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Nucleophilic displacement-reactions of the 4-sulfonyloxy group in derivatives having the D-*manno* configuration

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ABSTRACT

Methyl 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-(*p*-tolylsulfonyl) and 4-*O*-[(*p*-nitrophenyl)sulfonyl]-α-D-mannopyranosides (**9** and **10**) were prepared by three different routes from methyl α-D-mannopyranoside (**1**). The analogous 4-sulfonyloxy derivatives having HO-2 and HO-3 free (**14** and **15**) were also synthesized from **1**. Nucleophilic substitution of the sulfonyloxy group of **9**, **10**, **14**, and **15** by potassium thiocyanate in *N,N*-dimethylformamide was attempted. Compounds **9** and **10** gave a mixture of solvolysis products: methyl 2,3-di-*O*-benzoyl-6-deoxy-α-D-talopyranoside (**17**), methyl 3,4-di-*O*-benzoyl-6-deoxy-α-D-talopyranoside (**18**), and methyl 2,4-di-*O*-benzoyl-6-deoxy-α-D-talopyranoside (**19**), which are evidently formed by intramolecular displacement of the 4-sulfonate by backside attack of the C-2 benzoyloxy substituent, followed by benzoyl migration. The structure of compounds **17**–**19** was established by spectroscopic analysis, and then chemically confirmed. Although compound **14** decomposed during the substitution reaction, the 4-*p*-nitrophenylsulfonyl derivative **15** gave a 2:1 mixture of the 4-thiocyano derivatives with inversion [methyl 4,6-dideoxy-4-thiocyano-α-D-talopyranoside (**22**)] and retention [methyl 4,6-dideoxy-4-thiocyano-α-D-mannopyranoside (**23**)] of the C-4 configuration.

INTRODUCTION

We have recently reported a convenient procedure for the synthesis of 4-thio-D-galactofuranose[1] and 6-deoxy-4-thio-D-galactofuranose[2]. The key step in these syntheses was the substitution of a 4-sulfonyloxy group in a conveniently protected glucopyranoside derivative by a nucleophile precursor of the thiol. This reaction, when applied to 4-*O*-sulfonylmannopyranosides, should lead to derivatives of 4-thiotalose. However, an unusual rearrangement has been observed in the displacement reaction of the 4-mesylate of methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulfonyl-α-L-mannopyranoside by various nucleophiles such as sodium acetate[3], sodium azide[4], and potassium thiolbenzoate[5]. As a consequence of the rearrangement, the nucleophile becomes attached to C-5 with contraction of the pyranoside to a furanoside ring, and inversion of the configuration of C-4. A mechanism proposed for this unexpected ring-contraction[4] takes into account that, in the $^1C_4$ (L) conformation the C-5–O-5 bond is *trans*-antiparallel to the C-4–sulfonate bond, and the ring oxygen atom is thus in a favorable position for intramolecular, rearside attack on C-4. Nevertheless, 4-sulfonates of the *gluco* series, having the same stereochemistry as the *manno* derivatives at C-4

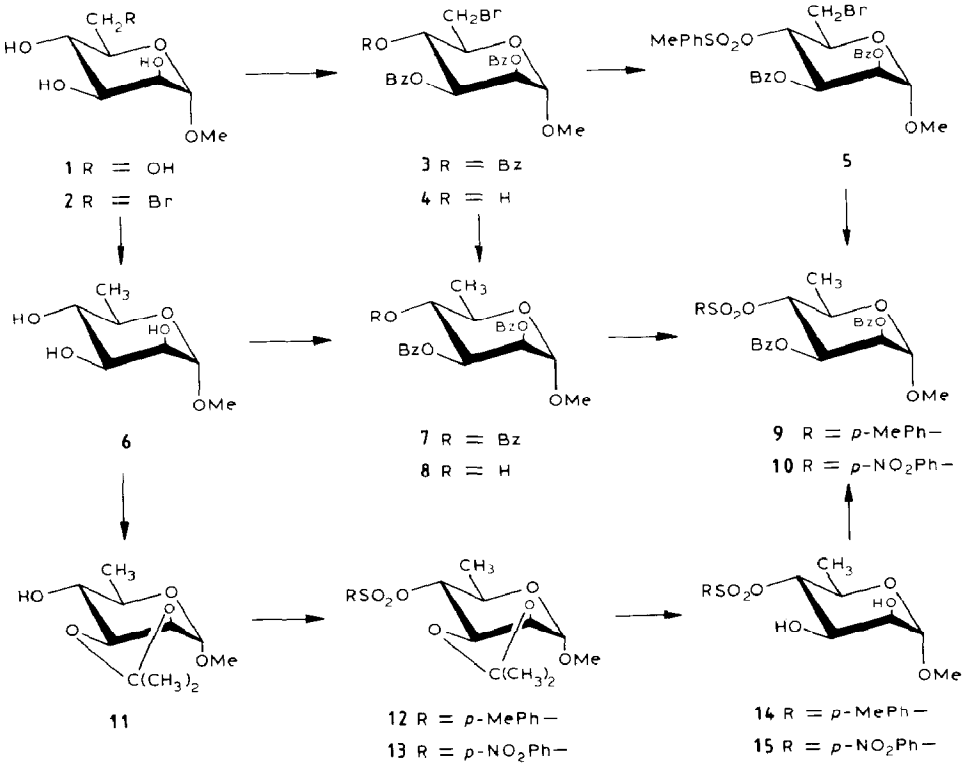
and C-5, did not rearrange during this substitution[12], indicating that other factors contribute to the stereochemical course of the reaction. Thus, the nature of the 2- and 3-substituents seems to have some influence, as the 4-mesylates of DL-oleandropyranoside and DL-amicetopyranoside having HO-4 and HO-5 in *erythro* relationship (as the *manno* derivatives), underwent ring contraction during the substitution[6] whereas methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-mannopyranoside reacted[7] with sodium benzoate to give the pyranoid 4-*O*-benzoyl derivative with retention of configuration at C-4. On the other hand, perbenzoylated 4-*O*-sulfonyl derivatives of methyl α-D-manno-[8] and α-L-rhamno-pyranosides[9] remained unreactive on treatment with sodium benzoate in refluxing DMF. In view of these controversial results, we undertook the study of the substitution reaction of 4-*O*-(*p*-tolylsulfonyl) and 4-*O*-(*p*-nitrophenylsulfonyl) derivatives of methyl 6-deoxy-α-D-mannopyranosides, having HO-2 and HO-3 free or benzoylated. In addition, convenient procedures for the preparation of such products, starting from methyl α-D-mannopyranoside, are described.

RESULTS AND DISCUSSION

Methyl 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-(*p*-tolylsulfonyl)-α-D-mannopyranoside (**9**) and its 4-*O*-[(*p*-nitrophenyl)sulfonyl] analog (**10**) were prepared by three alternative routes from methyl α-D-mannopyranoside (**1**). Two of these routes allowed us to evaluate the selectivity in the esterification reaction of the 6-bromo-6-deoxy (**2**) and 6-deoxy (**6**) derivatives of **1**, and also to compare the results with the selectivity observed for analogous compounds in the D-*gluco* series[12]. Compound **2** was obtained by treatment of **1** with carbon tetrabromide triphenylphosphine[10] and it was partially benzoylated with 2.3 molar equivalents of *N*-benzoylimidazole[11] in refluxing 1,2-dichloroethane. Two products were isolated from the reaction mixture by column chromatography: the 2,3,4-tribenzoate (**3**, 7% yield), previously described[12], and the 2,3-dibenzoate **4** (44% yield). The structure of **4** was assigned on the basis of its spectral data. Thus, the ^{13}C-n.m.r. spectrum of **4** showed a downfield shift for the C-3 and C-5 resonances (2.9 and 2.1 p.p.m. respectively) with respect to those of **3**, as expected[13] for the β-disposed carbon atoms of free and benzoylated HO-4.

Compound **2** was hydrogenated using Raney nickel as catalyst to give methyl 6-deoxy-α-D-mannopyranoside (**6**), which was also benzoylated with *N*-benzoylimidazole, affording the 2,3,4-tribenzoate (**7**) and the 2,3-dibenzoate (**8**), in 22 and 43% yield, respectively. These yields were similar to those reported[9] for the benzoylation of the enantiomer of **6** (L series), with benzoyl chloride–pyridine at low temperature. The product distribution in the benzoylation of **2** and **6** indicated a lower reactivity for the esterification of HO-4 in derivatives of the *manno* configuration, as described for related compounds[14].

The 5-bromomethyl group of **2**, being bulkier than the 5-methyl group of **6**, should generate a stronger *gauche* interaction in the benzoylation of HO-4 in **2** than in **6**, resulting in a lower amount of the perbenzoylated derivative of **2**. Similar results have been described for benzoylations of 6-bromo-6-deoxy and 6-deoxy derivatives having



the *gluco* configuration[2], which bear the same stereochemical relationship between HO-4 and the C-5 substituent. However, in the *gluco* series, the ratio of 2,3-di-*O*-benzoylated to tribenzoylated products were higher than in the mannopyranosides, under the same reaction conditions. This fact may be attributed to a lower reactivity of HO-2 in *manno* than in *gluco* compounds[14], because of its sterically unfavorable axial orientation, which makes HO-2 only slightly more reactive than HO-4.

Treatment of **3** with *p*-toluenesulfonyl chloride in pyridine afforded the crystalline tosylate **5**, in 73% yield. As observed for the sulfonylation of related compounds[1,2], the signal of C-4 in the ^{13}C-n.m.r. spectrum of **5** was shifted downfield (7.3 p.p.m.), and the β-carbon signals upfield (C-3 2.6 p.p.m. and C-5 2.5 p.p.m.), with respect to the same signals in the HO-4-free precursor **3**. Hydrogenation of **5** in the presence of Raney nickel gave crystalline methyl 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-(*p*-tolylsulfonyl)-α-D-mannopyranoside (**9**), which had the same melting point and optical rotation (absolute value), as values described for the L enantiomer[9]. Alternatively, compound **9** and its 4-*O*-(*p*-nitrophenyl)sulfonyl analog (**10**) were obtained by reaction of the dibenzoate **8** with tosyl chloride or *p*-nitrobenzenesulfonyl chloride (nosyl chloride). However, preparation of **10** by nosylation of **4** was not convenient, as on hydrogenolysis of the bromide the nitro group is reduced to the amine.

In order to improve the overall yield in the synthesis of **9** and **10** from **1**, we

followed an alternative route, via protection of HO-2 and HO-3 of **6** by acetonation prior to the sulfonylation of HO-4. Treatment of **6** with 2,2-dimethoxypropane, in the presence of a catalytic amount of *p*-toluenesulfonic acid, afforded methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**11**) in 85% yield. Reaction of **11** with tosyl chloride or nosyl chloride led to the corresponding tosylate **12** (64%) and nosylate **13** (72%). Hydrolysis of **12** and **13** with 2% HCl in methanol gave respectively methyl 6-deoxy-4-*O*-(*p*-tolylsulfonyl)-α-D-mannopyranoside (**14**) and methyl 6-deoxy-4-*O*-[(*p*-nitrophenyl)sulfonyl]-α-D-mannopyranoside (**15**). Benzoylation of **15** afforded the dibenzoate **10** in an overall yield at least 20% higher than obtained through the routes previously described.

The nucleophilic substitution was first studied for the 4-*O*-nosyl derivative **10**, using potassium thiocyanate as nucleophile, taking into account that, in aprotic solvents, this reagent is most convenient for the conversion of sulfonates into bivalent sulfur derivatives[12]. Treatment of **10** with KSCN in DMF solution for 6 h at 110° gave a mixture of three main products, which were isolated by column chromatography. The ^{1}H-n.m.r. spectra of the three products showed no signals for a nosyl group and the presence of a hydrogen atom interchangable by deuteration, suggesting a free HO group in the molecule. Moreover, the values determined for $J_{4,5}$ were between 0.7 and 1.5 Hz, indicating inversion of the C-4 configuration, from *manno* to *talo*. The spectroscopic data suggested that we were dealing with the three possible dibenzoylated isomers (**17**–**19**) of methyl 6-deoxy-α-D-talopyranoside. In effect, benzoylation of each isomer (**17**–**19**) afforded the same product: methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-talopyranoside (**20**). For a chemical confirmation of the D-*talo* structure of compounds **17**–**19**, one of the isomers (**17**) was *O*-debenzoylated with 5:2:1 MeOH–H_2O–Et_3N, and the resulting product was acetylated to afford crystalline methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-talopyranoside (**21**), whose physical constants were in good agreement with those reported[16]. Comparison of the ^{1}H-n.m.r. spectrum of **20** with that of each of the isomeric dibenzoates (**17**–**19**, Table I) allowed us to establish the location of the benzoates in those isomers. Thus, compound **17** showed the signal of HO-4 shifted upfield by 1.41 p.p.m. with respect to H-4 of the perbenzoate **20**, indicating that the unsubstituted hydroxyl group was HO-4, and **17** was therefore formulated as methyl 2,3-di-*O*-benzoyl-6-deoxy-α-D-talopyranoside. The structures of compounds **18** and **19** were similarly established as the 3,4- and 2,4-dibenzoates, respectively, by analysis of their spectra, which was facilitated by performing homonuclear and heteronuclear decoupling experiments.

Treatment of the 4-tosylate **9** with KSCN, in DMF at 110°, gave also a mixture of compounds **17**–**19**, although under the same conditions, reaction of **9** required a longer time (16 h). In contrast, it has been reported[9] that the L enantiomer of **9** remained unreactive under similar nucleophilic-displacement conditions.

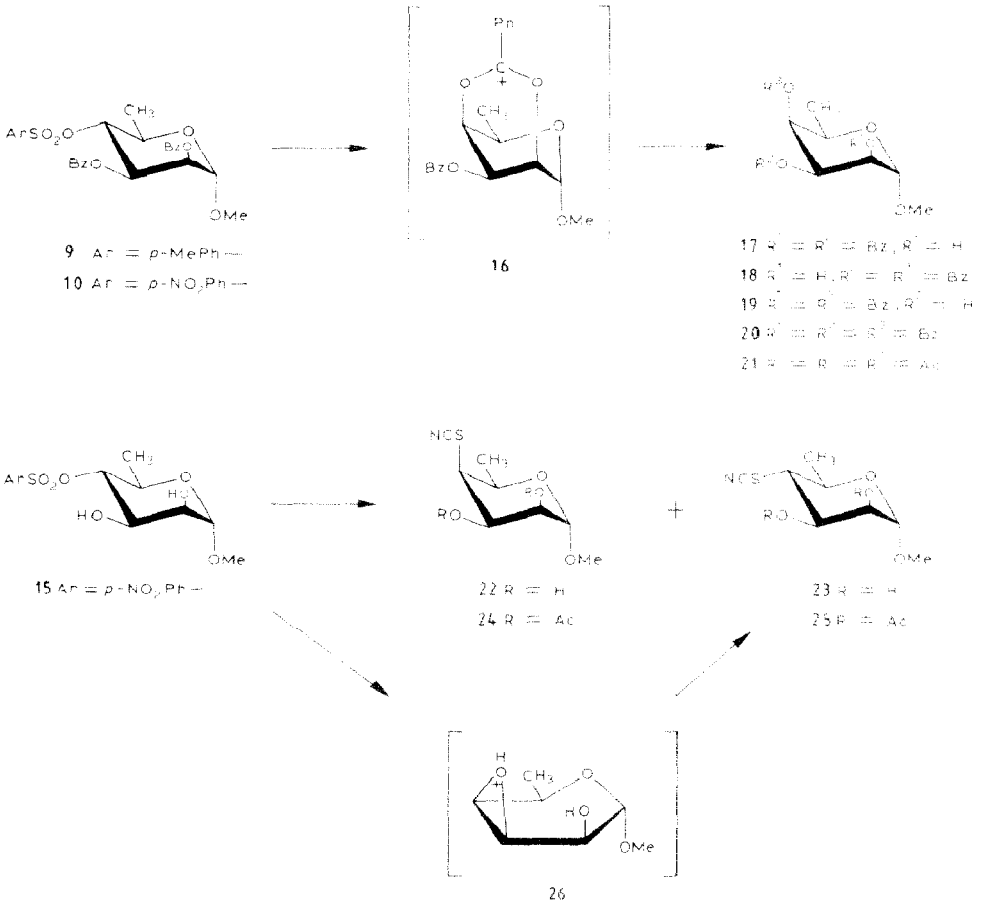
As no sulfur-containing products were obtained in the reaction of **9** or **10** with KSCN, the effect of heating a solution of **10** in the absence of KSCN was studied. Compound **10** dissolved in DMF was heated for 6 h at 110°, and the reaction was monitored by t.l.c., which revealed the formation of compounds **17**–**19** in a ratio similar

TABLE I

^{1}H-N.m.r. data for compounds **3**–**5**, **7**–**15**, **17**–**20**, and **22**–**25**

Compound	*δ, p.p.m.* J, *Hz*								
	H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{3,4}$)	*H-4* ($J_{4,5}$)	*H-5* ($J_{5,6}$)	*H-6* ($J_{5,6'}$)	*H-6'*	OCH_3	*Aromatic* (J_{ortho})
3	5.02 (2.0)	5.68 (2.5)	←5.78–5.94→		4.27	3.77	3.59	3.56	7.12–8.20
4	4.93	←5.34–5.64→		←3.64–4.65→				3.50	7.12–8.18
5[a]	4.87 (1.9)	5.49 (3.3)	5.68 (9.7)	5.23	4.09 (4.0)	3.82 (6.0)	3.60	3.43	6.74–8.10
7	4.92 (1.0)	5.67[b]	5.85 (10)	5.67[b] (8.8)	4.19 (6.3)	1.40		3.53	7.16–8.20
8	4.79 (2.0)	5.54 (3.0)	5.46 (10.0)	←3.6–4.0→		1.37		3.38	7.10–8.10
9[a]	4.81 (1.5)	5.52 (3.4)	5.68 (9.7)	5.02 (9.6)	4.07 (6.3)	1.50		3.46	6.80–8.16
10	4.81 (1.5)	5.49 (3.6)	5.71 (9.9)	5.00 (9.7)	4.14 (6.2)	1.55		3.46	7.08–8.10
11[c]	4.84 (<1.0)	←3.90–4.20→			3.58 (6.3)	1.24		3.33	
12[a,c]	4.85 (<1.0)	←3.98–4.18→		4.42 (10.1)	3.74 (6.3)	1.31		3.36	7.32, 7.84 (8.0)
13[c]	4.85 (<1.0)	←3.95–4.11→		4.47 (10.1)	3.79 (6.3)	1.38		3.37	8.11, 8.44 (8.3)
14[a]	4.64 (<1.0)	←3.64–4.05→		4.57 (9.1)	3.84[b] (6.2)	1.20		3.35	7.35, 7.88 (8.0)
15	4.64 (<1.0)	←3.62–4.00→		4.62 (9.0)	3.81[b] (6.2)	1.25		3.37	8.08, 8.50 (8.5)
17	4.93 (≅0)	←5.51–5.42→		3.98 (0.7)	4.17 (6.5)	1.40		3.47	7.20–8.19
18	4.92 (1.8)	4.03 (3.6)	5.51 (1.6)	5.66 (1.5)	4.31 (6.6)	1.31		3.48	7.14–8.12
19	4.99 (1.1)	5.27 (3.9)	4.41 (3.7)	5.45 (1.4)	4.22 (6.5)	1.33		3.46	7.12–8.18
20	4.95 (1.0)	5.55 (3.9)	5.68 (4.0)	5.39 (1.1)	4.30 (6.4)	1.28		3.41	7.08-8.10
22	4.66 (<1.0)	←3.66–3.94→			4.29 (6.5)	1.33		3.40	
23	4.74 (< 1.0)	←3.76–4.12→		(≅1.0) 2.96 (9.8)	3.94[b] (6.4)	1.49		3.40	
24[d]	4.61 (1.8)	4.80	4.92 (2.7)	3.74 (2.0)	4.32 (6.4)	1.22		3.33	
25[d]	4.63 (1.8)	5.20 (3.0)	5.34 (9.8)	3.09 (9.8)	4.05 (6.3)	1.54		3.45	

[a] CH_3Ph gave a singlet (3 H) at δ 20.9 for **5** and **9** and at δ 2.43 for **12** and **14**. [b] The δ value reported corresponds to the center of the multiplet of the overlapped signals. [c] The $(CH_3)_2C$ gave two singlets (3 H each) at δ 1.22–1.30 and 1.45–1.49. [d] CH_3CO gave a singlet (3 H) at δ 2.07–2.16.



to that observed for the reaction with KSCN, indicating that the talopyranoside dibenzoates **17**–**19** originated on solvolysis of the 4-sulfonyloxy group of **9** or **10**. It has been stated that 4-sulfonyloxy derivatives having the *manno* configuration are resistant to nucleophilic substitution. Thus, the perbenzoylated 4-*O*-sulfonyl derivative of methyl α-D-mannopyranoside did not react[8] when treated with sodium benzoate in refluxing DMF for 60 h. This, and other examples, have shown that the presence of a substituent *β-trans*-axial to the departing sulfonate group impedes direct replacement[17]. This *β-trans*-axial effect has been attributed to steric (1,3-diaxial) and polar interactions between the electronegative substituent and the charged nucleophile in the transition state of the reaction[17]. However, in the case of compounds **9** and **10**, intramolecular displacement of the sulfonate by rearside attack of the 2-benzoyloxy substituent, would involve a transition state of lower energy, as it is free of steric and dipolar repulsions, leading to the acyloxonium ion **16**. Examples of anchimeric assistance of acyloxy groups in the displacement of good leaving groups have been described. Thus, the solvolysis of sulfonyl derivatives of pyranoses by sodium fluoride in DMF takes place with participation of a *trans*-acyloxy group[18]. Also, Miljković and co-workers[7] observed the anchi-

meric assistance of a *β-trans*-axial benzoyloxy group in the reaction of 2-*O*-mesyl-D-galacto and 4-*O*-mesyl-D-manno-pyranosides with sodium benzoate in refluxing DMF. Although intramolecular displacement of sulfonate in **9** or **10** could be effected by participation of the benzoate at C-3, this assistance does not seem probable, since benzoylated 4-*O*-tosyl derivatives of the *gluco* series[1,2], having the same relative stereochemical relationship at C-3 and C-4 as **9** and **10**, were recovered unaltered after several h of heating at 110° in DMF. Furthermore, the attack of the axial 2-benzoyloxy on C-4 in **9** and **10** would take place without serious distortion of the favored $^4C_1$ conformation of the pyranoid ring, whereas an unfavorable chair inversion would be required for participation of the 3-benzoyloxy group in the displacement of the sulfonate at C-4. The intermediate benzoxonium ion **16** would also account for the three products formed (**17–19**), which would arise from the hydrolysis of **16**, during work-up of the reaction, followed by benzoyl migration between the *cis*-oriented oxygen functions at C-2, C-3, and C-4, as described for similar compounds[19].

Treatment of methyl 6-deoxy-4-*O*-(*p*-tolylsulfonyl)-α-D-mannopyranoside (**14**) with KSCN in DMF at 110° gave a complex mixture of products, which was not analyzed. However, the same reaction when applied to the 4-nosylate **15** led, after 6 h, to a mixture of two main products (R_F 0.48 and 0.22) which were separated by column chromatography. The less-polar component showed the signal for H-5 in a clear region of its ^{1}H-n.m.r. spectrum, showing $J_{4,5} \sim 1.0$ Hz, consistent with the change from the *manno* to the *talo* configuration. The ^{13}C-n.m.r. spectrum of this product showed the signal for the SCN carbon at δ 113.0, and the carbon atom linked to sulfur at δ 49.1, as in other thiocyanate derivatives[1,2]. The C-1 signal at a value (δ 100.3) close to that of its precursor **15**, excluded the possibility of ring contraction to the furanoid form. Therefore, the compound was formulated as methyl 4,6-dideoxy-4-thiocyano-α-D-talopyranoside (**22**), resulting from the normal substitution of the 4-*O*-tosyl group of **15** by thiocyanate. The ^{13}C-n.m.r. spectrum of the other component of the mixture (R_F 0.22) showed also the signals characteristic for the substitution by thiocyanate. In the ^{1}H-n.m.r. spectrum, the large values for $J_{3,4}$ (9.8 Hz) and $J_{4,5}$ (9.8 Hz) were consistent with a *manno* configuration for the compound, thus characterized as methyl 4,6-dideoxy-4-thiocyano-α-D-mannopyranoside (**23**). Compounds **22** and **23** were isolated in a 2:1 ratio. A similar ratio was obtained by acetylation of the crude substitution reaction-mixture, followed by chromatographic separation. The respective acetylated products **24** and **25** gave well-resolved ^{1}H-n.m.r. spectra (Table I), confirming the configurations proposed for **22** and **23**. The behavior of **15** contrasts with that of its benzoylated derivative **10**, which did not undergo substitution by thiocyanate, but intramolecular displacement of the sulfonate, through an acyloxonium ion **16**. However, neighboring-group participation could also account for the formation of the minor thiocyanate **23**, which retained the configuration of C-4 in the substitution reaction. Although anchimeric assistance of HO-2 does not seem probable on account of the long distance between HO-2 and C-4, HO-3, being *trans* to the 4-sulfonate, could attack C-4 with formation of the intermediate oxonium ion **26**. The attack of the thiocyanate ion on C-4 of **26** would lead to **23** as in the case of the oxirane opening reaction of methyl

3,4-anhydro-6-deoxy-α-D-talopyranoside by alkali[20]. The formation of the oxonium ion **26** would introduce a distortion (twisting) in the chair conformation of the pyranoid ring. This destabilizing factor could explain why compound **23** is the minor product of the reaction. On the other hand, a single electron-transfer mechanism could operate in the formation of **22** and **23** from **15**. This process may contribute in nucleophilic reactions, mainly when the leaving group is a nosylate[21].

The present results on nucleophilic substitution of 4-*O*-sulfonyl derivatives of mannopyranosides, as well as other reports in the literature, show that this reaction is not convenient for the incorporation of a nucleophile at C-4 with inversion of configuration. When the hydroxyl groups of those derivatives are free or acylated, they may participate to some extent and afford pyranoid products, resulting from the substitution of the 4-sulfonate with retention of the configuration at C-4, or from solvolysis of the 4-sulfonate to give the C-4 epimeric sugar. Ring-contraction products to the furanoid form are produced when there was no possibility of anchimeric assistance by neighboring groups. For 4-mesylates of methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside in particular, the formation of the furanoid product would be favored, as this may be stabilized by the presence of the fused isopropylidene five-membered ring[22].

TABLE II

^{13}C-N.m.r. data for compounds **2**–**15**, **17**–**20**, **22**, and **23**

Compound	*δ, p.p.m.*								
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	OCH_3	*C-aromatic*	C_6H_5CO *or* CH_3CO
2[a]	102.3	71.2*	71.7*	70.1	72.7	34.5	56.3		
3	98.6	70.3	70.0	69.7*	69.3*	31.9	55.6	128.1–133.4	165.3, 165.2 165.1
4	98.6	70.3	72.9	68.7	71.4	33.4	55.3	128.2–133.4	
5[b]	98.3	70.3	69.7	76.0	68.9	32.0	55.5	127.0–133.5	165.0, 164.5
6[a]	101.7	70.9*	71.1*	72.9	69.3	17.6	55.6		
7	98.5	69.9	71.8	70.7	66.5	17.7	55.3	128.1–133.3	165.2–165.4
8	98.4	70.8	73.1	71.9	68.5	17.7	55.0	128.2–133.2	165.3
9[b]	98.2	70.9	69.0	79.6	66.2	17.9	55.3	126.9–144.1	164.6, 165.1
10	98.1	70.6	68.6	81.5	66.0	17.7	55.3	123.8–142.3	164.9, 164.0
11[c]	97.9	75.6	78.4	74.2	65.5	17.4	54.7		
12[b,c]	97.7	75.6*	76.1*	83.3	63.3	17.3	54.9	127.9–134.4	
13[c]	97.6	75.2*	76.2*	85.2	63.0	17.2	55.0	123.8–143.0	
14[b]	99.9	70.8	69.4	83.2	64.9	17.2	55.0	127.9–132.8	
15	100.2	71.3	69.2	84.7	65.1	17.5	55.1	124.1–142.2	
17	99.0	69.9	68.6	69.9	66.4	16.3	55.2	128.2–133.4	165.2
18	102.1	68.2	68.0	71.8	64.7	16.4	55.3	128.1–133.3	
19	99.2	70.2	65.6	72.3	64.8	16.5	55.2	128.0–133.1	166.5, 167.2
20	99.4	68.0	66.7	69.4	64.8	16.4	55.3	128.0–132.9	164.9, 165.9 166.1
22[d]	100.3	70.6	67.6	49.1	62.0	16.1	54.9		
23[e]	100.3	70.2*	68.3*	53.3	66.8	18.9	55.2		

[a] Recorded in 1:1 D_2O–H_2O. [b] CH_2Ph appeared at ~21.5 p.p.m. [c] $(CH_3)_2C$ appeared ~109.5, and 26.2, 27.7 p.p.m. [d] SCN appeared at 113.0 and [e] 109.7 p.p.m. *Signals may be interchanged.

EXPERIMENTAL

General methods. — Melting points were determined in a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter for 1% solutions in $CHCl_3$ at 25°. ^1H- and ^{13}C-n.m.r. spectra were recorded with a Varian XL-100 spectrometer at 100.1 and 25.2 MHz, respectively, for solutions in $CDCl_3$ with Me_4Si as the internal standard. The ^1H-n.m.r. spectra of compounds **17**–**20** were determined with a Bruker AM-500 spectrometer. Data are shown in Tables I and II. I.r. spectra were recorded with a Perkin–Elmer 710B spectrophotometer; the polystyrene absorption at 1602 cm^{-1} was the reference. T.l.c. was performed on precoated aluminium plates (0.2 mm thickness) of Silica Gel 60F-254 (Merck) with 9:1 PhMe–EtOAc, unless otherwise indicated. Detection was effected by exposure of the plates to u.v. light or by spraying with 5% (v/v) H_2SO_4 in EtOH and subsequent heating. Silica Gel 60 (230–400 mesh, Merck) was used for column chromatography.

The following solvents were distilled before use: acetonitrile (from P_2O_5), dichloromethane (from P_2O_5), 1,2-dichloroethane (from P_2O_5), and pyridine (from KOH). *N,N*-Dimethylformamide (DMF) was purified by sequential drying[23] with 3-Å molecular sieves and distillation.

*Methyl 6-bromo-6-deoxy-α-*D*-mannopyranoside* (**2**). — To a suspension of methyl α-D-mannopyranoside (**1**, 1.0 g, 5.15 mmol) and CBr_4 (2.14 g, 6.45 mmol) in MeCN (6 mL), Ph_3P (2.04 g, 6.49 mmol) was slowly added, and the mixture was stirred for 48 h at room temperature. The solvent was evaporated and the residue extracted with water at 50° (3 × 100 mL). Upon concentration of the aqueous solution (30 mL) most of the Ph_3PO crystallized; it was filtered off and the filtrate evaporated. The residue was purified through a short column of silica gel with 1:1 EtOAc–PhMe, affording 0.77 g (58%) of compound **2**; $[\alpha]_D^{20}$ +57° (*c* 1.5, water), {lit.[24] $[\alpha]_D$ +52°}.

*Methyl 2,3-di-*O*-benzoyl-6-bromo-6-deoxy-α-*D*-mannopyranoside* (**4**). — To a suspension of compound **2** (0.26 g, 1.0 mmol) in 1,2-dichloroethane (8 mL), *N*-benzoylimidazole[25] (3.96 g, 2.30 mmol) was added and the stirred mixture was boiled under reflux for 24 h. The resulting solution was diluted with CH_2Cl_2 (200 mL) and extracted with 5% aq. HCl, water, sat. aq. $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$) and the solvent evaporated to afford a residue that showed two main spots on t.l.c. (R_F 0.62 and 0.37). The mixture was separated by column chromatography with 99:1 PhMe–EtOAc. The less-polar component (R_F 0.62) was isolated in 7% yield (40 mg) and characterized as methyl 2,3,4-tri-*O*-benzoyl-6-bromo-6-deoxy-α-D-mannopyranoside (**3**), which crystallized from EtOH; m.p. 182–184°, $[\alpha]_D^{20}$ −120°; {lit.[12] m.p. 181–182°, $[\alpha]_D$ −115°}.

The next fraction from the column afforded the other component of the mixture (R_F 0.37), identified as **4** (0.20 g, 44%). Crystallized from isopropyl ether–hexane compound **4** had m.p. 95–96°, $[\alpha]_D$ −15°.

Anal. Calc. for $C_{21}H_{21}BrO_7$: C, 54.21; H, 4.55. Found: C, 54.54; H, 4.66.

*Methyl 2,3-di-*O*-benzoyl-6-bromo-6-deoxy-4-*O*-(*p*-tolylsulfonyl)-α-*D*-mannopy-*

ranoside (**5**). — To a solution of **4** (0.86 g, 1.85 mmol) in pyridine (3 mL), tosyl chloride (1.38 g, 7.27 mmol) was slowly added. The mixture was kept at room temperature for 48 h, and then poured into ice–water (100 mL), affording compound **5** as an amorphous solid. Upon crystallization from EtOH (0.84 g, 73%) it had m.p. 109–110°, $[\alpha]_D^{20}$ −116°.

Anal. Calc. for $C_{28}H_{27}BrO_9S$: C, 54.29; H, 4.39. Found: C, 54.59; H, 4.54.

Methyl 6-deoxy-α-D-mannopyranoside (**6**). — Compound **2** (1.67 g, 6.50 mmol) dissolved in MeOH (80 mL) containing Et_3N (1.1 mL) was hydrogenated in the presence of Raney nickel (5.0 g) at 45 lb.in^{-2} for 8 h. The catalyst was filtered off and the solution was evaporated. The resulting syrup was chromatographed on silica gel (EtOAc) to give 1.06 g (91%) of compound **6**, $[\alpha]_D^{20}$ +69° (*c* 1, water) [lit.[26] $[\alpha]_D$ −67° for the L enantiomer].

Methyl 2,3-di-O-benzoyl-6-deoxy-α-D-mannopyranoside (**8**). — (**a**) *Starting from methyl 2,3-di-O-benzoyl-6-bromo-6-deoxy-α-D-mannopyranoside* (**4**). Compound **4** (0.10 g, 0.22 mmol) dissolved in MeOH (3 mL) containing Et_3N (0.03 mL) was hydrogenated using Raney nickel as described for the preparation of **6**. The resulting syrup was purified through a column of silica gel to give 66 mg (80%) of compound **8**: $[\alpha]_D^{20}$ −71° [lit.[9] +76° for the L enantiomer].

(*b*) *Starting from methyl 6-deoxy-α-D-mannopyranoside* (**6**). To a suspension of **6** (0.55 g, 3.10 mmol) in 1,2-dichloroethane (25 mL) heated to boiling under reflux, *N*-benzoylimidazole[25] (1.16 g, 6.77 mmol) was added and the heating was continued for 24 h. The procedure described for the preparation of **3** was then followed. The mixture, which showed two main spots on t.l.c. (R_f 0.74 and 0.49) was chromatographed on silica gel with 99:1 PhMe–EtOAc. The fastest-migrating component (R_f 0.74) was obtained as a syrup (0.33 g, 22%) and identified as methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-mannopyranoside (**7**), m.p. 131–132° (from EtOH), $[\alpha]_D^{20}$ −172°.

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.27; H, 5.54.

From the next chromatographic fraction (R_f 0.49), compound **8** (0.52 g, 43%) was isolated; it showed the same physical constants as those already indicated.

Methyl 2,3-di-O-benzoyl-6-deoxy-4-O-(p-tolylsulfonyl)-α-D-mannopyranoside (**9**). — Compound **5** (0.14 g, 0.22 mmol), dissolved in 1:1 MeOH–EtOAc (3 mL) containing Et_3N (0.11 mL) was hydrogenated using Raney nickel, as described for the preparation of **6**. Crystallization from EtOH afforded 0.10 g (84%) of compound **9**, m.p. 108–109°, $[\alpha]_D^{20}$ −158° [lit.[9] m.p. 107–109°, $[\alpha]_D$ +163° for the L enantiomer].

Methyl 2,3-di-O-benzoyl-6-deoxy-4-O-[(p-nitrophenyl)sulfonyl]-α-D-mannopyranoside (**10**). — To a solution of compound **8** (0.42 g, 1.08 mmol) in anhydrous pyridine (8 mL), 4-nitrobenzenesulfonyl chloride (0.85 g, 3.83 mmol) was added. The mixture was kept for 48 h at room temperature, and then poured into ice–water, affording an amorphous solid. Crystallization from EtOH gave compound **10** (0.47 g, 77%) having m.p. 139–140°, $[\alpha]_D^{20}$ −183°.

Anal. Calc. for $C_{27}H_{25}NO_{11}$: C, 56.74; H, 4.41. Found: C, 56.96; H, 4.56.

Methyl 6-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (**11**). — To a suspension of compound **6** (0.47 g, 2.63 mmol) in acetone (5 mL) and 2,2-dimethoxypropane (5 mL), *p*-toluenesulfonic acid (0.1 g) was added and the mixture was stirred until

dissolution of **6** was complete (~20 min). The solution was diluted with water (10 mL) and stirring was continued for 3 h, whereupon M $NaHCO_3$ (1 mL) was added. The solution was evaporated and the residue was extracted with ether. The extract was concentrated, affording syrupy compound **11**, which was purified through a column of silica gel with 4:1 PhMe–EtOAc. Compound **11** (0.48 g, 85%) had $[\alpha]_D^{20}$ +10° [lit.[27] $[\alpha]_D$ −12° for the L enantiomer].

*Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-(*p*-tolylsulfonyl)-α-*D*-mannopyranoside* (**12**). — To a solution of compound **11** (0.40 g, 1.83 mmol) in anhydrous pyridine (10 mL), tosyl chloride (1.0 g, 5.24 mmol) was added. The mixture was kept at room temperature for 4 days, and then poured into ice–water and extracted with CH_2Cl_2. The organic extract was washed with 5% aq. HCl, water, and aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a column of silica gel with 99:1 PhMe–EtOAc, to give 0.43 g (64%) of compound **12**, which, after crystallization from EtOH had m.p. 59–60°, $[\alpha]_D^{20}$ −23° [lit.[27] m.p. 61–62°; $[\alpha]_D$ +22° for the L enantiomer].

*Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-[(p-nitrophenyl)sulfonyl]-α-*D*-mannopyranoside* (**13**). — To a solution of compound **11** (0.22 g, 1.00 mmol) in anhydrous pyridine (5 mL), 4-nitrobenzenesulfonyl chloride (0.74 g, 3.33 mmol) was added. The mixture was kept for 48 h at room temperature and then poured into ice–water. The product was isolated as described for the preparation of **12**; yield 0.29 g (72%) of compound **13**, $[\alpha]_D^{20}$ −15°.

Anal. Calc. for $C_{16}H_{21}NO_9S$: C, 47.63; H, 5.25. Found: C, 47.25; H, 5.29.

*Methyl 6-deoxy-4-*O*-(p-tolylsulfonyl)-α-*D*-mannopyranoside* (**14**). — A solution of compound **12** (0.35 g, 0.95 mmol) in MeOH (2.7 mL) was treated with 2% HCl in MeOH (5.3 mL). The mixture was stirred for 8 h at 35°, whereupon no compound **12** was detected by t.l.c. The solution was made neutral with aq. $NaHCO_3$, and concentrated. The residue was extracted with CH_2Cl_2, and the organic extract was dried ($MgSO_4$) and evaporated to a syrup, which was purified by a column chromatography (4:1 PhMe–EtOAc), affording 0.25 g (80%) of compound **14**; $[\alpha]_D^{20}$ +78°.

Anal. Calc. for $C_{14}H_{20}O_7S$: C, 50.59; H, 6.06. Found: C, 50.62; H, 6.14.

Compound **14** (0.11 g, 0.34 mmol) dissolved in pyridine (3 mL) was benzoylated with BzCl (1.0 mL, 8.61 mmol), affording 0.15 g (85%) of compound **9**, which showed the same physical constants as those already described.

*Methyl 6-deoxy-4-*O*-[(p-nitrophenyl)sulfonyl]-α-*D*-mannopyranoside* (**15**). — Compound **13** (0.22 g, 0.54 mmol) was hydrolyzed with 2% HCl in MeOH (3 mL) as described for **14**, affording 0.18 g (91%) of syrupy **15**, $[\alpha]_D^{20}$ +38°.

Anal. Calc. for $C_{13}H_{17}NO_9S$: C, 42.97; H, 4.72. Found: C, 42.73; H, 4.46.

*Methyl 2,3-di-*O*-benzoyl-6-deoxy-α-*D*-talopyranoside* (**17**), *methyl 3,4-di-*O*-benzoyl-6-deoxy-α-*D*-talopyranoside* (**18**), *and methyl 2,4-di-*O*-benzoyl-6-deoxy-α-*D*-talopyranoside* (**19**). — *(a) Starting from methyl 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-[(p-nitrophenyl)sulfonyl]-α-*D*-mannopyranoside* (**10**). To a solution of **10** (0.42 g, 0.74 mmol) in dry DMF (4.2 mL), KSCN (0.49 g, 5.03 mmol) was added. The mixture was stirred under N_2 for 6 h at 110°, and then was poured into water and extracted with CH_2Cl_2. The organic extract was washed with water, dried ($MgSO_4$), and evaporated. The residue, which

showed three spots on t.l.c. (R_f 0.38, 0.33 and 0.26) was chromatographed on silica gel (99:1 PhMe–EtOAc). Fractions containing the fastest-migrating component (R_f 0.38) were pooled and evaporated, affording 104 mg (36%) of compound **17**; $[\alpha]_D^{20}$ −20°.

Anal. Calc. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.45; H, 5.60.

Evaporation of the fractions containing the product of R_f 0.33 gave 66 mg (23%) of compound **18**; $[\alpha]_D^{20}$ +119°.

Anal. Calc. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.55; H, 5.52.

From the next fraction from the column, the more-polar component (R_f 0.26) was isolated (52 mg, 18%), and identified as **19**. After recrystallization from isopropyl ether–hexane **19** it had m.p. 185–187°, $[\alpha]_D^{20}$ +64°.

Anal. Calc. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.39; H, 5.57.

In an additional experiment, a solution of compound **10** (25 mg, 0.04 mmol) in DMF (0.4 mL) was heated at 110° under N_2. After 4 h, the mixture was examined by t.l.c., which showed that the starting material had been completely converted into compounds **17** **19**.

(*b*) *Starting from methyl 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-(*p*-tolylsulfonyl)-α-*D*-mannopyranoside* (**9**). To a solution of **9** (0.13 g, 0.25 mmol) in dry DMF (1.3 mL), KSCN (0.15 g, 1.54 mmol) was added. After heating for 16 h at 110° under N_2, no starting **9** was detected by t.l.c., and the mixture was treated as described in (*a*), affording compounds **17** (31 mg, 33%), **18** (13 mg, 14%), and **19** (10 mg, 11%).

*Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-*D*-talopyranoside* (**20**). — To a solution of compound **17** (13 mg, 0.03 mmol) in dry pyridine (0.5 mL), BzCl (0.5 mL, 4.3 mmol) was slowly added at 0°. The mixture was kept for 90 min at room temperature, and then poured into water and extracted with CH_2Cl_2. The organic extract was washed with 5% aq. HCl, water, aq. $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated.

Compounds **18** (13 mg, 0.03 mmol) and **19** (13 mg, 0.03 mmol) were benzoylated as described for **17**, to afford the same product, which was also identical (^{1}H-n.m.r. spectrum) to the benzoate obtained from **17**. The three crude, syrupy products were pooled and purified by column chromatography, affording compound **20** (45 mg, 91%), $[\alpha]_D^{20}$ +50°.

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.45; H, 5.28.

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-*D*-talopyranoside* (**21**). — Compound **17** (38 mg, 0.10 mmol) was suspended in 5:2:1 MeOH–H_2O–Et_3N (2 mL) and stirred at room temperature until dissolution was complete. The solvent was evaporated and the residue was dried in a vacuum over P_2O_5, and then dissolved in 1:1 pyridine–Ac_2O (1 mL). The solution was stirred for 90 min and then evaporated. After two successive evaporations with toluene and MeOH, a syrup was obtained which crystallized upon addition of hexane to give 25 mg (67% from **17**) of compound **21**, m.p. 88–90°, $[\alpha]_D^{20}$ +74° [lit.[16] m.p. 91–92°, $[\alpha]_D^{20}$ −73°, for the L enantiomer].

*Methyl 4,6-dideoxy-4-thiocyano-α-*D*-talopyranoside* (**22**) *and methyl 4,6-dideoxy-4-thiocyano-α-*D*-mannopyranoside* (**23**). — To a solution of compound **15** (0.50 g, 1.37 mmol) in DMF (7.0 mL) KSCN (0.81 g, 8.31 mmol) was added. The mixture was heated for 6 h at 110°. The solution was diluted with CH_2Cl_2 (300 mL) and washed with

water (2 × 200 mL). The organic layer was dried ($MgSO_4$) and evaporated, affording a syrup (0.26 g) which showed two main spots on t.l.c. (R_F 0.48 and 0.22, 2:1 PhMe–EtOAc). A portion (25 mg) of this mixture was acetylated (see later), and the remaining material was chromatographed on silica gel (6:1 PhMe–EtOAc). The fastest-migrating component (R_F 0.48) was isolated (96 mg, 35%) and identified as compound **22**, which crystallized from EtOAc–hexane; m.p. 85–88°, $[\alpha]_D^{20}$ +43°; ν_{max} 3500–3100 (OH) and 2175 cm^{-1} (SCN).

Anal. Calc. for $C_8H_{10}NO_4S$: C, 44.44; H, 4.66. Found: C, 44.15; H, 4.93.

Fractions containing the slower migrating component (R_F 0.22) were pooled and evaporated, to afford 47 mg (17%) of compound **23**, $[\alpha]_D^{20}$ +24°; ν_{max} 3700–3000 (OH) and 2175 cm^{-1} (SCN).

Anal. Calc. for $C_8H_{10}NO_4S$: C, 44.44; H, 4.66. Found: C, 44.58; H, 4.75.

Acetylation of the crude reaction mixture of **15** with KSCN gave two products, which were separated by column chromatography (6:1 PhMe–EtOAc). The more-polar compound (R_F 0.44) was methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4-thiocyano-α-D-talopyranoside (**24**), isolated in 32% yield from **15**. The other component of the mixture (R_F 0.50) was repurified chromatographically, affording methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4-thiocyano-α-D-mannopyranoside (**25**, 12% yield from **15**).

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