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SYNTHESIS OF ANALOGS OF METHYL β-D-GALACTOPYRANOSIDE MODIFIED AT C-4

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ABSTRACT

Syntheses are reported of 4-substituted, 4-deoxy analogs of methyl β-D-galactopyranoside (the 4-amino-4-deoxy, 4-azido-4-deoxy, 4-bromo-4-deoxy, 4-chloro-4-deoxy, 4-deoxy-4-fluoro, 4-deoxy-4-iodo, and 4-thio derivatives) as potential substrates of D-galactose oxidase. These syntheses involved nucleophilic displacement of the 4-(*p*-bromophenylsulfonyl)oxy group of appropriate D-glucose derivatives, although the more reactive (trifluoromethylsulfonyl)oxy group was also utilized as a novel leaving-group. Formation of the bromo and iodo derivatives was accompanied by appreciable halogen exchange and a resulting overall retention of configuration, and formation of the thio compound was attended by competing reactions. Optical rotatory characteristics of the halogeno compounds, their triacetates, and tribenzoates are described, and "anomalous" behavior of the last group is noted.

RESULTS AND DISCUSSION

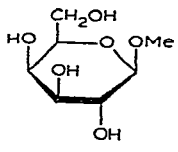
In conjunction with studies[1–3] on the stereochemistry of D-galactose oxidase, several analogs of methyl β-D-galactopyranoside (**1**) have been synthesized as potential substrates of the enzyme. That is, a group of glycosides has been prepared by replacement of the axially attached 4-hydroxyl group of **1** by a variety of other axial substituents. Some of these deoxy analogs (amino, chloro, and fluoro) are good to relatively poor substrates, whereas others (azido, bromo, iodo, and thio) are unaffected by D-galactose oxidase and do not serve as competitive inhibitors. The effectiveness of the 4-substituent as an enzyme-activating group appears to be a function of its size[3].

Synthesis of these 4-deoxy analogs involved SN2 displacement of the 4-sulfonyloxy group of a suitably protected derivative of methyl β-D-glucopyranoside. In general, the syntheses closely resembled those of related derivatives in other series[4–6]; the following discussion therefore emphasizes those results and observations that are particularly characteristic of the current study.

The (*p*-bromophenylsulfonyl)oxy (brosyloxy) group proved to be suitably reactive for the various substitutions described, although, in one synthesis, an even more facile leaving-group, the (trifluoromethylsulfonyl)oxy (triflyloxy)[7–10] group

was employed. Triflyl derivatives of carbohydrates do not appear to have been previously described and, based on the present results, the potential usefulness of such sulfonyl compounds merits further examination.

Partial benzoylation of methyl β-D-glucopyranoside, as for the α-anomer[11,12], afforded mainly the 2,3,6-tribenzoate (compound **2**). Several minor products were also isolated: the 2,6- and 3,6-dibenzoates and the 3,4,6-tribenzoate, as well as some tetrabenzoate (see also, ref. 12). Treatment of **2** with *p*-bromobenzenesulfonyl chloride then gave the main starting-compound for the SN2 reactions, namely, methyl 2,3,6-tri-*O*-benzoyl-4-*O*-brosyl-β-D-glucopyranoside (**3**).



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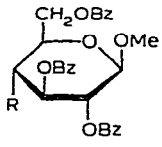
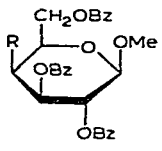
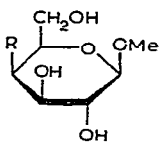


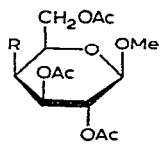
2 R = OH
3 R = *p*-$BrC_6H_4SO_2O$
7 R = F_3CSO_2O
17 R = I
31 R = Br



4 R = N_3 **23** R = Br
11 R = SBz **24** R = Cl
13 R = SCN **30** R = F
16 R = I



5 R = N_3 **19** R = H
6 R = NH_2 **21** R = Br
10 R = SH **22** R = Cl
15 R = I **27** R = F



8 R = N_3 **25** R = Br
9 R = NHAc **26** R = Cl
18 R = I **29** R = F
20 R = H

Methyl 4-azido-4-deoxy-β-D-galactopyranoside (**5**) *and methyl 4-amino-4-deoxy-β-D-galactopyranoside* (**6**). — The brosylate **3** in *N*,*N*-dimethylformamide (DMF) was treated with a suspension of sodium azide in DMF for 12 h at 95–100°, affording methyl 4-azido-2,4,6-tri-*O*-benzoyl-4-deoxy-β-D-galactopyranoside (**4**). Under the same reaction-conditions, methyl 2,3,6-tri-*O*-benzoyl-4-*O*-triflyl-β-D-glucopyranoside (**7**) gave a comparable yield of **4** in only 2–3 hours. Alkaline *O*-debenzoylation converted **4** into crystalline methyl 4-azido-4-deoxy-β-D-galactopyranoside (**5**), and hydrogenation of **5** over palladium black at room temperature and pressure afforded crystalline methyl 4-amino-4-deoxy-β-D-galactopyranoside (**6**). The p.m.r. spectrum of **4** and those of the peracetates (**8** and **9**) of **5** and **6** were consistent with the *galacto* configuration; this is most clearly evident from the small value observable for $J_{3,4}$ or $J_{4,5}$ (see Table I).

Methyl 4-thio-β-D-galactopyranoside (**10**). — The synthesis of thio sugars by nucleophilic displacement most commonly employs thioacetate, thiobenzoate, or thiocyano anions[13].

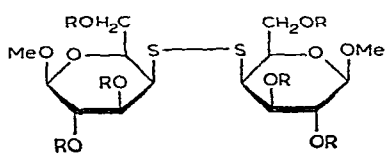
TABLE I

OBSERVED SPACINGS (Hz) FOR RING PROTONS OF β-D-*galacto* AND β-D-*gluco* DERIVATIVES[a] HAVING DIFFERENT SUBSTITUENTS AT C-4

Compound	*4-Substituent*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
4	azido	7.8	10.0	3.6	2.0
11	S-COPh	7.5	10.0	3.8	1.8
13	SCN	8.0	10.0	4.0	1.6
16	I	8.0	9.7	4.0	1.9
23	Br	8.0	10.0	3.8	1.8
24	Cl	8.0	10.0	3.4	1.5
30	F	8.0	9.8	2.8	1.2
Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside		7.7	10.0	3.2	1.2
17	I	7.8	10.0	9.5	10.0
31	Br	7.8	9.8	9.8	9.8
Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside		7.9	10.0	9.2	9.6

[a]The solvent was C_6D_6, except for the last three compounds, for which it was $CDCl_3$.

An attempt to displace the brosyloxy group of **3** with thioacetate in DMF resulted in the formation of a mixture of difficulty separable compounds that was not characterized. However, with thiobenzoate as the nucleophile, displacement was achieved in 4–6 h at a bath temperature of 95–100°, and purification of the reaction product on silica gel afforded crystalline methyl 2,3,6-tri-*O*-benzoyl-4-*S*-benzoyl-4-thio-β-D-galactopyranoside (**11**). As already noted in connection with the synthesis of **4**, the p.m.r. spectrum of **11** (see Table I) is consistent with the expectation that there had been a change of the *gluco* to the *galacto* configuration. Attempts to obtain the free thiol **10** by complete debenzoylation of **11** (which was a very slow process with methanolic ammonia, sodium methoxide, or lithium aluminum hydride) yielded an impure product. Acetylation of the latter gave crystalline material which proved to be the hexaacetate of the 4,4′-disulfide **12**. Similar results were obtained by



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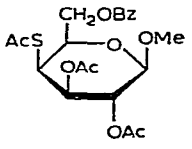
using an alternative route involving the 4-thiocyano derivative **13**, followed by alkaline hydrolysis[14]. These findings are analogous to those obtained[15] with methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4,6-di(thiocyano)-α-D-galactopyranoside (which was converted into a 4,6-cyclic disulfide diacetate), and afford another illustration of the facile, oxidative coupling of sugar thiols[13,16,17].

As already noted, complete debenzoylation of **11** occurs very slowly. After partial hydrolysis with sodium methoxide for two days, a major product was obtained which was purified by column chromatography on silica gel, followed by acetylation. Formation of this acetate, tentatively designated methyl 2,3-di-*O*-acetyl-4-*S*-acetyl-6-*O*-benzoyl-4-thio-β-D-galactopyranoside (**14**), showed that one of the benzoyl substituents of **11** is particularly stable. As benzoates are normally readily saponified



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(and this is true of the 2-, 3-, and 6-*O*-benzoyl groups of the 4-cyano derivative **13**), the group in **11** resistant to hydrolysis must be its *S*-benzoyl group. The p.m.r. spectrum of **14** suggested, however, that the benzoate group retained had migrated from the axially attached S-4 atom to O-6, possibly *via* a six-membered, 4,6-orthoester intermediate[18], during processing; the chemical shifts of the protons on C-6 of **11** and **14** are similar, whereas the signals for H-2, H-3, and H-4 of the latter are relatively more shielded, suggesting that O-6 of each is benzoylated, and that O-2, O-3, and S-4 of **14** are acetylated, not benzoylated.

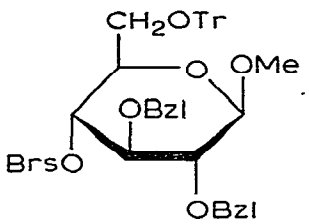
Methyl 4-deoxy-4-iodo-β-D-galactopyranoside (**15**). — When brosylate **3** in acetonitrile[19] was treated with an excess of tetrabutylammonium iodide at 95–100°, two crystalline products, **16** and **17**, were obtained*; compound **16** was the initial product, and this was gradually transformed by prolonged reaction into **17**. The p.m.r.-spectral characteristics of these compounds (especially $J_{3,4}$ and $J_{4,5'}$; see Table I) showed clearly that **16** is the expected methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-β-D-galactopyranoside, whereas **17** is its D-*gluco* epimer. Formation of the latter can be accounted for by nucleophilic attack of iodide at C-4 of **16**, inasmuch as ^{131}I exchange has been shown[20] to take place more rapidly at C-4 in the *galacto* than in the *gluco* series. Debenzoylation of **16** afforded crystalline **15**, and a crystalline triacetate (**18**) of **15** was also prepared.

Methyl 4-deoxy-β-D-xylo-hexopyranoside (**19**). — A mixture of the *galacto* and *gluco* iodides (**16** and **17**) was debenzoylated, and the product was then dehalogenated by hydrogenolysis over palladium black. As monitored by t.l.c., the hydrogenolysis proceeded more rapidly with the *gluco* than with the *galacto* diastereoisomer. Purification of the product through conversion into methyl 2,3,6-tri-*O*-acetyl-4-deoxy-β-D-*xylo*-hexopyranoside (**20**), followed by deacetylation, afforded the title compound (**19**).

*Use of a slightly higher reaction-temperature (100–120°) resulted in the formation of a third, minor product. The latter, which has not been obtained in a satisfactorily pure form, has been tentatively characterized by p.m.r. spectroscopy as a 3-deoxy-3-iodo derivative.

Methyl 4-bromo-4-deoxy-β-D-galactopyranoside (**21**) *and methyl 4-chloro-4-deoxy-β-D-galactopyranoside* (**22**). — Displacement of the brosylate group of **3** in acetonitrile with either tetrabutylammonium bromide or chloride yielded the 4-bromo-4-deoxy- (**23**) or 4-chloro-4-deoxy- (**24**) β-D-galactopyranoside tribenzoate, respectively. In each instance, the *galacto* configuration was confirmed by p.m.r. spectroscopy (see Table I). Halogen exchange was less pronounced in the formation of **23** than in that of its iodo analog (**17**), as indicated by the fact that only a small proportion of a second product was detected*, and this appeared to be completely absent in the synthesis of the chloride **24**. These observations are, therefore, in accord with the relatively greater nucleophilicity of iodide ion than of chloride or bromide ion[21] and also with its better leaving-group characteristics[22]. Crystalline triacetates **25** and **26** were prepared by *O*-debenzoylation of **23** and **24**, followed by acetylation.

Methyl 4-deoxy-4-fluoro-β-D-galactopyranoside (**27**). — The attempted use of tetrabutylammonium fluoride[19] in a displacement reaction with **3** was accompanied by the loss of benzoate, as well as of the brosyl group. As an alternative route to **27**, the approach recently described for synthesis of its α anomer (**23**) was adopted. That is, methyl 2,3-di-*O*-benzyl-4-*O*-brosyl-6-*O*-trityl-β-D-glucopyranoside (**28**) was prepared,



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(Brs = *p*-bromophenyl sulfonyl;
Bzl = benzyl;
Tr = trityl)

and treated with tetrabutylammonium fluoride in acetonitrile at 95–100°; for replacement of the brosyloxy group, a reaction period of two days sufficed, in contrast to the five days required with the mesyl derivative (**23**). The product was detritylated with hydrogen bromide, and the *O*-benzyl groups were then removed by hydrogenolysis, affording** crystalline **27**.

*From the coupling constants measured for this product, it is undoubtedly the 4-bromo-4-deoxy-D-*gluco* isomer (**31**) (see Table I).

**No *gluco* isomer was detected in this synthesis, indicating that, as with the chloro analog, halogen exchange did not follow the initial displacement by fluoride ion.

The p.m.r. spectrum of **29**, the triacetate of **27**, is consistent with the *galacto* configuration. Accordingly, as was observed for the α anomer **23**, the geminal coupling between H-4 and ^{19}F is 50 Hz, and H-3 and H-5 show coupling of 25 Hz with *trans*-disposed ^{19}F-4. Also consistent are the small couplings observed (see Table I) between the 3-, 4-, and 5-protons. Whereas no long-range, ^{19}F coupling[24,25] was detected in the p.m.r. spectrum of the α anomer[23], **25** shows two such interactions, one involving the fluorine atom with H-2 (1.1 Hz) and one with one H-6 (1.1 Hz). The 2,3,6-tri-*O*-benzoyl derivative (**30**) of **27** also shows these long-range interactions, although with smaller splittings (0.7 Hz). In addition, **30** displays a novel, axial–axial, five-bond coupling of about 0.5 Hz between ^{19}F-4 and H-1; this is much smaller than the ^5J values of 3.4–4.0 Hz reported[26] for equatorial ^{19}F-4 and equatorial H-1 in the α-D-*gluco* series.

Optical rotations of the halogenated derivatives. — The availability of the series of 4-deoxy-4-halogeno derivatives in this study has permitted a comparison of the effect of the different halogen substituents on rotatory and spectral characteristics of the compounds. Optical rotations ($[M]_D$) of the unesterified compounds (**15**, **21**, **22**, and **27**) and of their triacetates (**18**, **25**, **26**, and **29**) increase with increasing atomic weight (see Table II). An analogous trend is seen for the series of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl halides (see Table II). Hence, in both series, the upward progression parallels increasing polarizability of the halogen atom, from fluorine through iodine. Differences are also observed for 6-deoxy-6-halogeno derivatives (see Table II), although it is noteworthy that the trends are in opposite directions for the two groups of seemingly closely related compounds.

TABLE II

MOLECULAR ROTATIONS ($[M]_D$) OF HALOGEN DERIVATIVES

Parent compound	$[M]_D$ (*degrees*)			
	F	*Cl*	*Br*	*I*
Methyl 4-deoxy-4-halogeno-β-D-galactopyranoside[a]	−41.7	+18.5	+39.1	+77.5
2,3,6-triacetate[b]	−20.0	+104.8	+150.1	+326.8
2,3,6-tribenzoate[b]	+320.0	+318.7	+299.9	+293.8
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl halide[c]	+315.0	+609.2	+813.8	+1058.0
2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl halide[c]	+657.8	+670.4	+810.6	+981.3
1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-halogeno-β-D-glucopyranose[d]	+70.0	+66.1	+49.3	+45.8
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-halogeno-β-D-glucopyranoside[d]	—	−33.9	−3.8	+4.3

[a]Solvent, H_2O. [b]Solvent, $CHCl_3$. [c]Ref. 27. [d]Ref. 28.

O-Benzoyl derivatives **16**, **23**, **24**, and **30** are anomalous in this context, in that their optical rotations are all closely similar (see Table II). Among the D-glucopyranosyl halides, replacement of the acetate groups by benzoate has a noticeable, but

smaller, effect. However, in both series, there is a particularly large enhancement of the rotatory power of the fluoro derivative, and a progressively diminishing one for the chloro and other derivatives. Although this enhancement is undoubtedly due to the high polarizability of the phenyl groups themselves (see, for example, ref. 29), the 2-, 3-, and 6-*O*-benzoyl substituents obviously cannot contribute in a constant way to each of the derivatives. Possibly, the orientation of, for example, the 3-*O*-benzoyl group is altered with increasing size of the nearby halogen atom, causing graded change in the interaction between substituents and the incident light. In any event, the spin–spin coupling values (see Table I) suggest that these observations are not related to conformational change of the β-D-galactopyranosyl ring.

The marked influence of *O*-benzoyl groups on optical activity is clearly seen in the large variation in molecular rotation of the partially benzoylated compounds isolated, together with that of methyl 2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**2**); thus, $[M]_D$ (in chloroform) +393.9° (2,3,6-tri), −146.5° (3,4,6-tri), +56.0° (3,6-di), and −168.0° (2,6-di) [and +164.7° (2,3,4,6-tetra)]. Despite this wide range of values, however, some consistencies may be noted. It appears, for example, that the 2-*O*-benzoyl group is associated with a positive enhancement of rotatory power in the series; comparison of two different pairs of compounds gives the following results.

2,3,4,6 = +164.7°		2,3,6 = +393.9°	
− 3,4,6 = −146.7°	and	− 3,6 = +56.0°	
2 = +311.2°		2 = +337.9°	

Similarly, the 4-*O*-benzoyl group seems to be associated with a negative enhancement.

2,3,4,6 = +164.7°		3,4,6 = +146.5°	
−2,3, 6 = +393.9°	and	−3, 6 = +56.0°	
4 = −229.2°		4 = −202.5°	

Such observations as these provide additional examples of the varied effects that highly polarizable substituents may exert on optical activity. As shown by Korytnyk[29], Hudson's rules of isorotation may be modified to permit the correlation of anomers containing a halogen atom or phenyl group at C-1. In another study[30], "anomalously" large rotations of *O*-trityl derivatives have been correlated with specific shielding effects of the phenyl groups.

EXPERIMENTAL

General. — Column chromatography was performed with cellulose powder for aqueous systems, and silica gel (Macherey, Nagel and Co.) for nonaqueous systems. T.l.c. plates were prepared from Silica Gel G; solvents used were *A*, 9:1 (v/v) benzene–ether, and *B*, 3:2:1 propyl alcohol–ethyl acetate–water. Whatman No. 1 paper was used for descending chromatography, and the developing solvents were 4:1:5 (upper

layer) butyl alcohol–ethanol–water or 6:1:2 propyl alcohol–acetic acid–water[31]. Gas–liquid chromatography was conducted with a Hewlett–Packard 402 gas chromatograph having a column of silicone gum (4% U.C.W.) on Chromosorb W. P.m.r. spectra were recorded with a Varian HA-100 spectrometer, and mass spectra with a double-focusing, MS 902 AEI spectrometer operating at 70 eV with an ion-source temperature varied from 100–200°. Evaporations were performed under diminished pressure at, or below, 45°.

*Methyl 2,3,6-tri-*O*-benzoyl-β-*D*-glucopyranoside* (**2**). — A solution of compound **1** (18 g) in pyridine (60 ml) was cooled to −10°, and benzoyl chloride (31 ml) was added dropwise with continued cooling. The mixture was stirred at −10°, and more benzoyl chloride (31 ml) was added dropwise with continued cooling. The mixture was stirred for 10 h at −10°, and then the temperature was allowed to rise to 25°. T.l.c. with 1:1 benzene–ether showed the presence of five major compounds*. Water was added, the mixture was extracted with chloroform, and the extract was washed successively with 2M hydrochloric acid, water, 1M sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated, to afford a crystalline mass which was dissolved in benzene and transferred to a column of silica gel. Elution with 49:1 benzene–ether afforded methyl β-D-glucopyranoside tetrabenzoate (4.0 g, 7.1%) m.p. 161–162°, $[\alpha]_D$ +26.9° (*c* 2.15, chloroform); lit.[33] m.p. 158–160°, $[\alpha]_D$ +30.9° (chloroform). Elution with 9:1 benzene–ether gave methyl 2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**2**) (16 g, 34%), m.p. 148.5–150.5° (chloroform, petroleum ether), $[\alpha]_D$ +76.6° (*c* 2.0, chloroform); lit.[34] m.p. 145.5–146.5°, $[\alpha]_D$ +82.0° (chloroform).

*Methyl 3,4,6-tri-*O*-benzoyl-β-*D*-glucopyranoside.* — Continued elution of the silica gel with 9:1 benzene–ether afforded a syrup (1.5 g, 3%) $[\alpha]_D$ −29.1° (*c* 14.07, chloroform), identified by p.m.r. spectroscopy (solvent, C_5D_5N) as the title compound**: δ 7.0–8.26 (three PhCO groups); 6.26 (triplet, $J_{3,4} = J_{4,5}$ 9.3 Hz, H-4); 6.01 (triplet, $J_{3,4} = J_{3,2}$ 9.5 Hz, H-3); 4.89 (doublet, $J_{1,2}$ 8.0 Hz, H-1); 4.83 (multiplet, H-6*R* and H-6*S*); 4.4 (multiplet, H-5); 4.27 (quartet, $J_{2,1}$ 8 Hz, $J_{2,3}$ 9.5 Hz, H-2); and 3.62 (singlet, OCH_3).

Acetylation afforded a monoacetate (p.m.r. evidence), m.p. 162.5–163.5° (crystallized from methanol), $[\alpha]_D$ −42.0° (*c* 2.26, chloroform).

Anal. Calc. for $C_{30}H_{28}O_{10}$: C, 65.7; H, 5.1. Found: C, 65.9; H, 4.9.

*Methyl 3,6-di-*O*-benzoyl-β-*D*-glucopyranoside.* — Further elution with 9:1 benzene–ether afforded a compound (2.7 g, 4%) identified by p.m.r. spectroscopy (solvent, C_5D_5N) as methyl 3,6-di-*O*-benzoyl-β-D-glucopyranoside; m.p. 155–156° (crystallized from chloroform–petroleum ether), $[\alpha]_D$ +14.8° (*c* 2.34, chloroform).

Acetylation afforded the diacetate (identified by p.m.r. spectroscopy), m.p. 106–107° (crystallized from ethanol), $[\alpha]_D$ +21.5° (*c* 2.02, chloroform).

Anal. Calc. for $C_{25}H_{26}O_{10}$: C, 61.7; H, 5.4. Found: 61.5; H, 5.5.

*Williams and Richardson[32] noted that at least four compounds were detectable as products of the same reaction, although their isolation was not reported.

**Trimolar benzoylation of the α anomer affords[12], besides the 2,3,6-tribenzoate, the 2,4,6-tribenzoate, instead of the 3,4,6-isomer.

Methyl 2,6-di-O-benzoyl-β-D-glucopyranoside. — Finally, elution of the silica gel chromatogram with 1:1 benzene–ether afforded a compound (1.1 g, 4%) identified by p.m.r. spectroscopy (solvent, C_5D_5N) as the title compound. Recrystallized from chloroform–petroleum ether, it had m.p. 177–178°, $[\alpha]_D$ −42.1° (*c* 1.16, chloroform).

Acetylation afforded a diacetate (p.m.r. evidence); m.p. 167–168° (crystallized from methanol), $[\alpha]_D$ +54.8° (*c* 2.0, chloroform); lit.[35] m.p. 166°, $[\alpha]_D$ +54.8° (*c* 1.34, acetone).

Methyl 2,3,6-tri-O-benzoyl-4-O-(p-bromophenylsulfonyl)-β-D-glucopyranoside (**3**) — *p*-Bromobenzenesulfonyl chloride (15 g) was added to a solution of **2** (18 g) in pyridine (30 ml) at 45–50°, and the mixture was stirred for 24 h. T.l.c. in 1:1 benzene–ether then showed that the reaction was complete. Water was introduced dropwise with cooling, followed by ice–water, and the solid precipitate resulting was collected, washed with water, and dissolved in chloroform. The solution was washed successively with 2M hydrochloric acid, water, 1M sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated. Crystallization from chloroform–petroleum ether afforded **3** (12.5 g), m.p. 164–165° (dec.), $[\alpha]_D$ +23.2° (*c* 2.1, chloroform).

Anal. Calc. for $C_{34}H_{29}BrO_{11}S$: C, 56.3; H, 4.0; Br, 11.0; S, 4.4. Found: C, 56.3; H, 3.7; Br, 11.1; S, 4.3.

Methyl 4-azido-2,3,6-tri-O-benzoyl-4-deoxy-β-D-galactopyranoside (**4**). — A solution of compound **3** in *N*,*N*-dimethylformamide (DMF) (16 ml) was stirred with a suspension of sodium azide (3 g) at 95–105° (bath temp.). T.l.c. with 9:1 benzene–ether after 12 h showed that the reaction was about 90% complete (more-prolonged reaction caused the formation of a slower-moving fraction). After filtration, precipitation of more salts by addition of ether, and filtration, the filtrate was evaporated to dryness. Chromatography of the product on silica gel, with elution with 49:1 benzene–ether, afforded crystalline **4** (3.5 g, 96%), m.p. 157–158°. After recrystallization from benzene–petroleum ether or chloroform–petroleum ether, it had m.p. 158–159°; $[\alpha]_D$ −69.9° (*c* 2, chloroform); ν_{max}^{KBr} 2100 cm^{-1} (N=N=N); p.m.r. data: δ 6.8–8.2 (three PhCO) and 3.20 (OCH_3, H-1 to H-6, H-6′; see Table I).

Anal. Calc. for $C_{28}H_{25}N_3O_8$: C, 63.3; H, 4.7; N, 7.9. Found: C, 62.4; H, 4.7; N, 7.5.

Methyl 4-azido-4-deoxy-β-D-galactopyranoside (**5**). — *O*-Debenzoylation of **4** (1.0 g) with 0.1M sodium methoxide in methanol gave **5** (0.20 g, 49%) which, on recrystallization from methanol–ether containing a little hexane, had m.p. 169–172°, $[\alpha]_D$ −59.2° (*c* 1, water).

Anal. Calc. for $C_7H_{13}N_3O_5$: C, 38.4; H, 6.0; N, 19.2. Found: C, 39.0; H, 6.0; N, 19.7.

Methyl 2,3,6-tri-O-acetyl-4-azido-4-deoxy-β-D-galactopyranoside (**8**). — Acetylation of **5** (40 mg) with 1:2 acetic anhydride–pyridine gave **8** (50 mg); recrystallization from ethanol afforded crystals having m.p. 116–118°, $[\alpha]_D$ −60.9° (*c* 1.86, chloroform).

Anal. Calc. for $C_{13}H_{19}N_3O_8$: Mol. wt. 345. Found: $(M-59)^+$ [*i.e.*, $(M-CH_3COO)^+$] at *m/e* 286, followed by $(M-59-N_3)^+$ at *m/e* 244.

Methyl 2,3,6-tri-O-benzoyl-4-O-triflyl-β-D-glucopyranoside (**7**). — To a solution

of compound (**2**) (1.0 g) in pyridine (16 ml) cooled to 0° was added dropwise, with cooling, trifluoromethanesulfonyl anhydride [$(CF_3SO_2)_2O$] (0.63 g; prepared by distilling trifluoromethanesulfonic acid over phosphorus pentaoxide and collecting the fraction boiling at 80–82°). T.l.c. with 9:1 benzene–ether showed that a considerable proportion of **2** had been esterified*. The stirred solution was treated with cold water, shaken with chloroform, and the chloroform layer washed successively with 2M hydrochloric acid, water, 1M sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated to a syrup that darkened on standing. The syrup was transferred to a column of silica gel, and eluted with 9:1 benzene–ether. Fractions of **7** that were obtained also darkened on standing, but were crystallized and recrystallized from ethanol (0.6 g, 48%), m.p. 124–125° (dec.), $[\alpha]_D$ +25.7° (*c* 1.83, chloroform).

Anal. Calc. for $C_{29}H_{25}F_3O_{10}S$: C, 56.0; H, 4.1; F, 9.2; S, 5.2. Found: C, 56.4; H, 4.0; F, 8.3; S, 5.0.

Displacement of the triflyl group of **7** *by azide ion, to give* **4**. — To a solution of compound **7** (80 mg) in DMF (5 ml) was added sodium azide (0.2 g), and the suspension was heated at 95–100° (bath temp.). The reaction was allowed to proceed for 6 h, although t.l.c. with solvent *A* showed that the reaction was almost complete after 2 h. The mixture was evaporated, and the resulting syrup was chromatographed on silica gel, with elution with 9:1 benzene–ether. The purified product crystallized from chloroform–petroleum ether (yield 50 mg, 75%); it had m.p. (and mixed m.p.), $[\alpha]_D$, and p.m.r. and i.r. spectra indistinguishable from those of **4** prepared as already described.

*Methyl 4-amino-4-deoxy-β-*D*-galactopyranoside* (**6**). — To a solution of the azido derivative (**5**) (0.20 g) in water (5 ml) was added palladium black (60 mg), and the mixture was hydrogenated at atmospheric pressure for 13 h. Filtration through a Celite pad, and evaporation of the filtrate, gave a solid (0.15 g, 85%), m.p. 188–189°. Recrystallization from ethanol gave **6** as granular crystals, m.p. 194–195° (dec.), $[\alpha]_D$ ~0.0° (*c* 1, water).

Anal. Calc. for $C_7H_{15}NO_5$: C, 43.5; H, 7.8; N, 7.3. Found: C, 43.6; H, 7.8; N, 7.2.

*Methyl 4-acetamido-2,3,6-tri-*O*-acetyl-4-deoxy-β-*D*-galactopyranoside* (**9**). — Acetylation of **6** (15 mg) with acetic anhydride–pyridine gave syrupy **9**, purified on silica gel with ethyl acetate as the eluant. The p.m.r. spectrum is described in Table I.

*Methyl 2,3,6-tri-*O*-benzoyl-*S*-benzoyl-4-thio-β-*D*-galactopyranoside* (**11**). — To brosylate **3** (5.0 g) in DMF (20 ml) was added potassium thiobenzoate (2.2 g; recrystallized from ethanol), and the solution was heated for 3 h at 100–105° (bath temp.). T.l.c. with 9:1 benzene–ether then showed that the reaction was complete, and so the mixture was cooled and filtered. Ether was added to the filtrate until there was no further precipitation, the suspension was filtered, and the filtrate was evaporated,

*A prolonged reaction-time, or addition of more triflyl anhydride, caused formation of a number of unidentified side-products.

giving a yellow syrup which was chromatographed on silica gel by elution with benzene. The fast-moving fraction (3.0 g) crystallized from ethanol to give 2.4 g (56%) of **11**, m.p. 85–87°. Recrystallization from Cellosolve–methanol raised the m.p. to 87–90°, $[\alpha]_D$ +36.8° (*c* 2.2, chloroform).

Anal. Calc. for $C_{35}H_{30}O_9S$: C, 67.1; H, 4.8; S, 5.1. Found: C, 66.9; H, 4.8; S, 5.0.

Methyl 4-thio-β-D-galactopyranoside (**10**); *O-Debenzoylation of* **11**. — (*i*) *With ammonia in methanol.* Dry ammonia gas was bubbled into a solution of **11** (1 g) in methanol (200 ml), and the reaction was monitored by t.l.c. with (*a*) 9:1 benzene–ether, which showed the absence of **11**, and (*b*) 3:2:1 propyl alcohol–ethyl acetate–water, which showed the presence of **10**. After one week, the reaction was incomplete; therefore, the temperature was raised to 30° and, after 14 days, when a major spot was detected, the mixture was concentrated. Addition of ether caused precipitation of crude **10** (0.3 g, 89%). Attempted recrystallization from methanol or methanol–ether was unsuccessful.

(*ii*) *With lithium aluminum hydride.* A solution of compound **11** (0.5 g) in benzene (5 ml) was added slowly to a suspension of an excess of lithium aluminum hydride in ether. The excess of hydride was then decomposed with ethyl acetate, and the addition of water, followed successively by centrifugation, treatment of the supernatant liquor with Amberlite IR-120 (H^+) ion-exchange resin, and freeze-drying, afforded a clear syrup (0.14 g). Efforts to crystallize it failed. The p.m.r. spectrum of this syrup in D_2O showed the absence of benzoate groups: δ 3.7 (OCH_3), 4.48 (H-1), and 4.0 (H-6*R*, H-6*S*, unresolved).

(*iii*) *With sodium methoxide in methanol.* (*a*) *Prolonged reaction. O*-Debenzoylation of **11** (0.6 g) for ten days at room temperature with sodium methoxide–methanol gave an impure compound whose p.m.r. spectrum (in D_2O) showed weak, aromatic absorption (δ 8.0–8.4). Other resonances discernible were a doublet at δ 4.8 (*J* 7.8 Hz, H-1) and a broad triplet, typical of H-5 of *galacto* derivatives, at δ 3.6 (H-5). (*b*) *Brief* O- *and* S-*debenzoylation of* **11**. The *O*-debenzoylation of **11** (1.0 g) with methoxide was stopped after two days, and the solution was made neutral with Amberlite IR-120 (H^+) ion-exchange resin, and concentrated. Benzoates were extracted into benzene, and the aqueous layer was then extracted with chloroform. Evaporation of the aqueous layer gave a residue weighing 14 mg, whereas the chloroform-soluble material (0.17 g), by chromatography on silica gel with 3:1 benzene–ether as the eluant, afforded a minor fraction (7 mg), m.p. 165–166°, and a major fraction (70 mg). On acetylation of the latter, and purification of the peracetate on silica gel with 9:1 benzene–ether as the eluant, a crystalline compound, tentatively designated methyl 2,3-di-*O*-acetyl-4-*S*-acetyl-6-*O*-benzoyl-4-thio-β-D-galactopyranoside (**14**), was obtained. Recrystallized from ethanol, **14** had m.p. 146–147°, $[\alpha]_D$ −50.9° (*c* 2.5, chloroform).

The n.m.r. spectrum of **14** in $CDCl_3$ showed: δ 7.20–8.15 (one PhCO), 5.25 (quartet, $J_{3,4}$ 1 Hz, $J_{2,3}$ 10 Hz, H-3); 5.06 (quartet, $J_{1,2}$ 7 Hz, $J_{2,3}$ 10 Hz, H-2); 4.28 (doublet, $J_{1,2}$ 7 Hz, H-1); 4.56 (quartet, $J_{6R,5}$ 6.8 Hz, $J_{6R,6S}$ 11 Hz, H-6*R*);

4.40 (quartet, $J_{4,5}$ 1 Hz, $J_{3,4}$ 1 Hz, H-4); 4.29 (quartet, $J_{5,6}$, 5.6, $J_{6R,6S}$ 11 Hz, H-6*S*); 4.0 (H-5); 3.39 (singlet, OCH_3); 2.20 (singlet, probably *S*-Ac); and singlets at 1.97 and 1.88 (2 OAc).

Anal. Calc. for $C_{20}H_{24}O_9S$: C, 54.5; H, 5.5; S, 7.3. Found: C, 53.5; H, 4.9; S, 7.0.

Acetylation of **10**. *Formation of the dimeric hexaacetate* (**12**). — Acetylation of the combined products of *O*-debenzoylation (0.12 g) from reactions *i*, *ii*, and *iii* (believed to be methyl 4-thio-β-D-galactopyranoside, **10**) gave, after purification on silica gel with 1:1 benzene–ether as the eluant, crystalline **12** which, after recrystallization from ethanol (yield, 34 mg), had m.p. 202–203°, $[\alpha]_D$ −180.5° (*c* 1.13, chloroform).

Anal. Calc. for $C_{26}H_{38}O_{16}S_2$: C, 46.6; H, 5.7; S, 9.6. Found: C, 46.6; H,5.7; S, 10.4.

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-thiocyano-β-*D*-galactopyranoside* (**13**). — To a solution of brosylate **3** (1.0 g) in DMF (10 ml) was added potassium thiocyanate (1.1 g), and the mixture was stirred for 14 h at 95–100° (bath temp.); t.l.c. with 9:1 benzene–ether then showed that the reaction was complete. Ether was added to precipitate most of the salts, the suspension was filtered, and the material in the filtrate was chromatographed on silica gel. Elution with 9:1 benzene–ether, followed by evaporation of the eluate, afforded a syrupy fraction which crystallized from carbon tetrachloride–petroleum ether (0.23 g, 31%); m.p. 151–152°, $[\alpha]_D$ −41.5° (*c* 2, chloroform); $\nu_{max}^{CCl_4}$ 2150 cm^{-1} (–S–C≡N).

O-Debenzoylation and hydrolysis of the –SCN group in **13**. — Treatment of **13** (0.15 g) with sodium methoxide–methanol gave one major spot on t.l.c. Evaporation of the solvent was followed immediately by acetylation of the residue; purification of the product on silica gel, with elution with 9:1 benzene–ether, gave a fast-moving fraction (21 mg) as a syrup, and a crystalline material (19 mg) eluted with 1:1 benzene–ether. The R_F of the latter in solvents *A* and *B* was the same as that of **12**.

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-β-*D*-galactopyranoside* (**16**), *methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-β-*D*-glucopyranoside* (**17**), *and methyl 2,4,6-tri-*O*-benzoyl-3-deoxy-3-iodo-β-*D*-glucopyranoside* (**19**). — (*A*) *Reaction of brosylate* **3** *at 100–120° (bath temp.)*. To a solution of compound **3** (2 g) in acetonitrile (12 ml) was added tetrabutylammonium iodide (4 g), and the solution was boiled under reflux. The reaction was monitored by t.l.c. with 9:1 benzene–ether; this showed that a fast-moving compound formed initially was being converted into two other, slow-moving compounds. After 30 h, the incomplete reaction was stopped, the solvent was evaporated off, and the residue was dissolved in benzene. Addition of ether caused precipitation of salts. The suspension was filtered, the filtrate was concentrated, and the concentrate was transferred to a column of silica gel. Elution with 99:1 benzene–ether afforded, in sequence, crystalline **16** (0.34 g; m.p. 163–164°, from methanol); crystalline **17**, m.p. 130–131° (from ethanol), $[\alpha]_D$ +17.8° (*c* 1, chloroform); crystalline **19**, m.p. 146–147° (from methanol), $[\alpha]_D$ +3.7° (*c* 0.04, chloroform); and unreacted **3** (0.11 g).

(*B*) *Reaction of* **3** *with tetrabutylammonium iodide at 96–100°*. A solution of compound **3** (6 g) in acetonitrile (30 ml) was boiled under reflux with tetrabutylammonium iodide (25 g; recrystallized from acetone–ether) for 30 h, and the mixture was processed as in (*A*). Column-chromatographic separation afforded: (*i*) syrupy **16** (1.51 g, 30%), crystallizing from methanol to give 1.1 g (22%) of material which, after recrystallization from methanol, had m.p. 163–164°, $[\alpha]_D$ +47.7° (*c* 2, chloroform).

Anal. Calc. for $C_{28}H_{25}IO_8$: C, 54.6; H, 4.1; I, 20.6. Found: C, 55.5; H, 4.0; I, 20.5.

(*ii*) A mixture of **16** and **17** (p.m.r. evidence). A portion of this mixture was rechromatographed on silica gel with benzene as the eluant. Compound **17** crystallized from ethanol to give crystals having m.p. 131–133°, $[\alpha]_D$ +19.9° (*c* 0.78, chloroform).

Anal. Calc. for $C_{28}H_{25}IO_8$: C, 54.6; H, 4.1; I, 20.6. Found: C, 54.3; H, 4.0; I, 18.3.

*Methyl 4-deoxy-4-iodo-β-*D*-galactopyranoside* (**15**). — A solution of **16** (1.0 g) in benzene (10 ml) was diluted with methanol (dried over molecular sieves, type A-4), and the solution was made weakly basic with 0.1M sodium methoxide. T.l.c. with 9:1 benzene–ether showed that the reaction was complete within 12 h at room temperature. The solution was then treated with Amberlite IR-120 $(H)^+$ ion-exchange resin, and the suspension filtered; the filtrate was diluted with water, concentrated to remove most of the methanol, washed with benzene, and evaporated to a sticky, crystalline material which gave crystals from methanol–ether (0.39 g, 79%), m.p. 195–196° (dec.). Recrystallization from methanol afforded **15**, m.p. 200° (dec.), $[\alpha]_D$ +25.5° (*c* 1.0, water).

Anal. Calc. for $C_7H_{13}IO_5$: C, 27.7; H, 4.3; I, 41.7. Found: C, 28.1; H, 4.2; I, 42.4.

*Methyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-iodo-β-*D*-galactopyranoside* (**18**). — Compound **15** (60 mg) was acetylated, yielding crystals (70 mg, 83%), m.p. 87–88° (from ethanol–water), $[\alpha]_D$ +76.0° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{19}IO_8$: Mol. wt. 430. Found $(M-60)^+$ at *m/e* 370, and also $(M-59-128)^+$ [*i.e.*, $(M-CH_3COO-HI)^+$] at 243 (very intense).

*Methyl 4-deoxy-β-*D*-xylo-hexopyranoside* (**20**) *and its triacetate* (**21**). — Compound **17** (containing a small proportion of **16**) (0.60 g) was *O*-debenzoylated, affording a partially crystalline syrup (0.20 g). The mixture was dissolved in water, and the solution was stirred for 24 h with palladium black (0.10 g) under hydrogen at atmospheric pressure at 5–10°. The acidic suspension was filtered through a Celite pad, and the filtrate was made neutral with Dowex-1 (HCO_3^-) ion-exchange resin, the suspension filtered, and the filtrate freeze-dried. Acetylation with acetic anhydride–pyridine, followed by purification on a column of silica gel with 9:1 benzene–ether as the eluant, afforded methyl 2,3,6-tri-*O*-acetyl-4-deoxy-β-D-*xylo*-hexoside (**21**) (30 mg), $[\alpha]_D$ −23.2° (*c* 2.2, chloroform).

O-Deacetylation of **21** with sodium methoxide–methanol as in the foregoing experiment afforded crystalline **20**, m.p. 146–147° (ethyl acetate) (lit.[32] m.p. 145–147°).

Methyl 2,3,6-tri-O-benzoyl-4-bromo-4-deoxy-β-D-galactopyranoside (**24**). — A solution of compound **3** (6.0 g) and tetrabutylammonium bromide (25 g) in acetonitrile (30 ml) was heated for 30 h at 95–100° (bath temp.); t.l.c. with 9:1 benzene–ether then suggested that 95% of **3** had reacted. The solution was cooled, and concentrated to a small volume, and ether was added (to precipitate salts). The suspension was filtered, the filtrate was concentrated, and the residue was transferred to a column of silica gel which was eluted with 99:1 benzene–ether. The faster-moving, major fraction (**24**) (1.47 g, 31%) had, after recrystallization from methanol, m.p. 151–153°; $[\alpha]_D$ +52.7° (*c* 2, chloroform).

Anal. Calc. for $C_{28}H_{25}BrO_8$: C, 59.1; H, 4.4; Br, 14.0. Found: C, 59.7; H, 4.3; Br, 13.6.

The second major fraction contained **24** (0.75 g) and was rechromatographed. This procedure afforded a second product which, on recrystallization from ethanol had m.p. 132–134°, $[\alpha]_D$ +19.4° (*c* 1.23, chloroform). The p.m.r. spectrum of the compound in 3:1 $CDCl_3-C_6D_6$ showed δ 8.00, 7.30 (3 PhCO); 5.83 (H-3); 5.40 (H-2); 4.80 (H-6*R*); 4.60 (H-6*S*); 4.46 (H-1); 4.10 (H-4); 3.84 (H-5); and 3.35 (OCH_3); this suggested that this product is methyl 2,3,6-tri-*O*-benzoyl-4-bromo-4-deoxy-β-D-glucopyranoside (**31**).

Anal. Calc. for $C_{28}H_{25}BrO_8$: C, 59.1; H, 4.4; Br, 14.0. Found: C, 59.7; H, 4.3; Br, 13.8.

Methyl 4-bromo-4-deoxy-β-D-galactopyranoside (**22**) *and its triacetate* (**26**). — *O*-Debenzoylation of **24** (1.5 g) afforded **22** (0.51 g, 75%), m.p. 173°; recrystallization from methanol–ether gave crystals, m.p. 184–185°, $[\alpha]_D$ +15.2° (*c* 1, water).

Anal. Calc. for $C_7H_{13}BrO_5$: C, 32.7; H, 5.1; Br, 31.1. Found: C, 32.5; H, 5.4; Br, 30.6.

Acetylation of **22** (0.1 g) gave crystals (0.14 g) (recrystallized from methanol–ether), m.p. 99–100°, $[\alpha]_D$ +39.2° (*c* 1.55, chloroform).

Anal. Calc. for $C_{13}H_{19}{}^{79}BrO_8$: mol. wt. 382. Found: $(M-60)^+$ [*i.e.*, $M-AcOH^+$] at *m/e* 322; also $(M-60-{}^{79}Br)^+ = m/e$ 242 (very intense) and $(M-60-{}^{79}Br)^+ = m/e$ 243 (very intense). Calc. for $C_{13}H_{19}{}^{81}BrO_8$: mol. wt. 384. Found: $(M-60)^+$ at *m/e* 324 and $(M-60-H-{}^{81}Br)^+ = m/e$ 242; also $(M-60-{}^{81}Br)^+ = m/e$ 243.

Methyl 2,3,6-tri-O-benzoyl-4-chloro-4-deoxy-β-D-galactopyranoside (**25**). — To a solution of **3** (2.0 g) in acetonitrile (30 ml) was added tetrabutylammonium chloride (5 g), and the solution was boiled under reflux for 60 h and then evaporated to dryness. The residue was chromatographed on a column of silica gel with 49:1 benzene–ether; a major fraction was obtained, and crystallized from methanol (1.2 g, 83%); m.p. 131–132° $[\alpha]_D$ +60.7° (*c* 3, chloroform); p.m.r. spectral analysis showed δ 8.08, 7.02 (3 PhCO), and 3.22 (OCH_3).

Anal. Calc. for $C_{28}H_{25}ClO_8$: C, 64.1; H, 4.8; Cl, 6.8. Found: C, 64.3; H, 5.0; Cl, 7.4.

Methyl 4-chloro-4-deoxy-β-D-galactopyranoside (**23**) *and its triacetate* (**27**). —

O-Debenzoylation of **25** (1.0 g) gave **23** (0.32 g, 79%), m.p. 158–160°. Recrystallization from methanol–ether gave needles, m.p. 158–159°, $[\alpha]_D$ +8.7° (*c* 1, water).

Anal. Calc. for $C_7H_{13}ClO_5$: C, 39.5; H, 6.2; Cl, 16.7. Found: C, 39.3; H, 6.5; Cl, 16.3.

Acetylation of **23** (50 mg) gave **27** (60 mg, 76%); m.p. 96–97° (recrystallized from ethanol), $[\alpha]_D$ +30.9° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{19}ClO_8$: mol. wt. 338 for ^{35}Cl and 340 for ^{37}Cl. Found: $(M-59)^+$ [*i.e.*, $(M-CH_3COO)^+$] for ^{35}Cl (intense), centered at *m/e* 279; $(M-59)^+$ [*i.e.*, $(M-CH_3COO)^+$] for ^{37}Cl (less intense), centered at *m/e* 281; also $(M-60)^+$ [*i.e.*, $(M-CH_3COOH)^+$] for both isotopes.

*Methyl-2,3-di-*O*-benzyl-4-*O*-(*p*-bromophenylsulfonyl)-6-*O*-trityl-β-*D*-glucopyranoside* (**28**). — A solution of methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (prepared as for the α anomer[31]) (1 g) in pyridine (15 ml) was stirred for 36 h with chlorotriphenylmethane (1 g) at 40–50° (bath temp.), and then *p*-bromobenzenesulfonyl chloride (1.2 g) was added, and the mixture heated and stirred for an additional 36 h. Ice–water was added, followed by chloroform, and the organic layer was successively washed with hydrochloric acid, water, sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated to a syrup which was transferred to a column of silica gel and eluted with 1:3:5 benzene–petroleum ether–ether. A clear syrup of **28** (4.5 g) was isolated; $[\alpha]_D$ −7.1° (*c* 3.3, chloroform).

Preparation of tetrabutylammonium fluoride. — Tetrabutylammonium hydroxide (Eastman Kodak; 10% solution in water) was titrated to pH 4.8 with hydrofluoric acid (20% solution in water). The solution was concentrated *in vacuo*, and then freeze-dried for 4 days.

*Methyl 2,3-di-*O*-benzyl-4-deoxy-4-fluoro-6-*O*-trityl-β-*D*-galactopyranoside.* — To a solution of compound **28** (1 g) in dry acetonitrile (distilled over phosphorus pentaoxide) (10 ml) was added tetrabutylammonium fluoride (5.5 g) in acetonitrile (10 ml), and the solution was boiled under reflux for two days at 95–100° (bath temp.). The solvent was evaporated off, and the residual syrup was dissolved in benzene, the solution washed with water, dried (magnesium sulfate), and evaporated, and the resulting syrup chromatographed on a column of silica gel with 9:1 petroleum ether–ether as the eluant. This treatment afforded the title compound (0.22 g) which, after recrystallization from petroleum ether (b.p. 30–60°)—ether (yield 0.18 g, 30%), had m.p. 137–138°, $[\alpha]_D$ +21.6° (*c* 3, chloroform).

*Methyl 2,3-di-*O*-benzyl-4-deoxy-4-fluoro-β-*D*-galactopyranoside.* — To a solution of the foregoing trityl ether (0.5 g) in cold glacial acetic acid (15 ml) was added cold hydrobromic acid (32%, in acetic acid). The crystalline trityl bromide formed was filtered off, the solution was poured onto a water–ice mixture, and the resulting suspension was filtered. The filtrate was extracted with chloroform, and the extract was successively washed with 1M sodium hydrogen carbonate, water, dried (magnesium sulfate), and evaporated to a syrup which crystallized readily from toluene–petroleum ether; after recrystallization from the same solvent (yield 0.23 g, 76%), it had m.p. 105–106°, $[\alpha]_D$ −15.6° (*c* 2, chloroform).

Methyl 4-deoxy-4-fluoro-β-D-galactopyranoside (**27**). — The preceding compound (0.20 g) in ethanol (8 ml) was treated with hydrogen at room temperature and pressure in the presence of palladium black (0.10 g). After 2 h, the suspension was filtered through Celite, the Celite was washed with ethanol, and the filtrate and washings were combined and evaporated to give a crystalline residue. Recrystallization from ethyl acetate–ethanol afforded **27** (0.10 g, 96%), m.p. 155–156°, $[\alpha]_D$ −21.3° (*c* 1, water).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.9; H, 6.7; F, 9.7. Found: C, 43.3; H. 6.4; F, 9.5.

Methyl 2,3,6-tri-O-benzoyl-4-deoxy-4-fluoro-β-D-galactopyranoside (**30**). — Benzoyl chloride (0.2 ml) was added dropwise to a stirred solution of **27** (30 mg) in pyridine maintained at 0°, the reaction being monitored by t.l.c. with 9:1 benzene–ether. The excess of benzoyl chloride was then decomposed by dropwise addition of water, with stirring, and the solution was extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, water, sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated to dryness. The residue was passed through a short column of silica gel and eluted with 9:1 benzene–ether. On recrystallization from methanol, the product obtained (40 mg, 51%) had m.p. 134–135°, $[\alpha]_D$ +63.2° (*c* 2, chloroform).

Methyl 2,3,6-tri-O-acetyl-4-deoxy-4-fluoro-β-D-galactopyranoside (**29**). — A portion (25 mg) of **27** was acetylated with acetic anhydride–pyridine at room temperature. Evaporation of the solution *in vacuo* afforded a solid product which was purified by passage through a column of silica gel, with 4:1 benzene–ether as the eluant. The crystalline product (30 mg, 72%) obtained after recrystallization from ethanol had m.p. 95–97°, $[\alpha]_D$ −6.2° (*c* 1.7, chloroform).

Anal. Calc. for $C_{13}H_{19}FO_8$: mol. wt., 322. Found: $(M-60)^+$ [*i.e.*, $(M-CH_3CO_2H)^+$] 262 mass units.

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