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THE USE OF 2-*O*-ACYL-1-*O*-SULFONYL-D-GALACTOPYRANOSE DERIVATIVES IN β-D-GALACTOPYRANOSIDE SYNTHESIS

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ABSTRACT

Several 1-*O*-sulfonyl derivatives of D-galactopyranose having a participating benzoyl or *p*-methoxybenzoyl group at O-2 were synthesized from the corresponding D-galactopyranosyl chloride derivatives by use of silver *p*-toluenesulfonate or trifluoroethanesulfonate in acetonitrile. The reaction of the 1-*O*-sulfonyl-D-galactopyranose derivatives with several alcohols in various solvents at different times and temperatures served as model reactions to determine the best conditions for synthesizing stereoselectively β-D-galactopyranosides in high yields. This method was used to prepare, in good yield, several β-D-galactopyranosyl-containing disaccharides.

INTRODUCTION

Per-*O*-acyl-D-glycopyranosyl halides are being widely used for the synthesis of 1,2-*trans*-D-glycopyranosides by the Koenigs–Knorr or orthoester methods. Reaction yields and stereoselectivity are usually high only when simple or reactive alcohols are used. With aglycons of low reactivity (secondary alcohols), yields are lower and in some cases so is the stereoselectivity.

Wallace and Schroeder[1], and Shaban and Jeanloz[2] reported that D-glucopyranosyl halides having a 2-*O*-acyl group and ether functions on the other positions gave higher reaction rates and higher stereoselectivity than the corresponding peracyl derivatives. Hanessian[3] reported that per-*O*-acyl-D-glucopyranosyl halides can be activated by use of silver triflate to give β-D-glucopyranosides with good stereoselectivity and yields with short reaction times (4–8 h). In a recent article[4], we have shown that benzyl 2-*O*-benzoyl-per-*O*-benzyl-1-*O*-sulfonyl-D-mannopyranose derivatives are extremely reactive compounds that gave high yields of α-D-mannopyranosides with high stereoselectivity. The reaction rates were very high even with unreactive alcohols. In this report, we have extended the investigation to the reaction of 2-*O*-acyl-per-*O*-benzyl-1-*O*-sulfonyl-D-galactopyranose derivatives with various alcohols and carbohydrate aglycons to give β-D-galactopyranosides.

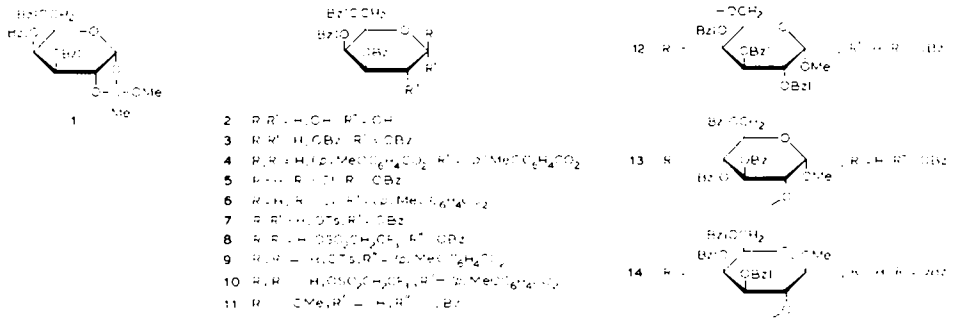

TABLE I

PHYSICAL CONSTANTS AND ANALYSIS FOR 1,2-DI-*O*-ACYL-3,4,6-TRI-*O*-BENZYL-D-GALACTOPYRANOSE DERIVATIVES

Constants and analysis	*Compound*	
	3	**4**
Acyl group	Benzoyl	*p*-Methoxybenzoyl
Formula	$C_{41}H_{38}O_8$	$C_{43}H_{42}O_{10}$
Yield (%)	90	90
$[\alpha]_D^{25}$ (°) (*c* 1, chloroform)	+65.2	−41.7
$\alpha:\beta$ Ratio[a]	43:57	0:100
Anal.		
Calc. C	74.75	71.82
H	5.84	5.83
Found C	74.56	71.84
H	5.84	5.89

RESULTS AND DISCUSSION

The 1,2-di-*O*-acyl-D-galactopyranose derivatives **3** and **4** (Table I) were prepared from 3,4,6-tri-*O*-benzyl-D-galactopyranose (**2**) by use of benzoyl or *p*-methoxybenzoyl chloride in pyridine. The diesters were converted into the corresponding 1-chlorides by conventional methods[4]. The 1-*O*-tosyl- (**7**) or -tresyl(trifluoroethanesulfonyl)-D-galactopyranose (**8**) derivatives were prepared by the action of silver *p*-toluenesulfonate or trifluoroethanesulfonate on the corresponding D-galactosyl chloride in acetonitrile at room temperature[4].

The glycosylation reactions were carried out in several solvents and with different alcohols at various temperatures to obtain the best yields with the highest stereoselectivity (Table II). In these model studies, the anomeric purity and yield were determined from ^{1}H-n.m.r. data for methyl and ^{13}C-n.m.r. data for the other aglycons. The β-methoxyl group of the methyl D-galactopyranosides gave a ^{1}H-n.m.r. signal at δ 3.44 and the α-methoxyl group one at δ 3.33. In the ^{13}C-n.m.r. spectra,

TABLE II

REACTION OF 2-*O*-ACYL-3,4,6-TRI-*O*-BENZYL-1-*O*-SULFONYL-D-GALACTOPYRANOSYL DERIVATIVES WITH ALCOHOLS

Compound no.	*Acyl group*	*Sulfonyl group*	*Alcohol*	*Solvent*	*Time (h)*	*Temp.*[a] *(°)*	*Yield (%)*	*β-D-Anomer (%)*
7	Bz	Ts	MeOH	AcCN	48	RT	92	> 95
7				CH_2Cl_2	48	RT	68	73
7				Et_2O	48	RT	77	90
7				$CDCl_3$	2	RT	78	92
7				AcCN	4	0	70	87
7			IsobuOH	AcCN	1.5	RT	> 90	> 98
7			$C_6H_{11}OH$	AcCN	18	RT	84	~ 90
7			2-[4-(*p*-Toluenesulfonamido)-phenyl]ethanol	AcCN	46	RT	> 90	> 98
8		Tre[a]	MeOH	AcCN	48	RT	Decomp.	
8				CH_2Cl_2–AcCN	4	0	92	> 90
9	(*p*)$MeOC_6H_4CO$	Ts	MeOH	CH_2Cl_2	48	RT	91	92
10		Tre[a]		CH_2Cl_2	4	0	71	> 95

[a]Abbreviations: RT, room temperature; Tre, trifluoroethylsulfonyl.

the C-1 atoms with β substituents were observed at 102–103 p.p.m., whereas the C-1α atoms were observed at 98–100 p.p.m. As shown in Table II, the stereoselectivity was not sensitive to the reaction time, temperature, solvent, C-2 substituent, C-1 sulfonate, or alcohol. The choice of solvent did in some cases affect the rate and overall yield of the reactions. The best conditions appeared to be the use of the 2-*O*-benzoyl-1-*O*-tosyl derivative **7** in acetonitrile at room temperature.

One reaction with methanol was carried out in a sealed 5-mm n.m.r. tube so that the reaction could be followed by ^{1}H-n.m.r. spectrometry. The reaction was almost over within the time necessary for preparing the sample and introducing it into the spectrometer (20 min). A small increase in the methoxyl group signal could be observed within the next 2 h. The formation of an orthoester intermediate could not be observed. Since *p*-toluenesulfonic acid was formed during these reactions and not removed, the failure to detect an orthoester was not unexpected. The mechanism of the reaction appears to be the same as that proposed for the corresponding 2-*O*-acyl-1-*O*-tosyl-D-mannopyranose derivatives[4], namely, that the reaction proceeds through an acyl oxonium ion-intermediate.

To investigate further the stereoselectivity of the reaction, methyl 3,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**11**) was prepared by treatment of 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-*O*-tosyl-D-galactopyranose (**7**) with methanol, and by rearrangement of 3,4,6-tri-*O*-benzyl-1,2-(1-methoxyethylidene)-α-D-galactopyranose (**1**) in chlorobenzene with catalytic amounts of methanol and 2,6-dimethylpyridinium perchlorate added[5], followed by debenzoylation. Both reactions gave crystalline **11**, in 90% yield from the 1-*O*-tosyl derivative **7**, and 80% yield from the orthoester **1**. However, the ^{1}H-n.m.r. spectra of the mother liquors showed only the β-D-glycoside present from the reaction of **7** and a 1:1 mixture of α- and β-D-anomers from the reaction of **1**. Thus, the stereoselectivity with the 1-*O*-tosyl derivative **7** was essentially 100% and that for the orthoester **1** ~90% of β-D anomer.

Several disaccharides **12**, **13**, and **14** having (1→6) and (1→2)-β-D-galactopyranosyl bonds were also synthesized. The ^{13}C-n.m.r. of the crude disaccharide fractions showed the stereoselectivity to be high (>95% of β-D anomer). The yields were somewhat variable, probably owing to the failure to exclude moisture completely during the reaction.

The results of the glycoside-forming reactions with **7** provide a general method of preparing β-D-galactopyranosides with high stereoselectivity, essentially irrespective of the structure and reactivity of the aglycon. Furthermore, the rates of reaction and the yields, when equivalent amounts of alcohol and glycosylating agent were used, were high if care was taken to exclude water from the reaction.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded with a Varian A-60-A spectrometer for solutions in chloroform-*d*, with tetramethylsilane as internal standard. ^{13}C-N.m.r. spectra were recorded with a Varian X100-15 spectrometer

operating in the pulsed Fourier-transform–proton-noise decoupled mode, for solutions in chloroform-*d* with tetramethylsilane as internal standard. Optical rotations were determined with a Perkin–Elmer model 141 polarimeter for solutions in jacketed, 1-dm cells kept at 25°, and melting points with a "Meltemp" apparatus equipped with a 76-mm immersion thermometer. T.l.c. was performed on "Bakeflex" silica gel 1B-F plates (2.5 × 3.0 cm) and column chromatography on V.W.R. silica gel (grade 950, 60–200 mesh).

3,4,6-Tri-O-*benzyl-1,2*-O-(*1-methoxyethylidene*)-α-D-*galactopyranose* (**1**). — 3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-D-galactopyranose[6] (14 g) was dissolved in dry toluene (50 mL) and potassium hydroxide (40 g, powder) was added. The mixture was heated to reflux, and benzyl chloride (60 mL) was added dropwise. The reaction mixture was heated under reflux for 2.5 h, cooled to room temperature, and water was added. The organic phase was diluted with toluene and washed with water until neutral. The toluene solution was evaporated to an oil, which was then steam distilled. The residue was extracted with chloroform, dried (anhydrous $MgSO_4$), and evaporated to a syrup, which crystallized from ether–hexane to give **1** (17 g, 87%), m.p. 84–86°, $[\alpha]_D^{25}$ +24.2° (*c* 1, chloroform); ^{1}H-n.m.r.: δ 7.5–6.9 (15 H), 5.68 and 5.51 (d, 1 H, $J_{1,2}$ 8 Hz), 3.4–3.3 (12 H), 3.22 and 3.25 (3 H), 1.55 and 1.58 (3 H).

Anal. Calc. for $C_{30}H_{34}O_7$: C, 71.13; H, 6.75. Found: C, 71.20; H, 6.73.

3,4,6-Tri-O-*benzyl*-D-*galactopyranose*[7] (**2**). — The orthoester **1** (6.0 g) was heated under reflux in 4:1 (v/v) 1,4-dioxane–M sulfuric acid (100 mL) until t.l.c. showed the deacetylation to be complete (4 h). The reaction mixture was neutralized with solid sodium hydrogencarbonate and evaporated to a syrup. The product was extracted with chloroform, and the extract was washed with water, dried (anhydrous Na_2SO_4) and evaporated to a syrup. Purification of the crude diol by use of a "Prep-500" (Waters Associates) chromatograph on silica gel and 2:1 (v/v) ethyl acetate–hexane as eluent gave syrupy diol **2** (4.0 g, 75%), $[\alpha]_D^{25}$ +48.5→53.0° (*c* 1, chloroform); ^{1}H-n.m.r.: δ 7.6–6.9 (15 H) and 5.5–3.0 (15 H, 2 H exchangeable with D_2O).

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 72.00; H, 6.68.

1,2-Di-O-*acyl-3,4,6-tri*-O-*benzyl*-D-*galactopyranose* (**3** *and* **4**). — A weighed amount of the diol **2** was dissolved in dry pyridine, and the acid chloride derivative (3–4 equiv.) was added. The solution was stirred at room temperature until the reaction was complete as shown by t.l.c. (~24–48 h). Water (1 mL) was added to decompose any remaining acid chloride and any acid anhydride that may have formed. The pyridine was evaporated *in vacuo* and the residue dissolved in dichloromethane. The organic phase was washed with dilute hydrochloric acid, sodium hydrogencarbonate solution, and water, dried ($MgSO_4$), and evaporated to a syrup. The crude diacyl derivatives were purified on a silica gel column with dichloromethane as the eluent. The products were syrups composed of one or two anomers (see Table 1).

Reaction of 2-O-*acyl-3,4,6-tri*-O-*benzyl*-α-D-*galactopyranosyl chloride derivatives with alcohols.* — The diacyl derivative (**3** or **4**, ~1 g) was dissolved in dry diethyl ether (20 mL). The solution, cooled to 0°, was saturated with dry hydrogen chloride,

and allowed to reach room temperature in the tightly stoppered container. After 48 h, the reaction was usually complete. Dry nitrogen was bubbled through the solution to remove the excess of hydrogen chloride, and the solution was then evaporated to a clear syrup. This was dissolved in dichloromethane, and the solution was washed with cold sodium hydrogencarbonate solution, cold water, dried (anhydrous $MgSO_4$), and evaporated to a syrup. The α-D-galactopyranosyl chloride derivatives were used in the coupling reactions without further purification, attempts to crystallize the compounds being not successful; ^{1}H-n.m.r.: δ 6.55 (d, 1 H, $J_{1,2}$ 3 Hz).

The suitable halide dissolved in acetonitrile was allowed to react with silver *p*-toluenesulfonate (or trifluoroethanesulfonate) (1 equiv.) to form the corresponding sulfonyl derivative. The acetonitrile was distilled off under vacuum (except for the case where acetonitrile served as the solvent for the reaction). The appropriate solvent was distilled onto the sulfonyl derivative. The reaction mixture was stirred and filtered to remove silver chloride. The solution was then mixed with 1 equiv. of an alcohol and allowed to react. The mixtures were isolated, and the crude glycosides analyzed by ^{1}H- or ^{13}C-n.m.r., or both. Results are shown in Table II.

*Methyl 3,4,6-tri-*O*-benzyl-β-*D*-galactopyranoside* (**11**). — Compound **7** (1.5 g) in acetonitrile was treated with methanol (0.1 g) for 15 h at room temperature as just described. The mixture was diluted with dichloromethane, and the solution was washed with sodium hydrogencarbonate solution, and water, dried ($MgSO_4$), and evaporated to a syrup. The crude syrup was *O*-debenzoylated with sodium ethoxide in ethanol at room temperature. The solution was neutralized with acetic acid, evaporated to a syrup, and dissolved in dichloromethane. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to a syrup. Chromatography on a silica gel column (10 × 1.5 cm) with chloroform gave **11**, which crystallized from ether–petroleum ether (1.1 g, 90%), m.p. 99–99.5°, $[\alpha]_D^{25}$ 5.4° (*c* 1, chloroform); ^{1}H-n.m.r.: δ 7.4–7.1 (15 H), 5.1–3.5 (13 H), 3.55 (3 H), and 2.4–2.2 (1 H exchangeable with D_2O); ^{13}C-n.m.r.: 104.3 (C-1β), 82.1 (C-3), 73.8 (C-5), 73.0 (C-4), 71.4 (C-2), 68.8 (C-6), 56.9 (OCH_3), 74.6, 73.6, and 72.5 p.p.m. (benzylic C, triplets in off-resonance ^{13}C-n.m.r.).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.42; H, 6.90.

*Methyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-*D*-galactopyranoside* (**12**). — Compound **7** (1.0 mmol) was mixed with methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside[8] (0.91 mmol) in acetonitrile. The reaction was processed as described for **11**. The crude disaccharide was chromatographed on silica gel with 19:1 (v/v) benzene–ether as eluent to give the pure disaccharide **12** which crystallized from ether (370 mg), m.p. 120–122°, $[\alpha]_D^{25}$ +18.7° (*c* 1, chloroform); ^{13}C-n.m.r.: 102.0 (C-1′β) and 98.8 p.p.m. (C-1α-OCH_3).

Anal. Calc. for $C_{62}H_{64}O_{12}$: C, 74.38; H, 6.44. Found: C, 74.57; H, 6.68.

*Methyl 2-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl)-3,4,6-tri-*O*-benzyl-α-*D*-glucopyranoside* (**13**). — Compound **7** (1 mmol) was mixed with methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside[9] (1 mmol) in acetonitrile. The reaction was processed as described for **11**. Purification on a silica gel column in 19:1 (v/v) benzene–

ether gave the disaccharide **13** which crystallized from ether (112 mg), m.p. 107–109°, $[\alpha]_D^{25}$ +40.8° (*c* 1, chloroform); ^{13}C-n.m.r.: 102.8 (C-1′β) and 99.9 p.p.m. (C-1α-OCH_3).

Anal. Calc. for $C_{62}H_{64}O_{12}$: C, 74.38; H, 6.44. Found: C, 74.60; H, 6.40.

*Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl)-β-*D*-galactopyranoside* (**14**). – Compound **11** (0.8 mmol) was coupled with **7** (0.8 mmol) in acetonitrile as described for the preparation of **9** to give the syrupy 2′-*O*-benzoyl disaccharide (0.7 g), $[\alpha]_D^{25}$ +27.3° (*c* 1, chloroform). *O*-Debenzoylation with sodium ethoxide in ethanol gave, after processing as described for **11**, **14** which crystallized from ether–petroleum ether (0.5 g, 70% total yield), m.p. 115–116°, $[\alpha]_D^{25}$ −10.7° (*c* 1, chloroform); ^{13}C-n.m.r.: 106.0 (C-1′β) and 104.3 p.p.m. (C-1β-OCH_3).

Anal. Calc. for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.58; H, 6.70.

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