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1,2-ACYLSPIROORTHOESTERS OF 3,4,6-TRI-*O*-ACETYL-α-D-GLUCOPYRANOSE*

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ABSTRACT

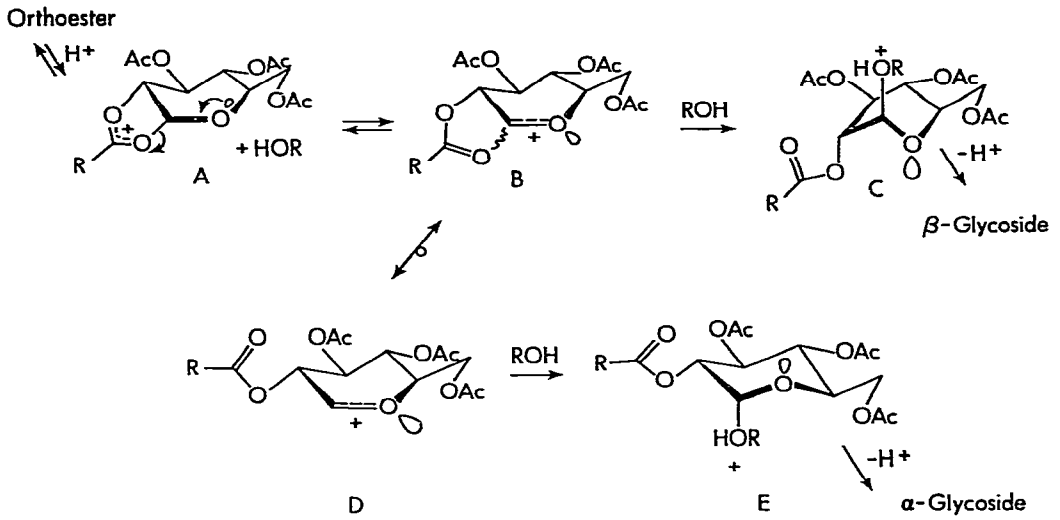
The 1,2-*O*-(2-oxa-3-oxocyclopentylidene) derivative of 3,4,6-tri-*O*-acetyl-α-D-glucopyranose was prepared in both the *exo* (**4**) and *endo* (**5**) forms. The compounds were prepared by bromide-ion promoted cyclization of 3,4,6-tri-*O*-acetyl-2-*O*-(3-carboxypropanoyl)-α-D-glucopyranosyl bromide. The similar acylorthoester derivatives of phthalic acid were prepared from 3,4,6-tri-*O*-acetyl-2-*O*-(2-carboxybenzoyl)-α-D-glucopyranosyl bromide. The cyclizations produced a much higher ratio of the *endo* forms than would have been expected from their relative thermodynamic stabilities. The configurations were established by nuclear Overhauser enhancement studies and their conformations deduced from ^{1}H-n.m.r. parameters. The greater stability of the *exo* isomers appears to have a stereoelectronic origin. Preliminary efforts to engage the acylorthoesters in reactions with isopropyl alcohol to form glycosides are reported. It was discovered that a carboxylic acid provides powerful catalysis for the β to α anomerization of *O*-acetylated glucopyranosides by stannic chloride.

INTRODUCTION

The development of a generally reliable synthesis of 1,2-*trans*-β-glycopyranosides in high yield remains an important challenge. The best methods now available, using glucose derivatives as an example, appear to be those involving the intermediate formation of a 1,2-orthoester[1,2]. All such methods, especially when applied to hindered and weakly nucleophilic alcohols, are susceptible to extensive formation of α- as well as β-glycoside[3–5]. Also, the nature of the acid used to catalyze the orthoester rearrangement may strongly influence the route of reaction[3,6].

The formation of a β-glycoside by way of a 1,2-orthoester is expected to proceed by the pathway outlined in Scheme 1. The 1,2-dioxenium ion (A) formed first

*Dedicated to Professor Stephen J. Angyal on the occasion of his retirement, and with gratitude for the great assistance provided through the very many important insights he has contributed to the development of modern carbohydrate chemistry and conformational analysis.
†In partial fulfilment of the Ph.D. degree.



Scheme 1. Reactive intermediates postulated for the acid-catalyzed alcoholysis of a 1,2-orthoester to *O*-acetylated anomeric glucopyranosides.

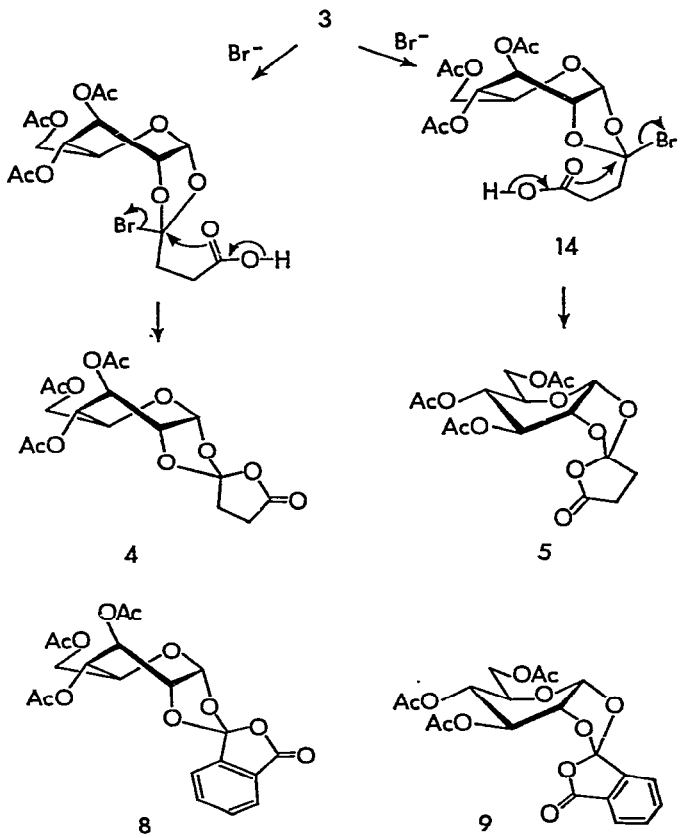
is attacked at the anomeric rather than the 2-position of the pyranose ring because of participation of O-5 in charge delocalization as indicated. Most probably, the reaction, in its first stage, involves bond rearrangement of the dioxenium ion (A) toward the glycosyloxonium ion (B). Nucleophilic attack at the β side of the anomeric center would be rendered favorable because of shielding of the α side by the newly formed 2-acetoxyl group, which can be expected to be electrostatically attracted to the carbonium center as depicted in B. Stereoelectronic demands appear[7] to require the development of the glycosidic bond to occur with a *p*-orbital of O-5 in an *anti*-periplanar orientation, as indicated in C. Should the shielding of the α side of the anomeric center be lost, as is indicated in D, then formation of α-glycoside (E) is expected to become the favored route of reaction[7].

It was considered of interest in this regard to prepare intramolecular 1,2-acyl-orthoesters such as could be derived from succinic acid (**4** and **5**) and phthalic acid (**8** and **9**) to inhibit the accumulation of stable orthoesters derived from external alcohol and, perhaps, favor reaction by way of the oxocarbonium ion of type B rather than type D.

DISCUSSION OF RESULTS

3,4,6-Tri-*O*-acetyl-2-*O*-(3-carboxypropanoyl)-α-D-glucopyranosyl bromide (**3**) was prepared from the readily available 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**1**) by way of its 2-*O*-(3-carboxypropanoyl) derivative (**2**). The intramolecular cyclization of **3** to produce the desired acylspiroorthoesters (**4** and **5**) in excellent yield was induced by bromide-ion catalysis[8]. The corresponding derivatives of phthalic acid

(**8** and **9**) were prepared similarly from **7**. Fractional crystallization allowed the isolation of the pure orthosuccinate **5** and orthophthalate (**8**). Attempts to obtain pure samples of **4** and **9** by chromatographic separation failed. The properties of these compounds were deduced from mixtures of the epimers.



The ^{1}H- and ^{13}C-n.m.r. parameters determined for compounds **4**, **5**, **8**, and **9** are reported in Table I, together with those for the structurally related compounds **10**–**13**. The *exo* and *endo* configurations were assigned to compounds **4** and **5** on the basis of nuclear Overhauser enhancement measurements.

The readily available form of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose (**10**) has been assigned the *exo*-configuration[8].

The great stability and uniformity of the magnetic field generated by a superconducting solenoid, and the high resolution achieved at fields up to 400 MHz, together with the computer-assisted, f.t. mode of operation, allows the precise (within 2%) measurement of nuclear Overhauser enhancements[9] and thereby often provides a convenient tool for estimating whether or not two or more hydrogen atoms are in close proximity. Thus, for example, the *exo* configuration of **10** could be readily

TABLE I

NUCLEAR MAGNETIC RESONANCE PARAMETERS[a]

Compound	*H-1*	$J_{1,2}$	*H-2*	$J_{2,3}$	*H-3*	$J_{3,4}$	*H-4*	$J_{4,5}$	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C*[b]	*Orthoester residue*
exo *Epimers*[c]																O ‖ -CH_2-CH_2-C-
4	5.82	5.5	4.44	3.0	5.18	3.0	4.92	9.5	97.32	73.52	69.68	67.98	67.43	62.99	126.47	(2.65 (m), 2.80 (m)
8	6.04	5.5	4.68	3.2	5.32	3.2	5.03	8.5	97.74	74.12	69.97	67.92	67.92	63.17	122.76	
																-O O- \ / CH_3-C-OCH_2-CH_3
10	5.71	5.5	4.31	2.9	5.17	2.9	4.90	9.5	97.06	73.39	70.42	68.45	67.18	63.22	121.41	1.70 (s), 3.54 (q), 1.17 (t)
11[d]	5.68	5.0	4.20	3.0	5.18	3.0	4.89	8.5	96.66	73.47	70.88	68.55	67.00	63.22	109.83	
12[e]	5.69	5.0	4.35	3.0	5.19	3.0	4.91	9.0								
endo *Epimers*																O ‖ -CH_2-CH_2-C-
5	5.80	6.2	4.40	4.5	5.46	7.2	5.01	9.7	99.20	76.74	73.22	67.25	68.48	61.95	127.27	2.48 (m), 2.75 (m)
9	6.07	6.0	4.65	4.5	5.63	7.5	5.11	10.0	99.93	77.23	73.33	67.30	68.70	62.00	122.93	
13[e]	5.61	5.5	4.25	4.7	5.56	7.0	4.99	9.5								

[a]All spectra were recorded in $CDCl_3$. Chemical shifts (δ) are reported in p.p.m. relative to internal Me_4Si. First-order coupling constants are in Hz for spectra measured at 100 MHz. [b]Quaternary carbon atom. [c]All of these isomers showed long-range coupling between H-2 and H-4 (1.0 Hz), as found by Coxon and Hall[11] for 1,2-*O*-alkylidene derivatives of glucose. The $B_{2,5}$ conformation is compatible (W-arrangement) with this coupling. [d]3,4,6-Tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucopyranose[18]. [e]The *exo* (**12**) and *endo* (**13**) isomers for 3,4,6-tri-*O*-acetyl-1,2-*O*-(2-oxacyclopentylidene)-α-D-glucopyranose[18].

confirmed by examining the effect of irradiating the methyl resonance (δ 1.70) of the orthoacetyl group. As expected, the signals for H-3, H-5 and the methylene hydrogen atoms of the ethoxyl group were uniquely enhanced, by 2.4, 9.5, and 5.6%, respectively. This result places the methyl group closer to H-5 than H-3, which would be in accordance with the $B_{2,5}$ conformation (however, as will be seen later, in a somewhat distorted form). Similarly, irradiation of the higher-field (δ 2.65) multiplet for the methylene protons of the succinyl residue of **4** resulted in 2.4 and 6.4% enhancements of the signals for H-3 and H-5, respectively. Alternatively, irradiation of H-5 of **4** caused a 2.1% enhancement of the signal for this methylene group. As expected, the signals for H-3 (6%) and the two H-6's (4.7%) were also enhanced. These measurements allow unequivocal assignment of the configuration of the quaternary carbon atom in **4**; that is, **4** is the *exo* isomer. In the case of **5**, irradiation of the multiplet at δ 2.48 caused enhancement of the signals for H-1 (4.0%) and H-2 (2.3%), as expected for the *endo* isomer. The conformational preferences for **4** and **5** are discussed in detail later. The configurations of the phthalic acid derivatives (**8** and **9**) are assigned on the basis of the n.m.r. parameters reported in Table I, when compared with those for compounds **4**, **5**, and **10**.

Under the conditions for the bromide-ion catalyzed cyclizations of **3** and **7**, the ratio of *exo* to *endo* acylorthoester found in the product varied somewhat from experiment to experiment, but in every instance the amount of the *exo* product was less than that in mixtures obtained when the isomers were equilibrated in dichloromethane containing a trace of trifluoroacetic acid. The *exo*-**4** and *endo*-**5** products were formed in a ratio of near 3:5, whereas the ratio was 5:1 for the equilibrium mixture. In the case of *exo*-**8** and *endo*-**9**, the ratio in the product was 3:2, whereas, in the equilibrium mixture, the ratio was 7:2. For the ethyl orthoacetate **10**, the ratio of *exo* to *endo* in the equilibrium mixture was the same as that found for **4** and **5**. The rapid equilibrations are expected to proceed by way of 1,2-dioxenium ions of the

TABLE II

CONFORMATIONS FOR THE 1,2-ACYLSPIROORTHOESTERS AS ESTIMATED[a] FROM VICINAL COUPLING-CONSTANTS[b]

	H-1,H-2	*H-2,H-3*	*H-3,H-4*	*H-4,H-5*
Compound **4** (exo)				
$^3J_{H,H}$ (Hz)	5.5	3.0	3.0	9.5
Torsion angle (°)	−38	−54	124	166
Compound **5** (endo)				
$^3J_{H,H}$ (Hz)	6.2	4.5	7.2	9.7
Torsion angle (°)	±33	−133	148	169

[a]Calculated by using the expression proposed by Abraham and co-workers[10]. [b]As derived from the observed spacings.

type **15**, with A = H. The faster formation of the thermodynamically less stable *endo*-**5** from **3** can be rationalized in terms of an SN2-type of replacement, as depicted by **14**, of *exo*-bromide formed from **15** (A = H) and bromide ion.

From the standpoint of repulsive nonbonded interactions, it could be expected that the more stable acylorthoester would be that with the "small" oxygen atom in the more crowded, *endo* disposition. However, as already noted, it is the *exo* isomer that is energetically more favorable.

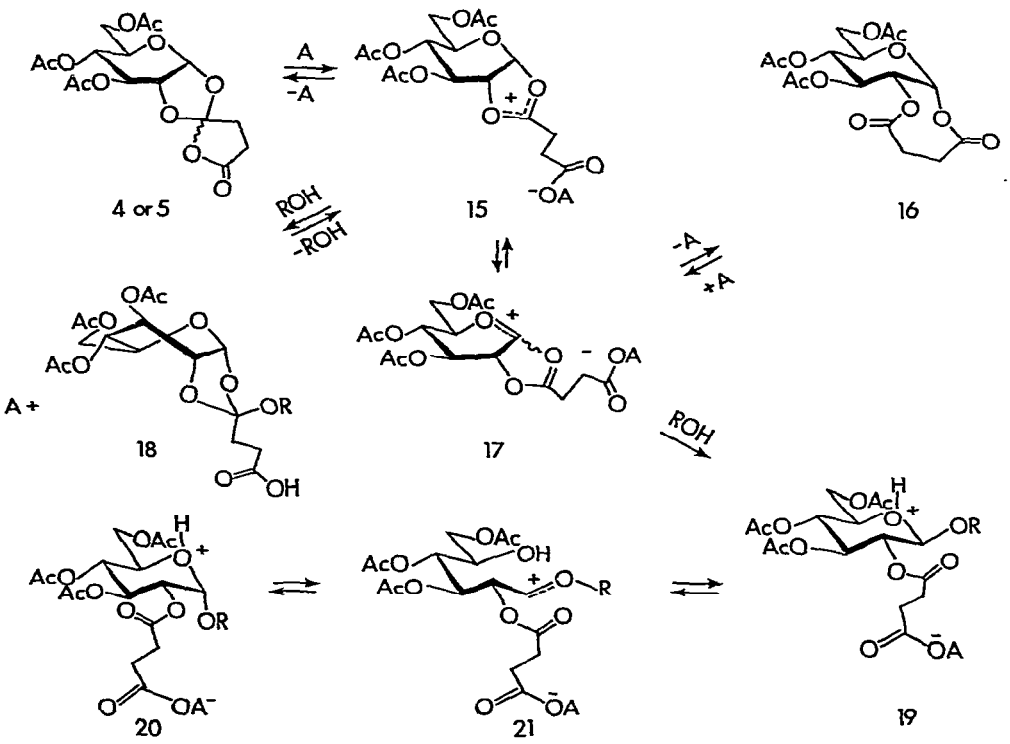
The modified Karplus relationship[10] used by Coxon and Hall[11] in a study of the conformations of 1,2-*O*-alkylidene pyranose derivatives provides the torsion angles given in Table II for the vicinal hydrogen atoms about the pyranose rings of the orthosuccinates **4** and **5**.

The difference in the coupling constants for vicinal hydrogen atoms about the pyranose rings of the orthosuccinates **4** and **5** requires the change in configuration at C-2 of the dioxolane ring to cause an appreciable change in the conformation of the pyranose ring. As already seen, the nuclear Overhauser enhancement experiment favors a $B_{2,5}$-like conformation for **4**. Indeed, inspection of a molecular model suggests that **4** probably exists in a somewhat flattened and slightly distorted $B_{2,5}$ conformation, which is inferred by the vicinal coupling-constants (Table II). In the case of **5**, the large values for $J_{H\text{-}3,H\text{-}4}$ and $J_{H\text{-}4,H\text{-}5}$ are suggestive of near *anti*-periplanar orientations between H-4 and its neighboring hydrogen atoms (H-3 and H-5). The value of 6.2 Hz for $J_{H\text{-}1,H\text{-}2}$ requires these hydrogen atoms to define a torsion angle of about 30°. On this basis, the favored conformation for the pyranose ring of **5** could be near the $^{1,4}B$ conformation, with H-1 and H-2 in *quasi*-axial and *quasi*-equatorial orientation, respectively. On this basis, it would be surprising that irradiation of the methylene group would cause stronger enhancement of the *quasi*-axial H-1 atom. On the other hand, the $^4C_1$(D) conformation for the pyranose ring, having the O-5–C-1–C-2 region strongly flattened so as to accommodate the dioxolane ring, also provides torsion angles compatible with the measured vicinal coupling-constants (Table II), but a decision in this regard could not be made on the basis of the coupling constants only.

In order to rationalize the fact that the *exo* compound **4** is thermodynamically more stable than its *endo* isomer **5**, it seems necessary to invoke a substantial driving-force for the oxygen atom at C-2 of the dioxolane ring to adopt as axial an orientation as possible, as indicated by the conformational formulas presented for **4** and **5** (also, the related structures **8** and **9**). The driving force presumably would be of a stereoelectronic origin, as is the case for the anomeric effect[12]. On this basis, a rationalization seems possible since, should the $B_{2,5}$ conformation of **4** be maintained in **5**, there would exist, as may be readily gauged from a molecular model, a severe nonbonded interaction between the *endo*-oxygen atom and H-5. Thus, the change in conformation for the pyranose ring would be expected to occur in order to relieve this interaction. Should the *endo* isomer (**5**) favor the flattened $^4C_1$-like conformation, then, as suggested by the conformational drawing, the *endo*-oxygen atom would be in a position to cause deshielding of H-3 of **5** as compared to H-3 of **4**. As may be seen

in Table I, this was indeed the case. Furthermore, this conformation would place H-1 in a somewhat more equatorial orientation than H-2, and these orientations would be more in line with the nuclear Overhauser enhancement which was observed on irradiation of the methylene-group hydrogen atoms of **5** than would be the case should the pyranose ring be in the $^{1,4}B$ conformation. It must be recognized that the conformations assigned to the pyranose rings of the acylorthoesters represent the weighted average of the conformers, with appreciable population in the conformational equilibria; these structures are probably not highly rigid.

It was expected that acylorthoesters would be highly prone to dissociation, either by thermal excitation alone or with the assistance of acid catalysis, to form dipolar species (**15**) when A is a neutral species (solvent or Lewis acid), or the cationic species when A is a proton. Recently, Wulff and co-workers[13] reported the synthesis and reactivity of 3,4,6-tri-*O*-acetyl-1,2-*O*-{1-[4-(4-biphenylyl)butanoyloxy]ethylidene}-α-D-glucopyranose.



In principle, the dioxenium ion (**15**) could lead to the cyclic structure **16**. However, this structure was not encountered either in the preparation of the acylorthoesters or in the product of their solvolysis. It may be expected that **15** would be in equilibrium with **17** so that, in the presence of an alcohol, a glycoside would be formed. Under conditions that would produce the dipolar species **17**, the α side could

be well shielded, and thus promote attack by the alcohol on the β side to form β-glycoside as the favored route of reaction.

Reaction of **4** and **5** with alcohol in the presence of a trace of trifluoromethanesulfonic acid as catalyst could lead to the formation of the orthoester **18**. However, a 2-molar excess of isopropyl alcohol did not provide a measurable amount of **18** under conditions that rapidly equilibrate **4** and **5**.

The acylorthoesters (**4** and **5**) were then heated at 150° in nitrobenzene with a one-molar excess of isopropyl alcohol. Only 60% of the orthoesters reacted in 18 h. An isopropyl ester was formed, together with glycoside (30% yield) in a $\beta:\alpha$ ratio of 5 to 1. Addition of 2,4,6-trimethylbenzoic acid had no apparent effect on the reaction. Addition of a slight excess of 2,6-lutidine completely suppressed the formation of glycoside. Judging from these results, further pursuit of this approach to the synthesis of β-glycosides should include a search for more-reactive acylspiroorthoesters.

Stannic chloride is known to promote the reaction of an acetylated sugar with alcohols to form glycosides[14,15]. It was therefore of interest to examine the reactions of these acylorthoesters promoted by this Lewis acid. Indeed, reaction of **5** was rapid at 25°, with dichloromethane as solvent, providing near-quantitative yields of isopropyl glycoside, but with the α anomer predominating. Examination of the course of reaction showed the system to provide strong conditions for $\beta \rightarrow \alpha$ glycoside anomerization. This was surprising, as Pacsu[16] had shown stannic chloride to be a very poor catalyst for this transformation, and this result was recently confirmed[15]. Indeed, isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**22**) (0.1M) in chloroform at 25° and in the presence of an equimolar amount of stannic chloride was found to anomerize very slowly (half-time of reaction about 1400 min). However, under the same conditions, isopropyl 3,4,6-tri-*O*-acetyl-2-*O*-(3-carboxypropanoyl)-β-D-glucopyranoside (**24**) and isopropyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-carboxybenzoyl)-β-D-glucopyranoside (**25**) were found to undergo rapid anomerization, with half-lives of 10 and 7 min, respectively.

These rapid rates of reaction were expected to originate in the liberation of a proton to form the protonated species **19** and **20** (A = $SnCl_4$) under superacid conditions, with subsequent anomerization, probably *via* the open-chair intermediate[17] (**21**). Indeed, when isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**22**) was subjected to the foregoing conditions, with the addition of one molar equivalent of acetic acid, anomerization was nearly 100 times faster ($t_{1/2}$ = 14 min) than in the absence of the acetic acid.

In contrast to the results obtained using the succinyl compounds **4** and **5**, the reaction of the phthaloyl compounds **8** and **9** produced high yields of 3,4,6-tri-*O*-acetyl-2-*O*-(2-carboxybenzoyl)-α-D-glucopyranosyl chloride when treated with stannic chloride in dichloromethane in the presence of 2 molar equivalents of isopropyl alcohol. It thus appears important to choose structures for the development of this approach to β-glycoside synthesis that can well separate the $-CO_2SnCl_4$ group from the anomeric center.

EXPERIMENTAL

General procedures and analytical methods. — These were the same as previously described[7].

*1,3,4,6-Tetra-*O*-acetyl-2-*O*-(3-carboxypropanoyl)-α-*D*-glucopyranose* (**2**). — A solution of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose[19] (**1**) (6.76 g, 19.4 mmol), succinic anhydride (5.77 g, 57.6 mmol), and 4-dimethylaminopyridine (0.2 g) in 40 mL of 1 : 1 (v/v) dichloromethane–pyridine was stirred for 2 h at room temperature by which time t.l.c. on silica gel with 10 : 10 : 1 ethyl acetate–hexane–ethanol indicated completion of reaction. Water (20 mL) was added and the solution was evaporated to dryness. Toluene (2 × 100 mL) was added to the residue and removed by distillation *in vacuo*.

The residue was dissolved in dichloromethane (100 mL) and the solution was washed successively with water (2 × 100 mL), 5% hydrochloric acid (200 mL), and water (100 mL). Drying and removal of solvent provided a syrupy product, yield 8.58 g (98%), that crystallized from ethyl acetate–hexane; m.p. 116–117°, $[\alpha]_D^{25}$ +93.4° (*c* 1, chloroform).

Anal. Calc. for $C_{18}H_{24}O_{13}$: C, 48.22; H, 5.39. Found: C, 47.96; H, 5.44.

*3,4,6-Tri-*O*-acetyl-1,2-*O*-[2-oxa-3-oxocyclopentylidene]-α-*D*-glucopyranose* [**4** (exo), **5** (endo)]. — A saturated solution of hydrogen bromide in acetic acid (40 mL, prepared at 0°) containing 3% (v/v) of acetic anhydride was added to a solution of **2** (8.50 g, 19.0 mmol) in dichloromethane (10 mL). The resulting solution was kept for 1.5 h at room temperature, and then the solvent was removed at a bath-temperature of 35°. Toluene (100 mL) was added to the residual yellow syrup and removed by distillation *in vacuo*. After repeating this treatment a second time, the product was dissolved in dichloromethane and the resulting solution was decolorized with charcoal, and evaporated to provide 3,4,6-tri-*O*-acetyl-2-*O*-(3-carboxypropanoyl)-α-D-glucopyranosyl bromide (**3**) as a white foam. The crude product resisted crystallization but appeared essentially pure (n.m.r.) and was used directly to prepare the title compounds. The material was dissolved in dry acetonitrile (30 mL) and to this solution 4-Å molecular sieve (5 g), tetraethylammonium bromide (3.2 g), and 2,6-lutidine (10 mL) were added and the mixture was stirred for 3 h at room temperature. Removal of the solids and evaporation of solvent left a yellow syrup that was dissolved in dichloromethane (150 mL). This solution was washed twice with water, dried, and evaporated to leave a syrup that crystallized from dichloromethane–diisopropyl ether as fluffy white needles; yield 4.43 g (60%), m.p. 125–135°. The ^{1}H-n.m.r. spectrum of this material showed it to consist of **5** and **4** in 5:3 ratio. Successive recrystallizations from ethyl acetate and dichloromethane–diethyl ether provided the pure *endo* isomer (**5**); m.p. 162–164°, $[\alpha]_D^{21}$ +135.6° (*c* 1.0, chloroform).

Anal. Calc. for $C_{16}H_{20}O_{11}$: C, 49.49; H, 5.19. Found: C, 49.32; H, 5.16.

*1,3,4,6-Tetra-*O*-acetyl-2-*O*-(2-carboxybenzoyl)-α-*D*-glucopyranose* (**6**). — A solution of **1** (11.66 g, 33.8 mmol), phthalic anhydride (7.49 g, 1.5 equiv.), and 4-dimethylaminopyridine (37 mg) in 45 mL of 2:1 (v/v) pyridine–dichloromethane was

kept for 9 h at room temperature, and then taken to dryness. The residual, clear syrup was dissolved in dichloromethane (100 mL) and the solution was washed with 5% hydrochloric acid (200 mL), and then water (100 mL). Removal of solvent left a white solid that crystallized from boiling ethanol (100 mL) in 90% yield (15.04 g). One recrystallization provided the analytical sample; m.p. 159–160°, $[\alpha]_D^{21}$ +107° (*c* 0.99, chloroform).

Anal. Calc. for $C_{22}H_{24}O_{13}$: C, 53.23; H, 4.87. Found: C, 52.98; H, 4.84.

3,4,6-Tri-O-acetyl-2-O-(2-carboxybenzoyl)-α-D-glucopyranosyl bromide (**7**). — Compound **6** (20.07 g, 40.47 mmol) was treated with hydrogen bromide under the same conditions as used for the preparation of **3**, producing **7** as a white foam that provided an unstable, crystalline product from ethanol–hexane; m.p. 140° (dec.), $[\alpha]_D^{24}$ +179.3° (*c* 1.0, chloroform).

Anal. Calc. for $C_{20}H_{21}BrO_{11}$: C, 46.44; H, 4.09; Br, 15.45. Found: C, 46.07; H, 3.98; Br, 15.70.

3,4,6-Tri-O-acetyl-1,2-O-phthalidylidene-α-D-glucopyranose [**8** (exo), **9** (endo)]. — The crude **7** appeared essentially pure on examination by t.l.c. (silica gel, 5:5:1 ethyl acetate–hexane–acetic acid) and was used directly for the preparation of the title compounds, as described for **4** and **5**, except that the mixture was stirred for 2 h at 50°, to give a yellow foam (90% yield).

The ^{1}H-n.m.r. spectrum showed it to consist of mixture (~2:3) of the *endo* (**9**) and *exo* (**8**) isomers. Crystallization from methanol provided 10.4 g of pure **8** (59%); m.p. 150.5–152°, $[\alpha]_D^{24}$ +84.3° (*c* 1.0, chloroform).

Anal. Calc. for $C_{20}H_{20}O_{11}$: C, 55.05; H, 4.62. Found: C, 55.03; H, 4.59.

Isopropyl 3,4,6-tri-O-acetyl-2-O-(3-carboxypropanoyl)-β-D-glucopyranoside (**24**). — Isopropyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside[20] (**23**; 800 mg, 2.3 mmol) was treated with succinic anhydride, as described for the preparation of **2**, to provide a pale-yellow solid; yield 1.03 g (99%). Crystallization from ethyl acetate–hexane provided the pure material; m.p. 116–117°, $[\alpha]_D^{25}$ +93.3° (*c* 1.0, chloroform).

Anal. Calc. for $C_{19}H_{28}O_{12}$: C, 50.89; H, 6.29. Found: C, 50.82; H, 6.31.

Isopropyl 3,4,6-Tri-O-acetyl-2-O-(2-carboxybenzoyl)-β-D-glucopyranoside (**25**). — Compound **23** (435 mg, 1.25 mmol) was treated with phthalic anhydride, under the conditions described for preparation of **6**, but for 36 h. The product crystallized from ethyl acetate–hexane (68% yield); m.p. 120–121°, $[\alpha]_D^{25}$ −9.9° (*c* 0.75, chloroform).

Anal. Calc. for $C_{23}H_{28}O_{12}$: C, 55.64; H, 5.68. Found: C, 55.78; H, 5.71.

Glycosidation reactions. — A. Solvolysis reactions. A solution of compound **5** (134 mg, 0.35 mmol) and isopropyl alcohol (0.70 mmol) in dry nitrobenzene (1.0 mL) was heated in a sealed tube for 18 h at 150°. Evaporation of solvent (100°, high vacuum) left a dark-yellow syrup whose ^{1}H-n.m.r. spectrum ($CDCl_3$) showed a 60% incorporation of the isopropyl group into the non-volatile product and near 40% of equilibrated starting-material (**4** and **5**). This material was *O*-deacetylated by treatment with 2:1:1 methanol–triethylamine–water overnight at room temperature. Evaporation and treatment of a methanolic solution of the product with Amberlite

IR-120 (H^+) resin gave a mixture of D-glucose and isopropyl D-glucopyranoside (30% yield) in a ratio of ~7:3 (^{1}H-n.m.r.). The relative intensities of the signals for these anomeric protons required the isopropyl β- and α-D-glucopyranosides to be present in a ratio of 5:1.

B. Reactions with stannic chloride. Stannic chloride (0.22 mmol) was added at room temperature to a stirred solution of **5** (85 mg, 0.22 mmol) and isopropyl alcohol (0.30 mmol) in dichloromethane (1.5 mL). After 1 h, 1:2 pyridine–water (1.5 mL) was added and the mixture was then diluted with dichloromethane. The solids were removed by filtration through a Celite filter-bed. Removal of the solvents was achieved by azeotropic evaporation of several portions of toluene. The yield of crude glycoside (90%) was estimated from the ^{1}H-n.m.r. ($CDCl_3$) spectrum by comparing the relative intensities of the signals of the methyl groups in the aglycon with those for the *O*-acetyl signals. *O*-Deacetylation, followed by treatment with Dowex 1 X8 (OH^-) resin, showed the product to be a 5:4 mixture of the α- and β-D-glucopyranosides, as determined from the relative intensities of their anomeric doublets (H-1α: δ 5.01, *J* 3.5 Hz; H-1β: δ 4.52, *J* 7.5 Hz). Under the same conditions, but with a reaction time of 15 h, a quantitative yield of a mixture of the isopropyl α- and β-glucopyranosides was recovered. The α:β ratio was 17:3.

Anomerization reactions. — Stannic chloride (1.0 mol equivalent) was added with vigorous mixing, at zero time, to a solution of the acylated isopropyl β-D-glucopyranoside (**22**, **24**, and **25**) (0.1M) in pure, dry chloroform (except in the case of the reaction of **22** catalyzed by an equimolar amount of acetic acid). The sample was transferred, *via* a syringe, to a thermostatted (25 ±0.2°) polarimeter cell and the rotation was monitored until it reached a constant maximum. The mixture was made neutral and processed as already described. The pseudo-first-order rate-constants for the $\beta \rightleftarrows \alpha$ anomerization were determined by using the standard, integrated polarimetric-rate expression and the half-times of reaction calculated from these constants.

The ^{1}H-n.m.r. spectra of the isolated products were, in all instance, consistent with a mixture of isopropyl 3,4,6-tri-*O*-acetyl-2-*O*-acyl-α- and -β-D-glucopyranosides in an α:β ratio of near 17:3.

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REFERENCES

1 J. E. WALLACE AND L. R. SCHROEDER, *J. Chem. Soc., Perkin Trans. 2*, (1977) 795–802.
2 P. J. GAREGG AND T. NORBERG, *Acta Chem. Scand., Ser. B*, 33 (1979) 116–118.
3 P. J. GAREGG AND I. KVARNSTRÖM, *Acta Chem. Scand., Ser. B*, 30 (1976) 655–658.
4 P. J. GAREGG AND I. KVARNSTRÖM, *Acta Chem. Scand., Ser. B*, 31 (1977) 509–513.
5 O. HINDSGAUL AND T. NORBERG, unpublished results from these laboratories, in preparation.

6 R. U. LEMIEUX AND H. DRIGUEZ, *J. Am. Chem. Soc.*, 97 (1975) 4069–5075.
7 R. U. LEMIEUX, K. B. HENDRIKS, R. V. STICK, AND K. JAMES, *J. Am. Chem. Soc.*, 97 (1975) 4056–4062.
8 R. U. LEMIEUX AND A. R. MORGAN, *Can. J. Chem.*, 43 (1965) 2199–2204.
9 R. RICHARZ AND K. WÜTHRICH, *J. Magn. Reson.*, 30 (1978) 147–150.
10 R. J. ABRAHAM, L. D. HALL, L. HOUGH, AND K. A. MCLAUCHLAN, *J. Chem. Soc.*, (1962) 3699–3705.
11 B. COXON AND L. D. HALL, *Tetrahedron*, 20 (1964) 1685–1695.
12 R. U. LEMIEUX AND S. KOTO, *Tetrahedron*, 30 (1974) 1933–1944.
13 G. WULFF, V. SCHRÖDER, AND W. SCHMIDT, *Angew. Chem. Int. Ed. Engl.*, 18 (1979) 309–310.
14 R. U. LEMIEUX AND W. P. SHYLUK, *Can. J. Chem.*, 31 (1953) 528–535.
15 S. HANESSIAN AND J. BANOUB, *Carbohydr. Res.*, 59 (1977) 261–267.
16 E. PACSU, *Ber.*, 61 (1928) 137–144.
17 J. JANSON AND B. LINDBERG, *Acta Chem. Scand.*, 14 (1960) 877–881.
18 R. U. LEMIEUX AND D. H. DETERT, *Can. J. Chem.*, 46 (1968) 1039–1040.
19 D. H. DETERT, Ph.D. Thesis, Department of Chemistry, University of Alberta, 1968.
20 W. J. HICKINBOTTOM, *J. Chem. Soc.*, (1928) 3140–3147.