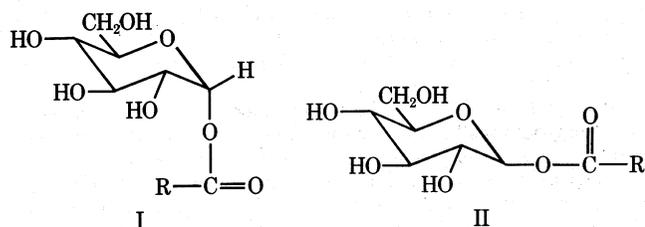


**Stereochemical Control in the Acylation of
2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose.
A Route to 1-*O*-Acyl- α - and - β -D-glucopyranoses**

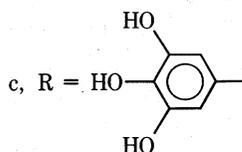
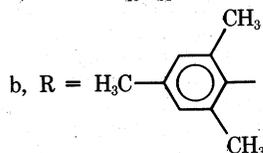
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A recent report² has implicated several D-glucosyl fatty acid esters as active plant growth regulating compounds. Although the stereochemistry of these natural products was not rigorously established, they were tentatively assigned the β -D configuration II.² To test the validity of this assignment, we



a, R = n -C₁₅H₃₁



set out to synthesize anomerically pure derivatives I and II containing long-chain fatty acid ester moieties.

In this paper we report the results of a study in which we have been able to control successfully the stereochemistry of 1-*O*-acylation of appropriately protected D-glucose to produce, selectively, in high yield (85–90%), α - and β -D-glucose esters Ia and IIa, respectively. Metalation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (TBG), III (5.40 g, 0.01 mol), in 125 ml of tetrahydrofuran (THF) at -30 to -40 °C using 1.1 equiv of *n*-butyllithium (1.6 M in hexane) followed by acylation with hexadecanoyl chloride produces a mixture of α - and β -D-anomeric esters IVa and IVb (noncrystalline mixture) in a

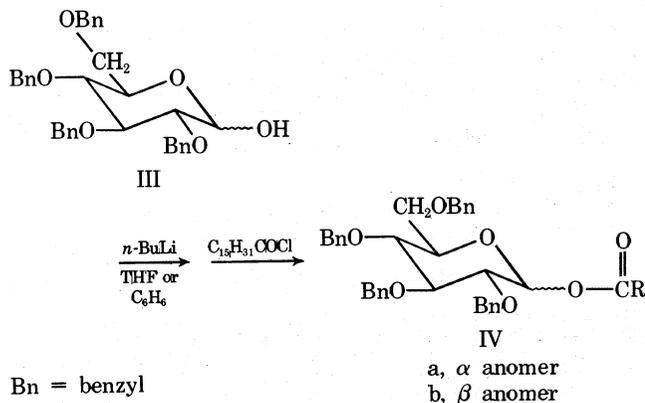


Table I. Stereochemical Distribution of Anomeric 1-*O*-Hexadecanoyl-D-TBG as a Function of Temperature and Solvent

Solvent	α	β	Temp, °C	Rotation
THF	90	10 (via ¹ H NMR)	-30 to -40	+45.9 (CH ₂ Cl ₂)
THF	70	30	25	+39.2
THF	70	30	45	
Benzene	50	50	0–5	+27.8
Benzene	26	74	40–45	+20.6
Benzene	11	89	62	+14.9

Table II. Anomeric Composition and ¹³C Chemical Shifts, δ (ppm, Me₄Si), of TBG and TBG-Li⁺ in Benzene and THF at 35 °C

	δ (benzene)		δ (THF)		% α (benzene)	% α (THF)
	α	β	α	β		
TBG	91.3	98.2	91.6	98.6	61	67
TBG-Li ⁺	89.1	95.9	88.8	96.1	50	52

ratio of 9:1, respectively, in chromatographically purified yields exceeding 95%. Other esters which we have prepared include benzoate, acetate, *cis*-9,10-octadecenoate, and octadecanoate; however, in this report we use the hexadecanoate as an illustrative example. Stereochemical assignment and relative amounts of IVa and IVb were readily determined by the measurement of the respective anomeric proton resonances at δ 6.65 (d, J = 2.62 Hz) and 5.85 (d, J = 6.75 Hz) in CCl₄ relative to internal standard Me₄Si.³ Increasing the temperature in the metalation and acylation reactions in THF changes somewhat the α : β ratio, but the α -D anomer, IVa, still predominates, e.g., at 45 °C the ratio is 2–2.5:1 (Table I). In studying the parameters which influence the stereochemical course of this reaction, we observed that a dramatic inversion in product ratio could be effected by changing the reaction medium. Thus, reaction of III in benzene at 60 °C produces a 1:8 ratio of IVa and IVb, respectively. Compound IVb was isolated from this reaction mixture by crystallization from absolute ethanol, mp 52–53 °C, $[\alpha]^{25D} +9.1^\circ$ (c 1.0, CH₂Cl₂). At lower temperatures, intermediate ratios are noted; however, IVb still predominates above 5 °C in benzene (Table I).

At first, interpretation of these data in terms of a solvent and temperature dependent equilibration of metalated anomeric TBG (α -TBG⁺Li⁻ and β -TBG⁻Li⁺) seemed attractive.⁴ Optical rotations of THF and benzene solutions containing TBG-Li⁺ were +31.6 and +33.4, respectively. These readings were relatively invariant with temperature change from 25 to 56 °C. Rotations obtained for the acetic acid quenched solutions of TBG-Li⁺ in THF and benzene were +36.8 and +37.0 whereas those of TBG were +46.8 and +53.6, respectively.⁵ Presumably, metalation of TBG has only a minor effect on the anomeric equilibrium position seen in a slight shift toward β -D-anomer formation. This is confirmed by ¹³C NMR spectroscopy which clearly shows the composition of the TBG and TBG-Li⁺ in benzene and THF. Table II lists the percentage of the α forms for both TBG and TBG-Li⁺ (generated with an equivalent amount of *n*-butyllithium) in benzene and THF determined by measurement of the corresponding α and β carbon resonances. Notice that both anomeric carbon shifts

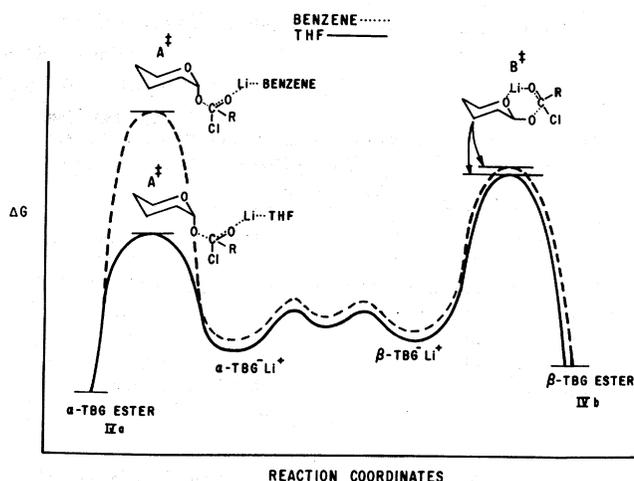


Figure 1. Pathway for the reaction of α and β TBG salts with acid chlorides.

are observed at higher fields in their salt forms, reminiscent of ionization. This result is in sharp contrast with the downfield shifts observed by deWit⁴ for D-glucose in D₂O. Furthermore, after metalation and quenching, the anomeric ratios appear to be approximately the same for both solvents (50:50). These findings lead us to believe that the stereochemical control of acylation occurs further along the reaction coordinate, i.e., through the agency of the activated complexes A[‡] (α form) and B[‡] (β form) (Figure 1). In THF solution, the lower energy pathway provided by THF-solvated A[‡] relative to the higher pathway given by intramolecularly bonded B[‡] leads to a predominance of product IVa. Conversely, in benzene intramolecular coordination in B[‡] becomes more important since it offers greater stabilization relative to the stabilization imparted to A[‡] by the relatively nonpolar, poorly solvating benzene. Thus in benzene, product IVb predominates.⁶

Glucosyl esters, especially the α -D anomers, have not been of easy access in the past. Only the gallate, Ic, has been prepared in 5% yield by the procedure of Schmidt⁷ and the mesitoate, Ib, in 17% yield by the procedure of Fletcher.⁸ Furthermore, Fletcher could not extend either procedure to less hindered systems because of the lack of stereospecificity in the acylation procedure employed⁸ and loss of desired product through rapid migration of the unhindered ester function from C-1 to C-2 under the nonneutral deblocking conditions.⁹

Hydrogenolysis of chromatographically purified (90% isomeric purity) IVa and isomerically pure IVb in absolute ethanol containing a catalytic amount of Pd black produced Ia and IIa in yields exceeding 90% (recrystallized from CHCl₃).

This synthetic sequence represents the first single pathway to pure, 1- α - and - β -D anomeric esters and the first general, high-yield route to pure unrearranged aliphatic 1-O-acyl- α -D-glucopyranoses Ia.

Experimental Section

Melting points are uncorrected. ¹³C NMR spectra were determined on a Bruker¹⁰ WH-90 spectrometer at 22.63 MHz. ¹H NMR spectra were determined on JEOL C-60H and Varian HA220 spectrometers. All chemical shifts are reported relative to internal Me₄Si. Ir spectra were recorded on a Perkin-Elmer 457 spectrometer. Rotational measurements were made on a Perkin-Elmer Model 141 polarimeter. GLC analyses of all glucose esters were performed on the corresponding trimethylsilyl derivatives prepared from Tri Sil Z reagent. The gas chromatograph used was a Hewlett-Packard Model 5750 equipped with flame ionization detection. 2,3,4,6-Tetra-O-benzyl-D-glucopyranose (TBG) was purchased from Pfanstiehl Chemical Co., mp 152–153 °C.

All reported compounds gave satisfactory elemental analyses.

General Procedure for the Preparation of 2,3,4,6-Tetra-O-benzyl-1-O-acyl- α -D-glucopyranose IVa. For this procedure we have chosen the hexadecanoyl ester as a representative example. Into a dry 250-ml three-neck flask, flushed with N₂, was placed 125 ml of freshly distilled anhydrous THF and 5.40 g (0.010 mol) of dry 2,3,4,6-tetra-O-benzyl-D-glucopyranose (TBG). The solution was magnetically stirred and the TBG was thoroughly dissolved within a few minutes at room temperature. The solution was then cooled to –30 to –40 °C and 6.8 ml (0.011 mol) of 1.6 M *n*-butyllithium in hexane was added. The homogeneous reaction mixture was stirred at this temperature for 3 min whereupon 3.0 g (0.011 mol) of hexadecanoyl chloride was added and the reaction continued for 20 min. The solution was then allowed to warm to room temperature, quenched with a saturated solution of ammonium chloride, and extracted with methylene chloride. The methylene chloride extracts were dried over sodium sulfate and the solvent removed to yield 7.8 g of crude ester (100%). The crude ester was eluted through an 18 × 0.75 in. column of Florisil with 50:50 methylene chloride–petroleum ether to give 7.7 g (97%) of a glassy solid. Attempts to crystallize this material failed. ¹H NMR in CDCl₃ showed the characteristic α and β anomeric proton resonances at δ 6.65 (d, J = 2.62 Hz) and 5.85 (d, J = 6.75 Hz) in the ratio of 9:1, respectively. The ratio of the sum of the α and β anomeric proton resonances to the 2-position methylene resonances of the aliphatic chain at δ 2.5 was 1:2, indicating monoesterification. Ir (neat film) C=O, 1745 cm⁻¹; [α]²⁵D +45.9° (c 1.0, CH₂Cl₂).

Preparation of 2,3,4,6-Tetra-O-benzyl-1-hexadecanoyl- β -D-glucopyranoses IVb. The preparation of the β -anomeric ester was similar to the above except that the reaction was carried out in anhydrous benzene. Metalation and solubilization of the TBG was carried out at 0 °C. Acylation was then effected at 62 °C for 20 min. Workup was essentially the same as above. Examination of the reaction mixture before crystallization by ¹H NMR indicated a ratio of α : β anomers of 11:89. The yield of crude ester was 95%. Crystallization of the product from absolute ethanol gave pure β anomer, mp 52–53 °C, in 85% yield. ¹H NMR in CDCl₃ showed the characteristic β -anomeric proton resonance at δ 5.85 (1 H, d, J = 6.75 Hz), 2.5 (2 H, t, J = 6.75 Hz, the 2 position CH₂ of the fatty acid chain); ir (neat film) C=O 1750 cm⁻¹; [α]²⁵D +9.1° (c 1.0, CH₂Cl₂).

Hydrogenolysis of IVa and IVb. IVa (90% α and 10% β) or compound IVb (100% β) (2 g, 0.0025 mol) were dissolved in 20 ml of absolute ethanol containing 75 mg of Pd black. The solutions were shaken on a Parr hydrogenator at room temperature for 8 h at 40 psi. Ia crystallized out of solution following hydrogenolysis of IVa in 92% yield. Recrystallization from CHCl₃ gave a solid which rearranged on melting, mp 98–108 °C, [α]²⁵D +66.9° (c 0.9, MeOH). ¹H NMR (CD₃OD), taken at 60 °C in a sealed tube because of the compounds' insolubility, showed resonances at δ 6.45 (1 H, d, J = 3.0 Hz, anomeric proton), 2.50 (2 H, t, J = 6.75 Hz, 2-position CH₂ protons of the aliphatic chain); ir (KBr pellet) C=O at 1740 cm⁻¹.

Ia was isolated in 96% yield after recrystallization from ethyl acetate: mp 108, 170–175 °C (double melting point); [α]²⁵D –1.17° (c 1.2, MeOH); ¹H NMR (CD₃OD) at 60 °C δ , 5.62 (1 H, d, J = 6.75 Hz, anomeric proton), 2.50 (2 H, t, J = 6.75 Hz, 2-position CH₂ protons of the aliphatic chain); ir (KBr pellet) shows three C=O peaks at 1760, 1750, and 1740 cm⁻¹.

The isomeric purity of Ia and IIa was confirmed by GLC analysis of the corresponding Me₄Si derivatives. Separation of these was made on a 6 ft × 0.25 in. glass column packed with 3% SP2100 and programmed from 180 to 250 °C, 6 °C/min. Under these conditions Ia and IIa have retention times of 12.0 and 12.5 min, respectively.

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Registry No.—Ia, 59473-41-5; IIa, 39848-71-0; α -III, 6564-72-3; β -III, 59531-24-7; α -III Li, 59473-42-6; β -III Li, 59531-25-8; IVa, 59473-43-7; IVb, 59473-44-8; hexadecanoyl chloride, 112-67-4.

References and Notes

- (1) Agricultural Research Service, U.S. Department of Agriculture.
- (2) N. Mandava and J. W. Mitchell, *Chem. Ind. (London)*, 930 (1972).
- (3) Further verification of assignment of IVa was made through comparison with the material prepared by the alternative route of esterification of TBG in CH₂Cl₂–pyridine. G. P. J. Glaudemans and H. G. Fletcher, Jr., *Methods Carbohydr. Chem.*, **6**, 373 (1972). Structure of IVb was confirmed through its debenzylated product Vb which was identical with the sample obtained

Notes

- through the 4,6-O-benzylidene-D-glucopyranose acylation, deblocking route. H. G. Fletcher, Jr., *ibid.*, 231 (1963).
- (4) A similar anionic equilibration has recently been observed for glucose: G. deWit, A. P. G. Klekoom, and H. vanBekum, *Tetrahedron Lett.*, 3943 (1975).
 - (5) The composition of TBG, e.g., the commercially available mp 149–150 °C material, in both benzene and THF has been determined by 220-MHz ¹H NMR to be approximately a 60:40 mixture of α and β anomeric forms. This ratio appears to remain approximately the same in the temperature range 17–56 °C.
 - (6) Note that addition of 4% HMPA to benzene v/v increases the solvating power of the medium enough to reverse the α : β product ratio to 2.3:1.
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 - (9) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 2849 (1956).
 - (10) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.