Acta Chemica Scandinavica, 1993: 47: 818–822
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904-213X

Simple Synthesis of β-D-Glucosyl Esters

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Bols, M. and Hansen, H. C., 1993. Simple Synthesis of β-D-Glucosyl Esters. – Acta Chem. Scand. 47: 818–822.

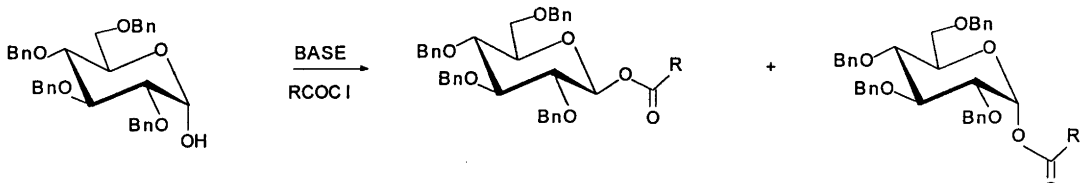
Acylation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**) with benzoyl chloride and triethylamine was found to give 1-*O*-benzoyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**2**) and 1-*O*-benzoyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (**3**) in a ratio of 2:9 while acylation of **1** with benzoyl chloride and pyridine gave **2** and **3** in the ratio 6:1. Slow addition of benzoyl chloride to **1** and triethylamine changed the ratio from 2:9 to 1:11. Similar acylation of **1** with either 2- or 4-chlorobenzoyl, acetyl or butanoyl chloride gave the corresponding 1-*O*-acyl-derivatives **4**, **5**, **6** or **7** with high predominance of the β-anomer. The rate of addition had to be decreased for the aliphatic acyl chlorides to provide good stereoselectivity. **3**, **5**, **6** and **7** was hydrogenolyzed to give 1-*O*-benzoyl, 1-*O*-4-chlorobenzoyl, 1-*O*-acetyl and 1-*O*-butanoyl-β-D-glucopyranoses **8**, **9**, **10** and **11**, respectively.

In our recent synthesis of 1-*O*-pivaloyl-β-D-glucopyranuronic acid we observed a surprising exclusive formation of the β-ester from the pyridine/DMAP catalyzed reaction between **1** and pivaloyl chloride (Scheme 1).[1] It was found that acylation of **1** under those conditions was only stereoselective when the acid chloride was sterically hindered, and that this, at least to some extent, was due to a much slower rate of reaction.[2] Pure β-glucosyl esters, besides having interest as naturally occurring compounds,[3] have recently received attention as glucosyl donors,[4,5] being more reactive than the α-anomers,[6] and we have attempted to develop a general stereoselective method based on simple acylation of **1**.

Glycosyl esters have previously been synthesized by substitution of glycosyl halides with silver[7] or cesium carboxylates,[6] reaction of glycosyl trichloroacetimidates with carboxylic acids[8] or by acylation of aldoses. While the last method is normally the simplest to perform, stereocontrol is typically poor unless an anomerically pure sugar is available and can be acylated without mutarotation.[9,10] However, two stereoselective acylation methods have been reported using either butyllithium/acyl chloride[11] or cesium fluoride/acyl fluoride.[12] The Mitsunobu reaction has also been used to convert aldoses into glycosyl esters in some cases with excellent stereoselectivity.[13] We now report the stereoselective synthesis of a number of β-glucosyl esters from the triethylamine-catalyzed reaction between **1** and some acyl chlorides.

Results and discussion

In our previous work we found that in the acylation of **1** in a system of **1**, pyridine, DMAP and acyl chloride in CH_2Cl_2, anomeric mixtures of esters were formed with the α-anomer predominating except when the acyl chloride was sterically hindered.[2] Omission of DMAP led to higher α/β-ratios (Table 1). This could be explained from the reaction rates (Scheme 3) since the rate constants of mutarotation of **1** fell threefold when DMAP was omitted. It should be clear that a slow rate of mutarotation, compared with the rate of acylation, resulted in the predominant formation of the α-ester so that an increase in the ratio $(k_1 + k_{-1})/k_2$ gave more β-ester formation. β-ester formation could even be expected to predominate when $k_1, k_{-1} < k_2, k_3$, because the β-alcohol has been shown to be more nucleophilic (i.e., $k_3 > k_2$).[14] The high



1

3: R = Ph
4: R = 2-ClC$_6$H$_4$
5: R = 4-ClC$_6$H$_4$
6: R = Me
7: R = Pr

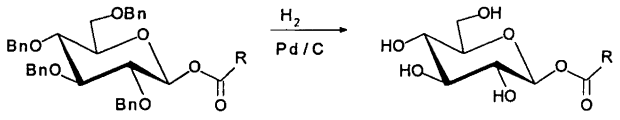
2: R = Ph

Scheme 1.

Table 1.

RCOCl R	Pyridine α/β	Pyridine/DMAP 1% α/β	Et_3N α/β	Et_3N^a α/β	Et_3N^b α/β	Et_3N^c α/β	Et_3N^d α/β
Me	10:1[e]	6:1[f]	2:1	1:2	1:10	1:15	1:20
Pr	10:1[e]	6:1[f]		2:3	1:12		
Ph	6:1[e]	3:1[f]	2:9	1:11			
2-ClC_6H_4				1:20			
4-ClC_6H_4				1:23			
Me_3C	1:6[f]	0:1[g]	0:1				
$t_{1/2}/min^{-1}$[h]	360	120			9		

[a]Acid chloride (4 equiv.) added in equal portions every 10 min over 100 min. [b]Acid chloride (2 equiv.) added continuously over 3 h. [c]Acid chloride (2 equiv.) added continuously over 3 h. [d]Acid chloride (2.5 equiv.) added continuously over 15 h. [e]Ref. 9. [f]Ref. 2. [g]Ref. 1. [h][1] = 0.17 M, [Base] = 1.1 M in CH_2Cl_2, $T = 22°C$.



8: R = Ph
9: R = 4-ClC_6H_4
10: R = Me
11: R = Pr

Scheme 2.

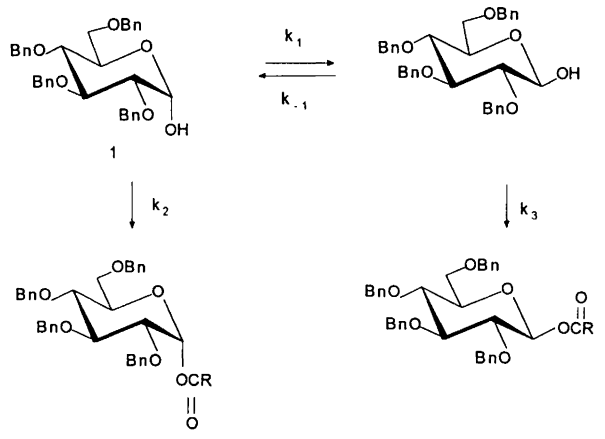
stereoselectivity in the reaction of pivaloyl chloride and **1** indicated that this difference in nucleophilicity (k_3/k_2) might be very large. Thus it was logical to attempt other bases to try to increase the $(k_1 + k_{-1})/k_2$ ratio. The rate of mutarotation of **1** was found to increase 45 times when pyridine was changed to Et_3N (Table 1). Acylation of **1** with benzoyl chloride and Et_3N as the base gave an α/β-ratio of 2:9, which was a reversal of the stereoselectivity when compared with pyridine[9] or pyridine/DMAP.[2] Et_3N was probably not a significantly better acylation catalyst than pyridine, since nucleophilic catalysis was absent. However, as a stronger base, Et_3N was a better catalyst for mutarotation than pyridine. Similar acylation of **1** with acetyl chloride gave a α:β ratio of 2:1, while pivaloyol chloride only gave β-ester (Table 1).

In order to develop a synthetically useful reaction we tried to increase β-selectivity further by decreasing the rate of acylation. Since the rate of acylation was equal to k[**1**][RCOCl], this could be done without affecting mutarotation simply by decreasing [RCOCl]. Thus by adding the acid chloride in 10 portions over 100 min to the solution of **1** and Et_3N, the result was large decreases in the α:β ratios. The benzoates **2** and **3** were obtained in a 1:11 ratio, and pure **3** could be crystallized in 82% yield. 2-Chlorobenzoyl chloride and 4-chlorobenzoyl chloride gave even higher stereoselectivity. Thus, the 2-chlorobenzoate **4** was obtained in 20:1 ratio over the α-anomer and was crystallized pure in 86% yield. The 4-chlorobenzoate **5** was obtained in a 23:1 ratio over the α-anomer and crystallized in 88% yield. The aliphatic acid chlorides gave lower stereoselectivity; the acetates were obtained with an α:β ratio 1:2 while the butanoates were obtained with an α:β ratio 2:3. However, lowering the concentration [**1**] even more by continuous addition of the acyl chloride over 3 h gave the β-acetate **6** in a 10:1 ratio over the α-anomer, and the β-butanoate **7** in 12:1 ratio over the α-anomer. Pure **7** could be crystallized in 70% yield. Even better, when the total volume of the reaction was decreased fivefold the β-acetate **6** was obtained in a 15:1 ratio.[15] By further decreasing the rate of addition by a factor of four the ratio could be increased to 20:1, however **6** could not be crystallized.

In Table 1 the acyl chlorides have been organised in increasing tendency to form β-ester under identical reaction conditions. This is also an order of decreasing reactivity. It should be noted that the less reactive acid chlorides do not have to be administered in small concentrations and over long periods to obtain good selectivity, and for many acid chlorides, this will probably be the case. The method can probably be applied to prepare the β-ester of most acid chlorides. As **1** can be acylated in pyridine to give mostly α-esters (with reactive acid chlorides) simple routes to both α and β-glucosyl esters now exist.

Mukaiyama has acylated **1** with acyl fluorides and cesium fluoride.[12] When **1** was added slowly to CsF and RCOF α-esters were mainly obtained, and when RCOF was slowly added to **1** and CsF mainly β-esters were obtained. The explanation was offered that cesium in the latter case chelated between 1-OH and the ring oxygen resulting in the β-ester. However, based on our results it seems likely that the β-selectivity observed was caused by CsF catalysis of the mutarotation of **1** so that only the more reactive β-anomer reacted. When **1** was added to CsF/RCOF, **1** was acylated before it was allowed to mutarotate significantly.

The β-esters **3**, **5**, **6** and **7** were hydrogenolyzed with 5% palladium-on-carbon, to give the unprotected β-esters **8**, **9**, **10** and **11** in 91%, 84%, 97% and 73% yield, respectively (Scheme 2). We were not able to deprotect 2-chlorobenzoate **4** succesfully owing to extensive dechlorination and cleavage of the glycosyl ester by the liberated HCl.



Scheme 3.

We believe that this method of preparing β-glucosyl esters is an improvement of existing methods in terms of simplicity and stereoselectivity. It is likely that it can be extended to other sugars and other acylation procedures when acylation rate and mutarotation are properly adjusted.

Experimental

General. NMR spectra were measured for solutions in $CDCl_3$ (internal Me_4Si) with a Bruker AC-250 instrument unless otherwise specified. Melting points were measured on a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer PE241 instrument. Microanalyses were performed by the Leo Microanalytical Laboratory. Column chromatography was performed on Kieselgel 60 (Merck 0.4–0.63 mm), using the flash technique. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection with 1% cerium sulfate and 1.5% molybdic acid in aqueous 10% H_2SO_4 at 200°C for 5 min. Evaporations were carried out *in vacuo* at 40°C, unless otherwise specified.

Determination of the rate of murarotation. The rate of mutarotation of **1** was determined as described by Swain and Brown[16] on a solution of **1** (170.3 mg) in 2 ml of a solution of 1.73 ml Et_3N in 10 ml CH_2Cl_2.

Acylation: general procedure. To a solution of **1** (1.0 g, 1.85 mmol) in CH_2Cl_2 (10 ml) were added base (12.4 mmol) and acid chloride (7.4 mmol). The solution was kept until TLC showed the disappearance of the starting material and then worked up by being washed with HCl (1 M, 30 ml), $NaHCO_3$ (saturated, 45 ml) and H_2O (30 ml). Drying ($MgSO_4$) and concentration left a product that was analyzed by ^1H NMR spectroscopy to determine the anomeric ratio. The procedures with slow addition of acid chloride were carried out as below for the preparation of **3**, **6** and **7**.

1-O-Benzoyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (**3**). 2,3,4,6-Tetra-*O*-benzyl-α-D-glucose (5.0 g, 9.25 mmol) was dissolved in CH_2Cl_2 (50 ml) and Et_3N (8.6 ml, 62 mmol). After 10 min of stirring 10 ml of a 100 ml solution of benzoyl chloride (4.9 ml, 37 mmol) and CH_2Cl_2 was added at 10 min intervals. After the last addition the final solution was stirred for 2 h at 25°C. The solution was washed with HCl (1 M, 120 ml), $NaHCO_3$ solution (sat., 120 ml) and H_2O (120 ml). Drying ($MgSO_4$) and concentration left an oily residue containing the α and β anomers in the ratio 1:11. Crystallization from Et_2O–pentane gave pure **3** (4.85 g, 82%). Recrystallization from Et_2O–pentane gave m.p. 93–93.5°C, $[\alpha]_D^{21} - 24.1°$ (*c* 1.0; $CHCl_3$). Lit.[17] m.p. 95–95.5°C, $[\alpha]_D^{22} - 23°$ (*c* 1.0; $CHCl_3$).

1-O-2-Chlorobenzoyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (**4**). **1** (5.0 g, 9.25 mmol) was dissolved in CH_2Cl_2 (50 ml) and Et_3N (8.6 ml, 62 mmol). After 10 min of stirring 10 ml of a 100 ml solution of 2-chlorobenzoyl chloride (3.65 ml, 37 mmol) and CH_2Cl_2 was added at 10 min intervals. After the last addition the final solution was stirred for 2 h at 25°C. The solution was washed with HCl (1 M, 120 ml), $NaHCO_3$ solution (sat., 120 ml) and H_2O (120 ml). Drying ($MgSO_4$) and concentration left an oily residue (α:β 1:20). Crystallization from Et_2O/pentane gave pure **4** (5.4 g, 86%). Recrystallization from Et_2O/pentane gave m.p. 107°C, $[\alpha]_D^{20} - 15.9°$ (*c* 1.0; $CHCl_3$). Lit.[8] m.p. 107–108°C, $[\alpha]_D^{20} - 16°$ (*c* 1.0; $CHCl_3$. Anal. $C_{41}H_{39}ClO_7$: C, H, Cl. ^1H NMR ($CDCl_3$): δ 3.61–3.88 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6a), 4.45–4.67 (m, 3 H, Bn), 4.75–4.95 (m, 5 H, Bn), 5.88 (d, 1 H, $J_{1,2} = 7.5$ Hz, H-1), 7.11–7.38 (m, 21 H, Ph, H-5′), 7.47 (dq, 2 H, H-3′ and H-4′), 7.87 (dd, 1 H, H-6′). ^{13}C NMR ($CDCl_3$): δ 67.95 (C-6), 73.4 (4 C, CH_2Ph), 74.9 (1 C, CH_2-OCH_2Ph), 75.6 (C-6), 73.4 (4 C, CH_2Ph), 74.9 (1 C, CH_2-OCH_2Ph), 75.6, 77.1, 80.7, 84.8 (C-5, C-4, C-3, C-2), 94.7 (C-1), 126.5–128.3 (20 C, Bn; 4 C), 131.3–133.1 (3 C), 137–138 (4 C, *ipso*-Ph).

1-O-4-Chlorobenzoyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (**5**). **1** (5.0 g, 9.25 mmol) was dissolved in CH_2Cl_2 (50 ml) and Et_3N (8.6 ml, 62 mmol). After 10 min of stirring 10 ml of a 100 ml solution of 4-chlorobenzoyl chloride (3.65 ml, 37 mmol) and CH_2Cl_2 was added at 10 min intervals. After the last addition the final solution was stirred for 2 h at 25°C. The solution was washed with HCl (1 M, 120 ml), $NaHCO_3$ solution (sat., 120 ml) and H_2O (120 ml). Drying ($MgSO_4$) and concentration left an oily residue containing α and β anomers in the ratio 1:23. Crystallisation from Et_2O–pentane gave pure **5** m.p. 87–88°C, $[\alpha]_D^{20} - 34°$ (*c* 1.0; $CHCl_3$) Anal. $C_{41}H_{39}ClO_7$: C, H, Cl. ^1H NMR ($CDCl_3$): δ 3.6–3.85 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6a), 4.41–4.65 (m, 3 H, Bn), 4.71–4.92 (m, 5 H, Bn), 5.83 (d, 1 H, $J_{12} = 7.5$ Hz, H-1), 7.1–7.37 (m, 20 H, Ph), 7.43 (q, 2 H), 7.97 (q, 2 H). ^{13}C NMR ($CDCl_3$): δ 68.0 (C-6), 73.5 (4 C, CH_2Ph), 75.0 (CH_2-OCH_2Ph), 75.6, 77.2, 80.8, 84.9 (C-5, C-4, C-3, C-2), 75.7 (1 C), 94.7 (C-1), 127.7–129.4 (20 C, Bn; 4 C),

131.4–131.9 (2 C, *C*–C=O, *C*–C-1), 137.7–138 (4 C, *ipso* Ph), 181.8 (1 C, C=O).

*1-O-Acetyl-2,3,4,6-tetra-O-benzyl-β-*D*-glucopyranose* (**6**). **1** (5.0 g, 9.25 mmol) was dissolved in CH_2Cl_2 (50 ml) and Et_3N (8.6 ml, 62 mmol). After 10 min of stirring a 15 ml solution of acetyl chloride (1.63 ml, 23.1 mmol) and CH_2Cl_2 was added dropwise over a period of 15 h. The solution was stirred for 2 h at 25°C. The solution was washed with HCl (1 M, 120 ml), $NaHCO_3$ solution (sat., 120 ml) and H_2O (120 ml). Drying ($MgSO_4$) and concentration left an oily residue containing α and β anomers in the ratio 1:15 (5.2 g, 96%). Attempts to crystallize this were not successful. $[\alpha]_D^{22}$ 13.2° (*c* 1.0; $CHCl_3$). Lit.[8] $[\alpha]_{578}^{20}$ 13.1° (*c* 1; $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.05 (s, 3 H, Me), 3.48–3.79 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6a), 4.42–4.7 (m, 3 H, Bn), 4.7–4.92 (m, 5 H, Bn), 5.61 (d, 1 H, $J_{1,2}$ = 8 Hz, H-1), 7.1–7.36 (m, 20 H, Ph). ^{13}C NMR ($CDCl_3$): δ 21.1 (1 C, CH_3–C=O), 68.0 (C-6), 73.5 (4 C, CH_2Ph), 75.0 (1 C, CH_2OBn), 75.4 (1 C), 75.7, 77.2, 81.0, 85.8 (C-5, C-4, C-3, C-2), 94.0 (C-1), 127.7–128.4 (20 C, Ph), 138–138.2 (4 C, *ipso* Ph), 169 (1 C, C=O).

*1-O-Butanoyl-2,3,4,6-tetra-O-benzyl-β-*D*-glucopyranose* (**7**). **1** (5.0 g, 9.25 mmol) was dissolved in CH_2Cl_2 (50 ml) and Et_3N (8.6 ml, 62 mmol). After 10 min of stirring an 80 ml solution of butanoyl chloride (1.95 ml, 18.5 mmol) and CH_2Cl_2 was added dropwise over a period of 3 h. The solution was stirred for 2 h at 25°C. The solution was washed with HCl (1 M, 120 ml), $NaHCO_3$ solution (sat., 120 ml) and water (120 ml). Drying ($MgSO_4$) and concentration left an oily residue containing α and β anomers in the ratio 1:12. Crystallization from Et_2O–pentane gave pure **7** (3.9 g, 70%). Recrystallization from Et_2O–pentane gave m.p. 70–71.5°C. $[\alpha]_D^{20}$ 11.7° (*c* 1.0; $CHCl_3$). Anal. $C_{38}H_{42}O_7$: C, H. ^1H NMR ($CDCl_3$): δ 0.93 (t, 3 H, Me), 1.65 (m, 2 H, CH_2), 2.29 (m, 2 H, CH_2C=O), 3.52–3.79 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6a), 4.43–4.7 (m, 3 H, Bn), 4.7–4.93 (m, 5 H, Bn), 5.62 (d, 1 H, $J_{1,2}$ = 8 Hz, H-1), 7.01–7.38 (m, 20 H, Ph). ^{13}C NMR ($CDCl_3$): δ 13.0 (1 C, Me), 18.0 (1 C, CH_2Me), 36.1 (1 C, CH_2C=O), 68.0 (C-6), 73.5 (4 C, CH_2Ph), 75.0 (1 C, CH_2OBn), 75.5 (1 C), 75.7, 77.2, 81.0, 84.8 (C-5, C-4, C-3, C-2), 93.9 (C-1), 127.7–128.4 (20 C, Ph), 137–138 (4 C, *ipso* Ph).

*1-O-Benzoyl-β-*D*-glucopyranose* (**8**). Hydrogenation (101 kPa) was performed with **3** (2.0 g, 3.1 mmol), EtOAc (40 ml), EtOH (20 ml) and Pd–C 5% (0.40 g) until the expected amount of H_2 had been consumed. Filtration and concentration left a syrup. On addition of Et_2O a white solid was obtained (0.8 g, 91%). Recrystallisation of this from MeOH–hexane gave m.p. 191–192°C, $[\alpha]_D^{20}$ −26.2° (*c* 1.0; water). Lit.[18] m.p. 193°C, $[\alpha]_D$ −26.8°.

*1-O-4-Chlorobenzoyl-β-*D*-glucopyranose* (**9**). Hydrogenation (101 kPa) was performed with **5** (2.0 g, 2.94 mmol), EtOAc (40 ml), EtOH (20 ml) and Pd–C 5% (0.40 g) until the expected amount of H_2 had been consumed. Filtration and concentration left a syrup. On addition of ether a white solid was obtained (0.79 g, 84%). Recrystallization of this from methanol–pentane gave m.p. 226–228°C, $[\alpha]_D^{20}$ −6.2° (*c* 1.0; EtOH). Anal. $C_{13}H_{15}ClO_7 \cdot 1/2\ H_2O$: C, H. ^1H NMR (CD_3OD): δ 3.26, 3.55 (m, 4 H, H-2, H-3, H-4, H-5), 3.7 (dd, 1 H, J_{56b} = 4 Hz, H-6b), 3.85 (d, 1 H, J_{6a6b} = 13 Hz, H-6a), 5.71 (d, 1 H, J_{12} = 7.5 Hz, H-1), 7.51 (d, 2 H, J_{23} = 8 Hz, H-3′), 8.07 (d, 2 H, H-2′).

*1-O-Acetyl-β-*D*-glucopyranose* (**10**). Hydrogenation (101 kPa) was performed with **6** (2.0 g, 3.43 mmol), EtOAc (40 ml), EtOH (20 ml) and Pd–C 5% (0.40 g) until the expected amount of H_2 had been consumed. Filtration and concentration left a syrup (0.74 g, 97%). $[\alpha]_D^{24}$ 15.1° (*c* 1.0; CH_3OH). Anal. $C_8H_{14}O_7 \cdot 1/2\ H_2O$: C, H. ^1H NMR (CD_3OD): δ 2.12 (s, 3 H, Me), 3.25–3.5 (m, 4 H, H-2, H-3, H-4, H-5), 3.69 (dd, 1 H, J_{56b} = 4.5 Hz, H-6b), 3.83 (br d, 1 H, J_{6a6b} = 11 Hz, H-6a), 5.48 (d, 1 H, J_{12} = 7.8 Hz, H-1 β). ^{13}C NMR (CD_3OD): δ 19.0 (1 C, Me), 60.2 (C-6), 68.9, 71.8, 75.7, 76.5 (C-5, C-4, C-3, C-2), 93.5 (C-1), 169.5 (1 C, C=O).

*1-O-Butanoyl-β-*D*-glucopyranose* (**11**). Hydrogenation (101 kPa) was performed with **7** (2.0 g, 3.28 mmol), EtOAc (40 ml), EtOH (20 ml) and Pd–C 5% (0.40 g) until the expected amount of H_2 had been consumed. Filtration and concentration left a syrup (0.60 g, 73%). $[\alpha]_D^{20}$ 9.0° (*c* 1.0; CH_3OH). Anal. $C_{10}H_{18}O_7 \cdot 1/3\ H_2O$: C, H. ^1H NMR (CD_3OD): δ 0.97 (t, 3 H, Me), 1.67 (m, 2 H, CH_2CH_3), 2.48 (dt, 2 H, CH_2–C=O), 3.22–3.46 (m, 4 H, H-2, H-3, H-4, H-5), 3.68 (dd, 1 H, J_{56b} = 4.5 Hz, H-6b), 3.83 (dd, 1 H, J_{6a6b} = 12 Hz, H-6a), 5.48 (d, 1 H, J_{12} = 8 Hz, H-1).

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15. The reaction with acetyl chloride and Et_3N probably takes place by a ketene mechanism with the formation of the ketene being rate-determining. The rate of acylation was thus $V = k[RCOCl][Et_3N]$ while the rate of mutarotation of **1** was $V = k[\mathbf{1}][Et_3N]$. When RCOCl was continuously added [RCOCl] could be expected to be constant and independent of the total volume (i.e., amount of solvent) since a steady state was maintained. Thus a decrease in reaction volume would increase the rate of acylation 1. order because $[Et_3N]$ was increased, but the rate of mutarotation would increase 2. order because both [**1**] and $[Et_3N]$ were increased. Thus a more concentrated reaction could be expected to give a lower $\alpha:\beta$ ratio.
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Received October 12, 1992.