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Regioselective Syntheses of Mono-O-acylglucoses[1,2]

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All isomeric 1α-, 1β-, 2-, 3-, 4-, and 6-mono-O-acyl-D-glucopyranoses (acyl group from caprinoyl through stearoyl) were synthesized in a regio- (and stereo-) selective manner. Gas–liquid chromatography (trimethylsilyl (TMS) derivatives), infrared, and ^{1}H-nuclear magnetic resonance data, which provided evidence for assignment of the position of the acyl chain, are described. Compounds previously reported to be 2-O-acyl and 3-O-acyl-D-glucoses were shown to be 6-O-acyl derivatives. In the 3- and 6-O-acyl derivatives, anomerization was slow and they were present largely as α-anomers, while the 2- and 4-O-acyl derivatives were mixtures of α- and β-anomers due to their rapid anomerization.

Some di-O-acyl-D-glucopyranoses (1β,6-, 2,3-, and 4,6-) and a new tri-O-acyl-D-glucopyranose (2,4,6-) were also prepared, all of them except for the 1β,6-di-O-acyl derivative were obtained as α-anomers.

Keywords——selective acylation; 2-O-acyl-D-glucopyranoses; 3-O-acyl-D-glucopyranoses; 4-O-acyl-D-glucopyranoses; 1β-O-acyl-D-glucopyranoses; 6-O-acyl-D-glucopyranoses; ^{1}H-NMR; IR; GLC; TLC

In spite of increasing interest in biochemical and chemical properties of acylsugars, the literature[4] on mono-O-acylglucoses is rather limited compared to the extensive studies in carbohydrate chemistry, and the reports are sometimes conflicting or unreliable.[4c,5,6] One of the reasons may be the easy acyl migration in acylglucoses during the process of removing protecting groups from protected acylglucoses and another may be misinterpretation of their chemical reactivity.

We sought to carry out the systematic synthesis of mono-O-acylglucoses to resolve the above confusion and to provide a basis for the synthetic utilization of D-glucose. There is also a biological interest, since it was reported[7] recently that palmitoyl to stearoyl derivatives of some disaccharides exhibited considerable antitumor activity against Ehrlich ascites carcinoma. Mainly for this reason, five fatty acids, capric to stearic, were chosen as the acyl chains.

As a strategy for the synthesis, in most cases we chose hydrogenolysis under neutral conditions for the removal of protecting group(s) to avoid acid- or base-catalyzed acyl migration. Of course, this method is not always 100% reliable, so the purity of the products was checked in every case by gas chromatography (GC) of their trimethylsilyl (TMS) derivatives.

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[2] Parts of this work were presented at the 97th and 98th Annual Meetings of the Pharmaceutical Society of Japan (1977, Tokyo and 1978, Okayama).

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[4] *a)* P.E. Pfeffer, E.S. Rothman, and G.G. Moore, *J. Org. Chem.*, **41**, 2925 (1976); *b)* P.E. Pfeffer, G.G. Moore, P.D. Hoagland, and E.S. Rothman, "Synthetic Methods for Carbohydrates," ed. by H.S. El Khadem, ACS, Sym. 39, p. 540 (1976), and references cited therein; *c)* J. Asselineau, *Bull. Soc. Chim.* France *Memoires*, **1955**, 937.

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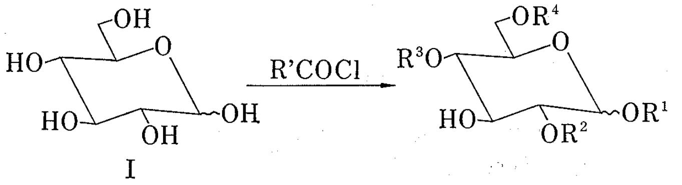

R'		R^1	R^2	R^3	R^4
a : C_9H_{19}	IIa—e :	H(α)	H	H	R'CO
b : $C_{11}H_{23}$	III :	H	R'CO	H	R'CO
c : $C_{13}H_{27}$	IV :	R'CO(β)	H	H	R'CO
d : $C_{15}H_{31}$	V :	R'CO	R'CO	H	R'CO
e : $C_{17}H_{35}$	VI :	H(α)	R'CO	R'CO	R'CO

Chart 1

6-O-Acyl-D-glucopyranoses

6-O-Acylglucoses were reported by Reinefeld and Korn,[8] who obtained IIa—e as major products by direct acylation of D-glucose (I) with acyl chlorides, together with two di-O-acyl and a tri-O-acyl derivatives as by-products. The latter were shown to be the 2,6-di-O-acyl (III), 1β,6-di-O-acyl (IV), and 1,2,6-tri-O-acyl (V) derivatives, although none of them was rigorously identified. Our reexamination under similar but not identical conditions substantially confirmed their results. The product showed three spots on thin-layer chromatography (TLC), corresponding to mono-, di-, and tri-O-acylglucoses, and these were separated by chromatography on silica gel.

The mono-O-acyl material was proved to be 6-O-acyl-D-glucopyranoses from the nuclear magnetic resonance (NMR) spectra in pyridine-d_5. Comparison of the ^{1}H-NMR (proton magnetic resonance (PMR)) signal ratio at δ 4.0—4.4 ppm and δ 4.5—5.2 ppm of the mono-O-acyl derivative (2: 4) with that of D-glucose (4: 2) indicated that two protons (C^6–H_2) were shifted *ca.* 0.5 ppm downfield by acylation, and the ^{13}C-NMR (CMR) spectra confirmed the pyranose structure.[9] 6-O-Acyl-D-glucopyranoses (IIa—e) (Table I) crystallized from acetone as the α-anomer, as indicated by their PMR signal at δ 5.80 ppm (J=3.5 Hz). However, on standing as a pyridine solution for 24 hr at room temperature, an additional signal at δ 5.22 ppm (J=7.5 Hz) appeared, indicative of the β-anomer. The approximately equal intensities of these two proton signals suggested equilibration between the α- and β-anomers in the solution, although the changes of optical rotation were small.

TABLE I. 6-O-Acyl-D-glucopyranoses (II)

Compd. II	Appearance	mp (°C)	$[\alpha]_D^{17}$ (c=2.0, pyridine) A[a]	B[a]	Yield[b] (%)	TLC Rf[c]	Tetra-acetates mp (°C)
Caprylate	Leaflets	134—138 (134—136)[d]	+87° (+98°)[d]	+81° (+60°)[d]	20	0.37	84—85
a	Leaflets	134—138 (133—135)	+86° (+87°)	+83° (+57°)	23	0.38	64—66
b	Leaflets	133—135 (135—136)	+75° (+74°)	+70° (+54°)	25	0.39	68—69
c	Leaflets	138—141 (136—137)	+70° (+76°)	+69° (+54°)	15	0.41	77—78
d	Leaflets	137—139 (134—136)	+64° (+70°)	+56° (+51°)	15	0.42	84—85
e	Granules	137—141 (137—138)	+63° (+65°)	+56° (+42°)	13	0.44	Gum
Oleate	Granules	126—128	+61°	+60°	11	0.44	Gum

a) A: measured within 1 hr after dissolving. B: after 24—48 hr.
b) After purification by several crystallizations, which involved significant losses.
c) Solvent system; $CHCl_3$: MeOH (8: 1).
d) Data in parentheses are given in ref. 8).

From the di-O-acyl fraction (in the cases of laurate and myristate) the 1β,6-di-O-acyl derivative (IV) was isolated; it exhibited an anomeric proton signal at δ 6.26 ppm (J=7.5 Hz), indicating that the second acyl group had been introduced at the 1β position. However, in contrast to previous work,[8] we could not isolate a 2,6-di-O-acyl or 1,2,6-tri-O-acyl deriva-

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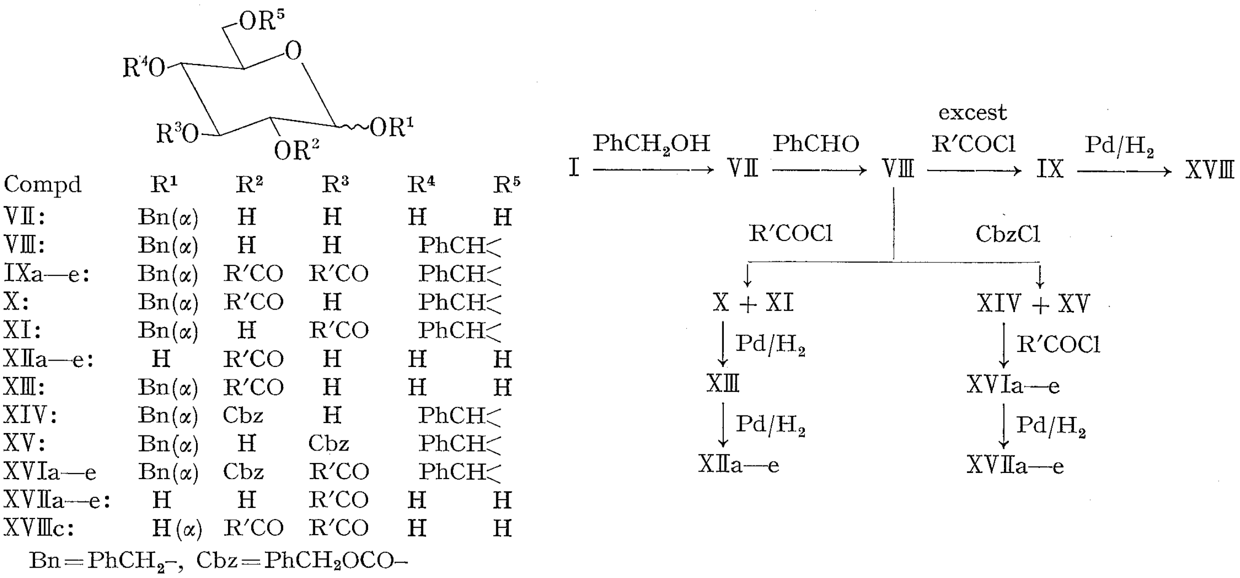
[8] E. Reinefeld and H.F. Korn, *Stärke*, **20**, 181 (1968).
[9] Details of the CMR spectra of acylglucoses will be reported in a separate paper.

tive; instead we isolated a new tri-O-acyl derivative which was assigned as the 2,4,6-tri-O-acyl derivative (VI) for the reasons described later.

2-O-Acyl- and 3-O-Acyl-D-glucopyranoses

2-O-Acyl- and 3-O-Acylglucoses were synthesized following the scheme shown in Chart 2.



Compd	R^1	R^2	R^3	R^4	R^5
VII:	Bn(α)	H	H	H	H
VIII:	Bn(α)	H	H	PhCH<	
IXa—e:	Bn(α)	R′CO	R′CO	PhCH<	
X:	Bn(α)	R′CO	H	PhCH<	
XI:	Bn(α)	H	R′CO	PhCH<	
XIIa—e:	H	R′CO	H	H	H
XIII:	Bn(α)	R′CO	H	H	H
XIV:	Bn(α)	Cbz	H	PhCH<	
XV:	Bn(α)	H	Cbz	PhCH<	
XVIa—e	Bn(α)	Cbz	R′CO	PhCH<	
XVIIa—e:	H	H	R′CO	H	H
XVIIIc:	H(α)	R′CO	R′CO	H	H

Bn=$PhCH_2$–, Cbz=$PhCH_2OCO$–

Chart 2

The key intermediate, benzyl 4,6-O-benzylidene-α-D-glucopyranoside (VIII) was prepared in 35% yield from D-glucose *via* benzyl α-D-glucoside (VII),[10] and identified by comparison of its physical data with those of the compound reported by Lubineau[11] shortly after we started this series of syntheses. He obtained VIII in a similar way in 14% yield from D-glucose.

Acylation of VIII with excess acyl chloride yielded the 2,3-di-O-acyl derivative (IX), whose PMR spectra (of IXc) exhibited signals of two protons geminal to acyloxy groups at δ 4.86 ppm (q, J=3.5 and 9.5 Hz) and at δ 5.63 ppm (t, J=9.5 Hz). Their coupling constants clearly indicate that the former signal corresponds to C^2–H and the latter to C^3–H.

On the other hand, partial acylation of VIII under cooling afforded the expected 2-O-acyl derivative (X) in *ca.* 50% yield with high regioselectivity, formation of the 3-O-acyl derivative

Table II. Benzyl 2,3-Di-O-acyl-4,6-O-benzylidene-α-D-glucopyranosides (IXa—e)

Compd. IX	Appearance	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
a	Needles	39—44	$C_{40}H_{58}O_8$	72.04	8.77	72.35	9.03
b	Needles	53—55	$C_{44}H_{66}O_8$	73.09	9.20	72.86	9.17
c	Needles	66—68	$C_{48}H_{74}O_8$	74.00	9.57	73.92	9.76
d	Needles	73—75	$C_{52}H_{82}O_8$	74.78	9.90	74.65	9.92
e	Needles	74—76	$C_{56}H_{90}O_8$	75.46	10.18	75.37	10.20

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[10] H.G. Fletcher, Jr., "Methods in Carbohydrate Chemistry," Vol. II, Academic Press, New York, 1963, p. 386.

[11] A. Lubineau, A. Thieffry, and A. Veyrieres, *Carbohydr. Research*, **46**, 143 (1976).

Table III. Benzyl 2-O-Acyl-4,6-O-benzylidne-α-D-glucopyranosides (Xa—e)

Compd. X	Appearance	mp (°C)	Formula	Analysis (%) Calcd. C		Found C	
				C	H	C	H
a	Needles	70—71	$C_{30}H_{40}O_7$	70.29	7.87	70.19	7.97
b	Needles	89—91	$C_{32}H_{44}O_7$	71.08	8.20	71.29	8.30
c	Needles	50—53	$C_{34}H_{48}O_7$	71.80	8.51	71.59	8.51
d	Needles	68—70	$C_{36}H_{52}O_7$	72.45	8.78	72.30	8.87
e	Granules	71—74	$C_{38}H_{56}O_7$	73.04	9.03	72.86	9.17

(XI) being negligible. The PMR signal at δ 4.78 ppm (q, J=4 and 10 Hz) (in Xb) confirmed the position of the acyloxy group.

Data for these di- and mono-O-acyl derivatives are listed in Tables II and III.

Hydrogenolysis of X in dioxane–methanol catalyzed by Pd-black afforded 2-O-acyl-D-glucopyranoses (XII). The intermediary formation of XIII in this reaction was shown by its chromatographic isolation, spectroscopic characterization, and conversion to XII under the same conditions. 2-O-Acyl-D-glucopyranoses (XIIa—e) (Table IV) were crystallized from acetone, and their PMR spectra showed that they exist in an equilibrium with approximately equal amounts of α- and β-anomers in pyridine-d_5 solution (δ 6.03 ppm, d, J=3.8 Hz and δ 5.36 ppm, d, J=7.5 Hz, respectively, for XIIc).

Table IV. 2-O-Acyl-D-glucopyranoses (XIIa—e)

Compd. XII	Appearance	mp (°C)	$[\alpha]_D^{18}$ (c=1.0, pyridine)	Formula	Analysis (%) Calcd. C		Found C	
					C	H	C	H
a	Needles	128—130(126—128)[a]	+38.2°	$C_{16}H_{30}O_7$	57.46	9.04	57.23	9.17
b	Needles	132—134(135—136)	+31.6°	$C_{18}H_{34}O_7$	59.64	9.46	59.42	9.43
c	Needles	127—131 —	+34.8°	$C_{20}H_{38}O_7$	61.51	9.81	61.06	9.80
d	Needles	127—130(132—133)	+32.7°	$C_{22}H_{42}O_7$	63.13	10.11	63.37	10.01
e	Granules	132—135(123—124)	+36.8°	$C_{24}H_{46}O_7$	64.54	10.38	64.21	10.50

a) Data in parentheses are given in ref. 5). These were proved to be mixtures of 6-O-acyl and 1β,6-di-O-acylglucoses (see the text).

Acylation of VIII with carbobenzoxy chloride (CbzCl) under cooling afforded in 80% yield a 4: 1 mixture of the 2-Cbz (XIV) and 3-Cbz (XV) derivatives, suggesting that the reaction with CbzCl is less regioselective than that with fatty acyl chloride. Chromatographic separation and PMR measurement of the products established their structures; the former (XIV) showed a quartet at δ 4.58 ppm (J=3.8 and 9.5 Hz) and the latter (XV) exhibited a triplet at δ 5.14 ppm (J=9.5 Hz). Acylation of XIV with acyl chloride yielded the 3-O-acyl-2-Cbz derivative (XVIa—e) which (for XVIc) exhibited a new triplet at δ 5.67 ppm (J=9.5 Hz) in addition to the signals due to the fatty acyl chain.

Hydrogenolysis of XVIa—e as described for 2-O-acyl-D-glucopyranoses furnished the desired 3-O-acyl-D-glucopyranoses (XVIIa—e) which crystallized as needles from acetone. Their PMR spectra indicated predominance of the α-anomer (δ 5.80 ppm, d, J=3.5 Hz) in pyridine-d_5 solution. Tables V and VI list the physical data for the above 3-O-acyl derivatives.

In 1959, Hess[5)] reported the preparation of 2-O-acylglucoses by direct acylation of D-glucose in $CHCl_3$–pyridine solution at low temperature, basing the proposed structures on

Table V. Benzyl 3-O-Acyl-2-O-carbobenzoxy-4,6-benzylidene-α-D-glucopyranosides (XVIa—e)

Compd. XVI	Appearance	mp (°C)	Formula	Analysis (%)			
				Calcd.		Found	
				C	H	C	H
a	Needles	38—40	$C_{38}H_{46}O_9$	70.57	7.17	70.27	7.18
b	Needles	78—79	$C_{40}H_{50}O_9$	71.19	7.47	71.18	7.27
c	Needles	57—58	$C_{42}H_{54}O_9$	71.77	7.74	71.48	7.58
d	Needles	66—68	$C_{44}H_{58}O_9$	72.30	8.00	72.50	8.19
e	Gum	—	$C_{46}H_{62}O_9$	—	—	—	—

Table VI. 3-O-Acyl-D-glucopyranoses (XVIIa—e)[a]

Compd. XVII	mp (°C)	$[\alpha]_D^{17}$ (c=1, MeOH)	Formula	Analysis (%)			
				Calcd.		Found	
				C	H	C	H
a	113—116 (133)[b]	+62°	$C_{16}H_{30}O_7$	57.46	9.04	57.21	9.41
b	118—121 (137)	+63°	$C_{18}H_{34}O_7$	59.64	9.46	59.63	9.59
c	119—121 (137)	+64°	$C_{20}H_{38}O_7$	61.51	9.81	61.22	10.05
d	110—113 (136)	+62°	$C_{22}H_{42}O_7$	63.13	10.11	63.15	10.33
e	116—119 (133)	+60°	$C_{24}H_{46}O_7$	64.54	10.38	64.67	10.50

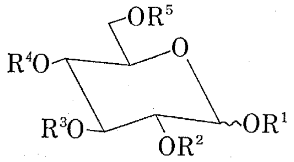
[a] 3-O-Acyl-D-glucopyranoses crystallized as needles from acetone.
[b] Data in parentheses are given ref. 6) as t_p's. These were found to be 6-O-acyl-D-glucopyranoses (see the text).

the observation that they did not form osazones. However, our reexamination of his work using lauroyl chloride showed that the product was not identical with 2-O-lauroylglucose prepared above, and that it was in fact 6-O-lauroyl-D-glucopyranose (IIb) accompanied by a small amount of 1β,6-di-O-lauroyl-D-glucopyranose (IVb), as determined by TLC and GC comparisons.

Hori,[6] in 1958, prepared 3-O-acylglucoses by the hydrolysis of 3-O-acyl-1,2; 5,6-di-O-isopropylidene-α-D-glucofuranosides (XIX) with hydrochloric acid. The reported melting points (data in parentheses in Table VI) were, however, closer to those of 6-O-acylglucoses than to those of 3-O-acylglucoses. Reexamination of his procedure and GC analysis of the product (as the TMS derivative) showed that the product was a mixture of 3-O-acyl- and 6-O-acylglucoses. 6-O-Acylglucoses crystallized out from this mixture on crystallization from MeOH or EtOH. We therefore conclude that the reported 3-O-acylglucoses are again actually 6-O-acylglucoses. This evidence suggested that 3→6 acyl migration occurs easily on acid treatment of 3-O-acylglucoses. (Details of acyl migration in acylglucoses will be discussed in a separate paper.)

4-O-Acyl-D-glucopyranoses

For regioselective synthesis of 4-O-acylglucoses (XXIII), the key intermediate VIII was converted to XXI by benzylation (Hakomori's method) followed by hydrolysis with 80% AcOH. Tritylation and acylation of XXI yielded benzyl 4-O-acyl-2,3-di-O-benzyl-6-O-trityl-α-D-glucopyranosides (XXII) which, after chromatographic purification on Florisil, were hydrogenolyzed as described above. Although this procedure afforded 4-O-acylglucoses, the products were always contaminated with 20—30% of 6-O-acylglucoses, as shown by GC of their TMS derivatives, suggesting that partial 4→6 acyl migration took place during the catalytic hydrogenation. Fractional crystallizations of the products from acetone furnished



Compd.	R¹	R²	R³	R⁴	R⁵
XX:	Bn(α)	Bn	Bn	PhCH<	
XXI:	Bn(α)	Bn	Bn	H	H
XXII:	Bn(α)	Bn	Bn	R′CO	Tr
XXIIIa—e:	H	H	H	R′CO	H
XXIV:	Bn(α)	Bn	Bn	H	Cbz
XXVc:	Bn(α)	Bn	Bn	R′CO	Cbz
XXVIc:	H(α)	H	H	R′CO	R′CO

Tr=(Ph)$_3$C–, Cbz=PhCH$_2$OCO–

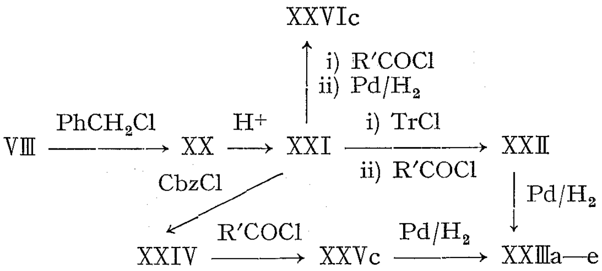


Chart 3

pure 4-O-acyl-D-glucopyranoses (XXIII), whose PMR spectra in pyridine-d_5 solution showed the presence of both α- and β-anomers in approximately equal amounts.

4-O-Acyl-D-glucopyranose (XXIIIc) was alternatively prepared as follows. Partial acylation of XXI with CbzCl gave the 6-Cbz derivative (XXIV) in 80% yield. Acylation of this with myristoyl chloride and subsequent hydrogenolysis of the resulting myristate under the conditions described above gave 4-O-myristoyl-D-glucopyranose (XXIIIc). However it was still contaminated with *ca.* 20% of 6-O-myristoylglucose (IIc), again suggesting partial 4→6 acyl migration during the hydrogenation step. 4-O-Acyl-D-glucopyranoses thus prepared are listed in Table VII.

Table VII. 4-O-Acyl-D-glucopyranoses (XXIIIa—e)

Compd. XXIII	mp (°C)	$[\alpha]_D^{17}$ (c=1, MeOH)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
a	113—115	+58°	$C_{16}H_{30}O_7$	57.46	9.04	57.43	9.14
b	117—119	+58°	$C_{18}H_{34}O_7$	59.64	9.46	59.45	9.58
c	114—117	+51°	$C_{20}H_{38}O_7$	61.51	9.81	61.23	10.05
d	122—125	+49°	$C_{22}H_{42}O_7$	63.13	10.11	63.16	10.35
e	119—123	+47°	$C_{24}H_{46}O_7$	64.54	10.38	64.15	10.41

1α-O-Acyl- and 1β-O-Acyl-D-glucopyranoses

Some 1α- and 1β-O-acylglucoses have already been reported. Nishikawa and Yoshimoto[12] synthesized 1α-O-glucosyl esters by the acylation of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (XXVII) with 50—85% stereoselectivity. In contrast, Pfeffer reported[4] the stereoselective (—89%) formation of the 1β-palmitoyl derivative (XXVIIId) by acylation of the Li salt of XXVII with palmitoyl chloride in benzene at high temperature (62°).

Our synthesis of 1β-O-acylglucoses was based on the report[13] that the stannic ester of XXVII, on acylation with acyl chloride, gave the 1β-O-acyl derivative exclusively. A reaction mixture of XXVII and $(Bu_3Sn)_2O$ was stirred with acyl chloride in pyridine. The proportion of the β-anomer in the product was roughly determined by comparison of the intensities of the two anomeric proton signals (δ 5.56 ppm, d, J=7.5 Hz for the β- and δ 6.30

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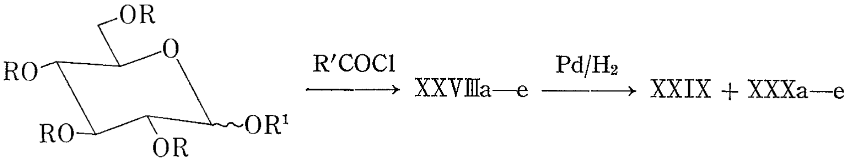
[12] Y. Nishikawa and K. Yoshimoto, *Chem. Pharm. Bull.* (Tokyo), 25, 624 (1977).
[13] T. Ogawa and M. Matsui, 20th Symposium on the Chemistry of Natural Products (Japan), 1976, Sendai, Abstract p. 91.



XXVII

Compd.	R^1	R
XXVII:	H(α)	Bn
XXVIIIa—e:	R′CO	Bn
XXIX:	R′CO(α)	H
XXXa—e:	R′CO(β)	H

Chart 4

ppm, d, $J=3.5$ Hz for the α-anomer) indicating 70% β and 30% α in every case. Hydrogenolysis of this mixture and GC analysis of the product (as the TMS derivative), however, revealed that the ratio of the anomers varied depending on the acyl chain length and reaction time, probably due to easy solvolytic cleavage of the 1β-O-acyl residue.[14] 1β-O-Acyl-D-glucopyranoses (XXXa—e) were eventually obtained in almost pure forms by fractional crystallizations of the crude product; their purities were confirmed by PMR and GC analyses. Data for 1α- and 1β-glucosyl esters thus prepared are listed in Table VIII.

TABLE VIII. 1β-O-Acyl-D-glucopyranoses (XXXa—e)

Compd. XXX	mp (°C)	$[\alpha]_D^{17}$ ($c=1$, MeOH)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H	*cf.* 1α-O-Acylglucoses[a] mp (°C)	$[\alpha]_D^{17}$ ($c=1$, pyridine)
a	105—107	−1.0°	$C_{16}H_{30}O_7$	57.46	9.04	57.16	9.25	—	—
b	104—107	−1.9°	$C_{18}H_{34}O_7$	59.64	9.46	59.80	9.68	74—76	+66.4°
c	105—107	−1.8°	$C_{20}H_{38}O_7$	61.51	9.81	61.43	10.01	113—115	+71.9°
d	112—113[b]	−4.2°[b]	$C_{22}H_{42}O_7$	63.13	10.11	63.19	10.29	108—110[c]	+69.0°[c]
e	113—114	−3.0°	$C_{24}H_{46}O_7$	64.54	10.38	64.45	10.58	112—113[d]	+67.6°[d]

a) Ref. 12).
b) Ref. 4). double mp 108° and 170—175°, $[\alpha]_D^{25}$ −1.17° ($c=1.2$, MeOH).
c) Ref. 4). mp 98—108°, $[\alpha]_D^{25}$ +66.9° ($c=0.9$, MeOH).
d) Ref. 4). mp 112—121°, $[\alpha]_D^{25}$ +72.9° ($c=1$, MeOH).

Thin-Layer Chromatography of Mono-O-acyl-D-glucopyranoses

All the mono-O-acyl-D-glucopyranoses had very similar *Rf* values (for example; myristates, 0.20—0.35; solvent, $CHCl_3$: MeOH=8: 1) so that it is difficult to identify them by TLC. The derivative with the highest *Rf* value (the 3-O-acyl derivative) is only distinguishable from those of the lowest *Rf* value (6-O- and 1α-O-acylglucose) if they have the same acyl chain. Increase of the acyl chain length slightly increased the *Rf* value.

Gas Chromatography of Mono-O-acyl-D-glucopyranoses

The TMS derivative of a purified mono-O-acylglucose gave a single peak on GC when the derivative was prepared from a fresh pyridine solution of acylglucose, although the PMR spectra suggested that 2- and 4-O-acylglucoses were mixtures of two anomers in pyridine-d_5 solution; this in turn suggests that the peaks of two anomers were not separable for these

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14) Solvolytic cleavage of 1β-O-acylglucoses in connection with acyl migration will be discussed in a separate paper.

acylglucoses. 6-O-Acylglucoses, after storage in pyridine for 24 hr, gave two peaks corresponding to α- and β-anomers, in agreement with the PMR evidence. The peaks in each series of acylglucoses showed a linear relationship between log. rt_R and acyl chain length. Some of the lines for independent series of acylglucoses in plots of log. rt_R *vs.* the carbon number of the acyl group were superimpossible, and the following three groups of lines were obtained: i) 1α-, 3-, and 4-O-acylglucoses ii) 1β-, and 2-O-acylglucoses, and iii) 6-O-acylglucose (α-anomer). These three groups were clearly distinguishable from each other (see Fig. 1).

Acetyl derivatives of the series of mono-O-acylglucoses also showed a linear relationship between log. rt_R and acyl chain length. However, the separation of isomers was poor; the tetra-acetates of 1β-, 2-, 3-, 4-, and 6-O-acyl derivatives gave the same rt_R, only the tetraacetyl-1α-O-acyl derivative being separated from the others (see Fig. 1).

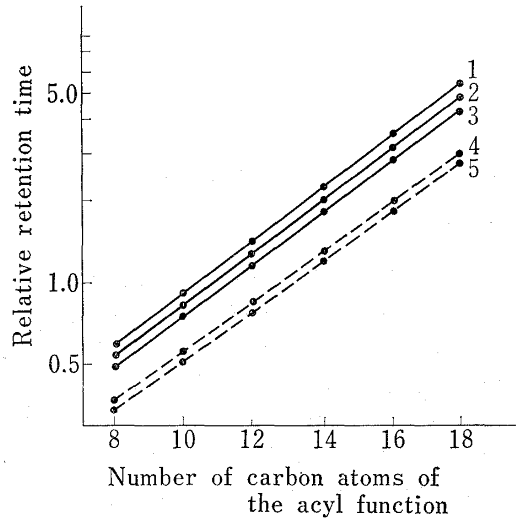

Fig. 1. Relationships between the Relative Retention Time[a] and Acyl Chain Length of Mono-O-acyl-D-glucopyranoses

1: 6-O-acyl-α-D-glucopyranoses,
2: 1β- and 2-O-acyl-D-glycopyranoses,
3: 1α-, 3-, and 4-O-acyl-D-glucopyranoses,
4: 1β-, 2-, 3-, 4-, and 6-O-acyl-D-glucopyranoses,
5: 1α-O-acyl-D-glucopyranoses.

a) Internal standard: sucrose 1.00 (TMS deriv. 3.9 min; Ac deriv. 3.5 min).
——: TMS derivative, 270°.
------: Ac derivative, 280°.

IR Spectra of Mono-O-acyl-D-glucopyranoses

The IR spectra of mono-O-acylglucoses provide appreciable information on the position of the acyl group in glucosyl esters. Table IX lists the ester carbonyl absorption bands of all isomeric mono-O-myristoyl-D-glucopyranoses.

The ester carbonyl of acylglucoses appears in the region of 1700—1750 cm^{-1}; 1α-O-acyl derivatives show the highest absorption (1740—1750 cm^{-1}), while 2-, 3-, and 4-O-acyl derivatives absorb at the lowest region (1700—1710 cm^{-1}). 6-O-Acyl derivatives gave a band at the normal ester carbonyl region (1720—1730 cm^{-1}). Unlike the others, the 1β-O-acyl derivative exhibited three characteristic absorption bands between 1730—1760 cm^{-1}, so it is easily distinguishable from the other isomers, all of which gave a single carbonyl absorption (see Fig. 2).

^{1}H-NMR Spectra of Mono-O-acyl-D-glucopyranoses

Since mono-O-acylglucoses were hardly soluble in $CDCl_3$, the NMR spectra were taken in pyridine-d_5 solution. Table IX shows the PMR specral data for all isomeric mono-O-myristoyl-D-glucopyranoses.

The anomeric proton of the β-anomer usually resonated at higher field by *ca.* 0.5 ppm than that of the α-anomer. Thus, 1α-O-acylglucoses exhibit a doublet at δ 6.8 ppm (J=3.8 Hz) and 1β-O-acyl derivatives at δ 6.2—6.3 ppm (J=7.5 Hz). The other mono-O-acylglucoses, except for the 2-O-acyl derivative, exhibit anomeric proton signals at δ 5.8—5.85 ppm (J=3.5 Hz) for the α-anomer and at δ 5.25—5.3 ppm (J=7.5 Hz) for the β-anomer, mostly as a doublet well separated from other proton signals. 2-O-Acylglucoses, however, exhibit a doublet for the α-anomer at δ 6.03 ppm (J=3.8 Hz) which is shifted downfield by *ca.* 0.2 ppm compared to the corresponding α-anomeric protons of the other isomers, apparently due to the presence of the *cis*-oriented neighboring ester carbonyl. The signal due to β-anomer appeared at δ 5.36 ppm (d, J=7.5 Hz), which is slightly shifted downfield due to the inductive effect of the acyloxy group.

Table IX. IR and NMR Spectra of Mono-O-tetradecanoyl-D-glucopyranoses

Compd.	IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1} Ester CO	NMR (δ ppm in pyridine-d_5) Anomeric H (d)		NMR (δ ppm in pyridine-d_5)
		α-Anomer	β-Anomer	$\rangle$C$\underline{\mathrm{H}}$-OCOR′
1α-(XXIXc)	1748[a]	6.80 (J=3.8 Hz)[a]		
1β-(XXXc)	1730, 1745, 1757[b]		6.23 (J=7.5 Hz)[b]	
(2-XIIc)	1706	6.03 (J=3.8 Hz)	5.36 (J=7.5 Hz)	5.70 (t, J=9.5 Hz, for β-anomer) 5.47 (q, J=3.8 and 9.5 Hz, for α-anomer)
3-(XVIIc)	1706	5.80 (J=3.5 Hz)	5.27 (J=7.5 Hz)[c]	6.17 (t, J=9.5 Hz)
4-(XXIIIc)	1706	5.83 (J=3.5 Hz)	5.30 (J=7.5 Hz)	5.63 (t, J=9.5 Hz)
6-(IIc)	1724	5.80 (J=3.5 Hz)	5.22 (J=7.5 Hz)[c]	Overlapped

a) *cf.* Ref. 4) for XXIXd: 1740 cm^{-1} (KBr disc), and δ 6.45 ppm (d, J=3.0 Hz) in CD$_3$OD at 60°.
b) *cf.* Ref. 4) for XXXd: 1740, 1750, 1760 cm^{-1} (KBr disc), and δ 5.62 ppm (d, J=6.5 Hz) in CD$_3$OD at 60°.
c) After 24 hr.

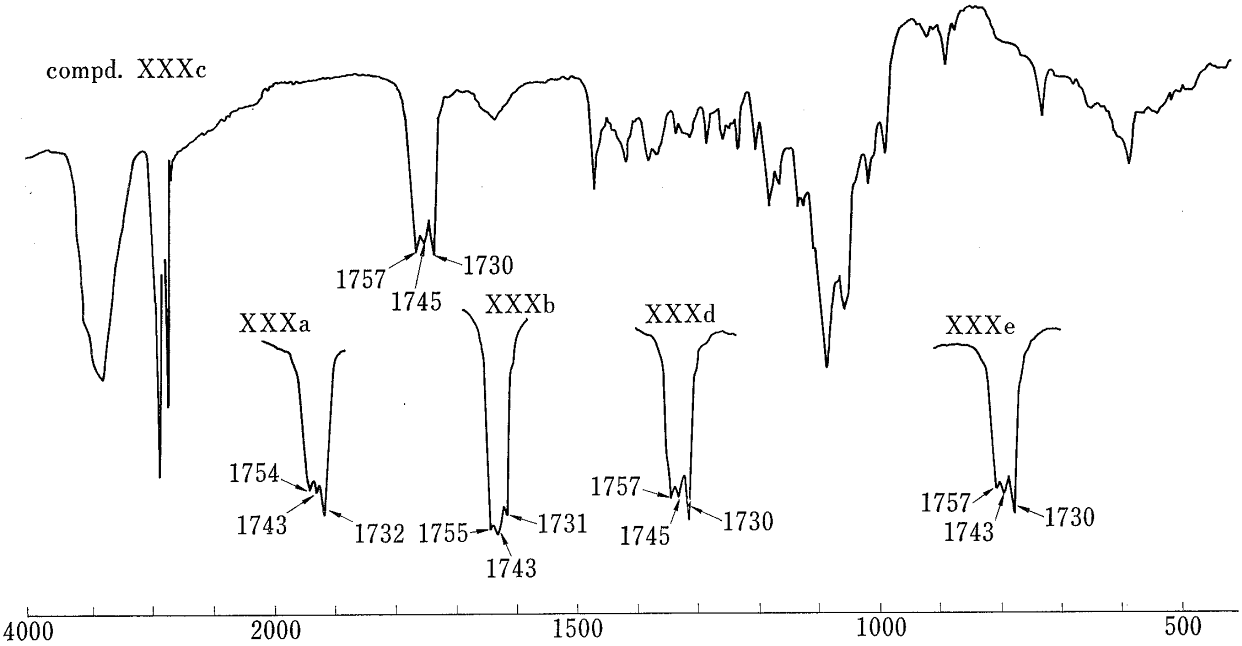

Fig. 2. IR Spectra of 1β-O-Acyl-D-glucopyranoses (in KBr Discs)

Signals due to the proton geminal to the acyloxy group provide additional information on the position of the acyl group. In 6-O-acylglucoses these were not well separated from other proton signals of the glucose moiety. However, 3-O-acyl- and 4-O-acylglucoses exhibit a clear triplet at δ 6.17 ppm (J=9.5 Hz) and at δ 5.63 ppm (J=9.5 Hz), respectively, the former at lower field than the signals of the anomeric protons (this is the lowest-field proton signal), and the latter between the two anomeric protons.

In 2-O-acylglucoses this proton signal showed a complex pattern as reported already[4b]: a triplet at δ 5.70 ppm (J=9.5 Hz) and a quartet at δ 5.47 ppm (J=3.8 and 9.5 Hz), corresponding to the β- and α-anomer, respectively.

In agreement with the above observations, 1β,6-di-O-myristoyl-D-glucopyranose (IV) showed an anomeric proton signal at δ 6.26 ppm (d, J=7.5 Hz).

2,3-Di-O-myristoyl-D-glucopyranose exhibited signals at δ 5.91 ppm (d, J=3.5 Hz) for the anomeric proton of the α-anomer, and at δ 6.31 ppm (d, J=9.5 Hz) and δ 5.32 ppm (q, J=3.5 and 9.5 Hz), indicative of protons geminal to the 3-O-acyl and 2-O-acyl (α-anomer) groupings, respectively. Since the signal due to the β-anomer was negligible, the compound was designated as 2,3-di-O-myristoyl-α-D-glucopyranose (XVIII).

4,6-Di-O-myristoyl-D-glucopyranose, which in turn was prepared by complete acylation and subsequent hydrogenolysis of XXI, clearly showed proton signals at δ 5.71 ppm (d, J=3.5 Hz, anomeric H for the α-anomer) and δ 5.52 ppm (t, J=9.5 Hz, C^4–H). C^6–H_2 was not distinguishable because of overlapping. The proton signal due to the β-anomer was again negligible, so the compound was assigned as 4,6-di-O-myristoyl-α-D-glucopyranose (XXVI).

The new tri-O-myristoylglucose obtained by direct acylation of D-glucose (see above) exhibited the anomeric proton signal at δ 6.00 ppm (d, J=3.5 Hz) and the signals of proton geminal to the acyloxy group at δ 5.63 ppm (t, J=9.5 Hz) and at δ 5.44 ppm (q, J=3.5 and 9.5 Hz), together with protons due to the D-glucose residue (δ 4—5 ppm, 4H) and the three acyl chains (δ 0.8—1.0, 9H; 1.0—1.8, 66H; 2.2—2.6 ppm, 6H) in pyridine-d_5. No proton signal due to the β-anomer was observed. Therefore it was designated as 2,4,6-tri-O-myristoyl-α-D-glucopyranose (VI). Figure 3 summarizes the PMR signal pattern of the above acylglucoses; this may be useful for the structure elucidation of unknown acylglucoses.

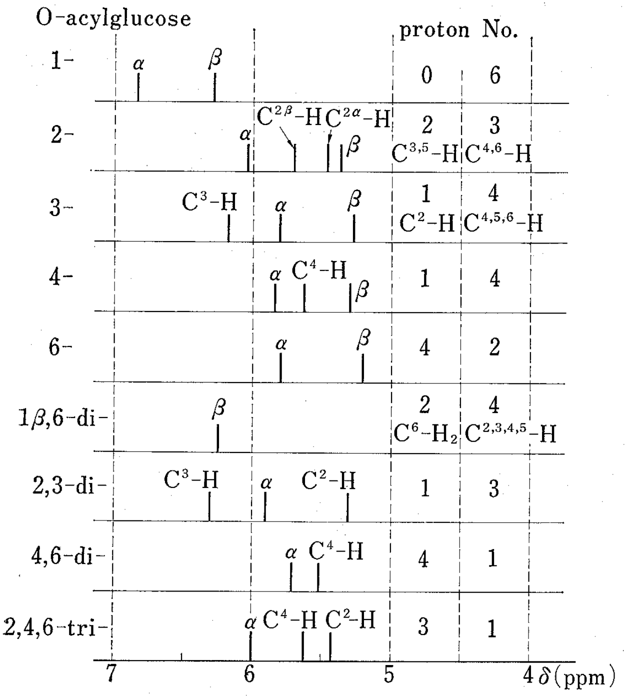

Fig. 3. ^{1}H-NMR Signals of Acylglucoses in Pyridine-d_5

Experimental

General——Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage mp apparatus, and are uncorrected. Acylglucoses usually show double mp's when measured in an open capillary:[6] the first one corresponds to t_p (transition point), at which the compound becomes liquid, and the second one is the temperature at which the liquid forms a meniscus; however the latter is not definitely observable. The melting points on a micro hot-stage are compatible with the first of these (t_p). IR spectra were taken in KBr discs with a JASCO IR-G spectrometer and are given in cm^{-1}. ^{1}H-NMR spectra were taken in pyridine-d_5 solution with TMS as an internal standard in a JNM-PMX-60 (60 MHz) or a JEOL JNM-PS-100 (100 MHz) spectrometer. Chemical shifts are given on the δ (ppm) scale: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were measured in pyridine or methanol with a JASCO DIP-SL automatic polarimeter. GLC analyses were carried out with a Shimadzu GC4CM-PF gas chromatograph with an FID detector, using N_2 (50 ml/min, 2.0 kg/cm^2) as a carrier gas. The TMS derivatives were prepared by the method of Sweeley *et al.*[15] A sample (1—2 mg) in dry pyridine (2 drops) was shaken vigorously with hexamethyldisilazane (2 drops) and trimethylsilyl chloride (1 drop). After 10 min at room temp., the mixture was centrifuged and the supernatant (1—2 μl) was directly injected into a glass column (2 m × 3 mm I.D.) packed with 1.5% OV-1 on Shimalite W (80—100 mesh). For TLC, Kieselgel GF$_{254}$ nach Stahl, type 60, and for column chromatography

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[15] C.C. Sweeley, R. Bentley, M. Makita, and W.W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).

Wakogel C-200 (silica gel) were used. All organic extracts were washed with water and dried over Na_2SO_4 before concentration.

6-O-Acyl-α-D-glucopyranoses (IIa—e)——Acyl chloride (1 mol eq.) in dioxane (20 ml) was added dropwise to a stirred solution of D-glucose (9.0 g) in pyridine (100 ml) at room temp., and stirring was continued for 5—7 hr at 100°. The progress of the reaction was monitored by TLC. When the spot corresponding to D-glucose became small, the mixture was evaporated to dryness and water was added. The acylglucose mixture was collected by extraction with EtOAc or by filtration (in the cases of palmitate and stearate) and chromatographed in $CHCl_3$. 6-O-Acyl-α-D-glucopyranose (II) was obtained from the $CHCl_3$–MeOH (15: 1) eluate and crystallized several times from acetone (see Table I). For IIb: IR: 3300 (OH), 1720 (–OCO–), 920, 893, 840. NMR (100 MHz): 5.82 (1H, d, $J=3.8$ Hz, C^1–H), 4.0—4.5 (2H, m, $C^{3,4}$–H), 4.5—5.0 (4H, m, $C^{2,4,6}$–H), 2.32 (2H, t, $J=7.5$ Hz, $-\mathrm{OCOC\underline{H}_2}-$),[16] 1.1—1.9 (18H, bs, $-(\mathrm{C\underline{H}_2})_9\mathrm{CH_3}$),[16] 0.88 (3H, t, $J=6.5$ Hz, $-CH_3$).[16]

6-O-Acyl-α-D-glucopyranose Tetraacetate——6-O-Acyl-α-D-glucopyranose (II, 50 mg) in pyridine (2 ml) was acetylated overnight with Ac_2O (1 ml) at room temp. Crystallization of the product from EtOH–H_2O gave the tetraacetate as needles (see Table I). NMR ($CDCl_3$, 100 MHz) of tetraacetyl IIb: 6.32 (1H, d, $J=4$ Hz, C^1–H), 5.47 (1H, t, $J=10$ Hz, C^3–H), 5.11 (1H, t, $J=10$ Hz, C^4–H), 5.02 (1H, q, $J=4$ and 10 Hz, C^2–H), 4.0—4.2 (3H, m, $C^{5,6}$–H), 2.16 (s), 2.03 (s), 2.01 (s), and 2.00 (s) (12H, $-OCOCH_3$).

1β,6-Di-O-acyl- (IVb, c) and 2,4,6-Tri-O-acyl-D-glucopyranose (VIb, c)——6-O-Lauroylglucose was removed as far as possible from the lauroylglucose mixture obtained above. The di- and tri-O-acyl fractions ($CHCl_3$ eluate) and the mother liquor from 6-O-lauroylglucose were combined, evaporated to dryness, and extracted with ether. The residue obtained on removal of the ether was chromatographed in *n*-hexane and eluted successively with *n*-hexane, benzene, $CHCl_3$, and MeOH, monitoring each fraction by TLC to yield 1β,6-di-O-lauroyl-D-glucopyranose (IVb) and 2,4,6-tri-O-lauroyl-α-D-glucopyranose (VIb). Di- and tri-O-myristates were obtained in the same way.

1β,6-Di-O-lauroyl-D-glucopyranose (IVb): mp 107—110°, colorless granules from MeOH, $Rf_1=0.66$ ($CHCl_3$: MeOH=8: 1), $Rf_2=0.33$ ($CHCl_3$: MeOH=95: 5) (lit.[8] mp 106—108°, $Rf_2=0.31$). IR: 3400(OH), 1748 and 1734 (–OCO–), 915, 867. NMR (100 MHz): 6.25 (1H, d, $J=7.5$ Hz, C^1–H), 4.7—4.9 (2H, m, C^6–H_2), 4.0—4.4 (4H, $C^{2,3,4,5}$–H).

2,4,6-Tri-O-lauroyl-α-D-glucopyranose (VIb): mp 92—93°, colorless granules from MeOH, $Rf_1=0.88$, $Rf_2=0.73$. IR: 3400 (OH), 1745, 1723, and 1694 (–OCO–), 925, 886. NMR (100 MHz): 5.98 (1H, d, $J=3.5$ Hz, C^1–H), 5.62 (1H, t, $J=9.5$ Hz, C^4–H), 5.43 (1H, q, $J=3.5$ and 9.5 Hz, C^2–H), 4.6—5.0 (2H, m, C^6–H_2). *Anal.* Calcd. for $C_{42}H_{78}O_9$: C, 69.38, H, 10.81. Found: C, 69.04, H, 10.62.

1β,6-Di-O-myristoyl-D-glucopyranose (IVc): mp 115—117°, colorless needles from MeOH, or mp 122—123°, colorless granules from acetone, $Rf_1=0.66$. IR: 3400 (OH), 1746 and 1733 (shoulder) (–OCO–), 913. NMR (100 MHz): 6.26 (1H, d, $J=7.5$ Hz, C^1–H), 4.7—4.9 (2H, m, C^6–H_2), 4.0—4.4 (4H, $C^{2,3,4,5}$–H).

2,4,6-Tri-O-myristoyl-α-D-glucopyranose (VIc): mp 97—99°, colorless granules from MeOH, $Rf_1=0.88$. IR: 3400 (OH), 1745, 1713, and 1695 (–OCO–), 923, 885. NMR (100 MHz): 6.00 (1H, d, $J=3.5$ Hz, C^1–H), 5.63 (1H, t, $J=9.5$ Hz, C^4–H), 5.44 (1H, q, $J=3.5$ and 9.5 Hz, C^2–H), 4.7—5.0 (2H, m, C^6–H_2). *Anal.* Calcd. for $C_{48}H_{90}O_9$: C, 71.06, H, 11.18. Found: C, 71.24, H, 11.00.

Benzyl α-D-Glucopyranoside (VII)——This was prepared according to the method of Fletcher, Jr.[10] as a pale yellow solid (yield, 60%).

Benzyl 4,6-O-Benzylidene-α-D-glucopyranoside (VIII)——Benzyl α-D-glucopyranoside (VII, 11 g), benzaldehyde (10 ml), and *p*-TsOH (0.3 g) in dimethylformamide (DMF) (10 ml) were heated under reduced pressure (30—40 mmHg) at 80—85° for 3 hr, then more benzaldehyde (1 ml) was added and the reaction was continued for a further 1 hr. The cooled mixture was poured into 1% $NaHCO_3$ (200 ml) and extracted with $CHCl_3$; this extract was passed through a short column of Florisil to remove some turbidity. Concentration of the eluate gave a pale yellow syrup which crystallized from EtOH to yield VIII (7.3 g, 50%) as colorless needles, mp 164—165°, $[\alpha]_D^{20}$ +104° ($c=1.02$, $CHCl_3$) (lit.[11] mp 161—162°, $[\alpha]_D^{20}$ +107° ($CHCl_3$)). Chromatography of the mother liquor gave an additional crop of VIII (0.8 g) (total yield, 55%). IR: 3020, 1602, 1582, and 1493. NMR (100 MHz): 7.2—7.5 (10H, bs, ArH), 5.44 (1H, s, $\mathrm{PhC\underline{H}}\langle{}^{\mathrm{O}}_{\mathrm{O}}$), 4.90 (1H, d, $J=4$ Hz, C^1–H), 4.74 (d) and 4.44 (d) (2H, $J=12$ Hz, $\mathrm{PhC\underline{H}_2O}-$).

Acylation of Benzyl 4,6-O-Benzylidene-α-D-glucopyranoside (VIII)——i) Acyl chloride (2 mol eq.) in dioxane (3 ml) was added dropwise for 1 hr to a stirred solution of VIII (300 mg) in pyridine (7 ml) at 0°, and the mixture was stirred for 4 hr at 10°. The mixture was poured into cold 1% $NaHCO_3$ and extracted with CH_2Cl_2. Concentration of the organic extract gave a gum which was chromatographed in benzene on Florisil (1.5 × 8 cm). The benzene eluate gave a small amount of the 2,3-di-O-acyl derivative (IX). Crystallization of the CH_2Cl_2 and $CHCl_3$ eluates from *n*-hexane gave the 2-O-acyl derivative (Xa—e) as needles (yield, 40—50%) (see Table III). Subsequent elution with $CHCl_3$–MeOH (1: 1) gave some starting material (VIII). Xa: IR: 3450 (OH), 1730 (–OCO–), 3020, 1582, and 1493. NMR (100 MHz): 7.34 (10H, bs, ArH), 5.52

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[16] The data on acyl chains are not shown hereafter.

(1H, s, PhC$\underline{\text{H}}\langle^{\text{O}}_{\text{O}}$), 5.14 (1H, d, $J=4$ Hz, C^{1}–H), 4.78 (1H, q, $J=4$ and 9.5 Hz, C^{2}–H), 4.72 (d) and 4.46 (d) (2H, $J=12$ Hz, PhC$\underline{\text{H}}_2$O–).

ii) The compound VIII (300 mg) was acylated as above with excess acyl chloride (5 mol eq.) and the reaction was carried out at room temp. for 4 hr. After work-up, the 2,3-di-O-acyl derivative (IXa—e) (see Table II) was obtained as colorless granules on crystallization from *n*-hexane or *n*-pentane (yield, 60—70%). IXc: IR: 1738 (–OCO–). NMR (60 MHz): 5.63 (1H, t, $J=9.5$ Hz, C^{3}–H), 5.54 (1H, s, PhC$\underline{\text{H}}\langle^{\text{O}}_{\text{O}}$), 5.08 (1H, d, $J=3.5$ Hz, C^{1}–H), 4.86 (1H, q, $J=3.5$ and 9.5 Hz, C^{2}–H), 4.73 (d) and 4.45 (d) (2H, $J=12$ Hz, PhC$\underline{\text{H}}_2$O–).

2-O-Acyl-D-glucopyranose (XIIa—e)——The 2-O-acyl derivative (X, 100 mg) and Pd-black (20 mg) in dioxane–MeOH (1:1) (8 ml) were shaken under H_2 at atmospheric pressure for 6 hr. The catalyst was removed by filtration, washed several times with MeOH, and the combined filtrate and washings were evaporated *in vacuo* to give a gummy residue. Chromatography of the residue and elution with $CHCl_3$–MeOH (15:1) gave 2-O-acyl-D-glucopyranose (XII), which crystallized as needles from acetone (yield, 80—85%). XIIc: IR: 3450 (OH), 1706 (–OCO–), 930, 904, 860. NMR (100 MHz): 6.03 (0.5H, d, $J=3.8$ Hz, C^{1}–H (α-anomer)), 5.70 (0.5H, t, $J=9.5$ Hz, C^{2}–H (β-anomer)), 5.47 (0.5H, q, $J=3.8$ and 9.5 Hz, C^{2}–H (α-anomer)), 5.36 (0.5H, d, $J=7.5$ Hz, C^{1}–H (β-anomer)), 4.91 (1H, t, $J=9.5$ Hz, C^{3}–H), 4.0—5.0 (4H, C^{4,5,6}–H).

2,3-Di-O-myristoyl-α-D-glucopyranose (XVIIIc)——The 2,3-di-O-myristoyl derivative (IXc, 100 mg) in EtOH (50 ml) was hydrogenated and worked up as above. Chromatography of the product gave 2,3-di-O-myristoyl-α-D-glucopyranose (XVIIIc) in the CH_2Cl_2–MeOH (15:1) eluate, and it was crystallized in needles from CH_2Cl_2, mp 118—120° (quantitative yield). IR: 3350 (OH), 1733 (shoulder) and 1717 (–OCO–), 924, 908, 868, 852. NMR (60 MHz): 6.31 (1H, t, $J=9.5$ Hz, C^{3}–H), 5.91 (1H, d, $J=3.5$ Hz, C^{1}–H), 5.32 (1H, q, $J=3.5$ and 9.5 Hz, C^{2}–H). *Anal.* Calcd. for $C_{34}H_{64}O_8$: C, 67.96; H, 10.74. Found: C, 67.74; H, 11.01.

Benzyl 4,6-O-Benzylidene-2-O- (XIV) and Benzyl 4,6-O-Benzylidene-3-O-Carbobenzoxy-α-D-glucopyranoside (XV)——A 30—35% solution of carbobenzoxy chloride in toluene (1.70 g) was added dropwise to a stirred solution of VIII (537 mg) in pyridine (10 ml) at 0° over 1.5 hr, and stirring was continued overnight at room temp. The mixture was poured into ice-water and the residue obtained from the organic extract was passed through a short column of Florisil (2×6 cm). The CH_2Cl_2 and $CHCl_3$ eluates were again chromatographed on silica gel (1.5×20 cm; solvents, $CHCl_3$–MeOH=10 ml: 3 drops) to give the 2-O-Cbz derivative (XIV, 330 mg) and 3-O-Cbz derivative (XV, 69 mg). Some starting material (110 mg) was recovered. XIV: colorless needles, mp 102—103° (from *n*-hexane), $Rf=0.50$ (solvent, $CHCl_3$: MeOH=10 ml: 3 drops). IR: 3450 (OH), 1747 (–OCO–), 1582, 1493. NMR ($CDCl_3$, 100 MHz): 7.30 (s) and 7.24 (s) (10H, ArH), 5.24 (1H, s, PhC$\underline{\text{H}}\langle^{\text{O}}_{\text{O}}$), 5.14 (1H, d, $J=3.8$ Hz, C^{1}–H), 5.06 (2H, s, PhC$\underline{\text{H}}_2$OCO–), 4.58 (1H, q, $J=3.8$ and 9.5 Hz, C^{2}–H), 4.68 (d) and 4.46 (d) (2H, $J=12$ Hz, PhC$\underline{\text{H}}_2$O–), 4.19 (1H, t, $J=9.5$ Hz, C^{3}–H), 4.17 (1H, q $J=5$ and 9 Hz, C^{5}–H), 3.90 (1H, t, $J=9$ Hz, C^{4}–H), 3.4—3.8 (2H, m, C^{6}–H_2). XV: colorless needles, mp 129—130° (from *n*-hexane), $Rf=0.60$ (solvent, $CHCl_3$: MeOH=10 ml: 3 drops). IR: 3450 (OH), 1750 (–OCO–), 1582, 1493. NMR ($CDCl_3$, 100 MHz): 7.28 (s) and 7.24 (s) (10H, ArH), 5.22 (1H, s, PhC$\underline{\text{H}}\langle^{\text{O}}_{\text{O}}$), 5.14 (1H, t, $J=9.5$ Hz, C^{3}–H), 5.11 (2H, s, PhC$\underline{\text{H}}_2$OCO–), 4.92 (1H, d, $J=3.8$ Hz, C^{1}–H), 4.74 (d) and 4.52 (d) (2H, $J=12$ Hz PhC$\underline{\text{H}}_2$O–), 4.21 (1H, q, $J=3.8$ and 9.5 Hz, C^{2}–H), 3.5—4.1 (4H, C^{4,5,6}–H).

Benzyl 3-O-Acyl-4,6-O-benzylidene-2-O-carbobenzoxy-α-D-glucopyranoside (XVIa—e)——Acyl chloride (3 mol eq.) was added dropwise to a stirred solution of 2-O-Cbz derivative (XIV, 110 mg) in pyridine (7 ml) at 0°, and stirring was continued overnight at room temp., then the mixture was poured into cold water and extracted with $CHCl_3$. Chromatography of the product in $CHCl_3$ gave the 3-O-acyl-2-O-Cbz derivative (XVI), which was crystallized from *n*-hexane as colorless needles (yield, 80—90%) (see Table V). XVIc: IR: 1755 and 1745 (–OCO–), 3020, 1582, and 1493. NMR ($CDCl_3$, 100 MHz): 5.67 (1H, t, $J=9.5$ Hz, C^{3}–H), 5.44 (1H, s, PhC$\underline{\text{H}}\langle^{\text{O}}_{\text{O}}$), 5.14 (1H, d, $J=3.8$ Hz, C^{1}–H), 5.06 (2H, s, PhC$\underline{\text{H}}_2$OCO–), 4.74 (1H, q, $J=3.8$ and 9.5 Hz, C^{2}–H), 4.71 (d) and 4.49 (d) (2H, $J=12$ Hz, PhC$\underline{\text{H}}_2$O–), 4.1—4.3 (1H, m, C^{5}–H), 3.8—4.1 (1H, m, C^{4}–H), 3.5—3.8 (2H, m, C^{6}–H_2).

3-O-Acyl-D-glucopyranose (XVIIa—e)——The 3-O-acyl-2-O-Cbz derivative (XVIa—e, 100 mg) in methanol–dioxane (1:1, 30 ml) was hydrogenated over Pd-black (40 mg) at room temp. and atmospheric pressure. After completion of the reaction (6—9 hr), the catalyst was removed by filtration, washed with methanol, and the combined filtrate and washings were evaporated to dryness. Chromatography of the residue in $CHCl_3$–MeOH (15:1) gave 3-O-acyl-D-glucopyranose (XVII), which was crystallized from acetone as colorless needles (quantitative yield) (see Table VI). XVIIb: IR: 3420 (OH), 1706 (–OCO–), 910, 890, 847. NMR (60 MHz): 6.17 (1H, t, $J=9.5$ Hz, C^{3}–H), 5.77 (0.9H, d, $J=3.5$ Hz, C^{1}–H (α-anomer)), 5.24 (0.1H, d, $J=7.5$ Hz, C^{1}–H (β-anomer)), 4.5—4.9 (1H, m, C^{2}–H), 4.0—4.5 (4H, C^{4,5,6}–H).

Benzyl 2,3,-Di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (XX)——The benzylidene derivative (VIII, 2 g) in dimethylsulfoxide (DMSO) (10 ml) was added to dymsyl anion solution prepared from DMSO (10 ml) and 50% NaH (1.5 g), and the mixture was stirred for 45 min at room temp. under argon. Benzyl chloride (60 ml) was then added dropwise, and the resulting mixture was stirred for 2.5 hr at room temp. under argon.

The mixture was then poured into cold water (150 ml) and extracted with ether. Concentration of the ethereal extract and crystallization of the residue from ether–*n*-hexane gave XX as colorless needles, mp 143—144° (yield, 91%) (lit.[11]) mp 137.5—138°). IR: 3020, 1582, and 1493. NMR ($CDCl_3$, 60 MHz): 7.2—7.5 (20H, ArH), 5.48 (1H, s, $\mathrm{PhC\underline{H}\langle{}^{O}_{O}}$), 4.77 (4H, s, $\mathrm{PhC\underline{H}_2O}$–), 4.72 (d) and 4.45 (d) (2H, J=12 Hz, $\mathrm{PhCH_2O}$–).

Benzyl 2,3-Di-O-benzyl-α-D-glucopyranoside (XXI)——Compound XX (150 mg) in 80% AcOH (10 ml) was heated under reflux for 30 min. The mixture was partially neutralized with 10% KOH and extracted with ether, which was then washed with H_2O, 5% $NaHCO_3$, and H_2O. Concentration of the solvent and crystallization of the residue from ether–*n*-hexane gave XXI as needles, mp 110—113° (yield, 80—85%) (lit.[11]) mp 111—111.5°). IR: 3350 (OH), 3020, 1585, and 1495, 916, 902, 854, 835. NMR ($CDCl_3$, 60 MHz): 7.30, 7.27, and 7.23 (15H, ArH), 4.78 (1H, d, J=3.5 Hz, C^1–H), 4.95 (d) and 4.58 (d) (2H, J=12 Hz, Ph-$\mathrm{C\underline{H}_2O}$–), 4.65 (d) and 4.38 (d) (4H, $\mathrm{PhC\underline{H}_2O}$–).

4-O-Acyl-D-glucopyranose (XXIIIa—e)——i) *Via* Tritylate: Compound XXI (675 mg) and TrCl (500 mg) in pyridine (15 ml) were heated at 80—85° for 6 hr then cooled. Acyl chloride (3 mol eq.) was added dropwise at 0° and the mixture was stirred overnight at room temp. The mixture was poured into cold water and extracted with CH_2Cl_2, then the residue obtained from the organic extract was dissolved in *n*-hexane and passed through a short Florisil column. The eluate, after removal of the solvent, was dissolved in MeOH–dioxane, and hydrogenated over Pd-black (200—300 mg) as described above. The product, which showed *ca.* 20—30% contamination with 6-O-acylglucose in GC, was chromatographed in $CHCl_3$–MeOH (15: 1) and the eluted mixture of 4-O-acyl and 6-O-acylglucose was crystallized several times from acetone to yield pure 4-O-acyl-D-glucopyranose (XXIII) as needles (yield, 35—40% from XXI) (see Table VII).

ii) *Via* Carbobenzoxy Derivative: A 30—35% toluene solution of CbzCl (3.40 g) was added dropwise to a stirred solution of XXI (1.35 g) in pyridine (4 ml) and CH_2Cl_2 (20 ml) at 0°, and the mixture was stirred overnight at room temp. The mixture was poured into cold water and extracted with CH_2Cl_2. Chromatography of the product in benzene on Florisil gave benzyl 2,3-di-O-benzyl-6-O-carbobenzoxy-α-D-glucopyranoside (XXIV), which was crystallized as needles from *n*-hexane–CH_2Cl_2, mp 65—67°, 1.37 g (yield, 78.5%). IR: 3400 (OH), 1747 (–OCO–), 3000, 1582, and 1493. NMR ($CDCl_3$, 60 MHz): 7.2—7.3 (20H, ArH), 5.11 (2H, J=12 Hz, $\mathrm{PhC\underline{H}_2O}$–), 4.78 (1H, d, J=3.5 Hz, C^1–H), 4.64 (d) and 4.42 (d) (2H, J=12 Hz, $\mathrm{PhC\underline{H}_2O}$–), 4.52 (2H, s, $\mathrm{PhC\underline{H}_2O}$–), proton ratio δ 3.2—4.0 to δ 4.2—5.2 was 4: 11.

The 6-O-Cbz derivative (XXIV, 582 mg) in pyridine (5 ml) and CH_2Cl_2 (5 ml) was acylated with excess myristoyl chloride for 2 days at room temp. After work-up as usual, the product in *n*-hexane was passed through a short column of Florisil to yield the 4-O-myristoyl-6-O-Cbz derivative as a colorless gum. This was dissolved in EtOH, hydrogenated over Pd-black and worked up as described above. The resulting mono-O-myristoylglucose was a 4: 1 mixture of the 4-O- and 6-O-myristoyl derivatives, as shown by GC of the TMS derivatives. Chromatography as described above and several crystallizations from acetone gave pure 4-O-myristoyl-D-glucopyranose (XXIIIc) as colorless needles, mp 114—117° (yield, 48% from XXIV). IR: 3450 (OH), 1706 (–OCO–), 940, 915, 855. NMR (100 MHz): 5.83 (0.5H, d, J=3.5 Hz, C^1–H (α-anomer)), 5.63 (1H, t, J=9.5 Hz, C^4–H), 5.30 (0.5H, d, J=7.5 Hz, C^1–H (β-anomer)), 4.78 (1H, t, J=9.5 Hz, C^3–H).

4,6-Di-O-myristoyl-α-D-glucopyranose (XXVIc)——An excess of myristoyl chloride (4 mol eq.) was added dropwise to a stirred solution of XXI (450 mg) in CH_2Cl_2 (6 ml) and pyridine (4 ml) at 0°, and the mixture was stirred overnight at room temp. The mixture was poured into ice-water and extracted with CH_2Cl_2. The product was chromatographed to give the 4,6-di-O-myristoyl derivative (530 mg) from the CH_2Cl_2 eluate as colorless needles, mp 38° (from *n*-hexane). IR: 1745 and 1725 (–OCO–), 3020, 1582, and 1493. NMR: ($CDCl_3$, 60 MHz): 7.30 and 7.18 (15H, ArH), 4.80 (1H, t, J=9.5 Hz, C^4–H), 4.78 (1H, d, J=3.5 Hz, C^1–H).

The CH_2Cl_2–MeOH (20: 1) eluate gave the 6-O-myristoyl derivative (220 mg).

The 4,6-di-O-myristoyl derivative obtained above was dissolved in EtOH, hydrogenated over Pd-black, and worked up as described above. Chromatography of the product gave 4,6-di-O-myristoyl-α-D-glucopyranose (XXVIc) from the CH_2Cl_2–MeOH (15: 1) eluate, and this was crystallized as needles from CH_2Cl_2, mp 97—98° (yield, 85%). IR: 3450 (OH), 1730 and 1690 (–OCO–), 940, 923, 898, 836. NMR (60 MHz): 5.71 (1H, d, J=3.5 Hz, C^1–H), 5.52 (1H, t, J=9.5 Hz, C^4–H), proton ratio δ 4.0—4.3 to 4.4—4.9 was 1: 4. *Anal.* Calcd. for $C_{34}H_{64}O_8$: C, 67.96; H, 10.74. Found: C, 68.23; H, 11.03.

1β-O-Acyl-D-glucopyranose (XXXa—e)——Tetra-O-benzyl-α-D-glucopyranose (XXVII, 1080 mg) and $(Bu_3Sn)_2O$ (1240 mg) in dry toluene (20 ml) were heated under reflux for 30 min then a half of the solvent was distilled off to remove water azeotropically, maintaining the bath temp. at 140°. Pyridine (2 ml) was added to the cooled mixture, then acyl chloride (2.6 mol eq.) was added dropwise. The mixture was stirred for 2 hr and kept overnight at room temp., then poured into water. This solution was extracted with ether and the extract was evaporated to dryness. The product was chromatographed in *n*-hexane, eluting successively with *n*-hexane, *n*-hexane–ether (4: 1), and ether. The *n*-hexane–ether eluate was again chromatographed rapidly on basic alumina to remove contaminating free carboxylic acid. 1β-O-Acyl-tetra-O-benzyl-D-glucose (XXVIII) was obtained from the *n*-hexane and *n*-hexane–benzene (1: 1) eluates (XXVIIIa—c were gums and XXVIIId—e were solids). All of them were contaminated with the 1α-O-acyl derivative, as shown by the NMR spectra. The 1-O-acyl derivative (XXVIII, 1.2—1.5 g) in EtOH (50 ml) was hydrogenated over Pd-black (500—750 mg) for 5—9 hr. Removal of the catalyst and the solvent gave a gum which was chromatographed in $CHCl_3$. The $CHCl_3$–MeOH (15: 1) eluate gave 1-O-acyl-D-glucopyranose (yield, 60—70% from XXVII), which was a 5: 1—1.25: 1 mixture of the 1β-O-acyl and 1α-O-acyl derivatives, as shown by GC of the TMS derivative. Several crystallizations of this material from acetone yielded pure 1β-O-acyl-D-glucopyranose as needles (see Table VIII). XXXc: 3400 (OH), 1730, 1745, and 1757 (–OCO–), 918, 887, 870. NMR (60 MHz): 6.23 (1H, d, $J=7.5$ Hz, C^1–H), 3.9—4.5 (6H, $C^{2,3,4,5,6}$–H).

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