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Regioselective Monoacylation of Some Glycopyranosides *via* Cyclic Tin Intermediates[1)]

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Selective mono-benzoylation of some pento- and hexo-pyranosides (Me β-L-Ara, Ph α-L-Ara, Me α-D-Xyl, Me β-D-Xyl, Me α-D-Glc, Me β-D-Glc, Me α-D-Gal, Me β-D-Gal, and Me α-D-Man) by using Bu_2SnO was examined in comparison with the results of the $(Bu_3Sn)_2O$ method and direct benzoylation. The Bu_2SnO method is particularly useful in that it selectively activates an equatorial hydroxyl group which bears an oxygenated function (OH or OMe) in a *cis* relationship at an adjacent position, even in the presence of a more reactive primary OH group. The various mono- and di-*O*-benzoyl derivatives prepared in this work were unambiguously identified by analysis of their ^{13}C-nuclear magnetic resonance spectra.

Keywords——regioselective acylation; dibutyltin oxide; bis-tributyltin oxide; cyclic tin intermediate; mono-*O*-acylglycopyranoside; *cis-vicinal* glycol; ^{13}C-NMR

Introduction

Recent developments in isolation techniques in the field of carbohydrate chemistry have resulted in the isolation of various acylglycosides and acylglycoses, including some of biological importance.[2)] Selective acylation of carbohydrates is not only necessary for the synthesis of such natural products but is also of great synthetic value because the products thus prepared may have further synthetic utility as versatile intermediates. Various methods and acylating agents have been introduced for this purpose;[3,4)] most of the methods are based on the blocking-deblocking technique for hydroxyl groups which are not directly involved in the reaction. Recently, however, tin compounds have been introduced for selective acylation without blocking-deblocking techniques. Several workers reported the use of dibutyltin oxide[5)] and bis-(tributyl)tin oxide[6)] for this purpose. Those methods are based on the principle that the O–Sn linkage formed as an intermediate has greater nucleophilicity than to the original O–H bond.

The dibutyltin oxide method was first introduced for selective acylation of ribonucleosides.[7)] Nashed and Anderson[5b)] recognized that in the case of a *cis-vic* glycol system a five-membered stannylene ring (**2**) is formed between the axial–equatorial pair and the reactivity of the equatorial OH group is enchanced much more than that of the axial one. Thus, they selectively obtained allyl 3-*O*-benzoyl-2,6-di-*O*-benzyl-α-D-galactopyranoside (**3**) from allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**1**) by benzoylation with benzoyl chloride in the presence of triethylamine after treatment with Bu_2SnO in methanol.[5b)] Interestingly, Munavu and Szmant[5a)] reported that in the case of methyl α-D-glucopyranoside (**4**), the 2-*O*-benzoate (**6**) was formed in 70% yield even in the presence of a more reactive primary hydroxyl group. They suggested that the formation of the five-membered stannylene ring (**5**) between two equatorial OH groups would be favored by coordination of the neighboring oxygen atom having axial orientation to the tin atom.

Later Ogawa and Matsui[6)] introduced the use of bis(tributyl)tin oxide for the selective acylation of some pyranosides. They suggested that the trialkyltin ether formed by the treatment of an OH group with $(Bu_3Sn)_2O$ is stabilized by coordination of a neighboring

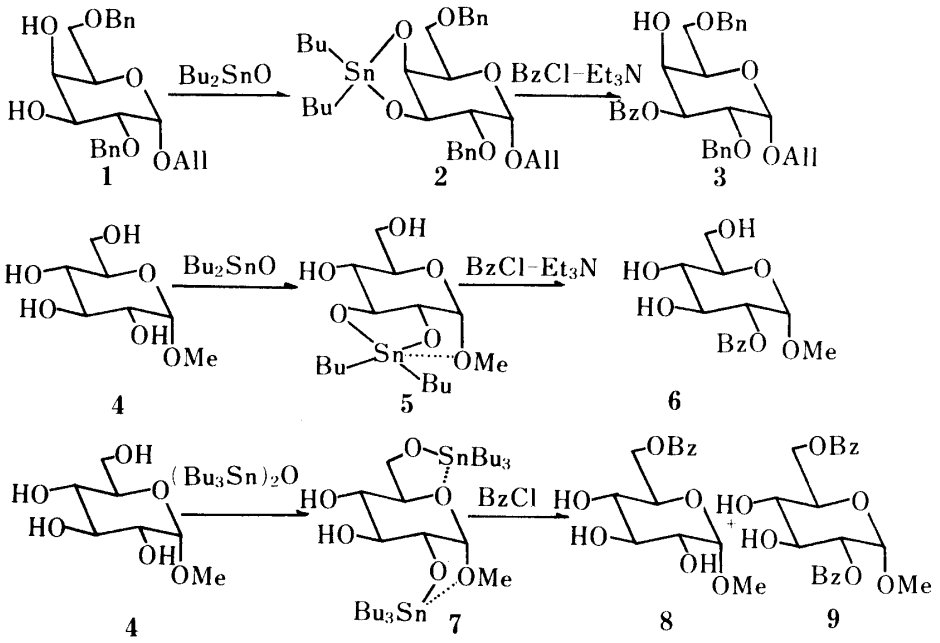


Chart 1

oxygen atom to the tin atom, but they also suggested that the reactivity of the primary tin ether is higher than that of the secondary one. Thus, they obtained the 6-*O*-benzoate (**8**) (73%) when methyl α-D-glucopyranoside (**4**) was treated with $(Bu_3Sn)_2O$ (1.5 eq) followed by subsequent benzoylation (3 eq of benzoyl chloride) at −15° to −10°C for 1.5 h, though an appreciable amount of 2,6-di-*O*-benzoate (**9**) was also formed.[6b]

Among the above methods, activation of OH groups by Bu_2SnO is particularly interesting, since this method would permit selective acylation of a particular secondary OH group of a pyranoside without the need to block a more reactive primary hydroxyl group, because for the cyclic tin intermediate, a five-membered ring would be more favorable than a six-membered ring. However, the utility of this method has been little studied from this point of view.

In this paper we describe the use of the Bu_2SnO method on Me α-D-Glc, Me β-D-Glc, Me β-L-Ara, Ph α-L-Ara, Me α-D-Xyl, Me β-D-Xyl, Me α-D-Gal, Me β-D-Gal, and Me α-D-Man[8] in comparison with the results of the $(Bu_3Sn)_2O$ method and of direct benzoylation.

Results and Discussion

In order to select the reaction conditions, we first repeated the reaction of Me α-D-Glc (**4**) by the two methods, *i.e*, with Bu_2SnO and $(Bu_3Sn)_2O$, and found that, contrary to Munavu and Szmant's original procedure for dibutyltin oxide,[5a] addition of triethylamine is not necessary; without triethylamine benzoylation proceeds more rapidly and more selectively to give only the 2-*O*-benzoate (**6**) in higher yield. Therefore, this modified procedure (method A) was applied to the other substrates.

The products of the bis(tributyl)tin oxide method (method B)[6b] depended on the reaction conditions of benzoylation, and this method was found to be appropriate to yield di-*O*-benzoates. In fact, Ogawa[6b] obtained 2,6-di-*O*-benzoate (**9**) in high yield (95%) from **4** on benzoylation of the intermediate at −10 to −5°C for 21 h. We observed that when 1 eq of benzoyl chloride was used, benzoylation was incomplete even when the reaction was carried out at 0°C, and under our conditions, 2 eq of the reagent was necessary to obtain a suifficient yield of mono-*O*-benzoate. However, if concentration of the reaction mixture was carried out above 50°C, the yield of di-*O*-benzoate was greatly increased.

TABLE I. Benzoylation of Methyl α-D-Glucopyranoside by the Bu_2SnO and $(Bu_3Sn)_2O$ Methods

Reagents		Mono-*O*-benzoate (%)	Composition (ratio)		2,6-Di-*O*-benzoate
			2-*O*-Benzoate	6-*O*-Benzoate	
Bu_2SnO,	a) BzCl, Et_3N	64.1 (70.0)[a]	92 (100)[a]	8 (0)[a]	11.7 (2.0)[a]
	b) BzCl, —	76.4	100	0	6.3
$(Bu_3Sn)_2O$,	BzCl, —				
	Evap. at 50 °C	65.2 (73.0)[b]	13 (0)[b]	87 (100)[b]	15.6 (20.0)[b]
	Evap. at 70 °C	32.3			31.9

a) R. M. Munavu and H. H. Szmant, *J. Org. Chem.*, **41**, 1832(1976).
b) T. Ogawa and M. Matsui, *Tetrahedron*, **37**, 2363(1981). Reaction at −15 to −10°C.

Identification of each product and exact determination of the proportions are the other problems. Until recently, these have been done either by isolation of each product by repeated chromatography or by transforming the products to crystalline derivatives followed by chromatography. Obviously these procedures cannot be done without considerable loss of some components. More importantly, the procedures are always possibly accompanied by acyl migration.[3a,b] Both factors prevent the accurate determination of the product composition in the original mixture. Gas chromatography (GC) of trimethylsilyl derivatives was successfully applied in some instances,[4,9] but in many cases regio-isomers of mono-*O*-benzoates give poorly separated or inseparable peaks, which again prevent the exact determination of the product composition.[4]

Recently it was shown that ^{13}C-NMR is a powerful tool for product analysis of such an isomeric mixture of carbohydrates, particularly by use of the acylation shift rule and shift parameters. Some complex mixtures of mono-*O*-acylglycosides were completely analyzed.[9,10] In the present case, for example, Fig. 1 shows a mono-*O*-benzoate mixture of Me β-L-Ara (**10**) obtained by method A; all the peaks can be identified by taking account of known acylation shifts and comparing the spectra with those of the non-acylated compounds. Although the intensity of each peak does not correspond to the proportion of the respective component due to the variability of nuclear Overhauser effects among the carbon atoms, we found that the intensity ratio of anomeric carbon signals (if the peaks are separated) is almost proportional

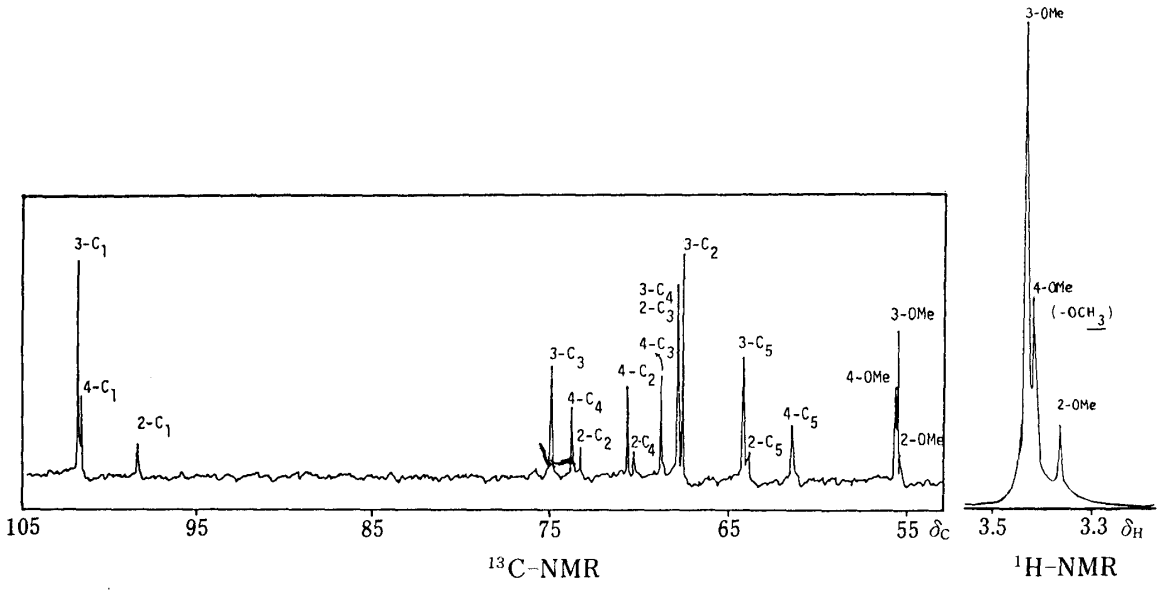
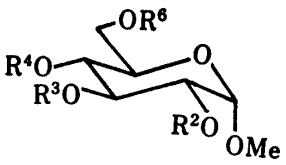
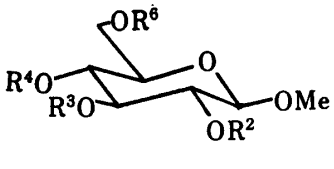


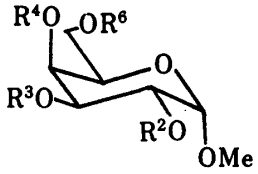
Fig. 1. NMR Spectrum of a Methyl Mono-*O*-benzoyl-β-L-arabinopyranoside Mixture obtained by Method A



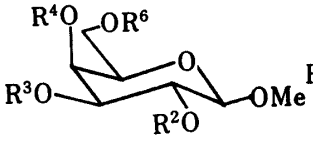
	R^2	R^3	R^4	R^6
4:	H	H	H	H
6:	Bz	H	H	H
8:	H	H	H	Bz
9:	Bz	H	H	Bz



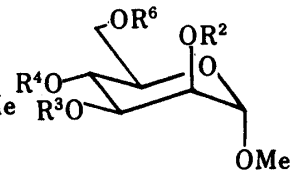
	R^2	R^3	R^4	R^6
34:	H	H	H	H
35:	H	H	H	Bz
36:	Bz	H	H	Bz



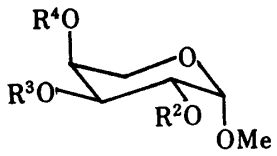
	R^2	R^3	R^4	R^6
37:	H	H	H	H
38:	Bz	H	H	H
39:	H	Bz	H	H
40:	H	H	H	Bz
41:	Bz	Bz	H	H
42:	Bz	H	H	Bz
43:	H	Bz	H	Bz
57:	Ts	H	H	H
58:	H	Ts	H	H



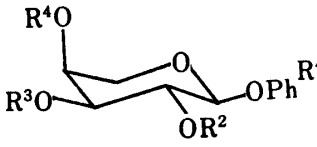
	R^2	R^3	R^4	R^6
44:	H	H	H	H
45:	H	Bz	H	H
46:	H	H	H	Bz
47:	H	Bz	H	Bz



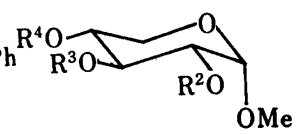
	R^2	R^3	R^4	R^6
48:	H	H	H	H
49:	H	Bz	H	H
50:	H	H	H	Bz
51:	H	Bz	H	Bz
52:	Bz	H	H	Bz



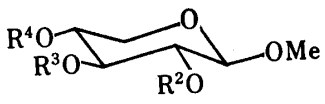
	R^2	R^3	R^4
10:	H	H	H
11:	Bz	H	H
12:	H	Bz	H
13:	H	H	Bz
14:	Bz	Bz	H
15:	Bz	H	Bz
16:	H	Bz	Bz



	R^2	R^3	R^4
17:	H	H	H
18:	H	Bz	H
19:	H	H	Bz
20:	Bz	Bz	H
21:	H	Bz	Bz



	R^2	R^3	R^4
22:	H	H	H
23:	Bz	H	H
24:	H	H	Bz
25:	Bz	Bz	H
26:	Bz	H	Bz



	R^2	R^3	R^4
27:	H	H	H
28:	Bz	H	H
29:	H	Bz	H
30:	H	H	Bz
31:	Bz	Bz	H
32:	Bz	H	Bz
33:	H	Bz	Bz

Chart 2

to the ratio of OMe peak areas from ^{1}H-NMR of the corresponding compound. Thus, by using either of the above methods or the combination, we can easily determined the proportions without separating the products into individual components. The possibility of acyl migration during the isolation procedures is thus minimized. Of course, the above assignments of the products were confirmed after rigorous purification of each component, where possible. The results are collected in Tables II—IV.

TABLE II. Yield and Composition Data of Mono-(mono-bz) and Di-*O*-benzoates(di-bz) obtained by Methods A, B, and C

Expt.	Compound	Method[a]	Mono-bz yield (%)	Composition				Di-bz yield (%)	Composition				
				2-bz	3-bz	4-bz	6-bz		2, 3	2, 4	2, 6	3, 4	3, 6
1	Me β-L-Ara	A	79.6[b]	10	61	29		14.0[b]	34	38		28	
2	Me β-L-Ara	B	50.7[b]	—	100	—		44.7[b]	32	37		31	
3	Me β-L-Ara	C	31.7[b]	47	31	22		25.6	100	—		Trace	
4	Ph α-L-Ara	A	73.1[c]	—	69	31		8.6	—	—		100	
5	Ph α-L-Ara	B	69.3	—	100	Trace		22.9	—	—		100	
6	Ph α-L-Ara	C	39.5[c]	—	69	31		31.5[c]	26	—		74	
7	Me α-D-Xyl	A	82.0[b]	64	—	36		—	—	—		—	
8	Me α-D-Xyl	B	72.0[b]	57	—	43		—	—	—		—	
9	Me α-D-Xyl	C	56.2	100	—	—		34.5[b]	57	43		—	
10	Me β-D-Xyl	A	77.7	—	—	100		15.5[b]	—	9		91	
11	Me β-D-Xyl	B	43.3	—	—	100		45.8[b]	—	56		44	
12	Me β-D-Xyl	C	44.6[b]	20	36	44		37.5[d]	45	27		28	
13	Me α-D-Glc	A	76.4	100	—	—	—	6.3	—	—	100	—	—
14	Me α-D-Glc	B	64.4[e]	12	—	—	88	9.4	—	—	100	—	—
15	Me β-D-Glc	A	86.2	—	—	—	100	Trace	—	—	—	—	—
16	Me β-D-Glc	B	79.2	—	—	—	100	15.7	—	—	100	—	—
17	Me α-D-Gal	A	67.5[b]	26	51	—	23	27.0[b]	(2,3+2,6)=76			—	24
18	Me α-D-Gal	B	58.6	—	—	—	100	32.4	—	—	43	—	57
19	Me β-D-Gal	A	53.1	—	100	—	—	21.3	—	—	—	—	100
20	Me β-D-Gal	B	42.0[b]	—	75	—	25	44.9	—	—	—	—	100
21	Me α-D-Man	A	64.5	—	100	—	—	30.3	—	—	—	—	100
22	Me α-D-Man	B	48.0[b]	Trace	40	—	60	50.5[b]	—	—	9	—	91

a) Method A, Bu_2SnO method; Method B, $(Bu_3Sn)_2O$ method; Method C, direct benzoylation.
b) Composition from OMe peak area.
c) Composition from H-1 intensity.
d) Composition from C-1 peak height.
e) Composition from GC peak area.

Pentopyranosides

The order of reactivity of OH groups of β-L-Ara towards benzoylation with benzoyl chloride in pyridine has been suggested to be 2-OH, 3-OH>4-OH,[11,12] though the relative reactivity of 2-OH and 3-OH is uncertain. Our result for the direct benzoylation of Me β-L-Ara (**10**) suggests that the 2-OH group is the most reactive, but the selectivity as well as the total yield of mono-*O*-benzoate was poor (Expt. 3). On the other hand, in method A, the 3-*O*-benzoate (**12**) was the major product, and the 4- and 2-*O*-benzoates (**13** and **11**) were minor products (Expt. 1). This is in accord with Nashed's proposal that the equatorial OH group in a *cis*-glycol system is more activated,[5b] provided that the reaction proceeds with *C*1 conformation. Method B was found to be more selective than method A, giving only the 3-*O*-benzoate (**12**), though the yield of mono-*O*-benzoate was lower, appreciable formation of di-*O*-benzoate being observed (Expt. 2).

The order of reactivity of OH groups of α-L-Ara is not known. Our result in the direct benzoylation of Ph α-L-Ara (**17**) showed that the 3-OH group was the most reactive and the order of reactivity was 3-OH>4-OH>2-OH, but the yield of mono-*O*-benzoates was low (Expt. 6). As compared to the direct benzoylation, the yield of mono-*O*-benzoates by method A was higher, but the percentage composition of 3- and 4-*O*-benzoates (**18** and **19**) was more or less the same (Expt. 4). This implies that the reactivity of the reactive OH groups was enhanced by using Bu_2SnO, though the selectivity was not altered. On the other hand, method B was more selective and gave only the 3-*O*-benzoate (**18**) in 69.3% yield (Expt. 5). The fact that method A is less regioselective than method B implies that the benzoyl cation can also attack, to some extent, the 4-O–Sn bond of the fused five-membered stannylene ring, probably due to deformation of the ring or a contribution of 1*C* form. The order of reactivity of OH

TABLE III. ^{13}C Chemical Shifts of Mono-*O*-benzoates of Some Pyranosides and their Acylation Shift Values (in Parentheses) in Pyridine-d_5

Mono-*O*-benzoate	Carbon number						OMe
	C-1	C-2	C-3	C-4	C-5	C-6	
Me β-L-Ara[a]	102.1	70.5	70.9	70.0	63.9		55.3
2-*O*-Benzoate[b]	98.8	73.5	67.9	70.4	63.9		55.3
	(−3.3)	(+3.0)	(−3.0)	(+0.4)	(0)		(0)
3-*O*-Benzoate[c]	102.2	67.6[f]	75.1	67.9[f]	64.1		55.4
	(+0.1)	(−2.9)	(+4.2)	(−2.1)	(+0.2)		(+0.1)
4-*O*-Benzoate[c]	102.0	70.8	68.9	74.0	61.4		55.5
	(−0.1)	(+0.3)	(−2.0)	(+4.0)	(−2.5)		(+0.2)
Ph β-L-Ara	102.8	72.1	74.4	69.3	67.2		
3-*O*-Benzoate[c]	101.7	69.1	76.6	65.9[f]	65.8[f]		
	(−1.1)	(−3.0)	(+2.2)	(−3.4)	(−1.4)		
4-*O*-Benzoate[c]	102.9	72.6[f]	72.6[f]	72.8[f]	64.9		
	(+0.1)	(+0.5)	(−1.8)	(+3.5)	(−2.3)		
Me α-D-Xyl[d]	101.5	73.6	75.3	71.3	63.0		55.1
2-*O*-Benzoate[c]	98.3	75.4	72.6	71.6	62.9		55.0
	(−3.2)	(+1.8)	(−2.7)	(+0.3)	(−0.1)		(−0.1)
4-*O*-Benzoate[c]	101.5	73.7[f]	72.1	73.8[f]	59.4		55.4
	(0)	(+0.1)	(−3.2)	(+2.5)	(−3.6)		(+0.3)
Me β-D-Xyl[d]	106.1	74.6	78.1	70.9	66.9		56.6
4-*O*-Benzoate[c]	106.1	74.9[f]	74.8[f]	73.7	63.3		56.7
	(0)	(+0.3)	(−3.2)	(+2.8)	(−3.6)		(+0.1)
Me α-D-Glc[c]	101.3	73.7	75.3	72.0	74.0	62.8	55.0
2-*O*-Benzoate[c]	98.1	75.6	72.6	72.1	74.2	62.5	54.8
	(−3.2)	(+1.9)	(−2.7)	(+0.1)	(+0.2)	(−0.3)	(−0.2)
6-*O*-Benzoate[c]	101.4	73.7	75.3	71.9	71.0	65.3	55.0
	(+0.1)	(0)	(0)	(−0.1)	(−3.0)	(+2.5)	(0)
Me β-D-Glc[c]	105.5	75.0	78.4	71.5	78.3	62.6	56.7
6-*O*-Benzoate[c]	105.6	75.0	78.3	71.5	75.2	65.2	56.7
	(+0.1)	(0)	(−0.1)	(0)	(−3.1)	(+2.6)	(0)
Me α-D-Gal[d]	101.7	70.5	71.6	70.9	72.5	62.6	55.1
2-*O*-Benzoate[b]	98.3	73.7	68.9	71.1	72.7	62.4	55.0
	(−3.4)	(+3.2)	(−2.7)	(+0.2)	(+0.2)	(−0.2)	(−0.1)
3-*O*-Benzoate[c]	101.7	68.3[f]	76.1	67.8[f]	72.3	62.1	55.2
	(0)	(−2.2)	(+4.5)	(−3.1)	(−0.2)	(−0.5)	(+0.1)
6-*O*-Benzoate[b]	101.7	70.3	71.3	70.8	69.5	65.5	55.2
	(0)	(−0.2)	(−0.3)	(−0.1)	(−3.0)	(+2.9)	(+0.1)
Me β-D-Gal[d]	106.1	72.5	75.2	70.1	76.8	62.3	56.6
3-*O*-Benzoate[c]	106.1	69.5	78.6	67.6	76.5	61.9	56.7
	(0)	(−3.0)	(+3.4)	(−2.5)	(−0.3)	(−0.4)	(+0.1)
6-*O*-Benzoate[c]	106.1	72.1	74.9	69.9	73.5	64.9	56.5
	(0)	(−0.4)	(−0.3)	(−0.2)	(−3.3)	(+2.6)	(−0.1)
Me α-D-Man[d]	102.3	71.8	72.8	68.7	74.7	62.8	54.6
2-*O*-Benzoate[b]	99.6	74.3	70.8	68.7	75.3	62.8	54.6
	(−2.7)	(+2.5)	(−2.0)	(0)	(+0.6)	(0)	(0)
3-*O*-Benzoate[c]	102.7	69.4	77.3	65.6	75.4	62.6	54.5
	(+0.4)	(−2.4)	(+4.5)	(−3.1)	(+0.7)	(−0.2)	(−0.1)
6-*O*-Benzoate[b]	102.7	71.9[f]	72.9	68.6	72.2[f]	65.5	54.5
	(+0.4)	(+0.1)	(+0.1)	(−0.1)	(−2.5)	(+2.7)	(−0.1)

a) K.Mizutani, R. Kasai, A. Hayashi, O. Tanaka, N. Yoshida, and T. Nakasima,Symposium Papers, 25th Symposium on the Chemistry of Natural Products, Tokyo, Oct. 1982,p.451.
b) Not isolated.
c) Isolated.
d) S. Seo, Y. Tomita, K. Tori, and Y. Yoshimura, *J. Am. Chem. Soc.*, **100**, 3331 (1978).
e) The data are cited from ref. 4.
f) Assignments may be reversed in each line.

groups of Me α-D-Xyl (**22**) was suggested to be 2-OH>4-OH>3-OH from di and tri-*O*-benzoylation[11,13] and selective sulfonylation[14] experiments. Our direct benzoylation confirmed that the 2-OH group is the most reactive, yielding only the 2-*O*-benzoate (**23**) together with a mixture

of di-*O*-benzoates (Expt. 9). Unexpectedly, methods A and B were both less regio-selective and gave a mixture of 2- and 4-*O*-benzoates (**23** and **24**) but in better yields (Expt. 7 and 8). Di-*O*-benzoate was not isolated when these two methods were used. Reduced regioselectivity in these methods would suggest a partial contribution of a cyclic intermediate (such as **53** and **54**) besides the major contribution of **55**.

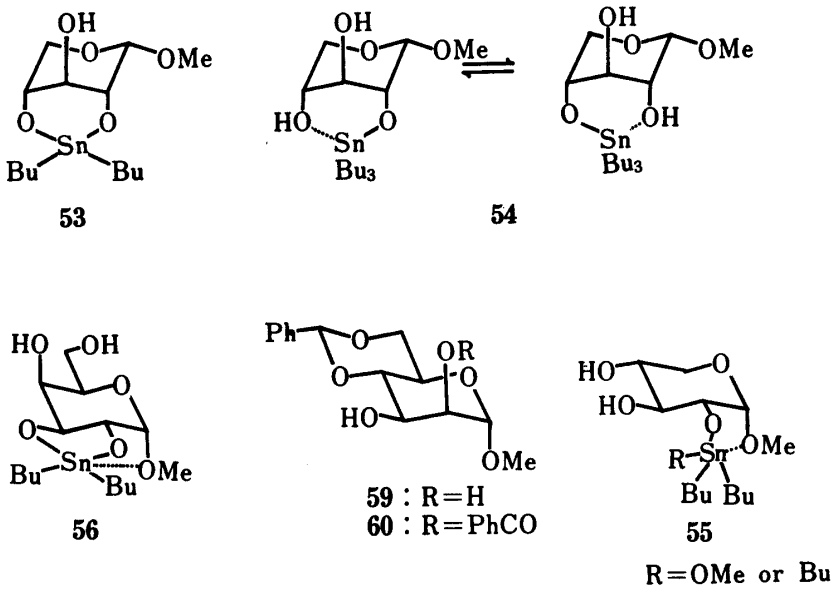
The order of reactivity of OH groups of Me β-D-Xyl (**27**) in selective sulfonylation was

TABLE IV. Observed and Calculated (in Parentheses) ^{13}C Chemical Shifts of Di-*O*-benzoates(di-bz) in Pyridine-d_5

Di-*O*-benzoate	Carbon number						
	C-1	C-2	C-3	C-4	C-5	C-6	OMe
Me β-L-Ara							
2,3-di-bz[b]	98.8	70.2	72.0	68.0	64.0		55.3
	(98.9)	(70.6)	(72.1)	(68.2)	(64.1)		(55.4)
2,4-di-bz[a]	98.7	73.9	66.0	73.9	61.3		55.5
	(98.7)	(73.8)	(65.9)	(74.4)	(61.4)		(55.5)
3,4-di-bz[a]	102.0	68.0	73.4	71.2	60.9		55.6
	(102.1)	(67.9)	(73.1)	(71.9)	(61.6)		(55.6)
Ph α-L-Ara							
2,3-di-bz[b]	99.2	70.8	74.1	66.0	63.5		
3,4-di-bz[b]	102.2	69.6[c]	74.0	69.5[c]	63.5		
	(101.8)	(69.6)	(74.8)	(69.4)	(63.5)		
Me α-D-Xyl							
2,3-di-bz[a]	97.9	73.0	74.8	68.9	62.7		55.1
2,4-di-bz[a]	98.2	74.8	69.1	73.3	59.4		55.4
	(98.3)	(75.5)	(69.4)	(74.1)	(59.3)		(55.3)
Me β-D-Xyl							
2,3-di-bz[a]	102.8	72.9	77.2	68.8	66.9		56.5
	(102.6)[d]	(73.6)[d]	(77.1)[d]	(68.4)[d]	(66.9)[d]		(56.5)[d]
2,4-di-bz[a]	102.4	74.7	71.6	72.9	62.4		56.2
	(102.6)[d]	(75.8)[d]	(72.3)[d]	(73.7)[d]	(63.3)[d]		(56.2)[d]
3,4-di-bz[a]	105.8	72.3	76.0	71.3	63.0		56.9
	(106.1)[d]	(72.8)[d]	(76.3)[d]	(71.3)[d]	(63.3)[d]		(56.9)[d]
Me α-D-Glc							
2,6-di-bz[b]	98.1	75.2	72.4	71.9	71.0	64.9	55.0
	(98.2)	(75.6)	(72.6)	(72.0)	(71.2)	(65.0)	(54.8)
Me β-D-Glc							
2,6-di-bz[b]	102.7	75.3[e]	76.0	71.5	75.6[c]	64.7	56.4
	(102.8)[c]	(74.6)[c]	(76.0)[c]	(71.9)[c]	(75.5)[c]	(64.3)[c]	(56.4)[c]
Me α-D-Gal							
2,3-di-bz[a]	98.3	71.4	72.4	68.2	72.9	61.8	55.0
	(98.3)	(71.5)	(72.4)	(68.0)	(72.5)	(61.9)	(55.1)
2,6-di-bz[a]	98.3	73.3	68.4	70.8	69.5	65.2	55.0
	(98.3)	(73.5)	(68.6)	(71.0)	(69.7)	(65.3)	(55.1)
3,6-di-bz[a]	101.6	68.0	75.4	67.4	69.3	65.1	55.2
	(101.7)	(68.1)	(75.8)	(67.7)	(69.3)	(65.0)	(55.3)
Me β-D-Gal							
3,6-di-bz[b]	105.9	69.3	78.1	67.3	73.3	64.5	56.7
	(106.1)	(69.1)	(78.3)	(67.4)	(73.2)	(64.5)	(56.6)
Me α-D-Man							
2,6-di-bz[a]	99.5	74.1	70.6	68.4	72.1	64.6	54.8
	(100.0)	(74.4)	(70.9)	(68.6)	(72.8)	(65.5)	(54.5)
3,6-di-bz[b]	102.6	69.3	77.0	65.5[c]	72.3	65.1[c]	54.7
	(103.1)	(69.5)	(77.4)	(65.5)	(72.9)	(65.3)	(54.4)

a) Not isolated.
b) Isolated.
c) These data were calculated from the acylation shifts of *O*-myristate (see ref. 4).
d) These were calculated by roughly estimating the shift parameters as 2-bz (C_1 −3.5, C_2 +1.0, C_3 −2.5, C_4 0, C_5 0, OMe 0) and 3-bz (C_1 0, C_2 −2.0, C_3 +1.5, C_4 −2.5, C_5 0, OMe 0).
e) Assignments may reversed in each line.

suggested to be 4-OH>3-OH>2-OH.[14] Direct monobenzoylation also showed that the 4-OH group was the most reactive (Expt. 12).[15] Methods A and B both gave only the 4-*O*-benzoate (**30**) with higher yields (Expt. 10 and 11). Probably because of the lack of formation of a cyclic tin intermediate, both dibutyl and bis(tributyl)tin oxide only enhanced the reactivity of the most reactive 4-OH group.



53 54 56 55

Chart 3

Hexopyranosides

The primary hydroxyl group of carbohydrates is the most reactive to direct acylation.[3a,b] Thus, mono-benzoylation of hexopyranosides with benzoyl chloride always gives the 6-*O*-benzoate as a major product, though the yield is usually low because of appreciable formation of di-*O*-benzoates, which are unavoidable even when a limited amount of acylating reagent is used.

Bis(tributyl)tin oxide enhances the reactivity of the most reactive 6-OH group.[6] Thus method B, except for the case of Me β-D-Gal (**44**), gave 6-*O*-benzoates (**8**, **35**, **40** and **50**) in good yields together with a di-*O*-benzoate. Increasing the amount of acylating agent or elevating the reaction temperature increased the proportion of di-*O*-benzoate, the second benzoyl group being introduced at the equatorial OH group having an axial oxygenated function at the adjacent position. Thus, Ogawa and Matsui[6b] prepared the 3,6-di-*O*-benzoate (**51**) from Me α-D-Man (**48**) in excellent yield by this method.

On the other hand, when Bu_2SnO (method A) is used, the order of reactivity of hydroxyl groups is profoundly changed. Me α-D-Gal (**37**) gave 3-, 2-, and 6-mono-*O*-benzoates (**39**, **38**, and **40**) in the ratio of 51:26:23, where the 3-*O*-benzoate (**39**) was a major product and the 6-*O*-benzoate (**40**) was a minor product, indicating that the reactivity order of OH groups in method A is 3-OH>2-OH>6-OH>4-OH (Expt. 17). On the other hand, the order suggested from the results of direct di- and tri-molar benzoylation[16] and sulfonylation[17] was 6-OH>3-OH >2-OH>4-OH. The above evidence clearly indicates that an equatorial hydroxyl group in a *cis-vic* glycol system is most activated by the formation of a five-membered stannylene ring as an intermediate when Bu_2SnO is used. Puzzlingly, Munavu and Szmant[5a] reported the formation of the 2-*O*-tosylate (**57**) on *p*-toluensulfonylation of the same intermediate, assuming a cyclic tin intermediate between 2-OH and 3-OH, which is stabilized by coordination of the 1α-OMe group (*cf.* **56**). Reinvestigation of their experiment and direct ^{13}C-NMR analysis of

the product revealed that the mono-*O*-tosylate fraction (57%) contained predominantly the 3-*O*-tosylate (**58**), which was only slightly contaminated with other *O*-tosylates.

With method, A, Me β-D-Gal (**44**) gave the 3-*O*-benzoate (**45**) in high yield with excellent selectivity (Expt. 19). Unexpectedly, method B also gave the 3-*O*-benzoate (**45**) though the selectivity was lower (Expt. 20). This was the only exceptional case in which the primary OH group was less reactive in method B.

Me α-D-Man (**48**) gave only the 3-*O*-benzoate (**49**) in the mono-*O*-benzoate fraction with method A (Expt. 21), while method B gave the 6-*O*-benzoate (**50**) as a major product (Expt. 22). Nashed and Anderson[5b] obtained the 2-*O*-benzoate (**60**) as a major product on benzoylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**59**) by the use of Bu_2SnO after repeated chromatography of the reaction mixture, and they claimed that this is an exception where an axial OH group is selectively acylated in preference to an equatorial one in the Bu_2SnO method. In conflict with this result, Nashed[18] later indicated that alkylation of the intermediate tin compound produced the 3-*O*-alkyl ether exclusively. This discrepancy may have been due to acyl migration of the initially formed 3-*O*-benzoate under base catalysis (triethylamine was used in their acylation) or during isolation.

In Me α-D-Glc (**4**), there is no *cis-vic* glycol, and instead 2-OH and 1-OMe are in a *cis* arrangement. Exclusive formation of the 2-*O*-benzoate (**6**) by method A (Expt. 13) strongly suggests that the 2-*O*-tin ester is stabilized by coordination of the neighboring 1α-OMe group to the tin atom.

Me β-D-Glc (**34**) has neither a *cis-vic* glycol nor a *cis* arrangement of OH and OMe; only the most reactive primary OH group was activated by treatment with Bu_2SnO, thus giving rise to the 6-*O*-benzoate (**35**) (Expt. 15).

Mechanism

Chart 4 shows our proposed mechanisms of enhancement of the reactivity of OH groups in methods A and B depending on the stereochemical arrangement of the OH groups. In most cases they are activated through the formation of a cyclic tin intermediate.

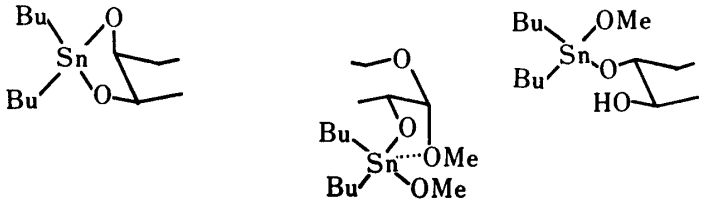
In the Bu_2SnO method, in contrast to Munavu's proposal,[5a] a stannylene ring may not be formed between two vicinal equatorial oxygen atoms. From our experimental results, we propose that stannylene ring formation is most favorable and stable at the *cis-vic* glycol to produce a five-membered ring. Me β-L-Ara (**10**), Ph α-L-Ara (**17**), Me α-D-Gal (**37**), Me β-D-Gal (**44**), and Me α-D-Man (**48**) are examples of this category, where the equatorial OH group is activated without exception. If there is no such sequence available for stannylene ring formation, the tin ester is stabilized by coordinating with the neighboring oxygen atom of the *cis* arrangement. Me α-D-Xyl (**22**) and Me α-D-Glc (**4**) are examples of this type. When neither sequence is available for ring formation, either covalent or coordination, Bu_2SnO only enhances the reactivity of the most reactive OH group. Me β-D-Xyl (**27**) and Me β-D-Glc (**34**) are examples of this.

In contrast, $(Bu_3Sn)_2O$ first enhances the reactivity of the most reactive OH group by forming a tin ether which, of course, is stabilized by coordination with the neighboring oxygen atom of the *cis* arrangement, and the reaction then proceeds in the similar way as for Bu_2SnO. According to Ogawa' ssuggestion[6] a 6-*O*-tin ether formed from a hexopyranoside is stabilized by coordination with the ring oxygen.

Conclusion

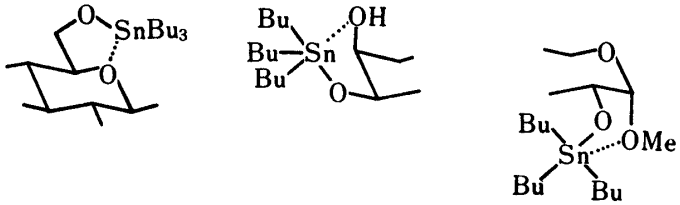
The major advantage of the Bu_2SnO method is that the reagent completely changes the order of reactivity of OH groups and activates a particular secondary OH in a *cis-vic* glycol system even in the presence of a more reactive primary OH group. By applying both methods, Bu_2SnO and $(Bu_3Sn)_2O$, it is possible to introduce an acyl group regioselectively into carbo-

activation of OH by Bu_2SnO



most favorable next most favorable least fgvorable

activation of OH by $(Bu_3Sn)_2O$



most favorable next most favorable least favorable

Chart 4

hydrates without the use of a blocking-deblocking technique. These methods should therefore have great synthetic value for synthetic intermediates and naturally occurring *O*-acylglycosides.

Experimental

General——Melting points were determined on a Yanagimoto micro hot stage melting point apparatus and are uncorrected. The infrared (IR) spectra were taken as KBr discs on a Jasco IR A202 spectrometer and data are given in cm^{-1}. ^1H-NMR (100 MHz) spectra were recorded with a JEOL FX-100 FT NMR spectrometer in pyridine-d_5 solution with tetramethylsilane as an internal standard. Column chromatography was performed on Wakogel C-200 (silica gel). For thin-layer chromatography (TLC), Kieselgel 60 F_{254} precoated plates were used and spots were developed by spraying 1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating the plates at 100°C until coloration took place.

Mono-benzoylation of Pyranosides——Method A (Bu_2SnO Method): Glycopyranoside (2.6—5.2 mmol) and Bu_2SnO (1 mol eq) in dry MeOH (12—20 ml) were heated under reflux until the mixture become homogeneous and clear (about 1 h). The mixture was refluxed for an additional 1 h, then the solvent was evaporated off *in vacuo* to leave a white solid, which was dissolved in dioxane (25—50 ml). Benzoyl chloride (1.1 mol eq) diluted with dioxane (5 ml) was added slowly to the above solution with stirring at room temperature. When the tin complex was insoluble in dioxane (in the cases of Me α-D-Gal (**37**), Me β-D-Gall (**44**), and Me α-D-Man (**48**)), it was suspended in dioxane and benzoyl chloride was added. The solution became clear upon addition of benzoyl chloride. Maximum conversions were checked by TLC. After 2—6 h, the solvent was evaporated off *in vacuo* to leave a syrup, which was subjected to column chromatography for further separation.

Method B [$(Bu_3Sn)_2O$ Method]: Glycopyranoside (2.6—5.2 mmol) was stannylated with $(Bu_3Sn)_2O$ (1—1.5 mol eq) by refluxing the mixture in toluene (25—50 ml) at 140°C for 2 h with continuous azeotropic removal of water. Then benzoyl chloride (1.5—2 mol eq) diluted with toluene (5 ml) was added dropwise (over 5—10 min) to the above solution at 0°C and stirring was continued at the same temperature. When maximum conversion was reached (2—5 h), AcOH (2 ml) was added to the mixture and the solvent was evaporated off *in vacuo* (below 50°C) to leave an oil which was subjected to column chromatography for further separation.

Method C (Direct Benzoylation): Glycopyranoside (0.6—3 mmol) was dissolved in pyridine (5—6 ml) and benzoyl chloride (1—1.5 mol eq) was added at 0°C under stirring. The mixture was brought to room temperature and stirring was continued for 3—48 h. Water was added to the cooled mixture and the whole was extracted three times with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to leave a syrup, which was subjected to chromatographic separation.

^{13}C-NMR Measurement——Natural abundance ^1H noise-decoupled ^{13}C FT NMR (at 25.0 MHz) spectra were recorded on a JEOL FX-100 FT NMR spectrometer using 5 mm spinning tubes at 24.5 °C. Samples

were dissolved in pyridine-d_5. Tetramethylsilane (TMS) served as an internal reference (δ 0). Concentrations were about 0.1—0.3 mmol/ml. FT NMR measurement conditions were as follows: spectral width, 6024 Hz; pulse flipping angle, 45°; acquisition time, 0.6997 s; number of data points, 8192. Accuracies of δ values were thus about ± 0.1 ppm.

Analysis of the mono-*O*-benzoate(s) was done by the use of known acylation shifts in relation to the spectrum of the non-acylated compound(s), and that of di-*O*-benzoate(s) was done by applying the additivity rule of shift parameters.

Product Analysis——The products obtained by one of the above procedures usually showed spots on TLC corresponding to the starting material, and mono- and di-*O*-benzoates. The product from each method was chromatographed (repeatedly if necessary); elution was carried out with benzene containing increasing amounts of ethyl acetate and finally with ethyl acetate. Mono-*O*-benzoate(s) (less mobile) and di-*O*-benzoate(s) (more mobile) fractions thus obtained were each subjected to ^{1}H-NMR and ^{13}C-NMR measurements, and gas chromatography (as TMS derivatives[4]) which allowed identification of each component of the mono- and di-*O*-benzoate fractions and determination of the composition. If the components showed separated spots on TLC, they were again chromatographed, and the resulting separated components were crystallized (where possible) from an appropriate solvent to give the pure compound. The homogeneity of the compounds thus obtained was confirmed by ^{13}C-NMR, ^{1}H-NMR, and TLC.

Methyl β-L-Arabinopyranoside (10)——3-*O*-Benzoate (**12**): Amorphous powder. NMR δ: 5.90 (1H, dd, J=3.4 and 9.1 Hz, H-3), 5.22 (1H, d, J=3.5 Hz, H-1), 4.81—5.12 (1H, H-4), 3.44 (3H, s, OMe).

2,3-Di-*O*-benzoate (**14**): Needles from EtOAc–light petroleum, mp 146—148°C. NMR δ: 6.43 (1H, dd, J=3.5 and 10.5 Hz, H-2), 6.15 (1H, dd, J=2.9 and 10.5 Hz, H-3), 5.50 (1H, d, J=3.5 Hz, H-1), 4.75—4.79 (1H, H-4), 3.88—4.16 (2H, H_2-5), 3.41 (3H, s, OMe). *Anal.* Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.23; H, 5.28. The following compounds were formed but not isolated: 2-*O*-benzoate (**11**), 4-*O*-benzoate (**13**), 2,4-di-*O*-benzoate (**15**), and 3,4-di-*O*-benzoate (**16**). These products showed an OMe peak at δ 3.38, 3.42, 3.39, and 3.43, respectively.

Phenyl α-L-Arabinopyranoside (17)[19]——3-*O*-Benzoate (**18**): Leaflets from CH_2Cl_2–*n*-hexane, mp 149—151°C. NMR δ: 5.91 (1H, dd, J=3.5 and 8.2 Hz, H-3), 5.69 (1H, d, J=5.6 Hz, H-1), 4.44 (1H, dd, J=4.9 and 12.0 Hz, H-5), 4.08 (1H, dd, J=2.5 and 12.0 Hz, H-5). IR: 3500, 1700, 1280. *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.38; H, 5.49.

4-*O*-Benzoate (**19**): Needles from CH_2Cl_2–light petroleum, mp 135—140°C. NMR δ: 5.80—6.00 (1H, H-4), 5.52 (1H, d, J=7.2 Hz, H-1), 4.52 (1H, dd, J=3.2 and 9.2 Hz, H-3), 4.44 (1H, dd, J=2.5 and 13.0 Hz, H-5), 4.06 (1H, dd, J=1.5 and 13.0 Hz, H-5). IR: 3540, 1725, 1280, 1225. *Anal.* Calcd for $C_{18}H_{18}O_6 \cdot 1/2H_2O$: C, 63.71; H, 5.64. Found: C, 63.88; H, 5.71.

3,4-Di-*O*-benzoate (**21**): Needles from iso-Pr_2O–light petroleum, mp 139—140°C. NMR δ: 6.15 (1H, dd, J=3.5 and 8.2 Hz, H-3), 5.74 (1H, d, J=6.5 Hz, H-1), 4.80—5.08 (1H, H-4), 4.49 (1H, dd, J=2.5 and 12.5 Hz, H-5), 4.20 (1H, dd, J=1.5 and 12.5 Hz, H-5). IR: 3350, 1720, 1280, 1225. *Anal.* Calcd for $C_{25}H_{22}O_7$: C, 69.11; H, 5.10. Found: C, 69.08; H, 5.03. The following compound was formed but not isolated: 2,3-di-*O*-benzoate (**20**), NMR δ: 5.84 (1H, d, J=6.2 Hz, H-1).

Methyl α-D-Xylopyranoside (22)——2-*O*-Benzoate (**23**): Prisms from iso-Pr_2O–*n*-hexane, mp 116.5—118°C (lit.[13] syrup). NMR δ: 5.55 (1H, dd, J=3.7 and 10 Hz, H-2), 5.31 (1H, d, J=3.7 Hz, H-1), 4.69 (1H, t, J=8.5 Hz, H-3), 3.38 (3H, s, OMe). IR: 3400, 2875, 1680, 1275. *Anal.* Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.93; H, 6.05.

4-*O*-Benzoate (**24**): Needles from AcOEt–*n*-hexane, mp 130—131°C. NMR δ: 5.50—5.75 (1H, H-4), 5.10 (1H, d, J=3.5 Hz, H-1), 4.67 (1H, t, J=8.9 Hz, H-3), 3.45 (3H, s, OMe). IR: 3500, 1705, 1320, 1280. *Anal.* Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.90; H, 5.99. The following compounds were formed but not isolated: 2,3-di-*O*-benzoate (**25**) and 2,4-di-*O*-benzoate (**26**). These products showed an OMe peak at δ 3.41 and 3.36, respectively.

Methyl β-D-Xylopyranoside (27)——4-*O*-Benzoate (**30**): Needles from AcOEt–light petroleum, mp 125—126°C. NMR δ: 5.48—5.79 (1H, H-4), 4.68 (1H, d, J=8.9 Hz, H-1), 3.59 (3H, s, OMe). IR: 3500, 3200, 1720, 1265. *Anal.* Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.95; H, 6.03. The following compounds were formed but not isolated: 2-*O*-benzoate (**28**), 3-*O*-benzoate (**29**), 2,3-di-*O*-benzoate (**31**), 2,4-di-*O*-benzoate (**32**), and 3,4-di-*O*-benzoate (**33**). These products showed an OMe peak at δ 3.50, 3.59, 3.51, 3.59, and 3.48, respectively.

Methyl α-D-Glucopyranoside (4)——2-*O*-Benzoate (**6**): Prisms from AcOEt–light petroleum, mp 177—179°C (lit. mp 179—180°C,[5a] 174—175°C[20]).

6-*O*-Benzoate (**8**): Prisms from AcOEt–light petroleum, mp 135—137°C (lit.[20] mp 127—129°C).

2,6-Di-*O*-benzoate (**9**): Needles from $CHCl_3$–*n*-hexane, mp 141—142°C (lit. mp 142—143°C,[13] 140—142°C[6b]).

Methyl β-D-Glucopyranoside (34)——6-*O*-Benzoate (**35**): Leaflets from AcOEt–light petroleum, mp 136—138°C (lit.[20] mp 131—132°C).

2,6-Di-*O*-benzoate (**36**): Needles from CH_2Cl_2–iso-Pr_2O, mp 170—172°C (lit.[21] mp 177—178°C).

Methyl α-D-Galactopyranoside (37)——6-*O*-Benzoate (**40**): Needles from AcOEt–light petroleum, mp 154—156°C (lit.[6a] mp 152—154°C). The following compounds were formed but not isolated: 2-*O*-benzoate

(**38**), 3-*O*-benzoate (**39**), 3,6-di-*O*-benzoate (**43**), and (2,3 and 2,6)-di-*O*-benzoates (**41** and **42**). These products showed an OMe peak at δ 3.41, 3.47, 3.49, and 3.45, respectively.

Methyl β-D-Galactopyranoside (**44**)——3-*O*-Benzoate (**45**):[22] Needles from AcOEt–light petroleum, mp 127—128°C. NMR δ: 5.60—5.80 (1H, H-3), 4.40 (1H, d, J=6.1 Hz, H-1), 3.64 (3H, s, OMe). IR: 3375, 1700, 1280. *Anal.* Calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.15; H, 6.06.

3,6-Di-*O*-benzoate (**47**): Crystals from AcOEt–light petroleum, mp 135—136°C (lit.[6b] mp 132—133°C). NMR δ: 5.62—5.92 (1H, H-3), 3.64 (3H, s, OMe). The following compound was formed but not isolated: 6-*O*-benzoate (**56**). It showed an OMe peak at δ 3.61.

Methyl α-D-Mannopyranoside (**48**)——3-*O*-Benzoate (**49**): Syrup. δ 6.07 (1H, dd, J=3.1 and 9.7 Hz, H-3), 5.18 (1H, d, J=2.0 Hz, H-1), 3.14 (3H, s, OMe).

3,6-Di-*O*-benzoate (**51**): Needles from AcOEt–light petroleum, mp 133—135°C (lit.[6b] mp 134—136°C). δ 6.11 (1H, dd, J=3.4 and 9.5 Hz, H-3), 3.42 (3H, s, OMe). The following compounds were formed but not isolated: 6-*O*-benzoate (**50**), and 2,6-di-*O*-benzoate (**52**). These products showed an OMe peak at δ 3.39 and 3.37, respectively.

Tosylation of Methyl α-D-Galactopyranoside (**37**) **by Method A**——Me α-D-Gal (0.5 g, 2.58 mmol) and Bu_2SnO (0.6 g, 2.58 mmol) in MeOH (12 ml) were heated under reflux for 1.5 h. Evaporation of the solvent *in vacuo* at 50°C from the mixture left a glassy solid which was suspended in dioxane (25 ml). *p*-Toluenesulfonyl chloride (0.5 g, 2.84 mmol) was added slowly to the stirred mixture at room temperature. Maximum conversion was checked by TLC. After 6 h, the solvent was evaporated off *in vacuo* to leave a syrup, which was subjected to column chromatography. Elution was carried out with benzene containing increasing amounts of ethyl acetate and finally with ethyl acetate. The benzene–ethyl acetate (1: 1) fraction gave a di-*O*-tosylate mixture (0.14 g, 10.3%) as a syrup, which was not further investigated. The ethyl acetate fraction gave the mono-*O*-tosylate (0.5 g, 56.4%), which was proved to be almost entirely 3-*O*-tosylate (>95 %). On keeping the product in MeOH, the 3-*O*-tosylate (**58**) crystallized out as prisms, mp 152—155°C. IR: 3300, 1450, 1335. ^{1}H-NMR δ_H: 8.06 (2H, d, J=8.3 Hz, ArH), 7.08 (2H, d, J=8.3 Hz, ArH), 5.42 (1H, dd, J=2.9 and 10 Hz, H-3), 5.17 (1H, d, J=3.7 Hz, H-1), 3.36 (3H, s, OMe), 2.08 (3H, s, ArMe). ^{13}C-NMR δ_C: 101.5 (C-1), 69.0 (C-2), 83.8 (C-3), 67.2 (C-4), 72.3 (C-5), 61.8 (C-6), 55.0 (OMe). *Anal.* Calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79. Found: C, 48.24; H, 5.76.

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