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Regioselective Monoalkylation of Non-protected Glycopyranosides by the Dibutyltin Oxide Method[1)]

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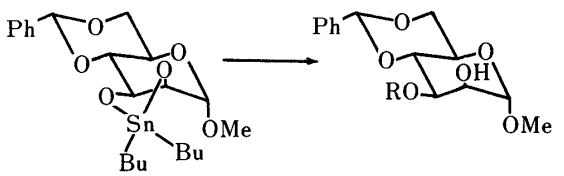
Regioselective monoalkylation of some pento- and hexopyranosides (Me β-L-Ara, Ph α-L-Ara, Me α-D-Xyl, Me β-D-Xyl, Me α-D-Glc, Me β-D-Glc, Me α-D-Gal, Me β-D-Gal, and Me α-D-Man) was examined by using the dibutyltin oxide method without protecting the hydroxyl groups. By this method, alkylation proceeds more or less in the same fashion as reported for acylation (through the formation of cyclic tin intermediates) and selectively activates an equatorial hydroxyl group which has an oxygenated function (OH or OMe) in a *cis* relationship at an adjacent position, even in the presence of a more reactive primary hydroxyl group. However, in some instances the position of activation is different. Various monoalkyl ethers thus prepared were identified by analyses of their carbon-13 nuclear magnetic resonance spectra.

Keywords——regioselective monoalkylation; glycopyranoside; dibutyltin oxide; *cis*-vicinal glycol; benzylation; allylation; methoxymethylation; methylation; ^{13}C-NMR

Introduction

Regioselective alkylation of sugar derivatives is of growing importance in the field of carbohydrate chemistry because of its usefulness for providing synthetic intermediates as protected units for polysaccharide and glycoprotein syntheses.[2a)] Usually, this is achieved by the following three successive procedures: protection of more reactive hydroxyl groups, alkylation with excess of an alkylating agent, and deprotection. However, in most cases the overall yields of the desired products are not satisfactory. A more efficient method, such as direct regioselective monoalkylation, is therefore needed.

The use of tin intermediates seems to be one of the most promising methods, since it was indicated that various tin ethers are formed regioselectively with enhanced reactivity of a particular hydroxyl group of a carbohydrate.[3)] For example, syntheses of some 3-alkyl ethers of partially protected methyl α-D-mannopyranoside were reported by Nashed,[3a)] who obtained the 3-benzyl, allyl, and methyl ethers (**2**) in 85, 79, and 76% yields, respectively, by treatment of methyl 4,6-benzylidene-α-D-mannopyranopyranoside with dibutyltin oxide



1 **2**: R = $PhCH_2$, $CH_2=CH-CH_2$, and CH_3

Chart 1

(Bu_2SnO) and subsequent alkylation with the appropriate alkyl halides in dimethylformamide (DMF). In this case, exclusive formation of the 3-alkyl ether was explained in terms of a five-membered cyclic tin intermediate (**1**) involving the *cis*-vicinal 2- and 3-hydroxyl groups, in which the reactivity of the equatorial 3-hydroxyl group is enhanced much more than that of the axial 2-hydroxyl group (Chart 1).

Ogawa *et al.*[2] reported the use of bis(tributyl)tin oxide [$(Bu_3Sn)_2O$] for selective alkylation of some glycopyranosides, but this method was found to be appropriate for the preparation of dialkyl ethers.

In a previous paper,[4] we reported the regioselective monoacylation of non-protected glycopyranosides by using the Bu_2SnO and $(Bu_3Sn)_2O$ methods. Of these, activation of hydroxyl groups by the Bu_2SnO method is particularly interesting, since this method permits the selective acylation of a particular secondary hydroxyl group of a pyranoside without the need to protect a more reactive primary hydroxyl group. It is expected that alkylation also occurs in a similar fashion. Therefore, the application of this method for the alkylation of non-protected glycopyranosides is of particular interest.

In this paper we describe the regioselective monoalkylation of non-protected glycopyranosides (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 β-D-Man)[5] by using the Bu_2SnO method.

Results and Discussion

In order to select the reaction conditions for non-protected sugars, methyl α-D-glucopyranoside was chosen as a substrate and alkylation was performed by using various solvents and at different temperatures (Table I). As the alkylating agents, benzyl bromide, allyl bromide, methoxymethyl chloride, and methyl iodide were used, since the benzyl group can be easily removed by hydrogenolysis over palladium, the allyl group by rhodium-catalyzed isomerization followed by mild acid hydrolysis, and the methoxymethyl group by acidic hydrolysis.[6] Methylation was performed since the monomethyl derivatives are helpful for analysis of various alkyl ethers.

Stannylation was carried out as described in a previous paper.[4] Compared with acylation, alkylation of the tin intermediate is slow and requires an excess of alkylating agent, a longer reaction time and a higher temperature.

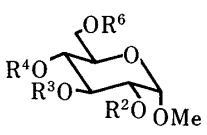
When benzylation of the tin intermediate of methyl α-D-glucopyranoside (**3**) was carried out under Nashed's conditions: *i.e.*, in dimethylformamide (DMF) at 100 °C, it was difficult to control the reaction and appreciable formation of dibenzyl ether was observed, even though

TABLE I. Alkylation of Methyl α-D-Glucopyranoside (**3**) by the Bu_2SnO Method

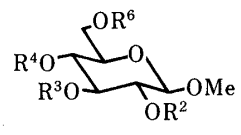
Reagent	eq mol	Solvent	Bath temp. (°C)	Time (h)	Monoalkyl deriv. (yield %)	Composition[a] 2-	3-	Dialkyl deriv. (yield %)
$PhCH_2Br$	6	DMF	100	8.0	Nil			32 (mix.)
$PhCH_2Br$	6	Dioxane	100	3.5	73.1	75	25	23 (mix.)
$PhCH_2Br$	6	CH_3CN	100	15.0	62.0	90	10	9 (mix.)
$CH_2=CHCH_2Br$	8	Dioxane	100	5.0	74.8	79	21	Trace
$CH_2=CHCH_2Br$	9	CH_3CN	100	20.0	46.0	100	Trace	3 (mix.)
CH_3OCH_2Cl	1.5	Dioxane	50	3.0	75.8	80	20	10 (2, 3)
CH_3OCH_2Cl	6	CH_3CN	0	1.0	36.0	100	Trace	14 (mix.)
CH_3I	18	Dioxane	100	16.0	72.6	56	44	20 (2, 3)

a) Composition of monoalkyl ethers was determined either from the OMe peak areas (^{1}H-NMR) or from the C-1 peak intensity (^{13}C-NMR).

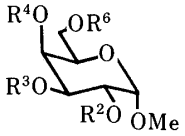
the reaction was not complete. Even at lower temperatures, formation of dibenzyl ethers was more favorable than monobenzyl ethers. When the solvent was changed to acetonitrile, benzylation proceeded selectively to give the 2-benzyl ether (**4a**) as the major product, and in the case of allylation and methoxymethylation only the 2-alkyl ethers (**7** and **9**) were formed,



	R^2	R^3	R^4	R^6
3:	H	H	H	H
4a:	Bn	H	H	H
4b:	Bn	Ac	Ac	Ac
5a:	H	Bn	H	H
5b:	Ac	Bn	Ac	Ac
6:	H	H	Bn	H
7:	All	H	H	H
8:	H	All	H	H
9:	MM	H	H	H
10:	H	MM	H	H
11:	MM	MM	H	H
12:	Me	H	H	H
13:	H	Me	H	H
14:	Me	Me	H	H

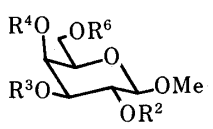


	R^2	R^3	R^4	R^6
22:	H	H	H	H
23a:	Bn	H	H	H
23b:	Bn	Ac	Ac	Ac
24:	H	Bn	H	H
25:	H	H	Bn	H
26:	H	H	H	Bn
27:	Bn	H	H	Bn
28:	MM	H	H	H
29:	H	MM	H	H
30:	H	H	H	MM
31:	Me	H	H	H
32:	H	Me	H	H
33:	H	H	H	Me

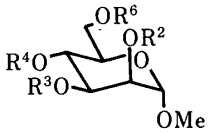


	R^2	R^3	R^4	R^6
37:	H	H	H	H
38:	H	Bn	H	H
39:	H	MM	H	H

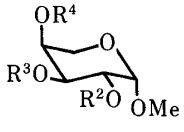
Bn: $C_6H_5CH_2-$
All: $CH_2=CHCH_2-$
MM: CH_3OCH_2-



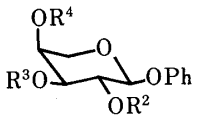
	R^2	R^3	R^4	R^6
40:	H	H	H	H
41:	H	Bn	H	H
42:	H	MM	H	H



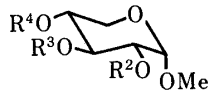
	R^2	R^3	R^4	R^6
43:	H	H	H	H
44:	Bn	H	H	H
45:	H	Bn	H	H
46:	MM	H	H	H
47:	H	MM	H	H
48:	MM	MM	H	H
49:	H	MM	MM	H



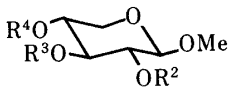
	R^2	R^3	R^4
50:	H	H	H
51:	H	Bn	H
52:	H	H	Bn
53:	H	MM	H
54:	H	H	MM
55:	MM	MM	H
56:	H	MM	MM



	R^2	R^3	R^4
57:	H	H	H
58:	H	Bn	H
59:	H	MM	H



	R^2	R^3	R^4
60:	H	H	H
61:	Bn	H	H
62:	H	Bn	H
63:	H	H	Bn
64:	All	H	H
65:	H	All	H
66:	H	H	All
67:	MM	H	H
68:	H	MM	H
69:	H	H	MM
70:	Me	H	H
71:	H	H	Me

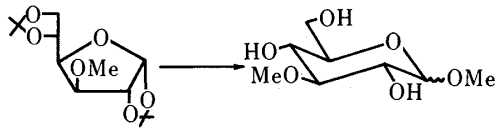


	R^2	R^3	R^4
74:	H	H	H
75a:	Bn	H	H
75b:	Bn	Ac	Ac
76a:	H	H	Bn
76b:	Ac	Ac	Bn
77a:	MM	H	H
77b:	MM	Ac	Ac
78:	H	MM	H
79a:	H	H	MM
79b:	Ac	Ac	MM

Chart 2

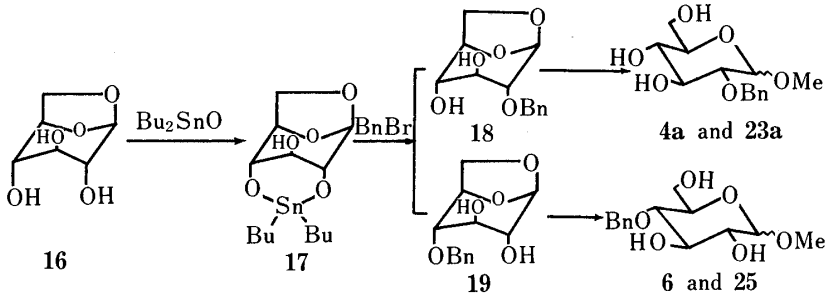
but the yields were not satisfactory (see Table I). On the other hand, when dioxane was used as the solvent, though the selectivity was a little inferior to that in acetonitrile, the monoalkyl ethers were obtained in higher yields. Therefore, dioxane was used as the solvent for the other substrates.

Identification of each product and determination of the product compositions were done as reported previously,[4] by analysis of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra. In most cases the mixtures of monoalkyl ethers obtained by the reaction could be



15 **13** and **32**

Chart 3



16 **17** **18** **19** **4a** and **23a** **6** and **25**

Chart 4

TABLE II. Alkylation of Some Glycopyranosides by Using the Bu_2SnO Method in Dioxane

Substrate	Reagent	eq mol	Temp. (°C)	Time (h)	Monoalkyl deriv. (yield %)	Composition 2-	3-	4-	6-	Dialkyl deriv. (yield %)
Me β-D-Glc	a) $PhCH_2Br$	6.0	100	5.0	61.9	49	13	—	38	Trace (2, 6)
(**22**)	b) CH_3OCH_2Cl	2.0	50	3.0	70.4	49	23	—	28	17.0 (mix.)
	c) CH_3I	18.0	100	16.0	56.7	10	17	—	73	Nil
Me α-D-Gal	a) $PhCH_2Br$	12.0	100	6.0	71.3	—	100	—	—	Nil
(**37**)	b) CH_3OCH_2Cl	1.5	50	1.5	89.6	—	100	—	—	Nil
Me β-D-Gal	a) $PhCH_2Br$	6.0	100	5.0	95.2	—	100	—	—	Nil
(**40**)	b) CH_3OCH_2Cl	1.5	50	1.0	93.0	—	100	—	—	Trace
Me α-D-Man	a) $PhCH_2Br$[a]	6.0	100	4.0	59.2	20	80	—	—	17.7 (mix.)
(**43**)	b) CH_3OCH_2Cl	1.5	50	2.0	76.5	39	61	—	—	20.5 (2, 3+3, 6)
Me α-D-Xyl	a) $PhCH_2Br$	6.0	100	2.5	96.8	59	6	35		Nil
(**60**)	b) $CH_2=CHCH_2Br$	8.5	100	3.5	76.2	62	8	30		Nil
	c) CH_3OCH_2Cl	2.0	50	1.5	89.3	56	13	31		Nil
	d) CH_3I	30.0	100	16.0	65.5	57	—	43		Nil
Me β-D-Xyl	a) $PhCH_2Br$	24.0	100	12.0	70.0	—	—	100		Nil
(**74**)	$PhCH_2Br$[a]	6.0	100	1.0	70.0	50	Trace	50		Trace (mix.)
	b) CH_3OCH_2Cl	2.0	50	1.0	80.4	51	7	42		17.0 (mix.)
Me β-L-Ara	a) $PhCH_2Br$	12.0	100	5.0	92.1	—	85	15		Nil
(**50**)	b) CH_3OCH_2Cl	2.0	50	1.3	81.5	—	74	26		18.0 (2, 3+3, 4)
Ph α-L-Ara	a) $PhCH_2Br$	18.0	100	12.0	73.5	—	100	—		Nil
(**57**)	b) CH_3OCH_2Cl	1.5	50	2.5	85.5	—	100	—		Nil

a) DMF was used as the solvent. In dioxane and with 6 mol eq of the reagent, the reaction did not proceed.

TABLE III. ^{13}C-Chemical Shifts of Mono-*O*-alkyl Ethers of Some Hexopyranosides and Their Alkylation Shift Values (in Parentheses) in Pyridine-d_5

Monoalkyl ethers	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3	OCH_3	OCH_2–R
Me α-D-Glc (**3**)	101.3	73.7	75.3	72.0	74.0	62.7	55.0		
2-Bn-ether (**4a**)	98.9	81.3	72.9	72.0	73.9	62.8	54.9		74.7
	(−2.4)	(+7.6)	(−2.4)	(±0)	(−0.1)	(+0.1)			
3-Bn-ether (**5a**)	101.3	73.3	84.1	71.0	73.9	62.4	54.9		75.1
	(±0)	(−0.4)	(+8.8)	(−1.0)	(−0.1)	(−0.3)			
4-Bn-ether[a] (**6**)	101.3	74.0	74.9	79.6	72.9	62.1	55.0		75.4
	(±0)	(+0.3)	(−0.4)	(+7.6)	(−1.1)	(−0.6)			
2-All-ether (**7**)	98.8	80.7	73.7	71.9	74.0	62.6	54.8		71.8
	(−2.5)	(+7.0)	(−1.6)	(−0.1)	(±0)	(−0.1)			
3-All-ether (**8**)	101.3	73.2	83.6	71.0	73.9	62.4	58.8		74.0
	(±0)	(−0.5)	(+8.3)	(−1.0)	(−0.1)	(−0.3)			
2-MM-ether (**9**)	100.0	80.2	73.7[c]	71.9	73.8[c]	62.6	55.0	54.8	97.7
	(−1.3)	(+6.5)	(−1.6)	(−0.1)	(−0.2)	(−0.1)			
3-MM-ether (**10**)	101.3	73.0	81.8	70.8	74.0	62.4	54.9	55.6	98.1
	(±0)	(−0.7)	(+6.5)	(−1.2)	(±0)	(−0.3)			
2-Me-ether (**12**)	98.3	82.8	74.0	71.9	74.0	62.7	54.8	58.4	
	(−3.0)	(+9.1)	(−1.3)	(−0.1)	(±0)	(±0)			
3-Me-ether (**13**)	101.4	73.4	85.8	71.0	74.1	62.5	55.0	61.0	
	(+0.1)	(−0.3)	(+10.5)	(−1.0)	(+0.1)	(−0.2)			
Me β-D-Glc (**22**)	105.5	74.9	78.2	71.4	78.2	62.6	56.7		
2-Bn-ether (**23a**)	105.2	83.1	77.5	71.2	78.1	62.5	56.6		74.6
	(−0.3)	(+8.2)	(−0.7)	(−0.2)	(−0.1)	(−0.1)			
3-Bn-ether (**24**)	105.4	74.8	86.7	70.6	78.0	62.3	56.6		75.1
	(−0.1)	(−0.1)	(+8.5)	(−0.8)	(−0.2)	(−0.3)			
4-Bn-ether[a] (**25**)	105.5	74.9	78.3	79.2	77.2	62.1	56.7		75.4
	(±0)	(±0)	(+0.1)	(+7.8)	(−1.0)	(−0.5)			
6-Bn-ether (**26**)	105.4	74.7	78.2	71.3	76.9	70.8	56.6		73.4
	(−0.1)	(−0.2)	(±0)	(−0.1)	(−1.3)	(+8.2)			
2-MM-ether (**28**)	104.7	78.9	77.2	71.5	78.2	62.4	56.7	55.7	97.1
	(−0.8)	(+4.0)	(−1.0)	(+0.1)	(±0)	(−0.2)			
3-MM-ether (**29**)	105.5	74.4	84.2	70.5	78.1	62.5	56.6	55.6	98.1
	(±0)	(−0.5)	(+6.0)	(−0.9)	(−0.1)	(−0.1)			
6-MM-ether (**30**)	105.5	74.8	78.3	71.3	76.6	67.8	56.6	54.9	96.6
	(−0.1)	(−0.1)	(+0.1)	(−0.1)	(−1.6)	(+5.2)			
2-Me-ether[a] (**31**)	105.2	84.9	77.5	71.4	78.1	62.5	56.6	60.6	
	(−0.3)	(+10.0)	(−0.7)	(±0)	(−0.1)	(−0.1)			
3-Me-ether (**32**)	105.5	74.6	88.4	70.6	78.1	62.4	56.7	60.9	
	(±0)	(−0.3)	(+10.2)	(−0.8)	(−0.1)	(−0.2)			
6-Me-ether (**33**)	105.4	74.8	78.3	71.3	76.9	72.9	56.7	59.1	
	(−0.1)	(−0.1)	(+0.1)	(−0.1)	(−1.3)	(+10.3)			
Me α-D-Gal (**37**)	101.5	70.3	71.5	70.8	72.4	62.5	55.0		
3-Bn-ether (**38**)	101.6	67.5	79.9	69.3	72.5	62.4	55.0		71.4
	(+0.1)	(−2.8)	(+8.4)	(−1.5)	(+0.1)	(−0.1)			
3-MM-ether (**39**)	101.5	68.8	77.7	68.8	72.3	62.3	55.0	55.2	96.3
	(±0)	(−1.5)	(+6.2)	(−2.0)	(−0.1)	(−0.2)			
Me β-D-Gal (**40**)	106.1	72.3	75.1	70.1	76.8	62.2	56.6		
3-Bn-ether (**41**)	106.0	71.2	83.0	66.7	76.6	62.1	56.6		71.8
	(−0.1)	(−1.1)	(+7.9)	(−3.4)	(−0.2)	(−0.1)			
3-MM-ether (**42**)	106.0	70.9	80.4	68.1	76.5	62.1	56.7	55.2	96.3
	(−0.1)	(−1.4)	(+5.3)	(−2.0)	(−0.3)	(−0.1)			
Me α-D-Man[b] (**43**)	102.5	71.9	72.9	68.9	75.1	63.1	54.4		
2-Bn-ether[a] (**44**)	102.3	77.3	69.4	69.0	75.4	63.1	54.5		71.9
	(−0.2)	(+5.4)	(−3.5)	(+0.1)	(+0.3)	(±0)			
3-Bn-ether (**45**)	102.6	68.6	81.3	67.5	75.2	63.0	54.5		73.0
	(+0.1)	(−3.3)	(+8.4)	(−1.4)	(+0.1)	(−0.1)			
2-MM-ether[a] (**46**)	100.9	78.2	72.2	69.0	75.2	62.9	54.5	55.2	97.7
	(−1.6)	(+6.3)	(−0.7)	(+0.1)	(+0.1)	(−0.2)			
3-MM-ether[a] (**47**)	102.5	70.1	79.1	67.2	75.2	62.9	54.5	55.3	96.6
	(±0)	(−1.8)	(+6.2)	(−1.7)	(+0.1)	(−0.2)			

a) These compounds were not isolated in pure form. *b*) The reported data are within ±0.1 ppm for all peaks except for Me α-D-Man (C_1 102.3, C_2 71.8, C_3 72.8, C_4 68.9, C_5 74.7, C_6 62.8, and OMe 54.6).[12] *c*) Assignments may be interchanged.

TABLE IV. ^{13}C-Chemical Shifts of Mono-*O*-alkyl Ethers of Some Pentopyranosides and Their Alkylation Shift Values (in Parentheses) in Pyridine-d_5

Monoalkyl ethers	C-1	C-2	C-3	C-4	C-5	OCH_3	OCH_3	OCH_2–R
Me α-D-Xyl (**60**)	101.5	73.7	75.5	71.4	63.1	55.1		
2-Bn-ether[a] (**61**)	99.1	81.0	73.0	71.3	62.7	54.9		74.3
	(−2.4)	(+7.3)	(−2.5)	(−0.1)	(−0.4)	(−0.2)		
3-Bn-ether[a] (**62**)	101.4	71.8	84.1	70.7	62.8	55.4		74.3
	(−0.1)	(−1.9)	(+8.6)	(−0.7)	(−0.3)	(+0.3)		
4-Bn-ether[a] (**63**)	101.3	73.5	73.2	79.3	60.5	54.9		74.3
	(−0.2)	(−0.2)	(−2.3)	(+7.9)	(−2.6)	(−0.2)		
2-All-ether[a] (**64**)	99.2	80.9	72.2	71.5	62.8	54.9		
	(−2.3)	(+7.2)	(−3.3)	(+0.1)	(−0.3)	(−0.2)		
3-All-ether[a] (**65**)	101.5	71.9	83.6	70.7	63.2	55.1		
	(±0)	(−1.8)	(+8.1)	(−0.7)	(+0.1)	(±0)		
4-All-ether[a] (**66**)	101.4	73.7	73.2	79.1	60.6	55.1		
	(−0.1)	(±0)	(−2.3)	(+7.7)	(−2.5)	(±0)		
2-MM-ether[a] (**67**)	100.2	80.1	73.8	71.4	62.6	55.0	55.2	97.8
	(−1.3)	(+6.4)	(−1.7)	(±0)	(−0.5)	(−0.1)		
3-MM-ether[a] (**68**)	101.4	72.7	81.4	70.4	62.9	55.1	55.5	97.9
	(−0.1)	(−1.0)	(+5.9)	(−1.0)	(−0.2)	(±0)		
4-MM-ether[a] (**69**)	101.2	73.8	73.5	78.0	61.0	55.0	55.2	97.4
	(−0.3)	(+0.1)	(−2.0)	(+6.6)	(−2.1)	(−0.1)		
2-Me-ether (**70**)	98.5	82.7	74.2	71.4	62.7	54.9	58.5	
	(−3.0)	(+9.0)	(−1.3)	(±0)	(−0.4)	(−0.2)		
4-Me-ether[a] (**71**)	101.3	73.5	74.1	80.9	60.1	55.1	58.9	
	(−0.2)	(−0.2)	(−1.4)	(+9.5)	(−3.0)	(±0)		
Me β-D-Xyl (**74**)	106.0	74.6	78.1	70.9	67.0	56.6		
2-Bn-ether[a] (**75a**)	105.9	83.2	77.7	71.1	67.1	56.6		74.9
	(−0.1)	(+8.6)	(−0.4)	(+0.2)	(+0.1)	(±0)		
4-Bn-ether (**76a**)	106.0	74.7	77.2	78.9	64.5	56.6		73.1
	(±0)	(+0.1)	(−0.9)	(+8.0)	(−2.5)	(±0)		
2-MM-ether[a] (**77a**)	105.4	78.9	77.5	71.1	67.0	56.7	55.2	97.2
	(−0.6)	(+4.3)	(−0.6)	(+0.2)	(±0)	(+0.1)		
3-MM-ether[a] (**78**)	106.0	73.9	83.4	70.1	66.8	56.6	55.6	97.8
	(±0)	(−0.7)	(+5.3)	(−0.8)	(−0.2)	(±0)		
4-MM-ether[a] (**79a**)	106.0	74.8	76.6	77.5	65.1	56.5	55.2	97.2
	(±0)	(+0.2)	(−1.5)	(+6.6)	(−1.9)	(−0.1)		
Me β-L-Ara (**50**)	102.0	70.4	70.8	70.0	63.8	55.3		
3-Bn-ether (**51**)	102.1	69.3	79.1	67.4	63.9	55.3		72.0
	(+0.1)	(−1.1)	(+8.3)	(−2.6)	(+0.1)	(±0)		
4-Bn-ether[a] (**52**)	102.1	70.8	67.5	78.3	60.9	55.3		72.3
	(+0.1)	(+0.4)	(−3.3)	(+8.3)	(−2.9)	(±0)		
3-MM-ether[a] (**53**)	102.0	68.8	76.6	68.4	63.9	55.2	55.2	96.3
	(±0)	(−1.6)	(+5.8)	(−1.6)	(+0.1)	(−0.1)		
4-MM-ether[a] (**54**)	101.9	70.6[b]	70.3[b]	76.4	62.1	55.1	55.4	96.8
	(−0.1)	(+0.2)	(−0.5)	(+6.4)	(−1.7)	(−0.2)		
Ph α-L-Ara (**57**)	102.7	72.0	74.4	69.3	67.2			
3-Bn-ether (**58**)	102.6	70.7	81.9	66.4	67.0			72.2
	(−0.1)	(−1.3)	(+7.5)	(−2.9)	(−0.2)			
3-MM-ether (**59**)	102.6	70.6	79.5	67.4	67.0		55.3	96.6
	(−0.1)	(−1.4)	(+5.1)	(−1.9)	(−0.2)			

a) These compounds were not isolated in pure form. *b*) Assignments may be interchanged.

completely analyzed by taking account of the deshielding of the substituted carbon atom due to the α-effect of alkylation[7] and the shielding due to the β-effect of alkylation[2d] at the neighboring carbon atoms in comparison with those of the non-alkylated compounds (see Tables III and IV). However, in some instances the shielding effect of an alkyl group on the neighboring carbon atoms is too small to permit unambiguous identification of the components. For example, the 3-alkyl ethers (**5a**, **8**, **10**, and **13**) of methyl α-D-glucopyranoside (**3**) and the 2-alkyl ethers (**23a** and **28**) of methyl β-D-glucopyranoside (**22**) can hardly be distinguished from the 4-alkyl ethers (**6** and **25**) of the same compounds, based only on their ^{13}C-NMR data. In such cases, detailed examination of the proton nuclear magnetic resonance (^{1}H-NMR) spectra of the acetyl derivatives is sometimes useful for identification of the product, since the coupling pattern of the methine protons in the acetates is more easily analyzed than that of the non-acetylated compounds. Thus, all methine protons of acetyl derivatives of methyl α-D-glucopyranoside 2- and 3-benzyl ethers (**4b** and **5b**) could be fully assigned by successive proton decoupling techniques (see Experimental).

Definitive confirmation of some of the 3-alkyl ethers, **13** and **32**, was achieved by direct comparisons with the corresponding authentic specimens prepared by methanolysis of methyl 3-*O*-methyl 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**15**).[8]

Furthermore, the 2-benzyl ethers (**4a** and **23a**, anomeric mixture) and 4-benzyl ethers (**6** and **25**, anomeric mixture) of methyl D-glucopyranoside were prepared from 1,6-anhydro-D-glucose (**16**) as shown in Chart 4. The identities of the major products (**4a** and **23a**) of benzylation of the glucosides with the 2-benzyl ethers were confirmed by comparison of the ^{13}C-NMR data. The identities were also confirmed by analyses of the ^{1}H-NMR spectra of the acetyl derivatives (**4b** and **23b**). The ^{13}C-NMR data of the 4-benzyl ether (**6** and **25**) did not coincide with those of any of the other benzylation products.

Dialkyl ethers obtained by the above experiments were assigned on the basis of the calculated ^{13}C-chemical shifts. The results are collected in Table V. The ratio of each component in the reaction products was determined by comparison of the C_1-OMe peak area

TABLE V. Observed and Calculated (in Parentheses)[a] ^{13}C-Chemical Shifts of Dialkyl Ethers in Pyridine-d_5

Dialkyl ethers	C-1	C-2	C-3	C-4	C-5	C-6	OMe	OMe	OCH_2–R
Me α-D-Glc									
2,3-Di-MM-ether	99.6	79.3[b]	79.4[b]	70.9	73.8	62.1	54.8	55.1, 55.6	97.6, 98.0
(**11**)	(100.0)	(79.5)	(80.2)	(70.7)	(73.8)	(62.3)	(54.8)		
2,3-Di-Me-ether	98.0	82.3	84.3	70.8	73.7	62.3	54.8	58.1, 60.9	
(**14**)	(98.4)	(82.5)	(84.5)	(70.9)	(74.1)	(62.5)	(54.8)		
Me β-D-Glc									
2,6-Di-Bn-ether	105.1	83.0	77.5	71.3	76.8	70.8	56.7		73.5
(**27**)	(105.1)	(82.9)	(77.5)	(71.1)	(76.9)	(70.7)	(56.5)		
Me α-D-Man									
2,3-Di-MM-ether	100.5	76.1	77.8	67.4	75.3	62.7	54.5	55.3, 55.3	96.9, 97.3
(**48**)	(100.9)	(76.4)	(78.4)	(67.3)	(75.3)	(62.7)	(54.4)		
3,6-Di-MM-ether	102.5	69.9	79.1	66.9	73.6	68.1	54.5	54.9, 55.3	96.6, 97.7
(**49**)									
Me β-L-Ara									
2,3-Di-MM-ether	100.5	74.5[b]	75.4[b]	68.3	63.5		55.1	55.1, 55.2	96.0, 97.5
(**55**)									
3,4-Di-MM-ether	101.7	69.0	75.3	74.7	61.8		55.3	55.0, 55.1	96.5, 97.7
(**56**)	(101.9)	(69.0)	(76.1)	(74.8)	(62.2)		(55.1)		

a) Calculated values were obtained by the summation of alkylation shifts of the appropriate monoalkyl ethers. *b*) Assignments may be reversed in each row.

(^{1}H-NMR) or C_1 peak intensity (^{13}C-NMR); the later was found to be proportional to the C_1-OMe peak area.

Hexopyranosides

The primary hydroxyl group of carbohydrate is the most reactive to direct acylation[9] and alkylation.[9a] However, when methyl α-D-glucopyranoside (**3**) is acylated by the Bu_2SnO method, the 2-acyl ester is the major and the 6-acyl ester is the minor product.[4,10] Similarly, in the alkylation of **3** by the Bu_2SnO method, the 2-alkyl ether was obtained as the major product. In contrast to the acylation, the minor product in the alkylation was found to be the 3-alkyl ether instead of the 6-alkyl ether. This may be rationalized by assuming a partial contribution of a cyclic tin intermediate **21**[11] as well as a major contribution of **20** (Chart 5).

Alkylation of methyl β-D-glucopyranoside (**22**) gave the 2-alkyl ether as the major product and the 6- and 3-alkyl ethers as minor products (see Table II). This is in contrast to acylation (Bu_2SnO method)[4] where the 6-acyl ester was the exclusive product. Since **22** has neither a *cis*-vicinal glycol nor a *cis*-arranged OMe group with respect to the neighboring hydroxyl group, it is difficult to form a stable cyclic tin intermediate in the *C*1 conformation and alkylation probably proceeds through the pathway shown in Chart 6. We assume that in a slow reaction the kinetically formed tin intermediate (**34**) may have enough time to isomerize to more reactive isomers, **35** and **36**. On the other hand, methylation proceeds in the same fashion as acylation, but the reason for this contradictory result is not clear.

Both methyl α-D-galactopyranoside (**37**) and methyl β-D-galactopyranoside (**40**) produce only the 3-alkyl ether in high yield with excellent selectivity (see Table II). This result again confirms the formation of a cyclic tin intermediate involving the *cis*-vicinal hydroxyls with enhancement of the reactivity of the equatorial hydroxyl group.

Methyl α-D-mannopyranoside (**43**) also gave the 3-alkyl ether as the major product, as expected (see Table II).

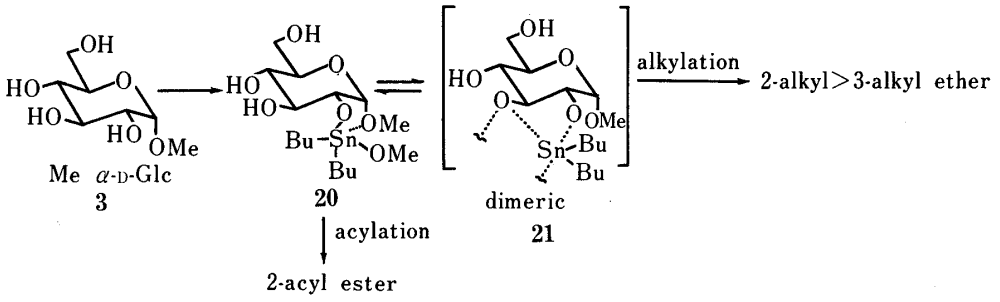


Chart 5

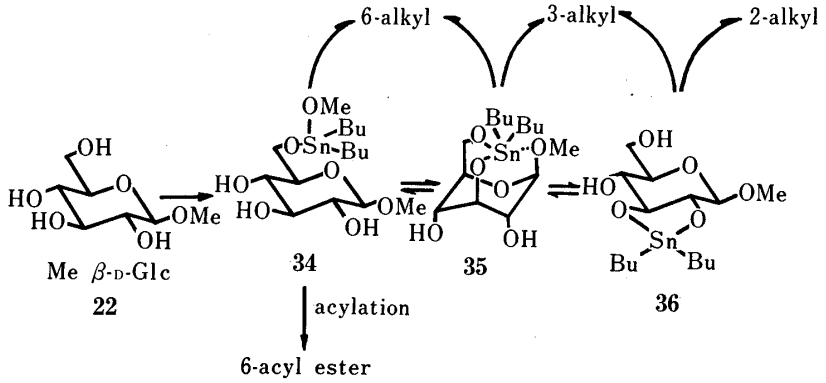


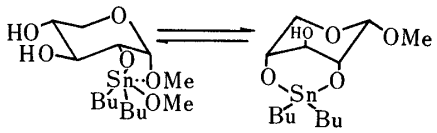
Chart 6

Pentopyranosides

The 2-hydroxyl group of methyl β-L-arabinopyranoside (**50**) is the most reactive to direct acrylation, but when acylation was carried out by using the Bu_2SnO method, the 3-hydroxyl group is acylated with the formation of a minor amount of the 4-acyl derivative.[4] Alkylation of methyl β-L-arabinopyranoside (**50**) also proceeded similarly to produce the 3-alkyl ether as the major product and the 4-alkyl ether as the minor product (see Table II).

The 3-hydroxyl group of phenyl α-L-arabinopyranoside (**57**) is the most reactive in both the Bu_2SnO method and direct acylation.[4] In alkylation, exclusive formation of 3-alkyl ether was also observed.

For methyl α-D-xylopyranoside (**60**) the 2-hydroxyl group was the most reactive to direct acylation.[4] When the Bu_2SnO method was used, reduced selectivity was observed,[4] though the yield of the monoacyl ester was higher. Alkylation by using the Bu_2SnO method also showed reduced regioselectivity, though the yield of the 2-alkyl ether was comparatively higher without formation of any dialkyl ether (see Table II). The reduced selectivity obtained by this method suggests a partial contribution of **73** as well as a major contribution of **72** (Chart 7).



72 **73**

Chart 7

The 4-hydroxyl group of methyl β-D-xylopyranoside (**74**) is the most reactive in both direct acylation and the Bu_2SnO method.[4] When benzylation was carried out in dioxane under the conditions given in Table II, this compound gave only the 4-benzyl ether (**76a**) in 70% yield, but after 20 h formation of the 2-benzyl ether (**75a**) was observed in addition to the 4-benzyl ether (**76a**). When DMF was used as the solvent, benzylation proceeded more rapidly and within 1 h, a 50 : 50 mixture of the 2- and 4-benzyl ethers (**75a** and **76a**) was obtained with a trace of the 3-benzyl ether. Methoxymethylation in dioxane gave the 2-, 3-, and 4-methoxymethyl ethers (**77a**, **78**, and **79a**) in a ratio of 51 : 7 : 42.

These results suggest that, under comparatively mild conditions, the reaction proceeds in the *C*1 conformation and gives only the 4-alkyl ether, *i.e.*, Bu_2SnO only enhances the reactivity of the most reactive hydroxyl group, but when the reaction conditions are comparatively drastic, the reaction might proceed in the 1*C* conformation as illustrated in Chart 7.

Conclusion

The major advantage of the Bu_2SnO method is that the reagent changes the order of reactivity of hydroxyl groups of carbohydrates and activates a particular secondary hydroxyl group in a *cis*-vicinal glycol system even in the presence of a more reactive primary hydroxyl group. By applying this procedure, it is possible to introduce an alkyl group regioselectively at a particular position of a carbohydrate, so that the procedure may serve as a good protecting method as well as a method for obtaining synthetic intermediates. This method should have a great value especially in the synthesis of complex sugars and their derivatives.

Experimental

Melting points were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in KBr discs on a Jasco IRA-2 spectrometer and the data are given in cm^{-1}. Unless otherwise stated, ^{1}H-NMR spectra (200 MHz) and ^{13}C-NMR spectra (at 50 MHz) were recorded with a

Varian Associates XL-200 FT NMR spectrometer in pyridine-d_5 solution with tetramethylsilane (TMS) as an internal standard, and the chemical shifts are given in δ values. Concentrations were about 0.1—0.3 mmol/ml. Column chromatography was performed on Wakogel C-200. For thin layer chromatography (TLC), Kieselgel $60F_{254}$ 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.

Monoalkylation of Pyranosides——Stannylation of glycopyranosides (1.0—2.6 mmol) were carried out with Bu_2SnO (1.5 mol eq) by refluxing in dry MeOH (10—20 ml) until the milky solution became homogeneous and clear (about 1 h). The mixture was refluxed for additional 2 h, then the solvent was evaporated off *in vacuo* to leave a glassy solid (stannylene derivative). For benzylation, allylation, and methylation, the stannylene derivative thus prepared was either dissolved or suspended in dry dioxane (1—20 ml) and the mixture was heated at 100 °C (bath temp.) with the addition of the appropriate alkyl halide (benzyl bromide, allyl bromide, and methyl iodide) (6—18 mol eq). When a large excess of reagent was used, 6 eq mol portions were added during the course of the reaction at 2—3 h intervals. Maximum conversions were checked by TLC. After 2—16 h, the solvent was evaporated off *in vacuo* to leave a syrupy residue. For methoxymethylation the tin complex was dissolved or suspended in dry dioxane, then methoxymethyl chloride (1.5—2.0 mol eq) was added and the mixture was stirred at 50 °C (both temp.) until maximum conversion was achieved (about 1—3 h). The solvent was evaporated off *in vacuo*.

The products obtained by the above experiments showed spots on TLC corresponding to the starting material and mono- and dialkyl ethers. The product mixture of each experiment was chromatographed. Elution was carried out with benzene, benzene containing increasing amounts of ethyl acetate, and finally with ethyl acetate. The monoalkyl ether (less mobile) and dialkyl ether (more mobile) fractions were separated and subjected to ^{1}H- and ^{13}C-NMR measurements which allowed identification of each component and determination of the composition. If the compounds showed separate spots on TLC, they were again chromatographed and the resulting individual components were crystallized (where possible) from an appropriate solvent to give the pure compound. The homogeneity of the compound thus obtained was confirmed by ^{1}H-NMR, ^{13}C-NMR, and TLC measurements.

Acetylation of some monoalkyl derivatives was carried out by using acetic anhydride–pyridine in the usual manner. Analyses of the acetylated derivatives were done by successive use of proton decoupling techniques.

Methyl α-D-Glucopyranoside Benzyl Ethers——2-Benzyl Ether (**4a**): Needles from hexane–AcOEt, mp 112—113 °C (lit.[2d] mp 118.5—120 °C). ^{1}H-NMR (60 MHz): 7.15—7.47 (5H, m, ArH), 5.06 (1H, d, J=3.0 Hz, H-1), 4.89 (2H, s, CH_2Ph), 3.76 (1H, dd, J=3.0, 9.2 Hz, H-2), 3.39 (3H, s, OMe). IR: 3400, 2900, 1460. *Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.18; H, 7.13.

2-Benzyl Ether Triacetate (**4b**): Syrup. ^{1}H-NMR: 7.23—7.46 (5H, m, ArH), 5.91 (1H, t, J=10.0 Hz, H-3), 5.37 (1H, t, J=10.0 Hz, H-4), 5.06 (1H, d, J=3.5 Hz, H-1), 4.79 and 4.70 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.51 (1H, dd, J=5.0, 12.0 Hz, H-6 ax.), 4.33 (1H, dd, J=2.5, 12.0 Hz, H-6 eq.), 4.06—4.16 (1H, m, H-5), 3.84 (1H, dd, J=3.5, 10.0 Hz, H-2), 3.36 (3H, s, OMe), 2.05 (9H, s, OAc × 3).

3-Benzyl Ether (**5a**): Needles from hexane–AcOEt, mp 117—118 °C. ^{1}H-NMR (60 MHz): 7.17—7.56 (5H, m, ArH), 6.03 (3H, br s, OH), 5.40 (2H, s, CH_2Ph), 5.03 (1H, d, J=3.0 Hz, H-1), 3.43 (3H, s, OMe). IR: 3500, 2875, 1440. *Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.00; H, 7.13.

3-Benzyl Ether Triacetate (**5b**): Syrup. ^{1}H-NMR: 7.24—7.48 (5H, m, ArH), 5.48 (1H, t, J=10.0 Hz, H-4), 3.27 (1H, dd, J=10.0, 3.5 Hz, H-2), 3.20 (1H, d, J=3.5 Hz, H-1), 4.91 and 4.81 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.49 (1H, dd, J=4.0, 12.0 Hz, H-6 ax.), 4.34 (1H, dd, J=2.5, 12.0 Hz, H-6 eq.), 4.30 (1H, t, J=10.0 Hz, H-3), 4.03—4.12 (1H, m, H-5), 3.39 (3H, s, OMe), 2.09 (9H, s, OAc × 3).

A mixture of dibenzyl ethers was also formed, but the components were not identified.

Methyl α-D-Glucopyranoside Allyl Ethers——2-Allyl Ether (**7**): Needles from $CHCl_3$–AcOEt, mp 130—131 °C. ^{1}H-NMR: 5.93—6.13 (1H, m, CH_2=CH–), 5.11 (1H, d, J=3.2 Hz, H-1), 3.67 (1H, dd, J=3.2, 9.2 Hz, H-2), 3.42 (3H, s, OMe). IR: 3325, 2875, 1710, 1620. *Anal.* Calcd for $C_{10}H_{18}O_6$: C, 51.27: H, 7.75. Found: C, 51.15; H, 7.63.

3-Allyl Ether (**8**): Syrup. ^{1}H-NMR: 6.01—6.20 (1H, m, CH_2=CH–), 5.00 (1H, d, J=3.1 Hz, H-1), 4.69 (2H, m, CH_2=CH–), 3.42 (3H, s, OMe).

A trace of diallyl ether was also formed but was not identified.

Methyl α-D-Glucopyranoside Methoxymethyl Ethers——2-Methoxymethyl Ether (**9**): Syrup. ^{1}H-NMR: 5.20 (1H, d, J=3.5 Hz, H-1), 5.10 and 4.91 (2H, ABq, J=6.5 Hz, OCH_2), 3.90 (1H, dd, J=3.5, 9.5 Hz, H-2), 3.47 (3H, s, OMe), 3.43 (3H, s, OMe). *Anal.* Calcd for $C_9H_{18}O_7 \cdot 1/2H_2O$: C, 43.72; H, 7.47. Found: C, 43.40; H, 7.36.

3-Methoxymethyl Ether (**10**): Prisms from ether, mp 104—105 °C. ^{1}H-NMR: 5.26 (2H, t, J=7.1 Hz, OCH_2), 5.08 (1H, d, J=3.2 Hz, H-1), 4.04 (1H, dd, J=3.2, 9.2 Hz, H-2), 3.55 (3H, s, OMe), 3.41 (3H, s, OMe). IR: 3300. *Anal.* Calcd for $C_9H_{18}O_7$: C, 45.37; H, 7.62. Found: C, 45.37; H, 7.59.

The 2,3-dimethoxymethyl ether (**11**) was also formed, but was not isolated; it showed OMe signals at δ 3.43, 3.38, and 3.51.

Methyl α-D-Glucopyranoside Methyl Ethers——2-Methyl Ether (**12**): Syrup. ^{1}H-NMR: 5.20 (1H, d, J=3.2 Hz, H-1), 3.59 (3H, s, OMe), 3.46 (3H, s, OMe).

3-Methyl Ether (**13**): Syrup. ^{1}H-NMR: 5.10 (1H, d, J=3.2 Hz, H-1), 3.88 (3H, s, OMe), 3.49 (3H, s, OMe).

The 2,3-dimethyl ether (**14**) was also formed, but was not isolated; it showed OMe signals at δ 3.45, 3.48, and 3.74.

Methyl β-D-Glucopyranoside Benzyl Ethers——2-Benzyl Ether (**23a**): Leaflets from AcOEt–light petroleum, mp 126—127 °C. ^{1}H-NMR: 7.22—7.60 (5H, m, ArH), 5.72 (3H, br s, OH), 5.20 and 5.03 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.64 (1H, d, J=7.8 Hz, H-1), 4.44 (1H, dd, J=2.9, 12.0 Hz, H-6 eq.), 4.27 (1H, dd, J=5.5, 12.0 Hz, H-6 ax.), 3.72—3.86 (1H, m, H-5), 3.54 (3H, s, OMe). IR: 3400, 3275, 2875. *Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.69; H, 7.00.

2-Benzyl Ether Triacetate (**23b**): Syrup. ^{1}H-NMR ($CDCl_3$): 7.33—7.22 (5H, m, ArH), 5.15 (1H, t, J=9.5 Hz, H-3), 4.98 (1H, t, J=9.5 Hz, H-4), 4.85 and 4.61 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.39 (1H, d, J=8.0 Hz, H-1), 4.29 (1H, dd, J=4.5, 12.0 Hz, H-6 ax.), 4.10 (1H, dd, J=2.5, 12.0 Hz, H-6 eq.), 3.78—3.60 (1H, m, H-5), 3.58 (3H, s, OMe), 3.40 (1H, dd, J=8.0, 9.5 Hz, H-2), 2.07, 2.00, and 1.90 (3H, each, s, OAc).

3-Benzyl Ether (**24**): Needles from hexane–benzene, mp 99—100 °C. ^{1}H-NMR: 7.20—7.58 (5H, m, ArH), 5.38 and 5.25 (2H, ABq, J=11.7 Hz, CH_2Ph), 4.62 (1H, d, J=7.5 Hz, H-1), 4.42 (1H, dd, J=3.0, 12.0 Hz, H-6 eq.), 4.27 (1H, dd, J=5.0, 12.0 Hz, H-6 ax.), 3.75—3.86 (1H, m, H-5), 3.54 (3H, s, OMe). IR: 3300, 2900. *Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.27; H, 7.06.

6-Benzyl Ether (**26**): Syrup. ^{1}H-NMR: 7.17—7.46 (5H, m, ArH), 6.49 (3H, br s OH), 4.67 (2H, s, CH_2Ph), 4.59 (1H, d, J=7.6 Hz, H-1), 4.24 (1H, dd, J=1.7, 10.6 Hz, H-6 eq.), 3.59 (3H, s, OMe). *Anal.* Calcd for $C_{14}H_{20}O_6 \cdot 1/2H_2O$: C, 57.33; H, 7.22. Found: C, 57.15; H, 6.77.

The 2,6-dibenzyl ether (**27**) was also formed, but was not isolated; it showed an OMe signal at δ 3.59.

Methyl β-D-Glucopyranoside Methoxymethyl Ethers——2-Methoxymethyl Ether (**28**): Needles from AcOEt, mp 109—111 °C. ^{1}H-NMR: 5.23 and 5.14 (2H, ABq, J=6.5 Hz, OCH_2), 4.71 (1H, d, J=7.9 Hz, H-1), 4.47 (1H, dd, J=5.5, 12.0 Hz, H-6 ax.), 3.88 (1H, dd, J=7.9, 9.0 Hz, H-2), 3.57 (3H, s, OMe), 3.53 (3H, s, OMe). IR: 3500, 3275, 3150, 2950. *Anal.* Calcd for $C_9H_{18}O_7$: C, 45.37; H, 7.62. Found: C, 45.23; H, 7.58.

6-Methoxymethyl Ether (**30**): Syrup. ^{1}H-NMR: 4.80 (2H, s, OCH_2), 4.62 (1H, d, J=7.9 Hz, H-1), 3.60 (3H, s, OMe). *Anal.* Calcd for $C_9H_{18}O_7 \cdot 1/2H_2O$: C, 43.72; H, 7.74. Found: C, 43.83; H, 7.46.

The 3-methoxymethyl ether (**29**) was also formed, but was not isolated; it showed OMe signals at δ 3.56 and 3.60. A small amount of dimethoxymethyl ether was also formed, but was not identified.

Methyl β-D-Glucopyranoside Methyl Ethers——6-Methyl Ether (**33**): Needles from AcOEt, mp 135—136 °C. ^{1}H-NMR: 4.63 (1H, d, J=7.6 Hz, H-1), 3.59 (3H, s, OMe), 3.38 (3H, s, OMe). IR: 3350, 2900. *Anal.* Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.06; H, 7.60.

The following compounds were also formed but were not isolated: the 2-methyl ether (**31**) and 3-methyl ether (**32**), which showed OMe signals at δ 3.90, 3.74, and at 3.56, 3.54 and anomeric protons at δ 4.62 (1H, d, J=7.6 Hz) and at 4.68 (1H, d, J=7.6 Hz), respectively.

Methyl α-D-Galactopyranoside Benzyl Ether——3-Benzyl Ether (**38**): Syrup. ^{1}H-NMR: 7.22—7.61 (5H, m, ArH), 5.19 (1H, d, J=3.9 Hz, H-1), 6.24 (3H, br s, OH), 4.89 and 4.98 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.80 (1H, dd, J=3.9, 10.0 Hz, H-2), 4.68—4.72 (1H, m, H-4), 4.15 (1H, dd, J=3.0, 10.0 Hz, H-3), 3.47 (3H, s, OMe). *Anal.* Calcd for $C_{14}H_{20}O_7$: C, 55.62; H, 7.34. Found: C, 55.39; H, 7.19.

Methyl α-D-Galactopyranoside Methoxymethyl Ether——3-Methoxymethyl Ether (**39**): Prisms from AcOEt, mp 117—118 °C. ^{1}H-NMR: 5.13 (1H, d, J=3.8 Hz, H-1), 5.08 and 4.97 (2H, ABq, J=6.5 Hz, OCH_2), 4.66 (1H, dd, J=3.8, 10.0 Hz, H-2), 3.43 (3H, s, OMe), 3.38 (3H, s, OMe). IR: 3400, 2950. *Anal.* Calcd for $C_9H_{18}O_7$: C, 45.37; H, 7.62. Found: C, 45.36; H, 7.58.

Methyl β-D-Galactopyranoside Benzyl Ether——3-Benzyl Ether (**41**): Needles from AcOEt, mp 136—137 °C. ^{1}H-NMR: 7.22—7.59 (5H, m, ArH), 5.03 and 4.94 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.65 (1H, d, J=7.5 Hz, H-1), 3.95 (1H, t, J=6.0 Hz, H-5), 3.83 (1H, dd, J=3.0, 9.0 Hz, H-3), 3.59 (3H, s, OMe). IR: 3300, 2900, 2850. *Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.99; H, 7.13.

Methyl β-D-Galactopyranoside Methoxymethyl Ether——3-Methoxymethyl Ether (**42**): Needles from AcOEt–light petroleum, mp 90—91 °C. ^{1}H-NMR: 5.16 and 5.01 (2H, ABq, J=6.1 Hz, OCH_2), 4.62 (1H, d, J=7.5 Hz, H-1), 3.58 (3H, s, OMe), 3.46 (3H, s, OMe). IR: 3400, 2950, 1640. *Anal.* Calcd for $C_9H_{18}O_7$: C, 45.37; H, 7.62. Found: C, 45.29; H, 7.61.

A trace of dimethoxymethyl ether was formed but was not identified.

Methyl α-D-Mannopyranoside Benzyl Ethers——3-Benzyl Ether (**45**): Syrup. ^{1}H-NMR: 7.20—7.58 (5H, m, ArH), 5.17 (1H, d, J=1.5 Hz, H-1), 5.00 and 4.88 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.72 (1H, t, J=10.0 Hz, H-4), 4.35 (1H, dd, J=5.8, 10.0 Hz, H-5), 4.19 (1H, dd, J=3.0, 10.0 Hz, H-3), 3.99 (3H, s, OMe).

The following compounds were also formed, but were not isolated: the 2-benzyl ether (**44**), which showed an OMe signal at δ 3.42, and a mixture of dibenzyl ethers which were not identified.

Methyl α-D-Mannopyranoside Methoxymethyl Ethers——The 2-methoxymethyl ether (**46**) and 3-methoxymethyl ether (**47**) showed a single spot on TLC and were not separable. These compounds showed OMe signals at δ 3.42 and 3.38, respectively. A mixture of 2,3- and 3,6-dimethoxymethyl ethers (**48** and **49**) was also formed in the ratio of 78 : 22 (determined from C-1 peak areas).

Methyl β-L-Arabinopyranoside Benzyl Ethers——3-Benzyl Ether (**51**): Needles from hexane–benzene, mp 119—120 °C. ^{1}H-NMR: 7.22—7.80 (5H, m, ArH), 5.25 (1H, d, J=3.4 Hz, H-1), 5.00 and 4.87 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.70 (1H, dd, J=3.4, 9.1 Hz, H-2), 4.38—4.42 (1H, m, H-4), 4.22 (1H, dd, J=3.4, 9.1 Hz, H-3), 3.90—4.04

(2H, m, H_2-5), 3.44 (3H, s, OMe). IR: 3425, 2900, 1710. *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.31; H, 7.18.

The 4-benzyl ether (**52**) was formed but was not isolated; it showed an OMe signal at δ 3.43.

Methyl β-L-Arabinopyranoside Methoxymethyl Ethers——The 3-methoxymethyl ether (**53**) and 4-methoxymethyl ether (**54**) showed a single spot on TLC and could not be separated. These compounds were identified and characterized by analyses of their ^{13}C-NMR spectra; they showed OMe signals at δ 3.42 and 3.38, respectively, in their ^{1}H-NMR spectra.

A mixture of 2,3- and 3,4-dimethoxymethyl ethers (**55** and **56**) was also formed but the components were not isolated; they showed OMe signals at δ 3.36, 3.40, 3.41, and at 3.34, 3.38, 3.39, respectively.

Phenyl α-L-Arabinopyranoside Benzyl Ether——3-Benzyl Ether (**58**): Needles from hexane–benzene, mp 119—120 °C. ^{1}H-NMR: 7.65—7.98 (10H, m, ArH), 5.40 (1H, d, J=7.2 Hz, H-1), 5.03 (2H, s, CH_2Ph), 4.78 (1H, dd, J=7.2, 9.0 Hz, H-2), 4.39—4.46 (1H, m, H-4), 4.33 (1H, dd, J=3.0, 12.1 Hz, H-5 ax.), 3.94 (1H, dd, J=3.4, 9.0 Hz, H-3), 3.82 (1H, dd, J=1.9, 12.1 Hz, H-5 eq.). IR: 3425, 2900 *Anal.* Calcd for $C_{18}H_{20}O_5$: C, 68.43; H, 6.37. Found: C, 68.07; H, 6.35.

Phenyl α-L-Arabinopyranoside Methoxymethyl Ether——3-Methoxymethyl Ether (**59**): Needles from hexane–AcOEt, mp 107—108 °C. ^{1}H-NMR: 7.00—7.38 (5H, m, ArH), 5.43 (1H, d, J=7.0 Hz, H-1), 5.20 and 5.06 (2H, ABq, J=6.9 Hz, OCH_2), 4.76 (1H, dd, J=7.0, 9.0 Hz, H-2), 4.41 (1H, m, H-4), 4.33 (1H, dd, J=3.1, 12.0 Hz, H-5 ax.), 4.15 (1H, dd, J=3.1, 9.0 Hz, H-3), 3.87 (1H, dd, J=1.0, 12.0 Hz, H-5 eq.). IR: 3500, 2950. *Anal.* Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.93; H, 6.76.

Methyl α-D-Xylopyranoside Benzyl Ethers——The 2-benzyl ether (**61**), 3-benzyl ether (**62**), and 4-benzyl ether (**63**) showed a single spot on TLC and could not be separated. The mixture showed OMe signals at δ 3.38, 3.42, and 3.39, respectively. These compounds were identified and characterized by analyses of their ^{13}C-NMR spectra.

Methyl α-D-Xylopyranoside Allyl Ethers——The 2-allyl ether (**64**), 3-allyl ether (**65**), and 4-allyl ether (**66**) showed a single spot on TLC, and were identified and characterized by analyses of their ^{13}C-NMR spectra. These compounds showed OMe signals at δ 3.40, 3.42, and 3.39, respectively.

Methyl α-D-Xylopyranoside Methoxymethyl Ethers——The 2-methoxymethyl ether (**67**), 3-methoxymethyl ether (**68**), and 4-methoxymethyl ether (**69**) also gave a single spot on TLC and were identified by analyses of their ^{13}C-NMR spectra. These compounds showed C_1-OMe signals at δ 3.38, 3.39, and 3.40, respectively.

Methyl α-D-Xylopyranoside Methyl Ethers——2-Methyl Ether (**70**): Prisms from hexane–CH_2Cl_2, mp 101—103 °C. ^{1}H-NMR: 5.06 (1H, d, J=3.5 Hz, H-1), 4.38 (1H, t, J=9.0 Hz, H-3), 3.48 (1H, dd, J=3.5, 9.0 Hz, H-2), 3.57 (3H, s, OMe), 3.38 (3H, s, OMe). IR: 3200, 2900, 1450, 1440. *Anal.* Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 46.90; H, 7.87.

The 4-methyl ether (**71**) was also formed, but was not isolated; it showed OMe signals at δ 3.54 and 3.37.

Methyl β-D-Xylopyranoside Benzyl Ethers——4-Benzyl Ether (**76a**): Needles from hexane–benzene, mp 90—91 °C. ^{1}H-NMR: 7.23—7.60 (5H, m, ArH), 5.00 and 4.87 (2H, ABq, J=12.0 Hz, CH_2Ph), 4.53 (1H, d, J=7.5 Hz, H-1), 4.25 (1H, t, J=9.0, H-3), 3.90 (1H, dd, J=7.5, 9.0 Hz, H-2), 3.58 (3H, s, OMe). IR: 3350, 2950, 2850. *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.41. Found: C, 61.31; H, 6.86.

4-Benzyl Ether Diacetate (**76b**): Syrup. ^{1}H-NMR ($CDCl_3$): 7.28—7.34 (5H, m, ArH), 5.16 (1H, t, J=9.0 Hz, H-3), 4.33 (1H, dd, J=7.5, 9.0 Hz, H-2), 4.59 (2H, s, CH_2Ph), 4.35 (1H, d, J=7.5 Hz, H-1), 4.01 (1H, dd, J=5.5, 12.0 Hz, H-5 eq.), 3.56—3.68 (1H, m, H-4), 3.46 (3H, s, OMe), 3.31 (1H, dd, J=10.0, 12.0 Hz, H-5 ax.), 2.05 and 2.02 (3H, each s, OAc). The 2-benzyl ether (**75a**) was also formed together with **76a** when DMF was used as the solvent, but it showed a single spot on TLC with the 4-benzyl ether (**76a**) and was characterized by ^{1}H-NMR analysis of acetyl derivatives of the mixture. It showed an OMe signal at δ 3.48.

2-Benzyl Ether Diacetate (**75b**): ^{1}H-NMR ($CHCl_3$): 7.27—7.33 (5H, ArH), 5.16 (1H, t, J=9.0 Hz, H-3), 4.58 (2H, s, CH_2Ph), 4.37 (1H, d, J=7.5 Hz, H-1), 4.01 (1H, dd, J=5.5, 12.0 Hz, H-5 ax.), 3.54 (3H, s, OMe), 3.34 (1H, dd, J=7.5, 9.0 Hz, H-2), 1.94 and 2.01 (3H each s, OAc).

Methyl β-D-Xylopyranoside Methoxymethyl Ethers——The 2-methoxymethyl ether (**77a**) and 4-methoxymethyl ether (**79a**) gave a single spot on TLC and could not be separated. The mixture showed OMe signals at δ 3.58 (6H), 3.53, and 3.38. These compounds were identified by analyses of their ^{13}C-NMR spectra and were characterized by successive proton decoupling experiments with the mixture of their acetyl derivatives.

2-Methoxymethyl Ether Diacetate (**77b**): ^{1}H-NMR ($CDCl_3$): 5.12 (1H, t, J=9.0 Hz, H-3), 4.91 (1H, t, J=9.0 Hz, H-4), 4.85 and 4.64 (2H, ABq, J=7.0 Hz, OCH_2), 4.32 (1H, d, J=7.0 Hz, H-1), 4.08 (1H, dd, J=5.2, 12.0 Hz, H-5), 3.74 (1H, dd, J=5.2, 9.0 Hz, H-5), 3.52 and 3.36 (3H each, s, OMe), 2.09 and 2.04 (3H each, s, OAc).

4-Methoxymethyl Ether Diacetate (**79b**): ^{1}H-NMR ($CDCl_3$): 5.16 (1H, t, J=9.0 Hz, H-3), 4.94 (1H, t, J=9.0 Hz, H-4), 4.85 and 4.64 (2H, ABq, J=7.0 Hz, OCH_2), 4.37 (1H, d, J=7.0 Hz, H-1), 4.15 (1H, dd, J=5.2, 12.0 Hz, H-5), 3.79 (1H, dd, J=5.2, 9.0 Hz, H-5), 3.55 (1H, dd, J=7.0, 9.0 Hz, H-2), 3.48 and 3.34 (3H each, s, OMe), 2.05 and 2.06 (3H each, s, OAc).

3-Methoxymethyl Ether (**78**): Leaflets from hexane–ether, mp 123—124 °C. ^{1}H-NMR: 3.35 and 5.07 (2H, ABq, J=6.0 Hz, OCH_2), 4.52 (1H, d, J=7.1 Hz, H-1), 4.25 (1H, dd, J=5.0, 10.9 Hz, H-3), 3.60 (3H, s, OMe), 3.55 (3H, s, OMe). IR: 3400, 3300. *Anal.* Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.85; H, 7.66.

Methyl D-Glucopyranoside 3-Methyl Ethers (13 and 32)[8]——This was obtained as a 3:2 anomeric mixture of α and β anomers in the form of a colorless syrup which showed C_1-H signals at δ 4.32 (d, J=7.5 Hz for β anomer) and 4.74 (d, J=3.5 Hz, for α anomer).

Benzylation of 1,6-Anhydro-D-Glucose (16) by the Bu_2SnO Method——A mixture of 1,6-anhydro-D-glucose (0.5 g, 3.09 mmol) and Bu_2SnO (1.15 g, 4.64 mmol) in dry MeOH (25 ml) was refluxed until the milky solution became homogeneous and clear (about 1 h), then refluxed for an additional 2 h. The solvent was evaporated off *in vacuo* to leave a white residue, which was suspended in dry dioxane (25 ml) and heated at 100 °C with the addition of benzyl bromide (3.2 mol eq). After 6 h, additional benzyl bromide (1.6 g, 3.0 mol eq) was added and the whole was heated at the same temperature for a further 10 h. Evaporation of the solvent *in vacuo* left a syrup, which was chromatographed. Elution was carried out with benzene, benzene containing increasing amounts of ethyl acetate, and finally with ethyl acetate. The benzene–ethyl acetate (1:1) eluate gave the monobenzyl ether mixture 387.6 mg (78.9%), and the ethyl acetate eluate gave the starting material (**16**), 193.5 mg. ^{13}C-NMR showed that the product was a mixture of 2- and 4-benzyl ethers (**18** and **19**). A portion of this mixture was subjected to preparative TLC with multiple development to separate the two products.

1,6-Anhydro-D-glucose 2-Benzyl Ether (**18**): Syrup. ^{1}H-NMR δ: 7.22—7.48 (5H, m, ArH), 5.92 (1H, s, H-1), 4.90 (1H, d, J=6.0 Hz, H-4), 4.77 and 4.85 (2H, ABq, J=11.5 Hz, CH_2Ph), 4.39 (1H, t, J=4.0 Hz, H-5), 4.29 (1H, dd, J=6.0, 0.5 Hz, H-2), 4.10 (1H, d, J=4.0 Hz, H-6), 3.81 (1H, t, J=6.0 Hz, H-3), 3.78 (1H, d, J=4.0 Hz, H-6), ^{13}C-NMR δ: 102.2 (C-1), 81.6 (C-2), 72.0 (C-3), 73.4 (C-4), 78.5 (C-5), 66.8 (C-6), 73.4 ($\underline{C}H_2$Ph).

1,6-Anhydro-D-glucose 4-Benzyl Ether (**19**): Syrup. ^{1}H-NMR δ: 7.23—7.54 (5H, m, ArH), 5.94 (1H, s, H-1), 4.92 (1H, d, J=6.0 Hz, H-4), 4.86 (2H, s, CH_2Ph), 4.51 (1H, m, H-5), 4.24 (1H, dd, J=6.0, 0.5 Hz, H-2), 4.13 (1H, d, J=4.0 Hz, H-6), 3.85 (1H, t, J=6.0 Hz, H-3), 3.77 (1H, d, J=4.0 Hz, H-6). ^{13}C-NMR δ: 104.5 (C-1), 73.5 (C-2), 71.6 (C-3), 81.9 (C-4), 75.5 (C-5), 66.6 (C-6), 74.3 ($\underline{C}H_2$Ph).

Methyl D-Glucopyranoside 2-Benzyl Ether (α and β Anomeric Mixture) (4a and 23a)——1,6-Anhydro-D-glucose 2-benzyl ether **18** (56.8 mg) was dissolved in 10% HCl in MeOH (10 ml) and the solution was refluxed for 12 h. Dilute aq. $KHCO_3$ was added to the mixture to make it just neutral, the solvent was evaporated off *in vacuo* and the residue was extracted with hot ethyl acetate to give a syrup (20 mg), which was identified by analyses of the ^{13}C-NMR spectra as a 51:49 mixture of **4a** and **23a**.

Methyl D-Glucopyranoside 4-Benzyl Ether (α and β Anomeric Mixture) (6 and 25)——1,6-Anhydro-D-glucose 4-benzyl ether (**19**) (65.1 mg) was treated with 10% HCl in MeOH as described above and worked up to give a residue (28.9 mg), which was identified by analyses of the ^{13}C-NMR spectra as a 66:34 mixture of **6** and **25**.

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