Enhanced reactivity of secondary hydroxyl groups in the O-alkylation of carbohydrate-related primary-secondary *vic*-glycols. Regioselective 2-O-benzylation of 1,3:2,4-di-O-ethylidene-*D*-glucitol

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Partial O-alkylation of 1,3:2,4-di-O-ethylidene-*D*-glucitol (**1a**), 1,2-O-isopropylidene-3-O-methyl-α-*D*-glucofuranose (**1b**), and *R*-(+)-1-O-benzylglycerol (**1c**) with benzyl chloride in a KOH/DMSO system results in products of monoalkylation at the secondary (**4a—c**) and at the primary hydroxyl (**2a—c**) in ratios of over 95:5 (**a**), ~2:1 (**b**), and ~1:1 (**c**), whereas (±)propane-1,2-diol (**1d**) gives only the product of 1-O-benzylation (**2d**). A qualitatively similar result is observed upon O-alkylation of diols (**1a—e**) with 2-methoxyethanol tosylate.

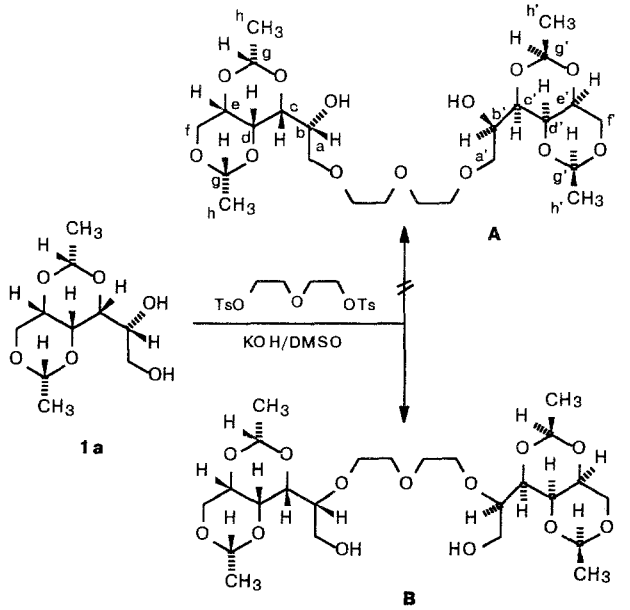
Key words: primary-secondary *vic*-diols; O-alkylation, regioselectivity; superbasic system; ^{13}C NMR spectra.

In our search for synthetic routes to crown ethers based on *D*-glucitol, we have observed an unusual case of preferential O-alkylation of the secondary hydroxyl group in 1,3:2,4-di-O-ethylidene-*D*-glucitol (**1a**). An attempt to prepare diol **A** (Scheme 1) by the condensation of 2 equivalents of glycol **1a** with one equivalent of diethylene glycol ditosylate in a superbasic system KOH/DMSO led to diol **B** as the main product and a minor admixture of the corresponding nine- and eighteen-membered crown ethers.[1]

The structure of product **B** has been established from the ^{13}C NMR spectrum and by identification of **B** with the corresponding compound, the structure of which was confirmed by its regio-controlled independent synthesis.[1]

The primary alkoxide group (RCH_2O^-) is normally more reactive as a nucleophile in S_N2 substitution reactions than the secondary group ($RR'CHO^-$).[2] At the same time, the enhanced reactivity of the hydroxyl group at C(2) in methyl-*D*-glucopyranosides, cellulose, nucleosides, and cyclodextrins in O-alkylation reactions in the presence of bases has been noted (see refs. 2—4 and the literature cited therein). This fact has been explained by the increased acidity of the hydroxyl at C(2) due to the influence of the neighboring electron-accepting acetal group: the pK_a value is 12.35 for 2-OH in unsubstituted methyl glucosides or 12.1 in α-, β-, and γ-cyclodextrins, whereas the 6-OH groups in derivatives of aldohexoses display pK_a values in the range of 15—16, which are comparable with those for the non-carbohydrate primary hydroxyls. Similar behavior has been observed for acyclic polyols: upon O-methylation of diethyldithioacetals derived from certain aldopentoses and aldohexoses using the Purdie procedure (MeI—Ag_2O/THF), the 2-OH group proved to be twice as active as the 6-OH group.[5] This result was attributed to the intermediate formation of a methylsulfonium ion resulting from attack of the sulfur atom by methyl

Scheme 1



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iodide, followed by methylation of the 2-OH group through a five-membered transition state. Generally, the regioselectivity of O-alkylation of the carbohydrate-related polyols depends on the reaction conditions (the pH of the medium, the nature of the cation in the base, the nature of the alkylating agent, the solvent, etc.). This points to the importance of such factors as kinetic and thermodynamic control, hydrogen bonding between hydroxyls and the neighboring oxygen-containing moieties, and chelating with the cations of the bases.[2–4] The combined action of these factors determines the preferred transition state and hence the regioselectivity of the reaction.

We could not find in the literature any examples in which the reactivity of the hydroxyl groups in primary-secondary vicinal glycols of type **1a** with both hydroxyls located outside the ring was inverted; at the same time, the activation of the secondary hydroxyl cannot be attributed to the influence of the neighboring electron-acceptor (acetal) or electron-donor (thioacetal) moiety.

In order to reveal whether the high regioselectivity observed in the O-alkylation of diol **1a** is related to the carbohydrate nature of the diol, we studied the relative reactivity of hydroxyls in both carbohydrate and non-carbohydrate primary-secondary *vic*-glycols. The study was carried out in a superbasic KOH/DMSO system at an equimolar ratio of glycols and alkylating agents, *i.e.*, under conditions of competition.

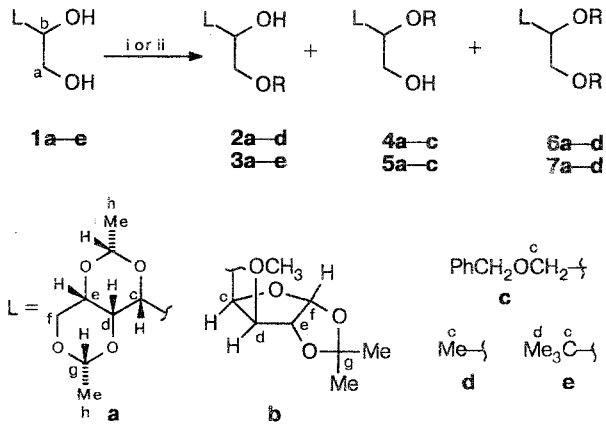
We used **1a** and 1,2-O-isopropylidene-3-O-methyl-α-*D*-glucofuranose (**1b**) as the models representing carbohydrate type diols.

The non-carbohydrate vicinal glycols, *R*-(+)-1-O-benzylglycerol (**1c**), (±)-propan-1,2-diol (**1d**), and 3,3-dimethylbutan-1,2-diol (**1e**), were chosen for comparison with **1a** and **1b**; the series **1c—1e** was selected in order to reveal how the additional oxygen function in **1c** and the steric factor in **1e** affect the behavior of the neighboring secondary HO group (Scheme 2).

Two alkylating agents, benzyl chloride (the «non-chelating» electrophile) and 2-methoxyethanol tosylate (the «chelating» electrophile), were used. The reaction of **1a—d** with $PhCH_2Cl$ proceeded readily at 20°C and with the base (powdered KOH) and the substrate in equimolar ratio. Increasing the amount of base caused an increase in the portion of diethers (**6a—c**) in the reaction products but did not alter the ratio of the isomeric monoethers; no detectable amount of the 2-substituted 1,2-propanediol **4d** was formed from diol **1d**. In the case of the alkylation of diols **1a—e** with an equimolar amount of 2-methoxyethanol tosylate, the reaction was forced to proceed successfully by taking the base and the substrate in a molar ratio of not less than 3:1 and by heating to 60°C.

The resulting products were fractionated by means of column chromatography on Al_2O_3. This allowed us to isolate diethers of the type **6** and **7** and the monoether **4a** in pure form, whereas the isomeric pairs of monoethers (**2b/4b, 2c/4c** and **3a/5a, 3b/5b, 3c/5c**) were isolated

Scheme 2



Reagents and conditions:

i. $PhCH_2Cl$/KOH—DMSO (20°C)
ii. $MeOCH_2CH_2OTs$/KOH—DMSO (60°C)

as mixtures. The structures of the compounds thus prepared and the ratios of the isomeric monoethers were established on the basis of ^{13}C NMR spectral data. The mixture of monoethers **2b** and **4b** was separated by TLC on Al_2O_3 (Brockman activity II).

The chemical shifts (CS) for the signals from the C atoms in the primary and secondary hydroxy groups calculated from the spectra of the original compounds **1a—e** and their alkylation products are listed in Table 1. The assignment of the signals was carried out taking their multiplicities and the effects of the substituents into account, and by comparing the CSs for the compounds under study. In addition, Table 1 lists the changes of CS values for the C atoms in the $—CH_2OH$ and —CHOH moieties in diols **1** caused by O-alkylation; these changes can point to the position of alkylation. There is a downfield shift of 6—9 ppm for the C atom bound to an alkoxy group whereas the signal from the C atom in the β-position relative to the alkoxy group shifts upfield by 1.5—3 ppm. Tables 2 and 3 summarize the assignments of the ^{13}C NMR signals for the original diols **1a—e**.

The capillary GLC analysis of the mixtures comprising the isomeric monoethers corroborated the NMR spectral data. In order to identify the peaks in the chromatograms, pure monoethers of the type **4a—c** and **5a—c** were independently synthesized using a regiocontrolled procedure. This included the transformation of diols **1a—c** into trityl ethers **8a—c**, the alkylation of the latter with $PhCH_2Cl$ or with $MeOCH_2CH_2OTs$ in the superbasic system to give the corresponding diethers of the type **9a—c** and **10a—c**, and deprotection of the latter. For the same purpose, diethers **6a,b** and **7a,b**

Table 1. Chemical shifts in the ^{13}C NMR spectra for carbon atoms of the primary (upper numbers) and secondary hydroxyl groups in glycols **1a—e** and products of their alkylation **2a—e** — **7a—e**. The changes in the chemical shifts are given in parentheses.

L	δ ($\Delta\delta = \delta_{alkylat.} - \delta_{nonalkylat.}$)						
		Alkylation with $PhCH_2Cl$			Alkylation with $MeOCH_2CH_2OTs$		
	1	**2**	**4**	**6**	**3**	**5**	**7**
a	64.0	72.4 (+8.4)	61.3 (−2.7)	70.7 (+6.7)	71.5 (+7.5)	61.2 (−2.8)	71.8 (+7.8)
	69.8	67.9 (−1.9)	77.2 (+7.4)	76.1 (+6.3)	66.8 (−3.0)	76.5 (+6.7)	75.4 (+5.6)
b	64.1	72.1 (+8.0)	62.1 (−2.0)	70.9 (+6.8)	72.8 (+8.7)	62.1 (−2.0)	71.6 (+7.5)
	68.8	68.0 (−0.8)	75.8 (+7.2)	75.0 (+6.2)	67.0 (−1.8)	76.7 (+7.9)	75.4 (+6.6)
c	64.0	72.7 (+8.2)	62.3 (−1.7)	70.3 (+6.3)	72.7 (+8.7)	62.6 (−1.4)	71.5 (+7.5)
	70.9	69.5 (−1.4)	78.1 (+7.2)	77.3 (+6.4)	69.5 (−1.4)	79.8 (+8.9)	78.5 (+7.6)
d	67.5	75.9 (+8.4)	—	74.3 (+6.8)	75.9 (+8.4)	—	74.8 (+7.3)
	68.0	66.5 (−1.5)	—	74.1 (+6.1)	64.7 (−3.3)	—	74.6 (+6.6)
e	63.1				69.4 (+6.3)	—	—
	79.6		Not studied		69.5 (−1.4)	—	—

Table 2. Chemical shifts in the ^{13}C NMR spectra for compounds **1a,b—7a,b**

Compound*	δ							
	C_a	C_b	C_c	C_d	C_e	C_f	C_g	C_h
1a	64.0	69.8	78.8	69.3	71.6	70.6	99.9 99.8	21.0 20.9
2a	72.4	67.9	77.4	68.1	69.7	69.4	98.3 98.2	20.6 20.4
3a	72.4	67.9	78.5	69.0	70.7	70.0	98.8	21.2
4a	61.3	77.2	76.5	68.0	69.6	69.2	98.3 98.2	20.7 20.5
5a	61.3	77.2	77.2	69.1	70.7	70.0	98.9 98.7	21.3 21.1
6a	71.8	75.4	76.3	68.1	69.8	69.3	98.4 98.3	20.8 20.6
7a	70.7	76.1	77.3	69.1	70.7	70.0	98.8	21.3 21.2
1b	64.1	68.8	79.7	81.3	83.9	104.9	111.5	26.5 26.0
2b	72.8	67.0	79.3	81.1	83.4	104.6	110.9	26.2 25.7
3b	72.1	68.0	79.7	81.6	84.4	105.1	111.7	26.8 26.3
4b	62.1	76.7	78.6	80.6	83.0	104.6	110.9	26.2 25.7
5b	62.1	75.8	79.4	80.9	83.5	104.9	111.7	26.6 26.2
6b	71.6	75.4	78.3	80.7	82.9	104.6	110.9	26.2 25.7
7b	70.9	75.0	78.5	80.8	83.2	104.8	111.1	26.4 26.0

*Solvents: CD_3OD **(1a)**, $(CD_3)_2CO$ **(3a, 5a, 7a)**, $CDCl_3$ in the remaining cases. The chemical shifts for compounds **2a** and **4a**, **2b** and **4b**, **3a** and **5a** were determined from spectra for **2/4** and **3/5** mixtures. Chemical shifts (δ) for compounds **3**, **5**, and **7**: 72—69 (OCH_2), 59—56 (CH_3O); for compounds **2**, **4**, and **6**: 138±0.2 (=C), 129—127 (=C), 73—71 (CH_2Ph).

were prepared by total alkylation. ^{13}C NMR spectra of these compounds appear in Table 4 (Scheme 3).

When we carried out this part of the study, we met with the necessity of removing the trityl protection from trityl-benzyl ethers **9a** and **9b** which contained some groups sensitive to the action of acids and others sensitive to hydrogenolysis. We succeeded in performing the selective deprotection of the primary HO group in **9a** and **9b** by short-term boiling (15 min) in the presence of a catalytic amount of pyridinium *para*-toluenesulfonate (PPTS) in methanol. Heating with PPTS in acetone has been used before to remove the dioxolane protection in acid-labile molecules (see refs. 6,7 and the literature cited therein); our data suggest that PPTS can be used for the finer differentiation of protective groups.

The results of the study on the partial O-alkylation of vicinal glycols are given in Table 5.

The relative rates of alkylation of the primary and secondary OH groups in glycols **1a—e** under the conditions used were estimated from the yields of the corresponding monoethers. The yields were calculated from the total weight of the fractions incorporating mixtures of the two isomeric monoethers, and from their ratios established from the matching data of ^{13}C NMR spectroscopy and capillary GLC. Under the competition conditions, *i.e.*, with an equimolar ratio of substrate and alkylating reagent, a portion of the latter is consumed to form the bis-alkylation product, as well as $PhCH_2OH$, $(PhCH_2)_2O$, or $MeOCH_2CH_2OH$, $(MeOCH_2CH_2)_2O$ upon reaction with KOH. In this case a portion of the

Table 3. Chemical shifts in the ^{13}C NMR spectra for compounds **1(c—e)÷7(c—e)**

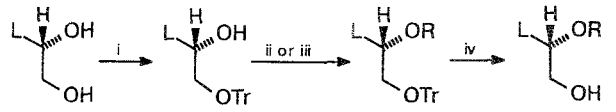
Compound*	δ			
	C_a	C_b	C_c	C_d
1c	64.0	70.9	71.7	
2c	72.7	69.5	71.4	
3c	71.2	69.3	71.2	
4c	62.6	79.8	70.2	
5c	62.3	78.1	69.9	
6c	71.5	78.5	70.3	
7c	70.3	77.3	70.3	
1d	67.5	68.0	18.5	
2d	75.9	64.7	18.3	
3d	75.9	66.5	18.7	
6d	74.8	74.6	16.7	
7d	74.3	74.1	17.3	
1e	63.1	79.6	33.5	26.0
3e	69.4	76.3	33.1	25.8

*Chemical shifts for compounds **2** and **4**, **3** and **5** were determined from spectra for **2/4** and **3/5** mixtures. Chemical shifts (δ) for compounds **3**, **5**, and **7**: 73—69 (OCH_2), 60—58 (CH_3O); for compounds **2**, **4**, and **6**: 138.2±0.5 (=C—), 129—127 (=CH); 73—71 (CH_2Ph).

unreacted glycol could not be isolated due to its high solubility. Therefore, the yields of the products calculated with respect to the starting amounts of the glycols are somewhat arbitrary. However, provided that the yields are calculated using the same procedure, they permit us to characterize quantitatively the reactivities of the primary and secondary hydroxyls in the objects selected.

The data presented in Table 5 indicate that the carbohydrate-related vicinal glycols **1a** and **1b** show a distinct tendency to be preferentially alkylated at the secondary OH groups. The alkylation of **1b** with benzyl chloride gives twice as much monoether **4b** as monoether

Scheme 3



1a—c **8a—c** **9a—c** **10a—c** **4a—c** **5a—c**

R = $PhCH_2$ (**9a—c**, **4a—c**)
R = $MeOCH_2CH_2$ (**10a—c**, **5a—c**)

Reagents and conditions:

i. TrCl/PyH; ii. $PhCH_2Cl$/KOH—DMSO (20°C)
iii. $MeOCH_2CH_2OTs$/KOH—DMSO (60°C)
iv. PPTS—MeOH, Δ, 10 min

2b, whereas the reaction of **1a** with $PhCH_2Cl$ proceeds regioselectively at the secondary hydroxyl to give the almost pure monoether **4a** (according to NMR data, the product is of 95 % purity) in a preparative yield of 52 %. This effect offers possibilities for selective protection in 1,3:2,4-di-O-ethylidene-*D*-glucitol **1a**. We used this fact for the synthesis of aza-crown ethers based on this readily available building block.[8] The lower selectivity of alkylation of **1a** with $MeOCH_2CH_2OTs$ in comparison with benzylation may be to some extent related to the chelating nature of this electrophile, although in the case of the alkylation of **1b** both alkylating reagents produce the regioisomeric monoethers **2b** and **4b** in equal ratios.

The formation of 2-O-alkylated products from diols **1d** and **1e** which incorporate no additional oxygen functions, as well as the formation of type **7** bis-alkylated

Table 4. Chemical shifts in the ^{13}C NMR spectra for compounds **8—10**

Compound*	δ							
	C_a	C_b	C_c	C_d	C_e	C_f	C_g	
8a	63.4	67.8	77.6	68.6	69.9	69.5	98.6	20.8;20.7
9a	62.3	75.7	76.6	68.3	70.1	69.6	98.7	21.1;20.8
10a	61.2	74.5	76.6	68.3	70.0	69.6	98.7;98.6	21.0;20.8
8b	65.2	68.3	79.4	81.5 57.8	84.4	105.0	111.5	26.7;26.3
9b	64.6	76.4	78.9	81.3 57.6	83.6	105.2	111.5	26.8;26.4
10b	63.6	75.3	78.7	83.6 57.3	81.1	105.0	111.4	26.6;26.3
8c	64.5	69.8	71.5					
9c	63.6	78.9	70.6					
10c	63.7	77.7	70.8					

*$(C_6H_5)_3C$: 144.4±0.2 (=C—), 129.0—126.5 (=C—H), 86.4±0.3 (Ph_3C—O); $C_6H_5CH_2$: 138.3±0.6 (=C—). 129.0—126.5 (=C—H), 72.6±0.7 (OCH_2); $CH_3O(CH_2)_2$: 73.4—69.1 [$(CH_2)_2O$]. 58.5±0.4 (CH_3O).

Table 5. Results of alkylation of vicinal glycols **1a—e**

Glycol	Reagent							
	$PhCH_2Cl$ (20°C)[a]				$MeOCH_2CH_2OTs$ (60°C)[b]			
	Yield (%)			Ratio	Yield (%)			Ratio
	2	**4**	**6**	**4:2**	**3**	**5**	**7**	**5:3**
1a	—	52.0	8.0	~1:0	15.1	32.2	20.1	2:1
	—	37.0	16.5[b]	~1:0				
1b	13.0	26.0	—	2:1	18.7	35.8	6.7	2:1
	6.0	12.0	50.0[b]	~2:1				
1c	13.3	13.3	20.0	~1:1	15.0	15.0	10.0	1:1
1d	30.0	—	4.0		36.0	—	15.5	—
1e	Not studied			—	85.7	—	—	—

[a]Ratio, mol/mol: [**1**]:[KOH] = 1:1.
[b]Ratio, mol/mol: [**1**]:[KOH] = 1:3.

products from the sterically hindered diol **1e** and $MeOCH_2CH_2OTs$ was not detected under the conditions used. Thus, O-alkylation of these non-carbohydrate diols proceeds preferentially, or even exclusively, at the primary hydroxyl.

As can be seen from Table 5, the compositions of the products resulting from O-benzylation of glycols **1a** and **1b** depend on the concentration of the alkali in the reaction medium. Thus, an increase in this concentration does not change the ratios of the monoethers, **4a**:**2a** or **4b**:**2b**; however, the portion of the corresponding diethers (**6a** and **6b**) increases. The latter fact may point both to the equalization of the alkylation rates of the primary and the secondary hydroxyls (under conditions when the difference in pK_a of the OH groups is no longer significant), and to the effect of alkylation of the secondary hydroxyl on the alkylation rate of the neighboring primary hydroxyl. Both possibilities have been discussed earlier in relation to similar effects observed during O-alkylation of aldopyranosides;[4,9–11] in this case (thermodynamic control conditions) the most acidic (due to the inductive effect of the neighboring acetal moiety) hydroxyl at C(2) undergoes selective deprotonation. In the case of glycols **1a** and **1b**, both the regioselectivity of monoalkylation and the effect of concentration on this reaction are likely to have a somewhat different explanation.

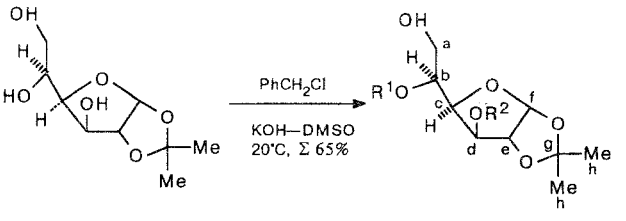
Of special interest is the alkylation of diol **1c**; the oxygen atom of the benzyloxy group in **1c** activates the neighboring secondary OH group in such a way that the competitive O-alkylation of this diol gives equal amounts of monoethers **4c** and **2c**.

The above data indicate that the enhancement of reactivity of the secondary OH groups relative to the primary OH groups (in S_N2 substitution reactions) is not just a feature of carbohydrate-related diols, but is more general. This behavior is probably due to the participation of oxygen atoms (the neighboring atoms or those close to the diol system) in intramolecular bonding with the OH groups, which influences the thermodynamic acidity of the hydroxyls and/or in the chelation with the metal cations in the corresponding alkoxides, which may stabilize the intermediate compounds involving the secondary oxanion. In turn, both of these factors may depend significantly on the nature of the solvent and on the concentrations of base and metal ions.

Evidently, the superbasic medium also contributes to the above effect. This is demonstrated by the results of partial O-benzylation of 1,2-O-isopropylidene-α-*D*-glucofuranose **11** in a KOH/DMSO system at 20°C. This reaction leads to a mixture of two isomeric products of alkylation at the secondary hydroxyls (compounds **12** and **13**, respectively); the primary hydroxyl of triol **11** does not react at all (Scheme 4).

The ratio of isomeric monoethers **12** and **13**, established from the ^{13}C NMR spectrum of the mixture thus obtained (Table 6), proved to be 1:1. O-Benzylation of triol **11** has been reported before;[12] in this case the alkoxide-anion was generated by the action of sodium on **11** in dioxane. Only the alkylation of the 3-OH occurred under these conditions, whereas the 5-OH and 6-OH hydroxyls did not undergo the reaction. The loss of selectivity in the change from the conditions reported in ref. 12 to a superbasic system may be due to the fact that in the former case O-benzylation proceeds under thermodynamic control, whereas in the latter case, it

Scheme 4



11

12 R^1 = H, R^2 = $PhCH_2$
13 R^1 = $PhCH_2$, R^2 = H

(**12**:**13** = 1:1)

Table 6. Chemical shifts in the ^{13}C NMR spectra for compounds **11—13*** ($CDCl_3$+CD_3OD, 1:1)

Compound	δ						
	C_a	C_b	C_c	C_d	C_e	C_f	C_g, C_h
11	65.0	70.3	81.0	75.4	85.1	106.0	111.6 27.2; 26.6
12	64.3	69.0	80.0	81.9	82.1	104.4	111.5 26.7; 26.1
13	62.0	77.5	79.5	75.1	85.1	105.0	111.7 26.7; 26.1

*Chemical shift for $PhCH_2$ (δ): 137.8 and 137.4 (=C—), 127.7—128.5 (=C—H), 73.2 and 72.2 (CH_2Ph).

proceeds under conditions where the acidities of the 3-OH and 5-OH groups level off (however, those of 6-OH and 5-OH are still different!). This comparison once more suggests the importance of the effect of the medium in the combined action of the factors influencing the preference of one or another transition state in the O-alkylation of diols and polyols.

Experimental

Preparative chromatography was carried out on neutral Al_2O_3 (Brockman activity II) using glass columns. TLC was performed using plates with an unfixed Al_2O_3 layer in ether—chloroform systems with a varying ratio of the components. Capillary GLC was carried out with a HP-5980 instrument equipped with a quartz capillary column 25 m in length, on a SE-30 stationary phase, with nitrogen as the carrier gas; the temperature was programmed from 50°C to 180°C. DMSO was twice distilled from powdered NaOH. For the experiments carried out in the superbasic medium, KOH was melted, cooled, and ground just before use. All of the reactions and the preliminary operations were carried out under argon. ^{13}C NMR spectra were recorded with a JEOL FX 90Q spectrometer (22.50 MHz for ^{13}C) in 5-mm tubes. $CDCl_3$ (δ 77.1), $(CD_3)_2CO$ (δ 29.8), and CD_3OD (δ 49.3) were used as solvents. The computer memory is 24 K. The pulse duration was 6 μs (45°) or 11 μs (90°). The inter-pulse delay varied from 2 s to 6 s. The differentiation between the signals from CH_3, CH_2, CH, and the quaternary C atom was achieved by employing the INEPT/COM procedure.

The starting vicinal glycols 1(a—d)

1,3:2,4-Di-O-ethylidene-*D*-glucitol (1a) was prepared using the procedure in ref. 1.

1,2-O-Isopropylidene-3-O-methyl-α-*D*-glucofuranose (1b) was prepared by methylation of 1,2:5,6-di-O-isopropylidene-α-*D*-glucofuranose with CH_3I under standard conditions of alkylation in the superbasic medium KOH/DMSO (see below) with subsequent removal of the acetal protection in an acid medium according to the procedure given in ref. 13. The yield of **1b** was 88 % over the two stages.

(±)1,2-Propandiol (1d) was used as a "pure" grade commercial reagent, b.p. 186—187 °C.

(±)-3,3-Dimethylbutane-1,2-diol (1e) was prepared according to a modified method[14] (the intermediate ketone was reduced with $NaBH_4$) in 40 % yield; bp 83—84°C (8 Torr); mp 46—48°C (literature data: b.p. 95°C (12 Torr), m.p. 47—48°C).

***R*-(+)-1-O-Benzylglycerol (1c)** was prepared from *S*-1,2-O-isopropylideneglycerol[11] by reaction with $PhCH_2Cl$ under standard alkylation conditions in the superbasic medium followed by removal of the acetal protection by a 1:1 (v/v) mixture of 5 % aqueous HCl and THF. The reaction was monitored by TLC (ether—hexane). The yield of **1c** amounted to 65.5 % over the two stages; bp 122—123 °C (0.7 Torr); n_D^{20} 1.5290. The ^{13}C NMR spectrum is given in Table 3.

1,3:2,4-Di-O-ethylidene-6-O-trityl-*D*-glucitol (8a) was prepared from **1a** according to the procedure in ref. 15, mp 92—93°C (from methanol), in 70 % yield. The ^{13}C NMR spectrum appears in Table 4.

1,2-O-Isopropylidene-3-O-methyl-6-O-trityl-α-*D*-glucofuranose (8b) was prepared from **1b** according to the procedure in ref. 16, m.p. 142—143 °C (from ether), in 70 % yield. The ^{13}C NMR spectrum appears in Table 4.

1-O-Benzyl-3-O-tritylglycerol (8c) was prepared from **1c** according to the procedure in ref. 16 as a colorless oil, R_f 0.48 (hexane—ether, 1:1), in 66 % yield. The ^{13}C NMR spectrum appears in Table 4.

Alkylation of glycols 1a—e in the superbasic medium (general procedure)

Alkylation with benzyl chloride. To a mixture of glycol **1** (10 mmol) and KOH (10 mmol) in 50 mL of DMSO, benzyl chloride was slowly added at 20°C, and the mixture was stirred for 8 h. After cooling the reaction mixture was poured into 100 mL of water; then the mixture was successively extracted with ether and with chloroform. The organic solutions were washed with water, dried with K_2CO_3, and the solvents were evaporated *in vacuo*. From the ethereal solution, a mixture of monoethers **2** and **4** and diether **6** were obtained. From the chloroform solution, an additional amount of the mixture of monoethers with an admixture of DMSO was obtained. The mixtures were separated by column chromatography or TLC, using an ether—chloroform mixture as the eluent.

Diethers **6** (the first fraction) and a mixture of monoethers **2** and **4** (the second fraction) were isolated as oils. The compositions of the mixtures containing monoethers were established by means of GLC and NMR. The results of the analyses and the yields of the products appear in Table 5. The relevant ^{13}C NMR spectra are presented in Tables 2 and 3.

In the case of glycols **1a** and **1b**, additional experiments were run at the molar ratio [KOH]:[**1**] of 3:1; the results are presented in Table 5. Monoethers **4a, 2b, 4b,** and **2d,** along with diethers **6a—d,** were isolated as pure compounds by means of preparative chromatography, whereas monoethers **2c** and **4c** were obtained as a mixture.

Alkylation with 2-methoxyethanol tosylate. To a mixture of glycol **1** (10 mmol) and KOH (30 mmol) in 50 mL of DMSO, 2-methoxyethanol tosylate (10 mmol) in 50 mL of DMSO was slowly added at 60°C, and the reaction mixture was stirred for 8 h. The reaction was worked-up in a way similar to that described above. The results are presented in Table 5. Monoethers **3d** and **3e,** along with diethers **7a—d,** were isolated as pure compounds whereas monoethers **3a** and **5a,** as well as **3c** and **5c,** were obtained as mixtures.

(+)-1-O-Benzylpropane-1,2-diol (2d), bp 98—100°C (20 Torr), n_D^{20} 1.5120; the relevant ^{13}C NMR spectrum appears in Table 3.

1,2-Di-O-benzylpropane-1,2-diol (6d), b.p. 119—120°C (1 Torr), n_D^{20} 1.5250; the relevant ^{13}C NMR spectrum appears in Table 3.

(±)-1-O-(2-Methoxyethyl)propane-1,2-diol (3d), b.p. 76—77°C (12 Torr); n_D^{20} 1.4560; the relevant ^{13}C NMR spectrum appears in Table 3.

All other products are oils; their ^{13}C NMR spectra appear in Tables 2 and 3.

The composition of the mixture of monoethers **2c** and **4c,** as well as that of **3c** and **5c,** was deduced from the ^{13}C NMR spectra (Tables 2 and 3).

Alkyl-trityl ethers 9a—c and 10a—c were prepared according to the above alkylation procedure.

5-O-Benzyl-1,3:2,4-di-O-ethylidene-6-O-trityl-*D*-glucitol (9a). The reaction of **8a** (4.76 g, 10 mmol), $PhCH_2Cl$ (2.53 g, 20 mmol), and KOH (1.68 g, 30 mmol) carried out at 20°C afforded 4.98 g (88 %) of **9a**, m.p. 162—163 °C (from ether).

5-O-Benzyl-6-O-trityl-1,2-isopropylidene-3-O-methyl-α-*D*-glucofuranose (9b). The reaction of **8b** (4.76 g, 10 mmol), $PhCH_2Cl$ (2.53 g, 20 mmol), and KOH (1.68 g, 30 mmol) carried out at 20°C afforded 3.67 g (65 %) of **9b** as a colorless oil, R_f 0.45 (hexane—ether, 1:1).

1,2-O-Dibenzyl-3-O-tritylglycerol (9c). The reaction of **8c** (4.23 g, 10 mmol), $PhCH_2Cl$ (2.53 g, 20 mmol), and KOH (1.68 g, 30 mmol) carried out at 20°C afforded 3.38 g (66 %) of **9c** as a colorless oil, R_f 0.60 (hexane—ether, 1:1).

1,3:2,4-Di-O-ethylidene-5-O-(2-methoxyethyl)-6-O-trityl-*D*-glucitol (10a). The reaction of **8a** (4.76 g, 10 mmol), $CH_3OCH_2CH_2OTs$ (4.6 g, 20 mmol), and KOH (1.68 g, 30 mmol) carried out at 60°C afforded 3.52 g (66 %) of **10a**, m.p. 123—124 °C (from ether).

1,2-Isopropylidene-5-O-(2-methoxyethyl)-3-O-methyl-6-O-trityl-α-*D*-glucofuranose (10b). The reaction of **8b** (4.76 g, 10 mmol), $CH_3OCH_2CH_2OTs$ (4.6 g, 20 mmol), and KOH (1.68 g, 30 mmol) carried out at 60 °C afforded 3.46 g (65 %) of **10b** as a yellow oil, R_f 0.5 (chloroform).

1-O-Benzyl-2-O-(2-methoxyethyl)3-O-tritylglycerol (10c). The reaction of **8c** (4.23 g, 10 mmol), $CH_3OCH_2CH_2OTs$ (4.6 g, 20 mmol), and KOH (1.68 g, 30 mmol) carried out at 60°C afforded 2.88 g (60 %) of **10c** as a yellow oil, R_f 0.38 (ether—chloroform, 1:1). The ^{13}C NMR spectra of ethers **9a—c** and **10a—c** are presented in Table 4.

Deprotection of alkyl-trityl ethers 9a—c and 10a—c was carried out by boiling them with PPTS (10 %) in methanol. Monoethers **4a—c** and **5a—c** were obtained in quantitative yields.

Benzylation of 1,2-O-isopropylidene-α-*D*-glucofuranose 11 was carried out under standard conditions. The resulting mixture of monoethers **12** and **13** (oil, yield 65 %) was analyzed by ^{13}C NMR. The relevant results appear in Table 6.

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