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CHIRAL COMPLEX FORMERS AND AGENTS FOR TRANSPHASE TRANSFER. COMMUNICATION 4.* APPLICATION OF O-ALKYLATION IN SUPERBASIC MEDIUM TO THE SYNTHESIS OF PODANDS AND CROWN ETHERS FROM 1,4;3,6-DIANHYDRO-D-MANNITOL

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The alkylation of 1,4:3,6-dianhydro-D-mannitol (I) has not been studied much; only the synthesis of diallyl [2] and dibenzyl [3] ethers and methylation using Ag_2O and CH_3I have been described [4]. In O-alkylation of (I) for the synthesis of podands and crown ethers, we have found that compound (I) does not undergo O-alkylation with tosylates of monoethyl ethers of mono- and diethylene glycols or with the corresponding bromides either in an organic solvent—50% aqueous alkali two-phase system under multiphase catalysis conditions, (catalysts TEBAC, TBAB, 18K6, B18K6), or by reaction with NaH in THF or dioxane. By the Hakomori method [5] that is traditional in carbohydrate chemistry, we could obtain acceptable results only by introducing substituents of relatively low bulk, i.e., for the synthesis of podands (II) and (III) (Table 1). When the alkylating agent contains a bulky substituent the relative yields of the monoalkylation products (IVa) and (Va) increase. Probably the endo location of the hydroxyl groups in diol (I) hinders attack by a second molecule of reagent.

We obtained much better yields of products of complete O-alkylation of (I) by reaction in superbasic medium, as previously proposed [6] for O-alkylation of aliphatic alcohols. This method (variant A) always gives a higher overall yield of alkylation product and a relatively lower yield of monoalkylation product than the Hakomori method (variant B) (see Table 1). The reaction is carried out with diol (I) and the alkylating agent in abs. DMSO in the presence of freshly melted and ground NaOH (60°C, 12 h); product yield 57-100%. Bromides give better results then tosylates, and NaOH is preferable to KOH. The preheating of NaOH to the melting point in an Ar stream increases the diether yield by 5-10%. This method gives more stable results than variant B, does not require careful drying of DMSO, and avoids the use of NaH.

*For previous communication, see [1].

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TABLE 1. Effect of Reaction Conditions on O-Alkylation of 1,4;3,6-Dianhydro-D-mannitol

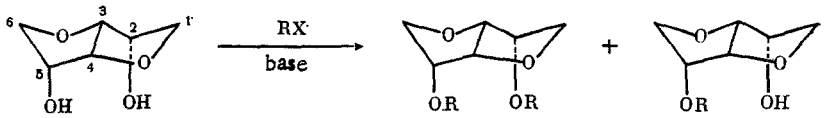
Alkylating agent, RX	Alkylation variant and product yields, %	
	NaOH/DMSO(A)	NaH/DMSO (B)
MeI	(II) – 69; (IIa) – 0	(II) – 31; (IIa) – 0
$EtOCH_2CH_2Br$	(III) – 90; (IIIa) – 0	(III) – 76; (IIIa) – 0
$EtOCH_2CH_2OTs$	(III) – 82; (IIIa) – 0	(III) – 70; (IIIa) – 0
$(EtO)_2CH_2CH_2Br$	(IV) – 90; (IVa) – 8	(IV) – 29; (IVa) – 20
$EtOCH_2CH_2OCH_2CH_2Br$	(V) – 57; (Va) – 10	(V) – 18; (Va) – 24
$EtOCH_2CH_2OCH_2CH_2OTs$	(V) – 50; (Va) – 8	(V) – 20; (Va) – 25
$THP-OCH_2CH_2Br$	(VI) – 100; (VIa) – 0	(VI) – 0; (VIa) – 40

TABLE 2. Properties of Monoethers Synthesized by O-Alkylation of Compound (I) (Variant B)

Compound	Mass spectrum m/z (M^+)	PMR spectrum δ, ppm ($CDCl_3$)	Found / Calculated, % C	Found / Calculated, % H	Empirical formula
(IVa) *	262	1.2 m (6H, CH_3), 2,6s (1H, OH), 3.50m (4H, C^1, C^6, CH_2O), 3.7 m (4H, CH_2CH_3), 4.1 m (4H, C^2, C^5, C^1, C^6) 4.5 m (2H, C^3, C^4), 4,63 t (1H, CHO)	54,48 / 54,95	8,49 / 8,45	$C_{12}H_{22}O_6$
(Va) **	262	1.06 m (3H, CH_3), 3,38q (2H, CH_2CH_3) 3,4–3,6 m (10H, CH_2O, C^1, C^6), 3,8q (2H, C^1, C^6), 4,0 m (2H, C^2, C^5, 4,1, (1H, OH), 4,34 m (2H, C^3, C^4)	53,92 / 54,95	8,47 / 8,45	$C_{12}H_{22}O_6$
(VIa) **	274	1.6 m (6H; CH_2–THP, 2,8 s (1H, OH). 3,3–3,6 m (8H, CH_2O, C^1, C^6), 3,85–4,10 m (4H, C^2, C^5, C^1, C^6), 4,48 m (2H, C^3, C^4), 4,65 t (1H, CH–O)	57.67 / 56,92	7.81 / 8,08	$C_{12}H_{22}O_6$

*Bp 138-140 (0.3 mm); mp 40°C (from Et_2O–C_6H_{14}).
**Product purified by chromatography on Al_2O_3.

The properties of the resulting diethers (II)-(VI) are described in [1]; the properties of the monoethers obtained by the Hakomori method are given in Table 2.

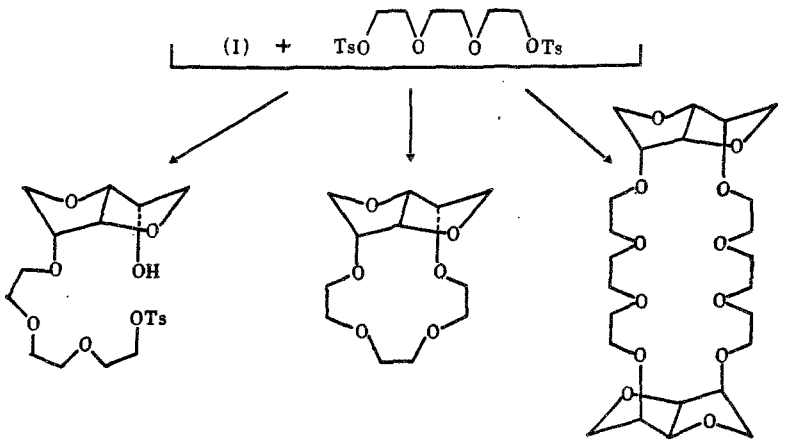


(I) (II)-(VI) (IIa)-(VIa)

An especially notable advantage of our method appears in the alkylation of diol (I) by the tetrahydropyranyl ether of ethylene bromohydrin; this reaction in superbasic medium gives pure diether (VI) in quantitative yield, whereas by the Hakomori method only monoether (VIa) can be obtained. Our method of synthesizing (VI) opens a convenient route to grafting 1,4;3,6-dianhydro-D-mannitol (I) to an ethylene glycol chain from each side at positions 2 and 5 [1].

The application of alkylation in superbasic medium to the synthesis of crown ethers from D-mannitol makes it possible to obtain crown ethers that under other conditons are obtained either not at all or in very low yield. Thus the condensation of diol (I) with triethylene glycol ditosylate in NaH/dioxane or NaH/THF gives the product of diol monoalkylation, tosyloxyalcohol (VII), while crown ethers (VIII) and (IX) are obtained in insignificant amounts (9.3 and 7.6% yield respectively). In superbasic medium, however, the reaction gives

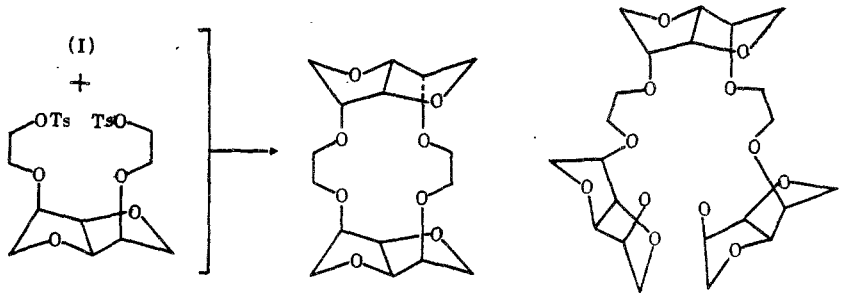
18-crown-6-ether (VIII) in 60% yield, while formation of the intermediate tosylate (VII) is not observed.



(VII) (VIII) (IX)

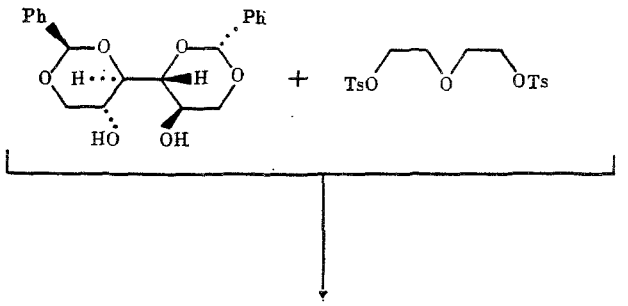
Apparently in the synthesis of crown ethers from diol (I) (as in podand synthesis) the rate of monoalkylation at one OH is significantly faster than at the other OH. The accelerating effect of NaOH may possibly be attributed to the fact that due to steric hindrance the OH^- anion is better able to deprotonate the second OH group in diol (I) than is the $CH_3SOCH_2^-$ anion.

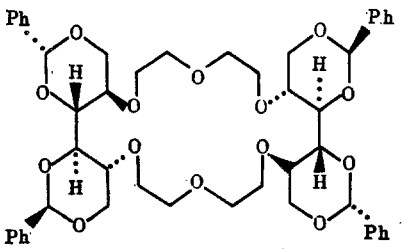
24-Crown-8-ether (XI), described in our preceding communication [1], can also be obtained by the Hakomori method by condensation of diol (I) with ditosylate (X) in 18.7% yield. But along with (XI) there is formed (XII), the condensation product of one molecule of (X) with two of (I). The reason for the formation of (XII) may also be the difference in the rates of mono- and dialkylation of diol (I).



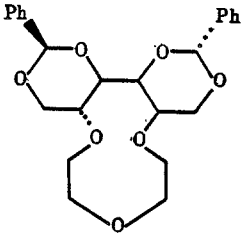
(X) (XI) (XII)

We used the above method to synthesize crown ethers from 1,3;4,6-di-O-benzylidene-D-mannitol (XIII). We obtained the chiral 22-crown-6-ether (XIV) in 28% yield (this has three axes of second-order symmetry), and 11-crown-3, (XV), in 19% yield.





(XIV)



(XV)

EXPERIMENTAL

Preparative chromatography was carried out on neutral Al_2O_3 (activity grade II) or Florisil. TLC was carried out on sheets with an unattached Al_2O_3 layer. DMSO was purified by two-fold distillation from powdered NaOH. For tests in superbasic medium NaOH was melted immediately before the reaction and when cool was crushed to powder. All reactions and preparative operations were carried out under Ar. PMR and ^{13}C NMR spectra were obtained with a Bruker WM-250 instrument in $CDCl_3$. Mass spectra were obtained with a Varian MAT-44S instrument by thermal desorption (200°C min), chemical ionization, and field evaporation from solution (FEFS). Values of $[\alpha]_D^{20}$ were determined with a Spectropol-1 instrument.

Preparation of compound (I) and the alkylating agents has been described in [1]. Diethylene glycol ditosylate was synthesized according to [7], mp 86-88°C. PMR spectrum (δ, ppm): 2.43 s (6H, CH_3), 3.50-3.65 m (4H, CH_2), 4.0-4.15 m (4H, CH_2-OTs), 7.28-7.87 m (8H, C_6H_4). Triethylene glycol ditosylate was synthesized according to [7], mp 79-81°C. PMR spectrum (δ, ppm): 2.43 s (6H, CH_3), 3.50-3.70 m (8H, CH_2), 4.07-4.22 (4H, CH_2-OTs), 7.25-7.87 m (8H, C_6H_4). 1,3;4,6-Di-O-benzylidene-D-mannitol (XIII) was synthesized according to [8] in 55.3% yield, mp 168-170°C (from EtOH), $[\alpha]_D^{20}$ −6.1° (c 0.70, Me_2CO). PMR spectrum (δ, ppm): 3.54-3.65 m (2H, CH-OH), 4.0 d (4H, CH_2), 4.22 d (2H, CH), 4.38 s (2H, OH), 5.52 s (2H, O-CH-O), 7.27-7.48 m (10H, C_6H_5). ^{13}C NMR spectrum (δ, ppm): 58.8 (CH), 70.55 (CH), 78.1 (CH_2), 100.34 (O-CH-O), 125, 49, 127.05, 127.71, 137.77 (C_6H_5).

General Alkylation Procedure by the Hakomori Method (Variant B). To a solution of 1.46 g (10 mmoles) of (I) in 50 ml of DMSO was added 0.6 g (25 mmoles) of NaH portionwise, and the mixture was stirred at 50°C until H_2 evolution stopped (2 h). To the resulting suspension 30 mmoles of tosylate or bromide was added with stirring, and the mixture was stirred for 12 h at 70°C. DMSO was distilled off in vacuum, and the residue was treated with a $CHCl_3$–H_2O mixture. The chloroform solution was evaporated in vacuum, and the residue was chromatographed on a column with Al_2O_3 (elution with Et_2O–$CHCl_3$ mixtures).

2,5-Di-O-(2-(2'-tosyloxyethoxy)-1,4:3,6-dianhydro-D-mannitol (X). To a solution of 0.95 g (4 mmoles) of 2,5-di-O-(2'-hydroxyethoxy)-1,4:3,6-dianhydro-D-mannitol [1] and 0.8 g (12 mmole) of Py in 20 ml of CH_2Cl_2 at 0°C was added 1.67 g (8 mmoles) of tosyl chloride, and the mixture was kept for 1 h at 0°C and 24 h at 20°C. The solution was washed with cold 10% HCl, saturated $NaHCO_3$ solution, and saturated NaCl solution, and evaporated in vacuum. The residue was dried by azeotropic distillation with benzene in vacuum. Compound (X) was obtained as a colorless oil, pure according to TLC, R_f 0.77 ± 0.05 ($CHCl_3$), yield 1.73 g (80%). PMR spectrum, (δ, ppm): 2.6 s (6H, CH_3), 3.68-3.80 m (12H, CH_2, C^1, C^6), 3.92-4.12 m (2H, C^2, C^5), 4.52-4.60 m (2H, C^3, C^4) 7.30-7.75 m (8H, C_6H_5).

Bisdianhydro-D-mannito-24-crown-8 (XI). To 0.43 g (18 mmoles) of NaH was added 10 ml of DMSO and the mixture was stirred at 50°C for 1 h. Then over the next 4 h, a solution of 1 g (7.5 mmole) of (I) and 4.2 g (2 mmoles) of ditosylate (X) in 100 ml of DMSO was added. The mixture was stirred at 75°C for 56 h, 2 ml of MeOH was added, DMSO was distilled off in vacuum, and the residue was treated with a $CHCl_3$–H_2O mixture. The chloroform layer was evaporated in vacuum. From the residue there were separated by preparative TLC 0.44 g (18.7%) of (XI) [1] with R_f 0.38 ± 0.05, and 0.54 g (16.4%) of (XII) as a colorless oil with R_f 0.20 ± 0.05 (Al_2O_3, $CHCl_3$:C_2H_5OH 100:1). PMR spectrum (δ, ppm): 3.65-3.80 m (20H, CH_2, C^1, C^6), 3.80-4.20 m (6H, C^2, C^5), 4.50-4.60 m (6H, C^3, C^4). Mass spectrum, m/z: 490 (M^+), 508 ($M^+ + NH_4^+$). $C_{22}H_{34}O_{12}$. Calculated, M 490.

General Procedure for Synthesis of Crown Ethers Derived from D-mannitol in Superbasic Medium. To a suspension of freshly melted NaOH (2.4 g, 60 mmoles) in 100 ml of abs. DMSO at 65°C was added very slowly (over 4 h) a solution of 10 mmoles of diol and 30 mmoles of difunc-

tional polyethylene glycol derivative (ditosylate, dihalide) in 50 ml of abs. DMSO. The mixture was stirred at 70-75°C for 64 h. DMSO was distilled off in vacuum, the solid residue was treated with a $CHCl_3$–water mixture, and the chloroform solution was evaporated in vacuum. The residue was chromatographed on a column with Al_2O_3 (elution with Et_2O–$CHCl_3$ mixtures).

1,4;3,6-Dianhydro-D-mannitol-18-crown-6 (VIII). From 1.46 g (10 mmoles) of (I), 5.49 g (12 mmoles) of $(TsOCH_2CH_2)_2O$ and 2.4 g (60 mmoles) of NaOH, (VIII) was obtained as a colorless oil with R_f 0.67 ± 0.05 (Al_2O_3, $CHCl_3$:CH_3OH 100:1), yield 1.38 g (50%). $[\alpha]D^{20}$ +37.18° (c 1.88), $CHCl_3$). PMR spectrum (δ, ppm): 3.65-3.80 m, (16H, CH_2, C^1, C^6), 3.80-4.20 m (2H, C^2, C^5), 4.51-4.62 m (2H, C^3, C^4). Mass spectrum, m/z: 260 (M^+), 278 ($M + NH_4^+$), 283 (260 + Na^+). $C_{12}H_{20}O_6$. Calculated: M 260.

Bis-1,3;4,6-di-O-benzylidene-D-mannitol-22-crown-6 (XIV) and 1,3:4,6-Di-O-benzylidine-D-mannitol-11-crown-3 (XV). From 3.58 g (10 mmoles) of diol (XIII), 5.49 g (12 mmoles) of $TsOCH_2CH_2)_2O$ and 2.4 g (60 mmoles) of NaOH, after separation by preparative TLC on Florisil ($CHCl_3$ elution), (XV) was separated as a colorless oil, with R_f 0.61 ± 0.05 (n-C_6H_{14}: EtOAc 1:2), $[\alpha]_D^{20}$ −38.3° (c 2.0, $CHCl_3$), yield 0.8 g (19%). PMR spectrum (δ, ppm): 3.32-4.58 m (16H, CH_2, CH), 5.56 s (2H, O–CH–O), 7.35-7.60 m (10H, C_6H_5). ^{13}C NMR spectrum (δ, ppm): 69.05 (CH), 69.9 (CH_2), 70.5 (CH), 76.6, 77.2, 77.7 (CH_2), 101.1 (O–CH–O), 126.4, 128.8, 129.9, 138.5 (C_6H_5). Mass spectrum, m/z: 428 (M^+), 446 ($M^+ + NH_4^+$), 451 ($M^+ + Na^+$). $C_{24}H_{28}O_7$. Calculated: M 428. Elution of the lower zone gave (XIV) as amorphous material with mp 35-37°C, R_f 0.45 ± 0.05 (n-C_6H_{14}–EtOAc 1:2). $[\alpha]_D^{20}$ −26.01° (c 2.0 $CHCl_3$), yield 1.2 g (28%). PMR spectrum, (δ, ppm): 3.35-4.55 m (32H, CH_2, CH), 5.58 s, (4H, O–CH–O), 7.32-7.58 m (20H, C_6H_5). ^{13}C NMR spectrum (δ, ppm): 69.1 (CH), 69.8 (CH_2), 70.5 (CH), 76.7, 77.2, 77.7 (CH_2), 101.01 (O–CH–O), 126.4, 128.8, 129.8, 138.6 (C_6H_5). Mass spectrum, m/z: 874 ($M^+ + NH_4^+$), 879 ($M^+ + Na^+$). $C_{48}H_{56}O_{14}$. Calculated: M 856.

Reaction of Diol (I) with $Ts(OCH_2CH_2)_3OTs$ in Presence of NaH in Dioxane. To a suspension of 0.68 g (24.2 mmoles) of NaH in 80 ml of abs. dioxane was added over 10 h a solution of 0.71 g (4.8 mmoles) of diol (I) and 2.17 g (4.5 mmoles) of $Ts(OCH_2CH_2)_3OTs$ in 220 ml of abs. dioxane. The mixture was boiled and stirred for 24 h, 5 ml of MeOH was added, and the solution was evaporated in vacuum. Chromatography on an Al_2O_3 column (elution by $CHCl_3$–MeOH mixture, gradient from $CHCl_3$ to 60:1 $CHCl_3$:MeOH) gave 0.1 g (9.3%) of 18-crown-6-ether (VIII), R_f 0.81 ± 0.05 ($CHCl_3$), and 0.18 g (7.6%) of 36-crown-12-ether (IX), R_f 0.60 ± 0.05 ($CHCl_3$), αD^{20} +10.3° (c 2.0, $CHCl_3$). Mass spectrum, m/z: 538 ($M^+ + NH_4^+$, 543 ($M^+ + Na^+$). $C_{24}H_{40}O_{12}$. Calculated M^+ 520. Elution of the third zone gave tosyloxyalcohol (VII) as a colorless oil, R_f 0.45 ± 0.05 ($CHCl_3$), yield 1.23 g (61%). PMR spectrum (δ, ppm): 2.6 s (3H, CH_3), 2.8 s (1H, OH), 3.65-3.80 m (16H, CH_2, C^1, C^6), 3.90-4.15 m (2H, C^2, C^5), 4.50-4.58 m (2H, C^3, C^4), 7.25-7.70 m (4H, C_6H_5). Found: C 52.78; H 7.36; S 7.66%. $C_{19}H_{28}SO_9$. Calculated: C 52.76 H 6.53; S 7.41%.

CONCLUSIONS

1. Using the sterically hindered secondary diols 1,4:3,6-dianhydro-D-mannitol and 1,3:4,6-di-O-benzylidene-D-mannitol as examples, we have shown the advantage of O-alkylation of alcohols in NaOH/DMSO superbasic medium over the NaH/DMSO system for the synthesis of crown ethers and podands.

2. New crown ethers, derived from 1,4:3,6-dianhydro-D-mannitol and 1,3:4,6-di-O-benzylidene-D-mannitol and having C_2 and D_2 symmetry, have been synthesized.

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