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Synthesis, Extraction Ability and Application in an Asymmetric Synthesis of Azacrown Ethers Derived from D-Mannitol

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Abstract

New chiral monoaza-15-crown-5 ethers have been synthesised from 1,2:5,6-di-O-isopropylidene-D-mannitol. The substituent at the nitrogen atom has a major influence on the cation extraction ability of the azacrown. These sugar-based crown ethers show asymmetric induction as chiral phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone (67% ee).

Introduction

Compounds derived from carbohydrates form a separate group of chiral crown ethers. Numerous macrocycles have been synthesized recently to study the relationship between molecular structure and complexing nature as well as chiral recognition ability [1]. Although some of these compounds showed enantioselectivity, only a few proved to be effective phase-transfer catalysts in enantioselective reactions [2]. We have previously reported the synthesis and investigation of monoaza-15-crown-5 type compounds and lariat ethers containing methyl-α-D-glucopyranose- and galactopyranose moieties [3]. Macrocycles built up of galactosides (**2**) were found to have stronger complexing ability with alkali metals and ammonium ions than compounds containing glucopyranose **1**. Furthermore, we have shown that substituents (alkyl-, alkoxy-, phenyl-, etc.) on the nitrogen atom have a significant effect on the coordinating ability of the molecules. The observed complexing properties of the chiral lariat ethers were similar, to a certain extent, to the achiral N-pivot lariat ethers reported by Gokel and coworkers [4]. Nevertheless, the main point is that these chiral ligands may exert asymmetric induction. This is true especially for lariat ethers that have oxygen [5a–d] or phosphorus [5e] containing end-groups on their side arm. D-Mannitol was found also to be a structurally suitable precursor for optically active crown ethers [6]. In the present paper we report on the synthesis, extractability and effect of D-mannitol containing monoaza-15-crown-5 type molecules in an asymmetric reaction.

Experimental

General procedures

Melting points were determined with a Büchi 510 apparatus and are uncorrected. Specific rotations were determined with a Perkin Elmer 241 polarimeter at 20 °C, and UV spectra were recorded with a Hitachi-Perkin Elmer 124 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM 250 instrument in $CDCl_3$, COSY techniques were used in some cases. The mass spectra were obtained on a Jeol JMS-01 SG-2 instrument using chemical ionization. Elemental analysis was performed on a Perkin Elmer 240 automatic analyzer. Analytical and preparative thin layer chromatography was performed on silica gel (60 GF-254, Merck), column chromatography was carried out using 70-230 mesh silica gel (Merck).

Synthesis

1,2:5,6-Di-O-isopropylidene-3,4-bis-O-[(2-chloroethoxy)ethyl]-D-mannitol (**4**): A solution of 5.24 g (20 mmol) of **3** and 13.6 g of tetrabutylammonium hydrogensulphate (2

equiv.) in 100 mL of bis(2-chloroethyl)ether as solvent and reagent was vigorously stirred at room temperature with 100 mL of 50% aq. NaOH solution for 14 h. The mixture was diluted with water (100 mL) and dichloromethane (100 mL), decanted and the aqueous phase was washed with dichloromethane (2 × 50 mL). The organic extracts were combined, washed with water (2 × 50 mL), dried and concentrated under vacuum. The resultant syrup was eluted through a silica gel column with dichloromethane-methanol (100:1–100:3) yielding **4** as a colourless oil, 8.54 g (90%); (lit. [6a] yield 75%); $[\alpha]_D^{20}$ = + 13.9 (c 16, CCl_4); (lit. $[\alpha]_D^{20}$ = + 14.9 [6a]). ^{1}H NMR ($CDCl_3$) [ppm] δ 1.34 (s, 6H, CH_3), 1.40 (s, 6H, CH_3), 3.60–3.67 (m, 12H, OCH_2), 3.72 (t, 4H, CH_2Cl), 3.77–3.79 (m, 2H, 3-CH and 4-CH), 3.99–4.02 (dd, 2H, 1,6-CH_2/H-a), 4.09–4.12 (dd, 2H, 1,6-CH_2/H-e), 4.21–4.25 (m, 2H, 2-CH and 5-CH).

1,2:5,6-Di-O-isopropylidene-3,4-bis-O-[(2-iodoethoxy)ethyl]-D-mannitol (**5**). The mixture of **4** (8.5 g, 17.9 mmol) and dry NaI (10.7 g, 71.6 mmol) in dry acetone (200 mL) was heated under reflux for 24 h. After cooling the precipitate was filtered and washed. The combined acetone solution in dichloromethane (100 mL), was washed with water (3 × 50 mL), dried (Na_2SO_4) and concentrated. Compound **5** was a yellow syrup, yield 10.6 g (90%). [α]D20 = + 10.1 (c = 2, $CHCl_3$); COSY ^{1}H NMR ($CDCl_3$) δ [ppm] 1.35 (s, 6H, CH_3), 1.41 (s, 6H, CH_3), 3.23 (t, 4H, CH_2I), 3.72 (t, 4H, CH_2), 3.60 (m, 6H, CH_2, 3-CH and 4-CH overlapped), 3.82 (m, 4H, CH_2) 4.01–4.04 (dd, 2H, J = 8.5, 6.2 Hz, 1,6-CH_2/H-a), 4.09–4.12 (dd, 2H, J = 8.5, 6.2 Hz, 1,6-CH_2/H-e), 4.21–4.25 (m, 2H, 2-CH and 5-CH); COSY ^{13}C NMR ($CDCl_3$) δ [ppm] 2.8 (CH_2I), 25.4 and 26.8 (CH_3), 66.6 (1,6-CH_2), 70.3 and 72.2 (OCH_2), 75.6 (2,5-CH), 80.7 (3,4-CH), 108.5 (CH_3—*C*—CH_3); Microanalysis: calculated for $C_{20}H_{36}O_8I_2$ m. w. = 658, C 36.47, H 5.47, I 38.6%; found C 36.55, H 5.42, I 38.70%.

General method for preparation of crown ethers **6a–h**. Anhydrous Na_2CO_3 (3.8 g, 36.2 mmol) was suspended in a solution of the corresponding primary amine (4.60 mmol) and the bisiodo compound **4** (3.03 g, 4.60 mmol) in dry acetonitrile (100 mL) under argon. The stirred reaction mixture was refluxed for 32–40 h and monitored by TLC. After cooling the precipitate was filtered and washed with acetonitrile. The combined acetonitrile solution was concentrated; the residue oil was dissolved in chloroform, washed with water, dried (Na_2SO_4) and concentrated. The residues were purified by column chromatography on silica gel with dichlorometane-methanol (100:1–100:10) to afford the title compounds.

N-Butyl-monoaza-15-crown-5-derivative **6a**. Yield: 53%; $[\alpha]_D^{20}$ = + 16.8 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 0,90 (t, 3H, CH_3), 1.31 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 2.70–2.87 (m, 6H, NCH_2), 3.43–3.70 (m, 16H, OCH_2 and CH_2), 3.77–3.80 (m, 2H, 3-CH and 4-CH), 3.97–4.03 (dd, 2H, 1,6-CH_2/H-a), 4.09–4.14 (dd, 2H, 1,6-CH_2/H-e), 4.18–4.23 (m, 2H, 2-CH and 5-CH); FAB-MS, m/z 476 (M^+ +1, 100%), 101(91); Microanalysis: calcd. for $C_{24}H_{45}NO_8$ m. w. = 475, C 60.63, H 9.47, N 2.95%; found C 60.60, H 9.51, N 2.98%.

N-Cyclohexyl-monoaza-15-crown-5 derivative **6b**. Yield: 35%; $[\alpha]_D^{20}$ = + 12.3 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.02–1.82 (m, 10H, cyclohexan CH_2), 1.36 (s, 6H, CH_3), 1.41 (s, 6H, CH_3), 2.67–2.82 (m, 4H, NCH_2), 3.47–3.73 (m, 12H, OCH_2), 3.77–3.82 (m, 2H, 3-CH and 4-CH), 3.92–4.01 (dd, 2H, 1,6-CH_2/H-a), 4.09–4.13 (dd, 2H, 1,6-CH_2/H-e), 4.21–4.25 (m, 2H, 2-CH and 5-CH), 5.31 (m, 1H, cyclohexan-CH); FAB-MS, m/z 502 (M^+ +1, 100%); Microanalysis: calcd. for $C_{26}H_{47}NO_8$ m. w. = 501, C 62.28, H 9.38, N 2.79%; found C 62.36, H 9.36, N 2.75%.

N-Benzyl-monoaza-15-crown-5 derivative **6c**. Yield: 51%; $[\alpha]_D^{20}$ = + 16.7 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.31 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 2.64–2.82 (m, 4H, NCH_2), 3.38 (d, 2H, CH_2Ph), 3.48–3.66 (m, 12H, OCH_2), 3.71–3.77 (m, 2H, 3-CH and 4-CH), 3.89–4.02 (dd, 2H, 1,6-CH_2/H-a), 4.09–4.13 (dd, 2H, 1,6-CH_2/H-e), 4.18–4.23 (m, 2H, 2-CH and 5-CH), 7.18–7.23 (m, 5H, ArH); FAB-MS, m/z 510 (M^+ +1, 26%), 91 (100), 101 (34); Microanalysis: calcd. for $C_{27}H_{43}NO_8$ m. w. = 509, C 63.65, H 8.45, N 2,75%; found C 63.56, H 8.49, N 2.80%.

N-2-Phenylethyl-monoaza-15-crown-5 derivative **6d**. Yield: 54%; $[\alpha]_D^{20}$ = + 12.4 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.31 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 2.73–2.92 (m, 6H, NCH_2), 3.50–3.68 (m, 14H, OCH_2 and CH_2), 3.72–3.77 (m, 2H, 3-CH and 4-CH), 3.90–4.03 (dd, 2H, 1,6-CH_2/H-a), 4.10–4.12 (dd, 2H, 1,6-CH_2/H-e), 4.22–4.25 (m, 2H, 2-CH and 5-CH), 7.19–7.21 (m, 5H, ArH); FAB-MS, m/z 524 (M^+ +1, 67%), 432 (49), 101 (100); Microanalysis: calcd. for $C_{28}H_{45}NO_8$ m. w. = 523, C 64.25, H 8.60, N 2,68%; found C 64.29, H 8.55, N 2.73%.

N-3-Hydroxypropyl-monoaza-15-crown-5 derivative **6e**. Yield: 48%; $[\alpha]_D^{20}$ = + 15.9 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.30 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 2.56–2.80 (m, 6H, NCH_2), 3.43–3.73 (m, 17H, OCH_2, CH_2 and OH), 3.77–3.82 (m, 2H, 3-CH and 4-CH), 3.96–4.02 (dd, 2H, 1,6-CH_2/H-a), 4.09–4.13 (dd, 2H, 1,6-CH_2/H-e), 4.21–4.24 (m, 2H, 2-CH and 5-CH); CI-MS, m/z 478 (M^+ +1, 96%), 432 (13), 101 (59), 59 (75); Microanalysis: calcd. for $C_{23}H_{43}NO_9$ m. w. = 477, C 57.86, H 9.02, N 2,94%; found C 57.85, H 9.05, N 2.86%.

N-4-Hydroxybutyl-monoaza-15-crown-5 derivative **6f**. Yield: 37%; $[\alpha]_D^{20}$ = + 14.4 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.34 (s, 6H, CH_3), 1.40 (s, 6H, CH_3), 1.64 (m, 4H, CH_2), 2.56–2.78 (m, 6H, NCH_2), 3.48–3.62 (m, 12H, OCH_2), 3.67 (m, 1H, OH), 3.71–3.76 (m, 2H, 3-CH and 4-CH), 3.89–4.01 (dd, 2H, 1,6-CH_2/H-a), 4.08–4.13 (dd, 2H, 1,6-CH_2/H-e), 4.19–4.24 (m, 2H, 2-CH and 5-CH); FAB-MS, m/z 492 (M^+ +1, 100%), 101(100); Microanalysis: calcd. for $C_{24}H_{45}NO_9$ m. w. = 491, C 58.66, H 9.16, N 2,85%; found C 58.61, H 9.21, N 2.81%.

N-2-Methoxyethyl-monoaza-15-crown-5 derivative **6g**. Yield: 48%; $[\alpha]_D^{20}$ = + 14.9 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.31 (s, 6H, CH_3), 1.36 (s, 6H, CH_3), 2.63–2.90 (m, 6H, NCH_2), 3.30 (s, 3H, OCH_3), 3.37–3.87 (m, 14H, OCH_2 and CH_2), 3.53–3.70 (m, 2H, 3-CH and 4-CH), 3.97–4.03 (dd, 2H, 1,6-CH_2/H-a), 4.09–4.13 (dd, 2H, 1,6-CH_2/H-e), 4.19–4.23 (m, 2H, 2-CH and 5-CH); CI-MS, m/z 478 (M^+ +1, 93%), 432 (36), 101 (69); Microanalysis:

calcd. for $C_{23}H_{43}NO_9$ m. w. = 477, C 57.86, H 9.02, N 2,94%; found C 57.92, H 8.95, N 2.92%.

N-3-Methoxypropyl-monoaza-15-crown-5 derivative **6h**. Yield: 28%; $[\alpha]_D^{20}$ = + 16.1 (c = 1, $CHCl_3$); COSY ^{1}H NMR ($CDCl_3$) δ [ppm] 1.32 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 1.70 (m, 2H, CH_2—CH_2OCH_3), 2.57 (t, 2H, NCH_2), 2.71 (m, 2H, NCH_2), 2.78 (m, 2H, NCH_2) 3.28 (s, 3H, OCH_3), 3.38 (t, 2H, CH_2—CH_2OCH_3), 3.42 (m, 2H, 3-CH and 4-CH), 3.61 (t, 4H, OCH_2) 3.52 (m, 2H, OCH_2), 3.66 (m, 2H, OCH_2), 3.72 (m, 2H, OCH_2), 3.95 (m, 2H, OCH_2), 3.89 (dd, 2H, J = 8.6, 6.2 Hz, 1,6-CH_2/H-a), 4.05 (dd, 2H, J = 8.6, 6.2 Hz, 1,6-CH_2/H-e), 4.19 (m, 2H, 2-CH and 5-CH); COSY ^{13}C NMR ($CDCl_3$) δ [ppm] 25.6 and 26.6 (CH_3), 27.6 (CH_2-CH_2-CH_2OCH_3), 53.3 (CH_2—CH_2—CH_2OCH_3), 54.4 (NCH_2), 58.6 (OCH_3), 66.6 (1,6-CH_2), 69.8 (NCH_2), 70.8 (CH_2-CH_2-CH_2OCH_3), 70.5 and 72.5 (OCH_2), 75.6 (2,5-CH), 80.7 (3,4-CH), 108.5 (CH_3—C—CH_3); FAB-MS, m/z 492 (M^+ +1, 100%), 432 (19), 101 (79); Microanalysis: calcd. for $C_{24}H_{45}NO_9$ m. w. = 491, C 58.66, H 9.16, N 2.85%; found C 58.74, H 9.20, N 2.80%.

N-Tosyl-monoaza-15-crown-5 derivative **7**. A mixture of bischloro podand **4** (5.8 g, 12.1 mmol), toluene-*p*-sulfonamide (2.1 g, 12.2 mmol) and anhydrous K_2CO_3 (8.4 g, 60.8 mmol) was stirred and refluxed in dry DMF (360 mL) for 32 h. After the reaction was complete, the precipitate was filtered off and washed with $CHCl_3$. The combined filtrate and washings were evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$, washed with water, and dried ($MgSO_4$). After removal of solvent, column chromatography of the residue on silica gel with dichlorometane-methanol (100:2–100:5) as the eluent gave the *N*-tosyl macrocycle **7** (3.2 g, 46%); m. p. 116–117 °C (ethanol); $[\alpha]_D^{20}$ = + 17.7 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.33 (s, 6H, CH_3), 1.38 (s, 6H, CH_3), 2.41 (s, 3H, CH_3), 3.31 (m, 4H, NCH_2), 3.46–3.72 (m, 12H, OCH_2), 3.72–3.78 (m, 2H, 3-CH and 4-CH), 3.90–3.95 (dd, 2H, 1,6-CH_2/H-a), 4.05–4.08 (dd, 2H, 1,6-CH_2/H-e), 4.18–4.20 (m, 2H, 2-CH and 5-CH), 7.28 (d, 2H, ArH) and 7.41 (d, 2H, ArH); Microanalysis: calcd. for $C_{27}H_{43}NO_{10}S$ m. w. = 573, C 56.54, H 7.50, N 2.44%; found C 56.60, H 7.47, N 2.49%.

Unsubstituted monoaza-15-crown-5 derivative **8**. Compound **7** (2.8 g, 4.89 mmol), anhydrous disodium phosphate (2.85 g, 20 mmol), and 4% sodium-amalgam (24 g, 41.8 mmol) were placed in dry methanol (30 mL). The mixture was heated at reflux under a nitrogen atmosphere for 20 hours while stirring rapidly. After cooling to room temperature, the resulting slurry was decanted into water (150 mL) and extracted with chloroform (4 × 70 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield **8** (1.80 g, 87%) as a colourless oil; $[\alpha]_D^{20}$ = + 16.4 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 1.34 (s, 6H, CH_3), 1.39 (s, 6H, CH_3), 2.58 (m, 1H, NH), 2.71–2.80 (m, 4H, NCH_2), 3.56–3.70 (m, 12H, OCH_2), 3.85 (m, 2H, 3-CH and 4-CH), 3.91–3.94 (dd, 2H, 1,6-CH_2/H-a), 4.12–4.15 (dd, 2H, 1,6-CH_2/H-e), 4.33–4.34 (m, 2H, 2-CH and 5-CH); FAB-MS, m/z 420 (M^+ +1, 100%), 101 (81); calcd. for $C_{20}H_{37}NO_8$ m. w. = 419. Microanalysis: calcd. for $C_{20}H_{37}NO_8$ m. w. = 419, C 57.28, H 8.83, N 3.34%; found C 57.34, H 8.85, N 3.29%.

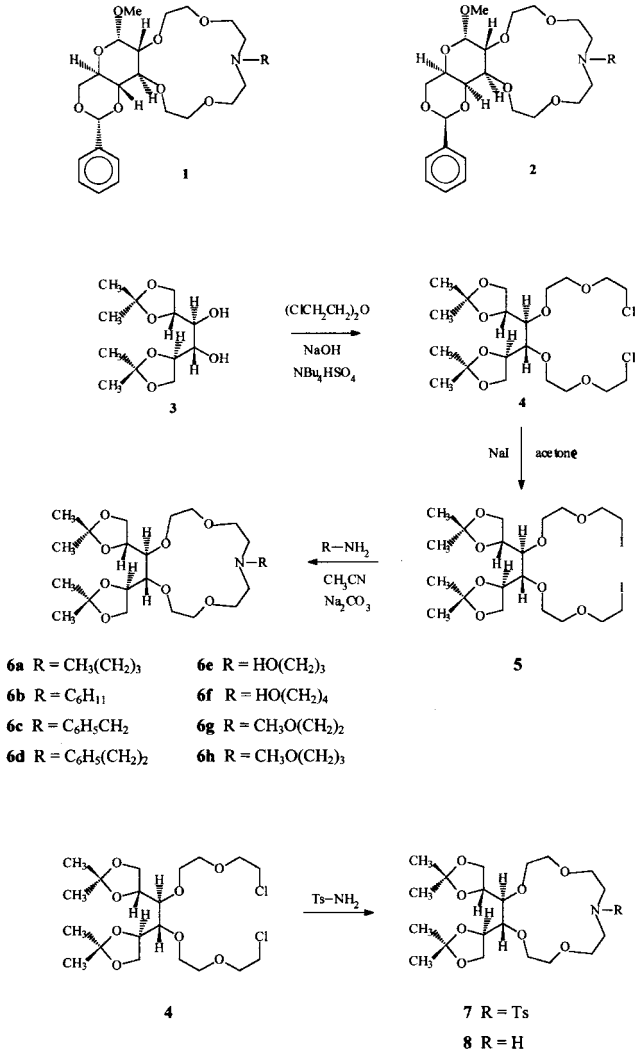


Figure 1. Synthesis of chiral crown ethers **6–8** from diisopropylidene-D-mannitol.

General procedure for the Michael addition. The reaction was performed as follows: The chalcone **9** (0.3 g, 1.44 mmol) and 2-nitropropane (0.3 ml, 3.36 mmol) were dissolved in dry toluene (3 mL), and crown ether catalyst (0.1 mmol) and sodium tert-butoxide (0.05 g, 0.5 mmol) were added. The mixture was stirred under an argon atmosphere at room temperature. After completing the reaction (48 h) a mixture of toluene (7 mL) and water (10 mL) was added. The organic phase was processed in the usual manner. The product was purified by preparative TLC on silica gel using hexane-ethyl acetate (10:1) as eluent. Mp. 146–148 °C; $[\alpha]_D^{20}$ = + 80.8 (c = 1, CH_2Cl_2) for pure (+)-(*S*) enantiomer [10]. ^{1}H NMR ($CDCl_3$) δ [ppm] 1.54 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.27 (dd, 1H, J = 17.2, 3.2 Hz, CH_2), 3.67 (dd, ^{1}H, J = 17.2, 10.4 Hz, CH_2), 4.15 (dd, 1H, J = 10.4, 3.2 Hz, CH), 7.18–7.32 (m, 5H, ArH), 7.42 (t, 2H, COPhH-*m*), 7.53 (t, 1H, COPhH-*p*), 7.85 (d, 2H, COPhH-*o*).

Results and discussion

Synthesis

The principle of the synthesis is shown in Figure 1. Hydroxyl groups at carbon atoms 3 and 4 of 1,2:5,6-di-O-isopropylidene-D-mannitol **3**, were alkylated with bis(2-chloro-ethyl)ether in a two-phase reaction (one phase was 50% NaOH, the second one was the ether itself) in the presence of 2 equivalents of tetrabutylammonium hydrogensulphate as a phase-transfer catalyst by the Gross method [7], and the bischloro podand **4** was obtained in 90% yield after 14 hours at 20 °C [6b]. The halogen exchange was performed by NaI in acetone, and the bisiodo derivative **5** was obtained in 90% yield after 24 hours reflux. This compound was a suitable substrate for the ring closing reaction by primary amines. The reaction was performed in acetonitrile in the presence of anhydrous Na_2CO_3. To avoid the intermolecular byproduct formation the reaction was performed in a diluted solution (2%). The crude product obtained after 32–40 hours of reflux was purified once or twice by column chromatography. On the nitrogen atom of 15-membered macrocycles obtained by this procedure there are different substituents depending on the type of the ring-closing amine applied. With butylamine, cyclohexylamine, benzylamine and 2-phenylethylamine compounds **6a**, **6b**, **6c**, and **6d**, respectively were obtained. We have also obtained lariat-ether type ionophores, which contain an electron donating heteroatom (oxygen) at the end of their side arm. Thus, **5** with 3-hydroxy-propylamine gave **6e**, with 4-hydroxy-butylamine gave **6f**, with 2-methoxy-ethylamine gave **6g** and with 3-methoxy-propylamine gave **6h** lariat-ethers. The yields of the ring closure product, after purification by chromatography, varied from 28–54%.

Unsubstituted compound **8** was obtained by a different route. The ring closing reaction of bischloro-podand **4** was performed by tosylamine at 150 °C in DMF in the presence of anhydrous K_2CO_3. After chromatographic purification macrocycle **7** was obtained in 42% yield. The tosyl group was removed by 4% sodium amalgam [8]. The structures of the ligands were confirmed via the analysis of their respective ^{1}H NMR, ^{13}C NMR (COSY) spectra and by CI-MS and FAB-MS. The (M^+ +1) fragment was present in all cases in the CI-MS and FAB-MS spectra. In the CI mass spectra of products **6a–d** and **6e–f** the fragments at 432 and 101 m/z that are due to the (sugar-based azacrown)-CH_2^+ and the $C_5H_9O_2$ fragments, respectively were of significant intensity.

Extraction ability

The complex forming ability of the new crown ethers (**6a–h**, **8**) was characterized by the extracting ability (EA%) of picrate salts (lithium, sodium, potassium and ammonium picrate) from water into dichloromethane by the method of Kimura [9]. Concentrations of the picrates in water were determined by UV spectroscopy. The extracting ability is determined mainly by the complex forming ability of the macrocycle, although some other factors can influence it, e.g., solubility, lipophilicity, etc. Table 1 contains data of compounds **6a–h** and **8**. The unsubstituted azacrown ether **8** has a surprisingly high extracting ability towards the cations investigated, but does not show a notable selectivity to any of the alkali- or ammonium cations (EA values are between 82–99%. We note, that here the selectivity means the difference between the alkali metal picrate extraction capabilities of host molecules). Side arms positioned at the nitrogen atom of the crown ring decrease the cation-binding ability, though differentiation ability among ions increases. Steric and electronic effects alike seem to play a part in these phenomena. Among compounds **6a–d**, *N*-benzyl **6c** has the smallest, and *N*-cyclohexyl substituted **6b** and the *N*-phenylethyl substituted **6d** the largest extracting ability. Among lariat ethers **6e–h** the smallest EA value belongs to 4-hydroxybutyl substituted **6f** (EA = 11–32%), having at the same time the best ion selectivity; e.g., it transports three times as much ammonium-picrate into the organic phase than lithium-picrate. The 3-hydroxypropyl substituted **6e**, having one CH_2 group less, has a somewhat better cation-binding ability (EA = 17–38%). The presence of hydrophilic end-groups on the side arm is disadvantageous from the complex forming point of view, probably due to the inhibiting effect by association with water molecules. This is supported by the fact, that when the free hydroxyl end-group is blocked, the extracting ability is improved; methyl ether derivatives **6g** and **6h** have EA values of 36–72% and 26–58% respectively. The length of the side chain is important in terms of the cation-binding ability. This becomes clear from the comparison of **6e** with **6f**, as well as **6g** with **6h**. Compound **6g** posessing two carbon atoms in the chain shows the largest coordinating ability among *N*-substituted crown ethers. These results may be due to the cooperation between the oxygen atom of the side arm and the complexing cations. It is worth mentioning that all of the investigated compounds form the most stable complex with ammonium-picrate. Complexes with ammonium cation are known to have a three-point hydrogen bridge connecting structure. In our case the ammonium cation is probably connected to the two oxygens of the crown ring and to the nitrogen atom. This bond appears to be stronger than the metal-heteroatom interaction.

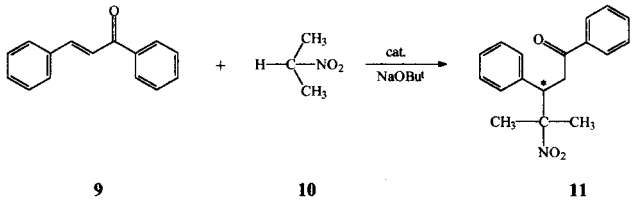
Asymmetric induction

Compounds **6a–h** and **8** used as chiral phase transfer catalysts proved to be effective in the addition of 2-nitropropane (**10**) to chalcone (**9**) (Figure 2). The reaction was carried out in toluene with solid sodium tertiary butoxide as base (35 mol%) and chiral catalyst (7 mol%) at room temperature. After the usual work-up procedure, the adduct (**11**) was isolated by preparative TLC, the asymmetric induction, expressed in terms of the enantiomeric excess (ee %), was monitored by ^{1}H NMR spectroscopy using (+)Eu(hfc)$_3$ as chiral shift reagent. The results given in Table 1 show that the (−)-(*R*)-enantiomer **11** is always in excess. Crown ethers **1** and **2** derived from glucoside and galactoside respectively, prefered the formation of the (+)-(*S*)-enantiomer in this Michael addition [5d]. This is pressumably connected to the

Table 1. Extracting ability and asymmetric induction of the crown ethers **8** and **6a–h**

Compound	R	Extractability (%)[a]				Asymmetric induction[b]	
		Li^+	Na^+	K^+	NH_4^+	Yield (%)[c]	ee (%)[d]
8	H	82	99	97	93	38	67
6a	$CH_3(CH_2)_3$	21	32	24	63	32	15
6b	C_6H_{11}	30	44	25	50	33	34
6c	$C_6H_5CH_2$	18	20	15	22	31	6
6d	$C_6H_5CH_2CH_2$	31	44	38	54	32	24
6e	$HO(CH_2)_3$	17	30	27	38	39	40
6f	$HO(CH_2)_4$	11	22	23	32	35	28
6g	$CH_3O(CH_2)_2$	36	69	67	72	34	16
6h	$CH_3O(CH_2)_3$	26	58	50	47	32	17

[a] Room temperature; aqueous phase (5 mL); [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = 1×10^{-2} M. Defined as % picrate extracted into the organic phase, determined by UV spectroscopy, error = ±1%.
[b] Reaction time 48 h, base $NaOBu^t$, 20 °C, (−)-(*R*) enantiomer is always in excess.
[c] Based on substance isolated by preparative TLC.
[d] Determined by ^1H NMR spectroscopy.



9 **10** **11**

Figure 2. Michael addition of 2-nitropropane to calcone.

relative configuration of the monosaccharides in the crown ether, which is 2,*R*,3*S* in glucose and galactose, and 3*S*,4*R* in D-mannitol.

From Table 1 it can be concluded that crown ethers derived from mannitol are weak phase transfer catalysts, this being proved by the fact that after 48 hours reaction the Michael adducts **11** formed in low yield, and that they showed moderate asymmetric induction. Earlier maximum values for glucoside **1** (R=$CH_3OCH_2CH_2$) and galactoside **2** (R=$CH_3OCH_2CH_2$) were 87% ee and 52% ee, respectively [5d]. The maximum enantiomeric excess of 67% in the group of mannitol derivatives was achieved by using the unsubstituted compound **8**. Side armed ligands proved to be weaker catalysts. Among them, the weakest was the *N*-benzyl substituted **6c** (6% ee), while the best catalyst was the *N*-3-hydroxypropyl substituted **6e** with 40% ee. The length of the side arm also plays a role in the asymmetric induction. This becomes obvious if one compares the *N*-benzyl substituted **6c** with *N*-2-phenylethyl **6d** (6% and 24% ee respectively), and compound **6e** (R = 3-hydroxypropyl, 40% ee) with **6f** (R = 4-hydroxy-buthyl, 28% ee). The numbers of the CH_2 units in the side chain of —$(CH_2)_3$— appears to be optimal in lariat ether type compounds **6e–h**.

In summary, it can be concluded that side arms have a decisive influence on the enantioselectivtiy by diminishing it compared to that of the unsubstituted analogue **8**. Experiments with the unsubstituted compound **8** are continuing.

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References

1. (a) J.F. Stoddart: *Chem. Soc. Rev.* **8**, 85 (1979); (b) J.F. Stoddart: *Top. Stereochem.* **17**, 207 (1987); (c) R. Miethchen and V. Fehring: *Liebigs Ann. Chem.* 553 (1997); (d) R. Miethchen and V. Fehring: *Synthesis* 94 (1998).
2. (a) M. Alonso-Lopez, J. Jimenez-Barbero, M. Martin-Lomas, S. Penades: *Tetrahedron* **44**, 1535 (1988); (b) D.A.H. van Maarschalkerwaart, N.P. Willard, U.K. Pandit: *Tetrahedron* **48**, 8825 (1992); (c) S. Aoki, S. Sasaki, and K. Koga: *Heterocycles* **33**, 493, (1992); (d) P.P. Kanakamma, N.S. Mani, U. Maitra, and V. Nair: *J. Chem. Soc., Perkin Trans 1*, 2339 (1995); (e) L. Tőke, P.Bakó, Gy. M. Keserû, M. Albert, and L. Fenichel: *Tetrahedron* **54**, 213 (1998) and references cited therein.
3. P. Bakó, and L. Tőke: *J. Incl. Phenom.* **23**, 195 (1995).
4. (a) G.W. Gokel: *Chem. Soc. Rev.* **21**, 39 (1992); (b) G.W. Gokel and O.F. Schall: Lariat Ethers. In *Comprehensive Supramolecular Chemistry*; G.W. Gokel (ed.), Pergamon Press, New York (1996), Vol. 1, pp 97–152.
5. (a) P. Bakó, T. Kiss, and L. Tőke: *Tetrahedron Lett.* **38**, 7259 (1997); (b) P. Bakó, K. Vízváardi, S. Toppet, E. van der Eycken, G.J. Hoornaert, and L. Tőke: *Tetrahedron* **54**, 14975 (1998); (c) P. Bakó, Z. Bajor, and L. Tőke: *J. Chem. Soc., Perkin Trans 1*, 3651 (1999); (d) P. Bakó, E. Czinege, T. Bakó, M. Czugler, and L. Tőke: *Tetrahedron: Asymmetry* **10**, 4539 (1999); (e) P. Bakó, T. Novák, K. Ludányi, B. Pete, L. Tőke, and Gy. Keglevich: *Tetrahedron: Asymmetry* **10**, 2373 (1999).
6. (a) J.-P. Joly and N. Moll: *J. Chromatogr.* **521**, 134 (1990); (b) M. Nazhaoui, B. Gross, and J.-P. Joly: *Tetrahedron Lett.* **34**, 1287 (1993); (c) J.-P. Joly, M. Nazhaoui, and B. Dumont: *Bull. Soc. Chim. Fr.* **131**, 369 (1994); (d) D.T. Gryko, P. Piatek, and J. Jurczak: *Synthesis*, 336 (1999); (e) M. Nazhaoui, J.-P. Joly, S. Kitane, and M. Berrade: *J. Chem. Soc., Perkin Trans 1*, 3845 (1998).
7. P. Di Cesare and B. Gross: *Synthesis*, 458 (1979).
8. F. Chavez, and A.D. Sherry: *J. Org. Chem.* **54**, 2990 (1989).
9. K. Kimura, T. Maeda, and T. Shono: *Talanta* **26**, 945 (1979).
10. P. Bakó, Á. Szöllősy, P. Bombicz, and L. Tőke: *Synlett*, 291 (1997).