B3654

DOKTORI ÉRTEKEZÉS

KIRÁLIS KORONAÉTEREKKEL KATALIZÁLT ENANTIOSZELEKTÍV SZINTÉZISEK

II. RÉSZ: MELLÉKELT KÖZLEMÉNYEK

Bakó Péter

Készült a
Budapesti Műszaki és Gazdaságtudományi Egyetem
Szerves Kémiai Technológia Tanszékén
2000

A tézisek alapját képező közlemények [B1-B22]

B1.
Bakó P., Fenichel L., Tőke L., Davison B.E.:
Novel Azacrown Ethers Incorporating Sugars; Synthesis and Complex Formation.
J. Chem. Soc. Perkin Trans 1., **1990**, 1235-1238

B2.
Bakó P., Fenichel L., Tőke L.:
A Novel Diaza-Crown Ether and Cryptands from Glucopyranose and Their Complex-Forming Properties.
Liebigs Ann. Chem., **1990**, 1161-1164

B3.
Bakó P., Fenichel L., Tőke L.:
The Complexing Ability of Crown Ethers Incorporating Glucose
J. Incl. Phenom., **1993**, *16*, 17-23.

B4.
Bakó P., Fenichel L., Tőke L., Davison B.E., Patel A.:
Elaboration of a Chiral 20-Crown-6 from a Glucofuranose Derivative and Its Complex with Alkali Cations.
Heteroatom Chem., **1994**, *5*, 415-419.

B5.
Bakó P. and Tőke L.:
Novel Monoaza- and Diazacrown Ethers Incorporating Sugar Units and Their Extraction Ability towards Picrate Salts.
J. Incl. Phenom., **1995**, *23*, 195-201.

B6.
Bakó P., Fenichel L. and Tőke L.:
Synthesis and Complex-Forming Properties of Crown Ethers Incorporating Glucuronic Acid Moieties.
J. Incl. Phenom., **1996**, *26*, 321-330.

B7.
Bakó P., Szöllősy Á., Bombicz P. and Tőke L.:
Asymmetric C-C Bond Forming Reactions by Chiral Crown Catalysts; Darzens Condensation and Nitroalkane Addition to the Double Bond
Synlett, **1997**, 291-292.

B8.
Bakó P., Szöllősy Á., Bombicz P. and Tőke L.:
Asymmetric Michael Addition of 2-Nitropropane to Chalcone Catalyzed by Chiral Crown Ethers Incorporating D-glucose Unit.
Heteroatom Chem., **1997**, *8*, 333-337.

B9.
Bakó P., Kiss T., Tőke L.:
Chiral Azacrown Ethers Derived from D-glucose as Catalysts for Enantioselective Michael Addition.
Tetrahedron Lett., **1997**, *38*, 7259-7262.

B10.
Tőke L., Bakó P., Keserű M.Gy., Albert M. and Fenichel L.:
Asymmetric Michael Addition and Deracemization of Enolate by Chiral Crown Ether
Tetrahedron, **1998**, *54*, 213-222.

B11.
Bakó P., Vizvárdi K., Bajor Z., Tőke L.:
Synthesis and application in asymmetric synthesis of azacrown ethers derived from D-glucose
Chem. Comm., **1998**, 1193-94.

B12.
Bakó P., Vizvárdi K., Toppet S., Van der Eycken E., Hoornaert G. J., Tőke L.:
Synthesis, Extraction Ability and Application in Asymmetric Synthesis of Azacrown Ethers Derived from D-glucose
Tetrahedron, **1998**, *54*, 14975-14988.

B13.
Bakó P., Novák T., Ludányi K., Pete B., Tőke L. és Keglevich Gy.:
D-Glucose-based azacrown ethers with a phosphonoalkyl side chain: application as enantioselective phase transfer catalysts
Tetrahedron:Asymmetry, **1999**, *10*, 2373-2380.

B14.
Bakó P., Czinege E., Bakó T., Czugler M., Tőke L.:
Asymmetric C-C bond forming reactions by chiral crown catalysts derived from D-glucose and D-galactose
Tetrahedron:Asymmetry, **1999**, *10*, 4539-4551

B15.
Novák T., Keglevich Gy., Imre T., Bakó P., Újszászy K., Ludányi K., Tőke L.:
Foszfonoalkil-oldalláncot tartalmazó azakoronák szintézise és komplexképzési tulajdonságainak vizsgálata.
Magyar Kémiai Folyóirat, **1999**, *1*, 16-21.

B16.
Keglevich Gy., Novák T., Bakó P., Újszászy K., Tőke L.:
Synthesis of Azacrown Ethers with P-Functionalized Side Chains
Phosphorus, Sulfur and Silicon, **1999**, *147*, 159.

B17.
Keglevich Gy., Novák T., Bakó P., Újszászy K., Ludányi K., Tóth K., Tőke L.:
New Type of Lariat Ethes: Synthesis and Cation Binding Ability of Phosphonoalkyl-Azacrown Ethers.
J. Incl. Phenom., **1999**, *34*, 299-309.

B18.
Bakó P., Bajor Z., Tőke L.:
Synthesis of novel chiral crown ethers derived from D-glucose and their application to an enantioselective Michael reaction
J. Chem. Soc., Perkin Trans 1., **1999**, *24*, 3651-3655

B19.
Novák T., Bakó P., Dobó A., Ludányi K., Tőke L. és Keglevich Gy.:
Modification of D-glucose-based 18-crown-6 ethers by phosphorylation and phosphonylation
Heteroatom Chem., (elfogadva)

B20.
Keglevich Gy., Novák T., Imre T., Bakó P., Tőke L., Újszászy K., Ludányi K.:
Synthesis and Cation Binding Ability of Azacrown Ethers with Phosphine or Phosphine Oxide Side Chain.
Heteroatom Chem., **1999**, *10*, 573-576

B21.
Novák T., Bakó P., Imre T., Keglevich Gy., Dobó A., Tőke L.:
Synthesis and Cation Binding Ability of the Phosphonoalkyl- and Phosphonoylalkyl Derivatives of Monoaza-18-crown-6
J. Incl. Phenom., (elfogadva)

B22.
Bakó P., Bakó T., Szöllősy Á., Bisztray K., Nagy K., Tőke L.:
Chiral Azacrown Ethers Derived from D-Mannitol
J. Incl. Phenom., (beküldve)

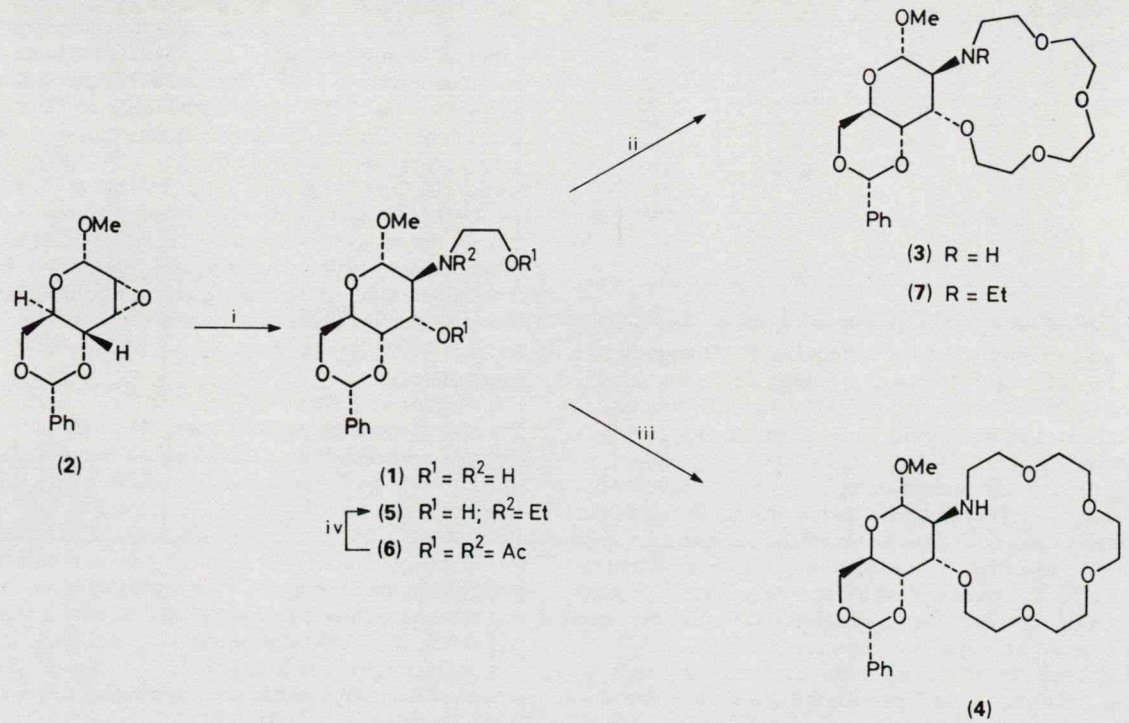
Novel Azacrown Ethers Incorporating Sugars: Synthesis and Complex Formation†

Péter Bakó, László Fenichel, and László Tőke
Department of Organic Chemical Technology, Technical University, Budapest, Hungary
Bruce E. Davison
Department of Applied Chemistry and Life Sciences, Polytechnic of North London, Holloway Road, London N7 8DB

Azacrown ethers derived from amino-deoxy sugars in which the sugar moiety forms part of the macrocycle, or is pendant from it, have been synthesised and their complexing ability towards cations compared.

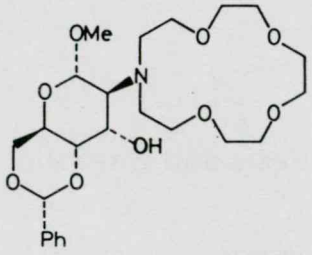
Several syntheses of chiral diazacrown ethers in which a sugar unit forms part of the macrocyclic ring have been previously reported.[1–3] We have recently published details of the synthesis of chiral monoazacrown ethers with pendant sugars bonded to the nitrogen atom of a previously constructed macrocycle.[4] We now report a synthesis of monoazacrown ethers by elaboration of sugar amines to give products in which the sugar forms part of the macrocyclic ring, and a comparative study of their complexing abilities with those of their pendant sugar counterparts.

The key intermediate, methyl 4,6-*O*-benzylidene-2-deoxy-2-(*N*-2-hydroxyethyl)amino-α-D-altropyranoside (**1**), was obtained by ring-opening of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**2**) with ethanolamine.[4] The Scheme shows the sequence of reactions employed to synthesise the macrocycles in which the sugars are incorporated. The products from cyclisation with the appropriate polyethylene bistosylates[5] were isolated and purified by preparative thin layer chromatography on Kieselgel 60 PF254 using toluene–methanol (5:1) as eluant. The 15-monoazatetraoxacrown-5 (**3**) was obtained as a crystaline material in 24% yield, while the 18-monoazapentaoxacrown-6 (**4**) resisted crystallisation. Since the yield of the 15-crown-5 (**3**) was affected by the undesired reaction of the bistosylate at the secondary amine, we carried

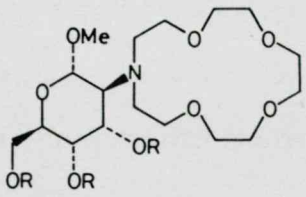


Scheme. *Reagents:* i, $H_2NCH_2CH_2OH$; ii, $TsO(CH_2CH_2O)_3Ts$, Bu^{t}ONa, Bu^{t}OH, dioxan, 20 h; iii, $TsO(CH_2CH_2O)_4Ts$, Bu^{t}OK, Bu^{t}OH, dioxan, 20 h; iv, $LiAlH_4$, THF

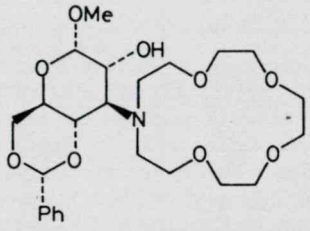
† This communication is a reprinted version of the corresponding article which appeared in *J. Chem. Soc., Perkin Trans. 1*, 1989, 2514. As the result of oversight in the Editorial Office, formulae (**8**)–(**13**) which should have appeared in this article were omitted. The Society apologizes for any inconvenience caused.



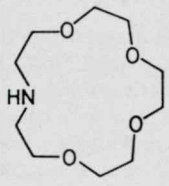
(8)



(9) R = H
(10) R = Ac
(11) R = Ts



(12)



(13)

Table. Association constants (log K_a) in $CDCl_3$ at 22 °C

Compound	log K_a (± 0.05)		
	Na^+	K^+	NH_4^+
(3)	4.73	4.54	4.45
(4)	5.18	4.84	4.90
(7)	4.96	4.64	4.56
(8)	5.84	5.45	5.53
(10)	5.41	4.98	4.78
(11)	6.02	5.42	5.27
(12)	6.11	5.61	4.98
(13)	6.03	5.52	5.72

out the synthesis on the *N*-ethyl derivative (**5**), the preparation of which was accomplished by acetylation of (**3**) to yield the triacetyl derivative (**6**), followed by reduction with lithium aluminium hydride. Condensation of (**5**) with triethylene glycol bistosylate resulted in a yield of 31% of the 15-(*N*-ethyl)-monoazatetraoxacrown-5 (**7**).

It was desired to compare the complex-forming abilities of the azoxacrowns (**5**)—(**7**) with those of the crowns in which the sugar moieties are pendant; to this end the benzylidene group of the previously described[4] *N*-altropyranosyl 15-monoazatetraoxacrown-5 (**8**) was removed with hot ethanoic acid[6] to yield the diol (**9**), from which the derivatives (**10**) and (**11**) were prepared by acetylation and tosylation respectively.

The Table shows the association constants for sodium, potassium, and ammonium ions with the new crowns, together with those of the previously described (**12**)[4] and (**13**),[5] as measured in chloroform by the u.v. technique developed by Cram.[7] As expected, the unsubstituted 15-crown-5 gave the strongest complexes. When the sugar is incorporated into the macrocyclic ring [compounds (**3**), (**4**), and (**7**)] there is a reduction in the log K_a values, but this is not so marked in the case of the pendant sugar crowns (**8**) and (**10**)—(**12**). The likely reason for these observations is an entropy effect due to the relative rigidity conferred on the ring by the fused sugar moiety in (**3**), (**4**), and (**7**) and concomitant steric hindrance to the binding of the ion, effects which are absent in the pendant sugar types. *N*-Alkylation as in (**7**) predictably increases the log K_a values for potassium and sodium ions by increasing the donor ability of the nitrogen ligand. A comparison of log K_a values for the substituted pendant sugar crowns (**10**) and (**11**) shows that the presence of acetyl groups produces poorer complexation than the benzylidene derivative (**8**) while tosyl groups cause a relative increase. Two possibilities are that there is additional bonding by the tosyl groups to the ion held in the cavity of the crown ether or that complexation is primarily to the tosyl group itself *i.e.* the complex is not of the classic crown ether type. The present work does not distinguish these two possibilities although the similarity of log K_a values would suggest that the former is the most likely explanation.

Experimental

Monoazacrown Ethers (**3**), (**4**), *and* (**7**).—*General procedure.* The hydroxyethylamino derivatives (**1**) or (**5**) (4.5 mmol) and sodium or potassium were dissolved in t-butanol (38 ml) under an atmosphere of argon and a solution of triethyleneglycol ditosylate or tetraethyleneglycol ditosylate (4.5 mmol) in dioxane was added during 3—4 h at 40 °C. The solution was cooled, the precipitated sodium or potassium tosylate removed by filtration, and the filtrate evaporated *in vacuo*. The residue was suspended in water (30 ml), washed with hexane (15 ml), and extracted with dichloromethane (3 × 20 ml). Evaporation of the extracts gave a residue (1.8—2.3 g) which was subjected to preparative thin layer chromatography using toluene–methanol (10:2) as eluant.

15-*Monoazatetraoxacrown*-5 (**3**) was obtained as crystals from ethanol (0.476 g, 24%), m.p. 54—56 C, $[\alpha]_D^{20}$ 31.5° (*c* 1, $CHCl_3$) (Found: C, 59.9; H, 7.5; N, 3.2%; M^+, 439. $C_{22}H_{33}NO_8$ requires C, 60.14; H, 7.52; N, 3.19%; M^+, 439); δ($CDCl_3$) 2.22 (1 H, br, s NH), 2.73—3.0 (2 H, q, NCH_2), 3.15 (1 H, d, 2-H), 3.41 (3 H, s, OCH_3), 3.50—4.40 (19 H, m, 8 × CH_2, 3 × CH), 4.60 (1 H, d, 1-H), 5.59 (1 H, s, PhC*H*), and 7.20—7.52 (5 H, m, Ph).

18-*Monoazapentaoxacrown*-6 (4), *oil*, (0.543 g, 25%), $[\alpha]_D^{20}$ 26.6° (*c* 0.96, $CDCl_3$) (Found: C, 58.9; H, 7.6; N, 2.95%; M^+, 483. $C_{24}H_{37}NO_9$ requires C, 59.63; H, 7.66; N, 2.90%; M^+, 483); δ($CDCl_3$) 2.28 (1 H, s, NH), 2.73—3.11 (3 H, m, NCH_2, 2-H), 3.43 (3 H, s, OCH_3), 3.50—4.40 (23 H, m, 10 × CH_2, 3 × CH), 4.56 (1 H, d, 1-H), 5.56 (1 H, s, PhC*H*), and 7.35—7.61 (5 H, m, Ph).

(N-*Ethyl*)-15-*monoazatetraoxacrown*-5 (7), *oil*, (0.658 g, 31%), $[\alpha]_D^{20}$ 56.0° (*c* 0.97, $CHCl_3$) (Found: C, 61.6; H, 7.95; N, 2.95%; M^+, 467. $C_{24}H_{37}NO_8$ requires C, 61.67; H, 7.92; N, 3.00%; M^+, 467); δ($CDCl_3$) 1.05 (3 H, t, CH_3), 2.40—2.92 (4 H, m, 2 × NCH_2), 3.08 (1 H, d, 2-H), 3.36 (3 H, s, OCH_3), 3.50—4.40 (19 H, m, 8 × CH_2, 3 × CH), 4.65 (1 H, d, 1-H), 5.54 (1 H, s, PhC*H*), and 7.25—7.62 (5 H, m, Ph).

Acknowledgements

The authors gratefully acknowledge the financial assistance of the International Department of the Technical University, Budapest and the British Council.

References

1 M. Pietraszkiewicz and J. Jurczak, *J. Chem. Soc., Chem. Commun.*, 1983, 132; M. Pietraszkiewicz, P. Salanski, and J. Jurczak, *ibid.*, 1983, 1184.
2 M. Pietraszkiewicz and J. Jurczak, *Tetrahedron*, 1984, **40**, 2967; M Pietraszkiewicz, P. Salanski, and J. Jurczak, *ibid.*, 1984, **40**, 2971.
3 P. Bako, L. Fenichel, and L. Toke, *Acta Chim. Acad. Sci. Hung.*, 1984, **115**, 323.
4 G. Toth, W. Dietrich, P. Bakó, L. Fenichel, and L. Tőke, *Carbohydr. Res.*, 1987, **168**, 141.
5 H. Maeda and Y. Nakatsuji, *J. Chem. Soc., Chem. Commun.*, 1981, 471.
6 R. L. Whistler and M. L. Wolfram, 'Methods in Carbohydrate Chemistry,' vol. I (Academic Press. N.Y., 1963) p. 214.
7 S. S. Moore, T. L. Tarnowski, M. Newcomb, and D. J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 6398.

Paper 9/03808F
Received 12*th July* 1989
Accepted 11*th September* 1989

A Novel Diaza-Crown Ether and Cryptands from Glucopyranose and Their Complex-Forming Properties

Péter Bakó, László Fenichel, László Tőke*

Department of Organic Chemical Technology, Technical University of Budapest, Műegyetem, P. O. Box 91, H-1521 Budapest

B2

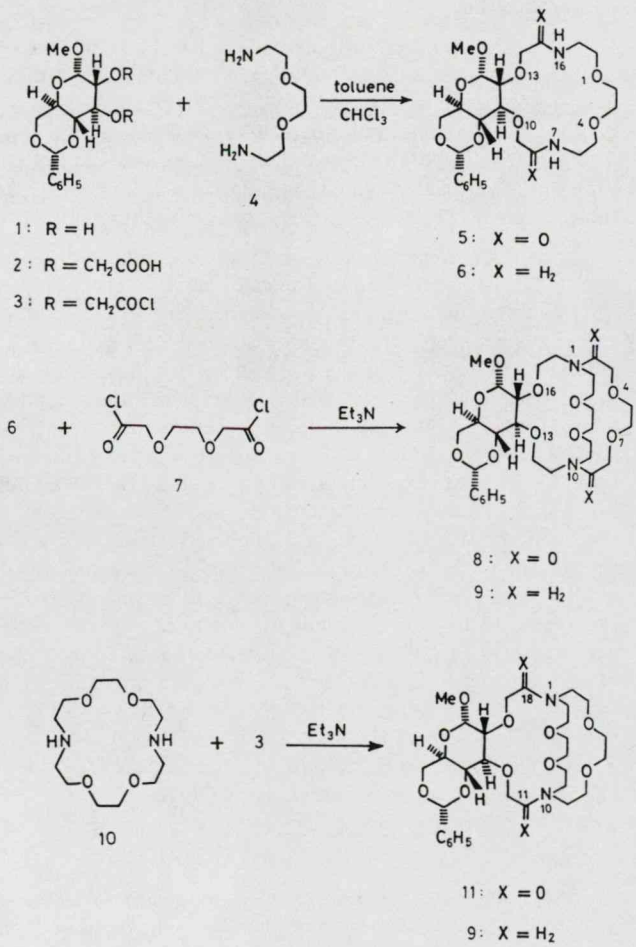
Received April 18, 1990

Key Words: Crown ether derivatives / Complex formation constants

Chiral diaza-crown ether **6** and cryptands of type [2.2.2] (**9**), containing one glucopyranoside unit, have been prepared. Two methods are described for the synthesis of **9**. The new cryptand **12** containing two glucopyranoside units has also been prepared. The association constants (K_a) of these compounds with Li, Na, K and NH_4 cations have been measured.

Sugar derivatives are cheap starting materials for the synthesis of chiral crown compounds[1–17].

Crown ethers considerably change their properties (complex forming ability, selectivity in transport processes) if instead of oxygen atoms "softer" nitrogen atoms are also incorporated into the macro ring[8–10]. Such chiral diaza-crown ethers built up from sugars were prepared first by Laidler and Stoddart from 1,2:5,6-di-*O*-isopropylidene-D-mannite[11] and later by Polish and Hungarian research workers from methyl 4,6-*O*-benzylidene-α-D-manno-, -galacto-, and -glucopyranoside[12–16].



Bicyclic cryptand molecules have particular complex-forming and selectivity porperties[17,18]. If these molecules are chiral, e.g. their synthesis starts from monoses, then they can also be used in the field of chiral recognition.

Pietraszkiewicz et al. have synthesized a chiral cryptand of type [2.2.1] from a monosaccharide[12–15]. The disadvantage of the method is that one of the reaction steps can be realized only at high pressure (8000 bar), and only small quantities of substance are formed because of the dimensions of the apparatus. The properties of the prepared compounds have not been reported.

We have synthesized crown amines and [2.2.2] cryptands using glucose as one of the starting compounds[16]. In this Paper we discuss both the experimental details and the data on complex-stability measurements. The synthesis of these compounds was carried out according to the high-dilution technique (developed by Lehn et al.)[17]. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was treated in *tert*-butyl alcohol with monochloroacetic acid in the presence of potassium *tert*-butoxide to give the diacid derivative **2** with 36% yield. We tried to perform the alkylation of the hydroxy groups in **1** also with ethyl bromoacetate by using solid KOH and phase-transfer catalysts, but obtained only poor yields.

Compound **2** was converted in chloroform with oxalyl dichloride into the respective bisacid chloride **3**. The reaction of **3** with 1,8-diamino-3,6-dioxaoctane[19,20] (**4**) was carried out in a 5:1 toluene/chloroform mixture by using the high-dilution technique. After purification by column chromatography the monocyclic bisamide **5** was obtained in 28% yield. **5** was reduced in THF with $LiAlH_4$ to give the chiral diaza-crown **6** (92%).

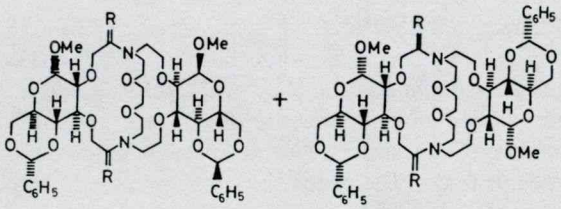
For the preparation of cryptand **9** two routes were developed. The first method essentially involves acylation of compound **6** with the bifunctional 1,6-dichlorocarbonyl-2,5-dioxahexane[17] (**7**) forming a bridge between the two nitrogen atoms. This reaction was carried out in 1:1 toluene/chloroform mixture in the presence of triethylamine accord-

 © VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1990 0170–2041/90/1212–1161 $ 3.50+.25/0

ing to the high-dilution technique. After chromatographic purification, the bicyclic bisamide derivative **8** was obtained in a yield of as low as 10%, probably due to steric hinderance of the reaction centers in **6**.

Another synthetic pathway gave better results. Thus, the reaction of the unsubstituted diaza-crown ether **10**[17] with the chiral diacid dichloride **3** in the way described above gave the bicyclic bisamide **11** in 21% yield, from which the chiral cryptand of type [2.2.2] (**9**) was obtained by reduction with $LiAlH_4$. Interesting to note that the reduction of bisamide of type [2.2.1] with $LiAlH_4$ can be realized only in a very poor yield, or it does not proceed at all according to ref.[15] but we succeeded in reducing the bisamide **11** of type [2.2.2] similarly with $LiAlH_4$ (87%).

A bicyclic cryptand built up from two moles of glucose was obtained by the reaction of the diaza-crown ether **6** with the chiral diacid dichloride **3**. The bicyclic bisamide **12** was obtained in 9% yield. In this reaction two diastereomers may be formed. After purification, TLC of compound **12** revealed two spots. These two components could neither be separated nor identified spectroscopically. The reduction of the isomeric mixture by $LiAlH_4$ yielded the stereoisomeric [2.2.2] cryptands **13a** and **13b** in a considerable yield.



a. b.

12: R = O

13: R = H_2

Complex-Forming Characteristics

The association constants for the compounds **5, 6, 9, 13** and **10** (the latter for comparison) were measured by Cram's method[21] using lithium, sodium, potassium and ammonium picrates as cation sources. The log K_a values are listed in Table 1.

Tab. 1. Association constants (log K_a) of diaza-crown compounds and cryptands in chloroform at 22°C

Host	log K_a			
	Li^+	Na^+	K^+	NH_4^+
5	3.87	4.60	4.25	4.11
6	6.39	6.31	5.82	6.65
10	6.85	6.45	6.59	8.81
9	6.26	8.88	9.37	9.57
13	5.57	6.34	6.26	6.35

The complex stability constants of sugar crown amine **6** for these ions are by 1.5 to 2.5 order of magnitude higher than those of bisamide **5** and the order of selectivity is also different. In the case of **5** the tendency to coordination of nitrogen incorporated into the carboxamide function decreases.

It can be seen from a comparison of the unsubstited crown amine **10** and compound **6** that the presence of the sugar unit diminishes the tendency to complex formation, especially in the case of the ammonium cation, and the selectivity is also decreased. This phenomenon may be attributed to the fact that the ring is flexible in molecule **10** while in the case of **6** the glucopyranoside unit makes the crown ring rigid and thus hinders complex formation. The steric hindrance may also contribute to the decrease of the stability which is most pronounced with the large ammonium cation.

It is remarkable that the stability constants for cryptand **9** are by 2.5 to 3.5 order of magnitude higher with the sodium cations but particularly with the potassium and ammonium cation, than the corresponding values for **6**. The cryptand, **13** built up from two glucose moieties, forms a weaker complex with each cation than compound **9** does. Probably, the two sugar moieties reduce the flexibility of the cryptand, and at the same time the effect of their steric hindrance increases. The same applies to the decrease in selectivity.

Data on the chiral recognition ability of the compounds described in this paper will be reported later.

We thank Dr. *József Tamás* for recording some of the mass spectra.

Experimental

^{1}H-NMR spectra: Perkin-Elmer R12 and Jeol FX-100 (in $CDCl_3$; TMS as internal standard). – UV spectra: Hitachi-Perkin-Elmer 124. – Mass spectra: Jeol JMS-OL SG-2. – Elemental analysis: Perkin-Elmer 240 automatic analyser. – TLC: Kieselgel 60 F_{254} or Al_2O_3 150 F_{254} Type T (Merck), eluent toluene/methanol mixtures (10:1–10:5); detection with Dragendorff's reagent[22]. – Column chromatography: Kieselgel 60 (0.2–0.063 mm) (Merck).

Methyl 4,6-O-Benzylidene-2,3-di-O-carboxymethyl-α-D-glucopyranoside (**2**): 14.0 g (0.36 mol) of metallic potassium was added to 300 ml of dry tBuOH under N_2 and stirred at 60°C until the reaction was completed (H_2 evolution stopped). After cooling, a solution of 20.0 g (0.07 mol) of **1** in 150 ml of dry tBuOH was added to the mixture which was heated at reflux with stirring for 1 h. A solution of 13.5 g (0.14 mol) of chloroacetic acid in 50 ml of dry tBuOH was then added, and the mixture was stirred at boiling temp. for 24 h. After cooling it was poured into ice/water, tBuOH was distilled off in vacuo, the aqueous residue was extracted three times with 40 ml of $CHCl_3$, and the combined extracts were acidified with HCl to pH = 1. The precipitate formed was filtered, dissolved in $CHCl_3$, repeatedly washed with water, dried with Na_2SO_4, and evaporated to dryness in vacuo to obtain 22 g of raw product, which gave 10.3 g (36%) of **2** after recrystallization from a mixture of 25 ml of acetone and 25 ml of benzene; m.p. 135–136°C, $[\alpha]_D^{22}$ = +88.1 (*c* = 1.1, in $CHCl_3$). – ^{1}H NMR: δ = 3.36 (s, 3H, OCH_3), 3.2–4.0 (m, 9H), 4.33 (s, 4H, OCH_2CO), 4.85 (d, *J* = 3.5 Hz, 1H, anomeric H), 5.40 (s, 1H, benzylidene H), 7.10–7.48 (m, 5H, aromatic H), 9.23 (broad, 2H, COOH).

$C_{18}H_{22}O_{10}$ (398.4) Calcd. C 54.27 H 5.52
Found C 54.41 H 5.44

Methyl 4,6-O-Benzylidene-2,3-di-O-chlorocarbonylmethyl-α-D-glucoyranoside (**3**): 10.0 g (25 mmol) of **2** was dissolved in 80 ml of

dry $CHCl_3$ and added to a solution of 15 m (176 mmol) of oxalyl dichloride in 80 ml of dry $CHCl_3$ (containing 3 drops of pyridine). The mixture was kept at room temp. for 40 h, then concentrated in vacuo. The remaining syrup was treated with anhydrous petroleum ether for a few hours to yield a white amorphous precipitate of 6.1 g (56%) of **3**; m.p. 141–150°C (dec.), $[\alpha]_D^{22}$ = +34.0 (*c* = 1.1 in $CHCl_3$). – ^{1}H NMR: δ = 3.44 (s, 3H, OCH_3), 3.3–4.4 (m, 9H, CH and CH_2 groups), 4.60 and 4.72 (s, 2H, OCH_2CO), 4.95 (d, *J* = 4 Hz, 1H, anomeric H), 5.43 (s, 1H, benzylidene H), 7.30–7.66 (m, 5H, aromatic H).

$C_{18}H_{20}Cl_2O_8$ (435.3) Calcd. C 49.66 H 4.63 Cl 16.31
Found C 49.38 H 4.68 Cl 16.24

Glucopyrano-Fused Derivative **5** *of 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-8,15-dione:* A solution of 3.3 g (7.5 mmol) of **3** in a mixture of 30 ml of dry $CHCl_3$ and 70 ml of dry toluene and a solution of 2.2 g (15.0 mmol) of **4** in 100 ml of dry toluene were added simultaneously under argon and with vigorous stirring to 200 ml of dry toluene during a period of 7–8 h. The mixture was left standing for about 12 h and then filtered. The filtrate was evaporated to dryness in vacuo to yield 4.9 g of a raw product which was purified by column chromatography (450 × 35 mm, Kieselgel 60, 100 g, eluent $CHCl_3$/MeOH, 10:1); yield 1.1 g (28%) of colorless **5**, m.p. 108–110°C (ethanol/heptane), $[\alpha]_D^{22}$ = +87.4 (*c* = 1 in $CHCl_3$). – ^{1}H NMR: δ = 3.41 (s, 3H, OCH_3), 3.43–3.90 (m, 18H), 4.12–4.40 (m, 4H, OCH_2CON), 4.87 (d, *J* = 4 Hz, 1H, anomeric H), 5.52 (s, 1H, benzylidene H), 7.31–7.48 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 510 (49.4) [M^+], 174 (25), 149 (40), 144 (22.5), 118 (32.5), 105 (66), 102 (82), 91 (82), 77 (46.6).

$C_{24}H_{34}N_2O_{10}$ (510.5) Calcd. C 56.46 H 6.71
Found C 56.31 H 6.62

Glucopyrano-Fused Derivative **6** *of 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane:* A solution of 2.0 g (3.92 mmol) of **5** in 20 ml of dry THF was added dropwise to a stirred suspension of 1.6 g (42.0 mmol) of $LiAlH_4$ in 50 ml of dry THF under argon. The mixture was stirred and heated at reflux for 2 h. After cooling, excess $LiAlH_4$ was decomposed with 15 ml of ethyl acetate and 10 ml of water. The precipitate was separated, washed with THF, and the combined filtrates were concentrated in vacuo; yield 1.73 g (92%) of **6** as a yellow syrup, $[\alpha]_D^{22}$ = +56.9 (*c* = 1, $CHCl_3$). – ^{1}H NMR: δ = 2.15–3.10 (m, 10H, NCH_2), 3.40 (s, 3H, OCH_3), 3.37–4.36 (m, 18H, CH_2 and CH groups), 4.82 (d, *J* = 4.5 Hz, 1H, anomeric H), 5.49 (s, 1H, benzylidene H), 7.22–7.45 (m, 5H, aromatic H).

$C_{24}H_{38}N_2O_8$ (482.6) Calcd. C 59.73 H 7.93
Found C 59.28 H 7.69

Glucopyrano-Fused Derivative **8** *of 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane-2,9-dione:* A solution of 4.2 g (8.7 mmol) of **6** in a mixture of 100 ml of dry toluene and 50 ml of dry $CHCl_3$ and a solution of 1.9 g (8.8 mmol) of **7** in 150 ml of dry toluene were added simultaneously dropwise to vigorously stirred dry toluene 300 ml [containing 2.3 g (22.7 mmol) of Et_3N] at room temp. during a period of 8 h. The reaction mixture was left standing for about 12 h, filtered, the filtrate was evaporated to dryness in vacuo, and the residue was eluated through a column (400 × 25 mm, 70 g Al_2O_3, activity II, neutral) with a mixture of benzene/petroleum ether (2:1); yield 0.5 g (10%), m.p. 101–102°C (benzene/petroleum ether), $[\alpha]_D^{22}$ = +64.2 (*c* = 1 in $CHCl_3$). – ^{1}H NMR: δ = 3.38 (s, 3H, OCH_3), 3.44–3.92 (m, 30H, CH and CH_2 groups), 4.2–4.32 (m, 4H, CH_2CON), 4.68 (d, *J* = 4 Hz, 1H, anomeric H), 5.44 (s, 1H, benzylidene H), 7.20–7.52 (m, 5H, aromatic H). – MS (75 eV): *m/z* (%) = 624 (100) [M^+].

$C_{30}H_{44}N_2O_{12}$ (624.7) Calcd. C 57.68 H 7.09 N 4.48
Found C 57.61 H 7.13 N 4.42

1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane (**10**): This was prepared according to the method of Lehn[7], with the exception that toluene was used as solvent instead of benzene for the high-dilution technique. The average yield of several reactions was 58% (ref.[17] 56%); m.p. 112–114°C (ref.[17] 115–116°C). The ^{1}H-NMR data agree with those published in the literature[17].

Glucopyrano-Fused Derivative **11** *of 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane-11,18-dione:* A solution of 4.6 g (17.5 mmol) of **10** in 300 ml of dry toluene and a solution of 7.6 g (17.6 mmol) of **3** in a mixture of 200 ml of dry $CHCl_3$ and 100 ml of dry toluene were added simultaneously dropwise to vigorously stirred dry toluene [600 ml, containing 4.5 g (44.4 mmol) of Et_3N] at room temp. over a period of 8 h. The reaction mixture was left standing for about 12 h, filtered, the filtrate was concentrated in vacuo, and the residue was purified by column chromatography (400 × 25 mm, 100 g of Al_2O_3, activity II, neutral) with a mixture of benzene/petoleum ether (2:1); yield 2.3 g (21%), m.p. 94–95°C (benzene/petroleum ether), $[\alpha]_D^{22}$ = +64.4, (*c* = 1 in $CHCl_3$). – ^{1}H NMR: δ = 3.37 (s, 3H, OCH_3), 3.44–3.92 (m, 30H, CH and CH_2 groups), 4.2–4.36 (m, 4H, CH_2CON), 4.66 (d, *J* = 4 Hz, 1H, anomeric H), 5.42 (s, 1H, benzylidene H), 7.21–7.5 (m, 5H, aromatic H). – MS (75 eV): *m/z* (%) = 624 (100) [M^+], 537 (20), 149 (37), 128 (41), 105 (31), 100 (33), 91 (36), 56 (75), 45 (47).

$C_{30}H_{44}N_2O_{12}$ (624.7) Calcd. C 57.68 H 7.09 N 4.48
Found C 57.53 H 7.10 N 4.41

Glucopyrano-Fused Derivative **9** *of 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane:* The reduction of **11** with $LiAlH_4$ was carried out as described for **6**; yield 84%. **9** is of greasy consistence; $[\alpha]_D^{22}$ = +12.3, (*c* = 1 in $CHCl_3$). – ^{1}H NMR: δ = 2.75 (m, 12H, NCH_2), 3.35 (s, 3H, OCH_3), 3.30–4.02 (m, 18H, CH and CH_2 groups), 4.54 (s, 8H, OCH_2CH_2O), 4.77 (d, *J* = 4 Hz, 1H, anomeric H), 5.49 (s, 1H, benzylidene H), 7.17–7.46 (m, 5H, aromatic H). – MS (75 eV): *m/z* (%) = 569 (49) [M^+], 521 (23), 319 (19), 315 (45), 301 (42), 158 (20), 144 (51), 128 (24), 114 (100), 100 (54), 91 (22).

$C_{30}H_{48}N_2O_{10}$ (596.7) Calcd. C 60.38 H 8.10 N 4.69
Found C 59.92 H 7.98 N 4.55

Bis(glucopyrano)-Fused Derivative **12** *of 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane-2,9-dione:* The reaction of 6.2 g (12.8 mmol) of **6** with 6.2 g (14.2 mmol) of **3** was carried out as described for **8**. After column chromatography, 1.0 g (9%) of **12** was obtained; m.p. 125–128°C ($CHCl_2$/petroleum ether), $[\alpha]_D^{22}$ = +48.9 (*c* = 1 in $CHCl_3$). – ^{1}H NMR: δ = 3.40 (s, 6H, OCH_3), 3.48–3.95 (m, 32H, CH and CH_2 groups), 4.12–4.5 (m, 4H, CH_2CON), 4.68 (d, *J* = 4 Hz, 2H, anomeric H), 5.48 (s, 2H, benzylidene H), 7.2–7.55 (m, 10H, aromatic H). – MS: *m/z* = 867 [M + Na]$^+$ (FAB-ionization technique).

$C_{42}H_{56}N_2O_{16}$ (844.9) Calcd. C 59.71 H 6.68 N 3.31
Found C 59.49 H 6.58 N 3.25

Bis(glucopyrano)-Fused Derivative **13** *of 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane:* The reduction of **12** with $LiAlH_4$ was performed as described for **6**; yield 83%, yellow substance of greasy consistence, $[\alpha]_D^{22}$ = +27.4 (*c* = 1 in $CHCl_3$). – ^{1}H NMR: δ = 2.75 (m, 12H, NCH_2), 3.38 (s, 6H, OCH_3), 3.23–4.3 (m, CH and CH_2), 4.68 (d, *J* = 4 Hz, 2H, anomeric H), 5.48 (s, 2H, benzylidene H), 7.2–7.4 (m, 10H, aromeric H).

$C_{42}H_{60}N_2O_{14}$ (816.9) Calcd. C 61.75 H 7.40 N 3.42
Found C 61.52 H 7.21 N 3.36

CAS Registry Numbers

1: 57701-27-6 / **2**: 92713-97-8 / **3**: 92713-98-9 / **4**: 929-59-9 / **5**: 92713-99-0 / **6**: 92762-33-9 / **7**: 31255-09-1 / **8**: 129570-32-7 / **9**: 129592-59-2 / **10**: 23978-55-4 / **11**: 129570-33-8 / **12a**: 129592-60-5 / **12b**: 129592-61-6 / **13a**: 129570-34-9 / **13b**: 129570-35-0 / lithium picrate: 18390-55-1 / sodium picrate: 3324-58-1 / potassium picrate: 573-83-1 / ammonium picrate: 131-74-8 / glucose: 50-99-7

[1] J. F. Stoddart *Synthetic Chiral Receptor Molecules from Natural Products* in *Progress in Macrocyclic Chemistry* (Izatt, Christensen, Ed.), vol. 2, p. 174–245, Wiley, New York 1981.

[2] J. F. Stoddart, *Chiral Crown Ethers, Topics in Stereochemistry* (Eliel, Wilen, Eds.), vol. 17, p. 207–279, Wiley, New York 1987.

[3] L. Tőke, L. Fenichel, P. Bakó, J. Szejtli, *Acta Chim. Acad. Sci. Hung.* **98** (1978) 357.

[4] P. Bakó, L. Fenichel, L. Tőke, M. Czugler, *Liebigs Ann. Chem.* **1981**, 1163.

[5] P. Bakó, L. Fenichel, L. Tőke, *Acta Chim. Acad. Sci. Hung.* **111** (1982) 297.

[6] P. Bakó, L. Fenichel, L. Tőke, G. Tóth, *Carbohydr. Res.* **147** (1986) 31.

[7] G. Tóth, W. Dietrich, P. Bakó, L. Fenichel, L. Tőke, *Carbohydr. Res.* **168** (1987) 141.

[8] J. M. Lehn, P. Vierling, *Tetrahedron Lett.* **21** (1980) 1323.

[9] K. Matsushima,. H. Kobayashi, Y. Nakatsuji, M. Okahara, *Chem. Lett.* **1983**, 701.

[10] H. Tsukube, *Bull. Chem. Soc. Jpn.* **57** (1984) 2685.

[11] D. A. Laidler, J. F. Stoddart, *J. Chem. Soc., Chem. Commun.* **1976**, 979.

[12] M. Pietraszkiewicz, J. Jurczak, *J. Chem. Soc., Chem. Commun.* **1983**, 132.

[13] M. Pietraszkiewicz, J. Salanski, J. Jurczak, *J. Chem. Soc., Chem. Commun.* **1983**, 1184.

[14] M. Pietraszkiewicz, J. Jurczak, *Tetrahedron* **40** (1984) 2967.

[15] M. Pietraszkiewicz, P. Salanski, J. Jurczak, *Tetrahedron* **40** (1984) 2971.

[16] P. Bakó, L. Fenichel, L. Tőke, *Acta. Chim. Hung.* **116** (1984) 323.

[17] B. Dietrich, J. M. Lehn, J. P. Sauvage, J. Blanzat, *Tetrahedron* **29** (1973) 1629.

[18] B. Dietrich, J. M. Lehn, J. P. Sauvage, *Tetrahedron* **29** (1973) 1647.

[19] D. Landini, F. Montanari, F. Rolla, *Synthesis* **1978**, 223.

[20] O. A. Gansow, A. R. Kausar, K. B. Triplett, *J. Heterocycl. Chem.* **18** (1981) 297.

[21] S. S. Moore, T. L. Tarnowski, M. Newcomb, D. J. Cram, *J. Am. Chem. Soc.* **99** (1977) 6398.

[22] L. Trézl, P. Bakó, L. Fenichel, I. Rusznák, *J. Chromatogr.* **269** (1983) 40.

[74/90]

Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **16**: 17–23, 1993.
© 1993 *Kluwer Academic Publishers. Printed in the Netherlands.*

The Complexing Ability of Crown Ethers Incorporating Glucose

PETER BAKÓ, LÁSZLÓ FENICHEL and LÁSZLÓ TÔKE*
Department of Organic Chemical Technology, Technical University of Budapest, H-1111 Budapest, Müegyetem rkp. 3, Hungary.

(Received: 30 December 1992; in final form: 17 May 1993)

Abstract. The complexing (in $CHCl_3$) and extracting abilities of 18-crown-6 type compounds (**1–15**) were measured with Li, Na, K and NH_4 cations. The substituents on the sugar part affected these properties significantly ($K_a = 10^3$–10^7). Some substituents, like acetyloxy groups (**3**) decreased whereas others, like tosyloxy groups (**10, 11**) significantly increased the complexing ability and thus changed the selectivity. The compound with four tosyloxy groups (**11**) shows an excellent picrate salt extracting ability in a CH_2Cl_2-water system.

Key words: Crown ether, complex formation, extraction ability.

1. Introduction

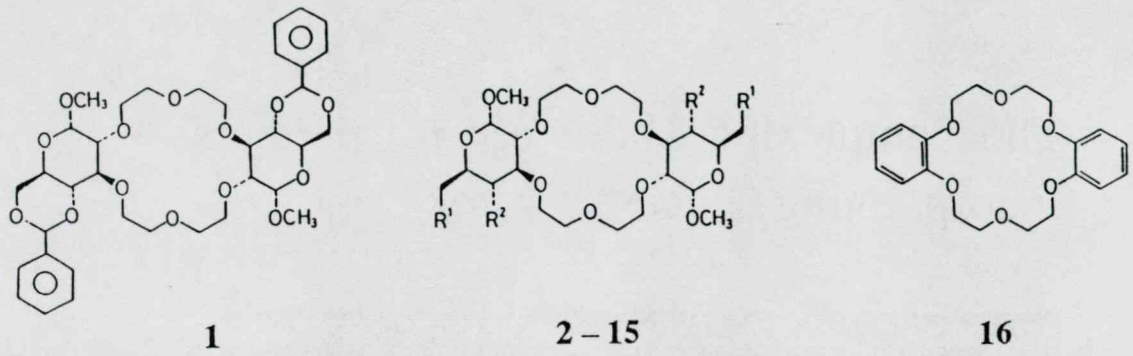
A variety of monosaccharides has been used as starting material for the synthesis of several types of chiral crown ethers [1, 2], and the stabilities of their complexes with metal and ammonium cations have been determined, mainly in a binary $CDCl_3$-water system [1, 3, 4].

In the case of metal, ammonium, methylammonium and *t*-butyl ammonium picrates, the values of the association constants (K_a) were determined by UV spectrophotometry, following the extraction of the aqueous solution of the picrate salt of the crown ether with deutero chloroform [1, 4]. The complexing ability of sugar crowns toward ammonium ions was measured with *t*-butyl ammonium thiocyanate by ^{1}H NMR spectroscopy [5, 6].

2. Experimental

The synthesis of the sugar-based crown ethers **1–15** has been described by us previously [7–10]; the dibenzo-18-crown-6 used for comparison is a Merck product. The complexing constants of the compounds with Li, Na, K and ammonium picrates were measured in chloroform, by UV spectrometry, using the method of Cram [4]. Most of the crown ethers were insoluble in water: solubilities were 0.5% of the total used. The distribution constants of the water-soluble crown ethers between water and chloroform were determined in independent experiments and these constants

* Author for correspondence.



1 **2 – 15** **16**

Fig. 1.

were taken into consideration in the calculations of K_a values [14, 15]. Although the host-guest stoichiometric ratio in the solution was unknown, for the similar 18-crown-6 type sugar crowns the literature describes 1 : 1 complexes only [1], and our calculations were based on this stoichiometry.

The complex forming ability of some glucopyranoside compounds having benzylidene, benzyloxy, acetoxy, and tosyloxy substituents was measured with metal picrates under the same conditions as in the case of the crown ethers. It has been found that these groups are not able to form complexes with alkali metal and ammonium picrates.

The alkali metal and ammonium picrates were prepared and purified by the method of Wong [11].

Extraction ability was measured by the method of Kimura *et al.* [12] with the above mentioned picrates in a CH_2Cl_2-water system, by means of UV spectrometry (using a Hitachi Perkin-Elmer 124 spectrometer).

3. Results and Discussion

3.1. Complexing Ability

In all the compounds investigated (**1–15**), the ring is always of the 18-crown-6 type, and the substituents on the sugar part vary (R^1 denotes the substituents on the two primary carbons, R^2 those on the two secondary carbons: Figure 1). Consequently, in this case one can study the effect of substituents on complexing ability (or salt extracting ability), i.e. the so-called lateral discrimination. The lateral groups may have a secondary interaction with the guest molecules. This interaction is a result of several factors: they may be steric effects or hydrophilic and hydrophobic effects (the crown ether also encounters water molecules during the measurement). These effects occur in a complex way, strengthening or weakening one another, and thus it is hard to predict scientifically the values of the resulting complexing constants.

We examined C.P.K. space-filling molecular models of the crown ethers substituted by different groups. The substituents were changed only on the 4C and 6C

TABLE I. Association constants of crown compounds (**1–15**) (log K_a in chloroform at 22°C.[a]

Crown compd.	R^1	R^2	log K_a			
			Li^+	Na^+	K^+	NH_4^+
1		$CH-C_6H_5$	4.14	4.05	5.04	4.12
2	OH	OH	4.04	4.50	4.85	4.01
3	OAc	OAc	3.57	3.20	4.46	3.58
4	Br	OBz	3.68	4.38	4.16	3.96
5	H	OH	4.75	5.05	4.78	4.56
6	Br	OH	3.57	3.95	4.40	3.53
7	OH	OBn	3.58	4.76	4.70	4.38
8	OTr	OAc	4.15	4.80	4.47	3.67
9	OH	OAc	3.75	3.62	4.37	3.59
10	OTs	OH	5.70	5.40	5.45	5.64
11	OTs	OTs	6.17	6.23	6.00	5.81
12	OMs	OH	4.47	4.16	4.65	4.33
13	OMe	OMe	3.18	4.21	4.35	3.91
14	OBu	OBu	4.25	4.33	4.38	3.82
15	OBn	OBn	3.56	4.01	4.09	3.72
16	dibenzo-18-crown-6		4.08	4.44	7.85	5.96

Ac = acetyl, Bz = benzoyl, Tr = trityl, Ts = tosyl, Ms = mesyl, Me = methyl, Bu = butyl, Bn = benzyl

[a] Aqueous phase (0.5 mL); [picrate] = 0.15 M; organic phase ($CHCl_3$, 0.2 mL); [crown ether] = 0.075 M; Ref. [4].

atoms of the pyranose residues (**1–15**). We found that these substituents did not induce conformational changes on the sugar ring and on the crown ring.

As a comparison, the properties of dibenzo-18-crown-6 (**16**) were also measured. As can be seen from Table I, the substituents found on the sugar parts affect the complexing ability significantly: the association constants, K_a, are in the 10^3–10^7 range. The weakest complexing ability is shown by the substances bearing two or four acetyloxy groups (**3**, **9**), bromine and benzoyloxy groups (**4**, **6**), four methoxy groups (**13**) or four benzyloxy groups (**15**).

Tetrabutoxy (**14**) and hexamethoxy ethers (**13**) have nearly identical properties, except that the lithium complex of **14** is an order of magnitude stronger than that of **13**.

There are substituents which promote complex formation with all cations: the presence of two tosyloxy groups (**10**) increases this ability by 1–1.5 orders of magnitude; that of four tosyloxy groups (**11**) by two orders of magnitude with respect to the benzylidene derivative (**1**).

As is known, the size of the 18-ring corresponds (on the basis of ion radii) to a selectivity sequence of $NH_4^+ \approx K^+ > Na^+ > Li^+$. This tendency also holds for our compounds: the majority forms the strongest complex with K^+. There are, however, substituents which change this characteristic sequence of the basic crown: the bromobenzoyloxy derivative (**4**), the unsubstituted (**5**), the benzyloxy (**7**), the trityloxy-acetyloxy (**8**) and the tetratosyloxy (**11**) derivatives all form the most stable complex with sodium. A comparison of the behaviour of **4** and **6** suggests that the crown ether becomes sodium selective on addition of benzoyloxy groups. A comparison of **8** and **9** indicates that the trityloxy groups increase the stability of the sodium complex by more than one order of magnitude.

Tosyloxy groups (**10**, **11**) not only enhance the complexing ability but also change the selectivity sequence, preferring primarily lithium and sodium, respectively.

In the case of the tetrasubstituted derivatives ($R^1 = R^2$), the stability of the complex with respect to K^+ decreases in the sequence of OTs > OCHPh > OH > OAc > OBu > OMe > OBn (Figure 2). Compared to the values measured with Na^+, some selectivity is shown by **1** and **3** (OCHPh and OAc), inasmuch as there is a 1–1.2 order of magnitude difference between the K_a values obtained with Na^+ and K^+ ions.

The stability of the disubstituted compounds ($R^2 = OH$) with respect to K^+ decreases in the sequence of OTs > OH > H > OMs > Br (Figure 3), and compared to the Na^+ values none of the compounds shows significant selectivity.

As can be seen, tosyloxy groups increase the stability of complexes with all cations, but suppress the differences thereby decreasing the selectivity.

We investigated the lipophilicity of compounds **1–15** by reverse- phase TLC on a silica gel plate modified by octadecyltrimethylsilane, with an ethanol-water (7 : 3) eluent. In this system the R_f values are characteristic of the lipophilicity of the crown ethers. We did not find any general connection between the lipophilicity and association constants (e.g. the order of lipophilicity is **1** > **10** > **3** but that of the K_a values is **10** > **1** > **3**).

3.2. Extraction Ability

Table II shows the extraction ability of picrate salts of compounds **1**, **2**, **3**, **4**, **7**, **10**, **11** and **16** in the CH_2Cl_2-water system. The tendencies are similar to those of complex formation; substituents affect the extraction ability to a great extent depending on the type of ions. Dibenzo-18-crown-6 (**16**) used as reference shows a notable selectivity with potassium ions.

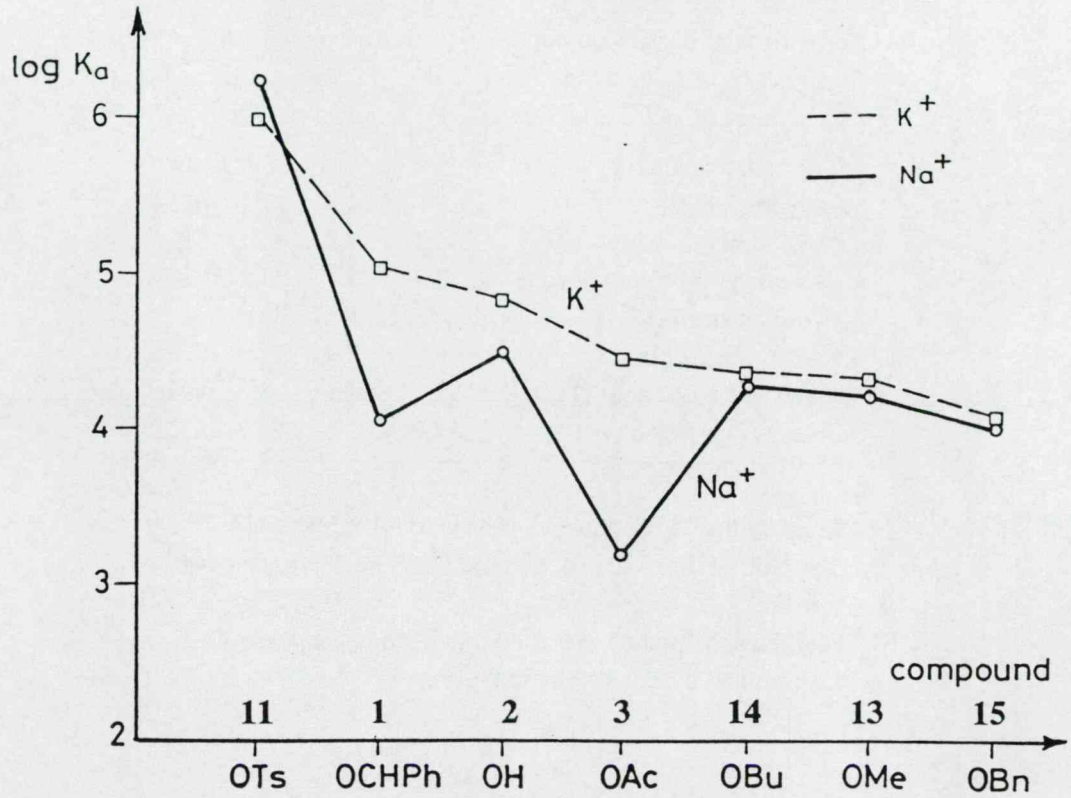


Fig. 2. Log K_a values for tetrasubstituted derivatives.

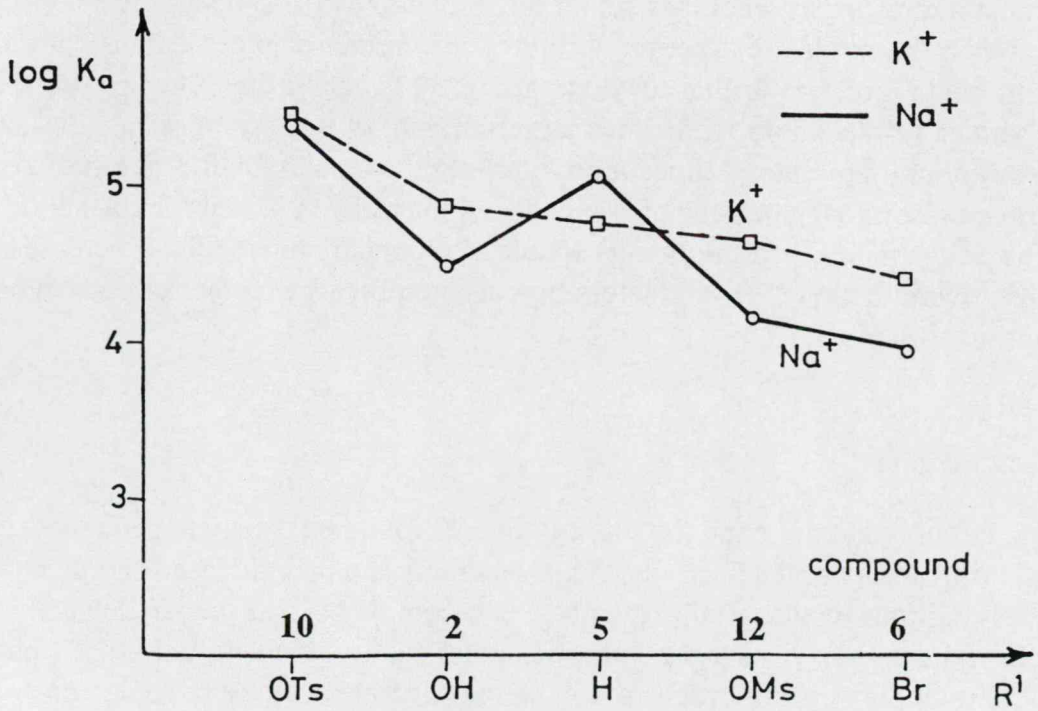


Fig. 3. Log K_a values for disubstituted derivatives.

SZTE Egyetemi Könyvtár SZEGED 13.

TABLE II. Extraction of alkali metal and ammonium picrates.[a]

Derivatives of bis(glucopyrano-sido)-18-crown-6	Extractability (%) [b]			
	Li^+	Na^+	K^+	NH_4^+
4,6-*O*-benzylidene- (**1**)	5.9	14.8	9.6	14.9
tetrahydroxy- (**2**)	6.7	4.4	7.1	12.9
4,4′,6,6′-tetra-*O*-acetyl- (**3**)	6.3	11.8	14.7	14.1
4-*O*-benzoyl-6-bromo- (**4**)	3.9	21.5	14.2	21.6
4,4′-di-*O*-benzyl- (**7**)	28.3	15.5	32.0	35.1
6,6′-di-*O*-tosyl- (**10**)	6.9	1.4	14.8	20.6
4,4′,6,6′-tetra-*O*-tosyl- (**11**)	99.5	93.2	98.5	99.6
dibenzo-18-crown-6 (**16**)	14.0	2.1	56.7	33.5

[a] Temperature 25°C; aqueous phase (10 mL); [picrate] = 5×10^{-3}M; organic phase (CH_2Cl_2, 10 mL); [crown ether] = 1×10^{-2}M.

[b] Defined as % picrate extracted into the organic phase. Determined by UV spectroscopy.

The dibenzyloxy derivative (**7**) is worth noting since its Li, Na and NH_4 picrate extraction ability is better than that of **16**, but shows only insignificant selectivity. The most interesting is a comparison of the ditosyloxy (**10**) and tetratosyloxy (**11**) derivatives: the modest extraction ability of the former changes dramatically on the introduction of two further tosyloxy groups (**11**), increasing it to an extremely large value: **11** takes up to 1.7 times larger amount of potassium picrate, 3 times more ammonium picrate, 7 times more lithium picrate, and finally, 44 times more sodium picrate into the organic phase than compound **16**. A probable explanation is that the polar Ar-SO_2 groups, being capable of secondary interactions, increase the stablity toward cations. These factors give us a chiral crown ether of outstanding extraction ability.

4. Conclusions

We have found that, by changing the subtituents found on the sugar parts only, the complexing ability and selectivity of crown ethers can be influenced significantly. By applying four tosyloxy substituents, a compound (**11**) was prepared which can be conceived to behave as a good phase transfer catalyst in the liquid-liquid phase, and this may play an important role in stereoselective syntheses. To demonstrate this assumption, further research is required.

References

1. J.F. Stoddart: *Synthetic Chiral Receptor Molecules from Natural Products* (Progress in Màcrocyclic Chemistry, Vol. 2, Ed. R. Izatt and J. Christensen), pp. 173–250, J. Wiley-Interscience, New York (1981).
2. J.F. Stoddart: *Chiral Crown Ethers* (Topics in Stereo-Chemistry, Vol. 17, Ed. E.L. Elied and S.H. Whilen), pp. 207–288, Wiley and Sons (1987).
3. K.E. Koeing, R.C. Helgeseon and D.J. Cram: *J. Am. Chem. Soc.* **98**, 4018 (1976).
4. S.S. Moore, T.L. Tarnowski, M. Newcomb and D.J. Cram: *J. Am. Chem. Soc.* **99**, 6398 (1977).
5. J.M. Timko, R.C. Helgeson, M. Newcomb, G.W. Gokel and D.J. Cram: *J. Am. Chem. Soc.* **96**, 7097 (1974).
6. J.M. Timko, S.S. Moore, D.M. Walba, P.C. Hiberty and D.J. Cram: *J. Am. Chem. Soc.* **99**, 4207 (1977).
7. L. Tôke, L. Fenichel, P. Bakó and J. Szejtli: *Acta Chim. Acad. Sci. Hung.* **98**, 357 (1978).
8. P. Bakó, L. Fenichel and L. Tôke: *Justus Liebigs Ann. Chem.* 1163 (1981).
9. P. Bakó, L. Fenichel and L. Tôke: *Acta Chim. Acad. Sci. Hung.* **111** (3), 297–304 (1982).
10. P. Bakó, L. Fenichel, L. Tôke and G. Tóth: *Carbohydrate Res.* **147**, 31 (1986).
11. K.H. Wong and H.L. Ng: *J. Coord. Chem.* **49**, 11 (1981).
12. K. Kimura, T. Maeda and T. Shono: *Talanta* **26**, 945 (1979).
13. T. Maeda, K. Kimuira and T. Shono: *Bull. Chem. Soc. Jpn.* **55**, 3506 (1982).
14. K.H. Wong, M. Bourgoin and J. Smid: *J. Chem. Soc. Chem. Commun.* 715 (1974).
15. M. Bourgoin, K.H. Wong, J.Y. Hull and J. Smid: *J. Am. Chem. Soc.* **97** 3462 (1975).

Heteroatom Chemistry
Volume 5, Number 4, 1994

Elaboration of a Chiral 20-Crown-6 from a Glucofuranose Derivative and Its Complex Formation with Alkali Cations

Peter Bakó, Laszló Fenichel, and Laszló Tōke*

Department of Organic Chemical Technology, Technical University of Budapest, H-1111 Budapest, Hungary

Bruce E. Davison and Alpana Patel

Department of Chemistry, Christopher Ingold University College London, London WC 1H, England

Received 9 March 1994; revised 20 June 1994

ABSTRACT

The synthesis of bis-(1,2-O-isopropylidene-6-O-triphenylmethyl-α-D-glucofuranosyl)-20-crown-6 (1) and its complexing ability with alkali and ammonium cations are described. The crown ether 1 was synthesized in a stepwise manner via the "half-crown" (2) using a blocking-deblocking procedure, in which the 3,3'-bridge was formed, followed after suitable manipulations, by formation of the 5,5'-bridge. An unusual feature of the complexing ability of the crown ether is that, although potassium and ammonium ions most closely approach the size of the complexing cavity, it is the sodium ion which forms the most stable complex. Compound 1 does not show chiral recognition toward two alkylammonium salts.

INTRODUCTION

It is known that chiral crown ethers functioning as hosts in complexation exhibit chiral recognition of enantiomers of alkylammonium salts as guests [1–6]. Certain macrocyclic compounds incorporating a sugar moiety show some enantiomer selectivity toward an (RS)-α-phenylethylammonium salt [2]. Compounds having *bis*-dinaphthyl units have a very high enantiomer selectivity for 1,2-diphenylethylamine and other amines [3,4]. Enantiomer selectivity of the chiral crown ethers was evaluated by a membrane electrode method [5,6].

Chiral crown ethers in which the chirality is carried by carbohydrate molecules incorporated into the macrocycle form a very important class of compounds [7–9]. Protected sugars bearing acetals, such as isopropylidene [10,11] and benzylidene [12–15] derivatives, have been used in the synthesis of several such chiral crown ethers, and the sugar moieties may be in the form of the open chain [10], the pyranose [12–15] or, more rarely, the furanose [11] ring.

In the majority of syntheses, the macrocycle has been constructed in a regioselective manner using one sugar residue and conventional ring formation or template ring closure, in which a metal ion participates. In those cases where two sugar residues are incorporated into the macrocycle, the ring closure reaction is often not regioselective, and stereoisomeric products result [13–15]. Similar preparative difficulties have been encountered in syntheses of the related aza crown compounds derived from amino sugars [16–18].

In order to increase the number of chiral compounds having different ring sizes and lipophilicities, we planned to synthesize chiral compounds with a 20-membered ring similarly to the chiral 18-crown-6 compounds synthesized and published earlier by us [14,15]. This new crown

*To whom correspondence should be addressed.

© 1994 VCH Publishers, Inc.

1042-7163/94/$5.00 + .25

TABLE 1 Effect of Different Bases on Yield of Half-Crown 2 and Formation of Monotosyl Ether 4

Base	Solvent	Yield% of 2	Formation of 4
aq KOH	THF	50	yes
NaOBu^t	THF-Bu^{t}OH	4.7	yes
NaH	THF	45	no
NaH	DMF	62	no

TABLE 2 Complex Formation Constants for Chiral Crown 1 with Ions in Chloroform at Room Temperature

Ion	Log Ka[a]
Li^+	3.85
Na^+	4.46
K^+	4.06
NH_4^+	3.92

[a]Error limit: ±0.03; the results are the average of triplet runs.

ether contains only six oxygen atoms in the ring. As a result, the complex-forming ability of the new ring of this type changes and may even be decreased compared to the 18-crown-6 compounds.

There are enantioselective reactions in which the chiral crown ether is being used as a phase transfer catalyst; e.g., carbohydrate-containing crown ethers have been used as catalysts in asymmetric Michael additions [19–21]. We have also obtained significant results in this field using 18-crown-6 incorporating glucopyranoside units [22]. Compared with the 20-membered ring, they may have other influences on the measure and direction of their enantioface differentiating ability in asymmetric reactions. Bradshaw et al. have found that the molecular conformation and flexibility play important roles in enantiomer recognition and in its function as a catalyst [23,24].

RESULTS AND DISCUSSION

Synthesis

The present article describes the regioselective synthesis of the chiral 20-crown-6 (**1**) from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**3**), in a stepwise manner using a blocking-deblocking process via the "half-crown" (**2**), in which the 3,3′-bridge is first formed, followed, after suitable manipulations, by formation of the 5,5′-bridge.

The protected sugar **3** contains a secondary hydroxyl group at position-3, which, as is well known, has a low reactivity. Since two molecules of **3** were to be coupled through this hydroxyl group using a base-catalyzed condensation with diethyleneglycol ditosylate, various base-solvent combinations were examined (see Table 1).

Using our earlier process [15] involving concentrated potassium hydroxide in tetrahydrofuran gave a reasonable yield (50%) of the desired half-crown **2**, but an additional by-product was formed, from which it could be separated only by chromatography. Isolation and characterization proved the by-product to be the monotosyl intermediate (**4**). On the other hand, a good yield of the 3,3′-bridged product **2** was obtained free from by-products using sodium hydride in dimethylformamide, the only contaminant being unreacted starting material from which **2** was easily separated by solvent extraction.

In the next stage, the 5,6-O-isopropylidene groups of **2** were removed using ethanoic acid in dioxane [26] to give the *bis*-diol (**5**) in 90% yield. In order to carry out the next stage of cyclization using the 5- and 5′-hydroxyl groups, it was necessary to protect the primary alcohol groups. Because it was intended to re-expose these groups after formation of the crown ether, triphenylmethyl protection was employed; the ditrityl derivative (**6**) was obtained in 95% yield using trityl chloride in dichloromethane in the presence of triethylamine.

Intramolecular ring closure leading to the target 20-crown-6 **1** was carried out by reaction of **6** with diethylene glycol ditosylate. This step proceeded in very poor yield, even with use of sodium hydride in dimethylformamide, chromatographic purification giving a 4% yield of the product. A probable reason for the difficulty of cyclization is steric inhibition by the triphenylmethyl groups.

COMPLEX FORMATION

The complex-forming properties of the crown **1** with lithium, sodium, potassium, and ammonium picrates were measured by the method of Cram [27]. The logarithms of the complex-formation constants (log K_a) in chloroform at room temperature are shown in Table 2. These values are of a similar order of magnitude to the values of 18-crown-6 having two glucopyranoside units (log K_a = 4–5) [25], and the ion selectivity is low; but, in spite of the large size of the ring, the most stable complex is formed with the sodium cation, even though the sizes of the potassium and ammonium ions most closely approach the diameter of the crown ring cavity (ion diameter of cations: Li^+ 1.2; Na^+ 1.9; K^+ 2.66; NH_4^+ 2.84 Å; the hole size of crown ethers: 12-crown-4 1.0–1.3; 15-crown-5 1.7–2.2; 18-crown-6 2.6–3.2 Å). The ionic diameter of K^+ corresponds to the inner dimensions of the 18-crown-6 ring. The hole of our ligand **1** is larger than that of 18-crown-6. The investigated cations are too small in comparison to the hole size of the 20-membered ring, and this is why they have play in the ring of **1**. The complex formation can be explained by the

flexibility of **1**, the cations being "wrapped up" by the crown ring.

The chiral recognition power of compounds can be measured by the membrane-transport process of racemic ammonium salts [28,29]. We have performed experiments using our new crown ether **1** to carry the enantiomers of a racemic mixture of 2-phenylethylammonium chloride or phenylglycine methyl ester hydrochloride, respectively, from the aqueous solution through chloroform (membrane) to the other aqueous phase, by Cram's method [29] in a co-axial cylinder cell apparatus. Compound **1** was able to transport the ammonium salts (49 and 42%, respectively, after 3 hours), but it did not show chiral recognition; we obtained the racemic mixture in the receiving phase.

The application of the new crown ether as a stereoselective catalyst in asymmetric reactions will be reported in a subsequent article.

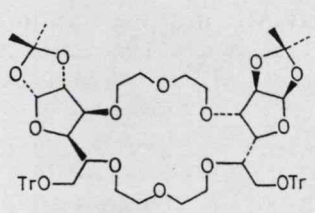
EXPERIMENTAL

1H NMR spectra: Perkin-Elmer R12 and JEOL FX-100 (in CDCl3), TMS as internal standard. UV spectra: Hitachi-Perkin-Elmer 124. Mass spectra: JEOL JMS-OL SG-2. Elemental analysis: Perkin-Elmer 240 automatic analyzer. TLC: Kieselgel 60 F254 or Al203 150 F254 Type T (Merck), eluent toluene/methanol mixtures (10:1–10:5); detection with Dragendorff's reagent [30]. Column chromatography: Kieselgel 60 (0.2–0.063 mm) (Merck).

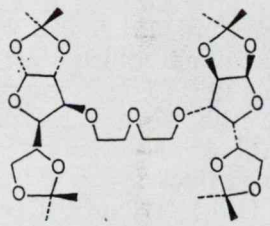
Preparation of 2,2'-di-O-(1,2:5,6-di-O-isopropylidene-D-glucofuranos-3-yl)diethylene Glycol **2** *Using Potassium Hydroxide as Base: Isolation of 3-O-(5'-p-toluenesulphonyloxy-3'-oxapentyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose* **4**

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (31.2 g, 0.12 mol) dissolved in tetrahydrofuran (450 mL) was placed in a round-bottomed flask equipped with a magnetic stirrer. Potassium hydroxide (20.2 g, 0.36 mol) in water (40.4 mL) was added and the mixture stirred under reflux for 2 hours. Diethyleneglycol ditosylate (24.8 g, 0.06 mol) was added, and the mixture was stirred under reflux for an additional 40 hours. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in methylene chloride (750 mL) and washed, respectively, with 2M hydrochloric acid (2 × 300 mL), 10% $NaHCO_3$ solution (300 mL), and saturated NaCl solution (300 mL). The solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to give a yellow syrup (27.5 g), which contained four components according to tlc. The product mixture was subjected to column chromatography on Kieselgel 60 using toluene-ethyl acetate (5:1) as eluent, giving three fractions: fraction 1 consisted of ethyleneglycol ditosylate (3.20 g); fraction 2 contained a by-product (3.45 g); fraction 3 contained a mixture of the unchanged di-O-isopropylidene-glucose **3** and the dissolved half-crown product **2**.

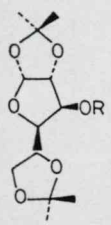
The syrupy mixture (18.70 g) obtained by evaporation of fraction 3 was boiled with petroleum ether for 0.5 hours, and the resulting suspension was allowed to stand for 10 hours at room temperature. Filtration gave unchanged 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (1.2 g). Evaporation of the filtrate gave the ethyleneglycol *bis*-glucose derivative (**2**) as a pale syrup (17.5 g, 50% yield). Evaporation of fraction 2 gave 3-O-[5'-*p*-toluenesulphonyloxy-3-oxapentyl]-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose as a pale syrup (3.45 g, 11.5%), $[\alpha]_D^{22} = -16.0°$ (c 5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.25 (12H, d, J = 10 Hz, isopropylidene CH_3). 2.30 (3H, s, C_6H_4–CH_3), 3.3–4.5 (14H, m, sugar protons), 3.5 (8H, s, 4 × crown–CH_2), 5.7 (1H, d, J = 4 Hz, 1-H), 7.2–7.7 (4H, m, aromatic-H). Anal. calcd. for $C_{23}H_{34}O_{11}S$ (518): C, 53.27; H, 6.61; S, 6.18. Found: C, 53.57; H, 6.58; S, 6.03.



1

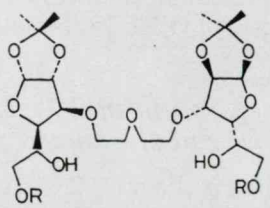


2



3 R = H

4 R = $(CH_2)_2O(CH_2)_2OTs$



5 R = H

6 R = CPh_3

Preparation of the Half-Crown **2** *Using Sodium tert- Butoxide as Base*

Metallic sodium (1.4 g, 0.06 mol) was caused to react with absolute *tert*-butyl alcohol (50 mL) under stirring and reflux, and a solution of the diacetal **3** (5.2 g, 0.02 mol) in absolute tetrahydrofuran (10 mL) was added. The mixture was maintained under reflux and stirring for an additional 2 hours, after which diethylene glycol ditosylate (4.14 g, 0.01 mol) in absolute tetrahydrofuran was added. After 25 hours at reflux, the reaction mixture was poured

into ice-water (100 mL), and the resulting suspension was evaporated to dryness in vacuo. The residue was extracted with chloroform (200 mL) and the extracts washed successively with 10% $NaHCO_3$ solution (100 mL) and water (100 mL). Drying of the chloroform extract over Na_2SO_4 gave, on evaporation, a yellow oil, from which was obtained by column chromatography, as before, the half-crown **2** (0.28 g, 4.7%). One of the two other compounds of the product mixture was shown to be the monotosyl by-product **4**.

Preparation of 2,2'-Di-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)diethylene Glycol **2** *without Formation of* **4**

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose **3** (2.84 g, 0.011 mol) was dissolved in absolute DMF (30 mL), and 55% paraffin-free sodium hydride (3.02 g, 0.069 mol) was added. After the mixture had been stirred for 1 hour at 60°C, a solution of diethylene glycol ditosylate (2.28 g, 0.006 mol) in absolute DMF (30 mL) was added. The reaction mixture was further diluted with DMF (20 mL), and the solution was maintained at 60°C for 30 hours. The reaction mixture was cooled, water (60 mL) added, and the resultant solution extracted with chloroform (3 × 50 mL). The combined chloroform phases were washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the title compound, as a thick syrup (2.0 g, 62%), $[\alpha]_D^{20} = -27.05°$ (c 5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28, 1.32, 1.40, 1.45 (8 × CH_3, 4 × s), 3.55–4.32 (18H, m, OCH_2CH_2O and other CH and CH_2 groups), 4.48 (2H, d, 2, 2'-H, J = 4 Hz), 5.88 (2H, d, anomeric-H, J = 4 Hz); **ms** *m/z* 575 (83.9), 474 (6.0), 373 (10.9), 101 (100), 59 (18.2), 45 (27.2%). Anal. calcd. for $C_{28}H_{46}O_{13}$ (590): C, 56.95; H, 7.80; O, 35.25. Found: C, 57.12; H, 7.60; O, 35.20.

Preparation of 2,2'-Di-O-(1,2-O-isopropylidene-α-D- glucofuranos-3-yl)diethylene Glycol **5**

The *bis*-diacetal **2** (6.81 g) was dissolved in dioxane (20 mL), and a solution of ethanoic acid (33 mL) in water (14 mL) was added. The reaction mixture was maintained under stirring at 65° for 2 hours. The solution was concentrated in vacuo, the residue dissolved in water (100 mL) and extracted with chloroform (2 × 10 mL). The aqueous phase was again concentrated and the acetic acid removed by azeotropic distillation with toluene to yield the title compound as a yellow syrup. (5.4 g, 92%), $[\alpha]_D^{20} = 16.2$ (c 5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (6H, s, 2 × CH_3), 1.45 (6H, s, 2 × CH_3); 3.55–4.12 (18H, m, OCH_2CH_2O, CH2, CH), 4.50 (2H, d, 2,2'-H, J = 4 Hz), 5.87 (2H, d, 2 × 1-H, J = 4 Hz) Anal. calcd. for $C_{22}H_{38}O_{13}$ (510): C, 51.67; H, 7.45. Found: C, 52.21; H, 7.30.

Preparation of 2,2'-Di-O-(1,2-O-isopropylidene-6-O-triphenylmethyl-α-D-glucofuranos-3-yl)diethylene Glycol **6**

Diethylene glycol-di-(1,2-O-isopropylidene-α-D-glucofuranos-3-yl) **5** (1.26 g, 2.5 mmol) dissolved in a mixture of dichloromethane (10 mL) and triethylamine (3 mL) was treated with triphenylmethyl chloride (1.38 g, 5.0 mmol) and stirred for 5 hours at room temperature. The reaction mixture was washed successively with water (10 mL), 2M HCl (10 mL), and 10% aq $NaHCO_3$ solution (10 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was digested with hot petroleum ether (10 mL), and the residue was dried in a vacuum desiccator to yield the title compound as a yellow amorphous solid (1.90 g, 78.5%), $[\alpha]_D^{20} = 20.1$ (c 5, $CHCl_3$), mp 96–101°; ^1H NMR ($CDCl_3$) δ 1.26 (6H, s, 2 × CH_3), 1.44 (6H, s, 2 × CH_3), 3.25–4.05 (18H, m, OCH_2CH_2O, CH, CH2), 4.46 (2H, d, 2,2'-H, J = 4 Hz), 5.78 (2H, d, C1-H, J = 4 Hz), 7.10–7.52 (30H, m, aromatic-H). Anal. calcd. for $C_{60}H_{64}O_{13}$ (992): C, 72.59; H, 6.45. Found: C, 72.50; H, 6.40 MS (70 eV) $m/z(M^+$ 992).

Preparation of bis-(1,2,-O-Isopropylidene-6-O-triphenylmethyl-α-D-glucofuranos-3,5-diyl)-20-crown-6 **1**

The diethylene glycol glucose derivative **5** (4.78 g, 4.9 mmol) was dissolved in absolute tetrahydrofuran (40 mL), and 55% petroleum-washed sodium hydride (1.28 g, 28.4 mmol) was added. The resulting suspension was stirred for 1 hour at 60°C, and diethyleneglycol ditosylate (2.03 g, 4.9 mmol) in absolute tetrahydrofuran (10 mL) was added. The mixture was stirred for an additional 40 hours at 60°C. The cooled solution was added dropwise into water (5 mL) to decompose unreacted sodium hydride. The mixture was filtered and the filtrate evaporated in vacuo. The residue was washed successively with water, 2M HCl, 10% aq $NaHCO_3$ solution, and finally dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using Kieselgel 60 with toluene-ethyl acetate (5:3) as eluent. The title crown ether was obtained as a white amorphous solid (0.21 g, 4%), mp 62–67°C. $[\alpha]_D^{20} = -17.2$ (c 3.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (6H, d, J = 4 Hz, 2 × CH3), 1.44 (6H, s, 2 × CH_3), 3.25–4.08 (26H, m, OCH_2CH_2O, CH; other CH_2), 4.48 (2H, d, J = 4 Hz, 2,2'-H), 5.75 (2H, d, J = 4 Hz, 2 × anomeric H), 7.10–7.52 (30H, m, Ph). Anal. calcd. for $C_{64}H_{22}O_{14}$ (1066): C, 72.18; H, 6.77. Found: C, 71.77; H, 6.91.

REFERENCES

[1] Evan P. Kyba, Joseph M. Timko, Lester J. Kaplan, Feike de Jong, George W. Gokel, Donald. J. Cram, *J. Am. Chem. Soc., 100*, 1978, 4555.

[2] W. David Curtis, Dale A. Laidler, J. Fraser Stoddart, Graham H. Jones, *J. Chem. Soc., Perkin Trans., I*, 1977, 1756.
[3] Koji Yamamoto, Hitoshi Fukushima, Yoshio Okamato, Koichi Hatada, Masao Nakazaki, *J. Chem. Soc., Chem. Commun.*, 1984, 1111.
[4] Koji Yamamoto, Koji Noda, Yoshio Okamoto, *J. Chem. Soc., Chem. Commun.*, 1985, 1065.
[5] Walter Bussmann, Jean-Marie Lehn, Urs Oesch, Pierre Plumeré, Wilhelm Simon, *Helv. Chim. Acta.*, *64*, 1981, 657.
[6] Yuta Yasaka, Takashi Yamamoto, Keiichi Kimura, Toshiyuki Shono, *Chem. Lett.*, 1980, 769.
[7] J. F. Stoddart, *Chem. Soc. Rev., 8*, 1979, 85.
[8] J. F. Stoddart: in R. M. Izatt, J. J. Christensen (eds): *Progress in Macrocyclic Chemistry*, Wiley-Interscience, New York, vol. 2, pp. 173–250 (1981).
[9] J. F. Stoddart: in E. L. Eliel, S. H. Wilen (eds): *Topics in Stereochemistry*, Wiley, New York, vol. 17, pp. 207–279 (1987).
[10] W. D. Curtis, D. A. Laidler, J. F. Stoddart, G. H. Jones, *J. Chem. Soc., Chem. Commun., 833*, 1975, 835.
[11] R. Aldag and G. Schröder, *Justus Liebig Ann. Chem.*, 1984, 1036.
[12] D. A. Laidler, J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1977, 481.
[13] W. Hain, R. Lehnert, H. Röttele, G. Schröder, *Tetrahedron Lett.*, 1978, 625.
[14] L. Tôke, L. Fenichel, P. Bakó, J. Szejtli, *Acta. Chim. Acad. Sci. Hung., 98*, 1978, 357.
[15] P. Bakó, L. Fenichel, L. Tôke, M. Czugler, *Justus Liebigs Ann. Chem.*, 1981, 1163.
[16] M. Pietraszkievicz, J. Jurczak, *J. Chem. Soc., Chem. Commun.*, 1983, 132.
[17] B. E. Davison, P. Bakó, L. Fenichel, L. Tôke, *J. Chem. Soc., Perkin Trans., I*, 1989, 2514; 1990.
[18] P. Bakó, L. Fenichel, L. Tôke, *Acta Chim. Acad. Sci. Hung., 116*, 1984, 323.
[19] Manuel Alonso-Lopez, Jesus Yimenez-Barbero, Manuel Martin-Lomas, Soledad Penades: *Tetrahedron, 44*, 1988, 1535.
[20] Shin Aoki, Shigeki Sasaki, Kenji Koga: *Heterocycles 33*, 1992, 493.
[21] Dave A. H. van Maarschalkerwaart, Nico P. Willard, Upendra K. Pandit: *Tetrahedron, 48*, 1992, 8825.
[22] The work is to be published in the near future.
[23] R. M. Izatt, C.-Y. Zhu, P. Huszthy, J. S. Bradshaw: in S. R. Cooper (ed): *Enantiomeric Recognition in Macrocycle-Primary Ammonium Cation Systems in Crown Ethers: Toward Future Application*, VCR Press, New York, 1993.
[24] Tingmin Wang, Jerald S. Bradshaw, Peter Huszthy, Xiaolan Kou, N. Kent Dalley, Reed M. Izatt: *J. Heterocyclic Chem., 31*, 1993, 1.
[25] Peter Bakó, László Fenichel, László Tôke: *J. Incl. Phenom., 16*, 1993, 17.
[26] R. E. Gramera, A. Park, R. L. Whistler, *J. Org. Chem., 28*, 1963, 3230.
[27] S. S. Moore, T. L. Tarnowski, M. Newcomb, and D. J. Cram, *J. Am. Chem. Soc., 99*, 1977, 9398.
[28] M. Zinic, L. Frkanec, V. Skaric, J. Trafton, G. W. Gokel: *J. Chem. Soc., Chem. Commun.*, 1990, 1726.
[29] M. Newcomb, I. L. Toner, R. C. Helgeson, D. J. Cram., *J. Am. Chem. Soc., 101*, 1979, 4941; *102*, 1980, 2043.
[30] L. Trézl, P. Bakó, L. Fenichel, I. Rusznák, *J. Chromatogr., 269*, 1983, 40.

-

Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **23**: 195–201, 1995.

© 1995 *Kluwer Academic Publishers. Printed in the Netherlands.*

B5

Novel Monoaza- and Diazacrown Ethers Incorporating Sugar Units and Their Extraction Ability towards Picrate Salts

PÉTER BAKÓ and LÁSZLÓ TÖKE*
Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, Müegyetem rkp. 3. Hungary.

(Received: 12 July 1995; in final form: 1 November 1995)

Abstract. A number of new 15- and 1 8-membered ring aza-crown (**4**, **5**, **8–13**, **17**, **18**) and lariat ethers (**6**, **7**) incorporating glucose or galactose units have been synthesized in good yields by a simple route. Their extracting abilities were measured with Li^+, Na^+, K^+ and NH_4^+ cations. The substituents at the nitrogen atom and the type of monosaccharide affected this property significantly.

Key words: Chiral crown ethers, extraction ability, aza-crown ethers, lariat ethers.

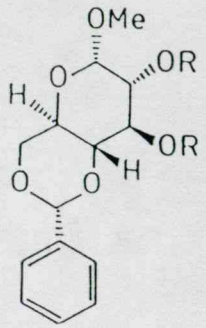
1. Introduction

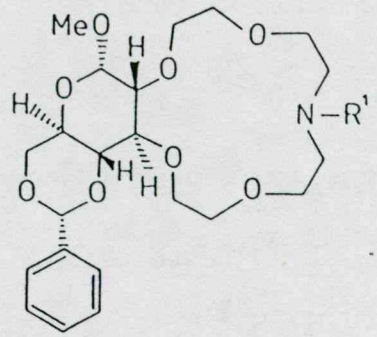
Asymmetric carbon–carbon bond forming reactions catalyzed by chiral crown ethers have recently attracted a great deal of attention [1–4]. The design of efficient catalysts for asymmetric induction has been a recent focus in synthetic organic chemistry. Many optically active crown ethers have been synthesised from monosaccharides. Carbohydrates including glucosides and galactosides as the source of chirality have been incorporated in crown ethers by Stoddart *et al.* [5–7]. Chiral monoaza- and diaza-crown ethers and cryptands containing monosaccharides have also been prepared [8–14].

Nitrogen atoms and side arms (among others side arms with heteroatoms) were built into the macrorings to enhance and regulate the cation binding properties as well as the lipophilicity. The latter compounds with heteroatoms, named lariat ethers or armed crown ethers, are known to display encapsulated complexation, high lipophilic character and unique guest specificity via macroring – side arm cooperativity [15–17].

In this paper we report the efficient synthesis of 15-membered monoazacrown ethers having different pendant arms (alkyl and aryl substituents) on the nitrogen atom (**4**, **5**, **8–11**, **17**, **18**) or functionalized pendant arms (lariat ethers: **6**, **7**) and 18-membered diazacrown ethers (**12**, **13**) from methyl-4,6-*O*-benzylidene-α-D-glucopyranoside and galactopyranoside.

* Author for correspondence.





1 R = H

2 R = $(CH_2)_2O(CH_2)_2Cl$

3 R = $(CH_2)_2O(CH_2)_2I$

4 R^1 = butyl

5 R^1 = decyl

6 R^1 = CH_2CH_2OH

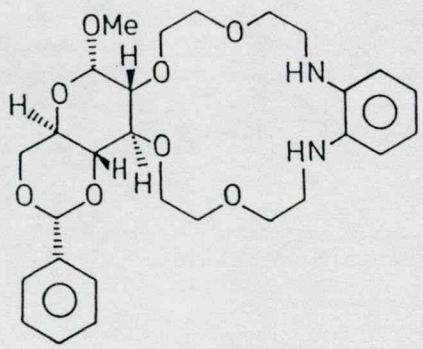
7 R^1 = CH_2COOCH_3

8 R^1 = cyclohexyl

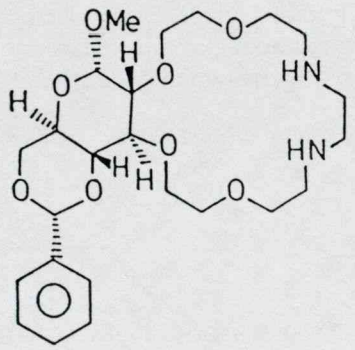
9 R^1 = benzyl

10 R^1 = Ph

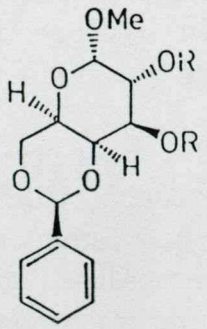
11 R^1 = α-naphthyl

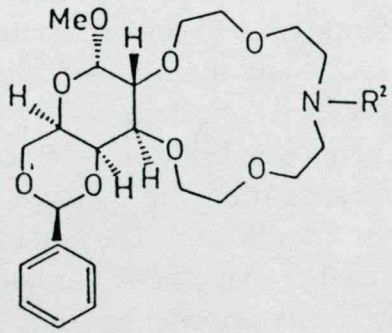


12



13





14 R = H

15 R = $(CH_2)_2O(CH_2)_2Cl$

16 R = $(CH_2)_2O(CH_2)_2I$

17 R^2 = benzyl

18 R^2 = decyl

Scheme 1.

Table I. Characterisation data of compounds and extraction of alkali metal and ammonium picrates for crown ethers **4–13**, **17** and **18**.

Comp.	Yield[a] (%)	$[\alpha]_D^{20}$ $CHCl_3$ $c = 1$	M.p. °C	Extractability (%)[b]			
				Li^+	Na^+	K^+	NH_4^+
3	92.7	29.5	oil	–	–	–	–
4	68.7	32.0	oil	28.7	58.2	26.9	55.9
5	44.3	31.6	58–60	32.7	77.2	47.0	67.4
6	60.0	41.7	oil	34.2	57.0	32.4	34.1
7	58.2	36.1	oil	30.5	61.2	49.5	45.8
8	70.6	30.1	oil	28.5	58.6	39.6	60.2
9	53.3	38.8	oil	6.5	44.0	15.2	13.7
10	33.7	42.3	126–28	5.9	13.7	6.5	0.9
11	37.0	32.7	48–51	5.6	22.4	8.9	0.1
12	57.7	29.7	60–61	16.2	23.3	20.1	6.1
13	37.8	40.1	56–58	55.6	66.7	59.9	66.8
15	88.0	98.7	oil	–	–	–	–
16	93.1	74.0	oil	–	–	–	–
17	37.7	94.2	oil	17.4	50.0	22.1	24.0
18	40.9	73.6	82–84	65.4	89.7	76.5	80.3

[a] After chromatography.
[b] R.t.; aqueous phase (10 mL); [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2 10 mL); [crown ether] = 1×10^{-2} M. Defined as % picrate extracted into the organic phase, determined by UV spectroscopy.

2. Experimental

^{1}H NMR spectra.: JEOL FX-100 (in $CDCl_3$), TMS as internal standard. UV spectra: Hitachi-Perkin Elmer 124. Mass spectra: JEOL JMS-OL SG-2. Column chromatography: Kieselgel 60 (0.063–0.2 mm, Merck), 23 × 440 mm, 75 g kieselgel, 2–2.5 g crude product, eluent: ethyl acetate–methanol (10 : 1–10 : 3) and toluene–methanol (3 : 1) in the case of compound **7**.

A typical experimental procedure is as follows. *Methyl* 4,6-*O*-*benzylidene*-2,3-*bis*-*O*-[(2-*chloroethoxy*)-*ethyl*]-α-D-*galactopyranoside* (**15**): A solution of **14** (21.8 g) and of tetrabutylammonium hydrogen sulfate (20.0 g) in bis[2-chloro-ethyl] ether (150 mL) was vigorously stirred at room temperature with a 50% aq. NaOH solution (150 mL) for 12 h. Dichloromethane (500 mL) and water (500 mL) were added to the reaction mixture. The organic phase was decanted and the aqueous phase washed with CH_2Cl_2. The organic phases were combined and washed with water, dried with $MgSO_4$, filtered and concentrated under vacuum. The resultant syrup was eluted through a silica gel column with ethyl acetate yielding **15** as a yellow syrup, 33.7 g (Data in Table I).

Methyl 4,6-*O*-*benzylidene*-2,3-*bis*-*O*-[(2-*iodoethoxy*)-*ethyl*]-α-D-*galacto-pyranoside* **16**. The mixture of **15** (20 g) and dry NaI (24.2 g) in dry acetone

(400 mL) was heated under reflux for 24 h. After cooling the precipitate was filtered and washed. The combined acetone solution was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (200 mL), washed with water, dried (Na_2SO_4), concentrated and dried in vacuum. Compound **16** was a yellow syrup; yield: 28 g (Data in Table I).

N-benzyl-monoaza-15-crown-5 derivative **17**. Dry Na_2CO_3 (8.0 g) was suspended in a solution of **16** (6.6 g) and benzylamine (1.12 g) in dry acetonitrile (200 mL). The stirred mixture was heated under reflux for 33 h. After cooling the precipitate was filtered and washed with acetonitrile. The combined acetonitrile solution was evaporated under vacuum. The residue oil was dissolved in $CHCl_3$ (60 mL), washed with water, dried (Na_2SO_4) and concentrated (5.6 g). Chromatography on silica gel with ethyl acetate–methanol (20 : 1–20 : 2) yielded a yellow oil **17**, yield: 1.94 g (Data in Table I).

The structure of all compounds was established by ^1H NMR, IR and MS spectroscopy. All products gave satisfactory microanalysis.

^1H NMR ($CDCl_3$, TMS, 100 MHz, ppm)

Compound **3**: 7.62–7.20 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.87 (d, 1H, J = 4 Hz, anomeric H); 4.35–3.48 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 3.20 (m, 4H, ICH_2).

Compound **4**: 7.53–7.10 (m, 5H, Ph); 5.44 (s, 1H, PhCH); 4.77 (d, 1H, J = 3.6 Hz anomeric H); 4.19 (d, 2H, J = 5 Hz, CH_2); 4.07–3.48 (m, 16H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.80–2.10 (m, 6H, NCH_2); 1.43–1.10 (m, 4H, CH_2); 0.84 (t, 3H, J = 6.6 Hz, CH_3).

Compound **5**: 7.52–7.20 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.22 (d, 2H, J = 5 Hz, CH_2); 4.0–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.75–2.40 (m, 6H, NCH_2); 1.25 (m, 16H, CH_2); 0.9 (t, J = 6 Hz, 3H, CH_3).

Compound **6**: 7.55–7.17 (m, 5H, Ph); 5.5 (s, 1H, PhCH); 4.75 (d, 1H, J = 3.6 Hz, anomeric H); 4.17 (d, 2H, J = 5 Hz, CH_2); 4.03–3.46 (m, 18H, CH and CH_2 groups); 3.41 (s, 3H, OMe); 2.47–2.83 (m, 6H, NCH_2); 1.95 (s, 1H, OH).

Compound **7**: 7.55–7.20 (m, 5H, Ph); 5.48 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.22 (d, 2H, J = 5 Hz, CH_2); 4.13–3.48 (m, 18H, CH and CH_2 groups); 3.42 (s, 3H, OMe); 3.38 (s, 3H, OMe); 3.03–2.63 (m, 4H, CH_2).

Compound **8**: 7.50–7.10 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.24 (d, 2H, J = 5 Hz, CH_2); 4.0–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.75 (m, 5H, NCH_2 and NCH); 1.72 (m, 4H, CH_2); 1.15 (m, 6H, CH_2).

Compound **9**: 7.50–7.15 (m, 10H, Ph); 5.50 (s, 1H, PhCH); 4.82 (d, 1H, J = 3.6 Hz, anomeric H); 4.25 (d, 2H, J = 5 Hz, CH_2); 4.0–3.46 (m, 18H, CH and CH_2 groups), 3.40 (s, 1H, OMe); 2.75 (m, 4H, NCH_2).

Compound **10**: 7.50–7.10 (m, 5H, Ph); 6.90–6.65 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.87 (d, 1H, J = 3.6 Hz, anomeric H); 4.22 (d, 2H, J = 5 Hz, CH_2); 4.07–3.48 (m, 20H, CH and CH_2 groups); 3.40 (s, 1H, OMe).

Compound **11**: 7.60–7.03 (m, 12H, Ph); 5.47 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.20 (d, 2H, J = 5 Hz, CH_2); 4.0–3.45 (m, 20H, CH and CH_2 groups); 3.40 (s, 3H, OMe).

Compound **12**: 7.55–7.10 (m, 5H, Ph); 6.80–6.50 (m, 4H, Ph); 5.48 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.26 (d, 2H, J = 5 Hz, CH_2); 4.10–3.45 (m, 22H, CH and CH_2 groups); 3.37 (s, 3H, OMe).

Compound **13**: 7.60–7.20 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.82 (d, 1H, J = 3.6 Hz, anomeric H); 4.25 (d, 2H, J = 5Hz, CH_2); 4.05–3.50 (m, 16H, CH, CH_2 groups and NH); 3.40 (s, 3H, OMe); 3.06–2.75 (m, 8H, NCH_2).

Compound **15**: 7.55–7.20 (m, 5H, Ph); 5.51 (s, 1H, PhCH); 4.90 (d, 1H, J = 4 Hz, anomeric H); 4.40–3.45 (m, 22H, CH and CH_2 groups); 3.40 (s, 3H, OMe).

Compound **16**: 7.60–7.10 (m, 10H, Ph); 5.50 (s, 1H, PhCH); 4.90 (d, 1H, J = 4 Hz, anomeric H); 4.40–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s 3H, OMe); 3.2 (t, 4H, ICH_2);

Compound **17**: 7.60–7.10 (m, 10H, Ph); 5.50 (s, 1H, PhCH); 4.90 (d, 1H, J = 4 Hz, anomeric H); 4.35–3.45 (m, 20H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.75 (t, 4H, NCH_2).

Compound **18**: 7.60–7.20 (m,5H, Ph); 5.55 (s, 1H, PhCH); 4.95 (d, 1H, J = 4 Hz, anomeric H); 4.50–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.60 (t, 4H, NCH_2); 2.35 (t, 2H, CH_2); 1.25 (m, 16H, CH_2); 0.85 (t, 3H, CH_3).

3. Results and Discussion

The vicinal free hydroxy groups in methyl 4,6-*O*-benzylidine-α-D-glucopyranoside (**1**) and in methyl 4,6-*O*-benzylidine-α-D-galactopyranoside (**14**) were alkylated by the method of Gross *et al.* [18] with bis(2-chloroethyl)ether ($Cl[CH_2]_2O[CH_2]_2Cl$ used as solvent and reagent) under liquid–liquid two-phase reaction conditions using tetrabutylammonium hydrogen sulfate (as a PT catalyst) and 50% aqueous NaOH to give **2** and **15**, respectively. The exchange of chlorine by iodine in **2** and

15 was carried out by NaI in acetone (reflux, 24 h). Reactions of the iodides **3** and **16** with different amines in acetonitrile in the presence of solid dry Na_2CO_3 were much faster than those of **2** and **15**. In dilute solutions (1–3%) the polycondensation type side reactions were suppressed and the intramolecular cyclization became the high yielding main reaction between the bis-iodo compounds and primary amines.The yields of the ring closure steps after chromatography are in Table I.

Treatment of **3** with various aliphatic amines (*n*-butylamine, *n*-decylamine, ethanolamine, glycine methyl ester, cyclohexylamine, or benzylamine, (CH_3CN, reflux, 32 h) gave the corresponding 15-membered monoaza-crown ethers **4**, **5**, **6**, **7**, **8** and **9** in good yields, with aromatic amines (aniline, α-naphthylamine). Compounds **10** or **11** were obtained in somewhat lower yields.

The 18-membered diazamacrocycles **12** and **13** were prepared by the reaction of **3** with *o*-phenylenediamine or ethylenediamine.

The galacto-derivatives **17** and **18** were synthesised from **16** under similar conditions.

The phase transfer abilities of the new azacrown ethers were characterized by extracting picrate salts (Li, Na, K and NH_4 picrate) from water into CH_2Cl_2. The concentrations of the picrates in CH_2Cl_2 we measured by UV spectroscopy [19, 20] (Table I).

It is worth noting that all the azacrowns prefer sodium ions in the complexation. The *N*-benzyl derivatives **9** and **17** show significant selectivity for the sodium cation among the four cations. The extraction ability depends signficantly on the substituents at the nitrogen atom. The highest values were observed in the case of **5** and **18** both having a decyl side arm at the nitrogen atom, the smallest values in the case of **10** and **11**, compounds having aromatic substituents.

A comparison of the behaviour of 18-membered ring crown ethers suggests that the nonsubstituted compound **13** forms stronger complexes with all cations than that of derivative **12** having an aromatic ring. On the other hand, derivatives in the galacto series **17** and **18** exhibit larger values for extraction than the corresponding compounds **5** and **9** of the glucoseries. This difference in the extraction abilities may be due to the difference in the structure of the two monosaccharide units. The 4-C—O bond in glucosides is in an equatorial position while that in galactosides is in an axial position. The axial orientation of the C—O bond at C(4) of the galactoside ring in both **17** and **18** causes *O*(4) to be available to participate, together with the ether heteroatoms of the macrocycle, in the complex formation, as a similar phenomenon was observed by Stoddart in the case of other crown ethers [21].

We are investigating the enantioselectivities of the new crown ethers as chiral catalysts in asymmetric reactions.

Acknowledgement

This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T 015677).

References

1. D. A. H. van Maarschalkerwaart, N. P. Willard, and U. K. Pandit: *Tetrahedron* **48**, 8825 (1992).
2. E. V. Dehmlow and V. Knufinke: *Liebigs Ann. Chem.* 282 (1992).
3. M. J. O'Donnell: *Asymmetric Phase Transfer Reactions in Catalytic Asymmetric Synthesis* (Ed.: I. Ojima) VCH Publishers, Inc., New York-Weinheim-Cambridge, pp. 367–387 (1993).
4. T. Wang, J. S. Bradshaw, P. Huszthy, X. Kou, N. K. Dalley, and R. M. Izatt: *J. Heterocyclic Chem.* **31**, 1 (1994).
5. J. F. Stoddart: *Chem. Soc. Rev.* **8**, 85 (1979)
6. J. F. Stoddart: *Synthetic Chiral Receptor Molecules from Natural Products* (Progress in Macrocycles Chemistry, Vol. 2, Ed. R. M. Izatt and J. J. Christensen), p. 173, Wiley (1981).
7. J. F. Stoddart: *Chiral Crown Ethers* (Topics in Stereochemistry, Vol. 17, Ed. E. L. Eliel and S. H. Wielen), p. 207, Wiley (1988).
8. D. A. Laidler and J. F. Stoddart: *J. Chem. Soc., Chem Commun.* 979 (1976).
9. H. F. Beckford, R. M. King, J. F. Stoddart, and R. F. Newton: *Tetrahedron Lett.* 171 (1978).
10. M. Pietraszkiewicz and J. Jurczak. *Tetrahedron* **40**, 2967 (1984).
11. M. Pietraszkiewicz, P. Salanski, and J. Jurczak: *Tetrahedron* **40**, 2971 (1984).
12. G. Tóth, W. Dietrich, P. Bakó, L. Fenichel, and L. Töke: *Carbohydr. Res.* **168**, 141 (1987).
13. P. Bakó, L. Fenichel, L. Töke, and B. E. Davison: *J. Chem. Soc. Perkin Trans. 1* 1235 (1990).
14. P. Bakó, L. Fenichel, and L. Töke: *Liebigs Ann. Chem.* 1161 (1990).
15. G. W. Gokel: *Chem. Soc. Rev.* **21**, 39 (1992) and references therein.
16. M. Zinic, S. Alihodzic, and Skaric: *J. Chem Soc. Perkin Trans. 1* 21 (1993).
17. M. Zinic, L. Frkanec, V. Skarin, Y. Trafton, and G. W. Gokel: *J. Chem. Soc. Chem. Commun.* 1726 (1990).
18. P. Di Cesare and B. Gross: *Synth. Commun.* 4581 (1979).
19. K. Kimura, T. Maeda, and T. Shono: *Talanta* **26**, 945 (1979).
20. T. Maeda, K. Kimura, and T. Shono: *Bull. Chem. Soc. Jpn.* **55**, 3506 (1982).
21. D. A. Laidlerl and J. F. Stoddart: *Carbohydr. Res.* **55**, C1 (1977).

Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **26**: 321–330, 1996.

© 1996 *Kluwer Academic Publishers. Printed in the Netherlands.*

B6

Synthesis and Complex-Forming Properties of Crown Ethers Incorporating Glucuronic Acid Moieties

PÉTER BAKÓ, LÁSZLÓ FENICHEL and LÁSZLÓ TÔKE*
Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, Mûegyetem rkp. 3, P.O. Box 91, Hungary.

(Received 6 February 1996; in final form: 30 May 1996)

Abstract. Crown ethers **1** and **4** of the 18-crown-6 type containing two glucose units have been oxidised by $KMnO_4$ into mono- and dicarboxylic acid derivatives (**5** and **11**), and derivatives with different lipophilicities of the above crown ethers, namely the acetyl, benzyl and butyl derivatives (**8–10**, **13**, **14**) and methyl esters (**6** and **12**) have been synthesized.

The association constants (K_a) with Li, Na, K and NH_4 cations measured in $CHCl_3$ indicate that complexing ability increases on introduction of carboxy groups, and selectivity changes in favour of the Na cation. These compounds were able to transport alkyl-ammonium salts through a $CHCl_3$ liquid membrane, displaying, however, no chiral recognition ability.

Key words: Chiral crown ethers, complex formation, glucuronic acids.

1. Introduction

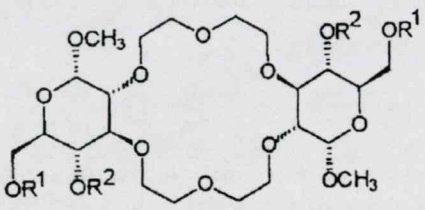
Following the pioneering publication of Cram [1], chiral crown ethers have been synthesised in great number, and their chiral recognition ability has been investigated on the enantiomers of organic ammonium salts [2–4]. Bradshaw *et al.* [5–8] determined the extent of chiral recognition from the kinetic and thermodynamic parameters of the complexes formed between chiral ligands containing pyridine units and the enantiomers of organic ammonium salts. This property can be utilised in the separation of enantiomers during transport through liquid membranes [9, 10].

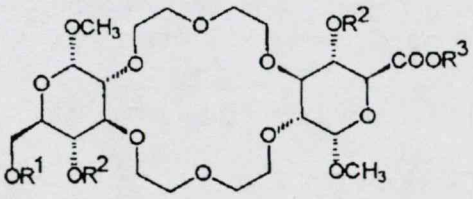
One of the most important group of chiral crown ethers is the monosaccharide based compounds [11–21]. The preparation and complex-forming properties of crown ethers **1** and **4** of the 18-crown-6 type containing two glucose units have been published by us earlier [22, 23]. This work deals with changes in the complex-forming properties and chiral recognition abilities of these sugar-based macrocycles caused by the formation of carboxy groups via oxidation. Chiral crown ether carboxylic acids have been prepared from L-(+)-tartaric acid bis(*N*,*N*-dimethylamide), and their complex-forming properties investigated by Lehn *et al.* [24].

* Author for correspondence.

2. Experimental

^{1}H NMR spectra: Perkin Elmer R12 and Jeol FX-100 (in $CDCl_3$, TMS as internal standard, 80 MHz, ppm). IR spectra: Perkin Elmer 237 in KBr pellets. UV spectra: Hitachi-Perkin-Elmer 124. Polarimeter: Perkin-Elmer 241. M.p.: Büchi 510 (uncorrected). Elemental analysis: Perkin-Elmer 240 automatic analyser. TLC: Kieselgel 60 F_{254} (Merck), eluent toluene-methanol mixtures (10 : 1–10 : 5), detection with Dragendorff's reagent. Column chromatography: Kieselgel 60 (0.2–0.063 mm, Merck).





1 $R^1 = R^2 = H$

2 $R^1 = R^2 = Ac$

3 $R^1 = R^2 = Bu$

4 $R^1 = H$, $R^2 = Bn$

5 $R^1 = R^2 = H$, $R^3 = H$

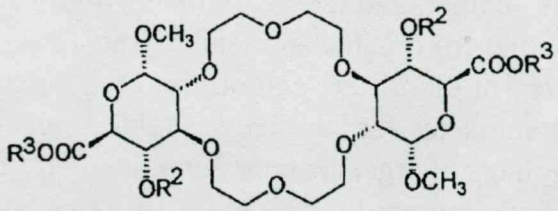
6 $R^1 = R^2 = H$, $R^3 = Me$

7 $R^1 = R^2 = H$, $R^3 = K$

8 $R^1 = R^2 = Ac$, $R^3 = H$

9 $R^1 = R^2 = Bu$, $R^3 = H$

10 $R^1 = H$, $R^2 = Bn$, $R^3 = H$



11 $R^2 = R^3 = H$

12 $R^2 = H$, $R^3 = Me$

13 $R^2 = Ac$, $R^3 = H$

14 $R^2 = Bn$, $R^3 = H$

Ac = acetyl, Bu = butyl, Bn = benzyl, Me = methyl

Methyl - 2,3 - dideoxy - α - D - glucopyranose[2,3 - b]methyl - 2,3 - dideoxy - α - D - glucurono - pyranose[2'3' - k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**5**)

Powdered $KMnO_4$ (0.12 g) was added to a stirred solution of **1** (0.5 g) in dry $CHCl_3$ (20 mL). After 4 h of stirring at room temperature further $KMnO_4$ (0.12 g) was added and the mixture was stirred for a further 18 h. The brown precipitate was filtered off by sintered glass filter, was suspended in water (20 mL), heated to boiling (to compress MnO_2), and, after recooling, MnO_2 was filtered off and washed with water. The combined filtrates and washes were stirred with Varion KS cation exchange resin (4 mL). The aqueous solution filtered off the resin was evaporated in vacuo, the residue was dried in a vacuum desiccator over P_2O_5, and then crystallised from an ethanol–petroleum ether mixture. *Yield* 0.35 g (68%) of **5**; m.p.: 78–80 °C, $[\alpha]_D^{22} = +77.8$ ($c = 1$ in $CHCl_3$). ^{1}H-NMR: 3.40 (s, 6H, 2 × OCH_3), 3.6–4.0 (m, 30H, CH_2 and CH groups), 4.83 (d, 2H, $J = 3.5$ Hz, anomeric H). *Elemental anal.: Calc.* for $C_{22}H_{38}O_{15}$; C 48.71, H 7.01. *Found;* C 48.50, H 7.20.

On titration with 0.1 N NaOH standard solution in the presence of phenolphthalein indicator, an equivalent amount (18.5 mL NaOH/g product) of alkali was consumed.

Methyl - 2,3 - dideoxy - α - D - glucopyranose[2,3 - b]methyl - 2,3 - dideoxy - α - D - methyl - glucuronopyranose[2'3' - k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**6**)

An ethereal solution (16 mL) of diazomethane (5 mmol) was added dropwise to a solution of **5** (0.54 g) in CH_2Cl_2 (10 mL) under stirring. After completing the reaction the excess of diazomethane was decomposed with 10% acetic acid solution. The CH_2Cl_2 phase was washed with 10% aqueous Na_2CO_3 solution and with water, and then, after drying over $MgSO_4$, it was evaporated. The raw product was chromatographed on Kieselgel (40 g) column (300 × 20 mm) with toluene–MeOH (10 : 2) as eluent. *Yield* 0.37 g (66.5%) of **6** (yellow syrup), $[\alpha]_D^{22} = +72.8$ ($c = 1$ in $CHCl_3$). ^{1}H-NMR: 3.38 (s, 3H, $COOCH_3$), 3.44 (s, 6H, 2 × OCH_3), 3.60–4.30 (m, 29H, CH_2 and CH protons), 4.82 (d, 2H, $J = 3.5$ Hz, anomeric H). *Elemental anal.: calc.* for $C_{23}H_{40}O_{15}$; C 49.64, H 7.19. *Found:* C 49.35, H 7.10.

Potassium salt of **5**: prepared in the same way as **5**, but without the treatment on the cation exchange resin. Yield: 0.39 g (71.1%). M.p.: 110 °C (from ethanol), $[\alpha]_D^{22} = +66.7$ ($c = 1$, H_2O).

Methyl - 2,3 - dideoxy - 4,6 - O - diacetyl - α - D - glucopyranose[2,3 - b]methyl - 2,3 - dideoxy - 4 - O - acetyl - α - D - glucuronopyranose[2'3' - k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**8**)

The potassium salt **5** (2.3 g) was dissolved in a mixture of pyridine (10 mL) and acetic anhydride (10 mL), and heated on a steam bath for 15 h. After cooling, the reaction mixture was evaporated in vacuo, the residue was dissolved in $CHCl_3$ (20 mL) and filtered through a filter paper. The filtrate was washed thrice with water and then stirred for 30 min with a little amount of water and Varion KS cation exchange resin (4 mL). After filtering off the resin, the chloroform phase was dried over $MgSO_4$ and then evaporated. *Yield* 1.6 g (61%) of **8**, m.p.: 119–122 °C (acetone–water 5 : 1), $[\alpha]_D^{22} = +50.2$ ($c = 1$, $CHCl_3$). ^{1}H-NMR: 2.0 (s, 9H, 3 × OAc), 3.40 (s, 6H, 2 × OCH_3), 3.3–4.5 (m, 27H, CH_2 and CH protons), 4.81 (d, 2H $J = 3.5$ Hz, anomeric H). *Elemental anal.: calc.* for $C_{28}H_{44}O_{18}$; C 50.29, H 6.58. *Found:* C 50.08, H 6.43.

*Methyl - 2,3 - dideoxy - 4,6 - O - dibutyl - α - D - glucopyranose[2,3 - b]methyl - 2,3 - dideoxy - 4 - O - butyl - α - D - glucuronopyranose[2'3' - k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**9**)*

The potassium salt **5** (1.74 g) was stirred with a mixture of butyl bromide (22 mL) and 50% NaOH (15 mL) for 70 h at 40 °C. The organic phase was evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (25 mL), washed with water, and then stirred for 30 min with a mixture of a little water and cation exchange resin. After filtration and separation the organic phase was washed again with water, dried over $MgSO_4$, and then evaporated to yield a yellow syrup of **9**. Yield 1.52 g (71.3%), $[\alpha]_D^{22} = +34.6$ ($c = 1$, $CHCl_3$). ^{1}H-NMR: 0.89 (t, 9H, 3 × CH_3), 1.11–1.89 (m, 18H, butyl-CH_2), 3.33 (s, 6H, 2 × OCH_3), 3.40–4.30 (m, 26H, CH_2 and CH protons), 4.77 (d, $J = 3.5$ Hz, 2H, anomeric H). *Elemental anal.: calc.* for $C_{34}H_{62}O_{15}$; C 57.46, H 8.73. *Found:* C 57.24, H 8.62.

*Methyl - 2,3 - dideoxy - 4 - O - benzyl - α - D - glucopyranose[2,3 - b]methyl - 2,3 - dideoxy - 4 - O - benzyl - α - D - glucuronopyranose[2'3'-k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**10**)*

Powdered $KMnO_4$ (0.26 g) was added to a solution of **4** (1.6 g) in dry $CHCl_3$ (20 mL) under stirring, and after 8 h of stirring at room temperature additional $KMnO_4$ (0.26 g) was added, and the mixture was stirred for a further 17 h. The precipitate was filtered off and washed twice with $CHCl_3$. The combined chloroform phases were washed three times with water (6 mL) each, and then stirred for 20 min with a mixture of water (5 mL) and cation exchange resin (5 mL). After filtering, the $CHCl_3$ phase was dried over $MgSO_4$, evaporated, and the residue was purified on a Kieselgel column (70 g, 350 × 25 mm, eluent: toluene–methanol 10 : 3) to give amorphous, white **10**. *Yield* 1.07 g (65.6%), $[\alpha]_D^{22} = +72.5$ ($c = 1$, $CHCl_3$). ^{1}H-NMR: 3.42 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.4–4.2 (m, 30H, CH_2 and CH protons), 4.85 (d, 2H, $J = 3.5$ Hz, anomeric H), 7.23 (s, 10H, aromatic protons),

9.44 (broad, 1H, COOH). *Elemental anal.: calc.* for $C_{36}H_{50}O_{15}$; C 59.83, H 6.92. *Found:* C 59.59, H 6.79.

*Bis(methyl - 2,3 - dideoxy - α - D - glucuronopyranose)[2,3 - b][2'3' - k] - 14,7,10,13,16 - hexaoxacyclooctadecane (**11**)*

Compound **1** (0.5 g) was dissolved in CH_3CN (15 mL), and $KMnO_4$ (0.3 g) was added. The mixture was stirred for 9 h, and after the introduction of an additional amount of $KMnO_4$, (0.3 g) for a further 9 h. The reaction mixture was processed by the method described for **5**. White, amorphous **11** was obtained with a yield of 0.42 g (80%). $[\alpha]_D^{22} = +92.3$ ($c = 1$, water). IR: 3380–3300, 2850, 1740, 1430, 1385, 1170–1010, 750 cm^{-1}. ^{1}H-NMR (D_2O): 3.40 (s, 6H, 2 × OCH_3), 3.30–4.48 (m, 28H, CH_2 and CH protons), 4.99 (d, 2H, $J = 5.1$ Hz, anomeric H). *Elemental anal.: calc.* for $C_{22}H_{36}O_{16}$; C 47.48, H 6.47. *Found:* C 47.29, H 6.39.

Alkali consumption in titration: 35.9 ml of 0.1 N NaOH/g of product (as expected).

*Bis(methyl - 2,3 - dideoxy - α - D - methylglucuronopyranose)[2,3 - b][2'3' - k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**12**)*

A procedure similar to the preparation of **6** was applied. A yellow syrup of **12** was obtained with a yield of 77%. $[\alpha]_D^{22} = +48.8$ ($c = 1.2$, $CHCl_3$). ^{1}H-NMR: 3.38 (s, 6H, 2 × $COOCH_3$), 3.44 (s, 6H, 2 × OCH_3), 3.35–4.56 (m, 26H, CH_2 and CH protons), 4.81 (d, 2H, $J = 3.5$ Hz, anomeric H). *Elemental anal.: calc.* for $C_{24}H_{40}O_{16}$; C49.31, H6.84. *Found:* C 49.12, H 6.70.

*Bis(methyl - 2,3 - dideoxy - 4 - O - acetyl - α - D - glucuronopyranose)[2,3 - b][2'3' - k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**13**)*

A procedure similar to the preparation of **8** was applied. An amorphous yellow product of **13** was obtained with a yield of 33%. $[\alpha]_D^{22} = +82.7$ ($c = 1$, $CHCl_3$). ^{1}H-NMR: 2.0 (s, 6H, 2 × OAc), 3.35 (s, 6H, 2 × OCH_3), 3.30–4.35 (m, 26H, CH_2 and CH protons), 4.75 (d, 2H, $J = 3.5$ Hz, anomeric H). IR: 3380–3300, 2850, 1740, 1430, 1360, 1230, 1175–1020, 755 cm^{-1}. *Elemental anal.: calc.* for $C_{26}H_{40}O_{18}$; C 48.77, H 6.25. *Found:* C 48.62, H 6.29.

*Bis(methyl - 2,3 - dideoxy - 4 - O - benzyl - α - D - glucuronopyranose)[2,3 - b][2'3' - k] - 1,4,7,10,13,16 - hexaoxacyclooctadecane (**14**)*

A procedure similar to the preparation of **10** was applied. Compound **14** was obtained as an amorphous solid with a yield of 68.3%. $[\alpha]_D^{22} = +90.0$ ($c = 1$, $CHCl_3$). ^{1}H-NMR: 3.40 (s, 6H, 2 × OCH_3), 3.48–4.10 (m, 24H, CH_2 and CH protons), 4.47 (s, 4H, 2 × CH_2Ph), 4.81 (d, 2H, $J = 3.5$ Hz, anomeric H), 7.28 (s,

10H, 2 × Ph), 9.23 (s, 2H, 2 × COOH). *Elemental anal.: calc.* for $C_{36}H_{48}O_{16}$; C 58.69, H 6.52. *Found:* C 58.47, H 6.50.

The association constants of the compounds with Li, Na, K and ammonium picrates were measured in $CHCl_3$, by UV spectrometry, using the method of Cram [25]. Most of the crown ethers were insoluble in water: solubilities were 1–2% of the total used. The distribution constants of the water-soluble crown acids between water and $CHCl_3$ were determined in independent experiments and these constants were taken into consideration in the calculations of K_a values.

Transport experiments were carried out in a conventional cell apparatus [9] consisting of an outer cylindrical glass vessel (46 mm i.d.) and a central glass tube (24 mm i.d.). The 0.01 M $CHCl_3$ solution (30 mL) of the host separated the inner aqueous phase (0.1 M HCl or NaOH, 8 mL) and the outer aqueous phase (0.08 M HCl, 15 mL) which contained $LiPF_6$ (0.4 M) and the racemic guest (0.08 M). The organic layer was stirred at a constant speed (60 r.p.m.), and transport was followed by monitoring the absorbance at 262 nm.

A 10% error was estimated in the transport experiments. The optical purity in the receiving phase was determined polarimetrically. The distribution of the water (NaOH) soluble crown acids between the water phase (NaOH) and $CHCl_3$ was determined polarimetrically.

3. Results and Discussion

3.1. SYNTHESIS

Tetrahydroxy crown ether **1** appeared to be suitable for the preparation of carboxylic acids by the oxidation of their hydroxymethyl groups. As oxidant, $KMnO_4$ was chosen since this reagent provides a mild oxidation condition in both neutral and alkaline media. The oxidation of **1** could be expected to yield two products: monocarboxylic acid **5** and dicarboxylic acid **11**. Pure monocarboxylic acid could not be prepared in water, acetonitrile etc., since under widely varying reaction conditions mixtures containing the starting substance or dicarboxylic acid were obtained. (The primary analysis of reaction products was performed by TLC and alkaline titration.) However, a uniform product could be obtained in the presence of dry $CHCl_3$ or CH_2Cl_2 as solvent, in solid–liquid phase transfer reaction.

This form of the reaction was interesting because only the starting crown ether could be dissolved in these solvents while $KMnO_4$ was insoluble, but the latter could be solubilised by the effect of the crown ether. Therefore, in this reaction, the crown ether was not only a substrate but a catalyst as well. We assumed that in dilute solution the primary product of oxidation is the potassium salt of the monocarboxylic acid, which is poorly soluble in $CHCl_3$ or CH_2Cl_2, and thus precipitates during the reaction. This led us to find the reaction conditions under which the main product is the monocarboxylic acid, **5**. In CH_2Cl_2 (with a substrate: $KMnO_4$ ratio of 1 : 1.5) a monocarboxylic acid yield of 87% was obtained after 5 h

of stirring and refluxing, whereas in $CHCl_3$ the yield was 68% after 18 h of stirring at room temperature. At the end of processing the reaction product, the free acid was released from the potassium salt by means of a cation exchange resin.

The synthesis of dicarboxylic acid **11** was easier to perform: crown ether **1** was treated with an excess of $KMnO_4$ (6.7 mole equivalents in water, 2.8 in acetonitrile) at room temperature for 18 to 20 h, to yield 80–84% of bis-glucuronic acid. Both products (**5** and **11**) could be titrated with 0.1 NaOH standard solution in the presence of phenolphthalein indicator, and an equivalent amount of alkali solution (18.4 mL/g and 35.9 mL/g, respectively) was consumed. In the ^{1}H-NMR spectrum the signal of acidic protons could not be assigned. In the IR spectra the carboxylic groups produced strong bands in the 1740–1745 cm^{-1} region. As a further confirmation of the structure, the reaction of monocarboxylic acid **5** with diazomethane (in ethanol–ether mixture) yielded monoester **6**, whereas that of **11** under similar conditions led to dimethyl ester **12**.

Uronic acid crown ethers **5** and **11** dissolve well in water, but are poorly soluble in chloroform (in fact, **11** is insoluble, and thus its complex forming properties could not be determined in chloroform). From the aspects of further investigations it appeared to be useful to convert **5** and **11** chemically into more lipophilic forms and to prepare derivatives that are soluble in chloroform.

Monocarboxylic acid **5** could not be acetylated either in acetic anhydride-pyridine or with acetic anhydride in the presence of $ZnCl_2$ catalyst. The desired result was obtained, however, by acetylating the potassium salt **7** of the monocarboxylic acid with acetic anhydride in pyridine (16 h, 90 °C) and liberating the acid on a cation exchange resin after processing the reaction product. Triacetate **8** was obtained with a yield of 61%, and, as expected, the product was soluble in chloroform.

Diacetate derivative **13** was obtained in a similar manner with a yield of 33% by acetylating the potassium salt of dicarboxylic acid **11**.

The tributyl ether of **5** was prepared in THF with an excess of butyl bromide in the presence of 50% sodium hydroxide solution. In the two-phase system the crown ether substrate itself played the role of phase transfer catalyst. The syrupy tributyl ether derivative **9** was obtained with a yield of 73% after 50 h stirring at 40 °C.

In certain cases a reverse order of synthesis proved to be more successful, according to which the substituent is built into the molecule first and then the product is oxidised into the corresponding uronic acid derivative. The previously described [22] 4,4′-di-*O*-benzyl crown ether **4** appeared to be suitable for the preparation of lipophilic crown-carboxylic acid derivatives that dissolve well in organic solvents, via the oxidation of its hydroxymethyl groups. Benzylated monocarboxylic acid **10** could be prepared with a yield of 65% in dry chloroform with 1.43 mole equivalents of $KMnO_4$ (25 h, room temperature), whereas the dicarboxylic acid derivative **14** was prepared in acetonitrile with a large excess of $KMnO_4$ (by refluxing for 18 h) with a yield of 83%. The products were not crystalline (syrup), and well soluble,

Table I. Association constants of chiral crown compounds (log K_a in $CHCl_3$, at 22 °C).

	1[a]	2[a]	3[b]	4[b]	5	8	9	10	12	13	14
Li^+	4.04	3.57	4.25	3.57	4.39	4.11	4.30	5.25	4.15	4.23	5.04
Na^+	4.50	3.20	4.33	4.20	5.50	5.13	4.57	5.97	5.15	4.74	5.45
K^+	4.85	4.46	4.38	4.70	5.37	4.83	4.48	5.62	4.97	4.60	5.17
NH_4^+	4.01	3.58	3.82	4.34	5.19	4.54	4.00	5.44	4.87	4.26	4.89

Aqueous phase (0.5 mL); [picrate] = 0.15 M; organic phase ($CHCl_3$, 0.2 mL); [crown ether] = 0.075 M; determination by UV spectroscopy: Ref. [25].
Error limit: ±0.03; the results are the average of triplet runs.
[a] Ref. [17]; [b] Ref. [22].

as expected, in chloroform and insoluble in water. The signals of the acidic protons in the ^{1}H-NMR spectra of both compounds appeared at δ 9.94 ppm.

3.2. Complex formation

The association constants (K_a) of glucuronic acid crown ethers obtained by oxidation were determined by the method of Cram [25] in chloroform, at room temperature, applying Li, Na, K and ammonium picrates as guest molecules. Table I shows the log K_a values of the above molecules together with those of starting substances **1** and **4** and of tetrasubstituted derivatives **2** and **3**, taken for comparison [17, 22, 23].

On comparing the K_a values of starting substance **1** and monocarboxylic acid **5**, it can be seen that the introduction of a carboxy group into the molecule increases the complex formation ability with respect to all cations, to the greatest extent with NH_4^+ and Na^+. A similar tendency can be observed from a comparison of tetraacetate **2** and triacetate monocarboxylic acid derivative **8**: the complex formation constant with respect to Na^+ has increased by nearly two orders. On the other hand, the K_a values of dicarboxylic acid diacetate **13** are lower than those of monocarboxylic acid **8**.

The dimethyl ester **12** and triacetate monocarboxylic acid derivative **8** show practically identical complexing properties with the small Li^+ and Na^+ ions, but the values of **12** are higher with K^+ and NH_4^+ having a larger ionic diameter.

An increase of 1 to 1.8 orders in the association constants can be observed with dibenzyl derivative **4** on the introduction of one carboxy group (**10**), but a decrease on the introduction of a second carboxy group (**14**) with respect to **10**. Note that with butyl substituted crown ether **3** the K_a values hardly increase on the introduction of a carboxy group (**9**).

As expected, the introduction of carboxy groups enhances the complex formation abilities of crown ethers in all cases with respect to all ions investigated. Lehn *et al.* established that the carboxylate groups in the crown ether increase the complex stability with cations and especially when they are close to the ring. It may be due

in part to two effects: the ion-pair interaction and electrostatic interaction between the carboxylate groups and the cations. The selectivities of complexation display electrostatic and hydrophobic effects [24]. In our compounds the carboxylic groups are further from the crown ring, so the interactions are weaker but the effect of the lateral discrimination of side chain carboxylic groups are perceptible. The relatively more modest increase in the complex formation abilities of dicarboxylic acids (**13, 14**) with respect to monoacids (**8, 10**) may be due to a mutual (intermolecular) hydrogen bonding among the carboxy groups.

It is worth noting that oxidation also affects the selectivities of crown ethers: whereas derivatives **1–4** form the strongest complexes with K ions (the ionic diameter of K^+ corresponds to the inner dimensions of the 18-crown-6 ring) the oxidised derivatives prefer Na ion complex formation. Generally for our uronic crowns the selectivity sequence is $Na^+ > K^+ > NH_4^+ > Li^+$.

3.3. CHIRAL RECOGNITION

Chiral recognition of crown ether derivatives can be investigated in the transport processes of racemic ammonium hydrochlorides through liquid membranes [9, 26]. In this work the transport of racemic phenylethylamine hydrochloride and phenylglycine methyl ester hydrochloride through chloroform membrane was measured by using the carboxy derivatives in question. Measurements were performed in a coaxial cylinder cell apparatus with the method of Cram [9].

These measurements are generally carried out in acidic media. Our transport experiments were performed also in acidic conditions using aqueous HCl as a receiving phase. In these cases the compounds **8, 9, 10, 13** and **14** remained completely in the $CHCl_3$ phase and so they did not disturb the UV determination of the transported amine salts. One of the aims of our synthetic work was to increase the lipophilicity of the crown acids by alkylation, acylation and aralkylation of the free hydroxyl groups, hoping that they remain in the organic phase. This was successful in the case of aqueous HCl receiving phase. These compounds were able to carry the above ammonium salts from the source phase to the aqueous acidic phase through the $CHCl_3$ membrane. Unfortunately, chiral recognition could not be observed: the receiving phase always contained a racemic mixture.

The methyl phenylglycinate salt was found to be better transported than the phenylethylamine salt by all crown acids. Good transporting abilities were found for these crown compounds. The percentage of the amine transported into the receiving phase related to the original source phase for methyl (±)-phenylglycinate * HCl (determined by UV) after 5 h, are: **8** (23.2%), **9** (19.6%), **10** (28.8%), **13** (22.5%) and **14** (22.0%).

The transporting capacities of crown ethers appear to be approximately proportional to their complex formation abilities; the greatest amounts of amine were transported by dibenzyl monocarboxylic acid derivative **10**, which forms the strongest complex with the ammonium ion. However, the crown carboxylic

acids with lipophilic groups allow acid-to-alkali transport (against pH) to occur, which may often be more selective [9]. Unfortunately the results of the transport experiments in the $CHCl_3$–aqeuous NaOH (receiving phase) system were not appreciable because of the solubility of the crown acids in aqueous NaOH.

Acknowledgement

This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T 015677).

References

1. E.P. Kyba, K. Koga, L.R. Sousa, M.G. Siegel, and D.J. Cram: *J. Am. Chem. Soc.* **95**, 2692 (1973).
2. P.G. Potvin and J.M. Lehn: *Design of Cation and Anion Receptors, Catalysts and Carriers* (Synthesis of Macrocycles: The Design of Selective Complexing Agents, Ed. R. M. Izatt and J. J. Christensen), pp. 167–239, Wiley-Interscience, New York (1987).
3. J.F. Stoddart: *Chiral Crown Ethers* (Topics in Stereochemistry, Vol. 17, Ed. E.L. Eliel and S.H. Wielen), pp. 207–279, Wiley-Interscience, New York (1987).
4. J. March: *Advanced Organic Chemistry*, p. 122, Wiley-Interscience, New York, (1992).
5. J.S. Bradshaw, P. Huszthy, C.W. McDaniel, M. One, C.-Y. Zhu, R.M. Izatt, and S. Lifson: *J. Coord. Chem.* **27**, 105 (1992).
6. R. M. Izatt, C.-Y. Zhu, P. Huszthy, and J.S. Bradshaw: 'Enantiomeric Recognition in Macrocycle-Primary Ammonium Cation Systems' in: *Crown Compounds: Toward Future Applications*, Ed. S.R. Cooper, p. 207, VCH Press, New York (1992).
7. C.-Y. Zhu, R.M. Izatt, T.-M. Wang, P. Huszthy, and J.S. Bradshaw: *Pure Appl. Chem.* **65**, 1485 (1993).
8. R.M. Izatt, C.-Y. Zhu, T.-M. Wang, P. Huszthy, J.K. Hathaway, X.-X. Zhang, J.C. Curtis, and J.S. Bradshaw: *J. Inc. Phenom* (in press).
9. M. Newcomb, I.L. Toner, R.C. Helgeson, and D.J. Cram: *J. Am. Chem. Soc.* **101**, 4941 (1979).
10. M. Zinic, L. Frkanec, V. Skaric, J. Trafton, and G.W. Gokel: *J. Chem.Soc. Chem. Commun.* 1726 (1990).
11. J.F. Stoddart: *Synthetic Chiral Receptor Molecules from Natural Products* (Progress in Macrocyclic Chemistry, Vol. 2, Eds. R.M. Izatt and J.J. Christensen), pp. 173–250, Wiley, New York, (1981).
12. M. Pietraszkiewicz, P. Salanski, J. Jurczak: *Tetrahedron* **40**, 2971 (1984).
13. W.D. Curtis, D.A. Laidler, J.F. Stoddart, and G.H. Jones: *J. Chem. Soc. Chem. Commun.* 835 (1975).
14. R. Aldag and G. Schröder: *Justus Liebigs Ann. Chem.* 1036 (1984).
15. B. Walz and G. Schröder: *Justus Liebigs Ann. Chem.* 426 (1985).
16. L. Tôke, L. Fenichel, P. Bakó, and J. Szejtli: *Acta. Chim. Acad. Sci. Hung.* **98**, 357 (1978).
17. P. Bakó, L. Fenichel, L. Tôke, and M. Czugler: *Justus Liebigs Ann. Chem.* 1163 (1981).
18. M. Pietraszkiewicz and J. Jurczak: *J. Chem. Soc. Chem. Commun.* 132 (1983).
19. P. Bakó, L. Fenichel, L. Tôke, and B.E. Davison: *J. Chem. Soc. Perkin Trans. 1*, 1235 (1990).
20. P. Bakó, L. Fenichel, and L. Tôke: *Acta Chim. Acad. Sci. Hung.* **116**, 323 (1984).
21. M.A. Lopez, J.Y. Barbero, M.M. Lomas, and S. Penades: *Tetrahedron* **44**, 1535 (1988).
22. P. Bakó, L. Fenichel, L. Tôke, and G. Tóth: *Carbohydr. Res.* **147**, 31 (1986).
23. P. Bakó, L. Fenichel, and L. Tôke: *J. Incl. Phenom.* **16**, 17 (1993).
24. J.P. Behr, J.M. Lehn, and P. Vierling: *J. Chem. Soc. Chem. Commun.* 621 (1976).
25. S.S. Moore, T.L. Tarnowski, M. Newcomb, and D.J. Cram: *J. Am. Chem. Soc.* **99**, 6398 (1977).
26. K. Yamamoto, H. Fukushima, Y. Okamoto, K. Hatada, and M. Nakazaki: *J. Chem. Soc. Chem. Commun.* 1111 (1984).

Asymmetric C-C Bond Forming Reactions by Chiral Crown Catalysts; Darzens Condensation and Nitroalkane Addition to the Double Bond

Péter Bakó[a], Áron Szöllõsy[b], Petra Bombicz[c] and László Tõke[a] *

[a] Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P. O. Box 91, Hungary, Fax: 36-1 463 3648, Email: P-Bako@ch.bme.hu

[b] NMR Laboratory of the Institute for General and Analytical Chemistry, Technical University of Budapest, H-1521 Budapest, Szt. Gellért tér 4, Hungary

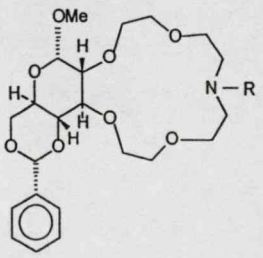
[c] Central Research Institute for Chemistry, Hung. Acad. of Sci., P.O.Box 17, H-1525 Budapest, Hungary

Received 20 December 1996

Abstract: A new, efficient crown ether **1** anellated to a sugar derivative has been prepared which shows significant asymmetric induction as phase transfer catalyst in the Michael addition of 2-nitropropane to chalcone (60% ee for the *S* antipode) and in the Darzens condensation of phenacyl chloride and benzaldehyde (64% ee), simultaneously changing the PT process from solid-liquid to liquid-liquid phase.

A number of papers have been published on the asymmetric C-C bond formation in the presence of chiral catalysts as phase transfer (PT) agents[1a-d]. Previously, we reported the asymmetric Michael addition of phenylacetate to acrylate catalyzed by chiral crown ethers incorporating two glucose units (85 % ee)[1d].

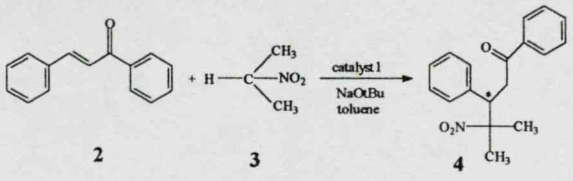
In this paper we wish to report the investigations of two new reactions: a Darzens condensation and the addition of nitroalkane to chalcone. It would bear great practical significance for both reactions (and reaction products) if asymmetric synthesis could be realized. Since the crown ethers having two glucoses[1d] have proved to be unsuccessful for these reactions, new catalysts have been synthesized[2]. These compounds are 15-membered monoaza-crown ethers **1** with one glycopyranoside unit, in which the substituents attached to the nitrogen exert a significant effect on the PT properties of the catalyst[2].



1

Compound	R
1a	C_6H_5
1b	$CH_2C_6H_5$
1c	CH_3-$(CH_2)_3$
1d	CH_3-$(CH_2)_9$
1e	CH_2CH_2OH
1f	C_6H_{11}
1g	$CH_2CO_2CH_3$

In the Michael addition the crown compounds **1** proved to be effective catalysts in the solid-liquid (SL) system, whereas in the Darzens condensation the medium had to be changed to a liquid-liquid (LL) system for appropriate results.



2 **3** **4**

The effect of certain catalysts on the stereoselective addition of nitroalkanes to methyl vinyl ketone[3a] and to enone[3b] was studied recently. The conventional addition of 2-nitropropane (**3**) to chalcone (**2**) to give the racemic nitroketone **4** is known in the literature[3c]. We studied this reaction in a binary SL system in the presence of various bases (35 mol %) and chiral catalysts (7 mol %)[4a]. The results obtained under such conditions are collected in Table 1.

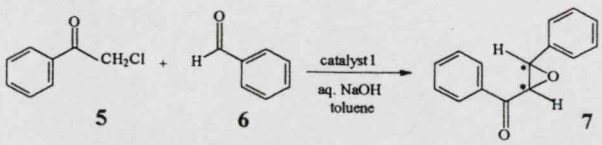
Table 1. Addition of 2-nitropropane (**3**) to chalcone (**2**) in toluene in the presence of catalysts **1**, at 20 °C

Entry	Catalyst	Base	Time (h)	Yield (%) [a]	$[\alpha]_D$ [b]	ee(%) [c]
1	**1b**	NaO-t-Bu	22	51	+38.4	46
2	**1f**	NaO-t-Bu	22	53	+39.1	48
3	**1g**	NaO-t-Bu	8	81	+43.0	52
4	**1g**	NaO-t-Bu	14	68	+43.4	53 [d]
5	**1e**	NaO-t-Bu	9	75	+49.1	60
6	**1e**	NaO-t-Bu	12	61	+44.5	58 [d]
7	**1e**	KO-t-Bu	5	80	+11.6	14
8	**1e**	KF	22	58	+8.2	10
9	**1e**	$KF+K_2CO_3$	3	81	+10.1	12

[a] Based on substance isolated by prep. TLC; [b] In CH_2Cl_2 (c 1.0) at ambient temperature; [c] Determined by ^{1}H-NMR spectroscopy in the presence of Eu(hfc)$_3$ as chiral shift reagent, [d] Reaction temperature: -10 °C.

In all cases the product with positive optical rotation was found to be in excess. It can be seen that under such conditions both chemical yield and optical purity depend on the substituent R of the catalyst. Compound **1e** (R=CH_2CH_2OH) showed the best asymmetric induction. The reaction was the fastest in the presence of $KF+K_2CO_3$ mixture (entry 9), but with low selectivity (12 % ee).

The greatest chiral induction could be achieved with NaO-t-Bu as a base: in the presence of catalyst **1e** at 20°C 60% ee was obtained for the (+)-antipode. The product of the highest optical purity was repeatedly recrystallized from toluene to prepare the pure enantiomer of positive optical rotation (purity was determined by ^{1}H-NMR)[4b]. The X-ray diffraction measurement of a single crystal of this substance[5] showed that the absolute configuration is *S*. The specific rotation of (+)-(*S*)-**4** is $[\alpha]_D^{20}$ + 80.8 (c = 1, CH_2Cl_2).



5 **6** **7**

The Darzens condensation taking place between phenacyl chloride (**5**) and benzaldehyde (**6**) could not be performed so far in a stereoselective manner[6]: in the presence of quininium benzyl chloride catalyst under PT conditions an optical purity of 8 % was the best result[7]. Using a SL system only a modest asymmetric induction (5 %) could be achieved in the presence of crown ethers **1**, consequently we changed the medium to a LL system[8](aqueous NaOH - toluene mixture , Table 2).

It can be seen that under such conditions both chemical yield and optical purity significantly depend on substituent R of the catalysts, **1e** (R = CH_2CH_2OH) has proved to be the most effective. The highest optical purity was obtained at -20°C (64 % ee with catalyst **1e**). This, on the basis of the optical rotation of the enantiomer corresponds to an absolute configuration of (2*R*,3*S*)[9]. The excellent properties of crown ether **1e** in both reactions are due most probably to the terminal OH group of substituent R (lariate ether type compound). The fact that catalysts **1** exerted no induction in SL system in the case of Darzens reaction, being effective in

LL system only, shows that the ion pair complexes leading to (2*R*,3*S*)-products are better stabilized under LL conditions.

Table 2. Asymmetric Darzens condensation of phenacyl chloride (5) with benzaldehyde (6) in the presence of chiral crown ethers 1

Entry	Catalyst	Time(h)	Temp.(°C)	Yield(%)[a]	$[\alpha]_{578}$[b]	ee(%)[c]
1	1a	1	22	42.8	-8.4	4
2	1b	1	22	67.6	-26.9	13
3	1c	1	22	38.6	-24.5	11
4	1c	16	22	84.3	-45.3	21
5	1d	3	22	61.8	-11.6	5
6	1e	1	22	87.8	-87.3	41[d]
7	1e	4	22	92.5	-90.3	42
8	1e	2	-10	80.4	-107.0	50
9	1e	4	-10	88.6	-126.0	59[d]
10	1e	4	-20	76.5	-137.0	64[d]

[a]Based on substance isolated by prep. TLC; [b]Maximum value $[\alpha]_{578}$ -214 (c=1, in CH_2Cl_2) for pure enantiomer[9]; [c]Enantiomeric excess was determined by optical rotation; [d]Determined by ^{1}H- NMR spectroscopy in the presence of Eu(hfc)$_3$ as chiral shift reagent.

Acknowledgement: This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T015677).

Notes and References

(1) (a) Maarschalkerwaart, D. A. H. van; Willard, N. P.; Pandit, U. K. *Tetrahedron* **1992,** *48,* 8825. (b) Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles* **1992,** *33,* 493, and references cited therein. (c) Brunet, E.; Poveda, A. M.; Rabasco, D.; Oreja, E.; Font, L. M.; Batra, M. S.; Rodriguez-Ubis, J. C. *Tetrahedron : Asymmetry* **1994,** *5,* 935. (d) Tõke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* **1995,** *36,* 5951, and references cited therein.

(2) Bakó, P; Tõke, L. *J. Incl. Phenom.* **1995,** *23,* 195.

(3) (a) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron : Asymmetry* **1993,** *4,* 173. (b) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994,** *35,* 8233. (c) Ono, N.; Kamimura, A.; Kaji, A. *Synthesis* **1984,** 226, and references cited therein.

(4) (a) The Michael addition was performed as follows: 0.3 g (1.44 mmol) of chalcone and 0.3 mL (3.36 mmol) of 2-nitropropane were dissolved in 3 mL of anhydrous toluene, and then 0.1 mmol of crown ether and 0.5 mmol of base were added. The mixture was stirred under Ar atmosphere. After completing the reaction a mixture of 7 mL of toluene and 10 mL of water was added. The organic phase was processed in the usual manner. The product was purified on silica gel by preparative TLC with hexane-ethyl acetate (10:1) as eluent. (b) We found that at 0.2 mol Eu(hfc)$_3$/substrate ratio the induced upfield shift of the methyl signals were 0.09 and 0.13 ppm for the *R* enantiomer while these values for the *S* antipode were 0.10 and 0.11 ppm. These shift differences at 500 MHz make possible to determine the enantiomeric purity within the limits of the NMR spectroscopy as quantitative analytical tool. In the case of the optically pure compound **4** the doubling of any signal could not be observed even at 0.3 and 0.45 Eu(hfc)$_3$/substrate ratio, and minor signals were not showed.

(5) Crystal data: $C_{18}H_{19}NO_3$, formula weight 297.34, orthorhombic; space group $P2_12_12_1$, unit cell dimension a=5.935(1)Å, b=14.539(1)Å, c=198.242(1)Å, α=90.00°, β=90.00°, γ=90.00°, V=1574.1(3)Å^3, z=4, D_{calc}=1.255 g/cm^3, F(000)=632, μ(CuK_α)=0.69 mm^{-1}, independent reflections 3189, R=0.0419, R_w=0.1085.

(6) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annunziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. 1,* **1982,** 1317.

(7) Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978,** 1089.

(8) Typical experimental procedure for the asymmetric Darzens condensation: A toluene solution (3 mL) of 0.2 g (1.3 mmol) of phenacyl chloride was treated with 0.2 g (1.9 mmol) of benzaldehyde and 0.1 mmol of catalyst in 0.6 mL of 30 % NaOH solution. The mixture was stirred under Ar atmosphere. After completing the reaction 7 mL of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed on a preparative silica gel plate of 2 mm thickness (Kieselgel 60 GF_{254}), using CH_2Cl_2 as eluent. ^{1}H-NMR (δ, 500 MHz, $CDCl_3$) 4.08 (1H, d, J 2 Hz), 4.29 (1H, d, J 2 Hz), 7.30-7.40 (5H, m aromatic), 7.48 (2H, t, aromatic), 7.60 (1H, t, aromatic), 8.01 (2H, m, aromatic).

(9) Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979,** *44,* 2312.

Heteroatom Chemistry
Volume 8, Number 4, 1997

Asymmetric Michael Addition of 2-Nitropropane to a Chalcone Catalyzed by Chiral Crown Ethers Incorporating a D-glucose Unit

Péter Bakó and László Töke*

Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P.O. Box 91, Hungary; Fax: 36-1 463 3648

Áron Szöllösy

NMR Laboratory of the Institute for General and Analytical Chemistry, Technical University of Budapest, H-1521 Budapest, Szt. Gellért tér 4, Hungary

Petra Bombicz

Central Research Institute for Chemistry, Hungary Academy of Science, P.O. Box 17, H-1525 Budapest, Hungary

Received 18 February 1997

ABSTRACT

Michael addition of 2-nitropropane **4** *to a chalcone* **3** *catalyzed by crown ethers incorporating two glucose units (of* **1** *type) afforded the adduct* **5** *with an R-enantiomer excess (28% ee) while the aza-crown ethers containing one glucose unit (of* **2** *type) gave the same adduct favoring the S-enantiomer under solid–liquid phase transfer conditions (SL-PT). It was proven that substituents at the N-atom of the crown ring in* **2** *have a significant effect on both the chemical yield and the enantioselectivity, and those having heteroatoms in the proper position of the side chain (***2e**, **2f***) showed the best results in this reaction: 65% ee for the S-antipode. The absolute configuration of (+)-4-methyl-4-nitro-1,3-diphenyl-1-pentanone (***5***), determined by X-ray diffraction, is also presented in this article.* © *1997 John Wiley & Sons, Inc.*

*To whom correspondence should be addressed.

INTRODUCTION

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral catalysts. Although many optically active crown ethers have been described in the literature [1], there have been relatively few attempts to use chiral crown ethers to catalyze asymmetric C–C bond formation reactions [2]. The Michael addition of carbon nucleophiles to conjugated enones is one of the most powerful methods for carbon–carbon bond formation. Due to its relevance in the synthesis of biologically active compounds, much effort has been centered on carrying out this reaction in a stereoselective way [3]. The effect of certain catalysts on the stereoselective addition of nitroalkanes to methyl vinyl ketone [4a] and to other enones [4b] was studied recently. The Michael addition of methyl phenylacetate to methyl acrylate had been described earlier by us, in a reaction in which the chiral crown ether catalyst **1b** showed very significant chiral induction (R = Bu, 80% ee) [5].

© 1997 John Wiley & Sons, Inc.
1042-7163/97/040333-05

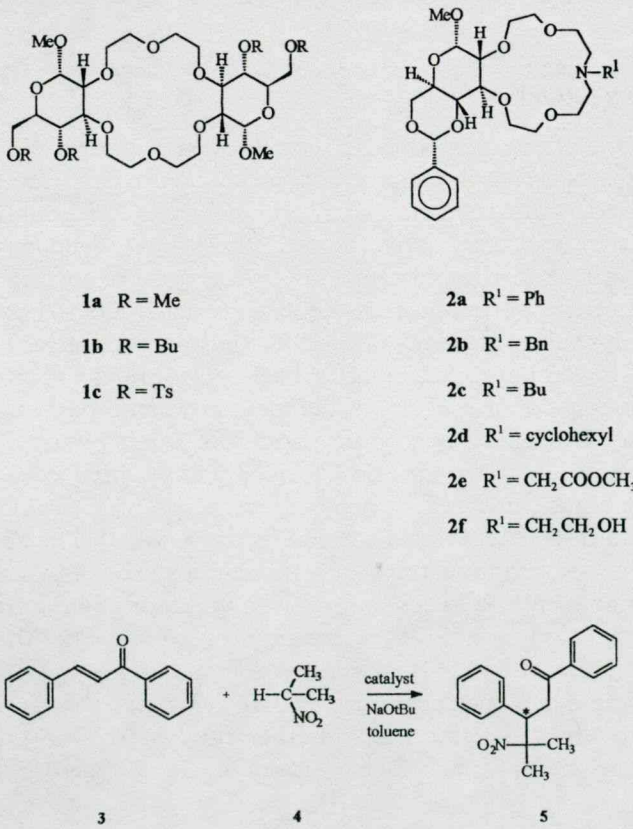
333
Egyetemi Könyvtár
SZEGED

As part of our investigations in this area, we have synthesized the novel class of D-glucose–based crown ether derivatives **2**. These compounds are 15-membered mono-aza-crown ethers with one glucopyranoside unit, in which the substituents attached to the nitrogen exert a significant effect on the phase transfer (PT) properties of the catalyst [6].

RESULTS AND DISCUSSION

The catalytic activity of macrocycles **1** and **2** in the asymmetric Michael addition reaction of 2-nitropropane (**4**) to the chalcone **3** was studied under SL-PT conditions (Scheme 1). Of course, this reaction yields a racemic product by conventional procedures [7]. Our experiments were carried out in toluene, employing solid sodium tert-butoxide as a base in the presence of 7 mol% of catalyst. The asymmetric inductions expressed in terms of enantiomeric excess (ee %) values were determined by ^{1}H-NMR spectroscopy with Eu(hfc)$_3$ as a chiral shift reagent and using preparative TLC in the workup procedure. The reactions were repeated under a variety of conditions. From the results presented in Table 1, several salient aspects of the reaction may be noted. First, the catalysts incorporating two glucopyranoside units **1a**, **1b** resulted in moderate chemical and relatively low optical yields for the R-enantiomer having negative rotatory power (runs 1–3). No conversion was observed in the presence of the tosyl-derivative **1c** (run 4). The highest optical purity (28% ee) was obtained at −20°C with catalyst **1b** (R = Bu).

It is interesting to note that, by use of aza-crown ethers **2**, the products with opposite configurations (*S*) were obtained. The catalyst having a phenyl group at the N-atom of the crown ring (**2a**) gave the lowest chemical and optical yields (run 5). The following three of the catalysts (**2b**, **2c**, **2d**) exerted roughly the same chiral induction (46% to 48% ee at room temperature), regardless of the quality of the substituents R (runs 6–8). The chemical yields dramatically increased, and higher enantioselectivities were obtained in the presence of catalysts **2e** and **2f** both having heteroatoms with lone pairs of electrons in the N-substituents. Among all the catalysts tested, the compound **2f** (R = CH_2CH_2OH) proved to be the best: optical purity of 61% for the *S*-antipode and a chemical yield of 85% were obtained at 20°C (run 11), and this value of ee could be improved to 65% ee by an increase of the amount of the catalyst used (from 7 mol% to 14 mol%). The above given temperature seemed to be the optimal temperature for the reaction because under or above this value the enantioselectivity was lower (runs 10, 12, and 14).



SCHEME 1

TABLE 1 Addition of 2-Nitropropane **4** to Chalcone **3** Catalyzed by Crown Ethers **1**[a] and **2**[b]

Run	*Catalyst*	*Temp. (°C)*	*Time (h)*	*Yield (%)*[c]	*ee (%)*[d]
1	**1a**	−20	42	31	9 (R)
2	**1b**	−20	30	44	28 (R)
3	**1b**	20	24	51	14 (R)
4	**1c**	20	68	0	—
5	**2a**	20	30	21	10 (S)
6	**2b**	20	22	39	46 (S)
7	**2c**	20	30	40	48 (S)
8	**2d**	20	22	42	47 (S)
9	**2e**	20	8	90	58 (S)
10	**2e**	−10	8	78	53 (S)
11	**2f**	20	9	85	61 (S)
12	**2f**	−10	10	71	55 (S)
13[e]	**2f**	22	8	91	65 (S)
14	**2f**	50	6	90	34 (S)
15[f]	**2f**	20	10	88	58 (S)

[a]Base: KF + K_2CO_3.
[b]Base: NaOBu^t.
[c]Based on substance isolated by preparative TLC.
[d]Determined by ^{1}H-NMR spectroscopy in the presence of Eu(hfc)$_3$ as chiral shift reagent; absolute configurations are given in parantheses.
[e]14 mol% of catalyst was used.
[f]Recovered catalyst was used; data are averages from two or more experiments and reproducible within 2%.

The crown amine catalysts **2** could be recovered from the reaction mixture by extracting them with aqueous hydrochloric acid, followed by treatment of the extracts with base. The last experiment of Table 1 (run 15) shows that the catalyst **2f** recovered by this procedure worked similarly as the original one in the reaction.

The effect of the quality of the bases with regard to the ee was examined, always with crown ether **2f** being used as the chiral source. The results of these experiments are presented in Table 2. It can be seen that the quality of the bases exerted significant influence on both the chemical yield and chiral induction. When a KF + K_2CO_3 mixture was used (run 2), the reaction was faster, and the chemical yield (91%) and selectivities (27% ee) were better than those in the case in which KF alone was used (run 1) (yield 58%, ee 22%). The application of the KOBu^t (run 3) and NaF + Na_2CO_3 mixture (run 4) resulted in a good chemical yield but showed very poor selectivities. The reaction was fast in the presence of NaH as well (run 6), but a series of by-products, so far not identified, were formed (yield 54%, ee 25%). The use of powdered NaOH resulted in a higher value of ee (41%) but with poor chemical yield (39%). The greatest degree of chiral induction could be achieved using NaOBu^t base at room temperature (61% ee). The increase of the amount of the base gave a somewhat lower selectivity (58% ee). The difference between influences of NaOBu^t (run 7) and KOBu^t (run 3) may be connected with the fact that crown ethers of type **2** form stronger complexes with Na ions than with K ions [6]. It can be seen that it is the *S*-enantiomer that is in excess in the products in all of the experiments listed in Table 2.

We also investigated the so-called deracemization of the racemic product (+/−)-**5** effected by chiral crown ether-NaOBu^t complexes. As it had been observed earlier by us, the position of the protonation–deprotonation equilibria for chiral CH-acids in the presence of chiral crown catalysts is dependent on the quality of the chiral catalysts, so that one of the antipodes can be in an excess at this point [5]. However, no such effect could be observed in the presence of the catalysts **1** either with KF + K_2CO_3 or with KOBu^t bases. The compounds **2** did not exert such an effect on the racemate **5** at room temperature either, but at −10°C, only slightly dependent on the conditions of the reaction, an excess for the *R*-enantiomer of **5** (4–7% ee) could be detected. Taking into account this result, one can explain the lower ee value for the *S*-enantiomer in the experiment carried out at −10°C (runs 10 and 12, in Table 1).

The product **5** of the highest optical purity (65% ee for *S*) was repeatedly recrystallized from toluene to prepare the pure enantiomer of positive optical rotation (purity was checked by ^{1}H-NMR spectroscopy). The single-crystal X-ray analysis of this substance showed that its absolute configuration is S. The specific rotation of (+)-(S)-**5** is $[\alpha]_D^{20}$ + 80,8 (*c* = 1, in CH_2Cl_2).

The X-ray crystal structure and labeling of (*S*)-**5** can be seen at the 50% probability level in the ZORTEP [10] diagram (Figure 1). The packing of **5** in the unit cell is drawn in a space-filling model with the nonhydrogen atom skeleton of the molecule. The two phenyl rings in the molecule are nearly perpendicular to each other with an angle of 91.95 (7)°. No noticeable intermolecular interactions could be observed within the sum of the van der Waals radii on the basis of this crystal structure model.

To explain the stereochemical outcome of the reaction, we suppose that there exists an equilibrium between ion pair complexes formed by the enolate-

TABLE 2 Addition of 2-Nitropropane **4** to Chalcone **3** catalyzed by Crown Ether **2f** in the Presence of Various Bases[a]

Run	*Base*	*Time (h)*	*Yield (%)*[b]	*ee (%)*[c]
1	KF	22	58	22 (S)
2	KF + K_2CO_3	3	91	27 (S)
3	KOBu^t	5	71	15 (S)
4	NaF + Na_2CO_3	10	82	12 (S)
5	NaOH	21	39	41 (S)
6	NaH	5	54	25 (S)
7	NaOBu^t	9	85	61 (S)
8[d]	NaOBu^t	8	89	58 (S)

[a]In toluene, at room temperature, 35 mol% of base was used.
[b]Based on substance isolated by prep. TLC.
[c]Determined by ^{1}H-NMR analysis.
[d]70 mol% of base was used.

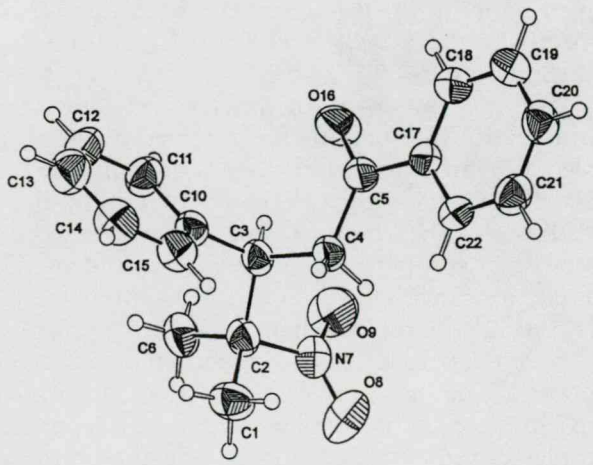


FIGURE 1 ZORTEP diagram of (S)-**5**.

TABLE 3 Crystal Data and Structure Refinement for (S)-5

Empirical formula	$C_{18}H_{19}NO_3$
Formula weight	297.34
Temperature	293(2) K
Wavelength	1.54184 Å
Crystal system	Ørthorhombic
Space group	P $2_12_12_1$
Unit cell dimensions	*a* = 5.935(1) Å alpha = 90.000°
	b = 14.539(1) Å beta = 90.000°
	c = 18.242(1) Å gamma = 90.000°
Volume	1574.1(3) Å^3
Z	4
Density (calculated)	1.255 Mg m^{-3}
Absorption coefficient	0.690 mm^{-1}
F(000)	632
Crystal size	0.35 × 0.18 × 0.09 mm
Theta range for data collection	3.89 to 74.92°
Index ranges	$-6 \leq h \leq 7$, $-18 \leq k \leq 18$, $-22 \leq l \leq 22$
Reflections collected	3824
Independent reflections	3189 [R(int) = 0.0128]
Absorption correction	semiempirical from ϕ-scan
Max. and min. transmission	0.940 and 0.771
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	3189/0/205
Goodness-of-fit on F 2	1.050
Final R indices [I > 2sigma(I)]	R1 = 0.0436, wR2 = 0.1129
R indices (all data)	R1 = 0.0630, wR2 = 0.1245
Absolute structure parameter	−0.1(3)
Largest diff. peak and hole	0.184 and −0.185 e Å^{-3}

metal ion-crown ether, and the result is believed to be controlled by the relative stability of these complexes. In this equilibrium, the ion pair with the lowest energy dominates. The anion of the ion pair is presumably trapped (so that the situation becomes frozen) by the attack of chalcone, resulting in the *S*-product excess.

The concepts of C_2 symmetry and catalyst-substrate steric interactions have played an important role in suggested mechanisms of asymmetric catalysis. The C_2 symmetry element often simplifies the synthesis of the catalysts and serves to reduce the number of competing diastereomeric intermediates in reactions involving their use. Most often, the models that adequately predict the stereochemical outcome of these reactions are based on the spatial orientation of groups within the disymmetric environment of the auxiliary or catalyst. Even so, examples of the electronic tuning of asymmetric catalysts are appearing in the literature with increasing frequency [8]. Furthermore, in several cases, good enantioselectivities have been obtained using chiral ligands without C_2 symmetry. Our examples with use of the catalysts **2** belong to this latter case. Unfortunately, a clear delineation of the steric and electronic effects is not possible in these systems [8].

It can be seen that the catalysts **2e** and **2f** provided the best chemical yields and the highest chiral induction. These types of heterocycles consisting of a side arm containing ester and hydroxy groups, respectively, named lariat ethers or armed crown ethers, are known to display special complexation, high lipophilic character, and unique quest specificity via tethering-side arm cooperativity [9].

EXPERIMENTAL

^{1}H-NMR Spectra. BRUKER DRX-500 AVANCE (in $CDCl_3$), TMS as internal standard. Polarimeter: Perkin-Elmer 241. TLC: preparative silica gel plates (20 × 20 cm) of 2 mm thickness, DC-Fertig-platten Sil G-200 UV_{254} (Macherey-Nagel), eluent hexane-ethyl acetate (10:1), development in UV light. Shift reagents: Eu(hfc)$_3$ (Aldrich).

Performance of The Michael Addition. Amounts of 0.3 g (1.44 mmol) of the chalcone and 0.3 mL (3.36 mmol) of 2-nitropropane were dissolved in 3 mL of anhydrous toluene, and the 0.1 mmol of crown ether and 0.5 mmol of base were added. The mixture was stirred under an Ar atmosphere. After completion of the reaction, a mixture of 7 mL of toluene and 10 mL of water was added. The organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated to dryness. The residue was purified by preparative TLC. The product **5** was a white crystalline solid, mp 146–148°C. ^{1}H-NMR ($CDCl_3$) δ 1.54 (3H, s, CH_3); 1.62 (3H, s, CH_3); 3.25–4.18 (3H, m, CH_2, and CH); 7.25 (5H, m, Ph); 7.52 (3H, m, Ph); 7.85 (2H, m, Ph).

The results of the experiments are presented in Tables 1 and 2. Data are averages of two or more experiments and are reproducible within 2%.

Determination of the Optical Purity. We found that at 0.2 mol Eu(hfc)$_3$/substrate ratio the induced upfield shifts of the methyl signals were 0.09 and 0.13 ppm for the R enantiomer, while those for the S antipode were 0.10 and 0.11 ppm. These shift differences at 500 MHz make it possible to determine the enantiomeric purity within the limits of the NMR spectroscopy as a quantitative analytical tool. In the case of the optically pure compound (*S*)-**5**, the doubling of any signal could not be observed, even at a 0.3 and 0.45 Eu(hfc)$_3$/substrate ratio, and minor signals were not in evidence.

X-ray Crystal Structure Determination of (*S*)-**5**. Determination of the unit cell parameters and collection of the symmetry-independent reflections of **5** were performed on an Enraf-Nonius CAD4 computer-controlled single-crystal diffractometer using graphite monochromated CuK_α radiation. The initial structure model was found by the direct method (program SHELXS86 [11]), with the structure refinement being carried out by SHELXL93 [12]. Anisotropic displacement parameters were refined for all of the nonhydrogen atoms. Hydrogen atoms were introduced in calculated positions and refined riding mode on the respective carbon atoms. Crystal data and structure refinements for (*S*)-**5** are listed in Table 3.

SUPPLEMENTARY MATERIAL

The fractional atomic coordinates with their anisotropic displacement parameters, full list of bond distances, angles and torsion angles, least-squares plane data, and F_0/F_c values are given in the supplementary material and are deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW England.

ACKNOWLEDGMENTS

This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T015677).

REFERENCES

[1] E. F. J. de Vries, P. Steenwinkel, J. Brussee, C. G. Kruse, A. van der Gen, *J. Org. Chem., 58,* 1993, 4315, and references cited therein.

[2] (a) Dave A. H. van Maarschalkerwaart, Nico P. Willard, Upendra K. Pandit, *Tetrahedron, 48,* 1992, 8825; (b) S. Aoki, S. Sasaki, K. Kaga, *Heterocycles, 33,* 1992, 493, and references cited therein; (c) M. J. O'Donnell: "Asymmetric Phase Transfer Reactions," in I. Ojima (ed): *Catalytic Asymmetric Synthesis,* VCH Publishers, New York, chap. 8, pp. 389–411 (1993).

[3] D. A. Oare, C. H. Heathcock, *Top. Stereochem., 20,* 1989, 227.

[4] (a) A. Latvala, S. Stanchev, A. Linden, M. Hesse, *Tetrahedron: Asymmetry, 4,* 1993, 173; (b) M. Yamaguchi, T. Shiraishi, Y. Igarashi, M. Hirama, *Tetrahedron Lett., 35,* 1994, 8233.

[5] L. Tōke, L. Fenichel, M. Albert, *Tetrahedron Lett., 36,* 1995, 5951, and references cited therein.

[6] P. Bakó, L. Tōke, *J. Incl. Phenom., 23,* 1995, 195.

[7] N. Ono, A. Kamimura, A. Kaji, *Synthesis,* 1984, 226, and references cited therein.

[8] (a) T. V. Rajan Babu, A. L. Casalnuovo, *J. Am. Chem. Soc., 118,* 1996, 6325; (b) C. Rosini, L. Franzini, A. Raffaelli, P. Salvadori, *Synthesis,* 1992, 503.

[9] G. W. Gokel, *Chem. Soc. Rev., 21,* 1992, 39 and references cited therein.

[10] L. Zsolnai, H. Pritzkow, ORTEP Program for Personal Computer. Original modified in Universität Heidelberg (1996).

[11] G. M. Sheldrick, *Acta Cryst., A46,* 1990, 467.

[12] G. M. Sheldrick, SHELXL93 Program for the Refinement of Crystal Structures, University of Göttingen, Germany (1993).

Pergamon

Tetrahedron Letters, Vol. 38, No. 41, pp. 7259-7262, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01686-9

B9

Chiral Azacrown Ethers Derived from D-glucose as Catalysts for Enantioselective Michael Addition

Péter Bakó, Tibor Kiss, László Tőke*

Department of Organic Chemical Technology and Organic Chemical Technology Research Group of the Hung. Acad. of Sciences at the Technical University of Budapest, H-1521 Budapest, P. O. Box 91, Hungary, Fax: 36-1 463 3648

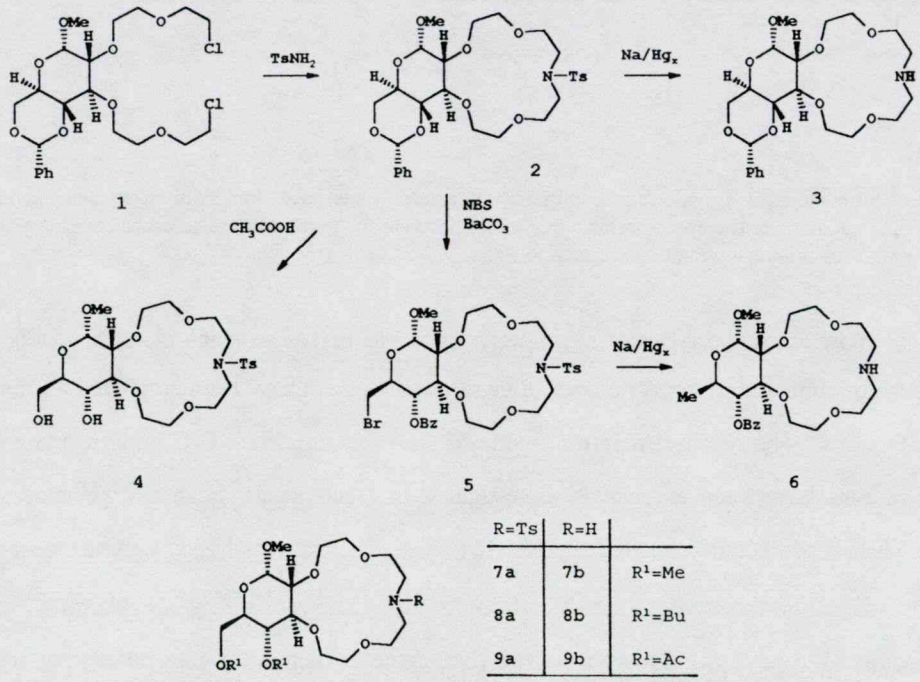
Abstracts: Chiral monoaza-crown ethers incorporating glucose units have been synthesized and applied as phase transfer catalysts in the enantioselective Michael addition of 2-nitropropane to a chalcone to give the corresponding adduct in enantiomeric excess up to 90%. © 1997 Elsevier Science Ltd.

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral catalysts. A number of chiral crown ethers have been employed as chiral catalysts in phase transfer reactions.[1] The Michael reaction is one of the most important C-C bond-forming reactions, and stereoselective variants have been extensively investigated in recent years. High asymmetric inductions have been reported in Michael addition of methyl phenylacetate to methyl acrylate catalyzed by chiral crown ethers.[2a-h] The effect of certain catalysts on the stereoselective addition of nitroalkanes to methyl vinyl ketone[2i] and to enones[2j] was studied recently. We have previously reported the synthesis of new 15-membered ring monoaza-crown ethers from glucose and galactose[3] and their application as catalysts in an asymmetric Michael addition[4,5] and in a Darzens condensation.[4] We first began investigating the addition of 2-nitropropane to a chalcone catalyzed by chiral macrocyclic polyethers under phase transfer conditions. The best result achieved in this reaction was 60% ee for the *S*-antipode.[4,5]

We now report on the synthesis of some new chiral monoaza-crown ethers incorporating glucose units (Scheme 1) and their asymmetric induction in the Michael addition mentioned above.

The chiral starting macrocycle **2** needed for the preparation of the derivatives **3-9** was obtained from the "half-crown" **1**[3,6] by treatment with 1 molar equivalents of p-toluenesulfonamide in DMF (in dilute solution 2-3%) in the presence of dry K_2CO_3 (reflux, 36 h) in 42% yield after chromatography. Compound **2** was deprotected to **3** by 4% sodium amalgam in the presence of dibasic sodium phosphate in methanol (reflux, 20 h) in a yield of 92%, as reported for similar compounds.[7] Our attempt to form **3** by reductive removal of the N-tosyl groups in **2** by $LiAlH_4$ in THF[8] was not successful and caused the macrocyclic ring to open. The benzylidene group was removed selectively from **2** with 96% aqueous acetic acid for 2 h at 100 °C, resulting in the dihydroxy compound **4** in 92% yield. Alkylation or acylation of **4** furnished compounds (**7a, 8a, 9a**), which

upon treatment with sodium amalgam gave the required crown amines (**7b, 8b, 9b**). The reaction of compound **4** with methyl iodide, in DMF, in the presence of barium oxide[9] (8 h, r.t.) resulted in the dimethyl derivative **7a**, followed by reduction to the corresponding amine **7b** in 78% overall yield. The dibutyl derivative **8a** was synthesized from **4** using butyl bromide in dry DMF containing NaH, for 40 h at 40 °C, cleavage of the tosyl group of **8a** furnished the amine **8b** in 58% overall yield. Crown ether **4** was also allowed to react with acetic anhydride in pyridine to yield the diacetyl derivative **9a**, reduction of which afforded the crown amine **9b** in 75% yield for the two steps.



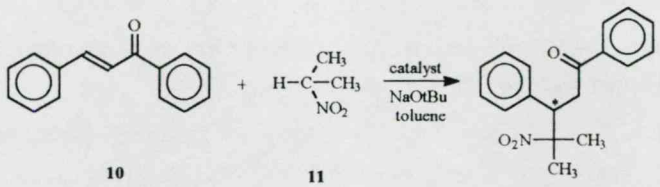
Scheme 1

The cleavage of the acetal ring in **2** can be performed in regioselective manner using Hanessian's method.[10] Treatment of **2** with boiling carbon tetrachloride containing N-bromo-succinimide, barium carbonate, and benzoyl peroxide for 3 h yielded 88% of the 4-benzoyl-6-bromo-6-deoxy derivative **5**. The structure of **5** was proved by the reduction with sodium amalgam to give the 4-benzoyl-6-deoxy derivative **6** whose ^{1}H NMR spectrum contained a doublet at δ 1.23 for the CH_3CH. All new compounds displayed satisfactory spectral and analytical data in full agreement with their structures.[11]

We examined the effect of these new compounds as chiral catalysts in the enantioselective Michael addition of 2-nitropropane **11** to chalcone **10** under solid-liquid phase transfer conditions (Scheme 2).

Our experiments were carried out in toluene employing solid sodium tert-butoxide as base in the presence of 7 mol% catalyst.[12] After preparative TLC work-up the asymmetric inductions expressed in terms of enantiomeric excess (ee) values were determined by optical rotation, the absolute configuration assigned by

comparison of specific rotation with literature value.[4,5] The results of these experiments are presented in Table 1.



10 11 12

Scheme 2

Table 1: Enantioselective Addition of 2-Nitropropane **11** to Chalcone **10** Catalyzed by Chiral Crown Ethers[a]

Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2**	26	28	4 (*S*)
2	**3**	11	73	61 (*S*)
3	**5**	24	20	6 (*S*)
4	**6**	9	77	55 (*R*)
5	**7a**	22	25	6 (*S*)
6	**7b**	15	68	34 (*S*)
7	**8a**	18	35	10 (*S*)
8	**8b**	9	82	90 (*S*)[d]
9	**9a**	28	23	5 (*S*)
10	**9b**	14	65	47 (*S*)

[a] In toluene, at room temperature, 35 mol% $NaOBu^t$ was used. [b] Based on substance isolated by preparative TLC; [c] Determined by optical rotation, absolute configuration are give in parantheses. [d] Checked by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent[5].

It can be seen that the crown ethers having tosyl groups on the N-atom (**2, 5, 7a, 8a, 9a**) resulted in a low chemical yield and very poor selectivities (entries 1, 3, 5, 7, 9). The catalytic activity and enantioselectivity dramatically increased in the presence of catalysts **3, 6, 7b, 8b, 9b** all having free NH group. It is probable that, the N-Ts amide part in the crown ring depreciates the complex-forming properties and its steric hindrance may play an essential role too. Among all the catalysts tested, the compound **8b** proved to be the best: optical purity of 90% for the *S*-antipode and a chemical yield of 82% were obtained (entry 8). It is interesting to note that, while all the catalysts, except **6**, gave the *S*-enantiomer, the 6-deoxy derivative **6** gave the product with opposite configuration ; the *R*-antipode was obtained in 55% ee (entry 4).

In conclusion, we have studied the enantioselective Michael addition of 2-nitropropane to a chalcone in the presence of glucose based monoaza-crown ethers as phase transfer catalysts. We have proved, both chemical yield and optical purity significantly depend on the substituents on the sugar part, the butyl groups proved to be the most effective (90% ee). Furthermore all of the successful catalysts have a free NH group in the cycle making probable the H-bond involvement in the transition state structures.

Further investigations including mechanistic studies are in progress.

Acknowledgements: This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T 015677).

References and Notes

1. O' Donnell, M. I. Asymmetric Phase Transfer Reactions; in *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH-Publishers, New York, 1993; pp. 389-411 and references cited therein.
2. (a) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (b) Alonso-López, M.; Jimenez-Barbero, J.; Martin-Lomas, M.; Penadés, S. *Tetrahedron* **1988**, *44*, 1535. (c) Takatsu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943. (d) van Maarschalkerwaart, D. A. H.; Willard, N. P.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 8825. (e) Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles* **1992**, *33*, 493. (f) Brunet, E.; Poveda, A. M.; Rabasco, D.; Oreja, E.; Font, L. M.; Batra, M. S.; Rodriguez-Ubis, J. C. *Tetrahedron: Asymmetry* **1994**, *5*, 935. (g) Kanakamma, P. P.; Mani, N. S.; Maitra, U.; Nair, V. *J. Chem. Soc. Perkin Trans I* **1995**, 2339. (h) Tőke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* **1995**, *36*, 5951. (i) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M.; *Tetrahedron:Asymmetry* **1993**, *4*, 173, and references cited therein. (j) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233, and references cited therein.
3. Bakó, P.; Tőke, L. *J. Incl. Phenom.* **1995**, *23*, 195.
4. Bakó, P.; Szöllősy, Á.; Bombicz, P.; Tőke, L. *Synlett* **1997**, 291.
5. Bakó, P.; Szöllősy, Á.; Bombicz, P.; Tőke, L. *Heteroatom Chem.* (in press).
6. Di Cesare, P.; Gross, B. *Synthesis* **1979**, 458.
7. (a) Vriesema, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110. (b) Chavez, F.; Sherry, A. D. *J. Org. Chem.* **1989**, *54*, 2990.
8. (a) Pietraszkiewicz, H.; Jurczak, J. *Tetrahedron* **1984**, *40*, 2967. (b) Lukyanenko, N. G.; Basok, S. S.; Filonova, L. K. *J. Chem. Soc. Perkin Trans I* **1988**, 3141.
9. Kuhn, R.; Baer, H. H.; Seelinger, A. *Ann.* **1958**, *611*, 236.
10. Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86.
11. For instance, **2**: mp 127-29°C; $[\alpha]_D^{20}$ + 15.6 (c=2, $CHCl_3$); MS (CI): m/z 594 (MH^+); ^1H NMR ($CDCl_3$) δ (ppm): 2.35 (s, 3H), 3.4 (s, 3H), 3.47-4.0 (m, 20H), 4.25 (d, J=4.8Hz, 2H), 4.82 (d, J=3.6Hz, 1H), 5.5 (s, 1H), 7.2-7.7 (m, 9H). **3**: mp 116-17°C; $[\alpha]_D^{20}$ + 46.6 (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$): 2.75 (t, 4H), 3.1 (s, 1H), 3.4 (s, 3H), 3.47-4.0 (m, 16H), 4.27 (d, J=4.8Hz, 2H), 4.86 (d, J=3.6 Hz, 1H), 5.52 (s, 1H), 7.2-7.5 (m, 5H). **6**: $[\alpha]_D^{20}$ + 19.3 (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.23 (d, J=2.5Hz, 3H), 2.45 (t, 4H), 3.05 (s, br, 1H), 3.4 (s, 3H), 3.45-4.0 (m, 13H), 4.47-4.95 (m, 4H), 7.22-7.4 (m, 5H). **8b**: $[\alpha]_D^{20}$ + 58.9 (c=1, $CHCl_3$); ^1H NMR: 0.9 (t, 6H), 1.14-1.73 (m, 12H), 2.45 (t, 4H), 2.8-3.05 (m, 5H), 3.4 (s, 3H), 3.45-4.8 (m, 14H), 4.9 (d, J=3.6Hz, 1H).
12. A typical experimental procedure is as follows:Under argon atmosphere, sodium tertiary butoxide (0.5 g, 0.5 mmol) was added to a solution of chalcone **10** (0.3 g, 1.44 mmol), 2-nitropropane (0.3 mL, 3.36 mmol) and crown ether (0.1 mmol) in anhydrous toluene (3 mL) and the mixture was stirred at room temperature. After completing the reaction 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 on silica gel by preparative TLC with hexane-ethyl acetate (10:1) as eluent (development in UV light).

(*Received in UK* 26 *June* 1997; *revised* 8 *August* 1997; *accepted* 15 *August* 1997)

Pergamon

Tetrahedron 54 (1998) 213–222

TETRAHEDRON

Asymmetric Michael Addition and Deracemization of Enolate by Chiral Crown Ether

László Tõke[a*], Péter Bakó[b], György M. Keserű[c], Melinda Albert[c] and László Fenichel[b]

[a]Organic Chemical Technology Research Group of the Hung. Acad. of Sciences at the Technical University of Budapest,

[b]Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P.O. Box 91, Hungary

[c]Chinoin Pharmacentical and Chemical Works Ltd., Tó u. 1-5, H-1045, Budapest, Hungary

Received 6 October 1997; revised 27 October 1997; accepted 30 October 1997

Abstract: Crown ethers anellated to glucose units have been used to catalyse the enantioselective Michael addition of methyl phenylacetate to methyl acrylate in high chemical yields in up to 84% enantiomeric excess. A novel CH-acid deracemization has also been discovered and the mechanistic rationale of the asymmetric induction is discussed.The proposed mechanism of the addition was also substantiated by molecular mechanics calculations. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Catalytic asymmetric C-C bond formation reactions are of special interest in organic synthesis.[1] The mechanism leading to asymmetric induction in transition states in the case of asymmetric reactions catalysed by chiral crown ether complexes is not well understood. Many optically active crown ethers have been synthesized, of which only a few have been applied as catalysts in asymmetric reactions,[2a-j] there is still a need for collecting further data for a better understanding of the mechanism of the chiral catalysis in these processes.

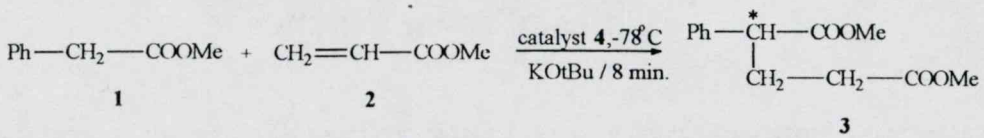
In this paper, in the Michael addition section we describe our contribution to the asymmetric carbon-carbon bond-forming reaction in the Michael addition of methyl phenylacetate (1) to methyl acrylate (2) catalyzed by chiral crown - potassium tert-butylate complex in a detailed form (Preliminary publication ref. 2j). The mechanism suggested by us for the reaction is substantiated by a molecular mechanics calculation, the details of which are also presented here under the Molecular modeling title.

To the best of our knowledge we are the first group who observed the time-dependency of the ee values in the reaction and gave a rationale explanation for it. The related experiments and the mechanistic reasonings are collected in the Deracemization section of the article.

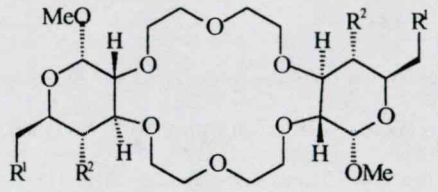
0040-4020/98/$19.00 © 1997 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(97)10271-X

Michael addition

The model reaction selected for testing the catalytic activity of the crown- macrocycles (**4**) was the addition of methyl phenylacetate (**1**) to methyl acrylate (**2**),[2a] employing potassium tertiary butoxyde as a base as well as the structure of crown ether catalysts **4** can be seen in Fig. 1.



1 **2** **3**



4

Figure 1

The crown ethers **4a-l** all have a C_2-symmetry axis obtained by alkylation under liquid - liquid phase transfer catalytic (PTC) conditions from crown ether **4a**. The synthetic procedures leading to **4a-j** were published earlier [3a-i] while syntheses of **4k,l** are collected in this Experimental.

The reactions were carried out at -78°C in toluene. The reagents were used in the following ratios : methyl phenylacetate : methyl acrylate : KOtBu :crown catalyst as 1.3 : 1 : 0.34 : 0.064. The asymmetric induction, expressed in terms of the enantiomeric excess (ee), was monitored by measuring the optical rotation of the product ester (**3**) and comparing to the literature value[2d] and by ^{1}H-NMR using (+)-Eu(fod)$_3$ as a chiral shift reagent. The results of the experiments are presented in Table 1.

Table 1. Asymmetric Michael addition of methyl phenylacetate to methyl acrylate in the presence of **4**, in toluene, for 8 min

Entry	Catalyst	R^1	R^2	Yield of **3** (%)	ee for *S*-**3** (%)	Notes
1	**4a**	OH	OH	44.0	7.5	
2	**4b**	OH	Bn	66.3	0.2	
3	**4c**	OTs	OH	67.5	0.4	
4	**4d**	Br	OH	37.1	1.2	
5	**4e**	Br	OBz	89.3	3.2	
6	**4f**	OTs	OTs	31.3	1.7	
7	**4g**	OAc	OAc	75.0	17.6	
8	**4h**	O—CH=O, Ph		59.5	17.5	
9	**4i**	OMe	OMe	100.0	76.4	
10	**4j**	OBu	OBu	100.0	80.0	
11	**4k**	O-hexyl	O-hexyl	69.3	46.0	
12	**4l**	O-octyl	O-octyl	69.2	29.2	
13	**4j**	OBu	OBu	47.0	25.3	solvent CH_2Cl_2
14	**4j**	OBu	OBu	82.3	84.4	time 1 min
15	**4j**	OBu	OBu	100.0	76.4	time 16 min
16	Dibenzo-18-crown-6			60.0	-	
17	no catalyst			43.5	-	

It can be seen that under such conditions all catalysts (derived from glucose) cause asymmetric induction leading to the product with the same (*S*) configuration. Both chemical yield and optical purity depend on the substituents (R^1 and R^2) of the catalyst. The crown ethers fully alkylated at the sugar units (**4i**, **4j**, **4k**) produced the best asymmetric induction (entry 9-11, Table 1). The catalyst **4j** (R^1=R^2=OBu) yielded the highest optical purity (entry 10, 80% ee). The yields and the ee-values are comparable to or better than those described in the literature for similar catalytic reactions.[2b,c,d]

To explain the stereochemical outcome of the reaction (Fig. 2) it can be supposed that there exists an equilibrium between ion pair complexes formed by the Z-enolate[2h] - metal ion - crown ether and the result is believed to be controlled by the relative stability of these complexes (at least at the very beginning of the reaction, see later).

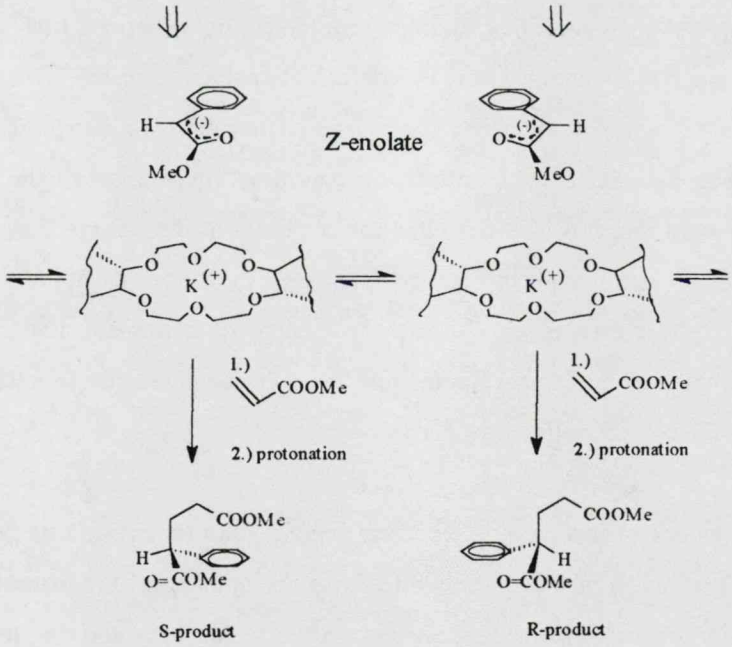


Figure 2.

In this equlibrium - because of the better fit of the Z-enolate in its Si-side-upwards - this ion-pair dominates, and after trapping the anion by the acrylate this situation will be frozen (trapped) resulting in the *S*-product-excess - after protonation of the adduct (anion) in a fast irreversible process. The result might also be modified by the solvent due to the different degree of the ion-pair aggregation and solvation (entry 13 in Table 1).

Molecular Modeling

Our proposed mechanism of the reaction was further analysed by molecular mechanics calculations. A relatively simple theoretical methodology to explain the observed stereoselectivity in asymmetric Michael additions was recently published by Brunet et al.[2h] Their calculations were limited to simple geometry

optimisation of feasible ion-pair complexes formed along the deprotonation. Since the stereoselectivity originates from the discrimination between these complexes, the rationalisation of the process requires their most stable conformation must be obtained. The computational effect of their limitation, however, is that the conformational space of intermediate complexes could not be explored and therefore the steric energies of local minima were compared. Although stereoselectivities calculated by this method were in fair agreement with the observed ones, the multiple minimum problem described above urged us to perform an extended conformational analysis on corresponding ion-pair complexes. The crown-ether **4i** was used as a model in our calculations.

According to the proposed mechanism our conformational analysis can be identified as a two-step process. Complexation of the potassium ion with the crown-ether **4i** is the first step of the reaction and therefore the conformational analysis of this complex should also be performed first. Due to the complexity of the system, this represents a challenging task. The conformational space of the crown ether cannot be treated without the consideration of the potassium ion complexed in its electrostatic field. The cyclic structure of the host revealed that a pseudosystematic algorithm for conformer generation might be optimal, the relative orientation of the potassium ion, however, requires the application of a Monte Carlo based random method. Conformational searches of such complexity can be adequately performed by the MacroModel package.[2k] The conformational space of the crown ether was explored using the systematic unbounded multiple minimum (SUMM) search algorithm. The positions of potassium ion were generated by Monte Carlo multiple minimum algorithm connected to the MOLS option of MacroModel.

SUMM algorithm

Within the framework of this method, conformer generation for cyclic structures is based on the ring-maker approach.[2l] The definition of a closure bond allows the opening of the macrocycle temporarily, in this opened state the variation of the torsional angles followed by reclosure of the ring leads to a new conformer. The resulting structure is then subjected to energy minimisation. The SUMM method[2m] operates by selecting values for torsional angle variation from a fixed set appropriate for a systematic search conducted at initially 120 deg resolution which can be increased along the process. This algorithm, therefore represents an intermediate between the fully systematic and random techniques, which is ideal for conformational searching.[2n]

MCMM/MOLS algorithm

Host-potassium interactions were studied by the particularly effective MCMM/MOLS algorithm using the low energy conformers of the crown ether **4i**. Minimum energy structures were calculated using Monte Carlo conformational search combined with the MOLS routine available in MacroModel.

The MOLS routine allows automatic docking of a ligand in a binding site by a combined conformational search procedure based on variation of the internal degrees of freedom of the crown ether (rotatable bonds). External degrees of freedom of the ligand (relative rotations and translations with respect to the fixed geometry

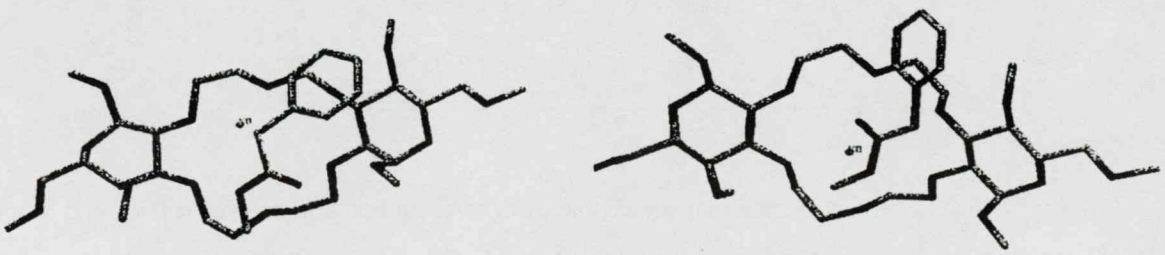
of the host) can be treated at the same time. In the case of metal ions only the degree of translational freedom should be considered.

The internal degrees of freedom of **4i** were varied using the previously described SUMM conformational search option of MacroModel. The combined MCMM/MOLS procedure was applied to allow the simultaneous random translation of the potassium ion with respect to the crown ether with increments of 0.5-1.0 Å for the translation of the centre of mass of the ligand along the *x,y,z* axes.

Finally, all these conformations were subjected to energy minimisation. The resulting minimum energy complex structures were sorted by energy and the unique structures within a 50 kJ/mol energy window above the global minimum were stored in a MacroModel multistructure file for further interactive study using the three-dimensional graphical interface of MacroModel.

Translations of potassium ion within the electrostatic field of the crown ether in combination with a 1000 step SUMM conformational search of the substrate enabled us to look for all possible low energy conformation for the potassium ion complex of **4I**. The most characteristic feature of the minimum energy complex is, that the potassium ion is located above the plane of the crown ether. This asymmetric orientation results, that attack of the anion formed from the phenylacetic acid ester could not take place with equal probability from the two sides of the crown ether. One can conclude that the anion would interact only from the more preferred side, and therefore further calculations concerning the other side might be omitted.

Conformational analyses of the corresponding ion-pair complexes were performed using an extended methodology. Backbone atoms of the crown ether as well as the potassium ion were fixed applying 35 kJ/A^2 constraint sets, which was introduced by a harmonic restoring potential. All substituents and the atoms of the anion were allowed free to move. The original MCMM/MOLS procedure was extended to the anion, in which the internal degrees of freedom were varied using the MCMM algorithm. Translation and rotation of the anion was allowed with respect to the crown ether with increments of 0.5-1.0 Å for the translation of the centre of mass of the ligand along the *x* ,*y* ,*z* axes and, 30-180 degrees for the rotation of the whole ligand around the *x*, *y*, *z* axes, respectively.



a b

Figure 3.

Minimum energy conformations of pro-*S* (a) and pro-*R* (b) complexes are depicted on Fig. 3. It is interesting to note, that the planar structure of the anion was distorted during the complexation with the potassium ion in both cases. The steric energy of the pro-*S* complex was found to be lower by 5.2 kJ/mol than that of the pro-*R* ion-pair. The enantioselectivity of 78% calculated from this energy difference is in good agreement with the corresponding experimental value (76.4%).

Comparing our result to previously reported values obtained by simple geometry optimisation clearly demonstrates, that exploring the conformational space of the complexes is a condition for quantitative prediction of selectivity. The accuracy of our method allows design of new and hopefully more selective chiral crown ethers for the catalysis of asymmetric Michael addition. Considering the fact, that the method suggested by Brunet et al. predicts the correct side of attack, it should be useful for preliminary qualitative analysis.

Deracemization

More important consequences were drawn from the observation that the ee values were dependent on time. It can be seen from Table 1. the reaction is very fast even at -78°C, as after one minute of reaction time 82.3% of the starting material (of the acrylate) has been converted into product, ee of which is as high as 85% (entry 14, Table 1). After 8 min time the reaction is completed, but at the same time the ee slightly decreased to ee 80%. After 16 min the ee value is 76 % (entry 15, Table 1).We also observed that the rate of the ee-decrease is somewhat retarded by the methyl phenylacetate excess because in its absence the ee value goes down more quickly to ee 40% (after 8 min reaction time) and - which is very important - the ee stabilises around this value further on with time (Table 2).

Table 2. Deracemization experiments with (±)-**3** (1.49 mmol) by KOtBu (0.39 mmol) and crown ether catalyst **4** (0.073 mmol), at -78°C, 8 min., in toluene

Entry	Catalyst	R^1=R^2	Notes	ee for S (%)
1	**4k**	O-hexyl	-	36.0
2	**4k**	O-hexyl	1.0 mmol of KOtBu	28.3
3	**4k**	O-hexyl	20°C	18.5
4	**4k**	O-hexyl	THF	23.2
5	**4k**	O-hexyl	(+)-**3**(ee 75% for S)	33.2
6	**4j**	O-Bu	-	39.9
7	**4j**	O-Bu	(+)-**3**(ee 75% for S)	40.5
8	**4j**	O-Bu	0.37 mmol of **1** also added	5.1

From these facts one can deduce that the ee values in Michael reaction are determined and shaped by two factors; the kinetically controlled result of the asymmetric C-C bond formation is continuously modified by another process; a deprotonation of the endproduct by the crown potassium base complex and reprotonation of the anion formed. Fig. 4. shows a possible arrangement of the anion before its protonation to give *S*-**3** and *R*-**3**.

It follows that the highest ee values are obtained at the very beginning of the reaction, which worsens with time so taking the conversion into account there is an optimum time for getting good yields still with highest possible ee. This seems to be true for all similar reactions in which the newly formed asymmetric carbon still has a C-H acidic proton.

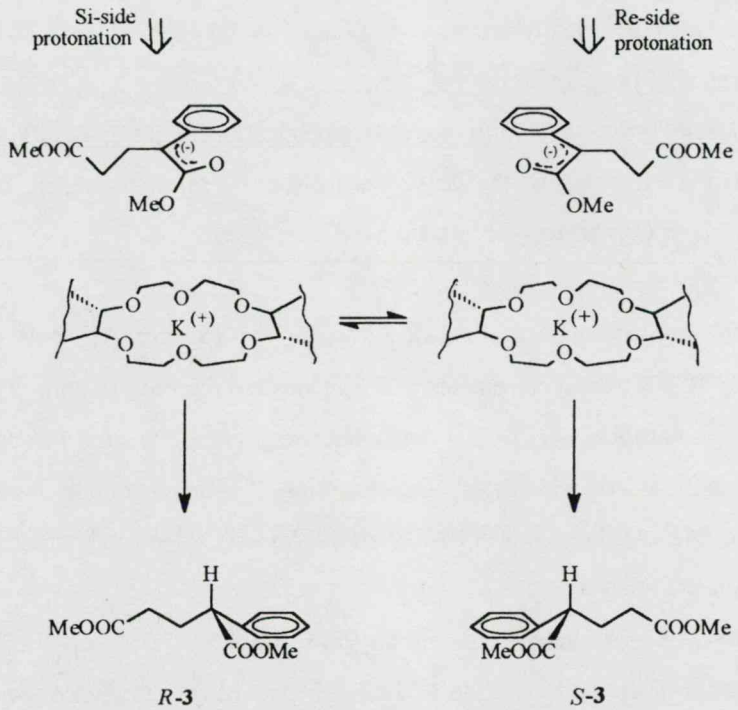


Figure 4.

On the other hand, the position of the deprotonation-protonation process in the presence of our chiral catalyst is around 40% for S so one can hope that placing the product-racemate into a mixture imitating the asymmetric Michael reaction conditions (of course the two reagents should be omitted) a so called deracemization occurs. And really it has been found that the (±)-**3** treated in this way quickly showed optical activity, the measure of which was increasing with time and after 8 minutes at -78°C its value corresponds to a product with almost 40% ee for *S* (entry 6, in Table 2). A similar tendency can be seen in the case of using tetra-O-hexyl-derivative **4k** (33-36% ee value, entry 1,5 in Table 2.).

Making the desired antipode from a racemate by deracemization is very attractive, modern route as one can get the racemate in a separate reaction using the best and cheapest synthetic method and subsequently, in a process called deracemization, both antipodes of the racemate (not only 50% of it) can be converted into the desired antipode, theoretically in 100% yield. The method has been reviewed excellently just recently [6b,c].

Good deracemization procedures have been published for CH-acids by Vedejs's,[4a,b] Hünig's,[5a-c]

Fehr's,[6a,b] Krause's[7] and Trost's[8] groups using one equvivalent of a chiral proton source for the enantioselective protonation of the enolates under kinetically controlled conditions. Successful deracemization experiments by catalytic enantioselective protonation of enolates are known from the literature and have been reviewed by Fehr.[6b]

For the explanation of our catalytic method we suppose that KOtBu; being practically insoluble in toluene at -78°C, goes into solution by a complex formation with the crown ether **4** and as a consequence, both the deprotonation of **3** and subsequently the reprotonation of the enolate from **3** (by t-BuOH or **3**) can proceed exclusively in the presence of the chiral crown **4**.

Further work is in progress on this novel deracemization to make it more useful for preparative purposes. We will also try to improve the ee values in Michael reactions and in other C-C bond forming reactions catalysed by chiral crown ether-potassium base complexes.

Experimental

Optical reactions are measured on a Perkin Elmer 241 polarimeter. ^{1}H-NMR spectra were recorded in $CDCl_3$ at 100 MHz JEOL FX 100 spectrometer. All δ values are reported in ppm, TMS was used as internal standard. Thin layer chromatography (TLC) is perfomed using silicagel coated plastic sheets (Merck silicagel 60 F_{254}) and UV and / or iodine reagent for detection. Chromatographic purification refers to flash chromatography using Merck silicagel 60 (70-230 mesh ASTM). Elemental analysis were performed on a Perkin Elmer 240 automatic analyzer.

Bis(methyl-2,3-dideoxy-4,6-di-O-hexyl-α-D-glucopyranosido[2,3-b][2',3'-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (4k). To a solution of 1g (1.9mmol) of the tetrahydroxy-compund **4a** in 7ml THF was added 14.8ml (105 mmol) hexyl bromide, 7.5ml 50% NaOH and 0.061g (0.19mmol) tetrabutylammonium bromide PT catalyst. This mixture was stirred at 40°C for 100 h. The water layer was extracted with dichloromethane (3x25ml), dried (Na_2SO_4), filtered off and concentrated *in vacuo*, to give 0.75g (45.8%) of **4k** as a yellow oil. $[\alpha]_D^{20}$ +47.3 (c=1, $CHCl_3$). ^{1}H-NMR δ: 4.77 (d, 2H, J=3.4Hz, 2x anomeric H), 3.73-3.46 (m, 28H, OCH_2 CH_2O, CH, other CH_2), 3.37 (s, 6H, 2xOMe), 1.81-1.10 (m, 40H, 20xCH_2), 0.86 (t, 12H, 4xCH_3) Anal. calcd. for $C_{46}H_{88}O_{14}$ (864), C 63.9, H 10.18, found C 64.00, H 10.15.

Bis(methyl-2,3-dideoxy-4,6-di-O-octyl-α-D-glucopyranosido[2,3-b][2',3'-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (4l). Terahydroxy compund **4a**: 2.0g (3.8mmol) in 15 ml THF octyl bromide: 40 ml (100mmol), 50% NaOH solution 15ml. The reaction procedure was performed in the same manner just like the previous one, **4l** was obtained as a thick oil. Yield: 2.75g (77.1%). $[\alpha]_D^{20}$ + 19.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR δ: 4.77 (d, 2H, J=3.5Hz, 2x anomeric H), 3.73-3.46 (m, 28H, OCH_2 CH_2O, CH, other CH_2), 3.37 (s, 6H, 2xOMe), 1.81-1.10 (m, 56H, 28xCH_2), 0.86 (t, 12H, 4xCH_3) Anal. calcd. for $C_{54}H_{104}O_{14}$ (976.1), C 66.42, H 10.65, found C 66.51, H 10.39.

Michael addition reactions. Methyl phenylacetate (1.49mmol) in dry toluene (1.0ml) was added to a

suspension of potassium tert-butoxide (0.93mmol) in toluene (1.0ml) under argon and the mixture was stirred for 15 minutes at -78°C. A solution of the crown-compound (0.073mmol) in toluene (1.5ml) was then added and the mixture stirred for another 15 minutes. A solution of methyl acrylate (1.14mmol) in toluene (1.0ml) was added and the mixture was stirred for 8 minutes, then was poured into saturated aq. NH_4Cl (10ml), extracted with toluene (3x10ml) and the combined extacts were dried. The residue obtained after removal of the solvent was subjected to silica gel column chromatography and was eluted with hexan-EtOAc 6:1 to yield the product. The ee was monitored by measuring the optical rotation of the product ester (**3**) and comparing that to the literature value.

Calculations. All computations were run on a SGI Indy R4400 workstation. Molecular mechanics calculations as well as conformational analyses were performed by the MacroModel 5.0 program package. The standard AMBER* force field was applied in all cases. Electrostatic energies were calculated using the built-in electrostatic energy equation with distance dependent dielectric constant. Due to the pure electrostatic interactions between the crown ether and the potassium ion, cut-off distances were set to 8 Å for van der Waals and 20 Å for electrostatic interactions. Atomic charges of the **4i**-potassium complex as well as the phenylacetic acid anion were obtained by ZINDO1[20] semiempirical calculations for the corresponding preoptimised geometry.

Conformational analyses were performed using the SUMM and MCMM/MOLS algorithm in 1000 steps. The final resolution of 30 deg with an energy window of 50 kJ/mol was used in SUMM calculation. Maximal and minimal ring closure distances were set to 3.5 Å and 0.5 Å respectively. Maximal translations and rotations were set to 0.5 Å and 30 deg, respectively in MCMM/MOLS calculations. Structure comparisons were based on the positions of nonhydrogen atoms in each case. Molecular mechanics energies were minimised using the Polaak-Ribiere conjugate gradient method with the convergence criterion set to 0.01 kJ/Å mol.

Deracemization experiments. A suspension of potassium-tert-butoxide (0.043g, 0.39mmol) in toluene (1.0ml) was added to a solution of racemic 2-phenyl-glutaric dimethyl ester (0.3g, 1.49mmol) in toluene (1.0ml). This mixture was stirred for 15 minutes at -78°C. A solution of the crown catalyst (0.073mmol) in toluene (1.5ml) was added and stirred for 8 minutes, then the mixture was poured into saturated aq. NH_4Cl (15ml), extracted with toluene (3x15ml) and the combined extacts were dried. After standard work-up and column chromatography the enantiomer mixture was obtained. The ee% was monitored by measuring the optical rotation of the deracemized product.

Acknowledgement. This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T 015677 and F 019261). We are grateful to Csaba Szántay, jr. (Central Sructure Research Laboratory, Chemical Works of Gedeon Richter Pharmaceutical Ltd.) for taking ^{1}H-NMR-spectra.

References

1. (a) Morrison, J.D.Ed, *Asymmetric Synthesis*, 5, Academic Press Inc. Ltd., 24-28 Oval Road, London NW1 7DX, 1985. (b) O'Donnell, M.J. *Catalytic Asymmetric Synthesis: Asymmetric Phase Transfer Reactions;* Ojima, I. Ed.: VCH-Publishers, New York, 8., pp 389-411, 1993.
2. (a) Cram, D.J.; Sogah, G.D.Y. *J. Chem. Soc. Chem. Commun.* **1981**, 625. (b) Alonso-Lopez, M.; Jimenez-Barbero, J.; Marin-Lomas, M.; Penadés, S. *Tetrahedron* **1988**, *44*, 1535. (c) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Letters* **1989**, *30*, 7229; *Heterocyicles* **1992**, *33*, 493. (d) Maarschalkerwart, D.A.H.; Willard, N.P.;Pandit, U.K. *Tetrahedron* **1992**, *48*, 8825. *Acta Chim. Hung. Models in Chemistry* **1992**, *129*, 843. (e) Demlow, E.V.; Knufinke, V. *Liebigs Ann. Chem.* **1992**, 283. (f) Loupy, A.; Zaparucha, A. *Tetrahedron* **1993**, *34*, 473. (g) Kumamato, T.; Aoki, S.; Nakajima, M.; Koga, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1431. (h) Brunet, E.; Poveda, A.M.; Rabasco, D.; Oreja, E.; Font, L.M.; Batra, M.S.; Rodriges-Ubis, J.C. *Tetrahedron: Asymmetry* **1994**, *5*, 935. (i) Kanakamma, P.P.; Mani, N.S.; Maitra, U.; Nair, V. *J. Chem. Soc., Perkin Trans.1* **1995**, 2339. (j) Töke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* **1995**, *36*, 5951. (k) MacroModel 5.0, Columbia University, New York 10027 USA. (l) Still, W.C.; Galynker, I. *Tetrahedron* **1981**, 37, 3981. (m) Goodman, J.M.; Still, W.C. *J. Comput. Chem.* **1991**, 12, 1110. (n) Kolossváry, I.; Guida, W.C. *J. Mol. Struct.* THEOCHEM **1994**, 91, 308. (o) Edwards, W.D.; Zerner,M. *Theor. Chim. Acta.* **1987**, 72, 347.
3. (a) Töke, L.; Fenichel, L.; Bakó, P.; Szeitli, J. *Acta. Chim. Acad. Sci. Hung.* **1978**, *98*, 357. Bakó, P.; Fenichel, L.; Töke, L.; Czugler, M. *Liebigs Ann. Chem.* **1981**, 1163. (b) Czugler, M.; Bakó, P.; Fenichel, L.; Töke, L. *Cristal Structure Commun.* **1981**, 511. (c) Bakó, P.; Fenichel, L.; Töke, L. *Acta. Chim. Hung.* **1982**, *111*, 297. (d) Bakó, P.; Fenichel, L.; Töke, L. *Acta. Chim. Hung.* **1984**, *116*. 323. (e) Bakó, P.; Fenichel, L.; Töke, L.; Tóth, G. *Carbohydrate Res.* **1986**, *147*, 31. (f) Bakó, P.; Fenichel, L.; Töke, L.; Davison, B.E. *J. Chem. Soc. Perkin Trans.1* **1990**, 1235. (g) Bakó, P.; Fenichel, L.; Töke, L. *Liebigs Ann. Chem.* **1990**, 1161. (h) Bakó, P.; Fenichel, L.; Töke, L. *J. Incl. Phenom.* **1993**, *16*, 17. (i) Bakó, P.; Fenichel, L.; Töke, L.; Davison, B.E.; Patel, A. *Heteroatom Chem.* **1994**, *5*, 415.
4. (a) Vedejs, E.; Lee, N.; Skata, T. *J. Am. Chem. Soc.* **1994**, *116*, 2175. (b) Vedejs, E.; Garcia-Rivas, J.A. *J. Org. Chem.* **1994**, *59*, 6517.
5. (a) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, V. *Chem. Ber.* **1993**, *126*, 1205. (b) Hünig, S.; Klaunzer, N.; Winner, H. *Chem. Ber.* **1994**, *127*, 165. (c) Gerlach, U.; Haubenreich, T.; Hünig, S. *Chem. Ber.* **1994**, *127*, 1269. (d) Gerlach, U.; Haubenreich, T.; Hünig, S. *Chem. Ber.* **1994**, *127*, 1281. (e) Gerlach, U.; Haubenreich, T.; Hünig, S. *Chem. Ber.* **1994**, *127*, 1289.
6. (a) Fehr, C.; Galindo, J. *Angew. Chem.* **1994**, *106*, 1967. (b) Fehr,C. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2566. (c) Stecher, H.; Faber, K. Synthesis **1997**, 1
7. Krause, N. *Angew. Chem.* **1994**, *106*. 1845.
8. Trost, B.M.;Organ, M.G. *J. Am. Chem. Soc.* **1994**, *116*. 1032

Synthesis and application in asymmetric synthesis of azacrown ethers derived from D-glucose

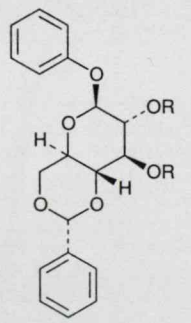
Péter Bakó,[a]† Kristóf Vizvárdi,[a] Zoltán Bajor[a] and László Tőke*[b]

[a] *Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, Hungary*
[b] *Organic Chemical Technology Research Group of the Hungarian Acadamy of Sciences at the Technical University of Budapest, H-1521 Budapest, Hungary*

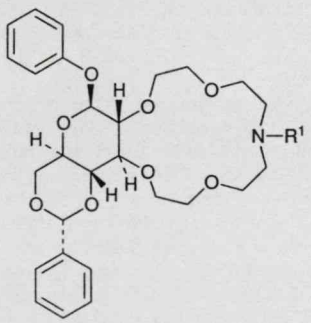
New chiral monoaza-15-crown-5 derivatives and lariat ethers anellated to phenyl β-D-glucoside have been synthesized which show significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone (84% ee) and in the Darzens condensation of phenacyl chloride with benzaldehyde (74% ee).

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral crown ether catalysts. Although many optically active crown ethers have been prepared, only a few have been used successfully as catalysts in asymmetric reactions.[1] Previously, we reported the asymmetric Michael addition of phenyl acetate to acrylate catalyzed by chiral crown ethers composed of two glucose units (85% ee).[1,2] The substituents on the sugar unit of the macrocycle[1,2] and the side arms at the nitrogen atom in the crown ring[3] play an important role in the catalytic activity of the crown ethers. The latter compounds with heteroatoms in the side arm, named lariat ethers or armed crown ethers, are known to display special complexation, high lipophilic character and unique guest specificity *via* macroring–side arm cooperativity.[4] It is therefore reasonable to study the effect of using different pendant arms on the chiral crown ether catalyst in asymmetric reactions.

We now report on the synthesis and application of new monoaza-15-crown-5 compounds **4–12**.



1 R = H
2 R = $(CH_2)_2O(CH_2)_2Cl$
3 R = $(CH_2)_2O(CH_2)_2I$



4 R^1 = Bu
5 R^1 = Pr^i_2CH
6 R^1 = C_6H_{11}
7 R^1 = $C_6H_{11}CH_2$
8 R^1 = Bn
9 R^1 = $Ph(CH_2)_2$
10 R^1 = $HO(CH_2)_2$
11 R^1 = $MeO(CH_2)_2$
12 R^1 = $HO(CH_2)_3$

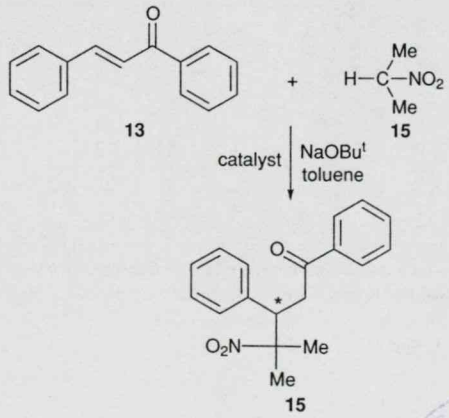
Their synthesis starts from phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside **1**. The vicinal free hydroxy groups in compound **1** were alkylated using the method of Di Cesare and Gross,[5] with bis(2-chloroethyl) ether acting as solvent and reagent, under liquid–liquid (LL) two-phase reaction conditions, in the presence of tetrabutylammonium hydrogen sulfate (as a phase transfer catalyst) and 50% aq. NaOH to give compound **2** (room temperature, 8 h, column chromatography). The exchange of chlorine for iodine in **2** was carried out using NaI in acetone (reflux, 24 h), resulting in the bis(iodide) derivative **3**. Compound **3** was cyclized with various primary amines: *n*-butylamine, 2,4-dimethylpentan-3-ylamine, cyclohexylamine, cyclohexylmethylamine, benzylamine, 2-phenylethylamine, ethanolamine, 2-methoxyethylamine and propanolamine, respectively, according to the method described previously,[6] which requires dry Na_2CO_3 in MeCN as solvent (reflux, 32–40 h, column chromatography). We thus obtained the corresponding 15-membered macrocycles **4–12**, the yields of the ring closure steps after chromatography being in the range 32–54% (Table 1). All structures were ascertained by ^1H NMR, ^{13}C NMR, COSY, mass and elemental analysis.‡

Table 1 Yield and characterisation data of compounds **2–12**

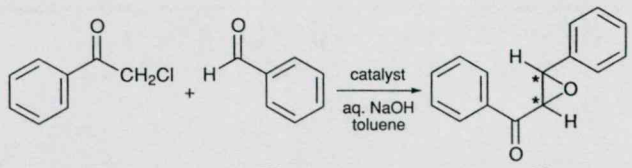
Compound	Yield (%)[a]	$[\alpha]^{20}$ (*c* 1, $CHCl_3$)	Mp/°C
2	29	−35.5	74–75
3	95	−28.6	58–59
4	44	−43.0	105–106
5	32	−35.4	58–60
6	39	−39.2	oil
7	32	−41.1	107–108
8	42	−34.9	oil
9	48	−44.3	153–55
10	48	−35.2	oil
11	54	−40.1	oil
12	45	−44.9	oil

[a] After column chromatography.

Compounds **4–12** were then used as phase transfer catalysts in different reactions in which enantiomeric mixtures can be formed. These catalysts proved to be effective in two reactions: the Michael addition of 2-nitropropane to chalcone (Scheme 1),



Scheme 1



16 17 18

Scheme 2

and the Darzens condensation of phenacyl chloride with benzaldehyde (Scheme 2).

The Michael addition was carried out in a solid–liquid (SL) system; in toluene, employing solid NaOBu^t as base (35 mol%) and chiral catalyst (7 mol%) at room temperature.§ After the usual work-up procedure the adduct was isolated by preparative TLC, and the asymmetric induction, expressed in terms of the enantiomeric excess (ee), was monitored by measuring the optical rotation of the product **15** and comparing it with literature values[3] and by ^{1}H NMR analysis using (+)-Eu(hfc)$_3$ as a chiral shift reagent. The results are shown in Table 2.

As can be seen, the substituents at the N-atom of the catalyst have a significant influence on both the chemical yield and the enentioselectivity. In all cases the (*S*)-(+)-adducts **15** were found to be in excess. The catalyst having the bulky 2,4-dimethylpentan-3-yl group at the N-atom gave the lowest chemical yield and chiral induction (entry 2), and the crown ether having a phenylethyl group (**9**) proved to be the best (entry 6). The methyl ether **11** showed a higher ee value than its free hydroxy analogue **10** (entry 8 and 7). The length of the side arm is decisive: catalyst **8** having a benzyl group shows poor chiral induction (6% ee), while compound **9** containing a phenylethyl group gives high enantioselectivity (84% ee).

The Darzens condensation (Scheme 2) was performed in a binary LL system, using a toluene–30% aq. NaOH (5:1) mixture.¶ The work-up procedure and determination of ee was carried out in a similar manner to that mentioned for the Michael addition. In all cases the epoxy ketone product **18** with a negative optical rotation was found to be in excess, which on the basis of the optical rotation of the pure enantiomer, corresponds to an absolute configuration of (2*R*,3*S*).[7] Low enantioselectivities were obtained using catalysts **4–8** (entries 1–5). The macrocycle **10** [R = $(CH_2)_2OH$] having the hydrophilic hydroxyethyl group at the N-atom gave 52% ee (entry 7) but this value was dramatically reduced (13% ee) for its methyl ether **11** (entry 8). It is interesting to note that the effect of the compound containing a free hydroxy group on the magnitude of the enantioselectivity for the Darzens condensation is the reverse of that for the Michael reactions (entries 7 and 8). The importance of the chain-length at the N-atom in the catalytic activity is reflected particularly in the experiment shown in entry 9: catalyst **12** [R = $(CH_2)_3OH$] proved to be the most effective, resulting in 74% ee at room temperature. With regard to the effectiveness of the crown ether structure for enantiomeric induction, we suppose that the substituent at the nitrogen atom of the catalyst takes part in the complexation of the salt of the anion by complexation of the cation in the third dimension, working as a pseudo-lariat ether, and as a consequence increases the effectiveness of the phase transfer process. Reactions running in the absence of chiral catalyst give only racemic products.

Table 2 Effect of chiral crown catalysts **4–12** on the asymmetric Michael addition and Darzens condensation

		Michael addition		Darzens condensation	
Entry	Catalyst	Yield (%)[a]	Ee (%)[b]	Yield (%)	Ee (%)[b]
1	**4**	61	27	92	4
2	**5**	15	4	33	3
3	**6**	50	23	94	4
4	**7**	53	24	70	8
5	**8**	56	6	88	4
6	**9**	78	82 (84)[c]	72	30
7	**10**	71	45	86	52 (53)[c]
8	**11**	65	60	72	13
9	**12**	42	6	68	74

[a] Based on isolation by preparative TLC. [b] Determined by optical rotation. [c] Determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ as chiral shift reagent.

The authors gratefully acknowledge Professor Dr Suzanne Toppet for NMR spectroscopic identification of the compounds, Dr Erik Van der Eycken and Professor Dr Georges J. Hoornaert for useful discussions (Laboratorium voor Organische Synthese, K. U. Leuven). This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T015677) and the Soros Foundation.

Notes and References

† E-mail: p-bako@chem.bme.hu

‡ *Selected data* for **2**: δ_H(250 MHz, $CDCl_3$, $SiMe_4$) 7.50–7.06 (m, 10 H, ArH), 5.56 (s, 1 H, Benzylidene-CH), 5.06 (d, *J* 7.6, 1 H, anomer-H), 4.36 (dd, *J* 10.5, 4.3, 1 H, H-6), 4.09–3.53 (m, 21 H, 8 CH_2O, 5 CH). For **3**: 7.50–7.05 (m, 10 H, ArH), 5.56 (s, 1 H, benzylidene-CH), 5.06 (d, *J* 7.6, 1 H, anomer-H), 4.38–4.36 (dd, *J* 10.5, 4.3, 1 H, H-6), 4.02–3.52 (m, 18 H, 8 CH_2O, 2 CH), 3.21–3.18 (m, 3 H, H-2, H-3, H-5). For **9**: 7.37–7.02 (m, 15 H, ArH), 5.54 (s, 1 H, benzylidene-CH), 5.06 (d, *J* 7.6, 1 H, anomer-H), 4.36 (dd, *J* 10.5, 4.3, 1 H, H-6), 4.10–3.57 (m, 15 H, 6 CH_2O and 3 CH), 3.54–3.47 (m, 2 H, H-2, H-5), 2.89–2.76 (m, 8 H, 3 NCH_2, CH_2Ph).

§ The Michael addition was performed as follows: 1.44 mmol of chalcone and 3.36 mmol of 2-nitropropane were dissolved in 3 ml of anhydrous toluene, and then 0.1 mmol of crown ether and 0.5 mmol of base were added. The mixture was stirred under an Ar atmosphere. After completing the reaction (8–40 h) a mixture of 7 ml of toluene and 10 ml of water was added. The organic phase was processed in the usual manner. The product was purified on silica gel by preparative TLC with hexane–ethyl acetate (10:1) as eluent; mp 146–148 °C, $[\alpha]_D^{20}$ + 68 (*c* 1, CH_2Cl_2) (84% ee) (lit.,[3] +80.8, for pure enantiomer), δ_H 7.85 (m, 2 H, Ph), 7.52 (m, 3 H, Ph), 7.25 (m, 5 H, Ph), 4.18–3.25 (m, 3 H, CH_2, CH), 1.62 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3).

¶ Typical experimental procedure for the asymmetric Darzens condensation: a toluene solution of 1.3 mmol of phenacyl chloride (3 ml) was treated with 1.9 mmol of benzaldehyde and 0.1 mmol of catalyst in 0.6 ml of 30% NaOH solution. The mixture was stirred under Ar atmosphere. After completing the reaction 7 ml of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed on preparative silica gel of 2 mm thickness (Kieselgel 60 GF_{254}), using CH_2Cl_2 as eluent; $(\alpha)_{578}^{20}$ −111 (*c* 1, CH_2Cl_2) (52% ee) (lit.,[7] −214, for pure enantiomer); δ_H 8.01 (m, 2 H, Ph), 7.60 (t, 1 H, Ph), 7.48 (t, 2 H, Ph), 7.40–7.30 (m, 5 H, Ph), 4.29 (d, *J* 2, 1 H), 4.08 (d, *J*, 1 H).

1 L. Tõke, P. Bakó, Gy. M. Keserû, M. Albert and L. Fenichel, *Tetrahedron*, 1998, **54**, 213 and references cited therein.
2 L. Tõke, L. Fenichel and M. Albert, *Tetrahedron Lett.*, 1995, **36**, 5951.
3 P. Bakó, Á. Szöllõsy, P. Bombicz and L. Tõke, *Heteroatom Chem.*, 1997, **8**, 333.
4 G. W. Gokel, *Chem. Soc. Rev.*, 1992, **21**, 39.
5 P. Di Cesare and B. Gross, *Synth. Commun.*, 1979, 4581.
6 P. Bakó and L. Tõke, *J. Inclusion Phenom.*, 1995, **23**, 195.
7 B. Marsman and H. Wynberg, *J. Org. Chem.*, 1979, **44**, 2312.

Received in Liverpool, UK, 16th March 1998; 8/02098A

B12

Pergamon

Tetrahedron 54 (1998) 14975–14988

TETRAHEDRON

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

Péter Bakó [a], Kristóf Vízvárdi [a,b], Suzanne Toppet [b], Erik Van der Eycken [b], Georges J. Hoornaert [b] and László Tőke [c]*

[a] Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P.O. Box 91, Hungary

[b] Laboratorium voor Organische Synthese, Department of Chemistry, K. U. Leuven, Celestijnenlaan 200F, B-3001 Heverlee, Belgium

[c] Organic Chemical Technology Research Group of the Hungarian Academy of Sciences at the Technical University of Budapest, H-1521 Budapest, P.O. Box 91, Hungary

Received 6 August 1998; revised 21 September 1998; accepted 8 October 1998

Abstract: A number of new chiral monoaza-15-crown-5 derivatives (**4-9**) and lariat ethers (**10-15**) anellated to phenyl-β-D-glucopyranoside have been synthesized. Their extracting ability was measured with alkali metal (Li, Na, K) and ammonium cations. The derivatives show significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone (82% ee) although in low yield, and in the Darzens condensation of phenacyl chloride with benzaldehyde (74% ee). The substituent at the nitrogen atom of the crown ethers has a major influence on both the extraction ability and the enantioselectivity. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

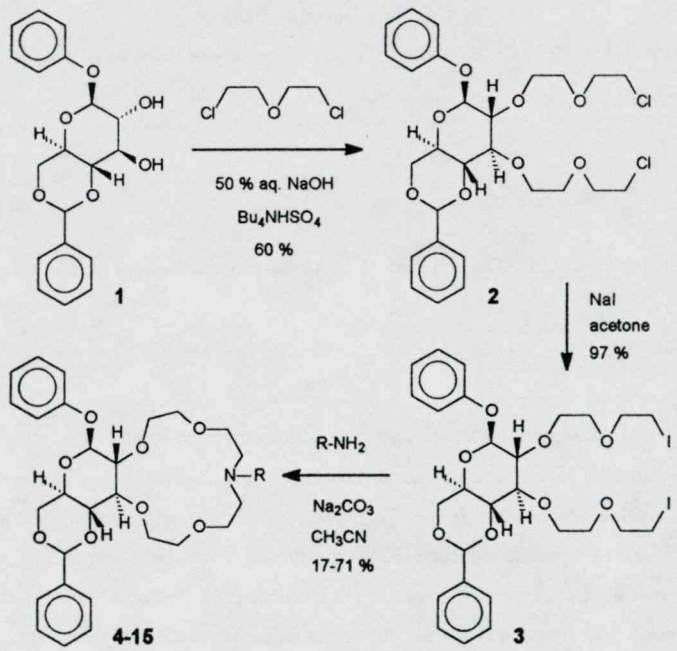
One of the most attractive types of catalytic asymmetric synthesis is enantioselective induction using chiral crown ethers. Although many optically active crown ethers have been synthesized, only a few have successfully been applied as catalysts in asymmetric reactions;[1] the collection of further information is still required to obtain a better understanding of the effect of the structure of the chiral catalyst in these processes. The chiral nature of the crown ether, the rigidity of the micro-environment of its cavity and the quality of the side arm are all expected to play an important role. Azacrown ethers with a side arm attached to the nitrogen atom in the macrocyclic ring may enhance and regulate the cation binding properties as well as the lipophilicity. Lariat (lasso) ethers or armed crown ethers having heteroatom containing podand arms are known to have highly lipophilic character and a unique guest specifity via macro-ring-side arm cooperativity.[2]

0040-4020/98/$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(98)00938-7

We have previously reported the synthesis and extracting ability of 15-membered ring monoaza-crown ethers and lariat ethers derived from methyl-α-D-glucopyranoside and methyl-α-D-galactopyranoside respectively.[3] These coronands have proved to be successful catalysts for an asymmetric Michael addition reaction and a Darzens condensation.[4,5] We have found that both the chemical yield and the optical purity depend on the substituent at the nitrogen atom, and the substituents of the sugar unit.

As part of a programme directed at the study of similar catalysts, we have prepared some new chiral monoaza-crown ethers and lariat ethers derived from phenyl-β-D-glucopyranoside. They possess differently structured pendant (**4-9**) or functionalized podand arms (lariat ethers **10-15**). The effects of these side arms on the extraction ability (complexing properties) and the catalysis in two chiral C-C bond forming reactions have been examined.

RESULTS AND DISCUSSION



Scheme 1

The starting protected monosaccharide, phenyl-4,6-O-benzylidene-β-D-glucopyranoside (**1**) was prepared in four steps according to the literature procedure.[7] The vicinal free hydroxy groups in compound **1** were alkylated by the method of Gross *et al.*[8] with bis(2-chloroethyl)ether as reagent and solvent. The liquid-liquid two-phase reaction using tetrabutylammonium hydrogen sulfate as phase transfer catalyst and 50% aqueous sodium hydroxide solution gave rise to the bis-chloro podand **2** (r.t., 8 h).

Exchange of the chlorines in **2** by iodines was carried out using sodium iodide in acetone (reflux, 48 h) yielding the bis-iodo derivative **3**. Compound **3** was cyclized with various primary amines: *n*-butylamine, *n*-hexylamine, 2,4-dimethyl-3-pentanamine, cyclohexylmethylamine, benzylamine, 2-phenylethylamine,

2-(2-methoxyphenyl)ethylamine, 2-(4-methoxyphenyl)ethylamine, 2-hydroxyethylamine, 2-methoxyethylamine, 3-hydroxypropylamine and 3-methoxypropylamine according to the method described previously.[3] The method requires dry Na_2CO_3 in acetonitrile as solvent (reflux, 24-48 h). In dilute solutions (1-3%) polycondensation side reactions are suppressed and the desired intramolecular cyclization reaction takes place preferably. In this way we obtained the corresponding 15-membered monoaza-crown ethers **4-15** in relatively high yields starting from **3** and the corresponding primary amine. The yields of the ring closure product, after purification by chromatography, vary from 17-71 %.

Extracting Properties

The phase transfer properties (in a liquid-liquid system) of the newly synthesized crown ethers were characterized by the extraction of picrate salts (lithium, sodium, potassium and ammonium picrate) from water into dichloromethane following the procedure described by Kimura *et al.*[9] The concentration of the picrates in water was measured by UV spectroscopy. The results are summarized in Table 1.

Table 1. Extraction of alkali metal and ammonium picrates with crown ethers

Compound	R	Extractability (%)[a]			
		Li^+	Na^+	K^+	NH_4^+
4	$CH_3(CH_2)_3$	60	63	59	76
5	$CH_3(CH_2)_5$	67	68	62	74
6	$(CH_3)_2(CH)_3(CH_3)_2$	15	47	49	56
7	$C_6H_{11}CH_2$	17	38	41	55
8	$C_6H_5CH_2$	13	24	24	33
9	$C_6H_5CH_2CH_2$	42	69	54	72
10	*o*-CH_3O-C_6H_4-CH_2CH_2	19	33	31	51
11	*p*-CH_3O-C_6H_4-CH_2CH_2	13	27	26	41
12	$HOCH_2CH_2$	14	41	39	47
13	$CH_3OCH_2CH_2$	44	72	71	76
14	$HOCH_2CH_2CH_2$	11	26	28	44
15	$CH_3OCH_2CH_2CH_2$	25	39	40	53

[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%.

The data collected in Table 1 show the transferred salt amount as a percentage of the initial salt concentration (extractability %). A higher value indicates a better phase transfer capability of the crown. The strongest complexes are formed with ammonium ion presumably due to the different and stronger coronate complexation (by three H-bonds via three-point interaction) whereas alkali metal cations only have metal-oxygen coordination interaction. Not withstanding the tighter cavity of 15-crown-5, the coronands form complexes of the same strength with Na^+ and K^+, probably due to the formation of 2:1 sandwich type complexes, with exception made for compound **9** which has a phenethyl group as side arm.

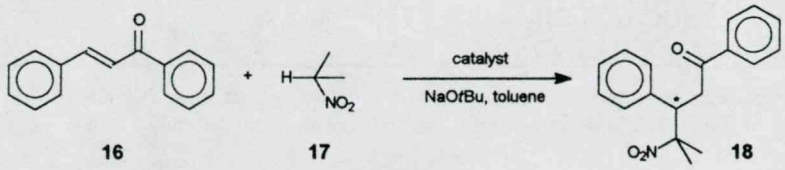
Of the crowns **4-9** lacking heteroatoms in the arm, the best extracting ability is displayed by **4** and **5**, probably because of the increased lipophilicity due to their butyl and hexyl side arms. The multi-branched arm (**6**) and the presence of the cyclohexylmethyl group (**7**) provide a weaker complexation because of steric hindrance. Benzyl substitution (**8**) lowers the extractability but the importance of the chain length of the side arm is shown by comparing **8** and **9** with the phenethyl arm extracting two, or in some cases three, times more ions. If the aromatic ring of the phenethyl arm is *ortho* or *para* substituted by a methoxy group (**9, 10, 11**) the extracting capability decreases significantly. This is presumably due to electronic and/or steric effects of the methoxy substituents in the interaction between the macrocyclic ring, the enfolding side arm and the cation.

Of the examined lariat ethers **12-15** compounds **12** and **14** having terminal hydroxy groups on the side arms show moderate extracting ability. The hydrophilic hydroxyl functions associated with water molecules possibly prevent the enfolding arm from participating in the complex formation. Indeed, the extracting ability increases significantly on methylation (**13, 15**) of the hydroxy groups. The highest extraction value is displayed by coronand **13** carrying a 'methoxyethyl-lasso'; This compound has the best arm length and a flexible hydrocarbon spacer between the nitrogen atom and the effective function at the terminal.

We can conclude that the phase transfer character of the newly synthesized crown ethers (**4-15**) strongly depends on the substituent at the nitrogen atom; a heteroatom-containing terminal group attached by two carbon atom appears to be ideal (**13**). Compound **9** also proved to be a good phase transfer agent but this is probably due to π-π interactions between the aromatic systems of the phenylethyl group and the picrate.

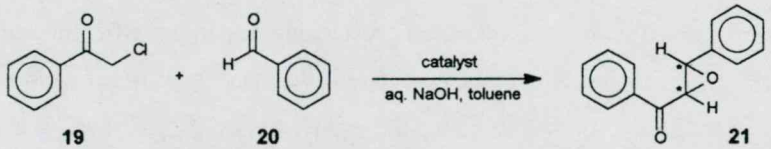
Asymmetric Induction

Compounds **4-15** were then used as chiral phase transfer catalysts. These catalysts proved to be effective in two reactions: the Michael addition of 2-nitropropane (**17**) to chalcone (**16**) (Scheme 2), and the Darzens condensation of phenacyl chloride (**19**) with benzaldehyde (**20**) (Scheme 3).



16 **17** **18**

Scheme 2



19 **20** **21**

Scheme 3

The Michael addition 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

(**18**) was isolated by preparative TLC or column chromatography; the asymmetric induction, expressed in terms of the enantiomeric excess (e.e.), was monitored by measuring the optical rotation of the product **18** and comparing it with literature data for the preferred pure enantiomer and by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent. The results given in Table 2 show that the (+)-(S)-adduct **18** is always in excess and moreover that the substituent on the nitrogen atom of the catalyst has a significant influence on both the chemical yield and the asymmetric induction.

Table 2. Results of the Michael addition of 2-nitropropane to chalcone and Darzens condensation of phenacyl chloride with benzaldehyde

Entry	Catalyst	Michael addition [a]		Darzens condensation [e]	
		Yield (%)	e.e. (%) [b]	Yield (%)	e.e. (%) [b]
1	**4**	19 [c]	27	92	4
2	**5**	6	23	94	5
3	**6**	2 [d]	2	40	2
4	**7**	10	24	70	8
5	**8**	16	6	88	12
6	**9**	18	82 (80 [f])	72	30
7	**10**	61	15	65	13
8	**11**	50	25	67	33
9	**12**	12 [c]	45	87	53
10	**13**	15	66 (61 [f])	72	13
11	**14**	12	6	68	74
12	**15**	18	48 (46 [f])	75	7

[a] Reaction time 45 h; [b] Determined by optical rotation; [c] Reaction time 8 h, [d] Reaction time 90 h; [e] Reaction time 2 h; [f] Determined by ^{1}H NMR spectroscopy.

Apparently, crown ethers **4-15** are weak catalysts in this Michael addition: after relatively long reaction times (8-45 h), adduct **18** is formed with low yield (2-61%). The weakest catalyst, compound **6** (entry 3) containing a bulky alkyl side arm, provided very low chemical (2%) and optical yield (e.e.: 2%). The use of crowns **10** and **11**, having methoxyphenylethyl group gave the highest yields (61%, 50% respectively) with moderate enantiomeric excess (e.e.: 15%, 25% respectively). Lariat ethers (**12**, **13**, **15**) display greater asymmetric induction (e.e.: 45%, 66%, 48% respectively). Comparing the obtained data for the latter compounds, it is clear that the methyl ethers give rise to higher enantioselectivity (66%, 48% respectively) than their hydroxy analogues (**12**, **14**, e.e.: 45%, 6% respectively). The results for catalysts **8** and **9** possessing benzyl and phenylethyl side groups indicate the importance of the length of the side arm on the nitrogen atom, the former gives 6%, the latter 82% e.e., the best result.

In the experiments in Table 3 the influence of the reaction conditions (reaction time, temperature, base) on the reaction catalyzed by crown **9** is shown. By increasing the reaction time (entries 1-3) and the concentration (entries 10 and 11) the chemical yield increases but the enantioselectivity diminishes. The use

of low temperature produces lower chemical yields (entries 4 and 5). The application of other bases (entries 6-8) results in higher yields and the asymmetric induction is not affected considerably.

Table 3. The effect of the reaction conditions in the Michael addition of 2-nitropropane to chalcone catalyzed by crown ether **9** and **13**

Entry	Time (h)	Temp. (°C)	Catalyst	Base	Yield (%) [a]	e.e. (%) [b]
1	48	20	**9**	NaO*t*Bu	18	82 (80 [c])
2	90	20	**9**	NaO*t*Bu	36	27
3	340	20	**9**	NaO*t*Bu	60	24
4	24	-20	**9**	NaO*t*Bu	17	22
5	65	-78	**9**	NaO*t*Bu	2	11
6	40	20	**9**	NaH	48	24
7	40	20	**9**	NaOEt	60	22
8	72	20	**9**	KO*t*Bu	71	25
9	160	20	**9**	KF	71	25
10	40	20	**13**	NaO*t*Bu	15	66 (61 [c])
11 [d]	40	20	**13**	NaO*t*Bu	61	19 (16 [c])

[a] Based on isolation by column chromatography; [b] Determined by optical rotation;
[c] Determined by ^{1}H NMR spectroscopy; [d] Two times concentrated reaction mixture

The Darzens condensation of phenacyl chloride (**19**) and benzaldehyde (**20**) was carried out in a binary liquid-liquid system, using a toluene - 30% aqueous NaOH (5:1) mixture. The work-up procedure and determination of enantiomeric excess was accomplished as mentioned for the Michael addition. In all cases the epoxy ketone product **21** with a negative optical rotation was found to be in excess (Table 2). This corresponds to an absolute configuration of 2*R*,3*S*.[10]

In this reaction crown compounds **4-15** proved to be effective phase transfer catalysts (except **6**): after 2 hour reaction, the obtained chemical yield is 65-94%. Coronands **4-7** having alkyl or cyclohexylmethyl substituents on the nitrogen atom of the crown ring did not provoke significant asymmetric induction (entries 1-4). The importance of the chain length of the side arm can be demonstrated by comparing the effects of crowns **8** (R=CH_2Ph) and **9** (R=CH_2CH_2Ph).

Compound **12**, possessing a hydroxyethyl arm gave rise to 53% e.e., but this value decreased dramatically (e.e.: 13%) when the methylated derivative (**13**) was applied. The highest asymmetric induction (e.e.: 74%) was generated by catalyst **14** (R=$(CH_2)_3OH$) with a more efficient arm length and again its methyl ether (**15**) afforded only 7% e.e. It is interesting to note that this tendancy in this liquid-liquid system is completely the opposite to that in the solid-liquid system of the Michael addition. In the toluene-water system the presence of the hydroxy group in the side arm of the catalyst is clearly beneficial.

In the demonstrated model reactions a C-H acidic compound is being deprotonated by a suitably chosen base generating a reactive anion in the presence of the chiral crown compound. When the base is added to the reaction mixture in solid form, it is soluble in the apolar solvent only to such an extent that the complexation with the crown occurs (solid-liquid phase transfer mechanism). It is followed by deprotonation

of the C-H acidic compound and reaction with the other reactant, all occuring in the chiral niche of the solubilizing crown which results in asymmetric induction.

In conclusion, no definite relation was found between the salt extracting ability (complex formation) of the synthesized coronands and their activity in the model asymmetric reactions. In a water-dichloromethane system the best exracting ability is related to the crown ethers having butyl and hexyl group on the nitrogen atom of the macrocyclic ring. On the other hand, these compounds proved to be ineffectual phase transfer catalysts in the solid-liquid system of the Michael addition. Compound **9** with a phenethyl substituent and compounds **13** and **15** with methoxyethyl and methoxypropyl podand arms showed the highest chiral induction but with low yields. In the Darzens condensation, satisfactory chemical yields were obtained in a liquid-liquid system; compounds **12** and **14** with hydroxyethyl and hydroxypropyl arms were the most effective catalysts with respect to enantioselectivity. We have proved that the substituents on the nitrogen atom had distinct importance in the asymmetric induction: the lariat ethers were good in both model reactions, probably due to the assistance of the heteroatom in the enfolding podand arm in cation complexation when a three-dimensional complex is formed improving the phase transfer process as well as the asymmetric induction.

EXPERIMENTAL

General. ^{1}H NMR (500, 400 and 250 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker AMX 400 (^{13}C) and Bruker WM 250 instruments in $CDCl_3$. DEPT (Distortionless enhancement by polarization transfer) and ^{13}C- ^{1}H correlation experiments (1D and 2D) were used for signal assignment. The mass spectra were obtained on a Kratos MS50TC instrument using DS90 data system. Chemical ionization was applied as ionization technique. Optical rotation was measured on a Perkin Elmer 241 polarimeter and on a Propol automatic polarimeter at 20 °C. Analytical and preparative thin layer chromatography was performed on silica gel (60 PF-224, Merck) and on aluminium oxide (F-254, Riedel-de-Haën, 60 PF-254 (Typ E), Merck) TLC plates. Column chromatography was carried out using 70-230 mesh silica gel (E. M. Merck) and 100-125 mesh aluminum oxide (Fluka). Melting point measurements were taken on a Büchi 510 and an electrothermal IA 9000 apparatus. Elemental analysis was performed on a Perkin Elmer 240 automatic analyzer.

The starting phenyl-4,6-O-benzylidene-β-D-glucopyranoside (**1**) was synthesized as described.[7]

Phenyl-4,6-*O*-benzylidene-2,3-bis[(2-chloroethoxy)ethyl]-β-D-glucopyranoside (2) (Scheme 1). A solution of 10.0 g (29.1 mmol) of compound **1** and 9.85 g (29.1 mmol) of tetrabutylammonium hydrogen sulfate in 73 mL (623 mmol) of bis(2-chloroethyl)ether was vigorously stirred with 109 mL of 50% NaOH solution at room temperature for 8 h. A mixture of 300 mL CH_2Cl_2 and 300 mL water was added to the reaction mixture. The organic layer was decanted and the aqueous one was washed with CH_2Cl_2. The organic phases were combined and washed with water, dried with $MgSO_4$, filtered and concentrated under vacuum. After the removal of the solvent and the bis(2-chloroethyl)ether, the product was purified by column chromatography on silica gel using hexane-ethyl acetate (80:20) as eluent to give 9.8 g (60.5%) of **2** as a white solid; M.p.: 74-75 °C (ethanol); $[\alpha]_D$ -37.8° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2904, 1600, 1496, 1364, 1242,

1142, 1093, 1022, 748, 695, 653; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.45-3.60 (m, 6H, H-2, H-5 and 2 CH_2 of the podand arm), 3.60-3.75 (m, 10H, H-3, H-4 and 4 CH_2 of the podand arm), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.92-4.12 (m, 4H, 2 OCH_2 of the podand arm), 4.37 (dd, 1H, *J*=10.5 Hz, 5Hz, H-6), 5.05 (d, 1H, *J*=7.6 Hz, H-1), 5.55 (s, 1H, PhCH), 7.00-7.10 (m, 3H, OPhH-*o* and OPhH-*p*), 7.30 (tm, 2H, *J*=7.4 Hz, OPhH-*m*), 7.37-7.43 (m, 3H, CHPhH-*m*-*p*), 7.49 (dm, 2H, *J*=7.6 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 42.6, 42.7 (2 CH_2Cl), 66.2 (C-5), 68.7 (C-6), 70.7, 70.8, 71.1, 71.2, 72.4, 72.5 (6 OCH_2 of the podand arm) 80.7 (C-3), 81.7 (C-4), 82.5 (C-5), 101.4 (PhCH), 101.9 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*) ; MS, m/z: 557 [M^++1] (6), 463 (20) 339 (88), 233 (27), 183 (100). Anal. Calcd for $C_{27}H_{34}O_8Cl_2$: C, 58.17; H, 6.15; Cl, 12.72. Found: C, 58.21; H, 6.12; Cl, 12.50.

Phenyl-4,6-*O*-benzylidene-2,3-bis[(2-iodoethoxy)ethyl]-β-D-glucopyranoside (3) (Scheme 1). A mixture of 10.0 g (18 mmol) of bis-chloro derivative **2** and 10.8 g (72 mmol) of dry NaI in 200 mL of dry acetone was stirred under reflux for 48 h. After cooling the precipitate was filtered and washed with acetone. The combined acetone solution was evaporated under vacuum. The residue was dissolved in 100 mL of CH_2Cl_2, washed with water, and dried over Na_2SO_4 to give **3** (12.9 g, 97.2%) as a white solid; M.p.: 58 °C; $[\alpha]_D$ -25.2° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2879, 1601, 1590, 1494, 1370, 1236, 1088, 1007, 744, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.19 (t, 4H, *J*=7 Hz, 2 CH_2I), 3.45-3.58 (m, 2H, H-2 and H-5), 3.60-3.75 (m, 10H, H-3, H-4 and 8 podand arm-H), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.93-4.12 (m, 4H, 4 podand arm-H), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.56 (s, 1H, PhCH), 7.00-7.10 (m, 3H, OPhH-*o* and OPhH-*p*), 7.30 (tm, 2H, *J*=7.4 Hz, OPhH-*m*), 7.37-7.43 (m, 3H, CHPhH-*m*-*p*), 7.49 (dm, 2H, *J*=7.6 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 2.8, 3.0 (2 CH_2I), 66.2 (C-5), 68.7 (C-6), 70.3, 70.4, 71.8, 71.9, 72.5, 72.6 (6 OCH_2 of the podand arm), 80.7 (C-3), 81.7 (C-4), 82.5 (C-5) 101.4 (PhCH), 101.9 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 741 [M^++1] (3), 647 (13), 541 (11), 431 (40), 305 (38), 183 (100). Anal. Calcd for $C_{27}H_{34}O_8I_2$: C, 43.80; H, 4.63; I, 34.28. Found: C, 43.70; H, 4.51; I, 34.21. The resulting compound was used without further purification.

General method for preparation of crown ethers **4-15**. 3.84 g (36.2 mmol) of dry Na_2CO_3 was suspended in a solution of 4.60 mmol of the corresponding primary amine and 3.45 g (4.6 mmol) of bis-iodo compound **3** in 100 mL of dry acetonitrile under argon. The stirred reaction mixture was refluxed for 24-48 h and monitored by TLC until the disappearance of the bis-iodo compound. After cooling the precipitate was filtered and washed with acetonitrile. The combined acetonitrile solution was concentrated at reduced pressure. The residue oil was dissolved in $CHCl_3$, washed with water and dried over Na_2SO_4 and the solvent evaporated under vacuum. The corresponding monoaza-crown ether was isolated by column chromatography or preparative TLC using silica gel or aluminium oxide.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-butyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (4). The purification was carried out by column chromatography with eluent $CHCl_3$:MeOH:NH_4OH = 97:2:1 on silica gel. Yield: 43.9 %; faint yellow crystals; M.p.: 105-106°C (ethanol); $[\alpha]_D$ -43.0° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2926, 2869, 1600, 1491, 1368, 1228, 1093, 1031, 749, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.90 (t, 3H, *J*=7.3 Hz, CH_3), 1.30 (m, 2H, *J*=7.2 Hz, $NCH_2CH_2CH_2$), 1.44 (m, 2H, *J*=7.6 Hz, $NCH_2CH_2CH_2$), 2.48 (t, 2H, *J*=7.4 Hz,

$NCH_2CH_2CH_2$), 2.65-2.88 (m, 4H, 2 NCH_2 of the macrocycle), 3.43-3.83 (m, 12H, H-2, H-3, H-4, H-5 and 4 OCH_2 of the macrocycle), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.95-4.14 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.0, 20.6, 29.6 ($CH_3CH_2CH_2$), 54.0, 54.1 (2 NCH_2 of the macrocycle), 56.5, (NCH_2), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 (6 OCH_2 of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.2 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 558 [M^++1] (100), 514 (8), 464 (33). Anal. Calcd for $C_{31}H_{43}O_8N$: C, 66.77; H, 7.77; N, 2.51. Found: C, 66.80; H, 7.71; N, 2.55.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-hexyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (5). The purification was carried out by column chromatography with eluent $CHCl_3$:MeOH:NH_4OH = 95:5:1 on silica gel. Yield: 39.3%; light yellow oil; $[\alpha]_D$= -39.2° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2926, 2872, 1600, 1491, 1368, 1233, 1093, 1030, 750, 696; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, *J*=6.6 Hz, $N(CH_2)_5CH_3$), 1.20-1.50 (m, 8H, $NCH_2(CH_2)_4CH_3$), 2.47 (t, 2H, *J*=7.5 Hz, $NCH_2(CH_2)_4CH_3$), 2.67-2.88 (m, 4H, 2 NCH_2 of the macrocycle), 3.44-3.85 (m, 12H, H-2, H-3, H-4, H-5 and 4 OCH_2 of the macrocycle), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.95-4.14 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.0 ($N(CH_2)_5CH_3$), 22.6, 27.1, 27.4, 31.8 ($NCH_2(CH_2)_4CH_3$), 54.0, 54.1 (2 NCH_2 of the macrocycle), 56.8 ($NCH_2(CH_2)_4CH_3$), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 (6 OCH_2 of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.2 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 586 [M^++1] (100), 514 (12), 492 (34). Anal. Calcd for $C_{33}H_{47}O_8N$: C, 67.67; H, 8.09; N, 2.39. Found: C, 67.70; H, 8.15; N, 2.30.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-3-(2,4-dimethyl)pentyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (6). The purification was carried out by column chromatography with eluent CH_2Cl_2:MeOH = 97:3 on silica gel or preparative TLC with eluent CH_2Cl_2:MeOH = 90:10 on silica gel. Yield: 17.7%; light yellow oil; $[\alpha]_D$ -35.4° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2926, 2870, 1600, 1491, 1368, 1230, 1093, 1030, 750, 696; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.84-0.95 (4d, 12H, *J*=6-7 Hz, 4 CH_3CH), 1.80-1.98 (m, 3H, 2 CH and 1 NCH), 2.80-2.97 (m, 4H, 2 NCH_2 of the macrocycle), 3.43-3.73 (m, 12H, H-2, H-3, H-4, H-5 and 4 OCH_2 of the macrocycle), 3.78 (t, 1H, *J*=10.5 Hz, H-6), 3.94-4.17 (m, 4H, 2 OCH_2 of the macrocycle), 4.35 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.3, 20.4, 21.3, 21.5 (4 CH_3), 29.2, 29.4 (*C*HC*H*C*H*) 54.8, 55.2 (2 NCH_2 of the macrocycle), 66.0 (C-5), 68.6 (C-6), 69.9, 70.2, 71.6, 72.0, 72.3, 72.4 (6 OCH_2 of the macrocycle), 75.7 (CHCHCH), 80.7, 81.4, 81.5 (C-2, C-3, C-4), 101.1 (PhCH), 102.1 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 600 [M^++1] (100), 556 (38), 506 (18). Anal. Calcd for $C_{34}H_{49}O_8N$: C, 68.09; H, 8.23; N, 2.33. Found: C, 68.12; H, 8.13; N, 2.30.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-cyclohexylmethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (7). The purification was carried out by column chromatography with eluent CH_2Cl_2:MeOH = 93:7 on silica gel. Yield: 32.2%; faint yellow crystals; M.p.: 104 °C (ethanol); $[\alpha]_D$ -41.1° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2923, 2871, 1600, 1493, 1456, 1349, 1240, 1132, 1086, 1008, 963, 754, 690; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.82-1.85 (m, 11H, cyclohex-H), 2.24 (d, 2H, *J*=7.0 Hz, NCH_2cyclohex), 2.60-2.85 (m, 4H, 2 NCH_2 of the macrocycle), 3.44-3.72, 3.73-3.85 (m, 12H, H-2, H-3, H-4, H-5, 4 OCH_2 of the macrocycle), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.93-4.13 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m-p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.1, 26.2 (2 cyclohex CH_2-β), 26.9 (cyclohex CH2-γ), 31.7, 31.8 (2 cyclohex CH2-α), 36.4 (cyclohex CH), 54.8, 54.9 (2 NCH_2 of the macrocycle), 63.8 (NCH_2cyclohex), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.2, 70.3, 72.4, 72.5 (6 OCH_2 of the macrocycle), 81.1, 81.5 (C-3, C-4), 81.8 (C-2), 101.2 (PhCH), 102.2 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 598 [M^++1] (100), 514 (31), 504 (35). Anal. Calcd for $C_{34}H_{47}O_8N$: C, 68.32; H, 7.92; N, 2.34. Found: C, 68.37; H, 7.85; N, 2.28.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-benzyl-1,4,7,10-tetraoxa-13-aza-cyclopentadecane (8). The purification was carried out by column chromatography with eluent $CHCl_3$:MeOH = 95:5 on silica gel or with eluent CH_2Cl_2:MeOH = 99.6:0.4 on aluminium oxide. Yield: 42.6%; light yellow oil; $[\alpha]_D$ -34.9° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2926, 2873, 1599, 1491, 1457, 1234, 1093, 1028, 962, 750, 695; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.72-2.95 (m, 4H, 2 NCH_2 of the macrocycle), 3.45-3.85 (m, 14H, H-2, H-3, H-4, H-5, NCH_2Ph and 4 OCH_2 of the macrocycle), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.95-4.15 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.6 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.4 Hz, OPhH-*p*), 7.19-7.41 (m, 10H, OPhH-*m*, CH_2PhH-*o-p-m*, CHPhH-*m-p*), 7.47 (dm, 2H, *J*=7.6 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 53.8, 53.9 (2 NCH_2 of the macrocycle), 60.7 (NCH_2Ph), 66.1 (C-5), 68.7 (C-6), 69.0, 69.1, 70.2, 70.3, 72.4, 72.5 (6 OCH_2 of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.8 (C-2), 101.2 (PhCH), 102.2 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 126.9 (CH_2PhC-*p*), 128.1 (2 CHPhC-*m*), 128.2 (2 CH_2PhC-*m*), 128.8 (2 CH_2PhC-*o*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 139.6 (CH_2PhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 592 [M^++1] (100), 514 (14), 498 (37). Anal. Calcd for $C_{34}H_{41}O_8N$: C, 69.02; H, 6.98; N, 2.37. Found: C, 68.90; H, 6.92; N, 2.31.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-(2-phenyl)ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (9). The purification was carried out by column chromatography, gradient elution with CH_2Cl_2:EtOAc:NH_4OH = 92:7:1 → 90:9:1 on silica gel or with eluent CH_2Cl_2:MeOH = 99.5:0.5 on aluminium oxide. Yield: 71%; white crystals; M.p.: 160 °C (ethanol); $[\alpha]_D$ -44.3° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2913, 2866, 1600, 1492, 1368, 1230, 1127, 1092, 1010, 751, 694; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.77 (s, 4H, $PhCH_2CH_2$, accidental equiv.), 2.76-2.95 (m, 4H, 2 NCH_2 of the macrocycle), 3.50 (m, 1H, H-5), 3.52 (t, 1H, *J*=8 Hz, H-2), 3.67 (m, 1H, H-3

or H-4), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.45-3.85 (m, 9H, 4 OCH_2 of the macrocycle and H-3 or H-4), 3.95-4.15 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.6 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.4 Hz, OPhH-*p*), 7.15-7.21 (m, 3H, CH_2PhH-*o*-*p*), 7.26 (tm, 2H, *J*=7.6 Hz, CH_2PhH-*m*), 7.30 (tm, 2H, *J*=7.5 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (dm, 2H, *J*=7.6 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 34.0 (NCH_2CH_2Ph), 54.1, 54.2 (2 NCH_2 of the macrocycle), 58.7 (NCH_2CH_2Ph), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 (6 OCH_2 of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.2 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 125.9 (CH_2PhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 128.3 (2 CH_2PhC-*m*), 128.7 (2 CH_2PhC-*o*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 140.5 (CH_2PhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 606 [M^++1] (100), 514 (49). Anal. Calcd for $C_{35}H_{43}O_8N$: C, 69.40; H, 7.15; N, 2.31. Found: C, 69.45; H, 7.22; N, 2.30.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-2-(2-methoxyphenyl)ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (10). The purification was carried out by column chromatography with eluent CH_2Cl_2:MeOH = 95:5 on silica gel or preparative TLC with eluent CH_2Cl_2:MeOH = 99.3:0.7 on aluminium oxide. Yield: 52.6%; faint yellow crystals; M.p.: 134 °C (ethanol); $[\alpha]_D$ -43.5° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2920, 2862, 2360, 1599, 1383, 1243, 1093, 752, 692; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.67-2.98 (m, 8H, $PhCH_2CH_2$ and 2 NCH_2 of the macrocycle), 3.44-3.85 (m, 16H, CH_2PhOCH_3, H-2, H-3, H-4, H-5, H-6 and 4 OCH_2 of the macrocycle), 3.95-4.15 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 6.82 (dm, 1H, *J*=8.1 Hz, CH_2PhH-*m*), 6.86 (tm, 1H, *J*=7.5 Hz, CH_2PhH-*m*), 7.02 (dm, 2H, *J*=7.9 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.4 Hz, OPhH-*p*), 7.13 (dm, 1H, *J*=7.4 Hz, CH_2PhH-*o*), 7.16 (tm, 1H, *J*=7.2 Hz, CH_2PhH-*p*), 7.30 (tm, 2H, *J*=7.7 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (m, 2H, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.2 ($NCH_2CH_2PhOCH_3$), 53.9, 54.0 (2 NCH_2 of the macrocycle), 55.2 ($NCH_2CH_2PhOCH_3$), 56.7 ($NCH_2CH_2PhOCH_3$), 66.1 (C-5), 68.7 (C-6), 69.3, 69.4, 70.3, 70.4, 72.4, 72.5 (6 OCH_2 of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.8 (C-2), 101.2 (PhCH), 102.2 (C-1), 110.2 (CH_2PhC-*m(3)*), 117.0 (2 OPhC-*o*), 120.4 (CH_2PhC-*m(5)*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 127.2 (CH_2PhC-*p*), 128.2 (2 CHPhC-*m*), 128.8 (CH_2PhC-*ipso*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 130.3 (CH_2PhC-*o(6)*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); 157.5 (CH_2PhC-*o(2)*); MS, m/z: 636 [M^++1] (100), 542 (24), 514 (40). Anal. Calcd for $C_{36}H_{45}O_9N$: C, 68.01; H, 7.13; N, 2.20. Found: C, 68.11; H, 7.20; N, 2.12.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-2-(4-methoxyphenyl)ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (11). The purification was carried out by column chromatography with eluent CH_2Cl_2:MeOH = 94:6 on silica gel or preparative TLC with eluent CH_2Cl_2:MeOH = 99.3:0.7 on aluminium oxide. Yield: 47.6%; faint yellow crystals; M.p.: 124-125 °C (ethanol); $[\alpha]_D$ -41.1° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2920, 2876, 1600, 1512, 1250, 1123, 1093, 823, 748, 696; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.72 (s, 4H, $PhCH_2CH_2$, accidental equiv.), 2.75-2.96 (m, 4H, 2 NCH_2 of the macrocycle), 3.44-3.84 (m, 16H, CH_2PhOCH_3, H-2, H-3, H-4, H-5, H-6 and 4 OCH_2 of the macrocycle), 3.95-4.13 (m, 4H, 4 OCH_2 of the macrocycle), 4.35 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 6.81 (d, 2H, *J*=8.6Hz, CH_2PhH-m), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.4 Hz, OPhH-*p*), 7.10 (d, 2H, *J*=8.6Hz, CH_2PhH-o), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 33.1

($NCH_2CH_2PhOCH_3$), 54.0, 54.1, (2 NCH_2 of the macrocycle), 55.2 ($NCH_2CH_2PhOCH_3$), 58.8 ($NCH_2CH_2PhOCH_3$), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.3, 72.4 (6 OCH_2 of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.1 (C-1), 113.7 (2 CH_2PhC-m), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-m), 129.0 (CHPhC-*p*), 129.5 (2 CH_2PhC-o), 129.6 (2 OPhC-*m*),), 132.5 (CH_2PhC-ipso), 137.2 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); 157.8 (CH_2PhC-*p*); MS, m/z: 636 [M^++1] (100), 542 (24), 514 (40). Anal. Calcd for $C_{36}H_{45}O_9N$: C, 68.01; H, 7.13; N, 2.20. Found: C, 68.10; H, 7.17; N, 2.17.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-hydroxyethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (12). The purification was carried out by column chromatography with eluent $CHCl_3$:MeOH:NH_4OH = 94:5:1 on silica gel. Light yellow oil. Yield: 48.0%; $[\alpha]_D$ -35.2° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3180-3600, 2920, 2875, 1600, 1491, 1236, 1093, 754, 694; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.63-2.87 (m, 6H, 3 NCH_2), 3.45-3.83 (m, 15H, H-2, H-3, H-4, H-5, H-6, CH_2OH and 4 OCH_2 of the macrocycle), 3.92-4.08 (m, 4H, 2 OCH_2 of the macrocycle), 4.35 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m-p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 55.0, 55.1 (2 NCH_2 of the macrocycle), 57.5, (NCH_2), 59.2 (CH_2OH), 66.0 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.3, 72.4 (6 OCH_2 of the macrocycle), 80.9, 81.5 (C-3, C-4), 81.8 (C-2), 101.2 (PhCH), 102.1 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 546 [M^++1] (100), 514 (14), 452 (27). Anal. Calcd for $C_{29}H_{39}O_9N$: C, 63.84; H, 7.20; N, 2.57. Found: C, 63.72; H, 7.25; N, 2.50.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-2-methoxyethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (13). The purification was carried out by column chromatography with eluent CH_2Cl_2:MeOH:NH_4OH = 97:2:1 on silica gel or with eluent CH_2Cl_2:MeOH = 99.2:0.8 on aluminium oxide. Yield: 53.8%; white crystals; M.p.: 57-58 °C (ethanol); $[\alpha]_D$ -40.1° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2920, 2876, 1600, 1496, 1388, 1239, 1093, 749, 695; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.70-3.00 (m, 4H, 2 NCH_2 of the macrocycle), 2.75 (t, 2H, *J*=6 Hz, $NCH_2CH_2OCH_3$), 3.33 (s, 3H, $NCH_2CH_2OCH_3$), 3.48 (t, 2H, *J*=6 Hz, $NCH_2CH_2OCH_3$), 3.45-3.84 (m, 12H, H-2, H-3, H-4, H-5 and 4 OCH_2 of the macrocycle), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.95-4.15 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m-p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 54.2, 54.3 (2 NCH_2 of the macrocycle), 55.7 ($NCH_2CH_2OCH_3$), 58.8 ($NCH_2CH_2OCH_3$), 66.1 (C-5), 68.7 (C-6), 68.9, 69.0, 70.3, 70.4, 72.3, 72.4 (6 OCH_2 of the macrocycle), 71.0 ($NCH_2CH_2OCH_3$), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.2 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 560 [M^++1] (100), 529 (4), 514 (21), 466 (32.). Anal. Calcd for $C_{30}H_{41}O_9N$: C, 64.38; H, 7.38; N, 2.50. Found: C, 64.45; H, 7.31; N, 2.55.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-hydroxypropyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (14). The purification was carried out by column chromatography with eluent CH_2Cl_2:MeOH =

93:7 on silica gel or preperative TLC with eluent CH_2Cl_2:MeOH = 98:2 on aluminium oxide. Yield: 38.4%; light yellow oil; $[\alpha]_D$ -44.9° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3120-3600, 2920, 2875, 1600, 1491, 1236, 1093, 756, 692; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.78 (m, 2H, $NCH_2CH_2CH_2$), 2.60-2.90 (m, 6H, $NCH_2CH_2CH_2$ and 2 NCH_2 of the macrocycle), 3.44-3.85 (m, 15H, $NCH_2CH_2CH_2$, H-2, H-3, H-4, H-5, H-6 and 4 OCH_2 of the macrocycle), 3.93-4.10 (m, 4H, 2 OCH_2 of the macrocycle), 4.35 (dd, 1H, *J*=10.5, 5 Hz, H-6), 4.83 (s, broad, 1H, OH), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.4 ($NCH_2CH_2CH_2$), 54.3 (2 NCH_2 of the macrocycle), 56.4 ($NCH_2CH_2CH_2$), 64.0 ($NCH_2CH_2CH_2$), 66.1 (C-5), 68.7 (C-6), 68.8, 68.9, 70.2, 70.3, 72.3, 72.5 (6 OCH_2 of the macrocycle), 80.9, 81.4 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.1 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 560 [M^++1] (100), 542 (3), 514 (4), 466 (30). Anal. Calcd for $C_{30}H_{41}O_9N$: C, 64.38; H, 7.38; N, 2.50. Found: C, 64.41; H, 7.31; N, 2.52.

Phenyl-4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*h*]-*N*-3-methoxypropyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (15). The purification was carried out by column chromatography with eluent CH_2Cl_2:MeOH = 95:5 on silica gel or preparative TLC with eluent CH_2Cl_2:MeOH = 99:1 on aluminium oxide. Yield: 66.0%; faint yellow crystals; M.p.: 78 °C (ethanol); $[\alpha]_D$ -44.1° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2922, 2876, 1600, 1496, 1388, 1239, 1093, 749, 695; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.72 (m, 2H, $NCH_2CH_2CH_2$), 2.56 (t, 2H, *J*=7.0 Hz, $NCH_2CH_2CH_2$), 2.66-2.88 (m, 4H, 2 NCH_2 of the macrocycle), 3.32 (s, 3H, OCH_3), 3.42 (t, 2H, *J*=6.3 Hz, $NCH_2CH_2CH_2$), 3.45-3.85 (m, 12H, H-2, H-3, H-4, H-5 and 4 OCH_2 of the macrocycle), 3.79 (t, 1H, *J*=10.5 Hz, H-6), 3.95-4.13 (m, 4H, 2 OCH_2 of the macrocycle), 4.36 (dd, 1H, *J*=10.5, 5 Hz, H-6), 5.06 (d, 1H, *J*=7.6 Hz, H-1), 5.54 (s, 1H, PhCH), 7.02 (dm, 2H, *J*=7.7 Hz, OPhH-*o*), 7.05 (tm, 1H, *J*=7.2 Hz, OPhH-*p*), 7.30 (tm, 2H, *J*=8.0 Hz, OPhH-*m*), 7.33-7.40 (m, 3H, CHPhH-*m*-*p*), 7.47 (dm, 2H, *J*=7.7 Hz, CHPhH-*o*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 27.7 ($NCH_2CH_2CH_2$), 53.2 ($NCH_2CH_2CH_2$), 54.1, 54.2 (2 NCH_2 of the macrocycle), 58.5 (OCH_3), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 (6 OCH_2 of the macrocycle), 70.9 ($NCH_2CH_2CH_2$), 81.0, 81.5 (C-3, C-4), 81.8 (C-2), 101.2 (PhCH), 102.2 (C-1), 117.0 (2 OPhC-*o*), 123.0 (OPhC-*p*), 126.0 (2 CHPhC-*o*), 128.2 (2 CHPhC-*m*), 129.0 (CHPhC-*p*), 129.6 (2 OPhC-*m*), 137.3 (CHPhC-*ipso*), 157.1 (OPhC-*ipso*); MS, m/z: 574 [M^++1] (100), 514 (6), 480 (31). Anal. Calcd for $C_{31}H_{43}O_9N$: C, 64.90; H, 7.55; N, 2.44. Found: C, 64.92; H, 7.61; N, 2.39.

General procedure for the Michael addition was performed as follows: 1.44 mmol of chalcone and 3.36 mmol of 2-nitropropane were dissolved in 3 mL anhydrous toluene, and then 0.1 mmol of crown ether and 0.5 mmol of base were added. The mixture was stirred under argon atmosphere. After completing the reaction (8-45 hours) a mixture of 7 mL of toluene and 10 mL of water was added. The organic phase was processed in the usual manner. The product was purified by preparative TLC or column chromatography on silica gel using hexane-ethyl acetate (10:1) and chloroform as eluent. M.p.: 146-148°C, $[\alpha]_D$ +80.8° (c 1, CH_2Cl_2) for pure (+)-(S) enantiomer;[5] ^1H NMR (400 MHz, $CDCl_3$) 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, 1H, *J*=17.2, 10.4 Hz, CH_2), 4.15 (dd, 1H, *J*=10.4, 3.2, CH) Hz, 7.18-7.32 (m, 5H, CHPhH), 7.42 (t, 2H, COPhH-*m*), 7.53 (t, 1H, COPhH-*p*), 7.85 (d, 2H, COPhH-*o*).

General procedure for the Darzens condensation: A toluene of 3 mL solution of 1.3 mmol of phenacyl chloride was treated with 1.9 mmol of benzaldehyde and 0.1 mmol of catalyst in 1.0 mL of 30% NaOH solution. The mixture was stirred under argon atmosphere. After completing the reaction 7 mL of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and the solvent evaporated. The product was isolated by preparative TLC or column chromatography using CH_2Cl_2 as eluent. $[\alpha]_D$ -214° (c 1, CH_2Cl_2) for pure 2*R*,3*S* enantiomer;[10] ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.08 (d, 1H, *J*=1.9 Hz, CH), 4.29 (d, 1H, *J*=1.9 Hz, CH), 7.35-7.45 (m, 5H, CHPhH), 7.49 (t, 2H, COPhH-*m*), 7.62 (t, 1H, COPhH-*p*), 8.01 (d, 2H, COPhH-*o*).

Acknowledgment: This work was supported by the Hungarian Academy of Sciences, the National Science Foundation (OTKA T015677), the Soros Foundation Hungary and the Katholieke Universiteit Leuven

REFERENCES

1. Tõke, L.; Bakó, P.; Keserû, M. Gy.; Albert, M.; Fenichel, L. *Tetrahedron* **1998**, *54*, 213 and references cited therein.
2. Gokel, G. W. *Chem. Soc. Rev.* **1992**, *21*, 39.
3. Bakó, P.; Tõke, L. *J. Incl. Phenom.* **1995**, *23*, 195.
4. Bakó, P.; Szöllõsy, Á.; Bombicz, P.; Tõke, L. *Synlett* **1997**, 291.
5. Bakó, P.; Szöllõsy, Á.; Bombicz, P.; Tõke, L. *Heteroatom Chem.* **1997**, *8*, 333.
6. Bakó, P.; Kiss, T.; Tõke, L. *Tetrahedron Lett.* **1997**, *38*, 7259.
7. (a) Fischer, E. *Ber.* **1916**, *46*, 584, (b) Zemplén, G.; Gerecs, A.; Hadácsy, I. *Ber.* **1936**, *69*, 1827, (c) Smits, E. *J. Chem. Soc., Perkin Trans 1.* **1996**, 2873, (d) Hall, D. M. *Carbohydr. Res.* **1980**, *86*, 158.
8. Di Cesare, P.; Gross, B. *Synth. Commun.* **1979**, 4581.
9. Kimura, K.; Maeda, T.; Shono, T. *Talanta* **1979**, *26*, 945.
10. Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312.

B13

Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2373–2380

TETRAHEDRON: *ASYMMETRY*

D-Glucose-based azacrown ethers with a phosphonoalkyl side chain: application as enantioselective phase transfer catalysts

Péter Bakó,[a,*] Tibor Novák,[a] Krisztina Ludányi,[b] Béla Pete,[c] László Tõke[c] and György Keglevich[a,*]

[a]*Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary*
[b]*Central Research Institute of Chemistry for the Hungarian Academy of Sciences, 1525 Budapest, Hungary*
[c]*Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary*

Received 18 May 1999; accepted 3 June 1999

Abstract

Five chiral α-D-glucose-based monoaza-15-crown-5 ethers with a phosphonoalkyl side chain **5a–e** have been synthesized. The substituent at the nitrogen atom has a major influence on the cation extraction ability of the azacrown. The new lariat ethers **5a–e** show significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Chiral crown ethers have received considerable attention due to their ability to serve as models for the study of chiral recognition in enzymatic reactions.[1] It has also been observed that the optically active crown ethers could be used as catalysts in enantioselective reactions.[2] A variety of such macrocycles has been synthesized, and much attention focused on systems derived from carbohydrates.[3] Crown ethers anellated to different pyranosidic or furanosidic carbohydrates have also been described.[4]

In recent papers, we have reported the synthesis of a novel class of D-glucose-based crown ethers and their application in asymmetric reactions. These compounds are 15-membered monoazacrown ethers anellated to a methyl-[5] or to a phenyl-4,6-*O*-benzylideneglucopyranoside[6] unit and are useful catalysts in asymmetric reactions. It is known that armed azacrown ethers, especially lariat ethers (azacrowns with heteroatom-containing podand arms) have a unique guest specificity via the macro-ring-side arm cooperativity.[7] We found that the presence of a substituent on the nitrogen atom played an important role in the cation binding ability, and hence in the catalytic activity of the azacrown ethers.[6b] In sugar-based azacrowns, the impact of alkyl and arylalkyl groups, as well as that of substituents containing an oxygen

* Corresponding authors. E-mail: p-bako@chem.bme.hu

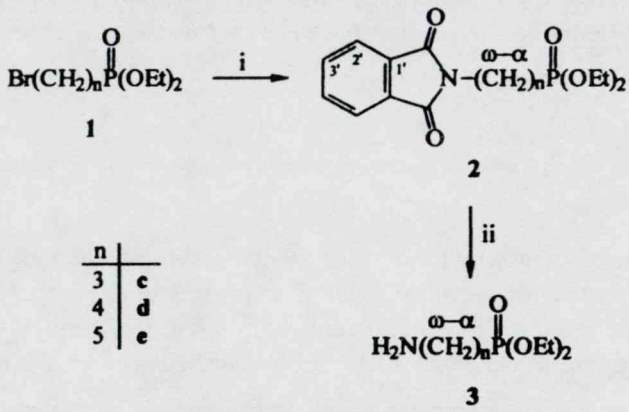
0957-4166/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(99)00224-4

atom, have been evaluated.[5a] The effects of phosphorus-containing side arms on the complexing abilities have been studied only in simple azacrown ethers.[8] As the lariat ethers incorporating a phosphonoalkyl substituent showed interesting cation binding properties, it was a challenge for us to synthesize D-glucose-based azacrown ethers with a phosphonoalkyl group on the nitrogen atom and to study their complexing properties and applicability in enantioselective reactions.

2. Results and discussion

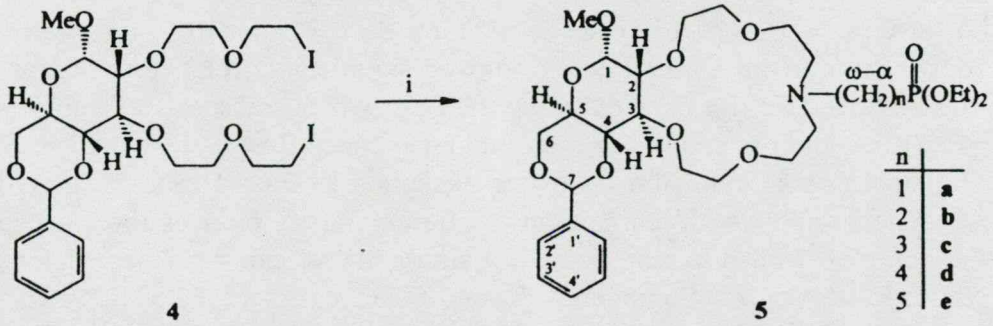
2.1. Synthesis of new azacrown ethers 5a–e

We used a method described previously[5a] for the synthesis of the new lariat ethers. The key intermediates, ω-aminoalkylphosphonates **3c–e** were prepared by the, in this case hitherto new, Gabriel synthesis (Scheme 1) in two steps. Intermediate **3a** (**3**, n=1) was also obtained through the corresponding phthalimido derivative **2a** (**2**, n=1) synthesized, in this case, by a different approach (see Experimental).



Scheme 1. Reagents and conditions: (i) potassium phthalimide, DMF, 100°C, 8 h; (ii) $(H_2N)_2 \cdot H_2O$, EtOH, 78°C, 1 h then HCl, 78°C, 30 min

Aminoethylphosphonate **3b** (**3**, n=2) was prepared by the Michael addition of ammonia to diethyl vinylphosphonate. The α-D-glucose-based bis-iodo podand[5a] **4** was cyclized with the aminoalkylphosphonates **3a–e** in boiling acetonitrile in the presence of sodium carbonate (Scheme 2). In dilute solutions, the polycondensation side reactions were suppressed and the desired intramolecular cyclization took place in high conversion to give the *N*-phosphonoalkyl azacrown ethers **5a–e** in fairly good yields (51–70%) after purification by chromatography. The products **5a–e** were characterized by ^{31}P, ^{1}H and ^{13}C NMR, as well as mass spectroscopic data. The ^{1}H and ^{13}C NMR spectral parameters were similar to those of azacrown derivatives described earlier.[6b] The molecular weights of **5a–e** were supported by CIMS and FABMS. The elemental composition was confirmed in all cases by HR-FAB. In the EI mass spectra of products **5a–e** we observed two different fragmentation patterns depending on the length of the hydrocarbon chain binding the P=O moiety to the azacrown ether. With compounds **5a** and **5b**, the fragments were formed mainly by bond fission in the 'sugar' part of the molecules, while in the case of azacrowns **5c–e**, the fragmentation occurred preferentially at the 'crown' part. The fragments at 452 and 156 *m/z* were of significant intensity in all cases (see Experimental) that are due to the (sugar-based azacrown)-CH_2^+ and the $C_7H_8O_4^+$ fragments, respectively. The latter one is the sugar residue from product **5a–e**. The $(CH_2)_nP(O)(OEt)_2^+$, the $CH_2N(CH_2)_nP(O)(OEt)_2^+$, as well as the $(CH_2)_2N(CH_2)_nP(O)(OEt)_2^+$ fragments could also be found in the mass spectra of products **5a–e**. The $M-H^+$, $M-Me^+$, $M-MeO^+$, $M-EtO^+$ and $M-P(O)(OEt)_2^+$ fragments were of low intensity.

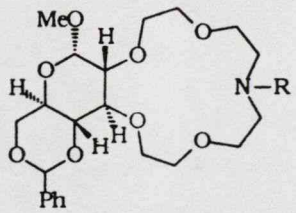


Scheme 2. Reagents and conditions: (i) $H_2N(CH_2)_nP(O)(OEt)_2$ (**3a–e**), CH_3CN, 82°C, 48 h

2.2. *Extracting properties of the new azacrown ethers* ***5a–e***

The phase transfer properties (in a liquid–liquid system) of the newly synthesized crown ethers **5a–e** were characterized by the extraction of picrate salts (lithium, sodium, potassium and ammonium picrates) from water into dichloromethane following the procedure described by Kimura et al.[9] The data collected in Table 1 show the amount of the transferred salt as the percentage of the initial salt concentration (extractability %). The concentration of the picrates in water was measured by UV spectroscopy. The unsubstituted azacrown ether **6** used as the reference compound[5c] has a surprisingly high extracting ability (EA) towards the cations investigated but does not show a notable selectivity to any of the alkali- or ammonium cations (EA: 87–98%).

Table 1
Extraction of alkali metal and ammonium picrates with different azacrown ethers



Compound	R	Extractability (%)[a]			
		Li^+	Na^+	K^+	NH_4^+
5a	$(CH_2)P(O)(OEt)_2$	8	29	16	5
5b	$(CH_2)_2P(O)(OEt)_2$	35	30	17	29
5c	$(CH_2)_3P(O)(OEt)_2$	4	15	24	43
5d	$(CH_2)_4P(O)(OEt)_2$	46	47	54	63
5e	$(CH_2)_5P(O)(OEt)_2$	38	59	59	63
6	H	87	87	96	98

[a] Room temperature; aqueous phase (5 ml); [picrate] = $5 \cdot 10^{-3}$ M; organic phase (CH_2Cl_2, 5 ml); [crown ether] = $1 \cdot 10^{-2}$ M. Defined as % picrate extracted into the organic phase, determined by UV spectroscopy. Error = ±1%.

As can be seen, the phosphonoalkyl side arms have significant influence on the EA of the azacrown ring. Introduction of the phosphonoalkyl substituents decreased the EA of the parent azacrown ether **6** in all cases. The impact of the long chains was smaller than that of the substituents with shorter chains (e.g. the EA values for compound **5d** (n=4) and **5a** (n=1) are 46–63% and 5–29%, respectively). For the potassium cation, the relative order of the EA values is the following: 96% for **6** (n=0), 59% for

5e (n=5), 54% for **5d** (n=4), 24% for **5c** (n=3), 17% for **5b** (n=2) and 16% for **5a** (n=1). On the other hand, the selectivity of derivatives **5a–e** was improved significantly relative to that of unsubstituted **6**. In this respect, compound **5c** (n=3) seems to be the best, which transports 10 times more ammonium picrate (EA=43%) into the organic phase than lithium picrate (EA=4%). Azacrown **5b** extracts twice as much lithium ion as potassium ion. With the exception of **5a** and **5b**, the azacrown ethers **5c–e** form the most stable complex with ammonium picrate among the picrates investigated. Regarding the stability of the complex with different cations, a similar trend can be observed for azacrowns **5c–e** as follows: $NH_4^+ > K^+ > Na^+ > Li^+$. Compounds **5a** and **5b** revealed the $Li^+ > Na^+ > NH_4^+ > K^+$ order. The complex effect of the *N*-substituents is presumably due to steric and electronic effects. The presence of the phosphonoalkyl side chain obviously means some kind of steric hindrance in the complexation. On the other hand, the phosphonoalkyl moiety affects the electron density on the nitrogen atom. While the phosphonomethyl substituent can be regarded as an electron-withdrawing group, the phosphonoalkyl substituents with longer carbon atom chains may increase the electron density on the nitrogen atom. The third effect may be the side arm cooperativity due to the oxygen atom of the phosphoryl moiety (Fig. 1). The length of the side arm is decisive.

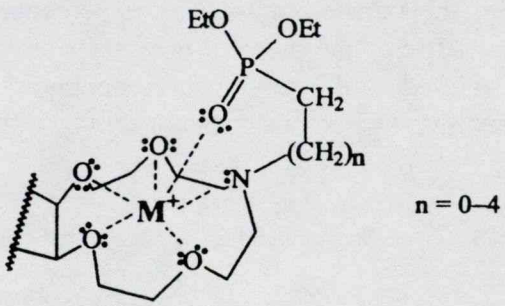
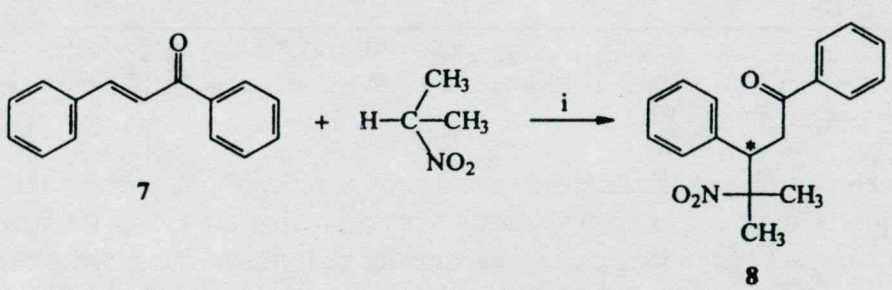


Figure 1.

2.3. *Chiral induction by the new azacrown ethers* **5a–e** *in an asymmetric Michael addition*

The compounds **5a–e** proved to be effective as chiral phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone **7** (Scheme 3). The Michael addition was carried out in toluene with solid sodium *tert*-butoxide as the base (35 mol%) in the presence of chiral catalyst **5a–e** (7 mol%) at room temperature. After the usual work-up procedure, the adduct **8** was isolated by preparative TLC. The asymmetric induction, expressed in terms of the enantiomeric excess (ee), was monitored by determining the specific rotation of product **8** and comparing it with the literature data for the pure enantiomer and by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent. The results given in Table 2 show that the (*S*)-(+)-adduct **8** was always in excess and, what is more important, that the substituent on the nitrogen atom of the catalyst has a significant influence on both the yield and the asymmetric induction.



Scheme 3. Reagents and conditions: (i) catalyst (**5a–e**), NaO*t*Bu, PhMe, 20°C, 48 h

Table 2
Addition of 2-nitropropane to chalcone (7) catalyzed by azacrown ethers 5a–e[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	5a	31	63
2	5b	42	61
3	5c	38	60
4	5d	39	82 (83)[d]
5	5e	40	79
6[5c]	6	53	61

[a] Base *t*-BuONa; reaction time 48 h; temperature 20 °C.
[b] Based on substance isolated by preparative TLC.
[c] Determined by specific rotation comparison.
[d] Determined by ^{1}H NMR spectroscopy.

Apparently, azacrown ethers **5a–e** are not very efficient phase transfer catalysts in the solid–liquid phase Michael addition mentioned above: after a 48 h period of stirring, adduct **8** was formed in only 31–42% chemical yield. The new products **5a–e** showed, however, significant asymmetric induction: an enantiomeric excess of 60–83% was detected (Table 2). As a comparison, use of the unsubstituted azacrown **6** reported earlier resulted in an enantiomeric excess of 61%.[5c] As can be seen, the length of the chain connecting the nitrogen atom and the P=O moiety has a major influence on the enantioselectivity. The catalysts having shorter side arms **5a** (n=1), **5b** (n=2) and **5c** (n=3) were as efficient as reference compound **6** (ee: 60–63%). The use of azacrowns with longer arms **5d** (n=4) and **5e** (n=5) resulted in a significant increase in the enantioselectivity (ee: 79–82%). Among the catalysts tested, lariat ether **5d**, connecting the phosphoryl group by a four carbon atom chain to the nitrogen, proved to be the best: an enantiomeric excess of 82% was observed for the (*S*)-(+)-**8** adduct. This compound (**5d**) seems to have the optimum length for the hydrocarbon spacer connecting the P=O moiety to the nitrogen atom of the azacrown. The phosphonobutyl side arm is flexible and can bend over to assist the complexation responsible for the asymmetric induction.

3. Experimental

The ^{31}P, ^{13}C and ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The coupling constants are given in hertz. EI-mass spectra were obtained on a Finnigan Automass 120 spectrometer at 70 eV. FAB measurements were conducted on a reverse geometry VG ZAB-2SEQ instrument using a 30 kV Cs^+ ion gun and 8 kV accelerating voltage.

The sugar-based bis-iodo podand **4** was synthesized as described earlier.[5a]

3.1. The preparation of ω-aminoalkylphosphonates 3a–e

3.1.1. Diethyl 1-aminomethylphosphonate 3a

Compound **3a** was synthesized from diethyl phthalimidomethylphosphonate **2a** obtained in the Arbuzov reaction of *N*-bromomethylphthalimide and triethyl phosphite[13] by reaction with hydrazine hydrate[14] as shown above for the preparation of aminopropylphosphonate **3c**. ^{31}P NMR ($CDCl_3$) δ 28.0; ^{13}C NMR ($CDCl_3$) δ 16.1 (J=5.4, CH_3), 37.4 (J=149.6, C_α), 61.6 (J=7.0, CH_2CH_3); MS, m/z 167 (M^+).

3.1.2. Diethyl 2-aminoethylphosphonate 3b

Compound **3b** was prepared by the Michael-type addition of ammonia to diethyl vinylphosphonate;[10] bp 96–100°C (0.4 mmHg) [lit.[11] 93–95°C (4.0 mmHg)]; ^{31}P NMR ($CDCl_3$) δ 30.8; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J*=7.2, 6H, Me), 1.85–1.93 (m, 2H, CH_2P), 2.92–3.01 (m, 2H, CH_2N), 4.01–4.13 (m, 4H, CH_2O); MS, *m/z* 181 (M^+).

3.1.3. Diethyl 3-aminopropylphosphonate 3c

A 75 mL DMF solution of 8.60 g (33.2 mmol) of bromopropylphosphonate **1c** and 9.21 g (49.8 mmol) of potassium phthalimide was stirred at 100°C for 8 h. The mixture was cooled to 25°C and the precipitated material filtered off. The filtrate was concentrated in vacuo and the residue so obtained taken up in 100 mL of chloroform. After extraction with 3×30 mL of water, the organic phase was dried ($MgSO_4$). Evaporation of the solvent afforded 10.6 g (93%) of **2c** in a purity of 95% (GC–MS). ^{31}P NMR ($CDCl_3$) δ 31.3; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J*=7.3, 6H, Me), 1.74–2.03 (m, 4H, $(CH_2)_2P$), 3.74 (t, *J*=7.1, 2H, CH_2N), 4.03–4.16 (m, 4H, CH_2O), 7.68–7.86 (m, 4H, Ar) [lit.[12] δ 1.32 (t, *J*=7, 6H, Me), 1.51–2.25 (m, 4H, $(CH_2)_2P$), 3.68 (m, 2H, CH_2N), 4.15 (m, 4H, CH_2O), 7.75 (m, 4H, Ar)]; ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=5.7, Me), 21.9 (*J*=4.4, C_β), 23.3 (*J*=143.1, C_α), 38.1 (*J*=19.7, C_γ), 61.6 (*J*=6.5, CH_2O), 123.1 ($C_{3'}$), 131.9 ($C_{1'}$), 133.9 ($C_{2'}$), 168.1 (C=O); MS, *m/z* (rel. int.) 325 (M^+, 2), 280 (6), 252 (5), 188 (6), 165 (21), 160 (54), 152 (100).

To 10.5 g (30.7 mmol) of **2c** in 130 mL of abs. ethyl alcohol was added 2.1 mL (42.4 mmol) of 98% hydrazine hydrate and the contents of the flask were stirred at reflux for 1 h. The volatile components were removed in vacuo and the oil so obtained distilled to give 2.10 g (51%) of **3c**. Bp 85–90°C (0.2 mmHg) [lit.[10] 114–116°C (1.5 mmHg)]; ^{31}P NMR ($CDCl_3$) δ 32.8; ^{13}C NMR ($CDCl_3$) δ 16.6 (*J*=5.7, Me), 23.2 (*J*=142.0, C_α), 26.6 (*J*=5.0, C_β), 42.7 (*J*=17.4, C_γ), 61.7 (*J*=6.6, CH_2O); MS, *m/z* 195 (M^+).

3.1.4. Diethyl ω-aminoalkylphosphonates 3d and 3e

Intermediates **3d** and **3e** were prepared in a similar way from bromoalkylphosphonates **1d** and **1e** via intermediates **2d** and **2e**, respectively.

2d: Yield 66%; ^{31}P NMR ($CDCl_3$) δ 32.1; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.0, 6H, Me), 1.65–1.89 (m, 6H, $(CH_2)_3P$), 3.70 (t, *J*=7.1, 2H, CH_2N), 4.03–4.16 (m, 4H, CH_2O), 7.68–7.88 (m, 4H, Ar) [lit.[12] δ 1.30 (t, *J*=7, 6H, Me), 1.47–2.10 (m, 6H, $(CH_2)_3P$), 3.63 (m, 2H, CH_2N), 4.05 (m, 4H, CH_2O), 7.75 (m, 4H, Ar)]; ^{13}C NMR ($CDCl_3$) δ 16.4 (*J*=5.5, Me), 19.8 (*J*=4.9, C_β), 25.1 (*J*=141.3, C_α), 29.3 (*J*=16.2, C_γ), 37.2 (C_δ), 61.6 (*J*=6.3, CH_2O), 123.2 ($C_{3'}$), 132.1 ($C_{1'}$), 134.0 ($C_{2'}$), 168.4 (C=O); MS, *m/z* (rel. int.) 339 (M^+, 7), 294 (10), 266 (4), 202 (2), 179 (47), 165 (62), 160 (100), 152 (75).

3d: Yield 73%; ^{31}P NMR ($CDCl_3$) δ 32.1; ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=5.8, Me), 25.1 (*J*=140.9, C_α), 26.0 (*J*=7.1, C_β), 32.0 (*J*=18.5, C_γ), 40.4 (C_δ), 61.3 (*J*=6.3, CH_2O); MS, *m/z* 209 (M^+).

2e: Yield 80%; ^{31}P NMR ($CDCl_3$) δ 32.6; ^{13}C NMR ($CDCl_3$) δ 16.4 (*J*=5.8, Me), 22.0 (*J*=5.1, C_β), 25.3 (*J*=140.6, C_α), 27.6 (*J*=17.0, C_γ), 28.0 (C_δ), 37.6 (C_ε), 61.5 (*J*=6.3, CH_2O), 123.1 ($C_{3'}$), 132.0 ($C_{1'}$), 133.9 ($C_{2'}$), 168.3 (C=O); MS, *m/z* (rel. int.) 353 (M^+, 3), 308 (6), 280 (1), 216 (4), 193 (32), 179 (16), 165 (67), 160 (100), 152 (46).

3e: Yield 89%; ^{31}P NMR ($CDCl_3$) δ 32.7; ^{13}C NMR ($CDCl_3$) δ 16.6 (*J*=5.7, Me), 22.4 (*J*=4.1, C_β), 25.7 (*J*=141.4, C_α), 27.9 (*J*=16.4, C_γ), 29.1 (C_δ), 40.0 (C_ε), 61.6 (*J*=5.8, CH_2O); MS, *m/z* 223 (M^+).

3.2. General procedure for the preparation of methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-h]-N-(O,O-diethyl phosphonoalkyl)-1,4,7,10-tetraoxa-13-azacyclopentadecanes 5a–e

Dry Na_2CO_3 (8.0 g, 75.5 mmol) was suspended in a solution of the corresponding ω-aminoalkylphosphonates **3a–e** (10.5 mmol) and bis-iodo compound **4** (6.60 g, 9.73 mmol) in dry acetonitrile

(200 mL) under argon. The contents of the flask were stirred at boiling point for 48 h until the disappearance of the bis-iodo compound. After cooling, the mixture was filtered and washed with acetonitrile. The combined acetonitrile solution was concentrated in vacuo. The oil so obtained was dissolved in 60 mL of chloroform, washed with 10 mL of water and dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by column chromatography (silica gel, 7% methanol in dichloromethane) to give lariat ethers **5a–e**.

5a: Yield 40%; $[\alpha]_D^{20}$ +39.6 (*c* 1, $CHCl_3$); mp 88–90°C; ^{31}P NMR ($CDCl_3$) δ 28.5; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J*=7.0, 6H, CH_2CH_3), 3.61 (s, 3H, MeO), 3.96–4.06 (m, 4H, OCH_2CH_3), 4.23 (d, *J*=5.8, 1H, C_6-H), 5.10 (d, *J*~3, 1H, C_1-H), 5.75 (s, 1H, C_7-H), 7.30–7.52 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.9 (*J*=6.2, CH_2CH_3), 51.2 (*J*=153.8, C_α), 54.5 (bd, *J*~16.0, CH_2NCH_2), 55.0 (CH_3O), 60.6 (*J*=6.5, CH_3CH_2), 96.9 (C_1), 100.7 (C_7), 125.9 ($C_{2'}$), 128.0 ($C_{3'}$), 128.7 ($C_{4'}$), 137.1 ($C_{1'}$); MS, *m/z* (rel. int.) 589 (M^+, 1), 588 (M–H, 1), 558 (M–31, 6), 544 (M–45, 3), 452 (100), 208 (12), 194 (17), 180 (7), 156 (29), 151 (8). CIMS, *m/z* (rel. int.) 590 (M+H, 10), 452 (100); FAB, 590 (M+H); HRFAB, (M+H) found: 590.2691, $C_{27}H_{45}NO_{11}P$ requires 590.2730.

5b: Yield 46%; $[\alpha]_D^{20}$ +51.1 (*c* 1, $CHCl_3$); mp 83–84°C; ^{31}P NMR ($CDCl_3$) δ 31.7; ^1H NMR ($CDCl_3$) δ 1.36 (t, *J*=7.0, 6H, CH_2CH_3), 3.45 (s, 3H, MeO), 4.09–4.17 (m, 4H, OCH_2CH_3), 4.27 (d, *J*=5.7, 1H, C_6-H), 5.02 (d, *J*=2.9, 1H, C_1-H), 5.56 (s, 1H, C_7-H), 7.36–7.50 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.4 (*J*=4.8, CH_2CH_3), 22.8 (*J*=140.5, C_α), 48.4 (C_β), 53.6 (CH_2NCH_2), 55.2 (MeO), 62.1 (*J*=6.5, OCH_2), 62.3 (C_5), 68.7 (C_6), 81.8 (C_2), 96.8 (C_1), 101.2 (C_7), 125.9 ($C_{2'}$), 128.2 ($C_{3'}$), 129.0 ($C_{4'}$), 136.9 ($C_{1'}$); MS, *m/z* (rel. int.) 602 (M–1, 3), 588 (M–15, 3), 572 (M–31, 6), 558 (M–45, 14), 466 (M–137, 3), 452 (14), 222 (26), 208 (75), 194 (30), 166 (25), 156 (100). CIMS, *m/z* (rel. int.) 604 (M+H, 28), 558 (37), 452 (100); FAB, 604 (M+H); HRFAB, (M+H) found: 604.2832, $C_{28}H_{47}NO_{11}P$ requires 604.2887.

5c: Yield 62%; $[\alpha]_D^{20}$ +43.0 (*c* 1, $CHCl_3$); mp 69–72°C; ^{31}P NMR ($CDCl_3$) δ 32.5; ^1H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.0, 6H, CH_2CH_3), 3.42 (s, 3H, MeO), 4.04–4.14 (m, 4H, OCH_2CH_3), 4.24 (d, *J*=5.3, 1H, C_6-H), 4.94 (d, *J*~2, 1H, C_1-H), 5.54 (s, 1H, C_7-H), 7.29–7.50 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=6.0, CH_2CH_3), 19.5 (C_β), 22.9 (*J*=140.7, C_α), 53.5 (CH_2NCH_2), 54.2 (*J*=15.7, C_γ), 55.0 (MeO), 61.7 (*J*=5.9, OCH_2), 62.2 (C_5), 68.6 (C_6), 81.7 (C_2), 96.9 (C_1), 101.0 (C_7), 125.8 ($C_{2'}$), 128.0 ($C_{3'}$), 128.8 ($C_{4'}$), 137.0 ($C_{1'}$); MS, *m/z* (rel. int.) 616 (M–H, 3), 602 (M–15, 3), 586 (M–31, 8), 572 (M–45, 12), 480 (M–137, 2), 452 (75), 236 (30), 222 (58), 208 (58), 180 (48), 156 (100). CIMS, *m/z* (rel. int.) 618 (M+H, 13), 572 (20), 452 (100); FAB, 618 (M+H); HRFAB, (M+H) found: 618.2957, $C_{29}H_{49}NO_{11}P$ requires 618.3043.

5d: Yield 50%; $[\alpha]_D^{20}$ +38.3 (*c* 1, $CHCl_3$); mp 58–60°C; ^{31}P NMR ($CDCl_3$) δ 33.3; ^1H NMR ($CDCl_3$) δ 1.34 (t, *J*=6.8, 6H, CH_2CH_3), 3.45 (s, 3H, MeO), 4.07–4.18 (m, 4H, OCH_2CH_3), 4.27 (d, *J*=5.3, 1H, C_6-H), 4.98 (d, *J*=2.5, 1H, C_1-H), 5.57 (s, 1H, C_7-H), 7.31–7.50 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.6 (*J*=5.4, CH_2CH_3), 20.8 (C_β), 24.6 (*J*=139.4, C_α), 26.4 (*J*=13.3, C_γ), 54.0 (CH_2N), 55.3 (MeO), 61.9 (*J*=7.2, OCH_2), 62.6 (C_5), 68.9 (C_6), 82.0 (C_2), 97.1 (C_1), 101.3 (C_7), 126.1 ($C_{2'}$), 128.3 ($C_{3'}$), 129.1 ($C_{4'}$), 137.2 ($C_{1'}$); MS, *m/z* (rel. int.) 630 (M–1, 4), 616 (M–15, 3), 600 (M–31, 13), 586 (M–45, 8), 494 (M–137, 3), 452 (88), 250 (18), 236 (43), 222 (88), 193 (46), 156 (100). CIMS, *m/z* (rel. int.) 632 (M+H, 12), 586 (5), 452 (100); FAB, 632 (M+H); HRFAB, (M+H) found: 632.3141, $C_{30}H_{51}NO_{11}P$ requires 632.3200.

5e: Yield 42%; $[\alpha]_D^{20}$ +21.2 (*c* 1, $CHCl_3$); syrup; ^{31}P NMR ($CDCl_3$) δ 32.5; ^1H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.1, 6H, CH_2CH_3), 3.43 (s, 3H, MeO), 4.02–4.12 (m, 4H, OCH_2CH_3), 4.26 (d, *J*=5.3, 1H, C_6-H), 4.97 (b s, 1H, C_1-H), 5.54 (s, 1H, C_7-H), 7.32–7.48 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=5.4, CH_2CH_3), 22.0 (*J*=4.9, C_β), 25.2 (*J*=140.5, C_α), 27.7 (*J*=16.8, C_γ), 28.6 (C_δ), 53.7 (CH_2N), 55.0 (MeO), 61.2 (*J*=6.4, OCH_2), 62.1 (C_5), 68.7 (C_6), 81.9 (C_2), 97.4 (C_1), 101.0 (C_7), 125.8 ($C_{2'}$), 128.0 ($C_{3'}$), 128.8 ($C_{4'}$), 137.0 ($C_{1'}$); MS, *m/z* (rel. int.) 644 (M–H, 7), 630 (M–15, 4), 614 (M–31, 13), 600 (M–45, 7), 508 (M–137, 6), 452 (86), 264 (21), 250 (38), 236 (100), 207 (36), 156 (77). CIMS,

m/z (rel. int.) 646 (M+H, 22), 600 (5), 452 (100); FAB, 646 (M+H); HRFAB, (M+H) found: 646.3335, $C_{31}H_{53}NO_{11}P$ requires 646.3356.

3.3. General procedure for the Michael addition of 2-nitropropane to chalcone in the presence of azacrown 5a–e

The corresponding azacrown **5a–e** (0.1 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) were added to the solution of chalcone **7** (0.3 g, 1.44 mmol) and 2-nitropropane (0.3 mL, 3.36 mmol) in dry toluene (3 mL). The mixture was stirred under an argon atmosphere at room temperature. After a reaction time of 48 h, a new portion of toluene (7 mL) was added and the mixture stirred with water (10 mL). The organic phase was washed with water (7 mL) and dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by preparative TLC (silica gel, hexane:ethyl acetate, 10:1, eluant) to give pure **8**; mp 146–148°C; $[\alpha]_D^{20}$ +80.8 (*c* 1.5, dichloromethane) for the pure (+)-(*S*)-enantiomer.[5b] ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.27 (dd, 1H, J_1=17.2, J_2=3.2, COCH), 3.67 (dd, 1H, J_1=17.2, J_2=10.4, COCH), 4.15 (dd, 1H, J_1=10.4, J_2=3.2, CH_2CH), 7.18–7.32 (m, 5H, CHPh), 7.42–7.85 (m, 5H, C(O)Ph).

References

1. (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009–1020; (b) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–114.
2. (a) Allwood, B. L.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1984**, *22*, 1461–1464; (b) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229–7230; (c) Cram, D. J.; Sogah, D. Y. *J. Am. Chem. Soc.* **1985**, *107*, 8301–8302; (d) Crosby, J.; Stoddart, J. F.; Sun, X.; Venner, M. R. W. *Synthesis* **1993**, 141–145.
3. (a) Stoddart, J. F. *Top. Stereochem.* **1987**, *17*, 207–288; (b) Coteron, J. M.; Vicent, C.; Bosso, C.; Penades, S. *J. Am. Chem. Soc.* **1993**, *115*, 10066–10076.
4. Tőke, L.; Bakó, P.; Keserű, M. Gy.; Albert, M.; Fenichel, L. *Tetrahedron* **1998**, *54*, 213–222 and references cited therein.
5. (a) Bakó, P.; Tőke, L. *J. Incl. Phenom.* **1995**, *23*, 195–201; (b) Bakó, P.; Szöllősy, Á.; Bombicz, P.; Tőke, L. *Synlett* **1997**, 291–292; (c) Bakó, P.; Kiss, T.; Tőke, L. *Tetrahedron Lett.* **1997**, *38*, 7259–7262.
6. (a) Bakó, P.; Vízvárdi, K.; Bajor, Z.; Tőke, L. *J. Chem. Soc., Chem. Commun.* **1998**, 1193–1194; (b) Bakó, P.; Vízvárdi, K.; Toppet, S.; Van der Eycken, E.; Hoornaert, G. J.; Tőke, L. *Tetrahedron* **1998**, *54*, 14975–14988.
7. Gokel, G. W. *Chem. Soc. Rev.* **1992**, *21*, 39–47.
8. Keglevich, Gy.; Novák, T.; Bakó, P.; Újszászy, K.; Ludányi, K.; Tóth, K.; Tőke, L. *J. Incl. Phenom.* **1999**, *34*, 299–309.
9. Kimura, K.; Maeda, T.; Shomo, T. *Talanta* **1979**, *26*, 945–949.
10. Rosowsky, A.; Forsch, R. A.; Moran, R. G.; Kohler, W.; Freisheim, J. H. *J. Med. Chem.* **1988**, *31*, 1326–1331.
11. Pudowik, A. N.; Denisowa, G. M. *Zh. Obshch. Khim.* **1953**, *23*, 263–267.
12. Chun, Y.-J.; Park, J.-H.; Oh, G.-M.; Hong, S.-I.; Kim, Y.-J. *Synthesis* **1994**, 909–910.
13. Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2531–2534.
14. Yamauchi, K.; Mitsuda, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3285–3286.

B14

Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4539–4551

TETRAHEDRON: *ASYMMETRY*

Asymmetric C–C bond forming reactions with chiral crown catalysts derived from D-glucose and D-galactose

Péter Bakó,[a] Erzsébet Czinege,[a] Tibor Bakó,[a] Mátyás Czugler[b] and László Tőke[c,*]

[a]*Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, PO Box 91, Hungary*

[b]*Central Research Institute of Chemistry for Hungarian Academy of Sciences, H-1525 Budapest, Hungary*

[c]*Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, PO Box 91, Hungary*

Received 20 October 1999; accepted 2 November 1999

Abstract

New chiral monoaza-15-crown-5 derivatives anellated to methyl-4,6-*O*-benzylidene-α-D-glucopyranoside **2a**, **2e**, **2g–i** and to methyl-4,6-*O*-benzylidene-α-D-galactopyranoside **3a**, **3e**, **3i** have been synthesized. These crown ethers showed significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone (87% ee), in the Darzens condensation of phenacyl chloride with benzaldehyde (71% ee) and in the self-condensation of phenacyl chloride (64% ee) to give **14**. The absolute configurations of (−)-(2*R*,3*S*)-epoxy-3-(4-chlorophenyl)-1-phenyl-1-propanone **12** and (−)-4-chloro-(2*R*,3*S*)-epoxy-1,3-diphenyl-1-butanone **14** have also been determined by X-ray diffraction. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Phase-transfer catalysis has been recognized as a practical methodology for organic synthesis due to its operational simplicity, mild reaction conditions, safety considerations, and environmental concerns. In addition, the development of novel phase-transfer catalyzed asymmetric reactions is of considerable industrial interest. One of the most up-to-date and interesting techniques of catalytic asymmetric synthesis is a phase-transfer reaction in which the enantioselectivity is generated by a chiral crown-ether catalyst.[1] A special group of optically active crown ethers are compounds whose carbohydrate moieties function as carriers of chirality. In the past two decades numerous macrocycles built up of one or more monosaccaride units have been synthesized.[2] Cheap natural sugars are attractive starting materials for organic syntheses. However, so far, only a limited number of asymmetric reactions have been demonstrated in which a sugar-based crown-ether catalyst produced a good enantiomeric excess.[1]

* Corresponding author. E-mail: toke.oct@chem.bme.hu

0957-4166/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(99)00485-1

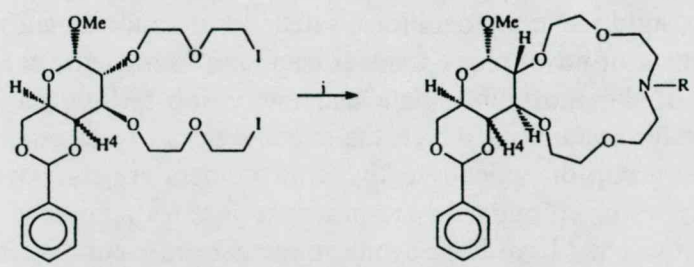
A synthesis of a new monoaza-15-crown-5 type macrocycle, containing D-glucopyranoside- and D-galactopyranoside units, respectively, has been recently reported.[3] Until now we have carefully examined two important reaction types, the Michael addition to an electrophilic double bond and the Darzens condensation, in which these crown ethers proved to be effective catalysts.[4] It was shown that the flexibility of the chiral macrocycle, the type of carbohydrate building blocks, the type of the substituents in the carbohydrate unit and at the nitrogen atom of the macrocycle play the most important roles in the generation of asymmetric induction. Furthermore, the so-called lariat ethers, in which the *N*-substituent contains an electron donating heteroatom (O, P) in the proper place, have also been studied.[5]

In the present paper, the synthesis of the crown ethers, the study of relationships between the catalysts' structure and their effect in the above mentioned reactions is disclosed with a more detailed experimental. Also included are experiments on the self-condensation of the phenacyl chloride reagent giving Darzens type products in a diastereoselective and enantioselective process.

2. Results and discussion

2.1. Synthesis

The new 15-crown-5 type compounds incorporating methyl-4,6-*O*-benzylidene-α-D-glucopyranoside and galactopyranoside as well as a nitrogen atom in the macrocycle, **2** and **3**, respectively, were synthesized using the same route as described by us previously.[3] The glucopyranoside based bis-iodo compound **1a** was cyclized with various primary amines, such as *n*-butylamine, 2-phenylethylamine, 3-hydroxypropylamine, 4-hydroxybutylamine and 2-methoxyethylamine (Scheme 1). The method requires dry sodium carbonate in acetonitrile solvent (reflux, 24–48 h). In dilute solutions (1–3%) polycondensation side reactions are suppressed and the desired intramolecular cyclization reaction takes place preferentially. After the usual work-up procedure and chromatographic purification, macrocycles **2a–i** were obtained in 44–64% yields. By the same method **3a**, **3e** monoaza-crown ethers and **3i** lariat ether were synthesized in 49–75% yields, starting from galactose-based bis-iodo compound **1b** and the corresponding primary amines. The structures of the ligands were confirmed via the analysis of their respective ^{1}H NMR, ^{13}C NMR spectra and by CIMS and FABMS. The $[M+H]^+$ fragment was present in all cases in the CIMS and FABMS spectra, the most intense in the CIMS spectra being *m/z* 452 fragment characteristic of the [crown-*N*-CH_2]$^+$ ion (see Experimental).



1a $H^4 = \beta$ **2** $H^4 = \beta$

1b $H^4 = \alpha$ **3** $H^4 = \alpha$

Scheme 1. Cyclization with amines. Glucose-based **2** and galactose-based crown ether **3**. Reagents and conditions: (i) CH_3CN, reflux, 28–36 h, RNH_2, R=butyl **2a**, **3a**, 2-phenylethyl **2e**, **3e**, 3-hydroxypropyl **2g**, 4-hydroxybutyl **2h**, 2-methoxyethyl **2i**, **3i**

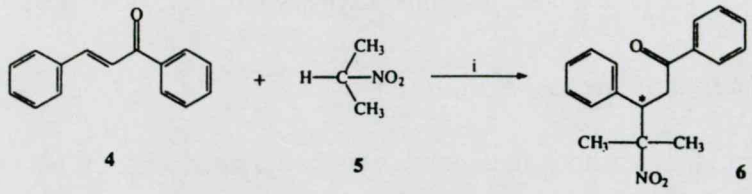
2.2. Asymmetric induction in Michael additions

The Michael addition of carbon nucleophiles to conjugated enones is one of the most powerful methods for carbon–carbon bond formation. Due to its relevance in the synthesis of biologically active compounds, much effort has been centered on carrying out this reaction in a stereoselective way.[6a] The stereoselective variants of the addition of enolates or their analogues to the carbon–carbon double bond of the α,β-unsaturated ketones or aldehydes have been extensively investigated in recent years.[6b,c] To the best of our knowledge, only one reaction is known in which significant asymmetric induction has been achieved with sugar-based crown-ether catalysts, and that is the Michael addition of methylphenylacetate to methylacrylate.[7] Now we describe our results with another Michael reaction, in which the new catalysts are also effective: the Michael addition of 2-nitropropane **5** to the chalcone **4** that was performed with 60–82% enantiomeric excess in a solid–liquid phase-transfer system[4] (Scheme 2). The addition was carried out in dry toluene, in the presence of a chiral catalyst (5 mol%) and solid sodium tertiary butoxide as base (35 mol%) at room temperature. After the usual work-up procedure, the adduct **6** was isolated by preparative TLC; the enantiomeric excess (ee%), was monitored by measuring the optical rotation of the product **6** and comparing the specifications with literature data for the preferred pure enantiomer and by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as a chiral shift reagent. For comparison purposes, our earlier results[4a,b] with **2b–d** and **2f** are also incorporated in Table 1. The results show that the type of the monosaccharide and the substituent at the nitrogen atom of the catalyst have the most significant influence on both the chemical yield and the enantiomeric excess.

Table 1
Addition of 2-nitropropane to chalcone catalyzed by chiral crown ethers[a]

Entry	Catalyst	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**	$CH_3(CH_2)_3$	40	41	58
2[e]	**2b**	C_6H_{11}	22	42	47
3[e]	**2c**	C_6H_5	30	21	10
4[e]	**2d**	$C_6H_5CH_2$	22	39	46
5	**2e**	$C_6H_5CH_2CH_2$	36	44	61
6[e]	**2f**	$HOCH_2CH_2$	20	51	62 (63[d])
7	**2g**	$HO(CH_2)_3$	28	53	85
8	**2h**	$HO(CH_2)_4$	48	52	85
9	**2i**	$CH_3OCH_2CH_2$	40	45	87 (88[d])
10	**3a**	$CH_3(CH_2)_3$	41	34	47
11	**3e**	$C_6H_5CH_2CH_2$	40	41	49
12	**3i**	$CH_3OCH_2CH_2$	38	34	52

[a] (+)-(*S*) enantiomer is always in excess; [b] Based on substance isolated by preparative TLC; [c] Determined by optical rotation; [d] Determined by ^{1}H NMR spectroscopy; [e] Lit. 4a, b



4 5 6

Scheme 2. Michael addition of 2-nitropropane to chalcone. Reagents and conditions: (i) catalyst **2** or **3**, NaOBu^t, toluene, 20°C

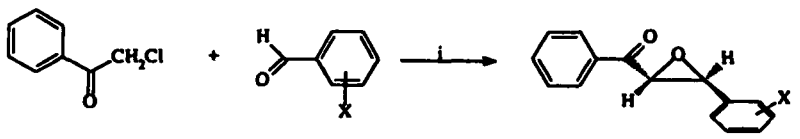
Among the glucopyranose derivatives **2a–i** it was the crown **2c** (phenyl group at the nitrogen) which gave the worst result (21% chemical yield, 10% ee). The catalytic effect was better with *N*-cyclohexyl and *N*-benzyl derivatives (**2b**, 47% ee; **2d**, 46% ee), and further increased with *N*-butyl (**2a**, 58% ee), and *N*-phenylethyl derivatives (**2e**, 61% ee). When the side arm cooperation in the complexation could operate (lariat ethers) again an increase in the ee value was detected: in the case of the *N*-2-hydroxyethyl derivative **2f** it was 62%, with the *N*-3-hydroxypropyl crown **2g** the ee value was 85%. However, further increase in the chain length did not increase the ee% value (**2h** has 85% ee). Interestingly we observed that the **2i** methylether derivative induced a higher enantioselectivity (87% ee) than its analogue containing a free hydroxyl group (61% ee). It can be seen that the chain length of the substituents is of crucial importance. In the case of the galactopyranose derivatives **3a**, **3e**, and **3i** the ee% observed were lower than those for the corresponding **2a**, **2e**, and **2i** (Table 1) in spite of the fact that the stability constants of the galactose containing crown ethers with sodium ion were found to be higher than those for the glucose derivatives.[3]

2.3. *Darzens condensation*

The Darzens reaction, which allows the generation of new stereocenters with complete diastereocontrol, is one of the most powerful methodologies for the synthesis of α,β-epoxy carbonyl and related compounds, and therefore has been recognized as one of most significant C–C bond forming processes in synthetic organic chemistry. Although many trials have been performed aimed at developing an asymmetric variant of the section in recent decades, many of them require a stoichiometric amount of a chiral source[8] and only a few examples which proceed catalytically are known.[9] The special attention paid to the Darzens reactions is justified by their pharmaceutical significance, e.g.: diltiazem is a widely prescribed cardiovascular drug.[10]

As already described in our preliminary report,[4a] the previously discussed chiral crown ethers proved to be effective asymmetric catalysts in the condensation of phenacyl chloride **7** with benzaldehyde **8a** (Scheme 3). This reaction was studied by many researchers, and in the presence of one of the most frequently used chiral phase-transfer catalysts benzyl quininium chloride 8% ee was achieved,[9a] while *N*-(4-trifluoromethylbenzyl)cinchoninium bromide resulted in 42% ee.[9d]

We performed the above reaction in both a liquid–liquid (LL) and solid–liquid (SL) system. Since our catalysts were more effective in LL phase-transfer conditions, this technique was studied thoroughly. Solvent, base, reaction time and temperature were varied until optimal reaction conditions were established. Reagents and the catalyst (5 mol%) were dissolved in toluene and reaction was initiated by adding 30% sodium hydroxide (volume ratio: 3:1, reaction time: 1–4 h). Following the usual work-up procedure, the pure epoxy ketone was separated by preparative TLC. The diastereomeric ratio of the product was determined by ^{1}H NMR spectroscopy, enantiomeric excess (ee%) by rotatory power measurements or by ^{1}H NMR in the presence of a chiral shift reagent. In each case the *trans*-epoxy ketone **9** was formed (de >98%) and its levorotatory enantiomer was found to be in excess. This corresponds to an absolute configuration of 2*R*,3*S*.[11] The most important results and reaction conditions are shown in Table 2. From



7 **8a** X = H **9** X = H

8b X = o-NO_2 **10** X = o-NO_2

8c X = p-NO_2 **11** X = p-NO_2

8d X = p-Cl **12** X = p-Cl

8e X = p-OMe **13** X = p-OMe

Scheme 3. Darzens condensation of phenacylchloride with benzaldehyde. Reagents and conditions: (i) crown-ether catalyst, 30% NaOH, toluene

Table 2
Asymmetric Darzens condensation of phenacyl chloride with benzaldehyde in the presence of chiral crown ethers[a]

Entry	Catalyst	Temperature (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**	22	4	74	21
2	**2c**	22	1	43	4
3	**2d**	22	1	67	13
4	**2e**	22	6	54	31
5	**2f**	22	1	90	42 (41[d])
6	**2f**	-5	2	88	59 (59[d])
7	**2f**	-20	4	76	64 (65[d])
8	**2g**	22	1	74	62
9	**2g**	-20	1	49	71 (72[d])
10	**2h**	22	1	65	26
11	**2i**	22	1	59	19
12[e]	**2f**	-20	3	44	39

[a] (-)-(2*R*,3*S*) enantiomer is always in excess; [b] Based on isolation by preparative TLC; [c] Determined by optical rotation; [d] Determined by ^{1}H NMR spectroscopy; [e] In SL system.

Table 2 it is obvious that, concerning asymmetric induction, the worst catalysts are **2c** (*N*-phenyl, 4% ee) and **2d** (*N*-benzyl, 13% ee). The compounds **2a** and **2e** possessing butyl and 2-phenylethyl side arms, respectively, were somewhat better catalysts (21% ee and 31% ee, respectively). The effect of the terminal hydroxyl groups was advantageous: 42% ee was achieved with 2-hydroxyethyl containing **2f**, and 62% ee with 3-hydroxypropyl substituted **2g**. However, further increases in chain length did not result in higher ees: in the presence of catalyst **2h** containing 4-hydroxybutyl substituent, the ee value of the epoxy ketone **9** dropped to 26%, there is an optimum in the chain length of the *N*-substituent.

The hydrophilic terminal group was found to have an important role in the toluene–water phase-transfer system: the free OH-group at the end of the substituent significantly decreased the catalytic effect, e.g. **2i** methylether derivative resulted in only 19% ee. Furthermore, from Table 2 it is obvious (entries 5–7 and 8–9) that a drop in the temperature increased the enantioselectivity: e.g. at room temperature with crown ether **2f** 42% ee was achieved, compared to 64% ee at −20°C. Maximum enantioselectivity (71% ee) was achieved with catalyst **2g** (having a 3-hydroxypropyl side arm) at −20°C. At temperatures lower than −20°C the reaction mixture solidified. An experiment carried out in a SL system (Table 2, entry 12), in the presence of NaOBu^t base, **2f** (possessing a 2-hydroxyethyl side arm) gave 39% ee.

We were also studying the Darzens condensation of phenacyl chloride with various substituted benzaldehydes under the same reaction conditions as previously described. Results of the reactions performed with catalyst **2g** at ambient temperature are summarized in Table 3. Reactions below room temperature could not be performed due to solubility problems. In the reaction with *o*-nitro-benzaldehyde (entry 1) the best chemical yield (71%) was obtained along with the lowest enantioselectivity (29% ee). One possible explanation is that the presence of an electron attracting group near the reaction center is advantageous regarding the chemical reaction itself, but its steric position is disadvantageous regarding the formation of a stereogenic carbon atom. Furthermore, it was observed that in the case of benzaldehydes with *para* electron attracting substituents the corresponding epoxy ketones[12] were obtained with approximately the same enantiomeric excess (*p*-NO_2 **11** 61% ee and *p*-Cl **12** 59% ee) as in the case of the unsubstituted benzaldehyde (62% ee). A methoxy group in the *para* position drastically decreased both the chemical yield (31%) and the enantioselectivity (12% ee). After repeated crystallization we managed to obtain pure levorotatory enantiomers of *trans-p*-NO_2 substituted **11** and *trans-p*-Cl substituted **12** epoxy ketones, and their specific rotatory power was determined. Their absolute configuration has not been studied so far, and is only assumed to be 2*R*,3*S*.[13] We have succeeded in obtaining a single crystal from the pure levorotatory enantiomer of *trans-p*-Cl substituted **12** epoxy ketone, and the subsequent X-ray studies (Fig. 1) confirmed its absolute configuration as 2*R*,3*S*.

Table 3
Asymmetric Darzens condensation of phenacyl chloride with substituted benzaldehyde in the presence of catalyst **2g**[a]

Entry	X	Yield (%)[b]	$[\alpha]_D$[c]	ee (%)[d]
1	o-NO_2	71	-48,7	29
2	p-NO_2	63	-161	61
3	p-Cl	54	-127	59
4	p-OMe	31	-16	12
5[e]	p-NO_2	29	-31	11

[a] At room temperature; [b] Based isolation by preparative TLC; [c] 20 °C, c=1, CH_2Cl_2; [d] Determined by ^{1}H NMR spectroscopy; [e] In SL system.

Scheme 4 describes a possible reaction path for the mechanism. Under the influence of the crown ether the sodium enolate gets solubilized in toluene thereby ensuring the chiral environment for the next step, in which the *Si* face of the enolate attacks the *Re* face of the aldehyde. The stereochemistry of the reaction is probably decided in this first, possibly slowest step, in which an intermediate with the 2*S*,3*S*

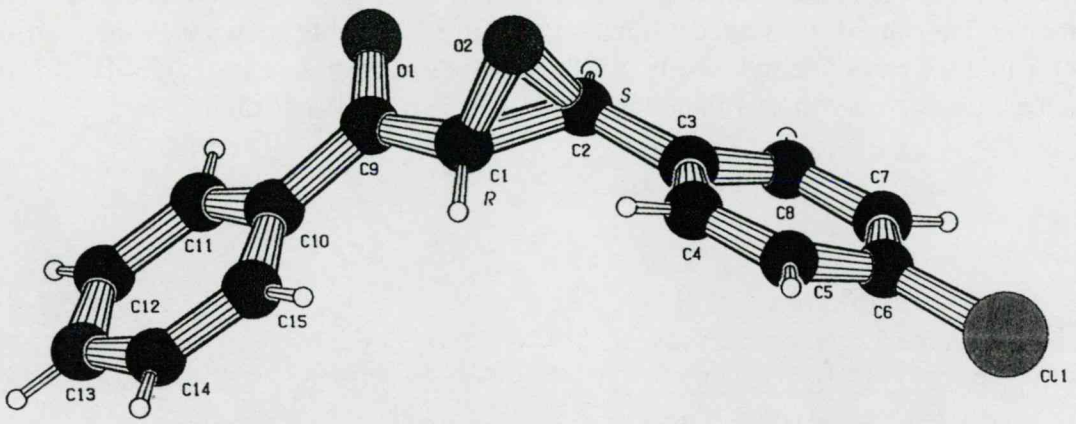
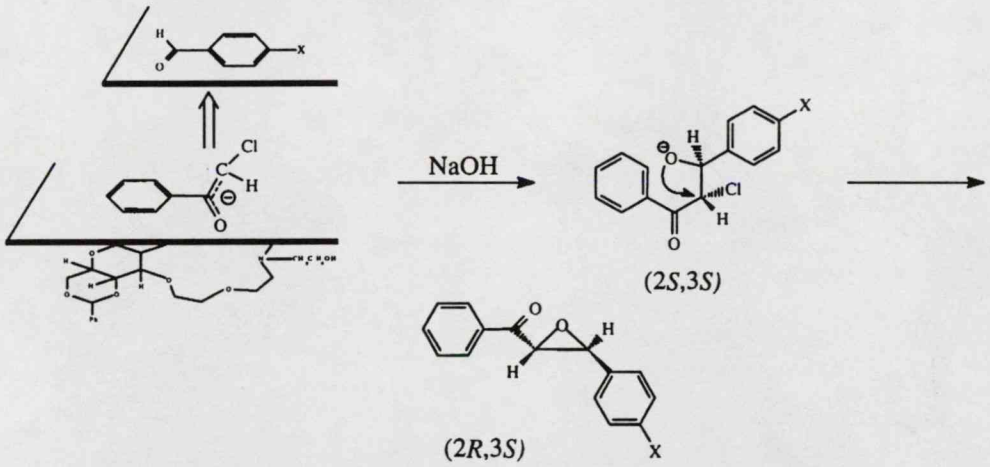


Fig. 1. Molecular structure of **12** with atomic labeling used in the X-ray analysis

configuration is formed. Following this, the configuration at C-2 is inverted to *R* by an S^{i}_{N} process, thus giving the end-product with 2*R*,3*S* stereochemistry.

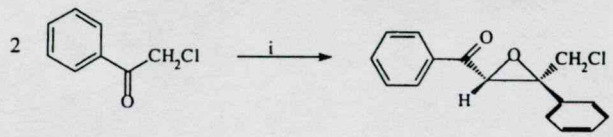


Scheme 4. Presumed reaction mechanism of the enantioselective Darzens condensation

2.4. *Self-condensation of phenacyl chloride*

During analysis of the by-products of the Darzens condensation, we have isolated an optically active by-product, which was found to be the base initiated self-condensation product of phenacyl chloride: 4-chloro-2,3-epoxy-1,3-diphenyl-butan-1-one (Scheme 5). This product has already been reported as a mixture of the racemic diastereomers.[14,15] The self-condensation of phenacyl chloride was then studied under the previously described conditions (toluene, 30% sodium hydroxide) in the presence of **2g** sugar-based crown-ether catalyst. By ^{1}H NMR spectroscopy we have shown that the ratio of *cis:trans* isomers was 23:77 in the condensation product, and these isomers were chromatographically separated. It was found that in the *trans* isomer the levorotatory enantiomer was in excess (64% ee). By repeated crystallization we have managed to isolate the pure levorotatory enantiomer, and obtained a single crystal. Crystal structure determinations of **12** and **14** showed that the stereogenic asymmetric carbons in both compounds (Figs. 1 and 2) have the respective 2*R*,3*S* configuration. The structures have normal bonding geometry. Intermolecular distances in the crystalline environment have only two peculiarities. One is that

in **12** there is a short H···H contact ($d_{H1\cdots H15}$=2.06 Å). The other is that both structures exhibit signs of the *chloro* effect.[16] The chloro substituted aromatic group in **12** probably causes the characteristic short *a* axis (~4.4 Å), while the chloromethyl moiety in **14** gives rise to numerous Cl···X (X=H, C, O) contacts, some of which are appreciably shorter than the sum of their van der Waals radii.



7 **14**

Scheme 5. Self-condensation of phenacyl chloride. Reagents and conditions: (i) crown-ether catalyst **2g**, 30% NaOH, toluene

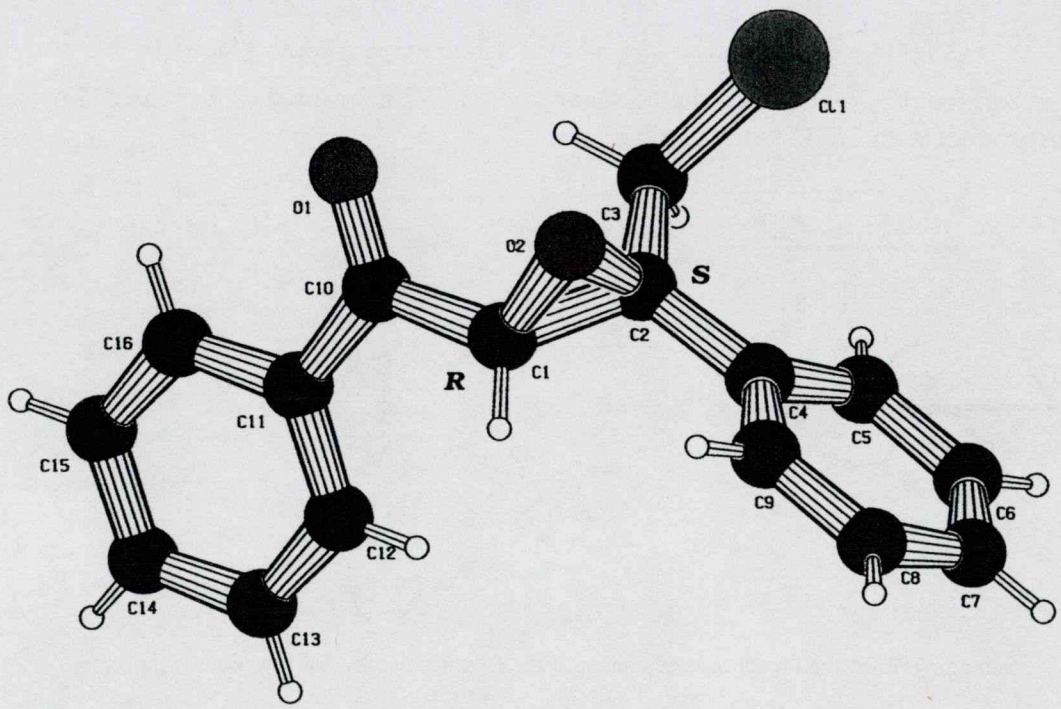


Fig. 2. Molecular structure of **14** with atomic labeling used in the X-ray analysis

Our research activity is being continued in field of the self-condensation of phenacyl chloride: the effect of other chiral catalysts in this reaction is being studied.

3. Experimental

3.1. General procedures

Melting points were determined with Büchi 510 apparatus and are uncorrected. Specific rotation was measured on a Perkin–Elmer 241 polarimeter at 20°C, and IR spectra were recorded on a Perkin–Elmer 237 spectrophotometer. NMR spectra were recorded on a Bruker WM 250 instrument in $CDCl_3$. The

mass spectra were obtained on a Jeol JMS-01 SG-2 instrument. Chemical ionization was applied as the ionization technique. 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).

3.2. *General method for preparation of crown ethers*

Dry Na_2CO_3 (3.84 g, 36.2 mmol) was suspended in a solution of 4.60 mmol of the corresponding primary amine and 3.45 g (4.6 mmol) of bis-iodo compound **1** in 110 mL of dry acetonitrile under argon. The stirred reaction mixture was refluxed for 24–48 h and monitored by TLC until the disappearance of the bis-iodo compound. After cooling, the precipitate was filtered and washed with acetonitrile. The combined acetonitrile solution was concentrated at reduced pressure. The residue oil was dissolved in $CHCl_3$, washed with water and dried over Na_2SO_4 and the solvent evaporated under vacuum. The corresponding monoaza-crown ether was isolated by column chromatography.

3.2.1. *Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-h]-N-butyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* **2a**

The column chromatography was carried out with eluent dichloromethane:methanol (100:5) on silica gel. Yield 64% (yellow oil); $[\alpha]_D^{20}$ +32 (c 1, $CHCl_3$); IR (neat) 2926, 2869, 1600, 1491, 1368, 1228, 1093, 1031, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.3 Hz, 3H, CH_3), 1.28–1.76 (m, 4H, $CH_3CH_2CH_2$), 2.65–2.88 (m, 6H, $3NCH_2$), 3.40 (s, 3H, OCH_3), 3.48–4.07 (m, 16H, CH and CH_2 groups), 4.33 (dd, J=10.5 Hz, 1H, H-6), 4.77 (d, J=3.6 Hz, 1H, anomeric-H), 5.48 (s, 1H, PhCH), 7.18–7.53 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.6, 29.6, ($CH_3CH_2CH_2$), 54.0, 54.5 (CH_2NCH_2), 55.0 (OCH_3), 56.5 (NCH_2), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 ($6OCH_2$ of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 96.9 (C-1), 100.9 (PhCH), 125.9 (PhC-*o*), 128.2 (PhC-*m*), 129.0 (PhC-*p*), 137.3 (PhC-*ipso*); FABMS *m/z* 496 (M+H). Anal. calcd for $C_{26}H_{41}NO_8$: C, 63.03; H, 8.28; N, 2.83%. Found: C, 62.98; H, 8.25; N, 2.81%.

3.2.2. *Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-h]-N-(2-phenyl)ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* **2e**

The purification was carried out by column chromatograpy with eluent chloroform:methanol (10:1) on silica gel. Yield 48% (yellow crystals); mp 73–75°C (ether); $[\alpha]_D^{20}$ +32.4 (c 1, $CHCl_3$); IR (KBr) 2913, 2866, 1600, 1492, 1368, 1230, 1127, 1092, 751, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76–2.88 (m, 8H, $3NCH_2$ and CH_2Ph), 3.43 (s, 3H, OCH_3), 3.48–3.86 (m, 17H, CH and CH_2 groups), 4.23 (dd, J=10.5 Hz, 1H, H-6), 4.76 (d, J=3.6 Hz, 1H, anomeric-H), 5.47 (s, 1H, PhCH), 7.12–7.53 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 34.0 (NCH_2CH_2Ph), 54.1, 54.3 (CH_2NCH_2), 58.7 (NCH_2CH_2Ph), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 ($6OCH_2$ of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 96.9 (C-1), 100.9 (PhCH), 125.9 (PhC-*o*), 126.0 (PhC-*o*), 128.2 (PhC-*m*), 128.3 (PhC-*m*), 129.0 (PhC-*p*), 129.6 (PhC-*p*), 137.3 (PhC-*ipso*), 140.5 (PhC-*ipso*); ClMS *m/z* (rel. int.) 544 (M+H, 29), 512 (72), 452 (100). Anal. calcd for $C_{30}H_{41}O_8N$: C, 66.29; H, 7.55; N, 2.58; Found: C, 66.31; H, 7.52; N, 2.57%.

3.2.3. *Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-h]-N-3-hydroxypropyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* **2g**

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:5→100:10) on silica gel. Yield: 58% (yellow crystals); mp 58–60°C; $[\alpha]_D^{20}$ +52.4 (c 1, $CHCl_3$); IR (neat) 3120–3600, 2920, 2875, 1600, 1491, 1236, 1093, 756, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67–1.98

(m, 2H, $NCH_2CH_2CH_2$), 2.25–2.43 (m, 2H, CH_2), 2.73–3.01 (m, 6H, $3NCH_2$), 3.43 (s, 3H, OCH_3), 3.52–3.90 (m, 13H, CH and CH_2 groups), 4.01–4.10 (m, 4H, $2OCH_2$), 4.26 (dd, J=10.5 Hz, 1H, H-6), 4.83 (d, J=3.6 Hz, 1H, anomeric-H), 5.0 (s, 1H, OH), 5.50 (s, 1H, PhCH), 7.27–7.43 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.4 ($NCH_2CH_2CH_2$), 54.3 (CH_2NCH_2), 56.4 ($NCH_2CH_2CH_2$), 64.0 ($NCH_2CH_2CH_2$), 66.1 (C-5), 68.7 (C-6), 68.8, 68.9, 70.2, 70.3, 72.3, 72.5 ($6OCH_2$ of the macrocycle), 80.9, 81.4 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.1 (C-1), 125.9 (PhC-*o*), 128.2 (PhC-*m*), 129.0 (PhC-*p*), 137.3 (PhC-*ipso*); FABMS *m/z* 498 (M+H, 100). Anal. calcd for $C_{25}H_{39}O_9N$: C, 60.36; H, 7.85; N, 2.82%. Found: C, 60.30; H, 7.79; N, 2.80%.

3.2.4. Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-h]-N-4-hydroxybutyl-1,4,7,10-tetraoxa-13-azacyclopentadecane 2h

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:1→100:5) on silica gel. Yield: 51% (yellow oil); $[\alpha]_D^{20}$ +38.4 (c 1, CH_2Cl_2); IR (neat) 3120–3600, 2920, 2875, 1600, 1491, 1236, 1093, 756, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54–1.70 (m, 4H, $2CH_2$), 2.47–2.91 (m, 6H, $3NCH_2$), 3.37 (s, 3H, OCH_3), 3.46–3.93 (m, 20H, CH and CH_2 groups), 4.24 (dd, J=10.5 Hz, 1H, H-6), 4.80 (d, J=3.6 Hz, 1H, anomeric-H), 5.48 (s, 1H, PhCH), 7.23–7.46 (m, 5H, Ph); FABMS *m/z* 512 (M+H). Anal. calcd for $C_{26}H_{41}O_9N$: C, 61.05; H, 8.02; N, 2.73%. Found: C, 61.15; H, 8.10; N, 2.70%.

3.2.5. Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-h]-N-2-methoxyethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane 2i

The purification was carried out by column chromatography with eluent dichloromethane:methanol (10:2) on silica gel. Yield: 44% (yellow crystals); mp 78–79°C (ether); $[\alpha]_D^{20}$ +41.6 (c 1.2, $CHCl_3$); IR (KBr) 2920, 2876, 1600, 1496, 1388, 1239, 1093, 749, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71–2.92 (m, 6H, $3NCH_2$), 3.31 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.46–3.90 (m, 19H, CH and CH_2 groups), 4.23 (dd, 1H, J=10.5 Hz, H-6), 4.82 (d, J=3.6 Hz, 1H, anomeric-H), 5.50 (s, 1H, PhCH), 7.23–7.46 (m, 5H, Ph); CIMS *m/z* (rel. int.) 498 (M+H, 15), 452 (100); FABMS *m/z* 498 (M+H). Anal. calcd for $C_{25}H_{39}O_9N$: C, 60.36; H, 7.85; N, 2.82%. Found: C, 60.28; H, 7.80; N, 2.78%.

3.2.6. Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-galactopyranosido[2,3-h]-N-butyl-1,4,7,10-tetraoxa-13-aza-cyclopentadecane 3a

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:1→100:5) on silica gel. Yield: 61% (yellow oil); $[\alpha]_D^{20}$ +91.8 (c 1, $CHCl_3$); IR (KBr) 2926, 2869, 1600, 1491, 1368, 1228, 1093, 1031, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J=7.3 Hz, 3H, CH_3), 1.27–1.74 (m, 4H, CH_2), 2.65–2.88 (m, 6H, $3NCH_2$), 3.40 (s, 3H, OCH_3), 3.48–4.14 (m, 18H, CH and CH_2 groups), 4.36 (dd, J=2.8 Hz, 1H, H-6), 4.86 (d, J=2.6 Hz, 1H, anomeric-H), 5.52 (s, 1H, PhCH), 7.18–7.52 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.6, 29.6 ($CH_3CH_2CH_2$), 54.0, 54.5 (CH_2NCH_2), 55.0 (OCH_3), 56.5 (NCH_2), 66.1 (C-5), 68.6 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 ($6OCH_2$ of the macrocycle), 81.1, 81.6 (C-3, C-4), 81.6 (C-2), 100.0 (C-1), 100.9 (PhCH), 125.9 (PhC-*o*), 128.2 (PhC-*m*), 129.0 (PhC-*p*), 137.2 (PhC-*ipso*); FABMS *m/z* 496 (M+H). Anal. calcd for $C_{26}H_{41}NO_8$: C, 63.03; H, 8.28; N, 2.83%. Found: C, 63.07; H, 8.25; N, 2.80%.

3.2.7. Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-galactopyranosido-[2,3-h]-N-(2-phenyl)ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane 3e

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:5→100:10) on silica gel. Yield: 49% (yellow syrup) $[\alpha]_D^{20}$ +103 (c 1, $CHCl_3$); IR (KBr) 2913,

2866, 1600, 1492, 1368, 1230, 1127, 1092, 751, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73–2.87 (m, 8H, $3NCH_2$ and CH_2Ph), 3.40 (s, 3H, OCH_3), 3.53–4.16 (m, 17H, CH and CH_2 groups), 4.26 (dd, J=2.8 Hz, 1H, H-6), 4.92 (d, J=2.6 Hz, 1H, anomeric-H), 5.46 (s, 1H, Ph*CH*), 7.18–7.51 (m, 10H, 2Ph); EI-MS *m/z* 544 (M+H, 17), 512 (80), 452 (100). Anal. calcd for $C_{30}H_{41}O_8N$: C, 66.30; H, 7.55; N, 2.58%. Found: C, 66.35; H, 7.51; N, 2.53%.

3.2.8. Methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-galactopyranosido[2,3-h]-N-2-methoxyethyl-1,4,7, 10-tetraoxa-13-azacyclopentadecane 3i

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:1→100:10) on silica gel. Yield: 75% (yellow oil); $[\alpha]_D^{20}$ +85.1 (c 1, $CHCl_3$); IR (neat) 2920, 2876, 1600, 1496, 1388, 1239, 1093, 749, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71–2.92 (m, 6H, $3NCH_2$), 3.32 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.51–3.93 (m, 19H, CH and CH_2 groups), 4.21 (dd, J=2.8 Hz, 1H, H-6), 4.92 (d, J=2.6 Hz, 1H, anomeric H), 5.50 (s, 1H, PhCH), 7.19–7.52 (m, 5H, Ph); CIMS *m/z* 498 (M+H, 9), 452 (100). Anal. calcd for $C_{25}H_{39}O_9N$: C, 60.36; H, 7.85; N, 2.82%. Found: C, 60.29; H, 7.80; N, 2.85%.

3.3. General procedure for the Michael addition of 2-nitropropane to chalcone in the presence of azacrown

The corresponding azacrown (0.1 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) were added to the solution of chalcone (0.3 g, 1.44 mmol) and 2-nitropropane (0.3 mL, 3.36 mmol) in dry toluene (3 mL). The mixture was stirred under argon atmosphere at room temperature. After a reaction time of 48 h, a new portion of toluene (7 mL) was added and the mixture stirred with water (10 mL). The organic phase was washed with water (7 mL) and dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by preparative TLC (silica gel, hexane:ethyl acetate, 10:1, eluant) to give pure adduct. Mp 146–148°C; $[\alpha]_D^{20}$ +80.8 (c 1.5, CH_2Cl_2) for the pure (+)-(*S*)-enantiomer.[4b] ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.27 (dd, 1H, J_1=17.2, J_2=3.2, COCH), 3.67 (dd, 1H, J_1=17.2, J_2=10.4, COCH), 4.15 (dd, 1H, J_1=10.4, J_2=3.2, CH_2CH), 7.18–7.32 (m, 5H, CHPh), 7.42–7.85 (m, 5H, C(O)Ph).

3.4. General procedure for Darzens condensation

A toluene solution (3 mL) of 1.3 mmol of phenyl chloride was treated with 1.9 mmol of benzaldehyde and 0.1 mmol of catalyst in 1.0 mL of 30% NaOH solution. The mixture was stirred under argon atmosphere. After completing the reaction 7 mL of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and solvent evaporated. The product was isolated by preparative TLC using CH_2Cl_2 as eluent. Results are collected in Table 2. $[\alpha]_{578}^{20}$ −214 (c 1, CH_2Cl_2) for pure 2*R*,3*S* enantiomer.[13] ^1H NMR ($CDCl_3$) δ 4.08 (d, 1H, J=1.9 Hz, CH), 4.29 (d, 1H, J=1.9 Hz, CH), 7.35–7.45 (m, 5H, CHPhH), 7.49 (t, 2H, COPhH-*m*), 7.62 (t, 1H, COPhH-*p*), 8.01 (d, 2H, COPhH-*o*). The ^1H NMR spectra of substituted (−)-(2*R*,3*S*)-epoxy-1,3-diphenyl-1-propanone **11** and **12** were essentially identical with those reported in the literature.[13]

3.4.1. trans-*(−)-2,3-Epoxy-3-(2-nitrophenyl)-1-phenyl-1-propanone 10*

Yield: 72% (colorless crystals); mp 69–70°C; $[\alpha]_D^{20}$ −48.7 (c 1, CH_2Cl_2); 29% ee. ^1H NMR $CDCl_3$ δ 4.23 (d, J=1.75 Hz, 1H), 4.63 (d, J=1.65 Hz, 1H), 7.27–8.22 (m, 9H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 57.7 (C-O), 59.6 (C-O), 124.9 (Ph, CH), 127.4 (Ph, CH), 128.5 (Ph, CH), 128.9 (Ph, CH), 129.5 (Ph, CH),

132.6 (Ph, CH), 134.1 (Ph, CH), 134.7 (Ph, CH), 135.4 (Ph, CH), 192.6 (C=O); FABMS *m/z* 270 (M+H). Anal. calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.08; N, 5.20%. Found: C, 66.90; H, 4.05; N, 5.18%.

3.4.2. trans-*(−)-2,3-Epoxy-3-(4-nitrophenyl)-1-phenyl-1-propanone* **11**

Yield: 63%; $[\alpha]_D^{20}$ −161 (c 1, CH_2Cl_2); 61% ee. Two crystallizations from ethanol and hexane gave the pure enantiomer, $[\alpha]_D^{20}$ −272 (c 1, CH_2Cl_2); (lit.[12] $[\alpha]_{557}^{20}$ −274, c 2, CH_2Cl_2); mp 138–140°C (lit.[12] 140–142°C).

3.4.3. (−)-(2R,3S)-Epoxy-3-(4-Chlorophenyl)-1-phenyl-1-propanone **12**

Yield: 54%; $[\alpha]_D^{20}$ −127 (c 0.33, CH_2Cl_2); 59% ee. Three crystallizations from ethanol and hexane gave the pure enantiomer, $[\alpha]_D^{20}$ −224 (c 1, CH_2Cl_2); (lit.[12] $[\alpha]_{577}^{20}$ −253, c 2.0, CH_2Cl_2); mp 64–66°C (lit.[13] 68°C).

3.4.4. trans-*(−)-2,3-Epoxy-3-(4-methoxyphenyl)-1-phenyl-1-propanone* **13**

Yield: 31%; mp 58–60°C (lit.[12] 60–63°C); $[\alpha]_D^{20}$ −16 (c 1, CH_2Cl_2); 12% ee (lit.[12] $[\alpha]_{577}^{20}$ −305, c 2.0, CH_2Cl_2, 90% ee); ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H, OCH_3), 4.08 (d, 1H, J=1.9 Hz, CH), 4.63 (d, 1H, J=1.9 Hz, CH), 7.38–8.01 (m, 9H, Ph). Anal. calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55%. Found: C, 75.61; H, 5.54%.

3.5. Self-condensation of phenacylchloride

A 6 mL toluene solution of 0.8 g (5.2 mmol) of phenacyl chloride and 0.1 g (0.2 mmol) of catalyst **2g** was treated with 2.0 mL of 30% NaOH solution. The mixture was stirred at room temperature for 1 h. After completing the reaction 14 mL of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and solvent evaporated. The product was purified by column chromatography (silica gel, CH_2Cl_2) to give 0.6 g (85%) of **14**. Mp 123–130°C; $[\alpha]_D^{20}$ −60.6 (c 1, CH_2Cl_2). Diastereomeric ratio *cis:trans*=23:77 (by ^{1}H NMR); separation by preparative TLC (silica gel, CH_2Cl_2) to give the pure *trans*-form of **14** (0.4 g); mp 122–124°C; $[\alpha]_D^{20}$ −74 (c 1, CH_2Cl_2); 64% ee. Two crystallizations from hexane afforded the pure enantiomer, (−)-(2*R*,3*S*)-epoxy-1,3-diphenyl-4-chlorobutan-1-one. Mp 124–126°C; $[\alpha]_D^{20}$ −116 (c 1, CH_2Cl_2); ^{1}H NMR δ 3.88 (d, J=12 Hz, 1H), 4.02 (d, J=15 Hz, 1H), 4.38 (s, 1H), 7.22–8.02 (m, 10H, Ph). ^{13}C NMR δ 44.1 (C-Cl), 65.4 (C-O), 66.1 (C-O), 126.3 (Ph, CH), 128.4 (Ph, CH), 128.6 (Ph, CH), 128.8 (Ph, CH), 129 (Ph, CH), 129.1 (Ph, CH), 134.4 (Ph, CH), 136.0 (Ph, CH), 193.6 (C=O). Anal. calcd for $C_{16}H_{13}ClO_2$: C, 70.40; H, 4.77; Cl, 13.0%. Found: C, 70.42; H, 4.76; Cl, 12.96%.

3.6. X-Ray crystal structure determinations[16–19]

Diffraction data were collected for both **12** and **14** at room temperature using Mo-Kα radiation. Initial structure models, obtained routinely by direct methods (SHELXS93), were smoothly refined to the final scattering model by using full-matrix least-squares and anisotropic displacement variables for non-H atoms. All hydrogen atoms both in **12** and **14** were positioned using geometric constrains and included within the final refinement cycles with so-derived contributions using SHELXL97. Pertinent crystallographic data for **12**: monoclinic $P2_1$ (no. 4), a=4.379(1), b=10.740(2), c=13.465(2) [Å], β=92.53(1) [°], V=632.6(2) [Å^3], Z=2, $D_{(calc)}$=1.358 [g/cm^3], data: N_{Tot}=2433, N_{Uniq}=1952, $R_{(int)}$=0.039, N_{Obs} [I>2.0$\sigma(I)$]=988, refinement: N_{ref}=1952, N_{par}=163, R=0.0550, R_w=0.1478, S=0.82; for **14**: monoclinic $P2_1$ (no. 4), a=6.990(1), b=5.053(1), c=18.544(2) [Å], β=91.74(1) [°], V=654.7(2) [Å^3], Z=2,

$D_{(calc)}$=1.383 [g/cm^3], data: N_{Tot}=4632, N_{Uniq}=3793, $R_{(int)}$=0.021, N_{Obs} [$I>2.0\sigma(I)$]=2215, refinement: N_{ref}=3793, N_{par}=172, R=0.0476, R_w=0.1178, S=0.91. Absolute configurations for both **12** and **14** were assigned on the basis of the refined Flack parameters (x=−0.02(14) for **12** and x=−0.03(8) for **14**).

Acknowledgements

This work was supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T029253, T026478 and in part T025910).

References

1. O'Donnell, M. I. *Asymmetric Phase-Transfer Reactions.* In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp. 389–411 and references cited therein.
2. (a) Tőke, L.; Fenichel, L.; Bakó, P.; Szejtli, J. *Acta Chim. Acad. Sci. Hung.* **1978**, *98*, 357–364. (b) Bakó, P.; Fenichel, L.; Tőke , L.; Czugler, M. *Liebigs Ann. Chem.* **1981**, 1163–1169. (c) Bakó, P.; Fenichel, L.; Tőke, L. *Acta Chim. Hung.* **1982**, *111*, 297–301. (d) Bakó, P.; Fenichel, L.; Tőke, L. *Acta Chim. Hung.* **1984**, *116*, 323–324. (e) Bakó, P.; Fenichel, L.; Tőke, L.; Tóth, G. *Carbohydrate Res.* **1986**, *147*, 31–38. (f) Stoddart, J. F. *Chiral Crown Ethers.* In *Top. Stereochem.* Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1987; 17, pp. 207–288. (g) Bakó, P.; Fenichel, L.; Tőke, L.; Davison, B. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1235–1238. (h) Bakó, P.; Fenichel, L.; Tőke, L. *Liebigs Ann. Chem.* **1990**, 1161–1163. (i) Bakó, P.; Fenichel, L.; Tőke, L. *J. Incl. Phenom.* **1994**, *16*, 17–26. (j) Coteron, J. M.; Vicent, C.; Bosso, C.; Penades, S. *J. Am. Chem. Soc.* **1993**, *115*, 10066–10076.
3. Bakó, P.; Tőke, L. *J. Incl. Phenom.* **1995**, *23*, 195–201.
4. (a) Bakó, P.; Szöllősy, Á.; Bombitcz, P.; Tőke, L. *Synlett* **1997**, 291–292. (b) Bakó, P.; Szöllősy, Á.; Bombitcz, P.; Tőke, L. *Heteroatom Chem.* **1997**, *8*, 333–337. (c) Bakó, P.; Vízvárdi, K.; Toppet, S.; Van der Eycken, E.; Hoornaert, G. J.; Tőke, L. *Tetrahedron* **1998**, *54*, 14975–14988.
5. Bakó, P.; Novák, T.; Ludányi, K.; Pete, B.; Tőke, L.; Keglevich, Gy. *Tetrahedron: Asymmetry* **1999**, *10*, 2373–2380.
6. (a) Oare, D. A.; Heathcock, C. H. *Top Stereochem.* **1989**, *20*, 87–99. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; p. 241. (c) Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051–2061.
7. (a) Alonso-Lopez, M.; Jimenez-Barbero, J.; Martin-Lomas, M.; Penades, S. *Tetrahedron* **1988**, *44*, 1535–1543. (b) Van Maarschalkerwaart, D. A. H.; Willard, N. P.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 8825–8840. (c) Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles* **1992**, *33*, 493–499. (d) Kanakamma, P. P.; Mani, N. S.; Maitra, U.; Nair, V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2339–2344. (e) Tőke, L.; Bakó, P.; Keseru, Gy. M.; Albert, M.; Fenichel, L. *Tetrahedron* **1998**, *54*, 213–222 and references cited therein.
8. Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* **1996**, 2411–2412 and references cited therein.
9. (a) Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978**, 1089–1092. (b) Colona, S.; Fornasier, R.; Pfeiffer, U. *J. Chem. Soc., Perkin Trans. 1* **1978**, 8–13. (c) Arai, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2145–2148. (d) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375–6386.
10. Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Tetrahedron* **1997**, *53*, 2421–2438 and references cited therein.
11. Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312.
12. Itsumo, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047–6049.
13. Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317–1324.
14. Wasserman, H. H.; Aubrey, N. E. *J. Am. Chem. Soc.* **1955**, *77*, 590–594.
15. Stevens, C. L.; Church, R. J.; Traynelis, V. J. *J. Org. Chem.* **1954**, *19*, 522–531.
16. Desiraju, G. R. *Crystal Engineering, Mater. Sci. Monog. 5* Elsevier: Oxford, 1990.
17. Sheldrick, G. M. *SHELXS-93 Program for Crystal Structure Solution;* University of Göttingen: Germany, 1997.
18. Sheldrick, G. M. *SHELXL-97 Program for Crystal Structure Refinement;* University of Göttingen: Germany, 1997.
19. Program PLATON, Spek, A. L. *Acta Cryst.* **1990**, *A46*, C-34.

Foszfonoalkil-oldalláncot tartalmazó azakoronák szintézise és komplexképzési tulajdonságainak a vizsgálata*

NOVÁK Tibor, KEGLEVICH György, IMRE Tímea és BAKÓ Péter

Budapesti Műszaki Egyetem, Szerves Kémiai Technológia Tanszék, 1521 Budapest

ÚJSZÁSZY Kálmán

Eötvös Loránd Tudományegyetem, Általános és Szervetlen Kémiai Tanszék, 1518 Budapest

LUDÁNYI Krisztina

Magyar Tudományos Akadémia Központi Kémiai Kutató Intézete, 1525 Budapest

TŐKE László

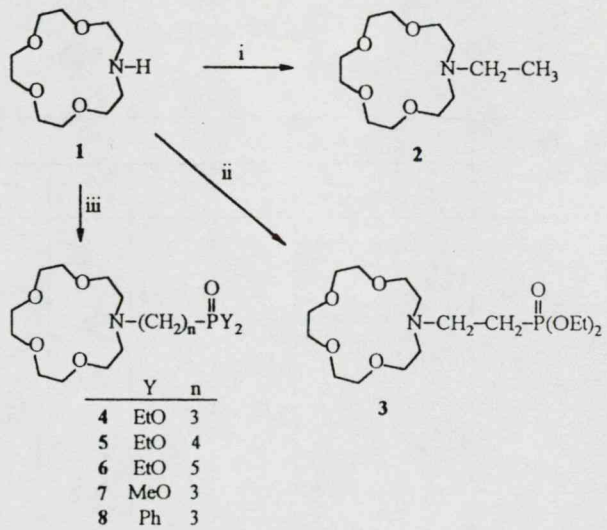
MTA, Szerves Kémiai Technológia Tanszéki Kutató Csoport, Budapesti Műszaki Egyetem, 1521 Budapest

Ismeretes, hogy a koronaéterek komplexképzési hajlama befolyásolható oldalláncok bevitelével. A foszfonoalkil-csoport azakoronák komplexképzési tulajdonságaira való hatását azonban még nem tanulmányozták átfogóan. Néhány foszfonometil-oldallánccal rendelkező mono- és diazakoronát azonban leírtak és ezek egy részének komplexképzési tulajdonságait is megvizsgálták.[2-5] Az említett lariátéterek között az oldallánc végén foszfincsoportot tartalmazó származékok is vannak.

Munkánk során új típusú, foszfonoalkil-csoportot tartalmazó azakoronákat szintetizáltunk és megvizsgáltuk ezek komplexképzési tulajdonságait. Felderítettük, hogy a funkciós-csoport és az oldallánc hosszúsága hogyan befolyásolja az azakorona komplexképzési hajlamát.

A foszfonoalkil-aza-15-korona-5 éterek és a bisz(foszfonoetil)-diaza-18-korona-6-éter szintézise és spektroszkópiás jellemzése

A foszfonoalkil-csoportot tartalmazó azakoronák a monoaza-15-korona-5-éter (**1**) *N*-alkilezésével készültek. Az azakorona (**1**) és a dietil-2-brómetil-foszfonát kálium-karbonát jelenlétében DMF-ban 90 °C-on megvalósított reakciója az azakorona etil-származékának (**2**) képződéséhez vezetett (1. ábra). A reakció körülményei között, a brómetil-foszfonát etilezőszerként viselkedett, ahelyett, hogy foszfonoetilezés játszódott volna le a nitrogénatomon. Az azakorona (**1**) dietil-vinilfoszfonáttal történő reakciójában azonban a várt foszfonoetil-származék (**3**) keletkezett (1. ábra).



	Y	n
4	EtO	3
5	EtO	4
6	EtO	5
7	MeO	3
8	Ph	3

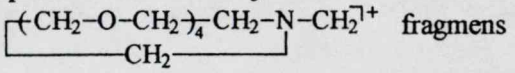
1. ábra

Reagensek és reakciókörülmények:
(i) $BrCH_2CH_2P(O)(OEt)_2$, K_2CO_3, DMF, 90 °C;
(ii) $CH_2{=}CHP(O)(OEt)_2$ (7.1 equiv.), C_6H_6, 80 °C;
(iii) $Br(CH_2)_nP(O)Y_2$, K_2CO_3, DMF, 90 °C.

A brómetil-foszfonáttal ellentétben, a három-, négy- és öt szénatomszámú brómalkil-foszfonátokat

*A közlemény egy angolul megjelent dolgozat fordítása.[1]

sikeresen hasznosítottuk a megfelelő lariátéterek (**4-6**) szintézisében. A ω-brómalkil-foszfonátokat *Arbuzov*-reakcióban állítottuk elő a megfelelő dibróm-alkán és trietil-foszfit reakciójában. Meghatároztuk az optimális reakciókörülményeket, hogy elkerüljük a difoszfonátok képződését. Az azakorona (**1**) brómalkil-foszfonátokkal megvalósított reakciója a várakozásnak megfelelően **4-6** lariátétereket eredményezte. Oszlopkromatográfiás tisztítás után 35–45 %-os hozammal kaptuk a termékeket (1. ábra). A lariátéterek szerkezetét ^{31}P-, ^{13}C- és ^{1}H-NMR-, valamint tömegspektrumokkal támasztottuk alá. A ^{13}C-NMR adatokat az 1. táblázatban tüntettük fel. A lariátéterek (**3-6**) oldalláncainak α-helyzetű szénatomján kb. 140 Hz-es foszfor-szén csatolásokat figyelhettünk meg; míg a β- és γ-helyzetű szénatomokon kb. 5, illetve 17 Hz-es csatolásokat mértünk. A CH_2N és CH_2O egységek hidrogénjelei a várakozásnak megfelelően, a δ_H 2.7–3.5 tartományban jelentkeztek. A lariátéterek (**3-6**) tömegspektrumában a molekulaionok ill. ezek protonvesztett formája látszott.

A  fragmens

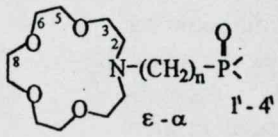
(*m/z* = 232) volt a báziscsúcs valamennyi esetben. A termékek (**3-6**) elemi összetételét nagyfelbontású tömegspektroszkópiával erősítettük meg. A fentieken kívül dimetil-foszfonát és difenil-foszfin-oxid funkcióscsoportot tartalmazó monoaza-koronaétereket (**7**, ill. **8**) is előállítottunk (1. ábra). A termékeket kb. 30% körüli termeléssel izoláltuk és szerkezetüket NMR-, valamint tömegspektrumokkal támasztottuk alá (1. táblázat). A lariátéterek (**7** és **8**) NMR-, és tömegspektroszkópiás jellemzői hasonlítottak a korábban bemutatott származékok adataihoz (**3-6**).

Az eddig bemutatott lariátétereken kívül kétkarú, a nitrogénatomokon helyettesített diaza-koronaétert is előállítottunk. A 7,16-diaza-18-korona-6 (**9**) dietil-vinil-foszfonáttal megvalósított reakciója közepes termeléssel vezetett a bisz(foszfonoetil)-származék (**10**) képződéséhez (2. ábra). A termék (**10**) szerkezetét ^{31}P-, ^{13}C- és ^{1}H-NMR, valamint tömegspektrumokkal igazoltuk.

Az általunk előállított lariátéterek új vegyületek, de a **3** és **10** termékek foszfonsav-származékai már korábbról is ismertek.[6,7]

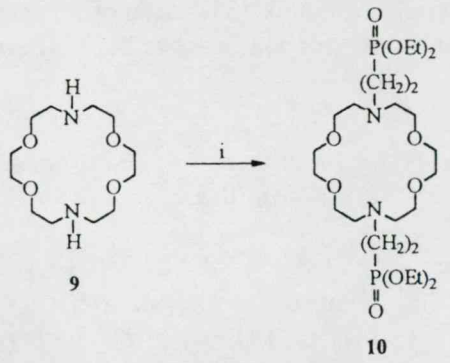
1. táblázat

A lariátéterek (3–8) ^{13}C NMR adatai ($CDCl_3$-ban)



Termék	δ_C (J_{PC} [Hz])													
	C_α	C_β	C_γ	C_δ	C_ε	C_2	C_3	C_5	C_6	C_8	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$
3	23.3 (136.6)	49.6	–	–	–	53.9	69.7[a]	70.0[a]	70.2[a]	70.8[a]	–	61.4 (6.3)	16.3 (5.9)	–
4	23.1 (141.9)	20.4 (4.6)	56.8 (18.0)	–	–	54.6	70.0[b]	70.1[b]	70.3[b]	70.9[b]	–	61.4 (6.5)	16.4 (5.9)	–
5	25.1 (140.5)	20.0 (5.0)	27.6 (16.3)	55.9	–	54.4	69.4[c]	69.8[c]	70.0[c]	70.6[c]		61.2 (6.3)	16.2 (6.0)	
6	25.6 (140.5)	22.3 (4.9)	28.3 (17.1)	26.8	56.6	54.5	69.9[d]	70.1[d]	70.4[d]	70.9[d]	–	61.4 (6.6)	16.4 (5.8)	–
7	21.8 (142.0)	20.1	56.5 (17.2)	–	–	52.1	69.7[e]	69.8[e]	70.1[e]	70.6[e]	–	54.4	–	–
8	27.0 (72.7)	19.4	56.7 (15.1)	–	–	54.4	69.7[f]	70.0[f]	70.2[f]	70.8[f]	133.0 (98.0)	130.7[g] (9.4)	128.5[g] (11.8)	131.5 (1.9)

[a-g] találomszerű hozzárendelés



9 10

2. ábra

Reagens és reakciókörülmény:
(i) CH_2=CHP(O)$(OEt)_2$ (8.5 equiv.), C_6H_6, forralás.

A foszfonoalkil-azakoronaéterek extrakciós tulajdonságai

A lariátéterek (**3-5** és **8**) komplexképző hajlamát *Kimura* és munkatársai által kidolgozott pikrát-extrakciós módszerrel jellemeztük.[8] Azt vizsgáltuk, hogy a helyettesített lariátéterek jelenlétében a lítium-, nátrium-, kálium- vagy ammóniumsó milyen hányada extrahálódik a vizes oldatból a diklórmetános fázisba [extrahálóképesség (EK)]. A mérések eredménye nem jellemzi pontosan a homogén fázisban tapasztalható komplexképző hajlamot, mégis bizonyos mértékben utal a komplexálóképességre. A vizes oldat pikrát-koncentrációját UV-spektroszkópiás módszerrel határoztuk meg. A mérés eredményeit a 2. táblázatban foglaltuk össze.

2. táblázat

Alkáli- és ammónium-pikrátok extrakciója koronaéterek (1, 3-5 és 8) jelenlétében[a]

Termék	Extrahálóképesség (%)[b]			
	Li^+	Na^+	K^+	NH_4^+
1	65	56	67	60
3	68	36	25	48
4	13	20	31	40
5	25	34	51	62
8	21	50	30	46

[a] hőmérséklet: 25°C; vizes fázis (5 ml); [pikrát]=5×10^{-3}M; szerves fázis (5 ml diklórmetán); [koronaéter]=1×10^{-2} M
[b] a szerves fázisba extrahált pikráthányaddal definiálva; meghatározás UV-spektroszkópiával, hiba: ≤5%

A viszonyítási alapnak tekintett monoaza-15-korona-5 (**1**) jelenlétében a pikrát 56–67%-a került át a vizes fázisból a szerves fázisba, de nem mutatott különösebb szelektivitást a vizsgált kationok körében. Látható, hogy a foszfonoalkil-csoport bevitele az azakorona-molekulába a kation-extrahálóképesség csökkenését eredményezte. A legnagyobb mértékű csökkenést a foszfonopropil-helyettesítőt tartalmazó koronánál (**4**) figyelhettük meg, de ez nem vonatkozik a káliumionra. Ezt a jelenséget azzal magyarázhatjuk, hogy a korona felé visszahajló kar sztérikusan gátolja a komplex-képződést. Az oldallánc bevitelével lejátszódó konformációs változásoknak szintén fontos szerepe lehet az extrahálóképesség csökkenésében. Másfelől azonban, a foszfonoalkil-csoport beépítésével a kation-szelektivitás jelentős mértékben nőtt: a **3** vegyület jelenléte esetén kétszerannyi ammónium-ion és háromszorannyi lítiumion került a szerves fázisba, mint káliumion. **4** lariátéter jelenlétében háromszorannyi ammóniumion került a szerves fázisba, mint lítiumion. Hasonló tendenciákat lehetett megfigyelni az **5** és **8** vegyületek alkalmazása esetén is. Érdemes összehasonlítani a foszfonoalkil-azakoronaéterek (**3-5**) jelenlétében mért kation-extrakciót a difenilfoszfin-oxid-csoportot tartalmazó származék (**8**) esetében mérttel: a foszfonoalkil-típusú koronaéterek (**3-5**) használata esetében 20–36% nátriumion került át a szerves fázisba, míg a foszfin-oxid-származék (**8**) jelenlétében ez a szám 50%. Ez a **8** vegyület jobb komplexképző sajátságaira vezethető vissza. A nitrogénatom helyettesítőjétől függően a következőképpen alakultak a szelektivitási sorrendek. A helyettesítetlen azakorona (**1**) esetében a sorrend $K^+\sim Li^+>NH_4^+>Na^+$ volt. A **3** származék esetében $Li^+>NH_4^+>Na^+>K^+$, míg a **4** és az **5** vegyület esetén $NH_4^+>K^+>Na^+>Li^+$ volt a sorrend. A foszfin-oxidra (**8**) $Na^+>NH_4^+>K^+>Li^+$ szelektivitási sorrendet mértünk.

Kísérleti rész

A ^{31}P-, ^{13}C- és az ^1H-NMR spektrumokat Bruker DRX-500 spektrométeren regisztráltuk (202.4, 125.7 és 500 MHz) 85%-os (külső) foszforsavoldat és (belső) tetrametil-szilán standard alkalmazásával. A csatolásokat Hz-ben adtuk meg. A tömeg-spektrumokat MS 25-RFA vagy ZAB-2SEQ készüléken vettük fel (70 eV).

Dietil-brómalkil-foszfonátok általános előállítási módja.

16.0 ml (0.0933 mol) trietil-foszfit és 0.467 mol dibróm-alkán elegyét 24 órán át 160 °C-on tartottuk. A dibróm-alkán feleslegét vákuumban eltávolítottuk és a maradékot 0.3–0.4 mm-en frakcionáltuk. Ily módon a következő vegyületeket állítottuk elő:

Dietil-(2-bróm-etil)-foszfonát

Termelés: 54%; fp.: 83–86 °C/0.4 mm (101 °C/0.8 mm[9]); ^{31}P-NMR ($CDCl_3$) δ 26.1.

Dietil-(3-bróm-propil)-foszfonát

Termelés: 57%; fp.: 97–101 °C/0.4 mm (94–95 °C/2 mm[10]); ^{31}P-NMR ($CDCl_3$) δ 31.3; MS, *m/z* 258 (M^+, 1%), 179 (99), 152 (100).

Dietil-(4-bróm-butil)-foszfonát

Termelés: 51%; fp.: 115–120 °C/0.4 mm (120 °C/0.01 mm[11]); ^{31}P-NMR ($CDCl_3$) δ 31.9; MS, *m/z* 272 (M^+, 5%), 193 (92), 165 (38), 137 (100).

Dietil-(5-bróm-pentil)-foszfonát

Termelés: 43%; fp.: 120–124 °C/0.3 mm; ^{31}P-NMR ($CDCl_3$) δ 32.3; MS, *m/z* 286 (M^+, 3%), 207 (42), 179 (21), 152 (100).

Dimetil-(3-bróm-propil)-foszfonát

Az előbbiekkel analóg módon állítottuk elő, de a trimetil-foszfitot és a 1,3-dibróm-propánt 7 órán át reagáltattuk 120 °C-on. Termelés: 41%; fp.: 94–98 °C/0.4 mm (96 °C/0.05 mm[12]); ^{31}P-NMR ($CDCl_3$) δ 33.5; MS, *m/z* 230 (M^+, 2%), 151 (48), 124 (100).

3-Bróm-propil-difenil-foszfin-oxid

Etil-difenil-foszfinit[13] és 1,3-dibróm-propán 150 °C-on kivitelezett reakciójával állítottuk elő. Reakcióidő: 2.5 óra. Termelés: 46% oszlopkromatográfiás tisztítás után (3% metanol kloroformban, szilikagél); ^{31}P-NMR ($CDCl_3$) δ 32.2; MS, *m/z* = (M^+, 2%), 243 (47), 215 (44), 201 (100).

A lariátéterek (4–8) általános előállítási módja

1.5 g (6.85 mmol) monoaza-15-korona-5[14], 10.3 mmol bróm-alkil-foszfonát (vagy bróm-alkil-foszfin-oxid), 0.95 g (6.85 mmol) vízmentes kálium-karbonát és 30 ml absz. dimetil-formamid (DMF) elegyét 8 órán át kevertettük 90 °C-on. Az elegyet szűrtük és a szűrletet vákumban bepároltuk. A maradékot 50 ml kloroformban felvettük és 3 ml vízzel pár percig kevertettük. A szerves fázist szárítottuk ($MgSO_4$), majd az oldószert eltávolítottuk. Az így kapott maradékot oszlopkromatográfiás módszerrel tisztítottuk (3% metanol kloroformban, szilikagél). Ily módon a következő vegyületeket állítottuk elő:

Dietil-(1,4,7,10-tetraoxa-13-aza-ciklopentadec-13-il-propil)-foszfonát (**4**)

Termelés: 45%; ^{31}P-NMR ($CDCl_3$): δ 33.2; ^{13}C-NMR, (1. táblázat); ^{1}H-NMR ($CDCl_3$): δ 1.27 (t, J=7.1, 6H, OCH_2CH_3), 1.61–1.82 (m, 4H, C(α)H_2, C(β)H_2), 2.48-2.57 (m, 2H, C(γ)H_2), 2.66–2.74 (m, 4H, C(2)H_2), 3.52–3.69 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 3.97–4.10 (m, 4H, OCH_2); MS, *m/z* = 396 (M^+–H, 2%), 382 (2), 352 (5), 336 (8), 232 (100) 179 (25); HRMS, $(M-H)^+_{mért}$ = 396.2101, a $C_{17}H_{35}NO_7P$-re számított 396.2151.

Dietil-(1,4,7,10-tetraoxa-13-aza-ciklopentadec-13-il-butil)-foszfonát (**5**)

Termelés: 41%; ^{31}P-NMR ($CDCl_3$) δ 32.6; ^{13}C-NMR, (1. táblázat); ^{1}H-NMR ($CDCl_3$) δ 1.11 (t, J=7.1, 6H, OCH_2CH_3), 1.34–1.42 (m, 4H, C(β)H_2, C(γ)H_2), 1.50–1.57 (m, 2H, C(α)H_2), 2.31–2.37 (m, 2H, C(δ)H_2), 2.55 (t, J=5.7, 4H, C(2)H_2), 3.38–3.48 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 3.83–3.91 (m, 4H, OCH_2); MS, *m/z* = 411 (M^+, 8%), 410 (M–H, 8), 396 (4), 366 (6), 350 (8) 232 (100), 193 (16); HRMS, $M^+_{mért}$ = 411.2332, a $C_{18}H_{38}NO_7P$-re számított 411.2386.

Dietil-(1,4,7,10-tetraoxa-13-aza-ciklopentadec-13-il-pentil)-foszfonát (**6**)

Termelés: 35%; ^{31}P-NMR ($CDCl_3$): δ 32.9; ^{13}C-NMR, (1. táblázat); MS, *m/z* = 425 (M^+, 4%), 410 (3), 380 (3), 364 (4), 232 (100), 207 (10); HRMS, $M^+_{mért}$ = 425.2473, a $C_{19}H_{40}NO_7P$-re számított 425.2542.

Dimetil-(1,4,7,10-tetraoxa-13-aza-ciklopentadec-13-il-propil)-foszfonát (**7**)

Termelés: 31%; ^{31}P-NMR ($CDCl_3$): δ 35.9; ^{13}C-NMR, (1. táblázat); ^{1}H-NMR ($CDCl_3$): δ 1.48–1.85 (m, 4H, C(α)H_2, C(β)H_2), 2.28–2.33 (m, 2H, C(γ)H_2), 2.33–2.57 (m, 4H, C(2)H_2), 3.33–3.62 (m, 22H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, CH_3O); MS, *m/z* = 369 (M^+, 1%), 368 (M^+–H, 1), 338 (3), 232 (100), 180 (39); HRMS, $M^+_{mért}$ = 369.1876, a $C_{15}H_{32}NO_7P$-re számított 369.1916.

(1,4,7,10-Tetraoxa-13-aza-ciklopentadec--13-il-propil)-difenil-foszfin-oxid (8)

Reakció idő: 20 óra; Termelés: 34%; ^{31}P-NMR ($CDCl_3$): δ 33.6; ^{13}C-NMR, (1. táblázat); ^{1}H-NMR ($CDCl_3$): δ 1.75–1.86 (m, 2H, C(β)H_2), 2.31–2.38 (m, 2H, C(α)H_2), 2.68–2.82 (m, 6H, C(γ)H_2, C(2)H_2), 3.52–3.69 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 7.39–7.76 (m, 10H, Ar); MS, *m/z* = 461 (M^+, 2%), 460 (M–H, 2), 400 (7), 311 (100), 243 (85); HRMS, $M^+_{mért}$ = 461.2249, a $C_{25}H_{36}NO_5P$-re számított 461.2331.

A monoaza 15-korona-5 reakciója dietil-2-brómetil-foszfonáttal az etilszármazék (2) képződéséhez vezetett 38%-os termeléssel. ^{13}C-NMR ($CDCl_3$): δ 12.0 (CH_2CH_3), 50.4 (CH_2CH_3), 53.9 (N–CH_2CH_2), 69.9 (O–CH_2), 70.0 (O–CH_2), 70.3 (O–CH_2), 70.9 (O–CH_2); MS, *m/z* = 247 (M^+–H, 18%), 232 (32), 114 (78), 100 (64), 73 (92), 58 (100), 45 (96) (247, 232, 114, 100, 73, 58, 45).[15]

Dietil-(1,4,7,10-tetraoxa-13-aza-ciklopentadec--13-il-etil)-foszfonát (3)

1.5 g (6.85 mmol) monoaza-15-korona-5 (1), 8.0 g (48.8 mmol) dietil-vinil-foszfonát (5) és 7.5 ml benzol elegyét 7 napig forraltuk. Az illékony komponenseket vákumban eltávolítottuk. Oszlopkromatográfiás tisztítás (3% metanol kloroformban, szilikagél) után 0.97 g (37%) terméket kaptunk. ^{31}P-NMR ($CDCl_3$): δ 31.2; ^{13}C-NMR, (1. táblázat); ^{1}H-NMR ($CDCl_3$): δ 1.13 (t, *J* = 7.1, 6H, OCH_2CH_3), 1.74–1.82 (m, 2H, C(α)H_2), 2.53–2.60 (m, 4H, C(2)H_2), 2.66–2.73 (m, 2H, C(β)H_2), 3.42–3.53 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 3.87–3.97 (m, 4H, OCH_2); MS, *m/z* = 382 (M^+–H, 8%), 368 (5), 338 (20), 322 (33), 232 (100), 166 (28); HRMS, $(M–H)^+_{mért}$ = 382.1955, a $C_{16}H_{33}NO_7P$-re számított 382.1995.

7,16-Bisz(dietil-foszfonoetil-)1,4,10,13-tetraoxa--7,16-diaza-ciklooktadekán (10)

0.5 g (1.90 mmol) diaza-18-korona-6 (9) és 5 g (32.5 mmol) dietil-foszfonát reakcióját 5 ml benzolban az 1→3 átalakításnál bemutatott körülmények között végeztük. Az előbbiekben ismertetett feldolgozási eljárás után 0.14 g (20%) terméket kaptunk, melynek tisztasága 95% volt. ^{31}P-NMR ($CDCl_3$): δ 31.3; ^{13}C-NMR ($CDCl_3$): δ 16.4 ($^3J_{PC}$ = 5.9, OCH_2CH_3), 23.1 ($^1J_{PC}$ = 136.9, CH_2P), 48.5 (CH_2CH_2P), 53.2 (NCH_2CH_2O), 61.4 ($^2J_{PC}$ = 6.3, OCH_2CH_3), 70.5 (OCH_2), 70.4 (OCH_2); ^{1}H-NMR ($CDCl_3$): δ 1.18 (t, *J* = 7.1, 12H, OCH_2CH_3), 1.74–1.87 (m, 4H, CH_2P), 2.55–2.75 (m, 12H, CH_2CH_2P, NCH_2CH_2O), 3.36–3.59 (m, 16H, CH_2OCH_2), 3.89–4.03 (m, 8H, OCH_2CH_3); MS, *m/z* = 590 (M^+, 15%), 529 (53), 515 (69), 453 (100); HRMS, $M^+_{mért}$=590.3001, a $C_{24}H_{52}N_2O_{10}P_2$-re számított 590.3097.

Azakoronák (1, 3-5 és 8) extrakcióképességének meghatározása

Az azakorona (1, 3-5 és 8) diklórmetános oldatát (c = 0.01 mol/l^{-1}) azonos mennyiségű (5 ml) pikrát vizes oldatával (c = 0.005 mol/l^{-1}) kevertettük 25 °C-on Erlenmeyer lombikban 40 percig. A fázisok minél teljesebb elválása érdekében az elegyet 2 órán át állni hagytuk. A fázisok elválasztása után a pikrát koncentrációjának meghatározása a vizes oldatban 354 nm-en mért abszorpció alapján történt. (ε = 14600 mol^{-1}cm^{-1}). Az extrahálóképesség (%) azt mutatja, hogy milyen mértékben került át a pikrát a vizes oldatból a szerves fázisba. Azakorona távollétében nem került kimutatható mennyiségű pikrát a szerves fázisba.

A szerzők köszönik a Magyar Tudományos Akadémia (AKP 96-2-583 2,4/26) és az OTKA (T 015677) támogatását. Novák T. köszönetét fejezi ki a Varga József Alapítványnak ösztöndíja folyósításáért.

Összefoglalás

Különféle szénatomszámú foszfonoalkil-oldalláncal rendelkező azakoronákat (3-8, 10) állítottunk elő, amelyek új típusú komplexképző ágensként jönnek számításba. A foszfortartalmú helyettesítő bevitele a monoaza-15-korona-5 vegyületbe (1) a kation-extrahálóképesség csökkenésével és a szelektivitás növekedésével járt.

Synthesis and complex forming ability of phosphonoalkyl-azacrown ethers. *T. Novák, Gy. Keglevich, T. Imre, P. Bakó, K. Újszászy, K. Ludányi and L. Tőke*

The synthesis of azacrown ethers with phosphonoalkyl side chains of two to five carbon atoms (3-8, 10), potentially useful as new type of complex forming agents, is described. Introduction of the phosphonoalkyl moiety into the parent monoaza-15-crown-5 (1) decreases the cation extraction ability, but results in an increase in the selectivity towards the cations examined.

IRODALOM

1 *Gy. Keglevich, T. Novák, P. Bakó, K. Újszászy, K. Ludányi, K. Tóth, L. Töke*: J. Incl. Phenom., közlésre elfogadva.

2 *M. Tazaki, K. Nita, M. Takagi, K. Ueno*: Chem. Lett., 571. 1982.

3 *B. Zhang, A. Clearfield*: J. Am. Chem. Soc., *119*. 2751. 1997.

4 *L. Burai, S. Jakab, R. Kiraly, I. Lázár, I. Tóth, E. Bruecher*: J. Chem. Soc. Dalton Trans., 1113. 1996.

5 *A. Carroy, C. R. Langick, J-M. Lehn, K. E. Matthes, D. Parker*: Helv. Chim. Acta, *69*. 580. 1986.

6 *E. Brunet, M. Huelva, J. C. Rodriguez-Ubis*: Tetrahedron Lett., *35*. 8697. 1994.

7 *E. Brunet, M. Huelva, R. Vazquez, O. Juanes, J. C. Rodriguez-Ubis*: Chem. – – Eur. J., *2*. 1578. 1996.

8 *K. Kimura, T. Maeda, T. Shono*: Talanta, *26*. 945. 1979.

9 *A.H. Ford-Moore, J.H. Williams*: J. Chem. Soc., 1465. 1947.

10 *Y. Okamoto, T. Okada, H. Sakurai*: Bull. Chem. Soc. Jpn., *48*. 484. 1975.

11 *D.G. Hewitt, G.L. Newland*: Aust. J. Chem., *30*. 579. 1977.

12 *P. Chabrier, T. Nguyen-Thanh, D. Le-Maitre, M. Perat:* C. R. Acad. Sci., Paris, Ser. *C, 267*. 732. 1968.

13 *F.M. Kharrasova, G. Kamai*: Zh. Obshch. Khim., *34*. 2195. 1964; CA *61*. 10705f. 1964.

14 *H. Maeda, Y. Nakatsuji*: J. Chem. Soc. Chem. Commun., 471. 1981.

15 *P-L. Kuo, M. Miki, I. Ikeda, M. Okahara*: Tetrahedron Lett., *44*. 4273. 1978.

Budapesti Műszaki Egyetem,
Szerves Kémiai Technológiai Tanszék
Érkezett: 1998. XII. 4.
Közlésre elfogadtuk: 1998. XII. 11.

B16

Phosphorus, Sulfur and Silicon, 1999, Vol. 147, pp. 159-159
Reprints available directly from the publisher
Photocopying permitted by license only

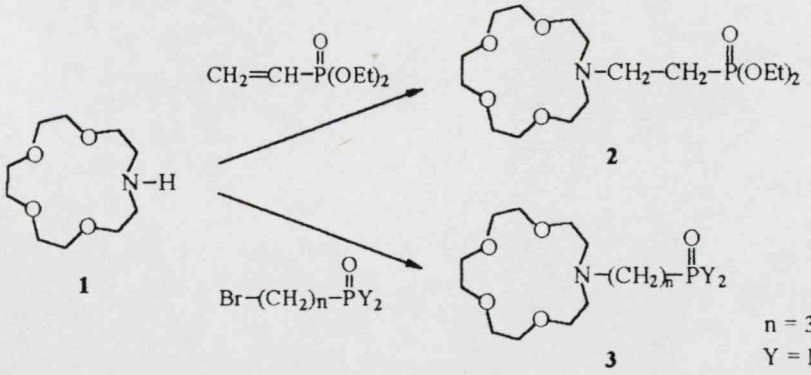
© 1999 OPA (Overseas Publishers Association) N.V.
Published by license under the
Gordon and Breach Science Publishers imprint.
Printed in Malaysia

Synthesis of Azacrown Ethers with P-Functionalized Side Chains

GYÖRGY KEGLEVICH[a], TIBOR NOVÁK[a], PÉTER BAKÓ[a], KÁLMÁN ÚJSZÁSZY[b] and LÁSZLÓ TÖKE[a]

[a]*Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary and* [b]*Department of General and Inorganic Chemistry, Eötvös University, 1117 Budapest, Hungary*

It is well-known that complex forming ability of azacrown ethers can be modified by side chains with electron-donating atoms. We aimed at the synthesis of lariat ethers with phosphonoalkyl side chains. The phosphonoalkyl arms of two to five carbon atoms were introduced into azacrown **1** by alkylation.



1 **2** **3**

The new products (**2** and **3**) were characterized by ^{31}P, ^{13}C and ^{1}H NMR, as well as mass spectroscopical methods. Complex forming ability of **2** and **3** was determined by the picrate extraction method[1]. Introduction of the phosphonoalkyl moiety into the parent azacrown (**1**) decreases the extraction ability, but results in an increase in the selectivity towards the cations examined.

This research was sponsored by the Hungarian Academy of Sciences (AKP no. 96/2-583 2,4/26).

References

[1] K. Kimura, T. Maeda and T. Shono, *Talanta*, **26**, 945 (1979).

Journal of Inclusion Phenomena and Macrocyclic Chemistry **34**: 299–309, 1999.
© 1999 *Kluwer Academic Publishers. Printed in the Netherlands.*

B17

New Type of Lariat Ethers: Synthesis and Cation Binding Ability of Phosphonoalkyl-Azacrown Ethers

GYÖRGY KEGLEVICH*, TIBOR NOVÁK and PÉTER BAKÓ
Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary.

KÁLMÁN ÚJSZÁSZY
Department of General and Inorganic Chemistry, Loránd Eötvös University, 1518 Budapest, Hungary.

KRISZTINA LUDÁNYI
Central Research Institute of Chemistry for Hungarian Academy of Sciences, 1525 Budapest, Hungary.

KLÁRA TÓTH
Department of General and Analytical Chemistry, Technical University of Budapest, 1521 Budapest, Hungary.

LÁSZLÓ TÕKE
Research Group of the Hungarian Academy of Sciences, Technical University of Budapest, 1521 Budapest, Hungary.

(Received: 5 July 1998; in final form: 15 September 1998)

Abstract. The synthesis of azacrown ethers with phosphonoalkyl side chains of two to five carbon atoms (**3–8, 10**), potentially useful as a new type of cation binding agent, is described. Introduction of the phosphonoalkyl moiety into the parent monoaza-15-crown-5 (**1**) decreases the cation extraction ability, but results in an increase in the selectivity towards the cations examined. The effect of the phosphonoalkyl-azacrown ethers on the properties of membranes used in ion-selective electrodes is also reported.

Key words: azacrown ethers, lariat ethers, phosphonoalkyl side chain, extraction ability.

1. Introduction

It is well known that the complexing ability of the crown ethers can be modified by the introduction of side chains. The effect of phosphorus containing substituents on the complexing ability of azacrown ethers is less studied. Several phosphonomethyl derivatives of monoaza- and diazacrown ethers showing uncommon selectivity

* Author for correspondence.

towards various metal ions have been described [1–3]. Other monoaza- and diazacrown ethers with one or two phosphorus containing side arms have also been synthesized [4]. These lariat ethers include phosphinoethyl or phosphinopropyl derivatives.

In this paper, new azacrown ethers with phosphonoalkyl side chains are described which have been synthesized to test their complex forming ability. We wished to assess the effect of the phosphorus function and the length of the carbon chain on the cation complexing ability of the azacrown moiety.

2. Experimental

The ^{31}P, ^{13}C and ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. Mass spectra were obtained on an MS-RFA instrument or on a ZAB-2SEQ spectrometer at 70 eV.

General procedure for the preparation of diethyl bromoalkylphosphonates
A mixture of 16.0 mL (0.0933 mol) of triethylphosphite and 0.467 mol of the corresponding dibromoalkane was heated at 160 °C for 24 h. Excess of the dibromoalkane was removed at 20 mmHg and the residue so obtained fractionated at 0.3–0.4 mmHg. The following products were thus synthesized:

Diethyl (2-bromoethyl)phosphonate
Yield: 54%; bp 83–86 °C/0.4 mmHg (lit. [5], 101 °C/0.8 mmHg); ^{31}P NMR ($CDCl_3$) δ 26.1.

Diethyl (3-bromopropyl)phosphonate
Yield: 57%; bp 97–101 °C/0.4 mmHg (lit. [6], 94–95 °C/2 mmHg); ^{31}P NMR ($CDCl_3$) δ 31.3; MS, *m/z* 258 (M^+, 1%), 179 (99), 152 (100).

Diethyl (4-bromobutyl)phosphonate
Yield: 51%; bp 115–120 °C/0.4 mmHg (lit. [7], 120 °C/0.01 mmHg); ^{31}P NMR ($CDCl_3$) δ 31.9; MS, *m/z* 272 (M^+, 5%), 193 (92), 165 (38), 137 (100).

Diethyl (5-bromopentyl)phosphonate
Yield: 43%; bp 120–124 °C/0.3 mmHg; ^{31}P NMR ($CDCl_3$) δ 32.3; MS, *m/z* 286 (M^+, 3%), 207 (42), 179 (21), 152 (100).

Dimethyl (3-bromopropyl)phosphonate was prepared similarly, but by the reaction of trimethylphosphite and 1,3-dibromopropane at 120 °C for 7h. Yield: 41%; bp 94–98 °C/0.4 mmHg (lit. [8], 96 °C/0.05 mmHg); ^{31}P NMR ($CDCl_3$) δ 33.5; MS, *m/z* 230 (M^+, 2%), 151 (48), 124 (100).

3-Bromopropyl-diphenylphosphine oxide was prepared by the reaction of ethyl diphenylphosphinite [9] and 1,3-dibromopropane. Yield: 46% after column chromatography (3% methanol in chloroform, silica gel); ^{31}P NMR ($CDCl_3$) δ 32.2; MS, *m/z* 322 (M^+, 2%), 243 (47), 215 (44), 201 (100).

2.1. GENERAL PROCEDURE FOR THE PREPARATION OF LARIAT ETHERS **4–8**

A mixture of 1.5 g (6.85 mmol) of monoaza-15-crown-5 [10], 10.3 mmol of the corresponding bromoalkylphosphonate (or bromoalkylphosphine oxide), 0.95 g (6.85 mmol) of dry potassium carbonate in 30 mL of dry dimethylformamide (DMF) was stirred at 90 °C for 8 h. Solid components were removed by filtration and the filtrate concentrated *in vacuo*. After the addition of 3 mL of water and 50 ml of chloroform, the organic phase was dried ($MgSO_4$). The residue obtained after evaporation was purified by repeated column chromatography (3% methanol in chloroform, silica gel). The following products were thus synthesized:

2.2. DIETHYL (1,4,7,10-TETRAOXA-13-AZA-CYCLOPENTADEC-13-YLPROPYL)PHOSPHONATE (**4**)

Yield: 45%; ^{31}P NMR ($CDCl_3$) δ 33.2; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.1, 6H, OCH_2CH_3), 1.61–1.82 (m, 4H, C(α)H_2, C(β)H_2), 2.48–2.57 (m, 2H, C(γ)H_2), 2.66–2.74 (m, 4H, C(2)H_2), 3.52-3.69 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 3.97–4.10 (m, 4H, OCH_2); MS, *m/z* 396 (M^+-H, 2%), 382 (2), 352 (5), 336 (8), 232 (100) 179 (25); HRMS, $(M\text{-}H)^+_{found}$ = 396.2101, $C_{17}H_{35}NO_7P$ requires 396.2151.

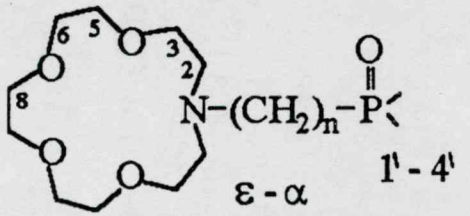
2.3. DIETHYL (1,4,7,10-TETRAOXA-13-AZA-CYCLOPENTADEC-13-YLBUTYL)PHOSPHONATE (**5**)

Yield: 41%; ^{31}P NMR ($CDCl_3$) δ 32.6; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.1, 6H, OCH_2CH_3), 1.34–1.42 (m, 4H, C(β)H_2, C(γ)H_2), 1.50–1.57 (m, 2H, C(α)H_2), 2.31–2.37 (m, 2H, C(δ)H_2), 2.55 (t, J = 5.7, 4H, C(2)H_2), 3.38–3.48 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 3.83–3.91 (m, 4H, OCH_2); MS, *m/z* 411 (M^+, 8%), 410 (M-H, 8), 396 (4), 366 (6), 350 (8) 232 (100), 193 (16); HRMS, M^+_{found} = 411.2332, $C_{18}H_{38}NO_7P$ requires 411.2386.

2.4. DIETHYL (1,4,7,10-TETRAOXA-13-AZA-CYCLOPENTADEC-13-YLPENTYL)PHOSPHONATE (**6**)

Yield: 35%; ^{31}P NMR ($CDCl_3$) δ 32.9; ^{13}C NMR, Table I; MS, *m/z* 425 (M^+, 4%), 410 (3), 380 (3), 364 (4), 232 (100), 207 (10); HRMS, M^+_{found} = 425.2473, $C_{19}H_{40}NO_7P$ requires 425.2542.

Table I. ^{13}C NMR data for lariat ethers **3–8** in $CDCl_3$ solutions



Compound	δ_C (J_{PC} in Hz)													
	C_α	C_β	C_γ	C_δ	C_ϵ	C_2	C_3	C_5	C_6	C_8	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$
3	23.3	49.6	–	–	–	53.9	69.7[a]	70.0[a]	70.2[a]	70.8[a]	–	61.4	16.3	
	(136.6)											(6.3)	(5.9)	
4	23.1	20.4	56.8	–	–	54.6	70.0[b]	70.1[b]	70.3[b]	70.9[b]	–	61.4	16.4	
	(141.9)	(4.6)	(18.0)									(6.5)	(5.9)	
5	25.1	20.0	27.6	55.9	–	54.4	69.4[c]	69.8[c]	70.0[c]	70.6[c]		61.2	16.2	
	(140.5)	(5.0)	(16.3)									(6.3)	(6.0)	
6	25.6	22.3	28.3	26.8	56.6	54.5	69.9[d]	70.1[d]	70.4[d]	70.9[d]	–	61.4	16.4	
	(140.5)	(4.9)	(17.1)									(6.6)	(5.8)	
7	21.8	20.1	56.5	–	–	52.1	69.7[e]	69.8[e]	70.1[e]	70.6[e]	–	54.4	–	–
	(142.0)		(17.2)											
8	27.0	19.4	56.7	–	–	54.4	69.7[f]	70.0[f]	70.2[f]	70.8[f]	133.0	130.7[g]	128.5[g]	131.5
	(72.7)		(15.1)								(98.0)	(9.4)	(11.8)	(1.9)

[a–g]Tentative assignments.

2.5. DIMETHYL (1,4,7,10-TETRAOXA-13-AZA-CYCLOPENTADEC-13-YLPROPYL)PHOSPHONATE (7)

Yield: 31%; ^{31}P NMR ($CDCl_3$) δ 35.9; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 1.48-1.85 (m, 4H, C(α)H_2, C(β)H_2), 2.28–2.33 (m, 2H, C(γ)H_2), 2.33–2.57 (m, 4H, C(2)H_2), 3.33–3.62 (m, 22H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, CH_3O); MS, *m/z* 369 (M^+, 1%), 368 (M^+-H, 1), 338 (3), 232 (100), 180 (39); HRMS, $M^{+\cdot}_{found}$ = 369.1876, $C_{15}H_{32}NO_7P$ requires 369.1916.

2.6. (1,4,7,10-TETRAOXA-13-AZA-CYCLOPENTADEC-13-YLPROPYL)-DIPHENYLPHOSPHINE OXIDE (8)

Reaction time: 20h; Yield: 34%; ^{31}P NMR ($CDCl_3$) δ 33.6; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 1.75–1.86 (m, 2H, C(β)H_2), 2.31–2.38 (m, 2H, C(α)H_2), 2.68–2.82 (m, 6H, C(γ)H_2, C(2)H_2), 3.52–3.69 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 7.39–7.76 (m, 10H, Ar); MS, *m/z* 461 (M^+, 2%), 460 (M-H, 2), 400 (7), 311 (100), 243 (85); HRMS, M^+_{found} = 461.2249, $C_{25}H_{36}NO_5P$ requires 461.2331.

The reaction of monoaza 15-crown-5 with diethyl (2-bromoethyl)phosphonate afforded ethyl derivative **2** in 38% yield. ^{13}C NMR ($CDCl_3$) δ 12.0 (CH_2CH_3), 50.4 (CH_2CH_3), 53.9 (N-CH_2CH_2), 69.9 (O–CH_2), 70.0 (O–CH_2), 70.3 (O–CH_2), 70.9 (O–CH_2); MS, *m/z* 247 (M^+–H, 18%), 232 (32), 114 (78), 100 (64), 73 (92), 58 (100), 45 (96) (lit. [11], 247, 232, 114, 100, 73, 58, 45).

2.7. DIETHYL (1,4,7,10-TETRAOXA-13-AZA-CYCLOPENTADEC-13-YLETHYL)PHOSPHONATE (3)

A solution of 1.5 g (6.85 mmol) of monoaza-15-crown-5 (**1**) and 8.0 g (48.8 mmol) of diethyl vinylphosphonate (prepared from diethyl (2-bromoethyl)phosphonate by a known method [5]) in 7.5 mL of benzene was stirred at the boiling point for 7 days. Volatile components were removed *in vacuo*. Column chromatography (as above) of the residue so obtained led to 0.97 g (37%) of product **3**. ^{31}P NMR ($CDCl_3$) δ 31.2; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.1, 6H, OCH_2CH_3), 1.74–1.82 (m, 2H, C(α)H_2), 2.53–2.60 (m, 4H, C(2)H_2), 2.66–2.73 (m, 2H, C(β)H_2), 3.42–3.53 (m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2), 3.87–3.97 (m, 4H, OCH_2); MS, *m/z* 382 (M^+–H, 8%), 368 (5), 338 (20), 322 (33), 232 (100), 166 (28); HRMS, $(M–H)^+_{found}$ = 382.1955, $C_{16}H_{33}NO_7P$ requires 382.1995.

2.8. 7,16-BIS(DIETHYLPHOSPHONOETHYL-)1,4,10,13-TETRAOXA-7,16-DIAZACYCLOOCTADECANE (10)

The reaction of 0.5 g (1.90 mmol) of diaza-18-crown-6 (**9**) and 5 g (32.5 mmol) of diethylphosphonate in 5 mL of benzene was carried out as described above for the **1**→**3** transformation. A similar work-up procedure afforded 0.14 g (20%) of

product **10** in a purity of 95%. ^{31}P NMR ($CDCl_3$) δ 31.3; ^{13}C NMR ($CDCl_3$) δ 16.4 ($^3J_{PC}$ = 5.9, OCH_2CH_3), 23.1 ($^1J_{PC}$ = 136.9, CH_2P), 48.5 (CH_2CH_2P), 53.2 (NCH_2CH_2O), 61.4 ($^2J_{PC}$ = 6.3, OCH_2CH_3), 70.5 (OCH_2), 70.4 (OCH_2); ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7.1, 12H, OCH_2CH_3), 1.74–1.87 (m, 4H, CH_2P), 2.55–2.75 (m, 12H, CH_2CH_2P, NCH_2CH_2O), 3.36–3.59 (m, 16H, CH_2OCH_2), 3.89–4.03 (m, 8H, OCH_2CH_3); MS, *m/z* 590 (M^+, 15%), 529 (53), 515 (69), 453 (100); HRMS, M^+_{found} = 590.3001, $C_{24}H_{52}N_2O_{10}P_2$ requires 590.3097.

2.9. PROCEDURE FOR THE DETERMINATION OF THE EXTRACTION ABILITY IN THE PRESENCE OF AZACROWN ETHERS **1**, **3–5** AND **8**

Equal volumes (5 mL) of a dichloromethane solution of the azacrown ether (**1**, **3–5** and **8**) (c = 0.01 mol L^{-1}) and of the aqueous alkali metal picrate (c = 0.005 mol L^{-1}) were introduced into an Erlenmeyer flask, which was then stoppered and shaken for 40 min at 25.0 °C. The mixture was then allowed to stand for at least 2 h in order to complete the phase separation. The phases were separated and the picrate concentration in the aqueous phase determined from its absorption at 354 nm (ϵ = 14600 mol^{-1} cm^{-1}). The extraction ability is given as % of the picrate extracted into the organic phase. In the control experiments carried out in the absence of azacrown ethers no detectable amounts of picrates were extracted into the organic phase.

2.10. PROCEDURE FOR THE ION-SELECTIVITY MEASUREMENTS

Membrane preparation: 5 mg of the azacrown ether (**1**, **4** and **8**) compound (ionophore), 66 mg of PVC powder of high molecular weight and 120 mg of *o*-nitrophenyl octyl ether were dissolved in 2 mL tetrahydrofuran (THF) and poured into a glass ring (diameter 28 mm) fixed on a glass plate [12]. A flexible membrane of ca. 0.2 mm thickness remained after the slow (ca. 24 h) evaporation of THF.

All membrane components except the azacrown ethers were purchased from Fluka AG, Buchs, Switzerland.

Electrodes: The membranes with diameter of 7 mm were incorporated into Philips IS 561 electrode bodies (Eindhoven, The Netherlands). As the inner electrolyte, 0.001 mol L^{-1} potassium chloride solution, while as the external reference electrode, Ag/AgCl electrode with 0.1 mol L^{-1} lithium acetate salt bridge electrolyte (Type 8201, Radelkis, Hungary) was used.

Selectivity determination: The potentiometric selectivity coefficients were determined by the separate solution method (SSM) [13] from the electromotive force (EMF) data measured in 0.1 mol L^{-1} chloride solutions of Li^+, Na^+, K^+ and NH_4^+. The EMF measurements were carried out at 25.0 °C with a Radiometer pHM 64 digital pH-meter (Coppenhagen, Denmark).

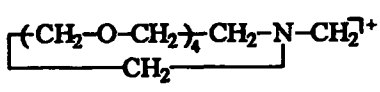
All solutions were prepared from chemicals of analytical grade and doubly quartz distilled water.

The activity coefficients of the solutions were calculated by the extended Debye-Hückel equation [14], while the liquid junction potential was estimated with the help of the Henderson formalism [14].

3. Results and Discussion

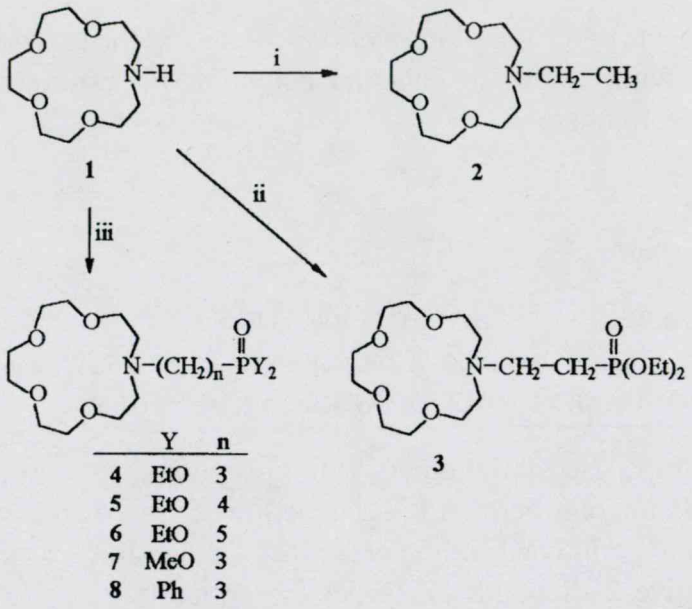
3.1. SYNTHESIS AND SPECTRAL CHARACTERIZATION OF *N*-PHOSPHONOALKYL-MONOAZA-15-CROWN-5 ETHERS AND AN *N,N*-DI(PHOSPHONOALKYL)-DIAZA 18-CROWN-6-ETHER

The monoaza-15-crown-5-based lariat ethers with phosphonyl function were synthesized by the *N*-alkylation of azacrown **1**. The reaction of azacrown **1** with diethyl (2-bromoethyl)phosphonate in DMF in the presence of potassium carbonate at 90 °C led to ethyl derivative **2** (Scheme 1). Under the conditions applied, the bromoethylphosphonate acted as an ethylating agent instead of phosphonoethylating the nitrogen atom. The expected product (**3**) could, however, be prepared in acceptable yield by reaction with diethyl vinylphosphonate (Scheme 1). In contrast to the bromoethylphosphonate, the bromoalkylphosphonates with three to five carbon atoms could be well utilized in the synthesis of the corresponding lariat ethers (**4–6**). The alkylating ω-bromoalkylphosphonates were prepared by the Arbuzov reaction of dibromoalkanes and triethyl phosphite according to our procedure. The synthesis had to be optimized to avoid the formation of the diphosphonates. *N*-Alkylation of azacrown **1** by the bromoalkylphosphonates afforded the lariat ethers (**4–6**) in 35–45% yield after repeated column chromatography (Scheme 1). The structure of the products was supported and characterized by ^{31}P, ^{13}C and ^{1}H NMR data, as well as MS and HRMS. The ^{31}C NMR spectral parameters are listed in Table I. The J_{PC} couplings are as large as ca. 140 Hz on C_α of the side chain of the lariat ethers (**3–6**); while values of ca. 5 Hz and 17 Hz were detected on C_β and C_γ, respectively. Protons of the CH_2N and CH_2O units appeared in the expected region, around δ_H 2.7 and 3.5, respectively. The EI mass spectra of the lariat ethers revealed the molecular ion only for **5** and **6**; in the case of **3** and **4** the molecular ion appeared in a deprotonated form. The



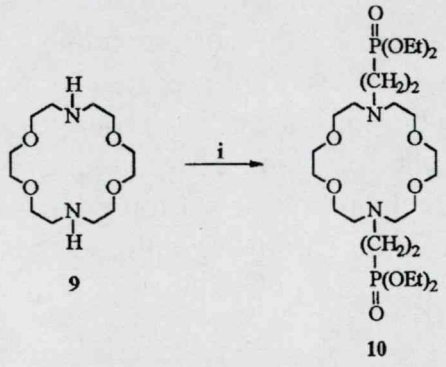
fragment (m/z = 232) was the base peak in all cases. Elemental composition of the products (**3–6**) was confirmed by HRMS.

To extend the range of the phosphonoalkyl-azacrown ethers, dimethylphosphonate **7** and diphenylphosphine oxide **8** were also synthesized using the bromoalkylation method (Scheme 1). The products isolated in ca. 33% yield were characterized by NMR and MS data (for ^{13}C NMR parameters see Table I). Lariat ethers **7** and **8** displayed similar NMR and mass spectroscopic features, as the other derivatives (**3–6**).



	Y	n
4	EtO	3
5	EtO	4
6	EtO	5
7	MeO	3
8	Ph	3

Scheme 1. Reagents and conditions: (i) $BrCH_2CH_2P(O)(OEt)_2$, K_2CO_3, DMFA, 90 °C; (ii) CH_2=CHP(O)$(OEt)_2$ (7.1 equiv.), C_6H_6, 80 °C; (iii) $Br(CH_2)_nP(O)Y_2$, K_2CO_3, DMFA, 90 °C.



Scheme 2. Reagent and conditions: (i) CH_2=CHP(O)$(OEt)_2$ (8.5 equiv.), C_6H_6, reflux.

A diazacrown ether with side chains on the two nitrogen atoms was also prepared. The reaction of 7,16-diaza-18-crown-6-ether (**9**) with diethyl vinylphosphonate afforded di(phosphonoethyl) derivative **10** in moderate yield (Scheme 2). The structure of the product (**10**) was confirmed by ^{31}P, ^{13}C and ^{1}H NMR, as well as mass spectrometry.

It is noted that the phosphonic acid derivatives of lariat ethers **3** and **10** are known compounds [15, 16]; their utilization as components of layered ion-exchangers has also been reported [15, 16].

3.2. EXTRACTION ABILITY OF THE PHOSPHONOALKYL-AZACROWN ETHERS

The complex forming ability of the lariat ethers (**3–5** and **8**) were characterized by the extracting ability (EA) of picrate salts (lithium, sodium, potassium and

ammonium picrate) from water into dichloromethane by the method of Kimura et al. [17]. The extraction ability may not accurately reflect the complexation ability in homogeneous solution, still it can be regarded as a good indicator of the cation binding ability. Concentrations of the picrates in water were determined by UV spectroscopy. The experimental data are shown in Table II. The unsubstituted azacrown ether (**1**) used as reference compound transports 56–67% of the picrate salts into the organic phase, but it does not show a notable selectivity with any of the alkali or ammonium ions. As can be seen, introduction of the phosphonoalkyl side arms results in a decreased extracting ability. The crown ether with the phosphonopropyl group (**4**) has the lowest values (except for potassium ion). A probable explanation for this effect may be that the bending side arms display a steric hindrance towards the cations. A change in the conformation of the azacrown ethers after introducing the side arms and protonation may also play important roles in the decreased extracting ability. On the other hand, selectivity of the monoazacrown ether (**1**) was improved significantly by introducing the phosphonoalkyl side chain: compound **3** transports two times more ammonium picrate and three times more lithium picrate into the organic phase, than potassium picrate. Lariat ether **4** extracts three times more ammonium picrate than lithium picrate. A similar trend can be observed for azacrown ether **5** and **8**. It is interesting to compare the extraction ability of the phosphonoalkyl azacrown ethers (**3, 4, 5**) with that of the diphenylphosphine oxide derivative (**8**): phosphonoalkyl species **3, 4, 5** form a relatively weak complex with the sodium ion (their EA values are 36%, 20% and 34%, respectively), while phosphine oxide **8** displays a better complex forming ability (EA = 50%) for the same cation. The sequence of selectivity was also changed by the substituents at the nitrogen atom: in the case of the unsubstituted azacrown ether (**1**) it is $K^+ \sim Li^+ > NH_4^+ > Na^+$. Compound **3** shows the order $Li^+ > NH_4^+ > Na^+ > K^+$, while derivatives **4** and **5** follow the order $NH_4^+ > K^+ > Na^+ > Li^+$. For phosphine oxide **8** the order of selectivity is $Na^+ > NH_4^+ > K^+ > Li^+$.

3.3. SELECTIVITY OF PVC MEMBRANE ELECTRODE CONTAINING PHOSPHONOALKYL-AZACROWN ETHERS (**1, 4, 8**)

The ion-selectivity of azacrown ethers **1, 4, 8** based on plasticized PVC membranes [12] was studied potentiometrically by the separate solution method [13] in 0.1 mol L^{-1} metal (M) chloride solutions. The selectivity coefficient values obtained by considering potassium as the primary ion are shown in Table III. From the data it is clear that the membrane with the unsubstituted azacrown ether (**1**) is selective for the ammonium ion and the order of selectivity is $NH_4^+ > K^+ > Na^+ > Li^+$. It is also seen that the membranes with the substituted azacrown ethers (**4** and **8**) lose the selectivity for the ammonium ion, and the sequence of selectivity changes in slight favour of the lithium ion.

Our research to synthesize new azacrown ethers with phosphinoalkyl side chains and to test their complex forming ability towards different cations is continuing.

Table II. Data for the extraction of alkali metal and ammonium picrates by crown ethers **1**, **3–5** and **8**[a]

Compound	Extractability (%)[b]			
	Li^+	Na^+	K^+	NH_4^+
1	65	56	67	60
3	68	36	25	48
4	13	20	31	40
5	25	34	51	62
8	21	50	30	46

[a]Temperature 25 °C; aqueous phase (5 mL); [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = 1×10^{-2} M.
[b]Defined as % picrate extracted into the organic phase. Determined by UV spectroscopy. Error limit: 5%.

Table III. Selectivity properties of azacrown ether (**1**, **4**, **8**) incorporated PVC membranes

Component of the membrane[a]	Potentiometric selectivity coefficient ($K^{Pot}_{K,M}$)			
	Li^+	Na^+	K^+	NH_4^+
1	0.60	0.95	1.00	8.51
4	1.20	0.93	1.00	0.83
8	1.26	1.02	1.00	1.10

[a]Composition of the membranes: 2.5 w/w% of substituted azacrown ether, 33 w/w% of PVC and 64.5 w/w% of 2-nitrophenyloctylether.

Acknowledgements

Gy. K. thanks the Hungarian Academy of Sciences for financing this project (Grant No. AKP 96-2-583 2,4/26). P. B. is grateful for the OTKA-support (No. T 015677). T. N. acknowledges the grant from the József Varga Foundation.

References

1. M. Tazaki, K. Nita, M. Takagi, and K. Ueno: *Chem. Lett.* 571 (1982).
2. B. Zhang and A. Clearfield: *J. Am. Chem. Soc.* **119**, 2751 (1997).
3. L. Burai, S. Jakab, R. Kiraly, I. Lázár, I. Tóth, and E. Bruecher:*J. Chem. Soc. Dalton Trans.* 1113 (1996).
4. A. Carroy, C. R. Langick, J-M. Lehn, K. E. Matthes, and D. Parker: *Helv. Chim. Acta* **69**, 580 (1986).

5. A. H. Ford-Moore and J. H. Williams: *J. Chem. Soc.* 1465 (1947).
6. Y. Okamoto, T. Okada, and H. Sakurai: *Bull. Chem. Soc. Jpn.* **48**, 484 (1975).
7. D. G. Hewitt and G. L. Newland: *Aust. J. Chem.* **30**, 579 (1977).
8. P. Chabrier, T. Nguyen-Thanh, D. Le-Maitre, M. Perat: *C. R. Acad. Sci.*, Paris, Ser. C, **267**, 732 (1968).
9. F. M. Kharrasova and G. Kamai: *Zh. Obshch. Khim.* **34**, 2195 (1964); *Chem. Abstr.* **61**, 10705f (1964).
10. H. Maeda and Y. Nakatsuji: *J. Chem. Soc. Chem. Commun.* 471 (1981).
11. P-L. Kuo, M. Miki, I. Ikeda, and M. Okahara: *Tetrahedron Lett.* **44**, 4273 (1978).
12. A. Craggs, G. J. Moody and J. D. R. Thomas: *J. Chem. Educ.* **51**, 541 (1974).
13. G. G. Guilbault, R. A. Durst, M. S. Frant, H. Freiser, E. H. Hansen, T. Light, E. Pungor, G. A. Rechnitz, N. M. Rice, T. J. Rohn, W. Simon, and J. D. R. Thomas: *Pure Appl. Chem.* **48**, 127 (1976).
14. P. C. Meier, D. Amman, W. E. Morf, and W. Simon: Medical and biological applications of electrochemical devices, J. Koryta (ed), John Wiley and Sons Ltd. (1980).
15. E. Brunet, M. Huelva, and J. C. Rodriguez-Ubis: *Tetrahedron Lett.* **35**, 8697 (1994).
16. E. Brunet, M. Huelva, R. Vazquez, O. Juanes, and J. C. Rodriguez-Ubis: *Chem. – Eur. J.* **2**, 1578 (1996).
17. K. Kimura, T. Maeda, and T. Shono: *Talanta* **26**, 945 (1979).

Synthesis of novel chiral crown ethers derived from D-glucose and their application to an enantioselective Michael reaction

Péter Bakó,[a] Zoltán Bajor[a] and László Tőke[b]*

[a] *Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P.O. Box 91, Hungary*
[b] *Organic Chemical Technology Research Group of the Hungarian Academy of Sciences at the Technical University of Budapest, H-1521 Budapest, P.O. Box 91, Hungary*

Received (in Cambridge, UK) 13th July 1999, Accepted 3rd November 1999

New chiral monoaza-15-crown-5 derivatives anellated to methyl 4,6-di-*O*-butyl-α-D-glucopyranoside have been synthesized from **1** using the 4,6-*O*-benzylidene protecting group (removed by acetic acid) and 2,3-di-*O*-benzyl groups (removed by catalytic hydrogenolysis). The alkylation of the hydroxy groups in **1** and **5** with benzyl chloride and bis(2-chloroethyl) ether, respectively, were carried out in two-phase reactions using phase-transfer (PT) catalysts. These sugar-based crown ethers showed significant asymmetric induction as chiral PT catalysts in the Michael addition of 2-nitropropane to chalcone (90% ee). The substituent at the nitrogen atom of the crown ethers has a major influence on both the chemical yield and the enantioselectivity.

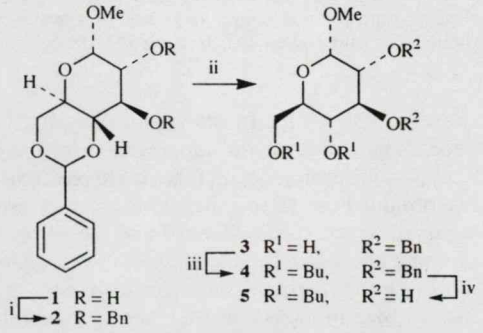
Introduction

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral crown ether catalysts. A number of chiral crown ethers have been employed as chiral catalysts in phase-transfer reactions.[1] A variety of such macrocycles have been synthesized and much attention was focussed on systems derived from carbohydrates. Crown ethers anellated to different pyranosidic or furanosidic carbohydrates have also been described.[2] The carbohydrate-containing chiral crown ethers have proved to be suitable models for the study of chiral induction in enantioselective reactions. Although many chiral crown ethers having different carbohydrate moieties have been synthesized in recent years, only a few have successfully been applied as catalysts in asymmetric reactions.[1]

The Michael reaction is one of the most important C–C bond-forming reactions, and stereoselective variants have been extensively investigated in recent years.[3] High asymmetric inductions have been reported in the Michael addition of methyl phenylacetate to methyl acrylate catalyzed by carbohydrate-containing chiral crown ethers.[4–8] We have previously reported the synthesis of new 15-membered-ring monoaza-crown ethers from glucose and galactose[9] and their application as chiral phase-transfer (PT) catalysts in an asymmetric Michael addition and in a Darzens condensation.[10,11] We first began investigating the Michael addition of 2-nitropropane to a chalcone catalyzed by chiral macrocyclic polyethers under phase-transfer conditions. The best result achieved in this reaction was 60% enantiomeric excess (ee) in the presence of monoaza-15-crown-5 ether containing a methyl 4,6-*O*-benzylidene-α-D-glucopyranoside unit,[11] and 82% ee generated by the crown catalyst anellated to phenyl β-D-glucopyranoside, respectively.[12] The chiral nature of the crown ether, the rigidity of the micro-environment of its cavity, the quality of the side arm attached to the nitrogen atom and the substituents on the sugar unit are all expected to play an important role. We have found that the presence of butyl substituents on the glucopyranose unit had an advantageous effect on both the chemical yield and the enantioselectivity. We have reported, in a preliminary communication, that use of the monoaza-crown ether containing a methyl 4,6-di-*O*-butyl-α-D-glucopyranoside unit (**13**, *N*-unsubstituted compound) as chiral PT catalyst resulted in 90% ee in the reaction of 2-nitropropane and chalcone.[13] In this paper we report the full details of this work and additionally discuss the synthesis and properties of a series of *N*-substituted analogues **8–11** (which in the event proved to be less effective than the *N*-substituted original).

Results and discussion

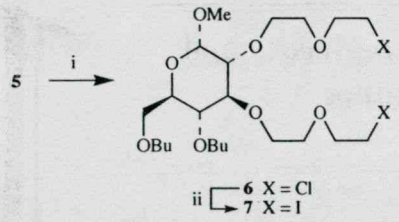
The general synthetic procedures for compounds **2–7** are summarized in Schemes 1 and 2.



Scheme 1 Synthesis of methyl 4,6-di-*O*-butyl-α-D-glucopyranoside **5** from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **1**. *Reagents and conditions*: i, benzyl chloride, 50% aq. NaOH, NBu_4Br, rt; ii, 96% CH_3CO_2H, reflux; iii, NaH, BuBr, DMF, rt; iv, 5% Pd/C EtOH, 50 °C.

The vicinal free hydroxy groups in methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **1** were treated with benzyl chloride, under PT conditions, in the presence of tetrabutylammonium hydroxide (PT catalyst). The reaction was carried out in a mixture of benzyl chloride (as reagent and solvent) and 50% aq. sodium hydroxide (10 h, room temp.) and we obtained the 2,3-di-*O*-benzyl ether **2** in a better yield (85%) than that obtained by the conventional method (in benzyl chloride, in the presence of powdered potassium hydroxide).[14] Removal of the 4,6-*O*-benzylidene group in compound **2** was effected by aq. acetic acid (2 h, 100 °C),[15] yielding the derivative **3** in 78% yield.[16] Alkylation of the two hydroxy groups in **3** with butyl bromide

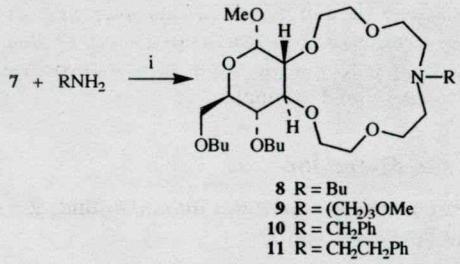
This journal is © The Royal Society of Chemistry 1999



Scheme 2 Synthesis of bisiodo podand **7** from compound **5**. *Reagents and conditions*: i, $O(CH_2CH_2Cl)_2$, 50% aq. NaOH, NBu_4Br, rt; ii, NaI, acetone, reflux.

in DMF, in the presence of sodium hydride (48 h, room temp.) afforded the 4,6-di-*O*-butyl derivative **4** in 74% yield. The benzyl protecting groups in **4** were removed by catalytic hydrogenolysis over palladium (5% Pd/C) in ethanol solution (12 h; 50 °C), giving compound **5** in quantitative yield.

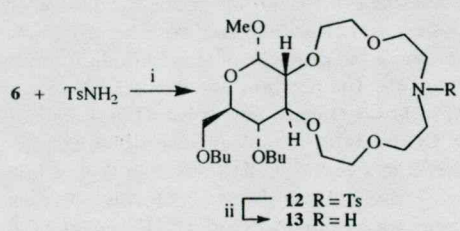
The hydroxy groups in **5** were alkylated by the method of Gross[17] with bis-(2-chloroethyl) ether as reagent and solvent (Scheme 2). The liquid–liquid two-phase reaction using tetrabutylammonium bromide as PT catalyst and 50% aq. sodium hydroxide gave rise to the bischloro podand **6** (8 h, room temp.) in 44% yield after chromatography. Exchange of the chlorines in **6** by iodines was carried out using sodium iodide in acetone (reflux, 40 h), yielding the bisiodo derivative **7**. Compound **7** was cyclized with various primary amines: *n*-butylamine, 3-methoxypropylamine, benzylamine and 2-phenylethylamine according to the method described previously[9] (Scheme 3). The method requires dry sodium carbonate in acetonitrile



Scheme 3 Synthesis of crown ethers **8–11** from **7**. *Reagents and conditions*: i, primary amines (*n*-butylamine to **8**, 3-methoxypropylamine to **9**, benzylamine to **10**, and 2-phenylethylamine to **11**), Na_2CO_3, CH_3CN, reflux.

as solvent (reflux, 32–40 h). In dilute solutions (1–3%) polycondensation side-reactions are suppressed and the desired intramolecular cyclization reaction takes place preferentially. In this way we obtained the 15-membered monoaza-crown ethers **8–11** in moderate yields starting from **7** and the corresponding primary amine. The yields of the ring-closure product, after purification by chromatography, varied from 40–46%.

The unsubstituted monoaza-crown ether **13** was synthesized by the method we described in our preliminary communication[13] (Scheme 4). The chiral starting macrocycle **12** needed for the preparation of the unsubstituted derivative **13** was obtained from the bischloro podand **6** by treatment with one molar equivalent of toluene-*p*-sulfonamide in DMF [in dilute



Scheme 4 Synthesis of crown ether **13** from **6**. *Reagents and conditions*: i, $TsNH_2$, K_2CO_3, DMF, reflux; ii, 4% Na/Hg_x, Na_2HPO_4, MeOH, reflux.

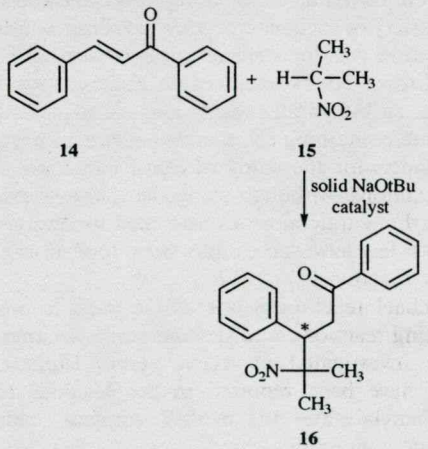
Table 1 Addition of 2-nitropropane to chalcone catalyzed by crown ethers **8–13**[a]

Run	Catalyst	Yield(%)[b]	ee(%)[c]
1	**8**	49	45 (*S*)
2	**9**	53	55 (54[d]) (*S*)
3	**10**	40	27 (*S*)
4	**11**	43	42 (*S*)
5	**12**	35	10 (*S*)
6	**13**	82	89 (90[d]) (*S*)

[a] Reaction time 24 h, base NaOBu^t, 20 °C. [b] Based on substance isolated by preparative TLC. [c] Determined by optical rotation. [d] Determined by ^{1}H NMR spectroscopy.

(2–3%) solution] in the presence of dry potassium carbonate (reflux, 32 h) in 52% yield after chromatography. Compound **12** was deprotected to **13** by 4% sodium amalgam in the presence of dibasic sodium phosphate in methanol (reflux, 20 h) in a yield of 85%, as reported for similar compounds.[18] Our attempt to form **13** by reductive removal of the *N*-tosyl group in **12** with $LiAlH_4$ in tetrahydrofuran (THF)[19] was not successful and caused the macrocyclic ring to open.The structure of products **8–13** was characterized by ^{1}H NMR and mass spectroscopic data. The ^{1}H spectral parameters are similar to those of aza-crown derivatives described earlier.[9] The relative molecular masses of new compounds were supported by CI-MS and FAB-MS. The fragment at *m/z* 476 was of significant intensity in all cases (see Experimental section) and is due to the (sugar-based-aza-crown-N-CH_2)$^+$ fragment.

Compounds **8–13** proved to be effective as chiral PT catalysts in the Michael addition of 2-nitropropane **15** to chalcone **14** (Scheme 5).



Scheme 5 The Michael addition of 2-nitropropane to chalcone. *Reagent and conditions*: NaOBu^t, toluene, rt.

The Michael addition was carried out in toluene with solid sodium *tert*-butoxide as base (35 mol%) and chiral catalyst (7 mol%), at room temperature. After the usual work-up procedure, the adduct **16** was isolated by preparative TLC; the asymmetric induction, expressed in terms of the ee, was monitored by measuring the optical rotation of the product **16** and comparing it with literature data for the preferred pure enantiomer[10] and by ^{1}H NMR spectroscopy using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-Eu(hfc)$_3$] as chiral shift reagent. The results, given in Table 1, show that the (*S*)-(+)-adduct **16** is always in excess and, moreover, that the substituent on the nitrogen atom of the catalyst has a significant influence on both the chemical yield and the asymmetric induction. It can be seen that the catalysts **8–11** resulted in moderate chemical yields from 40 to 53%; however, the enantioselectivity of the catalysts was rather different. Among the crown amines **8–11** the weakest catalyst was

the *N*-benzyl compound **10**, which gave 27% ee. This value increased in the presence of crown ether **11** having a phenylethyl side arm (42% ee) and *N*-butyl compound **8** (45% ee); the *N*-methoxypropyl derivative **9** (lariat ether) showed the highest enantioselection of 55% ee. The results for catalysts **10** and **11** possessing benzyl and phenylethyl side groups indicate the importance of the length of the side arm on the nitrogen atom. The *N*-tosyl crown amide **12** proved to be the weakest catalyst among all the crown ethers tested: chemical yield of 35% and optical purity of 10% ee were obtained. It is probable that the *N*-tosyl amide part in the crown ring reduces the complex-forming properties, and its steric hidrance may play an essential role too. The catalytic activity and enantioselectivity dramatically increased after the removal of the tosyl group: use of the unsubstituted aza-crown catalyst **13** resulted in a yield of 82% and enantioselectivity of 90% ee for the *S*-antipode. Therefore, compared with the unsubstituted compound, the enantioselectivity decreased in the case of *N*-substituted derivatives, most probably because of steric reasons but also because of the free NH group in the cycle making it probable that there is H-bond involvement in the transition-state structures. This finding is surprising in the light of our earlier findings with aza-crown ethers containing a 4,6-*O*-benzylidene group on the sugar moiety, when the substituents on the nitrogen mostly increased the chemical yield and the enantioselectivity.[10,11] The compounds presented here show a different picture, which can be explained by the structure of the molecule and which is different from those presented earlier. The crown ethers have no acetal ring and therefore they are more flexible. On the other hand, the two butyl groups on the glucopyranoside part considerably increase the lipophilicity of the molecule. Further investigations including mechanistic studies are now in progress.

Experimental

General procedures

Mps were determined with a Büchi 510 apparatus and are uncorrected. Specific rotations were determined with a Perkin-Elmer 241 polarimeter at 20 °C, and $[\alpha]_D$ values are given in units of deg cm^2 g^{-1}. IR spectra were recorded with a Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM 250 instrument for solutions in $CDCl_3$. *J*-Values are given in Hz. Mass spectra were obtained on a JEOL JMS-01 SG-2 instrument. Chemical ionization was applied as the ionization technique. Elemental analysis was performed on a Perkin-Elmer 240 automatic analyzer. Analytical and preparative TLC was performed on silica gel (60 GF-254, Merck); column chromatography was carried out using 70–230 mesh silica gel (Merck).

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 2

A solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **1** (20.0 g, 70.9 mmol) and tetrabutylammonium bromide (23.0 g, 71.4 mmol) in benzyl chloride (140.0 cm^3, 1.22 mol) was vigorously stirred with 50% aq. NaOH (140.0 cm^3, 2.67 mol) at room temperature for 10 h. The reaction mixture was added to a mixture of dichloromethane (450 cm^3) and water (450 cm^3). The organic layer was decanted and the aqueous one was washed with dichloromethane. The organic phases were combined, washed with water, dried (Na_2SO_4), and concentrated; the residue was crystallized from ethanol to give **2** (27.9 g, 85%), mp 97–98 °C (lit.,[14] 99 °C); $[\alpha]_D$ +23.3 (*c* 1, acetone) {lit.,[14] $[\alpha]_D$ +23.5 (*c* 1, acetone)}.

Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 3

Compound **2** (29.5 g, 63.7 mmol) was stirred with 96% acetic acid (300 cm^3) at 100 °C for 2 h. Water (100 cm^3) was then added and stirring was continued for 1 h. After cooling, the solution was evaporated to a syrup, water (2 × 40 cm^3) and toluene (2 × 60 cm^3) were added, and the mixture was evaporated to dryness again. The residue was dissolved in chloroform, and the solution was washed successively with aq. sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. Compound **3** was obtained as a syrup, which after crystallization gave solid material (17.9 g, 78%), mp 75–76 °C (from EtOH) (lit.,[16a] 73–74 °C); $[\alpha]_D$ +18.5 (*c* 1.5 $CHCl_3$) {lit.,[16a] $[\alpha]_D$ + 18.2 (*c* 1, $CHCl_3$)}.

Methyl 2,3-di-*O*-benzyl-4,6-di-*O*-butyl-α-D-glucopyranoside 4

A mixture of **3** (22.0 g, 58.8 mmol) in dry DMF (150 cm^3) and 60% NaH (6.0 g, 150 mmol) was stirred for 1 h under argon. After cooling of the mixture to 0 °C, dry butyl bromide (63.0 cm^3, 597.8 mmol) was added. The mixture was allowed to attain room temperature and then was stirred for a further 48 h. Excess of NaH was decomposed with methanol, and the solution was concentrated to a syrup. A solution of the residue in chloroform (150 cm^3) was washed with water (3 × 80 cm^3), dried (Na_2SO_4), and concentrated to give an oil, which was purified by column chromatography on silica gel using hexane–ethyl acetate (3:1) as eluent to afford syrupy *title compound* **4** (21.2 g, 74%), $[\alpha]_D$ +24.1 (*c* 1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2957, 2871 (Me, methylene), 1726 (sugar ring), 1454, 1366 (alkyl chain), 1094, 1057 (C–O), 1603, 737, 697 (Ar); δ_H ($CDCl_3$) 0.89 (6H, t, CH_3), 1.11–1.70 (12H, m, CH_2), 3.35 (3H, s, OCH_3), 3.38–3.86 (6H, m, CH and CH_2), 4.52–4.77 (4H, m, CH_2Ph), 4.82 (1H, d, *J* 3.5, anomer-H), 7.22–7.39 (10H, m, ArH); CI-MS *m/z* 487 (M^+ + 1, 98%) (Found: C, 71.45; H, 8.53. $C_{29}H_{42}O_6$ requires C, 71.60; H, 8.64%).

Methyl 4,6-di-*O*-butyl-α-D-glucopyranoside 5

A suspension of palladium catalyst absorbed on charcoal (5% Pd/C, 2.0 g) and compound **4** (29.1 g, 59.9 mmol) in absolute ethanol (300 cm^3) was shaken with hydrogen gas at 50 °C until the absorption of the gas ceased (12 h). Removal of the catalyst and concentration of the filtrate afforded the syrupy *title product* **5** (18.2 g, 99%), $[\alpha]_D$ +114.5 (*c* 1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3418br (OH), 2957, 2871 (Me, methylene), 1726 (sugar ring), 1464, 1367 (alkyl chain), 1126, 1053 (C–O); δ_H ($CDCl_3$) 0.82–0.98 (6H, m, CH_3), 1.21–1.70 (12H, m, CH_2), 3.38 (3H, s, OCH_3), 3.42–3.85 (8H, m, CH, CH_2 groups and OH), 4.76 (1H, d, *J* 4.8, anomer-H) (Found: C, 58.71; H, 9.75. $C_{15}H_{30}O_6$ requires C, 58.82; H, 9.80%).

Methyl 4,6-di-*O*-butyl-2,3-bis-*O*-[2-(2-chloroethoxy)ethyl]-α-D-glucopyranoside 6

A solution of compound **5** (16.1 g, 52.6 mmol) and tetrabutylammonium bromide (16.7 g, 52.6 mmol) in bis(2-chloroethyl) ether (92 cm^3, 831.4 mmol) was vigorously stirred with 50% aq. NaOH (92 cm^3) at room temp. for 10 h. The reaction mixture was then poured into a mixture of dichloromethane (330 cm^3) and water (330 cm^3) and the resulting solution was separated. The aqueous portion was washed with dichloromethane (2 × 200 cm^3); the combined organic layer and washings were then washed with water (3 × 180 cm^3), dried (Na_2SO_4), and evaporated to dryness. The syrup remaining was shaken with hexane (3 × 100 cm^3). The precipitate (Bu_4NBr) was filtered off, and the filtrate was evaporated to give a syrup, which was chromatographed on a column of silica gel (220 g) using diethyl ether–methanol (10:0.5) as eluent to give syrupy *product* **6** (12.1 g, 44%); $[\alpha]_D$ +61.5 (*c* 1, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2957, 2871 (Me, methylene), 1726 (sugar ring), 1460, 1357 (alkyl chain), 1100, 1051 (C–O), 749 (C–Cl); δ_H ($CDCl_3$) 0.90–0.94 (6H, m, CH_3), 1.34–1.40 (6H, m, CH_2), 1.52–1.64 (6H, m, CH_2), 3.38 (3H, s, OCH_3), 3.59–3.98 (22H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H) (Found: C, 53.02; H,

8.55; Cl, 13.36. $C_{23}H_{44}O_8Cl_2$ requires C, 53.18; H, 8.47; Cl, 13.48%).

Methyl 4,6-di-*O*-butyl-2,3-bis-*O*-[2-(2-iodoethoxy)ethyl]-α-D-glucopyranoside 7

A mixture of bischloro derivative **6** (6.0 g, 11.55 mmol) and anhydrous NaI (6.9 g, 47.1 mmol) in dry acetone (150 cm^3) was stirred under reflux for 40 h. After cooling, the precipitate was filtered off and washed with acetone. The combined acetone solution was evaporated. The residue was dissolved in dichloromethane (100 cm^3), and the solution was washed with water (3 × 50 cm^3) and dried (Na_2SO_4) to give compound **7** (7.8 g, 96%) as a syrup, $[\alpha]_D$ +46.3 (*c* 1, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2957, 2871 (Me, methylene), 1726 (sugar ring), 1105, 1052 (C–O), 1460, 1357 (alkyl chain), 545 (C–I); δ_H ($CDCl_3$) 0.85–0.96 (6H, m, CH_3), 1.32–1.40 (6H, m, CH_2), 1.52–1.64 (6H, m, CH_2), 3.27 (4H, t, CH_2I), 3.38 (3H, s, OCH_3), 3.45–4.10 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H).

General method for preparation of crown ethers 8–11

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 **7** (3.45 g, 4.60 mmol) in dry acetonitrile (100 cm^3) under argon. The stirred reaction mixture was refluxed for 32–40 h and monitored by TLC. After cooling, the precipitate was filtered off and washed with acetonitrile. The combined acetonitrile solution was concentrated; the residual oil was dissolved in chloroform, amd the solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with chloroform–methanol (10:0.5–10:2) to afford the title compounds.

***N*-Butyl-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 8.** Column chromatography gave *syrupy* **8** (1.1 g, 46%), $[\alpha]_D$ +57.4 (*c* 1, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2930, 2862 (Me, methylene), 1462, 1359 (alkyl chain), 1120, 1097, 1056 (C–O); δ_H ($CDCl_3$) 0.84–0.96 (9H, m, CH_3), 1.22–1.78 (16H, m, CH_2), 2.47–2.88 (6H, m, NCH_2), 3.38 (3H, s, OCH_3), 3.43–3.83 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H); EI-MS; *m/z* 519 (M^+, 17%), 488 ($M^+ - OCH_3$, 67), 476 ($M^+ - C_3H_7$, 91), 105 (100) (Found: C, 62.29; H, 10.12. $C_{27}H_{53}NO_8$ requires C, 62.42; H, 10.21%).

***N*-(3-Methoxypropyl)-2,3,5,6,8,9,11,12,14,15-decahydro-(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 9.** *Compound* **9** (0.84 g, 42%) was obtained as a syrup after chromatography, $[\alpha]_D$ +55.1 (*c* 1, $CHCl_3$); ν_{max} (neat film)/cm^{-1} 2930, 2862 (Me, methylene), 1462, 1360 (alkyl chain), 1120, 1100, 1056 (C–O); δ_H ($CDCl_3$) 0.84–0.96 (6H, m, CH_3), 1.32–1.42 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.47–2.88 (6H, m, NCH_2), 3.32 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.45–3.92 (22H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H); EI-MS *m/z* 535 (M^+, 8%), 504 ($M^+ - OCH_3$, 58), 476 ($M^+ - CH_2CH_2OCH_3$, 89), 105 (100) (Found: C, 60.48; H, 9.94; N, 2.58. $C_{27}H_{53}NO_9$ requires C, 60.56; H, 9.90; N, 2.61%).

***N*-Benzyl-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 10.** Column chromatography afforded *syrupy* **10** (1.0 g, 40%); $[\alpha]_D$ +56.2 (*c* 1.2, $CHCl_3$); ν_{max} (neat film)/cm^{-1} 2932, 2862 (Me, methylene), 1462, 1360 (alkyl chain), 1120, 1097, 1056 (C–O), 1600, 738, 700 (Ar); δ_H ($CDCl_3$) 0.84–0.97 (6H, m, CH_3), 1.32–1.44 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.62–2.90 (6H, m, NCH_2 and CH_2Ph), 3.38 (3H, s, OCH_3), 3.44–3.92 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H), 7.15–7.32 (5H, m, ArH); EI-MS *m/z* 553 (M^+, 13%), 536 ($M^+ - OCH_3$, 54), 476 ($M^+ - CH_2Ph$, 95), 105 (100) (Found: C, 65.00; H, 9.28; N, 2.52. $C_{30}H_{51}NO_8$ requires C, 65.09; H, 9.22; N, 2.53%).

***N*-(2-Phenylethyl)-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 11.** Column chromatography afforded syrupy **11** (1.2 g, 45%), $[\alpha]_D$ +51.3 (*c* 1, $CHCl_3$); ν_{max} (neat film)/cm^{-1} 2932, 2862 (Me, methylene), 1462, 1360 (alkyl chain), 1120, 1097, 1056 (C–O), 1600, 738, 700 (Ar); δ_H ($CDCl_3$) 0.84–0.97 (6H, m, CH_3), 1.32–1.44 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.62–2.91 (8H, m, NCH_2 and CH_2Ph), 3.38 (3H, s, OCH_3), 3.44–3.92 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H), 7.15–7.32 (5H, m, ArH); EI-MS *m/z* 567 (M^+, 13%), 536 ($M^+ - OCH_3$, 54), 476 ($M^+ - CH_2Ph$, 95), 105 (100) (Found: C, 65.38; H, 9.36; N, 2.42. $C_{31}H_{53}NO_8$ requires C, 65.60; H, 9.34; N, 2.47%).

***N*-Tosyl-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 12**

A mixture of bischloro podand **6** (2.6 g, 5.0 mmol), toluene-*p*-sulfonamide (0.86 g, 5.0 mmol) and anhydrous K_2CO_3 (3.5 g, 25.3 mmol) was stirred and refluxed in dry DMF (150 cm^3) for 32 h. After the reaction was complete, the precipitate was filtered off and washed with chloroform. The combined filtrate and washings were evaporated under reduced pressure, and the residue was dissolved in chloroform, washed with water, and dried ($MgSO_4$). After removal of the solvent, column chromatography of the residue on silica gel with toluene–methanol (10:1) as the eluent gave the *N-tosyl macrocycle* **12** as a yellow oil (1.6 g, 52%), $[\alpha]_D$ +33.4 (*c* 1.8, $CHCl_3$); δ_H ($CDCl_3$) 0.80–0.96 (6H, m, CH_3), 1.32–1.42 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.41 (3H, s, ArCH_3), 2.72–2.98 (4H, m, NCH_2), 3.40 (3H, s, OCH_3), 3.45–3.90 (18H, m, CH and CH_2 groups), 4.88 (1H, d, *J* 4.8, anomer-H), 7.22–7.70 (4H, m, ArH); MS (FAB) *m/z* 618 (MH^+) (Found: C, 58.44; H, 8.28; N, 2.21. $C_{30}H_{51}NO_{10}S$ requires C, 58.34; H, 8.26; N, 2.26%).

2,3,5,6,8,9,11,12,14,15-Decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 13

Compound **12** (1.4 g, 2.27 mmol), anhydrous disodium hydrogen phosphate (1.3 g, 9.10 mmol), and 4% sodium amalgam (11.0 g, 19.1 mmol) were placed in dry methanol (20 cm^3). The mixture was heated at reflux under a nitrogen atmosphere for 20 h while being stirred rapidly. After cooling to room temperature, the resulting slurry was decanted into water (80 cm^3) and extracted with chloroform (30 cm^3 × 4). The organic layers were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield compound **13** (0.89 g, 85%) as a yellow oil, $[\alpha]_D$ +58.9 (*c* 1.5, $CHCl_3$); δ_H ($CDCl_3$) 0.84–0.96 (6H, m, CH_3), 1.32–1.42 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.45 (1H, br s, NH), 2.82–2.98 (4H, m, NCH_2), 3.40 (3H, s, OCH_3), 3.44–3.92 (18H, m, CH and CH_2 groups), 4.83 (1H, d, *J* 4.8, anomer-H); MS (FAB) *m/z* 464 (MH^+) (Found: C, 59.50; H, 9.68; N, 3.08. $C_{23}H_{45}NO_8$ requires C, 59.61; H, 9.72; N, 3.02%).

General procedure for the Michael addition

This was performed as follows: Chalcone **14** (0.3 g, 1.44 mmol) and 2-nitropropane **15** (0.3 cm^3, 3.36 mmol) were dissolved in dry toluene (3 cm^3), 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 completion of the reaction (20–24 h) a mixture of toluene (7 cm^3) and water (10 cm^3) 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, and had mp 146–148 °C, $[\alpha]_D$ +80.8

(c 1, CH_2Cl_2) for pure (S)-(+)-enantiomer;[10] δ_H ($CDCl_3$) 1.54 (3H, s, CH_3), 1.63 (3H, s, CH_3), 3.27 (1H, dd, J 17.2 and 3.2, CH_2), 3.67 (1H, dd, J 17.2 and 10.4, CH_2), 4.15 (1H, dd, J 10.4 and 3.2, CH), 7.18–7.32 (5H, m, ArH), 7.42 (2H, t, COPh H-*m*), 7.53 (1H, t, COPh H-*p*), 7.85 (2H, d, COPh H-*o*).

Acknowledgements

This work was supported by the National Science Foundation (OTKA T 029253 and T 026478) and Hungarian Academy of Sciences.

References

1 M. I. O' Donnell, *Asymmetric Phase-transfer Reactions*, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, pp. 389–411 and references cited therein.
2 J. F. Stoddart, *Top. Stereochem.*, 1987, **17**, 207; J. M. Coteron, C. Vicent, C. Bosso and S. Penades, *J. Am. Chem. Soc.*, 1993, **115**, 10066.
3 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, 1994, p. 241; M. Wills and H. Tye, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3101; 1999, 1109.
4 M. Alonso-Lopez, J. Jimenez-Barbero, M. Martin-Lomas and S. Penades, *Tetrahedron*, 1988, **44**, 1535.
5 D. A. H. van Maarschalkerwaart, N. P. Willard and U. K. Pandit, *Tetrahedron*, 1992, **48**, 8825.
6 S. Aoki, S. Sasaki and K. Koga, *Heterocycles*, 1992, **33**, 493.
7 P. P. Kanakamma, N. S. Mani, U. Maitra and V. Nair, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2339.
8 L. Tőke, P. Bakó, Gy. M. Keserű, M. Albert and L. Fenichel, *Tetrahedron*, 1998, **54**, 213 and references cited therein.
9 P. Bakó and L. Tőke, *J. Inclusion Phenom.*, 1995, **23**, 195.
10 P. Bakó, Á. Szöllősy, P. Bombicz and L. Tőke, *Synlett*, 1997, 291.
11 P. Bakó, Á. Szöllősy, P. Bombicz and L. Tőke, *Heteroatom Chem.*, 1997, **8**, 333.
12 P. Bakó, K. Vizvárdi, S. Toppet, E. Van der Eycken, G. J. Hoornaert and L. Töke, *Tetrahedron*, 1998, **54**, 14975.
13 P. Bakó, T. Kiss and L. Tőke, *Tetrahedron Lett.*, 1997, **38**, 7259.
14 J. S. Brimacombe, in *Methods in Carbohydrate Chemistry*, ed. R. L. Whistler, M. L. Wolfrom and J. N. Bemillar, Academic Press, New York, 1963, vol. 6. p. 376.
15 R. W. Jeanloz, in *Methods in Carbohydrate Chemistry*, ed. R. L. Whistler, M. L. Wolfrom and J. N. Bemillar, Academic Press, New York, 1962, vol. 1. p. 231.
16 (*a*) B. H. Lipshutz and M. C. Morey, *J. Org Chem.*, 1981, **46**, 2419; (*b*) N. J. Davis and L. Flitsch, *J. Chem. Soc., Perkin Trans. 1*, 1994, 359.
17 P. Di Cesare and B. Gross, *Synth. Commun.*, 1979, 458.
18 F. Chavez and A. D. Sherry, *J. Org. Chem.*, 1989, **54**, 2990.
19 H. Pietraszkiewicz and J. Jurczak, *Tetrahedron*, 1984, **40**, 2967.

Paper 9/05670J

Heteroatom Chemistry folyóiratban elfogadva 1999 dec. 22.

Modification of D-glucose-based 18-crown-6 ethers by phosphorylation and phosphinylation

Tibor Novák,[1] Péter Bakó,[1] András Dobó,[2] Krisztina Ludányi,[2] László Tőke[3] and György Keglevich[1*]

[1] *Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary*

[2] *Research Institute for the Hungarian Academy Sciences, 1525 Budapest, Hungary*

[3] *Research Group of the Hungarian Academy of Sciences, Technical University of Budapest, 1521 Budapest, Hungary*

Received..... October 1999;

ABSTRACT: *The primary hydroxy groups of head–tail and head–head bis(sugar)-based crown ethers (1 and 3, respectively) were acylated by $(EtO)_2P(O)Cl$ and $Ph_2P(O)Cl$ in a selective manner. Cation binding ability of the bis-phosphorylated and phosphinylated macrocycles (2 and 4) was evaluated by the picrate extraction method.*

INTRODUCTION

It is well-known that the complex forming ability of the macrocycles can be modified by introduction of a side chain to the cycle. A number of phosphorylated crown ethers along with derivatives with exocyclic P-function(s) on the anellated ring have been described [1-3]. Our earlier research was focused on the synthesis of different azacrown ethers including sugar-anellated azacrowns with phosphorus containing side-chains [4-6]. These lariat-ethers were found to display a significant increase in the complex forming ability and in the selectivity towards the different cations. The sugar-based macrocycles are potential catalysts in enantioselective syntheses [6]. In this paper, we disclose our

results on the synthesis, spectral characterization and cation-binding ability of bis(glucose)-based crown ethers containing exocyclic P-functions on the sugar moiety.

RESULTS AND DISCUSSION

Reaction of head–tail type bis (D-glucose)-based crown **1** [7] with diethylphosphoryl chloride and with diphenylphosphinyl chloride in pyridine at room temperature furnished products **2a** and **2b**, respectively (Scheme 1). A similar acylation of head–head type sugar-anellated crown **3** [8] with the above reagents led to products **4a** and **4b** (Scheme 2). As it could be expected, the introduction of the P-functions was completely selective, only the primary hydroxy groups were involved in the acylation. Products **2a,b** and **4a,b** did not survive column chromatography, but could be filtered fast through a thin silica layer to afford the modified crown ethers in a 81–85% yield, in a purity of 93–96%. Compounds **2a,b** and **4a,b** were characterized by ^{31}P, ^{13}C and ^{1}H NMR, as well as FAB mass spectroscopy. The ^{13}C NMR spectral data were collected into Table 1. The assignments were confirmed by spectra obtained by the Attached Proton Test technique. The signals of the carbon atoms of both the glucose and the polyether rings, as well as those of the P-moieties appeared in the expected region. The FAB measurements confirmed the molecular weights in all instances, but the [M+H] peaks were of low intensity. The P-functionalized macrocycles (**2** and **4**) were found to undergo intensive deacylation under the circumstances of FAB. Due to this instability, the elemental composition could be confirmed by HR-FAB only in one case (**2b**).

We wished to study the effect of the phosphorus containing substituents on the complexing ability of the macrocycles. The cation binding ability of the bisphosphorilated (**2a**, **4a**) and phosphinylated (**2b**, **4b**) glucose-based crown ethers 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 et al. [9]. Although these values may not accurately reflect the complexation ability in homogeneous solution, still they can be regarded as good indicators of the cation binding ability. A higher value indicates a better phase transfer capability of the crown compounds. The experimental data are shown in Table 2. As a comparison, the properties of unsubstituted crown ethers (**1**, **3**) and the parent macrocycles bearing side arms with other heteroatoms (**5**, **6**) were also included [10]. As can be seen, introduction of the $P(O)(OEt)_2$ (**2a**, **4a**) and $P(O)Ph_2$ (**2b**, **4b**) functions resulted in a significant increase in the extracting ability (65–88%) for all of the cations examined as compared to the unsubstituted crown ethers **1** and **3** (EA = 4–14%), or to the compounds having tosyl-groups (**5**, EA = 7–21%) and acetyl groups (**6**, EA = 6–15%). A probable explanation is that, on one hand the phosphoryl groups may increase the lipophylity. On the other hand, the complex froming ability of compounds **2** and **4** may be increased due to secondary interactions between the P-moiety and the guest ion. No significant difference seemed to be between the complex forming ability of the "head–foot" and "head–head" isomers (**2a**, **2b** and **4a**, **4b**, respectively). The phosphinic derivatives (**2a**, **4a**) were found to form somewhat stronger complexes (73–88%) with the cations examined than the phosphates (**2b**, **4b**, 65–82%). Although the extracting ability of the new macrocycles was significantly improved, none of the compounds showed significant selectivity towards the cations. The crown ethers with diphenylphosphine oxide moiety (**2b**, **4b**) form the strongest complexes with ammonium ion (82% and 79%, respectively). The compounds with $P(O)(OEt)_2$ substituents (**2a**, **4a**) revealed the highest EA values for potassium and sodium ions, otherwise the $K^+ \sim Na^+ > NH_4^+ > Li^+$ order was followed.

EXPERIMENTAL

The ^{31}P, ^{13}C and ^{1}H NMR spectra were obtained on a Bruker DRX-500 instrument at 202.4, 125.7 and 500 MHz, respectively. The FAB measurements were performed on a ZAB-2SEQ spectrometer.

The starting macrocycles (**1** and **3**) were prepared as described earlier [7,8].

General procedure for the diacylation of bis(methyl-α-D-glucopyranoside)-18-crown-6 1 and 3

To 0.20 g (0.38 mmol) of macrocycle **1** or **3** in 15 mL of dry pyridine was added dropwise 0.11 mL (0.78 mmol) of $(EtO)_2P(O)Cl$ or 0.15 mL (0.78 mmol) of $Ph_2P(O)Cl$ and the mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue so obtained extracted with 40 mL of chloroform. The semicrystalline material obtained after concentration *in vacuo* was filtered through a 5 mm silica gel layer using 3% methanol in chloroform eluant to give the products (**2a,b** and **4a,b**) as syrupes after careful evaporation.

Product **2a**. Yield: 81%; ^{31}P NMR ($CDCl_3$) δ –0.34; ^{13}C NMR, Table 1; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J=7.0, 12H, OCH_2CH_3), 3.41 (s, 6H, OCH_3), 4.05–4.18 (m, OCH_2CH_3, overlapped by C(10)H, total intensity 10H), 4.83 (bs, 2H, C(1)H); FAB, 801 (M+H).

Product **2b**. Yield: 85%; ^{31}P NMR ($CDCl_3$) δ 24.3; ^{13}C NMR, Table 1; ^{1}H NMR ($CDCl_3$) δ 3.39 (s, 6H, OCH_3), 4.13–4.19 (m, 2H, C(10)H), 4.80 (d, J=3.2, 2H, C(1)H), 7.33–7.78 (m, 20H, Ar); FAB, 929 (M+H); HR-FAB, M^+_{found}=929.3095, $C_{46}H_{59}O_{16}P_2$ requires 929.3278.

Product **4a**. Yield: 84%; ^{31}P NMR ($CDCl_3$) δ –0.49; ^{13}C NMR, Table 1; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J=7.0, 12H, OCH_2CH_3), 3.39 (s, 6H, OCH_3), 4.0–4.12 (m, OCH_2CH_3 overlapped by C(10)H, total intensity 10H), 4.78 (d, J=3.2, 2H, C(1)H); FAB, 801 (M+H).

Product **4b**. Yield: 82%; ^{31}P NMR ($CDCl_3$) δ 26.3; ^{13}C NMR, Table 1; ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 6H, OCH_3), 4.15–4.22 (m, 2H, C(10)H), 4.80 (d, J=3.1, 2H, C(1)H), 7.35–7.80 (m, 20H, Ar); FAB, 929 (M+H).

ACKNOWLEDGMENTS

The authors are grateful for the OTKA-support of this research (Gr. no T 029235).

REFERENCES AND NOTES

[1] Markovskii, L. N.; Kalchenko, V. I.; Atmas, L. I. Zh Obshch Khim 1986, 56, 2419.

[2] Zabirov, N. G.; Sherbakova V. A.; Cherkasov, R. A. Zh Obshch Khim 1990, 60, 786.

[3] Chekhlov, A. N.; Zabirov, N. G.; Cherkasov, R. A.; Martynov, I. V. Izv Akad Nauk SSSR Ser Khim 1989, 2851.

[4] Keglevich, Gy.; Novák, T.; Bakó, P.; Újszászy, K.; Ludányi, K.; Tóth, K.; Tőke, L. J Inc Phenom 1999, 34, 299.

[5] Keglevich, Gy.; Novák, T.; Imre, T.; Bakó, P.; Újszászy, K.; Ludányi, K.; Tőke, L. Heteroatom Chem 1999, in press.

[6] Bakó, P.; Novák, T.; Ludányi, K.; Pete, B.; Tőke, L.; Keglevich, Gy. Tetrahedron Asymmetry 1999, 10, 2373.

[7] Bakó, P.; Fenichel, L.; Tőke, L.; Czugler, M. Liebigs Ann Chem 1981, 1163.

[8] Bakó, P.; Fenichel, L.; Tőke, L. Acta Chim Acad Sci Hung 1982, 111, 297.

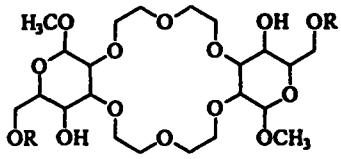
[9] Kimura, K.; Maeda, T.; Shono, T. Talanta 1979, 26, 945.

[10] Bakó, P.; Fenichel, L.; Tőke, L. J Incl Phenom 1993, 16, 17.

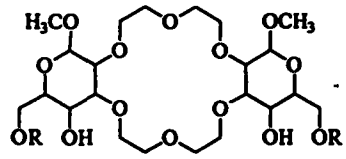
TABLE 1 ^{13}C NMR spectroscopic data of compounds **2a,b** and **4a,b** in $CDCl_3$ solution

Comp.	δ_C (J_{PC})														
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	OMe
2a	97.3	80.6	81.4	71.6	69.4	72.5	71.2	70.2	70.1	60.9	62.7 (5.8)	16.0 (7.1)	-	-	54.8
2b	97.6	80.6	81.6	72.0	69.7	72.5	71.1	70.4	70.2	61.0	135.5 (138.8)	128.2 (13.8)	131.1	131.2	54.9
4a	97.5	80.1	81.5	71.7	69.5	72.2	70.7	70.5	70.4	60.8	62.6 (5.7)	16.1 (7.1)	-	-	54.8
4b	97.7	80.3	81.6	71.8	69.7	72.4	70.9	70.7	70.5	61.1	135.4 (137.0)	128.2 (13.1)	131.1 (10.4)	131.2	54.9

TABLE 2 Extraction of alkali metal and ammonium picrates[a]



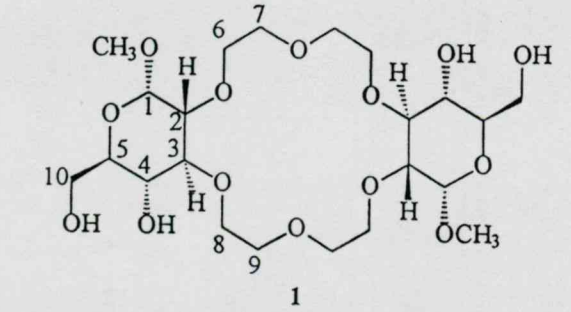
1, 2a, 2b, 5, 6



3, 4a, 4b

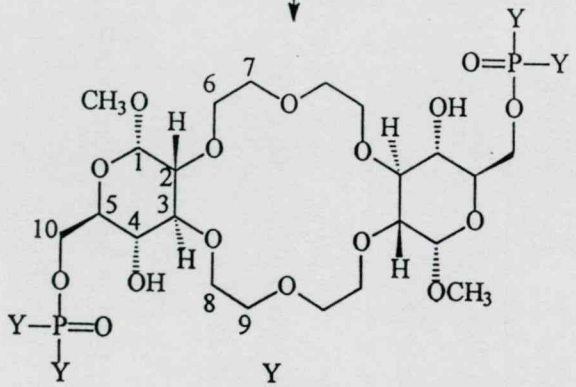
Comp.	*R*	*Extractability (%)*[b]			
		Li^+	Na^+	K^+	NH_4^+
1[c]	H	7	4	7	13
3[c]	H	6	5	6	14
2a	$P(O)(OEt)_2$	73	88	88	79
2b	$P(O)Ph_2$	69	70	72	82
4a	$P(O)(OEt)_2$	73	85	88	80
4b	$P(O)Ph_2$	72	65	71	79
5[c]	$SO_2PhCH_3(p)$	7	2	15	21
6[c]	$COCH_3$	6	12	15	14

[a] Temperature 20 °C; aqueous phase (5 mL); [picrate] = $5 \cdot 10^{-3}$ M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = $1 \cdot 10^{-2}$ M.
[b] Defined as % picrate extracted into the organic phase, determined by UV spectroscopy [9].
[c] Lit. [10].



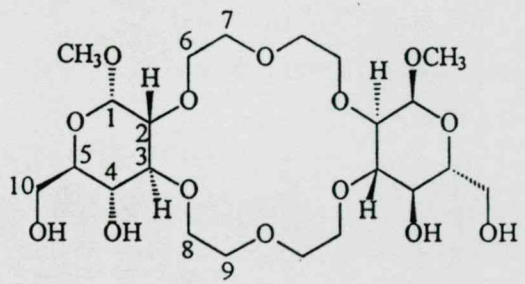
1

$ClP(O)Y_2$
Pyridine



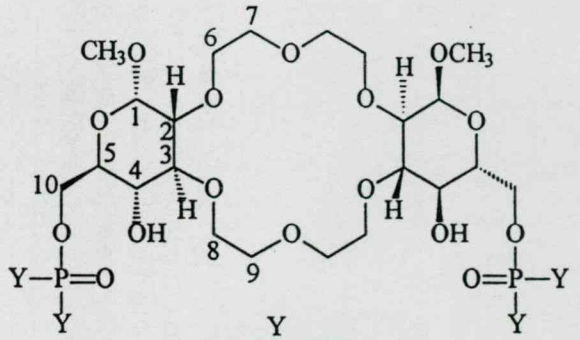
Y	
OEt	**2a**
Ph	**2b**

SCHEME 1



3

$ClP(O)Y_2$
Pyridine



Y	
OEt	**4a**
Ph	**4b**

SCHEME 2

Heteroatom Chemistry
Volume 10, Number 7, 1999

Synthesis and Cation Binding Ability of Azacrown Ethers with Phosphine or Phosphine Oxide Side Chain

György Keglevich,[1] Tibor Novák,[1] Tímea Imre,[1] Péter Bakó,[1] László Tőke,[1] Kálmán Újszászy,[2] and Krisztina Ludányi[3]

[1]*Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary*

[2]*Department of General and Inorganic Chemistry, Eötvös University, 1518 Budapest, Hungary*

[3]*Central Research Institute of Chemistry for Hungarian Academy of Sciences, 1525 Budapest, Hungary*

Received 29 March 1999; revised 2 June 1999

ABSTRACT: *The reaction of monoaza-15-crown-5* **1** *with bromoalkylphosphine oxides* **2** *and diphenylvinylphosphine oxide led to a new type of lariat ethers* (**3a–d**)*, one member of which* (**3a**) *was deoxygenated to the corresponding phosphine* (**4**)*. The substituent at the nitrogen atom had a great impact on the extraction ability of the azacrown.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 573–576, 1999

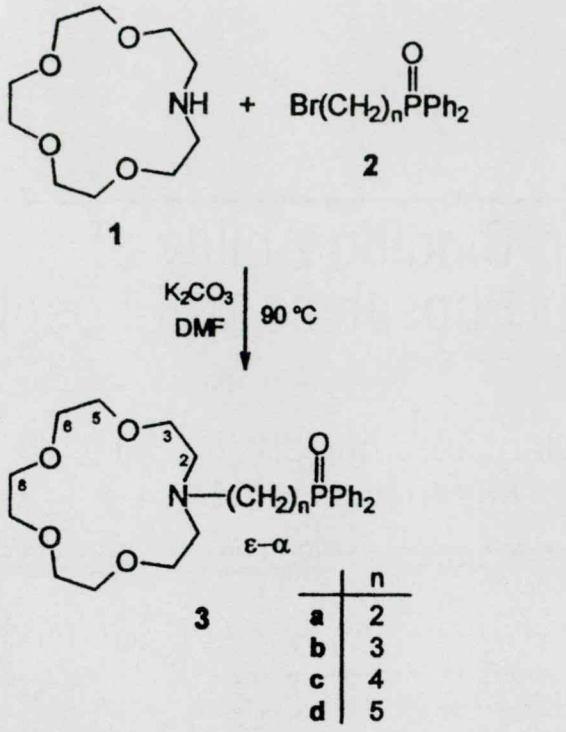
INTRODUCTION

In continuation of our current interest in the synthesis of macrocycles with phosphorus containing side chains [1,2], we present the preparation of the phosphine and the phosphine oxide derivatives of monoaza-15-crown-5. The few examples of monoaza- and diazacrown ethers with phosphorus containing side arm(s) described include phosphonomethyl- and phosphinoalkyl derivatives [3–5]. We attempted to evaluate the effect of the length of the carbon chain and the *P*-function on the complexing ability of the parent azacrown ring.

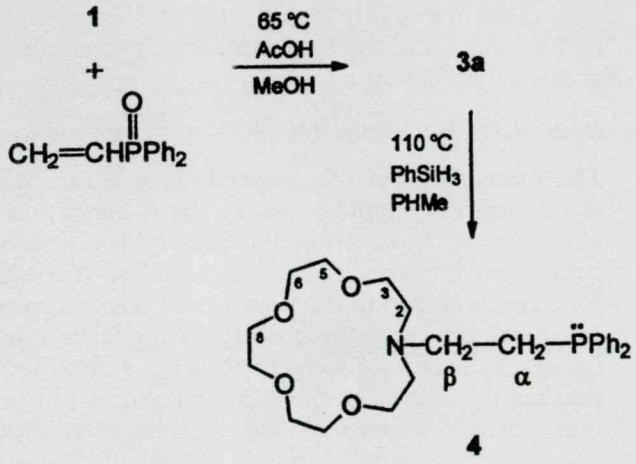
Correspondence to: György Keglevich.
Contract Grant Sponsor: Hungarian Academy of Sciences
Contract Grant Number: 96-2-583 2,4/26
Dedicated to Professor Alfred Schmidpeter on the occasion of his 70th birthday.
© 1999 John Wiley & Sons, Inc. CCC 1042-7163/99/070573-04

RESULTS AND DISCUSSION

The monoaza-15-crown-5-based lariat ethers with *P*-function were synthesized by the *N*-alkylation of azacrown **1**. The reaction of crown **1** with bromoalkyl-diphenylphosphine oxides **2a–d** in dimethylformamide (DMF) in the presence of potassium carbonate at 90°C gave the corresponding lariat ethers (**3a–d**) (Scheme 1). Products **3b–d** were obtained in reasonable yields (47–53%) after column chromatography, and because of side reactions of unknown nature, **3a** was isolated only in 12% yield. The reaction of crown **1** with diphenylvinylphosphine oxide in boiling methanol, in the presence of a catalytic amount of acetic acid, however, led to product **3a** in excellent yield (92%) (Scheme 2). With the exception of **3b** [1], the lariat ethers (**3a,c,d**) that were synthesized are new compounds and have been characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectrometry (MS) and high-resolution mass spectrometry (HRMS) data. The ^{31}P and ^{13}C NMR parameters are listed in Table 1. The chemical shifts, couplings, and mass spectroscopic fragmentation of phosphine oxides **3** showed close resemblance to the



SCHEME 1



SCHEME 2

corresponding features of phosphinic esters described earlier [1].

An additional lariat ether (4) with a phosphinoethyl substituent on the N atom was synthesized by the deoxygenation of phosphine oxide 3a using phenylsilane (Scheme 2). Earlier, phosphine 4 was synthesized by another approach [6]. The ^{31}P and ^{1}H NMR data of product 4 were similar to those reported [6]. In a nitrogen atmosphere, phosphine 4 can be stored for weeks. Oxidation of phosphine 4 by 30% hydrogen peroxide regenerated phosphine oxide 3a.

Having lariat ethers 3a–d and 4 in hand, it was possible to evaluate the effect of the length of the carbon chain and *P*-function on the cation binding ability of the azacrown ether (1). The complex forming ability of the lariat ethers (3a–d and 4) was characterized by the extracting ability (EA) of lithium, sodium, potassium, and ammonium picrates from water into dichloromethane in the presence of 3 or 4 by the method of Kimura et al. [7]. Concentrations of the picrates in water were determined by UV spectroscopy. The experimental data are shown in Table 2. The unsubstituted azacrown ether (1), which is used as the reference compound, transports 56–67% of the picrate salts into the organic phase, but it does not show a notable selectivity with any of the alkali or ammonium ions. As can be seen, the side arms with a diphenylphosphine oxide moiety at their end have a significant influence on the EA of the azacrown ring. In most cases, introduction of the $Ph_2P(O)$-alkyl side arm decreased the EA of the parent azacrown (1) (Table 2). In some cases, an increase in the EA, however, was observed (Table 2). The complex effect of the *N*-substituents is presumably due to steric and electronic effects. The length of the side arm is decisive; the highest extraction values (59–75%, except the EA for the lithium cation) were obtained for azacrown 3c, which incorporated four methylene units between the diphenylphosphine oxide moiety and the nitrogen atom. At the same time, compound 3b with a chain of three carbon atoms revealed the lowest values (21–50%, except the EA for the ammonium cation). The selectivity of the parent azacrown (1) was improved significantly by the introduction of the diphenylphosphine oxide side arm. Azacrown 3a with a two carbon atom chain showed the best selectivity because it transports two times more lithium picrate and sodium picrate (78% and 71%, respectively,) into the organic phase than potassium picrate or ammonium picrate (33 and 36%, respectively). Compound 3b distinguishes between lithium and sodium cations because it carries two times more sodium picrate (50%) than lithium picrate (21%) through the phase border. The sequence of selectivity was also changed for the different azacrown ethers (1, 3a–c); in the case of the base azacrown (1), the order is $K^+ \sim Li^+ > NH_4^+ > Na^+$. Product 3a revealed the $Li^+ > Na^+ > NH_4^+ \sim K^+$ order, and 3b followed the $Na^+ \sim NH_4^+ > K^+ > Li^+$ sequence. For 3c, an order of $NH_4^+ \sim Na^+ > K^+ > Li^+$ was detected.

It is interesting to compare the cation binding ability of phosphine oxide 3a with that of phosphine

TABLE 1 ^{31}P and ^{13}C NMR Data for the New Lariat Ethers

		$\delta_C(J_{PC})$												
Compound	δ_P	*C-α*	*C-β*	*C-γ*	*C-δ*	*C-ε*	*C-2*	*C-3*	*C-5*	*C-6*	*C-8*	*C-1′*	*C-2′*	*C-3′*	*C-4′*
3a	31.4	27.7 (69.2)	48.9				54.0	69.7[a]	70.1[a]	70.3[a]	70.9[a]	133.1 (98.8)	130.6[b] (9.4)	128.6[b] (11.5)	131.6 (1.7)
3c	33.4	29.6 (71.8)	19.6 (3.7)	28.4 (14.1)	56.1		54.7	69.7[c]	70.1[c]	70.3[c]	70.9[c]	133.1 (98.1)	130.9[d] (10.1)	128.8[b] (11.3)	131.8 (2.5)
3d	35.0	29.0 (73.1)	21.3 (2.0)	29.8 (8.4)	26.7	56.5	54.5	69.8[e]	70.0[e]	70.3[e]	70.9[e]	132.9 (98.2)	130.7′ (8.8)	128.6′ (11.4)	131.7

[a,c,e]Tentative assignment.
[b,d]May be reversed.

TABLE 2 Data for the Extraction of Alkali Metal and Ammonium Picrates by Azacrown Ethers **1**, **3a–c**, and **4**[a]

	Extractability (%)[b]			
Compound	Li^+	Na^+	K^+	NH_4^+
1	65	56	67	60
3a	78	71	33	36
3b	21	50	30	46 (Ref. [1])
3c	47	72	59	75
4	20	63	47	48

[a]Temperature 20°C; aqueous phase (5 mL); [picrate] = 0.005 M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = 0.01 M.
[b]Defined as % picrate extracted into the organic phase. Determined by UV spectroscopy. Error limit = 5%.

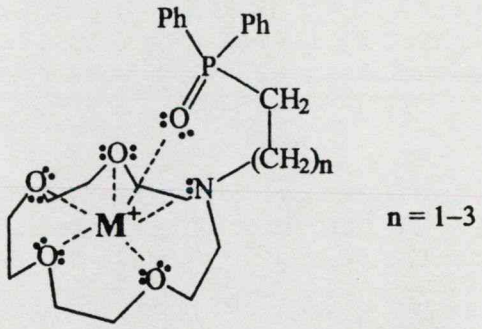


FIGURE 1 The effect of the P-functionalized side arm on the cation binding ability of the aracrown ring.

4. Removal of the oxygen atom from the phosphoryl group of **3a** resulted in a change of the EA values; phosphine **4** forms a weaker complex with the lithium cation than oxide **3a** does, but with the potassium and ammonium cations the complexes are stronger for **4** than for **3a** (Table 2). The selectivity also changed; compound **4** transports three times more sodium picrate than the lithium salt. The low value of 20% obtained for **4** can be explained by assuming that the short side arm cannot promote the complexation of the relatively small lithium cation. If there is an oxygen on the phosphorus atom (compound **3a**), the binding ability toward the lithium cation is improved.

It can be concluded that the *P*-functionalized side arms attached to the nitrogen atom have a significant effect on the cation binding ability of the monoaza-15-crown-5 ring, probably by the lateral discrimination [8] caused by the lone-pair electrons of the heteroatom (oxygen or phosphorus) at the end of the *N*-substituent. This effect is visualized for phosphine oxide **3b** in Figure 1. We plan to perform molecular mechanics calculations to explain the interaction between the complexing cation and the bending side arm. Although the extracting ability generally decreased, the selectivity always improved.

EXPERIMENTAL

^{31}P, ^{1}H, and ^{13}C NMR spectra were obtained on a Bruker DRX-500 spectrometer (at 202.4, 500, and 125.7 MHz, respectively) with 85% phosphoric acid (external) and tetramethylsilene (internal) standards in $CDCl_3$ solutions. Coupling constants are given in Hz. Mass spectra were recorded on a MS 25-RFA instrument at 70 eV.

Diphenylvinylphosphine oxide was prepared from diphenylphosphinic chloride and vinylmagnesium bromide as described earlier [9]. Diphenylvinylphosphine and monoaza-15-crown-5 were purchased from Aldrich.

General Procedure for the Preparation of ω-Bromoalkyl-diphenylphosphine Oxides **2a,c,d**

A mixture of 2.62 g, (11.4 mmol) of ethyl diphenylphosphinite [10] and 56.9 mmol of the corresponding dibromoalkane was heated at 150°C (oil bath) for 3 hours. The excess of dibromoalkane was removed at 20 mmHg, and the residue was purified by column

chromatography (silica gel, 3% methanol in chloroform) to give 2a,c,d.

(2a) Yield 46%; ^{31}P NMR ($CDCl_3$) δ 29.8; ^{13}C NMR ($CDCl_3$) δ 24.0 (C-2), 35.0 (J = 63.5, C-1), 129.1 (J = 11.9, C-3'), 130.8 (J = 9.4, C-2'), 131.9 (J = 99.3, C-1'), 132.4 (J = 2.2, C-4'); MS, *m/z* (rel. int.) 308 (M^+, 1), 228 (10), 201 (100).

(2c) Yield 53%; ^{31}P NMR ($CDCl_3$) δ 33.0; ^{13}C NMR ($CDCl_3$) δ 20.1 (C-2), 28.0 (J = 71.3, C-1), 32.8 (C-4), 33.1 (J = 14.7, C-3), 128.9 (J = 11.8, C-3'), 129.9 (J = 101.2, C-1'), 130.7 (J = 9.6, C-2'), 132.4 (C-4'); MS, *m/z* (rel. int.) 337 (M+H, 1), 257 (64), 201 (100).

(2d) Yield 42%; ^{31}P NMR ($CDCl_3$) δ 32.7; ^{13}C NMR ($CDCl_3$) δ 20.9 (J = 3.4, C-2), 29.5 (J = 14.5, C-3), 29.7 (J = 71.8, C-1), 32.3 (C-4), 33.5 (C-5), 128.8 (J = 11.3, C-3'), 130.8 (J = 9.0, C-2'), 131.8 (J = 1.7, C-4'), 133.1 (J = 98.1, C-1'); MS, *m/z* (rel. int.) 350 (M^+, 1), 271 (36), 215 (100), 201 (57).

General Procedure for the Preparation of (1,4,7,10-Tetraoxa-13-aza-cyclo-pentadec-13-ylalkyl)-diphenylphosphine Oxides 3a–d

A mixture of 0.5 g (2.28 mmol) of azacrown 1, 3.42 mmol of the corresponding bromalkylphosphine oxide, 0.32 g (2.28 mmol) of dry potassium carbonate in 30 mL of DMF was stirred at 85°C for 20 hours. The solid components were removed by filtration and the filtrate concentrated in vacuo. The residue was taken up in a mixture of 50 mL of chloroform and 2 mL of water. Then, the organic phase was dried (Na_2SO_4), and the solvent was evaporated. The remaining oil was purified by repeated column chromatography (silica gel, 3% methanol in chloroform) to give 3a–d.

(3c) Yield 51%; ^{31}P and ^{13}C NMR, Table 1; ^1H NMR ($CDCl_3$) δ 1.53–1.63 [m, 4H, C(β)H_2, C(γ)H_2], 2.22–2.31 [m, 2H, C(α)H_2], 2.45–2.51 [m, 2H, C(δ)H_2], 2.67 [t, J = 3.5, 4H, C(2)H_2], 3.53–3.67 [m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2], 7.51–7.73 (m, 10H, Ar); MS, *m/z* (rel. int.) 475 (M^+, 3), 474 (*M*-H, 4), 414 [*M*-$(CH_2O)_2$-H, 13), 326 [414-$(CH_2CH_2O)_2$,25], 325 (326-H, 33), 312 (326-CH_2, 22), 274 [*M*-P(O)Ph_2, 24], 257 [$(CH_2)_4$P(O)Ph_2, 95], 232 [*M*-$(CH_2)_3$P(O)Ph_2, 100], 201 [P(O)Ph_2, 60]: M^+_{found} = 475.2401, $C_{26}H_{38}NO_5P$ requires 475.2488.

(3d) Yield 47%; ^{31}P and ^{13}C NMR, Table 1; MS, *m/z* (rel. int.) 489 (M^+, 3), 488 (M-H, 5), 428 [M-$(CH_2O)_2$-H, 12], 340 [428-$(CH_2CH_2O)_2$, 21], 339 (340-H, 18), 326 (340-CH_2, 37), 288 [M-P(O)Ph_2, 27], 271 [$(CH_2)_5$P(O)Ph_2, 55], 232 [*M*-$(CH_2)_4$P(O)Ph_2, 100], 201 [P(O)Ph_2, 47]; M^+_{found} = 489.2579, $C_{27}H_{40}NO_5P$ requires 489.2644.

(3b) Yield 53%; spectroscopical data were similar to those reported earlier [1].

(3a) Yield 12%; preparation of 3a by the method described below was more efficient. A solution of 0.57 g (2.60 mmol) of azacrown 1, 0.59 g (2.60 mmol) of diphenylvinylphosphine oxide, and three drops of acetic acid in 30 mL of methanol was stirred at the boiling point for 10 days. Volatile components were removed in vacuo. Column chromatography (as above) of the oily residue led to 1.07 g (92%) of 3a. ^{31}P and ^{13}C NMR, Table 1; ^1H NMR ($CDCl_3$) δ 2.48–2.56 [m, 2H, C(α)H_2], 2.73 [d, J = 5.9, 4H, C(2)H_2], 2.88–2.94 [m, 2H, C(β)H_2], 3.56–3.69 [m, 16H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2], 7.45–7.78 (m, 10H, Ar); MS, *m/z* (rel. int.) 447 (M^+, 5), 446 (*M*-H, 3), 386 [*M*-$(CH_2O)_2$-H, 8], 298 [386-$(CH_2CH_2O)_2$, 30], 297 (298-H, 100), 284 (298-CH_2, 23), 246 [*M*-P(O)Ph_2, 70], 228 [$(CH_2)_2$P(O)Ph_2-H, 22], 201 [P(O)Ph_2, 94]; M^+_{found} = 447.2093, $C_{24}H_{34}NO_5P$ requires 447.2175.

Preparation of Phosphine 4

A solution of 0.2 g (0.447 mmol) of azacrown 1 and 0.20 mL (1.622 mmol) of phenylsilane in 5 mL of toluene was heated at 110°C under nitrogen for 4 days. Evaporation of the volatile components in vacuo left 0.20 g (98%) of 4 in a purity of 94%. ^{31}P NMR ($CDCl_3$) δ −19.1 [^{31}P NMR ($CDCl_3$) δ −19.3] [6]; ^1H NMR ($CDCl_3$) δ 2.22–2.43 (m, 2H, CH_2P), 2.59–3.09 (m, 6H, NCH_2), 3.46–3.80 (m, 16H, OCH_2), 7.16–7.56 (m, 10H, Ar); MS, *m/z* (rel. int.) 431 (M^+, 4), 372 [M-$(CH_2O)_2$+H, 3], 246 (*M*-PPh_2, 2), 232 (*M*-CH_2PPh_2, 100), 200 (CH_2PPh_2+H, 28), 185 (PPh_2, 24).

REFERENCES

[1] Keglevich, Gy.; Novák, T.; Bakó, P.; Újszászy, K.; Ludányi, K.; Tóth, K.; Tőke, L. J Inc Phenom 1999, 34, 299.

[2] Keglevich, Gy.; Novák, T.; Bakó, P.; Újszászy, K.; Tőke, L. Phosphorus Sulfur Relat Elem 1999, in press.

[3] Tazaki, M.; Nita, K.; Takagi, M.; Ueno, K. Chem Lett 1982, 571.

[4] Zhang, B.; Clearfield, A. J Am Chem Soc 1997, 119, 2751.

[5] Carroy, A.; Langick, C. R.; Lehn, J-M.; Matthes, K. E.; Parker, D. Helv Chim Acta 1986, 69, 580.

[6] Mclain, S. J. Inorg Chem 1986, 25, 3124.

[7] Kimura, K.; Maeda, T.; Shono, T. Talanta 1979, 26, 945.

[8] Lehn, J. M.; Vierling, P. Tetrahedron Lett 1980, 21, 1323.

[9] Collins, D. J.; Rowley, L. E.; Swan, J. M. Aust J Chem 1974, 27, 841.

[10] Kharrasova, F. M.; Kamai, G. Zh Obshch Khim 1964, 34, 2195.

Synthesis and Cation Binding Ability of the Phosphonoalkyl- and Phosphinoylalkyl Derivatives of Monoaza-18-Crown-6

TIBOR NOVÁK, PÉTER BAKÓ, TIMEA IMRE and GYÖRGY KEGLEVICH*
Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary.

ANDRÁS DOBÓ
Hungarian Academy of Sciences, Chemical Research Center, 1525 Budapest, Hungary.

LÁSZLÓ TŐKE
Research Group of the Hungarian Academy of Sciences, Technical University of Budapest, 1521 Budapest, Hungary.

(Received: 23. December 1999)

Abstract. Azacrown ethers with phosphonoalkyl- and phosphinoylalkyl side chains of two to five carbon atoms (**2–4**, **7** and **5–6**, **8**, respectively) were synthesized in acceptable yields. The cation binding ability of the new lariat ethers was evaluated by the picrate extraction method. Introduction of the P-functionalised N-substituent resulted in a decrease in the cation extraction ability in most cases, but the selectivity towards the cations examined was, in some instances, significantly increased.

Key words: Monoaza-18-crown-6, lariat ether, P-functionalised side chain, extraction ability.

1. Introduction

In the past few years a great number of azacrown macrocycles bearing functionalised pendant arms have been synthesized. These type of compounds, named lariat ethers [1], are known to be effective host molecules for alkali metal and alkaline earth metal cations due to the cooperative coordination function of the crown ring and the electron-donating side arm [1,2]. The selectivity for the different cations may be affected by the heteroatom(s) in the side chain and by the number of the methylene units connecting the functional group with the hetero atom to the azacrown ring [3]. The complex forming

ability of the macrocycles having P-functionalized pendant arms is relatively less studied. Some monoaza- and diazacrown ethers with phosphonomethyl side arms have been described [4–6]. According to the P-functions, these lariat ethers were mainly phosphonic acid derivatives [4,6]. A few examples of mono- and diazacrowns incorporating longer side arm(s) with the phosphine function are also known [7].

Recently we have reported the synthesis and cation extracting ability of monoaza-15-crown-5 ether having phosphonate, phosphine oxide or phosphine function in the side chain [8,9]. In the light of our favourable experiences with the above lariat ethers, it seemed to be promising to attach P-functionalised side arms to azacrown ethers of larger ring size. In this paper, we report the synthesis and cation binding ability of new lariat ethers with the phosphonic ester or phosphine oxide function that are based on the monoaza-18-crown-6 hetero ring. We wished to study the effect of the P-function and that of the length of the pendant arm on the cation binding ability of the parent macrocycle.

2. Experimental

The ^{31}P, ^{13}C and ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. Mass spectra were obtained on an MS-RFA instrument or on a ZAB-2SEQ spectrometer at 70 eV.

2.1. GENERAL PROCEDURE FOR THE PREPARATION OF LARIAT ETHERS (2–6)

A mixture of 1.0 g (3.80 mmol) of monoaza-18-crown-6 (1) [10], 5.70 mmol of the corresponding bromoalkylphosphonate [8] (or bromoalkylphosphine oxide [9]), 0.79 g (5.70 mmol) of dry potassium carbonate in 30 mL of dry acetonitrile was stirred at 90 °C for 8 h. Solid components were removed by filtration and the filtrate concentrated *in*

vacuo. The residue was purified by repeated column chromatography (3% methanol in chloroform, silica gel). The following products were thus synthesized:

2.2. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLPROPYL)PHOSPHONATE (2)

Yield: 58%; ^{31}P NMR ($CDCl_3$) δ 32.4; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.0, 6H, C(3')H_3), 1.65–1.81(m, 4H, C(α)H_2, C(β)H_2), 2.66–2.84 (m, 6H, C(2)H_2, C(γ)H_2), 3.52–3.75 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.10 (q, J = 6.94, 4H, C(2')H_2); MS, *m/z* 442 (M+H, 5), 396 (M–EtO, 7), 380 (M–EtO–O, 9), 336 (M–2EtO–O+H, 13), 276 (crown–CH_2, 100), 246 (30), 208 (38); $(M+H)^+_{found}$ = 442.2562, $C_{19}H_{41}NO_8P$ requires 442.2570.

2.3. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLBUTYL)PHOSPHONATE (3)

Yield: 45%; ^{31}P NMR ($CDCl_3$) δ 32.4; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.0, 6H, C(3')H_3), 1.52–1.66 (m, 4H, C(β)H_2, C(γ)H_2), 1.72–1.85 (m, 2H, C(α)H_2), 2.55–2.94 (m, 6H, C(2)H_2, C(δ)H_2), 3.48–3.80 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.08 (q, J = 7.0, 4H, C(2')H_2); MS FAB, *m/z* 456 (M+H, 5), 410 (M–EtO, 20), 394 (M–EtO–O, 25), 350 (M–2EtO–O+H, 50), 276 (crown–CH_2, 100), 246 (93), 208 (63); $(M+H)^+_{found}$ = 456.2712, $C_{20}H_{43}NO_8P$ requires 456.2726.

2.4. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLPENTYL)PHOSPHONATE (4)

Yield: 48%; ^{31}P NMR ($CDCl_3$) δ 32.7; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.0, 6H, C(3')H_3), 1.33–2.15 (m, 10H, C(α)H_2, C(β)H_2, C(γ)H_2, C(δ)H_2, C(ε)H_2), 2.52–2.78 (m, 4H, C(2)H_2), 3.43–3.76 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.07 (q, J = 7.1, 4H, C(2')H_2); MS, *m/z* 468 (M+H, 5), 424 (M–EtO, 5), 408 (M–EtO–O, 4), 364 (M–2EtO–O+H, 5), 276 (crown–CH_2, 100), 246 (36), 236 (36); $(M-H)^+_{found}$ = 468.2726, $C_{21}H_{43}NO_8P$ requires 468.2707.

2.5. (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLPROPYL)-DIPHENYLPHOSPHINE OXIDE (5)

Yield: 46%; ^{31}P NMR ($CDCl_3$) δ 34.1; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.59–1.71 (m, 2H, C(β)H_2), 2.22–2.30 (m, 2H, C(α)H_2), 2.97–3.03 (m, 6H, C(γ)H_2, C(2)H_2), 3.35–3.63 (m, 20H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 7.21–7.65 (m, 10H, Ar); MS, *m/z* 506 (M+H, 5), 444 (M–2CH_2O–H, 5), 400 (9), 311 (96), 276 (crown–CH_2, 53), 243 ($(CH_2)_3$–P(O)PPh_2, 100), 201 (P(O)Ph_2, 42); $(M+H)^+_{found}$ = 506.2640, $C_{27}H_{41}NO_6P$ requires 506.2672.

2.6. (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLBUTYL)-DIPHENYLPHOSPHINE OXIDE (6)

Yield: 44%; ^{31}P NMR ($CDCl_3$) δ 33.1; ^{13}C NMR, Table I; ^{1}H NMR ($CDCl_3$) δ 1.40–1.51 (m, 4H, C(β)H_2, C(γ)H_2), 2.20–2.29 (m, 2H, C(α)H_2), 2.45–2.54 (m, 2H, C(δ)H_2), 2.89–2.99 (m, 4H, C(2)H_2), 3.35–3.57 (m, 20H, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 7.27–7.67 (m, 10H, Ar); MS, *m/z* 520 (M+H, 4), 458 (M–2CH_2O–H, 6), 414 (10), 276

(crown–CH_2, 80), 257 (($(CH_2)_4$–P(O)PPh_2, 100), 201 (P(O)Ph_2, 71); $(M+H)^+_{found}$ = 520.2830, $C_{28}H_{43}NO_6P$ requires 520.2828.

2.7. GENERAL PROCEDURE FOR THE PREPARATION OF LARIAT ETHERS (7–8)

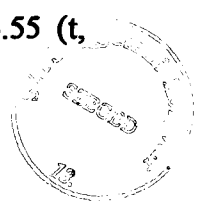
A solution of 1.0 g (3.80 mmol) of monoaza-18-crown-6 (1), 3.80 mmol of diphenylvinylphosphine oxide [9] (or diphenylvinylphosphonate [8]) and three drops of acetic acid in 30 mL of methanol was stirred at the boiling point for 10 days. Volatile components were removed *in vacuo*. The residue was purified by repeated column chromatography (3% methanol in chloroform, silica gel). The following products were thus synthesized:

2.8. DIETHYL (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLETHYL)PHOSPHONATE (7)

Yield: 69%; ^{31}P NMR ($CDCl_3$) δ 31.4; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7.0, 6H, C(3')H_3), 1.84–1.90 (m, 2H, C(α)H_2), 2.69–2.80 (m, 4H, C(2)H_2), 2.82–2.92 (m, 2H, C(β)H_2), 3.56–3.70 (m, 20H, C(2)H_2, C(3)H_2, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 4.09 (q, J = 7.4, 4H, C(2')H_2); MS, *m/z* 428 (M+H, 33), 382 (M–EtO, (22), 366 (M–EtO–O, 25), 322 (M–2EtO–O+H, 41), 276 (crown–CH_2, 100), 220 (95), 208 (95); $(M+H)^+_{found}$ = 428.2415, $C_{18}H_{39}NO_8P$ requires 428.2413.

2.9. (1,4,7,10,13-PENTAOXA-16-AZACYCLOOCTADEC-13-YLETHYL)-DIPHENYLPHOSPHINE OXIDE (8)

Yield: 58%; ^{31}P NMR ($CDCl_3$) δ 32.2; ^{13}C NMR, Table I; ^1H NMR ($CDCl_3$) δ 2.47–2.56 (m, 2H, C(α)H_2), 2.74 (t, J = 5.5, 4H, C(2)H_2), 2.86–2.95 (m, 2H, C(β)H_2), 3.55 (t,



J = 5.5, 4H, C(3)H_2), 3.57–3.67 (m, 16H, C(5)H_2, C(6)H_2, C(8)H_2, C(9)H_2), 7.45–7.79 (m, 10H, Ar); MS, *m/z* 492 (M+H, 6), 430 (M–2CH_2O–H, 6), 386 (10), 297 (100), 290 (M–P(O)Ph_2, 72), 201 (P(O)Ph_2, 74); $(M+H)^+_{found}$ = 492.2511, $C_{26}H_{39}NO_6P$ requires 492.2515.

2.10. PROCEDURE FOR THE DETERMINATION OF THE EXTRACTION ABILITY IN THE PRESENCE OF AZACROWN ETHERS 1–8

Equal volumes (5mL) of a dichloromethane solution of the azacrown ether (**1–8**) (c = 0.01 mol L^{-1}) and of the aqueous alkali metal picrate (c = 0.005 mol L^{-1}) were introduced into an Erlenmeyer flask, which was then stoppered and shaken for 40 min at 25 °C. The mixture was then allowed to stand for at least 2 h in order to complete the phase separation. The phases were separated and the picrate concentration in the aqueous phase determined from its absorption at 354 nm. (ε = 14600 $mol^{-1}cm^{-1}$). The extraction ability is given as % of the picrate extracted into the organic phase. In the control experiments carried out in the absence of azacrown ethers no detectable amounts of picrates were extracted into the organic phase. According to our experience, azacrowns **2-8** could only be detected in neglectable amounts in the aqueous phase.

3. Results and Discussion

3.1. SYNTHESIS AND SPECTRAL CHARACTERIZATION OF *N*-PHOSPHONOALKYL- AND *N*-PHOSPHINOYLALKYL-MONOAZA-18-CROWN-6 ETHERS

The monoaza-18-crown-6-based lariat ethers with phosphonyl- or phosphinoyl function were prepared by the N-alkylation of starting material **1**. The azacrown (**1**) was reacted with the bromoalkylphosphonates and bromoalkylphosphine oxides in acetonitrile at 90 °C to give phosphonates **2–4** and phosphine oxides **5** and **6**, respectively in 69–44%

yield after purification by column chromatography (Scheme 1). The lariat ethers with an ethylene chain (**7** and **8**) were synthesized by reacting azacrown **1** with diethyl vinylphosphonate and dipenyl-vinylphosphine oxide, respectively (Scheme 1). The structure of the products (**2–8**) was characterised by ^{31}P, ^{13}C and ^{1}H NMR data, as well as MS and HRMS. The ^{13}C NMR spectral parameters listed in Table I, as well as the mass spectroscopic features were similar to those reported for analogous derivatives [8, 9].

3.2. EXTRACTION ABILITY OF THE NEW LARIAT ETHERS (2–8)

The complex forming ability of the P-functionalized lariat ethers (**2–8**) 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 et al. [11]. The use of the EA values has been widely accepted as the indicator of the cation binding ability, since Pedersen introduced this approach [12]. Concentrations of the picrates in water were determined by UV spectroscopy. The experimental data are shown in Table II. The unsubstituted azacrown **1** used as reference compound has a rather good extracting ability with all cations, but it is hardly able to discriminate between them (EA=86–93%). In the case of the N-substituted compounds, the EA values are either similar to or lower than the values obtained using **1**. Crown ethers **3** and **6** having four methylene units between the nitrogen atom and the phosphorus function, as well as compound **5** with three methylene units revealed unchanged EA values (84–97%) within the error limit. These compounds did not display any selectivity towards the cations examined. In the case of azacrowns **7** and **8** with a short connecting chain (n=2), the presence of the N-substituents brought about a remarkable decrease in the extracting properties. At the same time, a significant discrimination could be observed between certain cations: e.g. **7** transports 35% of lithium picrate, while 82% each of potassium or ammonium picrate; **8** extracts 42% of lithium

picrate, but 94% of the potassium salt. Thus, the azacrowns with a shorter side arm discriminated between the cations to a higher extent than the compounds with longer side arms. Figure 1 revealing the situation for compounds **2-8** shows how the lone pair of the P=O function may assist in binding a metal cation. The complex effect of the N-substituents is presumably due to steric and electronic reasons. The presence of the N-phosphonoalkyl and N-phosphinoylalkyl substituents in the azacrown results in an increase in the electron density on the nitrogen atom due to the electronreleasing effect of the substituents under discussion. The phosphorus-containing side arm can influence the cation binding ability to a greater extent, when it is nearer to the parent crown ring.

Among the phosphonoalkyl-azacrown ethers (**2–4, 7**), compound **3** with a four carbon atom connecting chain formed the most stable complexes with all cations examined (84–94%). The EA-s for the alkali cations seem to be larger for the azacrowns with a phosphine oxide function (**5, 6, 8**) than for those with the phosphinic moiety (**2–4, 7**). All of the new macrocycles formed the strongest complexes with K^+ and NH_4^+ cation under our circumstances. The sequence for the cation binding ability was generally $K^+ \sim NH_4^+ > Na^+ > Li^+$. The trends discussed above seem to be comparable with those observed by us for the monoaza-15-crown-5 with similar N-substituents [8,9]. In these cases, the substituents had, however, a more significant influence on the EA values. This may be due to the better complexing ability of the azacrown with the 18-membered ring (**1**), incorporating the cations under discussion to a higher extent, as compared to that of the monoaza-15-crown-5. (The EA values for the cations examined are 86–93% and 56–67%, respectively.) Consequently, the introduction of the side arm is less efficient in the case of the macrocycle with a bigger ring size.

In the next part of our work, we shall focus on the synthesis and study of lariat ethers with other P-functions, such as phosphine, thiophosphine and the iminophosphine functional groups.

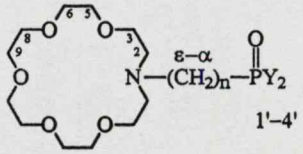
Acknowledgements

We are grateful for the OTKA-support (T 029253). T. N. thanks the grant from the József Varga Foundation.

References

1. G. W. Gokel: *Chem. Soc. Rev.* **21**, 39 (1992) and references cited therein.
2. (a) H. Tsukube, T. Inoue and K. Hori: *J. Org. Chem.* **59**, 8047 (1994).
   (b) T. Nabeshima, N. Tsukada, K. Nishijima, H. Ohshiro and Y. Yano: *J. Org. Chem.* **61**, 4342 (1996).
   (c) W. Walkowiak, W. A. Charewicz, S. I. Kang, I-W. Yang, M. J. Pugia and R. A Bartsch: *Anal. Chem.* **62**, 2018 (1990).
3. Y. Nakatsuji, T. Nakamura, M. Yonetani, H. Yuya and M. Okahara: *J. Am. Chem. Soc.* **110**, 531 (1988).
4. M. Tazaki, K. Nita, M. Takagi and K. Ueno: *Chem. Lett.* **1982**, 571.
5. B. Zhang and A. Clearfield: *J. Am. Chem. Soc.* **119**, 2751 (1997).
6. L. Burai, S. Jakab, R. Király, I. Lázár, I. Tóth and E. Bruecher: *J. Chem. Soc. Dalton Trans.* **1996**, 1113.
7. A. Carroy, C. R. Langick, J-M. Lehn, K. E. Matthes and D. Parker: *Helv. Chim. Acta* **69**, 580 (1986).
8. Gy. Keglevich, T. Novák, P. Bakó, K. Újszászy, K. Ludányi, K. Tóth and L. Tőke: *J. Incl. Phenom.* **34**, 299 (1999),
9. Gy. Keglevich, T. Novák, T. Imre, P. Bakó, L. Tőke, K. Újszászy and K. Ludányi: *Heteroatom Chem.* **10**, 573 (1999).
10. R. A. Schultz, B. D. White, D. M. Dishong, K. A. Arnold and G. W. Gokel: *J. Am. Chem. Soc.* **107**, 6659 (1985).
11. K. Kimura, T. Maeda and T. Shono: *Talanta* **26**, 945 (1979).
12. C. J. Pedersen: *J. Am. Chem. Soc.* **92**, 386 (1970).

Table I. ^{13}C NMR data for lariat ethers **2–8** in $CDCl_3$ solutions

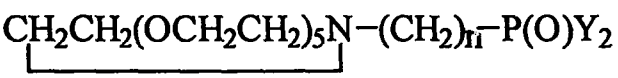


1'–4'

Comp.	Y	n	δ_C (J_{PC} in Hz)													
			C_α	C_β	C_γ	C_δ	C_ε	C_2	C_3	C_5	C_6	C_8	C_9	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$
7	EtO	2	23.0	48.3	–	–	–	53.2	69.4[a]	70.1[a]	70.4[a]	70.4[a]	70.6[a]	–	61.2	16.2	–
			(136.6)												(6.4)	(6.0)	
2	EtO	3	22.6	16.9	51.0	–	–	53.5	69.4[b]	69.5[b]	69.5[b]	69.5[b]	69.6[b]	–	61.4	16.1	–
			(141.2)	(3.8)	(15.4)										(6.1)	(5.9)	
3	EtO	4	24.5	19.9	24.3	50.4	–	53.6	69.3[c]	69.4[c]	69.5[c]	69.6[c]	69.7[c]	–	61.2	16.1	–
			(140.1)	(4.7)	(14.3)										(6.1)	(5.9)	
4	EtO	5	25.3	22.2	28.2	23.9	51.5	54.0	69.9[d]	69.9[d]	69.9[d]	70.0[d]	70.1[d]	–	61.4	16.4	–
			(140.0)	(3.8)	(16.4)										(6.5)	(5.9)	
8	Ph	2	26.9	47.6	–	–	–	53.4	69.2[e]	70.0[e]	70.3[e]	70.4[e]	70.5[e]	132.7	130.5[f]	128.5[f]	131.5
			(69.3)											(99.0)	(9.2)	(11.3)	()
5	Ph	3	26.6	16.8	71.8	–	–	53.8	69.4[g]	69.5[g]	69.7[g]	70.1[g]	70.2[g]	132.3	130.4[h]	128.5[h]	131.5
			(71.9)											(98.7)	(9.2)	(11.6)	(1.5)
6	Ph	4	28.7	19.3	25.5	50.9	–	53.8	69.5[i]	69.8[i]	69.9[i]	70.1[i]	70.2[i]	132.8	130.5[j]	128.4[j]	131.4
			(71.6)	(3.4)	(12.1)	(16.0)								(97.8)	(9.5)	(11.7)	(1.7)

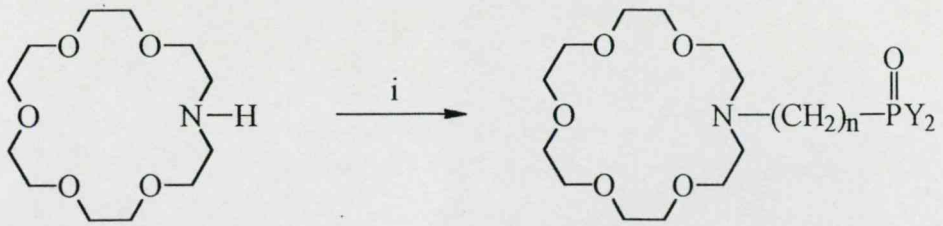
[a-j] Tentative assignments.

Table II. Data for the extraction of alkali metal and ammonium picrates by crown ethers **1–8**[a]



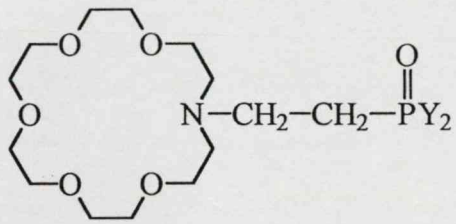
Compound	Y	n	Extractability (%)[b]			
			Li^+	Na^+	K^+	NH_4^+
1	H		86	88	93	93
7	EtO	2	35	66	82	82
2	EtO	3	69	74	89	91
3	EtO	4	84	85	94	94
4	EtO	5	76	78	87	95
8	Ph	2	42	75	94	85
5	Ph	3	88	91	95	90
6	Ph	4	86	89	97	92

[a] Temperature 25 °C; aqueous phase (5 mL); [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = 1×10^{-2} M.
[b] Defined as % picrate extracted into the organic phase. Determined by UV spectroscopy. Error limit: 5%.



1

	Y	n
2	EtO	3
3	EtO	4
4	EtO	5
5	Ph	3
6	Ph	4



	Y
7	EtO
8	Ph

Scheme 1. Reagents and conditions: (i) $Br(CH_2)_nP(O)Y_2$, K_2CO_3, acetonitrile, 90 °C; (ii) $CH_2{=}CHP(O)Y_2$, CH_3COOH (catalyst), methyl alcohol, 64 °C.

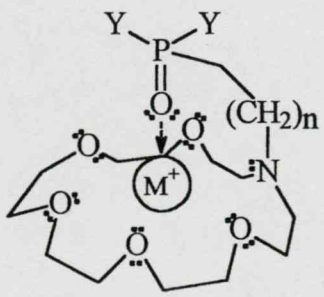


Fig 1. The effect of the P-functionalized side arm on the cation binding ability of the azacrown ring.

Chiral Azacrown Ethers Derived from D-Mannitol

PÉTER BAKÓ, TIBOR BAKÓ, KATALIN BISZTRAY
Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary.

ÁRON SZÖLLŐSY
NMR Laboratory of the Institute for General and Analytical Chemistry, Thecnical University of Budapest, 1521 Budapest, Hungary.

KORNÉL NAGY
Department of Physical Chemistry, Thecnical University of Budapest, 1521 Budapest, Hungary.

LÁSZLÓ TŐKE
Research Group of the Hungarian Academy of Sciences, Technical University of Budapest, 1521 Budapest, Hungary.

Abstact. 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%).

Key words. Chiral lariat ether, monoaza-15-crown-5, enantioselective synthesis.

Introduction

Compounds derived from carbohydrates form a separate group of chiral crown ethers. Numerous macrocycles have been synthetized 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 of them proved to be effective phase-transfer catalyst in enantioselective reactions [2]. D-mannitol was found to be a structurally suitable precursor for optically active crown ethers [3]. We have previously reported the synthesis and investigation of monoaza-15-crown-5 type compounds containing methyl-α-D-glucopyranose- and galactopyranose moieties [4]. 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. It was found that these ligands exert asymmetric induction in certain reactions. This is valid especially for lariat ethers that have oxygen [5a-d] or phosphorus [5e] containing end-group at their side arm. 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

2. 1. 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 ^{o}C, and UV spectra were recorded with a Hitachi-Perkin Elmer 124 spectrophotometer. ^{1}H NMR spectra were recorded an BRUKER WM 250 instrument in $CDCl_3$ COSY techniques were used in some cases. The mass spectra were obtained on Jeol JMS-01 SG-2 instrument. Chemical ionization was applied as ionization technique. 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).

2. 2. 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 tetraethylammonium hydrogensulphate (2 equiv.) in 100 mL of bis(2-chloroethyl)ether as solvent and reagent was vigorously stirred at room temperature with a 100 mL of 50 % aq. NaOH solution for 8 h. The mixture was diluted with water (100 mL) and dichloromethane (100 mL), decanted and the aqueous phase was washed with dichloromethane (2 x 50 mL). The organic extracts were combined, washed with water (2 x 50 mL), dried and concentrated under vacuom. 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. [3a] yield 75 %); $[\alpha]_D^{20}$ = + 13.9 (c 16, CCl_4); (lit. $[\alpha]_D^{20}$ = + 14.9 [3a]). ^{1}H NMR ($CDCl_3$) δ [ppm] 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), washed with water (3 x 50 mL), dried (Na_2SO_4) and concentrated. Compound **5** was a yellow syrup, yield 10.6 g (90 %). $[\alpha]_D^{20}$ = + 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 %; $[\alpha]_D^{20}$ = + 13.5 (c=1, $CHCl_3$); ^1H 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); CI-MS, m/z 477 (M^++1, 98 %); Microanalysis: calcd. for $C_{24}H_{45}NO_8$, 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, $CHCl_3$); ^1H 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); CI-MS, m/z 502 (M^++1, 71 %); calcd. for $C_{26}H_{47}NO_8$ m. w. = 501.

N-Benzyl-monoaza-15-crown-5 derivative **6c.** Yield: 51 %; $[\alpha]_D^{20}$ = + 16.7 (c 1, $CHCl_3$); ^1H 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); calcd. for $C_{27}H_{43}NO_8$ m. w. = 509.

N-2-Phenylethyl-monoaza-15-crown-5 derivative **6d.** Yield: 54 %; $[\alpha]_D^{20}$ = + 12.0 (c 1, $CHCl_3$); ^1H 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); CI-MS, m/z 524 (M^++1, 44 %), 432 (49), 101 (100); calcd. for $C_{28}H_{45}NO_8$ m. w. = 523.

N-3-Hydroxypropyl-monoaza-15-crown-5 derivative **6e.** Yield: 48 %; $[\alpha]_D^{20}$ = + 15.9 (c=1, $CHCl_3$); ^1H 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); calcd. for $C_{23}H_{43}NO_9$ m. w. = 477.

N-4-Hydroxybutyl-monoaza-15-crown-5 derivative **6f.** Yield: 37 %; $[\alpha]_D^{20}$ = + 14.4 (c=1, $CHCl_3$); ^1H 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); CI-MS, m/z 492 (M^++1); calcd. for $C_{24}H_{45}NO_9$ m. w. = 491.

N-2-Methoxyethyl-monoaza-15-crown-5 derivative **6g.** Yield: 48 %; $[\alpha]_D^{20}$ = + 14.9 (c=1, $CHCl_3$); ^1H 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); calcd. for $C_{23}H_{43}NO_9$ m. w. = 477.

N-3-Methoxypropyl-monoaza-15-crown-5 derivative **6h.** Yield: 28 %; $[\alpha]_D^{20}$ = + 16.1 (c=1, $CHCl_3$); COSY ^1H 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_2*OCH_3), 3.42 (m, 2H, 3-CH and 4-CH), 3.61 (t, 4H, NCH_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); calcd. for $C_{24}H_{45}NO_9$ m. w. = 491.

N-Tosyl-monoaza-15-crown-5 derivative 7. A mixture of bischloro podand 3 (5.77 g, 12.12 mmol), toluene-p-sulfonamide (2.1 g, 12.24 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 ^oC (ethanol); $[\alpha]_D^{20}$ = + 17.7 (c=1, $CHCl_3$); ^1H 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, S 5.58 %; found C 56.60, H 7.47, N 2.49, S 5.53 %.

Unsubstitueted 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 x 70 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield (1.80 g, 87 %) as a colourless oil; $[\alpha]_D^{20}$ = + 16.4 (c=1, $CHCl_3$); ^1H 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.

General procedure for the Michael addition. The reaction was performed as follows: The chalcone (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 (20-24 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 ^oC; $[\alpha]_D^{20}$ = + 80.8 (c=1, CH_2Cl_2) for pure (+)-(*S*) enantiomer [9]. ^1H 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, 1H, 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*).

3. Results and Discussion

3.1 SYNTHESIS

The principle of the synthesis is shown in Figure 1. Hydroxyl groups at the 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 tetrabuthylammonium hydrogensulphate as a phase-transfer catalyst by Gross method [6], and the bischloro podand **4** was obtained in 75% yield for 14 hours, at 20 °C [3b]. The halogen exchange was performed by NaI in acetone, and bisiodo derivative **5** was obtained in 90% yield after 24 hours reflux. This compound was a suitable substrate for ring closing reaction by primary amines. The reaction was performed in acetonitrile in the presence of anhydrous Na_2CO_3. To avoid intermolecular byproduct formation the reaction was performed in a diluted solution (2%). The raw product obtained after 36 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 applied ring-closing amine. With buthylamine, cyclohexylamine, benzylamine and 2-phenylethylamine we have obtained compounds **6a**, **6b**, **6c**, and **6d**, respectively. We have also obtained lariat-ether type isophores, which contain electrondonating heteroatom (oxygen) at the end of their side arm. Thus, from **5** with 3-hydroxy-propylamine **6e**, with 4-hydroxy-butylamine **6f**, with 2-methoxy-ethylamine **6g** and with 3-methoxy-propylamine **6h** lariat-ethers were synthetised. The yields of the ring closure product, after purification by chromatography, vary from 28-54 %.

Unsubstituted compound **8** was obtained by a different route. 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 amalgame [7].

The structures of the ligands were confirmed via the analysis of their respective ^1H 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 product **6a-d** and **6e-f** the fragments at 432 and 101 m/z were of significant intensity that are due to the (sugar-based azacrown)-CH_2^+ and the $C_5H_9O_2$ fragments, respectively.

3.2 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 [7]. Concentrations of the picrates in water were determined by UV spectroscopy. 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**. Unsubstituted crown ether **8** has the largest extracting ability, with small ionselectivity (EA values are between 76-88%, 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. Sterical and electronical effects alike seem to have part in these phenomena. Among compounds **6a-d,** N-benzyl **6c** has the smallest, and N-buthyl substituted **6a** the largest extracting ability. Among lariat ethers **6e-h** the largest EA value belongs to 4-hydroxy substituted **6f,** having at the same time the best ionselectivity; e.g. it transports three times as much ammonium-picrate into the organic phase than lithium-picrate does. 3-Hydroxypropyl substituted **6e,** having one $-CH_2-$ group less, has somewhat better cation-binding ability. Presence of hydrophyl 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 free hydroxyl end-group is blocked, 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 atom in the chain shows the largest coordinating ability among N-substituted crown ethers. 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 structures. 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.

Taking into account earlier results [4, 5e] and ranking the stability of various complexes according to the type of carbohydrates the following order can be established: galactoside > glucoside > mannitol.

Crown ethers **1** and **2** derived from glucoside and galactoside respectively, help in building up the (+)-(*S*)-enantiomer in the Michael reaction [5d]. Compounds **6a-h** obtained from D-mannitol on the other hand, prefer the formation of the (-)-(*R*)-enantiomer. This is

pressumably connected to the relative configuration of the monosacharide in the crown ether, which is 2*R*,3*S* in glucose and galactose, and 2*S*,3*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^1=$CH_3OCH_2CH_2$) and galactoside **2** (R^2=$CH_3OCH_2CH_2$) were 87% ee and 52% ee, respectively [5d]. 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** (8% ee), while the best catalyst was lariat ether **6e** (R=$HO(CH_2)_3$) with 40% ee. The length of the side arm also playes a role in the asymmetric induction. This becomes obvious if one compares the N-benzyl substituted **6c** with N-2-phenylethyl **6d** (8% and 24% ee respectively), and the compound **6e** (R=3-hydroxypropyl, 40% ee) with **6f** (R=4-hydroxy-buthyl, 30% 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** we certainly consider worth to continue.

Acknowledgement

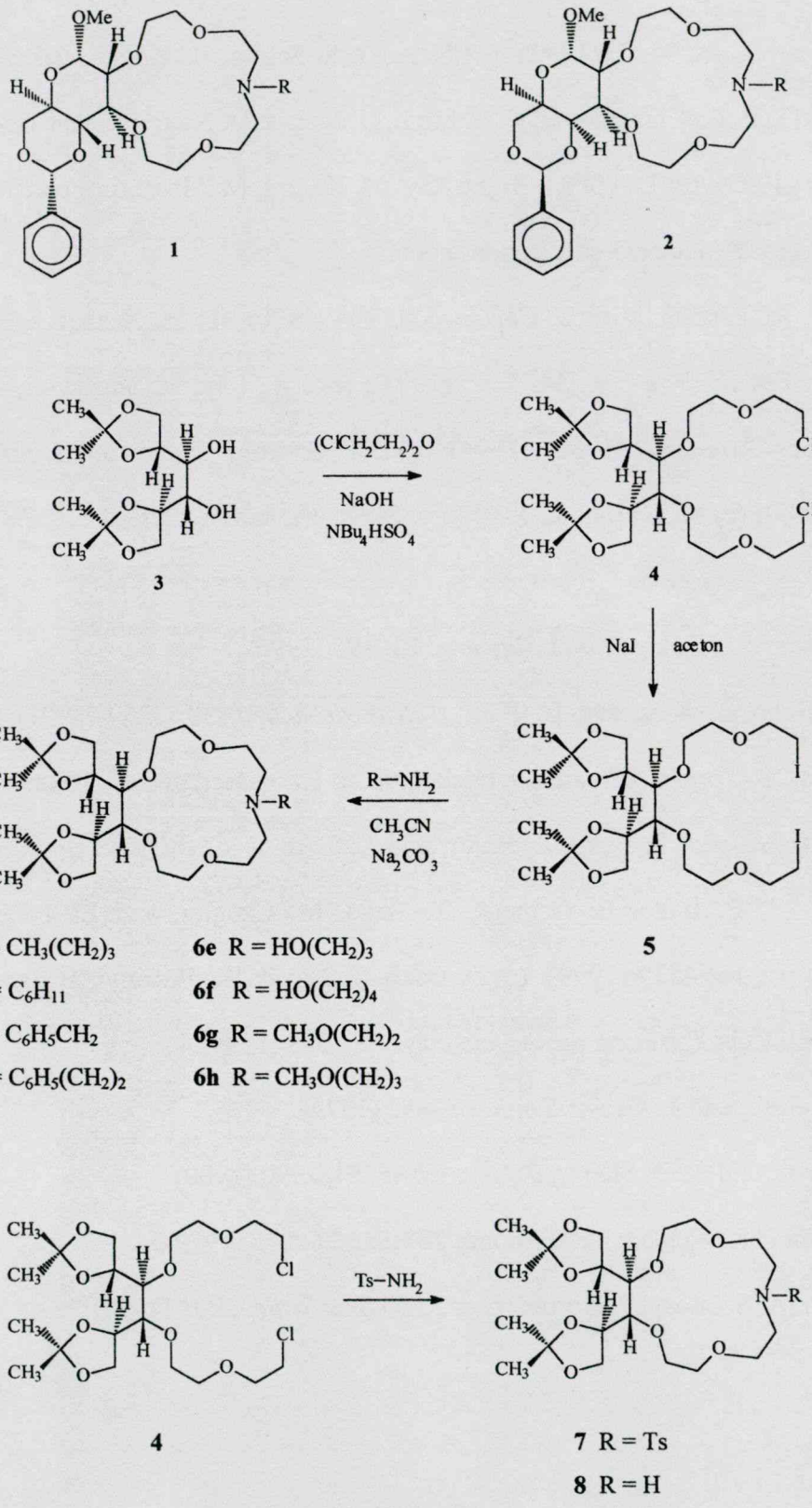
This work was supported by the and the National Science Foundation (OTKA T 029253 and T 026478) and Hungarian Academy of Sciences.

References

1. (a) J. F. Stoddart: *Chem. Soc. Rev.* **8**, 85 (1979); (b) J. F. Stoddart: *Top. Stereochem.* **17**, 207 (1987); (c) R. Miethen, and V. Fehring: *Liebigs Ann. Chem.* 553 (1997); (d) R. Meitchen 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, K. Koga: *Heterocycles*, **33**, 493, (1992); (d) P. P. Kanakamma, N. S. Mani, U. Maitra, V. Nair: *J. Chem. Soc., Perkin Trans 1.* 2339 (1995); (e) L. Tőke, P.Bakó, Gy. M. Keserű, M Albert, L. Fenichel: *Tetrahedron*, **54**, 213 (1998) and references cited therein.

3. (a) J.-P. Joly and N. Moll: *J. Chrom.* **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).
4. P. Bakó, and L. Tőke: *J. Incl. Phenom.* **23**, 195 (1995).
5. (a) P. Bakó, T. Kiss, and L. Tőke: *Tetrahedron Lett.* **38**, 7259 (1997); (b) P.Bakó, K. Vízvárdi, 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. P. Di Cesare, and B. Gross: *Synthesis*, 458 (1979).
7. F. Chavez, and A. D. Sherry: *J. Org. Chem.* **54**, 2990 (1989).
8. K. Kimura, T. Maeda, and T. Shono: *Talanta*, **26**, 945 (1979).
9. P. Bakó, Á. Szöllősy, P. Bombicz, and L. Tőke: *Synlett*, 291 (1997).



6a R = $CH_3(CH_2)_3$

6b R = C_6H_{11}

6c R = $C_6H_5CH_2$

6d R = $C_6H_5(CH_2)_2$

6e R = $HO(CH_2)_3$

6f R = $HO(CH_2)_4$

6g R = $CH_3O(CH_2)_2$

6h R = $CH_3O(CH_2)_3$

7 R = Ts

8 R = H

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

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	76	82	77	88	38	67
6a	$CH_3(CH_2)_3$	31	42	24	68	32	15
6b	C_6H_{11}	30	44	25	50	33	31
6c	$C_6H_5CH_2$	8	20	15	22	31	6
6d	$C_6H_5CH_2CH_2$	21	34	28	45	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.

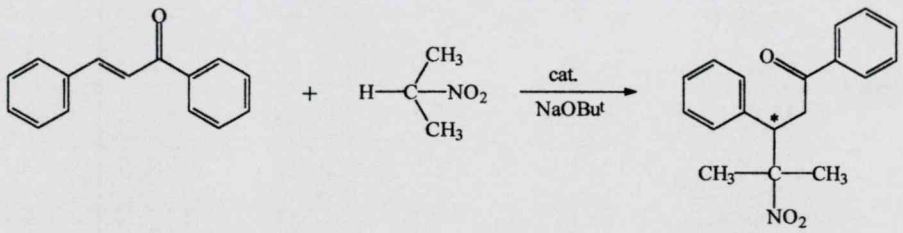


Figure 2. Michael addition 2-nitropropane to calcone