Monatsh Chem 139, 525–535 (2008)
DOI 10.1007/s00706-007-0799-7
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Synthesis of methyl-α-D-glucopyranoside-based azacrown ethers and their application in enantioselective reactions

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Received 25 June 2007; Accepted 4 September 2007; published online 11 April 2008

Abstract New chiral monoaza-15-crown-5 compounds anellated to methyl-4,6-*O*-(1-naphthyl)methylene-α-D-glucopyranoside (**2a**–**2b**), to methyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (**3a**–**3b**) and to methyl-α-D-glucopyranoside (**4a**–**4b**) have been synthesized. Several representatives of these crown ethers showed significant asymmetric induction as chiral phase transfer catalysts, among them **2a** proved to be the most efficient one inducing 90% *ee* in the *Michael* addition of 2-nitropropane to chalcone, 48% *ee* in the *Darzens* condensation of phenacyl-chloride with benzaldehyde and 89% *ee* in the epoxidation of chalcone with *tert*-butyl hydroperoxide. The catalytic results were compared with those obtained earlier with macrocycles **1a**–**1b** incorporating a 4,6-*O*-benzylidene protecting moiety. It occurred that the enantioselectivity is influenced to a great extent by the substituents on the C(4) and C(6) atoms of the monosaccharide. Lower enantioselectivities were obtained in the reactions of the chalcone analogues in the presence of catalyst **2a** than in the case of the proper chalcone.

Keywords Phase-transfer catalysis; Crown ether; Asymmetric catalysis; *Michael* addition.

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Introduction

The development of new methodologies for efficient asymmetric synthesis is of tremendous importance due to the increasing demand for optically active compounds [1]. One of the techniques of catalytic asymmetric synthesis currently attracting considerable interest is phase-transfer catalysis, in which the enantioselectivity is generated by a chiral crown ether [2]. Crown ethers with carbohydrate moieties form a special group of optically active macrocycles. Over the past three decades numerous macrocycles incorporating one or more monosaccharide units have been synthesized [3]. Unexpensive natural sugars are "green" and cheep starting materials in organic syntheses. Until now, only a limited number of asymmetric reactions have, however, been explored in which a sugar-based crown catalyst induced a good enantioselectivity [4]. Recently *Itoh et al*. published the synthesis of several α-D-glucose-based chiral macrocycles, the application of which in a *Michael* addition led to relatively high enantioselectivities [5].

The hexapyranoside-based 15-crown-5 lariat ethers described earlier by us possess special complexing ability due to their flexible side-arm containing a heteroatom at the end [6]. The overall complexing ability is influenced by the steric and electronic properties of the N-substituent. A few of the lariat ethers have been found to be efficient phase

transfer catalysts in certain types of asymmetric reactions [7]. Valuable information has been collected on the structure – enantioselectivity relationship. Regarding the carbohydrate moiety anellated to the azacrown ring, the glucopyranoside unit seemed to be more efficient than the galactopyranoside, mannopyranoside, altropyranoside and mannitol moieties [8]. Among the alkyl-, alkoxy-, aralkyl-, and other (*e.g.*, P-functionalized) N-substituents, the hydroxypropyl-, and in same cases, the methoxypropyl side arm was the most advantageous from the point of view of enantioselectivity. In these cases, the sugar moiety was protected by a 4,6-*O*-benzylidene group. The asymmetric induction brought about by macrocycles incorporating a methyl-4,6-*O*-benzylidene-α-D-glucopyranoside unit (**1a** and **1b**) has been thoroughly studied utilizing suitable model reactions [7, 8]. 4,6-Di-*O*-butylether derivatives have also been investigated as chiral catalysts [9].

The question emerged, how the change or elimination of the benzylidene group in macrocycles **1** may influence the catalytic properties, especially the enantioselectivity. In this paper, a number of new lariat ethers are introduced, where the 4- and 6-hydroxy groups of the α-methyl-glucopyranoside unit are free or protected in the form of acetals. The resulting species are (1-naphthyl)methylene- or isopropylidene derivatives.

Results and discussion

Synthesis

One of the starting materials, methyl-4,6-*O*-(1-naphthyl)methylene-α-D-glucopyranoside (**6**) was prepared by the reaction of methyl-α-D-glucopyranoside and 1-naphthaldehyde dimethyl acetal (**5**) in *DMF*, in the presence of camphorsulfonic acid as the catalyst. The crystalline dioxane-type acetal (**6**) was obtained in 58% yield. The equatorial position of the naphthyl-substituent was substantiated on the basis of the ^{1}H NMR spectrum and an analogy; the 2-naphthylmethylene acetal analogue is a known compound [10]. The starting 1-(dimethoxymethyl)naphthalene (**5**) was obtained in the reaction of 1-naphthaldehyde with trimethyl orthoformate in dry methanol in the presence of anhydrous zinc chloride catalyst.

The other starting sugar derivative, methyl-4,6-*O*-isopropylidene-α-D-glucoside (**9**) was synthesized by the reaction of methyl-α-D-glucopyranoside and 2,2-dimethoxypropane in acetone, using catalytic amounts of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (*DDQ*) in 70% yield [11]. Establishment of the crown ring in the 2 and 3 position of the glucopyranoside acetals (**6** and **9**) was accomplished in three steps, as described earlier [6, 12]. The vicinal hydroxy groups of **6** and **9** were alkylated with bis(2-chloroethyl) ether in the presence of tetrabutylammonium hydrogen sulfate and 50% aq. NaOH in a liquid–liquid two-phase system to give intermediate **7** and **10** which were purified by chromatography. The exchange of chlorine to iodine in intermediates **7** and **10** was accomplished in reaction with NaI in boiling acetone to afford bis-iodo derivative **8** and **11**, respectively. Compounds **8** and **11** were then cyclized with two kinds of primary amines, such as 3-aminopropanol and 3-methoxypropylamine, in boiling acetonitrile, in the presence of sodium carbonate to afford after purification by column chromatography azacrown ethers **2a**–**2b** and **3a**–**3b**, respectively. The yield of cyclizations reactions was 40–47% (Scheme 1).

The benzylidene protecting group in compounds **1a**–**1b** was removed by catalytic hydrogenation to give lariat ethers **4a**–**4b** with free hydroxy groups in positions 4 and 6.

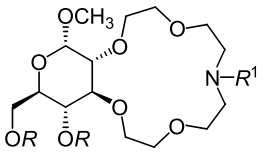
All intermediates and new products were characterized by ^{1}H, ^{13}C NMR and mass spectroscopy.

Asymmetric induction

Chiral crown ethers **2a**–**2b** and **3a**–**3b** were tested in a *Michael* addition, a *Darzens* condensation and an epoxidation reaction. In all cases, the products were isolated by preparative *TLC* after the usual work-up procedure. The enantiomeric excess (*ee*/%) was determined by measuring the optical rotation of the products or by ^{1}H NMR spectroscopy using (+)-Eu(*hfc*)$_3$ as a chiral shift reagent.

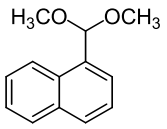
Michael addition of 2-nitropropane to chalcone

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 [13]. Perhaps, the most frequently studied model reaction is the *Michael* addition of methyl phenyl acetate to methyl acrylate carried out in the presence of a sugar-based crown ether, with which enantioselectivities of 53–70% were detected [14].



1

1a $R-R$ = CH–*Ph*, R^1 = $(CH_2)_3OH$ [4]
1b $R-R$ = CH–*Ph*, R^1 = $(CH_2)_3OCH_3$ [4]
2a $R-R$ = CH-(1)-*Naph*, R^1 = $(CH_2)_3OH$
2b $R-R$ = CH-(1)-*Naph*, R^1 = $(CH_2)_3OCH_3$
3a $R-R$ = $C(CH_3)_2$, R^1 = $(CH_2)_3OH$
3b $R-R$ = $C(CH_3)_2$, R^1 = $(CH_2)_3OCH_3$
4a R = H, R^1 = $(CH_2)_3OH$
4b R = H, R^1 = $(CH_2)_3OCH_3$



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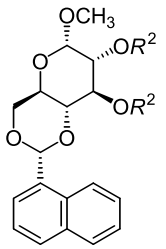
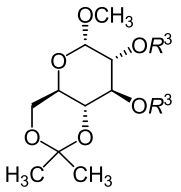




6 R^2 = H
7 R^2 = $(CH_2)_2O(CH_2)_2Cl$
8 R^2 = $(CH_2)_2O(CH_2)_2$**I**

9 R^3 = H
10 R^3 = $(CH_2)_2O(CH_2)_2Cl$
11 R^3 = $(CH_2)_2O(CH_2)_2$**I**

8 + R^1NH_2 —iii→ **2a-2b**

11 + R^1NH_2 —iii→ **3a-3b**

1a-1b —iv→ **4a-4b**

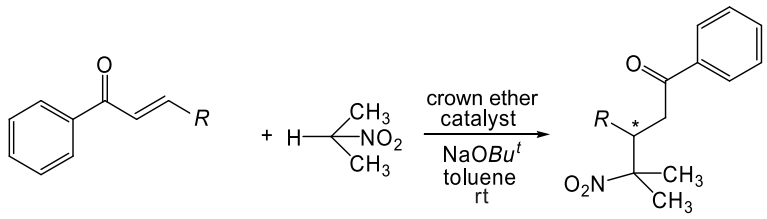
Reagent and condition: (i) $O(CH_2CH_2Cl)_2$, 50% aq. NaOH, NBu_4HSO_4, rt; (ii) NaI, acetone, reflux; (iii) Na_2CO_3, CH_3CN, reflux; and (iv) *Me*OH/CH_2CI_2, H_2, Pd/C

Scheme 1

Asymmetric induction due to glucose-based azacrown ethers (**1**) in the *Michael* addition of 2-nitropropane to chalcone was observed earlier [7, 9]. In the present study, the effect of glucose-based macrocycles **2a**–**2b**, **3a**–**3b**, and **4a**–**4b** was studied in the same model reaction. The solid-liquid phase transfer catalytic reaction was carried out at room temperature in dry toluene, in the presence of solid sodium *tert*-butylate (35 mol%) and one of the chiral catalysts prepared (7 mol%) (Scheme 2).

The experimental data are shown in Table 1.

It can be seen that the substituent in positions 4 and 6 of the catalyst and the side arm on the nitrogen atom of the ring have a significant influence on the asymmetric induction. While the use of 4,6-*O*-benzylidene derivatives as catalysts lead to *ee* values of 85 and 87% for the lariat ethers with hydroxypropyl and methoxypropyl side arms (**1a** and **1b**, respectively), the application of 1-naphthylmethylene derivatives **2a** and **2b** resulted in *ee* values of 90 and 68% (entries 3 and 4). It can be seen that the *N*-hydroxypropyl substituent was more favorable. Regarding the isopropylidene derivatives, the *ee* of



12a *R* = *Ph*
12b *R* = 1-naphthyl
12c *R* = 2-naphthyl
12d *R* = 2-pyridyl
12e *R* = *Me*

13a *R* = *Ph*
13b *R* = 1-naphthyl
13c *R* = 2-naphthyl
13d *R* = 2-pyridyl
13e *R* = *Me*

Scheme 2

Table 1 Enantioselectivities induced by chiral crown ether catalysts **1**–**4** in three reactions of the chalcone (**12a**)[a]

Entry	Cat.	*Michael* adduct (**13a**)		*Darzens* condensation (**15a**)		Epoxidation (**15a**)	
		Yield/%[b]	*ee*/% (*R*)	Yield/%[b]	*ee*/% (2*R*,3*S*)	Yield/%[b]	*ee*/%
1	**1a**	53	85[c]	74	62[c]	50	92 (2*R*,3*S*)[d]
2	**1b**	48	87[c]	62	21[c]	61	23 (2*R*,3*S*)[d]
3	**2a**	49	90	75	48	46	89 (2*R*,3*S*)
4	**2b**	16	68	54	14	43	38 (2*S*,3*R*)
5	**3a**	34	80	61	42	59	67 (2*R*,3*S*)
6	**3b**	17	55	52	18	39	19 (2*S*,3*R*)
7	**4a**	35	24	76	31	21	18 (2*R*,3*S*)
8	**4b**	30	16	61	14	26	9 (2*S*,3*R*)

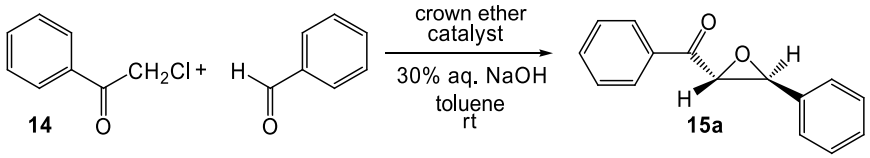
[a] The *ee*/% was determined by ^{1}H NMR spectroscopy, the absolute configurations were determined by comparing the measured optical rotations with the literature data
[b] Based on isolation by preparative *TLC*
[c] Ref. [4]
[d] Ref. [8b]

80% obtained with the *N*-hydroxypropyl lariat ether (**3a**) decreased to 55% on the ''methylation'' of the hydroxy group (**3b**) (entries 5 and 6). Elimination of the protecting groups led to modest enantioselectivities; the use of free bis-hydroxy derivatives **4a** and **4b** as the catalyst resulted in *ee* values of 24 and 16%, respectively (entries 7 and 8). This can be explained by the notion that without an acetal function the sugar unit has become more flexible and the lipophility was decreased. Presence of the acetal moiety also has a steric impact.

Darzens condensation

The glucose-based crown ethers (**1**–**4**) induced a moderate asymmetric induction in the condensation of phenacyl chloride (**14**) with benzaldehyde, which is a well studied model reaction (Scheme 3). The best results were obtained using *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (42% *ee*) [15], or a crown ether incorporating a glucopyranoside unit (62% *ee*) as a phase transfer catalyst [4].

We performed the above reaction in a liquid–liquid (LL) two-phase system. The reagents and the



Scheme 3

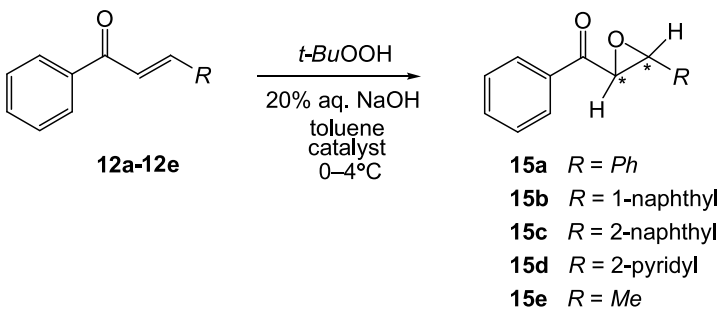
catalyst **1**–**4** (7 mol%) were dissolved in toluene and the reaction was initiated by adding 30% sodium hydroxide. After stirring for 1–4 h at room temperature, the *trans*-epoxyketone **15a** was formed in each case in a selective way (*de* > 98%). The predominant enantiomer was the one with negative optical rotation that corresponds to an absolute configuration of (2*R*,3*S*) [16]. Earlier, the best optical yield was achieved in the presence of catalyst **1a** giving the product (**15a**) after 2 h of stirring in an enantioselectivity of 62% (Table 1, entry 1) [4].

Nearly the same extent of asymmetric induction was detected with the hydroxypropyl naphthylmethylene and isopropylidene catalysts (**2a** and **3a**, respectively). In the former case, the *ee* was 48%, while in the latter case it was 42% (entries 3 and 5, respectively). In this series, the lowest value (an *ee* of 31%) was obtained with the unprotected catalyst **4a** (entry 7). In all cases investigated, ''methylation'' of the hydroxypropyl side arm led to lower optical yield; *ee* values of 21, 14, 18, and 14 were measured for catalysts **1b**, **2b**, **3b**, and **4b**, as shown by entries 2, 4, 6, and 8. In these instances, the yields were also significantly lower. A possible explanation is that the increase in the lipophylity is disadvantageous in the toluene-water two-phase system. At the same time, steric and electronic effects are also responsible for the above trends. The quality of the end-group of the bending side arm effects the complexation with the Na^+ cation that is accompanied by the corresponding $(PhC(O)CHCl)^-$ anion and hence influences the outcome of the *Darzens* condensation.

Asymmetric epoxidation of chalcone

Significant enantioselectivities were generated by the glucose-based crown ethers (**1**–**4**) in the epoxidation of the chalcone under phase transfer catalytic conditions (Scheme 4). The enantioselective epoxidation of α,β-unsaturated ketones employing chiral catalysts has received considerable attention in recent years [17]. A variety of methods have been developed including the use of polyphasic systems involving hydrogen peroxide in the presence of polyamino acids [18], alkyl peroxides in conjunction with lanthanoid-binaphthol complexes [19], tartrate-modified metal *tert*-butyl peroxides [20], and hydrogen peroxide in the presence of chiral platinium(II) complexes [21]. Good enantioselectivities were also reported using non-catalytic systems, like molecular oxygen in the presence of diethylzinc/chiral amino alcohols [22]. The use of chiral quaternary ammonium salts as phase-transfer catalyst in the transformation under discussion was also investigated [23].

In our experiments, the epoxidation of chalcone (**12a**) was carried out in a liquid–liquid two-phase system applying *tert*-butyl hydroperoxide (*TBHP*, 2 equiv.) in toluene, employing 20% aq. NaOH (3.5 equiv.) as the base and 7 mol% of glucopyranoside-based lariat ether **1**–**4** at a temperature of 0–4°C (Scheme 4). Table 1 summarizes the results obtained in the epoxidation of chalcone in the presence of chiral crown catalysts **1**–**4**. It can be seen that the yields and the enantioselectivities are significantly affected by the substituents of the carbohydrate moiety. In all experiments the *trans*-epoxyketone (**15**) was obtained and in most cases the (2*R*,3*S*) isomer of the epoxyketone was formed (with negative optical rotation). Presence of the catalysts having OCH_3 end-group **2b**, **3b**, and **4b** generated formation of the (2*S*,3*R*) isomer in excess (with positive optical rotation). The best *ee* values (92 and 89%) were detected in the presence of lariat ethers **1a** and **2a** containing an aryl group as protecting moiety in the sugar part. For the isopropylidene derivative **3a** only an *ee* of 67%, while for the unprotected lariat ether **4a** a low



Scheme 4

Table 2 Asymmetric *Michael* addition and epoxidation of chalcone analogues (**12b–12e**) mediated by chiral azacrown ether **2a**

Michael addition				Epoxidation			
Adduct	Yield/%[a]	$[\alpha]_D$/°g^{-1} cm^3 dm^{-1} [b]	*ee*/%[c]	Product	Yield/%[a]	$[\alpha]_D$/°g^{-1} cm^3 dm^{-1} [b]	*ee*/%[c]
13b	47	+92.1	35	**15b**	51	+63.0	56
13c	12	+68.8	43	**15c**	15	−153.2	64
13d	81	+118.2	79	**15d**	58	−113.7	45
13e	65	−23.5	64	**15e**	42	−3.2	51

[a] Based on isolation by preparative *TLC*
[b] In CH_2Cl_2 at 20°C
[c] Determined by ^{1}H NMR spectroscopy

ee of 18% was measured. All these were obtained for the *N*-hydroxypropyl derivatives **1a**, **2a**, and **3a**. Application of the catalysts with methoxy end-group (**1b**, **2b**, **3b**, and **4b**) led to decreased *ee* values (23, 38, 19, and 9%). The same trend was experienced in the *Darzens* condensations, but the decrease in *ee* due to the OH to OCH_3 change was more significant in the epoxidations.

Asymmetric Michael reaction and epoxidation of chalcone analogues

The *Michael* addition and epoxidation of a few chalcone analogues (**12b–12e**) were investigated in the presence of the best azacrown catalyst **2a**. The experimental results are listed in Table 2. It can be seen that the change of the phenyl ring (in the chalcone) to 1-naphthyl, 2-naphthyl, and methyl groups resulted in a decreased asymmetric induction in the *Michael* reaction during the formation of adducts **13b–13c** and **13e**. The *ee* values were 35 (**13b**), 43 (**13c**), and 64 (**13e**). The highest enantioselectivity was obtained in the case of the pyridyl-chalcone **13d** (79%). As the naphthyl groups are sterically demanding, the decrease in the enantioselectivity may be the consequence of steric effects. It is interesting that the product **13c** with 2-naphthyl substituent was formed with a somewhat higher enantioselectivity (43%) than the **13b** 1-naphthyl derivative (35%). It is noteworthy that while the *Michael* adducts **13b–13d** with aromatic substituents displayed positive specific rotations (suggesting the excess of the same enantiomer configuration in them), the methyl substituted **13e** was formed with negative specific rotation. The impact of the methyl group in **13e** on the specific rotation will be clarified at a later stage.

Table 2 summarizes the results obtained in the epoxidation of chalcone analogues in the presence of macrocycle **2a**. The corresponding *trans*-epoxy ketones **15b–15e** were obtained in all cases. The 1-naphthyl **15b**, 2-naphthyl **15c**, 2-pyridyl **15d**, and methyl- derivative **15e** were formed with 56, 64, 45, and 51% enantiomeric excesses. It is worth noting that a higher enantioselectivity was detected in the case of 2-naphthyl compound **15c** (64%) than with 1-napthtyl **15b** derivative (56%). The compounds **15c–15e** were formed with enantiomeric excesses with negative specific rotations, while the **15b** had a positive one.

Conclusions

Methyl-α-D-glucose based 15-crown-5 type lariat ethers were protected on C(4)-OH and C(6)-OH *via* acetal formation using different reagents. The 4,6-*O*-benzylidene (**1**), 4,6-*O*-(1)-naphthylidene (**2**), 4,6-*O*-isopropylidene (**3**) acetals, as well as unprotected lariat ether **4** were tested as chiral phase transfer catalyst in a *Michael* addition, a *Darzens* condensation and an epoxidation of the chalcone. The effect of the structural changes on the asymmetric induction was evaluated. The lariat ethers studied differ in polarity and lipophilicity (that is an important point of view in the case of phase transfer catalysts), but the decisive factor is the steric and electronic effect of the substituents on the asymmetric induction. In all the three reactions, the best asymmetric induction was achieved by the lariat ethers with 4,6-*O*-*Ar* moieties containing a hydroxypropyl substituent on the nitrogen atom. It is noteworthy that there was no significant difference between the effect of the benzylidene- and the naphthylidene derivatives (**1a** and **2a**, respectively) in the *Michael* addition and in the epoxidation of

chalcone. In the *Michael* addition, enantioselectivities of 85 (**1a**) and 90% (**2a**), while in the epoxidation, *ee* values of 92 (**1a**) and 89% (**2a**) were detected. In the *Darzens* condensation, the presence of the sterically demanding naphthyl group caused a significant decrease in the *ee* value: 62 (**1a**) *vs.* 48% (**2a**).

The use of catalysts with the smaller isopropylidene protecting group led to more modest results. Applying **3a**, *ee* values of 80, 42, and 67% were measured in the *Michael* addition, *Darzens* condensation and epoxidation, respectively. The lowest enantioselectivities was experienced in the case of macrocycles without any protecting groups (**4a**–**4b**). This may be caused on one hand by the lack of a sterically demanding protecting group while, on the other hand, by the more flexible hetero ring. Flexible ligands can match both guest enantiomers by adjusting its conformation, and therefore, provide little or no enantiomer recognition.

It is noteworthy that the use of lariat ethers with methoxypropyl N-substituent (**2b**, **3b**, and **4b**) in epoxidation reactions resulted in an enantiomeric excess, where the (2*S*,3*R*) antipode was predominant. The application of the hydroxypropyl-macrocycles (**1a**, **2a**, **3a**, and **4a**) induced the preferred formation of the (2*R*,3*S*) enantiomer.

Lower enantioselectivities were obtained in the reactions of the chalcone analogues in the presence of catalyst **2a** than in the case of the proper chalcone.

Experimental

Melting points were taken on using a Büchi 510 apparatus (compounds crystallized from ethanol). The specific rotation was measured with the help of a Perkin-Elmer 241 polarimeter at 22°C. NMR spectra were obtained on a Bruker 300 and a Bruker DRX-500 instrument in $CDC1_3$ with TMS as the internal standard. Mass spectra were registrated from m-nitrobenzyl alcohol (*NOBA*) matrix on a Varian MAT312 instrument. Analytical and preparative thin layer chromatography was performed on silica gel plates (60 GF-254, Merck), while column chromatography was carried out using 70–230 mesh silica gel (Merck). Chemicals and the shift reagent Eu(*hfc*)$_3$ were purchased from Aldrich Chem. Co.

1-Naphtaldehyde dimethyl acetal (**5**, $C_{13}H_{14}O_2$)

A mixture of 57.3 g 1-naphthaldehyde (366 mmol), 63.8 g freshly distilled trimethyl orthoformate (602 mmol), 153 cm^3 dry methanol and 0.37 g zinc chloride (3 mmol) was refluxed for 6 h under dry conditions. Part of the solvent (about 70 cm^3) was removed *in vacuo* and an additional portion 18.4 g of trimethyl orthoformate (173 mmol) was added. The reaction mixture was heated at reflux for overnight and was monitored by *TLC*. The excess of trimethyl orthoformate and the solvent was removed under reduced pressure, the residue was treated with 200 cm^3 5% aqueous $NaHCO_3$ and extracted with diethyl ether (3×100 cm^3). The combined ether extract was washed with water (100 cm^3), dried ($MgSO_4$) and concentrated to give intermediate **5** as brown syrup. Yield 70.4 g (95%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.27$ (d, $J = 8.2$ Hz, 1H, *Ar*H), 7.81 (d, $J = 7.5$ Hz, 1H, *Ar*H), 7.79 (d, $J = 8.2$ Hz, 1H, *Ar*H), 7.71 (d, $J = 7$ Hz, 1H, *Ar*H), 7.40–7.52 (m, 3H, *Ar*H), 5.89 (s, 1H, CH), 3.34 (s, 6H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 133.94$, 133.18, 130.92, 129.34, 128.61, 126.28, 125.75, 125.08, 124.90, 124.33 (*Ar*C), 102.40 (CH), 53.15 ($2OCH_3$) ppm; FAB-MS: $m/z = 202$ $[M]^+$; HRMS: m/z calcd for $C_{13}H_{14}O_2$ $[M]^+$ 202.0994, found 202.0997.

Methyl 4,6-O-(1-naphthyl)methylene-α-D-glucopyranoside (**6**, $C_{18}H_{20}O_6$)

To a solution of 20.0 g methyl-α-D-glucopyranoside (103 mmol), 26.0 g of 1-naphthaldehyde dimethyl acetal (128 mmol) in 150 cm^3 of dry *DMF* 4.5 g of 10-camphorsulfonic acid (19.4 mmol) was added in parts so the *pH* of mixture be 2–3. The reaction mixture was stirred at room temperature for 12 h, and then the methanol formed was removed by evaporating *in vacuo*. An additional 10.8 g 1-naphthaldehyde dimethyl acetal (53 mmol) was added. After 12 h reflux the mixture was concentrated *in vacuo*. The residue was taken up in dichloromethane (500 cm^3) and neutralized with solution of $NaHCO_3$ (so the *pH* of the mixture be 8), washed with water (3×200 cm^3). The organic phase was dried (Na_2SO_4). The crude product obtained in evaporation was purified by crystallization (from *Et*OH:hexane, 6:1). Yield 20.5 g (60%); $[\alpha]_D^{20} = +122.4^\circ\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 0.5$, $CHCl_3$); mp 221–223°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.19$ (d, $J = 8.5$ Hz, 1H, *Ar*H), 7.86 (d, $J = 8.2$ Hz, 2H, *Ar*H), 7.75 (d, $J = 7.1$ Hz, 1H, *Ar*H), 7.54 (t, $J = 7.3$ Hz, 1H, *Ar*H), 7.45–7.50 (m, 2H, *Ar*H), 6.09 (s, 1H, napht-CH), 4.84 (d, $J = 3.9$ Hz, 1H, H-1), 4.40 (dd, $J = 4.5$, 9.9 Hz, 1H, H-6), 3.98 (t, $J = 9.3$ Hz, 1H, H-4), 3.93 (dd, $J = 4.3$, 9.3 Hz, 1H, H-6) 3.88 (t, $J = 10.3$ Hz, 1H, H-3), 3.67–3.71 (m, 1H, H-5), 3.64 (t, $J = 9.3$ Hz, 1H, H-2), 3.50 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 133.86$, 132.18, 130.41, 129.93, 128.63, 126.38, 125.72, 124.98, 124.64, 124.03 (*Ar*C), 101.29 (napht-CH), 99.83 (C-1), 81.37 (C-4), 72.90 (C-2), 71.86 (C-3), 69.27 (C-6), 62.43 (C-5), 55.69 (OCH_3) ppm; FAB-MS: $m/z = 333$ $[M + 1]^+$, 355 $[M + Na]^+$; HRMS: m/z calcd for $C_{18}H_{20}O_6$ $[M]^+$ 332.1260, found 332.1253.

*General method for the preparation of compounds **7**, **10***

A solution of **6** or **9** (43.8 mmol) and 12.5 g tetrabutylammonium hydrogensulfate (36.9 mmol) in 93 cm^3 bis(2-chloroethyl)ether (650.3 mmol) was vigorously stirred with 93 cm^3 50% NaOH solution at room temperature for 18 h. To the reaction mixture were added 160 cm^3 CH_2Cl_2 and 160 cm^3 water. The organic layer was decanted and the aqueous phase was washed with CH_2Cl_2 (3×60 cm^3). The combined organic phases were washed with water and dried ($MgSO_4$).

After removal of the solvent and the excess of the bis(2-chloroethyl)ether, the product was purified by column chromatography (silica gel, CH_2Cl_2–*Me*OH (100:1 → 100:7) as the eluant), to give products **7** and **10**.

Methyl 4,6-O-(1-naphthyl)methylene-2,3-bis[(2-chloroethoxy)ethyl]-α-D-glucopyranoside (**7**, $C_{26}H_{34}Cl_2O_8$)
Yield 12.6 g (53%); $[\alpha]_D^{20} = +73.7°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); mp 132°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.16$ (d, $J = 8.3$ Hz, 1H, *Ar*H), 7.86 (d, $J = 8.1$ Hz, 2H, *Ar*H), 7.77 (d, $J = 7.1$ Hz, 1H, *Ar*H), 7.52 (t, $J = 7.2$ Hz, 1H, *Ar*H), 7.45–7.50 (m, 2H, *Ar*H), 6.07 (s, 1H, napht-CH), 4.90 (d, $J = 3.6$ Hz, 1H, H-1), 4.38 (dd, $J = 4.5$, 9.9 Hz, 1H, H-6), 3.95–3.98 (m, 1H, H-5), 3.92 (dd, $J = 4.4$, 9.5 Hz, 1H, H-6) 3.84–3.88 (m, 4H, 4 podand arm-H), 3.82 (t, $J = 9.2$ Hz, 1H, H-3), 3.77 (t, 2H, $J = 5.8$ Hz, 2 podand arm-H), 3.67–3.73 (m, 3H, H-4, 2 podand arm-H), 3.64 (t, $J = 5.9$ Hz, 2H, 2 podand arm-H), 3.52–3.59 (m, 5H, H-2, CH_2Cl, 2 podand arm-H), 3.48 (s, 3H, OCH_3), 3.39 (t, $J = 5.9$ Hz, 2H, CH_2Cl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 133.73$, 132.51, 130.47, 129.70, 128.56, 126.15, 125.66, 124.99, 124.16, 123.99 (*Ar*C), 100.56 (napht-CH), 99.22 (C-1), 82.26 (C-4), 80.69 (C-2), 79.12 (C-3), 72.19, 71.54, 71.32, 71.05, 70.93, 70.63 ($6OCH_2$ of the podand arm), 69.40 (C-6), 62.37 (C-5), 55.41 (OCH_3), 42.88, 42.64 ($2CH_2Cl$) ppm; FAB-MS: $m/z = 545$ $[M + 1]^+$, 547 $[M + 1]^+$, 567 $[M + Na]^+$ 569 $[M + Na]^+$; HRMS: m/z calcd for $C_{26}H_{34}Cl_2O_8$ $[M]^+$ 544.1631, found 544.1622.

Methyl 4,6-O-isopropylidene-2,3-bis[(2-chloroethoxy)ethyl]-α-D-glucopyranoside (**10**, $C_{18}H_{32}Cl_2O_8$)
Yield 11.6 (59%); $[\alpha]_D^{20} = +59.4°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.75$ (d, $J = 3.6$ Hz, 1H, H-1), 4.01 (dd, $J = 4.7$, 10.3 Hz, 1H, H-6), 3.82–3.87 (m, 2H, 2 podand arm-H), 3.74–3.80 (m, 3H, H-3, 2 podand arm-H), 3.68 (t, $J = 6.2$ Hz, 4H, 4 podand arm-H), 3.47–3.64 (m, 11H, H-4, H-5, H-6, $2CH_2Cl$, 4 podand arm-H), 3.38 (dd, $J = 3.3$, 8.9 Hz, 1H, H-2), 3.34 (s, 3H, OCH_3), 1.42 (s, 3H, CH_3), 1.34 (s, 3H, CH_3) ppm; FAB-MS: $m/z = 447$, 449 $[M + 1]^+$, 469, 471 $[M + Na]^+$; HRMS: m/z calcd for $C_{18}H_{32}Cl_2O_8$ $[M]^+$ 446.1474, found 446.1479.

*General method for the preparation of compounds **8**, **11***
A mixture of bis-chloro derivative **7** or **10** (36.4 mmol) and NaI (21.8 g, 145.3 mmol) in dry acetone (360 cm^3) was stirred under reflux for 22 h. After cooling, the precipitate was filtered and washed with acetone. The combined acetone solutions were evaporated in vacuum. The residue was dissolved in CH_2Cl_2 (200 cm^3), washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded the products **8** and **11** as yellow oils, which were used without further purification.

Methyl 4,6-O-(1-naphthyl)methylene-2,3-bis[(2-iodoethoxy)-ethyl]-α-D-glucopyranoside (**8**, $C_{26}H_{34}I_2O_8$)
Yield 24.9 (94%); $[\alpha]_D^{20} = +50.0°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); mp 81–82°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.16$ (d, $J = 8.3$ Hz, 1H, *Ar*H), 7.85 (d, $J = 7.9$ Hz, 2H, *Ar*H), 7.77 (d, $J = 7.0$ Hz, 1H, napht-H), 7.45–7.54 (m, 3H, *Ar*H), 6.07 (s, 1H, napht-CH), 4.91 (d, $J = 3.7$ Hz, 1H, H-1), 4.37 (dd, $J = 4.5$, 9.9 Hz, 1H, H-6), 3.95–3.98 (m, 1H, H-5), 3.92 (d, $J = 4.4$, 9.5 Hz, 1H, H-6), 3.84–3.88 (m, 4H, 4 podand arm-H), 3.82 (t, $J = 9.2$ Hz, 1H, H-3), 3.77 (t, $J = 6.8$ Hz, 2H, 2 podand arm-H), 3.64–3.72 (m, 3H, H-4, 2 podand arm-H), 3.50–3.58 (m, 5H, H-2, 4 podand arm-H), 3.48 (s, 3H, OCH_3), 3.27 (t, $J = 6.8$ Hz, 2H, CH_2I), 3.03 (t, $J = 6.9$ Hz, 2H, CH_2I) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 133.72$, 132.50, 130.46, 129.70, 128.57, 126.14, 125.64, 124.99, 124.14, 123.96 (*Ar*C), 100.51 (napht-CH), 99.22 (C-1), 82.22 (C-4), 80.59 (C-2), 79.14 (C-3), 72.22, 71.86, 71.60, 71.53, 70.63, 70.23 ($6OCH_2$ of the podand arm), 69.37 (C-6), 62.36 (C-5), 55.41 (OCH_3), 3.02, 2.95 ($2CH_2I$) ppm; FAB-MS: $m/z = 729$ $[M + 1]^+$, 751 $[M + Na]^+$; HRMS: m/z calcd for $C_{26}H_{34}I_2O_8$ $[M]^+$ 728.0343, found 728.0356.

Methyl 4,6-O-isopropylidene-2,3-bis[(2-iodoethoxy)ethyl]-α-D-glucopyranoside (**11**, $C_{18}H_{32}I_2O_8$)
Yield 21.1 (92%); $[\alpha]_D^{20} = +75.0°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.81$ (d, $J = 3.6$ Hz, 1H, H-1), 4.07 (dd, $J = 4.8$, 10.1 Hz, 1H, H-6), 3.88–3.93 (m, 2H, 2 podand arm-H), 3.79–3.85 (m, 3H, H-3, 2 podand arm-H), 3.74 (t, $J = 7.2$ Hz, 4H, 4 podand arm-H), 3.55–3.70 (m, 7H, H-4, H-5, H-6, 4 podand arm-H), 3.43 (dd, $J = 3.5$, 9.0 Hz, 1H, H-2), 3.40 (s, 3H, OCH_3), 3.22–3.28 (m, 4H, $2CH_2I$), 1.48 (s, 3H, CH_3), 1.40 (s, 3H, CH_3) ppm; FAB-MS: $m/z = 631$ $[M + 1]^+$, 653 $[M + Na]^+$; HRMS: m/z calcd for $C_{18}H_{32}I_2O_8$ $[M]^+$ 630.0187, found 630.0181.

*General method for the preparation of crown ethers **2**, **3***
A mixture of 3.84 g anhydrous Na_2CO_3 (36.2 mmol), the corresponding primary amine (4.60 mmol) and bis-iodo **8** or **11** (4.60 mmol) in 100 cm^3 dry acetonitrile was stirred and refluxed for 24–48 h, under argon. After cooling, the precipitate was filtered and washed with acetonitrile. The combined organic solutions were concentrated *in vacuo*. The residual oil was dissolved in $CHCl_3$, washed with water and dried (Na_2SO_4), and the solvent was evaporated. The crude monoaza-crown ether (**2** or **3**) was purified by column chromatography on silica gel using $CHCl_3$: *Me*OH (100:2 → 100:7) as the eluant.

Methyl 4,6-O-(1-naphthyl)methylene-2,3-dideoxy-α-D-glucopyranosido(2,3-h)-N-hydroxypropyl-1,4,7,10-tetraoxa-l3-azacyclopentadecane (**2a**, $C_{29}H_{41}NO_9$)
Yield 1.2 g (47%); $[\alpha]_D^{20} = +77.4°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 0.5$, $CHCl_3$); mp 98–100°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 8.13 (d, $J = 8.1$ Hz, 1H, *Ar*H), 7.85 (d, $J = 7.8$ Hz, 2H, *Ar*H), 7.77 (d, $J = 7.0$ Hz, 1H, *Ar*H), 7.45–7.52 (m, 3H, *Ar*H), 6.07 (s, 1H, napht-CH), 4.87 (d, $J = 3.4$ Hz, 1H, H-1), 4.38 (dd, $J = 4.4$, 9.8 Hz, 1H, H-6), 3.88–3.93 (m, 2H, H-5, H-6), 3.86 (m, 2H, OCH_2 of the macrocycle), 3.77–3.81 (m, 4H, $2OCH_2$ of the macrocycle), 3.73 (t, $J = 9.2$ Hz, 1H, H-3), 3.62–3.69 (m, 5H, H-4 and $2OCH_2$ of the macrocycle), 3.60 (t, $J = 5.2$ Hz, 2H, OCH_2 of the macrocycle), 3.54 (dd, $J = 3.1$, 8.1 Hz, 1H, H-2), 3.46 (s, 3H, OCH_3), 3.42–3.48 (m, 2H, $NCH_2CH_2CH_2$), 2.65–2.87 (m, 6H, $3NCH_2$), 1.60–1.72 (m,

2H, $NCH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 133.71, 132.52, 130.50, 129.61, 128.52, 126.06, 125.63, 125.00, 124.13, 123.69 (*Ar*C), 100.21 (napht-CH), 98.58 (C-1), 82.85 (C-4), 79.87 (C-2), 77.90 (C-3), 72.33, 70.67, 70.37, 69.37, 69.11, 68.91 ($6OCH_2$ of the macrocycle), 69.78 (C-6), 64.23 ($NCH_2CH_2CH_2$), 62.25 (C-5), 56.76 ($NCH_2CH_2CH_2$), 55.27 (OCH_3), 54.68, 54.37 ($2NCH_2$ of the macrocycle), 28.41 ($NCH_2CH_2CH_2$) ppm; FAB-MS: $m/z = 548$ $[M+H]^+$, 570 $[M+Na]^+$; HRMS: m/z calcd for $C_{29}H_{41}NO_9$ $[M]^+$ 547.2781, found 547.2792.

Methyl 4,6-O-(1-naphthyl)methylene-2,3-dideoxy-α-D-glucopyranosido(2,3-h)-N-methoxypropyl-1,4,7,10-tetraoxa-l3-azacyclopentadecane (**2b**, $C_{30}H_{43}NO_9$)
Yield 1.13 g (44%); $[\alpha]_D^{20} = +80.3°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); mp 106–108°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 8.13 (d, $J = 8.1$ Hz, 1H, *Ar*H), 7.84 (d, $J = 7.9$ Hz, 2H, *Ar*H), 7.78 (d, $J = 7.1$ Hz, 1H, *Ar*H), 7.45–7.52 (m, 3H, *Ar*H), 6.06 (s, 1H, napht-CH), 4.88 (d, $J = 3.6$ Hz, 1H, H-1), 4.38 (dd, $J = 4.4$, 9.7 Hz, 1H, H-6), 3.89–3.95 (m, 2H, H-5, H-6), 3.83–3.87 (m, 2H, OCH_2 of the macrocycle), 3.75–3.81 (m, 4H, $2OCH_2$ of the macrocycle), 3.73 (t, $J = 9.2$ Hz, 1H, H-3), 3.63–3.69 (m, 3H, H-4, OCH_2 of the macrocycle), 3.57–3.61 (m, 2H, OCH_2 of the macrocycle), 3.50–3.55 (m, 3H, H-2, OCH_2 of the macrocycle), 3.46 (s, 3H, OCH_3), 3.40 (t, $J = 6.3$ Hz, 2H, $NCH_2CH_2CH_2$), 3.31 (s, 3H, CH_2OCH_3), 2.56–2.85 (m, 6H, $3NCH_2$), 1.68–1.74 (m, 2H, $NCH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 133.70, 132.49, 130.50, 129.61, 128.52, 126.05, 125.63, 124.99, 124.14, 123.65 (*Ar*C), 100.21 (napht-CH), 98.53 (C-1), 82.81 (C-4), 79.96 (C-2), 77.94 (C-3), 72.28, 70.73, 70.33, 69.85, 69.37, 69.30 (OCH_2 of the macrocycle), 70.93 ($NCH_2CH_2CH_2$), 69.94 (C-6), 62.27 (C-5), 58.54 (CH_2OCH_3), 55.30 (OCH_3), 54.53 ($2NCH_2$ of the macrocycle), 53.53 ($NCH_2CH_2CH_2$), 27.63 ($NCH_2CH_2CH_2$) ppm; FAB-MS: $m/z = 562$ $[M+H]^+$, 584 $[M+Na]^+$; HRMS: m/z calcd for $C_{30}H_{43}NO_9$ $[M]^+$ 561.2938, found 561.2943.

Methyl 4,6-O-isopropylidene-2,3-dideoxy-α-D-glucopyranosido(2,3-h)-N-hydroxypropyl-1,4,7,10-tetraoxa-l3-azacyclopentadecane (**3a**, $C_{21}H_{39}NO_9$)
Yield: 0.83 g (40%); $[\alpha]_D^{20} = +77.0°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.79$ (d, $J = 3.6$ Hz, 1H, H-1), 4.08 (dd, $J = 4.8$, 10.1 Hz, 1H, H-6), 3.83–3.90 (m, 2H, OCH_2 of the macrocycle), 3.78–3.81 (m, 2H, OCH_2 of the macrocycle), 3.68–3.76 (m, 3H, H-3, OCH_2 of the macrocycle), 3.54–3.67 (m, 10H, H-2, H-4, H-5, H-6, $3OCH_2$ of the macrocycle), 3.41–3.43 (m, 2H, $NCH_2CH_2CH_2$), 3.39 (s, 3H, OCH_3), 2.70–2.83 (m, 6H, $3NCH_2$), 1.65–1.69 (m, 2H, $NCH_2CH_2CH_2$), 1.48 (s, 3H, CH_3), 1.39 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 99.24$ [$C(CH_3)_2$], 98.27 (C-1), 79.65 (C-2), 78.19 (C-3), 74.72 (C-4), 72.07, 70.36, 70.29, 69.76, 68.48, 68.40 ($6OCH_2$ of the macrocycle), 63.42 ($NCH_2CH_2CH_2$), 63.02 (C-6), 62.48 (C-5), 56.43 ($NCH_2CH_2CH_2$), 55.00 (OCH_3), 54.53, 54.30 ($2NCH_2$ of the macrocycle), 29.58, 29.11 ($2CH_3$), 28.04 ($NCH_2CH_2CH_2$) ppm; FAB-MS: $m/z = 450$ $[M+H]^+$, 472 $[M+Na]^+$; HRMS: m/z calcd for $C_{21}H_{39}NO_9$ $[M]^+$ 449.2625, found 449.2633.

Methyl 4,6-O-isopropylidene-2,3-dideoxy-α-D-glucopyranosido(2,3-h)-N-methoxypropyl-1,4,7,10-tetraoxa-l3-azacyclopentadecane (**3b**, $C_{22}H_{41}NO_9$)
Yield 0.88 g (42%); $[\alpha]_D^{20} = +87.0°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.81$ (d, $J = 3.6$ Hz, 1H, H-1), 4.08 (dd, $J = 4.8$, 10.1 Hz, 1H, H-6), 3.51–3.95 (m, 17H, H-2, H-3, H-4, H-5, H-6, $6OCH_2$ of the macrocycle), 3.42–3.43 (m, 2H, $NCH_2CH_2CH_2$), 3.41 (s, 3H, OCH_3), 3.32 (s, 3H, CH_2OCH_3), 2.58–2.86 (m, 6H, $3NCH_2$), 1.70–1.76 (m, 2H, $NCH_2CH_2CH_2$), 1.48 (s, 3H, CH_3), 1.40 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 99.28$ [$C(CH_3)_2$], 98.27 (C-1), 79.88 (C-2), 78.25 (C-3), 74.77 (C-4), 72.15, 70.43, 69.93, 69.27, 69.25, 68.87 ($6OCH_2$ of the macrocycle), 70.79 ($NCH_2CH_2CH_2$), 63.06 (C-6), 62.54 (C-5), 58.53 (CH_2OCH_3), 55.04 (OCH_3), 54.46, 54.43 ($2NCH_2$ of the macrocycle), 53.52 ($NCH_2CH_2CH_2$), 29.62 (CH_3), 29.16 ($NCH_2CH_2CH_2$), 27.24 (CH_3) ppm; FAB-MS: $m/z = 464$ $[M+H]^+$, 486 $[M+Na]^+$; HRMS: m/z calcd for $C_{22}H_{41}NO_9$ $[M]^+$ 4463.2781, found 463.2790.

*General procedure for the preparation of compounds **4a**, **4b***
Compound **1a** or **1b** (4.82 mmol) and 1:1 mixture of *Me*OH–CH_2Cl_2 (25 cm^3) were placed into a hydrogenation bottle, Pd/C (10%, 120 mg) was added, the air was replaced by argon and then the argon by hydrogen and the mixture was shaken under H_2 for 6 h at ambient temperature. The mixture was filtered through a Celite pad and the volatile components were removed under reduced pressure to furnish as a syrup **4a** or **4b**, which were used without further purification.

Methyl-2,3-dideoxy-α-D-glucopyranosido(2,3-h)-N-hydroxypropyl-1,4,7,10-tetraoxa-l3-azacyclopentadecane
(**4a**, $C_{18}H_{35}NO_9$)
Yield 1.77 g (90%); $[\alpha]_D^{20} = +81.0°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.10$ (d, $J =$ 3.6 Hz, 1H, H-1), 3.47–4.07 (m, 20H, $NCH_2CH_2CH_2$, H-2, H-3, H-4, H-5, 2H-6, $6OCH_2$ of the macrocycle), 3.43 (s, 3H, OCH_3), 2.45–2.81 (m, 6H, $3NCH_2$), 1.60–1.68 (m, 2H, $NCH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 96.68$ (C-1), 80.41 (C-2), 79.20 (C-3), 71.97 (C-4), 71.34, 70.96, 70.50, 70.05, 69.18, 69.10 ($6OCH_2$ of the macrocycle), 67.02 (C-5), 64.46 (CH_2OH), 62.06 (C-6), 55.06 (OCH_3), 54.78 ($2NCH_2$ of the macrocycle), 54.19 ($NCH_2CH_2CH_2$), 29.14 ($NCH_2CH_2CH_2$) ppm; FAB-MS: $m/z = 410$ $[M+H]^+$, 432 $[M+Na]^+$; HRMS: m/z calcd for $C_{18}H_{35}NO_9$ $[M]^+$ 409.2312, found 409.2325.

Methyl-2,3-dideoxy-α-D-glucopyranosido(2,3-h)-N-methoxypropyl-1,4,7,10-tetraoxa-l3-azacyclopentadecane
(**4b**, $C_{19}H_{37}NO_9$)
Yield 1.87 g (92%); $[\alpha]_D^{20} = +78.5°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.09$ (d, $J = 3.6$ Hz, 1H, H-1), 3.51–4.08 (m, 18H, H-2, H-3, H-4, H-5, 2H-6 and $6OCH_2$ of the macrocycle), 3.42 (t, $J = 6.0$ Hz, 2H, $NCH_2CH_2CH_2$), 3.43 (s, 3H, OCH_3), 3.32 (s, 3H, CH_2OCH_3), 2.63–2.84 (m, 4H, $2NCH_2$ of the macrocycle), 2.57 (t, $J = 7.1$ Hz, 2H, $NCH_2CH_2CH_2$), 1.72 (m, 2H, $NCH_2CH_2CH_2$) ppm; ^{13}C

NMR (75 MHz, $CDCl_3$): $\delta = 96.67$ (C-1), 80.40 (C-2), 79.20 (C-3), 71.95 (C-4), 71.35, 70.97, 70.50, 70.38, 69.23, 69.14 (6OCH_2 of the macrocycle), 70.90 ($NCH_2CH_2CH_2$), 67.01 (C-5), 62.04 (C-6), 58.53 (CH_2OCH_3), 55.06 (OCH_3), 54.28, 54.24 (2NCH_2 of the macrocycle), 53.17 ($NCH_2CH_2CH_2$), 29.07 ($NCH_2CH_2CH_2$) ppm; FAB-MS: $m/z = 424$ $[M+H]^+$, 446 $[M+Na]^+$; HRMS: m/z calcd for $C_{19}H_{37}NO_9$ $[M]^+$ 423.2468, found 423.2480.

General procedure for the Michael addition of 2-nitropropane to chalcones

The corresponding azacrown ether catalyst (0.1 mmol) and 0.05 g sodium *tert*-butoxide (0.5 mmol) was added to a solution of 1.44 mmol chalcone and 0.3 cm^3 2-nitropropane (3.36 mmol) in 3 cm^3 dry toluene. The mixture was stirred at room temperature under argon. After a reaction time of 20 to 42 h, a new portion of toluene (7 cm^3) and water (10 cm^3) were added and the mixture was stirred for several minutes. The organic phase was washed with water 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 as the eluant) to give pure adducts **13a**.

4-Methyl-3-phenyl-4-nitro-1-phenylpentan-1-one
(**13a**, $C_{18}H_{19}NO_3$)

Yield: 0.21 g (49%); $[\alpha]_D^{20} = +72.7^\circ\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2); 90% *ee* for (+)-(*R*) enantiomer [24]; mp 146–148°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.85$ (d, 2H, CO*Ph*H-*o*), 7.53 (t, 1H, CO*Ph*H-*p*), 7.42 (t, 2H, CO*Ph*H-*m*), 7.18–7.32 (m, 5H, CH*Ph*H), 4.15 (dd, $J = 10.4$, 3.3 Hz, 1H, CH), 3.67 (dd, $J = 17.2$, 10.4 Hz, 1H, CH_2), 3.27 (dd, $J = 17.2$, 3.2 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3), 1.54 (s, 3H, CH_3) ppm; HRMS: m/z calcd for $C_{18}H_{19}NO_3$ $[M]^+$ 297.1365, found 297.1367.

4-Methyl-3-(1-naphthyl)-4-nitro-1-phenylpentan-1-one
(**13b**, $C_{22}H_{21}NO_3$)

Yield: 0.23 g (47%); $[\alpha]_D^{20} = +92.1^\circ\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 35% *ee*; mp 131–133°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.47$ (d, 1H, napht-H), 7.82 (d, 2H, CO*Ph*H-*o*), 7.76 (d, 1H, napht-H), 7.61 (t, 1H, CO*Ph*H-*p*), 7.50 (t, 2H, CO*Ph*H-*m*), 7.33–7.38 (m, 5H, napht-H), 5.28 (dd, $J = 3.2$, 10.2 1H, CH), 3.86 (dd, $J = 10.2$, 17.4 Hz, 1H, CH_2), 3.45 (dd, $J = 3.2$, 17.4 Hz, 1H, CH_2), 1.66 (s, 3H, CH_3), 1.47 (s, 3H, CH_3) ppm; HRMS: m/z calcd for $C_{22}H_{21}NO_3$ $[M]^+$ 347.1521, found 347.1527.

4-Methyl-3-(2-naphthyl)-4-nitro-1-phenylpentan-1-one
(**13c**, $C_{22}H_{21}NO_3$)

Yield: 0.06 g (12%); $[\alpha]_D^{20} = +68.8^\circ\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 43% *ee*; mp 144–146°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.02$ (s, 1H, napht-H), 7.85 (d, 2H, CO*Ph*H-*o*), 7.76 (m, 2H, napht-H), 7.59 (t, 1H, CO*Ph*H-*p*), 7.49–7.52 (m, 2H, napht-H), 7.42–7.44 (m, 2H, napht-H), 7.41 (t, 2H, CO*Ph*H-*m*), 4.33 (dd, $J = 3.1$, 10.4 Hz, 1H, CH), 3.79 (dd, $J = 10.4$, 17.2 Hz, 1H, CH_2), 3.35 (dd, $J = 3.2$, 17.2 Hz, 1H, CH_2), 1.67 (s, 3H, CH_3), 1.57 (s, 3H, CH_3) ppm; HRMS: m/z calcd for $C_{22}H_{21}NO_3$ $[M]^+$ 347.1521, found 347.1532.

4-Methyl-4-nitro-1-phenyl-3-(2-pyridyl)pentan-1-one
(**13d**, $C_{17}H_{18}N_2O_3$)

Yield: 0.35 g (81%); yellow syrup; $[\alpha]_D^{20} = 118.2^\circ\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 79% *ee*; ^1H NMR (500 MHz, $CDCl_3$) $\delta = 8.48$ (d, 1H, pyr-H), 7.91 (d, 2H, CO*Ph*H-*o*), 7.64 (t, 1H, CO*Ph*H-*p*), 7.55 (t, 1H, pyr-H), 7.44 (t, 2H, CO*Ph*H-*m*), 7.38 (d, 1H, pyr-H), 7.15 (t, 1H, pyr-H), 4.35 (dd, $J = 2.0$, 10.7 Hz, 1H, CH), 4.24 (dd, $J = 10.7$, 17.3 Hz, 1H, CH_2), 3.11 (dd, $J = 2.0$, 17.3 Hz, 1H, CH_2), 1.77 (s, 3H, CH_3), 1.55 (s, 3H, CH_3) ppm; HRMS: m/z calcd for $C_{17}H_{18}N_2O_3$ $[M]^+$ 298.1317, found 298.1315.

3,4-Dimethyl-4-nitro-1-phenylpentan-1-one
(**13e**, $C_{13}H_{17}NO_3$)

Yield: 0.22 g (65%); yellow oil; $[\alpha]_D^{20} = -23.5^\circ\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 64% *ee*; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.93 (d, 2H, CO*Ph*H-*o*), 7.57 (t, 1H, CO*Ph*H-*p*), 7.47 (t, 2H, CO*Ph*H-*m*), 2.94–2.99 (m, 2H, CH, CH_2), 2.81 (dd, $J = 6.3$, 10.6 Hz, 1H, CH_2), 1.60 (s, 6H, $2CH_3$), 0.98 (d, 3H, CH_3) ppm; HRMS: m/z calcd for $C_{13}H_{17}NO_3$ $[M]^+$ 235.1208, found 235.1211.

General procedure for the Darzens condensation

To a solution of 0.2 g phenacyl chloride (1.3 mmol), 0.2 g benzaldehyde (1.9 mmol) and catalyst (0.1 mmol) in 3 cm^3 toluene, 1.0 cm^3 30% NaOH solution was added. The mixture was stirred under an argon atmosphere at room temperature for 1–4 h. After completion of the reaction toluene (7 cm^3) was added to the mixture and the organic phase was washed with 10% aqueous hydrochloric acid (2×10 cm^3) and then with water (10 cm^3), dried (Na_2CO_3) and the solvent was evaporated. The crude product (**15a**) was purified by preparative *TLC* using CH_2Cl_2 as eluant. Yield: 0.31 g (75%); $[\alpha]_D^{20} = -102.7\ g^{-1}\ cm^3\ dm^{-1}$ ($c =$ l, CH_2Cl_2), 48% *ee* for (2*R*,3*S*) enantiomer; mp 64–66°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.02$ (d, 2H, CO*Ph*H-*o*), 7.63 (t, 1H, CO*Ph*H-*p*), 7.50 (t, 2H, CO*Ph*H-*m*), 7.38–7.44 (m, 5H, CH*Ph*H), 4.30 (d, $J =$ 1.9 Hz, 1H, CH), 4.09 (d, $J = 1.9$ Hz, 1H, CH) ppm; HRMS: m/z calcd for $C_{15}H_{12}O_2$ $[M]^+$ 224.0837, found 224.0830.

General procedure for the epoxidation of chalcones

A mixture of 0.3 g chalcone (1.44 mmol), the appropriate catalyst (0.1 mmol) in 3 cm^3 toluene and 1 cm^3 20% aq. NaOH was treated with 0.5 cm^3 5.5 M *tert*-butyl hydroperoxide in decane (2.88 mmol). The mixture was stirred at 0–4°C for 1–10 h. New portion of toluene (7 cm^3) and water (10 cm^3) were added and the mixture was stirred for several times. The organic phase was washed with 10% aqueous hydrochloric acid (2×10 cm^3) and then with water (10 cm^3). The organic phase was dried (Na_2CO_3). The crude product obtained after evaporating the solvent was purified by preparative *TLC* (silica gel, hexane-ethyl acetate, 10:1 as the eluant) to give **15a** in a pure form. Results are collected in Table 1. Spectroscopic data of **15a** are given before.

2,3-Epoxy-1-phenyl-3-(1-naphthyl)propan-1-one
(**15b**, $C_{19}H_{14}O_2$)

Yield 0.20 g (51%); $[\alpha]_D^{20} = +63.0^\circ\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 56% *ee*; mp 106–107°C; ^1H NMR (500 MHz,

$CDCl_3$): $\delta = 8.01$ (d, 2H, CO*Ph*H-*o*), 7.93 (d, 1H, napht-H), 7.86 (t, 1H, CO*Ph*H-*p*), 7.81 (d, 1H, napht-H), 7.57 (t, 2H, CO*Ph*H-*m*), 7.41–7.48 (m, 5H, napht-H), 4.66 (d, $J = 1.5$ Hz, 1H, CH), 4.24 (d, $J = 1.6$ Hz, 1H, CH) ppm; HRMS: m/z calcd for $C_{19}H_{14}O_2$ $[M]^+$ 274.0994, found 274.0998.

2,3-Epoxy-1-phenyl-3-(2-naphthyl)propan-1-one (**15c**, $C_{19}H_{14}O_2$)
Yield 0.06 g (15%); $[\alpha]_D{}^{20} = -153.2°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 64% *ee*; mp 101–102°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.03$ (d, 2H, CO*Ph*H-*o*), 7.85–7.90 (m, 4H, napht-H), 7.62 (t, 1H, CO*Ph*H-*p*), 7.52–7.55 (m, 2H, napht-H), 7.49 (t, 2H, CO*Ph*H-*m*), 7.43 (d, 1H, napht-H), 4.40 (d, $J =$ 1.8 Hz, 1H, CH), 4.25 (d, $J = 1.6$ Hz, 1H, CH) ppm; HRMS: m/z calcd for $C_{19}H_{14}O_2$ $[M]^+$ 274.0994, found 274097.

2,3-Epoxy-1-phenyl-3-(2-pyridyl)propan-1-one (**15d**, $C_{14}H_{11}NO_2$)
Yield 0.19 g (58%); $[\alpha]_D{}^{20} = -113.7°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 45% *ee*; mp 93–94°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.65$ (d, 1H, pyr-H), 8.06 (d, 2H, CO*Ph*H-*o*), 7.77 (t, 1H, CO*Ph*H-*p*), 7.63 (t, 1H, pyr-H), 7.51 (t, 2H, CO*Ph*H-*m*), 7.42 (d, 1H, pyr-H), 7.32 (t, 1H, pyr-H), 4.60 (d, $J = 1.4$ Hz, 1H, CH), 4.23 (d, $J = 1.2$ Hz, 1H, CH) ppm; HRMS: m/z calcd for $C_{14}H_{11}NO_2$ $[M]^+$ 225.0790, found 225.0794.

2,3-Epoxy-1-phenylbutan-1-one (**15e**, $C_{10}H_{10}O_2$)
Yield 0.1 g (42%); yellow syrup; $[\alpha]_D{}^{20} = -3.2°\ g^{-1}\ cm^3\ dm^{-1}$ ($c = 1$, CH_2Cl_2), 51% *ee*; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 8.01 (d, 2H, CO*Ph*H-*o*), 7.62 (t, 1H, CO*Ph*H-*p*), 7.50 (t, 2H, CO*Ph*H-*m*), 3.99 (d, $J = 1.6$ Hz, 1H, CH), 3.21 (d, $J = 1.8$ Hz, 1H, CH), 1.51 (d, 3H, CH_3) ppm; HRMS: m/z calcd for $C_{10}H_{10}O_2$ $[M]^+$ 162.0681, found 162.0679.

Acknowledgements

The authors are grateful for the OTKA support of this research (Grant Nos. T 042514 and T 42933) and the joint founds from the European Union and the Hungarian State (GVOP-3.2.2.-2004-07-0006/3.0) *Dóra K. Menyhárd* is a *Bolyai* research fellow of the Hungarian Academy of Sciences.

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