Synthesis of *L*-arabinose-based crown ethers and their application as enantioselective phase transfer catalysts

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Abstract

New chiral monoaza-15-crown-5 type macrocycles anellated to 3,4-*O*-isopropylidene-β-*L*-arabinopyranose (**5a-b**), to β-*L*-arabinopyranose (**6**) and to 3,4-*O*-benzyliden-β-*L*-arabinopyranose (**11**) have been synthesized. The cation binding ability of the new lariat ethers was evaluated by the picrate extraction method in liquid-liquid system. Some representatives of these crown ethers showed moderate asymmetric induction as chiral phase transfer catalysts, among them **11** with a benzylidene group proved to be the most efficient one inducing 64% ee in the Michael addition of 2-nitropropane to chalcone and 61% ee in the addition of diethyl acetamidomalonate to *trans-β*-nitrostyrene. An induction of 65% ee was observed in the epoxidation of a chalcone analogue with *tert*-butyl hydroperoxide in the presence of catalyst **5a**.

Keywords: Asymmetric catalysis, chiral crown ether, phase transfer catalysis, Michael addition

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 attracting currently 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. Unexpensive natural sugars are „green" and cheep starting materials in organic syntheses. Over the past three decades, numerous macrocycles incorporating one or more monosaccharide units have been synthesized.[3] The hexopyranoside-based lariat ethers described earlier by us possess special complexing

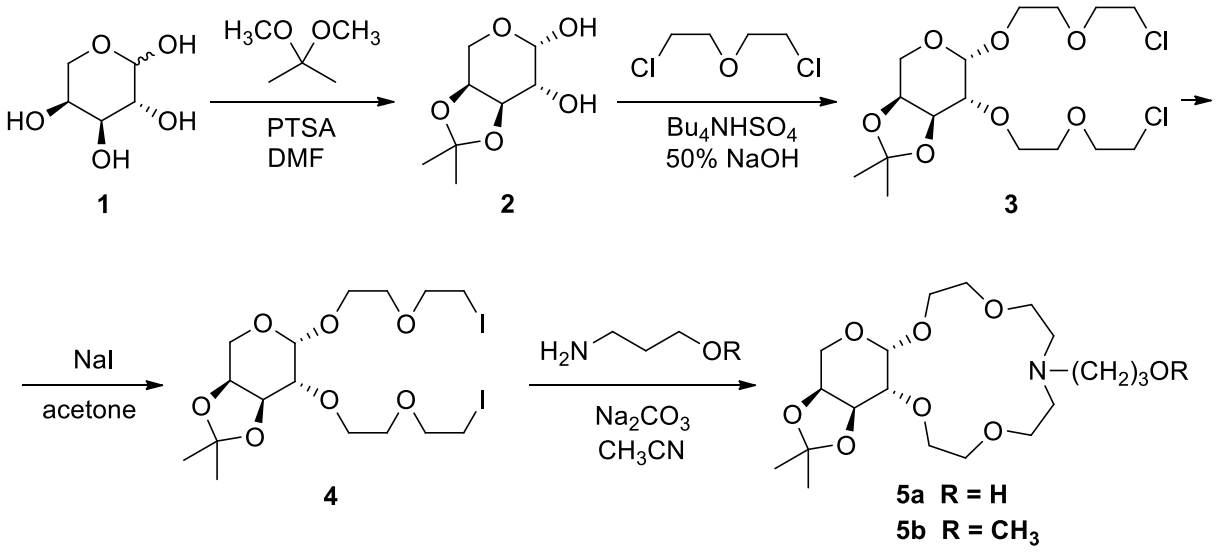
ability due to their flexible side arm containing a heteroatom at the end.[4] The overall complexing ability is influenced by the steric and electronic properties of the *N*-substituent. A few of the monosaccharide-based chiral lariat ethers have been found to be efficient phase transfer catalysts in certain types of asymmetric reactions.[5] A review has been recently published by us in this topic.[6] Valuable information has been accumulated on the structure - enantioselectivity relationship. Regarding the crown, a monoaza-15-crown-5 type structure seems to be advantageus. Beside this, the catalytic effect strongly depends on the carbohydrate moiety anellated to the azacrown ring and on the nature of the side arm of the crown ether. Among the alkyl-, alkoxy-, aralkyl- and other (e.g. *P*-functionalized) *N*-substituents, the hydroxypropyl, and in some cases, the methoxypropyl side arm was the most advantageous from the point of view of enantioselectivity.[6]

In this article, *L*-arabinose-based monoaza-15-crown-5 type chiral macrocycles with a hydroxypropyl- and methoxypropyl side arms (lariat ethers) are described.

Results and Discussion

Synthesis

The principle of the synthesis of macrocycles anellated to 3,4-*O*-isopropylidene-β-*L*-arabinopyranose is shown in Scheme 1.

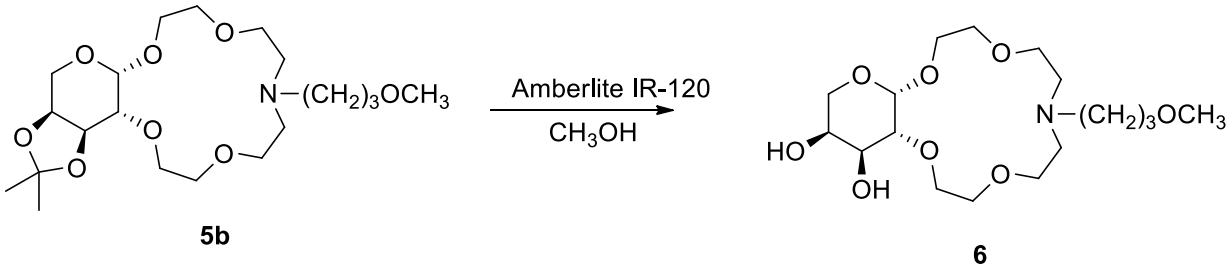


Scheme 1. Synthesis of macrocycles anellated to 3,4-*O*-isopropylidene-β-*L*-arabinopyranose.

The starting material, 3,4-*O*-isopropylidene-β-*L*-arabinopyranose (**2**) was prepared by the reaction of *L*-arabinose (**1**) with 2,2-dimethoxypropane in dry DMF in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst, at room temperature.[7] Beside compound **2**, different

byproducts (e.g. 1,2;3,4-di-*O*-isopropylidene-β-*L*-arabinopyranose) were also formed, which were removed by flash chromatography. The pure mono isopropylidene derivative (**2**) was obtained after cristallization in a yield of 70%. Anellation of the crown ring in positions 1 and 2 of the arabinopyranose acetals (**2**) was accomplished in three steps, as described earlier.[4] The vicinal hydroxyl groups of compound **2** were alkylated with bis(2-chloroethyl)ether in the presence of tetrabutylammonium hydrogen sulfate catalyst and 50% *aq.* NaOH in a liquid-liquid two-phase system by the Gross method[8] to give intermediate **3** which was purified by chromatography. The exchange of chlorine to iodine in intermediate **3** was accomplished in reaction with NaI in boiling acetone to afford bisiodo derivative **4**. Compound **4** was then cyclized with two kinds of primary amines, such as 3-aminopropanol and 3-methoxypropylamine, in boiling acetonitrile, in the presence of dry Na_2CO_3 to afford azacrown ethers **5a** and **5b,** respectively after purification by column chromatography. The yield of the cyclizations reactions was around 60% (Scheme 1).

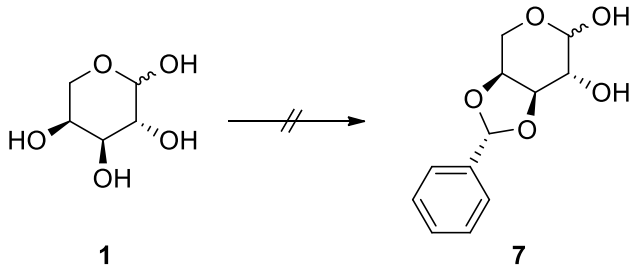
The isopropylidene protecting group in compound **5b** was removed by a cation exchanger resin (Amberlite IR-120) in methanol to give lariat ethers **6** with free hydroxyl groups in positions 3 and 4.



5b **6**

Scheme 2. Synthesis of a macrocycle anellated to β-*L*-arabinopyranose.

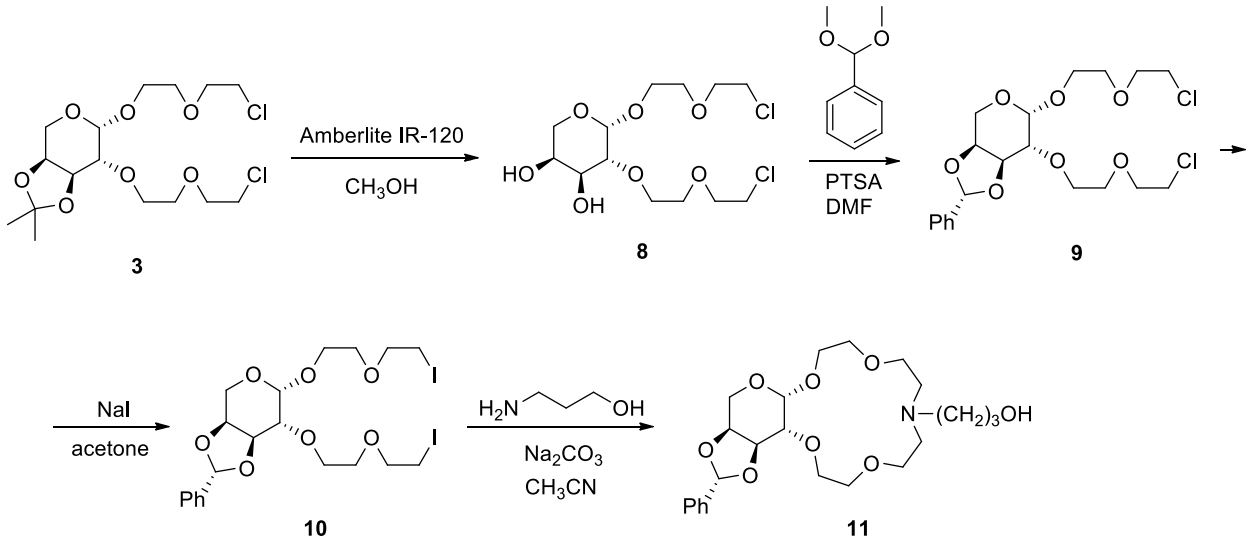
We wished to incorporate an aromatic moiety in the form of benzylidene acetal, instead of the isopropylidene group. Starting from *L*-arabinose, we tried out a few reagents (the $ZnCl_2$ complex of benzaldehyde, benzaldehyde-dimethylacetal), but we failed to synthesize the expected benzylidene acetal (**7**, Scheme 3).



1 **7**

Scheme 3. Experiments for preparation of 3,4-*O*-benzylidene-β-*L*-arabinopyranose.

The problem could be solved by starting from bischloro podand **3** instead of *L*-arabinose (Scheme 4). The isopropylidene protecting group was removed from compound **3** using cation exchanger resin (Amberlite IR-120) and the *L*-arabinose-based podand **8** so obtained was converted to derivative **9** using benzaldehyde-dimethylacetal. The yield was 75%. Then the chlorine atoms in compound **9** were exchanged to iodine to afford species **10**. The ring closure with 3-aminopropanol was performed as described earlier and the related azacrown ether **11** was obtained in a yield of 78%. The yield was better then that obtained for the isopropylidene analogue **5a**.



Scheme 4. Synthesis of a chiral crown ether anellated to 3,4-*O*-benzyliden-β-*L*-arabinopyranose.

Regarding the position of the phenyl ring in the benzylidene-acetal ring of compound **9**, the ratio of the isomers *endo*/*exo* was 85:15 on the basis of ^{1}H NMR. Chromatography afforded the pure *endo* isomer (δ = 5.94 ppm for the *endo* and δ= 6.27 ppm for the *exo* isomer)[9]. All intermediates and new products were characterized by ^{1}H NMR ^{13}C NMR, mass spectroscopy and elemental analysis.

Extracting properties

The phase transfer properties of the newly synthesized crown ethers were characterized by the extraction of picrate salts (lithium, sodium, potassium, rubidium, cesium and ammonium picrate) from water into dichloromethane (CH_2CH_2) by the method of Kimura.[10] The concentration of the picrates in the aqueous phase was determined by UV spectroscopy. The extracting ability (EA%) is mainly based on the complex forming ability of the macrocycle, although some other factors (e.g. solubility, lipophilicity, etc) may also influence it. Table 1 contains the EA data obtained with compounds **5a-b** and **6**, **11**. The data show the amount of the transferred salt as a percentage

of the initial salt concentration (Extractability %). A higher value indicates a better phase transfer capability of the crown.

Table 1. Extraction of alkali metal and ammonium picrates with *L*-arabinose-based crown ethers

	Extractability (%)[a]			
Cation	**5a**	**5b**	**6**	**11**
Li^+	16	27	6	31
Na^+	22	40	8	45
K^+	9	21	3	26
Rb^+	7	14	2	28
Cs^+	6	11	3	17
NH_4^+	16	31	2	38

[a] Room temperature; aqueous phase (5 mL); [picrate] = $5x10^{-3}$ M; organic phase (CH_2Cl_2 5 mL); [crown ether] = $1x10^{-2}$ M; Defined as % picrate extracted into the organic phase, determined by UV spectroscopy. Error = ±1%.

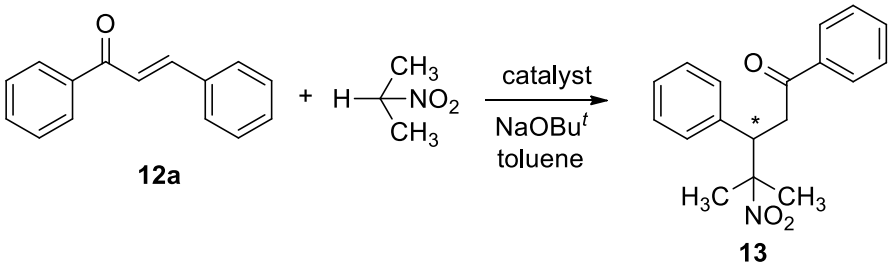
It is not surprising that from among the metal cations, all crown ethers form the strongest complex with the Na^+ cation as the size of this cation suits best the cavity of the 15-crown-5. With the cations of bigger size, the binding ability towards the crown ether is much weeker. By comparing the EA values of lariat ethers **5a** and **5b**, it can be seen that the change of the hydroxyl group at the end of the side arm (as in **5a**) to methoxy group (as in **5b**), the extracting ability is somewhat increased probably due to the increase in the lipophilicity. The smallest EA value (2-8%) was revealed by compound **6**, while the best extracting ability (17-45%) was detected with macrocycle **11**. The benzylidene moiety on the arabinose moiety has two effects. On the one hand, it increases the lipophilicity, on the other hand, it may be involved in a π-π interaction with the aromatic moiety of the picrates enhancing the formation of stronger complexes. The transport of NH_4^+ (2-38%) may not be compared with that of the metal cations, as the complexes with ammonium cation are known to have a structure with three-point hydrogen bridge connection. It can be concluded that the *L*-arabinose-based lariat ethers posses weak or medium extracting abilities as compared to the glucose analogues with a similar structure.[4a]

Asymmetric induction

The chiral crown compounds synthesized could also be tested in some model reactions as enantioselective phase transfer catalysts. In all cases, the products were isolated by preparative TLC after the usual work-up procedure. The enantiomer excess (ee) was determined by ^1H NMR spectroscopy or chiral HPLC.

The macrocycles **5a-b**, **6** and **11** were tested in the Michael addition of 2-nitropropane to chalcone (Scheme 5). 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 by us (7 mol%).[5b]



Scheme 5. Asymmetric addition of 2-nitropropane to chalcone

The experimental data are shown in Table 2.

Table 2. The effect of the *L*-arabinose-based crown catalyts on the enantioselectivity in the addition of 2-nitropropane to chalcone at room temperature

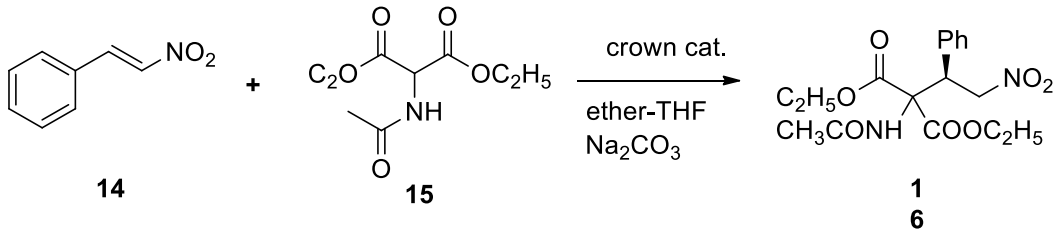
Entry	Catalyst	Time (h)	Yield of **13** (%) [a]	$[\alpha]_D$ [b]	ee (%) [c]
1	**5a**	8	46	- 39.6	49 (*S*)
2	**5b**	9	57	- 42.8	53 (*S*)
3	**6**	30	61	- 13.7	17 (*S*)
4	**11**	10	59	- 51.7	64 (*S*)

[a] Based on isolation by preparative TLC; [b] In CH_2Cl_2 at 20 °C; [c] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent. The absolute configurations were assigned by comparison of the specific rotation with the corresponding literature value[6a]

It can be seen that the *L*-arabinose-based macrocycles resulted in variable enantioselectivities (17-64%) in favour of the *S* antipode with 46-61% yields. The „methylation" of the hydroxypropyl side arm influenced the enantioselectivity to only a small extent; in the presence of catalyst **5a** (R=H) and **5b** ($R=CH_3$) the ee was 49 and 53%, respectively. The lowest enantiomer excess (17%) was observed with catalyst **6** that is without a protecting group, that can be explained by assuming that in the absence of an acetal ring, the molecule becomes more flexible. It is known that a more rigid structure is always better from the point of view of enantiomeric discrimination. It is also a significant change that the lipophilicity of catalyst **6** also decreased (lower solubility in toluene phase). The best result of 64% was obtained in the presence of **11** having a benzylidene protecting group and a hydroxypropyl side arm. Regarding the results obtained with catalysts **5a** and **11** (Table 2. entry 1 and 4), it can be seen that the

presence of a benzylidene acetal group is more advantageous from the point of view of enantioselectivity.

Another Michael reaction is the conjugate addition of diethyl acetamidomalonate **15** to *β*-nitrostyrene **14** under phase transfer catalytic conditions in the presence of L-arabinose-based lariat ethers (Scheme 6).

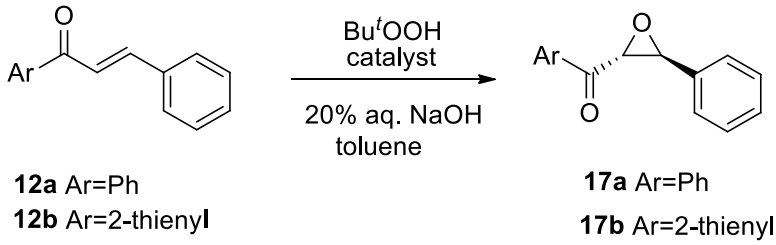


14 **15** **16**

Scheme 6. Asymmetric addition of diethyl acetamidomalonate to *β*-nitrostyrene.

The Michael addition was carried out in a solid-liquid two-phase system by employing 15 mol% of crown ether. The organic phase comprised the starting materials and the catalyst in a solvent mixture of THF-ether (4:1), while Na_2CO_3 used in two-fold excess formed the solid phase. Products **16** were obtained by preparative TLC, and the optical purity was measured by chiral HPLC.[11] The best results were obtained with catalyst **5a** having an isopropylidene group and species **11** having a benzylidene protecting group resulting in an ee of 52% and 61%, respectively. The *R* absolute configuration of Michael adduct **16** is characterized by a positive optical rotation.

The *L*-arabinose-based lariat ethers were also used as catalyst in the epoxidation of *trans*-chalcones (Scheme 7).[5e]



12a Ar=Ph
12b Ar=2-thienyl

17a Ar=Ph
17b Ar=2-thienyl

Scheme 7. Asymmetric epoxidation of *α,β*-enones.

In the experiments, the epoxidation of chalcones was carried out with *tert*-butyl hydroperoxide (TBHP, 2 equiv.) at 5 °C in toluene, in a liquid-liquid two-phase system, employing 20 % *aq.* NaOH (3.5 equiv) as base and 7 mol % of *L*-arabinose-based lariat ethers as catalyst. The reactions took place after 4-8 h in good yields (84-90%). The *trans*-epoxyketones **17a-b** were obtained in all experiments, with a configuration of (+)-(2*S*,3*R*). Regarding **17a**, the best results of 58 and 45% were obtained with catalyst **5a** and **11** respectively, that contained

hydroxypropyl side arms. In the presence of these catalysts (**5a** and **11**) product **17b** was formed with an enantioselectivity of 65 and 61%, respectively. It is interesting that the methylation of the hydrophilic functions in **5a** resulted in a dramatic decrease in the enantioselectivity as was demonstrated by the ee of 23 % for epoxyketone **17a** obtained in the presence of **5b**.

It can be concluded that the *L*-arabinose-based lariat ethers induced enantioselectivities of medium size in the asymmetric reactions studied. These results are more modest than those obtained with the *D*-glucose-based crown ethers.[5] In the future, we wish to study the enantiomeric discrimination ability of the lariat ethers synthesized toward chiral ammonium salts.

Experimental Section

General. Melting points were taken on using a Büchi 510 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20˚C. ^{1}H NMR spectra were recorded on a Bruker 300 and a Bruker DRX-500 or a Varian Inova 500 instrument in $CDC1_3$ with TMS as internal standard. The exact mass measurements were performed using Q-TOF Premier mass spectrometer (Waters Corporation, 34 Maple St, Milford, MA, USA) in positive electrospray ionization mode. Elemental analyses were determined on a Perkin-Elmer 240 automatic analyzer. 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.

1,2-Bis-*O*-[(2-chloroethoxy)ethyl]-3,4-*O*-isopropylidene-β-*L*-arabinopyranose (3). A mixture of the sugar derivative **2** (15.5 g, 83.0 mmol) and Bu_4NHSO_4 (20.9 g, 62.0 mmol) in bis(2-chloroethyl)ether (144 mL, 1.23 mol) was vigorously stirred with 50% *aq*. NaOH solution (157 mL, 2.7 mol) at room temperature for 10 hours. The reaction mixture was poured on a mixture of water (420 mL) and CH_2Cl_2 (420 mL). Then, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 270 mL) and the combined organic phases were dried (Na_2SO_4). After the removal of the solvent in vacuum, bis(2-chloroethyl)ether was removed by another distillation in vacuum. The crude product was purified by column chromatography on silica gel, using 1-5% MeOH in $CHCl_3$ as eluent. Yield: 14.0 g (44%), yellow oil. $[\alpha]_D^{20}$ = + 54.2 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.51-4.29 (m, 22H, 7 x OCH_2, 2 x CH_2Cl, H-1, H-2, H-3, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.37, 28.41, 42.70, 42.85, 61.78, 66.97, 68.05, 70.34, 70.68, 71.20, 71.22, 71.31, 71.75, 79.60, 101.96, 109.92. Anal. Calcd. for $C_{16}H_{28}Cl_2O_7$: C, 47.65 ; H, 7.00 %. Found: C, 47.61; H, 7.05%.

1,2-Bis-*O*-[(2-iodoethoxy)ethyl]-3,4-*O*-isopropylidene-β-*L*-arabinopyranose (4). The mixture of bischloro derivative **3** (5.9 g, 15.5 mmol), dry NaI (6.9 g, 46.2 mmol) and Na_2CO_3 (0.1 g, 1.0 mmol), in dry acetone (180 mL) was refluxed with stirring for 30 hours. Then the mixture was

cooled to room temperature and filtered, the residue was washed with acetone. The combined organic phases were evaporated. The residual oil was taken up in CH_2Cl_2 (100 mL), washed with water (3 x 40 mL), dried (Na_2SO_4) and evaporated. This procedure gave the pure product (**4**). Yield: 7.7 g (89%) yellow oil. $[\alpha]_D^{20}$ = + 47.5 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.25-4.25 (m, 22H, 7 x OCH_2, 2 x CH_2I, H-1, H-2, H-3, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 3.12, 3.16, 26.39, 30.92, 61.75, 67.01, 68.00, 70.33, 70.71, 71.15, 71.28, 71.31, 71.75, 79.58, 101.94, 109.93. Anal. Calcd. for $C_{16}H_{28}I_2O_7$: C, 32.78 **;** H, 4.81 %. Found: C, 32.71; H, 4.84%.

General method for the preparation of crown ethers (5a) and (5b)

Dry Na_2CO_3 (5.0 g, 47.5 mmol) was suspended in the solution of the corresponding primary amine (7.78 mmol) and bisiodo compound **4** (4.0 g, 7.1 mmol) in dry acetonitrile (100 mL). The stirred reaction mixture was refluxed for 42 h under argon. After cooling, the precipitate was filtered off and washed with acetonitrile. The combined organic phases were evaporated, the residual oil was taken up in $CHCl_3$ (50 mL) washed with water (2 x 30 mL), dried (Na_2SO_4) and finally evaporated. The oily crude product was purified by column chromatography (twice: on Al_2O_3 then on silica gel using 2 to 5% MeOH in $CHCl_3$ as eluent).

3,4-*O*-Isopropylidene-β-*L*-arabinopyranose-based crown ether (5a). Yield: 1.8 g (63%); yellow oil. $[\alpha]_D^{20}$ = + 74.1 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.68 (m, 2H, CH_2), 2.64-2.70 (m, 6H, 3 x NCH_2), 3.56-4.37 (m, 20H, 8 x OCH_2, H-1, H-2, H-3, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.26, 28.30, 28.46, 53.74, 53.81, 56.71, 64.01, 67.32, 68.45, 68.93, 69.96, 70.32, 70.84, 71.67, 73.13, 73.45, 78.46, 101.96, 109.96. MS: 406 $[M + H]^+$, 428 $[M + Na]^+$. Anal. Calcd. for $C_{19}H_{35}NO_8$: C, 56.28; H, 8.70%; Found. C, 56.22; H, 8.68%.

3,4-*O*-Isopropylidene-β-*L*-arabinopyranose-based crown ether (5b). Yield: 1.73 g (58%); yellow oil. $[\alpha]_D^{20}$ = +64.4 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.82 (m, 2H, CH_2), 2.40-2.80 (m, 6H, 3 x NCH_2), 3.56-4.37 (m, 23H, OCH_3, 8 x OCH_2, H-1, H-2, H-3, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.23, 26.34, 28.27, 53.44, 53.81, 54.56, 59.37, 65.88, 67.24, 67.45, 68.40, 69.08, 69.37, 70.00, 72.77, 73.03, 74.36, 78.71, 95.00, 109.14. MS: 420 $[M + H]^+$, 442 $[M + Na]^+$; Anal. Calcd. for $C_{20}H_{37}NO_8$: C, 57.26; H, 8.89%. Found: C, 57.21; H, 8.83%.

***L*-Arabinopyranose-based crown ether (6).** Crown ether **5b** (0.40 g, 0.96 mmol) was dissolved in methanol (10 mL), then Amberlite IR-120 resin (0.10 g) was added and the mixture was stirred. The methanol was slowly distillated from the mixture to remove the acetone formed. The crude product was purified by flash chromatography (silica gel, using 1-4% MeOH in $CHCl_3$ as an eluent). Yield: 0.22 g (60%); yellow oil. $[\alpha]_D^{20}$ = + 53.1 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.82 (m, 2H, CH_2), 2.40-2.80 (m, 6H, 3 x NCH_2), 3.56-4.37 (m, 23H, OCH_3, 8 x OCH_2, H-1, H-2, H-3, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.20, 53.42, 53.88, 54.60, 59.41, 65.84, 67.22, 67.44, 68.45, 69.05, 69.67, 70.03, 72.73, 73.10, 74.40, 78.70, 101.90. MS: 380 [M

+ H]$^+$, 402 [M + Na]$^+$. Anal. Calcd. for $C_{17}H_{33}NO_8$: C, 53.81; H, 8.77%. Found: C, 53.78; H, 8.79%.

1,2-Bis-*O*-[(2-chloroethoxy)ethyl]-β-*L*-arabinopyranose (8). Bischloro derivative **3** (9.1 g, 23.8 mmol) was dissolved in methanol (120 mL), then Amberlite IR-120 resin (1.1 g) was added and the mixture was stirred. Methanol was slowly distillated from the mixture to remove the acetone. The crude product was purified by flash chromatography (silica gel, using 10% EtOAc in hexan as eluent). Yield: 5.25 g (64%); yellow oil. $[\alpha]_D^{20}$ = + 66.4 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.51-4.27 (m, 22H, 7 x OCH_2, 2 x CH_2Cl, H-1, H-2, H-3, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.74, 42.83, 63.98, 66.91, 68.04, 70.32, 70.72, 71.18, 71.22, 71.26, 71.76, 79.61, 101.97. Anal. Calcd. for $C_{13}H_{24}Cl_2O_7$: C, 42.99; H, 6.66%. Found: C, 42.92; H, 6.69%.

1,2-Bis-*O*-[(2-chloroethoxy)ethyl]-3,4-*O*-benzylidene-β-*L*-arabinopyranose (9). The solution of bischloro derivative **8** (5.1 g, 14.9 mmol), benzaldehyde-dimethylacetal (11.2 mL, 73.3 mmol) and PTSA.H_2O (0.16 g) in dry DMF (100 mL) was stirred for 3 hours at 50 °C. The mixture was neutralized with NaOMe and was then poured on a mixture of water (100 mL) and $CHCl_3$ (60 mL). The phases were separated, the aqueous phase was extracted with $CHCl_3$ (3 x 30 mL) and the combined organic phases were washed with water (3 x 30 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by column chromatography (silica gel, using 1-6% MeOH in $CHCl_3$ as eluent). Yield: 4.8 g (75%) yellow oil. $[\alpha]_D^{20}$ = + 23.3 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.50-4.57 (m, 22H, 7 x OCH_2, 2 x CH_2Cl, H-1, H-2, H-3, H-4), 5.89 (s, 1H, PhCH, *endo*), 7.38-7.56 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.73, 42.83, 66.91, 68.04, 70.32, 70.71, 71.17, 71.22, 71.31, 71.78, 72.30, 79.59, 101.98, 109.90, 128.44, 129.00, 129.75, 130.10, 133.48, 134.46. Anal. Calcd. for $C_{20}H_{28}Cl_2O_7$: C, 53.22; H, 6.25%. Found: C, 53.20; H, 6.29%.

1,2-Bis-*O*-[(2-iodoethoxy)ethyl]-3,4-*O*-benzylidene-β-*L*-arabinopyranose (10). The chlorine - iodine change of derivative **9** (4.8 g, 11.2 mmol) was carried out as for isopropylidene derivative **4**. Yield: 5.2 g (75%) yellow oil. $[\alpha]_D^{20}$ = + 55.9 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.20-3.32 (m, 4H, 2 x CH_2I), 3.50-4.57 (m, 18H, 7 x OCH_2, H-1, H-2, H-3, H-4), 5.89 (s, 1H, PhCH, *endo*), 7.36-7.54 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 3.13, 3.17, 67.00, 67.99, 70.30, 70.71, 71.10, 71.25, 71.28, 71.81, 72.34, 79.60, 101.94, 109.90, 128.44, 128.99, 129.74, 130.11, 133.39, 134.44. Anal. Calcd. for $C_{20}H_{28}I_2O_7$: C, 37.87; H, 4.45%. Found: C, 37.82; H, 4.48%.

3,4-*O*-Benzylidene-β-*L*-arabinopyranose-based crown ether (11). The cyclization procedure for compound **10** (4.7 g, 7.62 mmol) was carried out as that for crown ethers **5a** and **5b**. Yield: 2.7 g (78%) yellow oil. $[\alpha]_D^{20}$ = + 64.0 (*c*. 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66-1.70 (m, 2H, CH_2), 2.70-2.75 (m, 6H, 3 x NCH_2), 3.47-4.30 (m, 20H, 8 x OCH_2, H-1, H-2, H-3, H-4), 5.90 (s, 1H, PhCH, *endo*), 7.35-7.49 (m, 5H, PhH). MS: 454 [M + H]$^+$, 476 [M + Na]$^+$. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.48, 54.29, 54.46, 56.63, 63.84, 68.85, 68.99, 69.26, 69.94, 70.13, 70.77, 71.43, 73.22, 75.88, 78.77, 103.78, 104.58, 126.15, 126.61, 126.78, 128.40, 129.26, 137.58. Anal. Calcd. for $C_{23}H_{35}NO_8$: C, 60.91; H, 7.78%. Found: C, 60.85; H, 7.92%.

General procedure for the Michael addition of 2-nitropropane to chalcones[5a-c]

The corresponding azacrown ether catalyst (0.10 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) were added to a solution of the 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 at RT under argon. After a reaction time of 8 to 30 h, a new portion of toluene (7 mL) and water (10 mL) was 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 eluent) to give adducts **13** in a pure form. Yield: 0.21 g (59%). m.p.: 146–148 °C. $[\alpha]_D^{20}$ = -51.7 (*c*. 1.0, CH_2Cl_2), 64% ee for the (-)-(*S*) enantiomer. Its spectral parameters were identical with those described.[5a]

General procedure for the addition of diethyl acetamidomalonate to *trans-β*-nitro-styrene[11]

The *trans-β*-nitrostyrene (0.15 g, 1.0 mmol), diethyl acetamidomalonate (**15)** (0.32 g, 1.5 mmol) and the crown ether (0.15 mmol) were dissolved in a mixture of anhydrous THF (0.6 mL) and Et_2O (2.4 mL) and dry Na_2CO_3 (0.22 g, 2.08 mmol) was added. The reaction mixture was stirred at room temperature. After completition of the reaction (2-7 h), the organic phase was concentrated in vacuo and the residue was dissolved in toluene (10 mL) and washed with cold 10% HCl (3 x 10 mL) and water (20 mL), dried (Na_2CO_3) and concentrated. The crude product was purified on silica gel by preparative TLC with hexane-EtOAc (3:1) as eluent. Enantioselectivities were determined by chiral HPLC analysis using a Chiralpack AD column, (20 ºC, 256 nm, 85/15 hexane/*i*-PrOH, 0.8 mL/min) in comparison with authentic racemic samples; t_R=17.8 min (major), t_R=27.7 min (minor).
Data for **16** Yield: 0.18 g (50%). $[\alpha]_D^{20}$ = +31.1 (*c*. 1.0, $CHCl_3$, 61% ee). M.p. 126-128 °C; Its spectral parameters were identical with those described.[11]

General procedure for the epoxidation of *α,β*-enones[5e-f]

To a solution of α,β-enones (1.44 mmol) and the appropriate catalyst (0.10 mmol) in toluene (3 mL) was added 20 % *aq.* NaOH (1 mL) and the mixture was treated with 0.5 mL 5.5 M *tert*-butyl hydroperoxide in decane (2.88 mmol). The mixture was stirred at 5 ºC for 4-8 hours. A new portion of toluene (7 mL) and water (2 mL) was added and the mixture was stirred for several minutes. The organic phase was washed with 10% aqueous hydrochloric acid (2 ×10 mL) and then with water (10 mL). 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 eluent) to give the chiral epoxyketone in a pure form. The enantiomer excess was determined by ^{1}H NMR spectroscopy in the presence of $Eu(hfc)_3$ as the chiral shift reagent.
Data for **17a**: Yield: 0.27 g (81%). m.p.: 146–148 °C. $[\alpha]_D^{20}$ = +175.9 (*c*. 1.0, CH_2Cl_2), 58% ee for the (+)-(2*S*,3*R*) enantiomer. Its spectral parameters were identical with those described.[5e]
Data for **17b**: Yield: 0.33 g (94%). $[\alpha]_D^{20}$ = +162 (*c*. 1.0, CH_2Cl_2), 65% ee for the (+)-(2*S*,3*R*) enantiomer. Its spectral parameters were identical with those described.[12]

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