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Synthesis of *ribo*-hexopyranoside- and altrose-based azacrown ethers and their application in an asymmetric Michael addition

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Dedicated to Professor Gábor Tóth on the occasion of his 70th birthday

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ABSTRACT

The synthesis of four new *ribo*-hexopyranoside-based chiral lariat ethers of monoaza-15-crown-5 type and two altropyranoside-based crown ethers were elaborated. Our syntheses utilized the regioselective ring opening of the oxiran moiety of the 2,3-anhydro sugars by nucleophilic reagents to afford the key intermediates. The reaction of methyl-2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside with ethanolamine is especially of interest to afford a 3-substituted altropyranoside. One of the *ribo*-hexopyranoside-based lariat ethers with a 4-methoxyphenyl substituent induced an enantioselectivity of 80% when used as catalyst in the Michael addition of diethyl acetamidomalonate to *trans*-β-nitrostyrene under phase transfer catalytic conditions.

1. Introduction

The enantiomer differentiation ability of the chiral crown ethers can be used in two main fields: one is the separation of racemic ammonium salts, the other is the application as chiral phase transfer catalysts in asymmetric syntheses. Crown ethers with carbohydrate moieties form a special group of optically active macrocycles. The incorporation of carbohydrates is advantageous in the synthesis of chiral macromolecules because the starting carbohydrate moieties are inexpensive and readily available as commercial products and they are biocompatible and can be obtained in enantiomerically pure form with known chiroptical properties. The basic chemistry of these compounds is well-explored. Carbohydrates have functionalities which can be used to establish secondary binding sites, as well as catalytic sites. This may be achieved most easily by building the macrocycle around the 'chiral ethylene glycol' unit of the carbohydrate making use of the hydroxyl groups on the vicinal C-atoms.[1–4]

Crown ethers containing a sugar unit in anellation with the macrocyclic ring have been built from various carbohydrates: from D-glucose,[5,6] D-galactose,[7,8] D-mannose,[9,10] D-altrose,[11] D- or L-xylose,[12,13] L-arabinose[14] and sugaralcohol (D-mannitol).[15,16] Thus, a broad scale of macrocycles based on carbohydrates with different chirality are available. These macrocycles may significantly differ from each other by the number of sugar units, the size of macrocyclic ring and the number and nature of the heteroatoms incorporated in the crown ring. However, until now, only a limited number of asymmetric reactions have been explored in which a sugar-based crown catalyst induced the enantioselectivity. The authors of this paper showed that the molecules of type monoaza-15-crown-5 are efficient catalysts in a few asymmetric reactions.[3,4]

In this study the syntheses of *ribo*-hexopyranoside-based chiral lariat ethers and macrocycles containing an altropyranoside unit are described. Both syntheses have the common feature that formation of the intermediates involves the regioselective ring opening of 2,3-anhydro-hexopyranosides. The application of the crown ethers prepared as chiral phase transfer catalysts in an asymmetric Michael addition is also discussed.

2. Results and discussion

2.1. Synthesis of *ribo*-hexopyranoside-based lariat ethers

The key intermediates for chiral macrocycles are *ribo*-hexopyranoside derivatives (**4** and **7**) that are suitable for the construction of the crown ring due to its vicinal hydroxyl groups. The synthesis of sugar **4** is shown in Scheme 1.

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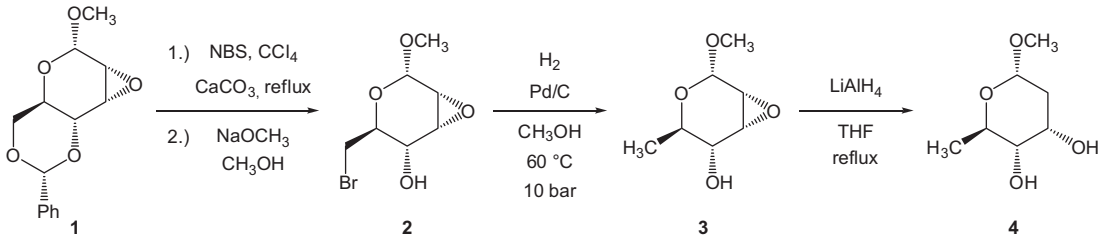
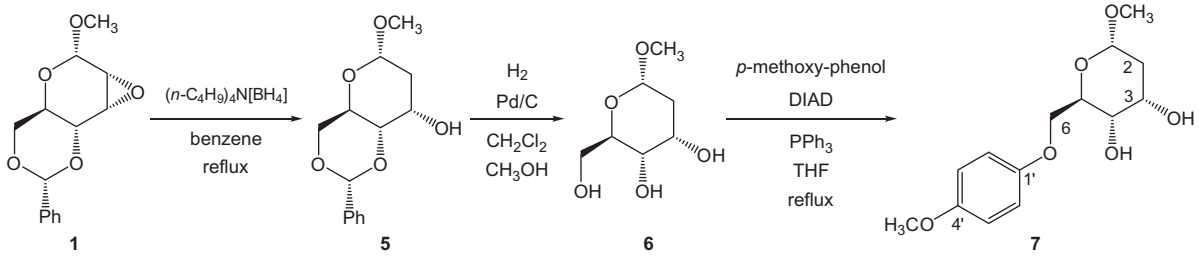


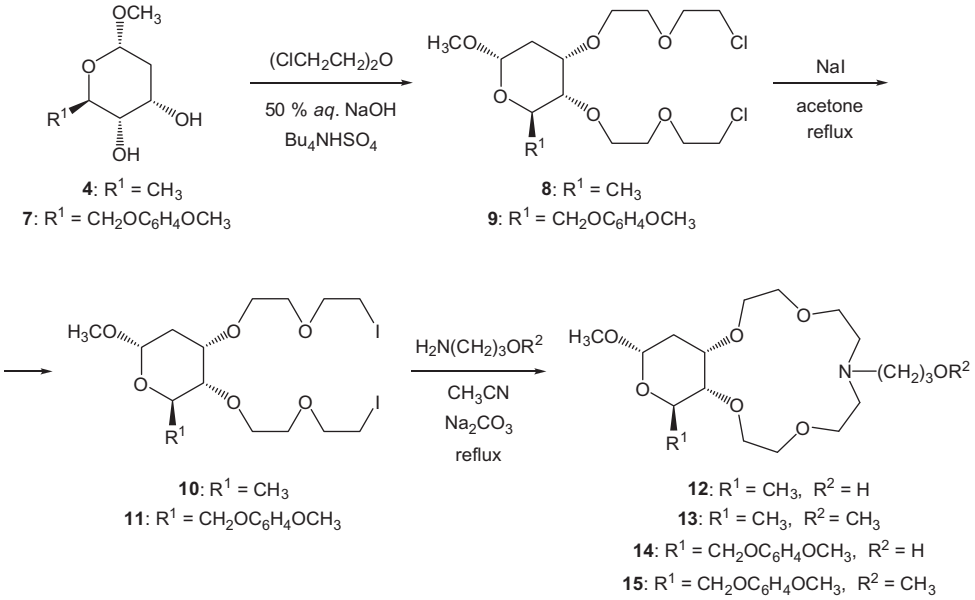
Scheme 1. Preparation of methyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside (**4**).

The opening of the benzylidene acetal ring of methyl-2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**1**)[17] was performed with *N*-bromosuccinimide (NBS),[18] the following reaction with sodium methylate resulted in the bromo sugar **2**.[19] The bromo function of intermediate **2** was removed by hydrogenolysis carried out in methanol, in the presence of Pd/C at 60°C. Debrominated species **3** was obtained in 65% yield after chromatography. The regioselective reductive ring opening was accomplished by $LiAlH_4$ in THF on the basis of an analogy described in the literature to afford methyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside (**4**)[20] in a yield of 46%. Our attempts to prepare sugar **4** by the reductive ring opening of species **1** ($LiAlH_4$), followed by the opening of the acetal ring by NBS were unsuccessful. Although the individual steps of the synthesis have been described as analogies, our method for the preparation of methyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside (**4**)[20] is novel. Synthesis of the another basic intermediate **7** can be seen in Scheme 2.

The reductive ring opening of the 2,3-anhydro derivative **1** prepared above was carried out with tetrabutylammonium tetrahydroborate (Bu_4NBH_4)[21] leading to diaxial ring opening product, methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**5**) in a yield of 59%.[22] Removal of the benzylidene acetal moiety in compound **5** was done by catalytic hydrogenation (Pd/C, MeOH, 10 bar) to furnish methyl-2-deoxy-α-D-*ribo*-hexopyranoside (**6**)[23] in an almost quantitative yield. Selective protection of the C-6 hydroxyl group was achieved by the Mitsunobu reaction using 4-methoxyphenol, diisopropyl-azodicarboxylate and triphenyl phosphine. Ether **7** was obtained in 60% yield after chromatography. The structure of compound **7** was proved by NMR spectrometry (DEPT-135, COSY, HMQC and HMBC spectra). The coupling of the *p*-methoxyphenyl moiety to the 6-CH_2O unit was clearly proven by the HMBC spectra, where both 6-CH_2 proton signals show characteristic crosspeaks with the C-1′ carbon signal. This correlation also made possible the



Scheme 2. Synthesis of methyl-2-deoxy-6-*O*-(4-methoxyphenyl)-α-D-*ribo*-hexopyranoside (**7**).



Scheme 3. Preparation of *ribo*-hexopyranoside-based lariat ethers **12–15**.

assignment of the C-1′ and C-4′ quaternary carbon signals, which are close to each other (153.08 and 154.03 ppm). Anellation of the crown ring to positions 2 and 3 of the α-D-*ribo*-hexopyranoside derivatives (**4** and **7**) was accomplished in three steps, in a similar way described earlier (Scheme 3).[24]

The vicinal hydroxyl groups of compounds **4** and **7** were alkylated with bis(2-chloroethyl) ether in the presence of tetrabutylammonium hydrogensulfate as the catalyst and 50% aq NaOH as the base in a liquid–liquid two-phase system by the Gross method[25] to give intermediates **8** and **9** in 45% and 52% yields respectively after chromatography. The exchange of chlorine to iodine in intermediates **8** and **9** was accomplished by the reaction with NaI in boiling acetone to afford bisiodo derivatives **10** and **11**, respectively. These compounds were 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 **12–15** after purification by column chromatography. It is interesting to note that the yields of 2,6-dideoxy-*ribo*-hexopyranoside-based lariat ethers (**12** and **13**) were relatively low (46% and 30%, respectively), while those of macrocycles having *p*-methoxyphenyl substituents (**14** and **15**) were much higher (79% and 84%, respectively). The difference in yields may be the consequence of the efficiency of the template effect within both reagents in the intramolecular ring closure reaction. The *p*-methoxyphenyl substituent may enhance the formation of the template effect (Scheme 3). The ring-closing step is facilitated by the sodium ion, which, by ion–dipole interaction 'wraps' the polyether-arms of the starting compound around itself in an intermediate complex and disposes the chain-ends to ring-closure. The *p*-methoxyphenyl substituent of the sugar is able to bend in the direction of the sodium cation and to stabilize this complex by the interaction of CH_3O group and Na^+.

In addition, the reactions to form macrocyclic compounds were performed under high dilution conditions. The low concentrations of reactants (3–4%) suppress the formation of acyclic oligomers with respect to cyclic products.

2.2. Synthesis of altropyranoside-based crown ethers

Methyl-2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**17**) was synthesised from sugar **16** by the method of Hicks and Fraser-Reid in one step (Scheme 4).[26] Using *N*-*p*-tosyl-imidazol and NaH in DMF, the yield of intermediate **17** was 44%. It is known that the oxirane ring of the anhydro sugars may be opened by reaction with nucleophilic agents (e.g., amines) when the amino sugar may be formed as a mixture of two isomers. The resulting new functionalities occupy the trans position and the ratio of the regioisomers depends on the structure and configuration of the starting epoxy sugar. The epoxides of rigid six-membered rings open up to place the new functionalities into a diaxial position according to the Fürst–Plattner rule.[27] Anhydro sugar **17** was reacted with ethanolamine at 140°C for 6 h to result in the formation of methyl 4,6-*O*-benzylidene-3-deoxy-3-(*N*-hydroxyethyl)amino-α-D-altropyranoside (**18**) by a regioselective ring opening (Scheme 4). The yield of product **18** was 79% after recrystallization.

The structure of compound **18** was proved by ^1H and ^{13}C NMR and on the basis of DEPT-135, COSY, HMQC, HMBC and H2BC spectra. The $J_{1,2} \leqslant 0.6$ Hz coupling constant of the H-1 (anomeric) proton shows that the methoxy group is in axial position in the dominant conformation of the molecule. However, the assignment of the crucial H-2 and H-3 signals and the corresponding carbon signals could not be done in the usual conventional way. The deduction of the coupling network cannot be started from H-1 because this signal practically has no coupling, and, furthermore, the H-2 proton also has a relatively weak coupling The C-2 and C-6 signals are isochronous and no signal separation could be detected at 11.47 T. Additionally, the C-3 and C-5 signals are also very close to each other. The structural determination was possible by applying the H2BC experiment[28,29] which is prominently useful in carbohydrate chemistry.[30] Correlation from H-2 and H-4 signals made it possible to assign the C-3 signal at 58.76 ppm and this chemical shift value indicates that C-3 has the nitrogen substituent. The analysis of the coupling constants shows that both H-2 and H-3 protons are equatorial and the 2-hydroxy and 3-hydroxyethylamino substituents occupy *trans*-diaxial positions. A further conclusion is that both H-4 and H-6_{ax} protons should be in axial position in the 1,3-dioxane ring and both of them have steric proximity with the H-7 signal, which was proven by the NOESY spectrum. The NOESY crosspeaks between H-4, H-6_{ax} and H-7 signals also serve as a proof for the axial position of the H-7 proton (and consequently, the equatorial position of the phenyl group) in the dominant conformation.

The amino sugar **18** was a suitable starting material for a few sugar-based azacrown ethers using ethylene glycol bistosylates as the ring forming reagents (Scheme 5).

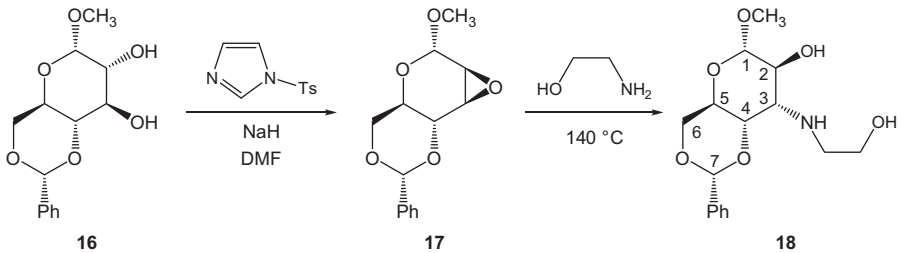
Using triethylene glycol ditosylate and tetraethylene glycol ditosylate in the presence of NaH in DMF, the 15-membered (**19**) and 18-membered (**20**) amino crown ethers were formed, respectively, in ca. 22% yield. The yields of the ring closure reactions are unusually low which may be due to the significant difference in the reactivity of the primary and secondary hydroxyl groups and therefore a lot of by-products may be also formed.

2.3. Application of the macrocycles in asymmetric synthesis

The crown compounds synthesized were tested as chiral phase transfer catalysts in a few asymmetric reactions. One of these reactions is the conjugate addition of diethyl acetamidomalonate (**22**) to *trans*-β-nitrostyrene (**21**) in the presence of chiral crown ethers **12–15** and **19–20** (Scheme 6).[31]

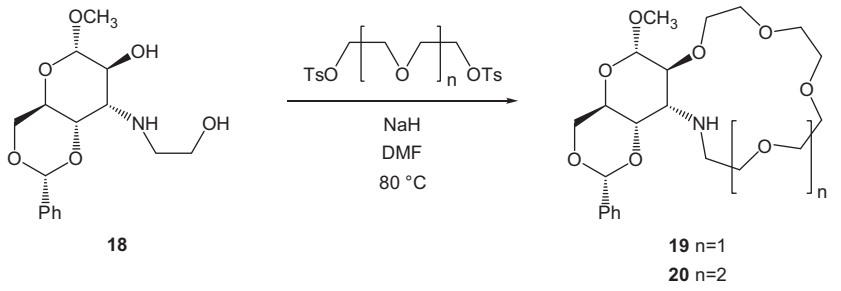
The Michael addition was carried out in a solid–liquid two-phase system employing 10 mol % of crown ether as the catalyst. The organic phase comprised of the starting materials and the catalyst in THF, while Na_2CO_3 used in twofold excess formed the solid phase. Product **23** was obtained by preparative TLC, while the optical purity was measured by chiral HPLC. The results are summarized in Table 1

As can be seen from Table 1, using catalysts **12–15**, **19** and **20**, the adduct **23** was formed in yields of 54–67%, but the ee values

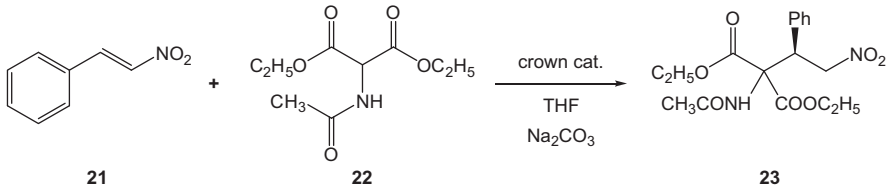


16 17 18

Scheme 4. Regioselective ring opening of the anhydrosugar **18** with ethanolamine.



Scheme 5. Synthesis of altrose-based crown-amines **19–20**.



Scheme 6. Addition of diethyl acetamidomalonate (**22**) to *trans*-β-nitrostyrene (**21**).

Table 1
Michael addition of diethyl acetamidomalonate (**22**) to *trans*-β-nitrostyrene (**21**) in the presence of catalyst **12–15** and **19–20**

Entry	Catalyst	Time (h)	Yield of **25**[a] (%)	$[\alpha]_D^{22}$[b]	ee[c] (%)
1	**12**	28	56	+7	20
2	**13**	24	67	−7.6	21
3	**14**	20	59	−35	80
4	**15**	21	56	−2	34
5	**19**	27	54	+11.7	26
6	**20**	21	41	0	0

[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, $c = 1$.
[c] Enantiomeric excesses were determined by chiral HPLC analysis in comparison with authentic racemic material.

were quite different. The macrocycles based on methyl-*ribo*-hexopyranoside (**12** and **13**) induced modest enantioselectivities of 20–21%. As the same time, there is a significant difference between the effect of the *p*-methoxyphenyl derivatives: lariat ether **15** with a methoxypropyl side arm induced an ee of 34%, while lariat ether **14** with a hydroxypropyl side arm brought about an ee of 80%. It seems that the substituent of the sugar moiety plays also a role in the discrimination of enantiomers. It is also possible that the heteroatom at the end of the substituent (e.g., O in the case of $–CH_2OC_6H_4–OCH_3$) takes also place in the formation of a transition complex. Overall, the properties of the side arm on the crown ring are of decisive importance.

The altrose-based monoaza-crown **19** induced only a modest enantioselectivity of ca. 26% and derivative **20** having a larger ring resulted in a racemic mixture. It is noteworthy that while catalysts **13–15** brought about the formation of the enantiomer with negative optical rotation (*S*), catalyst **12** with a hydroxypropyl side arm and the altropyranoside-based crown **19** induced the formation of the enantiomer with positive optical rotation (*R*).

2.4. Conclusion

The *ribo*-hexopyranosides with vicinal hydroxy groups (**4** and **7**) are key-intermediates in the synthesis of *ribo*-hexopyranoside-based macrocycles. Methyl 2,6-dideoxy-α-D-*ribo*-hexo-pyranoside (**4**) was prepared by the regio- and stereoselective opening of the 2,3-anhydro ring of compound **3** by $LiAlH_4$. The primary hydroxyl group of *ribo*-hexopyranoside **6** was successfully protected by the Mitsunobu reaction to afford compound **7**.

The opening of the epoxy ring of methyl-2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**17**) by ethanolamine took place in a regioselective manner to provide the 3-substituted altropyranoside derivative **18**.

From among the *ribo*-hexopyranoside-based lariat ethers, species **14** used as the catalyst induced an ee of 80% in the Michael addition of *trans*-β-nitrostyrene to diethyl acetamidomalonate. Altropyranoside-based crown ethers **19** and **20** were not found to be efficient enantioselective phase transfer catalysts.

The activity of the novel chiral macrocycles will be studied as catalysts in different asymmetric reactions.

3. Experimental

3.1. General procedures

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. NMR spectra were recorded on Bruker AV-300, DRX-500, and Varian Inova 500 instruments in $CDC1_3$ solution with TMS as the 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. 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.

3.2. Synthesis of chiral lariat ethers 12–15

Compound **1** was prepared acc. to lit.,[17] compound **2** to lit.[18,19]

3.2.1. Methyl-6-deoxy-2,3-anhydro-α-D-allopyranoside (3)

A solution of compound **2** (16.4 g, 68.4 mmol) in methanol (400 mL) containing triethyl amine (9.6 mL, 68.4 mmol) was stirred under an atmosphere of H_2 (10 bar) in the presence of Pd/C (4.9 g) at 60°C for 6 h. After cooling, the catalyst was filtered, and the filtrate concentrated in vacuo. The residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to give

3 (7.11 g, 65%). $[\alpha]_D^{22}$ +173.1 (*c* 1, $CHCl_3$). Lit.[32] $[\alpha]_D^{22}$ +165 (*c* 1, $CHCl_3$); mp: 98–99 °C; lit.[32] Mp: 99–100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm) 4.84 (d, *J* = 3 Hz, 1H), 3.68 (ddd, *J* = 15 Hz, 9 Hz, 6 Hz, 1H), 3.60–3.55 (m, 2H), 3.45 (s, 3H), 3.45–3.43 (m, 1H), 1.81 (br s, OH), 1.27 (d, *J* = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 94.68, 72.05, 66.14, 56.10, 54.90, 51.35, 17.65. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found C, 52.46; H, 7.60.

3.2.2. Methyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (4)

To a well-stirred solution of **3** (8.6 g, 53.7 mmol) in dry THF (100 mL) $LiAlH_4$ (4.10 g, 107.4 mmol) was added, then the mixture was refluxed for 16 h. After cooling, water (4 mL) was added dropwise with vigorous stirring. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel using $CHCl_3$/CH_3OH = 100:3 as an eluent to afford **4** (3.98 g, 46%); $[\alpha]_D^{22}$ +134.3 (*c* 1, CH_3OH). Lit.[20] $[\alpha]_D^{22}$ +126.5 (*c* 1, CH_3OH); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm) 4.59 (d, *J* = 3.5 Hz, 1H), 3.71 (ddd, *J* = 11.5 Hz, 5 Hz, 3.5 Hz, 1H), 3.50 (dq, *J* = 9 Hz, 6.5 Hz, 1H), 3.44 (s, 3H), 3.29 (ddd, *J* = 11 Hz, 9.5 Hz, 4.5 Hz, 1H), 2.19 (dt, *J* = 11,5 Hz, 5 Hz, 1H), 1.76 (br s, 2 OH), 1.64 (q, *J* = 11.5 Hz, 1H), 1.26 (d, *J* = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 97.30, 72.40, 66.40, 64.17, 55.28, 35.07, 17.62. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found C, 51.80; H, 8.73.

3.2.3. Tetrabutylammonium borohydride[21]

Tetrabutylammonium hydrogensulphate (13.58 g, 40.0 mmol) was dissolved in water (12 mL) and 5 M aqueous NaOH solution (10 mL) was added, then the mixture was cooled to rt and $NaBH_4$ (1.66 g, 44 mmol) was added during vigorous shaking. After all of the $NaBH_4$ was dissolved, the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried over K_2CO_3, then evaporated. The residue was crystallized from ethyl-acetate to give the product (10.39 g, 91%). Mp: 125–127 °C, Lit.[21] Mp: 125–127 °C.

3.2.4. Methyl-2-deoxy-4,6-*O*-benzilidene-α-D-*ribo*-hexopyranoside (5)[22]

A mixture of compound **1** (29.76 g, 0.113 mol) and tetrabutylammonium borohydride (87 g, 0.34 mol) in dry benzene (700 mL) was stirred and refluxed for 12 h. After cooling, the mixture was washed with water (3 × 150 mL), the organic phase was dried, then concentrated under reduced pressure. The residue was recrystallized from EtOAc to give **5** (17.64 g, 59%) as a solid. $[\alpha]_D^{22}$ +140 (*c* 2, $CHCl_3$); Lit.[33] $[\alpha]_D^{22}$ +141 (*c* 2.2, $CHCl_3$); Mp: 130–132 °C Lit.[33] Mp:130–131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm) 7.53–7.49 (m, 2H), 7.38–7.33 (m, 3H), 5.63 (s, 1H), 4.79 (d, *J* = 4 Hz, 1H), 4.33 (dd, *J* = 10 Hz, 5 Hz, 1H), 4.24 (td, *J* = 10 Hz, 5 Hz, 1H), 4.2–.17 (m, 1H), 3.76 (t, *J* = 10 Hz, 1H), 3.61 (dd, *J* = 10 Hz, 3 Hz, 1H), 3.41 (s, 3H), 3.01 (br s, OH), 2.20 (dd, *J* = 15 Hz, 2.5 Hz, 1H), 2.01 (dt, *J* = 15 Hz, 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 137.90, 128.83, 128.19, 126.25, 101.99, 98.38, 78.81, 68.93, 64.31, 58.15, 55.30, 35.26. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found C, 63.11; H, 6.83.

3.2.5. Methyl-2-deoxy-α-D-*ribo*-hexopyranoside (6)

A solution of **5** (14.66 g, 55 mmol) in a mixture of CH_2Cl_2 (80 mL) and CH_3OH (40 mL) was stirred under H_2 (10 bar) in the presence of Pd/C (2.2 g) at rt for 3.5 h. The catalyst was filtered, and the filtrate was concentrated in vacuo to give **6** (9.78 g, 99%) as a white solid; $[\alpha]_D^{22}$ +143 (*c* 1, $CHCl_3$); Lit.[23] $[\alpha]_D^{22}$ +143.1 (*c* 1, $CHCl_3$); Mp: 97–98 °C; Lit.[23] 98–99 °C. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm) 4.83 (d, *J* = 3 Hz, 1H), 4.02–3.98 (m, 1H), 3.93 (dd, *J* = 11.5 Hz, 3.5 Hz, 1H), 3.86 (dd, *J* = 11.5 Hz, 5 Hz, 1H), 3.72–3.67 (m, 1H), 3.50 (dd, *J* = 10.5 Hz, 3.5 Hz, 1H), 3.39 (s, 3H), 2.75 (br s, OH), 2.26 (br s, OH), 2.19 (dd, *J* = 14.5 Hz, 2.5 Hz, 1H), 2.10 (br s, OH), 1.91 (dt, *J* = 14.5 Hz, 3.5 Hz, 1H). ^{13}C NMR (D_2O, 75 MHz), δ (ppm): 100.93, 74.88, 73.83, 70.86, 63.41, 57.30, 39.32. Anal. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found C, 47.20; H, 7.90.

3.2.6. Methyl-2-deoxy-6-*O*-(4-methoxyphenyl)-α-D-*ribo*-hexopyranoside (7)

A mixture of **6** (4.4 g, 24.8 mmol), PPh_3 (16.26 g, 62 mmol), 4-methoxyphenol (15.4 g, 124 mmol) and diisopropyl-azodicarboxylate (12.21 mL, 62 mmol) in dry THF (200 mL), was stirred and refluxed under Ar atmosphere for 28 h. Then PPh_3 (6.51 g, 24.8 mmol) and diisopropyl-azodicarboxylate (4.88 mL, 24.8 mmol) were added and the mixture was refluxed for an additional 14 h. After cooling the solvent was evaporated, and the residue was purified by flash chromatography on silica gel using $CHCl_3$ as an eluent, then the pure product was isolated by repeated column chromatography on silica gel (hexane/EtOAc = 10:5) to give the product **7** (4.22 g, 60%) as a solid; mp: 44–48°C; $[\alpha]_D^{22}$ +113,7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 6.91 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.88 (d, *J* = 3 Hz, 1H), 4.34 (dd, *J* = 9.1 Hz, 5.6 Hz, 1H), 4.17 (dd, *J* = 9.1 Hz, 5.6 Hz, 1H), 4.03 (m, 1H), 3.94 (m, 1H), 3.76 (s, 3H), 3.58 (ddd, *J* = 10.7 Hz, 10.7 Hz, 3 Hz, 1H), 3.45 (d, *J* = 9.4 Hz, OH), 3.41 (s, 3H), 2.71 (d, *J* = 10 Hz, OH), 2.20 (dd, *J* = 15.1 Hz, 3 Hz, 1H), 1.98 (ddd, *J* = 15.1 Hz, 3 Hz, 3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 154.03, 153.08, 115.88, 114.59, 96.46, 68.68, 67.57, 67.32, 66.94, 55.72, 55.33, 34.74. HRMS calcd for $C_{14}H_{20}O_6$ 284.1260 found 284.1257.

3.2.7. General method for the preparation of compounds 8 and 9

A solution of compound **4** (3.98 g, 24.6 mmol) or **7** (6.99 g, 24.6 mmol) and tetrabutylammonium hydrogensulphate (8.34 g, 24.6 mmol) in bis(2-chloroethyl)ether (81 mL, 0.69 mol) was vigorously stirred with 50% aqueous NaOH solution (81 mL) at rt for 14 h. Then the mixture was poured into a mixture of CH_2Cl_2 (200 mL) and water (200 mL) and the phases were separated. The water layer was extracted with CH_2Cl_2 (2 × 100 mL), the combined organic layer was washed with water (80 mL), dried ($MgSO_4$) and the solvent was evaporated. The remaining bis(2-chloroethyl)ether was removed by vacuum distillation. The crude product was purified by column chromatography on silica gel (in the case of **8** $CHCl_3$, in the case of **9** hexane/EtOAc = 1:1 were eluents) to give product **8** and **9** as yellow syrups.

3.2.7.1. Methyl-2,6-dideoxy-3,4-bis[(2-chloroethoxy)ethyl]-α-D-*ribo*-hexopyranoside (8). Yield: 4.16 g, (45%); $[\alpha]_D^{22}$ +142 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm) 4.69 (d, *J* = 3 Hz, 1H), 3.77–3.72 (m, 5H), 3.70–3.64 (m, 5H), 3.64–3.60 (m, 6H), 3.59–3.54 (m, 1H), 3.50 (ddd, *J* = 12 Hz, 4.5 Hz, 3.5 Hz, 1H), 3.41 (s, 3H), 3.02 (ddd, *J* = 11 Hz, 9.5 Hz, 4.5 Hz, 1H), 2.30 (dt, *J* = 11.5 Hz, 4.5 Hz, 1H), 1.72 (q, *J* = 11.5 Hz, 1H), 1.24 (d, *J* = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 97.35, 72.42, 71.73, 71.27, 71.18, 71.10, 70.71, 70.35, 66.31, 64.10, 55.30, 42.82, 42.71, 35.03, 17.66. HRMS calcd for $C_{15}H_{28}Cl_2O_6$ 374.1263 found 374.1260.

3.2.7.2. Methyl-2-deoxy-6-*O*-(4-methoxyphenyl)-3,4-bis[(2-chloroethoxy)ethyl]-α-D-*ribo*-hexopyranoside (9). Yield: 6.36 g (52%); $[\alpha]_D^{22}$ +93,3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm) 6.90 (d, *J* = 9 Hz, 2H), 6.82 (d, *J* = 9 Hz, 2H), 4.76 (d, *J* = 4.5 Hz, 1H), 4.31–4.26 (m, 1H), 4.20 (dd, *J* = 10 Hz, 3.5 Hz, 1H), 4.16 (dd, *J* = 10 Hz, 2 Hz, 1H), 4.05 (dd, *J* = 6.5 Hz, 3 Hz, 1H), 3.83–3.77 (m, 4H), 3.76 (s, 3H), 3.74–3.76 (m, 11H), 3.50 (t, *J* = 6 Hz, 2H), 3.34 (s, 3H), 2.23 (dd, *J* = 15 Hz, 2.5 Hz, 1H), 1.83 (dt, *J* = 15 Hz, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 154.06, 153.12, 115.85, 114.50, 96.51, 71.80, 71.33, 71.24, 71.18, 70.72, 70.31, 68.62, 67.55, 67.30, 66.88, 55.70, 55.35, 42.85, 42.74, 34.78. HRMS calcd for $C_{22}H_{34}Cl_2O_8$ 496.1631 found 469.1634.

3.2.8. General method for the preparation of compounds 10 and 11

A mixture of bis-chloro derivative **8** or **9** (11 mmol) and NaI (6.60 g, 44 mmol) in dry acetone (120 mL) was stirred under reflux for 40 h. After cooling, the precipitate was filtered and washed with acetone. The combined acetone solutions were evaporated in vacuum. The residue was dissolved in a mixture of $CHCl_3$ (80 mL) and water (80 mL), the layers were separated and the organic phase was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded the products **10** and **11** as yellow oils, which were used without further purification.

3.2.8.1. Methyl-2,6-dideoxy-3,4-bis[(2-iodoethoxy)ethyl]-α-D-*ribo*-hexopyranoside (10). Yield: 6.08 g (99%); $[\alpha]_D^{22}$ +59.6 (*c* 1, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm) 4.70 (d, *J* = 3 Hz, 1H), 3.79–3.72 (m, 5H), 3.70–3.61 (m, 7H), 3.58–3.49 (m, 2H), 3.42 (s, 3H), 3.26 (td, *J* = 6.6 Hz, 2.1 Hz, 4H), 3.04 (ddd, *J* = 10.8 Hz, 9.4 Hz, 4.2 Hz, 1H), 2.30 (dt, *J* = 11.4 Hz, 4.5 Hz, 1H), 1.73 (q, *J* = 11.7 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 97.38, 72.40, 71.76, 71.29, 71.20, 71.11, 70.72, 70.33, 66.32, 64.09, 55.31, 35.07, 17.68, 3.17, 3.11. HRMS calcd for $C_{15}H_{28}I_2O_6$ 557.9975 found 557.9971.

3.2.8.2. Methyl-2-deoxy-6-*O*-(4-methoxyphenyl)-3,4-bis[(2-iodoethoxy)ethyl]-α-D-*ribo*-hexopyranoside (11). Yield: 7.41 g (99%); $[\alpha]_D^{22}$ +64.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm) 6.90 (d, *J* = 9 Hz, 2H), 6.83 (d, *J* = 9 Hz, 2H), 4.76 (d, *J* = 4.2 Hz, 1H), 4.33–4.26 (m, 1H), 4.21 (dd, *J* = 10.2 Hz, 3.6 Hz, 1H), 4.16 (dd, *J* = 10.2 Hz, 2.1 Hz, 1H), 4.07 (dd, *J* = 6 Hz, 3.1 Hz, 1H), 3.84–3.77 (m, 4H), 3.77 (s, 3H), 3.75–3.54 (m, 9H), 3.35 (s, 3H), 3.27 (t, *J* = 6.9 Hz, 2H), 3.12 (t, *J* = 6.9 Hz, 2H), 2.23 (dd, *J* = 15 Hz, 3 Hz, 1H), 1.84 (dt, *J* = 15 Hz, 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 154.02, 153.16, 115.88, 114.47, 96.52, 71.78, 71.30, 71.26, 71.15, 70.74, 70.27, 68.63, 67.59, 67.28, 66.86, 55.71, 55.32, 34.77, 3.16, 3.10.

HRMS calcd for $C_{22}H_{34}I_2O_8$ 680.0343 found 680.0338.

3.2.9. General method for the preparation of lariat ethers 12–15

A mixture of anhydrous Na_2CO_3 (3.43 g, 32.4 mmol), the corresponding primary amine: 3-hydroxypropylamine (0.41 mL, 5.4 mmol) or 3-methoxypropylamine (0.44 mL, 5.4 mmol) and bis-iodo compound **10** or **11** (5.4 mmol) in dry acetonitrile (90 mL) was stirred and refluxed for 30–40 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 ($MgSO_4$), and the solvent was evaporated. The crude monoaza-lariat ethers (**12–15**) were purified by column chromatography on silica gel using $CHCl_3/CH_3OH$ (100:5–100:10) as an eluent.

3.2.9.1. Metyl-2,3,4,6-tetradeoxy-α-D-*ribo*-hexopyranosido-[3,4-*h*]-*N*-(3-hydroxy)propyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (12). Yield: 0.93 g (46%); $[\alpha]_D^{22}$ +78.5 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz), δ (ppm) 4.90 (br s, OH), 4.60 (d, *J* = 3 Hz, 1H), 3.91 (td, *J* = 12 Hz, 4 Hz, 2H), 3.79 (t, *J* = 5 Hz, 2H), 3.67–3.56 (m, 9H), 3.55–3.49 (m, 3H), 3.41 (s, 3H), 3.16 (td, *J* = 10 Hz, 4 Hz, 1H), 2.84–2.73 (m, 4H), 2.67 (t, *J* = 5.5 Hz, 2H), 2.58–2.53 (m, 1H), 1.73–1.64 (m, 3H), 1.23 (d, *J* = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 97.59, 80.07, 73.01, 72.70, 70.05, 69.91, 69.32, 69.30, 69.27, 67.61, 63.88, 56.52, 54.75, 54.68, 54.26, 31.40, 28.29, 17.63; MS (EI): 378.3 $[M+H]^+$ 400.3 $[M+Na]^+$; HRMS calcd for $C_{18}H_{35}NO_7$ 377.2414 found 377.2410. Anal. Calcd for $C_{18}H_{35}NO_7$: C, 57.27; H, 9.35. Found C, 57.32; H 9.41.

3.2.9.2. Metyl-2,3,4,6-tetradeoxy-α-D-*ribo*-hexopyranosido-[3,4-*h*]-*N*-(3-methoxy)propyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (13). Yield: 0.63 g (30%). $[\alpha]_D^{22}$ +128.7 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz), δ (ppm): 4.60 (d, *J* = 3 Hz, 1H), 3.90 (td, *J* = 12 Hz, 4 Hz, 2H), 3.66–3.50 (m, 12H), 3.43–3.41 (m, 1H), 3.41 (s, 3H), 3.33 (s, 3H), 3.18 (td, *J* = 10.5 Hz, 4 Hz, 1H), 2.87–2.80 (m, 2H), 2.79–2.71 (m, 2H), 2.59–2.53 (m, 3H), 1.77–1.67 (m, 4H), 1.24 (d, *J* = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 97.50, 79.95, 73.00, 72.63, 70.94, 70.39, 70.27, 69.86, 69.69, 69.33, 67.66, 58.60, 54.70, 54.43, 54.38, 52.04, 31.55, 27.42, 17.65; MS (EI): 392.2 $[M+H]^+$, 414.2 $[M+Na]^+$.

HRMS calcd for $C_{19}H_{37}NO_7$ 391.2570 found 391.2573. Anal. Calcd for $C_{19}H_{37}NO_7$: C, 58.29; H, 9.53. Found C, 58.34; H, 9.47.

3.2.9.3. Methyl-6-*O*-(4-methoxyphenyl)-2,3,4-trideoxy-α-D-*ribo*-hexopyranosido-[3,4-*h*]-*N*-(3-hydroxy)propyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (14). Chromatography on silica gel using $CHCl_3$:CH_3OH = 100:7 as an eluent to afford **14** (2.13 g, 79%). $[\alpha]_D^{22}$ +137.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz), δ (ppm): 6.89 (d, *J* = 9 Hz, 2H), 6.81 (d, *J* = 9 Hz, 2H), 4.95 (br s, OH), 4.74 (d, *J* = 4 Hz, 1H), 4.34 (d, *J* = 9.5 Hz, 1H), 4.21 (dd, *J* = 10 Hz, 4 Hz, 1H), 4.16–4.11 (m, 2H), 3.91–3.83 (m, 2H), 3.81–3.74 (m, 6H), 3.72–3.45 (m, 12H), 3.33 (s, 3H), 2.87–2.56 (m, 5H), 2.24 (dd, *J* = 15 Hz, 2 Hz, 2H), 1.76 (dt, *J* = 15 Hz, 4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 153.84, 153.28, 115.78, 114.52, 97.97, 75.49, 71.22, 70.46, 70.29, 69.29, 68.96, 68.61, 68.51, 68.14, 65.79, 63.79, 56.52, 55.70, 55.17, 54.27, 54.20, 31.74, 28.41; MS (EI): 500.2 $[M+H]^+$, 522.0 $[M+Na]^+$

HRMS calcd for $C_{25}H_{41}NO_9$ 499.2781 found 499.2785. Anal. Calcd for $C_{25}H_{41}NO_9$: C, 60.10; H, 8.27. Found C, 60.06; H, 8.21.

3.2.9.4. Methyl-6-*O*-(4-methoxyphenyl)-2,3,4-trideoxy-α-D-*ribo*-hexopyranosido-[3,4-*h*]-*N*-(3-methoxy)propyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (15). Yield: 2.32 g (84%); $[\alpha]_D^{22}$ +120 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz), δ (ppm): 6.93 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.75 (d, *J* = 3.5 Hz, 1H), 4.49 (dd, *J* = 18 Hz, 10.5 Hz, 1H), 4.33–4.08 (m, 3H), 3.95–3.78 (m, 6H), 3.76 (s, 3H), 3.72–3.45 (m, 11H), 3.37 (s, 3H), 3.33 (s, 3H), 2.83–2.75 (m, 2H), 2.71–2.64 (m, 2H), 2.59–2.52 (m, 1H), 2.36–2.22 (m, 1H), 1.91–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 153.88, 153.16, 115.72, 114.55, 97.96, 75.85, 71.27, 70.78, 70.74, 70.22, 69.58, 69.39, 68.30, 68.26, 68.05, 65.78, 58.65, 55.70, 55.27, 54.70, 53.75, 53.70, 31.89, 27.18; MS (EI): 514.3 $[M+H]^+$, 536.2 $[M+Na]^+$; HRMS calcd for $C_{26}H_{43}NO_9$ 513.2938 found 513.2935. Anal. Calcd for $C_{26}H_{43}NO_9$: C, 60.80; H 8.44. Found C, 60.84; H 8.50.

3.3. Synthesis of altrose-based monoaza-15-crown-5 compounds (19–20)

3.3.1. Methyl-2,3-anhydro-4,6-*O*-benzilidene-α-D-mannopyranoside (17)[26]

Suspension of 60% NaH (4.2 g, 0.105 mol) was washed with dry hexane to remove the paraffin, and then was added to dry DMF (400 mL). To this suspension **16** (14.1 g, 0.05 mol) was added and the mixture was stirred for 1 h, then *N*-*p*-toluenesulfonyl imidazole (11.91 g, 0.054 mol) was added. After stirring for 2 h at rt the mixture was poured into ice-water (2000 mL). The precipitate was filtered and washed with water until the filtrate remained colourless. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc = 2:1 as an eluent to afford **17** (5.76 g, 44%); $[\alpha]_D^{22}$ +104 (*c* 1, $CHCl_3$); Lit.[35] $[\alpha]_D^{22}$ +103 (*c* 1, $CHCl_3$); Mp: 148 °C

^1H NMR ($CDCl_3$, 500 MHz), δ (ppm) 7.51–7.48 (m, 2H), 7.41–7.36 (m, 3H), 5.57 (s, 1H), 4.90 (s, 1H), 4.26 (d, *J* = 5.5 Hz, 1H), 3.76–3.66 (m, 3H), 3.49–3.47 (m, 1H), 3.47 (s, 3H), 3.17 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 137.80, 129.21, 128.30, 126.29, 102.02, 98.29, 78.80, 68.95, 66.98, 55.85,

54.81, 51.69. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H 6.10. Found C, 63.62; H 6.11.

3.3.2. Methyl-4,6-*O*-benzilidene-3-deoxy-3-(*N*-hydroxyethyl)amino-α-D-altropyranoside (18)

The mixture of freshly distillated ethanolamine (2.95 mL, 49.0 mmol) and **17** (1 g, 3.8 mmol) was stirred at 140°C under Ar for 5 h. After cooling, water (8 mL) was added, than the mixture was extracted with $CHCl_3$ (3 × 10 mL), the combined organic layer was washed with brine (5 mL), dried and concentrated in vacuo. The crude product was crystallized from diisopropylether–ethanol 6:1 to provide **18** (0.98 g, 79%); $[\alpha]_D^{22}$ +137 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.48 (m, 2H), 7.38 (m, 1H), 7.36 (m, 2H), 5.61 (s, 1H), 4.63 (s, 1H), 4.31 (dd, *J* = 10 Hz, 5 Hz, 1H), 4.24 (ddd, *J* = 10 Hz, 9.4 Hz, 5 Hz, 1H), 4.08 (dd, *J* = 9.4 Hz, 3.8 Hz, 1H), 4.00 (d, *J* = 3.1 Hz, 1H), 3.79 (dd, *J* = 10 Hz, 10 Hz, 1H), 3.51 (m, 2H), 3.42 (s, 3H), 3.20 (dd, *J* = 3.8 Hz, 3.1 Hz, 1H), 2.99 (ddd, *J* = 13.2 Hz, 8,5 Hz, 4 Hz, 1H), 2.77 (ddd, *J* = 13.2 Hz, 8,5 Hz, 4 Hz, 1H), 2.32 (br s, NH), 1.74 (br s, 2 OH);

^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 137.58, 129.42, 128.57, 126.38, 102.49, 102.45, 76.69, 69.63, 61.58, 59.11, 58.76, 55.89, 49.36.

MS (EI): 326.3 $[M+H]^+$, 348.4 $[M+Na]^+$; HRMS calcd for $C_{16}H_{23}NO_6$ 325.1525 found 325.1526. Anal. Calcd for $C_{16}H_{23}NO_6$: C, 59.06; H 7.13. Found C, 59.12; H, 7.18.

3.3.3. Methyl-4,6-*O*-benzilydene-2,3-dideoxy-α-D-altropyranosido-[2,3-*k*]-1,4,7,10-tetraoxa-13-azacyclopentadecane (19)

To a solution of **18** (1.30 g, 4 mmol) in dry DMF (40 mL) was added 60% NaH (0.96 g, 24 mmol) (previously washed with dry hexane to remove the paraffin) under Ar and the mixture was stirred at 80°C for 4 h. Then triethylene glycol ditosylate[34] (1.83 g, 4 mmol) was added, and the mixture was stirred at 80°C for 50 h. The solvent was removed by vacuum distillation, the residue was dissolved in a mixture of $CHCl_3$ and water, the water layer was extracted with $CHCl_3$ (3 × 20 mL), the combined organic phase was dried and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using $CHCl_3/CH_3OH$ = 100:2 as an eluent to give **19** (0.37 g, 21%); $[\alpha]_D^{22}$ +53.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm) 7.48 (dd, *J* = 7.5 Hz, 2 Hz, 2H), 7.37–7.32 (m, 3H), 5.57 (s, 1H), 4.64 (s, 1H), 4.28 (dd, *J* = 10 Hz, 5 Hz, 1H), 4.17 (td, *J* = 10 Hz, 5 Hz, 1H), 3.99 (dd, *J* = 9.5 Hz, 4 Hz, 1H), 3.92–3.84 (m, 1H), 3.86–3.83 (m, 1H), 3.79 (t, *J* = 10 Hz, 1H), 3.73–3.69 (m, 2H), 3.69–3.65 (m, 4H), 3.65–3.59 (m, 8H), 3.40 (s, 3H), 3.03 (t, *J* = 10 Hz, 2H), 1.87 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 137.99, 128.81, 128.15, 126.23, 101.98, 100.29, 78.86, 77.73, 72.16, 71.71, 71.20, 70.98, 70.87, 70.14, 69.64, 69.45, 58.54, 55.58, 48.03; MS (EI): 440.1 $[M+H]^+$ 462.0 $[M+Na]^+$.

HRMS calcd for $C_{22}H_{33}NO_8$ 439.2206 found 439.2210. Anal. Calcd for $C_{22}H_{33}NO_8$: C, 60.12; H, 7.57. Found C, 60.08; H, 7.61.

3.3.4. Methyl-4,6-*O*-benzilydene-2,3-dideoxy-α-D-altropyranosido-[2,3-*n*]-1,4,7,10,13-pentaoxa-16-azacyclopentadecane (20)

To a solution of **18** (0.98 g, 3 mmol) in dry DMF (40 mL) was added 60% NaH (0.72 g, 18 mmol) (previously washed with dry hexane to remove the paraffin) under Ar and the mixture was stirred at 80°C for 4 h. Then tetraethylene glycol ditosylate[34] (1.51 g, 3 mmol) was added, and the mixture was stirred at 80°C for 50 h. The solvent was removed by vacuum distillation, the residue was dissolved in a mixture of $CHCl_3$ and water, the water layer was extracted with $CHCl_3$ (3 × 20 mL), the combined organic phase was dried and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using $CHCl_3/CH_3OH$ = 100:1 as an eluent to afford **20** (0.32 g, 22%). $[\alpha]_D^{22}$ +101 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.48 (dd, *J* = 7.5 Hz, 2 Hz, 2H), 7.36–7.32 (m, 3H), 5.57 (s, 1H), 4.67 (d, *J* = 3.5 Hz, 1H), 4.28 (dd, *J* = 10 Hz, 5 Hz, 1H), 4.21–4.15 (m, 1H), 3.98 (dd, *J* = 10 Hz, 4 Hz, 1H), 3.87–3.56 (m, 20H), 3.46–3.44 (m, 1H), 3.40 (s, 3H), 2.99 (t, *J* = 5 Hz, 2H), 1.90 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 137.94, 128.87, 128.16, 126.29, 102.08, 100.80, 78.30, 77.39, 71.44, 71.02, 70.94, 70.88, 70.82, 70.67, 70.46, 69.53, 69.46, 58.65, 55.56, 48.33; MS (EI): 484.2 $[M+H]^+$ 506.1 $[M+Na]^+$; HRMS calcd for $C_{24}H_{37}NO_9$ 483.2468 found 483.2470. Anal. Calcd for $C_{24}H_{37}NO_9$: C, 59.61; H 7.71. Found C, 59.63; H, 7.68.

3.4. General procedure for the Michael addition[31]

trans-β-Nitrostyrene **21** (0.15 g, 1 mmol), diethyl acetamidomalonate **22** (0.33 g, 1.5 mmol) and the appropriate crown (0.1 mmol) were dissolved in anhydrous THF (3 mL) and dry Na_2CO_3 (2.08 mmol) was added. The reaction mixture was stirred at room temperature. After completion of the reaction (20 h), the organic phase was concentrated in vacuo and the residue was dissolved in toluene (10 mL) and washed with cold 10% HCl (3 × 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 an eluent. Enantiomeric excesses were determined by chiral HPLC analysis using a Chiralpack AD column (hexane/isopropanol 85:15, 0.8 mL/min, 220 nm) t_R = 17.8 min (major), t_R = 27.7 min (minor). Yield of **23** 59%; $[\alpha]_D^{22}$ −35.9 (*c* 1, $CHCl_3$, 80% ee). M.p. 135–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.69 (br s, NH), 5.50 (dd, *J* = 21.7, 12.2 Hz, 1H), 4.71–4.59 (m, 2H), 4.29 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.24 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.15 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.03 (dq, *J* = 10.7, 7.2 Hz, 1H), 2.12 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).[31]

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