Synthesis of novel chiral crown ethers derived from D-glucose and their application to an enantioselective Michael reaction

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

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

Received (in Cambridge, UK) 13th July 1999, Accepted 3rd November 1999

New chiral monoaza-15-crown-5 derivatives anellated to methyl 4,6-di-*O*-butyl-α-D-glucopyranoside have been synthesized from **1** using the 4,6-*O*-benzylidene protecting group (removed by acetic acid) and 2,3-di-*O*-benzyl groups (removed by catalytic hydrogenolysis). The alkylation of the hydroxy groups in **1** and **5** with benzyl chloride and bis(2-chloroethyl) ether, respectively, were carried out in two-phase reactions using phase-transfer (PT) catalysts. These sugar-based crown ethers showed significant asymmetric induction as chiral PT catalysts in the Michael addition of 2-nitropropane to chalcone (90% ee). The substituent at the nitrogen atom of the crown ethers has a major influence on both the chemical yield and the enantioselectivity.

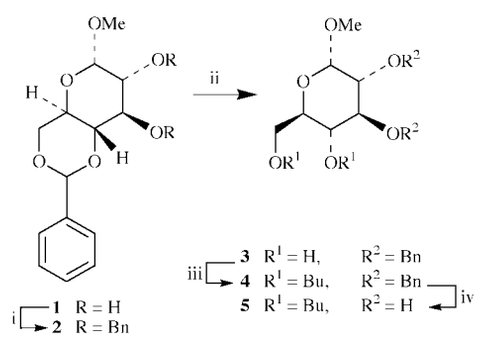
Introduction

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral crown ether catalysts. A number of chiral crown ethers have been employed as chiral catalysts in phase-transfer reactions.[1] A variety of such macrocycles have been synthesized and much attention was focussed on systems derived from carbohydrates. Crown ethers anellated to different pyranosidic or furanosidic carbohydrates have also been described.[2] The carbohydrate-containing chiral crown ethers have proved to be suitable models for the study of chiral induction in enantioselective reactions. Although many chiral crown ethers having different carbohydrate moieties have been synthesized in recent years, only a few have successfully been applied as catalysts in asymmetric reactions.[1]

The Michael reaction is one of the most important C–C bond-forming reactions, and stereoselective variants have been extensively investigated in recent years.[3] High asymmetric inductions have been reported in the Michael addition of methyl phenylacetate to methyl acrylate catalyzed by carbohydrate-containing chiral crown ethers.[4–8] We have previously reported the synthesis of new 15-membered-ring monoaza-crown ethers from glucose and galactose[9] and their application as chiral phase-transfer (PT) catalysts in an asymmetric Michael addition and in a Darzens condensation.[10,11] We first began investigating the Michael addition of 2-nitropropane to a chalcone catalyzed by chiral macrocyclic polyethers under phase-transfer conditions. The best result achieved in this reaction was 60% enantiomeric excess (ee) in the presence of monoaza-15-crown-5 ether containing a methyl 4,6-*O*-benzylidene-α-D-glucopyranoside unit,[11] and 82% ee generated by the crown catalyst anellated to phenyl β-D-glucopyranoside, respectively.[12] The chiral nature of the crown ether, the rigidity of the micro-environment of its cavity, the quality of the side arm attached to the nitrogen atom and the substituents on the sugar unit are all expected to play an important role. We have found that the presence of butyl substituents on the glucopyranose unit had an advantageous effect on both the chemical yield and the enantioselectivity. We have reported, in a preliminary communication, that use of the monoaza-crown ether containing a methyl 4,6-di-*O*-butyl-α-D-glucopyranoside unit (**13**, *N*-unsubstituted compound) as chiral PT catalyst resulted in 90% ee in the reaction of 2-nitropropane and chalcone.[13] In this paper we report the full details of this work and additionally discuss the synthesis and properties of a series of *N*-substituted analogues **8**–**11** (which in the event proved to be less effective than the *N*-substituted original).

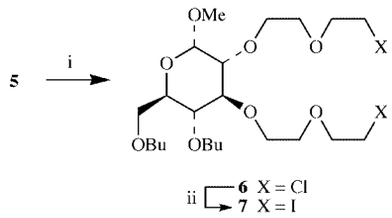
Results and discussion

The general synthetic procedures for compounds **2**–**7** are summarized in Schemes 1 and 2.



Scheme 1 Synthesis of methyl 4,6-di-*O*-butyl-α-D-glucopyranoside **5** from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **1**. *Reagents and conditions*: i, benzyl chloride, 50% aq. NaOH, NBu_4Br, rt; ii, 96% CH_3CO_2H, reflux; iii, NaH, BuBr, DMF, rt; iv, 5% Pd/C EtOH, 50 °C.

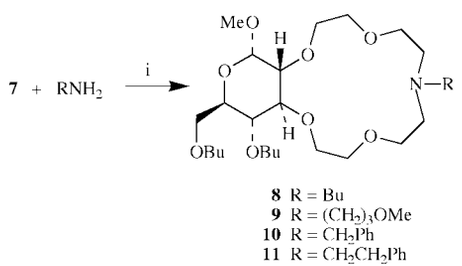
The vicinal free hydroxy groups in methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **1** were treated with benzyl chloride, under PT conditions, in the presence of tetrabutylammonium hydroxide (PT catalyst). The reaction was carried out in a mixture of benzyl chloride (as reagent and solvent) and 50% aq. sodium hydroxide (10 h, room temp.) and we obtained the 2,3-di-*O*-benzyl ether **2** in a better yield (85%) than that obtained by the conventional method (in benzyl chloride, in the presence of powdered potassium hydroxide).[14] Removal of the 4,6-*O*-benzylidene group in compound **2** was effected by aq. acetic acid (2 h, 100 °C),[15] yielding the derivative **3** in 78% yield.[16] Alkylation of the two hydroxy groups in **3** with butyl bromide



Scheme 2 Synthesis of bisiodo podand **7** from compound **5**. *Reagents and conditions*: i, $O(CH_2CH_2Cl)_2$, 50% aq. NaOH, NBu_4Br, rt; ii, NaI, acetone, reflux.

in DMF, in the presence of sodium hydride (48 h, room temp.) afforded the 4,6-di-*O*-butyl derivative **4** in 74% yield. The benzyl protecting groups in **4** were removed by catalytic hydrogenolysis over palladium (5% Pd/C) in ethanol solution (12 h; 50 °C), giving compound **5** in quantitative yield.

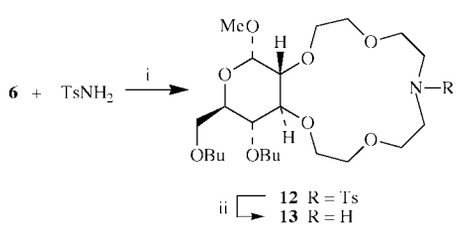
The hydroxy groups in **5** were alkylated by the method of Gross[17] with bis-(2-chloroethyl) ether as reagent and solvent (Scheme 2). The liquid–liquid two-phase reaction using tetrabutylammonium bromide as PT catalyst and 50% aq. sodium hydroxide gave rise to the bischloro podand **6** (8 h, room temp.) in 44% yield after chromatography. Exchange of the chlorines in **6** by iodines was carried out using sodium iodide in acetone (reflux, 40 h), yielding the bisiodo derivative **7**. Compound **7** was cyclized with various primary amines: *n*-butylamine, 3-methoxypropylamine, benzylamine and 2-phenylethylamine according to the method described previously[9] (Scheme 3). The method requires dry sodium carbonate in acetonitrile



Scheme 3 Synthesis of crown ethers **8**–**11** from **7**. *Reagents and conditions*: i, primary amines (*n*-butylamine to **8**, 3-methoxypropylamine to **9**, benzylamine to **10**, and 2-phenylethylamine to **11**), Na_2CO_3, CH_3CN, reflux.

as solvent (reflux, 32–40 h). In dilute solutions (1–3%) polycondensation side-reactions are suppressed and the desired intramolecular cyclization reaction takes place preferentially. In this way we obtained the 15-membered monoaza-crown ethers **8**–**11** in moderate yields starting from **7** and the corresponding primary amine. The yields of the ring-closure product, after purification by chromatography, varied from 40–46%.

The unsubstituted monoaza-crown ether **13** was synthesized by the method we described in our preliminary communication[13] (Scheme 4). The chiral starting macrocycle **12** needed for the preparation of the unsubstituted derivative **13** was obtained from the bischloro podand **6** by treatment with one molar equivalent of toluene-*p*-sulfonamide in DMF [in dilute



Scheme 4 Synthesis of crown ether **13** from **6**. *Reagents and conditions*: i, $TsNH_2$, K_2CO_3, DMF, reflux; ii, 4% Na/Hg_x, Na_2HPO_4, MeOH, reflux.

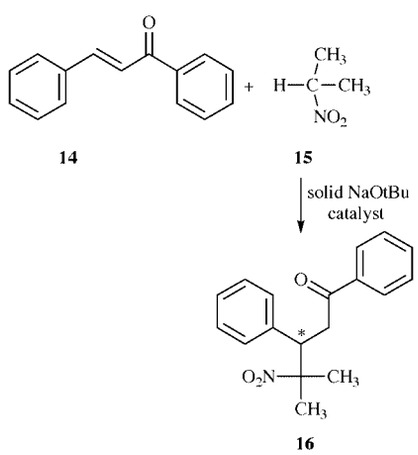
Table 1 Addition of 2-nitropropane to chalcone catalyzed by crown ethers **8**–**13**[a]

Run	Catalyst	Yield(%)[b]	ee(%)[c]
1	**8**	49	45 (*S*)
2	**9**	53	55 (54[d]) (*S*)
3	**10**	40	27 (*S*)
4	**11**	43	42 (*S*)
5	**12**	35	10 (*S*)
6	**13**	82	89 (90[d]) (*S*)

[a] Reaction time 24 h, base NaOBu^t, 20 °C. [b] Based on substance isolated by preparative TLC. [c] Determined by optical rotation. [d] Determined by ^{1}H NMR spectroscopy.

(2–3%) solution] in the presence of dry potassium carbonate (reflux, 32 h) in 52% yield after chromatography. Compound **12** was deprotected to **13** by 4% sodium amalgam in the presence of dibasic sodium phosphate in methanol (reflux, 20 h) in a yield of 85%, as reported for similar compounds.[18] Our attempt to form **13** by reductive removal of the *N*-tosyl group in **12** with $LiAlH_4$ in tetrahydrofuran (THF)[19] was not successful and caused the macrocyclic ring to open.The structure of products **8**–**13** was characterized by ^{1}H NMR and mass spectroscopic data. The ^{1}H spectral parameters are similar to those of aza-crown derivatives described earlier.[9] The relative molecular masses of new compounds were supported by CI-MS and FAB-MS. The fragment at *m*/*z* 476 was of significant intensity in all cases (see Experimental section) and is due to the (sugar-based-aza-crown-N-CH_2)$^+$ fragment.

Compounds **8**–**13** proved to be effective as chiral PT catalysts in the Michael addition of 2-nitropropane **15** to chalcone **14** (Scheme 5).



Scheme 5 The Michael addition of 2-nitropropane to chalcone. *Reagent and conditions*: NaOBu^t, toluene, rt.

The Michael addition was carried out in toluene with solid sodium *tert*-butoxide as base (35 mol%) and chiral catalyst (7 mol%), at room temperature. After the usual work-up procedure, the adduct **16** was isolated by preparative TLC; the asymmetric induction, expressed in terms of the ee, was monitored by measuring the optical rotation of the product **16** and comparing it with literature data for the preferred pure enantiomer[10] and by ^{1}H NMR spectroscopy using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-Eu(hfc)$_3$] as chiral shift reagent. The results, given in Table 1, show that the (*S*)-(+)-adduct **16** is always in excess and, moreover, that the substituent on the nitrogen atom of the catalyst has a significant influence on both the chemical yield and the asymmetric induction. It can be seen that the catalysts **8**–**11** resulted in moderate chemical yields from 40 to 53%; however, the enantioselectivity of the catalysts was rather different. Among the crown amines **8**–**11** the weakest catalyst was

the *N*-benzyl compound **10**, which gave 27% ee. This value increased in the presence of crown ether **11** having a phenylethyl side arm (42% ee) and *N*-butyl compound **8** (45% ee); the *N*-methoxypropyl derivative **9** (lariat ether) showed the highest enantioselection of 55% ee. The results for catalysts **10** and **11** possessing benzyl and phenylethyl side groups indicate the importance of the length of the side arm on the nitrogen atom. The *N*-tosyl crown amide **12** proved to be the weakest catalyst among all the crown ethers tested: chemical yield of 35% and optical purity of 10% ee were obtained. It is probable that the *N*-tosyl amide part in the crown ring reduces the complex-forming properties, and its steric hidrance may play an essential role too. The catalytic activity and enantioselectivity dramatically increased after the removal of the tosyl group: use of the unsubstituted aza-crown catalyst **13** resulted in a yield of 82% and enantioselectivity of 90% ee for the *S*-antipode. Therefore, compared with the unsubstituted compound, the enantioselectivity decreased in the case of *N*-substituted derivatives, most probably because of steric reasons but also because of the free NH group in the cycle making it probable that there is H-bond involvement in the transition-state structures. This finding is surprising in the light of our earlier findings with aza-crown ethers containing a 4,6-*O*-benzylidene group on the sugar moiety, when the substituents on the nitrogen mostly increased the chemical yield and the enantioselectivity.[10,11] The compounds presented here show a different picture, which can be explained by the structure of the molecule and which is different from those presented earlier. The crown ethers have no acetal ring and therefore they are more flexible. On the other hand, the two butyl groups on the glucopyranoside part considerably increase the lipophilicity of the molecule. Further investigations including mechanistic studies are now in progress.

Experimental

General procedures

Mps were determined with a Büchi 510 apparatus and are uncorrected. Specific rotations were determined with a Perkin-Elmer 241 polarimeter at 20 °C, and $[a]_D$ values are given in units of deg cm^2 g^{-1}. IR spectra were recorded with a Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM 250 instrument for solutions in $CDCl_3$. *J*-Values are given in Hz. Mass spectra were obtained on a JEOL JMS-01 SG-2 instrument. Chemical ionization was applied as the ionization technique. Elemental analysis was performed on a Perkin-Elmer 240 automatic analyzer. Analytical and preparative TLC was performed on silica gel (60 GF-254, Merck); column chromatography was carried out using 70–230 mesh silica gel (Merck).

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 2

A solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **1** (20.0 g, 70.9 mmol) and tetrabutylammonium bromide (23.0 g, 71.4 mmol) in benzyl chloride (140.0 cm^3, 1.22 mol) was vigorously stirred with 50% aq. NaOH (140.0 cm^3, 2.67 mol) at room temperature for 10 h. The reaction mixture was added to a mixture of dichloromethane (450 cm^3) and water (450 cm^3). The organic layer was decanted and the aqueous one was washed with dichloromethane. The organic phases were combined, washed with water, dried (Na_2SO_4), and concentrated; the residue was crystallized from ethanol to give **2** (27.9 g, 85%), mp 97–98 °C (lit.,[14] 99 °C); $[a]_D$ +23.3 (*c* 1, acetone) {lit.,[14] $[a]_D$ +23.5 (*c* 1, acetone)}.

Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 3

Compound **2** (29.5 g, 63.7 mmol) was stirred with 96% acetic acid (300 cm^3) at 100 °C for 2 h. Water (100 cm^3) was then added and stirring was continued for 1 h. After cooling, the solution was evaporated to a syrup, water (2 × 40 cm^3) and toluene (2 × 60 cm^3) were added, and the mixture was evaporated to dryness again. The residue was dissolved in chloroform, and the solution was washed successively with aq. sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. Compound **3** was obtained as a syrup, which after crystallization gave solid material (17.9 g, 78%), mp 75–76 °C (from EtOH) (lit.,[16a] 73–74 °C); $[a]_D$ +18.5 (*c* 1.5 $CHCl_3$) {lit.,[16a] $[a]_D$ + 18.2 (*c* 1, $CHCl_3$)}.

Methyl 2,3-di-*O*-benzyl-4,6-di-*O*-butyl-α-D-glucopyranoside 4

A mixture of **3** (22.0 g, 58.8 mmol) in dry DMF (150 cm^3) and 60% NaH (6.0 g, 150 mmol) was stirred for 1 h under argon. After cooling of the mixture to 0 °C, dry butyl bromide (63.0 cm^3, 597.8 mmol) was added. The mixture was allowed to attain room temperature and then was stirred for a further 48 h. Excess of NaH was decomposed with methanol, and the solution was concentrated to a syrup. A solution of the residue in chloroform (150 cm^3) was washed with water (3 × 80 cm^3), dried (Na_2SO_4), and concentrated to give an oil, which was purified by column chromatography on silica gel using hexane–ethyl acetate (3:1) as eluent to afford syrupy *title compound* **4** (21.2 g, 74%), $[a]_D$ +24.1 (*c* 1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2957, 2871 (Me, methylene), 1726 (sugar ring), 1454, 1366 (alkyl chain), 1094, 1057 (C–O), 1603, 737, 697 (Ar); δ_H ($CDCl_3$) 0.89 (6H, t, CH_3), 1.11–1.70 (12H, m, CH_2), 3.35 (3H, s, OCH_3), 3.38–3.86 (6H, m, CH and CH_2), 4.52–4.77 (4H, m, CH_2Ph), 4.82 (1H, d, *J* 3.5, anomer-H), 7.22–7.39 (10H, m, ArH); CI-MS *m/z* 487 (M^+ + 1, 98%) (Found: C, 71.45; H, 8.53. $C_{29}H_{42}O_6$ requires C, 71.60; H, 8.64%).

Methyl 4,6-di-*O*-butyl-α-D-glucopyranoside 5

A suspension of palladium catalyst absorbed on charcoal (5% Pd/C, 2.0 g) and compound **4** (29.1 g, 59.9 mmol) in absolute ethanol (300 cm^3) was shaken with hydrogen gas at 50 °C until the absorption of the gas ceased (12 h). Removal of the catalyst and concentration of the filtrate afforded the syrupy *title product* **5** (18.2 g, 99%), $[a]_D$ +114.5 (*c* 1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3418br (OH), 2957, 2871 (Me, methylene), 1726 (sugar ring), 1464, 1367 (alkyl chain), 1126, 1053 (C–O); δ_H ($CDCl_3$) 0.82–0.98 (6H, m, CH_3), 1.21–1.70 (12H, m, CH_2), 3.38 (3H, s, OCH_3), 3.42–3.85 (8H, m, CH, CH_2 groups and OH), 4.76 (1H, d, *J* 4.8, anomer-H) (Found: C, 58.71; H, 9.75. $C_{15}H_{30}O_6$ requires C, 58.82; H, 9.80%).

Methyl 4,6-di-*O*-butyl-2,3-bis-*O*-[2-(2-chloroethoxy)ethyl]-α-D-glucopyranoside 6

A solution of compound **5** (16.1 g, 52.6 mmol) and tetrabutylammonium bromide (16.7 g, 52.6 mmol) in bis(2-chloroethyl) ether (92 cm^3, 831.4 mmol) was vigorously stirred with 50% aq. NaOH (92 cm^3) at room temp. for 10 h. The reaction mixture was then poured into a mixture of dichloromethane (330 cm^3) and water (330 cm^3) and the resulting solution was separated. The aqueous portion was washed with dichloromethane (2 × 200 cm^3); the combined organic layer and washings were then washed with water (3 × 180 cm^3), dried (Na_2SO_4), and evaporated to dryness. The syrup remaining was shaken with hexane (3 × 100 cm^3). The precipitate (Bu_4NBr) was filtered off, and the filtrate was evaporated to give a syrup, which was chromatographed on a column of silica gel (220 g) using diethyl ether–methanol (10:0.5) as eluent to give syrupy *product* **6** (12.1 g, 44%); $[a]_D$ +61.5 (*c* 1, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2957, 2871 (Me, methylene), 1726 (sugar ring), 1460, 1357 (alkyl chain), 1100, 1051 (C–O), 749 (C–Cl); δ_H ($CDCl_3$) 0.90–0.94 (6H, m, CH_3), 1.34–1.40 (6H, m, CH_2), 1.52–1.64 (6H, m, CH_2), 3.38 (3H, s, OCH_3), 3.59–3.98 (22H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H) (Found: C, 53.02; H,

8.55; Cl, 13.36. $C_{23}H_{44}O_8Cl_2$ requires C, 53.18; H, 8.47; Cl, 13.48%).

Methyl 4,6-di-*O*-butyl-2,3-bis-*O*-[2-(2-iodoethoxy)ethyl]-α-D-glucopyranoside 7

A mixture of bischloro derivative **6** (6.0 g, 11.55 mmol) and anhydrous NaI (6.9 g, 47.1 mmol) in dry acetone (150 cm^3) was stirred under reflux for 40 h. After cooling, the precipitate was filtered off and washed with acetone. The combined acetone solution was evaporated. The residue was dissolved in dichloromethane (100 cm^3), and the solution was washed with water (3 × 50 cm^3) and dried (Na_2SO_4) to give compound **7** (7.8 g, 96%) as a syrup, $[\alpha]_D$ +46.3 (*c* 1, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2957, 2871 (Me, methylene), 1726 (sugar ring), 1105, 1052 (C–O), 1460, 1357 (alkyl chain), 545 (C–I); δ_H ($CDCl_3$) 0.85–0.96 (6H, m, CH_3), 1.32–1.40 (6H, m, CH_2), 1.52–1.64 (6H, m, CH_2), 3.27 (4H, t, CH_2I), 3.38 (3H, s, OCH_3), 3.45–4.10 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H).

General method for preparation of crown ethers 8–11

Anhydrous Na_2CO_3 (3.8 g, 36.2 mmol) was suspended in a solution of the corresponding primary amine (4.60 mmol) and the bisiodo compound **7** (3.45 g, 4.60 mmol) in dry acetonitrile (100 cm^3) under argon. The stirred reaction mixture was refluxed for 32–40 h and monitored by TLC. After cooling, the precipitate was filtered off and washed with acetonitrile. The combined acetonitrile solution was concentrated; the residual oil was dissolved in chloroform, amd the solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with chloroform–methanol (10 : 0.5–10 : 2) to afford the title compounds.

***N*-Butyl-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 8.** Column chromatography gave *syrupy* **8** (1.1 g, 46%), $[\alpha]_D$ +57.4 (*c* 1, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2930, 2862 (Me, methylene), 1462, 1359 (alkyl chain), 1120, 1097, 1056 (C–O); δ_H ($CDCl_3$) 0.84–0.96 (9H, m, CH_3), 1.22–1.78 (16H, m, CH_2), 2.47–2.88 (6H, m, NCH_2), 3.38 (3H, s, OCH_3), 3.43–3.83 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H); EI-MS; *m*/*z* 519 (M^+, 17%), 488 ($M^+ - OCH_3$, 67), 476 ($M^+ - C_3H_7$, 91), 105 (100) (Found: C, 62.29; H, 10.12. $C_{27}H_{53}NO_8$ requires C, 62.42; H, 10.21%).

***N*-(3-Methoxypropyl)-2,3,5,6,8,9,11,12,14,15-decahydro-(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 9.** *Compound* **9** (0.84 g, 42%) was obtained as a syrup after chromatography, $[\alpha]_D$ +55.1 (*c* 1, $CHCl_3$); ν_{max} (neat film)/cm^{-1} 2930, 2862 (Me, methylene), 1462, 1360 (alkyl chain), 1120, 1100, 1056 (C–O); δ_H ($CDCl_3$) 0.84–0.96 (6H, m, CH_3), 1.32–1.42 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.47–2.88 (6H, m, NCH_2), 3.32 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.45–3.92 (22H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H); EI-MS *m*/*z* 535 (M^+, 8%), 504 ($M^+ - OCH_3$, 58), 476 ($M^+ - CH_2CH_2OCH_3$, 89), 105 (100) (Found: C, 60.48; H, 9.94; N, 2.58. $C_{27}H_{53}NO_9$ requires C, 60.56; H, 9.90; N, 2.61%).

***N*-Benzyl-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 10.** Column chromatography afforded *syrupy* **10** (1.0 g, 40%); $[\alpha]_D$ +56.2 (*c* 1.2, $CHCl_3$); ν_{max} (neat film)/cm^{-1} 2932, 2862 (Me, methylene), 1462, 1360 (alkyl chain), 1120, 1097, 1056 (C–O), 1600, 738, 700 (Ar); δ_H ($CDCl_3$) 0.84–0.97 (6H, m, CH_3), 1.32–1.44 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.62–2.90 (6H, m, NCH_2 and CH_2Ph), 3.38 (3H, s, OCH_3), 3.44–3.92 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H), 7.15–7.32 (5H, m, ArH); EI-MS *m*/*z* 553 (M^+, 13%), 536 ($M^+ - OCH_3$, 54), 476 ($M^+ - CH_2Ph$, 95), 105 (100) (Found: C, 65.00; H, 9.28; N, 2.52. $C_{30}H_{51}NO_8$ requires C, 65.09; H, 9.22; N, 2.53%).

***N*-(2-Phenylethyl)-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 11.** Column chromatography afforded syrupy **11** (1.2 g, 45%), $[\alpha]_D$ +51.3 (*c* 1, $CHCl_3$); ν_{max} (neat film)/cm^{-1} 2932, 2862 (Me, methylene), 1462, 1360 (alkyl chain), 1120, 1097, 1056 (C–O), 1600, 738, 700 (Ar); δ_H ($CDCl_3$) 0.84–0.97 (6H, m, CH_3), 1.32–1.44 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.62–2.91 (8H, m, NCH_2 and CH_2Ph), 3.38 (3H, s, OCH_3), 3.44–3.92 (18H, m, CH and CH_2 groups), 4.82 (1H, d, *J* 4.8, anomer-H), 7.15–7.32 (5H, m, ArH); EI-MS *m*/*z* 567 (M^+, 13%), 536 ($M^+ - OCH_3$, 54), 476 ($M^+ - CH_2Ph$, 95), 105 (100) (Found: C, 65.38; H, 9.36; N, 2.42. $C_{31}H_{53}NO_8$ requires C, 65.60; H, 9.34; N, 2.47%).

N-Tosyl-2,3,5,6,8,9,11,12,14,15-decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 12

A mixture of bischloro podand **6** (2.6 g, 5.0 mmol), toluene-*p*-sulfonamide (0.86 g, 5.0 mmol) and anhydrous K_2CO_3 (3.5 g, 25.3 mmol) was stirred and refluxed in dry DMF (150 cm^3) for 32 h. After the reaction was complete, the precipitate was filtered off and washed with chloroform. The combined filtrate and washings were evaporated under reduced pressure, and the residue was dissolved in chloroform, washed with water, and dried ($MgSO_4$). After removal of the solvent, column chromatography of the residue on silica gel with toluene–methanol (10 : 1) as the eluent gave the *N-tosyl macrocycle* **12** as a yellow oil (1.6 g, 52%), $[\alpha]_D$ +33.4 (*c* 1.8, $CHCl_3$); δ_H ($CDCl_3$) 0.80–0.96 (6H, m, CH_3), 1.32–1.42 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.41 (3H, s, ArCH_3), 2.72–2.98 (4H, m, NCH_2), 3.40 (3H, s, OCH_3), 3.45–3.90 (18H, m, CH and CH_2 groups), 4.88 (1H, d, *J* 4.8, anomer-H), 7.22–7.70 (4H, m, ArH); MS (FAB) *m*/*z* 618 (MH^+) (Found: C, 58.44; H, 8.28; N, 2.21. $C_{30}H_{51}NO_{10}S$ requires C, 58.34; H, 8.26; N, 2.26%).

2,3,5,6,8,9,11,12,14,15-Decahydro(methyl 4,6-di-*O*-butyl-2,3-dideoxy-α-D-glucopyranosido)[2,3-*e*]-1,4,7,10-tetraoxa-13-azacyclopentadecine 13

Compound **12** (1.4 g, 2.27 mmol), anhydrous disodium hydrogen phosphate (1.3 g, 9.10 mmol), and 4% sodium amalgam (11.0 g, 19.1 mmol) were placed in dry methanol (20 cm^3). The mixture was heated at reflux under a nitrogen atmosphere for 20 h while being stirred rapidly. After cooling to room temperature, the resulting slurry was decanted into water (80 cm^3) and extracted with chloroform (30 cm^3 × 4). The organic layers were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield compound **13** (0.89 g, 85%) as a yellow oil, $[\alpha]_D$ +58.9 (*c* 1.5, $CHCl_3$); δ_H ($CDCl_3$) 0.84–0.96 (6H, m, CH_3), 1.32–1.42 (6H, m, CH_2), 1.52–1.66 (6H, m, CH_2), 2.45 (1H, br s, NH), 2.82–2.98 (4H, m, NCH_2), 3.40 (3H, s, OCH_3), 3.44–3.92 (18H, m, CH and CH_2 groups), 4.83 (1H, d, *J* 4.8, anomer-H); MS (FAB) *m*/*z* 464 (MH^+) (Found: C, 59.50; H, 9.68; N, 3.08. $C_{23}H_{45}NO_8$ requires C, 59.61; H, 9.72; N, 3.02%).

General procedure for the Michael addition

This was performed as follows: Chalcone **14** (0.3 g, 1.44 mmol) and 2-nitropropane **15** (0.3 cm^3, 3.36 mmol) were dissolved in dry toluene (3 cm^3), and crown ether catalyst (0.1 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) were added. The mixture was stirred under an argon atmosphere at room temperature. After completion of the reaction (20–24 h) a mixture of toluene (7 cm^3) and water (10 cm^3) was added. The organic phase was processed in the usual manner. The product was purified by preparative TLC on silica gel using hexane–ethyl acetate (10 : 1) as eluent, and had mp 146–148 °C, $[\alpha]_D$ +80.8

(c 1, CH_2Cl_2) for pure (*S*)-(+)-enantiomer;[10] δ_H ($CDCl_3$) 1.54 (3H, s, CH_3), 1.63 (3H, s, CH_3), 3.27 (1H, dd, J 17.2 and 3.2, CH_2), 3.67 (1H, dd, J 17.2 and 10.4, CH_2), 4.15 (1H, dd, J 10.4 and 3.2, CH), 7.18–7.32 (5H, m, ArH), 7.42 (2H, t, COPh H-*m*), 7.53 (1H, t, COPh H-*p*), 7.85 (2H, d, COPh H-*o*).

Acknowledgements

This work was supported by the National Science Foundation (OTKA T 029253 and T 026478) and Hungarian Academy of Sciences.

References

1 M. I. O' Donnell, *Asymmetric Phase-transfer Reactions*, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, pp. 389–411 and references cited therein.
2 J. F. Stoddart, *Top. Stereochem.*, 1987, **17**, 207; J. M. Coteron, C. Vicent, C. Bosso and S. Penades, *J. Am. Chem. Soc.*, 1993, **115**, 10066.
3 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, 1994, p. 241; M. Wills and H. Tye, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 3101; 1999, 1109.
4 M. Alonso-Lopez, J. Jimenez-Barbero, M. Martin-Lomas and S. Penades, *Tetrahedron*, 1988, **44**, 1535.
5 D. A. H. van Maarschalkerwaart, N. P. Willard and U. K. Pandit, *Tetrahedron*, 1992, **48**, 8825.
6 S. Aoki, S. Sasaki and K. Koga, *Heterocycles*, 1992, **33**, 493.
7 P. P. Kanakamma, N. S. Mani, U. Maitra and V. Nair, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 2339.
8 L. Tőke, P. Bakó, Gy. M. Keserű, M. Albert and L. Fenichel, *Tetrahedron*, 1998, **54**, 213 and references cited therein.
9 P. Bakó and L. Tőke, *J. Inclusion Phenom.*, 1995, **23**, 195.
10 P. Bakó, Á. Szöllősy, P. Bombicz and L. Tőke, *Synlett*, 1997, 291.
11 P. Bakó, Á. Szöllősy, P. Bombicz and L. Tőke, *Heteroatom Chem.*, 1997, **8**, 333.
12 P. Bakó, K. Vízvárdi, S. Toppet, E. Van der Eycken, G. J. Hoornaert and L. Töke, *Tetrahedron*, 1998, **54**, 14975.
13 P. Bakó, T. Kiss and L. Tőke, *Tetrahedron Lett.*, 1997, **38**, 7259.
14 J. S. Brimacombe, in *Methods in Carbohydrate Chemistry*, ed. R. L. Whistler, M. L. Wolfrom and J. N. Bemillar, Academic Press, New York, 1963, vol. 6. p. 376.
15 R. W. Jeanloz, in *Methods in Carbohydrate Chemistry*, ed. R. L. Whistler, M. L. Wolfrom and J. N. Bemillar, Academic Press, New York, 1962, vol. 1. p. 231.
16 (*a*) B. H. Lipshutz and M. C. Morey, *J. Org Chem.*, 1981, **46**, 2419; (*b*) N. J. Davis and L. Flitsch, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 359.
17 P. Di Cesare and B. Gross, *Synth. Commun.*, 1979, 458.
18 F. Chavez and A. D. Sherry, *J. Org. Chem.*, 1989, **54**, 2990.
19 H. Pietraszkiewicz and J. Jurczak, *Tetrahedron*, 1984, **40**, 2967.

Paper 9/05670J