1,6-Dideoxy-D-mannitol-based 20-crown-6 ethers: synthesis and influence of the substituents upon complexing properties toward phenylglycinium methyl esters

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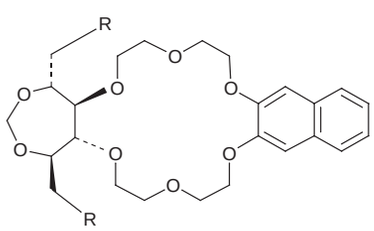
Ten novel homotopic 20-crown-6-ethers have been prepared from 1,3 : 4,6-di-*O*-benzylidene-D-mannitol. Substituents could be introduced on the alditol framework after the macrocyclisation in order to modify their complexing abilities. In one case, a low but significant enantiomeric excess (32% ee) in favour of L(*S*)-phenylglycine methyl ester could be ascertained when two bulky *vic*-triazole substituents were associated into the vicinity of the cavity. The formation of an adjacent *trans*-fused ring on C-3/C-4 of the mannitol framework mediated the complexing abilities of these macrocycles toward 2-phenylglycine methyl ester perchlorates.

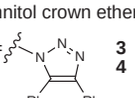
Introduction

In a recent paper[1] we reported the synthesis of several C_2-symmetric macrocycles prepared from technical D-mannitol. All these crown ethers were built from a common C_2-symmetric chiral 1,3-dioxepane scaffold obtained by methylenation of 1,3(*R*) : 4,6(*R*)-di-*O*-benzylidene-D-mannitol under basic conditions. The regioselective opening of this nicely crystalline *trans*-fused tricyclic acetal, either with *N*-bromosuccinimide (NBS) under free-radical conditions[2] or by reductive cleavage with sodium cyanoborohydride ($NaBH_3CN$) in acidic medium,[3] led, after *bis*-*O*-alkylation and cyclisation with dihydroxyaromatics, to macrocycles **1**–**5** with various functionalities on C-1/C-6 (*e.g.*, H, N_3, triazole, *O*Bn) of the 1,6-dideoxy-D-mannitol, or to macrocycles **6** and **7** with different aromatic moieties.

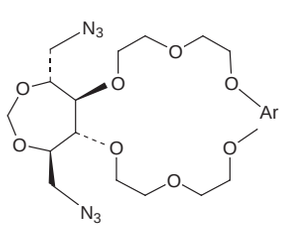


2,5-*O*-Methylene-D-mannitol crown ethers **1**–**5**

1 R = H
2 R = N_3
5 R = OBn

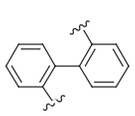
3, **4** R = 

3 R' = CO_2Me
4 R' = Ph



2,5-*O*-Methylene-D-mannitol crown ethers **6** and **7**

6 Ar = 

7 Ar = 

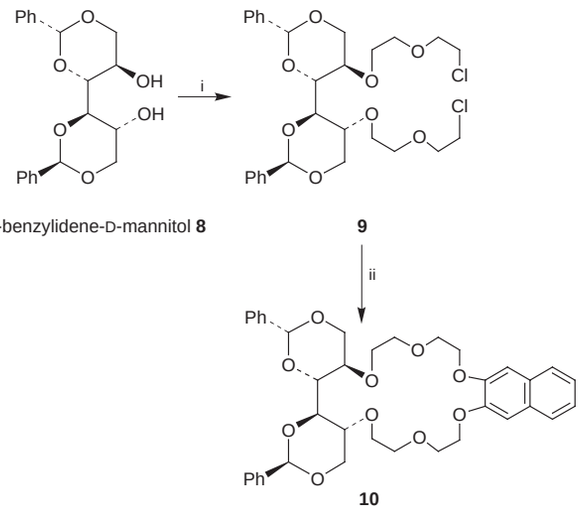
Apart from macrocycles **4**, but only to a small extent, these homotopic hosts did not extract enantiomers of racemic phenylglycinium methyl ester (our standard-guest) from molar lithium perchlorate in deuterium oxide into deuterochloroform. This absence of extraction of the 2-phenylglycinium methyl ester perchlorates was also established for the corresponding [20-6]-macrocycle **7** incorporating a flexible 2,2′-biphenyl moiety in the cavity. This rather surprising lack of interaction with salts of primary amino acid derivatives should be connected with the rigidity of the 1,3-dioxepane framework which presumably adopts a stable twist–chair (TC) conformation in solution. We concluded that this thermodynamically favoured TC conformation, which could be confirmed in the solid state for two derivatives, hinders the rotation around the C-3/C-4 axis necessary to create a regular co-ordination polyhedron into the vicinity of the ammonium cation. To ascertain this hypothesis, we decided to synthesise less rigid structures from 1,3(*R*) : 4,6(*R*)-di-*O*-benzylidene-D-mannitol. In this paper, which is the eleventh from our laboratory in the field,[2,4] we present the results of this work whose aim was the development of acid-stable hosts for enantiospecific complexation of primary ammonium cations.

Results and discussion

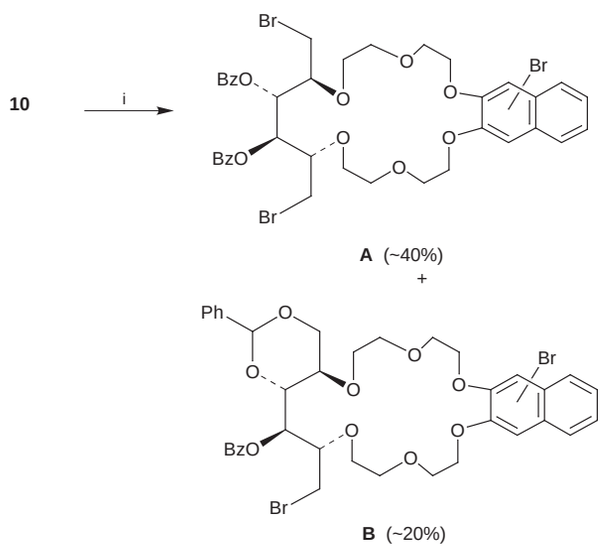
Synthesis

The synthesis of the first crown ether **10** in this series proceeded as outlined in Scheme 1. The easily obtainable 1,3(*R*) : 4,6(*R*)-di-*O*-benzylidene-D-mannitol **8** was converted into the half-crown **9**, which was first cyclised to the crown ether **10** by standard chemistry.[4a]

As the previously mentioned *trans*-fused tricyclic acetal, the C_2-symmetric chiral 20-crown-6-ether **10** was treated with NBS (2.2 mol equiv.) under free-radical conditions. After 1 h at reflux, TLC (*n*-hexane–ethyl acetate, 1 : 1) of the resulting crude solution showed two main products (R_f 0.67 and 0.58 respectively) besides unchanged starting material. The following asymmetric structures **A** and **B** (Scheme 2) are in fair agreement with the ^1H NMR and electron-impact mass (EI-MS) spectra of the two main products isolated from the reaction mixture by conventional chromatography.

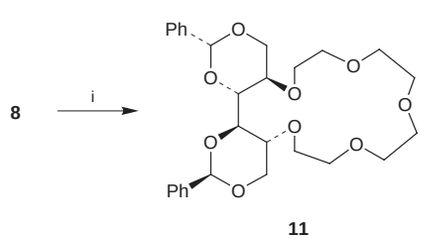


Scheme 1 Synthesis of crown ether **10** from 1,3(*R*):4,6(*R*)-di-*O*-benzylidene-D-mannitol **8**. *Reagents*: i, $(ClCH_2CH_2)_2O$, aq. NaOH; ii, 2,3-dihydroxynaphthalene, Cs_2CO_3, Bu^nOH.



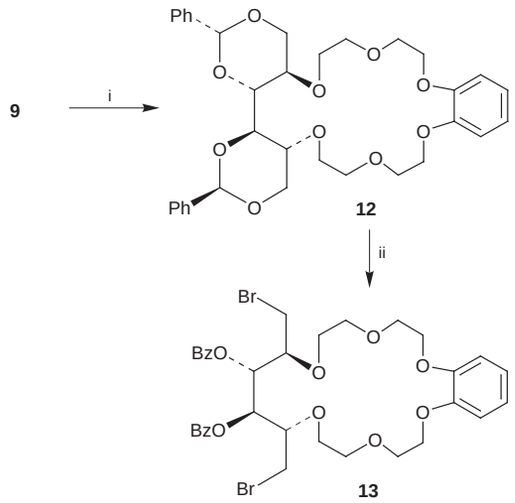
Scheme 2 Synthesis of **A** and **B** from crown ether **10**. *Reagents*: i, NBS, Bz_2O_2, *hv*, CCl_4, $CaCO_3$.

In order to obviate this difficulty and to obtain true homotopic hosts, we synthesised a macrocycle without an aromatic moiety, from the diol **8** and tetraethylene glycol ditosylate readily obtainable in the laboratory (Scheme 3).[5]



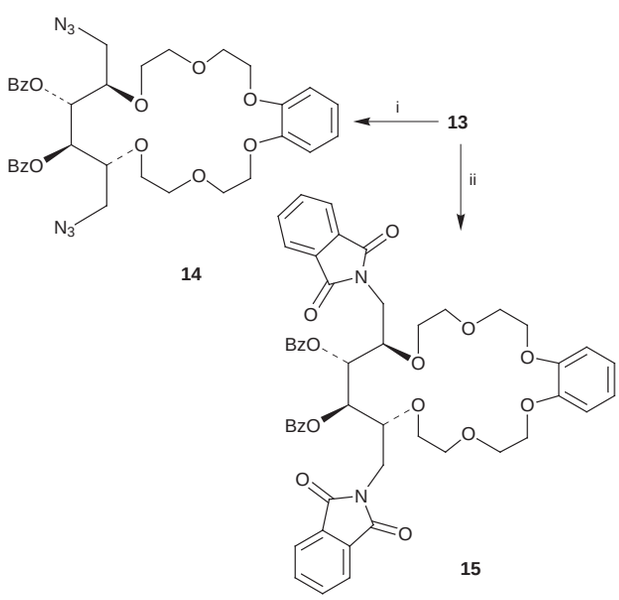
Scheme 3 Synthesis of the 17-crown-5 **11** from 1,3(*R*):4,6(*R*)-di-*O*-benzylidene-D-mannitol **8**. *Reagents*: i, NaH, tetraethylene glycol ditosylate, DMF.

Because of the poor yield of this reaction (~30%) and the very poor complexing properties of the 17-crown-5 **11**, we tried to optimise the cyclisation step of the dichloride **9** with pyrocatechol under different conditions (solvent and base) (see Scheme 4). The best yield (56%) was measured with caesium fluoride as base[6] in acetonitrile.



Scheme 4 Synthesis of the symmetric crown ethers **12** and **13** from dichloride **9**. *Reagents*: i, pyrocatechol, M_2CO_3 (M = K or Cs), Bu^nOH or CsF, MeCN; ii, NBS, Bz_2O_2, *hv*, CCl_4, $CaCO_3$.

The 1,6-dibromo-1,6-dideoxy-D-mannitol derivative **13** was isolated in only 36% after tedious purification. This rather poor result may be attributed mainly to the high polarity of this macrocycle towards the stationary phase (kieselgel). The two bromine atoms could then be easily displaced by sodium azide in DMF at 100 °C to give the diazide **14** in almost quantitative yield (Scheme 5).



Scheme 5 Synthesis of crown ethers **14** and **15** from crown **13**. *Reagents*: i, NaN_3, NH_4Cl, DMF; ii, K-phthalimide, DMF.

Alternatively, the two bromine atoms could be displaced by potassium phthalimide in the same solvent to give the corresponding bis-phthalimide **15** in 30% yield. The first step of this Gabriel synthesis was not optimised. From the diazide **14**, the C_2-symmetric triazoles **16**, **17** and **18** could be isolated after cyclisation with an excess of neat diphenylacetylene, followed by saponification and acetylation (Scheme 6).

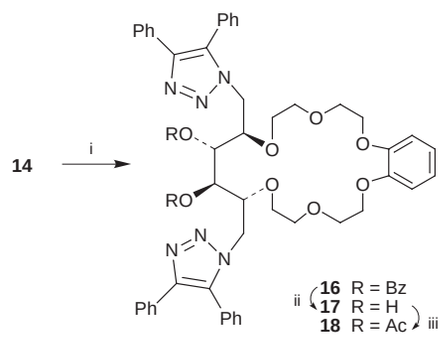
The *trans*-fused polycyclic crown ethers **19** and **20** were synthesised to check the influence of conformational restriction on complexation behaviour of the macrocycles (Schemes 7 and 8).

The last two syntheses were not optimised but afforded sufficient amounts of purified macrocycles to allow us to check their extraction behaviour toward D/L-phenylglycinium methyl esters by monoplate partitioning.

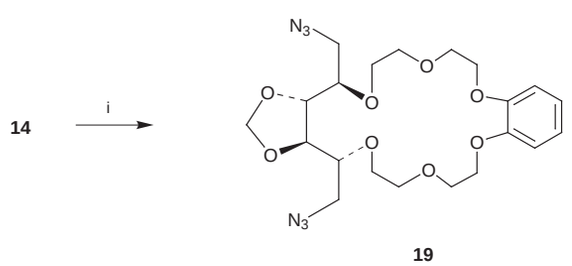
Table 1 Extraction data of the enantiomers of phenylglycine methyl ester perchlorate as guests by crown ethers **10**–**20** in $CDCl_3$ at 273 K

Crown ether (as host)	R (G/H) (quotient of guest to host)	CRF (Chiral Recognition Factor)	$\Delta\delta$ H^b (ppm) = $H^b_D - H^b_L$
10	1.0	1.20 (L)[a]	+0.20
11	nm[b]	[b]	
12	0.9	1.50 (L)	+0.16
13	1.2	1.30 (L)	+0.33
14	1.1	1.35 (L)	+0.26
15	1.0	1.30 (D)	+0.33
16	0.8	1.95 (L)	+0.37
17	0.5	1.20 (L)	0[c]
18	0.55	1.85 (L)	+0.31
19	[b]	[b]	
20	0.5	1.60 (L)	+0.19

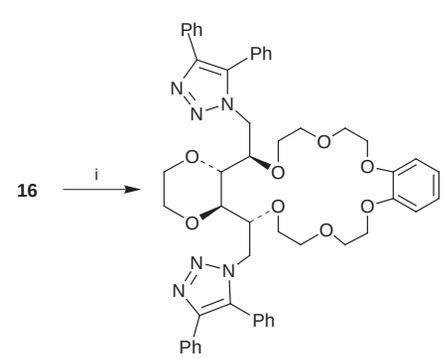
[a] The prominent enantiomer is in parentheses. [b] nm = non-measurable (~0). [c] Superimposed.



Scheme 6 Synthesis of crown ethers **16**, **17** and **18** from diazide **14**, *Reagents*: i, diphenylacetylene; ii, MeONa, MeOH; iii, Ac_2O, Pyr.



Scheme 7 Synthesis of crown ether **19** from compound **14**. *Reagents*: i, CH_2Br_2, NBu_4HSO_4, 50% aq. NaOH.



Scheme 8 Synthesis of crown ether **20** from compound **16**. *Reagents*: i, $ClCH_2CH_2Cl$, NBu_4HSO_4, 50% aq. NaOH.

Extraction experiments of phenylglycinium methyl ester perchlorates from $LiClO_4$ M (D_2O) to $CDCl_3$ at 273 K

Liquid–liquid extraction, also called monoplate partitioning, provides one of the fastest methods to evaluate the ability of an optically pure host to distinguish between enantiomers as guests. The guest salt is dissolved in the aqueous buffered phase first as a pure enantiomer and then as a racemic mixture.[7] A spectroscopic method (most often ^1H NMR) may be used to estimate the enantiomeric excess (ee) directly in the organic layer, but analytical HPLC with an appropriate chiral column is perhaps the best method especially for measuring high or low ee-values.[8] When complexation occurred, R was the molar quotient of *guest* to *host* in the organic phase, CRF (for Chiral Recognition Factor) the ratio of the pre-eminent enantiomer to the less complexed enantiomer in the organic phase, and $\Delta\delta$ the chemical-shift difference in ppm between the diastereotopic benzylic protons of the guest.[7] Our results for the extraction of aq. racemic phenylglycine methyl ester perchlorate (see Experimental section and ref. 1) by eleven chiral homotopic hosts dissolved in $CDCl_3$ at 273 K are summarised in Table 1.

Apart from host **11**, which is a 17-crown-5 without any measurable affinity in the test, most of the 20-crown-6 compounds described here were able to extract the phenylglycinium methyl esters perchlorates from D_2O at 0 °C. The temperature was decreased from ambient to slightly improve chiral recognition.[9] Complexation produced marked chemical shifts and multiplicity changes of ^1H NMR spectral bands of both host and guest, the more obvious one being the splitting of the benzylic proton of phenylglycine into two well separated singlets (see last column, Table 1) which allowed the estimation of CRF.[4f] High extraction (~1 : 1) ratios were related with lower enantioselectivity (hosts **10**, **12**, **13**, **14** and **15**). We observed that the introduction of a phthalimide moiety on C-1 and C-6 of D-mannitol in compound **15** reversed the enantioselectivity from L- and D-phenylglycine methyl ester. In compounds **16**, **17** and **18**, the best result was observed with the largest substituents (benzoate) on C-3 and C-4. From this point of view, it might be worth noting that another co-ordination site on C-3/C-4 as a second binding site endowed with a different selectivity could induce positive or negative allosteric co-operation.[10] The formation of an adjacent *trans*-fused ring on C-3/C-4 of the mannitol framework dramatically reduced the complexing abilities of the macrocycle **19**, even with small azide functions on C-1/C-6. We believe that this behaviour is likely to be relevant to those of the previously described 2,5-*O*-methylene-D-mannitol *trans*-fused crown ethers.[1] However, the *trans*-fused dioxane moiety restored the extraction capacity of macrocycle **20** with a medium enantioselectivity ($CRF_{20} > CRF_{17}$). A solid-state structure of compound **20** would need to be ascertained for us to understand the origin of this difference.

Conclusions

Homotopic 20-crown-6 ethers were successfully synthesised from D-mannitol and tested under conditions of monoplate partitioning near 0 °C with phenylglycinium methyl esters as guests. These hosts displayed much higher extraction capacities than did former [18-6] derivatives incorporating a chiral 1,3-dioxepane framework.[1] The enantioselectivity (CRF) of these new [20-6] macrocycles seemed to be more dependent on the nature of the substituents on C-3 and C-4 than those on C-1

and C-6. In the extreme, the formation of a methylene acetal between C-3 and C-4 completely froze the D-mannitol framework and also the *trans*-fused cavity, which lost its complexing behaviour. At least enantioselectivities were in the range of values actually found in the literature for especially designed receptors.[11] Further investigations with these macrocycles and related structures will be undertaken under HPLC conditions in order to evaluate their enantiomeric recognition of un-derivatised amino acids at various pH-values.[4d,4e]

Experimental

Preparative chromatography was performed on kieselgel from E. Merck, particle size 0.040–0.063 mm (230–400 mesh). Mps were determined on a Büchi apparatus in capillary tubes and are uncorrected; optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter in a 1 dm cell at room temp.; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 1000 spectrometer at room temp. Mass spectra were recorded on a Nermag R1010 instrument at 70 eV unless otherwise stated. Enantioselectivity in the complexation of the enantiomers of phenylglycine methyl esters by crown ethers was estimated with the help of 250 MHz ^{1}H NMR spectroscopy (Bruker AC 250). For this purpose, the crown ether (~50 μM) was dissolved in 1.0 cm^3 of $CDCl_3$ and shaken for 1 min with 1.0 cm^3 of 1 M $LiClO_4$ in D_2O containing 4 mol equiv. of racemic phenylglycine methyl ester hydrochloride at 0 °C. The mixture was allowed to settle for 30 min in crushed ice and the organic layer was then carefully separated, dried over anhydrous Na_2SO_4, filtered through a small cotton pad, and its ^{1}H NMR spectrum was immediately recorded at 27 °C. The CRFs were estimated by comparison of integrals of the separated benzylic protons of phenylglycine between δ 4.5 and 5.0. The molar ratio R of *guest* to *host* in the organic phase was estimated by comparison of suitable expanded aromatic signals. NMR *J*-values are given in Hz.

1,3:4,6-Di-*O*-benzylidene-2,5-bis-*O*-[(2-chloroethoxy)ethyl]-D-mannitol 9

To a vigorously cooled suspension of the diol **8** (7.16 g, 20.0 mmol) and Bu_4NHSO_4 (14.00 g, 2 mol equiv.) in bis-(2-chloroethyl) ether (150 cm^3) was added 50% aq. NaOH (150 cm^3) below 5 °C. The two-phase system was mechanically stirred for 16 h below 20 °C, the reaction being monitored by TLC with hexane–AcOEt (2:3). The mixture was then diluted with both ice-cooled water (500 cm^3) and CH_2Cl_2 (400 cm^3) and the organic phase was isolated. The aqueous phase was extracted twice with CH_2Cl_2 (150 cm^3), and the organic phases were combined, washed with water (2 × 75 cm^3), dried over $MgSO_4$, and concentrated under reduced pressure to remove the solvents and the excess of reagent. Rapid chromatography with hexane–AcOEt (3:2) yielded the bis-chloride **9** (9.82 g, 86%) as a gum, $[\alpha]_D$ −30.9 (*c* 3.8, $CHCl_3$); δ_H(250 MHz; $CDCl_3$) 3.56–3.66 (10 H, m, 5 × OCH_2), 3.67–3.74 (6 H, m, 2 × OCH*H*Cl, 2 × OCH*H*, 2- and 5-H), 3.79 (2 H, dd, $J_{1e,1a}$ 10, 1-, 6-H^a), 3.84–3.96 (2 H, m, 2 × OC*H*HCl), 4.08 (2 H, d, $J_{2,3}$ 9, 3-, 4-H), 4.44 (2 H, dd, $J_{1e,2}$ 5, 1-, 6-H^e), 5.55 (2 H, s, OC*H*PhO), 7.31–7.42 (6 H, m, ArH) and 7.51 (4 H, m, ArH).

1,3:4,6-Di-*O*-benzylidene-2,5-*O*-[naphthalene-2,3-diylbis-(oxyethyleneoxyethyl)]-D-mannitol 10

A solution of 2,3-dihydroxynaphthalene (1.14 g, 3.0 mol equiv.) in freshly distilled Bu^{n}OH (30 cm^3) was stirred for 20 min at room temp. under argon. To this solution were added, first, dried powdered Cs_2CO_3 (3.47 g, 4.5 mol equiv.) and then, after the mixture had been heated to a gentle reflux, the half-crown **9** (1.35 g, 2.36 mmol). The resulting suspension was boiled for 40 h, allowed to cool to room temp., and the Bu^{n}OH was evaporated off under reduced pressure. The remaining solids were dissolved in a mixture of CH_2Cl_2 (50 cm^3) and water (30 cm^3). The aqueous phase was extracted twice with CH_2Cl_2 (30 cm^3), and the organic phases were combined, washed with water (5 cm^3), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography with hexane–AcOEt (7:3) yielded the crown ether **10** (0.760 g, 49%) as a solid, mp 78–80 °C; $[\alpha]_D$ 71.7 (*c* 1.6, $CHCl_3$); *m*/*z* 658 (M$^+$); δ_H(250 MHz; $CDCl_3$) 3.64–4.17 (16 H, m, 6 × OCH_2, 2-, 5-H, 1-, 6-H^a), 4.21 (2 H, d, $J_{2,3}$ 9, 3-, 4-H), 4.28–4.36 (4 H, m, 2 × OCH_2), 4.45 (2 H, dd, $J_{1e,1a}$ 10, $J_{1e,2}$ 5, 1-, 6-H^e), 5.54 (2 H, s, 2 × OC*H*PhO), 7.19 (2 H, s, 1-, 4-H naphth.), 7.31–7.40 (8 H, m, 6 × ArH, 6-, 7-H naphth.), 7.50 (m, 4 H, ArH) and 7.69 (2 H, m, 8-, 5-H naphth.).

1,3:4,6-Di-*O*-benzylidene-2,5-*O*-[oxybis(ethyleneoxyethyl]-D-mannitol 11

To a solution of 1,3:4,5-di-*O*-benzylidene-D-mannitol **8** (3.58 g, 10 mmol) in abs. THF (125 cm^3) under argon was added 60% NaH (1.2 g, 1.5 mol equiv.) and the resulting mixture was magnetically stirred at room temp. until the solution turned white (*ca*. 1 h). Tetraethylene glycol ditosylate [37860-51-8] (6.03 g, 1.2 mol equiv.) was added in small portions and the mixture was stirred for 80 h under argon. The reaction was monitored by TLC (hexane–AcOEt, 1:1; R_f 0.22) and stopped by dilution with water (50 cm^3). The solvents were evaporated off under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 cm^3) and washed with water (2 × 25 cm^3). These aqueous phases were re-extracted with CH_2Cl_2 (2 × 15 cm^3). The organic phases were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica with CH_2Cl_2–EtOH (9:1) yielded the crown ether **11** (1.91 g, 37%) as a syrup; $[\alpha]_D$ −30.1 (*c* 2.2, $CHCl_3$); *m*/*z* 515 (M − H)$^+$; δ_H(400 MHz; $CDCl_3$) 3.5–3.85 (18 H, m, 8 × OCH_2, 1-, 6-H^a), 3.82–4.10 (2 H, m, 2-, 5-H), 4.21 (2 H, d, $J_{3,4}$ 8.8, 3-, 4-H), 4.41 (2 H, dd, $J_{1e,2}$ 5, $J_{1e,1a}$ 10.8, 1-, 6-H^e), 5.55 (2 H, s, 2 × OC*H*PhO), 7.33 (6 H, d, ArH) and 7.52 (4 H, d, ArH).

2,5-*O*-[Benzene-1,2-diylbis(oxyethyleneoxyethyl)]-1,3:4,6-di-*O*-benzylidene-D-mannitol 12

The same procedure was used as described for compound **10** except that pyrocatechol was used instead of 2,3-dihydroxynaphthalene and the reaction time was 48 h. From 0.81 g (3 mol equiv.) of catechol, 2.40 g (3 mol equiv.) of Cs_2CO_3, and 1.40 g (2.45 mmol) of dichloride **9** was obtained 1.00 g (67%) of crown ether **12** as a gum after chromatography on silica with *n*-hexane–AcOEt (1:1), $[\alpha]_D$ −47.3 (*c* 3.1, $CHCl_3$); *m*/*z* 608 (M)$^+$; δ_H(400 MHz; $CDCl_3$) 3.61–3.71 [8 H, m, 2 × (OCH_2 + $OCHH$), 2-, 5-H], 3.72–3.81 (2 H, m, 2 × OC*H*H), 3.85 (2 H, dd, $J_{1e,1a}$ 11, $J_{1e,2}$ 4.5, 1-, 6-H^a), 3.87–3.98 (4 H, m, 2 × OCH_2), 4.14–4.22 (6 H, m, 2 × OCH_2, 3-, 4-H), 4.39 (2 H, dd, $J_{1e,1a}$ 11, 1-, 6-H^e), 5.46 (2 H, s, 2 × OC*H*PhO), 6.91 (4 H, br s, catechol ring), 7.25–7.40 (6 H, m, ArH) and 7.48 (4 H, m, ArH).

2,5-*O*-[Benzene-1,2-diylbis(oxyethyleneoxyethyl)]-3,4-di-*O*-benzoyl-1,6-dibromo-1,6-dideoxy-D-mannitol 13

To a stirred solution of compound **12** (0.65 g, 1.07 mmol) in anhydrous CCl_4 (50 cm^3) under argon were added successively dried $CaCO_3$ (235 mg, 2.2 mol equiv.), NBS (420 mg, 2.35 mol equiv.) and a few crystals of Bz_2O_2. The resulting dispersion was immediately heated to reflux by an incandescent 500 W lamp for 30 min, cooled to 5 °C, and filtered through sintered glass under a fume board. The remaining succinimide and calcium salts were rinsed with CH_2Cl_2 (~50 cm^3) and the combined organic phases were washed successively with 0.2 M aq. $Na_2S_2O_5$ (10 cm^3), 5% aq. $NaHCO_3$ (10 cm^3) and water (10 cm^3), dried over $MgSO_4$, and finally evaporated under reduced pressure. The residue was chromatographed with *n*-hexane–AcOEt (4:1) to yield the dibromide **13** (0.48 g, 59%) as a gum, $[\alpha]_D$ +34.0 (*c* 1.5, $CHCl_3$); ν_{max}(neat/NaCl)/cm^{-1} 1724; δ_H(250 MHz; $CDCl_3$)

3.48 (2 H, dd, J_{gem} 12, $J_{1,2}$ 6, 1-, 6-H), 3.72 (2 H, dd, $J_{1',2}$ 3, 1-, 6-H′), 3.78–4.07 (14 H, m, 2-, 5-H, 6 × OCH_2), 4.21 (4 H, m, 2 × CH_2 near catechol ring), 5.69 (2 H, dd, $J_{2,3}$ 6.5, 3-, 4-H), 6.92 (4 H, br s, catechol ring), 7.32 (4 H, t, ArH), 7.49 (2 H, t, ArH) and 7.92 (4 H, d, ArH).

1,6-Diazido-2,5-*O*-[benzene-1,2-diylbis(oxyethyleneoxyethyl)]-3,4-di-*O*-benzoyl-1,6-dideoxy-D-mannitol 14

To a solution of the dibromide **13** (0.35 g, 0.46 mmol) in DMF (25 cm^3) were added sodium azide (0.12 g, 4 mol equiv.) and ammonium chloride (0.102 g, 4 mol equiv.). The resulting mixture was stirred and heated to 100 °C for 12 h, the reaction being monitored by TLC with *n*-hexane–AcOEt (1:1) since diazide **14** produced a typical brownish colour after charring with dil. sulfuric acid (H_2SO_4–MeOH, 1:1); the reaction product was cooled to room temp., DMF was evaporated off *in vacuo*, and the residue was dissolved in CH_2Cl_2 (50 cm^3). The solution was washed with distilled water (2 × 15 cm^3), decanted, dried over $MgSO_4$, and purified by chromatography on silica with *n*-hexane–AcOEt (3:1) to yield title compound **14** (0.300 g, 95%) as a homogeneous wax, $[\alpha]_D$ +57.3 (*c* 1.3, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 1724 and 2102; δ_H(250 MHz; $CDCl_3$) 3.28 (2 H, dd, J_{gem} 13, $J_{1,2}$ 6, 1-, 6-H), 3.59 (2 H, dd, $J_{1',2}$ 3, 1-, 6-H′), 3.76–4.06 (14 H, 6 × OCH_2, 2-, 5-H), 4.22 (4 H, m, 2 × OCH_2 near catechol ring), 5.66 (2 H, d, $J_{2,3}$ 6, 3-, 4-H), 6.73 (4 H, br s, catechol ring), 7.32 (4 H, t, ArH), 7.5 (2 H, t, ArH) and 7.91 (4 H, d, ArH); δ_C(62.896 MHz; $CDCl_3$) 165.54 (2 × Ph*C*=O), 149.27 (C-1, -2 catechol ring), 133.47 (C-4, -4′, Ph), 129.76 (C-2, -2′, -6, 6′, Ph), 129.12 (C-1, -1′, Ph), 128.49 (C-3, -3′, -5, -5′, Ph), 121.76 (C-4, -5, catechol ring), 115.11 (C-3, -6, catechol ring), 78.80 (C-2, -5), 70.78 (2 × OCH_2), 70.45 (C-3, -4), 70.34, 70.13 and 69.18 (6 × OCH_2) and 50.71 (C-1, -6).

2,5-*O*-[Benzene-1,2-diylbis(oxyethyleneoxyethyl)]-3,4-di-*O*-dibenzoyl-1,6-dideoxy-1,6-diphthalimido-D-mannitol 15

To a stirred solution of crown ether **13** (0.285 g, 0.37 mmol) in abs. DMF (20 cm^3) was added 0.206 g (1.37 mmol, 6 mol equiv.) of potassium phthalimide and the reaction mixture was heated immediately to 120 °C for 2.5 h, the reaction being monitored by TLC with *n*-hexane–AcOEt (1:1). After the mixture had cooled to room temp., the DMF was evaporated off *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 cm^3). The solution was washed with distilled water (3 × 15 cm^3), decanted, dried over $MgSO_4$, and purified by chromatography on silica with *n*-hexane–AcOEt (2:1) to yield title compound **15** (0.100 g, 30%) as a waxy solid; $[\alpha]_D$ +49.3 (*c* 1.4, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 1715; *m*/*z* 900 $(M + 2H)^+$; δ_H(2D; 250 MHz; $CDCl_3$) 3.57–3.71 (8 H, br t, 4 × OCH_2), 3.76–3.87 (2 H, m, 2 × OC*H*H), 3.88–4.03 (6 H, m, 2 × OCH*H*, 2 × OCH_2), 4.16 (2 H, J_{gem} 13.5, $J_{1,2}$ 4, 1-, 6-H), 4.28 (2 H, m, 2-, 5-H), 4.38 (2 H, dd, $J_{1',2}$ 6.5, 1-, 6-H′), 5.76 (2 H, s, 3-, 4-H), 6.78 (2 H, m, catechol ring), 6.87 (2 H, m, catechol ring), 7.22 (4 H, m, ArH), 7.38 (2 H, m, ArH), 7.63 (4 H, m, phthal.), 7.74 (4 H, m, phthal.) and 7.83 (4 H, d, ArH); δ_C(62.896 MHz; $CDCl_3$) 168.18 (4 × N*C*=O), 165.87 (2 × Ph*C*=O), 149.13 (C-1, -2, catechol ring), 133.76 (C-4, -4′, Ph), 132.97 (C-4, -4′, -5, -5′, phthal.), 132.15 (C-1, -1′, -2, -2′, phthal.), 129.66 (C-2, -2′, -6, -6′, Ph), 129.38 (C-1, -1′, Ph), 128.15 (C-3, -3′, -5, -5′, Ph), 123.14 (C-3, -3′, -6, -6′, phthal.), 121.52 (C-4, -5, catechol ring), 114.89 (C-3, -6, catechol ring), 77.7 (C-2, -5), 71.03 (2 × OCH_2), 70.75 (C-3, -4), 69.87, 69.64 and 69.0 (6 × OCH_2) and 30.38 (C-1, -6).

2,5-*O*-[Benzene-1,2-diylbis(oxyethyleneoxyethyl)]-3,4-di-*O*-benzoyl-1,6-dideoxy-1,6-bis(4,5-diphenyl-1,2,3-triazol-1-yl)-D-mannitol 16

To a stirred solution of diphenylacetylene (0.81 g, 5 mol equiv.) in CH_2Cl_2 (4 cm^3) was added diazide **14** (0.31 g, 0.45 mmol) and the reaction vessel was heated gradually to 120 °C, the reaction being monitored by TLC with *n*-hexane–AcOEt (1:1). After 48 h, the reaction mixture being cooled to room temp., the DMF was evaporated off *in vacuo*, and the residue was purified by chromatography on silica with *n*-hexane–AcOEt (7:3) to yield title compound **16** (0.357 g, 76%) as a solid; mp 103–105 °C; $[\alpha]_D$ +38.1 (*c* 1.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1724; *m*/*z* 1047 $(M)^+$; δ_H(2D; 250 MHz; $CDCl_3$) 3.28 (2 H, m, 2 × OC*H*H), 3.45–3.72 (6 H, m, 2 × OCH_2, 2 × OCH*H*), 3.77 (4 H, br t, 2 × OCH_2), 3.98–4.18 (4 H, m, 2 × OCH_2), 4.23–4.40 (4 H, m, $J_{1,2}$ ~8, 2-, 5-H, 1-, 6-H′), 4.53 (2 H, m, J_{gem} 10.5, 1-, 6-H), 5.49 (2 H, d, $J_{2,3}$ 3.5, 3-, 4-H), 6.86 (4 H, m, catechol ring), 7.17–7.31 (20 H, m, 4 × ArH + 16 H Ph on triazole), 7.42–7.53 (6 H, m, 2 × ArH + 4 H Ph on triazole) and 7.72 (4 H, d, ArH); δ_C(62.896 MHz; $CDCl_3$) 165.25 (2 × Ph*C*=O), 148.96 (C-1, -2, catechol ring), 143.98 (2 × C-1, triazole), 134.69 (2 × C1′, triazole), 133.31 (2 × C-4, Ph), 130.21 (2 × C-2, -6, Ph), 129.74 (C-1, -1′, Ph), 129.57 (2 × C-3, -5, Ph), 129.41 (2 × C-4, Ph on triazole), 129.09 (2 × C-2, -6, Ph on triazole), 128.56 (2 × *C*=C), 128.23 (2 × C-3, -5, -3′, -5′, Ph on triazole), 127.46 (2 × C-4′, Ph on triazole), 127.39 (2 × C=*C*), 126.59 (2 × C-2′, -6′, Ph on triazole), 121.51 (C-4, -5, catechol ring), 114.81 (C-3, -6, catechol ring), 78.19 (C-2, -5), 70.99 (2 × OCH_2), 70.57 (C-3, -4), 70.36, 69.64 and 68.89 (6 × OCH_2) and 48.99 (C-1, -6).

2,5-*O*-[Benzene-1,2-diylbis(oxyethyleneoxyethyl)]-1,6-dideoxy-1,6-bis(4,5-diphenyl-1,2,3-triazol-1-yl)-D-mannitol 17

To a solution of dibenzoate **16** (110 mg, 0.105 mmol) in abs. MeOH (25 cm^3) was added MeONa (~5 mg, 0.5 mol equiv.) and the mixture was magnetically stirred for 1 h at room temp. under argon. The reaction, which was monitored by TLC (*n*-hexane–AcOEt, 1:1), was stopped by addition of Amberlyst 15 resin (~300 mg). After 30 min of gentle stirring, the beads were removed by filtration on sintered glass, rinsed with methanol (~25 cm^3), and the solvents were evaporated off under reduced pressure. The residue was purified by elution through a neutral alumina column (EtOH–CH_2Cl_2, 1:1; 75 cm^3) to yield the diol **17** (79 mg, 90%) as a waxy solid from which an analytical sample could be obtained by preparative TLC (SiO_2; AcOEt); $[\alpha]_D$ +25.7 (*c* 0.6, $CHCl_3$); *m*/*z* 838 $(M)^+$; δ_H(2D; 250 MHz; $CDCl_3$) 1.27 (2 H, br s, 2 × O*H*), 3.16–3.28 (2 H, m, 2 × *O*CH*H*), 3.39–3.45 [m, 6 H, 2 × (OCH_2, *O*C*H*H)], 3.63–3.88 (6 H, m, 2 × *O*CH_2, 3-, 4-H), 3.94–4.10 (4 H, m, 2-, 5-H, 2 × OCH_2), 4.22 (2 H, dd, $J_{1,1'}$ 14, 1-, 6-H′), 4.58 (2 H, dd, $J_{1,2}$ 3, 1-, 6-H), 6.86 (4 H, m, catechol ring), 7.19–7.30 (6 H, m, Ph on triazole), 7.31–7.48 (10 H, Ph on triazole) and 7.52 (4 H, dd, Ph on trazole); δ_C(62.896 MHz; $CDCl_3$) 148.86 (C-1, -2, catechol ring), 144.08 (2 × C-1, Ph on triazole), 135.19 (2 × C-1′, Ph on triazole), 131.01 (2 × *C*=C), 130.50 (2 × C-2, -6, Ph on triazole), 129.66 (2 × C-4, Ph on triazole), 129.27 (2 × C-3, -5, Ph on triazole), 128.49 (2 × C-3′, -5′, Ph on triazole), 129.09 (2 × C-2, -6, Ph on triazole), 127.85 (2 × C=*C*), 127.71 (2 × C-4′, Ph on triazole), 126.88 (2 × C-2′, -6′, Ph on triazole), 121.92 (C-4, -5, catechol ring), 115.00 (C-3, -6, catechol ring), 80.18 (C-2, -5), 70.64, 70.23 and 69.75 (6 × OCH_2), 69.09 (C-3, -4), 68.81 (2 × OCH_2) and 48.66 (C-1, -6).

3,4-Di-*O*-acetyl-2,5-*O*-[benzene-1,2-diylbis(oxyethyleneoxyethyl)]-1,6-dideoxy-1,6-bis(4,5-diphenyl-1,2,3-triazol-1-yl)-D-mannitol 18

To a solution of the diol **17** (35 mg, 42 mm^3) in abs. pyridine (0.5 cm^3) were added acetic anhydride (1.5 cm^3) and 4-DMAP (~1 mg) and the mixture was stirred at room temp. under argon for 1 h. Usual work-up[1] and chromatography on silica gel with *n*-hexane–AcOEt (3:7) yielded diacetate **18** (40 mg, 95%) as a homogeneous wax, mp < 50 °C; $[\alpha]_D$ +23.4 (*c* 0.6, $CHCl_3$); *m*/*z* 922 $(M)^+$; δ_H(250 Hz; $CDCl_3$) 2.01 (6 H, s, 2 × CH_3), 3.12–3.27 (2 H, m, 2 × *O*CH*H*), 3.4–3.62 [6 H, m, 2 × (OCH_2 + *O*C*H*H)], 3.71 (4 H, t, 2 × OCH_2), 4.0–4.12 (6 H, m, 2-, 5-H, 2 × OCH_2), 4.22 (2 H, dd, $J_{1,1'}$ 14, 1′-, 6′-H), 4.43 (2 H, dd, $J_{1,1'}$

14, $J_{1,2}$ 4.5, 1-, 6-H), 5.13 (2 H, d, $J_{2,3}$ 4, 3-, 4-H), 6.85 (4 H, m, catechol ring), 7.20–7.28 (6 H, m, Ph on triazole), 7.42 (10 H, br s, Ph on triazole) and 7.53 (4 H, dd, Ph on triazole); δ_C(62.896 MHz; $CDCl_3$) 169.77 (2 × *C*OCH_3), 149.02 (C-1, -2, catechol ring), 144.12 (2 × C-1, Ph on triazole), 134.86 (2 × C-1′, Ph on triazole), 130.87 (2 × *C*=C), 130.45 (2 × C-2, -6, Ph on triazole), 129.64 (2 × C-4, Ph on triazole), 129.23 (2 × C-3, -5, Ph on triazole), 128.40 (2 × C-3′, -5′, Ph on triazole), 127.62 (2 × C-4′, Ph on triazole), 127.59 (2 × C=*C*), 126.72 (2 × C-2′, -6′, Ph on triazole), 121.61 (C-4, -5, catechol ring), 114.85 (C-3, -6, catechol ring), 78.25 (C-2, -5), 70.78 and 70.38 (4 × OCH_2), 70.23 (C-3, -4), 69.69 and 68.98 (4 × OCH_2), 48.78 (C-1, -6) and 20.62 (2 × CH_3).

1,6-Diazido-2,5-*O*-[benzene-1,2-diylbis(oxyethyleneoxyethyl)]-1,6-dideoxy-3,4-*O*-methylene-D-mannitol 19

To a solution of the diester **14** (100 mg, 0.145 mmol) in CH_2Br_2 (8 cm^3) were added 50% aq. NaOH (6 cm^3) and NBu_4HSO_4 (51 mg, 1 mol equiv.) and the reaction mixture was vigorously stirred at room temp. for 12 h. Usual work-up[1] and chromatography on silica gel with *n*-hexane–AcOEt (3:1) yielded unchanged starting material **14** (70 mg, 70% recovery) and then title compound **19** (10 mg, 14%) as a homogeneous wax, mp < 50 °C; $[a]_D$ +2.1 (*c* 1.6, $CHCl_3$); *m*/*z* 494 $(M)^+$; δ_H(250 MHz; $CDCl_3$) 3.45 (2 H, m, $J_{1,1'}$ 13, $J_{1,2}$ 6.5, 1-, 6-H), 3.52–3.67 (4 H, m, 2-, 5-H, 1-, 6-H′), 3.71–3.80 (6 H, m, 2 × OCH_2, 2 × OC*H*H), 3.81–4.01 (6 H, m, 2 × OCH_2, 2 × OC*H*H), 4.07 (2 H, d, $J_{2,3}$ 5, 3-, 4-H), 4.18 (4 H, t, 2 × OCH_2), 4.93 (2 H, s, OCH_2O) and 6.9 (4 H, s, catechol ring); δ_C(62.896 MHz; $CDCl_3$) 149.35 (C-1, -2, catechol ring), 121.84 (C-4, -5, catechol ring), 114.47 (C-3, -6, catechol ring), 95.3 (OCH_2O), 79.40 (C-2, -5), 77.65 (C-3, -4) 70.81, 70.12 and 69.98 (6 × OCH_2), 68.95 (2 × OCH_2) and 50.68 (C-1, -6).

2,5-*O*-[Benzene-1,2-diylbis(oxyethyleneoxyethyl]-1,6-dideoxy-1,6-bis(4,5-diphenyl-1,2,3-triazol-1-yl)-3,4-*O*-ethylene-D-mannitol 20

To a solution of the diester **16** (80 mg, 75 μmol) in 1,2-dichloroethane (7 cm^3) were added 50% aq. NaOH (7 cm^3) and NBu_4HSO_4 (26 mg, 1 mol equiv.) and the reaction mixture was vigorously stirred at room temp. for 24 h. Usual work-up[1] and preparative TLC on silica gel with *n*-hexane–AcOEt (1:3) yielded title compound **20** (~40 mg, 60%) as a homogeneous gum, $[a]_D$ +23.6 (*c* 0.5, $CHCl_3$); *m*/*z* 864 $(M + 2)^+$; δ_H(250 MHz; $CDCl_3$) 3.24–3.86 (18 H, m, 4 × OCH*H*, 4 × *O*CH_2, 2 × CH_2 dioxane, 3-, 4-H), 4.05 (4 H, br t, 2 × OCH_2), 4.18–4.45 (4 H, m, 2-, 5-H, 1-, 6-H′), 4.56 (2 H, dd, $J_{1,1'}$ 14, $J_{1,2}$ 4, 1-, 6-H), 6.85 (4 H, m, catechol ring), 7.18–7.36 (6 H, m, Ph on triazole), 7.44 (10 H, br s, Ph on triazole) and 7.53 (4 H, dd, Ph on triazole); δ_C(62.896 MHz; $CDCl_3$) 149.07 (C-1, -2, catechol ring), 144.0 (2 × C-1, Ph on triazole), 135.06 (2 × C-1′, Ph on triazole), 131.19 (2 × C=*C*), 130.54 (2 × C-2, -6, Ph on triazole), 129.61 (2 × C-4, Ph on triazole), 129.33 (2 × C-3, -5, Ph on triazole), 128.48 (2 × C-3′, -5′, Ph on triazole), 127.86 (2 × *C*=C), 127.66 (2 × C-4′, Ph on triazole), 126.86 (2 × C-2′, -6′, Ph on triazole), 121.74 (C-4, -5, catechol ring), 114.85 (C-3, -6, catechol ring), 79.27 (C-2, -5), 76.28 (C-3, -4), 70.4 and 69.65 (8 × OCH_2), 65.79 (2 × C, dioxane) and 48.76 (C-1, -6).

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