trans-Fused crown ethers from 2,5-*O*-methylene-D-mannitol: synthesis, X-ray diffraction structure and full nuclear magnetic resonance spectroscopic data of 1,6-diazido-1,6-dideoxy-2,5-*O*-methylene-3,4-*O*-naphthalene-2,3-diylbis(oxyethyleneoxyethylene)-D-mannitol and 3,4-di-*O*-acetyl-1,6-diazido-1,6-dideoxy-2,5-*O*-methylene-D-mannitol

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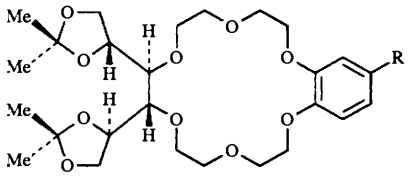
The crystalline compound **5**, named in the title and prepared from technical D-mannitol in 6 steps, has been fully investigated by different spectroscopic methods including MS, IR, ^{1}H, ^{13}C, ^{14}N and ^{15}N NMR. These results confirm the perfect C_2-symmetry in solution and provide the complete map of this chiral homotopic crown ether. X-ray diffraction analysis of compound **5** reveals it exists in a distorted chair conformation as one monocyclic precursor **14**. Treatment of compound **5** with acetylene derivatives gave the macrocycles **6** and **7** with bulky symmetric triazole substituents. The anomalous lack of complexing abilities of compounds **5**, **6**, and most related macrocycles towards phenylglycine methyl ester perchlorates could be explained by the rigidity of the dioxepane framework around the C-3/C-4 axis of D-mannitol.

Introduction

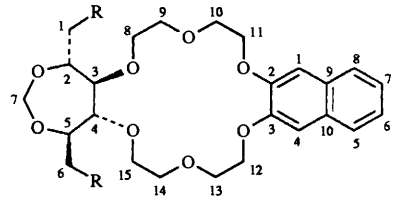
Carbohydrates and related compounds offer a wide range of inexpensive starting materials for the synthesis of numerous chiral intermediates.[1] Among them, D-mannitol, which is endowed with C_2-symmetry, offers unique synthetic opportunities. For instance, D-mannitol ketals have been extensively used for decades as sources of many synthons such as glyceraldehydes,[2] (*S*)-propanediol,[3] and (*R*)- and (*S*)-epichlorhydrin.[4] They also served as chiral frameworks for the synthesis of target molecules such as homotopic crown ethers,[5] chiral drugs,[6] and precursors to natural compounds.[7] We have already reported on the ability of simple 18-crown-6 ethers (**1**–**4**) immobilised on an analytical reversed phase to resolve racemic free amino acids:[5e,8]



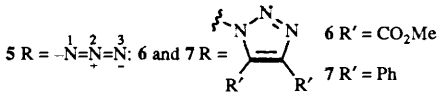
1 R = H; **2** R = Me; **3** R = NO_2; **4** R = Bu^t

Though most of these hosts manifested measurable enantioselectivity in solution towards phenylglycine methyl ester salts as guests,[9] the di-*O*-isopropylidene protective group proved to be too labile for valuable chromatographic applications. To obviate this difficulty and with the final aim to develop new chiral stationary phases, we decided to explore a novel crown ether family based on a far more acid-stable 2,5-*O*-methylene-D-mannitol framework.

This paper contains a full account of the synthesis, X-ray structure and full characterisation of compound **5** by ^{1}H, ^{13}C



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



5 R = $-\overset{1}{N}=\overset{2}{N}^+=\overset{3}{N}^-$; **6** and **7** R = ; **6** R′ = CO_2Me; **7** R′ = Ph

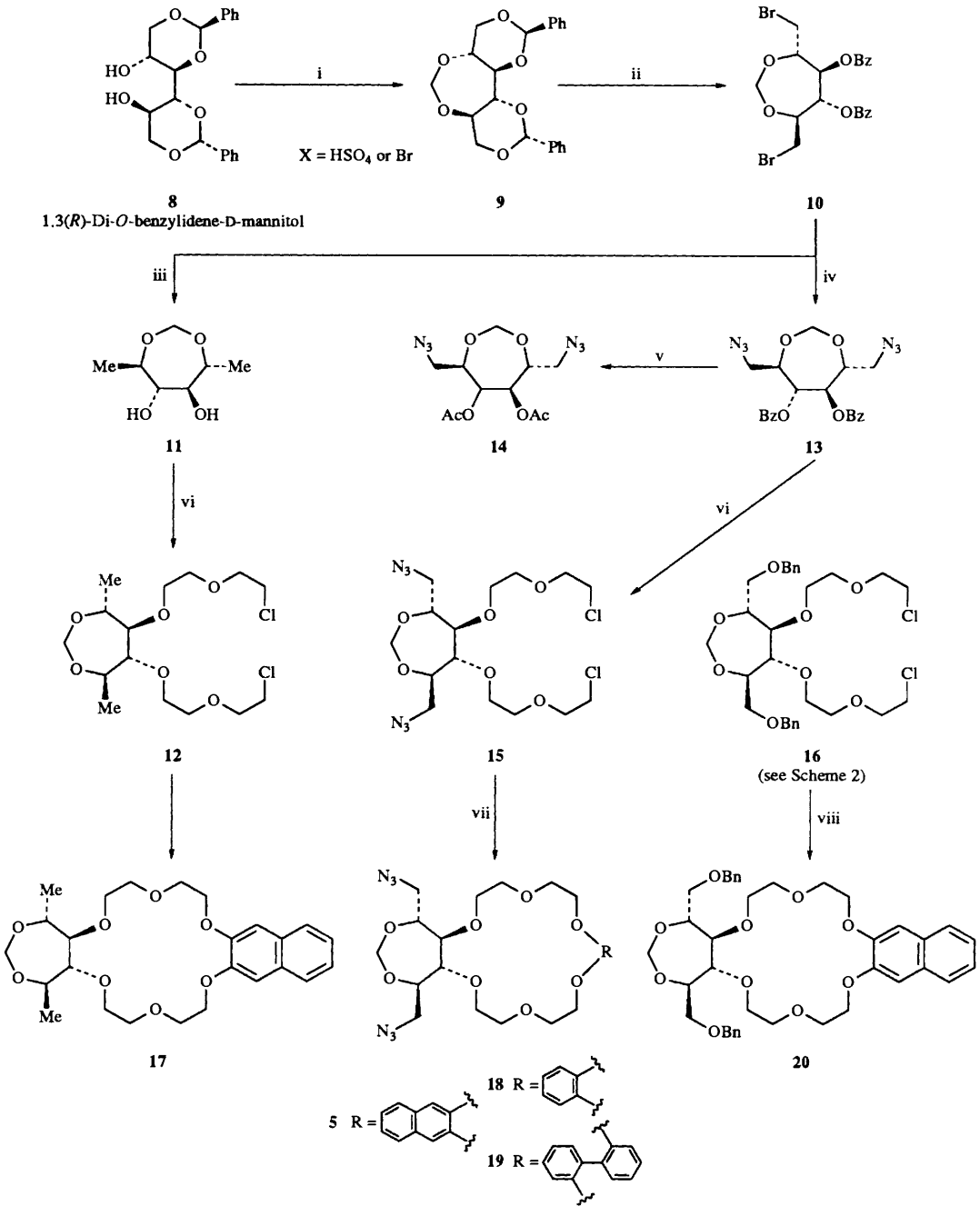
(including two-dimensional methods), ^{14}N and ^{15}N NMR spectroscopy and provides unequivocal proof of our assignments and useful information about the conformation of the seven-membered ring. Furthermore, the good reactivity of the azido groups could be exploited in cycloaddition reactions with acetylene derivatives to associate π-electron rich substituents (**6** and **7**) on each side of the cavity. Part of this work has been presented as a preliminary communication.[10]

Results and discussion

Synthesis

The synthesis of crown ethers **5**, **17**–**20** proceeded as outlined in Scheme 1. The methylenation of commercially,† or easily available 1,3(*R*):4,6(*R*)-di-*O*-benzylidene-D-mannitol[11] **8**, was performed with a *gem*-dihalide as both solvent and reagent under basic conditions with a tetrabutylammonium salt as catalyst. First attempts to use dichloromethane led to poor

† [28224-73-9] from Fluka Chemie AG, Switzerland.

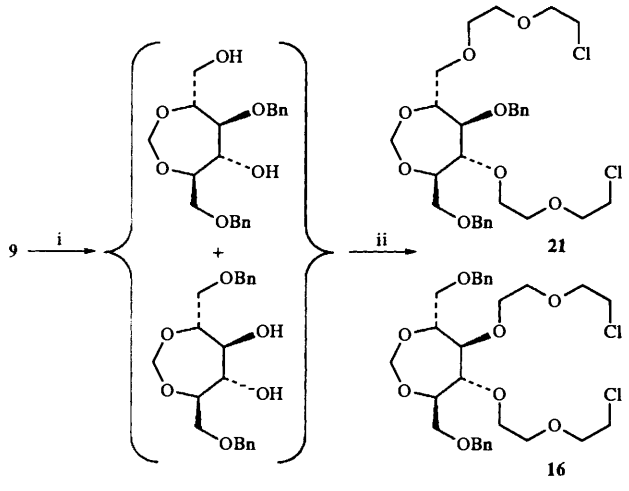


Scheme 1 Synthesis of crown ethers **5**, **17**–**20** from 1,3(*R*):4,6(*R*)-di-*O*-benzylidene-D-mannitol **8**. *Reagents*: i, CH_2Br_2, NBu_4X (X = HSO_4 or Br), 50% aq. NaOH; ii, NBS, CCl_4, $CaCO_3$; iii, $LiAlH_4$, THF; iv, DMF, NaN_3; v, KOH; then Ac_2O; vi, $(ClCH_2CH_2)_2O$, aq. NaOH; vii, dihydroxy aromatics, K_2CO_3, Bu^nOH; viii, 2,3-dihydroxynaphthalene, K_2CO_3, Bu^nOH.

yields even after 24 h of reaction at 25 °C.[12] This could be improved by the use of more reactive dibromomethane.[13] The nicely crystalline *trans*-fused tricyclic acetal **9** was previously synthesized in 1969 by Szarek and colleagues in a different way from 2,5-*O*-methylene-D-mannitol.[14] Surprisingly, regioselective opening of the benzylidene acetals of compound **9** with two mole equivalents of *N*-bromosuccinimide (NBS) in CCl_4 afforded the bis-bromide **10** as sole product in very good yield. As with compound **9**, ^1H NMR spectra of compound **10** agree with the C_2-symmetry of the dioxepane ring, where the 2,5-*O*-methylene protons are magnetically equivalent in solution at 300 K. Compound **10** could be quantitatively reduced by $LiAlH_4$ in refluxing tetrahydrofuran (THF) to the chiral diol **11**. As with compound **9**, diol **11** was previously isolated by Stoddart and Szarek in 1971 after a multistep synthesis from D-mannitol.[15] Alternatively, the two bromine atoms of compound **10** could be easily displaced with sodium azide in dimethylformamide (DMF) at 100 °C to give diazide **13**, which was converted into the highly crystalline diacetate **14** or into the half-crown **15** in good yield by using bis-(2-chloroethyl) ether as solvent and reagent under phase-transfer conditions.[16] Similar treatment of cyclic acetal **11** yielded the half-crown **12** which was cyclised in boiling butan-1-ol with 2,3-dihydroxynaphthalene with potassium carbonate as the sole base to give the crown ether **17** in 71% yield. In the same manner, but from half-crown **15** and 2,3-dihydroxynaphthalene, pyrocatechol, or 2,2′-biphenol, crown ethers **5**, **18** and **19** were isolated in 44, 75 and 25% yield, respectively. The good reactivity of the azide groups in crown **5** could be exploited in cyclisation reactions in neat dimethyl acetylenedicarboxylate

Table 1 Crystallographic data and instrumental setting

Compound	5	14
M	$C_{25}H_{32}N_6O_8$	$C_{11}H_{16}N_6O_6$
Formula weight	544.56	328.28
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a/Å	8.713(2)	6.491(2)
b/Å	10.079(2)	8.027(2)
c/Å	31.114(2)	30.518(2)
α,β,γ/°	90	90
V/Å^3	2732.2(6)	1590.0(6)
Z	4	4
D_c/g cm^{-3}	1.324	1.371
Radiation, λ/Å	1.540 56	1.540 56
μ/mm^{-1}	0.749	0.971
$F(000)$	1152	688
Crystal size/mm	0.2 × 0.2 × 0.5	0.4 × 0.4 × 1.0
θ-range for data collection/°	2.92–69.85	2.89–69.80
Index ranges	$0 \leqslant h \leqslant 10, 0 \leqslant k \leqslant 12, 0 \leqslant l \leqslant 37$	$0 \leqslant h \leqslant 10, 0 \leqslant k \leqslant 12, 0 \leqslant l \leqslant 37$
Reflections collected	2998	1811
Independent reflections	2479	1776
Refinement method	Full-matrix least-square on F	Full-matrix least-square on F
Data restraints/parameters	1793/0/481	1654/0/209
R	0.0550	0.0529
$R' = (\Sigma w\Delta^2/\Sigma wF_o^2)^{\frac{1}{2}}$	0.0492	0.1458
Goodness-of-fit	1.72	1.041
Largest difference peak and hole/e Å^{-3}	0.235 and −0.153	0.0563 and 0.1628



Scheme 2 Synthesis of 1,3-dioxepane half-crowns **16** and **21** from tricyclic acetal **9**. *Reagents*: i. $NaBH_3CN$, HCl, Et_2O–THF; ii, $(ClCH_2CH_2)_2O$, aq. NaOH.

(DMAD) or diphenylacetylene to give the bulky *vic*-triazoles **6** and **7** in excellent yields (95 and 88% respectively). Alternatively (see Scheme 2), the reductive cleavage of benzylidene groups[17] of compound **9**, whatever the acid employed (HCl, CF_3SO_3H), always gave a roughly 1:1 mixture of 1,6- and 1,4-isomers in only a poor yield. This TLC-homogeneous mixture was treated (as for pure compounds **11** and **13**) with bis-(2-chloroethyl) ether to give the separable isomers **16** and **21** by conventional chromatography. The isomer **21**, whose spectrum showed no C_2-symmetry, was discarded and only the dichloride **16** was cyclised onto 2,3-dihydroxynaphthalene to give the crown ether **20** in a modest 32% yield.

Table 2 Compared torsion angles (°) for the dioxepane ring of compounds **5** and **14**

Torsion angle	5	14
C(18)–O(7)–C(16)–C(17)	−144.9(4)	−145.4(2)
C(18)–O(7)–C(16)–C(15)	96.5(4)	95.1(3)
C(18)–O(8)–C(19)–C(21)	95.7(4)	95.9(3)
C(18)–O(8)–C(19)–C(20)	−143.0(4)	−143.1(3)
O(7)–C(16)–C(17)–N(1)	58.6(6)	66.6(3)
O(7)–C(16)–C(15)–C(21)	−67.5(5)	−67.7(3)
O(7)–C(16)–C(15)–O(5)	170.9(3)	174.4(2)
C(16)–C(17)–N(1)–N(2)	−76.0(6)	−159.5(3)
C(16)–O(7)–C(18)–O(8)	−48.0(5)	−49.9(3)
C(16)–C(15)–O(5)–C(14)	−115.0(4)	−124.3(3)
C(16)–C(15)–C(21)–C(19)	47.0(6)	52.9(3)
C(16)–C(15)–C(21)–O(6)	166.8(4)	173.7(2)
C(17)–N(1)–N(2)–N(3)	−172(5)	−178(4)
C(17)–C(16)–C(15)–O(5)	56.2(5)	57.3(3)
C(17)–C(16)–C(15)–C(21)	177.9(4)	175.2(2)
C(15)–O(5)–C(14)–C(13)	−164.5(4)	−176.1(3)
C(15)–C(21)–O(6)–C(22)	119.0(4)	113.2(3)
C(15)–C(21)–C(19)–C(20)	174.2(4)	169.4(2)
C(15)–C(21)–C(19)–O(8)	−67.3(5)	−73.7(3)
O(5)–C(15)–C(21)–O(6)	−70.0(4)	−66.7(3)
O(5)–C(15)–C(21)–C(19)	170.1(4)	172.4(2)
C(14)–O(5)–C(15)–C(21)	118.5(4)	113.0(3)
C(23)–C(22)–O(6)–C(21)	−168.3(4)	−171.9(3)
C(22)–O(6)–C(21)–C(19)	−117.7(4)	−123.2(3)
O(6)–C(21)–C(19)–C(20)	55.6(5)	50.9(3)
O(6)–C(21)–C(19)–O(8)	174.0(3)	167.8(2)
C(21)–C(19)–C(20)–N(4)	68.1(6)	−170.7(2)
C(21)–C(19)–O(8)–C(18)	95.7(4)	95.9(3)
C(19)–C(20)–N(4)–N(5)	90.3(6)	−81.0(4)
C(19)–O(8)–C(18)–O(7)	−46.0(5)	−43.5(3)
O(8)–C(19)–C(20)–N(4)	−51.0(6)	73.3(3)
N(1)–C(17)–C(16)–C(15)	174.5(4)	−175.9(3)
C(20)–N(4)–N(5)–N(6)	−167(4)	−170(3)

Crystal structure determinations

Crystallographic data are summarised in Table 1. Torsion angles are given in Table 2. The structure of crown ether **5** is shown in Fig. 1 and that of 1,3-dioxepane diacetate **14** in Fig. 2. Judging from these data, and especially from a comparison of the torsion angles (see Table 2), it clearly appears that the two dioxepane structures are quasi-superimposable when one excepts the azido groups on C-1/C-6. More precisely, the torsion angles around C-3/C-4 of the mannitol (*e.g.*, O-5–C-15–C-21–C-19 or C-16–C-15–C-21–O-6 in the crystal structure) are almost identical in the two structures (**5** and **14**) independently of the nature of the substituents on C-3/C-4. These results confirm the previous conclusions of former conformational

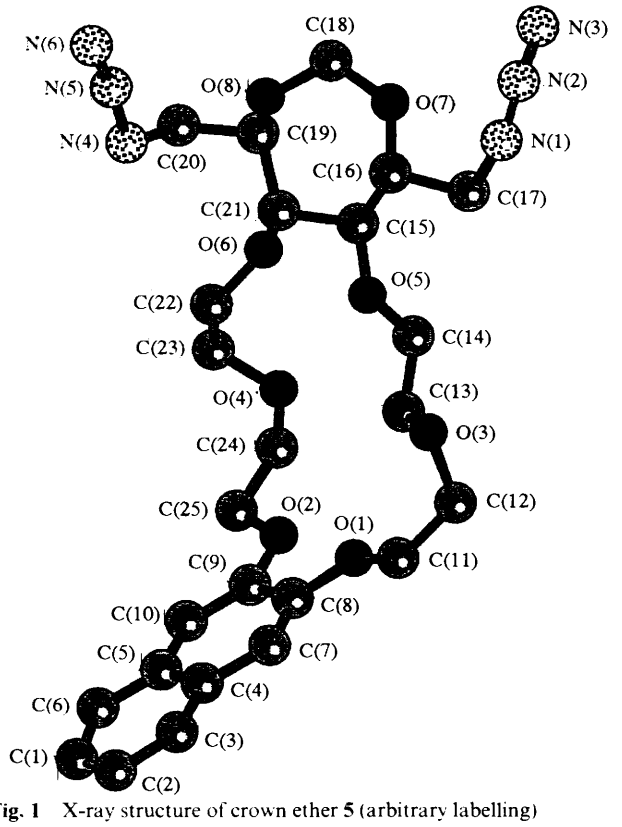


Fig. 1 X-ray structure of crown ether **5** (arbitrary labelling)

studies by Stoddart and co-workers on 1,3-dioxepanes derived from 2,5-*O*-methylene-D-mannitol,[18] in agreement with other studies based on rotational Raman,[19] ^{1}H and ^{13}C NMR[20] spectroscopy. These studies suggested that 1,3-dioxepane derivatives exist predominantly with the twist-chairs (TC) as lowest energy conformations, even at low temperature, except perhaps in rare cases such as when an azirine is *cis*-fused to the dioxepane ring.[21] The TC-conformation also appears to be the more stable conformation in the solid state. There is, however, a loss of reflection symmetry in the crystals.

Assignment of NMR spectra and conformations in $CDCl_3$

Two-dimensional NMR spectroscopy (including COSY, NOESY, HMQC and HMBC experiments) were used to confirm the structure of compound **5** and allowed the total assignment of the ^{1}H and ^{13}C signals to be made. For instance, Fig. 3 shows the 2D heteronuclear multiple quantum-filtered coherence (HMQC) spectrum of host **5** in $CDCl_3$ at room temp. The two-dimensional heterocorrelation showed 'three' carbon atoms bearing two magnetically non-equivalent protons: C-1 C-6 (at δ_C 51.87; δ_H 3.40 and 3.50), C-8 C-15 in the cavity (at δ_C 73.08; δ_H 3.80, 4.13) and C-10 C-13 (at δ_C 69.20; δ_H 3.9, 4.0). The assignment of these peaks was corroborated by additional two-dimensional NMR experiments which gave the connections between protons by nuclear Overhauser enhancement (NOE) effects and the connections between proton and carbon atoms through 2–3 bonds lengths [2D heteronuclear multiple-bond coherence (HMBC)]. As shown in Fig. 4, the NOESY experiment showed NOE effects between the methylene protons at δ 4.8 (on C-7) and 2-H at δ 3.8; also, the NOE effect between the protons at δ 3.8 (on C-2 C-5) and the proton at δ 4.13 (on C-8 C-15) indicates that they are in very close proximity. These results *in toto* are in agreement with the crystallographic data which revealed a TC-conformation for the 1,3-dioxepane ring in the solid state. In this conformation, 7-H and 2-H are pointed upward. More generally, the two-proton singlet between δ 4.5 and 5.1 is the most obvious characteristic common to all

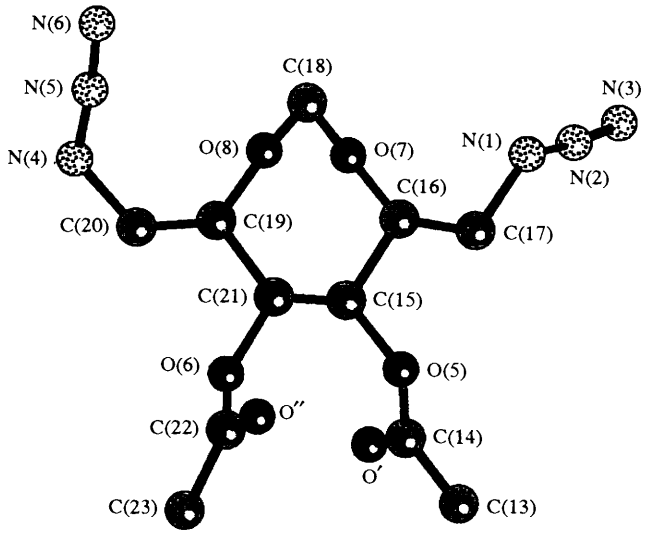


Fig. 2 X-Ray structure of dioxepane **14** (arbitrary labelling)

monocyclic 1,3-dioxepane derivatives **9**–**16** and to four of the seven *trans*-fused crown ethers (**15**, **17**, **18**, **20**). The failure to observe any chemical-shift difference between these two diastereotopic protons in most of these dioxepane derivatives agrees with the previous observations made by Stoddart and Szarek in this series.[15] A simulated spectrum was obtained with an improved LAOCOON program, the ring protons being analysed as a non-classical four-spin AA'BB' system (the AA' part being assigned to 2-H and 5-H and the BB' part to 3-H and 4-H). Best-fit computed coupling constants appeared to be: $J_{2,3} = J_{4,5} \sim 8$ Hz and $J_{3,4}$ 8.7 Hz. These values fairly confirm *trans*-diaxial relationships[22] between protons on C-2(5) and C-3(4), C-3 and C-4 of the D-mannitol framework, which are consistent with the revealed torsion angles (*e.g.*, O-6–C-21–C-19–O-8 = 174° ~ O-7–C-16–C-15–O-5 = 171° or C-16–C-15–C-21–O-6 = 167° ~ O-5–C-15–C-21–C-19 = 170°) in the slightly asymmetric crystal. Similar torsion angle values (170 ± 4°) and coupling constants could be also observed for the monocyclic diacetate **14**, whose ^{1}H spectrum was found to look in part like that of the already known 1,3,4,6-tetra-*O*-acetyl-2,5-methylene-D-[1,1,6,6-$^2H_4$]mannitol.[15] The ^{14}N NMR spectrum of compound **5** in [$^2H_6$]acetone showed only two resonance signals upfield from $MeNO_2$, one at −130.7 ppm assigned to the central nitrogen atom of the azide (N-2) and another, very broad, at ~ −175 ppm assigned to the terminal nitrogen atom (N-3).[23] The natural-abundance 50.653 MHz ^{15}N NMR and FT-IR spectra confirmed the presence of azide functionalities and, altogether with the ^{1}H and ^{13}C NMR spectra, confirm the perfect symmetry of compound **5** in solution at room temperature. In only two cases (compounds **6** and **7**) where bulky substituents are close to the dioxepane ring, did the diastereotopic methylene protons exhibit slight chemical-shift unequivalence (~ 0.05 ppm) with a small vicinal coupling constant (~ 3 Hz). All these facts demonstrate the existence of a rapid conformational equilibrium of the 1,6-dideoxy-2,5-*O*-methylene-D-mannitol framework between chair and degenerate chair forms, endowed in most of the cases with time-averaged C_2-symmetry. However, the case of compound **19** must be considered from another point of view. It is established that some strained 2,2'-bridged biphenyl derivatives may exist under two enantiomeric forms, thus demonstrating the non-coplanarity of the aromatic rings.[24] We explain the presence of a second, weaker singlet around δ 4.8, for the two *O*-methylene protons, by the formation of a less stable conformer or atropisomer (which could not be detected by conventional TLC whatever the developer employed), as for known diastereoisomers of racemic binaphthol.[25]

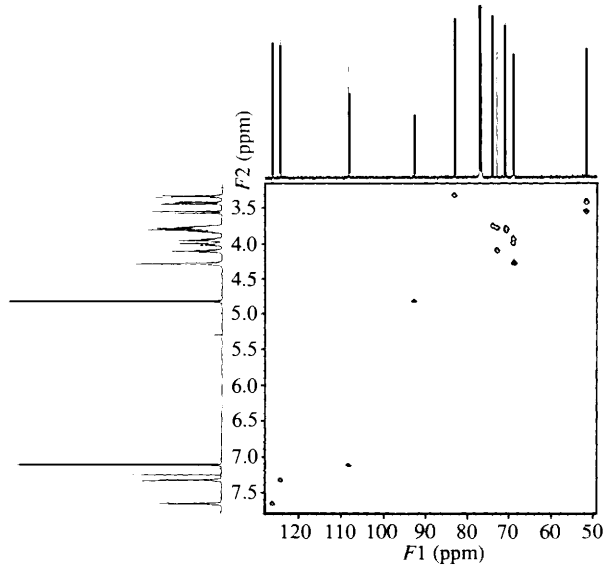


Fig. 3 HMQC spectrum of crown ether **5** in $CDCl_3$ at 499.843 MHz

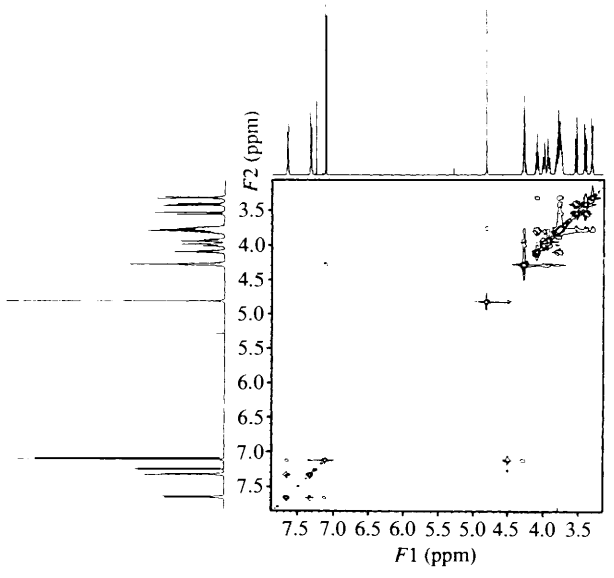


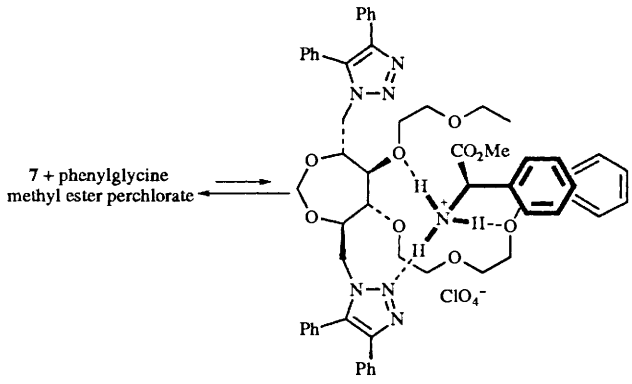
Fig. 4 NOESY spectrum of crown ether **5** at 499.843 MHz

Complexation experiments in $CDCl_3$

Furthermore, liquid–liquid extraction experiments were performed with racemic phenylglycine methyl ester perchlorate on crown ethers **5**–**7**, **17**–**20** at 0 °C. Surprisingly, and except for a single case (the macrocycle **7** but to only a small extent), only traces of the amino acid derivatives could be seen in the ^1H NMR spectra of the isolated and dried organic phases. This rather dramatic and anomalous behaviour was also seen with (±)-phenylalanine methyl ester, dopamine hydrochloride, and potassium picrate on compound **5**. Nevertheless, an apparent stoichiometry of ~0.4 (guest/host) without enantioselectivity was measured in the chloroform phase when host **7** was equilibrated with a four-fold excess of (±)-phenylglycine methyl ester perchlorate at 0 °C (pH ~3.7 ± 0.2).[9] The origin of this phenomenon is under investigation with the help of molecular modelling (BIOSYM) and might suggest the participation of one nitrogen atom of the triazole in the complexation.

Conclusions

The evidence so far available indicates that the rigid TC-conformations of the 1,3-dioxepane moiety of such *trans*-fused



[18]- or [20]-crown-**6** do not allow the movements necessary to create a regular co-ordination polyhedron around the ammonium cation. We are currently investigating parent structures incorporating an 'open' 1,6-dideoxy-D-mannitol framework, which are able to complex enantioselectively with primary ammonium cations, to investigate this hypothesis.

Experimental

Preparative chromatography was performed on silica 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 20 °C with $[\alpha]_D$-values given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 197 spectrometer at room temp. Crystallographic data were collected on a CAD4 Enraf-Nonius diffractometer in the θ–2θ scanning mode (θ < 70°) at room temp. Crystallographic data and instrumental setting are summarised in Table 1. The structures were solved and refined using the SHELXL 93 program.[26] Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.‡ Unless otherwise noted ^1H and ^{13}C spectra were recorded with a Bruker AC250 spectrometer operating at 250 and 62.9 MHz, respectively, and the ^{14}N spectra with a Bruker Aspect 3000 at 28.90 MHz. Me_4Si (^1H NMR) or $MeNO_2$ (^{14}N NMR) were used as internal references. *J*-Values are in Hz. The parameters for the two-dimensional NMR spectra of compound **5** were as follows: NOESY, 2D spectral width 3379.8 Hz, acquisition time 0.151 s, pulse width 11.9 μs, number of increments 256, relaxation delay 0.958 s; HMQC, 2D spectral width 18854.5 Hz, acquisition time 0.151 s, pulse width 11.9 μs, number of increments 256, relaxation delay 1.000 s; COSY, 2D spectral width 2287.0 Hz, acquisition time 0.224 s; all other parameters were the same as the above. The ^{15}N NMR spectrum of compound **5** was taken at 50.65 MHz on a Varian-500 and chemical shifts are reported upfield from $MeNO_2$ which was used as external standard. The 90° pulse width was 16.0 μs, the pulse interval was set at 5.0 s, and the temperature of the probe was 20 °C. The spectrum was obtained after 9408 transients in $CDCl_3$ at ~0.3 mol dm^{-3}. Mass spectra were recorded on a Nermag R1010 instrument at 70 eV, and elemental analyses were performed by the CNRS (Service Central de Microanalyse, Vernaison, France).

1,3(*R*):4,6(*R*)-Di-*O*-benzylidene-2,5-*O*-methylene-D-mannitol 9

To a solution of 1,3:4,6-di-*O*-benzylidene-D-mannitol **8**[11,12] (7.00 g, 19.5 mmol) and NBu_4HSO_4 (6.65 g, 19.5 mmol) in dibromomethane (80 cm^3) was added 50% aq. NaOH (50 cm^3).

‡ See Instructions for Authors, in the January issue.

The mixture was vigorously and mechanically stirred below 25 °C for 1 h. The emulsion was then diluted with ice-cold water (100 cm^3) and CH_2Cl_2 (100 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 30 cm^3), and the organic phases were combined, washed with water until neutral, dried over $MgSO_4$, and finally evaporated to dryness. The resulting solid was boiled with hot EtOH (~200 cm^3), the solution was cooled to room temperature and filtered on a paper, and the residue was dried *in vacuo* to give compound **9** as a solid (5.05 g, 69%), mp 242–243 °C; $[\alpha]_D$ −134.8 (*c* 1.3, $CHCl_3$) {lit.,[14] mp 255–257 °C; $[\alpha]_D$ −134.9 (*c* 1.7, $CHCl_3$)}; δ_H(250 MHz; $CDCl_3$) 3.86 (6 H, br s), 4.33 (2 H, dd), 4.85 (2 H, s, benzylidene), 5.52 (2 H, s, OCH_2O) and 7.34–7.5 (10 H, m, ArH).

3,4-Di-*O*-benzoyl-1,6-dibromo-1,6-dideoxy-2,5-*O*-methylene-D-mannitol 10

To a stirred dispersion of compound **9** (4.00 g, 10.8 mmol) in anhydrous CCl_4 (100 cm^3) under nitrogen were added successively dried $CaCO_3$[27] (2.38 g, 2.2 mol equiv.), NBS (4.14 g, 2.2 mol equiv.) and a few crystals of Bz_2O_2. The resulting mixture was immediately heated to reflux by an incandescent 500 W lamp for 30 min, cooled to 5 °C, and filtered under a fume board. The remaining succinimide and calcium salts were carefully washed with CH_2Cl_2 (~50 cm^3) and the combined organic phases washed successively with 37% aq. $NaHSO_3$ (25 cm^3), 5% aq. $NaHCO_3$ (25 cm^3) and water (25 cm^3), dried over $MgSO_4$ and finally evaporated under reduced pressure. The residue was purified by rapid chromatography with hexane–AcOEt (4:1) as eluent, which yielded compound **10** as a solid (4.63 g, 81%), mp 121 °C (from Pr^iOH) (Found: C, 47.8; H, 3.65; Br, 30.1. $C_{21}H_{20}Br_2O_6$ requires C, 47.75; H, 3.82; Br, 30.26%); $[\alpha]_D$ −108.0 (*c* 1.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1720; δ_H(250 MHz; $CDCl_3$) 3.47–3.61 (4 H, m and 6-H_2), 4.30 (2 H, m, 2-, 5-H), 5.04 (2 H, s, OCH_2O), 5.47 (2 H, dd, $J_{2,3}$ 7.5, 3-, 4-H), 7.41 (4 H, t, ArH), 7.56 (2 H, t, ArH) and 7.93 (4 H, d, ArH).

1,6-Dideoxy-2,5-*O*-methylene-D-mannitol 11

To a stirred dispersion of $LiAlH_4$ (0.60 g, 15.7 mmol) in THF (20 cm^3) at 0 °C was added dropwise a solution of the bis-bromide **10** (1.04 g, 1.97 mmol, 0.25 mol equiv.) in THF (10 cm^3). The mixture was allowed to warm up to room temp., the hydride excess was allowed to react with AcOEt (5 cm^3), and the suspension was filtered on a sintered glass, which was carefully rinsed with THF (~20 cm^3). The solvents were evaporated off under reduced pressure, the residue was dispersed in CH_2Cl_2 (50 cm^3) and extracted with distilled water (2 × 25 cm^3), and the aqueous phase was evaporated under reduced pressure with small volumes of toluene to yield the crude 1,3-dioxepane **11** (0.30 g, 94%) with a few inorganic salts as impurities: mp 117–118 °C (lit.,[15] 115–116 °C).

3,4-Bis-*O*-[2-(2-chloroethoxy)ethyl]-1,6-dideoxy-2,5-*O*-methylene-D-mannitol 12

To a stirred solution of the diol **11** (0.29 g, 1.79 mmol) and Bu_4NHSO_4 (1.22 g, 2 mol equiv.) in bis-(2-chloroethyl) ether (15 cm^3) was added 50% aq. NaOH (15 cm^3) at 0 °C. The two-phase system was vigorously and magnetically stirred below 5 °C for 14 h, the reaction being monitored by TLC with hexane–AcOEt (3:1). The mixture was diluted with ice-cooled water (50 cm^3) and CH_2Cl_2 (50 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 cm^3), the organic phases were combined, washed with water (2 × 20 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure, and the excess of reagent was removed under reduced pressure. Rapid chromatography with hexane–AcOEt (4:1) yielded gummy bis-chloride **12** (0.252 g, ~40%), $[\alpha]_D$ −6.7 (*c* 1.1, $CHCl_3$); δ_H(250 MHz; $CDCl_3$) 1.63 (6 H, d, $J_{1,2} = J_{6,5}$ = 6.5, 1- and 6-H_3), 3.02 (2 H, dd, $J_{2,3} = J_{3,4}$ = 7, 3-, 4-H), 3.52–3.83 (16 H, m, 4 × OC_2H_4O), 4.01 (2 H, m, 2-, 5-H) and 4.39 (2 H, s, OCH_2O).

1,6-Diazido-3,4-di-*O*-benzoyl-1,6-dideoxy-2,5-*O*-methylene-D-mannitol 13

To a solution of the 1,6-dibromo-1,6-dideoxy-2,5-*O*-methylene-D-mannitol **10** (0.90 g, 1.7 mmol) in anhydrous DMF (25 cm^3) were added sodium azide (0.45 g, 4 mol equiv.) and ammonium chloride (0.365 g, 4 mol equiv.). The resulting stirred mixture was heated to 100 °C for 1.5 h, the reaction being monitored by TLC with hexane–AcOEt (4:1) since product **13** produced a typical brownish colour after being burnt with dil. H_2SO_4; the mixture was cooled to room temp., DMF was evaporated off under reduced pressure, and the residue was redissolved in CH_2Cl_2 (50 cm^3). The solution was washed with distilled water (2 × 25 cm^3), decanted, dried over $MgSO_4$, and purified by elution through a neutral alumina column (~100 g) with AcOEt (100 cm^3). Evaporation of the solvents yielded diazide **13** as an homogeneous wax (0.731 g, 95%), $[\alpha]_D$ −67.6 (*c* 2.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1720 and 2102; δ_H(250 MHz; $CDCl_3$) 3.30 (2 H, dd, $J_{1',2}$ ~3, J_{gem} 13, 1-, 6-H), 3.47 (2 H, dd, $J_{1,2}$ 8.0, 1-, 6-H), 4.19 (2 H, m, 2-, 5-H), 5.04 (2 H, s, OCH_2O), 5.44 (2 H, d, $J_{2,3}$ 7.5, 3-, 4-H), 7.36 (4 H, t, ArH), 7.51 (2 H, t, ArH) and 7.87 (4 H, d, ArH).

3,4-Di-*O*-acetyl-1,6-diazido-1,6-dideoxy-2,5-*O*-methylene-D-mannitol 14

To a stirred solution of the diazide **13** (1.58 g, 3.49 mmol) in 96% EtOH (50 cm^3) was added finely ground 85% KOH (0.46 g, 1 mol equiv.). The mixture was heated under reflux for 1 h, cooled to room temp. and concentrated to dryness after addition of small volumes of abs. EtOH. The residue was then dissolved in acetic anhydride (40 cm^3), and the solution was boiled for 30 min and left overnight at room temp. while being stirred. Excess of reagent was removed under reduced pressure, the residue was redissolved in CH_2Cl_2 (50 cm^3), and the solution was cooled below 4 °C, carefully washed with 5% aq. $NaHCO_3$ (2 × 25 cm^3) and then with water until neutral (by pH stick), dried over $MgSO_4$, and finally concentrated under reduced pressure. Rapid chromatography with hexane–AcOEt (4:1) and recrystallisation from Pr^i_2O yielded *diacetate* **14** as long fine needles (0.90 g, 78%), mp 82–83 °C (Found: C, 40.1; H, 5.2; N, 25.9. $C_{11}H_{16}N_6O_6$ requires C, 40.25; H, 4.91; N, 25.60%); $[\alpha]_D$ −13.8, $[\alpha]_{365}$ −43.4 (*c* 1.9, $CHCl_3$); *m/z* 329 ($M + H^+$); ν_{max}(KBr)/cm^{-1} 1755 and 2107; δ_H(250 MHz; $CDCl_3$) 2.01 (6 H, s, 2 × Ac), 3.24 (2 H, dd, J_{gem} 13, 1-, 6-H), 3.34 (2 H, dd, $J_{1,2}$ 6.5, $J_{1',2}$ 3.5, 1-, 6-H'), 3.98 (2 H, m, $J_{2,3} = J_{4,5}$ = 6.0, 2-, 5-H), 4.91 (2 H, s, OCH_2O) and 4.97 (2 H, dd, $J_{3,4}$ 7.3, 3-, 4-H).

1,6-Diazido-3,4-bis-*O*-[2-(2-chloroethoxy)ethyl]-1,6-dideoxy-2,5-*O*-methylene-D-mannitol 15

To a stirred dispersion of the diester **13** (0.77 g, 1.7 mmol) and Bu_4NHSO_4 (1.10 g, 0.95 eq) in bis-(2-chloroethyl) ether (15 cm^3) was added 50% aq. NaOH (25 cm^3) at 0 °C. The two-phase system was vigorously and magnetically stirred below 5 °C for 3 h, the reaction being monitored by TLC with hexane–AcOEt (8:1). The mixture was diluted with ice-cooled water (50 cm^3) and CH_2Cl_2 (50 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 cm^3), the organic phases were combined, washed with water (2 × 20 cm^3), dried over $MgSO_4$, and concentrated under reduced pressure, and the excess of reagent was finally removed under reduced pressure. Rapid chromatography with hexane–AcOEt (9:1) yielded bis-chloride **15** as a gum (0.614 g, 79%), $[\alpha]_D$ −0.8 (*c* 3.0, $CHCl_3$); δ_H(250 MHz; $CDCl_3$) 3.36 (2 H, dd, $J_{2,3}$ 7.5, 3-, 4-H), 3.50 (2 H, dd, J_{gem} 13, $J_{1,2}$ 6.0, 1-, 6-H), 3.56–3.81 (18 H, m, 4 × OC_2H_4, 1-, 6-H'), 4.04 (2 H, m, 2-, 5-H) and 4.54 (2 H, s, OCH_2O).

1,6-Di-*O*-benzyl-3,4-bis-*O*-[2-(2-chloroethoxy)ethyl]-2,5-*O*-methylene-D-mannitol 16

To a stirred solution of compound **9** (1.000 g, 2.70 mmol) in abs. THF (30 cm^3) were added $NaBH_3CN$ (3.393 g, 10 mol equiv.) and powdered 4 Å molecular sieves (250 mg). To the vigorously stirred suspension at 0 °C under argon was added dropwise, over a period of 90 min, a saturated ethereal solution of HCl (50 cm^3 of ~0.5 mmol dm^{-3} solution obtained by extraction of 12 mol dm^{-3} HCl with diethyl ether and drying over $MgSO_4$). The mixture was then diluted with CH_2Cl_2 (200 cm^3) and filtered through a sintered glass filter. The filtrate was washed successively with 3% aq. ammonia and then with water until neutral (by pH stick), dried with $MgSO_4$, and finally concentrated under reduced pressure. The residue was boiled with hot EtOH (~20 cm^3), the solution was cooled to room temperature and filtered on a paper, and the concentrated filtrate was purified by rapid chromatography with hexane–AcOEt (1:1) to yield a TLC-homogeneous mixture of diols[28] (0.148 g, 15%) as shown in Scheme 2. As described for compounds **11** and **13**, but after 20 h from the diol mixture (0.14 g), were obtained by conventional chromatography with hexane–AcOEt (3:2) first compound **16** as a gum (0.080 g, 37%), $[\alpha]_D$ +6.3 (*c* 1.8, $CHCl_3$); δ_H(250 MHz; $CDCl_3$) 3.43–3.57 (8 H, m, 2-, 5-H, 3 × OCH_2), 3.58 (2 H, d, $J_{2,3}$ 5.5, 3-, 4-H), 3.62–3.82 (12 H, m, 1-, 6-H_2, 3 × OCH_2, 2 × OC*H*HCl), 3.97 (2 H, m, 2 × OCH*H*Cl), 4.57 (2 H, d, $J_{a,b}$ 12, C*H*^{a}H^{b}Ph), 4.63 (2 H, d, CH^a*H*^{b}Ph), 4.81 (2 H, s, OCH_2O) and 7.25–7.4 (10 H, m, Ph); then the regioisomer **21** as a gum (0.070 g, 32%), whose spectrum showed no C_2-symmetry: selected δ_H(250 MHz; $CDCl_3$) 4.58 (1 H, d, $J_{a,b}$ ~10, C*H*^{a}H^{b}Ph), 4.63 (1 H, d, CH^a*H*^{b}Ph), 4.73 (1 H, d, $J_{a,b}$ 11, C*H*$'^a$H$'^b$Ph), 4.82 (2 H, s, OCH_2O) and 4.87 (1 H, d, CH$'^a$*H*$'^b$Ph).

1,6-Dideoxy-2,5-*O*-methylene-3,4-*O*-[naphthalene-2,3-diylbis(oxyethyleneoxyethylene)]-D-mannitol 17

A solution of 2,3-dihydroxynaphthalene (0.314 g, 3 mol equiv.) in freshly distilled Bu^{n}OH (15 cm^3) was stirred for 30 min at room temp. To this solution were added, first, dried powdered K_2CO_3 (0.265 mg, 3 mol equiv.) and then, after the mixture having been heated to a gentle reflux, the half-crown **12** (0.24 g, 0.64 mmol). The resulting solution was boiled for 20 h, allowed to cool to room temp. and the Bu^{n}OH was evaporated off under reduced pressure. The remaining gum was dissolved in CH_2Cl_2 (50 cm^3), the solution was washed with water (2 × 20 cm^3), dried with $MgSO_4$, and concentrated to an oil, and the residue was prepurified by elution through an alumina column (~20 g) with AcOEt (50 cm^3). Rapid chromatography with hexane–AcOEt (7:2) yielded compound **17** (0.210 g, 71%) as a solid, mp 157–158 °C; $[\alpha]_D$ +45.1 (*c* 0.5, $CHCl_3$); *m/z* 462 (M^+); δ_H(400 MHz; 2D; $CDCl_3$) 1.29 (6 H, d, $J_{1,2}$ 6.5, 1-, 6-H_3), 3.02 (2 H, m, $J_{2,3}$ 7.5, 3-, 4-H), 3.61 (2 H, m, 2-, 5-H), 3.76–4.17 (12 H, m, 2 × OC_2H_4, 2 × CH_2O), 4.29 (4 H, t, OCH_2 onto naphth.), 4.71 (2 H, s, OCH_2O), 7.14 (2 H, s, 1-, 4-H naphth.), 7.34 (2 H, dd, 5-, 8-H naphth.) and 7.67 (2 H, dd, 6-, 7-H naphth.).

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

The same procedure was used as described for compound **17** except 2 mol equiv. only of K_2CO_3 were used and the reaction time was 30 h. Yield after chromatography on silica with hexane–AcOEt (4:1) from compound **15** (1.72 g, 3.76 mmol) was 1.024 g (50%) of compound **5** as a greyish solid; suitable crystals (0.91 g, 44%) for X-ray diffraction and further characterisations were obtained by slow recrystallisation from Pr^{i}OH–$CHCl_3$ (9:1: 30 cm^3); mp 105–106 °C (Found: C, 55.0; H, 6.05; N, 15.4. $C_{25}H_{32}N_6O_8$ requires C, 55.14; H, 5.92; N, 15.43%); $[\alpha]_D$ +44.0 (*c* 1; $CHCl_3$); *m/z* 544 (M^+); ν_{max}(KBr)/cm^{-1} 2107; δ_H(500 MHz; $CDCl_3$) 3.32 (2 H, m, $J_{2,3}$ = $J_{4,5}$ ~8, $J_{3,4}$ 8.7, 3-, 4-H), 3.42 (2 H, dd, J_{gem} 12.7, $J_{1,2}$ ~6, 1-, 6-H), 3.56 (2 H, dd, $J_{1',2}$ 2.5, 1-, 6-H'), 3.78 (2 H, m, 2-, 5-H), 3.73–3.86 (6 H, m, 2 × OCH_2, 2 × OCH*H*), 3.91–4.04 (4 H, m, 2 × OCH_2), 4.1 (2 H, m, 8-, 15-H), 4.28 (4 H, t, 11-, 12-H_2), 4.81 (2 H, s, 7-H_2), 7.12 (2 H, s, 1-, 4-H naphth.), 7.32 (2 H, m, 6-, 7-H naphth.) and 7.65 (m, 2 H, 5-, 8-H naphth.); δ_C 148.93 (C-2, -3 naphth.), 129.28 (C-9, -10 naphth.), 126.28 (C-5, -8 naphth.), 124.25 (C-6, -7 naphth.), 108.39 (C-1, -4 naphth.), 92.38 (OCH_2O), 83.28 (C-3, -4 mannitol), 74.10 (C-2, -5 mannitol), 73.08 (C-8, -15), 70.96 (C-9, -14), 69.20 (C-11, -12), 69.08 (C-10, -13), 51.87 (C-1, -6 mannitol); $\delta(^{15}N)$ −133.16 (N-2), −171.66 (N-1) and −315.55 (N-3).

1,6-Diazido-1,6-dideoxy-2,5-*O*-methylene-3,4-*O*-[*O*-phenylenebis(oxyethyleneoxyethylene)]-D-mannitol 18

The same procedure were used as described for compound **17** except 2 mol equiv. only of K_2CO_3 were used with catechol instead of 2,3-dihydroxynaphthalene. The reaction time was 18 h. Yield after chromatography on silica with hexane–AcOEt (1:1) from compound **15** (0.456 g, 1.00 mmoles) was 0.367 g (75%) of compound **18** as a solid; mp 95–97 °C (from Pr$^i_2$O); $[\alpha]_D$ +16.6 (*c* 1, $CHCl_3$); *m/z* 494 (M^+); ν_{max}(KBr)/cm^{-1} 2102; δ_H(250 MHz; $CDCl_3$) 3.32 (2 H, dd, $J_{2,3}$ 7, 3-, 4-H), 3.40 (2 H, dd, J_{gem} 13, $J_{1,2}$ 6.3, 1-, 6-H), 3.55 (2 H, dd, $J_{1',2}$ ~2.5, 1-, 6-H'), 3.69–3.81 (8 H, m, 4 × OCH_2), 3.84–3.97 (4 H, m, 2-, 5-H, 2 × OCH*H*), 4.05–4.22 (6 H, m, 2 × OCH_2, 2 × OC*H*H), 4.82 (2 H, s, OCH_2O) and 6.90 (4 H, pseudo-s, catechol).

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

A solution of 2,2'-dihydroxybiphenyl (0.162 g, 2 mol equiv.) in MeCN (10 cm^3) was stirred for 30 min under argon. To this solution was added, first, dry powdered Cs_2CO_3 (0.28 g, 2 mol equiv.), and then, the resulting mixture having been heated to reflux, the dichloride **15** (0.200 g, 0.43 mmol). The resulting suspension was boiled for 20 h, allowed to cool to room temp., and concentrated to a gum under reduced pressure; the gum was dissolved in CH_2Cl_2 (50 cm^3), the solution was washed with water (2 × 20 cm^3), dried with $MgSO_4$, and concentrated to an oil, which was finally purified by rapid chromatography on silica with hexane–AcOEt (2:1) to yield compound **19** (0.064 g, 25%) as a gum; $[\alpha]_D$ +1.2 (*c* 3.2, $CHCl_3$); *m/z* 570 (M^+); ν_{max}(KBr)/cm^{-1} 2102; δ_H(400 MHz; $CDCl_3$) 3.28–3.38 (2 H, m, 3-, 4-H), 3.38–3.83 (18 H, m), 3.91–4.25 (4 H, m, 2 × OCH_2), 4.82 (2 H, 2 s, OCH_2O), 6.88 (2 H, d, 3-, 3'-H biphenyl), 6.99 (2 H, t, 5-, 5'-H biphenyl), 7.17 (2 H, dd, 6-, 6'-H biphenyl) and 7.28 (2 H, m, 4-H biphenyl).

1,6-Di-*O*-benzyl-2,5-*O*-methylene-3,4-*O*-[naphthalene-2,3-diylbis(oxyethyleneoxyethylene)]-D-mannitol 20

The same procedure and stoichiometry were used as described for compound **17** except that the reaction time was 24 h. Yield after chromatography on silica with hexane–AcOEt (2:1) from compound **16** (0.080 g, 0.136 mmol) was 0.030 g (32%) of compound **20** as a solid besides recovered starting material (0.025 g): mp 115–117 °C; $[\alpha]_D$ +44.6 (*c* 0.25, $CHCl_3$); *m/z* 674 (M^+); δ_H(250 MHz; $CDCl_3$) 3.47 (2 H, d, $J_{2,3}$ = $J_{4,5}$ ~6, 3-, 4-H), 3.6–3.8 (12 H, m, 4 × OCH_2, 2 × OCH*H*, 2-, 5-H), 3.78 (2 H, m), 3.8–4.1 (6 H, m, 1-, 6-H_2, 2 × OC*H*H), 4.25 (4 H, t, 2 × OCH_2 onto naphth.), 4.53 (2 H, d, $J_{a,b}$ 12, C*H*^{a}H^{b}Ph), 4.63 (2 H, d, CH^a*H*^{b}Ph), 4.8 (2 H, s, OCH_2O), 7.12 (2 H, s, 1-, 4-H naphth.), 7.2–7.7 (12 H, m, 2 × Ph, 7-, 8-H naphth.) and 7.65 (2 H, m, 6-, 9-H naphth.).

1,6-Bis-(4,5-bismethoxycarbonyl-1,2,3-triazol-1-yl)-1,6-dideoxy-2,5-*O*-methylene-3,4-*O*-[naphthalene-2,3-diyl-bis(oxyethyleneoxyethylene)]-D-mannitol 6

A solution of the diazide **5** (0.114 g, 0.209 mmol) in DMAD (2 cm^3, 19 mol equiv.) was magnetically stirred at 60 °C for 1 h and

then allowed to cool to room temp. The reagent's excess was evaporated off under reduced pressure and the residue was purified by rapid chromatography on silica with hexane–AcOEt (1:1) to yield compound **6** (0.165 g, 95%) as a solid; mp 107–110 °C; $[\alpha]_D$ −73.1 (*c* 1.0, $CHCl_3$); *m/z* 828 (M^+); δ_H(400 MHz; 2D; $CDCl_3$) 3.27 (2 H, m, $J_{2,3}$ 6.5, 3-, 4-H), 3.76–4.22 (16 H, m, 7 × OCH_2, 2-, 5-H), 3.89 (3 H, s, OMe), 3.92 (3 H, s, OMe), 4.31 (4 H, t, $ArOCH_2$), 4.69 (4 H, dd, J_{gem} 14, J_{vic} 9.5, 1-, 6-H_2), 5.05 (1 H, d, $J_{a,b}$ 3, OCH^aH^bO), 5.08 (1 H, d, OCH^aH^bO), 7.13 (2 H, s, 1-, 4-H naphth.), 7.31 (2 H, dd, 5-, 8-H naphth.) and 7.66 (2 H, dd, 6-, 7-H naphth.).

1,6-Bis-(4,5-diphenyl-1,2,3-triazol-1-yl)-1,6-dideoxy-2,5-*O*-methylene-3,4-*O*-[naphthalene-2,3-diylbis(oxyethyleneoxyethylene)]-D-mannitol 7

To a refluxing solution of diphenylacetylene (1.245 g, 5 mol equiv.) in CH_2Cl_2 (5 cm^3) was added diazide **5** (0.380 g, 0.69 mmol) and, after the solvent had been carefully evaporated off, the mixture was heated to 120 °C for 48 h. After cooling, rapid chromatography of the reaction mixture on silica with hexane–AcOEt (1:1) gave TLC-homogeneous product **7** as a solid, which could be recrystallised from Pr^iOH–$CHCl_3$ (0.55 g, 88%); mp 224–225 °C (Found: C, 70.7; H, 5.6; N, 9.1. $C_{53}H_{52}N_6O_8$ requires C, 70.65; H, 5.82; N, 9.33%); $[\alpha]_D$ −23.7 (*c* 1.1, $CHCl_3$); *m/z* 901.3932 ($M + H^+$), $C_{53}H_{53}N_6O_8$ requires *m/z*, 901.3925; δ_H(400 MHz; 2D; $CDCl_3$) 3.32 (2 H, m, $J_{2,3}$ 7.0, 3-, 4-H), 3.70–3.78 (6 H, m), 3.78–3.96 (4 H, m), 4.06 (2 H, dd, J_{gem} 13.6, $J_{1,2}$ 6.0, 1-, 6-H), 4.12 (2 H, dd, $J_{1',2}$ 9.5, 1-, 6-H'), 4.19–4.24 (4 H, m), 4.27 (2 H, m, 2-, 5-H), 4.32 (2 H, s), 4.61 (1 H, d, $J_{a,b}$ 3, OCH^aH^bO), 4.65 (1 H, d, OCH^aH^bO), 7.10 (2 H, s, 1-, 4-H naphth.), 7.18–7.27 (10 H, m, Ph), 7.32 (2 H, dd, 5-, 8-H naphth.), 7.44–7.53 (10 H, m, Ph) and 7.65 (2 H, dd, 6-, 7-H naphth.).

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