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Polycyclic *trans*-Fused Crown Ethers From D-Mannitol

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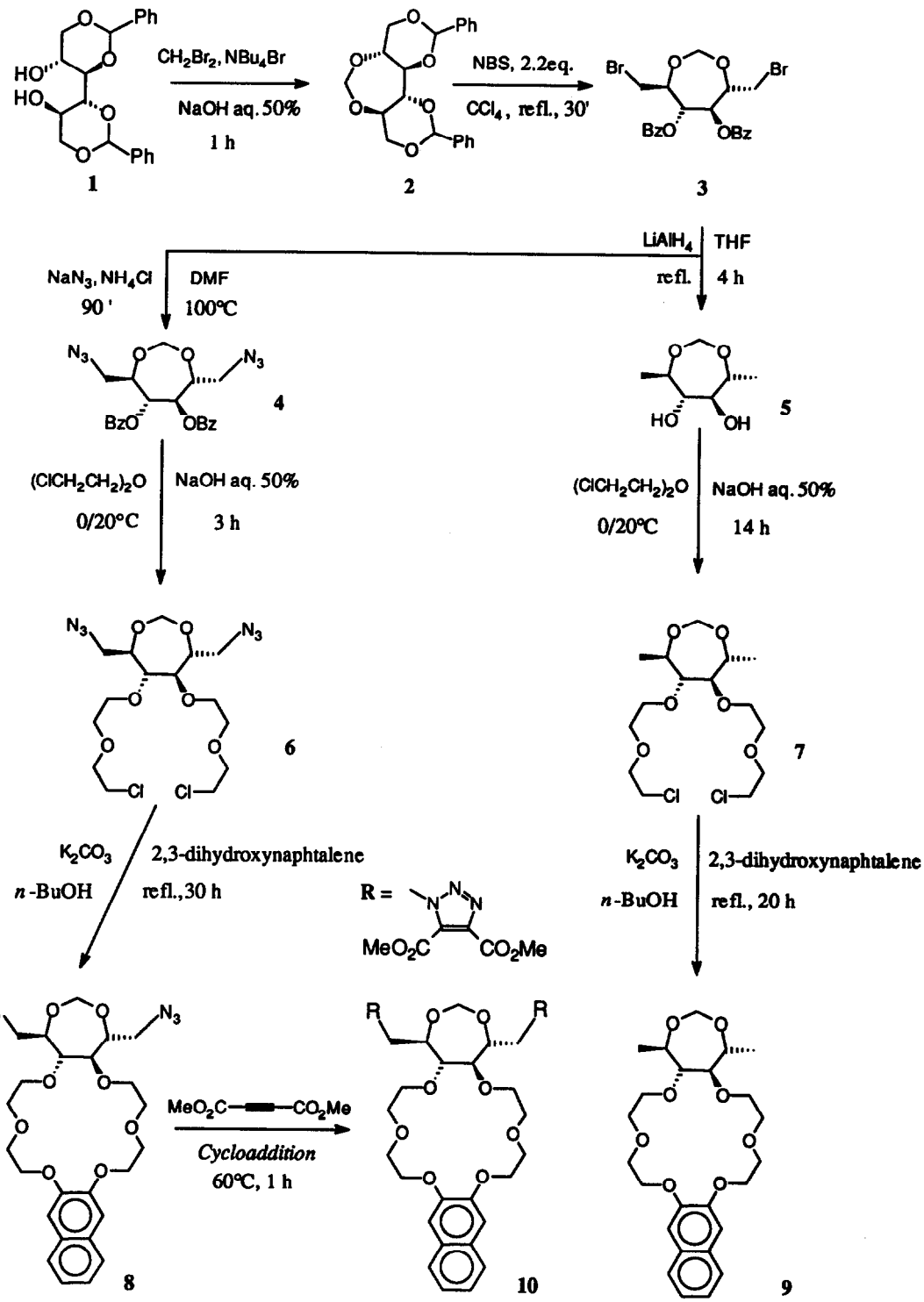
Abstract: New macrocyclic ethers, all bearing a common *trans*-fused chiral dioxepan moiety, were easily synthetized from 1,3:4,6-di-*O*-benzylidene-D-mannitol in 5 or 6 steps (3 examples). The influence of the substituent at C-1/C-6 positions upon conformation is discussed.

Protected sugars and alditols provide relatively inexpensive chiral frameworks for the formation of many convenient chiral intermediates.[1] Among them, D-mannitol has been used extensively for decades as a straightforward source of chiral synthons[2] and for the synthesis of chiral crown ethers with C_2 symmetry.[3] In a few cases, some of these macrocyclic **hosts** exhibited a certain enantioselectivity toward chiral primary amines[4] or allowed chromatographic resolution of some racemic free aminoacid **guests**.[5] In connection with our previous synthetic study in search of such homotopic host with improved chiral recognition capacities combined with better acid hydrolysis resistance,[6] we now report the synthesis and some spectroscopic properties of three new crown ethers bearing a *trans*-fused chiral dioxepan moiety from D-mannitol.

Readily available 1,3:4,6-di-*O*-benzylidene-D-mannitol **1**[7] was reacted in a two-phase system with CH_2Br_2 and tetra-*n*-butylammonium bromide as catalyst[8] to give the tricyclic acetal **2**[9] in 69% yield after purification by simple washing with warm EtOH. The regioselective opening of **2** with 2.2 eq. of NBS in CCl_4[10] afforded the chiral symmetric dioxepan **3** (or 1,6-dideoxy-1,6-dibromo-2,5-*O*-methylene-D-mannitol) in a 81% yield after rapid chromatography on silica-gel (*n*-hexane/AcOEt, 4/1). Compound **3** was easily and almost quantitatively converted by usual methods into the diazide **4** or into the diol **5** (prepurified by elution on neutral alumina with AcOEt), which were then reacted in a two-phase system with *bis*(2-chloroethyl)ether as solvent and reagent[11] to give respectively the half-crown ethers **6** and **7** in 80% and 65% yield. Finally, **6** and **7** were cyclized in boiling *n*-butanol under argon with 2,3-dihydroxynaphtalene with K_2CO_3 as base in 50% and 70% yield.[5]

In summary, crown ethers **8**[12] and **9** were synthetized in five steps from chiral diol **1** in respectively 21 and 25% overall yield as shown below.


CH2Br2, NBu4Br
NaOH aq. 50%
1 h
NBS, 2.2eq.
CCl4, refl., 30'
LiAlH4
THF
refl.
4 h
NaN3, NH4Cl
90 '
DMF
100°C
(ClCH2CH2)2O
0/20°C
NaOH aq. 50%
3 h
(ClCH2CH2)2O
0/20°C
NaOH aq. 50%
14 h
K2CO3
n-BuOH
2,3-dihydroxynaphtalene
refl.,30 h
K2CO3
n-BuOH
2,3-dihydroxynaphtalene
refl., 20 h
R =
MeO2C
CO2Me
MeO2C
CO2Me
Cycloaddition
60°C, 1 h
1
2
3
4
5
6
7
8
9
10

Furthermore, the two azido groups of crown ether **8** could be cyclized in neat dimethyl acetylenedicarboxylate to give the symmetric *bis*-triazol **10** in almost quantitative yield. Except for this product which showed two clearly distinguished resonances, namely one at δ = 5.04 for one *O*-methylene proton and one other at δ = 5.08 for the *gem*-proton, all other ^{1}H NMR spectra of dioxepan derivatives (**2** - **9**) exhibited a sharp characteristic two-proton singlet which was assigned to the isochronous 2,5-*O*-methylene proton according to previous studies:[13]

Compound	δ (ppm)	$[\alpha]_D$ (conc.)	m.p. (°C)
2	4.85[9a]	-135 (1.3)	243/244
3	5.03[b]	-108 (1.5)	121/122
4	5.04[b]	-68 (2.0)	wax[c]
5	4.75[14]	-83 (0.9)[14]	117/118
6	4.85[b]	-1 (3.0)	gum
7	4.69[b]	-7 (1.1)	gum
8	4.83[a]	+44 (1.0)	105/106
9	4.70[a]	+45 (0.5)	157/158
10	5.04, 5.08[ad]	-73 (1.0)	105/110

a: 400 MHz, b: 250 MHz, c: after filtration on neutral alumina, d: $J_{gem} \sim 3$ Hz.

Table 1. ^{1}H NMR chemical shifts of 2,5-*O*-methylene protons (r.t., $CDCl_3$/TMS), $[\alpha]_D$ (20°C, $CHCl_3$) and uncorrected melting points of dioxepan derivatives.

These results may be interpreted in two ways: either the dioxepan ring undergoes a fast ring-inversion or it exists predominantly in the more stable twist-chair (TC) or twist-boat (TB) conformations (depending of each compound structure).[15] The first results of the structural study of **8** (X-ray molecular structure) indicate that the TC conformation is favored in the **crystalline state**. On the other hand, the introduction of a bulky goup on C-1/C-6 positions (which may act as chiral barriers in future complexations), through convenient cycloaddition, caused the separation of the *O*-methylene-singlet of **10** into two slight doublets (AB-system). This fact strongly confirms that these dioxepan derivatives undergo a fast conformational inversion in **solution** (ring-inversion or/and *pseudo*-rotation) which can be in some cases significantly slowed by bulky substituents on the dioxepan ring.

We are now checking actively the complexation abilities and chiral recognition of crown ethers **8**, **9** and **10** and related compounds toward racemic aminoacids as their methylester salts or as the free form.

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12. Except for the compounds **4** and **5**, which were used after simple filtration over neutral alumina, yields cited herein are for isolated, pure materials, characterized by IR and ^1H NMR.
    For example, product **8**: colorless orthorhombic crystals (from *i*-PrOH/$CHCl_3$); m.p. 105/106°C; $[\alpha]_D$ = +44 (c=1, $CHCl_3$); IR (KBr) ν: 2105 cm^{-1} (N_3); ^1H NMR ($CDCl_3$, 400 MHz): δ/TMS: 3.32 (m, 1H, H-3, $J_{2,3}$ = 8.5 Hz), 3.42 (dd, 1H, H-1 or 1', J_{gem} = 12.7 Hz, $J_{1,2}$ = 6 Hz), 3.56 (dd, 1H, H1' or 1, $J_{1',2}$ = 2.5 Hz), 3.7 (m, 1H, H-2), 3.77-3.86 (m, 3H, 3/2 *O*-CH_2), 3.9-4.05 (m, 2H, 1 *O*-CH_2), 4.1 (m, 1H, 1/2 *O*-CH_2), 4.28 (*pseudo*-t, 1 *O*-CH_2), 4.83 (s, 1H, *O*-CHH-*O*), 7.13 (s, 1H, ar.), 7.34 (m, 1H, ar.), 7.66 (m, 1H, ar.); MS: *m/z* 544 (M^+); Analysis calc. for $C_{25}H_{32}N_6O_8$: C 55.13, H 5.92, N 15.43; found: C 55.01, H 6.05, N 15.40.

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