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Synthesis of a symmetric tetrakis-epoxide from a 3,4-D-mannitol bridged *o*,*o*-cyclophane

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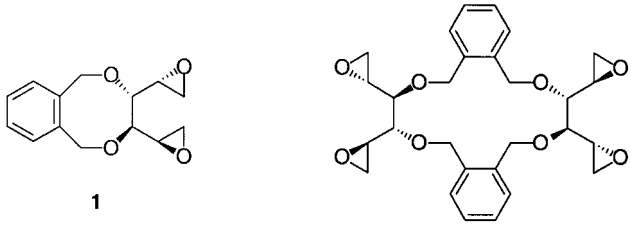
Abstract—The coupling reaction of 1,2:5,6-di-*O*-isopropylidene-D-mannitol with α,α′-dibromoxylene has been reinvestigated. We found reaction conditions leading to the 3,4-D-mannitol bridged *o*,*o*-cyclophane **3**, free of the 3,4-*O*-*o*-xylylene protected mannitol **2**. Compound **3** could be converted in 57% yield into tetrakis-epoxide **4**.

C_2 Symmetric bis-epoxides,[1] and bis-aziridines[1,2] easily prepared from 3,4-*O*-protected-D-mannitol are versatile building blocks for the synthesis of a wide range of compounds of biological interest. Their nucleophilic opening allows in particular the preparation of useful enantiopure synthons as α-hyroxyaldehydes,[3] α-aminoaldehydes or acids[4] as well as enantiopure polyhydroxylated nitrogen heterocycles, an important class of glycosidase inhibitors.[5] The products which result from the reaction of the bis-epoxides or bis-aziridines with nucleophiles are highly dependent on the flexibility of the six carbon skeleton. While 1,6-disubstituted compounds are easily prepared without desymmetrization by double nucleophilic opening of the conformationally restricted 3,4-di-*O*-isopropylidene-protected derivatives,[3,4] intramolecular cyclization towards either oxygen or nitrogen heterocycles follows in most cases opening of the conformationally flexible 3,4-di-*O*-benzyl compounds.[5,6]

In light of the significant influence of the 3,4-*O*-protecting group on the course of transformations, we were interested in the preparation of 3,4-*O*-*o*-xylylene protected derivatives such as bis-epoxides and bis-aziridines. Synthesis of bis-epoxide **1** (Scheme 1) had already been reported[7] using the Sharpless one pot orthoacetate method[8] in 73% yield from the corresponding tetrol. Since the preparation of the bis-acetonide precursor **2** (Scheme 2) was described in only poor yield (22%) by the reaction of 1,2:5,6-di-*O*-isopropylidene-D-mannitol with α,α′-dibromoxylene, we undertook the reinvestigation of the protection step. It turned out impossible to improve the yield of **2**, on the other hand we succeeded in synthesizing its dimer **3** in a satisfactory way. We report here the results of this study and the preparation of the new *o*,*o*-cyclophane-based homochiral tetrakis-epoxide **4** (Scheme 1).

When *O*-alkylation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol was carried out in the reported conditions[7] (NaOH, THF/H_2O, Bu_4NBr, 40°C), 3,4-*O*-*o*-xylylene protected diacetonide **2** was obtained as predicted in about 20% yield, along with 20% of what we identified as the dimer **3** of **2**, and unidentified higher oligomers. We think that the intermediate unsymmetrically substituted *o*-xylylene derivative **5** possessing an acidic benzylic proton and a benzylic leaving group is likely to generate oligomers in basic medium through a *o*-quinodimethane system,[9] thus in the presence of NaOH dimerization could compete with intramolecular cyclization towards **2** (Scheme 2).

When coupling was carried out in the presence of sodium hydride as the base, (NaH 2.5 equiv., Bu_4NBr cat, THF, 20°C), compound **2** was not formed, but dimer **3** was obtained in up to 48% yield, together with 20% of **6** which results from intermolecular dialkylation (Scheme 2). In this case, intramolecular cyclization is obviously not an easy process while the strongly basic conditions favor dimerization into the symmetrically functionalized sixteen membered tetraoxygenated ring **3**.



Scheme 1.

Keywords: tetrakis-epoxide; cyclophane; enantiomeric purity.

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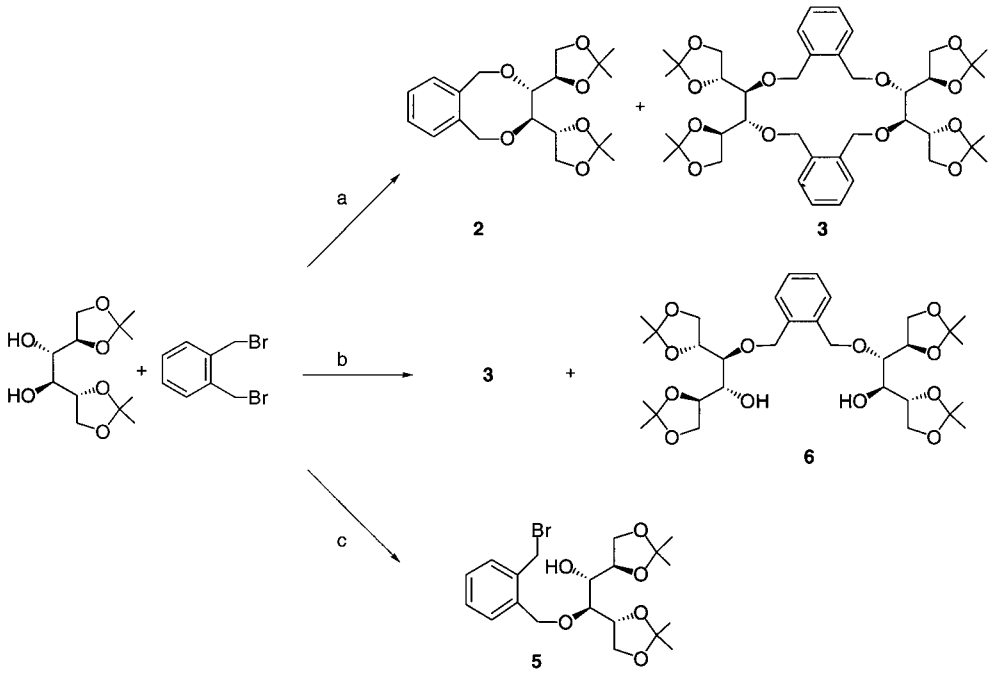
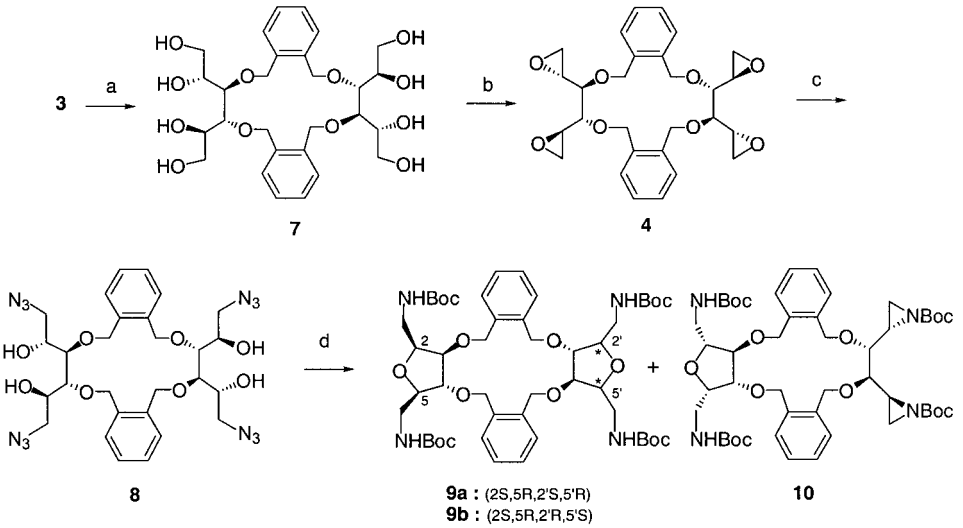


Scheme 2. (a) NaOH, Bu_4NBr, THF/H_2O, 40°C, 30 h. **2**: 20%, **3**: 20%; (b) NaH 2.5 equiv., Bu_4NBr cat., THF, 0°C, 30 min then 20°C overnight. **3**: 48%, **6**: 22%; (c) Bu_2SnO, CH_3CN, reflux 2 h, then $C_8H_8Br_2$, reflux 24 h.

In an effort to obtain 3,4-*O*-*o*-xylylene bis-epoxide **1** with increased overall yield we anticipated preparing **2** in two steps. The first, carried out in non-basic medium consisted of 1,2:5,6-di-*O*-isopropylidene-D-mannitol tin acetal mediated monoalkylation (Bu_2SnO, CH_3CN, then $C_8H_8Br_2$, reflux).[10] The only compound identified on the mass spectrum of the crude product was bromoalcohol **5** (FABMS, NaI: *m/z* 467, 469 (M+23)) besides unreacted tin acetal (*m/z* 515 (M+23)). Unfortunately, we were unable to obtain pure compound **5** since it partially decomposed due to its instability during purification. We did not find any trace of **2** among the degradation products.

Thus although we were unsuccessful in improving the yield of formation of 3,4-*O*-*o*-xylylene protected **2** we were able to satisfactorily prepare its cyclic dimer **3**. Removal of the isopropylidene protecting groups (70% acetic acid, 96% yield) converted compound **3** into the tetradiol **7**; then formation of epoxide **4** was achieved in 57% yield via a Mitsunobu reaction[11] (130°C, under 0.01 mm Hg) on the four terminal hydroxyl groups (Scheme 3). On the other hand, orthoacetate mediated epoxidation[8] led to only 11% of the tetrakis-epoxide **4** besides incompletely cyclized derivatives.

Epoxide **4** was converted into the tetrakis-azidoalcohol **8** in 86% yield through tetramethylguanidinium azide mediated nucleophilic opening. Reaction of **8** with



Scheme 3. (a) 70% acetic acid, 40°C, 4 h, 96%. (b) DIAD, toluene, 0°C, 30 min then 130°C, 0.01 mm Hg, 3 h, 57%. (c) Tetramethylguanidinium azide, DMF, 80°C, 3 h, 86%. (d) (i) PPh_3, toluene, 40°C, 3 h then 100°C, 20 h; (ii) $(CO_2tBu)_2O$, NEt_3, THF, 0°C, then rt, 3 h.

triphenylphosphine in refluxing toluene did not lead to the corresponding tetrakis-aziridine but to compounds **9** and **10** of which only bis-furan **9** could be isolated as a mixture of diastereoisomers **9a** and **9b**. We are able to propose a structure for **10**, deduced from mass spectrum data (CIMS, NH_3: *m/z* (%) 911 (100) (MH^+)) and ^1H and ^{13}C NMR spectra. We had previously observed the formation of small proportions of furan when the reaction with triphenylphosphine was carried out with conformationally flexible diazidodiols.[12,13]

In conclusion, we have accomplished a synthesis of the enantiopure tetrakis-epoxide **4** and tetrakis-azidoalcohol **8** starting from D-mannitol. These attractive cyclic templates could be considered as precursors of dendrimers[14] or serve as chiral chelating agents for catalytic asymmetric synthesis.[15]

1. Experimental

General directions. Prior to use, tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from CaH_2. CH_2Cl_2 and ethyl acetate (EtOAc) were filtered on K_2CO_3 prior to use. ^1H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded on a Brucker AM 250. Chemical shifts are reported in δ (ppm). Specific rotations were measured on a Perkin–Elmer 241C polarimeter with sodium (589 nm) or mercury (365 nm) lamps. Mass spectra were recorded by the Service de Spectrométrie de Masse, Ecole Normale Supérieure, Paris. All reactions were carried out under argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (200–500 μm); the solvent systems were given v/v. Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

1.1. Coupling of 1,2:5,6-di-*O*-isopropylidene-D-mannitol with α,α′-dibromo-*o*-xylene

To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (4.00 g, 15.2 mmol) in anhydrous THF (130 mL) was added at 0°C sodium hydride (0.91 g, 38.1 mmol). After 30 min stirring, α,α′-dibromo-*o*-xylene (4.83 g, 18.2 mmol) in THF (20 mL) was added dropwise at 0°C. After stirring the mixture at room temperature overnight, solvents were removed in vacuo, water was added (30 mL) and the residue extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with a saturated aqueous NH_4Cl solution then with brine, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography purification of the residue (cyclohexane/EtOAc, 4:1) afforded **3** R_f 0.65 (2.63 g, 48%) and compound **6** R_f 0.30 (2.11 g, 22%) as colourless oils.

1.1.1. Bis(1,2:5,6-di-*O*-isopropylidene-D-mannitol-3,4-diyl) bis xylylene-*o*,*o*-cyclophane (3). $[\alpha]_D=+18$ (*c* 0.995, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 1.33, 1.41 (2s, 24H, CH_3), 3.74 (brd, *J*=3.7 Hz, 4H, H-3, H-4), 3.93 (dd, *J*=8.3, 6.2 Hz, 4H, H-1, H-6), 4.02 (dd, *J*=8.3, 6.3 Hz, 4H, H-1′, H-6′), 4.25 (m, 4H, H-2, H-5), 4.68, 4.82 (AB, *J*=11.9 Hz, 8H, C*H*$_2$Ar), 7.1–7.4 (m, 8H$_{arom}$); ^{13}C NMR ($CDCl_3$), δ 25.4, 26.8 (CH_3), 67.0 (C-1, C-6), 71.8 (*C*H$_2$Ar), 75.1 (C-2, C-5), 80.7 (C-3, C-4), 109.0 (*C*(CH_3)$_2$), 127.8, 128.7 (CH_{arom}), 136.6 (Cq_{arom}); HRMS calcd for $C_{40}H_{57}O_{12}$ (MH^+) 729.3850, found 729.3845.

1.1.2. α,α′-Bis(1,2:5,6-di-*O*-isopropylidene-D-mannitol-3-yl)-*o*-xylene (6). $[\alpha]_D=-1$ (*c* 0.98, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 1.27, 1.32, 1.35, 1.38 (4s, 24H, CH_3), 2.85 (d, *J*=8.5 Hz, 2H, OH), 3.45 (td, *J*=8.3, 2.3 Hz, 2H, H-4), 3.7–4.1 (m, 12H, H-1, H-1′, H-3, H-5, H-6, H-6′), 4.21 (q, *J*=5.8 Hz, 2H, H-2), 4.82 (s, 4H, C*H*$_2$Ar), 7.2–7.4 (m, 4H$_{arom}$); ^{13}C NMR ($CDCl_3$), δ 25.3, 26.8 (CH_3), 65.9, 67.7 (C-1, C-6), 72.5 (*C*H$_2$Ar), 72.6, 75.4, 76.1, 78.6 (C-2, C-3, C-4, C-5), 108.8, 109.0 (*C*(CH_3)$_2$), 128.5, 130.1 (CH_{arom}), 136.2 (Cq_{arom}); HRMS calcd for $C_{32}H_{51}O_{12}$ (MH^+) 627.3381, found 627.3373.

1.2. Bis(D-mannitol) bis xylylene-*o*,*o*-cyclophane (7)

Tetraacetonide **3** (1.90 g, 5.21 mmol) was dissolved in 70% aqueous acetic acid (170 mL) and the solution was stirred for 4 h at 40°C. The solvent was removed under reduced pressure, then the residue was dissolved in a minimum amount of ethanol and tetradiol **7** was precipitated with diethylether. Filtration gave **7** as a white solid (1.41 g, 96%): mp 122–124°C; $[\alpha]_D=+42$ (*c* 1.00, MeOH). ^1H NMR (DMSO-d_6) δ 3.4–3.6 (m, 4H, H-1, H-6), 3.75 (dd, 4H, *J*=10.7, 4.6 Hz, H-1′, H-6′), 3.8–4.0 (m, 8H, H-2, H-3, H-4, H-5), 4.59 (t, *J*=5.5 Hz, 4H, OH), 4.85 (d, *J*=4.6 Hz, 4H, OH), 4.71, 4.90 (AB, *J*=12.2 Hz, 8H, C*H*$_2$Ar), 7.2–7.5 (m, 8H$_{arom}$); ^{13}C NMR (DMSO-d_6) δ 64.6 (C-1, C-6), 71.6 (C-2, C-5, *C*H$_2$Ar), 80.2 (C-3, C-4), 129.2, 129.9 (CH_{arom}), 138.3 (Cq_{arom}); CIMS, NH_3: *m/z* (%) 586 (100) (MNH_4^+).

1.3. Bis(1,2:5,6-dianhydro-D-mannitol-3,4-diyl) bis xylylene-*o*,*o*-cyclophane (4)

Tetradiol **7** (653 mg, 2.31 mmol) and triphenylphosphine (1.40 g, 5.32 mmol), dried in vacuo, were dissolved in anhydrous toluene (20 mL). The solution was cooled at 0°C and diisopropylazodicarboxylate (DIAD, 1.09 mL, 5.54 mmol) was added dropwise. After addition was complete, the mixture was allowed to stir at 0°C for 30 min, then toluene was removed under reduced pressure and the residue stirred at 125–130°C under 0.01 mm Hg for 3 h. Column chromatography purification (cyclohexane/EtOAc, 4:1) afforded **4** R_f 0.40 (330 mg, 57%) as a white solid: mp 130–132°C; $[\alpha]_D=-1$, $[\alpha]_{365}=-8$ (*c* 0.485, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 2.73 (dd, *J*=5.3, 3.9 Hz, 4H, H-1, H-6), 2.78 (dd, *J*=5.3, 2.8 Hz, 4H, H-1′, H-6′), 3.2–3.3 (m, 4H, H-2, H-5), 3.5–3.6 (m, 4H, H-3, H-4), 4.63, 4.66 (AB, *J*=11.5 Hz, 8H, C*H*$_2$Ar), 7.2–7.3 (m, 8H$_{arom}$); ^{13}C NMR ($CDCl_3$), δ 45.5 (C-1, C-6), 50.5 (C-2, C-5), 71.3 (*C*H$_2$Ar), 79.4 (C-3, C-4), 128.2, 129.9 (CH_{arom}), 136.6 (Cq_{arom}); HRMS calcd for $C_{28}H_{33}O_8$ (MH^+) 497.2164, found 497.2175.

1.4. Bis(1,6-diazido-1,6-dideoxy-D-mannitol-3,4-diyl) bis xylylene-*o*,*o*-cyclophane (8)

To a solution of tetrakis-epoxide **4** (330 mg, 1.32 mmol) in dry DMF (15 mL) was added tetramethylguanidinium

azide[16] (2.0 g, 12.6 mmol). After stirring at 80°C for 3 h, the solvent was removed in vacuo, then water (10 mL) was added and the mixture extracted with CH_2Cl_2 (15 mL). The extract was dried over $MgSO_4$, evaporated then purified by column chromatography (cyclohexane/EtOAc, 4:1) providing tetrakis-azidoalcohol **8** R_f 0.34 as colourless oil (360 mg, 86%). $[\alpha]_D=+42$ (*c* 0.79, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.21 (d, J=4.8 Hz, 4H, OH), 3.3–3.6 (m, 8H, H-1, H-1′, H-6, H-6′), 3.79 (brd, J=6.5 Hz, 4H, H-3, H-4), 3.9–4.1 (m, 4H, H-2, H-5), 4.62, 4.77 (AB, J=11.3 Hz, 8H, CH_2Ar), 7.2–7.3 (m, 8H$_{arom}$); ^{13}C NMR ($CDCl_3$) δ 53.9 (C-1, C-6), 70.4 (C-2, C-5), 71.4 (*C*H$_2$Ar), 78.4 (C-3, C-4), 128.8, 130.2 (CH$_{arom}$), 136.2 (Cq$_{arom}$); CIMS, NH_3: *m*/*z* (%) 686 (100) (MNH_4^+).

1.5. Reaction of tetrakis-azidoalcohol 8 with triphenylphosphine

A solution of tetrakis-azidoalcohol **8** (190 mg, 0.28 mmol) and triphenylphosphine (300 mg, 1.14 mmol) in dry toluene (4 mL) was stirred at 40°C for 2 h. The mixture was then heated to 90°C and stirred for 20 h under argon. After evaporation to dryness the crude residue was protected without further purification.

1.6. Protection with di-*tert*-butyl-dicarbonate

To a solution of the above residue (0.28 mmol) and triethylamine (160 μL, 1.14 mmol) in THF (10 mL), a solution of di-*tert*-butyl-dicarbonate (250 mg, 1.14 mmol) in THF (5 mL) was added under argon at 0°C. After 3 h stirring at 20°C, the solvent was evaporated, and the residue purified by column chromatography (cyclohexane/EtOAc/Et_3N, 4:1:0.01) to afford bis-aziridine furan **10** R_f 0.35 (54 mg, 20%) and bis-furan **9** R_f 0.20 (41 mg, 15%) as oils.

1.6.1. Bis-furan 9. ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 36 H, C(CH$_3$)$_3$), 3.2–3.7 (m, 8H, H-1, H-1′, H-6, H-6′), 3.80 (m, 4H), 4.10 (brs, 4H), 4.3–4.8 (m, 8H, CH_2Ar), 4.90, 5.05 (2 brs, 4H, N*H*Boc), 7.2–7.4 (m, 8H$_{arom}$); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH$_3$), 40.4, 42.9 (C-1, C-6), 69.3, 69.8, 70.4, 70.7 (*C*H$_2$Ar), 79.2, 79.4, 81.5, 81.6, 84.9, 85.2, 85.3, 85.9 (C-2, C-3, C-4, C-5), 79.4 (*C*(CH$_3$)$_3$), 128.1, 128.4, 128.7, 129.2, 129.8 (CH$_{arom}$), 134.5, 135.2, 135.4, 136.0 (Cq$_{arom}$), 156.1, 156.2 (CO); HRMS calcd for $C_{48}H_{76}O_{14}N_5$ (MNH_4^+) 946.5389, found 946.5392.

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