Stereospecific synthesis of 1,4-di-*O*-methyl-*myo*-inositol (liriodendritol)

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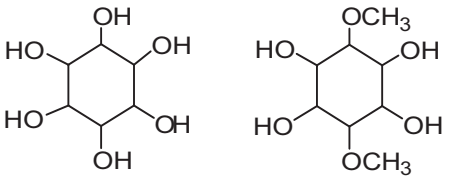
1,4-di-*O*-methyl-*myo*-inositol, a natural product, was synthesised starting from *p*-benzoquinone. The treatment of 5,6-dibromocyclohex-2-ene-1,4-diol with Na/ROH-system afforded a C_2-symmetric conduritol-B derivative key intermediate followed by acetylation. The OsO_4 oxidation and followed by acetylation gave the tetraacetates. The hydrolysis of the acetate groups furnished the desired the *myo*-inositol derivatives in high yield.

Keywords: liriodendritol, myoinositol, cyclitols, conduritol-B, natural product

Inositols and their derivatives are one of the most important classes of the biomolecules. Of the nine possible isomers, *myo, neo-,* D-*chiro,* L-*chiro-, scyllo-*, and *muco*-inositols **1** are naturally occurring.[1] These inositols, which have biological activities, occur in the phosphorylated form in animals. In plants they occur in phosphorylated, methylated or in the free forms. Some inositols including multiple phosphorylated groups have been reported as a Ca^{2+}-mobilising second messenger.[2,3] In addition, a number of inositol derivatives including one or more methylated groups **2**, (+)-pinpollitol, dambonitol and liriodendritol have been synthesised by different groups using the different synthetic methodologies.[4,5,6,7] Due to the importance of these natural products, the synthesis of inositols and its analogous including methyl ethers adds further relevance to this area. Therefore, there are many reported effective strategies for the synthesis of inositols.



1 **2**

Liriodendritol (1,4-di-*O*-methyl-*myo*-inositol) **12** is the first inositol ether known to occur in Nature. In 1955, Plouvier isolated it from the leaves of the tulip tree, *Liriodendron tulipifera L*. and named it liriodendritol.[6,7e,8]

This report describes an effective and concise strategy for the synthesis 1,4-di-*O*-methyl-*myo*-inositol (liriodendritol) **12** via conduritol B derivative from commercially available *p*-benzoquinone **3**. The inositols, conduritols and their derivatives have noteworthy biological properties, since they act as inhibitors of glycosidases.[9]

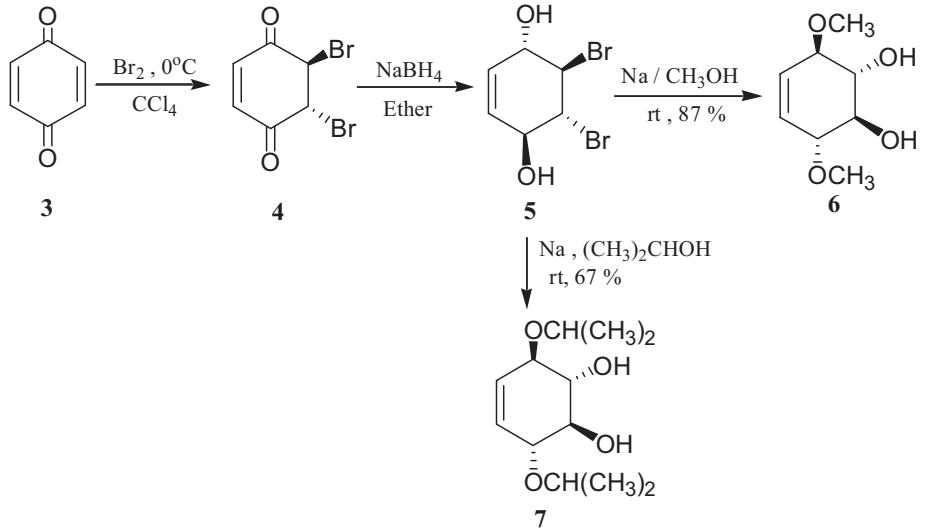
Results and discussion

5,6-dibromocyclohex-2-ene-1,4-diol was prepared using the procedure of Gal and Voorstad.[10b] Bromination of **3** (Scheme 1) followed by borohydride reduction of the resulting dibromide **4** gave the known compound diol **5.**[10] 5,6-Dibromocyclohex-2-ene-1,4-diol having the full *trans* structure is an intermediate for the synthesis of *myo*-inositols and was the key compound in the synthesis 1,4-di-*O*-methyl-*myo*-inositol.

The selective opining of the oxirans in "*anti*-benzene dioxide" (*trans*-3,4,5,6,-diepoxycyclohexene), derived from *p*-benzoquinone **3,** has been well-known with various nucleophiles by opening the epoxide at the allylic position.[11,12] In recent year, the known diacetoxydibromocyclohex-5-enes was obtained by acetylation of the corresponding diol **5** which was used as the enantiomer-pure building blocks for the synthesis of all the *myo*-inositol derivatives described.[13,14]

More recently, both compounds were showed as appropriate precursors for the synthesis of the *myo*-inositol phosphates.[15]

Treatment of dibromodiol **5** with a metallic sodium-methanol (or isopropanol) system leads in a stereocontrolled transformation to conduritol-B derivative **6** (or **7**) in 87% (67%) (Scheme 1).[16] Thus, by arranging from a conduritol-B derivative having full *trans* structure to a different



3 **4** **5** **6**

7

Scheme 1

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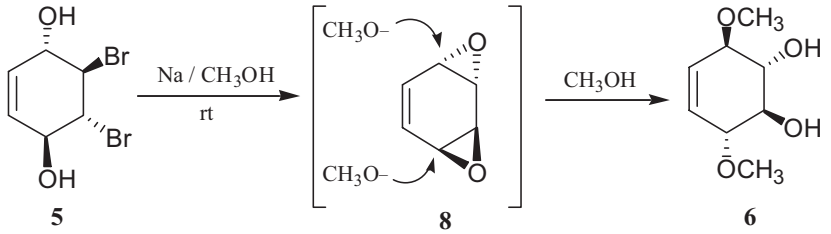


Scheme 2

conduritol-B derivative, all substituents are in a mutual *trans*-arrangement. The formation depends on nucleophilic ring opining of the *anti*-benzene dioxide which occurred as an intermediate product (Scheme 2).

Their C_2-symmetry makes conduritol-B derivatives ideal precursors for *myo*-inositol synthesis. On the other hand, due to the C_2-symmetric in the conduritol B systems, *cis*-hydroxylation of the double bound gives only one diastereoisomeric product. The acetylation by acetyl chloride of **6** under very mild conditions gave the alkoxy diacetates **9** as the sole isomer (in 95%). A six-line ^{13}C NMR spectrum of **9** confirms the proposed structure because of C_2-symmetry in the molecule. Dihydroxylation of the olefin in **9** leads access to **10**. *cis*-dihydroxlation is effected with *N*-methylmorpholine-*N*-oxide (NMO) and catalytic osmium tetroxide in polar solvent to give **10.** For further structure proof, **10** were converted into the corresponding tetraacetate derivatives (liriodendritol tetraacetate) **11** with acetyl chloride which was fully characterised by way of spectroscopic methods. The ^1H and ^{13}C NMR spectra of the tetraacetate **11** support the expected unsymmetrical structure. As the methoxy protons H_4 and H_1 resonate as a triplet (δ 3.66) and a doublet of doublets (δ 3.34), the acetoxy protons H_2, H_6, H_5, and H_3 resonate as a triplet (δ 5.67), (δ 5.25), (δ 5.02), and a doublet of doublets (δ 4.83), respectively. The oxidation of the double bond of some compounds including this ring system in the literature was achieved with ruthenium and sodium periodate.[15] Thus, *N*-methylmorpholine-*N*-oxide (NMO) and catalytic amounts of osmium tetroxide, for oxidation of the double bond of this type compounds, is a new alternative method for the synthesis of inositol. Finally, **11** were subjected to deacetylation reaction using NH_3/MeOH, but it did not give the expected hydrolysis product **12**.

Fortunately, the deacetylation of **11** was achieved in acid medium to give the desired racemic 1,4-di-*O*-methyl-*myo*-inositol (liriodendritol) **12** as a white powder (Scheme 3). All spectral data of **12** was in agreement with data given in the literature.[7a]

In summary, a concise and stereocontrolled approach to 1,4-di-*O*-methyl-*myo*-inositol (rac-liriodendritol) started from *p*-benzoquinone. This methodology provides us entry to high-scale and stereoselective synthesis of *myo*-inositol derivatives.

Experimental

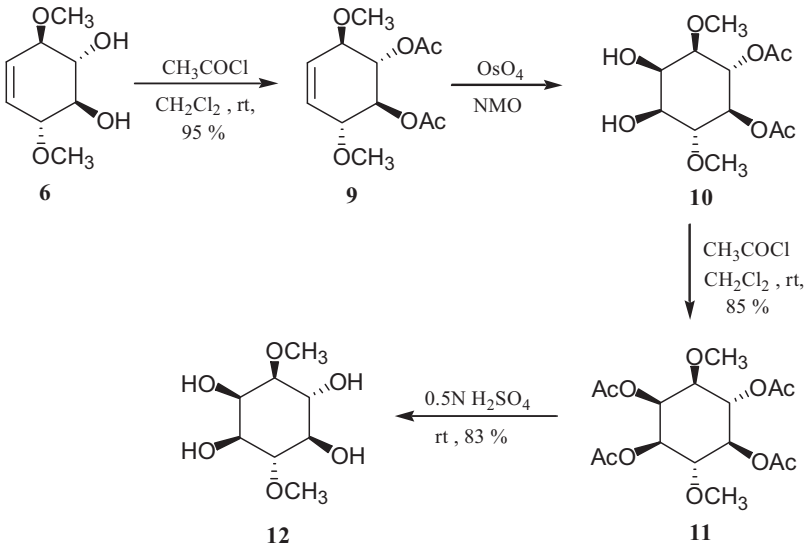
General

Melting points were determined on a Buchi 539 capillary melting apparatus and are uncorrected. IR spectra were obtained from KBr or film on a Mattson 1000 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on 400 (100) MHz Varian spectrometer and are reported in δ units with $SiMe_4$ as internal standard. Thin layer chromatography (TLC) was performed on E. Merck Silica Gel 60 F_{254} plate (0.2 mm). All column chromatography was performed on silica gel (60 mesh, Merck). Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyser. Methanol was distilled from magnesium metal activated with iodine.

(5RS,6RS)-5,6-dibromocyclohex-2-ene-1,4-dione **4:** The title compound was prepared in 84% yield as described in the literature.[10]

(*1RS,4RS,5SR,6SR)-5,6-dibromocyclohex-2-ene-1,4-diol* **5:** The titled compound was prepared in 70% yield as described in the literature.[10a]

(1RS,2RS,3RS,6RS)-3,6-dimethoxycyclohex-4-ene-1,2-diol (**6**): In a 250 ml round-bottomed flask fitted with a stirring bar at 0°C, sodium metal (*ca* 2 g) was added to dry methanol (100 ml) and the resulting suspension was stirred until all the sodium had disappeared and hydrogen liberation ceased. 5,6-dibromocyclohex-2-ene-1,4-diol **5** (7.5 g, 27.6 mmol) was added slowly and the mixture was stirred for 1 h at 0°C and stirring was continued for 24 h at room temperature to provide complete conversion. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 ml) and extracted with EtOAc



Scheme 3

(3 × 300 ml). The organic extracts were combined, dried (Na_2SO_4), and the solvent removed *in vacuo* to give 3,6-dimethoxycyclohex-4-ene-1,2-diol **6** as a colourless crystals (4.3 g, 87%); m.p. 49–50°C (Lit[16]; 48–49°C) (recrystallised from CH_2Cl_2/Et_2O): ^{1}H NMR (400 MHz $CDCl_3$ ppm) δ 5.65 (s, 2H, –CH=CH), 4.56 (s, 2H, –OH), 3.75 (br d, A part of AA'XX' system, J_{AX} = 5.9 Hz, 2H, –CH–OH), 3.55 (br d, × part of AA'XX' system, J_{AX} = 5.9 Hz, 2H, –CH–OCH_3), 3.36 (s, 6H, -OCH_3); ^{13}C NMR (100 MHz $CDCl_3$ ppm) δ 127.1 (x2), 81.2 (x2), 74.2 (x2), 57.2 (x2).

(1RS,2RS,3RS,6RS)-3,6-diisopropoxycyclohex-4-ene-1,2-diol (**7**): In a 250 ml round-bottomed flask fitted with a stirring bar at room temperature, sodium metal (*ca* 2.23 g) was added to dry 2-propanol (150 ml) and the resulting suspension was stirred until all the sodium had disappeared and hydrogen liberation ceased. 5,6-dibromocyclohex-2-ene-1,4-diol **5** (2.85 g, 10.5 mmol) was added slowly and the mixture was stirred for 24 h at room temperature to provide complete conversion. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 ml) and extracted with EtOAc (3 × 300 ml). The organic extracts were combined, dried (Na_2SO_4), and the solvent removed *in vacuo* to give 3,6-diisopropoxycyclohex-4-ene-1,2-diol **7** (4.23 g, 67%)**.** Colourless crystals, m.p. 125–127°C (recrystallised from CH_2Cl_2/Et_2O): IR (KBr): 3399, 2972, 2896, 1651, 1598, 1488, 1381, 1212, 1121, 1097, 1068, 983, 784 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$ ppm): δ 5.64 (s, 2H, –CH=CH), 3.92 (br d, A part of AA'XX' system, J_{AX} = 5.1 Hz, 2H, –CH–OH), 3.62 (br d, × part of AA'XX' system, J_{AX} = 5.1 Hz, 2H, –CH–$OCH(CH_3)_2$), 3.84 (heptet, 2H, $OCH(CH_3)_2$), 3.10 (s, 2H, –OH), 1.18 (d, 6H, J = 6.2 Hz, –$(CH_3)_2$), 1.17 (d, 6H, J = 5.9 Hz, –$(CH_3)_2$); ^{13}C NMR (100 MHz $CDCl_3$ ppm): δ 128.3 (x2), 77.3 (x2), 74.7 (x2), 71.6 (x2), 23.2 (x2), 22.7 (x2); EIMS *m/z* (%): 230 (0.5), 201 (4), 190 (7), 170 (79), 141 (34), 128 (67), 110 (48), 99 (46), 86 (100), 83 (46), 81 (16), 70 (11), 57 (14); Found: C, 62.90; H, 9.75. $C_{12}H_{22}O_4$ requires: C, 62.58; H, 9.63%.

(*1RS,2RS,3RS,6RS)-3,6-dimethoxycyclohex-4-ene-1,2-diyl diacetate* (**9**): 3,6-dimethoxycyclohex-4-ene-1,2-diol **6** (2.5 g, 14.4 mmol) of was dissolved in 20 ml of acetyl chloride and the resulting solution was stirred at room temperature during overnight. The excess of unreacted acetyl chloride was evaporated (60°C, 20 mmHg). The residue was dissolved in CH_2Cl_2 and filtered over silica gel. Evaporation of solvent gave 3,6-dimethoxycyclohex-4-ene-1,2-diyl diacetate **9** (3.5 g, 95%). M.p. 44–45°C (recrystallised from CH_2Cl_2/Et_2O): IR (KBr): 2949, 2831, 1753, 1371, 1242, 1222, 1097, 1048, 953, 784 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$ ppm): δ 5.74 (s, 2H, –CH=CH), 5.13 (m, 2H, –CHOAc), 4.03 (br d, 2H, –$CHOCH_3$), 3.29 (s, 6H, –OCH_3), 1.99 (s, 6H, –$OCOCH_3$); ^{13}C NMR (100 MHz $CDCl_3$ ppm): δ 170.3 (x2), 127.9 (x2), 78.7 (x2), 72.3 (x2), 56.5 (x2), 21.0 (x2); EIMS *m/z* (%): 258 (0.5), 198 (10), 156 (45), 155 (65), 142 (13), 138 (17), 127 (48), 114 (100), 113 (58), 100 (48), 99 (42), 95 (18), 81 (14), 71 (19), 55 (7)*;* Found: C, 55.73; H, 7.26 $C_{12}H_{18}O_6$ requires: C, 55.81; H, 7.02%;

DL-*2,3,5,6-tetra-O-acetyl-1,4-di-O-methyl-myo-inositol* (**11**): A 100 ml two-necked, round-bottomed flask, equipped with a magnetic stirrer and a nitrogen inlet, was charged with 1.16 g (14.2 mmol) of NMO, 4 ml of water, and 4 ml of acetone. To this solution were added ca. 10 mg of OsO4 (0.08 mmol) and 3.66 g (14.2 mmol) of diacetate **9**. The resulting mixture was stirred vigorously under nitrogen at 0°C. During the overnight stirring, the reaction mixture became homogeneous. After stirring 18 h, sodium bisulfite (100 mg) and 2 g of Florisil slurried in 1 ml of water were added, the slurry was stirred for 1 h, and the mixture was filtered through a short pad 2 g of celite in a 50 ml sintered glass funnel. The celite cake was washed with acetone (3 × 10 ml). The filtrates were combined and solvent was removed to give the crude diacetate-diol **11**. The same procedure as described above was applied for acetylation of **11** (4.75 g, 85%). M.p. 130–132°C (Lit[6d]; 139 or 155–156°C) (recrystallised from Ethyl acetate/hexane): IR (KBr): 2978, 2942, 2845, 1749, 1486, 1434, 1372, 1229, 1103, 1143, 1047, 945, 919, 718 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$ ppm): δ 5.67 (t, 1H, J = 2.6 Hz, H-2, –CHOAc), 5.25 (t, 1H, J = 10.0 Hz, H-6, –CHOAc), 5.02 (t, 1H, J = 9.9 Hz, H-5, –CHOAc), 4.83 (dd, 1H, J = 10.3 and 2.9 Hz, H-3, –CHOAc), 3.66 (t, 1H, J = 10.0 Hz, H-4, –CH-OMe), 3.42 (s, 3H, –OCH_3), 3.34 (dd, 1H, J = 9.9 and 2.9 Hz, H-1, –CH–OMe), 3.30 (s, 3H, –OCH_3), 2.14 (s, 3H, –$OCOCH_3$), 2.05 (s, 3H, –$OCOCH_3$), 2.04 (s, 3H, –$OCOCH_3$), 2.02 (s, 3H, –$OCOCH_3$); ^{13}C NMR (100 MHz $CDCl_3$ ppm): δ 170.5, 170.2, 170.1, 170.0, 78.6, 77.3, 72.7, 71.5, 71.3, 66.8, 60.9, 58.5, 21.1 (x2), 21.0 (x2); EIMS *m/z* (%): 376 (0.5), 334 (3), 317 (3), 243 (10), 224 (22), 213 (59), 182 (98), 171 (38), 158 (45), 155 (78), 140 (79), 129 (67), 114 (98), 99 (40), 87 (100), 75 (31); Found: C, 51.02; H, 6.37. $C_{16}H_{24}O_{10}$ requires: C, 51.06; H, 6.43%.

DL-*1,4-di-O-methyl-myo-inositol: rac-liriodendritol* (**12**): 154 mg (0.4 mmol) of tetraacetate **11** (0.11 g, 0.199 mmol) was dissolved in 5 ml of 0.5 N H_2SO_4. The resulting mixture was stirred at room temperature for 6 h. The acid was neutralised with $BaCO_3$. The solid material was filtered and the filtrate was concentrated under reduced pressure to yield 1,4-di-*O*-methyl-myo-inositol: rac-liriodendritol **12** (67 mg, 83%). M.p. 226–228°C (recrystallised from CH_3CH_2OH): ^{1}H NMR and ^{13}C NMR are agreement with data given in the literature.[7a] ^{1}H NMR (400 MHz CD_3OD ppm): δ 4.17–4.21 (br s, 4H, –OH), 3.81 (br s, 1H, –CHO), 3.63 (s, 3H, –OMe), 3.53 (br s, 1H, –CHO), 3.39 (br s, 1H, –CHO), 3.34 (s, 3H, –OMe), 3.14 (br s, 1H, –CHO), 3.05 (dd, 1H, J = 9.9 and 2.8 Hz, –CHO), 2.63 (t, 1H, J = 9.5 Hz, –CHO); ^{13}C NMR (100 MHz CD_3OD ppm): δ 82.5, 80.9, 74.4, 72.5, 71.3, 68.4, 54.6 (x2, –$OMe_{C\text{-}1}$ and –$OMe_{C\text{-}4}$).

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