Synthesis of *anti–anti* (*anti–syn*)-3,4:8,9-tetraacetoxy-11-oxa-tricyclo [4.4.1.0^{1,6}]undecanes

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Synthesis of *anti–anti*- and *anti–syn*-3,4:8,9-tetraacetoxy-11-oxa-tricyclo[4.4.1.0^{1,6}] undecanes have been achieved starting from naphthalene. The Birch reduction of naphthalene gave 1,4,5,8-tetrahydro-naphthalene in high yield. 1,4,5,8-Tetrahydro-naphthalene was selectively oxidised with *m*CPBA to give 11-oxa-tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene. OsO_4 oxidation followed by acetylation furnished the corresponding tetraacetates.

Keywords: hydroxy-skipped cyclitol, polycyclitol, epoxycyclitol

Inositols **1** and their derivatives are a most important class of biologically active natural products.[1,2] Due to the biological activities of inositols, their derivatives when phosphorylated, glycosylated and methylated have been extensively synthesised using diverse methods.[3–7] Thus, these compounds are of great deal of interest in inositol chemistry. Additionally, one of the major focuses of the synthetic inositol chemistry is the judicious design, synthesis and structure–activity relationship (SAR) studies of different structurally modified analogues of natural substrates of different metabolic enzymes and receptors.[8] Polyhydroxylated cycloalkanes such as cyclitols and carba-sugars have received an increased amount of attention due to their wide range of biological activities.[9–12] The synthesis of polycyclitols like **2** as new structural variants has been achieved.[13]

Polyhydroxylated cycloalkanes including epoxy ring are a concise intermediate for the synthesis of inositols. They are also known as biologically active compounds. 1,2-Anhydro-*myo*-inositol **3** (conduritol B epoxide) is of considerable interest because of its ability to act as an irreversible inhibitor of various β-glucosidases.[14] Cyclophellitol **4** is a β-glucosidase inhibitor isolated from the culture filtrate of a mushroom.[15,16] Nanda and Mahapatra have studied asymmetric synthesis of hydroxy-skipped bishomo-inositols **5** and reported their inhibitory effect on α- and β-glucosidases.[17] An effective strategy for the synthesis of –CH_2-bloked (or hydroxy-skipped) epoxypolycyclitols starting from naphthalene is now reported.

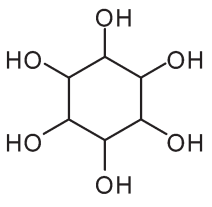
Results and discussion

We have introduced the synthesis of –CH_2-bloked (or hydroxy-skipped) polycyclitols starting from the aromatic compounds.[18,19] We have investigated the oxidation with OsO_4 of the decalin and indan rings including a diene unit. Oxidation of both compounds **6** and **8** gave the product mixtures (**7a, 7b** and other product from **6**; **9a** and **9b** from **8**) (Scheme 1). The structures of the products from both **6** and **8** were determined by NMR spectral data and X-ray diffraction analysis. The stereochemical course of the hydroxylation of **6** was from the *anti* position depending on the diene unit. However, the stereochemical course of the hydroxylation of **8** was from both the *anti* and *syn* position depending on the diene unit.

Ginsburg *et al.*[20] obtained the product mixtures from hydroxylation of 11,13-dioxo-12-methyl-12-aza[4.3.3]propella-3,8-diene **10** with osmium tetroxide. After acetylation of this mixtures, they reported the synthesis of the compound **11** as the major companent and confirmed its structure (Scheme 1). However, they did not isolated the other isomers. Shani and Sondheimer studied the bromination reactions of diene after opened of epoxide ring in compound **14**.[21] Recently, Mehta *et al.*[22,23] studied the bromination and oxidation reactions of dienes after opened of epoxide ring in compound **14**. Additionally, they put forward that oxidation and acetylation of one of two double bonds in sides followed epoxidation with *m*CPBA gave two isomers as *anti* and *syn* in a ratio of 10:1, respectively.[23] Both Mehta *et al.* and Ginsburg *et al.* could obtain only the major product from the product mixtures. Therefore, the reaction of epoxide **14** with OsO_4 was investigated.

Anti–anti- and *anti–syn*-3,4:8,9-tetraacetoxy-11-oxa-tricyclo [4.4.1.0^{1,6}]undecanes, **16a** and **16b**, were synthesised starting from naphthalene **12**. 1,4,5,8-Tetrahydro-naphthalene **13** was prepared from naphthalene **12** by reduction with sodium in liquid ammonia at low temperature.[21,24,25] Controlled epoxidation of **13** with *m*CPBA led selectively to 11-oxa-tricyclo [4.4.1.0^{1,6}]undeca-3,8-diene **14** in a yield of 81% as the sole product (Scheme 2). The structure of compound **14** was elucidated on the basis of ^{1}H and ^{13}C NMR spectroscopic data. In particular, a three-line ^{13}C NMR spectrum of **14** owing to C_{2v}-symmetry in the molecule confirms the proposed structure. The most conspicuous feature in the ^{13}C NMR spectrum is one line arising from the quaternary epoxide carbon-resonance at 60.5 ppm.

Diene-**14** is an ideal substrate for the synthesis of targeted compounds. if both double bonds were hydroxylated in *cis* manner one could theoretically obtain three isomeric component (all-*anti–anti*, all-*syn–syn* and *syn–anti*). The stereochemical course of the hydroxylation may be *syn* or *anti* with respect to the epoxy ring since compound **14** has C_{2v}-symmetry.



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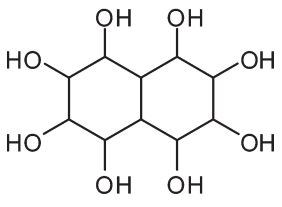

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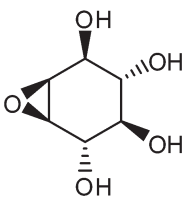

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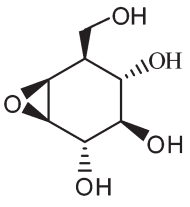

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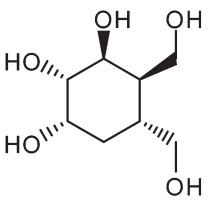

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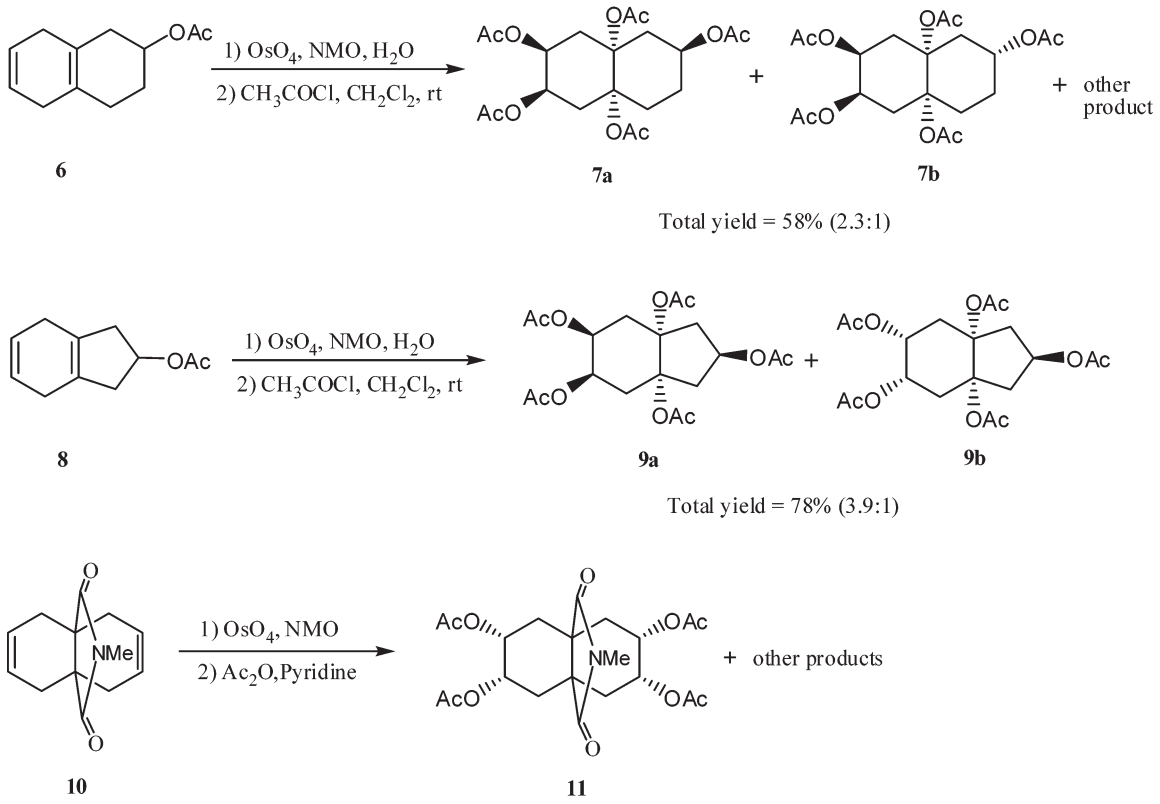
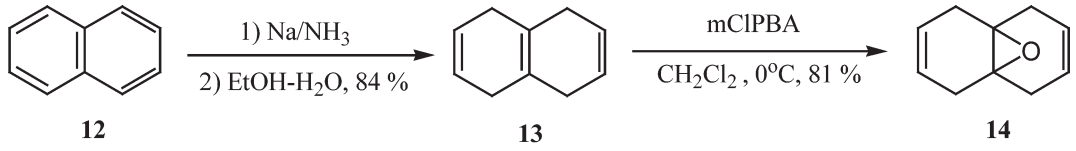


Scheme 1

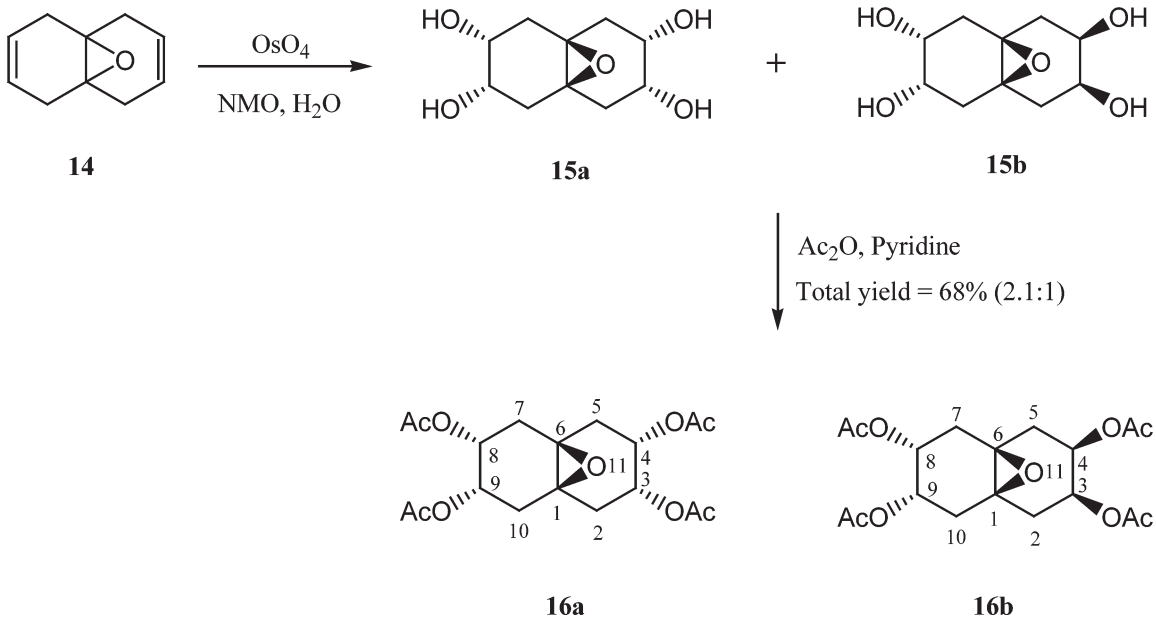


Scheme 2

cis-Hydroxylation of **14** with catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant at low temperature gave a mixture of diols as *anti–anti* **15a** and *anti–syn* **15b**. The diols were converted to epoxytetraacetate **16a** and **16b** with a pyridine/Ac_2O system for further characterisation (Scheme 3). An attempted chromatographic separation of the reaction mixture was unsuccussful. Compounds **16a** and **16b** were easily separated by crystallisation of the mixture in a ratio of 2.1:1, respectively. The formation of **16a** as major product is hindered due to the presence of an epoxy group in the *anti* position. While *anti–anti* and *anti–syn* isomers were obtained conformationally, a *syn–syn* isomer was not formed in the reaction.

The structures of the **16a** and **16b** were determined by NMR spectrums and extensive double resonance experiments. Both compounds also have the symmetric structures. The compound **16a** displays a five-line ^{13}C NMR spectrum because of C_{2v}-symmetry in the molecule. These are carbonyl carbons (δ 170.6, 4x C), carbons of CHO (67.6, C_3, C_4, C_8 and $C_{9)}$, quaternary epoxide carbons (58.3, C_1 and $C_{6)}$, methylenic carbons (32.7, C_2, C_5, C_7 and $C_{10)}$, and methyl carbons (21.2, 4x C). On the contrary, the compound **16b** displays an eight-line ^{13}C NMR spectrum because of Cs-symmetry in the molecule. These are carbonyl carbons (δ 170.8, 2x C and 170.4, 2x C), carbons of CHO (67.7 and 67.6, C_3, C_4, C_8 and $C_{9)}$, quaternary epoxide carbons (59.6, C_1 and $C_{6)}$, methylenic carbons (33.3 and 32.6, C_2, C_5, C_7 and $C_{10)}$, and methyl carbons (21.3, 4x C). Thus, these data are in full agreement with the proposed symmetric structures. In addition to, irradiation at the resonance frequency of the acetoxy protons (m 4.99) causes enhancement at the resonance signals of the methylenic protons resonating at dd 2.33 and dd 2.27 as well as of the other methylenic protons resonating at dd 2.03 and dd 1.98. Irradiation at the resonance frequency of the methylenic protons (dd 2.33 and dd 2.27) causes enhancement at the resonance signals of the acetoxy protons resonating at m 4.99. This NOE experiment clearly indicates that the *cis*-double acetate groups are in an *anti*-position with other *cis*-double acetate groups in **16b**.

The formation of **16a** as the major product may point to the intermediacy of a complex in which osmium is simultaneously bound to both double bonds of **14** in a diboat conformation. In addition, the observed high selectivity may be caused by hindering of the presence of an epoxy group in the *syn* position. As a result, the oxidation reaction of the 11-oxa-tricyclo [4.4.1.$0^{1,6}$]undeca-3,8-diene was studied and structures of the obtained products resulting from oxidation and the stereocontrolled preparation of epoxytetraacetates (or epoxypolycyclitols) starting from naphthalene was investigated.



14 **15a** **15b**

16a **16b**

Scheme 3

Experimental

Melting points were determined on a Büchi 539 capillary melting apparatus and are uncorrected. IR spectra were obtained from KBr or film on a Mattson 1000 FT-IR spectrophotometer. The ^{1}H 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. 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.

1,4,5,8-Tetrahydro-naphthalene (**13**): Prepared from Birch reduction of naphthalene in 84 % yield as described in the literature.[24,25]

11-Oxa-tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene (**14**): A solution of *m*-chloroperbenzoic acid (*m*CPBA) (5.32 g, 21.63 mmol, 70% purity) in dichloromethane (50 mL) was added dropwise to a solution of 1,4,5,8-tetrahydro-naphthalene **13** (2.38 g, 18.03 mmol) in dichloromethane (20 mL), the internal temperature being kept about –10 °C by the ice-salt cooling. The reaction was stirred at the same temperature for 5 h and was then quenched with a saturated solution of sodium hydrogen carbonate. The product was extracted with dichloromethane (3x50 mL); the combined extracts were washed with saturated sodium hydrogen carbonate solution and brine, and dried with anhydrous sodium sulfate. Removal of the solvent afforded the crude epoxide product. The usual chromatographic separation of the crude mixture with 30% ethyl acetate/hexane yielded successively the 11-oxa-tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene **14** (2.16 g) in 81% overall yield. White crystals, m.p. 59–61 °C (from ethyl acetate) (Lit[21]: m.p. 60–62 °C); ^{1}H NMR (400 MHz $CDCl_3$ ppm) δ 5.46 (m, 4H, –CH=CH), 2.51 (dd, A part of AB system, J = 16.7, 2.8 Hz, 4H, one of $–CH_2$), 2.36 (bd, B part of AB system, J = 16.7 Hz, 4H, one of $–CH_2$); ^{13}C NMR (100 MHz $CDCl_3$ ppm) δ 122.8 (2x –CH=CH), 60.5 (2x bridgehead-epoxy-C), 31.0 (4x $–CH_2$).

Anti–anti- and anti–syn-3,4:8,9-tetraacetoxy-11-oxa-tricyclo[4.4.1.0^{1,6}] undecanes (**16a** and **16b**): A 100 mL two-necked, round-bottomed flask, equipped with a magnetic stirrer and a nitrogen inlet, was charged with 1.75 g (14.8 mmol) of NMO, water (2 mL) and acetone solvent (20 mL). To this solution were added a catalytic amount of OsO_4 (*ca* 10 mg, 0.08 mmol) and 1.0 g (6.76 mmol) of 11-oxa-tricyclo [4.4.1.0^{1,6}]undeca-3,8-diene **14**. The resulting mixture was stirred vigorously under nitrogen at 0 °C. During the overnight stirring, the reaction mixture became homogeneous. After stirring for 18 h, sodium bisulfite (150 mg) and 3 g of Florisil sluried in 2 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 60 mL sintered glass funnel. The Celite cake was washed with acetone (3 × 15 mL). The filtrates were combined and evaporation of the solvent gave diols, which were dissolved in pyridine (10 mL). To the magnetically stirred solution was added Ac_2O (10 mL). The reaction mixture was stirred at room temperature for 12 h. The mixture was cooled to 0 °C and 4 N HCl solution (80 mL) was added and extracted with ether (3x50 mL). The combined organic extracts were washed with $NaHCO_3$ solution (10 mL) and water (45 mL) and then dried over Na_2SO_4. After the evaporation of the solvent, gave *anti–anti*-3,4:8,9-tetraacetoxy-11-oxa-tricyclo[4.4.1.0^{1,6}]undecane **16a** and *anti–syn*-3,4:8,9-tetraacetoxy-11-oxatricyclo[4.4.1.0^{1,6}] undecane **16b** (1.76 g, 68 % from **14**). Crystallisation of the mixture (1.76 g) from ethyl acetate permitted their separation (**16a**:1.20 g, **16b**: 0.56 g).

16a: Colourless oily; Found: C, 56.17; H, 6.78. $C_{18}H_{24}O_9$ requires: C, 56.24; H, 6.29 %; IR ($CHCl_3$, cm^{-1}): 3698, 2936, 1736, 1437, 1371, 1247, 1163, 1046, 734, 608; ^{1}H NMR (400 MHz $CDCl_3$ ppm) δ 4.92 (m, 4H, –CH-O), 2.23 (dd, A part of AB system, J = 15.5, 6.8 Hz, 4H, one of $–CH_2$), 1.99 (dd, B part of AB system, J = 15.5, 7.3 Hz, 4H, one of $–CH_2$), 1.98 (s, 12H, $–CH_3$); ^{13}C NMR (100 MHz $CDCl_3$ ppm) δ 170.6 (4x –C=O), 67.6 (4x -C-O), 58.3 (2x bridgehead-epoxy-C), 32.7 (4x $–CH_2$), 21.2 (4x $–CH_3$).

16b: White crystals, m.p. 160–162°C (from ethyl acetate); Found: C, 56.05; H, 6.71. $C_{18}H_{24}O_9$ requires: C, 56.24; H, 6.29 %; IR ($CHCl_3$, cm^{-1}): 3697, 2940, 1736, 1444, 1370, 1243, 1162, 1103, 1040, 915, 739, 629; ^{1}H NMR (400 MHz $CDCl_3$ ppm) δ 4.99 (m, 4H, –CH-O), 2.33 (dd, A part of AB system, J = 15.4, 7.0 Hz, 2H, one of $–CH_2$), 2.27 (dd, B part of AB system, J = 15.4, 5.8 Hz, 2H, one of $–CH_2$), 2.03 (dd, A part of AB system, J = 15.4, 6.2 Hz, 2H, one of $–CH_2$), 1.98 (dd, B part of AB system, J = 15.4, 6.2 Hz, 2H, one of $–CH_2$), 2.02 (s, 6H, $–CH_3$), 2.01 (s, 6H, $–CH_3$); ^{13}C NMR (100 MHz $CDCl_3$ ppm) δ 170.8 (2x –C=O), 170.4 (2x –C=O), 67.7 (2x –C-O), 67.6 (2x –C-O), 59.6 (2x bridgehead-epoxy-C), 33.3 (2x –CH2), 32.6 (2x –CH2), 21.3 (4x –CH3).

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