Novel Conformationally Locked Inositols: From Aromatics to Annulated Cyclitols

Goverdhan Mehta,* Ramesh S. Senaiar, and Mrinal K. Bera[a]

Abstract: A new family of ring-annulated inositols with "locked" conformations has been designed to deliver a range of these biologically important entities in "unnatural conformations" while retaining their "natural configurations". The simple "tool" of *trans* ring fusion has been used to "lock" the conformation of the annulated inositols. Short, simple syntheses of a range of these novel cyclitols have been achieved from readily available aromatic precursors such as tetralin and indane. Along the way, annulated C_2-symmetric cyclohexadiene-*trans*-diol (*trans*-CHD) derivatives have been prepared for the first time and serve as the pivotal building blocks for generating the oxy-functionalization pattern of inositols. The presence of chemo-differentiated hydroxyl groups in our novel inositols is expected to facilitate the installation of phosphate diversity to harness the biological potential of these entities.

Keywords: annulation · conformation analysis · cyclitols · dihydroxylation · signal transduction

Introduction

Inositols **1** occupy a preeminent position among biologically important entities known as cyclitols and constitute the only group of cyclohexanes substituted at each carbon atom for which all the possible (nine) diastereomers, five natural (*myo*, *scyllo*, D-*chiro*, L-*chiro*, and *neo*) and four synthetic (*cis*, *epi*, *allo*, and *muco*), are known.[1] The biological functions of derivatives of inositol are wide-ranging and diverse and include intercellular communication, phosphate storage and transfer, anti-cancer and involvement in covalent anchoring of proteins to membranes.[1a–c, 2] However, it is the pivotal role of inositol phosphate derivatives such as D-*myo*-inositol-1,4,5-triphosphate [Ins(1,4,5)P_3] and D-*myo*-inositol-1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P_4] as second messengers in intercellular signal transduction events through binding to specific receptors and mobilizing Ca^{2+} ions from intracellular stores that has generated contemporary interest in their chemistry and biology.[1, 2] The increased cytosolic Ca^{2+} concentration initiates a number of cell-type specific responses.[1b, 2] Thus, intervention and selective manipulation of physiological processes triggered by inositol polyphosphates has stimulated the search for new and designer analogues for unraveling the complex biological mechanisms and development of new pharmaceuticals.

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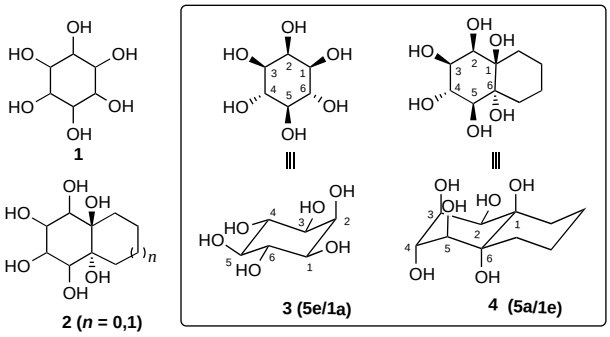
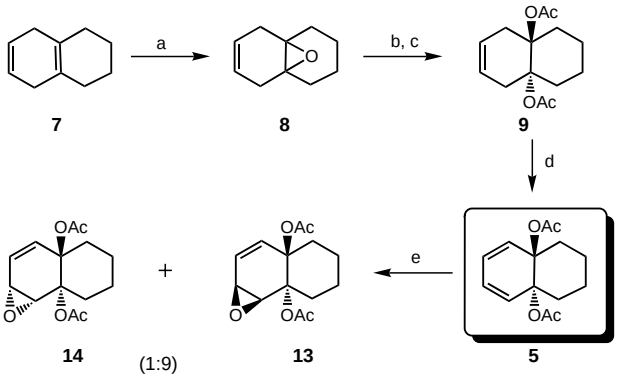
The quest for new synthetic analogues of inositols, though extensive,[3, 4] has largely centered on ring modification and sidearm and phosphate variation and studies with these structural variants continue to provide insights into structure–activity relationships. Here, we introduce a new family of ring-annulated bicyclic inositols **2** as novel entities with several unique attributes. The *trans*-fused bicyclic inositols **2**, unlike **1**, are rigid and can be locked in high-energy conformations (see below) which are unattainable in **1**.[5] For example, while the most abundant *myo*-inositol exists in the stable conformation **3** with five equatorial and one axial (5e/1a) hydroxyl group, the 1,6-annulated bicyclic *myo*-inositol **4** would be locked in the five axial and one equatorial (5a/1e) conformation. Secondly, the presence of two chemo-differentiated tertiary hydroxyl groups in **2** is expected to facilitate the generation of functional group diversity and phosphate variation, an essential but complicated feature of inositol chemistry.[1] It should be noted that selective phosphorylation of inositols is a cumbersome, multistep protocol which requires extensive protection–deprotection maneuvers. Lastly, a hydrophobic appendage in the form of an alicyclic ring in **2** could profoundly modulate the cell membrane permeability and receptor recognition parameters of the inositol moiety. Interestingly, the ring annulation maneuver on inositols, which leads to **2**, can be expected to alter their reactivity and biological profile and has not been attempted before.[3h] More importantly, the annulated inositols are destined to be locked in "unnatural conformations" while retaining their "natural configurations". In this paper, we describe a simple and versatile approach to several cyclohexa- and cyclopenta-annulated inositols **2** from readily



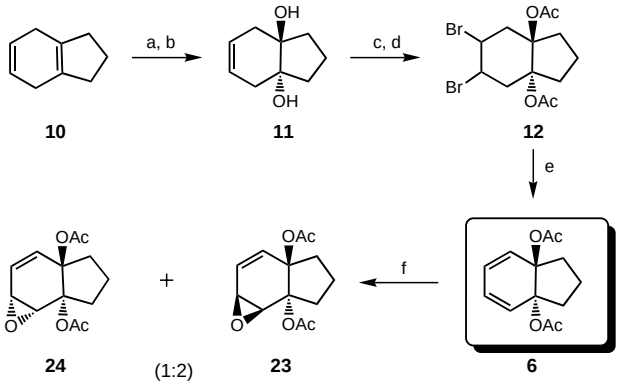
available aromatic precursors such as tetralin and indane. While the syntheses reported here are of racemic compounds, our overall strategy is amenable to chiral induction at several stages along the way.

In our general approach to **2**, annulated C_2-symmetric cyclohexadiene-*trans*-diol (*trans*-CHD) derivatives **5** and **6** were recognized as the pivotal building blocks and access to them from readily available precursors was first devised.[6, 7] For the synthesis of cyclohexa-annulated *trans*-CHD **5**, 1,4-dihydrotetralin (**7**) obtained from tetralin was subjected to regioselective epoxidation to give **8** followed by acid-catalyzed ring opening to a *trans* diol[8] and acetylation to furnish the *trans* diacetate **9** (Scheme 1). Allylic bromination of **9** and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)-mediated dehydrobromination delivered the desired C_2-symmetric cyclohexadiene-*trans*-diol diacetate **5**.[9] In a similar manner, cyclopenta-annulated cyclohexadiene-*trans*-diol derivative **6** was prepared from 1,4-dihydroindane (**10**) via *trans*-diol **11** (Scheme 2).[10] The allylic bromination-dehydrobromination sequence, successful in the case of **9**, led only to intractable products when implemented on **11** or its diacetate derivative. After some trials, a convenient route to the C_2-symmetric *trans*-CHD derivative **6** from **11** was established through addition of bromine and acetylation to **12** and double dehydrobromination in the presence of DBU.[9]

The C_2-symmetric bicyclic *trans*-CHD diacetates **5** and **6** served as the key starting materials for accessing the new family of inositols. The main theme in our approach was to generate the network of oxygen functionalities on the diene moiety in a stereoselective manner and with the minimum number of steps. Mono-epoxidation of **5** was stereoselective and furnished a readily separable mixture of diastereomeric epoxides **13** and **14** (9:1) (Scheme 1). Acid-catalyzed ring opening of the major epoxide **13** furnished bicyclic diols **15** (3:1) and **16**, which are annulated conduritol F and B derivatives, respectively (Scheme 3).[11, 12] The stereostructure of the acetate migration product **15**, though indicated through careful scrutiny of

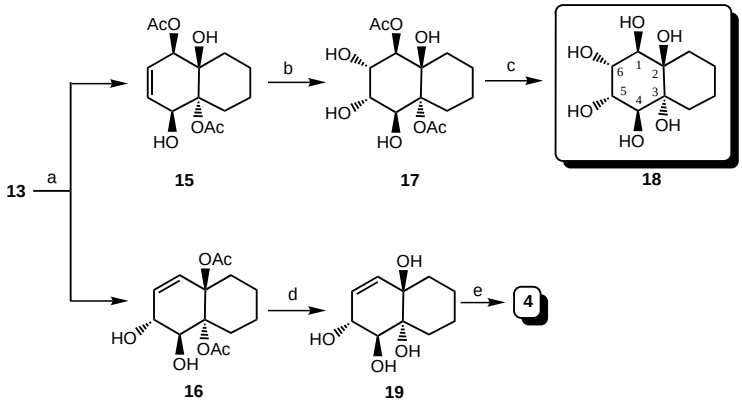


Scheme 1. a) *m*CPBA, CH_2Cl_2, −5 °C, 5 min, 85 %; b) 10 % AcOH, RT, 2 h, 90 %; c) Ac_2O, $BF_3 \cdot Et_2O$, RT, 2 h, 88 %; d) i) NBS, AIBN, CCl_4, reflux, 4 h; ii) DBU, DMSO, RT, 52 % (2 steps); e) *m*CPBA, CH_2Cl_2, 10 °C, 5–6 h, 73 % (based on recovered starting material).

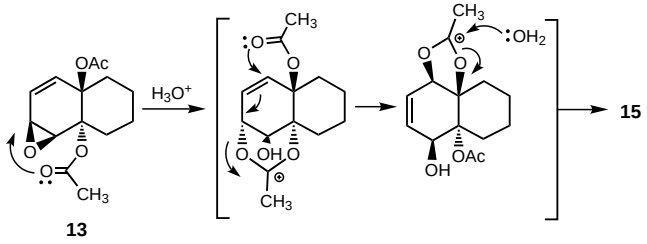


Scheme 2. a) MMPP (magnesium monoperoxyphthalate hexahydrate), THF/H_2O 1:1, 0 °C, 5 min, 85 %; b) 10 % AcOH, RT, 5 h, 90 %; c) $C_6H_5N^+ \cdot HBr_3^-$, CH_2Cl_2, 0 °C, 1 h, 66 %; d) Ac_2O, $BF_3 \cdot Et_2O$, RT, 1 h, 89 %; e) DBU, DMSO, RT, 4 h, 54 %; f) *m*CPBA, CH_2Cl_2, 0 °C, 3 d, 60 %.

the spectral data, was secured through X-ray crystallography studies. The origin of **15** from epoxide **13** can be traced to an intramolecular neighboring acetate-mediated opening of the epoxide ring followed by an S_N2' displacement by the distal acetate group as shown in Scheme 4. It is this eventful participation of both the acetate groups of **13** in the epoxide ring opening that generates the interesting *cis*-1,4-diol stereo-

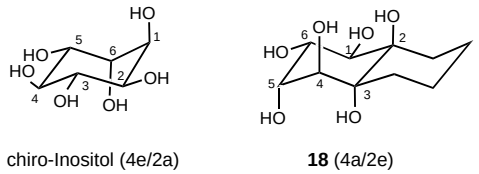


Scheme 3. a) 10 % AcOH, THF, 50 °C, 16 h, 80 %; b) OsO_4 (cat.), NMMO, acetone/water 4:1, RT, 2 h, 88 %; c) K_2CO_3, MeOH, RT, 2 h, 96 %; d) K_2CO_3, MeOH, RT, 1 h, 95 %; e) OsO_4 (cat.), NMMO, acetone/water 4:1, RT, 6 h, 80 %.



Scheme 4. Postulated mechanism of formation of **15**.

chemistry observed in **15** (Scheme 4).[13] The major product **15** from epoxide **13** was then subjected to stereospecific OsO_4-mediated dihydroxylation to furnish the inositol derivative **17** (Scheme 3). The stereochemical outcome of the dihydroxylation of **15** to give **17** was predictable and expected both on steric considerations and Kishi's rule[14] for the OsO_4-mediated dihydroxylation of allylic alcohols. Base hydrolysis of **17** led to the 2,3-cyclohexa-annulated *chiro*-inositol **18**.[15] The most stable conformation of *chiro*-inositol determined by X-ray crystallography is 4e/2a as shown in Scheme 5.[16] In contrast, the X-ray crystal structure of 2,3-cyclohexa-annulated *chiro*-inositol **18** exhibited a 4a/2e conformation and is displayed for comparison in Scheme 5.

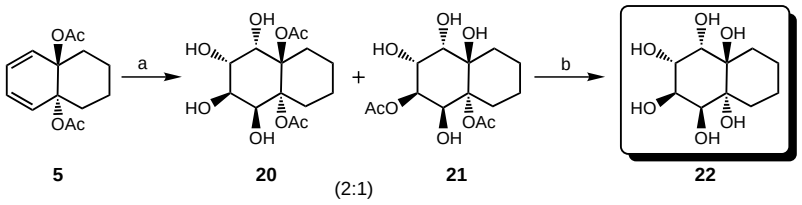


Scheme 5. Stable conformations of *chiro*-inositol and annulated *chiro*-inositol **18**.

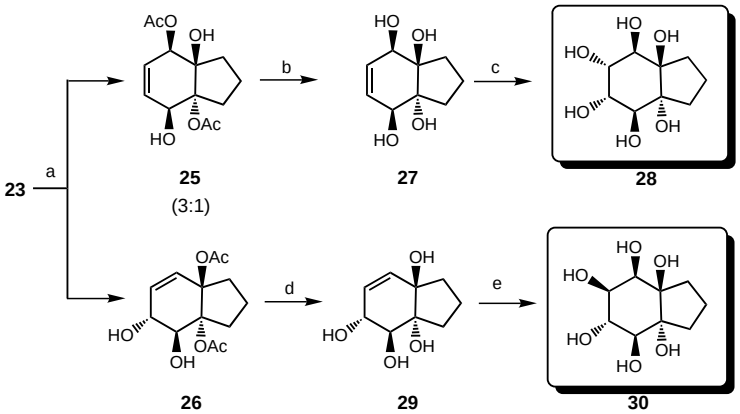
Attention was now turned to the minor diol **16** obtained from the cleavage of epoxide **13**. Acetate hydrolysis of **16** led to the tetrol **19**, which is an annulated conduritol B derivative (Scheme 3).[11] Catalytic OsO_4-mediated dihydroxylation of **19** was smooth and stereospecific and furnished the cyclohexa-annulated *myo*-inositol **4**. An X-ray crystal structure of **4** indicated that as per our design strategy it indeed had a 5a/1e ground state conformation in contrast with 5e/1a for *myo*-inositol **3**.[17] Once again, dihydroxylation of **19** occurred from the face opposite to the secondary allylic hydroxyl group.[14]

In an alternate sequence, bicyclic diene diacetate **5** was subjected to exhaustive dihydroxylation with catalytic OsO_4 to stereospecifically furnish the hexaoxygenated products **20** (2:1) and **21**, with the latter arising through 1,4-acetate migration (Scheme 6). Base hydrolysis of both **20** and **21** furnished 3,4-cyclohexa-annulated *chiro*-inositol **22**.[15] The stereostructure of **22** was evident from the C_2 symmetry present and this annulated *chiro*-inositol was locked in the 4a/2e conformation. It is noteworthy that starting from the same *trans*-CHD diacetate **5**, two inositols (**18** and **22**) with the *chiro*-configuration and 4a/2e conformation can be crafted by a tactic that is formally equivalent to altering the site of annulation (2,3- and 3,4-, respectively)[15] on *chiro*-inositol.

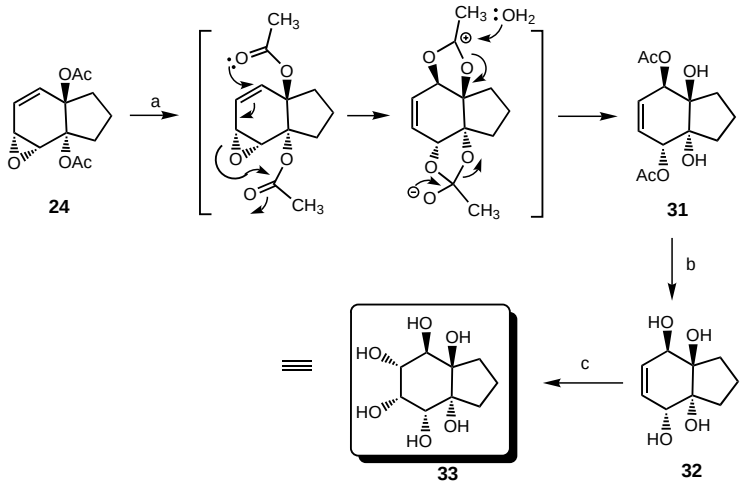
The elaboration of the cyclohexadiene-*trans*-diol derivative **6** to diverse cyclopenta-annulated inositols followed the protocols successfully implemented on **5** (see above). Epoxidation of **6** was less stereoselective (cf. **5**) and furnished a readily separable mixture (2:1) of epoxides **23** and **24** (Scheme 2). Acid-catalyzed ring opening of the major epoxide **23** furnished diols **25** and **26** in a 3:1 ratio (Scheme 7). The stereostructures of conduritol F **25** and conduritol B **26** derivatives[11] were secured through X-ray crystal structure determination. The major product was once again derived through complex acetate migration analogous to that observed for **13** (Scheme 4).[13] Acetate hydrolysis in **25** furnished the annulated conduritol F derivative **27**, and further catalytic OsO_4-mediated dihydroxylation led stereospecifically to the 2,3-cyclopenta-annulated[15] *chiro*-inositol **28**. Inositol **28** was firmly locked in 4a/2e conformation. Similarly, the minor epoxide cleavage product **26** was hydrolyzed to give conduritol B derivative **29**, and further dihydroxylation furnished the cyclopenta-annulated *myo*-inositol **30** which was locked in the 5a/1e ground state conformation (Scheme 7).[17] On acid cleavage the remaining minor epoxide **24** obtained from **6** furnished a single product **31** in which both the acetate



Scheme 6. a) OsO_4 (cat.), NMMO, acetone/water 4:1, 10 °C, 2 d, 70 %; b) K_2CO_3, MeOH, RT, 2 h, 90 %.



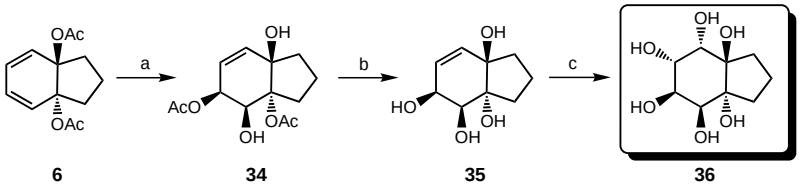
Scheme 7. a) 10 % AcOH, THF, 50 °C, 24 h, 60 %; b) K_2CO_3, MeOH, RT, 6 h, 81 %; c) OsO_4 (cat.), NMMO, acetone/water 4:1, RT, 4 h, 84 %; d) K_2CO_3, MeOH, RT, 4 h, 92 %; e) OsO_4 (cat.), NMMO, acetone/water 4:1, RT, 3 h, 86 %.



Scheme 8. a) 10% AcOH, THF, 50 °C, 24 h, 74%; b) K_2CO_3, MeOH, RT, 3 h, 95%; c) OsO_4 (cat.), NMMO, acetone/water 4:1, RT, 3 h, 83%.

groups had migrated (Scheme 8). Hydrolysis of **31** led to the conduritol E derivative **32**, and further OsO_4-mediated dihydroxylation furnished the annulated *allo*-inositol **33**. The stereostructure of **33** was secured through single-crystal X-ray structure determination and had a locked 3a/3e conformation.

Lastly, the annulated *trans*-CHD diol **6** was subjected to mono-dihydroxylation to stereospecifically give the diol **34** with concomitant 1,4-acetate migration (Scheme 9). The stereostructure of **34** was again secured through X-ray crystal structure determination. Acetate hydrolysis in **34** provided a conduritol F derivative **35**, and a second OsO_4-mediated dihydroxylation led to the 3,4-cyclopenta-annulated *chiro*-inositol **36**,[15] which adopts a 4a/2e conformation.



Scheme 9. a) OsO_4 (cat.), NMMO, acetone/water 4:1, 0 °C, 2 d, 48%; b) K_2CO_3, MeOH, RT, 8 h, 75%; c) OsO_4 (cat.), NMMO, acetone/water 4:1, RT, 6 h, 63%.

Conclusion

We have delineated short and efficient routes to ring-annulated C_2-symmetric *trans*-CHD diols **5** and **6** and harnessed them to craft a range of novel bicyclic inositols. Our design of these unusual entities employs the annulation stratagem for generating new "unnatural" conformations and structural diversity while retaining the "natural" configurations of the inositols. The availability of such bicyclic inositols with differentiated hydroxyl groups with new spatial orientations augurs well for further phosphate variations and biological evaluation.

Experimental Section

General methods: Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were recorded on JASCO FTIR 410. Proton (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were generally recorded on a JEOL JNM-LA 300 spectrometer. Mass spectra measurements were carried out on a JEOL JMS DX 303 spectrometer. Elemental analyses were carried out on a Carlo Erba Element Analyzer 1106. Analytical thin-layer chromatography (TLC) was performed on (10×5 cm) glass plates coated (250 μm) with Acme silica gel G or GF_{254} (containing 13% calcium sulfate as binder). Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by spraying sulfuric acid and heating the plates at 120 °C. Column chromatography was performed by using Acme silica gel (100–200 mesh) or neutral alumina. All solvents were freshly distilled over CaH_2 or Na/benzophenone as appropriate.

(4a*R,8a*R**)-1,2,3,4,4a,5,8,8a-Octahydro-4a,8a-naphthalenediol (9)**: Epoxide **8** (3 g, 0.02 mol)[8] was treated with 10% acetic acid (10 mL), and the resulting biphasic reaction mixture was stirred vigorously at room temperature. Upon complete consumption of the starting material (monitored by TLC), the acid was neutralized by careful addition of solid $NaHCO_3$, and the resulting diol was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×50 mL), brine (1×50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish the *trans* diol (3 g, 90%). The diol was dissolved in acetic anhydride (10 mL) and a catalytic amount of $BF_3 \cdot Et_2O$ (100 μL) was added at 0 °C. The resulting dark brown solution was stirred for 2 h under N_2 atmosphere. The reaction mixture was poured into ice-cold water (10 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×50 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish crystalline *trans* diacetate **9** (4.7 g), which was recrystallized from hexane/dichloromethane to give colorless needle-like crystals of **9** (4.54 g, 88%). M.p. 136–137 °C; IR (KBr): $\tilde{\nu} = 1727$ cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.15$ (m, 2H), 3.09 (s, 1H), 3.03 (s, 1H), 2.69 (s, 1H), 2.65 (s, 1H), 2.36 (s, 1H), 2.18 (s, 1H), 2.01 (s, 6H), 1.66–1.13 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.6$ (2C), 123.2 (2C), 80.8 (2C), 29.9 (2C), 28.5 (2C), 22.3 (2C), 20.8 (2C); MS (70 eV, EI): *m*/*z* (%): 252 [M^+]; elemental analysis calcd (%) for $C_{14}H_{20}O_4$ (252): C 66.64, H 7.99; found: C 66.56, H 8.03.

(4a*R,8a*R**)-8a-(Acetyloxy)-1,2,3,4,4a,8a-hexahydro-4-naphthalenyl acetate (5)**: *N*-Bromosuccinimide (706 mg, 3.97 mmol) and a catalytic amount of 2,2′-azabisisobutyronitrile (AIBN) (10 mg) were added to a solution of the *trans*-diacetate **9** (1 g, 3.97 mmol) in dry CCl_4 (10 mL), and the resulting reaction mixture was heated at reflux for 4 h under N_2. After the completion of the reaction, floating succinimide was filtered off and the filtrate was poured into ice-cold water (15 mL). The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were successively washed with 10% HCl, (2×10 mL), water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue (1.3 g) obtained was dissolved in dry DMSO (10 mL) and DBU (0.7 mL, 4.76 mmol) was added

gradually from a syringe at 5–10 °C under N_2 atmosphere, during which time the reaction mixture turned from pale yellow to dark brown. The reaction mixture was stirred at room temperature for further 2 h, before diluting with diethyl ether (20 mL) and pouring into ice-cold water (20 mL). The ether layer was separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with 10% HCl (2 × 10 mL), water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish the crude product (530 mg), which on chromatography over neutral alumina column (5% ethyl acetate/hexane) gave the crystalline *trans*-diene **5** (516 mg, 52%). M.p. 140–141 °C; IR (KBr): $\tilde{\nu}$ = 3052, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.09 (m, 2H), 5.91 (m, 2H), 2.56 (s, 1H), 2.51 (s, 1H), 2.03–1.83 (m, 2H), 1.97 (s, 6H), 1.77–1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2 (2C), 130.8 (2C), 124.1 (2C), 78.8 (2C), 26.7 (2C), 21.6 (2C), 20.2 (2C); MS (EI, 70 eV): *m*/*z*: 251 [M^++H]; elemental analysis calcd (%) for $C_{14}H_{18}O_4$ (250): C 67.18, H 7.25; found: C, 66.90, H, 7.52.

Compound 12: Pyridiniumbromide perbromide (8.22 g, 0.025 mmol) was added to a solution of the known[10] *trans*-diol **11** (3.6 g, 0.023 mol) in dry CH_2Cl_2 (50 mL), and the reaction mixture was stirred at 0 °C under N_2 atmosphere. After consumption of the starting material (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (50 mL) and poured into ice-cold water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed successively with saturated aqueous $Na_2S_2O_5$ solution (2 × 20 mL), water (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. Concentration of the solvent and purification of the resultant solid residue by silica gel chromatography afforded the dibromodiol (4.7 g, 66%). m.p. 106 °C; IR (thin film): $\tilde{\nu}$ = 3531, 3457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.89 (s, 2H), 2.87 (d, *J* = 16 Hz, 2H), 2.47 (s, 2H), 2.28 (d, *J* = 15.6 Hz, 2H), 1.86–1.80 (m, 4H), 1.62 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 80.0 (2C), 50.1 (2C), 35.8 (2C), 33.3 (2C), 18.9 (2C); MS (70 eV, EI): *m*/*z* (%): 314 [M^+]. The dibromodiol was dissolved in acetic anhydride (10 mL) and $BF_3 \cdot Et_2O$ (100 µL) was added at 0 °C and stirred at the same temperature for 1 h under N_2. On complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched by the careful addition of ice-cold water (50 mL) and diluted with CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed carefully with saturated aqueous $NaHCO_3$ (2 × 20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The residue obtained after concentration at reduced pressure was purified by silica gel chromatography to furnish the dibromodiacetate **12** (5.3 g, 89%) as a colorless crystalline solid. M.p. 127.3 °C; IR (thin film): $\tilde{\nu}$ = 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.76 (s, 2H), 3.20 (br s, 1H), 3.14 (br s, 1H), 2.69 (d, *J* = 3.9 Hz, 1H), 2.64 (d, *J* = 3.9 Hz, 1H), 2.57–2.53 (m, 2H), 2.01 (s, 6H), 1.8–1.6 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (2C), 86.7 (2C), 48.2 (2C), 30.7 (2C), 27.4 (2C), 23.3 (2C), 18.4; MS (70 eV, EI): *m*/*z* (%): 317 [M^+ – Br – H], 319 [M^+ – Br+H].

(3a*R,7a*R**)-2,3,3a,7a-Tetrahydro-1*H*-3a,7a-indenediol (6)**: Dibromodiacetate **12** (1 g, 2.51 mmol) was dissolved in dry DMSO (5 mL) and DBU (0.75 mL, 5.02 mmol) was added dropwise at 5–10 °C from a syringe under N_2 atmosphere, during which time the reaction turned dark brown. The reaction mixture was stirred at room temperature for further 2 h, before diluting with diethyl ether (30 mL) and pouring into ice-cold water (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with 10% HCl (2 × 20 mL), water (20 mL), brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resultant solid residue was purified by chromatography over neutral alumina (5% ethyl acetate/hexane) to furnish crystalline *trans*-diene **6** (319 mg, 54%). M.p. 139.5 °C; IR (KBr): $\tilde{\nu}$ = 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.43 (d, *J* = 10.2 Hz, 2H), 5.90 (d, *J* = 10.2 Hz, 2H), 2.41–2.35 (m, 2H), 2.09–1.99 (m, 2H), 1.94–1.84 (m, 2H), 1.94 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6 (2C), 128.9 (2C), 125.6 (2C), 87.2 (2C), 28.4 (2C), 21.7 (2C), 21.2; MS (70 eV, EI): *m*/*z* (%): 152 [M^+ – 2Ac+2].

Compounds 13 and 14: *m*CPBA (70%, 493 mg, 2 mmol) was added at 0 °C to a solution of **5** (500 mg, 2 mmol) in dry CH_2Cl_2 (10 mL), and the reaction mixture was stirred at room temperature for 5 h before quenching with 10% Na_2SO_3 (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a solid residue, which by TLC examination was found to be a mixture of two compounds. The residue was subjected to silica gel column chromatography (5% ethyl acetate/hexane) to furnish epoxides **13** (295 mg, 66%) and **14** (31 mg, 7%), along with recovered starting material **5** (80 mg), in an overall yield of 73%. Compound **13**: IR (thin film): $\tilde{\nu}$ = 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.13 (½ABq, *J* = 9.4, 3.7 Hz, 1H), 6.08 (d of ½ABq, *J* = 9.4, 3.7 Hz, 1H), 4.23 (d, *J* = 3.7 Hz, 1H), 3.33 (br s, 1H), 2.89 (d, *J* = 14.2 Hz, 1H), 2.41 (d, *J* = 14.2 Hz, 1H), 2.23–2.09 (m, 1H), 2.02 (s, 3H), 2.00 (s, 3H), 1.84–1.75 (m, 1H), 1.52–1.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 168.7, 134.7, 126.2, 80.7 (2C), 55.9, 46.7, 28.5, 25.5, 22.0, 21.7, 20.1, 19.7; MS (EI, 70 eV): *m*/*z* (%): 207 [M^+ – OAc]; elemental analysis calcd (%) for $C_{14}H_{18}O_5$ (266.2): C 63.15, H 6.81; found: C 62.85, H 6.90.

Compound **14**: IR (KBr): $\tilde{\nu}$ = 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.15 (d, *J* = 9.4 Hz, 1H), 5.95 (d, *J* = 9.4 Hz, 1H), 3.41 (d, *J* = 3.3 Hz, 1H), 3.28 (d, *J* = 3.3 Hz, 1H), 2.92 (d, *J* = 13.6 Hz, 1H), 2.50 (d, *J* = 13.6 Hz, 1H), 2.02 (s, 6H), 1.81–1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 168.7, 138.2, 124.4, 78.4, 77.7, 54.4, 47.6, 28.3, 27.2, 21.6, 21.2, 20.3, 20.0; MS (70 eV, EI): *m*/*z* (%): 267 [M^++H]; elemental analysis calcd (%) for $C_{14}H_{18}O_5$ (266.2): C 63.15, H 6.81; found: C 62.92, H 6.95.

Compounds 15 and 16: A solution of epoxide **13** (250 mg, 0.94 mmol) in THF (5 mL) was treated with 10% AcOH (2 mL), and the resulting mixture was stirred at 50 °C for 16 h. Upon completion of the reaction (monitored by TLC), the mixture was cooled and neutralized by the addition of solid $NaHCO_3$, followed by extraction with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a solid. Purification of the residue by column chromatography over silica gel (30% ethyl acetate/hexane) gave **15** (160 mg, 60%) and **16** (53 mg, 20%) as colorless crystalline solids in 80% overall yield. Compound **15**: m.p. 198–199 °C; IR (KBr): $\tilde{\nu}$ = 3478, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.98 (ddd, *J* = 10.2, 4.6, 2.2 Hz, 1H), 5.55 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.42 (d, *J* = 1.3 Hz, 1H), 4.68 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.14 (d, *J* = 11.1 Hz, 1H), 2.72 (d, *J* = 14.7 Hz, 1H), 2.45 (s, 1H), 2.26–2.05 (m, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 1.67–1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 169.3, 129.2, 124.6, 83.1 (2C), 73.6, 72.9, 64.8, 31.7, 24.5, 22.2, 21.0, 20.3; MS (70 eV, EI): *m*/*z* (%): 285 [M^++H]; elemental analysis calcd (%) for $C_{14}H_{20}O_6$ (284): C 59.14, H 7.09; found: C 59.08, H 7.04.

Compound **16**: m.p. 162–163 °C; IR (KBr): $\tilde{\nu}$ = 3402, 1737, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.21 (d, *J* = 10 Hz, 1H), 5.91 (dd, *J* = 10, 3.3 Hz, 1H), 5.54 (d, *J* = 8.4 Hz, 1H), 4.29 (br s, 1H), 3.04 (d, *J* = 9.6 Hz, 1H), 2.61 (d, *J* = 11.1 Hz, 1H), 2.21–2.09 (m, 2H), 2.04 (s, 3H), 2.00 (s, 3H), 1.87–1.78 (m, 2H), 1.66–1.22 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 167.7, 130.1, 129.7, 80.5, 79.9, 73.5, 70.5, 27.7, 24.5, 22.2, 21.8, 20.2, 19.8; MS (70 eV, EI): *m*/*z* (%): 242 [M^+ – Ac+H]; elemental analysis calcd (%) for $C_{14}H_{20}O_6$ (284.3): C 59.14, H 7.09; found: C 58.91, H 7.07.

Crystal data for compound 15: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: rhombohedral-hexagonal, space group: *R*3*c*, cell parameters: *a* = 27.761(2), *b* = 27.761(2), *c* = 9.956(10) Å, γ = 120(6)°, *V* = 6645.19 Å^3, *Z* = 18, ρ_{calcd} = 1.279 g cm^{-3}, *F*(000) = 2736, μ = 0.10 mm^{-1}, λ = 0.71 Å. *R*1 = 0.0491 for $F_o > 2\sigma(F_o)$ and 0.0499 for all 2111 data. *wR*2 = 0.1392, GOF = 1.097. There are four independent molecules in the asymmetric unit. An ORTEP drawing of compound **15** with 50% ellipsoidal probability level is shown in Figure 1.

Compound 17: OsO_4 (2 mg, 1 mol%) and 50% aqueous *N*-methylmorpholine *N*-oxide (NMMO) (130 µL, 0.56 mmol) were added to a solution of diol **15** (155 mg, 0.545 mmol) in acetone/water (4:1, 5 mL) at 0 °C, and the resulting pale yellow reaction mixture was stirred at room temperature for 2 h, before quenching with solid $NaHSO_3$. The resulting mixture was diluted with ethyl acetate (10 mL), filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography over silica gel (80% ethyl acetate/hexane) to afford the tetrol **17** (152 mg, 88%). IR (KBr): $\tilde{\nu}$ = 3391, 1727 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ = 5.19 (d, *J* = 10.2 Hz, 1H), 5.56 (d, *J* = 2.5 Hz, 1H), 4.10 (dd, *J* = 10.2, 4 Hz, 1H), 4.04 (dd, *J* = 4, 2.5 Hz, 1H), 2.28 (d, *J* =

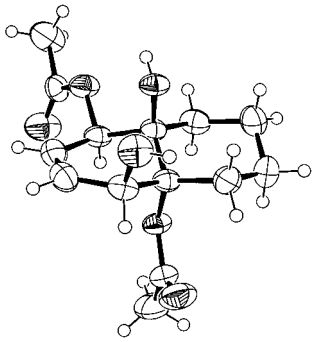


Figure 1. ORTEP drawing for **15**.

14.7 Hz, 1H), 2.06 (s, 3H), 1.95 (s, 3H), 1.92–1.86 (m, 1H), 1.55–1.21 (m, 6H); ^{13}C NMR (75 MHz, D_2O): δ = 175.5, 174.5, 83.7, 77.5, 76.1, 74.3, 71.2, 67.4, 30.1, 25.6, 22.9, 21.6, 20.1 (2C); MS (70 eV, EI): *m*/*z* (%): 319 [M^++H]; elemental analysis calcd (%) for $C_{14}H_{22}O_8$ (318.3): C 52.82, H 6.97; found: C 52.63, H 7.07.

Annulated *chiro*-inositol 18: Solid K_2CO_3 (78 mg, 0.566 mmol) was added to a solution of tetrol **17** (90 mg, 0.283 mmol) in methanol (3 mL), and the reaction mixture was stirred at room temperature for 2 h, before removal of methanol under reduced pressure. The residue obtained was dissolved in deionized water (2 mL) and the solution was passed though a Dowex 50W × 8 (H^+ form) ion exchange resin column and eluted with water. The eluent was concentrated under reduced pressure to give the annulated *chiro*-inositol **18** (63 mg, 96%). M.p. 209–210 °C; IR (KBr): $\tilde{\nu}$ = 3353 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 4.00 (dd, *J* = 3.6, 3.3 Hz, 1H), 3.89 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.61 (d, *J* = 9.9 Hz, 1H), 3.55 (d, *J* = 3.3 Hz, 1H), 2.05–1.95 (m, 1H), 1.66 (d, *J* = 13.2 Hz, 1H), 1.54–1.43 (m, 5H), 1.29 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ = 80.5, 78.8, 77.4, 77.1, 75.1, 72.3, 33.0, 32.1, 22.5, 22.1; MS (ES): *m*/*z* (%): 257 [M^++Na].

Crystal data for the compound 18: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P\bar{1}$, cell parameters: *a* = 12.558(3), *b* = 12.915(4), *c* = 13.859(4) Å, α = 87.959(6), β = 87.627(6), γ = 70.606(6)°, *V* = 2118.20 Å^3, *Z* = 8, ρ_{calcd} = 1.285 g cm^{-3}, *F*(000) = 882, μ = 0.11 mm^{-1}, λ = 0.71 Å. *R*1 = 0.0512 for 4439 $F_o > 4\sigma(F_o)$ and 0.0923 for all 7191 data, *wR*2 = 0.1563, GOF = 0.883, restrained GOF = 0.883 for all data. There are four independent molecules in the asymmetric unit. An ORTEP drawing of compound **18** with 50% ellipsoidal probability level is shown in Figure 2.

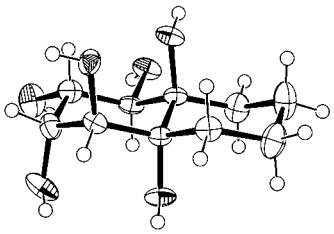


Figure 2. ORTEP drawing for **18**.

Compound 19: The tetrol **19** (35 mg, 95%) was obtained from diacetate **16** (53 mg, 0.187 mmol) by following a procedure similar to that described for the conversion of **17** to **18** but using K_2CO_3 (51 mg, 0.374 mmol) in methanol (2 mL) and purification over a silica gel (50% ethyl acetate/hexane). M.p. 202–203 °C; IR (thin film): $\tilde{\nu}$ = 3273 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 5.71 (d ½ABq, *J* = 10, 3.8 Hz, 1H), 5.61 (½ABq, *J* = 10, 3.8 Hz, 1H), 3.97 (d, *J* = 3.8 Hz, 1H), 3.53 (s, 1H), 2.09–2.00 (m, 1H), 1.65–1.29 (m, 7H); ^{13}C NMR (75 MHz, D_2O): δ = 134.6, 127.9, 77.7, 71.4, 70.9, 70.6, 32.7, 30.3, 20.4, 19.9; MS (70 eV, EI): *m*/*z* (%): 164 [M^+ – 2H_2O]; elemental analysis calcd (%) for $C_{10}H_{16}O_4$ (200.2): C 59.98, H 8.05; found: C 59.79, H 7.89.

Annulated *myo*-inositol 4: The annulated inositol **4** (18 mg, 80%) was obtained from the olefin **19** (20 mg, 0.1 mmol) by dihydroxylation following the procedure described above for the conversion of **15** to **17** but using OsO_4 (1 mg, 5 mol%) and NMMO (30 µL, 0.128 mmol) in acetone/water (4:1, 1 mL) and purification by silica gel column chromatography (10% methanol/ethyl acetate). M.p. 196–197 °C; IR (KBr): $\tilde{\nu}$ = 3308 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 3.98 (br s, 1H), 3.94 (m, 1H), 3.74 (m, 1H), 3.42 (br s, 1H), 2.08–2.00 (m, 1H), 1.65 (br d, *J* = 9.3 Hz, 1H), 1.51–1.28 (m, 5H), 1.24 (d, *J* = 14 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ 77.3, 76.2, 75.6, 74.8, 74.1, 68.4, 30.5, 30.1, 20.1, 19.6; MS (ES): *m*/*z* (%): 257 [M^++Na].

Crystal data for the compound 4: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P\bar{1}$, cell parameters: *a* = 6.113(1), *b* = 7.612(1), *c* = 11.667(2) Å, α = 102.326(4), β = 97.912(4), γ = 91.817(4)°, *V* = 524.39 Å^3, *Z* = 2, ρ_{calcd} = 1.484 g cm^{-3}, *F*(000) = 252.0, μ = 0.12 mm^{-1}, λ = 0.71 Å. *R*1 = 0.0498 for 892 $F_o > 4\sigma(F_o)$ and 0.0788 for all 1273 data *wR*2 = 0.0963, GOF = 1.100, restrained GOF = 1.100 for all data. An ORTEP drawing of compound **4** with 50% ellipsoidal probability level is shown in Figure 3.

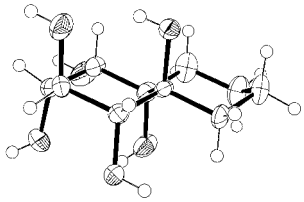


Figure 3. ORTEP drawing for **4**.

Compounds 20 and 21: A solution of the diene **5** (100 mg, 0.4 mmol) in acetone/water (4:1, 5 mL) was treated with OsO_4 (1 mg, 1 mol%) and NMMO (190 µL, 0.8 mmol), and the resulting solution was stirred at 10 °C for 2 d. The reaction was quenched by the addition of solid $NaHSO_3$. After dilution with ethyl acetate (20 mL), the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure to give a solid residue, which was indicated to be a mixture of two compounds by TLC. The isomers **20** and **21** were separated by chromatography over a silica gel (40% ethyl acetate/hexane) to furnish **20** (53 mg, 47%) and **21** (26 mg, 23%).

Compound **20**: m.p. 210–211 °C; IR (KBr): $\tilde{\nu}$ = 3419, 1731 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 4.50 (s, 2H), 3.78 (s, 2H), 2.38 (s, 1H), 2.34 (s, 1H), 2.01–1.97 (m, 2H), 1.96 (s, 6H), 1.5–1.4 (m, 2H), 1.13–1.06 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ = 172.5 (2C), 86.0 (2C), 71.4 (2C), 67.4 (2C), 24.8 (2C), 22.2 (2C), 19.5 (2C); MS (70 eV, EI): *m*/*z* (%): 223 [M^+ – 2H_2O – OAc]; elemental analysis calcd (%) for $C_{14}H_{22}O_8$ (318.3): C 52.82, H 6.97; found: C 52.96, H 7.27.

Compound **21**: m.p. 215–216 °C; IR (thin film): 3419 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 5.12 (dd, *J* = 10.6, 3 Hz, 1H), 4.89 (br s, 1H), 4.28–4.20 (m, 2H), 2.79 (br s, 1H), 2.60–2.55 (m, 2H), 2.16 (s, 3H), 2.14 (s, 3H), 1.85–1.30 (m, 5H); ^{13}C NMR (75 MHz, D_2O): δ = 170.9, 168.4, 85.0, 78.4, 74.1, 71.7, 71.6, 66.8, 30.3, 24.6, 22.2, 21.1, 19.9, 19.1; MS (70 eV, EI): *m*/*z* (%): 283 [M^+ – 2H_2O+H].

Annulated *chiro*-inositol 22: By following a procedure similar to that used for the conversion of **17** to **18**, tetrols **20** (45 mg, 0.158 mmol) and **21** (25 mg, 0.088 mmol) were separately hydrolyzed using K_2CO_3 (43 mg, 0.316 mmol for **20**, 24 mg, 0.176 mmol for **21**) in methanol to afford the annulated inositol **22** (34 mg, 18 mg, respectively, 90%). IR (thin film): 3364 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 3.95 (s, 2H), 3.51 (s, 2H), 2.00–1.91 (m, 2H), 1.52–1.38 (m, 4H), 1.18 (s, 1H), 1.14 (s, 1H); ^{13}C NMR (75 MHz, D_2O): δ = 78.8 (2C), 74.5 (2C), 69.2 (2C), 30.6 (2C), 19.8 (2C); MS (EI, 70 eV): *m*/*z* (%): 217 [M^+ – H_2O+H].

Compound 23 and 24: Mono-epoxidation of **6** was carried out by following a procedure similar to that described for **5** by treating the diene (1.2 g, 5.08 mmol) with *m*CPBA (70%, 1.25 g, 5.08 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, followed by chromatography over silica gel (elution with 10% ethyl acetate/hexane) to furnish mono-epoxides **23** (537 mg, 42%) and **24** (230 mg, 18%).

Compound **23**: m.p. 167 °C; IR (KBr): $\tilde{\nu} = 1730\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.44$ (d, $J = 9.3$ Hz, 1H), 6.06 (dd, $J = 9.8$ Hz, 3.9 Hz, 1H), 4.31 (d, $J = 4.2$ Hz, 1H), 3.31–3.29 (m, 1H), 2.68–2.61 (m, 1H), 2.34–2.24 (m, 2H), 1.97–1.79 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.5$, 169.1, 133.1, 127.4, 89.1, 86.1, 51.8, 47.5, 30.1, 27.4, 22.0, 21.9, 20.7; MS (70 eV, EI): m/z (%): 209 [$M^+ - Ac$]; elemental analysis calcd (%) for $C_{13}H_{16}O_5$ (252.2): C 61.09, H 6.39; found: C 61.47, H 6.36.

Copmound **24**: m.p. 170 °C; IR (thin film): $\tilde{\nu} = 1731\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.47$ (d, $J = 9.9$ Hz, 1H), 5.95 (d, $J = 9.9$ Hz, 1H), 3.68 (d, $J = 3.6$ Hz, 1H), 3.29 (s, 1H), 2.75–2.66 (m, 1H), 2.43–2.35 (m, 1H), 2.17–1.75 (m, 4H), 1.97 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 169.1, 168.9, 134.8, 125.3, 86.4, 85.5, 52.7, 48.0, 30.5, 29.3, 21.7, 21.2, 19.2; MS(70 eV, EI): m/z (%): 167 [$M^+ - 2\,Ac{+}H$].

Compounds 25 and 26: Epoxide **23** (500 mg, 1.98 mmol) was transformed into diols **25** (246 mg, 46%) and **26** (75 mg, 14%) by following a procedure similar to that used for the conversion of the epoxide **13** into diols **15** and **16** but using 10% AcOH (3 mL) and separation of the isomers by chromatography over silica gel (40% ethyl acetate/hexane).

Compound **25**: m.p. 99.6 °C; IR (KBr): $\tilde{\nu} = 3437, 1744, 1731\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.02–5.96$ (m, 1H), 5.62–5.57 (m, 2H), 4.80 (dd, $J = 10.8$, 4.8 Hz, 1H), 2.64–2.53 (m, 3H), 2.15 (s, 3H), 1.96 (s, 3H), 1.96–1.90 (m, 1H), 1.80–1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$, 169.4, 130.6, 125.5, 90.5, 81.4, 73.6, 64.5, 34.7, 26.6, 22.2, 21.1, 18.8; MS (70 eV, EI): m/z (%): 210 [$M^+ - Ac - H_2O{+}H$]; elemental analysis calcd (%) for $C_{13}H_{18}O_6$ (270.2): C 57.77, H 6.71; found: C 57.61, H 6.70.

Compound **26**: m.p. 150.3 °C; IR (KBr): $\tilde{\nu} = 3467, 1730, 1711\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.42$ (d, $J = 9.6$ Hz, 1H), 5.88 (dd, $J = 10.1$, 3 Hz, 1H), 4.55 (br s, 1H), 4.40 (br s, 1H), 2.59–2.28 (m, 3H), 2.11–1.95 (m, 1H), 1.99 (s, 3H), 1.95 (s, 3H), 2.11–1.95 (m, 1H), 1.89–1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.9$, 168.1, 131.9, 127.8, 89.6, 88.6, 73.2, 72.9, 30.02, 25.9, 22.3, 21.7, 19.8; MS (70 eV, EI): m/z (%): 228 [$M^+ - Ac{+}H$].

Crystal data for the compound 25: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: monoclinic, space group: $P12_1/m1$, cell parameters: $a = 10.4616(4)$, $b = 10.476(4)$, $c = 12.454(5)$ Å, $\beta = 101.117(8)°$, $V = 1339.40$ Å^3, $Z = 4$, $\rho_{calcd} = 1.34\ g\,cm^{-3}$, $F(000) = 576.0$, $\mu = 0.11\ mm^{-1}$, $\lambda = 0.71073$ Å. Total number of l.s. parameters = 433. $R1 = 0.1012$ for 1953 $F_o > 4\sigma(F_o)$ and 0.2277 for all 3949 data. $wR2 = 0.2523$, GOF = 1.252, restrained GOF = 1.252 for all data. An ORTEP drawing of compound **25** with 50% ellipsoidal probability is shown in Figure 4. There are two independent molecules in the asymmetric unit.

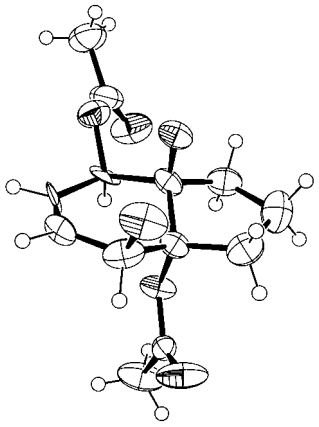


Figure 4. ORTEP drawing for **25**.

Crystal data for the compound 26: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: monoclinic, space group: $P2_1/c$, cell parameters: $a = 7.949(3)$, $b = 22.668(11)$, $c = 7.970(3)$ Å, $\beta = 112.605(8)°$, $V = 1325.81$ Å^3, $Z = 4$, $\rho_{calcd} = 1.354\ g\,cm^{-3}$, $F(000) = 576.0$, $\mu = 0.11\ mm^{-1}$, $\lambda = 0.71073$ Å. Total number of l.s. parameters = 244. $R1 = 0.0832$ for 2250 $F_o > 4\sigma(F_o)$ and 0.1002 for all 2680 data. $wR2 = 0.1882$, GOF = 1.227, restrained GOF = 1.227 for all data. An ORTEP drawing of compound **26** with 50% ellipsoidal probability is shown in Figure 5.

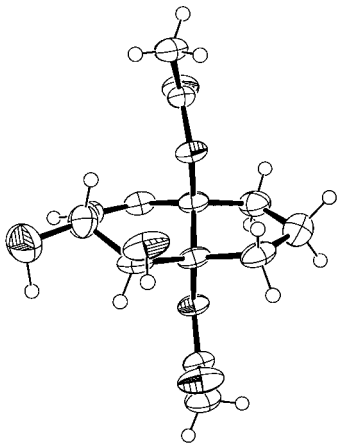


Figure 5. ORTEP drawing for **26**.

Compound 27: Diol **25** (230 mg, 0.85 mmol) was hydrolyzed with K_2CO_3 (234 mg, 1.7 mmol) in methanol (3 mL) at room temperature for 6 h. Removal of the solvent under reduced pressure gave a solid residue which was purified by chromatography over silica gel (70% ethyl acetate/hexane) to furnish the tetrol **27** (128 mg, 81%). IR (KBr): $\tilde{\nu} = 3399\ cm^{-1}$; ^1H NMR (300 MHz, D_2O): $\delta = 5.86–5.81$ (m, 1H), 5.65 (d, $J = 9.9$ Hz, 1H), 4.23 (s, 1H), 3.92 (s, 1H), 2.29–2.24 (m, 1H), 1.78 (br s, 4H), 1.58–1.52 (m, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta = 131.9$, 128.8, 82.5, 81.9, 71.4, 69.7, 33.9, 31.6, 18.9; MS (70 eV, EI): m/z (%): 150 [$M^+ - 2\,H_2O$]; elemental analysis calcd (%) for $C_9H_{14}O_4$ (186.2): C 58.05, H 7.58; found: C 58.14, H 7.71.

Annulated *chiro*-inositol 28: The tetrol **27** (128 mg, 0.688 mmol) was dihydroxylated by following a procedure similar to that described for **17** but using OsO_4 (2 mg, 1 mol%) and NMMO (175 µL, 0.75 mmol) in acetone/water (4:1, 3 mL), followed by chromatography over silica gel (10% methanol/ethyl acetate) to afford the annulated *chiro*-inositol **28** (127 mg, 84%). IR (KBr): $\tilde{\nu} = 3364\ cm^{-1}$; ^1H NMR (300 MHz, D_2O): $\delta = 4.02$ (s, 1H), 3.96–3.81 (m, 3H), 2.22–2.11 (m, 1H), 1.89–1.77 (m, 3H), 1.64–1.61 (m, 1H), 1.51–1.45 (m, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta = 86.9$, 83.7, 75.8, 72.6, 72.4, 70.7, 33.2, 31.3, 19.7; MS (70 eV, EI): m/z (%): 184 [$M^+ - 2\,H_2O$]; elemental analysis calcd (%) for $C_9H_{16}O_6$ (220.2): C, 49.09, H 7.32; found: C 48.69, H 7.29.

Compound 29: Diol diacetate **26** (75 mg, 0.278 mmol) was hydrolyzed with K_2CO_3 (76 mg, 0.556 mmol) in methanol (2 mL) by following a procedure similar to that used for the conversion of **16** to **19**. Purification of the resultant residue over silica gel (70% ethyl acetate/hexane) furnished **29** (47 mg, 92%). M.p. 124.6 °C; IR (thin film): $\tilde{\nu} = 3338\ cm^{-1}$; ^1H NMR (300 MHz, D_2O): $\delta = 5.99$ (d, $J = 10.2$, 1H), 5.76 (d, $J = 7.2$ Hz, 1H), 4.15 (s, 1H), 3.83 (s, 1H), 2.17–2.06 (m, 1H), 1.81–1.77 (m, 3H), 1.63–1.48 (m, 2H); ^{13}C NMR (75 MHz, D_2O): $\delta = 131.0$, 130.6, 80.3, 79.9, 75.8, 72.6, 33.4, 29.94, 19.8; MS (70 eV, EI): m/z (%): 167 [$M^+ - H_2O - H$].

Annulated *myo*-inositol 30: Tetrol **29** (45 mg, 0.242 mmol) was dihydroxylated with OsO_4 (1 mg, 2 mol%) and NMMO (70 µL, 0.29 mmol) in acetone/water (4:1, 2 mL) following a procedure described above for the conversion of **19** to **4**. Chromatography of the resultant residue over silica gel (10% methanol/ethyl acetate) afforded annulated *myo*-inositol **30** (45 mg, 86%). IR (KBr): $\tilde{\nu} = 3386\ cm^{-1}$; ^1H NMR (300 MHz, D_2O): $\delta =$ 4.06 (s, 1H), 3.96 (s, 2H), 3.79 (s, 1H), 2.20–2.13 (m, 1H), 1.80–1.61 (m, 4H), 1.47–1.42 (m, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta = 85.8$, 84.7, 76.5, 74.6, 73.7, 68.50, 33.6, 31.6, 18.7; MS (70 eV, EI): m/z (%): 166 [$M^+ - 3\,H_2O$].

Compound 31: Epoxide **24** (225 mg, 0.893 mmol) was converted to the diol **31** (178 mg, 74%) by following a procedure similar to that used for the major epoxide **23** but with 10% AcOH (3 mL) and purification over silica gel (40% ethyl acetate/hexane). M.p. 124.5 °C; IR (KBr): $\tilde{\nu} = 3452$, $1716\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.69$ (s, 2H), 5.67(s, 2H), 2.14 (s, 6H), 2.21–2.05 (m, 2H), 1.96–1.83 (m, 2H), 1.75–1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$ (2C), 128.0 (2C), 83.3 (2C), 73.8

(2C), 34.7 (2C), 21.1 (2C), 19.4; MS (70 eV, EI): m/z (%): 210 [M^+ – AcO – H_2O+H].

Compound 32: The diol diacetate **31** (175 mg, 0.648 mmol) was hydrolyzed with K_2CO_3 (178 mg, 1.296 mmol) in methanol (3 mL) by following a procedure similar to that used for the conversion of **16** to **19** to afford the tetrol **32** (114 mg, 95%). M.p. 114 °C; IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 5.49 (s, 2H), 4.21 (s, 2H), 1.91 – 1.71 (m, 6H); ^{13}C NMR (75 MHz, D_2O): δ = 131.0 (2C), 85.2 (2C), 71.2 (2C), 33.9 (2C), 19.5; MS (70 eV, EI): m/z (%): 150 [$M^+ - 2H_2O$].

Annulated *allo*-inositol 33: Tetrol **32** (100 mg, 0.537 mmol) was dihydroxylated by using OsO_4 (1 mg, 1 mol%) and NMMO (150 μL, 0.644 mmol) by following a procedure similar to that used for the conversion of **19** to **4**. Purification by chromatography over silica gel (10% methanol/ethyl acetate) led to **33**. M.p. 237 °C; IR (KBr): $\tilde{\nu}$ = 3382 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 3.96 (s, 1H), 3.78 – 3.68 (m, 3H), 1.87 – 1.59 (m, 6H); ^{13}C NMR (75 MHz, D_2O): δ = 87.7, 85.1, 75.7, 72.6, 72.2, 68.8, 33.2, 32.9, 19.7.

Crystal data for compound 33: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: monoclinic, space group: $P\,1\,2_1\,1$, cell parameters: a = 7.221(17), b = 11.507(27), c = 7.291(17) Å, β = 103.692(31)°, V = 588.63 Å^3, Z = 2, ρ_{calcd} = 1.242 g cm^{-3}, $F(000)$ = 236.0, μ = 0.10 mm^{-1}, λ = 0.71073 Å. Total number of l.s. parameters = 200. $R1$ = 0.0349 for 1436 $F_o > 4\sigma(F_o)$ and 0.0406 for all 1589 data. $wR2$ = 0.0815, GOF = 1.08, restrained GOF = 1.08 for all data. An ORTEP drawing of compound **33** with 50% ellipsoidal probability is shown in Figure 6.

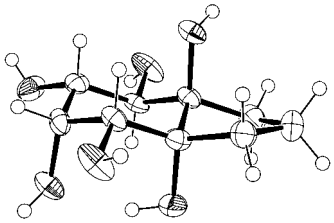


Figure 6. ORTEP drawing for **33**.

Compound 34: A solution of diene **6** (200 mg, 0.847 mmol) in acetone/water (4:1, 5 mL) was treated with OsO_4 (2 mg, 1 mol%) and NMMO (200 μL, 0.847 mmol), and the resulting mixture was stirred at 0 °C for 2 d. The reaction was quenched by the addition of solid $NaHSO_3$. After dilution with ethyl acetate (25 mL), the reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to yield a solid residue. Column chromatography over silica gel (elution with 50% ethyl acetate/hexane) furnished the diol diacetate **34** (109 mg, 48%). M.p. 122.7 °C; IR (KBr): $\tilde{\nu}$ = 3373, 1739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.12 (d, J = 10.2 Hz, 1H), 5.56 (d, J = 10.2 Hz, 1H), 5.29 (br s, 1H), 5.24 (br s, 1H), 2.41 (m, 2H), 2.14 (s, 3H), 1.98 (s, 3H), 2.04 – 1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 169.7, 131.9, 123.8, 89.3, 78.2, 70.5, 67.6, 32.6, 26.2, 22.0, 21.1, 18.8; MS (70 eV, EI): m/z (%): 186 [M^+ – 2Ac+2]; elemental analysis calcd (%) for $C_{13}H_{18}O_6$ (270.3): C 57.77, H 6.71; found: C 57.86, H 6.75.

Crystal data for the compound 34: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: monoclinic, space group: $P2_1/n$, cell parameters: a = 7.027(1), b = 8.318(1), c = 23.002(3) Å, β = 92.490(3)°, V = 1343.26 Å^3, Z = 4, ρ_{calcd} = 1.336 g cm^{-3}, $F(000)$ = 576.0, μ = 0.11 mm^{-1}, λ = 0.71073 Å. Total number of l.s. parameters = 244. $R1$ = 0.0458 for 1449 $F_o > 4\sigma(F_o)$ and 0.1048 for all 2815 data. $wR2$ = 0.0994, GOF = 0.820, restrained GOF = 0.820 for all data. An ORTEP drawing of compound **34** with 50% ellipsoidal probability is shown in Figure 7.

Compound 35: Diol diacetate **34** (100 mg, 0.370 mmol) was hydrolyzed with K_2CO_3 (102 mg, 0.74 mmol) in methanol (2 mL) followed by purification by chromatography over silica gel (10% methanol/ethyl acetate eluent) to give tetrol **35** (51 mg, 75%). M.p. 146.7 °C; IR (KBr): $\tilde{\nu}$ = 3364 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 5.88 (d, J = 10.2 Hz, 1H), 5.54 (d, J = 10.2 Hz, 1H), 4.38 (m, 1H), 4.02 (d, J = 4.8 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.69 – 1.67 (m, 3H), 1.53 – 1.43 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ = 130.6, 129.9, 81.3, 80.0, 72.3, 68.5, 33.1, 31.2 19.0; MS (70 eV, EI): m/z

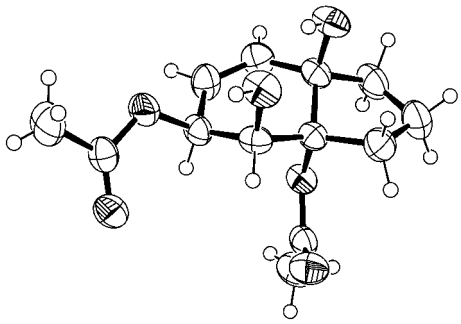


Figure 7. ORTEP drawing for **34**.

(%): 167 [$M^+ - H_2O - H$]; elemental analysis calcd (%) for $C_9H_{14}O_4$ (186.2): C 58.05, H 7.58; found: C 58.35, H 7.76.

Compound 36: Tetrol **35** (45 mg, 0.242 mmol) was subjected to a procedure similar to that detailed for the conversion of **19** to **4** but with OsO_4 (2 mg, 2 mol%) and NMMO (60 μL, 0.25 mmol) in acetone/water (4:1, 2 mL), followed by purification by chromatography over silica gel (10% methanol/ethyl acetate) to afford **36** (33 mg, 0.152 mmol). M.p. 188.6 °C; IR (KBr): $\tilde{\nu}$ = 3316 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ = 4.00 (s, 2H), 3.89 (s, 2H), 2.17 – 2.06 (m, 2H), 1.87 – 1.77 (m, 2H), 1.42 – 1.34 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ = 83.2 (2C), 74.5 (2C), 69.9 (2C), 31.1 (2C), 19.8; MS (70 eV, EI): m/z (%): 166 [$M^+ - 3H_2O$].

CCDC 196758 (**15**), -196759 (**18**), -196760 (**4**), -196755 (**25**), -196756 (**26**), -196757 (**33**), -196754 (**34**) contain the supplementary crystallographic data and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

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