

Solid and solution state conformations of (\pm)-3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol and (\pm)-3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-6-*O*-methyl-*allo*-inositol

Kana M. Sureshan^{*,†} and Yutaka Watanabe^{*}

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan

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Abstract—The synthesis and conformational studies of (\pm)-3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol and (\pm)-3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-6-*O*-methyl-*allo*-inositol are described. Solid state conformations of the title compounds have been studied by solving their X-ray crystal structures. The inositol ring in both the compounds deviate considerably from the ideal chair conformation to flattened chair conformation in the solid state. Their conformations in solution were studied by the use of ¹H NMR spectroscopy. These conformational analyses revealed that the title compounds adopt similar conformations in solid and solution states irrespective of the solvent polarity.

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1. Introduction

Conformations of small molecules play major roles in their crystal packing, physical, and chemical properties, chemical reactivity, biological activity, etc. While the solid-state conformation of a molecule depends on its inherent rigidity, steric interactions, intra- and inter-molecular interactions within the crystal lattice, the solution state conformation is further complicated by additional factors like solvent–solute interactions. Due to these reasons, conformations of molecules often differ in solution from that in solid states. While the knowledge of solid state conformation is important for successful crystal engineering, supramolecular synthesis etc., the knowledge of solution state conformation allows prediction of chemical reactivity, regioselectivity, and stereochemical outcome of a reaction in solution.

Thus, the study of conformation of molecules in both the states and their correlation constitutes an important area of chemical research. We have been interested in studying the solid and solution state conformations of various derivatives of hexahydroxy cyclohexanes (inositols). Inositol derivatives have been the subject of intense research in the recent past due to their established biological roles in cellular processes¹ and their use as synthons for natural products,² supramolecular assemblies,³ catalysts,⁴ gelators,⁵ metal complexing agents,⁶ etc. In view of this importance, there has been a greater deal of interest to synthesize various unnatural and less abundant inositols from different starting materials.⁷ During the synthetic efforts by different research groups, many X-ray crystal structures of various inositol derivatives have been solved which allowed prediction of reactivity in solution,⁸ rationalization of topochemical reactions,⁹ determination of absolute configuration,¹⁰ etc. But the majority of the solved structures are of *myo*-inositol derivatives owing to their natural abundance and excessive use in various fields of organic synthesis. The X-ray structures of inositol derivatives other than *myo*-inositol derivatives are

^{*} Corresponding authors. Tel.: +81 899236786; fax: +81 899279944; e-mail addresses: sureshankm@yahoo.co.in; wyutaka@dpc.ehime-u.ac.jp

[†] Present address: Department of Pharmacy, University of Bath, Bath, BA2 7AY, UK.

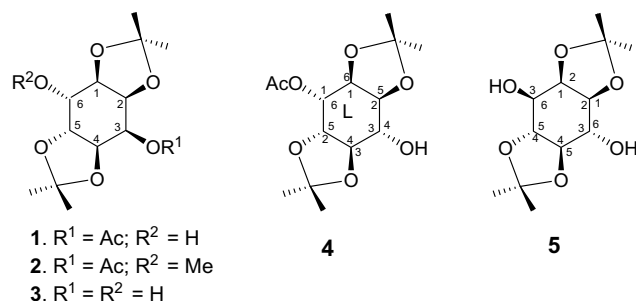


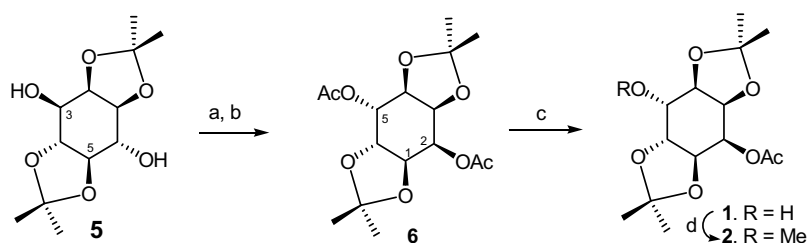
Chart 1. The outer numbering for **4** and **5** are *chiro*-inositol numbering and *myo*-inositol numbering, respectively, and the inner numbering is similar to that of *allo*-inositol derivatives **1–3** for brevity and consistency in comparison.

very few in the literature. As part of an ongoing program, we herein report, the solid and solution state conformations of two *allo*-inositol derivatives, namely, (\pm)-3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol (**1**) and (\pm)-3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-6-*O*-methyl-*allo*-inositol (**2**). Also, conformations of **1** and **2** are compared with that of structurally related 1L-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol (**3**),¹¹ 1L-1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol (**4**),¹² and 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**5**)¹³ (Chart 1).

2. Results and discussions

The preparation of compounds **1** and **2** from readily available racemic 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**5**) has been mentioned in a preliminary communication.¹⁴ Full details are given in the experimental section. The diol **5** was sulfonylated with 2.2 equiv of triflic anhydride and the crude di-triflate thus obtained was treated with KOAc in *N,N*-dimethylacetamide (DMA) to provide racemic diacetate, **6** (Scheme 1). Regioselective methanolysis of **6** provided the monoacetate **1**. The acetate **1** was methylated with methyl iodide in the presence of sodium hydride to afford the methyl ether **2** as the sole product.

Compound **1** crystallizes in orthorhombic crystal system with Pca_2 space group, whereas compound **2** crystallizes in monoclinic system with $P2_1/n$ space group.



Scheme 1. Reagents and conditions: (a) Ti_2O (2.2 equiv), Pyr, CH_2Cl_2 , -20°C ; (b) KOAc, DMA, 70°C ; (c) MeOH, Et_3N , reflux; (d) MeI, NaH, DMF, rt.

Each unit cell contains four molecules for both **1** and **2**. The solid state conformations of both these compounds showed many similarities owing to the similarity in their structure. The inositol ring deviated considerably from an ideal chair to a flattened chair conformation in both cases. The ring C–C bond lengths (1.491–1.554 Å in **1**; 1.502–1.542 Å in **2**) and C–O bond lengths (1.417–1.433 Å in **1**; 1.404–1.438 Å in **2**) are in the normal range. Both the ring valence angles (CCC) and CCO angles vary from those of a perfect chair. While the ring valence angles varied from 106.7° to 119.4° in **1** and from 105.2° to 119.0° in **2**, the CCO angles vary from 102.2° to 117.0° in **1** and from 101.7° to 115.3° in **2**. The valence angles C-1–C-2–C-3 (117.8° in **1**; 117.2° in **2**) and C-6–C-1–C-2 (119.4° in **1**; 119.0° in **2**) deviate much from the ideal tetrahedral angle due to the conformational strain offered by the five-membered *cis* ketal ring. Figures 1 and 2 show ORTEP diagrams of **1** and **2**, respectively.

A comparison of ring angles in **1** and **2** (Table 1) with those in structurally related *allo*-inositol derivative **3**, *chiro*-inositol derivative **4** and *myo*-inositol derivative **5** reveals that they all adopt similar conformations in the crystalline state. It is worthy to note that all of these compounds have one *cis* and one *trans* isopropylidene group at 1,2 and 4,5 positions in a cyclohexane skeleton, respectively.

As in the case of valence angles, the torsion angles in the carbocyclic skeleton also deviate much from that of a perfect chair. While the torsion angle C-3–C-4–C-5–C-6 expanded (73.0° in **1** and 74.0° in **2**), the torsion angles C-1–C-2–C-3–C-4 [36.5° (**1**); 42.7° (**2**)], C-5–C-6–C-1–C-2 [35.2° (**1**); 35.7° (**2**)] and C-6–C-1–C-2–C-3 [28.2° (**1**); 32.2° (**2**)] experienced compression. Furthermore, the torsion angles between vicinal oxygen atoms in **1** and **2** deviate from that of a perfect chair. The torsion angles in **1** and **2** are similar to the respective torsion angles (Table 2) in the structurally similar derivatives **3–5**, which are known to adopt flattened chair conformations in their crystals. Thus, the comparison of torsion angles and valence angles unequivocally establishes that compounds **1–5** have similar conformations in the solid state. Similar conformations of structurally similar derivatives **1–5** demonstrate that their conformations

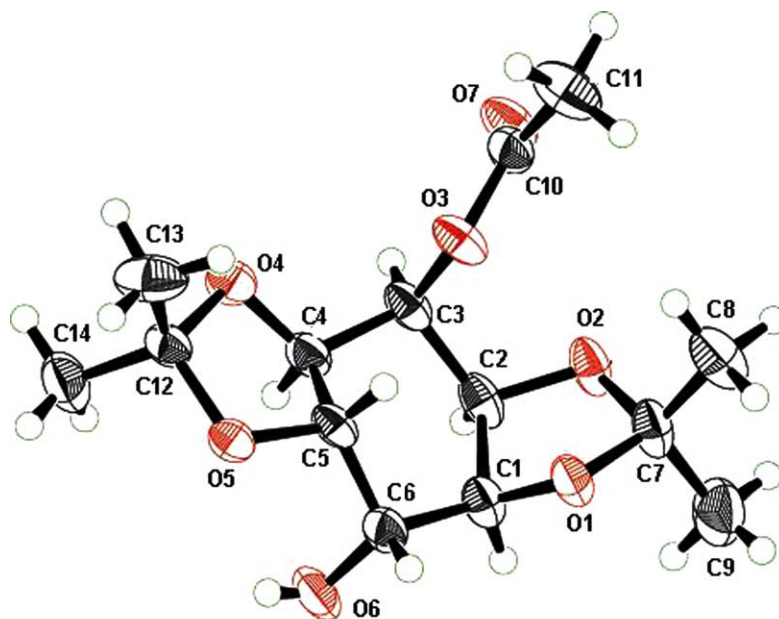


Figure 1. ORTEP diagram of 1.

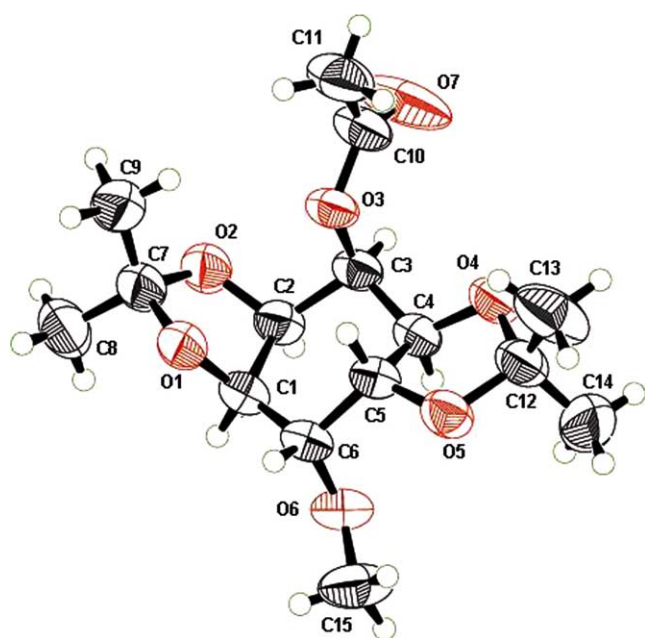


Figure 2. ORTEP diagram of 2.

in the solid state are determined by two isopropylidene (one *cis* and one *trans*) conformational locks. It is worthy to note that the relative configurations at the carbons that are not connected to isopropylidene group are different in **4** and **5**. This fact establishes that the relative configuration at the ring carbon atoms that are not connected to the isopropylidene group have negligible contribution toward the conformational preference of the derivatives **1–5** in the solid state.

Table 1. A comparison of ring (CCC) angles (°) of **1–5**

Ring angle	1	2	3^a	4^a	5^a
C-1-C-2-C-3	117.8	117.2	117.5	117.4	115.9
C-2-C-3-C-4	106.7	105.2	105.4	107.3	106.8
C-3-C-4-C-5	111.9	110.6	111.0	111.4	111.0
C-4-C-5-C-6	111.5	110.5	111.4	112.0	110.5
C-5-C-6-C-1	107.6	108.0	107.9	106.6	107.0
C-6-C-1-C-2	119.4	119.0	118.9	118.9	117.9

^a The ring angle values of **3**, **4** and **5** were taken from Refs. 11, 12, and 13, respectively. *allo*-Inositol numbering is used for **4** and **5** for brevity.

The crystal lattice of **1** is dominated by various intermolecular interactions. The free hydroxyl group [O(6)H(22)] of each molecule is hydrogen bonded [O(6)···O(7): 2.872 Å; H(22)···O(7): 2.276 Å; O(6)–H(22)···O(7): 146.04°] to the carbonyl oxygen [O(7)] of a neighboring molecule. In addition to this, there are various CH···O short contacts between adjacent molecules. For instance, O(1) is showing a definite CH···O bonding with H(2) of an adjacent molecule. The short interatomic distance [O(1)···H(2): 2.563 Å] and angle [O(1)···H(2)–C(2): 162°] nearing linearity are noteworthy. Two of the hydrogens on the acetyl group make CH···O contact with oxygens of the neighboring molecules; one with O-6 {O(6)···H(14): 2.538 Å; O(6)···H(14)–C(11): 138.63°} and the other with carbonyl oxygen O-7 [O(7)–H(15): 2.651 Å; O(7)···H(15)–C(11): 134°] of neighboring molecules. Both O(2) and O(4) are in short contact [O(2)···H(9): 2.709 Å; O(2)···H(9)–C(8): 140.35°, and O(4)···H(12): 2.641 Å; O(4)···H(12)–C(9): 159.75°] with one of the hydrogens

Table 2. Comparison of select torsion angles (°) in **1–5**

Torsion angle	1	2	3^a allo	4^a chiro	5^a myo
O-1-C-1-C-2-O-2	−27.9(5)	−32.7(2)	−34.5(4)	−35.4(7)	−36.5(1)
O-2-C-2-C-3-O-3	35.5(6)	43.1(2)	39.0(4)	−85.4(7)	−83.5(2)
O-3-C-3-C-4-O-4	−56.5(6)	−59.4(2)	−56.0(4)	68.7(7)	65.1(2)
O-4-C-4-C-5-O-5	−39.6(4)	−39.0(2)	−40.4(4)	−42.5(6)	−42.5(1)
O-5-C-5-C-6-O-6	−52.7(6)	−52.5(2)	−52.3(5)	−60.2(8)	66.2(2)
O-6-C-6-C-1-O-1	155.4(4)	157.7(1)	159.4(3)	166.8(5)	49.3(2)
C-1-C-2-C-3-C-4	36.5(6)	42.7(2)	41.9(5)	39.1(7)	42.8(2)
C-2-C-3-C-4-C-5	−58.1(5)	−62.9(2)	−61.1(4)	−57.4(7)	−60.1(2)
C-3-C-4-C-5-C-6	73.0(5)	74.0(2)	73.0(4)	71.5(6)	72.6(2)
C-4-C-5-C-6-C-1	−55.9(5)	−54.6(2)	−54.7(5)	−57.0(7)	−58.4(2)
C-5-C-6-C-1-C-2	35.2(6)	35.7(2)	36.2(5)	39.0(8)	42.3(2)
C-6-C-1-C-2-C-3	−28.2(7)	−32.2(2)	−32.4(5)	−33.0(9)	−36.9(2)

The signs of torsion angles are for the L-enantiomers shown in Chart 1. The number in parentheses is the standard deviation.

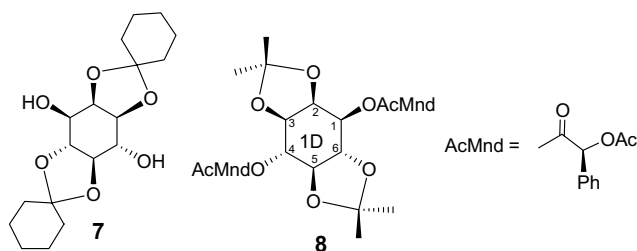
^a The torsion values of **3**, **4**, and **5** were taken from Refs. 11, 12, and 13, respectively. *allo*-Inositol numbering is used for **4** and **5** for brevity.

on the isopropylidene group connecting O-1 and O-2 of the neighboring molecule. Since there are no free hydroxyl groups present, there is no strong hydrogen bonding interaction in the crystal lattice of **2**. The lattice is dominated by CH···O hydrogen bonding that are relatively stronger than those in **1**. H-1, H-3, and H-4 make CH···O contact [H(3)···O(6): 2.409 Å; C(3)···H(3)–O(6): 154°, H(4)···O(7): 2.489 Å; C(4)···H(4)–O(7): 161.61°, and H(1)···O(7): 2.691 Å; C(1)···H(1)–O(7): 153.45°] with oxygens of neighboring molecules. Also, O(2) is in short contact [H(11)···O(2): 2.681 Å; C(9)···H(11)–O(2): 151.43°] with one of the hydrogens on the isopropylidene group connecting O-1 and O-2 of the neighboring molecule.

Extrapolation of solid state (crystal) structure to solution is often used to explain chemical reactivities, supramolecular interactions, etc. For instance, crystal structures have been used to explain the regioselectivity,^{8a} acyl migration^{8b} in solution state of inositol derivatives. To validate such an extrapolation, the solution state conformation has been studied by using ¹H NMR spectroscopy. 1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol (**5**)¹³ and 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (**7**, Chart 2)¹⁵ are reported to adopt similar conformations in solid and solution states. We have recently reported¹⁶ the consistency in conformation in solution and solid states of 1D-1,4-di-*O*-[(*S*)-*O*-acetylmandeloyl]-2,3:5,6-

di-*O*-isopropylidene-*myo*-inositol (**8**) and 1L-1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol (**4**).¹² It is reasonable to think that the presence of two ketal rings (one *cis* and one *trans*) in these derivatives could be responsible for their conformational freezing.

The ¹H NMR spectra of **1** and **2** in various solvents show well-resolved signals for the different ring protons. The vicinal coupling constants of the ring protons in **1** and **2** were determined to get an idea about their conformation in various solvents. The expected theoretical coupling constants of different sets of vicinal protons in **1** and **2** were calculated from the torsion angles between vicinal hydrogens in the crystalline state of **1** and **2**, using Altona's equation.^{17,‡} The conformations in solid and solution states of **1** and **2** were compared by comparing the observed coupling constants (³*J*_{HH}) and the calculated coupling constants (Table 3 and 4) based on torsion angle (ϕ) in the crystal structure. The observed coupling constants for all the protons in **1** and **2** in various solvents are in agreement with the respective calculated ones suggesting that their solid state conformations are retained in solution too. In addition, similar observed coupling constants for a particular proton (either in **1** or **2**) in all the solvents tested demonstrate that the conformation of **1** (or **2**) in all these solvents is the same irrespective of their polarity. It is worthy to note that the crystal state conformation of *allo*-inositol derivatives **1** and **2** are retained in Me₂SO, while that of their parent diol **3** has shown different conformations in crystal and in its Me₂SO solution.¹¹ It is interesting to note that the more crowded **1** and **2** show retention of their solid state conformation where as the less crowded **3** shows a varied conformation. Free hydroxyls form strong hydrogen bonds with Me₂SO molecules (solvation) and the solvated hydroxyl groups are more bulky (Chart 3) than the groups on axial oxygens (Me and Ac) in **2**. Based on

**Chart 2.**

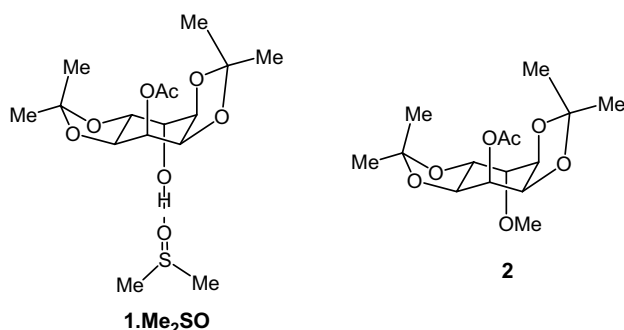
[‡] The equation $13.86 \cos^2 \phi - 0.81 \cos \phi + \Sigma \Delta \chi_i \{0.56 - 2.32 \cos^2 (\xi_i \cdot \phi + 17.9^\circ |\Delta \chi_i|)\}$ was used.

Table 3. Comparison of calculated and observed vicinal coupling constants, $^3J_{\text{HH}}$ (in Hz), of **1** in solvents of different polarity

H–H	Me ₂ CO- <i>d</i> ₆	CD ₃ OD	CDCl ₃	Me ₂ SO- <i>d</i> ₆	C ₆ D ₆	C ₅ D ₅ N	HH (ϕ°) torsion	J_{calcd}
H-1–H-2	5.86	5.6	^a	5.86	5.86	5.37	–28.9	5.3
H-2–H-3	5.86	5.37	5.12	5.37	5.37	5.37	32.1	5.0
H-3–H-4	2.44	2.44	2.50	2.44	2.44	2.44	–58.1	2.4
H-4–H-5	10.25	10.25	10.10	10.25	10.0	10.25	–166.3	9.0
H-5–H-6	2.44	2.93	3.1	2.44	2.93	2.44	–52.0	3.0
H-6–H-1	1.0	1.6	1.0	2.0	1.0	^a	–82.7	1.5

^a These values could not be measured due to the overlapping of signals.**Table 4.** Comparison of calculated and observed vicinal coupling constants, $^3J_{\text{HH}}$ (in Hz), of **2** in solvents of different polarity

H–H	Me ₂ CO- <i>d</i> ₆	CD ₃ OD	CDCl ₃	Me ₂ SO- <i>d</i> ₆	C ₆ D ₆	C ₅ D ₅ N	HH (ϕ°) torsion	J_{calcd}
H-1–H-2	5.37	^a	^a	5.86	5.6	^a	–29.5	5.2
H-2–H-3	5.37	5.3	5.3	5.37	5.3	^a	38.9	4.3
H-3–H-4	2.44	2.4	2.7	2.44	2.4	2.44	–62.9	2.0
H-4–H-5	10.25	10.2	10.26	10.25	10.2	10.25	–165.5	9.0
H-5–H-6	2.93	3.2	2.9	2.93	2.8	2.93	–50.7	3.1
H-6–H-1	1.9	^a	1.7	^a	2.0	^a	–83.6	1.4

^a These values could not be measured due to the overlapping of signals.**Chart 3.**

this argument, the sterically unfavorable axial orientation of these bulky solvated hydroxyl groups accounts for the different conformational behavior of **3** in Me₂SO. Similar conformation of **1**, the molecule with one protected and one free axial hydroxyl groups, in solid and its Me₂SO solution suggests that one axially disposed free hydroxyl group is not sufficient enough to overcome the conformational locking exerted by two isopropylidene groups.

In conclusion, we have presented the single crystal structures of two synthetically useful and important *allo*-inositol derivatives. Considerable conformational deviation from a chair to a flattened chair was observed for the inositol ring in both the cases. A comparison of their conformation in solid and solution states using NMR spectroscopy revealed that they adopt similar conformation in both the states. Attempts have been made, in the past, to explain the solution state behavior of inositol derivatives based on their crystal structure conformations. The results presented here give furtherance to such a practice.

3. Experimental

3.1. General

Chromatography refers to flash chromatography on a silica gel column using EtOAc–hexane as eluent. Crystal data collections for **1** and **2** were done on Rigaku AFC5R Diffractometer with graphite monochromated Mo K α radiation and Rigaku AFC7S Diffractometer with graphite monochromated Cu K α radiation, respectively. ¹H NMR spectra were recorded on a Bruker-DPX-400 (400 MHz) instrument. Chemical shifts (δ_{H} values relative to Me₄Si) and coupling constants (J values) are given in ppm and hertz, respectively.

3.2. (±)-3,6-Di-*O*-acetyl-1,2,4,5-di-*O*-isopropylidene-*allo*-inositol[§] (**6**)

To a cooled (–20 °C) soln of racemic diol **5**¹⁸ (520 mg, 2 mmol) in a mixture of pyridine (2 mL) and CH₂Cl₂ (20 mL), Tf₂O (740 μ L, 4.4 mmol) was added dropwise over a period of 5 min. The reaction mixture was stirred at that temperature for 1 h and then gradually allowed to attain rt and stirring continued at rt for overnight. The solvents were evaporated under diminished pressure and the residue thus obtained was re-dissolved in EtOAc and washed successively with, water, cold-dil HCl, aq NaHCO₃ and brine, dried over anhyd Na₂SO₄, and evaporated under diminished pressure. The crude ditriflate obtained was dissolved in dimethylacetamide

[§]This nomenclature was used for brevity and consistency. The correct name for **6**, based on cyclitol nomenclature, is 2,5-di-*O*-acetyl-1,6:3,4-di-*O*-isopropylidene-*allo*-inositol.

(DMA, 10 mL) and treated with KOAc (1.48 g, 15 mmol) at 70 °C overnight. DMA was evaporated under diminished pressure and the residue was dissolved in EtOAc and recovered by the usual extractive workup. The crude diacetate **6** was purified by crystallization from a mixture of EtOAc and hexane (640 mg, 93%: mp 140–141 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.33 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 2.11 (s, COCH₃), 2.12 (s, COCH₃), 3.93 (dd, 1H, 10.2, 2.6 Hz, H-4), 4.24 (dd, 1H, 5.7, 1.6 Hz, H-1), 4.27 (dd, 1H, 10.2, 3.4 Hz, H-5), 4.37 (t, 1H, 5.7 Hz, H-2), 5.64 (dd, 1H, 5.7, 2.6 Hz, H-3), 5.74 (dd, 1H, 3.3, 1.6 Hz, H-6); ¹³C NMR (100 MHz, CDCl₃): 20.5, 20.9, 24.8, 25.7, 26.4, 26.43, 65.9, 66.6, 70.6, 72.0, 72.6, 76.8, 109.9, 111.3, 169.1, 169.5. Anal. Calcd for C₁₆H₂₄O₈·1/3H₂O: C, 54.86; H, 7.10. Found: C, 54.77; H, 6.90.

3.3. (±)-3-*O*-Acetyl-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol (**1**)

Diacetate **6** (500 mg, 1.45 mmol) was refluxed in a mixture of MeOH (5 mL) and Et₃N (1 mL, 7.2 mmol) for 2 h. The solvents were evaporated and the residue thus obtained was purified by chromatography to give the pure monoacetate **1** (420 mg, 96%) as a white solid. A small fraction was recrystallized from EtOAc to give good quality crystals suitable for crystallographic studies: ¹H NMR (400 MHz, CDCl₃): δ 1.34 (s, 3H), 1.42 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 2.11 (s, COCH₃), 2.47 (br s, OH), 3.97 (dd, 1H, 10.1, 2.5 Hz, H-4), 4.21 (dd, 1H, 10.1, 3.1 Hz, H-5), 4.35–4.40 (m, 2H, H-2 and H-1), 4.54 (dd, 1H, 3.1, 1.0 Hz, H-6), 5.61 (dd, 1H, 5.1, 2.5 Hz, H-3); ¹³C NMR (100 MHz, CDCl₃): 21.0, 24.8, 25.8, 26.6, 65.3, 67.0, 71.4, 72.7, 72.72, 78.3, 109.4, 111.2, 169.6. Anal. Calcd for C₁₄H₂₂O₇: C, 55.62; H, 7.33. Found: C, 55.37; H, 7.49.

3.4. ¹H NMR data of **1** in other solvents

¹H NMR (CD₃OD): δ 1.32 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 2.09 (s, 3H), 4.05 (dd, H-4), 4.14 (dd, H-5), 4.31 (dd, H-1), 4.38–4.42 (m, H-2 and H-6), 5.54 (dd, H-3).

¹H NMR (Me₂SO-*d*₆): δ 1.26 (s, 3H), 1.31 (s, 3H), 1.33 (s, 3H), 1.39 (s, 3H), 2.04 (s, 3H), 3.95 (dd, H-4), 4.02 (dd, H-5), 4.20 (dd, H-1), 4.30–4.32 (m, H-6), 4.38 (dd, H-2), 5.45 (dd, H-3), 5.56 (d, 4.4 Hz, OH).

¹H NMR (Me₂CO-*d*₆): δ 1.29 (s, 3H), 1.33 (s, 6H), 1.43 (s, 3H), 2.06 (s, 3H, OCOCH₃), 4.04 (dd, H-4), 4.14 (dd, H-5), 4.32 (dd, H-1), 4.42 (t, H-2), 4.45 (dd, H-6), 5.57 (dd, H-3).

¹H NMR (C₅D₅N): δ 1.37 (s, 3H), 1.48 (s, 3H), 1.49 (s, 3H), 1.58 (s, 3H), 2.15 (s, COCH₃), 4.50 (dd, H-4), 4.54 (dd, H-5), 4.68 (t, H-2), 4.71–4.73 (m, H-1), 6.03 (dd, H-3).

¹H NMR (C₆D₆): δ 1.26 (s, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.48 (s, 3H), 1.90 (s, 3H), 3.88 (dd, H-4), 4.06 (dd, H-2), 4.33 (dd, H-1), 4.39 (dd, H-5), 4.54 (m, H-6), 5.87 (dd, H-3).

3.5. (±)-3-*O*-Acetyl-1,2:4,5-di-*O*-isopropylidene-6-*O*-methyl-*allo*-inositol (**2**)

To a stirred soln of acetate **1** (200 mg, 0.66 mmol) and NaH (16 mg, 0.66 mmol) in DMF (3 mL) at 0 °C, MeI (82 μL, 1.32 mmol) was added and the soln was stirred for 4 h allowing the mixture to attain rt gradually. Usual work up followed by chromatographic purification yielded the methyl ether **2** (190 mg, 91%). ¹H NMR (400 MHz, CDCl₃): δ 1.34 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 2.11 (s, COCH₃), 3.57 (s, 3H, OCH₃), 4.04 (dd, 1H, 10.3, 2.7 Hz, H-4), 4.10 (dd, 1H, 2.9, 1.7 Hz, H-6), 4.22 (dd, 1H, 10.3, 2.9 Hz, H-5), 4.30–4.35 (m, 2H, H-1 and H-2), 5.59 (dd, 1H, 5.3, 2.7 Hz, H-3); ¹³C NMR (100 MHz, CDCl₃): δ 21.1, 25.1, 25.9, 26.6, 26.7, 60.1, 67.2, 71.8, 72.8, 73.3, 74.4, 77.6, 109.7, 111.0, 169.7. Anal. Calcd for C₁₅H₂₄O₇: C, 56.95; H, 7.65. Found: C, 56.78; H, 7.71. FAB MS (+): M+H = 317.

3.6. ¹H NMR data of **2** in other solvents

¹H NMR (CD₃OD): δ 1.33 (s, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 2.08 (s, 3H), 3.55 (s, 3H, Me), 4.04 (m, H-1 and H-4), 4.19 (dd, H-5), 4.32–4.38 (m, H-2 and H-6), 5.53 (dd, H-3).

¹H NMR (Me₂SO-*d*₆): δ 1.27 (s, 3H), 1.30 (s, 3H), 1.33 (s, 3H), 1.39 (s, 3H), 2.04 (s, 3H), 3.47 (s, 3H, Me), 3.92 (dd, H-4), 4.05 (m, H-6), 4.08 (dd, H-5), 4.29–4.31 (m, H-1), 4.36 (dd, H-2), 5.44 (dd, H-3).

¹H NMR (Me₂CO-*d*₆): δ 1.30 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 2.06 (s, 3H, OCOCH₃), 3.54 (s, 3H, Me), 4.00 (dd, H-4), 4.04 (dd, H-6), 4.18 (dd, H-5), 4.33 (dd, H-1), 4.37 (t, H-2), 5.55 (dd, H-3).

¹H NMR (C₅D₅N): δ 1.37 (s, 3H), 1.42 (s, 3H), 1.46 (s, 3H), 1.56 (s, 3H), 2.13 (s, COCH₃), 3.57 (s, 3H, OCH₃), 4.20 (dd, H-4), 4.25 (m, H-6), 4.45 (dd, H-5), 4.45–4.55 (m, H-1 and H-2), 5.94 (dd, H-3).

¹H NMR (C₆D₆): δ 1.30 (s, 3H), 1.46 (s, 3H), 1.52 (s, 6H), 1.92 (s, 3H), 3.41 (s, 3H, OCH₃), 4.07 (dd, H-2), 4.08 (dd, H-4), 4.15 (t, H-6), 4.29 (dd, H-1), 4.51 (dd, H-5), 5.91 (dd, H-3).

3.7. X-ray data

Good crystals of **1** and **2** were obtained by slow evaporation of their EtOAc soln. The crystallographic data are given in Table 5. The structures were solved by direct methods using SIR92¹⁹ and all calculations were performed using TEXSAN.²⁰ All non-hydrogen atoms were

Table 5. Crystallographic data

	1	2
Formula	C ₁₄ H ₂₂ O ₇	C ₁₅ H ₂₄ O ₇
Formula weight	302.32	316.35
Crystal dimensions	0.30 × 0.30 × 0.10 mm	0.20 × 0.20 × 0.55 mm
Crystal system	Orthorhombic	Monoclinic
Space group	<i>Pca</i> 2 ₁	<i>P</i> 2 ₁ / <i>n</i>
Lattice parameters	<i>a</i> = 15.772(2) Å <i>b</i> = 5.561(2) Å <i>c</i> = 17.116(2) Å <i>V</i> = 1501.2(7) Å ³	<i>a</i> = 10.422(2) Å <i>b</i> = 8.594(1) Å <i>c</i> = 18.975(1) Å <i>V</i> = 1674.0(3) Å ³
<i>Z</i>	4	4
<i>D</i> _{calcd}	1.338 g/cm ³	1.255 g/cm ³
μ	$\mu(\text{Mo K}\alpha) = 1.07 \text{ cm}^{-1}$	$\mu(\text{Cu K}\alpha) = 8.37 \text{ cm}^{-1}$
Diffractometer	Rigaku AFC5R (rotating anode)	Rigaku AFC7S (sealed tube)
Radiation	Mo K α ($\lambda = 0.71069 \text{ Å}$) graphite monochromated	Cu K α ($\lambda = 1.54178 \text{ Å}$) graphite monochromated
Temperature	23.0 °C	23.0 °C
Collimator size	1.0 mm	1.0 mm
Take-off angle	6.0°	6.0°
Scan type	$\omega - 2\theta$	$\omega - 2\theta$
Scan width	(1.00 + 0.30 tan θ)°	(1.63 + 0.30 tan θ)°
$2\theta_{\text{max}}$	55.0°	120.1°
No. of reflections measured	Total = 2038; unique = 1908 (<i>R</i> _{int} = 0.00)	Total = 2859; unique = 2498 (<i>R</i> _{int} = 0.014)
Structure solution	Direct methods (SIR92)	Direct methods (SIR92)
Refinement	Full matrix least-squares (SHELXL-97)	Full matrix least-squares (SHELXL-97)
Function minimized	$\Sigma w(\text{Fo}^2 - \text{Fc}^2)^2$	$\Sigma w(\text{Fo}^2 - \text{Fc}^2)^2$
Least squares weights	$w = 1/[\sigma^2(\text{Fo}^2)]$	$w = 1/[\sigma^2(\text{Fo}^2)]$
No. variables	196	341
Residuals: <i>R</i> ₁ ; <i>R</i> _w	0.056; 0.084	0.045; 0.136
Goodness-of-fit indicator	1.25	1.25
Maximum peak in final diff. map	0.25 e/Å ³	0.13 e/Å ³
Minimum peak in final diff. map	0.00 e/Å ³	−0.15 e/Å ³

refined anisotropically. The co-ordinates of all atoms are deposited.[†]

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[†]Crystallographic data are deposited as CCDC 270011 and CCDC 270012. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033, e-mail deposit@ccdc.cam.ac.uk).

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