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Inositol Derivatives. 11. Synthesis of Dianhydroinositols[1]

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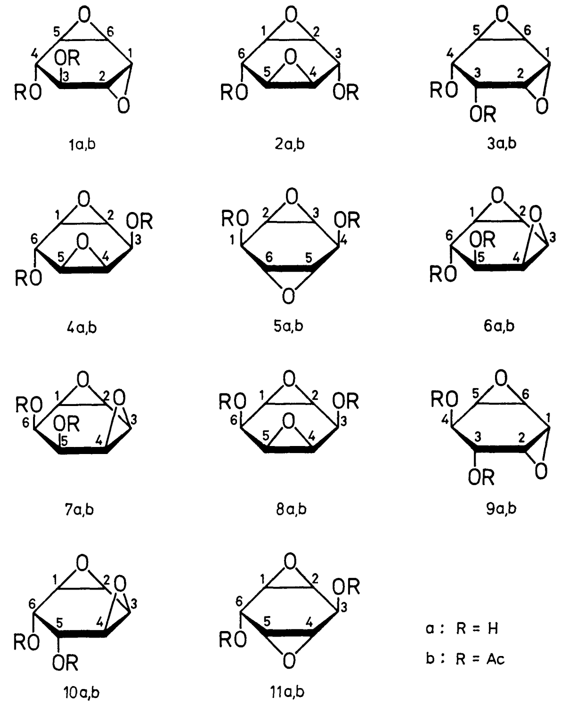
All the predicted isomers of 1,2:3,4- and 1,2:4,5-dianhydrocyclohexanehexols (5 racemates and 6 meso-compounds) were synthesized from appropriate inositol ditosylates and dimesylate by treatment with sodium methoxide.

A diepoxycyclohexane tumor inhibitor, crotepoxide was isolated from *Croton macrostachys*[2] and later from *Piper futokazura*,[3] and an antibiotic LL-Z 1220 was found to contain a *cis*-diepoxycyclohexene structure.[4] Recently, much interest has been taken in the reactivity and stereochemistry of highly mutagenic 7,8-dihydroxy-9,10-epoxide of benzo[*a*]pyrene and analogous substances.[5]

We have studied the structure-activity relationship of diepoxycyclohexanes by preparing diepoxycyclohexanediol as a model compound. We report herewith the details of synthetic studies on all the predicted diastereomers of dianhydrocyclohexanehexol (inositol).[6]

Sixteen isomers (5 racemates and 6 *meso*-compounds) are theoretically possible for dianhydroinositols: 1,2:3,4-(**1a**, **3a**, **6a**, **7a**, **9a**, and **10a**) and 1,2:4,5-dianhydrocyclohexanehexols (**2a**, **4a**, **5a**, **8a**, and **11a**), excluding isomers with a 1,3- or 1,4-anhydro ring.

None of these isomers has been described in literature, except for three of their *O*-cyclohexylidene derivatives.[7]

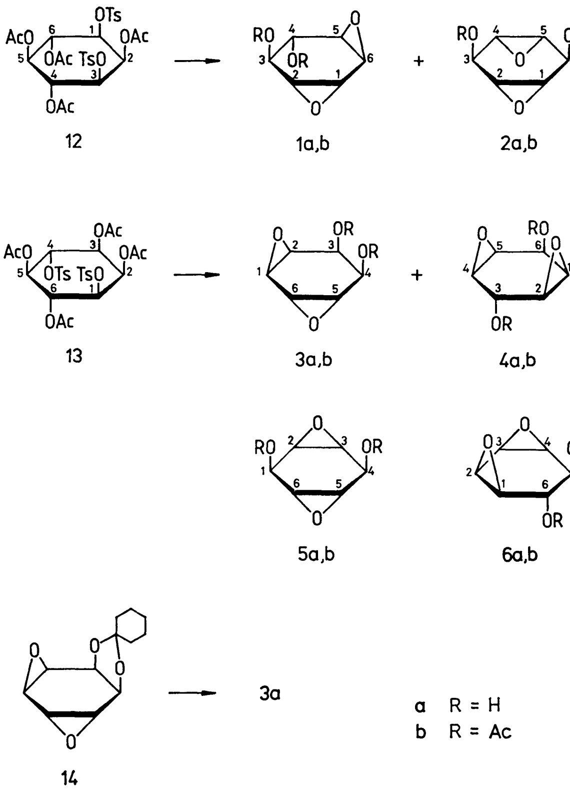


Scheme 1. The sixteen isomers of dianhydroinositol.[a]
a) Isomers **2**, **4**, **5**, **7**, **8**, and **10**, having a plane of symmetry, are meso forms. Of the five racemic diastereomers, **1**, **3**, **6**, **9**, and **11**, the enantiomer is depicted which allows clockwise assignment of positional numbers.

Seven isomers were synthesized from *myo*-inositol ditosylates and other four from *chiro*- and *muco*-inositol ditosylates and dimesylates. Structural elucidation of dianhydroinositols obtained was carried out by means of ^{1}H NMR spectroscopy and consideration of reaction mechanisms.

*1,2:5,6-Dianhydro-*chiro*- (**1**) and 1,2:4,5-Dianhydro-*muco*-inositols (**2**).* Treatment of tetra-*O*-acetyl-1,3-di-*O*-tosyl-*myo*-inositol (**12**)[8] with a slight excess of sodium methoxide in chloroform–methanol at ambient temperature led to the formation of two major and one minor components. The mixture was separated by column chromatography, giving syrupy **1a** and crystalline **2a** in 21 and 15% yields, respectively, which were further characterized by conversion into their crystalline di-*O*-acetyl derivatives (**1b** and **2b**).

We see from the reaction mechanism that the two diepoxy diols can be obtained from **12** through the displacement of tosyloxyl functions with anionic oxygens. Compounds **1a** and **2a** are interconvertible by migration of an oxirane ring in basic media.[9] Structures of the products were determined on the basis of the ^{1}H NMR spectra, taking advantage of the symmetry of molecules. A part



Scheme 2.

of the spectral data are given in Table 1.

In the spectrum of **1b** in deuteriochloroform ($CDCl_3$), a two-proton doublet of triplets at δ 3.18 and a two-proton doublet of doublets at δ 3.58 are attributed to magnetically equivalent H-1 and H-6, and H-2 and H-5, respectively. Appearance of a two-proton relatively narrow triplet at δ 5.11 due to H-3 and H-4 indicates that the acetoxyl and epoxy groups are arranged in trans positions.[10] In the spectrum of **2a** in deuterium oxide (D_2O), the six ring protons appear as a four-proton triplet (δ 3.29) and a two-proton quintet (δ 4.56), showing the presence of magnetically equivalent two epoxy and two hydroxyl groups. The spectral data are consistent with the assigned structures.

A crystalline mixture of the diepoxy diacetates derived by direct acetylation of the intact epoxydation products from **12** was shown to be a 4: 5 mixture of **1a** and **2a** by estimation of the relative intensity of the signals due to each acetoxyl group. On the other hand, when **1b** was *O*-deacetylated with methanolic sodium methoxide, the resulting reaction mixture was found to contain **1a** and **2a** in about 1: 1 ratio by visual observation on TLC. The results give an evidence for the proposed structures of **1a** and **2a**. It is difficult to decide which product is formed first from **12**, because of the ready isomerization resulting from an oxirane ring migration under the conditions in this synthesis.

*1,2: 5,6-Dianhydro-*allo*-(3), 1,2: 4,5-Dianhydro-*epi*-(4), and 2,3: 5,6-Dianhydro-*allo*-inositols (5).* Under similar conditions with use of sodium methoxide, tetra-*O*-acetyl-1,4-di-*O*-tosyl-*myo*-inositol (**13**)[11] gave, upon separation by column chromatography, three crystalline diepoxy diols **3a** (23%), **4a** (8%), and **5a** (21%). Four diepoxy diols (**3a**, **4a**, **5a**, and **6a**) might be formed from **13**, and two pairs interconvertible in basic media. Both **4a** and **5a** have a plane of symmetry. In the ^{1}H NMR spectrum of **3a**, two protons on C-3 and C-4 appear as a doublet of doublets and a doublet of doublets of doublets, coupled with each other at δ 4.06 and 4.35, respectively, indicating that **3a** should be a 1,3-diepoxide. The structure of **3a** was confirmed by identification with the compound obtained by a mild acid hydrolysis of 1,2: 5,6-dianhydro-3,4-*O*-cyclohexylidene-*allo*-inositol (**14**).[12] Under these conditions no epoxide group migration occurs. The results also show that **4a**, formed from **3a** by base-catalyzed isomerization, possesses the assigned structure demonstrated by the symmetric pattern of the signals due to the ring protons in its ^{1}H NMR spectrum. Thus, **4a** shows a four-proton narrow triplet (δ 3.45) and a two-proton broad singlet (δ 4.53), its two hydroxyl groups being found not to be magnetically equivalent by the spectrum of the diacetate **4b**. Compound **5a** exhibits three two-proton narrow multiplets for the methine protons, indicating the presence of a plane of symmetry. Thus, its structure was assigned as 2,3: 5,6-dianhydro-*allo*-inositol. Later, **6a** was found to be transformed completely into **5a** in basic media.

*1,2: 3,4- (7) and 1,2: 4,5-Dianhydro-*cis*-inositols (8).* Similar epoxidation of 1,2,5-tri-*O*-acetyl-3-*O*-benzoyl-4,6-di-*O*-tosyl-*myo*-inositol (**15**)[13] gave two diepoxy diols **7a** (4%) and **8a** (37%), together with 2,3-anhydro-6-*O*-tosyl-*epi*-inositol (**17**, 4%).[14] The structure of **17** was

TABLE 1. ^{1}H NMR DATA OF DIANHYDROINOSITOLS[a]

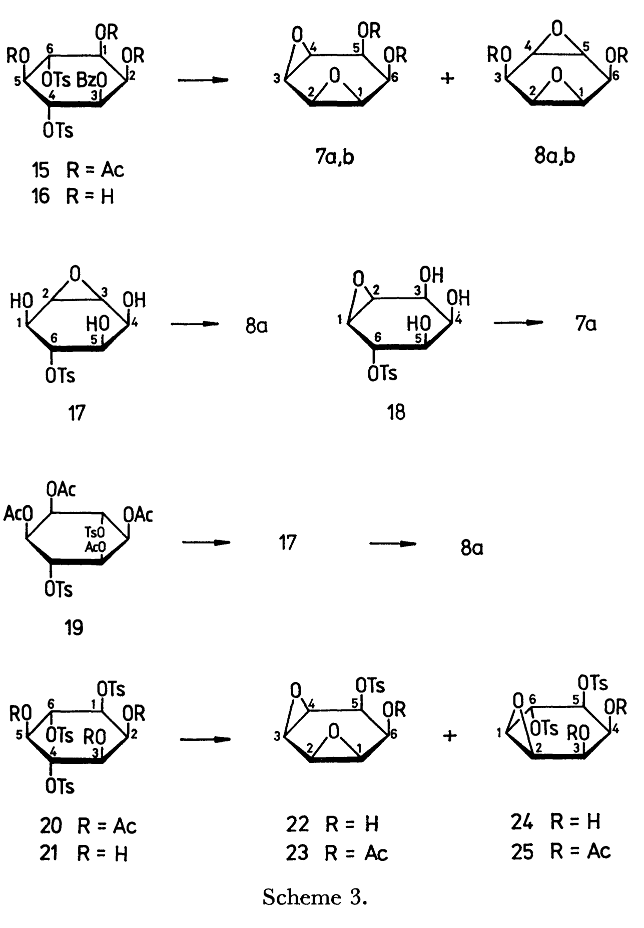
Formula	Diol[b]		Diacetate[c]		
	$\underline{H}C\overset{O}{—}C\underline{H}$	HO-C-$\underline{H}$	$\underline{H}C\overset{O}{—}C\underline{H}$	AcO-C-$\underline{H}$	OAc
1[d]	3.46 (2)	4.13 (2)	3.18 (2)	5.11 (2)	2.13 (6)
	3.66 (2)		3.58 (2)		
2	3.29 (4)	4.56 (2)	3.17 (4)	5.63 (2)	2.17 (6)
3	3.47 (2)	4.06 (1)	3.31 (2)	5.36 (1)	2.07 (3)
	3.72 (1)	4.35 (1)	3.64 (2)	5.72 (1)	2.16 (3)
	3.84 (1)				
4	3.45 (4)	4.53 (2)	3.34 (4)	5.60 (2)	2.16 (3)
					2.22 (3)
5	3.21 (2)	4.31 (2)	3.10 (2)	5.32 (2)	2.17 (6)
	3.51 (2)		3.44 (2)		
6	3.22 (1)	3.69 (1)	3.05 (1)	5.02 (1)	2.09 (3)
	3.46 (1)	4.12 (1)	3.2—3.7 (3)	5.44 (1)	2.12 (3)
	3.70 (2)				
7	3.46 (2)	4.15 (2)	3.31 (2)	5.30 (2)	2.13 (6)
	3.65 (2)		3.47 (2)		
8	3.51 (4)	4.48 (2)	3.50 (4)	5.52 (2)	2.22 (6)
9	3.46 (2)	3.94 (2)	3.39 (2)	5.36 (2)	2.12 (6)
	3.81 (2)		3.65 (2)		
10	3.31 (2)	3.95 (2)	3.22 (2)	5.28 (2)	2.10 (6)
	3.68 (2)		3.56 (2)		
11	3.26 (2)	4.47 (2)	3.13 (2)	5.44 (2)	2.17 (6)
	3.47 (2)		3.42 (2)		

a) Chemical shifts are given in terms of δ-values. Values in parentheses show number of protons.
b) Unless otherwise noted, the spectra were measured in D_2O. c) Measured in $CDCl_3$. d) The spectrum of the diol was measured in $CDCl_3$.

confirmed by conversion into **8a** on further treatment with sodium methoxide. Characterization of **7a** and **8a** was carried out by their ^{1}H NMR spectra. Thus, **8a** shows a four-proton doublet of doublets due to H-1, H-2, H-4, and H-5 appearing at δ 3.51, and a seven-line signal due to H-3 and H-6 at δ 4.48, confirming the assigned structure of **8a**. The spectrum of **7a** exhibits three two-proton narrow multiplets at δ 3.46, 3.65, and 4.15. The A_2B_2 pattern observed for H-1 and H-4, and H-5 and H-6 signals is compatible with the assigned structure of **7a**.

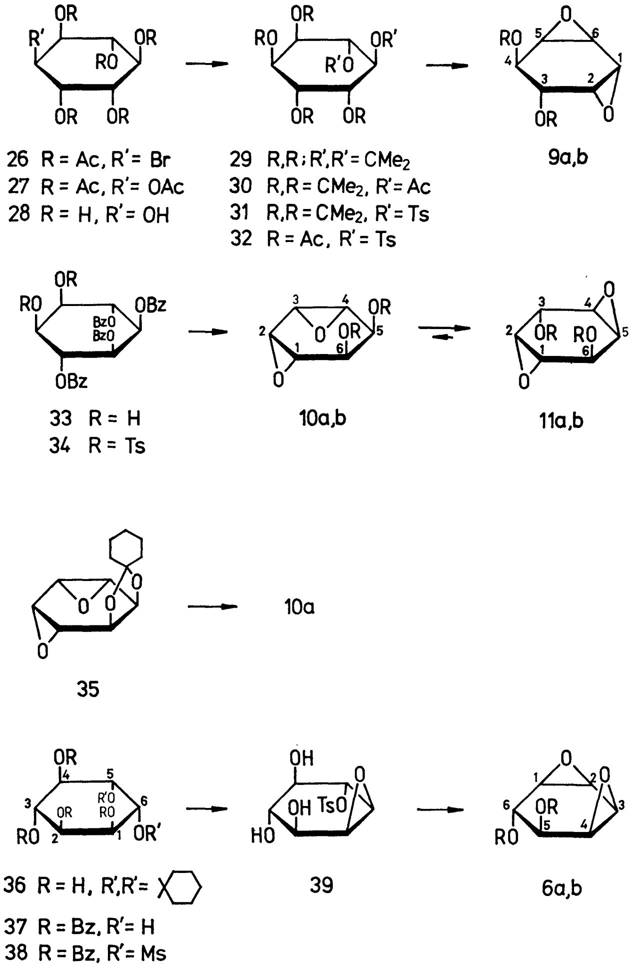
In contrast to the above results, when *O*-deacetylated compound, 1-*O*-benzoyl-4,6-di-*O*-tosyl-*myo*-inositol (**16**)13) was subjected to epoxidation, **7a** was obtained in 36% yield, together with a trace of **8a**. This might be accounted for by assuming an attack of the C-5 anionic oxygen at C-4 or C-6 giving 1,2-anhydro-6-*O*-tosyl-*epi*-inositol (**18**) as an intermediate for **7a**. In the case of **15**, **17** might be a major intermediate presumably resulting from an attack of the C-1 or C-3 anionic oxygen formed first by *O*-deacylation at C-6 or C-4. The evidence for these assumption was furnished by using tetra-*O*-acetyl-3,6-di-*O*-tosyl-*muco*-inositol (**19**)15) that would generate only **17** intermediary under the epoxidation conditions. In fact, **19** gave **8a** selectively in 36% yield.

In order to estimate the reactivity of *myo*-inositol ditosylates, we studied the epoxidation of tri-*O*-acetyl-1,4,6-tri-*O*-tosyl-*myo*-inositol (**20**) and its *O*-deacetylated compound (**21**).11)



Scheme 3.

Treatment of **20** with an excess of sodium methoxide in chloroform–methanol gave the diepoxide (**22**) preferentially in 50% yield. The corresponding *O*-acetyl derivative (**23**) revealed an ^{1}H NMR spectrum very similar to that of **7b**, suggesting it to be 1,2: 3,4-dianhydro-5-*O*-tosyl-*cis*-inositol. On the other hand, **21** reacted with sodium methoxide to give the monoepoxide (**24**) in 24% yield, together with a trace of **22**. The di-*O*-acetyl derivative (**25**) of **24** showed, in the ^{1}H NMR spectrum, a doublet of doublets and a doublet due to two protons on carbon atoms bearing the tosyloxyl functions at δ 4.58 and 4.96, respectively, showing that one of the tosyloxyls is adjacent to the epoxy group in trans orientation. These data allow us to assign the structure of **25** to 3,4-di-*O*-acetyl-1,2-anhydro-5,6-di-*O*-tosyl-*epi*-inositol. In the case of **20**, the C-3 acetoxyl seems to be *O*-deacylated first leading to the 3,4-epoxide, an intermediate for **22**. The preferential formation of the 3,4- or 4,5-epoxide is in line with that observed for **15** and **16**.



Scheme 4.

*1,2: 5,6-Dianhydro-*neo*-inositol (9).* Tetra-*O*-acetyl-3,4-di-*O*-tosyl-*chiro*-inositol (**32**), an intermediate compound for **9a**, was synthesized in the following sequences. Penta-*O*-acetyl-1-bromo-1-deoxy-*chiro*-inositol (**26**) derived by bromination of *myo*-inositol with acetyl bromide in acetic anhydride16) was treated with sodium acetate in boiling aqueous 2-methoxyethanol to give, after acetylation, hexa-*O*-acetyl-*chiro*-inositol (**27**)[17] in 65% yield. Hydrolysis of **27** with 4 M hydrochloric acid gave *chiro*-inositol (**28**) in 95% yield. Acetonation of **28** by the procedure of Angyal and MacDonald[18] gave the tri-*O*-isopropylidene derivative (**29**) in 30% yield, together with the desired 1,2: 5,6-di-*O*-isopropylidene derivative isolated as the di-*O*-acetyl derivative (**30**) in 18% yield. Compound **30** was *O*-deacylated with sodium methoxide and then tosylated to give the corresponding di-*O*-tosyl derivative (**31**) in 59% yield. On mild acid hydrolysis and successive acetylation **31** gave **32** in 95% yield.

By a similar treatment with sodium methoxide followed by acetylation, **32** gave crystalline di-*O*-acetyl-1,2: 5,6-dianhydro-*neo*-inositol (**9b**) in 48% yield, which was converted into the free diepoxy diol (**9a**) in 35% yield. The ^{1}H NMR spectrum of **9a** contains two-proton doublets of doublets at δ 3.46 and 3.81, and a two-proton singlet at δ 3.94. Characteristic A_2B_2 pattern of the former due to H-1, H-2, H-5, and H-6 supports the assigned structure.

*1,2: 3,4-Dianhydro-*allo*- (10) and 1,2: 4,5-Dianhydro-*neo*-inositols (11).* A similar epoxidation of tetra-*O*-benzoyl-1,2-di-*O*-tosyl-*muco*-inositol (**34**) derived from the corresponding tetra-*O*-benzoyl derivative (**33**)[19] is considered to afford **10a** and **11a**. However, the equilibrium between **10a** and **11a** in basic media was found to shift almost completely to the latter, **34** giving on epoxidation **11a** as the sole product in 39% yield. The ^{1}H NMR spectrum of **11a** showed three two-proton multiplets at δ 3.26, 3.47, and 4.47.

Preparation of **10a** was accomplished by mild acid hydrolysis of 1,2: 3,4-dianhydro-5,6-*O*-cyclohexylidene-*allo*-inositol (**35**).[11] When **10a** and **11a** were dissolved in 0.1 M methanolic sodium methoxide, respectively, only **10a** was detected in both reaction mixture at ambient temperature. This established the proposed structures of **10a** and **11a**. Compound **10a** showed, in the ^{1}H NMR spectrum, three two-proton multiplets at δ 3.31, 3.68, and 3.95.

*1,2: 3,4-Dianhydro-*epi*-inositol (6).* Tetra-*O*-benzoyl-1,2-di-*O*-mesyl-*chiro*-inositol (**38**) was prepared from 1,2-*O*-cyclohexylidene-*chiro*-inositol (**36**)[19] by benzoylation and removal of cyclohexylidene group followed by mesylation. Epoxidation between C-1 and C-6 of **38** was assumed to occur first, since the 6-OH and 1-OTs groups are located in diaxial positions in the favored conformation. In order to obtain **6a**, conditions for the next epoxidation should be carefully selected in order to suppress the epoxide migration to **5a**.

First, **38** was treated with 1.1 molar equiv. of sodium methoxide for the conversion into monoepoxide (**39**) which was then, without further purification, passed through a short column of Amberlite IRA-400 (OH^-) in a methanol solution several times until **39** disappeared in the effluent, subjected to monitoring by TLC. The crude product thus obtained consists of **6a** and a trace of **5a**, which were separated by column chromatography to give **6a** in 25% yield. Treatment of **6a** with sodium methoxide gave exclusively **5a**. The ^{1}H NMR spectrum of **6a** revealed two one-proton doublets of doublets at δ 3.69 and 4.12 attributable to H-5 and H-6, indicating that **6a** has an unsymmetric structure.

Experimental

All the compounds treated were racemic except for meso compounds. Diepoxy diols **1**, **3**, **6**, **9**, and **11** were synthesized as racemates. All the formulas depict one enantiomer of the respective racemates.

Unless otherwise stated, melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. Solutions were evaporated under reduced pressure at 40—50 °C. IR spectra were determined for potassium bromide disks with a JASCO IR-E spectrophotometer. ^{1}H NMR spectra were measured at 60 MHz on a Varian A-60D spectrometer in deuteriochloroform ($CDCl_3$) or deuterium oxide (D_2O) with reference to tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulfonate, respectively, as an internal standard, the peak positions being given in terms of δ. Values given for chemical shifts and coupling constants are of first-order. TLC was performed on silica gel (Wakogel B 10, Wako Pure Chemical Industries, Ltd.) using benzene–ethyl acetate (1: 2, v/v) as an eluent unless otherwise stated. Column chromatography was carried out on Wakogel C-200.

The synthetic reactions were not always conducted under optimum conditions. The isolated yields of the pure diepoxy diols are given for all cases.

*1,2: 5,6-Dianhydro-*chiro*- (1a) and 1,2: 4,5-Dianhydro-*muco*-inositols (2a).* *a)*: To a solution of tetra-*O*-acetyl-1,3-di-*O*-tosyl-*myo*-inositol (**12**)[8] (5 g) in a mixture of chloroform (50 ml) and methanol (40 ml) was added 1 M methanolic sodium methoxide (24 ml, 3 molar equiv.) and the mixture was allowed to stand at ambient temperature overnight. TLC indicated the formation of two major components (R_f 0.3 and 0.1) and one minor component (R_f 0.15). The reaction mixture was filtered in order to remove sodium *p*-toluenesulfonate precipitated, the filtrate being evaporated to dryness. The syrupy residue was dissolved in methanol (10 ml), mixed with silica gel (5 g), and the mixture was thoroughly dried with a rotary evaporator. The powder obtained was then transfered to the top of a silica-gel column (70 g) packed with benzene–ethyl acetate (1: 2, v/v), which was eluted with the same solvent system. Three fractions were separated according to examination by TLC. The faster-moving component (R_f 0.3) was obtained as a homogeneous syrup (**1a**) by removal of the solvent. The syrupy **1a** was treated with acetic anhydride (5 ml) in pyridine (10 ml) at ambient temperature overnight. The mixture was poured into ice–water (100 ml) and extracted with chloroform (3×20 ml). The extracts were washed with 1M hydrochloric acid, 10% aqueous sodium carbonate, and water, successively, and dried over anhydrous sodium sulfate. The solution was evaporated to give crystals which were recrystallized from chloroform–ethanol to give the diacetate (**1b**, 0.36 g, 21%) as rods, mp 125—127 °C.

Found: C, 52.58; H, 5.14%. Calcd for $C_{16}H_{12}O_6$: C, 52.63; H, 5.30%.

The second fraction consisting mainly of a minor component (R_f 0.15) did not crystallize and its characterization was not attempted.

The third fraction gave crystals which were recrystallized from methanol to give **2a** (0.17 g, 15%) as rods, mp 169—171 °C.

Found: C, 50.17; H, 5.51%. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.60%.

Acetylation of **2a** (60 mg) as described for **1b** gave, after crystallization from ethanol, the diacetate (**2b**, 58 mg, 76%) as plates, mp 108—109.5 °C.

Found: C, 52.90; H, 5.02%.

b): Compound **12** (2.5 g) was treated with sodium methoxide as described above. The crude product was shown by TLC to be a *ca.* 1:1 mixture of **1a** and **2a**. It was acetylated in the usual manner to give a crystalline mixture (0.33 g, 37%), which was found to be a 4:5 mixture of **1b** and **2b** estimation of the relative intensity of each acetyl signals in the ^{1}H NMR spectrum.

*1,2:5,6-Dianhydro-*allo*- (3a), 1,2:4,5-Dianhydro-*epi*- (4a), and 2,3:5,6-Dianhydro-*allo*-inositols (5a).* To a solution of tetra-*O*-acetyl-1,4-di-*O*-tosyl-*myo*-inositol (**13**)[11] (10 g) in a mixture of chloroform (100 ml) and methanol (80 ml) was added 1 M methanolic sodium methoxide (40 ml, 2.5 molar equiv.), and the mixture was allowed to stand at ambient temperature overnight. TLC showed the formation of three components: R_f 0.18, 0.15, and 0.05. The reaction mixture was processed as described in the epoxidation of **12** and the products were separated in a similar way by chromatography on silica gel with benzene–ethyl acetate (1:1, v/v) as an eluent. Three fractions were obtained. The first fraction gave crystals which were recrystallized from ethanol to give **3a** (0.48 g, 23%) as rods, mp 78—79 °C.

Found: C, 50.38; H, 5.60%.

Compound **3a** (80 mg) was acetylated in the usual way and the product was recrystallized from ethanol to give the diacetate (**3b**, 0.12 g, 90%) as plates, mp 121—121.5 °C.

Found: C, 52.60; H, 5.09%.

The second fraction gave crystals which were recrystallized from ethanol–ether to give **5a** (0.34 g, 15%) as needles, mp 75—76 °C. From the mother liquor, the second crop was obtained as prisms, mp 91—93 °C, weighing 0.13 g (total yield, 21%). These two dimorphic crystals were found to be identical by ^{1}H NMR spectroscopy.

Found: C, 50.16; H, 5.83%.

Acetylation of **5a** (0.18 g) gave, after recrystallization from ethyl acetate, the diacetate (**5b**, 0.22 g, 77%) as rods, mp 110—111.5 °C.

Found: C, 52.66; H, 5.02%.

The third fraction gave crystals which were recrystallized from ethanol to give **4a** (0.18 g, 8%) as plates, mp 124—124.5 °C.

Found: C, 50.42; H, 5.65%.

Acetylation of **4a** (24 mg) gave, after recrystallization from ethanol, the diacetate (**4b**, 28 mg, 73%), mp 136 °C.

Found: C, 52.47; H, 5.07%.

Compound **3a**, as well as **4a**, gave by TLC a *ca.* 3:2 mixture of **3a** and **4a** on treatment with methanolic sodium methoxide. Compound **5a**, however, remained unchanged under similar conditions.

*O-Decyclohexylidenation of 1,2:5,6-Dianhydro-3,4-O-cyclohexylidene-*allo*-inositol (14).*[12] A mixture of **14** (1 g) and 20% aqueous acetic acid (50 ml) was heated under reflux for 0.5 h. After having been cooled, the solution was neutralized with 5% aqueous sodium hydroxide and then evaporated to dryness. The residue was extracted with ethanol (50 ml) and the extract was concentrated to one half volume. TLC indicated the formation of **3a**, together with several minor components, but none of **4a**. The solution was filtered and the filtrate was chromatographed on silica gel (30 g) with benzene–ethyl acetate (1:2, v/v) as an eluent. The main fraction gave a syrup, which crystallized from methanol to give **3a** (0.24 g, 37%), mp 75—77 °C, identical with the compound obtained before.

*1,2:3,4- (7a) and 1,2:4,5-Dianhydro-*cis*-inositols (8a).* *a)*: 1,2,5-Tri-*O*-acetyl-3-*O*-benzoyl-4,6-di-*O*-tosyl-*myo*-inositol (**15**)[13] (3 g) was treated with 1 M methanolic sodium methoxide (11 ml, 2.5 molar equiv.) in a mixture of chloroform (18 ml) and methanol (12 ml) at ambient temperature overnight. TLC showed the formation of three components: one minor (R_f 0.2) and two major components (R_f 0.16 and 0.06). The reaction mixture was processed similarly and the products were fractionated as described in the separation of **1a** and **2a**. The faster-moving component, 2,3-anhydro-6-*O*-tosyl-*allo*-inositol (**17**), was obtained as needles (59 mg, 4.4%), mp 155—156 °C, after crystallization from ethanol–ether. ^{1}H NMR (D_2O): δ 2.47 (3H, s, tosyl CH_3), 3.8—4.4 (6H, m, methine protons).

Found: C, 49.65; H, 5.46%. Calcd for $C_{13}H_{16}O_7S$: C, 49.35; H, 5.11%.

The second fraction was evaporated and the residue was crystallized from ethanol–ether to give **7a** (26 mg, 4.3%) as needles, mp 103—104 °C.

Found: C, 50.00; H, 5.33%.

Acetylation of **7a** (25 mg) gave, after crystallization from ethanol, the diacetate (**7b**, 32 mg, 81%) as needles, mp 142.5—144 °C.

Found: C, 52.89; H, 5.12%.

The third fraction gave crystals which were recrystallized from methanol–ether to give **8a** (0.22 g, 37%) as plates, mp 178—180 °C.

Found: C, 50.39; H, 5.72%.

Acetylation of **8a** (24 mg) gave, after recrystallization from ethanol, the diacetate (**8b**, 24 mg, 63%) as plates, mp 153—154 °C.

Found: C, 52.86; H, 5.14%.

Compound **17** was found by TLC to be selectively converted into **8a** on treatment with methanolic sodium methoxide.

b): 1-*O*-Benzoyl-4,6-di-*O*-tosyl-*myo*-inositol (**16**)[13] (0.8 g) was treated similarly with 1 M methanolic sodium methoxide (3.4 ml, 2.5 molar equiv.) in a mixture of butanone (50 ml) and methanol (50 ml) at ambient temperature overnight. TLC indicated the formation of **7a** (R_f 0.2), together with traces of **8a** and **17**. The products were fractionated by chromatography on silica gel to give **7a** (70 mg, 36%), mp 101.5—103 °C.

The same results as described in (a) were obtained when **15** was treated with methanolic sodium methoxide in the solvent used for the epoxidation of **16**.

*Tetra-O-acetyl-3,6-di-O-tosyl-*muco*-inositol (19).* 3,6-Di-*O*-tosyl-*muco*-inositol[15] (0.2 g) was treated with acetic anhydride (2 ml) in pyridine (2 ml) at ambient temperature overnight. The reaction mixture was poured into ice-water and the resulting crystals were recrystallized from chloroform–ethanol to give **19** (0.26 g, 96%) as plates, mp 189—190 °C.

Found: C, 51.41; H, 5.03; S, 9.97%. Calcd for $C_{28}H_{32}O_{14}S_2$: C, 51.20; H, 4.91; S, 9.77%.

Reaction of 19 with Sodium Methoxide. Compound **19** (7 g) was treated with 1 M methanolic sodium methoxide (28 ml, 2.5 molar equiv.) in a mixture of chloroform (100 ml) and methanol (80 ml) at ambient temperature overnight. TLC showed the formation of one major component (R_f 0.06) and one minor one (R_f 0.11). The reaction mixture was processed similarly and the products were separated by chromatography on silica gel to give **8a** (0.55 g, 36%), mp 178—180 °C, as the main product. The minor component was obtained as needles (16 mg), mp 157—159 °C, after crystallization from ethanol; the IR spectrum showed no absorption in the region of tosyloxyl function. No further characterization was carried out owing to a minute amount.

*Reaction of Tri-O-acetyl-1,4,6-tri-O-tosyl-*myo*-inositol (20)*[11] *and Its O-Deacetylated Derivative (21)*[11] *with Sodium Methoxide.*

a): Compound **20** (0.3 g) was treated with 1 M methanolic sodium methoxide (0.33 ml, 2.5 molar equiv.) in a mixture of chloroform (10 ml) and methanol (2 ml) at ambient temperature overnight. TLC indicated the formation of one major component and one minor one. The reaction mixture was evaporated and the residue was extracted with hot ethyl acetate (3×10 ml). The extracts were evaporated and the residue was crystallized from chloroform–ethanol to give 1,2: 3,4-dianhydro-5-*O*-tosyl-*cis*-inositol (**22**, 59 mg, 50%) as plates, mp 176—177 °C.

Found: C, 52.76; H, 4.99; S, 10.36%. Calcd for $C_{13}H_{14}O_6S$: C, 52.32; H, 4.73: S, 10.75%.

Acetylation of **22** (40 mg) gave, after crystallization from chloroform–ethanol, the acetate (**23**, 36 mg, 79%) as needles, mp 173—174 °C. ^{1}H NMR ($CDCl_3$) δ 2.05 (3H, s, OAc), 2.47 (3H, s, tosyl CH_3), 3.25 (2H, m) and 3.43 (2H, m) (H-1, H-2, H-3, and H-4), 5.12 (2H, m, H-5 and H-6).

Found: C, 52.69; H, 4.74; S, 9.73%. Calcd for $C_{15}H_{16}O_7S$: C, 52.91; H, 4.74; S, 9.42%.

b): Compound **21** (0.5 g) was treated with 1 M methanolic sodium methoxide (1.5 ml, 2.5 molar equiv.) in a mixture of butanone (30 ml) and methanol (10 ml) at ambient temperature overnight. TLC indicated the formation of one major component, together with a trace of **22**. The reaction mixture was worked up as described above and the product was crystallized from ethanol–ether to give 1,2-anhydro-5,6-di-*O*-tosyl-*epi*-inositol (**24**, 90 mg, 25%) as prisms, mp 167—168 °C.

Found: C, 51.29; H, 4.79; S, 13.62%. Calcd for $C_{20}H_{22}O_9S_2$: C, 51.05; H, 4.72; S, 13.64%.

Acetylation of **24** (40 mg) gave, after crystallization from ethanol, the diacetate (**25**, 47 mg, 99%) as plates, mp 159—159.5 °C. ^{1}H NMR ($CDCl_3$) δ 2.05 (6H, s, two OAc), 2.49 (6H, s, two tosyl CH_3), 3.35 (1H, m, H-2), 3.45 (1H, d, $J_{1,2}$=3.5 Hz, H-1), 4.58 (1H, dd, $J_{4,5}$=2.5 Hz, $J_{5,6}$=9 Hz, H-5).

Found: C, 52.00; H, 4.72; S, 11.59%. Calcd for $C_{24}H_{26}O_{11}S_2$: C, 51.97; H, 4.73; S, 11.56%.

chiro-*Inositol (28).* Penta-*O*-acetyl-1-bromo-1-deoxy-*chiro*-inositol (**26**, 2.3 g), mp 114—116 °C, prepared by the modified method of McCasland and Horswill,[16] was treated with anhydrous sodium acetate (2.3 g) in boiling 90% aqueous 2-methoxyethanol (30 ml) for 18 h. The reaction mixture was evaporated to dryness and the residue was treated with acetic anhydride (10 ml) and pyridine (10 ml) at ambient temperature overnight. The reaction mixture was filtered to remove an insoluble matter. The filtrate was evaporated to give a syrup, which was purified by passing through a short alumina column with ethyl acetate. The eluate was evaporated and the syrupy product was crystallized from ethanol to give hexa-*O*-acetyl-*chiro*-inositol (**27**, 1.43 g, 65%) as crystals, mp 110—112 °C (lit,[16] 110—111 °C).

Compound **27** (5.6 g) was treated with boiling 4 M hydrochloric acid (100 ml) for 2.5 h. The reaction mixture was evaporated and the residue was crystallized from ethanol to give **28** (2.2 g, 95%) as crystals, mp 245—246 °C (lit,[16] 243 °C).

*Acetonation of **28**.* The reaction was carried out following the method of Angyal and MacDonald.[18] A mixture of finely powdered **28** (2 g), anhydrous zinc chloride (10 g), acetic acid (10 ml), and acetone (80 ml) was heated under reflux for 5.5 h. Pyridine (20 ml) was added to the cooled mixture, and the precipitates were removed by filtration and washed with chloroform (30 ml). The filtrate and washings were combined and evaporated to dryness. The residue was treated with acetic anhydride (10 ml) and pyridine (10 ml) and the reaction mixture was worked up by the usual method. The product was crystallized from ethanol to give 1,2: 3,4: 5,6-tri-*O*-isopropylidene-*chiro*-inositol (**29**, 0.99 g, 30%) as plates, mp 140 °C.

Found: C, 60.30; H, 8.05%. Calcd for $C_{15}H_{24}O_6$: C, 60.00: H, 8.05%.

The mother liquor of **29** was evaporated and the residue was crystallized from ethanol to give 3,4-di-*O*-acetyl-1,2: 5,6-di-*O*-isopropylidene-*chiro*-inositol (**30**, 0.69 g, 18%) as needles, mp 111—112 °C. ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, s) and 1.55 (3H, s) (isopropylidene CH_3), 2.06 (6H, s, two OAc), 5.06 (2H, dd, J=3 and 5 Hz, H-3 and H-4).

Found: C, 56.04; H, 6.84%. Calcd for $C_{16}H_{24}O_8$: C, 55.80; H, 7.04%.

*Tetra-*O*-acetyl-3,4-di-*O*-tosyl-*chiro*-inositol (32).* Compound **30** (0.65 g) was treated with a catalytic amount of methanolic sodium methoxide in a mixture of chloroform (5 ml) and methanol (5 ml) at ambient temperature overnight. The mixture was evaporated to dryness and the residue was treated with tosyl chloride (2.9 g) in pyridine (10 ml) at 40 °C for four days. The reaction mixture was poured into ice–water, and the resulting crystals were collected and recrystallized from chloroform–ethanol to give 1,2: 5,6-di-*O*-isopropylidene-3,4-di-*O*-tosyl-*chiro*-inositol (**31**, 0.63 g, 59%) as plates, mp 174—176 °C. ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, s) and 1.44 (3H, s) (isopropylidene CH_3), 2.45 (6H, s, two tosyl CH_3), 4.63 (2H, m, J=2.5 and 4 Hz, H-3 and H-4).

Found: C, 54.92; H, 5.86; S, 11.23%. Calcd for $C_{26}H_{32}O_{10}S_2$: C, 54.91; H, 5.68; S, 11.27%.

Compound **31** (0.55 g) was treated with 50% aqueous acetic acid (20 ml) at reflux for 2 h. The reaction mixture was evaporated to dryness and the residue was acetylated in the usual way. The product was recrystallized from chloroform–ethanol to give **32** (0.6 g, 94%) as needles, mp 216—216.5 °C.

Found: C, 51.48; H, 5.12; S, 9.74%. Calcd for $C_{28}H_{22}O_{14}S_2$: C, 51.20; H, 4.91; S, 9.77%.

*1,2: 5,6-Dianhydro-*neo*-inositol (9a).* Compound **32** (0.5 g) was treated with 1 M methanolic sodium methoxide (2 ml, 2.5 molar equiv.) in a mixture of chloroform (10 ml) and methanol (5 ml) at ambient temperature overnight. The reaction mixture was evaporated and the residue was acetylated in the usual manner. The product was crystallized from ethanol to give the diacetate (**5b**, 83 mg, 48%), mp 96—97 °C.

Found: C, 52.94; H, 5.47%.

Compound **5b** (80 mg) was treated with a catalytic amount of methanolic sodium methoxide in methanol (4 ml) and the mixture was then treated with Amberlite IR-120 (H^+) and evaporated to dryness. The residue was crystallized from ethanol–ether to give **5a** (18 mg, 35%) as plates, mp 121.5—122.5 °C.

Found: C, 49.88; H, 5.73%.

*1,2,3,6-Tetra-*O*-benzoyl-4,5-di-*O*-tosyl-*muco*-inositol (34).* 1,2,3,4,6-Tetra-*O*-benzoyl-*muco*-inositol (**33**)[19] (4 g) was treated with tosyl chloride (6.6 g, 5 molar equiv.) in pyridine (100 ml) at ambient temperature for 2 days. The reaction mixture was poured into ice–water and the precipitates were recrystallized from chloroform–ethanol to give **34** (5.6 g, 93%), mp 194—195 °C. ^{1}H NMR ($CDCl_3$): δ 2.32 (6H, s, two tosyl CH_3).

Found: C, 63.96; H, 4.59; S, 6.69%. Calcd for $C_{48}H_{40}O_{14}S_2$: C, 63.71; H, 4.46; S, 7.09%.

*1,2: 4,5-Dianhydro-*neo*-inositol (11a).* Compound **34** (7 g) was treated with 1 M methanolic sodium methoxide (20 ml, 2.5 molar equiv.) in a mixture of chloroform (40 ml) and methanol (50 ml) at ambient temperature overnight. The reaction mixture was worked up similarly and the product was purified by chromatography on silica gel with benzene–

ethyl acetate (1: 1, v/v) as an eluent. The product was crystallized from ethanol to give **11a** (0.44 g, 39%) as plates, mp 150—151 °C. Found: C, 50.30; H, 5.83%.

Compound **11a** (0.1 g) was converted into the diacetate (**11b**, 0.12 g, 83%) as plates, mp 138—139 °C, crystallized from ethanol. Found: C, 52.98; H, 5.14%.

*1,2: 3,4-Dianhydro-*allo*-inositol (10a).* 1,2: 3,4-Dianhydro-5,6-*O*-cyclohexylidene-*allo*-inositol (**35**)[12] was prepared in an improved yield (80%) from 1,2-*O*-cyclohexylidene-3,5-di-*O*-tosyl-*myo*-inositol by treatment with 2.5 molar equiv. of methanolic sodium methoxide in boiling 2-methoxyethanol. Compound **35** (1.2 g) was treated with boiling 20% aqueous acetic acid (50 ml) for 45 min. The reaction mixture was then processed as described in the preparation of **3a**. The crude product was purified by chromatography on silica gel with benzene–ethyl acetate (1: 2, v/v) as an eluent and crystallized from ethanol–ether to give **10a** (0.23 g, 30%) as crystals, mp 105—106 °C. Found: C, 50.22; H, 5.53%.

On acetylation, **10a** was converted into the syrupy diacetate (**10b**, 52 mg, 87%). Compound **10a** was found by TLC to give **11a** exclusively on treatment with methanolic sodium methoxide.

*1,2,3,4-Tetra-*O*-benzoyl-*chiro*-inositol (37).* 1,2-*O*-Cyclohexylidene-*chiro*-inositol (**36**)[19] (0.1 g) was treated with benzoyl chloride (0.41 ml, 12 molar equiv.) in pyridine (10 ml) at ambient temperature overnight. The reaction mixture was poured into ice–water to give crude tetra-*O*-benzoyl derivative as a white powder. It was treated with boiling 80% aqueous acetic acid (20 ml) for 2 h. The product was purified by chromatography on silica gel with butanone–toluene (1: 5, v/v) as an eluent. The main fraction gave crystals which were recrystallized from ethyl acetate–petroleum ether to give **37** (0.17 g, 72%) as needles, mp 148—150 °C.

Found: C, 68.26%; H, 4.82%. Calcd for $C_{34}H_{28}O_{10}$: C, 68.47; H, 4.73%.

*1,2,3,4-Tetra-*O*-benzoyl-5,6-di-*O*-mesyl-*chiro*-inositol (38).* *a)*: Compound **37** (0.1 g) was treated with mesyl chloride (0.1 ml, 8 molar equiv.) in pyridine (5 ml) at ambient temperature overnight. The reaction mixture was poured into ice-water and the precipitates were crystallized from chloroform–ethanol to give **38** (0.07 g, 55%) as crystals, mp 189—191 °C. ^{1}H NMR ($CDCl_3$): δ 3.04 (3H, s) and 3.36 (3H, s) (mesyl CH_3). Found: C, 57.38; H, 4.35; S, 8.60%. Calcd for $C_{36}H_{32}O_{14}S_2$: C, 57.34; H, 4.29; S, 8.52%.

b): Compound **36** (1.5 g) was treated with benzoyl chloride (8 ml, 12 molar equiv.) in pyridine (120 ml) at ambient temperature overnight and then at 60 °C for 0.5 h. The mixture was poured into ice–water and the resulting gum was extracted with chloroform. The extract was evaporated to give crude **37** (1.5 g), which was treated successively with boiling 80% aqueous acetic acid and with mesyl chloride (1.1 ml) in pyridine (30 ml) to give crude **38** (3.6 g). Recrystallization from chloroform–ethanol gave pure **38** (3.1 g, 72% yield based on **36** used), mp 189—191 °C.

*1,2: 3,4-Dianhydro-*epi*-inositol (6a).* A solution of **38** (1.04 g) in a mixture of chloroform (15 ml) and methanol (20 ml) was treated with 1 M methanolic sodium methoxide (1.6 ml, 1.1 molar equiv.) at ambient temperature overnight. TLC showed the formation of one major component (R_f 0.07) and one minor one (R_f 0.12). The reaction mixture was evaporated to dryness and the residue was dissolved in methanol (30 ml) and treated with Amberlite MB-3. The solution was evaporated to give a crude monoepoxide (**39**), which was without further purification dissolved in methanol (30 ml). The solution was passed through a short column of Amberlite IRA-400 (OH^-) several times until **39** disappeared in the effluent subjected to monitoring by TLC. TLC showed the formation of one major component (R_f 0.12) and two minor ones (R_f 0.15 and 0.07). The mixture was fractionated by chromatography on silica gel with benzene–ethyl acetate (1: 2, v/v) as an eluent. The first fraction gave a small amount of syrup, which crystallized to give **5a**, mp 108—110 °C, identical with the compound obtained before. The second fraction gave crystals, which were recrystallized from ethanol to give **6a** (49 mg, 25%) as plates, mp 132—134 °C.

Found: C, 50.14; H, 5.62%.

Acetylation of **6a** gave a syrupy diacetate **6b**.

Compound **6a** was shown by TLC to give **5a** exclusively on treatment with methanolic sodium methoxide.

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