BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 2597—2602 (1972)

Inositol Derivatives. IV.[1] Synthesis of Anhydro Derivatives of 1,2-*O*-Cyclohexylidene-inositol

Tetsuo SUAMI, Seiichiro OGAWA, Shuichi OKI, and Kumiko OHASHI
Department of Applied Chemistry, Faculty of Engineering, Keio University, Hiyoshi, Yokohama
(Received March 1, 1972)

A reaction of 1,2-*O*-cyclohexylidene-*myo*-inositol tosylates with sodium methoxide in an appropriate solvent gave nine anhydro derivatives (mono- 6 and di-epoxide 3). The structures of new compounds were determined by proton magnetic resonance (PMR) spectroscopy and the reaction sequences.

Recent discovery of cyclohexane diepoxide tumor inhibitor, crotepoxide,[2] stimulated us to investigate a preparation of anhydro derivatives of inositols, which are also useful intermediary compounds for a synthesis of inositol derivatives.

In 1947, Schöpf and Arnold[3] first reported a synthesis of 2,3-anhydro-*allo*-inositol from conduritol A by a treatment with peracid. Later, Nakajima *et al.*[4] described six inositol epoxides (conduritol epoxides) which were obtained from five conduritols derived from benzene-glycol. Very recently, Gero *et al.*[5] have described the preparation of 1L- and DL-1,2-anhydro-*chiro*- and 1L-1,2-anhydro-*myo*-inositol, and their biological activities were

1) Previous reports on inositol derivatives: T. Suami, S. Ogawa, T. Tanaka, and T. Otake, This Bulletin, **44**, 835 (1971); T. Suami, S. Ogawa, and S. Oki, *ibid.*, **44**, 2820 (1971); T. Suami, S. Ogawa, and S. Oki, *ibid.*, **44**, 2824 (1971).

2) S. M. Kupchan, R. J. Hemingway, P. Coggon, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **90**, 2982 (1968).

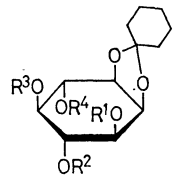
3) C. Schöpf and W. Arnold, *Ann. Chem.*, **558**, 123 (1947).

4) M. Nakajima, I. Tomida, N. Kurihara, and S. Takei, *Chem. Ber.*, **92**, 173 (1959); M. Nakajima and N. Kurihara, *ibid.*, **94**, 515 (1961).

5) D. Mercier, A. Olesker, and S. D. Gero, *Carbohyd. Res.*, **18**, 227 (1971).

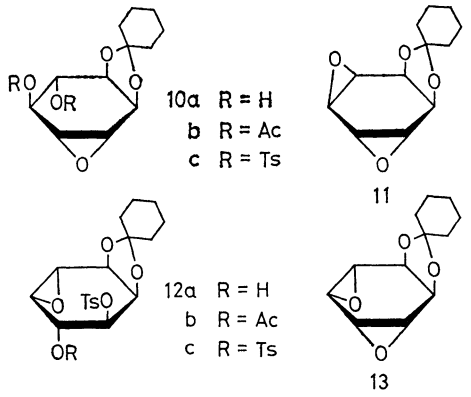
examined. However, inositol diepoxide has never been described until now.

In the present paper, we wish to report a synthesis of mono- and di-epoxides of inositols from 1,2-*O*-cyclohexylidene-*O*-*p*-toluenesulfonyl-*myo*-inositols[6] by a treatment with sodium methoxide in an appropriate solvent. The structures of new compounds were established mainly by way of their PMR spectroscopy and the reaction sequences.



	R^1	R^2	R^3	R^4
1	Ts	H	H	H
2	Ts	H	H	Ts
3	Ts	H	Ts	H
4	Ts	Ts	H	H
5	Bz	Ts	H	Ts
6	Bz	Ts	Ts	Ac
7	Ts	H	Ts	Ts
8	Ts	Ts	H	Ts
9	Bz	Ts	Ts	Ts

When 1,2-*O*-cyclohexylidene-3-*O*-*p*-toluenesulfonyl-*myo*-inositol (**1**) was treated with a slight excess of sodium methoxide in methanol at room temperature for 3 hr, 1,2-anhydro-5,6-*O*-cyclohexylidene-*chiro*-inositol (**10a**) was obtained almost exclusively in 80—90% yield.



Acetylation of **10a** with acetic anhydride and pyridine afforded the diacetate (**10b**). On treatment with *p*-toluenesulfonyl chloride in pyridine, **10a** gave the di-*O*-*p*-toluenesulfonate (**10c**). The PMR spectrum of **10b** in deuteriochloroform ($CDCl_3$) at 60 MHz (Fig. 1) was fully resolved by a first-order method and all signals were assigned unambiguously to the protons. The two protons (H-1 and H-2) attached to the epoxide ring appeared as two doublets ($J_{1,2}$ 3.0 Hz) at τ 6.73, and 6.51. Also small coupling constants ($J_{2,3}$ and $J_{1,6}$) were observed, which indicated that the epoxide ring was situated *trans* to the vicinal substituents.[7] The two protons (H-5 and H-6) appeared as double doublet and doublet ($J_{4,5}$ 8.0 Hz, $J_{5,6}$ 5.5 Hz) at τ 5.98 and 5.35, respectively. Therefore, the epoxide ring was shown to be located on C-1 and C-2. The remaining doublet and triplet ($J_{3,4}$ 8.0 Hz) at τ 5.06 and 4.80 were ascribed to H-3 and H-4, respectively. While, in the spectrum of **10c**, the two protons (H-1 and H-2) appeared as 2-proton singlet at τ 6.66. The triplet, 2-proton doublet, and triplet (J 6.0 Hz) appeared at τ 5.98, 5.33, and 5.16, which could be attributed to H-5, H-3 and H-6, and H-4, respectively. Consequently, the proposed structure was evidently confirmed by the PMR spectral data, and it was shown that a migration of an oxide-ring did not occur under the condition used.

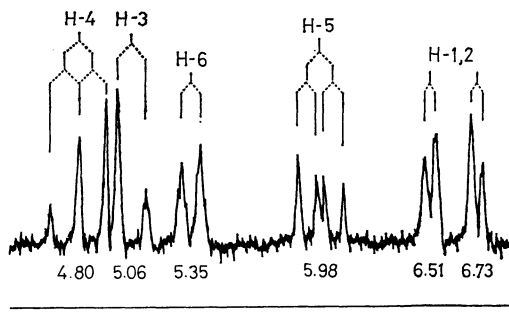


Fig. 1. Partial PMR spectrum of 3,4-*O*-acetyl-1,2-anhydro-5,6-*O*-cyclohexylidene-*chiro*-inositol (**10b**) in $CDCl_3$ at 60 MHz.

Five di-*O*-*p*-toluenesulfonyl derivatives of 1,2-*O*-cyclohexylidene-*myo*-inositol were then treated successively with sodium methoxide. The 3,6-di-*O*-*p*-toluenesulfonate (**2**)[6] was reacted with a slight excess of sodium methoxide in methanol overnight at room temperature to give the diepoxide (**11**) in 87% yield. The PMR spectrum of **11** in $CDCl_3$ (Fig. 2) revealed three multiplets (τ 6.73, 6.53, and 6.40) due to four protons attached to two epoxide rings, which was indicative of the unsymmetrical structure of **11**, hence, the epoxide rings were in *trans* arrangement each other. The two protons (H-3 and H-4) attached to the carbon atoms bonding to the cyclohexylidene group appeared at τ 5.59 and 5.36 as double doublet and broad doublet ($J_{3,4}$ 6.0 Hz, $J_{2,3}$ 3.0 Hz), respectively. Therefore, **11** was assigned to 1,2: 5,6-dianhydro-3,4-*O*-cyclohexylidene-*allo*-inositol.

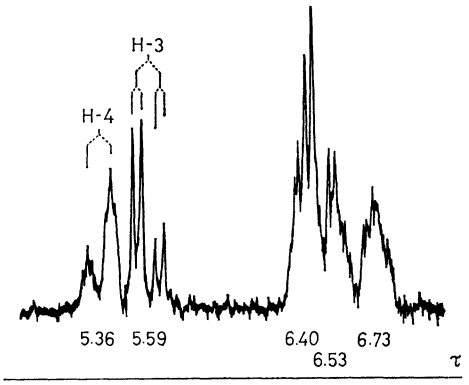


Fig. 2. Partial PMR spectrum of 1,2: 5,6-dianhydro-3,4-*O*-cyclohexylidene-*allo*-inositol (**11**) in $CDCl_3$ at 60 MHz.

By the similar treatment with sodium methoxide, the monoepoxide (**12a**) was obtained in a yield of 76% from the 3,5-di-*p*-toluenesulfonate (**3**).[6] A more drastic condition was needed for converting **3** into the

6) T. Suami, S. Ogawa, T. Tanaka, and T. Otake, This Bulletin, **44**, 835 (1971).

7) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 1481 (1968).

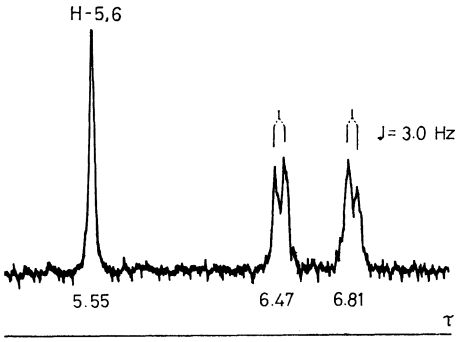
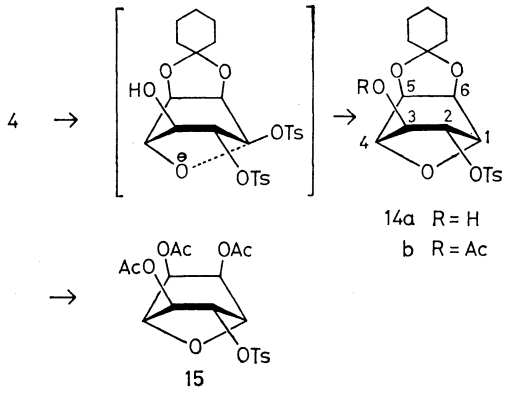


Fig. 3. Partial PMR spectrum of 1,2: 3,4-dianhydro-5,6-*O*-cyclohexylidene-*allo*-inositol (**13**) in $CDCl_3$ at 60 MHz.

diepoxide **13**. Thus, **3** was treated with an excess of sodium methoxide in boiling 2-methoxyethanol for 10 min to afford **13** in 28% yield. Monitoring the reaction using thin layer chromatography (tlc), **12a** was found to be an intermediate compound for further epoxidation to **13**. Compound **12a** was transformed into the monoacetate (**12b**) and di-*p*-toluenesulfonate (**12c**), respectively, by the usual way. Since **12c** was shown to be different from **10c**, **12a** must be either 1,2-anhydro-5,6-*O*-cyclohexylidene-4-*O*-*p*-toluenesulfonyl- or 1,2-anhydro-4,5-*O*-cyclohexylidene-6-*O*-*p*-toluenesulfonyl-*neo*-inositol. The latter can not give the diepoxide and could be excluded, therefore, **12a** was assigned to the former structure. And **13** was deduced to be 1,2: 3,4-dianhydro-5,6-*O*-cyclohexylidene-*allo*-inositol. The PMR spectrum of **13** in $CDCl_3$ (Fig. 3) revealed a simple pattern of signals for the ring protons, showing a symmetrical 1,3-*cis* diepoxide structure of **13**. The signals for H-4 and H-3 protons of **12b** appeared as two double doublets ($J_{3,4}$ 9.0 Hz, $J_{4,5}$ 2.0 Hz, and $J_{2,3}$ 1.5 Hz) at τ 5.17 and 4.43, respectively. In **12c**, the lower double doublet (H-3) upshifted[6] relatively by *ca.* 0.3 ppm (τ 4.78), comparing with that of **12b**, which showed that the acetoxy group was located at C-3 position in **12b**.



On a similar treatment, the 3,4-di-*p*-toluenesulfonate (**4**)[6] gave the monoepoxide (**14a**) in 67% yield. Compound **14a** was converted into the oily acetate (**14b**). Removal of the cyclohexylidene group of **14a** with boiling 80% aqueous acetic acid, followed by acetylation, afforded the triacetate (**15**) in 69% yield. By analogy, a structure of **14a** was initially considered to be 1,2-anhydro-4,5-*O*-cyclohexylidene-3-*O*-*p*-toluenesulfonyl-*epi*-inositol. However, the PMR spectra of **14a**, **14b**, and **15** in $CDCl_3$ lacked the signals of 1,2-epoxide ring protons in the region of τ 6.40—6.90[8] (Fig. 4). Furthermore, when **4** was treated with an excess of sodium azide in boiling 2-methoxyethanol for 20 hr, **14a** was surprisingly obtained in 73% yield almost exclusively. Under the azidation condition described above, all the *p*-toluenesulfonates studied so far[9] were smoothly converted into the expected azido compounds *via* intermediate 1,2-epoxides. Since the 1,2-epoxide structure could not account for both the unusual stability for the powerful nucleophilic reagent and the spectral data, **14a** was assumed to be 1,4-anhydro-5,6-*O*-cyclohexylidene-2-*O*-*p*-toluenesulfonyl-*chiro*-inositol. Therefore, it might be considered that in the compound **4** an attack of 5-hydroxyl group on C-4 is restricted by a stereochemical environment, and then, another hydroxyl group on C-6 attacks rear-side of C-3 in a boat conformation to form a transannular epoxide (1,4-anhydro ring).

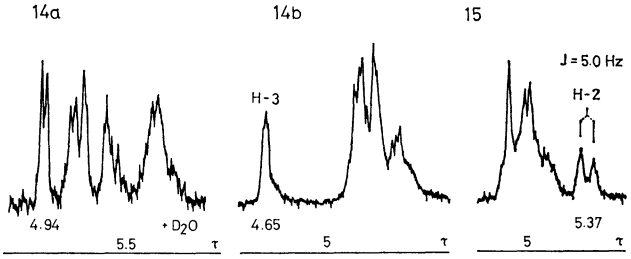


Fig. 4. Partial PMR spectra of 1,4-anhydro-5,6-*O*-cyclohexylidene-2-*O*-*p*-toluenesulfonyl-*chiro*-inositol (**14a**), its 3-*O*-acetate (**14b**), and 3,5,6-tri-*O*-acetyl-1,4-anhydro-2-*O*-*p*-toluenesulfonyl-*chiro*-inositol (**15**) in $CDCl_3$ at 60 MHz.

1-*O*-Benzoyl-2,3-*O*-cyclohexylidene-4,6-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**5**), which was obtained by a selective *p*-toluenesulfonylation of 1-*O*-benzoyl-2,3-*O*-cyclohexylidene-*myo*-inositol,[10] was subjected to an epoxidation to give the diepoxide (**16**) in 19% yield.

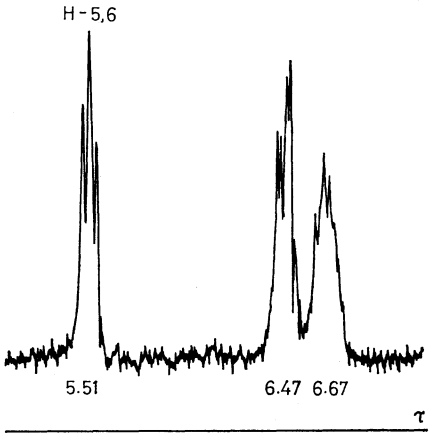


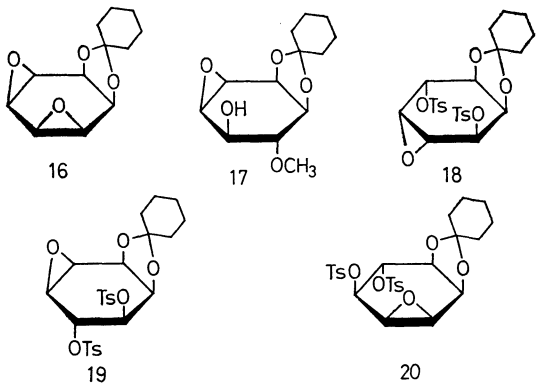
Fig. 5. Partial PMR spectrum of 1,2: 3,4-dianhydro-5,6-*O*-cyclohexylidene-*cis*-inositol (**16**) in $CDCl_3$ at 60 MHz.

8) Observed in the PMR spectra of eleven epoxides prepared in this study.

9) T. Suami, S. Ogawa, T. Tanaka, and S. Oki, in preparation. A part of the work had been reported at the Annual Meeting of the Chemical Society of Japan, Osaka, April, 1971.

10) T. Suami, S. Ogawa, K. Ohashi, and S. Oki, This Bulletin, in press.

Monitoring the reaction by tlc, it was found that **5** was slowly converted into **16** and **16** so formed gradually reacted with methoxide ion to give rise to a monomethyl ether (**17**). Thus, when **5** was treated with 7 molar equivalent of sodium methoxide in methanol at room temperature for 2 days, **17** was obtained mainly in 48% yield. Considering from the reaction sequence, **16** was assigned to 1,2:3,4-dianhydro-5,6-*O*-cyclohexylidene-*cis*-inositol. The PMR spectrum of **16** in $CDCl_3$ (Fig. 5) revealed symmetrical three multiplets due to three pairs of equivalent protons at τ 6.67, 6.47, and 5.51, supporting the *cis*-1,3-diepoxide structure. Compound **17** was assigned to 2,3-anhydro-4,5-*O*-cyclohexylidene-6-*O*-methyl-*epi*-inositol by the PMR spectral data. In the PMR spectrum of **17**, all the signals could not be well resolved by a first-order method, except those due to the two protons on C-4 and C-5. Thus, the double doublet at τ 5.39 was assigned to H-4 proton ($J_{3,4}$ 3.0 Hz, $J_{4,5}$ 7.0 Hz), which was closely related to that of **20** (τ 5.40, $J_{3,4}$ 2.5 Hz, $J_{4,5}$ 7.0 Hz). The broad doublet at τ 5.74 (H-5) seemed to be corresponding to that of **20** (τ 5.89).



From 4-*O*-acetyl-1-*O*-benzoyl-2,3-*O*-cyclohexylidene-*myo*-inositol (**6**),[10] **11** was obtained in a yield of 69% by similar treatment with sodium methoxide.

Three tri-*O*-*p*-toluenesulfonyl derivatives of 1,2-*O*-cyclohexylidene-*myo*-inositol were treated analogously with sodium methoxide. The 3,5,6-tri-*p*-toluenesulfonate (**7**)[6] gave the monoepoxide (**18**) in 60% yield, which was shown to be different from **10c**. And, **18** was assigned to 1,2-anhydro-4,5-*O*-cyclohexylidene-3,6-di-*O*-*p*-toluenesulfonyl-*neo*-inositol. In **7**, an oxide anion at C-4 seemed to attack preferentially the 5-carbon atom to give rise to the 4,5-epoxide derivative. The PMR spectrum of **18** in $CDCl_3$ showed three multiplets at τ 6.46, 5.81, and 4.91, which were ascribed to H-1 and H-2, H-4 and H-5, and H-3 and H-6, respectively.

While, the 3,4,6-tri-*p*-toluenesulfonate (**8**)[6] gave, on a similar treatment, the monoepoxide (**19**) in 84% yield. Two structures were possible for **19**: 1,2-anhydro-3,4-*O*-cyclohexylidene-5,6-di-*O*-*p*-toluenesulfonyl- and 1,2-anhydro-4,5-*O*-cyclohexylidene-3,6-di-*O*-*p*-toluenesulfonyl-*epi*-inositol. If **19** had the latter structure, its PMR spectrum should rather resemble that of **18** than that of **12c**, but, substantially the resemblance between the spectra of **19** and **12c** was observed. An oxide anion at C-5 was also expected to attack 6-carbon atom favorably, considering from the result obtained in the case of **4**. Then **19** was assigned to the former structure.

The similar treatment of 1-*O*-benzoyl-2,3-*O*-cyclohexylidene-4,5,6-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol (**9**)[10] with sodium methoxide afforded 2,3-anhydro-4,5-*O*-cyclohexylidene-1,6-*O*-*p*-toluenesulfonyl-*epi*-inositol (**20**) in 82% yield. The proposed structure was supported not only by the reaction sequence, but also by the PMR spectrum.

Experimental

Melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. IR spectra were measured on a Jasco IR-E spectrophotometer in KBr disks. PMR spectra were measured on a Varian A-60D spectrometer at a concentration of *ca.* 10% deuteriochloroform ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) with tetramethylsilane as an internal standard. Chemical shifts are expressed in τ-values and signals are expressed as s (singlet), dd (double doublet), t (triplet), and m (complex multiplet). Values given for coupling constants are first-order. Tlc was performed using silica gel (Wakogel B-10, Wako Pure Chemical Industries Ltd.) using methyl ethyl ketone and toluene or benzene and ethyl acetate as the solvent system. The compounds were detected by heating at 100°C after spraying 30% sulfuric acid. Evaporation was performed by a rotary evaporator below 50°C under diminished pressure. Unless otherwise noted, methanol solution of sodium methoxide (0.1 M) used in this experiment was prepared by dissolving sodium (0.23 g) in absolute methanol (100 m*l*). All the compounds described in this paper are racemic.

*1,2-Anhydro-5,6-*O*-cyclohexylidene-*chiro*-inositol (**10a**).* 1,2-*O*-Cyclohexylidene-3-*O*-*p*-toluenesulfonyl-*myo*-inositol (**1**)[6] (5.0 g) was dissolved in hot methanol (100 m*l*) and cooled to room temperature. To the solution was added methanol (20 m*l*) containing 1.5 molar equivalent of sodium methoxide, and the mixture was kept at room temperature for 3 hr. Then the solution was evaporated to dryness and the residue was partitioned between chloroform and water. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give practically pure crystals (2.63 g, 90%) of **10a**, mp 91—98°C. Recrystallization from ethanol–ether gave analytically pure needles (1.69 g, 58%), mp 109—110°C. PMR ($CDCl_3$): τ 6.68 (1-proton dd, $J_{1,2}$= 4.0 Hz, $J_{1,6}$=1.0 Hz, H-1), 6.50 (1-proton m, H-2), 5.90 (2-protons m, H-3,4), 5.60 (1-proton dd, $J_{4,5}$=4.0 Hz, $J_{5,6}$= 6.0 Hz, H-5), and 5.32 (1-proton d, H-6).

Found: C, 59.40; H, 7.29%. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49%.

*3,4-*O*-Acetyl-1,2-anhydro-5,6-*O*-cyclohexylidene-*chiro*-inositol (**10b**).* Compound **10a** (100 mg) was treated with acetic anhydride (0.5 m*l*) and pyridine (1 m*l*) overnight at room temperature. Then the mixture was poured into ice and water (25 m*l*), and the resulting colorless needles were collected by filtration: yield 124 mg (92%), mp 102—103°C. Recrystallization from ethanol afforded colorless prisms, which showed the same melting point.

Found: C, 59.25; H, 7.02%. Calcd for $C_{16}H_{22}O_7$: C, 58.88; H, 6.80%.

*1,2-Anhydro-5,6-*O*-cyclohexylidene-3,4-*O*-toluenesulfonyl-*chiro-inositol (**10c**).* To a solution of **10a** (100 mg) in dry pyridine (2 m*l*) was added *p*-toluenesulfonyl chloride (0.24 g, 3 molar equivalent) and the mixture was kept at room temperature for 2 days. Tlc indicated two main components, probably two mono-*p*-toluenesulfonates, together with **10a**.

Then an additional portion of *p*-toluenesulfonyl chloride (470 mg, 6 molar equivalent) in dry pyridine (2 m*l*) was added to the mixture and the solution was kept at 25°C for 3 days. Then the reaction mixture was poured into ice and water and the resulting oily product was extracted with chloroform several times. The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to give an oily residue which crystallized upon addition of chloroform–ethanol to afford colorless crystals, (90 mg, 40%) of **10c**, mp 110—111°C. Recrystallization from the same solvent gave an analytical sample, mp 115—117°C. PMR ($CDCl_3$): τ 7.55 (6-protons s, 2 OTs), 6.66 (2-protons s, H-1,2), 5.98 (1-proton t, $J_{4,5}=J_{5,6}=6.0$ Hz, H-5), 5.33 (2-protons d, $J_{2,3}=J_{1,6}=0$ Hz, $J_{3,4}=6.0$ Hz, H-3,6), and 5.16 (1-proton t, H-4).

Found: C, 56.60; H, 5.37; S, 11.78%. Calcd for $C_{26}H_{30}O_9S_2$: C, 56.70; H, 5.49; S, 11.64%.

1,2: 5,6-Dianhydro-3,4-O-cyclohexylidene-allo-*inositol (11).* (a) To a solution of 1,2-*O*-cyclohexylidene-3,6-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**2**)[6] (2.0 g) in methanol (40 m*l*) was added methanolic sodium methoxide (7.3 m*l*, 2 molar equivalent) and the reaction mixture was kept overnight at room temperature. The residue remaining on evaporation of the solvent was extracted several times with ethyl acetate, and the combined extracts were evaporated to give a crystalline product. The crystals were digested with methanol and collected by filtration: yield 0.70 g (87%), mp 142—144°C. Recrystallization from chloroform–ethanol gave an analytical sample, mp 143—144°C.

Found: C, 64.64; H, 7.46%. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.19%.

(b) Treatment of 4-*O*-acetyl-1-*O*-benzoyl-2,3-*O*-cyclohexylidene-5,6-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**6**)[10] (146 mg) with methanolic sodium methoxide (1.1 m*l*, 5 molar equivalent) in a mixture of chloroform (3 m*l*) and methanol (2 m*l*) similarly as described above afforded colorless plates (32 mg, 69%) of **11**, mp 141.5—143.5°C.

*1,2-Anhydro-5,6-*O-*cyclohexylidene-4-*O-p-*toluenesulfonyl-*neo-*inositol (12a).* To a solution of 1,2-*O*-cyclohexylidene-3,5-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**3**)[6] (0.20 g) in a mixture of chloroform (10 m*l*) and methanol (2 m*l*) was added methanolic sodium methoxide (1.1 m*l*, 3 molar equivalent) and the reaction mixture was kept overnight at room temperature. Then the mixture was processed similarly as described under the preparation of **11** to give the oily product, which crystallized upon addition of methanol. The crystals were digested with petroleum ether and collected by filtration: colorless needles, yield 0.11 g (76%), mp 142—144°C. An analytical sample was obtained by recrystallization from chloroform–ethanol: colorless prisms, mp 154—155°C.

Found: C, 57.75; H, 5.99; S, 8.38%. Calcd for $C_{19}H_{24}O_7S$: C, 57.55; H, 6.10; S, 8.09%.

*3-*O-*Acetyl-1,2-anhydro-5,6-*O-*cyclohexylidene-4-*O-p-*toluenesulfonyl-*neo-*inositol (12b).* Compound **12a** (62 mg) was acetylated with acetic anhydride (1 m*l*) and pyridine (2 m*l*) overnight at room temperature. The reaction mixture was then poured into ice and water and the precipitates were collected by filtration. Recrystallization from chloroform–ethanol gave colorless rods (58 mg, 85%) of **12a**, mp 149—150°C. PMR ($CDCl_3$): τ 8.14 (3-protons s, OAc), 7.53 (3-protons s, OTs), 6.82 and 6.55 (1-proton d, $J_{1,2}=4.0$ Hz, H-1 and H-2), 5.48 (2-protons m, H-5,6), 5.17 (1-proton dd, $J_{3,4}=9.0$ Hz, $J_{4,5}=2.0$ Hz, H-4), and 4.43 (1-proton dd, $J_{2,3}=1.5$ Hz, H-3).

Found: C, 57.53; H, 5.86; S, 7.44%. Calcd for $C_{21}H_{26}O_8S$: C, 57.50; H, 5.98; S, 7.31%.

*1,2-Anhydro-5,6-*O-*cyclohexylidene-3,4-di-*O-p-*toluenesulfonyl-*neo-*inositol (12c).* Compound **12a** (51 mg) in dry pyridine (2 m*l*) was treated with *p*-toluenesulfonyl chloride (74 mg, 3 molar equivalent) at room temperature for 3 days and then at 80—85°C for 10 min. The reaction mixture was poured into water (50 m*l*) and extracted with chloroform (20 m*l*) several times. The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to give an oily product. Tlc showed a main component together with several minor ones. Then the crude product was chromatographed on a column of silica gel (Wakogel C-200, 20 g) and eluted with methyl ethyl ketone–toluene (1:4). The main fractions were combined and evaporated to give a crystalline residue. Crystallization from chloroform–ethanol gave colorless prisms (48 mg, 47%) of **12c**, mp 168—168.5°C. PMR ($CDCl_3$): τ 7.55 (6-protons s, 2 OTs), 6.85 and 6.45 (1-proton dd, $J_{1,2}=4.0$ Hz, H-1 and H-2), 5.53 (2-protons s, H-5,6), 5.26 (1-proton dd, $J_{3,4}=9.0$ Hz, $J_{4,5}=1.5$ Hz, S-4), and 4.78 (1-proton dd, $J_{2,3}=1.5$ Hz, H-3).

Found: C, 56.66; H, 5.38; S, 11.71%. Calcd for $C_{26}H_{30}O_9S_2$: C, 56.70; H, 5.49; S, 11.64%.

*1,2: 3,4-Dianhydro-5,6-*O-*cyclohexylidene*-allo-*inositol (13).* To a solution of **3** (0.50 g) in 2-methoxyethanol (30 m*l*) was added methanolic sodium methoxide (2.7 m*l*, 3 molar equivalent) and the mixture was refluxed for 10 min. Monitoring the reaction by tlc, it was found that **12a**, as well as **3**, completely disappeared and **13** formed gradually underwent nucleophilic attack of methoxide ion to give rise to the slower moving component, probably a monomethyl ether. The brown reaction mixture was evaporated to dryness and the residue was extracted with ethyl acetate. Evaporation of the extracts gave a crystalline product which was chromatographed on a silica gel (20 g) and eluted with methyl ethyl ketone–toluene (1:4). The fractions containing the faster moving component were combined and evaporated to give colorless plates (56 mg, 28%) of **13**, mp 104—110°C. Recrystallization from ethyl acetate afforded an analytical sample, mp 111.5—112.5°C.

Found: C, 64.27; H, 6.95%. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.19%.

*1,4-Anhydro-5,6-*O-*cyclohexylidene-2-*O-p-*toluenesulfonyl-*chiro-*inositol (14a).* (a) To a solution of 1,2-*O*-cyclohexylidene-3,4-*O*-*p*-toluenesulfonyl-*myo*-inositol (**4**)[6] (100 mg) in a mixture of chloroform (3 m*l*) and methanol (4 m*l*) was added methanolic sodium methoxide (0.36 m*l*, 2 molar equivalent) and the reaction mixture was kept overnight at room temperature. The mixture was processed similarly as described under the preparation of **11** to give an oily product which crystallized upon addition of ethanol to give colorless prisms (47 mg, 67%) of **14a**, mp 114—115°C. Recrystallization from ethanol afforded an analytical sample. The melting point did not change. PMR ($CDCl_3$): τ 7.53 (3-protons s, OTs).

Found: C, 57.57; H, 6.23; S, 8.07%. Calcd for $C_{19}H_{24}O_7S$: C, 57.30; H, 6.06; S, 8.08%.

(b) A mixture of **4** (1.08 g), sodium azide (1.09 g) and 90% aqueous 2-methoxyethanol (20 m*l*) was refluxed for 20 hr. Then the reaction mixture was evaporated to dryness and dried by repeated co-distillation with toluene. The residue was extracted with hot ethyl acetate and the extracts were evaporated to give colorless crystals (0.55 g, 73%) of **14a**, mp 114—116°C. This compound was identified with the product obtained in (a) by IR and PMR spectral comparison.

Compound **14a** was acetylated with acetic anhydride and pyridine in the usual way to give the oily acetate (**14b**). Tlc indicated a single spot in methyl ethyl ketone–toluene (1:4). PMR ($CDCl_3$): τ 8.08 (3-protons s, OAc) and 7.55 (3-protons s, OTs).

3,5,6-Tri-O-acetyl-1,4-anhydro-2-O-p-toluenesulfonyl-chiro-inositol (**15**). Compound **14a** (0.21 g) was refluxed with 80% aqueous acetic acid (10 ml) for 3 hr. The reaction mixture was evaporated to dryness and the residue was treated with acetic anhydride (5 ml) and pyridine (5 ml) overnight at room temperature. Then the mixture was evaporated with toluene to give a yellow oil, which was dissolved in ethyl acetate and chromatographed on a column of aluminum oxide (5 g). The eluate was evaporated to give a oily product which crystallized by trituration with ethanol: colorless crystals, yield 0.16 g (69%), mp 124.5—125.5°C. An analytical sample was obtained by recrystallization from ethanol, mp 125—126°C. PMR ($CDCl_3$): τ 7.98 (6-protons s, 2 OAc), 7.86 (3-protons s, OAc) and 7.53 (3-protons s, OTs).

Found: C, 51.51; H, 5.14; S, 7.52%. Calcd for $C_{19}H_{22}O_{10}S$: C, 51.60; H, 4.98; S, 7.24%.

1,2: 3,4-Dianhydro-5,6-O-cyclohexylidene-cis-inositol (**16**). To a solution of 1-*O*-benzoyl-2,3-*O*-cyclohexylidene-4,6-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**5**)[10] (0.30 g) in a mixture of methanol (4 ml) and methyl ethyl ketone (6 ml) was added methanolic sodium methoxide (1.6 ml, 3.5 molar equivalent) and the mixture was kept overnight at room temperature. Then the reaction mixture was processed similarly as described under the preparation of **11** to give an oily product. Tlc indicated two main components. The crude mixture was then chromatographed on a column of silica gel (20 g) and eluted with methyl ethyl ketone–toluene (1:3). The fractions containing the slower moving component were combined and evaporated to give colorless plates (19 mg, 19%) mp 129—131°C. An analytical sample was obtained by recrystallization from ethyl acetate–petroleum ether, mp 130—131°C.

Found: C, 64.04; H, 7.29%. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.19%.

2,3-Anhydro-4,5-O-cyclohexylidene-6-O-methyl-epi-inositol (**17**). (a) To a solution of **5** (0.30 g) in a mixture of methanol (4 ml) and methyl ethyl ketone (6 ml) was added methanolic sodium methoxide (1.6 ml, 3.5 molar equivalent) and the solution was kept overnight at room temperature. Then an additional amount of methanolic sodium methoxide (1.6 ml) was added and, after 24 hr, the mixture was evaporated to dryness and the residue was processed similarly as described under the preparation of **11** to give crude crystals (66 mg, 48%). It was recrystallized from ethyl acetate–petroleum ether to afford colorless needles (48 mg) of **17**, mp 96—98°C. PMR ($CDCl_3$): τ 6.51 (2-protons m, H-2,3), 6.45 (3-protons s, OCH_3), and 6.10 (2-protons broad s, H-4,5).

Found: C, 61.16; H, 7.52%. Calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.87%.

(b) Compound **5** (0.40 g) was dissolved in a mixture of chloroform (8 ml) and methanol (4 ml) and methanolic sodium methoxide (1.12 ml, 3.5 molar equivalent) was added. The mixture was kept at room temperature for 17 days and then processed similarly as described in (a) to give colorless crystals (40 mg, 20%) of **17**.

1,2-Anhydro-4,5-O-cyclohexylidene-3,6-di-O-p-toluenesulfonyl-neo-inositol (**18**). To a solution of 1,2-*O*-cyclohexylidene-3,5,6-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol (**7**)[6] (0.20 g) in a mixture of chloroform (4 ml) and methanol (2 ml) was added methanolic sodium methoxide (0.56 ml, 2 molar equivalent) and the reaction mixture was kept at room temperature for 1 hr. Then the mixture was processed similarly as described under the preparation of **11** to give crude crystals. It was digested with methanol and collected by filtration: colorless needles, yield 91 mg (60%), mp 190—191°C. Recrystallization from chloroform–ethanol gave an analytical sample. The melting point did not change. PMR ($CDCl_3$); τ 7.57 (6-protons s, 2 OTs).

Found: C, 56.48; H, 5.39; S, 11.31%. Calcd for $C_{26}H_{30}O_9S_2$: C, 56.70; H, 5.49; S, 11.64%.

1,2-Anhydro-3,4-O-cyclohexylidene-5,6-di-O-p-toluenesulfonyl-epi-inositol (**19**). To a solution of 1,2-*O*-cyclohexylidene-3,4,6-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol (**8**)[6] (0.10 g) in a mixture of chloroform (2 ml) and methanol (1 ml) was added methanolic sodium methoxide (0.14 ml, 1 molar equivalent) and the mixture was kept overnight at room temperature. Then the reaction mixture was processed similarly as described under the preparation of **11**. The crude crystals was recrystallized from chloroform–methanol to give colorless needles (64 mg, 84%) of **19**, mp 184—184.5°C. Recrystallization from the same solvent gave an analytical sample. PMR ($CDCl_3$): τ 7.53 (6-protons s, 2 OTs), 6.76 (1-proton t, $J_{1,2}$= 3.5 Hz, $J_{2,3}$=4.0 Hz, H-2), 6.61 (1-proton d, $J_{1,6}$=0 Hz, H-1), 5.34 (1-proton dd, $J_{4,5}$=3.0 Hz, $J_{5,6}$=8.0 Hz, H-5), and 5.08 (1-proton d, H-6).

Found: C, 57.07; H, 5.83; S, 11.37%. Cacld for $C_{26}H_{30}O_9S_2$: C, 56.70; H, 5.49; S, 11.64%.

2,3-Anhydro-4,5-O-cyclohexylidene-1,6-di-O-p-toluenesulfonyl-epi-inositol (**20**). To a solution of 1-*O*-benzoyl-2,3-*O*-cyclohexylidene-4,5,6-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol (**9**)[10] (0.35 g) in a mixture of chloroform (5 ml) and methanol (5 ml) was added methanolic sodium methoxide (1.1 ml, 3 molar equivalent) and the mixture was kept at room temperature. After 15 min, colorless needles were crystallized out from the solution and the crystals were collected by filtration: yield 0.19 g (82%), mp 215.5—216°C. An analytical sample was obtained by recrystallization from chloroform–ethanol. The melting point did not change. PMR ($CDCl_3$): τ 7.56 and 7.53 (3-protons s, OTs), 6.52 (1-proton dd, $J_{2,3}$=4.0 Hz, $J_{3,4}$=2.5 Hz, H-3), 6.27 (1-proton d, $J_{1,2}$=0 Hz, H-2), and 5.40 (1-proton dd, $J_{4,5}$=7.0 Hz, H-4). (DMSO-d_6): τ 6.45 (2-protons m, H-2,3), 5.90 (1-proton t, $J_{4,5}$=$J_{5,6}$=7.5 Hz, H-5), 5.37 (1-proton dd, $J_{3,4}$=2.5 Hz, H-4), 5.33 (1-proton dd, $J_{1,6}$=9.5 Hz, H-6), and 4.79 (1-proton d, $J_{1,2}$=0 Hz, H-1).

Found: C, 56.36; H, 5.26; S, 11.50%. Calcd for $C_{26}H_{30}O_9S_2$: C, 56.70; H, 5.49; S, 11.64%.

The authors are grateful to Professor Sumio Umezawa for his kind advice, to Mr. Saburo Nakada for his elementary analyses, and to Mr. Tsunehisa Ueda for his preparative experiment. The financial support from the Ministry of Education for this work is gratefully acknowledged.