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p-Toluenesulfonylation of 1,2-*O*-Cyclohexylidene-*myo*-inositol[1]

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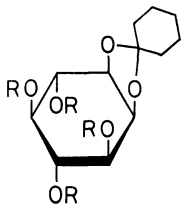
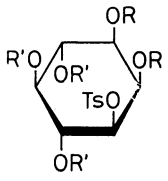
p-Toluenesulfonylation of 1,2-*O*-cyclohexylidene-*myo*-inositol (**1a**) afforded one mono (1), three di (1,4, 1,5, and 1,6), three tri (1,4,5, 1,4,6, and 1,5,6), and one tetra (1,4,5,6)-*O*-*p*-toluenesulfonyl derivatives of *myo*-inositol, and all the structures have been established by way of their proton magnetic resonance (PMR) spectra and the reaction sequences.

The sulfonate esters of carbohydrates are useful precursors for a wide variety of their derivatives.[2a,b] Therefore, selective sulfonylation at hydroxyl groups of sugars has been extensively studied.[2b] On the other hand, little information is, so far, known about the reactivities of the hydroxyl groups of cyclitols toward sulfonylation. Thus it seemed of interest to investigate a sulfonylation of inositols. In the present paper, we wish to report the *p*-toluenesulfonylation of 1,2-*O*-cyclohexylidene-*myo*-inositol (**1a**).[3]



1

a: R=H
b: R=Ac

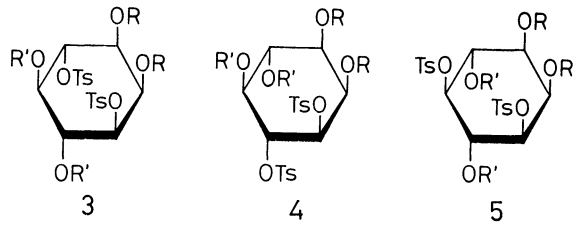


2

a: R=cyclohexylidene, R′=H
b: R=cyclohexylidene, R′=Ac
c: R=R′=H
d: R=R′=Ac

When **1a** was treated with 2 equivalents of *p*-toluenesulfonyl chloride in dry pyridine at 0—5°C for 24 hr and then at room temperature for 6 days, almost exclusively one isomer of the mono sulfonyl derivative (**2a**) was obtained in 41% yield. Acetylation of **2a** with acetic anhydride and pyridine gave tri-*O*-acetyl derivative (**2b**). Removal of cyclohexylidene group by refluxing of **2a** in 80% aqueous acetic acid afforded 1-*O*-*p*-toluenenesulfonyl-*myo*-inositol (**2c**),[4] and further acetylation of **2c** gave 1,2,4,5,6-penta-*O*-acetyl-3-*O*-*p*-toluenesulfonyl-*myo*-inositol (**2d**), which was identified with anauthentic sample.[5] Consequently, **2a** was assigned to1, 2-*O*-cyclohexylidene-3-*O*-*p*-toluenesulfonyl-*myo*-inositol. Although the same reaction was carried out with 1.5 or 3 equivalents of *p*-toluenesulfonyl chloride, **2a** was obtained in 39 or 36% yield, respectively. These results indicated that the hydroxyl group on C-3 was the most reactive one among four hydroxyl groups in **1a**, and were in accordance with the observed facilitation of acylation or sulfonylation by neighboring oxygen atoms in a cis position.[3] Other instance of this effect is the preferential *p*-toluenesulfonylation of 1,2:3,4-di-*O*-isopropylidene-*epi*-inositol in the 5-position.[6]

Then an isolation of the di-*O*-*p*-toluenesulfonyl esters was attempted. Compound **1a** was treated with



3 4 5

	R	R′
a:	cyclohexylidene	H
b:	cyclohexylidene	Ac
c:	H	H
d:	Ac	Ac

1) A part of this work was presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970 (See Abstracts of Papers of the Meeting, Vol. III, p. 1903).

2) a) R. S. Tipson, *Advan. Carbohyd. Chem.*, **8**, 107 (1953); b) D. H. Ball and F. W. Parrish, *ibid.*, **23**, 233 (1968); **24**, 139 (1969).

3) S. J. Angyal, M. E. Tate, and S. D. Gero, *J. Chem. Soc.*, **1961**, 4116.

4) S. J. Angyal, V. Bender, and J. H. Curtin, *J. Chem. Soc. (C)*, **1966**, 798.

5) S. J. Angyal, P. T. Gilham, and G. J. H. Melrose, *J. Chem. Soc.*, **1965**, 5252.

6) S. J. Angyal and P. T. Gilham, *ibid.*, **1957**, 3691.

2 equivalents of *p*-toluenesulfonyl chloride similarly a described before. After **2a** was obtained in 33% yield, its mother liquor was, then, subjected to a fractional crystallization to give a crystalline mixture of three di-esters in 41% yield. Further fractionations by a column chromatography using silica gel and recrystallization afforded chromatographically homogeneous three isomers of the di-esters (**3a**, **4a**, and **5a**). In another run, after isolating **2a** in 22% yield, the mixture was fractionated to give practically pure **3a**, **4a**, and **5a** in 20, 16 and 2.6% yield, respectively. Acetylation of **3a**, **4a**, and **5a** with acetic anhydride and pyridine gave the di-*O*-acetyl derivatives (**3b**), (**4b**), and (**5b**). Three isomers, (**3c**), (**4c**), and (**5c**), of di-*O*-*p*-toluenesulfonyl-*myo*-inositol were obtained by removal of cyclohexylidene group from **3b**, **4b**, and **5b**. On acetylation, **3c**, **4c**, and **5c** afforded tetra-*O*-acetyl derivatives (**3d**), (**4d**), and (**5d**), respectively.

In order to establish a configuration of the di-*O*-*p*-toluenesulfonyl derivatives, **2a** was further sulfonylated. When a course of the reaction with 1.5 equivalent of *p*-toluenesulfonyl chloride upon **2a**, as well as 2 equivalent upon **1a**, were monitored by a thin layer chromatography (TLC), both chromatograms were shown to be almost identical, except some traces of minor components. These results indicated that the three di-esters obtained must be derived from **2a**, and, accordingly, they should be either the 3,4-, 3,5- or 3,6-disulfonyl derivative. Also periodate oxidation was applied to an elucidation of the position of the sulfonyloxy groups in the di-esters. Compound **4a** was observed to react with periodate solution, however, neither **3a** nor **5a** would consume the reagent. So it might have been considered that the conformational rigidity of 1,2-*O*-cyclohexylidene-3,4 (or 3,6)-di-*O*-*p*-toluenesulfonyl-*myo*-inositol prevented a formation of the five membered periodate ester.[7]

Partial PMR spectrum of 3,4,5,6-tetra-*O*-acetyl-1,2-*O*-cyclohexylidene-*myo*-inositol (**1b**), as a reference compound, was shown in Fig. 1. The signals for the protons on C-1 and C-2, to which the cyclohexylidene group attached, are well upshifted and are separated

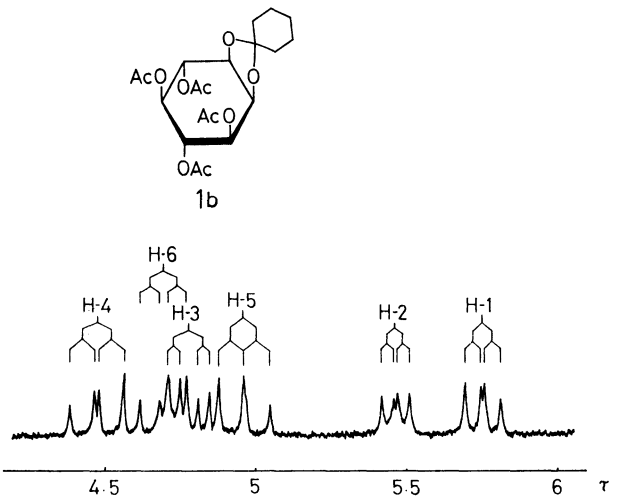


Fig. 1. Partial PMR spectrum of 3,4,5,6-tetra-*O*-acetyl-1,2-*O*-cyclohexylidene-*myo*-inositol (**1b**) (100 MHz, $CDCl_3$).

7) J. Corse and R. E. Lundin, *J. Org. Chem.*, **35**, 1904 (1970).

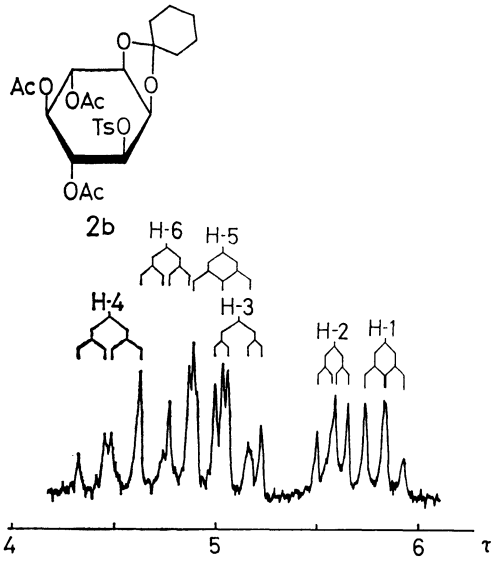


Fig. 2. Partial PMR spectrum of 4,5,6-tri- *O*-acetyl-1,2-*O*-cyclohexylidene-3-*O*-*p*-toluenesulfonyl-*myo*-inositol (**2b**) (60 MHz, $CDCl_3$).

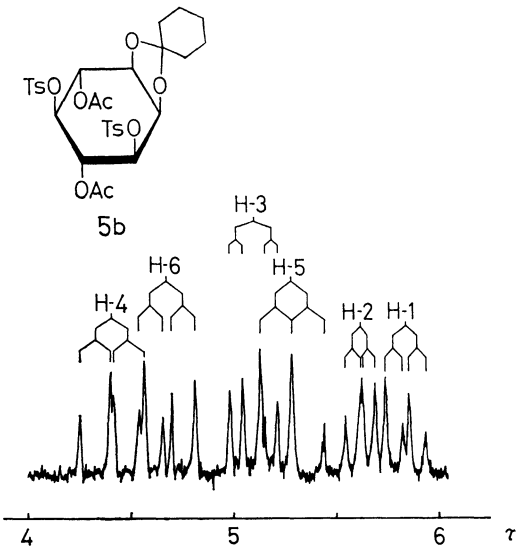


Fig. 3. Partial PMR spectrum of 4,6-di-*O*-acetyl-1,2-*O*-cyclohexylidene-3,5-di-*O*-p-toluenesulfonyl-*myo*-inositol (**5b**) (60 MHz, $CDCl_3$).

from those of the protons on the remaining carbon atoms. This simplified the assignment of signals. If it is assumed that the signal for H-1 (pseudoaxial) appears higher than that for H-2 (pseudoequatorial), all remaining signals could be adequately resolved by first-order method and assigned unambiguously to each proton, as listed in Tables 1 and 2. This assignment was further supported by the PMR spectrum of **2b** (Fig. 2). The spectral pattern is similar to that of **1b**, except that the signal for the H-3 proton is upshifted by 0.32 ppm. This can be easily understood by the fact that, in the case of **1b**, the acetoxy group on C-3 is substituted by a *p*-toluensulfonyloxy group. In the well resolved PMR spectrum of **5b** (Fig. 3), both signals for the H-3 and H-5 protons are upshifted by 0.32 ppm, comparing with those in the spectrum of **1b**. By analogy, these results might suggest that two

p-toluenesulfonyloxy groups are located at C-3 and C-5. While, in the PMR spectrum of **3b**, the quartet for the H-4 proton appears at τ 4.50, and this means that the *p*-toluenesulfonyloxy group is not located at C-4. Therefore, according to the observations of periodate oxidation and PMR spectra, **3a**, **4a**, and **5a** could be assigned to 1,2-*O*-cyclohexylidene-3,6-, 3,4- and 3,5-di-*O*-*p*-toluenesulfonyl-*myo*-inositol, respectively.

Table 1. Chemical shifts of methine protons[a)]

Compound	Chemical shifts (τ)					
	H-1	H-2	H-3	H-4	H-5	H-6
1b[b)]	5.75 q	5.46 q	4.78 q	4.47 q	4.96 t	4.69 q
2b	5.80 t	5.55 q	5.10 q	4.47 q	5.00 t	4.73 q
3b	5.84 t	5.59 q	5.14 q	4.50 q		
5b	5.83 q	5.61 t	5.10 q	4.41 t	5.28 t	4.67 q
5d	4.98 q	4.42 t	5.21 q	4.45 t	5.13 t	4.41 t
7b	5.81 t	5.59 q	5.21 q	4.54 q		

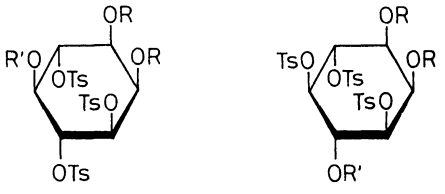
a) Measured at 60 MHz in $CDCl_3$, unless otherwise stated.
b) Measured at 100 MHz in $CDCl_3$. This compound should be named 1,4,5,6-tetra-*O*-acetyl-2,3-*O*-cyclohexylidene-*myo*-inositol, but it is not convenient for discussing the PMR spectrum.

Table 2. First-order coupling constants of methine protons

Compound	coupling constants (Hz)					
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,1}$
1b	5.5	3.8	9.9	8.3	8.9	6.6
2b	5.5	4.0	10.0	8.0	8.0	6.5
3b	5.5	3.5	9.5	8.0		6.5
5b	5.0	3.5	10.0	9.0	9.0	7.0
5d	2.7	3.0	10.5	9.5	9.5	10.5
7b	6.0	3.2	10.0	6.0		5.0

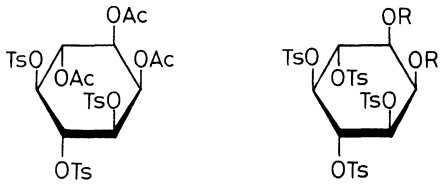
It is interesting to note that the coupling constants between H-1 and H-2 are of the order of 5.0—5.5 Hz, indicating the angle between the bridgehead hydrogen atoms of a cyclohexylidene ring of approximately 35—40° on the basis of Karplus equation.[8)] Judging from the other coupling constants observed, the six-membered ring was only slightly flattened from the chair conformation by the introduction of 1,2-*O*-cyclohexylidene group into *myo*-inositol derivatives.

When a reaction mixture of **1a** and 7 equivalents of *p*-toluenesulfonyl chloride in dry pyridine was kept at room temperature until its TLC indicated an absence of the di-esters, two tri-esters (**6a** and **7a**) were obtained in a pure state by fractional crystallizations in 28 and 6% yield, respectively. The TLC of its mother liquor showed a presence of considerable amount of the tetra-ester. On acetylation, **6a** and **7a** gave di-*O*-acetyl derivatives (**6b**) and (**7b**). On acid hydrolysis with aqueous acetic acid, **6a** and **7a** gave two isomers, (**6c**) and (**7c**), of tri-*O*-*p*-toluenesulfonyl-*myo*-inositol, which, on acetylation, afforded tri-*O*-acetyl derivatives (**6d**) and (**7d**), respectively. In another run, after **6a** was crystallized out in 24% yield, the mother liquor was evaporated and the residue was subjected to an acid hydrolysis with aqueous acetic acid. From the hydrolyzate, 1,4,5,6-tetra-*O*-*p*-toluenesulfonyl-*myo*-inositol (**9a**) was recovered in 21% yield, which was converted into di-*O*-acetyl derivative (**9b**). Then the mother liquor was evaporated and the residual oil was treated with a mixture of acetic anhydride and pyridine to afford, in addition to **7d** (5%), hitherto unknown tri-*O*-acetyl-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol (**8**) in 11% yield.



6 7

	R	R'
a :	cyclohexylidene	H
b :	cyclohexylidene	Ac
c :	H	H
d :	Ac	Ac



8 9

a : R=H
b : R=Ac

Now, sulfonylation of the three isomers of di-*O*-*p*-toluenesulfonyl derivative, **3a**, **4a**, and **5a**, were attempted for the purpose of obtaining informations on a position of sulfonyloxy groups in the tri-esters. By the TLC studies of sulfonylation products of the di-esters, it is apparent that both **6a** and **7a** were derived from **3a**, while, **6a** and **7a** were formed from **4a** and **5a**, respectively. In addition to each major component, an unidentified minor component was found in the reaction mixtures of **4a** and **5a**. Accordingly, **6a** and **7a** should be 1,2-*O*-cyclohexylidene-3,4,6- and -3,5,6-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol, respectively, while, the unidentified compound might be considered to be the 3,4,5-tri-ester. These structural assignments were also confirmed by PMR spectra, and the nucleophilic displacement reaction with an azide ion, which will be described later.

The PMR spectrum of **7b** reveals a quartet at τ 4.54, which is assigned to the signal for H-4 proton. Therefore the acetoxy group is located at C-4 in **7b** and **7b** must be the 3,5,6-tri-ester. On the other hand, the absence of a quartet in a lower field in the PMR spectrum of **6b** indicated that the sulfonyloxy group is in C-4 position, and ascertained the structural assignment of **6b**.

Theoretically, four tri-esters can be derived from **1a**: the 3,4,5-, 3,4,6-, 3,5,6-, and 4,5,6-esters. So that the unidentified tri-ester (**8**) must be either the 3,4,5-

8) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

TABLE 3. CHEMICAL SHIFTS OF ACETYL METHYL PROTONS[a]

Compound	Chemical Shifts (τ)			
1b	7.99	7.98	7.92	7.88
2b	8.10	8.01	7.93	
2d	8.07	8.01	7.99[b]	7.86
3b	8.14	8.01		
3d	8.16	8.13	8.10	7.86
4b	8.05	7.99		
4d	8.06	8.01	7.98	7.86
5b	8.22	8.04		
5d	8.17	8.05	8.03	7.90
6b	8.07			
6d	8.17	8.06	7.83	
7b	8.26			
7d	8.27	8.20	7.90	
8	8.08	8.02	7.92	
9b	8.22	7.98		

a) Measured at 60 MHz in $CDCl_3$.
b) Signal of two acetyl methyl protons.

or 4,5,6-tri-ester. Had **8** been the 4,5,6-tri-ester, two acetoxy groups on C-1 and C-3 should be spectroscopically equivalent and their signals should appear as one singlet. However, **8** shows three peaks at τ 8 region: τ 7.92, 8.02 and 8.08 (Table 3). Therefore, **8** should be 1,2,6-tri-*O*-acetyl-3,4,5-*O*-*p*-toluenesulfonyl-*myo*-inositol.

The remarkable facilitation of sulfonylation have not been observed among the hydroxyl groups of **1a** other than that on C-3. Some differences in the relative proportions of the isomeric sulfonyl esters obtained are seemed to be explained by a steric and an electronic effects on a hydroxyl group toward sulfonylation.

Experimental

Melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. Infrared (IR) spectra were taken in KBr disks. PMR spectra were measured on a Varian Associate A-60D (60 MHz) or HA-100D (100 MHz) spectrometer at a concentration of *ca.* 10% deuteriochloroform with tetramethylsilane as an internal standard. Chemical shifts are expressed in τ-values and signals are described as s (singlet), t (triplet), q (quartet), or m (complex multiplet). Values given for coupling constants are first-order. Thin layer chromatography (TLC) was done with silica gel (Wako-gel B-10, Wako pure chemical industries Ltd.) using toluene-methyl ethyl ketone (4 : 1 or 3 : 1 volume) as the solvent system. The compounds were detected by exposing the plates to iodine vapor; the relative proportions of the compounds were estimated visually. All solutions were concentrated by a rotary evaporator at 40—50°C under reduced pressure. Whenever pyridine was employed in a reaction, the residual pyridine was removed by repeated codistillation with dry toluene.

1,2-O-*Cyclohexylidene*-myo-*inositol* (***1a***). This compound was prepared from *myo*-inositol following the method of Angyal and his coworkers[3] and purified by recrystallization two times from ethanol, mp 178—179°C (lit,[3] 179°C).

3,4,5,6-Tetra-O-*acetyl-1,2*-O-*cyclohexylidene*-myo-*inositol* (***1b***). This compound was prepared from **1a** following the method of Angyal and his coworkers,[3] mp 117—118°C (lit,[3] 118°C).

1,2-O-*Cyclohexylidene-3*-O-p-*toluenesulfonyl*-myo-*inositol* (***2a***). A solution of **1a** (5.2 g) in dry pyridine (80 m*l*) was externally cooled to 0—5°C. *p*-Toluenesulfonyl chloride (7.6 g, 2.0 equiv.) was added in one portion and dissolved under stirring, and the temperature was maintained below 5°C for 24 hr. Then the reaction mixture was stored at room temperature (15—20°C) for 6 days. The mixture was, then, poured onto ice and water (500 m*l*), and, after 24 hr at room temperature, the resulting gum was collected by decantation. The crude product was dissolved in chloroform (150 m*l*) and washed with N hydrochloric acid, 10% aqueous sodium carbonate and water successively. After drying over anhydrous sodium sulfate, the solution was evaporated to yield a semisolid, which was recrystallized from ethanol to give colorless needles (3.4 g, 41%) of **2a**, mp 225—227°C (dec.). Two recrystallization from methanol afforded an analytical sample, mp 229—230.5°C (dec.).

Found: C, 54.80; H, 6.39; S, 7.41%. Calcd for $C_{19}H_{26}O_8S$: C, 55.06; H, 6.32; S, 7.74%.

Although TLC showed the presence of considerable amounts of di- and tri-esters in the mother liquor of **2a**, further isolation was not attempted in this experiment.

In another run, the sulfonylation was carried out with 1.5 equiv. of *p*-toluenesulfonyl chloride, and the reaction mixture was kept at 0—5°C for 3 days, followed by 2 days at room temperature. The yield of **2a** was 39%. When 3.0 equiv. of *p*-toluenesulfonyl chloride was used, the yield of **2a** was 36%.

4,5,6-Tri-O-*acetyl-1,2*-O-*cyclohexylidene-3*-O-p-*toluenesulfonyl*-myo-*inositol* (***2b***). Compound **2a** (0.20 g) was treated with a mixture of acetic anhydride (2 m*l*) and pyridine (2 m*l*) at room temperature overnight. Then the reaction mixture was poured onto ice and water (20 m*l*) and the resulting crystals were collected by filtration; yield 0.23 g (88%), mp 158—160.5°C. Two recrystallization from ethanol gave fine needles (0.20 g) of **2b**, which showed the same melting point. PMR: τ 7.54 (3, s, OTs C-CH_3).

Found: C, 55.78; H, 6.05; S, 5.74%. Calcd for $C_{25}H_{32}O_{11}S$: C, 55.54; H, 5.97; S, 5.93%.

1-O-p-*Toluenesulfonyl*-myo-*inositol* (***2c***). A mixture of **2a** (1.2 g) and 80% aqueous acetic acid (20 m*l*) was refluxed for 2 hr. After cooling, the resulting precipitates were collected by filtration, washed with ethanol and dried; yield 0.74 g (77%), mp 222.5—225°C (dec.). Recrystallization from acetic acid and water gave colorless needles of **2c**, which was identified with an authentic sample (lit,[4] mp 224°C) by a mixed melting point and comparing with IR spectra.

1,2,4,5,6-Penta-O-*acetyl-3*-O-p-*toluenesulfonyl*-myo-*inositol* (***2d***). Compound **2c** (0.10 g) was treated with a mixture of acetic anhydride (2 m*l*) and pyridine (2 m*l*) at room temperature overnight. Then the reaction mixture poured onto ice and water to give colorless crystals (0.15 g, 92%) of **2d**, mp 149.5—151°C. It was identified with an authentic sample (lit,[4] mp 151°C) by a mixed melting point and comparing with IR spectra.

1,2-O-*Cyclohexylidene-3,6-di*-O-p-*toluenesulfonyl*-myo-*inositol* (***3a***), *1,2*-O-*Cyclohexylidene-3,4-di*-O-p-*toluenesulfonyl*-myo-*inositol* (***4a***) *and* *1,2*-O-*Cyclohexylidene-3,5-di*-O-p-*toluenesulfonyl*-myo-*inositol* (***5a***). (a) A solution of **1a** (26.0 g) in dry pyridine (340 m*l*) was cooled to 0—5°C. *p*-Toluenesulfonyl chloride (38.0 g, 2.0 equiv.) was added in one portion and the solution was kept for 24 hr at 0—5°C, followed by 9 days at room temperature (15—20°C). Then the reaction mixture was poured onto ice and water (500 m*l*), and, after 2 days at room temperature, the water layer was separated from the resulting gum with decantation and extracted with chloroform

(2×200 ml). The extracts were washed with N hydrochloric acid, 10% aqueous sodium carbonate and water successively, and allowed to stand at room temperature overnight. The resulting crystals were collected and washed with ethanol; yield 13.9 g (33.4%), mp 225°C (dec.). Recrystallization from ethanol gave colorless needles (10.3 g, 24.7%) of **2a**, mp 229—230.5°C (dec.).

Then the gum (*ca.* 26 g) was dissolved in hot ethanol (150 ml) and kept at room temperature to give colorless crystals (10.4 g, 18.3%), which were shown to be a mixture of **3a** and **4a** by TLC. The mother liquor was evaporated and the residue was again dissolved in ethyl acetate (30 ml). Addition of benzene (60 ml) afforded the second crystals (8.45 g, 14.9%), which were composed of mainly **3a**. After 2 weeks, the third crystals (1.72 g, 3.0%) were obtained from the mother liquor and shown to be a mixture of **4a** and **5a** by TLC. Then the oily product which was obtained by evaporation of the filtrate was applied to the top of a column of silica gel (50 g, Wakogel C-200, Wako pure chemical industries Ltd.) packed in toluene-methyl ethyl ketone (5 : 1 volume). The column was eluted with the same solvent system, and the fractions were collected and combined according to the results of TLC. Evaporation of the eluates gave chromatographically pure crystals of **3a** (0.31 g), **4a** (0.53 g) and **5a** (0.78 g).

Further fractional crystallization of the first, second, and third crystals from methyl ethyl ketone and toluene gave **3a** (2.3 g), **4a** (3.6 g), and **5a** (0.9 g).

An analytical sample of **3a** was obtained by recrystallization from methyl ethyl ketone and toluene, and dried over phosphorus pentoxide *in vacuo* at 120°C; colorless granular crystals, mp 175—177.5°C.

Found: C, 55.05; H, 5.73; S, 11.41%. Calcd for $C_{26}H_{32}O_{10}S_2$: C, 54.91; H, 5.68; S, 11.28%.

Two recrystallization from methyl ethyl ketone and toluene afforded an analytical sample of **4a** as colorless cubic crystals, mp 173—175°C.

Found: C, 54.66; H, 5.63; S, 10.73%.

Recrystallization from methyl ethyl ketone and toluene gave an analytical sample of **5a** as colorless tiny needles, mp 182.5—184°C.

Found: C, 54.71; H, 5.65; S, 11.06%.

(b) Compound **1a** (26.0 g) was treated with *p*-toluenesulfonyl chloride (38.0 g) in dry pyridine (260 ml) similarly as described in (a). From the water layer, **2a** (9.3 g, 23%) was isolated. The gum was fractionally crystallized from ethyl acetate (45 ml) and benzene (100 ml) to give crystals (11.2 g, 19.6%) of **3a**, which were shown to be sufficiently pure for use in further synthetic experiment by TLC. The mother liquor was evaporated to give an oil which was crystallized from ethyl acetate and benzene to yield practically pure crystals (9.1 g, 16%) of **4a**, and, after long storage at room temperature, a crystalline mixture (8.5 g, 15%) of **3a**, **4a** and **5a** was obtained. Then the filtrate was evaporated and the resulting oil was subjected to a column chromatography similarly as described in (a). Four main components were obtained: a mixture of the tri-esters (0.59 g), **3a** (0.57 g), a mixture of **3a** and **4a** (2.92 g), and **5a** (0.43 g).

*Periodate Oxidation of **3a**, **4a**, and **5a**.* To a solution of 30 mg of 1,2-*O*-cyclohexylidene-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**3a**, **4a**, and **5a**) in 2 ml of methanol, a 1 ml portion of 50% aqueous methanolic solution of sodium metaperiodate (50 mg/ml) was added and the solution was kept for 2 days at room temperature in a dark place. The reaction mixture was analyzed directly by TLC. Judging from the results of TLC, both **3a** and **5a** did not react with periodate, and only **4a** was shown to react with periodate giving rise to another compound.

p-*Toluenesulfonylation of **2a**.* To a solution of **2a** (0.10 g) in dry pyridine (2 ml) was added *p*-toluenesulfonyl chloride (0.09 g, 1.5 equiv.) and the mixture was allowed to stand at room temperature for 4 days. The reaction mixture was analyzed directly by TLC. Monitoring by TLC, the chromatograms were found to be almost identical, except some traces of minor components, with that of the reaction mixture of **1a** and 2 equiv. of *p*-toluenesulfonyl chloride in pyridine prepared under the same condition. Even when an additional amount of *p*-toluenesulfonyl chloride was added to the mixture, both the chromatograms were identical, except some traces of minor components somewhat increased.

*4,5-Di-O-acetyl-1,2-O-cyclohexylidene-3,6-di-*O-p-*toluenesulfonyl*-myo-*inositol (**3b**).* Compound **3a** (0.20 g) was treated with a mixture of acetic anhydride (2 ml) and pyridine (3 ml) at 80°C for 1 hr. Then the reaction mixture was poured onto ice and water (10 ml) and the resulting precipitates were collected by filtration; yield 0.24 g (100%), mp 157—159°C. Two recrystallization from ethanol gave colorless needles (0.18 g, 78%) of **3b**, mp 158—160.5°C. PMR: τ 7.55 (6, s, OTs C–CH_3).

Found: C, 55.33; H, 5.39; S, 9.58%. Calcd for $C_{30}H_{36}O_{12}S_2$: C, 55.21; H, 5.56; S, 9.83%.

*5,6-Di-*O-*acetyl-1,2-*O-*cyclohexylidene-3,4-di-*O-p-*toluenesulfonyl*-myo-*inositol (**4b**).* Compound **4a** (0.45 g) was acetylated similarly as described under the preparation of **3b** to give crude crystals (0.45 g, 87%) of **4b**, mp 169—171.5°C. Two recrystallization from ethanol afforded colorless granular crystals (0.34 g, 66%), mp 170—170.5°C. PMR: τ 7.58 (6, s, OTs C–CH_3), 5.91 (1, t, H-1, J=5.5 Hz), 5.64 (1, q, H-2, J=3.5 and 5.5 Hz).

Found: C, 55.36; H, 5.66; S, 9.88%. Calcd for $C_{30}H_{36}O_{12}S_2$: C, 55.21; H, 5.56; S, 9.83%.

*4,6-Di-*O-*acetyl-1,2-*O-*cyclohexylidene-3,5-di-*O-p-*toluenesulfonyl*-myo-*inositol (**5b**).* Compound **5a** (0.13 g) was acetylated similarly as described under the preparation of **3b** to give crude crystals (0.15 g, 99%) of **5b**, mp 178.5—180°C. Two recrystallization from ethanol gave colorless needles (0.10 g, 67%), mp 166.5—168°C. Compound **5b** crystallized from ethanol in two allotropic forms: needles, mp 166.5—168°C, and rectangular plates, mp 179—180.5°C. PMR: τ 7.55 (6, s, OTs C–CH_3).

Found: C, 55.03; H, 5.61; S, 9.52%. Calcd for $C_{30}H_{36}O_{12}S_2$: C, 55.21; H, 5.56; S, 9.83%.

*1,4-Di-*O-p-*toluenesulfonyl*-myo-*inositol (**3c**).* A mixture of **3a** (0.20 g) and 80% aqueous acetic acid (10 ml) was refluxed for 2 hr. The reaction mixture was evaporated to give a crystalline residue, which was triturated with water and collected by filtration; yield 0.16 g (93%), mp 196—199°C. Recrystallization from acetic acid and water afforded colorless needles of **3c**, mp 198—200°C.

Found: C, 48.92; H, 5.02; S, 12.61%. Calcd for $C_{20}H_{24}O_{10}S_2$: C, 49.18; H, 4.95; S, 13.13%.

*1,6-Di-*O-p-*toluenesulfonyl*-myo-*inositol (**4c**).* A mixture of **4a** (0.25 g) and 80% aqueous acetic acid (10 ml) was refluxed for 2 hr. The reaction mixture was evaporated and the residue was dried by repeated codistillation with dry ethanol. Several attempts to crystallize amorphous glassy product of **4c** failed. Then it was dried over phosphorus pentoxide *in vacuo* at 110°C and analyzed; yield 0.22 g (76%), mp 155—160°C.

Found: C, 49.47; H, 5.41%. Calcd for $C_{20}H_{24}O_{10}S_2$: C, 49.18; H, 4.95%.

*1,5-Di-*O-p-*toluenesulfonyl*-myo-*inositol (**5c**).* Compound **5a** (0.29 g) was refluxed with 80% aqueous acetic acid (30 ml) for 2 hr. The reaction mixture was evaporated to dryness

and the residue was crystallized from ethanol to give colorless tiny needles (0.18 g, 71%) of **5c**, mp 211—212.5°C (dec.). Recrystallization from acetic acid and water afforded an analytical sample, mp 212—214°C (dec.).

Found: C, 48.99; H, 4.97; S, 12.85%. Calcd for $C_{20}H_{24}O_{10}S_2$: C, 49.18; H, 4.95; S, 13.13%.

*1,2,4,5-Tetra-O-acetyl-3,6-di-O-p-toluenesulfonyl-myo-inositol (**3d**).* Compound **3c** (0.24 g) was treated with a mixture of acetic anhydride (3 ml) and pyridine (4 ml) at 80°C for 1 hr. The the mixture was poured onto ice and water (20 ml) and the resulting precipitates were collected by filtration; yield 0.32 g (99%), mp 214—217°C. Recrystallization from chloroform and ethanol gave plates and needles (0.27 g, 84%) of **3d**, mp 216.5—217.5°C. PMR: τ 7.56 (6, s, OTs C–CH_3), 5.20 (1, q, H-3, J=3 and 10 Hz), 4.40 (1, t, H-2, J=*ca.* 3 Hz).

Found: C, 50.85; H, 5.13; S, 10.16%. Calcd for $C_{28}H_{32}O_{14}S_2$: C, 51.20; H, 4.91; S, 9.77%.

*1,2,5,6-Tetra-O-acetyl-3,4-di-O-p-toluenesulfonyl-myo-inositol (**4d**).* Crude **4c**, which was obtained from **4a** (1.01 g), was treated with a mixture of acetic anhydride (8 ml) and pyridine (10 ml) at room temperature overnight. Then the mixture was poured onto ice and water (20 ml) and the crystals were collected by filtration; yield 1.02 g (87%), mp 190—193°C. Recrystallization from ethyl acetate and ethanol gave colorless granular crystals of **4d**, mp 196—197.5°C. PMR: τ 7.54 (6, s, OTs C–CH_3), 5.40 (1, m, H-3), 5.07 (1, q, H-1, J=2.8 and 10 Hz).

Found: C, 51.07; H, 4.89; S, 9.64%. Calcd for $C_{28}H_{32}O_{14}S_2$: C, 51.20; H, 4.91; S, 9.77%.

*1,2,4,6-Tetra-O-acetyl-3,5-di-O-p-toluenesulfonyl-myo-inositol (**5d**).* Compound **5c** (47 mg) was treated with a mixture of acetic anhydride (0.5 ml) and pyridine (0.5 ml) at room temperature overnight. The mixture was poured onto ice and water and the resulting gum was crystallized from ethanol and water; yield 60 mg (95%), mp 160.5—162°C. Recrystallization from ethanol and water gave an analytical sample of **5d** as colorless needles, which showed the same melting point. PMR: τ 7.54 (6, s, OTs C–CH_3).

Found: C, 50.93; H, 4.88; S, 9.60%. Calcd for $C_{28}H_{32}O_{14}S_2$: C, 51.20; H, 4.91; S, 9.77%.

*1,2-O-Cyclohexylidene-3,4,6-tri-O-p-toluenesulfonyl-myo-inositol (**6a**) and 1,2-O-Cyclohexylidene-3,5,6-tri-O-p-toluenesulfonyl-myo-inositol (**7a**).* To a cooled solution of **1a** (26.0 g) in dry pyridine (380 ml), *p*-toluenesulfonyl chloride (133.5 g, 7.0 equiv.) was added in one portion, and the reaction mixture was stored at room temperature (10—15°C) for 10 days. Then any pyridine hydrochloride was removed by decantation and the solution was poured onto ice and water (1 *l*). After 2 days, the resulting gum was collected by filtration and dissolved in chloroform (300 ml). The chloroform solution was washed with N hydrochloric acid, 10% aqueous sodium carbonate, and water successively, and then, dried over anhydrous sodium sulfate. Then the solution was evaporated to yield a partly crystalline residue, which was triturated with chloroform and ethanol, and collected by filtration; yield 19.9 g (27.6%), mp 170—175°C. Recrystallization from chloroform and ethanol gave practically pure crystals (18.0 g) of **6a**, mp 173—177°C. An analytical sample was obtained by two recrystallizations from ethanol and dried over phosphorus pentoxide *in vacuo* at 120°C, mp 175—177.5°C.

Found: C, 54.93; H, 5.54; S, 12.70%. Calcd for $C_{33}H_{38}O_{12}S_3$: C, 54.83; H, 5.30; S, 13.30%.

From the mother liquor of **6a**, colorless plates were obtained after 1 week; yield 3.95 g (5.5%), mp 176—181°C. Two recrystallizations from chloroform and ethanol afforded an analytical sample of **7a** as colorless tiny plates, mp 183—184.5°C.

Found: C, 54.60; H, 5.27; S, 12.83%.

In another run, starting from **1a** (26.0 g), **6a** (18.2 g, (25.2%), and **7a** (2.67 g, 3.7%) were obtained from the reaction product. Then the mother liquor was evaporated and the residual oil was crystallized from methyl ethyl ketone and toluene to give a crystalline mixture (19.5 g) of mono- and di-esters. According to the result of TLC, considerable amount of tri- and tetra-esters were shown to be present in the mother liquor, but, further isolation of the isomer was not attempted.

*p-Toluenesulfonylation of **3a**, **4a**, and **5a**.* To a solution of 50 mg of 1,2-*O*-cyclohexylidene-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**3a**, **4a**, and **5a**) in 1 ml of dry pyridine was added 70 mg (4.0 equiv.) of *p*-toluenesulfonyl chloride and the mixture was allowed to stand at room temperature for 4 days. Then the reaction mixture was analyzed directly by TLC using toluene-methyl ethyl ketone (3:1) and benzene-ethyl acetate (9 : 4) as the solvent systems. Judging from the results of TLC, **3a** gave rise to **6a** and **7a**, while, **6a** and **7a** were formed from **4a** and **5a**, respectively. In addition to the major component, an unidentified product was found in the reaction mixture of **4a** and **5a**, which might be considered to be *1,2-O*-cyclohexylidene-*3,4,5*-tri-*O-p*-toluenesulfonyl-*myo*-inositol.

*5-O-Acetyl-1,2-O-cyclohexylidene-3,4,6-tri-O-p-toluenesulfonyl-myo-inositol (**6b**).* Compound **6a** (1.0 g) was treated with a mixture of acetic anhydride (5 ml) and pyridine (5 ml) at room temperature overnight. Then the reaction mixture was poured onto ice and water (30 ml) and the precipitates were collected by filtration; yield 1.0 g (95%), mp 177.5—179°C. Recrystallization from chloroform and ethanol afforded colorless cubic crystals (0.91 g) of **6b**, mp 179—180.5°C. PMR: τ 7.58 (9, s, OTs C–CH_3), 5.91 (1, t, H-1, J=5.5 Hz), 5.63 (1, q, H-2, J=3.5 and 5.5 Hz).

Found: C, 55.14; H, 5.47; S, 12.85%. Calcd for $C_{35}H_{36}O_{15}S_3$: C, 54.84; H, 5.27; S, 12.58%.

*4-O-Acetyl-1,2-O-cyclohexylidene-3,5,6-tri-O-p-toluenesulfonyl-myo-inositol (**7b**).* Compound **7a** (0.10 g) was acetylated similarly as described under the preparation of **6b** to give crystals (0.10 g, 95%) of **7b**, mp 194—195°C. Recrystallization from ethanol afforded colorless cubic crystals (0.09 g), mp 195.5—196°C. PMR: τ 7.59 (9, s, OTs C–CH_3).

Found: C, 55.05; H, 5.22; S, 12.79%. Calcd for $C_{35}H_{36}O_{15}S_3$: C, 54.84; H, 5.27; S, 12.58%.

*1,4,6-Tri-O-p-toluenesulfonyl-myo-inositol (**6c**).* A mixture of **6a** (2.0 g) and 80% aqueous acetic acid (40 ml) was refluxed for 2 hr. After cooling, the reaction mixture was poured into water (200 ml) and the resulting crystals were collected by filtration; yield 1.5 g (84%), mp 217—220°C. Recrystallization from ethanol gave two allotropic forms of crystals; needles and plates, mp 223—225.5°C. The melting point of the former is slightly lower than that of the latter. When the crystals were dissolved in 2-methoxyethanol and a crystallization was induced by addition of ethanol, colorless plates of **6c** were obtained homogeneously, mp 225.5—226.5°C.

Found: C, 50.68; H, 4.95; S, 14.92%. Calcd for $C_{27}H_{30}O_{12}S_3$: C, 50.47; H, 4.71; S, 14.97%.

*1,4,5-Tri-O-p-toluenesulfonyl-myo-inositol (**7c**).* A mixture of **7a** (0.51 g) and 80% aqueous acetic acid (10 ml) was refluxed for 2 hr. The reaction mixture was evaporated to dryness and the residue was digested with ethanol to give crystals (0.36 g, 81%) of **7c**, mp 205—211°C. Recrystallization from ethanol afforded colorless granular crystals, mp 208.5—210°C.

Found: C, 50.68; H, 4.87; S, 14.70%. Calcd for $C_{27}H_{30}O_{12}S_3$: C, 50.47; H, 4.71; S, 14.97%.

1,2,5-Tri-O-acetyl-3,4,6-tri-O-p-toluenesulfonyl-myo-inositol

(6d). Compound **6c** (0.10 g) was acetylated similarly as described under the preparation of **4d** to give crystal (0.12 g, 97%) of **6d**, mp 218.5—221°C. Recrystallization from chloroform and ethanol afforded colorless cubic crystals, which showed the same melting point. PMR: τ 7.56 (9, s, OTs C–CH_3), 5.49 (1, m, H-3), 4.48 (1, t, H-2, J=2.5 Hz).

Found: C, 51.40; H, 4.89; S, 12.69%. Calcd for $C_{33}H_{36}O_{15}S_3$: C, 51.56; H, 4.72; S, 12.49%.

1,2,4-Tri-O-*acetyl-3,5,6-tri*-O-p-*toluenesulfonyl*-myo-*inositol (7d).* Compound **7c** (0.10 g) was acetylated similarly as described under the preparation of **4d** to give crystals (0.11 g, 92%) of **7d**, mp 207—209°C (after melting and resolidifying at 180—185°C). Recrystallization from chloroform and ethanol afforded small needles, mp 210.5—212.5°C (after partly melting and showing a transition at 194—196°C). PMR: τ 7.56 (9, s, OTs C–CH_3), 5.27 (1, q, H-3, J=3 and 10 Hz).

Found: C, 51.57; H, 4.75; S, 12.30%. Calcd for $C_{33}H_{36}O_{15}S_3$: C, 51.56; H, 4.72; S, 12.49%.

1,2,6-Tri-O-*acetyl-3,4,6-tri*-O-p-*toluenesulfonyl*-myo-*inositol (8) and 1,4,5,6-Tetra*-O-p-*toluenesulfonyl*-myo-*inositol (9a).* A compound **1a** (5.0 g) was treated with *p*-toluenesulfonyl chloride (25.6 g, 7.0 equiv.) in dry pyridine (60 m*l*) and the reaction mixture was worked up similarly as described under the preparation of **6a** and **7a**. After **6a** (3.3 g, 24%) had been isolated by crystallization from chloroform and ethanol, the mother liquor was evaporated to dryness and the oily residue was refluxed with 80% aqueous acetic acid (50 m*l*) for 2 hr. The reaction mixture was kept for 2 days at room temperature and the resulting precipitates were collected by filtration. Then the mother liquor was again refluxed for additional 3 hr and the second crystals were obtained. The first and second crystals were combined and recrystallized two times from methyl ethyl ketone and ethanol to give colorless plates (3.3 g, 21%) of **9a**, mp 142—152°C (after sintering at 138°C). An analytical sample was obtained by recrystallization from methyl ethyl ketone and ethanol, mp 145—153°C.

Found: C, 51.59; H, 5.16; S, 15.54%. Calcd for $C_{34}H_{36}O_{14}S_4 \cdot C_2H_5OH$: C, 51.30; H, 5.03; S, 15.22%.

Then the mother liquor of **9a** was evaporated to dryness and the residue was treated with a mixture of acetic anhydride (10 m*l*) and pyridine (15 m*l*) overnight at room temperature. The reaction mixture was poured onto ice and water (100 m*l*) and, after 2 days, the resulting gum was filtered by suction. The gum was digested with chloroform and ethanol to give colorless needles (1.97 g), mp 173—177°C. Recrystallization from chloroform and ethanol afforded needles (1.6 g, 11%) of **8**, mp 194—194.5°C. PMR: τ 7.56 (9, s, OTs C–CH_3), 5.40 (1, q, H-3, J=3 and 9 Hz).

Found: C, 51.45; H, 4.53; S, 12.13%. Calcd for $C_{33}H_{36}O_{15}S_3$: C, 51.56; H, 4.72; S, 12.49%.

On addition of ethanol, the mother liquor gave plates (0.78 g, 5.3%) of **7d**, mp 202.5—206°C.

1,2-Di-O-*acetyl-3,4,5,6-tetra*-O-p-*toluenesulfonyl*-myo-*inositol (9b).* Compound **9a** (0.20 g) was acetylated as similarly as described under the preparation of **3d** to give crystals (0.23 g) of **9b**, mp 188.5—190.5°C. Recrystallization from ethanol afforded colorless needles (0.20 g, 91%), mp 189.5—190.5°C. PMR: τ 7.54 (12, s, OTs C–CH_3), 5.34 (1, q, H-3, J=3 and 8 Hz), 4.67 (1, t, H-2, J=*ca.* 3 Hz).

Found: C, 52.02; H, 4.77; S, 14.94%. Calcd for $C_{38}H_{40}O_{16}S_4$: C, 51.82; H, 4.58; S, 14.57%.

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