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SYNTHESIS OF 1,2:3,4- AND 1,2:4,5-DIANHYDROINOSITOLS*

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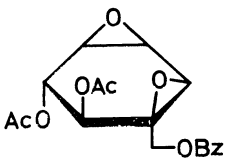
All eleven stereoisomers of dianhydroinositols (1 - 11), except 1,4-anhydro derivatives, have been synthesized from inositol disulfonates and their structures were established by PMR spectra together with a reaction mechanism. A migration of oxirane ring caused by participation of neighboring hydroxyl group induced an isomerization of the epoxide in an alkaline medium.

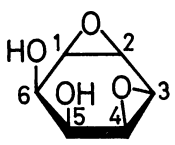
A significant tumor inhibitor, crotepoxide has been isolated from fruits of Croton macrostachys by Kupchan and his coworkers,[1,2] which contains a rare cyclohexane diepoxide structure. The same compound was obtained later by Takahashi[3,4] by the name of futoxide from Piper futokazura. Recently a new antibiotic LL-Z1220 was found to contain a similar cyclohexene diepoxide.[5,6] An existence of chemically active oxiranes in a cyclohexane ring system appears to play a major role in an appearance of the biological activities. Therefore, it is of great interest to explore the structure - activity relationship of cyclohexane diepoxides by exploiting a closely related dianhydroinositol as a model compound.



Crotepoxide

Eleven isomers are theoretically possible for dianhydroinositols: 1,2:3,4- (1 - 6) and 1,2:4,5-dianhydroinositols (7 - 11), excluding 1,4-anhydro compound. Among these eleven isomers, 2 has the most resembled structure to that of crotepoxide. But none of these compounds has been described in a literature, except the three of their O-cyclohexylidene derivatives.[7]

In this letter, we wish to report the preparation of all the predicted isomers of dianhydroinositols by treating an inositol disulfonate with sodium methoxide. Starting from myo-inositol disulfonates,[8-11] seven of the compounds have been



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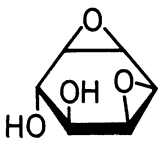

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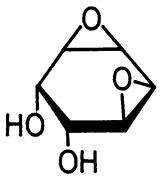

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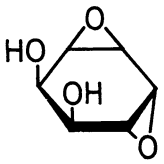

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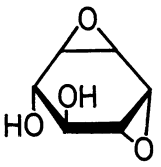

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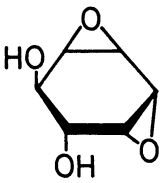

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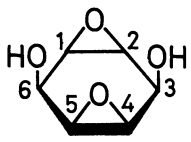

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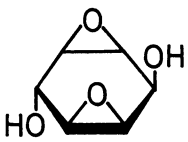

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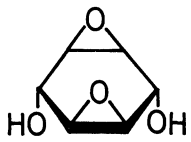

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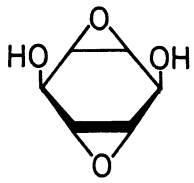

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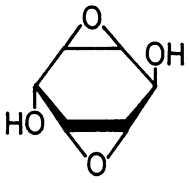

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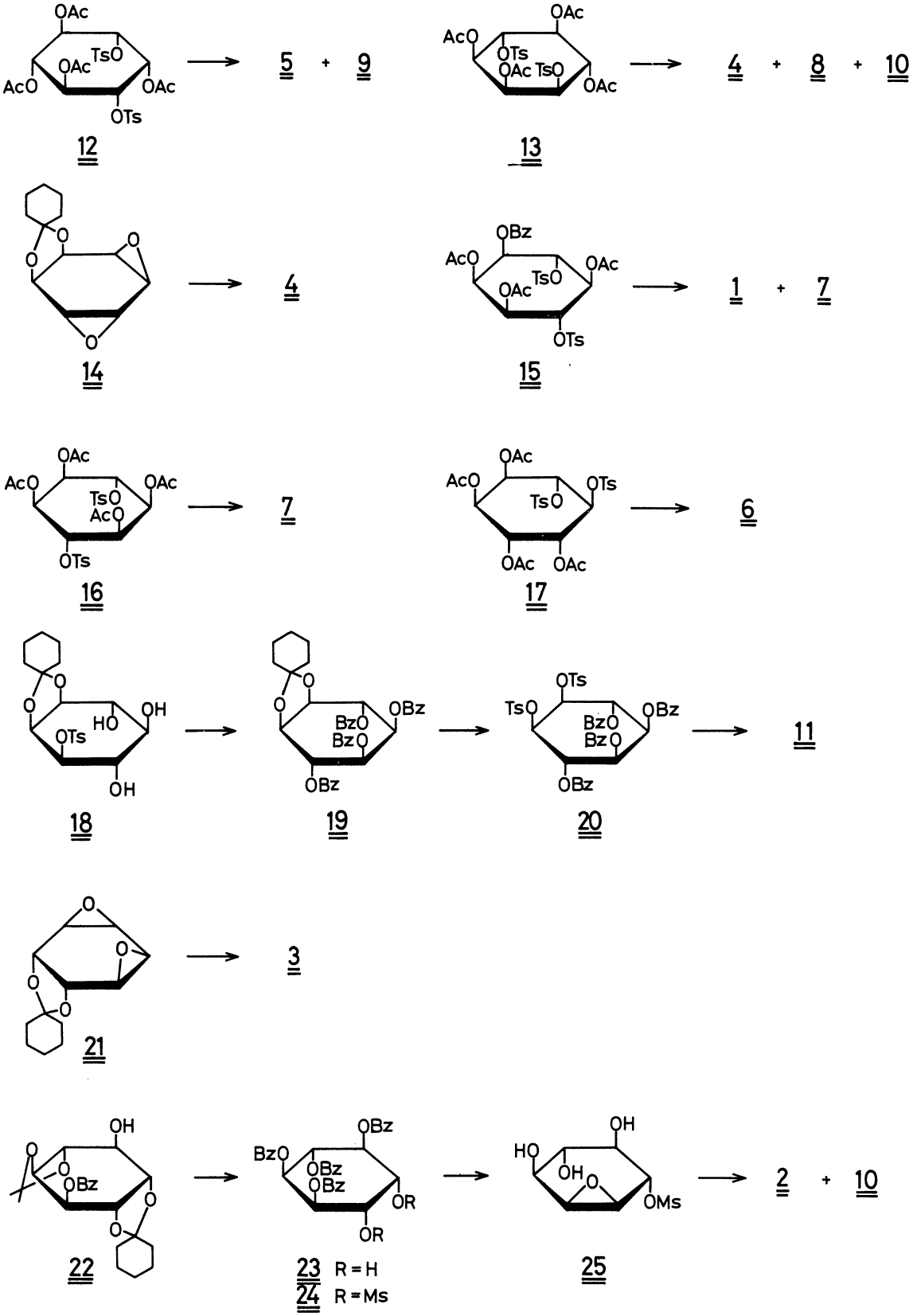
synthesized (1, 4, 5, 7, 8, 9 and 10) and from chiro- and muco-inositol disulfonates, other four isomers (2, 3, 6 and 11) have been prepared. Determinations of their anti-carcinoma activities are now in progress.

Treatment of 1,3-di-O-tosyl-myo-inositol tetraacetate (12)[8,9] with a slightly excess amount of sodium methoxide in a mixture of chloroform and methanol afforded two dianhydroinositols: 5 (21% yield) and 9 (15%), which were successfully separated by silica gel column chromatography. The structure of 9 was established by its PMR spectrum which revealed two sets of signals with a 2 : 1 relative intensity ascribed to the six ring protons, indicating a symmetrical structure. Syrupy 5 was converted to the crystalline diacetate and its structure was also established by PMR spectroscopic studies. It was observed that 5 and 9 were interconvertible via an oxirane ring migration in an alkaline medium.

From 1,4-di-O-tosyl-myo-inositol tetraacetate (13)[10], three dianhydroinositols: 4 (23%), 8 (8%) and 10 (21%) were prepared by the analogous method. Compounds 4 and 8 were interconvertible under a basic condition through a migration of oxirane ring. Compound 2 which was expected to be formed in this reaction was not obtained owing to rapid isomerization from 2 to 10. Compound 4 was identified with the compound derived from 1,2:5,6-dianhydro-3,4-O-cyclohexylidene-allo-inositol (14)[7] by mild acid hydrolysis. Structures of 8 and 10 were established by PMR spectra


OAc
TsO
OAc
AcO
OAc
OTs
12
5 + 9
OAc
AcO
OTs
OAc TsO
OAc
13
4 + 8 + 10
14
4
OBz
AcO
TsO
OAc
OAc
OTs
15
1 + 7
OAc
AcO
TsO
AcO
OAc
OTs
16
7
OAc
AcO
TsO
OTs
OAc OAc
17
6
OH
HO
OTs
OH
18
OBz
BzO
BzO
OBz
19
OTs
TsO
BzO
BzO
OBz
OBz
20
11
21
3
OH
OBz
22
OBz
BzO
OBz
OBz
OR
OR
23 R = H
24 R = Ms
OH
HO
OH
OMs
25
2 + 10

which showed an unsymmetrical structure for 8 and a symmetrical one for 10.

The analogous epoxidation of 3-O-benzoyl-4,6-di-O-tosyl-myo-inositol triacetate (15)[11] afforded 1 (4%), 7 (37%) and a monoepoxide (4%) which was found to be a precoursor for 7 by converting it into 7 on a further treatment with sodium methoxide. The structural assignments of 1 and 7 were carried out by PMR spectra, in which 1 revealed three sets of signals with equal intensities due to the three equivalent pairs of the ring protons and 7 showed two sets of signals with a 1 : 2 relative intensity for the ring protons. Also 7 was prepared selectively in 36% yield by epoxidation of 3,6-di-O-tosyl-muco-inositol tetraacetate (16)[12] with sodium methoxide.

Compound 6 was obtained in 35% yield by treatment of 3,4-di-O-tosyl-chiro-inositol (17)[13] with sodium methoxide.

Compound 11 was prepared by the following route. Treatment of 1,2-O-cyclohexylidene-3-O-tosyl-myo-inositol (18)[10] with sodium carbonate in boiling 80% aqueous 2-methoxyethanol for 3.5 hr, followed by benzoylation gave 1,2-O-cyclohexylidene-muco-inositol tetrabenzoate (19) in 65% yield. Removal of the cyclohexylidene group of 19, followed by tosylation afforded 1,2-di-O-tosyl-muco-inositol tetrabenzoate (20) in 60% yield. The analogous reaction of 18 with sodium methoxide afforded 11 exclusively in 39% yield. Another isomer 3 expected to be formed in this reaction was absent in the reaction mixture, owing to a complete isomerization (3 → 11) under the basic condition employed. This compound was prepared in another route where removal of cyclohexylidene group of 1,2:3,4-dianhydro-5,6-O-cyclohexylidene-allo-inositol (21)[7] was conducted in a mild acidic condition to suppress a migration of oxirane rings. Structures of 6, 11 and 3 were established by the PMR spectroscopy.

The last remaining isomer 2 seemed to isomerize readily to 10 under an alkaline condition, as was seen in the epoxidation of 13 with sodium methoxide. Therefore, following devices have been successfully adopted to the preparation of 2. Treatment of 18 with 2,2-dimethoxypropane in dimethylformamide (DMF) in the presence of a catalytic amount of p-toluenesulfonic acid gave a mixture of two positional isomers of the O-isopropylidene derivative. The 4,5-O-isopropylidene derivative which was obtained by silica gel column chromatography was treated with sodium benzoate in boiling DMF for 160 hr to give 3-O-benzoyl-1,2-O-cyclohexylidene-4,5-O-isopropylidene-chiro-inositol (22) in 37% yield. Compound 22 was hydrolyzed in a mild acidic condition to remove the isopropylidene group and subsequently benzoylated. Further hydrolysis of the benzoylated

product with 80% aqueous acetic acid afforded 1,2,3,4-tetra-O-benzoyl-chiro-inositol (23) in 67% yield. Mesylation of 23 gave 1,2-di-O-mesyl-chiro-inositol tetrabenzoate (24) in 55% yield. Treatment of 24 with 1.5 molar equivalent of sodium methoxide afforded the monoepoxide (25) predominantly. Then 25 was treated with Amberlite IRA-410 (OH^-) resin in methanol[14] to give 2 in 11% yield together with 10 in 7% yield without a serious intractable isomerization. While under the usual method with sodium methoxide 25 gave exclusively 10 in 60% yield. The PMR spectrum of 2 was consistent with the proposed structure. All the predicted isomers of dianhydroinositols have been synthesized and their melting points are listed in Table 1. The crystalline products described in Table 1 gave correct elemental analyses.

The formation of epoxide from the sulfonate involves an intramolecular displacement of leaving sulfonyloxy group by a vicinal trans hydroxyl group which is in a favorable position for the attack. The 1,2:3,4-diepoxides isomerize to 1,2:4,5-diepoxides, and vice versa, through an epoxide migration in an alkaline medium. The migration occurs by an attack of neighboring trans hydroxyl group on an oxirane ring, and this is known in carbohydrate chemistry[16]. An extent of the isomerization seems to be dependent on conformational stabilities of the diepoxides.

Table 1 Melting Points of Eleven Dianhydroinositols[15]

Configuration		Formula	Melting points (°C)	
			Diol	Diacetate
1,3-cis	(1,2,3,4,5,6/0)	1	103-104	142.5-144
	(1,2,3,4,5/6)	2	132-134	syrup
	(1,2,3,4/5,6)	3	105-106	syrup
1,3-trans	(1,2,5,6/3,4)	4	74-76	121-121.5
	(1,2,5/3,4,6)	5	syrup	125-127
	(1,2,6/3,4,5)	6	121.5-122.5	96-97
1,4-cis	(1,2,3,4,5,6/0)	7	170 (sublmd)	153-154
	(1,2,3,4,5/6)	8	124-124.5	136 (sublmd)
	(1,2,4,5/3,6)	9	169-171	108-109.5
1,4-trans	(1,2,3,6/4,5)	10	73-74	110-111.5
	(1,2,3/4,5,6)	11	150-151	138-139

REFERENCES AND FOOTNOTES

* A part of this work was presented at the 27th Annual Meeting of the Chemical Society of Japan, Nagoya, October, 1972 (See Abstracts of Papers of the Meeting, Vol. I, p. 528).

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15) The nomenclature used in this paper is based on the IUPAC-IUB Tentative Cyclitol Nomenclature Rule (J. Biol. Chem., 22, 5809 (1968)). Either one, the dianhydroinositol- or the diepoxycyclohexanediol-system can designate the configuration of the eleven isomers of diepoxydiol fairly unambiguously.

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