

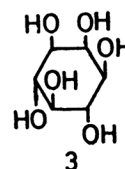
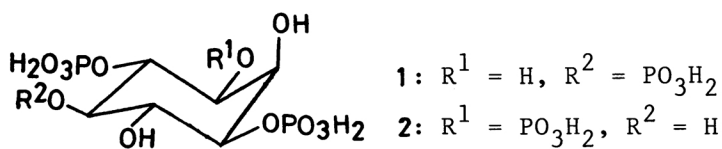
Synthesis of Optically Active myo-Inositol 1,3,4-Trisphosphate

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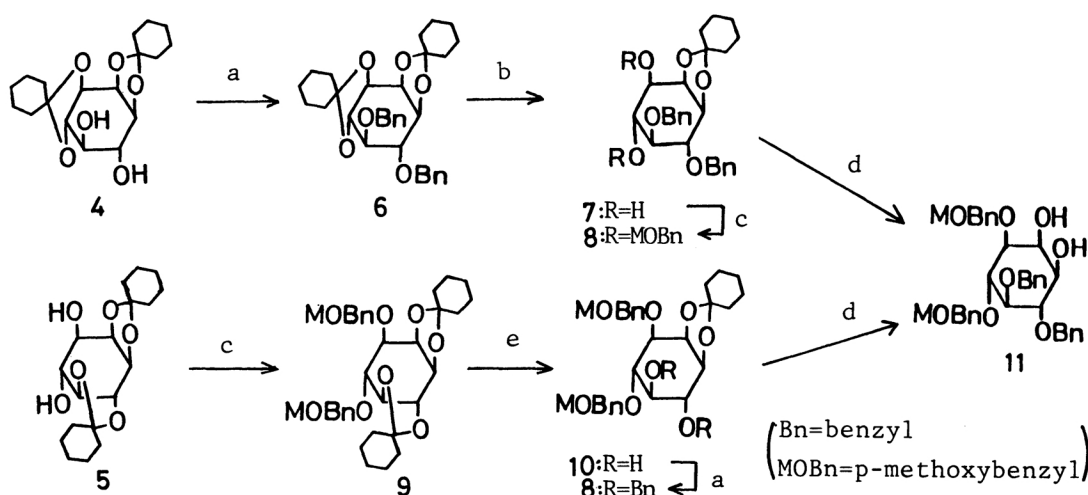
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Synthesis of optically active myo-inositol 1,3,4-trisphosphate has been accomplished. Efficiency of a chiral HPLC column for optical resolution of myo-inositols is shown.

It is now widely recognized that D-myo-inositol 1,4,5-trisphosphate (1) is a second messenger which mediates the release of calcium ion from intracellular stores.<sup>1)</sup> Some other inositol phosphates were found to exist temporarily as metabolites in a cellular signalling system.<sup>2)</sup> Irvine and co-workers reported that myo-inositol 1,3,4-trisphosphate (2) might be a new second messenger as well as 1,<sup>3b)</sup> although biological function of 2 is currently unclear yet.<sup>3)</sup> Preparation of 2 was enzymatically accomplished.<sup>4)</sup> Chemical synthesis of racemic 2 was also reported by two groups.<sup>5)</sup> We have now succeeded in the synthesis of optically active 2 by the entirely different pathway. In this communication, we describe the results and especially emphasize the efficiency of a chiral HPLC column for optical resolution of inositol derivatives.



The reaction<sup>6)</sup> of inositol 3 with ethoxycyclohexene in the presence of p-toluenesulfonic acid (TsOH) afforded a mixture of three biscyclohexylidene-myo-inositols, among which 4 and 5 were effectively utilized for the present purpose. Thus, 1,2:3,4-biscyclohexylidene derivative 4 was benzylated by treatment with sodium hydride and benzyl chloride in DMF at 60 °C for 2 h to give dibenzyl ether 6 in 98% yield. The selective removal of the cyclohexylidene group at C-3 and C-4 was achieved by the action of an equimolar amount of ethylene glycol in the presence of p-TsOH at room temperature to give 7 in 60% yield (75% yield based on recovered 6), which was then transformed to bis(p-methoxybenzyl)ether 8 in 93% yield by the reaction with sodium hydride and p-methoxybenzyl chloride. In a similar manner, the ether 8 was also obtained starting from 1,2:5,6-biscyclohexylidene derivative 5 by way of 9 and 10. Selective removal of the 5,6-cyclohexylidene group in 9 derived from 5 was much more difficult than that of the 3,4-cyclohexylidene group in 6. In

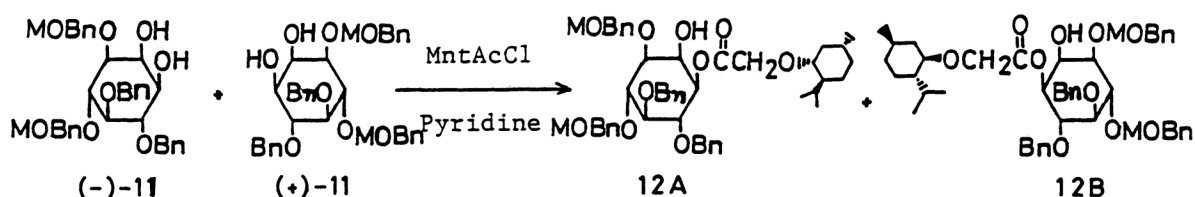


a, NaH/BnCl/DMF (98% for 6, 86% for 8); b, HO(CH<sub>2</sub>)<sub>2</sub>OH/TsOH/CHCl<sub>3</sub> (60%); c, NaH/MOBnCl/DMF 93% for 8, 94% for 9; d, HCl/MeOH (75%); e, I<sub>2</sub>/MeOH (66%)

fact, even careful treatment of 9 with ethylene glycol in the presence of p-TsOH as mentioned above resulted in the formation of a significant amount of tetrols resulting from removal of two cyclohexylidene groups. In the event, the I<sub>2</sub>-MeOH reagent<sup>7)</sup> afforded the monocyclohexylidene derivative 10 in 66% yield (80% yield based on recovered 9). Removal of the cyclohexylidene group at C-1 and C-2 in 8 was achieved by treatment with 0.1 M (1 M=1 mol dm<sup>-3</sup>) solution of hydrogen chloride in methanol to give 11 in 75% yield.

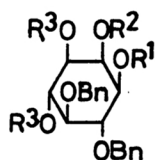
In order to obtain optically active 2, racemic 1,2-diol 11 was resolved by two methods. One method involves separation of diastereomeric *l*-menthoxyacetic esters 12A and 12B derived from racemic 11 by the selective reaction at C-1 with *l*-menthoxyacetyl chloride as reported from this laboratory.<sup>8)</sup> Both isomers 12A and 12B were converted to (-)- and (+)-11, respectively by treatment with ammonia in methanol.<sup>9)</sup> The other employing a chiral HPLC column, Chiralcel OD<sup>10)</sup> has now been found to be a promising method for optical resolution of inositol derivatives, especially 1,2-dihydroxy ones. Thus, highly efficient resolution of 11 was accomplished by the use of a 25 cm x 2 (i.d.) cm stainless steel tube packed with cellulose 3,5-dimethylphenylcarbamate derivative supported on silica gel<sup>11)</sup> (eluent: 2-propanol/hexane = 1/5, retention time (analytical column): (+)-11 = 15 min, (-)-11 = 25 min).

One enantiomer (-)-11 thus resolved was then benzylated at C-2 by way of methoxymethylated derivative 13 which was prepared effectively by the reaction of



(MntAcCl=*l*-menthoxyacetyl chloride)

(-)-11 with dibutyltin oxide and subsequent treatment with methoxymethyltriethylammonium chloride (81% yield).<sup>12)</sup> After benzylation of 13 (97% yield), the product 14 was transformed into the key synthetic intermediate D-2,5,6-tri-O-benzyl-myo-inositol 15 by the successive removal of the methoxybenzyl (DDQ, 86% yield)<sup>13)</sup> and methoxymethyl (0.1 M HCl-MeOH, 80% yield) groups.



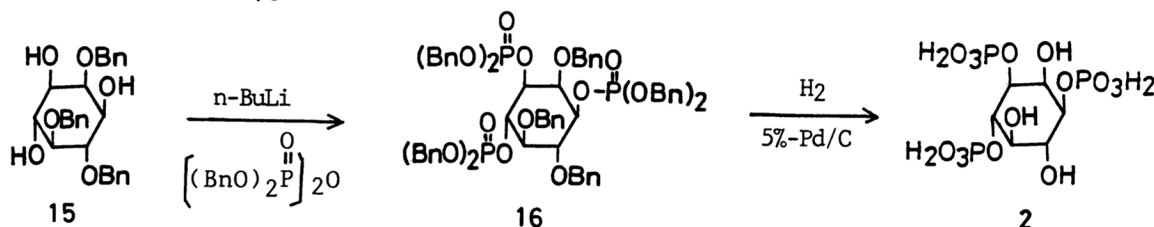
13: R<sup>1</sup>=MOM, R<sup>2</sup>=H, R<sup>3</sup>=MOBn

14: R<sup>1</sup>=MOM, R<sup>2</sup>=Bn, R<sup>3</sup>=MOBn

15: R<sup>1</sup>=R<sup>3</sup>=H, R<sup>2</sup>=Bn

(MOM=methoxymethyl)

Phosphorylation of 15 was efficiently carried out as reported recently from this laboratory<sup>14)</sup> by the exposure of it to butyllithium followed by addition of tetrabenzyl pyrophosphate giving rise to 16 in 70% yield.<sup>15)</sup> Finally, all of protective groups in 16 was deblocked in a single procedure with quite ease. Thus,



hydrogenolysis of 16 over 5%-Pd/C under a hydrogen atmosphere at room temperature for 24 h gave the expected product, D-myo-inositol 1,3,4-trisphosphate (2) in quantitative yield (as the hexaammonium salt),<sup>16)</sup>  $[\alpha]_D^{22} -6^\circ$  (c 0.5, H<sub>2</sub>O). The structure of 2 thus obtained was elucidated unambiguously by NMR analysis.<sup>17)</sup>

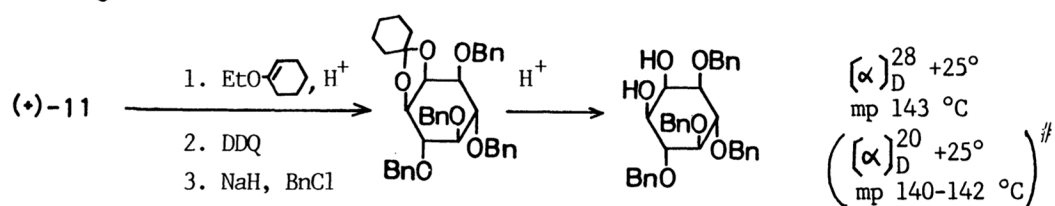
This work was partially supported by a Grant-in-Aid for Special Project Research (No. 61224008) from the Ministry of Education, Science and Culture. We would like to thank Eisai Co., Ltd. for NMR measurement. We are grateful Dr. Vacca for a preprint of his manuscript. We wish also to thank Advanced Instrumentation Center for Chemical Analysis, Ehime University, for the mass spectral and combustion analyses.

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- 9) The absolute configuration of (-)- and (+)-11 was confirmed by derivatization of (+)-11 to the known L-3,4,5,6-tetra-O-benzyl-myoinositol as shown below:



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- 10) Chiralcel OD was purchased from Daicel Chemical Industries, Ltd.
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- 15) After we submitted the article (Ref. 14), similar polyphosphorylation was reported by two groups where potassium hydride or sodium hydride was used as a base in place of butyl lithium or LDA used by us: J. P. Vacca, S. J. deSolms, and J. R. Huff, *J. Am. Chem. Soc.*, 109, 3478 (1987); D. C. Billington and R. Baker, *J. Chem. Soc., Chem. Commun.*, 1987, 1011; see also the report of S. J. deSolms et al. in Ref. 5.
- 16) The absolute configuration of naturally occurring 2 is not determined at the present time although it was assumed that it has the D configuration as same as our synthetic 2.<sup>4)</sup>
- 17) <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, reference: HOD = 4.86 ppm) 3.63 (dd, J<sub>4,5</sub> = J<sub>5,6</sub> = 9.5 Hz, H<sub>5</sub>), 3.92 (dd, J<sub>1,6</sub> = J<sub>5,6</sub> = 9.5 Hz, H<sub>6</sub>), 4.10 (ddd, J<sub>1,p</sub> = 11.0 Hz, J<sub>1,2</sub> = 2.5 Hz, H<sub>1</sub>), 4.19 (ddd, J<sub>3,p</sub> = J<sub>3,4</sub> = 9.5 Hz, J<sub>2,3</sub> = 2.5 Hz, H<sub>3</sub>), 4.39 (ddd, J<sub>4,p</sub> = 9.5 Hz, H<sub>4</sub>), and 4.5 (dd, H<sub>2</sub>).

(Received October 9, 1987)