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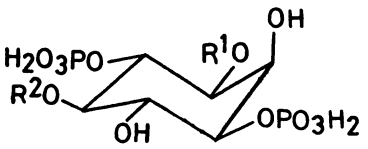
Synthesis of Optically Active myo-Inositol 1,3,4-Trisphosphate

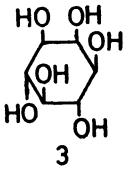
Shoichiro OZAKI,* Masayasu KOHNO, Hiroyuki NAKAHIRA,
Motonobu BUNYA, and Yutaka WATANABE
Department of Resources Chemistry, Faculty of Engineering,
Ehime University, Matsuyama 790

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.[1] Some other inositol phosphates were found to exist temporarily as metabolites in a cellular signalling system.[2] Irvine and co-workers reported that myo-inositol 1,3,4-trisphosphate (2) might be a new second messenger as well as 1,[3b] although biological function of 2 is currently unclear yet.[3] Preparation of 2 was enzymatically accomplished.[4] Chemical synthesis of racemic 2 was also reported by two groups.[5] 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.

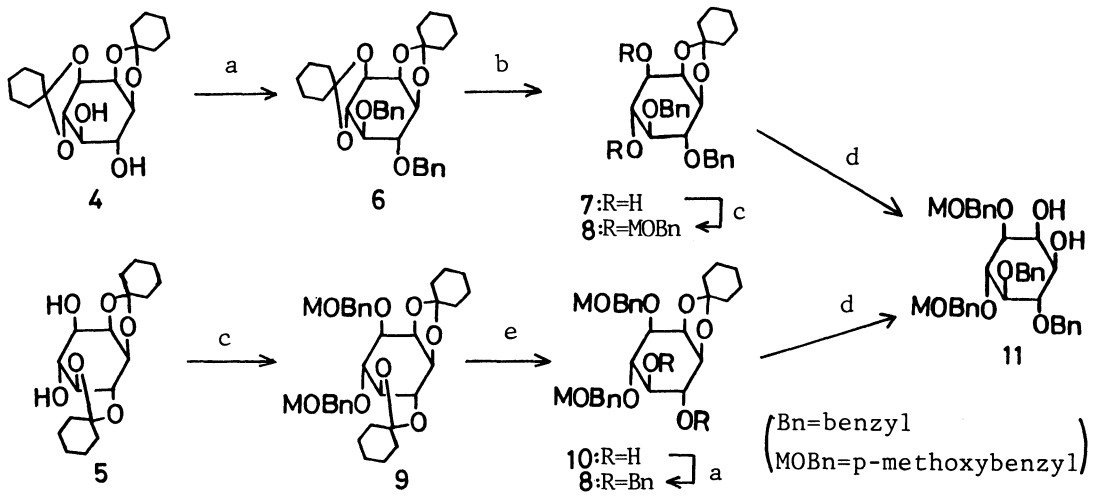


1: $R^1 = H$, $R^2 = PO_3H_2$
2: $R^1 = PO_3H_2$, $R^2 = H$



3

The reaction[6] 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

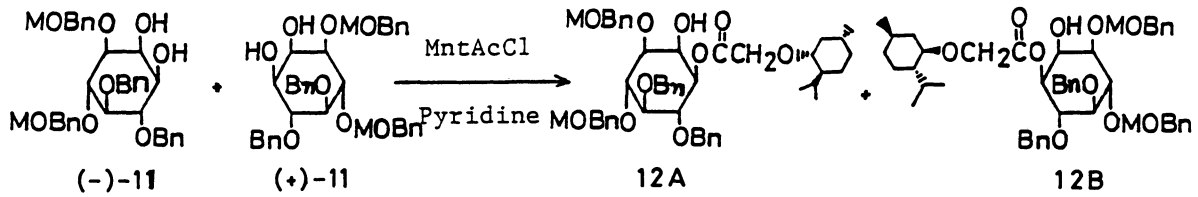


a, NaH/BnCl/DMF (98% for 6, 86% for 8); b, $HO(CH_2)_2OH$/TsOH/$CHCl_3$ (60%); c, NaH/MOBnCl/DMF 93% for 8, 94% for 9); d, HCl/MeOH (75%); e, I_2/MeOH (66%)

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_2-MeOH reagent[7] 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^{-3}) solution of hydrogen chloride in methanol to give 11 in 75% yield.

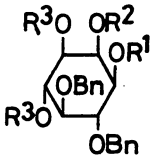
In order to obtain optically active 2, racemic 1,2-diol 11 was resolved by two methods. One method involves separation of diastereomeric ℓ-menthoxyacetic esters 12A and 12B derived from racemic 11 by the selective reaction at C-1 with ℓ-menthoxyacetyl chloride as reported from this laboratory.[8] Both isomers 12A and 12B were converted to (-)- and (+)-11, respectively by treatment with ammonia in methanol.[9] The other employing a chiral HPLC column, Chiralcel OD[10] 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[11] (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)

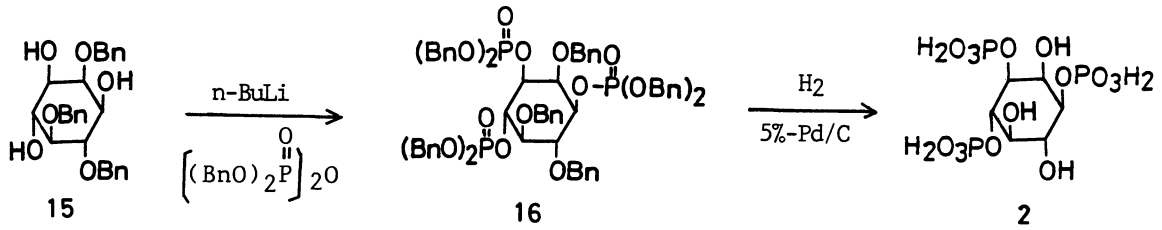
(-)-11 with dibutyltinoxide and subsequent treatment with methoxymethyltriethylammonium chloride (81% yield).[12] After benzylation of 13 (97% yield), the product 14 was transformed into the key synthetic intermediate D-2,5,6-tri-O-benzyl-myo-inositol 15 by the successive removal of the methoxybenzyl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



13: R^1=MOM, R^2=H, R^3=MOBn
14: R^1=MOM, R^2=Bn, R^3=MOBn
15: R^1=R^3=H, R^2=Bn

(MOM=methoxymethyl)

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



15 16 2

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),[16] $[\alpha]_D^{22}$ -6° (c 0.5, H_2O). The structure of 2 thus obtained was elucidated unambiguously by NMR analysis.[17]

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5) After completion of our synthesis of racemic 2, van Boom's report appeared: C. E. Dreef, G. A. van der Marel, and J. H. van Boom, Recl. Trav. Chim. Pays-Bas, 106, 161 (1987). We were also made aware in a personal communication with

Dr. J. P. Vacca, that his group completed a synthesis of 2, which is also racemic form: S. J. deSolms, J. P. Vacca, and J. R. Huff, Tetrahedron Lett., 28, 4503 (1987).

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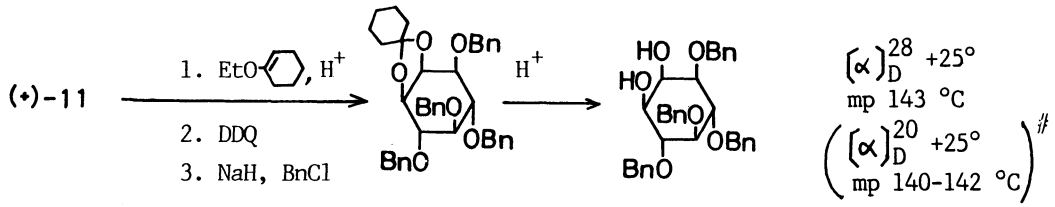
9) The absolute configuration of (-)- and (+)-11 was confirmed by derivatization of (+)-11 to the known L-3,4,5,6-tetra-O-benzyl-myo-inositol as shown below:



V. I. Shvets, B. A. Klyashchitskii, A. E. Stepanov, and R. P. Evstigneeva, Tetrahedron, 29, 331 (1973).

10) Chiralcel OD was purchased from Daicel Chemical Industries, Ltd.

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13) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., 23, 885 (1982).

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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.[4)]

17) ^{1}H NMR (400 MHz, D_2O, reference: HOD = 4.86 ppm) 3.63 (dd, $J_{4,5} = J_{5,6} = 9.5$ Hz, H_5), 3.92 (dd, $J_{1,6} = J_{5,6} = 9.5$ Hz, H_6), 4.10 (ddd, $J_{1,P} = 11.0$ Hz, $J_{1,2} = 2.5$ Hz, H_1), 4.19 (ddd, $J_{3,P} = J_{3,4} = 9.5$ Hz, $J_{2,3} = 2.5$ Hz, H_3), 4.39 (ddd, $J_{4,P} = 9.5$ Hz, H_4), and 4.5 (dd, H_2).

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