Tetrahedron Letters,Vol.27,No.27,pp 3157-3160,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

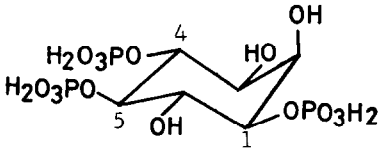
TOTAL SYNTHESIS OF OPTICALLY ACTIVE MYO-INOSITOL 1,4,5-TRIS(PHOSPHATE)

Shoichiro Ozaki,* Yutaka Watanabe, Tomio Ogasawara, Yoshihisa Kondo, Naokazu Shiotani, Hisayoshi Nishii, and Tomoko Matsuki

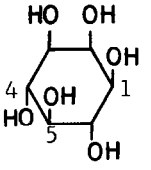
Department of Resources Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan

Abstract: Optically active myo-inositol 1,4,5-tris(phosphate) has been synthesized starting from myo-inositol.

Since the recent claim that D-myo-inositol 1,4,5-tris(phosphate) (1) acts as a cellular second messenger,[1] biological interest in it has been increased remarkably. Even though this material which is prepared by chemical hydrolysis of bovine brain phosphoinositides is commercially available, the isolation process is enormously tedious[2] and a supply of a large quantity of 1 is much difficult. It is also difficult to obtain radioactive derivatives of 1. Chemical synthesis of 1 must resolve such problems. In this communication, we describe the first total synthesis of optically active myo-inositol tris(phosphate) 1 starting from readily accessible myo-inositol (2) which is meso form.



1

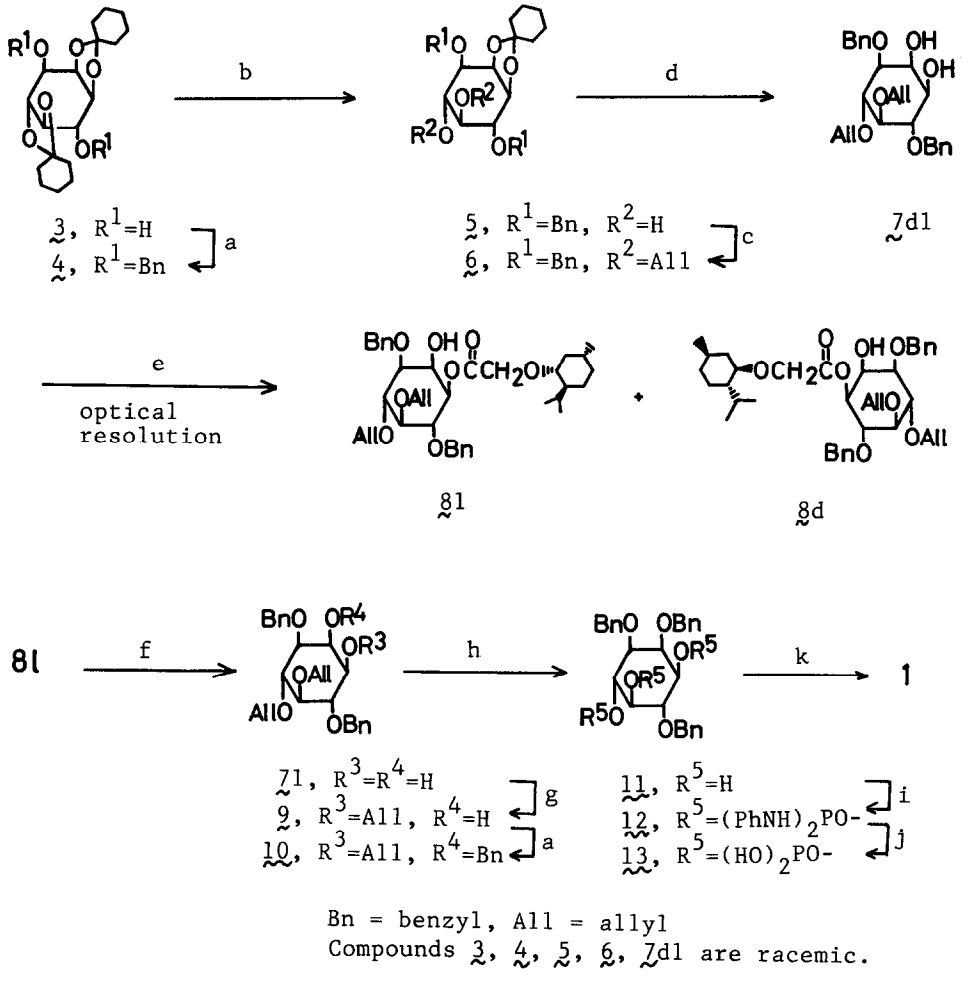


2

For the performance of our project, it was particularly necessary to explore the followings; 1) suitable protection of the six hydroxyl groups in myo-inositol, 2) convenient optical resolution, 3) efficient phosphorylation of the vicinal hydroxyl groups at the 4 and 5 positions. Concerning the first item, Gigg et al.[3] have very recently reported the synthesis of racemic 1,2,4-tri-O-benzyl-myo-inositol (racemic 11) which is the same intermediate that we prepared.[4]

Dibenzyl ether 4 was prepared by an ordinary procedure (Scheme 1, 90% yield) from 1,2:4,5-bis-O-cyclohexylidene-myo-inositol[5] which was readily derived from myo-inositol. Selective removal of the 4,5-cyclohexylidene group was achieved in 80% yield on treatment with ethylene glycol in the presence of p-toluenesulfonic acid in chloroform at room temperature.[6] Allylation on two

Scheme 1



Bn = benzyl, All = allyl
Compounds 3, 4, 5, 6, 7dl are racemic.

a, BnCl/NaH/DMF; b(4→5), $HO(CH_2)_2OH$ (1 eq.)/TsOH/$CHCl_3$/r.t.; c, AllBr/NaH/DMF; d(6→7dl), AcOH/H_2O/90°C; e, 1-Menthoxyacetylchloride/Pyridine; f, aq.NaOH/MeOH; g, AllBr/NaOH/Benzene/refl.; h(10→11), $RhCl(PPh_3)_3$/DABCO then HCl/MeOH; i, $(PhNH)_2P(O)Cl$/DMAP/Pyridine; j, i-AmONO/AcOH/Pyridine/Ac_2O; k(13→1), 5%-Pd-C/H_2/aq.MeOH

hydroxyl groups at C-4 and -5 in 5 (quantitative yield) followed by hydrolytic removal of the residual cyclohexylidene group (88% yield) gave the diol 7dl.

This racemic diol was subjected to optical resolution in the next step. There have been known several methods for resolution of myo-inositol derivatives.[7] Among them, the orthoester method developed by Shvets and co-workers[7b] has been shown to have some generality. However, yields of the formation of diastereomers are not always good, and orthoesters are inherently too sensitive towards acidic media to separate them by chromatography using silica gel which

provides a suitable tool for purifing a large quantity of a mixture of materials with similar Rf values. These considerations directed us to devise a more efficient resolution method which allows utilization of silica gel chromatography as well as recrystallization. After a number of examinations, we found that a diastereomeric mixture of the 1-ℓ-menthoxyacetyl derivatives 8d and 8l prepared in a regioselective manner by the reaction of the diol 7dl with the corresponding acid chloride, could be separated efficiently. Thus, recrystallization of the reaction mixture from hexane afforded the desired diastereomer 8l (mp 67.5-68.5 °C), free from the other 8d which was oily. Flash chromatography (SiO_2, hexane -ether 2:1) of the residue obtained from the mother liquor of the first recrystallization gave pure 8l (total 39% yield) and 8d (43% yield). Alkaline hydrolysis of 8l and 8d gave enantiomerically pure diols 7l ($[\alpha]_D^{16}$ -14.3°($CHCl_3$), 98% yield)[8] and 7d ($[\alpha]_D^{16}$ +14.2°($CHCl_3$), 99% yield), respectively. Optical purity of the diol 7l was checked by HPLC analysis of the menthoxyacetyl derivative prepared again from the resolved 7l and also by ^1H NMR analysis of Mosher's acid (R(+)-MTPA)[9] ester of 2-acetylated 7l.

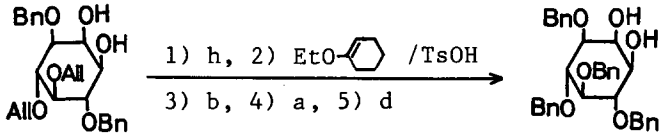
The optically pure diol 7l thus obtained was selectively transformed to 1-allylated alcohol 9 (76% yield) which was then benzylated to furnish the fully protected derivative 10 (98% yield) of myo-inositol. Deallylation of 10 by isomerization of double bond in the presence of Wilkinson catalyst and subsequent acidic methanolysis yielded the key intermediate, trihydroxy tribenzyl ether 11 ($[\alpha]_D^{16}$ +15.5° ($CHCl_3$), mp 117-9°C, 58% yield), whose structure was characterized by spectroscopic data (IR, NMR, MS) and combustion analysis. This pertinently protected triol 11 was subjected to phosphorylation by the use of dianilidophosphoric chloride[10] in the presence of DMAP in pyridine to give tris(phosphate) 12 (ca. 41% yield).[11] Successive deprotection of phosphoryl (isoamyl nitrite in pyridine-acetic acid— acetic anhydride 1:1:1)[12] and hydroxyl (H_2/5% Pd-C) groups in 12 gave the desired final product, D-myo-inositol 1,4,5-tris(phosphate) (ammonium salt) which was indistinguishable on cellurose TLC and PC from natural origin 1.[13] Study on ^1H and ^{13}C NMR spectra which involved spin decoupling and two-dimensional NMR experiments[14] supported unambiguously the structure of 1.[15]

At the present time, phosphorylation and subsequent deblocking reaction are not satisfactory. Improvement of these steps and biological assay of the synthetic 1 are now under way.

Acknowledgment: We would like to thank Prof. Y. Nagai and Dr. T. Takenawa of The University of Tokyo for their suggestion of chemical synthesis of 1 and encouragement, Prof. T. Yoshioka of Yokohama City University for his encouragement and gift of natural 1 (Sigma Chemical Company), and Dr. M. Sekine of Tokyo Institute of Technology for helpful suggestions concerning purification of 1. We thank also JEOL for recording the NMR spectra of synthetic 1. The use of Ehime University Advanced Instrumentation Center for Chemical Analysis facilities is appreciated.

References and Notes

1. H. Streb, R. F. Irvine, M. J. Berridge, and I. Schulz, Nature, 306, 67 (1983); M. J. Berridge and R. F. Irvine, ibid., 312, 315 (1984).
2. C. Grado and C. E. Ballou, J. Biol. Chem., 236, 54 (1961); R. V. Tomlinson and C. E. Ballou, ibid., 236, 1902 (1961).
3. J. Gigg, R. Gigg, S. Payne, and R. Conant, Carbohydr. Res., 140, c1 (1985).
4. We had already completed the synthesis of racemic 11 independently when their report appeared.
5. P. J. Garegg, T. Iversen, R. Johansson, and B. Lindberg, Carbohydr. Res., 130, 322 (1984).
6. Procedures described in the following literatures were modified: S. J. Angyal, M. E. Tate, and S. D. Gero, J. Chem. Soc., 1961, 4116; A. I. Lyutik, V. N. Krylova, S. P. Kozlova, B. A. Klyashchitskii, V. I. Shvets, R. P. Evstigneeva, and E. S. Zhdanovich, Zh. Obshch. Khim., 41, 2747 (1971) [J. Gen. Chem. USSR, 41, 2782 (1971)].
7. a) J. G. Molotkovsky and L. D. Bergelson, Tetrahedron Lett., 1971, 4791; b) V. I. Shvets, B. A. Klyashchitskii, A. E. Stepanov, and R. P. Evstigneeva, Tetrahadron, 29, 331 (1973); c) A. E. Stepanov, V. I. Shvets, and R. P. Evstigneeva, Bioorg. Khim., 2, 1618 (1976) [Soviet J. Bioorg. Chem., 2, 1165 (1976)]; d) A. E. Stepanov, B. A. Klyashchitskii, V. I. Shvets, and R. P. Evstigneeva, ibid., 2, 1627 (1976) [ibid., 2, 1172 (1976)]; e) P. J. Garegg and B. Lindberg, Carbohydr. Res., 139, 209 (1985).
8. The absolute configuration of 7 was confirmed by transforming it to 3,4,5,-6-tetra-O-benzyl-sn-myo-inositol (see Scheme 1 for conditions a, b, d, h) and comparing its $[\alpha]_D$ value (-22.3°) with reported one (-24.3°: ref. 7b).



9. J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).
10. V. N. Krylova, N. P. Gornaeva, G. F. Oleinik, and V. I. Shvets, Zh. Org. Khim., 16, 315 (1980) [J. Org. Chem. USSR, 16, 277 (1980)]; V. N. Krylova, A. I. Lyutik, N. P. Gornaeva, and V. I. Shvets, Zh. Obshch. Khim., 51, 210 (1981) [J. Gen, Chem. USSR, 51, 183 (1981)].
11. This phosphate 12 involved a trace of impurities. However, this was used without further purification.
12. M. Sekine and T. Hata, Tetrahedron Lett., 24, 5741 (1983).
13. Purchased from Amersham International plc.
14. The spectra were recorded on a JEOL JNM-GX400 spectrometer. ^1H NMR (12 mg in 0.4 ml D_2O, pH ca. 6, ext. ref. 4.80 ppm); δ = 4.31-4.24 (m, 2H), 4.05-3.99 (m, 2H), 3.92 (dd, $J_{1-6} = J_{5-6}$ = 9 Hz, 1H = H-6), 3.71 (dd, J_{3-4} = 10 Hz, J_{2-3} = 3 Hz, 1H = H-3). Chemical shift and coupling pattern of H-1, -2, -4, and -5 were disclosed mainly by two-dimensional correlation experiments as follows; δ = 4.28 (dd, J_{1-2} = 3 Hz, H-2), 4.26 (ddd, $J_{4-5} = J_{4-P4}$ = 9 Hz, H-4), 4.01 (ddd, J_{1-P1} = 9 Hz, H-1), 4.01 (ddd, J_{5-P5} = 9 Hz, H-5).
15. ^1H, ^{13}C, and ^{31}P NMR spectra of natural 1 have recently been reported by Lindon et al. (J. C. Lindon, D. J. Baker, R. D. Farrant, and J. M. Williams, Biochem. J., 233, 275 (1986)). These were different in chemical shift and coupling constant from those of the present synthetic 1 presumably because their sample was the potassium salt and measurement conditions (pH, concentration, and temperature) were different.

(Received in Japan 17 April 1986)