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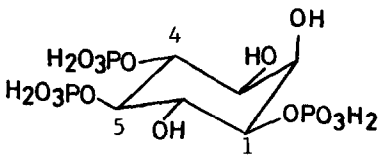
SYNTHESIS OF D-MYO-INOSITOL 1,3,4,5-TETRAKISPHOSPHATE

Shoichiro Ozaki,* Yoshihisa Kondo, Hiroyuki Nakahira,
Shinji Yamaoka, and Yutaka Watanabe

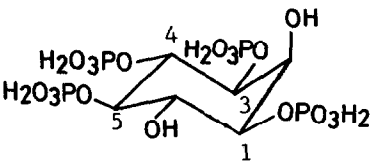
Department of Resources Chemistry, Faculty of Engineering,
Ehime University, Matsuyama 790, Japan

Abstract: Chemical synthesis of D-myo-inositol 1,3,4,5-tetrakisphosphate was accomplished starting from myo-inositol.

The role of D-myo-inositol 1,4,5-trisphosphate (Ins(1,4,5)P_3, 1) as the intracellular second messenger has now been accepted widely.[1] Recent explosive investigation on the cellular signalling system involving metabolism of inositol phosphates has claimed the existance of Ins(1,3,4,5)P_4 2 which seems to be a new second messenger,[2c] but its biological function is currently unclear.[1,2] Ins(1,3,4,5)P_4 2 was recently prepared enzymatically by the action of protein of Ins(1,4,5)P_3 kinase.[3] On the other hand, we have tried the chemical synthesis of 2 and now report an effective route for the synthesis of D-myo-inositol 1,3,4,5-tetrakisphosphate (2).

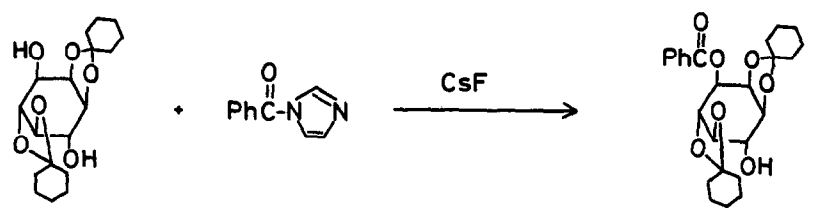


1



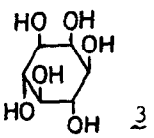
2

Racemic 1,2:4,5-biscyclohexylidene-myo-inositol 4 which can be readily available as crystals by the reaction of myo-inositol 3 with 1-ethoxycyclohexene in the presence of p-toluenesulfonic acid (p-TsOH) was selectively benzoylated at the 3 position (eq 1). Among benzoyl chloride, benzoic anhydride and benzoylimidazole[4] tested for the selective benzoylation, the last reagent

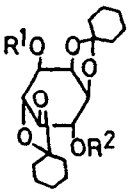


4 5 (1)

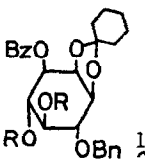
coupled with cesium fluoride[5] gave the best result. Thus, 4 was treated with benzoylimidazole (1.1 equiv) in the presence of cesium fluoride (2.0 equiv) in DMF at room temperature for 2 h to give 65% yield of the desired 5 accompanied with the starting diol 4. When benzoyl chloride or benzoic anhydride was used with or without DMAP, a significant amount of the other isomeric monobenzoate 6 was formed together with 5.



3



6: R^1=H, R^2=Bz
7: R^1=Bz, R^2=Bn
8: R^1=Bn, R^2=Bz

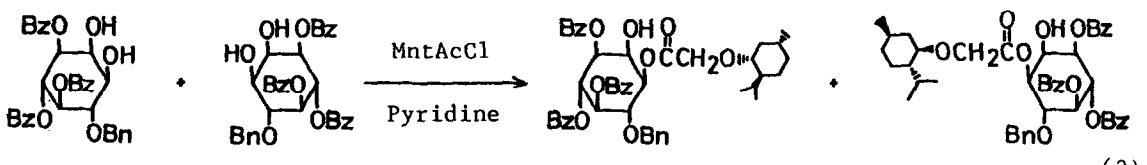


9: R=H
10: R=Bz

(Bn=benzyl, Bz=benzoyl) (6, 7, 8, 9, and 10 are racemic.)

The monobenzoate 5 thus obtained was then transformed into benzyl ether 7 (85% yield) by the reaction with benzyl trichloroacetimidate in the presence of trifluoromethanesulfonic acid.[6] The Williamson type ehter synthesis (NaH, benzyl chloride, DMF) for introduction of the benzyl group gave some products, among which DL-6-O-benzoyl-3-O-benzyl-myo-inositol (8) was obtained in 47% yield as a main product. At the next stage, selective removal of the cyclohexylidene group at the 4 and 5 positions in 7 was achieved by treatment with equimolar amount of ethylene glycol and a catalytic amount of p-TsOH in chloroform at room temperature to afford 4,5-diol derivative 9 in 80% yield. Benzoylation of 9 in pyridine (96% yield for 10) followed by hydrolysis in aq AcOH at 90-100 °C (quantitative yield) gave tribenzoyl derivative 11.

Racemic diol 11 was resolved by derivatizing to diastereomeric ℓ-menthoxyacetic esters as carried out in the synthesis of Ins(1,4,5)P_3[7] and Ins(2,4,5)-P_3[8] (eq 2). Thus, 11 was acylated by the reaction with ℓ-menthoxyacetyl chloride

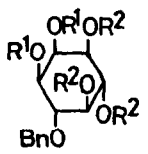


11α 11ℓ 11 12A 12B (2)

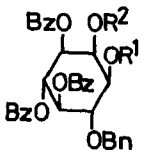
(MntAcCl=ℓ-menthoxyacetylchloride)

in pyridine at 0 °C for 10 min to afford the diastereomeric esters 12A and 12B in 83% yield. The desired ester 12A was obtained by medium pressure liquid chromatography in 37% yield based on racemic 11. In order to know the absolute configuration of 12A, another diastereomer 12B was utilized. Thus, menthoxyacetate 12B was first subjected to selective hydrazinolysis to give tribenzoate 11ℓ (86% yield) which was then converted to the 1,2-cyclohexylidene derivative 13 by treatment with 1-ethoxycyclohexene in the presence of a catalytic amount

of p-TsOH at 40 °C (85% yield). Removal of the benzoyl group in 13 (MeONa, MeOH, 91% yield for 14) followed by benzylation (NaH, benzyl chloride, DMF) afforded 15 which was in turn hydrolyzed (80% aq AcOH, 100 °C) without purification to L-3,4,5,6-tetra-O-benzyl-myo-inositol (16) in 70% yield from 14. Specific rotation ($[\alpha]_D^{15}$ +23.2° ($CHCl_3$)) and melting point (138-140 °C) of 16 supported the structure depicted below.[9] Consequently, the absolute configuration of 12A was verified as shown.



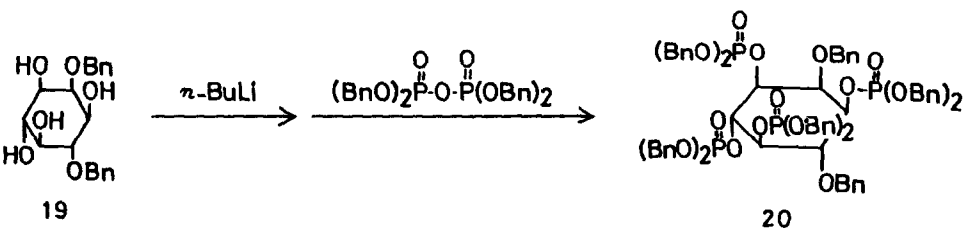
13: R^1=cyclohexylidene, R^2=Bz
14: R^1=cyclohexylidene, R^2=H
15: R^1=cyclohexylidene, R^2=Bn
16: R^1=H, R^2=Bn



17: R^1=MntAc, R^2=Bn
18: R^1=Bn, R^2=MntAc

The menthoxyacetyl group utilized for optical resolution of 11 was used at the next stage for the protection of the hydroxyl group at C-1. A desirable protective group of the hydroxyl group at C-2 in 12A is the benzyl. Introduction of this group was, however, much difficult because the hydroxyl group is substantially hindered and easy migration of the menthoxyacetyl group at C-1 to the C-2 position occurs under certain conditions. In the event, careful treatment of 12A with benzyl trichloroacetimidate (4 equiv) in the presence of TfOH[10] in dichloromethane and cyclohexane[6] furnished the desired benzyl ether 17 accompanied with a small amount of the regioisomeric 1,6-di-O-benzyl derivative 18 (66% yield).

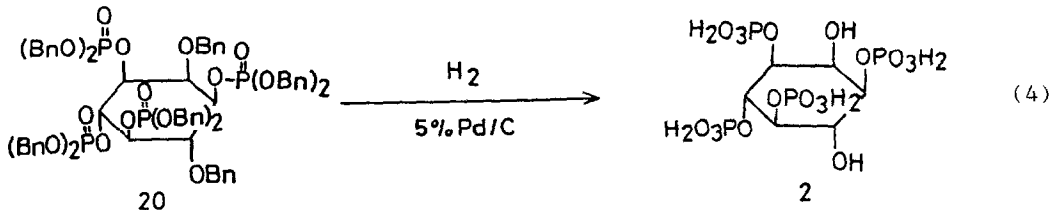
Dibenzyl ether 19 obtained by deacylation of 17 (MeONa, MeOH) was then subjected to phosphorylation. Phosphorylation of polyols is quite difficult, especially in the case of properly protected inositol derivatives which have the 1,2-dihydroxyl moiety,[11] probably because such diol systems bring about decrease of the reactivity and/or formation of cyclic phosphate in preference to second phosphorylation. As a solution to the problem, we have recently reported the polyphosphorylation of inositol derivatives by way of their lithium salts using tetrabenzyl pyrophosphate as a phosphorylating agent.[12] This phosphorylation method realized the rapid synthesis of the fully protected tetraphosphate 20 in a reasonable yield. Thus, D-2,6-di-O-benzyl-myo-inositol 19 was treated first with butyl lithium (4.8 equiv) in THF-DMSO (30:1) at -40 °C and the pyrophosphate (5.0 equiv) was immediately added to the resulting



19 → 20 (3)

solution. After changing the cooling bath for an ice-salt-water bath (0 °C), the solution was stirred for an additional 2 h to give 20 in 59% yield (eq 3).

Finally, removal of protective groups from 20 was achieved really simply in a single step by catalytic hydrogenolysis (H_2, 5% Pd/C, aq MeOH, eq 4) and 2 was isolated as the ammonium salt (79% yield calculated tentatively as the octa-ammonium salt of 2).[13] The structure of 2 thus obtained was elucidated unambiguously by NMR analysis.[14]



(4)

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9. Literature values: $[\alpha]_D^{20}$+25.0°, mp 140.2-142.1 °C: V. I. Shvets, B. A. Klyashchitskii, A. E. Stepanov, and R. P. Evstigneeva, Tetrahedron, 29, 331 (1973).
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12. Y. Watanabe, H. Nakahira, M. Bunya, and S. Ozaki, to be submitted to Tetrahedron Letters.
13. Specific rotation of 2: $[\alpha]_D^{24}$-13° (c 1.0, H_2O).
14. We obtained PMR spectrum of 2 similar to that reported by Cerdan et al.[3] We further characterized the structure by 2D NMR experiment.

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