A SHORT STEP AND PRACTICAL SYNTHESIS OF *MYO*-INOSITOL 1,3,4,5-TETRAKISPHOSPHATE

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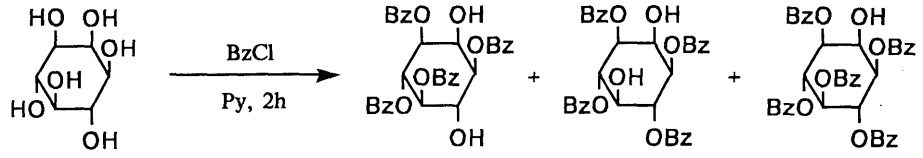
The reaction of *myo*-inositol with benzoyl chloride gave 1,3,4,5-tetra-O-benzoyl-*myo*-inositol as a major product which was conveniently converted to *myo*-inositol 1,3,4,5-tetrakisphosphate. The tetrabenzoate was optically resolved by means of chiral column chromatography using Chiralcel OD.

KEYWORDS *myo*-inositol 1,3,4,5-tetrakisphosphate; *myo*-inositol; benzoylation; phosphorylation; chiral column chromatography

Attempting an efficient synthesis of *myo*-inositol polyphosphates, it is important how quickly an adequately protected inositol derivative can be derived as a substrate for phosphorylation. In most cases of inositol phosphate synthesis ketals such as cyclohexylidene and isopropylidene groups were first formed from *myo*-inositol (**1**)[1] mainly because other suitable candidates for their synthesis are difficult to prepare regioselectively from **1**. Unfortunately, this route is rather indirect and tedious in some cases. In contrast, our recent work showed that 1,3-dichloro-1,1,3,3,-tetraisopropyldisiloxane reacted regioselectively with **1** to afford the 1,6:3,4-disiloxane derivative which was conveniently transformed to *myo*-inositol 1,3,4,6-tetrakisphosphate.[2] Such a straightforward protection of *myo*-inositol itself provides a short step synthesis of inositol phosphates. Along this line, the reaction of **1** with benzoyl chloride was examined. We report here the results and utilization of a benzoylated product for a convenient synthesis of *myo*-inositol 1,3,4,5-tetrakisphosphate (**7**) which apparently is an important metabolite in an intracellular signal transduction system.[3] An adequate supply of it has been needed for biological investigation.

Benzoylation of *myo*-inositol with 3.5 equivalent of benzoyl chloride in pyridine for 2 h afforded three main products **2**. The ratio of these products varied depending on reaction temperature. Thus, the reaction at 90 °C gave 33% of 1,3,4,5-tetra-O-benzoyl-*myo*-inositol (**2a**) accompanied with 14% of **2c**, a waste product. The yield of the latter increased when the reaction was conducted at 65 °C. At room temperature, the desired **2a** was obtained in a lower yield at and **2c** became a major product. These results may be explained in terms of the solubility of benzoylated inositols (*myo*-Inositol is sparingly soluble in pyridine at room temperature and the fewer benzoylated derivatives tend to be less soluble.).



	1	2a	2b	2c
r.t.		15 %	3 %	48 %
65°C		34 %	9 %	25 %
90 °C		33 %	13 %	14 %

Bz=benzoyl

Chart 1

Since 1,3,4,5-tetrabenzoate **2a** can be prepared in one step from *myo*-inositol which is readily available as a commercial chemical and its isolation in large quantities is easy, it may be quite promising as a synthetic intermediate for the synthesis of *myo*-inositol 1,3,4,5-tetrakis-phosphate (**7**). Thus, **2a** was benzylated by the reaction with benzyl trichloracetimidate in the presence of trifluoromethanesulfonic acid to give 2,6-dibenzyl ether **3** in 70% yield which was

then subjected to debenzoylation by the action of sodium methoxide under refluxing for 3 h to give 1,3,4,5-tetrol **4** in 72% yield. Four hydroxyl groups in **4** were then phosphorylated smoothly by the use of a new phosphitylating agent **5**.[4] Treatment of tetrol **4** with **5** (6 eq) in the presence of tetrazole (9 eq) at room temperature for 20 min formed the corresponding phosphite which after being stirred with a limited amount of water (20 eq) at the same temperature for 10 min was oxidized with *m*CPBA (9 eq) for 20 min (added at -40 °C and stirred at r.t.) to give the fully protected phosphate **6** in 90% yield. Finally, **6** was deprotected at once by hydrogenolysis (H_2, 10% Pd-C, r.t., 17 h) and *myo*-inositol 1,3,4,5-tetrakisphosphate **7** was isolated quantitatively as ammonium salt.

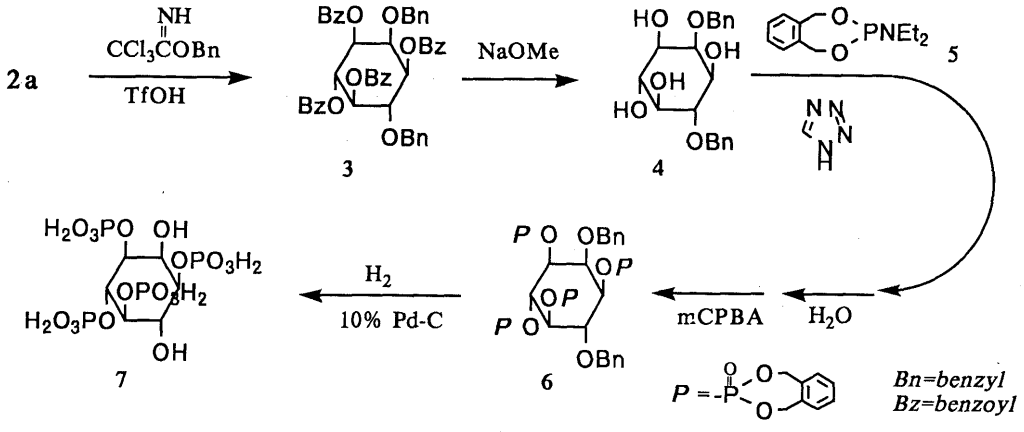


Chart 2

Optical resolution of 1,3,4,5-tetrabenzoate was accomplished by means of a chiral column chromatography using Chiralcel OD™ (Daisel Chemical Industries, Ltd.).[5] Thus, a short-step synthesis of D- and L-**7** has been formally accomplished.

Among reported methods for synthesizing **7**,[6] some groups[6b,e,f] suggested the use of an orthoformate derivative of **1**. The present synthesis route provides an alternative and practical method for synthesizing optically active *myo*-inositol 1,3,4,5-tetrakisphosphate.

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5) 1D-1,3,4,5-tetra-O-benzoyl-*myo*-inositol (**D-2a**): $[\alpha]_D^{22}$ -5.35°(c 2.4, $CHCl_3$); 1L-1,3,4,5-tetra-O-benzoyl-*myo*-inositol (**L-2a**): $[\alpha]_D^{22}$ +5.42°(c 2.5, $CHCl_3$). Absolute configurations of both enantiomers were determined by transforming them to 2,4-dibenzyl ethers **4** and comparing their specific rotation values with those reported for **4** (Ref. 6b and 6d).
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