A Short Step Synthesis of Optically Active *myo*-Inositol 1,3,4,5-Tetrakis(phosphate) and *myo*-Inositol 1,4,5-Tris(phosphate) from 1,3,5-Tri-*O*-benzoyl-*myo*-inositol

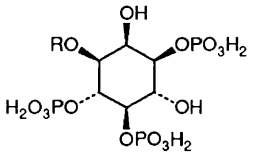
Yutaka Watanabe,* Takahiro Fujimoto, Tomoichi Shinohara and Shoichiro Ozaki*

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

A short and practical synthesis of *myo*-inositol 1,3,4,5-tetrakis(phosphate) and *myo*-inositol 1,4,5-tris(phosphate) has been achieved by direct benzoylation of *myo*-inositol, enantioselective tartaroylation and removal of acyl protecting groups with Grignard reagents.

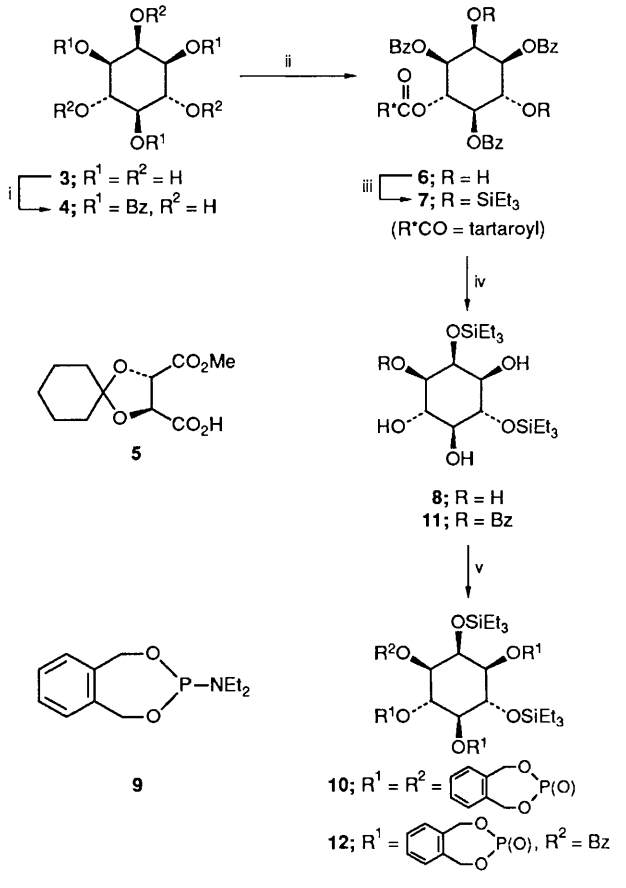
Recently, there have been many reports[1] on the synthesis of *myo*-inositol 1,3,4,5-tetrakis(phosphate) (IP_4, **1**) and *myo*-inositol 1,4,5-tris(phosphate) (IP_3, **2**), which are metabolites in the phosphoinositide cycle concerning a new intracellular signal transduction system.[2] Chemical synthesis of racemic IP_4 has been achieved in six or seven steps by several groups, whereas the synthesis of optically active IP_4 took 10 to 13 steps. This difference is attributed partly to the tedious derivatisation steps needed to form diastereoisomers, their separation, and removal of the chiral auxiliary. These facts have prevented a practical synthesis of optically active IP_4. Recently, we have found an efficient method for obtaining optically active inositol derivatives based on an enantioselective acylation using a tartaric acid monoester[3] instead of optical resolution. Coupling this methodology with a straightforward protection of the starting *myo*-inositol,[4] a short and practical synthesis of IP_4 has now been found. Optically active IP_3 has been also prepared concisely from the same synthetic intermediate. In this communication, these results are described.

Benzoylation of *myo*-inositol **3** with benzoyl chloride (2.5 equiv.) in pyridine at 90 °C readily yielded isolable symmetrical 1,3,5-tri-*O*-benzoyl-*myo*-inositol **4**;† the benzoate could



1; R = PO_3H_2
2; R = H

† *myo*-Inositol (3.0 g), benzoyl chloride (3.9 ml) and anhydrous pyridine (100 ml) were stirred together at 90 °C for 1 h; conventional work-up and flash chromatography (SiO_2, AcOEt : CH_2Cl_2, 1 : 6) gave **4** (1.2 g) in 15% yield, R_f 0.3 (AcOEt : CH_2Cl_2, 1 : 6), m.p. 133–5 °C (from benzene).



Scheme 1 *Reagents and conditions*: *i*, BzCl (2.5 equiv.), pyridine; *ii*, **5**, MsCl, *N*-methylmorpholine, dimethylaminopyridine, tetrahydrofuran; *iii*, Et_3SiCl, imidazole, dimethylformamide; *iv*, EtMgBr (for **8**), MeMgBr (for **11**), Et_2O; v, **9**, tetrazole, CH_2Cl_2, then *m*-chloroperbenzoic acid; Bz = PhCO; Ms = $MeSO_2$

be transformed to the unsymmetrical monotartaroylation product **6** in a highly enantioselective manner by treatment with **5**.[3] The tartrate **6** with 96% diastereoisomeric excess was then silylated with triethylsilyl chloride to afford the disilyl ether **7** in 98% yield. Fortunately, the ether **7** became optically pure after one recrystallisation from methanol, as judged from HPLC and NMR analyses; $[\alpha]_D^{24}$ + 7.55° (*c* 1.0, $CHCl_3$), mp. 139–141 °C.

Removal of the acyl groups from **7** by using usual nucleophilic reagents such as ammonia, sodium methoxide and lithium methoxide gave poor yields of the desired tetrol **8** and several migration products were formed. In order to prevent the attack on a silyl group (hard acid) by alkoxide, generated from the liberation of a benzoyl group, the magnesium salt of the alkoxide was chosen as the softer alkoxide. Thus, the silyl ether **7** was treated in diethyl ether with ethylmagnesium bromide (~35 molar equiv.) under reflux for 3 h to give the tetrol **8** in 89% yield with complete retention of both silyl groups at the 2 and 6 positions. Phosphorylation of **7** was carried out successfully by a new amidite method[5] using *O*-xylylene phosphoramidite **9** to give **10** in 90% yield. Treatment of the fully protected phosphate **10** under hydrogenolysis conditions over Pd–C in aqueous MeOH resulted in the removal of all protective groups at once to afford D-*myo*-inositol 1,3,4,5-tetrakis(phosphate) **1** in quantitative yield, potassium salt, $[\alpha]_D^{20}$ −3.83° (*c* 3.6, H_2O, pH 5.4).‡

The deblocking method using a Grignard reagent employed above for the removal of acyl groups in **7** was applied for the selective deprotection of **7**. Thus, methylmagnesium bromide (~35 molar equiv.) in place of the ethyl Grignard used for obtaining tetrol **8**, was reacted with **7** under reflux in diethyl ether for 2 h to give 1,4,5-triol **11** in 74% yield which retained the benzoyl group at the 3 position. Treatment of **7** with ethylmagnesium iodide (20 equiv.) at room temperature for 2 h also gave **11** in 47% yield together with **8** in 28% yield. It was observed during the deprotection of the acyl groups that methylmagnesium iodide was much less reactive than ethylmagnesium bromide. These differences in reactivity seem to be attributed to both alkyl and halide moieties. The triol 11 was then derived to the final D-*myo*-inositol 1,4,5-tris(phosphate) **2**, potassium salt, (80% overall yield), $[\alpha]_D^{23}$ −9.4° (*c* 1.2, H_2O, pH 6.9),‡ in a manner similar to that used in the synthesis of **1**, except for additional treatment with sodium methoxide for removal of the remaining benzoyl group.

In summary, both optically active IP_4 and IP_3 have been effectively synthesised in the shortest number of steps among the reported synthetic methods.[1,6] In the present approach, a promising method for removal of an acyl group which is effective even in the presence of a silyl group at the neighbouring position has been exploited. The usefulness of this deblocking method is under investigation.

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‡ ^1H ^{13}C and ^{31}P NMR spectra fully agreed with those of IP_4 and IP_3 obtained by other methods (S. Ozaki, Y. Kondo, H. Nakahira, S. Yamaoka and Y. Watanabe, *Tetrahedron Lett.*, 1987, **28**, 4691; S. Ozaki, Y. Watanabe, T. Ogasawara, Y. Kondo, N. Shiotani, H. Nishii and T. Matsuki, *Tetrahedron Lett.*, 1986, **27**, 3157).