# Synthesis of (1-Deoxy-4,6-*O*-bisphosphoryl-β-D-mannopyranosyl)methane Phosphonate as an Analogue of L-*myo*-Inositol-1,4,5-trisphosphate

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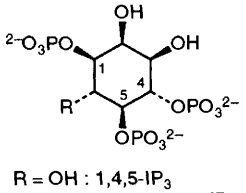
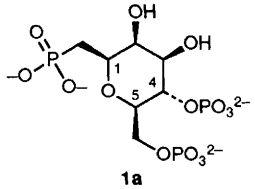
Synthesis of the α- and β-anomers of the title compound starting from D-mannose is reported.

Since the discovery that D-*myo*-inositol-1,4,5-trisphosphate plays a pivotal role as a second messenger in transmembrane signalling that mobilizes calcium ions from intracellular storage, intensive research efforts have been expended from the standpoints of both fundamental interests and potential pharmacological intervention for therapeutic utilities.[1–6] As a part of our efforts in understanding the molecular recognition aspect of the inositol phosphate-dependent signal tranduction, including phospholipase C, inositol-1,4,5-trisphosphate receptor, and the metabolic enzymes, we have been studying the synthesis of various unnatural inositol analogues. The unnatural L-inositol-1,4,5-trisphosphate was synthesized and reported to have a poor ability to release calcium ions. Removal of the hydroxy group at the 6 position of the natural agonist was also reported to have calcium releasing potency 100 times weaker than the natural agonist.[7] We have constructed structures of *myo*-inositol and several hexopyranoses on the basis of MM2 calculations, and compared their geometries using computer graphics. It has been found that the L-isomer of the *myo*-inositol-1,4,5-trisphosphate has a molecular size and shape very similar to those of D-mannose-1,4,6-trisphosphate, whereas the natural D-isomer matches well with D-galactose-1,2,6-trisphosphate. The superimposition root mean square (RMS) in both pairs is *ca.* 0.055–0.063, and their volume differences less than 2%.[8] Thus, we have decided to synthesize D-mannose-1,4,6-trisphosphate[9] and the corresponding phosphonate analogues, and herein report the synthesis of the title compound **1**.

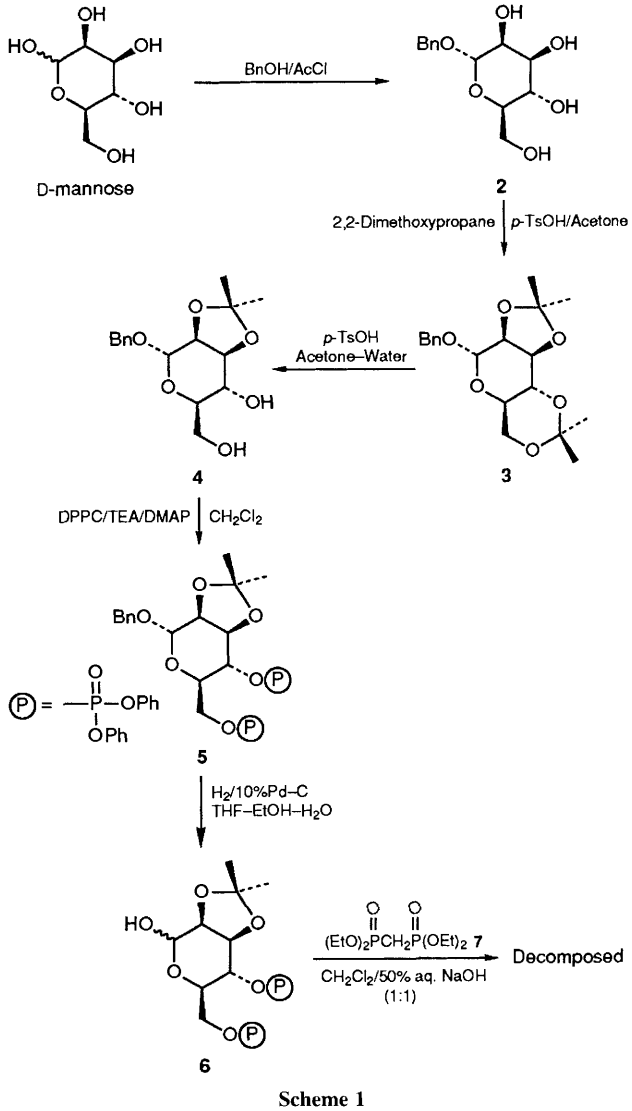
D-Mannose was converted to benzyl α-D-mannopyranoside **2** in 90% yield essentially according to the literature proce-



R = OH : 1,4,5-IP$_3$
R = H : 6-Deoxy-1,4,5-IP$_3$



**1a**



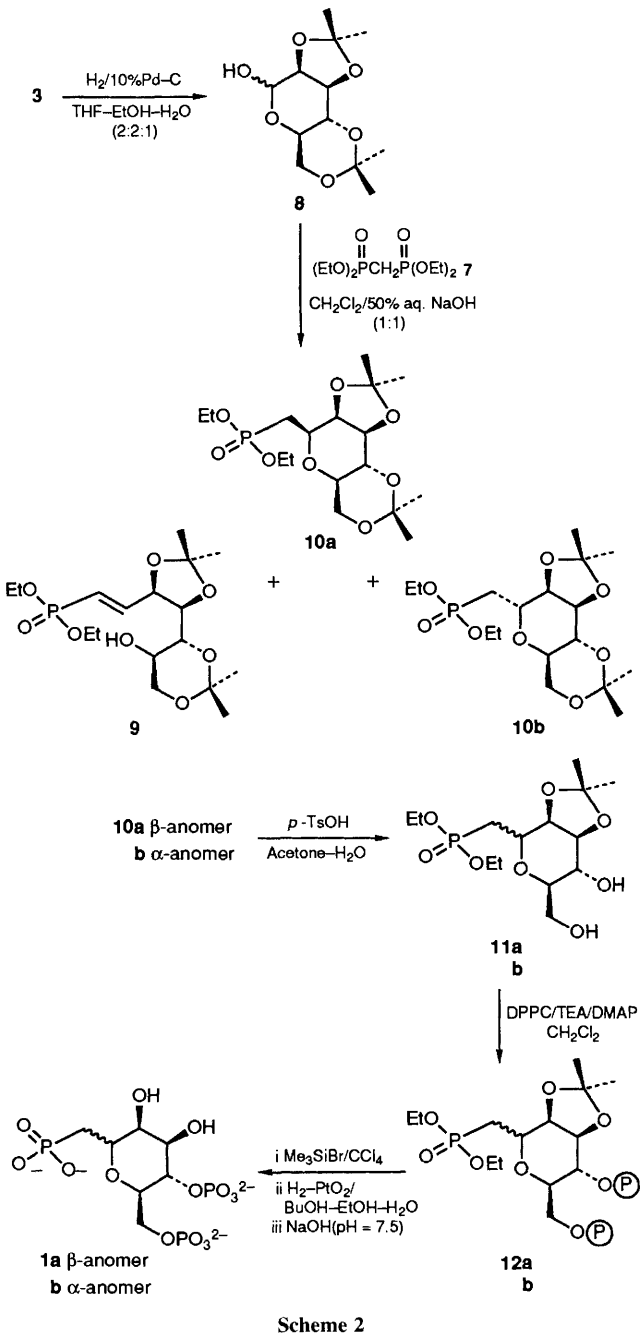

**Scheme 1**

dure.[10] Treatment of compound **2** with 2,2-dimethoxypropane in acetone in the presence of a catalytic amount of toluene-*p*-sulfonic acid gave benzyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside **3**. When subjected to the controlled hydrolysis conditions first described by Evans *et al.*,[11] the diacetonide **3** was converted to benzyl 2,3-*O*-isopropylidene-α-D-mannopyranoside in good yield. The 4,6-dihydroxy groups in compound **4** were readily phosphorylated by means of diphenyl phosphorochloridate in the presence of 4-dimethylaminopyridine and triethylamine to provide **5**. Although formation of cyclic phosphate is known to occur sometimes for diols and polyols under these conditions,[12] it was not a problem in the present case. The benzyl protecting group in compound **5** was efficiently removed by hydrogenolysis to give compound **6**. However, all attempts to introduce the desired phosphonate functionality at the anomeric position have failed. Apparently, the starting material did not survive the modified Wittig reaction conditions[13] (Scheme 1).

As an alternative (Scheme 2), when compound **8**, obtained from **3** *via* hydrogenolysis, was treated with tetraethyl methylene bisphosphonate and NaOH under two-phase conditions[14] a smooth reaction took place to give a mixture of unsaturated phosphonate **9** and the epimers of the cyclic sugar phosphonate **10**.†

The ratio of the cyclic products **10a** and **b**, obtained in 44% yield, was found to be 1:2.7 in favour of the β-anomer. The stereochemical assignments were made on the basis of the $^1$H NMR resonance of the C-5 proton, which is expected to be sensitive to the steric environment of the anomeric position because of the 1,3-interactions. The C-5 proton peak in the α-anomer appears at δ 3.15 as a ddd, as opposed to δ 3.40 in the β-anomer, clearly showing that the C-5 proton in the α-anomer experiences the steric upfield shift. In addition, the chemical shifts for the anomeric protons in the *C*-glycopyranosides were reported to occur at the lower field in the *cis*-1,2-substituted isomers than the *trans*-1,2-substituted. In the present case, the anomeric proton chemical shifts are observed at δ 4.28 in the *cis*-1,2-substituted β-anomer **10a**, and at δ 4.15 in the *trans*-1,2-substituted α-anomer **10b**. The fact that the $^{13}$C NMR resonance of the anomeric carbon appears at δ 76.5 in the β-anomer and at δ 75.5 in the α-anomer is also consistent with the general observation that the C-1 chemical shift of the α-anomer appears at the higher field than that of the β-anomer.[15,16]

The question whether or not the acyclic compound **9** might be an intermediate to the cyclic product **10** cannot be unequivocally answered at this time. When compound **9** was treated with sodium methoxide in methanol over an extended period, the formation of compound **10** was not observed.




**Scheme 2**

We have also examined the possible epimerization between the cyclic compounds **10a** and **b** by $^1$H NMR spectroscopy. Treatment of either anomer with sodium methoxide in methanol for 4 days resulted in no detectable epimerization.[17–19]

Compound **10a** was hydrolysed with *p*-TsOH in aqueous acetone to give **11a**, which was phosphorylated with diphenyl phosphorochloridate to yield the desired product **12a** in 87% yield. Compound **10b** was similarly converted to product **12b** through **11b**. Compounds **12a** and **b** have been thoroughly characterized, and all the spectral data are fully consistent with assigned structures. In the final steps of the synthesis, **12a** and **b** each was successively treated with an excess of bromotrimethylsilane,[20] and hydrogen over $PtO_2$ to yield (1-deoxy-4,6-bisphosphoryl-β-D-mannopyranosyl)methane phosphonate **1a** and its α-anomer.‡ These phosphonates are currently

† *Spectroscopic data* for **9**: $^1$H NMR ($CDCl_3$) 1.31 (6H, t, *J* 7.1 Hz), 1.38 and 1.41 (each, 3H, s), 1.46 (6H, s), 2.98 (1H, bs), 3.60–3.94 (3H), 3.84 (1H), 4.07 (5H, m), 4.70 (1H, m), 6.02 (1H, d,d,d, *J* 20.2, 17.1 and 1.6 Hz), 6.76(1H, d,d,d, *J* 21.8, 17.1 and 4.3 Hz); $^{31}$P NMR ($CDCl_3$) 18.9; IR (neat) 3359, 2940, 1639, 1450, 1379, 1106 and 762 cm$^{-1}$; MS(EI) *m/z* 395 ($MH^+$), 379.

**10a**: $^1$H NMR ($CDCl_3$) 1.32 (6H, t, *J* 7.0 Hz), 1.35, 1.42, 1.51 and 1.52 (each 3H, s), 2.01 (1H, d,d,d, *J* 15.3, 15.3 and 8.2 Hz), 2.16 (1H, d,d,d, *J* 15.3, 15.3 and 5.0 Hz), 3.40 (1H, d,d,d, *J* 10.8, 10.0 and 5.5 Hz), 3.72 (1H, d,d, *J* 10.8 and 10.8 Hz), 3.86 (1H, d,d, *J* 10.8 and 5.5 Hz), 3.97 (1H, d,d, *J* 10.0 and 6.8 Hz), 4.10 (4H, q, *J* 7.0 Hz), 4.19–4.28 (3H, m, $J_{1H-2H}$ 4.8 Hz by *J*-resolved 2D spectrum); $^{13}$C NMR ($CDCl_3$) 16.4, 16.5, 19.0, 25.4, 27.6, 29.0, 29.6, 61.8, 62.7, 64.5, 69.7, 72.1, 75.4, 76.5, 99.6 and 110; MS(FAB) *m/z* 395 ($M^{+1}$), 379.

**10b**: $^1$H NMR ($CDCl_3$) 1.32 (6H, t, *J* 7.1 Hz), 1.35, 1.42, 1.50 and 1.54 (each 3H, s), 2.21 (1H, d,d,d, *J* 18.4, 15.4 and 6.7 Hz), 2.32 (1H, d,d,d, *J* 18.4, 15.4 and 6.7 Hz), 3.15 (1H, d,d,d, *J* 10.2, 10.2 and 5.6 Hz), 3.70 (1H, d,d, *J* 10.2 and 7.0 Hz), 3.71 (1H, d,d, *J* 10.2 and 10.2 Hz), 3.88 (1H, d,d, *J* 10.2 and 5.6 Hz), 4.10 (4H, q, *J* 7.1 Hz), 4.05–4.16 (2H, m), 4.21 (1H, d,d, *J* 5.1 and 2.2 Hz); $^{13}$C NMR ($CDCl_3$) 16.3 16.4, 18.8, 26.3, 28.4, 28.5, 29.0, 61.5, 61.9, 62.0, 69.8, 72.1, 72.9, 75.5, 76.0, 99.6 and 109.5; $^{31}$P NMR ($CDCl_3$) 28.3; MS(EI) *m/z* 394 ($M^+$), 379.

‡ $^{31}$*P NMR data* for: **12a** ($CDCl_3$) δ 27.0, −11.3 and −12.1; **12b** ($CDCl_3$) 27.7, −11.4 and −12.0; **1a** ($D_2O$) 23.2, 5.2 and 4.9; **1b** ($D_2O$) 17.2. 5.3 and 5.2.

undergoing biological evaluation for their possible activity in inositol-1,4,5-trisphosphate induced calcium release.

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