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Direct mono-phosphorylation of 1,3-diols. A synthesis of FTY720-phosphate

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Abstract—A novel method for selective and direct phosphorylation of various 1,3-diols using silver(I) oxide, tetrabenzyl pyrophosphate (TBPP), and tetrahexylammonium iodide affording mono-phosphates was developed. We applied the present method to the synthesis of FTY720-phosphate.

FTY720[1] (**1**, Fig. 1) is a novel immunosuppressive compound, which is currently undergoing clinical phase III trials for prevention of kidney graft rejection. Unlike other standard immunosuppressants (e.g., Cyclosporin A or FK506), **1** possesses an inhibitory action on migration of T- and B-lymphocytes from the thymus and secondary lymphoid tissues.[2] Recently, it was revealed that **1** is rapidly mono-phosphorylated in vivo to form FTY720-phosphate (**2**, Fig. 1), which is an agonist for four sphingosine-1-phosphate (S1P) receptors ($S1P_{1,3,4,5}$) out of five ($S1P_{1-5}$) and responsible for the biological activity of **1**.[3,4] We believe that complementary agonists for each S1P receptor will be valuable tools to ascertain the mechanism of immunosuppressive action of **1**, and provide further information to researchers. For this purpose, it is important to develop a convenient method for mono-phosphorylation of **1** and to synthesize various analogs of **2**.

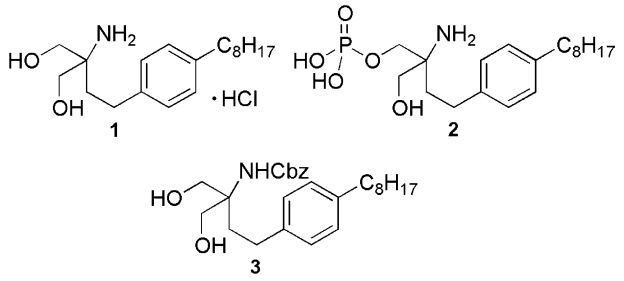

Figure 1. FTY720 (**1**), FTY720-phosphate (**2**), and N-protected FTY720 (**3**).

Compound **1** has a propan-1,3-diol moiety. Because **1** has the two hydroxyls in it, to properly protect one of the hydroxyls has been needed before the phosphorylation of the other. Indeed, we and other groups[3,5,6] reported the synthesis of **2**; however, the protection to prevent the formation of the bisphosphorylated byproduct complicated their syntheses. Accordingly, it will be valuable to develop a synthetic method for direct mono-phosphorylation of diols without protecting one of the hydroxyls. We required a selective and convenient method of phosphorylation with wide adaptability for several kinds of substrates having the propane-1,3-diol moiety.

There have been numerous reports[7,8] on the phosphorylation of alcohols for the syntheses of nucleotides, phosphorylated inositols, etc. The use of phosphoramidite,[7a–d] one of frequently used reagents, on N-protected FTY720 (**3**) gave no mono-phosphate but a cyclic phosphate.[9] Other highly useful reagents, the pyrophosphate[7e–h] or the chlorophosphate,[7i–l] require strong bases such as butyl lithium and sodium hydride, and the bases make their reactivity too high. A method for selective mono-phosphorylation of inositol derivatives using dibutyltin oxide and pyrophosphate[7h] has been

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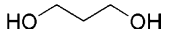
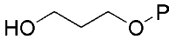
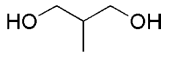
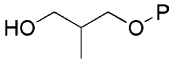
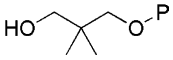
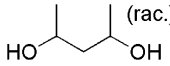
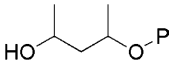
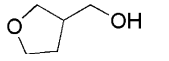
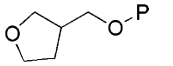
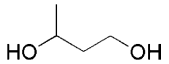
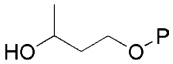
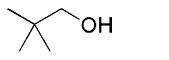
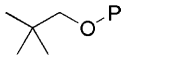
reported; however, the method failed to give an intermediate for **2**. Under a similar condition described in the literature, compound **3** was converted into an oxazolidinone formed by cyclization of the carbamate moiety and one of the hydroxyls. As described above, traditional phosphorylation methods using phosphoramidite or pyrophosphate were ineffective for mono-phosphorylation of **3**.

On the other hand, Bouzide and Sauve[10] reported a method for mono-protection and mono-tosylation of symmetrical diols utilizing chelation and Lewis acidity of silver(I) oxide.[11] We leveraged this intermolecular chelating system between silver(I) oxide and diol for mono-phosphorylation of propane-1,3-diols with tetrabenzyl pyrophosphate[12] (TBPP) as a phosphatic donor. In this communication, we describe a concise procedure to obtain mono-phosphates from various non-protected diols without any oxidative reagents or strong bases under a mild condition, and the application of the present method to provide **2**.

In our initial investigation, reactivity and selectivity of our method were evaluated in the phosphorylation of simple diols. The present procedure[13] is as follows. To a solution of a diol, TBPP and silver(I) oxide in dichloromethane was added tetrahexylammonium iodide.[14] The mixture was stirred at ambient temperature. After purification, the corresponding mono-phosphate was obtained. Although 2 equiv of the phosphorylating reagent was used, bisphosphorylated byproducts of simple diols were not detected. The results are summarized in Table 1.

Propane-1,3-diols underwent smooth conversion to the corresponding mono-phosphorylated alcohol derivatives in 69–76% yields (entry 1–3). When 1.1 equiv of the phosphorylating reagent was used, the desired mono-phosphate was obtained in a slightly low yield (entry 4). Although the phosphorylations of secondary alcohol (entry 5) and mono-ol (entry 6), which has a similar structure to the diol in entry 2 except lacking the other hydroxyl, proceeded in a slightly low yield, 1-methylpropan-1,3-diol including both a primary and a secondary alcohol was selectively mono-phosphorylated at the primary alcohol in a good yield (entry 7). These results suggested that steric requirement for the chelation between silver(I) oxide and two hydroxyls would have a crucial role for the smooth reaction. As expected, 2,2-dimethyl-1-propanol (entry 8), which is a model compound of a hindered alcohol and lacks an internal chelatable hydroxyl, had no reactivity for phosphorylation.

Table 1. Direct mono-phosphorylation of 1,3-diols

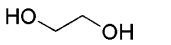
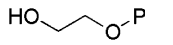
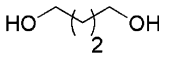
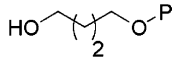
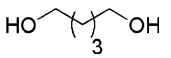
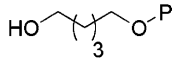
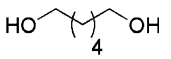
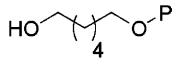
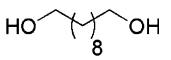
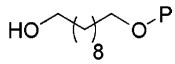
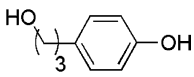
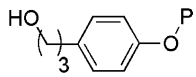
Entry[a]	Substrate	Product[b]	Yield[c,d]
1			69
2			74
3			76
4[e]			55
5			44[f]
6			43
7			76
8			N.R.[g]

[a] Conditions: TBPP (2 equiv), Ag_2O (2 equiv), tetrahexylammonium iodide (2 equiv) in DCM at room temperature for 20 h.
[b] P = P(O)(OBn)$_2$.
[c] Isolated yield.
[d] No bisphosphorylated byproduct was observed.
[e] 1.1 equiv of all reagents was used.
[f] No diastereoselectivity was observed.
[g] No reaction.

Next we examined the reaction on other 1,*n*-diols and a substrate having a competing phenol group (Table 2). Although ethylene glycol (entry 1) gave little phosphorylated product, 1,4-butanediols (entry 2) was efficiently phosphorylated in a similar yield to that of 1,3-propanediol (Table 1, entry 1). As for a series of 1,*n*-diols, increasing the number of the carbon atoms between the two hydroxyls resulted in a decrease of the yields for the reaction; the treatment of 1,10-decanediol (entry 5) failed to give the corresponding mono-phosphate, suggesting that the present method was applicable to mono-phosphorylation of 1,*n*-diols (n = 3–6). The phenolic hydroxyl of 3-(4-hydroxyphenyl)-1-propanol (entry 6) was selectively phosphorylated over the aliphatic hydroxyl in an excellent yield. This selectivity to the phenolic hydroxyl could be attributed to its higher acidity; therefore, the method would be useful for the selective phosphorylation on the phenol moiety without any protection of aliphatic hydroxyls.

On the basis of the result on the simple alcohols, we applied the method to the synthesis of **2** as shown in Scheme 1. We examined the phosphorylation of

Table 2. Direct mono-phosphorylation of diols

Entry[a]	Substrate	Product[b]	Yield[c,d]
1			Trace
2			71
3			43
4			31
5			Trace
6			97

[a] Conditions: TBPP (2 equiv), Ag_2O (2 equiv), tetrahexylammonium iodide (2 equiv) in DCM at room temperature for 20 h.
[b] P = P(O)(OBn)$_2$.
[c] Isolated yield.
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