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Selective phosphorylation of diols with a Lewis acid catalyst

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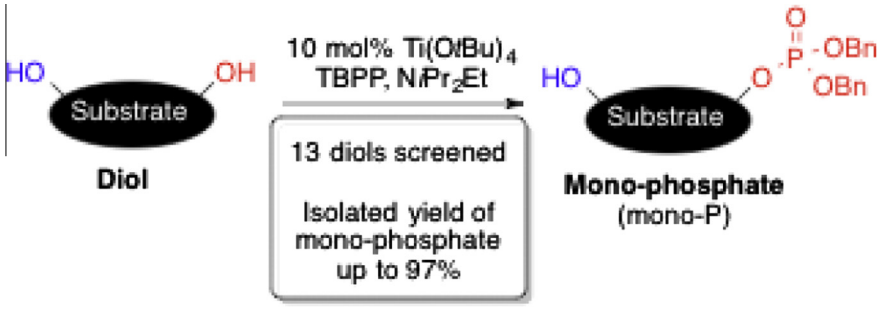
ABSTRACT

We report a method for the Lewis acid catalyzed phosphorylation of diols with pyrophosphates. Titanium alkoxides were found to be effective catalysts in the selective mono-phosphorylation for a range of diols. Diols of varying chain lengths and substituents were screened, to study the factors that influence mono- versus di-phosphorylation. It was discovered that 2-alkyl-2-amino-1,3-propanediols can be selectively mono-phosphorylated in up to 97% isolated yield. This structural core is mono-phosphorylated in numerous immunomodulating compounds including the FDA-approved drug, FTY720.



The mono-functionalization of polyols has been of particular interest to synthetic chemists due to the plethora of natural products and pharmaceuticals that require this transformation for their synthesis. These reactions are often hampered by low yields due to reactivity at multiple hydroxyl groups, yet selective strategies exist for the acylation,[1] alkylation,[2] benzoylation,[3] phosphorylation,[4] silyation,[5] and tosylation[6] of polyols. These reactions rely on enzymes,[7] organocatalysts[8] or reagents such as silver(I) oxide,[6a] organotin compounds,[3a] or borinic acids[6b] to facilitate the modification of one hydroxyl group in the polyol.

The discovery of FTY720 (Fingolimod, Gilenya) highlighted the need for synthetic methods for the functionalization of diols. FTY720 is the first orally available drug approved for the treatment of relapse-remitting Multiple Sclerosis.[9] In 2002 it was discovered that the key immunomodulating compound was not the diol FTY720, but the mono-phosphate FTY720-P, which is generated in vivo by sphingosine kinase (see Fig. 1).[10] FTY720-P is a mimic of spingosine-1-P and acts as a high affinity agonist for four of the five spingosine-1-phosphate G-protein coupled receptors resulting in the sequestration of lymphocytes in secondary lymphoid organs.[11] FTY720 was generated as a structural analogue of myriocin, a natural product with immunosuppressive activity 10-100 times greater than Cyclosporine A.[12] Researchers found that the key structural element for the immunomodulating response was a 2-alkyl-2-amino-1,3-propanediol. Interestingly, FTY720 was created as a simplified analogue of myriocin lacking any stereogenic centers, however the active drug (FTY720-P) is chiral upon mono-phosphorylation and only the (*S*)-enantiomer is medicinally relevant.[13] The reported chemical syntheses of FTY720-P generate the compound as a racemate,[4a] utilize chiral HPLC for enantiomer separation,[14] use enzymatic acylation in the

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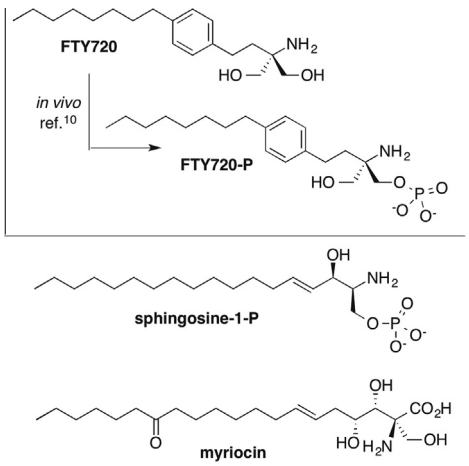


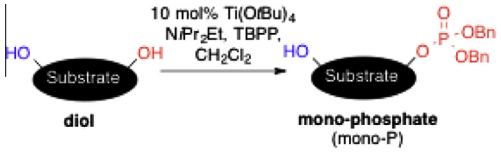
Figure 1. FTY720, FTY720-P, and structurally related immuno modulating natural products.

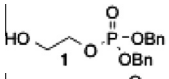
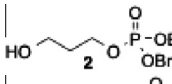
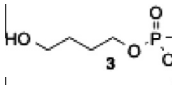
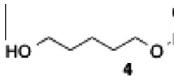
desymmetrization of the diol,[15] or use a Sharpless asymmetric epoxidation followed by functional group interconversions.[16] We sought a method for the direct phosphorylation of 2-alkyl-2-amino-1,3-propanediols to facilitate a rapid synthesis of FTY720-P and its analogues.

Catalytic methods for the phosphorylation of alcohols include the use of P(III) reagents (such as phosphoramidites[17]) followed by oxidation, or P(V) reagents (such as chlorophosphates[18] or pyrophosphates[19]). We sought to test our recently disclosed method on the Lewis acid catalyzed phosphorylation of alcohols with pyrophosphates on the mono-phosphorylation of diols.[19] We began this study by examining if the carbon chain length between the two hydroxyls of a diol would have an effect on the selectivity of mono-phosphorylation (see Table 1). All reactions were run with 10 mol % of the Lewis acid catalyst ($Ti(OtBu)_4$), 1.2 equiv of phosphorylating agent (tetrabenzyl pyrophosphate (TBPP)), and 1.5 equiv of proton scavenger ($NiPr_2Et$) in CH_2Cl_2 and quenched after 4 h.[20] When two or three carbon-bridged diols were tested, 75% of **1** and 71% of **2** are isolated along with 8% and 17% of the di-phosphate (Table 1, entries 1 and 2). As the carbon chain is increased to four or five carbons, the yield of mono-phosphate is decreased to 64% of **3** and 65% of **4**, respectively, (Table 1, entries 3 and 4). This is due to an increase in di-phosphate yield of 26% and 22%, respectively. Takeda and co-workers reported that a similar chain length screen using an excess of silver(I) oxide, tetrahexylammonium iodide (THAI), and TBPP resulted in comparable yields for **2** and **3** (69% and 71%, respectively), but decreased yields of **1** and **4** (trace and 43%, respectively).[4a]

To determine if the selectivity for mono-phosphorylation of 1,3-propane diols could be increased, we examined the effect of methyl substitutions on the three-carbon chain (see Table 2). A single methyl substitution on carbon-2 (C-2) increases the mono-phosphorylation yield from 71% of **2** to 84% of **5** (Table 2, entry 1). This trend can be further exploited by addition of a second methyl substituent, which results in the selective formation of **6** in 90% yield. Adding methyl substituents adjacent to the hydroxyl group (C-1 and/or C-3) also had an effect on the mono-phosphorylation selectivity. The addition of substituents at these positions can break the symmetry and results in hydroxyl groups of differing reactivity (primary, secondary, or tertiary alcohols). The primary hydroxyl group is preferred in a ratio of 4:1 over the secondary hydroxyl in the formation of **7** (Table 2, entry 3). In the case of secondary versus tertiary alcohols, only the secondary alcohol is phosphorylated to deliver **8** in 85% yield. We had previously reported that tertiary alcohols are poor substrates for phosphorylation using $Ti(OtBu)_4$, as witnessed by the low yield of **9**.

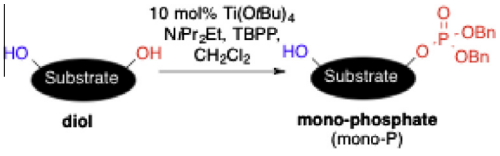
Table 1
Effect of chain length on the mono-phosphorylation of diols

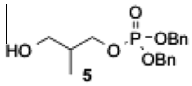
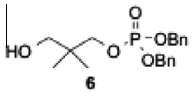
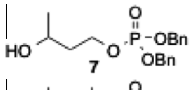
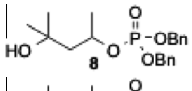
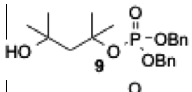
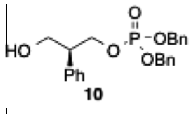
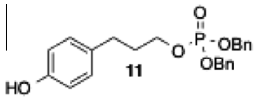


Entry	Mono-P product	Isolated yield mono-P[a]
1		75%
2		71%
3		64%
4		65%

[a] Reactions performed with 1.2 equiv of TBPP and 1.5 equiv of Hünig's Base at room temperature for 4 h.

Table 2
Effect of substituents on the mono-phosphorylation of diols



Entry	mono-P product	Isolated yield mono-P[a]
1		84%
2		90%
3		90% (4:1 ratio[b])
4		85%
5		21%[c]
6		81%
7		84% (15:1 ratio[b])

[a] Reactions performed with 1.2 equiv of TBPP and 1.5 equiv of Hünig's Base at room temperature for 4 h.

[b] The major mono-phosphate product is depicted for unsymmetrical diols. The product ratio was determined by ^1H NMR.

[c] Compound slowly decomposes during isolation.