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Selective phosphorylation of diols with a Lewis acid catalyst

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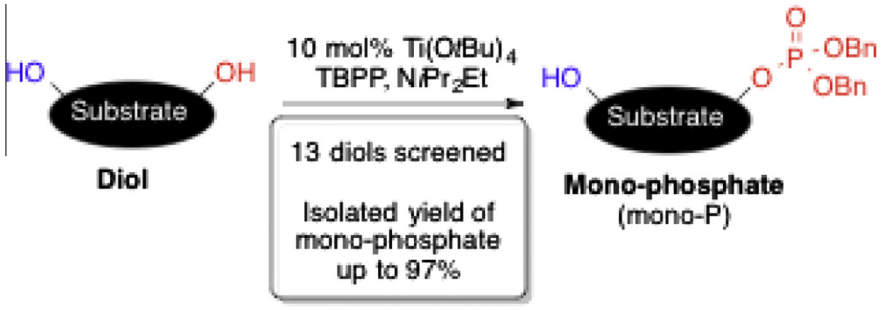
ABSTRACT

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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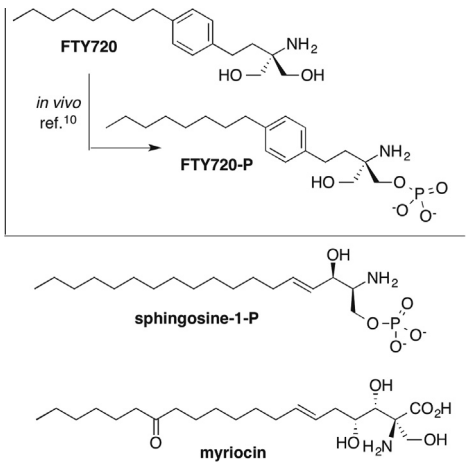


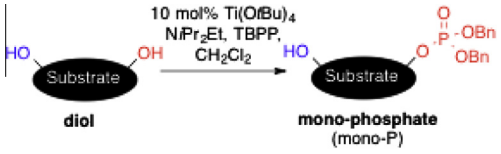
Figure 1. FTY720, FTY720-P, and structurally related immuno modulating natural products.

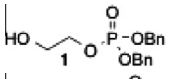
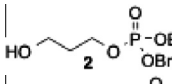
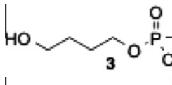
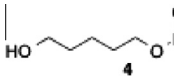
desymmetrization of the diol,[15] or use a Sharpless asymmetric epoxidation followed by functional group interconversions.[16] We sought a method for the direct phosphorylation of 2-alkyl-2-amino-1,3-propanediols to facilitate a rapid synthesis of FTY720-P and its analogues.

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**.

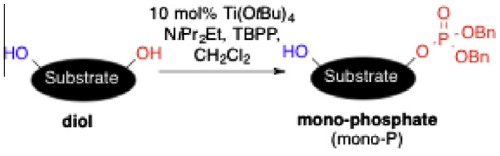
Table 1
Effect of chain length on the mono-phosphorylation of diols

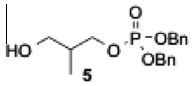
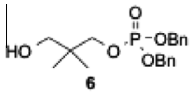
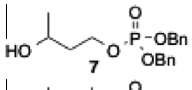
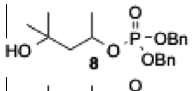
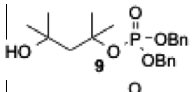
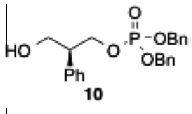
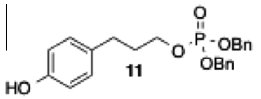


Entry	Mono-P product	Isolated yield mono-P[a]
1		75%
2		71%
3		64%
4		65%

[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.

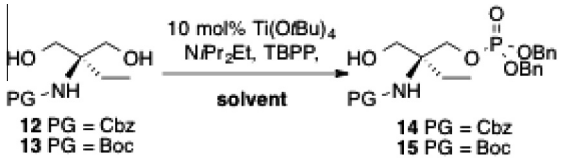
[c] Compound slowly decomposes during isolation.

Aromatic substituents were also examined for their effect on selectivity. Phenyl substitution at C-2 did not alter the high yield of mono-phosphorylation as witnessed by the 81% isolated yield of **10** (Table 2, entry 6). We were also interested in studying the competition between a phenolic and primary hydroxyl. When 3-(4-hydroxyphenyl)-1-propanol was subjected to the standard reaction conditions, 84% yield of mono-phosphate was isolated in a 15:1 ratio favoring phosphorylation of the primary hydroxyl (as depicted in **11**). This result is complimentary to the work of Takeda and coworkers who report this same substrate reacts with silver(I) oxide, THAI, and TBPP to yield a reaction at the phenolic hydroxyl, exclusively.[4a]

With a series of encouraging results for the selective mono-phosphorylation of 1,3-propane diols, we turned our attention to analogues of FTY720. Inexpensive and readily available 2-amino-2-ethyl-1,3-propanediol was amine protected with *tert*-butoxycarbonyl (Boc) and carboxybenzyl (Cbz) protecting groups (**12** and **13**).[21] When either of these amine-protected diols was subjected to our standard reactions conditions, 78% of the mono-phosphate was formed (Table 3, entries 1 and 2). Analysis of the crude NMR for both reactions showed recovered starting material. We were excited to observe that by extending the duration of the reaction to 16 h, we could obtain 96% of **14** and 93% of **15**, with no detectable di-phosphate. Takeda and co-workers found that when Cbz-protected FTY720 was subjected to phosphorylation with silver(I) oxide, THAI, and TBPP, 60% of the desired mono-phosphate was formed along with 22% di-phosphate and 12% of a cyclized byproduct.[4a] It is interesting to note that similar yields of **14** are formed when 10 mol % of the more commonly available $Ti(OiPr)_4$ is used in the phosphorylation of **12** (generating 92% isolated yield of **14**).[22] We are hopeful that the use of titanium alkoxides as Lewis acid catalysts will afford high levels of selectivity in the synthesis of FTY720-P and its analogues.

Due to the diverse solubility of potential FTY720 analogues, we examined the effect of solvent on the reaction rate and selectivity. (see Table 3, entries 5–10). We found that when **12** was subjected to phosphorylation in CH_2Cl_2, toluene, THF, or DMF **14** was isolated in high yield. There is a slight drop in yield when the reaction is performed in Et_2O, CH_3CN, or pentane (77%, 80%, and 63%, respectively). We were pleased that a variety of solvents with different boiling points, polarity, and dielectric constants were suitable for the mono-phosphorylation of **12**.

Table 3
Mono-phosphorylation of *N*-protected 2-amino-2-ethyl-1,3-propane diols



Entry	PG	Solvent	Time (h)	Isolated yield **14** or **15**[a] (%)
1	Cbz	CH_2Cl_2	4	78
2	Boc	CH_2Cl_2	4	78
3	Cbz	CH_2Cl_2	16	96
4	Boc	CH_2Cl_2	16	93
5	Cbz	Toluene	16	97
6	Cbz	Et_2O	16	77
7	Cbz	CH_3CN	16	80
8	Cbz	DMF	16	93
9	Cbz	Pentane	16	63
10	Cbz	THF	16	96

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

In conclusion, we have demonstrated that titanium alkoxides are effective catalysts for the mono-phosphorylation of diols. We have found that the propensity to stop at mono-phosphorylation is even greater when the carbon chain length separating the two hydroxyls is two or three carbons and bears additional substituents. We have also demonstrated that this reaction can generate up to 97% yield of a mono-phosphate in a model system for FTY720-P. This method should aid in the selective chemical mono-phosphorylation of FTY720-P and its analogues.[23] We are currently exploring the use of other Lewis acid catalysts including chiral catalysts to enable a desymmetrization of FTY720 to form (*S*)-FTY720-P.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.047.

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20. General procedure for the phosphorylation of diols. The diol (0.49 mmol) was dissolved in 1.0 mL of CH_2Cl_2. *N,N*-Diisopropylethylamine (0.130 mL,

0.746 mmol) was added to the solution, followed by tetrabenzylpyrophosphate (0.320 g, 0.594 mmol). Ti(O*t*Bu)$_4$ (19 μL, 0.049 mmol, 10 mol %) was added and the reaction was stirred for 4 h at room temperature. To quench the reaction, the crude solution was filtered through a 5 mL plastic syringe containing 2 mL of 20:1 Silica/$MgSO_4$ and washed with 60 mL of 75% EtOAc/hexanes. The filtrate was concentrated under reduced pressure. The crude product was purified using silica gel chromatography. See Supporting information for characterization data and spectra.

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22. In the phosphorylation of secondary alcohols, there is contaminant phosphorylation of isopropanol when Ti(O*i*Pr)$_4$ is employed as the catalyst (see Ref. 17a). None of this byproduct was detected in the phosphorylation of **12**.

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