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Efficient Synthesis of Phosphorylated Prodrugs with Bis(POM)-phosphoryl Chloride

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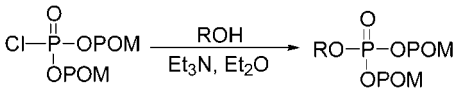
ABSTRACT



An efficient method for the synthesis of phosphorylated prodrugs is described. The preparation of various bis-pivaloyloxymethyl (POM) phosphate triesters was accomplished in moderate to good yields with the use of bis(POM) phosphoryl chloride under mild conditions.

Enzymatic phosphorylation of biologically active molecules is of major regulatory importance in living systems. As a result, many cellular drug targets display high-affinity interactions with phosphorylated molecules but are unable to bind to their unphosphorylated counterparts. This has greatly limited drug development because phosphorylated compounds are generally not effective at penetrating cell membranes and thus are not bioactive. One general strategy[1] to circumvent this problem involves masking the phosphate in a form that neutralizes its negative charge and can enhance cell permeability. Upon cell entry, the mask is removed enzymatically and the compound converted to a biologically active form. Of the various approaches developed for reversibly masking phosphate compounds, the bis-pivaloyloxymethyl (bisPOM) strategy[2] has received considerable attention and appears to be especially useful. While bisPOM derivatives are generally quite stable in buffer and plasma, they are readily transformed to free phosphate derivatives inside various cell types. The application of bisPOM phosphates in the antiviral and anticancer arena has shown promise. However, the synthesis of these derivatives tends to be cumbersome and low-yielding. Two general approaches to bisPOM derivatives have been described. The first method[2a−e] involves conversion of the hydroxy compound to the phosphate followed by double alkylation with the iodomethyleneoxyester. This is a four- to five-step procedure that usually proceeds in <10% overall yield. The second method[2f−i] involves direct reaction of the hydroxy compound with bisPOM-phosphate diester. While sometimes successful, this reaction usually affords low yields even with unhindered primary alcohols. We recently attempted both methods in an effort to make a coenzyme A prodrug, and the final reactions in either route showed unacceptable yields (<10%).[3]

In response to this challenge, we hypothesized that it might be possible to prepare and use the chlorophosphoryl-bisPOM reagent **5** for improved generation of bis(POM) derivatives. Approach to **5** began with trimethyl phosphate **1**, which was converted to the trisPOM derivative **2** by transesterification[4b] (Scheme 1). Hydrolysis of one of the POM groups[4] over two steps to generate the bisPOM phosphate **4** was followed

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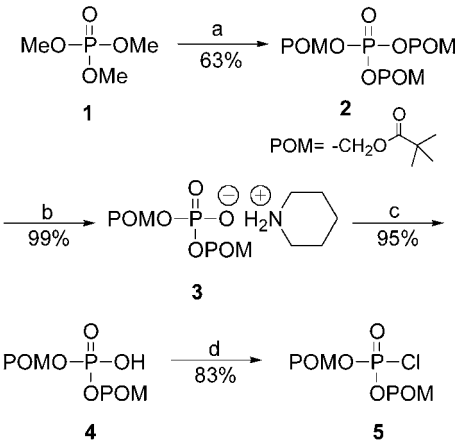
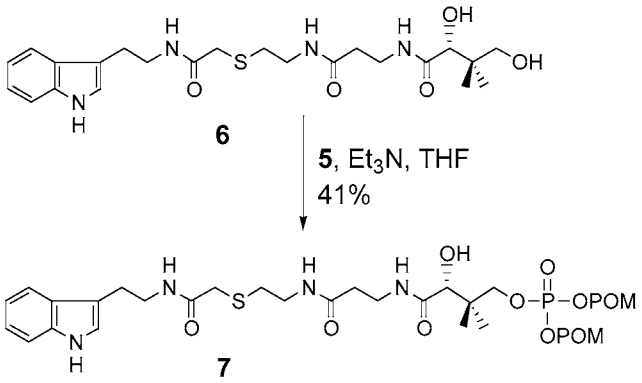
Scheme 1 [a]



[a] Conditions: (a) NaI, chloromethyl pivalate, CH_3CN, reflux; (b) piperidine, rt; (c) cation exchange column; (d) oxalyl chloride, DMF (cat), DCM.

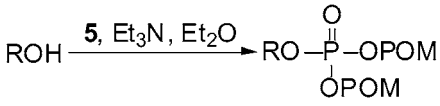
by reaction with oxalyl chloride resulting in relatively clean formation of **5**, which was stable upon freezer storage for several weeks. In an initial examination of the utility of **5**, we attempted to prepare the possible prodrug indole-pantetheine derivative **7**. Related to a pantetheine analogue in a previous study,[3] **7** was not accessible using the standard methods (unpublished data). However, reaction of **6** and **5** in the presence of triethylamine led to a 41% yield of the bisPOM derivative **7** (Scheme 2). To explore the generality

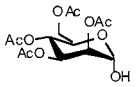
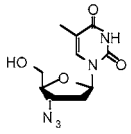
Scheme 2



of this finding, we examined the use of **5** to convert a series of alcohols to the corresponding bisPOM derivatives as shown. As can be seen (Table 1), simple primary alcohols in the presence of **5** undergo smooth conversion to bisPOM derivatives in 80−90% yields (entries 1 and 2). More hindered alcohols including secondary alcohols generally proceed in ∼40% yield (entries 3 and 4). Some of the target compounds prepared in this study, including bisPOM-phosphoAZT[1] and bisPOM-mannose-1-phosphate[2a] (entries 5 and 4), have been shown or predicted to possess therapeutic potential.

Table 1. Bis(POM) Phosphorylation of Alcohols



entry	substrate(ROH)	rxn time	yield[b]
1	n-BuOH	4h	90%
2	Benzyl alcohol	3h	81%
3	2-Butanol	15h	45%
4		18h	41%[c]
5		24h	47%

[a] Conditions: 1.0 equiv of substrate, 5.0 equiv of **5**, 10.0 equiv of Et_3N, Et_2O. [b] Yields of pure and isolated products. [c] This yield is based on the converted starting material.

In summary, we believe that the use of chlorophosphoryl-bisPOM **5** in the generation of bisPOM phosphate triesters represents a significant advance over previous approaches to bisPOM-containing compounds. Given the increasing interest of generating masked phosphate derivatives as biological tools and as antiviral and anticancer agents, it is expected that **5** may be usefully applied to a wide range of important systems. Moreover, it is anticipated that alternative acyloxy phosphate esters in addition to the pivaloyl type may be prepared in a related fashion with the appropriate phosphoryl chloride reagent.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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