

Selective Lewis Acid Catalyzed Assembly of Phosphonomethyl Ethers: Three-Step Synthesis of Tenofovir

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(5) Supporting Information

ABSTRACT: Described herein is a novel Lewis acid catalyzed rearrangement—coupling of oxygen heterocycles and bis-(diethylamino)chlorophosphine that provides direct formation of the phosphonomethyl ether functionality found in several important antiretroviral agents. A wide range of dioxolanes and 1,3-dioxanes may be employed, furnishing the desired products in good yield. The utility of this method is demonstrated in a novel synthesis of tenofovir, an antiretroviral drug used in the treatment of HIV/AIDS and hepatitis B.

O ver 35 million people are infected with HIV/AIDS worldwide, 28 million of whom are in developing nations.¹ Accessibility to effective treatments is limited in these regions, even with help from organizations such as the Bill and Melinda Gates Foundation (BMGF) and the Clinton Health Access Initiative (CHAI).² Tenofovir disoproxil fumarate (1, TDF) has emerged as an effective treatment for HIV/AIDS,³ and it is preferred over alternative HIV medications because it is less toxic and has a lower rate of resistance.⁴ Approved by the FDA in 2001, it is part of the first-line treatment against HIV/AIDS in combination with other antiretroviral drugs.⁵

Tenofovir (2), the active constituent of TDF, is a nucleoside analogue reverse transcriptase inhibitor that is released in vivo by phosphonate ester hydrolysis.⁶ It has been proposed that the electronegative nature of the β -oxygen atom facilitates phosphorylation by kinases.⁷ The phosphonomethyl ether core found in tenofovir and other antiretrovirals such as adefovir dipivoxil and cidofovir (Figure 1a) is typically synthesized via multistep processes involving protecting groups, a substitution reaction of a tosyloxymethyl ether of a phosphonate diester, and the use of bases that are either expensive or difficult to handle on industrial scale.⁸ Herein, we report a novel catalytic rearrangement—coupling of readily available starting materials that furnishes the critical phosphonomethyl ether functionality directly (Figure 1b) and enables a three-step synthesis of tenofovir.

We initially envisioned generation of the phosphonomethyl ether by effecting nucleophilic ring opening of a cyclic phosphonate (phostone), in analogy to a carbohydrate-derived phostone ring opening reported by Moravcova and co-workers (Scheme 1).^{9,10} Phostone **3** ($R = CH_3$) was generated from the ring expansion of the corresponding dioxolane by treatment with diethylchlorophosphite under Lewis acidic conditions.¹¹ Use of adenine as the nucleophile in the substitution reaction of **3** would have been ideal, as this would directly furnish the core structure of the antiretrovirals shown in Figure 1a. Unfortu-





Figure 1. (a) Antiretroviral pharmaceuticals; (b) a novel Lewis acid catalyzed rearrangement-coupling that assembles the common phosphonomethyl ether core.

nately, the desired reactivity was not observed using a variety of different bases (e.g., Cs_2CO_3 , K_2CO_3 , NaH, NaOH). Other nucleophiles such as iodide and organolithium reagents were also ineffective.¹²

We were drawn, however, to the structure of the putative phosphonium intermediate in this process. Specifically, we

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Scheme 1. Initial Design: Phosphonomethyl Ether Formation via Nucleophilic Phostone Ring Opening



envisioned an analogous intermediate starting from bis(diethylamino)chlorophosphine (Figure 1b). In this case, reaction at the ethyl groups would be unlikely; instead, we hypothesized that direct chloride attack onto the phosphonium ring would furnish the corresponding phosphonomethyl ether in a single step.

Several transition-metal- and lanthanide-based Lewis acid catalysts were evaluated for the rearrangement–coupling of dioxolane 4a in the presence of excess bis(diethylamino)-chlorophosphine.¹³ Zinc(II) catalysts, particularly ZnCl₂ and Zn(OTf)₂, gave optimal results. 4-Methyl-1,3-dioxolane 4a was chosen as a development substrate for several reasons: it would probe group selectivity, does not display a strong electronic or steric bias, and, following the rearrangement, would form the phosphonomethyl ether core of tenofovir. Indeed, the predicted product 5a was generated in 10:1 selectivity over minor isomer 6a (Table 1). Increasing the temperature to 130 °C gave

 Table 1. Evaluation of Lewis Acids and Reaction

 Temperatures for the Dioxolane Rearrangement^a

4a + (Et ₂ N) ₂ PCI	THF, 24 h	O	0 0 P NEt ₂ 6a
entry	Lewis acid	temp (°C)	yield (%) ^b
1	$ZnCl_2$	100	21 ^c
2	$ZnCl_2$	100	33
3	$ZnCl_2$	120	41
4^d	$ZnCl_2$	120	51
5 ^e	$ZnCl_2$	120	53
6	$Zn(OTf)_2$	120	57
7^d	$Zn(OTf)_2$	120	40
8	$ZnCl_2$	130	50
9	$Zn(OTf)_2$	130	61
10	$ZnCl_2$	140	52
11	$Zn(OTf)_2$	140	59

^{*a*}Dioxolane (0.8 mmol), chlorophosphine (1.9 mmol), ZnX₂ (20 mol % relative to dioxolane, unless otherwise noted), THF (0.3 mL); see the Supporting Information. ^{*b*}Isolated yield after purification (SiO₂ chromatography). ^{*c*}1.2 equiv of phosphine. ^{*d*}60 mol % ZnX₂. ^{*e*}100 mol % ZnX₂.

significant improvement in yield; however, no further improvement was observed at or above 140 °C. These studies thus established our standard conditions (130 °C, 20 mol % $Zn(OTf)_2$).

We propose that the mechanism of the reaction initially involves interaction of $Zn(OTf)_2$ with the chlorine atom to increase the electrophilicity at phosphorus (Scheme 2). The less sterically hindered oxygen of the dioxolane then reacts with the activated chlorophosphine to generate oxonium intermediate 7. Phosphorus attack onto oxocarbenium 8^{14} in an intramolecular Michaelis–Arbuzov-type reaction then proceeds Scheme 2. Proposed Mechanism of the Reaction



to generate cyclic phosphonium intermediate **9**. Finally, chloride attack furnishes the phosphonomethyl ether product. In this framework, the minor isomer is generated by initial reaction at the more sterically hindered oxygen.

To probe the initial Lewis acid–chlorophosphine interaction, we conducted ³¹P NMR studies.¹⁵ Mixing a 1:1 ratio of chlorophosphine and ZnCl₂ (chosen for solubility reasons) in THF- d_8 at ambient temperature resulted in no detectable change in chemical shift. In order to enhance the putative interaction, we conducted further experiments in CD₂Cl₂, a noncoordinating solvent. Indeed, we found a dramatic downfield shift in the ³¹P NMR spectrum (158.8 to 234.6 ppm). These results support the formation of a (Et₂N)₂PCl–ZnX₂ complex and is consistent with previous NMR studies.¹⁶

We evaluated the rearrangement conditions for a variety of substituted dioxolanes and 1,3-dioxanes (Table 2). In the case of the 4-substituted substrates, even a methyl group was sufficient in biasing reaction to the less sterically hindered oxygen, yielding the desired product in a 10:1 ratio (entries 1 and 11). Higher selectivity was observed for the substrates bearing a phenyl or geminal dimethyl group at the 4-position (entries 3, 12, and 13), possibly a result of the larger size of the phenyl ring or geminal dimethyl group (relative to methyl), decreasing the degree of coordination of the more sterically encumbered oxygen to the chlorophosphine. Interestingly, a decrease in selectivity was observed for 4-((benzyloxy)methyl)-1,3-dioxolane (entry 4). It is postulated that the benzyloxy group can direct reaction at the more sterically hindered oxygen of the dioxolane by coordinating to phosphorus. Electronic effects may also play a significant role in this case.

Generally, we observed higher yields for the 2-substituted dioxolanes (entries 5–8), possibly due to the groups in this position stabilizing the oxonium intermediate. Additionally, we obtained higher yields at lower concentration (1.0 M vs 2.5 M) for these substrates; no significant concentration effect was observed for the 4-substituted substrates.¹³ A lower yield was observed with 2-vinyl dioxolane 4i due to partial alkene isomerization in the product, giving an internal olefin (entry 9). Highly sterically hindered substrates, bearing geminal dimethyl groups, were also tolerated under these conditions (entries 6 and 12).

To demonstrate the utility of this method, we developed a novel and efficient synthesis of tenofovir.¹⁷ The first step of the route involves reaction of enantiomerically pure (R)-4a,

Table 2. Zn(OTf)₂-Catalyzed Rearrangement of Substituted Dioxolanes and 1,3-Dioxanes^a

$ \begin{array}{c} R_2 \\ \searrow O \\ O \\ & & & \\ O \\ & & & \\ O_n \\ R_1 \\ 1 \text{ equiv} \end{array} $	+ Et ₂ N + P-Cl Et ₂ N 2.4 equiv	Zn(OTf) ₂ (20 mol %) THF, 130 °C, 24 h Cl √	$ \begin{array}{c} $
entry	substrate	product	yield (%) ^b
1	0 4a	$\underset{\textbf{5a}}{\overset{\textbf{O}}{\underset{\textbf{F}_{2}}{\overset{\textbf{O}}{\underset{T}}}}}}}}}{\overset{\textbf{O}}{\overset{\textbf{O}}{\underset{\textbf{O}}{\overset{\textbf{O}}{\underset{T}}{\overset{\textbf{O}}{\underset{T}}{\overset{O}{\underset{T}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}$	61 (10:1)
2	o ↓ 4b	$\underset{\textbf{bb}}{\overset{O}{\overset{H}{\underset{l}}}} \overset{O}{\underset{\substack{H}{\underset{l}}{\overset{H}{\underset{l}}{\underset{l}}}}} \overset{O}{\underset{\substack{H}{\underset{l}}{\underset{l}}{\underset{l}{\underset{l}}{\underset{l}}{\underset{l}}}} \overset{O}{\underset{l}{\underset{l}}{\underset{l}{\underset{l}}{\underset{l}}{\underset{l}}}} \overset{O}{\underset{l}{\underset{l}}{\underset{l}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}}} \overset{O}{\underset{l}{\underset{l}}{\underset{l}}{\underset{l}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}{\underset{l}}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}}{\underset{l}}{\underset{l}}{\underset{l}}}{\underset{l}}{\underset{l}}{\underset{l}}{\underset{l}}}{\underset{l}}}{\underset{l}$	73
3	o ↓ 4c Ph	$\begin{array}{c} O\\ CI & \overbrace{}^{O} & \overbrace{}^{P} \\ \mathbf{5c} & Ph \end{array} $	50 (>20:1)
4	O ↓ 4d OBn	$\begin{array}{c} O\\ H\\ CI \\ \hline \\ 5d \end{array} \begin{array}{c} O\\ P\\ P\\ NEt_2 \\ NEt_2 \end{array}$	55 (4:1)
5 ^c	}_0 0 4e	$\underset{\textbf{5e}}{\overset{O}{\overset{H}}} \overset{O}{\underset{NEt_2}{\overset{O}{\overset{H}}}} $	83
6 ^c	4f	$\underset{\mathbf{5f}}{\overset{O}{\underset{P}{\overset{O}{\underset{NEt_2}}}}}$	67
7 ^c	Ph O 4g	$\begin{array}{c} O\\ H\\ CI \\ \mathbf{5g} Ph \end{array} \begin{array}{c} O\\ P\\ \mathbf{NEt}_2\\ \mathbf{NEt}_2 \end{array}$	76
8 ^c	o o 4h	$\begin{array}{c} & & O \\ & & P \\ & P \\ & P \\ & NEt_2 \\ & \\ & Sh \end{array}$	81
9 ^c			49 ^d
10		$\begin{array}{c} O\\ CI & O \\ P_{NEt_2} \\ Sj \end{array}$	67
11		$\begin{array}{c} O \\ CI \\ & \downarrow \\ \mathbf{5k} \end{array} \xrightarrow{O \\ V \\ NEt_2} \\ O \\ NEt_2 \\ NEt_2 \end{array}$	77 (10:1)
12		$\underset{\textbf{SI}}{\overset{O}{\overset{H}{\underset{NEt_2}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{NEt_2}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{NEt}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{NEt}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{NEt}{\overset{H}{\underset{NEt}{\overset{H}{\underset{NEt}{\overset{H}{NEt}{NEt}{\overset{H}{\underset{NEt}{NEt}{\overset{H}{\underset{NEt}{NEt}{\overset{H}{NEt}{NEt}{\overset{H}{NEt}{NEt}{\overset{H}{NEt}{NEt}{NEt}{\overset{H}{NEt}{NEt}{NEt}{NEt}{NEt}{NEt}{NEt}{NEt$	65 (>20:1)
13	O O 4m	$CI \xrightarrow{O} P_{h} NEt_2$ 5m Ph	66 (>20:1)

^{*a*}Dioxolane (0.8 mmol), chlorophosphine (1.9 mmol), Zn(OTf)₂ (20 mol %), THF (0.3 mL); see the Supporting Information. ^{*b*}Isolated yield after purification (SiO₂ chromatography). Values in parentheses represent isomeric ratios. ^{*c*}0.8 mL of THF. ^{*d*}23% of internal alkene isomer also isolated.

prepared from (R)-(-)-1,2-propanediol and paraformaldehyde, under the standard rearrangement conditions to afford enantiomerically pure phosphonomethyl ether (R)-**5a** in 72% yield (Scheme 3).¹⁸

Scheme 3. Synthesis of Tenofovir via Zn(OTf)₂-Catalyzed Dioxolane Rearrangement



Alkylation with adenine using potassium phosphate (K_3PO_4), followed by hydrolysis of the phosphonamide under mild conditions (2 N HCl, 80 °C), affords tenofovir monohydrate ($2 \cdot H_2O$) in 41% yield over two steps after recrystallization. The overall yield of the synthesis starting from (R)-4a is 27%. The advantages of this synthetic route include rapid formation of the phosphonomethyl ether core, a late-stage introduction of adenine, mild hydrolysis conditions, and recrystallization of the final product by simple pH adjustment. Moreover, the final two steps require no chromatographic purification.

In summary, we have developed a protocol that allows for direct access to a variety of phosphonomethyl ether compounds. This novel rearrangement—coupling utilizes reagents that either are commercially available or can be accessed using inexpensive starting materials. Moreover, all of the atoms contained in the starting materials are transferred to the product. Dioxolane and 1,3-dioxane substrates bearing substituents at either the 2- or 4-position are tolerated, generating the corresponding products in good yield. Finally, this transformation enables a new, three-step synthesis of tenofovir, demonstrating the utility of this method and its potential for accessing other antiretroviral compounds containing the phosphonomethyl ether motif.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data (¹H, ¹³C, ³¹P NMR; HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Use of Cs₂CO₃, K₂CO₃, NaH, NaOH, organolithium reagents, or iodide resulted in either recovery or decomposition of phostone starting material.

(13) For a full evaluation of Lewis acid catalysts and other reaction conditions, see the Supporting Information for details.

(14) We cannot rule out the possibility that oxonium 7 undergoes chloride attack to generate the corresponding chloromethyl ether intermediate; however, since *gem*-dimethyl groups are tolerated in the 2-position, it is more likely that the mechanism proceeds via oxocarbenium intermediate 8.

(15) For full details, see the Supporting Information.

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