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

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

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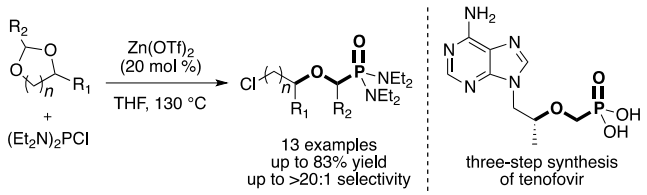
Supporting Information Placeholder



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 with up to >20:1 group selectivity. The two components are commercially available or easily prepared from inexpensive precursors, and all of the atoms in these coupling partners are transferred to the product. 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.

Over 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] In 1998, Gilead Sciences developed an elegant five-step synthesis of TDF starting from (*S*)-glycidol, two steps of which assemble the phosphonomethyl ether functionality.[9] The

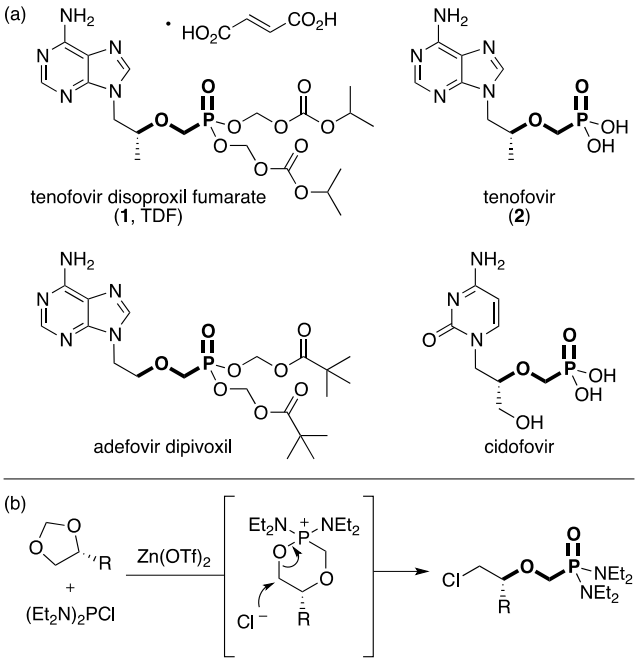


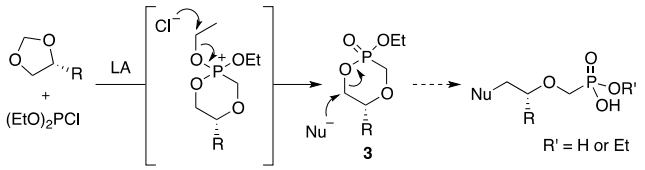
Figure 1. (a) Antiretroviral pharmaceuticals; (b) a novel Lewis acid catalyzed rearrangement–coupling that assembles the common phosphonomethyl ether core.

current manufacturing process is very similar to this route.[10] 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).[11,12] Phostone **3** (R=CH_3) was generated from the ring expansion of the corresponding dioxolane by treatment with diethylchlorophosphite under Lewis acidic conditions.[13] 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. Unfortunately, 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.

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

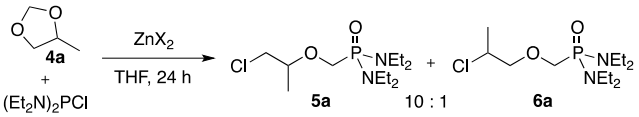


We were drawn, however, to the structure of the putative phosphonium intermediate in this process. Specifically, we envisioned an analogous intermediate starting from bis(diethylamino)chlorophosphine (Figure 1b). In this case, reaction at the ethyl groups would be unlikely; instead, we hypothesized that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

We evaluated a variety of Lewis acid catalysts for the rearrangement of dioxolane **4a** in the presence of excess bis(diethylamino)chlorophosphine.[14] 4-Methyl-1,3-dioxolane **4a** was chosen as a development substrate because 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). Zinc(II) catalysts, particularly $ZnCl_2$ and $Zn(OTf)_2$, gave optimal results. Increasing the temperature to 130 °C gave 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**[15] in an intramolecular Michaelis–Arbuzov-type reaction then proceeds to generate cyclic phosphonium intermediate **9**. Finally, chloride attack furnishes the phosphonomethyl ether product. In this framework, the minor isomer would be generated by initial reaction at the more sterically hindered oxygen.

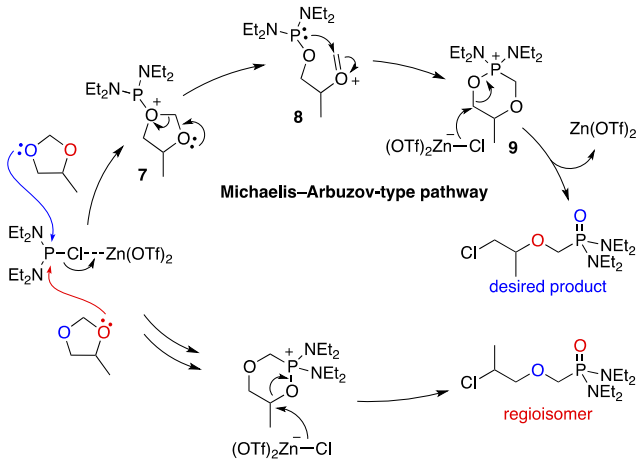
Table 1. Evaluation of Lewis Acids and Reaction Temperatures for the Dioxolane Rearrangement[a]



Entry	Lewis Acid	Temperature (°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

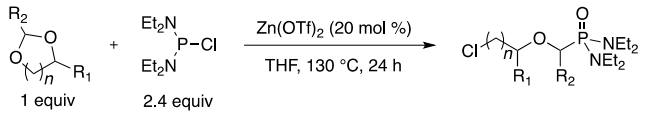
[a] Dioxolane (0.8 mmol), chlorophosphine (1.9 mmol), ZnX_2 (20 mol %, unless otherwise noted), THF (0.03 mL); see the Supporting Information. [b] isolated yield after purification (SiO_2 chromatography). [c] 1.2 equiv phosphine. [d] 60 mol % ZnX_2. [e] 100 mol % ZnX_2

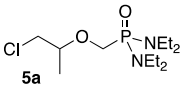
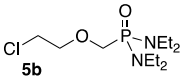
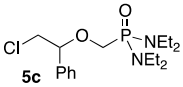
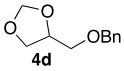
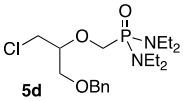
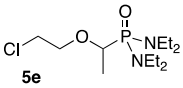
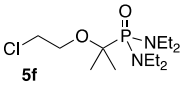
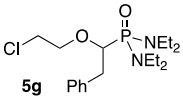
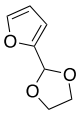
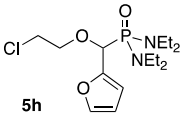
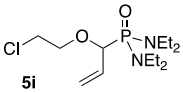
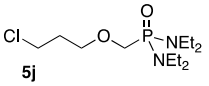
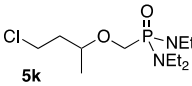
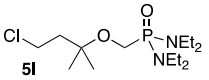
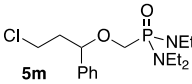
Scheme 2. Proposed Mechanism of the Reaction



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

Table 2. $Zn(OTf)_2$-Catalyzed Rearrangement of Substituted Dioxolanes and 1,3-Dioxanes[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **4a**	 **5a**	61 (10:1)
2	 **4b**	 **5b**	73
3	 **4c**	 **5c**	50 (>20:1)
4	 **4d**	 **5d**	55 (4:1)
5[c]	 **4e**	 **5e**	83
6[c]	 **4f**	 **5f**	67
7[c]	 **4g**	 **5g**	76
8[c]	 **4h**	 **5h**	81
9[c]	 **4i**	 **5i**	49[d]
10	 **4j**	 **5j**	67
11	 **4k**	 **5k**	77 (10:1)
12	 **4l**	 **5l**	65 (>20:1)
13	 **4m**	 **5m**	66 (>20:1)

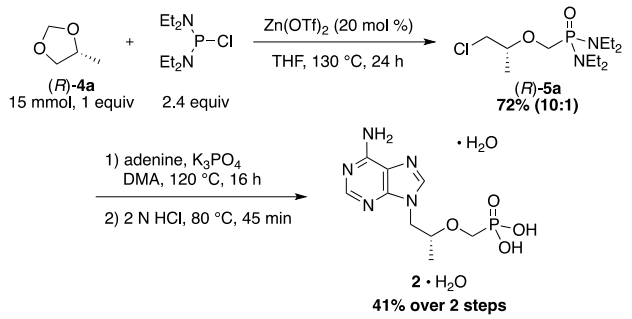
[a] Dioxolane (0.8 mmol), chlorophosphine (1.9 mmol), $Zn(OTf)_2$ (20 mol %), THF (0.3 mL); see the Supporting Information. [b] Isolated yield after purification (SiO_2 chromatography). Values in parentheses represent isomeric ratios. [c] 0.8 mL of THF. [d] 23% of an alkene isomer also isolated.

10:1 ratio (entries 1 and 11). Higher selectivity was observed for the 4-phenyl substituted substrates (entries 3 and 13), possibly a result of greater stabilization of the oxocarbenium intermediate by the aromatic ring and/or the larger size of the phenyl ring (relative to methyl). 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), suggesting that the groups in this position stabilize 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. 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. The first step of the route involves reaction of enantiomerically pure (*R*)-**4a**, 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).[16] 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**•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 latter two steps are telescoped, obviating the need for intermediary chromatographic purification.

Scheme 3. Synthesis of Tenofovir via $Zn(OTf)_2$-Catalyzed Dioxolane Rearrangement



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-positions 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 (^{1}H, ^{13}C, ^{31}P 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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(14) See the Supporting Information for details.

(15) 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**.

(16) Enantioselectivity was determined by chiral HPLC of an intermediate that was further functionalized. See the Supporting Information for details.