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Rapid, mild method for phosphonate diester hydrolysis: development of a one-pot synthesis of tenofovir disoproxil fumarate from tenofovir diethyl ester

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ABSTRACT

A rapid, low temperature hydrolysis of tenofovir diethyl ester mediated by TMSCl and NaBr was identified and demonstrated to be superior to the current production method, TMSBr-mediated hydrolysis. This mild phosphonate ester hydrolysis was then coupled to alkylation of the phosphonic acid, providing a one-pot procedure for formation of tenofovir disoproxil from tenofovir diethyl ester. The hydrolytic conditions developed here dramatically improve the synthesis of tenofovir disoproxyl and will lead to lower cost HIV/AIDS treatment in the developing world.

1. Introduction

Recently the WHO reported that the number of people being treated for HIV/AIDS in the developing world passed three million, up from around 250,000 in 2002. With over 20 million people infected with HIV/AIDS in the developing world, the rapid expansion of treatment programs promises to continue. As the number of patients on treatment grows, and safer, more effective treatments become incorporated into treatment recommendations, the cost of medications is putting increasing strain on the budgets available for treatment programs. The Clinton Health Access Initiative (CHAI) is focused on making the best medications available to patients at the best price possible in a commercially sustainable marketplace. Profit margins for the sale of first-line HIV/AIDS medications for treatment naïve patients in the developing world are quite low, and the cost of products in the marketplace are directly linked to the cost of manufacturing those products. For newer drugs, such as tenofovir, market price improvements will be the result of continued scale-up, utilizing lower priced sources of high quality raw materials and intermediates, and manufacturing process improvements, with the latter holding the potential for large scale reduction in price. In order to speed the market price reduction of tenofovir resulting from improved manufacturing efficiencies, CHAI and its partners are engaged in active research to develop an optimal process for its preparation.

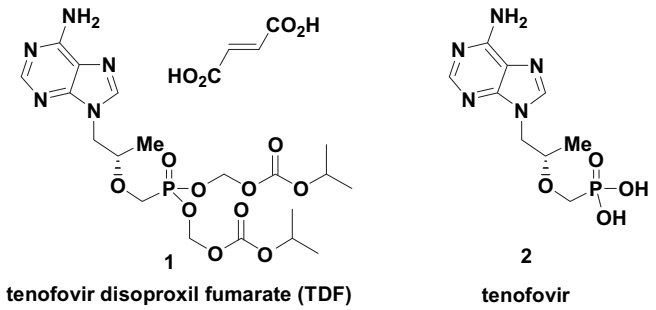

Figure 1. Structures of the potent HIV/AIDS prodrug TDF and active drug product tenofovir.

Tenofovir, **2** (Fig. 1), is a potent nucleotide reverse transcriptase inhibitor (NRTI) used in the first-line treatment of HIV in the US, in combination with emtricitabine and efavirenz[1,2] to form the

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backbone of HAART (highly active anti-retroviral therapy).[3] The use of tenofovir in the first-line treatment of HIV is considered superior to treatments utilizing Nevirapine due to a lower incidence of toxicity and lower rate of resistance development.[4] However, until recently, the cost of tenofovir has limited the practicality of using TDF in first-line therapy in the developing world.

Tenofovir is administered as a prodrug, tenofovir disoproxil fumarate **1**, TDF marketed under the name Viread (Gilead). The bis-isopropoxyl carbonate phosphonate ester of tenofovir has significantly enhanced oral bioavailability due to improved lipophillicity of the molecule.[5] The isopropyl carbonates are hydrolyzed in vivo by ubiquitous esterases to produce **2**, which undergoes phosphorylation to form the active tenofovir diphosphate drug substance. The required active pharmaceutical ingredient is thus **1**.

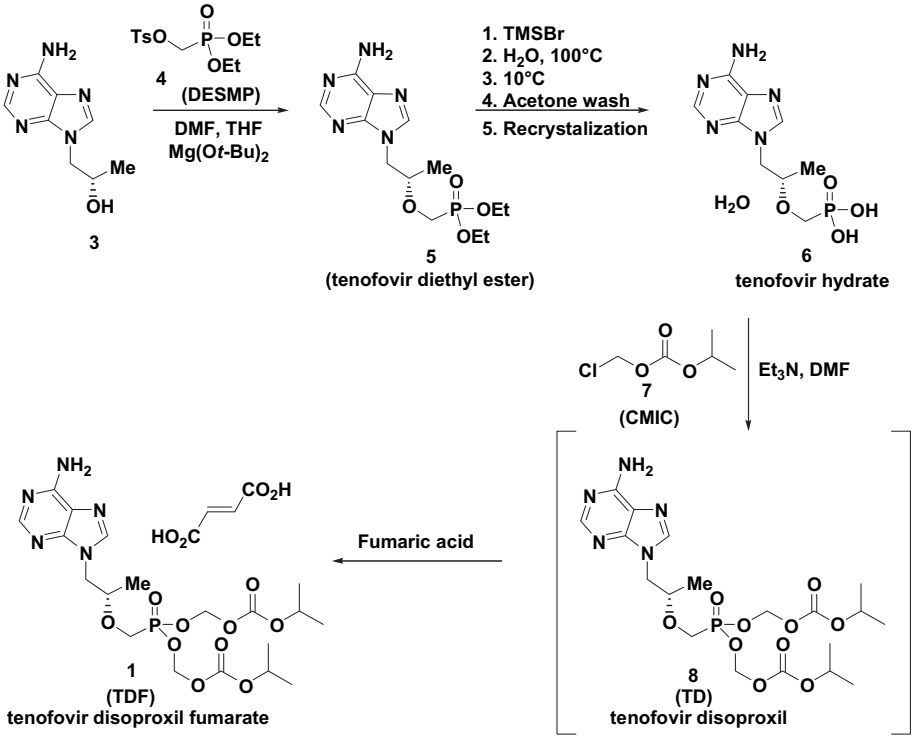
The current process for preparation of the phosphonate ester prodrug TDF (Scheme 1) is achieved on scale by an S_N2 addition of the chiral adenine-based alcohol **3** to the tosylated phosphonate ester **4** (DESMP) to produce **5** as indicated in Scheme 1. To obtain **6**, tenofovir hydrate, an acid catalyzed hydrolysis of the ethyl phosphonate esters is employed in the presence of a nucleophilic halogen such as bromide. This hydrolysis step has been particularly problematic for the manufacturing process, requiring the use of an expensive reagent, TMSBr, or the use of aqueous HBr. The reaction suffers from long cycle times, difficult to handle reagents, and results in a low yield over the DESMP coupling and hydrolysis. Once prepared the phosphonic acid is recrystallized as the hydrate to isolate **6**. To provide the active pharmaceutical ingredient **1**, recrystallized **6** is treated with **7** (CMIC), chloromethyl isopropylcarbonate, in the presence of Et_3N installing the isopropyl carbonate ester groups. Recrystallization as the fumarate salt affords TDF **1** completing the synthesis.

CMIC-mediated alkylation of the phosphonic acid. We identified reaction conditions that rapidly hydrolyzed **5** forming the desired phosphonic acid in under 8 h. TMSCl was used to activate the phosphonic esters, which were displaced via attack by bromide, supplied in the form of NaBr. In addition, we have shown that the phosphonic acid formed in situ under these reaction conditions can be converted directly into TDF, **1** following protocols identical to those used for the conversion of **6** to **1**. These process improvements, coupled with additional process improvements identified by CHAI,[6] are likely to decrease the manufacturing cost of TDF and have an immediate and major impact on the annual cost of HIV/AIDS treatment in the developing world.

2. Results and discussion

Phosphonate esters and their corresponding acids have emerged as important functional groups in the pharmaceutical industry. For example, these functional groups can be found in top selling approved pharmaceutical agents such as Fosamax (Merck), Actonel (Procter and Gamble), and Monurol. Numerous antiviral agents and anti-cancer agents currently under development capitalize on the favorable pharmacological properties of acyclic nucleotide phosphonates. In general, for discovery and process chemistry, phosphonates are installed as diethyl phosphonate esters. The esters are subsequently hydrolyzed affording the phosphonic acids. If a prodrug is required, such as with tenofovir, the requisite ester is installed via alkylation.

Examination of the recent literature shows that the overwhelming majority of alkyl phosphonate ester hydrolyses are carried out by treatment with trimethylsilyl bromide. A variety of solvents have been successfully used for this transformation, including non-polar



Scheme 1. Published manufacturing process (Gilead) of TDF from **3**.

To decrease the overall processing time for production of **1** from **5** we investigated alternative conditions for the hydrolysis of the diethyl phosphonate ester **5**. We focused on identifying rapid reaction conditions that could be compatible with the in situ

solvents such as dichloromethane and polar solvents including acetonitrile, DMF, and NMP. Buffering of the reaction condition via addition of 2,6-lutidine[7–9] can help suppress unwanted side reactions such as oxonium ion formation from glycosidic linkages. Analysis of

reaction rates and temperatures shows that hydrolysis occurs in these solvents at temperatures between 23 °C and 55 °C with reaction times varying between 24 h and 72 h.[7–56]

The known mechanisms for TMSBr-mediated hydrolysis occur via rapid activation of the phosphonate ester by silylation, followed by either rate determining loss of an alkyl carbocation (S_N1) or S_N2 displacement of the alkyl chain by a nucleophile.[57] The partitioning between the S_N1 and S_N2 reaction pathways is dictated by two factors, the stability of the carbocationic species and the accessibility of the electrophilic center by the nucleophile. With methyl and ethyl phosphonate esters, the S_N2 pathway predominates.[58,59]

Hydrolysis of the diethyl esters of tenofovir **5** is challenging.[60–64] Harsh conditions such as 12 equiv of TMSBr in refluxing acetonitrile provide hydrolysis over 8 h with a 79% isolated yield of **6**.[61] Treatment of **5** with 4.5 equiv of TMSCl in chlorobenzene in a sealed vessel at 125 °C for 9 h provides **6** in 75% isolated yield.[60,64] Use of 48% aqueous HBr (7.5 equiv) at 90 °C for 5 h leads to a 70% isolated yield of **6**.[63] These examples demonstrate the harshness of reaction conditions and the large excesses of reagents required to provide good conversion of **5** to **6** in a timely manner. Our goal was to identify reaction conditions capable of generating **6** with less corrosive and hazardous reagents than TMSBr and HBr, lower temperatures and stoichiometric amounts of reagents.

Since nucleophilic displacement is rate determining for TMSBr-mediated hydrolysis, the use of TMSCl in conjunction with exogenous nucleophiles[65] was investigated for the hydrolysis of **5**. A 6 h treatment of **5** in *N*-methylpyrrolidone (NMP) at 55 °C with 4 equiv of bromide or iodide[57] in the presence of 4 equiv TMSCl, followed by quenching with H_2O leads to substantial formation of **2** (Table 1, entries 7 and 8). Examination of earlier time points in the reaction shows that at 2 h the iodide-mediated reaction had generated 90 area % **2** and the bromide-mediated reaction had produced 18 area % **2**. Addition of all other exogenous nucleophiles examined, including acetate, azide, and chloride under otherwise identical reaction conditions (Table 1, entries 1, 2, and 5) did not lead to appreciable formation of **2**.

Table 1
Effect of exogenous nucleophiles on hydrolysis of **5**

Entry	Nucleophile	**2** (area %)[a]
1	NaOAc	0
2	NaN_3	1
3	$KSCOCH_3$	1
4	$KSCO_2Et$	1
5	NaCl	2
6	PhSH	4
7	NaI	85
8	NaBr	98

Reactions were performed at 0.58 mmol scale (1 M in NMP, 4 equiv TMSCl, 60 °C, 6 h).
[a] Area percent of **2** determined by HPLC analysis.

These results are consistent with nucleophilic attack as the rate determining step. Good nucleophiles such as iodide rapidly hydrolyze **5** whereas poor nucleophiles, such as acetate and chloride, generated **5** at substantially slower rates. Of particular interest was the reactivity of azide (Table 1, entry 2). Based on Swain–Scott nucleophilicity parameters, *n*, azide (n=5.78) is a comparable nucleophile to bromide (n=5.79)[66] and should provide comparable hydrolytic rates. Azide, however, is found to provide much slower hydrolysis than bromide. The poor performance of azide can be attributed to its reactivity toward silylation. As a strong nucleophile but poor leaving group (conjugate acid pK_a of 4.75 versus −7.7 for bromine), azide can react with trimethylsilyl chloride or the silylated phosphonate ester to generate trimethylsilyl azide ($TMSN_3$). In solvents with high dielectric constants, $TMSN_3$ formation can be very rapid, occurring in under 2 h at room temperature.[67] The less reactive $TMSN_3$ no longer rapidly silylates **5**, decreasing the amount of activated phosphonate ester and slowing the reaction. We thus predict that optimal nucleophiles for hydrolysis will have Swain–Scott nucleophilicity parameters comparable or greater than bromide (n=5.79) and conjugate acid pK_a's less than chloride (pK_a=−5.7).

The counter ion of the exogenous nucleophile can play a role in reaction rate by influencing both solubility of the nucleophile and reactivity. To determine the optimal counter ion for maximizing the rate of TMSCl/halide-mediated hydrolysis of **5**, the lithium, sodium, and potassium salts of chlorine, bromine, and iodine were examined. Table 2 provides a time course for formation of **2**. The reaction rates do not trend with solubility of the salts in organic solvents, such as methanol.[68] For example the solubility of LiBr, NaBr, and KBr in methanol at 25 °C is 139, 17.4, and 2.2 g/100 g of solvent, respectively.[68] Similar trends are seen with chloride and iodide. If solubility alone were the principle factor in the rate of hydrolysis, then LiBr (Table 2, entry 4) would be anticipated to be a substantially better nucleophile than NaBr (Table 2, entry 5). However the softer sodium counter ion leads to a more solvent separated ion pair in solution, increasing reaction rate. In the case of KBr-mediated hydrolysis of **5** (Table 2, entry 6), the increase in reactivity for of the softer more solvent separated KBr ion pair is insufficient to counteract the very low solubility of the salt in organic solvent.

Table 2
Effect of halide counter ion on the time course for hydrolysis of **5**

Entry	Salt	**2** (area %)[a]			
		0 h	2 h	4 h	6 h
1	LiCl	0	0	0	2
2	NaCl	0	1	1	2
3	KCl	1	1	1	2
4	LiBr	1	8	20	32
5	NaBr	0	18	92	98
6	KBr	1	1	2	7
7	LiI	0	17	38	52
8	NaI	82	90	88	85
9	KI	89	91	88	90

Reactions were performed at 0.58 mmol scale (1 M in NMP, 4 equiv TMSCl, 4 equiv salt, 60 °C).
[a] Area percent of **2** determined by HPLC analysis.

Hydrolysis is also sensitive to the nature of the silylating agent used. If silylation is rapid and reversible, than the more reactive the silylating group used in the reaction, the farther the equilibrium will lie on the silylated phosphonate intermediate side, accelerating the reaction rate. Hydrolysis was thus carried out in the presence of a number of different silylating groups and the amount of phosphonate diester **5**, intermediate ethyl phosphonate monoester **9**, and phosphonic acid **2** present after quenching with water were determined by HPLC. Unreactive silyl chlorides such as TBDPSCl (Table 3, entry 1) lead to minimal hydrolysis over 6 h. More reactive silyl chlorides, such as TESCl (Table 3, entry 4) and TMSCl (Table 3, entry 7), increased the rate of hydrolysis. Highly reactive silyl triflates (Table 3, entries 6 and 8) were substantially more reactive than the corresponding silyl chlorides (Table 3, entries 1 and 7). For example TMSOTf leads to complete hydrolysis of **5** in under 2 h with no phosphonate monoester **9** detectable whereas TMSCl produced 18 area % **2** and 54 area % **9**, with 28 area % starting material **5** remaining after 2 h.

As silylation reversibly activates the phosphonate ester enabling nucleophilic attack, we examined the ability of Lewis acids to

Table 3
Effect of silylating agent reactivity on the hydrolysis **5**

Entry	Silylating agent	**5** (area %)[a]	**9** (area %)[a]	**2** (area %)[a]
1	TBDPSCl	84	10	0
2	TBSCl	84	12	0
3	TIPSCl	71	27	0
4	TESCl	69	26	2
5	$SiCl_4$	0	1	78
6	TBSOTf	0	1	97
7	TMSCl	0	2	98
8	TMSOTf	0	0	99

Reactions were performed at 0.58 mmol scale (1 M in NMP, 4 equiv silylating agent, 4 equiv NaBr, 60 °C, 6 h).
[a] Area percent determined by HPLC analysis.

Table 4
Effect of Lewis acids on phosphonate ethyl ester hydrolysis

Entry	Lewis acid	**5** (area %)[a]	**9** (area %)[a]	**2** (area %)[a]
1	$ZnCl_2$	97	1	1
2	$FeCl_3$	96	0	1
3	$MnCl_2$	95	3	1
4	AgOTf	94	1	0
5	$CuCl_2$	90	1	5
6	$AlCl_3$	84	15	0
7	$BF_3{\cdot}OEt_2$	36	60	4
8	$MgCl_2$	27	71	0
9	$TiCl_4$	1	87	3

Reactions were performed at 0.58 mmol scale (1 M in NMP, 4 equiv NaBr, 4 equiv Lewis acid, 60 °C, 6 h).
[a] Area percent determined by HPLC analysis.

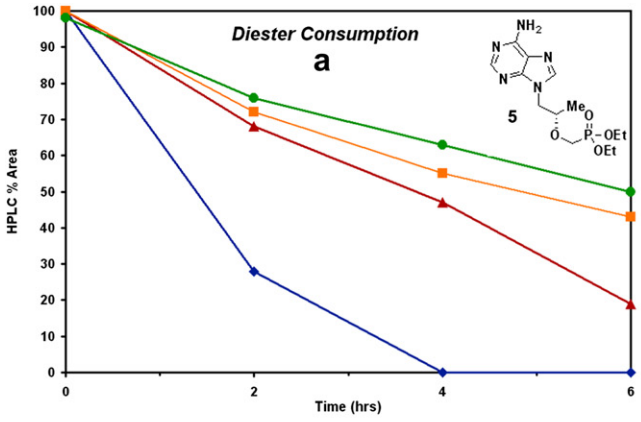
similarly activate the phophonate ester to hydrolysis ($A_{AL}2$ mechanism).[69] Table 4 shows the results for various Lewis acids in the NaBr-mediated hydrolysis of **5**. Weak Lewis acids did not provide appreciable hydrolysis of the diethyl phosphonate ester (Table 4, entries 1–5). Strong Lewis acids, such as the oxophilic Lewis acid $TiCl_4$, lead to substantial formation of **9** (Table 4, entries 7 and 9). Further conversion to **2** is likely prevented due to the insolubility of the metal salt of **9**. While Lewis acids do not appear to be effective reagents for complete hydrolysis to the phosphonic acid, strong Lewis acids do provide a selective route for phosphonate monoester formation.

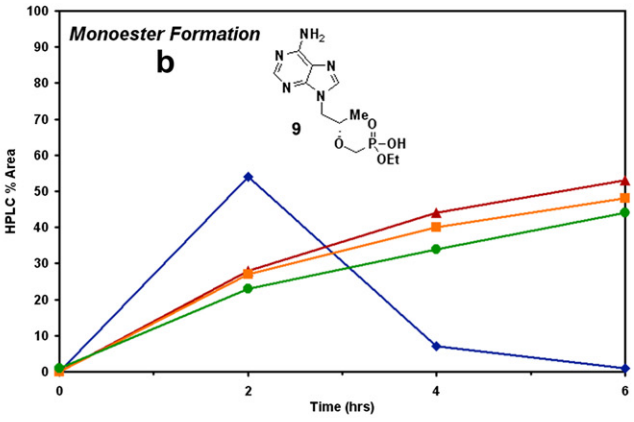
Based on our screen of exogenous nucleophile, counter ion, and activating group, we identified NaBr/TMSCl as the optimal reagents for rapid, low temperature hydrolysis of **5**. NaI and KI lead to more rapid hydrolysis of **5** at 60 °C than NaBr and in the case of NaI, rapid hydrolysis at room temperature. However, the use of iodide as the

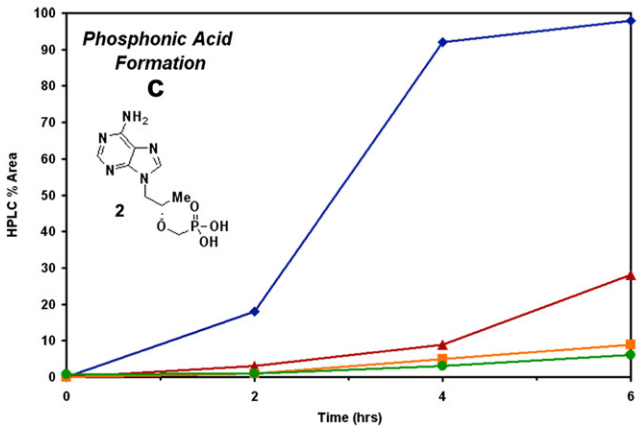
Table 5
Solvent effects on NaBr/TMSCl-mediated hydrolysis of **5**

Entry	Solvent	Dielectric constant (ε)[a]	**5** (area %)[b]	**9** (area %)[b]	**2** (area %)[b]
1	NMP	32	0	2	98
2	DMF	37	0	2	98
3	MeCN	36	77	17	1
4	DCE	10	88	9	0
5	PhMe	2	88	2	0
6	EtOAc	6	96	1	0
7	DMSO	47	0	1	0

Reactions were performed at 0.58 mmol scale (1 M solvent, 4 equiv NaBr, 4 equiv TMSCl, 60 °C, 6 h).
[a] Dielectric constants (ε) taken from Refs. 66,70–73.
[b] Area percent determined by HPLC analysis.







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entry	eq. H_2O	**5** (area %)[a]	**9** (area %)[a]	**2** (area %)[a]
1	0	0	1	98
2	2	19	53	28
3	4	43	48	9
4	8	50	44	6

Figure 2. The addition of water negatively effects the hydrolysis rate of phosphonate diethyl ester. (a) Consumption of diester **5**. (b) Formation of monoester **9**. (c) Formation of phosphonic acid **2**. (d) Data in table form. Reactions were performed at 0.58 mmol scale (1 M in NMP, 4 equiv NaBr, 4 equiv TMSCl, 60 °C, 6 h). [a]Area percent determined by HPLC analysis. Symbols: ◆, no H_2O; ▲, 2 equiv H_2O; ■, 4 equiv H_2O; ●, 8 equiv H_2O.

nucleophile consistently generated approximately 10 area% of a new uncharacterized impurity. Presumably this impurity is formed via alkylation with the ethyl iodide generated during the hydrolysis. NaBr was thus selected over NaI and KI as it provided rapid, quantitative conversion to **2** without formation of significant levels of this impurity. Silyl triflates were also shown to provide more rapid hydrolysis of **5** than the corresponding reaction with TMSCl. However, the silyl triflates are substantially more difficult to handle and more costly than TMSCl. Therefore the optimal activating agent selected for hydrolysis was TMSCl.

Solvent plays a major role in the hydrolysis of **5** as is seen in Table 5. However the effect of solvent is complex and difficult to predict as it impacts the solubility of **5** and NaBr, the stability of the activated intermediate and thus its concentration in solution, and the nucleophilicity of bromide in the reaction. A screen of polar aprotic and non-polar aprotic solvents shows that NMP and DMF are the only suitable solvents for hydrolysis (Table 5, entries 1 and 2). The high dielectric constant (ε) of both of these solvents (DMF ε=37, NMP ε=32) sufficiently stabilizes both the activated silyl intermediate and facilitates solvent separated bromide ion pairs. Both of these effects are expected to increase reaction rate. In acetonitrile, which also has a high dielectric constant (ε=32), the reaction is slow. This can be attributed to the observable poor solubility of sodium bromide and the phosphonate diester **5**. DMSO, with its high dielectric constant leads to formation of numerous byproducts and none of the desired phosphonic acid, **2**. Presumably TMSCl and NaBr activate DMSO, likely resulting in the formation of *N*-oxides, alkylation of the adenine nitrogens, and generation of dimethylsulfide. Thus DMF and NMP appeared to be optimal, manufacturing friendly solvents for hydrolysis of **5**.

both NaBr and TMSCl (Table 6, entry 9). If longer reaction times are used, stoichiometric amounts (Table 6, entry 8) of NaBr can be effectively used in the reaction, yielding 97.5±1.5 area% **2** (n=9). It is interesting to note that iodide can be used catalytically for the reaction. Presumably ethyl iodide is formed and converted into volatile ethyl chloride in situ. Further optimization of this process may provide a robust catalytic approach to hydrolysis of **5**. The use of stoichiometric NaBr, however, provides a robust, reproducible process with an outstanding purity profile. A representative HPLC trace of the reaction end point is shown in Figure 3, demonstrating the high purity of crude **2** from the reaction.

Table 6
Effect of nucleophile stoichiometry and silylating reagent on the hydrolysis of **5**

Entry	Salt	Equivalents of salt	Equivalents of TMSCl	Time (h)	Temp (°C)	**5** (area %)[a]	**9** (area %)[a]	**2** (area %)[a]
1	NaI	4	4	6	60	0	0	85
2	NaI	3	4	6	23	0	5	89
3	NaI	2	4	6	23	5	40	51
4	NaI	0.2	4	6	60	23	54	22
5	NaI	0.2	4	6	23	91	7	1
6	NaBr	1	4	6	60	9	47	43
7	NaBr	2	4	6	60	1	21	79
8	NaBr	2.1	4	12	60	0	0	100
9	NaBr	4	4	6	60	0	2	98
10	NaBr	4	1	6	60	68	26	1
11	NaBr	4	2	6	60	28	52	16
12	NaBr	2	2	6	60	38	48	10

Reactions were performed at 0.58 mmol scale (1 M in NMP).
[a] Area percent determined by HPLC analysis.

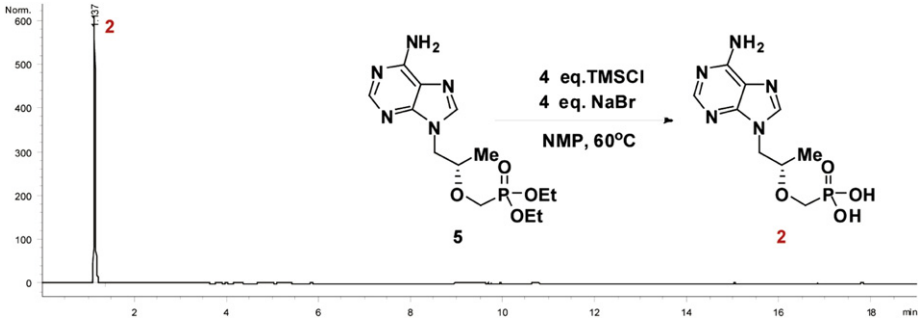

Figure 3. Hydrolysis of **5** with NaBr is extremely clean, providing high quality, anhydrous **2**.

The reaction was found to be highly sensitive to water. Addition of 2 equiv of water was sufficient to dramatically slow the reaction rate as seen in Figure 2. The addition of excess water completely inhibited formation of the phosphonic acid **2** and led to significant accumulation of the phosphonate monoester **9**. Hydrolysis of TMSCl by water is insufficient to rationalize the decrease in rate since the addition of excess TMSCl does not recover reactivity. For example, hydrolysis of **5** in the presence of 2 equiv of water and 8 equiv of TMSCl provides identical results after 6 h to hydrolysis of **5** with 2 equiv of water and 4 equiv of TMSCl. The HCl generated from water hydrolysis of the TMSCl is likely inhibiting silylation of **5**, decreasing the concentration of the reactive intermediate and slowing the reaction rate. Under anhydrous conditions the TMSCl/NaBr-mediated reaction in NMP is extremely robust and highly reproducible, providing 96±2% conversion of **5** to **2** in 6 h with no failed attempts.

In order to minimize reagent use, the effect of stoichiometry of the nucleophile and activating group was investigated. Table 6 indicates high yielding conversion of **5** to **2** in 6 h with 4 equiv of

The high purity of **2** in conjunction with the stoichiometric use of NaBr suggested that hydrolysis could be coupled to alkylation of **2** generating **8** (TD) directly from **5**. To facilitate formation of **8** from **2** it was necessary to ensure complete removal of the excess TMSCl. This could be accomplished via co-distillation with anhydrous ethyl acetate. Given the anhydrous conditions, the phosphonate silyl ester **10** had to be solvolyzed to release the required phosphonic acid **2**. Treatment with isopropyl alcohol hydrolyzed **10** and the trimethylsilyl isopropyl ether generated was removed by distillation. The phosphonic acid, **2**, produced in situ was then ready to proceed with the **7** (CMIC) mediated alkylation to form **8**. Addition of **7** and Et_3N generated **8** in 6 h at 61% in situ yield. This is comparable to in situ yields obtained from a 6 h treatment of isolated purified **6** with Et_3N and CMIC. Following a standard, unoptimized aqueous work up protocol, **8** was isolated in 31% overall yield from **5**. The impurity profile generated for the conversion of **5** directly to **8** (Fig. 4) is identical to the profile for conversion of isolated purified **6** to **8**. This reaction demonstrates the feasibility of coupling hydrolysis to CMIC-mediated alkylation in a single reaction vessel.

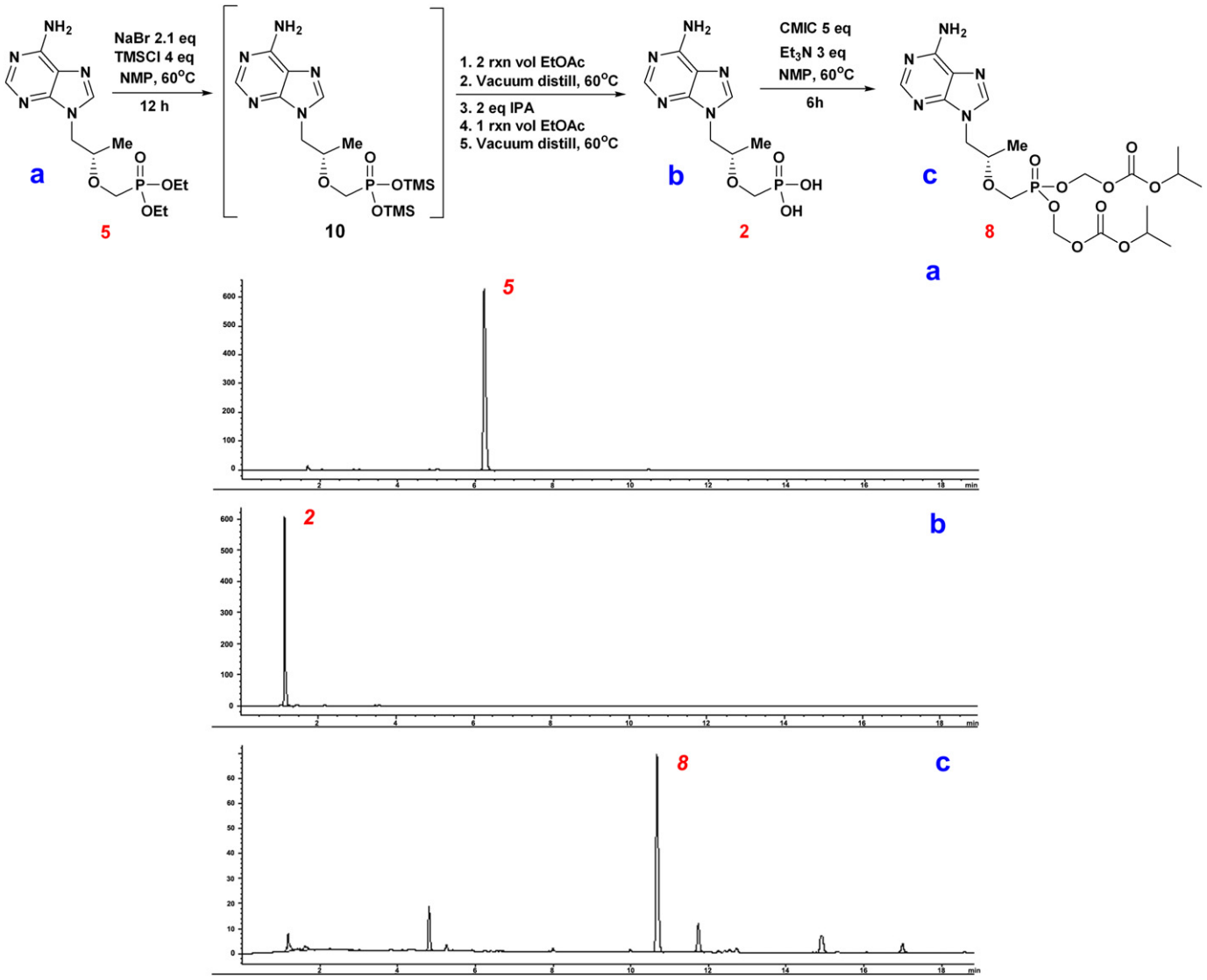

Figure 4. One-pot conversion of **5** to **8**. HPLC traces of the reaction at each stage are shown. Reactions were performed at 2.91 mmol scale (1 M in NMP, 60 °C). Area percent determined by HPLC analysis.

3. Conclusion

Herein we demonstrate a rapid mild, method for the hydrolysis of the diethyl phosphonate ester of tenofovir **5** to tenofovir **2**. This reaction relies on rapid, reversible silylation of the phosphonate ester by TMSCl, generating a reactive intermediate, which is hydrolyzed in the rate determining step by bromide supplied to the reaction as NaBr. The reaction solvent is NMP and at 60 °C the reaction is complete in under 6 h. This reaction is a substantial improvement over the current manufacturing process as it is (1) much faster, offering an increase in production capacity, (2) occurs at a much lower temperature, requiring less energy expenditure, and (3) uses less reactive, corrosive reagents, decreasing the potential for lot failure due to reagent sensitivity. In addition, we have shown that the optimized conditions are amenable to in situ hydrolysis followed by CMIC-mediated alkylation. Optimization and implementation of this two-step one-pot process commercially would substantially shorten the TDF manufacturing process by removing four steps. Therefore, this process improvement has the potential to impact the treatment of HIV/AIDS in the developing world by ultimately lowering the current cost of providing treatment with the front-line drug, tenofovir, as well as combination therapies, to a more affordable level.

4. Experimental

4.1. General procedure for the formation of tenofovir (2)

Sodium bromide (0.240 g, 2.33 mmol) and **5** (0.2 g, 0.58 mmol) are placed into a dry reaction vessel containing a magnetic stir bar. *N*-Methylpyrrolidone (NMP, 580 μL, 1 M) and trimethylsilyl chloride (TMSCl, 300 μL) are added to the mixture. The vessel is capped, stirred vigorously, and heated to 60 °C. The reaction mixture was maintained at 60 °C for 6 h. Samples (approximately 25 μL) were removed from the reaction mixture at 0 h, 2 h, 4 h, and 6 h and quenched with 20% v/v aqueous acetonitrile (1.5 mL). The samples (1 μL volume) were then analyzed by HPLC. HPLC conditions: UV detection λ=254 nm, Zorbax RX-C18, 3.5 μm, 4.6×100 mm, flow rate 1.5 mL/min, gradient elution H_2O, 0.05% v/v formic acid/MeCN 0.05% v/v formic acid, 95:5 to 45:55 (linear gradient) over 18 min run time. Typical retention times, **5**: t_R=5.28 min, **9**: t_R=2.0–2.2 min, **2**: t_R=1.13 min. Compound **2** generated following this protocol

matched authentic, commercial **2** in all respects (HPLC t_R, MS). ESI-MS [M+H] observed m/z=520.3, calculated m/z=520.2.

4.2. General procedure for the one-pot synthesis of tenofovir disoproxil (8) from 5

A dry round bottom flask equipped with a reflux condenser and a magnetic stir bar was charged with **5** (8.0107 g, 23.33 mmol, 1.0 equiv) and sodium bromide (5.0505 g, 49.08 mmol, 2.10 equiv) under Ar atmosphere. *N*-Methylpyrrolidone (NMP, 23.3 mL) and TMSCl (11.9 mL, 93.8 mmol, 4.02 equiv) were added to the flask and the mixture was stirred. The flask was capped and stirred vigorously while heating to 60 °C. The reaction mixture was maintained at 60 °C for 12 h and monitored by HPLC for complete conversion to **2** (for HPLC conditions see General procedure for the formation of tenofovir). When complete (less than 2 area % of **5** and **9** combined), the reaction mixture is diluted with EtOAc (35 mL) and stirred for 5 min. The EtOAc and remaining TMSCl were then removed by vacuum distillation at 60 °C. EtOAc (35 mL) was again added, stirred for 5 min, and removed by vacuum distillation at 60 °C. Isopropanol (3.6 mL, 47 mmol, 2.0 equiv) was then added to the reaction mixture and was stirred for 15 min. The mixture was diluted with EtOAc (35 mL) and the volatile reagents removed by vacuum distillation at 60 °C. Chloromethyl isopropylcarbonate, **7**, (15.6 mL, 118 mmol, 5.03 equiv) and Et_3N (9.8 mL, 70 mmol, 3.0 equiv) were added to the mixture and the reaction mixture is stirred at 60 °C for 6 h. Analytical samples (25 μL) were collected immediately after addition of **7** and Et_3N to the reaction mixture and every subsequent 2 h. Samples were immediately quenched with 20% v/v aqueous acetonitrile (1.5 mL) and analyzed by HPLC. HPLC conditions: UV detection λ=254 nm, Zorbax RX-C18, 3.5 μm, 4.6×100 mm, flow rate 1.5 mL/min, gradient elution H_2O, 0.05% v/v formic acid/MeCN 0.05% v/v formic acid, 95:5 to 45:55 over 18 min run time. Typical retention times; **2**: t_R=1.13 min, mono isoproxyl phosphonate ester (assigned by ESI-MS [M+H] m/z=403.9): t_R=4.81 min, **8**: t_R=10.72 min. The reaction was considered complete when HPLC analysis showed less than 15 area % of the mono isoproxyl phoshonate ester. The reaction was diluted in EtOAc (35 mL), stirred for 5 min, and the ethyl acetate and remaining Et_3N are removed by vacuum distillation at 60 °C. The reaction mixture was diluted in EtOAc (140 mL) and extracted with water (70 mL). The organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtered, and concentrated to dryness in vacuo. The resulting light brown oil **8** (TD, 11.87 g) was assayed by HPLC to give a potency corrected yield of 31%. Compound **8** produced following this protocol matched authentic **8** in all respects (HPLC, MS, ^{1}H NMR). Compound **2**: HPLC t_R=10.72 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H, CH), 7.98 (s, 1H, CH), 5.63 (m, 4H, CH_2), 4.91 (m, 2H, C*H*(CH_3)$_2$), 4.36 (dd, J=3.0, 14.4 Hz, 1H, CH), 4.14 (dd, J=7.3, 14.4 Hz, 1H, CH), 3.94 (m, 2H, C*H*H and C*H*), 3.71 (dd, J=9.1, 13.7 Hz, 1H, CH*H*), 1.30 (d, J=15 Hz, 12H, CH(CH_3)$_2$), 1.27 (s, 3H, CH_3), 1.21 (d, J=7.4 Hz, 3H, CH_3); ESI-MS [M+H] observed m/z=520.3, calculated m/z=520.2.

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Supplementary data

Experimental procedure and complete data sets for all hydrolysis experiments, ^{1}H NMR spectra for compounds **1**, **2**, **5**, and **8** are available. ESI-MS spectra for compounds **2**, **5**, **8**, reaction intermediate **9**, impurities, as well as HPLC traces of a representative hydrolysis and coupling reaction time course are included. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.08.037. These data include MOL files and InChIKeys of the most important compounds described in this article.

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