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Preparation of Phosphonooxymethyl Prodrugs of HIV-1 Attachment Inhibitors

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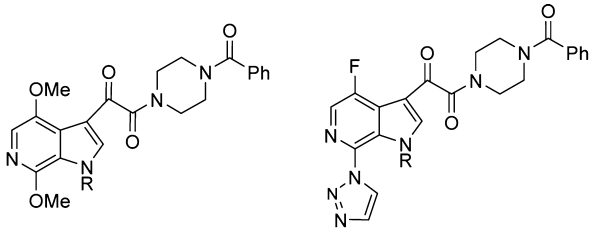
ABSTRACT: A practical and scalable synthesis of phosphonooxymethyl prodrugs of HIV-1 attachment inhibitors is described. Starting from azaindoles **1** and **2**, this two-step sequence features an efficient alkylation using chloromethyl phosphate **5** and an exceptionally mild deprotection for *tert*-butyl phosphates. After a salt formation, the API is formed in 82% and 70% overall yield for **3a** and **4a**, respectively. This chemistry was used to prepare multikilogram quantities of API.

INTRODUCTION

HIV/AIDS is a global epidemic infecting over 34 million people. About 2.7 million new cases are reported each year, and AIDS is responsible for over 1.8 million deaths annually.[1] There are currently over 25 single antiviral agents approved for HIV-1 spanning seven different classes of therapies, as well as multiple fixed-dose combinations.[2] While the use of combination antiretroviral therapy (cART) has led to extensive progress in reducing morbidity and mortality, significant challenges around drug resistance and tolerability underline the importance of developing new approaches for additional viral targets.[3] One new class of agents for combating HIV/AIDS is HIV-1 attachment inhibitors, belonging to the general class of HIV-1 entry inhibitors.[4] HIV-1 attachment inhibitors prevent entry to the host cell by binding to the viral envelope gp120 and interfering with the interaction with the human cellular receptor CD4.[5,6]

In a program directed towards targeting viral gp120,[7] two promising HIV-1 attachment inhibitors have been studied (**1** and **2**, Figure 1).[8] An unfortunate limitation of these molecules



1, R = H
3, R = $CH_2OP(O)(OH)_2$
3a, R = $CH_2OP(O)(OH)_2$ - Lysine

2, R = H
4, R = $CH_2OP(O)(OH)_2$
4a, R = $CH_2OP(O)(OH)_2$ - Lysine

Figure 1. HIV attachment inhibitors.

is their poor aqueous solubility, which limits exposure. In an effort to improve this characteristic, a water-soluble prodrug strategy[9−11] was examined by the use of a phosphonooxymethyl moiety attached to the azaindole N-1 position.[12] Once in the intestines, phosphonooxymethyl prodrugs[13] are hydrolyzed by alkaline phosphatase in the brush border membrane,[13a,14] leading to a readily labile hemiaminal, which rapidly degrades to deliver the parent drug and a molecule of formaldehyde. This manuscript details the development of an efficient and scaleable conversion of HIV-1 attachment inhibitors **1** and **2** to phosphonooxymethyl prodrugs **3** and **4** to support early toxicology studies and phase I clinical studies.

RESULTS AND DISCUSSION

HIV-1 attachment inhibitor **3** is a phosphonooxymethyl prodrug, derived from its parent compound **1**, through an alkylation employing **5** to afford the di-*tert*-butylphosphate **6**.[15] Acid-promoted deprotection of **6** affords the prodrug **3** (Scheme 1). The initial conditions for the alkylation of **1** required 5 equiv of the alkylating agent **5** and relied upon the use of 3 equiv of sodium hydride and 1 equiv of iodine to generate NaI *in situ* and thus effect a Finkelstein reaction to render **5** more electrophilic. In this manner, **6** was produced in 70−80% yield and 92 HPLC area % purity after column chromatography. There were a number of issues to be addressed to make this process more amenable to scale-up. Foremost was the excess of the expensive and mutagenic alkylating agent **5**. The use of sodium hydride poses a pyrophoric risk, and its reaction with liberated HI evolves hydrogen gas. Furthermore, this reaction is highly exothermic, albeit addition-controlled. Preliminary experiments verified that the charge of alkylating agent **5** could be reduced to 1.5 equiv and that sodium iodide was an effective substitute for iodine; thus the sodium hydride stoichiometry was reduced to 1.5 equiv, and the highly exothermic reaction of sodium hydride with HI was eliminated.

To address scale-up issues, a more efficient alkylation reaction was developed using a weaker inorganic base in a polar aprotic solvent. Although acetone, acetonitrile, and DMF all proved to be acceptable solvents for the alkylation, DMSO was ultimately chosen for its superior reaction profile and ease of removal during workup. Potassium carbonate was chosen as the inorganic base among other common inorganic bases that performed well. The azaindole **1** proved sufficiently nucleophilic to react under these conditions without the addition of an iodine source, and the charge of alkylating agent **5** was reduced

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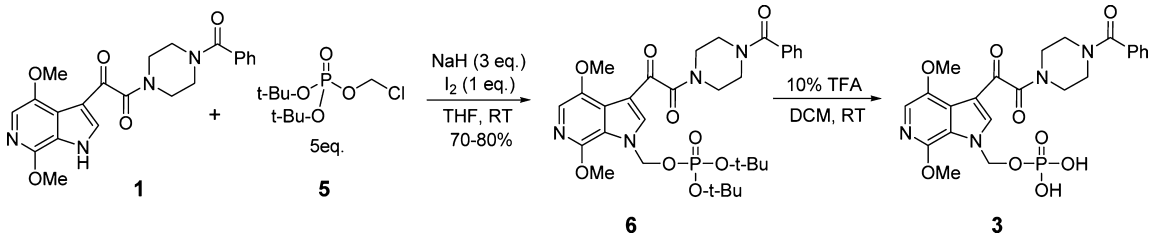
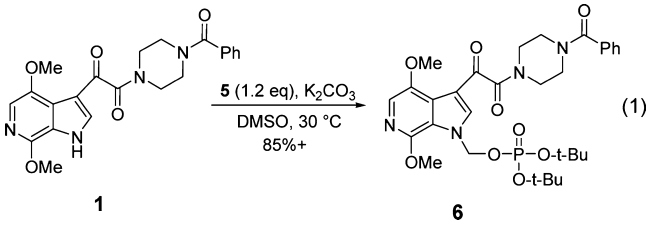
Scheme 1



to 1.2 equiv.[16] The protected prodrug **6** was obtained in 84% yield after aqueous workup and crystallization from *n*-butyl acetate (eq 1), eliminating the requirement for chromatographic purification. The HPLC area % purity of material obtained by this method improved dramatically to >98%, although 11% of **6** remained in the mother liquor.



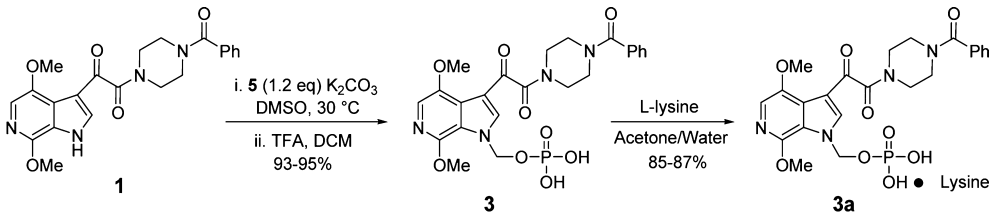
The di-*tert*-butylphosphate **6** was readily deprotected through the action of TFA in methylene chloride at room temperature, affording crystalline **3** in 98% yield and >99.5 HPLC area % purity after a solvent switch to methanol. Given the excellent crystallization properties from methanol for compound **6** and the ability to use methylene chloride both in the coupling step and in the deprotection, a telescoped alkylation/deprotection strategy was explored. Thus, simply treating the rich methylene chloride organic stream containing **6** with TFA followed by a solvent switch to methanol produced **3** directly in 93−96% yield and in 97.4 HPLC area % purity. This telescoped approach circumvented the significant loss of **6** to the mother liquor of the previous process. Conversion of the free acid **3** to the L-lysine salt **3a** was achieved in 82−87% yield, upgrading the purity to 99.7 HPLC area % (Scheme 2). This process was successfully scaled up to prepare 1.1 kg of **3a**.

The alkylation of azaindole **2** proved considerably more challenging than that of **1** due in part to the electron-withdrawing fluorine atom and triazole ring, which renders the azaindole less nucleophilic. Additionally, the triazole ring may sterically hinder the nucleophilic site. Table 1 highlights the preliminary studies for the conversion of **2** to **7**. Adapting the above conditions (2 equiv of **5**, K_2CO_3, DMSO) to azaindole **2** led to only 24% conversion to the di-*tert*-butylphosphate **7** (entry 1). This heterogeneous reaction mixture becomes a thick emulsion with time. The addition of potassium iodide modestly improves the conversion to 32% (entry 2). The conversion responded well to increasing the number of equivalents of alkylating agent **5** with the optimum conversion of 89% achieved using 8 equiv (entry 4). Nonetheless, this excessive amount of alkylating agent was considered unacceptable. Increasing the concentration from 0.1 g/mL of DMSO to 0.2 g/mL of DMSO did improve the conversion (48%, entry 5), with additional concentration to 0.4 g/mL having a negative effect on conversion (17%, entry 6) as the mixture becomes exceedingly thick and mixing is not effective.

The choice of counterion for both the carbonate base and the iodide salt proved key for solving this problem. When the reaction was run at 0.1 g/mL in DMSO, very little differentiation was observed, except that lithium proved completely ineffective (Figure 2). However, a key observation was made with respect to the rubidium and cesium counterions: *the thick emulsion previously observed was now a much more fluid suspension*. Hence, the effect of reaction concentration could then be re-examined with regard to these counterions. When the reactions were run at 0.2 g/mL, 55% and 49% conversion was obtained for rubidium and cesium, respectively, similar to the conversion achieved using the potassium counterion (Figure 3). However, when the reactions were run at 0.4 g/mL, the rubidium and cesium counterions afforded 45% and 72% conversion, respectively. This is considerably better than the potassium case. *A counterion effect is indeed operative when the* reaction *is run at higher concentration*. As the counterion effect is likely related to the solubility properties of the carbonate base, iodide salt, and the corresponding salt of substrate **2**, additional screening of solvents could be expected to augment conversion.

A detailed solvent screen identified DMPU and NMP as superior solvents with NMP chosen for its relative cost and ease of removal downstream. A 93% conversion was achieved using only 2 equiv of **5** in NMP when employing the cesium counterion (Figure 4). Lowering the reaction temperature from 40 to 30 °C and utilizing potassium iodide instead of cesium iodide improved the conversion to 97% while minimizing impurities. This methodology provide 75−81% isolated yield of crystalline di-*tert*-butylphosphate **7** with ∼95 HPLC area % purity[17] after a simple workup and crystallization from *n*-butyl acetate.

Scheme 2



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Scheme 3

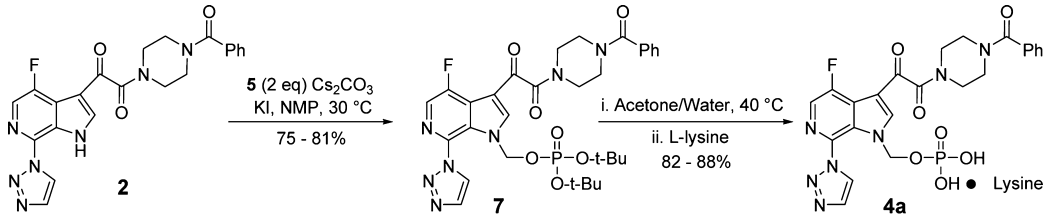
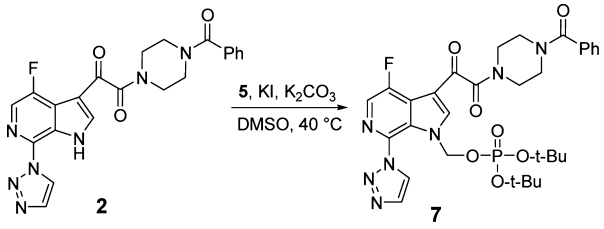


Table 1. Preliminary studies for the conversion of 2 to 7



entry	equiv of **5**	iodine source	concn (g/mL)	conv (%)
1	2	none	0.1	24
2	2	KI	0.1	32
3	4	KI	0.1	57
4	8	KI	0.1	86
5	2	KI	0.2	48
6	2	KI	0.4	17

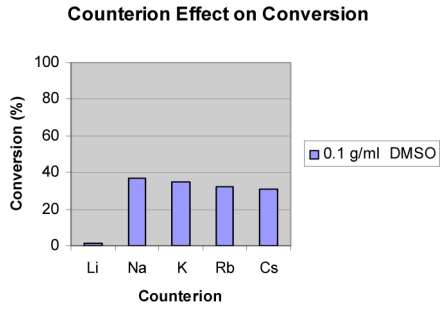


Figure 2. Counterion effect on conversion.

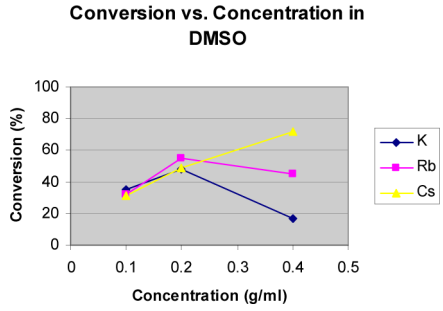


Figure 3. Conversion versus concentration in DMSO.

Deprotection of the di-*tert*-butylphosphate **7** proved challenging due to the instability of prodrug **4** under acidic conditions. Treatment of **7** with TFA in methylene chloride led to rapid deprotection; however, ~20 HPLC area % of byproducts was generated necessitating milder deprotection conditions. Strong acids afforded similar results, while weaker acids afforded no reaction. *Gratifyingly, stirring 7 in aqueous acetone at 40 °C led to complete deprotection after 24 h.*[18] Byproduct formation, while still an issue, is typically limited to

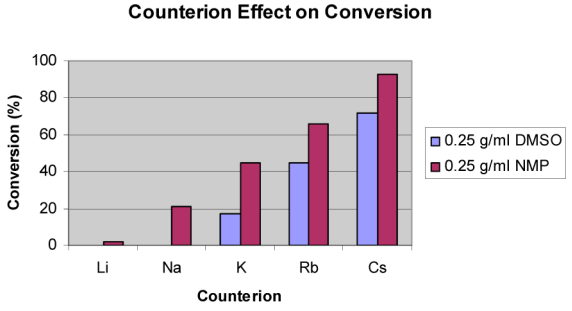


Figure 4. Counterion effect on conversion.

5%, and the reaction mixture could be held for over 12 h at room temperature with only minimal degradation. Isolation as the L-lysine salt **4a** proceeded in 82−88% yield and 98.5 HPLC area % purity (Scheme 3). This process was scaled to prepare 3.2 kg of **4a**.

CONCLUSIONS

We have developed a practical and scalable process for the conversion of HIV-1 attachment inhibitors **1** and **2** to phosphonooxymethyl prodrugs **3** and **4**, generating multiple kilograms of API to support early toxicology studies and phase I clinical studies. This research effort has brought to light an unusual concentration-dependent counterion effect and highlights extremely mild deprotection conditions for *tert*-butyl phosphates.

EXPERIMENTAL SECTION

Analytical Methods. Alkylating agent **5** was prepared according to the method of Mäntylä.[15] ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance or a Bruker DRX NMR spectrometer. Chemical shifts in DMSO-d_6, CD_3OD, and $CDCl_3$ were reported in ppm relative to residual deuterated solvent for ^{1}H and the deuterated solvent for ^{13}C. Chemical shifts in D_2O were reported in ppm relative to an external standard for ^{13}C. Coupling constants (J) are given in hertz. High-resolution mass spectra were obtained on a Waters LCT TOF or Waters QTOF TOF mass spectrometer using positive ion electrospray ionization (ESI). HPLC analyses were collected on a Shimadzu LC-10AT liquid chromatograph using a SPD-10AV UV−vis detector and the results are reported as area percent (area %).

Preparation of 3 from 1. A mixture of **1** (1.40 kg, 3.31 mol), K_2CO_3 (0.919 kg, 6.65 mol), and DMSO (7.00 L) was stirred, resulting in a light brown suspension. Di-*tert*-butyl chloromethyl phosphate **5** (1.03 kg, 3.98 mol) was added over 15 min, and the reaction mixture was heated to 30 °C for 29 h. Additional K_2CO_3 (0.460 kg, 3.33 mol) and *tert*-butyl chloromethyl phosphate **5** (0.432 g, 1.67 mol) were added to drive the reaction to completion. The reaction was stirred for an additional 14 h followed by cooling to 15 °C. DCM (14.0 L)

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was added followed by a slow quench with water (14.0 L) maintaining <20 °C, which resulted in a biphasic mixture. The product-rich bottom layer was separated, washed with water (14.0 L), and treated with trifluoroacetic acid (3.89 L, 49.1 mol). The resulting mixture was stirred for 1 h and cooled to 0 °C, then methanol (21.0 L) was added while maintaining <20 °C, and the mixture was cooled to 0 °C. The mixture was concentrated under vacuum to a volume of 14 L (200 mmHg, < 30 °C). The solution was seeded with **3** (10 g) and then stirred 7 h at room temperature. The resulting slurry was filtered, and the wet cake was washed with THF (16.6 L) and then dried in a vacuum oven at 50 °C, resulting in a pale yellow to white powder (1.69 kg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.55 (s, 1H), 7.44 (s, 5H), 6.12 (d, J = 10.6 Hz, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 3.80−3.22 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 185.49, 169.26, 166.06, 146.20, 145.60, 140.64, 135.50, 129.68, 128.41, 127.04, 123.46, 121.17, 120.08, 114.32, 72.43, 56.92, 53.32, 45.22, 40.50.

Preparation of 3a from 3. A mixture of **3** (1.00 kg, 1.88 mol), L-lysine (0.275 kg, 1.88 mol), and water (6.0 L) was heated to 50 °C, resulting in a hazy solution that was filtered through a 10 μm polish filter before addition of acetone (20.0 L) while maintaining >40 °C. The solution was seeded with **3a** (5 g) and cooled to room temperature over 5 h, resulting in a slurry. The slurry was stirred 1 h at room temperature and then filtered, and the wet cake was washed with acetone (6.3 L) and dried in a vacuum oven at 25 °C with a bleed of moist air, resulting in a fluffy white powder (1.08 kg, 85%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.38 (s, 1H), 7.49 (m, 6H), 6.13 (d, J = 10.5 Hz, 2H), 4.06 (s, 3H), 3.92 (s, 3H), 4.00−3.40 (m, 8H), 3.58 (t, J = 6 Hz, 1H), 2.92 (t, J = 7.5 Hz, 2H), 1.90−1.40 (m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 186.1, 173.2, 171.8, 167.8, 147.4, 146.4, 141.0, 135.4, 130.4, 128.8, 127. 2, 124.6, 122.3, 120.2, 114.6, 73.2, 56.6, 54.7, 53.1, 46.0, 41.6, 39.2, 30.5, 27.0, 22.0. HRMS m/z: (M-lysine + H)$^+$ calcd for $C_{23}H_{26}N_4O_9P$ 533.1437, found 533.1437. Anal. Calcd: C, 51.32; H, 5.79; N, 12.38; P, 4.56. Found: C, 48.54; H, 5.32; N, 11.76; P, 4.04. Melting point 170 °C.

Preparation of 7 from 2. A mixture of **2** (3.01 kg, 6.73 mol), Cs_2CO_3 (6.56 kg, 20.1 mol), KI (2.23 kg, 13.4 mol), and NMP (7.5 L) was stirred, resulting in a light brown suspension. Di-*tert*-butyl chloromethyl phosphate **5** (3.64 kg, 14.1 mol) was added over 15 min, and the reaction mixture was heated to 30 °C for 20 h and then cooled to 5 °C. *n*-BuOAc (18.0 L) was added followed by a slow quench with water (30.0 L) maintaining <15 °C, which resulted in a biphasic mixture that was separated. The product rich top layer was seeded with **7** (40 g) and stirred for 3.5 h at room temperature, resulting in a slurry. The slurry was filtered, and the wet cake was washed with MTBE (6.3 L) and then dried in a vacuum oven at 50 °C, resulting in a yellow/white powder (3.55 kg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.27 (s, 1H), 8.22 (s, 1H), 7.90 (s, 1H), 7.42, (s, 5H), 5.92, (d, J = 14.9 Hz, 2H), 4.02−3.40 (m, 8H), 1.24 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.75, 170.64, 152.07, 144.03, 134.91, 133.96, 131.82, 130.21, 128.68, 128.27, 128.00, 127.07, 125.81, 124.01, 113.82, 84.00, 83.93, 73.97, 46.12, 41.90, 29.57, 29.53.

Preparation of 4a from 7. A mixture of **7** (3.51 kg, 5.24 mol), IPA (7.0 L) and water (7.0 L) was heated to 40 °C and stirred for 20 h before being cooled to 20 °C. L-Lysine (0.730 kg, 4.99 mol) was added, resulting in a solution that was filtered through a 10 μm polish filter. IPA (9.5 L) was added followed by seeding with **4a** (36 g) and stirring for 30 min. IPA (3.5 L) was added over 1 h, and the mixture was heated to 50 °C, resulting in a thin slurry. The slurry was seeded with **4a** (36 g), and IPA (7.0 L) was added over 2 h with stirring for 16 h, resulting in a slurry that was heated to 70 °C for 2 h and then cooled to 50 °C. IPA (11.6 L) was added over 1 h, and then additional IPA (23.6 L) was added over 2 h followed by aging for 1 h. The slurry was cooled to 20 °C over 2 h and held overnight prior to filtration. The wet cake was washed with IPA (35.2 L) and dried in a vacuum oven at 50 °C, resulting in a white powder (3.23 kg, 88%). ^{1}H NMR (500 MHz, CD_3OD, 50 °C) δ 8.94 (s, 1H), 8.87 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.83 (m, 5H), 5.81 (d, J = 12.5 Hz, 2H), 4.30−3.70 (m, 8H), 4.08 (t, J = 6.5 Hz, 1H), 3.67 (t, J = 10 Hz, 2H), 2.26 (m, 2H), 2.07 (m, 2H), 1.88 (m, 2H); ^{13}C NMR (125 MHz, D_2O, 30 °C) δ 185.2, 174.9, 173.3, 166.8, 153.1, 146.8, 134.8, 134.3, 131.3, 131.1, 130.3, 129.3, 128.9, 128.7, 128.5, 127.2, 124.2, 112.6, 74.0, 54.9, 47.9, 47.2, 46.4, 45.9, 42.7, 42.2, 42.0, 41.7, 39.5, 30.3, 26.8, 21.8 (some signals doubled due to rotamers). MS m/z: (M-lysine + H)$^+$ calcd for $C_{23}H_{22}FN_7O_7P$ 558.1302, found 558.1293. Anal. Calcd: C, 48.75; H, 5.07; N, 17.63; P, 4.33. Found: C, 49.02; H 4.90; N, 17.90; P, 4.37. Melting point 193 °C.

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Notes

The authors declare no competing financial interest.

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