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Di-*tert*-butyl Phosphonate Route to the Antiviral Drug Tenofovir

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ABSTRACT: Di-*tert*-butyl oxymethyl phosphonates were investigated regarding their suitability for preparing the active pharmaceutical ingredient tenofovir (PMPA). First, an efficient and simple access to the crystalline di-*tert*-butyl(hydroxymethyl)-phosphonate was developed. O-Mesylation gave high yields of the active phosphonomethylation reagent. For the synthesis of tenofovir, a two-step sequence was developed using $Mg(O^tBu)_2$ as the base for the alkylation of (*R*)-9-(2-hydroxypropyl)adenine. Subsequent deprotection could be achieved with aqueous acids. (Di-*tert*-butoxyphosphoryl)methyl methanesulfonate showed to be the most efficient electrophile tested, affording PMPA in 72% yield on a 5 g scale. The developed protocol could also be applied for the preparation of the hepatitis B drug adefovir (64% yield/1 g scale).

KEYWORDS: *tenofovir, phosphites, oxymethyl phosphonates, adefovir, antivirals*

1. INTRODUCTION

The nucleotide reverse transcriptase inhibitor tenofovir (**1**, PMPA), which was described by Balzarini in 1993,[1] currently belongs to the most frequently applied human immunodeficiency virus (HIV) medications. To enable oral application and to increase bioavailability, a prodrug unit is required, which led to the development of tenofovir disoproxil fumarate (**2**, TDF), which was approved by the FDA for HIV treatment in 2001 and later in 2008 for hepatitis B virus therapy.[2] In 2010, tenofovir alafenamide fumarate (**3**, TAF) (Figure 1) was launched, which showed fewer side effects and better tolerability than TDF.[3]

In the course of the 2020 COVID-19 pandemic, testing tenofovir as potential medication for SARS-CoV2 also moved in the focus of attention. It could be demonstrated that the triphosphate of tenofovir inhibits the RNA-dependent RNA polymerase of this virus *in vitro*.[4] These results were supported by a study, which investigated the incidence and severity of COVID-19 from 77,590 HIV-positive persons receiving antiretroviral therapy. There was a lower risk of COVID-19, less related hospitalization, and even no mortality for people who were treated with Truvada [TDF + FTC (emtricitabine)] than for people who had taken other antiviral drugs.[5] There is also an ongoing clinical study in Spain with 4000 medical workers investigating Truvada as potential prophylaxis for COVID-19.[6] Thus, the demand for tenofovir could further rise in the future. Because of a lack of a diverse set of industrial syntheses of tenofovir, raw material dependency can lead to unsteady prices and drug shortages. Therefore, diversification of the synthetic portfolio is an attractive goal.

The state-of-the-art synthesis of PMPA has been reported by Ripin *et al.* in 2010 (Scheme 1).[7] (*R*)-9-(2-Hydroxypropyl)-adenine (HPA, **4**) is alkylated with diethyl(*p*-toluenesulfonyloxymethane)phosphonate (DESMP, **5**), followed by a one-pot deprotection of the phosphonic acid ester. Ripin *et al.* reported that using $Mg(O^tBu)_2$ as a base showed the best conversion (>90%) for alkylation. Telescoping the two steps proved to be beneficial to circumvent the inconvenient workup and the continuous extraction of the water-soluble phosphonate ester **6**. Furthermore, the costs of the deprotection step could be reduced by replacing the hitherto used expensive TMSBr[8] by TMSCl/NaBr. However, the workup was still elaborate, as several filtration and extraction steps were required, while simultaneously avoiding any moisture. Despite a reported significant loss of the product in the magnesium salt cake (up to 15%), PMPA·H_2O could be isolated in 59% yield.

In 2016, Riley *et al.* reported that $Mg(O^tBu)_2$ could be replaced by *in situ* generation from MeMgCl and ^{t}BuOH. The group developed an improved method to isolate the phosphonate diester **6** after continuous extraction in 85% yield. Subsequent deprotection with HBr/acetic acid afforded PMPA·H_2O in 67% yield (57% over two steps) (Scheme 1).[9] Recently, Derstine *et al.* published a new approach for making PMPA on a multigram scale. They found conditions to alkylate HPA with the free phosphonic acid of DESMP by using NaO^tBu as a base in dimethylformamide (DMF). This very efficient process gave PMPA in 70% yield.[10]

It is conspicuous that all reports investigating the challenging synthesis of PMPA focused only on DESMP or the derived free acid **7** as alkylating agents with HPA. One big selling point is of course the fact that DESMP can be made from cheap commodity chemicals and has an industrial well-established process. Nevertheless, the overall yield starting from diethyl phosphite (**8**) has been reported to be only 60−70% with varying degrees of purity (Scheme 2).[11]

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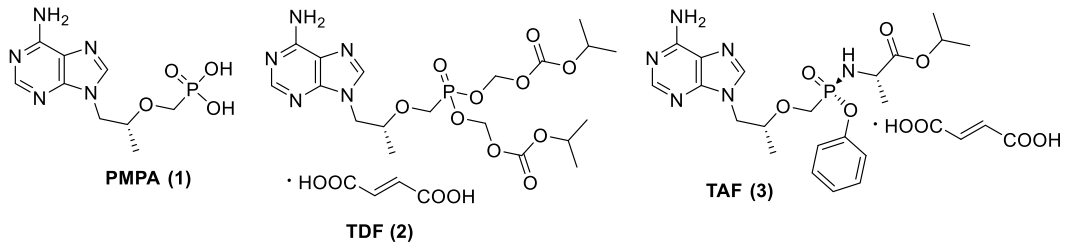
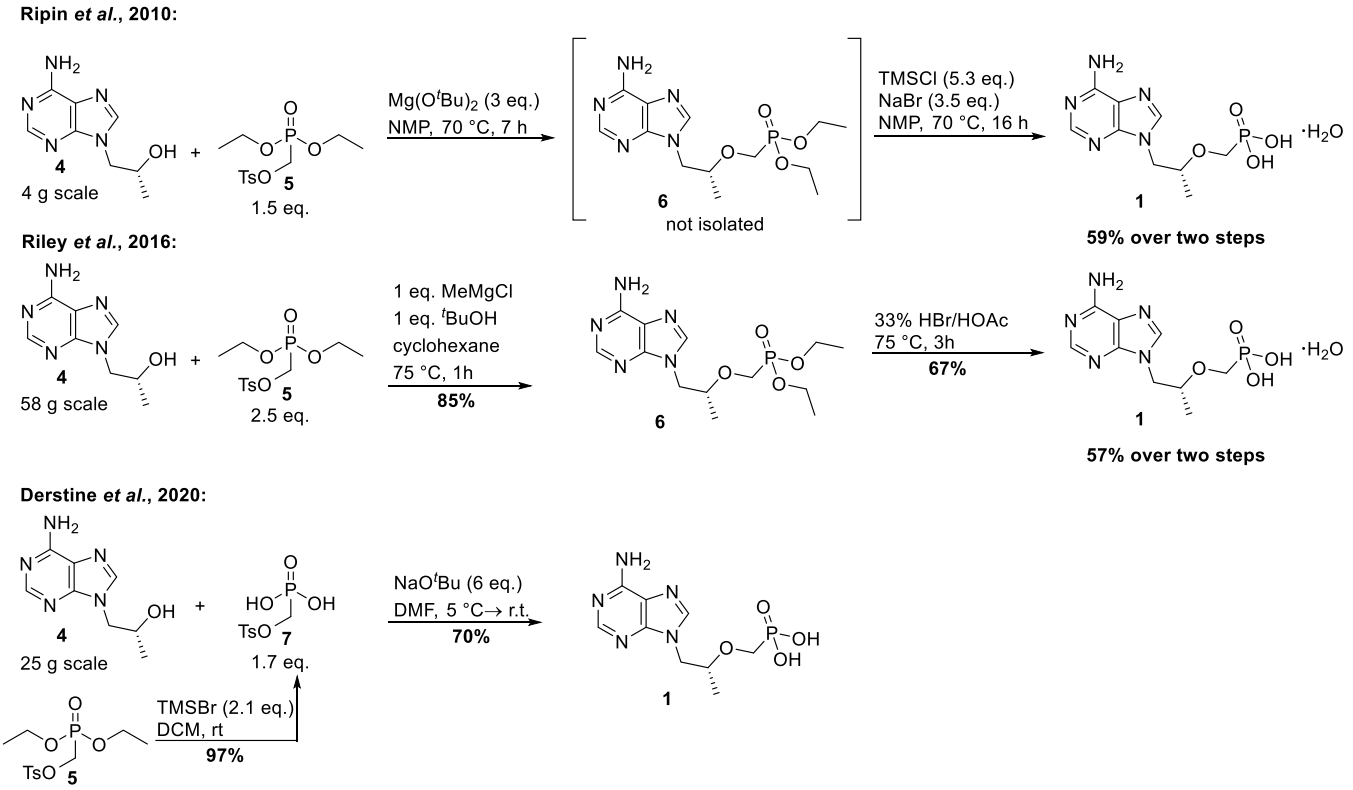
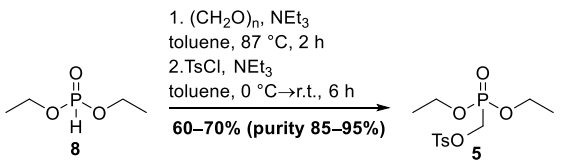


Figure 1. Structures of tenofovir (PMPA, **1**), TDF (**2**), and TAF (**3**).

Scheme 1. Overview to Hitherto Known Scalable PMPA Syntheses



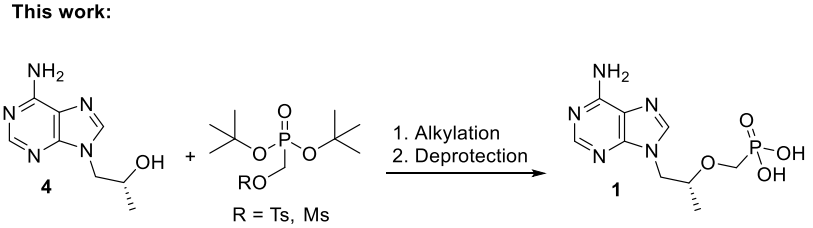
Scheme 2. Industrial Synthesis of DESMP (5)



The biggest drawback of using DESMP in the synthesis of PMPA remains the deprotection of the diethyl ester. Besides expensive (TMSBr[6]) or excessive amounts of reagents (TMSCl/NaBr[7]), an elaborate workup including several filtrations and extractions is necessary. Silicon-containing byproducts have also been reported.[12] Other conditions (aq. HBr, dry HCl gas, $AlCl_3$,[13] or HOAc/HBr[9]) led to lower yields. There is no variation in the alkyl group of oxymethyl phosphonates reported in the literature other than the use of diisopropyl ester, which requires similar conditions for the deprotection as the diethyl ester **6**.[14,15]

Tert-butyl phosphonates[16,17] are also known for being deprotected under aqueous acidic conditions. In this report, the synthesis of di-*tert*-butyl oxymethyl phosphonates and their suitability for preparing PMPA was investigated. An industrially feasible process was the aim of this work (Scheme 3).

Scheme 3. Proposed Synthesis for PMPA Using di-*tert*-butyl Oxymethyl Phosphonates



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2. RESULTS AND DISCUSSION

2.1. Synthesis of di-*tert*-butyl Phosphite. Di-*tert*-butyl phosphite (**9**) is commercially available but expensive. It can be synthesized by adding PCl_3 to a cooled solution of *tert*-butanol in the presence of a base (triethylamine, pyridine, or dimethylaniline) in a nonpolar solvent (ligroin, petroleum ether, and diethyl ether). The reported yields vary widely (40–77%).[18−23] Chemoselectivity (triester **10** *vs* diester **9**, Figure 2) also proved to be an issue.[24]

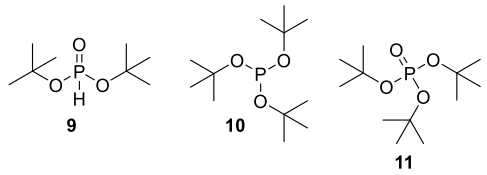
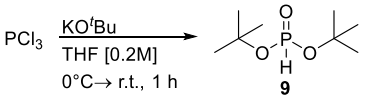


Figure 2. Structures of di-*tert*-butyl phosphite (**9**), tri-*tert*-butyl phosphite (**10**), and tri-*tert*-butyl phosphate (**11**).

Mark and Van Wazer, who focused their investigations on the selective synthesis of tri-*tert*-butyl phosphite (**10**), enlightened more details about the reaction of PCl_3 and *tert*-butanol. They proved that almost only triester **10** forms in the reaction. Nevertheless, **10** decomposes quickly at 50 °C under reduced pressure yielding the diester **9**. Furthermore, they reported that triester **10** was prone to rapid aerial oxidation to tri-*tert*-butyl phosphate (**11**, Figure 2). In terms of the selective synthesis of the diester, **11** represents an undesired byproduct, which can only be avoided by strict exclusion of oxygen during preparation and workup. The reported varying yields could be explained by the fact that diester **9** has been reported to be very sensitive to incautious heating and some product is lost during distillation.[19,20] In order to make *tert*-butyl phosphite interesting for an industrial application, the development of a more efficient synthesis was attempted.

It appeared worth trying the reaction of KO^{t}Bu with PCl_3 instead of *tert*-butanol and an organic base. As a benefit, KO^{t}Bu would combine both the reagent and base, while only potassium chloride would be accumulated as a coproduct. In initial experiments, PCl_3 was added to a KO^{t}Bu/tetrahydrofuran (THF) solution while cooling. Following the reaction by ^{1}H/^{31}P NMR spectroscopy also revealed the formation of triester, diester, and phosphate. However, when the order of addition was reversed, predominant diester formation was observed and none of the potential impurities **10** and **11** could be detected using ^{31}P NMR spectroscopy. Furthermore, adding solid KO^{t}Bu instead of a THF solution, which was slightly more convenient regarding handling, gave similar results. For the workup, the reaction mixture was quenched with saturated $NaHCO_3$ solution to maintain a basic pH in order to prevent acid-catalyzed cleavage of the *tert*-butyl groups. It is worth mentioning that despite a second aqueous washing step, all the product remained in the organic phase and no further extraction was necessary. Using 3.0 equiv of KO^{t}Bu, 98% of crude **9** (^{31}P NMR purity: 75%) was obtained after workup (Table 1, entry 1). Further investigations revealed that subsequent reduction of the equivalents of KO^{t}Bu improved the purity of the crude product (Table 1, entries 2−5). When the reaction was performed with 2.5 equiv of KO^{t}Bu, 76% of crude **9** could be obtained showing a high purity in ^{1}H and ^{31}P NMR spectroscopies (see the Supporting Information for details).

Table 1. Screening Equivalents of KO^{t}Bu for the Synthesis of di-*tert*-butyl Phosphite[a]



#	KO^{t}Bu (equiv)	IY [%][b]	purity [%][c]
1	3.0	98	75
2	2.9	85	91
3	2.7	84	95
4	2.5	76	97
5	2.3	69	99

[a]All reactions were performed on a 3 g scale. [b]Crude isolated yield. [c]Determined by ^{31}P NMR-spectroscopy.

Using the water-soluble THF as the solvent required large amounts of sodium sulfate for drying. Therefore, less polar alternative solvents were investigated. CPME (cyclopentyl methyl ether), 2-Me-THF, and even MTBE showed similar results regarding yield and purity (Table 2).

Table 2. Solvent Screening for the Synthesis of di-*tert*-butyl Phosphite[a]

#	solvent	KO^{t}Bu (equiv)	IY [%][b]	purity [%][c]
1	THF	2.5	76	97
2	2-Me-THF	2.5	75	99
3	CPME	2.5	77	99
4	MTBE	2.5	78	99

[a]All reactions were performed on 3 g scale. [b]Crude isolated yield. [c]Determined by ^{31}P NMR spectroscopy.

By focusing on MTBE and 2-Me-THF as solvents, substitution of KO^{t}Bu by the cheaper sodium salt further increased the yield of **9** (Table 3). When the reaction in MTBE was scaled up, an increasing byproduct formation was observed, whereas in Me-THF, the purity remained constant.

The obtained crude di-*tert*-butyl phosphite was used for hydroxymethylation without prior distillation to avoid an additional loss of products.

2.2. Hydroxymethylation of di-*tert*-butyl Phosphite. A procedure for hydroxymethylation of di-*tert*-butyl phosphite has already been reported in the patent literature.[25,26] According to this procedure, **9** was stirred in the presence of aq. formaldehyde solution, triethylamine, and water at r.t. to give crude **12** in 99% yield. A ^{31}P NMR spectrum showed about 10% of impurities (Scheme 4).

For the workup, it was necessary to coevaporate the reaction mixture several times with MeOH and DCM in order to remove water and triethylamine. Optimization attempts by replacing triethylamine by K_2CO_3 or omitting the additional water led to increased byproduct formation. In search for a simpler method, the combination of paraformaldehyde with K_2CO_3 in acetonitrile showed promising results. After performing some optimization studies (see the Supporting Information for more details), nearly pure **12** could be isolated in 99% yield after workup, which only consisted of a single filtration and subsequent solvent removal *in vacuo* (Scheme 5).

It should be mentioned that only commercial or freshly distilled di-*tert*-butyl phosphite was used up to this point. When using the crude di-*tert*-butyl phosphite obtained through the newly developed protocol mentioned above, the purity was

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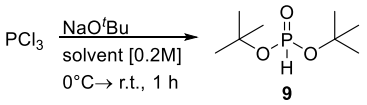
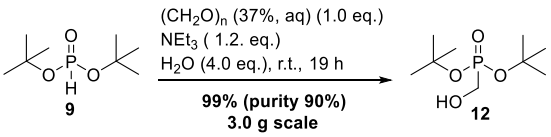
Table 3. Scale Up of the di-*tert*-butyl Phosphite Synthesis Using NaO^{t}Bu



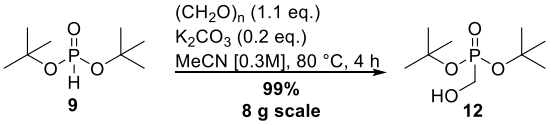
#	scale [grams of PCl_3]	solvent	NaO^{t}Bu (equiv)	IY [%][a]	purity [%][b]
1	3	MTBE	2.5	80	97
2	6	MTBE	2.5	82	90
3	3	2-Me-THF	2.5	86	95
4	9	2-Me-THF	2.5	85	95

[a]Crude isolated yield. [b]Determined by ^{31}P NMR spectroscopy.

Scheme 4. Hydroxymethylation of di-*tert*-butyl Phosphite Using aq. Formaldehyde Solution

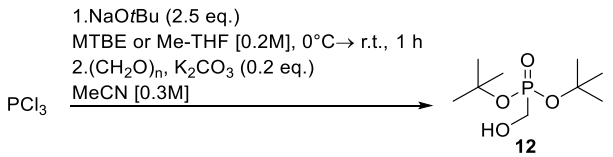


Scheme 5. Hydroxymethylation of di-*tert*-butyl Phosphite Using Paraformaldehyde



determined first by ^{31}P NMR spectroscopy in order to adjust the amount of paraformaldehyde. This was crucial, as excess paraformaldehyde caused additional byproduct formation. During further investigations, it turned out that **12** can be recrystallized from MeCN. When the filtered and concentrated reaction mixture was stored in a freezer, crystalline **12** could be isolated in 71% (based on PCl_3) (Table 4, entry 1).

Table 4. Telescoped Synthesis of di-*tert*-butyl(hydroxymethyl)phosphonate from PCl_3



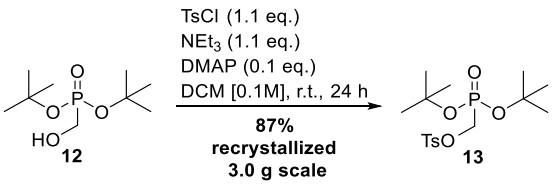
#	scale [grams of 9][a]	$(CH_2O)n$ (equiv)	T [°C]	t [h]	IY [%][b]
1	6.6 (95)	1.1	80	5	71
2[c]	7.2 (90)	1.0	70	20	66
3[c]	3.8 (95)	1.0	70	20	72
4[c]	11.3 (95)	1.0	70	20	71

[a]Purity [%] determined by ^{31}P NMR spectroscopy. [b]After recrystallization and based on PCl_3. [c]Flask gas room filled with argon.

Because of the volatility of the releasing formaldehyde, the reactions were usually performed in a closed flask equipped with a septum and a nitrogen-filled balloon for pressure compensation. However, there were always small amounts of paraformaldehyde precipitating on the bottom of the septum. Therefore, a slight excess of paraformaldehyde (0.1 equiv) had to be used. Depending on the scale and reactor size, the precipitating paraformaldehyde could lead to variable conversion and made unwelcome additional purification necessary. To circumvent this issue at least under laboratory conditions, it was efficient to fill the gas room of the flask and the balloon with argon. Paraformaldehyde precipitation could not be observed anymore, and consequently, the equivalents of paraformaldehyde could be further decreased to 1.0 equiv, while temperature and time were also adjusted. Crude **9** derived from the esterification in MTBE could be hydroxymethylated in 66% yield (Table 4, entry 2), while crude **9** derived from the esterification in Me-THF furnished **12** in 72% (Table 4, entry 3). Upscaling to an 11 g reaction afforded **12** in 71% yield. There are still opportunities for optimization of this two-step sequence. With a more accurate method for determining the purity of crude di-*tert*-butyl phosphite (*e.g.*, gas chromatography), the equivalents of paraformaldehyde could be adjusted more precisely to produce less byproducts.

2.3. Tosylation and Mesylation of 12. Sulfonylation of the hydroxyl group of **12** has only been described for the expensive triflate.[25] Tosylation and mesylation of **12** should be investigated as more economic alternatives. Under optimized conditions, (di-*tert*-butoxyphosphoryl)methyl 4-methylbenzenesulfonate (**13**) could be obtained in 87% yield after recrystallization from EtOH (Scheme 6). It should be noted

Scheme 6. Tosylation of di-*tert*-butyl(hydroxymethyl)phosphonate



that **13** is prone to rapid dealkylation in the presence of acids. When the reaction was performed without DMAP, traces of tosyl chloride present in the crude product were sufficient to slowly release HCl during recrystallization in EtOH, which led to dealkylation.

The mesylation of **12** proceeded more efficiently than the tosylation under similar conditions. Furthermore, no recrystallization was necessary, as the excess of mesyl chloride completely hydrolyzed during the aqueous workup and no byproducts formed. Crystalline (di-*tert*-butoxyphosphoryl)-methyl methanesulfonate (**14**) could be obtained in 97% yield even on a multigram scale (Scheme 7).

2.4. Synthesis of PMPA Using Di-*tert*-butyl Oxymethyl Phosphonates 13 and 14. For screening the alkylation of HPA, the focus was laid on using mesylate **14** because of its more efficient preparation. Performing the reaction in DMF and using other bases than $Mg(O^tBu)_2$ such as KO^{t}Bu, NaO^{t}Bu, or NaH led to product mixtures containing

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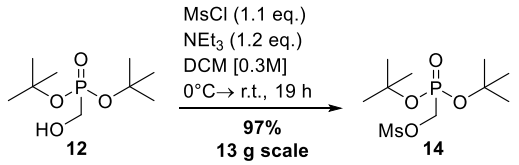
Scheme 7. Mesylation of di-*tert*-butyl(hydroxymethyl)phosphonate



both N-and O-alkylated HPA, bis-alkylated HPA, and both isomers of 9-propenyladenine, which probably had formed because of transesterification and subsequent elimination. The best results were achieved with $Mg(O^tBu)_2$ as the base. In the first screening, different aprotic polar solvents [DMF, dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA), and *N*-methylpyrrolidone (NMP)] were investigated, while an excess of mesylate **14** (2.5 equiv) was used to accomplish a complete conversion of HPA.

The best results were observed when O-alkylation was performed in NMP or DMA at 90 °C. Mainly, monoester **16** formation occurred along with only small amounts of byproducts. Summing up the monoester **16** and diester **15**, 95 and 96% (Figure 3) PMPA formation could be detected, respectively (see the Supporting Information for further details).

For further optimizations, DMA was chosen as the solvent. Regarding the amount of $Mg(O^tBu)_2$, it turned out that 3.0 equiv was crucial to achieve high conversions (>90%). Between 2.0 and 1.5 equiv of mesylate **14**, the conversion varied between 90 and 98%, and only decreased noticeably below 1.5 equiv (see Supporting Information for further details).

To cleave off the *tert*-butyl groups in order to generate PMPA, aqueous hydrochloric acid was added to the crude reaction mixture. Dealkylation was complete after stirring for 24 h at r.t. When the reaction was performed on a larger scale (1 g), DMA was first removed *in vacuo* and aqueous acid (3 N HCl) was added to the residue. At 60 °C, dealkylation was already complete after 2 h. The pH was adjusted to 2.8−3.0 with NaOH solution to precipitate PMPA·H_2O, which was dried afterward, as described in the literature.[10] On a 1 g scale, the conversion of HPA was slightly higher when using 1.7 equiv of **14** instead 1.5 equiv, while the isolated yields were similar (64 and 65%, respectively, Table 5, entries 1 and 2). Despite the high conversions of HPA, large amounts of PMPA·H_2O did not precipitate and remained in the mother liquor.

Several attempts were undertaken to isolate more PMPA from the mother liquor. When the mother liquor was concentrated and cooled again, mostly inorganic salts precipitated along with traces of PMPA. The same was observed when small amounts of water were added to the residue of the lyophilized mother liquor. The addition of cosolvents like MeOH, EtOH, ^{i}PrOH, or MeCN to the mother liquor also led only to the precipitation of PMPA/salt mixtures from which PMPA could not be easily separated. Derstine *et al.* have carefully observed that NaCl, which forms during pH adjustment, has a large effect on keeping PMPA in solution.[10] Therefore, in a further experiment, aqueous H_2SO_4 was used for dealkylation and the pH was adjusted with conc. aqueous NH_3 (25 wt %) in order to see how $(NH_4)_2SO_4$ formation affects the solubility of PMPA. Only slightly more PMPA (69%) could be isolated in this way (Table 5, entry 3). Nevertheless, performing the reaction on a 5 g scale, 72% of PMPA could be obtained (Table 5, entry 4).

Using the tosylate **13** for the alkylation of HPA, similar conversions could be observed in DMA, DMSO, and DMF (see Supporting Information for more details). When the reaction was performed in DMF on a 1 g scale, a 96% conversion of HPA was detected after 23 h. After conducting dealkylation and workup in the same way as described for the mesylate **14**, PMPA could be isolated in 68% yield (Scheme 8).

All in all, there was no significant difference in the isolated yield when using mesylate **14** or tosylate **13** for preparing PMPA.

2.5. Further Application. Both newly reported di-*tert*-butyl phosphonates **13** and **14** could also be easily converted quantitatively to the corresponding free phosphonic acids by

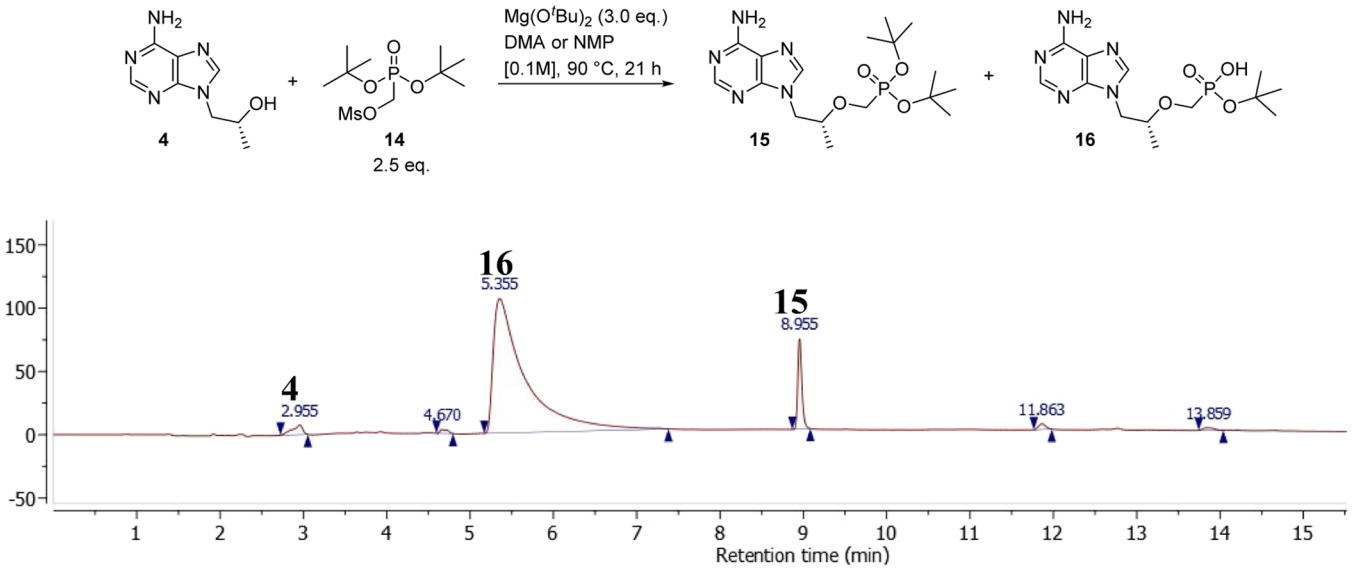


Figure 3. High-performance liquid chromatography (HPLC) chromatogram of the alkylation of HPA with mesylate **14** after 21 h in DMA at 90 °C (λ = 254 nm).

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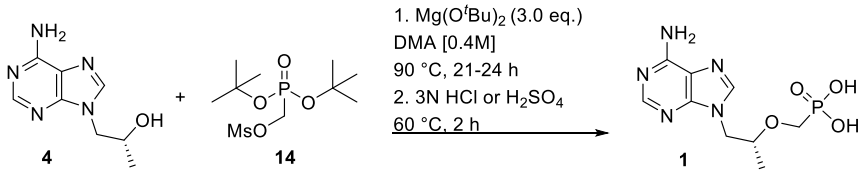
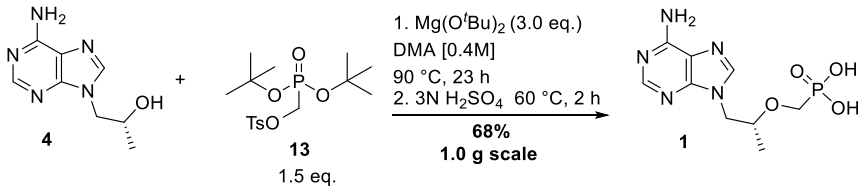
Table 5. Two-Step Sequence for Making PMPA from HPA and Mesylate 14



#	scale [grams of 4]	14 (equiv)	t [h]	Conversion [%][a]	IY [%]
1[b]	1.0	1.7	23	96	64
2[b]	1.0	1.5	21	92	65
3[c]	1.0	1.5	24	91	69
4[c]	5.0	1.5	22	91	72

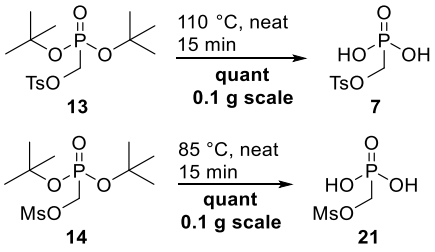
[a]Determined by HPLC (λ = 254 nm). [b]Dealkylation/pH adjustment performed with 3 N HCl/NaOH (40 wt %). [c]Dealkylation/pH adjustment performed with 3 N H_2SO_4/NH_3 (25 wt %).

Scheme 8. Two-Step Sequence for Making PMPA from HPA and Tosylate 13



just heating them for a few minutes even under solvent-free conditions (Scheme 9). In the case of tosylate **13**, the method affords an alternative to the recently reported synthesis by Derstine *et al.*, where the diethyl ester **5** was dealkylated with TMSBr.[10]

Scheme 9. Dealkylation of 13 and 14 to the Free Phosphonic Acid by Heating in the Neat Form



In general, other nucleotide-like APIs having an oxy-methyl phosphonate moiety are industrially prepared similar to PMPA.[27,28] The hepatitis B inhibitor adefovir **22**, which was described first by A. Holy and I. Rosenberg in 1987,[29] only differs in one methyl group from tenofovir. Applying the newly developed protocol to 9-(2-hydroxyethyl)adenine (HEA, **23**), 87% conversion could be detected after 22 h at 90 °C. After dealkylation and workup, adefovir could be isolated in 64% yield (Scheme 10). It should be noted that when 3 N H_2SO_4/NH_3 was used for dealkylation/pH adjustment, the formation of an insoluble adefovir salt was observed.

3. CONCLUSIONS

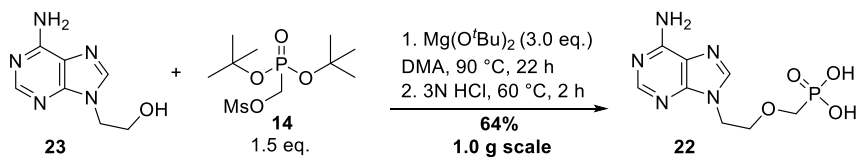
A new practical two-step sequence for the synthesis of tenofovir was developed using the hitherto unknown (di-*tert*-butoxyphosphoryl)methyl 4-methylbenzenesulfonate (**13**) and (di-*tert*-butoxyphosphoryl)methyl methanesulfonate (**14**). These crystalline key intermediates could be synthesized in gram amounts using straightforward chemistry and avoiding any chromatography step. The newly developed *tert*-butyl phosphite synthesis allowed for a simple and multigram preparation of a sufficiently pure starting material. The crude di-*tert*-butyl phosphite was hydroxymethylated through an optimized protocol, whereby crystalline di-*tert*-butyl-(hydroxymethyl)phosphonate could directly be obtained from the filtered reaction mixture.

While the manufacturing costs of the *tert*-butyl oxymethyl phosphonates are probably higher than those of the commonly used ethyl derivative, higher expenses can probably be compensated by much smoother and more economic conditions for deprotection and by a simpler overall process. Furthermore, the use of mesylate instead of tosylate as the leaving group in the alkylation of HPA is more atom-economical. The protocol developed herein allows for a quick and efficient access to compounds showing an oxymethyl phosphonate moiety, which can also be beneficial for prospective research.

4. EXPERIMENTAL SECTION

All employed chemicals were commercially available and used without prior purification. Anhydrous THF, 2-Me-THF,

Scheme 10. Synthesis of Adefovir 22 Using HEA and Mesylate 14



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CPME, and MTBE were freshly distilled over potassium (DCM over CaH_2) under a nitrogen atmosphere. Anhydrous DMF, DMA, DMSO, and NMP were purchased from Acros (AcroSeal). Oven-dried glassware was dried in an oven at 150 °C overnight, closed with a plug and a septum while still hot, cooled to room temperature, and then purged with nitrogen. NMR spectra were recorded on a Bruker AVANCE-III HD instrument (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz, ^{31}P NMR: 121 MHz) or a Bruker AVANCE-III HD instrument (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz, ^{31}P NMR: 162 MHz) with a 5 mm BBFO probe. The chemical shifts δ were expressed in ppm downfield from tetramethylsilane (^{1}H NMR, ^{13}C NMR). Deuterated solvents ($CDCl_3$, DMSO-d_6) served as the internal reference. The reported signal splittings were abbreviated as follows: s_b = broad singlet, s = singlet, d = doublet, and t = triplet. Coupling constants J are reported in Hz. For ^{31}P NMR purity analyses, the analyte (15 mg) was dissolved in the deuterated solvent indicated (0.7 mL). ESI-MS spectra were recorded on a 1260-series Infinity II HPLC system (Agilent-Technologies) with a binary pump and integrated diode array detector coupled to a liquid chromatography/mass selective detector (LC/MSD) Infinity-lab LC/MSD (G6125B LC/MSD) mass spectrometer. For high-resolution (HR) mass spectra, an Agilent 6545 Q-TOF spectrometer and a suitable external calibrant was used. Analytical HPLC was carried out with an Agilent 1260 Infinity system equipped with a binary pump, a diode array detector, and LC/MSD Infinitylab LC/MSD (G6125B LC/MSD) mass spectrometer. An ACE C18 pentafluorophenyl column (3 μm, 4.6 mm × 150 mm, 40 °C) with gradient elution using acetonitrile/water (+0.1% formic acid) or phosphate buffer (20 mM, pH = 2.5)/MeOH as the solvent with a flow rate of 1.0 mL/min was used. Gas chromatography was performed on an Agilent 8890 gas chromatograph equipped with a 5977 Gas chromatography−mass spectrometry detector. An Agilent Technologies HP 5MS UI column (30 m × 0.25 mm × 0.25 μm) as a stationary phase with helium as a carrier gas and a flow rate of 1.2 mL/min was used. The following parameters were used: inlet temperature 250 °C, transfer-line temperature 250 °C, ion-source temperature 230 °C, MS-quadrupole temperature 150 °C, and an initial oven temperature of 40 °C for 2 min with a temperature ramp of 50 °C/min to 320 °C over 5.6 min followed by 7.4 min hold. IR spectroscopy was conducted on a Bruker Tensor 27 Fourier transform infrared-spectrometer using a diamond attenuated total reflection (ATR) unit. Thin-layer chromatography was performed on Merck F_{254} silica gel plates. Spots were visualized with UV light (λ = 254 nm) or stained with appropriate reagents. Melting points are uncorrected and were taken by using a Krüss KSP1N digital melting point apparatus. Water content determination was conducted with a Xylem TitroLine 7500 Karl-Fischer Titrator.

4.1. Di-*tert*-butyl Phosphite, 8. An oven-dried Schlenk flask was charged with dry 2-Me-THF (300 mL) under a nitrogen atmosphere and cooled in an ice bath. PCl_3 (99%, 6.0 mL, 67.9 mmol, 1.0 equiv) was added, and the solution was stirred for 3 min while cooling. Under nitrogen reverse flow, NaO^{t}Bu (98%, 16.32 g, 166.4 mmol, 2.5 equiv) was added in small portions over 5 min while stirring vigorously. The ice bath was removed, and the thick colorless suspension was stirred for 1 h at r.t. Saturated $NaHCO_3$ solution (200 mL) was added, and the mixture was stirred for 5 min. The two-phase mixture was transferred into a separating funnel and shaken vigorously. The aqueous phase was drained and the organic phase was washed again with a fresh portion of sat. $NaHCO_3$-solution (200 mL). The organic phase was separated and dried over $NaSO_4$, and all volatiles were removed *in vacuo* at 30 °C. Crude **9** was obtained as a colorless, slightly turbid liquid (11.26 g, 57.98 mmol, 85%), which was used for the next step without further purification. M ($C_8H_{19}O_3P$) = 194.21 g/mol. Boiling range: 27−31 °C (0.3 mbar) (lit. 72−78 °C (13−16 mbar)[19]) R_f (SiO_2): 0.46 (EtOAc), stained with $KMnO_4$. IR (ATR) ν: 2980, 1371, 1263, 1173, 958 cm^{-1}. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 6.90 (d, $^1J_{P-H}$ = 681 Hz, 1H, −P−H), 1.47 (s, 18H, $-C(CH_3)_3$) ppm. ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ = 82.9 (d, $^2J_{C-P}$ = 7.4 Hz, $-O-C(CH_3)_3-$), 30.5 (d, $^3J_{C-P}$ = 4.6 Hz, $-CH_3$) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 3.18 ppm. GC−MS m/z: 83.1 (100%). The spectrometric data are consistent with literature values.[22,24]

4.2. Di-*tert*-butyl(hydroxymethyl)phosphonate, 12. **Variant 1**: According to a method reported by Grimmond *et al.*,[25] a round-bottomed flask was charged with di-*tert*-butyl phosphite (commercially available, 96%, 3.24 g, 16.0 mmol, 1.0 equiv), NEt_3 (2.6 mL, 19 mmol, 1.2 equiv), and H_2O (1 mL). Aqueous formaldehyde solution (37%, 1.20 mL, 16.0 mmol 1.0 equiv) was added afterward, and the solution was stirred for 24 h at r.t. (reaction control by GC or ^{31}P NMR spectroscopy). MeOH (5 mL) was added, and all volatiles were removed *in vacuo* at 40 °C. This procedure was repeated twice and then performed again with DCM (3 × 5 mL), furnishing the crude product as a slight yellowish waxy solid (3.51 g, 14.5 mmol, 91%, yield corrected based on ^{31}P NMR). **Variant 2**: A round-bottomed flask was charged with crude di-*tert*-butyl phosphite (95%, purity estimated by ^{31}P NMR, 11.25 g, 55.0, mmol, 1.0 equiv), paraformaldehyde (97%, 1.70 g, 1.0 equiv), K_2CO_3 (anhydrous, ground, stored in a desiccator, 1.60 g, 11.59 mmol, 0.2 equiv), and MeCN (HPLC grade, 170 mL). The gas-filled compartment of the flask was purged with argon for 15 s and immediately closed with a septum equipped with an argon-filled balloon. The colorless suspension was heated at 70 °C for 20 h (reaction control by GC or ^{31}P NMR spectroscopy). The reaction mixture was cooled to r.t., filtered, and concentrated *in vacuo* at 40 °C to half of the original volume. The flask was stored in a freezer overnight at −24 °C when **12** crystallized out (if no crystallization took place, slight shaking or inoculating helped). The supernatant mother liquor was decanted, and the solid was washed twice with cold MeCN (−24 °C, 2 × 5 mL). The solid was dried *in vacuo* at 30 °C to afford **12** (8.90 g). Concentrating the mother liquor and storing in a freezer overnight yielded a second pure crystallisate (1.97 g). In total, 10.87 g (48.47 mmol, 71% related to PCl_3) of **12** was obtained. M ($C_9H_{21}O_4P$) = 224.24 g/mol. mp 100.0−102.7 °C. R_f (SiO_2): 0.32 (EtOAc), stained with $KMnO_4$. IR (ATR) ν: 3309, 2980, 1394, 1238, 1167, 1038, 975 cm^{-1}. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ 3.74 (d, $^1J_{P-H}$ = 6.6 Hz, 2H, $-PCH_2-$), 2.57 (s_B, 1H, −OH), 1.52 (s, 18H, $-C(CH_3)_3$) ppm. ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ 82.9 (d, $^2J_{C-P}$ = 9.0 Hz, $-C(CH_3)_3-$), 60.1 (d, $^1J_{C-P}$ = 164 Hz, $-P-CH_2-$), 30.6 (d, $^3J_{C-P}$ = 3.8 Hz, $-C(CH_3)_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 16.4 ppm. GC−MS m/z: 113.1 (100%). ESI-MS m/z: 247.1 (100%, $[M + Na]^+$). The spectrometric data are consistent with literature values.[30]

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4.3. (Di-*tert*-butoxyphosphoryl)methyl 4-Methylbenzenesulfonate, 13. In an oven-dried Schlenk flask, di-*tert*-butyl(hydroxymethyl)phosphonate (3.00 g, 13.4 mmol, 1.0 equiv), NEt_3 (2.1 mL, 14.7 mmol, 1.1 equiv), and DMAP (0.16 g, 1.34 mmol, 0.1 equiv) were dissolved in dry DCM (100 mL) under a nitrogen atmosphere. Tosyl chloride (2.81 g, 14.7 mmol, 1.1 equiv) was added, and the solution was stirred under a nitrogen atmosphere at r.t. for 24 h (99% conversion by ^{31}P NMR spectroscopy). The reaction mixture was washed with saturated $NaHCO_3$ solution (70 mL), and the organic phase was separated. After drying over $NaSO_4$, all volatiles were removed *in vacuo* at 30 °C [**CAUTION!** High temperatures can lead to decomposition (dealkylation)]. The crude product (4.93 g) was dissolved in warm EtOH (17 mL, max 50 °C), cooled to r.t., and stored in a freezer (−24 °C) overnight. The supernatant mother liquor was decanted, and the crystallized solid was washed with two portions of cold (−24 °C) EtOH (2 × 3 mL). After drying *in vacuo* at 30 °C, **13** was obtained as a colorless solid in 87% yield (4.41 g, 11.7 mmol, 87%). For longer storage, it is recommended to store the compound in a refrigerator or freezer. *M* ($C_{16}H_{27}O_6PS$) = 378.42 g/mol. mp 74.4−76.5 °C (decomposition). R_f (SiO_2): 0.21 (EtOAc/cyclohexane = 1:2). IR (ATR) ν: 2979, 1365, 1251, 1180, 1170, 1022, 972 cm^{-1}. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 7.82−7.77 (m, 2H, H-2), 7.37−7.33 (m, 2H, H-3), 4.01 (d, $^2J_{H-P}$ = 9.9 Hz, 2H, −P−CH_2), 2.45 (s, 3H, Ar-CH_3), 1.46 (s, 18H, −$(CH_3)_3$) ppm. ^{13}C NMR, HMBC, HSQC (101 MHz, $CDCl_3$): δ 145.3 (C-1), 132.2 (C-4), 130.0 (C-3), 128.3 (C-2, 84.3 (d, $^2J_{C-P}$ = 8.6 Hz, −$C(CH_3)_3$), 64.1 (d, $^1J_{C-P}$ = 174 Hz, −P−CH_2−), 30.4 (d, $^3J_{C-P}$ = 4.0 Hz, −$C(CH_3)_3$), 21.8 (s, Ar-CH_3) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.7 ppm. ESI-HRMS: calcd for $[M + Na]^+$, *m/z*: 401.1158; found, *m/z*: 401.1154.

4.4. (Di-*tert*-butoxyphosphoryl)methyl Methanesulfonate, 14. In an oven-dried Schlenk flask, di-*tert*-butyl-(hydroxymethyl)phosphonate (12.94 g, 57.71 mmol, 1.0 equiv) was dissolved in dry DCM (200 mL) under a nitrogen atmosphere. NEt_3 (9.70 mL, 69.2 mmol, 1.2 equiv) was added, and the solution was cooled in an ice bath. Mesyl chloride (4.90 mL, 63.5 mmol, 1.1 equiv) was added drop-wise to the solution within 4 min, the ice bath was removed, and the solution was stirred at r.t. for 19 h (reaction control by thin-layer chromatography). The reaction mixture was washed twice with sat. $NaHCO_3$ solution (2 × 150 mL), and the organic phase was separated. After drying over Na_2SO_4, all volatiles were removed *in vacuo* at 30 °C [**CAUTION!** High temperatures can lead to decomposition (dealkylation)]. The title compound **14** was obtained as an orange-brown oil (16.92 g, 55.97 mmol, 97%), which solidified after a while. For longer storage, it is recommended to store the compound in a refrigerator or freezer. *M* ($C_{10}H_{23}O_6PS$) = 302.32 g/mol. mp 52.2−55.0 °C (decomposition). R_f (SiO_2): 0.55 (EtOAc), stained with $KMnO_4$. IR (ATR) ν: 2983, 1359, 1260, 1174, 965 cm^{-1}. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ 4.28 (d, $^1J_{P-H}$ = 8.7 Hz, 2H, −P−CH_2−), 3.12 (s, 3H, −CH_3), 1.53 (s, 18H, −$C(CH_3)_3$) ppm. ^{13}C NMR, HMBC, HSQC (75 MHz, $CDCl_3$): δ 84.5 (d, $^2J_{C-P}$ = 8.5 Hz, −$C(CH_3)_3$−), 64.2 (d, $^1J_{C-P}$ = 174 Hz, −P−CH_2−), 38.2 (−CH_3), 30.5 (d, $^3J_{C-P}$ = 3.9 Hz, −$C(CH_3)_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.2 ppm. ESI-HRMS: calcd for $[M + H]^+$, *m/z*: 303.1026; found, *m/z*: 303.1026.

4.5. Tenofovir (PMPA), 1. *4.5.1.* ***Variant 1*** *Using Mesylate* ***14.*** An oven-dried Schlenk flask was charged with HPA (**4**, >98%, 5.00 g, 25.9 mmol 1.0 equiv) and magnesium *tert*-butoxide (93%, 14.24 g, 77.64 mmol, 3.0 equiv) under a nitrogen atmosphere. Dry DMA (65 mL) was added, and the suspension was stirred at 90 °C for 30 min. While purging with nitrogen, (di-*tert*-butoxyphosphoryl)methyl methanesulfonate (**14**, 11.74 g, 38.82 mmol, 1.5 equiv) was added portion-wise within 1 min. The reaction mixture was stirred at 90 °C for 22 h (90% conversion of HPA detected by HPLC at 254 nm). All volatiles were removed *in vacuo* at 50−60 °C, and 1.5 M H_2SO_4 (50 mL) was added to the orange-brownish residue. During heating to 60 °C, a yellowish solution formed. After 4 h (complete dealkylation to PMPA detected by HPLC at λ = 254 nm), the solution was cooled in an ice bath. Additional water (20 mL) was added, and the pH was adjusted to pH = 2.8−3 using conc. NH_3 solution (25 wt %, 3 mL). A colorless to slight yellowish suspension formed, which was stirred while cooling for 1 h and then stored in a refrigerator overnight. The next day, the suspension was vacuum-filtered and washed with ice-cold water (4 × 4 mL) and ice-cold acetone (3 × 4 mL). The filtered solid was first dried on the air and then at 80 °C under high vacuum for 4 h to obtain PMPA as a colorless powder (5.36 g, 18.6 mmol, 72%, HPLC-purity (254 nm): ≥99%, q-^{31}P NMR assay: (98.37 ± 1.95)%). *M* ($C_9H_{14}N_5O_4P$) = 287.22 g/mol. mp 271−274 °C (decomposition) (lit. 276−278 °C[31]). Water content: 2.3% (determined by Karl-Fischer Titrator). R_f (C_{18}−SiO_2): 0.38 (H_2O). IR (ATR) ν: 3383, 3216, 3108, 2933, 1696, 1666, 1616, 1410, 1237, 1074, 933 cm^{-1}. ^{1}H NMR, COSY (300 MHz, DMSO-d_6): δ = 8.17 (s, 1H, H-8), 8.15 (s, 1H, H-2), 7.43 (s_B, 2H, −NH_2), 4.29 (dd, ^2J = 14.3 Hz, ^3J = 4.0 Hz, 1H, −NCH_aH−), 4.16 (dd, ^2J = 14.3 Hz, ^3J = 5.6 Hz, 1H, −NCH_bH−), 3.95−3.85 (m, 1H, −$CH(CH_3)O$−), 3.66−3.51 (m, 2H, −OCH_2P−), 1.02 (d, ^3J = 6.2 Hz, 3H, −CH_3) ppm. ^{13}C NMR, HMBC, HSQC (75 MHz, DMSO-d_6): δ 155.5 (C-6), 151.7 (C-2), 149.7 (C-4), 141.9 (C-8), 118.2 (C-5), 75.3 (d, $^3J_{C-P}$ = 12.1 Hz, −$CH(CH_3)O$−), 64.5 (d, $^1J_{C-P}$ = 162 Hz, −OCH_2P−), 46.5 (−NCH_2−), 17.0 (−CH_3) ppm. ^{31}P NMR (121 MHz, DMSO-d_6): δ 16.2 ppm. ESI-MS *m/z*: 288.1 (100%, $[M + H]^+$). The spectrometric data are consistent with literature values.[10]

4.5.2. ***Variant 2*** *Using Tosylate* ***13.*** An oven-dried Schlenk flask was charged with HPA (**4**, >98%, 1.00 g, 5.18 mmol, 1.0 equiv) and magnesium *tert*-butoxide (93%, 2.85 g, 15.5 mmol, 3.0 equiv) under a nitrogen atmosphere. Dry DMF (12 mL) was added, and the suspension was stirred at 80 °C for 25−30 min. While purging with nitrogen, (di-*tert*-butoxyphosphoryl)-methyl 4-methylbenzenesulfonate (**13**, 2.94 g, 7.76 mmol, 1.5 equiv) was added portion-wise within 1 min. The reaction mixture was stirred at 80 °C for 23 h (95% conversion of HPA detected by HPLC at λ = 254 nm). All volatiles were removed *in vacuo*, and 1.5 M H_2SO_4 (10 mL) was added to the orange-brownish residue. During heating to 60 °C, a yellowish solution formed. After 4 h (complete dealkylation to PMPA detected by HPLC at λ = 254 nm), the solution was cooled in an ice bath and the pH was adjusted to pH = 2.8−3 using conc. NH_3 solution (25%, 0.6 mL, additional water (2−3 mL) was added for better stirring). A colorless to slight yellowish suspension formed, which was stirred for one further hour while cooling and then stored in a refrigerator overnight. The suspension was vacuum-filtered, and the filter cake was washed with ice-cold water (3 × 2 mL) and ice-cold acetone (3 × 2 mL). The filtered solid was first dried on the air and then at 80

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°C under high vacuum for 4 h. PMPA was obtained as a colorless powder (1.01 g, 3.52 mmol, 68%).

4.6. {[(4-Methylbenzenesulfonyl)oxy]methyl}-phosphonic Acid, 7. In an oven-dried Schlenk flask, di-*tert*-(butoxyphosphoryl)methyl 4-methylbenzenesulfonate (**13**, 0.099 g, 0.26 mmol) was heated to 100 °C while purging with nitrogen. After the solid has melted, it was stirred for further 15 min and then cooled to r.t. Compound **7** was obtained as a colorless resin (0.070 g, 0.26 mmol, quant.), which formed as a colorless solid by trituration. *M* ($C_8H_{11}O_6PS$) = 266.20 g/mol. mp 133.8−134.8 °C. R_f (SiO_2): 0.19 (EtOAc+10% HOAc), stained with Seebach-reagent. IR (ATR) ν: 1365, 1239, 1178, 1026, 939 cm^{-1}. ^1H NMR, COSY (400 MHz, DMSO-d_6): δ 7.84−7.75 (m, 2H, H-2), 7.53−7.45 (m, 2H, H-3), 3.95 (d, $^2J_{P-H}$ = 10.0 Hz, 2H, $-CH_2-$), 2.43 (s, 3H, $-CH_3$) ppm. ^{13}C NMR, HMBC, HSQC (75 MHz, DMSO-d_6): δ 145.4 (C-1), 131.3 (C-4), 130.3 (C-3), 128.0 (C-2), 64.0 (d, $^2J_{C-P}$ = 159 Hz, $-CH_2-$), 21.2 (-CH_3) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ 9.5 ppm. ESI-MS *m*/*z*: 266.9 (100%, $[M + H]^+$). The spectrometric data are consistent with literature values.[10]

4.7. {[(Methylsulfonyl)oxy]methyl}phosphonic Acid, 21. In an oven-dried Schlenk flask, (di-*tert*-butoxyphosphoryl)-methyl methanesulfonate (**14**, 0.10 g, 0.33 mmol) was heated to 85 °C while purging with nitrogen. After the solid has melted, it was stirred for a further 15 min and then cooled to r.t. **21** was obtained as a reddish oil (0.063 g, 0.33 mmol, quant.), which formed a colorless to slight reddish solid by trituration. *M* ($C_2H_7O_6PS$) = 190.11 g/mol. mp 94.2−96.5 °C. R_f ($C_{18}-SiO_2$): 0.46 (H_2O + 3% HOAc). IR (ATR) ν: 1365, 1178, 1026, 1011, 939 cm^{-1}. ^1H NMR, COSY (400 MHz, DMSO-d_6): δ = 4.23 (d, $^2J_{P-H}$ = 9.6 Hz, 2H, $-P-CH_2-$), 3.22 (s, 3H,$-CH_3$) ppm. ^{13}C NMR, HMBC, HSQC (101 MHz, DMSO-d_6): δ = 64.2 (d, $^1J_{C-P}$ = 160 Hz,$-P-CH_2-$), 36.5 (s, $-CH_3$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): ? = 10.4 ppm. ESI-HRMS: calcd for $[M + H]^+$, *m*/*z*: 190.9774; found, *m*/*z*: 190.9776.

4.8. Adefovir (PMEA), 22. An oven-dried Schlenk flask was charged with HEA (**23**, >98%, 1.00 g, 5.58 mmol, 1.0 equiv) and magnesium *tert*-butoxide (93%, 3.07 g, 16.7 mmol, 3.0 equiv) under a nitrogen atmosphere. Dry DMA (12 mL) was added, and the suspension was stirred at 90 °C for 30 min. While purging with nitrogen, (di-*tert*-butoxyphosphoryl)-methyl methanesulfonate (**14**, 2.53 g, 8.37 mmol, 1.5 equiv) was added portion-wise within 1 min. The reaction mixture was stirred at 90 °C for 22 h (conversion of HEA 87% detected by HPLC at λ = 254 nm). All volatiles were removed *in vacuo* at 50−60 °C, and 3 N HCl (10 mL) was added to the orange-brownish residue. During heating to 60 °C, an orange solution formed. After 4 h (complete dealkylation to PMEA detected by HPLC at λ = 254 nm), the solution was cooled in an ice bath and the pH was adjusted to pH = 2.8−3.0 using NaOH solution (40 wt %, 4−5 drops). A colorless to slight yellowish thick suspension formed [additional water (3 mL) was added for better stirring], which was stirred while cooling for 1 h and then stored in a refrigerator overnight. The suspension was vacuum-filtered and washed with ice-cold water (4 × 2 mL) and ice-cold acetone (3 × 2 mL). The filtered solid was first dried on the air and then at 80 °C under high vacuum for 3 h to obtain PMEA [0.98 g, 3.59 mmol, 64%, HPLC-purity (254 nm): ≥99%]. q-^{31}P NMR assay: (99.31 ± 1.29)%. *M* ($C_8H_{12}N_5O_4P$) = 273.19 g/mol. mp 276−278 °C (decomposition) (lit. 282−284 °C[32]). Water content: 1.1% (determined by Karl-Fischer Titrator). R_f ($C_{18}-SiO_2$): 0.60 (H_2O). IR (ATR) ν: 3059, 2983, 1698, 1519, 1411, 1153, 1122, 1056, 1041 cm^{-1}. ^1H NMR, COSY (400 MHz, D_2O): δ 8.41 (s, 1H, H-8), 8.38 (s, 1H, H-2), 4.51 (t, ^3J = 5.0 Hz, 2H, $-NCH_2-$), 3.98 (t, ^3J = 5.0 Hz, 2H, $-OCH_2-$), 3.63 (d, ^2J = 8.7 Hz, 2H, $-OCH_2P-$) ppm. ^{13}C NMR, HMBC, HSQC (101 MHz, D_2O): δ 150.2 (C-6), 148.6 (C-4), 145.2 (C-8), 144.8 (C-2), 117.9 (C-5), 70.3 (d, $^3J_{C-P}$ = 11.6 Hz, $-CH_2O-$), 66.9 (d, $^1J_{C-P}$ = 157 Hz, $-OCH_2P-$), 44.0 ($-NCH_2-$) ppm. ^{31}P NMR (121 MHz, D_2O): δ 15.6 ppm. ESI-MS *m*/*z*: 274.0 (100%, $[M + H]^+$). The spectrometric data are consistent with literature values.[32]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00473.

Optimization studies, chromatograms, quantitative NMR data, PMI, E-factor, atom economy calculations, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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