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The di-*tert*-Butyl Oxymethylphosphonate Route to the Antiviral Drug Tenofovir

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Di-*tert*-butyl oxymethyl phosphonates were investigated regarding their suitability of preparing the active pharmaceutical ingredient tenofovir (PMPA). First, an efficient and simple method for making the crystalline di-*tert*-butyl (hydroxymethyl)phosphonate was developed. Its *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 phosponate deprotection could be achieved with aqueous

acids. (Di-*tert*-butoxyphosphoryl)methyl methanesulfonate showed to be most efficient electrophile, 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 in 1 g scale).

1. Introduction

The nucleotide reverse transcriptase inhibitor tenofovir (**1**, PMPA), which was discovered by A. Holy in 1993[1], currently belongs to the most frequently applied 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, Viread®) 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, Vemlidy®) (Figure 1) was launched which showed fewer side effects and better tolerability than TDF.[3]

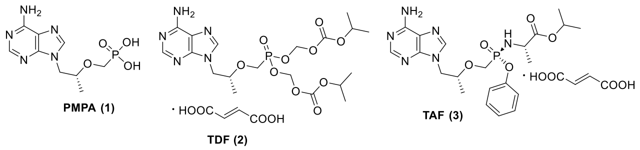
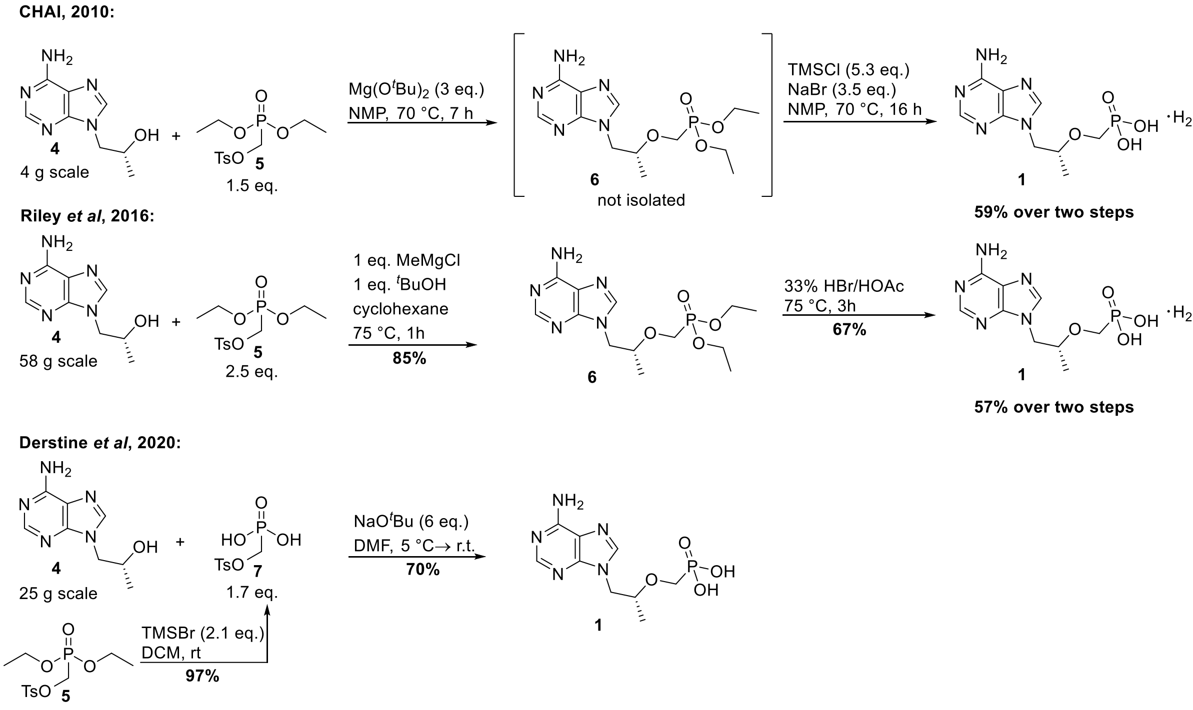


Figure 1: Structures of tenofovir (PMPA, 1), tenofovir disoproxil fumarate (TDF, 2) and tenofovir alafenamid fumarate (TAF, 3).

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 77590 HIV-positive persons receiving anti-retroviral therapy. There was a lower risk for 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 of tenofovir could further rise in future. Due to 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.

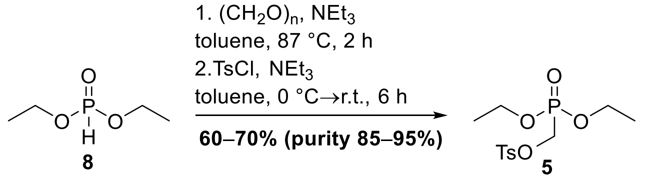
The state-of-the-art synthesis of PMPA has been reported by the Clinton Health Access Initiative (CHAI) in 2010 (Scheme 1). (*R*)-9-(2-Hydroxypropyl)adenine (HPA, **4**) undergoes a base-mediated alkylation with diethyl (*p*-toluenesulfonyloxymethane)phosphonate (DESMP, **5**) followed by a one-pot deprotection of the phosphonic acid ester. CHAI reported that using $Mg(O^tBu)_2$ as a base showed the best conversion (>90%) for the alkylation. Telescoping the two steps showed to be beneficial to circumvent the inconvenient work-up 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[7] by TMSCl/NaBr. However, the work up was still elaborate as several filtration and extraction steps were required while simultaneously avoiding any moisture. Despite a reported significant loss of product in the magnesium salt cake (up to 15%) $PMPA\cdot H_2O$ could be isolated in 59% yield.[8]



Scheme 1: Overview to hitherto scalable PMPA syntheses.

In 2016, Riley *et al.* reported that Mg(O^{t}Bu)$_2$ could be substituted through its *in situ* generation by using 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 were able to find conditions to alkylate HPA with the free phosphonic acid of DESMP (**7**) by using NaO*t*Bu as base in DMF. This very efficient process furnished PMPA in 70% yield.[10]

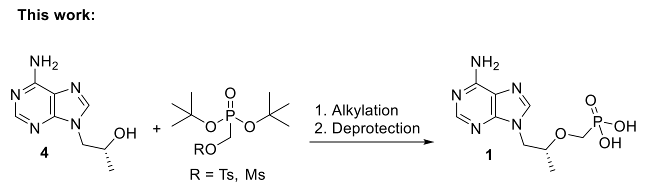
It is conspicuous that all reports investigating the challenging synthesis of PMPA focused only DESMP (**5**) or the derived free acid **7** as alkylating agents with HPA. One big selling point is of course the fact that DESMP can be made from cheap commodity chemicals and has an industrial well-established 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]



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. Beside expensive (TMSBr[6]) or excessive amounts of reagents (TMSCl/NaBr[8]) an elaborate work-up including several filtrations and extractions is necessary. Silicon-containing byproducts have also been reported when using silyl agents.[12] Other conditions (aq. HBr, dry HCl gas, $AlCl_3$[13], or HOAc/HBr[9]) led to lower yields. There is no variation of the alkyl group of oyxmethyl phosphonates reported in literature 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 (**1**) was investigated. An industrially feasible process was the aim of this work (Scheme 3).



Scheme 3: Proposed synthesis for PMPA using tert-butyl oxymethyl phosphonates.

2. Discussion/results

2.1 Synthesis of di-*tert*-butyl phosphite

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

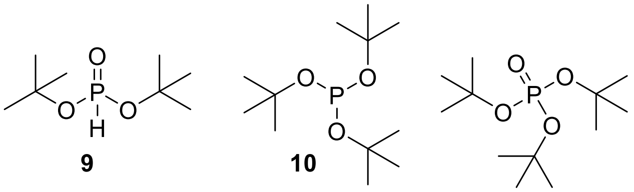

9 **10** **11**

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

V. Mark and J. R. 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 oxidation by air oxygen resulting in the formation of tri-*tert*-butyl phosphate (**11**). In terms of the selective synthesis of the diester, **11** represents an undesired byproduct which can only be circumvented by strict exclusion of oxygen during preparation and work-up. 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 to use potassium *tert*-butoxide in the reaction with PCl$_3$ instead of *tert*-butanol and an organic base. As a benefit, KO^{t}Bu would combine both reagent and base while only potassium chloride would be accumulated as a co-product. In initial experiments, PCl$_3$ was added to a KO^{t}Bu/THF solution while cooling. Following the reaction by ^{1}H/^{31}P-NMR spectroscopy revealed also the formation of triester, diester and phosphate However, when the order of addition was reversed, predominant diester formation could be observed. Furthermore, adding solid KO^{t}Bu instead of a THF-solution, which was slightly more convenient regarding handling, gave similar results. For the work-up, 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 eq. of KO^{t}Bu, 98% of crude **9** (^{31}P-NMR purity: 75%) was obtained after work-up (Table 1, entry 1). During further investigations it turned out that subsequent reduction of the equivalents of KO^{t}Bu improved the purity of the crude product (Table 1, entry 2–5). When the reaction was performed with 2.5 eq. of KO^{t}Bu, 76% of crude **9** could be obtained showing a high purity in the ^{1}H & ^{31}P-NMR spectrum (see the supporting information for more details).

Table 1: Screening equivalents of KOtBu for the synthesis of di-tert-butyl phosphite.

#	KOtBu (eq.)	yield [%]a	purity [%]b

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

All reactions were performed on a 3 g scale; a crude isolated yield; b determined by 31P-NMR-spectroscopy.

Using the water-soluble THF as solvent had the drawback that large amounts of sodium sulfate had to be used for drying the organic phase. Therefore, less water-soluble alternative solvents were investigated for the reaction. CPME (cyclopentyl methyl ether), Me-THF and even MTBE showed similar results regarding yield and purity (Table 2).

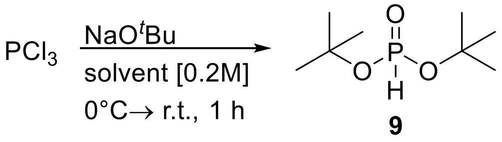
Table 2: Solvent screening for the synthesis of tert-butyl phosphite.

#	**solvent**	**KO^{t}Bu (eq.)**	**Yield [%][a]**	**Purity [%][b]**
1	THF	2.5	76	97
2	Me-THF	2.5	75	99
3	CPME	2.5	77	99
4	MTBE	2.5	78	99

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

By focusing on MTBE and 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.

Table 3: Scale-up of the tert-butyl phosphite synthesis using NaOtBu.



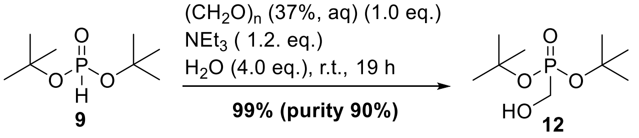
#	scale [g PCl_3]	solvent	NaO^tBu (eq.)	IY [%][a]	Purity [%][b]
1	3	MTBE	2.5	80	97
2	6	MTBE	2.5	82	90
3	3	Me-THF	2.5	86	95
4	9	Me-THF	2.5	85	95

[a] crude isolated yield; [b] determined by ^{31}P-NMR-spectroscopy.

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

2.2 Hydroxymethylation of *tert*-butyl phosphite

A procedure for the hydroxymethylation of *tert*-butyl phosphite has already been reported in patent literature.[25,26,26] According to this procedure, **9**[1] was stirred in the presence of aq. formaldehyde-solution, triethylamine and water at r.t. to furnish crude **12** in 99% yield. A ^{31}P-NMR-spectrum showed about 10% of impurities (Scheme 4).



Scheme 4: Hydroxymethylation of tert-butyl phosphite using aq. formaldehyde solution.

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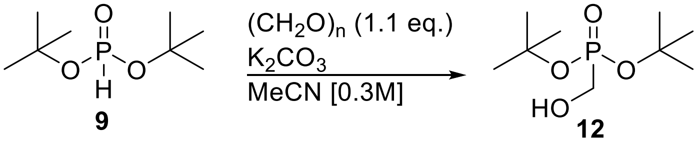
[1] For this reaction commercial available tert-butyl phosphite (96%) was used.

For the work-up it was necessary to co-evaporate 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, it turned out that using solid paraformaldehyde along with K_2CO_3 as base and acetonitrile as solvent showed promising results (Table 4). The reaction was followed by ^{1}H- and ^{31}P-NMR spectroscopy, which revealed incomplete conversion after 19 h at 50 °C using 10 mol% K_2CO_3 (Table 4, entry 1). Doubling the amount of base furnished complete conversion in the same time along with only small amounts of byproducts (Table 4, entry 2). Performing the reaction on a larger scale required higher temperature (60 °C) for completion in the same time (Table 4, entry 3). Further increasing of the temperature shortened reaction time significantly without increasing byproduct formation (Table 4, entry 4). When the reaction was performed on an 8 g scale, nearly pure **9** could be isolated in 99% yield after work-up which only consisted of a single filtration and subsequent solvent removal in vacuo (Table 4, entry 5).

Table 4: Hydroxymethylation of tert-butyl phosphite using solid paraformaldehyde and K_2CO_3 in MeCN.



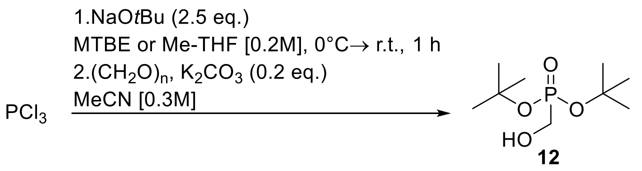
#	Scale [g 9]	K_2CO_3 (eq.)	*T* [°C]	*t* [h]	BP [%][a]	conversion [%][b]
1	0.2	0.1	50	19	4	89
2	0.2	0.2	50	19	2	98
3	1.0	0.2	60	23	2	98

4	1.0	0.2	80	3	2	98
5	8.0	0.2	80	4	1	99[c]

[a] phosphorus-containing byproducts [b] determined by ^{31}P-NMR spectroscopy; [c] 99% isolated yield after work-up

It should be mentioned that only commercially or freshly distilled di-*tert*-butyl phosphite was used up to this point. When using crude di-*tert*-butyl phosphite, obtained from the newly developed protocol mentioned above, the purity was 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** could 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 5, entry 1).

Table 5: Telescoped synthesis of di-tert-butyl (hydroxymethyl)phosphonate from PCl_3.



#	scale [g 9][a]	$(CH_2O)_n$ (eq.)	*T* [°C]	*t* [h]	IY [%][b]
1	6.6 (95)	1.1	80	5	71
2[d]	7.2 (90)	1.0	70	20	66
3[d]	3.8 (95)	1.0	70	20	72
4[d]	11.3 (95)	1.0	70	20	71

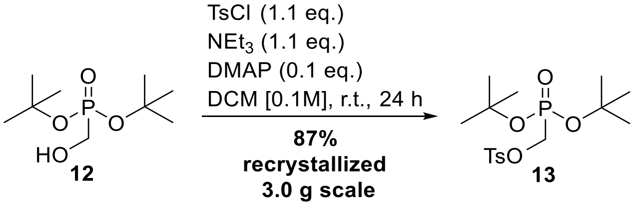
[a] purity [%] determined by ^{31}P-NMR-spectroscopy; [b] after recrystallization and based on PCl_3,; [d] flask gas room filled with argon

Due to 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 eq.) had to be used. Depending on 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 eq. while temperature and time were also adjusted. Crude **9** derived from the esterification in MTBE could be hydroxymethylated in 66% yield (Table 5, entry 2) while crude **9** derived from the esterification in Me-THF furnished **12** in 72% (Table 5, entry 3). Up-scaling to a 11 g reaction afforded **12** in 71% yield. There is still space for optimization of this two-step sequence. With a more accurate method for determining the purity of crude *tert*-butyl phosphite (e.g. gas chromatography), the equivalents of paraformaldehyde could be adjusted more precisely giving less byproducts.

2.3 Tosylation and mesylation of **12**

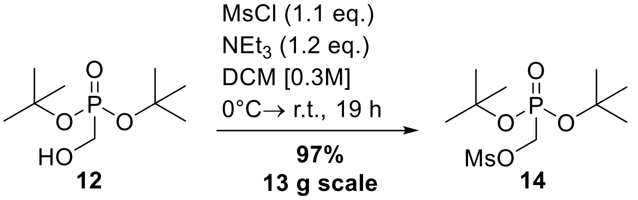
Sulfonation of the hydroxyl group of **12** has only been described for the expensive triflate.[25] Tosylation and mesylation of **12** should be investigated as more economic alternatives. Under optimized conditions, (di-*tert*-butoxyphosphoryl)methyl 4-methylbenzenesulfonate (**13**) could be obtained in 87% yield after recrystallization from EtOH (Scheme 5). It should be noted 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.



Scheme 5: Tosylation of di-tert-butyl (hydroxymethyl)phosphonate.

The mesylation of **12** proceeded more efficiently than the tosylation under similar conditions. Furthermore, no recrystallization was necessary as excessive mesyl chloride completely hydrolyzed during the aqueous work-up and no byproducts formed. Crystalline (di-*tert*-butoxyphosphoryl)methyl methanesulfonate (**14**) could be obtained in 97% yield even on multigram scale (Scheme 6).



Scheme 6: Mesylation of di-tert-butyl (hydroxymethyl)phosphonate.

2.4 Synthesis of PMPA using *tert*-butyl oxymethyl phosphonates 13 and 14.

For screening the alkylation of HPA, the focus was laid on using mesylate **14** due to its more efficient preparation. Performing the reaction in DMF and using other bases than $Mg(O^tBu)_2$ such as KOtBu, NaOtBu or NaH led to product mixtures containing both *N*-and *O*-alkylated HPA, bisalkylated HPA and both isomers of 9-propenyladenine which probably had formed due to transesterification and subsequent elimination. The best results were achieved with Mg(O^{t}Bu)$_2$ as the base. In a first screening, different aprotic polar solvents were investigated while an excess of mesylate **14** (2.5 eq.) was used to accomplish complete conversion of HPA. After stirring for 20 h at 80 °C in DMF, 96% conversion of HPA could be detected by HPLC. At lower temperatures the reaction proceeded much slower (63% conversion after 21 h at 70 °C). Besides the desired diester **15**, formation of the monoester **16** could be detected which had probably formed by thermal decomposition. Furthermore, the respective amidine of both esters (Figure 4, **17** and **18**) as well as the formylated diester (Figure 4, **19**) could be detected. Summing up the mono-and diester and supposing that the amidines also hydrolyze under aqueous acidic conditions 92% of potential PMPA had formed (Table 6, entry 2).

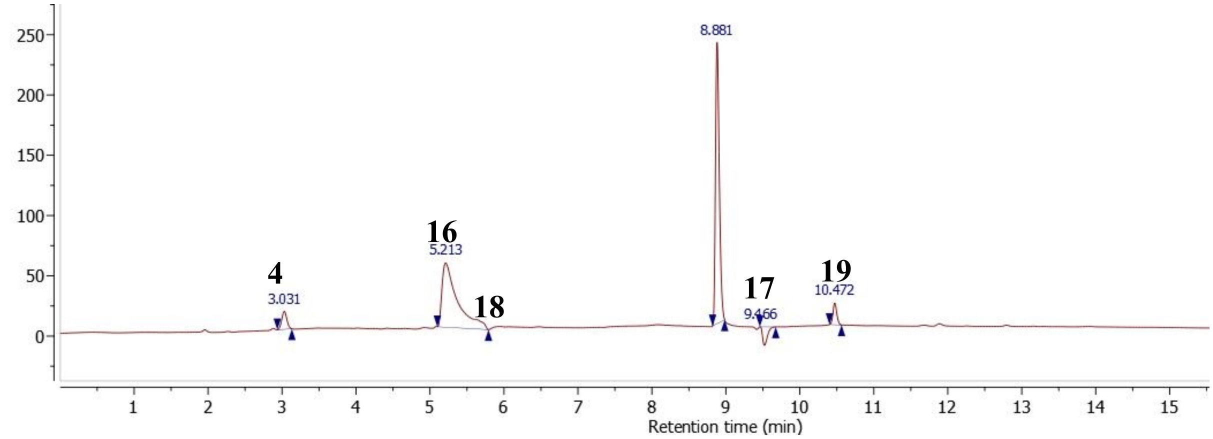


Figure 3: HPLC-Chromatogram of the alkylation of HPA with mesylate XX after 21 h in DMF at 80 °C (λ = 254 nm).

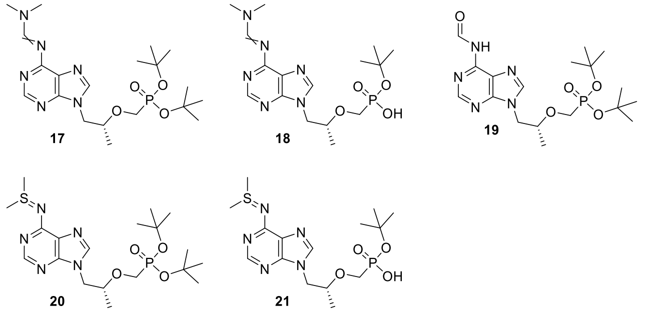
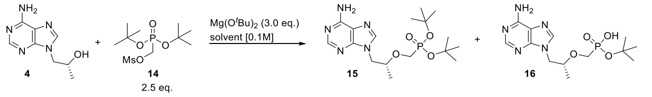


Figure 4: Occuring Impurities during alkylation of HPA with mesylate 14 in DMF and DMSO.

In DMSO, a slightly lower conversion of HPA (93%) could be achieved at 70 °C after 21 h. A larger percentage of diester **15** could be detected which was attributed to the lower temperature. The observed sulfinimides **20** and **21** **(**Figure 4) had formed in a reaction with DMSO. These compounds should also get hydrolyzed under acidic conditions, so that overall 87% of PMPA had formed in this reaction.

Table 6: Solvent screening of the alkylation of HPA with mesylate XX in presence of Mg(OtBu)$_2$.



#	solvent	*T* [°C]	*t* [h]	**4**^{a}	**16**^{a}	**15**^{a}	BP^{a}	"PMPA"
1	DMF	80	21	4	43	49	4	92
2	DMSO	70	21	7	5	76	12^{b}	87
3	NMP	90	21	4	81	14	1	95
4	DMA	90	21	2	88	8	2	96

All reactions were performed in a 0.02 g scale; ^{a} peak area [%] (λ = 254 nm); ^{b} include 6% of sulfinimids; BP = byproducts

The best results were observed when the *O*-alkylation was performed in *N*-methylpyrrolidone (NMP) or dimethyl acetamide (DMA) at 90 °C. Mainly monoester formation occurred along with only small amounts of byproducts. 95% and 96% (Figure 5) PMPA-formation could be detected, respectively (Table 6, entry 3 & 4).

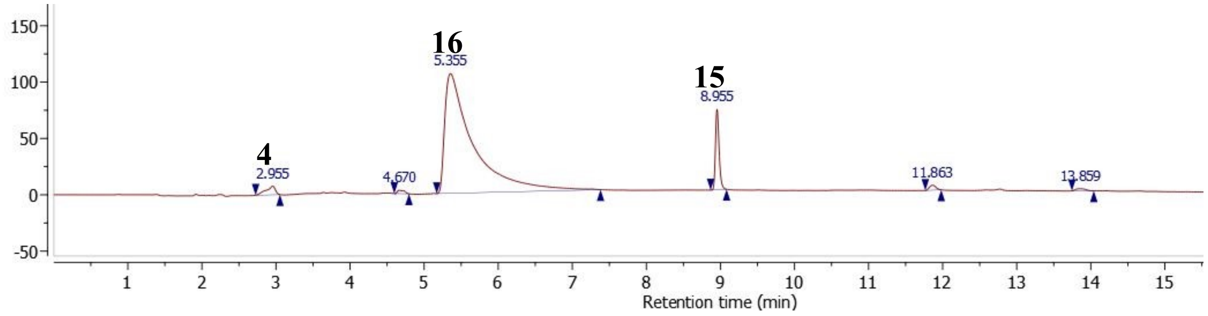


Figure 5: HPLC-Chromatogram of the alkylation of HPA with mesylate XX after 21 h in DMA at 90 °C (λ = 254 nm).

For further optimizations DMA was chosen as solvent. Regarding the amount of $Mg(O^{t}Bu)_2$, it turned out that 3.0 equivalents were crucial to achieve high conversions (Table 7).

Table 7: Screening of $Mg(O^{t}Bu)_2$ equivalents for the alkylation of HPA with mesylate 14 in DMA.

#	$Mg(O^{t}Bu)_2$ (eq.)	conversion [%][a]
1	4.0	95
2	3.5	94
3	3.0	97
4	2.5	65
5	2.0	32

All reactions were performed in a 0.02 g scale with 2.5 eq. mesylate and stirred for 21 h in DMA at 90 °C; [a] determined by HPLC (λ = 254 nm);

No significant difference in terms of conversion could be observed when the equivalents of mesylate were reduced from 2.5 to 2.0 (Table 8). Between 2.0 and 1.5 eq. the conversion varied between 90% and 98%. Below 1.5 equivalents the conversion decreased noticeably. The varying conversion could arise from the low purity of $Mg(O^tBu)_2$ (93%) which can have a big effect in such small scale reactions.

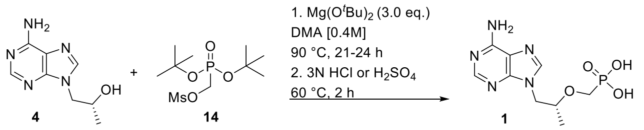
Table 8: Screening equivalents of mesylate 14 for the alkylation of HPA.

#	**XX (eq.)**	**conversion [%][a]**
1	2.5	94–98
2	2.0	96–98
3	1.7	91–96
4	1.5	90–94
5	1.3	79–83

All reactions were performed twice in a 0.02 g scale with 3.0 eq. of $Mg(O^tBu)_2$ and stirred for 21 h in DMA at 90 °C; [a] determined by HPLC ($\lambda = 254$ nm)

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 (3N HCl) was added to the residue. At 60 °C, the dealkylation was already complete after 2 h. The pH was adjusted to 2.8–3.0 with NaOH-solution to precipitate $PMPA\cdot H_2O$ which was dried afterwards as described in literature.[10] On a 1 g scale, the conversion of HPA was slightly higher when using 1.7 eq. of **14** instead 1.5 eq. while the isolated yields were similar, 64% and 65%, respectively (Table 9, entry 1 & 2). Despite the high conversions of HPA, large amounts of PMPA·H_2O did not precipitate and remained in the mother liquor.

Table 9: Two-step-sequence for making PMPA from HPA and mesylate **14**.



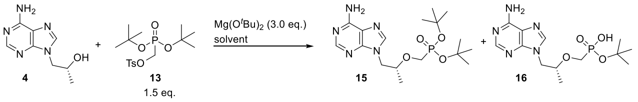
#	scale [g 4]	XX (eq.)	*t* [h]	Conversion [%][a]	IY [%]
1[b]	1.0	1.7	23	96	64
2[b]	1.0	1.5	21	92	65
3[c]	1.0	1.5	24	91	69
4[c]	5.0	1.5	22	91	72

[a] determined by HPLC (λ = 254 nm), [b] dealkylation/pH-adjustment performed with 3N HCl/NaOH (40wt%); [c] dealkylation/pH-adjustment performed with 3N H_2SO_4/NH_3 (25wt%)

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 co-solvents to the mother liquor like MeOH, EtOH, *i*PrOH or MeCN also led only to the precipitation of a PMPA/salt mixtures from which PMPA could not be easily separated. As Derstine *et al.* have carefully analyzed, 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 the dealkylation and the pH was adjusted with conc. aqueous NH_3 (25 wt-%) in order to see how the forming $(NH_4)_2SO_4$ effects the PMPAsolubility. Only slightly more PMPA (69%) could be isolated in this way (Table 9, entry 3). Nevertheless, performing the reaction on a 5 g scale, 72% of PMPA could be obtained (Table 9, entry 4).

Using the tosylate **13** for the alkylation of HPA similar conversions could be observed in DMA, DMSO and DMF (Table 10).

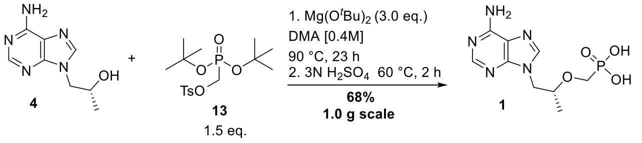
Table 10: Solvent screening of coupling HPA with tosylate **13** in presence of Mg(OtBu)$_2$.



#	**solvent**	***T*** **[°C]**	***t*** **[h]**	**4**^{a}	**16**^{a}	**15**^{a}	**BP**^{a}	**"PMPA"**
1	DMA	80	21	6	80	12	2	92
2	DMSO	70	21	3	39	50	8	90
3	DMF	80	21	4	82	12	2	94

All reactions were performed in a 0.02 g scale; ^{a} peak area [%] (λ = 254 nm); BP = byproducts

When the reaction was performed in DMF on a 1 g scale 96% conversion of HPA was detected after 23 h. After conducting the dealkylation and work-up in the same way as described for the mesylate, PMPA could be isolated in 68% yield (Scheme 7).

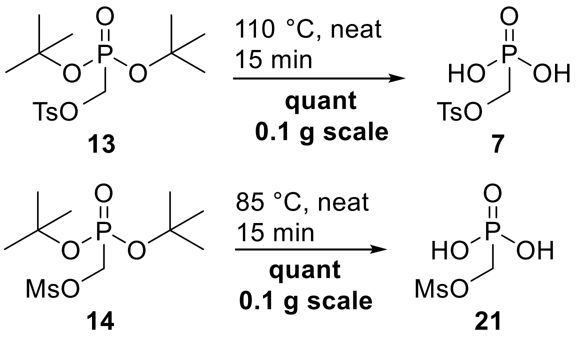


Scheme 7: Two-step-sequence for making PMPA from HPA and tosylate **13**.

All in all, there was no significant difference regarding isolated yield between the usage of mesylate **14** and tosylate **13** for preparing PMPA.

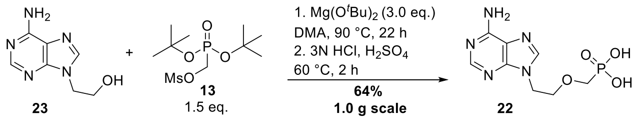
2.5 Further application

Both newly reported di-*tert*-butyl oxymethylphosphonates **13** and **14** could be also easily converted quantitatively to their free phosphonic acid by just heating them for a few minutes even under solvent free conditions (Scheme 8). 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 8: Dealkylation of **13** and **14** to the free phosphonic acid by heating neat.

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 (Hepsera®, **22**) differs only in one methyl group from tenofovir. Applying the newly developed protocol on 9-(2-hydroxyethyl)adenine (**23**) 87% conversion could be detected after 22 h at 90 °C. After dealkylation and work-up, adefovir could be isolated in 64% yield (Scheme 9). It should be noted that when 3N H_2SO_4/NH_3 was used for dealkylation/pH adjustment, the formation of an insoluble adefovir-salt was observed.



Scheme 9: Synthesis of adefovir (**22**) using (di-tert-butoxyphosphoryl)methyl methanesulfonate (**13**).

3. Conclusion

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 a simple and multigram preparation of 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.

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

Experimental section

All employed chemicals were commercially available and used without prior purification. Anhydrous THF, Me-THF, CPME, MTBE were freshly distilled over potassium (DCM over CaH_2) under nitrogen atmosphere. Anhydrous DMF, DMA, DMSO and NMP were purchased from Acros (AcroSeal™). Oven-dried glass ware 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 internal reference. The reported signal splittings were abbreviated as follows: s_b = broad singlet, s = singlet, d = doublet, t = triplet. Coupling constants J are reported in Hz. 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 LC/MSD Infinitylab 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. A ACE C18 PFP column (3 µm, 4.6 mm x 150 mm, 40 °C) with gradient elution using acetonitrile/ water (+0.1% formic acid) as solvent and a flow rate of 1.0 mL/min was used. Gas chromatography was performed on an Agilent 8890 gas chromatograph equipped with a 5977 GC/MS detector. An Agilent Technologies HP 5MS UI column (30 m x 0.25 mm x 0.25 µm) as stationary phase with helium as 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 FTIR-spectrometer using a diamond 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.

Di-*tert*-butyl phosphite, 8. An oven-dried Schlenk flask was charged with dry Me-THF (300 mL) under nitrogen atmosphere and cooled in an ice-bath. PCl_3 (99%, 6.0 mL, 67.9 mmol, 1.0 eq) was added and the solution was stirred for three minutes while cooling. Under nitrogen reverse flow, NaO*t*Bu (98%, 16.32 g, 166.4 mmol, 2.5 eq.) was added in small portions over five minutes while stirring properly. The ice-bath was removed and the thick colorless suspension stirred for one hour at r.t.. Saturated $NaHCO_3$-solution (200 mL) was added and the mixture was stirred for five minutes. 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, dried over $NaSO_4$ and all volatiles were removed in vacuo at 30 °C. Crude **9** was obtained as a colorless, slight murky liquid (11.26 g, 57.98 mmol, 85%) which was used for the next step without 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, $^1J_{P\text{-}H}$ = 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, $^2J_{C\text{-}P}$ = 7.4 Hz, -O-

C(CH_3)$_3$-), 30.5 (d, $^3J_{C\text{-}P}$ = 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]

Di-*tert*-butyl (hydroxymethyl)phosphonate, 12. Variant 1: According to a method from Grimmond *et al.*[25]: A round-bottomed flask was charged with di-*tert*-butyl phosphite (96%[2], 3.24 g, 16.0 mmol, 1.0 eq.), NEt_3 (2.6 mL, 19 mmol, 1.2 eq.) and H_2O (1 mL). Aqueous formaldehyde solution (37%, 1.20 mL, 16.0 mmol 1.0 eq.) was added afterwards 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 x 5 mL) furnishing the crude product as slight yellowish waxy solid (3.51 g, 14.5 mmol, 91%[3]). **Variant 2**: A round-bottomed flask was charged with crude di-*tert*-butyl phosphite (95%[4], 11.25 g, 55.0, mmol, 1.0 eq.), paraformaldehyde (97%, 1.70 g, 1.0 eq.), K_2CO_3[5] (1.60 g, 11.59 mmol, 0.2 eq.) and acetonitrile (*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 a balloon full of argon. 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 during **12** crystallized out (if no crystallization took place, slightly shaking or inoculating helped). The supernatant mother liquor was decanted and the solid was washed twice with cold MeCN (-24 °C, 2 x 5 mL). The solid was dried in vacuo at 30 °C to afford

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[2] Commercially available

[3] Yield was corrected by ^{31}P-NMR spectroscopy.

[4] Purity was estimated by ^{31}P-NMR spectroscopy

[5] anhydrous, grinded and stored in desiccator

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. **Melting range:** 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, $^1J_{P\text{-}H}$ = 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, $^2J_{C\text{-}P}$ = 9.0 Hz, -$\mathit{C}(CH_3)_3$-), 60.1 (d, $^1J_{C\text{-}P}$ = 164 Hz, -P-CH_2-), 30.6 (d, $^3J_{C\text{-}P}$ = 3.8 Hz, -$C(\mathit{C}H_3)_3$) 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.[29]

(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 eq.), NEt_3 (2.1 mL, 14.7 mmol, 1.1 eq.) and DMAP (0.16 g, 1.34 mmol, 0.1 eq.) were dissolved in dry DCM (100 mL) under nitrogen atmosphere. Tosyl chloride (2.81 g, 14.7 mmol, 1.1 eq.) was added and the solution stirred under 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 x 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. **Melting range:** 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, $^2J_{H\text{-}P}$ = 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, $^2J_{C\text{-}P}$ = 8.6 Hz, -*C*$(CH_3)_3$), 64.1 (d, $^1J_{C\text{-}P}$ = 174 Hz, -P-CH_2-), 30.4 (d, $^3J_{C\text{-}P}$ = 4.0 Hz, -C(*C*$H_3)_3$), 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.

(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 eq.) was dissolved in dry DCM (200 mL) under nitrogen atmosphere. NEt_3 (9.70 mL, 69.2 mmol, 1.2 eq.) was added and the solution was cooled in an ice-bath. Mesyl chloride (4.90 mL, 63.5 mmol, 1.1 eq.) was dripped into the solution within four minutes, the ice bath was removed and the solution stirred at r.t. for 19 h (reaction control by TLC). The reaction mixture was washed twice with sat. $NaHCO_3$-solution (2 x 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 a 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. **Melting range:** 52.2–55.0 °C (decomposition). **R_f (SiO_2):** 0.55 (EtOAc), stained with $KMnO_4$. **IR (ATR):** *v* = 2983, 1359, 1260, 1174, 965 cm^{-1}. **^{1}H-NMR, COSY** (400 MHz, $CDCl_3$): *δ* = 4.28 (d, $^1J_{P\text{-}H}$ = 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, $^2J_{C\text{-}P}$ = 8.5 Hz, -*C*$(CH_3)_3$-), 64.2 (d, $^1J_{C\text{-}P}$ = 174 Hz, -P-CH_2-), 38.2 (-CH_3), 30.5 (d, $^3J_{C\text{-}P}$ = 3.9 Hz, -C(*C*$H_3)_3$) 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.

Tenofovir (PMPA), 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 eq.) and magnesium *tert*-butoxide (93%, 14.24. g, 77.64 mmol, 3.0 eq.) under 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 eq.) was added portion wise within one minute. 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 1.5M H_2SO_4 (50 mL) was added to the orange-brownish residue. During heating to 60 °C a yellowish solution formed. After four hours (complete dealkylation to PMPA detected by HPLC at 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 (25wt%, 3 mL). A colorless to slight yellowish suspension formed which was stirred while cooling for one hour and then stored in a refrigerator overnight. The next day, the suspension was vacuum-filtered and washed with ice-cold water (4 x 4 mL) and ice-cold acetone (3 x 4 mL). The filtered solid was first dried on the air and then at 80 °C under high vacuum for four hours to obtain PMPA as a colorless powder (5.36 g, 18.6 mmol, 72%). **Variant 2** using tosylate **13**: An oven-dried Schlenk flask was charged with HPA (**4**, >98%, 1.00 g, 5.18 mmol, 1.0 eq.) and magnesium *tert*-butoxide (93%, 2.85 g, 15.5 mmol, 3.0 eq.) under 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 eq.) was added portion wise within one minute. 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 1.5M H_2SO_4 (10 mL) was added to the orange-brownish residue. During heating to 60 °C a yellowish solution formed. After four hours (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 x 2 mL) and ice-cold acetone (3 x 2 mL). The filtered solid was first dried on the air and then then at 80 °C under high-vacuum for four hours. PMPA was obtained as a colorless powder (1.01 g, 3.52 mmol, 68%). ***M*** ($C_9H_{14}N_5O_4P$) = 287.22 g/mol. **Melting range:** 271–274 °C (decomposition), (Lit.: 276–278 °C[30]). **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, -C*H*(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, $^3J_{C\text{-}P}$ = 12.1 Hz, -*C*H(CH_3)O-), 64.5 (d, $^1J_{C\text{-}P}$ = 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-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.. **7** was obtained as a colorless resin (0.070 g, 0.26 mmol, quant.) which formed a colorless solid by trituration. ***M*** ($C_8H_{11}O_6PS$) = 266.20 g/mol. **Melting range**: 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}. **^{1}H-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, $^2J_{P\text{-}H}$ = 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, $^2J_{C\text{-}P}$ = 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]

{[(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 further 15 min and then cooled to r.t.. **21** was obtained as 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. **Melting range:** 94.2–96.5 °C. **R$_f$ (C$_{18}$-SiO$_2$):** 0.46 (H$_2$O + 3% HOAc). **IR (ATR):** ν = 1365, 1178, 1026, 1011, 939 cm^{-1}. **^{1}H-NMR, COSY** (400 MHz, DMSO-d$_6$): δ = 4.23 (d, $^2J_{P\text{-}H}$ = 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, $^1J_{C\text{-}P}$ = 160 Hz,-P-CH$_2$-), 36.5 (s, -CH$_3$) ppm. **^{31}P-NMR** (162 MHz, DMSO-d$_6$): δ = 10.4 ppm. **ESI-HRMS:** Calcd for [M+H]$^+$: *m/z* = 190.9774, found: *m/z* = 190.9776.

Adefovir (PMEA), 22. An oven-dried Schlenk flask was charged with HEA (**23**, >98%, 1.00 g, 5.58 mmol, 1.0 eq.) and magnesium *tert*-butoxide (93%, 3.07 g, 16.7 mmol, 3.0 eq.) under 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 (**XX**, 2.53 g, 8.37 mmol, 1.5 eq.) was added portion wise within one minute. The reaction mixture stirred at 90 °C for 22 h (conversion of HEA 87% detected by HPLC at 254 nm). All volatiles were removed in vacuo at 50–60 °C and 3N HCl (10 mL) was added to the orange-brownish residue. During heating to 60 °C an orange solution formed. After four hours (complete dealkylation to PMEA detected by HPLC at 254 nm) the solution was cooled in an ice bath and the pH was adjusted to pH = 2.8-3 using NaOH-solution (40wt%, 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 one hour and then stored in a refrigerator overnight. The suspension was vacuum-filtered and washed with ice-cold water (4 x 2 mL) and ice-cold acetone (3 x 2 mL). The filtered solid was first dried on the air and then at 80°C under high vacuum for three hours to obtain PMEA (0.98 g, 3.59 mmol, 64%). ***M*** ($C_8H_{12}N_5O_4P$) = 273.19 g/mol. **Melting range:** 276–278°C (decomposition), (Lit.: 282–284 °C[31]). **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}. **^{1}H-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, $^3J_{C\text{-}P}$ = 11.6 Hz, -CH_2O-), 66.9 (d, $^1J_{C\text{-}P}$ = 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.[31]

Associated content

Supporting Information

Chromatograms and NMR-spectra (PDF).

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