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Synthesis and antimalarial activity of chain substituted pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098

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Abstract—Fosmidomycin is a promising antimalarial drug candidate with a unique chemical structure and a novel mode of action. Chain substituted pivaloyloxymethyl ester derivatives of Fosmidomycin and its acetyl analogue FR900098 have been synthesized and their in vitro antimalarial activity versus the Chloroquine sensitive strain 3D7 of *Plasmodium falciparum* has been determined.

1. Introduction

Malaria is a parasitic tropical infection disease which affects approximately 40% of the world's population. According to estimations by the World Health Organisation, 1.5–3 million people die of malaria every year, most of them children. Almost all of the fatal cases are caused by *Plasmodium falciparum*, the causative agent of *Malaria tropica*. As the parasites' resistance to established antimalarial drugs steadily increases, the need for the development of novel chemotherapeutic principles is growing. New classes of compounds displaying novel modes of action have to be developed. Fosmidomycin (**I**) and its more active acetyl analogue FR900098 (**II**) are potent, selective inhibitors of the 1-desoxy-D-xylulose-5-phosphate (DOXP) reductoisomerase, a key enzyme of the DOXP/MEP pathway of isoprenoid biosynthesis.[1,2] The DOXP/MEP pathway, which leads to isopentenyl diphosphate (IPP), the common precursor of isoprenoids, is for instance present in algae, higher plants, bacteria and the malaria parasite *P. falciparum*, but not in humans and mammalians.[3] As in humans IPP is synthesized via the mevalonate pathway, inhibitors of the DOXP/MEP pathway are expected to be well tolerated (Fig. 1).

In previous studies, Fosmidomycin and FR900098 have been shown to inhibit the growth of multidrug-resistant strains of *P. falciparum* in vitro. Furthermore, **I** and **II** have been proved to cure mice infected with the rodent malaria parasite *Plasmodium vinckei*

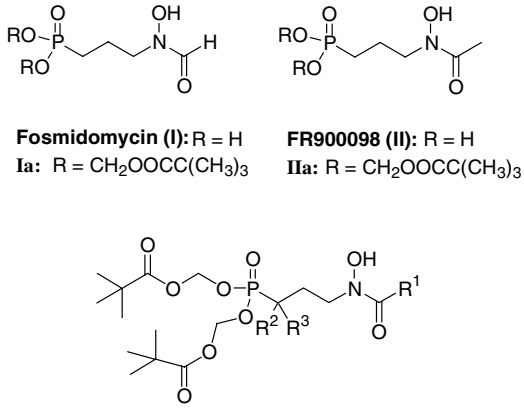

Figure 1. Pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098.

Keywords: Malaria; Targets; Fosmidomycin; Pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098.
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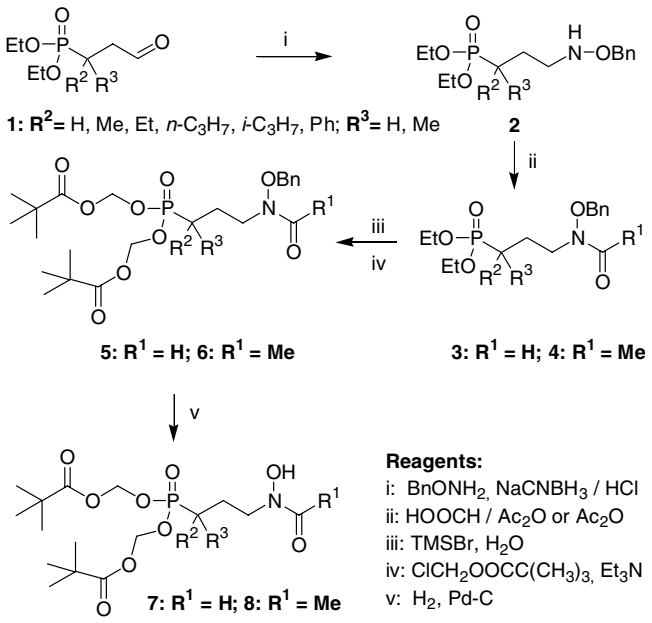
by intraperitoneal or oral treatment.[2] Clinical trials conducted in Thailand and Gabon have shown that Fosmidomycin is efficient in the treatment of acute, uncomplicated *Malaria tropica*.[4] However, due to their low lipophilicity and the dissociation of the phosphonic acid group at physiological pH values, **I** suffers from low oral bioavailability with absorption rates of approximately 30%.[5] Furthermore, Fosmidomycin's short plasma half time of 2.5 h requires the repeated administration of relatively high dosages.[5] Recently, Schlitzer described acyloxyalkyl and alkoxycarbonyloxyethyl ester prodrugs of FR900098 with improved in vivo antimalarial activity.[6] As hydroxyurea and carboxylic acid analogues of **I** and **II** recently prepared in our group are inactive, the phosphonic acid and hydroxamic acid functionalities seem to be essential for the antimalarial activity.[7,8] So far only very little research efforts have been dedicated to the structural modifications of the carbon spacer between the functional groups. Recently, we discovered that α-phenylfosmidomycin displays high activity against *P. falciparum*.[9] In a publication, which is online available since January 2006, Van Calenbergh et al. confirmed the results of our patent.[10] In order to get a better understanding of the structure activity relationships and to increase the lipophilicity, we investigated the synthesis and antimalarial activity of chain substituted pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098. Pivaloyloxymethyl esters of phosphonic acids are known to be hydrolysed by non-specific esterases to liberate the biologically active phosphonic acid, formaldehyde and pivalic acid.[11] In contrast to the hygroscopic nature of phosphonohydroxamic acids, the corresponding bis(pivaloyloxymethyl) esters are stable and non-hygroscopic compounds.

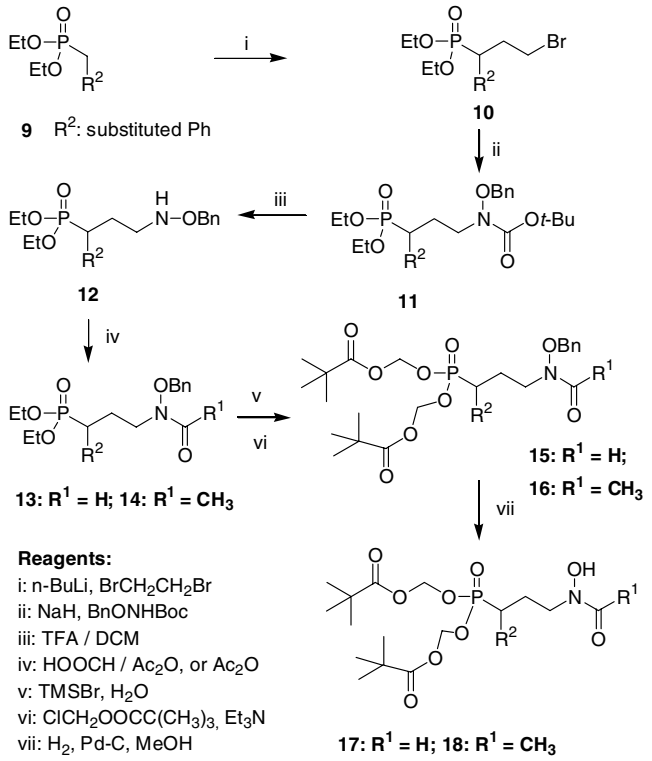
2. Results and discussion

2.1. Synthesis

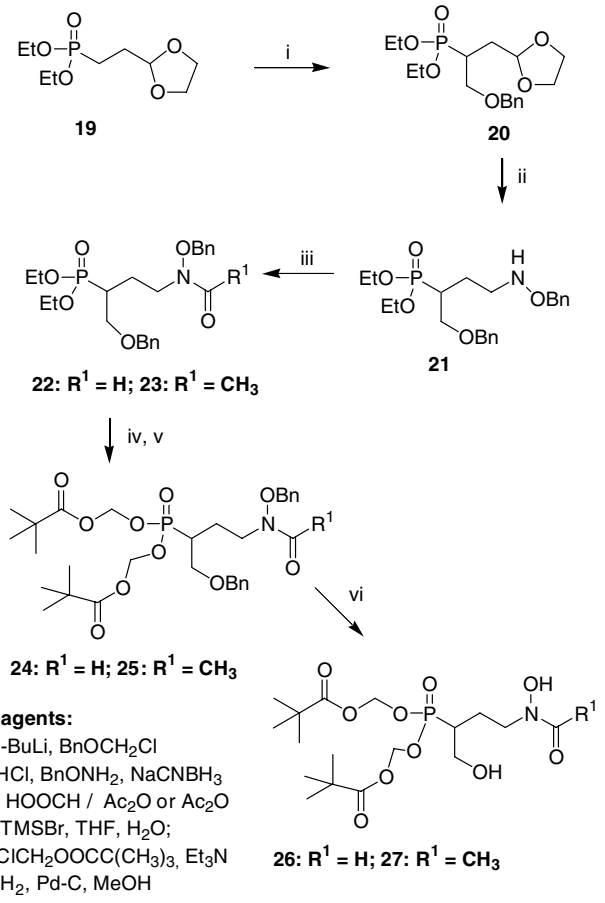
The pivaloyloxymethyl ester prodrugs (**Ia**, **IIa**) of Fosmidomycin (**I**) and FR900098 (**II**) were synthesized according to the method of Schlitzer.[6] Three different synthetic routes have been developed for the synthesis of the target compounds as shown in Schemes 1–3. Starting materials **1** were prepared by reactions of α,β-unsaturated aldehydes with triethyl phosphite and ethanol followed by acidic hydrolysis of the diethyl acetal intermediates according to a literature procedure.[12] Reactions of **1** with *O*-benzylhydroxylamine and subsequent reduction of the resulting *O*-benzyloximes with sodium cyanoborohydride in presence of hydrochloric acid afforded N,O-substituted hydroxylamines **2** in excellent yields of 92–97%.[7] Treatment of **2** with acetic-formic anhydride or acetic anhydride furnished hydroxamic acids **3** and **4** in 92–99% and 73–89% yield, respectively.[8] Dealkylation of **3** and **4** by bromotrimethylsilane and subsequent alkylation of the crude acids with chloromethyl pivalate led to phosphonic acid esters **5** and **6**.[6,13] Cleavage of the *O*-benzyl group was accomplished by catalytic hydrogenation on Pd–C to provide compounds **7** and **8** in high yields (Scheme 1). Precursors **9** were prepared by reactions of triethyl phosphite with substituted benzyl chlorides and bromides. Alkylation of **9** with 1,2-dibromoethane led to compounds **10**, which were reacted with *N*-Boc-*O*-Bn-hydroxylamine in presence of sodium hydride. Cleavage of the Boc-protecting



Scheme 1. Synthesis of chain substituted pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098.



Scheme 2. Synthesis of aryl substituted pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098.



Scheme 3. Synthesis of hydroxymethyl substituted pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098.

group in **11** with TFA in dichloromethane and subsequent formylation or acetylation afforded hydroxamic acids **13** and**14**.[8]

As described above, cleavage of the phosphonic ester functionality by bromotrimethylsilane followed by alkylation of the crude phosphonic acids with chloromethyl pivalate led to pivaloyloxymethyl esters **15** and **16**. Finally, catalytic hydrogenation on Pd–C furnished compounds **17** and **18** (Scheme 2). Alkylation of dioxolane **19** with benzylchloromethyl ether provided compound **20**.[14] Acidic hydrolysis of **20**, oximation and subsequent reduction with sodium cyanoborohydride in presence of hydrochloric acid furnished N,O-substituted hydroxylamine **21** in a high yield of 89%.[7,12] Conversion of **21** into the target compounds **26** and **27** was accomplished as described for compounds **7**, **8**, **17** and **18** (Scheme 3). The hydroxymethyl group could contribute to improve the activity of compounds **26** and **27** by additional hydrogen bonding.

2.2. Biological activity

The in vitro antimalarial activity of analogues **7**, **8**, **17**, **18**, **26** and **27** was evaluated by 8-[^{3}H]hypoxanthine incorporation assay according to the method of Desjardins using the Chloroquine-sensitive strain 3D7 of *P. falciparum*.[15] IC_{50} values as well as the inhibition of parasite growth at 25 μM and 0.5 μM have been determined. The antimalarial activity was compared to the pivaloyloxymethyl esters (**Ia**, **IIa**) of the leads Fosmidomycin (**I**) and FR900098 (**II**) (Tables 1–3).

Table 1. IC_{50} values of pivaloyloxymethyl ester analogues of Fosmidomycin and FR-900098 against *P. falciparum*

Compound	Activity against *P. falciparum*		
	IC_{50}[a] (μM)	*n*	SEM[b]
7a	0.7	3	0.2
7b	0.6	3	0.2
8a	0.7	3	0.2
8b	0.7	3	0.2
26	6.7	3	0.9
27	3.7	3	0.4
17a	0.3	3	0.1
Ia	2.1	6	1.1
IIa	0.4	6	0.1

[a] Mean values of 3 or 6 independent determinations.
[b] Standard errors of the means.

Table 2. Inhibition of *P. falciparum* growth (%) at 25 μM

Compound	R^1	R^2	R^3	Inhibition of *P. falciparum* growth		
				Inhib.[a] (%)	*n*	SEM[b]
7a	H	CH_3	H	97	3	2
7b	H	Ph	H	98	3	2
7c	H	CH_2CH_3	H	57	5	5
7d	H	$CH(CH_3)_2$	H	55	5	2
7e	H	$CH_2CH_2CH_3$	H	29	5	2
7f	H	CH_3	CH_3	12	5	2
8a	CH_3	CH_3	H	97	3	2
8b	CH_3	Ph	H	97	3	2
8c	CH_3	CH_2CH_3	H	39	5	5
8d	CH_3	$CH(CH_3)_2$	H	32	5	2
8e	CH_3	$CH_2CH_2CH_3$	H	27	5	2
8f	CH_3	CH_3	CH_3	23	5	2

[a] Mean values of 3 or 5 independent determinations.
[b] Standard errors of the means.

Table 3. Inhibition of *P. falciparum* growth (%) at 0.5 μM

Compound	R^1	R^2	Inhib.[a] (%)	*n*	SEM[b]
17a	H	3,4-F–Ph	43.7	4	2.2
18a	CH_3	3,4-F–Ph	37.9	4	3.6
17b	H	2-F–Ph	31.7	4	3.9
17c	H	2,6-CH_3–Ph	2.0	4	2.7
7b	H	Ph	39	4	0.9

[a] Mean values of 4 independent determinations.
[b] Standard errors of the means.

2.3. Structure–activity relationships

In contrast to the higher activity of FR900098 compared to Fosmidomycin, most of the tested formyl derivatives were significantly more active than their acetyl analogues.[2,6,16] A considerable loss of antimalarial activity was observed with the ethyl, propyl, isopropyl and dimethyl substituted pivaloyloxymethyl ester anlogues (**7c–f**, **8c–f**). In contrast, the methyl and phenyl substituted derivatives (**7a**, **b**, **8a**, **b**) were approximately as active as the FR900098 prodrug **IIa**, which exhibits an IC_{50} value of 0.4 μM. These promising results encouraged us to investigate the activity of the hydroxymethyl substituted derivatives **26** and **27** as well as the activity of substituted phenyl analogues (**17a–c**, **18a**). However, the replacement of methyl by hydroxymethyl resulted in a significant reduction of activity. In contrast, the substituted phenyl derivatives (**17a**, **b**, **18a**) are approximately as active as **7b**, but slightly less plasmodicidal as **IIa**, whereas electron-donating substituents lead to a significant reduction of antiplasmodial activity (**17c**).

3. Conclusion

The introduction of substituents into the α-position to the phosphonic acid moiety of Fosmidomycin and FR900098 as well as masking the phosphonic acid functionality as pivaloyloxymethyl esters led to a series of promising analogues with comparable in vitro antimalarial activity. This is noteworthy since former attempts to introduce substituents in β- and γ-position had resulted in almost inactive compounds.[14] To the best of our knowledge, the 3,4-difluorophenyl substituted analogue of Fosmidomycin (**17a**) is one of the most active analogues reported so far. Furthermore, it should be mentioned that all derivatives were tested as racemates. Therefore, a resolution of the racemic compounds should lead to an additional improvement of the antimalarial activity. As the pivaloyloxymethyl ester prodrugs are transformed into the corresponding active phosphonic acids by non specific esterases, no animal experiments were necessary so far.[11] Further investigations regarding the bioavailability of the most active compounds are intended.

4. Materials and methods

4.1. Experimental

Melting points were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as internal standard and DMSO-d_6 or $CDCl_3$ as solvents. Mass spectra were recorded on a Micromass VG 70-250S mass spectrometer (HRFAB), a Finnigan MAT 311 A mass spectrometer (EI) or a Varian MS 1200 L mass spectrometer (ESI).

4.2. Bispivaloyloxymethyl esters of Fosmidomycin and FR900098[6a]

4.3. General procedure for the preparation of (3-benzyloxyamino-propyl)-phosphonic acid diethyl esters 2a–f

A solution of the respective aldehyde **1** (30 mmol) in MeOH (20 mL) was treated with *O*-benzylhydroxylamine (30 mmol) and stirred for 1 h. After addition of further 430 mL of MeOH, the mixture was treated portionwise with $NaBH_3CN$ (90 mmol). Over a period of 30 min, HCl (37%, 30 mL) was added dropwise under ice cooling. The mixture was allowed to warm up to room temperature, followed by treatment with additional 20 mmol of $NaBH_3CN$. After an overall time of 2 h, the solution was concentrated and aqueous KOH (10%) was added under ice cooling until an alkaline reaction was observed. The aqueous solution was extracted 3 times with CH_2Cl_2 (50 mL). The organic layers were combined, dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel using EtOAc/MeOH (95:5) as an eluent to give (3-benzyloxyamino-propyl)-phosphonic acid diethyl esters **2** as colourless oils.

4.3.1. (3-Benzyloxyamino-1-methyl-propyl)-phosphonic acid diethyl ester (2a). Yield: 93%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.36–7.25 (m, 5H), 6.64 (t, 1H, J = 5.9 Hz), 4.59 (s, 2H), 4.03–3.93 (m, 4H), 2.96–2.88 (m, 1H), 2.84–2.76 (m, 1H), 2.00–1.81 (m, 2H), 1.44–1.32 (m, 1H), 1.22 (t, 6H, J = 7.1 Hz), 1.03 (dd, 3H, $^3J_{H\text{-}P}$ = 18.5 Hz, $J_{H\text{-}H}$ = 7.1 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 138.9, 128.5, 128.4, 127.7, 75.5, 61.3 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 49.1 (d, $^3J_{C\text{-}P}$ = 13.2 Hz), 27.8 (d, $^2J_{C\text{-}P}$ = 3.6 Hz), 27.8 (d, $^1J_{C\text{-}P}$ = 140.4 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.1 Hz), 13.5 (d, $^2J_{C\text{-}P}$ = 5.1 Hz). IR: 3242 cm^{-1} (N–H), 1233 cm^{-1} (P=O). Anal. Calcd for ($C_{15}H_{26}NO_4P$): C, 57.13; H, 8.31; N, 4.44. Found: C, 56.87; H, 8.14; N, 4.45. HRFAB-MS $C_{15}H_{26}NO_4P$ $[M+H]^+$: calculated 316.1677; found 316.1680.

4.3.2. (3-Benzyloxyamino-1-phenyl-propyl)-phosphonic acid diethyl ester (2b). Yield: 92%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.34–7.22 (m, 10H), 6.63 (t, 1H, J = 5.3 Hz), 4.57 (dd, 2H, J_{AB} = 11.8 Hz), 4.01–3.91 (m, 2H), 3.86–3.76 (m, 1H), 3.76–3.66 (m, 1H), 3.27 (dt, 1H, $J_{H\text{-}P}$ = 3.8 Hz, $J_{H\text{-}H}$ = 11.1 Hz), 2.70–2.62 (m, 1H), 2.60–2.52 (m, 1H), 2.25–2.14 (m, 1H), 2.02–1.91 (m, 1H), 1.19 (t, 3H, J = 7.1 Hz), 1.01 (t, 3H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 138.7, 136.7 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 128.6, 128.6, 128.5, 128.3,

127.8, 127.2, 127.2, 75.6, 62.0 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 61.6 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 49.3 (d, $^3J_{C\text{-}P}$ = 15.8 Hz), 40.9 (d, $^1J_{C\text{-}P}$ = 137.3 Hz), 27.6 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 16.6 (d, $^3J_{C\text{-}P}$ = 5.6 Hz), 16.4 (d, $^3J_{C\text{-}P}$ = 5.6 Hz). IR: 3243 cm^{-1} (N–H), 1242 cm^{-1} (P═O). Anal. Calcd for $C_{20}H_{28}NO_4P$: C, 63.65; H, 7.48; N, 3.71. Found: C, 63.15; H, 7.46; N, 3.56. HRFAB-MS $C_{20}H_{28}NO_4P$ $[M+H]^+$: calculated 378.1834; found 378.1819.

4.3.3. (3-Benzyloxyamino-1-ethyl-propyl)-phosphonic acid diethyl ester (2c). Yield: 97%. ^1H NMR (DMSO-d_6), δ (ppm): 7.36–7.25 (m, 5H), 6.64 (t, 1H, J = 5.85 Hz), 4.60 (s, 2H), 4.02–3.93 (m, 4H), 2.93–2.80 (m, 2H), 1.84–1.71 (m, 2H), 1.66–1.51 (m, 2H), 1.49–1.37 (m, 1H), 1.21 (t, 3H, J = 7.1 Hz), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 138.8, 128.4, 128.3, 127.7, 75.5, 61.2 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 61.1 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 49.5 (d, $^3J_{C\text{-}P}$ = 9.7 Hz), 34.3 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 25.4 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 21.3 (d, $^2J_{C\text{-}P}$ = 3.6 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.6 Hz), 12.0 (d, $^3J_{C\text{-}P}$ = 8.7 Hz). IR: 3243 cm^{-1} (N–H), 1238 cm^{-1} (P═O). HRFAB-MS $C_{16}H_{28}NO_4P$ $[M+H]^+$: calculated 330.1834; found 330.1834.

4.3.4. [1-(2-Benzyloxyamino-ethyl)-2-methyl-propyl]-phosphonic acid diethyl ester (2d). Yield: 93%. ^1H NMR (DMSO-d_6), δ (ppm): 7.36–7.25 (m, 5H), 6.63 (t, 1H, J = 5.85 Hz), 4.59 (s, 2H), 4.00–3.92 (m, 4H), 2.96–2.88 (m, 1H), 2.86–2.78 (m, 1H), 2.11–1.97 (m, 1H), 1.81–1.53 (m, 3H), 1.21 (t, 6H, J = 7.1 Hz), 0.94 (t, 6H, J = 6.6 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 138.8, 128.4, 128.4, 127.7, 75.5, 61.1 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 60.9 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 50.6 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 39.1 (d, $^1J_{C\text{-}P}$ = 134.8 Hz), 27.3 (d, $^2J_{C\text{-}P}$ = 2.5 Hz), 22.6 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 21.3 (d, $^3J_{C\text{-}P}$ = 13.2 Hz), 19.5 (d, $^3J_{C\text{-}P}$ = 2.5 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.6 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.6 Hz). IR: 3242 cm^{-1} (N–H), 1234 cm^{-1} (P═O). Anal. Calcd for $C_{16}H_{26}NO_4P$: C, 59.46; H, 8.81; N, 4.08. Found: C, 58.99; H, 8.84; N, 4.46. HRFAB-MS $C_{17}H_{30}NO_4P$ $[M+H]^+$: calculated 344.1990; found 344.2017.

4.3.5. [1-(2-Benzyloxyamino-ethyl)-butyl]-phosphonic acid diethyl ester (2e). Yield: 94%. ^1H NMR (DMSO-d_6), δ (ppm): 7.36–7.25 (m, 5H), 6.63 (t, 2H, J = 5.85 Hz), 4.59 (s, 2H), 4.02–3.92 (m, 4H), 2.93–2.80 (m, 2H), 1.89–1.70 (m, 2H), 1.61–1.48 (m, 2H), 1.43–1.27 (m, 3H), 1.21 (t, 6H, J = 7.1 Hz), 0.85 (t, 3H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 138.8, 128.4, 128.4, 127.7, 75.5, 61.2 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 49.5 (d, $^3J_{C\text{-}P}$ = 9.2 Hz), 32.8 (d, $^1J_{C\text{-}P}$ = 137.8 Hz), 30.6 (d, $^2J_{C\text{-}P}$ = 3.6 Hz), 26.0 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 20.4 (d, $^3J_{C\text{-}P}$ = 8.6 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.1 Hz), 14.4. IR: 3244 cm^{-1} (N–H), 1235 cm^{-1} (P═O). Anal. Calcd for $C_{17}H_{30}NO_4P$: C, 59.46; H, 8.81; N, 4.08. Found: C, 59.38; H, 8.57; N, 4.24.

4.3.6. (3-Benzyloxyamino-1,1-dimethyl-propyl)-phosphonic acid diethyl ester (2f). Yield: 94%. ^1H NMR (DMSO-d_6), δ (ppm): 7.35–7.25 (m, 5H), 6.57 (t, 1H, J = 6.4 Hz), 4.59 (s, 2H), 4.03–3.96 (m, 4H), 2.89–2.84 (m, 2H), 1.65–1.57 (m, 2H), 1.22 (t, 6H, J = 7.1 Hz), 1.05 (d, 6H, $^3J_{H\text{-}P}$ = 16.5 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 138.9, 128.4, 128.4, 127.7, 75.4, 61.6 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 47.1 (d, $^3J_{C\text{-}P}$ = 8.1 Hz), 34.5, 33.2 (d, $^1J_{C\text{-}P}$ = 141.9 Hz), 22.4 (d, $^2J_{C\text{-}P}$ = 2.5 Hz), 16.8 (d, $^3J_{C\text{-}P}$ = 5.6 Hz). IR: 3246 cm^{-1} (N–H), 1232 cm^{-1} (P═O). HRFAB-MS $C_{16}H_{28}NO_4P$ $[M+H]^+$: calculated 330.1834; found 330.1832.

4.4. General procedure for the preparation of [3-(*N*-Benzyloxy-*N*-*tert*-butoxycarbonylamino)-propyl]-phosphonic acid diethyl esters 11a–c

A solution of **9** (40 mmol) in dry toluene (50 mL) was cooled down to −78 °C, treated with 40 mmol of *n*-butyllithium (2.7 M solution in heptane) and stirred for 1 h. 1,2-Dibromethane (160 mmol) was added in one portion and the mixture was allowed to warm up to room temperature. After stirring overnight, water (100 mL) was added and the product extracted with EtOAc (2× 50 mL). The organic layer was dried over Na_2SO_4, evaporated and the resulting residue (**10**) was purified by column chromatography on silica gel with EtOAc as eluent. For the alkylation step, NaH (20 mmol) was added to a solution of *O*-Bn-*N*-Boc-hydroxylamine in anhydrous THF (20 mL) at room temperature. After 30 min, a solution of the appropriate alkylating agent **10** (10 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was refluxed for 8 h and cooled down to room temperature. EtOAc (100 mL) was added and the organic layer was washed twice with water (30 mL), dried over Na_2SO_4 and evaporated. The resulting oil was purified by column chromatography (EtOAc/*n*-hexane, 80:20) on silica gel to give compounds **11** as colourless oils.

4.4.1. [3-(*N*-Benzyloxy-*N*-*tert*-butoxycarbonylamino)-1-(3,4-difluorophenyl)-propyl]-phosphonic acid diethyl ester (11a). Yield: 76%. ^1H NMR (DMSO-d_6), δ (ppm): 7.46–7.27 (m, 7H), 7.17–7.09 (m, 1H), 4.74 (s, 2H), 4.03–3.92 (m, 2H), 3.89–3.74 (m, 2H), 3.35–3.22 (m, 2H), 3.18–3.09 (m, 1H), 2.28–2.16 (m, 1H), 2.03–1.19 (m, 1H), 1.38 (s, 9H), 1.18 (t, 3H, J = 7.1 Hz), 1.05 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 156.3, 152.9 (dd, $^1J_{C\text{-}F}$ = 246.8 Hz), 150.0 (dd, $^1J_{C\text{-}F}$ = 246.9 Hz), 135.7, 132.9, 129.8, 129.0, 128.9, 125.9, 118.6 (dd, $^2J_{C\text{-}F}$ = 18.0 Hz, $^3J_{C\text{-}F}$ = 6.0 Hz), 118.7 (dd, $^2J_{C\text{-}F}$ = 17.0 Hz, $^3J_{C\text{-}F}$ = 2.6 Hz), 82.0, 77.5, 63.1 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 62.5 (d, $^2J_{C\text{-}P}$ = 7.4 Hz), 47.9 (d, $^3J_{C\text{-}P}$ = 17.0 Hz), 41.5 (d, $^1J_{C\text{-}P}$ = 140.3 Hz), 28.7, 27.6 (d, $^2J_{C\text{-}P}$ = 2.8 Hz), 16.8 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.8 Hz). IR: 1701 cm^{-1} (C═O), 1246 cm^{-1} (P═O). Anal. Calcd for $C_{25}H_{34}F_2NO_6P$: C, 58.47; H, 6.67; N, 2.73. Found: C, 58.69; H, 6.83; N, 2.49.

4.4.2. 3-(*N*-Benzyloxy-*N*-*tert*-butoxycarbonylamino)-1-(2-fluorophenyl)-propyl]-phosphonic acid diethyl ester (11b). Yield: 74%. ^1H NMR (DMSO-d_6), δ (ppm): 7.45–7.39 (m, 1H), 7.38–7.30 (m, 6H), 7.25–7.16 (m, 2H), 4.75 (dd, 2H, J_{AB} = 11.7 Hz), 4.02–3.92 (m, 2H), 3.90–3.72 (m, 2H), 3.48 (ddd, 1H, $J_{H\text{-}P}$ = 23.1 Hz, J_{AB} = 11.5 Hz), 3.33–3.27 (m, 1H), 3.24–3.17 (m, 1H), 2.35–2.25 (m, 1H), 2.12–2.01 (m, 1H), 1.36 (s, 9H), 1.18 (t, 3H, J = 7.1 Hz), 1.03 (t, 3H, J = 7.1 Hz). ^{13}C

NMR ($CDCl_3$), δ (ppm): 159.1 (dd, $^1J_{C\text{-}F}$ = 246.3 Hz, $^3J_{C\text{-}P}$ = 8.3 Hz), 154.3, 133.5, 127.6, 126.7 (dd, $^3J_{C\text{-}P}$ = 7.9 Hz, $^3J_{C\text{-}F}$ = 3.5 Hz), 122.3, 120.7 (dd, $^2J_{C\text{-}P}$ = 14.5 Hz, $^3J_{C\text{-}F}$ = 6.6 Hz), 113.3 (dd, $^2J_{C\text{-}F}$ = 22.9 Hz, $^4J_{C\text{-}P}$ = 2.5 Hz), 79.4, 60.6 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 60.1 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 45.9 (d, $^3J_{C\text{-}P}$ = 17.8 Hz), 30.9 (d, $^1J_{C\text{-}P}$ = 141.9 Hz, $^3J_{C\text{-}F}$ = 2.4 Hz), 27.7, 24.7 (d, $^2J_{C\text{-}P}$ = 2.2 Hz), 14.3 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 13.6 (d, $^3J_{C\text{-}P}$ = 5.9 Hz). IR: 1712 cm^{-1} (C═O), 1242 cm^{-1} (P═O). Anal. Calcd for $C_{25}H_{35}FNO_6P$: C, 60.60; N, 2.83; H, 7.12. Found: C, 60.88; N, 2.90; H, 7.32.

4.4.3. [3-(*N*-Benzyloxy-*N*-*tert*-butoxycarbonylamino)-1-(2,6-dimethylphenyl)-propyl]-phosphonic acid diethyl ester (11c). Yield: 78%. ^1H NMR (DMSO-d_6), δ (ppm): 7.39–7.29 (m, 5H), 7.16–7.11 (m, 1H), 7.09–7.04 (m, 1H), 7.00–6.94 (m, 1H), 4.74 (s, 2H), 3.99–3.89 (m, 2H), 3.84–3.74 (m, 1H), 3.71–3.61 (m, 1H), 3.33–3.23 (m, 2H), 3.19–3.12 (m, 1H), 2.34–2.23 (m, 4H), 2.20 (s, 3H), 2.13–2.00 (m, 1H), 1.37 (s, 9H), 1.18 (t, 3H, J = 7.1 Hz), 1.00 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 156.8, 135.9 (d, $^2J_{C\text{-}P}$ = 3.3 Hz), 135.8, 134.8 (d, $^3J_{C\text{-}P}$ = 8.1 Hz), 133.6 (d, $^3J_{C\text{-}P}$ = 7.3 Hz), 130.7, 129.7, 128.9, 128.8, 128,2, 128.1, 81.8, 77.4, 63.1 (d, $^2J_{C\text{-}P}$ = 7.4 Hz), 62.2 (d, $^2J_{C\text{-}P}$ = 7.4 Hz), 48.2 (d, $^3J_{C\text{-}P}$ = 17.9 Hz), 36.9 (d, $^1J_{C\text{-}P}$ = 138.8 Hz), 28.6, 28.4, 27.7, 21.6, 20.1, 16.8 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 16.6 (d, $^3J_{C\text{-}P}$ = 6.0 Hz). IR: 1710 cm^{-1} (C═O), 1246 cm^{-1} (P═O). Anal. Calcd for $C_{27}H_{40}NO_6P$: C, 64.14; H, 7.97; N, 2.77. Found: C, 64.22; H, 8.07; N, 2.51.

4.5. General procedure for the preparation of (3-benzyloxyamino-propyl)-phosphonic acid diethyl esters 12a–c

A mixture of CH_2Cl_2 (20 mL) and trifluoro acetic acid (20 mL) was added to **11** (10 mmol) and the mixture was stirred at room temperature for 8 h. The solvent was removed under reduced pressure, the resulting residue was treated with a saturated $NaHCO_3$-solution (5 mL) and extracted with EtOAc (2× 50 mL). After drying over Na_2SO_4, the organic layer was evaporated and the crude product was purified by column chromatography on silica gel with EtOAc to give **12** as colourless oils or solids, respectively.

4.5.1. [3-Benzyloxyamino-1-(3,4-difluorophenyl)-propyl]-phosphonic acid diethyl ester (12a). Yield: 76%. ^1H NMR ($CDCl_3$), δ (ppm): 7.42–6.96 (m, 8H), 4.69 (dd, 2H, J_{AB} = 2.63 Hz), 4.15–3.75 (m, 4H), 3.30–3.13 (m, 1H), 2.97–2.84 (m, 1H), 2.79–2.64 (m, 1H), 2.46–2.27 (m, 1H), 2.14–1.97 (m, 1H), 1.29 (t, 3H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 150.0 (dd, $^1J_{C\text{-}F}$ = 245.9 Hz), 147.1 (dd, $^1J_{C\text{-}F}$ = 249.2 Hz), 137.9, 133.4, 128.9, 128.8, 125.8, 118.6 (dd, $^2J_{C\text{-}F}$ = 17.8 Hz, $^3J_{C\text{-}F}$ = 6.4 Hz), 118.4 (dd, $^2J_{C\text{-}F}$ = 17.4 Hz, $^3J_{C\text{-}F}$ = 2.7 Hz), 76.9, 63.1 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 62.5 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 49.6 (d, $^3J_{C\text{-}P}$ = 15.3 Hz), 41.5 (d, $^1J_{C\text{-}P}$ = 140.5 Hz), 28.0 (d, $^2J_{C\text{-}P}$ = 2.7 Hz), 16.8 (d, $^3J_{C\text{-}P}$ = 5.5 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.5 Hz). IR: 3242 cm^{-1} (N–H), 1242 cm^{-1} (P═O). Anal. Calcd for $C_{20}H_{26}F_2NO_4P$: C, 58.11; H, 6.34; N, 3.39. Found: C, 58.12; H, 6.25; N, 3.46.

4.5.2. [3-Benzyloxyamino-1-(2-fluorophenyl)-propyl]-phosphonic acid diethyl ester (12b). Yield: 70%. ^1H NMR (DMSO-d_6), δ (ppm): 7.47–7.39 (m, 1H), 7.36–7.13 (m, 8H), 6.65 (t, 1H, J = 4.8 Hz), 4.55 (dd, 2H, J_{AB} = 15.5 Hz), 4.03–3.93 (m, 2H), 3.89–3.72 (m, 2H), 3.62 (ddd, 1H, $J_{H\text{-}P}$ = 22.1 Hz, J_{AB} = 10.9 Hz), 2.72–2.63 (m, 1H), 2.60–2.52 (m, 1H), 2.26–2.16 (m, 1H), 2.06–1.94 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz), 1.04 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 161.0 (dd, $^1J_{C\text{-}F}$ = 245.0 Hz, $^3J_{C\text{-}P}$ = 8.2 Hz), 137.8, 129.8, 128.6 (dd, $^3J_{C\text{-}P}$ = 8.5 Hz, $^3J_{C\text{-}F}$ = 3.2 Hz), 128.4, 127.8, 124.4, 123.2 (dd, $^2J_{C\text{-}F}$ = 14.8 Hz, $^2J_{C\text{-}F}$ = 6.7 Hz), 115.3 (d, $^2J_{C\text{-}F}$ = 22.8 Hz), 76.4, 62.5 (d, $^2J_{C\text{-}P}$ = 6.7 Hz), 62.0 (d, $^2J_{C\text{-}P}$ = 7.3 Hz), 49.7 (d, $^3J_{C\text{-}P}$ = 15.5 Hz), 32.9 (d, $^1J_{C\text{-}P}$ = 141.0 Hz), 27.2 (d, $^2J_{C\text{-}P}$ = 2.6 Hz), 16.4 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 16.2 (d, $^3J_{C\text{-}P}$ = 5.6 Hz). IR: 3248 cm^{-1} (N–H), 1232 cm^{-1} (P═O). Anal. Calcd for $C_{20}H_{27}FNO_4P$: C, 60.75; H, 6.88; N, 3.54. Found: C, 60.23; H, 6.59; N, 3.72.

4.5.3. [3-Benzyloxyamino-1-(2,6-dimethylphenyl)-propyl]-phosphonic acid diethyl ester (12c). Yield: 75%. Mp: 53.3 °C. ^1H NMR (DMSO-d_6), δ (ppm): 7.35–7.24 (m, 5H), 7.17–7.13 (m, 1H), 7.06–7.02 (m, 1H), 7.97–7.91 (m, 1H), 6.63 (t, 1H, J = 4.8 Hz), 4.56 (dd, 2H, J_{AB} = 16.8 Hz), 4.01–3.91 (m, 2H), 3.84–3.74 (m, 1H), 3.70–3.60 (m, 1H), 3.49 (ddd, 1H, J_{H-P} = 22.9 Hz, J_{AB} = 10.9 Hz), 2.71–2.61 (m, 1H), 2.50–2.43 (m, 1H), 2.28–2.15 (m, 7H), 2.03–1.92 (m, 1H), 1.20 (t, 3H, J = 7.1 Hz), 1.00 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 138.2, 135.9 (d, $^2J_{C\text{-}P}$ = 3.2 Hz), 134.7 (d, $^3J_{C\text{-}P}$ = 8.2 Hz), 134.2 (d, $^3J_{C\text{-}P}$ = 6.5 Hz), 130.5, 128.9, 128.8, 128.7, 128.2, 128.1, 128.0, 76.8, 62.9 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 62.1 (d, $^2J_{C\text{-}P}$ = 7.4 Hz), 50.0 (d, $^3J_{C\text{-}P}$ = 16.0 Hz), 50.5 (d, $^3J_{C\text{-}P}$ = 16.0 Hz), 36.9 (d, $^1J_{C\text{-}P}$ = 138.8 Hz), 28.3, 21.5, 20.1, 16.8 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 16.6 (d, $^3J_{C\text{-}P}$ = 5.7 Hz). IR: 3263 cm^{-1} (N–H), 1230 cm^{-1} (P═O). Anal. Calcd for $C_{22}H_{32}NO_4P$: C, 65.17; H, 7.95; N, 3.45. Found: C, 64.92; H, 7.41; N, 3.45.

4.5.4. (3-Benzyloxyamino-1-benzyloxymethyl-propyl)-phosphonic acid diethyl ester (21). Dioxolane **19** (50 mmol) was dissolved in dry toluene (50 mL), cooled down to −78 °C and treated with 50 mmol of *n*-butyllithium (2.5 M solution in toluene). After stirring for 1 h under nitrogen atmosphere, benzylchlormethylether (50 mmol) was added in one portion. The reaction mixture was allowed to warm up to room temperature and stirred overnight. A solution of NH_4Cl (10%, 50 mL) was added and the product was extracted with diethyl ether. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure and the remaining oil was purified by column chromatography on silica gel using EtOAc and *n*-hexane (9:1) as eluents. The resulting dioxolane **20** was reacted with 2 M HCl (100 mL) and acetone (10 mL) at 50 °C for 3 h. Acetone was removed and the aqueous layer was extracted with dichloromethane (3× 30 mL). Afterwards, the organic layer was dried over $MgSO_4$ and the solvent was evaporated. Without further purification, the resulting crude aldehyde was converted into the corresponding

hydroxylamine **21** as described for compounds **2**. Yield: 45%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.35–7.47 (m, 10H), 4.81 (s, 2H), 4.58 (s, 2H), 4.21–4.10 (m, 4H), 3.88–3.76 (m, 1H), 3.74–3.63 (m, 1H), 3.28–3.09 (m, 2H), 2.41–2.26 (m, 1H), 2.21–1.93 (m, 2H), 1.32 (t, 6H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 138.4, 128.8, 128.2, 128.1, 76.6, 73.6, 62.2 (d, $^2J_{C\text{-}P}$ = 6.4 Hz), 62.1 (d, $^2J_{C\text{-}P}$ = 6.4 Hz), 50.5 (d, $^3J_{C\text{-}P}$ = 10.1 Hz), 35.9 (d, $^1J_{C\text{-}P}$ = 138.2 Hz), 25.1 (d, $^2J_{C\text{-}P}$ = 3.4 Hz), 16.8 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), IR: 3249 cm^{-1} (N–H), 1232 cm^{-1} (P═O). Anal. Calcd for $C_{22}H_{32}NO_5P$: C, 62.69; H, 7.65; N, 3.32. Found: C, 62.29; H, 7.75; N, 3.20.

4.6. General procedure for the preparation of [3-(benzyloxy-formyl-amino)-propyl]-phosphonic acid diethyl esters 3a–f, 13a–c and 22

Formic acid (500 mmol) was treated with acetic acid anhydride (50 mmol) and stirred under exclusion of humidity. After 20 min, the solution was cooled to 0 °C, and the respective hydroxylamine **2**, **12**, **21** (10 mmol), dissolved in dry THF (20 mL), was added dropwise. After 10 min, the mixture was allowed to warm up to room temperature and stirred for another hour. The solution was treated with EtOAc (200 mL) and successively washed with water (3× 50 mL), with aqueous KOH (0.1 M, 3× 25 mL) and once again with water. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc to give [3-(benzyloxy-formyl-amino)-propyl]-phosphonic acid diethyl esters **3**, **13**, **22** as colourless oils.

4.6.1. [3-(Benzyloxy-formyl-amino)-1-methyl-propyl]-phosphonic acid diethyl ester (3a). Yield: 97%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.33–7.94 (m, 1H), 7.45–7.36 (m, 5H), 4.91 (dd, 2H, J_{AB} = 16.1 Hz), 4.03–3.93 (m, 4H), 3.80–3.50 (m, 2H), 2.40–1.93 (m, 1H), 1.88–1.74 (m, 1H), 1.56–1.40 (m, 1H), 1.21 (t, 6H, J = 7.1 Hz), 1.07 (dd, 3H, $^3J_{H\text{-}P}$ = 18.4 Hz, $J_{H\text{-}H}$ = 7.1 Hz). ^{13}C NMR (DMSO-d_6): 163.1, 130.0, 129.1, 128.8, 77.1, 61.5 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 61.4 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 41.2, 27.5 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 27.3, 16.7 (d, $^3J_{C\text{-}P}$ = 5.6 Hz), 13.2. IR: 1680 cm^{-1} (C═O), 1241 cm^{-1} (P═O). HRFAB-MS $C_{16}H_{26}NO_5P$ $[M+H]^+$: calculated 344.1627; found 344.1638.

4.6.2. [3-(Benzyloxy-formyl-amino)-1-phenyl-propyl]-phosphonic acid diethyl ester (3b). Yield: 92%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.28–7.65 (m, 1H), 7.40–7.26 (m, 10H), 4.83 (s, 2H), 4.02–3.88 (m, 2H), 3.86–3.66 (m, 2H), 3.55–3.39 (m, 1H), 3.36–3.25 (m, 1H), 3.23–3.09 (m, 1H), 2.33–2.22 (m, 1H), 2.15–2.00 (m, 1H), 1.17 (t, 3H, J = 7.1 Hz), 1.01 (t, 3H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 162.6, 135.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 134.6, 129.4, 129.1, 129.0, 128.6, 128.4, 128.3, 127.0 (d, $^3J_{C\text{-}P}$ = 2.5 Hz), 76.0, 61.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 61.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 41.5, 40.4 (d, $^1J_{C\text{-}P}$ = 132.8 Hz), 26.6 (d, $^2J_{C\text{-}P}$ = 3.6 Hz), 16.1 (d, $^3J_{C\text{-}P}$ = 5.6 Hz), 15.9 (d, $^3J_{C\text{-}P}$ = 5.6 Hz). IR: 1680 cm^{-1} (C═O), 1245 cm^{-1} (P═O). Anal. Calcd for $C_{21}H_{28}NO_5P$: C, 62.21; H, 6.96; N, 3.45. Found: C, 61.76; H, 7.08; N, 3.67. HRFAB-MS $C_{20}H_{28}NO_4P$ $[M+H]^+$: calculated 406.1783; found 406.1769.

4.6.3. [3-(Benzyloxy-formyl-amino)-1-ethyl-propyl]-phosphonic acid diethyl ester (3c). Yield: 99%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.25 + 8.01 (2s, 1H), 7.45–7.36 (m, 5H), 4.91 (s, 2H), 4.03–3.94 (m, 4H), 3.75–3.52 (m, 2H), 1.93–1.82 (m, 1H), 1.74–1.56 (m, 3H), 1.52–1.39 (m, 1H), 1.21 (t, 6H, J = 7.1 Hz), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 163.0, 129.9, 129.1, 128.8, 77.1, 61.4 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 61.3 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 40.5, 34.0 (d, $^1J_{C\text{-}P}$ = 138.9 Hz), 24.9 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 24.8 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 20.9, 16.7 (d, $^3J_{C\text{-}P}$ = 5.1 Hz), 11.9 (d, $^3J_{C\text{-}P}$ = 8.6 Hz). IR: 1679 cm^{-1} (C═O), 1239 cm^{-1} (P═O). HRFAB-MS $C_{17}H_{28}NO_5P$ $[M+H]^+$: calculated 358.1783; found 358.1791.

4.6.4. {1-[2-(Benzyloxy-formyl-amino)-ethyl]-2-methyl-propyl}-phosphonic acid diethyl ester (3d). Yield: 96%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.25 + 8.00 (2s, 1H), 7.45–7.36 (m, 5H), 4.91 (s, 2H), 4.04–3.94 (m, 4H), 3.75–3.52 (m, 2H), 2.11–1.99 (m, 1H), 1.87–1.62 (m, 3H), 1.22 (t, 6H, J = 7.1 Hz), 0.95–0.93 (m, 6H). ^{13}C NMR ($CDCl_3$), δ (ppm): 162.9, 129.5, 129.1, 128.7, 77.6, 61.6 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 61.3 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 43.5, 39.8 (d, $^1J_{C\text{-}P}$ = 137.8 Hz), 27.4 (d, $^2J_{C\text{-}P}$ = 2.6 Hz), 22.4, 21.5 (d, $^3J_{C\text{-}P}$ = 13.7 Hz), 19.1, 16.5 (d, $^3J_{C\text{-}P}$ = 5.6 Hz), 16.5 (d, $^3J_{C\text{-}P}$ = 5.6 Hz). IR: 1680 cm^{-1} (C═O), 1237 cm^{-1} (P═O). HRFAB-MS $C_{18}H_{30}NO_5P$ $[M+H]^+$: calculated 372.1940; found 372.1976.

4.6.5. {1-[2-(Benzyloxy-formyl-amino)-ethyl]-butyl}-phosphonic acid diethyl ester (3e). Yield: 93%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.24 + 8.01 (2s, 1H), 7.45–7.37 (m, 5H), 4.03–3.94 (m, 4H), 3.75–3.52 (m, 2H), 1.94–1.81 (m, 1H), 3.79–3.47 (m, 3H), 3.43–3.28 (m, 3H), 1.21 (t, 6H, J = 7.1 Hz), 0.85 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 163.0, 129.5, 129.1, 128.7, 77.7, 61.7 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 61.6 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 42.5, 33.5 (d, $^1J_{C\text{-}P}$ = 140.4 Hz), 30.5, 25.6, 20.6 (d, $^3J_{C\text{-}P}$ = 9.7 Hz), 16.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 14.0. IR: 1679 cm^{-1} (C═O), 1234 cm^{-1} (P═O). HRFAB-MS $C_{18}H_{30}NO_5P$ $[M+H]^+$: calculated 372.1940; found 372.1940.

4.6.6. [3-(Benzyloxy-formyl-amino)-1,1-dimethyl-propyl]-phosphonic acid diethyl ester (3f). Yield: 98%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.21 + 8.02 (2s, 1H), 7.45–7.36 (m, 5H), 4.90 (s, 2H), 4.06–3.98 (m, 4H), 3.70–3.49 (m, 2H), 1.75–1.67 (m, 2H), 1.23 (t, 6H, J = 7.1 Hz), 1.08 (d, 6H, $^3J_{H\text{-}P}$ = 16.5 Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 162.5, 134.8, 129.4, 128.6, 128.4, 76.7, 61.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 43.7, 33.5, 32.7 (d, $^1J_{C\text{-}P}$ = 142.4 Hz), 21.7 (d, $^2J_{C\text{-}P}$ = 2.0 Hz), 16.3 (d, $^3J_{C\text{-}P}$ = 5.1 Hz). IR: 1681 cm^{-1} (C═O), 1239 cm^{-1} (P═O). HRFAB-MS $C_{17}H_{28}NO_5P$ $[M+H]^+$: calculated 358.1783; found 358.1777.

4.6.7. [3-(Benzyloxy-formyl-amino)-1-(3,4-difluoro-phenyl)-propyl]-phosphonic acid diethyl ester (13a). Yield: 95%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.37–7.80 (m, 1H),

7.45–6.93 (m, 8H), 5.11–4.65 (m, 2H), 4.18–3.73 (m, 4H), 3.58–3.33 (m, 1H), 3.08–2.93 (m, 1H), 2.53–2.35 (m, 1H), 2.23–1.85 (m, 2H), 1.28 (t, 3H, J = 7.2 Hz), 1.14 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 163.5, 151.1 (dd, $^1J_{C\text{-}F}$ = 244.6 Hz), 150.1 (dd, $^1J_{C\text{-}F}$ = 246.5 Hz), 136.9, 132.6, 129.9, 129.6, 129.2, 125.9, 118.5 (dd, $^2J_{C\text{-}F}$ = 19.6 Hz, $^3J_{C\text{-}F}$ = 5.2 Hz), 117.8 (dd, $^2J_{C\text{-}F}$ = 18.3 Hz, $^3J_{C\text{-}F}$ = 4.1 Hz), 78.4, 63.2 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 62.6 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 42.7 (d, $^3J_{C\text{-}P}$ = 14.7 Hz), 41.6 (d, $^1J_{C\text{-}P}$ = 141.0 Hz), 27.6 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 16.8 (d, $^3J_{C\text{-}P}$ = 5.9 Hz), 16.7 (d, $^3J_{C\text{-}P}$ = 5.9 Hz). IR: 1682 cm^{-1} (C═O), 1242 cm^{-1} (P═O). EI-MS $C_{21}H_{26}F_2NO_5P$: calculated 441; found 441.

4.6.8. [3-(Benzyloxy-formyl-amino)-1-(2-fluoro-phenyl)-propyl]-phosphonic acid diethyl ester (13b). Yield: 98%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.27–7.63 (m, 1H), 7.52–7.00 (m, 9H), 5.06–4.65 (m, 2H), 4.16–3.75 (m, 4H), 3.68–3.11 (m, 3H), 2.57–2.10 (m, 2H), 1.28 (t, 3H, J = 7.3 Hz), 1.11 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 163.4, 161.4 (dd, $^1J_{C\text{-}F}$ = 244.5 Hz, $^3J_{C\text{-}P}$ = 7.6 Hz), 134.6, 129.9, 129.8, 129.5, 129.1, 124.9, 115.9 (dd, $^2J_{C\text{-}F}$ = 22.2 Hz), 78.2, 63.1 (d, $^2J_{C\text{-}P}$ = 7.4 Hz), 62.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 42.8 (d, $^3J_{C\text{-}P}$ = 16.7 Hz), 33.4 (d, $^1J_{C\text{-}P}$ = 143.4 Hz), 26.7, 16.7 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 16.6 (d, $^3J_{C\text{-}P}$ = 5.7 Hz). IR: 1682 cm^{-1} (C═O), 1231 cm^{-1} (P═O). EI-MS $C_{21}H_{26}F_2NO_5P$: calculated 423; found 423.

4.6.9. [3-(Benzyloxy-formyl-amino)-1-(2,6-dimethyl-phenyl)-propyl]-phosphonic acid diethyl ester (13c). Yield: 94%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.28–7.46 (m, 1H), 7.42–6.92 (m, 8H), 5.05–4.62 (m, 2H), 4.13–3.75 (m, 4H), 3.71–3.28 (m, 3H), 2.52–2.33 (m, 2H), 2.31 (s, 3H), 2.25 (s, 3H), 1.28 (t, 3H, J = 7.2 Hz), 1.06 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 162.8, 136.1 (d, $^2J_{C\text{-}P}$ = 2.3 Hz), 134.8, 134.7, 133.1, 130.9, 129.8, 129.5, 129.1, 128.6, 128.4, 78.2, 63.2 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 62.4 (d, $^2J_{C\text{-}P}$ = 7.9 Hz), 42.9, 37.0 (d, $^1J_{C\text{-}P}$ = 138.9 Hz), 27.4, 21.5, 19.9, 16.8 (d, $^3J_{C\text{-}P}$ = 6.2 Hz), 16.5 (d, $^3J_{C\text{-}P}$ = 5.8 Hz). IR: 1682 cm^{-1} (C═O), 1244 cm^{-1} (P═O). Anal. Calcd for $C_{23}H_{32}NO_5P$: C, 63.73; H, 7.44; N, 3.23. Found: C, 63.40; H, 7.67; N, 3.00.

4.6.10. [3-(Benzyloxy-formyl-amino)-1-benzyloxymethyl-propyl]-phosphonic acid diethyl ester (22). Yield: 85%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.26–7.84 (m, 1H), 7.51–7.16 (m, 10H), 5.10–4.70 (m, 2H), 4.51 (s, 2H), 4.14–4.02 (m, 4H), 3.88–3.42 (m, 4H), 2.24–1.93 (m, 3H), 1.35–1.21 (m, 6H). ^{13}C NMR ($CDCl_3$), δ (ppm): 163.5, 136.2, 134.7, 129.9, 129.5, 129.1, 128.8, 128.2, 77.2, 73.7, 68.7, 62.4 (d, $^2J_{C\text{-}P}$ = 6.4 Hz), 62.33 (d, $^2J_{C\text{-}P}$ = 6.4 Hz), 43.1, 35.8 (d, $^1J_{C\text{-}P}$ = 133.6 Hz), 24.7, 16.8 (d, $^3J_{C\text{-}P}$ = 6.2 Hz). IR: 1674 cm^{-1} (C═O), 1236 cm^{-1} (P═O). Anal. Calcd for $C_{23}H_{32}NO_6P$: C, 61.46; H, 7.18; N, 3.12. Found: C, 61.12; H, 7.44; N, 2.96.

4.7. General procedure for the preparation of [3-(acetyl-benzyloxy-amino)-propyl]-phosphonic acid diethyl esters 4a–f, 14a and 23

Acetic acid anhydride (20 mmol) was added to a solution of the respective hydroxylamine (**2**, **12**, **21**; 10 mmol) in dry THF (10 mL) and stirred at room temperature for 2 h. After addition of EtOAc (100 mL), the organic layer was washed twice with aqueous KOH (0.1 M, 50 mL), water (50 mL) and 3 times with aqueous 1 M HCl. The organic layer was dried over $MgSO_4$, evaporated, and the residue was purified by column chromatography on silica gel with EtOAc to give [3-(acetyl-benzyloxy-amino)-propyl]-phosphonic acid diethyl esters **4**, **14** and **23** as colourless oils.

4.7.1. [3-(Acetyl-benzyloxy-amino)-1-methyl-propyl]-phosphonic acid diethyl ester (4a). Yield: 78%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.46–7.37 (m, 5H), 4.88 (dd, 2H, J_{AB} = 15.8 Hz), 4.02–3.92 (m, 4H), 3.81–3.74 (m, 1H), 3.67–3.60 (m, 1H), 2.04–1.91 (m, 4H), 1.87–1.73 (m, 1H), 1.51–1.39 (m, 1H), 1.20 (t, 6H, J = 7.1 Hz), 1.07 (dd, 3H, $^3J_{H\text{-}P}$ = 18.4 Hz, $J_{H\text{-}H}$ = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 172.3, 134.5, 129.2, 129.0, 128.7, 76.4, 61.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 61.6 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 43.3, 28.5 (d, $^1J_{C\text{-}P}$ = 142.4 Hz), 27.6, 20.5, 16.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 13.4 (d, $^2J_{C\text{-}P}$ = 5.1 Hz). IR: 1662 cm^{-1} (C═O), 1234 cm^{-1} (P═O). Anal. Calcd for $C_{17}H_{28}NO_5P$: C, 57.13; H, 7.90; N, 3.92. Found: C, 57.00; H, 7.57; N, 4.07.

4.7.2. [3-(Acetyl-benzyloxy-amino)-1-phenyl-propyl]-phosphonic acid diethyl ester (4b). Yield: 73%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.41–7.25 (m, 10H), 4.78 (dd, 2H, J_{AB} = 18.3 Hz), 4.00–3.89 (m, 2H), 3.86–3.76 (m, 1H), 3.75–3.66 (m, 1H), 3.59–3.49 (m, 1H), 3.38–3.33 (m, 1H), 3.23–3.12 (m, 1H), 2.32–2.21 (m, 1H), 2.11–2.01 (m, 1H), 1.96 (s, 3H), 1.17 (t, 3H, J = 7.1 Hz), 1.01 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 172.2, 135.2 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 134.4, 129.4, 129.3, 129.2, 128.9, 128.7, 128.6, 128.6, 127.4 (d, $^3J_{C\text{-}P}$ = 3.1 Hz), 76.3, 62.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 61.9 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 43.8, 42.2 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 26.9 (d, $^2J_{C\text{-}P}$ = 2.0 Hz), 20.5, 16.4 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 16.2 (d, $^3J_{C\text{-}P}$ = 6.1 Hz). IR: 1665 cm^{-1} (C═O), 1245 cm^{-1} (P═O). Anal. Calcd for $C_{22}H_{30}NO_5P$: C, 63.00; H, 7.21; N, 3.34. Found: C, 62.70; H, 7.32; N, 3.48.

4.7.3. [3-(Acetyl-benzyloxy-amino)-1-ethyl-propyl]-phosphonic acid diethyl ester (4c). Yield: 83%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.47–7.36 (m, 5H), 4.88 (s, 2H), 4.03–3.93 (m, 4H), 3.78–3.62 (m, 2H), 2.02 (s, 3H), 1.93–1.82 (m, 1H), 1.74–1.56 (m, 3H), 1.52–1.40 (m, 1H), 1.21 (t, 6H, J = 7.1 Hz), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 172.2, 134.5, 129.3, 129.0, 128.7, 76.32 (d, $^1J_{C\text{-}P}$ = 140.4 Hz), 25.0, 21.4 (d, $^2J_{C\text{-}P}$ = 4.1 Hz), 20.5, 16.5 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 12.0 (d, $^2J_{C\text{-}P}$ = 10.2 Hz). IR: 1665 cm^{-1} (C═O), 1239 cm^{-1} (P═O). HRFAB-MS $C_{18}H_{30}NO_5P$ $[M+H]^+$: calculated 372.1940; found 372.1958.

4.7.4. {1-[2-(Acetyl-benzyloxy-amino)-ethyl]-2-methyl-propyl}-phosphonic acid diethyl ester (4d). Yield: 73%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.45–7.37 (m, 5H), 4.87 (s, 2H), 4.03–3.94 (m, 4H), 3.79–3.72 (m, 1H), 3.68–3.61 (m, 1H), 2.02 (s, 3H), 1.86–1.62 (m, 3H), 1.21 (t, 6H, J = 7.1 Hz), 0.95–0.92 (m, 6H). ^{13}C NMR ($CDCl_3$), δ (ppm): 172.1, 129.3, 129.0, 128.7, 76.2, 61.6

(d, $^2J_{C\text{-}P}$ = 7.1 Hz), 61.2 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 44.8, 39.9 (d, $^1J_{C\text{-}P}$ = 137.3 Hz), 27.5 (d, $^2J_{C\text{-}P}$ = 2.6 Hz), 22.3, 21.5 (d, $^3J_{C\text{-}P}$ = 14.3 Hz), 20.6, 19.1 (d, $^2J_{C\text{-}P}$ = 2.5 Hz), 16.6 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 16.5 (d, $^3J_{C\text{-}P}$ = 5.6 Hz). IR: 1665 cm^{-1} (C═O), 1239 cm^{-1} (P═O). HRFAB-MS $C_{19}H_{32}NO_5P$ $[M+H]^+$: calculated 386.2096; found 386.2117.

4.7.5. {1-[2-(Acetyl-benzyloxy-amino)-ethyl]-butyl}-phosphonic acid diethyl ester (4e). Yield: 79%. ^1H NMR (DMSO-d_6), δ (ppm): 7.45–7.37 (m, 5H), 4.87 (s, 2H), 4.03–3.93 (m, 4H), 3.78–3.62 (m, 2H), 2.02 (s, 3H), 1.93–1.46 (m, 4H), 1.43–1.28 (m, 3H), 1.21 (t, 6H, J = 7.1 Hz), 0.85 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 172.2, 134.5, 129.3, 129.0, 128.7, 76.3, 61.6 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 61.5 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 43.8, 33.5 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 30.5, (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 25.5, 20.6 (d, $^3J_{C\text{-}P}$ = 10.2 Hz), 20.5, 16.5 (d, $^3J_{C\text{-}P}$ = 5.1 Hz), 14.0. IR: 1664 cm^{-1} (C═O), 1238 cm^{-1} (P═O). HRFAB-MS $C_{19}H_{32}NO_5P$ $[M+H]^+$: calculated 386.2096; found 386.2108.

4.7.6. [3-(Acetyl-benzyloxy-amino)-1,1-dimethyl-propyl]-phosphonic acid diethyl ester (4f). Yield: 89%. ^1H NMR (DMSO-d_6), δ (ppm): 7.45–7.36 (m, 5H), 4.87 (s, 2H), 4.05–3.98 (m, 4H), 3.70–3.66 (m, 2H), 2.00 (s, 3H), 1.73–1.65 (m, 2H), 1.22 (t, 6H, J = 7.1 Hz), 1.07 (d, 6H, $^3J_{H\text{-}P}$ = 16.5 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 172.2, 134.6, 129.2, 128.9, 128.7, 76.3, 61.9 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 41.6, 34.0, 33.4 (d, $^1J_{C\text{-}P}$ = 141.4 Hz), 22.3 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 20.6, 16.6 (d, $^3J_{C\text{-}P}$ = 6.1 Hz). IR: 1665 cm^{-1} (C═O), 1230 cm^{-1} (P═O). HRFAB-MS $C_{18}H_{30}NO_5P$ $[M+H]^+$: calculated 372.1940; found 372.1977.

4.7.7. [3-(Acetyl-benzyloxy-amino)-1-(3,4-difluoro-phenyl)-propyl]-phosphonic acid diethyl ester (14a). Yield: 95%. ^1H NMR ($CDCl_3$), δ (ppm): 7.41–6.93 (m, 8H), 4.72 (s, 2H), 4.13–3.73 (m, 4H), 3.66–3.32 (m, 2H), 3.10–2.89 (m, 1H), 2.51–2.34 (m, 1H), 2.22–2.08 (m, 1H), 2.04 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz), 1.14 (t, 3H, J = 6.6 Hz).^{13}C NMR ($CDCl_3$): 164.9, 150.2 (dd, $^1J_{C\text{-}F}$ = 243.6 Hz, $^2J_{C\text{-}F}$ = 13.1 Hz), 149.7 (dd, $^1J_{C\text{-}F}$ = 247.1 Hz, $^2J_{C\text{-}F}$ = 16.5 Hz), 134.2, 132.5, 130.9, 128.8, 129.1, 129.2, 125.4, 118.1 (dd, $^2J_{C\text{-}F}$ = 17.1 Hz, $^3J_{C\text{-}F}$ = 6.2 Hz), 117.3 (dd, $^2J_{C\text{-}F}$ = 17.1 Hz, $^3J_{C\text{-}F}$ = 2.8 Hz), 76.6, 62.8 (d, $^2J_{C\text{-}P}$ = 7.3 Hz), 62.2 (d, $^2J_{C\text{-}P}$ = 6.5 Hz), 43.8, 41.6 (d, $^1J_{C\text{-}P}$ = 139.8 Hz), 27.0, 20.4, 16.4 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 16.3 (d, $^3J_{C\text{-}P}$ = 5.4 Hz). IR: 1663 cm^{-1} (C═O), 1242 cm^{-1} (P═O). Anal. Calcd for $C_{22}H_{28}F_2NO_5P$: C, 58.02; H, 6.20; N, 3.08. Found: C, 58.24; H, 6.19; N, 3.36.

4.7.8. [3-(Acetyl-benzyloxy-amino)-1-benzyloxymethyl-propyl]-phosphonic acid diethyl ester (23). Yield: 79%. ^1H NMR ($CDCl_3$), δ (ppm): 7.42–7.27 (m, 10H), 4.80 (s, 2H), 4.51 (s, 2H), 4.14–4.02 (m, 4H), 3.93–3.57 (m, 4H), 2.22–1.91 (m, 6H), 1.31–1.22 (m, 6H). ^{13}C NMR ($CDCl_3$), δ (ppm): 172.7, 138.4, 134.9, 129.6, 129.3, 129.1, 128.8, 128.1, 76.7, 73.6, 68.8, 62.3 (d, $^2J_{C\text{-}P}$ = 6.3 Hz), 62.1 (d, $^2J_{C\text{-}P}$ = 6.3 Hz), 44.2, 35.9 (d, $^1J_{C\text{-}P}$ = 139.7 Hz), 24.7 (d, $^2J_{C\text{-}P}$ = 3.0 Hz), 21.0, 16.8 (d, $^3J_{C\text{-}P}$ = 5.9 Hz). IR: 1660 cm^{-1} (C═O), 1234 cm^{-1} (P═O). HRFAB-MS $C_{24}H_{34}NO_6P$ $[M+H]^+$: calculated 463.5155; found 463.5124.

4.8. General procedure for the preparation of [3-(acyl-benzyloxy-amino)-propyl]-(2,2-dimethyl-propionyloxy-methoxy)- phosphinoyloxymethyl esters 5a–f, 6a–f, 15a–c, 16a, 24 and 25

Trimethylsilylbromide (15 mmol) was added to a stirred solution of phosphonic acid diethyl esters **3**, **4**, **13**, **14**, **22** and **23** (3 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After 1 h, the solution was allowed to warm up to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dry THF (10 mL) and treated with water (0.1 mL). After 5 min, the solvent was evaporated and the residue was dried in vacuo overnight. For the alkylation step, the resulting oil was dissolved in anhydrous DMF (20 mL), treated with triethylamine (9 mmol) and stirred for 5 min. Chloromethyl pivalate (30 mmol) was added and the mixture was stirred at 70 °C for 2 h. Another 3 mmol of triethylamine and 5 mmol of chloromethyl pivalate were added and the solution was stirred for further 2 h. The procedure of adding triethylamine and chloromethyl pivalate was repeated once again. After an overall time of 6 h, the mixture was allowed to cool down and stirred overnight at room temperature. Diethyl ether (100 mL) was added and the solution was successively washed with water (50 mL), twice with saturated aqueous $NaHCO_3$-solution (50 mL) and again with water (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography on silica gel (Et_2O) to give [3-(acyl-benzyloxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl esters **5**, **6**, **15**, **16**, **24** and **25** as colourless products.

4.8.1. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-methyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (5a). Yield: 30%. ^1H NMR ($CDCl_3$), δ (ppm): 8.16 (s, 1H), 7.38 (m, 5H), 5.71–5.64 (m, 4H), 4.85 (s, 2H), 3.82–3.52 (m, 2H), 2.25–2.09 (m, 1H), 2.02–1.89 (m, 1H), 1.73–1.57 (m, 1H), 1.24–1.15 (m, 21H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 163.1, 134.3, 129.5, 129.2, 128.8, 81.5 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 77.8, 41.7 (d, $^3J_{C\text{-}P}$ = 14.2 Hz), 38.8, 28.9 (d, $^1J_{C\text{-}P}$ = 142.4 Hz), 27.0, 26.9, 12.8. IR: 1753 cm^{-1} (C═O), 1680 cm^{-1} (C═O), 1255 cm^{-1} (P═O). Anal. Calcd for $C_{24}H_{38}NO_9P$: C, 55.92; H, 7.43; N, 2.72. Found: C, 55.80; H, 7.51; N, 2.72.

4.8.2. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-phenyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (5b). Yield: 43%. ^1H NMR ($CDCl_3$), δ (ppm): 8.18–7.60 (m, 1H), 7.38–7.27 (m, 10H), 5.60 (ddd, 2H, $^3J_{H\text{-}P}$ = 12.0 Hz, J_{AB} = 17.0 Hz), 5.41 (ddd, 2 H, $^3J_{H\text{-}P}$ = 11.7 Hz, J_{AB} = 24.7 Hz), 4.98–4.64 (m, 2H), 3.54–3.07 (m, 3H), 2.50–2.39 (m, 1H), 2.32–2.16 (m, 1H), 1.21 (s, 9H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.8, 176.8, 163.0, 134.2, 133.5, 129.5, 129.4, 129.3, 129.1, 128.9,

128.7, 127.9, 81.9 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 81.7 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 77.8, 42.2 (d, $^{1}J_{C\text{-}P}$ = 138.4 Hz), 42.1, 38.7, 38.7, 26.8, 26.8, 26.6. IR: 1753 cm^{-1} (C═O), 1680 cm^{-1} (C═O), 1260 cm^{-1} (P═O). Anal. Calcd for $C_{29}H_{40}NO_9P$: C, 60.30; H, 6.98; N, 2.42. Found: C, 59.93; H, 7.07; N, 2.42.

4.8.3. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-ethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (5c). Yield: 27%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.16 (s, 1H), 7.44–7.32 (m, 5H), 5.72–5.64 (m, 4H), 5.02–4.78 (m, 2H), 3.83–3.40 (m, 2H), 2.14–1.67 (m, 4H), 1.59–1.44 (m, 1H), 1.23 (s, 18H), 0.99 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 163.0, 134.4, 129.5, 129.1, 128.8, 81.4 (d, $^{2}J_{C\text{-}P}$ = 6.6 Hz), 77.6, 42.1, 38.8, 35.6 (d, $^{1}J_{C\text{-}P}$ = 142.4 Hz), 26.9, 24.7, 20.9 (d, $^{2}J_{C\text{-}P}$ = 3.6 Hz), 11.8 (d, $^{3}J_{C\text{-}P}$ = 10.2 Hz). IR: 1753 cm^{-1} (C═O), 1680 cm^{-1} (C═O), 1257 cm^{-1} (P═O). Anal. Calcd for $C_{25}H_{40}NO_9P$: C, 56.70; H, 7.61; N, 2.64. Found: C, 56.63; H, 7.71; N, 2.66.

4.8.4. 2,2-Dimethyl-propionic acid {1-[2-(benzyloxy-formyl-amino)-ethyl]-2-methyl-propyl}-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (5d). Yield: 33%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.15 (s, 1H), 7.38 (m, 5H), 5.73–5.64 (m, 4H), 5.03–4.79 (m, 2H), 3.80–3.39 (m, 2H), 2.24–2.09 (m, 1H), 2.05–1.69 (m, 3H), 1.23 (s, 18H), 1.02–0.95 (m, 6H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 162.9, 134.3, 129.6, 129.1, 128.8, 81.4 (d, $^{2}J_{C\text{-}P}$ = 6.1 Hz), 81.2 (d, $^{2}J_{C\text{-}P}$ = 6.1 Hz), 77.5, 43.2, 40.4 (d, $^{1}J_{C\text{-}P}$ = 142.4 Hz), 38.8, 27.3 (d, $^{2}J_{C\text{-}P}$ = 2.6 Hz), 26.9, 22.2 (d, $^{2}J_{C\text{-}P}$ = 2.0 Hz), 21.3 (d, $^{3}J_{C\text{-}P}$ = 13.2 Hz), 19.0. IR: 1753 cm^{-1} (C═O), 1680 cm^{-1} (C═O), 1255 cm^{-1} (P═O). Anal. Calcd for $C_{26}H_{42}NO_9P$: C, 57.45; H, 7.79; N, 2.58. Found: C, 57.42; H, 7.89; N, 2.60.

4.8.5. 2,2-Dimethyl-propionic acid {1-[2-(benzyloxy-formyl-amino)-ethyl]-butyl}-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (5e). Yield: 23%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.15 (s, 1H), 7.38 (m, 5H), 5.68 (d, 4H, $^{3}J_{H\text{-}P}$ = 12.5 Hz), 5.05–4.77 (m, 2H), 3.81–3.36 (m, 2H), 2.12–1.77 (m, 3H), 1.73–1.59 (m, 1H), 1.52–1.30 (m, 3H), 1.23 (s, 18H), 0.89 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 163.0, 134.4, 129.6, 129.1, 128.8, 81.5 (d, $^{2}J_{C\text{-}P}$ = 6.1 Hz), 81.4 (d, $^{2}J_{C\text{-}P}$ = 6.1 Hz), 77.6, 42.2, 38.8, 34.1 (d, $^{1}J_{C\text{-}P}$ = 142.4 Hz), 30.0 (d, $^{2}J_{C\text{-}P}$ = 2.0 Hz), 26.9, 25.3 (d, $^{2}J_{C\text{-}P}$ = 2.0 Hz), 20.4 (d, $^{3}J_{C\text{-}P}$ = 10.7 Hz), 13.9. IR: 1753 cm^{-1} (C═O), 1680 cm^{-1} (C═O), 1252 cm^{-1} (P═O). HRFAB-MS $C_{26}H_{42}NO_9P$ [M+H]$^{+}$: calculated 544.2675; found 544.2643.

4.8.6. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1,1-dimethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (5f). Yield: 22%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.13 (s, 1H), 7.38 (m, 5H), 5.74–5.63 (m, 4H), 4.84 (s, 2H), 3.75–3.44 (m, 2H), 1.93–1.81 (m, 2H), 1.24–1.15 (m, 24H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 162.9, 134.4, 129.5, 129.1, 128.8, 81.5 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 77.7, 40.1, 38.8, 33.6 (d, $^{1}J_{C\text{-}P}$ = 139.9 Hz), 33.5, 26.9, 21.7. IR: 1753 cm^{-1} (C═O), 1680 cm^{-1} (C═O), 1256 cm^{-1} (P═O). Anal. Calcd for $C_{25}H_{40}NO_9P$: C, 56.70; H, 7.61; N, 2.64. Found: C, 56.49; H, 7.38; N, 2.67.

4.8.7. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-methyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (6a). Yield: 35%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.39–7.37 (m, 5H), 5.71–5.63 (m, 4H), 4.82 (s, 2H), 3.85–3.76 (m, 1H), 3.73–3.66 (m, 1H), 2.23–2.10 (m, 1H), 2.07 (s, 3H), 2.02–1.88 (m, 1H), 1.71–1.58 (m, 1H), 1.22 + 1.21 (2s, 18H), 1.23–1.16 (m, 21H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 172.3, 134.4, 129.3, 129.0, 128.7, 81.5 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 81.4 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 76.5, 43.1, 38.7, 29.1 (d, $^{1}J_{C\text{-}P}$ = 141.4 Hz), 27.1, 26.9, 20.5, 12.9 (d, $^{2}J_{C\text{-}P}$ = 6.1 Hz). IR: 1753 cm^{-1} (C═O), 1666 cm^{-1} (C═O), 1258 cm^{-1} (P═O). HRFAB-MS $C_{25}H_{40}NO_9P$ [M+H]$^{+}$: calculated 530.2519; found 530.2542.

4.8.8. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-phenyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (6b). Yield: 64%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.37–7.27 (m, 10H), 5.59 (ddd, 2H, $^{3}J_{H\text{-}P}$ = 12.2 Hz, J_{AB} = 15.0 Hz), 5.40 (ddd, 2H, $^{3}J_{H\text{-}P}$ = 12.2 Hz, J_{AB} = 22.8 Hz), 4.68 (dd, 2H, J_{AB} = 11.2 Hz), 3.60–3.42 (m, 2H), 3.17 (ddd, 1H, $^{2}J_{H\text{-}P}$ = 23.9 Hz, J_{AB} = 11.5 Hz), 2.48–2.37 (m, 1H), 2.34–2.22 (m, 1H), 1.98 (s, 3H), 1.20 (s, 9H), 1.16 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.8, 172.2, 134.3, 133.8 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 129.4, 129.3, 129.2, 129.0, 128.8, 128.8, 128.7, 127.8, 127.8, 81.9, (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 81.7 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 76.4, 43.6, 42.4 (d, $^{1}J_{C\text{-}P}$ = 138.4 Hz), 38.7, 38.6, 26.8, 26.8, 26.3, 20.4. IR: 1753 cm^{-1} (C═O), 1667 cm^{-1} (C═O), 1260 cm^{-1} (P═O). Anal. Calcd for $C_{30}H_{42}NO_9P$: C, 60.90; H, 7.16; N, 2.37. Found: C, 60.89; H, 7.15; N, 2.48.

4.8.9. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-ethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (6c). Yield: 29%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.40–7.37 (m, 5H), 5.71–5.64 (m, 4H), 4.83 (s, 2H), 3.84–3.70 (m, 2H), 2.13–1.96 (m, 4H), 1.91–1.69 (m, 3H), 1.60–1.46 (m, 1H), 1.22 (s, 18H), 0.99 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 172.2, 134.4, 129.3, 129.0, 128.7, 81.4 (d, $^{2}J_{C\text{-}P}$ = 6.6 Hz), 81.4 (d, $^{2}J_{C\text{-}P}$ = 6.6 Hz), 76.4, 43.5, 38.7, 35.7 (d, $^{1}J_{C\text{-}P}$ = 138.4 Hz), 26.9, 24.6, 21.0 (d, $^{2}J_{C\text{-}P}$ = 4.1 Hz), 20.5, 11.8 (d, $^{3}J_{C\text{-}P}$ = 10.2 Hz). IR: 1753 cm^{-1} (C═O), 1666 cm^{-1} (C═O), 1252 cm^{-1} (P═O). Anal. Calcd for $C_{26}H_{42}NO_9P$: C, 57.45; H, 7.79; N, 2.58. Found: C, 57.37; H, 7.84; N, 2.59.

4.8.10. 2,2-Dimethyl-propionic acid {1-[2-(acetyl-benzyloxy-amino)-ethyl]-2-methyl-propyl}-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (6d). Yield: 43%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.40–7.36 (m, 5H), 5.71–5.65 (m, 4H), 4.83 (s, 2H), 3.83–3.70 (m, 2H), 2.23–2.11 (m, 1H), 2.07 (s, 3H), 2.00–1.76 (m, 3H), 1.22 (s, 18H), 1.00 (d, 3H, J = 7.1 Hz), 0.98 (d, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 172.1, 134.5, 129.4, 129.0, 128.7, 81.4 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 81.3 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 76.3, 44.6, 40.5 (d, $^{1}J_{C\text{-}P}$ = 135.3 Hz), 38.7, 27.3 (d, $^{2}J_{C\text{-}P}$ = 2.0 Hz), 26.9, 22.0 (d,

$^{2}J_{C\text{-}P}$ = 3.1 Hz), 21.3 (d, $^{3}J_{C\text{-}P}$ = 14.2 Hz), 20.5. IR: 1753 cm^{-1} (C=O), 1667 cm^{-1} (C=O), 1252 cm^{-1} (P=O). Anal. Calcd for $C_{27}H_{44}NO_9P$: C, 58.16; H, 7.95; N, 2.51. Found: C, 58.03; H, 8.01; N, 2.54.

4.8.11. 2,2-Dimethyl-propionic acid {1-[2-(acetyl-benzyloxy-amino)-ethyl]-butyl}-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (6e). Yield: 46%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.40–7.36 (m, 5H), 5.71–5.64 (m, 4H), 4.83 (s, 2H), 3.83-3.70 (m, 2H), 2.09–1.96 (m, 4H), 1.93–1.77 (m, 2H), 1.73–1.59 (m, 1H), 1.51–1.31 (m, 3H), 1.22 (s, 18H), 0.88 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 172.2, 134.5, 129.3, 129.0, 128.7, 81.4 (d, $^{2}J_{C\text{-}P}$ = 6.1 Hz), 81.4 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 76.4, 43.5, 38.7, 34.1 (d, $^{1}J_{C\text{-}P}$ = 138.4 Hz), 33.0 (d, $^{2}J_{C\text{-}P}$ = 4.1 Hz), 26.9, 25.2, 20.5, 20.4 (d, $^{3}J_{C\text{-}P}$ = 10.7 Hz), 14.0. IR: 1753 cm^{-1} (C=O), 1666 cm^{-1} (C=O), 1247 cm^{-1} (P=O). HRFAB-MS $C_{27}H_{44}NO_9P$ [M+H]$^{+}$: calculated 558.2832; found 558.2811.

4.8.12. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1,1-dimethyl-propyl]-(2,2-dimethyl-propionyloxy-methoxy)-phosphinoyloxymethyl ester (6f). Yield: 38%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.40–7.36 (m, 5H), 5.69 (ddd, 4H, J_{AB} = 20.3 Hz, $^{3}J_{HP}$ = 12.1 Hz), 4.82 (s, 2H), 3.77–3.73 (m, 2H), 2.05 (s, 3H), 1.92–1.83 (m, 2H), 1.22 (s, 18H), 1.19 (d, 6H, $^{3}J_{HP}$ = 17.8 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.8, 172.2, 134.5, 129.3, 129.0, 128.7, 81.5 (d, $^{2}J_{C\text{-}P}$ = 7.1 Hz), 76.4, 41.3, 38.7, 33.6 (d, $^{1}J_{C\text{-}P}$ = 139.4 Hz), 33.3, 26.9, 21.7, (d, $^{2}J_{C\text{-}P}$ = 2.0 Hz), 20.6. IR: 1752 cm^{-1} (C=O), 1667 cm^{-1} (C=O), 1251 cm^{-1} (P=O). Anal. Calcd for $C_{26}H_{42}NO_9P$: C, 57.45; H, 7.79; N, 2.58. Found: C, 57.36; H, 7.65; N, 2.64.

4.8.13. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(3,4-difluoro-phenyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (15a). Yield: 32%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.30–7.56 (m, 1H), 7.47–6.89 (m, 8H), 5.69 (m, 4H), 5.02–4.63 (m, 2H), 3.58-3.04 (m, 3H), 2.52–2.33 m, 1H), 2.21–2.05 (m, 1H), 1.21 (s, 9H), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$): 176.8, 163.1, 149.9 (dd, $^{1}J_{C\text{-}F}$ = 248.3 Hz, $^{2}J_{C\text{-}F}$ = 11.7 Hz), 134.0, 130.1, 129.5, 129.3, 128.8, 125.7, 118.5 (dd, $^{2}J_{C\text{-}F}$ = 17.8 Hz, $^{3}J_{C\text{-}F}$ = 4.2 Hz), 117.8 (dd, $^{2}J_{C\text{-}F}$ = 17.8 Hz, $^{3}J_{C\text{-}F}$ = 3.0 Hz), 81.8, 78.0, 41.8 (d, $^{3}J_{C\text{-}P}$ = 18.8 Hz), 38.7, 29.7, 26.8. IR: 1753 cm^{-1} (C=O), 1682 cm^{-1} (C=O), 1259 cm^{-1} (P=O). Anal. Calcd for $C_{29}H_{38}F_2NO_9P$: C, 56.77; H, 6.24; N, 2.28. Found: C, 57.02; H, 6.43; N, 2.47.

4.8.14. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(2-fluoro-phenyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (15b). Yield: 39%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.17 (s, 0.5H), 7.62 (s, 0.5 H), 7.40–7.26 (m, 5H), 7.11–7.03 (m, 2H), 7.01–6.96 (m, 1H), 5.55 (ddd, 2H, $J_{H\text{-}P}$ = 13.0 Hz, J_{AB} = 18.2 Hz), 5.44 (d, 2H, $J_{H\text{-}P}$ = 12.2 Hz), 4.80 (dd, 2H, J_{AB} = 12.5 Hz), 3.48-3.20 (m, 3H), 2.31–2.07 (m, 8H), 1.13 (s, 9H), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$): 176.8, 163.0, 161.0 (dd, $^{1}J_{C\text{-}F}$ = 247.6 Hz, $^{3}J_{C\text{-}P}$ = 10.9 Hz), 134.2, 129.5, 129.1, 128.7, 128.2, 124.6, 120.9 (dd, $^{2}J_{C\text{-}F}$ = 14.7 Hz, $^{2}J_{C\text{-}P}$ = 7.7 Hz), 115.7 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz), 81.8 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz), 77.8, 42.1 (d, $^{3}J_{C\text{-}P}$ = 14.4 Hz), 38.7, 33.7 (d, $^{1}J_{C\text{-}P}$ = 143.7 Hz), 26.8, 25.9. IR: 1753 cm^{-1} (C=O), 1682 cm^{-1} (C=O), 1263 cm^{-1} (P=O). Anal. Calcd for $C_{29}H_{39}FNO_9P$: C, 58.48; H, 6.60; N, 2.35. Found: C, 58.40; H, 6.70; N, 2.56.

4.8.15. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(2,6-dimethyl-phenyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (15c). Yield: 34%. ^{1}H NMR (DMSO-d_6), δ (ppm): 8.17 (s, 0.5H), 7.62 (s, 0.5 H), 7.40–7.26 (m, 5H), 7.11–7.03 (m, 2H), 7.01–6.96 (m, 1H), 5.55 (ddd, 2H, $J_{H\text{-}P}$ = 13.0 Hz, J_{AB} = 18.2 Hz), 5.44 (d, 2H, $J_{H\text{-}P}$ = 12.2 Hz), 4.80 (dd, 2H, J_{AB} = 12.5 Hz), 3.48–3.20 (m, 3H), 2.31–2.07 (m, 8H), 1.13 (s, 9H), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$): 176.8, 162.9, 135.9 (d, $^{2}J_{C\text{-}P}$ = 2.7 Hz), 134.6 (d, $^{3}J_{C\text{-}P}$ = 8.5 Hz), 130.8, 129.5, 129.1, 128.7, 128.5, 128.0, 81.9 (d, $^{3}J_{C\text{-}P}$ = 6.1 Hz), 81.6 (d, $^{3}J_{C\text{-}P}$ = 6.7 Hz), 77.8, 42.0 (d, $^{3}J_{C\text{-}P}$ = 14.2 Hz), 38.6, 36.7 (d, $^{3}J_{C\text{-}P}$ = 135.6 Hz), 29.7, 26.8, 21.1, 19.5. IR: 1757 cm^{-1} (C=O), 1682 cm^{-1} (C=O), 1262 cm^{-1} (P=O). Anal. Calcd for $C_{31}H_{44}NO_9P$: C, 61.48; H, 7.32; N, 2.31. Found: C, 61.28; H, 7.35; N, 2.52.

4.8.16. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-(3,4-difluoro-phenyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (16a). Yield: 34%. ^{1}H NMR (DMSO-d_6), δ (ppm): 7.40–7.31 (m, 7H), 7.23–7.17 (m, 2H), 5.57 (ddd, 2H, $J_{H\text{-}P}$=13.0 Hz, J_{AB} = 17.3 Hz), 5.50 (d, 2H, $J_{H\text{-}P}$ = 12.5 Hz), 4.77 (dd, 2H, J_{AB} = 15.33 Hz), 3.63–3.47 (m, 2H), 3.39–3.32 (m, 1H), 2.33–2.22 (m, 1H), 2.15–2.05 (m, 1H), 1.91 (s, 3H), 1.13 (s, 9H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$): 176.8, 172.3, 150.3 (dd, $^{1}J_{C\text{-}F}$ = 246.2 Hz), 150.0 (dd, $^{1}J_{C\text{-}F}$ = 244.8 Hz), 134.1, 131.0, 129.2, 129.1, 128.8, 125.6, 118.2 (dd, $^{2}J_{C\text{-}F}$ = 18.2 Hz, $^{3}J_{C\text{-}F}$ = 6.8 Hz), 117.4 (dd, $^{2}J_{C\text{-}F}$ = 17.2 Hz, $^{3}J_{C\text{-}F}$ = 2.9 Hz), 81.8 (d, $^{2}J_{C\text{-}P}$ = 8.7 Hz), 76.3, 43.4, 41.6 (d, $^{1}J_{C\text{-}P}$ = 140.2 Hz), 38.7, 26.8, 26.4, 20.4. IR: 1753 cm^{-1} (C=O), 1666 cm^{-1} (C=O), 1257 cm^{-1} (P=O). Anal. Calcd for $C_{30}H_{42}F_2NO_9P$: C, 59.11; H, 6.78; N, 2.30. Found: C, 59.11; H, 6.69; N, 2.16.

4.8.17. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-benzyloxymethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (24). Yield: 41%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.35–7.85 (m, 1H), 7.49–7.21 (m, 10H), 5.72–5.52 (m, 4H), 4.88 (s, 2H), 4.48 (s, 2H), 3.86-3.49 (m, 4H), 2.39–2.23 (m, 1H), 1.99–1.78 (m, 2H), 1.17 (s, 18H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.4, 163.0, 138.2, 135.0, 129.9, 129.1, 128.8, 128.6, 127.9, 127.8, 81.7, 77.0, 72.6, 67.4, 41.8, 38.5, 34.4 (d, $^{1}J_{C\text{-}P}$ = 134.5 Hz), 26.8, 23.7. IR: 1753 cm^{-1} (C=O), 1676 cm^{-1} (C=O), 1257 cm^{-1} (P=O). Anal. Calcd for $C_{31}H_{44}NO_{10}P$: C, 60.26; H, 7.30; N, 2.25. Found: C, 59.89; H, 7.13; N, 2.25.

4.8.18. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-benzyloxymethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (25). Yield: 44%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.48–7.25 (m, 10H), 5.66–5.53 (m, 4H), 4.84 (s, 2H), 4.48 (s, 2H), 3.78-3.50

(m, 4H), 2.37–2.21 (m, 1H), 1.99 (s, 3H), 1.96–1.76 (m, 2H), 1.13 (s, 18H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.5, 138.2, 135.0, 129.7, 129.0, 128.8, 128.6, 127.9, 127.8, 81.7, 75.7, 72.6, 67.4, 43.0, 38.5, 35.5 (d, $^1J_{C\text{-}P}$ = 138.5 Hz), 26.8, 23.6 (d, $^2J_{C\text{-}P}$ = 2.7 Hz), 20.7. IR: 1758 cm^{-1} (C═O), 1668 cm^{-1} (C═O), 1257 cm^{-1} (P═O). Anal. Calcd for $C_{32}H_{46}NO_{10}P$: C, 60.46; H, 7.29; N, 2.20. Found: C, 60.19; H, 7.49; N, 1.99.

4.9. General procedure for the preparation of 2,2-dimethyl-propionic acid [3-(acyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl esters 7a–f, 8a–f, 17a–c, 18a, 26 and 27

One millimole of the O-protected hydroxamic acids **5**, **6**, **15, 16**, **24** and **25** was dissolved in freshly distilled methanol (50 mL). After addition of the Pd–C catalyst, hydrogen gas was added to generate a pressure of 3 bar and the mixture was hydrogenated for one hour. The suspension was filtered through an SPE tube RP-18 purchased from Supelco. The filtrate was evaporated to give 2,2-dimethyl-propionic acid [3-(acyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl esters **7**, **8**, **17**, **18**, **26** and **27** as pale yellow oils.

4.9.1. 2,2-Dimethyl-propionic acid (2,2-dimethyl-propionyloxymethoxy)-[3-(formyl-hydroxy-amino)-1-methyl-propyl]-phosphinoyloxymethyl ester (7a). Yield: 85%. ^{1}H NMR (DMSO-d_6), δ (ppm): 10.03 (s, 0.5H), 9.58 (s, 0.5H), 8.23 (s, 0.5H), 7.92 (s, 0.5H), 5.65–5.56 (m, 4H), 3.58-3.38 (m, 2H), 2.03–1.89 (m, 2H), 1.58–1.39 (m, 1H), 1.17 (s, 18H), 1.07 (dd, 3H, $^3J_{H\text{-}P}$ = 19.4 Hz, $J_{H\text{-}H}$ = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 163.2, 81.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.5 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 44.1 (d, $^3J_{C\text{-}P}$ = 12.2 Hz), 38.7, 28.7 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 27.0, 26.8, 13.7 (d, $^2J_{C\text{-}P}$ = 5.1 Hz). IR: 1754 cm^{-1} (C═O), 1673 cm^{-1} (C═O), 1231 cm^{-1} (P═O). Anal. Calcd for $C_{17}H_{32}NO_9P$: C, 48.00; H, 7.58; N, 3.29. Found: C, 48.12; H, 7.75; N, 3.48.

4.9.2. 2,2-Dimethyl-propionic acid (2,2-dimethyl-propionyloxymethoxy)-[3-(formyl-hydroxy-amino)-1-phenyl-propyl]-phosphinoyloxymethyl ester (7b). Yield: 90%. ^{1}H NMR (DMSO-d_6), δ (ppm): 9.99 (s, 0.5H), 9.58 (s, 0.5H), 8.18 (s, 0.5 H), 7.60 (s, 0.5H), 7.38–7.24 (m, 5H), 5.57 (ddd, 2H, $^3J_{H\text{-}P}$ = 10.6 Hz, J_{AB} = 17.3 Hz), 5.44 (ddd, 2 H, $^3J_{H\text{-}P}$ = 12.5 Hz, J_{AB} = 7.6 Hz), 3.42–3.10 (m, 3H), 2.31–2.18 (m, 1H), 2.15–1.98 (m, 1H), 1.16 (s, 9H), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 176.9, 163.4, 156.4, 133.3 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 129.3, 129.2, 129.1, 129.1, 128.8, 128.1, 128.1, 127.8, 81.9 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 46.7 (d, $^3J_{C\text{-}P}$ = 16.3 Hz), 41.0 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 38.8, 38.7, 27.1 (d, $^2J_{C\text{-}P}$ = 4.1 Hz), 26.9, 26.8. IR: 1754 cm^{-1} (C═O), 1673 cm^{-1} (C═O), 1259 cm^{-1} (P═O). Anal. Calcd for $C_{22}H_{34}NO_9P$: C, 54.21; H, 7.03; N, 2.87. Found: C, 54.09; H, 7.20; N, 2.72.

4.9.3. 2,2-Dimethyl-propionic acid (2,2-dimethyl-propionyloxymethoxy)-[1-ethyl-3-(formyl-hydroxy-amino)-propyl]-phosphinoyloxymethyl ester (7c). Yield: 94%. ^{1}H NMR (DMSO-d_6), δ (ppm): 10.02 (s, 0.5H), 9.58 (s, 0.5H), 8.23 (s, 0.5H), 7.91 (s, 0.5H), 5.66–5.56 (m, 4H), 3.59–3.44 (m, 2H), 1.93–1.78 (m, 2H), 1.73–1.40 (m, 3H), 1.17 (s, 18H), 0.92 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 163.4, 81.7 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 81.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 44.9 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 38.8, 34.9 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 23.9 (d,$^2J_{C\text{-}P}$ = 2.0 Hz), 21.6 (d, $^2J_{C\text{-}P}$ = 4.1 Hz), 11.8 (d, $^2J_{C\text{-}P}$ = 12.2 Hz). IR: 1754 cm^{-1} (C═O), 1673 cm^{-1} (C═O), 1231 cm^{-1} (P═O). Anal. Calcd for $C_{18}H_{34}$ NO_9P: C, 49.20; H, 7.80; N, 3.19. Found: C, 49.03; H, 7.84; N, 3.40.

4.9.4. 2,2-Dimethyl-propionic acid (2,2-dimethyl-propionyloxymethoxy)-{1-[2-(formyl-hydroxy-amino)-ethyl]-2-methyl-propyl}-phosphinoyloxymethyl ester (7d). Yield: 93%. ^{1}H NMR (DMSO-d_6), δ (ppm): 10.01 (s, 0.5H), 9.59 (s, 0.5H), 8.23 (s, 0.5H), 7.89 (s, 0.5H), 5.67–5.57 (m, 4H), 3.60–3.45 (m, 2H), 2.13–2.00 (m, 1H), 1.89–1.61 (m, 3H), 1.17 (s, 18H), 0.98–0.89 (m, 6H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 176.8, 163.6, 81.8 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 45.8 (d, $^3J_{C\text{-}P}$ = 4.1 Hz), 40.4 (d, $^1J_{C\text{-}P}$ = 134.3 Hz), 38.8, 27.9 (d, $^2J_{C\text{-}P}$ = 4.1 Hz), 26.9, 21.7 (d, $^3J_{C\text{-}P}$ = 14.2 Hz), 20.8 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 18.9 (d, $^2J_{C\text{-}P}$ = 5.1 Hz). IR: 1754 cm^{-1} (C═O), 1673 cm^{-1} (C═O), 1230 cm^{-1} (P═O). Anal. Calcd for $C_{19}H_{36}NO_9P$: C, 50.33; H, 8.00; N, 3.09. Found: C, 50.09; H, 8.26; N, 3.24.

4.9.5. 2,2-Dimethyl-propionic acid (2,2-dimethyl-propionyloxymethoxy)-{1-[2-(formyl-hydroxy-amino)-ethyl]-butyl}-phosphinoyloxymethyl ester (7e). Yield: 91%. ^{1}H NMR (DMSO-d_6), δ (ppm): 10.01 (s, 0.5H), 9.58 (s, 0.5H), 8.22 (s, 0.5H), 7.90 (s, 0.5H), 5.66–5.56 (m, 4H), 3.61-3.43 (m, 2H), 1.96–1.79 (m, 2H), 1.75–1.31 (m, 5H), 1.17 (s, 18H), 0.84 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 176.8, 163.4, 81.8 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 81.5 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 44.9 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 38.8, 33.2 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 30.8 (d, $^2J_{C\text{-}P}$ = 5.1 Hz), 26.9, 24.3 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 20.4 (d, $^3J_{C\text{-}P}$ = 12.2 Hz), 13.9. IR: 1754 cm^{-1} (C═O), 1673 cm^{-1} (C═O), 1231 cm^{-1} (P═O). Anal. Calcd for $C_{19}H_{36}NO_9P$: C, 50.33; H, 8.00; N, 3.09. Found: C, 50.05; H, 8.23; N, 3.29.

4.9.6. 2,2-Dimethyl-propionic acid (2,2-dimethyl-propionyloxymethoxy)-[3-(formyl-hydroxy-amino)-1,1-dimethyl-propyl]-phosphinoyloxymethyl ester (7f). Yield: 89%. ^{1}H NMR (DMSO-d_6), δ (ppm): 10.03 (s, 0.5H), 9.57 (s, 0.5H), 8.19 (s, 0.5H), 7.93 (s, 0.5H), 5.66–5.59 (m, 4H), 3.56-3.46 (m, 2H), 1.80–1.67 (m, 2H), 1.17 (s, 18H), 1.11 (d, 6H, $^3J_{H\text{-}P}$ = 17.8 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 162.9, 81.7 (d, $^2J_{C\text{-}P}$ = 8.1 Hz), 81.5 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 43.9, 38.8, 35.1 (d, $^2J_{C\text{-}P}$ = 8.1 Hz), 33.8 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 26.9, 22.3 (d, $^2J_{C\text{-}P}$ = 2.0 Hz). IR: 1754 cm^{-1} (C═O), 1673 cm^{-1} (C═O), 1231 cm^{-1} (P═O). Anal. Calcd for $C_{18}H_{34}NO_9P$: C, 49.20; H, 7.80; N, 3.19. Found: C, 49.18; H, 8.00; N, 3.18.

4.9.7. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-methyl-propyl]-(2,2-dimethyl-propionyloxy-methoxy)-phosphinoyloxymethyl ester (8a). Yield: 90%. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.98 (s, 1H), 5.71–5.60 (m, 4H), 4.19–4.08 (m, 1H), 3.44–3.35

(m, 1H), 2.20–1.96 (m, 5H), 1.75–1.62 (m, 1H), 1.25–1.18 (m, 21H). ^{13}C NMR ($CDCl_3$), δ (ppm): 177.0, 176.9, 172.7, 81.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 45.4 (d, $^3J_{C\text{-}P}$ = 10.2 Hz), 38.8, 28.8 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 27.1 (d, $^2J_{C\text{-}P}$ = 2.0 Hz), 26.9, 26.8, 20.5, 13.9 (d, $^2J_{C\text{-}P}$ = 5.1 Hz). IR: 1755 cm^{-1} (C=O), 1622 cm^{-1} (C=O), 1234 cm^{-1} (P=O). Anal. Calcd for $C_{18}H_{34}NO_9P$: C, 49.20; H, 7.80; N, 3.19. Found: C, 48.93; H, 7.91; N, 3.35.

4.9.8. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-phenyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (8b). Yield: 92%. ^{1}H NMR (DMSO-d_6), δ (ppm): 9.71 (s, 1H), 7.36–7.24 (m, 5H), 5.57 (ddd, 2H, $^3J_{H\text{-}P}$ = 12.8 Hz, J_{AB} = 16.4 Hz), 5.44 (ddd, 2 H, $^3J_{H\text{-}P}$ = 12.4 Hz, J_{AB} = 7.9 Hz), 3.43-3.33 (m, 2H), 3.25–3.17 (m, 1H), 2.27–2.16 (m, 1H), 2.09–1.99 (m, 1H), 1.91 (s, 3H), 1.16 (s, 9H), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 172.9, 134.7 (d, $^2J_{C\text{-}P}$ = 8.1 Hz), 133.5, 129.3, 129.2, 129.0, 128.7, 128.0, 127.7, 82.0 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.9 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 46.6, 41.8 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 38.7, 28.7, 26.8, 26.8, 26.4 (d, $^2J_{C\text{-}P}$ = 4.1 Hz), 20.6. IR: 1754 cm^{-1} (C=O), 1621 cm^{-1} (C=O), 1243 cm^{-1} (P=O). Anal. Calcd for $C_{23}H_{36}NO_9P$: C, 55.08; H, 7.24; N, 2.79. Found: C, 54.65; H, 7.31; N, 2.66.

4.9.9. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-ethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (8c). Yield: 88%. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.08 (s, 1H), 5.72–5.60 (m, 4H), 4.18–4.08 (m, 1H), 3.42-3.33 (m, 1H), 2.22–2.04 (m, 4H), 1.83–1.67 (m, 3H), 1.55–1.41 (m, 1H), 1.24 + 1.23 (2s, 18H), 0.99 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 176.8, 172.8, 81.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.4 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 45.9 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 38.8, 35.8 (d, $^1J_{C\text{-}P}$ = 136.3 Hz), 26.9, 26.8, 24.3 (d, $^2J_{C\text{-}P}$ = 2.0 Hz), 22.1 (d, $^2J_{C\text{-}P}$ = 5.1 Hz), 20.6, 11.9 (d, $^3J_{C\text{-}P}$ = 13.2 Hz). IR: 1755 cm^{-1} (C=O), 1630 cm^{-1} (C=O), 1241 cm^{-1} (P=O). Anal. Calcd for $C_{19}H_{36}NO_9P$: C, 50.33; H, 8.00; N, 3.09. Found: C, 50.27; H, 8.30; N, 3.19.

4.9.10. 2,2-Dimethyl-propionic acid {1-[2-(acetyl-hydroxy-amino)-ethyl]-2-methyl-propyl}-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (8d). Yield: 83%. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.06 (s, 1H), 5.73–5.64 (m, 4H), 4.18–4.08 (m, 1H), 3.39-3.31 (m, 1H), 2.19–1.99 (m, 5H), 1.83–1.66 (m, 2H), 1.24 (s, 18H), 1.00 (d, 3H, J = 6.9 Hz), 0.94 (d, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 176.8, 172.8, 81.7 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 81.3 (d, $^2J_{C\text{-}P}$ = 8.1 Hz), 46.7 (d, $^3J_{C\text{-}P}$ = 5.1 Hz), 40.3 (d, $^1J_{C\text{-}P}$ = 134.3 Hz), 3878, 38.8, 27.9 (d, $^2J_{C\text{-}P}$ = 4.1 Hz), 26.9, 21.7 (d, $^3J_{C\text{-}P}$ = 14.2 Hz), 21.1, 20.6, 18.8 (d, $^3J_{C\text{-}P}$ = 6.1 Hz). IR: 1755 cm^{-1} (C=O), 1624 cm^{-1} (C=O), 1231 cm^{-1} (P=O). Anal. Calcd for $C_{20}H_{38}NO_9P$: C, 51.38; H, 8.19; N 3.00. Found: C, 50.76; H, 8.00; N, 3.08.

4.9.11. 2,2-Dimethyl-propionic acid {1-[2-(acetyl-hydroxy-amino)-ethyl]-butyl}-(2,2-dimethyl-propionyl-oxymethoxy)-phosphinoyloxymethyl ester (8e). Yield: 91%. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.09 (s, 1H), 5.72–5.60 (m, 4H), 4.17–4.08 (m, 1H), 3.41–3.32 (m, 1H), 2.21–2.04 (m, 4H), 1.92–1.60 (m, 3H), 1.52–1.28 (m, 3H), 1.24 + 1.23 (2s, 18H), 0.91 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 176.8, 172.7, 81.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 81.4 (d, $^2J_{C\text{-}P}$ = 8.1 Hz), 45.9 (d, $^3J_{C\text{-}P}$ = 5.1 Hz), 38.9, 38.8, 34.0 (d, $^1J_{C\text{-}P}$ = 137.3 Hz), 30.9 (d, $^2J_{C\text{-}P}$ = 5.1 Hz), 26.8, 24.7 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 20.6, 20.4 (d, $^3J_{C\text{-}P}$ = 13.2 Hz), 13.8. IR: 1755 cm^{-1} (C=O), 1623 cm^{-1} (C=O), 1235 cm^{-1} (P=O). Anal. Calcd for $C_{20}H_{38}NO_9P$: C, 51.38; H, 8.19; N, 3.00. Found: C, 51.10; H, 8.42; N, 3.10.

4.9.12. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1,1-dimethyl-propyl]-(2,2-dimethyl-propionyloxy-methoxy)-phosphinoyloxymethyl ester (8f). Yield: 92%. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.21 (s, 1H), 5.75–5.57 (m, 4H), 3.83–3.73 (m, 2H), 2.12 (s, 3H), 1.99–1.84 (m, 2H), 1.24 (s, 18H), 1.00 (d, 6H, $^3J_{H-P}$ = 17.3 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.8, 172.0, 81.7 (d, $^2J_{C\text{-}P}$ = 7.1 Hz), 45.1 (d, $^3J_{C\text{-}P}$ = 5.1 Hz), 38.8, 34.9, 33.9 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 26.9, 22.5, 20.6. IR: 1755 cm^{-1} (C=O), 1632 cm^{-1} (C=O), 1234 cm^{-1} (P=O). Anal. Calcd for $C_{19}H_{36}NO_9P$: C, 50.33; H, 8.00; N, 3.09. Found: C, 49.93; H, 8.24; N, 3.23.

4.9.13. 2,2-Dimethyl-propionic acid [1-(3,4-difluoro-phenyl)-3-(formyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (17a). Yield: 87%. ^{1}H NMR (DMSO-d_6), δ (ppm): 10.00 (s, 0.5H), 9.57 (s, 0.5H), 8.24–7.93 (m, 0.5H), 7.78–7.57 (m, 0.5H), 7.50–7.03 (m, 3H), 5.66–5.40 (m, 4H), 3.65-3.40 (m, 3H), 2.34–1.91 (m, 2H), 1.15 (s, 9H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 177.4, 177.3, 164.0, 163.7, 162.0, 150.4 (dd, $^1J_{C\text{-}F}$ = 248.1 Hz), 131.1, 126.1, 118.4, 117.9, 82.3, 47.1 (d, $^3J_{C\text{-}P}$ = 15.8 Hz), 44.6 (d, $^3J_{C\text{-}P}$ = 14.2 Hz), 41.1 (d, $^1J_{C\text{-}P}$ = 141.4 Hz), 40.6 (d, $^1J_{C\text{-}P}$ = 142.7 Hz), 39.1, 30.1 (d, $^2J_{C\text{-}P}$ = 3.1 Hz), 27.2. IR: 1753 cm^{-1} (C=O), 1674 cm^{-1} (C=O), 1256 cm^{-1} (P=O). EI-MS $C_{21}H_{26}F_2NO_5P$ $[M+H]^+$: calculated 524, found 524.

4.9.14. 2,2-Dimethyl-propionic acid [1-(2-fluoro-phenyl)-3-(formyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (17b). Yield: 84%. ^{1}H NMR (DMSO-d_6), δ (ppm): 9.99 (m, 0.5H), 9.61 (m, 0.5H), 8.16 (m, 0.5H), 7.58 (m, 0.5H), 7.42–7.30 (m, 2H), 7.25–7.15 (m, 2H), 5.59 (ddd, 2H, $J_{H\text{-}P}$ = 13.5 Hz, J_{AB} = 15.5 Hz), 5.50 (d, 2 H, $J_{H\text{-}P}$ = 12.2 Hz), 3.68-3.53 (m, 1H), 3.29-3.15 (m, 2H), 2.36–2.24 (m, 1H), 2.16–2.05 (m, 1H), 1.15 (s, 9H), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.8, 163.6, 160.9, 156.2 (dd, $^1J_{C\text{-}F}$ = 246.0 Hz, $^3J_{C\text{-}P}$ = 8.90 Hz), 129.6, 124.8, 115.9 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 82.0, 46.7 (d, $^3J_{C\text{-}P}$ = 16.2 Hz), 44.7 (d, $^3J_{C\text{-}P}$ = 11.4 Hz), 38.8, 33.1 (d, $^1J_{C\text{-}P}$ = 145.1 Hz), 26.8, 26.1. IR: 1753 cm^{-1} (C=O), 1674 cm^{-1} (C=O), 1243 cm^{-1} (P=O). Anal. Calcd for $C_{22}H_{33}FNO_9P$: C, 52.28; H, 6.58; N, 2.77. Found: C, 52.25; H, 6.66; N, 2.86.

4.9.15. 2,2-Dimethyl-propionic acid [1-(2,6-dimethyl-phenyl)-3-(formyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (17c). Yield: 87%. ^{1}H NMR (DMSO-d_6), δ (ppm): 9.98

(m, 0.5H), 9.60 (m, 0.5H), 8.18 (m, 0.5H), 7.44 (m, 0.5H), 7.11–7.03 (m, 2H), 6.99–6.95 (m, 1H), 5.56 (ddd, 2H, $J_{H\text{-}P}$ = 13.0 Hz, J_{AB} = 17.6 Hz), 5.44 (d, 2H, $J_{H\text{-}P}$ = 12.0 Hz), 3.53–3.44 (m, 1H), 3.26-3.09 (m, 2H), 2.33–2.23 (m, 4H), 2.21–2.07 (m, 4H), 1.15 (s, 9H), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 155.3, 136.2, 134.2, 131.0, 128.7, 81.6, 45.9, 38.8, 29.7, 26.8, 21.1, 19.5. IR: 1753 cm^{-1} (C═O), 1674 cm^{-1} (C═O), 1254 cm^{-1} (P═O). ESI-MS $C_{24}H_{38}NO_9P$ $[M+H]^+$: calculated 516, found 516.

4.9.16. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-(3,4-difluoro-phenyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (18a). Yield: 89%. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.21–6.91 (m, 3H), 5.70–5.39 (m, 4H), 4.08-3.05 (m, 3H), 2.63–2.39 (m, 1H), 2.32–1.78 (m, 4H), 1.22 (s, 9H), 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.9, 173.1, 148.8, 132.2, 125.7, 118.2, 118.1, 117.5, 81.9 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 45.7, 41.0 (d, $^1J_{C\text{-}P}$ = 138.7 Hz), 38.8, 29.7, 27.8, 26.8. IR: 1753 cm^{-1} (C═O), 1622 cm^{-1} (C═O), 1246 cm^{-1} (P═O). EI-MS $C_{23}H_{34}F_2NO_9P$ $[M+H]^+$: calculated 538, found 538.

4.9.17. 2,2-Dimethyl-propionic acid [1-benzyloxymethyl-3-(formyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (26). Yield: 87%. ^{1}H NMR (DMSO-d_6), δ (ppm): 9.99 (s, 0.5H), 9.55 (s, 0.5H), 8.25–8.18 (m, 0.3H), 8.08–7.87 (m, 0.7H), 5.68–5.52 (m, 4H), 4.97 (br s, 1H), 3.75-3.43 (m, 3H), 3.24–3.13 (m, 1H), 2.09–1.63 (m, 3H), 1.17 (s, 18H). ^{13}C NMR (DMSO-d_6), δ (ppm): 176.5, 162.1, 161.3, 157.5, 82.7, 59.2, 58.9, 47.9, 44.7, 38.6, 37.7 (d, $^1J_{C\text{-}P}$ = 136.1 Hz), 26.8, 25.8 (d, $^2J_{C\text{-}P}$ = 3.0 Hz). IR: 3240 cm^{-1} (O–H), 1753 cm^{-1} (C═O), 1668 cm^{-1} (C═O), 1242 cm^{-1} (P═O). Anal. Calcd for $C_{17}H_{32}NO_{10}P$: C, 46.26; H, 7.31; N, 3.17. Found: C, 46.09; H, 7.32; N, 3.25.

4.9.18. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-benzyloxymethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (27). Yield: 92%. ^{1}H NMR (DMSO-d_6), δ (ppm): 9.73 (s, 1H), 5.68–5.57 (m, 4H), 4.96 (br s, 1H), 3.75-3.49 (m, 4H), 2.08–1.75 (m, 6H), 1.19 (s, 18H). ^{13}C NMR ($CDCl_3$), δ (ppm): 176.5, 170.6, 81.7, 58.9 (d, $^2J_{C\text{-}P}$ = 13.5 Hz), 45.9 (d, $^3J_{C\text{-}P}$ = 12.7 Hz), 38.6, 37.6 (d, $^1J_{C\text{-}P}$ = 138.5 Hz), 26.9, 23.1 (d, $^2J_{C\text{-}P}$ = 2.1 Hz), 20.7. IR: 3219 cm^{-1} (O–H), 1753 cm^{-1} (C═O), 1627 cm^{-1} (C═O), 1236 cm^{-1} (P═O). Anal. Calcd for $C_{18}H_{34}NO_{10}P$: C, 47.47; H, 7.52; N, 3.08. Found: C, 47.13; H, 7.68; N, 3.05.

4.10. Determination of in vitro antimalarial activity

4.10.1. Culture of *P. falciparum*. The *P. falciparum* 3D7 strain was maintained in continuous culture, according to Trager and Jensen and DasGupta et al.[15,17,18] The parasites were grown in human red blood cells (RBCs blood group A positive), RPMI 1640 medium supplemented with 25 mM HEPES, 20 mM sodium bicarbonate, and 0.5% AlbuMAX (Invitrogen, Karlsruhe, Germany) at 5% hematocrit. The flasks were gassed with 90% N_2, 5% O_2 and 5% CO_2 and incubated at 37 °C. The development of the cultures and the percentage of infected RBC's were determined by light microscopy of Giemsa-stained thin smears.

4.10.2. Preparation of drug solutions. Twenty micromole of the respective compounds was solved in 400 µl DMSO and further diluted with water/ethanol (50/50) to obtain the particular concentration.

4.10.3. Determination of parasite growth inhibition. The tests were carried out in 96-well microtitre plates under strict aseptic conditions, according to literature.[15,17] Dilutions of each compound were added to 250 µl of a suspension of *P. falciparum* infected erythrocytes (1.5% hematocrit, 1.5–2% parasitemia). The plates were flushed with a gas mixture consisting of 90% N_2, 5% O_2 and 5% CO_2, closed tightly and incubated at 37 °C for 24 h. Afterwards, 0.1 µCi 8-[^{3}H]hypoxanthine was added to each well. The plates were flushed with the above-mentioned gas mixture, incubated for additional 24 h at 37 °C and subsequently harvested with a cell harvester system (Inotech, Dottikon, Switzerland). Infected erythrocytes were washed four times with distilled water before they were analysed for incorporated radioactivity in a multidetector liquid scintillation counter (Wallac, Turku, Finland).

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