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Amino acid based prodrugs of a fosmidomycin surrogate as antimalarial and antitubercular agents

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ABSTRACT

Fosmidomycin is a natural antibiotic with promising IspC (DXR, 1-deoxy-D-xylulose-5-phosphate reductoisomerase) inhibitory activity. This enzyme catalyzes the first committed step of the non-mevalonate isoprenoid biosynthesis pathway, which is essential in *Plasmodium falciparum* and *Mycobacterium tuberculosis*. Mainly as a result of its high polarity, fosmidomycin displays suboptimal pharmacokinetic properties. Furthermore, fosmidomycin is inactive against *M. tuberculosis* as a result of its inability to penetrate the bacterial cell wall. Temporarily masking the phosphonate moiety as a prodrug has the potential to solve both issues. We report the application of two amino acid based prodrug approaches on a fosmidomycin surrogate. Conversion of the phosphonate moiety into tyrosine-derived esters increases the *in vitro* activity against asexual blood stages of *P. falciparum*, while phosphonodiamidate prodrugs display promising antitubercular activities. Selected prodrugs were tested *in vivo* in a *P. berghei* malaria mouse model. These results indicate good *in vivo* antiplasmodial potential.

1. Introduction

Despite considerable international efforts, malaria and tuberculosis (TB) control and elimination remain major challenges. According to the World Health Organization (WHO), 216 million malaria cases and 445,000 malaria-related deaths were reported worldwide in 2016, of which 90% occurred in Africa. Malaria incidence has decreased significantly since 2010. Since 2014, however, the number of malaria cases is steadily increasing.[1] TB is the world's deadliest infectious disease. In 2016, > 10 million cases of TB and almost 2 million TB-related deaths, of which approximately 400,000 among people co-infected with HIV, were reported. TB mortality rates have dropped by 37% between 2010 and 2016. However, the proportion of multidrug-resistant (MDR) TB cases is steadily increasing. Approximately 5% of active TB cases are MDR, of which 6% are extensively drug-resistant (XDR).[2,3] In 2009, the first totally drug-resistant (TDR) strains have been detected in India.[4] Due to the rising problem of acquired resistance against all currently available antimalarial and antitubercular agents, there is a pressing need for novel therapies. Over the past forty years, only one new synthetic antimalarial (tafenoquine) has been launched on the market.[5] Plenty of research is being conducted on antitubercular drugs, recently resulting in the approval of bedaquiline (2012) and delamanid (2014). However, no new first-line drug has been approved since the introduction of the current short-course chemotherapy in the 1970s.[6] Compounds with a completely novel mechanism of action (MOA) are preferably pursued, as resistance against these compounds is expected

Abbreviations: AA, amino acid; ANP, acyclic nucleoside phosphonate; BAIB, bis(acetoxy)iodobenzene; 9-BBN, 9-borabicyclo[3.3.1]nonane; CDI, 1,1′-carbonyldiimidazole; cHx, cyclohexyl; DCM, dichloromethane; DIPEA, diisopropylethylamine; DMF, dimethylformamide; dpi, days post infection; DXP, 1-deoxyxylulose 5-phosphate; DXR, 1-deoxyxylulose 5-phosphate reductoisomerase; EDC, *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide; Et_3N, triethylamine; EtOH, ethanol; HATU, hexafluorophosphate azabenzotriazole tetramethyl uronium; HOBt, hydroxybenzotriazole; HRMS, high-resolution mass spectrometry; ip, intraperitoneal; MDR, multidrug-resistant; MeCN, acetonitrile; MEP, methylerythritolphosphate; MOA, mechanism of action; MST, mean survival time, *Mtb*, *Mycobacterium tuberculosis*; PK, pharmacokinetic; PyBOP, (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; RBC, red blood cell; SAR, structure-activity relationship; SPB, sodium perborate; TB, tuberculosis; TBS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TDR, totally drug-resistant; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; THF, tetrahydrofuran; TMSBr, trimethylsilyl bromide; WHO, world health organization; XDR, extensively drug-resistant

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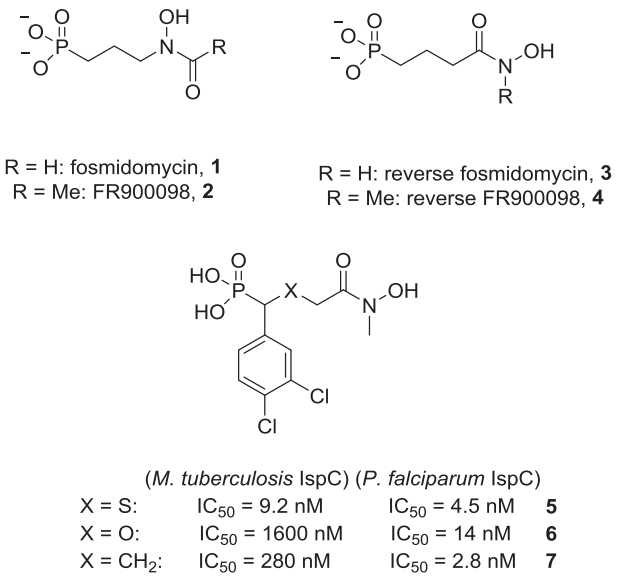


Fig. 1. Structural formulae of fosmidomycin, FR900098, their reverse analogues and α-aryl derivatives.

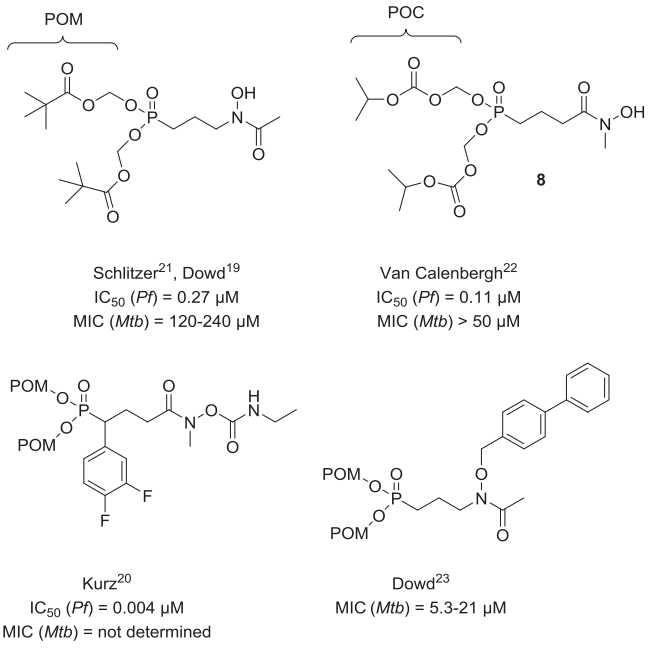


Fig. 2. *In vitro* antiplasmodial and antitubercular activities of representative prodrug derivatives of fosmidomycin analogues.

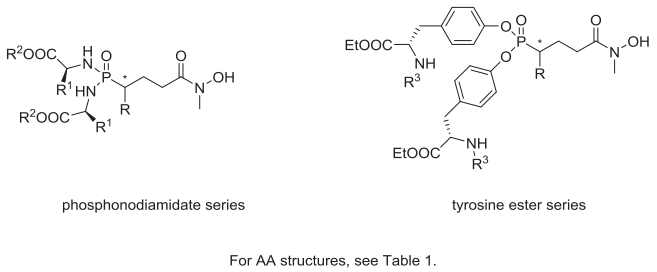


Fig. 3. Target compounds: phosphonodiamidate and tyrosine ester series.

to develop more slowly in comparison with compounds acting on previously addressed targets or pathways.

An interesting pathway in this respect is the non-mevalonate isoprenoid biosynthesis pathway, also known as the methylerythritolphosphate (MEP) or 1-deoxyxylulose 5-phosphate (DXP) pathway.[7,8] This pathway is essential in a number of pathogens, including *Plasmodium* parasites, the causative agents of malaria, and *Mycobacterium tuberculosis* (*Mtb*), the causative agent of TB. Humans synthesize the essential isoprenoid building blocks via the evolutionarily distinct mevalonate pathway. Since the two pathways utilize non-homologous enzymes, selective interference is possible.[9] 1-Deoxy-D-xylulose-5-phosphate reductoisomerase (DXR) is the most extensively studied enzyme of the non-mevalonate pathway and catalyzes the first committed reaction step.[7,10–12] Fosmidomycin (**1**, Fig. 1) and FR900098 (**2**, Fig. 1) are natural antibiotics and potent inhibitors of DXR.[13]

Significant research has been devoted to expanding the structure–activity relationship (SAR) of these phosphonate antibiotics. This has also resulted in a number of analogues with improved DXR inhibitory activity, including the α-aryl derivatives **5–7** (Fig. 1).[10,12,14,15] Fosmidomycin (**1**, Fig. 1) is a highly hydrophilic compound, mainly due to its phosphonate functionality, which is charged at physiological pH. As a result, fosmidomycin exhibits suboptimal pharmacokinetic (PK) properties including moderate oral bioavailability (20–40%), a short plasma half-life (< 2 h) and high rates of parasite recrudescence after monotherapy.[16,17] The poor permeation by passive diffusion of fosmidomycin additionally results in a lack of activity against pathogens not actively importing the drug, including *Mtb*. In an attempt to improve these properties, a number of prodrugs of fosmidomycin (analogues) have been reported and have been shown to possess enhanced *in vitro* antimalarial and antitubercular activity.[10,12,18] A selection of representative prodrug derivatives is shown in Fig. 2 [19–23]

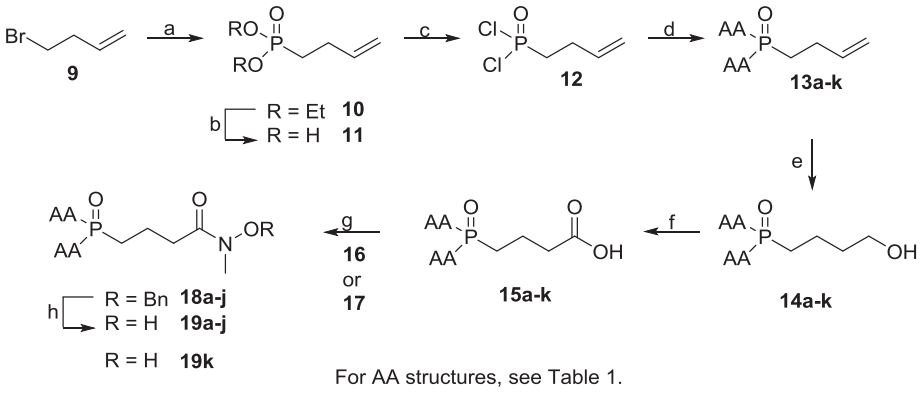
This article reports on the synthesis, *in vitro* and *in vivo* antimalarial, and *in vitro* antitubercular activity, of two prodrug series of the fosmidomycin surrogate **4** and the α-aryl analog **7** (Fig. 1): the phosphonodiamidates and tyrosine-derived esters (Fig. 3). Both series are inspired by phosphonate and phosphate prodrug strategies successfully applied in the nucleoside field.[24,25] The phosphonodiamidate prodrug approach, developed by McGuigan *et al.*, has been shown to increase cellular uptake of antivirals.[26,27] This approach has also proven to be valid in *Mtb*, as it enables cellular uptake of acyclic nucleoside phosphonates (ANPs), resulting in highly active antituberculosis agents.[28]

The putative cleavage mechanism of these phosphonodiamidates relies on two enzymatic steps, catalyzed by carboxypeptidase and phosphoramidase.[24] The tyrosine prodrug approach, developed by McKenna and coworkers, has been shown to lead to significantly enhanced oral bioavailability of ANPs. Release of the prodrug promoiety is mediated by enzymatic or chemical hydrolysis.[29] We hypothesized that corresponding prodrugs of **4** and **7** (Fig. 1) could exhibit enhanced *in vitro* antimalarial and antitubercular activity as a result of increased cellular uptake.

2. Results and discussion

2.1. Synthesis

The synthesis of the phosphonamidates started from 4-bromo-1-butene **9** (Scheme 1). Substitution with diethyl phosphite yielded diethylphosphonate **10**. TMSBr-mediated deprotection, followed by chlorination with oxalyl chloride provided phosphonic dichloride **12**. Treatment with the appropriate amino acid (AA) derivatives (For AA structures, see Table 1) yielded the symmetric phosphonamides **13a-k**. Hydroboration-oxidation with 9-BBN produced primary alcohols **14a-k**, which were subsequently converted to carboxylic acids **15a-k** using TEMPO-BAIB oxidation. EDC-coupling with benzyl-protected hydroxylamine **16** gave protected hydroxamates **18a-j**. Catalytic hydrogenolysis afforded the corresponding free hydroxamates **19a-j**. For the synthesis of the benzyl L-leucine diamidate **19k** orthogonal protection of the hydroxamate was required. Therefore, carboxylic acid **15k** was



Scheme 1. Synthesis of NH-linked amino acid based prodrugs. Reagents and conditions: (a) (i) $(EtO)_2PH$, NaH, THF, 0 °C; (ii) 4-bromo-1-butene **9** (78%); (b) (i) TMSBr, DCM; (ii) H_2O, THF; (c) oxalyl chloride, DMF, DCM, 50 °C; (d) AA alkyl ester HCl, DIPEA, pyridine, DCM (35–80%); e) (i) 9-BBN, THF; (ii) SPB·H_2O, H_2O (24–86%); (f) TEMPO, BAIB, $NaHCO_3$, $MeCN/H_2O$ (34–84%); (g) EDC.HCl, HOBt, BnONHMe (**16**) or TBSONHMe (**17**), Et_3N, DCM (33–91%); (h) H_2, Pd/C, solvent (50%-quantitative).

EDC coupled with TBS-protected hydroxylamine **17.**

Interestingly, during the coupling of **15k** with **17**, the silyl group was unexpectedly removed *in situ*, immediately yielding final compound **19k** in an acceptable yield of 33%. For the synthesis of L-alanine ethyl ester prodrug derivative **28**, hydroboration of the terminal alkene intermediate was attempted using a range of different reaction conditions, but failed to produce the desired product. Therefore, an alternative synthesis route was envisaged (Scheme 2).

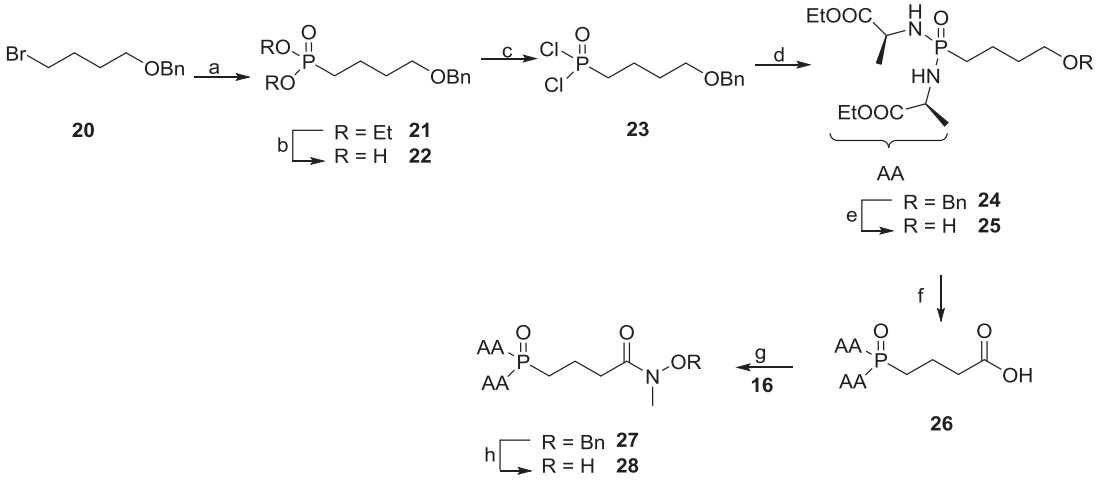
The synthesis of **28** started from benzyl 4-bromobutyl ether **20**. Arbuzov reaction with triethyl phosphite yielded phosphonate **21**. TMSBr-mediated deprotection followed by chlorination with oxalyl chloride produced phosphonic dichloride **23**. Treatment with L-alanine ethyl ester yielded phosphonamide **24**, which was converted into the primary alcohol **25** upon hydrogenation. TEMPO-BAIB oxidation and EDC coupling of the resulting carboxylic acid **26** with benzyl-protected hydroxylamine **16** gave protected hydroxamate **27**. Debenzylation by hydrogenation afforded final compound **28**. Tyrosine based prodrugs **37a** and **37b** (Table 1) were synthesized as described in our previous work using a cross metathesis synthetic approach (Scheme 3).[22]

In addition, two prodrug promoieties were selected for the synthesis of prodrugs of the α-3,4-dichlorophenyl analog **7** (Fig. 1). Their synthesis started from 3,4-dichlorobenzyl bromide **38** (Scheme 4). Arbuzov reaction with triethyl phosphite yielded diethylphosphonate **39**. Alkylation with allyl bromide in the presence of *n*-butyllithium afforded **40**. Transformation into the corresponding phosphonamides **43a-b** was performed using the same reaction sequence as before (**40** → **41** → **42** → **43**). Hydroboration with BH_3, followed by TEMPO-BAIB oxidation gave carboxylic acids **45a-b**. Attempts to couple the carboxylic acids **45a-b** with TBDPS-protected hydroxylamine **46** using a number of different coupling agents, including EDC, HATU, CDI and PyBOP, failed to yield acceptable amounts of desired products. Eventually, the desired compounds **47a-b** were obtained via the mixed anhydride method using ethyl chloroformate.[30] Also in this case, the silyl protecting groups were removed *in situ* to yield the corresponding free hydroxamic acids **47a-b**.

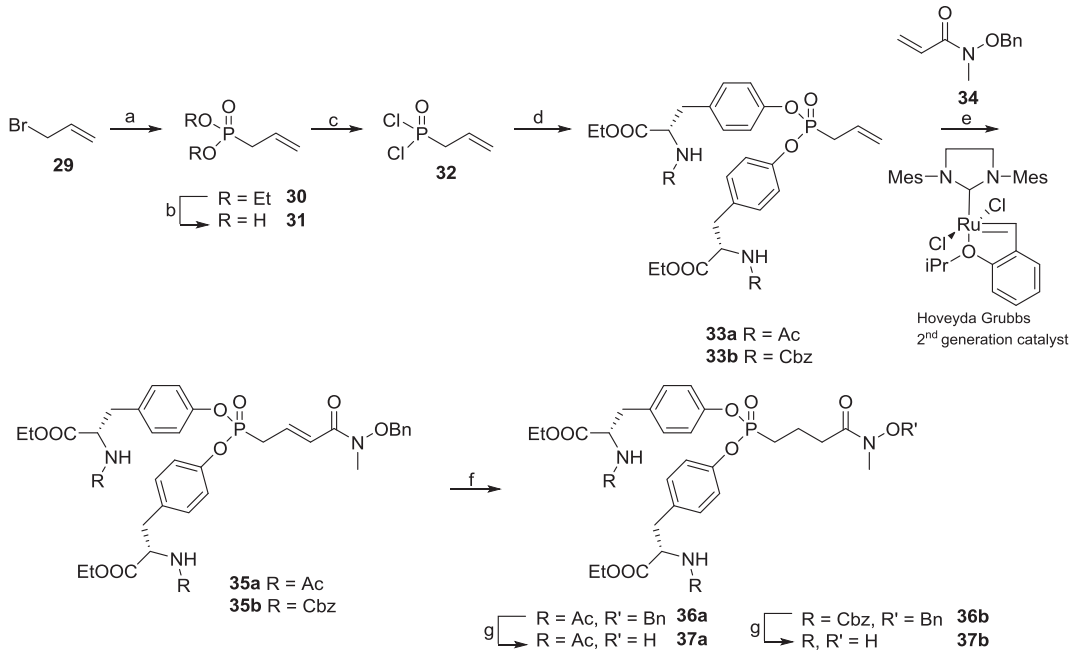
2.2. Biological evaluation

Table 1 summarizes the *in vitro* inhibitory activity on the growth of *M. tuberculosis* (H37Rv) and asexual blood stages of *P. falciparum* (*Pf*-K1). The cytotoxicity of all compounds was assessed using human fibroblasts (MRC-5). Of the phosphonamidate prodrugs evaluated against *P. falciparum*, only L-lysine derivative **19e** displayed submicromolar activity. All other phosphonamidates displayed antiplasmodial activity comparable or inferior to fosmidomycin. Furthermore, derivatives **19i-k** suffered from MRC-5 cell toxicity. Interestingly, tyrosine esters **37a** and **37b** displayed better antiplasmodial activity than fosmidomycin. Both **19e**

and **37b** are positively charged at physiological pH, which does not seem to hamper transport into the infected red blood cells (RBCs). Ethyl ester L-leucine derivative **19g** and ethyl ester L-alanine derivative **28** displayed moderate antitubercular activities, with MIC values of 50 μM and 20 μM. All other compounds did not show any activity against *M. tuberculosis*, presumably as a result of lack of uptake or efflux. This observation led us to also test the L-alanine and *N*-acetyl L-tyrosine prodrug derivatives of α-3,4-dichlorophenyl analog **7**, which compared



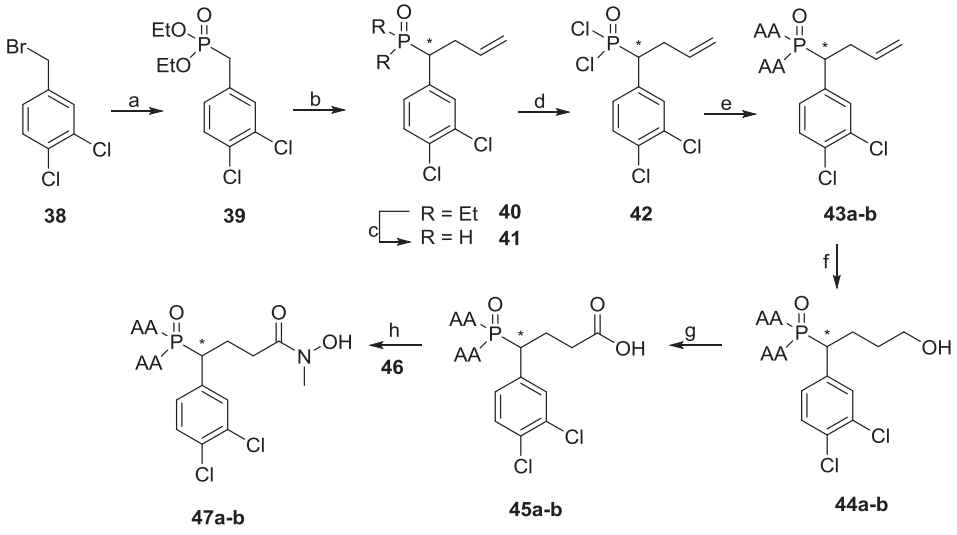
Scheme 2. Synthesis of NH-linked L-alanine based prodrug. Reagents and conditions: (a) $(EtO)_3P$, reflux, 71%; (b) (i) TMSBr, DCM; (ii) H_2O, THF; (c) oxalyl chloride, DMF, DCM, 50 °C; (d) L-Ala OEt.HCl, DIPEA, pyridine, DCM (37% over 3 steps); (e) H_2, Pd/C, EtOH (89%); (f) TEMPO, BAIB, $NaHCO_3$, $MeCN/H_2O$ (53%); (g) EDC.HCl, HOBt, BnONHMe (**16**), Et_3N, DCM (79%); (h) H_2, Pd/C, EtOH (91%).



Scheme 3. Synthesis of O-linked L-tyrosine based prodrugs. Reagents and conditions: (a) triethyl phosphite, 150 °C (97%); (b) (i) TMSBr, DCM; (ii) H_2O, THF; (c) oxalyl chloride, DMF, DCM, 45 °C; (d) *N*-acetyl L-tyrosine OEt or *N*-Cbz L-tyrosine OEt, DIPEA, pyridine, DCM (60–68% over 3 steps); (e) Hoveyda–Grubbs second generation catalyst, toluene, 70 °C (67%); (f) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF (50–65%); (g) H_2, Pd/C, EtOH (55–90%).

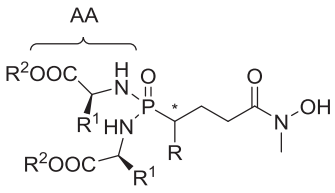
to fosmidomycin is more active against *Pf*DXR (IC_{50} = 2.8 nM) and equally active against *Mtb*DXR (IC_{50} = 280 nM).[14,15] Surprisingly, however, compound **47a** was inactive against *M. tuberculosis* and the antiplasmodial activity of **47b** was clearly inferior to that of derivative **37a**. These results are in marked contrast to the previously reported activities of prodrugs of the corresponding α-3,4-difluorophenyl analog with antiplasmodial IC_{50} values up to 4 nM.[20]

Compounds **8**, **19e** and **37a**, belonging to different prodrug classes, were selected for evaluation in a *P. berghei* malaria mouse model. The isopropyloxycarbonyloxymethyl (POC) prodrug **8** (Fig. 2) was previously reported by us to display excellent *in vitro* antiplasmodial activity (*Pf* –K1 IC_{50} of 110 nM)[22]. The compounds were dosed intraperitoneally (ip) at 50 mg/kg for 5 consecutive days. Chloroquine (10 mg/kg for 5 days) was included as reference treatment. Parasitemia was determined on days 4, 7, 11 and 14 on surviving animals using flow cytometry. Percentage reduction of parasitemia and mean survival time (MST) of mice compared to vehicle-treated infected controls is used as a measure for drug activity (Table 2). The results in Table 2 show that compound **19e** failed to show relevant activity. On the other hand, **37a** resulted in 82% suppression of parasitemia at 4 days post infection (dpi), which dropped to 66% at 7 dpi and 50% at 14 dpi. The mean survival time was 12.7 days. In line with its potent *in vitro* antiplasmodial activity data, compound **8** was superior to the others, resulting in 99% suppression of parasitaemia at 4 dpi, which dropped slightly to 92% at 7 dpi and 75% at 14 dpi. The overall MST was 15.3 days. These data demonstrate that the tyrosine ester prodrug **37a** exhibits moderate *in vivo* antiplasmodial activity, while POC-prodrug **8** compares favorably with the reference chloroquine treatment. The weak *in vivo* activity of **19e** is possibly the result of chemical instability, metabolic instability and/or insufficient bioactivation.

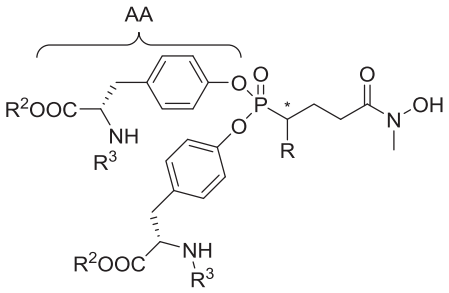


Scheme 4. Synthesis of prodrugs of α-3,4-dichlorophenyl analog 7. Reagents and conditions: (a) $(OEt)_3P$, reflux, 92%; (b) (i) *n*-BuLi, THF, −78 °C; (ii) allyl bromide (70%); (c) (i) TMSBr, DCM; (ii) H_2O, THF; (d) oxalyl chloride, DMF, DCM, 50 °C; (e) AA alkyl ester HCl, DIPEA, pyridine, DCM (43–98% over 3 steps); (f) (i) $BH_3{\cdot}THF$, THF; (ii) $SPB{\cdot}H_2O$, H_2O (35–80%); (g) TEMPO, BAIB, $NaHCO_3$, $MeCN/H_2O$ (66–79%); (h) (i) 4-methylmorpholine, ethyl chloroformate, −20 °C; (ii) TBDPSONHMe (**46**) (23–36%).

Table 1
***In vitro* biological evaluation of amino acid based prodrugs**[a].



phosphonodiamidate series



tyrosine ester series

Compound	Amino acid (AA)	Ester (R^2)	R	Pf-K1IC_{50} [μM]	H37RvMIC [μM]	MRC-5[μM]
1	–	–	–	1.73[31]	> 500[19]	> 64
phosphonodiamidate series						
19a	L-Val	Et	H	12.7	> 50	> 64
19b	L-Phe	Et	H	4.71 (± 0.05)	> 50	> 64
19c	L-Pro	Et	H	10.2 (± 8.2)	> 50	> 64
19d	L-iLe	Et	H	2.00	> 50	> 64
19e	L-Lys	Et	H	0.96 (± 0.35)	> 50	> 64
19f	L-Leu	Me	H	1.76	> 50	> 64
19g	L-Leu	Et	H	3.91 (± 2.85)	50	> 64
19h	L-Leu	iPr	H	4.97	> 50	> 64
19i	L-Leu	Pentyl	H	2.37	> 50	7.46
19j	L-Leu	cHx	H	4.56	> 50	7.65
19k	L-Leu	Bn	H	2.02 (± 0.89)	> 50	7.94 (± 3.22)
28	L-Ala	Et	H	5.06 (± 0.54)	20	> 64
47a	L-Ala	Et	3,4-dichlorophenyl	> 36.6	> 50	> 64
tyrosine ester series						
37a	*N*-Acetyl L-Tyr	Et	H	0.31	> 50	> 64
37b	L-Tyr	Et	H	0.23	> 50	> 64
47b	*N*-Acetyl L-Tyr	Et	3,4-dichlorophenyl	> 41.1	> 50	36.9 (± 5.5)

[a] values for which standard deviations are given are the calculated mean values of at least two measurement results.

Table 2
In vivo biological evaluation of selected prodrug derivatives in *P. berghei* infected mice.

Treatment (ip for 5 consecutive days)	mean % suppression of infected RBC at 4 dpi [a] 4 dpi	mean % infected RBC								MST[b]
		4 dpi	SURVIVORS	7 dpi	SURVIVORS	11dpi	SURVIVORS	14 dpi	SURVIVORS	
Vehicle		17.1	6/6	19.0	4/6	44.0	3/6	64.6	2/6	11.2
chloroquine (10 mg/kg)	98.6	0.2	6/6	0.6	6/6	11.9	6/6		0/6	14.0
19e (50 mg/kg)	0.6	17.1	6/6	30.1	2/6	34.7	2/6		0/6	8.7
8 (50 mg/kg)	99	0.2	6/6	0.04	6/6	3.7	6/6	16.4	4/6	15.3
37a (50 mg/kg)	82	3.0	6/6	6.5	6/6	29.2	3/6	32.6	2/6	12.7

[a] dpi = days post infection.
[b] MST = mean survival time.

3. Conclusion

In conclusion, we report here on the synthesis, antiplasmodial and antimycobacterial activity of a series of 14 amino acid-based prodrug derivatives of fosmidomycin surrogate **4** (Fig. 1) and 2 prodrug derivatives of the α-3,4-dichlorophenyl analog **7** (Fig. 1). Ethyl L-alanine and ethyl L-leucine diamidate derivatives resulted in moderate *in vitro* inhibitory activity of *M. tuberculosis* (H37Rv) growth. These findings suggests that a phosphonamidate prodrug approach may enable uptake of fosmidomycin surrogate **4** in mycobacterial cells. Furthermore, both L-tyrosine-derived ester prodrug derivatives of **4** displayed potent *in vitro* antiplasmodial (*Pf*-K1) activity. Preliminary *in vivo* experiments indicate that the promising *in vitro* activity of the POC-prodrug **8** and *N*-acetyl L-tyrosine ester **37a** is reflected in the *P. berghei* malaria mouse model, while the L-lysine derivative **19e** failed to show significant *in vivo* activity despite its promising *in vitro* activity.

4. Experimental section

4.1. General

All reactions were performed using oven dried round-bottomed flasks sealed with rubber septa, unless otherwise stated. Reactions were magnetically stirred using teflon-coated stir bars. Where appropriate, reactions were carried out in dry solvents and under an inert nitrogen atmosphere. Dropwise addition of reagents or solutions was carried out using a syringe pump. Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure homogeneous materials. Reagents were purchased at the highest commercial quality and used without additional purification, unless otherwise stated. Hexanes for flash column chromatography were distilled prior to use. Reactions were monitored by thin layer chromatography (TLC) carried out on precoated Macherey-Nagel® SIL G/UV254 plates using ultraviolet light (254 nm

wave length) as visualizing agent and either potassium permanganate or ceric ammonium molybdate (CAM) as developing agents. Flash column chromatography was performed manually using Grace Davisil® silica gel (40–60 μm particle size) or automatically using a Grace Reveleris X2 purification system with flash cartridges. NMR spectra were recorded at 25 °C on a Varian Mercury-300 spectrometer. ^{1}H NMR spectra were calibrated using either TMS as a reference (TMS: ^{1}H NMR = 0.00) or residual undeuterated solvent as an internal reference (METHANOL: ^{1}H NMR = 3.31). ^{13}C NMR spectra were calibrated using residual undeuterated solvent as an internal reference (CHLOROFORM-*d*: ^{13}C NMR = 77.16, METHANOL-*d4*: ^{13}C NMR = 49.00). In ^{31}P NMR, signals are referenced to the CHLOROFORM-*d* lock resonance frequency according to IUPAC referencing, with H_3PO_4 set to 0.00 ppm. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad signal. Chemical shifts are expressed in ppm and coupling constants are given in Hertz (Hz). Weak carbon signals were assigned using HSQC experiments. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier XE TOF equipped with an electrospray ionization (ESI-MS) interface and a modular Lockspray TM interface. Samples were infused in a MeCN/water (1:1) + 0.1% formic acid mixture at a rate of 100 μL/min. LC-MS analyses were carried out on a Waters AutoPurification System equipped with PDA and ESI-MS detection and using a Waters CORTECS C18 Column (4.6 × 100 mm, 2.7 μm) and a water/acetonitrile/formic acid linear gradient system at a flow rate of 1.44 mL/min. Preparative HPLC purifications were carried out on a Waters AutoPurification System equipped with PDA and ESI-MS detection and using a Waters Xbridge C18 column (19 × 250 mm, 5 μm) and a water/acetonitrile/formic acid linear gradient system at a flow rate of 20 mL/min.

5. Materials

Final compound **8** and protected hydroxylamines **16** and **46** have been previously reported by us.[22] Hydroxylamine **17** was synthesized in the same way as **46**.

5.1. General procedure 1 for TMSBr-mediated deprotection

Phosphonate ethyl ester (1 eq) was dissolved in DCM (0.1 M) and cooled to 0 °C in an ice bath. TMSBr (5 eq) was added and the solution was subsequently stirred for 10 min at 0 °C and 2 h at RT. ^{31}P NMR confirmed completion of the reaction, after which all volatiles were removed *in vacuo*. The crude oil was dissolved in THF (0.3 M) and treated with H_2O (3 M). The reaction was stirred for 1 h at RT, after which all volatiles were removed *in vacuo*. The residue was coevaporated three times with toluene in order to remove all traces of water. The resulting crude material was dried overnight at high vacuum and immediately used in the next reaction without further purification or characterization.

5.2. General procedure 2 for phosphonic dichloride formation

A solution of crude phosphonic acid (1 eq) in DCM (0.4 M) was heated to 50 °C. After addition of a catalytic amount of DMF, oxalyl chloride (5 eq) was added dropwise over 30 min. After 3 h at 50 °C, ^{31}P NMR confirmed completion of the reaction, after which all volatiles were removed *in vacuo*. The resulting crude material was immediately used in the next reaction without further purification or characterization.

5.3. General procedure 3 for phosphonamide formation

A solution of crude phosphonic dichloride (1 eq) in DCM (0.2 M) was cooled to 0 °C in an ice bath. DIPEA (6 eq) was added to a solution of the corresponding amino acid (2.5 eq) in DCM (0.3 M). Anhydrous pyridine (1 eq) was added to the first solution, followed by addition of the second to the first solution. The reaction mixture was stirred overnight, slowly warming to RT. After overnight stirring, the reaction mixture was further diluted with DCM and washed with 0.1 M HCl (aq. soln.) and $NaHCO_3$ (sat. aq. soln.). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by column chromatography with appropriate eluents.

5.4. General procedure 4 for hydroboration-oxidation

9-BBN in THF 0.5 M (4 eq) was added to terminal alkene (1 eq). The resulting solution was allowed to stir overnight at RT, after which H_2O (0.13 M) and SPB·H_2O (8 eq) were added. The reaction mixture was stirred vigorously at RT for 3 h, after which LC-MS confirmed completion of the reaction. The reaction mixture was filtered and concentrated *in vacuo*. The products were purified by column chromatography with appropriate eluents.

5.5. General procedure 5 for TEMPO-BAIB oxidation

To a solution of primary alcohol (1 eq) in MeCN (0.2 M) were added consecutively H_2O (0.2 M), TEMPO (0.3 eq), BAIB (3 eq) and $NaHCO_3$ (1.5 eq). The reaction was protected from light and stirred overnight at RT. The reaction mixture was partially evaporated *in vacuo* in order to remove MeCN. The crude was further diluted with H_2O, the pH of the reaction was subsequently lowered to pH 2 with 1 M HCl (aq. soln.) and the reaction mixture was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* The products were purified by column chromatography with appropriate eluents.

5.6. General procedure 6 for EDC-mediated coupling

EDC.HCl (1.3 eq) and HOBt (1 eq) were added to a solution of acid (1 eq) in DCM (0.3 M). A solution of hydroxylamine (1.3 eq) and Et_3N (4 eq) in DCM (0.6 M) was added to the first solution and the reaction was allowed to stir overnight at RT. The reaction mixture was further diluted with DCM and washed with H_2O, citric acid (1 M aq. soln.) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by column chromatography with appropriate eluents.

5.7. General procedure 7 for hydrogenation

Benzyl protected compounds (1 eq) were dissolved in MeOH, EtOH, iPrOH or EtOAc (+formic acid, 1 eq) (0.05 M). A catalytic amount of Pd/C was added to the reaction mixture. The reaction was stirred for 30 min under a hydrogen atmosphere, after which TLC analysis confirmed complete conversion of the starting material. The reaction mixture was filtered and all volatiles were removed *in vacuo*. The products were purified by column chromatography with appropriate eluents.

5.8. General procedure 8 for cross metathesis

Phosphonate esters (1 eq) and benzyl-protected hydroxamate (4 eq) were dissolved in toluene (0.1 M). This solution was heated to 70 °C. Grubbs Hoveyda 2 catalyst (0.05 eq) was dissolved in a small amount of toluene and a volume corresponding to 0.01 eq of catalyst was added to the reaction mixture every hour. After overnight stirring at 70 °C, all volatiles were removed *in vacuo* and the resulting crude was purified by flash column chromatography with appropriate eluents.

5.9. General procedure 9 for nickel boride reduction

Unsaturated compounds (1 eq) were dissolved in THF (0.1 M).The resulting solution was cooled to 0 °C in an ice bath and $NiCl_2{\cdot}6H_2O$ (2 eq) and $NaBH_4$ (4 eq) were subsequently added. After 1 h, HRMS confirmed complete conversion of the starting material. The reaction was quenched with NH_4Cl (sat. aq. soln.) and was vigorously stirred at RT for 2 h until a clear blue solution was obtained. The reaction mixture was extracted three times with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by column chromatography with appropriate eluents.

5.10. Diethyl but-3-en-1-ylphosphonate (**10**)

A solution of diethyl phosphite (0.64 mL, 5.0 mmol) in dry THF (5 mL) was cooled to 0 °C in an ice bath. NaH (0.20 g, 5.0 mmol) was added gradually and the reaction mixture was allowed to warm to RT. After 1 h, 4-bromo-1-butene (0.76 mL, 7.5 mmol) was added. The reaction was quenched with NH_4Cl (sat. aq. soln.) after overnight stirring and extracted three times with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (DCM → 4% MeOH in DCM) yielded pure **10** as a colorless oil (78%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.26 (t, J = 7.1 Hz, 6H), 1.69–1.83 (m, 2H), 2.21–2.35 (m, 2H), 3.94–4.14 (m, 4H), 4.91–5.04 (m, 2H), 5.79 (ddt, J = 16.9, 10.4, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 16.39 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 24.96 (d, $^1J_{C\text{-}P}$ = 140.5 Hz), 26.46 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 61.41 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 115.01, 137.17 (d, $^3J_{C\text{-}P}$ = 18.4 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm = 31.45. HRMS (ESI-MS): calculated for $C_8H_{18}O_3P$ $[M + H]^+$: 193.0988, found: 193.0987.

5.11. But-3-en-1-ylphosphonic acid (**11**)

Following general procedure 1, **10** (0.58 g, 3.0 mmol) afforded **11** as a crude material, which was dried overnight at high vacuum and immediately used in the next reaction without further purification or characterization.

5.12. But-3-en-1-ylphosphonic dichloride (**12**)

Following general procedure 2, **11** (0.54 g, 4.0 mmol) afforded **12** as a crude material, which was immediately used in the next reaction without further purification or characterization.

5.13. Diethyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis (3-methylbutanoate) (**13a**)

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13a** (71%) as a faint yellow oil after purification by column chromatography (DCM → 3% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.87 (dd, J = 9.5, 6.9 Hz, 6H), 0.98 (dd, J = 6.8, 5.5 Hz, 6H), 1.23–1.33 (m, 6H), 1.75–1.89 (m, 2H), 2.01–2.18 (m, 2H), 2.30–2.45 (m, 2H), 2.83–3.00 (m, 2H), 3.73–3.91 (m, 2H), 4.09–4.28 (m, 4H), 5.00–5.06 (m, 1H), 5.10 (dq, J = 17.1, 1.6 Hz, 1H), 5.87 (ddt, J = 16.9, 10.3, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.23, 17.3, 17.5, 19.0, 27.1 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 28.7 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 32.0 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 32.2 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 57.7, 58.5, 61.0, 61.1, 115.4, 137.8 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 173.9 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 174.1 (d, $^3J_{C\text{-}P}$ = 2.3 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.67. HRMS (ESI-MS): calculated for $C_{18}H_{36}N_2O_5P$ $[M + H]^+$: 391.2356, found: 391.2367.

5.14. Diethyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis (3-phenylpropanoate) (**13b**)

Following general procedure 3, crude **12** (0.35 g, 2.0 mmol) afforded **13b** (44%) as a yellow oil after purification by column chromatography (DCM → 3.5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.18–1.29 (m, 6H), 1.41–1.61 (m, 2H), 1.98–2.17 (m, 2H), 2.46 (dd, J = 13.0, 11.1 Hz, 1H), 2.83–3.10 (m, 5H), 4.02–4.30 (m, 6H), 4.87–4.98 (m, 2H), 5.67 (ddt, J = 16.9, 10.4, 6.3 Hz, 1H), 7.08–7.34 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 14.3, 26.9 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 28.5 (d, $^1J_{C\text{-}P}$ = 115.2 Hz), 40.8 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 41.3 (d, $^3J_{C\text{-}P}$ = 4.61 Hz), 53.9, 54.3, 61.41, 61.44, 115.3, 127.08, 127.11, 128.6, 129.7, 129.8, 136.4, 136.7, 137.6 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 173.3, 173.5 (d, $^3J_{C\text{-}P}$ = 2.3 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.75. HRMS (ESI-MS): calculated for $C_{26}H_{36}N_2O_5P$ $[M + H]^+$: 487.2356, found: 487.2348.

5.15. Diethyl (but-3-en-1-ylphosphoryl)(S)-di-L-prolinate (**13c**)

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13c** (80%) as a yellow oil after purification by column chromatography (toluene → 70% acetone in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.27 (t, J = 7.1 Hz, 6H), 1.71–2.05 (m, 8H), 2.08–2.34 (m, 2H), 2.34–2.68 (m, 2H), 3.12–3.39 (m, 3H), 3.53 (dq, J = 9.3, 6.6 Hz, 1H), 4.10–4.21 (m, 4H), 4.21–4.33 (m, 2H), 4.90–5.09 (m, 2H), 5.86 (ddt, J = 16.9, 10.3, 6.3 Hz, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 25.1 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 25.2 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 25.9 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 26.1 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 31.6 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 31.9 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 46.1, 47.0 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 59.1 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 59.4 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 60.8, 60.9, 114.6, 138.1 (d, $^3J_{C\text{-}P}$ = 18.4 Hz), 174.5, 174.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.09. HRMS (ESI-MS): calculated for $C_{18}H_{32}N_2O_5P$ $[M + H]^+$: 387.2043, found: 387.2050.

5.16. Diethyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)] (2S,2′S,3R,3′R)-bis(3-methylpentanoate) (**13d**)

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13d** (35%) as a faint yellow foam after purification by column chromatography (DCM → 2.5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.84–1.01 (m, 12H), 1.01–1.23 (m, 2 H), 1.23–1.33 (m, 6 H), 1.33–1.52 (m, 2 H), 1.71–1.91 (m, 4 H), 2.27–2.44 (m, 2 H), 2.81–2.99 (m, 2 H), 3.86 (dddd, J = 17.6, 11.0, 9.7, 4.7 Hz, 2 H), 4.06–4.29 (m, 4 H), 4.98–5.16 (m, 2 H), 5.86 (ddt, J = 16.9, 10.3, 6.4 Hz, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 11.8, 11.9, 14.4, 15.57, 15.60, 24.9, 25.2, 27.2 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 28.8 (d, $^1J_{C\text{-}P}$ = 111.7 Hz), 39.3 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 39.5 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 57.2, 578.0, 61.1, 61.2, 115.5, 137.9 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 173.9, 174.1 (d, $^3J_{C\text{-}P}$ = 2.3 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.43. HRMS (ESI-MS): calculated for $C_{20}H_{40}N_2O_5P$ $[M + H]^+$: 419.2669, found: 419.2678.

5.17. Diethyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis (6{[(benzyloxy)carbonyl] amino} hexanoate) (**13e**)

Following general procedure 3, crude **12** (1.0 g, 6.0 mmol) afforded **13e** (59%) as a yellow oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.18–1.32 (m, 6H), 1.32–1.66 (m, 10H), 1.69–1.87 (m, 4H), 2.22–2.41 (m, 2H), 2.88–3.06 (m, 2H), 3.09–3.26 (m, 4H), 3.81–4.01 (m, 2H), 4.09–4.26 (m, 4H), 4.97–5.05 (m, 2H), 5.08 (s, 4H), 5.23–5.42 (m, 2H), 5.72–5.90 (m, 1H), 7.28–7.38 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 22.0, 22.2, 27.0 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 28.7 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 28.9, 29.1, 33.9, 34.5, 40.6, 40.8, 52.3, 53.1, 61.4, 61.6, 66.6, 115.6, 128.1, 128.6, 136.9, 137.6 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 156.7, 174.2, 174.3. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.43. HRMS (ESI-MS): calculated for $C_{36}H_{54}N_4O_9P$ $[M + H]^+$: 717.3623, found: 717.3592.

*5.18. Dimethyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis (4-methylpentanoate) (**13f**)*

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13f** (59%) as a yellow foam after purification by column chromatography (DCM → 3.5% MeOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.89–0.98 (m, 12H), 1.40–1.87 (m, 8H), 2.25–2.42 (m, 2 H), 2.80 (br s, 2 H), 3.72 (d, J = 3.2 Hz, 6 H), 3.90–4.03 (m, 2 H), 5.02 (dq, J = 10.2, 1.4 Hz, 1 H), 5.09 (dq, J = 17.1, 1.6 Hz, 1 H), 5.85 (ddt, J = 16.9, 10.3, 6.4 Hz, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 22.1, 22.2, 22.8, 22.9, 24.7, 24.8, 27.1 (d, $^{2}J_{C-P}$ = 3.5 Hz), 28.6 (d, $^{1}J_{C-P}$ = 112.9 Hz), 44.1, 44.2, 44.3, 51.3, 52.0, 52.2, 115.51, 137.8 (d, $^{3}J_{C-P}$ = 16.1 Hz), 175.5, 175.56, 175.60. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.85. HRMS (ESI-MS): calculated for $C_{18}H_{36}N_2O_5P$ $[M + H]^+$: 391.2356, found: 391.2353.

*5.19. Diethyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis (4-methylpentanoate) (**13g**)*

Following general procedure 3, crude **12** (0.86 g, 5.0 mmol) afforded **13g** (62%) as a colorless foam after purification by column chromatography (DCM → 4.5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.88–1.00 (m, 12H), 1.28 (td, J = 7.1, 5.1 Hz, 6H), 1.42–1.87 (m, 8H), 2.25–2.43 (m, 2 H), 2.71–2.84 (m, 2 H), 3.88–4.01 (m, 2 H), 4.08–4.26 (m, 4 H), 4.98–5.05 (m, 1 H), 5.09 (dq, J = 17.1, 1.6 Hz, 1 H), 5.85 (ddt, J = 17.0, 10.3, 6.4 Hz, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 22.1, 22.2, 22.8, 22.9, 24.7, 24.8, 27.1 (d, $^{2}J_{C-P}$ = 3.5 Hz), 28.7 (d, $^{1}J_{C-P}$ = 112.9 Hz), 44.1 (d, $^{3}J_{C-P}$ = 5.8 Hz), 44.3 (d, $^{3}J_{C-P}$ = 4.6 Hz), 51.3, 52.1, 61.2, 61.3, 115.4, 137.8 (d, $^{3}J_{C-P}$ = 16.1 Hz), 175.0. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.56. HRMS (ESI-MS): calculated for $C_{20}H_{40}N_2O_5P$ $[M + H]^+$: 419.2669, found: 419.2659.

*5.20. Diisopropyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis(4-methylpentanoate) (**13h**)*

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13h** (56%) as a faint yellow foam after purification by column chromatography (DCM → 4% iPrOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.85–1.03 (m, 12H), 1.19–1.31 (m, 12H), 1.39–1.63 (m, 4H), 1.65–1.97 (m, 4H), 2.23–2.45 (m, 2 H), 2.84 (br s, 2 H), 3.90 (td, J = 8.5, 6.2 Hz, 2 H), 4.97–5.12 (m, 4H), 5.85 (ddt, J = 17.0, 10.3, 6.4 Hz, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 21.8, 21.9, 22.1, 22.2, 22.7, 22.8, 24.66, 24.72, 27.1 (d, $^{2}J_{C-P}$ = 3.5 Hz), 28.7 (d, $^{1}J_{C-P}$ = 112.9 Hz), 44.0 (d, $^{3}J_{C-P}$ = 5.8 Hz), 44.3 (d, $^{3}J_{C-P}$ = 5.8 Hz), 51.4, 52.2, 68.7, 68.9, 115.3, 137.8 (d, $^{3}J_{C-P}$ = 15.0 Hz), 174.49, 174.52. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.48. HRMS (ESI-MS): calculated for $C_{22}H_{44}N_2O_5P$ $[M + H]^+$: 447.2982, found: 447.2963.

*5.21. Dipentyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis (4-methylpentanoate) (**13i**)*

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13i** (37%) as a yellow oil after purification by column chromatography (petroleum ether → 40% EtOAc in petroleum ether). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.87–0.99 (m, 18H), 1.28–1.39 (m, 8 H), 1.45–1.84 (m, 12H), 2.26–2.42 (m, 2 H), 2.79 (t, J = 11.2 Hz, 2 H), 3.87–4.03 (m, 2 H), 4.03–4.20 (m, 4 H), 4.98–5.04 (m, 1 H), 5.08 (dq, J = 17.1, 1.6 Hz, 1 H), 5.85 (ddt, J = 16.9, 10.3, 6.4 Hz, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 22.2, 22.3, 22.4, 22.8, 22.9, 24.7, 24.8, 27.1 (d, $^{2}J_{C-P}$ = 3.5 Hz), 28.7 (d, $^{1}J_{C-P}$ = 111.7 Hz), 28.1, 28.4, 44.2 (d, $^{3}J_{C-P}$ = 5.8 Hz), 44.4 (d, $^{3}J_{C-P}$ = 5.8 Hz), 51.3, 52.1, 65.4, 65.5, 115.5, 137.8 (d, $^{3}J_{C-P}$ = 15.0 Hz), 175.1 (d, $^{3}J_{C-P}$ = 2.3 Hz), 175.2 (d, $^{3}J_{C-P}$ = 3.5 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.59. HRMS (ESI-MS): calculated for $C_{26}H_{52}N_2O_5P$ $[M + H]^+$: 503.3608, found: 503.3595.

*5.22. Dicyclohexyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)] (2S,2′S)-bis(4-methylpentanoate) (**13j**)*

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13j** (75%) as a yellow oil after purification by column chromatography (petroleum ether → 60% EtOAc in petroleum ether). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.86–1.02 (m, 12H), 1.23–1.62 (m, 16H), 1.66–1.88 (m, 12H), 2.23–2.45 (m, 2 H), 2.70–2.88 (m, 2 H), 3.82–4.03 (m, 2 H), 4.69–4.86 (m, 2 H), 5.01 (dq, J = 10.2, 1.4 Hz, 1 H), 5.08 (dq, J = 17.1, 1.6 Hz, 1 H), 5.84 (ddt, J = 17.0, 10.3, 6.4 Hz, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 22.2, 22.3, 22.7, 22.8, 23.8, 24.7, 24.8, 25.4, 27.1 (d, $^{2}J_{C-P}$ = 3.5 Hz), 28.7 (d, $^{1}J_{C-P}$ = 111.7 Hz), 31.6, 31.7, 44.2 (d, $^{3}J_{C-P}$ = 5.8 Hz), 44.4 (d, $^{3}J_{C-P}$ = 5.8 Hz), 51.4, 52.2, 73.6, 73.7, 115.4, 137.8 (d, $^{3}J_{C-P}$ = 15.0 Hz), 174.4, 174.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.42. HRMS (ESI-MS): calculated for $C_{28}H_{52}N_2O_5P$ $[M + H]^+$: 527.3608, found: 527.3632.

*5.23. Dibenzyl 2,2′-[(but-3-en-1-ylphosphoryl)bis(azanediyl)](2S,2′S)-bis (4-methylpentanoate) (**13k**)*

Following general procedure 3, crude **12** (0.69 g, 4.0 mmol) afforded **13k** (56%) as a yellow oil after purification by column chromatography (toluene → 75%EtOAc in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.79–0.99 (m, 12H), 1.34–1.81 (m, 8H), 2.19–2.39 (m, 2 H), 2.75–2.94 (m, 2 H), 3.93–4.06 (m, 2 H), 4.95–5.19 (m, 6 H), 5.78 (ddt, J = 16.9, 10.3, 6.4 Hz, 1 H), 7.29–7.36 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 21.9, 22.0, 22.65, 22.73, 24.56, 24.59, 27.0 (d, $^{2}J_{C-P}$ = 3.5 Hz), 28.5 (d, $^{1}J_{C-P}$ = 112.9 Hz), 43.8, 43.9, 44.0, 51.3, 52.0, 66.8, 67.0, 115.3, 128.28, 128.33, 128.5, 128.56, 128.63, 135.4, 135.5, 137.7 (d, $^{3}J_{C-P}$ = 16.1 Hz), 174.67, 174.72. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.54. HRMS (ESI-MS): calculated for $C_{30}H_{44}N_2O_5P$ $[M + H]^+$: 543.2982, found: 543.2967.

*5.24. Diethyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)}(2S,2′S)-bis(3-methylbutanoate) (**14a**)*

Following general procedure 4, **13a** (0.75 g, 1.9 mmol) afforded **14a** (86%) as a transparent wax after purification by column chromatography (EtOAc → 8% EtOH in EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.81–0.92 (m, 6H), 0.92–1.02 (m, 6H), 1.28 (app td, J = 7.1, 4.3 Hz, 6H), 1.59–1.87 (m, 6H), 2.00–2.17 (m, 2H), 2.88–3.08 (m, 2H), 3.64 (t, J = 5.7 Hz, 2H), 3.72–3.87 (m, 2H), 4.09–4.31 (m, 4H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.4, 17.6, 19.06, 19.09, 19.2 (d, $^{2}J_{C-P}$ = 3.5 Hz), 28.8 (d, $^{1}J_{C-P}$ = 112.9 Hz), 32.1 (d, $^{3}J_{C-P}$ = 5.8 Hz), 32.2 (d, $^{3}J_{C-P}$ = 4.6 Hz), 33.2 (d, $^{3}J_{C-P}$ = 15.0 Hz), 57.8, 58.6, 61.2, 61.4, 174.1. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.78. HRMS (ESI-MS): calculated for $C_{18}C_{38}N_2O_6P$ $[M + H]^+$: 409.2462, found: 409.2479.

*5.25. Diethyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)}(2S,2′S)-bis(3-phenylpropanoate) (**14b**)*

Following general procedure 4, **13b** (558 mg, 1.15 mmol) afforded **14b** (83%) as a transparent oil after purification by column chromatography (toluene → 10% EtOH in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.23 (app q, J = 7.1 Hz, 6H), 1.33–1.48 (m, 6H), 1.86–2.07 (br s, 1H), 2.46 (dd, J = 11.1, 11.0 Hz, 1H), 2.79–3.19 (m, 5H), 3.52 (t, J = 5.7 Hz, 2H), 3.97–4.29 (m, 6H), 7.07–7.12 (m, 2H), 7.17–7.34 (m, 8H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 14.3, 19.0 (d, $^{2}J_{C-P}$ = 4.6 Hz), 28.5 (d, $^{1}J_{C-P}$ = 112.9 Hz), 33.2 (d, $^{3}J_{C-P}$ = 15.0 Hz), 40.8, 41.2, 54.0, 54.3, 61.4, 61.5, 61.6, 127.1, 128.6, 129.8, 129.8, 136.5, 136.8. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ

ppm 29.67. HRMS (ESI-MS): calculated for $C_{26}H_{38}N_2O_6P$ $[M + H]^+$: 505.2462, found: 505.2447.

5.26. Diethyl [(4-hydroxybutyl)phosphoryl](S)-di-L-prolinate (14c)

Following general procedure 4, **13c** (985 mg, 2.55 mmol) afforded **14c** (67%) as a transparent oil after purification by column chromatography (EtOAc → 20% EtOH in EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.16–1.35 (m, 6H), 1.57–1.81 (m, 6H), 1.81–2.05 (m, 6H), 2.09–2.26 (m, 2H), 3.13–3.39 (m, 3H), 3.44–3.56 (m, 1H), 3.62 (t, J = 5.8 Hz, 2H), 4.11–4.20 (m, 4H), 4.20–4.33 (m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.9 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 25.7 (d, $^1J_{C\text{-}P}$ = 114.0 Hz), 25.2, 25.3, 31.6 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 31.9 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 33.5 (d, $^3J_{C\text{-}P}$ = 13.8 Hz), 46.1 (d, $^2J_{C\text{-}P}$ = 2.3 Hz), 47.1 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 59.1 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 59.5 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 60.9, 61.0, 61.4, 174.5, 174.7. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 31.59. HRMS (ESI-MS): calculated for $C_{18}H_{34}N_2O_6P$ $[M + H]^+$: 405.2149, found: 405.2152.

5.27. Diethyl2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)} (2S,2′S,3R,3′R)-bis(3-methyl pentanoate) (14d)

Following general procedure 4, **13d** (603 mg, 1.44 mmol) afforded **14d** (61%) as a transparent oil after purification by column chromatography (EtOAc → 8% EtOH in EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.83–0.97 (m, 12H), 1.03–1.22 (m, 2 H), 1.28 (td, J = 7.1, 4.3 Hz, 6 H), 1.33–1.50 (m, 2 H), 1.59–1.87 (m, 8 H), 2.86–3.04 (m, 2 H), 3.61–3.69 (m, 2 H), 3.77–3.92 (m, 2 H), 4.08–4.29 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 11.8, 11.9, 14.3, 15.57, 15.60, 19.2 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 24.9, 25.1, 28.8 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 33.3 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 39.3 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 39.4 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 57.2, 58.0, 61.2, 61.5, 174.08, 174.12, 174.2. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.43. HRMS (ESI-MS): calculated for $C_{20}H_{42}N_2O_6P$ $[M + H]^+$: 437.2775, found: 437.2763.

5.28. Diethyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)}(2S,2′S)-bis(6-{[(benzyloxy) carbonyl]amino}hexanoate) (14e)

Following general procedure 4, **13e** (2.51 g, 3.50 mmol) afforded **14e** (63%) as a transparent oil after purification by column chromatography (petroleum ether → acetone → 10% EtOH in acetone). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (app tt, J = 7.1, 1.6 Hz, 6H), 1.28–1.84 (m, 18H), 2.86 (br s, 1H), 3.00–3.26 (m, 6H), 3.54–3.63 (m, 2H), 3.80–4.00 (m, 2H), 4.04–4.25 (m, 4H), 5.07 (s, 4H), 5.37–5.60 (m, 2H), 7.25–7.37 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.25, 14.28, 19.2 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 22.2, 28.7 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 29.0, 29.1, 33.1 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 33.9 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 34.4 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 40.7, 40.8, 52.3, 53.1, 60.5, 61.4, 61.5, 66.5, 128.1, 128.5, 136.9, 156.7, 156.8, 174.3, 174.4. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.35. HRMS (ESI-MS): calculated for $C_{36}H_{56}N_4O_{10}P$ $[M + H]^+$: 735.3729, found: 735.3717.

5.29. Dimethyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)} (2S,2′S)-bis(4-methylpentanoate) (14f)

Following general procedure 4, **13f** (911 mg, 2.33 mmol) afforded **14f** (24%) as a transparent oil after purification by column chromatography (toluene → 15% MeOH in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.88–1.00 (m, 12H), 1.42–1.80 (m, 12H), 2.83–3.00 (m, 2 H), 3.64 (t, J = 5.7 Hz, 2 H), 3.72 (app d, J = 2.3 Hz, 6 H), 3.88–4.01 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 19.1 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 22.0, 22.1, 22.8, 22.9, 24.66, 24.72, 28.6 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 33.2 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 44.0 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 44.1 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 51.3, 52.0, 52.2, 61.4, 175.59, 175.62, 175.7. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.82. HRMS (ESI-MS): calculated for $C_{18}H_{38}N_2O_6P$ $[M + H]^+$: 409.2462, found: 409.2480.

5.30. Diethyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)}(2S,2′S)-bis(4-methylpentanoate) (14g)

Following general procedure 4, **13g** (0.13 g, 0.30 mmol) afforded **14g** (76%) as a transparent oil after purification by column chromatography (toluene → 10% EtOH in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.90–0.98 (m, 12H), 1.28 (td, J = 7.1, 4.4 Hz, 6H), 1.42–1.80 (m, 12H), 2.88–3.11 (m, 2 H), 3.62 (t, J = 5.6 Hz, 2 H), 3.87–3.98 (m, 2 H), 4.10–4.23 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 19.1 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 22.0, 22.1, 22.7, 22.8, 24.6, 24.7, 28.6 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 33.2 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 43.9, 44.0, 44.1, 51.2, 52.0, 61.2, 175.2. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.57. HRMS (ESI-MS): calculated for $C_{20}H_{42}N_2O_6P$ $[M + H]^+$: 437.2775, found: 437.2758.

5.31. Diisopropyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)} (2S,2′S)-bis(4-methylpentanoate) (14h)

Following general procedure 4, **13h** (991 mg, 2.22 mmol) afforded **14h** (62%) as a transparent oil after purification by column chromatography (toluene → 10% iPrOH in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.88–1.00 (m, 12H), 1.20–1.30 (m, 12H), 1.37–1.81 (m, 12H), 2.78–2.94 (m, 2 H), 3.64 (t, J = 5.8 Hz, 2 H), 3.82–3.96 (m, 2 H), 4.94–5.09 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 19.1 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 21.8, 21.9, 22.1, 22.2, 22.8, 22.9, 24.7, 28.7 (d, $^1J_{C\text{-}P}$ = 111.7 Hz), 33.2 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 44.0 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 44.2 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 51.4, 52.2, 61.4, 68.86, 68.93, 174.60, 174.63, 174.79, 174.83. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.49. HRMS (ESI-MS): calculated for $C_{22}H_{46}N_2O_6P$ $[M + H]^+$: 465.3088, found: 465.3107.

5.32. Dipentyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)} (2S,2′S)-bis(4-methylpentanoate) (14i)

Following general procedure 4, **13i** (706 mg, 1.41 mmol) afforded **14i** (51%) as a transparent oil after purification by column chromatography (toluene → EtOAc → 30% acetone in EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.85–1.01 (m, 18H), 1.26–1.42 (m, 8 H), 1.42–1.79 (m, 16H), 2.78–3.00 (m, 3 H), 3.64 (t, J = 5.6 Hz, 2 H), 3.84–4.01 (m, 2 H), 4.01–4.17 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.0, 19.1 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 22.1, 22.2, 22.4, 22.7, 22.9, 24.7, 24.8, 28.7 (d, $^1J_{C\text{-}P}$ = 111.7 Hz), 28.08, 28.11, 28.3, 33.2 (d, $^3J_{C\text{-}P}$ = 13.8 Hz), 44.1, 44.2, 44.3, 51.3, 52.1, 61.4, 65.4, 65.5, 175.18, 175.22, 175.3. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.49. HRMS (ESI-MS): calculated for $C_{26}H_{54}N_2O_6P$ $[M + H]^+$: 521.3714, found: 521.3690.

5.33. Dicyclohexyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)} (2S,2′S)-bis(4-methyl pentanoate) (14j)

Following general procedure 4, **13j** (1.41 g, 2.67 mmol) afforded **14j** (70%) as a transparent oil after purification by column chromatography (toluene → EtOAc → 30% acetone in EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.91–0.97 (m, 12H), 1.25–1.91 (m, 32H), 2.75–2.92 (m, 2 H), 3.64 (t, J = 5.7 Hz, 2 H), 3.85–4.97 (m, 2 H), 4.70–4.84 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 19.1 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 22.2, 22.3, 22.8, 22.9, 23.8, 24.76, 24.80, 25.4, 28.7 (d, $^1J_{C\text{-}P}$ = 111.7 Hz), 31.6, 31.7, 33.3 (d, $^3J_{C\text{-}P}$ = 13.8 Hz), 44.2 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 44.4 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 51.4, 52.3, 61.5, 73.7, 73.8, 174.5 (d, $^3J_{C\text{-}P}$ = 3.5 Hz), 174.7 (d, $^3J_{C\text{-}P}$ = 2.3 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.38. HRMS (ESI-MS): calculated for $C_{28}H_{54}N_2O_6P$ $[M + H]^+$: 545.3714, found: 545.3732.

*5.34. Dibenzyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)} (2S,2′S)-bis(4-methylpentanoate) (**14k**)*

Following general procedure 4, **13k** (1.26 g, 2.32 mmol) afforded **14k** (61%) as a faint yellow oil after purification by column chromatography (EtOAc → 40% acetone in EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.82–0.95 (m, 12H), 1.33–1.77 (m, 12H), 2.85–2.98 (m, 1H), 3.06 (dd, J = 14.1, 10.9 Hz, 1H), 3.56 (t, J = 5.8 Hz, 2 H), 3.98 (dtd, J = 10.8, 8.5, 8.5, 6.1 Hz, 2 H), 5.05–5.19 (m, 4 H), 7.29–7.37 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 19.1 (d, $^{2}J_{C-P}$ = 4.6 Hz), 22.0, 22.1, 22.7, 22.8, 24.6, 28.6 (d, $^{1}J_{C-P}$ = 111.7 Hz), 33.1 (d, $^{3}J_{C-P}$ = 15.0 Hz), 43.8, 43.9, 51.3, 52.0, 61.2, 66.9, 67.0, 128.3, 128.4, 128.5, 128.6, 128.7, 135.4, 135.6, 174.8 (d, $^{3}J_{C-P}$ = 3.5 Hz), 174.9 (d, $^{3}J_{C-P}$ = 2.3 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.73. HRMS (ESI-MS): calculated for $C_{30}H_{46}N_2O_6P$ $[M + H]^+$: 561.3088, found: 561.3093.

*5.35. 4-(Bis{[(S)-1-ethoxy-3-methyl-1-oxobutan-2-yl]amino}phosphoryl) butanoic acid (**15a**)*

Following general procedure 5, **14a** (664 mg, 1.63 mmol) afforded **15a** (81%) as an off-white wax after purification by column chromatography (toluene → 7.5% EtOH in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.81–0.93 (m, 6H), 0.97 (t, J = 7.0 Hz, 6H), 1.23–1.33 (m, 6H), 1.78–1.99 (m, 4H), 2.01–2.18 (m, 2H), 2.38–2.50 (m, 2H), 3.10–3.23 (m, 1H), 3.34 (dd, J = 13.7, 11.1 Hz, 1H), 3.71–3.89 (m, 2H), 4.08–4.28 (m, 4H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.4, 17.4, 17.6, 18.6 (d, $^{2}J_{C-P}$ = 3.5 Hz), 19.1, 28.3 (d, $^{2}J_{C-P}$ = 112.9 Hz), 32.1 (d, $^{2}J_{C-P}$ = 4.6 Hz), 32.2 (d, $^{2}J_{C-P}$ = 5.8 Hz), 34.6 (d, $^{3}J_{C-P}$ = 15.0 Hz), 58.0, 58.6, 61.28, 61.33, 173.9 (d, $^{3}J_{C-P}$ = 2.3 Hz), 174.1 (d, $^{3}J_{C-P}$ = 2.3 Hz), 175.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 31.84. HRMS (ESI-MS): calculated for $C_{18}H_{36}N_2O_7P$ $[M + H]^+$: 423.2255, found: 423.2274.

*5.36. 4-(Bis{[(S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl]amino} phosphoryl)butanoic acid (**15b**)*

Following general procedure 5, **14b** (0.15 g, 0.30 mmol) afforded **15b** (66%) as a transparent oil after purification by column chromatography (DCM → 6% EtOH in DCM + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.18–1.27 (m, 6H), 1.30–1.64 (m, 4H), 2.17 (br t, J = 6.3 Hz, 2H), 2.52–2.64 (m, 1H), 2.73–2.86 (m, 2H), 3.02 (ddd, J = 18.6, 13.5, 5.3 Hz, 2H), 3.54 (br t, J = 11.1 Hz, 1H), 3.99–4.26 (m, 6H), 7.06–7.11 (m, 2H), 7.17–7.34 (m, 8H), 10.31 (br s, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 14.3, 19.0 (d, $^{2}J_{C-P}$ = 4.6 Hz), 28.5 (d, $^{1}J_{C-P}$ = 107.8 Hz), 33.2 (d, $^{3}J_{C-P}$ = 15.0 Hz), 40.8, 41.2, 54.0, 54.3, 61.4, 61.5, 61.6, 127.1, 128.6, 129.75, 129.84, 136.5, 136.8. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 31.01. HRMS (ESI-MS): calculated for $C_{26}H_{36}N_2O_7P$ $[M + H]^+$: 519.2255, found: 519.2274.

*5.37. 4-{Bis[(S)-2-(ethoxycarbonyl)pyrrolidin-1-yl]phosphoryl}butanoic acid (**15c**)*

Following general procedure 5, **14c** (0.37 g, 0.90 mmol) afforded **15c** (84%) as a faint yellow oil after purification by column chromatography (toluene → 25% EtOH in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.26 (t, J = 7.1 Hz, 6H), 1.79–2.05 (m, 10H), 2.08–2.27 (m, 2H), 2.32–2.53 (m, 2H), 3.14–3.38 (m, 3H), 3.46–3.59 (m, 1H), 4.15 (qd, J = 7.1, 1.8 Hz, 4H), 4.25–4.34 (m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.8 (d, $^{2}J_{C-P}$ = 3.5 Hz), 25.2 (d, $^{3}J_{C-P}$ = 5.8 Hz), 25.25 (d, $^{1}J_{C-P}$ = 114.0 Hz), 25.31 (d, $^{3}J_{C-P}$ = 6.9 Hz), 31.6 (d, $^{3}J_{C-P}$ = 5.8 Hz), 31.9 (d, $^{3}J_{C-P}$ = 5.8 Hz), 34.9 (d, $^{3}J_{C-P}$ = 13.8 Hz), 46.1 (d, $^{2}J_{C-P}$ = 2.3 Hz), 47.0 (d, $^{2}J_{C-P}$ = 4.6 Hz), 59.1 (d, $^{2}J_{C-P}$ = 5.8 Hz), 59.6 (d, $^{2}J_{C-P}$ = 5.8 Hz), 60.9, 61.1, 174.4 (d, $^{3}J_{C-P}$ = 2.3 Hz), 174.5, 175.2. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 32.63. HRMS (ESI-MS): calculated for $C_{18}H_{32}N_2O_7P$ $[M + H]^+$: 419.1942, found: 419.1941.

*5.38. 4-(Bis{[(2S,3R)-1-ethoxy-3-methyl-1-oxopentan-2-yl]amino} phosphoryl)butanoic acid (**15d**)*

Following general procedure 5, **14d** (0.33 g, 0.75 mmol) afforded **15d** (82%) as a transparent oil after purification by column chromatography (toluene → 8% EtOH in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.81–1.02 (m, 12H), 1.02–1.23 (m, 2 H), 1.28 (td, J = 7.1, 4.8 Hz, 6 H), 1.34–1.51 (m, 2 H), 1.72–2.01 (m, 6 H), 2.36–2.47 (m, 2 H), 3.17–3.35 (m, 1 H), 3.37–3.52 (m, 1 H), 3.75–3.93 (m, 2 H), 4.06–4.29 (m, 4 H), 11.38 (br s, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 11.78, 11.81, 14.3, 15.5, 18.4 (d, $^{2}J_{C-P}$ = 3.5 Hz), 24.8, 25.0, 28.1 (d, $^{1}J_{C-P}$ = 112.9 Hz), 34.5 (d, $^{3}J_{C-P}$ = 16.1 Hz), 39.1 (d, $^{3}J_{C-P}$ = 4.6 Hz), 39.3 (d, $^{3}J_{C-P}$ = 4.6 Hz), 57.2, 57.9, 61.18, 61.21, 173.8 (d, $^{3}J_{C-P}$ = 2.3 Hz), 173.9 (d, $^{3}J_{C-P}$ = 2.3 Hz), 175.0. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 31.77. HRMS (ESI-MS): calculated for $C_{20}H_{40}N_2O_7P$ $[M + H]^+$: 451.2568, found: 451.2589.

*5.39. 4-(Bis{[(S)-6-{[(benzyloxy)carbonyl]amino}-1-ethoxy-1-oxohexan-2 yl)amino]phosphoryl} butanoic acid (**15e**)*

Following general procedure 5, **14e** (968 mg, 1.32 mmol) afforded **15e** (48%) as a faint yellow oil after purification by column chromatography (toluene → 10% EtOH in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.18–1.29 (m, 6H), 1.30–1.93 (m, 16H), 2.24–2.46 (m, 2 H), 3.04–3.21 (m, 4 H), 3.22–3.59 (m, 2 H), 3.78–4.00 (m, 2 H), 4.00–4.24 (m, 4 H), 4.96–5.16 (m, 4 H), 5.32–5.55 (m, 2 H), 7.12–7.36 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 18.5, 22.2, 27.4, 28.1 (d, $^{1}J_{C-P}$ = 114.0 Hz), 29.1, 33.9, 34.3, 40.7, 40.8, 52.4, 53.0, 61.4, 61.5, 66.5, 128.1, 128.5, 136.9, 156.7, 156.8, 174.1, 174.3, 175.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 30.26, 30.87. HRMS (ESI-MS): calculated for $C_{36}H_{54}N_4O_{11}P$ $[M + H]^+$: 749.3521, found: 749.3556.

*5.40. 4-(Bis{[(S)-1-methoxy-4-methyl-1-oxopentan-2-yl]amino} phosphoryl)butanoic acid (**15f**)*

Following general procedure 5, **14f** (210 mg, 0.514 mmol) afforded **15f** (43%) as a transparent oil after purification by column chromatography (toluene → 10% MeOH in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.83–1.03 (m, 12H), 1.39–1.95 (m, 10H), 2.34–2.46 (m, 2 H), 3.22 (t, J = 10.5 Hz, 1 H), 3.33–3.45 (m, 1 H), 3.72 (app d, J = 3.3 Hz, 6 H), 3.86–4.01 (m, 2 H), 10.48 (br s, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 18.4 (d, $^{2}J_{C-P}$ = 3.5 Hz), 22.0, 22.1, 22.7, 22.8, 24.6, 28.1 (d, $^{1}J_{C-P}$ = 112.9 Hz), 34.6 (d, $^{3}J_{C-P}$ = 16.1 Hz), 43.8, 43.9, 44.0, 51.3, 51.9, 52.3, 175.3, 175.37, 175.42, 175.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 31.29. HRMS (ESI-MS): calculated for $C_{18}H_{36}N_2O_7P$ $[M + H]^+$: 423.2255, found: 423.2253.

*5.41. 4-(Bis{[(S)-1-ethoxy-4-methyl-1-oxopentan-2-yl]amino}phosphoryl) butanoic acid (**15g**)*

Following general procedure 5, **14g** (98 mg, 0.22 mmol) afforded **15g** (55%) as a faint yellow oil after purification by column chromatography (toluene → 10% EtOH in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.90–0.96 (m, 12H), 1.22–1.34 (m, 6H), 1.38–1.98 (m, 10H), 2.36–2.46 (m, 2 H), 3.11 (t, J = 10.8 Hz, 1 H), 3.30 (dd, J = 14.2, 10.7 Hz, 1 H), 3.85–3.99 (m, 2 H), 4.11–4.26 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 18.5 (d, $^{2}J_{C-P}$ = 3.5 Hz), 22.1, 22.2, 22.8, 22.9, 24.7, 28.2 (d, $^{1}J_{C-P}$ = 112.9 Hz), 34.6 (d, $^{3}J_{C-P}$ = 16.1 Hz), 43.9 (d, $^{3}J_{C-P}$ = 5.8 Hz), 44.1 (d, $^{3}J_{C-P}$ = 5.8 Hz), 51.4, 52.0, 61.35, 61.39, 175.0, 175.1, 175.5. ^{31}P

NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.66. HRMS (ESI-MS): calculated for $C_{20}H_{40}N_2O_7P$ $[M + H]^+$: 451.2568, found: 451.2552.

5.42. 4-(Bis{[(S)-1-isopropoxy-4-methyl-1-oxopentan-2-yl]amino} phosphoryl)butanoic acid (15h)

Following general procedure 5, **14h** (598 mg, 1.29 mmol) afforded **15h** (51%) as a faint yellow oil after purification by column chromatography (DCM → 7% iPrOH in DCM + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.90–0.98 (m, 12H), 1.19–1.29 (m, 12H), 1.37–1.98 (m, 10H), 2.32–2.46 (m, 2 H), 2.99–3.11 (m, 1 H), 3.16–3.35 (m, 1 H), 3.81–3.96 (m, 2 H), 4.94–5.10 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 18.6 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 21.8, 21.92, 22.1, 22.2, 22.8, 22.9, 24.7, 28.3 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 34.6 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 43.9 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 44.2 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 51.5, 52.2, 68.96, 69.04, 174.5 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 174.6 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 175.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.43. HRMS (ESI-MS): calculated for $C_{22}H_{44}N_2O_7P$ $[M + H]^+$: 479.2881, found: 479.2894.

5.43. 4-(Bis{[(S)-4-methyl-1-oxo-1-(pentyloxy)pentan-2-yl]amino} phosphoryl)butanoic acid (15i)

Following general procedure 5, **14i** (346 mg, 0.660 mmol) afforded **15i** (51%) as a faint yellow oil after purification by column chromatography (toluene → 40% acetone in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.85–1.01 (m, 18H), 1.24–1.40 (m, 8 H), 1.43–1.99 (m, 14H), 2.28–2.49 (m, 2 H), 3.07 (t, *J* = 10.5 Hz, 1 H), 3.21–3.32 (m, 1 H), 3.84–4.01 (m, 2 H), 4.01–4.18 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 18.6 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 22.15, 22.21, 22.4, 22.8, 22.9, 24.7, 28.10, 28.13, 28.3 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 34.6 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 44.0, 44.2, 51.4, 52.1, 65.5, 65.6, 175.1, 175.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.62. HRMS (ESI-MS): calculated for $C_{26}H_{52}N_2O_7P$ $[M + H]^+$: 535.3507, found: 535.3487.

5.44. 4-(Bis{[(S)-1-(cyclohexyloxy)-4-methyl-1-oxopentan-2-yl]amino} phosphoryl)butanoic acid (15j)

Following general procedure 5, **14j** (953 mg, 1.80 mmol) afforded **15j** (34%) as a yellow oil after purification by column chromatography (toluene → 40% acetone in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.88–0.98 (m, 12H), 1.25–1.62 (m, 16H), 1.65–1.92 (m, 14H), 2.34–2.50 (m, 2 H), 3.07 (t, *J* = 10.6 Hz, 1 H), 3.31–3.44 (m, 1 H), 3.82–3.97 (m, 2 H), 4.71–4.84 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 18.5 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 22.16, 22.22, 22.7, 22.8, 23.8, 24.7, 25.4, 28.3 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 31.5, 31.6, 34.6 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 43.9 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 44.2 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 51.4, 52.1, 73.7, 73.8, 174.35, 174.41, 174.44. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.56. HRMS (ESI-MS): calculated for $C_{28}H_{52}N_2O_7P$ $[M + H]^+$: 559.3507, found: 559.3503.

5.45. 4-(Bis{[(S)-1-(benzyloxy)-4-methyl-1-oxopentan-2-yl]amino} phosphoryl)butanoic acid (15k)

Following general procedure 5, **14k** (65 mg, 0.12 mmol) afforded **15k** (55%) as a transparent oil after purification by column chromatography (petroleum ether → 50% acetone in petroleum ether + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.79–0.95 (m, 12H), 1.30–1.91 (m, 10H), 2.29–2.36 (m, 2 H), 3.01 (t, *J* = 10.9 Hz, 1 H), 3.16–3.27 (m, 1 H), 3.86–4.05 (m, 2 H), 5.06–5.19 (m, 4 H), 7.30–7.37 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 18.4 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 22.0, 22.1, 22.7, 22.8, 24.6, 28.1 (d, $^1J_{C\text{-}P}$ = 111.7 Hz), 34.5 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 43.65, 43.73, 43.8, 51.4, 52.0, 66.99, 67.04, 128.4, 128.5, 128.6, 128.7, 135.5, 135.6, 174.7, 175.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.72. HRMS (ESI-MS): calculated for $C_{30}H_{44}N_2O_7P$ $[M + H]^+$: 575.2881, found: 575.2872.

5.46. O-(tert-butyldimethylsilyl)-N-methylhydroxylamine (17)

N-methyl hydroxylamine hydrochloride (1.84 g, 22.0 mmol) was dissolved in DCM (22 mL). DIPEA (8.70 mL, 50.0 mmol) was added, followed by addition of TBSCl (3.01 g, 20.0 mmol). After overnight stirring at RT, the reaction mixture was further diluted with DCM and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (hexanes → 40% EtOAc in hexanes) yielded pure 17 as a transparent liquid (18%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.04–0.10 (m, 6H), 0.84–0.92 (m, 9H), 2.66 (s, 3H), 5.00 (br s, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm −5.5, 18.1, 26.4, 41.9. HRMS (ESI-MS): calculated for $C_7H_{20}NOSi$ $[M + H]^+$: 162.1309, found: 162.1310.

5.47. Diethyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-bis(3-methylbutanoate) (18a)

Following general procedure 6 using hydroxylamine 16, **15a** (545 mg, 1.29 mmol) afforded **18a** (70%) as a faint yellow oil after purification by column chromatography (DCM → 4.5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.81–1.02 (m, 12H), 1.27 (app q, *J* = 7.2 Hz, 6H), 1.62–1.78 (m, 2 H), 1.83–2.00 (m, 2 H), 2.01–2.19 (m, 2 H), 2.44–2.58 (m, 2 H), 3.20 (s, 3 H), 3.31–3.49 (m, 2 H), 3.74–3.88 (m, 2 H), 4.05–4.27 (m, 4 H), 4.83 (s, 2 H), 7.38 (s, 5 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.3, 17.5, 18.1 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 19.1, 28.7 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 32.0 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 32.1 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 32.4 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 33.5 (w), 57.7, 58.5, 60.9, 61.0, 76.3, 128.8, 129.0, 129.3, 134.5, 173.9 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 174.1 (d, $^3J_{C\text{-}P}$ = 2.3 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.68. HRMS (ESI-MS): calculated for $C_{26}H_{45}N_3O_7P$ $[M + H]^+$: 542.2990, found: 542.2989.

5.48. Diethyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-bis(3-phenylpropanoate) (18b)

Following general procedure 6 using hydroxylamine **16**, **15b** (0.11 g, 0.22 mmol) afforded **18b** (72%) as a transparent oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.17–1.25 (m, 6H), 1.27–1.83 (m, 4H), 2.30–2.37 (m, 2H), 2.57–2.68 (m, 1H), 2.81–3.12 (m, 5H), 3.18 (s, 3 H), 4.00–4.17 (m, 5H), 4.17–4.29 (m, 1H), 4.80 (s, 2H), 7.08–7.45 (m, 15H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 18.0 (d, $^2J_{C\text{-}P}$ = 2.3 Hz), 28.6 (d, $^1J_{C\text{-}P}$ = 115.2 Hz), 32.4 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 33.6 (w), 40.8 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 41.2 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 53.9, 54.2, 61.2, 61.3, 76.3, 126.89, 126.94, 128.5, 128.8, 129.1, 129.4, 129.7, 129.8, 136.6, 136.8, 173.3, 173.41. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.62. HRMS (ESI-MS): calculated for $C_{34}H_{45}N_3O_7P$ $[M + H]^+$: 638.2990, found: 638.3000.

5.49. Diethyl ({4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphoryl) (S)-di-L-prolinate (18c)

Following general procedure 6 using hydroxylamine **16**, **15c** (0.41 g, 0.98 mmol) afforded **18c** (78%) as a faint yellow oil after purification by column chromatography (DCM → 7.5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (td, *J* = 7.1, 2.5 Hz, 6H), 1.69–2.03 (m, 9H), 2.05–2.26 (m, 3H), 2.47–2.57 (m, 2H), 3.18 (s, 3H), 3.21–3.36 (m, 3H), 3.44–3.57 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 4H), 4.19–4.34 (m, 2H), 4.83 (s, 2H), 7.33–7.43 (m, 5H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.2 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 25.2, 25.4, 26.1 (d, $^1J_{C\text{-}P}$ = 111.7 Hz), 31.6 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 31.9 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 32.8 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 33.5 (w), 46.2 (d, $^2J_{C\text{-}P}$ = 2.3 Hz), 47.0 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 59.1 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 59.5 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 60.8, 60.9, 76.4, 128.8, 129.1, 129.4, 174.6 d, $^3J_{C\text{-}P}$ = 2.3 Hz), 174.7. ^{31}P

NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.55. HRMS (ESI-MS): calculated for $C_{26}H_{41}N_3O_7P$ $[M + H]^+$: 538.2677, found: 538.2659.

5.50. Diethyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)] (2S,2′S,3R,3′R)-bis(3-methylpentanoate) (18d)

Following general procedure 6 using hydroxylamine **16**, **15d** (0.24 g, 0.53 mmol) afforded **18d** (76%) as a transparent oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.79–1.04 (m, 12H), 1.04–1.20 (m, 2 H), 1.21–1.33 (m, 6 H), 1.34–1.48 (m, 2 H), 1.63–1.97 (m, 6 H), 2.51 (br t, *J* = 6.6 Hz, 2 H), 3.20 (s, 3 H), 3.74–3.93 (m, 2 H), 4.02–4.30 (m, 4 H), 4.82 (s, 2 H), 7.36–7.40 (m, 5 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 11.9, 12.0, 14.4, 15.6, 18.2 (d, $^2J_{C-P}$ = 3.5 Hz), 24.9, 25.1, 28.8 (d, $^1J_{C-P}$ = 112.9 Hz), 32.5 (d, $^3J_{C-P}$ = 15.0 Hz), 33.6 (w), 39.2 (d, $^3J_{C-P}$ = 4.6 Hz), 39.4 (d, $^3J_{C-P}$ = 4.6 Hz), 57.1, 58.0, 61.0, 61.1, 76.4, 128.9, 129.1, 129.4, 134.6, 174.0, 174.1, 174.2. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.42. HRMS (ESI-MS): calculated for $C_{28}H_{49}N_3O_7P$ $[M + H]^+$: 570.3303, found: 570.3327.

5.51. Diethyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-bis(6-{[(benzyloxy)carbonyl]amino} hexanoate) (18e)

Following general procedure 6 using hydroxylamine **16**, **15e** (475 mg, 0.630 mmol) afforded **18e** (91%) as a transparent oil after purification by column chromatography (DCM → 6% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.19–1.28 (m, 6H), 1.31–1.94 (m, 16H), 2.38–2.51 (m, 2 H), 3.01–3.27 (m, 8 H), 3.41–3.56 (m, 1 H), 3.81–4.02 (m, 2 H), 4.05–4.24 (m, 4 H), 4.76 (s, 2 H), 5.07 (app d, *J* = 2.5 Hz, 4 H), 5.36–5.64 (m, 2 H), 7.20–7.44 (m, 15H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.9, 22.1, 22.2, 28.5 (d, $^1J_{C-P}$ = 112.9 Hz), 28.8, 29.0, 32.2 (d, $^3J_{C-P}$ = 15.0 Hz), 33.4 (w), 33.8 (d, $^3J_{C-P}$ = 4.6 Hz), 34.3 (d, $^3J_{C-P}$ = 4.6 Hz), 40.6, 40.7, 52.2, 53.0, 61.3, 61.4, 66.4, 66.5, 76.2, 128.1, 128.5, 128.8, 129.1, 129.4, 134.4, 136.9, 137.0, 156.6, 156.7, 174.3, 174.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.14. HRMS (ESI-MS): calculated for $C_{44}H_{63}N_5O_{11}P$ $[M + H]^+$: 868.4256, found: 868.4297.

5.52. Dimethyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)] (2S,2′S)-bis(4-methylpentanoate) (18f)

Following general procedure 6 using hydroxylamine **16**, **15f** (93 mg, 0.22 mmol) afforded **18f** (83%) as a transparent oil after purification by column chromatography (DCM → 5% MeOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.89–0.98 (m, 12H), 1.39–1.95 (m, 10H), 2.51 (t, *J* = 6.6 Hz, 2 H), 2.88 (t, *J* = 10.4 Hz, 1 H), 3.20 (s, 3 H), 3.23–3.32 (m, 1 H), 3.70 (app d, *J* = 6.4 Hz, 6 H), 3.89–4.03 (m, 2 H), 4.83 (s, 2 H), 7.39 (s, 5 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 18.1 (d, $^2J_{C-P}$ = 3.5 Hz), 22.0, 22.1, 22.8, 22.9, 24.66, 24.74, 28.7 (d, $^1J_{C-P}$ = 111.7 Hz), 32.4 (d, $^3J_{C-P}$ = 15.0 Hz), 33.7, 43.9, 44.0, 44.1, 51.1, 52.0, 52.2, 76.4, 128.9 129.2, 129.4, 134.5, 175.6, 175.68, 175.71. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.52. HRMS (ESI-MS): calculated for $C_{26}H_{45}N_3O_7P$ $[M + H]^+$: 542.2990, found: 542.2990.

5.53. Diethyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-bis(4-methylpentanoate) (18g)

Following general procedure 6 using hydroxylamine **16**, **15g** (0.17 g, 0.37 mmol) afforded **18g** (83%) as a transparent oil after purification by column chromatography (DCM → 7% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.87–1.01 (m, 12H), 1.26 (q, *J* = 7.3 Hz, 6H), 1.41–1.98 (m, 10H), 2.50 (t, *J* = 6.7 Hz, 2 H), 2.85 (br t, *J* = 10.0 Hz, 1 H), 3.15–3.24 (m, 1 H), 3.19 (s, 3 H), 3.86–4.01 (m, 2 H), 4.08–4.25 (m, 4 H), 4.82 (s, 2 H), 7.38 (s, 5 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 18.2, 22.1, 22.2, 22.8, 22.9, 24.7, 24.8, 28.8 (d, $^1J_{C-P}$ = 112.9 Hz), 32.4 (d, $^3J_{C-P}$ = 15.0 Hz), 33.6 (w), 44.0 (d, $^3J_{C-P}$ = 5.8 Hz), 44.11 (d, $^3J_{C-P}$ = 5.8 Hz), 51.2, 52.1, 61.1, 61.2, 76.4, 128.9, 129.1, 129.4, 134.6, 175.1–175.2 (m). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.29. HRMS (ESI-MS): calculated for $C_{28}H_{49}N_3O_7P$ $[M + H]^+$: 570.3303, found: 570.3289.

5.54. Diisopropyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)] (2S,2′S)-bis(4-methylpentanoate) (18h)

Following general procedure 6 using hydroxylamine 16, 15 h (0.31 g, 0.65 mmol) afforded 18 h (72%) as a transparent oil after purification by column chromatography (DCM → 4% iPrOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.90–0.97 (m, 12H), 1.20–1.28 (m, 12H), 1.37–1.94 (m, 10H), 2.50 (t, *J* = 6.7 Hz, 2 H), 2.85 (t, *J* = 10.6 Hz, 1 H), 3.09–3.26 (m, 1 H), 3.19 (s, 3 H), 3.83–3.97 (m, 2 H), 4.82 (s, 2 H), 5.00 (dq, *J* = 12.3, 6.2 Hz, 2 H), 7.38 (s, 5 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 18.1 (d, $^2J_{C-P}$ = 4.6 Hz), 21.7, 21.75, 21.79, 22.0, 22.1, 22.7, 22.8, 24.57, 24.63, 28.8 (d, $^1J_{C-P}$ = 111.7 Hz), 32.3 (d, $^3J_{C-P}$ = 15.0 Hz), 33.5 (w), 43.8 (d, $^3J_{C-P}$ = 4.6 Hz), 44.0 (d, $^3J_{C-P}$ = 5.8 Hz), 51.2, 52.1, 68.5, 68.6, 76.3, 128.7, 129.0, 129.3, 134.5, 174.50, 174.54. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.17. HRMS (ESI-MS): calculated for $C_{30}H_{53}N_3O_7P$ $[M + H]^+$: 598.3616, found: 598.3590.

5.55. Dipentyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)] (2S,2′S)-bis(4-methylpentanoate) (18i)

Following general procedure 6 using hydroxylamine **16**, **15i** (0.16 g, 0.30 mmol) afforded **18i** (61%) as a transparent oil after purification by column chromatography (toluene → 40% acetone in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.85–0.99 (m, 18H), 1.25–1.42 (m, 8 H), 1.42–1.96 (m, 14H), 2.50 (t, *J* = 6.6 Hz, 2 H), 2.86 (t, *J* = 10.5 Hz, 1 H), 3.19 (s, 3 H), 3.26 (dd, *J* = 14.7, 10.7 Hz, 1 H), 3.89–4.03 (m, 2 H), 4.03–4.17 (m, 4 H), 4.82 (s, 2 H), 7.38 (s, 5 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 18.2 (d, $^2J_{C-P}$ = 4.6 Hz), 22.1, 22.2, 22.4, 22.8, 22.9, 24.7, 24.8, 28.8 (d, $^1J_{C-P}$ = 111.7 Hz), 28.1, 28.3, 32.4 (d, $^3J_{C-P}$ = 15.0 Hz), 44.1 (d, $^3J_{C-P}$ = 4.6 Hz), 44.2 (d, $^3J_{C-P}$ = 5.8 Hz), 51.2, 52.1, 65.3, 65.4, 76.4, 128.9, 129.1, 129.4, 175.21, 175.24, 175.3. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.32. HRMS (ESI-MS): calculated for $C_{34}H_{61}N_3O_7P$ $[M + H]^+$: 654.4242, found: 654.4250.

5.56. Dicyclohexyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)] (2S,2′S)-bis(4-methylpentanoate) (18j)

Following general procedure 6 using hydroxylamine **16**, **15j** (0.35 g, 0.63 mmol) afforded **18j** (71%) as a transparent oil after purification by column chromatography (toluene → 30% acetone in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.85–1.01 (m, 12H), 1.25–1.59 (m, 16H), 1.60–1.94 (m, 14H), 2.50 (t, *J* = 6.6 Hz, 2 H), 2.87 (t, *J* = 10.6 Hz, 1 H), 3.19 (s, 3 H), 3.21–3.29 (m, 1 H), 3.82–4.07 (m, 2 H), 4.70–4.80 (m, 2 H), 4.82 (s, 2H), 7.14–7.24 (m, 1 H), 7.38 (s, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 18.2 (d, $^2J_{C-P}$ = 3.5 Hz), 22.2, 22.3, 22.8, 22.9, 23.8, 24.7, 24.8, 25.4, 28.8 (d, $^1J_{C-P}$ = 112.9 Hz), 31.6, 32.4 (d, $^3J_{C-P}$ = 15.0 Hz), 33.9, 44.0 (d, $^3J_{C-P}$ = 5.8 Hz), 44.3 (d, $^3J_{C-P}$ = 6.9 Hz), 51.3, 52.2, 73.5, 73.6, 76.4, 128.9, 129.1, 129.4, 174.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.25. HRMS (ESI-MS): calculated for $C_{36}H_{61}N_3O_7P$ $[M + H]^+$: 678.4242, found: 678.4269.

*5.57. Diethyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl) bis(azanediyl)](2S,2′S)-bis(3-methylbutanoate) (**19a**)*

Following general procedure 7 in EtOH, **18a** (0.48 g, 0.89 mmol) afforded **19a** (quantitative) as a transparent oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.82–0.93 (m, 6H), 0.97 (app t, *J* = 6.9 Hz, 6H), 1.28 (app td, *J* = 7.1, 4.6 Hz, 6H), 1.68–1.85 (m, 2H), 1.85–2.19 (m, 4H), 2.55–2.70 (m, 2H), 3.23 (s, 3H), 3.27–3.47 (m, 2H), 3.59–3.84 (m, 2H), 4.06–4.31 (m, 4H), 10.28 (br s, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.31, 14.34, 17.3, 17.5, 18.7 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 19.2, 28.2 (d, $^{1}J_{C\text{-}P}$ = 112.9 Hz), 31.3 (d, $^{3}J_{C\text{-}P}$ = 11.5 Hz), 31.9 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 32.1 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 35.9, 58.0, 58.5, 61.2, 173.0, 173.8, 173.9. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 31.73. HRMS (ESI-MS): calculated for $C_{19}H_{39}N_3O_7P$ $[M + H]^+$: 452.2520, found: 452.2503.

*5.58. Diethyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl) bis(azanediyl)](2S,2′S)-bis(3-phenylpropanoate) (**19b**)*

Following general procedure 7 in EtOH, **18b** (0.10 g, 0.16 mmol) afforded **19b** (69%) as a transparent oil. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.21–1.28 (m, 6H), 1.33–1.64 (m, 4H), 2.20–2.47 (m, 2H), 2.60–2.78 (m, 2H), 2.89–2.98 (m, 1H), 3.02–3.10 (m, 1H), 3.18 (s, 3H), 3.81–3.96 (m, 2H), 4.05–4.28 (m, 4H), 7.01–7.10 (m, 2H), 7.16–7.35 (m, 8H), 10.11 (br s, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 14.3, 18.8 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz), 28.1 (d, $^{1}J_{C\text{-}P}$ = 114.0 Hz), 31.7 (d, $^{3}J_{C\text{-}P}$ = 12.7 Hz), 35.8, 40.6 (d, $^{3}J_{C\text{-}P}$ = 2.3 Hz), 40.8 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 54.1, 54.5, 61.3, 61.6, 127.1, 128.5, 129.5, 130.0, 136.5, 137.0, 173.1, 173.4, 173.8. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.63, 30.23. HRMS (ESI-MS): calculated for $C_{27}H_{39}N_3O_7P$ $[M + H]^+$: 548.2520, found: 548.2534.

*5.59. Diethyl ({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)(S)-di-L-prolinate (**19c**)*

Following general procedure 7 in EtOH, **18c** (0.36 g, 0.67 mmol) afforded **19c** (97%) as a transparent oil after purification by column chromatography (DCM → 8% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.27 (t, *J* = 7.1 Hz, 6H), 1.78–2.06 (m, 10H), 2.06–2.28 (m, 2H), 2.60–2.71 (m, 2H), 3.17–3.38 (m, 3H), 3.24 (s, 3H), 3.43–3.55 (m, 1H), 4.09–4.20 (m, 4H), 4.20–4.27 (m, 2H), 10.44 (br s, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 18.2 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 24.6 (d, $^{1}J_{C\text{-}P}$ = 112.9 Hz), 25.2 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 25.4 (d, $^{3}J_{C\text{-}P}$ = 6.91 Hz), 30.8 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 31.6 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 31.9 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 35.7, 46.4, 47.0 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 59.0 (d, $^{2}J_{C\text{-}P}$ = 5.8 Hz), 59.7 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 61.0, 61.2, 173.0, 174.2, 174.4. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 30.41, 32.53. HRMS (ESI-MS): calculated for $C_{19}H_{35}N_3O_7P$ $[M + H]^+$: 448.2207, found: 448.2211.

*5.60. Diethyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl) bis(azanediyl)] (2S,2′S,3R,3′R)-bis(3-methylpentanoate) (**19d**)*

Following general procedure 7 in EtOH, **18d** (0.23 g, 0.40 mmol) afforded **19d** (51%) as a transparent oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.85–1.02 (m, 12H), 1.03–1.22 (m, 2 H), 1.22–1.34 (m, 6 H), 1.35–1.47 (m, 2 H), 1.67–2.02 (m, 6 H), 2.62 (br t, *J* = 6.4 Hz, 2 H), 3.22–3.50 (m, 2 H), 3.23 (s, 3 H), 3.68–3.89 (m, 2 H), 4.07–4.30 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 11.7, 11.8, 14.3, 15.6, 15.7, 18.7 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz), 24.8, 24.9, 28.2 (d, $^{1}J_{C\text{-}P}$ = 112.9 Hz), 31.3 (d, $^{3}J_{C\text{-}P}$ = 11.5 Hz), 35.9, 39.0 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 39.2 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 57.3, 57.8, 61.2, 173.0, 173.7, 173.8. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 29.59, 31.46. HRMS (ESI-MS): calculated for $C_{21}H_{43}N_3O_7P$ $[M + H]^+$: 480.2833, found: 480.2823.

*5.61. (5S,5′S)-5,5′-[({4-[Hydroxy(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)]bis(6-ethoxy-6-oxohexan-1-aminium) (**19e**)*

18e (0.47 g, 0.54 mmol) was dissolved in EtOH (0.05 M). A catalytic amount (approximately 50 mg) of Pd/C was added to the reaction mixture. The reaction was stirred for 2 h under a hydrogen atmosphere, after which HRMS confirmed complete conversion of the starting material. The reaction mixture was filtered and all volatiles were removed *in vacuo*. The resulting crude was dissolved in EtOH (5 mL) and cooled to 0 °C in an ice bath. HCl 2 M in Et_2O (4 eq) was added dropwise, after which the reaction mixture was allowed to warm to RT. All volatiles were subsequently removed *in vacuo*, after which precipitation in EtOAc/DCM afforded **19e** (76%) as a white powder. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.21–1.33 (m, 6H), 1.36–2.01 (m, 16H), 2.56–2.84 (m, 6 H), 3.18–3.36 (m, 4 H), 3.61–4.01 (m, 7 H), 4.06–4.28 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 18.7, 22.2, 22.3, 28.3 (d, $^{1}J_{C\text{-}P}$ = 112.9 Hz), 31.9, 32.0, 32.7, 34.1, 34.5 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 36.2, 41.2, 41.7, 52.4, 53.2, 61.3, 173.2, 174.2, 174.3. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 30.18. HRMS (ESI-MS): calculated for $C_{21}H_{45}N_5O_7P$ $[M + H]^+$: 510.3051, found: 510.3053.

*5.62. Dimethyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-bis(4-methylpentanoate) (**19f**)*

Following general procedure 7 in MeOH, **18f** (92 mg, 0.17 mmol) afforded **19f** (78%) as a white powder after purification by column chromatography (DCM → 6% MeOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.89–0.99 (m, 12H), 1.43–1.81 (m, 8H), 1.84–1.98 (m, 2 H), 2.63 (t, *J* = 5.8 Hz, 2 H), 3.15–3.29 (m, 1 H), 3.23 (s, 3 H), 3.73 (app d, *J* = 3.0 Hz, 6 H), 3.84–3.99 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 19.0 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 21.9, 22.0, 22.8, 22.9, 24.68, 24.74, 28.1 (d, $^{1}J_{C\text{-}P}$ = 111.7 Hz), 31.0 (d, $^{3}J_{C\text{-}P}$ = 9.2 Hz), 35.9, 43.8, 43.85, 43.91, 51.3, 51.9, 52.3, 173.0, 175.4. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.39, 30.75. HRMS (ESI-MS): calculated for $C_{19}H_{39}N_3O_7P$ $[M + H]^+$: 452.2520, found: 452.2509.

*5.63. Diethyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl) bis(azanediyl)](2S,2′S)-bis(4-methylpentanoate) (**19g**)*

Following general procedure 7 in EtOH, **18g** (0.15 g, 0.27 mmol) afforded **19g** (57%) as a transparent oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.94 (dt, *J* = 6.5, 2.4 Hz, 12H), 1.28 (td, *J* = 7.1, 4.3 Hz, 6H), 1.42–1.82 (m, 8H), 1.83–2.02 (m, 2 H), 2.62 (br t, *J* = 6.7 Hz, 2 H), 3.16–3.38 (m, 2 H), 3.24 (s, 3 H), 3.79–3.97 (m, 2 H), 4.09–4.28 (m, 4 H), 10.30 (br s, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 19.1 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 21.9, 22.8, 22.9, 24.65, 24.74, 28.1 (d, $^{1}J_{C\text{-}P}$ = 111.7 Hz), 30.9 (d, $^{1}J_{C\text{-}P}$ = 9.2 Hz), 35.9, 43.76, 43.84, 43.9, 51.3, 51.9, 61.4, 172.9, 175.0. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.34, 30.73. HRMS (ESI-MS): calculated for $C_{21}H_{43}N_3O_7P$ $[M + H]^+$: 480.2833, found: 480.2810.

*5.64. Diisopropyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-bis(4-methylpentanoate) (**19h**)*

Following general procedure 7 in iPrOH, **18h** (0.33 g, 0.55 mmol) afforded **19h** (75%) as a transparent oil after purification by column chromatography (DCM → 7% iPrOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.90–0.99 (m, 12H), 1.19–1.29 (m, 12H), 1.38–1.63 (m, 4H), 1.66–1.81 (m, 4H), 1.86–2.05 (m, 2 H), 2.65 (t, *J* = 6.5 Hz, 2 H), 3.00–3.20 (m, 2 H), 3.24 (s, 10/11 of 3 H), 3.35 (s, 1/11 of 3 H), 3.74–3.92 (m, 2 H), 5.02 (m, 2 H). ^{13}C NMR (75 MHz,

CHLOROFORM-*d*) δ ppm 19.2 (d, $^{2}J_{C\text{-}P}$ = 5.8 Hz), 21.8, 21.89, 21.92, 22.01, 22.86, 22.91, 24.7, 24.8, 27.9 (d, $^{1}J_{C\text{-}P}$ = 110.6 Hz), 30.3 (d, $^{3}J_{C\text{-}P}$ = 8.1 Hz), 35.8, 43.85, 43.93, 44.02, 51.5, 52.1, 69.0, 69.1, 172.8, 174.4. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.08, 30.83. HRMS (ESI-MS): calculated for $C_{23}H_{47}N_3O_7P$ $[M + H]^+$: 508.3146, found: 508.3140.

5.65. Dipentyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl) bis(azanediyl)](2S,2′S)-bis(4-methylpentanoate) (19i)

Following general procedure 7 in EtOAc (+formic acid, 1 eq), **18i** (102 mg, 0.156 mmol) afforded **19i** (50%) as a transparent oil after purification by column chromatography (toluene → 50% acetone in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.84–1.01 (m, 18H), 1.24–1.42 (m, 8 H), 1.42–1.80 (m, 12H), 1.86–2.06 (m, 2 H), 2.64 (br t, *J* = 5.8 Hz, 2 H), 3.05–3.19 (m, 2 H), 3.24 (s, 3 H), 3.79–3.97 (m, 2 H), 4.01–4.16 (m, 4 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 19.1 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 22.1, 22.4, 22.8, 22.9, 24.7, 24.8, 27.9 (d, $^{1}J_{C\text{-}P}$ = 111.7 Hz), 28.11, 28.14, 28.4, 30.5 (d, $^{3}J_{C\text{-}P}$ = 8.1 Hz), 35.8, 44.0, 44.1, 51.4, 52.1, 65.56, 65.63, 172.9, 175.0. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.18, 30.83. HRMS (ESI-MS): calculated for $C_{27}H_{55}N_3O_7P$ $[M + H]^+$: 564.3772, found: 564.3795.

5.66. Dicyclohexyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)] (2S,2′S)-bis(4-methylpentanoate) (19j)

Following general procedure 7 in EtOAc (+formic acid, 1 eq), **18j** (0.16 g, 0.24 mmol) afforded **19j** (65%) as a faint yellow oil after purification by column chromatography (toluene → 50% acetone in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.87–1.01 (m, 12H), 1.25–1.61 (m, 16H), 1.64–2.02 (m, 14H), 2.50–2.76 (m, 2 H), 2.95–3.16 (m, 2 H), 3.24 (s, 3 H), 3.73–3.97 (m, 2 H), 4.62–4.84 (m, 2 H), 10.38 (br s, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 19.2 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 22.1, 22.8, 22.9, 23.8, 24.7, 24.8, 25.4, 27.9 (d, $^{1}J_{C\text{-}P}$ = 111.7 Hz), 30.3 (d, $^{3}J_{C\text{-}P}$ = 8.1 Hz), 31.6, 31.7, 35.8, 44.0, 44.1, 44.2, 51.4, 52.1, 73.85, 73.94, 172.8, 174.32. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.00, 30.92. HRMS (ESI-MS): calculated for $C_{29}H_{55}N_3O_7P$ $[M + H]^+$: 588.3772, found: 588.3799.

5.67. Dibenzyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-bis(4-methylpentanoate) (19k)

Following general procedure 7 using hydroxylamine **17**, **15k** (159 mg, 0.276 mmol) afforded **19k** (33%) as a transparent oil after purification by column chromatography (toluene → 50% acetone in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.82–0.94 (m, 12H), 1.32–1.94 (m, 10H), 2.58 (t, *J* = 6.44 Hz, 2 H), 3.01–3.18 (m, 2 H), 3.21 (s, 6/7 of 3 H), 3.31 (s, 1/7 of 3 H), 3.83–4.01 (m, 2 H), 5.05–5.20 (m, 4 H), 7.28–7.40 (m, 10H), 10.22 (br s, 1 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 19.11 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 21.9, 22.8, 22.9, 24.68, 24.72, 27.8 (d, $^{1}J_{C\text{-}P}$ = 110.6 Hz), 30.3 (d, $^{3}J_{C\text{-}P}$ = 8.1 Hz), 35.8, 43.7–43.9 (m), 51.4, 52.1, 67.2, 67.3, 128.48, 128.51, 128.6, 128.7, 128.76, 128.80, 135.4, 135.6, 172.8, 174.7. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.20, 30.83. HRMS (ESI-MS): calculated for $C_{31}H_{47}N_3O_7P$ $[M + H]^+$: 604.3146, found: 604.3168.

5.68. Diethyl [4-(benzyloxy)butyl]phosphonate (21).

Benzyl 4-bromobutyl ether **20** (1.9 mL, 10 mmol) and triethyl phosphite (3.00 mL, 17.5 mmol) were refluxed under neat conditions for 24 h. ^{31}P NMR confirmed completion of the reaction, after which all volatiles were removed *in vacuo*. The resulting crude was purified by column chromatography (DCM → 80% acetone in DCM), yielding pure **21** as a colorless oil (71%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.31 (t, *J* = 7.1 Hz, 6H), 1.66–1.85 (m, 6H), 3.48 (t, *J* = 6.0 Hz, 2H), 3.99–4.17 (m, 4H), 4.49 (s, 2H), 7.27–7.38 (m, 5H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 16.6, 16.7, 19.6 (d, $^{2}J_{C\text{-}P}$ = 5.8 Hz), 25.6 (d, $^{1}J_{C\text{-}P}$ = 140.5 Hz), 30.7 (d, $^{3}J_{C\text{-}P}$ = 16.1 Hz), 61.5, 61.6, 69.7, 73.1, 127.7, 127.8, 128.5, 138.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 32.12. HRMS (ESI-MS): calculated for $C_{15}H_{26}O_4P$ $[M + H]^+$: 301.1563, found: 301.1552.

5.69. [4-(Benzyloxy)butyl]phosphonic acid (22)

Following general procedure 1, **21** (0.39 g, 1.3 mmol) afforded **22** as a crude material, which was dried overnight at high vacuum and immediately used in the next reaction without further purification or characterization.

5.70. [4-(Benzyloxy)butyl]phosphonic dichloride (23)

Following general procedure 2, **22** (0.32 g, 1.3 mmol) afforded **23** as a crude material, which was immediately used in the next reaction without further purification or characterization.

5.71. Diethyl 2,2′-({[4-(benzyloxy)butyl]phosphoryl}bis(azanediyl)) (2S,2′S)-dipropionate (24)

Following general procedure 3, crude **23** (1.12 g, 4.00 mmol) afforded **24** (37%) as a yellow oil after purification by column chromatography (DCM → 40% acetone in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.22–1.31 (m, 6H), 1.33–1.42 (m, 6H), 1.64–1.80 (m, 6H), 2.91–3.11 (m, 2H), 3.38–3.56 (m, 2H), 3.89–4.08 (m, 2H), 4.08–4.26 (m, 4H), 4.49 (s, 2H), 7.23–7.38 (m, 5H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.21, 14.24, 20.0 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz), 21.6 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 21.7 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 29.2 (d, $^{1}J_{C\text{-}P}$ = 112.9 Hz), 30.6 (d, $^{3}J_{C\text{-}P}$ = 16.1 Hz), 48.5, 49.0, 61.3, 61.4, 69.8, 73.1, 127.6, 127.8, 128.4, 138.5, 174.7 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 174.8 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.02. HRMS (ESI-MS): calculated for $C_{21}H_{36}N_2O_6P$ $[M + H]^+$: 443.2305, found: 443.2283.

5.72. Diethyl 2,2′-{[(4-hydroxybutyl)phosphoryl]bis(azanediyl)}(2S,2′S)-dipropionate (25)

Following general procedure 7 in EtOH, **24** (129 mg, 0.290 mmol) afforded **25** (89%) as a transparent oil after purification by column chromatography (DCM → 10% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.28 (td, *J* = 7.1, 3.6 Hz, 6H), 1.34–1.45 (m, 6H), 1.57–1.82 (m, 6H), 3.16–3.34 (m, 2H), 3.63 (t, *J* = 5.6 Hz, 2H), 3.84–4.09 (m, 2H), 4.10–4.24 (m, 4H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.18, 14.21, 19.1 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 21.4 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 21.6 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 28.6 (d, $^{1}J_{C\text{-}P}$ = 114.0 Hz), 33.2 (d, $^{3}J_{C\text{-}P}$ = 16.1 Hz), 48.5, 48.9, 61.25, 61.33, 174.76, 174.83, 174.9. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 29.88. HRMS (ESI-MS): calculated for $C_{14}H_{30}N_2O_6P$ $[M + H]^+$: 353.1836, found: 353.1848.

5.73. 4-(Bis{[(S)-1-ethoxy-1-oxopropan-2-yl]amino}phosphoryl)butanoic acid (26)

Following general procedure 5, **25** (392 mg, 1.11 mmol) afforded **26** (53%) as a yellow oil after purification by column chromatography (toluene → 25% EtOH in toluene + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.21–1.32 (m, 6H), 1.33–1.48 (m, 6H), 1.53–1.63 (m, 2H), 1.71–1.97 (m, 4H), 2.28–2.47 (m, 2H), 3.37–3.66 (m, 2H), 3.88–4.10 (m, 2H), 4.10–4.27 (m, 4H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 18.3 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz), 21.3 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 21.4 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 28.0 (d, $^{1}J_{C\text{-}P}$ = 112.9 Hz), 34.6 (d, $^{3}J_{C\text{-}P}$ = 16.1 Hz), 48.6, 49.0, 61.4, 174.5 (d, $^{3}J_{C\text{-}P}$ = 3.5 Hz), 174.7 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 175.7. ^{31}P NMR (121 MHz, CHLOROFORM-*d*)

δ ppm 30.82. HRMS (ESI-MS): calculated for $C_{14}H_{28}N_2O_7P$ $[M + H]^+$: 367.1629, found: 367.1633.

5.74. Diethyl 2,2′-[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(azanediyl)](2S,2′S)-dipropionate (27)

Following general procedure 6 using hydroxylamine **16**, **26** (0.15 g, 0.42 mmol) afforded **27** (79%) as a transparent oil after purification by column chromatography (DCM → 10% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.27 (td, *J* = 7.1, 6.0 Hz, 6H), 1.34–1.45 (m, 6H), 1.62–1.76 (m, 2H), 1.80–1.98 (m, 2H), 2.50 (t, *J* = 6.6 Hz, 2H), 3.12–3.22 (m, 1H), 3.20 (s, 3H), 3.28–3.40 (m, 1H), 3.92–4.11 (m, 2H), 4.11–4.23 (m, 4H), 4.83 (s, 2H), 7.28–7.44 (m, 5H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 14.3, 18.0 (d, $^2J_{C\text{-}P}$ = 3.5 Hz), 21.5 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 21.7 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 28.6 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 32.3 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 33.5 (w), 48.5, 49.0, 61.3, 61.4, 76.3, 128.9, 129.1, 129.4, 134.5, 174.7 (d, $^3J_{C\text{-}P}$ = 3.5 Hz), 174.9 (d, $^3J_{C\text{-}P}$ = 4.6 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 28.56. HRMS (ESI-MS): calculated for $C_{22}H_{37}N_3O_7P$ $[M + H]^+$: 486.2364, found: 486.2345.

5.75. Diethyl 2,2′-[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl) bis(azanediyl)](2S,2′S)-dipropionate (28)

Following general procedure 7 in EtOH, **27** (133 mg, 0.275 mmol) afforded **28** (91%) as a transparent oil after purification by column chromatography (DCM → 8% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.18–1.33 (m, 6H), 1.40 (dd, *J* = 10.5, 7.1 Hz, 6H), 1.67–2.03 (m, 4H), 2.50–2.72 (m, 2H), 3.24 (s, 3H), 3.44–3.61 (m, 2H), 3.86–4.04 (m, 2H), 4.09–4.26 (m, 4H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 14.3, 18.6 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 21.35, 21.41, 28.1 (d, $^1J_{C\text{-}P}$ = 112.9 Hz), 31.6 (d, $^3J_{C\text{-}P}$ = 11.5 Hz), 36.0, 48.7, 48.9, 61.5, 173.2, 174.6, 174.7. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 28.83, 20.64. HRMS (ESI-MS): calculated for $C_{15}H_{31}N_3O_7P$ $[M + H]^+$: 396.1894, found: 396.1907.

5.76. Diethyl 3,3′-{[(allylphosphoryl)bis(oxy)]bis(4,1-phenylene)} (2S,2′S)-bis(2-acetamidopropanoate) (33a)

Following general procedure 3, crude allyl phosphonic dichloride (0.32 g, 2.0 mmol) afforded 33a (60%) as a transparent oil after purification by column chromatography (DCM → 4% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.21–1.29 (m, 6H), 1.98 (app d, *J* = 1.2 Hz, 6H), 2.87–3.17 (m, 6H), 4.05–4.28 (m, 4H), 4.79–4.89 (m, 2H), 5.27–5.37 (m, 2H), 5.81–5.97 (m, 1H), 5.98–6.08 (m, 2H), 6.98–7.16 (m, 8H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 23.3, 31.9 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 37.3, 53.2, 61.8, 120.7 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 121.5 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 126.2 (d, $^2J_{C\text{-}P}$ = 12.7 Hz), 130.8, 133.2, 149.4 (d, $^2J_{C\text{-}P}$ = 2.3 Hz), 149.5 (d, $^2J_{C\text{-}P}$ = 2.3 Hz), 169.7, 171.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 20.40. HRMS (ESI-MS): calculated for $C_{29}H_{38}N_2O_9P$ $[M + H]^+$: 589.2309, found: 589.2309.

5.77. Diethyl 3,3′-{[(allylphosphoryl)bis(oxy)]bis(4,1-phenylene)} (2S,2′S)-bis(2-{[(benzyloxy)carbonyl]amino}propanoate) (33b)

Following general procedure 3, crude allyl phosphonic dichloride (79 mg, 0.50 mmol) afforded 33b (68%) as a yellow wax after purification by column chromatography (toluene → 1toluene/3EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.22 (t, *J* = 7.1 Hz, 6H), 2.85–3.00 (m, 2H), 3.00–3.15 (m, 4H), 4.15 (q, *J* = 4.1 Hz, 4H), 4.55–4.65 (m, 2H), 5.09 (s, 4H), 5.19–5.36 (m, 4H), 5.80–5.99 (m, 1H), 6.98–7.14 (m, 8H), 7.25–7.39 (m, 10H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 31.8 (d, $^1J_{C\text{-}P}$ = 141.7 Hz), 37.6, 54.9, 61.7, 67.1, 120.8 (d, $^3J_{C\text{-}P}$ = 3.5 Hz), 121.5 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 126.3 (d, $^2J_{C\text{-}P}$ = 11.5 Hz), 128.25, 128.34, 128.7, 130.8, 133.0, 136.3, 149.5 (d, $^2J_{C\text{-}P}$ = 8.1 Hz), 155.7, 171.4. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 20.28. HRMS (ESI-MS): calculated for $C_{41}H_{46}N_2O_{11}P$ $[M + H]^+$: 773.2834, found: 773.2856.

5.78. Diethyl 3,3′-{[({(E)-4-[(benzyloxy)(methyl)amino]-4-oxobut-2-en-1-yl}phosphoryl)bis(oxy)]bis(4,1-phenylene)}(2S,2′S)-bis(2-acetamidopropanoate) (35a)

Following general procedure 8, 33a (0.73 g, 1.2 mmol) afforded 35a (67%) as a yellow oil after purification by column chromatography (toluene → 15% EtOH in toluene). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.24 (t, *J* = 7.1 Hz, 6H), 1.98 (d, *J* = 1.5 Hz, 6H), 2.97–3.18 (m, 6H), 3.26 (s, 3H), 4.09–4.24 (m, 4H), 4.74–4.88 (m, 4H), 6.05 (br t, *J* = 6.6 Hz, 2H), 6.57–6.68 (m, 1H), 6.80–6.96 (m, 1H), 6.99–7.14 (m, 8H), 7.32–7.44 (m, 5H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 23.3, 30.7 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 33.9, 37.2, 53.2, 61.7, 76.7, 120.7 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 124.9 (d, $^3J_{C\text{-}P}$ = 13.8 Hz), 128.9, 129.2, 129.4, 130.9, 133.4, 134.0 (d, $^2J_{C\text{-}P}$ = 11.5 Hz), 134.3, 149.3 (d, $^2J_{C\text{-}P}$ = 10.4 Hz), 166.1, 169.8, 171.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 18.11. HRMS (ESI-MS): calculated for $C_{38}H_{47}N_3O_{11}P$ $[M + H]^+$: 752.2943, found: 752.2948.

5.79. Diethyl 3,3′-{[({(E)-4-[(benzyloxy)(methyl)amino]-4-oxobut-2-en-1-yl}phosphoryl)bis(oxy)] bis(4,1-phenylene)}(2S,2′S)-bis(2 {[(benzyloxy)carbonyl]amino}propanoate) (35b)

Following general procedure 8, 33b (0.55 g, 0.71 mmol) afforded 35b (67%) as a yellow wax after purification by column chromatography (toluene → EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.13–1.29 (m, 6H), 2.87–3.16 (m, 6H), 3.25 (s, 3H), 4.07–4.20 (m, 4H), 4.53–4.64 (m, 2H), 4.81 (s, 2H), 5.08 (s, 4H), 5.22–5.32 (m, 2H), 6.57–6.68 (m, 1H), 6.86–6.98 (m, 1H), 6.98–7.12 (m, 8H), 7.27–7.43 (m, 15H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 30.6 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 33.9, 37.6, 54.9, 61.7, 67.1, 76.7, 120.7 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 124.9 (d, $^3J_{C\text{-}P}$ = 13.8 Hz), 128.2, 128.3, 128.7, 128.9, 129.2, 129.43, 130.9, 133.2, 134.0 (d, $^2J_{C\text{-}P}$ = 11.5 Hz), 134.3, 136.3, 149.3 (d, $^2J_{C\text{-}P}$ = 9.2 Hz), 155.7, 166.1, 171.3. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 18.08. HRMS (ESI-MS): calculated for $C_{50}H_{55}N_3O_{13}P$ $[M + H]^+$: 936.3467, found: 936.3480.

5.80. Diethyl 3,3′-{[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(oxy)]bis(4,1-phenylene)}(2S,2′S)-bis(2-acetamidopropanoate) (36a)

Following general procedure 9, 35a (0.30 g, 0.32 mmol) afforded 36a (50%) as a yellow oil after purification by column chromatography (DCM → 7.5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (t, *J* = 7.1 Hz, 6H), 1.95–2.02 (m, 6H), 2.02–2.20 (m, 4H), 2.54 (br t, *J* = 6.3 Hz, 2H), 3.01–3.16 (m, 4H), 3.21 (s, 3H), 4.08–4.25 (m, 4H), 4.75–4.93 (m, 4H), 5.95–6.10 (m, 2H), 7.00–7.13 (m, 8H), 7.36 (s, 5H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.6 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 23.3, 25.5 (d, $^1J_{C\text{-}P}$ = 140.5 Hz), 32.2 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 33.5, 37.2, 53.2, 61.7, 76.3, 120.7 (d, $^3J_{C\text{-}P}$ = 3.5 Hz), 128.9, 129.2, 129.4, 130.8, 133.0, 134.5, 149.5 (d, $^2J_{C\text{-}P}$ = 9.2 Hz), 169.8, 171.5. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 25.68. HRMS (ESI-MS): calculated for $C_{38}H_{49}N_3O_{11}P$ $[M + H]^+$: 754.3099, found: 754.3118.

5.81. Diethyl 3,3′-{[({4-[(benzyloxy)(methyl)amino]-4-oxobutyl} phosphoryl)bis(oxy)]bis(4,1-phenylene)}(2S,2′S)-bis(2-{[(benzyloxy) carbonyl]amino}propanoate) (36b)

Following general procedure 9, 35b (95 mg, 0.10 mmol) afforded 36b (65%) as a transparent oil after purification by column chromatography (toluene → 1toluene/1EtOAc). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.21 (t, *J* = 7.1 Hz, 6H), 1.98–2.14 (m, 4H), 2.54 (br t,

J = 6.3 Hz, 2H), 2.99–3.11 (m, 4H), 3.20 (s, 3H), 4.14 (q, J = 7.1 Hz, 4H), 4.59 (q, J = 6.1 Hz, 2H), 4.80 (s, 2H), 5.09 (s, 4H), 5.21–5.30 (m, 2H), 6.91–7.18 (m, 8H), 7.30–7.41 (m, 15H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 17.6 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 25.5 (d, $^{1}J_{C\text{-}P}$ = 140.5

Hz), 32.2 (d, $^{3}J_{C\text{-}P}$ = 16.1 Hz), 33.5, 37.6, 54.9, 61.7, 67.1, 76.3, 120.8 (d, $^{3}J_{C\text{-}P}$ = 3.5 Hz), 128.2, 128.3, 128.7, 128.9, 129.2, 129.4, 130.80, 132.83, 136.4, 149.5 (d, $^{2}J_{C\text{-}P}$ = 9.2 Hz), 155.7, 171.4. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 25.25. HRMS (ESI-MS): calculated for $C_{50}H_{57}N_3O_{13}P$ $[M + H]^+$: 938.3624, found: 938.3642.

5.82. Diethyl 3,3′-{[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(4,1-phenylene)}(2S,2′S)-bis(2-acetamidopropanoate) (37a)

Following general procedure 7 in EtOH, 36a (95 mg, 0.10 mmol) afforded 37a (55%) as a faint yellow powder after purification by column chromatography (DCM → 6% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.25 (t, J = 7.1 Hz, 6H), 1.88–2.03 (m, 6H), 2.03–2.23 (m, 4H), 2.45–2.66 (m, 2H), 2.94–3.38 (m, 7H), 4.07–4.27 (m, 4H), 4.76–4.89 (m, 2H), 6.19–6.38 (m, 2H), 7.08 (s, 8H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 18.0, 23.2, 25.0 (d, $^{1}J_{C\text{-}P}$ = 139.4 Hz), 31.4, 36.0, 37.3, 53.3, 61.8, 120.6 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 130.9, 133.4, 149.3 (d, $^{2}J_{C\text{-}P}$ = 8.1 Hz), 170.0, 171.6, 172.8. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers at δ ppm 24.81, 26.00. HRMS (ESI-MS): calculated for $C_{31}H_{43}N_3O_{11}P$ $[M + H]^+$: 664.2630, found: 664.2628.

5.83. Diethyl 3,3′-{[({4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(4,1-phenylene)}(2S,2′S)-bis(2-aminopropanoate) (37b)

Following general procedure 7 in EtOH, 36b (0.13 g, 0.14 mmol) afforded 37b (90%) as a faint yellow oil after purification HPLC (5% MeCN in H_2O + 0.2% formic acid → MeCN). ^{1}H NMR (300 MHz, METHANOL-d_4) δ ppm 1.19–1.35 (m, 6H), 1.89–2.33 (m, 4H), 2.59–2.76 (m, 2H), 3.17–3.26 (m, 7H), 4.12–4.39 (m, 6H), 7.21 (br d, J = 7.6 Hz, 4H), 7.27–7.38 (m, 4H), 8.31 (br s, 1H). ^{13}C NMR (75 MHz, METHANOL-d_4) δ ppm 14.4, 18.8 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 26.0 (d, $^{1}J_{C\text{-}P}$ = 139.4 Hz), 32.9 (d, $^{3}J_{C\text{-}P}$ = 17.3 Hz), 36.3, 36.8, 55.2, 63.6, 122.3 (d, $^{3}J_{C\text{-}P}$ = 3.5 Hz), 132.2, 133.1, 151.0 (d, $^{2}J_{C\text{-}P}$ = 9.2 Hz), 170.1, 174.5. ^{31}P NMR (121 MHz, METHANOL-d_4) rotamers at δ ppm 26.74, 26.90. HRMS (ESI-MS): calculated for $C_{27}H_{39}N_3O_9P$ $[M + H]^+$: 580.2418, found: 580.2432.

5.84. Diethyl (3,4-dichlorobenzyl)phosphonate (39)

3,4-dichlorobenzyl bromide **38** (3.8 mL, 26 mmol) and triethyl phosphite (4.3 mL, 25 mmol) were refluxed under neat conditions for 24 h. ^{31}P NMR confirmed completion of the reaction, after which all volatiles were removed *in vacuo*. The resulting crude was purified by column chromatography (toluene → EtOAc), yielding pure **39** as a colorless oil (92%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.27 (t, J = 7.1 Hz, 6H), 3.09 (d, J = 21.7 Hz, 2H), 4.05 (dq, J = 8.3, 7.0 Hz, 4H), 7.13–7.17 (m, 1H), 7.36–7.41 (m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 16.5 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 33.1 (d, $^{1}J_{C\text{-}P}$ = 138.2 Hz), 62.5 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 129.3 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 130.5 (d, $^{4}J_{C\text{-}P}$ = 2.3 Hz), 131.7 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 132.1, 132.3. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 24.81. HRMS (ESI-MS): calculated for $C_{11}H_{16}Cl_2O_3P$ $[M + H]^+$: 297.0209, found: 297.0218.

5.85. Diethyl [1-(3,4-dichlorophenyl)but-3-en-1-yl]phosphonate (40)

A solution of **39** (1.49 g, 5.00 mmol) in dry THF (50 mL) was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 3.44 mL) was added dropwise. After 1 h, allyl bromide (0.48 mL, 5.5 mmol) was added. The reaction mixture was allowed to warm to RT. After overnight stirring, the reaction was quenched with H_2O and partially evaporated *in vacuo* in order to remove THF. The reaction mixture was subsequently extracted three times with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (toluene → EtOAc) yielded pure **40** as a yellow oil (70%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.16 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 2.52–2.70 (m, 1H), 2.72–2.92 (m, 1H), 2.93–3.11 (m, 1H), 3.78–4.12 (m, 4H), 4.86–5.02 (m, 2H), 5.55 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 7.11–7.17 (m, 1H), 7.33–7.39 (m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 16.36, 16.44, 16.5, 33.9 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz), 43.9 (d, $^{1}J_{C\text{-}P}$ = 138.2 Hz), 62.3 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 62.7 (d, $^{2}J_{C\text{-}P}$ = 8.1 Hz), 117.6, 128.7 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 130.4 (d, $^{3}J_{C\text{-}P}$ = 2.3 Hz), 131.3 (d, $^{4}J_{C\text{-}P}$ = 6.9 Hz), 132.5 (d, $^{4}J_{C\text{-}P}$ = 2.3 Hz), 134.7 (d, $^{3}J_{C\text{-}P}$ = 16.1 Hz), 136.3 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz). ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 26.59. HRMS (ESI-MS): calculated for $C_{14}H_{20}Cl_2O_3P$ $[M + H]^+$: 337.0522, found: 337.0535

5.86. [1-(3,4-dichlorophenyl)but-3-en-1-yl]phosphonic acid (41)

Following general procedure 1, **40** (0.10 g, 0.30 mmol) afforded **41** as a crude material, which was dried overnight at high vacuum and immediately used in the next reaction without further purification or characterization.

5.87. [1-(3,4-dichlorophenyl)but-3-en-1-yl]phosphonic dichloride (42)

Following general procedure 2, **41** (84 mg, 0.30 mmol) afforded **42** as a crude material, which was immediately used in the next reaction without further purification or characterization.

5.88. Diethyl 2,2′-({[1-(3,4-dichlorophenyl)but-3-en-1-yl]phosphoryl}bis(azanediyl))(2S,2′S)-dipropionate (43a)

Following general procedure 3, crude **42** (95 mg, 0.30 mmol) afforded **43a** (43%) as a yellow oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.19–1.44 (m, 12H), 2.50–3.23 (m, 6H), 3.68–4.25 (m, 6H), 4.92–5.07 (m, 2 H), 5.49–5.67 (m, 1 H), 7.12–7.30 (m, 1 H), 7.37–7.45 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 14.16, 14.21, 21.26, 21.32, 21.35, 21.43, 22.08, 22.13, 22.39, 22.44, 34.0 (d, $^{2}J_{C\text{-}P}$ = 9.2 Hz), 46.8 (d, $^{1}J_{C\text{-}P}$ = 109.4 Hz), 46.9 (d, $^{1}J_{C\text{-}P}$ = 109.4 Hz), 48.7, 49.2, 49.4, 61.4, 61.48, 61.54, 117.7, 128.5, 128.60, 128.63, 130.65, 130.68, 131.05, 131.14, 131.2, 131.3, 132.68, 132.71, 132.8, 134.9, 135.0, 135.1, 135.2, 137.4 (app t, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 174.25, 174.32, 174.4, 174.5, 174.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) diastereoisomers at δ ppm 25.87, 25.90. HRMS (ESI-MS): calculated for $C_{20}H_{30}Cl_2N_2O_5P$ $[M + H]^+$: 479.1264, found: 479.1256

5.89. Diethyl 3,3′-[({[1-(3,4-dichlorophenyl)but-3-en-1-yl]phosphoryl}bis(oxy))bis(4,1-phenylene)](2S,2′S)-bis(2-acetamidopropanoate) (43b)

Following general procedure 3, crude **42** (1.27 g, 4.00 mmol) afforded **43b** (98%) as a transparent oil after purification by column chromatography (DCM → 5% EtOH in DCM). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.20–1.29 (m, 6H), 1.94–2.00 (m, 6H), 2.72–2.90 (m, 1H), 2.96–3.17 (m, 5H), 3.33–3.49 (m, 1H), 4.11–4.23 (m, 4H), 4.76–4.88 (m, 2H), 4.98–5.11 (m, 2H), 5.54–5.71 (m, 1H), 5.93–6.07 (m, 2H), 6.70–6.85 (m, 3H), 6.91–7.08 (m, 6H), 7.38–7.46 (m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 23.3, 34.0 (d, $^{2}J_{C\text{-}P}$ = 2.3 Hz), 37.2, 37.3, 44.2 (d, $^{1}J_{C\text{-}P}$ = 138.2 Hz), 53.2, 61.7, 61.8, 115.6, 118.5, 120.4 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 120.5 (d, $^{3}J_{C\text{-}P}$ = 4.6 Hz), 127.5, 128.9 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 130.5, 130.7, 130.8, 131.6, 131.7, 133.2, 133.3, 133.8, 134.0, 134.9 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 149.2–149.6 (m) 155.5, 169.8, 171.5, 171.9. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) diastereoisomers at δ ppm 19.69, 19.72. HRMS (ESI-MS): calculated for $C_{36}H_{42}Cl_2N_2O_9P$ $[M + H]^+$: 747.1999, found: 747.2014

*5.90. Diethyl 2,2′-({[1-(3,4-dichlorophenyl)-4-hydroxybutyl]phosphoryl} bis(azanediyl))(2S,2′S)-dipropionate (**44a**)*

A solution of **43a** (48 mg, 0.10 mmol) in dry THF (1 mL) was cooled to 0 °C in an ice bath, after which BH_3·THF 1 M (0.30 mL, 0.30 mmol) was added. The reaction mixture was allowed to warm to RT. After 3 h, H_2O (1 mL) and SPB·H_2O (50 mg, 0.50 mmol) were added. The reaction mixture was stirred vigorously at RT for 3 h, after which LC-MS confirmed completion of the reaction. The reaction mixture was filtered and the resulting filtrate was extracted three times with EtOAc. Column chromatography (DCM → 10% EtOH in DCM) yielded pure **44a** as a transparent oil (35%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.14–1.60 (m, 12H), 1.83–2.34 (m, 4H), 2.84–3.14 (m, 2 H), 3.22–3.40 (m, 1 H), 3.54–3.65 (m, 2 H), 3.70–4.26 (m, 6 H), 7.20–7.29 (m, 1 H), 7.37–7.49 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.18, 14.22, 21.29, 21.34, 21.9, 22.0, 22.37, 22.4, 26.0, 30.2, 30.3, 30.4, 30.5, 46.2 (d, $^1J_{C\text{-}P}$ = 110.6 Hz), 46.3 (d, $^1J_{C\text{-}P}$ = 109.4 Hz), 48.6, 48.8, 49.3, 61.4, 61.5, 61.6, 128.5, 128.56, 128.62, 130.7, 130.8, 131.0, 131.1, 131.15, 131.24, 132.8, 137.7, 137.79, 137.84, 137.9, 174.4, 174.5, 174.6, 174.76, 174.83. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) diastereoisomers at δ ppm 26.90, 27.01. HRMS (ESI-MS): calculated for $C_{20}H_{32}Cl_2N_2O_6P$ $[M + H]^+$: 497.1370, found: 497.1391

*5.91. Diethyl 3,3′-[({[1-(3,4-dichlorophenyl)-4-hydroxybutyl]phosphoryl} bis(oxy))bis(4,1-phenylene)](2S,2′S)-bis(2-acetamidopropanoate) (**44b**)*

A solution of **43b** (75 mg, 0.10 mmol) in dry THF (1 mL) was cooled to 0 °C in an ice bath, after which BH_3·THF 1 M (0.20 mL, 0.20 mmol) was added. The reaction mixture was allowed to warm to RT. After 3 h, H_2O (1 mL) and SPB·H_2O (30 mg, 0.30 mmol) were added. The reaction mixture was stirred vigorously at RT for 3 h, after which LC-MS confirmed completion of the reaction. The reaction mixture was filtered and the resulting filtrate was extracted three times with EtOAc. Column chromatography (DCM → 10% EtOH in DCM) yielded pure **44b** as a white foam (80%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.24 (app td, *J* = 7.1, 3.5 Hz, 6H), 1.45–1.57 (m, 2H), 1.78 (br s, 1H), 1.97 (s, 6H), 2.03–2.24 (m, 1H), 2.35–2.45 (m, 1H), 2.94–3.17 (m, 4H), 3.29–3.47 (m, 1H), 3.60 (t, *J* = 6.0 Hz, 2H), 4.07–4.23 (m, 4H), 4.74–4.90 (m, 2H), 5.97–6.12 (m, 2H), 6.78–6.88 (m, 2H), 6.92–7.08 (m, 6H), 7.19–7.29 (m, 1H), 7.38–7.50 (m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 23.3, 26.4, 30.3 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 30.4 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 37.3, 37.4, 43.8 (d, $^1J_{C\text{-}P}$ = 138.2 Hz), 43.9 (d, $^1J_{C\text{-}P}$ = 137.1 Hz), 53.2, 61.8, 62.0, 120.4 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 120.5 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 128.8 (d, $^3J_{C\text{-}P}$ = 6.9 Hz), 130.7, 130.8, 131.5 (d, $^4J_{C\text{-}P}$ = 6.9 Hz), 132.0 (d, $^4J_{C\text{-}P}$ = 3.5 Hz), 132.9 (d, $^5J_{C\text{-}P}$ = 2.3 Hz), 133.2, 133.3, 135.5 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 149.5 (d, $^2J_{C\text{-}P}$ = 10.4 Hz), 169.8, 171.56, 171.60. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) δ ppm 20.36. HRMS (ESI-MS): calculated for $C_{36}H_{44}Cl_2N_2O_{10}P$ $[M + H]^+$: 765.2105, found: 765.2141.

*5.92. 4-(Bis{[(S)-1-ethoxy-1-oxopropan-2-yl]amino}phosphoryl)-4-(3,4-dichlorophenyl)butanoic acid (**45a**)*

Following general procedure 5, **44a** (60 mg, 0.12 mmol) afforded **45a** (66%) as a transparent oil after purification by column chromatography (DCM → 5% EtOH in DCM + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.15–1.46 (m, 12H), 2.01–2.57 (m, 4H), 3.02–3.36 (m, 2 H), 3.60–4.25 (m, 7 H), 7.15–7.32 (m, 1 H), 7.37–7.49 (m, 2 H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 14.16, 14.19, 14.22, 21.1, 21.2, 21.26, 21.32, 21.7, 21.8, 22.36, 22.39, 22.7, 25.2, 25.6, 25.9, 29.4, 29.5, 31.5, 31.6, 31.7, 31.8, 31.9, 32.8, 44.8 (d, $^1J_{C\text{-}P}$ = 111.7 Hz), 45.4 (d, $^1J_{C\text{-}P}$ = 110.6 Hz), 49.26, 49.29, 61.6, 128.8, 128.9, 130.8, 132.15, 132.24, 132.4, 132.5, 132.59, 132.64, 132.8, 132.85, 132.88, 132.91, 136.8, 136.85, 136.89, 136.94, 174.4–174.6 (m) 175.6. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) diastereoiosmers at δ ppm 27.99, 28.41. HRMS (ESI-MS): calculated for $C_{20}H_{30}Cl_2N_2O_7P$ $[M + H]^+$: 511.1162, found: 511.1154

*5.93. 4-(Bis{4-[(S)-2-acetamido-3-ethoxy-3-oxopropyl]phenoxy} phosphoryl)-4-(3,4-dichlorophenyl)butanoic acid (**45b**)*

Following general procedure 5, **44b** (0.69 g, 0.90 mmol) afforded **45b** (79%) as white foam after purification by column chromatography (DCM → 6% EtOH in DCM + 0.1% acetic acid). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.19–1.31 (m, 6H), 1.95–1.99 (m, 6H), 2.12–2.43 (m, 3H), 2.48–2.68 (m, 1H), 2.93–3.17 (m, 4H), 3.44–3.67 (m, 1H), 4.08–4.25 (m, 4H), 4.7 6–4.92 (m, 2H), 6.22–6.43 (m, 2H), 6.83–7.08 (m, 6H), 7.13–7.28 (m, 3H), 7.37–7.50 (m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 23.1, 25.4, 30.9, 31.0, 31.1, 31.3, 37.2–37.5 (m), 42.0 (d, $^1J_{C\text{-}P}$ = 137.1 Hz), 42.1 (d, $^1J_{C\text{-}P}$ = 138.2 Hz), 53.2, 61.85, 61.91, 120.2 (d, $^3J_{C\text{-}P}$ = 3.5 Hz), 120.5 (d, $^3J_{C\text{-}P}$ = 2.3 Hz), 128.9 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 130.69, 130.74, 130.9, 131.5 (d, $^4J_{C\text{-}P}$ = 8.1 Hz), 132.3 (d, $^4J_{C\text{-}P}$ = 3.5 Hz), 133.1, 133.2, 133.3, 133.4, 134.5, 134.6 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 149.4 (d, $^2J_{C\text{-}P}$ = 10.4 Hz), 170.29, 170.34, 170.4, 171.6, 171.8, 175.1, 175.3. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) diastereoisomers at δ ppm 19.67, 19.84. HRMS (ESI-MS): calculated for $C_{36}H_{42}Cl_2N_2O_{11}P$ $[M + H]^+$: 779.1898, found: 779.1898.

*5.94. Diethyl 2,2′-[({1-(3,4-dichlorophenyl)-4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(azanediyl)](2S,2′S)-dipropionate (**47a**)*

A solution of **45a** (61 mg, 0.12 mmol) and 4-methylmorpholine (0.015 mL, 0.13 mmol) in dry THF (2.5 mL) was cooled to − 20 °C, after which ethyl chloroformate (0.023 mL, 0.24 mmol) was added. After 20 min at − 20 °C, a solution of hydroxylamine **46** (0.14 g, 0.48 mmol) in dry THF was added dropwise. The reaction was allowed to warm to RT. After 3 days, HRMS confirmed completion of the reaction, after which the reaction was quenched with H_2O and partially concentrated *in vacuo*. The resulting crude was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (DCM → 5% EtOH in DCM) yielded pure **47a** as a faint yellow oil (23%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.14–1.44 (m, 12H), 2.03–2.70 (m, 4H), 2.99–3.31 (m, 5H), 3.63–4.30 (m, 7H), 7.15–7.26 (m, 1H), 7.36–7.49 (m, 2 H), 9.66 (br s, 1H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.18, 14.21, 14.3, 21.3, 22.4, 26.1, 30.2, 36.1, 48.6, 49.0, 49.4, 61.6, 128.6, 130.8, 131.3, 131.5, 132.8, 137.9, 138.0, 173.3, 173.5, 174.2–174.6 (m), 174.7, 174.8. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers of diastereoiosmers at δ ppm 26.05, 26.65, 27.24, 27.97. HRMS (ESI-MS): calculated for $C_{21}H_{33}Cl_2N_3O_7P$ $[M + H]^+$: 540.1428, found: 540.1439

*5.95. Diethyl 3,3′-{[({1-(3,4-dichlorophenyl)-4-[hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(4,1-phenylene)}(2S,2′S)-bis(2-acetamidopropanoate) (**47b**)*

A solution of **45b** (128 mg, 0.165 mmol) and 4-methylmorpholine (0.020 mL, 0.18 mmol) in dry THF (1.7 mL) was cooled to − 20 °C, after which ethyl chloroformate (0.039 mL, 0.41 mmol) was added. After 20 min at − 20 °C, a solution of hydroxylamine **46** (0.14 g, 0.50 mmol) in dry THF was added dropwise. The reaction was allowed to warm to RT. After 3 days, HRMS confirmed completion of the reaction, after which the reaction was quenched with H_2O and partially concentrated *in vacuo*. The resulting crude was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (DCM → 6% EtOH in DCM) yielded pure **47b** as a transparent oil (36%). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.19–1.28 (m, 6H), 1.94 (s, 6H), 2.25–2.44 (m, 2H), 2.48–2.64 (m, 2H), 2.91–3.11 (m, 4H), 3.13 (s, 3H), 3.46–3.67 (m, 1H), 4.08–4.24 (m, 4H), 4.72–4.87 (m, 2H), 6.19–6.43 (m, 2H), 6.77–6.88 (m, 2H), 6.92–7.08 (m, 6H), 7.20–7.25 (m, 1H), 7.35–7.49

(m, 2H). ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 23.1, 25.3, 29.8, 36.0, 37.3, 43.1 (d, $^{1}J_{C-P}$ = 137.1 Hz), 53.3, 61.8, 120.1–120.7 (m), 128.9, 130.7, 130.8, 131.5 (d, $^{4}J_{C-P}$ = 8.1 Hz), 132.0 (d, $^{4}J_{C-P}$ = 3.5 Hz), 132.8, 133.3, 133.4, 135.4 (d, $^{2}J_{C-P}$ = 6.9 Hz), 149.2, 149.4, 170.1, 171.5, 172.7. ^{31}P NMR (121 MHz, CHLOROFORM-*d*) rotamers of diastereoisomers at δ ppm 19.66, 19.79, 20.39. HRMS (ESI-MS): calculated for $C_{37}H_{45}Cl_2N_3O_{11}P$ $[M + H]^+$: 808.2163, found: 808.2186.

5.96. Biological evaluation

5.96.1. Antiplasmodial susceptibility testing[32]

Chloroquine resistant *P. falciparum*-K1 parasites were cultured in human erythrocytes (O +) at 37 °C under a low oxygen atmosphere (3% O2, 4% CO2, and 93% N2) in RPMI-1640, supplemented with 10% human serum. Infected human red blood cells (200 µL, 1% parasitaemia, 2% haematocrit) were added to each well and incubated for 72 h. After incubation, test plates were frozen at −20 °C. Parasite multiplication was measured by the Malstat method. One hundred microliters of Malstat™ reagent was transferred in a new plate and mixed with 20 µL of the hemolysed parasite suspension for 15 min at RT. Then, 20 µL of nitro blue tetrazolium chloride (NBT) at 2 mg/mL/PES at 0.1 mg/mL solution was added and the plate was incubated again for 2 h at RT in the dark. Absorbance was read at 655 nm in a Biorad 3550-UV microplate reader. As a positive control, chloroquine was included (IC_{50} = 0.13 µM).

5.96.2. Antitubercular susceptibility testing[33]

In vitro antimycobacterial activity was evaluated by a colorimetric resazurin microtiter assay based on a *M. tuberculosis* H37Rv laboratory strain. Volumes of 100 µL of 7H9-Supplemented broth (Middlebrook 7H9 broth + 10% OADC + 0.5% glycerol + 0.1% casitone) were dispensed in each well of a sterile, flat-bottomed 96-well plate. A 2-fold serial dilution of each compound was made directly in the plate with final concentrations ranging from 50 µM to 3.12 µM. Bacterial isolates were freshly subcultured on LJ medium. The inoculum was prepared in 7H9-S broth, adjusted spectrophotometrically to a no. 1 McFarland tube standard, and further diluted 1:10 in 7H9-S broth for the test. A volume of 100 µL of bacteria was added to each well. A growth control (medium and bacteria), a drug control (medium and compound) and a sterile control (only medium) were also included. All of the outer-perimeter wells were filled with 200 µL of sterile deionized water to minimize evaporation of the medium in the test wells during incubation. The plate was subsequently covered, sealed in a plastic bag, and incubated at 37 °C under a normal atmosphere. After 7 days of incubation, 30 µL of resazurin solution was added to each well, and the plate was reincubated overnight. A change in color from blue to pink indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in color. Bacterial replication was analyzed by visual reading.

5.96.3. *In vitro cytotoxicity assay.*[32]

The *in vitro* cytotoxicity on the MRC-5 *Homo sapiens* long fibroblast cell line (ATCC® CCL-171™) was assessed for each analogue by a resazurin-based cytotoxicity assay. Briefly, the MRC-5 cells were cultured in 75 cm^2 sterile Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal calf serum in a 5% CO_2 atmosphere at 37 °C. When a semi-confluent layer of cells was formed, the cells were trypsinized, washed with sterile PBS, seeded into a transparent, flat-bottomed 96-well plate at a density of 4×10^4 cells per well and left for recovery at 37 °C, 5% CO_2 for at least 24 h. For each compound, a two-fold serial dilution was made in complete DMEM with final concentrations ranging from 128 µM to 0.5 µM. Subsequently, the MRC-5 cells were exposed to the compounds by adding 100 µL of the serial dilutions to the wells. Test plates were incubated for 24 h in an atmosphere of 5% CO_2 at 37 °C. For the resazurin assay, the cells were washed 2 times with 200 µL PBS and 100 µL resazurin working solution was added per well. Subsequently, the plates were left for incubation at 37 °C, 5% CO_2 for 3 h. The irreversible reduction of resazurin to resorufin is proportional to aerobic respiration and the quantity of resorufin produced is proportional to the number of viable cells. To monitor the viable cell number after compound exposure, each well was analyzed using a microplate fluorometer equipped with a 560 nm excitation / 590 nm emission filter set. Tamoxifen was included as positive control (IC_{50} = 11.09 µM).

5.96.4. In vivo assay

The *in vivo* antiplasmodial activity of compounds **19e**, **37a** and **8** was evaluated in the *Plasmodium berghei* (GFP ANKA-strain) mouse model after intraperitoneal (IP) dosing at 50 mg/kg s.i.d. for 5 consecutive days. Chloroquine was used as reference treatment at 10 mg/kg IP for 5 days. The animals were observed for the occurrence/presence of clinical or adverse effects during the course of the experiment. In case of very severe clinical signs, either due to toxicity or malaria, animals were euthanized for welfare reasons. Parasitemia was determined on days 4, 7, and 14 on surviving animals using flow cytometry (10 µL of blood in 2000 µL of PBS). Percentage reduction of parasitemia compared to vehicle-treated infected controls is used as a measure for drug activity, and the mean survival time (MST) was calculated. Additional information and data are included in the Supporting Information.

Author contributions

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Conflict of interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data (^{1}H NMR, ^{13}C NMR and LC-MS spectra for the final compounds, additional information and data on the in vivo assay (PDF)) to this article can be found online at https://doi.org/10.1016/j.bmc.2019.01.016.

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