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Cyclic Phosphinamides and Phosphonamides, Novel Series of Potent Matrix Metalloproteinase Inhibitors with Antitumour Activity

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Abstract—The design, synthesis, and structure–activity relationship (SAR) of a series of novel nonpeptidic cyclic phosphon- and phosphinamide-based hydroxamic acids as inhibitors of matrix metalloproteinases MMP-1, MMP-3, and MMP-9 are presented. Based on modelling studies and X-ray analysis, a model of the binding mode of these novel compounds in the MMP active site was obtained. This model provided a rational explanation for the observed SAR data, which included a systematic study of different S1′ directed substituents, zinc-complexing groups, chirality, and variation of the cyclic phosphon- and phosphinamide rings. The in vivo effect of four compounds in a human fibrosarcoma mouse model (HT1080) was evaluated and compared to that of a reference compound, Prinomastat. Inhibition of tumour growth was observed for all four compounds.

Introduction

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endoproteinases responsible for degradation of extracelluar matrix components in tissue remodelling during pregnancy, wound healing, and angiogenesis. However, uncontrolled expression and activity of the MMPs lead to pathological destruction of connective tissue, and MMPs have been implicated in a number of diseases such as multiple sclerosis,[1] osteoarthritis,[2] psoriasis,[3] and tumor growth and metastasis.[4] Consequently, MMPs are attractive therapeutic targets and considerable effort has been made to discover inhibitors of MMP activity useful for treatment of the above-mentioned diseases.

More than 20 different MMPs have been found to date. According to their location, substrate preferences, and structural similarities the MMPs can be divided into five groups: collagenases (MMP-1, MMP-8, MMP-13), stromelysins (MMP-3, MMP-10, MMP-11), gelatinases (MMP-2, MMP-9), membrane-type MMPs, and others. It is still the subject of debate which MMPs are involved in which diseases. However, some studies suggest that inhibitors of MMP-13 show potential for reducing cartilage loss in osteoarthritis,[2] while inhibitors of the gelatinases MMP-2 and MMP-9 may prevent cancer tumour growth[5] through inhibition of the angiogenetic process.

In this paper, we describe the design and synthesis of novel, potent, and in vivo active cyclic phosphon- and phosphinamides. The in vitro SAR data of these new MMP inhibitors are discussed and a molecular modelling analysis of their possible binding in the MMP enzymes is presented. Furthermore, the in vivo effect of the cyclic phosphon- and phosphinamides in a human fibrosarcoma mouse model (HT1080) is presented.

Molecular modelling and compound design

One of the first low-molecular non-peptidic MMP inhibitors reported was the sulphonamide hydroxamic acid

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CGS-27023A (**1**, Fig. 1).[6] In addition to the investigation of sulfonamides, MacPherson et al. also showed that substituting an amide bond for the sulphonamide bond caused the loss of all activity.[6] Accordingly, it was speculated that either both sulphonamide oxygens made crucial H-bonds to the enzyme or the geometry of the active sulphonamide rotamer was crucial for activity.[6]

In order to discriminate between these two possible explanations, Pikul et al. investigated phosphinamide-based hydroxamic acids (**2**, Fig. 1).[7] The phosphinamide bond mimics the geometry and conformational freedom of the sulphonamide bond but provides only one oxygen for interaction with the enzyme. The phosphinamide-based hydroxamic acid compounds are highly potent MMP inhibitors and it was concluded that only one of the oxygens and the geometry of the sulphonamide bond was essential for the activity of CGS-27023A.[7]

A recent study has described the synthesis of novel cyclic phosphonamide-based hydroxamic acids where the amide nitrogen atom is connected to the carbon α to the hydroxamic acid (**3**, Fig. 1); these compounds are also potent MMP inhibitors.[8]

Structural information of the binding of CGS-27023A to the active site of the MMPs came from the determination by NMR of the three-dimensional structure of CGS-27023A bound to MMP-1 (pdb-codes 3ayk and 4ayk).[9] The information about the bio-active conformation of CGS-27023A played a crucial role in our design of the novel cyclic phosphon- and phosphinamide inhibitors presented here. Furthermore, structural information on the binding of the phosphinamide-based inhibitors has also been presented.[7,10]

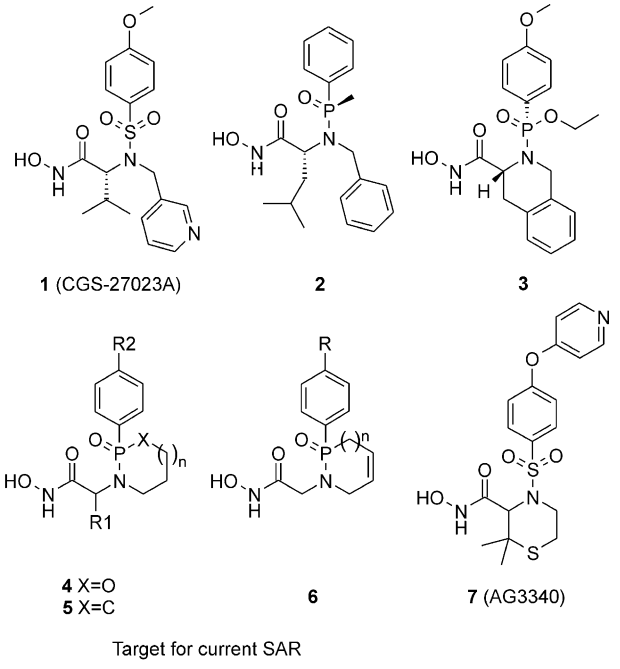


Figure 1. Structures of MMP inhibitors.

The structure of CGS-27023A bound to MMP-1 showed that the zinc atom in the active site was chelated by the two oxygen atoms of the hydroxamic acid.[9] Furthermore, one of the sulphonamide oxygens formed a hydrogen bond with the NH of Leu181[9] (MMP-1 numbering[11]). A similar hydrogen bond acceptor is present in almost all MMP inhibitors and was early on recognised as highly important for inhibitory activity.[11] One possible explanation for this critical hydrogen bond is that the NH of Leu181 (MMP-1) is 'electrostatic hot' due to the complexation of the Leu181 carbonyl oxygen to a nearby structural calcium ion.[11,12] Finally, the methoxyphenyl group was positioned in the S1′ pocket of the enzyme. This pocket is a relatively narrow hydrophobic channel. Several studies have shown that the S1′ pocket size differs in the MMPs and is therefore often described as a 'selectivity pocket'.[11,13,14] Thus, MMP-1, MMP-7, and MMP-11 have a relatively small S1′ pocket whereas MMP-2, MMP-3, and MMP-9 have a deep S1′ pocket.

The three-dimensional structure of the phosphinamide-based MMP inhibitor **2** bound to MMP-3 revealed the same binding interactions as those found for CGS-27023A.[7,10] Comparison of the binding of these inhibitors led to the suggestion that CGS-27023A might experience some unfavourable interactions with MMP enzymes by placing the sulfonyl oxygen not involved in a H-bond close to the hydrophobic isobutyl side chain of Leu164 (MMP-3, Leu81 in MMP-1).[7] The phosphinamide-based inhibitors had a methyl group at this position, and the observation that a methyl-to-ethyl switch resulted in a 6–10-fold decrease of potency against both MMP-1 and MMP-3 led to the conclusion that the arrangement of substituents at the phosphorus center of **2** shown in Figure 1 seemed to be quite optimal.[7]

In our search for conformationally restrained MMP inhibitors we speculated that, despite the observations described above, the MMP enzymes would be able to accommodate cyclic phosphonamide/phosphinamide-based hydroxamic acids (**4**–**6**, Fig. 1). These compounds proved highly interesting based on a computational evaluation. First, a conformational analysis of **4** and **5** [with R1 = H, R2 = methoxy, and an (*R*)-configuration at the phosphorus atom] using the program MacroModel revealed that low-energy conformations (approx. 1 kcal/mol above the global minimum) of both cyclic phosphon- and phosphinamide hydroxamic acids almost perfectly emulated the bioactive conformation of CGS-27023A found in the MMP-1 complex (Fig. 2). Second, superposition of these low-energy conformations on CGS-27023A in the MMP-1 complex indicated that the cyclic phosphonamide/phosphinamide ring system would *not* clash significantly with the enzyme. The only steric overlap seemed to be between one of the protons in the methylene group, which in the cyclophosphonamides is adjacent to the ring oxygen, and the α proton of Asn180 (MMP-1). Consequently, we decided to further explore the feasibility of cyclic phosphonamide/phosphinamide-based hydroxamic acids as MMP inhibitors.

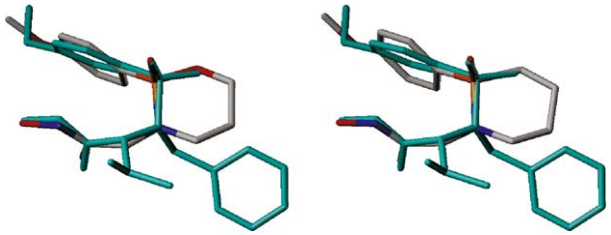


Figure 2. Superposition of low-energy conformations of (a) **4** and (b) **5** analogues (atom colours) on the CGS-27023A (shown in cyan) conformation found in 3ayk.pdb. The heavy atoms of the hydroxamic acid moiety, the phosphorous atom, the double bonded oxygen, and the four-carbon of the aromatic ring were superimposed on the corresponding atoms of CGS-27023A. The RMS values were 0.36 and 0.24 Å, respectively.

Chemistry

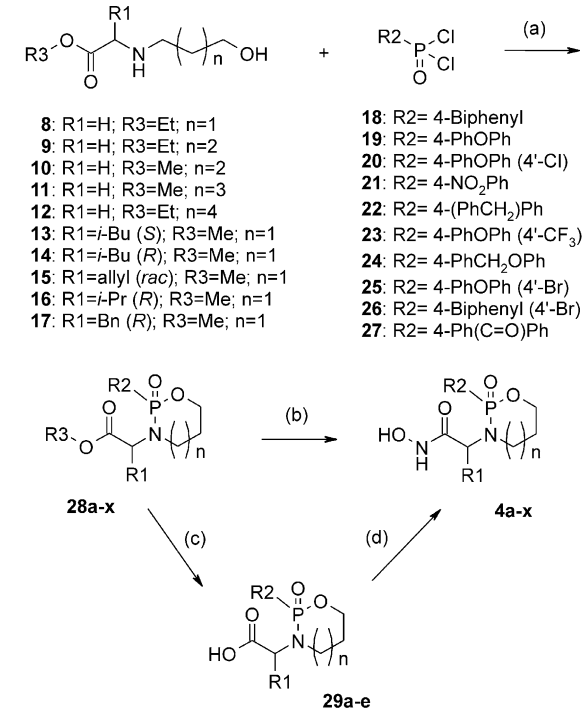
Synthesis of cyclophosphonamides

The cyclophosponamide hydroxamic acids were prepared by cyclization of *N*-hydroxyalkyl amino acid esters (**8**–**17**) with phosphonyl dichlorides (**18**–**27**), followed by conversion of the ester group to a hydroxamic acid (Scheme 1). Esters **28f**–**x** (R1 = H) were converted directly to the corresponding hydroxamic acids **4f**–**x** by treatment with hydroxylamine and NaOMe in methanol. However, this method was not suitable for compounds **28a**–**28e**, probably due to steric hindrance. Instead, these compounds were hydrolyzed to carboxylic acids **29** before conversion to hydroxamic acids **4** by the mixed anhydride method.

Cyclophosphonamides **4** prepared from achiral aminoalcohols **8**–**12** (R1 = H) were prepared as racemates. The cyclisation of chiral aminoalcohols **13**–**17**, in which R1≠H, resulted in diastereomeric cyclophosphonamides **4a**–**e** (Table 1) that were separable by flash chromatography. Except for **4d**, these compounds were enantiomerically pure.

The aminoalcohols **8**–**12** with R1 = H were prepared by alkylation of excess ω-aminoalcohol with methyl or ethyl bromoacetate. Amino propanols **13**–**17** with R1 substituents were prepared from the corresponding amino acid esters according to Scheme 2. First, the amino acid ester was protected with a 2-nitrobenzenesulfonyl or a benzyl group and subsequently alkylated, which gave the hydroxypropyl compounds **35**–**39**. Removal of the protecting group using standard conditions afforded the substituted amino alcohol.

Phosphonyl dichlorides **18**–**27** were prepared by chlorination of the corresponding alkyl aryl phosphonates (**40**–**49**), preferably with PCl_5[15] (Scheme 3). This method was not suitable for substrates **47** and **48**, which underwent ring-substitution of the bromine atom with chlorine, and for substrate **49**, which decomposed to unidentifiable products. In these cases, the alkyl aryl phosphonate was converted to a bis(trimethylsilyl) aryl phosphonate[16] that was subsequently chlorinated with oxalyl chloride[17] in the presence of a catalytic amount of DMF. Aryl phosphonates were prepared from aryl bromides or aryl triflates by palladium-catalyzed phosphonation.[18]



	n	R1	R2
a	1	*i*-Pr	4-MeO-Ph
b	1	Bn	4-MeO-Ph
c	1	*i*-Bu	4-MeO-Ph
d	1	allyl	4-MeO-Ph
e	1	*i*-Pr	4-PhOPh (4'-Cl)
f	2	H	4-Biphenyl
g	2	H	Phenyl
h	2	H	4-MeO-Ph
i	2	H	4-Biphenyl (4'-Br)
j	2	H	4-PhOPh
k	2	H	4-PhOPh (4'-Cl)
l	2	H	4-PhOPh (4'-Br)

	n	R1	R2
m	2	H	4-PhOPh (4'-CF_3)
n	2	H	$PhCH_2Ph$
o	2	H	4-Ph(C=O)Ph (4'-Cl)
p	2	H	4-$PhCH_2OPh$
q	2	H	4-PhCONHPh (4'-Cl)
r	1	H	4-MeO-Ph
s	3	H	4-MeO-Ph
t	4	H	4-MeO-Ph
u	1	H	4-PhOPh
v	3	H	4-PhOPh
w	1	H	4-Biphenyl (4'-Br)
x	3	H	4-Biphenyl (4'-Br)

Scheme 1. (a) NMM, CH_2Cl_2; (b) NaOMe, $TMSONH_2$, MeOH; (c) NaOH, MeOH; (d) isobutylchloroformate, $TMSONH_2$, THF.

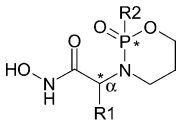
Compound **4q** was synthesized via a 4-nitrophenyl phosphonamide ester **28y** intermediate (Scheme 4). The nitro group was reduced to the amine and subsequently benzoylated with 4-chlorobenzoylchloride. Finally, hydroxylaminolysis of the ester gave compound **4q**.

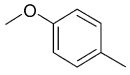
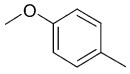
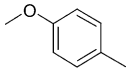
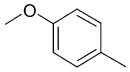
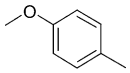
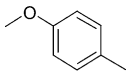
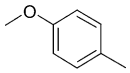
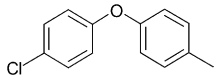
Synthesis of cyclophosphinamides

As the phosphonamide hydroxamic acids proved to be potent MMP inhibitors (vide infra), we then proceeded to synthesize the corresponding phosphinamides. These compounds were obtained by a ring-closing metathesis strategy by procedures described by Gouverneur and co-workers.[19]

Dichloroarylphosphines **50a**–**c**, prepared by standard methods,[20] were treated with unsaturated alcohols (Scheme 5). In the case of allyl alcohol, the resulting diallyl arylphosphonites underwent a thermal Arbuzov-

Table 1. In vitro results for a series of six-membered cyclophosphonamide MMP inhibitors: effect of stereochemistry and α substituent



Compd[a]	R1	R2	IC_{50} (nM)		
			MMP-1	MMP-3	MMP-9
4a	*i*-Pr		500	40	20
4b	Benzyl		320	25	16
(*R,R*)-**4c**	*i*-Bu		400	63	25
(*S,R*)-**4c**	*i*-Bu		> 10,000	7900	> 10,000
(*R,S*)-**4c**	*i*-Bu		> 10,000	> 10,000	> 10,000
(*S,S*)-**4c**	*i*-Bu		> 10,000	7900	10,000
4d[b]	Allyl		790	63	32
4e	*i*-Pr		130	16	0.63

[a]The stereochemistry at the two chiral centres (P,α) is (R,R) unless otherwise specified.
[b]A racemic mixture of the most potent diastereomer.

type rearrangement to yield allyl alkenyl(aryl)phosphinates, **51**(**d**,**f**,**h**). Esters of higher ω-alkenols were treated with the corresponding bromides to effect rearrangement to alkyl alkenyl(aryl)phosphinates, **51**(**e**,**g**). In turn, these phosphinates were cleaved with phosphorus pentachloride, and amidated with *N*-allylglycine ethyl ester, and the resulting phosphinamides **52**(**d**,**e**,**h**) cyclized in the presence of Grubb's catalyst to the phosphinamides **53**(**d**,**e**,**h**). Alternatively, the phosphinate **51f**,**g** was cleaved and amidated with allyl amine yielding phosphinamides **54f**,**g**. After ring closing metathesis using Grubb's catalyst, the resulting phosphinamides **55f** were alkylated with ethyl bromoacetate, yielding esters **53f**. Alkylation prior to RCM was also feasible as shown by the transformations of alkyl phosphinamide **54g** to dialkyl phosphinamide **52g** and further to azaphosphorepene **53g**. For the synthesis of saturated heterocycles, the ring double bond was hydrogenated using Palladium on charcoal without adverse fission of the C–N bond of the cyclic phosphinamides **53d**–**g**, (Scheme 6). In all cases, hydroxylaminolysis of the ethyl esters **53** and **56** finally afforded hydroxamic acids **6d**–**h** and **5d**–**g**, respectively.

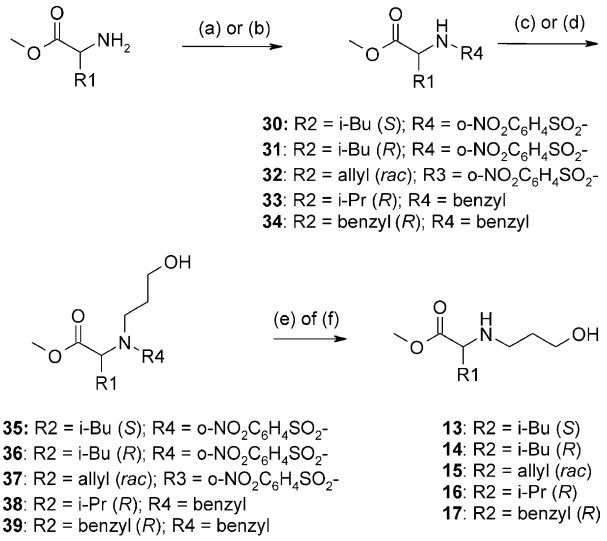
Analysis of stereochemistry

The absolute configuration of the carboxylic precursor to **4a** (**29a**) was established using X-ray analysis (data not shown). It was found that both the α carbon and the phosphorus atom had an (*R*)-configuration, which should also apply to **4a**. Similar to other studies,[7,8] this structure elucidation was used to assign the stereochemistry of other compounds by characteristic signal patterns in ^{1}H NMR.

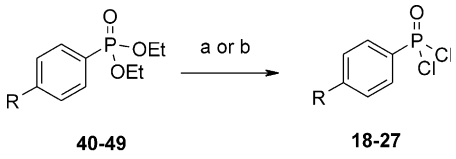
Results and Discussion

In vitro structure–activity relationships

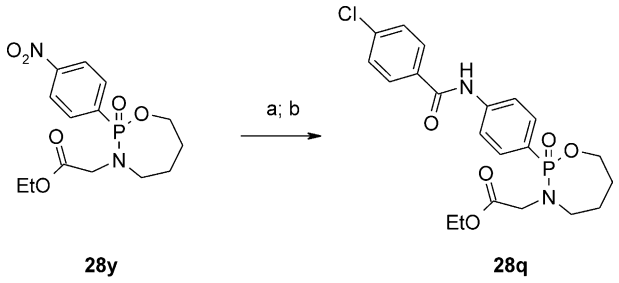
A schematic overview of the in vitro SAR is shown in Figure 3. In general, the two series (cyclophosphonamides and cyclophosphinamides) of MMP inhibitors described in the present work were equally potent in vitro. However, the SARs of the two series were slightly different. The modelling-based binding mode proposed for the cyclophosphonamides and cyclophosphinamides is shown in Figure 4.



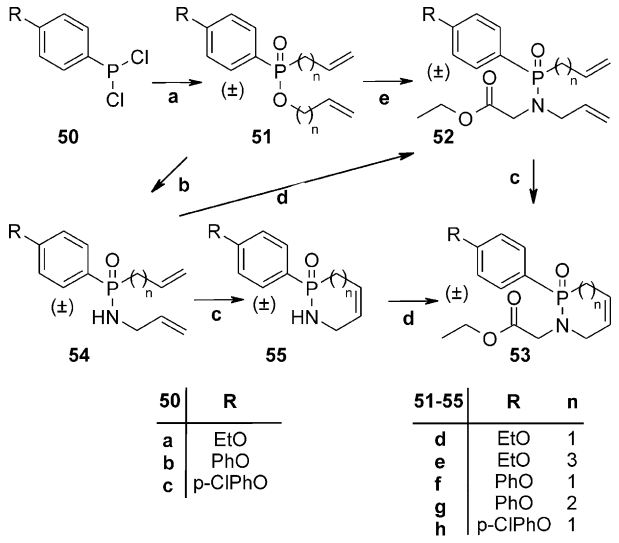
Scheme 2. 2-Nitrobenzenesulfonic chloride; Et_3N, CH_2Cl_2; (b) PhCHO, $NaBH_3CN$, MeOH; (c) $CsCO_3$, 3-bromopropanol, DMF; (d) Allylbromide, DIPEA, DMF; then 9-BBN, THF; H_2O_2, NaOH; (e) K_2CO_3, PhSH, MeCN, (f) H_2, Pd-C.



Scheme 3. (a) PCl_5 (for the preparation of **18–24**); (b) TMSCl, NaI; then $(COCl)_2$, DMF (cat.) (for the preparation of **25–27**).



Scheme 4. (a) H_2/Pd-C; (b) 4-Cl-benzoylchloride, Et_3N.



Scheme 5. (a) (i) $CH_2CH(CH_2)_nOH$, Et_2O, pyridine; (ii) $CH_2CH(CH_2)_nBr$, 130 °C, 16 h; (b) (i) PCl_5, DCM; (ii) allylamine, triethylamine, DCM (c) Grubb's catalyst, DCM (d) (i) *n*BuLi, THF; (ii) Ethyl bromoacetate; (e) (i) PCl_5, DCM; (ii) *N*-allylglycine ethyl ester, triethylamine, DCM.

Hydroxamic acids and carboxylic acids were prepared and tested as zinc binding groups. As expected, the in vitro potencies of the hydroxamic acids were 100–1000-fold higher than the corresponding carboxylic acids (data not shown). Furthermore, *N*-methylation of the hydroxamic acid resulted in a decreased potency (data not shown).

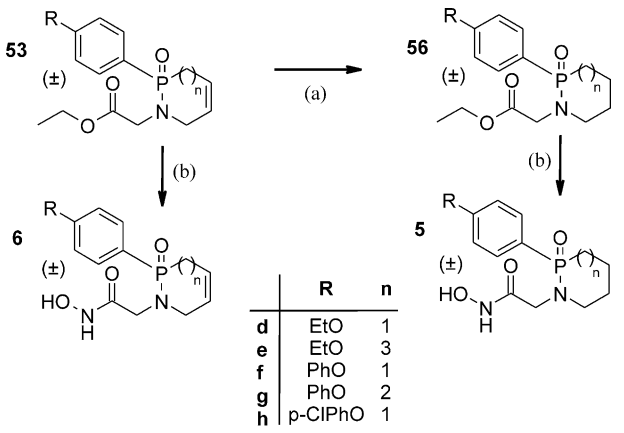
Although we did not find any carboxylic acids equipotent to their hydroxamic acid counterparts, a recent study of tetrahydroisoquinoline-3-carboxylates as MMP-8 inhibitors has indicated that this is sometimes possible by optimization of the S1′-directed substituent.[21]

Effect of stereochemistry. All compounds presented in this study have a chiral centre at the phosphorus atom. Compounds with only this chiral centre were tested as racemates.

Compounds with two chiral centres (the phosphorus atom and the carbon atom α to the hydroxamic acid) were prepared as pure stereoisomers. Determination of the absolute configuration (see Chemistry section) revealed that the most potent stereoisomers had the (*R,R*)-configuration. This result was in excellent agreement with our modelling studies as well as previous studies which all indicate that the (*R*)-configuration at the phosphorus atom is preferred for binding of the cyclic phosphonamide/phosphinamide-based hydroxamic acids to the MMP enzymes.[7,8] Furthermore, it is well known for more bulky substituents, that an (*R*)-configuration at the α carbon is important for activity.[6,8,13,22] Stereoisomers with another configuration than (*R,R*) were in general 100–1000 times less potent (Table 1).

Effect of the phosphorus substituent. Our modelling studies based primarily on earlier work[6,7] indicated that the aromatic phosphorus substituent (R2, Fig. 1) would be placed in the S1′ pocket, generally believed to confer affinity and selectivity (Fig. 4).

The in vitro data obtained for our cyclic phosphonamide-based hydroxamic acids (Table 2) support our hypothesis that the aromatic phosphorus substituent is placed in the S1′ pocket. Increasing the size of the relatively hydrophobic phosphorus substituent from phenyl to *p*-methoxyphenyl to *p*-phenoxyphenyl (**4g**, **4h**, and **4j**) dramatically increased the affinity towards the deep S1′



Scheme 6. (a) H_2, 5% Pd on C, EtOH; (b) NH_2OTMS, KOH, MeOH, 0 °C.

pocket enzymes MMP-3 (IC_{50}: 5000, 200, 13 nM) and MMP-9 (IC_{50}: 1600, 32, 0.40 nM) as well as the selectivity against the short S1′ pocket MMP-1 (MMP-9/MMP-1 ratio: 41 for *p*-methoxyphenyl and 1000 for *p*-phenoxyphenyl). These observations correspond very well with those in other studies,[6,8,21,23] strongly suggesting that the increase in affinity and selectivity is indeed due to improved enzyme–ligand interactions between the phosphorus substituent and the deep and relatively narrow hydrophobic S1′ pocket.

An increased affinity towards MMP-1, although less dramatic, was also observed when increasing the phosphorus substituent from *p*-methoxyphenyl (IC_{50}: 1300 nM, **4h**) to *p*-phenoxyphenyl (IC_{50}: 400 nM, **4j**). This was somewhat surprizing as MMP-1 has a short S1′ pocket which one might expect would not be able to

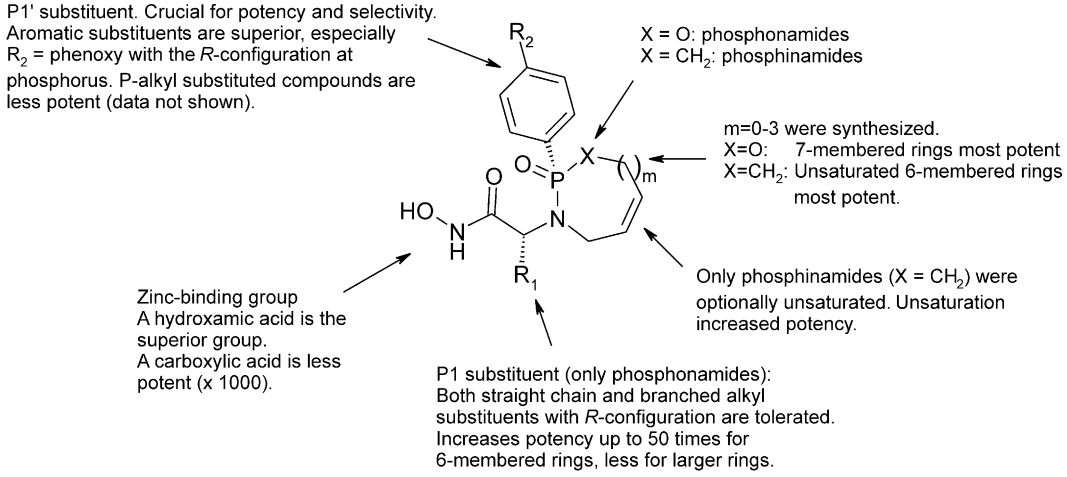


Figure 3. An overview of structure–activity relationships of the cyclic phosphon- and phosphinamides.

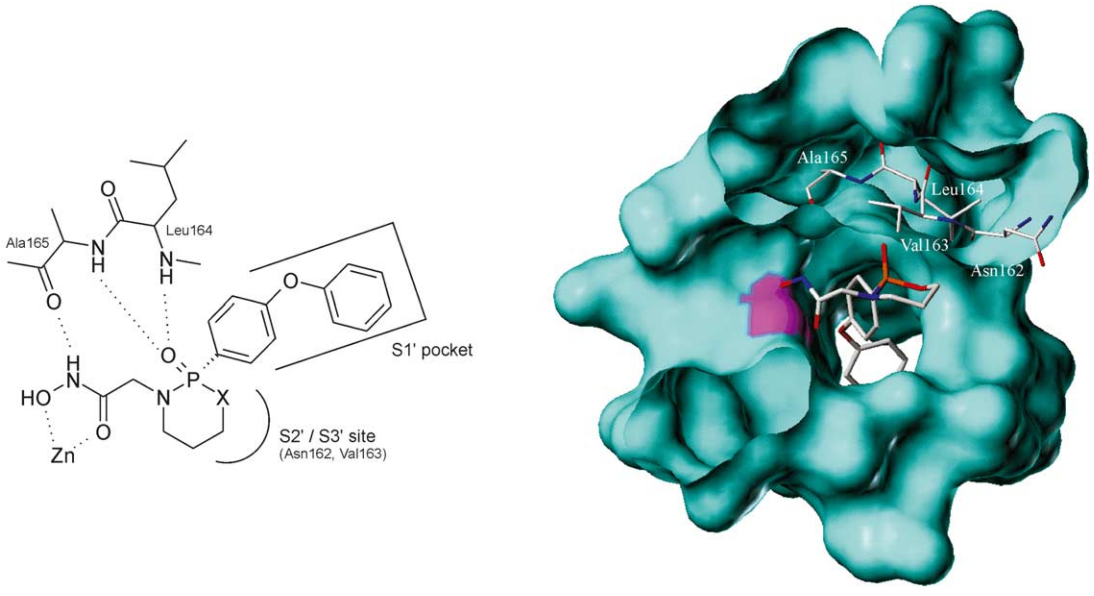
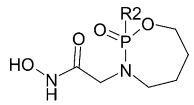
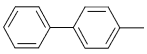
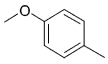
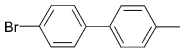
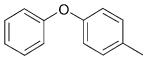
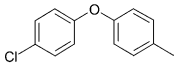
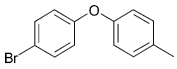
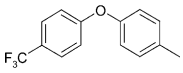
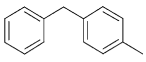
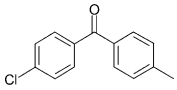
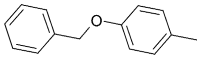
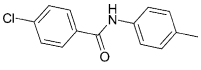


Figure 4. (a) Schematic view of the expected binding mode of the cyclic phosphon- and phosphinamides in MMP-3; (b) docking model of the MMP-3-**4u** complex. Using the same atoms as in Figure 2, a low-energy conformation of the cyclic phosphonamide inhibitor **4u** was superimposed on the conformation of **2** found in the MMP-3–**2** complex. (1b3d.pdb). The RMS value was 0.37 Å. A MOLCAD surface of the residues surrounding the inhibitor was generated using Sybyl 6.9. The position of the catalytic zinc is indicated by the magenta part of the surface.

Table 2. In vitro results for a series of seven-membered cyclophosphonamide MMP inhibitors: effect of *P*-substituent (R2)



Compd	R2	IC_{50} (nM)		
		MMP-1	MMP-3	MMP-9
1		160	40	79
7		79	6.3	5.0
4f		4000	200	79
4g			5000	1600
4h		1300	200	32
4i		6300	79	63
4j		400	13	0.40
4k		400	40	1.0
4l		400	32	2.5
4m		1600	40	4.0
4n		> 10,000	200	160
4o		> 10,000	200	20
4p		> 10,000	50	79
4q		> 10,000	100	10

accommodate the *p*-phenoxyphenyl substituent. However, similar observations have been reported.[8] The superposition of low-energy conformations of **4j** on CGS-27023A bound to MMP-1 indicates that the S1′ pocket of MMP-1 is in fact able to accommodate the *p*-phenoxyphenyl substituent even without undergoing the significant rearrangement of the S1′ loop proposed for some MMP-1 inhibitors with extended P1′ substituents — a rearrangement which results in a more open MMP-1 S1′ pocket by repositioning the Arg which normally blocks the S1′ pocket.[11,13] It should be noted that the *p*-phenoxyphenyl substituent is quite unique in this respect as other biphenyls (**4n**, **4o**, **4p**, and **4q**) are not tolerated in the MMP-1 S1′ pocket (Table 2).

Effect of ring size. In the case of larger P1′ substituents (*p*-phenoxyphenyl and *p*-bromo-biphenyl) the optimal ring size for the cyclic phosphonamide was a seven-membered ring with six- and eight-membered rings somewhat less potent (Table 3). For the smaller P1′ substituent *p*-methoxyphenyl, seven- and eight-membered rings were essentially equipotent and six- and nine-membered somewhat less potent.

We speculated that the variation in activity with varying ring size may be due to additional hydrophobic interactions between the ring and residues Val163 and Asn162 (MMP-3, numbering[7,8]) forming part of the S2′/S3′ site and/or less steric overlap due to increased ring flexibility. However, the reason for the apparent preference for seven-membered rings in the phosphonamide series is difficult to pinpoint.

Effect of the α substituent. As mentioned above, an (*R*)-configuration was important α to the hydroxamic acid; inversion of the stereochemistry resulted in a 200–400-fold reduction in potency (Table 1). The optimal substituents with respect to in vitro activity were isopropyl, allyl, isobutyl, and benzyl.

The (*R*)-α substitutions increased the potency roughly by a factor of 10–50 in the compounds containing a 6-membered phosphonamide ring. Interestingly, (*R*)-α substitutions in compounds containing a seven-membered phosphonamide ring only resulted in a more modest increase in potency (data not shown).

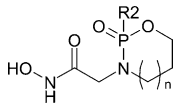
The cyclophosphinamides. In the phosphinamide series, the influence of ring size was not the same for saturated and unsaturated cyclophosphinamides (Table 4). For saturated compounds, seven- and eight-membered rings appeared to be almost equipotent, and somewhat more potent than six-membered rings, as observed for the saturated cyclophosphonamides. In contrast, unsaturated cyclophosphinamides with six-membered rings gave the most in vitro potent compounds, seven- and eight-membered rings being up to 10-fold less potent (compare **6f** with **6g**). The most potent cyclophosphinamides seem to be those with an unsaturated six-membered ring. One possible explanation could be that the unsaturated six-membered ring does not contain the methylene CH_2 group which could clash with the α proton of Asn180 (MMP-1).

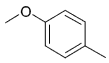
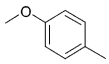
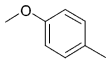
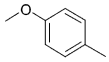
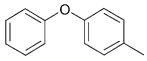
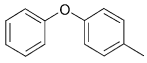
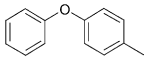
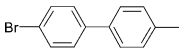
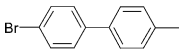
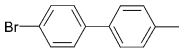
The effect of the aromatic phosphorus substituent was the same as for the cyclic phosphonamides. No cyclophosphinamides with an α substituent were prepared.

In vivo antitumour activity

The most potent compounds in vitro had a *p*-phenoxyphenyl as the P1′ substituent. However, based on in vitro pharmacokinetic analyses we were concerned about the metabolic stability of the *p*-phenoxyphenyl. Accordingly, compounds where the 4-position of the *p*-phenoxyphenyl group, the most likely point of metabolic attack, was blocked by a halogen, were tested in an in vivo antitumor model. Introduction of this halo-

Table 3. In vitro results for a series of cyclophosphonamide MMP inhibitors: effect of ring size



Compd	R2	*n*	IC_{50} (nM)		
			MMP-1	MMP-3	MMP-9
4r		1	> 10,000	790	630
4h		2	1300	200	32
4s		3	2000	100	32
4t		4	3200	320	160
4u		1	1600	40	4.0
4j		2	400	13	0.40
4v		3	790	32	4.0
4w		1	> 10,000	130	100
4i		2	6300	79	63
4x		3	> 10,000	500	320

gen did indeed increase the stability of the compounds in the in vitro pharmacokinetic assay (data not shown).

The compounds were tested in a human fibrosarcoma mouse model (HT1080) (see Experimental). The mice were treated therapeutically for 14–16 days with 50 mg/kg/day ip daily starting day 3 to 6 after tumour inoculation. The compounds were well tolerated by the animals, and there were no signs of weight loss or other adverse effects.

Good tumour growth inhibition was observed for both the cyclophosphonamides (**4k**, **4l**, and **4e**) and the cyclophosphinamide (**6h**) as well as for the reference compound Prinomastat (**7**, AG3340) (Table 5). The tumour growth curves for **4l** and **6h** are shown in Figure 5. For compounds **4k**, **4l**, **6h**, and Prinomastat the inhibition of tumour growth was statistically significant ($p < 0.05$, one-way analysis of variance). Compound **4e** also reduced tumour growth, however without reaching statistical significance. The in vitro activities of the compounds tested in the HT1080 cancer model are also summarised in Table 5.

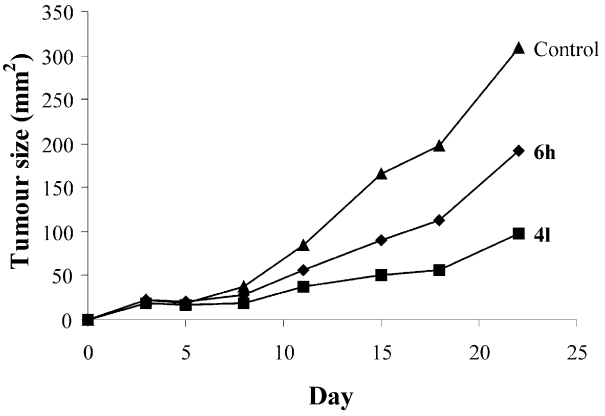


Figure 5. Tumour growth inhibitory effect in a human fibrosarcoma mouse model (HT1080). Comparison of the effect of a cyclophosphonamide **4l** and a cyclophosphinamide **6h** to a control group. The tumour sizes are mean values. The mice were dosed 50 mg/kg/d ip for 2 weeks from day 5. The tumour reduction is given in Table 5.

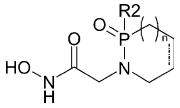
The tumour growth inhibition of **4k**, **4l**, **4e**, and **6h** was comparable to that of the reference compound Prinomastat. However, although the compounds showed a clear tendency to reduce tumour growth, they did not stop the tumour growth entirely. This may be explained by the somewhat short $T_{1/2}$ (0.7–1.6 h) for all the compounds and/or tumour growth which is not dependent on MMP activity.

The observation that tumour growth does not stop entirely suggests that administration of MMP inhibitors to patients in earlier stages would be more efficient. It could also be interesting to combine MMP inhibitors with conventional cytostatics to benefit from the anti-angiogenic mechanism of the MMP inhibitors.

Conclusion

The design and synthesis of novel cyclic phosphon- and phosphinamide-based hydroxamic acids were described. It was shown that these compounds were very potent (nM) MMP inhibitors in vitro. Variation of the phosphorus S1′ directed substituent produced compounds with altered selectivity for the MMPs reported herein. Modelling studies and X-ray analysis revealed that an (*R*)-configuration at the phosphorus atom and at the α

Table 4. In vitro results for a series of cyclophosphinamide MMP inhibitors



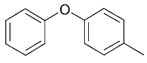
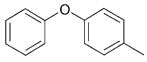
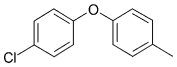
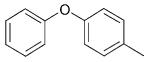
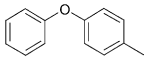
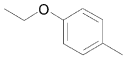
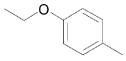
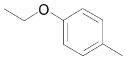
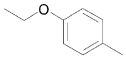
Compd	*R2*	*Satd.*	*n*	IC_{50} (nM)		
				MMP-1	MMP-3	MMP-9
5f		Yes	1	10,000	160	13
6f		No	1	2500	20	0.63
6h		No	1	3200	32	1.3
5g		Yes	2	4000	40	5.0
6g		No	2	7900	100	10
5d		Yes	1	> 10,000	3200	1300
6d		No	1	> 10,000	320	320
5e		Yes	3	> 10,000	200	160
6e		No	3	> 10,000	1000	1300

Table 5. In vitro and in vivo results for compounds tested in the HT1080 mice cancer model

Compd	IC_{50} (nM)			$T_{1/2}$ (ip) h	Tumour growth inhibition (%)	Statistical significance
	MMP-1	MMP-3	MMP-9			
4k	400	40	1.0	1.0	−43	$p < 0.05$
4l	400	32	2.5	1.3	−48	$p < 0.05$
6h	3200	32	1.3	0.7	−29	$p < 0.05$
4e	130	16	0.63	1.2	−33	$p > 0.05$
7	79	6.3	5.0	1.6	−38	$p < 0.05$

carbon, when substituted, was essential for activity. The influence of ring size on potency was explored. We found that seven-membered cyclophosphonamides and unsaturated six-membered cyclophosphinamides provided the most potent inhibitors. A model of the binding mode of these novel compounds in the active site of MMPs was presented. Finally, four compounds were tested in a human fibrosarcoma mouse model (HT1080). The compounds all showed antitumour activity in this cancer model, the effects being comparable to that of Prinomastat. This suggested that these novel cyclic phosphon- and phosphinamide-based MMP inhibitors may have potential for the treatment of cancer.

Experimental

Computational procedures

All calculations were performed on a Silicon Graphics O_2 R10000 workstation. The conformational analyses were carried out using the Monte Carlo (Mcrlo) routine of MacroModel (Schrödinger Inc.). The structures in the conformational analyses were energy-minimized with the truncated Newton conjugate gradient (TNCG) method using the MMFF94s force field (default convergence criteria). The solvent was set to water using the SLVNT command. The hydroxamic acid was protonated in the conformational analyses. The resulting structures were visualized with Sybyl (Tripos Inc.). Superposition of the cyclic phosphon- and phosphinamides on the conformation of CGS-27023A found in 3ayk.pdb[9] was done using the Fit Atoms feature in Sybyl. All visual inspection of the novel compounds positioned in the MMP active site was done within Sybyl.

Chemistry

Phenylphosphonic dichloride and 4-methoxyphenylphosphonic dichloride were obtained from TCI. Drying of solvents was effected by adding oven dried molecular sieves to commercial, dry solvents. 'Diastereomer 1'; refers to the less polar of two possible diastereomers as determined by TLC. 'Diastereomer 2'; refers to the more polar diastereomer. All melting points are uncorrected. NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C in the solvent specified. Chemical shift values (δ, in ppm) are quoted relative to internal tetramethylsilane (δ = 0 ppm) or deuteriochloroform δ = 76.81 ppm). The mass spectra were obtained on a Micromass LCT time-of-flight mass spectrometer operating in either positive or negative ion electrospray mode, with a cone voltage of 30 V. The instrument was operated at a resolution of 5000 FWHM. All spectra were recorded at the Department of Spectroscopy at LEO Pharma.

General procedure A: formation of hydroxamic acids from carboxylic acids

A solution of carboxylic acid **29** (2.9 mmol) in THF (45 mL) was cooled to −10 °C under argon. NMM (0.3 mL, 3.0 mmol) and isobutyl chloroformate (0.4 mL, 3.0 mmol) were then added with stirring. After stirring overnight at −10 °C, *O*-trimethylsilyl hydroxylamine (0.4 mL, 3.2 mmol) was added, and the mixture was left at −10 °C for 5 h. The mixture was then acidified with 4 M acetic acid and extracted with EtOAc/H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (typically chloroform/methanol/NH_3 (25%) 90:10:1) or crystallisation to afford the hydroxamic acid **4**.

General procedure B: formation of hydroxamic acids from esters

To a solution of ester **28** (0.20 mmol) in dry methanol (2 mL) was added *O*-trimethylsilyl-hydroxylamine (72 μL, 0.60 mmol) and sodium methoxide (1.4 M, 214 μL, 0.30 mmol). After stirring at room temperature for 1 h, the solution was acidified with 4 M AcOH to pH 4, concentrated under reduced pressure and extracted with EtOAc/H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (typically chloroform/methanol/NH_3 (25% aq.) 90:10:1) or crystallisation to afford the hydroxamic acid **4**.

(2*R*,α*R*)-*N*-Hydroxy-(4-methoxyphenyl)-α-(1-methylethyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide (4a). Prepared from **29a** using procedure A in 19% yield after chromatography and recrystallization in acetone, mp 183.5 °C (dec.). ^{1}H NMR (CD_3OD) δ 7.60 (m, 2H), 7.06 (m, 2H), 4.36 (m, 1H), 4.11 (m, 1H), 3.85 (s, 3H), 3.71 (m, 1H), 3.42 (m, 2H), 2.30 (m, 1H), 2.11 (m, 1H), 1.86 (m, 1H), 1.12 (d, 3H), 0.96–0.88 (d, 3H). ^{13}C NMR (DMSO-d_6) δ 167.2 (d), 161.4 (d), 132.6 (d), 122.8 (d), 114.1 (d), 67.3 (d), 60.1 (d), 55.1, 41.5, 26.5 (d), 26.2 (d), 19.5, 19.0. HRMS calcd for $C_{15}H_{24}N_2O_5P$ (M + H) 343.1423, found 343.1428.

(2*R*,α*R*)-*N*-Hydroxy-2-(4-methoxyphenyl)-2-oxo-α-phenylmethyl-1,3,2-oxazaphosphorinane-3-acetamide (4b). Prepared from **29b** using procedure A in 15% yield as a white solid (crystallized from methanol). ^{1}H NMR (CD_3OD) δ 7.64 (m, 2H), 7.32–7.15 (m, 5H), 7.04 (m, 2H), 4.21 (m, 2H), 4.10 (m, 1H), 3.84 (s, 3H), 3.83 (m, 1H), 3.43 (m, 1H), 3.31 (m, 1H), 3.06 (dd, 1H), 1.87 (m, 2H). HRMS calcd for $C_{19}H_{24}N_2O_5P$ (M + H) 391.1423, found 391.1440.

(2*R*,α*R*)-*N*-Hydroxy-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide [(*R*,*R*)-4c]. Prepared from (*R*,*R*)-**29c** using procedure A in 48% yield. ^{1}H NMR (DMSO-d_6) δ 11.0–9.7 (bs, 1H), 9.2–8.6 (bs, 1H), 7.56 (m, 2H), 7.02 (m, 2H), 4.25 (m, 1H), 4.07 (m, 1H), 3.92 (m, 1H), 3.81 (s, 3H), 3.60 (m, 1H), 3.12 (m, 1H), 1.90–1.35 (m, 5H), 0.93 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 168.0, 161.6, 132.8, 122.4, 114.1, 67.2, 55.2, 52.1, 41.1, 26.7, 24.0, 22.8, 21.9. HRMS calcd for $C_{16}H_{25}N_2O_5P$ (M + H) 357.1579, found 357.1592.

(2*S*,α*R*)-*N*-Hydroxy-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide [(*S*,*R*)-4c]. Prepared from (*S*,*R*)-**29c** using procedure A in 76% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–9.8 (bs, 1H), 9.5–8.6 (bs, 1H), 7.67 (m, 2H), 7.05 (m, 2H), 4.25 (m, 2H), 3.81 (s, 3H), 3.66 (m, 1H), 3.48 (m, 1H), 3.11 (m, 1H), 2.00 (m, 1H), 1.91 (m, 1H), 1.51 (m, 1H), 1.28 (m, 2H), 0.68 (d, 3H), 0.52 (d, 3H). ^{13}C NMR (DMSO-d_6) δ 168.1, 162.0, 133.5, 121.9, 113.9, 66.5, 55.3, 52.0, 40.1, 37.3, 25.8, 23.7, 22.3, 21.8. HRMS calcd for $C_{16}H_{25}N_2O_5P$ (M-H) 355.1423, found 355.1439.

(2*R*,α*S*)-*N*-Hydroxy-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide [(*R*,*S*)-4c]. Prepared from (*R*,*S*)-**29c** using procedure A in 63% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–9.7 (s, 1H), 9.2–8.6 (s, 1H), 7.55 (m, 2H), 7.02 (m, 2H), 4.25 (m, 1H), 4.07 (m, 1H), 3.92 (m, 1H), 3.81 (s, 3H), 3.61 (m, 1H), 3.12 (m, 1H), 1.83 (m, 1H), 1.66 (m, 3H), 1.42 (m, 1H), 0.93 (m, 6H). ^{13}C NMR (DMSO-d_6) d 168.1, 161.5, 132.8, 122.5, 114.1, 67.2, 55.2, 52.1, 41.1, 26.8, 24.0, 22.8, 21.9. HRMS calcd for $C_{16}H_{25}N_2O_5P$ (M + H) 357.1579, found 357.1585.

(2*S*,α*S*)-*N*-Hydroxy-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide [(S,S)-4c]. Prepared from (*S*,*S*)-**29c** using procedure A in 73% yield. ^{1}H NMR (DMSO-d_6) δ 11.0–9.8 (bs, 1H), 9.6–8.5 (bs, 1H), 7.67 (m, 2H), 7.06 (m, 2H), 4.25 (m, 2H), 3.81 (s, 3H), 3.66 (m, 1H), 3.46 (m, 1H), 3.11 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.51 (m, 1H), 1.40–1.15 (m, 2H), 0.68 (d, 3H), 0.52 (d, 3H). ^{13}C NMR (DMSO-d_6) δ 168.1, 162.0, 133.5, 122.0, 113.9, 66.5, 55.3, 52.0, 40.1, 37.3, 25.8, 23.7, 22.3, 21.8. HRMS calcd for $C_{16}H_{25}N_2O_5P$ (M + H) 357.1579, found 357.1592.

(2*R, α*R*)-(±)-*N*-Hydroxy-α-allyl-2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide (4d).** Prepared from **29d** using procedure A in 53% yield. ^{1}H NMR (DMSO-d_6) δ 11.0–9.9 (s, 1H), 9.3–8.7 (s, 1H), 7.56 (m, 2H), 7.03 (m, 2H), 7.76 (m, 1H), 5.13 (m, 2H), 4.24 (m, 1H), 4.11 (m, 1H), 3.94 (m, 1H), 3.81 (s, 3H), 3.61 (m, 1H), 3.14 (m, 1H), 2.50 (m, 2H), 1.87 (m, 1H), 1.69 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 167.4, 161.6, 134.4, 132.8, 122.5, 117.4, 114.1, 67.1, 55.2, 53.6, 41.1, 34.2, 26.6. HRMS calcd for $C_{15}H_{21}N_2O_5P$ (M + H) 341.1266, found 341.1256.

(2*R*,α*R*)-*N*-Hydroxy-2-[4-(4-chlorophenyloxy)-phenyl]-α-(2-methylethyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide (4e). Prepared from **29e** using procedure A in 26% yield after chromatography. Recrystallized from methanol to afford a slightly coloured solid, mp 188.5–190 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 10.64 (bs, 1H), 8.81 (s, 1H), 7.58 (m, 2H), 7.49 (m, 2H), 7.14 (m, 2H), 7.07 (m, 2H), 4.28 (m, 1H), 3.97 (m, 1H), 3.66 (m, 1H), 3.52 (m, 1H), 3.14 (m, 1H), 2.16 (m, 1H), 1.94 (m, 1H), 1.70 (m, 1H), 1.01 (d, 3H), 0.82 (d, 3H). ^{13}C NMR (DMSO-d_6) δ 167.0 (d), 159.1 (d), 154.2, 133.1 (d), 130.0, 128.2, 126.3 (d), 121.4, 117.8 (d), 67.5 (d), 60.0, 41.5, 26.4 (d), 26.1, 19.5, 19.0. HRMS calcd for $C_{20}H_{25}ClN_2O_5P$ (M + H) 439.1189, found 439,1176.

(±)-*N*-Hydroxy-2-(4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetamide (4f). Prepared from **28f** using procedure B in 55% yield as a colourless foam. ^{1}H NMR (DMSO-d_6) δ 11.0–8.5 (bs, 2H), 7.91 (m, 2H), 7.75 (m, 2H), 7.71 (m, 2H), 7.50 (m, 2H), 7.41 (m, 1H), 4.39 (m, 1H), 4.09 (m, 1H), 4.86 (dd, 1H), 3.58 (dd, 1H), 2.93 (m, 2H), 1.90–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.8, 142.9, 139.4, 131.7, 130.2, 129.1, 128.1, 126.9, 126.5, 64.8, 46.5, 29.0, 25.9. HRMS calcd for $C_{18}H_{21}N_2O_4P$ (M + H) 361.1317, found 361.1293.

(±)-*N*-Hydroxy-2-oxo-2-phenyl-1,3,2-oxazaphosphorepane-3-acetamide (4g). Prepared from 28g using procedure B in 65% yield as a colourless oil. ^{1}H NMR (DMSO-d_6) δ 11.0–8.5 (bs, 2H), 7.83 (m, 2H), 7.49 (m, 3H), 4.37 (m, 1H), 4.06 (m, 1H), 3.83 (dd, 1H), 3.56 (dd, 1H), 2.91 (m, 2H), 1.85–1.45 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.7, 131.5, 131.3, 131.0, 128.2, 64.7, 46.5, 46.4, 29.0, 25.9. HRMS calcd for $C_{12}H_{17}N_2O_4P$ (M−H) 283.0848, found 283.0879.

(±)-*N*-Hydroxy-2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetamide (4h). Prepared from **28h** using procedure B in 47% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.5–11.0 (bs, 2H), 7.75 (m, 2H), 7.00 (m, 2H), 4.33 (m, 1H), 4.05 (m, 1H), 3.80 (m, 3H), 3.80 (m, 1H), 3.55 (dd, 1H), 2.88 (m, 2H), 1.85–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.7, 161.5, 132.8, 122.7, 113.6, 64.4, 55.1, 46.4, 46.3, 28.9, 25.8. HRMS calcd for $C_{13}H_{19}N_2O_5P$ (M−H) 313.0954, found 313.0969.

(±)-*N*-Hydroxy-2-(4′-bromo-4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetamide (4i). Prepared from **28i** using procedure B in 49% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–9.8 (s, 1H), 9.3–8.7 (s, 1H), 7.91 (m, 2H), 7.76 (m, 2H), 7.68 (m, 4H), 4.39 (m, 1H), 4.10 (m, 1H), 3.86 (dd, 1H), 3.57 (dd, 1H), 2.92 (m, 2H), 1.90–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.6, 141.5, 138.4, 131.8, 131.7, 130.6, 128.9, 126.3, 121.6, 64.7, 46.4, 46.3, 28.9, 25.8. HRMS calcd for $C_{18}H_{20}BrN_2O_4P$ (M + H) 439.0422, found 439.0446.

(±)-*N*-Hydroxy-2-oxo-2-(4-phenoxyphenyl)-1,3,2-oxazaphosphorepane-3-acetamide (4j). Prepared from **28j** using procedure B in 60% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–10.1 (bs, 1H), 9.3–8.5 (bs, 1H), 7.82 (m, 2H), 7.44 (m, 2H), 7.22 (m, 1H), 7.10 (m, 2H), 7.03 (m, 2H), 4.35 (m, 1H), 4.05 (m, 1H), 3.82 (m, 1H), 3.54 (m, 1H), 2.91 (m, 2H), 1.88–1.43 (m, 4H).

(±)-*N*-Hydroxy-2-[4-(4-chlorophenoxy)-phenyl]-2-oxo-1,3,2-oxazaphosphorepane-3-acet-amide (4k). Prepared from **28k** using procedure B in 83% as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–9.8 (s, 1H), 9.2–8.7 (s, 1H), 7.84 (m, 2H), 7.48 (m, 2H), 7.13 (m, 2H), 7.06 (m, 2H), 4.35 (m, 1H), 4.06 (m, 1H), 3.82 (dd, 1H), 3.54 (dd, 1H), 2.91 (m, 2H), 1.90–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.6, 159.0, 154.4, 133.3, 130.0, 128.0, 126.1, 121.2, 117.5, 64.6, 46.4, 28.9, 25.8. HRMS calcd for $C_{18}H_{20}ClN_2O_5P$ (M + H) 411.0876, found 411.0879.

(±)-*N*-Hydroxy-2-[4-(4-bromophenoxy)-phenyl]-2-oxo-1,3,2-oxazaphosphorepane-3-acetamide (4l). Prepared

from **28l** using procedure B in 78% yield as a white solid (recrystallized from methanol). ^{1}H NMR (DMSO-d_6) δ 11.5–8.0 (bs, 2H), 7.83 (m, 2H), 7.60 (m, 2H), 7.07 (m, 4H), 4.35 (m, 1H), 4.04 (m, 1H), 3.80 (m, 1H), 3.55 (dd, 1H), 2.91 (m, 2H), 1.90–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.6, 158.9, 154.9, 133.3, 132.9, 126.2, 121.5, 117.6, 116.0, 64.6, 46.4, 28.9, 25.8. HRMS calcd for $C_{18}H_{21}BrN_2O_5P$ (M + H) 455.0371, found 455.0392.

(±)-*N*-Hydroxy-2-[4-(4-trifluormethylphenoxy)-phenyl]-2-oxo-1,3,2-oxazaphosphorepa-ne-3-acetamide (4m). Prepared from **28m** using procedure B in 69% yield as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.5–8.0 (bs, 2H), 7.90 (m, 2H), 7.78 (m, 2H), 7.24 (m, 2H), 7.18 (m, 2H), 4.37 (m, 1H), 4.07 (m, 1H), 3.84 (dd, 1H), 3.56 (dd, 1H), 2.92 (m, 2H), 1.90–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.6, 159.2, 157.8, 133.4, 127.5, 127.2, 124.1, 124.1, 118.9, 118.8, 64.7, 46.4, 28.9, 25.8. HRMS calcd for $C_{19}H_{21}F_3N_2O_5P$ (M + H) 445.1140, found 445.1139.

(±)-*N*-Hydroxy-2-benzylphenyl-2-oxo-1,3,2-oxazaphosphorepane-3-acetamide (4n). Prepared from **28n** using procedure B in 71% yield as a colorless foam. ^{1}H NMR (DMSO-d_6) δ 9.95 (bs, 1H), 9.02 (bs, 1H), 7.73 (m, 2H), 7.40–7.15 (m, 7H), 4.34 (m, 1H), 4.04 (m, 1H), 3.98 (s, 2H), 3.80 (dd, 1H), 3.53 (dd, 1H), 2.88 (m, 2H), 1.90–1.40 (m, 4H).

(±)-*N*-Hydroxy-2-(4-chlorobenzoylphenyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetamide (4o). Prepared from **28o** using procedure A in 64% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0-9.5 (bs, 1H), 9.5–8.5 (bs, 1H), 8.01 (m, 2H), 7.84–7.75 (m, 4H), 7.65 (m, 2H), 4.42 (m, 1H), 4.12 (m, 1H), 3.87 (dd, 1H), 3.59 (dd, 1H), 2.93 (m, 2H), 1.93–1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 194.9, 167.2, 139.5, 138.6, 136.4 (d), 135.8, 132.2, 131.8 (d), 129.6 (d), 129.4, 65.6 (d), 47.1, 29.5, 26.5. HRMS calcd for $C_{19}H_{21}ClN_2O_5P$ (M + H) 423.0876, found 423.0890.

(±)-*N*-Hydroxy-2-oxo-2-(4-phenylmethoxyphenyl)-1,3,2-oxazaphosphorepane-3-acetamide (4p). Prepared from **28p** using procedure B in 79% yield as a colorless oil. ^{1}H NMR (DMSO-d_6) δ 11.0–9.8 (bs, 1H), 9.2–8.6 (bs, 1H), 7.75 (m, 2H), 7.40 (m, 5H), 7.08 (m, 2H), 5.16 (s, 2H), 4.32 (m, 1H), 4.03 (m, 1H), 3.80 (dd, 1H), 3.53 (dd, 1H), 2.89 (m, 2H), 1.90-1.45 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.7, 160.5, 136.6, 132.8, 128.4, 127.8, 127.6, 123.0, 114.4, 69.2, 64.5, 46.3, 28.9, 25.7. HRMS calcd for $C_{19}H_{23}N_2O_5P$ (M + H) 391.1423, found 391.1429.

(±)-*N*-Hydroxy-2-*N*-(4-chlorobenzoyl)-4-aminophenyl-2-oxo-1,3,2-oxazaphosphorepa-ne-3-acetamide (4q). Prepared from **28q** using procedure B in 58% yield as a colorless foam. ^{1}H NMR (DMSO-d_6) δ 11.0–9.5 (s, 1H), 9.5–8.1 (bs, 1H), 8.00 (m, 2H), 7.95–7.75 (m, 4H), 7.62 (m, 2H), 4.37 (m, 1H), 4.09 (m, 1H), 3.81 (dd, 1H), 3.57 (dd, 1H), 2.91 (m, 2H), 1.85-1.50 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.7, 164.6, 141.6, 136.5, 133.3, 131.7, 129.6, 128.4, 126.1, 119.5, 64.6, 46.5, 46.3, 28.9, 25.8. HRMS calcd for $C_{19}H_{22}ClN_3O_5P$ (M + H) 438.0985, found 438.1010.

(±)-*N*-Hydroxy-2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorinane - 3 - acetamide (4r). Prepared from **28r** using procedure B in 43% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–8.0 (m, 2H), 7.71 (m, 2H), 7.04 (m, 2H), 4.30 (m, 1H), 4.06 (m, 1H), 3.82 (s, 3H), 3.46 (m, 2H), 3.21 (m, 2H), 2.01 (m, 1H), 1.85 (m, 1H). HRMS calcd for $C_{12}H_{18}N_2O_5P$ (M + H) 301.0953, found 301.0927.

(±)-*N*-Hydroxy-2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorocane-3-acetamide (4s). Prepared from **28s** using procedure B in 69% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–9.9 (bs, 1H), 9.2–8.7 (bs, 1H), 7.82 (m, 2H), 7.00 (m, 2H), 4.22 (m, 1H), 3.89 (m, 2H), 3.80 (s, 3H), 3.42 (dd, 1H), 2.91 (m, 2H), 1.90–1.20 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 166.5, 161.6, 133.1, 123.0, 113.6, 65.3, 55.3, 44.7, 44.6, 28.1, 24.6, 24.1. HRMS calcd for $C_{14}H_{21}N_2O_5P$ (M + H) 329.1266, found 329.1254.

(±)-*N*-Hydroxy-2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphoronane-3-acetamide (4t). Prepared from **28t** using procedure B in 66% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.0–9.8 (s, 1H), 9.3–8.6 (s, 1H), 7.90 (m, 2H), 7.01 (m, 2H), 4.43 (m, 1H), 4.01 (m, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.39 (dd, 1H), 2.86 (m, 1H), 2.61 (m, 1H), 1.90–1.60 (m, 2H), 1.55–1.05 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 166.4, 161.6, 133.5, 122.4, 113.7, 59.6, 55.3, 44.0, 41.5, 27.3, 23.9, 18.5, 17.9. HRMS calcd for $C_{15}H_{23}N_2O_5P$ (M−H) 341.1267, found 341.1267.

(±)-*N*-Hydroxy-2-oxo-2-(4-phenoxyphenyl)-1,3,2-oxazaphosphorinane-3-acetamide (4u). Prepared from **28u** using procedure B in 39% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.5–8.5 (m, 2H), 7.78 (m, 2H), 7.45 (m, 2H), 7.23 (m, 1H), 7.11 (m, 2H), 7.05 (m, 2H), 4.32 (m, 1H). ^{13}C NMR (CD_3OD) δ 168.6 (d), 163.2, 156.9, 135.4 (d), 131.3, 125.9, 124.0 (d), 121.3, 118.7 (d), 68.9 (d), 49.9–48.1 (2*CH_2), 27.1 (d). HRMS calcd for $C_{17}H_{20}N_2O_5P$ (M + H) 363.1110, found 363.1087.

(±)-*N*-Hydroxy-2-oxo-2-(4-phenoxyphenyl)-1,3,2-oxazaphosphorocane-3-acetamide (4v). Prepared from **28v** using procedure B in 32% yield as a colourless foam. ^{1}H NMR (DMSO-d_6) δ 10.1 (bs, 1H), 8.89 (bs, 1H), 7.89 (m, 2H), 7.44 (m, 2H), 7.22 (m, 1H), 7.09 (m, 2H), 7.02 (m, 2H), 4.23 (m, 1H), 4.04–3.80 (m, 2H), 3.43 (m, 1H), 2.94 (m, 2H), 1.89–1.20 (m, 6H).

(±)-*N*-Hydroxy-2-(4′-bromo-4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetamide (4w). Prepared from **28w** using procedure B in 62% yield as a colourless oil. ^{1}H NMR (DMSO-d_6) δ 10.4 (bs, 1H), 9.0 (bs, 1H), 7.93–7.74 (m, 4H), 7.69 (bs, 4H), 4.36 (m, 1H), 4.13 (m, 1H), 3.69–3.13 (m, 4H), 2.06 (m, 1H), 1.86 (m, 1H). HRMS calcd for $C_{17}H_{19}BrN_2O_4P$ (M + H) 425.0266, found 425.0267.

(±)-*N*-Hydroxy-2-(4′-bromo-4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorocane-3-acetamide (4x). Prepared from **28x** using procedure B in 50% yield as a colourless oil. MS calcd for $C_{19}H_{22}BrN_2O_4P$ 452.05, Found $[M-H]^- = 451$.

General procedure C: preparation of *N*-(hydroxyalkyl)-glycine ethyl- or methyl esters

To an ice-cooled solution of the aminoalcohol (100 mmol) in dry THF (200 mL) was added methyl or ethyl bromoacetate (16.7 mmol) with stirring. After stirring for 4 h, the mixture was concentrated and purified by flash chromatography (methanol or ethanol in dichloromethane).

***N*-(3-Hydroxypropyl)-glycine ethyl ester (8).**[24] Prepared from 3-amino-1-propanol and ethyl bromoacetate in 72% yield as a colourless oil, following procedure C. ^{1}H NMR (DMSO-d_6) δ 4.09 (q, 2H), 3.44 (t, 2H), 3.28 (s, 2H), 2.55 (t, 2H), 2.5–3.5 (bs, 2H), 1.53 (m, 2H), 1.19 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 172.1, 59.8, 59.3, 50.4, 46.1, 32.6, 14.1.

***N*-(4-Hydroxybutyl)-glycine ethyl ester (9).** Prepared from 4-amino-1-butanol and ethyl bromoacetate in 89% yield as a colourless oil, following procedure C. ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 3.60 (t, 2H), 3.41 (s, 2H), 3.14 (bs, 2H), 2.66 (t, 2H), 1.64 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 172.5, 62.5, 51.9, 50.2, 49.3, 31.6, 27.8.

***N*-(4-Hydroxybutyl)-glycine methyl ester (10).** Prepared from 4-amino-1-butanol and methyl bromoacetate in 65% yield as a colourless oil, following procedure C. ^{1}H NMR ($CDCl_3$) δ 4.20 (q, 2H), 3.61 (t, 2H), 3.39 (s, 2H), 3.02 (bs, 2H), 2.67 (t, 2H), 1.64 (m, 4H), 1.28 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 172.0, 62.6, 60.9, 50.4, 49.4, 31.8, 28.0, 14.2.

***N*-(5-Hydroxypentyl)-glycine methyl ester (11).**[25] Prepared from 5-amino-1-pentanol and methyl bromoacetate in 88% yield as a colourless oil, following procedure C. ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.63 (t, 2H), 3.41 (s, 2H), 2.62 (t, 2H), 1.97 (bs, 2H), 1.66–1.34 (m, 6H). ^{13}C NMR δ 173.3, 62.9, 52.1, 51.1, 49.8, 32.8, 30.0, 23.7.

***N*-(6-Hydroxyhexyl)-glycine ethyl ester (12).** Prepared from 6-amino-1-hexanol and ethyl bromoacetate in 82% yield as a colorless oil, following procedure C. ^{1}H NMR ($CDCl_3$) δ 4.19 (q, 2H), 3.62 (t, 2H), 3.38 (s, 2H), 2.60 (t, 2H), 1.93 (bs, 2H), 1.54 (m, 4H), 1.37 (m, 4H), 1.28 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 172.6, 62.7, 60.8, 50.9, 49.5, 32.7, 29.9, 27.0, 25.6, 14.2.

General procedure D: preparation of *N*-(3-hydroxypropyl)-amino acid methyl esters 13–15

The syntheses were based on the method described in the literature.[26] 2-Nitrosulfonyl chloride (13.9 g, 63 mmol) was added with stirring to an ice-cooled solution of amino acid methyl ester hydrochloride (63 mmol) and triethylamine (20 mL, 143 mmol) in DCM (500 mL). The mixture was allowed to warm to room temperature and stirred overnight. The resulting solution was washed with water, dried and concentrated. The resulting *N*-(2-nitrophenylsulfonyl)-amino acid methyl ester was used without purification.

Cesium carbonate (12,35 g, 35 mmol) was added to a solution of the *N*-(2-nitrophenylsulfonyl)-amino acid methyl ester (35 mmol) in DMF (160 mL). The reaction mixture heated to 60 °C then 3-bromopropanol (4,75 mL, 52.5 mmol) was added dropwise with stirring. The mixture was heated overnight, was then diluted with water and extracted three times with ethyl acetate. The combined organic phases were washed with calcium chloride solution (3 mol/l), water, brine, dried ($MgSO_4$) and concentrated. The resulting *N*-(3-hydroxypropyl)-*N*-(2-nitrophenylsulfonyl)-amino acid methyl ester was purified by chromatography eluting with ethyl acetate–light petroleum.

Potassium carbonate (3.6 g, 26 mmol) was added to a solution of the resulting *N*-(3-hydroxypropyl)-*N*-(2-nitrophenylsulfonyl)-amino acid methyl ester (8 mmol) and phenylthiol (1 mL, 9 mmol) in acetonitrile (40 mL). The reaction mixture was stirred at room temperature overnight, then reduced under vacuum and the residue taken up in diethyl ether. Hydrochloric acid solution (1 M) was added and the mixture stirred for 10 min. The organic layer was removed and washed with water, the combined aqueous layers were washed with diethyl ether followed by basification with solid potassium carbonate. The product was extracted from the basic aqueous layer with DCM (several washes), the combined DCM phases were dried and concentrated. The resulting *N*-(3-hydroxypropyl)-amino acid methyl ester was purified by chromatography eluting with methanol in DCM.

***N*-(3-hydroxypropyl)-L-leucine methyl ester (13).**[27] Prepared from L-leucine methyl ester hydrochoride. according to procedure D, with the following intermediates.

***N*-(2-nitrophenylsulfonyl)-L-leucine methyl ester (30).** Yield: 92%.

***N*-(3-hydroxypropyl)-*N*-(2-nitrophenylsulfonyl)- L-leucine methyl ester (35).** Yield: 45%.

***N*-(3-hydroxypropyl)-L-leucine methyl ester (13).** Yield: 44%. ^{1}H NMR ($CDCl_3$) δ 3.80 (t, 2H), 3.73 (s, 3H), 3.31 (t, 1H), 2.93 (m, 1H), 2.93 (bs, 2H), 2.59 (m, 1H), 1.69 (m, 3H), 1.46 (m, 2H), 0.92 (d, 3H), 0.91 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 176.0, 64.0, 59.9, 51.8, 48.1, 42.7, 31.0, 24.9, 22.8, 22.1.

***N*-(3-hydroxypropyl)-D-leucine methyl ester (14).** Prepared from D-leucine methyl ester hydrochoride, according to procedure D, with the following intermediates

***N*-(2-nitrophenylsulfonyl)-D-leucine methyl ester (31).** Yield: 85%

***N*-(3-hydroxypropyl)-*N*-(2-nitrophenylsulfonyl)-D-leucine methyl ester (36).** Yield: 52%

***N*-(3-hydroxypropyl)-D-leucine methyl ester (14).** Yield: 60%. ^{1}H NMR ($CDCl_3$) δ 3.80 (t, 2H), 3.73 (s, 3H), 3.31 (t, 1H), 2.95 (m, 1H), 2.64 (bs, 2H), 2.59 (m, 1H), 1.69 (m, 3H), 1.46 (m, 2H), 0.92 (d, 3H), 0.91 (d, 3H).

^{13}C NMR ($CDCl_3$) δ 176.0, 64.1, 59.9, 51.7, 48.2, 42.7, 31.1, 24.9, 22.8, 22.1.

***N*-(3-hydroxypropyl)-(D, L)-allylglycine methyl ester (15).** Prepared from D,L-allylglycine methyl ester hydrochoride, according to procedure D, with the following intermediates.

***N*-(2-nitrophenylsulfonyl)-(D,L)-allylglycine methyl ester (32).** Yield: 82%

***N*-(3-hydroxypropyl)-*N*-(2-nitrophenylsulfonyl)-(D,L)-allylglycine methyl ester (37).** Yield: 25%.

***N*-(3-hydroxypropyl)-(D,L)-allylglycine methyl ester (15).** Yield: 20%. Compound **15**: ^{1}H NMR ($CDCl_3$) δ 5.73 (m, 1H), 5.13 (m, 1H), 5.08 (m, 1H), 3.79 (t, 2H), 3.73 (s, 3H), 3.37 (m, 1H), 2.94 (m, 1H), 2.64 (m, 1H), 2.55 (bs, 2H), 2.40 (m, 2H), 1.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 174.7, 133.2, 118.5, 64.0, 60.8, 51.8, 48.0, 37.7, 31.0.

***N*-Benzyl-D-valine methyl ester (33).** Benzaldehyde (12.7 g, 119 mmol) was added to an ice-cooled mixture of methyl-D-valinate hydrochloride (20.0 g, 119 mmol) and $NaBH_3CN$ (7.48 g, 119 mmol) in 350 mL methanol and stirred overnight at rt. The reaction mixture was cooled in an ice-bath, acidified to pH 1 with concentrated HCl and stirred for 3.5 h at 0 °C. The solvent was removed in vacuo and water was added to the residue. The pH was adjusted to 9.3 with saturated Na_2CO_3, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure, affording 21.2 g of crude product, which was purified by flash chromatography to give 16.1 g (61%) *N*-benzyl-D-valine methyl ester (**33**) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37–7.18 (m, 5H), 3.83 (d, 1H), 3.71 (s, 3H), 3.58 (d, 1H), 3.02 (d, 1H), 1.92 (m, 1H), 1.80 (s, 1H), 0.95 (d, 3H), 0.93 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 175.8, 140.1, 128.3, 128.2, 127.0, 66.6, 52.6, 51.4, 31.7, 19.3, 18.7.

***N*-Benzyl-D-phenylalanine methyl ester (34).** In a procedure similar to the above, D-phenylalanine methyl ester was converted to 34 in 81% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.30–7.10 (m, 10H), 3.81 (d, 1H), 3.64 (s, 3H), 3.63 (d, 1H), 3.54 (t, 1H), 2.96 (m, 2H), 1.77 (bs, 1H).

***N*-Benzyl-*N*-(3-hydroxypropyl)-D-valine methyl ester (38).** A solution of **33** (16.1 g, 72.8 mmol), allyl bromide (17.6 g, 145.5 mmol) and diisopropylethylamine (18.8 g, 145.5 mmol) in dry DMSO (75 mL) was heated overnight at 40 °C. The reaction mixture was diluted with water and extracted three times with ethylacetate. The combined extracts were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure, affording 19.7 g of crude *N*-benzyl-*N*-allyl-D-valine methyl ester. Purification by flash chromatography gave 13.1 g (69%) of a colorless oil.

A solution of *N*-benzyl-*N*-allyl-D-valine methyl ester (13 g, 50 mmol) in 40 mL dry THF was added to an ice-cooled solution of 9-BBN (149 mL, 0.5 M in THF) under argon. After stirring at rt for 4.5 h, the solution was cooled to 0 °C and quenched with 40 mL water. After stirring another 15 min, aqueous NaOH (20%, 30 mL) was added dropwise followed by aqueous H_2O_2 (30%, 21 mL). The mixture was stirred for 1.5 h at 0 °C, then neutralized with 4 M HCl and concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted five times with EtOAc. Combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 17.1 g of **38** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.38–7.20 (m, 5H), 4.07 (d, 1H), 3.74 (s, 3H), 3.63 (m, 2H), 3.29 (d, 1H), 3.05 (d, 1H), 2.82 (m, 1H), 2.56 (bs, 1H), 2.44 (m, 1H), 2.16 (m, 1H), 1.87 (m, 1H), 1.56 (m, 1H), 1.03 (d, 3H), 0.87 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 172.4, 139.4, 128.9, 128.4, 127.2, 69.1, 62.3, 54.9, 50.7, 48.8, 29.5, 27.4, 20.1, 19.6.

***N*-Benzyl-*N*-(3-hydroxypropyl)-D-phenylalanine methyl ester (39).** In a procedure similar to the above, **34** was converted to **39** in 38% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.34–7.14 (m, 8H), 7.10 (m, 2H), 3.93 (d, 1H), 3.75 (dd, 1H), 3.67 (s, 3H), 3.63–3.55 (m, 3H), 3.5–2.0 (bs, 1H), 3.15 (dd, 1H), 2.91 (m, 2H)(, 2.72 (m, 1H), 1.85–1.50 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 172.5, 138.6, 138.0, 129.2, 129.0, 128.4, 128.4, 127.3, 126.5, 63.5, 62.6, 55.2, 51.4, 49.1, 34.9, 29.2.

***N*-(3-Hydroxypropyl)-D-valine methyl ester (16).** A solution of crude **38** (17.1 g) in 120 mL ethanol was hydrogenated over Pd on carbon (10%) for 2.5 h. The catalyst was filtered off through Celite, and the filtrate was concentrated to an oil. Purification by flash chromatography gave 6.4 g (68%) of **16** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 3.81 (t, 2H), 3.73 (s, 3H), 3.5–2.0 (bs, 2H), 3.05 (d, 1H), 2.98 (m, 1H), 2.55 (m, 1H), 1.92 (m, 1H), 1.69 (m, 2H), 0.94 (d, 3H), 0.93 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 175.1, 67.4, 64.3, 51.6, 48.8, 31.6, 30.9, 19.4, 18.6.

***N*-(3-Hydroxypropyl)-D-phenylalanine methyl ester (17).** In a procedure similar to the above, **39** was converted to **17** in 32% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 1H), 7.27 (m, 2H), 7.15 (m, 2H), 3.71 (m, 2H), 3.68 (s, 3H), 3.54 (m, 1H), 2.92 (m, 3H), 2.58 (m, 1H), 1.64 (m, 2H), 3.20–1.60 (bs, 2H).

General procedure E: preparation of phosphonyl dichlorides

The diethyl aryl phosphonate was added neat to ice-cooled PCl_5 (2.2 equivalents) under an argon atmosphere over 15 min while stirring. After complete addition, the suspension was heated to 110–120 °C for 4–5 h. During this period, a clear solution was obtained. Volatiles were removed in vacuo, and the phosphonyl dichloride was purified by Kugelrohr distillation or used immediately without purification (not distillable)

General procedure F: preparation of phosphonyl dichlorides

Chlorotrimethylsilane (8.54 mmol) was added dropwise to a solution of diethyl aryl phosphonate (4.27 mmol) and NaI (8.54 mmol) in dry CH_3CN (4 mL). The resulting dark suspension was heated at 40 °C for 45

min. The precipitated NaCl was filtered off, and the filtrate was concentrated in vacuo to remove excess chlorotrimethylsilane. The residue was dissolved in dry CH_2Cl_2 (5 mL) containing a few drops of DMF, and oxalylchloride (12.81 mmol) was added dropwise (gas evolution). After complete addition, the reaction mixture was stirred at rt for 1 h. The solvent and other volatiles were removed in vacuo, and the residue was either purified by Kugelrohr distillation or used immediately without purification (not distillable).

4-Biphenyl phosphonic dichloride (18). Prepared from 40 in quantitative yield (crude) using general procedure E. Used without further purification. ^{1}H NMR ($CDCl_3$) δ 8.04 (m, 2H), 7.78 (m, 2H), 7.62 (m, 2H), 7.47 (m, 3H). MS (EI+): *m*/*z* 270 (M^+), 235, 152.

4-Phenoxyphenyl phosphonic dichloride (19). Prepared from **41** using general procedure E in 72% yield. Distilled at 200 °C/0.08 mmHg. ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2H), 7.44 (m, 2H), 7.26 (m, 1H), 7.15–7.00 (m, 4H). MS (EI+) *m*/*z* 286 (M^+), 251, 169, 139, 77.

4-(4-Chlorophenoxy)phenyl phosphonic dichloride (20). Prepared from **42** using general procedure E in 83% yield. Distilled at 200–225 °C/0.08–0.10 mmHg. ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.39 (m, 2H), 7.12–7.00 (m, 4H). MS (EI+): *m*/*z* 320 (M^+), 285, 175, 168, 139, 111, 99.

4-Nitrophenyl phosphonic dichloride (21). Prepared from **43** using general procedure E. Distilled at 175–190 °C/0.06 mmHg. (Flaky solid at rt). MS (EI+): *m*/*z* 239 (M^+), 204, 193.

4-(Phenylmethyl)phenyl phosphonic dichloride (22). Prepared from **44** using general procedure E in 88% yield. Distilled at 250 °C/0.08 mmHg. ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.45–7.13 (m, 7H), 4.07 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 148.7 (d), 139.1, 132.1 (d), 130.6 (d), 129.6 (d), 129.0, 128.8, 126.7, 42.0.

4-(4-Trifluoromethylphenoxy)phenyl phosphonic dichloride (23). Prepared from **45** using general procedure E in 90% yield. Distilled at 250 °C/ 0.07 mmHg. ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.69 (m, 2H), 7.15 (m, 4H). MS (EI+): *m*/*z* 354 (M^+), 335, 319, 236.

4-(Phenylmethoxy)phenyl phosphonic dichloride (24). Prepared from **46** using general procedure E in 31% yield. Distilled at 225–250 °C/0.09 mmHg. MS (EI^+): *m*/*z* 300 (M^+), 265, 210, 175, 91.

4-(4-Bromophenoxy)phenyl phosphonic dichloride (25). Prepared from **47** using general procedure F in 60% yield. Distilled at 225–250 °C/0.06–0.08 mmHg. MS (EI+): *m*/*z* 364 (M^+), 329.

4′-Bromo-4-biphenyl phosphonic dichloride (26). Prepared from **48** in quantitative yield (crude) using general procedure F. Used directly without further purification.

4-(4-Chlorobenzoyl)phenyl phosphonic dichloride (27). Prepared from **49** in quantitative yield (crude) using general procedure F. Used directly without further purification.

General procedure G: formation of esters 28

A solution of amino alcohol (**8**–**17**) (0.42 mmol) and NMM (0.85 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 °C under argon, and a solution phosphonyldichloride (**18**–**27**) (0.42 mmol) in dry CH_2Cl_2 (10 mL) was added. The mixture was stirred at 0 °C for 1 h, then at rt overnight. After quenching with water, the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (chloroform/methanol) to afford the target compounds **28**.

Methyl (2*R*,α*R*)-2-(4-methoxyphenyl)-α-(1-methylethyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (diastereomer 1) (28a). Prepared from 4-methoxyphenylphosphonic dichloride and **16** in 30% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 2H), 6.94 (m, 2H), 4.44 (m, 1H), 4.20 (m, 1H), 3.85 (t, 1H), 3.84 (s, 3H), 3.45 (s, 3H), 3.43 (m, 2H), 2.16 (m, 2H), 1.96 (m, 1H), 1.14 (d, 3H), 0.90 (d, 3H).

Methyl (2*R*,α*R*)-2-(4-methoxyphenyl)-2-oxo-α-phenylmethyl-1,3,2-oxazaphosphorinane-3-acetate (diastereomer 1) (28b). Prepared from 4-methoxyphenylphosphonic dichloride and **17** in 33% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 2H), 7.35–7.15 (m, 5H), 6.93 (m, 2H), 4.59 (m, 1H), 4.30–4.00 (m, 2H), 3.83 (s, 3H), 3.50 (s, 3H), 3.50–3.25 (m, 3H), 3.14 (dd, 1H), 1.87 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 172.2, 162.5, 136.8, 133.8, 129.4, 128.4, 126.7, 121.7, 113.9, 66.2, 58.5, 55.3, 51.6, 41.1, 36.3, 26.7.

Methyl (2*R*,α*R*)-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (diastereomer 1) [(*R*,*R*)-28c]. Prepared from 4-methoxyphenylphosphonic dichloride and **14** in 42% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2H), 6.95 (m, 2H), 4.43 (m, 1H), 4.34 (m, 1H), 4.17 (m, 1H), 3.84 (s, 3H), 3.56 (s, 3H), 3.37 (m, 2H), 2.10–1.55 (m, 5H), 1.03 (d, 3H), 0.97 (d, 3H).

Methyl (2*S*,α*R*)-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (diastereomer 2) [(S,*R*)-28c]. Prepared from 4-methoxyphenylphosphonic dichloride and **14** in 39% yield as a colorless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 2H), 6.95 (m, 2H), 4.56 (m, 1H), 4.19 (m, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 3.54 (m, 1H), 3.20 (m, 1H), 2.17 (m, 1H), 2.02 (m, 1H), 1.56 (m, 2H), 1.36 (m, 1H), 0.79 (d, 3H), 0.63 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 173.7, 162.5, 133.8, 122.2, 113.9, 66.0, 55.4, 55.3, 52.0, 40.4, 38.5, 26.5, 24.5, 22.8, 21.5.

Methyl (2*R*,α*S*)-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (diastereomer 1) [(*R*,*S*)-28c]. Prepared from 4-methoxyphenylphosphonic dichloride and **13** in 33% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ

7.75 (m, 2H), 6.95 (m, 2H), 4.38 (m, 2H), 4.17 (m, 1H), 3.84 (s, 3H), 3.56 (s, 3H), 3.38 (m, 2H), 2.10–1.55 (m, 5H), 1.02 (d, 3H), 0.97 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 173.5, 162.5, 133.8, 121.7, 113.9, 66.7, 55.7, 55.3, 51.6, 41.2, 38.6, 26.9, 24.7, 23.1, 21.7.

Methyl (2*S*,α*S*)-2-(4-methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (diastereomer 2) [(*S*,*S*)-28c]. Prepared from 4-methoxyphenylphosphonic dichloride and **13** in 26% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.74 (m, 2H), 6.94 (m, 2H), 4.56 (m, 1H), 4.20 (m, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 3.55 (m, 1H), 3.19 (m, 1H), 2.17 (m, 1H), 2.03 (m, 1H), 1.54 (m, 2H), 1.37 (m, 1H), 0.78 (d, 3H), 0.63 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 173.7, 162.5, 133.9, 122.2, 113.9, 66.0, 55.4, 55.3, 52.0, 40.4, 38.5, 26.5, 24.5, 22.8, 21.5.

(±)-Methyl (2*R,α*R*)-α-allyl-2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (diastereomers 1) (28d).** Prepared from 4-methoxyphenylphosphonic dichloride and **15** in 35% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2H), 6.95 (m, 2H), 5.91 (m, 1H), 5.15 (m, 2H), 4.41 (m, 2H), 4.15 (m, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 3.36 (m, 2H), 2.80–2.50 (m, 2H), 2.15–1.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 172.3, 162.5, 134.1, 133.8, 121.8, 117.9, 113.9, 66.7, 57.0, 55.3, 51.7, 41.3, 34.4, 26.7.

Methyl (2*R*,α*R*)-2-[4-(4-chlorophenoxy)-phenyl]-α-(2-methylethyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (diastereomer 1) (28e). Prepared from **9c** and **16** in 29% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 2H), 7.33 (d, 2H), 7.01 (m, 2H), 6.97 (m, 2H), 4.46 (m, 1H), 4.22 (m, 1H), 3.88 (t, 1H), 3.47 (s, 3H), 3.42 (m, 2H), 2.17 (m, 2H), 1.96 (m, 1H), 1.14 (d, 3H), 0.92 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 172.3, 160.3, 154.5, 133.6, 130.0, 129.5, 125.5, 121.1, 117.8, 66.8, 63.1, 51.1, 41.0, 27.2, 26.7, 19.4, 19.3.

(±)-Methyl 2-(4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetate (28f). Prepared from **9a** and **10** in 48% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.67 (m, 2H), 7.60 (m, 2H), 7.45 (m, 2H), 7.37 (m, 1H), 4.59 (m, 1H), 4.38 (dd, 1H), 4.18 (m, 1H), 3.89 (dd, 1H), 3.71 (s, 3H), 3,21 (m, 1H), 2.95 (m, 1H), 1.95–1.60 (m, 4H). ^{13}C NMR ($CDCl_3$) d 171.9, 144.4, 140.3, 131.8, 129.2, 128.9, 127.9, 127.3, 127.0, 65.3, 51.9, 48.5, 47.5, 29.5, 26.6.

(±)-Ethyl 2-oxo-2-phenyl-1,3,2-oxazaphosphorepane-3-acetate (28g). Prepared from phenylphosphonic dichloride and **9** in 68% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.46 (m, 3H), 4.57 (m, 1H), 4.35 (m, 1H), 4.17 (m, 1H), 4.15 (q, 2H), 3.85 (dd, 1H), 3.15 (m, 1H), 2.93 (m, 1H), 1.90–1.60 (m, 4H), 1.22 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.3, 131.6, 131.3, 130.6, 128.3, 65.3, 61.0, 48.6, 47.4, 29.5, 26.5, 14.2.

(±)-Methyl 2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetate (28h). Prepared from 4-methoxyphenylphosphonic dichloride and **10** in 60% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2H), 6.95 (m, 2H), 4.54 (m, 1H), 4.35 (m, 1H), 4.12 (m, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.90–3.70 (m, 1H), 3.15 (m, 1H), 2.91 (m, 1H), 1.90–1.60 (m, 4H). ^{13}C NMR ($CDCl_3$) d 171.9, 162.3, 133.2, 122.0, 113.8, 65.2, 55.3, 51.9, 48.4, 47.4, 29.5, 26.5.

(±)-Ethyl 2-(4′-bromo-4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetate (28i). Prepared from **26** and **9** in 50% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 2H), 7.62 (m, 2H), 7.57 (m, 2H), 7.46 (m, 2H), 4.58 (m, 1H), 4.38 (m, 1H), 4.20 (m, 1H), 4.16 (q, 2H), 3.85 (dd, 1H), 3.20 (m, 1H), 2.95 (m, 1H), 2.0–1.6 (m, 4H), 1.24 (t, 3H). ^{13}C NMR ($CDCl_3$) d 171.3, 143.1, 139.2, 132.0, 131.9, 129.8, 128.8, 126.8, 122.3, 65.4, 61.0, 48.6, 47.4, 29.5, 26.6, 14.2.

(±)-Methyl 2-oxo-2-(4-phenoxyphenyl)-1,3,2-oxazaphosphorepane-3-acetate (28j). Prepared from **19** and **10** in 60% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.37 (m, 2H), 7.16 (m, 1H), 7.03 (m,4H), 4.54 (m, 1H), 4.37 (m, 1H), 4.15 (m, 1H), 3,85 (dd, 1H), 3.70 (s, 3H), 3.16 (m, 1H), 2.94 (m, 1H), 1.77 (m, 4H).

(±)-Ethyl 2-[4-(4-chlorophenoxy)-phenyl]-2-oxo-1,3,2-oxazaphosphorepane-3-acetamide (28k). Prepared from **20** and **9** in 90% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.32 (m, 2H), 7.01 (m, 2H), 6.97 (m, 2H), 4.52 (m, 1H), 4.37 (m, 1H), 4.16 (m, 1H), 4.16 (q, 2H), 3.82 (dd, 1H), 3.15 (m, 1H), 2.94 (m, 1H), 1.95–1.60 (m, 4H), 1.24 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.3, 160.1, 154.6, 133.5, 130.0, 129.3, 125.1, 121.1, 117.8, 65.3, 61.0, 48.4, 47.3, 29.5, 26.5, 14.2.

(±)-Ethyl 2-[4-(4-bromophenoxy)-phenyl]-2-oxo-1,3,2-oxazaphosphorepane-3-acetate (28l). Prepared from **25** and **9** in 84% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2H), 7.47 (m, 2H), 7.01 (m, 2H), 6.92 (m, 2H), 4.54 (m, 1H), 4.38 (m, 1H), 4.16 (m, 1H), 4.16 (q, 2H), 3.82 (dd, 1H), 3.14 (m, 1H), 2.94 (m, 1H), 1.95–1.60 (m, 4H), 1.24 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.4, 160.0, 155.3, 133.5, 132.9, 125.2, 121.4, 117.9, 116.7, 65.3, 61.0, 48.4, 47.3, 29.5, 26.5, 14.2.

(±)-Ethyl 2-oxo-2-[4-(4-trifluormethylphenoxy)-phenyl]-1,3,2-oxazaphosphorepane-3-acetate (28m). Prepared from **23** and **9** in 88% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.94 (m, 2H), 7.61 (m, 2H), 7.09 (m, 4H), 4.55 (m, 1H), 4.39 (m, 1H), 4.17 (m, 1H), 4.16 (q, 2H), 3.83 (dd, 1H), 3.16 (m, 1H), 2.95 (m, 1H), 2.00–1.55 (m, 4H), 1.24 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.4, 159.3, 159.0, 133.6, 127.3, 126.2, 119.0, 118.9, 65.4, 61.1, 48.4, 47.4, 29.5, 26.5, 14.2.

(±)-Ethyl 2-oxo-2-[4-(phenylmethyl)phenyl-1,3,2-oxazaphosphorepane-3-acetate (28n). Prepared from **22** and **9** in 44% yield as a colorless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 2H), 7.40–7.10 (m,

7H), 4.55 (m, 1H), 4.33 (m, 1H), 4.23–4.06 (m, 1H), 4.13 (q, 2H), 4.00 (s, 2H), 3.83 (dd, 1H), 3.14 (m, 1H), 2.92 (m, 1H), 2.00–1.55 (m, 4H), 1.20 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.1 (d), 144.7 (d), 140.0, 131.3 (d), 128.7, 128.6 (d), 128.3, 126.0, 65.0 (d), 60.7, 48.3 (d), 47.2 (d), 41.7, 29.2, 26.3, 13.9.

(±)-Ethyl 2-(4-chlorobenzoylphenyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetate (28o). Prepared from **27** and **9** in 59% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 8.06 (m, 2H), 7.81 (m, 2H), 7.75 (m, 2H), 7.48 (m, 2H), 4.59 (m, 1H), 4.39 (m, 1H), 4.20 (m, 1H), 4.17 (q, 2H), 3.86 (dd, 1H), 3.15 (m, 1H), 2.96 (m, 1H), 1.95-1.60 (m, 4H), 1.25 (t, 3H).

(±)-Ethyl 2-oxo-2-(4-phenylmethoxyphenyl)-1,3,2-oxazaphosphorepane-3-acetate (28p). Prepared from **24** and **9** in 38% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.37 (m, 5H), 7.01 (m, 2H), 5.10 (s, 2H), 4.53 (m, 1H), 4.34 (m, 1H), 4.14 (m, 1H), 4.14 (q, 2H), 3.82 (dd, 1H), 3.14 (m, 1H), 2.92 (m, 1H), 1.95–1.60 (m, 4H), 1.22 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.4, 161.4, 136.5, 133.2, 128.7, 128.1, 127.5, 122.4, 114.7, 70.0, 65.2, 61.0, 48.6, 47.4, 29.5, 26.5, 14.2.

(±)-Ethyl 2-*N*-(4-chlorobenzoyl)-4-aminophenyl-2-oxo-1,3,2-oxazaphosphorepane-3-acetate (28q). A solution of **28y** in methanol was hydrogenated with Pd on carbon (10%) for 1 h at atm pressure. Filtration and concentration afforded ethyl 2-(4-aminophenyl)-2-oxo-1,3,2-oxazaphosphorepane-3-acetate. This crude aniline was dissolved in CH_2Cl_2 with 3 equivalents triethylamine, the solution was cooled to 0 °C, and 2 equivalents of 4-chlorobenzoylchloride were added neat. After stirring overnight at rt, the mixture was concentrated under reduced pressure, redissolved in ethylacetat and washed with water and brine. After filtration and evaporation, the title compound was purified by flash chromatography. Yield: 61% (colourless oil). ^{1}H NMR ($CDCl_3$) δ 9.49 (s, 1H), 7.92 (m, 2H), 7.71 (m, 4H), 7.36 (m, 2H), 4.50 (m, 1H), 4.25–4.00 (m, 2H), 4.12 (q, 2H), 3.83 (dd, 1H), 3.07 (m, 1H), 2.87 (m, 1H), 1.90–1.55 (m, 4H), 1.21 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2, 165.3, 141.6, 138.0, 133.1, 132.0, 129.2, 128.7, 125.3, 120.3, 65.4, 61.1, 48.8, 47.4, 29.4, 26.5, 14.2.

(±)-Ethyl 2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (28r). Prepared from 4-methoxyphenyl phosphonic dichloride and **8**, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 6.96 (m, 2H), 4.49 (m, 1H), 4.30–4.05 (m, 3H), 3.98 (dd, 1H), 3.84 (s, 3H), 3.65 (dd, 1H), 3.41 (m, 1H), 3.28 (m, 1H), 2.07 (m, 2H), 1.23 (t, 3H).

(±)-Methyl 2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorocane-3-acetate (28s). Prepared from 4-methoxyphenylphosphonic dichloride and **11** in 41% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 6.95 (m, 2H), 4.46 (m, 2H), 4.03 (m, 1H), 3.84 (s, 3H), 3.73 (dd, 1H), 3.69 (s, 3H), 3.16 (m, 1H), 3.00 (m, 1H), 1.95–1.65 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 171.7, 162.2, 133.3, 122.2, 113.7, 66.0, 55.3, 51.8, 46.2, 45.4, 28.7, 25.2, 24.4.

(±)-Ethyl 2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphoronane-3-acetate (28t). Prepared from 4-methoxyphenylphosphonic dichloride and **12** in 7% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.94 (m, 2H), 6.95 (m, 2H), 4.55 (m, 2H), 4.19 (m, 2H), 4.01 (m, 1H), 3.84 (s, 3H), 3.70 (dd, 1H), 3.10 (m, 1H), 3.81 (m, 1H), 2.00–1.40 (m, 8H), 1.28 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2, 162.3, 133.8, 121.7, 113.8, 60.9, 60.5, 55.3, 45.9, 42.3, 27.7, 24.3, 19.1, 18.5, 14.2.

(±)-Ethyl 2-oxo-2-(4-phenoxyphenyl)-1,3,2-oxazaphosphorinane-3-acetate (28u). Prepared from **19** and **8** in 44% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.38 (m, 2H), 7.18 (m, 1H), 7.04 (m, 4H), 4.50 (m, 1H), 4.23 (m, 1H), 4.14 (q, 2H), 4.02 (dd,1H), 3.68 (dd, 1H), 3.41 (m, 1H), 3.28 (m, 1H), 2.12 (m, 1H), 2.03 (m, 1H), 1.23 (t, 3H).

(±)-Methyl 2-oxo-2-(4-phenoxyphenyl)-1,3,2-oxazaphosphorocane-3-acetate (28v). Prepared from **19** and **11** in 12% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.36 (m, 2H), 7.16 (m, 1H), 7.03 (m, 4H), 4.47 (m, 2H), 4.05 (m, 1H), 3.72 (m, 1H), 3.69 (s, 3H), 3.19 (m, 1H), 3.02 (m, 1H), 2.10–1.35 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 171.6, 160.6, 155.9, 133.5, 129.9, 124.7, 124.2, 119.9, 117.6, 66.1, 51.8, 46.0, 45.4, 28.6, 25.1, 24.4.

(±)-Ethyl 2-(4′-bromo-4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetate (28w). Prepared from **26** and **8** in 62% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.72–7.42 (m, 6H), 4.53 (m, 1H), 4.26 (m, 1H), 4.15 (q, 2H), 4.06 (dd, 1H), 3.74 (dd, 1H), 3.47 (m, 1H), 3.31 (m, 1H), 2.16 (m, 1H), 2.03 (m, 1H), 1.23 (t, 3H).

(±)-Methyl 2-(4′-bromo-4-biphenylyl)-2-oxo-1,3,2-oxazaphosphorocane-3-acetate (28x). Prepared from **25** and **11** in 30% yield as a colourless oil, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 2H), 7.63 (m, 2H), 7.58 (m, 2H), 7.47 (m, 2H), 4.50 (m, 2H), 4.07 (m, 1H), 3.77 (m, 1H), 3.71 (s, 3H), 3.23 (m, 1H), 3.05 (m, 1H), 2.00–1.33 (m, 6H).

(±)-Ethyl 2-oxo-2-(4-nitrophenyl)-1,3,2-oxazaphosphorepane-3-acetate (28y). Prepared from **21** and **9** in 49% yield as a white solid, according to procedure G. ^{1}H NMR ($CDCl_3$) δ 8.28 (m, 2H), 8.12 (m, 2H), 4.59 (m, 1H), 4.40 (m, 1H), 4.30–4.10 (m, 1H), 4.17 (q, 2H), 3.82 (dd, 1H), 3.10 (m, 1H), 2.94 (m, 1H), 2.00–1.65 (m, 4H), 1.25 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.1, 149.8, 138.0, 132.6, 123.1, 65.9, 61.3, 48.4, 47.4, 29.4, 26.6, 14.2.

General procedure H: formation of carboxylic acids 29 from the esters 28

A solution of ester **28** (0.26 mmol) in methanol (2 mL) and aqueous sodium hydroxide (2 M, 2 mL) was stirred overnight at rt, acidified with 4 M AcOH and extracted with EtOAc/H_2O. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated

under reduced pressure. The residue was purified by chromatography (chloroform/methanol/acetic acid 80:20:1) or by crystallization to afford the carboxylic acid **29**.

(2*R*,α*R*)-2-(4-Methoxyphenyl)-α-(1-methylethyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetic acid (29a). Prepared from **28a** in 91% yield as a crude, white solid, according to procedure H. Recrystallized in acetone/ether. ^{1}H NMR (CD_3OD) δ 7.72 (m, 2H), 7.07 (m, 2H), 4.46 (m, 1H), 4.27 (m, 1H), 3.89 (s, 3H), 3.73 (t, 1H), 3.67–3.36 (m, 2H), 2.21 (m, 2H), 1.98 (m, 1H), 1.16 (d, 3H), 1.02 (d, 3H). ^{13}C NMR (CD_3OD) 174.5 (d), 164.4 (d), 134.6 (d), 122.6 (d), 115.3 (d), 68.9 (d), 65.0 (d), 55.9, 42.6, 28.3 (d), 27.9 (d), 20.1, 19.8.

(2*R*,α*R*)-2-(4-Methoxyphenyl)-2-oxo-α-phenylmethyl-1,3,2-oxazaphosphorinane-3-acetic acid (29b). Prepared from **28b** in 46% yield as a white solid, according to procedure H. ^{1}H NMR (CD_3OD) δ 7.79 (m, 2H), 7.40–7.20 (m, 5H), 7.04 (m, 2H), 4.50 (m, 1H), 4.17 (m, 2H), 3.87 (s, 3H), 3.60–3.30 (m, 3H), 3.14 (dd, 1H), 1.91 (m, 2H). ^{13}C NMR (CD_3OD) δ 164.8, 139.2, 135.3, 130.9, 129.8, 128.0, 122.7, 115.5, 68.8, 56.3, 43.3, 37.9, 28.1.

(2*R*,α*R*)-2-(4-Methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetic acid (*R,R*)-29c. Prepared from (*R,R*)-**28c** in 90% as a white solid, according to procedure H. ^{1}H NMR (CD_3OD) δ 7.82 (m, 2H), 7.07 (m, 2H), 4.46 (m, 1H), 4.23 (m, 2H), 3.89 (s, 3H), 3.43 (m, 2H), 2.04 (m, 2H), 1.84 (m, 2H), 1.69 (m, 1H), 1.05 (d, 3H), 1.03 (d, 3H).

(2*S*,α*R*)-2-(4-Methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetic acid ((*S,R*)-29c). Prepared from (*S,R*)-**28c** in 98% yield as a white solid, according to procedure H. ^{1}H NMR (CD_3OD) δ 7.79 (m, 2H), 7.09 (m, 2H), 4.58 (m, 1H), 4.36 (m, 1H), 4.01 (m, 1H), 3.90 (s, 3H), 3.57 (m, 1H), 3.31 (m, 1H), 2.27 (m, 1H), 2.14 (m, 1H), 1.62 (m, 2H), 1.42 (m, 1H), 0.82 (d, 3H), 0.59 (d, 3H).

(2*R*,α*S*)-2-(4-Methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetic acid ((*R,S*)-29c). Prepared from (*R,S*)-**28c** in 76% yield as a white solid, according to procedure H. ^{1}H NMR (DMSO-d_6) δ 7.67 (m, 2H), 7.03 (m, 2H), 4.28 (m, 1H), 4.10 (m, 2H), 3.81 (s, 3H), 3.23 (m, 2H), 2.00–1.60 (m, 5H), 0.94 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 174.0, 161.8, 133.2, 122.5, 114.1, 67.3, 55.2, 55.2, 41.1, 38.1, 26.6, 24.1, 23.2, 21.4.

(2*S*,α*S*)-2-(4-Methoxyphenyl)-α-(2-methylpropyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetic acid [(*S,S*]-29c). Prepared from (*S,S*)-**28c** in 80% yield as a white solid, according to procedure H. ^{1}H NMR (DMSO-d_6) δ 7.64 (m, 2H), 7.05 (m, 2H), 4.36 (m, 1H), 4.20 (m, 1H), 3.90 (m, 1H), 3.81 (s, 3H), 3.37 (m, 1H), 3.12 (m, 1H), 2.10 (m, 1H), 1.95 (m, 1H), 1.75–1.20 (m, 3H), 0.75 (d, 3H), 0.51 (d, 3H). ^{13}C NMR (DMSO-d_6) δ 174.1, 163.1, 162.0, 133.4, 122.8, 114.0, 66.4, 55.4, 54.9, 40.3, 37.6, 25.8, 24.0, 22.8, 21.0.

(±)-α-Allyl-2-(4-methoxyphenyl)-2-oxo-1,3,2-oxazaphosphorinane-3-acetic acid (29d). Prepared from **28d** in 78% yield as a white solid, according to procedure H. ^{1}H NMR (CD_3OD) δ 7.78 (m, 2H), 7.02 (m, 2H), 5.95 (m, 1H), 5.20 (m, 1H), 5.12 (m, 1H), 4.38 (m, 1H), 4.20 (m, 2H), 3.85 (s, 3H), 3.38 (m, 2H), 2.66 (m, 2H), 2.06 (m, 1H), 1.91 (m, 1H).

(2*R*,α*R*)-2-[4-(4-Chlorophenoxy)-phenyl]-α-(2-methylethyl)-2-oxo-1,3,2-oxazaphosphori-nane-3-acetic acid (29e). Prepared from **28e** in 70% yield as a white solid, according to procedure H. ^{1}H NMR (CD_3OD) δ 7.75 (m, 2H), 7.39 (m, 2H), 7.05 (m, 4H), 4.43 (m, 1H), 4.25 (m, 1H), 3.67 (t, 1H), 3.60–3.30 (m, 2H), 2.30–2.05 (m, 2H), 1.95 (m, 1H), 1.10 (d, 3H), 0.97 (d, 3H). ^{13}C NMR (CD_3OD) δ 175.4, 162.0, 156.0, 135.0, 131.2, 130.6, 126.2, 122.4, 119.0, 69.1, 65.7, 42.8, 28.3, 27.9, 20.1, 20.0.

General procedure I: preparation of diethyl aryl phosphonates 40–49

Diethyl aryl phosphonates were prepared according to literature starting from aryl bromides or aryl triflates.[18a] All aryl phosphonates were purified by column chromatography with ethyl acetate as the eluent.

Diethyl 4-biphenyl phosphonate (40). Prepared from bromobiphenyl in 76% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.68 (m, 2H), 7.61 (m, 2H), 7.50–7.35 (m, 3H), 4.15 (m, 4H), 1.35 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 145.2 (d), 140.0, 132.3 (d), 129.0, 127.6 (d), 127.3, 127.0 (d), 125.7, 62.2 (d), 16.4 (d).

Diethyl 4-phenoxyphenyl phosphonate (41). Prepared from 4-phenoxyphenyl trifluoromethanesulfonate in 87% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 2H), 7.38 (m, 2H), 7.19 (m, 1H), 7.05 (m, 2H), 7.01 (m, 2H), 4.11 (m, 4H), 1.31 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 161.4 (d), 155.5, 133.9 (d), 130.0, 124.6, 121.8 (d), 120.1, 117.6 (d), 62.2 (d), 16.3 (d).

Diethyl 4-(4-chlorophenoxy)-phenyl phosphonate (42). Prepared from 4-bromo-4′-chloro phenyl ether in 75–90% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H), 7.35 (m, 2H), 7.02 (m, 2H), 6.99 (m, 2H), 4.12 (m, 4H), 1.33 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 160.9 (d), 154.2, 134.0 (d), 130.1, 129.7, 122.6 (d), 121.3, 117.7 (d), 62.1 (d), 16.4 (d).

Diethyl 4-nitrophenyl phosphonate (43). Prepared from 1-bromo-4-nitrobenzene in 96% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 8.31 (m, 2H), 8.01 (m, 2H), 4.18 (m, 4H), 1.35 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 150.3 (d), 135.9 (d), 133.0 (d), 123.4 (d), 62.8 (d), 16.4 (d).

Diethyl 4-(phenylmethyl)phenyl phosphonate (44). Prepared from phenyl-(4-bromophenyl)methane in 85% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.72 (m, 2H), 7.35–7.14 (m, 7H), 4.10

(m, 4H), 4.02 (s, 2H), 1.31 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 145.9 (d), 140.0, 132.0 (d), 129.0, 129.0 (d), 128.6, 126.4, 126.0 (d), 62.0 (d), 42.0, 16.3 (d).

Diethyl 4-trifluoromethylphenoxyphenyl phosphonate (45). Prepared from 4-(4-trifluoromethylphenoxy)-phenyltrifluoromethanesulfonate in 51% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.63 (m, 2H), 7.12 (m, 2H), 7.09 (m, 2H), 4.14 (m, 4H), 1.34 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 159.8 (d), 158.9, 134.1 (d), 127.4 (q), 126.3 (q), 124.0 (q), 23.7 (d), 119.3, 118.7 (d), 62.2 (d), 16.4 (d).

Diethyl 4-(phenylmethoxy)-phenyl phosphonate (46). Prepared from 4-(phenylmethoxy)-phenyltrifluoromethanesulfonate in 85% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2H), 7.46–7.29 (m, 5H), 7.03 (m, 2H), 5.09 (s, 2H), 4.09 (m, 4H), 1.30 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 162.1 (d), 136.2, 133.8 (d), 128.7, 128.2, 127.5, 119.8 (d), 114.9 (d), 70.0, 62.0 (d), 16.3 (d).

Diethyl 4-(4-bromophenoxy)-phenyl phosphonate (47). Prepared from 4-bromophenyl ether in 49% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 2H), 7.49 (m, 2H), 7.02 (m, 2H), 6.94 (m, 2H), 4.12 (m, 4H), 1.33 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 160.8 (d), 154.8, 134.0 (d), 133.1, 122.7 (d), 121.7, 117.7 (d), 117.2, 62.1 (d), 16.4 (d).

Diethyl 4′-bromo-4-biphenyl phosphonate (48). Prepared from 4,4′-dibromobiphenyl in 41% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.64 (m, 2H), 7.59 (m, 2H), 7.47 (m, 2H), 4.15 (m, 4H), 1.34 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 143.9 (d), 138.9, 132.4 (d), 132.1, 128.9, 127.0 (d), 127.6 (d), 122.6, 62.2 (d), 16.4 (d).

Diethyl 4-(4-benzoyl)-phenyl phosphonate (49). Prepared from 4-(chlorobenzoyl)-phenyltrifluoromethanesulfonate in 88% yield as a colourless oil, according to procedure I. ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.83 (m, 2H), 7.76 (m, 2H), 7.48 (m, 2H), 4.16 (m, 4H), 1.36 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 194.7, 140.6 (d), 139.6, 135.1, 132.9 (d), 131.8 (d), 131.5, 129.5 (d), 128.9, 62.5 (d), 16.4 (d).

General procedure J: dichlorophosphinylation

The aromatic compound was heated at reflux with trichlorophosphine (1 molar equivalent) and either aluminium chloride (0.1 molar equivalent) or tin(IV)chloride (0.1 molar equivalent) for 3 days under a stream of escaping argon. Unreacted trichlorophosphine was removed by distillation at atmospheric pressure. The crude product was distilled quickly at 0.05 mmHg, and the distillate carefully redistilled at 0.05 mmHg to give a lower boiling fraction of unreacted aromatic, and the desired dichloroarylphosphine as the higher boiling product.

Dichloro-(4-ethoxyphenyl)phosphine (50a). Prepared from fenethole by dichlorophosphinylation with tin(IV) chloride in 40% yield. The oil collected at 70–8 °C/0.05 mmHg was sufficiently pure for the following step. ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 2H), 6.98 (m, 2H), 4.09 (q, 2H), 1.44 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 162.8, 132.3 (d), 131.4 (d), 114.9 (d), 63.8, 14.6.

Dichloro-(4-phenoxyphenyl)phosphine (50b). Prepared from phenyl ether by dichlorophosphinylation with aluminium chloride in 9% yield as an oil distilling at 150 °C/0.05 mmHg (Kugelrohr oven). ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.40 (m, 2H), 7.20 (m, 1H), 7.12–7.02 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 161.9, 155.3, 133.8 (d), 132.4 (d), 130.1, 124.8, 120.3, 117.8 (d).

Dichloro-(4-(4-chlorophenoxy)-phenyl)-phosphine (50c). Prepared by dichlorophosphinylation with aluminium chloride of 4-chlorophenyl phenyl ether in 14% yield as an oil of bp: 125–135 °C/0.05 mmHg. ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.35 (m, 2H), 7.05 (m, 2H), 7.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 161.3, 153.9, 132.4 (d), 130.1, 129.9, 121.5, 117.9 (d).

General procedure K: allyl/Arbuzov sequence

The (aryl)dichlorophosphine was dissolved at 0.25 M in dry diethyl ether under argon and ice cooling. Pyridine (2.2 molar equivalents) was added, followed by allyl alcohol (2.2 molar equivalents). After 2 h at room temperature, the mixture was filtered under minimal exposure to air, the filter washed with additional dry diethyl ether, and the filtrate concentrated in vacuo. Solvent residues were removed in high vacuum. The residue was heated at 130 °C overnight and chromatographed on silica gel in a gradient of ethyl acetate in toluene rising from 0 to 100%. Fractions containing product were identified by TLC (iodine vapour), combined, and concentrated in vacuo, yielding the pure product as an oil.

(±)-Allyl Allyl-(4-ethoxyphenyl)-phosphinate (51d). Prepared from **50a** by the allyl/Arbuzov sequence in 53% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 2H), 6.96 (m, 2H), 5.91 (m, 1H), 5.77 (m, 1H), 5.32 (m, 1H), 5.20 (m, 1H), 5.17–5.00 (m, 2H), 4.53 (m, 1H), 4.30 (m, 1H), 4.08 (q, 2H), 2.78 (m, 2H), 1.44 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 162.3 (d), 133.8 (d), 133.3 (d), 127.4 (d), 121.1 (d), 120.3 (d), 117.5, 114.5 (d), 64.9 (d), 63.6, 36.2 (d), 14.7.

(±)-Allyl allyl(phenoxyphenyl)phosphinate (51f). Prepared from **50b** by the allyl/Arbuzov sequence in 70% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.72 (m, 2H), 7.40 (m, 2H), 7.20 (m, 1H), 7.12–7.00 (m 4H), 5.92 (m, 1H), 5.77 (m, 1H), 5.33 (m, 1H), 5.21 (m, 1H), 5.21–5.05 (m, 2H), 4.56 (m, 1H), 4.33 (m, 1H), 2.87–2.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 161.5 (d), 155.4, 133.9 (d), 133.1 (d), 130.1, 127.2 (d), 124.6, 123.6 (d), 120.5 (d), 120.2, 117.7, 117.5 (d), 65.0 (d), 36.2 (d).

(±)-Allyl allyl(4-(4-chlorophenoxy)phenyl)phosphinate (51h). Prepared from **50c** by the allyl/Arbuzov sequence in 42% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 2H), 7.35 (m, 2H), 7.10–6.97 (m, 4H), 5.92 (m, 1H), 5.77 (m, 1H), 5.33 (m, 1H), 5.22 (m, 1H), 5.20–5.02 (m, 2H), 4.56 (m, 1H), 4.33 (m, 1H), 2.80 (dd, 2H). ^{13}C NMR ($CDCl_3$) δ 161.0 (d), 154.1, 134.0 (d), 133.1 (d),

130.1, 129.8, 127.1 (d), 124.2 (d), 121.4, 120.5 (d), 117.7, 117.6 (d), 65.0 (d), 36.2 (d).

(±)-But-3-enyl but-3-enyl(4-phenoxyphenyl)phosphinate (51g). The aryl-dichloro-phosphine **50b** was dissolved at 0.25 M in dry diethyl ether under argon and ice cooling. Pyridine (2.2 molar equivalents) was added, followed by but-3-enol (2.2 molar equivalents). After two h at room temperature, the mixture was filtered under minimal exposure to air, the filter washed with additional dry diethyl ether, and the filtrate concentrated in vacuo. Solvent residues were removed in high vacuum. 4-bromobut-1-ene (1 molar equivalent) was added, the solution heated at 120 °C overnight and chromatographed on silica gel in a gradient of ethyl acetate in toluene rising from 0 to 100%. Fractions containing product were identified by TLC (iodine vapour), combined, and concentrated in vacuo, yielding the pure 3-butenyl aryl(3-butenyl)phosphinate as an oil. ^{1}H NMR ($CDCl_3$) δ 7.71 (m, 2H), 7.40 (m, 2H), 7.20 (m, 1H), 7.11–6.99 (m, 4H), 5.89–5.70 (m, 2H), 5.20–4.92 (m, 4H), 4.08 (m, 1H), 3.82 (m, 1H), 2.56–2.17 (m, 4H), 2.11–1.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 161.4 (d), 155.5, 137.3 (d), 133.8, 133.7 (d), 130.1, 124.6, 124.2 (d), 120.2, 117.7 (d), 117.5, 115.0, 63.4 (d), 35.0 (d), 29.2 (d), 25.9 (d).

(±)-Pent-4-enyl 4-ethoxyphenyl(pent-4-enyl)phosphinate (51e). In a procedure similar to the above, aryl-dichlorophosphine **50a** was treated first with pent-4-enol and then with 5-bromopent-1-ene to afford the pure 4-pentenyl aryl(4-pentenyl)phosphinate **51e** in 66% yield. ^{1}H NMR ($CDCl_3$) δ 7.67 (m, 2H), 6.96 (m, 2H), 5.85–5.63 (m, 2H), 5.07–4.90 (m, 4H), 4.09 (q, 2H), 4.00 (m, 1H), 3.74 (m, 1H), 2.20–2.02 (m, 4H), 2.00–1.50 (m, 6H), 1.44 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 162.1 (d), 137.5, 137.5, 133.5 (d), 121.9 (d), 115.6, 115.2, 114.6 (d), 63.6, 63.5 (d), 34.5 (d), 29.9 (d), 29.8, 29.2 (d), 21.1 (d), 14.7.

General procedure L: amidation

The alkenyl arylakenylphosphinate was dissolved under argon in dry dichloromethane (to 0.5 M), and phosphorpentachloride (1.05 molar equivalents) was added. After stirring at room temperature for 3 h, volatiles were removed in vacuo, and a high vacuum (0.04 mmHg) was applied for 15 min. The residue was redissolved under argon in dry dichloromethane (to 0.5 M), and the allylic amine (2 molar equivalents) was added, followed by triethylamine (2 molar equivalents). After 3 h, the mixture was evaporated onto silica gel (1 g of silica gel per 100 mg of product) and eluted with a gradient of methanol in ethyl acetate rising from 0% to 10%. Fractions containing product were identified by TLC (iodine vapour), and combined. Removal of solvents in vacuo yielded the pure product as an oil.

(±)-*N*-Allyl-*N*-ethoxycarbonylmethyl-allyl(4-ethoxyphenyl)-phosphinamide (52d). Prepared from **51d** by amidation with *N*-allyl-glycine ethyl ester in 62% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2H), 6.96 (m, 2H), 5.92–5.63 (m, 2H), 5.20–5.06 (m, 4H), 4.16 (q, 2H), 4.08 (q, 2H), 3.86 (dd, 1H), 3.71 (dd, 1H), 3.59 (m, 2H), 2.96 (m, 2H), 1.43 (t, 3H), 1.26 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2 (d), 162.0 (d), 134.2 (d), 133.9 (d), 128.3 (d), 122.0 (d), 120.0 (d), 118.8, 114.5 (d), 63.6, 60.9, 50.2 (d), 46.4 (d), 35.0 (d), 14.7, 14.2.

(±)-*N*-Allyl-*N*-ethoxycarbonylmethyl-4-ethoxyphenyl(pent-4-enyl)phosphinamide (52e). Prepared from **51e** by amidation with *N*-allyl-glycine ethyl ester in 35% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 2H), 6.96 (m, 2H), 5.80–5.61 (m, 2H), 5.20–5.08 (m, 2H), 5.04–4.92 (m, 2H), 4.15 (q, 2H), 4.08 (q, 2H), 3.83 (dd, 1H), 3.70 (dd, 1H), 3.57 (m, 2H), 2.16–1.40 (m, 6H), 1.43 (t, 3H), 1.25 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2 (d), 161.9 (d), 137.5, 134.3 (d), 133.7 (d), 122.6 (d), 118.6, 115.6, 114.5 (d), 63.6, 60.9, 50.1 (d), 46.3 (d), 34.7 (d), 27.6 (d), 21.4 (d), 14.7, 14.2.

(±)-*N*-Allyl-allyl(4-phenoxyphenyl)phosphinamide (54f). Prepared by amidation of **51f** with allylamine in 82% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 2H), 7.39 (m, 2H), 7.19 (m, 1H), 7.10–6.99 (m, 4H), 6.00–5.75 (m, 2H), 5.27–5.05 (m, 4H), 3.68–3.36 (m, 2H), 2.90–2.65 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 161.2, 155.6, 136.4 (d), 134.4 (d), 130.0, 128.5 (d), 124.5 (d), 124.5, 120.2, 120.1 (d), 117.6 (d), 115.8, 42.7, 36.8 (d).

(±)-*N*-Allyl-but-3-enyl(4-phenoxyphenyl)phosphinamide (54g). Prepared from **51g** by amidation with allylamine in 67% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 2H), 7.39 (m, 2H), 7.19 (m, 1H), 7.11–6.99 (m, 4H), 5.98–5.71 (m, 2H), 5.55 (m, 1H), 5.10 (m, 1H), 5.03 (m, 1H), 4.97 (m, 1H), 3.73–3.37 (m, 2H), 2.74 (q, 1H), 2.37 (m, 1H), 2.21 (m, 1H), 2.11–1.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 161.2 (d), 155.6, 137.5 (d), 136.4 (d), 134.2 (d), 130.0, 124.9 (d), 124.5, 120.1, 117.7 (d), 115.8, 115.2, 42.9, 29.3 (d), 26.4 (d).

(±)-*N*-Allyl-*N*-(ethoxycarbonyl)methyl-allyl(4-(4-chlorophenoxy)phenyl)phosphinamide (52h). Prepared from **51h** by amidation with *N*-allyl-glycine ethyl ester in 85% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.35 (m, 2H), 7.03 (m, 2H), 7.00 (m, 2H), 5.93–5.63 (m, 2H), 5.22–5.08 (m, 4H), 4.17 (q, 2H), 3.88 (dd, 1H), 3.78 (dd, 1H), 3.60 (m, 2H), 2.97 (m, 2H), 1.26 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.1 (d), 160.7 (d), 154.2, 134.1 (d), 133.9 (d), 130.1, 129.7, 128.0 (d), 125.5 (d), 121.3, 120.2 (d), 119.0, 117.6 (d), 61.0, 50.2 (d), 46.3 (d), 34.9 (d), 14.2.

General procedure M: ring closing metathesis

The diene was dissolved to 0.01 M in dichloromethane, and Grubb's catalyst, benzylidene-bis-(tricyclohexylphosphine)-dichloro-ruthenium (0,02 molar equivalents), was added. When the reaction had gone to completion (within 2 h at reflux), silica gel (1 g silica gel per 100 mg product) was added, volatiles removed in vacuo, and the residue eluted in a gradient of methanol in ethyl acetate rising from 0 to 10%. Fractions containing product were identified by TLC (iodine vapour), combined, and concentrated in vacuo to give the pure product as an oil.

(±)-Ethyl 2-(4-ethoxyphenyl)-2-oxo-azaphosphorin-4-ene-1-acetate (53d). Prepared from **52d** by ring closing metathesis in 82% yield as an oil. ^{1}H NMR ($CDCl_3$) δ

7.76 (m, 2H), 6.93 (m, 2H), 5.90–5.70 (m, 2H), 4.18–4.00 (m, 2H), 4.07 (q, 2H), 3.89 (m, 2H), 3.85 (dd, 1H), 3.61 (dd, 1H), 2.73–2.60 (m, 2H), 1.42 (t, 3H), 1.19 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 170.2 (d), 161.9 (d), 133.4 (d), 126.4 (d), 123.6 (d), 120.0 (d), 114.5 (d), 63.6, 60.9, 50.2, 48.3 (d), 28.2 (d), 14.7, 14.1.

(±)-Ethyl 2-(4-ethoxyphenyl)-2-oxo-azaphosphoroc-6-ene-1-acetate (53e). Prepared from **52e** by ring closing metathesis in 35% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2H), 6.94 (m, 2H), 5.76 (m, 1H), 5.55 (m, 1H), 4.28 (m, 1H), 4.16 (q, 2H), 4.06 (q, 2H), 3.76–3.64 (m, 2H), 3.54 (dd, 1H), 2.65 (m, 1H), 2.30–1.60 (m, 5H), 1.42 (t, 3H), 1.25 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.6 (d), 161.7 (d), 132.8 (d), 129.2, 128.0, 124.7 (d), 114.5 (d), 63.5, 60.9, 47.4 (d), 47.3 (d), 25.6 (d), 24.0 (d), 21.5 (d), 14.7, 14.2.

(±)-2-Oxo-2-(4-phenoxyphenyl)-azaphosphorin-4-ene (55f). Prepared by ring closing metathesis of **54f** in 87% yield. ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 2H), 7.38 (m, 2H), 7.17 (m, 1H), 7.10–6.96 (m, 4H), 5.97–5.69 (m, 2H), 4.07 (m, 1H), 3.84 (m, 1H), 3.13 (bs, 1H), 2.83–2.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 160.9 (d), 155.7, 133.3 (d), 130.0, 127.5 (d), 126.4 (d), 124.4, 120.0 (d), 120.0, 117.7 (d), 43.2 (d), 27.1 (d).

(±)-Ethyl 2-oxo-2-(4-phenoxyphenyl)-azaphosphorep-5-ene-1-acetate (53g). Prepared from **52g** by ring closing metathesis in 21% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.38 (m, 2H), 7.18 (m, 1H), 7.10–7.00 (m, 4H), 5.87–5.68 (m, 2H), 4.26–4.07 (m, 3H), 3.83–3.54 (m, 3H), 2.85–2.20 (m, 4H), 1.25 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2 (d), 161.0 (d), 155.7, 133.5 (d), 131.7, 130.0, 127.1, 124.4, 120.0, 117.9 (d), 61.0, 47.5 (d), 44.9 (d), 27.9 (d), 22.0 (d), 14.2.

(±)-Ethyl 2-(4-(4-chlorophenoxy)-phenyl)-2-oxo-azaphosphorin-4-ene-1-acetate (53h). Prepared from **52h** by ring closing metathesis in 67% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2H), 7.34 (m, 2H), 7.05–6.95 (m, 4H), 5.90–5.70 (m, 2H), 4.11 (m, 2H), 4.02–3.80 (m, 3H), 3.65 (dd, 1H), 2.68 (m, 2H), 1.20 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 170.1 (d), 160.5 (d), 154.3, 133.5 (d), 130.0, 128.1, 127.3 (d), 126.5 (d), 121.3, 119.9 (d), 117.7 (d), 61.0, 50.4, 48.1, 28.1 (d), 14.1.

General procedure N: alkylation

To the phosphonamide suspended at 0 °C in dry THF at 0.5 M was added butyl lithium (1.15 molar equivalents of a 1.6 M solution in hexanes). The clear solution obtained was cooled to −78 °C, ethyl bromoacetate (1.6 molar equivalents) was added, and the reaction mixture left to reach room temperature. The next day, aqueous work up with phosphate buffer at pH 7 and ethyl acetate followed by chromatography in a gradient of ethyl acetate in hexane rising from 0 to 10% afforded the pure product as an oil.

(±)-*N*-Allyl-*N*-(ethoxycarbonyl)methyl-but-3-enyl(4-phenoxyphenyl)phosphinamide (52g). Prepared from **54g** by alkylation with ethyl bromoacetate in 59% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.39 (m, 2H), 7.19 (m, 1H), 7.11–6.97 (m, 4H), 5.90–5.63 (m, 2H), 5.23–4.92 (m, 4H), 4.16 (q, 2H), 3.79 (m, 2H), 3.60 (m, 2H), 2.50–2.00 (m, 4H), 1.25 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.1 (d), 161.1 (d), 155.6, 137.5 (d), 134.0 (d), 133.8 (d), 130.0, 125.1 (d), 124.5, 120.1, 118.8, 117.7 (d), 115.0, 61.0, 50.0 (d), 46.3 (d), 27.5 (d), 26.2, 14.2.

(±)-Ethyl 2-oxo-2-(4-phenoxyphenyl)-azaphosphorin-4-ene-1-acetate (53f). Prepared by alkylation of **55f** as an oil. ^{1}H NMR ($CDCl_3$) δ 7.79 (m, 2H), 7.38 (m, 2H), 7.18 (m, 1H), 7.10–6.96 (m, 4H), 6.00–5.67 (m, 2H), 4.24–4.06 (m, 3H), 3.91 (m, 1H), 3.89 (dd, 1H), 3.65 (dd, 1H), 2.74–2.62 (m, 2H), 1.20 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 170.1 (d), 161.0 (d), 155.6, 133.4 (d), 130.0, 126.5 (d), 126.5 (d), 124.5, 120.1, 119.9 (d), 117.6 (d), 61.0, 50.3, 48.2 (d), 28.2 (d), 14.1.

General procedure O: hydrogenation

The cyclic olefin, 70 mg, was shaken in ethyl acetate (2 mL) with 10% palladium on carbon (30 mg) under hydrogen at 1 atm, until the calculated amount of hydrogen had been absorbed. Filtration through a pad of Celite and removal of solvent yielded the corresponding saturated product in a pure state.

(±)-Ethyl 2-(4-ethoxyphenyl)-2-oxo-azaphosphorinane-1-acetate (56d). Prepared from **53d** by hydrogenation in 51% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.81 (m, 2H), 6.95 (m, 2H), 4.20–4.00 (m, 2H), 4.08 (q, 2H), 3.63 (dd, 1H), 3.37 (dd, 1H), 3.35 (m, 1H), 3.12 (m, 1H), 2.20–1.80 (m, 6H), 1.43 (t, 3H), 1.21 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 170.5 (d), 162.1 (d), 134.2 (d), 122.2 (d), 114.6 (d), 63.6, 60.9, 49.3, 48.9, 28.8 (d), 26.7 (d), 20.7 (d), 14.7, 14.2.

(±)-Ethyl 2-(4-ethoxyphenyl)-2-oxo-azaphosphorocane-1-acetate (56e). Prepared from **53e** by hydrogenation in 51% yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 2H), 6.93 (m, 2H), 4.23 (m, 1H), 4.08 (q, 2H), 4.06 (q, 2H), 3.54 (dd, 1H), 3.47–3.14 (m, 2H), 2.29–1.15(m, 10H), 1.42 (t, 3H), 1.19 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2 (d), 161.6 (d), 133.2 (d), 125.3 (d), 114.3 (d), 63.5, 60.8, 45.6 (d), 44.5 (d), 28.5 (d), 26.4, 26.1, 23.3, 22.3 (d), 14.7, 14.1.

(±)-Ethyl 2-oxo-2-(4-phenoxyphenyl)-azaphosphorinane-1-acetate (56f). Prepared by hydrogenation of **53f** in practically quantitative yield. ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2H), 7.39 (m, 2H), 7.19 (m, 1H), 7.10–6.97 (m, 4H), 4.12 (m, 2H), 3.67 (dd, 1H), 3.42 (dd, 1H), 3.36 (m, 1H), 3.14 (m, 1H), 2.20–1.77 (m, 6H), 1.22 (t, 3H).

(±)-2-Oxo-2-(4-phenoxyphenyl)-azaphosphorepane-1-acetate (56g). Prepared from **53g** by hydrogenation in quantitative yield as an oil. ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.38 (m, 2H), 7.17 (m, 1H), 7.10–6.97 (m, 4H), 4.12 (q, 2H), 4.02 (dd, 1H), 3.62 (dd, 1H), 3.37 (m, 1H), 3.16 (m, 1H), 2.34–1.50 (m, 8H), 1.21 (t, 3H).

General procedure P: hydroxaminolysis

To the ethyl ester, dissolved at 0.7 M in dry methanol at 0 °C, was added *O*-trimethylsilyl hydroxylamine (2 molar equivalents), followed by potassium hydroxide

monohydrate (2 molar equivalents) dissolved at 1 M in dry methanol. When TLC indicated complete conversion, aqueous work up with phosphate buffer at pH 2 and ethyl acetate, and drying with magnesium sulphate, followed by addition of silica gel (1 g of silica gel per 100 mg of crude product), removal of volatiles in vacuo, and elution with a gradient of methanol in chloroform rising from 0 to 15%, afforded fractions containing the hydroxamic acid (identified on TLC plates with ferrichloride spray), which were combined, and concentrated in vacuo to give the pure hydroxamic acid.

(±)-*N*-Hydroxy-2-(4-ethoxyphenyl)-2-oxo-azaphosphorinane-1-acetamide (5d). Prepared from **56d** by hydroxylaminolysis in 51% yield as an oil. ^{1}H NMR (DMSO-d_6) δ 11.5–9.5 (bs, 1H), 9.5–8.0 (bs, 1H), 7.76 (m, 2H), 7.04 (m, 2H), 4.09 (q, 2H), 3.60-3.10 (m, 3H), 2.97 (m, 1H), 2.10–1.65 (m, 6H), 1.34 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 165.5, 161.3, 133.7, 122.3, 114.5, 63.2, 49.2, 48.6, 27.3, 25.7, 20.4, 14.4. HRMS calcd for $C_{14}H_{22}N_2O_4P$ (M + H) 313.1317, found 313.1316.

(±)-*N*-Hydroxy-2-(4-ethoxyphenyl)-2-oxo-azaphosphorocane-1-acetamide (5e). Prepared from **56e** by hydroxylaminolysis in 65% yield as an oil. ^{1}H NMR (DMSO-d_6) δ 11.0–9.5 (bs, 1H), 9.5–8.5 (bs, 1H), 7.74 (m, 2H), 6.99 (m, 2H), 4.07 (q, 2H), 3.55 (m, 1H), 3.40–3.10 (m, 3H), 2.24 (m, 1H), 2.00-1.20 (m, 9H), 1.34 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 166.7, 160.7, 132.9, 125.4, 114.1, 63.1, 45.3, 44.7, 27.3, 26.0, 25.5, 23.1, 22.1, 14.5. HRMS Calcd. for $C_{16}H_{26}N_2O_4P$ (M + H) 341.1630, found 341.1611.

(±)-*N*-hydroxy-2-oxo-2-(4-phenoxyphenyl)-azaphosphorinane-1-acetamide (5f). Prepared by hydroxylaminolysis of **56f** as an oil. ^{1}H NMR (CD_3CN) δ 7.71 (m, 2H), 7.37 (m, 2H), 7.17 (m, 1H), 7.00 (m, 4H), 3.40 (dd, 1H), 3.24 (m, 1H), 3.19 (t, 1H), 3.00 (m, 1H), 2.00–1.65 (m, 6H). ^{13}C NMR (CD_3CN) δ 167.3, 162.2, 156.4, 135.0, 131.0, 125.5, 125.3, 120.8, 118.6, 51.7, 50.2, 28.3, 26.8, 21.1. HRMS calcd for $C_{18}H_{222}N_2O_4P$ (M + H) 361.1317, found 361.1300.

(±)-*N*-Hydroxy-2-oxo-2-(4-phenoxyphenyl)-azaphosphorepane-1-acetamide (5g). Prepared from **56g** by hydroxaminolysis in 40% yield as an oil. ^{1}H NMR (DMSO-d_6) δ 11.5–9.5 (bs, 1H), 9.5–8.5 (bs, 1H), 7.82 (m, 2H), 7.45 (m, 2H), 7.22 (m, 1H), 7.10 (m, 2H), 7.04 (m, 2H), 3.50 (dd, 1H), 3.40–3.00 (m, 3H), 2.06 (m, 2H), 1.90–1.40 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 166.7, 159.7, 155.2, 133.5, 130.2, 127.8, 124.3, 119.7, 117.3, 48.8, 47.8, 30.0, 29.3, 28.7, 20.4. HRMS Calcd. for $C_{19}H_{24}N_2O_4P$ (M + H) 375.1473, found 375.1496.

(±)-*N*-Hydroxy-2-(4-ethoxyphenyl)-2-oxo-azaphosphorin-4-ene-1-acetamide (6d). Prepared from **53d** by hydroxaminolysis in 40% yield as an oil. ^{1}H NMR (DMSO-d_6) δ 11.5–9.5 (bs, 1H), 9.5–8.5 (bs, 1H), 7.65 (m, 2H), 7.01 (m, 2H), 5.73 (m, 2H), 4.08 (q, 2H), 3.90–3.60 (m, 2H), 3.48 (dd, 1H), 3.25 (dd, 1H), 2.68 (m, 1H), 2.50 (m, 1H), 1.33 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 165.6, 161.0, 132.7, 126.3, 123.9, 119.8, 114.3, 63.2, 50.1, 47.3, 27.1, 14.4. HRMS calcd for $C_{14}H_{20}N_2O_4P$ (M + H) 311.1160, found 311.1182.

(±)-*N*-Hydroxy-2-(4-ethoxyphenyl)-2-oxo-azaphosphoroc-6-ene-1-acetamide (6e). Prepared from **53e** by hydroxylaminolysis in 48% yield as an oil. ^{1}H NMR (DMSO-d_6) δ 11.5–9.5 (bs, 1H), 9.5–8.5 (bs, 1H), 7.82 (m, 2H), 6.99 (m, 2H), 5.63 (m, 2H), 4.08 (q, 2H), 3.75–3.40 (m, 3H), 3.18 (dd, 1H), 2.60–1.50 (m, 6H), 1.34 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 166.6, 160.8, 132.6, 128.8, 128.7, 125.2, 114.1, 63.1, 46.1, 45.7, 24.9, 23.6, 21.3, 14.4. HRMS Calcd. for $C_{16}H_{24}N_2O_4P$ (M + H) 339.1473, found 339.1486.

(±)-*N*-Hydroxy-2-oxo-2-(4-phenoxyphenyl)-azaphosphorin-4-ene-1-acetamide (6f). Prepared by hydroxaminolysis of **53f** as an oil. ^{1}H NMR (CD_3CN) δ 11.0–8.0 (bs, 2H), 7.69 (m, 2H), 7.41 (m, 2H), 7.21 (m, 1H), 7.04 (m, 4H), 5.76 (m, 2H), 3.90 (m, 1H), 3.68 (m, 2H), 3.24 (m, 1H), 2.62 (m, 2H). ^{13}C NMR (CD_3CN) δ 167.5, 162.1, 156.6, 134.5, 131.2, 127.6, 126.6, 125.7, 121.0, 120.4, 118.7, 51.5, 49.7, 28.0. HRMS calcd for $C_{18}H_{20}N_2O_4P$ (M + H) 359.1160, found 359.1155.

(±)-*N*-Hydroxy-2-oxo-2-(4-phenoxyphenyl)-azaphosphorep-5-ene-1-acetamide (6g). Prepared from **53g** by hydroxylaminolysis in 15% yield as an oil. ^{1}H NMR (DMSO-d_6) δ 11.5–9.5 (bs, 1H), 9.5–8.5 (bs, 1H), 7.87 (m, 2H), 7.45 (m, 2H), 7.22 (m, 1H), 7.09 (m, 4H), 5.74 (m, 2H), 3.75–3.50 (m, 3H), 3.26 (dd, 1H), 2.60–2.00 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 166.5, 159.8, 155.2, 133.3, 131.1, 130.2, 127.6, 127.2, 124.4, 119.6, 117.4, 46.2, 44.0, 26.5, 21.5. HRMS calcd for $C_{19}H_{20}N_2O_4P$ (M−H) 371.1161, found 371.1170.

(±)-*N*-Hydroxy-2-(4-(4-chlorophenoxy)-phenyl-2-oxo-azaphosphorin-4-ene-1-acetamide (6h). Prepared from **53h** by hydroxaminolysis in 30% yield after recrystallization from methanol/ethyl acetate. Mp: 161.5–162.5 °C (dec.) ^{1}H NMR (DMSO-d_6) δ 11.0–9.5 (s, 1H), 9.5–8.5 (s, 1H), 7.75 (m, 2H), 7.48 (m, 2H), 7.12 (m, 2H), 7.07 (m, 2H), 5.73 (m, 2H), 3.77 (m, 2H), 3.51 (dd, 1H), 3.30 (m, 1H), 2.85–2.40 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 165.5, 159.3, 154.2, 133.1, 130.0, 128.2, 127.8, 126.4, 121.4, 119.7, 117.6, 50.2, 47.0, 27.0. Anal. calcd for $C_{18}H_{18}Cl_2N_2O_4P$: C, 55.04; H, 4.62. Found: C, 55.09; H, 4.66.

Enzyme assays

MMP-1 and MMP-9, derived from human dermal fibroblasts, were obtained from Chemicon (CA, USA). MMP-3, derived from human synovial fibroblasts, was purchased from Biogenesis (England, UK). The metalloproteinases were activated immediately before the assay by incubation with amino phenyl mercuric acetate (APMA) (Sigma, MO, USA), as recommended by the producers, and were diluted in buffer (50 mM Tris, 200 mM NaCl, 5 mM $CaCl_2$, 1 μM $ZnCl_2$, pH 7.5 for MMP-3 and MMP-9, or 50 mM Tris, 200 mM NaCl, 100 mM $CaCl_2$, 1 μM $ZnCl_2$, pH 7.5, for MMP-1). The final concentration of the enzyme was 190 ng/mL (MMP-1), 330 ng/mL (MMP-3), and 50 ng/mL (MMP-9).

The compounds were tested for their inhibitory properties against each metalloproteinase with a fluorogenic assay, by measuring the fluorescent products formed by

the cleavage of the substrate in the presence of different concentrations of the inhibitors.

In the assay with MMP-9, fluorescein-conjugated gelatine (Molecular Probes, OR, USA), which is so heavily labelled that the fluorescence is quenched in the uncleaved substrate, was diluted in buffer to the final concentration of 50 μg/mL. The Dnp-Pro-β-cyclohexyl-Ala-Gly - Cys(Me) - His - Ala - Lys(*N* - Me - Abz) - NH_2 peptide (Bachem, Switzerland), which is quenched by 2,4-dinitrophenyl (Dnp), was diluted in buffer to the final concentration of 50 μM in the assays with MMP-1 and MMP-3.

The formation of free fluorescein from the uncleaved, quenched substrate was monitored by excitation at 485 nm and emission at 530 nm. The formation of the free *N*-methyl-antranilyl moiety (*N*-Me-Abz) was monitored by excitation at 350 nm and emission at 450 nm. The maximal enzymatic activity measured in the absence of inhibitors was approximately 10000 units in all assays, as determined after a total incubation time of 3 h for MMP-3, and 24 h for MMP-1 and MMP-9.

Test compounds

For the enzyme assays, the compounds were dissolved in DMSO at the concentration of 10 μM and were stored at −20 °C. For the experiments, the compounds were diluted in buffer to the concentrations of 0.1 nM to 10 μM. The final concentration of DMSO was 0.1% v/v.

Statistical methods

For the enzyme assays, the data are means of at least two independent experiments. The IC_{50} values were calculated from the dose–response curves for each inhibitor.

In vivo experiments

For dilution of the test compounds, a mixture of 2% carboxymethylcellulose and demineralised water was used.

Cells

HT 1080 is a human fibrosarcoma cell line that overexpresses MMP. The cells are semi-adherent and were cultured in Dulbecco's modified Eagle Medium supplemented with 100 IU of penicillin/streptomycin, sodium bicarbonate, glucose and 10% FBS. Medium was changed twice a week. Before inoculation, cells were harvested from sub-confluent monolayers. The viability of the HT 1080 cells was between 60 and 80%, determined by the eosin exclusion test.

Animal models

Animals and animal welfare. All of the animal experiments were conducted according to the guidelines and ethical standards of the Danish Committee for Animal Experiments. Female athymic NMRI nu/nu mice 6 weeks of age were purchased from M&B (Ry, Denmark). The mice were allowed an acclimatization period of 1–3 weeks before start of the experiments. The nude mice were housed in Scantainers under semi-sterile conditions where light was controlled on a 12 h light–dark cycle. They were given free access to food (Altromin 1324), sterilized by irradiation and filtered (0.2 mM) drinking water. All handling of the mice was performed in a laminar flow bench. The bodyweight of the animals was recorded twice weekly.

HT 1080 xenografts

NMRI nu/nu mice were injected with a single cell suspension of 2×10^6 cells in 0.2 mL of medium subcutaneously in each flank and tumour size was measured twice weekly using a digital caliper. The tumor area was used as expression of tumor size and was calculated from two perpendicular dimensions (d_1 & d_2). The test compounds were given intraperitoneally for 2 weeks starting day 3–6, when the tumour size was 22–24 mm^2. There were no signs of weight loss (data not shown) or other adverse effects after 2 weeks of dosing.

Mice were sacrificed at the end of the treatment or previously in case of (a) large tumours, (b) ulceration of tumours or (c) for humane reasons.

Statistical methods

Tumour area (A) was calculated as the product of the two diameters:

$$A = d_1 \times d_2$$

For mice with only one tumour, the area of this tumour at each day of observation was calculated and used in the statistical analysis. For mice with both left and right flank tumours the average of the two tumour areas was calculated and used in the statistical analysis. For each animal, an individual curve of the tumour areas observed during the experiment was plotted against time. The trend was an increasing growth rate of the tumours. In order to ensure an approximate linear correspondence between tumour data and time, the observations were transformed by taking the square root of the tumour areas. As a summary measure of the repeated measurements of tumour areas during the experiment, the estimated slope of the individual curve of the square root transformed data was used. The slope was interpreted to be a measure of tumour growth and was estimated using linear regression analysis. Comparison with controls was expressed as T/C% and calculated as follows:

$$[A/B - 1]^*100 \text{ where}$$

A = (overall mean tumour size at baseline + mean trend of treatment*intended days of treatment)
B = (overall mean tumour size at baseline + mean trend of control*intended days of treatment)

Overall mean tumour size at baseline = pooling all treatments this is the mean of all baseline values. For each mouse the baseline value is calculated as the square root of the (mean) area of the tumour(s).

Statistical evaluation of differences in tumour growth between groups of animals was performed using a one-way analysis of variance with correction for multiplicity by Bonferroni. A p value of less than 0.05 was considered significant.

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