Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2541–2552

TETRAHEDRON: *ASYMMETRY*

Synthesis of optically active oxazoles from phosphorylated 2*H*-azirines and *N*-protected amino acids or peptides

Francisco Palacios,* Ana María Ochoa de Retana, José Ignacio Gil and José María Alonso

Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain

Received 20 September 2002; accepted 23 October 2002

Abstract—A simple synthesis of optically active phosphorylated oxazoles **8**, **10**, **11**, and **12** containing amino acid residues from 2*H*-azirine-phosphine oxides **1** or -phosphonates **6** is described. Ring-opening reaction of 2*H*-azirines derived from phosphine oxides **1** and phosphonates **6** with *N*-protected amino acids **2** gives functionalized phosphorylated ketamides **3** and **7**. Cyclization of ketamides **3** and **7** with triphenylphosphine and hexachloroethane in the presence of triethylamine leads to the formation of racemic and optically active phosphorylated oxazoles containing *N*-protected amino acid residues **8** and **10**. Deprotection of these oxazoles gives aminoalkyl oxazoles **11** and **12**. 2*H*-Azirines **1** and **6** also react with *N*-protected peptides **13** and give functionalized ketamides **14** and **15**, ring closure of which leads to the formation of phosphorylated oxazoles containing peptide residues **16** and **17**.

1. Introduction

Oxazoles are widely used intermediates for functional transformations.[1] Simple oxazoles are common units in a wide variety of polyoxazole marine natural products possessing biological activity,[2] while aminoalkyl oxazoles derived from amino acids **I** are very important substrates because they are constituents of peptide-based alkaloids and antibiotics with remarkable cytotoxic and/or antitumor properties.[3,4] Additionally, amino acid residues play an important role in connecting the heterocyclic moieties in the formation of polyazole natural products. Therefore, the preparation of optically active oxazoles **I** is an interesting goal in synthetic organic chemistry. Furthermore, it is known that phosphorus substituents regulate important biological functions,[5] and that molecular modifications involving the introduction of organophosphorus functionalities could increase their biological activity, in a similar way to that reported for other pharmaceuticals.[5] For these reasons, optically active oxazoles with amino acid residues, which contain a phosphorus substituent (**II**, Fig. 1) are expected to play a similar role to that observed in the isosteric analogues **I**, and could possess biological activity and be used in the preparation of new complex polyoxazole derivatives containing phosphorus substituents. However, as far as we know, no examples of racemic or optically active oxazoles with amino acid residues and containing a phosphorus substituent have been described.

In this context, we have described new methods for the preparation of five-[6] and six-[7] membered phosphorus substituted nitrogen heterocycles from functionalized phosphine oxides and phosphonates and the synthetic uses of amino phosphorus derivatives as starting materials for the preparation of acyclic compounds[8] and phosphorus-containing heterocycles.[9] Recently, we reported the first asymmetric synthesis of 2*H*-azirines[10] derived from phosphine oxides by alkaloid-mediated Neber reaction of tosyl oximes,[11,12] as well as their dimerization to phosphorylated pyrazines[13] and the ring opening of azirines with carboxylic acids followed by the cyclization of the corresponding adducts to oxazoles **IV** (Scheme 1).[14] Continuing with our interest in

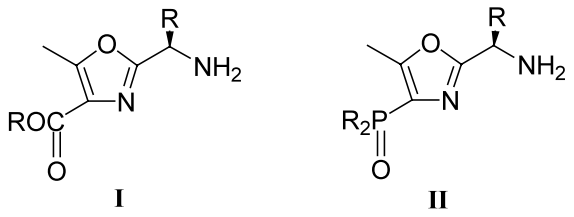
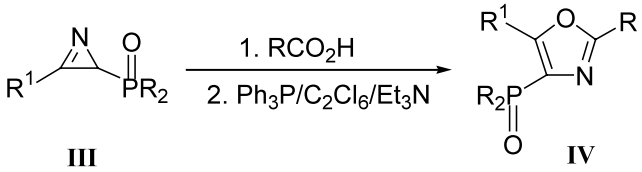


Figure 1.

* Corresponding author. Tel.: 34-945-013103; fax: 34-945-013049; e-mail: qoppagaf@vc.ehu.es

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00686-9



Scheme 1.

the synthesis of new phosphorus substituted heterocycles, we report herein an easy and high yielding synthesis of racemic and optically active 4-(2-aminoalkyloxazolyl)phosphine oxides (**II**, Fig. 1, R = Ph) and -phosphonates (**II**, Fig. 1, R = OEt) from easily available azirines. Azirines are thus very interesting reagents for the activation and amidation of *N*-protected amino acids via azirine–oxazolone intermediates and have been successfully applied to peptide synthesis.[15–17]

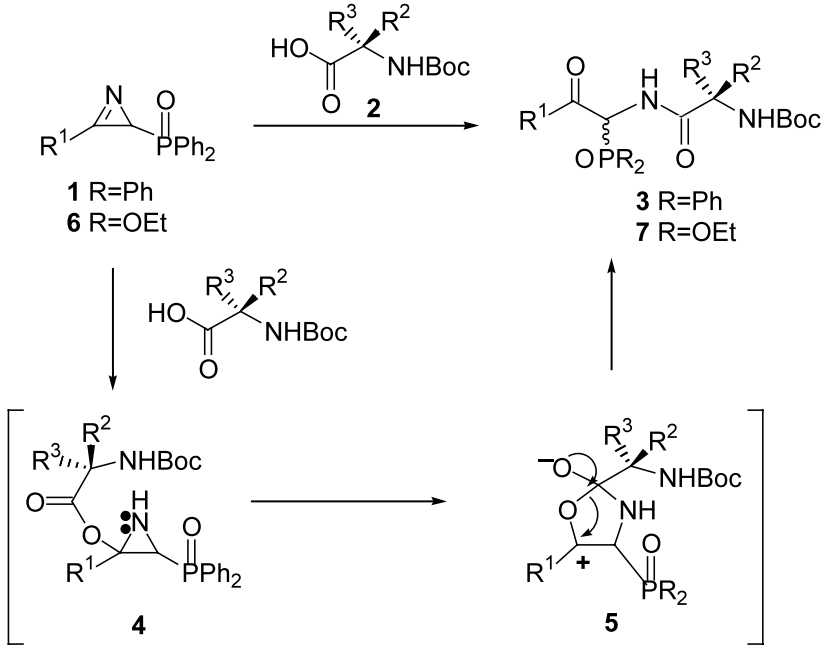
2. Results and discussion

2.1. Reaction of azirines 1 and 6 with *N*-protected amino acids 2. Synthesis of α-ketamides 3 and 7

Ring opening and selective cleavage of the N–C double bond of amino-azirines[15,16] and of phosphorus substituted azirines,[14] can be achieved with carboxylic acids. In the case of amino-azirines the process has been extended to *N*-protected amino acids.[15,17] As far as we know, no ring-opening reaction of azirines containing phosphorus substituents with *N*-protected amino acid has been reported. For this reason, we explored the reaction of phosphorylated azirines with *N*-protected amino acids and peptides. Given the increasing interest in 'phosphapeptides' in organic and medicinal chemistry,[18,19] this reaction can be used as a model for the introduction of amino phosphorus moieties into peptides. Furthermore, the functionalized ketamides generated can be used for the regioselective preparation of the previously unknown racemic and optically active phosphorylated oxazoles containing amino alkyl residues.

Firstly, we explored the reaction of azirines with racemic *N*-Boc protected amino acids.[20] Reaction of 3-methyl-2*H*-azirinyl phosphine oxide **1a** ($R^1 = CH_3$) with *N*-Boc-glycine **2a** ($R^2 = R^3 = H$), at low temperature (−80°C) in THF led to the formation of α-ketamide containing a phosphine oxide group in the α-position **3aa** ($R^1 = CH_3$, $R^2 = R^3 = H$) (Scheme 2, Table 1, entry 1). The reaction can be extended both to Cα-substituted (±)-*N*-Boc-alanine **2b** ($R^2 = CH_3$, $R^3 = H$; $R^2 = H$, $R^3 = CH_3$) and to (±)-*N*-Boc-serine **2c** ($R^2 = CH_2OH$, $R^3 = H$; $R^2 = H$, $R^3 = CH_2OH$) obtaining (1:1) diastereoisomeric mixtures[21] of α-ketamides **3ab** ($R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$; $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$) and **3ac** ($R^1 = CH_3$, $R^2 = CH_2OH$, $R^3 = H$; $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2OH$) (Scheme 2, Table 1, entries 2 and 3). Spectroscopic data were in agreement with the assigned structure of compounds **3**. Mass spectrometry of **3ab** showed the molecular ion peak, while in the ^{31}P NMR spectrum phosphine oxide groups resonated at $\delta_P = 32.4$ and 33.1 ppm for both diastereoisomers. The formation of adducts **3** could be explained by protonation of the nitrogen atom of the azirine, then nucleophilic addition of the carboxylate to the aziridinium ion, followed by ring expansion of aziridine **4** to give the zwitterionic oxazolone **5**, which underwent ring opening to form ketamides **3**.

The scope of the reaction was not limited to racemic *N*-protected amino acids **3aa**–**3ac**, given that azirine



Scheme 2.

Table 1. α-Ketamides **3** and **7**

Entry	Compound	R	R^1	R^2	R^3	Yield (%)[a]	$[\alpha]_D^{22}$[b]
1	**3aa**	C_6H_5	CH_3	H	H	73	–
2	(±)-**3ab**	C_6H_5	CH_3	H[c]	CH_3[c]	65	–
3	(±)-**3ac**	C_6H_5	CH_3	H[c]	CH_2OH[c]	65	–
4	(+)-**3ad**	C_6H_5	CH_3	CH_3	H	58	+34.0
5	(−)-**3ae**	C_6H_5	CH_3	H	CH_3	62	−34.0
6	(+)-**3af**	C_6H_5	CH_3	CH_2OH	H	48	+32.4
7	(−)-**3ag**	C_6H_5	CH_3	H	CH_2OH	66	−32.4
8	(−)-**3ah**	C_6H_5	CH_3	H	$CH_2C_6H_5$	56	−11.4
9	(±)-**7ab**	OC_2H_5	CH_3	H[c]	CH_3[c]	68	–
10	(+)-**7ad**	OC_2H_5	CH_3	CH_3	H	71	+21.0
11	(−)-**7ae**	OC_2H_5	CH_3	H	CH_3	66	−21.0
12	(−)-**7ag**	OC_2H_5	CH_3	H	CH_2OH	52	−11.0
13	(+)-**7bd**	OC_2H_5	C_2H_5	CH_3	H	72	+24.4
14	(−)-**7bg**	OC_2H_5	C_2H_5	H	CH_2OH	50	−9.5

[a] Yields refer to isolated compounds.
[b] Degrees (for concentration, see Section 4).
[c] Racemic.

phosphine oxide **1a** ($R^1=CH_3$) also reacted with optically active isomers of *N*-Boc-(*R*)-alanine **2d** ($R^2=CH_3$, $R^3=H$) or (*S*)-alanine **2e** ($R^2=H$, $R^3=CH_3$), of *N*-Boc-(*R*)-serine **2f** ($R^2=CH_2OH$, $R^3=H$) or (*S*)-serine **2g** ($R^2=H$, $R^3=CH_2OH$) and with *N*-Boc-(*S*)-phenylalanine **2h** ($R^2=H$, $R^3=CH_2C_6H_5$) to give, respectively, optically active α-ketamides (+)-**3ad** ($R^1=CH_3$, $R^2=CH_3$, $R^3=H$), (−)-**3ae** ($R^1=CH_3$, $R^2=H$, $R^3=CH_3$), (+)-**3af** ($R^1=CH_3$, $R^2=CH_2OH$, $R^3=H$), (−)-**3ag** ($R^1=CH_3$, $R^2=H$, $R^3=CH_2OH$) and (−)-**3ah** ($R^1=CH_3$, $R^2=H$, $R^3=CH_2C_6H_5$), which were obtained, as in the case of the racemic compounds, as 1:1 diastereoisomeric mixtures[21] (Scheme 2, Table 1, entries 4–8). Enantiomerically enriched azirine phosphine oxide **1a** ($R^1=CH_3$)[11] was also treated with optically active *N*-Boc-(*R*)- **2d** or (*S*)-amino acids **2e** and **2g** but enantiomerically enriched ketamides **3** were not obtained and (1:1) diastereoisomeric mixtures[21] were obtained instead. These results could be explained by epimerization of Cα-carbon to the phosphine oxide group, due to the acid character of the methinic hydrogen in this position.

The process can also be extended to azirines derived from phosphonates **6**.[12a] In this case shorter periods of time (2 h) and higher temperatures (70°C) were required. Heating racemic or enantiomerically enriched azirines **6a** ($R^1=CH_3$), and **6b** ($R^1=C_2H_5$), with *N*-Boc-protected-(±)-alanine **2b**, -(*R*)-alanine **2d** or -(*S*)-alanine **2e** and with *N*-Boc-(*S*)-serine **2g** led to the formation[22] of racemic and optically active α-ketamides containing a diethoxyphosphoryl group in the α-position **7ab**–**7bg**, which were obtained, as before, as 1:1 diastereoisomeric mixtures[21] (Scheme 2, Table 1, entries 9–14). This formation of phosphapeptides[18,19] can be regarded as a peptide chain elongation which introduces an α-ketamine containing a phosphonate group or a phosphine oxide to the C-terminal end of the amino acid.

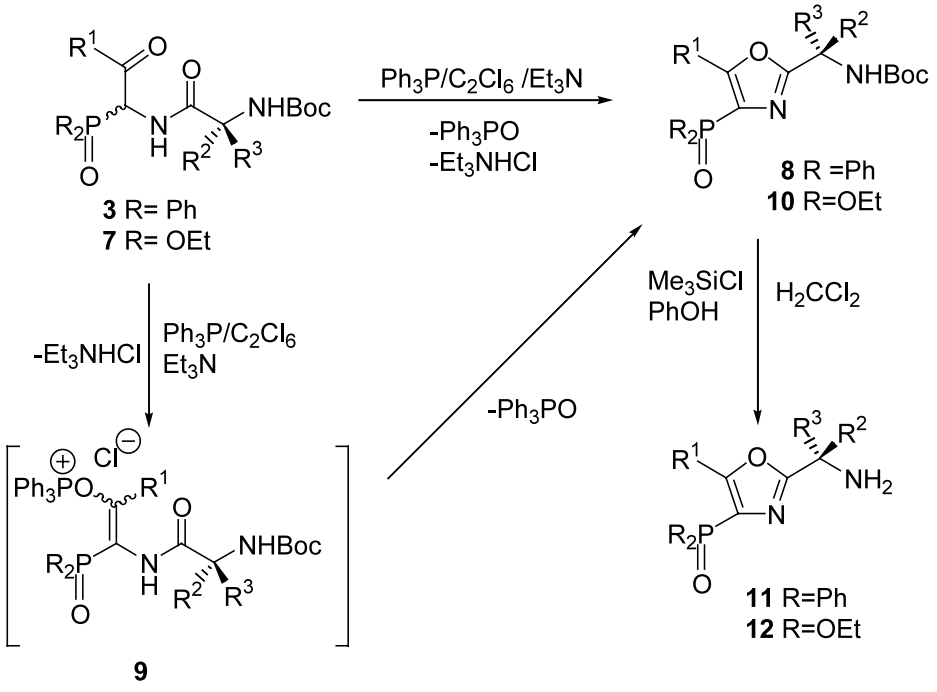
2.2. Synthesis of racemic and optically active phosphorus substituted aminoalkyl oxazoles 8 and 11

Next we explored the ring closure of ketamides containing a phosphine oxide **3**, or phosphonate substituent **7** for the preparation of the previously unknown and potentially useful racemic and optically active phosphorylated oxazoles containing amino alkyl residues **II** (Fig. 1). The best results were observed when triphenylphosphine dichloride, generated 'in situ' from the reaction of the phosphine with hexachloroethane, was used.[23,24] Adducts **3** were treated with triphenylphosphine and hexachloroethane in the presence of triethylamine in THF to give oxazole phosphine oxides **8** in good yields and in a regioselective fashion (Scheme 3, Table 2). Spectroscopic data were in agreement with the assigned structure of compounds **8**. Mass spectrometry of (+)-**8ad** showed the molecular ion peak, while in the ^{31}P NMR spectrum the phosphine oxide group resonated at $\delta_P=18.3$ ppm. The ^{13}C NMR spectrum of oxazole (+)-**8ad** showed doublets at $\delta_C=126.3$ ppm ($^1J_{PC}=141.5$ Hz) for C-4, and at $\delta_C=163.8$ ppm ($^3J_{PC}=17.1$ Hz) for C-2. The formation of oxazoles **8** could be explained by deprotonation of ketamides **3** by means of dichlorotriphenylphosphorane (Ph_3PCl_2), generated in situ from triphenylphosphine and hexachloroethane,[25] to give an intermediate enamide **9** (Scheme 3) followed by the loss of triphenylphosphine oxide and subsequent ring closure.[24]

Cyclization is quite general, allowing the preparation of racemic and optically active oxazole phosphine oxides (4-position) bearing aminoalkyl groups in the 2-position of the ring derived not only from glycine **8aa** ($R^1=CH_3$, $R^2=R^3=H$) (Scheme 3, Table 2, entry 1), but also from (±)-alanine **8ab** ($R^1=CH_3$, $R^2=CH_3$, $R^3=H$; $R^1=CH_3$, $R^2=H$, $R^3=CH_3$), (*R*)-alanine (+)-**8ad** ($R^1=CH_3$, $R^2=CH_3$, $R^3=H$) or (*S*)-alanine (−)-**8ae** ($R^1=CH_3$, $R^2=H$, $R^3=CH_3$) (Scheme 3, Table 2,

entries 2–4), and from (*S*)-phenylalanine (–)-**8ah** ($R^1=CH_3$, $R^2=H$, $R^3=CH_2C_6H_5$) (Scheme 3, Table 2, entry 5). As far as we know, this process represents the first synthesis of optically active oxazoles derived from amino acids and containing a phosphorus substituent.

Likewise the cyclization of functionalized ketamides derived from α-aminophosphonates **7** with triphenylphosphine–hexachloroethane and triethylamine gave (±)-oxazole **10ab** ($R^1=CH_3$, $R^2=CH_3$, $R^3=H$; $R^1=CH_3$, $R^2=H$, $R^3=CH_3$) (Scheme 3, Table 2, entry 6) when racemic ketamide **7ab** was used and optically active oxazole phosphonates containing aminoalkyl groups in the 2-position of the ring derived from (*R*)-alanine (+)-**10ad** ($R^1=CH_3$, $R^2=CH_3$, $R^3=H$) and (+)-**10bd** ($R^1=C_2H_5$, $R^2=CH_3$, $R^3=H$) or from (*S*)-alanine (–)-**10ae** ($R^1=CH_3$, $R^2=H$, $R^3=CH_3$) (Scheme 3, Table 2, entries 7–9) when optically active ketamides (+)-**7ad**, (+)-**7bd**, (–)-**7ae** were used. The deprotection of the terminal *N*-Boc group of oxazoles **8** and **10** was studied. In the case of oxazole phosphine oxides **8**, the best results were obtained when the reaction was performed with chlorotrimethylsilane (1 M) and phenol (3 M) in dichloromethane[26] to give (2-aminomethyl-5-methyloxazol-4-yl) phosphine oxide **11aa** ($R^1=CH_3$, $R^2=R^3=H$) and enantiomerically pure oxazole (–)-**11ae** derived from (*S*)-alanine ($R^1=CH_3$, $R^2=H$, $R^3=CH_3$) in good yields (Scheme 3, Table 2, entries 10 and 11). However, in the case of oxazole phosphonate **10ad** the deprotection was accomplished[27] with HCl 3 M in refluxing AcOEt and optically active oxazole (+)-**12ad** derived from (*R*)-alanine ($R^1=CH_3$, $R^2=CH_3$, $R^3=H$) was obtained (Scheme 3, Table 2, entry 12).



Scheme 3.

Table 2. Phosphorylated oxazoles **8**, **10**, **11** and **12**

Entry	Compound	R	R^1	R^2	R^3	Yield (%)[a]	$[\alpha]_D^{22}$[b]
1	**8aa**	C_6H_5	CH_3	H	H	68	–
2	(±)-**8ab**	C_6H_5	CH_3	H[c]	CH_3[c]	70	–
3	(+)-**8ad**	C_6H_5	CH_3	CH_3	H	72	+43.4
4	(–)-**8ae**	C_6H_5	CH_3	H	CH_3	66	–43.4
5	(–)-**8ah**	C_6H_5	CH_3	H	$CH_2C_6H_5$	73	–11.0
6	(±)-**10ab**	OC_2H_5	CH_3	H[c]	CH_3[c]	45	–
7	(+)-**10ad**	OC_2H_5	CH_3	CH_3	H	56	+39.7
8	(–)-**10ae**	OC_2H_5	CH_3	H	CH_3	50	–39.7
9	(+)-**10bd**	OC_2H_5	C_2H_5	CH_3	H	46	+34.5
10	**11aa**	C_6H_5	CH_3	H	H	81	–
11	(–)-**11ae**	C_6H_5	CH_3	H	CH_3	74	–8.0
12	(+)-**12ad**	OC_2H_5	CH_3	CH_3	H	46	+15.0

[a] Yields refer to isolated compounds.
[b] Degrees (for concentration, see Section 4).
[c] Racemic.

2.3. Synthesis of phosphorylated oxazoles 16 and 17 with peptide residues

The ring opening of azirines can be extended to *N*-protected peptides.[20] Treatment of 3-methyl-2*H*-azirinyl phosphine oxide **1a** ($R^1=CH_3$) with both a optically active *N*-protected dipeptide *N*-Boc-(*S*)-glycine-phenylalanine **13a** (Pep = Gly-Phe) and with a *N*-protected tripeptide *N*-Boc-(*S*)-alanine-glycine-glycine **13b** (Pep = Ala-Gly-Gly) at low temperature (−80°C) in THF led to the formation of optically active α-ketamides containing a phosphine oxide group in the α-position (−)-**14aa** ($R^1=CH_3$, Pep = Gly-Phe) and (+)-**14ab** ($R^1=CH_3$, Pep = Ala-Gly-Gly), which were obtained as 1:1 diastereoisomeric mixtures[21] in moderate yields (Scheme 4, Table 3, entries 1 and 2). Spectroscopic data were in agreement with the assigned structure of compounds **14** and the formation of adducts **14** could be explained, as before (Scheme 2), by formal addition of the carboxylic acid moiety of the *N*-protected peptide to the reactive carbon–nitrogen azirine double bond to give an unstable aziridine intermediate, followed by ring opening of zwitterionic oxazolone. The process can also be extended to azirine-phosphonates. Heating at 70°C (2 h) azirine **6b** ($R^1=C_2H_5$) with *N*-Boc-(*S*)-glycine-phenylalanine **13a** (Pep = Gly-Phe) gave a 1:1 diastereoisomeric mixture[21] of optically active α-ketamide containing a phosphonate group in the α-position (−)-**15ba** (Scheme 4, Table 3, entry 3).[22] This formation of phosphapeptides **14** and **15** can be regarded as a peptide chain elongation which introduces an α-ketamine containing a phosphine oxide or a phosphonate group to the C-terminal end of the peptide. Ketamide (−)-**14aa** was then treated with triphenylphosphine and hexachloroethane in the presence of triethylamine and optically active oxazole phosphine oxide containing a peptide residue (−)-**16aa** was obtained (Scheme 4, Table 3, entry 4). In a similar manner oxazole phosphonate (−)-**17ba** was prepared from α-ketamide (−)-**15ba** derived from phosphonate (Scheme 4, Table 3, entry 5). The formation of enantiomerically pure functionalized oxazoles **16** and **17** could also be explained through a similar mechanism to that reported for oxazoles derived from amino acids **8** and **10** (Scheme 3). This strategy describes the first preparation of optically active peptide-based oxazoles containing phosphinoyl **16** or phosphoryl substituents **17**.

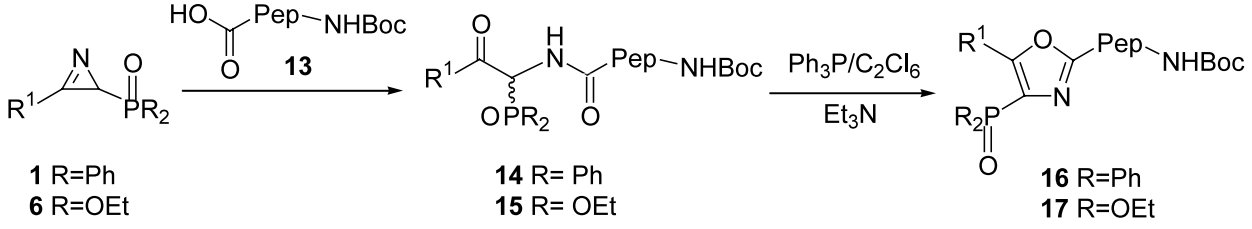
3. Conclusions

In conclusion, the first asymmetric synthesis of optically active oxazoles containing amino alkyl residues and with phosphine oxides **8** and **11** or phosphonate groups **10** and **12** has been described. The process involves a two-step procedure involving the ring opening of 2*H*-azirines derived from phosphine oxides **1** or phosphonates **6** with *N*-protected amino acids **2**, followed by dehydration and ring closure of the first-formed α-ketamides **3** and **7**. This strategy can also be extended to *N*-protected peptides **13** to give the first family of phosphorylated optically active oxazoles **16** and **17** with peptide side chains. Functionalized oxazoles containing amino acid **8**–**12** and peptide residues **16** and **17** as well as phosphorylated α-ketamides phosphapeptides **3**, **7**, **14**, and **15** are important synthons in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry.[3,4,18,19]

4. Experimental

4.1. General methods

Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100



Scheme 4.

Table 3. α-Ketamides **14** and **15** and phosphorylated oxazoles **16** and **17**

Entry	Compound	R	R^1	Peptide	Yield (%)[a]	$[\alpha]_D^{22}$,[b]
1	(−)-**14aa**	C_6H_5	CH_3	(*S*)-Gly-Phe	55	−10.7
2	(+)-**14ab**	C_6H_5	CH_3	(*S*)-Ala-Gly-Gly	51	+3.3
3	(−)-**15ba**	OC_2H_5	C_2H_5	(*S*)-Gly-Phe	48	−3.9
4	(−)-**16aa**	C_6H_5	CH_3	(*S*)-Gly-Phe	52	−6.6
5	(−)-**17ba**	OC_2H_5	C_2H_5	(*S*)-Gly-Phe	50	−3.6

[a] Yields refer to isolated compounds.
[b] Degrees (for concentration, see Section 4).

digital melting point apparatus and are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Varian VXR 300 MHz spectrometer using $CDCl_3$ solutions with TMS as an internal reference for ^{1}H and ^{13}C NMR spectra and phosphoric acid (85%) as external standard for ^{31}P NMR spectra. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on Hewlett–Packard 5971 and 5973 spectrometers, and obtained by APCI on a Hewlett–Packard 1100 spectrometer. Infrared spectra (IR) were recorded using a Nicolet IRFT Magna 550 spectrometer. $[\alpha]_D^{22}$ were taken on a Perkin–Elmer 341 polarimeter using a Na/HaI lamp. Elemental analyses were performed in a LECO CHNS-932 apparatus. Azirines **1a**[11] and **6a**,**b**[12a] were synthesized according to literature procedures.

4.2. General procedure for synthesis of 2-*tert*-butoxycarbonylamino-3-alkyl-*N*-(1-diphenylphosphinoyl-2-oxopropyl)alkylamide 3

To a −80°C solution of 3-alkyl-2*H*-azirin-2-yl diphenylphosphine oxide **1** (5 mmol) in THF (5 ml), a solution of *N*-protected amino acid **2** (15 mmol) in THF (5 ml) was added under a nitrogen atmosphere. Then, the mixture was allowed to warm to room temperature and stirred for 1–4 days. The solvent was evaporated in vacuo, and the subsequent residue was purified by flash column chromatography eluting with AcOEt.

4.2.1. 2-*tert*-Butoxycarbonylamino-*N*-(1-diphenylphosphinoyl-2-oxopropyl)acetamide (3aa). Yield 1.57 g (73%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and *N*-*tert*-butoxycarbonylglycine **2a** (2.63 g, 15 mmol) as described in the general procedure: mp 182–183°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.18 (s, 3H), 3.62 (m, 2H), 4.98 (d, $^3J_{HH}=7.5$ Hz, 1H), 5.77 (dd, $^2J_{PH}=9.0$ Hz, $^3J_{HH}=7.5$ Hz, 1H), 7.39–7.95 (m, 11H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 29.8, 44.0, 60.7 (d, $^1J_{PC}=65.0$ Hz), 80.1, 128.4–132.8 (m), 155.7, 169.4 (d, $^3J_{PC}=4.0$ Hz), 200.6 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 30.8 ppm; IR (KBr): 3423, 3211, 1724, 1699, 1668, 1228, 1182 cm^{-1}; MS (CI): *m*/*z* 431 (M^++1, 7). Anal. calcd for $C_{22}H_{27}N_2O_5P$: C, 61.39; H, 6.32; N, 6.51. Found C, 61.43; H, 6.31; N, 6.53.

4.2.2. (±)-2-*tert*-Butoxycarbonylamino-*N*-(1-diphenylphosphinoyl-2-oxopropyl)propanamide (3ab). Yield 1.44 g (65%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and (±)-*N*-*tert*-butoxycarbonylalanine **2b** (2.84 g, 15 mmol) as described in the general procedure: mp 146–147°C (hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, $^3J_{HH}=6.9$ Hz, 6H), 1.38 (s, 18H), 2.09 and 2.15 (2s, 6H), 4.03 (m, 2H), 5.02 (2d, $^3J_{HH}=7.2$ Hz, 2H), 5.76, 5.80 (2dd, $^2J_{PH}=9.6$ Hz, $^3J_{HH}=7.2$ Hz, 2H), 7.41–7.92 (m, 22H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 18.0, 28.2, 29.7, 49.8, 50.6, 60.4 (d, $^1J_{PC}=66.0$ Hz), 80.0 and 80.2, 128.4–132.8 (m), 155.1, 172.7 (d, $^3J_{PC}=4.5$ Hz), 200.3, 200.8 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 32.4 and 33.1 ppm; IR (KBr): 3423, 3310, 3211, 3070, 2979, 1725, 1715, 1672, 1202, 1175 cm^{-1}; MS (CI): *m*/*z* 445 (M^++1, 12). Anal. calcd for $C_{23}H_{29}N_2O_5P$: C, 62.15; H, 6.58; N, 6.30. Found C, 62.11; H, 6.60; N, 6.31.

4.2.3. (±)-2-*tert*-Butoxycarbonylamino-3-hydroxy-*N*-(1-diphenylphosphinoyl-2-oxopropyl)propanamide (3ac). Yield 1.50 g (65%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and (±)-*N*-*tert*-butoxycarbonylserine **2c** (3.08 g, 15 mmol) as described in the general procedure: mp 74–75°C (hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 18H), 2.20 and 2.16 (2s, 6H), 3.40–3.49 and 3.69–3.77 (2m, 4H), 4.08 (t, $^3J_{HH}=7.5$ Hz, 2H), 5.36 and 5.53 (2d, $^3J_{HH}=6.6$ Hz, 2H), 5.80 (2dd, $^2J_{PH}=9.6$ Hz, $^3J_{HH}=6.6$ Hz, 2H), 7.41–7.90 (m, 22H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 29.5, 55.7 and 56.0, 60.6 (d, $^1J_{PC}=67.5$ Hz), 62.4 and 62.7, 80.0, 127.8–132.8 (m), 155.6, 171.1 (d, $^3J_{PC}=13.6$ Hz), 200.8 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 30.7 and 31.2 ppm; IR (KBr): 3525, 3429, 3310, 3197, 3051, 2979, 1724, 1712, 1664, 1175 cm^{-1}; MS (CI): *m*/*z* 461 (M^++1, 13). Anal. calcd for $C_{23}H_{29}N_2O_6P$: C, 59.99; H, 6.35; N, 6.08. Found C, 59.92; H, 6.33; N, 6.09.

4.2.4. (+)-2-(*R*)-*tert*-Butoxycarbonylamino-*N*-(1-diphenylphosphinoyl-2-oxopropyl)propanamide (3ad). Yield 1.29 g (58%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*R*)-alanine **2d** (2.84 g, 15 mmol) as described in the general procedure: $[\alpha]_D^{22}=+34.0$ (*c* 1.00, CH_2Cl_2). For spectroscopic data see compound **3ab**.

4.2.5. (−)-2-(*S*)-*tert*-Butoxycarbonylamino-*N*-(1-diphenylphosphinoyl-2-oxopropyl)propanamide (3ae). Yield 1.38 g (62%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*S*)-alanine **2e** (2.84 g, 15 mmol) as described in the general procedure: $[\alpha]_D^{22}=-34.0$ (*c* 1.00, CH_2Cl_2). For spectroscopic data see compound **3ab**.

4.2.6. (+)-2-(*R*)-*tert*-Butoxycarbonylamino-3-hydroxy-*N*-(1-diphenylphosphinoyl-2-oxopropyl)propamide (3af). Yield 0.64 g (28%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*R*)-serine **2f** (3.08 g, 15 mmol) as described in the general procedure: $[\alpha]_D^{22}=+32.4$ (*c* 0.87, CH_2Cl_2). For spectroscopic data see compound **3ac**.

4.2.7. (−)-2-(*S*)-*tert*-Butoxycarbonylamino-3-hydroxy-*N*-(1-diphenylphosphinoyl-2-oxopropyl)propanamide (3ag). Yield 1.52 g (66%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*S*)-serine **2g** (3.08 g, 15 mmol) as described in the general procedure: $[\alpha]_D^{22}=-32.4$ (*c* 0.21, CH_2Cl_2). For spectroscopic data see compound **3ac**.

4.2.8. (−)-2-(*S*)-*tert*-Butoxycarbonylamino-*N*-(1-diphenylphosphinoyl-2-oxopropyl)phenyl propanamide (3ah). Yield 1.46 g (56%) obtained as a white solid from compound **1a** (1.28 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*S*)-phenylalanine **2h** (3.98 g, 15 mmol) as described in the general procedure: mp 63–64°C (hexane/AcOEt); $[\alpha]_D^{22}=-11.4$ (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 18H), 2.02 and 2.16 (2s, 6H), 2.69 (m, 4H), 4.23 (m, 2H), 4.85 (d, $^3J_{HH}=7.8$ Hz,

2H), 5.76 and 5.80 (2dd, $^2J_{PH}=9.9$ Hz, $^3J_{HH}=7.8$ Hz, 2H), 7.91–7.12 (m, 32H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 29.7, 37.8, 55.2 and 55.9, 60.1 (d, $^1J_{PC}=66.5$ Hz), 79.9, 126.6–136.3 (m), 155.1, 171.5 (d, $^3J_{PC}=13.5$ Hz), 200.9 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 31.6 and 32.5 ppm; IR (KBr): 3443, 3283, 3175, 1719, 1704, 1666, 1367, 1176 cm^{-1}; MS (CI): m/z 521 (M^++1, 27). Anal. calcd for $C_{29}H_{33}N_2O_5P$: C, 66.91; H, 6.39; N, 5.38. Found C, 66.86; H, 6.39; N, 5.39.

4.3. General procedure for synthesis of diethyl 3-alkyl-(2-*tert*-butoxycarbonylaminoalkanoylamino)-2-oxoalkylphosphonate 7

To diethyl 3-alkyl-2*H*-azirinyl phosphonate **6** (5 mmol) without solvent, the *N*-protected amino acid **2** (7.5 mmol) was added under a nitrogen atmosphere, at room temperature and with continuous stirring. The mixture was heated at 70°C for 2 h. Then, the subsequent residue was purified by flash column chromatography eluting with hexane/AcOEt affording **7** and a small proportion (10–20%) of pyrazine phosphonates.[13]

4.3.1. Diethyl (±)-1-(2-*tert*-butoxycarbonylaminopropanoylamino)-2-oxopropylphosphonate (7ab). Yield 1.29 g (68%) obtained as a colorless oil from compound **6a** (0.96 g, 5 mmol) and (±)-*N*-*tert*-butoxycarbonylalanine **2b** (1.42 g, 7.5 mmol) as described in the general procedure: R_f 0.39 (AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 12H), 1.39 (s, 18H), 2.36 (2s, 6H), 4.10 (m, 10H), 5.07 (2d, $^3J_{HH}=7.2$ Hz, 2H), 5.76 (dd, $^2J_{PH}=23.3$ Hz, $^3J_{HH}=8.5$ Hz, 2H), 7.11 (d, $^3J_{HH}=8.5$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2, 18.3, 28.2, 28.9 (d), 49.9 (2s), 57.1 (2d, $^1J_{PC}=140.5$ Hz), 63.6 (2s), 80.1, 155.2, 172.3 (d, $^3J_{PC}=5.0$ Hz), 199.2 (d, $^2J_{PC}=16.2$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 15.7 and 15.8 ppm; IR (NaCl): 3270, 2861, 1725, 1709, 1679, 1590, 1165, 1113 cm^{-1}; MS (CI): m/z 381 (M^++1, 5). Anal. calcd for $C_{15}H_{29}N_2O_7P$: C, 47.36; H, 7.68; N, 7.36. Found C, 47.42; H, 7.67; N, 7.36.

4.3.2. Diethyl (+)-1-(2-(*R*)-*tert*-butoxycarbonylaminopropanoylamino)-2-oxopropylphosphonate (7ad). Yield 1.35 g (71%) obtained as a colorless oil from compound **6a** (0.96 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*R*)-alanine **2d** (1.42 g, 7.5 mmol) as described in the general procedure: $[\alpha]_D^{22}=+21.0$ (c 1.75, CH_2Cl_2). For spectroscopic data see compound **7ab**.

4.3.3. Diethyl (−)-1-(2-(*S*)-*tert*-butoxycarbonylaminopropanoylamino)-2-oxopropylphosphonate (7ae). Yield 1.25 g (66%) obtained as a colorless oil from compound **6a** (0.96 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*S*)-alanine **2e** (1.42 g, 7.5 mmol) as described in the general procedure: $[\alpha]_D^{22}=-21.0$ (c 1.75, CH_2Cl_2). For spectroscopic data see compound **7ab**.

4.3.4. Diethyl (−)-1-(2-(*S*)-*tert*-butoxycarbonylamino-3-hydroxypropanoylamino)-2-oxopropyl phosphonate (7ag). Yield 1.04 g (42%) obtained as a colorless oil from compound **6a** (0.96 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*S*)-serine **2g** (1.54 g, 7.5 mmol) as described in the general procedure: R_f 0.33 (AcOEt/MeOH 10%); $[\alpha]_D^{22}=-11.0$ (c 0.39, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (m, 12H), 1.39 (s, 18H), 2.32 (2s, 6H), 3.80–4.26 (m, 14H), 4.55 (s, 2H), 5.22 (dd, $^2J_{PH}=23.3$ Hz, $^3J_{HH}=8.4$ Hz, 2H), 5.71 (d, $^3J_{HH}=7.5$ Hz, 2H), 7.61 (d, $^3J_{HH}=8.4$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2, 28.2, 28.7, 55.7 (2s), 58.2 (d, $^1J_{PC}=141.0$ Hz), 62.9, 64.0, 80.4, 155.9, 171.2 (d, $^3J_{PC}=5.0$ Hz), 199.2 (d, $^2J_{PC}=27.7$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 16.2 and 16.6 ppm; IR (NaCl): 3310, 2924, 2852, 1723, 1710, 1699, 1591, 1164 cm^{-1}; MS (CI): m/z 397 (M^++1, 4). Anal. calcd for $C_{15}H_{29}N_2O_8P$: C, 45.45; H, 7.37; N, 7.07. Found C, 45.40; H, 7.38; N, 7.08.

4.3.5. Diethyl (+)-1-(2-(*R*)-*tert*-butoxycarbonylaminopropanoylamino)-2-oxobutylphosphonate (7bd). Yield 1.42 g (72%) obtained as a colorless oil from compound **6b** (1.03 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*R*)-alanine **2d** (1.42 g, 7.5 mmol) as described in the general procedure: R_f 0.48 (AcOEt); $[\alpha]_D^{22}=+24.4$ (c 0.47, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (t, $^3J_{HH}=7.2$ Hz, 6H), 1.18–1.36 (m, 18H), 1.39 (s, 18H), 2.52 and 2.95 (2m, 4H), 4.12 (m, 10H), 4.98 (d, $^3J_{HH}=7.5$ Hz, 2H), 5.18 (dd, $^2J_{PH}=22.7$ Hz, $^3J_{HH}=8.4$ Hz, 2H), 7.07 (d, $^3J_{HH}=8.5$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.5, 16.2, 18.2, 28.2, 34.9 (d, $^3J_{PC}=3.5$ Hz), 50.0 (2s), 57.0 (2d, $^1J_{PC}=139.5$ Hz), 63.5, 80.2, 155.3, 172.2 (d, $^3J_{PC}=5.5$ Hz), 202.4 (d, $^2J_{PC}=13.6$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 16.0 and 16.1 ppm; IR (NaCl): 3287, 2981, 2937, 2860, 1772, 1709, 1680, 1167, 977 cm^{-1}; MS (CI): m/z 395 (M^++1, 4). Anal. calcd for $C_{16}H_{31}N_2O_7P$: C, 48.72; H, 7.92; N, 7.10. Found C, 48.77; H, 7.93; N, 7.09.

4.3.6. Diethyl (−)-1-(2-(*S*)-*tert*-butoxycarbonylamino-3-hydroxypropanoylamino)-2-oxobutylphosphonate (7bg). Yield 0.89 g (35%) obtained as a colorless oil from compound **6b** (1.03 g, 5 mmol) and *N*-*tert*-butoxycarbonyl-(*S*)-serine **2g** (1.54 g, 7.5 mmol) as described in the general procedure: R_f 0.50 (AcOEt); $[\alpha]_D^{22}=-9.5$ (c 2.15, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (t, $^3J_{HH}=7.2$ Hz, 6H), 1.27 (m, 12H), 1.40 (s, 18H), 2.54 and 2.83 (2m, 4H), 3.75–4.28 (m, 14H), 4.71 (s, 2H), 5.22 (dd, $^2J_{PH}=22.6$ Hz, $^3J_{HH}=8.6$ Hz, 2H), 5.72 (d, $^3J_{HH}=7.5$ Hz, 2H), 7.60 (d, $^3J_{HH}=8.6$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.3, 16.2, 28.1, 34.7, 55.7 (2s), 57.1 (d, $^1J_{PC}=140.0$ Hz), 62.8, 63.6, 80.2, 155.7, 170.9 (d, $^3J_{PC}=5.0$ Hz), 202.1 (d, $^2J_{PC}=24.7$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 16.4 and 16.8 ppm; IR (NaCl): 3250, 2938, 2860, 1725, 1711, 1679, 1382, 1165, 979 cm^{-1}; MS (CI): m/z 511 (M^++1, <1). Anal. calcd for $C_{16}H_{31}N_2O_8P$: C, 46.83; H, 7.61; N, 6.83. Found C, 46.78; H, 7.60; N, 6.84.

4.4. General procedure for synthesis of (5-alkyl-2-*tert*-butoxycarbonylaminoalkyl)oxazol-4-yl diphenylphosphine oxide 8

To a room temperature solution of triphenylphosphine (1.70 g, 6.5 mmol) and hexachloroethane (1.54 g, 6.5 mmol), in THF a solution of 2-*tert*-butoxycarbonylamino-3-alkyl-*N*-(1-diphenylphosphinoyl-2-oxopropyl)-

alkylamide **3** was added under a nitrogen atmosphere. The mixture was stirred at that temperature for 5 min. After that, triethylamine (2.10 ml, 15 mmol) was added dropwise for 10 min. The subsequent mixture was heated at THF reflux for 20 h. The solvent was evaporated in vacuo and the residue was diluted with water and extracted with CH_2Cl_2. The organic layers where dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography eluting with AcOEt.

4.4.1. (2-*tert*-Butoxycarbonylaminomethyl-5-methyl)-oxazol-4-yl diphenylphosphine oxide (8aa). Yield 1.40 g (68%), obtained as a white solid from compound **3aa** (2.15 g, 5 mmol) as described in the general procedure: mp 104–105°C (hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.52 (s, 3H), 4.34 (d, $^3J_{HH}$= 5.1 Hz, 2H), 5.28 (s, 1H), 7.82–7.36 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 28.2, 37.8, 80.1, 126.3 (d, $^1J_{PC}$=142.0 Hz), 128.3–133.2 (m), 155.5, 159.4 (d, $^2J_{PC}$=27.1 Hz), 160.3 (d, $^3J_{PC}$=17.0 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.3 ppm; IR (KBr): 3264, 3078, 2980, 1712, 1553, 1275, 1188 cm^{-1}; MS (CI): *m*/*z* 413 (M^++1, 48). Anal. calcd for $C_{22}H_{25}N_2O_4P$: C, 64.07; H, 6.11; N, 6.79. Found C, 63.11; H, 6.12; N, 6.78.

4.4.2. (±)-[2-(1-*tert*-Butoxycarbonylaminoethyl)-5-methyl]-oxazol-4-yl diphenylphosphine oxide (8ab). Yield 1.47 g (69%), obtained as a white solid from compound **3ab** (2.22 g, 5 mmol), as described in the general procedure: mp 120–121°C (hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.43 (d, $^3J_{HH}$=7.2 Hz, 3H), 2.50 (s, 3H), 4.85 (q, $^3J_{HH}$=7.2 Hz, 1H), 5.00 (s, 1H), 7.48–7.34 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 20.1, 28.3, 44.7, 80.0, 126.3 (d, $^1J_{PC}$= 141.5 Hz), 128.3–133.6 (m), 154.9, 159.1 (d, $^2J_{PC}$=26.7 Hz), 163.8 (d, $^3J_{PC}$=17.1 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.3 ppm; IR (KBr): 3337, 2992, 2945, 1719, 1540, 1175 cm^{-1}; MS (CI): *m*/*z* 427 (M^++ 1, 33). Anal. calcd for $C_{23}H_{27}N_2O_4P$: C, 64.78; H, 6.38; N, 6.57. Found C, 64.71; H, 6.37; N, 6.58.

4.4.3. (+)-[2-(1-(*R*)-*tert*-Butoxycarbonylaminoethyl)-5-methyl]oxazol-4-yl diphenylphosphine oxide (8ad). Yield 1.53 g (72%), obtained as a white solid from compound **3ad** (2.22 g, 5 mmol), as described in the general procedure: $[\alpha]_D^{22}$=+43.4 (*c* 1.00, CH_2Cl_2). For spectroscopic data see compound **8ab**.

4.4.4. (−)-[2-(1-(*S*)-*tert*-Butoxycarbonylaminoethyl)-5-methyl]oxazol-4-yl diphenylphosphine oxide (8ae). Yield 1.41 g (66%), obtained as a white solid from compound **3ae** (2.22 g, 5 mmol), as described in the general procedure: $[\alpha]_D^{22}$=−43.4 (*c* 1.00, CH_2Cl_2). For spectroscopic data see compound **8ab**.

4.4.5. (−)-[2-(1-(*S*)-*tert*-Butoxycarbonylamino-2-phenylethyl)-5-methyl]oxazol-4-yl diphenylphosphine oxide (8ah). Yield 1.83 g (73%), obtained as a white solid from compound **3ah** (2.60 g, 5 mmol), as described in the general procedure: mp 115–116°C (hexane/AcOEt); $[\alpha]_D^{22}$=−11.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.51 (s, 3H), 3.11 (d, $^3J_{HH}$= 7.2 Hz, 2H), 5.09 (q, $^3J_{HH}$=7.2 Hz, 1H), 5.16 (s, 1H), 6.90–7.73 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 28.1, 39.8, 49.8, 79.9, 126.1 (d, $^1J_{PC}$=141.9 Hz), 126.7–135.7 (m), 154.8, 159.2 (d, $^2J_{PC}$=26.7 Hz), 162.0 (d, $^3J_{PC}$=17.1 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.8 ppm; IR (KBr): 3250, 3058, 2979, 2939, 1719, 1188 cm^{-1}; MS (CI): *m*/*z* 503 (M^++1, 45). Anal. calcd for $C_{29}H_{31}N_2O_4P$: C, 69.31; H, 6.22; N, 5.57. Found C, 69.39; H, 6.21; N, 5.56.

4.5. General procedure for synthesis of diethyl [5-alkyl-2-(1-*tert*-butoxycarbonylaminoalkyl)]oxazol-4-yl phosphonate 10

To a room temperature solution of triphenylphosphine (1.70 g, 6.5 mmol) and hexachloroethane (1.54 g, 6.5 mmol), in toluene a solution of diethyl 3-alkyl-(2-*tert*-butoxycarbonylaminoalkanoylamino)-2-oxoalkylphosphonate **7** was added under a nitrogen atmosphere. The mixture was stirred at that temperature for 5 min. After that, triethylamine (2.10 ml, 15 mmol) was added dropwise slowly for 10 min. The subsequent mixture was heated at toluene reflux and stirred for 20 h. The solvent was evaporated in vacuo and the residue was purified by precipitating in cold ethyl ether. The ethereal layers were concentrated in vacuo and the residue was ground with cold water and filtered. The aqueous layer was concentrated again affording the compounds **10** as colorless oils.

4.5.1. Diethyl (±)-[2-(1-*tert*-butoxycarbonylaminoethyl)-5-methyl]oxazol-4-yl phosphonate (10ab). Yield 0.81 g (45%), obtained as a colorless oil from compound **7ab** (1.90 g, 5 mmol), as described in the general procedure method: R_f 0.45 (AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, $^3J_{HH}$=7.0 Hz, 6H), 1.38 (s, 9H), 1.45 (d, $^3J_{HH}$=7.0 Hz, 3H), 2.49 (d, $^4J_{HH}$=1.8 Hz, 3H), 4.08 (m, 4H), 4.84 (q, $^3J_{HH}$=7.0 Hz, 1H), 5.14 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.4, 16.2 (d, $^3J_{PC}$=6.5 Hz), 20.2, 28.2, 44.7, 62.5 (d, $^2J_{PC}$=5.5 Hz), 79.9, 124.0 (d, $^1J_{PC}$=41.5 Hz), 154.8, 158.5 (d, $^2J_{PC}$=39.3 Hz), 164.1 (d, $^3J_{PC}$=21.2 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.6 ppm; IR (NaCl): 3260, 2917, 2861, 1700, 1521, 1162, 1027 cm^{-1}; MS (CI): *m*/*z* 363 (M^++1, 7). Anal. calcd for $C_{15}H_{27}N_2O_6P$: C, 49.72; H, 7.51; N, 7.73. Found C, 49.79; H, 7.52; N, 7.72.

4.5.2. Diethyl (+)-[2-(1-(*R*)-*tert*-butoxycarbonylaminoethyl)-5-methyl]oxazol-4-yl phosphonate (10ad). Yield 1.01 g (56%), obtained as a colorless oil from compound **7ad** (1.90 g, 5 mmol), as described in the general procedure: R_f 0.45 (AcOEt); $[\alpha]_D^{22}$=+39.7 (*c* 0.3, CH_2Cl_2). For spectroscopic data see compound **10ab**.

4.5.3. Diethyl (−)-[2-(1-(*S*)-*tert*-butoxycarbonylaminoethyl)-5-methyl]oxazol-4-yl phosphonate (10ae). Yield 0.91 g (50%), obtained as a colorless oil from compound **7ae** (1.90 g, 5 mmol), as described in the general procedure: R_f 0.45 (AcOEt); $[\alpha]_D^{22}$=−39.7 (*c* 0.3, CH_2Cl_2). For spectroscopic data see compound **10ab**.

4.5.4. Diethyl (+)-[2-(1-(*R*)-*tert*-butoxycarbonylamino-ethyl)-5-ethyl]oxazol-4-yl phosphonate (10bd). Yield 0.87 g (46%), obtained as a colorless oil from compound **7bd** (1.97 g, 5 mmol), as described in the general procedure: R_f 0.40 (AcOEt); $[\alpha]_D^{22}=+34.5$ (*c* 0.33, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, $^3J_{HH}=7.5$ Hz, 3H), 1.29 (t, $^3J_{HH}=7.0$ Hz, 6H), 1.38 (s, 9H), 1.45 (d, $^3J_{HH}=7.0$ Hz, 3H), 2.92 (dq, $^3J_{HH}=7.5$ Hz, $^4J_{HH}=1.8$ Hz, 2H), 4.08 (m, 4H), 4.86 (q, $^3J_{HH}=7.0$ Hz, 1H), 5.17 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 16.2 (d, $^3J_{PC}=6.5$ Hz), 19.1, 20.2, 28.2, 44.7, 62.5 (d, $^2J_{PC}=5.5$ Hz), 79.9, 123.3 (d, $^1J_{PC}=243.9$ Hz), 154.8, 163.4 (d, $^2J_{PC}=39.8$ Hz), 164.1 (d, $^3J_{PC}=21.2$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.7 ppm; IR (NaCl): 3254, 2917, 2861, 1702, 1519, 1165, 1119 cm^{-1}; MS (CI): *m*/*z* 377 (M^++1, 10). Anal. calcd for $C_{16}H_{29}N_2O_6P$: C, 51.06; H, 7.77; N, 7.44. Found C, 50.94; H, 7.76; N, 7.45.

4.6. General procedure for synthesis of (5-alkyl-2-aminoalkyl)oxazol-4-yl diphenylphosphine oxide 11

To a solution previously prepared and kept under anhydrous Na_2CO_3 of chlorotrimethylsilane 1 M and phenol 3 M in CH_2Cl_2 (15 mmol) a solution of protected oxazole **8** was added at room temperature and under a nitrogen atmosphere. The mixture was stirred at that temperature for 24 h. Then, it was washed with a NaOH 2N solution (10 ml) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under vacuum. The crude residue was ground in hexane/ether and, after filtering, was washed with the same mixture of solvents. The products were crystallized from hexane/AcOEt.

4.6.1. (2-Aminomethyl-5-methyl)oxazol-4-yl diphenylphosphine oxide (11aa). Yield 1.26 g (81%), obtained as a white solid from compound **8aa** (2.06 g, 5 mmol) as described in the general procedure: mp 131–132°C (hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (s, 2H), 2.57 (d, $^4J_{PH}=1.8$ Hz, 3H), 3.89 (s, 2H), 7.39–7.85 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 39.4, 126.2 (d, $^1J_{PC}=142.0$ Hz), 128.3–133.6 (m), 159.1 (d, $^2J_{PC}=26.7$ Hz), 163.9 (d, $^3J_{PC}=16.6$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.7 ppm; IR (KBr): 3376, 3303, 2932, 1593, 1440, 1195, 1129 cm^{-1}; MS (EI): *m*/*z* 312 (M^+, 77). Anal. calcd for $C_{17}H_{17}N_2O_2P$: C, 65.38; H, 5.49; N, 8.97. Found C, 65.31; H, 5.49; N, 8.98.

4.6.2. (−)-[2-(1-(*S*)-Aminoethyl)-5-methyl]oxazol-4-yl diphenylphosphine oxide (11ae). Yield 1.21 g (74%), obtained as a white solid from compound **8ae** (2.22 g, 5 mmol), as described in the general procedure: mp 126–127°C (hexane/AcOEt); $[\alpha]_D^{22}=-8.0$ (*c* 0.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, $^3J_{HH}=6.9$ Hz, 3H), 1.87 (s, 2H), 2.51 (s, 3H), 4.07 (q, $^3J_{HH}=6.9$ Hz, 1H), 7.36–7.82 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 21.6, 45.5, 125.9 (d, $^1J_{PC}=142.1$ Hz), 128.3–133.6 (m), 159.0 (d, $^2J_{PC}=26.7$ Hz), 166.9 (d, $^3J_{PC}=17.1$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.8 ppm; IR (KBr): 3350, 3283, 3058, 1593, 1188, 1173 cm^{-1}; MS (EI): *m*/*z* 326 (M^+, 51). Anal. calcd for $C_{18}H_{19}N_2O_2P$: C, 66.25; H, 5.87; N, 8.58. Found C, 66.21; H, 5.87; N, 8.59.

4.7. Synthesis of diethyl (+)-2-(*R*)-aminoethyl)-5-methyl-oxazol-4-yl phosphonate (12ad)

To a solution of compound **10ad** (1.81 g, 5 mmol) in AcOEt, a solution of HCl 3 M (5 ml, 15 mmol) was added dropwise slowly. The mixture was heated at AcOEt reflux for 15 h. Then, the solution was extracted with water and the aqueous layer was concentrated in vacuo. The crude residue was purified by silica gel column chromatography eluting with AcOEt/MeOH affording compound **12ad**. 0.60 g (46%), obtained as a white solid from compound **11ad** (1.81 g, 5 mmol) as described in the general procedure: R_f 0.25 (AcOEt/MeOH 25%); $[\alpha]_D^{22}=+15.0$ (*c* 0.10, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, $^3J_{HH}=6.8$ Hz, 6H), 1.77 (dd, $^3J_{HH}=6.1$ Hz, $^3J_{NH}=42.4$ Hz, 3H), 1.78 (s, 2H), 2.51 (s, 3H), 4.20 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 16.2 (d, $^3J_{PC}=6.5$ Hz), 17.5, 45.1, 63.2 (d, $^2J_{PC}=5.0$ Hz), 127.6 (d, $^1J_{PC}=226.1$ Hz), 158.4 (d, $^2J_{PC}=36.3$ Hz), 160.0 (d, $^3J_{PC}=22.1$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 10.6 ppm; IR (KBr): 3383, 3269, 1646, 1228, 1036 cm^{-1}; MS (CI): *m*/*z* 263 (M^++1, 82). Anal. calcd for $C_{10}H_{19}N_2O_4P$: C, 45.80; H, 7.30; N, 10.68. Found C, 45.90; H, 7.31; N, 10.66.

4.8. General procedure for synthesis of *N*-Boc-peptides 13 (see Ref. 3)

4.8.1. (+)-2-(*S*)-[*N*-(2-*tert*-Butoxycarbonylamino)acetyl-amino]-3-phenylpropionic acid 13a. Yield 1.29 g (80%), obtained as a white solid from Gly-Phe (1.11 g, 5 mmol) as described in the general procedure: mp 141–142°C (hexane/diethyl ether); $[\alpha]_D^{22}=+31.2$ (*c* 1.00, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9H), 2.97 (q, $^3J_{HH}=5.4$ Hz, $^2J_{HHgem}=13.5$ Hz, 1H), 3.09 (q, $^3J_{HH}=5.4$ Hz, $^2J_{HHgem}=13.5$ Hz, 1H), 3.59 (q, $^3J_{HH}=6.3$ Hz, $^2J_{HHgem}=16.8$ Hz, 1H), 3.79 (q, $^3J_{HH}=6.3$ Hz, $^2J_{HHgem}=16.8$ Hz, 1H), 4.77 (t, $^3J_{HH}=5.4$ Hz, 1H), 5.42 (s, 1H), 6.81 (d, $^3J_{HH}=6.3$ Hz, 1H), 7.07–7.20 (m, 5H), 9.21 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 37.3, 43.6, 45.1, 80.5, 127.0–135.8 (m), 156.3, 170.0 and 173.5 ppm; IR (KBr): 3469, 3370, 3032, 1728, 1626. 1560 cm^{-1}; MS (CI): *m*/*z* 341 (M^++3, 2), 339 (M^++1, 7). Anal. calcd for $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.24; H, 7.79; N, 8.29.

4.8.2. (−)-2-(*S*)-[*N*-(2-*tert*-Butoxycarbonylaminopropi-onylamino)acetylamino]acetic acid 13b. Yield 0.97 g (64%), obtained a a white solid from Ala-Gly-Gly (1.02 g, 5 mmol) as described in the general procedure: mp 76–77°C (hexane/diethyl ether); $[\alpha]_D^{22}=-7.9$ (*c* 0.52, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, $^3J_{HH}=7.2$ Hz, 3H), 1.36 (s, 9H), 3.67 (s, 2H), 3.74 (d, $^2J_{HHgem}=3.0$ Hz, 2H), 3.88 (q, $^3J_{HH}=7.2$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 28.7, 43.5, 52.2, 66.9, 80.9, 158.1, 171.7, 176.5 ppm; IR (KBr): 3400, 3356, 3310, 1750, 1692, 1672, 1626, 1527 cm^{-1}; MS (CI): *m*/*z* 304 (M^++1, 8). Anal. calcd for $C_{12}H_{21}N_3O_6$: C, 47.52; H, 6.98; N, 13.85. Found C, 47.47; H, 6.99; N, 13.87.

4.9. General procedure for synthesis of peptide containing α-ketamides 14

To a solution of 3-alkyl-2*H*-azirinyl-2-phosphine oxide **1** (1.28 g, 5 mmol) in THF (5 ml), a solution of *N*-Boc-peptide **13** (15 mmol) in THF (5 ml) is added under a nitrogen atmosphere, at −80°C and with continuous stirring. The mixture was stirred allowing to warm to room temperature for 4 days. The solvent was concentrated under vacuum, and the residue was purified by flash column chromatography eluting with AcOEt.

4.9.1. (−)-2-(*S*)-(2-*tert*-Butoxycarbonylaminoethanoylamino) - *N* - (1 - diphenylphosphinoyl - 2 - oxopropyl) - 3-phenylpropanamide (14aa). Yield 1.18 g (41%) obtained as a white solid from *N*-Boc-(*S*)-GlyPhe **13a** (4.83 g, 15 mmol) as described in the general procedure: mp:110–111°C; $[\alpha]_D^{22}=-10.7$ (*c* 0.68, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 18H), 1.99 and 2.11, (2s, 6H), 2.58 (d, $^3J_{HH}=6.3$ Hz, 4H), 2.74 (dd, $^3J_{HH}=7.2$ Hz, $^2J_{HHgem}=13.8$ Hz, 2H), 2.87 (dd, $^3J_{HH}=6.9$ Hz, $^2J_{HHgem}=13.8$ Hz, 2H),), 3.63 (m, 4H), 4.70 and 4.80 (dq, $^3J_{HH}=7.2$ Hz, 2H), 5.34 and 5.41 (2s, 2H), 5.84 and 5.76 (2dd, $^2J_{PH}=11.4$ Hz, $^3J_{HH}=9.3$ Hz, 2H), 6.45 and 6.75 (2d, $^3J_{HH}=6.9$ Hz, 2H), 6.87–8.06 (m, 32H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 29.7, 37.9, 44.0, 54.0 (2s), 60.4 (2d, $^1J_{PC}=65.5$ Hz), 80.0 (2s), 126.8–136.1 (m), 155.9, 169.4 and 170.9 (2d, $^3J_{PC}=4.0$ Hz), 200.6 (2s) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 31.2 and 31.7 ppm; IR (KBr): 3277, 3071, 2979, 2939, 1732, 1724, 1708, 1659, 1540, 1169 cm^{-1}; MS (CI): *m*/*z* 578 (M^++1, 26). Anal. calcd for $C_{31}H_{36}N_3O_6P$: C, 64.46; H, 6.28; N, 7.27. Found C, 64.44; H, 6.29; N, 7.28.

4.9.2. (+)-2-[-2-(*S*)-(2-*tert*-Butoxycarbonylamino)propanoylamino]ethanoylamino - *N* - (1 - diphenylphosphinoyl-2-oxopropyl)acetamide (14ab). Yield 1.06 g (38%) obtained as a white solid from *N*-Boc-(*S*)-AlaGlyGly (4.55 g, 15 mmol) as described in the general procedure: mp 66–67°C (hexane/AcOEt); $[\alpha]_D^{22}=+3.3$ (*c* 1.63, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (m, 24H), 2.02 (s, 6H), 2.53 (s, 2H), 3.59–4.06 (m, 8H), 4.20 (dq, $^3J_{HH}=6.2$ Hz, $^3J_{HH}=6.7$ Hz, 2H), 5.61 (d, $^3J_{HH}=6.0$ Hz, 2H), 5.76 (dd, $^2J_{PH}=10.3$ Hz, $^3J_{HH}=9.4$ Hz, 2H), 7.28 (s, 2H), 7.38–7.87 (m, 20H), 8.13 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 28.3, 29.7, 42.9, 50.5, 60.8 (d, $^1J_{PC}=64.5$ Hz), 80.0, 128.4–132.9 (m), 155.8, 168.8, 169.6 (d, $^3J_{PC}=4.0$ Hz), 173.9, 200.8 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 31.4 and 31.5 ppm; IR (KBr): 3265, 3071, 2975, 2928, 1731, 1724, 1708, 1657, 1540, 1175 cm^{-1}; MS (CI): *m*/*z* 559 (M^++1, 5). Anal. calcd for $C_{27}H_{35}N_4O_7P$: C, 58.06; H, 6.32; N, 10.03. Found C, 57.93; H, 6.31; N, 10.03.

4.10. Synthesis of diethyl (−)-1-[2-(*S*)-(2-*tert*-butoxycarbonylaminoethanoylamino)-3-phenylpropanoylamino]-2-oxobutylphosphonate (15ba)

To diethyl 3-alkyl-2*H*-azirinyl phosphonate **6** (5 mmol) without solvent, the *N*-Boc-peptide **13** (7.5 mmol) is added under a nitrogen atmosphere, at room temperature and with continuous stirring. The mixture was heated at 70°C for 2 h and the subsequent residue was purified by flash column chromatography eluting with AcOEt affording a small proportion (10–20%) of pyrazine phosphonates[13] and **15ba** (1.13 g, 43%) obtained as colorless oil from *N*-Boc-(*S*)-GlyPhe **13a** (4.83 g, 15 mmol), as described in the general procedure: R_f 0.37; $[\alpha]_D^{22}=-3.9$ (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 and 0.98 (2t, $^3J_{HH}=7.0$ Hz, 6H), 1.21 (m, 12H), 1.37 and 1.38 (2s, 18H), 2.38–3.12 (m, 8H), 3.71 (m, 4H), 3.96–4.25 (m, 10H), 5.18–5.11 (2dd, $^2J_{PH}=22.0$ and 21.5 Hz, $^3J_{HH}=8.2$ and 8.5 Hz, 2H), 7.12–7.91 (m, 14H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.4, 16.2, 28.2, 34.7 (d, $^3J_{PC}=15.6$ Hz), 37.9 and 38.2, 44.1, 53.8 and 54.1 (2s), 57.1 (d, $^1J_{PC}=141.5$ Hz), 63.5, 80.0 (2s), 126.8–136.2 (m), 155.9, 169.5 and 169.7 (2s), 170.4 and 170.5 (2d, $^3J_{PC}=5.0$ and 6.0 Hz), 202.4 (d, $^2J_{PC}=26.7$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 16.0 and 16.1 ppm; IR (NaCl): 3255, 3065, 2983, 2935, 1730, 1724, 1708, 1682, 1165 cm^{-1}; MS (CI): *m*/*z* 528 (M^++1, 3). Anal. calcd for $C_{24}H_{38}N_3O_8P$: C, 54.64; H, 7.26; N, 7.97. Found C, 54.69; H, 7.25; N, 7.96.

4.11. General procedures for synthesis of peptide containing oxazoles 16 and 17

To a room temperature solution of triphenylphosphine (1.70 g, 6.5 mmol) and hexachloroethane (1.54 g, 6.5 mmol), in toluene a solution of peptide containing α-ketamides **14** and **15** was added under a nitrogen atmosphere. The mixture was stirred at that temperature for 5 min. After that, triethylamine (2.10 ml, 15 mmol) was added dropwise for 10 min. The mixture was heated at toluene reflux for 1–3 days. The solvent was evaporated in vacuo and the residue was diluted with water and extracted with CH_2Cl_2. The organic layers where dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography eluting with AcOEt.

4.11.1. (−)-2-[(1-(*S*)-*tert*-Butoxycarbonylaminoethanoylamino)-2-phenylethyl]-5-methyloxazol-4-yl diphenylphosphine oxide 16aa. Yield 1.45 g (52%) obtained as a white solid from compound **14aa** (2.89 g, 5 mmol) as described in the general procedure: mp 74–75°C; $[\alpha]_D^{22}=-6.6$ (*c* 0.50, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.51 (s, 3H), 3.20 (t, $^3J_{HH}=5.8$, 4.9 Hz, 2H), 3.75 (m, 2H), 5.18 (s, 1H), 5.47 (q, $^3J_{HH}=6.0$, 7.2 Hz), 6.83–7.77 (m, 16H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 28.2, 39.4, 44.3, 48.4, 80.2, 126.9–135.5 (m), 155.9, 159.3 (d, $^2J_{PC}=26.7$ Hz), 161.5 (d, $^3J_{PC}=17.1$ Hz), 169.0 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.6 ppm; IR (KBr): 3277, 3071, 2979, 2939, 1732, 1724, 1708, 1659, 1540, 1169 cm^{-1}; MS (CI): *m*/*z* 560 (M^++1, 53). Anal. calcd for $C_{31}H_{34}N_3O_5P$: C, 66.55; H, 6.12; N, 7.51. Found C, 66.48; H, 6.11; N, 7.51.

4.11.2. Diethyl (−)-2-[(1-(*S*)-*tert*-butoxycarbonylaminoethanoylamino)-2-phenylethyl]-5-ethyloxazol-4-yl phosphonate 17ba. Yield 1.27 g (50%) obtained as a colorless oil from compound **15ba** (2.63 g, 5 mmol) as described in the general procedure: R_f 0.38; $[\alpha]_D^{22}=-3.6$ (*c* 0.30, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, $^3J_{HH}=$

7.5 Hz, 3H), 1.30 (q, $^3J_{HH}=7.1$ Hz, 6H), 1.45 (s, 9H), 2.93 (m, 2H), 3.20 (d, $^3J_{HH}=6.3$ Hz, 2H), 3.82 (m, 2H), 4.08 (m, 4H), 5.12 (s, 1H), 5.48 (q, $^2J_{HH}=7.0$, 1H), 6.74–7.26 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7, 16.2 (d, $^3J_{PC}=4.5$ Hz), 19.1, 28.3, 40.0, 48.5, 62.5 (d, $^2J_{PC}=4.5$ Hz), 80.3, 123.0 (d, $^1J_{PC}=241.2$ Hz), 127.0–135 (m), 155.8, 161.8 (d, $^3J_{PC}=20.7$ Hz), 163.8 (d, $^2J_{PC}=39.8$ Hz), 168.9 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 10.2 ppm; IR (NaCl): 3283, 2979, 2925, 1712, 1672, 1513, 1367, 1255, 1162, 1029 cm^{-1}; MS (CI): m/z 510 (M^++1, 100). Anal. calcd for $C_{24}H_{36}N_3O_7P$: C, 56.57; H, 7.12; N, 8.25. Found C, 56.62; H, 7.12; N, 8.24.

Acknowledgements

The present work has been supported by the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, BQU2000-0217) and by the Universidad del País Vasco (UPV, G11/99). J.I.G. and J.M.A. thank the Universidad del País Vasco and the Ministerio de Educación y Cultura (Madrid) for predoctoral fellowships.

References

1. For recent reviews on oxazoles, see: (a) Lewis, J. R. *Nat. Prod. Rep.* **2001**, *18*, 95–128; (b) Boyd, G. V. *Prog. Heterocyclic Chem.* **1999**, *11*, 213–229; (c) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *115*, 417–437; (d) Hartner, F. W. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W., Eds.; Elsevier: Oxford, 1996; Vol. 3, pp. 261–318.
2. For recent contributions, see: (a) Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, *43*, 935–938; (b) Berger, R.; Shoop, W. L.; Pivnichny, J. V.; Warmke, L. M.; Zakson-Aiken, M.; Owens, K. A.; de Montigny, P.; Schamatz, D. M.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T.; Coletti, S. L. *Org. Lett.* **2001**, *3*, 3715–3718; (c) Yokokawa, F.; Asano, T.; Shiori, T. *Tetrahedron* **2001**, *57*, 6311–6327; (d) Radspieler, A.; Liebscher, J. *Tetrahedron* **2001**, *57*, 4867–4871; (e) Yokokawa, F.; Asano, T.; Shiori, T. *Org. Lett.* **2000**, *2*, 4169–4172.
3. For recent reviews, see: (a) Lewis, J. R. *Nat. Prod. Rep.* **2000**, *17*, 57–84; (b) Davies, J. S. *Amino Acids Pept. Proteins* **2000**, *31*, 285–335; (c) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249–263; (d) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 371–395; (e) Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1–10.
4. For recent contributions, see: (a) Wipf, P.; Methot, J. L. *Org. Lett.* **2001**, *3*, 1261–1264; (b) Xia, Z.; Smith, C. D. *J. Org. Chem.* **2001**, *66*, 3459–3466; (c) Ducruet, A. P.; Rice, R. L.; Tamura, K.; Yokokawa, F.; Yokokawa, S.; Wipf, P.; Lazo, J. S. *Bioorg. Med. Chem.* **2000**, *8*, 1451–1466; (d) Vogt, A.; Wang, A. S.; Johnson, C. S.; Fabisiak, J. P.; Wipf, P.; Lazo, J. S. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 530–537; (e) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897–6900; (f) Haberhauer, G.; Smgyi, L.; Rebek, J. *Tetrahedron Lett.* **2000**, *41*, 5013–5016; (g) Vedejs, E.; Barda, D. *Org. Lett.* **2000**, *2*, 1033–1035; (h) Bertram, A.; Pattenden, G. *Synlett* **2000**, 1519–1521.
5. For reviews, see: (a) Engel, R. *Handbook of Organophosphorus Chemistry*; Marcel Dekker: New York, 1992; (b) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur* **1991**, *63*, 193–215; (c) Toy, A. D. F.; Walsh, E. N. *Phosphorus Chemistry in Everyday Living*; American Chemical Society: Washington, DC, 1987; p. 333.
6. (a) Palacios, F.; Aparicio, D.; de los Santos, J. M.; Vicario, J. *Tetrahedron* **2001**, *57*, 1961–1972; (b) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1999**, *55*, 13767–13778; (c) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **1998**, *54*, 2281–2288; (d) Palacios, F.; Pagalday, J.; Piquet, V.; Dahan, F.; Baceiredo, A.; Bertrand, G. *J. Org. Chem.* **1997**, *62*, 292–296.
7. (a) Palacios, F.; Aparicio, D.; García, J.; Vicario, J.; Ezpeleta, J. M. *Eur. J. Org. Chem.* **2001**, 3357–3365; (b) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; García, J.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 3105–3116.
8. (a) Palacios, F.; Oyarzabal, J.; Pascual, S.; Ochoa de Retana, A. M. *Org. Lett.* **2002**, *4*, 769–772; (b) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941–1946; (c) Palacios, F.; Aparicio, D.; García, J.; Rodríguez, E.; Fernandez, A. *Tetrahedron* **2001**, *57*, 3131–3141; (d) Palacios, F.; Herran, E.; Rubiales, G. *J. Org. Chem.* **1999**, *64*, 6239–6246.
9. (a) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; López de Munain, R. *Tetrahedron Lett.* **2002**, *43*, 5917–5919; (b) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 3091–3104; (c) Barluenga, J.; López, F.; Palacios, F. *Tetrahedron Lett.* **1987**, *28*, 4327–4328.
10. For recent reviews on azirines, see: (a) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; de los Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219–269; (b) Gilchrist, T. L. *Aldrichim. Acta* **2001**, *34*, 51–55; (c) Zwannenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 94–124; (d) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401–2414.
11. Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213–3217.
12. (a) For the asymmetric synthesis of 2*H*-azirine-2-phosphonates from oximes, see: Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I. *Tetrahedron Lett.* **2000**, *41*, 5363–5366; (b) For the asymmetric synthesis of regioisomeric mixtures of 2*H*-azirine-2-phosphonates and -3-phosphonates from aziridines, see: Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655–658; (c) Davis, F. A.; McCoull, W. *Tetrahedron Lett.* **1999**, *40*, 249–252.
13. Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Lopez de Munain, R. *Org. Lett.* **2002**, *4*, 2405–2408.
14. Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Alonso, J. M. *J. Org. Chem.* **2002**, *67*, 7283–7288.
15. For a review, see: Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238–264.
16. For recent contributions, see: (a) Koch, K. N.; Linden, A.; Heimgartner, H. *Tetrahedron* **2001**, *57*, 2311–2326; (b)

Koch, K. N.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 1881–1900; (c) Koch, K. N.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 233–257; (d) Lehmann, J.; Linden, A.; Heimgartner, H. *Tetrahedron* **1999**, *55*, 5359–5376.

17. (a) Breitenmoser, R. A.; Hirt, T. R.; Luykx, R. T. N.; Heimgartner, H. *Helv. Chim. Acta* **2001**, *84*, 972–979 and references cited therein; (b) Straasler, C.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1997**, *80*, 1528–1554; (c) Villalgordo, J. M.; Heimgartner, H. *Helv. Chim. Acta* **1997**, *80*, 748–766; (d) Bucher, C.; Heimgartner, H. *Helv. Chim. Acta* **1996**, *79*, 1903–1915; (e) Bucher, C.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 935–946; (f) Villalgordo, J. M.; Heimgartner, H. *Helv. Chim. Acta* **1992**, *75*, 1866–1871; (g) Wipf, P.; Heimgartner, H. *Helv. Chim. Acta* **1990**, *73*, 13–24; (h) Sahebi, M.; Wipf, P.; Heimgartner, H. *Tetrahedron* **1989**, *45*, 2999–3010; (i) Wipf, P.; Heimgartner, H. *Helv. Chim. Acta* **1988**, *71*, 140–154.
18. For reviews, see: (a) Kafarski, P.; Lejczak, B. *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; Kukhar, V. P.; Hudson, H. R., Eds.; Wiley: Chichester, 2000; pp. 173–195 and 407–435; (b) Hiratake, J.; Oda, J. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211–218.
19. For recent contributions, see: (a) Cristau, H. J.; Coulombeau, A.; Genevis-Borella, A.; Pirat, J. L. *Tetrahedron Lett.* **2001**, *42*, 4491–4494; (b) Georgiadis, D.; Dive, V.; Yiotakis, A. *J. Org. Chem.* **2001**, *66*, 6604–6610; (c) Wallace, E. M.; Moliterni, J. A.; Moskal, M. A.; Neubart, A. D.; Marcopulos, N.; Stamford, L. B.; Trapani, A. J.; Savage, P.; Chou, M.; Jeng, A. Y. *J. Med. Chem.* **1998**, *41*, 1513–1523; (d) Meyer, J. H.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4600–4609; (e) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502–509; (f) Lohse, P. A.; Felber, R. *Tetrahedron Lett.* **1998**, *39*, 2067–2070; (g) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8177–8190.
20. The protection of amino acids **2** and peptides **13** was performed with the di-*tert*-butoxycarbonyl group (Boc) by using (^{t}BuOCO$_2$)O, NaOH, H_2O, ^{t}BuOH. See: Keller, O.; Keller, W. E.; Look, G. V.; Wersin, G. *Org. Synth. Coll. Vol. VII* **1990**, 70–75.
21. The ratio of both diastereoisomers was determined by ^{31}P NMR.
22. A small proportion of pyrazine phosphonates (10–20%) were also obtained as a result of dimerization of the starting azirines **6**.[13]
23. (a) Vorbrüeggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353–9372; (b) Vorbrüeggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471–4474.
24. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.
25. Appel, R.; Schöler, H. *Chem. Ber.* **1977**, *110*, 2382–2384.
26. Kaiser, E.; Tam, J. P.; Kubiak, T. M.; Merrifield, R. B. *Tetrahedron Lett.* **1988**, *29*, 303–306.
27. Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285–2286.