A Regioselective Route to 5-Substituted Isoxazole- and Isoxazoline-3-phosphonates

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Received 2 October 2008; revised 17 October 2008

Abstract: 5-Substituted 3-(diethoxyphosphoryl)isoxazoles and -2-isoxazolines were synthesized regioselectively by 1,3-dipolar cycloaddition of (diethoxyphosphoryl)formonitrile oxide to monosubstituted alkynes and alkenes. By applying this methodology to an *N*-(*tert*-butoxycarbonyl)-substituted allylglycine methyl ester, we prepared the precursors of two diastereomeric 3-phosphono-2-isoxazolin-5-yl-substituted amino acids, which are bioisosteres of potent NMDA receptor antagonists.

Key words: cycloadditions, regioselectivity, phosphonates, isoxazoles, heterocycles

Isoxazole- and 2-isoxazoline-3-carboxylates are synthetic targets of the utmost importance in the pharmaceutical industry, since such heterocyclic moieties represent the core structures of numerous compounds provided with different biological activities. Recent reports indicate the isoxazole-3-carboxylate chemotype as the structural motif of derivatives capable of inhibitory activity at the 11β-hydroxysteroid dehydrogenase, which could be used to treat diabetes,[2] and against enzymes involved in bacterial lysine biosynthesis[3] as well as potent serotonin reuptake inhibitors, which could lead to novel antidepressants.[4] On the other hand, the 2-isoxazoline-3-carboxylate moiety is present in natural compounds such as calafianin,[5–7] a spiroisoxazoline derivative produced by the marine sponge *Aplysia gerardogreeni* and provided with antimicrobial activity. Furthermore, some 2-isoxazoline-3-carboxyamides linked to the piperazine nucleus have been found to be quite potent α1a/α1d adrenoreceptor antagonists.[8]

Nevertheless, the glutamatergic field is the one where the isoxazole- and 2-isoxazoline-3-carboxylate cores are present with a substantial number of representatives. The heterocyclic moiety has been used both to rigidify the glutamate skeleton and to homologate the structure of glutamic acid.[9] The most appealing achievement has been the discovery of 2-amino-3-(3-carboxy-5-methylisoxazol-4-yl)propionic acid (ACPA), which turned out to be a very potent and highly selective agonist of the AMPA receptors, the ionotropic glutamate receptor subtypes named after the acronym of its most selective agonist.[9] Subsequently, the racemate has been resolved and the eutomer turned out to be the one with the *S* configuration at the stereogenic center, namely (*S*)-ACPA [(*S*)-**1**, Figure 1].[10] A number of analogues with different substituents at C-5 were prepared and tested at ionotropic and metabotropic glutamate receptors.[10,11]

Recently, we took as a lead compound tricholomic acid [(+)-**2**, Figure 1], a naturally occurring glutamate analogue present in different species of poisonous mushrooms,[12–14] to prepare and test its higher homologues **3a**,**b** and **4a**,**b**.[15,16] While the pharmacological profile of (+)-**2** largely resembles that of the endogenous neurotransmitter,[17] the one-carbon elongation of the chain connecting the two pharmacophoric entities, i.e. the amino acid moiety and the distal carboxylate group, brought about a noticeable selectivity for AMPA receptors.[15] A further one-carbon elongation of the spacer connecting the two pharmacophoric entities resulted in a marked increase in both affinity and selectivity for the NMDA receptors, accompanied by a switch in the pharmacological behavior from agonist to antagonist.[16,18]

It is amply documented[19] that the replacement of the distal carboxylate group of NMDA antagonists by the bioisosteric phosphonate moiety significantly increases the potency. As a matter of fact, such a bioisosteric modification transforms a weak NMDA antagonist such as (*R*)-2-aminoadipic acid (**5**) into the quite potent (*R*)-2-amino-5-phosphonopentanoic acid (**6**, AP-5, Figure 1).[19] The same trend is observed on passing from 4-(3-carboxypropyl)piperazine-2-carboxylic acid (**7**) to 4-(3-phosphonopropyl)piperazine-2-carboxylic acid (**8**, CPP, Figure 1), which is a commonly used pharmacological tool to characterize NMDA receptors.[19]

In connection with our ongoing medicinal chemistry project aimed at the discovery of novel potent NMDA antagonists, we planned the synthesis of compounds **9a**,**b** and **10a**,**b** (Figure 1), the phosphonate analogues of derivatives **3a**,**b** and **4a**,**b**.

As a preliminary exploratory investigation, we tested the 1,3-dipolar cycloaddition of (diethoxyphosphoryl)formonitrile oxide (**12**), generated in situ from the corresponding oxime **11**, to monosubstituted alkynes **13a–d** and alkenes **14a–d** (Scheme 1). Herein we describe the highly regioselective synthesis of 5-substituted isoxazoles **15a–d** and 5-substituted 2-isoxazolines **16a–d** bearing at the 3-position the diethyl phosphonate moiety (Scheme 1). Subsequently, we reacted the 1,3-dipole **12**

SYNTHESIS 2009, No. 4, pp 0591–0596
Advanced online publication: 27.01.2009
DOI: 10.1055/s-0028-1083343; Art ID: Z22308SS

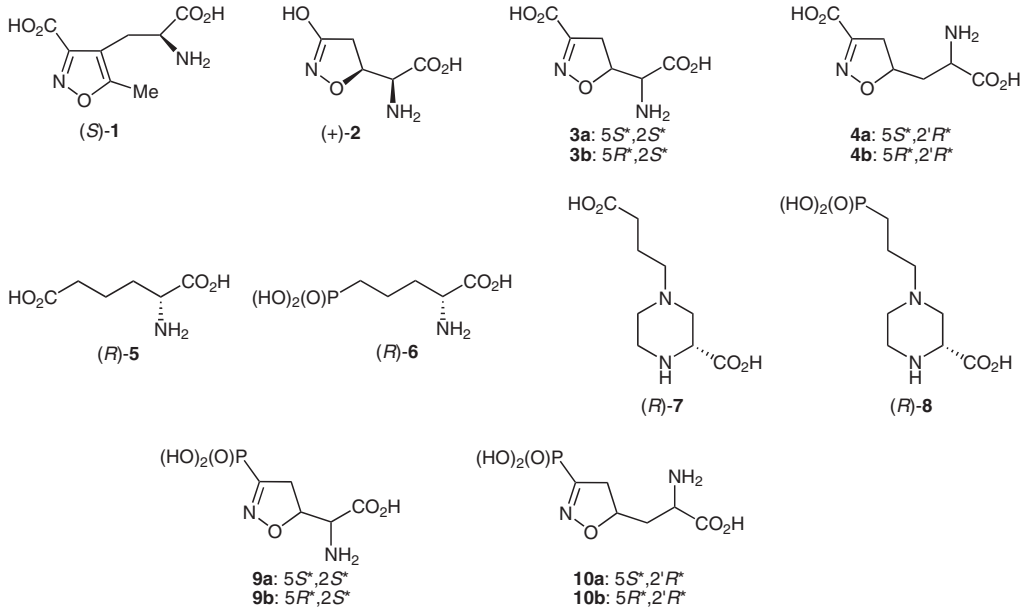
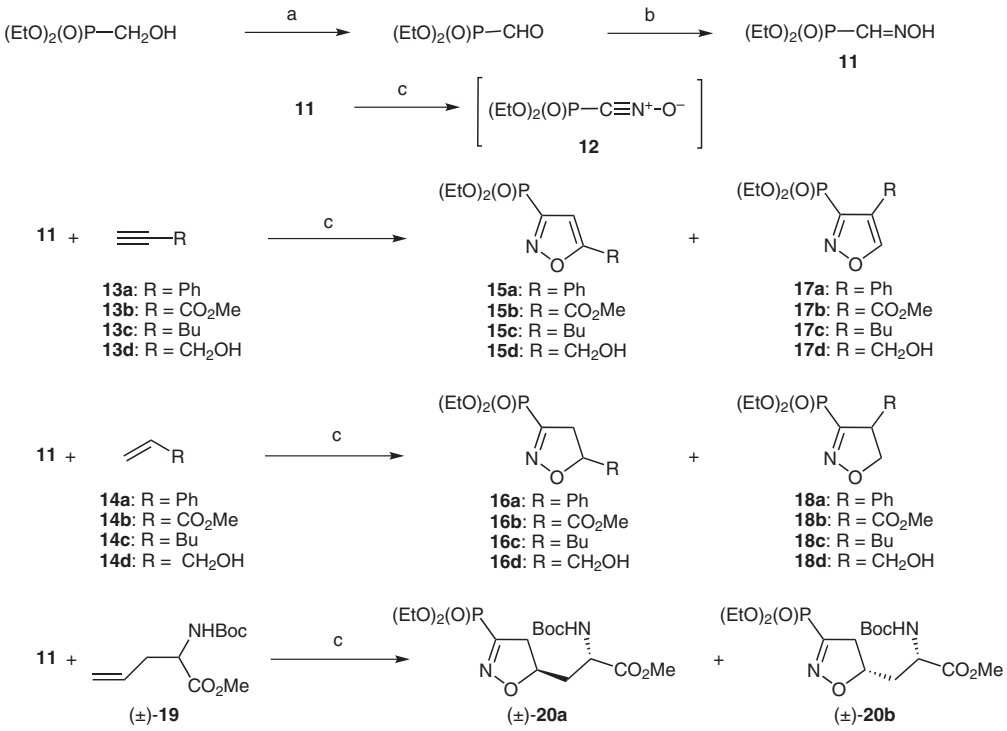


Figure 1 Structures of reference compounds **1**, (+)-**2**, **3a**,**b**, **4a**,**b**, (*R*)-**5**, (*R*)-**6**, (*R*)-**7**, and (*R*)-**8** and target compounds **9a**,**b** and **10a**,**b**



Scheme 1 *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, –78 °C; (b) $NH_2OH{\cdot}HCl$, CH_2Cl_2, –15 °C; (c) NaClO, CH_2Cl_2.

with a suitably protected allylglycine to yield cycloadducts **20a**,**b**, intermediates of final amino acids **10a**,**b**.

Nitrile oxides can be generated in a variety of ways, e.g. dehydration of primary nitroalkanes (Mukaiyama's procedure),[20] thermolysis of hydroximoyl halides,[21] and oxidation of oximes with a variety of oxidizing reagents.[22] Usually, the most practical and scalable method is the in situ technique based on the dehydrohalogenation of hydroximoyl halides by treatment with a base (Huisgen's procedure).[23] Serious drawbacks are associated with this protocol since hydroximoyl halides are usually strong irritants, causing severe skin allergies even when handled with care. In addition, the competing dimerization to furoxan prevents its application to sluggish dipolarophiles. This limitation can be partially overcome through a slow generation of the nitrile oxide either by a dropwise addition of a base or by using a solid base in a heterogeneous medium. According to a recent report, nitrile oxides can be efficiently generated in situ from the corresponding aldoximes by using bleach as the chlorinating agent,

which also provides the basic conditions to perform the dehydrochlorination step.[24]

A careful survey of the literature shows that phosphorylnitrile oxides have been generated both by dehydrochlorination of the (diisopropoxyphosphoryl)hydroximoyl chloride[25,26] and dehydration of diethyl (nitromethyl)phosphonate.[27] Nevertheless, the two reagents could only be prepared in low yield by rather complicated procedures.[28,29]

Recent papers reported the synthesis of some (diethoxyphosphoryl)nitrones and their 1,3-dipolar cycloaddition to an array of dipolarophiles.[30,31] The procedure is based on the Swern oxidation of the commercially available diethyl (hydroxymethyl)phosphonate to yield diethyl formylphosphonate, which in turn was condensed with *N*-alkylhydroxylamines. Diethyl formylphosphonate was not characterized, but directly condensed with the *N*-alkylhydroxylamines, since it is chemically unstable, and at –10 °C undergoes decomposition to carbon monoxide and diethyl phosphite.[32]

Following the same strategy, we prepared diethyl formylphosphonate, which was immediately reacted with hydroxylamine at –30 °C to give (diethoxyphosphoryl)formaldehyde oxime (**11**) in 63% yield (Scheme 1). To a dichloromethane solution of oxime **11** and a threefold excess of dipolarophile, bleach was added dropwise. All the cycloaddition reactions reported in Scheme 1 were run under comparable conditions and the reactions were allowed to proceed until disappearance of the (diethoxyphosphoryl) formaldehyde oxime. Major isomers **15a–d** and **16a–d** were isolated after column chromatography, and fully characterized by spectroscopic and analytical methods, whereas minor regioisomers **17a–d** and **18a–d** were detected by high-resolution gas chromatography and identified through their mass spectra. The ratios of the regioisomeric pairs **15a–d/17a–d** and **16a–d/18a–d** were evaluated by high-resolution gas chromatography–FID analysis and the relative percentages are reported in Table 1.

Table 1 Cycloaddition between (Diethoxyphosphoryl)formonitrile Oxide **12** and Dipolarophiles **13a–d** and **14a–d**

Dipolarophile	R	Products (ratio)[a]	Yield[b] (%)
13a	Ph	**15a/17a** (99.9:0.1)	48
13b	CO_2Me	**15b/17b** (96.4:3.6)	41
13c	Bu	**15c/17c** (94.4:5.6)	25
13d	CH_2OH	**15d/17d** (96.4:3.6)	36
14a	Ph	**16a/18a** (99.7:0.3)	26
14b	CO_2Me	**16b/18b** (98.8:1.2)	22
14c	Bu	**16c/18c** (98.4:1.6)	18
14d	CH_2OH	**16d/18d** (97.6:2.4)	36

[a] Ratio determined by HRGC-FID analysis of the crude reaction mixture.
[b] Yield of isolated product **15** or **16**.

The almost unidirectional behavior observed in the cycloaddition of nitrile oxide **12** to monosubstituted alkynes **13** and alkenes **14** parallels the results obtained with the thoroughly studied benzonitrile oxide.[22] As an application of this methodology, we then prepared the two diastereomeric cycloadducts **20a** and **20b** (Scheme 1), direct precursors of amino acids **10a** and **10b**, which are bioisosteres of the potent NMDA receptor antagonists **4a** and **4b**. The cycloaddition reaction was carried out following the above described procedure and using (±)-**19**, a suitably protected allylglycine, as the dipolarophile. The two cycloadducts **20a** and **20b** were formed in 46% overall yield and in a 52:48 ratio, as established by HPLC analysis of the crude reaction mixture. Flash chromatography allowed the recovery of the unchanged alkene and the separation of the two diastereomers **20a** and **20b**. The stereochemistry of the cycloadducts was assigned by comparing their ^{1}H NMR spectra with those of the corresponding 3-ethoxycarbonyl analogues.[33] In particular, we took into account the two hydrogens of the methylene group of the side chain, which give rise to an overlapped multiplet resonating in the region of δ = 2.10–2.22, in the case of diastereomer **20a**, while they resonate as two distinct signals in the case of **20b**, appearing as a multiplet in the region of δ = 1.74–2.00 and a doublet of doublets of doublets at δ = 2.16.

All reagents were purchased from Sigma. *N*-Boc-protected allylglycine methyl ester (±)-**19** was prepared according to a literature procedure.[33] TLC analyses were performed on commercial silica gel 60 F_{254} aluminum sheets; spots were visualized by spraying with a dilute alkaline $KMnO_4$ soln. ^{1}H NMR (300 MHz), ^{13}C NMR (75.5 MHz), and ^{31}P NMR (121.5 MHz) spectra were recorded on a Varian Mercury 300 spectrometer of samples in $CDCl_3$ soln at 20 °C. The HRGC-FID analyses were performed using an Agilent Technologies (Palo Alto, CA) model HP 6890 series equipped with a split–splitless injector, electronic pressure control, HP 6890 autosampler, and flame ionization detector (FID). The column used was an HP5 (5% phenyl methyl silicone) fused-silica capillary column (15 m, 0.32 mm i.d., 0.25 μm film thickness), which was also obtained from Agilent Technologies. H_2 and He were used as the carrier and preparation gas, respectively. The flow rate of H_2 was 1.3 mL/min; air He and H_2 were of high-purity grade. Temperature programming was used for the successful elution of all the peaks of interest. The column temperature was programmed from an initial 100–280 °C at 10 °C/min; the total analysis time was 20 min. The injector and detector temperatures were 280 and 300 °C, respectively. The injector was operated in split mode with a split rate of 30:1. The HRGC-MS analyses were performed using a Varian ion trap Saturn 2100 with MSn-option and multi CI option coupled with a Varian 3800 gas chromatograph. The column and the method used were the same as that described above. The ion trap was operated in full scan mode, detecting ions between *m*/*z* = 50 and 650. The HPLC analysis was performed using a Varian model Prostar chromatograph with autosampler and UV-DAD detector (ProStar 335). Separation was obtained on a normal-phase column (LichroCart 125-4, Lichrospher Si 60 5 μm from Merck). The injection was effected through a 10μL loop. Mobile phase: A = *n*-hexane, B = *i*-PrOH; gradient: 20–50% of B in 10 min; flow rate: 1.0 mL/min (47 bar); column temperature 25 °C; detection at 220 nm; run time 10 min.

(Diethoxyphosphoryl)formaldehyde Oxime (11)

DMSO (44 mmol, 3.1 mL) was added to a soln of oxalyl chloride (22 mmol, 1.86 mL) in CH_2Cl_2 (90 mL), cooled at –78 °C under N_2. After 2 min, a soln of diethyl(hydroxymethyl)phosphonate (20 mmol, 2.95 mL) in CH_2Cl_2 (20 mL) was added dropwise. After 15 min, Et_3N (170 mmol, 23.7 mL) was added dropwise. The temperature was increased to –15 °C over 3.5 h. MS (7.2 g, diameter ~2 mm, pore diameter 3 Å, water adsorption capacity ≥15%) were added to the reaction flask followed by $NH_2OH{\cdot}HCl$ (70 mmol, 4.86 g). The mixture was stirred at –15 °C overnight. The white suspension was washed with 1 N HCl (150 mL). After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by column chromatography (EtOAc); this afforded compound **11**.

Yield: 2.27 g (63%); yellow oil; R_f = 0.39 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.2 Hz, 6 H), 4.13 (dq, J = 7.2, 7.2 Hz, 4 H), 7.50 (d, J = 38.5 Hz, 1 H), 11.43 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 ($J_{C–P}$ = 6.2 Hz), 63.4 (d, $J_{C–P}$ = 6.0 Hz), 141.7 (d, $J_{C–P}$ = 220.8 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 9.52.

Anal. Calcd for $C_5H_{12}NO_4P$: C, 33.16; H, 6.68; N, 7.73. Found: C, 33.42; H, 6.75; N, 7.60.

Cycloaddition of 11 to Alkynes 13; General Procedure

Oxime **11** (145 mg, 0.8 mmol) was added to a soln of alkyne **13** (2.4 mmol) in CH_2Cl_2 (3.5 mL). While the mixture was cooled in an ice bath, a 3.5% soln of NaOCl (3.4 mL, 1.6 mmol) was added slowly, dropwise. The reaction mixture was stirred at 25 °C for 2 h. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried (Na_2SO_4). HR–GCMS analysis of the crude material, obtained after evaporation of the solvent, showed the formation of regioisomers **15** and **17**. The relative ratios of **15** and **17** were determined by HRGC-FID analysis and are reported in Table 1. The crude material was purified by flash column chromatography (silica gel) to give isoxazoles **15**. The yields are reported in Table 1.

Isoxazole 15a

R_f = 0.3 (PE–EtOAc, 1:1); HRGC: t_R = 10.58 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (td, J = 0.6, 7.0 Hz, 6 H), 4.22–4.35 (m, 4 H), 6.82 (d, J = 1.2 Hz, 1 H), 7.45–7.51 (m, 3 H), 7.78–7.82 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (m), 63.9 (m), 102.2 (m), 126.3, 126.7, 129.4, 131.0, 156.6 (d, $J_{C–P}$ = 210.9 Hz), 171.1 (d, $J_{C–P}$ = 10.2 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 5.60.

Anal. Calcd for $C_{13}H_{16}NO_4P$: C, 55.52; H, 5.73; N, 4.98. Found: C, 55.48; H, 5.92; N, 4.73.

Isoxazole 17a

HRGC retention time: 8.94 min.

Isoxazole 15b

R_f = 0.35 (PE–EtOAc, 1:1); HRGC: t_R = 6.87 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, J = 7.0 Hz, 6 H), 3.98 (s, 3 H), 4.20–4.33 (m, 4 H), 7.18 (d, J = 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (m), 53.4 (m), 64.2 (m), 111.9 (m), 156.7, 157.0 (d, $J_{C–P}$ = 212.0 Hz), 161.0 (d, $J_{C–P}$ = 10.0 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 3.49.

Anal. Calcd for $C_9H_{14}NO_6P$: C, 41.07; H, 5.36; N, 5.32. Found: C, 41.34; H, 5.46; N, 5.11.

Isoxazole 17b

HRGC: t_R = 6.42 min.

Isoxazole 15c

R_f = 0.65 (EtOAc); HRGC: t_R = 7.29 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.3 Hz, 3 H), 1.36 (t, J = 7.0 Hz, 6 H), 1.32–1.46 (m, 2 H), 1.63–1.75 (m, 2 H), 2.75–2.85 (m, 2 H), 4.16–4.32 (m, 4 H), 6.28 (d, J = 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 16.5 (m), 22.3, 26.4, 29.7, 63.7 (m), 103.5 (m), 155.8 (d, $J_{C–P}$ = 211.8 Hz), 175.0 (d, $J_{C–P}$ = 10.5 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 6.30.

Anal. Calcd for $C_{11}H_{20}NO_4P$: C, 50.57; H, 7.72; N, 5.36. Found: C, 50.78; H, 7.79; N, 5.11.

Isoxazole 17c

HRGC: t_R = 7.00 min.

Isoxazole 15d

R_f = 0.3 (EtOAc); HRGC: t_R = 7.53 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.0 Hz, 6 H), 4.12–4.26 (m, 4 H), 4.58 (br s, 1 H), 4.76 (s, 2 H), 6.46 (d, J = 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (m), 56.3 (m), 64.1 (m), 104.2 (m), 155.4 (d, $J_{C–P}$ = 212.7 Hz), 174.1 (d, $J_{C–P}$ = 10.0 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 5.83.

Anal. Calcd for $C_8H_{14}NO_5P$: C, 40.86; H, 6.00; N, 5.96. Found: C, 41.13; H, 6.10; N, 5.77

Isoxazole 17d

HRGC: t_R = 5.17 min.

Cycloaddition of 11 to Alkenes 14; General Procedure

Oxime **11** (145 mg, 0.8 mmol) was added to a soln of alkene **14** (2.4 mmol) in CH_2Cl_2 (3.5 mL). While the mixture was cooled in an ice bath, a 3.5% soln of NaOCl (3.4 mL, 1.6 mmol) was added slowly, dropwise. The reaction mixture was stirred at 25 °C for 2 h. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried (Na_2SO_4). HR–GCMS analysis of the crude material, obtained after evaporation of the solvent, showed the formation of regioisomers **16** and **18**. The relative ratios of **16** and **18** were determined by HRGC-FID analysis and are reported in Table 1. The crude material was purified by flash column chromatography (silica gel) to give isoxazolines **16**. The yields are also reported in Table 1.

Isoxazoline 16a

R_f = 0.53 (EtOAc); HRGC: t_R = 10.09 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, J = 7.0 Hz, 3 H), 1.39 (t, J = 7.0 Hz, 3 H), 3.19 (ddd, J = 1.5, 8.5, 17.3 Hz, 1 H), 3.62 (ddd, J = 1.5, 11.4, 17.3 Hz, 1 H), 4.18–4.31 (m, 4 H), 5.66 (dd, J = 8.5, 11.4 Hz, 1 H), 7.26–7.41 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (m), 44.9 (d, $J_{C–P}$ = 18.5 Hz), 63.9 (m), 83.0 (m), 126.0, 128.8, 129.1, 139.9, 151.0 (d, $J_{C–P}$ = 213.5 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 6.20.

Anal. Calcd for $C_{13}H_{18}NO_4P$: C, 55.12; H, 6.41; N, 4.94. Found: C, 55.01; H, 6.55; N, 4.73.

Isoxazoline 18a

HRGC: t_R = 9.21 min.

Isoxazoline 16b
R_f = 0.33 (EtOAc); HRGC: t_R = 7.67 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.0 Hz, 6 H), 3.47 (m, 2 H), 3.79 (s, 3 H), 4.16–4.28 (m, 4 H), 5.08 (dd, *J* = 10.0, 10.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (m), 41.2 (d, J_{C-P} = 19.1 Hz), 53.2 (m), 64.1 (m), 77.8 (m), 151.0 (d, J_{C-P} = 212.4 Hz), 169.8.

^{31}P NMR (122 MHz, $CDCl_3$): δ = 4.87.

Anal. Calcd for $C_9H_{16}NO_6P$: C, 40.76; H, 6.08; N, 5.28. Found: C, 41.05; H, 5.91; N, 5.14.

Isoxazoline 18b
HRGC: t_R = 6.63 min.

Isoxazoline 16c
R_f = 0.52 (EtOAc); HRGC: t_R = 7.54 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.20–1.40 (m, 10 H), 1.40–1.60 (m, 1 H), 1.60–1.80 (m, 1 H), 2.79 (ddd, *J* = 1.8, 8.2, 17.3 Hz, 1 H), 3.20 (ddd, *J* = 1.8, 10.8, 17.3 Hz, 1 H), 4.14–4.26 (m, 4 H), 4.58–4.70 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 16.5 (m), 22.6, 27.6, 34.8, 41.7 (d, J_{C-P} = 17.9 Hz), 63.8 (m), 82.1 (m), 151.1 (d, J_{C-P} = 214.3 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 6.98.

Anal. Calcd for $C_{11}H_{22}NO_4P$: C, 50.18; H, 8.42; N, 5.32. Found: C, 50.45; H, 8.46; N, 5.07.

Isoxazoline 18c
HRGC: t_R = 6.97 min.

Isoxazoline 16d
R_f = 0.23 (EtOAc); HRGC: t_R = 6.95 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (td, *J* = 0.6, 7.0 Hz, 6 H), 2.90 (br s, 1 H), 3.10 (ddd, *J* = 1.8, 7.9, 17.3 Hz, 1 H), 3.19 (ddd, *J* = 1.4, 10.8, 17.3 Hz, 1 H), 3.58 (dd, *J* = 4.4, 12.3 Hz, 1 H), 3.75 (dd, *J* = 3.5, 12.3 Hz, 1 H), 4.12–4.26 (m, 4 H), 4.76 (dddd, *J* = 3.5, 4.4, 7.9, 10.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (m), 38.3 (d, J_{C-P} = 18.5 Hz), 63.2, 63.9 (m), 82.0 (m), 151.5 (d, J_{C-P} = 214.1 Hz).

^{31}P NMR (122 MHz, $CDCl_3$): δ = 6.47.

Anal. Calcd for $C_8H_{16}NO_5P$: C, 40.51; H, 6.80; N, 5.91. Found: C, 40.77; H, 6.98; N, 5.66.

Isoxazoline 18d
HRGC: t_R = 5.83 min.

Diethyl (5*R,2′*S**)-5-[2′-(*tert*-Butoxycarbonylamino)-2′-(methoxycarbonyl)ethyl]-4,5-dihydroisoxazole-3-phosphonate (20a) and Diethyl (5*R**,2′*R**)-5-[2′-(*tert*-butoxycarbonylamino)-2′-(methoxycarbonyl)ethyl]-4,5-dihydroisoxazole-3-phosphonate (20b)**
Oxime **11** (1.81 g, 10 mmol) was added to a soln of **19** (4.59 g, 20 mmol) in CH_2Cl_2 (45 mL). While the mixture was cooled in an ice bath, a 3.5% soln of NaOCl (42.6 mL, 20 mmol) was added slowly, dropwise. The reaction mixture was stirred at 25 °C for 2 h. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried (Na_2SO_4). The crude material was purified by flash column chromatography (silica gel, cyclohexane–EtOAc, 1:1); this gave unchanged alkene (2.20 g), **20a** (0.96 g), and **20b** (0.91 g).

Isoxazoline 20a
Yellow oil; R_f = 0.42 (EtOAc); HPLC: t_R = 6.44 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (td, *J* = 0.6, 7.0 Hz, 3 H), 1.36 (td, *J* = 0.6, 7.0 Hz, 3 H), 1.42 (s, 9 H), 2.10–2.22 (m, 2 H), 2.88 (ddd, *J* = 1.5, 7.3, 17.3 Hz, 1 H), 3.33 (ddd, *J* = 1.5, 10.9, 17.3 Hz, 1 H), 3.75 (s, 3 H), 4.14–4.28 (m, 4 H), 4.35 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 4.78 (dddd, *J* = 7.3, 7.3, 7.3, 10.9 Hz, 1 H), 5.34 (d, *J* = 6.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (m), 28.4, 37.6, 42.3 (d, J_{C-P} = 18.1 Hz), 51.2, 52.8 (m), 63.8 (m), 78.3, 80.3, 151.3 (d, J_{C-P} = 214.4 Hz), 155.5, 172.3.

^{31}P NMR (122 MHz, $CDCl_3$): δ = 6.38.

Anal. Calcd for $C_{16}H_{29}N_2O_8P$: C, 47.06; H, 7.16; N, 6.86. Found: C, 47.25; H, 7.23; N, 6.61.

Isoxazoline 20b
Yellow oil; R_f = 0.40 (EtOAc); HPLC: t_R = 7.79 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.0 Hz, 3 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 1.43 (s, 9 H), 1.74–2.00 (m, 1 H), 2.16 (ddd, *J* = 4.7, 8.8, 14.0 Hz, 1 H), 2.85 (ddd, *J* = 1.5, 7.9, 17.3 Hz, 1 H), 3.30 (ddd, *J* = 1.5, 10.8, 17.3 Hz, 1 H), 3.74 (s, 3 H), 4.14–4.28 (m, 4 H), 4.38–4.50 (m, 1 H), 4.76 (dddd, *J* = 4.4, 7.9, 8.8, 10.8 Hz, 1 H), 5.32 (d, *J* = 6.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (m), 28.4, 37.6, 42.4 (d, J_{C-P} = 18.1 Hz), 51.5, 52.7 (m), 63.8 (m), 78.7, 80.2, 151.4 (d, J_{C-P} = 214.1 Hz), 155.6, 172.5.

^{31}P NMR (122 MHz, $CDCl_3$): δ = 6.27.

Anal. Calcd for $C_{16}H_{29}N_2O_8P$: C, 47.06; H, 7.16; N, 6.86. Found: C, 47.32; H, 7.21; N, 6.68.

Acknowledgment

This work was financially supported by MIUR (PRIN 2005, Rome) and Università degli Studi di Milano (FIRST).

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