Ethyl 2-(Diisopropoxyphosphoryl)-2*H*-azirine-3-carboxylate: Reactions with Nucleophilic 1,3-Dienes

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Abstract: Ethyl 2-(diisopropoxyphosphoryl)-2*H*-azirine-3-carboxylate, the first example of an azirine bearing simultaneously ester and phosphonate groups was generated in situ and reacted with a number of 1,3-dienes. Cycloadducts or their ensuing rearranged products were isolated in moderate yields.

Key words: 2*H*-azirines, aza-Diels–Alder cycloaddition, dienophiles, phosphonates

2*H*-Azirines have generated a great deal of interest due to their versatility as building blocks in the synthesis of important classes of heterocyclic compounds,[1,2] and amino acids.[3] 2*H*-Azirines carrying ester groups are especially important not only due to their structural similarity to naturally occurring azirines with biological activity, like azirinomycin[4] and (–)-(*R*)-dysidazirine antibiotics,[5] but also for being excellent precursors in the synthesis of α-[6] and β-amino acid[7] derivatives. Azirines with C=O, P=O or heteroaromatic groups conjugated with the C=N bond, are effective dienophile partners[8–10] in Diels–Alder cycloadditions, producing bicyclic and tricyclic compounds. 2*H*-Azirines devoid of electron-withdrawing groups only react with specially activated dienes such as 1,3-diphenylisobenzofuran in refluxing toluene[11a,b] or under Lewis acid catalysis.[11c,d]

Excitatory amino acids are the most common neurotransmitters in the mammalian central nervous system thus their receptors have been exploited in the treatment of several pathological conditions affecting the brain, such as Parkinson's and Alzheimer's diseases.[12] (*S*)-2-Amino-3-phosphonopropanoic acid [(*S*)-AP-3, **1**, Figure 1] is known to be a modulator for the *N*-methyl-D-aspartate (NMDA) receptor site.

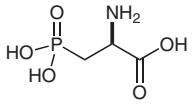

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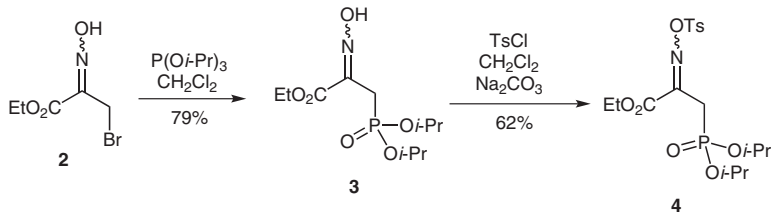
Figure 1 (*S*)-2-Amino-3-phosphonopropanoic acid

In connection with our work on 2*H*-azirines, we envisaged that 2-(dialkoxyphosphoryl)-2*H*-azirine-3-carboxylates would be excellent dienophiles for Diels–Alder cycloadditions, introducing simultaneously the biologically important phosphonate group[13] into cycloadducts. This class of compounds has not been previously synthesized, despite of being closely related to (*S*)-AP-3 **1**.

This paper reports the unprecedented generation of ethyl 2-(diisopropoxyphosphoryl)-2*H*-azirine-3-carboxylate (**5**) and its interception by a number of electron-rich buta-1,3-dienes producing mono-, di-, and tricyclic aziridines, carrying the α-amino-β-phosphonate carboxylate moiety.

The oxime **3** was obtained from ethyl bromopyruvate oxime (**2**)[14] and triisopropyl phosphite. Its treatment with tosyl chloride in the presence of sodium carbonate led to β-phosphonic tosyloxime ester **4** (Scheme 1). The corresponding 2*H*-azirine **5** was obtained under Neber conditions, but could not be isolated from the reaction medium. Although monofunctional 2*H*-azirine-2-phosphonates[15]



Scheme 1 Preparation of β-phosphonic tosyloxime ester

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have been produced and isolated before under similar reaction conditions, manipulation of the reaction mixture in the present case, however, led to decomposition, according to ^{1}H NMR analysis.

In a typical procedure tosyloxime **4** was solubilized in benzene mixed with potassium carbonate (10 equiv), triethylamine (0.3 equiv), and a 1,3-diene and stirred for four days at room temperature. The primary cycloadducts **6a**,**b**,**d**,**e** were obtained in 9–59% yield. Derivative **7** was obtained in the case of reaction with the Danishefsky diene in 39% yield, by rearrangement of the primary cycloadduct **6c** (Scheme 2). In case **6f**, the silyl group cleaved during chromatography giving **8**.

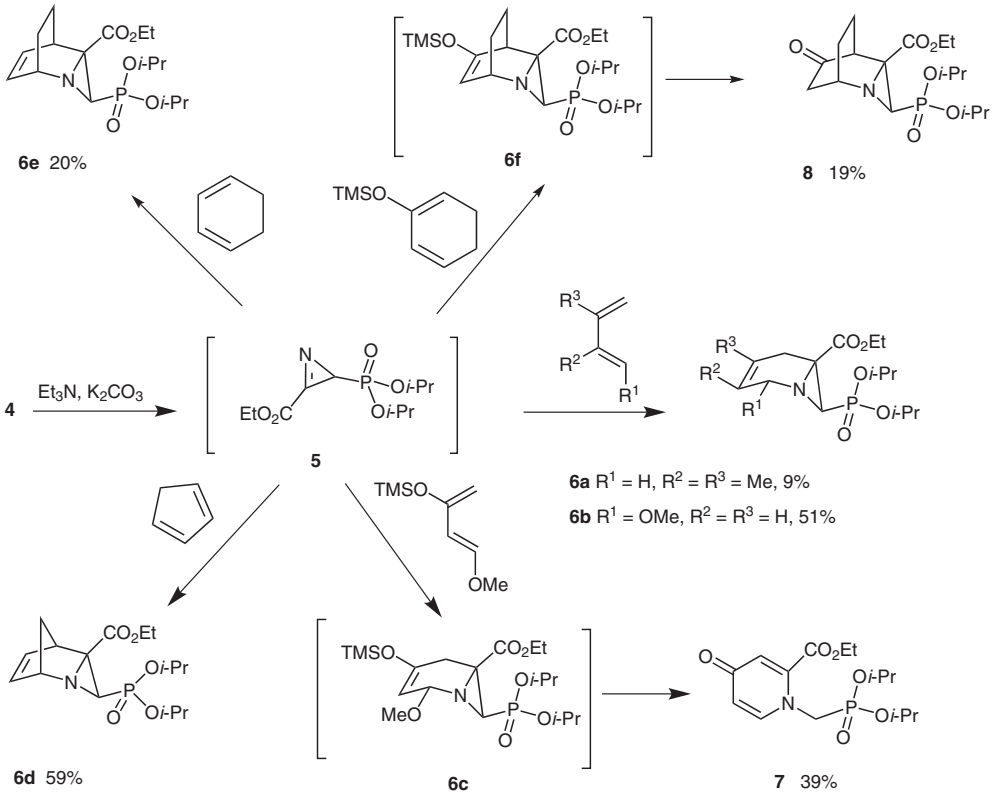
The moderate yields are certainly the reflection of the two-step sequence in the one-pot procedure together with the instability of the azirine because of the presence of the two electron-withdrawing substituents in the ring.

Cycloadduct **6a**, obtained from reaction of azirine **5** with 2,3-dimethylbuta-1,3-diene, was isolated in very low yield, even in the presence of a large excess of diene (5 equiv). Difficulties of the same type had been reported by Davis in reaction of a 2*H*-azirine-3-phosphonate with 2,3-dimethylbuta-1,3-diene, where 100 equivalents of the diene were required.[9]

Reaction of the azirine **5** with 1-methoxybuta-1,3-diene evidenced that the regioselectivity of the cycloaddition is governed by electronic effects. ^{1}H and ^{13}C NMR data of product **6b** are in accordance with the electron-withdrawing effect of the two heteroatoms attached to C2; H2 is at $\delta_H = 4.80$ and C2 at $\delta_C = 85.6$. The cycloaddition products were obtained as single isomers, presumably formed by *endo*-selective processes, as generally observed in reactions of 2*H*-azirines with 1,3-dienes.[8] Furan and their derivatives are exceptions due to retro-Diels–Alder cycloadditions of the initially formed *endo*-cycloadduct that isomerize to the *exo*-products.[11b] The low-field resonance of H3 in the tricyclic products obtained by reaction of 2*H*-azirines with cyclopentadiene is a clear feature of the *endo* selectivity.[8] This can be ascribed to the anisotropy of the backside double bond over H3, due to constraints of the tricyclic structure. The chemical shift value of H3 in compound **6d** correspond to such an effect appearing at $\delta_H = 1.62$.

Features of pyridinone **7**, obtained by rearrangement of **6c**, are the two hydrogens of the CH_2 group, coupling to the phosphorus nucleus with $J = 12.0$ Hz; the signal at $\delta_H = 6.45$, assigned to H5, shows a doublet of doublets ($^3J = 3.0$ Hz to H3 and $^2J = 7.6$ Hz to H6) and two doublets at $\delta_H = 7.35$, corresponding to H6, and at $\delta_H = 7.03$, corresponding to H3, show matching couplings to H5. Rearrangements of this type have been noticed before in bicyclic adducts obtained from the Danishefsky diene and 2*H*-azirines bearing electrophilic groups.[16]

In summary, cycloaddition reactions of ethyl 2-(diisopropoxyphosphoryl)-2*H*-azirine-3-carboxylate to nucleophilic dienes produced, in moderate yields, a number of functionalized six-membered-ring fused aziridines. These may eventually be valuable intermediates at the synthesis of interesting biological compounds related to (*S*)-AP3. Studies to improve the reaction efficiency as well as the



Scheme 2 Generation of azirine **5** and its cycloaddition reactions with 1,3-dienes

development of an asymmetric synthesis or generation of the azirine are ongoing.

^{1}H and ^{13}C NMR spectra (100.6 or 75.5 MHz) were recorded on a Bruker Avance III 400 (400 MHz) spectrometer or on a Bruker WM AMX (300 MHz), using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1640-FT spectrophotometer. Samples were run as thin films. Mass spectra were recorded on a VG Autospec M. Purification of crude samples was performed by dry flash chromatography, using silica gel purchased from Carlo Erba (35–70 mμ).

Ethyl 3-(Diisopropoxyphosphoryl)-2-(hydroxyimino)propanoate (3)

To ethyl bromopyruvate oxime (4.7 g, 22 mmol) dissolved in CH_2Cl_2 (30 mL) was added P(O*i*-Pr)$_3$ (6 mL, 24 mmol) and the mixture stirred at 35 °C for 16 h. H_2O (30 mL) was added and the mixture stirred at r.t. for a further 30 min and the organic phase was dried ($MgSO_4$) and evaporated under vacuum. The oily residue was subjected to dry-flash chromatography (silica gel, CH_2Cl_2–EtOAc, 10:1), affording **3** (5.13 g, 79%) as a as colorless oil.

IR(neat): 3167, 2982, 2936, 1720, 1252, 995 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.30 (m, 15 H, 5 Me), 3.29 (d, $^1J_{PH}$ = 24.0 Hz, 2 H), 4.19–4.29 (m, 2 H, OCH_2), 4.66–4.74 (m, 2 H, 2 OCH).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.1 (Me), 23.6 (Me), 23.7 (Me), 24.6 (Me), 24.6 (d, $^1J_{PC}$ = 83.8 Hz), 61.5 (OCH_2), ~71.1 (d, $^2J_{PC}$ = 13.6 Hz, OCH), 143.6 (C=N), 163.9 (CO).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{23}NO_6P$: 296.1263; found: 296.1258.

Ethyl 3-(Diisopropoxyphosphoryl)-2-[(tosyloxy)imino]propanoate (4)

To a soln of **3** (4.5 g, 15 mmol) in CH_2Cl_2 (40 mL) was added Na_2CO_3 (4.8 g, 45 mmol) followed by TsCl (3.24 g, 17 mmol) and the mixture stirred until the disappearance of the starting oxime (~4 h). The insolubles were removed by filtration and the solvent was evaporated to afford a residue that was subjected to dry-flash chromatography (silica gel, hexanes–CH_2Cl_2–EtOAc, increasing polarity) to product **4** (4.2 g, 62%) as a pale yellow thick oil.

IR(neat): 2983, 1737, 1386, 1267, 1194, 993 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19–1.30 (m, 15 H, 5 Me), 2.38 (s, 3 H, PhMe), 3.25 (d, $^1J_{PH}$ = 24.0 Hz, 2 H), 4.23 (q, *J* = 6.0 Hz, 2 H, OCH_2), 4.57–4.64 (m, 2 H, 2 OCH), 7.28 (d, *J* = 6.0 Hz, 2 H), 7.83 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.8 (Me), 21.6 (Me), 23.4 (Me), 23.5 (Me), 23.6 (Me), 23.7 (Me), 26.5 (d, $^1J_{PC}$ = 135.8 Hz, PCH_2), 62.8 (OCH), ~72.0 (d, $^2J_{PC}$ = 12.1 Hz, OCH), 131.7 (C, Ar), 145.7 (C, Ar), 152.1 (C=N), 161.1 (CO).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{29}NO_8PS$: 450.1351; found: 450.1346.

Cycloaddition Reactions; General Procedure

To a soln of tosyloxime **4** (0.3 g, 0.69 mmol) in benzene (5 mL) was added Et_3N (30 μL, 0.33 equiv), K_2CO_3 (0.96 g, 6.9 mmol, 10 equiv), and the diene (1.0 equiv to large excess). [Cyclopentadiene was used in large excess (1 mL), other dienes were used in excess: the Danishefsky diene (1.5 equiv), 1-methoxybuta-1,3-diene (2 equiv), 2,3-dimethylbuta-1,3-diene (1.5 equiv or 5 equiv).] The mixture was stirred at r.t. for 4 d. Evaporation of the solvent gave the crude product, which was subjected to dry-flash chromatography (silica gel, petroleum ether–Et_2O, polarity gradient or EtOAc–MeOH, 3:1 for **7**) affording products **6**–**8** as oils.

Ethyl 7-(Diisopropoxyphosphoryl)-3,4-dimethyl-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (6a)

(i) 2,3-Dimethybuta-1,3-diene (1.5 equiv); yield: 0.020 g (8%).

(ii) 2,3-Dimethybuta-1,3-diene (5.0 equiv); yield: 0.025 g (9%).

IR (neat): 3458, 2981, 2933, 1753 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29–1.33 (m, 15 H, 5 Me), 1.52 (br s, 3 H, Me), 1.63 (br s, 3 H, Me), 2.16 (d, *J* = 17.3 Hz, 1 H, H7), 2.38 (br d, *J* = 17.3 Hz, 1 H, H5), 2.70 (d, *J* = 17.6 Hz, 1 H, H5), 3.23 (d, *J* = 17.0 Hz, 1 H, H2), 3.73 (d, *J* = 17.0 Hz, 1 H, H2), 4.16–4.26 (m, 2 H, OCH_2), 4.68–4.80 (m, 2 H, 2 OCH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.1 (Me), 15.4 (Me), 17.5 (Me), 22.6 (Me), 22.9 (Me), 23.95 (Me), 23.05 (Me), 23.1 (Me), 28.4 (d, $^3J_{PC}$ = 19 Hz, CH_2, C5), 33.1 (d, $^1J_{PC}$ = 216 Hz, C7), 45.0 (d, $^2J_{PC}$ = 5.0 Hz, C6), 51.6 (d, $^3J_{PC}$ = 6.6 Hz, CH_2, C2), 60.3 (CH_2O), 69.8 (d, $^3J_{PC}$ = 6.0 Hz, COH), 69.9 (d, $^3J_{PC}$ = 6.3 Hz, COH), 118.7 (C3 or C4), 119.1 (C4 or C3), 168.7 (CO).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{31}NO_5P$: 360.1940; found: 360.1927.

Ethyl 7-(Diisopropoxyphosphoryl)-2-methoxy-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (6b)

Yield: 0.125 g (51%).

IR (neat): 3467, 2980, 2931, 1754, 1731 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.28 (m, 15 H, 5 Me), 2.30 (d, *J* = 16.6 Hz, 2 H, H5, H7), 2.78 (dd, *J* = 6.1, 18.5 Hz, 1 H, H5), 3.61 (s, 3 H, OMe), 4.16–4.18 (m, 2 H, OCH_2), 4.68 (br s, 2 H, 2 OCH), 4.80 (s, 1 H, H2), 5.39 (d, *J* = 10.0 Hz, 1 H, H3), 5.62–5.63 (m, 1 H, H4).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4 (Me), 24.1 (Me), 24.2 (CH_2, C5), 24.4 (Me), 24.42 (Me), 24.6 (Me), 33.2 (d, $^1J_{PC}$ = 217 Hz, C7), 45.6 (d, $^2J_{PC}$ = 4.5 Hz, C6), 57.3 (OMe), 61.8 (OCH_2), 71.3 (d, $^2J_{PC}$ = 6.8 Hz) 71.5 (d, $^2J_{PC}$ = 6.8 Hz, OCH), 85.6 (C2), 123.1 (C3 or C4), 124.5 (C4 or C3), 168.0 (CO).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{29}NO_6P$: 362.1732; found: 362.1731.

Ethyl 3-(Diisopropoxyphosphoryl)-2-azatricyclo[3.2.1.0^{2,4}]oct-6-ene-4-carboxylate (6d)

Yield: 0.140 g (59%).

IR (neat): 3467, 2981, 2937, 1741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27–1.34 (m, 15 H, 5 Me), 1.62 (d, *J* = 12.5 Hz, 1 H, H3), 1.71 (t, *J* = 8.6 Hz, 1 H, H8), 2.43 (d, *J* = 8.6 Hz, 1 H, H8), 3.29 (br s, 1 H, H5), 4.24–4.29 (m, 3 H, OCH_2, H1), 4.67–4.78 (m, 2 H, 2 OCH), 5.71–5.73 (m, 1 H, H6 or H7), 6.18–6.22 (m, 1 H, H7 or H6).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5 (Me), 24.3 (Me), 24.4 (Me), 24.43 (Me), 24.5 (Me), 45.8 (d, $^1J_{PC}$ = 205 Hz, C3), ~48 (C6), 49.6 (C5), 59.4 (d, *J* = 3.0 Hz, C8), 62.0 (OCH_2), 67.6 (d, $^3J_{PC}$ = 7.5 Hz, C1), 71.3 (d, $^2J_{PC}$ = 6.8 Hz, OCH), 71.5 (d, $^2J_{PC}$ = 6.8 Hz, OCH), 128.8 (C5 or C6), 133.3 (C6 or C5), 172.0 (CO).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{27}NO_5P$: 344.1627; found: 344.1615.

Ethyl 3-(Diisopropoxyphosphoryl)-2-azatricyclo[3.2.2.0^{2,4}]non-6-ene-4-carboxylate (6e)

Yield: 0.088 g (20%).

IR (neat): 2933, 1749, 1653, 1281 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (m, 1 H, H8 or H9), 1.24–1.34 (m, 16 H, 5 Me, 1 H, H9 or H8), 1.52 (d, *J* = 13.2 Hz, 1 H, H3), 1.69 (m, 1 H, H8 or H9), 2.1 (m, 1 H, H9 or H8), 3.12 (m, 1 H, H5), 3.99 (m, 1 H, H1), 4.26 (m, 2 H, $CO_2CH_2CH_3$), 4.66–4.81 (m, 2 H, 2 OCH), 5.68 (m, 1 H, H6 or H7), 6.22 (m, 1 H, H7 or H6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2\mathit{C}H_3$), 19.8 (C8 or C9), 23.6 (C9 or C8), 23.82, 23.9, 24.0, 24.0 (4 Me), 31.0 (d, $^1J_{PC}$ = 212.5 Hz, C3), 32.9 (d, *J* = 2.6 Hz, C5), 52.3 (d, $^3J_{PC}$ = 9.2 Hz, C1), 61.4 ($CO_2\mathit{C}H_2CH_3$), 70.7 (d, $^2J_{PC}$ = 6.3 Hz, OCH), 71.0 (d, $^2J_{PC}$ = 6.3 Hz, OCH), 125.1 (C6 or C7), 130.1 (C7 or C6), 125.5 (q, C2), 169.2 (C=O).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{29}NO_5P$: 358.1783; found: 358.1784.

Ethyl 1-[(Diisopropoxyphosphoryl)methyl]-4-oxo-1,4-dihydropyridine-2-carboxylate (7)
Yield: 0.092 g (39%).

IR (neat): 3440, 2983, 2938, 1733, 1633, 1573 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.27 (m, 12 H, 4 Me), 1.36 (t, *J* = 7.2 Hz, 3 H, Me), 3.73 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.63–4.71 (m, 2 H, 2 OCH), 4.71 (d, *J* = 12.0 Hz, 2 H, H1′), 6.45 (dd, *J* = 3.0, 7.6 Hz, 1 H, H5), 7.03 (d, *J* = 3.0 Hz, 1 H, H3), 7.35 (d, *J* = 7.6 Hz, 1 H, H6).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.3 (Me), 24.21 (Me), 24.27 (Me), 24.32 (Me), 49.7 (d, $^1J_{PC}$ = 156 Hz, C1′, CH_2), 63.3 (CH_2O), 73.0 (d, $^2J_{PC}$ = 7.5 Hz, OCH), 119.7 (C5), 123.3 (C3), 140.2 (C2), 162.9 (CO), 179.5 (CO).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{25}NO_6P$: 346.1419; found: 346.1419.

Ethyl 3-(Diisopropoxyphosphoryl)-6-oxo-2-azatricyclo[3.2.2.0^{2,4}]nonane-4-carboxylate (8)
Yield: 0.077 g (19%).

IR (neat): 3459, 3274, 3054, 1734, 1602 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29–1.30 (m, 15 H, 5 Me), 1.73–1.80 (m, 2 H), 1.88 (d, *J* = 9.3 Hz, 1 H, H3), 2.07–2.32 (m, 4 H), 3.07 (br s, 1 H, H1), 3.79 (br s, 1 H, H5), 4.26 (m, 2 H, $C\mathit{H}_2CH_3$), 4.75 (m, 2 H, 2 OCH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0 (Me), 18.5 (C8 or C9), 23.8 (Me), 23.92 (Me), 23.96 (Me), 24.0 (Me), 24.6 (CH_2), 33.5 (d, $^1J_{PC}$ = 213.3 Hz, C3), 39.6 (C8 or C9), 43.7 (d, $^3J_{PC}$ = 2.0 Hz, C5), 45.8 (d, $^2J_{PC}$ = 4.0 Hz, C4), 49.7 (d, $^3J_{PC}$ = 8.0 Hz, C1), 61.8 (OCH), 71.4 (d, $^2J_{PC}$ = 6.0 Hz, OCH), 167.0 (C=O), 207.6 (C=O).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{29}NO_6P$: 374.1732; found: 374.1729.

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References

(1) For reviews, see: (a) Palacios, F.; Ochoa de Retana, A. M.; Marigorta, E. M.; de los Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219. (b) Gilchrist, T. L. *Aldrichimica Acta* **2001**, *34*, 51. (c) Palacios, F.; Ochoa de Retana, A. M.; Marigorta, E. M.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401.

(2) (a) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; Gonçalves, A. M. d' A. R.; Beja, J. A.; Paixão, A. M.; Silva, M. R.; Alte da Veiga, L. *J. Org. Chem.* **2002**, *67*, 66. (b) Davis, F. A.; Liang, C.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. (c) Banert, K.; Kohler, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 174.

(3) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238.

(4) Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48.

(5) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103.

(6) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Filigheddu, S. N.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 3857. (c) Zwanenburg, B.; Thi, L. J. *Pure Appl. Chem.* **1996**, *68*, 735. (d) Davis, F. A.; Liu, H.; Reddy, C. V. *Tetrahedron Lett.* **1996**, *37*, 5473.

(7) (a) Righi, G.; D'Achielle, R. *Tetrahedron Lett.* **1996**, *37*, 6893. (b) Lim, Y.; Lee, W. K. *Tetrahedron Lett.* **1995**, *36*, 8431. (c) Tanner, D.; Bergsson, C.; Dhaliwal, H. K. *Tetrahedron Lett.* **1990**, *31*, 1903.

(8) Alves, M. J.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 299.

(9) (a) Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655. (b) Bickley, J. F.; Gilchrist, T. L.; Mendonça, R. *ARKIVOC* **2002**, *(vi)*, 192.

(10) Alves, M. J.; Gil Fortes, A.; Lemos, A.; Martins, C. *Synthesis* **2005**, 555.

(11) (a) Nair, V. J. *J. Org. Chem.* **1972**, *37*, 2508. (b) Hassner, A.; Anderson, D. J. *J. Org. Chem.* **1974**, *39*, 2031. (c) Ray, C. A.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2001**, *42*, 9289. (d) Ray, C. A.; Risberg, E.; Somfai, P. *Tetrahedron* **2002**, *58*, 5983.

(12) (a) Young, A. B.; Greenamyre, J. T.; Hollingsworth, Z.; Albin, R.; D'Amato, C.; Shoulson, I.; Penny, J. B. *Science* **1988**, *241*, 981. (b) Reyes-Rangel, G.; Marañón, V.; Avila-Ortiz, C. G.; Parrodi, C. A.; Quintero, L.; Juaristi, E. *Tetrahedron* **2006**, *62*, 8404.

(13) (a) Engel, R. In *Handbook of Organophosphorus Chemistry*; Dekker Inc.: New York, **1992**. (b) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.

(14) (a) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1283. (b) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.

(15) (a) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213. (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I. *Tetrahedron Lett.* **2000**, *41*, 5363. (c) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; López de Munain, R. *Org. Lett.* **2002**, *4*, 2405. (d) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2525. (e) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; López de Munain, R. *Tetrahedron: Asymmetry* **2003**, *14*, 689. (f) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron* **2004**, *60*, 8937.

(16) Alves, M. J.; Gil Fortes, A.; Costa, F. T.; Duarte, V. C. M. *Tetrahedron* **2007**, *63*, 11167.