Synthesis of a Novel Class of β-Lactam Derivatives of 1-Aminophosphonates by Staudinger Ketene–Imine [2+2]-Cycloaddition Reaction

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Abstract: A novel class of β-lactam derivatives of 1-aminophosphonates was synthesized by Staudinger [2+2] cycloaddition reaction of ketenes with imines derived from 1-aminophosphonates. Treatment of aromatic aldehydes with ammonia and diethyl phosphite followed by a reaction with ketenes, which are generated from the appropriate acid chloride and a tertiary amine, gave a novel class of β-lactam derivatives of 1-aminophosphonates. The major or, in some cases, sole product of the cycloaddition is the *cis*-β-lactam.

Key words: 1-aminophosphonates, β-lactams, ketenes, imines, [2+2]-cycloaddition reaction

α-Functionalized phosphonic acids have attracted growing attention because of their novel applications in industry, agriculture and medicine, and as synthetic intermediates.[1–4] Among α-functionalized phosphonic acids, 1-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. 1-Aminophosphonic acids are considered to be mimics of the corresponding 1-aminocarboxylic acids in biological systems.[5] Indeed, a number of potent antibiotics,[7] enzyme inhibitors,[8] and pharmacological agents[9] are 1-aminophosphonic acids or peptide analogues.

The β-lactam skeleton is still attracting a lot of attention due to its applications as antimicrobial agents and elastase inhibitors.[10] Due to the constant need for new drugs displaying broader antibacterial activity, numerous penicillin derivatives have been prepared and examined for antibacterial activity. Penams, carbapenems, cephalosporins, clavulanic acids, and oxapenams constitute a variety of new β-lactam-containing ring systems that are reported to show antibacterial properties (Figure 1).[11]

A large number of synthetic methods for the preparation of β-lactams have been developed.[12] Of these methods, the Staudinger reaction, in particular, has provided useful and economical access to β-lactams, mainly due to the ready availability of both Schiff bases and ketenes.[13] The key step in the Staudinger synthesis of β-lactams is the [2+2] cycloaddition of ketenes, which are generated from the appropriate acid chloride and a tertiary amine, with imines.

In contrast to extensive studies on the synthesis of 1-aminophosphonates and β-lactam derivatives,[14–18] relatively few papers have reported the synthesis of such compounds containing two functionalities in the same molecule.[19] The conjunction of two functionalities may afford powerful biological activity.

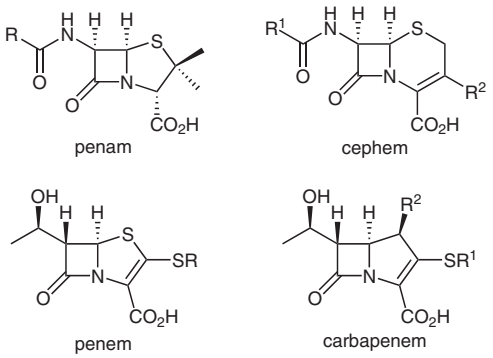
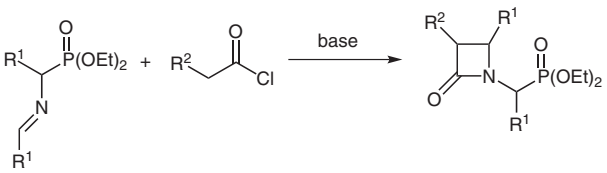


Figure 1

Recently, we have reported that the reaction of diethyl *N*-(arylmethylene)-1-aminoaryl methylphosphonate with diethyl phosphite in the presence of chlorotrimethylsilane or acetyl chloride gives bis[1-diethoxyphosphorylalkyl]amine as the sole product (Scheme 1).[20]

Scheme 1

We were interested in studying the synthesis of a novel class of b-lactam derivatives of 1-aminophosphonates through the Staudinger reaction of 1-iminophosphonates with ketenes (Scheme 2).



Scheme 2

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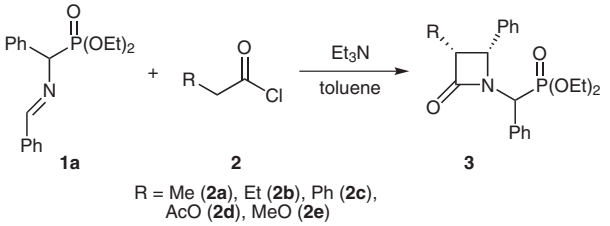
Treatment of diethyl *N*-(phenylmethylene)-1-aminophenyl methylphosphonate (**1a**), which was chosen as a model compound and prepared by our previous reported method,[21] with various acid chlorides was studied in the presence of triethylamine in toluene, and the progress of the reaction was monitored by TLC (Scheme 3).



Scheme 3

Treatment of **1a** with propanoyl (**2a**), butanoyl (**2b**) and phenylacetyl (**2c**) chlorides in the presence of triethylamine in anhydrous toluene at room temperature for 24 hours, failed. When the reaction was carried out with acetoxy acetyl chloride (**2d**) in the presence of triethylamine in anhydrous toluene for 12 hours at room temperature, compound **3d** was obtained in 64% isolated yield. The structure of **3d** was confirmed by NMR data and elemental analysis. In the ^{31}P NMR spectrum, two singlet peaks appeared at δ = 18.43 and 18.81 ppm. The major, or sole, product of the Staudinger [2+2]-cycloaddition reaction of ketenes with imines was the *cis*-β-lactam.[10] On the other hand, due to the presence of the stereogenic center at the α-position of the phosphonate moiety, compound **3d** can exist as two diastereoisomers. The diastereomeric excess of 28% for **3d** was calculated from the integrated areas of the ^{31}P NMR peaks. The ^{1}H NMR spectrum contains two sets of doublet peaks at δ = 4.87 (J_{H-P} = 21 Hz) and 5.13 (J_{H-P} = 21.7 Hz) ppm, which corresponds to the hydrogen CH-P in the two diastereoisomers. The ^{1}H NMR spectrum also contains two doublet peaks at δ = 5.04 (J = 5 Hz) and 5.74 (J = 5 Hz) ppm, which corresponds to the *cis* hydrogens (g and d) in **3d** for a single diastereoisomer. The signals for the *cis* hydrogens of the second diastereoisomer showed two doublet peaks at δ = 5.34 (J = 4.7 Hz) and 5.85 (J = 4.7 Hz) ppm. The ^{13}C NMR spectrum exhibited a two sets of doublet peaks at δ = 54.1 (J_{C-P} = 153.4 Hz) and 56.2 (J_{C-P} = 156.6 Hz) ppm for the two diastereoisomers. The [2+2] cycloaddition reaction of **1a** with methoxyacetyl chloride (**2e**) in the presence of triethylamine converted the Schiff base **1a** into the corresponding *cis*-β-lactam **3e** at room temperature after 12 hours in good isolated yield (80%) in about 20% diastereomeric excess. The results are summarized in Table 1.

Treatment of a range of derivatives of diethyl *N*-(arylmethylene)-1-aminoaryl methylphosphonates **1** with various acyl chlorides in toluene at room temperature were examined (Table 1). As shown in Table 1, the reaction of diethyl *N*-(4-methoxyphenylmethylene)-1-amino (4-methoxyphenyl) ethylphosphonate (**1b**) with a mixture of methoxyacetyl chloride (**2e**) and triethylamine in toluene at room temperature afforded the corresponding β-lactam derivative **3g** in 80% isolated yield (entry 6). Treatment of **1b** with phenoxyacetyl chloride (**2f**) in the presence of triethylamine in toluene gave **3h** in 72% isolated yield in about 35% diastereomeric excess (entry 8). The reaction of diethyl *N*-(4-fluorophenylmethylene)-1-amino (4-fluorophenyl) ethylphosphonate (**1c**) with a mixture of methoxyacetyl chloride (**2e**) and triethylamine in toluene at room temperature, afforded the corresponding β-lactam derivative **3i** in 80% isolated yield (entry 9).

In summary, we have developed a novel synthesis of β-lactam derivatives of 1-aminophosphonates by using the Staudinger [2+2]-cycloaddition reaction of ketenes with imines derived from 1-aminophosphonates. The major, or sole, product of the cycloaddition is the *cis*-β-lactam. Using this method, a series of β-lactam derivatives of 1-aminophosphonates was synthesized in good to excellent yields. Some of the major advantages of this protocol are the simple procedure, easy work-up, good yields, and catalyst-free reaction conditions.

All chemicals were commercial products and were either distilled or recrystallized before use. NMR spectra were recorded with a 250 Bruker Avance instrument with chemical shifts (δ) being reported as ppm and couplings expressed in hertz; the chemical shift data are given relative to $CHCl_3$ (δ = 7.26 ppm) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are recorded relative to the $CDCl_3$ resonance (δ = 77.0 ppm). Silica gel column chromatography was carried out with Merck Silica gel 60 (Merck No. 10184). Merck Silica gel 60 F254 plates (No. 5744) were used for preparative TLC.

Synthesis of Diethyl *N*-(Arylmethylene)-1-aminoaryl Methylphosphonate (1); General Procedure

Obtained according to our previously published article.[21]

The aldehyde (15 mmol) was added to NH_4OH (30%, 15 mL) and the solution was stirred for 5 h at reflux. During this time, a white precipitate formed. The precipitate was removed by filtration and dried. Diethyl phosphite (828 mg, 6 mmol) was added to this solid and the resulting solution was stirred for 2–5 h at 70 °C. Chromatography on silica gel (EtOAc–*n*-hexane, 5:5) gave the pure product diethyl *N*-(arylmethylene)-1-aminoaryl methyl phosphonate **1** as a colorless oil.[21]

Synthesis of Novel β-Lactam Derivatives of 1-Aminophosphonates (3); General Procedure

A solution of the acid chloride **2** (3.5 mmol) in anhydrous toluene (10 mL) was slowly added to a solution of diethyl *N*-(arylmethylene)-1-aminoaryl methylphosphonate **1** (1 mmol) and Et_3N (4.5 mmol) in anhydrous toluene (10 mL) at 0–5 °C. The reaction mixture was then allowed to warm to r.t. and the reaction mixture was stirred for 12–24 h. The reaction mixture washed with H_2O (2 × 15 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4 and the organic solvent was removed by distillation under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (EtOAc–*n*-hexane, 1:5→5:1) to give a diastereomeric mixture of β-lactams **3** in 64–80% yields. All products gave satisfactory spectral data in accord with the assigned structures.

Table 1 Reaction of Diethyl *N*-(Arylmethylene)-1-aminoaryl Methylphosphonates **1** with Acyl Chlorides **2** in Toluene at Room Temperture

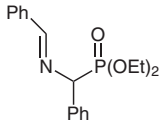
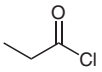
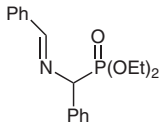
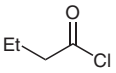
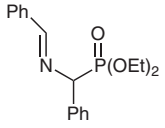
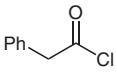
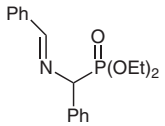
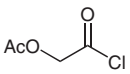
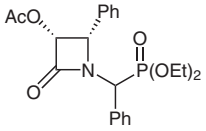
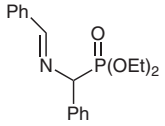
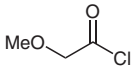
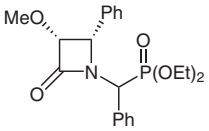
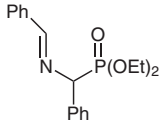
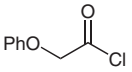
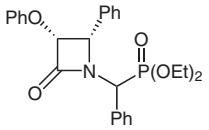
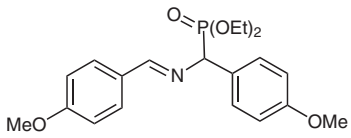
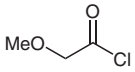
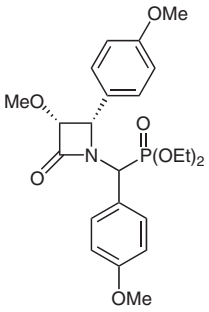
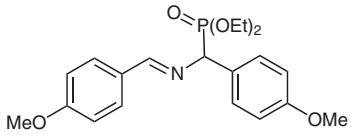
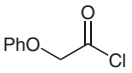
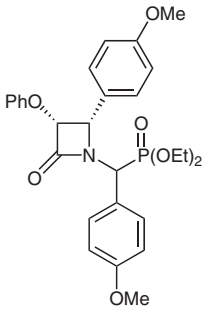
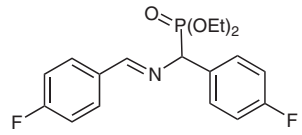
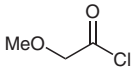
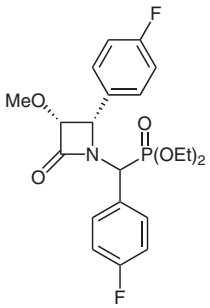
Entry	Compound **1**	Compound **2**	Product **3**	Time (h)	Yield (%)[a]	^{31}P NMR of **3**
1	 **1a**	 **2a**	–[c]	24	–	–
2	 **1a**	 **2b**	–[c]	24	–	–
3	 **1a**	 **2c**	–[c]	24	–	–
4	 **1a**	 **2d**	 **3d**	14	64	18.43, 18.81 (28%)
5	 **1a**	 **2e**	 **3e**	12	80	18.70, 19.11 (20%)
6	 **1a**	 **2f**	 **3f**	12	70	18.59, 19.02 (4%)
7	 **1b**	 **2e**	 **3g**	12	80	18.87, 19.37 (8%)
8	 **1b**	 **2f**	 **3h**	12	72	18.83, 19.31 (35%)

Table 1 Reaction of Diethyl *N*-(Arylmethylene)-1-aminoaryl Methylphosphonates **1** with Acyl Chlorides **2** in Toluene at Room Temperture (continued)

Entry	Compound **1**	Compound **2**	Product **3**	Time (h)	Yield (%)[a]	^{31}P NMR of **3**
9	 **1c**	 **2e**	 **3i**	14	80	18.33, 18.72 (32%)

[a] Yields refers to the isolated pure products after column chromatography.
[b] ^{31}P NMR δ shifts and *de* in parentheses.
[c] Unknown mixture.

1-[(Diethoxyphosphoryl)phenylmethyl]-2-oxo-4-phenylazetidin-3-yl Acetate (3d)
Colorless oil; mixture of two diastereoisomers.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.02–1.45 (m, 12 H), 1.61 (s, 3 H), 1.63 (s, 3 H), 3.75–4.08 (m, 6 H), 4.10–4.30 (m, 2 H), 4.87 (d, *J* = 21 Hz, 1 H), 5.04 (d, *J* = 5 Hz, 1 H), 5.13 (d, *J* = 21.7 Hz, 1 H), 5.34 (d, *J* = 4.7 Hz, 1 H), 5.74 (d, *J* = 5 Hz, 1 H), 5.85 (d, *J* = 4.7 Hz, 1 H), 7.0–7.55 (m, 20 H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.1–16.5 (m), 19.8, 54.1 (d, $J_{P–C}$ = 153.4 Hz), 56.2 (d, $J_{P–C}$ = 156.6 Hz), 62.6–63.7 (m), 127.7, 127.9, 128.3, 128.4–129.0 (m), 129.6–129.9 (m), 131.1, 131.9, 132.6, 164.9 (b-lactam CO), 169.0 (acetoxy CO).

^{31}P NMR ($CDCl_3$, 101.25 MHz, H_3PO_4): δ = 18.43 (major), 18.81 (minor).

Anal. Calcd for $C_{22}H_{26}NO_6P$: C, 61.23; H, 6.08; N, 3.25. Found: C, 61.08; H, 6.15; N, 3.20.

Diethyl [(3-Methoxy-2-oxo-4-phenylazetidin-1-yl)phenylmethyl]phosphonate (3e)
White powder; mixture of two diastereoisomers.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.0–1.25 (m, 9 H), 1.33 (t, *J* = 7 Hz, 3 H), 3.02 (s, 3 H), 3.03 (s, 3 H), 3.37–3.55 (q, *J* = 7 Hz, 1 H), 3.65 (q, *J* = 7 Hz, 1 H), 3.73–4.05 (m, 5 H), 4.05–4.25 (m, 1 H), 4.59 (d, *J* = 4.7 Hz, 1 H), 4.71 (d, *J* = 4.5 Hz, 1 H), 4.83 (d, *J* = 4.7 Hz, 1 H), 4.85 (d, *J* = 21 Hz, 1 H), 5.10 (d, *J* = 21.7 Hz, 1 H), 5.16 (d, *J* = 4.7 Hz, 1 H), 6.96–7.18 (m, 8 H), 7.25–7.40 (m, 10 H), 7.40–7.53 (m, 2 H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 15.7–16.6 (m), 53.5 (d, $J_{P–C}$ = 152.8 Hz), 55.4 (d, $J_{P–C}$ = 156.6 Hz), 57.9, 58.0, 62.3–63.6 (m), 85.0, 85.5, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3–128.8 (m), 128.9, 129.4–129.9 (m), 131.3, 132.2, 133.6, 166.8 (b-lactam CO), 166.9 (b-lactam CO).

^{31}P NMR ($CDCl_3$, 101.25 MHz, H_3PO_4): δ = 18.70 (minor), 19.11 (major).

Anal. Calcd for $C_{21}H_{26}NO_5P$: C, 62.51; H, 6.50; N, 3.47. Found: C, 62.32; H, 6.40; N, 3.40.

Diethyl [(3-Phenoxy-2-oxo-4-phenylazetidin-1-yl)phenylmethyl]phosphonate (3f)
Colorless oil; mixture of two diastereoisomers.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.0–1.20 (m, 9 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 3.75–4.10 (m, 6 H), 4.10–4.28 (m, 2 H), 4.90 (d, *J* = 21.3 Hz, 1 H), 5.05 (d, *J* = 4.7 Hz, 1 H), 5.16 (d, *J* = 21.5 Hz, 1 H), 5.33 (d, *J* = 4.2 Hz, 1 H), 5.36 (d, *J* = 4.5 Hz, 1 H), 5.46 (d, *J* = 4.5 Hz, 1 H), 6.65 (d, *J* = 7.7 Hz, 4 H), 6.79 (t, *J* = 7.5 Hz, 2 H), 6.95–7.15 (m, 14 H), 7.15–7.27 (m, 4 H), 7.27–7.42 (m, 4 H), 7.44–7.58 (m, 2 H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.1–16.6 (m), 53.9 (d, $J_{P–C}$ = 154.1 Hz), 55.9 (d, $J_{P–C}$ = 156.6 Hz), 62.4 (d, $J_{P–C}$ = 7.5 Hz), 62.9 (d, $J_{P–C}$ = 7.6 Hz), 63.3 (d, $J_{P–C}$ = 6.9 Hz), 63.5 (d, $J_{P–C}$ = 6.9 Hz), 63.8 (d, $J_{P–C}$ = 2.5 Hz), 64.1, 115.5, 121.9, 127.6, 127.8, 128.2, 128.3, 128.4, 128.6, 128.7, 128.9, 129.1, 129.2, 129.7, 129.8, 131.2, 132.1, 132.9, 156.7, 165.7 (d, $J_{P–C}$ = 5.0 Hz), 165.8 (d, $J_{P–C}$ = 5.0 Hz).

^{31}P NMR ($CDCl_3$, 101.25 MHz, H_3PO_4): δ = 18.59 (52%), 19.02 (48%).

Anal. Calcd for $C_{26}H_{28}NO_5P$: C, 67.07; H, 6.07; N, 3.01. Found: C, 66.95; H, 6.15; N, 3.05.

Diethyl {(4-Methoxyphenyl)-[2-(4-methoxyphenyl)-3-methoxy-4-oxoazetidin-1-yl]methyl}phosphonate (3g)
Colorless oil; mixture of two diastereoisomers.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.02–1.18 (m, 9 H), 1.25–1.37 (t, *J* = 7 Hz, 3 H), 3.03 (s, 3 H), 3.05 (s, 3 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 3.77 (s, 6 H), 3.80–4.02 (m, 6 H), 4.02–4.23 (m, 2 H), 4.53 (d, *J* = 4.5 Hz, 1 H), 4.66 (dd, *J* = 3.2, 1.5 Hz, 1 H), 4.73 (d, *J* = 5 Hz, 1 H), 4.78 (d, *J* = 20.7 Hz, 1 H), 5.05 (d, *J* = 21.5 Hz, 1 H), 5.09 (s, 1 H), 6.53 (d, *J* = 8.7 Hz, 2 H), 6.64 (d, *J* = 8.7 Hz, 2 H), 6.77–6.9 (m, 4 H), 6.96–7.12 (m, 4 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 7.37 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.1–16.5 (m), 52.6 (d, $J_{P–C}$ = 154.7 Hz), 54.6 (d, $J_{P–C}$ = 158.5 Hz), 55.1, 55.2, 58.0, 58.1, 62.4–63.4 (m), 84.9, 85.4, 113.2, 113.3, 113.5, 113.9, 123.4, 124.0, 125.4, 125.6, 130.0, 130.3, 130.9–131.4 (m), 159.3–159.5 (m), 159.6, 159.7, 159.8, 166.8 (d, $J_{P–C}$ = 5.0 Hz), 167.0 (d, $J_{P–C}$ = 5.0 Hz).

^{31}P NMR ($CDCl_3$, 101.25 MHz, H_3PO_4): δ = 18.87 (minor), 19.37 (major).

Anal. Calcd for $C_{23}H_{30}NO_7P$: C, 59.59; H, 6.53; N, 3.02. Found: C, 59.53; H, 6.45; N, 2.96.

Diethyl {(4-Methoxyphenyl)-[2-(4-methoxyphenyl)-3-phenoxy-4-oxoazetidin-1-yl]methyl}phosphonate (3h)
Colorless oil; mixture of two diastereoisomers.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.00–1.28 (m, 9 H), 1.35 (t, *J* = 7 Hz, 3 H), 3.65 (s, 3 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 3.78 (s, 3 H), 3.8–4.05 (m, 5 H), 4.05–4.25 (m, 3 H), 4.82 (d, *J* = 20.7 Hz, 1 H), 4.96 (d, *J* = 4.7 Hz, 1 H), 5.19 (d, *J* = 21.7 Hz, 1 H), 5.31 (d, *J* = 4.5 Hz, 2 H), 5.40 (d, *J* = 4.7 Hz, 1 H), 6.45–6.62 (m, 6 H), 6.62–6.92 (m, 8 H), 6.93–7.15 (m, 8 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 7.42 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.1–16.6 (m), 53.0 (d, J_{P-C} = 154.3 Hz), 54.9 (d, J_{P-C} = 158.5 Hz), 55.0–55.2 (m), 62.5 (d, J_{P-C} = 7.5 Hz), 62.9 (d, J_{P-C} = 6.9 Hz), 62.6–63.7 (m), 81.4, 81.9, 113.1, 113.2, 113.5, 114.0, 115.5, 121.9, 123.3, 123.9, 124.8, 125.0, 129.1, 130.2, 130.5, 130.9–131.5 (m), 156.9, 159.4, 159.6–159.9 (m), 165.6 (d, J_{P-C} = 5.0 Hz), 165.7 (d, J_{P-C} = 5.0 Hz).

^{31}P NMR ($CDCl_3$, 101.25 MHz, H_3PO_4): δ = 18.83 (major), 19.31 (minor).

Anal. Calcd for $C_{28}H_{32}NO_7P$: C, 62.25; H, 6.43; N, 2.79. Found: C, 62.32; H, 6.35; N, 2.70.

Diethyl {(4-Fluorophenyl)-[2-(4-fluorophenyl)-3-methoxy-4-oxo-azetidin-1-yl]methyl}phosphonate (3i)

Colorless oil; mixture of two diastereoisomers.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.98–1.25 (m, 9 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 3.02 (s, 6 H), 3.73–4.05 (m, 6 H), 4.07–4.23 (m, 2 H), 4.56 (d, *J* = 4.75 Hz, 1 H), 4.68 (dd, *J* = 4.5, 1.5 Hz, 1 H), 4.77 (d, *J* = 4.7 Hz, 1 H), 4.78 (d, *J* = 21.3 Hz, 1 H), 5.11 (d, *J* = 21.5 Hz, 1 H), 5.17 (d, *J* = 5.0 Hz, 1 H), 6.63–6.88 (m, 4 H), 6.93–7.22 (m, 8 H), 7.23–7.36 (m, 2 H), 7.37–7.48 (m, 2 H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.0–16.5 (m), 52.3 (J_{P-C} = 155.3 Hz), 54.6 (J_{P-C} = 157.8 Hz), 58.0, 58.1, 62.4–63.2 (m), 63.3–63.7 (m), 85.0, 85.5, 114.5, 114.6–115.0 (m), 115.1, 115.3, 115.5, 115.8, 127.3, 128.1 (J_{C-F} = 3.1 Hz), 129.4 (J_{C-F} = 2.5 Hz), 130.4 (J_{C-F} = 8.2 Hz), 130.7 (J_{C-F} = 8.2 Hz), 131.4–131.9 (m), 160.4–160.8 (m), 164.5–164.8 (m), 166.7 (d, J_{P-C} = 5.0 Hz), 166.8 (d, J_{P-C} = 5.0 Hz).

^{31}P NMR ($CDCl_3$, 101.25 MHz, H_3PO_4): δ = 18.33 (d, J_{P-F} = 2.2 Hz; major), 18.72 (d, J_{P-F} = 2.6 Hz; minor).

Anal. Calcd for $C_{21}H_{24}NO_5F_2P$: C, 57.38; H, 5.51; N, 3.19. Found: C, 57.52; H, 5.35; N, 3.20.

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References

(1) (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349. (b) Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211. (c) Schug, K. A.; Lindner, W. *Chem. Rev.* **2005**, *105*, 67. (d) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177. (e) Palacios, F.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2004**, *8*, 1481.

(2) Dingwall, J. G.; Campell, C. D.; Baylis, E. K. UK Pat. Appl., 1 542 938, **1979**; *Chem. Abstr.* **1979**, *88*, 105559j.

(3) Kafarski, P.; Lejczak, B.; Tyka, R.; Koba, L.; Pliszczak, E.; Wieczorek, P. *J. Plant Growth Regul.* **1995**, *14*, 199.

(4) Ishiguri, Y.; Yamada, Y.; Kato, T.; Sasaki, M.; Mukai, K. Eur. Pat. Appl., EP 82-301905, **1982**; *Chem. Abstr.* **1983**, *98*, 102686u.

(5) (a) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603. (b) Maier, L.; Lea, P. J. *Phosphorus Sulfur Relat. Elem.* **1983**, *17*, 1. (c) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845. (d) Hilderbrand, R. L. In *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, **1982**. (e) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.

(6) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Chem. Rev.* **2004**, *104*, 5823.

(7) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29.

(8) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652.

(9) Hassal, C. H. In *Antibiotics*, Vol. 6; Hahn, F. E., Ed.; Springer Verlag: Berlin, **1983**, 1.

(10) (a) Poole, K. *Cell. Mol. Life Sci.* **2004**, *61*, 2200. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (c) Dürkheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (d) *Chemistry and Biology of β-Lactam Antibiotics*, Vols. 1-3; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, **1982**.

(11) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, Vol. 2; Lukacs, G., Ed.; Springer-Verlag: Berlin, **1993**.

(12) (a) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49. (b) Hegedus, L. S. *Acc. Chem. Res.* **1996**, *28*, 299. (c) Barrett, M. A.; Sturgess, M. A. *Tetrahedron* **1988**, *44*, 5615.

(13) Staüdinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51.

(14) (a) Kukhar, V. P.; Hudson, H. R. In *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons: Chichester, **2000**. (b) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263. (c) Kaboudin, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1749.

(15) Gancarz, R.; Wieczorek, J. S. *Synthesis* **1978**, 625.

(16) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

(17) Worms, K. H.; Schmidt-Dunker, M. In *Organic Phosphorus Compounds*, Vol. 7; Kosolapoff, G. M.; Marier, L., Eds.; John Wiley & Sons: New York, **1976**, 1.

(18) Barycki, J.; Mastalerz, P.; Soroka, M. *Tetrahedron Lett.* **1970**, *36*, 3147.

(19) (a) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2002**, *43*, 4633. (b) Koster, W. H.; Zahler, R.; Chang, H. W.; Cimarusti, C. M.; Jacobs, G. A.; Perri, M. *J. Am. Chem. Soc.* **1983**, *105*, 3743. (c) Shiozaki, M.; Masuko, H. *Heterocycles* **1984**, *22*, 1727. (d) Campbell, M. M.; Carruthers, N. I.; Mickel, S. J. *Tetrahedron* **1982**, *38*, 2513. (e) Stevens, C. V.; Vekemans, W.; Moonen, K.; Rammeloo, T. *Tetrahedron Lett.* **2003**, *44*, 1619.

(20) (a) Kaboudin, B.; Moradi, K. *Synthesis* **2006**, 2339. (b) Kaboudin, B.; Jafari, E. *Synthesis* **2006**, 3063. (c) Kaboudin, B.; Moradi, K.; Sardarian, A. R. *ARKIVOC* **2007**, *(xiii)*, 210. (d) Kaboudin, B.; Jafari, E. *Synthesis* **2006**, 1823.

(21) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2689.