Microwave-assisted synthesis of peptidyl phosphorus ylides

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Dedicated to Professor Fišera on his 60th anniversary
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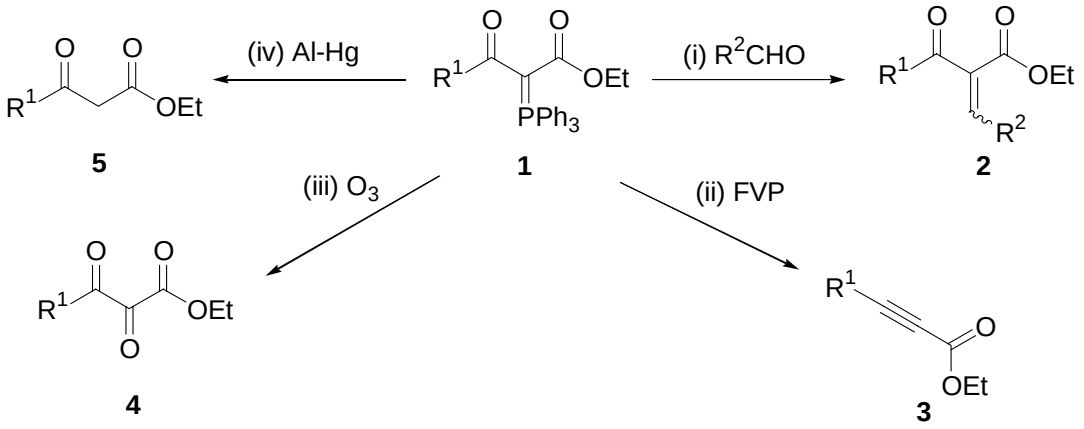
Abstract
Chiral *N*-Boc- and Cbz-protected (α-aminoacyl)benzotriazoles **6a–g** microwaved for 10 minutes with ethyl (triphenylphosphoranylidene)acetate **7** produce chiral phosphorus ylides **8a–g** in 65–90% yield. Reactions of diastereomeric chiral phosphorus ylides (**15**, **16**) demonstrated preservation of chirality.

Keywords: Phosphorus ylide, *N*-(α-aminoacyl)benzotriazoles, microwave, benzotriazole methodology

Introduction

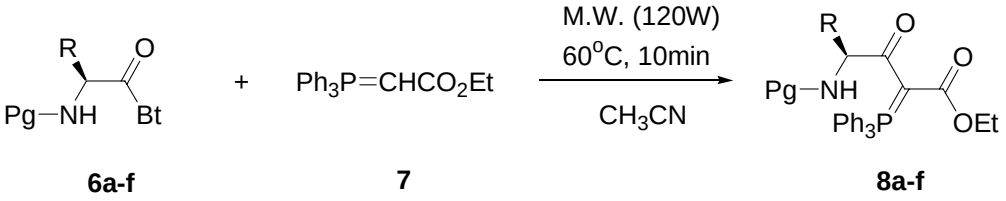
Peptidyl phosphorus ylides have attracted considerable attention as important intermediates for the preparation of peptidyl α-keto esters and α-keto amides, which are potential inhibitors for proteolytic enzymes[1a,1b] and leukotriene A_4 hydrolase.[1c] Acyl phosphorus ylides **1** have been used for (i) synthesis of olefins **2**, (ii) preparation of alkynes **3** by flash vacuum pyrolysis (FVP),[2] (iii) formation of tricarbonyl compounds **4** by oxidation with O_3[3a] or oxone®,[3b] and (iv) direct reduction with Al-Hg to obtain β-keto esters **5**.[4]

Diverse acyl phosphorus ylides **1** are readily prepared by reactions of phosphorus ylides with acyl chlorides in the presence of a base.[3,5] Peptidyl phosphorus ylides are commonly prepared in a one-pot sequence by activation of the carboxyl group in *N*-protected amino acids with CDI[6] or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCl)/DMAP,[3,5b,7] but the bases used are a potential source of low yields and problems with other functional groups. Thus, the development of a new method for the acylation of amino acid-derived phosphorus ylides without the use of base is desirable.



Scheme 1

N-Protected (α-aminoacyl)benzotriazoles are effective chiral acylating reagents for the convenient preparation of amino amides,[8a] amino sulfonamides,[8b] amino thiol esters,[8c] small peptides carrying side-chains in the first component with alkyl groups,[8d] small peptides with multi-functional groups,[8e] and amino ketones.[8f] We now demonstrate acylation of phosphorus ylides with *N*-protected (aminoacyl)benzotriazoles under microwave irradiation utilizing a single mode cavity synthesizer,[8g,8h] which helps to ensure reproducibility and safety. Microwave heating is also an effective technique for promoting a variety of reactions and shortening reaction times while reducing pollution.



Pg = Boc (*t*-butoxycarbonyl), Cbz (benzyloxycarbonyl)
Amino acid with R = *L*-Ala, *L*-Val, *L*-Phe, *L*-Asp(OMe), *L*-Trp

Scheme 2

Results and Discussion

Preparation of N-protected (α-aminoacyl)benzotriazoles

The starting *N*-(Boc-α-aminoacyl)benzotriazole **6a**,[8a] *N*-(Cbz-α-aminoacyl)benzotriazoles **6b**–**f** (*L*-configuration), **6g** (*D*-configuration), and **9a**–**c** (non-chiral) were prepared in 72–95% yields from the corresponding N-protected amino acids following recently developed procedures.[8d,8e] Compound **6e**, **6g,** and **9a**–**c** are novel, and characterized by NMR, microanalysis, and optical rotation.

Preparation of peptidyl phosphorus ylides 8a–g

Microwave reactions were carried out in a standard 50 mL round bottom flask under controlled, safe and reproducible conditions. The single mode microwave irradiation was used at a fixed temperature and irradiation power, which automatically maintained the temperature.

Optimization of the reaction conditions was investigated using the reaction of Cbz-*L*-Ala-Bt (**6b**) with **7** in CH_2Cl_2, CH_3CN, or toluene as choices of solvent with different combinations of temperature, time and irradiation power using a round bottom flask as well as a sealed heavy-walled Pyrex tube. The optimized reaction of **6b** with **7** at 60 ^oC (120 W) in CH_3CN for 10 min utilizing a round bottom flask gave the desired product **8b** in 88% yield in pure form after water-wash work-up. By contrast, reactions performed in CH_2Cl_2 at 36 ^oC and 70 W irradiation power gave no detectable **8b** within 30 minutes. In toluene, at 110 ^oC with 200 W, signals for **8b** were observed in the ^1H NMR spectrum along with signals of by-products, and the yield of **8b** was estimated as <30%. For comparison, when thermal reactions of **6b** and **6d** with **7** in refluxing CH_3CN were carried out, 12 hours was required to give the corresponding products **8b** and **8d** in 86, 79% yield, respectively. Although these yields are satisfactory, the microwave protocol is beneficial for significantly shortening the reaction time and reducing the amount of solvent required. The above optimized microwave reaction condition (60 ^oC, 120W, CH_3CN, 10 min.) was applied to the preparation of peptidyl phosphorus ylides **8a–g** (Table 1). The results exhibited fast and clean microwave acylation, and use of N-protected (α-aminoacyl)benzotriazoles **6a–g** avoided the use of base.

Compound **8a** was previously prepared in 54% yield by reaction of the corresponding Boc-protected *N*-carboxyanhydride with **7**.[10] Althought this method offers reactions without preactivation of N-protected amino acids, several steps are required to prepare the starting *N*-carboxyanhydride. Direct couplings of Cbz-Ala-OH and Cbz-Val-OH with **7** were carried out in the presence of EDCl/DMAP to produce compound **8b**, **8c** in 46% and 45% yield, respectively.[2b] The preparation of 12 ylides by this method produced average of yields 47%. By our method, compound **8a**,**b**,**c** were obtained in 64, 88, and 88% yield, respectively providing higher yields over the yields using the previously reported methods.

Unfortunately, attempts failed to produce the corresponding acyl phosphorus ylides from the *N*-(Cbz-α-aminoacyl)benzotriazole prepared from Cbz-glutamine (Cbz-Glu-Bt[8e]), instead hydrolysis of Cbz-Glu-Bt regenerated Cbz-glutamine. In case of Fmoc-Ala-Bt, a reaction gave a complex mixture from which Fmoc-Bt was isolated by column chromatography (SiO_2). The formation of Fmoc-Bt could be explained by a nucleophilic substitution with the benzotriazole anion, generated by the coupling reaction, at the carbonyl carbon in the Fmoc group.

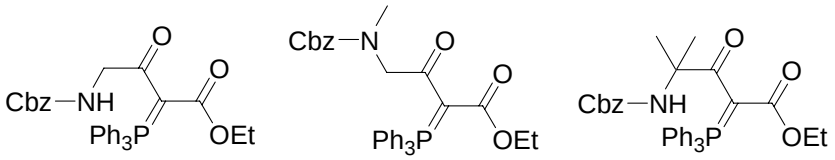
Table 1. Preparation of chiral phosphorus ylides

Product	Amino acid	Pg	R	Yield [a] (%)	Lit. yield (%)
8a	*L*-Ala	Boc	CH_3	65	54[c]
8b	*L*-Ala	Z	CH_3	88 (86)	46[d]
8c	*L*-Val	Z	$CH(CH_3)_2$	88[c]	45[d]
8d	*L*-Phe	Z	$CH_2C_6H_5$	89 (79)[b]	–
8e	*L*-Asp(OMe)	Z	CH_2CO_2Me	90	–
8f	*L*-Trp	Z	CH_2-Indol-3-yl	70	–
8g	*D*-Ala	Z	CH_3	69	–

[a] Isolated yield. [b] Yields obtained in refluxing CH_3CN. [c] Lit[10] Boc-Protected *N*-carboxyanhydride with **7**. [d] Lit.[2b] EDCl, DMAP with Cbz-Ala-OH or Cbz-Val-OH.

Preparation of non-chiral peptidyl phosphorus ylides 10, 11, 12

Reactions of non-chiral compounds **10–12** were carried out under the optimized microwave condition (60 °C, 120W, CH_3CN, 10 min.). Reaction of Cbz-Gly-Bt (**9a**) with **7** produced compound **10** in 80% yield. *N*-methylated Gly-Bt (Cbz-Sar-Bt, **9b**) reacted with **7** to give **11** in 89% yield. When Cbz-Aib-Bt (**9c**) was used under the optimized conditions, compound **12** was obtained in 3% yield. Extension of the reaction time resulted in decomposition of **9c** and no improvement of the yield was observed. Apparently, the formation of **12** was inhibited by steric hindrance from the two methyl groups at the α-position.

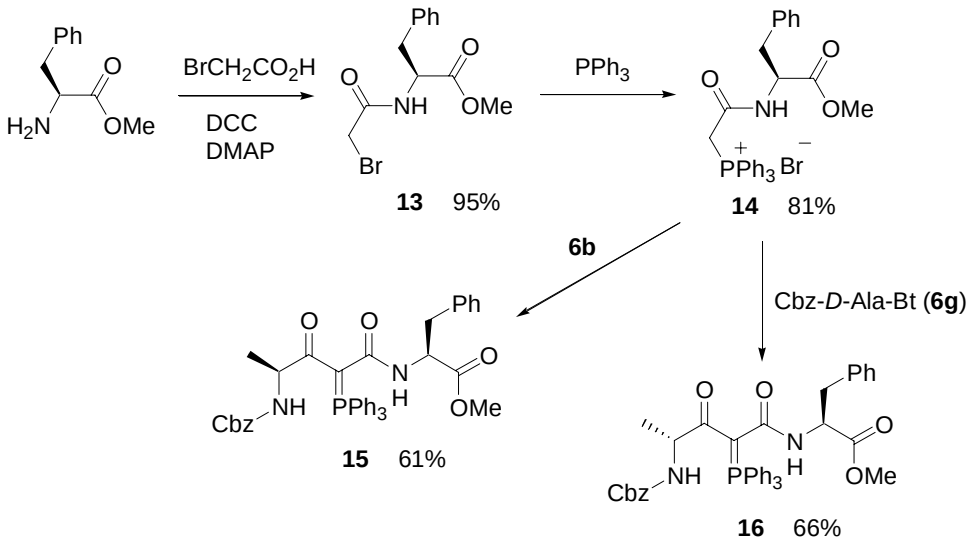


Scheme 3

Preparation of diastereomeric peptidyl phosphorus ylides

Synthesis of **15** (*LL*-config.) and **16** (*DL*-config.) was performed to test retention of the original chirality during the formation of acylphosphorus ylides. Compound **14** was prepared by following a reported procedure[6] for a similar compound prepared with valine benzyl ester; a coupling of *L*-phenylalanine methyl ester with α-bromoacetic acid in the presence of DCC/DMAP gave **13**[9] in 95% yield. Preparation of **14** was achieved by a reaction with triphenylphosphine in THF/Et_2O (1:3) to give the corresponding phosphonium salt **14**. Diastereomeric acylphosphorus ylide **15** was obtained in 61% yield under microwave conditions (60 °C, 120W, CH_3CN, 10 min.) with Cbz-*L*-Ala-Bt (**6b**) in the presence of 1 equivalent of Et_3N. Similarly, reaction of **14** with Cbz-*D*-Ala-Bt (**6g**) gave diastereomer **16** in 66% yield. The extent

of preservation of original chirality was estimated as >95% by the ^{1}H NMR spectra of the (*LL*) and (*DL*) diastereomers, **15** and **16** respectively. While enantiopure alanine methyl on the (*LL*) diastereomer (**15**) showed at 0.99 ppm, alanine methyl on the (*DL*) diastereomer (**16)** showed at 0.86 ppm. Additionally the ^{13}C NMR spectra of the two diastereomers showed a broadening of some signals, and a complex series of signals in the aromatic region, especially between 131.5 to 132.2 ppm. Upon a heated ^{13}C NMR experiment, to 60 ^{o}C, of the (*DL*) diastereomer (**16**), sharpening of the signals occurred and the complex signals separated to show two sets of doublets. In a ^{31}P NMR experiment, two broad singlets at room temperature merged at 60 ^{o}C to form one sharp singlet, indicating the presence of two rotomeric forms. These results confirmed the preservation of chirality.



Scheme 4

Conclusions

In conclusion, the preparation of peptidyl phosphorus ylides (**8a–g**, **10**, **11**, **12**, **15**, and **16**) utilizing *N*-(Boc- or Cbz-*α*-aminoacyl)benzotriazoles (**6a–g**, **9a–c**) converted from the corresponding *N*-protected amino acids was demonstrated under microwave irradiation without base. These results show an application of versatile benzotriazole methodology offering fast and effective synthesis of peptidyl phosphorus ylides using advantageous microwave heating. This procedure utilizes versatile *N*-protected (α-aminoacyl)benzotriazoles to avoid the use of base plus microwave irradiation to reduce reaction times.

Experimental Section

General Procedures. Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$ with TMS for ^1H (300 MHz) and ^{13}C (75 MHz) as the internal reference, unless otherwise specified. *N*-Boc- and Cbz-Amino acids purchased from Fluka and amino acids purchased from Acros, were used without further purification. Acetonitrile was purchased from Aldrich, and used without distillation. Microwave heating was carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, NC), producing continuous irradiation at 2455 MHz.

General procedure for the preparation of N-protected (aminoacyl)benzotriazoles Compound **6a** (Boc protecting group),[8a] **6b–f** (Cbz protecting group),[8d,8e] and **9a–c**[8d] were prepared by previously reported procedures. Compound **6e**, **6g,** and **9a–c** are all novel, and details of their properties and NMR data are described below.

Methyl (3*S*)-4-(1*H*-1,2,3-benzotriazol-1-yl)-3-{[(benzyloxy)carbonyl]amino}-4-oxobutanoate (Cbz-Asp(OMe)-Bt, 6e). Colorless needles (from chloroform/hexane), 86% yield, mp 72–74 °C. $[\alpha]^{23}_D$ = –23.4 (*c* 1.75, CH_2Cl_2). ^1H NMR δ 3.23 (dd, *J* = 16.6, 4.8 Hz, 1H), 3.38 (dd, *J* = 16.6, 4.8 Hz, 1H), 3.65 (s, 3H), 5.14 (s, 2H), 5.90–5.97 (m, 1H), 6.11 (br s, 1H), 7.35 (br s, 5H), 7.51–7.56 (m, 1H), 7.65–7.71 (m, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.27 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR δ 37.2, 51.7, 52.2, 67.4, 114.4, 120.3, 126.6, 128.1, 128.2, 128.5, 130.9, 131.2, 135.9, 145.9, 155.7, 169.2, 170.4. Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.76; H, 4.66; N, 14.58.

Benzyl *N*-[(1*R*)-2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Cbz-*D*-Ala-Bt, 6g). White crystals (from ethyl acetate/hexanes), 85% yield, mp 94–96 °C. $[\alpha]^{23}_D$ = +80.2 (*c* 2.08, CH_2Cl_2). ^1H NMR δ 1.69 (d, *J* = 7.0 Hz, 3H), 5.11 (d, *J* = 12.2 Hz, 1H, A part of AB system), 5.17 (d, *J* = 12.2 Hz, 1H, B part of AB system), 5.65 (d, *J* = 6.9 Hz, 1H), 5.81 (quintet, *J* = 7.1 Hz, 1H), 7.10–7.45 (m, 5H), 7.50–7.56 (m, 1H), 7.64–7.70 (m, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR δ 18.9, 50.5, 67.1, 114.3, 120.3, 126.4, 128.1 (2C), 128.4, 130.6, 131.1, 136.0, 145.9, 155.6, 172.2. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.82; H, 4.97; N, 17.25.

Benzyl *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)-2-oxoethyl]carbamate (Cbz-Gly-Bt, 9a). White microcrystals (from chloroform/hexane), 98% yield, mp 106–108 °C. ^1H NMR δ 5.10 (d, *J* = 5.7 Hz, 1H), 5.20 (s, 2H), 5.55 (s, 1H), 7.35–7.39 (m, 5H), 7.51–7.56 (m, 1H), 7.66–7.71 (m, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR δ 45.0, 67.7, 114.3, 120.6, 126.8, 128.4, 128.5, 128.8, 131.1, 136.2.146.2, 156.7, 168.6. Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 61.98; H, 4.57; N, 17.99.

Benzyl *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)-2-oxoethyl]-*N*-methylcarbamate (Cbz-Sar-Bt, 9b). (two rotomeric forms) Colorless crystals (from ethyl acetate/hexane), 84% yield, mp 45–46 °C. ^1H NMR δ 3.17 (s, 3H), 5.12 (s, 1H), 5.15 (s, 1H), 5.17 (s, 1H), 5.23 (s, 1H), 7.20–7.26 (m, 2H), 7.34–7.44, (m, 3H), 7.51–7.57 (m, 2H), 7.65–7.72 (m, 2H), 8.13–8.15 (m, 1H), 8.23–8.28

(m, 1H). ^{13}C NMR δ 35.8, 36.3, 52.4, 52.8, 67.6, 67.8, 114.1, 120.3, 126.4, 126.5, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 130.7, 130.8, 131.0, 136.2, 136.4, 145.9, 156.1, 156.9, 167.8, 167.9. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.82; H, 4.99; N, 17.30.

Benzyl *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)-1,1-dimethyl-2-oxoethyl]carbamate (Cbz-Aib-Bt, 9c). Colorless needles (from chloroform/hexane), 80% yield, mp 98–100 °C. ^{1}H NMR δ 1.88 (s, 6H), 4.90 (s, 2H), 5.77 (br s, 1H), 7.11–7.20 (m, 5H), 7.47–7.53 (m, 1H), 7.62–7.67 (m, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR δ 26.0, 58.9, 66.8, 115.0, 119.9, 126.0, 127.8, 128.0, 128.3, 130.5, 131.9, 135.9, 144.8, 155.3, 172.6. Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.73; H, 5.22; N, 16.55.

General procedure for the preparation of peptidyl ylides under the microwave irraditation

A dry 50 mL round bottom flask with a magnetic stir bar was equipped with a condenser, and the apparatus was charged with a solution of N-protected (aminoacyl)benzotriazole **6** (1.1 mmol) and ethyl (triphenylphosphoranylidene)acetate **7** (0.348 g, 1.0 mmol) in acetonitrile (1 mL). The flask containing the reaction mixture was exposed to microwave irradiation (120 W) for 10 min at a temperature of 60 °C. The reaction mixture was cooled with high-pressure air through an inbuilt system in the instrument until temperature had fallen below 30 °C (ca. 2 min). The reaction mixture was diluted with ethyl acetate, and the organic solution was washed with saturated aqueous Na_2CO_3 solution, water, and dried over $MgSO_4$ to give a crude product, which was purified by column chromatography on silica gel with hexane/ethyl acetate (1:1).

Procedure for the preparation of 8b, 8d under the conventional heating

A dry 50 mL round bottom flask with a stir bar was attached to a condenser, and the apparatus was charged with a solution of N-protected (aminoacyl)benzotriazole **6** (1.1 mmol) and ethyl (triphenyl phosphoranylidene)acetate **7** (0.348 g, 1.0 mmol) in acetonitrile (15 mL). The reaction mixture was heated in an oil bath at 70–80 °C for about 12 hours until the starting materials were completely consumed (Monitored by TLC, hexanes:ethyl acetate = 1:1). After concentration under reduced pressure, the residue was diluted with ethyl acetate, and the organic solution was washed with saturated Na_2CO_3 solution, water, and dried over $MgSO_4$ to give a crude product, which was purified by column chromatography on silica gel with hexane/ethyl acetate (1:1).

Ethyl (*S*)-4-*tert*-butoxycarbonylamino-3-oxo-2-(triphenylphosphanylidene)pentanoate (8a). Colorless microcrystals (from ethyl acetate/hexanes), 65% yield, mp 153–155 °C (lit.[10] mp 153–155 °C). $[\alpha]^{23}_D$ = +0.2 (*c* 1.67, CH_2Cl_2). ^{1}H NMR δ 0.75 (t, *J* = 7.0 Hz, 3H), 1.38 (s, 9H), 1.43 (d, *J* = 6.3 Hz, 3H), 3.65–3.95 (m, 2H), 5.38–5.51 (m, 2H), 7.44–7.68 (m, 15H). ^{13}C NMR δ 13.7, 20.1, 28.3, 51.9 (J_{CP} = 8.0 Hz), 58.6, 68.9 (J_{CP} = 110.5 Hz), 78.3, 126.1 (J_{CP} = 93.3 Hz), 128.5 (J_{CP} = 12.6 Hz), 131.7, 133.0 (J_{CP} = 9.7 Hz), 155.2, 166.7 (J_{CP} = 15.5 Hz), 195.5.

Ethyl (4*S*)-4-{[(benzyloxy)carbonyl]amino}-3-oxo-2-(triphenylphosphanylidene)pentanoate (8b). Colorless microcrystals (from chloroform/hexane), 86% yield, mp 140–142 °C (lit.[2b] 140–142 °C). $[\alpha]^{23}_D$ = +25.4 (*c* 1.58, CH_2Cl_2) (lit.[2b] $[\alpha]^{20}_D$ = +20.3 [*c* 1.0005, CH_2Cl_2]). ^{1}H NMR δ 0.75 (t, *J* = 7.0 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 3.69–3.82 (m, 2H), 5.06 (s, 2H), 5.49

(quintet, J = 7.1 Hz, 1H), 5.85 (d, J = 7.6 Hz, 1H), 7.27–7.68 (m, 20H). ^{13}C NMR δ 13.7, 20.4, 52.4 (J_{CP} = 8.6 Hz), 58.6, 65.9, 68.8 (J_{CP} = 111.1 Hz), 126.0 (J_{CP} = 93.3 Hz), 127.6 (3C), 128.2, 128.5 (J_{CP} = 12.6 Hz), 131.8 (J_{CP} = 2.9 Hz), 133.0 (J_{CP} = 9.7 Hz), 137.1, 155.4, 166.7 (J_{CP} = 14.3 Hz), 194.7. Anal. Calcd for $C_{33}H_{32}NO_5P$: C, 71.60; H, 5.83; N, 2.53. Found: C, 71.39; H, 5.78; N, 2.40.

Ethyl (4*S*)-4-{[benzyloxy)carbonyl]amino-5-methyl-3-oxo-2-(triphenylphosphoranylidene) hexanoate (8c). Colorless crystals (from ethyl acetate/hexanes), 88% yield, mp 88–90 °C (lit.[2b] 88–91 °C). $[\alpha]^{23}_D$ = +28.0 (*c* 1.66, CH_2Cl_2). ^{1}H NMR δ 0.68 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H), 2.42–2.45 (m, 1H), 3.68–3.85 (m, 2H), 5.06 (s, 2H), 5.52–5.56 (m, 1H), 5.68 (d, J = 8.9 Hz, 7.39–7.20 (m, 5H), 7.51–7.40 (m, 10H), 7.80–7.63 (m, 5H). ^{13}C NMR δ 13.8, 15.9, 20.7, 32.3, 58.6, 60.4 (*J*cp = 8.5 Hz), 66.0, 69.8 (*J*cp = 111.0 Hz), 126.0 (*J*cp = 93.9 Hz), 127.6 (3C), 128.2, 128.5 (*J*cp = 12.6 Hz), 131.8 (*J*cp = <2 Hz), 133.0 (*J*cp = 9.7 Hz), 137.1, 156.6, 166.8 (*J*cp = 14.2 Hz).

Ethyl (4*S*)-4-{[(benzyloxy)carbonyl]amino}-3-oxo-5-phenyl-2-(triphenylphosphanylidene) pentanoate (8d). Colorless foam, 79% yield, mp 51–53 °C. $[\alpha]^{23}_D$ = +0.58 (*c* 1.66, CH_2Cl_2). ^{1}H NMR δ 0.71 (t, J = 7.1 Hz, 3H), 2.83 (dd, J = 13.2, 7.7 Hz, 1H), 3.40 (dd, J = 13.2, 4.4 Hz, 1H), 3.70–3.85 (m, 2H), 4.95 (d, J = 12.8 Hz, 1H, A part of AB system), 5.02 (d, J = 12.8 Hz, 1H, B part of AB system), 5.58 (d, J = 8.9 Hz, 1H), 5.80–5.87 (m, 1H), 7.16–7.32 (m, 10H), 7.41–7.47 (m, 5H), 7.53–7.66 (m, 10H). ^{13}C NMR δ 13.7, 39.8, 56.8(J_{CP} = 8.6 Hz), 58.7, 65.9, 70.1 (J_{CP} = 108.8 Hz), 125.9 (J_{CP} = 93.9 Hz) 126.0, 127.5, 127.9, 128.2, 128.5 (J_{CP} = 12.6 Hz), 129.7, 131.7 (J_{CP} = 2.9 Hz) 133.1 (J_{CP} = 9.7 Hz), 137.1, 138.0, 155.7, 166.9 (J_{CP} = 14.3 Hz), 193.5. Anal. Calcd for $C_{39}H_{36}NO_5P$: C, 74.39; H, 5.76; N, 2.22. Found: C, 74.10; H, 5.83; N, 2.58.

1-Ethyl 6-methyl (4*S*)-4-{[(benzyloxy)carbonyl]amino}-3-oxo-2-(triphenyl phosphanylidene)hexanedioate (8e). Colorless microcrystals (from ethyl acetate/hexanes), 90% yield, mp 116–118 °C. $[\alpha]^{23}_D$ = +0.84 (*c* 1.91, CH_2Cl_2). ^{1}H NMR δ 0.72 (t, J = 6.9 Hz, 3H), 2.82 (dd, J = 14.3, 6.7 Hz, 1H), 3.09 (dd, J = 14.3, 3.4 Hz, 1H), 3.56 (s, 3H), 3.69–3.85 (m, 2H), 5.06 (s, 2H), 5.76–5.81 (m, 1H), 5.91 (d, J = 8.1 Hz, 1H), 7.22–7.72 (m, 20H). ^{13}C NMR δ 13.6, 38.6, 51.5, 53.6 (J_{CP} = 9.2 Hz), 58.8, 66.1, 69.3 (J_{CP} = 109.4 Hz), 125.6 (J_{CP} = 93.9 Hz), 127.5, 127.6, 128.2, 128.5 (J_{CP} = 12.6 Hz), 131.8 (J_{CP} = 2.9 Hz), 133.1 (J_{CP} = 9.7 Hz), 136.9, 155.6, 166.7 (J_{CP} = 14.3 Hz), 171.5, 191.8. Anal. Calcd for $C_{35}H_{34}NO_7P$: C, 68.73; H, 5.60; N, 2.29. Found: C, 68.66; H, 5.65; N, 2.22.

Ethyl (*S*)-4-benzyloxycarbonylamino-5-(1*H*-indol-3-yl)-3-oxo-2-(triphenyl-phosphanylidene)pentanoate (8f). White microcrystals (from chloroform/hexanes), 71% yield, mp 88–90 °C. $[\alpha]^{23}_D$ = +40.0 (*c* 1.67, CH_2Cl_2). ^{1}H NMR δ 0.72 (t, J = 7.0 Hz, 3H), 3.26 (dd, J = 14.7, 6.9 Hz, 1H), 3.51 (dd, J = 14.7, 4.5 Hz, 1H), 3.68–3.83 (m, 2H), 4.97 (s, 2H), 5.70–5.80 (m, 1H), 5.80–5.91 (m, 1H), 6.91 (s, 1H), 7.00–7.40 (m, 15H), 7.40–7.60 (m, 9H), 7.71 (d, J = 7.6 Hz, 1H), 7.90 (s, 1H). ^{13}C NMR δ 13.7, 28.8, 56.5 (J_{CP} = 8.6 Hz), 58.8, 68.3 (J_{CP} = 96.3 Hz), 110.9, 111.5, 119.0, 121.3, 122.9, 125.9 (J_{CP} = 93.3 Hz), 127.6, 127.9, 128.2, 128.5 (J_{CP} = 12.6 Hz), 131.6, 132.0, 132.1, 133.0 (J_{CP} = 9.7 Hz), 135.9, 137.0, 155.8, 166.9 (J_{CP} = 13.7 Hz),

193.9. Anal. Calcd for $C_{41}H_{37}N_2O_5P$: C, 73.64; H, 5.58; N, 4.19. Found: C, 73.07; H, 5.58; N, 4.16. HRMS *m/z* Calcd for $C_{41}H_{37}N_2O_5P$ 669.2513 ($M+H^+$), Found 5569.2523.

Ethyl (*R*)-4-benzyloxycarbonylamino-3-oxo-2-(triphenylphosphanylidene)-pentanoate (8g). Colorless crystals (from ethyl acetate/hexane), 69% yield, mp 135–137 °C. $[\alpha]^{23}_D$ = –17.5 (c 2.08, CH_2Cl_2). ^{1}H NMR δ 0.75 (t, *J* = 7.1 Hz, 3H), 1.48 (d, *J* = 7.1 Hz, 3H), 3.66–3.88 (m, 2H), 5.06 (s, 2H), 5.50 (quintet, *J* = 6.7 Hz, 1H), 5.86 (d, *J* = 7.7 Hz, 1H), 7.26–7.68 (m, 20H). ^{13}C NMR δ 13.7, 20.3, 52.4 (J_{CP} = 8.6 Hz), 58.6, 65.8, 68.8 (J_{CP} = 110.5 Hz), 125.8 (J_{CP} = 93.9 Hz), 127.5, 127.6, 128.2, 128.5 (J_{CP} = 12.6 Hz), 131.7, 131.8 (J_{CP} = 2.9 Hz), 132.9 (J_{CP} = 9.7 Hz), 137.0, 155.4, 166.7 (J_{CP} = 14.3 Hz), 194.8. Anal. Calcd for $C_{33}H_{32}NO_5P$: C, 71.60; H, 5.83; N, 2.53. Found: C, 71.20; H, 5.89; N, 2.56.

Ethyl 4-benzyloxycarbonylamino-3-oxo-2-(triphenylphosphanylidene)butanoate (10). White microcrystals (from ethyl acetate/hexanes), 80% yield, mp 134–136 °C (lit.[10] mp 134–136 °C). ^{1}H NMR δ 0.75 (t, *J* = 7.0 Hz, 3H), 3.70–3.82 (m, 2H), 4.60 (d, *J* = 4.0 Hz, 2H), 5.06 (s, 2H), 5.85 (s, 1H), 7.22–7.70 (m, 20H). ^{13}C NMR δ 13.8, 49.3 (J_{CP} = 8.6 Hz), 58.6, 66.1, 68.9 (J_{CP} = 112.8 Hz) 125.7 (J_{CP} = 93.3 Hz), 127.6, 127.7, 128.6 (J_{CP} = 12.6 Hz), 131.9 (J_{CP} = 2.9 Hz), 133.1 (J_{CP} = 9.7 Hz), 136.9, 156.1, 167.3 (J_{CP} = 14.3 Hz), 190.3. Anal. Calcd for $C_{32}H_{30}NO_5P$: C, 71.23; H, 5.60; N, 2.60. Found: C, 71.11; H, 5.79; N, 2.63.

Ethyl 4-(benzyloxycarbonyl-methyl-amino)-3-oxo-2-(triphenylphosphanylidene)butanoate (11). (two rotomeric forms) White microcrystals (from ethyl acetate/hexanes), 89% yield, mp 133–135 °C. ^{1}H NMR δ 0.64 (d, *J* = 7.0 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H), 2.83 (s, 3H), 2.85 (s, 3H), 3.74 (quintet, *J* = 7.1 Hz, 2H), 4.69 (s, 2H), 5.04 (s, 1H), 5.06 (s, 1H), 7.25–7.70 (m, 20H). ^{13}C NMR δ 13.5, 13.7, 35.5, 36.1, 57.1 (J_{CP} = 8.6 Hz), 57.5 (J_{CP} = 8.0 Hz), 58.2, 66.3, 66.6, 68.6 (J_{CP} = 109.9 Hz), 68.9 (J_{CP} = 111.7 Hz), 125.9 (J_{CP} = 93.3 Hz), 126.0 (J_{CP} = 93.3 Hz), 126.9, 127.2, 127.4, 127.5, 128.1, 128.1, 128.3 (J_{CP} = 12.6 Hz), 128.3 (J_{CP} = 12.6 Hz), 131.5, 131.5, 131.6, 131.8, 131.9, 132.9, 133.0, 133.1, 137.0, 137.3, 156.6, 156.7, 167.5 167.7, 167.9, 191.1 (J_{CP} = 3.4 Hz), 191.6 (J_{CP} = 3.4 Hz). HRMS *m/z* Calcd for $C_{33}H_{32}NO_5P$ 554.2091 ($M+H^+$), Found 554.2106.

Ethyl 4-benzyloxycarbonylamino-4-methyl-3-oxo-2-(triphenylphosphanylidene)pentanoate (12). White crystals (from ethyl acetate/hexanes), 3% yield, mp 80–81 °C. ^{1}H NMR ($CDCl_3$) δ 0.56 (t, *J* = 7.1 Hz, 3H), 1.63 (s, 6H), 3.58 (q, *J* = 7.1 Hz, 2H), 5.14 (br s, 2H), 6.79 (s, 1H), 7.25–7.68 (m, 20H). ^{13}C NMR ($CDCl_3$) δ 13.5, 25.0, 58.7, 60.1, 60.2, 65.6, 68.9 (J_{CP} = 109.4 Hz), 127.0 (J_{CP} = 93.9 Hz), 127.4, 127.5, 128.3, 128.5 (J_{CP} = 12.0 Hz), 131.4 (J_{CP} = 2.9 Hz), 132.9 (J_{CP} = 9.7 Hz), 137.4, 155.8, 167.2 (J_{CP} = 13.2 Hz), 198.2. HRMS *m/z* Calcd for $C_{34}H_{34}NO_5P$ 568.2247 ($M+H^+$), Found 568.2269.

[(*S*)-1-Methoxycarbonyl-2-phenyl-ethylcarbamoyl)-methyl]-triphenylphosphonium bromide (14). White crystal (from dichloromethane/hexanes), 81% yield, mp 155–157 °C, $[\alpha]^{23}_D$ = –9.7 (*c* 2.08, CH_2Cl_2). ^{1}H NMR (DMSO-d_6) δ 2.83 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.97 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.56 (s, 3H), 4.38–4.43 (m, 1H), 5.02–5.09 (m, 2H), 7.13–7.35 (m, 5H), 7.50–7.91 (m, 15H), 9.07 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 30.6 (J_{CP} = 57.3 Hz), 36.5, 52.0, 54.3, 118.6 (J_{CP} = 88.2 Hz), 126.7, 128.3, 129.1, 129.9 (J_{CP} = 13.2 Hz), 133.7 (J_{CP} = 10.3 Hz), 134.8,

136.5, 163.0 (J_{CP} = 4.6 Hz), 170.9. Anal. Calcd for $C_{30}H_{29}BrNO_3P$: C, 64.06; H, 5.20; N, 2.49. Found: C, 63.76; H, 5.18; N, 2.41.

Methyl-(*S*)-2-[(*S*)-4-benzyloxycarbonylamino-3-oxo-2-(triphenylphosphanylidene)pentanoylamino]-3-phenyl-propionate (15). (two rotomeric forms) White crystals (from dichloromethane/hexanes), 61% yield, mp 65–68 °C, $[\alpha]^{23}_D$ = –20.0 (*c* 2.08, CH_2Cl_2). ^{1}H NMR δ 0.99 (d, *J* = 4.8 Hz, 3H), 1.87 (s, 1H), 2.99 (dd, *J* = 13.5, 8.5 Hz, 1H), 3.12 (dd, *J* = 13.5, 5.2 Hz, 1H), 3.61 (s, 3H), 4.65-4.72 (m, 1H) 4.95-5.06 (m, 2H), 5.66 (br s, 1H), 7.23-7.70 (m, 26H). ^{13}C NMR δ 20.4, 38.1, 50.5, 51.7, 53.6, 65.9, 72.2 (J_{CP} = 116.8 Hz), 126.1 (d, J_{CP} = 93.3 Hz,), 126.3, 127.5, 127.6, 128.0, 128.1, 128.2, 128.3, 128.5 (J_{CP} = 12.6 Hz), 129.2, 131.5, 131.7, 131.9, 132.9 (J_{CP} = 9.7 Hz), 136.6, 137.0, 155.1, 168.5, 172.6, 191.2. Anal. Calcd for $C_{41}H_{39}N_2O_6P$: C, 71.71; H, 5.72; N, 4.08. Found: C, 71.85; H, 5.81; N, 3.75.

Methyl-(*S*)-2-[(*R*)-4-benzyloxycarbonylamino-3-oxo-2-(triphenylphosphanylidene)-pentanoylamino]-3-phenyl-propionate (16). (two rotomeric forms) White crystals (from dichloromethane/hexanes), 66% yield, mp 46–48 °C, $[\alpha]^{23}_D$ = +4.4 (*c* 2.08, CH_2Cl_2). ^{1}H NMR δ 0.86 (d, *J* = 6.7 Hz, 3H), 1.90 (s, 1H), 2.98 (dd, *J* = 13.8, 7.9 Hz, 1H), 3.11 (dd, *J* = 13.6, 5.4 Hz, 1H), 3.61 (s, 3H), 4.67-4.74 (m, 1H) 5.03 (br s, 2H), 5.60 (br s, 1H), 7.15-7.70 (m, 26H). ^{13}C NMR δ 20.3, 38.1, 50.6, 51.8 (J_{CP} = 4.6 Hz), 53.7, 66.1, 72.8 (J_{CP} = 119.7 Hz), 126.5 (J_{CP} = 93.9 Hz,), 126.5, 127.7, 127.8,128.3, 128.4, 128.5, 128.7 (J_{CP} = 12.6 Hz), 129.2, 131.7, 131.9, 131.9, 132.0, 132.1, 133.2 (J_{CP} = 9.7 Hz), 136.7, 137.1, 155.3, 169.2, 172.8, 191.5. [^{13}C NMR ($CDCl_3$, 60 °C, aromatic region) δ 127.0 (J_{CP} = 93.7 Hz,), 126.5, 127.8,128.3, 128.4, 128.5 (J_{CP} = 12.1 Hz), 128.7 (J_{CP} = 12.6 Hz), 129.3, 131.8 (J_{CP} = 3.3 Hz), 131.9 (J_{CP} = 3.0 Hz), 132.2 (J_{CP} = 9.8 Hz), 133.4 (J_{CP} = 9.8 Hz), 136.7, 137.1.]. Anal. Calcd for $C_{41}H_{39}N_2O_6P$: C, 71.71; H, 5.72; N, 4.08. Found: C, 71.34; H, 5.89; N, 3.51.

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