# The Carbenoid Approach to Peptide Synthesis

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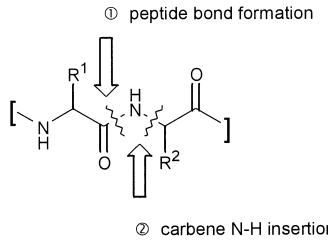
**Abstract:** A different approach to the synthesis of dipeptides is described based on the formation of the NHCHR$^1$CONH−CHR$^2$CO bond by carbenoid N−H insertion, rather than the formation of the peptide bond itself. Thus decomposition of triethyl diazophosphonoacetate catalysed by rhodium(II) acetate in the presence of N-protected amino acid amides **8** gives the phosphonates **9.** Subsequent Wadsworth–Emmons reaction of **9** with aldehydes in the presence of DBU gives dehydro dipeptides **10**. The reaction has been extended to a simple two-step procedure, without the isolation of the intermediate phosphonate, for conversion of a range of amino acid amides **11** into dehydro dipeptides **12** and to an *N*-methylamide **11h**, and for conversion of a dipeptide to tripeptide (**13** → **14**). Direct conversion, by using methyl diazophenylacetate, of amino acid amides to phenylglycine-containing dipeptides **19** proceeds in good chemical yield, but with poor diastereoselectivity.

**Keywords:** amino acids · carbenoids · insertions · peptides · rhodium

## Introduction

Peptides and proteins play a central role in all living organisms, and hence the synthesis of such compounds has emerged as a subject in its own right.[1] In fact, peptide synthesis is so highly developed that chemists rarely, if ever, consider any approach other than the formation of the amide bond (Scheme 1, disconnection 1). We now report a new approach to peptide synthesis that involves the formation of the CONH−CHRCO bond by a metal-carbene N−H insertion reaction (Scheme 1, disconnection 2), and its application in synthesis.




Scheme 1. Alternative disconnections for dipeptides.

The N−H insertion reactions of metallocarbenoids have been known for some time. Early work by Yates involved the copper/bronze-catalysed decomposition of diazoacetophenone in the presence of aniline or piperidine to give $\alpha$-anilinoacetophenone and $\alpha$-piperidinoacetophenone in 33% and 80% yield, respectively.[2] Further copper-mediated intermolecular N−H carbenoid insertion reactions followed, but it was the 1974 report by Paulissen and co-workers, that rhodium(II) acetate was an effective catalyst for N−H insertion reactions of carbenoids, which stimulated much of the subsequent work in this area.[3] In particular, following the original report from the Merck group in 1978,[4] the intramolecular rhodium-carbenoid insertion into a $\beta$-lactam N−H bond has become a standard synthetic route to a range of bicyclic $\beta$-lactams.[5]

We have recently described the application of carbenoid N−H insertion reactions in the preparation of $\alpha$-amino acids, $\alpha$-aminophosphonates and phosphonoglycines (Scheme 2),[6, 7] and therefore were attracted by the possibility of using such N−H insertions in a synthesis of dipeptides which, unusually, does not rely on formation of the peptide bond itself.

Two approaches that start from readily available N-protected amino acid amides **1** were considered (Scheme 3, Pg = protecting group). The first was the use of diazoesters, which would lead directly to dipeptides **2** (Scheme 3, path a).

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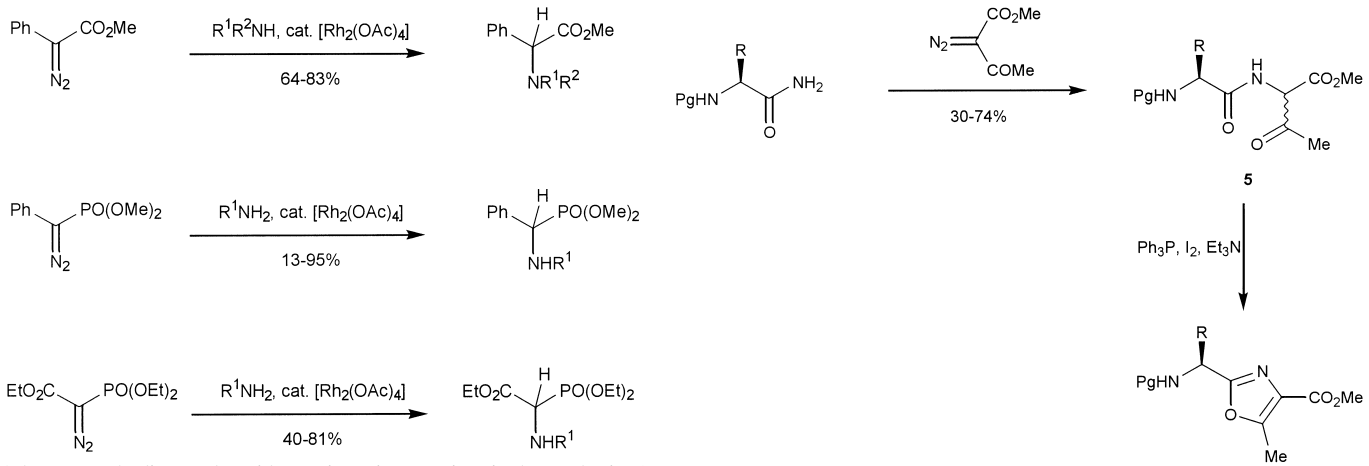
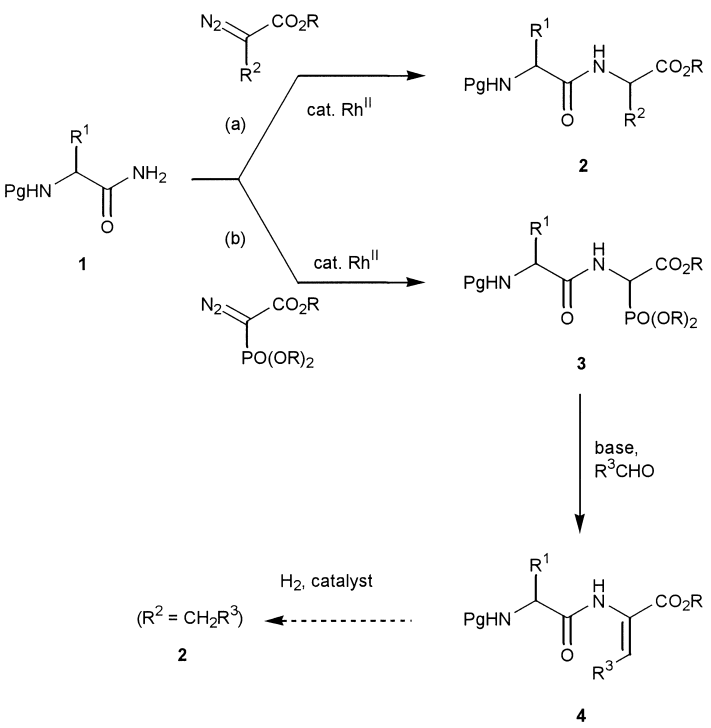


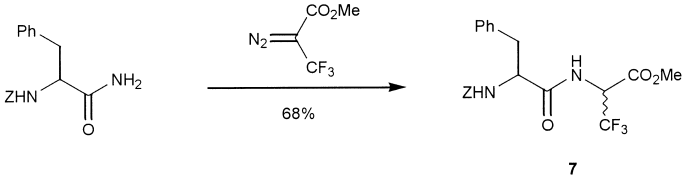

Scheme 2. Rhodium carbenoid N–H insertion reactions in the synthesis of amino acid and aminophosphonate derivatives.




Scheme 3. Possible approaches to dipeptides using rhodium carbenoid N–H insertion reactions.

The second involves diazophosphonoacetate as the carbenoid precursor, to give the phosphonates **3**, Wadsworth–Emmons reaction of which leads to the dehydro dipeptide **4** (Scheme 3, path b). Stereoselective hydrogenation of dehydro dipeptide **4** would, of course, provide an alternative route to the dipeptide **2** ($R^2 = CH_2R^3$).

Our initial work on the N–H insertion reactions of amino acid amides employed methyl 2-diazo-3-oxobutanoate as the carbenoid precursor. This resulted in a regioselective N–H insertion reaction to give the dipeptides **5**, which were subsequently dehydrated to the oxazoles **6** (Scheme 4).[8, 9] In addition to our own work in the area, there is another reported example of this approach that resulted in the synthesis of the dipeptide Z-Phe-$\beta,\beta,\beta$-trifluoroAla-OMe **7** by reaction of *N*-Z-phenylalaninamide with methyl 2-diazo-3,3,3-trifluoropropionate catalysed by rhodium(II) acetate (Scheme 4).[10] We now report the details of our new approach to peptide synthesis,[11] concentrating on the preparation of dehydro dipeptides **4** (Scheme 3b).



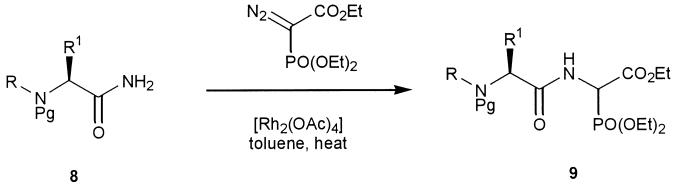

Scheme 4. Carbenoid insertions into the N–H bond of primary amides.

## Results and Discussion

A range of N-protected $\alpha$-amino acid amides was prepared from the corresponding acids by using standard techniques; the subsequent insertion reactions were initially carried out on amino acids with simple alkyl side chains to prevent competing carbenoid reactions. The key N–H insertion reaction was carried out by treating a mixture of the N-protected amino acid amide **8** and triethyl diazophosphonoacetate with a catalytic amount of rhodium(II) acetate in toluene, and resulted in the formation of the phosphonates **9**. Initial reactions were carried out in toluene under reflux, and gave the phosphonates **9** in good yield (Table 1). However, at these temperatures decomposition of the diazophosphonate appears to compete with N–H insertion, and although the product phosphonates **9** gave satisfactory spectroscopic data they could never be obtained analytically pure. The N–H insertion reaction was completely regioselective in that no products resulting from insertion into the carbamate N–H bond or C–H bonds were observed. Although related phosphonates have been prepared by the synthesis of the corresponding $\alpha$-aminophosphonate, $H_2NCH(CO_2R)$-$PO(OR^1)_2$, followed by standard peptide coupling[12, 13] this new method has the advantage of simplicity.

To complete the synthesis of dehydro dipeptides, the phosphonates **9** were subjected to the Wadsworth–Emmons reaction with aldehydes. Although various protocols have

Table 1. Formation of phosphonates **9** from amides **8**.

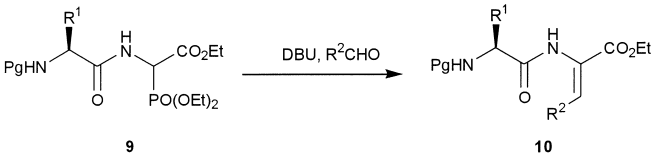



**8** **9**

| Starting amino acid | Amide | Pg | R | $R^1$ | Phosphonate | Yield [%][a] |
|---|---|---|---|---|---|---|
| Gly | **8a** | Z | H | H | **9a** | 81 |
| Ala | **8b** | Boc | H | Me | **9b** | 88 |
| Ala | **8c** | Z | H | Me | **9c** | 80 |
| Val | **8d** | Boc | H | *i*Pr | **9d** | 80 |
| Leu | **8e** | Boc | H | *i*Bu | **9e** | 82 |
| Pro | **8f** | Z | $-(CH_2)_3-$ | | **9f** | 80 |

[a] The phosphonates **9** could not be obtained analytically pure; yield refers to material that is homogeneous by TLC and that gave satisfactory spectroscopic data.

Table 2. Formation of dehydrodipeptides **10** from phosphonates **9**.




**9** **10**

| Phosphonate | Pg | $R^1$ | $R^2$ | Dehydro-dipeptide | | Yield [%] |
|---|---|---|---|---|---|---|
| **9a** | Z | H | Ph | Z-Gly-ΔPhe-OEt | **10a** | 82 |
| **9b** | Boc | Me | Ph | Boc-Ala-ΔPhe-OEt | **10b** | 88 |
| **9e** | Boc | *i*Bu | Ph | Boc-Leu-ΔPhe-OEt | **10c** | 88 |
| **9e** | Boc | *i*Bu | *i*Pr | Boc-Leu-ΔLeu-OEt | **10d** | 80 |
| **9e** | Boc | *i*Bu | Ar[a] | Boc-Leu-ΔTrp(Boc)-OEt | **10e** | 79 |

[a] Ar = *N*-Boc-indol-3-yl.

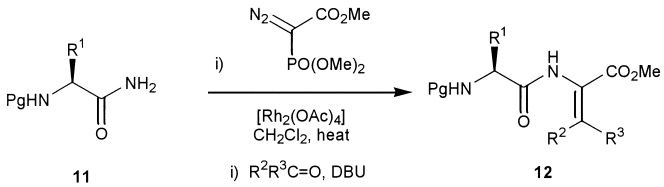
been developed for the synthesis of dehydro amino acid derivatives by using the Wadsworth–Emmons reaction, we used the Schmidt method with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base.[14] This is highly *Z* selective, and gave the corresponding *Z*-dehydro dipeptides **10** in good yield (Table 2) with benzaldehyde, isobutyraldehyde, or *N*-Boc-indole-3-carboxaldehyde as the carbonyl component.

There is no need to purify the phosphonates before carrying out the subsequent olefination reaction. If the N–H insertion reaction with trimethyl diazophosphonoacetate is carried out over a longer period of time at a lower temperature (dichloromethane, reflux), a cleaner reaction mixture ensues. After a brief aqueous work-up, the N–H insertion product can be used directly in the Wadsworth–Emmons reaction. In this way, a range of amides **11** derived from Leu, Phe, Ser, Tyr and Trp were converted into dehydro dipeptides **12** by using benzaldehyde, isobutyraldehyde, *N*-Boc-indole-3-carboxaldehyde, acetaldehyde or acetone as the carbonyl component (Table 3). In the case of Ser and Tyr, the side chain OH groups had to be protected; without this *O*-protection the insertion reaction was more complex, presumably as a result of competing O–H insertion.[15] No competing attack of the rhodium carbenoid on the aromatic rings of Phe, Tyr or Trp was observed. However, in the case of Trp, indole-N-protection was necessary to achieve a high yield in the Wadsworth–Emmons reaction. Use of *N*-Boc-methioninamide failed to give any N–H insertion product; the reaction mixture immediately turned purple, presumably due to catalyst poisoning.

The reaction sequence could be extended to include *N*-methyl amides such as **11h**, which gave the dehydro dipeptide **12h** of an *N*-methyl amino acid (Scheme 5). Finally, in order to demonstrate the selectivity of the carbenoid N–H insertion reaction, the dipeptide amide Boc-Ala-Leu-$NH_2$ (**13**) was treated with trimethyl diazophosphonoacetate to give an N–H insertion product, which was immediately subjected to Wadsworth–Emmons reaction with benzaldehyde to give the tripeptide Boc-Ala-Leu-ΔPhe-OMe (**14**) in 50% yield over the two steps (Scheme 5).

The carbenoid approach to dipeptides was applied to the synthesis of the dehydro dipeptide fragment of Mm-2 **15** ($Ar^1$ = 3,4-dihydroxyphenyl), a blood pigment of the tunicate *Molgula manhattensis*.[16] Although this compound has been synthesized previously,[16] the projected disconnection (Scheme 6) to the protected dehydro dipeptide **16** ($Ar^2$ = 3,4-dibenzyloxyphenyl) differs from the published strategy. The phosphonate **17**, prepared from *N*-Boc-leucinamide (**8e**)

Table 3. Formation of dehydro dipeptides **12** from amides **11**.




**11** **12**

| Starting amino acid | Amide | Pg | $R^1$ | $R^2$ | $R^3$ | Dehydrodipeptide | | Yield [%] |
|---|---|---|---|---|---|---|---|---|
| Leu | **11a** | Z | *i*Bu | Ph | H | Z-Leu-ΔPhe-OMe | **12a** | 65 |
| Leu | **11b** | Ac | *i*Bu | Ph | H | Ac-Leu-ΔPhe-OMe | **12b** | 37 |
| Phe | **11c** | Boc | $CH_2Ph$ | *i*Pr | H | Boc-Phe-ΔLeu-OMe | **12c** | 60 |
| Ser | **11d** | Boc | $CH_2OTBS$[a] | Ar[b] | H | Boc-Ser(TBS)-ΔTrp(Boc)-OMe | **12d** | 77 |
| Ser | **11d** | Boc | $CH_2OTBS$ | Me | Me | Boc-Ser(TBS)-ΔVal-OMe | **12e** | 30 |
| Tyr | **11e** | Boc | $CH_2$-$C_6H_4$-OTBS | *i*Pr | H | Boc-Tyr(TBS)-ΔLeu-OMe | **12f** | 61 |
| Trp | **11f** | Boc | $CH_2Ar$[b] | Me | H | Boc-Trp(Boc)-ΔAbu-OMe[c] | **12g** | 86 |

[a] TBS = *tert*-butyldimethylsilyl. [b] Ar = *N*-Boc-indol-3-yl. [c] Abu = 2-aminobutanoic acid.



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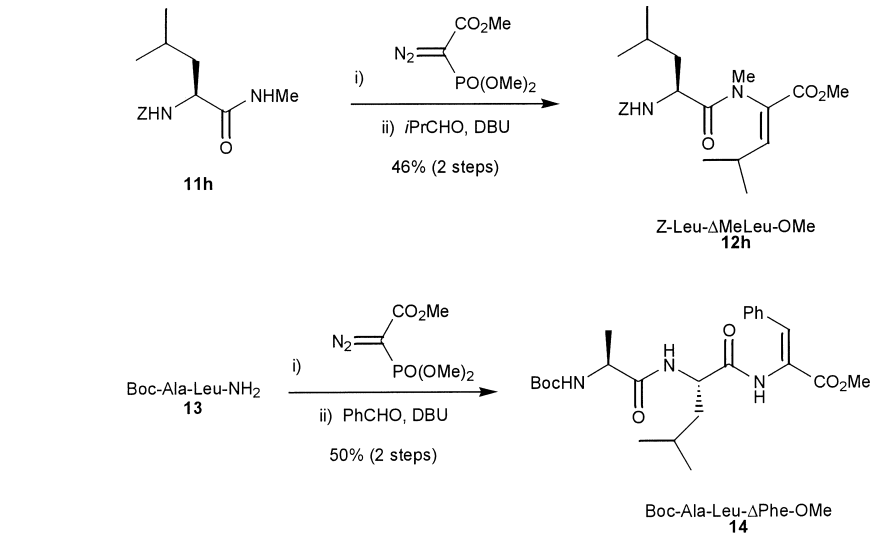
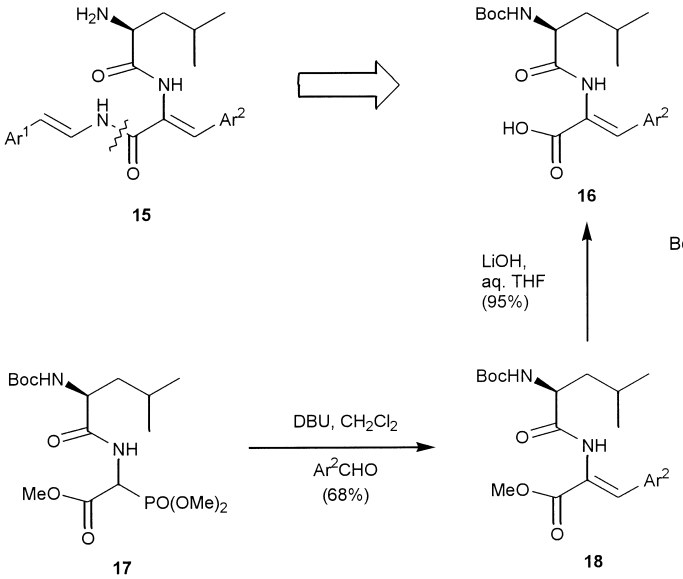


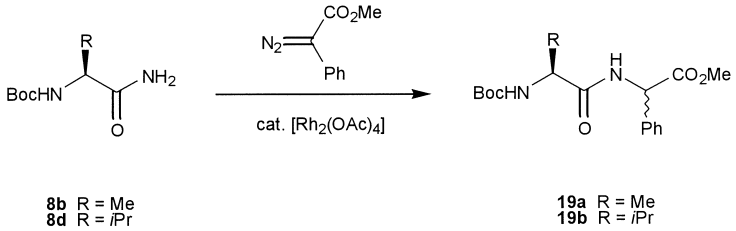

Scheme 5. N–H Insertion/Wadsworth – Emmons reaction sequence.




Scheme 6. Synthesis of the dehydro dipeptide fragment **16** of Mm-2.

and trimethyl phosphonoacetate in exactly the same way as its triethyl analogue **9e**, reacted readily with 3,4-dibenzyloxybenzaldehyde to give the required dipeptide **18** ($Ar^2 = 3,4$-dibenzyloxyphenyl) as a single *Z* diastereomer. Hydrolysis of ester **18** gave the required acid **16** in 95% yield (Scheme 6).

Having established the carbenoid-based route to dehydro dipeptides (Scheme 3b), we briefly investigated the alternative route to dipeptides (Scheme 3a). Thus, *N*-Boc-Ala-$NH_2$ (**8b**) and the valine-derived analogue **8d** were treated with methyl 2-diazophenylacetate in the presence of rhodium(II) acetate. The N–H insertion reaction proceeded chemoselectively and gave the expected dipeptides—*N*-Boc-alanylphenylglycine methyl ester **19a** and its valine analogue **19b**—in 55% and 66% yield, respectively (Scheme 7). The dipeptides **19** were formed as mixtures of diastereomers as evidenced by the presence of two sets of signals in their $^1$H NMR spectra. By integration of the methyl ester singlets in the $^1$H NMR spectra it was possible to determine the diastereoselectivity of the insertion reaction for the formation of **19a** and **19b** as 24% and 20% *de*, respectively. Hence, this preliminary study shows that, perhaps not surprisingly, the existing stereocentre in the amino acid amide **8** causes little asymmetric induction in the insertion reaction. This clearly raises the question of the use of chiral catalysts in the N–H insertion reaction. We and others have explored a wide range of chiral copper- and rhodium-based catalysts for carbenoid transformations, and although to date there is only the reported example of an intramolecular N–H insertion reaction with a chiral catalyst,[17] we are pursuing the use of such catalysts to increase the stereoselectivity of the N–H insertion reactions that lead directly to dipeptides (Scheme 3a and Scheme 7).




Scheme 7. Synthesis of Boc-Ala-Phg-OMe and Boc-Val-Phg-OMe dipeptides.

In summary, we have shown that carbenoid N–H insertion reactions can be applied in a different approach to peptides that does not involve the formation of the peptide bond itself; whilst the method is unlikely to supplant traditional peptide chemistry, we believe that it may find use in the synthesis of peptide sequences that incorporate non-coded amino acids such as *N*-methyl and dehydro derivatives.[18]

## Experimental Section

Commercially available reagents were used throughout without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with b.p. 40–60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Analytical thin-layer chromatography was carried out by using aluminium-backed plates coated with Merck Kieselgel 60 $GF_{254}$. Plates were visualized under UV light (at 254 and/or 360 nm). Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60.
Fully characterized compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000–600 $cm^{-1}$ using a Nicolet Magna FT-550 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded using Bruker 250, 300 and 400 MHz instruments ($^1$H frequencies, corresponding $^{13}$C frequencies are 63, 75 and 100 MHz). High- and low-resolution mass spectra were recorded on a Kratos HV3 instrument, or at the EPSRC Mass Spectrometry Service (Swansea). Rotations were recorded on an Optical Activity PolAAR 2001 polarimeter.

**N-Protected amino acid amides**: These were prepared by published methods for the racemization-free conversion of N-protected amino acids into the corresponding amides.[19–21]

**N–H insertion reactions of N-protected amino acid amides**: A solution of triethyl diazophosphonoacetate (1.4 mmol) and the N-protected amino acid amide **8** (1.4 mmol) in dry toluene (5 mL) was treated with rhodium(II) acetate (2 mol%). The mixture was heated under reflux for 2 h and evaporated, and the residue chromatographed on silica gel (ethyl acetate/ether) to give the *insertion product*.

**Ethyl 2-[(benzyloxycarbonylamino)acetyl]amino-2-(diethoxyphosphoryl)acetate (9a)**: This compound was prepared in 81% yield from Z-Gly-$NH_2$ **8a**[22] as a waxy solid. IR ($CHCl_3$): $\tilde{\nu}=2983$, 1739, 1698, 1694, 1265, 1047 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta=7.37-7.34$ (m, 5H; ArH), 6.82 (br, 1H; N*H*CH), 5.41 (s, 1H; NH), 5.14 (s, 2H; PhC$H_2$), 5.13 (dd, $J=$ 21.8 Hz, 9.0 Hz, 1H; CHP), 4.11–4.10 (m, 6H; $OCH_2$), 3.97 (d, $J=5.7$ Hz, 2H; NHC$H_2$), 1.39–1.29 (m, 9H; $CH_2Me$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta=169.3$, 166.4, 156.5, 136.3, 128.3, 127.9, 127.8, 66.7, 63.8 (d, $J=6.8$ Hz, $CH_2OP$), 63.7 (d, $J=6.8$ Hz, $CH_2OP$), 62.1, 50.5 (d, $J=141.6$ Hz, CHP), 44.0, 16.2 (d, $J=6.7$ Hz, *Me*$CH_2OP$), 13.9; $^{31}P$ NMR (101.3 MHz, $CDCl_3$): $\delta=17.1$; MS (EI): *m/z* (%): 430 (1) $[M]^+$, 127 (10), 107 (28), 91 (59), 44 (100); (found: 430.1505 $[M]^+$; $C_{18}H_{27}N_2O_8P$ calcd 430.1528).

**Ethyl 2-[(S)-(2-*tert*-butoxycarbonylamino)propanoyl]amino-2-(diethoxyphosphoryl)acetate (9b)**: Compound **9b** was prepared in 88% yield from Boc-Ala-$NH_2$ **8b**[21] as a yellow waxy solid. $[\alpha]_D^{23}$ −13.9 ($c=1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2980$, 1732, 1694, 1674, 1250, 1167, 1024 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta=6.91$ (brs, 1H; NH), 5.22 (brs, 1H; CHP), 4.17–4.03 (m, 7H; CH, $OCH_2$), 1.33 (s, 9H; Boc), 1.27–1.13 (m, 12H; $CH_2Me$ and CH*Me*); NH not observed; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta=173.8$, 164.6, 153.6, 78.1, 67.4, 61.8 (d, $J=7.0$ Hz, $CH_2OP$), 61.7 (d, $J=7.0$ Hz, $CH_2OP$), 53.5, 50.5 (d, $J=140.6$ Hz, CHP), 26.3, 16.6 (d, $J=6.0$ Hz, *Me*$CH_2OP$), 14.3, 12.1; $^{31}P$ NMR (101.3 MHz, $CDCl_3$): $\delta=16.9$; MS (EI): *m/z* (%): 411 (18) $[M+H]^+$, 327 (8), 301 (10), 266 (13), 224 (89), 197 (15), 152 (18), 88 (22), 57 (93), 44 (100); (found: 410.1827 $[M]^+$; $C_{16}H_{31}N_2O_8P$ calcd 410.1818).

**Ethyl 2-[(S)-(2-benzyloxycarbonylamino)propanoyl]amino-2-(diethoxyphosphoryl)acetate (9c)**: Compound **9c** was prepared in 80% yield from Z-Ala-$NH_2$ **8c**[21] as a waxy solid. $[\alpha]_D^{23}$ −11.0 ($c=1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2982$, 1741, 1682, 1674, 1252, 1047 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta=7.36$ (s, 5H; ArH), 6.90 (brs, 1H; NH), 5.30 (s, 1H; NH), 5.15 (dd, $J=$ 21.2 Hz, 8.7 Hz, 1H; CHP), 5.12 (s, 2H; PhC$H_2$), 4.19–4.08 (m, 7H; NHC*H*, $OCH_2$), 1.41 (d, $J=7.0$ Hz, 3H; CH*Me*), 1.37–1.23 (m, 9H; $CH_2Me$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta=172.8$, 166.3, 155.7, 136.3, 128.2, 127.8, 127.7, 66.5, 63.6 (d, $J=6.8$ Hz, $CH_2OP$), 63.5, 50.9 (d, $J=139.2$ Hz, CHP), 49.3, 18.6, 16.1 (d, $J=6.8$ Hz, *Me*$CH_2OP$), 13.8; $^{31}P$ NMR (101.3 MHz, $CDCl_3$): $\delta=16.8$; MS (EI): *m/z* (%): 444 (6) $[M]^+$, 266 (9), 224 (49), 197 (10), 155 (12), 91 (100); (found: 444.1665 $[M]^+$; $C_{19}H_{29}N_2O_8P$ calcd 444.1661).

**Ethyl 2-[(S)-2-*tert*-butoxycarbonylamino-3-methylbutanoyl]amino-2-(diethoxyphosphoryl)acetate (9d)**: Compound **9d** was prepared in 80% yield from Boc-Val-$NH_2$ **8d**[23] as a colourless solid. $[\alpha]_D^{23}$ −9.2 ($c=1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=1712$, 1673, 1670, 1249, 1169, 1023 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta=6.75$ (brs, 1H; NH), 5.22 (dd, $J=21.1$ Hz, 8.6 Hz, 1H; CHP), 5.05 (brs, 1H; NH), 4.28–4.09 (m, 6H; $OCH_2$), 3.95 (brs, 1H; NHC*H*), 2.04 (sept, $J=6.7$ Hz, 1H; C*H*$Me_2$), 1.44 (s, 9H; Boc), 1.35–1.23 (m, 9H; $CH_2Me$), 1.00–0.92 (m, 6H; $CHMe_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta=173.7$, 165.1, 154.6, 77.1, 67.3, 61.7 (d, $J=6.8$ Hz, $CH_2OP$), 61.6 (d, $J=6.8$ Hz, $CH_2OP$), 53.5, 50.5 (d, $J=140.9$ Hz, CHP), 38.4, 26.4, 22.9, 16.6 (d, $J=6.7$ Hz, *Me*$CH_2OP$), 14.2, 12.1; $^{31}P$ NMR (101.3 MHz, $CDCl_3$): $\delta=17.0$; MS (EI): *m/z* (%): 438 (18) $[M]^+$, 327 (8), 301 (10), 266 (13), 224 (89), 197 (15), 152 (18), 88 (22), 57 (93), 44 (100); (found: 438.2129 $[M]^+$; $C_{18}H_{35}N_2O_8P$ calcd 438.2131).

**Ethyl 2-[(S)-2-*tert*-butoxycarbonylamino-4-methylpentanoyl]amino-2-(diethoxyphosphoryl)acetate (9e)**: Compound **9e** was prepared in 82% yield from Boc-Leu-$NH_2$ **8e**[20] as a yellow oil. $[\alpha]_D^{23}$ −18.7 ($c=1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2980$, 1749, 1717, 1683, 1253, 1167, 1027 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta=6.48$ (brs, 1H; NH), 6.05 (brs, 1H; NH), 5.15 (dd, $J=22.1$ Hz, 10.4 Hz, 1H; CHP), 4.27–4.14 (m, 7H; NHC*H*, $OCH_2$), 1.64–1.61 (m, 2H; C$H_2$CHMe$_2$), 1.51–1.49 (m, 1H; C*H*Me), 1.35 (s, 9H; Boc), 1.34–1.29 (m, 9H; $CH_2Me$), 0.96–0.93 (m, 6H; $CHMe_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta=173.9$, 167.9, 157.1, 81.2, 65.1 (d, $J=7.4$ Hz, $CH_2OP$), 65.0 (d, $J=6.7$ Hz, $CH_2OP$), 63.0, 54.5, 51.9 (d, $J=133.6$ Hz, CHP), 42.6, 29.5, 26.0, 24.2, 23.1, 17.5 (d, $J=5.1$ Hz, *Me*$CH_2OP$), 15.3, 14.7; $^{31}P$ NMR (101.3 MHz, $CDCl_3$): $\delta=16.9$; MS (EI): *m/z* (%): 453 (100) $[M+H]^+$, 397 (42), 353 (10), 131 (47), 86 (49); (found: 453.2366 $[M+H]^+$; $C_{19}H_{38}N_2O_8P$ calcd 453.2366).

**Ethyl 2-[(S)-2-(1-benzyloxycarbonylpyrrolidin-2-yl)carbonyl]amino-2-(diethoxyphosphoryl)acetate (9f)**: Compound **9f** was prepared in 80% yield from Z-Pro-$NH_2$ **8f**[24] as a colourless waxy solid (80%). $[\alpha]_D^{23}$ −57.2 ($c=1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2981$, 1735, 1697, 1677, 1241, 1177, 1029 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta=7.37-7.30$ (m, 5H; ArH), 5.17–5.16 (m, 2H; PhC$H_2$), 5.11 (dd, $J=21.2$ Hz, 8.8 Hz, 1H; CHP), 4.27–4.11 (m, 6H; OC$H_2$Me), 3.54 (brs, 1H; NH), 3.47 (brs, 1H; NCH), 2.21 (m, 1H; CH), 1.98–1.90 (m, 2H; CH), 1.58–1.56 (m, 3H; CH), 1.38–1.28 (m, 9H; $CH_2Me$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta=171.5$, 166.4, 155.8, 136.4, 128.4, 127.9, 127.7, 67.1, 63.7 (d, $J=6.7$ Hz, $CH_2OP$), 60.4, 50.7 (d, $J=145.6$ Hz, CHP), 46.9, 31.1, 28.7, 24.4, 16.3 (d, $J=6.7$ Hz, *Me*$CH_2OP$), 13.9; $^{31}P$ NMR (101.3 MHz, $CDCl_3$): $\delta=16.95$; MS (EI) *m/z* (%): 470 (4) $[M]^+$, 335 (8), 231 (6), 204 (10), 160 (32), 91 (100), 70 (12), 44 (11); (found: 470.1827 $[M]^+$; $C_{21}H_{31}N_2O_8P$ calcd 470.1825).

**General procedure for Wadsworth–Emmons reactions**: A solution of the appropriate triethyl aminophosphonoacetate **9** (0.66 mmol) and DBU (0.1 mL, 0.66 mmol) in anhydrous dichloromethane was treated with the appropriate aldehyde (1.3 mmol). The reaction mixture was stirred overnight and evaporated, and the residue was purified by chromatography on silica gel (ether/light petroleum) to give the dehydrodipeptide **10**.

**Z-Gly-ΔPhe-OEt (10a)**: Dipeptide **10a** was prepared in 82% yield from **9a** and benzaldehyde as a yellow oil. IR ($CHCl_3$): $\tilde{\nu}=1710$, 1685, 1643, 1262 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta=7.90$ (s, 1H; CH=C), 7.36–7.16 (m, 11H; ArH, NH), 5.75 (s, 1H; NH), 4.97 (s, 2H; PhC$H_2$), 4.12 (q, $J=$ 7.0 Hz, 2H; $OCH_2$), 3.85 (s, 2H; $CH_2$), 1.20 (t, $J=7.0$ Hz, 3H; $CH_2Me$); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta=168.4$, 165.0, 156.9, 136.2, 133.0, 129.9, 129.7, 128.6, 128.3, 127.9, 127.7, 125.9, 124.0, 67.2, 61.8, 44.8, 14.2; MS (EI): *m/z* (%): 383 (82) $[M+H]^+$, 292 (51), 275 (39), 249 (100), 191 (21), 108 (19); (found: 383.1610 $[M+H]^+$; $C_{21}H_{23}N_2O_5$ calcd 383.1607).

**Boc-Ala-ΔPhe-OEt (10b)**: Dipeptide **10b** was prepared in 88% yield from **9b** and benzaldehyde as a yellow oil. $[\alpha]_D^{25}$ −21.7 ($c=1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2981$, 1715, 1690, 1645, 1265 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta=8.04$ (s, 1H; CH=C), 7.41–7.38 (m, 2H; ArH), 7.29–7.21 (m, 4H; ArH, NH), 5.31 (s, 1H; NH), 4.31 (m, 1H; NHC*H*), 4.14 (q, $J=7.3$ Hz, 2H; $OCH_2$), 1.32 (s, 9H; Boc), 1.22 (t, $J=7.3$ Hz, 3H; $CH_2Me$), 1.14 (d, $J=$ 7.0 Hz, 3H; CH*Me*); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta=171.9$, 165.1, 155.7, 132.9, 132.6, 129.8, 129.4, 128.8, 124.3, 80.1, 61.7, 50.3, 28.3, 18.2, 14.2; MS (EI): *m/z* (%): (100) $[M+H]^+$, 307 (55), 263 (27); (found: 363.1920 $[M+H]^+$; $C_{19}H_{27}N_2O_5$ calcd 369.1920).

**Boc-Leu-ΔPhe-OEt (10c)**: Dipeptide **10c** was prepared in 88% yield from **9e** and benzaldehyde as a yellow oil. $[\alpha]_D^{25}$ −18.8 ($c=1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2960$, 1735, 1709, 1677, 1265 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta=7.66$ (s, 1H; CH=C), 7.50–7.48 (m, 2H; ArH), 7.40–7.31 (m, 4H; ArH, NH), 4.84 (s, 1H; NH), 4.29 (q, $J=7.0$ Hz, 2H; $OCH_2$), 4.23 (brs, 1H; NHC*H*), 1.79–1.72 (m, 2H; C$H_2$CHMe$_2$), 1.55 (m, 1H; C*H*Me$_2$), 1.47 (s, 9H; Boc), 1.34 (t, $J=7.0$ Hz, 3H; $CH_2Me$), 0.99–0.94 (m, 6H; $CHMe_2$); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta=171.7$, 165.1, 155.9, 133.7, 132.6, 129.9, 129.4, 128.6, 124.4, 80.2, 61.7, 53.3, 40.9, 28.4, 24.7, 22.9, 22.1, 14.3; MS (EI): *m/z* (%): 405 (69) $[M+H]^+$, 349 (85), 305 (100), 259 (15), 191 (30), 131 (15), 86 (55); (found: 405.2389 $[M+H]^+$; $C_{22}H_{33}N_2O_5$ calcd 405.2389).

**Boc-Leu-ΔLeu-OEt (10d)**: Dipeptide **10d** was prepared in 80% yield from **9e** and isobutyraldehyde as a yellow oil. $[\alpha]_D^{25}$ −18.3 ($c=0.5$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2976$, 1725, 1685, 1645, 1245 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta=7.34$ (s, 1H; NH), 6.50 (d, $J=10.5$ Hz, 1H; CH=C), 4.85 (s, 1H; NH), 4.21 (q, $J=7.3$ Hz, 2H; $OCH_2$), 4.18 (s, 1H; NHC*H*), 2.59 (m, 1H; C*H*Me$_2$), 1.79–1.74 (m, 3H; C*H*Me$_2$, C$H_2$CHMe$_2$), 1.46 (s, 9H; Boc), 1.29 (t, $J=7.3$ Hz, 3H; $CH_2Me$), 1.06–1.03 (m, 6H; $CHMe_2$), 0.99–0.95 (m, 6H; $CHMe_2$); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta=171.6$, 164.6, 155.8, 145.1, 123.4, 80.1, 61.1, 53.1, 52.9, 40.8, 28.1, 27.7, 24.6, 22.8, 21.9, 21.8, 14.0; MS (EI): *m/z* (%): 371 (100) $[M+H]^+$, 315 (85), 297 (70), 271 (61), 225 (12), 157 (13), 86 (52); (found: 371.2546 $[M+H]^+$; $C_{19}H_{35}N_2O_5$ calcd 371.2546).

**Boc-Leu-ΔTrp(Boc)-OEt (10e)**: Dipeptide **10e** was prepared in 79% yield from **9e** and *N-tert*-butoxycarbonylindole-3-carboxaldehyde as a yellow oil. $[\alpha]_D^{25}$ −11.3 ($c=0.5$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=2991$, 1725, 1695, 1665, 1235 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta=8.12$ (d, $J=7.6$ Hz, 1H; indole



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7-H), 7.81(s, 1H; NH), 7.79 (s, 1H; indole 2-H), 7.70 (d, $J = 8.7$ Hz, 1H; indole 4-H), 7.35–7.22 (m, 3H; indole 5/6-H, CH=C), 4.81 (s, 1H; NH), 4.32 (q, $J = 7.0$ Hz, 2H; $OCH_2$), 4.26 (m, 1H; NHC*H*), 1.76 (m, 2H; C$H_2$CHMe$_2$), 1.68 (m, 1H; C*H*Me$_2$), 1.64 (s, 9H; Boc), 1.32 (s, 9H; Boc), 1.37 (t, $J = 7.0$ Hz, 3H; $CH_2$*Me*), 0.97 (m, 6H; CH*Me*$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 171.4$, 165.0, 155.9, 149.3, 134.8, 129.6, 127.9, 125.0, 123.7, 123.4, 123.1, 119.0, 115.3, 114.1, 84.5, 80.2, 61.6, 53.4, 40.7, 28.3, 28.2, 24.8, 23.2, 21.8, 14.3; MS (EI): *m*/*z* (%): 544 (49) $[M+H]^+$, 488 (19), 444 (100), 388 (15), 344 (22), 231 (10), 131 (31), 86 (54); (found: 544.3023 $[M+H]^+$; $C_{29}H_{41}N_3O_7$ calcd 544.3023).

**General procedure for the N–H insertion—Wadsworth–Emmons reaction sequence**: A solution of trimethyl diazophosphonoacetate (125 mg, 0.6 mmol) in dichloromethane (2.5 mL) was added over 10 min, under nitrogen, to a stirred solution of N-protected amino acid amide **11** (0.43 mmol) and rhodium(II) acetate (23 mg, 10 mol% with respect to the diazo compound) in dichloromethane (3 mL), which was heated at reflux. After 24 h the mixture was cooled to room temperature and diluted with ethyl acetate. The solution was washed in turn with water, saturated sodium bicarbonate solution and brine. The organic layer was then dried with magnesium sulfate and evaporated to yield the crude insertion product. A solution of DBU (140 mg, 1 mmol) in dichloromethane (1 mL) was then added to a stirred solution of the crude insertion product (ca. 0.43 mmol) in dichloromethane (0.5 mL), under nitrogen. After 10 min, a solution of aldehyde or ketone (0.78 mmol) in dichloromethane (0.5 mL) was added to the reaction mixture. The reaction was followed by TLC (ethyl acetate), and when complete the mixture was diluted with ethyl acetate. The solution was washed in turn with water, saturated sodium bicarbonate solution and brine. The organic layer was dried with magnesium sulfate and evaporated to yield the crude product, which was purified by flash column chromatography (mixtures of ethyl acetate/hexane).

**Z-Leu-ΔPhe-OMe (12a)**: Peptide **12a** was prepared in 65% overall yield starting from Z-Leu-NH$_2$ **11a**[24] and benzaldehyde. $[\alpha]_D^{28}$ −13.4 ($c = 2.36$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3430$, 2959, 1717, 1645, 1505, 1438, 1266, 1106, 1045, 909 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$ (s, 1H; CH=C), 7.48–7.42 (m, 3H; ArH and NH), 7.36–7.29 (m, 8H; ArH), 5.14 (br s, 3H; PhC$H_2$ and NH), 4.32 (br d, $J = 5.1$ Hz, 1H; NHC*H*), 3.80 (s, 3H; OMe), 1.78–1.70 (m, 2H; C$H_2$CHMe$_2$), 1.55 (m, 1H; C*H*Me$_2$), 0.96 (m, $J = 6.4$ Hz, 6H; CH*Me*$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 170.6$, 165.4, 156.4, 136.0, 133.6, 132.8, 129.7, 129.5, 128.6, 128.4, 128.3, 128.1, 123.4, 67.3, 53.8, 52.6, 40.6, 24.7, 22.8, 21.9; MS (EI): *m*/*z* (%): 424 (1) $[M]^+$, 316 (63), 228 (82), 203 (60), 177 (40), 131 (52), 117 (100), 91 (85); (found: 424.2568 $[M]^+$; $C_{24}H_{28}N_2O_5$ calcd 424.1998).

**Ac-Leu-ΔPhe-OMe (12b)**: Peptide **12b** was prepared in 37% overall yield starting from Ac-Leu-NH$_2$ **11b**[25] and benzaldehyde. $[\alpha]_D^{28}$ −25.7 ($c = 0.54$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 2959$, 2361, 1718, 1700, 1666, 1601, 1506, 1437, 1370, 1266, 1202, 929 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 8.37$ (br s, 1H; CH=C), 7.44 (d, $J = 5.6$ Hz, 2H; ArH), 7.34–7.27 (m, 3H; ArH), 6.56 (d, $J = 8.0$ Hz, 1H; NH), 4.73 (dd, $J = 8.2$ Hz, 14.2 Hz, 1H; NHC*H*), 3.80 (m, 1H; NH), 3.76 (s, 3H; OMe), 1.85 (s, 3H; Ac), 1.78–1.65 (m, 2H; C$H_2$CHMe$_2$), 1.53 (m, 1H; C*H*Me$_2$), 0.93 (m, 6H; CH*Me*$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 171.5$, 170.7, 165.3, 133.4, 133.2, 129.8, 129.5, 128.5, 124.3, 52.5, 51.7, 40.7, 24.7, 22.8, 22.7, 22.4; MS (EI): *m*/*z* (%): 332 (4) $[M]^+$, 301 (9), 271 (22), 191 (25), 177 (100), 117 (63), 91 (41); (found: 332.1730 $[M]^+$; $C_{18}H_{24}N_2O_4$ calcd 332.1736).

**Boc-Phe-ΔLeu-OMe (12c)**: Peptide **12c** was prepared in 60% overall yield starting from Boc-Phe-NH$_2$ **11c**[21] and isobutyraldehyde. $[\alpha]_D^{28}$ −16.2 ($c = 2.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3421$, 2968, 1716, 1698, 1495, 1438, 1368, 1255, 1160, 1029, 929 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (br s, 1H; NH), 7.29–7.19 (m, 5H; ArH), 6.47 (d, $J = 10.4$ Hz, 1H; CH=C), 5.18 (d, $J = 8.2$ Hz, 1H; NH), 4.48 (m, 1H; NHC*H*), 3.70 (s, 3H; OMe), 3.15 (dd, $J = 6.7$ Hz, 13.9 Hz, 1H; PhC*H*H), 3.05 (dd, $J = 7.2$ Hz, 13.9 Hz, 1H; PhCH*H*), 2.40 (m, 1H; C*H*Me$_2$), 1.38 (s, 9H; Boc), 0.98 (d, $J = 6.6$ Hz, 3H; =CHCH*Me*Me), 0.96 (d, $J = 6.7$ Hz, 3H; =CHCHMe*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 164.9, 155.6, 145.9, 136.6, 129.4, 128.6, 122.9, 80.2, 55.9, 52.2, 38.0, 28.2, 27.7, 21.6, 21.5; MS (EI): *m*/*z* (%): 391 (1) $[M]^+$, 335 (32), 303 (32), 241 (31), 164 (62), 142 (73), 120 (96), 91 (38), 57 (100); (found: 391.2246 $[M]^+$; $C_{21}H_{31}N_2O_5$ calcd 391.2238).

**Boc-Ser(TBS)-ΔTrp(Boc)-OMe (12d)**: Peptide **12d** was prepared in 77% overall yield starting from Boc-Ser(TBS)-NH$_2$ **11d** and *N*-*tert*-butoxycarbonylindole-3-carboxaldehyde; $[\alpha]_D^{28}$ +3.9 ($c = 4.04$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3410$, 2982, 2954, 2931, 2859, 1719, 1695, 1644, 1483, 1371, 1255, 1154, 1088, 1020, 839 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 8.41$ (br s, 1H; NH), 8.14 (d, $J = 8.0$ Hz, 1H; indole 7-H), 7.88 (s, 1H; indole 2-H), 7.71 (s, 1H; CH=C), 7.68 (d, $J = 7.3$ Hz, 1H; indole 4-H), 7.38–7.26 (m, 2H; indole 5-H, 6-H), 4.47 (br s, 1H; NH), 4.31 (m, 1H; NHC*H*), 4.12 (dd, $J = 4.4$ Hz, 9.9 Hz, 1H; C*H*HOSi), 3.86 (s, 3H; OMe), 3.79 (dd, $J = 7.7$ Hz, 9.9 Hz, 1H; CH*H*OSi), 1.68 (s, 9H; Boc), 1.45 (s, 9H; Boc), 0.85 (s, 9H; *t*BuSi), 0.13 (s, 3H; MeSi), 0.095 (s, 3H; MeSi); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 169.1$, 165.1, 155.6, 149.1, 134.9, 129.4, 127.7, 125.0, 124.0, 123.2, 122.9, 118.9, 115.3, 113.9, 84.5, 80.1, 62.8, 55.8, 52.5, 28.3, 28.2, 25.8, 18.0, −5.4, −5.6; MS (FAB): *m*/*z* (%): 618 (30) $[M+H]^+$, 518 (55), 216 (77), 174 (100); (found: 618.3193 $[M+H]^+$; $C_{31}H_{48}N_3O_8Si$ calcd 618.3211).

**Boc-Ser(TBS)-ΔVal-OMe (12e)**: Peptide **12e** was prepared in 30% overall yield starting from Boc-Ser(TBS)-NH$_2$ **11d** and acetone. $[\alpha]_D^{28}$ +13.9 ($c = 1.04$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3421$, 2945, 2852, 1710, 1680, 1485, 1367, 1163, 1081, 937, 841 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (br s, 1H; NH), 5.37 (br s, 1H; NH), 4.19 (br s, 1H; NHC*H*), 4.04 (dd, $J = 4.0$ Hz, 9.8 Hz, 1H; C*H*HOSi), 3.70 (s, 3H; OMe), 3.69 (m, 1H; CH*H*OSi), 2.15 (s, 3H; =CMe), 1.81 (s, 3H; =CMe), 1.44 (s, 9H; Boc), 0.88 (s, 9H; *t*BuSi), 0.09 (s, 3H; MeSi), 0.08 (s, 3H; MeSi); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 169.2$, 164, 155.5, 146.1, 120.6, 80.1, 63.1, 55.5, 51.7, 28.3, 25.8, 22.5, 21.2, 18.1, −5.5, −5.6; MS (FAB): *m*/*z* (%): 431 (42) $[M+H]^+$, 375 (54), 331 (63), 174 (64); (found: 430.2506 $[M]^+$; $C_{20}H_{38}N_2O_6Si$ calcd 430.2499).

**Boc-Tyr(TBS)-ΔLeu-OMe (12f)**: Peptide **12f** was prepared in 61% overall yield starting from Boc-Tyr(TBS)-NH$_2$ **11e** and isobutyraldehyde. $[\alpha]_D^{28}$ −8.4 ($c = 2.76$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3677$, 3411, 3027, 2965, 2929, 2858, 1716, 1700, 1608, 1516, 1475, 1419, 1260, 1209, 1014, 927, 794, 737, 661 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.21$ (br s, 1H; NH), 7.10 (d, $J = 8.5$ Hz, 2H; ArH), 6.76 (d, $J = 8.5$ Hz, 2H; ArH), 6.72 (d, $J = 10.4$ Hz, 1H; CH=C), 5.01 (br s, 1H; NH), 4.39 (br, X of ABX system, 1H; NHC*H*), 3.73 (s, 3H; OMe), 3.11–2.99 (AB of ABX, $J = 14.0$ Hz, 6.9 Hz, 7.0 Hz, 2H; $CH_2$Ar), 2.45 (m, 1H; C*H*Me$_2$), 1.42 (s, 9H; Boc), 1.01 (d, $J = 6.5$ Hz, 3H; =CHCH*Me*Me), 0.99 (d, $J = 6.5$ Hz, 3H; =CHCHMe*Me*), 0.97 (s, 9H; *t*BuSi), 0.18 (s, 6H; MeSi); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 170.3$, 164.9, 155.5, 154.7, 145.8, 130.3, 129.1, 122.8, 120.2, 80.2, 56.1, 52.3, 37.1, 28.2, 27.8, 25.6, 21.6, 18.2, −4.5; MS (CI): *m*/*z* (%): 521 (65) $[M+H]^+$, 465 (20), 250 (25), 223 (28), 146 (55), 144 (100), 132 (32), 86 (42), 72 (58); (found: 521.3056 $[M+H]^+$; $C_{27}H_{45}N_2O_6Si$ calcd 521.3047).

**Boc-Trp(Boc)-ΔAbu-OMe (12g)**: Peptide **12g** was prepared in 86% overall yield starting from Boc-Trp(Boc)-NH$_2$ **11f** and acetaldehyde; $[\alpha]_D^{28}$ −7.4 ($c = 3.70$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3684$, 3418, 3018, 2984, 1723, 1690, 1602, 1505, 1438, 1453, 1370, 1212, 1159, 1088, 1018, 928, 909, 749, 669 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 8.13$ (br d, $J = 8.2$ Hz, 1H; indole 7-H), 7.61 (d, $J = 7.7$ Hz, 1H; indole 4-H), 7.48 (s, 1H; indole 2-H), 7.40 (s, 1H; NH), 7.35–7.20 (m, 2H; indole 5-H, 6-H), 6.77 (q, $J = 7.2$ Hz, 1H; CH=C), 5.18 (br s, 1H; NH), 4.59 (br d, $J = 5.0$ Hz, 1H; NHC*H*), 3.69 (s, 3H; OMe), 3.26 (dd, $J = 6.9$ Hz, 14.8 Hz, 1H; C*H*Hindole), 3.19 (dd, $J = 6.3$ Hz, 14.8 Hz, 1H; CH*H*indole), 1.67 (d, $J = 7.2$ Hz, 3H; =CMe), 1.65 (s, 9H; Boc), 1.42 (s, 9H; Boc); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 169.7$, 164.5, 155.5, 149.5, 135.6, 134.4, 130.3, 125.8, 124.6, 124.4, 122.7, 119.0, 115.3, 83.6, 80.4, 54.7, 52.2, 28.2, 28.1, 27.8, 14.5; MS (FAB): *m*/*z* (%): 502 (20) $[M+H]^+$, 390 (14), 284 (20), 203 (30), 170 (25), 159 (32), 130 (100), 116 (41); (found: 502.2554 $[M+H]^+$; $C_{26}H_{36}N_3O_7$ calcd 502.2553).

**Z-Leu-ΔMeLeu-OMe (12h)**: Peptide **12h** was prepared in 46% overall yield (as a mixture of amide bond rotamers and double bond isomers) starting from Z-Leu-NHMe **11g**[26] and isobutyraldehyde; IR ($CHCl_3$): $\tilde{\nu} = 3684$, 3400, 3018, 2960, 2871, 1731, 1704, 1658, 1525, 1438, 1309, 1217, 1092, 1027, 928, 749, 668 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) (all signals reported; mixture of isomers/rotamers): $\delta = 7.35–7.25$ (m, 20H; ArH), 6.64 (br s, 1H; NH), 6.54 (br s, 1H; NH), 6.35 (br d, $J = 4.2$ Hz, 1H; NH), 6.29 (br d, $J = 4.8$ Hz, 1H; NH), 6.25 (d, $J = 10.0$ Hz, 1H; CH=C), 6.21 (d, $J = 11.5$ Hz, 1H; CH=C), 5.71 (d, $J = 10.4$ Hz, 1H; CH=C), 5.59 (d, $J = 10.5$ Hz, 1H; CH=C), 5.25–5.08 (m, 8H; $PhCH_2$), 4.26–4.05 (m, 4H; NHC*H*), 3.71 (s, 3H; OMe), 3.66 (s, 3H; OMe), 3.63 (s, 3H; OMe), 3.59 (s, 3H; OMe), 2.70–2.68 (m, 6H; NMe), 2.63–2.61 (m, 6H; NMe), 1.70–1.49 (m, 16H; C$H_2$C*H*Me$_2$), 1.06–0.78 (m, 48H; CH*Me*$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 174.9$, 174.8, 174.7, 163.4, 163.1, 162.8, 162.5, 149.9, 149.4, 148.7, 148.3, 139.5, 137.4, 137.3, 137.2, 136.7, 136.6, 136.4, 136.3, 136.2, 136.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.5, 127.3, 70.9, 70.8, 70.1, 69.9, 57.6, 57.5, 57.4, 52.1, 51.7, 43.7, 43.6, 43.5, 27.9, 26.2, 25.8, 25.7, 25.6, 25.5, 24.7, 24.6, 23.6, 23.6, 23.5, 23.4, 22.5, 21.8, 21.7, 21.6, 21.5; MS (EI): *m*/*z* (%): 404 (1) $[M]^+$, 347

(100), 171 (74), 114 (74), 91 (73), 57 (61); (found: 404.2328 $[M]^+$; $C_{22}H_{32}N_2O_5$ calcd 404.2311).

**Boc-Ala-Leu-ΔPhe-OMe (14)**: Peptide **14** was prepared in 50% overall yield starting from Boc-Ala-Leu-$NH_2$ (**13**)[27] and benzaldehyde. $[\alpha]_D^{25}$ −44.1 ($c = 2.00$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3421$, 3303, 2955, 1705, 1490, 1424, 1357, 1270, 1152, 927 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.15$ (br s, 1H; NH), 7.48–7.43 (br d, $J = 6.7$ Hz, 2H; ArH), 7.37 (s, 1H; CH=C), 7.32–7.26 (m, 3H; ArH), 6.91 (br d, $J = 6.0$ Hz, 1H; NH), 5.15 (br d, $J = 4.6$ Hz, 1H; NH), 4.61 (ddd, $J = 5.6$ Hz, 8.9 Hz, 14.2 Hz, 1H; NHC*H*), 4.17 (br, 1H; NHC*H*), 3.78 (s, 3H; OMe), 1.81–1.54 (m, 3H; C$H_2$C*H*$Me_2$), 1.38 (s, 9H; Boc), 1.31 (d, $J = 7.0$ Hz, 3H; CH*Me*), 0.92 (m, 6H; CH$Me_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 173.1$, 170.9, 165.4, 155.7, 133.6, 133.4, 129.9, 129.5, 128.5, 124.2, 80.4, 52.5, 51.9, 50.3, 40.2, 28.2, 24.7, 22.9, 21.9, 17.9; MS (FAB): *m/z* (%): 462 (75) $[M+H]^+$, 406 (12), 285 (20), 229 (100), 201 (44), 178 (31); (found: 461.2531 $[M]^+$; $C_{24}H_{35}N_3O_6$ calcd 461.2526).

**Methyl 2-[(S)-2-*tert*-butoxycarbonylamino-4-methylpentanoylamino]-2-(dimethoxyphosphoryl)acetate (17)**: Trimethyl diazophosphonoacetate (0.88 g, 4.2 mmol) in toluene (5 mL) was added dropwise over a period of 10 min to a stirred solution of amide **8e** (0.89 g, 3.9 mmol) and rhodium(II) acetate (0.17 g, 0.039 mmol) in boiling toluene (50 mL). The reaction was monitored by TLC and had gone to completion within 1 h. The solvent was evaporated and the residue purified by column chromatography (1:1 ethyl acetate/light petroleum elution) to yield a colourless oil (0.89 g, 56%) (ref. [13] foam). $[\alpha]_D^{25}$ −28.6 ($c = 1.16$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3440$, 3306, 3063, 2955, 1755, 1694 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.09$ (m, 1H; NH), 5.19 (m, 1H; CHP), 4.96 (m, 1H; NHC*H*), 4.20 (br s, 1H; NH), 3.78 (m, 9H; OMe), 1.66 (m, 2H; C$H_2$CHMe$_2$), 1.47 (m, 1H; C*H*Me$_2$), 1.43 (s, 9H; Boc), 0.93 (m, 6H; CH$Me_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 172.4$, 166.8, 155.5, 80.2, 54.6, 54.2 (d, $J = 6.0$ Hz, *Me*OP), 54.1 (d, $J = 5.5$ Hz, *Me*OP), 53.3, 52.3, 50.0 (d, $J = 146.7$ Hz, CHP), 40.9, 28.2, 24.7, 22.9, 21.8; MS (EI): *m/z* (%): 410 (2) $[M]^+$, 367 (4), 337 (8), 182 (43), 130 (45), 86 (100).

**Methyl 3-(3,4-dibenzyloxyphenyl)-2-[(S)-2-*tert*-butoxycarbonylamino-4-methylpentanoylamino]propenoate (18)**: DBU (1.06 g, 7.0 mmol) was added to a solution of phosphonate **17** (1.37 g, 3.3 mmol) in dichloromethane (14 mL), and the mixture was stirred at room temperature for 10 min. 3,4-Dibenzyloxybenzaldehyde (1.17 g, 3.7 mmol) was added in one portion, and the reaction was stirred for 2 h. The solvent was evaporated, and the residue purified by column chromatography (ethyl acetate elution) and recrystallized (ethyl acetate/light petroleum) to yield the **18** as colourless crystals (1.51 g, 75%). M.p. 65–67 °C; $[\alpha]_D^{25}$ +6.3 ($c = 0.95$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3292$, 2955, 2874, 1728, 1681 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (s, 1H; NH), 7.47–7.28 (m, ArH, 11H; CH=C), 7.16–7.12 (m, 2H; ArH), 6.89 (d, $J = 8.3$ Hz, 1H; ArH), 5.16 (s, 2H; PhC$H_2$), 5.14 (s, 2H; PhC$H_2$), 4.92 (br d, $J = 7.1$ Hz, 1H; NH), 4.28 (br s, 1H; NHC*H*), 3.80 (s, 3H; OMe), 1.77–1.74 (m, 2H; C$H_2$CHMe$_2$), 1.51 (m, 1H; C*H*Me$_2$), 1.43 (s, 9H; Boc), 0.95 (m, 6H; CH$Me_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 171.5$, 165.7, 155.8, 150.4, 148.6, 137.1, 136.9, 133.3, 128.5, 128.4, 127.9, 127.8, 127.4, 127.3, 126.9, 124.3, 122.1, 116.8, 114.2, 80.3, 71.4, 70.9, 53.5, 52.5, 40.7, 28.3, 24.7, 23.0, 21.9; MS (EI): *m/z* (%): 603 (27) $[M+H]^+$, 602 (6) $[M]^+$, 548 (14), 547 (33), 503 (52), 131 (52), 108 (94), 106 (58), 86 (100); (found: 603.3070 $[M+H]^+$; $C_{35}H_{43}N_2O_7$ calcd 603.3070); elemental analysis calcd (%) for $C_{35}H_{43}N_2O_7$: C 69.7, H 7.0, N 4.7; found C 69.7, H 7.0, N 4.8.

**3-(3,4-Dibenzyloxyphenyl)-2-[(S)-2-*tert*-butoxycarbonylamino-4-methylpentanoylamino]propenoic acid (16)**: A solution of lithium hydroxide (0.22 g, 9.2 mmol) in water (25 mL) was added to a stirred solution of ester **18** (1.1g, 1.84 mmol) in THF (75 mL). The mixture was stirred for 4 h, and then acidified with 3 M hydrochloric acid. Ammonium chloride solution was added,and the acid was extracted into ethyl acetate. The organic layer was dried ($Na_2SO_4$) and concentrated. The crude material was purified by column chromatography (ethyl acetate elution) and recrystallized (ethyl acetate/light petroleum) to yield the **16** as a colourless crystalline solid (1.03 g, 95%). M.p. 124–126 °C; $[\alpha]_D^{25}$ −30.5 ($c = 1.09$ in $CHCl_3$); IR ($CH_2Cl_2$): $\tilde{\nu} = 3407$, 3270, 3059, 2993, 2960, 1690, 1518 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.95$ (br s, 1H; $CO_2H$), 7.94 (s, 1H; NH), 7.50–7.27 (m, ArH, 11H; CH=C), 7.14–7.12 (m, 2H; ArH), 6.87 (d, $J = 8.3$ Hz, 1H; ArH), 5.13 (br s, 5H; PhC$H_2$ NH), 4.38 (br s, 1H; NHC*H*), 1.73 (m, 2H; C$H_2$CHMe$_2$), 1.52 (m, 1H; C*H*Me$_2$), 1.43 (s, 9H; Boc), 0.94 (m, 6H; CH$Me_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 171.9$, 156.2, 150.2, 148.5, 137.2, 136.9, 128.4, 128.3, 127.7, 127.5, 127.2, 124.4, 116.7, 114.0, 80.2, 71.3, 70.8, 53.4, 40.8, 28.3, 24.7, 23.2, 21.6; the signals for 2 Ar*C*H and 3 quaternary C atoms were not observed as discrete non-overlapped signals; MS (FAB): *m/z* (%): 612 (43) $[M+H+Na]^+$, 611 (100) $[M+Na]^+$, 589 (19) $[M+H]^+$, 588 (34) $[M]^+$, 512 (36), 511 (92), 376 (27), 284 (39), 107 (76); (found: 611.2741 $[M+Na]^+$; $C_{34}H_{40}N_2O_7 \cdot Na$ calcd 611.2733); elemental analysis calcd (%) for $C_{34}H_{40}N_2O_7 \cdot 1.5\,H_2O$: C 66.3, H 7.0, N 4.5; found C 66.6, H 6.6, N 4.5.

**Boc-Ala-Phg-OMe (19a)**: Boc-Ala-$NH_2$ **8b** (58.8 mg, 0.31 mmol) followed by rhodium(II) acetate (2 mol%) was added to a stirred solution of methyl 2-(diazo)phenylethanoate (50 mg, 0.28 mmol) in dry dichloromethane (4 mL) under a nitrogen atmosphere. After stirring for 1 h, the solvent was removed under reduced pressure to yield a green oil. This crude product was then subjected to flash silica-gel chromatography with light petroleum and ethyl acetate (7:3) as eluant to yield an inseparable diastereomeric mixture (24% *de* by NMR) of the **19a** as a colourless oil (52 mg, 55%). IR (film): $\tilde{\nu} = 3423$, 3321, 3055, 2979, 1744, 1710, 1677, 1538, 1505, 1456, 1067, 742 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (br s, 1H; NH), 7.34 (m, 5H; ArH), 5.55 (m, 1H; NHC*H*), 5.05 (m, 1H; NH), 4.24 (m, 1H; NHC*H*), 3.71 and 3.70 (s, 3H; OMe; ratio 62:38), 1.43 (s, 9H; Boc), 1.35 (d, $J = 4.4$ Hz, 3H; CH*Me*); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 172.1$, 171.1, 155.6, 136.3, 128.9, 128.5, 127.2, 80.2, 56.4, 52.7, 49.9, 28.3, 17.9; MS (EI): *m/z* (%): 336 (42) $[M]^+$, 281 (77), 237 (42), 221 (29), 203 (26), 144 (71), 132 (30), 121 (55), 106 (100), 88 (76), 77 (37), 57 (95); (found: 336.1684 $[M]^+$; $C_{17}H_{24}N_2O_5$ calcd 336.1685).

**Boc-Val-Phg-OMe (19b)**: Boc-Val-$NH_2$ **8e** (67.5 mg, 0.31 mmol) followed by rhodium(II) acetate (2 mol%) was added to a stirred solution of methyl 2-(diazo)phenylethanoate (50 mg, 0.28 mmol) in dry chloroform (4 mL) under a nitrogen atmosphere. After stirring for 1 h the solvent was removed under reduced pressure to yield a green oil. This crude product was then subjected to flash silica-gel chromatography with light petroleum and ethyl acetate (4:1) as eluant to yield an inseparable diastereomeric mixture (20% *de* by NMR) of the **19b** as a colourless oil (67 mg, 66%). IR (film): $\tilde{\nu} = 3423$, 3321, 3055, 2979, 1744, 1711, 1677, 1537, 1506, 1456, 1017, 738 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (m, 5H; ArH), 7.03 (br s, 1H; NH), 5.55 (m, 1H; NHC*H*), 5.06 (br s, 1H; NH), 3.98 (m, 1H; NHC*H*), 3.72 and 3.71 (s, 3H; OMe; ratio 60:40), 2.15 (m, 1H; C*H*Me$_2$), 1.42 (s, 9H; Boc), 0.90 (d, $J = 6.8$ Hz, 3H; CH*Me*), 0.86 (d, $J = 6.8$ Hz, 3H; CH*Me*); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 171.1$, 171.0, 155.8, 136.3, 128.9, 128.4, 127.2, 80.0, 59.7, 56.5, 52.7, 30.9, 28.3, 19.2, 17.7; MS (CI): *m/z* (%): 365 (65) $[M+H]^+$, 309 (46), 265 (58), 172 (9), 116 (25), 106 (37), 91 (11), 72 (100), 57 (80); (found: 365.2070 $[M+H]^+$; $C_{19}H_{29}N_2O_5$ calcd 365.2076).

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