Introduction of Allylic Side Chains onto Peptides by Pd(0)-Catalyzed "Ester Enolate Claisen Rearrangement"

Uli Kazmaier

Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Federal Republic of Germany

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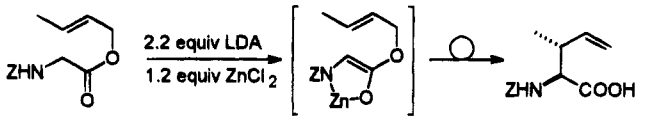
Allylic esters of peptides undergo an ester enolate Claisen rearrangement upon treatment with LDA in the presence of various metal salts (see Table 1). Best results are obtained using zinc chloride. In the presence of a catalytic amount of Pd(0) the rearrangement products are formed in high yields. Addition of Pd(II) has no significant influence on the yield and stereoselectivity of the reaction. In contrast to the rearrangement without Pd(0) the catalyzed reaction probably proceeds via intermolecular allylic alkylation as is shown in a cross experiment of different allylic esters. The methodology is not limited to dipeptides, but can also be applied to larger peptides as is illustrated in the rearrangement of tripeptide **11**. No epimerization of chiral centers is observed under the reaction conditions used.

In 1983 Seebach developed a fascinating new concept for peptide synthesis: the introduction of alkyl side chains onto a given peptide.[1] This methodology allows an extremely economical modification of sarcosine subunits of linear[2] as well as cyclic peptides.[3] In an application of this technique, the immunosuppressive cyclic undecapeptide cyclosporin was alkylated in a highly regio- as well as stereoselective fashion.[4] Another interesting approach using this concept of side chain introduction was described by Reetz with the stereoselective addition of cuprates to vinylic pseudopeptides.[5] Herein we report our initial investigations of peptide allylation using a modified ester enolate Claisen rearrangement developed in our laboratory.[6]

The first synthesis of allylic amino acids by Claisen rearrangement was described in 1975 by Steglich *et al.*[7] The reaction proceeds *via* an oxazole intermediate and is especially suitable for the synthesis of α-alkylated allylic amino acids.[8] In 1982 the Ireland–Claisen rearrangement[9] of glycine allylic esters was studied by Bartlett and co-workers.[10] In the meantime this elegant methodology has found various applications in amino acid synthesis.[11]

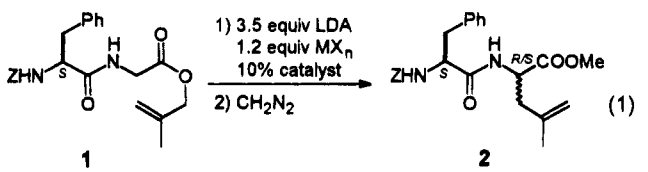
In a previous paper we described another variation of the ester enolate Claisen rearrangement, one that is especially suitable for α-amino acid synthesis (Scheme 1). Deprotonation of *N*-protected glycine allyl esters with LDA at −78 °C and subsequent addition of metal salts such as zinc chloride presumably results in the formation of a chelated zinc enolate which undergoes Claisen rearrangement upon warming to room temperature.[12]

Scheme 1



Due to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeds with a high degree of diastereoselectivity, independent of the substitution pattern and the protecting groups used. In contrast to the corresponding lithium enolates, the chelated enolates are quite stable and can be warmed up to room temperature without decomposition. We therefore tried to apply this methodology to peptides.

As a first example we investigated the rearrangement of allylic ester **1** (eq 1 and Table 1) in the presence of zinc chloride (entry 1). Subsequent esterification of the rearrangement product with diazomethane results in the



1 2 (1)

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Table 1. Rearrangement of Dipeptide 1 in the Presence of Various Metal Salts (MX_n) and 10 Mol % Catalyst

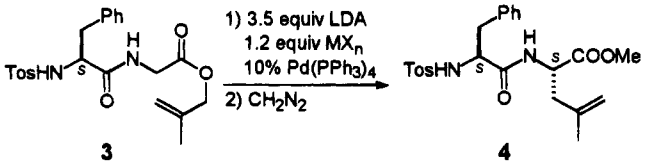
entry	MX_n	catalyst	diastereomeric ratio (*S,S*):(*S,R*)	yield (%)
1	$ZnCl_2$	–	62:38	28
2	$ZnCl_2$	$PdCl_2$(cod)	65:35	20
3	$ZnCl_2$	$Pd(PPh_3)_4$	50:50	75
4	$SnCl_2$	$Pd(PPh_3)_4$	70:30	36
5	$CoCl_2$	$Pd(PPh_3)_4$	35:65	35
6	$AlCl_3$	$Pd(PPh_3)_4$	40:60	50

formation of unsaturated dipeptide **2** in only moderate yields. The (*S,S*)-diastereomer is formed preferentially.

Since the tremendous work done by Overman on rearrangement catalysis,[13,14] many applications, especially of Pd(II)-catalyzed rearrangements, are described in the literature. In our case addition of 10 mol % Pd(II) results in a decrease in yield without affecting the stereoselectivity (Table 1, entry 2).[15] Because Pd(II) is known to form stable complexes with peptides,[16] the formation of a less reactive palladium enolate, which does not rearrange, is probable. In contrast, Pd(0) (10 mol %) catalyzes the reaction in the expected manner (entry 3).

To verify the influence of the chelated metal on the diastereoselectivity of the rearrangement, various metal salts (MX_n) were employed (Table 1, entries 4–6). Although the yields are in general lower in comparison to zinc chloride, better selectivities are obtained. Addition of tin chloride (entry 4) also leads to the preferential formation of the (*S,S*)-diastereomer, while cobalt chloride (entry 5) and aluminum chloride (entry 6) generate the opposite (*S,R*)-diastereomer, probably because of a different complex geometry.

This methodology is suitable for various *N*-protecting groups. So far the best results are obtained with *N*-Tosyl protected peptides like **3** (eq 2). Rearrangement in the presence of zinc chloride or tin chloride provides dipeptide **4** in very good yields.

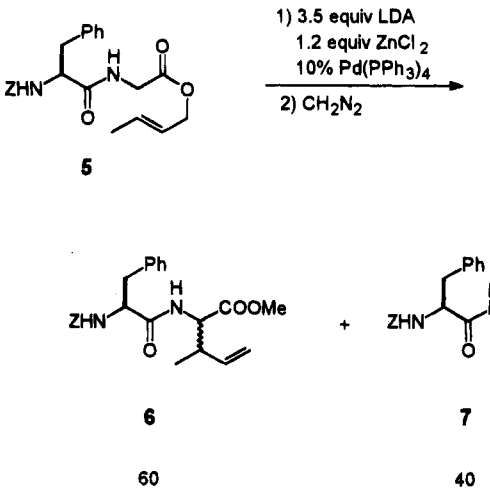


3 4

(2)

MX_n		
$ZnCl_2$	85%	65% ds
$SnCl_2$	82%	66% ds

An important question regarding the mechanism of the rearrangement now arises. In the presence of Pd(0), does the rearrangement still proceed in a [3,3]-sigmatropic fashion or by intermolecular allylic alkylation *via* a π-allylpalladium complex?[17] In order to distinguish between these two possibilities, the rearrangement of crotyl ester **5** (eq 3) was investigated.



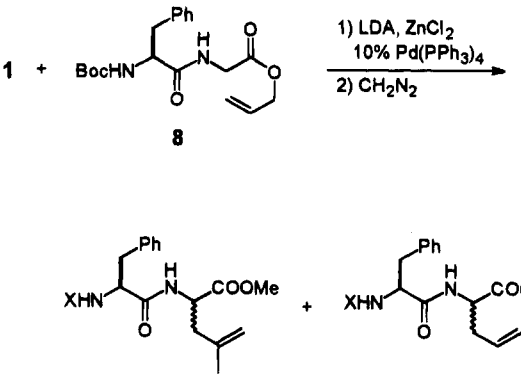
5

(3)

6 60 7 40

The rearrangement products **6** and **7** are formed in comparable amounts. This fact, as well as the nearly complete lack of diastereoselectivity in the newly generated amino acid of **6** (*syn:anti* 2:1) is a clear indication for a π-allylpalladium intermediate.[18] Similar observations had been made by Kellogg for the Pd(0)-catalyzed rearrangement of imines of amino acid allylic esters.[19] The minor product **7** is formed with clean *trans* double bond geometry. No *cis* product was detected by NMR.

To confirm the intermolecular pathway *via* a dissociated π-allylic complex, a second experiment with a mixture of allyl esters **1** and **8** was carried out (eq 4). All four possible diastereomeric peptides (**2**, **9**, **10a**, and **10b**) are formed in this cross reaction in comparable ratios. These results make an intermolecular process probable.



8

(4)

78%

2 X=Z **10a** X=Z
9 X=Boc **10b** X=Boc

Dipeptide **2** was also used to check if racemization of chiral peptides occurs during the reaction. Catalytic hydrogenation yields phenylalanyl–leucine methyl ester

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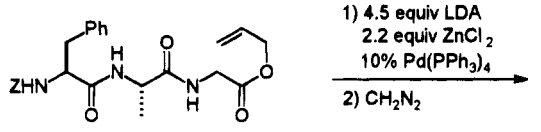
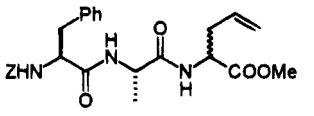
which was analyzed by chiral GC (Chirasil-L-Val) after trifluoroacetylation. *No racemization was observed!* As described by Seebach et al. the chiral centers of peptides are protected by deprotonation of the amide bonds.[1] This also seems to be the case with our chelate complexes even at room temperature.

To show that our methodology is not limited to dipeptides but can also be applied to larger peptides, allyl ester **11** was also subjected to rearrangement (eq 5). The expected product **12** was formed as a nearly 1:1 diastereomeric mixture in reasonable yields.



11 (5)



54%

12

In summary, we have shown that Claisen rearrangement of chelated allylic ester enolates is not only a powerful method for amino acid synthesis, but can also be applied to peptides. In the presence of a catalytic amount of Pd(0) the rearrangement products are formed in high yields. The reaction probably proceeds *via* intermolecular allylic alkylation as was confirmed by cross reactions. No racemization was observed under the reaction conditions used. Further investigations, in particular on the stereochemical control of the rearrangement, are in progress.

Experimental Section

General Procedure. All reactions were carried out in oven-dried glassware (100 °C) under an atmosphere of argon. All solvents were dried before use. THF was distilled from sodium–benzophenone, and diisopropylamine from calcium hydride. LDA solutions were prepared from freshly distilled diisopropylamine and commercially available butyllithium solution (15% in hexane) in THF at −20 °C directly before use. The starting materials and the products were purified by flash chromatography on silica gel (32–63 μm). Mixtures of ethyl acetate and hexanes were used as eluants. TLC was performed on commercial precoated silica gel 60 F_{254} plates (Merck). Visualization was accomplished with UV light, iodine, and potassium permanganate solution. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer. Chemical shifts were reported in δ relative to $CHCl_3$ as an internal reference. GC analyses were performed on a Hewlett-Packard 5890 Series II instrument equipped with a chiral fused silica coating Chirasi-L-Val column (25 m × 0.25 mm, Chrompack). Diastereomer ratios were determined by NMR and analytical HPLC using a Knauer Eurosphere column (250 × 4 mm, Si80, 5 μm, flow: 2 mL/min) and a Knauer UV detector.

General Procedure for the Rearrangement of Dipeptide Allyl Esters. In a typical experiment a solution of 2 mmol of LDA in 4 mL of absolute THF was added at −78 °C under argon to a mixture of 0.6 mmol of dipeptide allyl ester and 0.7 mmol (95 mg) of zinc chloride in 5 mL of THF. A clear pale yellow solution was formed. After 10 min a solution of 0.06 mmol (70 mg) $Pd(PPh_3)_4$ in 1 mL of THF was added before the mixture was allowed to warm up to room temperature. After stirring for 16 h the clear brown solution was diluted with ether and hydrolyzed with 10% aqueous HCl. The organic layer was washed with water and the rearrangement product was extracted twice with 15% NaOH solution. Acidification of the aqueous solution and reextraction of the product with ether gave the crude dipeptide acid, which was esterified by addition of a solution of diazomethane in ether. The product was purified by flash chromatography.

[*N*-(Benzyloxycarbonyl)phenylalanyl]-4,5-didehydroleucine Methyl Ester (2). Following the general procedure, rearrangement of 246 mg (0.6 mmol) of [*N*-(Benzyloxycarbonyl)phenylalanyl]glycine methallyl ester (**1**) yields 210 mg of the crude acid which was purified after esterification by flash chromatography (R_f 0.27, hexanes–EtOAc 7/3) to give 190 mg of **2** (75%) as a colorless foam. Major diastereomer (HPLC retention time 18.61 min, hexanes–EtOAc 83/17): ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.19 (m, 10H), 6.22 (d_{br}, J = 7.2 Hz, 1H), 5.43 (d_{br}, 1H), 5.07 (s, 2H), 4.73 (s, 1H), 4.62 (m, 1H), 4.57 (s, 1H), 4.47 (m, 1H), 3.70 (s, 3H), 3.08 (dd, J = 13.7, 6.3 Hz, 1H), 2.99 (dd, J = 13.7, 6.5 Hz, 1H), 2.46 (dd, J = 13.9, 5.5 Hz,1H), 2.28 (dd, J = 13.9, 8.3 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.00, 170.63, 155.93, 140.18, 136.40, 136.23, 129.33, 128.69, 128.65, 128.53, 128.17, 128.00, 127.00, 114.65, 67.06, 56.12, 52.25, 50.69, 40.43, 38.53, 21.79. Minor diastereomer (HPLC retention time 21.56 min, hexanes–EtOAc 83/17) (selected signals): ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (d_{br}, 1H), 5.06 (s, 2H), 3.69 (s, 3H), 2.39 (dd, J = 14.0, 5.8 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.21, 170.80, 140.21, 136.46, 129.44, 50.53, 40.28. Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.71; H, 6.78; N, 6.57.

[*N*-(*p*-Toluenesulfonyl)phenylalanyl]-4,5-didehydroleucine Methyl Ester (4). Following the general procedure, rearrangement of 260 mg (0.6 mmol) of [*N*-(*p*-Toluenesulfonyl)-phenylalanyl]glycine methallyl ester (**3**) yields 240 mg of the crude acid which was purified after esterification by flash chromatography (R_f 0.18, hexanes–EtOAc 7/3) to give 225 mg of **4** (85%) as a colorless oil. Major diastereomer (HPLC retention time 25.08 min, hexanes–EtOAc 85/15): ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2H), 7.18 (m, 5H), 6.98 (m, 2H), 6.58 (d, J = 7.4 Hz, 1H), 5.16 (d_{br}, 1H), 4.72 (t, J = 1.6 Hz, 1H), 4.58 (s, 1H), 4.55 (m, 1H), 3.92 (m_{br}, 1H), 3.70 (s, 3H), 2.98 (dd, J = 14.0, 7.0 Hz, 1H), 2.90 (dd, J = 14.0, 6.2 Hz, 1H), 2.47 (dd, J = 12.8, 6.2 Hz, 1H), 2.39 (s, 3H), 2.28 (dd, J = 12.8, 6.1 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.71, 169.85, 143.74, 140.12, 136.21, 135.30, 129.77, 129.36, 129.21, 128.87, 128.82, 127.18, 114.64, 57.60, 52.29, 50.86, 40.37, 38.47, 21.80. Minor diastereomer (HPLC retention time 26.19 min, hexanes–EtOAc 85/15) (selected signals): ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 6.92 (m, 2H), 6.83 (d, J = 7.4 Hz, 1H), 5.05 (d_{br}, 1H), 4.85 (t, J = 1.5 Hz, 1H), 2.36 (dd, J = 12.8, 6.1 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.01, 170.11, 139.97, 135.88, 135.15, 127.13, 115.05, 57.78, 52.33, 50.76, 40.32, 38.20, 21.51. Anal. Calcd for $C_{23}H_{28}N_2O_5S$: C, 62.14; H, 6.35; N, 6.30; S, 7.21. Found: C, 61.99; H, 6.31; N, 6.40; S, 7.16.

[*N*-(Benzyloxycarbonyl)phenylalanyl]-4,5-didehydroisoleucine Methyl Ester (6). Following the general procedure, rearrangement of 246 mg (0.6 mmol) of [*N*-(Benzyloxycarbonyl)phenylalanyl]glycine crotyl ester (**5**) yields 230 mg of the crude acid mixture which was purified after esterification by flash chromatography (R_f 0.37, hexanes–EtOAc 6/4) to give 206 mg of a mixture of **6** and **7** (81%) as a colorless oil. Major diastereomer (HPLC retention time 17.89 min, hexanes–EtOAc 85/15): ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.18 (m, 10H), 6.35 (d_{br}, J = 8.1 Hz, 1H), 5.59 (ddd, J = 17.3, 10.7, 7.7 Hz, 1H), 5.48 (d_{br}, J = 6.2 Hz, 1H), 5.09 (d, J = 12.3 Hz, 1H), 5.04 (d, J = 18.0 Hz, 1H), 5.03 (d, J = 12.3 Hz, 1H), 4.94 (dd, J = 10.7, 1.7 Hz, 1H), 4.48 (m, 2H), 3.67 (s, 3H), 3.06 (m, 2H), 2.58 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz,

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$CDCl_3$) δ 171.04, 170.60, 155.95, 138.25, 136.32, 136.18, 129.35, 129.29, 128.77, 128.70, 128.54, 128.20, 128.03, 127.02, 116.31, 67.10, 56.14, 52.16, 40.64, 38.29, 15.47. Minor diastereomer (HPLC retention time 19.09 min, hexanes–EtOAc 85/15) (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (d_{br}, 1H), 5.52 (ddd, J = 18.0, 10.3, 7.7 Hz, 1H), 3.69 (s, 3H), 2.47 (m, 1H), 0.93 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.23, 170.66, 137.61, 116.91, 56.04, 52.03, 40.57, 38.57, 15.57. Anal. Calcd for $C_{24}H_{28}N_2O_5$ (mixture **6** + **7**): C, 67.91; H, 6.65; N, 6.60. Found: C, 67.94; H, 6.59; N, 6.63.

[*N*-(Benzyloxycarbonyl)phenylalanyl]-2-(2-butenyl)glycine Methyl Ester (7): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.16 (m, 10H), 6.41 (d_{br}, 1H), 5.37 (m, 3H), 5.05 (s, 2H), 4.48 (m, 2H), 3.70 (s, 3H), 3.06 (m, 2H), 2.49 (m, 2H), 1.58 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.73, 170.80, 155.97, 136.45, 136.26, 130.11, 129.38, 128.70, 128.64, 128.52, 128.16, 128.00, 127.00, 124.24, 67.04, 56.19, 52.26, 52.09, 38.67, 35.19, 17.90.

[*N*-(*tert*-Butyloxycarbonyl)phenylalanyl]-4,5-didehydroleucine Methyl Ester (9). Following the general procedure, rearrangement of 225 mg (0.6 mmol) of [*N*-(*tert*-butyloxycarbonyl)phenylalanyl]glycine methallyl ester yields 195 mg of the crude acid which was purified after esterification by flash chromatography (R_f 0.29, hexanes–EtOAc 7/3) to give 165 mg of **9** (71%) as a colorless oil. Major diastereomer (HPLC retention time 12.27 min, hexanes–EtOAc 83/17): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.17 (d_{br}, 1H), 4.98 (d_{br}, 1H), 4.76 (s, 1H), 4.59 (s, 1H), 4.57 (m, 1H), 4.37 (m, 1H), 3.71 (s, 3H), 3.12 (dd, J = 14.1, 6.5 Hz, 1H), 3.03 (dd, J = 14.1, 6.3 Hz, 1H), 2.49 (dd, J = 14.7, 5.5 Hz, 1H), 2.30 (dd, J = 14.7, 6.1 Hz, 1H), 1.67 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.87, 170.67, 155.39, 140.27, 136.49, 129.36, 128.67, 126.97, 114.73, 80.20, 55.62, 52.29, 50.93, 40.29, 38.34. Minor diastereomer (HPLC retention time 13.50 min, hexanes–EtOAc 83/17) (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (d_{br}, 1H), 2.39 (dd, J = 14.5, 6.0 Hz,1H), 1.65 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.80, 170.62, 140.32, 129.32, 50.87, 40.17. Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.60; H, 7.74; N, 7.17. Found: C, 64.49; H, 7.72; N, 7.23.

[*N*-(Benzyloxycarbonyl)phenylalanyl]-2-(2-propenyl)glycine Methyl Ester (10a). Following the general procedure, rearrangement of 240 mg (0.6 mmol) of [*N*-(benzyloxycarbonyl)phenylalanyl]glycine allyl ester yields 220 mg of the crude acid which was purified after esterification by flash chromatography (R_f 0.25, hexanes–EtOAc 7/3) to give 185 mg of **10a** (73%) as a colorless oil. Major diastereomer (HPLC retention time 23.60 min, hexanes–EtOAc 83/17): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.16 (m, 10 H), 6.33 (d_{br}, J = 6.9 Hz, 1H), 5.55 (ddt, J = 14.3, 10.2, 7.1 Hz, 1H), 5.35 (d_{br}, 1H), 5.08 (s, 2H), 5.03 (m, 2H), 4.58 (dt, J = 7.7, 7.3 Hz, 1H), 4.46 (q_{br}, 1H), 3.70 (s, 3H), 3.10 (d, J = 14.0 Hz, 1H), 3.03 (d, J = 14.0 Hz, 1H), 2.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.47, 170.47, 155.87, 136.27, 136.18, 131.85, 129.38, 128.71, 128.55, 128.21, 128.04, 127.06, 119.28, 67.10, 56.13, 52.34, 51.78, 38.41, 36.34. Minor diastereomer (HPLC retention time 22.66 min, hexanes–EtOAc 83/17) (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (d_{br}, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.60, 170.34, 129.30, 128.76, 52.24, 51.59, 36.20. Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.19; H, 6.30; N, 6.74.

[*N*-(*tert*-Butyloxycarbonyl)phenylalanyl]-2-(2-propenyl)glycine Methyl Ester (10b). Following the general procedure, rearrangement of 218 mg (0.6 mmol) of [*N*-(*tert*-butyloxycarbonyl)phenylalanyl]glycine allyl ester (**8**) yields 195 mg of the crude acid which was purified after esterification by flash chromatography (R_f 0.28, hexanes–EtOAc 7/3) to give 175 mg **10b** (78%) as a colorless oil. Major diastereomer (HPLC retention time 14.51 min, hexanes–EtOAc 83/17): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.17 (m, 5H), 6.41 (d_{br}, 1H), 5.52 (m, 1H), 5.02 (m, 3H), 4.60 (dt, J = 7.8, 7.2 Hz, 1H), 4.40 (m, 1H), 3.69 (s, 3H), 3.07 (dd, J = 13.8, 7.2 Hz, 1H), 3.00 (dd, J = 13.8, 7.0 Hz, 1H), 2.49 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.23, 170.87, 155.32, 136.64, 131.96, 129.38, 128.63, 126.92, 119.19, 80.23, 55.74, 52.21, 51.78, 38.28, 36.80, 28.25. Minor diastereomer (HPLC retention time 14.98 min, hexanes–EtOAc 83/17) (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d_{br}, 1H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$)-δ 171.53, 170.73, 131.88, 129.30, 119.28, 52.68, 51.56, 36.40. Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.73 H, 7.38; N, 7.41.

[*N*-(Benzyloxycarbonyl)phenylalanyl]alanyl]-2-(2-propenyl)glycine Methyl Ester (12). Following the general procedure, 2 mmol of LDA in 4 mL absolute THF was added at −78 °C under argon to a mixture of 187 mg (0.4 mmol) of dipeptide allyl ester **11** and 110 mg (0.8 mmol) of zinc chloride in 5 mL of THF. After addition of 45 mg (0.04 mmol) $Pd(PPh_3)_4$ in 1 mL of THF the mixture was allowed to warm up to room temperature overnight. Workup as usual gave 135 mg of the crude acid which was purified after esterification by flash chromatography (R_f 0.20, hexanes–EtOAc 1/1) to give 100 mg of **12** (54%) as a colorless foam. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.20 (m, 10H), 7.15 (d, J = 6.3 Hz, 1H), 6.70 (d, J = 6.0 Hz, 1H), 5.68 (ddt J = 16.5, 9.6, 7.0 Hz,-1H), 5.48 (d_{br}, 1H), 5.08 (m, 2H), 5.09 (d, J = 12.1 Hz, 1H), 5.03 (d, J = 12.1 Hz, 1H), 4.63–4.45 (m, 3H), 3.72 (s, 3H), 3.09 (d, J = 14.3 Hz, 1H), 3.03 (d, J = 14.3 Hz, 1H), 2.50 (m, 2H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.41, 170.79, 155.93, 136.17, 136.12, 132.07, 129.28, 128.76, 128.71, 128.54, 128.22, 128.03, 127.13, 119.28, 67.22, 56.27, 52.39, 51.86, 48.93, 38.43, 36.31, 18.37. Minor diastereomer (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 6.6 Hz, 1H), 6.84 (d, J = 7.0 Hz, 1H), 5.52 (d_{br}, 1H), 3.71 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.79, 170.84, 132.15, 128.21, 128.13, 119.17, 67.13, 51.76, 48.81, 36.39, 18.26. Anal. Calcd for $C_{26}H_{31}N_3O_6$: C, 64.84; H, 6.49; N, 8.73. Found: C, 64.72; H, 6.61; N, 8.83.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for starting materials (compound **1**, **3**, **5**, **8**, **11**) (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.