Modifications of Peptides by Chelate Claisen Rearrangements of Manganese Enolates

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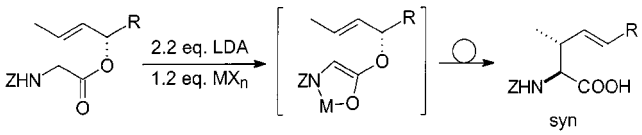
Deprotonation of allylic esters of peptides at –70 °C in the presence of metal salts results in the formation of metal peptide enolate complexes, which undergo Claisen rearrangement on warming to room temperature to produce stereoselectively modified peptides. By far the best results are obtained with manganese enolates. With these enolates, the amino acids incorporated in the peptide chain have no significant influence on the rearrangement, neither on the yield nor on the stereochemical outcome. Therefore, this protocol is extremely suitable for the stereoselective modification of peptides by using esters of chiral allylic alcohols. α-Alkylated amino acids can be incorporated into peptides as well.

Introduction

Peptides and cyclopeptides containing unusual amino acids are quite common in nature, and are often found in marine organisms.[1] Many of these peptides show antibiotic activity[2] and are therefore of great interest from a pharmaceutical point of view.[3] For straightforward approaches towards these targets, efficient target screenings, as well as optimizations of lead structures, flexible synthetic concepts are necessary.

Three fundamentally different protocols are suitable for the synthesis of modified peptides: (a) The classical method of preparing modified peptides is to incorporate non-proteinogenic amino acids or other building blocks into the peptide backbone through standard peptide couplings. (b) Another possibility is to modify functionalized amino acids in the side chain; the great advantage of such side-chain modifications is that the stereogenic center in the newly formed amino acid is derived from that in the precursor amino acid;[4] a disadvantage is that suitable precursors are necessary. (c) Direct modifications can be carried out on the peptide backbone by substitution of NH[5] and/or CH hydrogens or by replacing the carbonyl oxygen with other groups, e.g. sulfur.[6] Substitution reactions at the α-carbon of a glycine subunit are especially attractive as they allow the direct introduction of various types of side chains into peptides. As reactive intermediates, either glycine cation equivalents[7] or glycine anions (glycine enolates) can be used.[8] The major drawback associated with this concept is a lack of control over the stereochemical outcome of the C–C coupling step. As shown by Seebach et al., the best results are obtained in enolate alkylations of cyclic peptides, presumably because one face of the enolate is shielded by the peptide ring.[9]

For quite some time we have been investigating syntheses of γ,δ-unsaturated amino acids.[10] One approach towards these structures is based on a variation of the Claisen rearrangement and proceeds via chelated amino acid ester enolates (Scheme 1).[11] Because the enolate geometry is fixed by chelation and the Claisen rearrangement shows a strong preference for the *chair-like* transition state, the *syn*-configured rearrangement products are formed in a highly stereoselective fashion. If esters of chiral allylic alcohols are used, the corresponding enantiomerically pure amino acids are obtained.[12]



Scheme 1

Therefore, we became interested in ascertaining whether this Claisen protocol could also be applied to backbone modifications of peptides. Our early investigations were carried out using zinc enolates, which generally give the best results in the rearrangement of amino acids.[13] With peptides, the yields obtained were modest, although they could be increased (to 70–80%) by addition of Pd^0 catalysts. However, under these conditions, the allylations of the peptide chains proceed via π-allylpalladium intermediates. This intermolecular process results in significantly reduced diastereoselectivities and also leads to the formation of regioisomers if substituted allylic esters are used. Therefore, we undertook an extensive investigation of various metals in order to find suitable chelate complexes that undergo Claisen rearrangement without the assistance of a palladium catalyst.

Results and Discussion

Preparation of Peptide Allylic Esters

The peptide allylic esters used as substrates for the ester enolate Claisen rearrangements were prepared according to two major protocols (Scheme 2).

Procedure 1: Esterification of the corresponding *N*-protected dipeptides (PG: protecting group) with the appropri-

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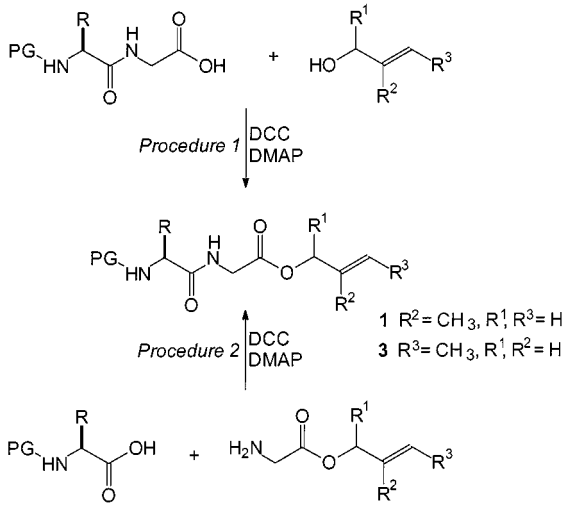


Scheme 2

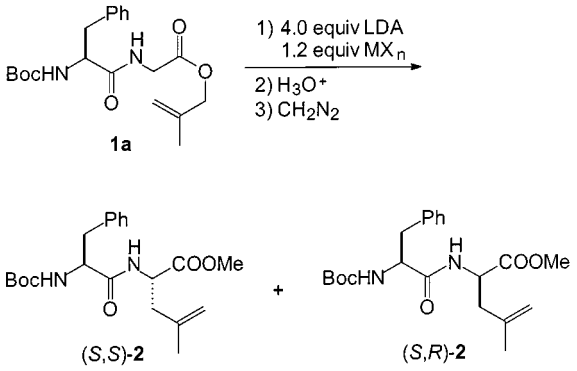
ate allylic alcohols using DCC/DMAP, according to Steglich et al.[14] This approach is highly flexible with respect to the alcohols that can be used and was mainly applied to the preparation of methylallylic ester **1** as well as several chiral allylic esters ($R^1 \neq H$).

Procedure 2: To achieve variations in the peptide chain, a fragment condensation of several protected amino acids with glycine crotyl ester was used for the synthesis of esters **3**. These crotyl esters are especially interesting as their rearrangements give rise to isoleucine derivatives with the simultaneous generation of two stereogenic centers in a single step.

In the course of our investigations concerning the influence of the protecting group, we became interested in the synthesis of *N*-tosylated and Tfa (trifluoroacetyl)-protected peptide esters. The introduction of such strongly electron-withdrawing groups results in an increase in the acidity of the *N*-terminus of the peptide chain. Regioselective palladium-catalyzed allylic alkylations[15] at this position under very mild conditions provide suitable substrates for subsequent ring-closing metatheses.[16] With tosylated amino acids, the fragment condensations (Procedure 2) using DCC gave only moderate isolated yields. In these cases, better results were obtained using carbonyldiimidazole[17] as the coupling reagent. Peptide couplings of Tfa-protected amino acids are not a trivial matter either. During their activation, oxazolinones can be formed as intermediates, which leads to (partial) epimerization of the α-stereogenic center.[18] To avoid this problem, Tfa-protected peptide esters were prepared from the corresponding Boc derivatives. Cleavage of the Boc group using trifluoroacetic acid and subsequent addition of trifluoroacetic anhydride allows a one-pot formation of the desired substrates.

Peptide Claisen Rearrangements

As a first example, we investigated the rearrangement of methylallyl ester **1** (Scheme 3) in the presence of various metal salts (Table 1). The rearrangement was generally performed as follows. The peptide ester **1a** was dissolved in



Scheme 3

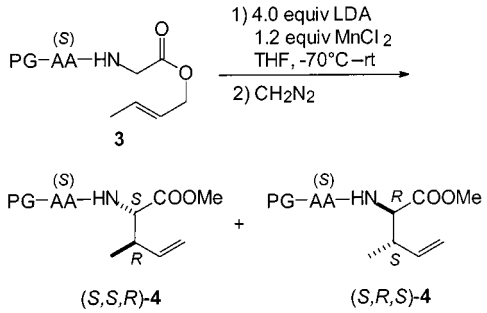
Table 1. Chelate Claisen rearrangement of dipeptide allylic ester **1**

Entry	MX_n	Diastereomeric ratio		Yield
		(*S*,*S*)	(*S*,*R*)	[%]
1	$Al(OiPr)_3$	18	82	19
2	$Ti(OiPr)_4$	10	90	32
3	$Ti(OiPr)_3Cl$	21	79	37
4	$TiCp_2Cl_2$	33	67	37
5	$CoCl_2$	63	37	30
6	$SnCl_2$	70	30	52
7	$MgCl_2$	50	50	59
8	$ZnCl_2$	60	40	62
9	$MnCl_2$	60	40	86

THF, the metal salt was added, and the mixture was cooled to –70 °C. A freshly prepared solution of LDA in THF was then slowly added and the resulting mixture was allowed to warm to room temperature and left to stand overnight. Hydrolysis and subsequent esterification of the rearrangement product with diazomethane furnished the unsaturated dipeptide ester **2**.

Interestingly, the isopropoxides of aluminum and titanium gave relatively good selectivities, although the yields obtained were only moderate.[19] In these cases, the (*S*,*R*) diastereomer was formed preferentially. In contrast, no significant selectivity was observed with most of the other metal salts used, although they gave much better yields. By far the best results were obtained when manganese salts were used for chelation.[20]

This trend was also observed with other peptide methylallyl esters. In the course of our investigations, we also found the reason for the low yields occasionally encountered. With certain substrates, we observed an isomerization of the terminal allylic double bond to the more highly substituted and therefore clearly more stable vinylic position. Because the resulting vinyl esters are unable to undergo the Claisen rearrangement, these isomerized products were isolated from the reaction mixture. To avoid this problem, we switched to the corresponding crotyl esters **3**, in which there should be no driving force for this isomerization. The results obtained with these esters using the manganese enol-



Scheme 4

Table 2. Chelate enolate Claisen rearrangement of peptide esters **3**

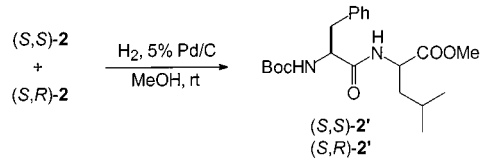
Entry	Ester	PG	AA	Selectivity		Yield
				(*S*,*S*,*R*)	(*S*,*R*,*S*)	[%]
1	**3a**	Boc	Phe	62	38	93
2	**3b**	Tfa	Phe	63	37	75
3	**3c**	Tos	Phe	56	40	92
4	**3d**	Z	Val	60	40	92
5	**3e**	Boc	Val	37	63	95
6	**3f**	Tos	Ile	35	65	83
7	**3g**	Boc	Met	33	67	89
8	**3h**	Boc	Lys(BOC)[a]	42	58	77[b]
9	**3i**	Boc	β-Phe	55	45	96[b]

[a] 5 equiv. of base were used. – [b] LHMDS was used as base.

ates (Scheme 4) are presented in Table 2. Irrespective of the protecting groups (PG) used,[21] the yields obtained with these manganese enolates were good to excellent throughout. This was even true for peptides containing functionalized side chains (Entries 7 and 8) and β-amino acids (Entry 9). In all examples investigated to date, the simple diastereoselectivity of the rearrangement has been found to be very high (95% *syn*)[22] and comparable with the results obtained using amino acids. No significant induced diastereoselectivity has been observed.[23] Clearly, the *N*-terminal amino acid (AA) has no notable influence on the rearrangement. This is also reflected in the high yields obtained, which are virtually independent of the peptide used.

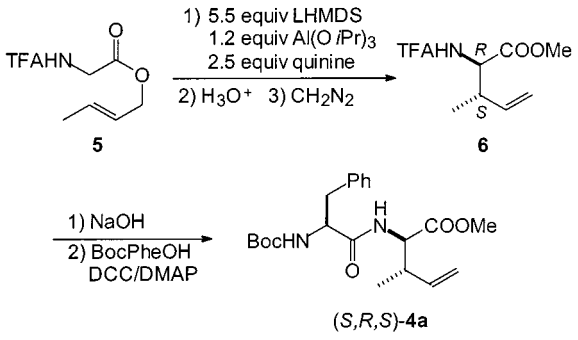
Determination of Configuration

The methylallyl ester **1** was selected for study as its rearrangement generates only one stereogenic center and the resulting dehydroleucine derivative **2** can easily be converted into the corresponding leucine peptide **2′** by catalytic hydrogenation (Scheme 5). In order to determine the configuration at the newly formed stereogenic center, (*S*,*S*)-**2′** was also prepared by classical peptide coupling. The diastereomeric ratio was determined by HPLC using a chiral column (Daicel OD-H). As reported previously,[8,13] no epimerization of the stereogenic center in the peptide substrate was observed.



Scheme 5

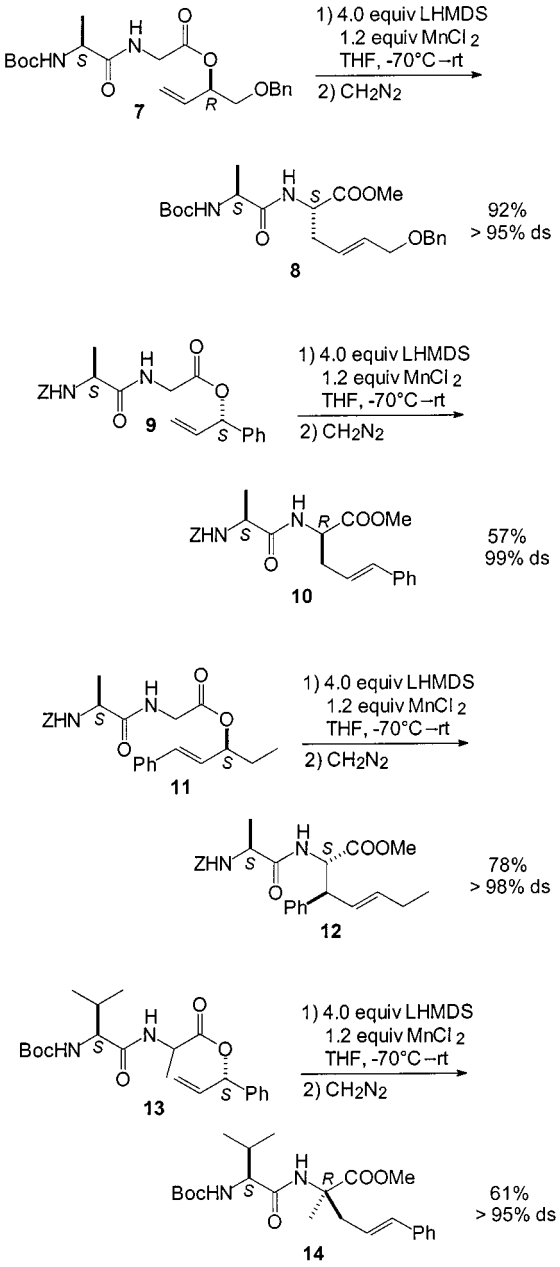
Under these conditions, rearrangement of the crotyl esters can provide up to four different isomeric products. If the rearrangement proceeds via the *chair-like* transition state, the *syn* (2*R*,3*S* or 2*S*,3*R*) products are formed preferentially, whereas the *boot-like* transition state gives rise to the *anti* (2*R*,3*R* or 2*S*,3*S*) product. In all examples investigated to date, the *syn* product has been formed with high diastereoselectivity, typically 95% *de* or higher. Only in the case of the rearrangement product **4c** (obtained from **3c**) could the minor diastereomer (5%) be observed by NMR. In order to verify that the *syn* product had indeed been formed, we synthesized several diastereomeric dipeptides **4** in a stepwise manner. Rearrangement of Boc-glycine crotyl ester and subsequent esterification gave the Boc-protected *syn* dehydroisoleucine ester (95% *de*). Cleavage of the protecting group and standard peptide coupling with the *N*-terminal amino acids provided reference samples. In order to determine the absolute configuration, the (*R*)-*allo*-isoleucine derivative **6** was obtained with high *ee* (86%) and in almost diastereomerically pure form (98% *de*) by an asymmetric Claisen rearrangement in the presence of quinine (Scheme 6).[24] Saponification of the protecting group and coupling with, for example, Boc-protected phenylalanine, gave the required peptide (*S*,*R*,*S*)-**4a** with high diastereomeric excess. The (*R*) derivative was selected for study since it gives better separation of HPLC peaks in cases where the major, sometimes broad peak is the second eluted. In all examples investigated to date, the (*S*,*S*) isomer has been found to elute ahead of the corresponding (*S*,*R*) diastereomer.



Scheme 6

Asymmetric Claisen Rearrangements

Because the influence of the adjacent amino acid on the rearrangement can be neglected, the use of esters of chiral allylic alcohols allows the stereoselective synthesis of pep-



Scheme 7

tides (Scheme 7). The stereochemical outcomes of rearrangements of chiral amino acid esters have been investigated previously,[12] and therefore it is possible to confidently predict the configuration that will be obtained. This approach is especially interesting if the appropriate chiral alcohols are readily available. The requisite alcohol for ester **7** was obtained from tartaric acid,[25] while the others were prepared by enzymatic kinetic resolution[26] using an immobilized lipase (*candida antarctica*). The corresponding esters were prepared according to Procedure 1.

Using LHMDS as a base,[27] the corresponding dipeptides were obtained not only in good to excellent yields, but also in a highly diastereoselective fashion. In most cases, only one diastereomer could be detected by HPLC and NMR. As expected, the rearrangement also proved to be suitable for the generation of (*S*)- and (*R*)-configured amino acids. Not only linear, but branched side chains can be introduced as well. Example **11** illustrates that the results obtained with the crotyl esters can also be achieved with other *trans* configured esters. Therefore, various substituents can be placed at the chiral β-position, such as the phenyl group shown here (**12**). This protocol is also suitable for the direct introduction of α-alkylated amino acids into peptides (**14**). These derivatives show higher resistances towards proteases and are therefore of potential interest with regard to the development of peptide-based pharmaceuticals.[28] Because of the steric hindrance of these amino acids, their introduction into peptides by classical peptide coupling reactions is often problematic and consequently special coupling reagents and methods have to be employed.[29] Using the present peptide Claisen rearrangement, even these sterically hindered peptides can be obtained.

In summary, we have shown that manganese enolates are extremely suitable for the modification of peptides through chelate Claisen rearrangements. The yields obtained are good to excellent in most cases and are independent of the peptides and the protecting groups used. Because the adjacent amino acids do not have any significant influence on the rearrangement, use of chiral esters offers easy access to diastereomerically pure peptides.

Experimental Section

General: All reactions were carried out in oven-dried glassware (100 °C) under an atmosphere of argon. All solvents were dried prior to use. THF was distilled from sodium-benzophenone, and diisopropylamine from calcium hydride. LDA solutions were prepared from freshly distilled diisopropylamine and commercially available *n*-butyllithium solution (15% in hexane) in THF at –20 °C immediately prior to use. The starting materials and the products were purified by flash column chromatography on silica gel (32–63 μm). Mixtures of ethyl acetate and hexane were used as eluents. – TLC was performed on commercial precoated silica gel 60 F_{254} plates (Merck). Visualization was accomplished with UV light, by exposure to iodine, or by treatment with potassium permanganate solution. – ^1H and ^{13}C NMR spectra were recorded on Bruker AC-300 or Bruker Avance 300 spectrometers. Chemical shifts are reported in δ units relative to $CHCl_3$ as an internal reference. – Diastereomer ratios were determined by NMR and analytical HPLC using a Daicel OD-H chiral column (flow rate: 0.5 mL/min) and a Shimadzu diode-array detector. Where selected signals are quoted for the second diastereomer, these were extracted from the NMR spectra of the mixtures.

General Procedures for the Synthesis of Dipeptide Allyl Esters

Procedure 1: To a cooled (–15 °C) solution of the allylic alcohol (10 mmol), a solution of DMAP (1 mmol) and DCC (10 mmol) in dichloromethane (DCM) was added. The resulting clear solution was stirred for 20 min, and then a solution of the appropriate dipeptide (10 mmol) in DCM (20 mL) was added. The precipitated DCU was filtered off and washed with DCM. The organic layer was washed with 1 N HCl and with satd. $NaHCO_3$ solution and the aqueous washings were extracted once with DCM. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated

in vacuo. The crude product was purified by flash column chromatography and/or by crystallization.

Procedure 2: To a cooled (–20 °C) solution of the *N*-protected amino acid (10 mmol), a solution of DMAP (1 mmol) and DCC (10 mmol) in DCM was added. Meanwhile, the glycine ester hydrochloride (11 mmol) was suspended in DCM (20 mL) in a separate flask, *N*-methylmorpholine (12 mmol) was added, and the resulting mixture was stirred vigorously for 5 min. This solution was then added to the activated amino acid at –20 °C and the resulting mixture was allowed to warm to room temperature overnight. Work-up was carried out as described for Procedure 1.

General Procedure for the Rearrangement of Dipeptide Allyl Esters: Typically, a solution of LDA (1 mmol) in absolute THF (2 mL) was added to a mixture of the dipeptide allyl ester (0.25 mmol) and manganese chloride (38 mg, 0.3 mmol) in THF (5 mL) at –70 °C under argon. A cloudy, light-brown solution resulted, which was allowed to warm to room temperature overnight. After stirring for 16 h, the clear brown solution was diluted with diethyl ether and hydrolyzed with 1 N HCl solution under vigorous stirring until the organic layer was almost colorless. After separation of the phases, the organic layer was washed with water and the rearrangement product was extracted with two aliquots of 1 N NaOH solution. Acidification of the aqueous solution and re-extraction of the product with DCM gave the crude dipeptide acid, which was esterified by adding a solution of diazomethane in diethyl ether. The product was purified by flash chromatography.

2-Methylallyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanylglycinate (1a): Ester **1a** was prepared according to General Procedure 1 on a 15.0 mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 63:37) to give 5.38 g (14.2 mmol, 95%) of ester **1a** as a colorless solid. Crystallization from DCM/diethyl ether/hexane gave colorless needles, m.p. 113 °C. – $[\alpha]_D^{20} = -2.7$ ($c = 0.6$, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 1-H), 1.74 (s, 3 H, 11-H), 3.02 (dd, J = 13.9, 7.0 Hz, 1 H, 12-H), 3.12 (dd, J = 13.9, 6.4 Hz, 1 H, 12-H), 3.96 (dd, J = 18.3, 5.1 Hz, 1 H, 6-H), 4.06 (dd, J = 18.3, 5.4 Hz, 1 H, 6-H), 4.41 (br. s, 1 H, 4-H), 4.54 (s, 2 H, 8-H), 4.94 (s, 1 H, 10-H), 4.96 (s, 1 H, 10-H), 5.07 (d, J = 7.9 Hz, 1 H, BocNH), 6.58 (t, J = 5.1 Hz, 1 H, NH), 7.18–7.30 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.39 (q, C-11), 28.23 (q, C-1), 38.39 (t, C-12), 41.26 (t, C-6), 55.67 (d, C-4), 68.60 (t, C-8), 80.28 (s, C-2), 113.64 (t, C-10), 126.91, 128.62, 129.29 (d, arom. C), 136.64 (s, C-13), 139.21 (s, C-9), 155.41 (s, C-3), 169.17, 171.61 (s, C-5, C-7). – $C_{20}H_{28}N_2O_5$ (376.45): calcd. C 63.81, H 7.50, N 7.44; found C 63.88, H 7.53, N 7.41.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanyl-(*RS*)-γ,δ-didehydroleucinate [(*S*,*RS*)-2]: Ester **2** was prepared from **1** (95 mg, 0.25 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 1. 80:20, 2. 70:30) to give 84 mg (0.215 mmol, 86%) of ester **2** as a colorless foam. Diastereomeric ratio (*S*,*S*)/(*S*,*R*): 60:40. – HPLC (hexane/2-propanol, 87:13): t_R(*S*,*S*): 20.84 min, t_R(*S*,*R*): 23.97 min. – (*S*,*S*)-**2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, 1-H), 1.65 (s, 3 H, 12-H), 2.28 (dd, J = 14.0, 8.3 Hz, 1 H, 9-H), 2.45 (dd, J = 14.0, 6.0 Hz, 1 H, 9-H), 3.03 (d, J = 6.5 Hz, 2 H, 13-H), 3.68 (s, 3 H, 8-H), 4.36 (br. s, 1 H, 4-H), 4.54–4.61 (m, 1 H, 6-H), 4.57 (s, 1 H, 11-H), 4.73 (s, 1 H, 11-H), 4.99 (br. s, 1 H, BocNH), 6.33 (d, J = 7.6 Hz, 1 H, NH), 7.16–7.29 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.54 (q, C-12), 28.01 (q, C-1), 38.12 (t, C-13), 40.26 (t, C-9), 50.27 (d, C-6), 51.98 (q, C-8), 55.48 (d, C-4), 79.97 (s, C-2), 114.45 (t, C-11), 126.68, 128.41, 129.17 (d, arom. C), 136.38 (s, C-14), 139.95 (s, C-10), 155.57 (s, C-3), 170.65, 171.75 (s, C-5, C-7). – (*S*,*R*)-**2**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 1-H), 1.63 (s, 3 H, 12-H), 3.69 (s, 3 H, 8-H), 6.20 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.04 (t, C-9), 50.41 (d, C-6), 114.40 (t, C-11), 139.92 (s, C-10), 170.83, 171.95 (s, C-5, C-7). – $C_{21}H_{30}N_2O_5$ (390.48): calcd. C 64.60, H 7.74, N 7.17; found C 64.76, H 7.71, N 7.16.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanyl-(*S*)-leucinate [(*S*,*S*)-2′]: Ester (*S*,*S*)-**2′** was prepared on a 6.2 mmol scale according to General Procedure 2. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 2.2 g (5.7 mmol, 92%) of ester **2′** as a colorless oil. – HPLC (hexane/2-propanol, 85:15): t_R(*S*,*S*): 17.47 min. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.1 Hz, 3 H, 11-H), 0.87 (d, J = 5.9 Hz, 3 H, 11-H), 1.35–1.59 (m, 3 H, 9-H, 10-H), 1.38 (s, 9 H, 1-H), 3.04 (d, J = 6.8 Hz, 2 H, 12-H), 3.66 (s, 3 H, 8-H), 4.32 (m, 1 H, 4-H), 4.53 (m, 1 H, 6-H), 5.00 (br. s, 1 H, BocNH), 6.29 (d, J = 8.1 Hz, 1 H, NH), 7.17–7.29 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.66, 22.49 (q, C-11), 24.42 (d, C-10), 28.00 (q, C-1), 37.86 (t, C-12), 41.37 (t, C-9), 50.53 (d, C-6), 51.95 (q, C-8), 55.46 (d, C-4), 80.03 (s, C-2), 126.67, 128.37, 129.14 (d, arom. C), 136.37 (s, C-13), 155.14 (s, C-3), 170.70, 172.56 (s, C-5, C-7).

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanyl-(*RS*)-leucinate [(*S*,*RS*)-2′]: For analytical purposes, 30 mg of ester (*S*,*RS*)-**2** was dissolved in 5 mL of MeOH. After addition of 5 mg of 5% Pd/C, the mixture was subjected to hydrogenation (45 psi H_2). After filtration and evaporation of the solvent, the diastereomeric mixture (60:40) was analyzed by HPLC (hexane/2-propanol, 85:15): t_R(*S*,*S*): 17.46 min, t_R(*S*,*R*): 18.70 min.

Crotyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanylglycinate (3a): Ester **3a** was prepared according to General Procedure 1 on a 3.25-mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 1.19 g (3.16 mmol, 97%) of ester **3a** as a colorless solid, m.p. 90 °C. – $[\alpha]_D^{20} = -3.0$ (c = 2.6, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 9 H, 1-H), 1.52 (dd, J = 6.3, 0.9 Hz, 3 H, 11-H), 2.76–2.83 (m, 1 H, 12-H), 2.93 (dd, J = 13.9, 6.5 Hz, 1 H, 12-H), 3.78 (dd, J = 18.3, 5.2 Hz, 1 H, 6-H), 3.84 (dd, J = 18.3, 5.6 Hz, 1 H, 6-H), 4.22 (m, 1 H, 4-H), 4.35 (d, J = 6.4 Hz, 2 H, 8-H), 4.89 (br. s, 1 H, BocNH), 5.35 (dtq, J = 15.2, 6.4, 1.4 Hz, 1 H, 9-H), 5.60 (dq, J = 15.2, 6.3 Hz, 1 H, 10-H), 6.37 (br. s, 1 H, NH), 6.98–7.13 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.79 (q, C-11), 28.30 (q, C-1), 38.48 (t, C-12), 41.39 (t, C-6), 55.85 (d, C-4), 66.20 (t, C-8), 80.36 (s, C-2), 124.48 (d, C-9), 126.78, 128.92, 129.37 (d, arom. C), 132.36 (d, C-10), 136.71 (s, C-13), 155.44 (s, C-3), 169.32, 171.63 (s, C-5, C-7). – $C_{20}H_{28}N_2O_5$ (376.45): calcd. C 63.81, H 7.50, N 7.44; found C 63.59, H 7.52, N 7.41.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanyl-(*R*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*R*,*S*)-4a]: For analytical purposes, ester (*S*,*R*,*S*)-**4a** was prepared from methyl *N*-trifluoroacetyl-(*R*)-*allo*-γ,δ-didehydroisoleucinate (**6**).[24] To a solution of 66 mg (0.3 mmol) of ester **6** in DCM (3 mL) was added 0.6 mL of 0.5 N NaOH solution. After the base had been consumed, the mixture was diluted with H_2O (10 mL) and the amine was extracted with two aliquots of DCM. The combined organic layers were dried and used directly for the peptide coupling step according to Procedure 2. Yield: 82 mg (0.21 mmol, 70%). – HPLC (hexane/2-propanol, 90:10): t_R(*S*,*R*,*S*): 9.21 min.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4a]: 4a was prepared from ester **3a**

(113 mg, 0.30 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 109 mg (0.28 mmol, 93%) of ester **4a** as a colorless foam. Diastereomeric ratio (*S*,*S*,*R*)/(*S*,*R*,*S*): 62:38. Crystallization from diethyl ether/hexane gave colorless crystals of (*S*,*R*,*S*)-**4a**, m.p. 105 °C. – HPLC (hexane/2-propanol, 90:10): t_R(*S*,*S*,*R*): 8.41 min, t_R(*S*,*R*,*S*): 9.10 min. – (*S*,*R*,*S*)-**4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 7.0 Hz, 3 H, 12-H), 1.38 (s, 9 H, 1-H), 2.47 (m, 1 H, 9-H), 3.04 (d, *J* = 6.9 Hz, 2 H, 13-H), 3.68 (s, 3 H, 8-H), 4.37 (br. s, 1 H, 4-H), 4.48 (dd, *J* = 8.0, 5.6 Hz, 1 H, 6-H), 4.95 (br. s, 1 H, BocNH), 4.95 (d, *J* = 17.3 Hz, 1 H, 11-H), 5.04 (d, *J* = 10.3 Hz, 1 H, 11-H), 5.54 (ddd, *J* = 17.3, 10.3, 8.1 Hz, 1 H, 10-H), 6.34 (d, *J* = 7.3 Hz, 1 H, NH), 7.17–7.31 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.33 (q, C-12), 28.01 (q, C-1), 38.06 (t, C-13), 40.34 (d, C-9), 51.81 (q, C-8), 55.74 (d, C-6), 55.97 (d, C-4), 79.94 (s, C-2), 116.15 (t, C-11), 126.74, 128.48, 129.04 (d, arom. C), 136.38 (s, C-14), 138.02 (d, C-10), 154.95 (s, C-3), 170.74, 171.04 (s, C-5, C-7). – (*S*,*S*,*R*)-**4a**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 7.0 Hz, 3 H, 12-H), 1.39 (s, 9 H, 1-H), 2.56 (m, 1 H, 9-H), 3.65 (s, 3 H, 8-H), 4.52 (dd, *J* = 8.6, 5.5 Hz, 1 H, 6-H), 5.60 (ddd, *J* = 17.0, 10.5, 7.7 Hz, 1 H, 10-H), 6.36 (d, *J* = 8.6 Hz, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.52 (q, C-12), 38.03 (t, C-13), 40.67 (d, C-9), 51.99 (q, C-8), 56.06 (d, C-6), 116.30 (t, C-11), 138.23 (d, C-10). – $C_{21}H_{30}N_2O_5$ (390.48): calcd. C 64.60, H 7.74, N 7.17; found C 64.62, H 7.79, N 7.15.

Crotyl *N*-Trifluoroacetyl-(*S*)-phenylalanylglycinate (3b): Ester **3b** was prepared from the Boc derivative **3a**. To a solution of ester **3a** (1.0 g, 2.66 mmol) in DCM (5 mL) at 0 °C was added trifluoroacetic acid. After 2 h, the solution was concentrated to dryness. The residue was redissolved in DCM and then pyridine (650 mg, 8.0 mmol) and trifluoroacetic anhydride (1.3 g, 6.0 mmol) were added. After 12 h, the reaction mixture was diluted with DCM (30 mL) and washed twice with water. The solvent was then evaporated and the crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30). Yield: 980 mg (2.60 mmol, 98%) of ester **3b** as colorless needles, m.p. 92–93 °C. – $[\alpha]_D^{20}$ = +0.8 (*c* = 0.6, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (dd, *J* = 6.5, 0.8 Hz, 3 H, 10-H), 3.06 (dd, *J* = 13.8, 8.0 Hz, 1 H, 11-H), 3.10 (dd, *J* = 13.8, 8.0 Hz, 1 H, 11-H), 3.91 (dd, *J* = 18.2, 5.1 Hz, 1 H, 5-H), 3.98 (dd, *J* = 18.2, 5.3 Hz, 1 H, 5-H), 4.54 (d, *J* = 6.7 Hz, 2 H, 7-H), 4.68 (m, 1 H, 3-H), 5.54 (dtq, *J* = 15.2, 6.7, 1.6 Hz, 1 H, 8-H), 5.79 (dq, *J* = 15.2, 6.6 Hz, 1 H, 9-H), 6.10 (br. s, 1 H, NH), 7.18 (d, *J* = 7.1 Hz, 1 H, TfaNH), 7.23–7.30 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.74 (q, C-10), 38.48 (t, C-11), 41.43 (t, C-5), 54.67 (d, C-3), 66.44 (t, C-7), 115.58 (q, *J* = 287.4 Hz, C-1), 124.13 (d, C-8), 127.53, 128.87, 129.23 (d, arom. C), 132.70 (d, C-9), 135.19 (s, C-12), 168.75, 169.26 (s, C-4, C-6). – $C_{17}H_{19}F_3N_2O_4$ (372.35): calcd. C 54.84, H 5.14, N 7.52; found C 54.81, H 5.26, N 7.51.

Methyl *N*-Trifluoroacetyl-(*S*)-phenylalanyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4b]: Ester **4b** was prepared from ester **3b** (130 mg, 0.35 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 101 mg (0.26 mmol, 75%) of ester **4b** as a colorless foam. Diastereomeric ratio (*S*,*S*,*R*)/(*S*,*R*,*S*): 63:37. Crystallization from diethyl ether/hexane gave colorless needles, m.p. 100 °C. – HPLC (silica, hexane/ethyl acetate, 80:20, 2 mL/min): t_R(*S*,*S*,*R*): 9.50 min, t_R(*S*,*R*,*S*): 10.39 min. – (*S*,*S*,*R*)-**4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.0 Hz, 3 H, 11-H), 2.45 (m, 1 H, 8-H), 3.05 (dd, *J* = 20.0, 8.0 Hz, 1 H, 12-H), 3.12 (dd, *J* = 20.0, 6.4 Hz, 1 H, 12-H), 3.69 (s, 3 H, 7-H), 4.52 (dd, *J* = 8.4, 5.1 Hz, 1 H, 5-H), 4.79 (m, 1 H, 3-H), 4.89 (d, *J* = 17.0 Hz, 1 H, 10-H), 4.98 (d, *J* = 10.4 Hz, 1 H, 10-H), 5.49 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1 H, 9-H), 6.43 (d, *J* = 8.4 Hz, 1 H, NH), 7.18–7.32 (m, 5 H, arom. H), 7.57 (d, *J* = 7.4 Hz, 1 H, TfaNH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.08 (q, C-11), 38.40 (t, C-12), 40.12 (d, C-8), 51.95 (q, C-7), 54.49 (d, C-3), 56.13 (d, C-5), 115.40 (q, *J* = 287.5 Hz, C-1), 116.30 (t, C-10), 127.19, 128.59, 129.15 (d, arom. C), 135.16 (s, C-13), 137.76 (d, C-9), 156.86 (q, *J* = 37.9 Hz, C-2), 168.90, 170.96 (s, C-4, C-6). – (*S*,*R*,*S*)-**4b**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 7.0 Hz, 3 H, 11-H), 2.59 (m, 1 H, 8-H), 3.69 (s, 3 H, 7-H), 5.57–5.63 (m, 1 H, 9-H), 6.30 (d, *J* = 8.3 Hz, 1 H, NH). – $C_{18}H_{21}F_3N_2O_4$ (386.37): calcd. C 55.96, H 5.48, N 7.25; found C 55.68, H 5.39, N 7.13.

Crotyl *N*-Tosyl-(*S*)-phenylalanylglycinate (3c): To a solution of 1.72 g (6.00 mmol) of *N*-tosyl-(*S*)-phenylalanine in THF (20 mL) was added carbonyldiimidazole (1.02 g, 6.30 mmol). The reaction mixture was stirred for 30 min, and then glycine crotyl ester hydrochloride (1.10 g, 6.60 mmol) was added. After stirring for 10 h, the mixture was diluted with diethyl ether and the organic layer was washed with 1 N HCl and satd. aq. $NaHCO_3$ solution. The aqueous washings were extracted twice with diethyl ether. The combined organic layers were then dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 2.07 g (4.56 mmol, 76%) of ester **3c** as a colorless foam. Crystallization from diethyl ether/hexane gave colorless crystals, m.p. 105 °C. – $[\alpha]_D^{20}$ = –43.6 (*c* = 2.9, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (dd, *J* = 6.5, 1.2 Hz, 3 H, 13-H), 2.38 (s, 3 H, 1-H), 2.89 (dd, *J* = 14.1, 7.8 Hz, 1 H, 14-H), 2.97 (dd, *J* = 14.1, 5.8 Hz, 1 H, 14-H), 3.85 (dd, *J* = 18.2 Hz, 4.8 Hz, 1 H, 8-H), 3.87–3.94 (m, 1 H, 6-H), 4.03 (dd, *J* = 18.2, 5.9 Hz, 1 H, 8-H), 4.54 (d, *J* = 6.6 Hz, 2 H, 10-H), 5.16 (d, *J* = 6.9 Hz, 1 H, TosNH), 5.55 (dtd, *J* = 15.3, 6.6, 1.5 Hz, 1 H, 11-H), 5.79 (dq, *J* = 15.3, 6.5 Hz, 1 H, 12-H), 6.89–6.92 (m, 1 H, NH), 6.91 (d, *J* = 7.8 Hz, 2 H, 3-H), 7.08–7.15 (m, 1 H, arom. H), 7.47 (d, *J* = 8.3 Hz, 2 H, 4-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.52 (q, C-13), 21.29 (q, C-1), 38.03 (t, C-14), 41.24 (t, C-8), 57.61 (d, C-6), 65.95 (t, C-10), 124.20 (d, C-11), 126.94 (d, C-3), 128.60, 128.94 (d, arom. C), 129.51 (d, C-4), 132.09 (d, C-12), 135.01 (s, C-15), 135.52 (s, C-2), 143.51 (s, C-5), 168.87, 170.40 (s, C-7, C-9). – $C_{22}H_{26}N_2O_5S$ (430.48): calcd. C 61.38, H 6.08, N 6.51; found C 61.45, H 5.98, N 6.54.

Methyl *N*-Tosyl-(*S*)-phenylalanyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4c]: Ester **4c** was prepared from ester **3c** (87 mg, 0.20 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 60:40) to give 82 mg (0.18 mmol, 92%) of ester **4c** as a colorless foam. Diastereomeric ratio (*S*,*S*,*R*)/(*S*,*R*,*S*): 56:44. Crystallization from ethyl acetate/diethyl ether/hexane gave colorless needles of (*S*,*R*,*S*)-**4c**, m.p. 105–106 °C. – HPLC (hexane/2-propanol, 90:10): t_R(*S*,*S*,*R*): 29.83 min, t_R(*S*,*R*,*S*): 31.44 min. – (*S*,*R*,*S*)-**4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.9 Hz, 3 H, 14-H), 2.36 (s, 3 H, 1-H), 2.55 (m, 1 H, 11-H), 2.84 (dd, *J* = 14.1, 8.0 Hz, 1 H, 15-H), 2.97 (dd, *J* = 14.1, 5.8 Hz, 1 H, 15-H), 3.66 (s, 3 H, 10-H), 3.90 (m, 1 H, 6-H), 4.49 (dd, *J* = 8.7, 5.4 Hz, 1 H, 8-H), 5.01 (d, *J* = 10.8 Hz, 1 H, 13-H), 5.02 (d, *J* = 16.7 Hz, 1 H, 13-H), 5.20 (d, *J* = 6.7 Hz, 1 H, TosNH), 5.59 (ddd, *J* = 17.4, 9.9, 8.0 Hz, 1 H, 12-H), 6.88–6.97 (m, 1 H, NH), 6.89 (d, *J* = 7.8 Hz, 2 H, 3-H), 7.07–7.16 (m, 5 H, arom. H), 7.45 (d, *J* = 8.3 Hz, 2 H, 4-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.40 (q, C-14), 21.27 (q, C-1), 38.12 (t, C-15), 40.57 (d, C-11), 51.81 (q, C-10), 56.07 (d, C-8), 57.77 (d, C-6), 116.22 (t, C-13), 126.90 (d, C-

3), 128.52, 128.62, 128.90 (d, arom. C), 129.49 (d, C-4), 135.06 (s, C-2), 135.55 (s, C-16), 138.00 (d, C-12), 143.43 (s, C-5), 169.84, 170.93 (s, C-7, C-9). – (*S*,*S*,*R*)-**4c**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 7.0 Hz, 3 H, 14-H), 3.65 (s, 3 H, 10-H), 4.43 (dd, *J* = 8.4, 5.3 Hz, 1 H, 8-H), 5.34 (d, *J* = 7.7 Hz, 1 H, TosNH), 6.68 (d, *J* = 8.3 Hz, 1 H, NH), 7.53 (d, *J* = 8.3 Hz, 1 H, 4-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.55 (q, C-14), 38.35 (t, C-15), 40.37 (d, C-11), 51.84 (q, C-10), 56.17 (d, C-8), 57.52 (d, C-6), 115.98 (t, C-13), 126.87 (d, C-3), 129.10 (d, C-4), 135.12 (s, C-2), 136.08 (s, C-16). – Selected signals of the *anti* diastereomers: (*S*,*S*,*S*)-**4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3 H, 14-H). – (*S*,*R*,*R*)-**4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.7 Hz, 3 H, 14-H). – $C_{23}H_{28}N_2O_5S$ (444.50): calcd. C 62.14, H 6.35, N 6.30; found C 61.91, H 6.34, N 6.28.

Crotyl *N*-Benzyloxycarbonyl-(*S*)-valylglycinate (3d): Ester **3d** was prepared according to General Procedure 2 on a 6.0 mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 1.45 g (4.0 mmol, 67%) of ester **3d** as a colorless solid. Crystallization from diethyl ether/hexane gave colorless needles, m.p. 123–124 °C. – $[\alpha]_D^{20}$ = –9.5 (*c* = 1.7, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H, 13-H), 0.99 (d, *J* = 6.8 Hz, 3 H, 13-H), 1.72 (d, *J* = 6.4 Hz, 3 H, 11-H), 2.14 (m, 1 H, 12-H), 3.94 (dd, *J* = 18.0, 4.8 Hz, 1 H, 6-H), 4.08 (dd, *J* = 18.0, 5.3 Hz, 1 H, 6-H), 4.12 (m, 1 H, 4-H), 4.57 (d, *J* = 6.5 Hz, 2 H, 8-H), 5.06 (d, *J* = 12.3 Hz, 1 H, 2-H), 5.12 (d, *J* = 12.2 Hz, 1 H, 2-H), 5.52–5.63 (m, 2 H, 9-H, ZNH), 5.81 (dq, *J* = 15.2, 6.4 Hz, 1 H, 10-H), 6.85 (br. s, 1 H, NH), 7.28–7.34 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.76 (q, C-11, C-13), 19.37 (q, C-13), 31.32 (d, C-12), 41.41 (t, C-6), 60.43 (d, C-4), 66.35 (t, C-8), 67.22 (t, C-2), 124.57 (d, C-9), 128.18, 128.34, 128.71 (d, arom. C), 132.54 (d, C-10), 136.41 (s, C-1), 156.68 (s, C-3), 169.69, 171.91 (s, C-5, C-7). – $C_{19}H_{26}N_2O_5$ (362.42): calcd. C 62.97, H 7.23, N 7.73; found C 62.99, H 7.30, N 7.61.

Methyl *N*-Benzyloxycarbonyl-(*S*)-valyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4d]: Ester **4d** was prepared from ester **3d** (109 mg, 0.30 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 104 mg (0.276 mmol, 92%) of ester **4d** as a colorless foam. Diastereomeric ratio (*S*,*S*)/(*S*,*R*): 60:40. Crystallization from ethyl acetate/diethyl ether gave colorless needles of (*S*,*R*,*S*)-**4d**, m.p. 148–149 °C. – HPLC (hexane/2-propanol, 85:15): t_R(*S*,*S*,*R*): 12.11 min, t_R(*S*,*R*,*S*): 14.41 min. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3 H, 14-H), 0.95 (d, *J* = 6.9 Hz, 3 H, 14-H), 1.02 (d, *J* = 6.9 Hz, 3 H, 12-H), 2.13 (m, 1 H, 13-H), 2.62 (m, 1 H, 9-H), 3.69 (s, 3 H, 8-H), 4.04 (br. s, 1 H, 4-H), 4.61 (dd, *J* = 8.6, 5.0 Hz, 1 H, 6-H), 5.02 (d, *J* = 17.1 Hz, 1 H, 11-H), 5.03 (d, *J* = 10.2 Hz, 1 H, 11-H), 5.08 (s, 2 H, 2-H), 5.31 (br. s, 1 H, ZNH), 5.66 (ddd, *J* = 16.9, 10.6, 7.7 Hz, 1 H, 10-H), 6.40 (d, *J* = 8.6 Hz, 1 H, NH), 7.30–7.34 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.46 (q, C-12), 17.41, 19.25 (q, C-14), 31.01 (d, C-13), 40.66 (d, C-9), 52.12 (q, C-8), 55.85 (d, C-6), 60.31 (d, C-4), 67.08 (t, C-2), 116.39 (t, C-11), 128.06, 128.17, 128.52 (d, arom. C), 136.21 (s, C-1), 138.39 (d, C-10), 156.28 (s, C-3), 170.80, 171.36 (s, C-5, C-7). – $C_{20}H_{28}N_2O_5$ (376.45): calcd. C 63.81, H 7.50, N 7.44; found C 63.82, H 7.52, N 7.35.

Crotyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-valylglycinate (3e): Ester **3e** was prepared according to General Procedure 2 on a 27.6 mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 68:32) to give 7.90 g (24.0 mmol, 87%) of ester **3e** as a colorless solid, m.p. 63 °C. – $[\alpha]_D^{20}$ = –11.2 (*c* = 0.2, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 3 H, 13-H), 0.94 (d, *J* = 6.7 Hz, 3 H, 13-H), 1.39 (s, 9 H, 1-H), 1.68 (d, *J* = 6.5 Hz, 3 H, 11-H), 2.11 (m, 1 H, 12-H), 3.97–4.07 (m, 3 H, 4-H, 6-H), 4.52 (dd, *J* = 6.6, 0.7 Hz, 2 H, 8-H), 5.13 (br. s, 1 H, BocNH), 5.53 (dtq, *J* = 15.3, 6.6, 1.5 Hz, 1 H, 9-H), 5.76 (dq, *J* = 15.2, 6.5 Hz, 1 H, 10-H), 6.72 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.47, 18.97 (q, C-11, C-13), 28.06 (q, C-1), 30.66 (d, C-12), 40.98 (t, C-6), 59.55 (d, C-4), 65.87 (t, C-8), 79.68 (s, C-2), 124.21 (d, C-9), 132.02 (d, C-10), 155.62 (s, C-3), 169.23, 171.70 (s, C-5, C-7). – $C_{16}H_{28}N_2O_5$ (328.41): calcd. C 58.51, H 8.60, N 8.53; found C 58.60, H 8.61, N 8.56.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-valyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4e]: Ester **4e** was prepared from ester **3e** (100 mg, 0.30 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 97 mg (0.28 mmol, 95%) of ester **4e** as a colorless foam. Diastereomeric ratio (*S*,*S*,*R*)/(*S*,*R*,*S*): 37:63. Crystallization from diethyl ether/hexane gave (*S*,*R*,*S*)-**4e** as a colorless solid, m.p. 121 °C. – HPLC (hexane/2-propanol, 95:5): t_R(*S*,*S*,*R*): 8.62 min, t_R(*S*,*R*,*S*): 11.17 min. – (*S*,*R*,*S*)-**4e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.9 Hz, 3 H, 14-H), 0.92 (d, *J* = 6.8 Hz, 3 H, 14-H), 1.02 (d, *J* = 6.9 Hz, 3 H, 12-H), 1.40 (s, 9 H, 1-H), 2.13 (m, 1 H, 13-H), 2.62 (m, 1 H, 9-H), 3.68 (s, 3 H, 8-H), 3.96 (br. s, 1 H, 4-H), 4.59 (dd, *J* = 8.7, 5.2 Hz, 1 H, 6-H), 4.99–5.04 (br. s, 1 H, BocNH), 5.02 (d, *J* = 15.3 Hz, 1 H, 11-H), 5.03 (d, *J* = 11.8 Hz, 1 H, 11-H), 5.66 (ddd, *J* = 15.3, 11.6, 7.6 Hz, 1 H, 10-H), 6.58 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.46 (q, C-12), 17.34, 19.30 (q, C-14), 28.25 (q, C-1), 30.63 (d, C-13), 40.67 (d, C-9), 52.04 (q, C-8), 55.83 (d, C-6), 60.33 (d, C-4), 80.01 (s, C-2), 116.31 (t, C-11), 138.43 (d, C-10), 155.72 (s, C-3), 171.25, 171.46 (s, C-5, C-7). – (*S*,*S*,*R*)-**4e**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.8 Hz, 3 H, 14-H), 3.71 (s, 3 H, 8-H), 3.88 (m, 1 H, 4-H), 6.35 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.55 (q, C-12), 19.15 (q, C-14), 40.61 (d, C-9), 55.94 (d, C-6). – $C_{17}H_{30}N_2O_5$ (342.44): calcd. C 59.63, H 8.83, N 8.18; found C 59.56, H 8.78, N 8.12.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-valyl-(*R*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*R*,*S*)-4e]: For analytical purposes, ester **4e** was also prepared from methyl *N*-trifluoroacetyl-(*R*)-*allo*-γ,δ-didehydroisoleucinate (**6**) as described for ester **4a**. – HPLC (hexane/2-propanol, 95:5): t_R(*S*,*R*,*S*): 11.11 min.

Crotyl *N*-Tosyl-(*S*)-isoleucylglycinate (3f): Ester **3f** was prepared on a 6.0 mmol scale as described for **3c**. Flash column chromatography gave 1.90 g (4.8 mmol, 80%) of a colorless oil. Crystallization from DCM/diethyl ether/hexane gave a colorless solid, m.p. 149–150 °C. – $[\alpha]_D^{20}$ = –5.3 (*c* = 0.8, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.9 Hz, 3 H, 17-H), 0.80 (t, *J* = 7.3 Hz, 3 H, 16-H), 1.05 (ddq, *J* = 13.4, 9.6, 7.3 Hz, 1 H, 15-H), 1.48 (dqd, *J* = 13.4, 7.4, 6.0 Hz, 1 H, 15-H), 1.70 (dd, *J* = 6.3, 1.3 Hz, 3 H, 13-H), 1.70–1.75 (m, 1 H, 14-H), 2.38 (s, 3 H, 1-H), 3.55 (dd, *J* = 8.2 Hz, 5.6 Hz, 1 H, 6-H), 3.76 (dd, *J* = 18.3, 5.2 Hz, 1 H, 8-H), 3.84 (dd, *J* = 18.3, 5.0 Hz, 1 H, 8-H), 4.53 (dd, *J* = 6.6, 1.0 Hz, 2 H, 10-H), 5.28 (d, *J* = 8.3 Hz, 1 H, TosNH), 5.56 (dtd, *J* = 15.2, 6.6, 1.3 Hz, 1 H, 11-H), 5.78 (dq, *J* = 15.3, 6.3 Hz, 1 H, 12-H), 6.42 (br. s, 1 H, NH), 7.25 (d, *J* = 8.1 Hz, 2 H, 3-H), 7.70 (d, *J* = 8.3 Hz, 2 H, 4-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.06 (q, C-16), 15.05 (q, C-17), 17.51 (q, C-13), 21.26 (q, C-1), 24.13 (t, C-15), 37.69 (d, C-14), 41.08 (t, C-8), 61.27 (d, C-6), 66.03 (t, C-10), 124.08 (d, C-11), 127.20 (d, C-3), 129.38 (d, C-4), 132.28 (d, C-12), 136.31 (s, C-2), 143.47 (s, C-5), 168.90, 170.28 (s, C-7, C-9). –

$C_{19}H_{28}N_2O_5S$ (396.51): calcd. C 57.56, H 7.12, N 7.06; found C 57.67, H 7.09, N 6.95.

Methyl *N*-Tosyl-(*S*)-isoleucyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4f]: Ester **4f** was prepared from ester **3f** (80 mg, 0.20 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 60:40) to give 68 mg (0.17 mmol, 83%) of ester **4f** as a colorless foam. Diastereomeric ratio (*S*,*S*,*R*)/(*S*,*R*,*S*): 35:65. – Crystallization from ethyl acetate/diethyl ether/hexane gave (*S*,*R*,*S*)-**4f** as colorless needles, m.p. 138–139 °C. – HPLC (hexane/2-propanol, 85:15): t_R(*S*,*S*,*R*): 12.12 min, t_R(*S*,*R*,*S*): 14.54 min. – (*S*,*R*,*S*)-**4f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 6.8 Hz, 3 H, 17-H), 0.78 (d, *J* = 7.3 Hz, 3 H, 18-H), 0.98 (d, *J* = 6.9 Hz, 3 H, 14-H), 0.97–1.06 (m, 1 H, 16-H), 1.38 (m, 1 H, 16-H), 1.74–1.82 (m, 1 H, 15-H), 2.36 (s, 3 H, 1-H), 2.56 (m, 1 H, 11-H), 3.59 (dd, *J* = 8.0, 4.9 Hz, 1 H, 6-H), 3.68 (s, 3 H, 10-H), 4.38 (dd, *J* = 8.5, 5.0 Hz, 1 H, 8-H), 5.02 (d, *J* = 11.7 Hz, 1 H, 13-H), 5.02 (d, *J* = 15.3 Hz, 1 H, 13-H), 5.33 (d, *J* = 8.1 Hz, 1 H, TosNH), 5.61 (ddd, *J* = 15.3, 11.7, 7.7 Hz, 1 H, 12-H), 6.55 (d, *J* = 8.4 Hz, 1 H, NH), 7.21 (d, *J* = 8.1 Hz, 2 H, 3-H), 7.67 (d, *J* = 8.2 Hz, 2 H, 4-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.15 (q, C-17), 15.21 (q, C-18), 15.25 (q, C-14), 21.25 (q, C-1), 24.12 (t, C-16), 37.84 (d, C-15), 40.58 (d, C-11), 51.82 (q, C-10), 55.84 (d, C-8), 61.38 (d, C-6), 116.13 (t, C-13), 127.13 (d, C-3), 129.36 (d, C-4), 136.27 (s, C-2), 138.01 (d, C-12), 143.36 (s, C-5), 169.73, 170.90 (s, C-7, C-9). – (*S*,*S*,*R*)-**4f**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 7.0 Hz, 3 H, 14-H), 3.54 (m, 1 H, 6-H), 3.71 (s, 3 H, 10-H), 4.35 (dd, *J* = 8.4, 5.0 Hz, 1 H, 8-H), 4.94 (d, *J* = 17.0 Hz, 1 H, 13-H), 4.98 (d, *J* = 10.9 Hz, 1 H, 13-H), 5.61 (ddd, *J* = 16.6, 10.6, 7.7 Hz, 1 H, 12-H), 6.13 (d, *J* = 8.4 Hz, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.10 (q, C-17), 23.85 (t, C-16), 38.19 (d, C-15), 40.34 (d, C-11), 51.87 (q, C-10), 56.03 (d, C-8), 60.99 (d, C-6), 115.98 (t, C-13), 129.35 (d, C-4), 136.70 (s, C-2), 137.93 (d, C-12), 143.28 (s, C-5), 169.93, 170.83 (s, C-7, C-9). – $C_{20}H_{30}N_2O_5S$ (410.53): calcd. C 58.51, H 7.37, N 6.82; found C 58.47, H 7.42, N 6.78.

Crotyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-methionylglycinate (3g): Ester **3g** was prepared according to General Procedure 2 on a 16.3 mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 4.54 g (13.9 mmol, 77%) of ester **3g** as a colorless oil. – $[\alpha]_D^{20}$ = –6.6 (*c* = 2.0, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, 1-H), 1.69 (dd, *J* = 6.4, 1.5 Hz, 3 H, 11-H), 1.90 (m, 1 H, 12-H), 2.00–2.13 (m, 1 H, 12-H), 2.07 (s, 3 H, 14-H), 2.56 (br. s, 2 H, 13-H), 3.95 (dd, *J* = 18.2, 5.3 Hz, 1 H, 6-H), 4.05 (dd, *J* = 18.2, 5.6 Hz, 1 H, 6-H), 4.30 (br. s, 1 H, 4-H), 4.53 (d, *J* = 6.6 Hz, 2 H, 8-H), 5.29 (d, *J* = 8.1 Hz, 1 H, BocNH), 5.53 (dtq, *J* = 15.3, 6.6, 1.5 Hz, 1 H, 9-H), 5.77 (dq, *J* = 15.3, 6.4 Hz, 1 H, 10-H), 6.81 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.18 (q, C-14), 17.70 (q, C-11), 28.26 (q, C-1), 30.05 (t, C-13), 31.65 (t, C-12), 41.25 (t, C-6), 53.27 (d, C-4), 66.13 (t, C-8), 80.19 (s, C-2), 124.35 (d, C-9), 132.31 (d, C-10), 155.54 (s, C-3), 169.31, 171.81 (s, C-5, C-7). – $C_{16}H_{28}N_2O_5S$ (360.47): calcd. C 53.31, H 7.83, N 7.77, S 8.90; found C 53.32, H 7.80, N 7.65, S 8.99.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-methionyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4g]: Ester **4g** was prepared from ester **3g** (72 mg, 0.20 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 60:40) to give 67 mg (0.18 mmol, 89%) of ester **4g** as a colorless foam. Diastereomeric ratio (*S*,*S*,*R*)/(*S*,*R*,*S*): 33:67. Crystallization from diethyl ether/hexane gave (*S*,*R*,*S*)-**4g** as a colorless solid, m.p. 74 °C. – HPLC (hexane/2-propanol, 85:15): t_R(*S*,*S*,*R*): 12.84 min, t_R(*S*,*R*,*S*): 14.35 min. – (*S*,*R*,*S*)-**4g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.0 Hz, 3 H, 12-H), 1.40 (s, 9 H, 1-H), 1.88 (m, 1 H, 13-H), 2.00–2.09 (m, 1 H, 13-H), 2.06 (s, 3 H, 15-H), 2.51 (br. s, 2 H, 14-H), 2.64 (m, 1 H, 9-H), 3.68 (s, 3 H, 8-H), 4.25 (br. s, 1 H, 4-H), 4.57 (dd, *J* = 8.6, 5.1 Hz, 1 H, 6-H), 5.04 (d, *J* = 17.2 Hz, 1 H, 11-H), 5.04 (d, *J* = 10.0 Hz, 1 H, 11-H), 5.22 (d, *J* = 8.0 Hz, 1 H, BocNH), 5.67 (ddd, *J* = 17.4, 10.0, 7.5 Hz, 1 H, 10-H), 6.74 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.02 (q, C-12), 15.16 (q, C-15), 28.05 (q, C-1), 29.91 (t, C-14), 31.28 (t, C-13), 40.22 (d, C-9), 51.86 (q, C-8), 53.33 (d, C-4), 55.72 (d, C-6), 79.99 (s, C-2), 116.11 (t, C-11), 138.20 (d, C-10), 155.28 (s, C-3), 171.05, 171.14 (s, C-5, C-7). – (*S*,*S*,*R*)-**4g**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.8 Hz, 3 H, 12-H), 2.78 (m, 1 H, 9-H), 3.69 (s, 3 H, 8-H), 5.02–5.09 (m, 2 H, 11-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.68 (d, C-9), 51.97 (q, C-8), 55.97 (d, C-6), 116.82 (t, C-11), 137.36 (d, C-10). – $C_{17}H_{30}N_2O_5S$ (374.50): calcd. C 54.52, H 8.08, N 7.48, S 8.56; found C 54.49, H 8.18, N 7.44, S 8.58.

Crotyl $N^{\alpha}N^{\varepsilon}$-Bis(*tert*-butyloxycarbonyl)-(*S*)-lysylglycinate (3h): Ester **3h** was prepared according to General Procedure 2 on a 10.0 mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 1. 70:30, 2. 60:40) to give 3.81 g (8.3 mmol, 83%) of ester **3h** as a colorless oil. – $[\alpha]_D^{20}$ = –11.0 (*c* = 2.0, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35–1.45 (m, 4 H, 13-H, 14-H), 1.39 (s, 18 H, 1-H, 18-H), 1.60–1.64 (m, 1 H, 12-H), 1.68 (dd, *J* = 6.3, 1.3 Hz, 3 H, 11-H), 1.75–1.82 (m, 1 H, 12-H), 3.06 (br. s, 2 H, 15-H), 3.97 (dd, *J* = 18.2, 5.1 Hz, 1 H, 6-H), 4.03 (dd, *J* = 18.2, 5.3 Hz, 1 H, 6-H), 4.09 (m, 1 H, 4-H), 4.53 (d, *J* = 6.6 Hz, 2 H, 8-H), 4.68 (br. s, 1 H, BocN$^{\varepsilon}$H), 5.20 (br. s, 1 H, BocN$^{\alpha}$H), 5.53 (dtq, *J* = 15.3, 6.6, 1.5 Hz, 1 H, 9-H), 5.76 (dq, *J* = 15.2, 6.5 Hz, 1 H, 10-H), 6.78 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.50 (q, C-11), 22.26 (t, C-13), 28.08, 28.20 (q, C-1, C-18), 29.41 (t, C-14), 31.80 (t, C-12), 39.72 (t, C-15), 41.02 (t, C-6), 54.05 (d, C-4), 65.90 (t, C-8), 78.87 (s, C-17), 79.87 (s, C-2), 124.20 (d, C-9), 132.04 (d, C-10), 155.51, 155.93 (s, C-3, C-16), 169.25, 172.17 (s, C-5, C-7). – $C_{22}H_{39}N_3O_7$ (457.56): calcd. C 57.75, H 8.59, N 9.18; found C 57.94, H 8.71, N 8.85. – HRMS (FAB): $C_{22}H_{39}N_3NaO_7$ [M^+ + Na]: calcd. 480.2672; found 480.2662. – MS (FAB): *m*/*z* (%) = 480 (100), 459 (12), 458 (46), 402 (12), 346 (23), 121 (50).

Methyl N^{α},N^{ε}-Bis(*tert*-butyloxycarbonyl)-(*S*)-lysyl-(*RS*)-*allo*-γ,δ-didehydroisoleucinate [(*S*,*RS*)-4h]: Ester **4h** was prepared from ester **3h** (220 mg, 0.48 mmol) according to a modification of the general procedure for rearrangements, employing LHMDS (2.5 mmol) as a base. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 65:35) to give 182 mg (0.37 mmol, 77%) of ester **4h** as a colorless oil. Diastereomeric ratio (*S*,*S*,*R*)/(*S*,*R*,*S*): 42:58. – HPLC (hexane/2-propanol, 85:15): t_R(*S*,*S*,*R*): 9.93 min, t_R(*S*,*R*,*S*): 10.86 min. – (*S*,*R*,*S*)-**4g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.0 Hz, 3 H, 12-H), 1.32–1.46 (m, 4 H, 14-H, 15-H), 1.40 (s, 18 H, 1-H, 19-H), 1.57–1.61 (m, 1 H, 13-H), 1.77–1.81 (m, 1 H, 13-H), 2.62 (m, 1 H, 9-H), 3.06 (m, 2 H, 16-H), 3.68 (s, 3 H, 8-H), 4.05 (br. s, 1 H, 4-H), 4.56 (dd, *J* = 8.7, 5.3 Hz, 1 H, 6-H), 4.62 (br. s, 1 H, BocN$^{\varepsilon}$H), 5.03 (d, *J* = 17.0 Hz, 1 H, 11-H), 5.08 (d, *J* = 9.1 Hz, 1 H, 11-H), 5.20 (br. s, 1 H, BocN$^{\alpha}$H), 5.66 (ddd, *J* = 17.5, 9.8, 7.6 Hz, 1 H, 10-H), 6.69 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.20 (q, C-12), 22.28 (t, C-14), 28.07, 28.20 (q, C-1, C-19), 29.49 (t, C-15), 31.50 (t, C-13), 39.67 (t, C-16), 40.35 (d, C-9), 51.84 (t, C-8), 54.27 (d, C-4), 55.73 (d, C-6), 78.89 (s, C-18), 79.88 (s, C-2), 116.05 (t, C-11), 138.25 (d, C-10), 155.48, 155.93 (s, C-3, C-17), 171.30, 171.61 (s, C-5, C-7). –

(*S*,*S*,*R*)-**4h**: selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7.0 Hz, 3 H, 12-H), 2.66 (m, 1 H, 9-H), 3.69 (s, 3 H, 8-H), 6.58 (br. s, 1 H, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.80 (q, C-12), 51.97 (t, C-8), 55.82 (d, C-6), 116.73 (t, C-11), 137.43 (d, C-10), 171.46, 171.89 (s, C-5, C-7). – $C_{23}H_{41}N_3O_7$ (471.59): calcd. C 58.58, H 8.76, N 8.91; found C 58.46, H 8.73, N 8.88.

Crotyl *N*-(*tert*-Butyloxycarbonyl)-(*R*,*S*)-β-phenylalanylglycinate (3i): Ester **3i** was prepared according to General Procedure 2 on a 3.0 mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 1.04 g (2.76 mmol, 92%) of ester **3i** as a colorless solid. Crystallization from diethyl ether/hexane gave colorless crystals, m.p. 107–109 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 1-H), 1.69 (dd, *J* = 6.4, 1.5 Hz, 3 H, 12-H), 2.71 (br. s, 2 H, 5-H), 3.83 (dd, *J* = 18.3, 5.0 Hz, 1 H, 7-H), 3.94 (dd, *J* = 18.3, 5.3 Hz, 1 H, 7-H), 4.51 (d, *J* = 6.6 Hz, 2 H, 9-H), 5.00 (br. s, 1 H, BocNH), 5.51 (dtq, *J* = 15.3, 6.6, 1.5 Hz, 1 H, 10-H), 5.76 (dq, *J* = 15.3, 6.4 Hz, 1 H, 11-H), 6.02 (br. s, 1 H, 4-H), 6.25 (br. s, 1 H, NH), 7.18–7.31 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.52 (q, C-12), 28.10 (q, C-1), 41.07 (t, C-7), 42.21 (t, C-5), 51.98 (d, C-4), 65.95 (t, C-9), 79.39 (s, C-2), 124.14 (d, C-10), 125.82, 127.13, 128.37 (d, arom. C), 132.14 (d, C-11), 141.73 (s, C-13), 155.16 (s, C-3), 169.27, 170.24 (s, C-6, C-8). – $C_{20}H_{28}N_2O_5$ (376.45): calcd. C 63.81, H 7.50, N 7.44; found C 64.03, H 7.52, N 7.58.

Methyl *N*-(*tert*-Butyloxycarbonyl)-(*R*,*S*)-β-phenylalanyl-*allo*-γ,δ-didehydroisoleucinate (4i): Ester **4i** was prepared from ester **3i** (57 mg, 0.15 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 65:35) to give 56 mg (0.14 mmol, 96%) of ester **4h** as a colorless foam. Diastereomeric ratio *like*/*unlike* 55:45. Crystallization from diethyl ether/hexane gave colorless crystals, m.p. 130–132 °C (mixture of stereoisomers). – *like*-**4i:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 7.0 Hz, 3 H, 13-H), 1.41 (s, 9 H, 1-H), 2.54 (m, 1 H, 10-H), 2.73 (d, *J* = 5.6 Hz, 2 H, 5-H), 3.68 (s, 3 H, 9-H), 4.53 (dd, *J* = 8.5, 5.2 Hz, 1 H, 7-H), 4.92–5.03 (m, 2 H, 12-H, BocNH), 5.02 (d, *J* = 10.0 Hz, 1 H, 12-H), 5.57 (ddd, *J* = 17.7, 10.0, 7.7 Hz, 1 H, 11-H), 5.84 (m, 1 H, 4-H), 6.03 (br. s, 1 H, NH), 7.21–7.35 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.56 (q, C-13), 28.32 (q, C-1), 40.63 (t, C-10), 42.53 (t, C-5), 51.42 (d, C-4), 52.06 (q, C-9), 55.91 (d, C-7), 79.14 (s, C-2), 116.20 (t, C-12), 125.97, 127.26, 128.54 (d, arom. C), 138.16 (d, C-11), 141.32 (s, C-14), 155.19 (s, C-3), 171.37, 171.53 (s, C-6, C-8). – *unlike*-**4i:** selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.0 Hz, 3 H, 13-H), 1.63 (s, 9 H, 1-H), 2.42 (m, 1 H, 10-H), 3.70 (s, 3 H, 9-H), 4.83 (d, *J* = 16.9 Hz, 1 H, 12-H). – $C_{21}H_{30}N_2O_5$ (390.48): calcd. C 64.60, H 7.74, N 7.17; found C 64.51, H 7.72, N 7.10.

(*R*)-1-(Benzyloxymethyl)allyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-alanylglycinate (7): The requisite allylic alcohol was obtained according to a literature procedure.[25] Ester **7** was prepared according to General Procedure 1 on a 6.1 mmol scale. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 1. 70:30, 2. 60:40) to give 1.77 g (5.2 mmol, 86%) of ester **7g** as a colorless oil. – $[\alpha]_D^{20}$ = –18.2 (*c* = 2.1, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.9 Hz, 3 H, 14-H), 1.40 (s, 9 H, 1-H), 3.51 (d, *J* = 5.6 Hz, 2 H, 11-H), 4.02 (d, *J* = 5.4 Hz, 2 H, 6-H), 4.21 (br. s, 1 H, 4-H), 4.48 (d, *J* = 12.2 Hz, 1 H, 12-H), 4.53 (d, *J* = 12.2 Hz, 1 H, 12-H), 5.18 (br. s, 1 H, BocNH), 5.21 (dd, *J* = 10.5, 0.6 Hz, 1 H, 10-H), 5.29 (d, *J* = 17.3 Hz, 1 H, 10-H), 5.48 (m, 1 H, 8-H), 5.77 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1 H, 9-H), 6.85 (br. s, 1 H, NH), 7.22–7.33 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.19 (q, C-14), 28.09 (q, C-1), 41.13 (t, C-6), 49.75 (d, C-4), 70.85 (t, C-11), 72.99 (t, C-12), 74.24 (d, C-8), 79.88 (s, C-2), 118.41 (t, C-10), 127.41, 127.54, 128.19 (d, arom. C), 132.39 (d, C-9), 137.51 (s, C-13), 155.25 (s, C-3), 168.78, 172.79 (s, C-5, C-7). – $C_{21}H_{30}N_2O_6$ (406.48): calcd. C 62.05, H 7.44, N 6.89; found C 61.61, H 7.46, N 6.81.

Methyl (*S*)-2-[*N*-(*tert*-Butyloxycarbonyl)-(*S*)-alanyl]amino-6-benzyloxyhex-(4*E*)-enoate (8): Ester **8** was prepared from ester **7** (488 mg, 1.20 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 65:35) to give 461 mg (1.10 mmol, 92%) of ester **8** as a colorless foam. Diastereomeric ratio (*S*,*S*)/(*S*,*R*): >95:5. – HPLC (hexane/2-propanol, 70:30): t_R(*S*,*S*): 17.85 min, t_R(*S*,*R*): 19.47 min. – (*S*,*S*)-**8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 7.0 Hz, 3 H, 15-H), 1.40 (s, 9 H, 1-H), 2.45 (m, 1 H, 9-H), 2.58 (m, 1 H, 9-H), 3.69 (s, 3 H, 8-H), 3.92 (d, *J* = 5.5 Hz, 2 H, 12-H), 4.14 (br. s, 1 H, 4-H), 4.45 (s, 2 H, 13-H), 4.61 (m, 1 H, 6-H), 5.08 (br. s, 1 H, BocNH), 5.52–5.69 (m, 2 H, 10-H, 11-H), 6.72 (d, *J* = 7.3 Hz, 1 H, NH), 7.21–7.33 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.86 (q, C-15), 28.06 (q, C-1), 34.91 (t, C-9), 49.85 (d, C-4), 51.52 (d, C-6), 52.13 (q, C-8), 69.96 (t, C-12), 71.86 (t, C-13), 79.89 (s, C-2), 127.06, 127.79 (d, C-10, C-11), 127.79, 128.14, 128.24, 130.93 (d, arom. C), 137.94 (s, C-14), 155.22 (s, C-3), 171.61, 172.15 (s, C-5, C-7). – HRMS (FAB): $C_{22}H_{33}N_2O_6$ [M^+ + H]: calcd. 421.2328; found 421.2326; $C_{22}H_{32}N_2O_6Na$ [M^+ + Na]: calcd. 443.2147; found 443.2127. – MS (FAB): *m*/*z* (%) = 443 (63), 421 (77), 329 (26), 321 (100), 308 (23), 307 (97), 289 (48), 257 (40), 217 (39), 213 (40).

(*S*)-1-Phenylallyl Alcohol: (*S*)-1-Phenylallyl alcohol was obtained from the racemic alcohol (11.5 g, 86 mmol) by means of enzymatic kinetic resolution (16 mL vinyl acetate, 1 g Novozym 435). The alcohol was isolated by flash column chromatography and was used directly without further purification. Yield: 3.5 g (26 mmol, 30%), 99.8% *ee*. The enantiomeric excess was determined by GC (column: β-cyclodextrin, 105 °C isotherm): t_R(*R*): 32.04 min, t_R(*S*): 32.67 min. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (br. s, 1 H, OH), 5.17 (ddd, *J* = 10.2, 1.3, 1.3 Hz, 1 H, 3-H), 5.33 (ddd, *J* = 17.0, 1.3, 1.3 Hz, 1 H, 3-H), 6.03 (ddd, *J* = 16.5, 10.1, 6.1 Hz, 1 H, 2-H), 7.24–7.37 (m, 6 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.11 (d, C-1), 114.91 (t, C-3), 126.16, 127.53, 128.35 (d, arom. C), 140.04 (d, C-2), 142.40 (s, C-4).

(*S*)-1-Phenylallyl *N*-Benzyloxycarbonyl-(*S*)-alanylglycinate (9): Ester **9** was prepared from (*S*)-1-phenylallyl alcohol (400 mg, 3.00 mmol) according to General Procedure 1. For analytical purposes, the (*S*,*RS*) derivative was also prepared. The crude product was purified by flash column chromatography (hexane/ethyl acetate: 1. 70:30, 2. 60:40) to give 590 mg (1.50 mmol, 50%) of ester **9** as a colorless solid, m.p. 95–98 °C. – $[\alpha]_D^{20}$ = –45.7 (*c* = 1.3, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.1 Hz, 3 H, 12-H), 4.01 (dd, *J* = 13.8, 5.2 Hz, 1 H, 6-H), 4.05 (dd, *J* = 13.8, 5.2 Hz, 1 H, 6-H), 4.27 (m, 1 H, 4-H), 5.04 (d, *J* = 12.2 Hz, 1 H, 2-H), 5.10 (d, *J* = 12.2 Hz, 1 H, 2-H), 5.25 (dd, *J* = 10.5, 1.2 Hz, 1 H, 10-H), 5.28 (dd, *J* = 17.1, 1.1 Hz, 1 H, 10-H), 5.36 (br. s, 1 H, ZNH), 5.97 (ddd, *J* = 16.9, 10.4, 5.9 Hz, 1 H, 9-H), 6.27 (d, *J* = 5.9 Hz, 1 H, 8-H), 6.62 (br. s, 1 H, NH), 7.29–7.34 (m, 10 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.24 (q, C-12), 41.25 (t, C-6), 50.24 (d, C-4), 66.89 (t, C-2), 77.34 (d, C-8), 117.41 (t, C-10), 126.91, 127.86, 127.99, 128.25, 128.31, 128.43 (d, arom. C), 135.33 (d, C-9), 135.90 (s, C-1), 137.90 (s, C-11), 155.95 (s, C-3), 168.49, 172.20 (s, C-5, C-7). – $C_{22}H_{24}N_2O_5$ (396.44): calcd. C 66.65, H 6.10, N 7.07; found C 66.87, H 6.24, N 6.75.

Methyl (*R*)-2-[*N*-Benzyloxycarbonyl-(*S*)-alanyl]amino-5-phenylpent-(4*E*)-enoate (10): Ester **10** was prepared from ester **9** (80 mg, 0.20 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 65:35) to give 45 mg (0.11 mmol, 57%) of ester **10** as a colorless solid, m.p. 111–113 °C. Diastereomeric ratio (*S*,*S*)/(*S*,*R*) 1:99. – HPLC (hexane/2-propanol, 85:15): t_R(*S*,*S*): 19.54 min, t_R(*S*,*R*): 24.89 min. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 7.0 Hz, 3 H, 13-H), 2.62 (m, 1 H, 9-H), 2.71 (m, 1 H, 3-H), 3.71 (s, 3 H, 8-H), 4.29 (m, 1 H, 4-H), 4.71 (td, *J* = 7.0, 6.2 Hz, 1 H, 6-H), 4.95 (d, *J* = 12.2 Hz, 1 H, 2-H), 5.05 (d, *J* = 12.0 Hz, 1 H, 2-H), 5.48 (d, *J* = 6.9 Hz, 1 H, ZNH), 6.01 (dd, *J* = 15.5, 7.7 Hz, 1 H, 10-H), 6.41 (d, *J* = 15.6 Hz, 1 H, 11-H), 6.82 (br. s, 1 H, NH), 7.19–7.34 (m, 10 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.69 (q, C-13), 35.61 (t, C-9), 50.42 (d, C-4), 51.77 (d, C-6), 52.43 (q, C-8), 66.90 (t, C-2), 123.25 (d, C-10), 126.18, 127.46, 127.52, 127.95, 128.03, 128.08, 128.42, 128.47 (d, arom. C), 134.20 (d, C-11), 136.09 (s, C-1), 136.69 (s, C-12), 155.86 (s, C-3), 171.89, 172.02 (s, C-5, C-7). – $C_{23}H_{26}N_2O_5$ (410.47): calcd. C 67.30, H 6.38, N 6.83; found C 66.94, H 6.55, N 6.63. HRMS (FAB): $C_{23}H_{26}N_2O_5$ [M^+ + H]: calcd. 411.1911; found 411.1921. $C_{23}H_{26}N_2NaO_5$ [M^+ + Na]: calcd. 433.1730; found 433.1768. – MS (FAB): *m*/*z* (%) = 434 (27), 433 (100), 412 (24), 411 (87), 410 (15), 367 (13).

(*S*)-1-Phenyl-1-penten-3-ol: (*S*)-1-Phenyl-1-penten-3-ol was obtained from the racemic alcohol (1.35 g, 8.32 mmol) by means of enzymatic kinetic resolution as described above. Yield: 503 mg (3.08 mmol, 37%), 99.9% *ee*. The enantiomeric excess was determined by GC (column: β-cyclodextrin, 120 °C isotherm): t_R(*S*): 46.55 min. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3 H, 6-H), 1.65 (m, 2 H, 5-H), 1.72 (s, 1 H, OH), 4.19 (dt, *J* = 6.4, 5.9 Hz, 1 H, 4-H), 6.11 (dd, *J* = 16.0, 6.7 Hz, 1 H, 3-H), 6.56 (d, *J* = 15.9 Hz, 1 H, 2-H), 7.19–7.43 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.51 (q, C-6), 30.02 (t, C-5), 74.17 (d, C-4), 126.24, 127.39, 128.35 (d, arom. C), 130.20, 132.09 (d, C-2, C-3), 136.56 (s, C-1).

(*S*)-1-Phenyl-1-penten-3-yl *N*-Benzyloxycarbonyl-(*S*)-alaninylglycinate (11): Ester **11** was prepared from (*S*)-1-phenyl-1-penten-3-ol (500 mg, 3.08 mmol) according to General Procedure 1. For analytical purposes, the (*S*,*RS*) derivative was also prepared. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 60:40) to give 0.80 g (1.89 mmol, 61%) of ester **11** as a colorless solid. Crystallization from diethyl ether/hexane gave colorless needles, m.p. 113–114 °C. – $[\alpha]_D^{20}$ = –87.7 (*c* = 0.9, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.37 (d, *J* = 7.0 Hz, 3 H, 14-H), 1.74 (m, 2 H, 12-H), 4.00–4.06 (m, 2 H, 6-H), 4.29 (m, 1 H, 4-H), 5.05 (d, *J* = 12.2 Hz, 1 H, 2-H), 5.11 (d, *J* = 12.2 Hz, 1 H, 2-H), 5.39 (br. s, 1 H, ZNH), 6.07 (dd, *J* = 15.9, 7.5 Hz, 1 H, 9-H), 6.59 (d, *J* = 15.9 Hz, 1 H, 10-H), 6.66 (br. s, 1 H, NH), 7.20–7.37 (m, 10 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.31 (q, C-13), 18.31 (q, C-14), 27.34 (t, C-12), 41.28 (t, C-6), 50.24 (d, C-4), 66.89 (d, C-2), 77.56 (d, C-2), 126.36, 126.41, 127.88, 127.90, 128.00, 128.33, 128.39, 133.20 (d, C-9, C-10, arom. C), 155.76 (s, C-3), 168.88, 172.18 (s, C-5, C-7). – $C_{24}H_{28}N_2O_5$ (424.49): calcd. C 67.91, H 6.65, N 6.60; found C 67.77, H 6.65, N 6.63.

Methyl *syn*-(*R*)-2-[*N*-Benzyloxycarbonyl-(*S*)-alanyl]amino-3-phenylhept-(4*E*)-enoate (12): Ester **12** was prepared from ester **11** (318 mg, 0.75 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 60:40) to give 256 mg (0.58 mmol, 78%) of ester **12** as a colorless foam. Diastereomeric ratio (*S*,*S*)/(*S*,*R*): >98:2. – HPLC (hexane/2-propanol, 95:5): t_R(*S*,*S*): 24.71 min, t_R(*S*,*R*): 31.74 min. – $[\alpha]_D^{20}$ = 23.4 (*c* = 1.1, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H, 13-H), 1.21 (d, *J* = 6.8 Hz, 3 H, 15-H), 1.99 (m, 2 H, 12-H), 3.63 (s, 3 H, 8-H), 3.68 (m, 1 H, 9-H), 4.12 (m, 1 H, 4-H), 4.86 (dd, *J* = 8.5, 7.9 Hz, 1 H, 6-H), 5.00 (d, *J* = 8.4 Hz, 1 H, 2-H), 5.07 (d, *J* = 8.4 Hz, 1 H, 2-H), 5.11 (d, *J* = 10.4 Hz, 1 H, ZNH), 5.58–5.65 (m, 2 H, 10-H, 11-H), 6.35 (d, *J* = 7.3 Hz, 1 H, NH), 7.13–7.37 (m, 10 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.32 (q, C-13), 17.86 (q, C-15), 25.30 (t, C-12), 50.07 (d, C-4), 51.31, 51.75 (q, C-8; d, C-9), 56.14 (d, C-6), 66.80 (t, C-2), 126.45, 127.04, 127.71, 127.84, 128.01, 128.34, 128.49 (d, C-11, arom. C), 155.56 (s, C-3), 171.34, 171.50 (s, C-5, C-7). – HRMS (FAB): $C_{25}H_{31}N_2O_5$ [M^+ + H]: calcd. 439.2223; found 439.2253; $C_{25}H_{30}N_2NaO_5$ [M^+ + Na]: calcd. 461.2042; found 461.2069. – MS (FAB): *m*/*z* (%) = 462 (13), 461 (46), 440 (27), 439 (100), 395 (11).

(*S*)-1-Phenylallyl *N*-(*tert*-Butyloxycarbonyl)-(*S*)-valyl-(*RS*)-alaninate (13): Ester **13** was prepared from (*S*)-1-phenylallyl alcohol (800 mg, 6.00 mmol) according to General Procedure 1. For analytical purposes, the (*S*,*RS*) derivative was also prepared. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 76:24) to give 2.14 g (5.28 mmol, 88%) of ester **13** as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.8 Hz, 1.5 H, 14-H), 0.87 (d, *J* = 6.8 Hz, 1.5 H, 14-H), 0.92 (d, *J* = 6.9 Hz, 3 H, 14-H), 1.35 (d, *J* = 7.1 Hz, 1.5 H, 12-H), 1.41 (s, 9 H, 1-H), 1.44 (d, *J* = 7.2 Hz, 1.5 H, 12-H), 2.14 (m, 1 H, 13-H), 3.93 (m, 1 H, 4-H), 4.63 (m, 1 H, 6-H), 5.04 (br. s, 1 H, BocNH), 5.22–5.31 (m, 2 H, 10-H), 5.91–6.03 (m, 1 H, 9-H), 6.23 (d, *J* = 5.8 Hz, 0.5 H, 8-H), 6.25 (d, *J* = 7.0 Hz, 0.5 H, 8-H), 6.43 (br. s, 0.5 H, NH), 6.53 (d, *J* = 7.4 Hz, 0.5 H, NH), 7.28–7.43 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.46, 17.63, 18.23, 18.44, 19.18 (q, C-12, C-14), 28.27 (q, C-1), 30.74, 39.97 (d, C-13), 48.07, 48.17 (d, C-6), 59.78 (d, C-4), 77.32 (d, C-8), 79.28 (s, C-2), 117.48, 117.51 (t, C-10), 126.97, 127.04, 128.33, 128.38, 128.60 (d, arom. C), 135.59 (d, C-9), 138.05, 138.35 (s, C-11), 155.74 (s, C-3), 170.88, 171.04, 171.62, 171.71 (s, C-5, C-7). – $C_{22}H_{32}N_2O_5$ (404.50): calcd. C 65.32, H 7.97, N 6.96; found C 65.35, H 8.10, N 6.84.

Methyl (*R*)-2-[*N*-*tert*-Butyloxycarbonyl-(*S*)-valyl]amino-2-methyl-5-phenylpent-(4*E*)-enoate (14): Ester **14** was prepared from ester **13** (405 mg, 1.00 mmol) according to the general procedure for rearrangements. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 70:30) to give 255 mg (0.61 mmol, 61%) of ester **14** as a colorless foam. Diastereomeric ratio (*S*,*S*)/(*S*,*R*): <5:95 (NMR). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3 H, 15-H), 0.93 (d, *J* = 6.9 Hz, 3 H, 15-H), 1.38 (s, 9 H, 1-H), 1.58 (s, 3 H, 13-H), 2.11 (m, 1 H, 14-H), 2.73 (dd, *J* = 14.0, 7.5 Hz, 1 H, 9-H), 3.02 (dd, *J* = 14.0, 7.5 Hz, 1 H, 9-H), 3.72 (s, 3 H, 8-H), 3.86 (br. s, 1 H, 4-H), 4.99 (br. s, 1 H, BocNH), 6.01 (dt, *J* = 15.6, 7.5 Hz, 1 H, 10-H), 6.41 (d, *J* = 15.8 Hz, 1 H, 11-H), 6.67 (s, 1 H, NH), 7.15–7.34 (m, 5 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.30, 19.00 (2 q, C-15), 22.62 (q, C-13), 28.01 (q, C-1), 30.40 (d, C-14), 39.77 (t, C-9), 52.41 (q, C-8), 59.91 (d, C-4; s, C-6), 79.69 (s, C-2), 123.40 (d, C-10), 126.03, 127.21, 128.24 (d, arom. C), 134.11 (d, C-11), 136.75 (s, C-12), 155.61 (s, C-3), 170.55, 173.84 (s, C-5, C-7). – $C_{23}H_{34}N_2O_5$ (418.53): calcd. C 66.01, H 8.19, N 6.69; found C 66.01, H 8.15, N 6.61.

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