Photochemically Induced Electron Transfer (PET) Catalyzed Radical Cyclization: A Practical Method for Inducing Structural Changes in Peptides by Formation of Cyclic Amino Acid Derivatives

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A new radical cyclization reaction of unsaturated amino acid derivatives is presented. The reaction is induced by photoelectron transfer (PET) catalysis and proceeds, in comparison to commonly applied methods, under mild, nonoxidizing, and nontoxic conditions in neutral medium. This type of radical cyclization reaction can be used in peptide chemistry for inducing structural changes in peptides.

Introduction

Over the last 15 years, the activation of molecules by single electron transfer (SET) has proved to be an important concept in developing new reactions. Many useful applications in selective synthesis even for complex compounds have been found.[1] In our investigations, we are interested in developing new SET-catalyzed reactions of synthetic importance.[2]

Besides the light-induced formation of radical cations as intermediates in cycloaddition reactions,[3] the generation of radicals under nonoxidative, nontoxic, and mild conditions via photoinduced electron transfer (PET) is of great value.[4] By one-electron oxidation an intermediate radical cation is formed, which subsequently fragments into an electrophilic leaving group and a neutral radical.

On the basis of this principle, α-silylmethylamino derivatives can act as starting materials for α-aminomethyl radicals. Upon irradiation of α-silylmethylamino derivatives with UV/vis light in the presence of a sensitizer, α-silylmethylamino radical cations are formed, which readily undergo fragmentation by loss of the trimethylsilyl group, leading to free α-aminomethyl radicals. These radicals can act as reactive intermediates in many different types of reactions, for example radical cyclization reactions[5] leading to piperidine or pyrrolidine structures.[6] In contrast to other methods,[7] the generation of α-aminomethyl radicals by PET can be performed under mild, nonoxidative, and nontoxic conditions.

The lifetime of the intermediate α-silylmethylamino radical cation is decisive for the success of these reactions. Recently, we investigated the PET-catalyzed intermolecular addition of α-silylmethyl carbamates to acceptor-substituted olefins, which is possible only by prolongation of the lifetime of the intermediate radical cation using a co-sensitization protocol.[8]

Here, we report PET-catalyzed radical cyclization reactions of unsaturated *N*-trimethylsilylmethyl amino acid derivatives and their application in peptide chemistry.[9] Besides carrying the trimethylsilylmethyl group, the nitrogen function of the amino acid derivative has to be acylated by a protecting group, another amino acid, or a peptide to achieve an oxidation potential in the range 1.4−1.6 V (vs Ag/AgCl).[10] It is not necessary to activate

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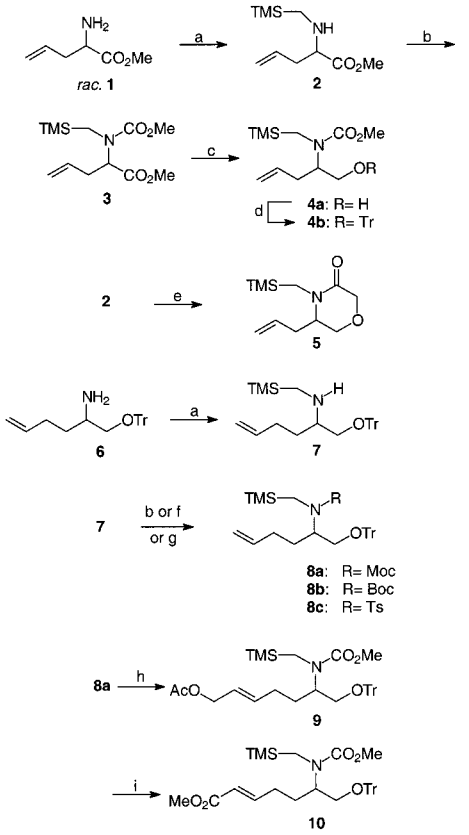
Scheme 1. Synthesis of PET Precursors 3, 4a,b, 5, 8a−c, and 10[a]



[a] Reagents and conditions: (a) $TMSCH_2Cl$, KI, Na_2CO_3, MeCN, 83 °C, 12 h, 55−60%. (b) $ClCO_2Me$, NaOH (0.8 N), MTBE, 0 °C, 0.5 h 98%. (c) $NaBH_4$, MeOH, THF, 98%. (d) Ph_3CCl, Py, 7d, 28%. (e) (1) $NaBH_4$, MeOH, THF, 94%. (2) $ClCH_2COCl$, toluene, NEt_3, 0 °C, 2 h, then KOH (50%), Bu_4NI, 10 h, 64%. (f) Boc_2O, NEt_3, MeOH, 65 °C, 99%. (g) TsCl, NEt_3, CH_2Cl_2, 12 h, 65%. (h) $AcOCH_2CH{=}CHCH_2OAc$, $Cl_2(PCy_3)_2Ru{=}CHPh$ 5 mol %, CH_2Cl_2, 40 °C,12 h. (i) (1) KCN, MeOH. (2) MnO_2, pentane/CH_2Cl_2 (1:1). (3) MnO_2, NaCN, HOAc, MeOH, 12 h, 75% (4 steps).

the double bond acting as radical acceptor with an electron-withdrawing group. Photoexcited 9,10-anthracene dicarbonitrile (ADC) and biphenyl (BP) as co-sensitizer were used to induce the reaction.

Results and Discussion

As model compounds, the amino acid derivatives **3**−**5** were synthesized as shown in Scheme 1 starting from racemic allylglycine methyl ester **1**. After *N*-alkylation (→ **2**), the nitrogen atom was acylated to give the *N*-Moc derivative **3**. Reduction of ester **3** led to **4a**, which was tritylated to give **4b**. Morpholinone **5** was obtained from **2** by ester reduction, subsequent treatment with chloroacetyl chloride, and cyclization. Additionally, the model compounds **8a**−**c** and **10** were synthesized starting from homoallylglycinol trityl ether **6**.[11] In the same manner as above, after *N*-alkylation (→ **7**), the nitrogen atom was acylated to give the *N*-Moc, *N*-Boc, or *N*-Ts derivatives **8a**−**c**. **10** was generated from **8a** via cross olefin metathesis[12] (→ **9**) followed by deprotection and oxidation[13] of the allyl alcohol (Scheme 1).

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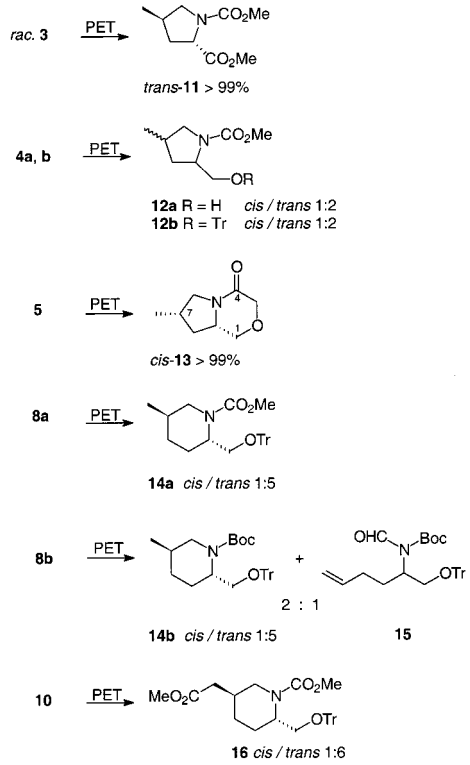
Table 1. Results of the PET-Catalyzed Radical Cyclization of 3, 4a,b, 5, 8a,b, and 10

amino acid	product	yield (%)	ratio *cis*/*trans*
3	**11**	51	<1:99
4a	**12a**	34	1:2
4b	**12b**	45	1:2
8a	**14a**	54	1:5
8b	**14b**[a]	30	1:5
10	**16**	65	1:6
5	**13**	45	>99:1

[a] The product contains **15** (12%).

Scheme 2. PET Reactions of 3, 4a,b, 5, 8a,b, and 10[a]



[a] Reagents and conditions: 20 mol % BP, 30 mol % ADC, MeOH/MeCN (2:3), irradiation $\lambda > 345$ nm. BP: biphenyl, ADC: 9,10-anthracenedicarbonitrile.

The irreversible oxidation potentials of compounds **3**−**5**, **8a**,**b**, and **10** are close to 1.4 V (vs Ag/AgCl) except for **8c**, for which no discrete oxidation potential was measurable. In all cases except for **8c** the corresponding pyrrolidines **11**−**13** or piperidines **14a**,**b** and **16** were formed on radiation (UV/vis) in the presence of ADC (20 mol %) and BP (30 mol %) (Scheme 2, Table 1).

The cyclization products **11**−**14** and **16** were obtained in moderate to good yield, but **8c** did not react.[14] The ring size strictly depends on the length of the side chain. The diastereoselectivity is moderate to good, except for **11** and **13**, where the diastereoselectivity is excellent.[15] The major diastereomer has *trans* configuration (see Table 1), except for **13**, which is *cis* configurated. The relative

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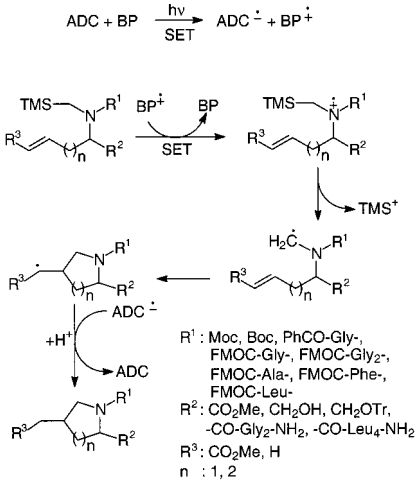
Scheme 3. Mechanism of the PET Reaction

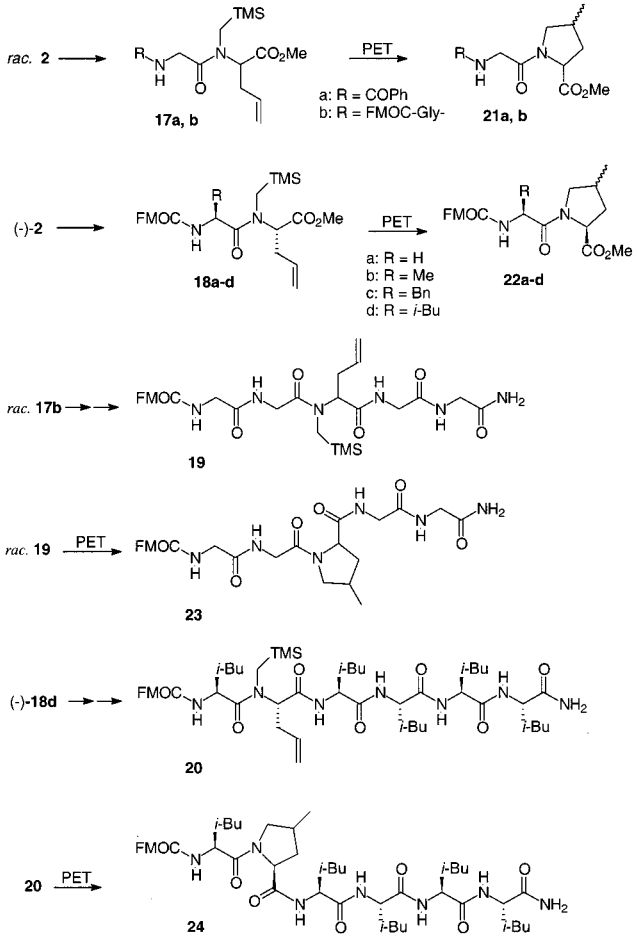


configuration of the compounds shown in Table 1 was confirmed by NOE experiments. The size of the *N*-protecting group does not influence the diastereoselectivity but the reaction rate of the cyclization. Bulky protecting groups such as Boc in **8b** favor the open chain product **15**.[16] An acceptor-substituted double bond improves the yield as well as the diastereoselectivity. The PET-catalyzed radical cyclization is completed within an hour. In the case of **13**, however, an extremely long reaction time (12 h) is observed due to the decrease in the fragmentation reaction rate. This observation was supported by our results with similar cyclic compounds such as morpholinediones, piperazinediones, and oxazolidinones.[17]

On the basis of our results and previous studies,[4c] we propose a mechanism starting with a SET process between the primary electron donor BP ($E_{ox} = 1.98$ V vs. SCE) and the photoexcited ADC ($E_{red}(S1) = 2.0$ V vs SCE) (Scheme 3).[18] In a subsequent SET reaction, the BP-radical cation oxidizes the α-silymethylcarbamate (e.g., **3**) or the α-silylmethylamide (e.g., **19**), leading to the desired radical cation (Scheme 3). After α-desilylation,[19] supported by the attack of methanol, the neutral radical is intramolecularly captured by the double bond. Finally, the reduction of the secondary radical by the ADC radical anion followed by protonation completes the reaction.

Because of the mild conditions for the formation of proline derivatives (e.g., **11**), it was our aim to apply this PET-catalyzed cyclization to influence the secondary structure of peptides by the in situ formation of a proline residue. Proline influences the peptide structure[20] by acting as a β-sheet breaker, an α-helix breaker, or a weak α-helix former depending on its position in the peptide.[21] It is also frequently found in β-turns.[22] Therefore, we expected structural changes in the peptide backbone (of proteins or oligopeptides) upon the PET-catalyzed cyclization reaction of oligopeptides containing the appropriate proline precursors.

Scheme 4. Synthesis of 17a,b, 18a−d, 19, and 20 and Their PET Reaction[a]



[a] Reagents and conditions: for details see text.

For these investigations we synthesized di- and oligopeptides starting from the enantiomerically pure unsaturated *N*-silylmethyl amino acid (−)-**2** derived from enantiomerically pure (−)-**1**.[23] The peptides **17**−**20** are readily accessible by means of a peptide coupling reaction and, in the case of **19** and **20**, by further saponification[24] of the ester followed by another peptide formation (Scheme 4).

The oxidation pontentials of **17**−**20** are close to +1.6 V (vs Ag/AgCl). As shown in Scheme 4 and Table 2, the PET-catalyzed cyclization was successful for all peptides. The 4-methylproline-containing peptides were obtained in 24−86% yield. No exceptions were found, even though it is known that Z-protecting groups act as quenchers of the PET reaction.[25] The stereochemistry of the com-

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Table 2. Results of the PET-Catalyzed Cyclization of the Peptides 17−20

peptide	product	R	yield (%)	ratio *cis*/*trans*
17a	**21a**	PhCO	24	1:3
18a	**22a**	H	33	1:2
18b	**22b**	Me	57	1:2
18c	**22c**	Bn	51	2:3
18d	**22d**	*i*-Bu	70	1:2
17b	**21b**	FMOC-Gly	55	1:2
19	**23**		86	1:3
20	**24**		64	2:1

pounds shown in Table 2 was confirmed by NOE and two-dimensional NMR experiments.

Obviously, the observed diastereoselectivity is not influenced by the side chain of neighboring amino acids. However, it reflects the approach of the intermediate radical toward the double bond which is determined by the predominant conformation of the peptide chain (e.g., **20**).

The influence of a proline moiety on the conformation of oligoleucines has already been reported.[26] Therefore, we were able to show structural changes during the transformation of **20** to **24** by CD spectroscopy. Due to the specific absorptions of peptides, one can distinguish between α-helix (two maxima at 190 and 215 nm, two minima at 205 and 225 nm), *β*-sheet (one maximum at 195 nm, one minimum at 202 nm), and random chain conformation (one maximum at 220 nm, one minimum at 195 nm). It is also possible to calculate the relative amount of each conformation in mixed spectra.[27] Because of the limited chain length of **20** and **24**, we observed for these peptides only spectra of the mixed type. The CD spectrum of **20** shows two maxima at 185 and 213 nm and two minima at 200 and 237 nm, which changes after the reaction giving **24**, showing one maximum at 190 nm, one minimum at 203 nm, and a shoulder at 230 nm. Therefore, we can conclude a change in the secondary structure during the transformation of **20** to **24** caused by the PET-catalyzed cyclization reaction.[28]

While the conformational consequences of a proline residue within an oligopeptide chain are well known, we considered whether an additional methyl group at postion 4 of the proline changes this situation. Therefore, we performed a conformational search using the molecular mechanics software TINKER[29] with the CHARMM22[30] force field, which is especially designed to perform protein simulations. Calculations on three individual compounds have been performed, namely, on AcO-Leu(1)-Leu(2)-Leu(3)-Pro(4)-Leu(5)-NHMe and the two 4-methyl proline derivatives (methyl group *cis* or *trans* to the backbone). The terminating groups used in the calculation (acetyl at the *N*-terminus, *N*-methylamide at the C-terminus) were chosen because of the availability of high-quality force field parameters. For each of the three compounds, ~20 000 conformations were generated.

An analysis of the low-energy conformations found in these calculations shows that all three compounds behave similarly. All the low-energy conformations display a hydrogen bond (NH···O distance <200 pm) between the amino group of Leu(2) and the carbonyl group of Leu(5), which is characteristic for a *β*-turn. This clearly demonstrates that there is no special effect of the methyl group.

Conclusion

The PET-catalyzed radical cyclization reaction is easily carried out under nonoxidative, nontoxic, and mild conditions. This reaction is applicable to peptides. The proline-containing peptides resulting from this cyclization reaction are of potential interest with respect to the photochemically induced structural changes in their secondary structure. In a simple example, we were able to demonstrate this effect on the relative amount of α-helix in the secondary structure during the transformation of **20** to **24** by the PET-catalyzed reaction. Therefore, we expect that this PET-catalyzed cyclization is also applicable to the formation of *β*-turn mimetics.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 200, 400, or 500 MHz. (Bruker), and ^{13}C NMR spectra were recorded at 50.3 MHz. Optical rotations were measured on a digital polarimeter (Perkin-Elmer) at room temperature. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ (0.2 mm) sheets which were developed with ethanolic molybdophosphoric acid, a solution of $KMnO_4$ in water, or UV light. Flash chromatography (FC) was performed on Merck (0.04−0.063 mm) silica. All chemicals were of the highest commercial available purity and were used without further purification. Solvents used for chromatography were distilled before use. Photolyses were performed with a light source system consisting of a Hanovia 976C1010 1000 W xenon arc lamp, a Müller-Elektronik LAX 1000 lamp housing, and a Schott WG345 long-pass filter. The system was designed for use with wavelengths (*λ*) greater than 345 nm.

General Procedure for Photolysis (Procedure P). The unsaturated amino acid derivatives {0.1−0.4 mmol/L in MeOH/MeCN (2:3, 50 mL)}, 20 mol % of ADC (9,10-anthracenedicarbonitrile), and 30 mol % of BP (biphenyl) were vigorously mixed in a 100 mL Schlenk tube. Before the reaction is started, the solution was evacuated until gas evolution stopped and purged for 10 min with Ar to free it from O_2. Then the solution was irradiated for 60−80 min under Ar with a 1000 W xenon arc lamp (*λ* > 345 nm), while being monitored by TLC. After the reaction was finished, the products were purified by FC. ADC and BP were reisolated nearly quantitatively.

General Procedure for Peptide Formation (Procedure F). One equivalent of the *C*-protected amino acid, 1.2 equiv of the *N*-protected amino acid, and 1.2 equiv of HABT (1-hydroxy-7-azabenzotriazole) were dissolved in a minimum amount of absolute MeCN. At 0 °C 1.2 equiv of DIC (diisopropyl carbodiimide) followed by 1.2 equiv of DIEA (diisopropylethylamine) were added to the mixture. After 0.5 h the mixture was allowed to warm to room temperature. During the reaction a precipitate was formed. After the reaction was finished, the mixture was dissolved in 50−100 mL of MTBE (methyl *tert*-butyl ether) and was subsequently washed twice with 10% citric acid, twice with saturated Na_2CO_3 solution, and with saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was evaporated. Separation of the products was effected by FC unless otherwise stated.

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(28) Furthermore the CD spectra, NMR spectra, and the dramatic change in the solubility during the formation of **24** are hints for the change in the secondary structure. **24** is less soluble in MeOH, $CDCl_3$, and CH_2Cl_2 than **20**. The ^{1}H NMR signals of **24** are broadened, whereas the NMR signals of **20** are sharp.

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L-2-(Trimethylsilanylmethylamino)-pent-4-ene Carboxylic Acid Methyl Ester (H-(*N*-Trimethylsilanylmethyl-2-allyl)-Gly-OMe) (−)-(2). L-allylglycine methyl ester (−)-(**1**) (600 mg, 4.6 mmol), chloromethyltrimethylsilane (0.71 mL, 5.1 mmol), KI (846 mg, 5.1 mmol), and Na_2CO_3 (540 mg, 5.1 mmol) were dissolved in absolute MeCN (20 mL). After 12 h at 83 °C the solvent was evaporated and the residue was dissolved in MTBE. After filtration the solvent was evaporated. FC with MTBE/hexane (1:5, $R_f = 0.42$) afforded (−)-**2** (544 mg, 55%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.77 (dtd, J = 18, 8, 8 Hz, 4-H), 5.08 (dd, J = 18, 3 Hz, 5-H), 5.06 (dd, J = 8, 3 Hz, 5-H′), 3.71 (s, CO_2Me), 3.26 (t, J = 6 Hz, 2-H), 2.40 (dd, J = 8, 6 Hz, 3-H_2); CH_2TMS: 2.03, 1.98 (2 d, J = 14 Hz), 0.04 (s). ^{13}C NMR ($CDCl_3$): δ 175.2 (s, C-1), 133.8 (d, C-4), 117.5 (t, C-5), 64.7 (d, C-2), 51.4 (q, CO_2*Me*), 38.0 (t, C-3); CH_2TMS 37.2 (t), −2.7 (q). HRMS calcd for $C_9H_{18}NO_2$ (M^+ − Me) 200.1107, found 200.1101. $[\alpha]_D^{RT}$ −39° (c = 0.38, MTBE). Racemic **2** was prepared analogously from racemic **1**.

2-(Methoxycarbonyl(trimethylsilanyl)methylamino)-pent-4-ene Carboxylic Acid Methyl Ester (*rac*-3). Methyl chloroformate (125 μL, 1.6 mmol) was added slowly under stirring at 0 °C to a suspension of *rac*-**2** (320 mg, 1.5 mmol) in MTBE (10 mL) and water (10 mL). Afterward a 0.8 N NaOH solution (2 mL) was added. After 0.5 h, MTBE (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with MTBE (3 × 20 mL). Removal of the solvent afforded *rac*-**3** (405 mg, 98%) as a colorless oil. No further purification was necessary. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74 (m_c, 4-H), 5.12 (dd, J = 16, 3 Hz, 5-H), 5.08 (dd, J = 8, 3 Hz, 5-H′), 4.7−4.3 (m, 2-H), 3.69 (s, CO_2Me), 3.66 (s, CO_2Me), 2.8−2.4 (m, 3-H_2, CH_2TMS), 0.04 (s, TMS). ^{13}C NMR ($CDCl_3$): δ 171.3 (s, C-1), 157.1 (s, *C*O_2Me), 133.8 (d, C-4), 117.9 (t, C-5), 60.7 (d, C-2), 52.3 (q, CO_2*Me*), 51.9 (q, CO_2*Me*), 36.6 (t, C-3). CH_2TMS: 33.6 (t), −1.4 (q). HRMS: calcd for $C_{12}H_{23}NO_4Si$ (M^+) 273.1396, found 273.1397.

(1-Hydroxymethylbut-3-enyl)trimethylsilanylmethylcarbamic Acid Methyl Ester (*rac*-4a). MeOH (2 mL) was slowly added under stirring to a suspension of *rac*-**3** (190 mg, 0.7 mmol) and $NaBH_4$ (133 mg, 3.5 mmol) in THF (10 mL). After complete reduction MeOH (10 mL) was added. After the evolution of H_2 had ceased, the solvent was evaporated. The crude product was suspended in MTBE (20 mL), and a saturated solution of NH_4Cl (30 mL) was added. The organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 20 mL). Removal of the solvent afforded *rac*-**4a** (168 mg, 98%) as a colorless oil. No further purification was necessary. ^{1}H NMR (400 MHz, 55 °C, $CDCl_3$): δ 5.78 (ddt, J = 17, 10, 7 Hz, 3-H), 5.11 (ddd, J = 17, 3, 2 Hz, 4-H), 5.06 (d, J = 10 Hz, 4-H′), 3.85 (br, CH_2OH), 3.7−3.6 (m, 1-H, CH_2-O*H*), 3.69 (s, CO_2Me), 2.68, 2.54 (2d, J = 15 Hz, CH_2TMS), 2.36 (t, J = 7 Hz, 2-H_2), 0.08 (s, TMS). ^{13}C NMR ($CDCl_3$): δ 157.9 (s, *C*O_2Me), 134.6 (d, C-3), 117.5 (t, C-4), 63.7 (t, *C*H_2-OH), 52.4 (q, CO_2*Me*). CH_2TMS: 33.2 (t), −1.4 (q), C-2 and C-1 were not detected. HRMS: calcd for $C_{11}H_{23}NO_3Si$ (M^+) 245.1447, found 245.1450.

Trimethylsilanylmethyl(1-trityloxymethylbut-3-enyl)-carbamic Acid Methyl Ester (*rac*-4b). At 80 °C *rac*-**4a** (180 mg, 0.73 mmol) and triphenylchloromethane (245 mg, 0.88 mmol) were stirred in pyridine (5 mL). After 7 days MTBE (50 mL) was added and the mixture was washed with 10% citric acid (3 × 20 mL). Drying over $MgSO_4$, removal of the solvent, and purification by FC with MTBE/hexane (1:1, R_f = 0.28) afforded *rac*-**4b** (100 mg, 28%) as a colorless oil. ^{1}H NMR (200 MHz, 55 °C, $CDCl_3$): δ 7.5−7.2 (m, Tr), 5.73 (ddt, J = 17, 10, 7 Hz, 3-H), 5.09 (ddd, J = 17, 3, 2 Hz, 4-H), 5.02 (d, J = 10 Hz, 4-H′), 4.32 (br, 1-H), 3.71 (s, CO_2Me), 3.22 (d, J = 7 Hz, CH_2OR), 2.32 (m_c, 2-H_2). CH_2TMS: 2.42 (s), 0.13 (s). ^{13}C NMR (55 °C, $CDCl_3$): δ 157.4 (s, *C*O_2Me), 144.1 (s, Tr), 135.0 (d, C-3), 128.8, 127.7, 127.0 (3d, Tr), 116.8 (t, C-4), 86.9 (s, Tr), 64.0 (t, CH_2OR), 57.6 (d, C-1), 52.0 (q, CO_2*Me*), 34.4 (t, C-2); CH_2TMS: 35.3 (t), −1.1 (q). HRMS: calcd for $C_{30}H_{37}NO_3Si$ (M^+) 487.2543, found 487.2544.

5-Allyl-4-trimethylsilanylmethylmorpholin-3-one (*rac*-5). Reduction of *rac*-2 with $NaBH_4$. The same procedure as for *rac*-**4a** was used. Without further purification 2-((trimethylsilanyl)methylamino)-pent-4-enol was obtained as a colorless oil (yield 94%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74 (ddt, J = 18, 10, 7 Hz, 4-H), 5.07 (m_c, 5-H_2), 3.63 (dd, J = 10, 4 Hz, 1-H), 3.57 (dd, J = 10, 6 Hz, 1-H′), 2.58 (m_c, 2-H), 2.20 (ddbr, J = 12, 7 Hz, 3-H). CH_2TMS: 2.01 (s), 0.02 (s). ^{13}C NMR ($CDCl_3$): δ 135.0 (d, C-4), 117.6 (t, C-5), 62.0 (t, C-1), 61.2 (d, C-2), 36.3 (t, C-3). CH_2TMS: 35.5 (t), −2.8 (q). HRMS: calcd for $C_8H_{18}NSi$ (M^+ − OMe) 156.1209, found 156.1209; calcd for $C_6H_{16}NOSi$ (M^+ − C_3H_5) 146.1001, found 146.0997.

Formation of the Morpholinone *rac*-5. At 0 °C a solution of chloroacetyl chloride (203 mg, 1.8 mmol) in toluene (5 mL) was added to a solution of the amino alcohol (336 mg, 1.8 mmol) and NEt_3 (5 mL) in toluene (20 mL). After 2 h at room temperature a catalytic amount of Bu_4NI and 20 mL of a KOH solution (50%) were added. After 10 h the organic layer was separated, and the aqueous layer was extracted with MTBE (3 × 20 mL). Purification by FC with MTBE/hexane (1:1, R_f = 0.35) afforded *rac*-**5** (260 mg, 64%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 4.14, 4.04 (2d, J = 16 Hz, 2-H_2), 3.82 (dd, J = 12, 2 Hz, 6-H), 3.64 (dd, J = 12, 3 Hz, 6-H′), 3.09 (m_c, 5-H); 5-allyl: 5.69 (ddt, J = 17, 10, 6 Hz), 5.12 (d, J = 17 Hz), 5.10 (d, J = 10 Hz), 2.44 (t br, J = 6 Hz); CH_2TMS: 3.35, 2.23 (2d, J = 15 Hz), 0.05 (s). ^{13}C NMR ($CDCl_3$): δ 165.6 (s, C-3), 67.7 (t, C-2), 65.5 (t, C-6), 57.6 (d, C-5); 5-allyl: 133.4 (d), 118.8 (t), 34.5 (t); CH_2TMS: 37.2 (t), −1.3 (q). HRMS: calcd for $C_{11}H_{21}NO_2Si$ (M^+ − H) 227.1342, found 227.1345.

2-((Trimethylsilanyl)methylamino)hex-5-enyl Trityl Ether (*rac*-7). The same procedure as for the preparation of *rac*-**2** was used. 2-Aminohex-5-enyl trityl ether (*rac*-**6**)[31] (1.2 g, 5 mmol), chloromethyltrimethylsilane (0.69 mL, 5 mmol), KI (0.83 g, 5 mmol), and Na_2CO_3 (0.53 g, 5 mmol) afforded *rac*-**7** (1.3 g, 60%) as a colorless oil. Purification was achieved by FC with MTBE/hexane (1:5, R_f = 0.37). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (ddt, J = 16, 10, 6 Hz, 5-H), 4.94 (dd, J = 16, 2 Hz, 6-H), 4.91 (dd, J = 10, 2 Hz, 6-H′), 3.18 (dd, J = 9, 4 Hz, 1-H), 3.00 (dd, J = 9, 6 Hz, 1-H), 2.60 (m, 2-H), 1.97 (m_c, 4-H), 1.56 (dt, J = 14, 6 Hz, 3-H), 1.43 (dt, J = 14, 7 Hz, 3-H); Tr: 7.5−7.2 (m); CH_2TMS: 1.94, 1.84 (2d, J = 12 Hz), 0.04 (s). ^{13}C NMR ($CDCl_3$): δ 138.9 (d, C-5), 114.3 (t, C-6), 64.1 (t, C-1), 60.9 (d, C-2), 30.3 (t, C-4), 26.9 (t, C-3); Tr: 144.3 (s), 128.7, 127.7, 126.9 (3d), 86.2 (s); CH_2TMS: 36.4 (t), −2.6 (q). HRMS: calcd for $C_{29}H_{38}NOSi$ (M^+ + H) 444.2773, found 444.2727.

Trimethylsilanylmethyl(1-trityloxymethylpent-4-enyl)-carbamic Acid Methyl Ester (*rac*-8a). The same procedure as for *rac*-**3** was used. *rac*-**7** (226 mg, 0.5 mmol), methyl chloroformate (42 μL, 0.55 mmol), and 1 N NaOH (1 mL) afforded *rac*-**8a** (240 mg, 96%) as a colorless oil, which was purified by FC with MTBE/hexane (1:10, R_f = 0.48). ^{1}H NMR (200 MHz, C_6D_6, 80 °C): δ 5.83 (ddt, J = 16, 10, 7 Hz, 4-H), 5.06 (ddd, J = 16, 4, 2 Hz, 5-H), 5.00 (ddd, J = 10, 4, 2 Hz, 5-H), 4.33 (m_c, 1-H), 3.73 (s, CO_2Me), 3.21 (d, J = 8 Hz, −OCH_2), 2.08 (m_c, 3-H_2), 1.62 (m_c, 2-H_2); Tr: 7.5−7.2 (m); CH_2-TMS: 2.51, 2.41 (2d, J = 14 Hz), 0.05 (s, TMS). ^{13}C NMR ($CDCl_3$, 55 °C): δ 157.6 (s, *C*O_2Me), 137.9 (d, C-4), 114.8 (t, C-5), 64.3 (t, -OCH_2), 57.1 (d, C-1), 52.0 (q, CO_2*Me*), 30.5 (t, C-3), 27.0 (t, C-2); Tr: 144.1 (s), 128.8, 127.7, 126.9 (3d), 86.9 (s). CH_2TMS: 34.6 (t), −1.0 (q). HRMS: calcd for $C_{31}H_{39}NO_3Si$ (M^+) 501.2699, found 501.2687.

Trimethylsilanylmethyl(1-trityloxymethylpent-4-enyl)-carbamic Acid *tert*-Butyl Ester (*rac*-8b). *rac*-**7** (150 mg, 0.34 mmol), Boc_2O (148 mg, 0.67 mmol), and NEt_3 (0.5 mL) were heated to reflux. After the reaction was finished, removal of the solvent and residual reagents under reduced pressure afforded *rac*-**8b** (184 mg, 99%) as a colorless oil. No further purification was necessary. ^{1}H NMR (200 MHz, C_6D_6, 55 °C): δ 5.84 (ddt, J = 18, 10, 7 Hz, 4-H), 5.03 (ddd, J = 18, 4, 2 Hz, 5-H), 5.03 (ddd, J = 10, 4, 2 Hz, 5-H′), 4.22 (m_c, 1-H), 3.14 (d, J = 7 Hz, −OCH_2), 2.05 (m_c, 3-H_2), 1.59 (m_c, 2-H_2), 1.49 (s, Boc); Tr: 7.5−7.2 (m); CH_2TMS: 2.51, 2.39 (2d, J = 14 Hz), 0.08 (s). ^{13}C NMR ($CDCl_3$, 55 °C): δ 156.1 (s, Boc), 138.1 (d, C-4), 114.8 (t, C-5), 79.1 (s, Boc), 64.7 (t, −OCH_2), 57.0 (d, C-1), 30.5 (t, C-3), 29.6 (t, C-2), 28.6 (q, Boc); Tr: 144.2 (s, Tr), 128.8, 127.7, 126.9 (3d), 86.8 (s); CH_2TMS: 34.9 (t), −0.8 (q). HRMS: calcd for $C_{34}H_{46}NO_3Si$ (M^+) 544.3247, found 544.3245.

4-Methyl-*N*-trimethylsilanylmethyl-*N*-(1-trityloxymethylpent-4-enyl)benzene Sulfonamide (*rac*-8c). *rac*-**7** (100 mg, 0.23 mmol), tosyl chloride (47 mg, 0.25 mmol), NEt_3 (0.5 mL), and CH_2Cl_2 (10 mL) were stirred for 12 h. The crude mixture was added to a saturated solution of NaCl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). Purification by FC with MTBE/hexane (1:10, R_f = 0.48) afforded *rac*-**8c** (90 mg, 65%) as a colorless oil. ^{1}H NMR (200 MHz, C_6D_6, 55 °C): δ 7.65 (d, J = 8 Hz, Ts), 7.4−7.1 (m, Ts, Tr), 5.76 (ddt, J = 18, 10, 6 Hz, 4-H), 5.0−4.9 (m, 5-H), 3.98 (m_c, 1-H), 3.03 (d, J = 6 Hz, −OCH_2), 2.41 (s, Ts), 2.0−1.4 (m, 2-H_2, 3-H_2); CH_2TMS: 2.53, 2.40 (2d, J = 16 Hz), 0.07 (s). ^{13}C NMR ($CDCl_3$, 55 °C): δ 142.6 (s, Ts), 137.8 (d, C-4), 136.9 (s, Ts), 129.4 (d, Ts), 127.3 (d, Ts), 114.9 (t, C-5), 63.8 (t, −OCH_2), 58.6 (d, C-1), 30.6 (t, C-3), 29.7 (t, C-2), 21.5 (q, Ts); Tr: 143.5 (s), 128.6, 127.7, 126.9 (3d), 86.9 (s); CH_2TMS: 35.3 (t), −1.1 (q). HRMS: calcd for $C_{35}H_{40}NO_3SSi$ (M^+ − Me) 582.2498, found 582.2497.

Preparation of *rac*-10: Acetic Acid 6-(Methoxycarbonyl(trimethylsilanyl)methylamino)-7-trityloxymethylhept-2-enyl Ester (*rac*-9). Cross Metathesis. *rac*-**8a** (158 mg, 0.36 mmol), but-2-ene-1,4-diol diacetate (115 mg, 0.72 mmol), and [Ru][32] (44 mg, 5 mol %) were dissolved in CH_2Cl_2 (5 mL) and heated for 12 h at 40 °C. Purification by FC with MTBE/hexane (1:4, R_f = 0.22) afforded *rac*-**9** (180 mg, 87%). ^{1}H NMR (200 MHz, 55 °C, $CDCl_3$): δ 7.5−7.2 (m, Tr), 5.79 (dt, J = 16, 6 Hz, 2-H), 5.54 (dt, J = 16, 6 Hz, 3-H), 4.51 (d, J = 6 Hz, 1-H_2), 4.22 (m_c, 6-H), 3.69 (s, CO_2Me), 3.16 (d, J = 7 Hz, 7-H_2), 2.04 (s, Ac), 2.02 (m_c, 4-H_2), 1.67 (m_c, 5-H_2); CH_2-TMS: 2.44, 2.35 (2d, J = 14 Hz), 0.00 (s). ^{13}C NMR (55 °C, $CDCl_3$): δ 170.4 (s, Ac), 157.5 (s, *C*O_2Me), 134.9 (d, C-2), 124.9 (d, C-3), 64.8 (t, C-1), 64.4 (t, C-7), 57.2 (d, C-6), 52.0 (q, CO_2*Me*), 29.2 (t, C-4), 29.0 (t, C-5), 20.7 (q, Ac); Tr: 144.1 (s), 128.9, 127.7, 127.0 (3d), 87.0 (s); CH_2TMS: 34.9 (t), −1.0 (q). HRMS: calcd for $C_{34}H_{43}NO_5Si$ (M^+) 573.2911, found 573.2923.

6-(Methoxycarbonyl(trimethylsilanyl)methylamino)-7-trityloxyhept-2-enoic Acid Methyl Ester (*rac*-10). Transesterification of the Acetate Group. The allyl acetate *rac*-**9** (180 mg, 0.3 mmol) was stirred with KCN (10 mg) in absolute MeOH (50 mL). After complete transesterification the solvent was evaporated. MTBE (20 mL) was added to the crude mixture. Filtration over Celite afforded (6-hydroxy-1-trityloxymethylhex-4-enyl)(trimethylsilanyl)methylcarbamic acid methyl ester (160 mg, 96%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.5−7.2 (m, Tr), 5.63 (m_c, 4-H, 5-H_2), 4.26 (m_c, 1-H), 4.05 (d, J = 4 Hz, 6-H_2), 3.69 (s, CO_2Me), 3.16 (d, J = 7 Hz, −CH_2OR), 2.03 (m_c, 3-H_2), 1.58 (m_c, 2-H_2); CH_2TMS: 2.44, 2.34 (2d, J = 14 Hz), 0.00 (s). ^{13}C NMR ($CDCl_3$): δ 157.5 (s, *C*O_2Me), 131.7 (d, C-5), 130.2 (d, C-4), 64.4 (t, *C*H_2OR), 63.4 (t, C-6), 57.1 (d, C-1), 52.0 (q, CO_2*Me*), 29.3 (t, C-3), 29.0 (t, C-2); Tr: 144.1 (s), 128.8, 127.7, 127.0 (3d), 87.1 (s); CH_2TMS: 34.7 (t), −1.1 (q). HRMS: calcd for $C_{32}H_{41}NO_4Si$ (M^+) 531.2805, found 531.2811.

Oxidation of the Allyl Alcohol. Allyl alcohol (160 mg, 0.3 mmol) and MnO_2 (524 mg, 6 mmol) were stirred in pentane/CH_2Cl_2 (1:1, 10 mL) overnight. The crude oily aldehyde (150 mg) obtained after filtration was used without purification for the next step. MnO_2 (524 mg, 6 mmol), NaCN (40 mg, 0.8 mmol), HOAc (13 μL), and the aldehyde (150 mg) were stirred in absolute MeOH (10 mL). After complete reaction and removal of the solvent, MTBE was added. Filtration over Celite afforded *rac*-**10** (141 mg) as a colorless oil. No further purification was necessary. Overall yield starting from *rac*-**8a**: 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4−7.2 (m, Tr), 6.91 (dt, J = 16, 7 Hz, 3-H), 5.80 (d, J = 16 Hz, 2-H), 4.22 (m_c, 6-H), 3.73 (s, CO_2Me), 3.69 (s, CO_2Me), 3.15 (m_c, 7-H_2), 2.15 (td, J = 8, 7 Hz, 4-H_2), 1.7−1.5 (m, 5-H_2); CH_2TMS: 2.40, 2.34 (2d, J = 14 Hz), −0.02 (s). ^{13}C NMR ($CDCl_3$): δ 166.7 (s, C-1), 157.4 (s, *C*O_2Me), 148.0 (d, C-3), 121.5 (d, C-2), 64.2 (t, C-7), 56.9 (d, C-6), 52.1 (q, CO_2*Me*), 51.1 (q, CO_2*Me*), 28.9 (t, C-4), 28.2 (t, C-5); Tr: 143.9 (s), 128.7, 127.7, 127.0 (3d), 87.0 (s); CH_2TMS: 34.7 (t), −1.1 (q). HRMS: calcd for $C_{32}H_{38}NO_5Si$ (M^+ − Me) 544.2519, found 544.2519.

(31) Compound **6** was prepared according to ref 11.

(32) [Ru]: $Cl_2(PCy_3)Ru$=CHPh, Cy = cyclohexyl, see also refs 12a,b.

(2,4-*trans*)-4-Methylpyrrolidine-1,2-dicarboxylic Acid Dimethyl Ester (*rac*-11). Following the procedure P, *rac*-**3** (0.5 mmol, 136 mg), BP (23 mg) and ADC (22 mg) yielded after purification by FC with MTBE/hexane (1:1, R_f = 0.23) *rac*-**11** (52 mg, 51%, 1:1 mixture of rotamers) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41/4.34 (dd, J = 8, 3 Hz, 2-H), 3.8−3.6 (m, 4-H, 5-H), 3.72, 3.68 (2s, 2 × CO_2*Me*), 3.03/2.95 (dd, J = 11, 9 Hz, 5-H′), 2.39 (m_c, 4-H′), 2.09 (ddd, J = 9, 6, 3 Hz, 3-H), 1.84 (m_c, 3-H′), 1.05/1.03 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 173.2/173.1 (s, 2-*C*O_2Me), 155.4/154.9 (s, 1-*C*O_2Me), 59.3/59.0 (d, C-2), 53.6/53.2 (t, C-5), 52.5, 52.2 (q, 1-, 2-CO_2*Me*), 38.6/37.5 (t, C-3), 32.1/31.1 (d, C-4), 17.3 (q, 4-Me). HRMS: calcd for $C_8H_{15}NO_4$ (M^+) 201.1001, found 201.1000.

2-Hydroxymethyl-4-methylpyrrolidine-1-carboxylic Acid Methyl Ester (*rac*-12a). Following the procedure P, *rac*-**4a** (24 mg, 0.1 mmol), BP (5 mg), and ADC (5 mg) yielded after purification by FC with EtOAc/CH_2Cl_2 *rac*,*cis*- and *trans*-**12a** (34%). *rac*,*cis*-**12a** (R_f = 0.25, 2 mg) was eluted first as an oil, followed by *rac*,*trans*-**12a** (R_f = 0.21, 4 mg) as the second fraction.

(2,4-*cis*)-4-Methylprolinol (*rac*,*cis*-12a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (m_c, 2-H), 3.8−3.7 (m, 5-H, CH_2OH), 3.72 (s, CO_2*Me*), 3.60 (dd, J = 12, 7 Hz, CH_2OH), 2.80 (t, J = 10 Hz, 5-H′), 2.2−2.1 (m, 3-H, 4-H), 1.26 (m_c, 3-H′), 1.02 (d, J = 6 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 67.4 (t, *C*H_2OH), 61.9 (d, C-2), 54.2 (t, C-5), 52.6 (q, CO_2*Me*), 37.1 (t, C-3), 32.1 (d, C-4), 16.7 (q, 4-Me), carbonyl *C* was not detected. HRMS: calcd for $C_7H_{12}NO_2$ (M^+ − CH_2OH) 142.0868, found 142.0863.

(2,4-*trans*)-4-Methylprolinol (*rac*,*trans*-12a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 (m_c, 2-H), 3.72 (s, CO_2*Me*), 3.64 (m_c, CH_2OH), 3.52 (dd, J = 10, 7 Hz, 5-H), 3.01 (dd, J = 10, 8 Hz, 5-H′), 2.30 (m_c, 4-H), 1.8−1.5 (m, 3-H_2), 1.02 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 67.7 (t, *C*H_2OH), 60.2 (d, C-2), 54.2 (t, C-5), 52.7 (q, CO_2*Me*), 36.4 (t, C-3), 31.8 (d, C-4), 17.9 (q, 4-Me), carbonyl *C* was not detected. HRMS: calcd for $C_7H_{12}NO_2$ (M^+ − CH_2OH) 142.0868, found 142.0863.

4-Methyl-2-trityloxymethylpyrrolidine-1-carboxylic Acid Methyl Ester (*rac*-12b). Following the procedure P, *rac*-**4b** (73 mg, 0.15 mmol), BP (7 mg), and ADC (7 mg) yielded after purification by FC with MTBE/hexane (1:4, R_f = 0.30) a 1:2 mixture of *rac*,*cis*- and *trans*-**12b** (28 mg, 45%) as a colorless oil. HRMS: calcd for $C_{27}H_{28}NO_3$ (M^+ − H) 414.2069, found 414.2066. *rac*,*trans*-**12b**: ^{1}H NMR (400 MHz, 58 °C, $CDCl_3$): δ 7.6−7.1 (m, Tr), 4.0−3.8 (m, 2-H), 3.40 (s, CO_2Me), 3.52 (dd, J = 10, 7 Hz, CH_2OR), 3.3−3.1 (m, 5-H, CH_2OR), 2.95 (m_c, 5-H′), 2.4−2.1 (m, 3-H, 4-H), 1.7−1.5 (m, 3-H′), 1.02 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 155.6 (s, *C*O_2Me), 64.5 (t, CH_2OR), 57.7 (d, C-2), 54.0 (t, C-5), 52.0 (q, CO_2*Me*), 18.0 (q, 4-Me); Tr: 144.4 (s), 128.8, 127.9, 127.0 (3d), 86.8 (s); (C-3 and C-4 were not detected). *rac*,*cis*-**12b**: ^{1}H NMR (400 MHz, 58 °C, $CDCl_3$): δ 7.6−7.1 (m, Tr), 4.0−3.8 (m, 2-H), 3.40 (sbr, CO_2Me), 3.3−3.1 (m, 5-H, CH_2OR), 2.85 (t, J = 10 Hz, 5-H′), 2.4−2.1 (m, 3-H, 4-H), 1.7−1.5 (m, 3-H′), 1.06 (d, J = 7 Hz, 4-Me).

5-Methyl-2-trityloxymethylpiperidine-1-carboxylic Acid Methyl Ester (*rac*-14a). Following the procedure P, *rac*-**8a** (86 mg, 0.17 mmol), BP (9 mg), and ADC (9 mg) yielded after purification by FC with MTBE/hexane (10:1, R_f = 0.17) a 1:5 mixture of *rac*,*cis*- and *trans*-**14a** (52 mg, 51%) as a colorless oil. *rac*,*trans*-**14a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.4−7.1 (m, Tr), 4.42 (m_c, 2-H), 3.7−3.6 (m, 6-H), 3.65 (s, CO_2Me), 3.17 (dd, J = 10, 8 Hz, CH_2OR), 3.00 (dd, J = 8, 6 Hz, CH_2OR), 2.72 (dd, J = 13, 3 Hz, 6-H′), 1.70 (m_c, 3-H, 5-H), 1.40 (m_c, 3-H′, 4-H), 1.14 (m_c, 4-H′), 0.88 (d, J = 7 Hz, 5-Me). ^{13}C NMR ($CDCl_3$): δ 157.3 (s, *C*O_2Me), 61.5 (t, *C*H_2OR), 52.4 (q, CO_2*Me*), 50.8 (d, C-2), 44.8 (t, C-6), 27.3 (d, C-5), 25.4 (t, C-4), 20.4 (t, C-3), 16.6 (q, 5-*Me*); Tr: 144.1 (s), 128.7, 127.7, 127.0 (3d), 86.5 (s). HRMS: calcd for $C_{28}H_{30}NO_3$ (M^+ − H) 428.2226, found 428.2227.

5-Methyl-2-trityloxymethylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (*rac*-14b). Following the procedure P, *rac*-**8b** (105 mg, 0.19 mmol), BP (9 mg), and ADC (9 mg) yielded after purification by FC with MTBE/pentane (1:3) a 1:5 mixture of *rac*,*cis*- and *trans*-**14b** and **15.** *rac*-**14b** (R_f = 0.29,

26 mg, 30%) was eluted first as an oil and *rac*-**15** (oily, R_f = 0.19, 11 mg, 12%) as a second fraction. *rac,trans*-**14b**: ^{1}H NMR (400 MHz, 55 °C, $CDCl_3$): δ 7.5−7.0 (m, Tr), 4.46 (dddd, J = 7, 7, 5, 3 Hz, 2-H), 3.64 (d, J = 14 Hz, 6-H), 3.21 (dd, J = 9, 7 Hz, CH_2OR), 3.10 (dd, J = 9, 7 Hz, CH_2OR), 2.81 (dd, J = 14, 4 Hz, 6-H′), 1.84 (m_c, 3-H), 1.74 (m_c, 5-H), 1.6−1.4 (m, 3-H′, 4-H), 1.49 (s, Boc), 1.22 (m_c, 4-H′), 0.97 (d, J = 7 Hz, 5-Me). ^{13}C NMR ($CDCl_3$): δ 61.6 (t, -*C*H_2O), 50.5 (d, C-2), 44.6 (t, C-6), 27.5 (d, C-5), 25.6 (t, C-4), 20.6 (t, C-3), 16.6 (q, 5-*Me*); Tr: 144.1 (s), 128.7, 127.7, 126.9 (3d), 86.3 (s); Boc: 155.8 (s), 79.0 (s), 28.6 (q). MS (EI, 200 °C): *m*/*z* (%) 410 (2), 368 (1), 341 (4), 243 (Tr^+, 90), 228 (M^+ − Tr, 10), 198 (78), 183 (35), 165 (50), 142 (94), 105 (32), 98 (93), 81 (86), 69 (100), 57 (92). HRMS: calcd for $C_{19}H_{15}$ (Tr^+) 243.1173, found 243.1178; calcd for $C_{12}H_{22}NO_3$ (M^+ − Tr) 228.1600, found 228.1602.

Formyl(1-trityloxymethylpent-4-enyl)carbamic Acid *tert*-Butyl Ester (*rac*-15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4−7.2 (m, Tr), 5.73 (ddt, J = 16, 10, 6 Hz, 4-H), 4.97 (dd, J = 16, 2 Hz, 5-H), 4.94 (dd, J = 10, 2 Hz, 5-H′), 4.80 (m_c, 1-H), 3.39 (m_c, CH_2OR), 3.20 (dd, J = 8, 5 Hz, CH_2OR), 1.97 (m_c, 3-H_2), 1.83 (m_c, 2-H), 1.59 (m_c, 2-H′), 1.43 (s, Boc). ^{13}C NMR ($CDCl_3$): δ 163.9 (d, formyl), 137.5 (d, C-5), 115.2 (t, C-6), 63.5 (t, C-1), 30.4 (t, C-4), 28.4 (t, C-3); Tr: 143.9 (s), 128.6, 127.9, 126.9 (3d), 86.4 (s); Boc: 152.9 (s), 83.8 (s), 28.0 (q). HRMS: calcd for $C_{31}H_{34}NO_4$ (M^+ − H) 484.2488, found 484.2488.

5-Methoxycarbonylmethyl-2-trityloxymethylpiperidine-1-carboxylic Acid Methyl Ester (*rac*-16). Following the procedure P, *rac*-**10** (90 mg, 0.16 mmol), BP (7 mg), and ADC (7 mg) yielded after purification by FC with MTBE/hexane (1:3, R_f = 0.23) a 1:6 mixture of *rac,cis*- and *trans*-**16** (51 mg, 65%) as a colorless oil. *rac,trans*-**16**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.5−7.3 (m, Tr), 4.54 (m_c, 2-H), 3.86 (d br, J = 14 Hz, 6-H), 3.75 (s, CO_2Me), 3.66 (s, CO_2Me), 3.28 (dd, J = 8, 7 Hz, CH_2OR), 3.14 (dd, J = 8, 6 Hz, CH_2OR), 2.84 (dd, J = 14, 3 Hz, 6-H′), 2.50 (dd, J = 14, 8 Hz, 5-CH_2R), 2.37 (dd, J = 14, 7 Hz, 5-CH_2R), 2.18 (m_c, 5-H), 1.80 (m_c, 3-H), 1.58 (ddd, J = 14, 8, 3 Hz, 3-H′), 1.52 (ddt, J = 14, 8, 4 Hz, 4-H), 1.36 (dbr, J = 14 Hz, 4-H′). ^{13}C NMR ($CDCl_3$): δ 173.2 (s, *C*O_2Me), 157.0 (s, *C*O_2Me), 61.2 (t, *C*H_2OR), 52.5 (q, CO_2*Me*), 51.5 (q, CO_2*Me*), 50.7 (d, C-2), 43.0 (t, C-6), 35.1 (t, 5-CH_2R), 29.6 (d, C-5), 23.5 (t, C-4), 20.6 (t, C-3); Tr: 144.0 (s), 128.6, 127.8, 127.0 (3d), 86.5 (s). HRMS: calcd for $C_{30}H_{34}NO_3$ (M^+ + H) 488.2437, found 488.2433.

7-Methyltetrahydropyrrolo[2,1-*c*][1,4]oxazine-4-one (*rac*-13). Following the procedure P (but irradiation time 12 h), *rac*-**5** (80 mg, 0.35 mmol), BP (16 mg), and ADC (16 mg) yielded after purification by chromatography on SEPHADEX LH-20 with CH_2Cl_2/MeOH gradient (50:1 → 1:1) *rac*-**13** (4 mg, 7%, GC yield 45%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (d, J = 16 Hz, 3-H), 4.14 (dd, J = 12, 4 Hz, 1-H), 4.02 (d, J = 16 Hz, 3-H′), 3.80 (m_c, 9-H), 3.65 (dd, J = 11, 9 Hz, 6-H), 3.24 (t, J = 12 Hz, 1-H′), 3.19 (d, J = 11 Hz, 6-H′), 2.32 (m_c, 7-H), 2.07 (dt, J = 12, 6 Hz, 8-H), 1.14 (d, J = 7 Hz, 7-Me), 1.10 (dt, J = 16, 12 Hz, 8-H′). ^{13}C NMR ($CDCl_3$): δ 69.0 (t, C-1), 67.0 (t, C-3), 57.9 (d, C-9), 51.9 (t, C-6), 37.3 (t, C-8), 31.7 (d, C-7), 17.9 (q, 7-*Me*) (C-4 was not detected). HRMS: calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0943. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.45; N, 9.03. Found: C, 61.23; H, 8.36; N, 8.93.

Benzoyl-Gly-(*N*-Trimethylsilanylmethyl-2-allyl)-Gly-OMe (*rac*-17a).[33] Following the procedure F, *rac*-**2** (108 mg, 0.5 mmol), hippuric acid (116 mg, 0.6 mmol), HABT (82.6 mg), DIC (0.093 mL), DIEA (0.102 mL), and MeCN (10 mL) were used in the coupling reaction. Purification by FC with MTBE/hexane (1:1, R_f = 0.23) afforded *rac*-**17a** (85 mg, 45%, 1:1 mixture of rotamers) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.38/3.81 (dd, J = 9, 6 Hz, 2-H), 3.73/3.72 (s, CO_2-Me); 2-allyl: 5.9−5.6 (m), 5.3−5.0 (m), 2.9−2.5 (m); CH_2TMS: 3.03 (d, J = 16 Hz), 2.9−2.5 (m), 0.17/0.06 (s); benzoyl-Gly-: 7.83 (dd, J = 8, 1 Hz), 7.5−7.3 (m, N−H, Ph), 4.28 (t, J = 4 Hz), 4.18 (dd, J = 12, 4 Hz). ^{13}C NMR ($CDCl_3$): δ 170.2/169.8 (s, *C*O_2Me), 62.3/59.3 (d, C-2), 52.5/52.2 (q, CO_2*Me*); 2-allyl: 134.0/132.0 (d), 119.7/118.4 (t), 33.4/33.2 (t); CH_2TMS: 40.7/35.6 (t), −0.7/−1.9 (q); benzoyl-Gly-:167.9/167.4 (s), 167.2/167.0 (s), 133.8/133.7 (s), 131.6, 128.5/128.4, 127.0 (3d), 42.1/41.9 (t). HRMS: calcd for $C_{19}H_{28}N_2O_4Si$ (M^+) 376.1818, found 376.1819.

FMOC-Gly-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OMe (18a). Following the procedure F, (−)-**2** (108 mg, 0.5 mmol), FMOC-Gly-OH (178 mg, 0.6 mmol), HABT (82.6 mg), DIC (0.093 mL), DIEA (0.102 mL), and MeCN (10 mL) were used in the coupling reaction. Purification was achieved by dissolving the crude product in a minimum amount of MTBE and filtering off the urea. **18a** (244 mg, 99%, 1:1 mixture of rotamers) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.3−3.8 (m, 2-H), 3.74 (s, CO_2Me); 2-allyl: 5.9−5.6 (m), 5.15 (m_c), 2.9−2.5 (m); CH_2TMS: 2.96, 2.70 (2d, J = 16 Hz), 0.17/0.08 (s, TMS); FMOC-Gly-: 7.76 (d, J = 8 Hz), 7.62 (m_c), 7.40, 7.31 (2t, J = 8 Hz), 4.38 (m_c), 4.3−3.8 (m). ^{13}C NMR ($CDCl_3$): δ 170.2/169.8 (s), 167.7/167.2 (s) 156.0 (s), 143.8 (s), 141.2 (s), 134.0/132.0 (d), 127.6 (d), 126.9 (d), 125.1 (d), 119.8 (d), 119.6/118.2 (t), 67.0 (t), 62.1/59.2 (d), 52.4/52.1 (q), 47.0 (d), 42.9/42.7 (t), 40.4 (t), 33.3/33.2 (t); CH_2TMS: 35.6 (t) −0.7/−1.9 (q). HRMS: calcd for $C_{27}H_{34}N_2O_5Si$ (M^+) 494.2237, found 494.2232.

FMOC-Ala-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OMe (18b). Following the procedure F, (−)-**2** (108 mg, 0.5 mmol), FMOC-Ala-OH (186 mg, 0.6 mmol), HABT (82.6 mg), DIC (0.093 mL), DIEA (0.102 mL), and MeCN (10 mL) were used in the coupling reaction. Purification by FC with MTBE/hexane (1:3, R_f = 0.28) afforded **18b** (90 mg, 35%, 1:1 mixture of rotamers) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (m_c)/3.63 (dd, J = 9, 8 Hz, 2-H), 3.74/3.68 (s, CO_2Me); 2-allyl: 5.75 (m_c), 5.15 (m_c), 2.9−2.5 (m); CH_2TMS: 3.09, 2.67 (2d, J = 16 Hz)/2.63, 2.50 (2d, J = 15 Hz), 0.16/0.07 (s, TMS); FMOC-Ala-: 7.76, 7.60 (2d, J = 8 Hz), 7.40, 7.31 (2t, J = 8 Hz), 4.74 (q, J = 7 Hz), 4.35 (m_c), 4.21 (m_c), 1.35/1.33 (d, J = 7 Hz). ^{13}C NMR ($CDCl_3$): δ 170.1 (s, *C*O_2Me), 143.9/143.8 (s), 141.3 (s), 134.1/132.6 (d), 127.6 (d), 127.0 (d), 125.2 (d), 119.6 (d), 119.4/118.5 (t), 67.0/66.8 (t), 62.6/60.0 (d), 52.5/52.1 (q), 47.2/46.7 (d), 42.3 (t), 35.8 (t), 34.1/33.2 (t), 19.7/19.3 (q), −0.7/−2.1 (q, TMS), (−*C*ONR$_2$ and −N*C*OOR were not detected). HRMS: calcd for $C_{28}H_{36}N_2O_5Si$ (M^+) 508.2393, found 508.2389.

FMOC-Phe-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OMe (18c). Following the procedure F, (−)-**2** (108 mg, 0.5 mmol), FMOC-Phe-OH (232 mg, 0.6 mmol), HABT (82.6 mg), DIC (0.093 mL), DIEA (0.102 mL), and MeCN (10 mL) were used in the coupling reaction. Purification by FC with MTBE/hexane (1:4, R_f = 0.26) afforded **18c** (220 mg, 75%, 1:1 mixture of rotamers) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, J = 8 Hz, FMOC), 7.57 (dbr, J = 8 Hz, FMOC), 7.40 (t, J = 8 Hz, FMOC), 7.3−7.2 (m, FMOC, Phe), 5.9−5.6 (m, NH, allyl), 5.43 (ddt, J = 17, 10, 7 Hz, allyl), 5.2−5.0 (m, allyl, Phe), 4.84 (q, J = 7 Hz, Phe), 4.63 (tbr, J = 8 Hz, 2-H), 4.4−4.1 (m, 3H, FMOC), 3.70 (m_c, 2-H), 3.73/3.61 (s, CO_2Me), 3.2−2.4 (m, allyl, CH_2TMS, Phe), 2.15 (m_c, allyl), 0.19/0.09 (s, TMS). ^{13}C NMR ($CDCl_3$): δ 171.3 (s), 170.2/169.9 (s), 155.3/155.1 (s), 143.7/143.6 (s), 141.1/141.0 (s), 136.3/136.0 (s), 134.4/132.5 (d), 129.4/129.3 (d), 128.4/128.3 (d), 127.5/126.9 (d), 125.0/124.9 (d), 119.8 (d), 118.9/117.5 (t), 67.0/66.7 (t), 62.5/60.0 (d), 52.2/51.8 (q), 51.6 (d), 47.0/46.9 (d), 41.4 (t), 39.9/39.6 (t), 35.8 (t), 33.7/33.2 (t), −0.7/−2.3 (q, TMS). HRMS: calcd for $C_{34}H_{40}N_2O_5Si$ (M^+) 584.2707, found 584.2707.

FMOC-Leu-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OMe [(−)-18d]. Following the procedure F, (−)-**2** (285 mg, 1.3 mmol), FMOC-Leu-OH (561 mg, 1.6 mmol), HABT (216 mg), DIC (0.252 mL), DIEA (0.270 mL), and MeCN (10 mL) were used in the coupling reaction. Purification by FC with MTBE/hexane (1:4, R_f = 0.29) afforded (−)-**18d** (420 mg, 76%, 1:1 mixture of rotamers) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8 Hz, FMOC), 7.60 (d, J = 8 Hz, FMOC), 7.40 (t, J = 8 Hz, FMOC), 7.31 (t, J = 8 Hz, FMOC), 5.75 (m_c, allyl), 5.63/5.45 (d, J = 9 Hz, NH), 5.15 (m_c, allyl), 4.79 (ddd, J = 9, 9, 4 Hz, Leu), 4.6 (m_c, 2-H, Leu), 4.35 (m_c, FMOC), 4.16 (m_c, FMOC), 3.67 (m_c, 2-H), 3.70 (s, CO_2Me), 3.10, 2.67 (2 d, J = 16 Hz, CH_2TMS), 2.63 (d, J = 15 Hz, CH_2TMS), 2.85−2.45

(33) For simplification the following abbreviations for the amino acids are used: 2-(trimethylsilanylamino)pent-4-enoic acid: H-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OH; 4-methylpyrrolidine-2-carboxylic acid (4-methylprolin): H-Mpr-OH.

(m, allyl, CH_2TMS), 1.75−1.3 (m, Leu), 1.1−0.9 (m, Leu), 0.16/0.07 (s, TMS). ^{13}C NMR ($CDCl_3$): δ 172.5/171.4 (s), 170.1/170.0 (s), 155.8/155.7 (s), 143.9/143.8 (s), 143.6 (s), 141.1 (s), 134.2/132.7 (d), 127.5 (d), 126.9 (d), 125.0 (d), 119.8 (d), 119.3/118.2 (t), 66.9/66.6 (t), 62.4/60.0 (d), 52.3/51.9 (q), 49.5/48.7 (d), 47.0 (d), 43.4/42.8 (t), 41.8 (t), 35.6 (t), 33.9/33.2 (t), 24.3 (d), 23.5/23.4 (d), 21.7/21.3 (q), −0.8/−2.3 (q, TMS). HRMS: calcd for $C_{31}H_{42}N_2O_5Si$ (M^+) 550.2863, found 550.2864. $[\alpha]_D$ −69° (*c* 1.4, $CHCl_3$).

FMOC-Gly-Gly-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OMe (*rac*-17b). Following the procedure F, *rac*-**2** (350 mg, 1.6 mmol), FMOC-Gly-Gly-OH (691 mg, 1.9 mmol), HABT (265 mg), DIC (0.302 mL), DIEA (0.332 mL), and MeCN (10 mL) were used in the coupling reaction. Purification by FC with CH_2Cl_2/MeOH (50:1, R_f = 0.14) afforded *rac*-**17b** (880 mg, 98%, 1:1 mixture of rotamers) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77, 7.61 (2d, J = 8 Hz, FMOC), 7.40, 7.31 (2t, J = 8 Hz, FMOC), 6.96 (d br, J = 16 Hz, NH), 5.81 (ddt, J = 18, 10, 7 Hz, allyl)/5.70 (ddt, J = 17, 10, 7 Hz, allyl), 5.47 (m_c, NH), 5.25−5.1 (m, allyl), 4.41 (m_c, FMOC), 4.29/3.83 (dd, J = 10, 6 Hz, 2-H), 4.24 (t br, J = 7 Hz, FMOC), 4.2−3.9 (m, 2 × Gly), 3.74/3.72 (s, CO_2Me), 2.96 (d, J = 16 Hz, CH_2TMS), 2.85−2.55 (m, allyl, CH_2TMS), 0.16/0.05 (s, TMS). ^{13}C NMR ($CDCl_3$): δ 170.1/169.7 (s, *C*O_2Me), 62.1/59.2 (d, C-2), 52.4/52.1 (q, CO_2*Me*); FMOC: 156.4, 143.7, 141.1 (3 s), 127.5, 126.9, 125.0, 119.8 (4d), 67.1 (t), 46.9 (d); 2-allyl: 133.9/132.0 (d), 119.6/118.2 (t), 33.3/33.1 (t); Gly: 168.8 (s), 167.5/167.0 (s), 44.1 (t), 41.4/41.2 (t); CH_2TMS: 40.5/35.5 (t), −0.8/−1.9 (q). HRMS: calcd for $C_{29}H_{37}N_3O_6Si$ (M^+) 551.2452, found 551.2439.

FMOC-Gly-Gly-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-Gly-Gly-NH_2 (*rac*-19). Saponification of the Methyl Ester *rac*-17b. A solution of LiOH (0.3 N, 16 mL) was added to a solution of *rac*-**17b** (880 mg, 1.6 mmol) in THF (20 mL) at 0 °C. After 30 min at 0 °C the reaction mixture was added to HCl (0.3 N, 50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The colorless solid (704 mg) obtained after evaporation of the solvent was used without purification for the next step. Peptide coupling: 150 mg (0.28 mmol) of the solid, HABT (41 mg, 0.28 mmol), DIC (0.048 mL, 0.28 mmol), and DIEA (0.047 mL, 0.28 mmol) were dissolved in DMF (5 mL). After 30 min a suspension of H-Gly-Gly-NH_2*HCl (94 mg, 0.56 mmol) and DIEA (0.031 mL, 0.18 mmol,) in DMF (2 mL) was added. After 2 h the reaction mixture was added to Et_2O (10 mL), and the crude product was obtained by filtration. Purification by FC with CH_2Cl_2/MeOH (50:1 → 1:1) afforded *rac*-**19** (105 mg, 57%, 5:1 mixture of rotamers) as a colorless powder. ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (s br, NH), 7.75 (d, J = 8 Hz, FMOC), 7.6 (m_c, FMOC), 7.38, 7.29 (2t br, J = 8 Hz, FMOC), 6.98, 6.56 (2s br, NH), 5.8−5.6 (m, allyl), 5.15 (m_c, allyl), 4.54 (dd, J = 10, 6 Hz, 2-H), 4.4 (m_c, FMOC), 4.25−3.6 (m, FMOC, 4 × Gly, CH_2TMS, 2-H), 3.01, 2.80 (2 d, J = 16 Hz, CH_2TMS), 2.9−2.45 (m, CH_2TMS, allyl), 0.18/0.01 (s, TMS). ^{13}C NMR ($CDCl_3$): δ 173.0/172.5 (s, *C*O_2Me), 63.5/60.2 (d, C-2); FMOC: 156.9, 143.7, 141.2 (3 s), 127.7, 127.0, 125.1, 119.9 (4 d), 67.1 (t), 47.0 (d); 2-allyl: 133.8/133.1 (d), 119.4/118.2 (t), 33.0/32.7 (t); CH_2TMS: 41.2/35.7 (t), −0.6/−1.6 (q, TMS); Gly: 170.7, 170.2, 169.3, 168.0 (4s), 44.1, 43.5, 42.6, 41.7 (4t). MS (FAB, *m*-nitrobenzyl alcohol): *m*/*z* (%) 673 (M^+ + Na, 10), 651 (M^+ + H, 20), 520 (M^+ − [NH-Gly-Gly-NH_2], 30).

FMOC-Leu-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-Leu-Leu-Leu-Leu-NH_2 (20). Saponification of the Methyl Ester (−)-18d. A solution of LiOH (4 N, 5 mL) was added to a solution of (−)-**18d** (590 mg, 1.1 mmol) in THF (10 mL) and water (5 mL). After 5 h HCl (6 N, 3 mL) was added, followed by a saturated Na_2CO_3 solution (5 mL) and a solution of FMOC−Cl (312 mg) in THF (5 mL). After 3 h the reaction mixture was acidified (pH = 2) and extracted with EtOAc (10 × 20 mL). Purification by FC with CH_2Cl_2/MeOH (gradient, 50:1 → 1:1) afforded FMOC-Leu-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OH (424 mg, 72%) as a colorless solid. IR (ATR, cm^{-1}): ν 3307 (w), 1718 (s), 1640 (m), 1599 (m), 759 (m), 740 (s). HRMS: calcd for $C_{30}H_{40}N_2O_5Si$ 536.2707, found 536.2707. Peptide coupling: Following the procedure F, FMOC-Leu-(*N*-trimethylsilanylmethyl-2-allyl)-Gly-OH (250 mg. 0.47 mmol), H-Leu-Leu-Leu-Leu-NH_2*CF_3CO_2H (247 mg, 0.42 mmol), HABT (64 mg), DIC (0.073 mL), DIEA (0.100 mL), and MeCN (10 mL) were used in the coupling reaction. Purification by crystallization (MeOH, Et_2O) afforded **20** (512 mg, 81%, 1:2 mixture of rotamers) as a colorless powder. ^1H NMR (400 MHz, D_3COD): δ 7.8 (m_c, FMOC), 7.6 (m_c, 6 H, FMOC), 7.4 (m_c, 6 H, FMOC), 7.3 (m_c, 6 H, FMOC), 5.9 (m_c, 1 H, 2-H), 5.7 (m_c, 2 H), 5.2−5.0 (m, 6 H), 4.7−4.55 (m, 3 H), 4.4−4.0 (m, 12 H), 3.00 (d, J = 16 Hz, 1 H), 2.6−2.45 (m, 11 H), 1.8−1.45 (m, 45 H), 1.0−0.8 (m, 90 H), 0.16 (s, 9 H, TMS), 0.07 (s, 18 H, TMS). IR (ATR, cm^{-1}): ν 3355 (m), 1526 (s), 1350 (s), 803 (m), 731 (m). MS (FAB, *m*-nitrobenzyl alcohol): *m*/*z* (%) 1011 (M^+ + Na, 12), 989 (M^+ + H, 30), 973 (M^+ − Me, 100). CD (*c* = 0.76 mM in TFE) λ_{max} [nm] (mol. ellip.): 186 (210681), 200 (−47663), 213 (39469), 237 (−42408).

Benzoyl-Gly-Mpr-OMe (*rac*-21a). Following the procedure P, *rac*-**17a** (82 mg, 0.22 mmol), BP (10 mg), and ADC (10 mg) yielded after purification by FC with $CHCl_3$/EtOAc (2:1, R_f = 0.29) a 1:3 mixture of *rac*,*cis*- and *trans*-**21a** (14 mg, 24%) as a colorless oil. HRMS: calcd for $C_{16}H_{20}N_2O_4$ (M^+) 304.1423, found 304.1424. *rac*,*trans*-**21a**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, J = 8 Hz, Ph), 7.54, 7.47 (2 t, J = 8 Hz, Ph), 7.24 (s br, NH), 4.66 (dd, J = 10, 2 Hz, 2-H), 4.4−4.2 (m, Gly), 3.85 (m_c, 5-H), 3.77 (s, CO_2Me), 3.13 (dd, J = 9, 9 Hz, 5-H′), 2.6 (m_c, 4-H), 2.20 (ddd, J = 13, 6, 2 Hz, 3-H), 1.91 (dt, J = 13, 10 Hz, 3-H′), 1.16 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 172.2 (s, *C*O_2Me), 167.2 (s, Gly), 133.8 (s, Ph), 133.6, 128.5, 127.1 (3d, Ph), 59.1 (d, C-2), 52.8 (t, C-5), 52.3 (q, CO_2*Me*), 42.4 (t, Gly), 36.7 (t, C-3), 32.5 (d, C-4), 17.2 (q, 4-*Me*). Differing values of *rac*,*cis*-**21a**: ^1H NMR: δ 4.49 (dd, J = 10, 10 Hz, 2-H), 3.78 (s, CO_2Me), 3.22 (dd, J = 10, 10 Hz, 5-H′), 2.5 (m_c, 3-H), 2.45 (m_c, 4-H), 1.65 (dt, J = 12, 10 Hz, 3-H′), 1.19 (d, J = 7 Hz, 4-Me). ^{13}C NMR: δ 172.4 (s, *C*O_2Me), 59.6 (d, C-2), 53.1 (t, C-5), 52.4 (q, CO_2*Me*), 37.1 (t, C-3), 33.8 (d, C-4), 16.8 (q, 4-*Me*).

FMOC-Gly-Mpr-OMe (22a). Following the procedure P, **18a** (88 mg, 0.18 mmol), BP (10 mg), and ADC (10 mg) yielded after purification by FC with MTBE/hexane (3:1, R_f = 0.33) a 1:2 mixture of *cis*- and *trans*-**22a** (25 mg, 33%) as a colorless oil. HRMS: calcd for $C_{24}H_{26}N_2O_5$ (M^+) 422.1842, found 422.1845. *trans*-**22a**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.81, 7.65 (2d, J = 8 Hz, FMOC), 7.44, 7.35 (2t, J = 8 Hz, FMOC), 5.80 (m_c, NH), 4.64 (dd, J = 10, 2 Hz, 2-H), 4.41 (d, J = 8 Hz, FMOC), 4.27 (t br, J = 8 Hz, FMOC), 4.1 (m_c, Gly), 3.9−3.7 (m, 5-H), 3.75 (s, CO_2Me,), 3.07 (dd, J = 9, 9 Hz, 5-H′), 2.45 (m_c, 4-H), 2.18 (ddd, J = 13, 6, 2 Hz, 3-H), 1.88 (dt, J = 13, 10 Hz, 3-H′), 1.14 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 172.2 (s, *C*O_2Me), 58.9 (d, C-2), 52.6 (t, C-5), 52.2 (q, CO_2*Me*), 36.6 (t, C-3), 32.3 (d, C-4), 17.0 (q, 4-*Me*); FMOC: 156.1, 143.7, 141.1 (3 s), 127.5, 127.0, 125.0, 119.8 (4d), 67.0 (t), 46.9 (d); Gly: 166.9 (s), 43.2 (t br). Differing values of *cis*-**22a**: ^1H NMR: δ 4.46 (dd, J = 9, 9 Hz, 2-H), 3.9−3.7 (m, 5-H), 3.76 (s, CO_2Me,), 3.15 (m_c, 5-H′), 2.6−2.3 (m, 3-H, 4-H), 1.62 (dt, J = 12, 10 Hz, 3-H′), 1.17 (d, J = 7 Hz, 4-Me). ^{13}C NMR: δ 172.2 (s, *C*O_2Me), 59.4 (d, C-2), 52.8 (t, C-5), 52.7 (q, CO_2*Me*), 36.8 (t, C-3), 33.7 (d, C-4), 16.7 (q, 4-*Me*).

FMOC-Ala-Mpr-OMe (22b). Following the procedure P, **18b** (60 mg, 0.12 mmol), BP (5 mg), and ADC (5 mg) yielded after purification by FC with MTBE/hexane (3:2, R_f = 0.13) a 1:2 mixture of *cis*- and *trans*-**22b** (30 mg, 57%) as a colorless oil. HRMS: calcd for $C_{25}H_{28}N_2O_5$ (M^+) 436.1998, found 436.2001. *trans*-**22b**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.81, 7.64 (2d, J = 8 Hz, FMOC), 7.44, 7.31 (2t, J = 8 Hz, FMOC), 5.75 (d br, J = 8 Hz, NH), 4.66 (dd, J = 9, 3 Hz, 2-H), 4.6 (m_c, Ala), 4.38 (d br, J = 7 Hz, FMOC), 4.26 (t br, J = 7 Hz, FMOC), 3.82 (dd, J = 9, 8 Hz, 5-H), 3.78 (s, CO_2Me), 3.27 (dd, J = 9, 9 Hz, 5-H′), 2.55 (m_c, 4-H), 2.16 (ddd, J = 12, 6, 3 Hz, 3-H), 1.89 (dt, J = 12, 9 Hz, 3-H′), 1.45 (m_c, Ala), 1.13 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 172.3 (s, *C*O_2Me), 58.7 (d, C-2), 53.5 (t, C-5), 52.2 (q, CO_2*Me*), 36.4 (t, C-3), 32.6 (d, C-4), 17.2 (q, 4-*Me*); FMOC: 155.6, 143.8, 141.3 (3 s), 127.7, 127.0, 125.1, 119.9 (4 d), 67.0 (t), 47.1 (d); Ala: 171.3 (s), 48.2 (d), 18.4 (q). Differing values for *cis*-**22b**: ^1H NMR: δ 5.81 (d br, J = 8 Hz, NH), 4.49 (dd, J = 8, 8 Hz, 2-H), 3.94 (dd, J = 10, 8 Hz, 5-H), 3.79 (s, CO_2Me), 3.18 (dd, J = 10, 10 Hz, 5-H′), 2.5 (m_c, 3-H), 2.4

(m_c, 4-H), 1.6 (m_c, 3-H′), 1.16 (d, J = 7 Hz, 4-Me). ^{13}C NMR: δ 172.3 (s, *C*O_2Me), 59.5 (d, C-2), 54.0 (t, C-5), 52.3 (q, CO_2*Me*), 37.0 (t, C-3), 34.0 (d, C-4), 16.6 (q, 4-*Me*).

FMOC-Phe-Mpr-OMe (22c). Following the procedure P, **18c** (97 mg, 0.17 mmol), BP (8 mg), and ADC (8 mg) yielded after purification by FC with MTBE/hexane (1:1 R_f = 0.16) a 2:3 mixture of *cis*- and *trans*-**22c** (30 mg, 51% yield on 70% conversion) as a colorless oil. HRMS: calcd for $C_{31}H_{32}N_2O_5$ (M^+) 512.2311, found 512.2312. *trans*-**22c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8 Hz, FMOC), 7.6−7.25 (m, FMOC, Phe), 5.8−5.6 (m, NH), 4.79/4.75 (q, J = 8 Hz, Phe), 4.63 (dd, J = 9, 3 Hz, 2-H), 4.5−4.2 (m, 3 H, FMOC), 3.78 (s, CO_2Me), 3.40 (t br, J = 8 Hz, 5-H), 3.2−3.1 (m, 5-H, Phe), 3.05 (m_c, Phe), 2.5−2.3 (m, 4-H), 2.12 (ddd, J = 12, 6, 3 Hz, 3-H), 1.83 (dt, J = 12, 9 Hz, 3-H′), 1.15 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 172.2 (s, *C*O_2Me), 58.9 (d, C-2), 53.6 (t, C-5), 52.1 (q, CO_2*Me*), 36.5 (t, C-3), 32.6 (d, C-4), 17.0 (q, 4-Me); FMOC: 155.6, 143.8, 141.2 (3 s), 127.6, 127.0, 125.1, 119.9 (4 d), 67.1 (t), 47.1 (d); Phe: 170.3, 136.0 (2 s), 129.8, 129.7, 128.4 (3 d), 53.8 (d), 39.0 (t). Differing values for *cis*-**22c**: ^{1}H NMR: δ 3.86 (ddbr, J = 9, 8 Hz, 5-H), 3.79 (s, CO_2Me), 2.68 (dd, J = 9, 9 Hz, 5-H′), 2.5−2.3 (m, 3-H, 4-H′), 1.54 (ddd br, J = 9, 9, 9 Hz, 3-H′), 1.15 (d, J = 7 Hz, 4-Me). ^{13}C NMR: δ 172.2 (s, *C*O_2Me), 59.8 (d, C-2), 52.6 (t, C-5), 52.2 (q, CO_2*Me*), 37.0 (t, C-3), 33.7 (d, C-4), 17.3 (q, 4-*Me*).

FMOC-Leu-Mpr-OMe (22d). Following the procedure P, (−)-**18d** (100 mg, 0.18 mmol), BP (8 mg), and ADC (8 mg) yielded after purification by FC with MTBE/hexane (1:1, R_f = 0.23) a 1:2 mixture of *cis*- and *trans*-**22d** (60 mg, 70%) as a colorless oil. HRMS: calcd for $C_{25}H_{28}N_2O_5$ (M^+) 478.2468, found 478.2468. *trans*-**22d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76, 7.59 (2d, J = 8 Hz, FMOC), 7.39, 7.30 (2 t, J = 8 Hz, FMOC), 5.46 (d br, J = 9 Hz, NH), 4.61 (dd, J = 9, 3 Hz, 2-H), 4.53 (ddd, J = 14, 9, 5 Hz, Leu), 4.5−4.3 (m, FMOC), 4.21 (tbr, J = 8 Hz, FMOC), 3.77 (dd, J = 9, 8 Hz, 5-H), 3.73 (s, CO_2Me), 3.29 (dd, J = 9, 9 Hz, 5-H′), 2.5 (m_c, 4-H), 2.11 (ddd, J = 12, 6, 3 Hz, 3-H), 1.9−1.7 (m, 3-H′, Leu), 1.55 (m_c, Leu), 1.09 (d, J = 7 Hz, 4-Me), 1.03/0.98 (d, J = 6 Hz, Leu). ^{13}C NMR ($CDCl_3$): δ 172.4 (s, *C*O_2Me), 58.8 (d, C-2), 53.5 (t, C-5), 52.2 (q, CO_2*Me*), 36.6 (t, C-3), 32.7 (d, C-4), 17.3 (q, 4-*Me*); FMOC: 155.3, 143.9, 141.3 (3 s), 127.7, 127.1, 125.2, 120.0 (4 d), 67.1 (t), 47.2 (d); Leu: 171.6 (s), 50.8 (d), 42.0 (t, C-8), 24.6 (q), 22.0 (d). Differing values for *cis*-**22d**: ^{1}H NMR: δ 4.43 (dd, J = 9, 9 Hz, 2-H), 3.98 (dd, J = 9, 7 Hz, 5-H), 3.74 (s, CO_2Me), 3.12 (dd, J = 10, 9 Hz, 5-H′), 2.4 (m_c, 3-H), 2.35 (m_c, 4-H), 1.12 (d, J = 7 Hz, 4-Me). ^{13}C NMR: δ 172.5 (s, *C*O_2Me), 59.5 (d, C-2), 54.1 (t, C-5), 52.3 (q, CO_2*Me*), 37.2 (t, C-3), 34.1 (d, C-4), 16.7 (q, 4-*Me*).

FMOC-Gly-Gly-Mpr-OMe (*rac*-21b). Following the procedure P, *rac*-**17b** (60 mg, 0.11 mmol), BP (5 mg), and ADC (5 mg) yielded after purification by FC with CH_2Cl_2/MeOH (50:1 → 10:1) a 1:2 mixture of *rac,cis*- and *trans*-**21b** (25 mg, 55%) as a colorless oil. HRMS: calcd for $C_{26}H_{29}N_3O_6$ (M^+) 479.2056, found 479.2055. *rac,trans*-**21b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8 Hz, FMOC), 7.6 (m_c, FMOC), 7.38, 7.30 (2t br, J = 8 Hz, FMOC), 6.9 (m_c, NH), 5.6 (m_c, NH), 4.56 (dd br, J = 10, 3 Hz, 2-H), 4.45 (m_c, FMOC), 4.42 (d, J = 7 Hz, FMOC), 4.2−3.6 (m, 5 H, 5-H, 2 × Gly), 3.75 (s, CO_2Me), 3.01 (dd, J = 9, 9 Hz, 5-H′), 2.5 (m_c, 4-H), 2.21 (ddd, J = 13, 6, 3 Hz, 3-H), 1.80 (ddd, J = 13, 10, 10 Hz, 3-H′), 1.08 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 172.1 (s, *C*O_2Me), 59.1 (d, C-2), 52.8 (t, C-5), 52.4 (q, CO_2*Me*), 36.6 (t, C-3), 32.4 (d, C-4), 17.1 (q, 4-*Me*); FMOC: 156.4, 143.8, 141.3 (3 s), 127.7, 127.1, 125.1, 120.0 (4 d), 67.0 (t), 47.1 (d); Gly: 168.9, 166.7 (2 s), 44.2, 41.8 (2 t br). Differing values for *rac,cis*-**21b**: ^{1}H NMR: δ 3.76 (s, CO_2Me), 3.12 (m_c, 5-H′), 2.5−2.3 (m, 3-H, 4-H), 1.56 (ddd, J = 12, 10, 10 Hz, 3-H′), 1.11 (d, J = 7 Hz, 4-Me). ^{13}C NMR: δ 172.3 (s, *C*O_2Me), 59.5 (d, C-2), 53.2 (t, C-5), 53.0 (q, CO_2*Me*), 37.0 (t, C-3), 33.7 (d, C-4), 16.8 (q, 4-*Me*).

FMOC-Gly-Gly-Mpr-Gly-Gly-NH$_2$ (*rac*-23). Following the procedure P, *rac*-**19** (80 mg, 0.12 mmol), BP (6 mg), and ADC (6 mg) yielded after purification by crystallization (Et_2O/MeOH) a 1:3 mixture of *rac,cis*- and *trans*-**23** (60 mg, 86%) as a colorless powder. MS (FAB, *m*-nitrobenzyl alcohol): *m*/*z* (%) 601 (M^+ + Na, 100). *rac,trans*-**23**: ^{1}H NMR (500 MHz, $CD_3OD/CDCl_3$): δ 7.69 (d, J = 8 Hz, FMOC), 7.55 (m_c, FMOC), 7.33, 7.24 (2t br, J = 8 Hz, FMOC), 4.4−4.3 (m, 2-H, FMOC), 4.16 (t, J = 7 Hz, FMOC), 4.1−3.6 (m, 5-H, 4 × Gly), 3.02 (dd, J = 9, 9 Hz, 5-H′), 2.5 (m_c, 4-H), 2.09 (ddd, J = 13, 6, 4 Hz, 3-H), 1.78 (ddd, J = 13, 9, 9 Hz, 3-H′), 1.03 (d, J = 7 Hz, 4-Me). ^{13}C NMR ($CDCl_3$): δ 170.0 (s, *C*ONR), 60.8 (d, C-2), 53.1 (t, C-5), 36.2 (t, C-3), 32.5 (d, C-4), 16.8 (q, 4-*Me*); FMOC: 157.1, 143.5, 141.0 (3 s), 127.5, 126.8, 124.7, 119.7 (4 d), 66.7 (t), 47.1 (d); Gly: 168.5 (s), 43.6, 42.6, 41.7, 41.4 (4 t). Differing values for *cis*-**23**: ^{1}H NMR: δ 4.2 (m_c, 2-H), 3.10 (dd, J = 10, 10 Hz, 5-H′), 2.35 (m_c, 3-H, 4-H), 1.6−1.4 (m, 3-H′), 1.08 (d, J = 7 Hz, 4-Me). ^{13}C NMR: δ 61.7 (d, C-2), 53.3 (t, C-5), 36.9 (t, C-3), 33.5 (d, C-4) 16.1 (q, 4-*Me*).

FMOC-Leu-Mpr-Leu-Leu-Leu-Leu-NH$_2$ (24). Following the procedure P, **20** (95 mg, 0.1 mmol), BP (4 mg), and ADC (4 mg) yielded after purification by crystallization (MeOH/water) a 2:1 mixture of *cis*- and *trans*-**24** (56 mg, 64%) as a colorless powder. No NMR spectra were obtained. Qualitative amino acid analysis (**22d** and a mixture of Pro and Leu was used as reference): L-Leu (t_R = 7.276, greatest peak), *trans*-L-4-methylprolin (t_R = 12.933), *cis*-L-4-methylprolin (t_R = 13.675, double area of *trans* isomer). IR (CH_2Cl_2): ν (cm^{-1}) 3272 (m), 1632 (s), 1533 (m), 1450 (m). MS (FAB, *m*-nitrobenzyl alcohol): *m*/*z* (%) 939 (M^+ + Na). CD (c = 0.23 mM in TFE) λ_{max} [nm] (mol. ellip.): 190 (114567), 203 (−94283), 230 (sh, −27275).

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