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Synthesis of α-Amino-γ-lactams through Pd-Catalzed Intramolecular Allylic Alkylation of Sarcosine Allyl Amides

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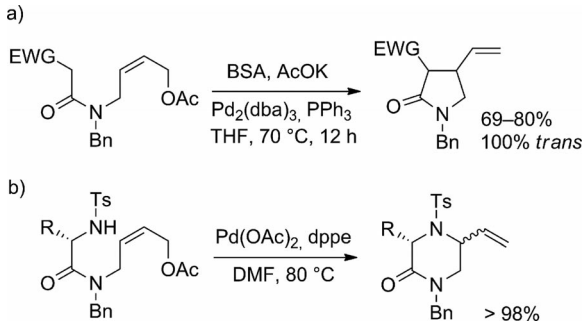
N-Protected amino acid allyl amides with an allylic leaving group can be used as substrates in palladium-catalyzed allylic alkylation. Whereas intermolecular allylations proceed with excellent yields under standard conditions for enolate reactions, the intramolecular version is not a trivial issue. *N*-Protected glycine amides preferentially form piperidinones through *N*-allylation, but the corresponding sarcosine derivatives provide γ-lactams in acceptable to good yields in dichloromethane, especially when the corresponding titanium enolates are formed.

Introduction

Allylic alkylations are definitely one of the most popular palladium-catalyzed reactions,[1] and a wide range of mechanistic investigations as well as synthetic applications have been reported during the last decades.[2] In addition to intermolecular alkylations, a variety of intramolecular protocols have also been developed that have provided access to macrocycles,[3] polycycles,[4] or heterocycles[5] of different ring size. In general, a stabilized carbanion (malonate, β-keto ester, disulfone, etc.) is generated in a molecule containing an allylic leaving group such as an allyl carbonate or a vinyl epoxide. According to this protocol, Poli et al. investigated cyclizations of functionalized malonamides in great detail (Scheme 1, a).[6] They observed, that strongly electron-withdrawing groups (COOR, COR, CN, SO_2Ph) gave the cyclic product in yields of 70–80%, whereas weaker electron-withdrawing groups such as chloride failed to undergo cyclization. In the latter case the formation of the dienamide under the basic conditions was the major side reaction.[7] The yield could be increased by transmetallation of the carbanion to Ti[8] or by using phase-transfer conditions.[9] This approach gives direct access to γ-lactams in a highly diastereoselective fashion. Such γ-lactams are not only interesting as synthetic building blocks, but are also found in a number of natural products.[10] In addition, γ-lactams can also be introduced into, for example, peptidic drugs, optimizing the pharmacological properties of these compounds.[11] Their incorporation, in general, results in a rigidification of the peptide backbone, and freezing of the active conformation can improve the biological activity.[12] For this purpose it would be advantageous if such intramolecular allylic alkylations could be carried out with amino acid derivatives. The analogous reactions using *N*-protected amino acid amides were also investigated by Poli et al., but with these substrates not a *C*-allylation but rather an *N*-allylation of the deprotonated amide was observed (Scheme 1, b).[13]



Scheme 1. Intramolecular allylic alkylations of *N*-allylamides.

Our group is also involved in natural product synthesis focusing on peptidic structures, and our aim is the development of new synthetic protocols for the synthesis of unusual and/or highly functionalized amino acids and peptides.[14] For an efficient modification of natural products or drugs (for SAR studies) it is important to introduce the desired variations as late as possible in the synthesis to save both human and financial resources. The ideal situation would be the modification of a natural product/drug precursor in the very last step. An early realization of this approach was reported by Seebach et al. with the stereoselective methylation of cyclosporine in 1993.[15] During the last years we developed several protocols for transition-metal-catalyzed allylic alkylations of chelated amino acid ester enolates.[16] Besides the popular Pd-catalysts, Rh-[17] and Ru complexes[18] can also be applied, and the great advantage of the chelated ester enolates results from their much higher

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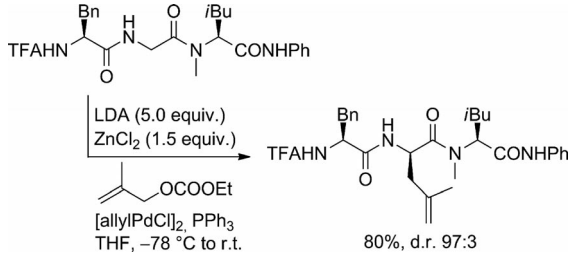
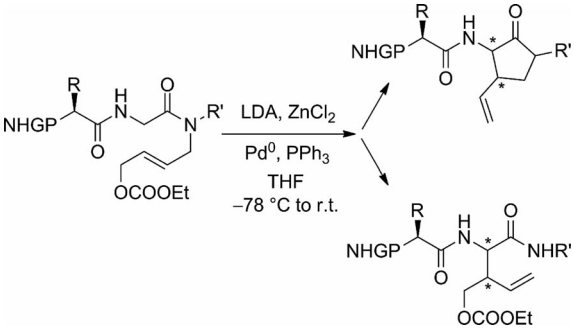
stability and reactivity.[19] The generally used glycine ester enolates react with π-allyl complexes at –78 °C (or even lower), allowing side reactions such as isomerizations to be suppressed.[20] The substrate spectrum could also be increased by using deprotonated peptide esters, which can be regio- and stereoselectively allylated at a C-terminal glycine unit.[21] The stereochemical outcome of this process can be controlled by the stereogenic centers of the peptide chain. Very recently, we could show that peptides can also be allylated at a central glycine unit, as long as it is connected to a secondary amino acid (proline or *N*-alkyl amino acid), which allows the formation of an amide enolate (Scheme 2).[22]



Scheme 2. Stereo- and regioselective allylic alkylation of peptides.

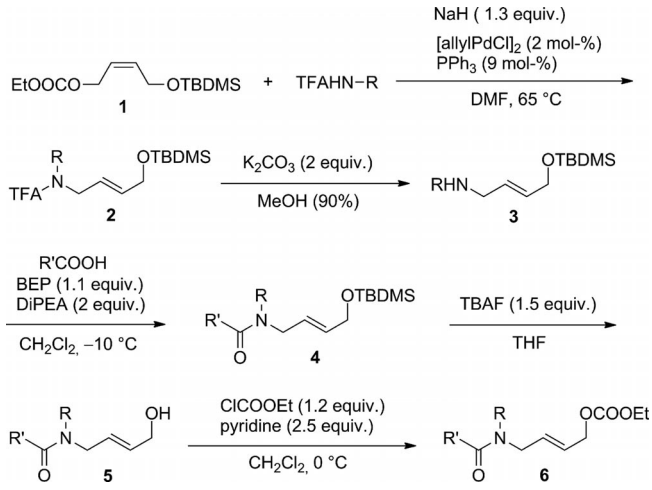
Results and Discussion

We were interested to see whether the reaction conditions developed for intramolecular allylic alkylations were also suitable for intramolecular reactions of peptidic *N*-allyl amides. This approach would allow the direct incorporation of γ-lactams into a peptide chain. Alternatively, the *N*-alkylated amides may undergo a Claisen rearrangement,[23] resulting in the formation of allylated peptides (Scheme 3).[24]



Scheme 3. Possible reaction pathways of peptidic *N*-allylamides.

To investigate the reaction behavior of such allyl amides, we synthesized a selection of amino acid derivatives with different *N*-protecting groups (Scheme 4). The yields obtained in the different reaction steps are summarized in Table 1. Starting from monosilyl-protected allyl carbonate **1**,[25] the amine functionality was introduced through Pd-catalyzed *N*-allylation of *N*-trifluoroacetylated amines.[26] This approach allowed the introduction of different *N*-alkyl groups (**2a**–**c**). Saponification of the trifluoroacetic acid (TFA) group resulted in free secondary amines **3**, which could be coupled to a range of protected amino acids. In general, 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) was used as coupling reagent, giving excellent yields for secondary amines and *N*-alkylated amino acids.[27] However, other coupling reagents such as propylphosphonic anhydride (T_3P) could also be used with comparable success (entry 6).[28] The carbonate functionality was introduced according to standard procedures in high overall yield.



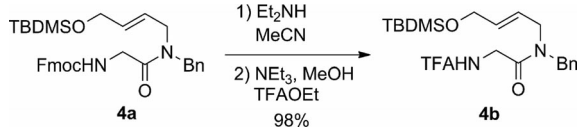
Scheme 4. Synthesis of several *N*-alkyl allylamides.

Because the TFA-protected glycine derivatives always gave the best results in allylic alkylations, we first tried to obtain the corresponding TFA-amide **4b** by using this protocol. Unfortunately, the yields obtained were moderate (max. 40%), probably because of competitive azlactone formation. Therefore, we decided to make a detour via the corresponding Fmoc amide **4a**, which could be converted into the TFA-derivative **4b** in almost quantitative yield (Scheme 5).

Table 1. Preparation of allyl amides **6**.

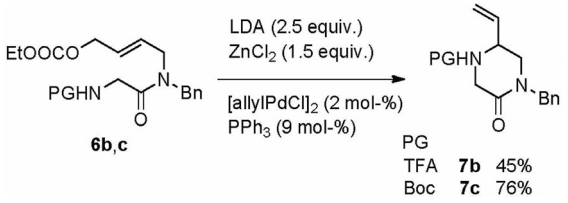
Entry	R	Yield [%]				R′COOH	Yield [%]				
		2		**3**			**4**		**5**		**6**
1	Bn	**2a**	88	**3a**	99	Fmoc-Gly	**4a**	76			
2	Bn					TFA-Gly	**4b**	98	**5b**	93	**6b** 96
3	Bn					Boc-Gly	**4c**	84	**5c**	82	**6c** 96
4	Bn					Boc-β-Ala	**4d**	85	**5d**	85	**6d** 94
5	Bn					Boc-Sar	**4e**	81	**5e**	93	**6e** 90
6	Me	**2b**	64	**3b**	91	Boc-Sar	**4f**	99[a]	**5f**	84	**6f** 85
7	$(CH_2)_2OTHP$	**2c**	95	**3c**	89	Boc-Sar	**4g**	94	**5g**	99	**6g** 85

[a] T_3P was used as coupling reagent.



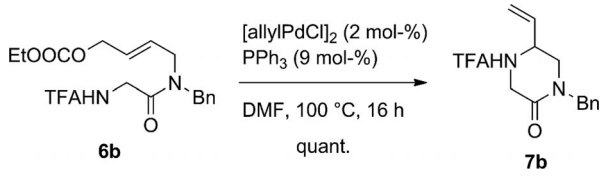
Scheme 5. Synthesis of TFA-protected glycine allylamide **4b**.

With these allylamides in hand, we first undertook experiments concerning the desired intramolecular allylation. Amide **6b** was subjected to the optimized reaction conditions for intermolecular allylic alkylation. However, in contrast to these, no reaction was observed at low temperature, and when the reaction mixture was warmed to room temperature only 25% starting material could be recovered. Clearly the long reaction time and high temperature results in cleavage of the TFA group by the base. We made similar observations previously during our work on peptide Claisen rearrangements.[24] When the reaction mixture was heated to reflux, the starting material was completely consumed and piperidinone **7b** was obtained in moderate yield (Scheme 6). The same reaction was also carried out with the Boc-protected derivative **6c**, which was expected to be more stable towards decomposition, and in this case the corresponding product **7c** was obtained in higher yield. These results are consistent with the observations described by Poli et al.[13]



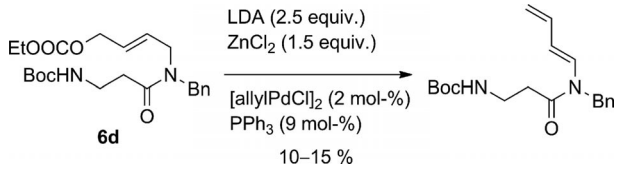
Scheme 6. Intramolecular *N*-allylation of allylamides **6**.

Whereas Boc-protected derivative **6c** required strong base for deprotonation, the TFA-derivative **6b** probably does not. Based on the high acidity of the latter, it should be deprotonated by the alcoholate formed in the π-allyl complex formation step. To investigate this option, we heated **6b** in the presence of the Pd-catalyst without additional base and found that, indeed, piperidinone **7b** was obtained in quantitative yield under these completely neutral reaction conditions (Scheme 7).



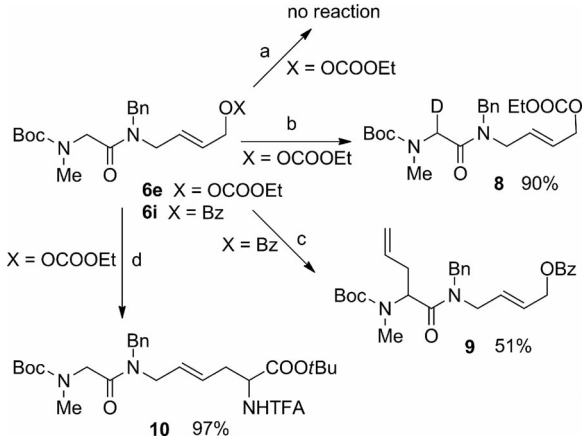
Scheme 7. Intramolecular *N*-allylation of TFA-protected allylamide **6b**.

Considering that this was actually not the reaction we were looking for, we next tried to roll back this undesired side reaction by replacing the glycine by a β-alanine. Here, the *N*-allylation should result in the formation of a seven-membered ring, a process that is probably slower than the six-membered ring cyclization. Unfortunately, this reaction also failed and, although we varied a wide range of reaction parameters (base, chelating metal salt, solvent, temperature), in all cases a more or less inseparable mixture of products was obtained. As one of them, the dienylamide could be detected, which was obtained through elimination under the strong basic reactions conditions (Scheme 8).[7]



Scheme 8. Formation of dienylamides.

Another option to suppress amide deprotonation/cyclization is replacement of the acidic proton by an alkyl group. In this case the amount of base can be reduced (in theory) to slightly more than 1 equiv. Therefore, we next examined the use of *N*-methylated analogue **6e** (sarcosine, Sar). As expected, no *N*-allylation occurred but, interestingly, also no elimination such as in Scheme 8 was observed (Scheme 9). Only starting material was recovered, even when the reaction mixture was heated to reflux overnight. This observation made us question whether the enolate was formed at all. To investigate this, we deprotonated **6e** with various amounts of LHMDS and quenched the reaction mixture with D_2O. Interestingly, with 1.5 equiv. of base no D-incorporation at the α-position of the sarcosine was observed. Clearly, under these conditions the enolate is not formed, which explains the recovery of the starting material in the previous example. Even with 2.5 equiv. base only



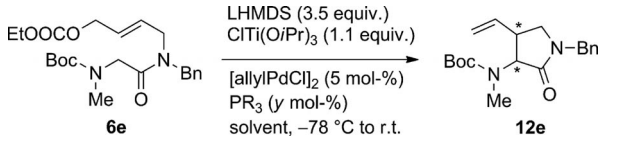
Scheme 9. Reactions of sarcosin allyl amides. *Reagents and conditions:* (a) 1. LHMDS (1.5 equiv.), $ZnCl_2$ (1.5 equiv.), $[allylPdCl]_2$ (2 mol-%), PPh_3 (4 mol-%), THF, –78 °C to room temp.; 2. THF, 55 °C, 16 h. (b) 1. LHMDS (3.5 equiv.), $ZnCl_2$ (1.5 equiv.), $[allylPdCl]_2$ (2 mol-%), PPh_3 (4 mol-%), THF, –78 °C, 3 h; 2. D_2O. (c) 1. LHMDS (3.5 equiv.), $ZnCl_2$ (1.5 equiv.), allyl ethyl carbonate (1.0 equiv.), $[allylPdCl]_2$ (2 mol-%), PPh_3 (4 mol-%), THF, –78 °C to room temp., 16 h. (d) 1. TFA-Gly-O*t*Bu (1.0 equiv.), LHMDS (2.5 equiv.), $ZnCl_2$ (1.5 equiv.), THF, –78 °C, 30 min; 2. **6e**, $[allylPdCl]_2$ (1 mol-%), PPh_3 (4.5 mol-%), THF, –78 °C to room temp., 16 h.

around 50% D-incorporation occurred, but with 3.5 equiv. LHMDS incorporation was complete (**8**). Clearly, a relatively large excess of base is required for complete deprotonation. However, even under these conditions the Pd-catalyzed cyclization failed.

We therefore carried out two further control experiments. We subjected **6i** to an intermolecular allylation by using allyl ethyl carbonate. The benzoate **6i** was chosen to achieve selective ionization of the more reactive allyl carbonate. Although the yield was moderate, the desired allylation product **9** was obtained without problems. Clearly, the enolate is sufficiently reactive to undergo allylation, and the failure of the cyclization is not a problem of the enolate *per se*. To investigate the reactivity of the allyl carbonate subunit, **6e** was reacted with a chelated enolate according to our standard procedure for enolate allylation reactions. In this case, allylation product **10** was obtained almost quantitatively, clearly indicating that the sarcosine amide **6e** is an excellent substrate for allylic alkylations. We can therefore exclude the possibility that the allyl amide forms some enolate-Pd complexes that are inactive under the reaction conditions.

We next focused on variation of the reaction conditions, mainly by changing the solvent, the chelating metal salt, and the Pd/ligand ratio (Table 2). In general, enolate chemistry is performed in ether solvents such as tetrahydrofuran (THF), diethyl ether, or dioxane. With the zinc enolate no cyclization product could be obtained in any of these solvents, whereas with $ClTi(OiPr)_3$ traces of **12e** could be determined in THF. We increased the amount of catalyst to 5% (10 mol-% Pd^0) to obtain a reasonable amount of product (entry 1). A further improvement was obtained by switching from THF to toluene (entry 2), and most surprisingly to dichloromethane (entry 3). Although one may expect that the latter solvent can be (at least in part) deprotonated under the rather basic reaction conditions, in this case the product could be obtained for the first time in preparatively acceptable yield. Other titanium salts [$Ti(OiPr)_4$, $TiCl_4$, Cp_2TiCl_2] were less effective under the same reaction conditions (26–36% yield), and many other metal salts [$CoCl_2$, CuBr, $Bi(OTf)_2$ $Mg(OTf)_2$] failed completely. A comparable result was also obtained in dichloroethane (entry 4), but considering its higher toxicity, dichloromethane was used for the further optimizations. When the LHMDS solution in dichloromethane was warmed to room temperature before the allyl amide was added, a slight clouding was observed, probably caused by deprotonation/chlorocarbene formation. But this side effect could be suppressed by preparing the LHMDS solution at a temperature below –25 °C, resulting in a slightly increased yield (entry 5). It is worth mentioning, that all attempts to use other bases (LDA, LTMP) failed.

Table 2. Thiol addition towards allylated dipeptides **6** and **7**.



6e **12e**

Entry	Solvent	PR_3 (mol-%)	Ratio Pd/PR_3	Yield [%]
1	THF	PPh_3 (22.5)	1:2.25	trace
2	toluene	PPh_3 (22.5)	1:2.25	30
3	CH_2Cl_2	PPh_3 (22.5)	1:2.25	45[a]
4	$ClCH_2CH_2Cl$	PPh_3 (22.5)	1:2.25	45
5	CH_2Cl_2	PPh_3 (22.5)	1:2.25	51[b]
6	CH_2Cl_2	PPh_3 (12.5)	1:1.25	32[b]
7	CH_2Cl_2	PPh_3 (17.5)	1:1.75	45[b]
8	CH_2Cl_2	PPh_3 (27.5)	1:2.75	59[b]
9	CH_2Cl_2	PPh_3 (37.5)	1:3.75	67[b]
10	CH_2Cl_2	PPh_3 (52.5)	1:5.25	75[b]
11	CH_2Cl_2	$P(OPh)_3$ (52.5)	1:5.25	61[b]
12	CH_2Cl_2	XPHOS (17.5)	1:1.75	61[b]

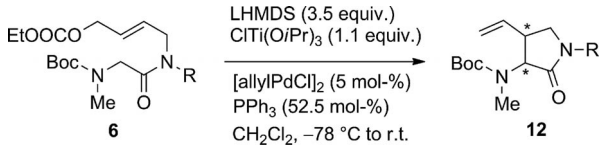
[a] Base solution prepared at –20 °C and warmed to room temperature. [b] Base solution prepared at –20 °C without warming to room temperature.

In general, in allylic alkylations of chelated enolates, a Pd/phosphine ratio of at least 1:2 is required to avoid precipitation of Pd^0, but it is not clear that this ratio is also best for nonchelating enolates, as formed from **6e**. It should be mentioned that, in contrast to chelated enolates, "normal" enolates of esters and amides are critical nucleophiles in Pd-catalyzed allylic alkylations, because they can form inactive Pd-enolates. Although, this does not seem to be the case with our allylamide enolates, as established from the results of the control experiments, the amount of phosphine might have an influence by competing with the enolate for the coordination sides at the Pd. Therefore, we systematically varied the amount of phosphine used (entries 5–10). Whereas the yield dropped upon reducing the Pd/PPh_3 ratio, it also increased significantly when up to a fivefold excess of PPh_3 was used. A higher excess gave no further improvement. These results indicate that the enolate might coordinate to the Pd-catalyst and that this coordination might be suppressed by a large phosphine excess. If this is the case, one might also expect the outcome of the reaction to be influenced by the type of phosphine used. Replacing the PPh_3 by the less electron-donating $P(OPh_3)_3$ resulted in a slightly reduced yield (entry 11). The same result was obtained with the sterically hindered XPHOS ligand (entry 12), whereas performing the reaction with dppe and carbene ligands such as isopropyl-NHC failed. It should be mentioned that other Pd sources such as $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ could also be used, but could not compete with the optimized $[AllylPdCl]_2$/PPh_3 system.

With these optimized reaction conditions in hand, we subjected allylamides **6e**–**h** to the same conditions (Table 3). The yields obtained were comparable, with the THP-protected derivative **6g** giving an excellent yield of 88%. To establish whether the latter good result was influenced by the presence of the THP group, we also investigated the reaction of the free alcohol. In this case the yield dropped to 50%, which might be caused by an interaction of the alcoholate formed with the π-allyl complex, however, the result was still in a preparatively useful range.

In all the examples investigated, the *anti*-configured product was formed preferentially (*anti*/*syn* ratio of 3–5:1), whereas the highest selectivity was observed with the *N*-

Table 3. Thiol addition towards tetrapeptide **12** containing an allyl glycine subunit.



Entry	**6**	R	**12**	Yield [%]	*anti*/*syn*
1	**6e**	Bn	**12e**	75	87:13
2	**6f**	Me	**12f**	69	76:24
3	**6g**	CH_2CH_2OTHP	**12g**	88	82:18
4	**6h**	CH_2CH_2OH	**12h**	50	78:22

benzylated derivative **6e** used in the optimization studies. For structure elucidation, the diastereomeric products were separated by preparative HPLC, and NOE experiments were carried out with the major diastereomer. No NOE was observed between the α- and the β-proton, which is a clear indication of their *anti*-orientation. For the *syn* isomer a strong NOE should be expected.[29] In addition, the coupling constants for these protons are in the range of 9.6 to 10.8 Hz, which is also typical for *trans*-oriented protons in γ-lactams (coupling constants of 6.5–8.0 Hz are generally observed for the *cis* isomers).[30]

Conclusions

We have demonstrated that intramolecular allylic alkylations using functionalized amino acid allyl amides are not trivial. The reactions do not proceed under standard conditions that are generally used for reactions of enolates, but good to high yields are obtained with the corresponding titanium enolates in dichloromethane as solvent. Applications of this protocol for the direct introduction of γ-lactams into peptides are under investigation.

Experimental Section

General Remarks: All air- and moisture-sensitive reactions were carried out in dried glassware under a nitrogen atmosphere. THF was distilled from sodium-benzophenone. LHMDS solutions were prepared from freshly distilled HMDS and commercially available *n*-butyllithium (1.6 M in hexane) in THF before use. The products were purified by flash chromatography on silica gel columns (40–63 μm). Mixtures of hexanes and ethyl acetate were generally used as eluents. Analytical TLC was performed on precoated silica gel plates (Macherey–Nagel, Polygram SIL G/UV254). Visualization was accomplished with UV-light or $KMnO_4$ solution. The diastereomeric ratios were determined by HPLC with a chiral column (Chiracel ODH). ^1H and ^{13}C NMR spectra were recorded with a Bruker AV II-400 [400 MHz (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$ or CD_3OD. Chemical shifts are reported in ppm (δ) with respect to TMS, and $CHCl_3$ or CH_3OH was used as the internal standard. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) by using the CI technique. Elemental analyses were performed at Saarland University.

[(*Z*)-4-*tert*-Butyldimethylsilyloxy-2-butenyl] Ethyl Carbonate (1): Monosilyl-protected (2*Z*)-butendiol (5.00 g, 24.7 mmol) and pyridine (5.0 mL, 61.8 mmol, 2.5 equiv.) were dissolved in dichloromethane (50 mL) and the solution was cooled to 0 °C before ethyl chloroformate (2.8 mL, 29.6 mmol, 1.2 equiv.) was added. After complete consumption of the alcohol (TLC), 1 N $KHSO_4$ solution was added. After separation of the layers, the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 9:1) to give **1** (6.56 g, 24.0 mmol, 97%) as a colorless oil. ^1H NMR ($CDCl_3$): δ = 5.75 (dtt, *J* = 11.4, 5.8, 1.4 Hz, 1 H, 3-H), 5.60 (dtt, *J* = 11.3, 6.6, 1.6 Hz, 1 H, 2-H), 4.70 (dt, *J* = 6.6, 1.2 Hz, 2 H, 1-H), 4.29 (dt, *J* = 5.8, 1.6 Hz, 2 H, 4-H), 4.19 (q, *J* = 7.1 Hz, 2 H, 9-H), 1.31 (t, *J* = 7.1 Hz, C-10), 0.91 (s, 9 H, 6-H), 0.07 (s, 6 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.1 (s, C-8), 134.4 (d, C-3), 123.7 (d, C-2), 64.0 (t, C-9), 63.6 (t, C-1), 59.6 (t, C-4), 25.9 (q, C-6), 18.2 (s, C-5), 14.3 (q, C-10), –5.27 (q, C-7) ppm. $C_{13}H_{26}O_4Si$ (274.43): calcd. C 56.90, H 9.55; found C 56.51, H 9.04.

General Procedure for the *N*-Allylation of Trifluoroacetamides: Allylpalldium chloride dimer (7.3 mg, 0.02 mmol, 2 mol-%) and triphenylphosphine (23.5 mg, 0.09 mmol, 9 mol-%) were dissolved in DMF (10 mL) and stirred at room temperature for 15 min before carbonate **1** was added (1.0 mmol). The TFA-amide (1.3 mmol) and sodium hydride (31 mg, 1.3 mmol) were also dissolved in DMF (7 mL), before the catalyst/carbonate solution was added. The reaction mixture was stirred at room temperature until complete consumption of **1** was observed (1–3 h, TLC). In the case of *N*-benzylamide, the reaction mixture was heated to reflux overnight. The solvent was removed in vacuo and the crude product was purified by flash chromatography.

***N*-Benzyl-4-[*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]trifluoracetamide (2a):** Allylamide **2a** (7.97 g, 20.6 mmol, 88%) was obtained as a yellow oil as a mixture of rotamers according to the general procedure for *N*-allylations from **1** (6.44 g, 23.4 mmol) and *N*-benzyltrifluoroacetamide (6.19 g, 30.5 mmol) after flash chromatography (hexanes/ethyl acetate, 98:2). HRMS (CI): calcd. for $C_{19}H_{28}F_3NO_2Si$ $[M]^+$ 387.1848; found 387.1808. $C_{19}H_{28}F_3NO_2Si$ (387.51): calcd. C 58.89, H 7.28, N 3.61; found C 58.21, H 7.21, N 7.21.

Major Rotamer: ^1H NMR ($CDCl_3$): δ = 7.40–7.29 (m, 3 H, 1-H, 2-H), 7.14 (m, 2 H, 3-H), 5.77–5.56 (m, 2 H, 7-H, 8-H), 4.62 (s, 2 H, 5-H), 4.20 (dd, *J* = 4.1, 1.5 Hz, 2 H, 9-H), 3.92 (d, *J* = 5.2 Hz, 2 H, 6-H), 0.92 (s, 9 H, 12-H), 0.08 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 135.0 (d, C-4), 134.8 (d, C-8), 129.0 (d, C-3), 128.3 (d, C-2), 127.3 (d, C-1), 122.8 (d, C-7), 62.6 (t, C-9), 48.5 (t, C-5), 46.8 (t, C-6), 25.8 (q, C-12), 18.4 (s, C-11), –5.30 (q, C-10) ppm.

Minor Rotamer (selected signals): ^1H NMR ($CDCl_3$): δ = 4.61 (s, 2 H, 5-H), 4.15 (dd, *J* = 3.9, 1.5 Hz, 2 H, 9-H), 0.91 (s, 9 H, 12-H), 0.07 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 135.3 (d, C-4), 134.7 (d, C-8), 128.9 (d, C-3), 128.2 (d, C-2), 128.0 (d, C-1), 122.0 (d, C-7), 62.8 (t, C-9), 47.7 (t, C-5), 25.9 (q, C-12), –5.26 (q, C-10) ppm.

4-[*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]-*N*-methyl-trifluoracetamide (2b): Allylamide **2a** (5.98 g, 19.2 mmol, 64%) was obtained as a pale-yellow oil as a mixture of rotamers according to the general procedure for *N*-allylations from **1** (8.23 g, 30.0 mmol) and *N*-methyltrifluoroacetamide (4.96 g, 39.0 mmol) after flash chromatography (hexanes/ethyl acetate, 98:2). HRMS (CI): calcd. for $C_{13}H_{25}F_3NO_2Si$ $[M + H]^+$ 312.1562; found 312.1621. $C_{13}H_{24}F_3NO_2Si$ (311.42): calcd. C 50.14, H 7.77, N 4.50; found C 50.14, H 7.31, N 4.70.

Major Rotamer: ^1H NMR ($CDCl_3$): δ = 5.77 (dtt, *J* = 15.3, 2.9, 1.3 Hz, 1 H, 4-H), 5.64 (dtt, *J* = 15.3, 6.3, 1.7 Hz, 1 H, 3-H), 4.20

(dd, J = 2.9, 1.3 Hz, 2 H, 5-H), 4.04 (d, J = 6.2 Hz, 2 H, 2-H), 3.08 (q, $J_{1,F}$ = 1.5 Hz, 3 H, 1-H), 0.91 (s, 9 H, 8-H), 0.07 (s, 6 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 134.5 (d, C-4), 122.1 (d, C-3), 62.8, 62.6 (t, C-5), 50.4 (t, C-2), 34.0 (q, C-1), 25.9 (q, C-8), 18.4 (s, C-7), –5.28 (q, C-6) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 4.00 (d, J = 6.0 Hz, 2 H, 2-H), 2.98 (s, 3 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 134.6 (d, C-4), 122.6 (d, C-3), 62.8, 62.6 (t, C-5), 25.9 (q, C-8), 18.4 (s, C-7), –5.32 (q, C-6) ppm.

4-[*tert*-Butyldimethylsilyloxy-(2*E*)-buten-1-yl]-*N*-[2-(tetrahydropyran-2-yloxy)ethyl]trifluoracetamide (2c): Allylamide **2c** (7.31 g, 17.2 mmol, 95%) was obtained as a yellow oil as a mixture of rotamers according to the general procedure for *N*-allylations from **1** (5.00 g, 18.2 mmol) and *N*-[2-(tetrahydropyran-2-yloxy)ethyl]-trifluoroacetamide (5.71 mg, 23.7 mmol) after flash chromatography (hexanes/ethyl acetate, 9:1 to 8:2). HRMS (CI): calcd. for $C_{19}H_{35}F_3NO_4Si$ $[M + H]^+$ 429.2243; found 426.2296. $C_{19}H_{34}F_3NO_4Si$ (425.56): calcd. C 53.62, H 8.05, N 3.29; found C 53.93, H 8.00, N 3.57.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.76 (dt, J = 15.4, 4.3 Hz, 1 H, 10-H), 5.64 (m, 1 H, 9-H), 4.58 (dd, J = 4.3, 3.6 Hz, 1 H, 5-H), 4.18–4.15 (m, 4 H, 8-H, 11-H), 3.92 (dt, J = 10.3, 6.0 Hz, 1 H, 6-H_a), 3.79 (t, J = 8.0 Hz, 1 H, 1-H_a), 3.68–3.50 (m, 4 H, 1-H_b, 6-H_b, 7-H), 1.79–1.70 (m, 2 H, 3-H_a, 4-H_a), 1.60–1.51 (m, 4 H, 2-H, 3-H_b, 4-H_b), 0.91 (s, 9 H, 14-H), 0.07 (s, 6 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 156.8 (q, $J_{15,F}$ = 35.8 Hz, C-15), 134.4 (d, C-10), 123.2 (d, C-9), 116.4 (q, $J_{16,F}$ = 288.0 Hz, C-16), 98.9 (d, C-5), 64.7 (t, C-6), 62.6 (t, C-11), 62.2 (t, C-1), 48.8 (t, C-8), 46.0 (t, C-7), 30.5 (t, C-4), 25.8 (q, C-14), 25.3 (t, C-2), 19.4 (t, C-3), 18.3 (s, C-13), –5.38 (q, C-12) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 3.79 (2t, J = 8.0 Hz, 1 H, 1-Ha), 0.90 (s, 9 H, 14-H), 0.07 (s, 6 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 157.0 (q, $J_{15,F}$ = 35.6 Hz, C-15), 134.2 (d, C-10), 122.5 (d, C-9), 98.9 (d, C-5), 65.7 (t, C-6), 62.9 (t, C-11), 62.1 (t, C-1), 50.1 (t, C-8), 46.2 (t, C-7), 30.4 (t, C-4), 25.8 (q, C-14), 25.2 (t, C-2), 19.2 (t, C-3), –5.33 (q, C-12) ppm.

Cleavage of the TFA-Protecting Group. General Procedure: The TFA-protected amide **2** (1.0 equiv.) was dissolved in methanol–water (9:1) before potassium carbonate (1.5 to 2 equiv.) was added. After complete consumption of **2** (TLC) the solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The clear solution was washed with water and the aqueous layer was extracted four times with ethyl acetate. The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the crude product was used without further purification.

Benzyl[4-*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]amine (3a): Allylamine **3a** (5.32 g, 18.3 mmol, >99%) was obtained as a yellow oil according to the general procedure for TFA-cleavage from **2a** (7.07 g, 18.3 mmol). ^{1}H NMR ($CDCl_3$): δ = 7.33–7.30 (m, 4 H, 2-H, 3-H), 7.25 (m, 1 H, 1-H), 5.83–5.69 (m, 2 H, 7-H, 8-H), 4.17 (dd, J = 4.6, 1.3 Hz, 2 H, 9-H), 3.80 (s, 2 H, 5-H), 3.28 (dd, J = 5.7, 1.0 Hz, 2 H, 6-H), 1.47 (br. s, 1 H, NH), 0.91 (s, 9 H, 12-H), 0.07 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 140.3 (s, C-4), 131.2, 128.6 (2d, C-7, C-8), 128.4, 128.2 (2d, C-2, C-3), 126.9 (d, C-1), 63.5 (t, C-9), 53.3 (t, C-5), 50.6 (t, C-6), 25.7 (q, C-12), 18.4 (s, C-11), –5.19 (q, C-10) ppm. HRMS (CI): calcd. for $C_{17}H_{30}NOSi$ $[M + H]^+$ 292.2052; found 292.2100. $C_{17}H_{29}NOSi$ (291.50): calcd. C 70.04, H 10.03, N 4.80; found C 69.74, H 9.56, N 5.32.

[4-*tert*-Butyldimethylsilyloxy-(2*E*)-buten-1-yl]methylamine (3b): Allylamine **3b** (2.36 g, 10.9 mmol, 91%) was obtained as a yellow oil according to the general procedure for TFA-cleavage from **2b** (3.75 g, 12.0 mmol). ^{1}H NMR ($CDCl_3$): δ = 5.79–5.67 (m, 2 H, 3-H, 4-H), 4.16 (dd, J = 3.5, 1.4 Hz, 2 H, 5-H), 3.21 (d, J = 4.9 Hz, 2 H, 2-H), 2.43 (s, 3 H, 1-H), 1.65 (br. s, 1 H, NH), 0.90 (s, 9 H, 8-H), 0.07 (s, 6 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 131.0, 128.6 (2d, C-3, C-4), 63.5 (t, C-5), 53.3 (t, C-2), 36.0 (q, C-1), 26.0 (q, C-8), 18.4 (s, C-7), –5.20 (q, C-6) ppm. HRMS (CI): calcd. for $C_{11}H_{25}NOSi$ $[M]^+$ 215.1705; found 215.1697.

[4-*tert*-Butyldimethylsilyloxy-(2*E*)-buten-1-yl][2-(tetrahydropyran-2-yloxy)ethyl]amine (3c): Allylamine **3c** (4.67 g, 14.2 mmol, 89%) as a yellow oil was obtained according to the general procedure for TFA-cleavage from **2c** (6.75 g, 15.9 mmol). ^{1}H NMR ($CDCl_3$): δ = 5.81–5.47 (m, 2 H, 9-H, 10-H), 4.59 (dd, J = 4.3, 2.9 Hz, 1 H, 5-H), 4.17 (dd, J = 4.5, 1.0 Hz, 2 H, 11-H), 3.89–3.83 (m, 2 H, 1-Ha, 6-H_a), 3.55–3.48 (m, 2 H, 1-H_b, 6-H_b), 3.27 (d, J = 5.6 Hz, 2 H, 8-H), 2.80 (dd, J = 4.3, 2.6 Hz, 2 H, 7-H), 1.83 (m, 1 H, 3-H_a), 1.71 (m, 1 H, 4-H_a), 1.60–1.50 (m, 5 H, 2-H, 3-H_b, 4-H_b, NH), 0.90 (s, 9 H, 14-H), 0.06 (s, 6 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 131.0, 128.7 (2d, C-9, C-10), 99.1 (d, C-5), 67.0 (t, C-6), 63.5 (t, C-11), 62.4 (t, C-1), 51.2 (t, C-8), 48.9 (t, C-7), 30.6 (t, C-4), 25.9 (q, C-14), 25.4 (t, C-2), 19.6 (t, C-3), 18.4 (s, C-13), –5.20 (q, C-12) ppm. HRMS (CI): calcd. for $C_{17}H_{36}NO_3Si$ $[M + H]^+$ 330.2420; found 330.2457. $C_{17}H_{35}NO_3Si$ (329.55): calcd. C 61.96, H 10.70, N 4.25; found C 61.95, H 10.68, N 4.36.

Amide Coupling Using 2-Bromo-1-ethylpyridinium Tetrafluoroborate (BEP). General Procedure: Amine **3** (1 equiv.) was dissolved in dichloromethane (1 mL/mmol) under N_2 before BEP (1.1 equiv.) and the amino acid (1.1 equiv.) were added. The solution was cooled to –10 °C then diisopropylamine (2.0 equiv.) was added dropwise. After stirring at –10 °C for 20 min, the mixture was warmed to room temperature overnight. The solvent was removed in vacuo and the crude product was purified by flash chromatography.

***N*-Fluorenylmethoxycarbonyl-glycyl-{*N*-benzyl-*N*-[4-*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]}amide (4a):** Allylamide **4a** (2.33 g, 4.08 mmol, 76%) was obtained as a pale-yellow oil as a mixture of rotamers according to the general procedure for peptide couplings from **3a** (1.56 g, 5.35 mmol), Fmoc-Gly-OH (1.75 g, 5.89 mmol), BEP (1.61 g, 5.89 mmol), and diisopropylamine (1.38 g, 10.7 mmol) after flash chromatography (hexanes/ethyl acetate, 9:1 to 7:3). HRMS (CI): calcd. for $C_{34}H_{43}N_2O_4Si$ $[M + H]^+$ 571.2947; found 571.2974. $C_{34}H_{42}N_2O_4Si$ (570.79): calcd. C 71.54, H 7.42, N 4.91; found C 70.79, H 7.24, N 5.22.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.76 (d, J = 7.4 Hz, 2 H, 19-H), 7.62 (d, J = 7.0 Hz, 2 H, 22-H), 7.42–7.15 (m, 9 H, 1-H, 2-H, 3-H, 20-H, 21-H), 5.87 (br. s, 1 H, NH), 5.65 (m, 2 H, 7-H, 8-H), 4.65 (s, 2 H, 5-H), 4.40 (d, J = 7.4 Hz, 2 H, 16-H), 4.26 (t, J = 7.3 Hz, 1 H, 17-H), 4.17 (m, 2 H, 9-H), 4.11 (m, 2 H, 14-H), 3.83 (d, J = 3.9 Hz, 2 H, 6-H), 0.91 (s, 9 H, 12-H), 0.07 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.2 (s, C-13), 156.1 (s, C-15), 143.9 (s, C-18), 141.3 (s, C-23), 136.7 (s, C-4), 132.9 (d, C-8), 129.1, 128.7, 128.2, 127.9, 127.7, 127.0, 126.3 (5d, C-1, C-2, C-3, C-20, C-21), 125.2 (d, C-22), 122.7 (d, C-7), 119.9 (d, C-19), 67.1 (t, C-16), 62.6 (t, C-9), 48.7 (t, C-5), 47.2, 47.1 (2t, C-6, d, C-17), 42.6 (t, C-14), 25.9 (q, C-12), 18.3 (s, C-11), –5.31 (q, C-10) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 4.46 (s, 2 H, 5-H), 4.40 (d, J = 7.4 Hz, 2 H, 16-H), 4.08 (d, J = 3.8 Hz, 2 H, 6-H), 0.07 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.1 (s, C-13), 135.5 (s, C-4), 133.8 (d, C-8), 129.1, 128.7, 128.2, 127.9, 127.7, 127.0, 126.3 (5d, C-1, C-2, C-3, C-20, C-21), 123.6 (d, C-7), 62.9 (t, C-9), 49.0 (t, C-5), 42.7 (t, C-14), –5.26 (q, C-10) ppm.

***N*-Trifluoroacetyl-glycyl-{*N*-benzyl-*N*-[4-*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]}amide (4b):** Allylamide **4b** was obtained by

treating a solution of **4a** (1.28 g, 2.13 mmol) in acetonitrile (35 mL) with diethylamine (17 mL). After stirring for 30 min at room temperature all starting material was consumed (TLC). The solvent was removed in vacuo and the residue was dissolved in methanol (25 mL). Triethylamine (1.19 mL, 8.52 mmol) and ethyl trifluoroacetate (1.27 mL, 10.7 mmol) were added and the solution was stirred at room temperature for 3 d. The clear solution was concentrated in vacuo and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 9:1 to 7:3) to give **4b** (931 mg, 2.09 mmol, 98%) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{17}H_{23}F_3N_2O_3Si$ [M – C_4H_8]$^+$ 388.1430; found 388.1469. $C_{21}H_{31}F_3N_2O_3Si$ (444.56): calcd. C 56.74, H 7.03, N 6.30; found C 56.79, H 6.80, N 6.80.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.61 (br. s, 1 H, NH), 7.40–7.30 (m, 3 H, 1-H, 2-H), 7.26 (m, 2 H, 3-H), 5.69 (m, 2 H, 7-H, 8-H), 4.63 (s, 2 H, 5-H), 4.18–4.15 (m, 4 H, 9-H, 14-H), 3.81 (dd, J = 5.1, 1.4 Hz, 2 H, 6-H), 0.91 (s, 9 H, 12-H), 0.07 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.5 (s, C-13), 156.8 (q, $J_{15,F}$ = 35.8 Hz, C-15), 136.2 (s, C-4), 133.4 (d, C-8), 128.8 (d, C-2), 128.3 (d, C-3), 127.9 (d, C-1), 122.2 (d, C-7), 115.5 (q, $J_{16,F}$ = 287.3 Hz, C-16), 62.4 (t, C-9), 49.0 (t, C-5), 47.3 (t, C-6), 41.4 (t, C-14), 25.9 (q, C-12), 18.3 (s, C-11), –5.33 (q, C-10) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.17 (d, J = 7.0 Hz, 2 H, 3-H), 4.47 (s, 2 H, 5-H), 4.07 (d, J = 5.2 Hz, 2 H, 6-H), 0.90 (s, 9 H, 12-H), 0.06 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 134.9 (s, C-4), 134.4 (d, C-8), 129.2 (d, C-2), 128.1 (d, C-1), 126.3 (d, C-3), 123.0 (d, C-7), 62.8 (t, C-9), 47.4 (t, C-6), 41.5 (t, C-14) ppm.

***N*-*tert*-Butyloxycarbonyl-glycyl-{*N*-benzyl-*N*-[4-*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]}amide (4c):** Allylamide **4c** (3.76 g, 8.40 mmol, 84%) was obtained as a colorless oil as a mixture of rotamers according to the general procedure for peptide couplings from **3a** (2.92 g, 10.0 mmol), Boc-Gly-OH (1.93 g, 11.0 mmol), BEP (3.01 g, 11.0 mmol), and diisopropylamine (2.59 g, 20.0 mmol) after flash chromatography (hexanes/ethyl acetate, 8:2 to 7:3). HRMS (CI): calcd. for $C_{24}H_{41}N_2O_4Si$ [M + H]$^+$ 449.2791; found 449.2884. $C_{24}H_{40}N_2O_4Si$ (448.67): calcd. C 64.25, H 8.99, N 6.24; found C 64.51, H 8.88, N 6.29.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.36–7.28 (m, 3 H, 1-H, 2-H), 7.22 (m, 2 H, 3-H), 5.67–5.44 (m, 3 H, 7-H, 8-H, NH), 4.60 (s, 2 H, 5-H), 4.16 (m, 2 H, 9-H), 4.03 (s, 2 H, 14-H), 3.77 (d, J = 4.2 Hz, 2 H, 6-H), 1.45 (s, 9 H, 17-H), 0.90 (s, 9 H, 12-H), 0.06 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.6 (s, C-13), 155.7 (s, C-15), 136.8 (s, C-4), 132.9 (d, C-8), 128.6 (d, C-2), 128.2 (d, C-3), 127.5 (d, C-1), 122.9 (d, C-7), 79.5 (s, C-16), 62.6 (t, C-9), 48.6 (t, C-5), 47.2 (t, C-6), 42.2 (t, C-14), 28.3 (q, C-17), 25.9 (q, C-12), 18.3 (s, C-11), –5.31 (q, C-10) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.14 (d, J = 7.2 Hz, 2 H, 3-H), 4.44 (s, 2 H, 5-H), 4.00 (d, J = 5.2 Hz, 2 H, 6-H), 1.43 (s, 9 H, 17-H), 0.89 (s, 9 H, 12-H), 0.05 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 135.7 (s, C-4), 133.6 (d, C-8), 129.0 (d, C-2), 127.8 (d, C-1), 126.4 (d, C-3), 123.8 (d, C-7), 62.9 (t, C-9), 49.0 (t, C-5), 47.0 (t, C-6), 42.4 (t, C-14), –5.27 (q, C-10) ppm.

***N*-*tert*-Butyloxycarbonyl-β-alanyl-{*N*-benzyl-*N*-[4-*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]}amide (4d):** Allylamide **4d** (3.16 g, 6.80 mmol, 85%) was obtained as a colorless oil as a mixture of rotamers according to the general procedure for peptide couplings from **3a** (2.33 g, 8.00 mmol), Boc-β-Ala-OH (1.67 g, 8.80 mmol), BEP (1.67 g, 8.80 mmol), and diisopropylamine (2.07 g, 16.0 mmol) after flash chromatography (hexanes/ethyl acetate, 8:2 to 7:3). HRMS (CI): calcd. for $C_{25}H_{42}N_2O_4Si$ [M]$^+$ 462.2914; found 462.2908. $C_{25}H_{42}N_2O_4Si$ (462.70): calcd. C 64.89, H 9.15, N 6.05; found C 64.47, H 9.53, N 6.15.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.38–7.30 (m, 3 H, 1-H, 2-H), 7.24 (m, 2 H, 3-H), 5.69–5.55 (m, 2 H, 7-H, 8-H), 5.38 (br. s, 1 H, NH), 4.60 (s, 2 H, 5-H), 4.18 (m, 2 H, 9-H), 3.82 (d, J = 4.0 Hz, 2 H, 6-H), 3.46 (t, J = 5.7 Hz, 2 H, 14-H), 2.59 (t, J = 5.7 Hz, 2 H, 15-H), 1.45 (s, 9 H, 18-H), 0.93 (s, 9 H, 12-H), 0.08 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.9 (s, C-13), 156.0 (s, C-16), 137.3 (s, C-4), 132.3 (d, C-8), 128.6 (d, C-2), 128.1 (d, C-3), 127.4 (d, C-1), 123.6 (d, C-7), 79.0 (s, C-17), 62.7 (t, C-9), 48.2 (t, C-5), 48.0 (t, C-6), 36.4 (t, C-14), 33.2 (t, C-15), 28.4 (q, C-18), 25.9 (q, C-12), 18.3 (s, C-11), –5.29 (q, C-10) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.15 (d, J = 7.1 Hz, 2 H, 3-H), 4.49 (s, 2 H, 5-H), 4.02 (d, J = 3.8 Hz, 2 H, 6-H), 3.46 (t, J = 5.7 Hz, 2 H, 14-H), 2.59 (t, J = 5.7 Hz, 2 H, 15-H), 1.44 (s, 9 H, 18-H), 0.92 (s, 9 H, 12-H), 0.08 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 136.4 (s, C-4), 133.2 (d, C-8), 128.9 (d, C-2), 127.6 (d, C-1), 126.3 (d, C-3), 124.4 (d, C-7), 63.1 (t, C-9), 49.8 (t, C-5), 46.7 (t, C-6), 36.3 (t, C-14), 33.4 (t, C-15), 25.9 (q, C-12), –5.23 (q, C-10) ppm.

***N*-*tert*-Butyloxycarbonyl-sarcosyl-{*N*-benzyl-*N*-[4-*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]}amide (4e):** Allylamide **4e** (6.00 g, 13.0 mmol, 81%) was obtained as a colorless oil as a mixture of three rotamers according to the general procedure for peptide couplings from **3a** (4.69 g, 16.1 mmol), Boc-Sar-OH (3.35 g, 17.7 mmol), BEP (4.85 g, 17.7 mmol) und diisopropylamine (4.16 g, 32.0 mmol) after flash chromatography (hexanes/ethyl acetate, 8:2 to 7:3). HRMS (CI): calcd. for $C_{25}H_{43}N_2O_4Si$ [M + H]$^+$ 463.2947; found 463.2948. $C_{25}H_{42}N_2O_4Si$ (462.70): calcd. C 64.89, H 9.15, N 6.05; found C 64.29, H 8.85, N 6.43.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.37–7.29 (m, 3 H, 1-H, 2-H), 7.24 (m, 2 H, 3-H), 7.16 (d, J = 7.3 Hz, 2 H, 3-H), 5.68–5.56 (m, 2 H, 7-H, 8-H), 4.59, 4.50, 4.45 (s, 2 H, 5-H), 4.16, 4.10, 4.07 (s, 2 H, 9-H), 4.00 (br. s, 2 H, 14-H), 3.80 (d, J = 9.8 Hz, 2 H, 6-H), 2.95, 2.91 (s, 3 H, 18-H), 1.48, 1.43 (s, 9 H, 17-H), 0.91, 0.90 (s, 9 H, 12-H), 0.07, 0.06 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.0, 168.8, 168.7 (s, C-13), 156.2, 155.7 (s, C-15), 137.2, 136.5 (s, C-4), 133.4, 132.4, 132.2 (d, C-8), 129.0, 128.9, 128.5 (d, C-2), 128.2 (d, C-3), 127.5, 127.3 (d, C-1), 126.4, 126.2 (d, C-3), 123.8, 123.6 (d, C-7), 79.8 (s, C-16), 64.5, 62.8, 62.5 (t, C-9), 50.8, 50.2, 50.0, 49.3, 49.1, 48.5, 47.5, 47.1, 47.0 (t, C-5, C-6, C-14), 35.8, 35.6 (q, C-18), 28.3 (q, C-17), 25.9 (q, C-12), 18.4 (s, C-11), –5.29, –5.25 (q, C-10) ppm.

***N*-*tert*-Butyloxycarbonyl-sarcosyl-{*N*-4-[*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]-*N*-methyl}amide (4f):** Allylamide **4f** (456 mg, 1.18 mmol, >99%) was obtained as a colorless oil as a mixture of rotamers from **3b** (330 mg, 1.53 mmol) and Boc-Sar-OH (223 mg, 1.18 mmol). The reaction was carried out in ethyl acetate (2 mL), and T_3P (1.05 mL, 1.77 mmol) in combination with diisopropylamine (618 μL, 3.54 mmol) was used as coupling reagent. Flash chromatography (hexanes/ethyl acetate, 9:1 to 1:1). HRMS (CI): calcd. for $C_{19}H_{39}N_2O_4Si$ [M + H]$^+$ 387.2634; found 387.2664. $C_{19}H_{38}N_2O_4Si$ (386.60): calcd. C 59.03, H 9.91, N 7.25; found C 59.36, H 9.70, N 7.48.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.70–5.55 (m, 2 H, 7-H, 8-H), 4.16 (m, 2 H, 9-H), 4.03–3.95 (m, 4 H, 4-H, 6-H), 2.91–2.89 (m, 6 H, 13-H, 14-H), 1.45 (s, 9 H, 1-H), 0.89 (s, 9 H, 12-H), 0.05 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.2 (s, C-5), 156.3 (s, C-3), 133.0 (d, C-8), 124.5 (d, C-7), 79.8 (s, C-2), 63.1 (t, C-9), 50.2 (t, C-6), 49.0 (t, C-4), 35.5, 33.6 (2q, C-13, C-14), 28.3 (q, C-1), 25.9 (q, C-12), 18.3 (s, C-11), –5.31 (q, C-10) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 3.85 (d, $^3J_{6,7}$ = 8.4 Hz, 2 H, 6-H), 1.41 (s, 9 H, 1-H), 0.89 (s, 9 H, 12-H), 0.05 (s, 6 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.6 (s, C-5), 155.7 (s, C-3), 132.1 (d, C-8), 123.7 (d, C-7), 79.7 (s, C-2), 62.8 (t, C-9), 50.4 (t, C-6), 49.2 (t, C-4), 35.6, 33.5 (2q, C-13, C-14), 25.9 (q, C-12), 18.4 (s, C-11), –5.25 (q, C-10) ppm.

***N*-*tert*-Butyloxycarbonyl-sarcosyl-{*N*-4-[*tert*-butyldimethylsilyloxy-(2*E*)-buten-1-yl]-*N*-(2-tetrahydropyran-2-yloxyethyl)}amide (4g):** Allylamide **4g** (6.59 g, 13.2 mmol, 94%) was obtained as a colorless oil as a mixture of three rotamers according to the general procedure for peptide couplings from **3c** (4.66 g, 14.1 mmol), Boc-Sar-OH (2.94 g, 15.6 mmol), BEP (4.27 g, 15.6 mmol) and diisopropylamine (4.93 mL, 28.2 mmol) after flash chromatography (hexanes/ethyl acetate, 9:1 to 6:4). ^{1}H NMR ($CDCl_3$): δ = 5.72–5.60 (m, 2 H, 9-H, 10-H), 4.58 (dd, *J* = 3.9, 3.1 Hz, 1 H, 5-H), 4.19–3.96 (m, 6 H, 8-H, 11-H, 16-H), 3.83 (m, 2 H, 6-H), 3.63 (m, 1 H, 1-H$_a$), 3.51–3.48 (m, 3 H, 1-H$_b$, 7-H), 2.93, 2.90 (s, 3 H, 20-H), 1.81–1.70 (m, 2 H, 3-H$_a$, 4-H$_a$), 1.59–1.47 (m, 13 H, 2-H, 3-H$_b$, 4-H$_b$, 19-H), 1.43 (s, 9 H, 19-H), 0.92, 0.91 (s, 9 H, 14-H), 0.08, 0.07 (s, 6 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.9, 168.8, 168.6 (s, C-15), 156.3, 156.2 (s, C-17), 132.7, 131.9, 131.7 (d, C-10), 125.0, 124.4, 124.2 (d, C-9), 99.0, 98.9 (d, C-5), 79.7 (s, C-18), 65.9, 65.8, 65.0, 63.2, 63.1, 63.0, 62.9, 62.7, 62.4, 62.3, 62.2, 62.1 (3t, C-1, C-6, C-11), 50.7, 50.0, 49.9, 49.7, 49.6, 47.0 (2t, C-8, C-16), 46.2, 46.1, 45.9 (t, C-7), 35.7, 35.6, 35.4 (q, C-20), 30.6, 30.4 (t, C-4), 28.4 (q, C-19), 25.9 (q, C-14), 25.4, 25.3 (t, C-2), 19.5, 19.4, 19.3 (t, C-3), 18.4 (s, C-13), –5.24, –5.29 (q, C-12) ppm. HRMS (CI): calcd. for $C_{25}H_{49}N_2O_6Si$ [M + H]$^+$ 501.3315; found 501.3338. $C_{25}H_{48}N_2O_6Si$ (500.74): calcd. C 59.96, H 9.66, N 5.59; found C 60.09, H 9.51, N 5.61.

Cleavage of the Silyl Protecting Group. General Procedure: The silylated allyl amide **4** was dissolved in anhydrous THF (1 mL/mmol) then a solution of tetrabutylammoniumfluoride (1.5 equiv.) in anhydrous THF (7 ml/mmol) was added. After stirring for 30 min and complete consumption of the starting material (TLC), the solvent was removed in vacuo and the crude product was purified by flash chromatography.

***N*-Trifluoroacetyl-glycyl-{*N*-benzyl-*N*-[4-hydroxy-(2*E*)-buten-1-yl]}amide (5b):** According to the general procedure for silyl group cleavage, alcohol **5b** (639 mg, 1.93 mmol, 93%) was obtained from **4b** (923 mg, 2.08 mmol) after flash chromatography (hexanes/ethyl acetate, 3:7 to ethyl acetate) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{15}H_{17}F_3N_2O_3$ [M]$^+$ 330.1191; found 330.1155. $C_{15}H_{17}F_3N_2O_3$ (330.30): calcd. C 54.54, H 5.19, N 8.48; found C 54.33, H 5.38, N 8.52.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.62 (br. s, 1 H, NH), 7.40–7.30 (m, 3 H, 1-H, 2-H), 7.26 (m, 2 H, 3-H), 5.80–5.60 (m, 2 H, 7-H, 8-H), 4.64 (s, 2 H, 5-H), 4.21–4.12 (m, 4 H, 9-H, 11-H), 3.83 (dd, *J* = 5.2, 1.3 Hz, 2 H, 6-H), 1.58 (s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.5 (s, C-10), 157.0 (q, $J_{12;F}$ = 37.9 Hz, C-12), 136.1 (s, C -4), 132.6 (d, C-8), 128.8 (d, C-2), 128.2 (d, C-3), 127.9 (d, C-1), 123.8 (d, C-7), 115.5 (q, $J_{13,F}$ = 287.0 Hz, C-13), 62.2 (t, C-9), 49.1 (t, C-5), 47.3 (t, C-6), 41.3 (t, C-11) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.58 (br. s, 1 H, NH), 7.17 (d, *J* = 7.1 Hz, 2 H, 3-H), 4.48 (s, 2 H, 5-H), 4.07 (d, *J* = 5.8 Hz, 2 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 156.9 (q, $J_{12,F}$ = 37.5 Hz, C-12), 134.8 (s, C-4), 133.4 (d, C-8), 129.2 (d, C-2), 128.2 (d, C-1), 126.3 (d, C-3), 124.6 (d, C-7), 62.5 (t, C-9), 49.4 (t, C-5), 47.5 (t, C-6), 41.4 (t, C-11) ppm.

***N*-*tert*-Butyloxycarbonyl-glycyl{*N*-benzyl-*N*-[4-hydroxy-(2*E*)-buten-1-yl]}amide (5c):** According to the general procedure for silyl group cleavage, alcohol **5c** (1.50 g, 4.49 mmol, 82%) was obtained from **4c** (2.47 g, 5.50 mmol) after flash chromatography (hexanes/ethyl acetate, 3:7 to EE) as a yellow oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{18}H_{27}N_2O_4$ [M]$^+$ 335.1965; found 335.1969.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.37–7.27 (m, 3 H, 1-H, 2-H), 7.22 (d, *J* = 6.7 Hz, 2 H, 3-H), 5.77–5.54 (m, 3 H, 7-H, 8-H, NH), 4.61 (s, 2 H, 5-H), 4.16 (m, 2 H, 9-H), 4.04–4.02 (m, 4 H, 6-H, 11-H), 1.64 (s, 1 H, OH), 1.45 (s, 9 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.8 (s, C-10), 155.9 (s, C-12), 136.7 (s, C-4), 132.5 (d, C-8), 128.6 (d, C-2), 128.2 (d, C-3), 127.6 (d, C-1), 124.6 (d, C-7), 79.7 (s, C-13), 62.4 (t, C-9), 48.9 (t, C-5), 47.2 (t, C-6), 42.2 (t, C-11), 28.3 (q, C-14) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.15 (d, *J* = 7.3 Hz, 2 H, 3-H), 4.61 (s, 2 H, 5-H), 3.80 (d, *J* = 4.4 Hz, 2 H, 6-H), 1.44 (s, 9 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.7 (s, C-10), 155.7 (s, C-12), 135.6 (s, C-4), 132.9 (d, C-8), 129.0 (d, C-2), 127.8 (d, C-1), 126.4 (d, C-3), 125.3 (d, C-7), 79.6 (s, C-13), 62.6 (t, C-9), 49.3 (t, C-5), 47.1 (t, C-6), 42.3 (t, C-11) ppm.

***N*-*tert*-Butyloxycarbonyl-β-alanyl-{*N*-benzyl-*N*-[4-hydroxy-(2*E*)-buten-1-yl]}amide (5d):** According to the general procedure for silyl group cleavage, alcohol **5d** (1.48 g, 4.25 mmol, 85%) was obtained from **4d** (2.31 g, 5.00 mmol) after flash chromatography (hexanes/ethyl acetate, 1:1 to ethyl acetate) as a yellow oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{19}H_{29}N_2O_4$ [M + H]$^+$ 349.2083; found 349.2082. $C_{19}H_{28}N_2O_4$ (348.44): calcd. C 65.49, H 8.10, N 8.04; found C 64.90, H 8.34, N 7.93.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.37–7.27 (m, 3 H, 1-H, 2-H), 7.22 (d, *J* = 6.6 Hz, 2 H, 3-H), 5.75–5.55 (m, 2 H, 7-H, 8-H), 5.31 (br. s, 1 H, NH), 4.60 (s, 2 H, 5-H), 4.13 (d, *J* = 3.8 Hz, 2 H, 9-H), 3.83 (dd, *J* = 5.1, 1.1 Hz, 2 H, 6-H), 3.44 (m, 2 H, 11-H), 2.58 (m, 2 H, 12-H), 1.63 (s, 1 H, OH), 1.43, 1.42 (s, 9 H, 15-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.9 (s, C-10), 156.0 (s, C-13), 137.3 (s, C-4), 132.2 (d, C-8), 128.6 (d, C-2), 128.1 (d, C-3), 127.4 (d, C-1), 126.0 (d, C-7), 79.2 (s, C-14), 62.5 (t, C-9), 48.5 (t, C-5), 46.8 (t, C-6), 36.6 (t, C-11), 33.1 (t, C-12), 28.4 (q, C-15) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.13 (d, *J* = 7.1 Hz, 2 H, 3-H), 4.49 (s, 2 H, 5-H), 4.01 (d, *J* = 4.2 Hz, 2 H, 6-H), 1.43, 1.42 (s, 9 H, 15-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.7 (s, C-10), 155.7 (s, C-12), 136.3 (s, C-4), 132.5 (d, C-8), 128.9 (d, C-2), 127.7 (d, C-1), 126.3 (d, C-3), 125.4 (d, C-7), 62.8 (t, C-9), 50.1 (t, C-5), 48.2 (t, C-6), 36.3 (t, C-11), 33.4 (t, C-12) ppm.

***N*-*tert*-Butyloxycarbonyl-sarcosyl-{*N*-benzyl-*N*-[4-hydroxy-(2*E*)-buten-1-yl]}amide (5e):** According to the general procedure for silyl group cleavage, alcohol **5e** (3.30 g, 9.48 mmol, 93%) was obtained from **4e** (4.71 g, 10.2 mmol) after flash chromatography (hexanes/ethyl acetate, 1:1 to ethyl acetate) as a yellow oil as a mixture of three rotamers. ^{1}H NMR ($CDCl_3$): δ = 7.37–7.29 (m, 3 H, 1-H, 2-H), 7.25, 7.17 (m, 2 H, 3-H), 5.78–5.58 (m, 2 H, 7-H, 8-H), 4.59, 4.50, 4.46 (s, 2 H, 5-H), 4.12–3.81 (m, 6 H, 6-H, 9-H, 11-H), 2.98, 2.96, 2.94 (s, 3 H, 15-H), 1.46, 1.42 (s, 9 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.2, 168.7, 168.5 (s, C-10), 156.2, 155.7 (s, C-12), 137.1, 136.1 (s, C-4), 132.8, 132.5, 132.0 (d, C-8), 128.9, 128.5 (d, C-2), 128.2 (d, C-3), 127.7, 127.6, 127.4 (d, C-1), 126.4, 126.2 (d, C-3), 125.6, 125.3, 124.9 (d, C-7), 80.0, 79.9 (s, C-13), 62.6, 62.5, 62.3 (t, C-9), 50.8, 50.7, 50.0, 49.6, 49.3, 48.9, 48.7, 47.4, 47.3, 47.2 (3t, C-5, C-6, C-11), 35.9, 35.7, 35.6 (q, C-15), 28.3 (q, C-14) ppm. HRMS (CI): calcd. for $C_{19}H_{28}N_2O_4$ [M]$^+$ 348.2049; found 348.2066. $C_{19}H_{28}N_2O_4$ (348.44): calcd. C 65.49, H 8.10, N 8.04; found C 64.79, H 8.10, N 7.91.

***N*-*tert*-Butyloxycarbonyl-sarcosyl-{*N*-[4-hydroxy-(2*E*)-buten-1-yl]-*N*-methyl}amide (5f):** According to the general procedure for silyl

group cleavage, alcohol **5f** (265 mg, 0.97 mmol, 84%) was obtained from **4f** (450 mg, 1.16 mmol) after flash chromatography (hexanes/ethyl acetate, 1:1 to ethyl acetate) as a yellow oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{13}H_{24}N_2O_4$ $[M]^+$ 272.1736; found 272.1730.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.78 (m, 1 H, 8-H), 5.65 (m, 1 H, 7-H), 4.16 (br. s, 2 H, 9-H), 4.04–3.97 (m, 4 H, 4-H, 6-H), 2.94–2.92 (m, 6 H, 10-H, 11-H), 1.69 (t, J = 5.2 Hz, 1 H, OH), 1.45 (s, 9 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.3 (s, C-5), 156.3 (s, C-3), 132.5 (d, C-8), 125.9 (d, C-7), 79.9 (s, C-2), 62.8 (t, C-9), 50.2 (t, C-6), 49.1 (t, C-4), 35.6, 33.8 (2q, C-10, C-11), 28.3 (q, C-1) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 3.87 (br. s, 2 H, 6-H), 1.75 (br. s, 1 H, OH), 1.42 (s, 9 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 156.2 (s, C-3), 131.8 (d, C-8), 125.3 (d, C-7), 62.6 (t, C-9), 50.4 (t, C-6), 50.0 (t, C-4), 35.8, 34.0 (2q, C-10, C-11) ppm.

***N*-*tert*-Butyloxycarbonyl-sarcosyl-{*N*-[4-hydroxy-(2*E*)-buten-1-yl]-*N*-(2-tetrahydropyran-2-yloxyethyl)}amide (5g):** According to the general procedure for silyl group cleavage, alcohol **5g** (3.82 g, 9.89 mmol, 99%) was obtained from **4g** (5.00 g, 10.0 mmol) after flash chromatography (hexanes/ethyl acetate, 1:1 to ethyl acetate) as a yellow oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{19}H_{35}N_2O_6$ $[M + H]^+$ 387.2450; found 387.2425. $C_{19}H_{34}N_2O_6$ (386.48): calcd. C 59.05, H 8.87, N 7.25; found C 59.04, H 8.92, N 6.87.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.77–5.66 (m, 2 H, 9-H, 10-H), 4.55 (br. s, 1 H, 5-H), 4.15–3.95 (m, 6 H, 8-H, 11-H, 13-H), 3.82 (m, 2 H, 6-H), 3.61 (m, 1 H, 1-Ha), 3.54–3.46 (m, 3 H, 1-Hb, 7-H), 2.90 (s, 3 H, 17-H), 1.78–1.67 (m, 2 H, 3-Ha, 4-Ha), 1.53–1.49 (m, 4 H, 2-H, 3-Hb, 4-Hb), 1.43 (s, 9 H, 16-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.1 (s, C-12), 156.3 (s, C-14), 132.1 (d, C-10), 126.2 (d, C-9), 99.0 (d, C-5), 79.8 (s, C-15), 65.9, 62.7, 62.4 (3t, C-1, C-6, C-11), 50.7, 50.1, 49.6, 47.5 (2t, C-8, C-13), 46.4 (t, C-7), 35.7 (q, C-17), 30.4 (t, C-4), 28.3 (q, C-16), 25.3 (t, C-2), 19.6 (t, C-3) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, 16-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.9 (s, C-12), 156.2 (s, C-14), 131.7 (d, C-10), 126.6 (d, C-9), 99.1 (d, C-5), 80.0 (s, C-15), 62.8, 62.6, 62.3 (3t, C-1, C-6, C-11), 50.6, 49.9, 49.8, 47.4 (2t, C-8, C-13), 46.6 (t, C-7), 35.6 (q, C-17), 30.6 (t, C-4), 25.2 (t, C-2), 19.3 (t, C-3) ppm.

Synthesis of Allyl Carbonates. General Procedure: A solution of allyl alcohol **5** and pyridine (2.5 equiv.) in dichloromethane (0.7 mL/mmol) was cooled to 0 °C before ethyl chloroformate (1.2 equiv.) was added. The mixture was warmed to room temperature overnight, then 1 N $KHSO_4$ (3 mL/mmol) was added and the aqueous layer was extracted thrice with dichloromethane. The combined organic layers were washed with 1M $CuSO_4$, H_2O and brine, dried (Na_2SO_4), and the solvents evaporated in vacuo. The crude product was purified by flash chromatography.

***N*-Trifluoroacetyl-glycyl-{*N*-benzyl-*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]}amide (6b):** According to the general procedure for allyl carbonate formation, **6b** (706 mg, 1.76 mmol, 96%) was obtained from **5b** (608 mg, 1.84 mmol) after flash chromatography (hexanes/ethyl acetate, 7:3 to 6:4) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{18}H_{22}F_3N_2O_5$ $[M + H]^+$ 403.1436; found 403.1468. $C_{18}H_{21}F_3N_2O_5$ (402.36): calcd. C 53.73, H 5.26, N 6.96; found C 53.93, H 5.34, N 87.01.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.58 (br. s, 1 H, NH), 7.40–7.30 (m, 3 H, 1-H, 2-H), 7.22 (m, 2 H, 3-H), 5.79–5.65 (m, 2 H, 7-H, 8-H), 4.63–4.58 (m, 4 H, 5-H, 9-H), 4.24–4.15 (m, 4 H, 11-H, 14-H), 3.82 (dd, J = 3.6, 3.6 Hz, 2 H, 6-H), 1.33 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.5 (s, C-13), 156.9 (q, $J_{15,F}$ = 37.9 Hz, C-15), 154.8 (s, C-10), 136.0 (s, C-4), 128.9 (d, C-2), 128.3 (d, C-3), 128.0 (d, C-8), 127.9 (d, C-1), 127.7 (d, C-7), 66.5 (t, C-9), 64.2 (t, C-11), 49.1 (t, C-5), 46.9 (t, C-6), 41.3 (t, C-14), 14.2 (q, C-12), (C-16 not detected) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.55 (br. s, 1 H, NH), 7.13 (d, J = 7.0 Hz, 2 H, 3-H), 4.46 (s, 2 H, 5-H), 4.07 (d, J = 5.5 Hz, 2 H, 6-H), 1.31 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 134.7 (s, C-4), 129.3 (d, C-2), 128.4 (d, C-8), 127.3 (d, C-7), 126.4 (d, C-1), 126.3 (d, C-3), 66.9 (t, C-9), 64.3 (t, C-11), 49.4 (t, C-5), 47.3 (t, C-6), 41.4 (t, C-14) ppm.

***N*-*tert*-Butyloxycarbonyl-glycyl-{*N*-benzyl-*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]}amide (6c):** According to the general procedure for allyl carbonate formation, **6c** (1.53 g, 3.76 mmol, 96%) was obtained from **5c** (1.31 g, 3.92 mmol) after flash chromatography (hexanes/ethyl acetate, 7:3 to 6:4) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{21}H_{31}N_2O_6$ $[M + H]^+$ 407.2137; found 407.2206. $C_{21}H_{30}N_2O_6$ (406.47): calcd. C 62.05, H 7.44, N 6.89; found C 61.93, H 7.64, N 6.95.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.37–7.27 (m, 3 H, 1-H, 2-H), 7.21 (d, J = 6.6 Hz, 2 H, 3-H), 5.78–5.53 (m, 2 H, 7-H, 8-H), 5.53 (br. s, 1 H, NH), 4.60–4.58 (m, 4 H, 5-H, 9-H), 4.22 (q, J = 7.1 Hz, 2 H, 11-H), 4.04–4.00 (m, 4 H, 6-H, 14-H), 1.46 (s, 9 H, 17-H), 1.32 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.7 (s, C-13), 155.7 (s, C-15), 154.8 (s, C-10), 136.6 (s, C-4), 128.7 (d, C-2), 128.2 (d, C-3), 129.2, 127.9 (2d, C-1, C-8), 126.8 (d, C-7), 79.6 (s, C-16), 66.7 (t, C-9), 64.2 (t, C-11), 48.6 (t, C-5), 46.9 (t, C-6), 42.2 (t, C-14), 28.3 (q, C-17), 14.2 (q, C-12) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.13 (d, J = 7.2 Hz, 2 H, 3-H), 5.50 (br. s, 1 H, NH), 4.43 (s, 2 H, 5-H), 4.20 (q, J = 7.1 Hz, 2 H, 11-H), 3.79 (br. s, 2 H, 6-H), 1.44 (s, 9 H, 17-H), 1.31 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 135.4 (s, C-4), 128.4, 127.7 (2d, C-1, C-8), 129.1 (d, C-2), 127.2 (d, C-7), 126.4 (d, C-3), 67.1 (t, C-9), 64.1 (t, C-11), 49.3 (t, C-5), 46.9 (t, C-6), 42.3 (t, C-14) ppm.

***N*-*tert*-Butyloxycarbonyl-β-alanyl-{*N*-benzyl-*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]}amide (6d):** According to the general procedure for allyl carbonate formation, **6d** (1.46 g, 3.47 mmol, 94%) was obtained from **5d** (1.29 g, 3.70 mmol) after flash chromatography (hexanes/ethyl acetate, 7:3 to 6:4) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{22}H_{33}N_2O_6$ $[M + H]^+$ 421.2294; found 421.2338. $C_{22}H_{32}N_2O_6$ (420.50): calcd. C 62.84, H 7.67, N 6.66; found C 62.78, H 8.00, N 6.72.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.36–7.28 (m, 3 H, 1-H, 2-H), 7.20 (d, J = 6.8 Hz, 2 H, 3-H), 5.78–5.60 (m, 2 H, 7-H, 8-H), 5.32 (br. s, 1 H, NH), 4.60–4.58 (m, 4 H, 5-H, 9-H), 4.21 (q, J = 7.1 Hz, 2 H, 11-H), 4.01 (d, J = 5.8 Hz, 2 H, 6-H), 3.87 (br. s, 2 H, 6-H), 3.44 (t, J = 5.8 Hz, 2 H, 14-H), 2.56 (t, J = 5.5 Hz, 2 H, 15-H), 1.42 (s, 9 H, 18-H), 1.32 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.0 (s, C-13), 156.0 (s, C-16), 154.9 (s, C-10), 137.1 (s, C-4), 129.1 (d, C-8), 128.6 (d, C-2), 128.1 (d, C-3), 127.5 (d, C-1), 126.3 (d, C-7), 79.1 (s, C-17), 66.8 (t, C-9), 64.2 (t, C-11), 48.2 (t, C-5), 47.8 (t, C-6), 36.3 (t, C-14), 33.4 (t, C-15), 28.4 (q, C-18), 14.2 (q, C-12) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 7.11 (d, J = 7.2 Hz, 2 H, 3-H), 4.47 (s, 2 H, 5-H), 4.19 (q, J = 7.1 Hz, 2 H, 11-H), 3.44 (t, J = 5.8 Hz, 2 H, 14-H), 1.43 (s, 9 H, 18-H), 1.31 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.8 (s, C-13), 154.8 (s, C-10), 136.1 (s, C-4), 129.9 (d, C-8), 129.0 (d, C-2),

127.7 (d, C-1), 126.8 (d, C-7), 126.3 (d, C-3), 67.2 (t, C-9), 64.1 (t, C-11), 50.0 (t, C-5), 46.5 (t, C-6), 36.4 (t, C-14), 33.2 (t, C-15) ppm.

***N-tert*-Butyloxycarbonyl-sarcosyl-{*N*-benzyl-*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]}amide (6e):** According to the general procedure for allyl carbonate formation, **6e** (1.14 g, 2.71 mmol, 90%) was obtained from **5e** (1.05 g, 3.00 mmol) after flash chromatography (hexanes/ethyl acetate, 7:3 to 6:4) as a colorless oil as a mixture of three rotamers. ^{1}H NMR ($CDCl_3$): δ = 7.37–7.30 (m, 3 H, 1-H, 2-H), 7.23 (m, 2 H, 3-H), 7.15 (d, $^3J_{3,2}$ = 7.4 Hz, 2 H, 3-H), 5.80–5.61 (m, 2 H, 7-H, 8-H), 4.60–4.44 (m, 4 H, 5-H, 9-H), 4.21, 4.19 (q, $^3J_{11,12}$ = 7.1 Hz, 2 H, 11-H), 4.08–3.98 (m, 4 H, 6-H, 14-H), 3.84, 3.80 (br. s, 2 H, 6-H), 2.92, 2.90, 2.95 (s, 3 H, 18-H), 1.42 (s, 9 H, 17-H), 1.32, 1.30 (t, $^3J_{12,11}$ = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.0 (s, C-13), 156.2 (s, C-15), 154.8 (s, C-10), 137.0, 136.1 (s, C-4), 129.7, 129.3, 128.9, 128.3, 127.7, 127.6, 127.4, 127.0, 126.4, 126.2 (5d, C-1, C-2, C-3, C-7, C-8), 79.9 (s, C-16), 67.2, 66.9 (t, C-9), 64.2, 64.1, 64.0 (t, C-11), 50.2, 50.0, 49.6 (t, C-14), 49.3, 48.8, 48.6 (t, C-5), 47.3, 47.0, 46.9 (t, C-6), 35.6 (q, C-18), 28.3 (q, C-17), 14.2 (q, C-12) ppm. HRMS (CI): calcd. for $C_{22}H_{32}N_2O_6$ $[M]^+$ 420.2260; found 420.2224. $C_{22}H_{32}N_2O_6$ (420.50): calcd. C 62.84, H 7.67, N 6.66; found C 62.65, H 7.73, N 6.61.

***N-tert*-Butyloxycarbonyl-sarcosyl-{*N*-methyl-*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]}amide (6f):** According to the general procedure for allyl carbonate formation, **6f** (271 mg, 0.79 mmol, 85%) was obtained from **5f** (252 mg, 0.93 mmol) after flash chromatography (hexanes/ethyl acetate, 9:1 to 3:7) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{12}H_{20}N_2O_6$ $[M - t\mathrm{Bu}]^+$ 288.1321; found 288.1285. $C_{16}H_{28}N_2O_6$ (344.40): calcd. C 55.80, H 8.19, N 8.13; found C 55.79, H 8.09, N 8.18.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.78–5.67 (m, 2 H, 7-H, 8-H), 4.60 (d, J = 8.4 Hz, 2 H, 9-H), 4.19 (q, J = 7.1 Hz, 2 H, 11-H), 4.04–3.91 (m, 4 H, 4-H, 6-H), 2.92–2.90 (m, 6 H, 13-H, 14-H), 1.46 (s, 9 H, 1-H), 1.30 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.3 (s, C-5), 154.9, 154.8 (2s, C-3, C-10), 129.9 (d, C-8), 126.7 (d, C-7), 79.9 (s, C-2), 67.2 (t, C-9), 64.1 (t, C-11), 50.2 (t, C-6), 48.9 (t, C-4), 35.6, 33.7 (2q, C-13, C-14), 28.3 (q, C-1), 14.2 (q, C-12) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 4.66 (d, J = 8.7 Hz, 2 H, 9-H), 4.20 (q, J = 7.1 Hz, 2 H, 11-H), 1.42 (s, 9 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 129.6 (d, C-8), 126.2 (d, C-7), 66.9 (t, C-9), 64.2 (t, C-11), 50.3 (t, C-6), 50.0 (t, C-4), 35.5, 33.8 (2q, C-13, C-14) ppm.

***N-tert*-Butyloxycarbonyl-sarcosyl-{*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]-*N*-(2-tetrahydropyran-2-yloxyethyl)}amide (6g):** According to the general procedure for allyl carbonate formation, **6g** (3.71 g, 8.09 mmol, 86%) was obtained from **5g** (3.68 g, 9.52 mmol) after flash chromatography (hexanes/ethyl acetate, 1:1 to 3:7) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{22}H_{38}N_2O_8$ $[M]^+$ 458.2628; found 458.2632. $C_{22}H_{38}N_2O_8$ (458.55): calcd. C 57.62, H 8.35, N 6.11; found C 57.76, H 8.34, N 6.45.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.79–5.65 (m, 2 H, 9-H, 10-H), 4.60–4.53 (m, 3 H, 5-H, 11-H), 4.20–3.90 (m, 6 H, 8-H, 13-H, 16-H), 3.79 (m, 2 H, 6-H), 3.59 (m, 1 H, 1-H_a), 3.49–3.42 (m, 3 H, 1-H_b, 7-H), 2.89 (s, 3 H, 20-H), 1.76–1.66 (m, 2 H, 3-H_a, 4-H_a), 1.54–1.50 (m, 4 H, 2-H, 3-H_b, 4-H_b), 1.43 (s, 9 H, 19-H), 1.27 (t, J = 7.1 Hz, 3 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.0 (s, C-15), 156.3 (s, C-17), 154.8 (s, C-12), 130.4 (d, C-10), 126.2 (d, C-9), 98.9 (d, C-5), 79.7 (s, C-18), 67.3 (t, C-11), 65.0, 62.3 (2t, C-1, C-6), 64.0 (t, C-13), 50.6, 49.9 (2t, C-8, C-16), 46.2 (t, C-7), 35.7 (q, C-20), 30.6 (t, C-4), 28.3 (q, C-19), 25.3 (t, C-2), 19.3 (t, C-3), 14.2 (q, C-14) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 2.86 (s, 3 H, 20-H), 1.39 (s, 9 H, 19-H), 1.28 (t, J = 7.1 Hz, 3 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.7 (s, C-15), 156.0 (s, C-17), 154.8 (s, C-12), 130.0 (d, C-10), 125.8 (d, C-9), 99.0 (d, C-5), 79.8 (s, C-18), 67.0 (t, C-11), 65.9, 62.1 (2t, C-1, C-6), 64.1 (t, C-13), 50.0, 49.6 (2t, C-8, C-16), 47.1 (t, C-7), 35.5 (q, C-20), 30.4 (t, C-4), 28.4 (q, C-19), 25.2 (t, C-2), 19.5 (t, C-3) ppm.

***N-tert*-Butyloxycarbonyl-sarcosyl-{*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]-*N*-(2-hydroxyethyl)}amide (6h):** THP-protected alcohol **6g** (1.20 g, 2.61 mmol) was dissolved in methanol (20 mL), *p*-toluenesulfonic acid (20 mg, 0.1 mmol) was added and, after stirring for 30 min, when all **6g** was consumed (TLC), solid $NaHCO_3$ (420 mg, 5 mmol) was added. After evaporation of the solvent, the residue was dissolved in ethyl acetate and water was added. The aqueous layer was extracted thrice with diethyl ether, the combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 1:1 to ethyl acetate) to give **6h** (835 mg, 2.23 mmol, 85%) as a colorless oil as a mixture of rotamers. HRMS (CI): calcd. for $C_{17}H_{31}N_2O_7$ $[M + H]^+$ 375.2131; found 375.2122. $C_{17}H_{30}N_2O_7$ (374.43): calcd. C 54.53, H 8.08, N 7.48; found C 54.54, H 7.99, N 7.53.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.81–5.67 (m, 2 H, 4-H, 5-H), 4.62 (d, J = 4.0 Hz, 2 H, 6-H), 4.20 (q, J = 7.1 Hz, 2 H, 8-H), 4.11–3.95 (m, 4 H, 3-H, 11-H), 3.75 (m, 2 H, 1-H), 3.51 (m, 2 H, 2-H), 3.03 (br. s, 1 H, OH), 2.91 (s, 3 H, 15-H), 1.45 (s, 9 H, 14-H), 1.31 (t, J = 7.1 Hz, 3 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.6 (s, C-10), 156.2 (s, C-12), 154.8 (s, C-7), 130.4 (d, C-5), 126.4 (d, C-4), 80.1 (s, C-13), 67.3 (t, C-6), 64.1 (t, C-8), 61.6 (t, C-1), 50.1, 47.2 (2t, C-3, C-11), 50.0 (t, C-2), 35.6 (q, C-15), 28.3 (q, C-14), 14.2 (q, C-9) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 4.59 (d, J = 5.6 Hz, 2 H, 6-H), 3.42 (m, 2 H, 2-H), 2.96 (s, 3 H, 15-H), 1.42 (s, 9 H, 14-H), 1.29 (t, J = 7.1 Hz, 3 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.3 (s, C-10), 156.6 (s, C-12), 154.9 (s, C-7), 129.3 (d, C-5), 126.3 (d, C-4), 66.8 (t, C-6), 64.2 (t, C-8), 60.2 (t, C-1), 50.7, 49.6 (2t, C-3, C-11), 48.9 (t, C-2), 36.3 (q, C-15) ppm.

***N-tert*-Butyloxycarbonyl-sarcosyl-{*N*-[4-benzoyloxy-(2*E*)-buten-1-yl]-*N*-benzyl}amide (6i):** Alcohol **5e** (1.05 g, 3.00 mmol) was dissolved in dichloromethane (30 mL) together with pyridine (363 µL, 4.50 mmol) and the solution was cooled to 0 °C before DMAP (37 mg, 0.30 mmol, 10 mol-%) and benzoyl chloride (519 µL, 4.50 mmol) were added. The mixture was warmed to room temperature overnight, then 1*N* $KHSO_4$ (10 mL) was added and the aqueous layer was extracted thrice with dichloromethane. The combined organic layers were washed with 1M $CuSO_4$, H_2O, and brine, dried (Na_2SO_4), and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 8:2 to 7:3) to give **6i** (1.38 g, 2.95 mmol, 98%) as a colorless oil as a mixture of three rotamers. ^{1}H NMR ($CDCl_3$): δ = 8.05 (d, J = 7.5 Hz, 2 H, 12-H), 7.57 (d, J = 7.0 Hz, 1 H, 14-H), 7.45 (m, 2 H, 13-H), 7.36–7.16 (m, 5 H, 1-H, 2-H, 3-H), 5.85–5.70 (m, 2 H, 7-H, 8-H), 4.80 (m, 2 H, 9-H), 4.52, 4.47, 4.61 (s, 2 H, 5-H), 4.11–4.01 (m, 4 H, 6-H, 16-H), 3.88, 3.84 (br. s, 2 H, 6-H), 2.95 (s, 3 H, 20-H), 1.47, 1.43, 1.41 (s, 9 H, 19-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.1, 169.0 (s, C-15), 166.2, 166.1 (s, C-10), 156.2, 155.7 (s, C-17), 137.1, 137.0, 136.2 (s, C-4), 133.2, 133.1, 133.0 (d, C-14), 130.0 (s, C-11), 129.6, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.6, 127.4, 127.0, 126.5, 126.3 (6d, C-1, C-2, C-3, C-7, C-8, C-13), 79.9 (s, C-18), 64.4, 64.2, 64.1 (t, C-9), 50.8, 50.7, 50.2 (t, C-16), 49.7, 49.5, 49.0, 48.8 (t, C-5), 47.5, 47.4, 47.2, 47.1 (t, C-6),

35.8, 35.7, 35.6 (q, C-20), 28.3 (q, C-19) ppm. HRMS (CI): calcd. for $C_{26}H_{32}N_2O_5$ $[M]^+$ 452.2311; found 452.2333.

1-Benzyl-4-trifluoracetyl-5-vinylpiperazin-2-one (7b): Allylpalladium chloride dimer (0.7 mg, 2.0 μmol, 2 mol-%) and triphenylphosphine (2.4 mg, 9.0 μmol, 9 mol-%) were dissolved in DMF (1 mL) and the solution was stirred at room temperature for 15 min. This solution was added to a solution of allyl carbonate **6b** (40 mg, 0.10 mmol) in DMF (2 mL) and the mixture was heated to 100 °C overnight. The solvent was removed in vacuo and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 8:2 to 7:3) to give **7b** (34 mg, 0.10 mmol, >99%) as a colorless oil as a mixture of three rotamers. ^{1}H NMR ($CDCl_3$): δ = 7.38–7.26 (m, 5 H, 1-H, 2-H, 3-H), 5.53 (ddd, J = 15.2, 10.5, 4.2 Hz, 1 H, 8-H), 5.32 (dd, J = 15.1, 1.4 Hz, 1 H, 9-H_{cis}), 5.29 (dd, J = 15.0, 1.1 Hz, 1 H, 9-H_{cis}), 5.24, 4.72 (br. s, 1 H, 7-H), 5.09 (d, J = 10.1 Hz, 1 H, 9-H_{trans}), 5.05 (dd, J = 10.1, 1.1 Hz, 1 H, 9-H_{trans}), 4.91, 4.87 (d, J = 14.4 Hz, 1 H, 10-H_a), 4.85 (d, J = 18.9 Hz, 1 H, 5-H_a), 4.47 (d, J = 17.7 Hz, 1 H, 5-H_a), 4.35 (d, J = 13.9 Hz, 1 H, 10-H_b), 4.19 (d, J = 17.7 Hz, 1 H, 5-H_b), 3.93 (d, J = 18.8 Hz, 1 H, 5-H_b), 3.64 (dd, J = 12.8, 3.8 Hz, 1 H, 6-H_a), 3.56 (dd, J = 13.0, 4.3 Hz, 1 H, 6-H_a), 3.30 (d, J = 12.9 Hz, 1 H, 6-H_b) ppm. ^{13}C NMR ($CDCl_3$): δ = 163.4, 162.8 (s, C-11), 156.9 (q, $J_{16,F}$ = 37.6 Hz, C-12), 155.3 (q, $J_{12,F}$ = 27.9 Hz, C-12), 135.3, 135.2 (s, C-4), 131.7, 131.1 (d, C-8), 128.9, 128.7 (d, C-2), 128.2, 127.3, 126.4, 126.3 (2d, C-1, C-3), 119.9, 119.6 (t, C-9), 116.0 (q, $J_{13,F}$ = 286.6 Hz, C-13), 52.7, 49.9 (d, C-7), 50.1, 49.9 (t, C-10), 48.3, 47.0 (t, C-6), 45.5, 44.5 (t, C-5) ppm. HRMS (CI): calcd. for $C_{15}H_{15}F_3N_2O_2$ $[M]^+$ 312.1086; found 312.1086. $C_{15}H_{15}F_3N_2O_2$ (312.29): calcd. C 57.69, H 4.84, N 8.97; found C 57.71, H 5.11, N 8.79.

1-Benzyl-4-*tert*-butyloxycarbonyl-5-vinylpiperazin-2-one (7c): A fresh prepared LHMDS solution in THF (3 mL), obtained from HMDS (90 mg, 0.56 mmol) and BuLi (1.6 M in hexane, 0.31 mL, 0.50 mmol) at –20 °C, was added to a solution of allyl carbonate **6c** (81 mg, 0.20 mmol) and zinc chloride (41 mg, 0.30 mmol) in THF (3 mL) at –78 °C and the mixture was stirred at this temperature for 30 min. A solution of allylpalladium chloride dimer (1.5 mg, 4.0 μmol, 2 mol-%) and triphenylphosphine (2.1 mg, 8.0 μmol, 4 mol-%) in THF (3 mL) was added at –78 °C and the reaction mixture was warmed to room temperature overnight. To complete the reaction, the mixture was subsequently heated to reflux for another 7 h, before it was cooled to room temperature and hydrolyzed with NH_4OAc buffer (5 mL). The aqueous layer was separated and extracted thrice with diethyl ether. The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the crude product was purified by flash chromatography (hexanes/ethyl acetate, 7:3 to 6:4) to give **7c** (50 mg, 0.15 mmol, 76%) as a yellow oil as a mixture of rotamers.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 7.36–7.25 (m, 5 H, 1-H, 2-H, 3-H), 5.53 (ddd, J = 17.3, 10.5, 4.2 Hz, 1 H, 8-H), 5.18 (dd, J = 10.5, 1.4 Hz, 1 H, 9-H_{trans}), 5.02 (dd, J = 17.3, 1.4 Hz, 1 H, 9-H_{trans}), 4.82–4.78 (m, 2 H, 7-H, 10-H_a), 4.42 (d, J = 14.5 Hz, 1 H, 10-H_b), 4.33 (d, J = 18.3 Hz, 1 H, 5-H_a), 3.91 (d, J = 18.3 Hz, 1 H, 5-H_b), 3.56 (dd, J = 12.5, 4.5 Hz, 1 H, 6-H_a), 3.19 (dd, J = 12.5, 1.7 Hz, 1 H, 6-H_b), 1.46 (s, 9 H, 14-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.5 (s, C-11), 153.8 (s, C-12), 135.9 (s, C-4), 133.6 (d, C-8), 128.7, 128.6 (d, C-2/C-3), 127.9 (d, C-1), 117.7 (t, C-9), 80.9 (s, C-13), 49.9 (2d, C-7, C-10), 48.4 (t, C-6), 45.3 (t, C-5), 28.3 (q, C-14) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 5.56 (ddd, J = 17.2, 10.5, 4.2 Hz, 1 H, 8-H) ppm.

***N*-*tert*-Butyloxycarbonyl-α-deuterio-sarcosyl-{*N*-benzyl-*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]}amide (8):** *n*BuLi (1.6 M toluene, 0.44 mL, 0.70 mmol) was added to hexamethyldisilazane (157 μL, 0.76 mmol) in THF (2 mL) at –78 °C. After stirring 30 min at this temperature, carbonate **6c** (84 mg, 0.20 mmol) was added in THF (2 mL) and the reaction mixture was stirred for 3 h before D_2O (1 mL) was added. The cooling bath was removed and the mixture was warmed to room temperature and then diluted with diethyl ether. The aqueous layer was extracted with diethyl ether, the combined organic layers were dried (Na_2SO_4), and the solvents evaporated in vacuo to give **8** (75 mg, 0.18 mmol, 90%) as a colorless oil as a mixture of rotamers. ^{1}H NMR ($CDCl_3$): δ = 7.33–7.13 (m, 5 H, 1-H, 2-H, 3-H), 5.80–5.60 (m, 2 H, 7-H, 8-H), 4.58–4.56 (m, 4 H, 5-H, 9-H), 4.47, 4.42 (m, 2 H, 5-H), 4.19, 4.17 (q, J = 7.1 Hz, 2 H, 11-H), 4.06–3.94 (m, 3 H, 6-H, 14-H), 3.83, 3.78 (br. s, 2 H, 6-H), 2.93, 2.89 (s, 3 H, 18-H), 1.45, 1.41, 1.40 (s, 9 H, 17-H), 1.30, 1.28 (t, J = 7.1 Hz, 3 H, 12-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.0, 168.9, 168.7, 168.5 (s, C-13), 156.1, 155.6 (s, C-15), 154.8 (s, C-10), 137.0, 136.9, 136.1, 135.9 (s, C-4), 129.7, 129.2, 129.0, 128.9, 128.8, 128.5, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 126.9, 126.8, 126.4, 126.3, 126.2 (5d, C-1, C-2, C-3, C-7, C-8), 79.8 (s, C-16), 67.1, 66.8, 66.6 (t, C-9), 64.1, 64.0 (t, C-11), 49.3, 48.7, 48.5 (t, C-5), 47.2, 47.1, 46.9, 46.8 (t, C-6), 35.6, 35.7, 35.5 (q, C-18), 28.2 (q, C-17), 14.2 (q, C-12) ppm. HRMS (CI): calcd. for $C_{22}H_{31}DN_2O_6$ $[M]^+$ 421.2323; found 421.2329. $C_{22}H_{31}DN_2O_6$ (421.51): calcd. C 62.69, H 7.89, N 6.65; found C 62.82, H 7.75, N 6.88.

General Procedure for Pd-Catalyzed Allylic Alkylations: Zinc chloride (204 mg, 1.5 mmol) was heated in a Schlenk tube with the heat gun until dry. After cooling to room temperature, the salt was dissolved in THF (5 mL) before the amino acid ester or amide (1.0 mmol) as added. In a second Schlenk tube, hexamethyldisilazane (450 mg, 0.58 mL, 2.8 mmol) was dissolved in THF (5 mL). The the stirred solution was cooled to –78 °C before *n*BuLi (1.6 M in hexane, 1.56 mL, 2.5 mmol) was added. The cooling bath was removed for 10 min and, after cooling again to –78 °C, the glycine ester/amide and zinc chloride solution was added at this temperature. After stirring for 30 min, a solution of allylpalladium chloride dimer (3.66 mg, 0.01 mmol, 1 mol-%), triphenylphosphine (11.8 mg, 0.045 mmol, 4.5 mol-%) and the corresponding allyl carbonate (0.5 mmol) in THF (5 mL) was added at –78 °C. The reaction mixture was warmed to room temperature overnight, then diluted with diethyl ether (20 mL) and hydrolyzed with 1 N HCl (10 mL). The aqueous layer was extracted thrice with diethyl ether, the combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the crude product was purified by flash chromatography.

***N*-*tert*-Butyloxycarbonyl-α-allyl-sarcosyl-{*N*-benzyl-*N*-[4-ethoxycarbonyloxy-(2*E*)-buten-1-yl]}amide (9):** According to the general procedure for Pd-catalyzed allylic alkylations, allylated sarcosine derivative **9** was obtained from benzoate **6i** (136 mg, 0.3 mmol) and allyl ethyl carbonate (39 mg, 0.30 mmol) using 3.5 equiv. of LHMDS. After purification by flash chromatography (hexanes/ethyl acetate, 9:1 to 7:3), **9** (75 mg, 0.15 mmol, 51%) was obtained as yellow oil as a mixture of rotamers. ^{1}H NMR ($CDCl_3$): δ = 8.05 (m, 2 H, 12-H), 7.57 (m, 1 H, 14-H), 7.46 (m, 2 H, 13-H), 7.36–7.22 (m, 5 H, 1-H, 2-H, 3-H), 7.11 (d, J = 7.3 Hz, 2 H, 3-H), 5.81–5.70 (m, 3 H, 7-H, 8-H, 22-H), 5.21 (t, J = 8.0 Hz, 1 H, 16-H), 5.15–4.78 (m, 5 H, 9-H, 16-H, 23-H), 4.54 (s, 2 H, 5-H), 4.00 (m, 2 H, 6-H), 2.80, 2.77, 2.76 (s, 3 H, 20-H), 2.55 (m, 2 H, 21-H), 1.43, 1.30, 1.29 (s, 9 H, 19-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.6, 169.8 (s, C-15), 166.2, 166.1 (s, C-10), 155.6, 155.5 (s, C-17), 137.3, 137.1, 136.7 (s, C-4), 134.1, 134.0, 133.9 (d, C-22), 133.1, 133.0 (d, C-14), 130.1, 130.0 (s, C-11), 129.6, 129.4, 129.1, 129.0, 128.9, 128.8, 128.6, 128.4, 128.3, 128.1, 127.7, 127.6, 127.4, 127.2, 127.1, 126.8, 126.6, 126.3 (6d, C-1, C-2, C-3, C-7, C-8, C-13), 118.1, 117.8

(t, C-23), 80.5, 80.1, 80.0 (s, C-18), 64.4, 64.1 (t, C-9), 54.0, 49.9, 49.5 (d, C-16), 48.4 (t, C-5), 47.7, 47.1, 46.6 (t, C-6), 33.7, 33.5 (q, C-20), 29.4 (t, C-21), 28.4, 28.3, 28.1 (q, C-19) ppm. HRMS (CI): calcd. for $C_{29}H_{36}N_2O_5$ $[M]^+$ 492.2624; found 492.2600. $C_{29}H_{36}N_2O_5$ (492.61): calcd. C 70.71, H 7.37, N 5.69; found C 70.53, H 6.96, N 6.26.

Pd-Catalyzed Intramolecular Allylations. General Procedure: The LHMDS solution was prepared from HMDS (157 μL, 0.76 mmol) and *n*BuLi (0.44 mL, 0.70 mmol) in dichloromethane (2 mL) at –78 °C. After the addition of BuLi, the cooling bath was removed and the reaction mixture was warmed to –25 °C, before it was cooled again to –78 °C. A solution of the corresponding allyl substrate **6** (0.20 mmol) and chlorotitaniumtriisopropoxide (1 M in hexane, 0.22 mL, 0.22 mmol) in THF (2 mL) was added at this temperature. After stirring for 30 min, a solution of allylpalladiumchloride dimer (3.7 mg, 10.0 μmol, 5 mol-%) and triphenylphosphine (27.5 mg, 105 μmol, 52.5 mmol-%) in dichloromethane (1 mL) was added. The reaction mixture was warmed to room temperature overnight before it was hydrolyzed with a mixture of 2 N NaOH and satd. potassium sodium tartrate solution. The solution was stirred until the layers separated, then the aqueous layer was separated and extracted twice with dichloromethane. The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the crude product was purified by flash chromatography.

1-Benzyl-3-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-4-vinylpyrrolidin-2-one (12e): According to the general procedure for Pd-catalyzed intramolecular allylations, pyrrolidin-2-one **12e** (48 mg, 0.25 mmol, 75%) was obtained from allyl carbonate **6e** (84 mg, 0.2 mmol) after flash chromatography (hexanes/ethyl acetate, 9:1 to 1:1) as a pale-yellow oil as a mixture of rotamers. Ratio *anti*/*syn* = 86:14. ^{1}H NMR ($CDCl_3$): δ = 7.33–7.28 (m, 3 H, 14-H, 15-H), 7.24 (d, J = 6.5 Hz, 2 H, 13-H), 5.69 (m, 1 H, 2-H), 5.13–5.06 (m, 2 H, 1-H_a, 1-H_b), 4.66 (d, J = 9.5 Hz, 1 H, 6-H), 4.51–4.40 (m, 3 H, 6-H, 11-H), 3.27 (br. s, 1 H, 4-H_a), 3.14–2.95 (m, 2 H, 3-H, 4-H_b), 2.86, 2.83 (s, 3 H, 10-H), 1.45, 1.42 (s, 9 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.5, 170.2 (s, C-5), 155.9, 155.3 (s, C-7), 136.0 (d, C-2), 135.8 (s, C-12), 128.7 (d, C-14), 128.3, 128.1 (d, C-13), 127.7, 127.5 (d, C-15), 117.9, 117.6 (t, C-1), 80.3, 80.0 (s, C-8), 63.8, 63.0 (d, C-6), 47.7 (t, C-4), 47.1, 47.0 (t, C-11), 41.6, 41.1 (d, C-3), 31.9 (q, C-10), 28.2 (q, C-9) ppm. HPLC (Chiracel ODH; hexane/*i*PrOH, 90:10; 1 mL/min): (*anti*)-**12e**: t_R = 33.96, 75.48 min; (*syn*)-**12e**: t_R = 38.81, 51.68 min. HRMS (CI): calcd. for $C_{19}H_{26}N_2O_3$ $[M]^+$ 330.1943; found 330.1926.

3-[(*tert*-Butyloxycarbonyl)methylamino]-1-methyl-4-vinylpyrrolidin-2-one (12f): According to the general procedure for Pd-catalyzed intramolecular allylations, pyrrolidin-2-one **12f** (35 mg, 0.14 mmol, 69%) was obtained as a colorless oil as a mixture of rotamers from allyl carbonate **6f** (69 mg, 0.20 mmol) after flash chromatography (hexanes/ethyl acetate, 1:1 to 3:7). Ratio *anti*/*syn* = 88:20. HPLC (Chiracel ODH; hexane/*i*PrOH, 90:10; 1 mL/min): (*anti*)-**12f**: t_R = 15.35, 19.20 min; (*syn*)-**12f**: t_R = 12.89, 15.35 min. HRMS (CI): calcd. for $C_{13}H_{22}N_2O_3$ $[M]^+$ 254.1630; found 254.1604. $C_{13}H_{22}N_2O_3$ (254.33): calcd. C 61.39, H 8.72, N 11.01; found C 61.56, H 8.68, N 11.41.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.80 (m, 1 H, 2-H), 5.18–5.10 (m, 2 H, 1-H), 4.53 (d, J = 10.3 Hz, 1 H, 6-H), 3.38 (dd, J = 8.9, 8.9 Hz, 1 H, 4-H_a), 3.11 (dd, J = 9.3, 9.3 Hz, 1 H, 4-H_b), 3.00 (m, 1 H, 3-H), 2.88–2.75 (m, 6 H, 10-H, 11-H), 1.41 (s, 9 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.4 (s, C-5), 155.3 (s, C-7), 136.2 (d, C-2), 117.9 (t, C-1), 80.3 (s, C-8), 63.1 (d, C-6), 50.5 (t, C-4), 41.7 (d, C-3), 30.1, 30.0 (2q, C-10, C-11), 28.2 (q, C-9) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 4.32 (br. s, 1 H, 6-H), 1.42 (s, 9 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7 (s, C-5), 155.9 (s, C-7), 136.3 (d, C-2), 117.6 (t, C-1), 80.0 (s, C-8), 64.0 (d, C-6), 41.2 (d, C-3), 28.3 (q, C-9) ppm.

3-[(*tert*-Butyloxycarbonyl)methylamino]-1-(2-tetrahydropyran-2-yloxyethyl)-4-vinylpyrrolidin-2-one (12g): According to the general procedure for Pd-catalyzed intramolecular allylations, pyrrolidin-2-one **12g** (65 mg, 0.18 mmol, 88%) was obtained as a colorless oil as a mixture of rotamers from allyl carbonate **6g** (92 mg, 0.20 mmol) after flash chromatography (hexanes/ethyl acetate, 9:1 to 4:6). Ratio *anti*/*syn* = 82:18. HPLC (Chiracel ODH; hexane/*i*PrOH, 90:10; 1 mL/min): (*anti*)-**12g**: t_R = 41.35, 59.13 min; (*syn*)-**12g**: t_R = 49.49, 52.01 min. HRMS (CI): calcd. for $C_{19}H_{33}N_2O_5$ $[M + H]^+$ 369.2345; found 369.2380. $C_{19}H_{32}N_2O_5$ (368.47): calcd. C 61.93, H 8.75, N 7.60; found C 62.10, H 8.96, N 7.90.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.80 (ddd, J = 17.5, 9.8, 8.2 Hz, 1 H, 2-H), 5.19–5.11 (m, 2 H, 1-H), 4.67 (d, J = 10.8 Hz, 1 H, 6-H), 4.58 (s, 1 H, 13-H), 3.90–3.80 (m, 2 H, 12-Ha, 17-H_a), 3.71–3.35 (m, 5 H, 4-H_a, 11-H, 12-H_b, 17-H_b), 3.27 (dd, J = 9.8, 9.8 Hz, 1 H, 4-H_b), 3.00 (ddd, J = 18.3, 9.1, 9.1 Hz, 1 H, 3-H), 2.84 (s, 3 H, 10-H), 1.80–1.70 (m, 2 H, 14-H_a, 15-H_a), 1.58–1.48 (m, 4 H, 14-H_b, 15-Hb, 16-H), 1.43 (s, 9 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.5 (s, C-5), 156.0 (s, C-7), 136.4 (d, C-2), 117.9 (t, C-1), 98.9 (d, C-13), 80.3 (s, C-8), 65.4, 62.6, 62.5 (d, C-6, 2t, C-12, C-17), 49.8 (t, C-4), 43.2 (t, C-11), 42.1 (d, C-3), 30.7 (q, C-10, t, C-14), 28.3 (q, C-9), 25.4 (t, C-16), 19.6 (t, C-15) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 3.26 (dd, J = 9.8, 9.8 Hz, 1 H, 4-H_b), 2.80 (s, 3 H, 10-H), 1.45 (s, 9 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 136.9 (d, C-2), 117.7 (t, C-1), 110.0 (d, C-13), 80.0 (s, C-8), 41.7 (d, C-3) ppm.

3-[(*tert*-Butyloxycarbonyl)methylamino]-1-(2-hydroxyethyl)-4-vinylpyrrolidin-2-one (12h): According to the general procedure for Pd-catalyzed intramolecular allylations, pyrrolidin-2-one **12h** (29 mg, 0.10 mmol, 50%) was obtained as a colorless oil as a mixture of rotamers from allyl carbonate **6h** (75 mg, 0.20 mmol) after flash chromatography (hexanes/ethyl acetate, 1:1 to 1:9). Ratio *anti*/*syn* = 78:22. HPLC (Chiracel ODH; hexane/*i*PrOH, 90:10; 1 mL/min): (*anti*)-**12g**: t_R = 33.37, 36.04 min; (*syn*)-**12g**: t_R = 36.04, 54.87 min. HRMS (CI): calcd. for $C_{14}H_{24}N_2O_4$ $[M]^+$ 284.1736; found 284.1734.

Major Rotamer: ^{1}H NMR ($CDCl_3$): δ = 5.77 (m, 1 H, 2-H), 5.20–5.10 (m, 2 H, 1-H), 4.40 (d, J = 9.6 Hz, 1 H, 6-H), 3.77 (m, 2 H, 12-H), 3.56–3.45 (m, 2 H, 4-H_a, 11-H_a), 3.36 (m, 1 H, 11-H_b), 3.25 (dd, J = 9.8, 9.8 Hz, 1 H, 4-H_b), 3.07 (ddd, J = 17.8, 8.9, 8.9 Hz, 1 H, 3-H), 2.84 (s, 3 H, 10-H), 1.42 (s, 9 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.7 (s, C-5), 155.9 (s, C-7), 136.5 (d, C-2), 118.1 (t, C-1), 80.5 (s, C-8), 64.2 (d, C-6), 60.2 (t, C-12), 50.0 (t, C-4), 46.5 (t, C-11), 41.7 (d, C-3), 33.4 (q, C-10), 28.3 (q, C-9) ppm.

Minor Rotamer (selected signals): ^{1}H NMR ($CDCl_3$): δ = 3.24 (dd, J = 9.8, 9.8 Hz, 1 H, 4-H_b), 1.43 (s, 9 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.9 (s, C-5), 155.3 (s, C-7), 136.1 (d, C-2), 117.6 (t, C-1), 80.4 (s, C-8), 60.6 (t, C-12), 49.8 (t, C-4), 46.6 (t, C-11), 42.2 (d, C-3), 33.4 (q, C-10), 28.3 (q, C-9) ppm.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra of all new compounds.

Acknowledgments

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