Application of the Ester Enolate Claisen Rearrangement in the Synthesis of Amino Acids Containing Quaternary Carbon Centers

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Ester enolate Claisen rearrangement of highly substituted amino acid allylic esters **4** allows for the synthesis of sterically demanding amino acids **5** with β-quaternary carbon centers. Because of enolate fixation by chelation, the rearrangement occurs in a highly diastereoselective fashion. The methodology is suitable not only for glycine derivatives but also for allylic esters of various amino acids. In this case amino acids with two vicinal quaternary carbon centers are created. With unsymmetrically substituted allylic esters like **4k**−**n** the rearrangement proceeds with a high degree of diastereoselectivity.

Introduction

Amino acids containing quaternary β-carbon centers are, in addition to α-alkylated amino acids, an especially interesting class of nonproteinogenic amino acids. The most common representative, *tert*-leucine, occurs as a building block in various complex natural products like bottromycin A,[1] milnamide A,[2] the related hemiasterlins[3] or the discodermins.[4] Recently, *tert*-leucine was used as a precursor for the synthesis of chiral auxiliaries[5] and ligands[6] applied to asymmetric synthesis. While various methods are known for the synthesis of α-alkylated amino acids,[7] there are fewer procedures available for the formation of amino acids containing quaternary β-centers.[8] During the last years numerous investigations have been undertaken into the synthesis of *tert*-leucine[9] and its derivatives.[10] But the stereoselective generation of amino acids with chiral β-carbon centers is not a trivial issue and is therefore not yet well developed. Besides Michael- and cycloadditions, the sigmatropic rearrangement processes are suitable for this purpose.[11] The major procedures applied to amino acid syntheses are the rearrangement of amino acid allylic esters *via* oxazole-intermediates,[12] developed by Steglich,[13] and the Ireland−Claisen rearrangement,[14,15] investigated by Bartlett.[16]

In a previous communication we described a new variation of the ester enolate Claisen rearrangement, one that is especially suitable for α-amino acid synthesis.[17] Deprotonation of *N*-protected amino acid allylic esters

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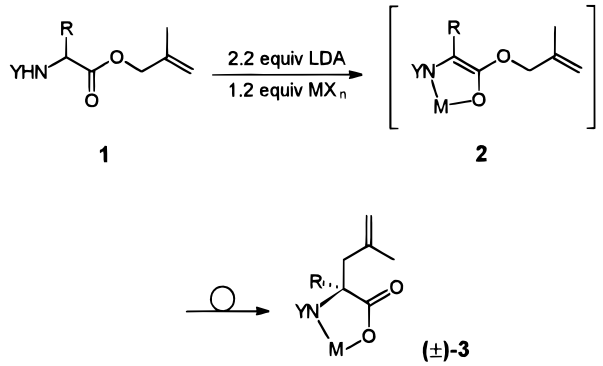
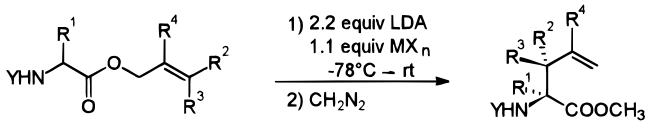
Scheme 1



Scheme 2



(Scheme 1) such as **1** with LDA at −78 °C and subsequent addition of a metal salt (MX_n) presumably results in the formation of a chelated metal enolate **2,** which undergoes Claisen rearrangement upon warming to room temperature, giving rise to unsaturated amino acid **3**.

In contrast to the corresponding lithium enolates, which do not show this rearrangement, due to decomposition during warming, the chelate enolates are much more stable. Otherwise, the metal enolates are clearly superior to silylketene acetals, both in terms of their reactivity and selectivity.[16] The driving force for the accelerated rearrangement of the chelate enolates is probably the transformation of the high-energy ester enolate **2** into a chelate bridged, stabilized carboxylate **3**. Due to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeds with a high degree of diastereoselectivity, independent of the substitution pattern and the protecting groups Y used. This method is suitable for acyclic as well as cyclic allylic esters[18] and can also be applied to peptides.[19]

In this article our investigations into the stereoselective synthesis of sterically demanding amino acids using this chelate enolate Claisen rearrangement are presented.[20]

Results and Discussion

Because of the promising results obtained with *E*-configured glycine allylic esters, the chelate ester enolate rearrangement was also applied to the rearrangement of highly substituted allylic esters like **4** (Scheme 2), giving rise to amino acids containing quaternary β-carbon centers. Starting from amino acids other than glycine ($R^1 \neq H$) allows for the generation of two vicinal quaternary centers in one step.

The influence of the protecting group Y, the substitution pattern, as well as the metal salt MX_n, used for chelation of the ester enolate, were investigated. The results are listed in Table 1.

Various metal salts can be used for chelation (Table 1, entries 1−4), but in general best results are obtained with zinc chloride and methylaluminum dichloride. Therefore zinc chloride was applied for this purpose in standard reactions because it is less expensive and easier to handle. The rearrangement can be applied to acyclic as well as to cyclic substrates (entries 5−8). That this methodology is not limited to glycine esters is illustrated with the rearrangement of various amino acid allylic esters (entries 9−15). Aliphatic as well as aromatic side chains are suitable, and the extremely sterically demanding α-alkylated amino acids[21] are obtained in good yields. The influence of the protecting group Y was investigated for the phenylalanine derivative (entries 11−14), and no significant dependence on the protecting group is observed for the rearrangement. This makes the method of general value for the synthesis of various *N*-protected amino acids and peptides.

In addition to the equally substituted allylic esters ($R^1 = R^2$) the unsymmetrically substituted esters ($R^1 \neq R^2$) are especially interesting substrates. Their rearrangement allows the diastereoselective generation of chiral β-quaternary carbon centers (Table 2).

The rearrangement of the *E*-configured esters (entries 15−17) resulted in the formation of the *syn*-configured amino acid in a highly diastereoselective fashion. The observed diastereoselectivity (≥95% ds) is in good agreement with the selectivities observed for other *E*-configured allylic esters,[17] and results from a preferential rearrangement *via* a *chairlike* transition state.[22] On the other hand, the rearrangement of the *Z*-configured neryl ester **4n** (entry 18) gave rise to the opposite diastereomer, although with a significantly lower degree of selectivity. The lower diastereoselectivity may result from interactions of the *cis*-oriented side chain and the chelated enolate. These interactions should destabilize the *chairlike* transitions state with the consequence that the *boatlike* transition state should become more favored.

To prove this possibility, the acetylenic substrates **4o** and **4p** were also subjected to rearrangement (Scheme 3).[23] Because of the acidic acetylenic proton, 3.5 equiv of LDA were used for the rearrangement of these substrates. While the *E*-configured ester **4o** gave the expected product **5o** in a highly diastereoselective fashion, the oppositely configured *Z*-ester **4p** unexpectedly yields the same product, although less selectively.

The formation of the same product from these complementary precursors can be explained by a change of the transition state geometry (Scheme 4).

The *E*-configured ester **4o** rearranges preferentially *via* the expected *chairlike* transition state **A**. In the case of the *Z*-configured ester **4p** strong steric interactions could arise in the corresponding transition state **C** between the triple bond and the presumably solvated chelated metal. The system can switch to the *boatlike* transition state **D** to avoid these possible interactions, accepting the less dramatic interaction of the axial hydrogen and the chelate. This has the consequence that the *syn* product **5o** is also produced preferentially.

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(23) It should be noted that the ester **4o** and should be prepared directly before use or should be stored at −50 °C to avoid decomposition.

Table 1. Ester Enolate Claisen Rearrangement of Amino Acid Allylic Esters 4

entry	substrate	Y	R^1	R^2	R^3	R^4	MX_n	product	yield[a]
1	**4a**	Cbz	H	CH_3	CH_3	H	$ZnCl_2$	**5a**	81%
2	**4a**	Cbz	H	CH_3	CH_3	H	$AlMeCl_2$	**5a**	78%
3	**4a**	Cbz	H	CH_3	CH_3	H	$MgCl_2$	**5a**	75%
4	**4a**	Cbz	H	CH_3	CH_3	H	$Al(OiPr)_3$	**5a**	36%
5	**4b**	Boc	H	$-(CH_2)_4-$		H	$ZnCl_2$	**5b**	64%
6	**4b**	Boc	H	$-(CH_2)_4-$		H	$AlMeCl_2$	**5b**	62%
7	**4c**	Boc	H	$-(CH_2)_5-$		H	$ZnCl_2$	**5c**	45%
8	**4c**	Boc	H	$-(CH_2)_5-$		H	$AlMeCl_2$	**5c**	69%
9	**4d**	Boc	CH_3	CH_3	CH_3	H	$ZnCl_2$	**5d**	68%
10	**4e**	Cbz	Bn	CH_3	CH_3	H	$ZnCl_2$	**5e**	69%
11	**4f**	Boc	Bn	CH_3	CH_3	H	$ZnCl_2$	**5f**	64%
12	**4g**	TFA	Bn	CH_3	CH_3	H	$ZnCl_2$	**5g**	67%
13	**4h**	Ts	Bn	CH_3	CH_3	H	$ZnCl_2$	**5h**	75%
14	**4i**	TFA	Ph	CH_3	CH_3	H	$ZnCl_2$	**5i**	69%

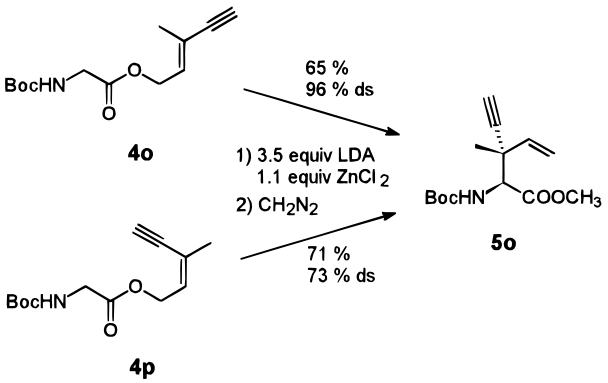
[a] Isolated yield after esterification with diazomethane.

Table 2. Ester Enolate Claisen Rearrangement of Unsymmetrical Substituted Amino Acid Allylic Esters 4 in the Presence of Zinc(II) Chloride

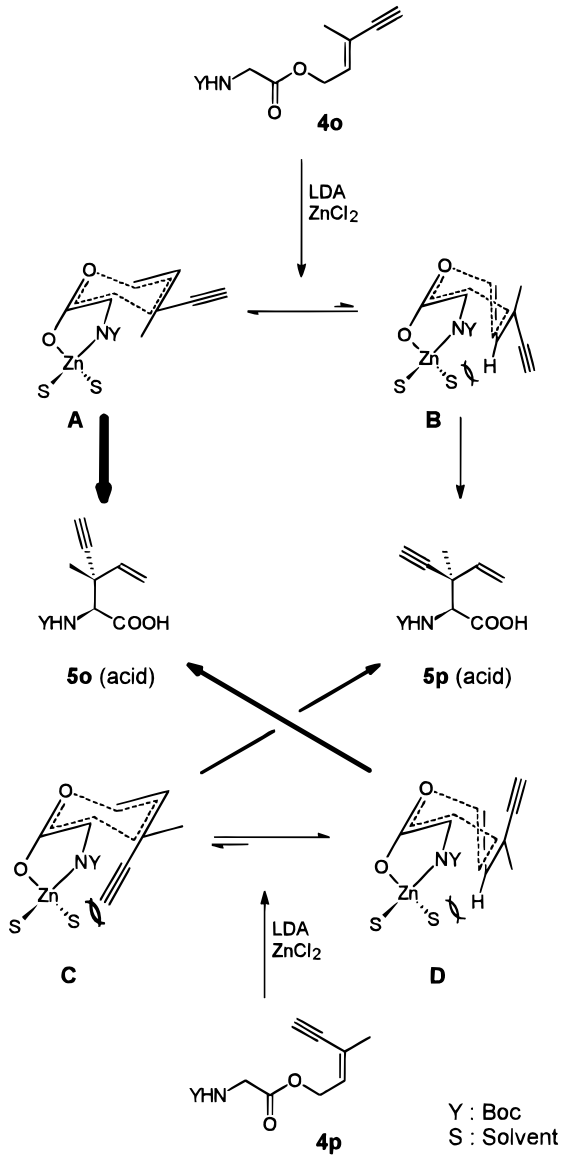
entry	substrate	Y	R^1	R^2	R^3	R^4	product	% yield[a]	% ds
15	**4k**	Boc	H	C≡C-*p*Tol	CH_3	H	**5k**	65	96[b]
16	**4l**	TFA	CH_3	Ph	CH_3	CH_3	**5l**	62	96[b]
17	**4m**	Boc	H	$(CH_2)_2CH{=}C(CH_3)_2$	CH_3	H	**5m**	46	95[c]
18	**4n**	Boc	H	CH_3	$(CH_2)_2CH{=}C(CH_3)_2$	H	**5n**	43	73[c]

[a] Isolated yield after esterification with diazomethane. [b] Determined by HPLC. [c] Determined by NMR.

Scheme 3



Scheme 4



Introduction of bulky substituents (aryl or trialkylsilyl groups) on the acetylenic moiety has no further influence on the reaction, e.g. rearrangement of the *Z*-configured analogue of ester **4k** also proceeded preferentially *via* the *boatlike* transition state. Yield and diastereoselectivity were comparable to the results obtained with the basic ester **4p**.

Conclusion

In conclusion it has been shown, that the ester enolate Claisen rearrangement of amino acid allylic esters is a suitable method for the synthesis of sterically demanding amino acids with even two vicinal quaternary carbon centers. Because of the fixation of the enolate geometry by chelation, the rearrangement proceeds in a highly diastereoselective fashion. Further investigations, particularly into the asymmetric synthesis of quaternary amino acids by rearrangement of chiral allylic esters and rearrangements in the presence of chiral ligands,[24] are in progress.

Experimental Section

General Procedure. General procedures and methods for characterization have been described previously.[19] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-300

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spectrometer. Chemical shifts were reported in δ relative to $CHCl_3$ as an internal reference. Melting points were determined on a Tottoli melting point apparatus and are uncorrected.

Preparation of the Amino Acid Allylic Esters. The allylic ester derivatives **4** used as substrates were synthesized by coupling of *N*-protected amino acids and the corresponding allylic alcohol using dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine.[25]

3-Methyl-2-butenyl *N*-(Benzyloxycarbonyl)glycinate (4a). 4a was obtained from *N*-(benzyloxycarbonyl)glycine and 3-methyl-2-butenol in 86% yield (after flash chromatography, ethyl acetate/hexanes 3/7) as a colorless oil: ^{1}H NMR δ 7.35 (m, 5H), 5.35 (t_{br}, 1H), 5.29 (tq, J = 6.0, 1.4 Hz, 1H), 5.13 (s, 2H), 4.64 (d, J = 7.4 Hz, 2H), 3.96 (d, J = 5.6 Hz, 2H), 1.73 (s, 3H), 1.68 (s, 3H); ^{13}C NMR δ 170.2, 156.2, 140.6, 136.2, 128.5, 128.2, 128.1, 117.5, 66.9, 62.8, 42.8, 25.6, 17.87. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.04; H, 6.86; N, 5.01.

(2-Cyclopentylideneethyl) *N*-(*tert*-Butyloxycarbonyl)glycinate (4b). 4b was obtained from *N*-(*tert*-butyloxycarbonyl)glycine and 2-cyclopentylideneethanol in 76% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 5.40 (tt, J = 7.2, 2.3 Hz, 1H), 5.04 (s_{br}, 1H), 4.60 (d, J = 7.2 Hz, 2H), 3.88 (d, J = 5.8 Hz, 2H), 2.26 (m, 4H), 1.68 (m, 4H), 1.42 (s, 9H); ^{13}C NMR δ 170.3, 155.6, 151.4, 113.5, 79.9, 63.6, 42.7, 33.8, 28.8, 26.1, 25.9. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.60; H, 8.66; N, 5.11.

(2-Cyclohexylideneethyl) *N*-(*tert*-Butyloxycarbonyl)glycinate (4c). 4c was obtained from *N*-(*tert*-butyloxycarbonyl)glycine and 2-cyclohexylideneethanol in 73% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 5.25 (t, J = 7.3 Hz, 1H), 5.06 (t_{br}, 1H), 4.63 (d, J = 7.3 Hz, 2H), 3.87 (d, J = 5.4 Hz, 2H), 2.17 (m, 2H), 2.09 (m, 2H), 1.53 (m, 6H), 1.42 (s, 9H); ^{13}C NMR δ 170.3, 155.6, 147.6, 114.6, 79.9, 61.4, 42.5, 37.0, 29.0, 28.3, 27.7, 26.5. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.23; H, 8.74; N, 4.86.

3-Methyl-2-butenyl *N*-(*tert*-Butyloxycarbonyl)alaninate (4d). 4d was obtained from *N*-(*tert*-butyloxycarbonyl)-alanine and 3-methyl-2-butenol in 93% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 5.31 (tq, J = 7.2, 1.4 Hz, 1H), 5.06 (d_{br}, 1H), 4.69 (d, J = 7.2 Hz, 2H), 4.27 (m, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.42 (s, 9H), 1.35 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.3, 155.1, 139.5, 118.2, 79.7, 62.1, 49.3, 28.3, 25.7, 18.7, 18.0. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.82; H, 8.92; N, 5.55.

3-Methyl-2-butenyl *N*-(Benzyloxycarbonyl)phenylalaninate (4e). 4e was obtained from *N*-(benzyloxycarbonyl)-phenylalanine and 3-methyl-2-butenol in 68% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 7.34 (s, 5H), 7.24 (m, 3H), 7.10 (dd, J = 7.0, 1.6 Hz, 2H), 5.27 (m, 2H), 5.10 (s, 2H), 4.61 (m, 3H), 3.12 (m, 2H), 1.77 (s, 3H), 1.70 (s, 3H); ^{13}C NMR δ 171.4, 155.6, 139.9, 136.4, 135.8, 129.4, 128.5, 128.1, 128.0, 127.0, 118.1, 66.9, 62.3, 54.9, 38.3, 25.7, 18.0. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.11; H, 6.67; N, 3.84.

3-Methyl-2-butenyl *N*-(*tert*-Butyloxycarbonyl)phenylalaninate (4f). 4f was obtained from *N*-(*tert*-butyloxycarbonyl)phenylalanine and 3-methyl-2-butenol in 84% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 7.24 (m, 3H), 7.12 (dd, J = 6.3, 1.4 Hz, 2H), 5.29 (tt, J = 7.3, 1.4 Hz, 1H), 4.93 (d_{br}, J = 7.4 Hz, 1H), 4.59 (m, 3H), 3.06 (m, 2H), 1.76 (s, 3H), 1.69 (s, 3H), 1.41 (s, 9H); ^{13}C NMR δ 171.8, 155.1, 139.6, 136.1, 129.4, 128.4, 126.9, 118.2, 62.1, 54.5, 38.4, 28.3, 25.7, 18.0. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.17; H, 8.11; N, 4.27.

3-Methyl-2-butenyl *N*-(Trifluoroacetyl)phenylalaninate (4g). 4g was obtained from *N*-(trifluoroacetyl)phenyl alanine and 3-methyl-2-butenol in 76% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a white solid: mp 35−36 °C: ^{1}H NMR δ 7.27 (m, 3H), 7.08 (m, 2H), 6.83 (s_{br}, 1H), 5.33 (td, J = 7.4, 1.2 Hz, 1H), 4.85 (q, J = 6.6 Hz, 1H), 4.70 (dd, J = 12.0, 7.4 Hz, 1H), 4.65 (dd, J = 12.0, 7.4 Hz, 1H), 3.24 (dd, J = 14.0, 5.7 Hz, 1H), 3.16 (dd, J = 14.0, 5.4 Hz, 1H), 1.79 (s, 3H), 1.73 (s, 3H); ^{13}C NMR δ 169.2, 156.5 (q, J = 37.5 Hz), 140.7, 134.7, 129.3, 128.7, 127.5, 117.5, 115.7, (q, J = 287.6 Hz), 62.9, 53.6, 37.2, 25.7, 18.0. Anal. Calcd for $C_{16}H_{18}NO_3F_3$: C, 58.36; H, 5.51; N, 4.15. Found: C, 58.32; H, 5.66; N, 4.17.

3-Methyl-2-butenyl *N*-(*p*-Tolylsulfonyl)phenylalaninate (4h). 4h was obtained from *N*-(*p*-tolylsulfonyl)phenylalanine and 3-methyl-2-butenol in 79% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 7.46 (d, J = 8.3 Hz, 2H), 7.23 (m, 5H), 7.08 (m, 2H), 5.09 (m, 2H), 4.35 (d, J = 7.3 Hz, 2H), 4.18 (dt, J = 9.0, 6.0 Hz, 1H), 3.02 (d, J = 6.0 Hz, 2H), 2.39 (s, 3H), 1.73 (s, 3H), 1.61 (s, 3H); ^{13}C NMR δ 170.7, 143.4, 140.7, 139.5, 135.0, 129.5, 128.4, 127.2, 127.1, 117.6, 62.4, 56.6, 39.5, 25.6, 21.5, 17.9. Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 64.88; H, 6.46; N, 3.66.

3-Methyl-2-butenyl *N*-(Trifluoroacetyl)phenylglycinate (4i). 4i was obtained from *N*-(trifluoroacetyl)phenylglycine and 3-methyl-2-butenol in 86% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a white solid: mp 80−81 °C: ^{1}H NMR δ 7.36 (s, 6H), 5.55 (d, J = 7.1 Hz, 1H), 5.26 (t, J = 7.3 Hz, 1H), 4.71 (dd, J = 12.1, 7.3 Hz, 1H), 4.59 (dd, J = 12.1, 7.3 Hz, 1H), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR δ 169.5, 156.3 (q, J = 38.00 Hz), 140.8, 134.9, 129.1, 129.0, 127.2, 117.3, 115.6 (q, J = 287.7 Hz), 63.4, 56.6, 25.6, 17.9. Anal. Calcd for $C_{15}H_{16}NO_3F_3$: C, 57.14; H, 5.11; N, 4.44. Found: C, 57.27; H, 5.31; N, 4.39.

(*E*)-3-Methyl-5-(4-methylphenyl)pent-2-en-4-ynyl *N*-(*tert*-Butyloxycarbonyl)glycinate (4k). 4k was obtained from *N*-(*tert*-butyloxycarbonyl)glycine and (*E*)-3-methyl-5-(4-methylphenyl)pent-2-en-4-ynol[26] in 93% yield (after flash chromatography, ethyl acetate/hexanes 3/7) as a pale yellow oil: ^{1}H NMR δ 7.31 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 5.97 (td, J = 7.3, 1.4 Hz, 1H), 5.05 (t_{br}, 1H), 4.75 (d, J = 7.3 Hz, 2H), 3.91 (d, J = 5.4 Hz, 2H), 2.33 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H), 1.44 (s, 9H); ^{13}C NMR δ 170.1, 155.7, 138.4, 131.5, 129.1, 128.8, 124.2, 120.0, 90.3, 88.9, 80.0, 61.3, 42.5, 28.3, 21.4, 17.8. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.88; H, 7.25; N, 3.97.

(*E*)-2-Methyl-3-phenyl-2-butenyl *N*-(Trifluoroacetyl)alaninate (4l). 4l was obtained from *N*-(trifluoroacetyl)-alanine and (*E*)-2-methyl-3-phenyl-2-butenol[27] in 80% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 7.38−7.31 (m, 2H), 7.25−7.22 (m, 1H), 7.16−7.09 (m, 2H), 7.08 (s_{br}, 1H), 4.88 (s, 2H), 4.68 (q, J = 7.2 Hz, 1H), 2.03 (s, 3H), 1.61 (s, 3H); 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR δ 171.6, 156.8 (q, J = 37.6 Hz), 143.7, 137.9, 128.2, 127.8, 126.7, 125.9, 115.3 (q, J = 287.4 Hz), 67.0, 48.8, 20.7, 18.0, 16.3. Anal. Calcd for $C_{16}H_{18}NO_3F_3$: C, 58.36; H, 5.51; N, 4.25. Found: C, 58.33; H, 5.39; N, 4.26.

Geranyl *N*-(*tert*-Butyloxycarbonyl)glycinate (4m). 4m was obtained from *N*-(*tert*-butyloxycarbonyl)glycine and geraniol in 88% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 5.32 (td, J = 7.0, 1.1 Hz, 1H), 5.05 (m, 2H), 4.65 (d, J = 7.0 Hz, 2H), 3.89 (d, J = 5.5 Hz, 2H), 2.04 (m, 4H), 1.69 (s, 3H), 1.67 (d, J = 1.1. Hz, 3H), 1.59 (s, 3H), 1.44 (s, 9H); ^{13}C NMR δ 170.3, 155.7, 143.0, 131.9, 123.7, 117.8, 79.9, 62.1, 42.5, 39.5, 28.3, 26.3, 25.6, 17.6, 16.5. Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.49; H, 9.38; N, 4.51.

Neryl *N*-(*tert*-Butyloxycarbonyl)glycinate (4n). 4n was obtained from *N*-(*tert*-butyloxycarbonyl)glycine and nerol in 85% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: ^{1}H NMR δ 5.32 (t, J = 6.6 Hz, 1H), 5.05 (m, 2H), 4.61 (d, J = 7.4 Hz, 2H), 3.87 (d, J = 5.1 Hz, 2H), 2.06 (m, 4H), 1.74 (d, J = 1.1 Hz, 3H), 1.66 (s, 3H), 1.57 (s,

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(26) Obtained by Pd(II)-catalyzed coupling of pent-2-en-4-yn-1-ol and iodotoluene.

(27) Obtained by DIBAL-Reduction of the corresponding ethyl ester: Gallagher, G., Jr.; Webb, R. L. *Synthesis* **1974**, 122.

3H), 1.42 (s, 9H); ^{13}C NMR δ 170.2, 155.6, 143.2, 132.2, 123.5, 118.6, 79.8, 61.9, 42.5, 32.1, 28.3, 26.6, 26.0, 23.4, 17.6. Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.63; H, 9.34; N, 4.55.

(*E*)-3-Methylpent-2-en-4-ynyl *N*-(*tert*-Butyloxycarbonyl)glycinate (4o). 4o was obtained from *N*-(*tert*-butyloxycarbonyl)glycine and (*E*)-3-methylpent-2-en-4-yn-1-ol in 85% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a pale yellow oil: ^{1}H NMR δ 5.96 (td, J = 7.1, 1.4 Hz, 1H), 5.05 (t_{br}, 1H), 4.69 (d, J = 7.1 Hz, 2H), 3.89 (d, J = 5.7 Hz, 2H), 2.87 (s, 1H), 1.85 (s, 3H), 1.42 (s, 9H); ^{13}C NMR δ 170.2, 155.7, 131.1, 122.8, 85.2, 80.1, 76.4, 61.0, 42.4, 28.3, 17.5. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.68; H, 7.63; N, 5.65.

(*Z*)-3-Methylpent-2-en-4-ynyl *N*-(*tert*-Butyloxycarbonyl)glycinate (4p). 4p was obtained from *N*-(*tert*-butyloxycarbonyl)glycine and (*Z*)-3-methylpent-2-en-4-yn-1-ol in 83% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as colorless needles: mp 78°C: ^{1}H NMR δ 5.81 (t, J = 6.8 Hz, 1H), 5.10 (t_{br}, 1H), 4.80 (d, J = 6.8 Hz, 2H), 3.87 (d, J = 5.6 Hz, 2H), 3.19 (s, 1H), 1.87 (s, 3H), 1.40 (s, 9H); ^{13}C NMR δ 170.2, 155.7, 131.3, 122.9, 83.2, 81.1, 79.9, 63.5, 42.3, 28.3, 22.9. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.36; H, 7.63; N, 5.47.

General Procedure for Ester Enolate Claisen Rearrangement. A 2.5 mmol amount of a freshly prepared LDA solution in 5 mL of THF was added to a stirred mixture of 1 mmol of allylic ester and 1.1 mmol of the corresponding metal salt in dry THF at −78 °C. The mixture was allowed to warm up to room temperature overnight. The resulting clear solution was diluted with ether and hydrolyzed with 1 N hydrochloric acid. After separation of the aqueous layer the crude *N*-protected amino acids were directly converted into the methyl ester by addition of a solution of diazomethane in ether. After evaporation of the solvent the crude product was purified by flash chromatography (ethyl acetate/hexanes).

Methyl 2-[*N*-(Benzyloxycarbonyl]amino]-3,3-dimethyl-4-pentenoate (5a). 5a was obtained from **4a** following the general rearrangement procedure in 81% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 7.34 (m, 5H), 5.81 (dd, J = 17.3, 10.8 Hz, 1H), 5.27 (d, J = 9.5 Hz, 1H), 5.08 (s, 2H), 5.08 (d, J = 10.8 Hz, 1H), 5.03 (d, J = 17.3 Hz, 1H), 4.22 (d, J = 9.5 Hz, 1H), 3.71 (s, 3H), 1.09 (s, 6H); ^{13}C NMR δ 171.6, 156.1, 142.8, 136.3, 128.5, 128.2, 128.1, 114.0, 67.1, 61.5, 51.8, 40.3, 24.3, 23.4. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.94; H, 7.31; N, 4.77.

Methyl *N*-(*tert*-Butyloxycarbonyl)(1′-vinylcyclopentyl)-glycinate (5b). 5b was obtained from **4b** following the general rearrangement procedure in 64% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 5.67 (dd, J = 17.3, 10.7 Hz, 1H), 5.15 (d, J = 10.7 Hz, 1H), 5.05 (d, J = 17.3 Hz, 1H), 5.01 (d, J = 9.4 Hz, 1H), 4.17 (d, J = 9.4 Hz, 1H), 3.68 (s, 3H), 1.50−1.76 (m, 8H), 1.40 (s, 9H); ^{13}C NMR δ 172.1, 155.5, 140.2, 115.3, 79.8, 60.2, 52.6, 51.7, 35.1, 33.3, 28.3, 23.4, 22.8. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.44; H, 8.82; N, 4.87.

Methyl *N*-(*tert*-Butyloxycarbonyl)(1′-vinylcyclohexyl)-glycinate (5c). 5c was obtained from **4c** following the general rearrangement procedure in 64% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 5.52 (dd, J = 17.5, 11.0 Hz, 1H), 5.27 (dd, J = 11.0, 1.5 Hz, 1H), 5.04 (dd, J = 17.5, 1.5 Hz, 1H), 4.96 (d_{br}, J = 9.8 Hz, 1H), 4.21 (d, J = 9.8 Hz, 1H), 3.67 (s, 3H), 1.58−1.17 (m, 10 H), 1.38 (s, 9H); ^{13}C NMR δ 172.0, 155.5, 140.5, 117.0, 79.7, 60.1, 51.6, 43.2, 34.0, 31.4, 28.8, 26.0, 21.9, 21.6. Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.63; H, 8.99; N, 4.66.

Methyl 2-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,3,3-trimethyl-4-pentenoate (5d). 5d was obtained from **4d** following the general rearrangement procedure in 68% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 5.91 (dd, J = 17.4, 10.9 Hz, 1H), 5.16 (dd, J = 10.9, 1.0 Hz, 1H), 5.11 (dd, J = 17.4, 1.0 Hz, 1H), 4.89 (s_{br}, 1H), 3.68 (s, 3H), 1.55 (s, 3H), 1.39 (s, 9H), 1.07 (s, 3H), 1.02 (s, 3H); ^{13}C NMR δ 173.38, 155.19, 143.15, 114.68, 79.61, 63.97, 51.92, 42.35, 28.29, 23.03, 22.95, 21.82. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.25; N, 5.16. Found: C, 62.09; H, 9.24; N, 5.02.

Methyl 2-[*N*-(Benzyloxycarbonyl)amino]-2-benzyl-3,3-dimethyl-4-pentenoate (5e). 5e was obtained from **4e** following the general rearrangement procedure in 69% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 7.33 (m, 4H), 7.20−7.10 (m, 6H), 6.02 (dd, J = 17.7, 10.5 HZ, 1H), 5.84 (s_{br}, 1H), 5.10 (d, J = 12.5 Hz, 1H), 5.06 (d, J = 17.7 Hz, 1H), 5.05 (d, J = 10.5 Hz, 1H), 5.00 (d, J = 12.5 Hz, 1H), 4.03 (d, J = 14.1 Hz, 1H), 3.69 (s, 3H), 3.33 (d, J = 14.1 Hz, 1H), 1.22 (s, 3H), 1.17 (s, 3H); ^{13}C NMR δ 172.4, 154.8, 144.1, 137.3, 137.1, 130.1, 130.0, 128.5, 128.1, 126.4, 113.1, 70.2, 66.2, 52.1, 46.0, 34.1, 24.2, 23.5. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.43; H, 7.43; N, 3.67. Found: C, 72.29; H, 7.31; N, 3.67.

Methyl 2-[*N*-(*tert*-Butyloxycarbonyl)amino]-2-benzyl-3,3-dimethyl-4-pentenoate (5f). 5f was obtained from **4f** following the general rearrangement procedure in 64% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 7.20 (m, 5H), 6.03 (dd, J = 16.6, 10.5 Hz, 1H), 5.68 (s_{br}, 1H), 5.04 (d, J = 16.6 Hz, 1H), 5.02 (d, J = 10.6 Hz, 1H), 4.01 (d, J = 14.0 Hz, 1H), 3.70 (s, 3H), 3.30 (d, J = 14.0 Hz, 1H), 1.40 (s, 9H), 1.21 (s, 3H), 1.15 (s, 3H); ^{13}C NMR δ 172.7, 154.4, 144.3, 137.5, 130.1, 127.9, 126.3, 112.8, 78.9, 70.0, 52.0, 46.0, 34.1, 28.4, 24.3, 23.5. Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.11; H, 8.34; N, 3.97.

Methyl 2-[*N*-(Trifluoroacetyl)amino]-2-benzyl-3,3-dimethyl-4-pentenoate (5g). 5g was obtained from **4g** following the general rearrangement procedure in 67% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 7.44 (s_{br}, 1H), 7.20 (m, 3H), 7.09 (dd, J = 7.0, 1.6 Hz, 2H), 6.00 (dd, J = 17.2, 10.8 Hz, 1H), 5.12 (d, J = 10.8 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 4.08 (d, J = 14.2 Hz, 1H), 3.80 (s, 3H), 3.40 (d, J = 14.2 Hz, 1H), 1.26 (s, 3H), 1.22 (s, 3H); ^{13}C NMR δ 172.0, 156.2 (q, J = 36.2 Hz), 143.0, 135.7, 129.6, 128.3, 127.0, 115.7 (q, J = 289.9 Hz), 114.1, 72.1, 52.7, 46.3, 33.8, 24.3, 23.6. MS (EI, 70 eV) m/z (rel intensity) 344 (M^+ + H, 1.2), 343 (M^+, 0.2), 275 (12), 274 (18), 230 (31), 215 (13), 214 (55), 192 (11), 171 (13); HRMS m/z (M^+) calcd 343.1395, obsd 343.1376.

Methyl 2-[*N*-(*p*-Tolylsulfonyl)amino]-2-benzyl-3,3-dimethyl-4-pentenoate (15h) was obtained from **4h** following the general rearrangement procedure in 75% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a colorless oil: $_1$H NMR δ 7.39 (d, J = 8.4 Hz, 2H), 7.19−7.06 (m, 7H), 5.76 (dd, J = 17.6, 10.5 Hz, 1H), 5.20 (s, 1H), 5.06 (dd, J = 10.5, 1.1 Hz, 1H), 5.04 (dd, J = 17.6, 1.1 Hz, 1H), 3.62 (d, J = 15.4 Hz, 1H), 3.51 (d, J = 15.4 Hz, 1H), 3.52 (s, 3H), 2.34 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H); ^{13}C NMR δ 171.7, 143.3, 142.0, 140.6, 136.8, 129.6, 128.1, 126.6, 125.9, 114.8, 73.1, 51.9, 45.5, 37.3, 23.62, 23.58, 21.5. Anal. Calcd for $C_{21}H_{27}NO_4S$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.72; H, 7.04; N, 3.57.

Methyl 2-[*N*-(Trifluoroacetyl)amino]-2-phenyl-3,3-dimethyl-4-pentenoate (5i). 5i was obtained from **4i** following the general rearrangement procedure in 78% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 8.44 (d, J = 7.3 Hz, 2H), 7.70 (m, 3H), 6.94 (s_{br}, 1H), 5.77 (dd, J = 17.4, 10.8 Hz, 1H), 5.33 (d, J = 10.8 Hz, 1H), 5.27 (d, J = 17.4 Hz, 1H), 3.77 (s, 3h), 1.18 (s, 3H), 1.07 (s, 3H); ^{13}C NMR δ 169.0, 156.3 (q, J = 37.7 Hz), 142.7, 133.92, 127.9, 127.8, 127.7, 116.1, 115.8 (q, J = 289.3 Hz), 68.7, 52.6, 44.5, 22.8, 22.7. Anal. Calcd for $C_{16}H_{18}NO_3F_3$: C, 58.38; H, 5.51; N, 4.25. Found: C, 58.33; H, 5.56; N, 4.19.

Methyl (±)-(2*S*,3*S*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-methyl-5-(4-methylphenyl)-3-vinyl-4-pentynoate (5k). 5k was obtained from **4k** following the general rearrangement procedure in 65% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil. The diastereomeric ratio was determined by HPLC (ethyl acetate/hexanes 15/85; $t_{R(major)}$: 6.12 min, $t_{R(minor)}$: 10.48 min): ^{1}H NMR δ 7.34 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.83 (dd, J = 16.8, 10.0 Hz, 1H), 5.51 (d, J = 16.8 Hz, 1H), 5.23 (d_{br}, 1H), 5.20 (d, J = 10.0 Hz, 1H), 4.38 (d, J = 9.7 Hz, 1H), 3.76 (s, 3H), 2.34 (s,

3H), 1.47 (s, 3H), 1.42 (s, 9H); ^{13}C NMR δ 170.5, 155.2, 139.5, 138.3, 131.6, 129.0, 119.9, 115.8, 87.7, 86.5, 78.0, 60.4, 52.0, 43.5, 28.3, 25.4, 21.4. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N 3.93. Found: C, 70.44; H, 7.56; N, 4.02.

Methyl (±)-(2*S*,3*S*)-2-[*N*-(Trifluoroacetyl)amino]-3-phenyl-2,3,4-trimethyl-4-pentenoate (5l). 5l was obtained from **4l** following the general rearrangement procedure in 69% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil. The diastereomeric ratio was determined by HPLC (ethyl acetate/hexanes 7/93; $t_{R(\text{major})}$: 3.07 min, $t_{R(\text{minor})}$: 4.13 min): ^{1}H NMR δ 7.38−7.21 (m, 5H), 7.11 (s_{br}, 1H), 5.35 (s, 1H), 5.31 (d, J = 0.8 Hz, 1H), 3.31 (s, 3H), 1.95 (s, 3H), 1.71 (s, 3H), 1.59 (d, J = 0.8 Hz, 3H); ^{13}C NMR δ 170.8, 156.2 (q, J = 36.7 Hz), 145.3, 141.0, 128.6, 128.5, 128.2, 127.6, 127.5, 117.6, 115.6 (q, J = 288.8 Hz), 115.5, 66.7, 54.2, 52.3, 22.7, 21.7, 18.4. MS (EI, 70 eV) m/z (rel intensity) 344 (M^+ + H, 1.5), 343 (M^+, 0.5), 275 (12), 284 (4), 171 (20), 156 (10), 146 (28), 145 (100), 133 (22), 117 (36) HRMS m/z (M^+) calcd 343.1395, obsd 343.1346.

Methyl (±)-(2*S*,3*R*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3,7-dimethyl-3-vinyl-6-octenoate (5m). 5m was obtained from **4m** following the general rearrangement procedure in 46% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 5.73 (dd, J = 17.3, 10.6 Hz, 1H), 5.19 (d, J = 10.6 Hz, 1H), 5.04 (d_{br}, 1H), 5.03 (d, J = 17.3 Hz, 1H), 5.01 (t, J = 10.4 Hz, 1H), 4.20 (d, J = 9.6 Hz, 1H), 3.69 (s, 3H), 1.90 (m, 2H), 1.66, (s, 3H), 1.56 (s, 3H), 1.42 (s, 9H), 1.40 (m, 2H), 1.06 (s, 3H); ^{13}C NMR δ 172.1, 155.4, 141.5, 131.6, 124.2, 115.4, 79.9, 60.3, 51.6, 43.4, 38.1, 28.7, 25.7, 22.6, 18.5, 17.6. Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N 4.30. Found: C, 66.28; H, 9.76; N, 4.22.

Methyl (±)-(2*S*,3*S*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3,7-dimethyl-3-vinyl-6-octenoate (5n). 5n was obtained from **4n** following the general rearrangement procedure in 43% yield (after flash chromatography, ethyl acetate/hexanes 15/85) as a colorless oil: ^{1}H NMR δ 5.72 (dd, J = 17.2, 9.9 Hz, 1H), 5.18 (t, J = 9.5 Hz, 1H), 5.03 (d, J = 17.3 Hz, 1H), 5.02 (m, 2H), 4.22 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 1.91 (m, 2H), 1.65 (s, 3H), 1.56 (s, 3H), 1.41 (s, 9H), 1.38 (m, 2H), 1.04 (s, 3H); ^{13}C NMR δ 172.0, 155.4, 141.9, 131.6, 124.2, 114.9, 79.8, 59.9, 51.7, 43.4, 37.2, 28.3, 25.6, 22.5, 19.4, 17.6. Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N 4.30. Found: C, 66.39; H, 9.55; N, 4.17.

Methyl (±)-(2*S*,3*S*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-methyl-3-vinyl-4-pentynoate (5o). 5o was obtained from **4o** (and as the major product from **4p**) following the general rearrangement procedure in 76% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a pale yellow oil: ^{1}H NMR δ 5.74 (dd, J = 16.8, 10.0 Hz, 1H), 5.45 (d, J = 16.8 Hz, 1H), 5.18 (d_{br}, 1H), 5.17 (d, J = 10.0 Hz, 1H), 4.28 (d, J = 9.7 Hz, 1H), 3.75 (s, 3H), 2.41 (s, 1H), 1.40 (s, 9H), 1.39 (s, 3H); ^{13}C NMR δ 170.4, 155.2, 139.0, 115.9, 83.1, 80.0, 74.4, 59.9, 52.0, 42.8, 28.3, 25.2. Anal. Calcd for $C_{14}H_{21}NO_4$ (mixture **5o**/**5p**): C, 62.90; H, 7.92; N 5.24. Found: C, 62.70; H, 7.89; N, 5.29.

Methyl (±)-(2*S*,3*R*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-methyl-3-vinyl-4-pentinoate (5p). 5p was obtained as a mixture with **5o** from **4p** (and as the minor product) following the general rearrangement procedure in 79% yield (after flash chromatography, ethyl acetate/hexanes 2/8) as a pale yellow oil: ^{1}H NMR δ 5.76 (dd, J = 16.1, 9.8 Hz, 1H), 5.47 (d, J = 16.1 Hz, 1H), 5.16 (m, 2H), 4.29 (d, J = 8.8 Hz, 1H), 3.65 (s, 3H), 2.43 (s, 1H), 1.42 (s, 9H), 1.40 (s, 3H); ^{13}C NMR δ 170.4, 155.1, 138.2, 115.7, 83.0, 80.1, 74.5, 59.9, 51.6, 43.3, 28.2, 26.1. Anal. Calcd for $C_{14}H_{21}NO_4$ (mixture **5o**/**5p**): C, 62.90; H, 7.92; N 5.24. Found: C, 62.70; H, 7.89; N, 5.29.

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