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Synthesis of Sterically High Demanding α-Alkylated Amino Acids *via* Claisen Rearrangement of Chelated Enolates

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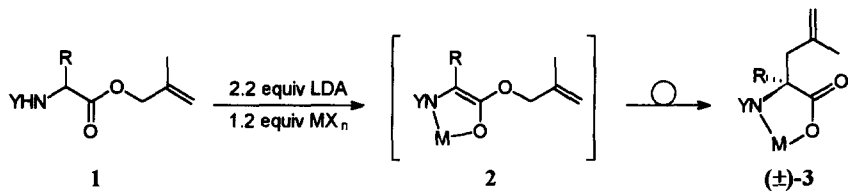
Abstract: Ester enolate Claisen rearrangement of chelated *N*-protected amino acid allylic esters **1** and **4** results in the formation of α-alkylated γ,δ-unsaturated amino acids **3** and **5** in good yields and in a highly diastereoselective fashion.

INTRODUCTION

Under the amino acids containing quaternary carbon centers the α-alkylated amino acids are an especially interesting class of nonproteinogenic amino acids,[1] particularly in view of their activity as enzyme inhibitors.[2] γ,δ-Unsaturated amino acids are also of great interest not only as naturally occurring amino acids,[3] but also as intermediates for the synthesis of complex amino acids and peptides.[4] Various methods are known for the synthesis of the α-alkylated amino acids,[5] and besides the *N*-sulfonylimine ene reaction[6] and the nucleophilic allylation of glycine cation equivalents,[7] the sigmatropic rearrangement processes are well suited for the introduction of the unsaturated side chains. The first synthesis of allylic amino acids by Claisen rearrangement was described in 1975 by Steglich.[8] The reaction proceeds *via* an oxazole intermediate and is especially suitable for the synthesis of α-alkylated allylic amino acids.[9] In 1982 the Ireland-Claisen rearrangement[10] of glycine allylic esters was studied by Bartlett and coworkers.[11] In the meantime this elegant methodology has found various applications in amino acid synthesis.[12]

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.[13] Deprotonation of *N*-protected glycine allylic esters (Scheme 1, R = H) like **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** (Scheme 1).



1 **2** **(±)-3**

Scheme 1

In contrast to the corresponding lithium enolates, which do not show this rearrangement, because they decompose during the 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.[11] 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[14] and can also be applied to peptides.[15] Herein the application of this methodology for the synthesis of sterically high demanding α-alkylated γ,δ-unsaturated amino acids ($R \neq H$) is described.[16]

RESULTS AND DISCUSSION

Because of the good results obtained with glycine allylic esters the chelate ester enolate rearrangement was also applied to the rearrangement of esters of other amino acids **1** (Scheme 1, $R \neq H$). The influence of the protecting group Y, the side chain R, as well as the metal salt MX_n, used for chelation of the ester enolate, was investigated. The results are listed in Table 1. No 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.

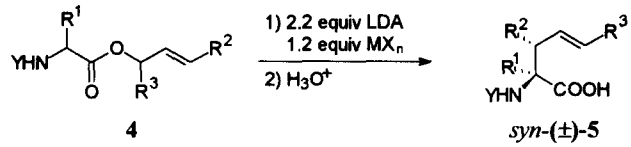
Table 1: Rearrangement of various amino acid allylic esters **1**

Entry	Ester	Y	R	MX_n	Yield (%)[a]
1	**1a**	Z	H	$ZnCl_2$	92
2	**1b**	BOC	CH_3	$ZnCl_2$	81
3	**1b**	BOC	CH_3	$MgCl_2$	73
4	**1c**	Z	C_2H_5	$ZnCl_2$	87
5	**1c**	Z	C_2H_5	$MgCl_2$	80
6	**1d**	Z	$CH(CH_3)_2$	$ZnCl_2$	39
7	**1e**	Z	CH_2Ph	$ZnCl_2$	63
8	**1f**	TFA	CH_2Ind[b]	$ZnCl_2$	34
9	**1f**	TFA	CH_2Ind[b]	$MgCl_2$	79
10	**1g**	Z	$(CH_2)_4NHBOC$	$ZnCl_2$	69
11	**1h**	BOC	$(CH_2)_2SCH_3$	$ZnCl_2$	80

[a] Isolated yield after esterification with diazomethane and flash chromatography
[b] Ind = 3-Indolyl

Overall, best results are obtained in the presence of zinc chloride as the chelating metal salt. Among all the other metal salts which can be employed,[13] in particular magnesium chloride gives comparable yields in many cases (entry 3,5). For the tryptophan derivative **1f** the yield was even higher (entries 9 and 10). This example also shows that this methodology is not restricted to amino acids with aliphatic or aromatic side chains, but can also be applied to derivatives of functionalized amino acids like tryptophan (**1f**)[17], lysine (**1g**)[18] or methionine (**1h**)[19]. These examples had been chosen, because especially the tryptophan and lysine derivatives are critical substrates for α-alkylation reactions.[20] The α-alkylated methionine derivative **3i** is also an interesting substrate, because it can be converted easily into other amino acids like ethyl glycine (Raney-Ni)[19a] or vinyl glycine (*via* an oxidation-elimination pathway).[21]

Due to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeds with a high degree of diastereoselectivity. This was confirmed by rearrangement of several *N*-protected amino acid allylic esters **4** (Scheme 2). Independent of the metal salt used for chelation, the rearrangement products *syn*-**5** are obtained in even higher diastereoselectivities (Table 2) in comparison to the results obtained with the corresponding glycine derivatives **4a** (R^1 = H).[13]



4 *syn*-(±)-5

Scheme 2

Table 2: Rearrangement of amino acid allylic esters **4**

Entry	Ester	Y	R^1	R^2	R^3	MX_n	Yield (%)	de (%)
1	**4a**	TFA	H	CH_3	H	$ZnCl_2$	86	88[a]
2	**4a**	TFA	H	CH_3	H	$MgCl_2$	81	82[a]
3	**4b**	TFA	CH_3	CH_3	H	$ZnCl_2$	84	96[a]
4	**4b**	TFA	CH_3	CH_3	H	$MgCl_2$	83	90[a]
5	**4c**	TFA	CH_3	Ph	H	$ZnCl_2$	65	94[a]
6	**4d**	TFA	CH_3	CH_3	C_2H_5	$ZnCl_2$	84	92[a]
7	**4d**	TFA	CH_3	CH_3	C_2H_5	$MgCl_2$	89	94[a]
8	**4e**	TFA	Ph	CH_3	H	$ZnCl_2$	94	95[a]
9	**4f**	Z	$(CH_2)_4NHBOC$	CH_3	H	$ZnCl_2$	74	94[b]

[a] Diastereomer ratio determined by GC with a chiral fused silica coating Chirasi-*L*-Val column.
[b] Diastereomer ratio determined by NMR spectroscopy.

Further investigations, especially into the asymmetric synthesis by rearrangement of chiral allylic esters and rearrangements in the presence of chiral ligands[22] are in progress.

CONCLUSION

In conclusion, we have shown that the ester enolate Claisen rearrangement of chelated amino acid allylic esters is a powerful methodology for the introduction of unsaturated side chains onto amino acids. Due to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeds with a high degree of diastereoselectivity, independent of the substitution pattern and the protecting groups used.

EXPERIMENTAL SECTION

General. All reactions were carried out in oven-dried glassware (100°C) under an atmosphere of argon. All solvents were dried before used. THF was distilled from sodium-benzophenone and diisopropylamine from calcium hydride. LDA solutions were prepared from freshly distilled diisopropylamine and commercially available butyllithium solution (15% in hexane) in THF at -20°C directly before use. The starting materials and the products were purified by flash chromatography on silica gel (32 - 63 μm). Mixtures of ethyl acetate and hexanes were used as eluants. TLC was performed on commercial precoated silica gel 60 F_{254} plates (Merck). Visualization was accomplished with iodine and potassium permanganate solution. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WH-200 and a Bruker AC-300 spectrometer. Chemical shifts were reported in δ relative to $CHCl_3$ as an internal reference. GC analyses were performed on a Hewlett-Packard 5890 Series II instrument equipped with a chiral fused silica coating Chirasi-L-Val column (25m × 0.25 mm, Chrompack). Diastereomeric ratios were also determined by NMR spectroscopy. Melting points were determined on a Tottoli melting point apparatus and are uncorrected.

Preparation of the amino acid allylic esters. The allylic ester derivatives **1** and **4** used as substrates were synthesized by coupling *N*-protected amino acids and the corresponding allylic alcohol using dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine.[23]

***N-t*-Butyloxycarbonyl-alanine (2-methyl)propenyl ester (1b): 1b** was obtained from *N-t-butyl*oxycarbonyl-alanine and (2-methyl)propenol in 96% yield (after flash chromatography, ethyl acetate / hexanes 3 / 7) as a colorless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ 5.08 (d_{br}, 1H), 4.96 (d, J = 0.7 Hz, 1H), 4.91 (s, 1H), 4.59 (d, J = 13.1 Hz, 1H), 4.47 (d, J = 13.1 Hz, 1H), 4.38 (m, 1H), 1.73 (s, 3H), 1.42 (s, 9H), 1.38 (d, J = 7.3 Hz, 3H). ^{13}C NMR (50MHz, $CDCl_3$): δ 173.00, 155.01, 139.39, 133.28, 79.,78, 68.35, 49.22, 28.26, 19.36, 18.65. $C_{12}H_{21}NO_4$ (243.30): calcd. C, 59.24; H, 8.79; N, 5.76; found C, 59.32; H, 8.86; N, 5.71.

***N*-Benzyloxycarbonyl-ethylglycine (2-methyl)propenyl ester (1c): 1c** was obtained from *N*-benzyloxycarbonyl-ethylglycine and (2-methyl)propenol in 88% yield (after flash chromatography, ethyl acetate / hexanes 3 / 7) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.35 (s, 5H), 5.33 (d_{br}, J = 7.6 Hz, 1H), 5.11 (s, 2H), 4.99 (s, 1H), 4.95 (s, 1H), 4.59 (d, J = 13.1 Hz, 1H), 4.53 (d, J = 13.1 Hz, 1H), 4.39 (dd, J = 13.1, 7.4 Hz, 1H), 1.91 (m, 1H), 1.75 (s, 3H), 1.72 (m, 1H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 172.09, 155.89, 139.37, 136.33, 128.53, 128.16, 128.09, 113.64, 68.54, 66.98, 55.07, 25.90, 19.42, 9.47. $C_{16}H_{21}NO_4$ (291.35): calcd. C, 65.96; H, 7.27; N,4.81; found C, 65.88; H, 7.26; N, 4.73.

***N*-Benzyloxycarbonyl-valine (2-methyl)propenyl ester (1d): 1d** was obtained from *N*-benzyloxycarbonyl-valine and (2-methyl)propenol in 73% yield (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ 7.23 (m, 5H), 5.20 (d, J = 8.9 Hz, 1H), 5.00 (s, 2H), 4.88 (s, 1H,), 4.83 (s, 1H), 4.44 (s, 2H), 4.24 (dd, J = 9.0, 4.6 Hz, 1H), 2.08 (dq, J = 6.6, 4.7 Hz, 1H), 1.64 (s, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.70, 156.05, 139.30, 136.26, 128.48, 128.12, 128.05, 113.77, 68.47, 66.99, 59.09, 31.28, 19.46, 18.97, 17.43. $C_{17}H_{23}NO_4$ (305.37): calcd. C, 66.86; H, 7.59; N,4.59; found C, 66.88; H, 7.46; N, 4.60.

***N*-Benzyloxycarbonyl-phenylalanine (2-methyl)propenyl ester (1e): 1e** was obtained from *N*-Benzyloxycarbonyl-phenylalanine and (2-methyl)propenyl alcohol in 81% yield (after flash chromatography, ethyl acetate / hexanes 2 / 8) as colorless needles, mp 46 - 47°C. ^{1}H NMR (200MHz, $CDCl_3$): δ 7.32 (s, 5H), 7.20 (m, 3H), 7.10 (m, 2H), 5.26 (d, J = 8.2 Hz, 1H), 5.08 (s, 2H), 4.93 (bs, 2H), 4.69 (dd, J = 8.3, 6.0 Hz, 1H), 4.51 (s, 2H), 3.13 (d, J = 5.6 Hz, 1H), 3.11 (d, J = 5.8 Hz, 1H), 1.69 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$): δ 171.20, 155.80, 139.12, 136.23, 135.66, 129.25, 128.56, 128.46, 128.11, 128.01, 127.08, 113.81, 68.68, 66.92, 54.89, 38.25, 19.41. $C_{21}H_{23}NO_4$ (353.42): calcd. C, 71.37; H, 6.56; N, 3.96; found C, 71.32; H, 6.60; N, 3.94.

***N*-Trifluoroacetyl-tryptophane (2-methyl)propenyl ester (1f): 1f** was obtained from *N*-trifluoroacetyl-tryptophane and (2-methyl)propenol in 73% yield (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless solid, mp 113 - 114°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.20 (s_{br}, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.17 (m, 2H), 6.98 (s, 1H), 6.92 (d, J = 7.3 Hz, 1H), 4.97 (m, 3H), 4.55 (d, J = 12.8 Hz, 1H), 4.49 (d, J = 12.8 Hz, 1H), 3.44 (d, J = 5.3 Hz, 2H), 1.71 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 170.02, 156.70 (q, J = 37.5 Hz), 138.85, 136.22, 127.36, 122.94, 122.57, 119.99, 118.30, 115.60 (q, J = 287.8 Hz), 114.25, 111.41, 108.86, 69.37, 53.49, 27.27, 19.36. $C_{17}H_{17}F_3N_2O_3$ (353.42): calcd. C, 57.63; H, 4.84; N, 7.91; found C, 57.71; H, 4.96; N, 7.92.

***α*-*N*-Benzyloxycarbonyl-*ε*-*N*-*t*-*butyl*oxycarbonyl-lysine (2-methyl)propenyl ester (1g): 1g** was obtained from *α*-*N*-benzyloxycarbonyl-*ε*-*N*-*t*-*butyl*oxycarbonyl lysine and (2-methyl)propenol in 84% yield (after flash chromatography, ethyl acetate / hexanes 3 / 7) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.33 (s, 5H), 5.46 (d, J = 7.4 Hz, 1H), 5.09 (s, 2H), 4.96 (s, 1H), 4.93 (s, 1H), 4.61 (t_{br}, 1H), 4.53 (s, 2H), 4.38 (m, 1H), 3.07 (m, 2H), 1.86 (m, 2H), 1.73 (s, 3H), 1.43 (m, 4H), 1.41 (s, 9H).

^{13}C NMR (75MHz, $CDCl_3$): δ 172.06, 156.01, 139.26, 136.22, 128.56, 128.45, 128.26, 128.09, 128.04, 113.60, 79.11, 68.51, 66.94, 53.79, 39.98, 32.16, 29.54, 28.35, 22.33, 19.36. $C_{23}H_{34}N_2O_6$ (434.53): calcd. C, 63.57; H, 7.89; N, 6.45; found C, 63.54; H, 7.75; N, 6.40.

***N*-*t*-Butyloxycarbonyl-methionine (2-methyl)propenyl ester (1h): 1h** was obtained from *N-t-butyl*-oxycarbonyl-methionine and (2-methyl)propenol in 70% yield (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ 5.14 (s_{br}, 1H), 4.96 (s, 1H), 4.91 (s, 1H), 4.55 (d, J = 14.0 Hz, 1H), 4.50 (d, J = 14.0 Hz, 1H), 4.41 (m, 1H), 2.52 (t, J = 7.6 Hz, 2H), 2.06 (s, 3H), 1.90 (m, 2H), 1.73 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.99, 155.30, 139.30, 113.64, 79.35, 68.62, 52.89, 32.21, 30.00, 28.28, 19.46, 15.43. $C_{14}H_{25}NO_4S$ (303.42): calcd. C, 55.42; H, 8.30; N, 4.62; S, 10.57; found C, 55.34; H, 8.43; N, 4.55, S 10.31.

***N*-Trifluoroacetyl-glycine crotyl ester (4a): 4a** was obtained from *N*-trifluoroacetyl-glycine and crotyl alcohol in 60% yield (after crystallization from dichloromethane / hexanes) as colorless needles, mp 62 - 63°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 6.96 (s_{br}, 1H), 5.84 (dt, J = 17.4, 6.9 Hz, 1H), 5.58 (dq, J = 17.4, 6.8 Hz, 1H), 4.61 (d, J = 6.9 Hz, 2H), 4.11 (d, J = 5.1 Hz, 2H), 1.72 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 168.0, 157.1 (q, J = 44.2 Hz), 133.1, 123.9, 115.6 (q, J = 281.5 Hz), 66.8, 41.3, 17.7. $C_8H_{10}F_3NO_3$ (225.17): calcd. C, 42.67; H, 4.48; N, 6.22; found C, 42.62; H, 4.41; N, 6.20.

***N*-Trifluoroacetyl-alanine crotyl ester (4b): 4b** was obtained from *N*-trifluoroacetyl-alanine and crotyl alcohol in 78% yield (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.13 (s_{br}, 1H), 5.80 (dtq, J = 15.3, 6.5, 1.1 Hz, 1H), 5.56 (dtq, J = 15.3, 6.6, 1.5 Hz, 1H), 4.59 (d, J = 6.6 Hz, 1H), 4.58 (d, J = 6.6 Hz, 1H), 4.55 (q, J = 7.1 Hz, 1H), 1.71 (dd, J = 6.5, 1.1 Hz, 3H), 1.47 (d, J = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.26, 156.50 (q, J = 37.7 Hz), 132.68, 124.00, 115.61 (q, J = 287.5 Hz), 66.70, 48.67, 17.71, 17.60. $C_9H_{12}F_3NO_3$ (239.19): calcd. C, 45.19; H, 5.06; N, 5.86; found C, 45.09; H, 4.97; N, 5.97.

***N*-Trifluoroacetyl-alanine cinnamyl ester (4c): 4c** was obtained from *N*-trifluoroacetyl-alanine and cinnamyl alcohol in 72% yield (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.25-7.41 (m, 5H), 7.11 (s_{br}, 1H), 6.69 (d, J = 15.9 Hz, 1H), 6.26 (dt, J = 15.9, 6.6 Hz, 1H), 4.84 (d, J = 6.6 Hz, 2H), 4.65 (dq, J = 7.1, 7.1 Hz, 1H), 1.53 (d, J = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.30, 156.84 (q, J = 39.6 Hz), 135.85, 135.50, 128.69, 128.41, 126.72, 121.77, 115.66 (d, J = 287.6 Hz), 66.66, 48.76, 17.86. $C_{14}H_{14}F_3NO_3$ (301.27): calcd. C, 55.82; H, 4.68; N, 4.65; found C, 55.92; H, 4.87; N, 4.65.

***N*-Trifluoroacetyl-alanine (*t*-2-hexen-4-yl) ester (4d): 4d** was obtained from *N*-trifluoroacetyl-alanine and *t*-2-hexen-4-ol in 70% yield (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.08 (s_{br}, 1H), 5.75 (ddq, J = 15.1, 6.6, 1.8 Hz, 1H), 5.40 (dqd, J = 15.1, 6.6, 1.6 Hz, 1H), 5.16 (dt, J = 7.0, 1.6 Hz, 1H), 4.55 (q, J = 7.1, 1H), 1.69 (dd, J = 6.5, 1.3 Hz, 3H), 1.54-1.69 (m, 2H), 1.47 (d, J = 7.2 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 170.94, 156.70 (q, J = 37.4 Hz), 130.50, 128.39, 115.61 (q, J = 287.6 Hz), 78.64, 48.91, 27.39, 17.96, 17.63, 9.37. $C_{11}H_{16}F_3NO_3$ (267.25): calcd. C, 49.44; H, 6.03; N, 5.24; found C, 49.48; H, 5.99; N, 5.11.

***N*-Trifluoroacetyl-phenylglycine crotyl ester (4e): 4e** was obtained from *N*-trifluoroacetyl-phenylglycine and crotyl alcohol in 86% yield (after flash chromatography, ethyl acetate / hexanes 1 / 9) as colorless needles, mp 94 - 95°C. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.33 (s, 6H), 5.74 (dq, J = 15.2, 6.5 Hz, 1H), 5.54 (d, J = 7.0 Hz, 1H), 5.48 (dt, J = 15.2, 6.6 Hz, 1H), 4.64 (dd, J = 12.1, 6.6 Hz, 1H), 4.54 (dd, J = 12.1, 6.6 Hz, 1H), 1.68 (dd, J = 6.5, 1.2 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 169.32, 156.26 (q, J = 39.1 Hz), 134.81, 132.81, 129.20, 129.14, 127.23, 123.79, 115.76 (q, J = 265.3 Hz), 67.14, 56.65, 17.70. $C_{14}H_{14}F_3NO_3$ (301.27): calcd. C, 55.82; H, 4.68; N, 4.65; found C, 55.92; H, 4.87; N, 4.65.

***α*-*N*-Benzyloxycarbonyl-*ε*-*N*-*t*-*butyl*oxycarbonyl-lysine crotyl ester (4f): 4f** was obtained from *α*-*N*-benzyloxycarbonyl-*ε*-*N*-*t*-*butyl*oxycarbonyl lysine and crotyl alcohol in 80% yield (after flash chromatography, ethyl acetate / hexanes 3 / 7) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.33 (s, 5H), 5.76 (dt, J = 15.1, 6.5 Hz, 1H), 5.53 (dq, J = 15.1, 6.1 Hz, 1H), 5.15 (d, J = 6.4 Hz, 1H), 5.08 (s, 2H), 4.61 (t_{br}, 1H), 4.54 (d, J = 6.1 Hz, 2H), 4.33 (m, 1H), 3.07 (m, 2H), 1.80 (m, 2H), 1.70 (d, J = 6.1 Hz, 3H), 1.41 (s, 9H), 1.38 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$): δ 172.19, 156.06, 155.97, 136.32, 132.13, 129.62, 128.50, 128.32, 128.14, 128.09, 124.54, 79.15, 66.96, 66.06, 53.82, 40.10, 32.28, 29.57, 28.41, 22.35, 17.25. $C_{23}H_{34}N_2O_6$ (434.53): calcd. C, 63.57; H, 7.89; N, 6.45; found C, 63.51; H, 7.83; N, 6.37.

General procedure for the ester enolate Claisen rearrangement. 2.5 mmol of a freshly prepared LDA solution in 5 ml THF was added to a stirred mixture of 1 mmol allylic ester **1** or **4** 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 rearrangement product was directly converted into the methyl ester of **3** or **5** respectively by addition of a solution of diazomethane in ether. After evaporation of the solvent the crude product was purified by flash chromatography.

***N-t-Butyl*oxycarbonyl-2-(2-methyl-propenyl)alanine methyl ester (3b):** Following the general rearrangement procedure **3b** was obtained from **1b** in 81% yield ($ZnCl_2$) or 73% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 5.38 (s_{br}, 1H), 4.86 (s, 1H), 4.71 (s, 1H), 3.73 (s, 3H), 2.83 (m, 1H), 2.53 (d, J = 13.6 Hz, 1H), 1.67 (s, 3H), 1.56 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.89, 154.26, 141.01, 115.64, 79.91, 59.34, 52.39, 44.48, 28.36, 24.18, 23.27. $C_{13}H_{23}NO_4$ (257.33): calcd. C, 60.68; H, 9.01; N, 5.44; found C, 60.62 ; H, 8.89; N, 5.37.

***N*-Benzyloxycarbonyl-2-(2-methyl-propenyl)ethylglycine methyl ester (3c):** Following the general rearrangement procedure **3c** was obtained from **1c** in 87% yield ($ZnCl_2$) or 80% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.32 (m, 5H), 5.87 (s_{br}, 1H), 5.10 (d, J = 12.4 Hz, 1H), 5.02 (d, J = 12.4 Hz, 1H), 4.76 (s, 1H), 4.61 (s, 1H), 3.73 (s, 3H), 3.10 (d, J = 13.8 Hz, 1H), 2.45 (d, J = 13.6 Hz, 1H), 2.40 (dq, J = 14.0, 7.4 Hz, 1H), 1.78 (dq, J = 14.1, 7.2 Hz, 1H), 1.58 (s, 3H), 0.73 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.00, 153.80, 140.92, 136.67, 128.40, 127.95, 127.88, 114.98, 66.14, 64.62, 52.49, 43.08, 28.95, 23.03, 8.21. $C_{17}H_{23}NO_4$ (305.37): calcd. C, 66.86; H, 7.59; N, 4.59; found C, 66.93; H, 7.58; N, 4.60.

***N*-Benzyloxycarbonyl-2-(2-methyl-propenyl)valine methyl ester (3d):** Following the general rearrangement procedure **3d** was obtained from **1d** in 39% yield ($ZnCl_2$) or 17% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.33 (m, 5H), 5.98 (s_{br}, 1H), 5.07 (d, J = 12.4 Hz, 1H), 4.99 (d, J = 12.4 Hz, 1H), 4.73 (s, 1H), 4.64 (s, 1H), 3.73 (s, 3H), 3.22 (d, J = 14.0 Hz, 1H), 2.64 (d, J = 13.8 Hz, 1H), 2.60 (m, 1H), 1.56 (s, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 173.44, 154.10, 141.34, 136.95, 128.41, 127.95, 114.72, 66.86, 66.15, 52.23, 40.03, 34.24, 17.80, 17.72. $C_{18}H_{25}NO_4$ (319.40): calcd. C, 67.69; H, 7.89; N, 4.39; found C, 67.70; H, 7.88; N, 4.30.

***N*-Benzyloxycarbonyl-2-(2-methyl-propenyl)phenylalanine methyl ester (3e):** Following the general rearrangement procedure **3e** was obtained from **1e** in 63% yield ($ZnCl_2$) or 59% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.39 (s, 5H), 7.18 (m, 3H), 6.94 (m, 2H), 5.76 (s, 1H), 5.22 (d, J = 12.4 Hz, 1H), 5.08 (d, J = 12.4 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 3.76 (s, 3H), 3.72 (d, J = 13.5 Hz, 1H), 3.34 (d, J = 13.8 Hz, 1H), 3.09 (d, J = 13.4 Hz, 1H), 2.65 (d, J = 13.8 Hz, 1H), 1.64 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 173.03, 154.28, 140.83, 136.86, 136.03, 129.68, 128.47, 128.21, 128.08, 126.89, 115.32, 66.26, 65.32, 52.38, 43.37, 41.50, 23.04. $C_{22}H_{25}NO_4$ (367.44): calcd. C, 71.91; H, 6.86; N, 3.81; found C, 71.83; H, 6.82; N, 3.89.

***N*-Trifluoroacetyl-2-(2-methyl-propenyl)tryptophan methyl ester (3f):** Following the general rearrangement procedure **3f** was obtained from **1f** in 34% yield ($ZnCl_2$) or 79% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 4 / 6) as a pale yellow oil. ^1H NMR (300MHz, $CDCl_3$): δ 8.14 (s_{br}, 1H), 7.52 - 7.09 (m, 5H), 6.88 (s, 1H), 4.88 (s, 1H), 4.76 (s, 1H), 3.98 (d, J = 14.7 Hz, 1H), 3.73 (s, 3H), 3.49 (d, J = 14.1 Hz, 1H), 3.40 (d, J = 14.6 Hz, 1H), 2.80 (d, J = 14.1 Hz, 1H), 1.64 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 172.98, 155.76 (q, J = 37.5 Hz), 140.80, 135.83, 127.48, 122.90, 122.58, 120.00, 118.31, 117.85 (q, J = 270.6 Hz), 114.24, 111.38, 108.91, 66.28, 53.03, 42.51, 31.06, 22.67. $C_{18}H_{19}F_3N_2O_3$ (368.36): calcd. C, 55.69; H, 5.20; N, 7.60; found C, 55.72; H, 5.08; N, 7.54.

***syn*-α-*N*-Benzyloxycarbonyl-ε-*N*-*t*-*butyl*oxycarbonyl-2-(2-methyl-propenyl)lysine methyl ester (3g):** Following the general rearrangement procedure **3g** was obtained from **1g** in 69% yield ($ZnCl_2$) (after flash chromatography, ethyl acetate / hexanes 15 / 85) as a colorless oil. ^1H NMR (300MHz, $CDCl_3$): δ 7.34 (s, 5H), 5.90 (s_{br}, 1H), 5.10 (d, J = 12.3 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.77 (s, 1H), 4.61 (s, 1H), 4.54 (s_{br}, 1H), 3.74 (s, 3H), 3.08 (d, J = 13.7 Hz, 1H), 3.05 (m, 2H), 2.45 (d, J = 13.7 Hz, 1H), 2.42 (m, 1H), 1.76 (td, J = 12.0, 4.7 Hz, 2H), 1.58 (s, 3H), 1.43 (s, 9H), 1.32 (m, 2H), 0.97 (m, 1H). ^{13}C NMR (75MHz, $CDCl_3$): δ 174.00, 155.95, 154.03, 140.76, 136.68, 128.46, 128.05, 128.02, 115.23, 79.08, 66.29, 63.99, 52.63, 43.46, 40.21, 35.41, 29.64, 28.43, 23.06, 21.16. $C_{24}H_{36}N_2O_6$ (448.56): calcd. C, 64.26; H, 8.09; N, 6.25; found C, 64.18; H, 8.16; N, 6.31.

***N*-*t*-*butyl*oxycarbonyl-2-(2-methyl-propenyl)methionine methyl ester (3h):** Following the general rearrangement procedure **3h** was obtained from **1h** in 80% yield ($ZnCl_2$) or 47% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^1H NMR (300MHz, $CDCl_3$): δ 5.64 (s, 1H), 4.82 (s, 1H), 4.66 (s, 1H), 3.74 (s, 3H), 3.12 (d, J = 13.6 Hz, 1H), 2.73 (m, 1H), 2.44 (m, 1H), 2.42 (d, J = 13.2 Hz, 1H), 2.15 (m, 2H), 2.04 (s, 3H), 1.64 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (75MHz, $CDCl_3$): δ 173.78, 153.65, 140.75, 115.34, 79.25, 63.36, 52.52, 43.34, 35.33, 28.74, 28.35, 23.06, 15.44. $C_{15}H_{27}NO_4S$ (317.44): calcd. C, 56.75; H, 8.57; N, 4.41; found C, 56.68; H, 8.57; N, 4.35.

***syn*-*N*-Trifluoroacetyl-2-(1-methyl-propenyl)glycine methyl ester (5a):** Following the general rearrangement procedure **5a** was obtained from **4a** in 86% yield ($ZnCl_2$) or 81% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^1H NMR (300MHz, $CDCl_3$): δ 6.81 (s_{br}, 1H), 5.76 (ddd, J = 17.5, 10.6, 6.9 Hz, 1H), 5.13 (d, J = 10.6 Hz, 1H), 5.12 (d, J = 17.5 Hz, 1H), 4.64 (dd, J = 9.3, 3.9 Hz, 1H), 3.78 (s, 3H), 2.74 (m, 1H), 1.10 (d, J = 6.9 Hz, 1H).

^{13}C NMR (75MHz, $CDCl_3$): δ 170.27, 155.25 (q, J = 37.9 Hz), 137.27, 117.32, 115.82 (q, J = 286.6 Hz), 71.27, 69.17, 63.39, 56.20, 42.57, 40.66, 20.88, 15.40. $C_9H_{12}F_3NO_3$ (239.19): calcd. C, 45.19; H, 5.06; N, 5.86; found C, 45.17; H, 5.08; N, 5.72.

***syn*-*N*-Trifluoroacetyl-2-(1-methyl-propenyl)alanine methyl ester (5b):** Following the general rearrangement procedure **5b** was obtained from **4b** in 84% yield ($ZnCl_2$) or 83% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.03 (s_{br}, 1H), 5.65 (ddd, J = 16.8, 9.0, 6.3 Hz, 1H), 5.13 (dd, J = 16.8, 1.3 Hz, 1H), 5.12 (dd, J = 9.0, 1.4 Hz, 1H), 3.77 (s, 3H), 2.81 (dq, J = 7.0, 7.0 Hz, 1H), 1.70 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 172.01, 156.51 (q, J = 37.5 Hz), 137.44, 118.05, 114 (q, J = 286.7 Hz), 63.13, 52.80, 45.01, 19.88, 15.10. $C_{10}H_{14}F_3NO_3$ (253.22): calcd. C, 47.47; H, 5.57; N, 5.53; found C, 47.46; H, 5.55; N, 5.54.

***syn*-*N*-Trifluoroacetyl-2-(1-phenyl-propenyl)alanine methyl ester (5c):** Following the general rearrangement procedure **5c** was obtained from **4c** in 65% yield ($ZnCl_2$) or 54% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.38 - 7.25 (m, 3H), 7.16 (dd, J = 7.8, 1.6 Hz, 2H), 6.98 (s_{br}, 1H), 6.25 (ddd, J = 16.7, 9.9, 9.9 Hz, 1H), 5.28 (dd, J = 10.1, 1.3 Hz, 1H), 5.22 (d, J = 16.9 Hz, 1H), 3.87 (d, J = 9.8 Hz, 1H), 3.70 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.75, 155.80 (q, J = 38.2 Hz), 137.55, 134.36, 128.68, 128.63, 127.91, 119.67, 113.50 (q, J = 279.2 Hz), 63.46, 57.13, 52.64, 19.38. $C_{15}H_{16}F_3NO_3$ (315.29): calcd. C, 57.14; H, 5.11; N, 4.44; found C, 57.08; H, 5.20; N, 4.48.

***syn*-*N*-Trifluoroacetyl-2-(1-phenyl-2-pentenyl)alanine methyl ester (5d):** Following the general rearrangement procedure **5d** was obtained from **3d** in 84% yield ($ZnCl_2$) or 89% yield ($MgCl_2$) respectively (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.00 (s_{br}, 1H), 5.58 (dt, J = 15.3, 6.5 Hz, 1H), 5.20 (tdd, J = 15.3, 9.2, 1.4 Hz, 1H), 3.75 (s, 3H), 2.68 (dq, J = 9.2, 7.0 Hz, 1H), 2.00 (qdd, J = 7.5, 6.4, 1.3 Hz, 2H), 1.66 (s, 3H), 1.04 (d, J = 7.0Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.97, 156.05 (q, J = 36.7 Hz), 136.41, 127.99, 115.62 (q, J = 288.8 Hz), 63.10, 52.59, 44.29, 25.46, 19.87, 15.55, 13.58. $C_{12}H_{18}F_3NO_3$ (281.28): calcd. C, 51.24; H, 6.45; N, 4.98; found C, 51.18; H, 6.45; N, 5.03.

***syn*-*N*-Trifluoroacetyl-2-(1-methyl-propenyl)phenylglycine methyl ester (5e):** Following the general rearrangement procedure **5e** was obtained from **4e** in 94% yield ($ZnCl_2$) (after flash chromatography, ethyl acetate / hexanes 2 / 8) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.48 - 7.25 (m, 6H), 5.70 (ddd, J = 17.2, 10.2, 6.9 Hz, 1H), 5.22 (d, J = 17.1 Hz, 1H), 5.17 (d, J = 10.2 Hz, 1H), 3.80 (s, 3H), 3.68 (dq, J = 7.0, 7.0 Hz, 1H), 1.14 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.18, 155.62 (q, J = 36.6 Hz), 137.42, 135.87, 128.44, 128.23, 127.12, 117.97, 115.64 (q, J = 288.9 Hz), 68.79, 53.23, 42.85, 15.80. $C_{15}H_{16}F_3NO_3$ (315.29): calcd. C, 57.14; H, 5.11; N, 4.44; found C, 57.15; H, 5.08; N, 4.49.

***syn*-α-*N*-Benzyloxycarbonyl-ε-*N*-*t*-*butyl*oxycarbonyl-2-(1-methyl-propenyl)lysine methyl ester (5f):** Following the general rearrangement procedure **5f** was obtained from **4f** in 74% yield ($ZnCl_2$) (after flash chromatography, ethyl acetate / hexanes 15 / 85) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.33 (s, 5H), 5.77 (s_{br}, 1H), 5.65 (ddd, J = 15.6, 8.8, 6.7 Hz, 1H), 5.08 (d, J = 12.6Hz, 1H), 5.04 (d, J = 15.6 Hz, 1H), 5.02 (d, J = 8.8 Hz, 1H), 4.98 (d, J = 12.6 Hz, 1H), 4.64 (t_{br}, 1H), 3.72 (s, 3H), 3.04 (m, 2H), 2.83 (t, J = 7.1 Hz, 1H), 2.43 (t, J = 10.3 Hz, 1H), 1.96 (m, 2H), 1.41 (s_{br}, 10H), 1.22 (m, 2H), 1.00 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 173.08, 155.98, 154.42, 138.65, 136.66, 128.47, 128.05, 127.99, 116.66, 78.95, 66.37, 66.26, 52.52, 44.40, 40.08, 31.61, 29.62, 28.43, 21.28, 15.38. $C_{24}H_{36}N_2O_6$ (448.56): calcd. C, 64.26; H, 8.09; N, 6.25; found C, 64.31; H, 8.13; N, 6.24.

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