Application of the Asymmetric Chelate Enolate Claisen Rearrangement to the Synthesis of Unsaturated Polyhydroxylated Amino Acids

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Received 10 February 1998

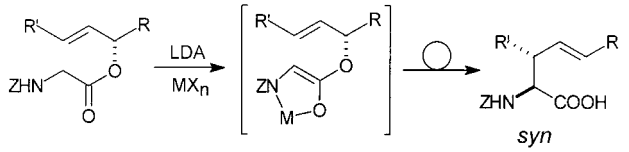
Abstract: Ester enolate Claisen rearrangement of chelated *N*-protected chiral allylic amino acid esters results in the formation of polyhydroxylated γ,δ-unsaturated amino acids in good yields and with a high degree of chirality transfer.

Key words: allylic esters, chelates, Claisen rearrangement, enolates, unsaturated amino acids

Polyhydroxylated amino acids are an important class of natural products. For example, polyoxamic acid is part of many polyoxines, which are potent antifungal agents.[1] These interesting synthetic targets[2] can act as enzyme inhibitors or as antimetabolites.[3] They are also found as substructures in naturally occurring antibiotics[4] and take part in the biosynthesis of important bioactive substances.[5] In addition, polyhydroxylated amino acids are valuable tools in the design of polyhydroxylated piperidine alkaloids.[6]

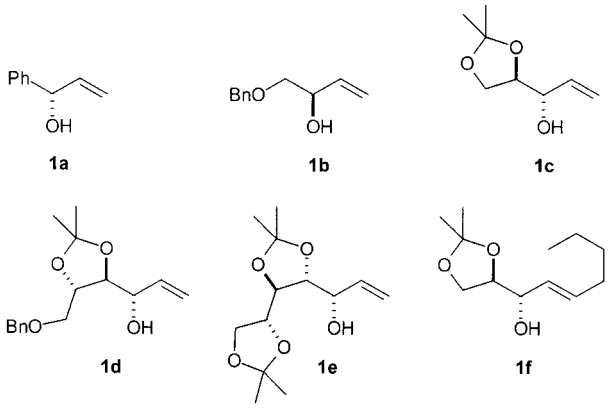
Polyhydroxylated amino acids can be obtained via introduction of suitable side chains into glycine residues and/or via functionalization of double bonds.[7] The unsaturated amino acids, needed for this approach, can be obtained e.g. by sigmatropic rearrangement reactions.[8]

Recently, we have developed a new variation of the ester enolate Claisen rearrangement proceeding via chelated allylic ester enolates.[9] Deprotonation of *N*-protected glycine allyl esters with LDA at –78°C and subsequent addition of metal salts, such as zinc chloride, presumably results in the formation of a chelated zinc enolate, which undergoes Claisen rearrangement upon warming to room temperature (Scheme 1). 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. This method is suitable for various types of allylic esters and can also be applied to peptides.[10] If the reaction is carried out in the presence of chiral bidentate ligands, chiral γ,δ-unsaturated amino acids are obtained in high yields and in a highly stereoselective fashion.[11]



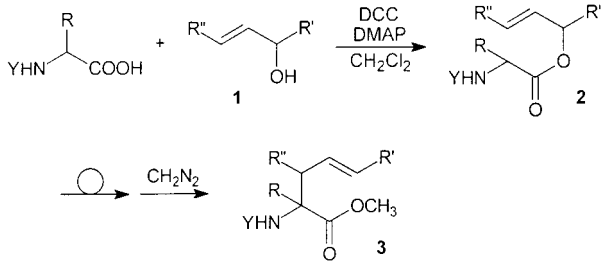
Scheme 1

Herein we describe the ester enolate Claisen rearrangement of functionalized chiral allylic amino acid esters which gives rise to the corresponding chiral amino acids with high enantio- as well as diastereoselectivities.[12] The



syntheses of the chiral allylic alcohols **1a–1f** used is described in the previous paper.[13]

Esterification of these alcohols with protected amino acids in the presence of DCC/DMAP[14] gave the corresponding chiral allylic esters **2** in high yields (Scheme 2, Table 1). This procedure is suitable for the generation of glycine esters, and other amino acid esters[15] as well. These are of special interest because they allow the stereoselective synthesis of functionalized unsaturated α-alkylated amino acids.[16]



Scheme 2

For the investigation of the ester enolate Claisen rearrangement, a solution of the allylic ester **2** in THF was deprotonated with an excess of base (2.5 equiv) in the presence of a chelating metal salt. Best results were obtained when lithium diisopropylamide (LDA) was used as a base, and $ZnCl_2$ for the chelation of the ester enolate (Table 2). If other metal salts such as $MgCl_2$ or $Al(OiPr)_3$ were used for chelate formation, generally lower yields were observed (entries 3 and 4), and the allylic alcohols **1** were obtained as byproducts. After warming the reaction mixture overnight to room temperature, the mixture was hydrolyzed with 1 N $KHSO_4$ solution. For this purpose $KHSO_4$ is superior to HCl, because no cleavage of the acid labile ketal moieties was observed under these condi-

Table 1. Preparation of Chiral Allylic Esters **2**

Allylic Alcohol	Y	R	Yield (%)	Config. (allyl Pos.)	Ester
1a	Z	H	83	*S*	**2a**
ent-**1a**	Z	H	79	*R*	ent-**2a**
1b	Boc	H	98	*R*	**2b**
1c	Z	H	83	*S*	**2c**
1d	Boc	H	82	*S*	**2d**
1e	Z	H	92	*R*	**2e**
1f	Z	H	93	*S*	**2f**
1a	Z	Me	96	*S*	**2g**
ent-**1a**	Z	Ph	95	*R*	**2h**
1a	Z	Bn	80	*S*	**2i**
1c	Z	Me	94	*S*	**2k**
1c	Z	Et	86	*S*	**2l**

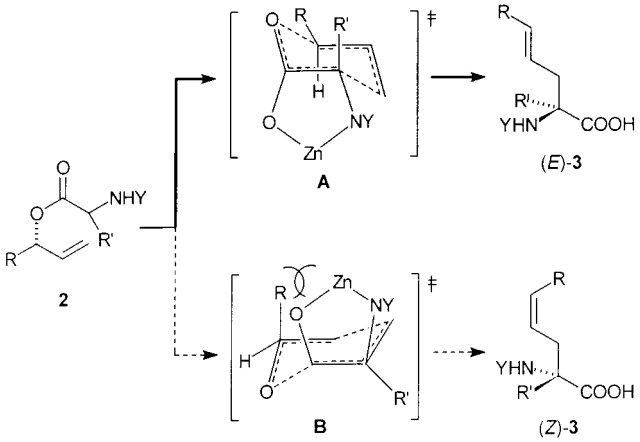
Table 2. Chelate Claisen Rearrangement of Chiral Allylic Esters **2**

Entry	Ester	MXn	Yield (%)	Select. (%)	Amino Acid Ester
1	**2a**	$ZnCl_2$	89	99.3	(*R*)-**3a**
2	ent-**2a**	$ZnCl_2$	93	>99	(*S*)-**3a**
3	**2b**	$Al(OiPr)_3$	5	n.d.	**3b**
4	**2b**	$MgCl_2$	6	n.d.	**3b**
5	**2b**	$ZnCl_2$	95	>99	(*S*)-**3b**
6	**2c**	$ZnCl_2$	92	>98	(*R*)-**3c**
7	**2d**	$ZnCl_2$	77	99.7	(*R*)-**3d**
8	**2e**	$ZnCl_2$	85	>99	(*S*)-**3e**
9	**2f**	$ZnCl_2$	71	98	(*R*)-**3f**
10	**2g**	$ZnCl_2$	95	>99	(*R*)-**3g**
11	**2h**	$ZnCl_2$	92	>99	(*R*)-**3h**
12	**2i**	$ZnCl_2$	85	>98	(*S*)-**3i**
13	**2k**	$ZnCl_2$	82	>99	(*S*)-**3k**
14	**2l**	$ZnCl_2$	82	>99	(*R*)-**3l**

tions. The rearrangement generally proceeded with very good yields and selectivities, as shown in Table 2.

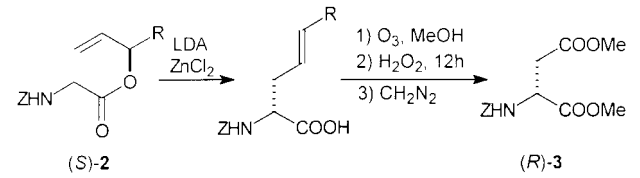
For the determination of the stereoselectivity of the rearrangement, the crude reaction products were esterified with diazomethane, and the resulting methyl esters were analyzed by HPLC (chiral HPLC column Daicel OD-H). The observed ee and ds values were, without exception, ≥98% (Table 2).[17] This is also true for the rearrangement of allylic ester **2f**. In this case two new stereogenic centers were formed, and therefore in principle four stereoisomers should be expected. Out of these four isomers only two were observed in a *syn/anti* ratio of 98:2.

The high degree of chirality transfer of these chelated ester enolates can be explained by a closer look at the corresponding transition states (Scheme 3). Like in most sigmatropic rearrangements, the *chair-like* transition state is highly preferred, whereas two diastereomeric chairs are possible for esters of secondary allylic alcohols. In the favored transition state **A**, the substituent R is orientated in an equatorial position, while in transition state **B** strong steric interactions between the axial R and the chelate-complex may occur. As a result of the highly ordered transition state, the [3.3]-sigmatropic rearrangement also determines the double bond geometry in the rearranged product. *E*-Olefins are obtained if the reaction proceeds via transition state **A**, while the disfavored transition state **B** gives rise to *Z*-configurated olefins. The exclusive formation of the *E*-configurated amino acids, obtained in our reactions, clearly demonstrates the high preference for the favored transition state **A**.



Scheme 3

The absolute configuration of the rearrangement products was determined by ozonolysis of the double bond, giving rise to the corresponding aspartic acid derivative (Scheme 4). Comparison with derivatives of the natural amino acid confirms the mechanism proposed.



Scheme 4

In conclusion we have shown that the chelate enolate Claisen rearrangement is a versatile method for the synthesis of even highly functionalized amino acids. As illustrated, the rearrangement is not limited to allylic esters of glycine, but can also be applied to the synthesis of α-alkylated amino acids **3g–l** without problems. We were also able to show that allylic esters with sterically highly demanding substituents take part in the rearrangement in good yields (**2d,e**). Therefore, it is possible to introduce protected polyhydroxylated substituents into amino acids in one step and in a highly diastereoselective fashion. The observed yields and selectivities are almost independent of the protecting groups. All rearrangements proceeded with almost 100% *trans*-selectivity, no *cis*-configurated product was observed by HPLC or NMR.

All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from sodium benzophenone, CH_2Cl_2 and i-Pr_2NH from CaH_2. The starting materials and the products were purified by flash chromatography on silica gel (32–63 μm). Mixtures of EtOAc and petroleum ether (40–

Table 3. Analytical and Spectroscopic Data of Compounds **2** and **3**

Compound	$[\alpha]_D^{20}$ (*c*, Solvent)	^{1}H NMR (300 MHz, $CDCl_3$) δ, *J* (Hz)	^{13}C NMR (75 MHz, $CDCl_3$) δ
2a	–43.0 (2.0, $CHCl_3$)	3.99 (dd, *J* = 18.3, 5.5, 1H, C*H*$_2$N), 4.09 (dd, *J* = 18.3, 5.7, 1H, C*H*$_2$N), 5.12 (s. 2H, PhC*H*$_2$), 5.28 (d, *J* = 10.3, 2H, CH=CH*H*^{t}, N*H*), 5.31 (d, *J* = 17.1, 1H, CH=CH-*H*^{c}), 6.01 (ddd, *J* = 17.1, 10.6, 6.0, 1H, C*H*=CH$_2$), 6.21 (m, 1H, C*H*OCO), 7.35 (s_{br}, 10H, Ar*H*)	43.00 (t, *C*H$_2$N), 67.14 (t, PhCH$_2$), 77.45 (d, *C*HOCO), 116.61 (t, CH=*C*H$_2$), 127.18, 128.11, 128.20, 128.47,128.55, 128.66 (6d, Ar*C*), 135.62 (d, *C*H=CH$_2$), 136.26, 138.20 (2s, quart. Ar*C*), 156.23 (s, O*C*ON), 169.05 (s, *C*OO)
ent-**2a**	+ 42.1 (0.5, $CHCl_3$)	3.99 (dd, *J* = 18.3, 5.5, 1H, C*H*$_2$N), 4.08 (dd, *J* = 18.3, 5.7, 1H, C*H*$_2$N), 5.12 (s, 2H, PhC*H*$_2$), 5.28 (d, *J* = 10.3, 2H, CH=CH*H*^{t}, N*H*), 5.31 (d, *J* = 17.3, 1H, CH=CH-*H*^{c}), 6.01 (ddd, *J* = 17.3, 10.4, 5.9, 1H, C*H*=CH$_2$), 6.23 (m, 1H, C*H*OCO), 7.35 (s_{br}, 10H, Ar*H*)	42.99 (t, *C*H$_2$N), 67.13 (t, PhCH$_2$), 77.45 (d, *C*HOCO), 116.61 (t, CH=*C*H$_2$), 127.17, 128.10, 128.20, 128.47, 128.55, 128.65 (6d, Ar*C*), 135.62 (d, *C*H=CH$_2$), 136.26, 138.20 (2s, quart. Ar*C*), 156.23 (s, O*C*ON), 169.04 (s, *C*OO)
2b	–4.3 (1.0, $CHCl_3$)	1.45 [s, 9H, C(C*H*$_3$)$_3$], 3.52–3.62 (m, 4H, C*H*$_2$OBn, C*H*$_2$N), 4.53 (d, *J* = 12.2, 1H, PhC*H*$_2$), 4.57 (d, *J* = 12.2, 1H, PhC*H*$_2$), 5.01 (s_{br}, 1H, N*H*), 5.26 (d, *J* = 11.0, 1H, CH=CH*H*^{t}), 5.33 (d, *J* = 17.3, 1H, CH=CH*H*^{c}), 5.53 (dd, *J* = 11.0, 5.9, 1H, C*H*OCO), 5.82 (ddd, *J* = 17.1, 10.7, 6.1, 1H, C*H*=CH$_2$), 7.26–7.,37 (m, 5H, Ar*H*)	28.28 (q, *C*H$_3$), 42.52 (t, *C*H$_2$N), 71.07 (t, *C*H$_2$O), 73.99 (t, Ph*C*H$_2$), 74.28 (d, *C*HOCO), 79.93 [s, *C*(CH$_3$)$_3$], 118.56 (t, CH=*C*H$_2$), 127.62, 127.74, 128.41 (3d, Ar*C*), 132.68 (d, *C*H=CH$_2$), 137.75 (s, quart. Ar*C*), 155.56 (s, O*C*ON), 169.58 (s, *C*OO)
2c	–1.24 (5.5, $CHCl_3$)	1.35 (s, 3H, C*H*$_3$), 1.41 (s, 3H, C*H*$_3$), 3.80 (dd, *J* = 8.4, 6.3, 1H, C*H*$_2$O), 3.99–4.04 (m, 3H, C*H*$_2$O, C*H*$_2$N), 4.21 (dt, *J* = 11.2, 6.2, 1H, C*H*OC), 5.12 (s, 2H, PhC*H*$_2$), 5.29–5.40 (m, 4H, N*H*, C*H*OCO, CH=C*H*$_2$), 5.81 (ddd, *J* = 17.2, 10.6, 6.6, 1H, C*H*=CH$_2$), 7.31–7.35 (m, 5H, Ar*H*)	26.18 (q, *C*H$_3$), 26.32 (q, *C*H$_3$), 42.91 (t, *C*H$_2$N), 65.58 (t, *C*H$_2$O), 67.17 (t, PhCH$_2$), 75.22 (d, *C*HOC), 76.34 (d, *C*HOCO), 110.05 [s, *C*(CH$_3$)$_2$], 119.71 (t, CH=*C*H$_2$), 128.11, 128.22, 128.55 (3d, Ar*C*), 131.72 (d, *C*H=CH$_2$), 136.22 (s, quart. Ar*C*), 156.22 (s, O*C*ON), 169.02 (s, *C*OO)
2d	–13.8 (3.6, $CHCl_3$)	1.38 (s, 3H, C*H*$_3$), 1.40 (s, 3H, C*H*$_3$), 1.43 [s, 9H, C(C*H*$_3$)$_3$], 3.57 (dd, *J* = 10.3, 5.2, 1H, C*H*$_2$OBn), 3.61 (dd, *J* = 10.3, 3.7, 1H, C*H*$_2$OBn), 3.86 (d, *J* = 5.4, 2H, C*H*$_2$N), 3.97 (dd, *J* = 8.1, 4.0, 1H, C*H*OC), 4.06 (ddd, *J* = 8.1, 5.2, 2.9, 1H, C*H*OC), 4.55 (d, *J* = 12.4, 1H, PhC*H*$_2$), 4.59 (d, *J* = 12.4, 1H, PhC*H*$_2$), 4.91 (s_{br}, 1H, N*H*), 5.28 (d, *J* = 10.5, 1H, CH=CH*H*^{t}), 5.32 (ddd, *J* = 17.4, 1.1, 1.1 Hz, 1H, CH=CH*H*^{c}), 5.42 (dddd, *J* = 6.6, 4.4, 1.1, 1.1, 1H, C*H*OCO), 5.81 (ddd, *J* = 17.3, 10.5, 6.6, 1H, C*H*=CH$_2$), 7.27–7.36 (m, 5H, Ar*H*)	26.62 (q, *C*H$_3$), 26.85 (q, *C*H$_3$), 28.07 [s, C(*C*H$_3$)$_3$], 42.28 (t, *C*H$_2$N), 70.26 (t, *C*H$_2$O), 73.31 (t, PhCH$_2$), 74.90 (d, *C*HOC), 78.48 (d, *C*HOC), 78.76 (d, *C*HOCO), 79.79 [s, *C*(CH$_3$)$_3$], 109.85 [s, *C*(CH$_3$)$_2$], 119.66 (t, CH=*C*H$_2$), 127.53, 128.18 (2d, Ar*C*), 131.38 (d, *C*H=CH$_2$), 137.64 (s, quart. Ar*C*), 155.31 (s, O*C*ON), 169.07 (s, *C*OO)
2c	+ 5.1 (0.44, $CHCl_3$)	1.34–1.41 (m, 12H, C*H*$_3$), 3.68 (t, *J* = 7.8, 1H, C*H*$_2$N), 3.93–4.24 (m, 6H, C*H*$_2$N, C*H*O), 5.12 (s, 2H, PhC*H*$_2$), 5.29 (s_{br}, 1H, N*H*), 5.36–5.42 (m, 2H, CH=C*H*$_2$), 5.52 (dd, *J* = 7.8, 3.2, 1H, C*H*OCO), 5.93 (ddd, *J* = 17.7, 8.9, 8.9, 1H, C*H*=CH$_2$), 7.30–7.36 (m, 5H, Ar*H*)	25.18, 26.60, 26.91, 27.18 (4q, *C*H$_3$), 42.99 (t, *C*H$_2$N), 67.13 (t, Ph*C*H$_2$), 67.66 (t, *C*H$_2$O), 75.87, 76.93, 78.55, 81.15 (4d, *C*HO), 109.93, 110.29 [2s, *C*(CH$_3$)$_2$], 121.45 (t, CH=*C*H$_2$), 128.10, 128.52, 129.19 (3d, Ar*C*), 131.07 (d, *C*H=CH$_2$), 136.25 (s, quart. Ar*C*), 156.21 (s, O*C*ON), 169.01 (s, *C*OO)
2f	+ 24.2 (2.5, $CHCl_3$)	0.88 (t, *J* = 7.0, 3H, CH$_2$C*H*$_3$), 1.25–1.33 (m, 4H, C*H*$_2$), 1.34 [s, 3H, C(C*H*$_3$)$_2$], 1.39 [s, 3H, C(C*H*$_3$)$_2$], 2.05 (m, 2H, C = CHC*H*$_2$), 3.77 (dd, *J* = 7.9, 6.8, 1H, C*H*$_2$N), 3.91–4.13 (m, 4H, C*H*$_2$O, C*H*$_2$N, C*H*OC), 5.12 (s, 2H, PhC*H*$_2$), 5.26 (m_c, 1H, N*H*), 5.33–5.46 (m, 2H, CHOC*H*=CH, C*H*OCO), 5.81 (dt, *J* = 14.3, 7.1, 1H, CH=C*H*CH$_2$), 7.35 (m, 5H, Ar*H*)	13.96 (q, CH$_2$*C*H$_3$), 22.20 (t, *C*H$_2$CH$_3$), 25.40, 26.43 [2q, C(*C*H$_3$)$_2$], 30.99 (t, *C*H$_2$), 32.12 (t, *C*H$_2$), 43.14 (t, *C*H$_2$N), 65.72 (t, *C*H$_2$O), 67.25 (t, Ph*C*H$_2$), 75.54 (d, *C*HO), 76.83 (d, *C*HO), 110.06 [2s, *C*(CH$_3$)$_2$], 123.25 (d, CH=*C*HCH$_2$), 128.22, 128.32, 128.66 (3d, Ar*C*), 136.42 (s, quart. Ar*C*), 137.97 (d, CHO*C*H=CH), 156.29 (s, O*C*ON), 169.17 (s, *C*OO)
2g	– 40.3 (0.6, $CHCl_3$)	1.39 (d, *J* = 7.2, 1.5H, C*H*$_3$), 1.47 (d, *J* = 7.2, 1.5H, C*H*$_3$), 4.47 (m_c, 1H, C*H*N), 5.10 (s, 1H, PhC*H*$_2$), 5.11 (s, 1H, PhC*H*$_2$), 5.27 (m, 2H, CH=CH*H*^{t}, N*H*), 5.34 (m_c, 1H, CH=CH*H*^{c}), 6.00 (ddd, *J* = 16.1, 10.7, 5.3, 1H, C*H*=CH$_2$), 6.28 (m, 1H, C*H*OCO), 7.34 (s_{br}, 10H, Ar*H*)	18.55, 18.77 (2q, *C*H$_3$), 49.74 (d, *C*HN), 68.88 (t, Ph*C*H$_2$), 72.21, 77.32 (2d, *C*HOCO), 117.41, 117.51 (2t, CH=*C*H$_2$), 126.95, 127.04, 128.05, 128.12, 128.31, 128.36, 128.49 (7d, Ar*C*), 135.63 (d, *C*H=CH$_2$), 136.26, 138.14, 138.20 (3s, quart. Ar*C*), 155.52 (s, O*C*ON), 171.85 (s, *C*OO)
2h	– 26.0 (2.7, $CHCl_3$)	5.06 (d, *J* = 12.1, 1H, PhC*H*$_2$), 5.12 (d, *J* = 12.1, 1H, PhC*H*$_2$), 5.26 (d, *J* = 10.4, 1H, CH=CH*H*^{t}), 5.28 (d, *J* = 17.1, 1H, CH=CH*H*^{c}), 5.46 (d, *J* = 7.5, 1H, C*H*N), 5.83 (d, *J* = 7.3, 1H, N*H*), 5.97 (ddd, *J* = 17.0, 10.6, 6.3, 1H, C*H*=CH$_2$), 6.23 (d, *J* = 5.9, 1H, C*H*OCO), 6.96 (d, *J* = 6.1, 2H, Ar*H*), 7.28–7.38 (m, 13H, Ar*H*)	67.17 (t, Ph*C*H$_2$), 76.43, 77.85 (2d, *C*HN, *C*HOCO), 117.9 (t, CH=*C*H$_2$), 126.56, 127.31, 128.09, 128.20, 128.38, 128.55, 128.89 (7d, Ar*C*), 135.58 (d, *C*H=CH$_2$), 136.09, 136.36, 137.94 (3s, quart. Ar*C*), 155.33 (s, O*C*ON), 169.67 (s, *C*OO)

Table 3. (continued)

Compound	$[\alpha]_D^{20}$ (*c*, Solvent)	^{1}H NMR (300 MHz, $CDCl_3$) *δ*, *J* (Hz)	^{13}C NMR (75 MHz, $CDCl_3$) *δ*
2i	+ 45.3 (3.1, $CHCl_3$)	3.16 (d, *J* = 5.9, 2H, PhCH_2C), 4.70 (m_c, 0.5H, C*H*N), 4.74 (m_c, 0.5H, C*H*N), 5.08 (s, 2H, PhCH_2O), 5.25–5.35 (m, 3H, N*H*, CH=CH_2), 5.95 (ddd, *J* = 16.9, 10.7, 6.3, 1H, C*H*=CH_2), 6.25 (d, *J* = 6.3, 1H, C*H*OCO), 7.09–7.35 (m, 15H, Ar*H*)	37.91, 38.28 (2t, PhCH_2C), 54.67, 54.89 (2d, *C*HN), 66.92 (t, PhCH_2O), 77.38, 77.50 (2d, *C*HOCO), 117.50, 117.67 (2t, CH=CH_2), 126.96, 127.05, 127.36, 128.03, 128.13, 128.32, 128.48, 128.55, 128.61, 129.32, 129.41 (11d, Ar*C*), 135.29, 135.43 (2d, *C*H=CH_2), 136.23, 138.10, 138.17 (3s, quart. Ar*C*), 155.58 (s, O*C*ON), 170.51 (s, *C*OO)
2k	–4.4 (2.1, $CHCl_3$)	1.34 (s, 3H, CH_3), 1.41–1.46 [m, 6H, C(CH_3)$_2$], 380–3.82 (m, 1H, CH_2O), 4.02 (m_c, 1H, CH_2O), 4.19 (m_c, 1H, C*H*OC), 4.43 (m_c, 1H, C*H*N), 5.11 (s_{br}, 2H, PhCH_2O), 5.29–5.36 (m, 4H, N*H*, C*H*OCO, CH=CH_2), 5.77–5.82 (m, 1H, C*H*=CH_2), 7.31–7.35 (m, 5H, Ar*H*)	18.66, 18.80 (q, *C*H_3), 25.10, 25.20, 26.38 [3q, C(*C*H_3)$_2$], 49.82 (d, *C*HN), 65.57, 65.75 (2t, *C*H_2O), 66.96 (t, Ph*C*H_2), 109.93, 110.06 [2s, *C*(CH$_3$)$_2$], 119.34 (t, CH=*C*H_2), 128.12, 128.20, 128.54 (3d, Ar*C*), 131.95 (d, *C*H=CH_2), 136.26 (s, quart. Ar*C*), 155.54 (s, O*C*ON), 171.95 (s, *C*OO)
2l	–3.7 (3.1, $CHCl_3$)	0.94 (m, 3H, CH_2CH_3), 1.34 [s, 3H, C(CH_3)$_2$], 1.41 [s, 3H, C(CH_3)$_2$], 1.71–1.75 (m, 2H, CH_2CH$_3$), 3.79 (m_c, 1H, CH_2O), 3.98–4.08 (m, 1H, CH_2O), 4.18–4.22 (m, 1H, C*H*OC), 4.37–4.39 (m, 1H, C*H*N), 5.11 (s, 2H, PhCH_2O), 5.29–5.38 (m, 4H, N*H*, C*H*OCO, CH=CH_2), 5.82 (ddd, *J* = 17.2, 10.6, 6.5, 1H, C*H*=CH_2), 7.30–7.39 (m, 5H, Ar*H*)	9.37, 9.50 (2q, CH_2*C*H$_3$), 25.12, 25.22 [2q, C(*C*H$_3$)$_2$], 25.79, 25.87 (2t, *C*H_2CH$_3$), 26.34, 26.37 [2q, C(*C*H$_3$)$_2$], 54.99 (d, *C*HN), 65.72, 65.82 (2t, *C*H_2O), 75.06, 75.11 (2d, *C*HOC), 76.27, 76.37 (2d, *C*HOCO), 109.93, 110.06 [2s, *C*(CH$_3$)$_2$], 119.44, 119.71 (2t, CH=*C*H_2), 128.11, 128.20, 128.56 (3d, Ar*C*), 132.01 (d, *C*H=CH_2), 136.27 (s, quart. Ar*C*), 155.83 (s, O*C*ON), 171.35 (s, *C*OO)
3a	- 39.9 (1.4, $CHCl_3$)	2.67–2.76 (m, 2H, CH=CHCH_2), 3.77 (s, 3H, OCH_3), 4.55 (dd, *J* = 13.6, 5.9, 1H, C*H*N), 5.09 (d, *J* = 12.2, 1H, PhCH_2O), 5.14 (d, *J* = 12.2, 1H, PhCH_2O), 5.38 (d, *J* = 7.8, 1H, N*H*), 6.06 (dt, *J* = 15.4, 7.6, 1H, CH=C*H*CH$_2$), 6.46 (d, *J* = 15.7, 1H, PhC*H*=CH), 7.24–7.33 (m, 10H, Ar*H*)	36.13 (t, CH=CH*C*H$_2$), 52.44 (q, OCH$_3$), 53.67 (d, *C*HN), 67.04 (t, PhCH$_2$), 123.37 (d, CH=*C*HCH$_2$), 126.32, 127.01, 128.10, 128.18, 128.53, 128.56 (6d, Ar*C*), 134.28 (d, Ph*C*H=CH), 136.11, 136.26 (2s, quart. Ar*C*), 155.74 (s, O*C*ON), 172.15 (s, *C*OO)
ent-**3a**	+ 39.9 (1.3, $CHCl_3$)	2.68–2.78 (m, 2H, CH=CHCH_2), 3.77 (s, 3H, OCH_3), 4.55 (dd, *J* = 13.6, 5.9, 1H, C*H*N), 5.09 (d, *J* = 12.2, 1H, PhCH_2O), 5.14 (d, *J* = 12.2, 1H, PhCH_2O), 5.38 (d, *J* = 7.8, 1H, N*H*), 6.06 (dt, *J* = 15.4, 7.6, 1H, CH=C*H*CH$_2$), 6.46 (d, *J* = 15.7, 1H, PhC*H*=CH), 7.24–7.35 (m, 10H, Ar*H*)	36.13 (t, CH=CH*C*H$_2$), 52.44 (q, OCH$_3$), 53.67 (d, *C*HN), 67.04 (t, PhCH$_2$), 123.37 (d, CH=*C*HCH$_2$), 126.32, 127.01, 128.10, 128.18, 128.53, 128.56 (6d, Ar*C*), 134.28 (d, Ph*C*H=CH), 136.11, 136.26 (2s, quart. Ar*C*), 155.74 (s, O*C*ON), 172.15 (s, *C*OO)
3b	+ 16.2 (0.5, $CHCl_3$)	1.43 [s, 9H, C(CH_3)$_3$], 2.47 (ddd, *J* = 13.5, 6.7, 6.7, 1H, CH=CHCH_2), 2.57 (ddd, *J* = 13.5, 6.7, 6.7, 1H, CH=CHCH_2), 3.73 (s, 3H, OCH_3), 3.97 (*J* = 5.5, 2H, CH=CHCH_2O), 4.37 (m_c, 1H, C*H*N), 4.48 (s, 2H, PhCH_2O), 5.03 (s_{br}, 1H, N*H*), 5.60 (dt, *J* = 15.4, 6.7, 1H, CH=C*H*CH$_2$), 5.70 (dt, *J* = 15.4, 5.4, 1H, CH=C*H*CH$_2$O), 7.24–7.37 (m, 5H, Ar*H*)	28.30 [q, C(*C*H$_3$)$_3$], 35.44 (t, CH=CH*C*H$_2$), 52.21 (q, OCH$_3$), 53.10 (d, *C*HN), 70.23 (t, CH=CH*C*H$_2$O), 72.02 (t, Ph*C*H$_2$), 79.75 [s, *C*(CH$_3$)$_3$], 127.39 (d, CH=*C*HCH$_2$), 127.60, 127.75, 128.37 (3d, Ar*C*), 131.10 (d, CH=*C*HCH$_2$O), 138.27 (s, quart. Ar*C*), 155.17 (s, O*C*ON), 172.48 (s, *C*OO)
3c	–9.1 (0.1, $CHCl_3$)	1.36 [s, 3H, C(CH_3)$_2$], 1.40 [s, 3H, C(CH_3)$_2$], 2.47–2.62 (m, 2H, CH=CHCH_2), 3.52 (dd, *J* = 7.9, 1H, CH_2O), 3.74 (s, 3H, OCH_3), 4.05 (dd, *J* = 8.1, 6.3, 1H, CH_2O), 4.44 (dd, *J* = 13.6, 6.7, 2H, C*H*N, C*H*OC), 5.10 (s_{br}, 2H, PhCH_2O), 5.34 (d, *J* = 8.0, 1H, N*H*), 5.56 (dt, *J* = 15.4, 6.8, 1H, CH=C*H*CH$_2$), 5.65 (dd, *J* = 15.3, 6.7, 1H, CH=C*H*CHO), 7.34 (s_{br}, Ar*H*)	25.79 [q, C(*C*H$_3$)$_2$], 26.61 [q, C(*C*H$_3$)$_2$], 35.20 (t, CH=CH*C*H$_2$), 52.37 (q, OCH$_3$), 53.36 (d, *C*HN), 67.04 (t, PhCH$_2$), 69.32 (t, *C*H$_2$O), 76.44 (d, *C*HO), 109.32 [s, *C*(CH$_3$)$_2$], 127.81 (d, CH=*C*HCH$_2$), 128.07, 128.18, 128.50 (3d, Ar*C*), 132.45 (d, CH=*C*HCHO), 136.22 (s, quart. Ar*C*), 155.64 (s, O*C*ON), 171.79 (s, *C*OO)
3d	+ 15.3 (1.1, $CHCl_3$)	1.40 [s, 3H, C(CH_3)$_2$], 1.42 [s, 9H, C(CH_3)$_3$], 1.44 [s, 3H, C(CH_3)$_2$], 2.43–2.53 (m, 2H, CH=CHCH_2), 3.58 (d, *J* = 4.0, 2H, CH_2O), 3.68 (s, 3H, OCH_3), 3.83 (dt, *J* = 8.6, 4.0, 1H, OCH$_2$C*H*O), 4.17 (ddd, *J* = 8.5, 6.6, 1.8, 1H, CH=CHC*H*O), 4.35 (m_c, 1H, C*H*N), 4.59 (s, 2H, PhCH_2O), 5.04 (s_{br}, 1H, N*H*), 5.57 (dt, *J* = 15.4, 6.3, 1H, CH=C*H*CH$_2$), 5.64 (dd, *J* = 15.4, 6.6, 1H, CH=C*H*CHO), 7.24–7.37 (m, 5H, Ar*H*)	26.89 [q, C(*C*H$_3$)$_2$], 26.92 [q, C(*C*H$_3$)$_2$], 28.26 [q, C(*C*H$_3$)$_3$], 35.30 (t, CH=CH*C*H$_2$), 52.20 (q, OCH$_3$), 52.91 (d, *C*HN), 69.47 (t, PhCH$_2$), 73.52 (t, *C*H$_2$O), 78.61 [s, *C*(CH$_3$)$_3$], 78.79 (d, *C*HOC), 80.10 (d, *C*HOC), 109.30 [s, *C*(CH$_3$)$_2$], 12763, 127.65, 127.68 (3d, Ar*C*), 128.32 (d, CH=*C*HCH$_2$), 131.63 (d, CH=*C*HCHO), 137.92 (s, quart. Ar*C*), 155.06 (s, O*C*ON), 172.25 (s, *C*OO)

Table 3. (continued)

Compound	$[\alpha]_D^{20}$ (*c*, Solvent)	^{1}H NMR (300 MHz, $CDCl_3$) *δ*, *J* (Hz)	^{13}C NMR (75 MHz, $CDCl_3$) *δ*
3e	+ 7.2 (0.3, $CHCl_3$)	1.31 [s, 3H, C(C*H*$_3$)$_2$], 1.36 [s, 3H, C(C*H*$_3$)$_2$], 1.38 [s, 6H, C(C*H*$_3$)$_2$], 2.57–2.58 (m, 2H, CH=CHC*H*$_2$), 3.59 (dd, *J* = 7.4, 7.1, 1H, C*H*$_2$O), 3.75 (s, 3H, OC*H*$_3$), 3.87 (m$_c$, 1H, C*H*$_2$O), 4.04–4.11 (m, 2H, C*H*OC), 4.28 (dd, *J* = 7.8, 6.0, 1H, CH=CHC*H*O), 4.50 (dt, *J* = 8.5, 5.3, 1H, C*H*N), 5.10 (s, 2H, PhC*H*$_2$O), 5.35 (d, *J* = 8.5, 1H, N*H*), 5.37–5.80 (m, 2H, CH=C*H*), 7.26–7.36 (m, 5H, Ar*H*)	25.18, 26.50, 26.89, 26.94 [4q, C(*C*H$_3$)$_2$], 35.15 (t, CH=CH*C*H$_2$), 52.40 (q, O*C*H$_3$), 53.19 (d, *C*HN), 67.04 (t, Ph*C*H$_2$), 67.22 (t, *C*H$_2$O), 76.50, 79.63, 80.15 (3d, *C*HOC), 109.34 [s, *C*(CH$_3$)$_2$], 109.85 [s, *C*(CH$_3$)$_2$], 127.50, 128.52, 128.80, 128.81 (4d, CH=*C*HCH$_2$, Ar*C*), 132.51 (d, CH=*C*HCHO), 136.24 (s, quart. Ar*C*), 155.74 (s, O*C*ON), 171.93 (s, *C*OO)
3f	+ 3.7 (1.0, $CHCl_3$)	0.79 (t, *J* = 6.2, 3H, CH$_2$C*H*$_3$), 1.20 (m, 6H, C*H*$_2$), 1.31 [s, 3H, C(C*H*$_3$)$_2$], 1.34 [s, 3H, C(C*H*$_3$)$_2$], 2.35 (m$_c$, 1H, CH=CHC*H*C), 3.45 (t, *J* = 7.9, 1H, C*H*$_2$O), 3.64 (s, 3H, OC*H*$_3$), 3.98 (dd, *J* = 7.9, 6.2, 1H, C*H*$_2$O), 4.25–4.40 (m, 2H, C*H*OC, C*H*N), 5.00 (d, *J* = 13.0, 1H, PhC*H*$_2$O), 5.07 (d, *J* = 13.0, 1H, PhC*H*$_2$O), 5.16 (d, *J* = 7.7, 1H, N*H*), 5.33–5.51 (m, 2H, CH=C*H*), 7.28 (s$_{br}$, 5H, Ar*H*)	18.34 (q, CH$_2$*C*H$_3$), 22.42 (t, *C*H$_2$CH$_3$), 25.86 [q, C(*C*H$_3$)$_2$], 26.64 [q, C(*C*H$_3$)$_2$], 29.22 (t, *C*H$_2$), 30.17 (t, *C*H$_2$), 45.87 (d, CH=CH*C*HC), 51.99 (q, O*C*H$_3$), 57.38 (d, *C*HN), 67.06 (t, Ph*C*H$_2$), 69.59 (t, *C*H$_2$O), 76.44 (d, *C*HOC), 109.36 [s, *C*(CH$_3$)$_2$], 128.18, 128.51, 128.53 (3d, Ar*C*), 131.49 (d, CH=*C*H), 132.96 (d, CH=*C*H), 136.21 (s, quart. Ar*C*), 155.73 (s, O*C*ON), 171.68 (s, *C*OO)
3g	–10.5 (0.7, $CHCl_3$)	1.63 (s, 3H, C*H*$_3$), 2.75 (dd, *J* = 14.0, 7.3, 1H, CH=CHC*H*$_2$), 2.97 (m$_c$, 1H, CH=CHC*H*$_2$), 3.76 (s, 3H, OC*H*$_3$), 5.07 (d, *J* = 12.3, 1H, PhC*H*$_2$), 5.13 (d, *J* = 12.3, 1H, PhC*H*$_2$), 5.57 (s$_{br}$, 1H, N*H*), 6.02 (dt, *J* = 15.4, 7.7, 1H, PhCH=C*H*), 6.42 (d, *J* = 15.8, 1H, PhC*H*=CH), 7.19–7.35 (m, 10H, Ar*H*)	23.36 (q, *C*H$_3$), 40.51 (t, CH=CH*C*H$_2$), 52.71 (q, O*C*H$_3$), 59.94 (s, *C*N), 66.51 (t, Ph*C*H$_2$), 123.5 (d, PhCH=*C*H), 126.29, 127.50, 128.04, 128.09, 128.51 (5d, Ar*C*), 134.44 (d, Ph*C*H=CH), 136.50, 136.98 (2s, quart. Ar*C*), 154.73 (s, O*C*ON), 174.22 (s, *C*OO)
3h	+ 15.3 (1.0, $CHCl_3$)	3.39 (dd, *J* = 13.6, 7.7, 1H, CH=CHC*H*$_2$), 3.72 (s$_{br}$, 4H, CH=CHC*H*$_2$, OC*H*$_3$), 5.00 (d, *J* = 12.3, 1H, PhC*H*$_2$), 5.13 (d, *J* = 12.3, 1H, PhC*H*$_2$), 6.04 (dt, *J* = 15.4, 7.7, 1H, PhCH=C*H*), 6.39 (s$_{br}$, 1H, N*H*), 6.48 (d, *J* = 15.4, 1H, PhC*H*=CH), 7.21–7.90 (m, 15H, Ar*H*)	37.27 (t, CH=CH*C*H$_2$), 53.28 (q, O*C*H$_3$), 65.49 (s, *C*N), 66.55 (t, Ph*C*H$_2$), 123.65 (d, PhCH=*C*H), 126.01, 126.33, 127.47, 128.02, 128.06, 128.50, 128.63 (7d, Ar*C*), 134.55 (d, Ph*C*H=CH), 136.55, 137.15, 139.56 (3s, quart. Ar*C*), 154.15 (s, O*C*ON), 172.56 (s, *C*OO)
3i	– 10.5 (3.1, $CHCl_3$)	2.79 (dd, *J* = 13.9, 7.7, 1H, CH=CHC*H*$_2$), 3.15 (d, *J* = 13.4, 1H, PhC*H*$_2$C), 3.41 (dd, *J* = 13.9, 7.7, 1H, CH=CHC*H*$_2$), 3.66 (d, *J* = 13.4, 1H, PhC*H*$_2$C), 3.76 (s, 3H, OC*H*$_3$), 5.11 (d, *J* = 12.3, 1H, PhC*H*$_2$O), 5.20 (d, *J* = 12.3, 1H, PhC*H*$_2$O), 5.67 (s$_{br}$, 1H, N*H*), 5.98 (dt, *J* = 15.4, 7.7, 1H, PhCH=C*H*), 6.44 (d, *J* = 15.4, 1H, PhC*H*=CH), 6.95–7.88 (m, 15H, Ar*H*)	39.25 (t, Ph*C*H$_2$C), 40.94 (t, CH=CH*C*H$_2$), 52.64 (q, O*C*H$_3$), 65.65 (s, *C*N), 66.32 (t, Ph*C*H$_2$O), 123.55 (d, PhCH=*C*H), 126.30, 126.95, 127.42, 128.28, 128.52, 128.77, 129.73 (7d, Ar*C*), 134.12 (d, Ph*C*H=CH), 135.98, 136.84, 137.12 (3s, quart. Ar*C*), 154.41 (s, O*C*ON), 172.69 (s, *C*OO)
3k	+ 7.7 (1.0, $CHCl_3$)	1.36 [s, 3H, C(C*H*$_3$)$_2$], 1.39 [s, 3H, C(C*H*$_3$)$_2$], 1.56 (s, 3H, C*H*$_3$), 2.59 (dd, *J* = 14.0, 6.0, 1H, CH=CHC*H*$_2$), 2.84 (m, 1H, CH=CHC*H*$_2$), 3.46 (dd, *J* = 7.9, 7.9, 1H, C*H*$_2$O), 3.73 (s, 3H, OC*H*$_3$), 4.02 (dd, *J* = 8.1, 6.3, 1H, C*H*$_2$O), 4.41 (m$_c$, 1H, C*H*O), 5.04 (d, *J* = 12.3, 1H, PhC*H*$_2$), 5.09 (d, *J* = 12.3, 1H, PhC*H*$_2$), 5.45–5.62 (m, 3H, CH=C*H*N*H*), 7.30–7.36 (m, 5H, Ar*H*)	23.27 (q, *C*H$_3$), 25.83 [q, C(*C*H$_3$)$_2$], 26.66 [q, C(*C*H$_3$)$_2$], 39.47 (t, CH=CH*C*H$_2$), 52.72 (q, O*C*H$_3$), 59.63 (s, *C*N), 66.52 (t, Ph*C*H$_2$), 69.36 (t, *C*H$_2$O), 76.18 (d, *C*HO), 109.29 [s, *C*(CH$_3$)$_2$], 127.95 (d, CH=*C*HCH$_2$), 128.09, 128.15, 128.52 (3d, Ar*C*), 132.76 (d, CHO*C*H=CH), 136.43 (s, quart. Ar*C*), 154.57 (s, O*C*ON), 174.07 (s, *C*OO)
3l	– 10.9 (0.7, $CHCl_3$)	0.74 (t, *J* = 7.4, 3H, CH$_2$C*H*$_3$), 1.33 [s, 3H, C(C*H*$_3$)$_2$], 1.36 [s, 3H, C(C*H*$_3$)$_2$], 1.77 (dq, *J* = 7.4, 7.4, 1H, C*H*$_2$CH$_3$), 2.28 (dq, *J* = 7.4, 7.4, 1H, C*H*$_2$CH$_3$), 2.51 (dd, *J* = 14.2, 5.7, 1H, CH=CHC*H*$_2$), 3.03 (*J* = 13.8, 6.1, 2H, CH=CHC*H*$_2$), 3.40 (dd, *J* = 8.1, 7.7, 1H, C*H*$_2$O), 3.74 (s, 3H, OC*H*$_3$), 3.97 (dd, *J* = 8.1, 6.3, 1H, C*H*$_2$O), 4.36 (m$_c$, 1H, C*H*O), 4.99–5.09 (m, 2H, PhC*H*$_2$), 5.45 (dt, *J* = 15.4, 5.5, 1H, CHOCH=C*H*), 5.61 (dd, *J* = 15.4, 6.3, 1H, CHOC*H*=CH), 5.74 (s, 1H, N*H*) 7.29–7.34 (m, 5H, Ar*H*)	8.11 (q, CH$_2$*C*H$_3$), 25.62 [q, C(*C*H$_3$)$_2$], 26.44 [q, C(*C*H$_3$)$_2$], 28.18 (t, *C*H$_2$CH$_3$), 37.74 (t, CH=CH*C*H$_2$), 52.56 (q, O*C*H$_3$), 64.30 (s, *C*N), 66.08 (t, Ph*C*H$_2$), 69.11 (t, *C*H$_2$O), 76.38 (d, *C*HO), 109.98 [s, *C*(CH$_3$)$_2$], 127.78, 127.90, 128.01, 128.31 (4d, CH=*C*HCH$_2$, Ar*C*), 132.02 (d, CHO*C*H=CH), 136.33 (s, quart. Ar*C*), 153.80 (s, O*C*ON), 173.27 (s, *C*OO)

60 °C) were generally used as eluents. TLC: commercially precoated Polygram© SIL-G/UV 254 plates (Macherey–Nagel). Visualization was accomplished with UV light, I_2, and $KMnO_4$ soln. ^1H and ^{13}C NMR: Bruker AC-300 spectrometer. Enantiomeric and diastereomeric ratios were determined by analytical HPLC using a Knauer Eurosphere column (250 × 4 mm, Si80, 5 μm, flow: 2 mL/min), as well as a Chiracel-OD-H column (Daicel) (0.5 mL/min) and a Knauer UV detector. Optical rotations were measured on a Perkin–Elmer polarimeter PE 241.

Synthesis of Amino Acid Allylic Esters 2; General Procedure:
The allylic ester derivatives used as substrates were synthesized by the method described by Steglich et al.[14] To a solution of allylic alcohol **1** (1 mmol) in CH_2Cl_2 (5 mL) was added DMAP (0.1 mmol). The mixture was stirred for 5 min, before a solution of DCC (1.1 mmol) in CH_2Cl_2 (3 mL) was added, followed by the *N*-protected amino acid (1.1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at r.t. overnight. The precipitate was filtered off, and the filtrate was washed with 1 N $KHSO_4$, sat. $NaHCO_3$ and brine. After evaporation of the solvent in vacuo, the residue obtained was purified by flash chromatography (EtOAc/petroleum ether).

Chelate Enolate Claisen Rearrangement; General Procedure:
Freshly prepared LDA solution (2.5 mmol) in THF (7 mL) was added to a stirred solution of the allylic ester (1 mmol) and $ZnCl_2$ (1.1 mmol) in anhyd THF at –78 °C. The mixture was allowed to warm to r.t. overnight. The resulting clear solution was diluted with Et_2O and hydrolyzed with 1 N $KHSO_4$. After separation of the aqueous layer, the crude rearrangement product was extracted with 1 N NaOH. After acidification of the aqueous layer with 1 N $KHSO_4$, the product was extracted twice with Et_2O and the solvent was removed in vacuo. For determination of selectivity the crude product was treated with a solution of diazomethane in Et_2O and purified by flash chromatography on silica gel (EtOAc/petroleum ether).

Determination of Configuration via Ozonolysis:
Starting from allylic ester **2a** (*S*-configuration) (82 mg, 0.25 mmol) and following the general procedure for the chelate enolate Claisen rearrangement, the crude amino acid **3a** (80 mg) was obtained. This amino acid was dissolved in MeOH (30 mL), and after addition of 2,3-dimethylbutene (31 mg, 0.37 mmol) the solution was cooled to –60 °C. After ozonolysis for 5 min, the mixture was allowed to warm to r.t. overnight. The solvent was removed in vacuo, and the residue obtained was dissolved in EtOAc. After washing the organic layer with 1 N HCl, the product was extracted twice with 1 N NaOH. The aqueous solution was acidified with 1 N HCl and extracted twice with EtOAc. After drying (Na_2SO_4) and evaporation of the solvent, Z-Asp was obtained, which was converted into the corresponding dimethyl ester with diazomethane. HPLC analysis using a Chiracel-OD-H column (Daicel) (hexane/EtOH 8:2; 0.5 mL/min), and comparison with samples obtained from (*S*)-Asp and (*R/S*)-Asp ($t_{R(S)}$: 20.27 min; $t_{R(R)}$: 22.95 min), determined the configuration of the rearrangement product to be (*R*).

We thank Prof. Dr. G. Helmchen for his generous support of this work. Financial support by the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie is gratefully acknowledged.

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