Stereoselective Synthesis of β-Branched Phenylalanine Derivatives via Chelate-Claisen Rearrangement

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Abstract: Ester enolate Claisen rearrangement of chelated N-protected chiral amino acid cinnamyl esters results in the formation of substituted phenylalanine derivatives with unsaturated side chains in good yields and with a high degree of chirality transfer.

Key words: amino acids, chelates, esters, rearrangements, stereoselective synthesis

In human metabolism peptides fulfill important functions as neurotransmitters or substrates for enzymes, which makes them interesting lead structures for the development of peptide based drugs. Nevertheless their use is restricted, because of their polarity the resorption is often bad. Further more fast elimination via the liver or kidneys can also be a problem, and finally peptides underlie metabolic degradation in the gastrointestinal tract and are not stable. Hence different precautions have to be taken to avoid these disadvantages. One possibility is the introduction of amino acids with unnatural side chains into peptides.[1] For example, the incorporation of β-branches increases the stability against enzymymatic degradation.[2] β-Alkylated amino acids are also found widespread in nature, for example in bottromycin, which contains nearly exclusively branched amino acids.[3] Therefore, these unusual amino acids are interesting building blocks for peptidomimetics, and not surprisingly, a wide range of different protocols for their stereoselective synthesis has been developed in the last decades.[4]

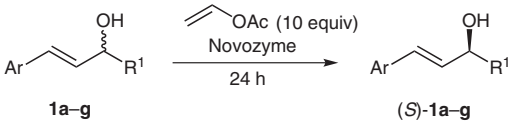
Our group is also involved in the synthesis of unnatural amino acids, especially those with functionalized side chains, using chelated amino acid ester enolates. These chelated enolates can then be utilized for various reactions, for example, Michael additions,[5] aldol reactions,[6] or palladium-[7] and rhodium-catalyzed allylic alkylations,[8] which all allow the stereoselective introduction of β-substituents.

Especially for the introduction of γ,δ-unsaturated side chains the Claisen rearrangement is a very suitable method. In 1975 Steglich[9] reported the first rearrangement of allylic amino acid esters via oxazoles and Bartlett[10] was successful in Ireland–Claisen rearrangement using the same intermediates a few years later. In the 1990s we developed a new protocol for the ester enolate Claisen rearrangement using chelated ester enolates.[11] Because of the fixed enolate geometry, due to chelation, and the preferred chair-like transition state the rearrangement proceeds with a high degree of diastereoselectivity. By using amino acid esters of chiral allylic alcohols, optically active amino acids can be obtained with excellent 1,3-chirality transfer.[12]

Herein we report on an application of the chelate enolate Claisen rearrangement towards the synthesis of β-alkylated phenylalanines, which are interesting candidates for the modification of natural products such as bottromycin.

These phenylalanine analogues are easily accessible from substituted cinnamyl alcohols **1**, which can be obtained enantiomerically pure from the racemate (see experimental) via enzymatic kinetic resolution using Novozyme 435® (Table 1).[13] In the presence of vinyl acetate the *R*-configured acetates were formed and the desired *S*-configured allylic alcohols remained in high optical purity.

Table 1 Enzymatic Kinetic Resolution with Novozyme 435®



1a–g (*S*)-**1a–g**

Entry	Substrate	Ar	R^1	Product	Yield (%)	ee (%)
1	**1a**	Ph	Me	(*S*)-**1a**	49	98
2	**1b**	Ph	Et	(*S*)-**1b**	42	>99
3	**1c**	4-$MeOC_6H_4$	Me	(*S*)-**1c**	46	>99
4	**1d**	naphthyl	Me	(*S*)-**1d**	49	>99
5	**1e**	4-MeC_6H_4	Me	(*S*)-**1e**	47	99
6	**1f**	4-BrC_6H_4	Me	(*S*)-**1f**	44	99
7	**1g**	4-BrC_6H_4	Et	(*S*)-**1g**	44	–[a]

[a] No separation of the enantiomers was accomplished, neither by GC nor by HPLC.

In the next step the allylic alcohols (*S*)-**1a–g** were coupled with either Boc-protected glycine or alanine under Steglich's conditions[14] to provide the chiral allylic amino acid esters (*S*)-**2a–h**. The esters were subsequently subjected to the chelate ester enolate Claisen rearrangement. Deprotonation at –78 °C with LDA in the presence of $ZnCl_2$ resulted in the formation of chelated metal enolates,

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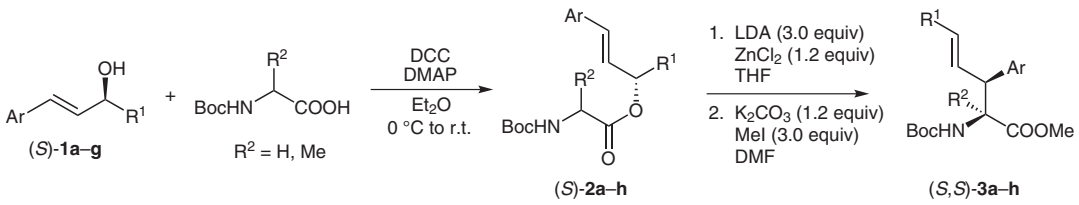
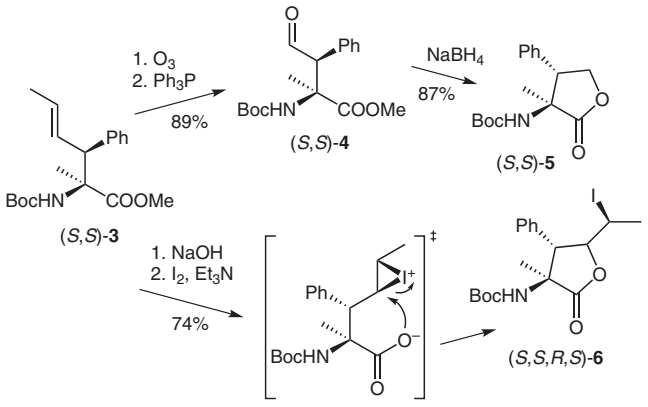
Table 2 DCC-Coupling and Claisen Rearrangement Products



Entry	Alcohol	Amino acid	Ester	Ar	R^1	R^2	Yield (%)	Product	Yield (%)	ee (%)	ds (%)
1	(*S*)-**1a**	BocGlyOH	(*S*)-**2a**	Ph	Me	H	99	(*S*,*S*)-**3a**	84	>99	>99
2	(*S*)-**1a**	BocAlaOH	(*S*)-**2b**	Ph	Me	Me	96	(*S*,*S*)-**3b**	87	>99	>99
3	(*S*)-**1b**	BocAlaOH	(S)-**2c**	Ph	Et	Me	96	(*S*,*S*)-**3c**	88	>99	>99
4	(*S*)-**1c**	BocGlyOH	(*S*)-**2d**	4-$MeOC_6H_4$	Me	H	97	(*S*,*S*)-**3d**	69	>99	97
5	(*S*)-**1d**	BocGlyOH	(*S*)-**2e**	2-naphthyl	Me	H	93	(*S*,*S*)-**3e**	79	>99	99
6	(*S*)-**1e**	BocGlyOH	(*S*)-**2f**	4-MeC_6H_4	Me	H	94	(*S*,*S*)-**3f**	84	98	>99
7	(*S*)-**1f**	BocAlaOH	(*S*)-**2g**	4-BrC_6H_4	Me	Me	99	(*S*,*S*)-**3g**	83	>99	98
8	(*S*)-**1g**	BocAlaOH	(*S*)-**2h**	4-BrC_6H_4	Et	Me	90	(*S*,*S*)-**3h**	89	97	>99

which undergo Claisen rearrangement upon warming to room temperature and afford the γ,δ-unsaturated amino acid esters (*S*,*S*)-**3a**–**h** in good yields and excellent diastereo- and enantioselectivities (Table 2).[12] The alanine derived allyl esters provide directly the corresponding α-alkylated amino acids.[15]

Finally we chose (*S*,*S*)-**3b** as an example to build up some other interesting derivatives. Ozonolysis of the double bond side chain and reductive workup with PPh_3 yielded aldehyde (*S*,*S*)-**4** in 89%. Reduction of this aldehyde with $NaBH_4$ gave the five-membered lactone (*S*,*S*)-**5** directly in 87% yield from the in situ developing alcohol. Of course lactone formation also took place if $NaBH_4$ was used as reducing reagent in the ozonolysis but the overall yield for (*S*,*S*)-**5** was higher with aldehyde (*S*,*S*)-**4** as isolated intermediate. Furthermore (*S*,*S*)-**3b** underwent an iodolactonization on saponification of the methyl ester resulting in the iodolactone (*S*,*S*,*R*,*S*)-**6** in 74% yield and 88% ds (Scheme 1).[16]



Scheme 1 Derivatization of rearrangement product (*S*,*S*)-**3**

In conclusion, starting from the chiral allylic alcohols (*S*)-**1a**–**g** we could synthesize a variety of optically active γ,δ-unsaturated amino acids (*S*,*S*)-**3a**–**h**. With lactone (*S*,*S*)-**5** and iodolactone (*S*,*S*,*R*,*S*)-**6** derivatives with constrained side chains were also accessible.

All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from $LiAlH_4$. The products were purified by flash chromatography on silica gel. TLC: commercially precoated Polygram® SIL-G/UV 254 plates. Visualization was accomplished with UV-light, I_2, or $KMnO_4$ solution. Melting points are uncorrected. ^1H and ^{13}C NMR were recorded on a Bruker DRX-500 spectrometer using $CDCl_3$ as solvent. Selected signals in the NMR spectra for the minor isomers are extracted from the spectra of the isomeric mixture. Enantio- and diastereomeric excesses were determined on an analytical HPLC using a Trentec Reprosil-100 Chiral-NR 8 μm column or a Chiracel OD-H column and a Shimadzu UV detector. As references, the racemic amino acids were obtained via rearrangement of the racemic allylic esters, which allows the differentiation between enantiomers and diastereomers. Optical rotations were measured on a Perkin-Elmer polarimeter PE 241. High-resolution mass spectra were recorded on a Finnigan MAT 95 (CI) mass spectrometer. Elemental analyses were carried out at the department of chemistry, University of Saarbrücken.

Compounds **1a** and **1b** were prepared via Grignard reaction from cinnamyl aldehyde. Compounds **1c**–**f** were prepared by carbonyl olefination of the *p*-substituted benzaldehyde derivatives using the Horner[17] or Wittig reagent derived from chloroacetone, and subsequent Luche reduction.[18] Compound **1g** was obtained from *p*-bromobenzaldehyde by Knoevenagel reaction and conversion of the resulting cinnamyl acid to the corresponding α,β-unsaturated ethyl ketone,[19] which was finally reduced by the Luche protocol.

Enzymatic Kinetic Resolution with Novozyme 435® of 1a–g; General Procedure I

The racemic allylic alcohol **1** (1.0 equiv) was dissolved in vinyl acetate (10 equiv) and Novozyme 435® (5 weight%) was added. After shaking for 24 h, the enzyme was filtered off and washed with

Et_2O (3 × 20 mL).The solvent was removed by rotary evaporation and the enantiopure alcohol was separated from the corresponding acetate by column chromatography (silica gel, hexanes–EtOAc).

(*S*,*E*)-4-Phenylbut-3-en-2-ol [(*S*)-1a][20]
Yield: 49%; 98% ee; white solid; mp <30 °C; R_f = 0.41 (hexanes–EtOAc, 1:1); ee was determined by HPLC (Chiracel OD-H, hexanes–*i*-PrOH, 90:10, flow 1 mL/min): t_R (*R*)-**1a** = 8.26 min, t_R (*S*)-**1a** = 12.48 min; $[\alpha]_D^{20}$ –27.0 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-Phenylpent-1-en-3-ol [(*S*)-1b][21]
Yield: 42%; 99% ee; colorless oil; ee was determined by HPLC (Chiracel OD-H, hexanes–*i*-PrOH, 90:10, flow 1 mL/min): t_R (*R*)-**1b** = 7.01 min, t_R (*S*)-**1b** = 10.20 min; $[\alpha]_D^{20}$ –4.5 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-(4-Methoxyphenyl)pent-1-en-3-ol [(*S*)-1c][22]
Yield: 46%, >99% ee; white solid; mp 81 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 97:3, flow 2 mL/min): t_R (*R*)-**1c** = 8.54 min, t_R (*S*)-**1c** = 8.96 min; $[\alpha]_D^{20}$ –38.5 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-4-(Naphthalen-2-yl)but-3-en-2-ol [(*S*)-1d]
Yield: 49%, >99% ee; white solid; mp 85 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*R*)-**1d** = 22.51, t_R (*S*)-**1d** = 23.52 min; $[\alpha]_D^{20}$ –26.1 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, ^3J = 6.4 Hz, 3 H), 1.67 (br s, 1 H), 4.54 (ddq, ^3J = 6.4, 6.4 Hz, ^3J = 1.1 Hz, 1 H), 6.38 (dd, ^3J = 15.9 Hz, ^3J = 6.4 Hz, 1 H), 6.72 (d, ^3J = 15.9 Hz, 1 H), 7.44 (m, 2 H), 7.58 (dd, ^3J = 8.6 Hz, ^4J = 1.7 Hz, 1 H), 7.71 (br s, 1 H), 7.78 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 (q), 69.0 (d), 123.5 (d), 125.9 (d), 126.3 (d), 126.4 (d), 127.6 (d), 127.9 (d), 128.2 (d), 129.5 (d), 133.0 (s), 133.6, 133.9 (s, d), 134.1 (s).

HRMS (CI): *m*/*z* calcd for $C_{14}H_{14}O$ $[M]^+$: 198.1045; found: 198.1002.

(*S*,*E*)-1-*p*-Tolylpent-1-en-3-ol [(*S*)-1e][23]
Yield: 47%; 99% ee; colorless oil; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*R*)-**1e** = 16.54 min, t_R (*S*)-**1e** = 17.89 min; $[\alpha]_D^{20}$ –22.8 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-4-(4-Bromophenyl)but-3-en-2-ol [(*S*)-1f][23]
Yield: 44%, 99% ee; white solid; mp 62 °C; ee was determined after derivatization to the appropriate acetate using Ac_2O by GC (Chirasil-Dex CB, T_0 [3 min] = 80 °C, 2 °C/min to T = 200 °C [20 min], injector = 250 °C, detector = 275 °C): t_R (*S*)-**1f** = 47.12 min, t_R (*R*)-**1f** = 48.00 min; $[\alpha]_D^{20}$ –25.5 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-1-(4-Bromophenyl)pent-1-en-3-ol [(*S*)-1g]
Yield: 44%; 99% ee; colorless oil; $[\alpha]_D^{20}$ –4.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.5 Hz, 3 H), 1.58 (br s, 1 H) 1.64 (m, 2 H), 4.19 (ddt, ^3J = 6.5, 6.5 Hz, ^3J = 1.0 Hz, 1 H), 6.19 (dd, ^3J = 15.9 Hz, ^3J = 6.6 Hz, 1 H), 6.50 (d, ^3J = 15.9 Hz, 1 H), 7.22 (m, 2 H), 7.41 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.7 (q), 30.2 (t), 74.2 (d), 121.3 (s), 128.0 (d), 129.1 (d), 131.7 (d), 133.1 (d), 135.7 (s).

HRMS (CI): *m*/*z* calcd for $C_{11}H_{13}BrO$ $[M]^+$: 240.0150; found: 240.0159.

DCC-Coupling Reactions with Boc-Protected Glycine or Alanine; General Procedure II
The enantiopure alcohol (*S*)-**1** (1.0 equiv) was dissolved together with BocGlyOH or BocAlaOH (1.0 equiv) in Et_2O (15 mL/mmol). After the addition of DMAP (0.2 equiv), the solution was cooled to 0 °C and DCC (1.2 equiv) was added in one portion. The mixture was allowed to stir and warmed overnight up to r.t. The precipitated DCU was filtered through a pad of Celite, washed with Et_2O (50 mL) and the combined organic layers were concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc) to afford the allylic amino acid ester.

(*S*,*E*)-4-Phenylbut-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate [(*S*)-2a]
From BocGlyOH (1.72 g, 9.82 mmol), allylic alcohol (*S*)-**1a** (1.46 g, 9.82 mmol), DMAP (0.24 g, 1.96 mmol), and DCC (2.43 g, 11.8 mmol), the allylic ester (*S*)-**2a** (3.00 g, 9.82 mmol, ~100%, 98% ee) was obtained as a white solid; mp 87 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 97:3, flow 1 mL/min): t_R (*R*)-**2a** = 17.81 min, t_R (*S*)-**2a** = 20.28 min; $[\alpha]_D^{20}$ –53.8 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, ^3J = 6.5 Hz, 3 H), 1.38 (s, 9 H), 3.82 (dd, ^2J = 18.3 Hz, ^3J = 5.2 Hz, 1 H), 3.88 (dd, ^2J = 18.3 Hz, ^3J = 5.5 Hz, 1 H), 4.94 (br s, 1 H), 5.52 (dq, ^3J = 6.5, 6.5 Hz, 1 H), 6.10 (dd, ^3J = 16.0 Hz, ^3J = 6.9 Hz, 1 H), 6.54 (d, ^3J = 16.0 Hz, 1 H), 7.18 (m, 1 H), 7.24 (m, 2 H), 7.30 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3 (q), 28.3 (q), 42.7 (t), 72.3 (d), 79.9 (s), 126.6 (d), 128.0 (s), 128.1 (d), 128.6 (d), 132.2 (d), 136.1 (s), 155.7 (s), 169.6 (s).

HRMS (CI): *m*/*z* calcd for $C_{17}H_{24}NO_4$ $[M + H]^+$: 306.1705; found: 306.1690.

Anal. Calcd for $C_{17}H_{23}NO_4$ (305.37): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.75; H, 7.44; N, 4.25.

(*S*)-[(*S*,*E*)-4-Phenylbut-3-en-2-yl] 2-(*tert*-Butoxycarbonylamino)propanoate [(*S*)-2b]
From BocAlaOH (1.78 g, 9.39 mmol), allylic alcohol (*S*)-**1a** (1.40 g, 9.39 mmol), DMAP (0.23 g, 1.88 mmol), and DCC (2.33 g, 11.3 mmol), the ester (*S*)-**2b** (2.88 g, 9.03 mmol, 96%, >99% ee) was obtained as a white solid; mp 80–82 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 90:10, flow 1 mL/min): t_R (*S*)-**2b** = 19.07 min; $[\alpha]_D^{20}$ –95.3 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (d, ^3J = 7.2 Hz, 3 H), 1.37 (m, 12 H), 4.24 (m, 1 H), 4.98 (d, ^3J = 5.0 Hz, 1 H), 5.49 (ddq, ^3J = 6.5, 6.5 Hz, ^4J = 0.9 Hz, 1 H), 6.10 (dd, ^3J = 15.9 Hz, ^3J = 6.8 Hz, 1 H), 6.54 (d, ^3J = 15.9 Hz, 1 H), 7.18 (m, 1 H), 7.24 (m, 2 H), 7.30 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.7 (q), 20.4 (q), 28.3 (q), 49.4 (d), 72.1 (d), 79.8 (s), 126.6 (d), 128.0 (d), 128.2 (d), 128.6 (d), 132.0 (d), 136.2 (s), 155.1 (s), 172.6 (s).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{26}NO_4$ $[M + H]^+$: 320.1862; found: 320.1837.

Anal. Calcd for $C_{18}H_{25}NO_4$ (319.40): C, 67.69; H, 7.89; N, 4.39. Found: C, 67.82; H, 7.80; N, 4.39.

(*S*)-[(*S*,*E*)-1-Phenylpent-1-en-3-yl] 2-(*tert*-Butoxycarbonylamino)propanoate [(*S*)-2c]
From BocAlaOH (0.85 g, 4.50 mmol), allylic alcohol (*S*)-**1b** (0.73 g, 4.50 mmol), DMAP (0.11 g, 0.90 mmol) and DCC (1.11 g, 5.40 mmol) allylic ester (*S*)-**2c** (1.45 g, 4.34 mmol, 96%, >99% ee) was obtained as a waxy solid; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 97:3, flow 1 mL/min): t_R (*S*)-**2** = 40.20 min; $[\alpha]_D^{20}$ –73.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.4 Hz, 3 H), 1.37 (d, ^3J = 7.2 Hz, 3 H), 1.42 (s, 9 H), 1.75 (m, 2 H), 4.32 (m, 1 H), 5.03 (br s, 1 H), 5.35 (m, 1 H), 6.09 (dd, ^3J = 15.9 Hz, ^3J = 7.4 Hz, 1 H), 6.59 (d, ^3J = 15.9 Hz, 1 H), 7.23 (m, 1 H), 7.30 (m, 2 H), 7.35 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.5 (q), 18.7 (q), 27.6 (t), 28.3 (q), 49.4 (d), 77.1 (d), 79.7 (s), 126.6 (d), 126.9 (d), 128.0 (d), 128.6 (d), 133.0 (d), 136.3 (s), 155.1 (s), 172.7 (s).

HRMS (CI): *m*/*z* calcd for $C_{19}H_{27}NO_4$ $[M]^+$: 333.1940; found: 333.1934.

(*S*,*E*)-4-(4-Methoxyphenyl)but-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate [(*S*)-2d]

From BocGlyOH (182 mg, 1.04 mmol), allylic alcohol (*S*)-**1c** (185 mg, 1.04 mmol), DMAP (25.7 mg, 0.21 mmol), and DCC (258 mg, 1.25 mmol), the ester (*S*)-**2d** (340 mg, 1.01 mmol, 97%, >99% ee) was obtained as a colorless oil; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 97:3, flow 1 mL/min): t_R (*S*)-**2d** = 36.24 min; $[\alpha]_D^{20}$ –2.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, ^3J = 6.5 Hz, 3 H), 1.43 (s, 9 H), 3.79 (s, 3 H), 3.87 (dd, ^2J = 18.6 Hz, ^3J = 5.6 Hz, 1 H), 3.93 (dd, ^2J = 18.4 Hz, ^3J = 5.7 Hz, 1 H), 4.99 (br s, 1 H), 5.55 (dq, ^3J = 6.6, 6.6 Hz, 1 H), 6.01 (dd, ^3J = 15.9 Hz, ^3J = 7.1 Hz, 1 H), 6.54 (d, ^3J = 15.9 Hz, 1 H), 6.83 (m, 2 H), 7.29 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (q), 28.3 (q), 42.7 (t), 55.3 (q), 72.6 (d), 79.9 (s), 114.0 (d), 125.8 (d), 127.8 (d), 128.8 (s), 131.9 (d), 155.7 (s), 159.6 (s), 169.7 (s).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{25}NO_5$ $[M]^+$: 335.1733; found: 335.1711.

Anal. Calcd for $C_{18}H_{25}NO_5$ (335.40): C, 64.46; H, 7.51; N, 4.18. Found: C, 64.35; H, 7.49; N, 4.25.

(*S*,*E*)-4-(Naphthalen-2-yl)but-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate [(*S*)-2e]

From BocGlyOH (180 mg, 1.03 mmol), allylic alcohol (*S*)-**1d** (188 mg, 1.03 mmol), DMAP (25.7 mg, 0.21 mmol), and DCC (256 mg, 1.24 mmol), the ester (*S*)-**2e** (325 mg, 0.96 mmol, 93%, >99% ee) was obtained as a white solid; mp 82 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 90:10, flow 1 mL/min): t_R (*S*)-**2e** = 51.92 min; $[\alpha]_D^{20}$ –111.6 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 1.46 (d, ^3J = 6.5 Hz, 3 H), 3.90 (dd, ^2J = 18.5 Hz, ^3J = 5.5 Hz, 1 H), 3.96 (dd, ^2J = 18.5 Hz, ^3J = 5.8 Hz, 1 H), 5.01 (br s, 1 H), 5.63 (dq, ^3J = 6.5, 6.5 Hz, 1 H), 6.28 (dd, ^3J = 15.9 Hz, ^3J = 6.9 Hz, 1 H), 6.76 (d, ^3J = 15.9 Hz, 1 H), 7.44 (m, 2 H), 7.56 (dd, ^3J = 8.6 Hz, ^4J = 1.7 Hz, 1 H), 7.72 (br s, 1 H), 7.78 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (q), 28.3 (q), 42.7 (t), 72.4 (d), 79.9 (s), 123.4 (d), 126.1 (d), 126.3 (d), 126.9 (d), 127.6 (d), 128.0 (d), 128.2 (d), 128.4 (d), 132.2 (s), 133.2 (s), 133.5 (d, s), 155.7 (s), 169.7 (s).

HRMS (CI): *m*/*z* calcd for $C_{21}H_{25}NO_4$ $[M]^+$: 355.1784; found: 355.1767.

(*S*,*E*)-4-*p*-Tolylbut-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate [(*S*)-2f]

BocGlyOH (178 mg, 1.10 mmol), allylic alcohol (*S*)-**1e** (193 mg, 1.10 mmol), DMAP (26.9 mg, 0.22 mmol), and DCC (270 mg, 1.31 mmol) yielded (*S*)-**2f** (295 mg, 0.92 mmol, 94%, >99% ee) as a white solid; mp 67 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 90:10, flow 1 mL/min): t_R (*S*)-**2f** = 34.14 min; $[\alpha]_D^{20}$ –143.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, ^3J = 6.5 Hz, 3 H), 1.52 (s, 9 H), 2.40 (s, 3 H), 3.95 (dd, ^2J = 18.4 Hz, ^3J = 5.4 Hz, 1 H), 4.02 (dd, ^2J = 18.3 Hz, ^3J = 5.6 Hz, 1 H), 5.09 (br s, 1 H), 2.64 (dq, ^3J = ^3J = 6.5 Hz, 1 H), 6.18 (dd, ^3J = 15.9 Hz, ^3J = 7.0 Hz, 1 H), 6.65 (d, ^3J = 15.9 Hz, 1 H), 7.19 (m, 2 H), 7.34 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (q), 21.2 (q), 28.3 (q), 42.7 (t), 72.5 (d,), 79.9 (s), 126.5 (d), 127.0 (d), 129.3 (d), 132.1 (d), 133.3 (s), 137.9 (s), 155.6 (s), 169.6 (s).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{25}NO_4$ $[M]^+$: 319.1784; found: 319.1781.

(*S*)-[(*S*,*E*)-4-(4-Bromophenyl)but-3-en-2-yl] 2-(*tert*-Butoxycarbonylamino)propanoate [(*S*)-2g]

From BocAlaOH (369 mg, 1.95 mmol), allylic alcohol (*S*)-**1f** (443 mg, 1.95 mmol), DMAP (47.6 mg, 0.39 mmol), and DCC (483 mg, 2.34 mmol), the ester (*S*)-**2g** (750 mg, 1.95 mmol, 100%, >99% ee) was obtained as a white solid; mp 51 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 90:10, flow 1 mL/min): t_R (*S*)-**2g** = 16.03 min; $[\alpha]_D^{20}$ –76.7 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, ^3J = 7.2 Hz, 3 H), 1.41 (d, ^3J = 6.6 Hz, 3 H), 1.42 (s, 9 H), 4.29 (m, 1 H), 5.01 (d, ^3J = 5.4 Hz, 1 H), 5.51 (ddq, ^3J = 6.4, 6.4 Hz, ^4J = 0.6 Hz, 1 H), 6.13 (dd, ^3J = 15.9 Hz, ^3J = 6.7 Hz, 1 H), 6.52 (d, ^3J = 15.9 Hz, 1 H), 7.21 (m, 2 H), 7.41 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.6 (q), 20.3 (q), 28.3 (q), 49.4 (d), 71.9 (d), 79.8 (s), 121.8 (s), 128.1 (d), 129.0 (d), 130.7 (d), 131.7 (d), 135.1 (s), 155.1 (s), 172.6 (s).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{25}BrNO_4$ $[M + H]^+$: 398.0967; found: 398.0920.

Anal. Calcd for $C_{18}H_{24}BrNO_4$ (398.30): C, 54.28; H, 6.07; N, 3.52. Found: C, 54.62; H, 6.05; N, 3.77.

(*S*)-[(*S*,*E*)-1-(4-Bromophenyl)pent-1-en-3-yl] 2-(*tert*-Butoxycarbonylamino)propanoate [(*S*)-2h]

BocAlaOH (329 mg, 1.74 mmol), allylic alcohol (*S*)-**1g** (420 mg, 1.74 mmol), DMAP (42.6 mg, 0.35 mmol), and DCC (431 mg, 2.09 mmol) yielded (*S*)-**2h** (643 mg, 1.56 mmol, 90%, 99% ee) as a colorless solid; mp 62 °C; ee was determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 97:3, flow 1 mL/min): t_R (*R*)-**2h** = 20.15 min, t_R (*S*)-**2h** = 20.79 min; $[\alpha]_D^{20}$ –75.6 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.4 Hz, 3 H), 1.37 (d, ^3J = 7.2 Hz, 3 H), 1.42 (s, 9 H), 1.74 (m, 2 H), 4.31 (m, 1 H), 5.02 (d, ^3J = 4.9 Hz, 1 H), 5.33 (dt, ^3J = 6.6, 6.6 Hz, 1 H), 6.07 (dd, ^3J = 15.9 Hz, ^3J = 7.2 Hz, 1 H), 6.52 (d, ^3J = 15.9 Hz, 1 H), 7.21 (m, 2 H), 7.41 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.5 (q), 18.7 (q), 27.5 (t), 28.3 (q), 49.4 (d), 76.8 (d), 79.8 (s), 121.8 (s), 127.8 (d), 128.1 (d), 131.7 (2 d), 135.2 (d), 155.1 (s), 172.2 (s).

Anal. Calcd for $C_{19}H_{26}BrNO_4$ (412.32): C, 55.35; H, 6.36; N, 3.40. Found: C, 55.39; H, 6.21; N, 3.78.

Chelate Ester Enolate Claisen Rearrangement of Allylic Esters (*S*)-2a–h; General Procedure III

A stirred solution of the allylic ester (*S*)-**2** (1.0 equiv) and $ZnCl_2$ (1.2 equiv) in anhyd THF (5 mL/mmol) was cooled to –78 °C. A freshly prepared LDA solution (3.0 equiv) in anhyd THF (0.9 mL/mmol) was also cooled to –78 °C and added dropwise to the solution of the allylic ester via transfer cannula. The solution was allowed to warm overnight up to r.t.. The mixture was diluted with Et_2O (50 mL) and quenched with aq 1 M $KHSO_4$ (20 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried (Na_2SO_4). The solvent was removed in vacuo, the residue dissolved in anhyd DMF (5 mL/mmol), and K_2CO_3 (1.2 equiv) was added. The suspension was cooled to 0 °C and MeI (3.0 equiv) was added dropwise. The reaction mixture was stirred at r.t. for 5 h, diluted with EtOAc (30 mL), and washed with H_2O (3 × 15 mL). The organic layer was dried (Na_2SO_4), the solvent removed in vacuo,

and the crude product was purified by column chromatography (silica gel, hexanes–EtOAc).

(2*S*,3*S*,*E*)-Methyl 2-(*tert*-Butoxycarbonylamino)-3-phenylhex-4-enoate [(*S*,*S*)-3a]

According to general procedure III, allylic ester (*S*)-**2a** (400 mg, 1.31 mmol), $ZnCl_2$ (214 mg, 1.57 mmol), DIPA (398 mg, 3.93 mmol), *n*-BuLi (2.46 mL, 3.93 mmol, 1.6 M in hexanes), K_2CO_3 (218 mg, 1.57 mmol), and MeI (558 mg, 3.93 mmol) reacted to give (*S*,*S*)-**3a** (349 mg, 1.10 mmol, 84%, >99% ds, >99% ee); white solid; mp 67–68 °C; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*S*,*S*)-**3a** = 8.49 min; $[\alpha]_D^{20}$ +64.7 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 1.66 (dd, ^3J = 6.2 Hz, ^4J = 1.2 Hz, 3 H), 3.63 (s, 3 H), 3.66 (m, 1 H), 4.57 (m, 1 H), 4.79 (d, ^3J = 8.0 Hz, 1 H), 5.57 (dq, ^3J = 15.0 Hz, ^3J = 6.3 Hz, 1 H), 5.68 (ddq, ^3J = 15.2 Hz, ^3J = 8.6 Hz, ^4J = 1.5 Hz, 1 H), 7.16 (m, 2 H), 7.21 (m, 1 H), 7.29 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.0 (q), 28.2 (q), 51.6 (d), 51.8 (q), 57.9 (d), 79.9 (s), 127.1 (d), 128.0 (d), 128.5 (d), 128.6 (d), 129.0 (d), 139.7 (s), 155.2 (s), 172.2 (s).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{26}NO_4$ $[M + H]^+$: 320.1862; found: 320.1845.

Anal. Calcd for $C_{18}H_{25}NO_4$ (319.40): C, 67.69; H, 7.89; N, 4.39. Found: C, 68.08; H, 7.78; N, 4.00.

(2*S*,3*S*,*E*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-methyl-3-phenylhex-4-enoate [(*S*,*S*)-3b]

According to general procedure III, allylic ester (*S*)-**2b** (1.42 g, 4.45 mmol), $ZnCl_2$ (0.73 g, 5.34 mmol), DIPA (1.36 g, 13.4 mmol), *n*-BuLi (8.38 mL, 13.4 mmol, 1.6 M in hexanes), K_2CO_3 (0.74 g, 5.34 mmol), and MeI (1.90 g, 13.4 mmol) reacted to give (*S*,*S*)-**3b** (1.29 g, 3.88 mmol, 87%, >99% ds, >99% ee); white solid; mp 104–105 °C; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*S*,*S*)-**3b** = 4.86 min; $[\alpha]_D^{20}$ +15.6 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 1.47 (s, 3 H), 1.63 (dd, ^3J = 6.5 Hz, ^4J = 1.0 Hz, 3 H), 3.55 (m, 1 H), 3.58 (s, 3 H), 4.94 (br s, 1 H), 5.50 (m, 1 H), 5.79 (m, 1 H), 7.10 (m, 2 H,), 7.19 (m, 1 H), 7.25 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (q), 20.2 (q), 28.3 (q), 52.0 (q), 56.8 (s), 62.5 (d), 79.7 (s), 127.4 (d), 128.0 (d), 128.5 (d), 129.0 (d), 129.9 (d), 139.1 (s), 154.6 (s), 173.5 (s).

HRMS (CI): *m*/*z* calcd for $C_{19}H_{28}NO_4$ $[M + H]^+$: 334.2018; found: 334.2041.

Anal. Calcd for $C_{19}H_{27}NO_4$ (333.43): C, 68.44; H, 8.16; N, 4.20. Found: C, 68.38; H, 8.00; N, 3.89.

(2*S*,3*S*,*E*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-methyl-3-phenylhept-4-enoate [(*S*,*S*)-3c]

According to general procedure III, allylic ester (*S*)-**2c** (500 mg, 1.50 mmol), $ZnCl_2$ (245 mg, 1.80 mmol), DIPA (455 mg, 4.50 mmol), *n*-BuLi (2.81 mL, 3.93 mmol, 1.6 M in hexanes), K_2CO_3 (249 mg, 1.80 mmol), and MeI (639 mg, 4.50 mmol) reacted to give (*S*,*S*)-**3c** (457 mg, 1.32 mmol, 88%, >99% ds, >99% ee white solid; mp 51 °C; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*S*,*S*)-**3c** = 5.24 min; $[\alpha]_D^{20}$ +12.1 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.4 Hz, 3 H), 1.33 (s, 9 H), 1.47 (s, 3 H), 1.98 (m, 2 H), 3.54 (m, 1 H), 3.58 (s, 3 H), 4.94 (br s, 1 H), 5.52 (dt, ^3J = 15.0 Hz, ^3J = 6.4 Hz, 1 H), 5.76 (m, 1 H), 7.11 (m, 2 H), 7.19 (m, 1 H), 7.26 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6 (q), 20.1 (q), 25.6 (t), 28.3 (q), 51.9 (q), 56.6 (s), 62.5 (d), 79.7 (s), 125.8 (d), 127.4 (d), 128.5 (d), 129.0 (d), 136.9 (d), 139.1 (s), 154.6 (s), 173.4 (s).

HRMS (CI): *m*/*z* calcd for $C_{20}H_{29}NO_4$ $[M]^+$: 347.2097; found: 347.2091.

Anal. Calcd for $C_{20}H_{29}NO_4$ (347.45): C, 69.14; H, 8.41; N, 4.03. Found: C, 68.79; H, 8.23; N, 3.98.

(2*S*,3*S*,*E*)-Methyl 2-(*tert*-Butoxycarbonylamino)-3-(4-methoxyphenyl)hex-4-enoate [(*S*,*S*)-3d]

According to general procedure III, allylic ester (*S*)-**2d** (250 mg, 0.75 mmol), $ZnCl_2$ (121 mg, 0.89 mmol), DIPA (226 mg, 2.24 mmol), *n*-BuLi (1.40 mL, 2.24 mmol, 1.6 M in hexanes), K_2CO_3 (122 mg, 0.89 mmol), and MeI (318 mg, 2.24 mmol) reacted to give (*S*,*S*)-**3d** (181 mg, 0.52 mmol, 69%, 97% ds, >99% ee); white solid; mp 54 °C; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*S*,*R*)-**3d** = 12.96 min, t_R (*S*,*S*)-**3d** = 16.50 min; $[\alpha]_D^{20}$ +79.8 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 1.66 (m, 3 H), 3.62 (m, 4 H), 3.76 (s, 3 H), 4.51 (m, 1 H), 4.78 (d, ^3J = 8.5 Hz, 1 H), 5.55 (dq, ^3J = 15.2 Hz, ^3J = 6.1 Hz, 1 H), 5.65 (ddq, ^3J = 15.2 Hz, ^3J = 8.4 Hz, ^4J = 1.3 Hz, 1 H), 6.83 (m, 2 H), 7.07 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (q), 28.2 (q), 50.6 (d), 51.8 (q), 55.2 (q), 58.0 (d), 79.9 (s), 114.1 (d), 128.2 (d), 128.9 (d), 129.3 (d), 131.6 (s), 155.2 (s), 158.6 (s), 172.3 (s).

HRMS (CI): *m*/*z* calcd for $C_{19}H_{28}NO_5$ $[M + H]^+$: 350.1967; found: 350.1977.

Anal. Calcd for $C_{19}H_{27}NO_5$ (349.43): C, 65.31; H, 7.79; N, 4.01. Found: C, 65.28; H, 7.72; N, 3.67.

(2*S*,3*S*,*E*)-Methyl 2-(*tert*-Butoxycarbonylamino)-3-(naphthalen-2-yl)hex-4-enoate [(*S*,*S*)-3e]

According to general procedure III, allylic ester (*S*)-**2e** (250 mg, 0.74 mmol), $ZnCl_2$ (120 mg, 0.88 mmol), DIPA (224 mg, 2.21 mmol), n-BuLi (1.38 mL, 2.21 mmol, 1.6 M in hexanes), K_2CO_3 (122 mg, 0.88 mmol), and MeI (314 mg, 2.21 mmol) reacted to give (*S*,*S*)-**3e** (206 mg, 0.58 mmol, 79%, 99% ds, >99% ee); white solid; mp 93 °C; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 μm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*S*,*R*)-**3e** = 18.21 min; t_R (*S*,*S*)-**3e** = 23.37 min; $[\alpha]_D^{20}$ +113.4 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9 H), 1.69 (d, ^3J = 6.3 Hz, 3 H), 3.64 (s, 3 H), 3.83 (m, 1 H), 4.66 (m, 1 H), 4.84 (d, ^3J = 8.2 Hz, 1 H), 5.63 (m, 1 H), 5.77 (dd, ^3J = 15.2 Hz, ^3J = 8.6 Hz, 1 H), 7.32 (d, ^3J = 8.4 Hz, 1 H), 7.45 (m, 2 H), 7.62 (br s, 1 H), 7.79 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (q), 28.1 (q), 51.7 (d), 51.9 (q), 57.8 (d), 80.0 (s), 125.8 (d), 125.9 (d), 126.2 (d), 126.8 (d), 127.6, 127.7 (3 d), 128.4 (d), 128.9 (d), 132.6 (s), 133.4 (s), 137.1 (s), 155.2 (s), 172.3 (s).

HRMS (CI): *m*/*z* calcd for $C_{22}H_{28}NO_4$ $[M + H]^+$: 370.2018; found: 370.1998.

Anal. Calcd for $C_{22}H_{27}NO_4$ (369.46): C, 71.52; H, 7.37; N, 3.79. Found: C, 71.19; H, 7.41; N, 3.44.

(2*S*,3*S*,*E*)-Methyl 2-(*tert*-Butoxycarbonylamino)-3-*p*-tolylhex-4-enoate [(*S*,*S*)-3f]

According to general procedure III, allylic ester (*S*)-**2f** (250 mg, 0.78 mmol), $ZnCl_2$ (128 mg, 0.94 mmol), DIPA (238 mg, 2.35 mmol), *n*-BuLi (1.47 mL, 2.35 mmol, 1.6 M in hexanes), K_2CO_3 (130 mg, 0.94 mmol), and MeI (334 mg, 2.35 mmol) reacted to give (*S*,*S*)-**3f** (219 mg, 0.66 mmol, 84%, >99% ds, 98% ee); colorless oil;

diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*R*,*R*)-**3f** = 7.63 min; t_R (*S*,*S*)-**3f** = 8.69 min; $[\alpha]_D^{20}$ +57.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 1.65 (d, ^3J = 6.2 Hz, 3 H), 2.29 (s, 3 H), 3.63 (m, 4 H), 4.53 (m, 1 H), 4.78 (d, ^3J = 8.4 Hz, 1 H), 5.56 (dq, ^3J = 15.1 Hz, ^3J = 6.1 Hz, 1 H), 5.66 (ddq, ^3J = 15.1 Hz, ^3J = 8.5 Hz, ^4J = 1.3 Hz, 1 H), 7.04 (m, 2 H), 7.10 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (q), 21.0 (q), 28.2 (q), 51.0 (d), 51.8 (q), 57.9 (d), 79.9 (s), 127.8 (d), 128.2 (d), 129.2 (d), 129.4 (d), 136.5 (s), 136.7 (s), 155.2 (s), 172.3 (s).

HRMS (CI): *m*/*z* calcd for $C_{19}H_{28}NO_4$ $[M + H]^+$: 334.2018; found: 334.2013.

Anal. Calcd for $C_{19}H_{27}NO_4$ (333.43): C, 68.44; H, 8.16; N, 4.20. Found: C, 68.23; H, 8.42; N, 4.30.

(2*S*,3*S*,*E*)-Methyl 3-(4-Bromophenyl)-2-(*tert*-butoxycarbonylamino)-2-methylhex-4-enoate [(*S*,*S*)-3g]

According to general procedure III, allylic ester (*S*)-**2g** (350 mg, 0.91 mmol), $ZnCl_2$ (149 mg, 1.09 mmol), DIPA (276 mg, 2.73 mmol), *n*-BuLi (1.71 mL, 2.73 mmol, 1.6 M in hexanes), K_2CO_3 (151 mg, 1.09 mmol), and MeI (387 mg, 2.73 mmol) reacted to give (*S*,*S*)-**3g** (301 mg, 0.73 mmol; 83%, 98% ds, >99% ee) as a colorless oil; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*S*,*R*)-**3g** = 4.27 min; t_R (*S*,*S*)-**3g** = 5.52 min; $[\alpha]_D^{20}$ +38.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 1.51 (s, 3 H), 1.68 (dd, ^3J = 6.5 Hz, ^4J = 1.5 Hz, 3 H), 3.62 (m, 4 H), 4.99 (br s, 1 H), 5.55 (dq, ^3J = 15.0 Hz, ^3J = 6.4 Hz, 1 H), 5.79 (m, 1 H), 7.01 (m, 2 H), 7.42 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (q), 20.5 (q), 28.3 (q), 52.1 (q), 56.0 (q), 62.3 (d), 79.9 (s), 121.3 (s), 127.5 (d), 130.4 (d), 130.6 (d), 131.6 (d), 138.4 (s), 154.5 (s), 173.3 (s).

HRMS (CI): *m*/*z* calcd for $C_{19}H_{27}BrNO_4$ $[M + H]^+$: 412.1123; found: 412.1123.

Anal. Calcd for $C_{19}H_{26}BrNO_4$ (412.32): C, 55.35; H, 6.36; N, 3.40. Found: C, 55.67; H, 6.33; N, 3.38.

(2*S*,3*S*,*E*)-Methyl 3-(4-Bromophenyl)-2-(*tert*-butoxycarbonylamino)-2-methylhept-4-enoate [(*S*,*S*)-3h]

According to general procedure III, allylic ester (*S*)-**2h** (350 mg, 0.85 mmol), $ZnCl_2$ (139 mg, 1.02 mmol), DIPA (258 mg, 2.55 mmol), *n*-BuLi (1.59 mL, 2.55 mmol, 1.6 M in hexanes), K_2CO_3 (143 mg, 1.02 mmol), and MeI (362 mg, 2.55 mmol) reacted to give (*S*,*S*)-**3h** (323 mg, 0.76 mmol, 89%, >99% ds, 97% ee); colorless oil; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 99:1, flow 2 mL/min): t_R (*R*,*R*)-**3h** = 4.17 min; t_R (*S*,*S*)-**3h** = 4.91 min; $[\alpha]_D^{20}$ +39.2 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.5 Hz, 3 H), 1.39 (s, 9 H), 1.51 (s, 3 H), 2.03 (m, 2 H), 3.60 (m, 1 H), 3.63 (s, 3 H), 4.98 (br s, 1 H), 5.57 (dt, ^3J = 15.1 Hz, ^4J = 6.4 Hz, 1 H), 5.75 (ddt, ^3J = 14.9 Hz, ^3J = 9.6 Hz, ^4J = 1.2 Hz, 1 H), 7.02 (m, 2 H), 7.42 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (q), 20.4 (q), 25.6 (t), 28.3 (q), 52.0 (q), 55.9 (q), 62.4 (d), 79.9 (s), 121.3 (s), 125.4 (d), 130.7 (d), 131.6 (d), 137.4 (d), 138.4 (s), 154.5 (s), 173.3 (s).

HRMS (CI): *m*/*z* calcd for $C_{20}H_{29}BrNO_4$ $[M + H]^+$: 426.1280; found: 426.1253.

Anal. Calcd for $C_{20}H_{28}BrNO_4$ (426.35): C, 56.34; H, 6.62; N, 3.29. Found: C, 56.42; H, 6.44; N, 3.29.

(2*S*,3*S*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-methyl-4-oxo-3-phenylbutanoate [(*S*,*S*)-4]

Amino acid derivative (*S*,*S*)-**3b** (250 mg, 0.75 mmol) was dissolved in anhyd CH_2Cl_2 (20 mL) and cooled to –78 °C. Ozone was bubbled through the solution until a blue color remained and excess of ozone was removed by bubbling N_2 through the solution. Then PPh_3 (216 mg, 0.82 mmol) was added and the mixture was allowed to warm overnight up to r.t. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, hexanes–EtOAc, 8:2) to yield aldehyde (*S*,*S*)-**4** (222 mg, 0.67 mmol, 89%, >99% ds, >99% ee) as a white solid; mp 102 °C; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 97:3, flow 1 mL/min): t_R (*S*,*S*)-**4** = 14.84 min; $[\alpha]_D^{20}$ –67.6 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 1.56 (s, 3 H), 3.73 (s, 3 H), 4.54 (br s, 1 H), 5.02 (br s, 1 H), 7.18 (m, 2 H), 7.32 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (q), 28.2 (q), 52.8 (q), 60.9, 61.4 (s, d), 80.2 (s), 128.1 (d), 128.5 (d), 130.8 (d), 132.3 (s), 154.2 (s), 173.3 (s), 198.4 (d).

HRMS (CI): *m*/*z* calcd for $C_{17}H_{23}NO_5$ $[M]^+$: 321.1576; found: 321.1582.

***tert*-Butyl (3*S*,4*S*)-3-Methyl-2-oxo-4-phenyltetrahydrofuran-3-ylcarbamate [(*S*,*S*)-5]**

Aldehyde (*S*,*S*)-**4** (150 mg, 0.47 mmol) was dissolved in trifluoroethanol (5 mL) and after cooling to 0 °C, $NaBH_4$ (17.7 mg, 0.47 mmol) was added. The cooling bath was removed and the mixture allowed to stir at r.t. for 1 h. The solution was diluted with Et_2O (30 mL), quenched with aq 1 M $KHSO_4$ (10 mL), and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc, 7:3) to yield lactone (*S*,*S*)-**5** (119 mg, 0.41 mmol, 87%, >99% ds, >99% ee) as a white solid; mp 145 °C; diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–i-PrOH, 97:3, flow 1 mL/min): t_R (*S*,*S*)-**5** = 23.38 min; $[\alpha]_D^{20}$ –60.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 3 H), 1.48 (s, 9 H), 4.49 (dd, ^3J = 10.7 Hz, ^3J = 7.9 Hz, 1 H), 4.61 (m, 2 H), 4.74 (br s, 1 H), 7.16 (m, 2 H), 7.34 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 (q), 28.3 (q), 45.7 (d), 59.3 (s), 67.0 (t), 80.9 (s), 127.9 (d), 128.1 (d), 128.8 (d), 134.2 (s), 176.3 (s); the signals for Boc(C=O) are missing because of low intensity.

HRMS (CI): *m*/*z* calcd for $C_{16}H_{21}NO_4$ $[M]^+$: 291.1471; found: 291.1458.

Anal. Calcd for $C_{16}H_{21}NO_4$ (291.35): C, 65.96; H, 7.27; N, 4.81. Found: C, 65.69; H, 7.16; N, 4.91.

***tert*-Butyl (3*S*,4*S*,5*R*)-5-[(*S*)-1-Iodoethyl]-3-methyl-2-oxo-4-phenyltetrahydrofuran-3-ylcarbamate [(*S*,*S*,*R*,*S*)-6]**

Amino acid derivative (*S*,*S*)-**3b** (147 mg, 0.44 mmol) was dissolved in 1,4-dioxane (2.5 mL) and aq 1 M NaOH (0.53 mL) was added. After stirring overnight, the mixture was heated up to 40 °C to complete the saponification. The solution was concentrated in vacuo and the residue dissolved in H_2O (20 mL). After washing with Et_2O (3 × 10 mL), the aqueous layer was acidified with aq 1 M $KHSO_4$ to pH 2 and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo. The residue was dissolved in THF (5 mL), Et_3N (67 µL, 0.48 mmol) was added and the solution cooled to 0 °C. After the addition of I_2 (135 mg, 0.53 mmol), the cooling bath was removed and the solution was allowed to stir at r.t. overnight. The mixture was diluted with Et_2O (15 mL) and washed several times with a 5% $Na_2S_2O_3$ solution to remove the excess of I_2. The ethereal layer was dried

(Na_2SO_4) and the solvent evaporated in vacuo. After column chromatography (silica gel, hexanes–EtOAc, 7:3), the iodolactone (*S*,*S*,*R*,*S*)-**6** (145 mg, 0.33 mmol, 74%, 88% ds, >99% ee) was obtained as a white solid; mp 162–164 °C (dec.); diastereo- and enantioselectivities were determined by HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes–*i*-PrOH, 97:3, flow 1 mL/min): t_R (*S*,*S*,*R*,*S*)-**6** = 7.66 min, t_R (*S*,*S*,*S*,*R*)-**6** = 16.41 min; $[\alpha]_D^{20}$ –49.2 (*c* = 1.0, $CHCl_3$).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{25}I\,NO_4$ $[M + H]^+$: 446.0828; found: 446.0736.

Anal. Calcd for $C_{18}H_{24}INO_4$ (445.30): C, 48.55; H, 5.43; N, 3.15. Found: C, 48.70; H, 5.37; N, 3.29.

Major Diastereomer (*S*,*S*,*R*,*S*)-6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3 H), 1.48 (s, 9 H), 2.06 (d, ^3J = 6.7 Hz, 1 H), 3.74 (m, 1 H), 4.26 (d, $^3J_{10,7}$ = 4.3 Hz, 1 H), 4.72 (br s, 1 H), 5.09 (dd, ^3J = 11.4 Hz, ^3J = 4.7 Hz, 1 H), 7.16 (m, 2 H), 7.30 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (q), 22.7 (d), 25.5 (q), 28.3 (q), 56.6 (d), 63.5 (q), 85.5 (d), 128.1 (d), 128.7 (d), 128.8 (s), 129.9 (d), 154.3 (s); the signals for Boc [$C(CH_3)_3$] and lactone (C=O) are missing because of low intensity.

Minor Diastereomer (*S*,*S*,*S*,*R*)-6

^{1}H NMR (400 MHz, $CDCl_3$): δ (selected signals) = 1.00 (s, 3 H), 1.55 (s, 9 H), 1.99 (d, ^3J = 6.9 Hz, 1 H), 4.18 (d, ^3J = 10.4 Hz, 1 H), 4.68 (br s, 1 H), 4.94 (dd, ^3J = 10.3 Hz, ^3J = 5.3 Hz, 1 H), 7.36 (m, 3 H).

^{13}C NMR: Signals of the minor diastereomer could not be detected.

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