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Synthesis of Tubuphenylalanines via Ireland–Claisen Rearrangement

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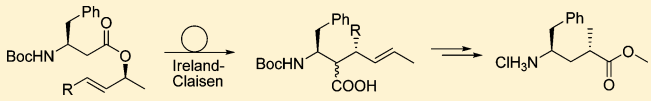
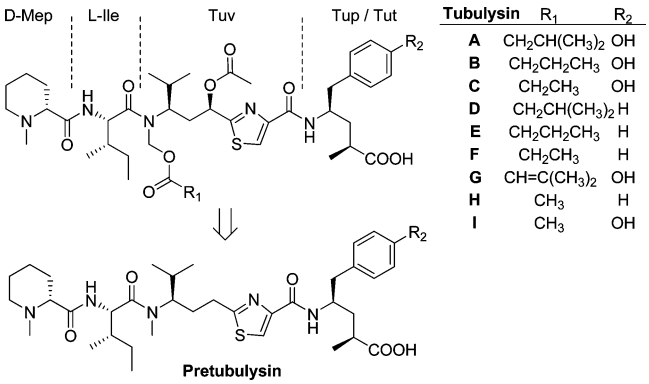
Supporting Information

ABSTRACT: The Ireland–Claisen rearrangement is the central step in the synthesis of tubuphenylalanine, a key building block of the highly antitumor-active tubulysins. The rearrangement of substituted β-amino acid allyl esters, in combination with subsequent decarboxylation and oxidative cleavage of the double bond, allows the highly stereoselective introduction of substituents into the α-position of the resulting γ-amino acids.



INTRODUCTION

In 2000, Höfle and Reichenbach reported the isolation of a new group of peptide secondary metabolites from myxobacteria called tubulysins.[1] From the bacteria *Angiococcus disciformis* An d48 and *Archangium gephyra* nine different tubulysins (**A**–**I**) were isolated (Figure 1), which show powerful inhibition of



Tubulysin	R_1	R_2
A	$CH_2CH(CH_3)_2$	OH
B	$CH_2CH_2CH_3$	OH
C	CH_2CH_3	OH
D	$CH_2CH(CH_3)_2$	H
E	$CH_2CH_2CH_3$	H
F	CH_2CH_3	H
G	$CH{=}C(CH_3)_2$	OH
H	CH_3	H
I	CH_3	OH

Figure 1. Tubulysins and pretubulysin.

tubulin polymerization,[2] leading to apoptosis.[3,4] The mode of action differs from that of other tubulin binders such as paclitaxel or the epothilones, and the bioactivity is significantly higher, with IC_{50} values in the low nanomolar or even picomolar range toward various cancer cell lines.[2]

Compared to other tubulin binders, the structure is relatively simple, consisting of *N*-methylpipecolic acid (Mep), isoleucine (Ile), the unusual amino acid tubuvaline (Tuv), and a chain-extended analogue of phenylalanine or tyrosine, called tubuphenylalanine (Tup) or tubutyrosine (Tut). All tubulysins contain an acetoxy group in the tubuvaline unit and differ in the substitution pattern of the *N*,*O*-acetal, the unique structural motive of these peptides. Recently, 23 "new tubulysins" have been discovered from *Angiococcus disciformis* An d48 and *Cystobacter* SBCb004, missing (in part) these tubuvaline substituents.[5] Probably, these new structures are biosynthetic intermediates, and one of them, pretubulysin D (Figure 1) also shows biological activity in the subnanomolar range toward various tumor cell lines.[6] Its activity is only slightly lower compared to the more complex tubulysins,[7] and it also shows a strong antiangiogenic effect.[8]

In the meantime, a few syntheses of tubulysins themselves,[9−11] as well as to their derivates are described in the literature.[12−17] SAR-studies clearly indicate, that the *N*,*O*-acetal is not necessary for the high biological activity,[9,18,19] but at least a *N*-methyl group should be present for good activity.[14,19] The *N*-terminus is rather conserved, while the *C*-terminal Tup allows a range of modifications.[19] Therefore, this subunit seems to be the ideal position not only to generate new derivatives but also to introduce labels (photo affinity, fluorescence, etc.) for biological studies.[20]

For this purpose a highly flexible stereoselective synthesis is desirable, allowing not only modifications at the phenyl ring, but also at the methyl substituent. During the syntheses of the tubulysins and their derivatives, a few synthetic routes toward tubuphenylalanine have been developed. While the stereogenic center at the γ-position can easily be obtained from phenylalanine, the stereoselective introduction of the α-methyl group is synthetically the greater challenge. Some approaches are based on more or less stereoselective hydrogenations of unsaturated precursors, and subsequent separation of the diastereomers.[6,11,21,22] Menthol was found to be a suitable auxiliary for the separation of α-epimeric tubuphenylalanine derivatives.[6,22,23] Alternatively, the α-methyl group can also be introduced by ring-opening of chiral aziridines with deprotected SAMP-hydrazones[12] or by more or less diastereoselective methylation of a phenylalanine-derived lactame.[24] Two other approaches generate the stereogenic center at the γ-position via stereoselective addition, either toward an Evans auxiliary based chiral hydrazine[25] or a phenylacetaldimine generated from chiral (*R*)-*tert*-butanesulfinamide.[9] Another new synthesis describes the synthesis of tubuphenylalanine starting from (−)-citronellol, which allows the synthesis of tubuphenylalanine on a gram scale but in a rather long reaction sequence.[26]

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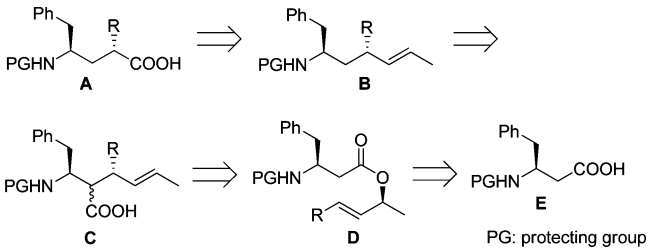
RESULTS AND DISCUSSION

Although a range of different approaches has been developed, each protocol has some drawbacks, either concerning yield or stereo- or chemoselectivity. Therefore, we decided to develop an independent approach that would allow us to also vary the α-position, taking advantage of the Claisen rearrangement. Based on the pioneering work by Robert Ireland in Claisen rearrangements,[27−30] we developed a version, especially suitable for α-amino acids, proceeding via chelated amino acid ester enolates.[31−34] Because of the fixed enolate geometry in the chelate complex, the rearrangement proceeds with excellent diastereoselectivity and chirality transfer, as far as chiral allylic esters are applied.[35,36] This approach was used for the synthesis of highly functionalized amino acids[37,38] but was limited to α-amino acids. Our retrosynthetic plan toward tubuphenylalanine and α-derivatives thereof is shown in Scheme 1.

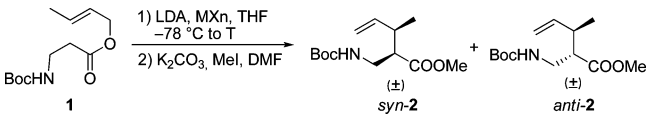
Scheme 1



The carboxylic acid **A** should be accessible via oxidative cleavage of alkene **B**, which can be obtained from **C** by radical decarboxylation. β-Amino acid **C** should be the product of a Claisen rearrangement of allylic ester **D**, easily available from β-amino acid **E**.

Based on our good results obtained with chelated ester enolates, we tried to transfer this protocol to β-amino acid esters. As a model reaction, we decided to investigate the Claisen rearrangement of the crotyl ester of Boc-protected β-alanine **1** (Table 1).[39] According to Ireland, the simple

Table 1. Claisen Rearrangements of β-Alanine Crotyl Ester



entry	MX_n	T (°C)	yield (%)	ratio *syn:anti*
1		rt		
2	$ZnCl_2$	rt	35	96:4
3	$ClTi(Oi\text{-}Pr)_3$	rt	24	98:2
4	$ClSiMe_3$	60	86	86:14

diastereoselectivity observed should provide important informations on the enolate geometry. If a chelate complex is formed, an excellent diastereoselectivity should be observed, as usually found for α-amino acids.

The Claisen rearrangement was investigated in the presence of several metal salts. For analytical purposes, the rearrangement product was directly converted into the known methyl ester **2**.[39]

As expected, no rearrangement product was obtained in the absence of a chelating metal salt (Table 1, entry 1). The lithium salt was found to be unstable and the ester enolate decomposed completely during warm up. Quite different was the situation if $ZnCl_2$ was added for chelation (Table 1, entry 2). In a clean reaction, the rearrangement product was obtained with very high diastereoselectivity but very moderate yield. No decomposition was observed here, and starting material could be recovered. A similar situation was observed with the titanium enolate (Table 1, entry 3). Here the selectivity could even be increased, but the reaction was incomplete. Obviously, the chelates of the β-amino acid esters are less reactive compared to the α-amino analogous, which generally undergo Claisen rearrangement in the range of −20 °C to rt. While ester enolates of α-amino acids can be heated overnight without decomposition (an additional positive effect of chelate formation), this behavior is not observed with β-amino acid esters, indicating that these chelate complexes are less stable. Therefore, we decided to apply the Ireland−Claisen rearrangement to our system. Indeed, after heating the silylketene acetals formed to 60 °C for 2 h, the desired rearrangement product was obtained in very high yield, albeit with significant lower selectivity, which is in perfect agreement with the results described by Knight et al.[39] For our purpose, the simple diastereoselectivity of the rearrangement process does not play a major role, since the carboxylic acid functionality is removed in the next reaction step according to Scheme 1. Only the chirality transfer from a chiral allyl alcohol should work perfectly.

To prove this option, we synthesized chiral allylic esters of *N*-protected prolonged phenylalanine, easily obtained via Arndt−Eistert homologation.[40] One of the easiest ways to obtain the requested chiral alcohols is given with the enzymatic kinetic resolution of racemic alcohols, using Novozym 435, an immobilized *Candida antarctica* lipase. According to Kazlauskas,[41] in racemic allylic alcohols of type **1** the (*R*)-configured enantiomer is selectively acylated, while the (*S*)-isomers remain untouched. In general, the ee's of both products are excellent, and it is no problem to separate them, e.g., by flash chromatography. The only critical point of rather small alcohols such as **3a** is their high volatility (bp 120 °C), and therefore, the isolated yield of the enantiomerically pure alcohol (*S*)-**3a** and the acetate (*R*)-**4a** (similar boiling point) can be low. Therefore, we decided to abstain from workup and to subject the reaction mixture of the kinetic resolution directly to the esterification with prolonged Boc-protected phenylalanine. To get a high diastereoselectivity in the allylic ester, we allowed the reaction mixture to proceed slightly >50% conversion, and indeed, the requested allyl ester **5a** was obtained in acceptable yield and a high diastereomeric ratio (Table 2). To get access to α-modified tubuphenylalanines, we also subjected the racemic alcohols **3b** and **3c** to the same protocol, getting comparable results.

The allylic esters **5** obtained were subsequently subjected to the Ireland−Claisen rearrangement, giving rise to the rearrangement products **6** in consistently excellent yield. As in our control experiment, the diastereoselectivities were also modest in these cases, but as already mentioned, the configuration of the carboxyl group is irrelevant because it is removed in the next step. The carboxylic acids where subjected to a Barton decarboxylation.[42] It should be mentioned that the esterification[43] with 2-mercaptopyridine *N*-oxide should be carried out in the absence of light to avoid decomposition of the rather labile ester. The crude product was subjected to a BEt_3-initiatized radical reaction in the dark using *t*-BuSH as a

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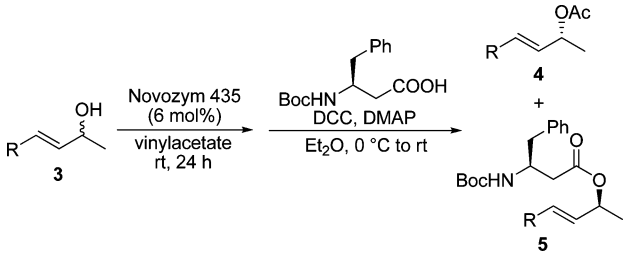
Table 2. Syntheses of Chiral Allyl Esters



entry	3	R	5	yield (%)	dr
1	**3a**	Me	**5a**	38	>97:3
2	**3b**	Et	**5b**	39	>98:2
3	**3c**	$TBDMSOCH_2$	**5c**	35	>99:1

hydrogen source.[44] In all examples, good to very high yields were obtained, indicating the reliability of this protocol.

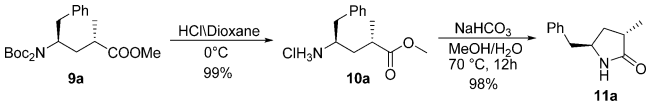
In the next step, the double bond of **7** had to be subjected to an oxidative cleavage to get access to the carboxylic acid. To avoid γ-lactam ring formation, we first converted the Boc-protected amide into a double protected amide **8**. Subsequent ozonolysis using a protocol developed by Marshall[45] provided the protected desired tubuphenylalanine derivatives **9** in good yields and almost perfect diastereoselectivity (Table 3).

For analytical purposes and to determine the absolute configuration of the new introduced α-substituent, we subjected **9a** to a *N*-deprotection giving rise to the hydrochloride of the tubuphenylalanine methyl ester **10a** which was described previously in the literature (Scheme 2).[22] Our analytical data were in accordance to the data reported. In addition, deprotonation of **10a** resulted in the formation of the corresponding lactam **11a**, which is also a known compound.[15]

CONCLUSION

In conclusion, we have developed a straightforward protocol toward tubuphenylalanine and derivatives thereof, based on an Ireland–Claisen rearrangement. All reaction steps proceed with high yield, and the desired products can be obtained with high optical purity. This protocol should be general applicable to various kinds of substituted tubuphenylalanine derivatives and should also give access to the other stereoisomers by starting from the enantiomeric allylic alcohols.

Scheme 2

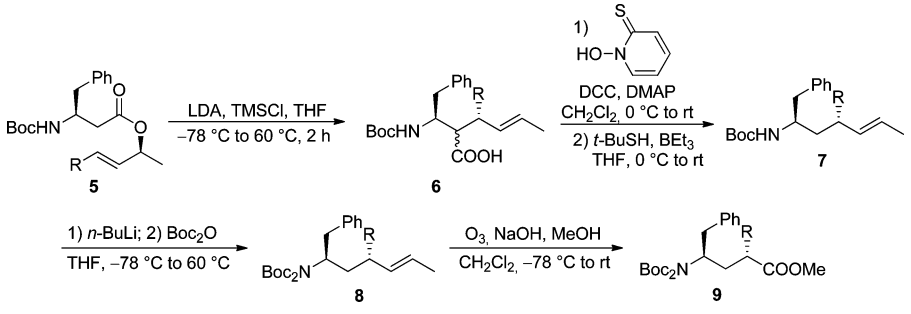


EXPERIMENTAL SECTION

General Remarks. Reactions with dry solvents were carried out in oven-dried glassware (100 °C) under nitrogen. Solvents were dried as follows: THF was distilled from $LiAlH_4$, CH_2Cl_2 from CaH_2, MeOH from Mg, and toluene from Na. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of EtOAc and hexanes were generally used as eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates. Visualization was accomplished with UV light, $KMnO_4$ solution, or ninhydrine. ^1H NMR and ^{13}C NMR spectra were obtained at room temperature at 400 and 100 MHz, respectively. Chemical shifts are expressed in ppm relative to internal solvent. Selected signals of minor isomers are extracted from the NMR spectra of the isomeric mixtures. The enantiomeric and diastereomeric ratios were determined by HPLC using a chiral column (Reprosil 100 Chiral-NR 8 μm). Melting points are uncorrected. High-resolution mass were recorded on a quadrupole mass spectrometer.

(*S*,*E*)-Pent-3-en-2-yl (*S*)-3-(*tert*-butoxycarbonylamino)-4-phenylbutanoate (5a). A mixture of racemic alcohol **3a** (1.68 g, 19.5 mmol) in vinyl acetate (9 mL, 97.5 mmol) was shaken in the presence of Novozym 435 (100 mg, 6 wt %) for 24 h at room temperature. The enzyme was filtered off, and the resulting solution was diluted with 70 mL of dry diethyl ether. (*S*)-3-(*tert*-Butoxycarbonylamino)-4-phenylbutanoic acid (3.00 g 10.7 mmol), DMAP (130 mg, 1.00 mmol), and DCC (2.43 g, 11.8 mmol) in dry diethyl ether (30 mL) were added at 0 °C, and the mixture was allowed to warm to room temperature overnight. The precipitate was filtered off, and the organic layer was washed twice with 1 M $KHSO_4$, H_2O, satd $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (hexanes/ethyl acetate 9:1) provided allylic ester **5a** (258 mg, 0.741 mmol, 38%, 97% ds) as a colorless oil. R_f = 0.21 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D$ = −24.9 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.5 Hz, 3 H), 1.40 (s, 9 H), 1.71 (ddd, *J* = 6.5, 1.7, 0.7 Hz, 3 H), 2.39 (dd, *J* = 15.8, 6.0 Hz, 1 H), 2.48 (dd, *J* = 15.8, 5.8 Hz, 1 H), 2.80 (dd, *J* = 13.5, 7.5 Hz, 1 H), 2.89 (m, 1 H), 4.14 (m, 1 H), 5.03 (bs, 1 H), 5.34 (dq, *J* = 6.3, 6.3 Hz, 1 H), 5.49 (ddq, *J* = 15.3, 7.0, 1.5 Hz, 1 H), 5.74 (dqd, *J* = 15.3, 6.5, 1.0 Hz, 1 H), 7.16–7.24 (m, 3 H), 7.28 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 20.2, 28.3, 37.9, 40.3, 48.9, 71.5, 79.2, 126.5, 128.4, 128.5, 129.4, 130.6, 137.8, 155.1, 170.9. HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min): t_R = 11.52 min (3%), t_R = 12.39 min (97%). HRMS (CI) *m*/*z*: calcd for $C_{20}H_{30}NO_4$ $(M + H)^+$:

Table 3. Syntheses of Protected Tubuphenylalanines



5	6	yield (%)	dr	7	yield (%)	8	yield (%)	9	yield (%)	dr
5a	**6a**	93	2:1	**7a**	85	**8a**	88	**9a**	82	>97:3
5b	**6b**	91	2:1	**7b**	93	**8b**	83	**9b**	79	>99:1
5c	**6c**	93	1:1	**7c**	78	**8c**	86	**9c**	81	>98:2

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348.2169, found 348.2186. Anal. Calcd for $C_{20}H_{29}NO_4$ (347.45): C 69.14; H, 8.41; N, 4.03; found C 69.20; H, 8.25; N, 4.21.

(*S*,*E*)-Hex-3-en-2-yl (*S*)-3-(*tert*-Butoxycarbonylamino)-4-phenylbutanoate (5b). According to ester **5a**, allylic ester **5b** was prepared from racemic alcohol **3b** (200 mg, 2.00 mmol), vinyl acetate (0.93 mL, 10.0 mmol), Novozym 435 (12 mg, 6 wt %), (*S*)-3-(*tert*-butoxycarbonylamino)-4-phenylbutanoic acid (307 mg, 1.10 mmol), DMAP (13.0 mg, 100 μmol), and DCC (248 mg, 1.20 mmol). Purification by flash chromatography (hexanes/ethyl acetate 9:1) resulted in the isolation of **5b** (277 mg, 0.77 mmol, 39%, >98% ds) as a colorless oil. R_f: 0.21 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D = -25.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.5 Hz, 3 H), 1.29 (d, *J* = 6.3 Hz, 3 H), 1.40 (s, 9 H), 2.06 (qdd, *J* = 7.3, 7.3, 1.0 Hz, 2 H), 2.39 (dd, *J* = 15.6, 6.0 Hz, 1 H), 2.48 (dd, *J* = 15.6, 5.5 Hz, 1 H), 2.80 (dd, *J* = 13.3, 7.8 Hz, 1 H), 2.91 (dd, *J* = 13.1, 5.5 Hz, 1 H), 4.14 (bs, 1 H), 5.07 (d, *J* = 7.3 Hz), 5.36 (dq, *J* = 7.0, 7.0 Hz, 1 H), 5.46 (ddt, *J* = 15.3, 7.0, 1.8 Hz, 1 H), 5.78 (dtd, *J* = 15.3, 8.3, 0.75 Hz, 1 H), 7.17−7.23 (m, 3 H), 7.28 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 20.3, 25.1, 28.3, 37.9, 40.3, 48.9, 71.6, 79.3, 126.5, 128.3, 128.4, 129.4, 135.3, 137.8, 155.1, 170.9. HPLC (hexane/*i*-PrOH 95:5, 1 mL/min): t_R = 8.49 min (2%), t_R = 9.61 min (98%). HRMS (CI): *m*/*z* calcd for $C_{21}H_{32}NO_4$ $(M + H)^+$ 362.2326, found 362.2312. Anal. Calcd for $C_{21}H_{31}NO_4$ (361.48): C, 69.78; H, 8.64; N, 3.87. Found: C 69.84; H, 9.16; N, 4.31.

(*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)pent-3-en-2-yl (*S*)-3-(*tert*-Butoxycarbonylamino)-4-phenylbutanoate (5c). According to ester **5a**, allylic ester **5c** was prepared from racemic alcohol **3c**[46] (1.51 g, 7.00 mmol), vinyl acetate (3.24 mL, 35.0 mmol), Novozym 435 (91 mg, 6 wt.%), (*S*)-3-(*tert*-butoxycarbonylamino)-4-phenylbutanoic (1.07 g, 3.85 mmol), DMAP (43.0 mg, 350 μmol), and DCC (867 mg, 4.20 mmol). Purification by flash chromatography (hexanes/ethyl acetate 9:1) gave rise to **5c** (1.17 g, 2.45 mmol, 35%, >99% ds) as a colorless oil. R_f: 0.18 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D = -20.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 6 H), 0.91 (s, 9 H), 1.31 (d, *J* = 6.5 Hz, 3 H), 1.40 (s, 9 H), 2.40 (dd, *J* = 15.8, 5.8 Hz, 1 H), 2.49 (dd, *J* = 15.8, 5.5 Hz, 1 H), 2.80 (dd, *J* = 13.3, 7.5 Hz, 1 H), 2.91 (dd, *J* = 12.8, 6.0 Hz, 1 H), 4.14 (m, 1 H), 4.18 (m, 2 H), 5.07 (d, *J* = 7.3 Hz, 1 H), 5.42 (dqd, *J* = 6.5, 6.5, 0.5 Hz, 1 H), 5.71 (ddt, *J* = 15.6, 6.0, 1.5 Hz, 1 H), 5.80 (dtd, *J* = 15.3, 4.3, 0.75 Hz, 1 H), 7.18 (m, 2 H), 7.22 (m, 1 H), 7.28 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3, 18.4, 20.2, 25.9, 28.3, 37.8, 40.3, 48.8, 62.8, 70.8, 79.2, 126.5, 128.5, 128.8, 129.4, 131.8, 137.8, 155.1, 170.9. HPLC (hexane/*i*-PrOH 95:5, 1 mL/min): t_R = 8.43 min (1%), t_R = 9.44 min (99%). HRMS (CI): *m*/*z* calcd for $C_{26}H_{44}NO_5Si$ $(M + H)^+$ 478.2983, found 478.2995. Anal. Calcd for $C_{26}H_{43}NO_5Si$ (477.71): C, 65.37; H, 9.07; N, 2.93. Found: C, 65.11; H, 8.90; N, 2.82.

(3*R*,*E*)-2-[(*S*)-1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]-3-methylhex-4-enoic Acid (6a). To a solution of freshly distilled diisopropylamine (0.87 mL, 6.19 mmol) in abs THF (6 mL) in a dry Schlenk tube was added *n*-butyllithium (3.75 mL, 6.00 mmol, 1.6 M in hexane) at −30 °C under nitrogen. After 5 min at this temperature, the mixture was allowed to warm to room temperature for 30 min and was cooled to −78 °C again. In a second Schlenk tube allylic ester **5a** (721 mg, 2.07 mmol) was dissolved in abs THF (6 mL) under nitrogen and cooled to −78 °C. The base solution was slowly transferred to the substrate solution at −78 °C via a transfer cannula. After 30 min, TMSCl (0.78 mL, 6.17 mmol) was added, and stirring was continued for 60 min at this temperature. The cooling bath was removed, and the reaction mixture was warmed to room temperature and heated to 60 °C for 2 h. After being cooled to room temperature, the mixture was diluted with diethyl ether and hydrolyzed with 1 M HCl. The organic layer was further washed with 1 M HCl, H_2O, satd $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (hexanes/ethyl acetate 7:3) afforded unsaturated acid **6a** (668 mg, 1.92 mmol, 93%, 67% ds) as a white solid. Mp: 131−133 °C. R_f: 0.26 (hexanes/ethyl acetate 7:3). $[\alpha]^{20}_D$ = 33.6 (*c* 1.0, $CHCl_3$). 1:1 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$), major diastereomer: δ 1.14 (d, *J* = 6.8 Hz, 3 H), 1.35 (s, 4.5 H), 1.42 (s, 4.5 H), 1.66 (bs, 3 H), 2.27 (dd, *J* = 10.2, 3.1 Hz, 0.5 H), 2.49−2.81 (m, 2.5 H), 2.98 (dd, *J* = 13.9, 3.6 Hz, 1 H), 4.05 (m, 1 H), 4.54 (d, *J* = 8.0 Hz, 0.5 H), 5.46 (m, 2 H), 5.64 (d, *J* = 9.3 Hz, 0.5 H), 7.19−7.24 (m, 3 H), 7.28 (m, 2 H). Minor diastereomer (selected signals): δ 0.99 (d, *J* = 6.5 Hz, 3 H), 1.26 (s, 4.5 H), 1.30 (s, 4.5 H), 1.63 (d, *J* = 6.3 Hz, 3 H), 2.92 (dd, *J* = 13.5, 5.8 Hz, 1 H), 3.95 (m, 1 H), 5.08 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$), major diastereomer: δ 17.9, 19.3, 28.4, 37.2, 41.3, 51.3, 52.2, 79.0, 126.2, 126.4, 128.3, 129.5, 132.2, 137.9, 155.0, 179.8. Minor diastereomer (selected signals): δ 27.8, 51.8. HRMS (CI): *m*/*z* calcd for $C_{20}H_{30}NO_4$ $(M + H)^+$ 348.2169, found 348.2198. Anal. Calcd for $C_{20}H_{29}NO_4$ (347.45): C, 69.14; H, 8.41; N, 4.03. Found: C 69.01; H, 8.37; N, 3.90.

(3*R*,*E*)-2-[(*S*)-1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]-3-ethylhex-4-enoic Acid (6b). According to **6a**, unsaturated acid **6b** was prepared from diisopropylamine (0.23 mL, 1.66 mmol), *n*-butyllithium (1.00 mL, 1.60 mmol, 1.6 M in hexane), allylic ester **5b** (200 mg, 0.55 mmol) and TMSCl (0.21 mL, 1.66 mmol). Purification by flash chromatography (hexanes/ethyl acetate 7:3) provided **6b** (184 mg, 0.51 mmol, 91%, 67% ds) as a white solid; mp. 133−135 °C. R_f: 0.23 (hexanes/ethyl acetate 7:3). $[\alpha]^{20}_D$= −23.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), major diastereomer: δ 0.87 (bs, 3 H), 1.36 (s, 9 H), 1.40 (m, 1 H), 1.55 (m, 1 H), 1.69 (bs, 3 H), 2.28 (bs, 1 H), 2.80−2.85 (m, 2 H), 2.96 (m, 1 H), 4.02 (m, 1 H), 4.52 (d, *J* = 8.8 Hz, 1 H), 5.38 (m, 1 H), 5.45 (dq, *J* = 15.0, 6.0 Hz, 1 H), 7.19−7.22 (m, 3 H), 7.28 (m, 2 H). Minor diastereomer (selected signals): δ 1.24 (s, 9 H), 1.69 (bs, 3 H), 2.40 (bs, 1 H), 2.67 (m 2 H), 3.94 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$), major diastereomer: δ 11.9, 18.0, 25.9, 28.3, 37.9, 44.2, 51.9, 52.7, 79.2, 16.3, 128.3, 128.3, 129.5, 30.7, 138.1, 155.0, 178.2. Minor diastereomer (selected signals): δ 11.9, 26.0, 28.0, 53.2, 53.8, 80.5, 128.0, 130.4. HRMS (CI) *m*/*z* calcd for $C_{21}H_{32}NO_4$ $(M + H)^+$: 362.2326, found 362.2327. Anal. Calcd for $C_{21}H_{31}NO_4$ (361.48): C, 69.78; H, 8.64; N, 3.87. Found: C, 69.32; H, 8.57; N, 3.95.

(3*R*,*E*)-2-[[(*S*)-1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]-3-(*tert*-butyldimethylsilyloxymethyl)hex-4-enoic Acid (6c). The unsaturated acid **6c** was prepared according to **6a** from diisopropylamine (0.82 mL, 5.80 mmol), *n*-butyllithium (3.50 mL, 5.60 mmol, 1.6 M in hexane), allylic ester **5c** (924 mg, 1.93 mmol), and TMSCl (0.73 mL, 5.80 mmol). Purification by flash chromatography (hexanes/ethyl acetate 8:2) gave rise to unsaturated acid **6c** (854 mg, 1.79 mmol, 93%, 50% ds) as a white solid. Mp: 55−57 °C. R_f: 0.25 (hexanes/ethyl acetate 8:2). $[\alpha]^{20}_D = -8.8$ (*c* 1.0, $CHCl_3$). Diastereomeric ratio 1:1.[47] ^{1}H NMR (400 MHz, $CDCl_3$), diastereomer I: δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.34 (s, 9 H), 1.68 (d, *J* = 6.0 Hz, 3 H), 2.59−2.69(m, 2 H), 2.82−3.01 (m, 2 H), 3.63 (m, 2 H), 4.02 (bs, 1 H), 4.74 (d, *J* = 9.0 Hz, 1 H), 5.45−5.66 (m, 2 H), 7.18−7.21 (m, 3 H), 7.27 (m, 2 H). Diastereomer II (selected signals): δ 0.01 (s, 6 H), 0.82 (s, 9 H), 1.40 (s, 9 H), 2.63 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$), diastereomer I: δ −5.57, 18.1, 18.2, 25.8, 28.3, 38.2, 44.5, 49.4, 52.2, 66.2, 79.1, 126.3, 127.7, 128.3, 129.6, 129.8, 138.1, 155.1, 175.7. Diastereomer II (selected signals): δ −5.49, 18.2. HRMS (CI): *m*/*z* calcd $C_{26}H_{44}NO_5Si$ $(M + H)^+$ 478.2983, found 478.2970. Anal. Calcd for $C_{26}H_{43}NO_5Si$ (477.71): C, 65.37; H, 9.07; N, 2.93. Found: C, 64.81; H, 8.28; N, 3.07.

***tert*-Butyl [(2*R*,4*S*,*E*)-4-Methyl-1-phenylhept-5-en-2-yl]-carbamate (7a).** To a solution of unsaturated acid **6a** (299 mg, 861 μmol), 2-mercaptopyridine *N*-oxide (109 mg, 857 μmol), and DMAP (11.0 mg, 90 μmol) in dry dichloromethane (4 mL) was added DCC (204 mg, 989 μmol) in dichloromethane (2 mL) at 0 °C in the dark. The mixture was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ether. The organic layer was filtered, washed with satd $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated in vacuo to yield the green-yellow Barton ester.

The crude product was taken up in dry THF (4 mL) and was treated with *t*-BuSH (960 μL, 8.53 mmol) in the dark. At 0 °C, BEt_3 (260 μL, 260 μmol, 1 M in hexane) was added under air, and the mixture was stirred for 1.5 h before it was diluted with ether. The organic layer was washed with 6 M HCl, H_2O, satd $NaHCO_3$, H_2O, and brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash chromatography (hexanes/ethyl acetate 9:1) resulted in the isolation of **7a** (222 mg, 732 μmol, 85%) as a colorless oil. R_f: 0.28 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D$ =

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+10.9 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.8 Hz, 3 H), 1.27 (m, 1 H), 1.34 (m, 1 H), 1.40 (s, 9 H), 1.64 (dd, *J* = 6.3, 1.0 Hz, 3 H), 2.21 (m, 1 H), 2.76 (m, 2 H), 3.83 (m, 1 H), 4.28 (bs, 1 H), 5.18 (dd, *J* = 15.2, 8.0 Hz, 1 H), 5.38 (dqd, *J* = 15.3, 6.3, 0.7 Hz, 1 H), 7.15−7.22 (m, 3 H), 7.27 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 21.4, 28.4, 33.7, 41.5, 41.7, 49.8, 78.8, 124.2, 126.1, 128.2, 129.6, 136.1, 138.4, 155.7. HRMS (CI): *m*/*z* calcd $C_{19}H_{30}NO_2$ $(M + H)^+$ 304.2271, found 304.2293. Anal. Calcd for $C_{19}H_{29}NO_2$ (303.44): C, 75.21; H, 9.63; N, 4.62. Found: C, 75.14; H, 9.33; N, 4.95.

***tert*-Butyl [(2*R*,4*S*,*E*)-4-Ethyl-1-phenylhept-5-en-2-yl]-carbamate (7b).** The alkene **7b** was prepared according to **7a** from unsaturated acid **6b** (100 mg, 277 μmol), *N*-mercaptopyridine *N*-oxide (36 mg, 283 μmol), DMAP (3.0 mg, 25 μmol), DCC (66 mg, 320 μmol), *t*-BuSH (312 μL, 2.77 mmol), and BEt_3 (83 μL, 83 μmol, 1 M in hexane). Purification by flash chromatography (hexanes/ethyl acetate 9:1) provided **7b** (81 mg, 255 μmol, 92%) as a colorless oil. R_f: 0.25 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D$ = +1.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, *J* = 7.3 Hz, 3 H), 1.15−1.33 (m, 4 H), 1.42 (s, 9 H), 1.66 (d, *J* = 6.0 Hz, 3 H), 1.94 (bs, 1 H), 2.72 (dd, *J* = 13.3, 6.8 Hz 1 H), 2.80 (dd, *J* = 13.3, 5.3 Hz, 1 H), 3.81 (bs, 1 H), 4.30 (d, *J* = 8.0 Hz, 1 H), 5.02 (dd, *J* = 14.6, 9.5 Hz, 1 H), 5.38 (dq, *J* = 15.0, 6.5 Hz, 1 H), 7.16−7.22 (m, 3 H), 7.27 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 17.9, 28.4, 29.7, 39.4, 41.3, 41.9, 49.7, 78.7, 125.9, 126.1, 128.1, 129.6, 134.5, 138.5, 155.1. HRMS (CI): *m*/*z* calcd $C_{20}H_{32}NO_2$ $(M + H)^+$ 318.2428, found 318.2432. Anal. Calcd for $C_{20}H_{31}NO_2$ (317.47): C, 75.67; H, 9.84; N, 4.41. Found: C, 75.28; H, 9.81; N, 4.53.

***tert*-Butyl [(2*R*,4*S*,*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-1-phenylhept-5-en-2-yl]carbamate (7c).** The alkene **7c** was prepared according to **7a** from unsaturated acid **6c** (132 mg, 276 μmol), *N*-mercaptopyridine *N*-oxide (36 mg, 283 μmol), DMAP (3.0 mg, 25 μmol), DCC (66 mg, 320 μmol), *t*-BuSH (312 μL, 2.77 mmol), and BEt_3 (83 μL, 83 μmol, 1 M in hexane). Purification by flash chromatography (hexanes/ethyl acetate 9:1) provided **7c** (94 mg, 217 μmol, 79%) as a colorless oil. R_f: 0.26 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D$ = +13.0 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ −0.01 (s, 3 H), −0.01 (s, 3 H), 0.86 (s, 9 H), 1.33 (m, 1 H), 1.41 (s, 9 H), 1.45 (m, 1 H), 1.63 (d, *J* = 6.3 Hz, 3 H), 2.23 (m, 1 H), 2.72 (dd, *J* = 13.5, 7.3 Hz, 1 H), 2.85 (dd, *J* = 13.3, 5.3 Hz, 1 H), 3.30 (m, 1 H), 3.47 (dd, *J* = 9.8, 5.5 Hz,1 H), 3.80 (m, 1 H), 4.44 (d, *J* = 8.3 Hz, 1 H), 5.10 (dd, *J* = 15.3, 8.5 Hz, 1 H), 5.42 (dq, *J* = 15.1, 6.5 Hz, 1 H), 7.15−7.21 (m, 3 H), 7.27 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4, −5.3, 18.1, 18.3, 25.9, 28.4, 35.4, 42.1, 42.3, 49.8, 67.0, 78.7, 126.1, 127.1, 128.1, 129.6, 131.5, 138.4, 155.7. HRMS (CI): *m*/*z* calcd $C_{25}H_{44}NO_3Si$ $(M + H)^+$ 434.3085, found 434.3118. Anal. Calcd for $C_{25}H_{43}NO_3Si$ (433.69): C, 69.23; H, 9.99; N, 3.23. Found: C, 69.06; H, 9.54; N, 3.58.

Di-*tert*-butyl [(2*R*,4*S*,*E*)-4-Methyl-1-phenylhept-5-en-2-yl]-iminodicarbonate (8a). To a solution of alkene **7a** (160 mg, 527 μmol) in dry THF (4 mL) was added *n*-butyllithium (430 μL, 688 μmol, 1.6 M in hexane) at −78 °C. After 30 min at this temperature, di-*tert*-butyl dicarbonate (195 mg, 894 μmol) in THF (2 mL) was added in one portion, and the reaction mixture was allowed to warm to room temperature overnight before it was heated to 60 °C for 3 h. The reaction mixture was hydrolyzed with satd NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with 1 M HCl and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (hexanes/ethyl acetate 95:5) provided **8a** (187 mg, 463 μmol, 88%) as a colorless oil. R_f: 0.30 (hexanes/ethyl acetate 95:5). $[\alpha]^{20}_D$ = −50.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.8 Hz, 3 H), 1.38 (m, 1 H), 1.41 (s, 18 H), 1.62 (dd, *J* = 6.3, 1.3 Hz, 3 H), 1.92 (ddd, *J* = 14.1, 10.0, 4.0 Hz, 1 H), 2.13 (m, 1 H), 2.79 (dd, *J* = 13.4, 6.7 Hz,1 H), 3.11 (dd, *J* = 13.3, 8.8 Hz, 1 H), 4.38 (m, 1 H), 5.19 (ddq, *J* = 15.1, 6.5, 1.5 Hz, 1 H), 5.36 (dqd, *J* = 15.1, 6.3, 0.8 Hz, 1 H), 7.14−7.19 (m, 3 H), 7.24 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 21.4, 27.9, 34.1, 39.9, 40.5, 57.2, 81.6, 123.9, 126.0, 128.1, 129.5, 136.1, 139.2, 153.2. HRMS (CI): *m*/*z* calcd $C_{24}H_{38}NO_4$ $(M + H)^+$ 404.2795, found 404.2783. Anal. Calcd for $C_{24}H_{37}NO_4$ (403.27): C, 71.43; H, 9.24; N, 3.47. Found: C, 71.53; H, 9.24; N, 3.67.

Di-*tert*-butyl [(2*R*,4*S*,*E*)-4-Ethyl-1-phenylhept-5-en-2-yl]-iminodicarbonate (8b). The double-protected amine **8b** was prepared according to **8a** from alkene **7b** (328 mg, 1.03 mmol), *n*-butyllithium (0.84 mL, 1.34 mmol, 1.6 M in hexane), and di-*tert*-butyl dicarbonate (383 mg, 1.76 mmol). Purification by flash chromatography (hexanes/ethyl acetate 95:5) gave rise to **8b** (357 mg, 860 μmol, 83%) as a colorless oil. R_f: 0.19 (hexanes/ethyl acetate 95:5). $[\alpha]^{20}_D$ = −59.9 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.4 Hz, 3 H), 1.24−1.44 (m, 3 H), 1.48 (s, 18 H), 1.70 (dd, *J* = 6.4, 1.6 Hz 3 H), 1.91 (m, 1 H), 2.07 (ddd, *J* = 14.0, 10.6, 3.3 Hz, 1 H), 2.87 (dd, *J* = 13.3, 6.8 Hz, 1 H), 3.18 (dd, *J* = 13.3, 8.8 Hz, 1 H), 4.44 (m, 1 H), 5.10 (ddq, *J* = 15.0, 8.8, 1.5 Hz, 1 H), 5.41 (dq, *J* = 15.0, 6.3 Hz, 1 H), 7.21−7.26 (m, 3 H), 7.31 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 18.0, 27.9, 28.6, 37.8, 40.6, 41.7, 57.0, 81.5, 125.7, 126.0, 128.1, 129.5, 134.5, 139.2, 153.1. HRMS (CI): *m*/*z* calcd $C_{25}H_{40}NO_4$ $(M + H)^+$ 418.2952, found 418.2951. Anal. Calcd for $C_{25}H_{39}NO_4$ (403.27): C, 71.81; H, 9.41; N, 3.35. Found: C, 72.01; H, 10.11; N, 3.72.

Di-*tert*-butyl [(2*R*,4*S*,*E*)-4-(*tert*-Butyldimethylsilyloxymethyl)-1-phenylhept-5-en-2-yl]iminodicarbonate (8c). The double-protected amine **8c** was prepared according to **8a** from alkene **7c** (49 mg, 113 μmol), *n*-butyllithium (92 μL, 147 μmol, 1.6 M in hexane), and di-*tert*-butyl dicarbonate (62 mg, 284 μmol). Purification by flash chromatography (hexanes/ethyl acetate 95:5) gave rise to **8c** (52 mg, 97 μmol, 86%) as a colorless oil. R_f: 0.25 (hexanes/ethyl acetate 95:5). $[\alpha]^{20}_D$ = −28.9 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ −0.01 (s, 3 H), −0.01 (s, 3 H), 0.87 (s, 9 H), 1.35 (m, 1 H), 1.41 (s, 18 H), 1.63 (dd, *J* = 6.6, 1.5 Hz, 3 H), 2.21 (m, 1 H), 2.18 (m, 1 H), 2.82 (dd, *J* = 13.3, 6.8 Hz, 1 H), 3.13 (dd, *J* = 13.3, 8.8 Hz, 1 H), 3.44 (d, *J* = 6.0 Hz, 2 H), 4.37 (m, 1 H), 5.13 (ddq, *J* = 15.3, 8.8. 1.8 Hz, 1 H), 5.41 (dqd, *J* = 15.3, 6.5, 0.5 Hz, 1 H), 7.15−7.19 (m, 3 H), 7.23 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3, 18.1, 18.4, 25.9, 28.0, 34.2, 40.6, 42.1, 56.9, 67.4, 81.6, 126.0, 127.1, 128.1, 129.5, 131.8, 139.2, 153.1. HRMS (CI): *m*/*z* calcd $C_{30}H_{52}NO_5Si$ $(M + H)^+$ 534.3609, found 534.3622. Anal. Calcd for $C_{30}H_{51}NO_5Si$ (533.81): C, 67.50; H, 9.63; N, 2.62. Found: C, 67.87; H, 9.43; N, 2.60.

(2*S*,4*R*)-Methyl 4-[Bis(*tert*-butoxycarbonyl)amino]-2-methyl-5-phenylpentanoate (9a). Through a solution of double-protected amine **8a** (207 mg, 513 μmol) and a NaOH solution (1.03 mL, 2.58 mmol, 2.5 M in dry MeOH) in dichloromethane (4 mL) was bubbled ozone at −78 °C until the characteristic blue color and a yellow precipitate appeared. The mixture was diluted with H_2O (3.5 mL) and ether (3.5 mL), warmed to room temperature, and extracted twice with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (hexanes/ethyl acetate 9:1) gave rise to **9a** (177 mg, 420 μmol, 82%, 97% ds) as a colorless oil. R_f: 0.25 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D$ = −30.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, *J* = 7.3 Hz, 3 H), 1.39 (s, 18 H), 1.95 (ddd, *J* = 14.3, 9.8, 5.0 Hz, 1 H), 2.02 (ddd, *J* = 14.3, 10.0, 4.5 Hz, 1 H), 2.51 (m, 1 H), 2.82 (dd, *J* = 13.5, 6.3 Hz,1 H), 3.14 (dd, *J* = 13.5, 9.5 Hz, 1 H), 3.64 (s, 3 H), 4.45 (m, 1 H), 7.14−7.19 (m, 3 H), 7.25 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 27.9, 36.4, 36.6, 39.9, 51.6, 57.1, 81.8, 126.2, 128.2, 129.4, 138.7, 153.1, 176.6. HPLC (hexane/*i*-PrOH 9:1, 0.5 mL/min): t_R = 10.89 min (97%), t_R = 12.87 min (3%). HRMS (CI): *m*/*z* calcd $C_{23}H_{36}NO_6$ $(M + H)^+$ 422.2537, found 422.2548. Anal. Calcd for $C_{23}H_{35}NO_6$ (421.24): C, 65.53; H, 8.37; N, 3.32. Found: C, 65.14; H, 8.40; N, 3.42.

(2*S*,4*R*)-Methyl 4-[Bis(*tert*-butoxycarbonyl)amino]-2-ethyl-5-phenylpentanoate (9b). Ester **9b** was prepared according to **9a** from double-protected amine **8b** (63.1 mg, 151 μmol) and NaOH solution (0.3 mL, 0.75 mmol, 2.5 M in dry MeOH) in dichloromethane (1.2 mL). Purification by flash chromatography (hexanes/ethyl acetate 9:1) provided **9b** (52 mg, 119 μmol, 79%, 99% ds) as a colorless oil. R_f: 0.26 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D$ = −35.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.4 Hz, 3 H), 1.39 (s, 18 H), 1.51−1.54 (m, 1 H), 1.58−1.65 (m, 1 H), 1.89 (ddd, *J* = 15.0, 10.8, 4.3 Hz, 1 H), 2.09 (ddd, *J* = 14.3, 11.0, 3.5 Hz, 1 H), 2.36 (m, 1 H), 2.81 (dd, *J* = 13.6, 5.8 Hz, 1 H), 3.15 (dd, *J* = 13.6, 9.5 Hz, 1

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H), 3.64 (s, 3 H), 4.41 (m, 1 H), 7.13−7.18 (m, 3 H), 7.23 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 26.3, 27.9, 34.2, 40.0, 43.7, 51.4, 57.1, 81.8, 126.1, 128.2, 129.4, 137.7, 153.1, 176.1. HPLC (hexane/*i*-PrOH 9:1, 0.5 mL/min): t_R = 15.83 min (99%), t_R = 17.67 min (1%). HRMS (CI): *m*/*z* calcd $C_{24}H_{38}NO_6$ $(M + H)^+$ 436. 2694, found 436.2727. Anal. Calcd for $C_{24}H_{37}NO_6$ (435.55): C, 66.18; H, 8.56; N, 3.22. Found: C 65.56; H, 8.76; N, 3.59.

(2*R*,4*R*)-Methyl 4-[Bis(*tert*-butoxycarbonyl)amino]-2-(*tert*-butyldimethylsilyloxymethyl)-5-phenylpentanoate (9c). Ester **9c** was prepared according to **9a** from double protected amine **8c** (72.0 mg, 135 μmol) and NaOH solution (0.27 mL, 0.68 mmol, 2.5 M in dry MeOH) in dichloromethane (1.1 mL). Purification by flash chromatography (hexanes/ethyl acetate 9:1) provided **9c** (60 mg, 109 μmol, 81%, 98% ds) as a colorless oil. R_f: 0.32 (hexanes/ethyl acetate 9:1). $[\alpha]^{20}_D$ = −32.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.01 (s, 3 H), −0.01 (s, 3 H), 0.85 (s, 9 H), 1.39 (s, 18 H), 1.92 (ddd, *J* = 14.6, 10.5, 4.3 Hz, 1 H), 2.10 (ddd, *J* = 14.6, 11.4, 3.8 Hz, 1 H), 2.64 (m, 1 H), 2.81 (dd, *J* = 13.5, 5.8 Hz, 1 H), 3.16 (dd, *J* = 13.4, 9.7 Hz, 1 H), 6.64 (s, 3 H), 3.71 (m, 2 H), 4.44 (m, 1 H), 7.14−7.18 (m, 3 H), 7.23 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.5, 18.2, 25.7, 27.9, 31.4, 40.0, 45.6, 51.5, 56.9, 65.0, 81.8, 126.2, 128.2, 129.4, 138.6, 153.0, 174.4. HPLC (hexane/*i*-PrOH 95:5 to 9:1 in 20 min, 0.5 mL/min): t_R = 13.40 min (98%), t_R = 19.33 min (2%). HRMS (CI): *m*/*z* calcd $C_{29}H_{50}NO_7Si$ $(M + H)^+$ 552.3351, found 552.3315. Anal. Calcd for $C_{29}H_{49}NO_7Si$ (551.79): C, 63.12; H, 8.95; N, 2.54. Found: C, 62.59; H, 9.20; N, 2.82.

(2*S*,4*R*)-Methyl 4-Amino-2-methyl-5-phenylpentanoate Hydrochloride (10a).[6,22] A HCl solution (1.05 mL, 4.20 mmol, 4 M in dioxane) was added to ester **9a** (177 mg 420 μmol) at 0 °C under nitrogen atmosphere. After complete conversion (TLC control), the solvent was removed in vacuo and **10a** (107 mg, 415 μmol, 99%) was obtained as a white solid: mp 136−138 °C; $[\alpha]^{20}_D$ = +11.4 (*c* 1.0, $CHCl_3$) [+11.2 (*c* 1.0, MeOH)].[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ −1.15 (d, *J* = 6.8 Hz, 3 H), 1.80 (ddd, *J* = 13.3, 9.0, 3.8 Hz, 1 H), 1.99 (ddd, *J* = 14.3, 10.5, 3.3 Hz, 1 H), 2.93 (dd, *J* = 14.0, 9.3 Hz, 1 H), 2.97 (m, 1 H), 3.29 (dd, *J* = 13.7, 5.4 Hz, 1 H), 3.61 (s, 3 H), 3.64 (m, 1 H), 7.24−7.28(m, 3 H), 7.32 (m, 2 H), 8.55 (bs, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 35.9, 36.0, 39.8, 51.9, 52.2, 127.3, 128.9, 129.3, 135.4, 175.7. HRMS (CI): *m*/*z* calcd $C_{13}H_{20}NO_2$ $(M - Cl)^+$ 222.1489, found 222.1496. Anal. Calcd for $C_{13}H_{20}ClNO_2$ (257.76): C, 60.58; H, 7.82; N, 5.43. Found: C, 60.29; H, 7.48; N, 5.16.

(3*S*,5*R*)-5-Benzyl-3-methylpyrrolidin-2-one (11a).[15] To a solution of **10a** (31.0 mg, 120 μmol) in MeOH (1 mL) was added a solution of $NaHCO_3$ (30.0 mg, 257 μmol) in H_2O (1 mL), and the mixture was stirred for 4 h at room temperature and 12 h at 70 °C. The solvent was removed in vacuo, and the residue was extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated to dryness to yield the lactam **21** (22.3 mg, 118 μmol, 98%) as a white solid. R_f: 0.14 (hexanes/ethyl acetate 1:1). $[\alpha]^{20}_D$= −55.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, *J* = 7.3 Hz, 3 H), 1.88 (ddd, *J* = 12.8, 7.8, 7.8 Hz, 1 H), 2.11 (ddd, *J* = 12.8, 8.8, 3.8 Hz, 1 H), 2.43 (m, 1 H), 2.72 (dd, *J* = 13.3, 7.8 Hz, 1 H), 2.80 (dd, *J* = 13.6, 6.0 Hz, 1 H), 3.81 (m, 1 H), 6.03 (bs, 1 H), 7.17 (m, 2 H), 7.25 (m, 1 H), 7.31 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 34.9, 35.0, 42.7, 53.3, 126.8, 128.7, 129.1, 137.6, 180.3. HRMS (CI): *m*/*z* calcd $C_{12}H_{16}NO$ $(M + H)^+$ 190.1226, found 190.1211.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR data of all new compounds **5**−**9** and HPLC chromatograms of **5** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Robert E. Ireland.

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