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Synthesis of Chlamydocin by Chelate-Claisen Rearrangement

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Chelate-Claisen rearrangement of a chiral allylic ester allows the synthesis of the unusual epoxyketo amino acid Aoe found in chlamydocin, one representative of a group of peptide-based HDAc inhibitors.

Introduction

Cyclic peptides are found in wide variety as secondary metabolites of marine organisms and fungi. Many of them show interesting biological activities (antibiotic and antitumor activities) and are therefore highly interesting from a pharmaceutical point of view.[1] An interesting family of cyclotetrapeptides contains Aoe [(2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid], an unusual lipophilic amino acid containing an epoxyketone functionality. A typical representative of this family is chlamydocin;[2] other members are HC-toxin,[3] WF-3161,[4] Cyl-1 and Cyl-2,[5] and the trapoxins (Figure 1).[6] All members of this family share three structural features: 1) a proline or a pipecolic acid residue, 2) at least one (*R*)-configured amino acid, and 3) the unusual amino acid Aoe. Several groups have shown that reduction or hydrolysis of the epoxide moiety results in complete loss of activity, suggesting that this reactive group might react irreversibly with a receptor through covalent bond formation.[2,6,7] This notion has been challenged, though, with the isolation of a biologically active fungal metabolite that is structurally identical to chlamydocin except that the (9*S*)-epoxide is replaced by a (9*S*)-hydroxy group.[8] The epoxy functionality is also completely removed in the microsporins, which nevertheless showing promising antitumor activity.[9] The structurally related apicidins, also containing the simplified amino acid Aoda, are in addition highly active against plasmodium species (malaria parasites).[10]

The molecular target of all these cyclic peptides is histone deacetylase (HDAc), a nuclear isozyme that regulates gene transcription through a dynamic process of acetylation and deacetylation of lysine residues of histones.[11] Blockade of the deacylating process causes hyperacetylation of histones and unregulated gene activity, resulting in untimely cell death.

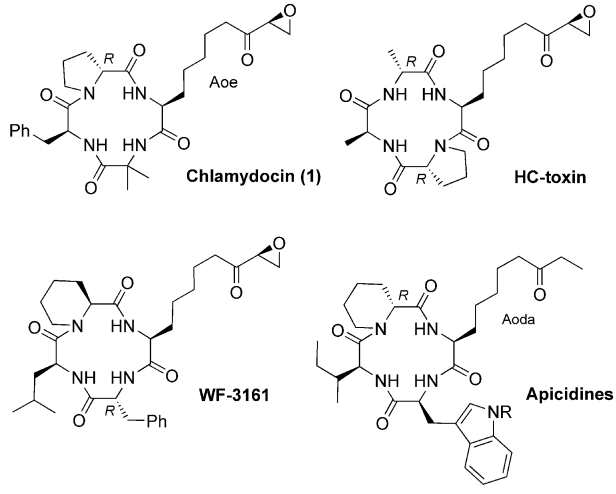

Figure 1. Naturally occurring cyclic peptides showing HDAc inhibition.

These cyclic peptides are therefore of strong interest both to medicinal and to natural products chemists, and several syntheses directed both towards the natural products themselves and towards the unusual amino acids Aoe and Aoda have been developed. Rich et al. were the first to report on a synthesis of racemic Aoe through alkylation of an imino glycinate[12] and its incorporation into chlamydocin[13] and HC-toxin.[14] The first enantioselective synthesis of Aoe was reported by Schmidt et al., who used a phosphonate condensation combined with an asymmetric hydrogenation of the obtained dehydroamino acid.[15]

Jacquier[16] and Katsuki[17] modified the Rich approach by using chiral modified glycinates to generate the stereogenic center, while Baldwin[18] and Schreiber[19] started with a suitable enantiomerically pure amino acid precursor that was prolonged by radical[18] or cuprate addition.[19] Several syntheses for the structurally related but simpler Aoda were also reported, either using Schöllkopf's bislac-

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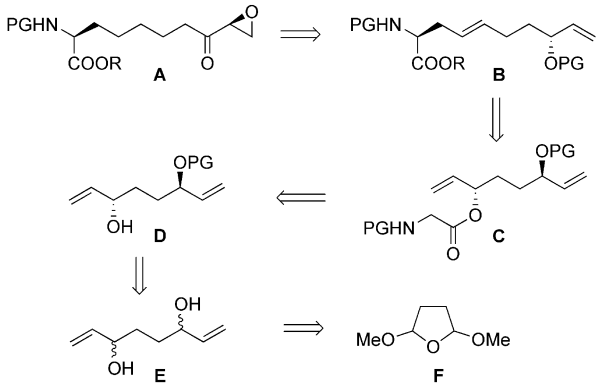
tim ether protocol[20] to generate the stereogenic center,[21] or starting from suitable optically active amino acid precursors.[22]

Our group is also involved in amino acid and peptide synthesis, investigating reactions of metal-chelated enolates.[23] These enolates are excellent nucleophiles for transition-metal-catalyzed allylic alkylations,[24] giving rise to γ,δ-unsaturated amino acids. The same structural motif can be obtained through a chelate-enolate Claisen rearrangement,[25] an approach well suited for highly functionalized amino acids[26] and peptides.[27] Here we wish to report on an application of this protocol for the synthesis of Aoe and chlamydocin. Our retrosynthetic plan is shown in Scheme 1. The protected Aoe (**A**) should be accessible from the doubly unsaturated amino acid **B** through regioselective epoxidation of the allylic alcohol and subsequent hydrogenation of the remaining double bond. The stereogenic center of this amino acid should be generated through a chelate-Claisen rearrangement of chiral allylic ester **C**. Alcohol **D** should be accessible from diol **E** through monoprotection and kinetic resolution of the stereoisomeric mixture formed by vinyl-Grignard addition to the dialdehyde obtained from THF derivative **F**.



Scheme 1. Retrosynthesis plan for the synthesis of Aoe.

Results and Discussion

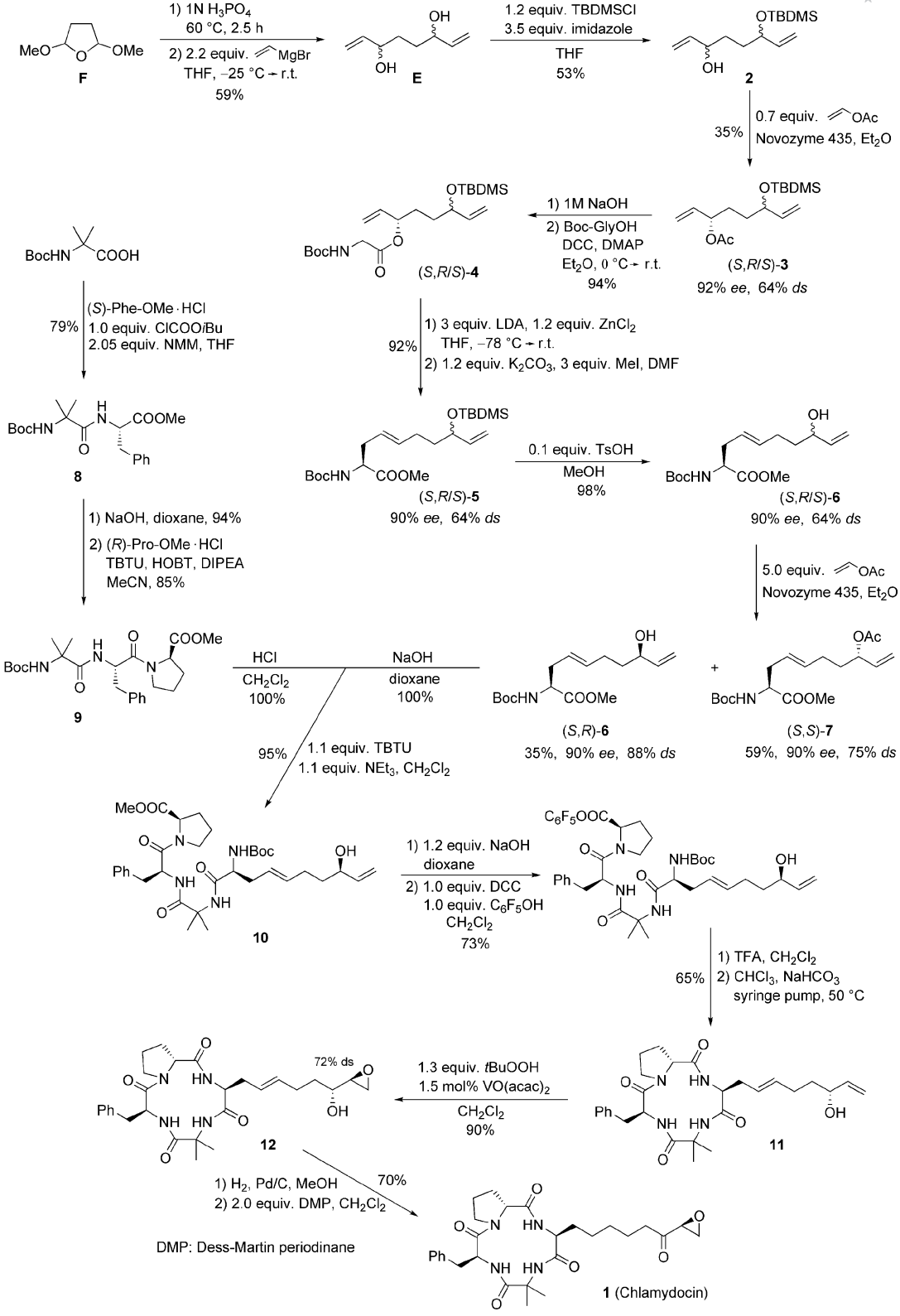
As outlined in this retrosynthetic plan, **F** was subjected to a proton-catalyzed ring cleavage,[28] giving rise to the corresponding dialdehyde, which was directly subjected to the Grignard addition to afford the diallyl alcohol **E** (Scheme 2).

Terminal allylic alcohols are excellent substrates for enzymatic kinetic resolutions with immobilized *Candida antarctica* lipase (Novozyme 435). According to the Kazlauskas rule, the (*S*)-configured alcohol should undergo the esterification more rapidly than its enantiomer.[29] In an idealized situation, a diol such as **E** should provide a mixture of the diacylated (*S*,*S*)-diol, the monoprotected (*R*,*S*)-diol, and the unreacted (*R*,*R*) isomer. The monoacylated (*R*,*S*)-alcohol is the one required for the synthesis of Aoe. Unfortunately, though, the stereoselectivity with which this monoprotected alcohol was formed was unsatisfying (70% *ds*), although a wide range of reaction conditions were used. Similar observations were also made by Unelius et al. when investigating the acylation of comparable dipropargylic diols.[30] They switched from the standard acyl donor vinyl acetate to ethyl octanoate, but with our substrate no significant improvement was observed. It should also be mentioned that attempts to saponify the racemic diacetate selectively with Novozyme and *Candida rugosa* lipase were also unsuccessful. This is quite different from the behavior of other terminal allylic alcohols,[31] and we assumed that the polar hydroxy group might be not compatible with the apolar binding pocket of the lipase.

We therefore decided to protect one of the hydroxy functionalities as a silyl ether (**2**; Scheme 2) to remove this polarity, and indeed, esterification of this monoallyl alcohol gave the required acetate **3** in 92% *ee* (relative to the acetate-bearing stereocenter) as a nearly 2:1 diastereomeric mixture. Only a slight excess of vinyl acetate was used in this case, to ensure that the esterification would stop after consumption of one enantiomer. Saponification of the acetate and coupling with Boc-glycine gave rise to allylic ester **4**. Deprotonation and transmetallation of the lithium enolate with $ZnCl_2$ resulted in the formation of a chelated enolate, which underwent Claisen rearrangement on warming up to room temperature. Esterification of the obtained crude amino acid provided the methyl ester **5** in excellent yield.

Cleavage of the silyl protecting group in **5** could be achieved with TsOH, giving rise to the allyl alcohol **6** in nearly quantitative yield. Although the alcohol functionality is later on oxidized to the ketone, so the configuration of this stereogenic center is "uninteresting", we subjected **6** to a second enzymatic kinetic resolution, because we wanted to use this stereogenic center to control the subsequent epoxidation. Novozyme-catalyzed esterification gave rise to the (*S*,*S*)-acetate **7** in 59% yield (75% *ds*), together with the diastereomerically enriched (88% *ds*) allyl alcohol (*S*,*R*)-**6**.[32] Saponification of the methyl ester and peptide coupling with the tripeptide **9** provided the chlamydocin linear precursor **10**.

The cyclization was carried out by the pentafluorophenyl ester protocol developed by Schmidt et al.[33] The peptide ester **10** was saponified and coupled with pentafluorophenol to provide the active ester, which was directly subjected to the cyclization step. The Boc protecting group was removed with trifluoroacetic acid, and the resulting TFA salt was added slowly at 50 °C to a vigorously stirred suspension of $CHCl_3$/$NaHCO_3$, giving rise to the cyclization product **11** in 65% yield. The next step, the epoxidation of the allyl alcohol moiety, proved to be more problematic than expected. No reaction was observed under Sharpless' conditions with the Ti complex,[34] even after 1 week, but the V-catalyzed process[35] gave the desired product **12** in excellent yield with 72% *ds*. Catalytic hydrogenation of the double bond and oxidation of the alcohol functionality by the Dess–Martin protocol[36] completed the synthesis of chlamydocin (**1**).



Scheme 2. Synthesis of chlamydocin (**1**).

Conclusions

In conclusion, we have been able to show that the chelate-Claisen rearrangement is an excellent method for the stereoselective synthesis of unusual amino acids such as Aoe and an important tool for natural products synthesis. Further applications directed towards modified chlamydocins and

other members of this interesting class of cyclic peptides are currently under investigation.

Experimental Section

General Remarks: All air- or moisture-sensitive reactions were carried out under argon in oven-dried (65 °C) glassware, which was freshly heated under vacuum before use. Dry solvents were distilled before use: THF was distilled from $LiAlH_4$, CH_2Cl_2 from CaH_2. The products were purified by flash chromatography on silica gel columns (Macherey–Nagel, silica gel 60, 50–200 μm). Analytic TLC was performed on pre-coated silica gel plates (Macherey–Nagel Polygram Sil G/UV_{254}), and UV light, $KMnO_4$ solution, or iodine were used for visualization. Melting points were determined with a melting point apparatus (Büchi) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV-400 spectrometer [400 MHz (^1H), 100 MHz (^{13}C)] in $CDCl_3$ as solvent. Chemical shifts are reported in ppm (δ), and $CDCl_3$ was used for calibration. Diastereomeric ratios were determined by GC (Shimadzu GC 2010, Chirasil-DEX-CB column 25 m × 0.25 μm, N_2 as carrier gas) or HPLC (Shimadzu HPLC 10 A VP, Trentec ReproSil 100 Chiral-NR column 250 × 4.6 mm/8 μm). HRMS spectra were recorded with a Finnigan MAT 95 spectrometer by the CI technique. Elemental analyses were performed at Saarland University.

6-(*tert*-Butyldimethylsilyloxy)octa-1,7-dien-3-ol (2): Diallyl alcohol **E**[37] (6.00 g, 42.2 mmol) was dissolved in dry THF (150 mL), and imidazole (10.1 g, 50.6 mmol) was added, followed by the addition of *tert*-butylchlorodimethylsilane (7.62 g, 50.6 mmol). The reaction mixture was allowed to stir overnight and washed thrice with brine, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 9:1 → 8:2 → 1:1) to afford the monoprotected alcohol **2** (5.57 g, 21.7 mmol, 53%) as a colorless oil.

Unreacted diallyl alcohol **E** (1.20 g, 8.44 mmol, 20%) and the doubly protected alcohol (3.07 g, 8.28 mmol, 20%) were also isolated. R_f = 0.44 (hexanes/EtOAc, 70:30). Major diastereomer: ^1H NMR (400 MHz): δ = 0.03 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.58 (m, 5 H), 4.08 (m, 1 H), 4.15 (m, 1 H), 5.03 (m, 1 H), 5.08 (m, 1 H), 5.13 (m, 1 H), 5.21 (m, 1 H), 5.81 (m, 2 H) ppm. ^{13}C NMR (100 MHz): δ = –4.8, – 4.4, 18.2, 25.9, 32.2, 33.2, 72.9, 73.5, 114.0, 114.6, 141.2, 141.3 ppm. Minor diastereomer: ^1H NMR (400 MHz, selected signals): δ = 0.02 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H) ppm. ^{13}C NMR (100 MHz, selected signals): δ = –4.9, –4.4, 32.5, 33.9, 73.2, 73.6, 114.1, 114.5, 141.1, 141.2 ppm. HRMS (CI) calcd. for $C_{14}H_{29}O_2Si$ $[M + H]^+$: 215.1937; found 215.1929.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)octa-1,7-dien-3-yl Acetate [(*S*,*R*/*S*)-3]: Silyl ether **2** (10.0 g, 39.0 mmol) was dissolved in Et_2O (150 mL), vinyl acetate (2.16 mL, 23.4 mmol) and Novozyme 435 (0.50 g) were added, and the mixture was shaken for 22 h. The enzyme was filtered off and washed twice with Et_2O, and the combined layers were concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 98:2 → 80:20) to yield acetate (*S*,*R*/*S*)-**3** (3.97 g, 13.3 mmol, 34%) as a colorless oil. R_f = 0.61 (hexanes/EtOAc, 70:30). Major diastereomer: ^1H NMR (400 MHz): δ = –0.01 (s, 6 H), 0.85 (s, 9 H), 1.55 (m, 4 H), 2.03 (s, 3 H), 4.08 (m, 1 H), 5.00 (m, 1 H), 5.12 (m, 4 H), 5.77 (m, 2 H) ppm. ^{13}C NMR (100 MHz): δ = –4.9, 18.2, 21.2, 25.8, 29.4, 33.1, 73.1, 74.6, 114.0, 116.7, 136.5, 141.2, 170.3 ppm. Minor diastereomer: ^1H NMR (400 MHz, selected signal): δ = 0.01 (s, 6 H) ppm. ^{13}C NMR (100 MHz, selected signals): δ = –4.4, 29.6, 33.3, 73.3, 74.7, 116.6, 136.5, 141.3 ppm. GC (Chirasil-Dex CB,T_0 [3 min] = 80 °C, 2 °C min^{-1} up to T = 200 °C [20 min], injector = 250 °C, detector = 275 °C): minor diastereomers: t_R = 35.13′, t_R = 35.30′; major diastereomers: t_R = 35.84′, t_R = 36.09′. HRMS (CI) calcd. for $C_{16}H_{31}O_3Si$ $[M + H]^+$: 299.2042; found 299.2010.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)octa-1,7-dien-3-yl 2-(*tert*-Butoxycarbonylamino)acetate [(*S*,*R*/*S*)-4]: Acetate (*S*,*R*/*S*)-**3** (3.90 g, 13.1 mmol) was dissolved in 1,4-dioxane (50 mL), and NaOH (1 M, 15.7 mL, 15.7 mmol) was added at 0 °C. The solution was allowed to stir overnight at room temperature and was then concentrated in vacuo, and the residue was dissolved in EtOAc. After three washes with water, the aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo to provide the alcohol (3.16 g, 12.3 mmol, 94%), which was directly used as crude product for the esterification.

N-Boc-glycine (1.42 g, 8.08 mmol) and the alcohol (2.20 g, 8.08 mmol) were dissolved in Et_2O (120 mL), DMAP (0.20 g, 1.62 mmol) was added, and the solution was cooled to 0 °C. DCC (2.00 g, 9.69 mmol) was added in one portion, and the reaction mixture was allowed to warm to room temperature overnight. The precipitated DCU was filtered through a pad of celite, washed with Et_2O, and the combined ethereal layers were concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc, 85:15) to afford (*S*,*R*/*S*)-**4** (3.34 g, 8.08 mmol, 100%) as a colorless oil. R_f = 0.35 (hexanes/EtOAc, 80:20). Major diastereomer: ^1H NMR (400 MHz): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 1.43 (s, 9 H), 1.59 (m, 4 H), 3.88 (m, 2 H), 4.09 (m, 1 H), 4.97 (br. s, 1 H), 5.02 (m, 1 H), 5.20 (m, 4 H), 5.73 (m, 2 H) ppm. ^{13}C NMR (100 MHz): δ = –4.9, 18.2, 25.8, 28.3, 29.4, 33.0, 42.6, 75.9, 79.9, 114.1, 117.4, 135.9, 141.1, 155.6, 169.9 ppm. Minor diastereomer: ^{13}C NMR ($CDCl_3$, 100 MHz, selected signals): δ = –4.4, 29.6, 33.2, 73.2, 76.0, 117.3, 135.9, 141.2 ppm. HRMS (CI) calcd. for $C_{21}H_{40}NO_5Si$ $[M + H]^+$: 414.2678; found 414.2648.

Methyl (*S*,*E*)-2-(*tert*-Butoxycarbonylamino)-8-(*tert*-butyldimethylsilyloxy)deca-4,9-dienoate [(*S*,*R*/*S*)-5]: A stirred solution of allylic ester (*S*,*R*/*S*)-**4** (3.00 g, 7.26 mmol) and $ZnCl_2$ (1.19 g, 8.73 mmol) in dry THF (40 mL) was cooled to –78 °C. A freshly prepared LDA solution (21.8 mmol) in dry THF (20 mL) was also cooled to –78 °C and added dropwise by transfer cannula to the solution of the allylic ester (*S*,*R*/*S*)-**4**. The solution was allowed to warm to room temperature overnight. The mixture was diluted with Et_2O and quenched with $KHSO_4$ solution (1 M). The aqueous layer was extracted thrice with Et_2O, and the combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo and the residue was dissolved in dry DMF (30 mL), after which potassium carbonate (1.20 g, 8.73 mmol) was added. The suspension was cooled to 0 °C, and methyl iodide (3.09 g, 21.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 5 h, diluted with EtOAc, and washed thrice with water. The organic layer was dried with Na_2SO_4, the solvent was removed in vacuo, and the crude product was purified by column chromatography (silica gel, hexanes/EtOAc, 90:10) to yield the desired methyl ester (*S*,*R*/*S*)-**5** (2.82 g, 6.60 mmol, 91%) as a colorless oil. R_f = 0.53 (hexanes/EtOAc, 90:10). Major diastereomer: ^1H NMR (400 MHz): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 1.42 (s, 9 H), 1.50 (m, 2 H), 2.02 (m, 2 H), 2.41 (m, 2 H), 3.70 (s, 3 H), 4.06 (m, 1 H), 4.30 (m, 1 H), 4.96 (d, J = 7.7 Hz, 1 H), 5.00 (m, 1 H), 5.11 (m, 1 H), 5.26 (m, 1 H), 5.51 (m, 1 H), 5.75 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = –4.8, 18.2, 25.9, 28.3, 35.6, 37.6, 52.1, 53.2, 73.3, 79.8, 113.8, 123.5, 135.1, 141.6, 155.2, 172.7 ppm. Minor

diastereomer: ^{13}C NMR (100 MHz, selected signals): δ = –4.3, 28.2, 37.7, 73.3 ppm. HRMS (CI) calcd. for $C_{22}H_{42}NO_5Si$ [M + H]$^+$: 428.2832; found 428.2844. $C_{22}H_{41}NO_5Si$ (427.66): calcd. C 61.79, H 9.66, N 3.28; found C 61.80, H 9.53, N 3.45.

Methyl (*S*,*E*)-2-(*tert*-Butoxycarbonylamino)-8-hydroxydeca-4,9-dienoate [(*S*,*R*/*S*)-6]: Methyl ester (*S*,*R*/*S*)-**5** (2.48 g, 5.80 mmol) was dissolved in methanol (50 mL), followed by the addition of *p*-TsOH. After 1 h the solution was concentrated in vacuo, dissolved in Et_2O, and washed thrice with water. The ethereal layer was dried with Na_2SO_4, and the solvent was removed in vacuo. Purification of the residue by column chromatography (silica gel, hexanes/EtOAc, 70:30) afforded (*S*,*R*/*S*)-**6** (1.78 g, 5.68 mmol, 98%) as a colorless oil. R_f = 0.10 (hexanes/EtOAc, 70:30). Major diastereomer: ^{1}H NMR (400 MHz): δ = 1.41 (s, 9 H), 1.56 (m, 2 H), 1.63 (br. s, 1 H), 2.09 (dt, *J* = 7.2 Hz, 2 H), 2.43 (m, 2 H), 3.71 (s, 3 H), 4.08 (m, 1 H), 4.30 (m, 1 H), 5.05 (d, *J* = 7.7 Hz, 1 H), 5.09 (ddd, *J* = 10.4, 2.7, 1.4 Hz, 1 H), 5.20 (ddd, *J* = 17.2, 2.6, 1.3 Hz, 1 H), 5.30 (m, 1 H), 5.53 (m, 1 H), 5.84 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 28.3, 28.6, 35.5, 36.3, 52.2, 53.2, 72.5, 79.9, 114.7, 124.0, 134.7, 141.0, 155.2, 172.2 ppm. Minor diastereomer: ^{13}C NMR (100 MHz, selected signals): δ = 28.5, 35.6, 36.2, 72.5, 114.7, 124.2, 134.6, 141.0 ppm.

Methyl (2*S*,8*R*,*E*)-2-(*tert*-Butoxycarbonylamino)-8-hydroxydeca-4,9-dienoate [(*S*,*R*)-6] and Methyl (2*S*,8*S*,*E*)-8-Acetoxy-2-(*tert*-butoxycarbonylamino)deca-4,9-dienoate [(*S*,*S*)-7]: Allylic alcohol (*S*,*R*/*S*)-**6** (1.40 g, 4.47 mmol) was dissolved in vinyl acetate (2.06 mL, 22.3 mmol), and Novozyme 435 (0.07 g) was added. After the reaction mixture had been shaken for 2 d, the enzyme was filtered off, the system was washed with Et_2O, and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 75:25) to provide allyl alcohol (*S*,*R*)-**6** (0.49 g, 1.57 mmol, 35%) and acetate (*S*,*S*)-**7** (0.95 g, 2.66 mmol, 59%), both as colorless oils.

Compound (*S*,*R*)-6: R_f = 0.19 (hexanes/EtOAc, 70:30). $[\alpha]_D^{20}$ = +5.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 1.42 (s, 9 H), 1.57 (m, 2 H), 1.63 (br. s, 1 H), 2.09 (m, 2 H), 2.42 (m, 2 H), 3.71 (s, 3 H), 4.09 (m, 1 H), 4.30 (m, 1 H), 5.05 (d, *J* = 7.3 Hz, 1 H), 5.09 (m, 1 H), 5.21 (m, 1 H), 5.30 (m,1 H), 5.53 (m, 1 H), 5.84 (ddd, *J* = 17.0, 10.4, 6.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 28.5, 35.6, 36.2, 52.2, 53.2, 72.5, 79.9, 114.7, 124.2, 134.6, 141.0, 155.2, 172.7 ppm. HRMS (CI) calcd. for $C_{16}H_{28}NO_5$ [M + H]$^+$: 314.1967; found 314.1928. HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes/^{i}PrOH 97:3, flow = 1 mL min^{-1}): t_R (*R*,*R*)-**6** = 40.28′, t_R (*R*,*S*)-**6** = 44.97′, t_R (*S*,*R*)-**6** = 46.65′, t_R (*S*,*S*)-**6** = 53.48’ (determined after conversion of the alcohol functionality to the corresponding *p*-nitrophenyl ester).

Compound (*S*,*S*)-7: R_f = 0.28 [hexanes/EtOAc, 70:30]. $[\alpha]_D^{20}$ = +18.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 1.41 (s, 9 H), 1.63 (m, 2 H), 2.01 (m, 2 H), 2.02 (s, 3 H), 2.42 (m, 2 H), 3.70 (s, 3 H), 4.31 (m, 1 H), 5.03 (d, *J* = 7.5 Hz, 1 H), 5.18 (m, 3 H), 5.29 (m, 1 H), 5.49 (m, 1 H), 5.73 (m, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 21.2, 28.1, 28.3, 33.7, 33.5, 52.2, 53.2, 74.1, 79.8, 116.8, 125.5, 133.8, 136.2, 155.2, 170.2, 172.6 ppm. HRMS (CI) calcd. for $C_{18}H_{29}NO_6$ [M]$^+$: 355.1995; found 355.1956.; $C_{18}H_{29}NO_6$ (355.43): calcd. C 60.83, H 8.22, N 3.94; found C 60.98, H 8.15, N 4.15. HPLC (Reprosil 100 Chiral-NR 8 µm, hexanes/^{i}PrOH 97:3, flow = 1 mL min^{-1}): t_R (*R*,*R*)-**7** = 39.66′, t_R (*R*,*S*)-**7** = 43.64′, t_R (*S*,*R*)-**7** = 46.35′, t_R (*S*,*S*)-**7** = 51.96’ (determined after conversion of the acetate functionality to the corresponding *p*-nitrophenyl ester).

***N*-Boc-Aib-(*S*)-Phe-OMe (8):**[38] *N*-Boc-AibOH (4.58 g, 22.5 mmol) was dissolved in dry THF (100 mL), *N*-methylmorpholine (2.47 mL, 22.5 mmol) was added, and the solution was cooled to –20 °C. Isobutyl chloroformate (2.92 mL, 22.5 mmol) was added dropwise, together with further *N*-methylmorpholine (2.60 mL, 23.6 mmol). (*S*)-Phenylalanine methyl ester hydrochloride (4.86 g, 22.5 mmol) was added in one portion. After warming up to room temperature overnight, the suspension was washed with saturated $NaHCO_3$ solution and $KHSO_4$ solution (1 M). The organic layer was dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by recrystallization from petroleum ether/CH_2Cl_2 to provide **8** (6.48 g, 17.8 mmol, 79%) as a white solid. Spectroscopic data were in accordance with those reported in the literature.[39]

***N*-Boc-Aib-(*S*)-Phe-(*R*)-Pro-OMe (9):**[40] Dipeptide **8** (2.37 g, 6.50 mmol) was dissolved in 1,4-dioxane (30 mL), and NaOH (1 M, 7.15 mL, 7.15 mmol) was added at 0 °C. After complete conversion (monitored by TLC), the solvent was removed in vacuo and the residue was dissolved in water. The aqueous solution was extracted thrice with Et_2O and then acidified to pH 2 with $KHSO_4$ solution (1 M). The resulting emulsion was extracted thrice with EtOAc, and the combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo, and the carboxylic acid (2.28 g, 6.50 mmol, 100%) was used as crude product for the peptide coupling.

The free acid (0.91 g, 2.58 mmol), TBTU (0.83 g, 2.58 mmol), and HOBt (0.40 g, 2.58 mmol) were suspended in CH_3CN (20 mL). DIPEA (0.68 g, 5.29 mmol) was added, followed by the addition of (*R*)-proline methyl ester hydrochloride (0.39 g, 2.35 mmol) in one portion. The reaction mixture was allowed to stir overnight. The resulting suspension was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and $KHSO_4$ solution (1 M). The organic layer was dried with Na_2SO_4, the solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, hexanes/EtOAc, 40:60). Tripeptide **9** (0.92 g, 1.99 mmol, 85%) was obtained as a white solid; m.p. 97–98 °C. R_f = 0.29 (hexanes/EtOAc, 30:70). $[\alpha]_D^{20}$ = +102.5 (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz): δ = 1.39 (m, 15 H), 1.83 (m, 4 H), 2.60 (m, 1 H), 2.89 (dd, *J* = 12.9, 9.7 Hz, 1 H), 3.06 (dd, *J* = 12.9, 4.9 Hz, 1 H), 3.48 (m, 1 H), 3.65 (s, 3 H), 4.27 (dd, *J* = 8.2, 3.9 Hz, 1 H), 4.89 (ddd, *J* = 9.7, 8.4, 4.9 Hz, 1 H), 4.94 (br. s, 1 H), 6.92 (d, *J* = 8.3 Hz, 1 H), 7.20 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 24.3, 24.9, 26.2, 28.3, 28.9, 39.7, 46.7, 52.1, 52.5, 56.6, 58.7, 80.0, 126.9, 128.3, 129.6, 136.4, 154.2, 169.8, 172.1, 173.9 ppm. Minor rotamer: ^{1}H NMR (400 MHz, selected signals): δ = 2.22 (m, 4 H), 2.83 (m, 1 H), 3.11 (dd, *J* = 14.0, 4.8 Hz, 1 H), 3.56 (m, 1 H), 3.68, (s, 3 H), 4.72 (m, 1 H), 4.82 (br. s, 1 H), 6.72 (d, *J* = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, selected signals): δ = 22.5, 28.2, 31.0, 37.8, 46.5, 51.7, 56.5, 59.2, 126.6, 128.3, 129.2, 136.9, 170.6, 172.8, 174.0 ppm. HRMS (CI) calcd. for $C_{24}H_{35}N_3O_6$ [M]$^+$: 461.2526; found 461.2623. $C_{24}H_{35}N_3O_6$ (461.56): calcd. C 62.45, H 7.64, N 9.10; found C 62.65, H 7.43, N 8.81.

Tetrapeptide 10: Allylic alcohol (*S*,*R*)-**6** (0.47 g, 1.50 mmol) was dissolved in 1,4-dioxane (10 mL), and NaOH (1 M, 1.65 mL, 1.65 mmol) was added at 0 °C. After complete conversion (monitored by TLC) the solvent was removed in vacuo and the residue was dissolved in water. The aqueous solution was extracted thrice with Et_2O and then acidified to pH 2 with $KHSO_4$ solution (1 M). The resulting emulsion was extracted thrice with EtOAc, and the combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo, and the acid (0.45 g, 1.50 mmol, 100%) obtained was used as crude product for the peptide coupling.

Tripeptide **9** (0.79 mg, 1.70 mmol) was dissolved in CH_2Cl_2, and HCl solution in 1,4-dioxane (4 M, 4.25 mL, 17.0 mmol) was added dropwise at 0 °C. After 15 min at that temperature the reaction mixture was allowed to stir at room temperature until Boc removal

was complete (monitored by TLC). The solvent was removed in vacuo, and the resulting hydrochloride salt was added to a stirred emulsion of sat. $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was extracted thrice with CH_2Cl_2 and dried with Na_2SO_4, and the solvent was removed in vacuo. The obtained amine (0.60 g, 1.65 mmol) and the acid (0.45 g, 1.50 mmol) were dissolved in dry CH_2Cl_2, and TBTU (0.53 g, 1.65 mmol) was added at 0 °C. After the addition of Et_3N (0.17 g, 1.65 mmol), the mixture was allowed to warm to room temperature overnight. The reaction mixture was washed with $KHSO_4$ solution (1 M), sat. $NaHCO_3$ solution, and water. The organic layer was dried with Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc, 30:70 → 10:90) to yield tetrapeptide **10** (0.91 g, 1.42 mmol, 95%) as a viscous oil. R_f = 0.09 (hexanes/EtOAc, 30:70). $[\alpha]_D^{20}$ = +17 (*c* = 1.0, $CHCl_3$). Major rotamer/diastereomer: ^{1}H NMR (400 MHz): δ = 1.38 (s, 9 H), 1.41 (s, 3 H), 1.47 (s, 3 H), 1.53 (m, 3 H), 1.81 (m, 3 H), 2.09 (m, 2 H), 2.36 (m, 2 H), 2.47 (br. s, 1 H), 2.65 (m, 1 H), 2.88 (m, 1 H), 2.98 (dd, *J* = 13.0, 5.2 Hz, 1 H), 3.49 (m, 1 H), 3.61 (s, 3 H), 3.98 (br. s, 1 H), 4.05 (m, 1 H), 4.24 (m, 1 H), 4.84 (m, 1 H), 5.02 (m, 1 H), 5.15 (m, 2 H), 5.34 (m, 1 H), 5.50 (m, 1 H), 5.80 (m, 1 H), 6.76 (s, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 7.15 (m, 5 H) ppm. ^{13}C NMR (100 MHz): δ = 24.3, 25.5, 28.2, 28.4, 28.9, 35.2, 36.2, 39.2, 46.7, 52.1, 52.5, 54.4, 56.9, 58.7, 72.0, 80.1, 114.2, 125.0, 126.8, 128.3, 129.5, 134.5, 136.3, 141.2, 155.6, 169.8, 170.9, 172.1, 173.5 ppm. Minor rotamer and diastereomer: ^{1}H NMR (400 MHz, selected signals): δ = 1.37, 1.39 (2 × s, 9 H), 1.43, 1.44 (2 × s, 6 H), 2.81 (m, 1 H), 3.05 (m, 1 H), 3.64, 3.66 (2 × s, 3 H), 3.89 (br. s, 1 H), 4.39 (m, 1 H), 4.62 (m, 1 H), 4.98 (m, 1 H), 6.63, 6.70, 6.74 (3 × s, 1 H), 6.82, 6.98 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, selected signals): δ = 22.4, 24.8, 24.9, 31.0, 36.2, 39.1, 46.6, 46.9, 52.5, 52.6, 56.8, 59.0, 59.2, 72.1, 114.1, 114.3, 126.5, 126.8, 128.2, 129.2, 129.7, 136.4, 136.9, 169.7, 170.6, 170.8, 172.2, 172.7, 174.1 ppm. HRMS (CI) calcd. for $C_{34}H_{51}N_4O_8$ $[M + H]^+$: 643.3707; found 643.3519.

Cyclotetrapeptide 11

Preparation of the Pentafluorophenol Ester: Tetrapeptide **10** (500 mg, 0.78 mmol) was dissolved in 1,4-dioxane (10 mL), and NaOH (1 M, 0.85 mL, 0.85 mmol) was added at 0 °C. After complete saponification (monitored by TLC), the solvent was removed in vacuo and the residue was dissolved in water. The aqueous solution was extracted thrice with Et_2O and then acidified to pH 2 with $KHSO_4$ solution (1 M). The resulting emulsion was extracted thrice with EtOAc, and the combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo to afford the crude acid (442 mg, 0.70 mmol, 90%). The acid (315 mg, 0.50 mmol) was dissolved in Et_2O, pentafluorophenol (92.0 mg, 0.50 mmol) was added, and the solution was cooled to 0 °C. After addition of DCC (104 mg, 0.50 mmol) the reaction mixture was allowed to warm up to room temperature overnight. The precipitated DCU was filtered through a pad of celite, washed with Et_2O, and the combined ethereal layers were concentrated in vacuo. Filtration through a small pad of silica gel (hexanes/EtOAc, 40:60) yielded the pentafluorophenol ester of **10** (290 mg, 0.36 mmol, 73%), which was directly subjected to the cyclization step.

Cyclization: The active ester (111 mg, 0.14 mmol) was dissolved in dry CH_2Cl_2, and trifluoroacetic acid (0.14 mL) was added at 0 °C. After Boc removal was complete (monitored by TLC), the solvent was removed in vacuo. The residue was dissolved in CH_3CN (10 mL) and added by syringe pump at 50 °C over 5 h to a rigorously stirred emulsion of saturated $NaHCO_3$ solution (12.5 mL) and $CHCl_3$ (87.5 mL). After the addition was complete the mixture was stirred for 30 min at the same temperature. The aqueous layer was extracted thrice with CH_2Cl_2, and the combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo, and after purification by column chromatography (silica gel, hexanes/EtOAc, 30:70), cyclic tetrapeptide **11** (46 mg, 0.09 mmol, 65%) was obtained as a white foam. R_f = 0.12 (hexanes/EtOAc, 30:70). $[\alpha]_D^{20}$ = –84 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 1.22 (s, 3 H), 1.47 (m, 2 H), 1.64 (m, 5 H), 2.00 (m, 2 H), 2.07 (m, 1 H), 2.21 (m, 2 H), 2.41 (m, 1 H), 2.84 (dd, *J* = 13.5, 5.7 Hz, 1 H), 3.13 (m, 2 H), 3.74 (m, 1 H), 3.99 (m, 1 H), 4.14 (dt, *J* = 10.2, 7.5 Hz, 1 H), 4.55 (m, 1 H), 4.99 (m, 1 H), 5.04 (m, 1 H), 5.11 (m, 1 H), 5.27 (m, 1 H), 5.46 (m, 1 H), 5.75 (m, 1 H), 6.08 (s, 1 H), 7.06 (d, *J* = 10.5 Hz, 1 H), 7.14 (m, 5 H), 7.41 (d, *J* = 10.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 23.5, 24.7, 24.9, 26.3, 28.4, 32.2, 35.8, 36.3, 46.9, 53.4, 54.2, 57.7, 58.7, 72.2, 114.5, 124.8, 126.6, 128.5, 129.0, 133.8, 137.0, 141.0, 171.2, 172.8, 174.0, 175.6 ppm. HRMS (CI) calcd. for $C_{28}H_{39}N_4O_5$ $[M + H]^+$: 511.2920; found 511.2945.

Epoxy Alcohol 12: Cyclic tetrapeptide **11** (64 mg, 125 μmol) was dissolved in dry CH_2Cl_2 (1 mL), and $VO(acac)_2$ (496 μL, 1.88 μmol) was added dropwise as a CH_2Cl_2 solution [1 mg $VO(acac)_2$/1 mL dry CH_2Cl_2]. After 5 min a solution of *tert*-BuOOH in decane (5.5 M, 30.2 μL, 163 μmol) was added, and the solution was allowed to stir overnight at room temperature. The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 97:3) to afford epoxy alcohol **12** (60 mg, 114 μmol, 90%) as a yellowish oil. R_f = 0.11 (CH_2Cl_2/MeOH, 97:3). ^{1}H NMR (400 MHz): δ = 1.31 (s, 3 H), 1.60 (m, 3 H), 1.74 (m, 2 H) 1.74 (s, 3 H), 2.15 (m, 2 H), 2.31 (m, 2 H), 2.49 (m, 1 H), 2.66 (dd, *J* = 4.9, *J* = 2.8 Hz, 0.3 H), 2.70 (dd, *J* = 5.0, *J* = 4.0 Hz, 0.7 H), 2.77 (m, 1 H), 2.94 (m, 2 H), 3.21 (m, 2 H), 3.81 (m, 2 H), 4.21 (dt, *J* = 10.2, 7.4 Hz, 1 H), 4.63 (m, 1 H), 5.13 (td, *J* = 10.1, 5.8 Hz, 1 H), 3.39 (m, 1 H), 5.54 (m, 1 H), 5.97 (br. s, 1 H), 7.11 (d, *J* = 10.3 Hz, 1 H), 7.22 (m, 5 H), 7.45 (d, *J* = 10.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 23.5, 24.7, 25.0, 26.4, 28.3, 32.2, 32.8, 35.8, 43.5, 45.0, 47.0, 53.4, 54.2, 54.4, 57.9, 58.8, 67.8, 125.1, 126.7, 128.6, 129.0, 133.6, 137.0, 171.7, 172.8, 174.0, 175.6 ppm. HRMS (CI) calcd. for $C_{28}H_{38}N_4O_6$ $[M]^+$: 526.2791; found 526.2772.

Chlamydocin (1): Epoxy alcohol **12** (20 mg, 38.0 μmol) was dissolved in MeOH (5 mL), and the system was stirred under hydrogen in the presence of Pd on charcoal (5%, 1.08 mg). After the hydrogenation was complete (monitored by TLC), the catalyst was filtered off and washed with EtOAc, and the solvent was removed in vacuo. The residue was dissolved in dry CH_2Cl_2 (1 mL) and added to a solution of DMP (32.2 mg, 76.0 μmmol) in dry CH_2Cl_2 (1 mL). After 3 h the precipitated solid was filtered off, and the residue was filtered through a short pad of silica gel ($CHCl_3$/MeOH, 99:1) to provide **1** (14 mg, 26.6 μmol, 70%). R_f = 0.20 ($CHCl_3$/MeOH, 99:1). Major diastereomer: ^{1}H NMR (400 MHz): δ = 1.28 (m, 4 H), 1.32 (s, 3 H), 1.67 (m, 6 H), 1.75 (s, 3 H), 2.15 (m, 1 H), 2.33 (m, 3 H), 2.84 (dd, *J* = 5.8, 2.5 Hz, 1 H), 2.93 (dd, *J* = 13.8, 6.0 Hz, 1 H), 2.97 (dd, *J* = 5.8, 4.7 Hz, 1 H), 3.22 (m, 2 H), 3.40 (dd, *J* = 4.6, 2.5 Hz, 1 H), 3.83 (m, 1 H), 4.17 (m, 1 H), 4.64 (m, 1 H), 5.14 (td, *J* = 10.1, 5.8 Hz, 1 H), 5.95 (s, 1 H), 7.08 (d, *J* = 9.4 Hz, 1 H), 7.22 (m, 5 H), 7.49 (d, *J* = 10.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 22.7, 23.5, 24.8, 25.0, 25.3, 26.5, 28.9, 29.7, 35.8, 35.9, 46.1, 47.0, 53.4, 54.3, 57.8, 58.8, 126.7, 128.6, 129.0, 137.0, 171.8, 172.8, 174.4, 175.6, 207.6 ppm. Minor diastereomer: ^{13}C NMR (100 MHz, selected signals): δ = 22.8, 23.6, 29.4, 36.3, 54.3, 174.3 ppm. No signals could be detected in ^{1}H NMR; only a slight splitting of the amide protons was observed. HRMS (CI) calcd. for $C_{28}H_{39}N_4O_6$ $[M + H]^+$: 527.2870; found 527.2867.

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[32] In principle the (*S*,*S*)-acetate **7**, with the "wrong" stereogenic center for the epoxidation, could have been inverted by use of chemical procedures such as oxidation and chiral reduction after cleavage of the acetate functionality to increase the yield of the desired allyl alcohol (*S*,*R*)-**6**. In our case we decided to use (*S*,*S*)-**7** as a precursor for (*S*)-Aoda [as present in, for example, apicidine (Figure 1)], the synthesis of which is currently under investigation.
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