Total Synthesis and Absolute Configuration of Minalemine A, a Guanidine Peptide from the Marine Tunicate *Didemnum rodriguesi*

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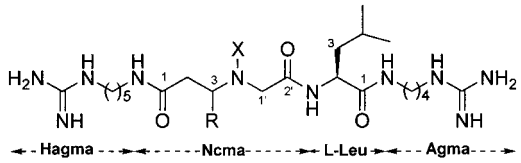
The total synthesis of the 3*S*,2*S* and 3*R*,2*S* diastereomers (**1a** and **1b**) of minalemine A and the identification of the natural compound as the 3*R*,2*S* isomer is described. The key step in the synthesis is the preparation of the two enantiomers of the *β*-amino diacid 3-(*N*-carboxymethyl)-aminodecanoic acid (Ncma), which were obtained by stereoselective alkylation with allyl bromide of two nonanoic acid imides bearing chiral oxazolidinones as chiral auxiliaries. Natural minalemine A shows identical ^{1}H NMR and very similar ^{13}C NMR spectra compared to the two synthetic diastereomers. Sufficient differences in their chromatographic behavior to allow conclusive identification were not found. However, the corresponding *N*-2-naphthoyl amides presented quite distinct circular dichroism spectra (CD), and these confirmed the 3*R*,2*S* configuration for the natural minalemines and the *R* configuration for the constituent *β*-amino diacid, Ncma.

Introduction

Marine tunicates belonging to the genus *Didemnum* (Phylum Chordata, class Ascidiacea) have proven to be a particularly rich source of structurally diverse and biologically potent marine metabolites.[1] Most of these metabolites are nitrogen-containing compounds derived from amino acids, such as cyclic and acyclic peptides, and aromatic alkaloids. Some representative examples of the first group are the hexapeptides comoramides A and B and the heptapeptides mayotamides A and B,[2] isolated from *D. molle*. Recent examples of aromatic alkaloids are the novel predator antideterrant didemnimides A−D[3] and the aromatic alkaloids granulatimide and isogranulatimide,[4] from the Brazilian ascidian *D. granulata*.

As a result of our studies on the biologically active extracts from the tunicate *D. rodriguesi*, we reported some time ago the guanidinic peptide caledonin A[5] and, more recently, the isolation of minalemines A−F,[6] the first examples in nature of sulfamic acid guanidine derivatives.

Minalemines are relatively small peptide-like compounds (Figure 1) that consist of L-leucine and an amino diacid, 3-(*N*-carboxymethyl)aminodecanoic acid (Ncma), which can be viewed either as an *N*-carboxymethyl long chain *β*-amino acid or as a nitrogen-modified glycine. In minalemines, these two amino acids are linked by an amide bond between the L-Leu amino group and the carboxyl group on the nitrogen side chain of Ncma. The two remaining carboxyl groups are bonded to the amino group of two different α,*ω*-aminoguanidines: the carboxyl group of leucine is bonded to agmatine (Agma) and the carboxyl group of the *β*-amino acid is bonded to homoagmatine (Hagma). The individual minalemines differ in the chain length of the *β*-amino acid Ncma (10, 11, or 12 carbons) and in the presence or absence of a sulfamic acid group on the nitrogen of the same residue (Figure 1).



minalemine	X	R
A	H	C_7H_{15}
B	H	C_8H_{17}
C	H	C_9H_{19}
D	SO_3H	C_7H_{15}
E	SO_3H	C_8H_{17}
F	SO_3H	C_9H_{19}

Figure 1. Structure of minalemines.

Their structures, elucidated by spectroscopic (1D and 2D NMR) and spectrometric (MS) methods, are characterized by the presence of two asymmetric carbons. The absolute stereochemistry at C-2 in the leucine residue was determined to be *S* by acid hydrolysis of minalemine A and comparison with authentic standards by chiral GC.

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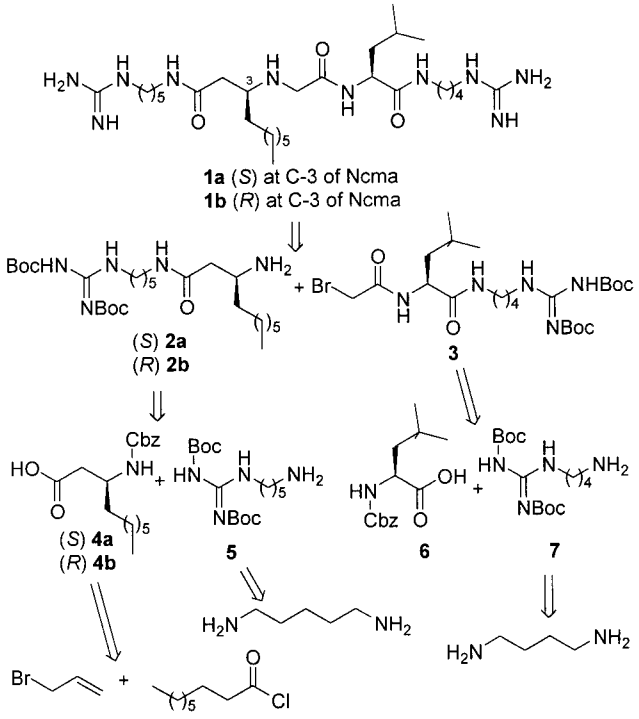
Scheme 1



However, the absolute configuration at C-3 in the *β*-amino acid Ncma could not be established and remains unknown.

In this paper we present our results on the stereospecific synthesis of the two enantiomers of the *β*-amino acid Ncma and, subsequently, of the two diastereomers (3*S*,2*S*)-**1a** and (3*R*,2*S*)-**1b** of minalemine A (Scheme 1). Comparison of the spectroscopic properties of the two synthetic diastereomers with those of the natural compound unambiguously proved that the absolute configuration of natural minalemine A is 3*R*,2*S*.

Results and Discussion

Leucine is commercially available, and protected agmatine and homoagmatine can be prepared by guanilation of cadaverine and putrescine, respectively. For this reason the main synthetic problem in this study involved the stereoselective synthesis of the two enantiomers of the *β*-amino acid Ncma (**4a/4b**) and their coupling to the other structural fragments, as shown in Scheme 1.

According to this retrosynthetic analysis, the last synthetic step is the connection of the chiral fragments **2a** and **2b** with the bromide **3** by N-alkylation of the primary amino group of **2**. Compounds **2a** and **2b** were easily prepared by coupling of the two enantiomers of Ncma, **4a** and **4b**, with protected Hagma **5**. Compound **3** was synthesized by the sequential coupling of Cbz-protected[7] L-leucine **6** with protected Agma **7** followed by treatment with bromoacetic acid.

In this way, the synthesis is highly convergent since both diastereomers **1a** and **1b** are prepared from a common fragment **3**. In addition, the coupling steps involving leucine are performed at the N-terminus, thus avoiding potential racemization at its chiral center.

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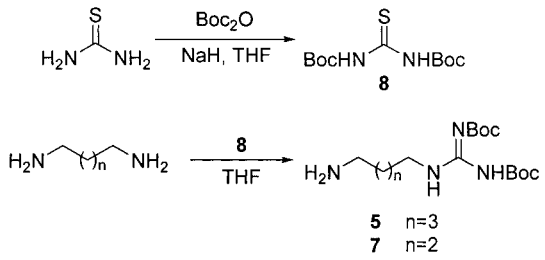
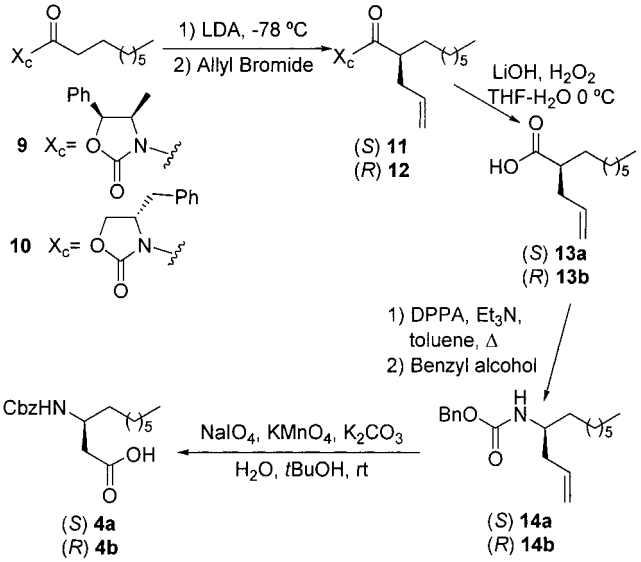
Scheme 2



Scheme 3



Protected agmatine **7** and protected homoagmatine **5** were prepared by guanilation of the corresponding α,*ω*-diamines with the thiourea derivative **8** (Scheme 2). *N*,*N*′-Di-*tert*-butoxycarbonyl thiourea **8** was obtained by treatment of thiourea with sodium hydride and a slight excess of di-*tert*-butyl dicarbonate (BOC_2O).[8] Reaction of cadaverine and putrescine with reagent **8** smoothly afforded the required protected α,*ω*-aminoguanidines Hagma (**5**) and Agma (**7**) respectively, in high yields.

The strategy for the stereocontrolled synthesis of the long chain *β*-amino acids[9,10] **4a/4b** hinges on the stereoselective alkylation of a long chain acid derivatized with an Evans' chiral auxiliary (Scheme 3).[11] This reaction guarantees a high degree of optical purity in the two

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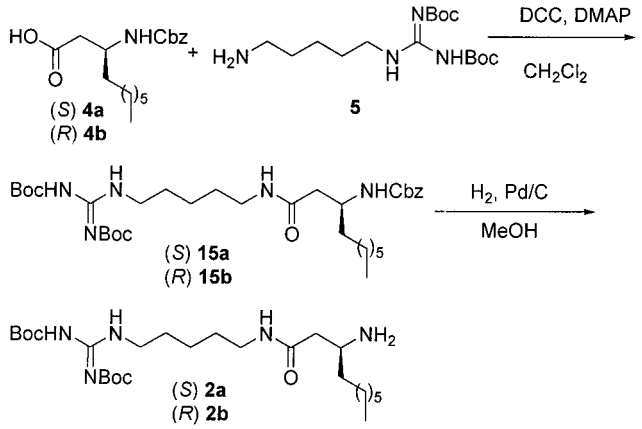
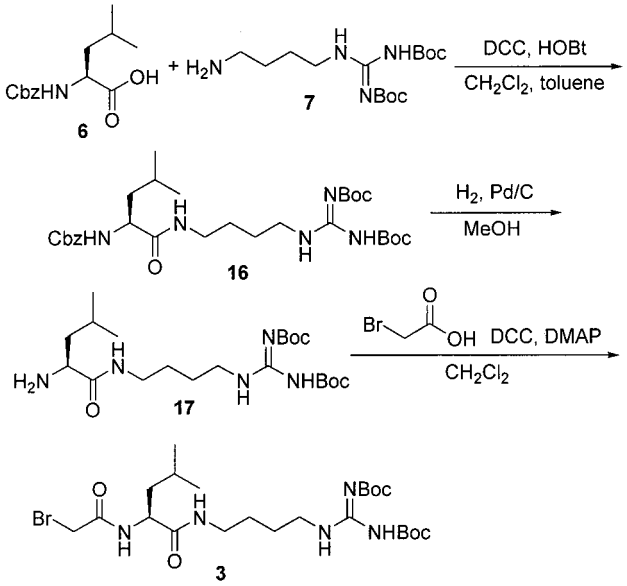
Scheme 4



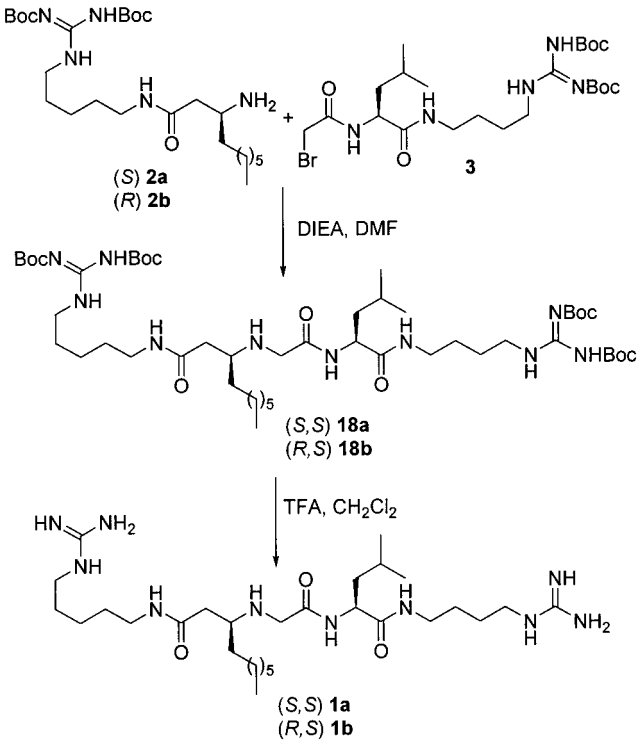
enantiomers. It also provides functional groups that can be easily modified to the target compounds by suitable reactions: the carboxyl group of **13** can be converted to an amine group, as in **14**, and thereafter the terminal olefin can be converted to the acid, **4**. The chiral auxiliaries selected for the preparation of each enantiomer are shown in Scheme 3 and were prepared by reaction of L-phenylalaninol and commercially available (1*S*,2*R*)-norephedrine with diethyl carbonate in the usual way.[12] L-Phenylalaninol was easily prepared by reduction of L-phenylalanine with the iodine−borohydride system proposed by Meyers.[13] Thus, both oxazolidinones were sequentially treated with *n*-butyllithium and nonanoyl chloride to give the imides **9** and **10** in good yields. Compounds **9** and **10** were alkylated by sequential treatment with LDA and allyl bromide to give compounds **11** and **12**.[14] Their ^{1}H NMR spectra showed no appreciable signals of their diastereomers, thus ensuring high optical purity at the new chiral center. Acids **13a** and **13b** were obtained in high yield after cleavage of the chiral auxiliaries with lithium hydroperoxide. The carboxylic acid group of **13** was converted into the protected carboxybenzyl amino group through a Curtius-type rearrangement[15] by treatment with diphenylphosphoryl azide (DPPA) and subsequent trapping of the isocyanate intermediate with benzyl alcohol. The protected amines **14a** and **14b** afforded the acids **4a/4b** by oxidative cleavage of the double bond using the conditions proposed by Lemieux and Rudloff ($NaIO_4$ and a catalytic amount of $KMnO_4$ in a basic medium).[16] Cbz-N-protected-β-amino acids **4a** and **4b** were obtained in an optically pure form in an overall yield of 53%.

Having obtained all of the components required for the final synthesis, we proceeded to their assembly in the following way. Coupling of the two enantiomers of the N-protected β-amino acid (**4a** and **4b**) with protected Hagma **5** (Scheme 4) using the DCC/DMAP protocol afforded **15a** and **15b** in moderate yields. Hydrogenolysis

Scheme 5



Scheme 6



of **15a** and **15b** provided compounds **2a** and **2b** in nearly quantitative yield.

On the other hand, Cbz-protected L-leucine **6** was coupled with protected Agma **7** using the DCC/HOBt protocol to provide **16** in moderate yield (Scheme 5). Deprotection of **16** by hydrogenolysis and further coupling of **17** with bromoacetic acid in the presence of DCC (Scheme 5) afforded compound **3**.

Subsequently, reaction of each enantiomer **2a**/**2b** with **3** in the presence of Hunig's base in DMF provided the fully protected minalemine A derivatives **18a** and **18b** in moderate yield (Scheme 6). When this reaction was carried out with model compounds, such as β-alanine, the dialkylation product was obtained in relative high yield. However, the reaction with fragments **2a/2b** only af-

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forded the monoalkylation product in moderate yield. We ascribed this behavior to the long chain β-amino acid steric hindrance. Since we obtained enough material for the final reaction, we did not attempt to optimize the reaction yield. Finally, complete deprotection was achieved by acidolysis of the *tert*-butyl carbamates in a TFA/dichloromethane solution to afford the diastereomers **1a** and **1b**, which were isolated and purified by HPLC and handled as trifluoroacetates for all further work.

Comparison between Synthetic 1a and 1b and Natural Minalemine A. Despite all our efforts to find appropriate experimental conditions for the effective chromatographic separation of diastereoisomers **1a** and **1b** for their comparison with natural minalemine A, we could not distinguish the two compounds by chromatographic methods. Thus, TLC and analytical reversed-phase HPLC showed, in all attempts, only a single spot (e.g., *n*-BuOH/AcOH/H_2O, 12:3:5; $R_f = 0.5$) and a single peak (μ-Bondapak C-18 MeOH/H_2O/TFA, 60:40:0.1; t_R = 9.8 min), respectively, for both compounds. This behavior is also coincident with that shown by natural minalemine A. Normal-phase HPLC could not be performed effectively as a result of the low solubility of the salts in normal organic solvent systems.

We also attempted to carry out the identification by comparison of the specific optical rotations. Unfortunately, however, the values measured for diastereoisomers **1a** and **1b** (−2.4, c = 0.56 and −9.9, c = 1.23, respectively) are significantly different from the value reported for the natural product (−22.8, c = 0.002), thus rendering this method ineffective in this case.

This difference in the optical rotation values warrants further comment. In our opinion, the discrepancy does not solely arise from the different concentrations of the solutions used in the experiment but principally from the nature and concentration of the anion accompanying the natural minalemines.[17] The synthetic diastereoisomers were prepared as trifluoroacetate salts, but the counterion of the natural sample is not known.

A detailed comparison of the ^{1}H and ^{13}C NMR spectra of **1a** and **1b** with those of natural minalemine A, measured in the same spectrometer, showed only tiny differences in a few chemical shifts. These differences are smaller than 0.06 ppm in the ^{1}H NMR spectrum and 0.2 ppm in the ^{13}C NMR spectrum and are of limited use for our purpose. Thus, the ^{1}H NMR spectra of minalemine A are practically identical to those of the synthetic compounds **1a** and **1b**. On the other hand, the profile of the plots for the ^{13}C NMR chemical shifts show some differences in the carbons close to the asymmetric carbon under scrutiny (C-3 of Ncma), and this points to a greater similarity between natural minalemine A and **1b** (Figure 2). Diastereomer **1b** displays chemical shifts for C-2, C-3, and C-4 of Ncma that are virtually identical to those of minalemine A, while **1a** shows larger differences in these signals. In fact, it is in this region of the spectra where the differences in chemical shifts are most marked. Therefore, if minalemine A is identical to **1b**, its absolute configuration should be 3*R*,2*S* and that of Nmca at C-3 should be *R*.

Nevertheless, the limited significance of these data prompted us to confirm the proposed stereochemistry by other means, particularly by circular dichroism (CD). The

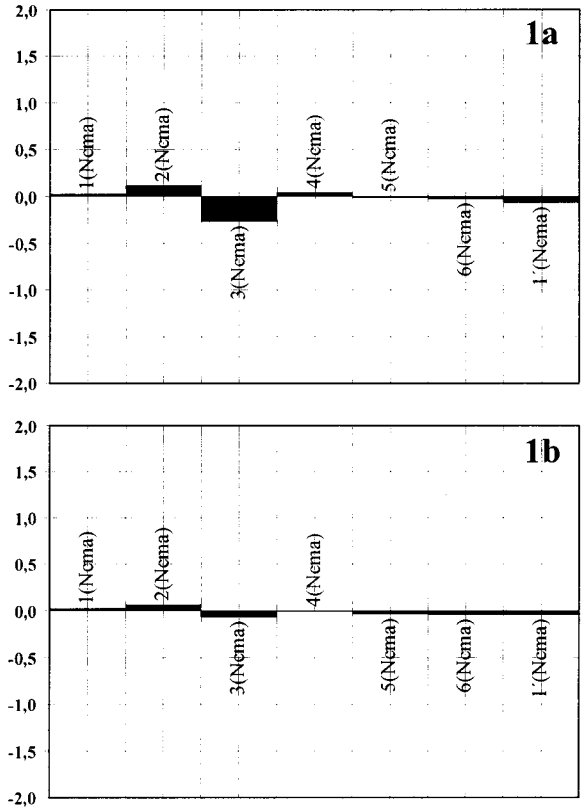

Figure 2. Difference in ^{13}C NMR chemical shifts between minalemine A and compound **1a** and between minalemine A and compound **1b**. The *x*-axis represents the carbon number and the *y*-axis represents $\Delta\delta$ ($\Delta\delta = \delta_{\text{minalemine A}} - \delta_{\text{synthetic compound}}$).

CD spectra of natural minalemine A and the synthetic samples (**1a** and **1b**) are all very weak as a result of the absence of a strong chromophore, and unfortunately this makes meaningful comparisons impossible. To overcome this drawback, and after several unsuccessful attempts, we managed to introduce a naphthoic acid group as an auxiliary chromophore on the secondary amine group close to the C-3 chiral center of the three compounds. This was achieved by dissolving the synthetic diastereomers **1a** and **1b** and minalemine A in pyridine and adding 2-naphthoyl chloride. The mixture was allowed to react for 24 h (Scheme 7). Purification by reversed-phase HPLC afforded derivatives **1c**, **1d**, and **1e**, respectively, and these showed identical retention times under a variety of conditions.

The CD and UV spectra of these three derivatives were found to be very useful for comparisons (Figure 3). The CD curves of **1d** and **1e** are practically superimposable and present a positive band centered at 231 nm, while **1c** shows a rather different CD spectrum with a positive band at 250 nm. These data confirm the coincidence of minalemine A with **1b**, the absolute configuration of the natural minalemines as 3*R*,2*S*, and the absolute configuration of the Ncma residue as *R*.

Experimental Section

General Procedures. THF was distilled from the Na/benzophenone system. Flash chromatography was carried out with silica gel 60 (230−400 mesh). TLC chromatography was done with silica gel 60 F_{254} on coated aluminum or glass plates. Compounds were visualized using UV light, iodine vapor, $KMnO_4$ aqueous solution, or a ninhydrin ethanolic solution.

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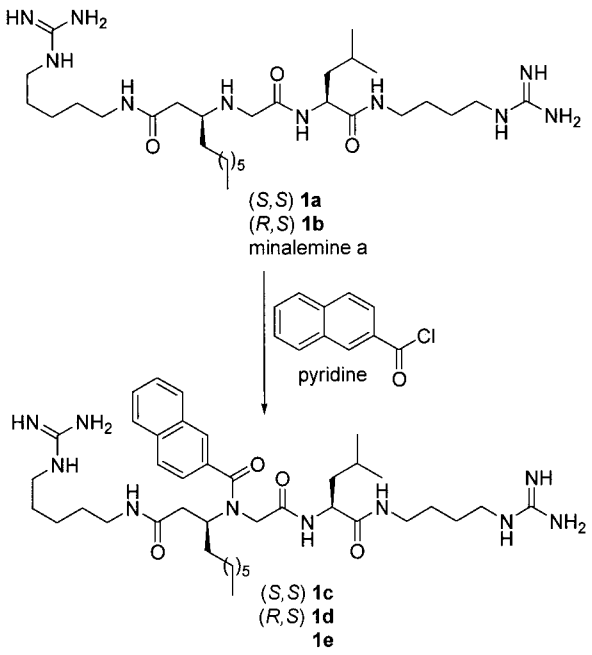
Scheme 7



Semipreparative HPLC purifications were done using a system with a μ-Porasil (7.8 mm × 300 mm) column for normal-phase separations, while the reversed-phase separations were performed either with a μ-Bondapack C_{18} (7.8 mm × 300 mm) or a Nova-Pack HR-C_{18} column. A differential refractometer and/or a diode array were used as detectors.

^{1}H NMR and ^{13}C NMR were recorded on 500, 400, or 300 MHz spectrometers. All chemical shifts (δ) are reported in ppm relative to TMS using the residual solvent signal as internal reference: δ 7.26 and 77.0 ppm for the $CHCl_3$ ^{1}H and ^{13}C signals, respectively, and δ 3.30 and 49.05 ppm for the MeOH ^{1}H and ^{13}C signals, respectively. Coupling constants (J) are given in Hz and are apparent. Optical rotations were measured on a polarimeter using a cell of 1 dm path length.

***N*,*N*′-Bis-*tert*-butoxycarbonylthiourea (8).** To a stirred solution of thiourea (571 mg, 7.50 mmol) in THF (150 mL) under argon at 0 °C were added hexane and sodium hydride (1.35 g, 33.8 mmol, 60% in mineral oil). After 5 min, the ice bath was removed, and the reaction mixture was stirred at room temperature for 10 min. The mixture was cooled to 0 °C again, di-*tert*-butyl dicarbonate (3.60 g, 16.5 mmol) was added, and the ice bath was removed after 30 min of stirring at that temperature. The resulting slurry was stirred for another 2 h at room temperature. Then the reaction was quenched with an aqueous solution of saturated $NaHCO_3$ (10 mL). The reaction mixture was poured into water (250 mL) and extracted with EtOAc (3 × 70 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give **8** as a white solid (1.78 g, 86% yield). Mp 127−129 °C. ^{1}H NMR ($CDCl_3$) 1.50 (brs, 18 H). ^{13}C NMR 27.4, 83.5, 149.8, 177.3. EI-HRMS calcd for $[C_{11}H_{20}N_2O_4S]^+$ 276.1144, found 276.1136. Anal. Calcd for $C_{11}H_{20}N_2O_4S$: C, 47.81; H, 7.29; N, 10.13; S, 11.60. Found: C, 47.94; H, 7.63; N, 9.84; S, 11.51.

Di-Boc-homoagmatine (5). To a vigorously stirred solution of 1,5-diaminopentane (1.02 g, 10 mmol) in DMF (30 mL) at room temperature was added a solution of **8** (273 mg, 1 mmol) in DMF (30 mL) dropwise through an addition funnel. Once the addition was finished, the reaction mixture was poured into water and extracted with a mixture of hexanes/diethyl ether 1:1 (10 × 50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo, to give **5** as a colorless oil (318 mg, 92% yield). ^{1}H NMR ($CDCl_3$) 1.36−1.48 (m, 4H), 1.50 (brs, 18 H), 1.53−1.61 (m, 2H), 2.70 (t, J = 6.9, 2H), 3.42 (q, J = 7.1, 2H). ^{13}C NMR 26.7, 30.6, 30.8, 31.4, 36.0, 43.3, 44.5, 81.7, 85.5, 155.8, 158.6, 166.1. EI-HRMS calcd for $[C_{16}H_{32}N_4O_4]^+$ 344.2423, found 344.2410.

Di-Boc-agmatine (7). To a vigorously stirred solution of 1,4-diaminobutane (880 mg, 10 mmol) in DMF (30 mL) was added a solution of **8** (276 mg, 1 mmol) in DMF (25 mL) dropwise using an addition funnel. After 30 min the addition had finished. The mixture was diluted with H_2O and extracted with a mixture of EtOAc/diethyl ether 1:1 (10 × 30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in a vacuum to give **7** as a colorless oil (300 mg, 91% yield). ^{1}H NMR ($CDCl_3$) 1.22−1.56 (m, 22H), 2.71 (brs, 1H), 3.17−3.41(m, 4H), 8.02 (brs, 1H), 8.30 (brs, 1H). ^{13}C NMR ($CDCl_3$) 26.2, 28.1, 30.5, 40.6, 41.5, 79.0, 82.9, 153.1, 156.0, 163.4. EI-HRMS calcd for $[C_{15}H_{30}N_4O_4]^+$ 330.2267, found 330.2266.

(4*R*,5*S*)-5-Phenyl-4-methyl-3-(1′-oxononanoyl)-2-oxazolidinone (9). To a stirred solution of (4*R*,5*S*)-5-phenyl-4-methyl-2-oxazolidinone (0.53 g, 3 mmol) in dry THF (30 mL) under argon atmosphere at −78 °C was added *n*-BuLi (1.6 M in hexanes, 2.15 mL, 3.6 mmol) dropwise. After 10 min, nonanoyl chloride (0.65 mL, 3.6 mmol) was added, and the reaction mixture was stirred for another 30 min. Then, the mixture was allowed to warm to room temperature, a saturated solution of NH_4Cl was added, and the stirring was continued for another 10 min. The reaction mixture was made basic with 1 M NaOH and extracted with CH_2Cl_2 (30 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes 1:3) to give **9** as a colorless oil (789.3 mg, 83% yield). ^{1}H NMR ($CDCl_3$) 0.85−0.89 (m, 6H), 1.25−1.36 (m, 10H), 1.62−1.70 (m, 2H), 2.84−3.01 (m, 2H), 4.76 (q, J = 6.9, 1H), 5.66 (d, J = 7.3, 1H), 7.27−7.42 (m, 5 H). ^{13}C NMR ($CDCl_3$) 14.0, 14.4, 22.5, 24.2, 29.0, 29.2, 31.7, 35.5, 78.8, 125.5, 128.5, 128.6, 133.3, 152.9, 173.0. EI-HRMS calcd for $[C_{19}H_{27}NO_3]^+$ 317.1991, found 317.1990. $[\alpha]^{23}_D$ = +38.1 (*c* 1.3, $CHCl_3$).

(*S*)-4-Phenylmethyl-3-(1′-oxononanoyl)-2-oxazolidinone (10). This compound was obtained following the same procedure as for compound **9**. Thus, (*S*)-4-phenylmethyl-2-oxazolidinone (1.14 g, 6.45 mmol) and nonanoyl chloride (1.4 mL, 7.7 mmol) afforded after workup and purification by flash chromatography (EtOAc/hexanes 1:30) compound **10** as a colorless oil (1.87 g, 92% yield). ^{1}H NMR ($CDCl_3$) 0.89 (t, J = 6.9, 3H), 1.29−1.40 (m, 10H), 1.65−1.71 (m, 2H), 2.77 (dd, J = 13.4 and 9.5, 1H), 2.85−3.01 (m, 2H), 3.29 (dd, J = 13.4 and 3.3, 1H), 4.14−4.21 (m, 2H), 4.67 (m, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) 14.0, 22.6, 24.2, 29.0, 29.1, 29.3, 31.7, 35.4, 37.8, 55.0, 66.0, 127.2, 128.8, 129.3, 135.3, 153.4, 173.3. EI-HRMS calcd for $[C_{19}H_{27}NO_3]^+$ 317.1990, found 317.1991. $[\alpha]^{23}_D$ = +45.3 (*c* 1.37, $CHCl_3$).

(4*R*,5*S*)-3-((2′*S*)-2′-Allyl-1′-oxononanoyl)-5-phenyl-4-methyl-2-oxazolidinone (11). A freshly prepared solution of LDA (0.6 M, 2.96 mL, 1.87 mmol) in anhydrous THF under argon atmosphere was cooled to −78 °C. A solution of compound **9** (0.54 g, 1.7 mmol) in dry THF (0.34 mL) was added dropwise, and once the addition was finished the stirring was continued for 1 h. Then, allyl bromide (0.44 mL, 5.1 mmol) was slowly added to the yellow solution. The temperature was allowed to rise from −60 to −40 °C, and the solution turned to colorless. The CO_2/acetone bath was removed, and the mixture was stirred for 1 h at 0 °C. Saturated NH_4Cl solution was added, and the mixture was stirred for another 10 min. The crude reaction was extracted with diethyl ether (3 × 5 mL), and the organic phase was dried over $MgSO_4$, filtered, and concentrated in a vacuum. The remaining yellow oil was purified by flash chromatography (EtOAc/hexanes 1:30) to give **11** as a colorless oil (398 mg, 66% yield). ^{1}H NMR ($CDCl_3$) 0.86 (d, J = 6.5, 3H), 0.89 (d, J = 6.1, 3H), 1.19−1.32 (m, 10H), 1.51 (m, 1 H), 2.32 (m, 1H), 2.42 (m, 1H), 3.93 (m, 1H), 4.81 (q, J = 6.7, 1H), 5.01−5.09 (m, 2H), 5.65 (d, J = 7.3, 1H), 5.82 (m, 1H) 7.28−7.44 (m, 5H). ^{13}C NMR ($CDCl_3$) 14.0, 14.5, 22.6, 27.2, 29.1, 29.6, 31.6, 31.7, 36.7, 42.3, 54.9, 78.6, 116.9, 125.2, 125.6, 125.8, 128.6, 133.3, 135.2, 152.68, 175.8. EI-HRMS calcd for $[C_{22}H_{31}NO_3]^+$ 357.2304, found 357.2308. $[\alpha]^{23}_D$ = +12.0 (*c* 1.0, $CHCl_3$).

(*S*)-3-((2′*R*)-Allyl-1′-oxononanoyl)-4-phenyl-methyl-2-oxazolidinone (12). Compound **12** was synthesized following

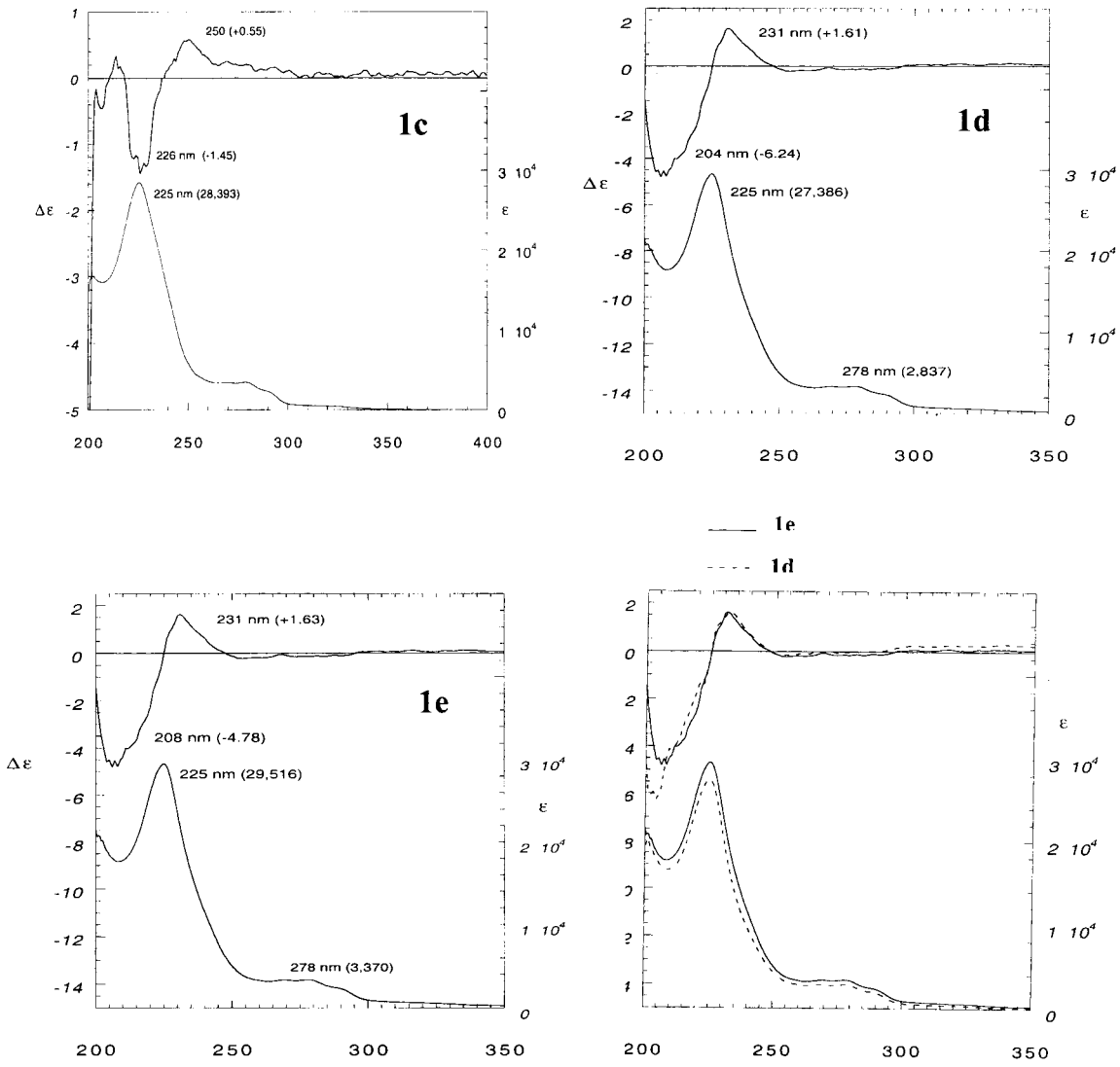


Figure 3. UV and CD spectra of compounds **1c**, **1d**, and **1e**.

the same procedure as for **11**. Thus, compound **10** (0.8 g, 2.54 mmol) and allyl bromide (0.7 mL, 7.62 mmol) afforded after workup and purification by flash chromatography (EtOAc/hexanes 1:30) compound **12** as a colorless oil (709 mg, 78% yield). ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 6.8, 3H), 1.28 (brs, 10H), 1.51 (m, 1H), 1.42 (m, 1H), 2.34 (m, 1H), 2.46 (m, 1H), 2.67 (dd, J = 13.1 and 10.0, 1H), 3.92 (m, 1H), 4.10−4.20 (m, 2H), 4.69 (m, 1H), 5.03−5.12 (m, 2H), 5.83 (m, 1H), 7.22−7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) 14.0, 22.5, 27.2, 29.1, 29.6, 31.5, 31.7, 36.7, 38.0, 42.3, 55.4, 65.8, 117.0, 127.2, 128.8, 129.3, 135.3, 135.4, 153.1, 176.1. EI-HRMS calcd for $[C_{22}H_{31}NO_3]^+$ 357.2303, found 357.2302. $[\alpha]^{26}_D$ = +47.8 (*c* 1.09, $CHCl_3$).

(2*S*)-2-Allylnonanoic Acid (13a). To a vigorously stirred solution of **11** (0.57 g, 1.6 mmol) in a mixture of THF/H_2O 4:1 (8 mL) at 0 °C were added H_2O_2 (30%, 1.45 mL, 12.8 mmol) and LiOH (76.7 mg, 3.2 mmol) dissolved in H_2O (5 mL). After 10 min, the ice bath was removed, and the mixture was stirred for 1 h. The mixture was treated with a solution of Na_2SO_3 (1.61 g, 12.8 mmol) in water, and then it was stirred for another 10 min. The aqueous residue was basified with a solution of $NaHCO_3$ (5%) and extracted with CH_2Cl_2 (3 × 25 mL). From the organic phase the chiral auxiliary was recovered. The aqueous phase was acidified with HCl (6 M) until pH 1, and the mixture was extracted with diethyl ether (4 × 25 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in a vacuum. Compound **13a** was obtained as a yellowish oil (305 mg, 96% yield). ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 6.7, 3H), 1.23−1.32 (m, 10H), 1.50 (m, 1H), 1.62 (m, 1H), 2.27 (m, 1H), 2.39 (m, 1H), 2.45 (m, 1H), 5.02−5.10 (m, 2H), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$) 14.0, 22.6, 27.2, 29.1, 29.4, 31.5, 31.8, 36.1, 45.2, 116.8, 135.2, 182.5. EI-HRMS calcd $[C_{12}H_{22}O_2]^+$ 198.1620, found 198.1621. $[\alpha]^{21}_D$ = −8.1 (*c* 2.78, $CHCl_3$).

(2*R*)-2-Allylnonanoic Acid (13b). Compound **10** (2.25 g, 6.3 mmol) was submitted to the same procedure as for **11** to give **13b** as a yellowish oil (1.14 g, 91% yield). NMR and EI-HRMS data are identical to that of its enantiomer **13a**. $[\alpha]^{21}_D$ = +8.6 (*c* 3.02, $CHCl_3$).

(4*S*)-4-Benzyloxycarbonyl-undec-1-ene (14a). To a stirred solution of **13a** (197 mg, 1 mmol) in dry toluene (10 mL) under argon atmosphere were added Et_3N (0.14 mL, 1 mmol) and diphenyl phosphoryl azide (DPPA) (0.2 mL, 1 mmol). The mixture was refluxed for 8 h. Benzyl alcohol (0.5 mL) was then added, and the reflux was continued for another 15 h. Finally, the mixture was allowed to reach room temperature, it was dissolved in EtOAc, and then it was sequentially washed with H_2O (3 × 20 mL) and brine (2 × 20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in a vacuum. The residue was purified by flash chromatography (EtOAc/hexanes 1:30) to give **14a** as a white crystalline solid (251 mg, 83% yield). Mp 71−72 °C. ^{1}H NMR ($CDCl_3$) 0.86 (t, J = 6.7, 3H), 1.23−1.31 (m, 10H), 1.46 (brs, 1H), 1.61 (brs, 1H), 2.13−2.27 (m, 2H), 3.69 (d, J = 6.1, 1H), 4.53 (d, J = 8.5, 1H), 5.03−5.08 (m, 4H), 5.73 (m, 1H), 7.27−7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) 14.1, 22.6, 25.8, 29.2, 29.4, 31.8, 34.6, 39.4, 50.7, 66.5, 117.7, 128.0, 128.4, 134.3, 136.7, 156.0. EI-HRMS calcd for $[C_{19}H_{29}NO_2]^+$ 303.2198, found 303.2202. $[\alpha]^{23}_D$ = −18.1 (*c* 1.0,

$CHCl_3$). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.61. Found: 75.26; H, 9.53; N, 4.62.

(4*R*)-4-Benzyloxycarbonyl-undec-1-ene (14b). Compound **13b** (580 mg, 2.95 mmol) was submitted to the same Curtius-like reaction, giving **14b** as a white crystalline solid (742 mg, 83% yield). Mp, NMR, and EI-HRMS data are identical to those of its enantiomer. $[\alpha]^{23}_D = +19.5$ (*c* 1.10, $CHCl_3$).

(3*S*)-3-Benzyloxycarbonylamino-decanoic Acid (4a). To a vigorously stirred solution of $NaIO_4$ (1.42 g, 6.7 mmol) in H_2O (30 mL) was added $KMnO_4$ (237 mg, 0.15 mmol). K_2CO_3 (112.5 mg, 0.81 mmol), *t*-BuOH (7.5 mL), and compound **14a** (0.23 g, 0.74 mmol) in *t*-BuOH (7.5 mL) were added to the purple solution. After 2 h of stirring at room temperature the solution turned to pink. Ethylenglycol (0.2 mL, 3.25 mmol) was added, and the stirring was maintained for another 2 h. Finally the solution was treated with HCl (1.5 M) until pH 1 and extracted with EtOAc (4 × 30 mL). The combined organic layer was washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in a vacuum. Compound **4a** was obtained as white solid (235 mg, 99% yield). Mp 89−92 °C. ^{1}H NMR ($CDCl_3$) 0.81 (t, J = 6.8, 3H), 1.19 (brs, 10H), 1.48 (brs, 10H), 2.53 (brs, 2H), 3.90 (brs, 1H), 5.03−5.13 (m, 2H), 7.23−7.31-(m, 5H). ^{13}C NMR ($CDCl_3$) 14.0, 22.6, 26.1, 29.1, 29.2, 31.7, 34.3, 38.8, 48.0, 66.7, 128.1, 128.5, 136.4, 155.9, 176.5. EI-HRMS calcd for $[C_{18}H_{27}NO_4]^+$ 321.1940, found 321.1931. $[\alpha]^{23}_D = -12.3$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.27; H, 8.47; N, 4.36. Found: C, 67.26; H, 8.67; N, 4.49.

(3*R*)-3-Benzyloxycarbonylamino-decanoic Acid (4b). Compound **14b** (349 mg, 1.15 mmol) was submitted to the same procedure as for **14a** to give **4b** as a white solid (343 mg, 93% yield). Mp, NMR, and EI-HRMS data are identical to those of its enantiomer 4**a**. $[\alpha]^{25}_D = +10.0$ (*c* 0.48, $CHCl_3$).

Peptide 15a. To a stirred solution of **4a** (321 mg, 1 mmol) in CH_2Cl_2 cooled at 0 °C with an ice bath were sequentially added amine **5** (434 mg, 1.26 mmol), DCC (227 mg, 1.1 mmol), and DMAP (cat.). The mixture was stirred at 0 °C for 10 min and then at room temperature for 19 h. The DCU was filtered off, and the solution was concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane 1:1) to give compound **15a** as a white solid (404 mg, 62% yield). Mp 72−75 °C. ^{1}H NMR ($CDCl_3$) 0.84 (t, J = 6.8, 3H), 1.19−1.63 (m, 34H), 2.35 (dd, J = 14.8 and 6.1, 2H), 2.44 (dd, J = 14.9 and 4.4, 1H), 3.19 (dd, J = 13.1 and 6.3, 2H), 3.37 (dd, J = 12.4 and 6.7, 2H), 3.84 (d, J = 5.4, 1H), 5.05 (brs, 2H), 5.50 (d, J = 8.3, 1H), 5.88 (brs, 1H), 7.25−7.32 (m, 5H), 8.31 (brs, 1H). ^{13}C NMR ($CDCl_3$) 14.0, 22.6, 24.0, 24.9, 25.6, 26.2, 28.0, 28.2, 28.5, 29.0, 29.1, 29.3, 31.7, 33.9, 34.6, 39.1, 40.6, 41.0, 49.0, 66.4, 127.8, 127.9, 128.4, 136.6, 153.3, 156.1, 156.2, 163.5, 170.8. FAB-HRMS calcd for $[C_{34}H_{58}N_5O_7 + H]^+$ 648.4336, found 648.4339. $[\alpha]^{25}_D = -5.7$ (*c* 2.10, $CHCl_3$).

Peptide 15b. Using the same procedure as for **15a**, but starting from **4b** (96.3 mg, 0.3 mmol) and **5** (100 mg, 0.3 mmol), isomer **15b** (105 mg, 54% yield) was obtained as a white solid. Mp, NMR, and FAB-HRMS data are identical to those of its enantiomer **15a**. $[\alpha]^{24}_D = +4.8$ (*c* 1.02, $CHCl_3$).

Peptide 2a. To a stirred solution of **15a** (375 mg, 0.6 mmol) in MeOH (15 mL) was added Pd (10% on activated charcoal, 250 mg), and the mixture was stirred under hydrogen atmosphere at normal pressure for 5 h. The crude was filtered through Celite, and the filtrate was concentrated in a vacuum. Compound **2a** was obtained as a colorless oil (303 mg, 98% yield) and was used without further purification. ^{1}H NMR ($CDCl_3$) 0.88 (t, J = 6.9, 3H), 1.26−1.62 (m, 34H), 2.16 (d, J = 11.8, 1H), 2.37 (d, J = 15.5, 1H), 3.12 (brs, 1H), 3.25 (dd, J = 12.8 and 6.6, 2H), 3.41 (dd, J = 12.4 and 7.4, 2H), 8.30 (brs, 1H). ^{13}C NMR ($CDCl_3$) 14.0, 22.5, 24.2, 24.9, 25.6, 25.9, 28.0, 28.2, 28.5, 29.0, 29.1, 29.4, 31.7, 33.9, 38.4, 38.8, 40.6, 43.0, 48.8, 50.3, 79.1, 83.0, 153.2, 156.0, 163.5, 172.0. FAB-HRMS calcd for $[C_{28}H_{54}N_2O_6 + H]^+$ 514.3982, found 514.3992. $[\alpha]^{22}_D = +7.6$ (*c* 2.57, $CHCl_3$).

Peptide 2b. Following the same previous procedure from **15b** (256 mg, 0.4 mmol) compound **2b** (197 mg, 96% yield) was obtained. $[\alpha]^{23}_D = -4.9$ (*c* 1.05, $CHCl_3$).

Peptide (16). *N*-Cbz-L-leucine was obtained using literature procedures[7] as a yellow oil. A solution of *N*-Cbz-L-leucine in toluene was prepared and titrated with NaOH 0.1 M using phenolphthalein as indicator. To a stirred solution of compound **7** (881 mg, 2 mmol) in CH_2Cl_2 at 0 °C were sequentially added a solution of *N*-Cbz-L-leucine (0.7 M, 2.86 mL, 2 mmol), HOBt (270.3 mg, 2 mmol), and DCC (433.3 mg, 2.1 mmol). After 10 min the ice bath was removed, and the stirring was continued overnight at room temperature. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane 1:3) to afford **16** as a colorless oil that solidified on standing (84 mg, 42% yield). Mp 56−60 °C. ^{1}H NMR ($CDCl_3$) 0.90 (d, J = 5.9, 6H), 1.46−1.67 (m, 25H), 3.21−3.37 (m, 4H), 4.12 (m, 1H), 5.06 (brs, 2H), 5.26 (d, J = 8.1, 1H), 6.34 (brs, 1H), 7.27−7.35 (m, 5H), 8.31 (brs, 1H). ^{13}C NMR 22.0, 22.9, 24.7, 26.4, 26.6, 28.0, 39.1, 40.3, 41.5, 53.6, 67.0, 79.4,83.2, 128.0, 128.2, 128.5, 136.2, 153.2, 156.2, 163.3, 172.1. FAB-HRMS calcd for $[C_{29}H_{47}N_5O_7 + H]^+$ 578.3509, found 578.3528. $[\alpha]^{27}_D = -14.5$ (*c* 1.15, $CHCl_3$).

Peptide 17. To a stirred solution of compound **16** (84 mg, 0.14 mmol) in MeOH (15 mL) was added Pd (10% on activated carbon). The mixture was stirred under hydrogen atmosphere at 1 atm for 5 h. The crude was filtered through Celite, and the filtrate was concentrated in vacuo. Compound **17** was obtained as a colorless oil (62 mg, 100% yield). ^{1}H NMR ($CDCl_3$) 0.90 (d, J = 6.1, 3H), 0.93 (d, J = 6.2, 3H), 1.25−1.70 (m, 25H), 3.19−3.48 (m, 5H), 7.39 (s, 1H), 8.30 (d, J = 4.6, 1H). ^{13}C NMR ($CDCl_3$) 21.2, 23.4, 24.8, 26.5, 26.9, 28.0, 28.2, 38.5, 40.4, 43.9, 53.4, 79.2, 83.1, 153.2, 156.1, 163.5, 175.6. EI-HRMS calcd for $[C_{21}H_{41}N_5O_5]^+$ 443.3108, found 443.3122. $[\alpha]^{23}_D = -14.7$ (*c* 4.97, $CHCl_3$).

Compound 3. To a stirred solution of bromoacetic acid (66 mg, 0.47 mmol) in CH_2Cl_2 (1 mL) cooled at 0 °C were sequentially added compound **17** (150 mg, 0.34 mmol), DCC (76.3 mg, 0.37 mmol), and a catalytic amount of DMAP. The ice bath was removed after 10 min, and the mixture was concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes 1:1). Compound **3** was obtained as a white solid (129 mg, 67% yield). Mp 115−118 °C. ^{1}H NMR ($CDCl_3$) 1.00 (brs, 6H), 1.45 (brs, 18H), 1.47−1.65 (m, 7 H), 3.14−3.36 (m, 4H), 3.76 (s, 2H), 4.36 (dd, J = 8.3 and 5.8, 1H), 6.62 (t, J = 5.7, 1H), 7.13 (d, J = 8.3, 1H), 8.27 (t, J = 5.1, 1H). ^{13}C NMR ($CDCl_3$) 22.2, 22.8, 24.7, 26.4, 26.6, 28.0, 28.2, 28.6, 39.2, 40.3, 41.1, 52.3, 79.4, 83.2, 153.2, 156.1, 163.3, 166.0, 171.4. FAB-HRMS calcd for $[C_{23}H_{42}N_5O_6Br + H]^+$ 566.2376, found 566.2394. $[\alpha]^{23}_D = -21.4$ (*c* 1.59, $CHCl_3$).

Peptide 18a. To a stirred solution of **2a** (250 mg, 0.5 mmol) in DMF (0.5 mL) was added DIEA (0.13 mL, 0.75 mmol) dropwise, and the mixture was cooled to 0 °C. Then compound **3** (282 mg, 0.5 mmol) was added, and the mixture was stirred for 2 h at room temperature. The crude was poured into water, and the resulting mixture was extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and concentrated in a vacuum. The residue was purified by normal-phase HPLC, column μ-Porasil 7.8 mm × 300 mm; mobile phase OEtAc/MeOH 9.5:0.5; isocratic; flow 2 mL/min. Compound **18a** was obtained as a light orange solid (215 mg, 43% yield). ^{1}H NMR ($CDCl_3$) 0.83 (t, J = 6.8, 3H), 0.87 (d, J = 6.1, 3H), 0.89 (d, J = 6.2, 3H), 1.20−1.66 (m, 51H), 2.13 (dd, J = 14.8 and 8.0, 1H), 2.33 (dd, J = 14.9 and 3.5, 1H), 2.92 (brs, 1H), 3.13−3.35 (m, 10H), 4.38 (dd, J = 13.7 and 8.2, 1H), 6.65 (t, J = 5.3, 1H), 6.86 (t, J = 5.3, 1H), 7.73 (d, J = 8.3, 1H), 8.28 (brs, 1H). ^{13}C NMR ($CDCl_3$) 13.9, 22.00, 22.5, 22.8, 24.1, 24.7, 25.9, 26.4, 26.6, 27.9, 28.2, 28.3, 28.5, 29.0, 29.1, 29.5, 31.6, 33.8, 38.9,-39.0, 40.2, 40.3, 40.6, 48.7, 51.5, 55.1, 79.1, 83.0, 153.1, 156.0, 163.4, 172.1, 171.6, 171.9. FAB-HRMS calcd for $[C_{49}H_{92}N_{10}O_{11} + H]^+$ 997.7025, found 997.7073. $[\alpha]^{24}_D = -8.3$ (*c* 0.98, $CHCl_3$).

Peptide 18b. Using the same procedure as for **18a**, compound **2b** (190 mg, 0.37 mmol) was treated with DIEA (0.1 mL, 0.5 mmol) and compound **3** (211 mg, 0.37 mmol). After the same workup and purification, compound **18b** was obtained as a light orange solid (82 mg, 22% yield). ^{1}H NMR ($CDCl_3$) 0.86 (t, J = 6.9, 3H), 0.89 (d, J = 6.1, 3H), 0.92 (d, J = 6.0, 3H), 1.13−1.70 (m, 51 H), 2.17 (dd, J = 10.7 and 5.5, 1H), 2.46 (dd, J = 14.9 and 2.9, 1H), 2.95 (brs, 1H), 3.23−3.47

(m, 10H), 4.44 (m, 1H), 6.50(brs, 1H), 7.17 (brs, 1H), 7.85 (d, $J = 8.4$, 1H), 8.31 (brs, 1H). ^{13}C NMR ($CDCl_3$) 14.0, 21.8, 22.6, 23.0, 24.1, 24.8, 25.8, 26.6, 28.0, 28.3, 28.6, 29.0, 29.1, 29.6, 31.7, 39.1, 39.3, 40.5, 40.6, 41.1, 49.0, 52.0, 55.4, 79.3, 83.1, 153.2, 156.1, 163.5, 171.1, 171.6, 172.5. FAB-HRMS calcd for $[C_{49}H_{92}N_{10}O_{11} + H]^+$ 997.7025, found 997.6988. $[\alpha]^{24}_D = -21.3$ (*c* 0.52, $CHCl_3$).

(*S,S*) Diastereoisomer (1a). A solution of **18a** (34 mg, 0.034 mmol) in a mixture of CH_2Cl_2/TFA 1:1 (3 mL) was stirred for 3 h. The mixture was concentrated in vacuo several times after adding several portions of diethyl ether. The residue was purified by reversed-phase HPLC, μ-Bondapack C_{18} 7.8 mm × 300 mm; mobile phase MeOH/H_2O/TFA (60:40:0.1); isocratic; flow 2 mL/min. Compound **1a** was obtained as a solid (21 mg, 55% yield). ^{1}H NMR (MeOD) 0.93 (t, $J = 6.8$, 3H), 0.97 (d, $J = 6.6$, 3H), 1.00 (d, $J = 6.6$, 3H), 1.34−1.46 (m, 12H), 1.56−1.66 (m, 11H), 1.72 (m, 1H), 1.79 (m, 1H), 2.61 (dd, $J = 16.4$ and 7.2, 1H), 2.73 (dd, $J = 16.2$ and 4.2, 1H), 3.19−3.25 (m, 8H), 3.55 (m, 1H), 3.92 (d, $J = 15.7$, 1H), 3.97 (d, $J = 15.7$, 1H), 4.41 (dd, $J = 9.3$ and 5.8, 1H). ^{13}C NMR (MeOD) 14.3, 21.9, 23.3, 23.6, 25.0, 25.9, 26.3, 27.1, 27.5, 29.4, 29.8, 30.0, 30.3, 31.6, 32.8, 34.9, 39.7, 40.2, 42.1, 42.3, 42.4, 46.6, 53.7, 57.7, 158.7, 166.6, 172.4, 174.5. FAB-HRMS calcd for $[C_{29}H_{60}N_{10}O_3 + H]^+$ 597.4928, found 597.4918. $[\alpha]^{24}_D = -2.4$ (*c* 0.56, MeOH).

(*R,S*) Diastereoisomer (1b). Compound **18b** (30 mg, 0.03 mmol) was also deprotected using CH_2Cl_2/TFA 1:1 (3 mL), and the reaction product was submitted to the same purification process as for **1a** to afford compound **1b** (80 mg, 45% yield). ^{1}H NMR (MeOD) 0.94 (t, $J = 6.9$, 3H), 0.97 (d, $J = 6.6$, 3H), 1.00 (d, $J = 6.6$, 3H), 1.34−1.46 (m, 12H), 1.56−1.66 (m, 1H), 1.72 (m, 1H), 1.79 (m, 1H), 2.61 (dd, $J = 16.5$ and 7.1, 1H), 2.79 (dd, $J = 16.4$ and 4.4, 11H), 3.19−3.26 (m, 8H), 3.55 (m, 1H), 3.92 (d, $J = 15.7$, 1H), 3.98 (d, $J = 15.7$, 1H), 4.41 (dd, $J = 8.2$ and 6.6, 1H). ^{13}C NMR (MeOH) 14.3, 21.9, 23.3, 23.6, 25.0, 25.9, 26.3, 27.1, 27.5, 29.4, 29.8, 30.1, 30.3, 31.7, 32.8, 35.0, 39.7, 40.2, 42.1, 42.2, 42.4, 46.5, 53.7, 57.5, 158.7, 166.6, 172.4, 174.5. FAB-HRMS calcd for $[C_{29}H_{60}N_{10}O_3 + H]^+$ 597.4928, found 597.4917. $[\alpha]^{24}_D = -9.9$ (*c* 1.23, MeOH).

Procedure for Derivatization of 1a, 1b, and Minalemine A. Synthesis of Compounds 1c, 1d, and 1e. To a stirred solution of **1a** (1 mg, 0.002 mmol) in pyridine (0.15 mL) was added an excess of 2-naphthoyl chloride. The mixture was stirred for 48 h, concentrated in vacuo, and purified by reversed-phase HPLC, column NovaPack HR-C_{18} 7.8 mm × 300 mm; mobile phase MeOH/H_2O/TFA (70:30:0.1); isocratic; flow 2 mL/min, affording **1c** (0.51 mg, 43% yield); $t_R = 11.0$ min. ESI-LRMS $m/z = 865.6$ $[M + TFA]^+$.

Derivatization of **1b** (1 mg, 0.002 mmol) by the same procedure as for **1a** and purification using the same conditions as for **1c** afforded **1d** (0.54 mg, 45% yield). $t_R = 11.0$ min. ESI-LRMS $m/z = 865.6$ $[M + TFA]^+$.

Minalemine A (1 mg, 0.002 mmol) was derivatized with the same procedure as that followed for **1a**. Purification using the same conditions as for **1c** gave **1e** (0.48 mg, 40% yield). $t_R = 11.0$ min. ESI-LRMS $m/z = 865.6$ $[M + TFA]^+$.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and DEPT spectra of natural minalemine A, **1a**, **1b**, and all the synthetic intermediates and mass spectra, UV, and CD spectra of **1c**, **1d**, and **1e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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