Synthesis of the Marine Natural Product *N*α-(4-Bromopyrrolyl-2-carbonyl)-L-homoarginine, a Putative Biogenetic Precursor of the Pyrrole−Imidazole Alkaloids

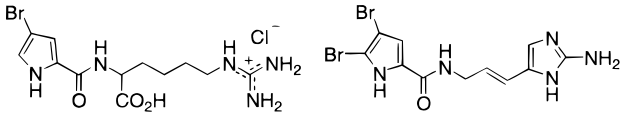
Thomas Lindel,*,† Matthias Hochgürtel,† Michael Assmann,‡ and Matthias Köck*,‡,⊥

Pharmazeutisch-chemisches Institut der Universität, INF 364, D-69120 Heidelberg, Germany, and Institut für Organische Chemie, Johann Wolfgang Goethe-Universität, Marie-Curie-Strasse 11, D-60439 Frankfurt, Germany

Received April 12, 2000

Lysine is proposed as an alternative biosynthetic precursor of the pyrrole−imidazole alkaloids frequently found in marine sponges. As a putative key intermediate, the natural product *N*α-(4-bromopyrrolyl-2-carbonyl)-L-homoarginine (**1**) from the sponge *Agelas wiedenmayeri* was synthesized in the solid phase starting from Fmoc/Pmc-protected L-homoarginine and in solution starting from readily available L-lysine methyl ester.

Pyrrole−imidazole alkaloids continue to be isolated from marine sponges and represent one of the most prominent groups of natural products exclusive to the marine environment.[1] The underlying $C_{11}N_5$ building block consists of a pyrrolyl-2-carbonyl unit being connected via an amide linkage to a 2-amino-5-(3-amino)propylimidazole partial structure. Recently, *N*α-(4-bromopyrrolyl-2-carbonyl)-homoarginine (**1**) was isolated from the marine sponge *Agelas wiedenmayeri*,[2a] together with known pyrrole−imidazole alkaloids such as oroidin (**2**).[3] In this paper, we describe solid-[2b] and solution-phase syntheses of **1** and the determination of its absolute configuration. After the discovery of the aplysinamisines I and II from *Aplysina cauliformis*,[4] **1** and **2** constitute a new pair of natural products pointing at a biogenetic relationship between lysine and 2-amino-5-(3-amino)propenylimidazoles in marine sponges. Oroidin (**2**) contributes to the survival of the genus *Agelas* by protecting the sponge against predation by the reef fish *Thalassoma bifasciatum*.[5]

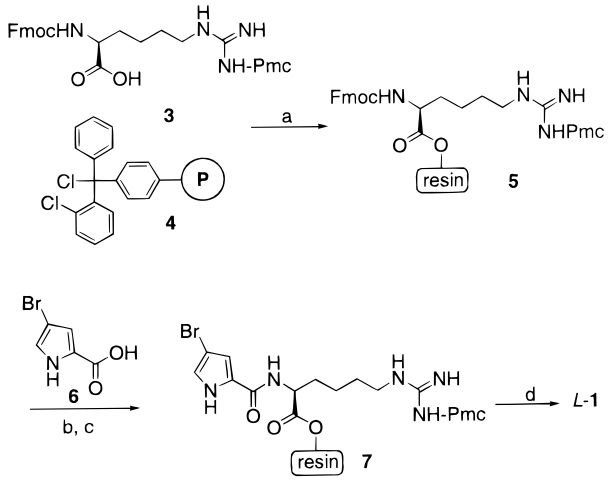


1 **2** (oroidin)

The solid-phase synthesis of **1** (Scheme 1) was achieved starting from (Fmoc/Pmc)-protected L-homoarginine (**3**), which was coupled to 2-chlorotrityl chloride polystyrene resin (**4**), forming compound **5**. After removal of the Fmoc-protecting group with 40% piperidine in DMF, 4-bromopyrrole-2-carboxylic acid (**6**) was attached using DIC/HOBt as coupling reagents. Finally, treatment of the product **7** with 98% TFA led to the removal of the Pmc group and to the cleavage of *N*α-(4-bromopyrrolyl-2-carbonyl)-L-homoarginine (L-**1**) from the resin. The overall yield was 72%.

Alternatively, reaction of L-lysine methyl ester (**8**, Scheme 2) with the bis-Boc-protected pyrazole-1*H*-carboxamidine

Scheme 1. Solid-Phase Synthesis of L-**1**[a]



[a] (a) **4**, CH_2Cl_2, *i*-Pr_2NEt, room temperature, 3 h; (b) piperidine/DMF, room temperature, 3 × 20 min; (c) **6**, DIC, HOBt, DMF, room temperature, 5 h; (d) TFA, room temperature, 30 min, 72% from **3**.

11[6] regioselectively gave the protected homoarginine **12**, which was further converted to the methyl ester **14** via reaction with the pyrrolyltrichloromethyl ketone **13**.[7] Treatment of **14** with HCl(g)/Et_2O led to the selective removal of the Boc groups. Hydrolysis with 8 N HCl provided the natural product L-**1** as the hydrochloride in 60% overall yield. Reaction of **8** with **9** in acetonitrile/*N*,*N*-diisopropylethylamine[8] led to the selective acylation of the ϵ-amino group to **10**.

The UV maxima of **1** in aqueous phosphate buffer, pH 7, were observed at 272 (ϵ 3.99) and 202 (ϵ 3.89) nm, while the CD spectrum (Figure 1) exhibited only one significant minimum. The still undetermined absolute configuration of the natural product **1** was established as L on the basis of negative Cotton effects at 216 nm (Δϵ −1.6) for the synthetic L-**1** and at 214 nm (Δϵ −1.6) for the natural product **1**. At 270 nm, the CD is not intense enough to be useful for the assignment of the absolute stereochemistry of the *N*α-pyrrolylcarbonyl amino acid **1**; L-**1** shows a negative optical rotation.

Several alternatives have been discussed with regard to the biosynthesis of the pyrrole−imidazole alkaloids. While the pyrrole part is generally expected to derive from

* To whom correspondence should be addressed. (T.L.) Tel.: + 49(0)-6221/54-4857. Fax: + 49(0)6221/54-6430. E-mail: thomas.lindel@urz.uni-heidelberg.de. (M.K.) Tel.: +49(0)69/798-29143. Fax: +49(0)69/798-29128. km@org.chemie.uni-frankfurt.de.

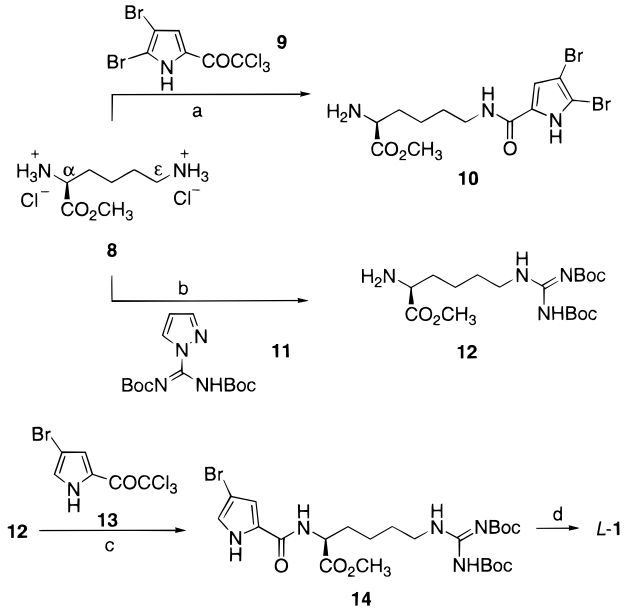
† Pharmazeutisch-chemisches Institut der Universität.

‡ Institut für Organische Chemie, Johann Wolfgang Goethe-Universität.

⊥ Present address: Alfred-Wegener-Institut, Am Handelshafen 12, D-27570 Bremerhaven. E-mail: mkoeck@awi-bremerhaven.de.

10.1021/np000160o CCC: $19.00
Published on Web 09/23/2000

Scheme 2. Solution-Phase Synthesis of L-**1**[a]



[a] (a) **9**, *i*-Pr_2NEt, CH_3CN, room temperature, 3 h, 75%; (b) **11**, *i*-Pr_2NEt, CH_3CN, room temperature, 24 h, 80%; (c) **13**, *i*-Pr_2NEt, CH_3CN, 24 h, 89%; (d) 8 N HCl, room temperature, 4 h, 85%.

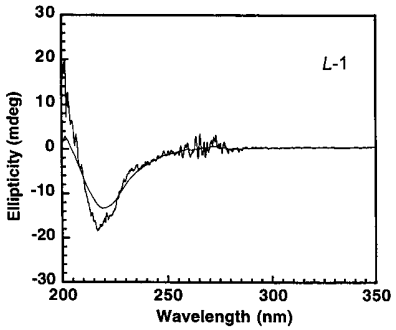


Figure 1. CD spectrum of synthesized natural product L-**1** (2,2,2-trifluoroethanol, $c = 1.5$ mM).

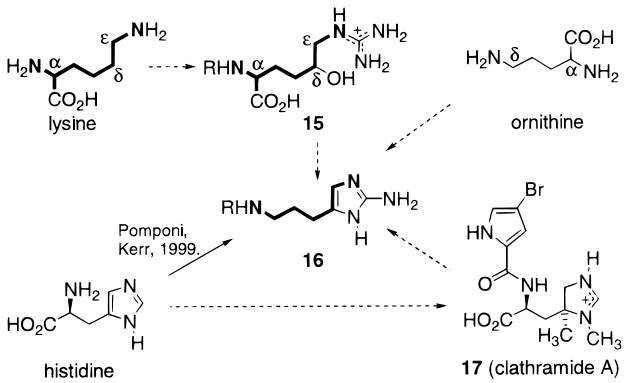


Figure 2. Proposal of the lysine-derived δ-hydroxyhomoarginine (**15**) as an alternative biogenetic precursor of the 2-amino-5-(3-amino)-propylimidazoles.

proline/ornithine, different proposals have been put forward for the 2-amino-5-(3-amino)propylimidazole part. Recently, the first experimental study on the biosynthesis of the pyrrole−imidazole alkaloid stevensine was performed by Pomponi, Kerr, and co-workers.[9] The incorporation of histidine might proceed via an analogue of clathramide A[10] (**17**, Figure 2) isolated from the oroidin source *Agelas clathrodes*. The *C*-methylation of the imidazoline ring of **17** could provide the carbon atom required for chain elongation, for example, via a cyclopropanoid intermediate. Kitagawa et al.[11] and Braekman et al.[12] proposed ornithine as a biogenetic precursor, with the carboxyl carbon atom being incorporated into the imidazole ring and the α- and δ-amino groups incorporated into the imidazole ring and the side chain, respectively.

The discovery of the aplysinamisines and of the homoarginine derivative **1**, together with the co-occurrence of lysine and bromopyrroles in marine sponges,[13] points to the existence of an alternative biosynthesis (Figure 2). In analogy to the role of 4-hydroxyarginine as a biosynthetic precursor of the 2-aminoimidazoline anatoxin-a(s),[14] δ-hydroxyhomoarginine (**15**) is postulated as an intermediate in the biosynthesis of 5-(3-aminopropyl)-2-aminoimidazoles. Intramolecular cyclization of **15** would lead to a 2-aminoimidazoline, which would be further oxidized and undergo decarboxylation. The aminohomohistamine **16** with its saturated side chain is a partial structure of the marine natural product aerophobin-2 from *Aplysina aerophoba*.[15] Horne et al. have shown that by oxidation of **16** (R = dibromopyrrolyl-2-carbonyl) the vinyl double bond of oroidin (**2**) can be introduced.[16] The formation of the putative intermediate **15** could occur via the guanidinylation of lysine to an analogue of the natural product **1**, followed by δ-hydroxylation.

Experimental Section

General Experimental Procedures. The melting points are uncorrected. NMR chemical shifts refer to those of residual solvent signals based on $\delta_{TMS} = 0$. FABMS were obtained with nitrobenzyl alcohol as matrix. Solvents were purified and dried according to standard procedures.[17] Column chromatography was carried out on Si gel 60 (60−200 mesh, Merck) and on Sephadex LH-20 (Pharmacia). HPLC separation columns (analytical: 4.6 × 250 mm, 5 μm; preparative: 20 × 250 mm, 7 μm) were pre-filled with Kromasil RP_{18} (Knauer GmbH). CD spectra were obtained using the JASCO spectropolarimeter J-710. Thin-layer chromatography (TLC) was performed on Si gel (precoated Si gel plate F_{254} Merck).

4-Bromopyrrole-2-carboxylic Acid (6). Ethyl pyrrole-2-carboxylate[18] was brominated and then hydrolyzed according to Anderson and Lee.[19] After purification by preparative reversed-phase HPLC (gradient: 5 min A, 0−40% B in 45 min; A: 10% MeCN/H_2O + 0.1% TFA, B: 100% MeCN + 0.1% TFA; flow rate 10 mL/min) **6** was frozen in liquid nitrogen and freeze-dried to afford 1.19 g (33%) of a white-gray powder; mp 142 °C (dec); t_R 12.73 min (gradient: 20−60% MeCN/H_2O + 0.1% TFA in 40 min; flow rate 1 mL/min); UV (MeOH) λ_{max} (log ϵ) 264 (4.05) nm; IR (KBr) ν_{max} 3357, 3133, 2924, 1685, 1550, 1432, 1366, 1326, 1206, 1121 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 12.11 (1H, N*H*), 7.10 (1H, C*H*), 6.75 (1H, C*H*); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 161.0 (1C, *C*OOH), 123.8 (1C, NH*C*CO), 123.3 (1C, NH*C*HCBr), 115.8 (1C, CBr*C*HC), 95.7 (1C, *C*Br); ESIMS (neg) *m/z* 188 (100) 190 (99); HRFABMS *m/z* 188.9420 $[M + H]^+$ (calcd for $C_5H_4N_1O_2{}^{79}Br$, 188.9426).

(2*S*)-2-{[1-(4-Bromo-1*H*-pyrrol-2-yl)methanoyl]amino}-6-guanidinohexanoic Acid (L-1). To a suspension of 2-chlorotrityl chloride resin (**4**, 1.00 g, copoly(styrene-2% DVB), 200−400 mesh, Novabiochem) in CH_2Cl_2 (4 mL) Fmoc−Homoarg-(Pmc)−OH (**3**, 500 mg, 0.74 mmol, BACHEM), dissolved in CH_2Cl_2 (1 mL), was added. During the addition of *N*,*N*-diisopropylethylamine (380 μL, 2.22 mmol), the yellow reaction mixture turned immediately violet. After shaking for 3 h at room temperature a 3-fold excess of *N*,*N*-diisopropylethylamine and MeOH (3 mL) was added, and the mixture was shaken for 15 min. After filtering off the liquid phase, the resin was washed (2 × 5 min each time) with CH_2Cl_2 (10 mL), *i*-PrOH (10 mL), and Et_2O (10 mL). The resin was then resuspended for 3 × 20 min in DMF (5 mL) and shaken at room temperature. For removal of the Fmoc-protecting group, the resin was

shaken 3 × 20 min each time with a solution of piperidine in DMF (40%, 5 mL). Afterward the resin was washed 4 × 5 min with DMF (10 mL). Then a solution of 4-bromopyrrole-2-carboxylic acid (**6**, 422 mg, 2.22 mmol) and 1-hydroxybenzotriazol (450 mg, 3.33 mmol) in DMF (5 mL) was added, and the mixture was shaken for 2 min at room temperature. After the addition of *N*,*N*-diisopropylcarbodiimide (404 μL, 2.59 mmol), the mixture was allowed to shake for 5 h at room temperature. The reaction mixture was then removed using air pressure, and the remaining resin was washed twice for 5 min with CH_2Cl_2 (10 mL), *i*-PrOH (10 mL), and Et_2O (10 mL). Finally, the resin was treated with 98% TFA (5 mL) and shaken for 30 min at room temperature. The liquid phase was collected, and the resin was washed (2 × 5 min each) with H_2O (2 × 10 mL) and MeCN (2 × 10 mL). Both the acid reaction solution and washings were combined, frozen with liquid nitrogen, and freeze-dried. The obtained crude white powder was purified by preparative reversed-phase HPLC (gradient: 5 min A, 0−40% B in 45 min; A: 10% MeCN/H_2O + 0.1% TFA, B: 100% MeCN + 0.1% TFA; flow rate 10 mL/min). The purified HPLC fraction was frozen and freeze-dried yielding 100 mg (72%) of L-**1** as white powder; t_R 7.85 min (gradient: 20−60% MeCN/H_2O + 0.1% TFA in 40 min; flow rate 1 mL/min); UV (H_2O) λ_{max} (log ϵ) 271 (4.06) nm; CD (H_2O) λ ($\Delta\epsilon$) 216 (−1.6) nm; IR (KBr) ν_{max} 3379, 3199, 2943, 2871, 1670, 1520, 1386, 1203, 1136 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz,) δ 11.87 (1H, N*H*), 8.14 (1H, N*H*), 7.41 (1H, N*H*), 6.96 (1H, C*H*), 6.91 (1H, C*H*), 4.25 (dt, J = 4.9 Hz, 1H, C*H*), 3.05 (d, J = 5.3 Hz, 2H, CH_2NH), 1.73 (m, 2H, CHCH_2), 1.47 (m, 2H, CH_2CH$_2$NH), 1.37 (m, 2H, CHCH$_2$CH_2); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 174.9 (1C, *C*OOH), 159.2 (1C, *C*ONH), 157.0 (1C, N*C*NHNH$_2$), 126.9 (1C, NH*C*CO), 121.1 (1C, NH*C*HCBr), 111.9 (1C, CBr*C*HC), 95.0 (1C, *C*Br), 52.8 (1C, *C*H), 40.6 (1C, *C*H$_2$NH), 31.2 (1C, CH*C*H$_2$), 28.3 (1C, *C*H$_2$CH$_2$NH), 22.9 (1C, CHCH$_2$*C*H$_2$); ESIMS (neg) *m*/*z* 358 (82), 360 (82); HRFABMS *m*/*z* 360.0663 [M + H]$^+$ (calcd for $C_{12}H_{19}N_5O_3{}^{79}Br$, 360.0672).

(2*S*)-2-Amino-6-[1-(4,5-dibromo-1*H*-pyrrol-2-yl-methanoyl)amino]hexanoic Acid Methyl Ester (10). To a solution of L-lysine methyl ester hydrochloride (**8**, 200 mg, 0.86 mmol) in acetonitrile (3 mL) was added 2,2,2-trichloro-1-(4,5-dibromo-1*H*-pyrrol-2-yl)ethanone (**9**, 318 mg, 0.86 mmol) and *N*,*N*-diisopropylethylamine (0.3 mL, 1.81 mmol). After 3 h at room temperature, the solvent was evaporated, and the crude residue was purified by column chromatography (Si gel, $CHCl_3$/MeOH/NH_{3aq} 40:10:1) to yield **10** as colorless oil (265 mg, 75%); R_f 0.5 ($CHCl_3$/MeOH/NH_{3aq} 40:10:1); UV (MeOH) λ_{max} (log ϵ) 204 (3.92), 218 (3.84, sh), 236 (3.79, sh), 274 (4.15) nm; IR (KBr) ν_{max} 3369, 3300, 3116, 2939, 2857, 1734, 1628, 1560, 1525 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 8.05 (1H, t, J = 5.3 Hz, N*H*COC), 6.88 (1H, s, CBrC*H*C), 3.60 (3H, s, CO$_2$CH_3), 3.30 (1H, m, C*H*CH$_2$), 3.18 (2H, m, CH_2NH), 1.60−1.25 (6H, m, CHCH_2CH_2CH_2); ^{13}C NMR (DMSO-d_6, 90.6 MHz) δ 176.1 (1C, *C*O$_2$CH$_3$), 158.9 (1C, NH*C*O), 128.5 (1C, NH*C*CO), 112.3 (1C, CBr*C*HC), 104.4 (1C, *C*Br), 97.6 (1C, *C*Br), 53.8 (1C, *C*H), 51.4 (1C, O*C*H$_3$), 38.4 (1C, *C*H$_2$NH), 34.1 (1C, CH*C*H$_2$), 29.0 (1C, *C*H$_2$CH$_2$NH), 22.6 (1C, CHCH$_2$*C*H$_2$); FABMS *m*/*z* 410/412/414 (10/19/10) [M + H]$^+$, 251/252/253 (4/10/4), 154 (20), 136 (22), 84 (100); HRFABMS *m*/*z* 409.9707 (calcd for $C_{12}H_{18}N_3O_3{}^{79}Br_2$, 409.9715); *anal.* C 35.76%, H 4.47%, N 10.28%, calcd for $C_{12}H_{17}N_3O_3Br_2$, C 35.46%, H 4.17%, N 10.22%.

(2*S*)-2-Amino-6-[*N*,*N*′-bis(*tert*-butoxycarbonyl)guanidino]hexanoic Acid Methyl Ester (12). To a solution of L-lysine methyl ester hydrochloride (**8**, 1.16 g, 5.00 mmol) and *N*,*N*-diisopropylethylamine (1.85 mL, 10.5 mmol) in MeCN (25 mL) was added 1*H*-pyrazole-1-[*N*,*N*′-bis(*tert*-butoxycarbonyl)]-carboxamidine (**11**, 1.55 g, 5.00 mmol). After 24 h at room temperature, the reaction mixture was filtered, and the solvent was evaporated. The crude residue was purified by column chromatography (Si gel, $CHCl_3$/MeOH 20:1) to yield **12** as colorless oil (1.61 g, 80%); R_f = 0.4 ($CHCl_3$/MeOH 10:1); $[\alpha]^{20}_D$ +11° (*c* 0.01, MeOH); UV (MeOH) λ_{max} (log ϵ) 216 (3.98), 236 (4.09) nm; IR (KBr) ν_{max} 3333, 3140, 2979, 2865, 1728, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 11.49 (1H, br s, NH), 8.31 (1H, br s, NH), 3.72 (3H, s, O*C*H$_3$), 3.43 (3H, m, C*H*, CH_2NH), 2.17 (2H, br s, NH_2), 1.50 (9H, s, C(CH_3)$_3$), 1.49 (9H, s, C(CH_3)$_3$), 1.80−1.41 (6H, m, CH_2CH_2CH_2); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 176.4 (1C, *C*O$_2$CH$_3$), 163.6 (1C, *C*O), 156.1 (1C, NH*C*NNH), 153.3 (1C, *C*O), 83.0 (1C, *C*(CH$_3$)$_3$), 79.2 (1C, *C*(CH$_3$)$_3$), 54.2 (1C, *C*H), 51.9 (1C, O*C*H$_3$), 40.6 (1C, *C*H$_2$NH), 34.5 (1C, CH*C*H$_2$), 28.8 (1C, *C*H$_2$CH$_2$NH), 28.3 (3C, C(*C*H$_3$)$_3$), 28.0 (3C, C(*C*H$_3$)$_3$), 23.0 (1C, CHCH$_2$*C*H$_2$); FABMS *m*/*z* 403 (4) [M + H]$^+$, 203 (75), 126 (12), 84 (40), 60 (12), 57 (100); HRFABMS *m*/*z* 403.2570 (calcd for $C_{18}H_{35}N_4O_6$, 403.2557); *anal.* C 53.42%, H 8.43%, N 13.62%, calcd for $C_{18}H_{34}N_4O_6$, C 53.72%, H 8.51%, N 13.92%.

(2*S*)-2-{[1-(4-bromo-1*H*-pyrrol-2-yl)methanoyl]amino}-6-[*N*,*N*′-bis(*tert*-butoxycarbonyl)guanidino]hexanoic Methyl Ester (14). To a solution of **12** (400 mg, 1.00 mmol) in MeCN (3 mL) was added 2,2,2-trichloro-1-(4-bromo-1*H*-pyrrol-2-yl)ethanone (**13**, 270 mg, 1.00 mmol) and *N*,*N*-diisopropylethylamine (0.20 mL, 1.10 mmol). After 24 h at room temperature, the solvent was evaporated, and the crude residue was purified by column chromatography (Si gel, $CHCl_3$/MeOH 50:1) to yield **14** as colorless foam (511 mg, 89%); R_f 0.6 ($CHCl_3$/MeOH 10:1); $[\alpha]^{20}_D$ −10° (*c* 0.02, MeOH); UV (MeOH) λ_{max} (log ϵ) 208 (4.26), 234 (4.37), 270 (4.01) nm; IR (KBr) ν_{max} 3331, 2979, 1721, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 11.48 (1H, br s, NH), 10.64 (1H, br s, NH), 8.33 (1H, br s, NH), 6.89 (1H, m, CBrC*H*C), 6.84 (1H, m, NH), 6.74 (1H, m, NHC*H*CBr), 4.72 (1H, m, NHC*H*CO$_2$CH$_3$), 3.76 (3H, s, O*C*H$_3$), 3.38 (2H, m, CH_2NH), 1.56 (18H, s, C(CH_3)$_3$), 2.00−1.30 (6H, m, CH_2CH_2CH_2); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 172.8 (1C, *C*O$_2$CH$_3$), 163.4 (1C, *C*O), 160.1 (1C, *C*ONHCH), 156.1 (1C, NH*C*NNH), 153.2 (1C, CO), 125.4, (1C, CH*C*CO), 122.0 (1C, CBr*C*HNH), 112.2 (1C, CBr*C*HC), 96.8 (1C, *C*Br), 83.0 (1C, *C*(CH$_3$)$_3$), 79.2 (1C, *C*(CH$_3$)$_3$), 52.3 (1C, *C*H), 52.0 (1C, O*C*H$_3$), 40.3 (1C, *C*H$_2$NH), 31.8 (1C, CH*C*H$_2$), 28.4 (1C, *C*H$_2$-CH$_2$NH), 28.2 (3C, C(*C*H$_3$)$_3$), 27.9 (3C, C(*C*H$_3$)$_3$), 22.6 (1C, CHCH$_2$*C*H$_2$); FABMS *m*/*z* 574/576 (0.6/0.5) [M + H]$^+$, 374/376 (6/7). 84 (16), 57 (100); HRFABMS *m*/*z* 574.1914 (calcd for $C_{23}H_{37}N_5O_7{}^{79}Br$, 574.1876).

(2*S*)-2-{[1-(4-Bromo-1*H*-pyrrol-2-yl)methanoyl]amino}-6-guanidinohexanoic Acid Methyl Ester. A solution of **14** (100 mg, 0.17 mmol) in MeOH (20 mL) was saturated with HCl gas at 0 °C and stirred for 30 min at room temperature. The solvent was evaporated, and the residue was purified by column chromatography (Si gel, *n*-BuOH/HOAc/H_2O 3:1:1) to yield L-**1** methyl ester as pale yellow solid (64 mg, 90%); R_f = 0.5 (Si gel, *n*-BuOH/HOAc/H_2O 3:1:1); $[\alpha]^{20}_D$ −9° (*c* 0.01, MeOH); UV (MeOH) λ_{max} (log ϵ) 204 (4.05), 234 (3.98, sh), 276 (4.34) nm; IR (KBr) ν_{max} 3416, 3266, 3177, 2950, 2863, 1734, 1653 cm^{-1}; ^1H NMR (MeOH-d_4, 250 MHz) δ 6.94 (1H, s, C*H*), 6.93 (1H, s, C*H*), 4.54 (1H, m, C*H*), 3.73 (3H, s, O*C*H$_3$), 3.18 (2H, t, J = 6.5 Hz, CH_2NH), 1.92 (2H, m, CHCH_2), 1.63 (2H, m, CH_2CH$_2$NH), 1.50 (2H, m, CHCH$_2$CH_2); ^{13}C NMR (MeOH-d_4, 63 MHz) δ 174.2 (1C, *C*O$_2$H), 162.5 (1C, *C*ONHCH), 158.6 (1C, NH*C*NNH), 127.0 (1C, CH*C*CO), 123.2 (1C, CBr*C*HNH), 114.2 (1C, CBr*C*HC), 97.6 (1C, *C*Br), 53.5 (1C, *C*H), 52.8 (1C, O*C*H$_3$), 42.3 (1C, *C*H$_2$NH), 32.0 (1C, CH*C*H$_2$), 29.3 (1C, *C*H$_2$-CH$_2$NH), 24.2 (1C, CHCH$_2$*C*H$_2$); FABMS *m*/*z* 374/376 (99/100) [M + H]$^+$; HRFABMS *m*/*z* 376.0793 (calcd for $C_{13}H_{21}N_5O_3{}^{79}Br$, 376.0807).

(2*S*)-2-{[1-(4-Bromo-1*H*-pyrrol-2-yl)methanoyl]amino}-6-guanidinohexanoic Acid (L-1). Compound **14** (200 mg, 0.35 mmol) was suspended in aqueous HCl (8 N, 8 mL) and stirred 4 h at room temperature. The solution was concentrated in vacuo to dryness and purified by column chromatography (Si gel, *n*-BuOH/HOAc/H_2O 3:1:1) to afford L-**1** as pale orange solid (118 mg, 85%); R_f 0.6 (*n*-BuOH/HOAc/H_2O 3:1:1); $[\alpha]^{20}_D$ −11° (*c* 0.03, MeOH); UV (aqueous phosphate buffer, pH 7) λ_{max} (log ϵ) 202 (3.89), 272 (3.99) nm; CD (CF_3CH_2OH) λ ($\Delta\epsilon$) 217 (−1.8) nm; IR (KBr) ν_{max} 3330, 3277, 3199, 2940, 2863, 1718, 1633 cm^{-1}; ^1H NMR (MeOH-d_4, 250 MHz) δ 6.94 (1H, s, C*H*), 6.93 (1H, s, C*H*), 4.54 (1H, m, C*H*), 3.18 (2H, t, J = 6.5 Hz, CH_2NH), 2.05−1.93 (1H, m, CHCH_2), 1.89−1.75 (1H, m, CHCH_2), 1.71−1.56 (2H, m, CH_2CH$_2$NH), 1.55−1.41 (2H, m, CHCH$_2$CH_2); ^{13}C NMR (MeOH-d_4, 63 MHz) δ 175.5 (1C, *C*OOH), 162.5 (1C, N*C*NHNH$_2$), 158.6 (1C, *C*ONH), 127.1 (1C, NH*C*CO), 123.1 (1C, NH*C*HCBr), 114.2 (1C, CBr*C*HC), 97.6 (1C, *C*Br), 53.4 (1C, *C*H), 42.3 (1C, *C*H$_2$NH), 32.2 (1C, CH*C*H$_2$),

29.3 (1C, CH_2CH_2NH), 24.3 (1C, $CHCH_2CH_2$); FABMS *m*/*z* 382/384 (84/86) $[M + Na]^+$, 360/362 (80/80) $[M]^+$; HRFABMS *m*/*z* 382.0486 (calcd for $C_{12}H_{18}N_5O_3{}^{79}BrNa$, 382.0491).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (Li 597/2-2 and Ko 1314/3-1 to 3-4). T.L. and M.H. thank Professor Dr. Richard Neidlein for generous support. Damian Kokot is thanked for technical assistance. M.A. and M.K. are grateful to Ellen Lichte for performing HPLC analyses and acknowledge the support of Professor Dr. Christian Griesinger.

References and Notes

(1) (a) For a summary, see: Gribble, G. W. *Fortschr. Chem. Org. Naturst.* **1996**, *68*, 137−141. (b) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335−346. (c) Urban, S.; de Almeida Leone, P.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731−735, and references therein.

(2) (a) Assmann, M.; Lichte, E.; van Soest, R. W. M.; Köck, M. *Org. Lett.* **1999**, *1*, 455−457. (b) First presented at the 2nd Euroconference on Marine Natural Products, Assmann, M.; Lichte, E.; van Soest, R. W. M.; Köck, M. Presentations OP-10 and PD-2, Santiago de Compostela, Spain, 1999.

(3) (a) Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *J. Chem. Soc., Chem. Commun.* **1971**, 1129−1130. (b) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Chem. Soc., Chem. Commun.* **1973**, 78−79.

(4) Rodríguez, A. D.; Piña, I. C. *J. Nat. Prod.* **1993**, *56*, 907−914.

(5) (a) Chanas, B.; Pawlik, J. R.; Lindel, T.; Fenical, W. *J. Exp. Mar. Biol. Ecol.* **1996**, *208*, 185−196. (b) Lindel, T.; Hoffmann, H.; Hochgürtel, M.; Pawlik, J. R. *J. Chem. Ecol.* **2000**, *26*, 1477−1496. (c) Assmann, M.; Lichte, E.; Pawlik, J. R.; Köck, M. *Mar. Ecol. Prog. Ser.* **2000**, in press.

(6) Bernatowicz, M. S.; Wu. Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389−3392.

(7) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300−1302.

(8) Drake, B.; Patek, M.; Lebl, M. *Synthesis* **1994**, 579−582.

(9) Andrade, P.; Willoughby, R.; Pomponi, S. A.; Kerr, R. G. *Tetrahedron Lett.* **1999**, *40*, 4775−4778.

(10) (a) Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. *Tetrahedron* **1996**, *52*, 13713−13720. (b) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. *J. Nat. Prod.* **1998**, *61*, 122−125.

(11) Kitagawa, I.; Kobayashi, M.; Kitanaka, I.; Kido, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321−2328.

(12) Braekman, J.-C., Daloze, D.; Stoller, C.; van Soest, R. W. M. *Biochem. Syst. Ecol.* **1992**, *20*, 417−431.

(13) Li, C. J.; Schmitz, F. J.; Kelly-Borges, M. *J. Nat. Prod.* **1998**, *61*, 387−389.

(14) Hemscheidt, T.; Burgoyne, D. L.; Moore, R. E. *J. Chem. Soc., Chem. Commun.* **1995**, 205−206.

(15) Cimino, G.; De Rosa, S.; De Stefano, S.; Self, R.; Sodano, G. *Tetrahedron Lett.* **1983**, 24, 3029−3032.

(16) Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1998**, *63*, 1248−1253.

(17) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed., Pergamon: Oxford, 1988.

(18) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51*, 100−102.

(19) Anderson, H. J.; Lee, S.-F. *Can. J. Chem.* **1965**, *43*, 409−414.

NP000160O