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Tetrahedron 60 (2004) 961–965
Tetrahedron

Synthesis of barettin

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Received 11 August 2003; revised 20 October 2003; accepted 13 November 2003

Abstract—The indole alkaloid barettin (with bromine in 6-position), isolated from the marine sponge *Geodia Barretti*, has been synthesised via a Horner–Wadsworth–Emmons type reaction from 6-bromoindole-3-carboxaldehyde to introduce the dehydro-functionality. Subsequent deprotection and cyclisation afforded the natural product in *Z*-conformation.

1. Introduction

The structure of the pharmacologically active indole alkaloid barettin, isolated in 1986 from the cold water sponge *Geodia barretti* by Lidgren et al.,[1] has been the subject of debate during several years. The originally proposed structure for barettin, the diketopiperazine **1**, was disproved by an independent total synthesis of **1**, as well as the *E*-isomer **2** a year later (Fig. 1).[2] However, a recent publication by Sölter et al.[3] presented isolation and structure elucidation of a diketopiperazine from *G. barretti*, collected in Norway. The German group found the diketopiperazine to be a condensation product of 6-bromo-Δ-tryptophan[4] and arginine, i.e. compound **3**, which they believed represented the actual structure of barettin. Now we have indeed confirmed these findings after a reinvestigation of isolated material, combined with a total synthesis of compound **3**.

2. Results and discussion

Synthesis of arginine-containing peptides is often very laborious due to problems with the basic guanidino group in the arginine side chain. In our case, the guanidino group was protected by *tert*-butoxycarbonyl groups, via the excellent method by Bernatowicz et al.[5] Thus the Cu(II)-ornithine[6] complex (prepared from L-ornithine·HCl) is guanylated at N^{δ} with a protected derivative of 1-guanylpyrazole, N^{1}-[*N*,*N*′-bis(*tert*-butoxycarbonyl)amidino]pyrazole (**4**) to give the Cu(II)-complex of N^{ω},$N^{\omega'}$-bis(*tert*-butoxycarbonyl)-protected arginine derivative **5** in good yields, prepared as described in the literature.[5] Compound **5** was further N^{α}-protected with di-*t*-butyl dicarbonate in the presence of ethylenediaminetetraacetic acid (EDTA) to afford N^{α}-(*tert*-butoxycarbonyl)-N^{ω},$N^{\omega'}$-bis(*tert*-butoxycarbonyl)-L-arginine (**6**) in a reasonable yield (79%) (Scheme 1).

Using this protected arginine derivative, the saturated analogue of **3** (i.e. **9**) was prepared via standard peptide coupling procedures with 6-bromo-D,L-tryptophan methyl ester (**7**), obtained via esterification of commercially available 6-bromo-D,L-tryptophan. Removal of the protecting groups of the resulting dipeptide **8** with trifluoroacetic acid (TFA) and subsequent cyclisation[7] afforded

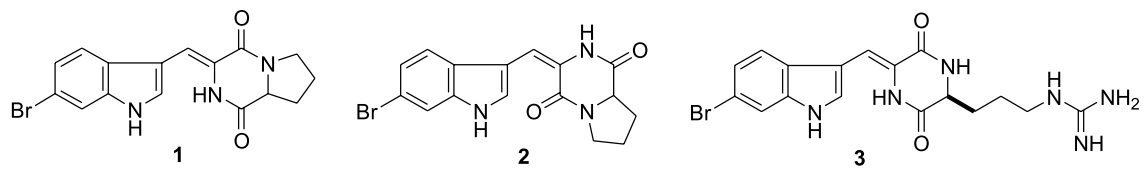

Figure 1.

Keywords: *Geodia Barretti*; Barettin; *N*-Boc protection of arginine; HWE-reaction.
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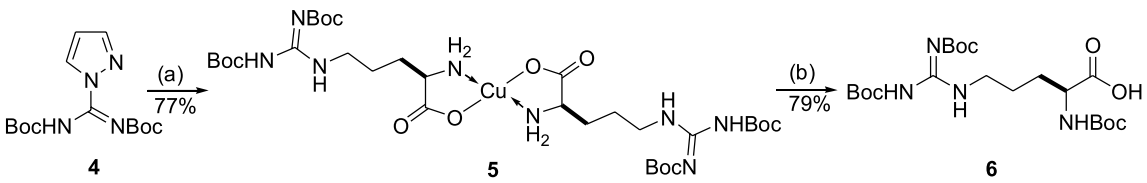
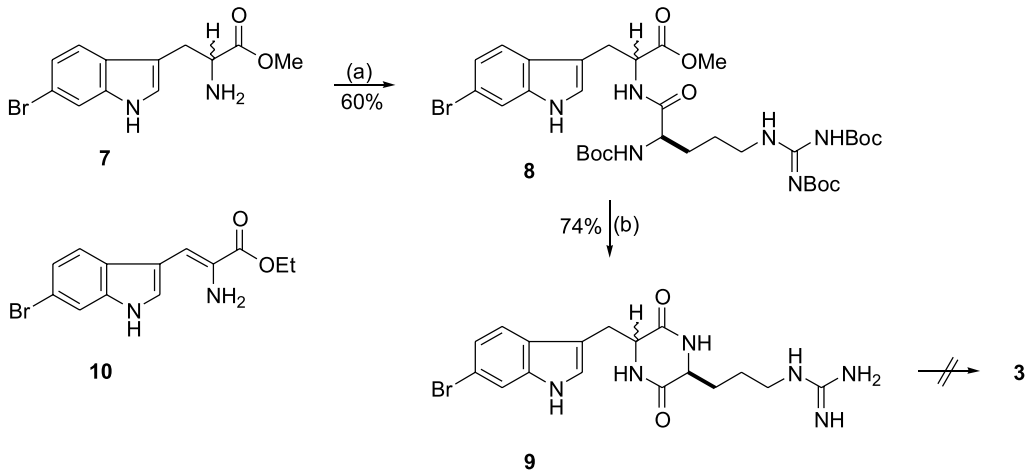
doi:10.1016/j.tet.2003.11.031



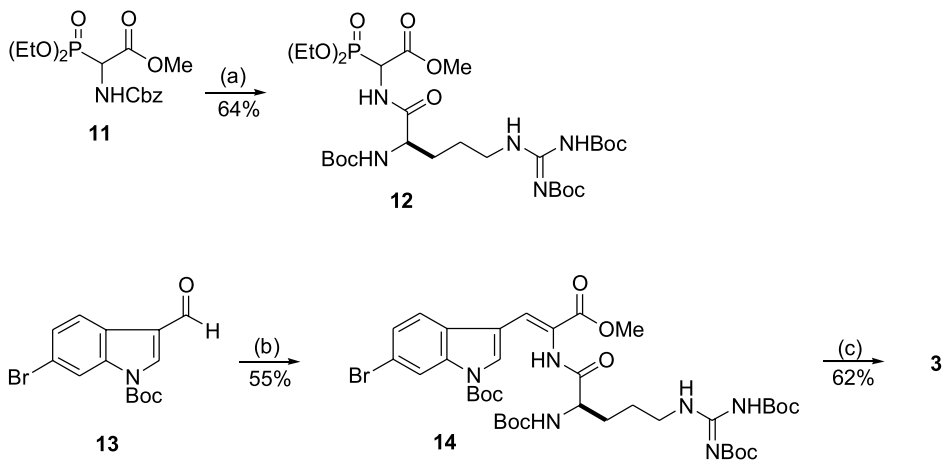
Scheme 1. (a) $Cu(Orn)_2{\cdot}CuCl_2$, DIEA, formamide/dioxane, rt 5 h. (b) $EDTA{\cdot}4Na{\cdot}2H_2O$, $NaHCO_3$, Boc_2O, H_2O/acetone, rt 12 h.

cyclo-6-bromo-D,L-Trp-L-Arg or 8,9-dihydrobarettin (**9**) as a mixture of diastereomers. Although 8,9-dihydrobarettin has previously been identified as a congener of barettin in *G. barretti*, the specific rotation of the natural product still remains to be determined.[8] Here, no efforts were made to separate the diastereomeric mixture. However, despite several attempts, using e.g. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and trichloroisocyanuric acid (TCCA), we were not able to dehydrogenate **9** to compound **3**. Neither did it prove to be possible to use 6-bromo-Δ-tryptophan ethyl ester[9] (**10**) as starting material, since all attempted peptide coupling with compounds **6** and **10** failed (Scheme 2).

Another route towards functionalised dehydroamino acids involves Horner–Wadsworth–Emmons type reactions. Hydrogenolysis of methyl 2-benzyloxycarbonylamino-2-(diethoxyphosphinyl)-acetate (**11**)[10] afforded the free amine which was immediately reacted with the amino acid derivative **6** in presence of 1-ethyl-3-(3′-dimethylamino-propyl)carbodiimide hydrochloride (EDCI), which gave the dipeptide **12** in 64% yield. The phosphonoglycinate **12** was further condensed with 6-bromo-1-(*tert*-butoxycarbonyl)-indole-3-carboxaldehyde (**13**)[11] using 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as the base to furnish the desired compound **14**. The yield in this particular reaction has so far been only moderate, usually around 55%. Although the low yield might indicate formation of the *E*-isomer, we were only able to detect the desired *Z*-isomer of **14**. However, there are indications in the literature that *Z*-isomers are formed predominately using DBU as the base in this type of reactions.[12] Using potassium *tert*-butoxide (*t*-BuOK) as



Scheme 2. (a) **6**, EDCI, HOBt, DIEA, CH_2Cl_2, rt 18 h. (b) (i) TFA, CH_2Cl_2, rt 12 h. (ii) 0.1 M HOAc/1-BuOH, NMM, reflux 6 h.



Scheme 3. (a) (i) H_2, Pd/C, EtOH, 4.5 h. (ii) **6**, EDCI, HOBt, DIEA, CH_2Cl_2, rt 18 h. (b) **12**, DBU, CH_2Cl_2, −78° to rt 20 h. (c) (i) TFA, CH_2Cl_2, rt 12 h. (ii) 0.1 M HOAc/1-BuOH, NMM, reflux 6 h.

base in the same reaction resulted in an even lower yield. Several acidic hydrogen atoms present in compound **12** might also account for the poor yield but variation of the amount of base used failed to improve the results.

The four Boc-protecting groups in **14** were removed by treatment with TFA at ambient temperature overnight. The solvent was then removed and the residue in the flask dissolved in 1-butanol containing 0.1 M acetic acid, with addition of *N*-methylmorpholine (NMM). After 5 h at reflux the solvents were removed, giving barettin (**3**) in 62% yield (Scheme 3).

The analytical data of this synthetic material agreed completely with those of the natural product.[8] The NMR data of **3** are in agreement with those reported by Sölter et al.[3,13]

3. Experimental

3.1. General

NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively. NMR spectra were recorded in DMSO-d_6 or $CDCl_3$, using the solvent signal as reference. δ Values are given in ppm, coupling constants are given in Hz. The IR spectra were acquired using a FT-IR instrument. Optical rotation values were determined in a polarimeter equipped with a 1 mL cell measuring 10 cm using the emission wavelength of a sodium lamp; concentrations are given in g/100 mL. High-resolution mass spectroscopic (HRMS) analyses were performed by E. Nilsson, University of Lund, Sweden. Melting points were determined on a capillary melting point apparatus. Chromatographic separations were performed on silica gel 60 (230–400 mesh). All reagents used were purchased from Aldrich, Lancaster, Merck or Biosynth and were used as received. All solvents were purified by distillation or were of analytical grade.

3.1.1. N^{α}-(*tert*-Butoxycarbonyl)-N^{ω},$N^{\omega'}$-bis(*tert*-butoxycarbonyl)-L-arginine (6). To a suspension of $Cu[Arg^{\omega,\omega}(Boc)_2]_2$ (**5**)[5] (4.03 g, 5.00 mmol), EDTA·4Na·2H_2O (2.23 g, 6.00 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in H_2O (30 mL), a solution of Boc_2O (2.40 g, 11.0 mmol) in acetone (30 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 h when the solvent was evaporated. The aqueous mixture was acidified with 5% $KHSO_4$, until ~pH 3. The resulting gummy precipitate was extracted with EtOAc (3×40 mL) and the combined organic phases were washed with H_2O (100 mL), brine (100 mL) and dried over $MgSO_4$. Evaporation furnished a yellow oil which was purified by column chromatography using hexane/EtOAc (60:40) as eluent, yielding **6** as a colourless glass (3.77 g, 79%): $[\alpha]_D^{21}$ +7° (*c* 0.1, MeOH); IR (KBr): 3332, 2980, 1722, 1634, 1616, 1368, 1332, 1158, 1136, 1052 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.53 (s, 1H), 11.49 (s, 1H), 8.29–8.25 (m, 1H), 7.08 (d, *J*=8.0 Hz, 1H), 3.85–3.82 (m, 1H), 3.27–3.25 (m, 2H), 1.57–1.35 (m, 31H); ^{13}C NMR (DMSO-d_6): δ 174.1 (s), 163.1 (s), 155.6 (s), 155.3 (s), 152.1 (s), 82.9 (s), 78.1 (s), 78.0 (s), 53.3 (d), 39.6 (t), 28.2 (q), 28.1 (t), 28.0 (q), 27.6 (q), 25.5 (t). HRMS (FAB+) *m/z* calcd for $C_{21}H_{39}N_4O_8$ $(M+H)^+$ 475.2768, found 475.2767.

3.1.2. 6-Bromo-D,L-tryptophan methyl ester·HCl (7). 6-Bromo-D,L-tryptophan (1.42 g, 5.00 mmol) was suspended in MeOH (18 mL) at 0 °C. $SOCl_2$ (0.37 mL, 5.05 mmol) was added dropwise and the mixture kept at 0 °C for an additional 0.5 h. The solution was refluxed for 1.5 h and thereafter allowed to cool. The solvent was evaporated leaving a quantitative yield of 6-bromo-D,L-tryptophan methyl ester·HCl (**7**) as a pinkish solid: mp 240.0–242.5 °C; IR (KBr): 3274, 2876, 1743, 1590, 1500, 1445, 1246, 1105, 1080, 802 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.37 (s, 1H), 8.70 (br s, 2H), 7.57 (d, *J*=1.6 Hz, 1H), 7.50 (d, *J*=8.5 Hz, 1H), 7.30 (d, *J*=2.3 Hz, 1H), 7.15 (dd, *J*=1.7, 8.5 Hz, 1H), 4.22 (t, *J*=6.3 Hz, 1H), 3.63 (s, 3H), 3.38–3.34 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 169.7 (s), 137.1 (s), 126.1 (d), 126.0(s), 121.5 (d), 119.9 (d), 114.1 (d), 113.9 (s), 106.8 (s), 52.7 (q), 52.6 (d), 25.8 (t). HRMS (FAB+) *m/z* calcd for $C_{12}H_{14}N_2O_2^{79}Br$ $(M+H)^+$ 297.0239, found 206.0232.

3.1.3. N^{α}-(Boc)-N^{ω},$N^{\omega'}$-bis(Boc)-L-Arg-6-bromo-D,L-TrpOMe (8). A mixture of 6-bromo-D,L-tryptophan methyl ester·HCl (**7**) (999 mg, 3.00 mmol), arginine derivative **6** (1.42 g, 3.00 mmol), EDCI (690 mg, 3.60 mmol) and HOBt (486 mg, 3.60 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C. Et_3N (0.84 mL, 6.00 mmol) was added and the solution was allowed to reach room temperature overnight. The reaction mixture was transferred to a separatory funnel, additional CH_2Cl_2 (15 mL) was added and the organic phase was washed with H_2O (2×20 mL), brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography (hexane/EtOAc 60:40) to give the protected dipeptide **8** as a clear oil (1.36 g, 60%): IR (KBr): 3333, 2979, 2936, 1723, 1647, 1620, 1368, 1163, 1135 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.50 (s, 1H), 11.01 (d, *J*=5.0 Hz, 1H), 8.26–8.19 (m, 2H) 7.51 (s, 1H) 7.45 (d, *J*=8.5 Hz, 1H) 7.19 (dd, *J*=2.0, 8.4 Hz, 1H), 7.12 (dd, *J*=1.2, 8.4 Hz, 1H), 6.86–6.76 (m, 1H), 4.53–4.51 (m, 1H), 4.02–3.97 (m, 1H), 3.59–3.54 (m, 3H), 3.25–2.98 (m, 4H), 1.47–1.34 (m, 31H); ^{13}C NMR (DMSO-d_6): δ 172.0 (s), 171.9 (s), 171.8 (s), 163.1 (s), 155.2 (s), 152.1 (s), 136.9 (136.8) (s), 126.1 (126.0) (s), 125.0 (124.9) (d), 121.2 (d), 119.8 (119.7) (d), 113.9 (d), 113.7 (s), 109.7 (109.6) (s), 82.8 (s), 78.1 (s), 78.1 (s), 52.8 (52.7) (d), 51.8 (51.7) (q), 39.7 (39.6) (t), 31.2 (d), 29.3 (t), 28.1 (q), 28.0 (q), 27.6 (q), 27.0 (26.8) (t), 25.1 (24.9) (t). Figures within brackets refer to doublets arising due to the presence of diastereomers. HRMS (FAB+) *m/z* calcd for $C_{33}H_{50}N_6O_9^{79}Br$ $(M+H)^+$ 753.2823, found 753.2835.

3.1.4. 8,9-Dihydrobarettin (9). The dipeptide **8** (1.14 g, 1.52 mmol) was dissolved in CH_2Cl_2 (15 mL) and TFA (2.32 mL, 30.31 mmol) was added at room temperature. The reaction mixture was stirred for 5 h, and then evaporated to dryness. The residue was dissolved in 1-butanol (15 mL) containing 0.1 M AcOH. NMM (0.17 mL, 1.52 mmol) was added and the reaction mixture was refluxed for 12 h and thereafter allowed to cool. The reaction mixture was washed with H_2O (2×20 mL), brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated affording cyclo-6-bromo-D,L-Trp-L-Arg or 8,9-dihydrobarettin (**9**) as a yellowish solid (474 mg 74%): IR (KBr):

3339, 3201, 2959, 2934, 2873, 1668 (br), 1456, 1330, 1202, 1136, 802 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.08 (s, 1H), 11.02 (s, 1H), 8.15 (br s, 2H), 8.01 (s, 1H), 7.92 (s, 1H), 7.54–7.51 (m, 4H), 7.45 (t, J=5.5 Hz, 1H), 7.24 (t, J=5.3 Hz, 1H), 7.30–6.70 (m, 6H), 7.10–7.05 (m, 4H), 4.13–4.03 (m, 2H), 3.63–3.59 (m, 1H), 3.32–2.97 (m, 3H), 3.03–2.97 (m, 4H), 2.81–2.71 (m, 2H), 1.55–1.27 (m, 4H), 1.10–0.62 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 168.0 (167.4) (s), 167.0 (166.7) (s), 156.9 (156.8) (s), 136.8 (136.7) (s), 126.9 (126.7) (s), 125.7 (125.5) (d), 121.2 (121.1) (d), 120.8 (120.7) (d), 113.8 (113.7) (d), 113.6 (113.5) (s), 109.0 (108.8) (s), 55.4 (55.3) (d), 53.3 (52.9) (d), 40.4 (40.2) (t), 29.2 (t), 28.7 (28.6) (t), 23.5 (23.1) (t). Figures within brackets refer to doublets arising due to the presence of diastereomers. HRMS (FAB+) m/z calcd for $C_{17}H_{22}N_6O_2^{79}Br$ $(M+H)^+$ 421.0988, found 421.0996.

3.1.5. 6-Bromo-Δ-tryptophan metyl ester (10). 2-Nitro-pent-2-enoic acid ethyl ester[14] (1.59 g, 8.40 mmol) was mixed with 6-bromoindole (1.37 g, 7.00 mmol) under a nitrogen atmosphere at ambient temperature. A mixture of Et_2O/hexane (1:1) was added after 12 h and the yellow precipitate formed was collected and washed with further Et_2O/hexane (1:1) to give 3-(6-bromo-1*H*-indol-3-yl)-2-nitro-acrylic acid ethyl ester (808 mg), which was used without further purification. A second crop was collected from the mother liquid (362 mg) to give a total yield of 1.17 g (54%).

$SnCl_2{\cdot}2H_2O$ (2.36 g, 10.5 mmol) was dissolved in 3 M HCl in MeOH (20 mL) at 0 °C. 3-(6-Bromo-1*H*-indol-3-yl)-2-nitro-acrylic acid ethyl ester (1.02 g, 3.00 mmol) was added to the solution in small portions during 0.5 h. The mixture was kept at 0 °C for 1 h. The precipitate formed was collected by filtration and washed with a small amount of ether. The hydrochloride of **10** was obtained as a pinkish solid (560 mg, 54%): mp 189 °C (dec); IR (KBr): 3140, 2996, 2502, 1675, 1653, 1565, 1272, 1145 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.32 (s, 1H), 8.19 (d, J=2.8 Hz, 1H), 7.75 (d, J=1.7 Hz, 1H), 7.75–7.24 (br, 3H), 7.56 (s, 1H), 7.29 (dd, J=1.7, 8.5 Hz, 1H), 4.33 (q, J=7.1, 14.1 Hz, 2H), 1.39 (t, J=7.1 Hz, 3H); ^{13}C NMR (DMSO): δ 164.0 (s), 136.6 (s), 129.9 (d), 126.0 (s), 123.3 (d), 120.0 (d), 119.0 (d), 118.1 (s), 115.1 (s), 114.7 (d), 107.8 (s), 61.6 (t), 14.2 (q). HRMS (FAB+) m/z calcd for $C_{13}H_{13}N_2O_2^{79}Br$ $(M)^+$308.0160, found 308.0160.

3.1.6. Methyl 2-(N^{α}-(Boc)-N^{ω},$N^{\omega'}$-bis(Boc)-L-arginyl-amino)-2-(diethoxyphosphinyl)-acetate (12). A solution of compound **11**[10] (2.13 g, 5.94 mmol) in EtOH (60 mL) was hydrogenated in the presence of Pd/C (5%; 213 mg) at room temperature for 4.5 h. The reaction mixture was filtered through celite and the filtrate evaporated leaving a clear oil. The free amine was immediately dissolved in CH_2Cl_2 (10 mL) and added to an ice-cold mixture of the arginine derivative **6** (2.56 g, 5.40 mmol), HOBt (803 mg, 5.94 mmol), EDCI (1.14 mg, 5.94 mmol) and DIEA (1.03 mL, 5.94 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was allowed to reach room temperature. After 15 h the solvent was evaporated and the residue was taken up in EtOAc (150 mL) then washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$ and evaporated. Purification by column chromatography with EtOAc/hexane (70:30) as eluent afforded the title compound **12** as a clear oil. Yield: 2.35 g (64%): $[\alpha]_D^{21}$ −7° (c 0.2, MeOH); IR (KBr): 3332, 2978, 2933, 1752, 1719, 1680, 1639, 1617, 1367, 1330, 1252, 1164, 1134, 1050, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.45 (s, 1H), 8.34–8.30 (m, 1H), 7.27–7.19 (m, 1H), 5.42–5.32 (m, 1H), 5.19 (d, J=8.9 Hz, 1H), 4.22–4.06 (m, 4H), 3.78 (s, 3H), 3.43–3.39 (m, 2H), 1.86–1.27 (m, 38 H). MS (ESI) m/z 680 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{28}H_{53}N_5O_{12}P$ $(M+H)^+$ 682.3428, found 682.3439.

3.1.7. N^{α}-(Boc)-N^{ω},$N^{\omega'}$-bis(Boc)-L-Arg-6-bromo-Δ-(1-Boc)TrpOMe (14). The arginine derivative **12** (710 mg, 1.04 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise to a solution of DBU (0.31 mg, 2.09 mmol) in CH_2Cl_2 (5 mL) at −78 °C under a nitrogen atmosphere. After 30 min 6-bromo-1-(*tert*-butoxycarbonyl)-indole-3-carboxaldehyde (**13**)[11] (338 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was allowed to reach room temperature. After 18 h the mixture was evaporated to dryness and the residue dissolved in EtOAc (20 mL), washed with H_2O (2×20 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$ and evaporated, leaving a yellow oil which was purified by column chromatography. Elution with hexane/EtOAc (80:20 to 60:40) afforded **14** as a yellow oil (490 mg, 55%): $[\alpha]_D^{21}$+ 74° (c 0.2, MeOH); IR (KBr): 3330, 2978, 2933, 1721, 1641, 1619, 1368, 1333, 1251, 1155, 1135, 1051 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.46 (s, 1H), 8.52–8.41 (m, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 7.83 (s, 1H), 7.67 (s, 1H), 7.53 (d, J=8.5 Hz, 1H), 7.39 (dd, J=1.7, 8.5 Hz, 1H), 5.72 (d, J=8.1 Hz, 1H), 4.51–4.37 (m, 1H), 3.81 (s, 3H), 3.60–3.55 (m, 1H), 3.49–3.39 (m, 1H), 2.02–1.86 (1H), 1.72–1.25 (m, 39H); ^{13}C NMR ($CDCl_3$): δ 171.0 (s), 165.3 (s), 163.4 (s), 156.8 (s), 155.9 (s), 153.4 (s), 148.9 (s), 135.6 (s), 128.6 (d), 128.3 (s), 126.5 (d), 124.6 (d), 123.2 (s), 120.4 (d), 118.8 (s), 118.7 (d), 114.1 (s), 85.2 (s), 83.4 (s), 80.2 (s), 79.6 (s), 54.4 (d), 52.8 (q), 40.0 (t), 29.1 (t), 28.5 (q), 28.3 (q), 28.2 (q), 26.1 (t). MS (ESI) m/z 849 and 851 $(M-H)^-$; HRMS (FAB+) m/z calcd for $C_{38}H_{56}N_6O_{11}^{79}Br$ $(M+H)^+$ 851.3190, found 851.3199.

3.1.8. Barettin (3). TFA (0.91 mL) was added a solution of compound **7** (500 mg, 0.59 mmol) in CH_2Cl_2 (10 mL) and stirred at room temperature for 8 h. The solvent was evaporated and the residue dissolved in 1-BuOH (10 mL) containing 0.1 M HOAc. After addition of NMM (0.06 mL, 0.59 mmol) the reaction mixture was heated at reflux for 4.5 h. The mixture was allowed to cool and thereafter washed with H_2O (2×15 mL), brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded barettin (**3**) as a dark yellow solid (153 mg, 62%). The NMR data of **3** are in agreement with those reported by Sölter et al.[3,13] $[\alpha]_D^{26}$ −32.5° (c 2, MeOH), [lit[1] $[\alpha]_D$ −25° (c 3, MeOH)].

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