Total Syntheses of the Benzodiazepine Alkaloids Circumdatin F and Circumdatin C

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Total syntheses of circumdatin F and circumdatin C, which both possess a 3*H*-quinazolin-4-one as well as a 1,4-benzodiazepin-5-one moiety, are described. A tripeptide derivative was synthesized as a key intermediate and dehydrated to a benzoxazine by reaction with triphenylphosphine, iodine, and a tertiary amine. The natural products were attained via rearrangements to an amidine intermediate, deprotection with 45% HBr in acetic acid, and cyclization on silica gel.

Introduction

In 1999, several new fused benzodiazepine alkaloids were isolated from a terrestrial isolate of the fungus *Aspergillus ochraceus*.[1] Circumdatin F (**1**) and C (**2**) are prototypical members, while others such as circumdatin D (**3**) and E (**4**) feature an additional tetrahydropyrrole ring (Figure 1). The related alkaloid, asperlicin (**5**), produced by *Aspergillus alliaceus*, is a potent cholecystokinin antagonist,[2] and benzomalvin A (**6**), isolated from a fungus culture of *Penicillium* sp, showed inhibitory activity against substance P at the guinea pig, rat, and human neurokinin NK1 receptors, respectively.[3] Sclerotigenin (**7**) was recently isolated from organic extracts of sclerotia of *Penicillium sclerotigenum* (NRRL 3461),[4] a potential antiinsectan benzodiazepine alkaloid. The total syntheses of asperlicin (**5**)[5] and benzomalvin A (**6**)[6] have been reported, and a synthesis of sclerotigenin (**7**)[7] was reported already 20 years ago, i.e., before its identification as a natural product. Now we wish to report the total syntheses of circumdatin F (**1**) and C (**2**).

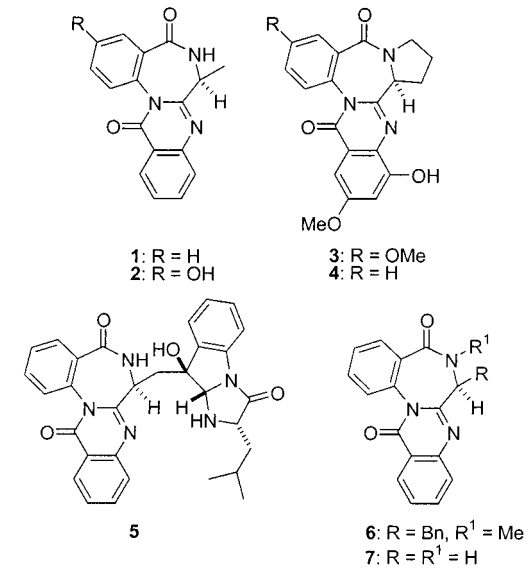

Figure 1.

Results and Discussion

Retrosynthetically, compounds **1** and **2** could formally be biosynthesized from two appropriately substituted anthranilic acid units and L-alanine. Dehydration of a peptide precursor **X** (Figure 2) represents a route to the quinazoline ring of these natural products.[8] However, the aza-Wittig disconnection[6] might be useful, but the precursor **Y** will require additional manipulation of protecting groups.

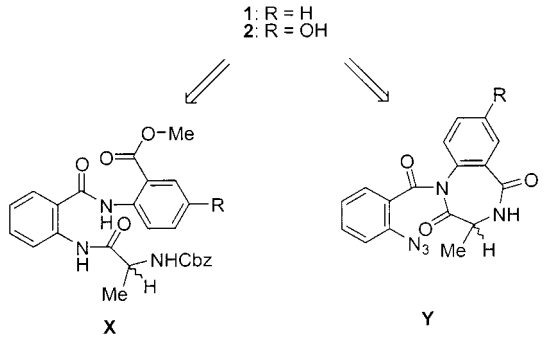

Figure 2.

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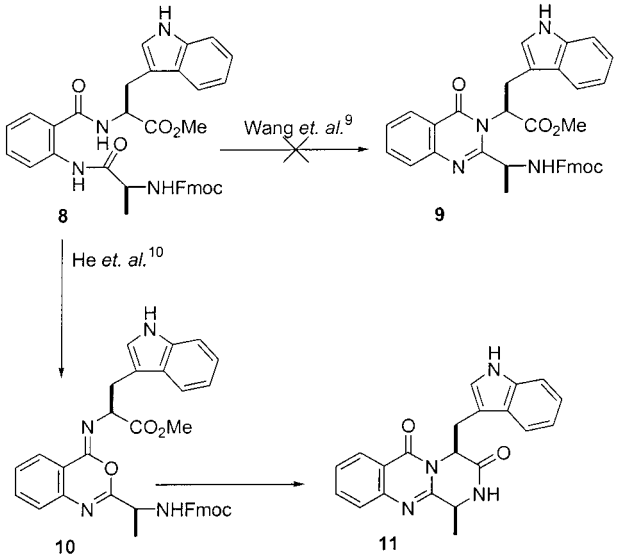
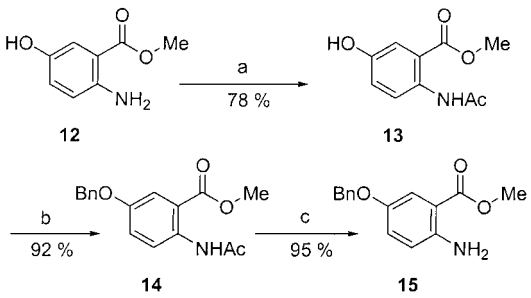
Scheme 1



Scheme 2[a]

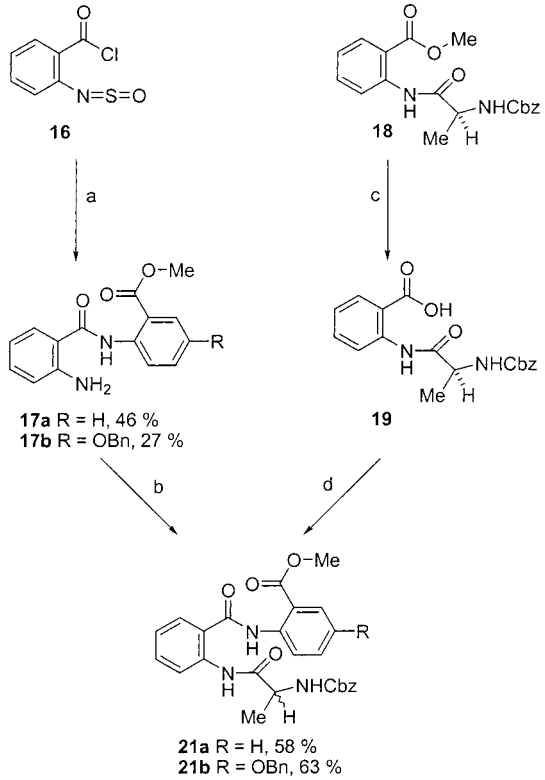


[a] Reagents and conditions: (a) Ac_2O, EtOH, 40−50 °C, 3 h; (b) BnBr, K_2CO_3, acetone, reflux, 3.5 h; (c) $HCl_{(g)}$ in MeOH, reflux, 8 h.

Wang and Ganesan have reported[9] a route to fumiquinazoline G (**11**), wherein the protected tripeptide **8** was used as a key intermediate (Scheme 1) in the cyclization step. These workers proposed the cyclization product to be a quinazolin-4-one **9**, but He and Snider showed[10] it rather to be the 4-imino-4*H*-3,1-benzoxazine **10**. We considered this synthetic strategy to be useful for syntheses of circumdatin F (**1**) and C (**2**), but rather than to create two six-membered rings, we wanted to induce cyclization involving one six-membered and one seven-membered ring.

Circumdatin C (**2**) can be considered as derived from 5-hydroxyanthranilic acid, and several suitably protected 5-hydroxy derivatives of, e.g., methyl anthranilate are known.[11,12] The benzylated derivative **15**[11] was prepared from the known 2-amino-5-hydroxybenzoic acid methyl ester **12**,[12] obtained by esterification of commercially available 2-amino-5-hydroxybenzoic acid in 95% yield followed by *N*-acetylation with acetic anhydride in ethanol to the *N*-acetyl derivative **13** (Scheme 2). Compound **13** was *O*-benzylated with benzyl bromide and K_2CO_3 in acetone to compound **14**, which was treated with HCl in methanol at reflux to give methyl 5-(benzyloxy)anthranilate **15** in an overall yield of 65% from 2-amino-5-hydroxybenzoic acid. *N*-Acetylation and *O*-benzylation of 4-amino-2-hydroxybenzoic acid methyl ester are known according to this methodology.[13]

Scheme 3[a]



[a] Reagents and conditions: (a) methyl anthranilate or **15**, toluene, rt, 48 h; (b) Cbz-L-Ala, DCC, CH_2Cl_2, rt; (c) LiOH, MeOH/THF/H_2O (3:1:1), rt, 3 h; (d) methyl anthranilate or **15**, PCl_3, toluene, reflux, 3h.

N-Sulfinylanthraniloyl chloride (**16**),[14a] previously described as a sulfinamide anhydride,[14b] was prepared from anthranilic acid and thionyl chloride and treated with methyl anthranilate or compound **15** to yield 2-(2-amino-benzoylamino)-benzoic acid methyl ester (**17a**)[15] or 2-(2-amino-benzoylamino)-5-benzyloxybenzoic acid methyl ester (**17b**), respectively. Condensation of **17a,b** with *N*-Cbz-L-alanine[16] and DCC afforded the tripeptide derivatives **21a,b** (=**X**, Figure 2) in 58% and 63% yield, respectively (Scheme 3).

In a second synthetic approach the tripeptide derivatives **21a,b** were made via condensation of *N*-Cbz-L-alanine[16] with methyl anthranilate under standard coupling conditions with DCC and *N*-hydroxybenzotriazole, which resulted in 57% yield of the corresponding amide **18** (Scheme 3). Hydrolysis of the ester functionality using LiOH yielded the acid **19**[17] in 82% yield. Construction of analogues of the acid **19** were executed according to this protocol.[18]

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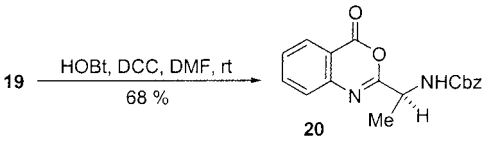
Scheme 4



When peptide coupling reagents such as DCC[19] or 1-methyl-2-chloropyridinium iodide[20] were used on compound **19** the sole product was an intramolecular cyclization to the benzoxazinone derivative **20**[17] (Scheme 4) and no coupling products **21a,b** were detected. The acid **19** was treated with PCl_3 and then heated with methyl anthranilate or compound **15** in toluene to give the tripeptide derivatives **21a,b** in 41% and 43% yield, as racemates.

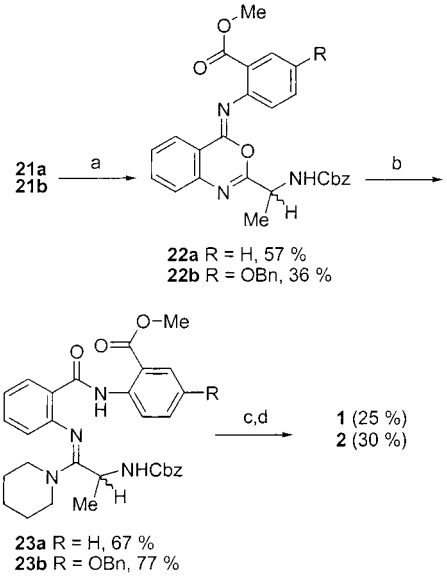
Cyclization of the tripeptide derivatives **21a,b** with PPh_3 and I_2 in the presence of $EtN(i\text{-}Pr)_2$ in CH_2Cl_2 at room temperature gave the 4-imino-4*H*-3,1-benzoxazines **22a,b** in 57% and 36% isolated yields, respectively, after separation on silica gel. A further less pure quantity of the component **22a** was isolated in 20% yield. According to ^1H NMR, this material contained starting material (15%) but could nevertheless be used directly in the synthesis of circumdatin F (**1**) without purification until the last step. Similarly compound **22b** and starting material (95:5) was isolated in 38% yield and could be converted to circumdatin C (**2**) in the same fashion as compound **22a**.

When compounds **22a,b** were treated with 20% piperidine in EtOAc at room temperature, the amidine carboxamides **23a,b** were isolated in 67% and 77% yield, respectively, and used immediately in the deprotection by heating at 50 °C with 45% HBr in HOAc. During the deprotection of **23b** both the benzyl- and the Cbz-group were removed, as expected by the use of strong acid.[21] It is presumed that the HBr salts of deprotected **23a,b** cyclize to 3*H*-quinazolin-4-one, which quickly eliminate methanol thus yielding circumdatin F (**1**) and C (**2**) in 25% and 30% yield, respectively, from the amidine carboxamides **23a,b** (Scheme 5).

The spectra of the synthetic **1** and **2** were identical with the published spectroscopic data.[1] Due to low solubility in MeOH-d_4 we did ran spectra in $CDCl_3$ and DMSO-d_6, respectively. The specific optical rotation of the synthetic circumdatin C ($[\alpha]^{20}_D$ −91° (*c* 0.17, MeOH)) differed from the reported value for natural circumdatin C ($[\alpha]^{22}_D$ −75° (*c* 0.16, MeOH)).[1a] Synthetic circumdatin F gave the optical rotation, $[\alpha]^{20}_D$ −55° (*c* 0.94, $CHCl_3$), no value for the natural circumdatin F has been published.

In conclusion, the total synthesis of circumdatin F (**1**) has been achieved in 5 steps and 5.5% overall yield from **17a**, and circumdatin C (**2**) was attained in 10 steps and 0.9% overall yield from 2-amino-5-hydroxybenzoic acid.

Scheme 5[a]



[a] Reagents and conditions: (a) PPh_3, I_2, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, rt, 6 h; (b) 20% piperidine in EtOAc, rt, 5 h; (c) 45% HBr in HOAc, 60 °C, 1h; (d) SiO_2, triethylamine or $EtN(i\text{-}Pr)_2$, EtOAc, rt.

Experimental Section

General Aspects. NMR spectra were recorded at 300 MHz for ^1H and 75 or 125 MHz for ^{13}C; δ values are given in ppm, coupling constants are reported in hertz. Infrared spectra were recorded on a FT-IR instrument. Mass spectra were recorded using a GC/MS system operating in the electron impact (EI) mode at 70 eV. Only fragments larger than 20% of the base peak are given. The element compositions were determined by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. HRMS analyses were performed by Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden. Melting points were measured using the capillary method and are uncorrected. All reagents were of commercial quality and were used as received. All solvents were purified by distillation or were HPLC grade. Reactions were monitored by thin-layer chromatography, on aluminum plates coated with silica gel with fluorescent indicator. Separations by flash chromatography were preformed on silica gel. 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.

2-(2-Amino-benzoylamino)-benzoic Acid Methyl Ester (17a). Methyl anthranilate (1.16 g, 7.7 mmol) dissolved in toluene (20 mL) was added dropwise to a solution of compound **16**[14a] (2.02 g, 10 mmol) in toluene (20 mL) at room temperature. The mixture was stirred at ambient temperature for 48 h, poured into cold water (50 mL), and extracted with $CHCl_3$ (50 mL × 2). The organic phases were washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and dried (Na_2SO_4). The solution was concentrated under reduced pressure to afford an oily residue, which was purified by flash chromatography (20% diethyl ether in hexane as eluent) to give compound **17a** (0.95 g, 46%) as a light yellow solid: mp 116−117 °C (lit.[15], mp 128 °C); IR (KBr) 3474, 3364, 1684, 1660, 1519, 1450, 1262, 765, 743 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.96 (s, 3H), 5.52 (br s, 2H), 6.74 (dd, *J* = 8.3, 1.0, 1H), 6.79 (ddd, *J* = 8.0, 7.0, 1.1, 1H), 7.11 (ddd, *J* = 8.1, 7.1, 1.1, 1H), 7.28 (ddd, *J* = 8.3, 7.0, 1.4, 1H), 7.59 (ddd, *J* = 8.6, 7.1, 1.6, 1H), 7.75 (dd, *J* = 8.0, 1.4, 1H), 8.08 (dd, *J* = 8.1, 1.6, 1H), 8.83 (dd, *J* = 8.6, 1.0, 1H), 11.83 (s, 1H); δ_C (75 MHz, $CDCl_3$) 52.6 (q), 115.5 (s), 116.0 (s), 117.3 (d), 117.8 (d), 120.7 (d), 122.6 (d), 127.9 (d), 131.2 (d), 133.1 (d), 134.8 (d), 142.1 (s), 149.8 (s), 168.3 (s), 169.1 (s).

2-(2-Amino-benzoylamino)-5-benzyloxybenzoic Acid Methyl Ester (17b). Compound **17b** was prepared similarly to compound **17a** using compound **15**, but compound **17b** was purified by recrystallization from 35% ethyl acetate in hexane: yield, 27%; mp 149−150 °C; IR (KBr) 3475, 3360, 1686, 1660, 1523, 1227, 1008, 836, 753, 692 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.86 (s, 3H), 5.15 (s, 2H), 6.52 (s, 2H), 6.63 (ddd, *J* = 7.9, 7.1, 0.9, 1H), 6.78 (d, *J* = 8.3, 1H), 7.23 (ddd, *J* = 8.3,

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7.0, 1.2, 1H), 7.26−7.52 (m, 6H), 7.54 (d, J = 3.0, 1H), 7.59 (d, J = 8.0, 1H), 8.33 (d, J = 9.1, 1H), 11.02 (s, 1H); δ_C (75 MHz, DMSO-d_6) 52.6 (q), 69.6 (t), 114.1 (s), 115.1 (d), 115.5 (d), 116.9 (d), 118.8 (s), 121.0 (d), 123.0 (d), 127.4 (d), 127.7 (d), 127.9 (d), 128.4 (d), 132.5 (d), 133.8 (s), 136.7 (s), 150.3 (s), 153.5 (s), 167.1 (s), 167.6 (s).

2-[2-(*N*-Benzyloxycarbonyl-L-alanyl)-benzoylamino]-benzoic Acid Methyl Ester (21a). Method A. DCC (180 mg, 0.87 mmol) dissolved in CH_2Cl_2 (3 mL) was added to a solution of compound **17a** (195 mg, 0.72 mmol) and *N*-Cbz-L-Ala[16] (193 mg, 0.86 mmol) in CH_2Cl_2 (6 mL) at 0 °C, and the mixture was stirred at ambient temperature overnight. After filtration through Celite, the organic phase was washed with 2 M HCl (10 mL), saturated $NaHCO_3$ (10 mL), and water (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford a solid residue, which was purified by flash chromatography (30% ethyl acetate in hexane as eluent) to give compound **21a** (200 mg, 58%) as a white solid: $[\alpha]^{20}_D$ −21° (c 1.05, $CHCl_3$); mp 147−148 °C; IR (KBr) 3298, 2928, 1697, 1651, 1583, 1540, 1445, 1268, 1066, 754 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.55 (d, J = 7.1, 3H), 3.97 (s, 3H), 4.41−4.54 (m, 1H), 5.14 and 5.17 (AB q, J = 12.3, 2H), 5.60 (d, J = 6.4, 1H), 7.15 (ddd, J = 8.3, 7.2, 1.0, 1H), 7.20−7.45 (m, 6H), 7.47−7.60 (m, 2H), 7.89 (d, J = 7.1, 1H), 8.10 (dd, J = 8.0, 1.6, 1H), 8.69 (d, J = 8.3, 1H), 8.78 (d, J = 8.4, 1H), 11.78 (s, 1H), 12.09 (s, 1H); δ_C (75 MHz, $CDCl_3$) 19.3 (q), 52.1 (d), 52.8 (q), 67.2 (t), 115.8 (s), 120.8 (s), 120.8 (d), 121.7 (d), 123.4 (d), 123.7 (d), 127.3 (d), 128.1 (d), 128.2 (d), 128.7 (d), 131.2 (d), 133.3 (d), 134.9 (d), 136.5 (s), 140.2 (s), 141.3 (s), 155.9 (s), 167.8 (s), 169.1 (s), 171.3 (s). Anal. Calcd for $C_{26}H_{25}N_3O_6$: C, 65.68; H, 5.30; N, 8.84. Found: C, 65.79; H, 5.28; N, 8.81.

Method B. PCl_3 (105 mg, 0.76 mmol) was added to a mixture of **19** (113 mg, 0.33 mmol) and methyl anthranilate (67 mg, 0.44 mmol) in toluene (3 mL, distilled over Na) under N_2. The mixture was heated at reflux for 3 h and then concentrated under reduced pressure to afford a solid residue, which was purified as in method A to give compound **21a** (60 mg, 41%).

2-[2-(*N*-Benzyloxycarbonyl-L-alanyl)-benzoylamino]-5-benzyloxy-benzoic Acid Methyl Ester (21b). Method A. Compound **21b** was prepared similarly to compound **21a** using compound **17b**, but compound **21b** was purified by recrystallization from ethyl acetate/chloroform (4:1) in 52% yield. The evaporated mother liquor was purified by flash chromatography (40% ethyl acetate in hexane as eluent) to give additional **21b** (230 mg, 11%): total yield, 63% as a white solid; $[\alpha]^{20}_D$ −8.6° (c 1.0, $CHCl_3$); mp 192−193 °C; IR (KBr) 3318, 1697, 1538, 1285, 1229, 1067, 1016, 751, 698 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.31 (d, J = 7.3, 3H), 3.83 (s, 3H), 4.00−4.13 (m, 1H), 4.89 and 5.00 (AB q, J = 12.5, 2H), 5.12 (s, 2H), 7.19 (dd, J = 9.0, 3.0, 1H), 7.24−7.48 (m, 11H), 7.53 (d, J = 3.0, 1H), 7.58 (ddd, J = 8.4, 7.2, 1.4, 1H), 7.88 (d, J = 7.1, 1H), 7.95 (d, J = 6.5, 1H), 8.08 (d, J = 9.0, 1H), 8.43 (d, J = 8.3, 1H), 11.01 (s, 1H), 11.31 (s, 1H); δ_C (125 MHz, DMSO-d_6) 17.8 (q), 52.3 (d), 53.2 (q), 66.3 (t), 70.2 (t), 116.3 (d), 120.9 (d), 121.4 (d), 121.9 (s), 122.6 (s), 123.9 (d), 125.2 (d), 128.2 (d), 128.3 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.8 (d), 129.0 (d), 132.7 (s), 133.0 (d), 137.2 (s), 137.3 (s), 139.0 (s), 155.1 (s), 156.5 (s), 167.1 (s), 167.6 (s), 172.2 (s). Anal. Calcd for $C_{33}H_{31}N_3O_7$: C, 68.15; H, 5.37; N, 7.22. Found: C, 68.22; H, 5.32; N, 7.18.

Method B. Compound **21b** was prepared similarly to compound **21a** using compound **17b**, but compound **21b** was purified by flash chromatography (40% ethyl acetate in hexane as eluent): yield, 43%.

***N*-{2-[1-*N*-(Benzyloxycarbonyl)-aminoethyl]-4*H*-3,1-benzoxazin-4-ylidene}-benzoic Acid Methyl Ester (22a).** Ph_3P (1.57 g, 6.0 mmol), I_2 (1.52 g, 6.0 mmol), and *N*, *N*-diisopropylethylamine (2.0 mL, 11.6 mmol) were added to a solution of compound **21a** (570 mg, 1.2 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature for 6 h and quenched with aqueous Na_2CO_3 (25 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The dark residue was purified by flash chromatography (30% ethyl acetate in hexane with 2% Et_3N) to give compound **22a** (310 mg, 57%) as a light yellow solid: $[\alpha]^{20}_D$ −16° (c 0.93, $CHCl_3$); mp 126−127 °C; IR (KBr) 3308, 1719, 1684, 1540, 1251, 1080, 736 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (d, J = 6.9, 3H), 3.76 (s, 3H), 4.47 (q, J = 6.9, 1H), 5.10 (s, 2H), 5.61 (d, J = 6.8, 1H), 7.00 (d, J = 7.9, 1H), 7.17 (ddd, J = 8.1, 7.0, 1.1, 1H), 7.27−7.56 (m, 8H), 7.64 (ddd, J = 7.7, 6.9, 1.4, 1H), 7.98 (dd, J = 7.9, 1.4, 1H), 8.28 (d, J = 7.6, 1H); δ_C (75 MHz, $CDCl_3$) 19.7 (q), 49.0 (d), 52.1 (q), 67.1 (t), 119.2 (s), 121.6 (s), 122.8 (d), 123.8 (d), 126.6 (d), 127.0 (d), 128.3 (d), 128.4 (d), 128.7 (d), 128.9 (d), 131.3 (d), 133.2 (d), 134.1 (d), 136.5 (s), 141.9 (s), 146.2 (s), 147.1 (s), 155.6 (s), 159.8 (s), 166.8 (s); GC/MS (EI) m/z (rel intensity) 457 (M^+, 1%), 279 (100). Anal. Calcd for $C_{26}H_{23}N_3O_5$: C, 68.26; H, 5.07; N, 9.19. Found: C, 68.20; H, 4.96; N, 9.11.

***N*-{2-[1-*N*-(Benzyloxycarbonyl)-aminoethyl]-4*H*-3,1-benzoxazin-4-ylidene}-5-benzyloxy-benzoic Acid Methyl Ester (22b).** Compound **22b** was prepared similarly to compound **22a** using compound **21b**: yield, 36% as a white solid; $[\alpha]^{20}_D$ −21° (c 1.1, $CHCl_3$); mp 154−155 °C; IR (KBr) 3284, 1731, 1682, 1543, 1497, 1268, 1231, 1069, 1014, 748 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.26 (d, J = 6.9, 3H), 3.69 (s, 3H), 4.20−4.32 (m, 1H), 5.00 (s, 2H), 5.10 (s, 2H), 7.02−7.59 (m, 15H), 7.69−7.83 (m, 2H), 8.14 (d, J = 7.5, 1H); δ_C (75 MHz, DMSO-d_6) 17.5 (q), 48.8 (d), 51.9 (q), 65.4 (t), 69.6 (t), 115.2 (d), 118.7 (s), 119.9 (d), 123.1 (s), 124.2 (d), 126.1 (d), 126.2 (d), 127.6 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.3 (d), 128.4 (d), 128.6 (d), 134.2 (d), 136.8 (s), 136.9 (s), 139.0 (s), 141.6 (s), 145.6 (s), 154.2 (s), 155.6 (s), 160.5 (s), 165.9 (s). Anal. Calcd for $C_{33}H_{29}N_3O_6$: C, 70.33; H, 5.19; N, 7.45. Found: C, 70.26; H, 5.09; N, 7.36.

Amidine Carboxamide (23a). Piperidine (distilled from CaH_2, 1.5 mL) was added to a solution of compound **22a** (275 mg, 0.60 mmol) in EtOAc (6 mL). The reaction mixture was stirred at room temperature for 5 h and concentrated under reduced pressure to an yellow oil. The residue was purified by flash chromatography (30% ethyl acetate in hexane) to give compound **23a** (220 mg, 67%) as a light yellow oil: δ_H (300 MHz, $CDCl_3$) 1.35 (d, J = 6.8, 3H), 1.35−1.63 (m, 6H), 2.96−3.30 (m, 4H), 3.73 (s, 3H), 4.74−4.89 (m, 1H), 4.99 and 5.13 (AB q, J = 12.2, 2H), 6.62−6.78 (m, 2H), 7.03 (dd, J = 7.5, 7.4, 1H), 7.10 (dd, J = 8.0, 7.1, 1H), 7.24−7.39 (m, 6H), 7.57 (dd, J = 8.4, 7.1, 1H), 7.95 (d, J = 7.4, 1H), 8.02 (d, J = 7.8, 1H), 8.65 (d, J = 8.4, 1H), 11.96 (s, 1H); δ_C (75 MHz, $CDCl_3$) 21.6 (q), 24.3 (t), 25.9 (t), 48.0 (d), 49.3 (t), 52.4 (q), 66.7 (t), 117.6 (s), 121.7 (d), 121.9 (d), 122.9 (d), 123.5 (d), 125.5 (s), 128.1 (d), 128.2 (d), 128.6 (d), 130.8 (d), 131.2 (d), 132.0 (d), 134.0 (d), 136.8 (s), 140.8 (s), 149.4 (s), 156.1 (s), 161.5 (s), 166.6 (s), 168.0 (s). The product thus obtained was used without further purification.

Amidine Carboxamide (23b). Compound **23b** was prepared similarly to compound **23a** using compound **22b**: yield, 77% as a colorless oil; δ_H (300 MHz, $CDCl_3$) 1.36 (d, J = 6.8, 3H), 1.42−1.58 (m, 6H), 3.00−3.27 (m, 4H), 3.72 (s, 3H), 4.76−4.88 (m, 1H), 4.95−5.20 (m, 4H), 6.63−6.76 (m, 2H), 7.02 (dd, J = 8.1, 7.0, 1H), 7.21 (dd, J = 9.2, 3.0, 1H), 7.24−7.53 (m, 11H), 7.55 (d, J = 3.0 1H), 8.06 (dd, J = 7.9, 1.4, 1H), 8.51 (d, J = 9.2, 1H), 11.79 (s, 1H); δ_C (75 MHz, $CDCl_3$) 21.5 (q), 24.3 (t), 25.9 (t), 48.0 (d), 49.2 (t), 52.5 (q), 66.7 (t), 70.6 (t), 116.0 (d), 119.1 (s), 121.0 (d), 121.7 (d), 121.9 (d), 125.2 (s), 125.4 (d), 127.7 (d), 128.1 (d), 128.2 (d), 128.2 (d), 128.5 (d), 128.8 (d), 131.2 (d), 131.9 (d), 134.3 (s), 136.8 (s), 136.8 (s) 149.4 (s), 154.1 (s), 156.1 (s), 161.5 (s), 166.2 (s), 167.5 (s). The product thus obtained was used without further purification.

Circumdatin F (1). Compound **23a** (190 mg, 0.35 mmol) was dissolved in 45% HBr in HOAc (5 mL) and heated to 60 °C. Upon cessation of gas evolution (less than 1 h), diethyl ether (5 + 5 mL) was added to precipitate the hydrobromide of compound **23a**. The mixture was left in an ice bath for a couple of hours. The resulting orange precipitate was collected and dried. Triethylamine (0.06 mL, 0.43 mmol) was added to a solution of the HBr salt of deprotected **23a** (135 mg, 0.28 mmol) dissolved in EtOAc (3 mL), and within 15 min, silica gel (600 mg, silica gel 60, 230−400 mesh ASTM, Merck) was added. The mixture was stirred at room temperature overnight. After filtration through Celite, the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography (60% ethyl acetate in hexane) to give

compound **1** (25 mg, 25%) as a white solid: $[\alpha]^{20}_D$ −55° (*c* 0. 94, $CHCl_3$); IR (KBr) 3278, 3180, 2962, 1685, 1654, 1615, 1449, 1363, 1261, 1096, 1018, 780 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.73 (d, *J* = 6.6, 3H), 4.32−4.48 (m, 1H), 7.22 (br d, *J* = 5.3, 1H), 7.81−7.56 (m, 6H), 7.96 (d, *J* = 7.2, 1H), 8.26 (d, *J* = 7.9, 1H); δ_C (75 MHz, $CDCl_3$) 15.5 (q), 50.1 (d), 121.6 (s), 127.6 (d), 127.7 (d), 127.9 (d), 128.5 (d), 129.1 (d), 130.1 (d), 130.8 (s), 131.5 (d), 133.7 (s), 135.0 (d), 146.3 (s), 155.2 (s), 161.8 (s), 168.2 (s); GC/MS (EI) *m*/*z* (rel intensity) 292 (M^+ + 1, 18%), 291 (M^+, 100), 249 (66), 248 (64), 247 (37), 220 (24), 146 (32), 124 (21); HRMS (EI) *m*/*z* calcd for $C_{17}H_{13}N_3O_2$ 291.1008, found 291.0989.

Circumdatin C (2). Circumdatin C was prepared similarly to circumdatin F (**1**) using compound **23b** and *N*,*N*-diisopropylethylamine as a base. Compound **2** was isolated by chromatography on silica gel column (75% ethyl acetate in hexane) as a beige solid: yield, 30%; $[\alpha]^{20}_D$ −91° (*c* 0. 17, MeOH) (lit.[1a], $[\alpha]^{20}_D$ −75° (*c* 0.16, MeOH)); IR (KBr) 3336, 3183, 3072, 2940, 1673, 1656, 1605, 1387, 1290, 1252, 1214, 778 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.52 (d, *J* = 6.7, 3H), 4.30−4.40 (m, 1H), 7.01 (dd, *J* = 8.8, 2.9, 1H), 7.11 (d, *J* = 2.9, 1H), 7.41 (d, *J* = 8.8, 1H), 7.58 (ddd, *J* = 8.0, 7.0, 1.1, 1H), 7.73 (d, *J* = 8.0, 1H), 7.88 (ddd, *J* = 8.4, 6.9, 1.5, 1H), 8.17 (dd, *J* = 8.0, 1.1, 1H), 8.69 (d, *J* = 5.9, 1H), 10.18 (s, 1H); δ_C (75 MHz, DMSO-d_6) 14.9 (q), 49.5 (d), 114.1 (d), 117.8 (d), 120.9 (s), 124.4 (s), 126.7 (d), 127.3 (d), 127.3 (d), 130.0 (d), 132.4 (s), 134.9 (d), 145.9 (s), 156.8 (s), 157.2 (s), 161.1 (s), 166.6 (s). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.34; H, 4.21; N, 13.61.

Supporting Information Available: Experimental data, ^1H and ^{13}C NMR spectral data for **12**, **13**, **14**, **15**, **18**, **19**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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