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Exploitation of a Tuned Oxidation with *N*-Haloimides in the Synthesis of Caulibugulones A−D

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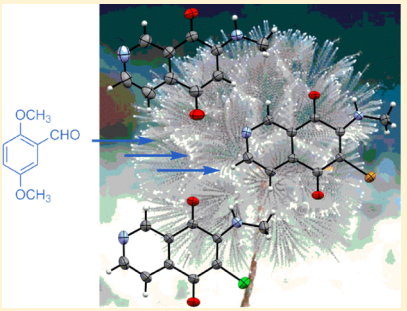
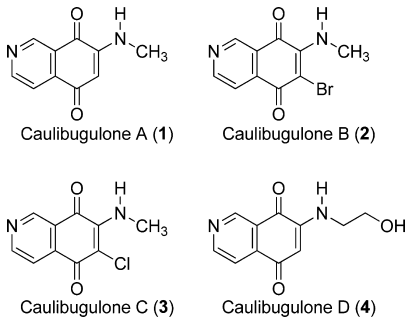
Supporting Information

ABSTRACT: Marine alkaloids caulibugulones A−D were synthesized in six steps starting from the readily available 2,5-dimethoxybenzaldehyde. Pomeranz−Fritsch reaction of *N*-(2,5-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide proceeded smoothly to give 5,8-dimethoxyisoquinoline, which was oxidized to isoquinolinediones by a tunable oxidation reaction with *N*-haloimides. Therefore, NBS furnished direct conversion to the isoquinoline-5,8-dione; alternatively, *N*-haloimides of cyanuric acid provided both oxidation and halogenation generating 6,7-dihaloisoquinoline-5,8-diones. Aminolyses of these isoquinolinediones with methylamine or ethanolamine produced the isoquinolinedione alkaloids caulibugulones A−D in 24−57% overall yield.



Caulibugulones A−D (**1**−**4**, Scheme 1) are simple isoquinolinedione alkaloids that were isolated from the marine bryozoan *Caulibugula intermis* Harmer (Bugulidae) in 2004, at Palau in the Indo-Pacific northwest, by Milanowski and co-workers.[1] Despite their simplicity and high activity against tumor cells[1] there are only two syntheses, at the same year of their isolation, by the Wipf[2] and Alagille[3] groups. These compounds attracted our attention because of their high activity against cdc25 phosphatases,[1,4] acting by at least two different mechanisms,[4] showing great potential as a leading compound in the development of new drugs for cancer therapy.[5,6]

Scheme 1. Structures of Caulibugulones A−D Isolated from the Marine Bryozoan *Caulibugula intermis* Harmer (Bugulidae)



All syntheses exploited the same key intermediate, 5,8-dimethoxyisoquinoline (**8**), prepared in four steps in 83% overall yield from the easily accessible 2,5-dimethoxybenzaldehyde (**5**, Scheme 2). Using the bespoken oxidation/halogenation step with adequate *N*-haloimide for each case, followed by aminolyses with the correspondent amine, the isoquinoline **8** furnished all four desired caulibugulones in two steps with 29−68% yield (Schemes 3 and 4).

The synthesis of caulibugulones began with the preparation of **8** by reductive amination of 2,5-dimethoxybenzaldehyde (**5**) with 2,2-dimethoxyethanamine in the presence of $NaBH_4$ to afford the benzylamine **6**, which was activated for the Pomeranz−Fritsch reaction by derivatization with *o*-nosyl chloride.[7,8] When the nosyl amide **7** was submitted to the Pomeranz−Fritsch reaction in HCl/dioxane, it consecutively cyclized, underwent methanol elimination, and 2-nitrobenzenesulfinic acid elimination to furnish 5,8-dimethoxyisoquinoline (**8**).[7,8] Apparently, the corresponding tosyl amide (**9**) has a higher S−N bond cleavage energy and stops at the formation of the 2-tosyl-1,2-dihydroisoquinoline intermediate (**10**, Scheme 2) under the same conditions.[8−11] This result is supported by Miyata and co-worker's findings about the N−S bond cleavage ability of arylsulfonamides.[12] In this case, the velocity of solvolysis is related not only to the electronic factor as could be supposed at a first glance, but also to a steric and/or solvent factor.[12] It was only possible to generate isoquinoline **8** from **10** after treatment with *t*-BuOK/*t*-BuOH at 80 °C for 30 min.[10]

5,8-Dimethoxyisoquinoline (**8**) was then converted to isoquinoline-5,8-diones (**11**−**13**) by reaction with *N*-haloimides (Scheme 3). Thereafter, caulibugulones A−D were promptly prepared from **11**−**13** after subsequent reaction with the corresponding amines. An interesting aspect of the oxidation/halogenation step was the chemoselectivity of the process. As shown by Chi and co-workers in closely related compounds,[13] 5,8-dimethoxyisoquinoline (**8**) could be trans-

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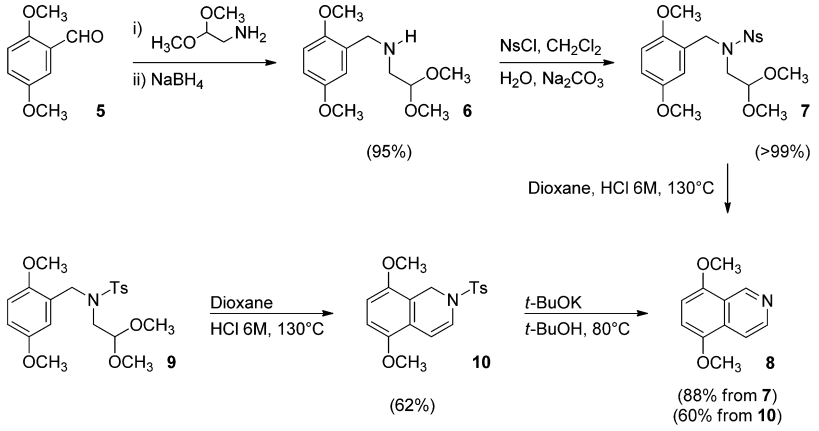
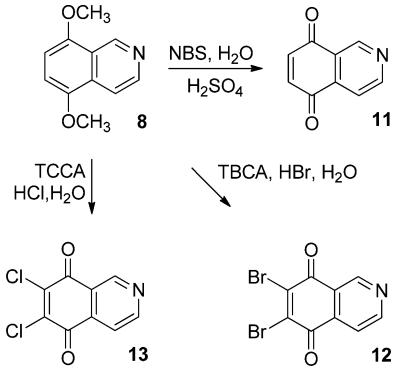
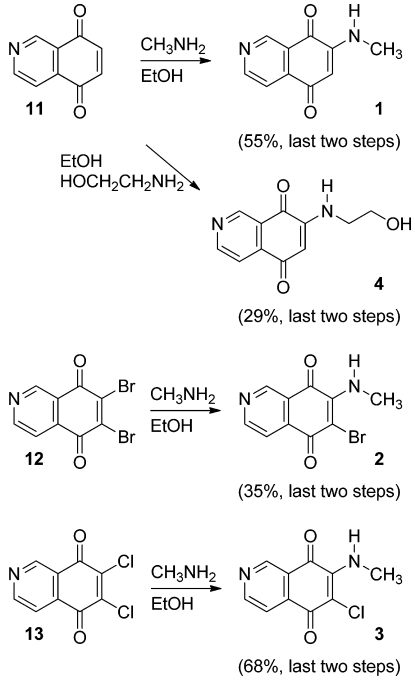
Scheme 2. Nosylamide-Based Activation of the Pomeranz–Fritsch Reaction for the Synthesis of Compound 8



Scheme 3. Preparation of Isoquinoline-5,8-diones (11–13) by Selective Oxidation with *N*-Haloimides



Scheme 4. Aminolysis Step for the Preparation of Caulibugulones A–D (1–4)



formed into isoquinoline-5,8-dione (**11**) by treatment with $NBS/H_2O/H_2SO_4$, although in a much longer time in our case (48 h instead of 5 min). Nevertheless, 6,7-dibromoisoquinoline-5,8-dione (**12**) could not be prepared in this way despite all attempted modifications concerning reaction time, acid concentration, solvent, or temperature.

On the other hand, when *N*-haloimides derived from isocyanuric acid were applied,[14,15] both oxidation and halogenations at positions 6 and 7 were simultaneously achieved. Thus, the reaction of 5,8-dimethoxyisoquinoline (**8**) and trichloroisocyanuric acid (TCCA), in H_2O/HCl at room temperature, furnished 6,7-dichloroisoquinoline-5,8-dione (**13**). Similarly, the reaction of 5,8-dimethoxyisoquinoline (**8**) and tribromoisocyanuric acid (TBCA), in H_2O/HBr at room temperature, furnished 6,7-dibromoisoquinoline-5,8-dione (**12**).

Unfortunately, all isoquinolinediones (**11–13**) have insufficient stability to be isolated in reasonable or reproducible yields and purities using this methodology; thus we proceeded without their isolation directly toward caulibugulones. This findings corroborate the experimental data of Wipf and coworkers,[2] which also reported difficulties in isolating and characterizing isoquinoline-5,8-dione (**11**) using a different reaction condition.[2] Therefore, in all cases, the corresponding isoquinoline-5,8-dione reaction media was treated with the related amine (methylamine or ethanolamine), and the resulting caulibugulone was isolated without further problems in 36–86% yield from **8**, as a ~4:1 mixture of isomers. In all cases, the caulibugulone/isocaulibugulone mixture was efficiently resolved by PLC.[16]

In the case of 6,7-dihaloisoquinoline-5,8-diones (**12** and **13**), an amine addition followed by halogen elimination is expected to occur. On the other hand, in the case of the isoquinoline-5,8-dione (**11**), a conjugate addition to the α,β-unsaturated carbonyl moiety followed by tautomerization of the diketo derivative to the hydroquinone, and an in situ oxidation probably takes place.[17] It is noteworthy to mention that, despite mechanism differences, the presented regiochemistry of both reactions is quite similar. The observed regioselection for the addition at position 7 vary within 4:1 and 6:1 for all isoquinoline-5,8-diones. All NMR spectra and high-resolution mass data are in complete accordance with literature.[1−3]

Interestingly, despite the spectroscopic conditions described in the literature,[1] all caulibugulones were sufficiently soluble in $CDCl_3$ to perform all NMR experiments furnishing adequate spectra (Table 1). The structures of caulibugulones B (**2**) and C (**3**) were also unambiguously assigned by X-ray crystallography (Figure 1).[16] Thus, the regiochemistry of the nucleophilic addition of the amines was confirmed concurrently by 2D-

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Table 1. ^{13}C NMR Chemical Shift (in ppm) Comparison among Natural Caulibugulones (I)[1] and Synthesized in This Work (II)

	caulibugulone											
	A			B			C			D		
position	I[a]	II[a]	II[d]	I[b]	II[b]	II[d]	I[b]	II[b]	II[d]	I[c]	II[c]	II[d]
1	147.4	148.0	147.9	148.1	148.4	148.5	148.4	148.6	148.4	148.3	148.4	148.1
3	155.5	156.3	156.3	156.1	156.1	156.3	156.1	156.7	156.1	156.9	157.1	156.5
4	120.1	119.9	119.0	118.8	119.2	119.5	119.2	119.4	119.3	119.3	119.4	119.6
4a	141.0	140.7	139.3	138.4	138.2	138.0	138.2	139.0	138.4	140.1	140.2	139.2
5	181.1	181.3	180.9	174.8	174.5	174.8	173.4	175.3	175.3	181.5	181.7	181.2
6	100.7	100.8	101.2	[e]	[e]	[e]	[e]	[e]	[e]	101.0	101.6	101.7
7	150.7	150.7	148.8	146.4	[e]	146.9	148.4	146.9	144.9	149.6	149.7	[e]
8	181.0	181.5	181.2	180.5	180.1	179.8	180.1	180.9	179.9	182.2	182.5	[e]
8a	125.8	125.6	124.3	124.4	123.1	123.6	123.8	123.9	123.5	125.6	125.7	124.4
9	29.3	29.4	29.2	32.5	33.0	33.3	33.0	32.9	32.7	45.2	45.5	44.5
10										59.7	60.0	60.1

Spectral data were acquired in

[a]$CD_3OD/CDCl_3$ (1:1), [b]pyridine-d5, [c]CD_3CN or [d]$CDCl_3$. [e]Signal not observed.

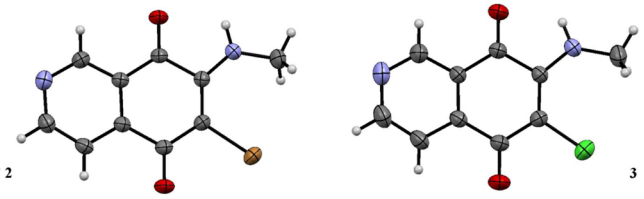

Figure 1. ORTEP representations of caulibugulone B (**2**) (left) and caulibugulone C (**3**) (right). Ellipsoids displayed at 50% probability.[16]

NMR data and XRD experiments. Crystals of both compounds, and also of caulibugulone A (**1**),[16] were obtained by slow evaporation of dichloromethane solutions. The ORTEP drawings of caulibugulone B (**2**) and caulibugulone C (**3**) are shown in Figure 1 and fully corroborate all 2D-NMR data.[16]

In summary, the synthesis of the naturally occurring caulibugulones A–D was accomplished in six steps with 25–57% overall yield and provided sufficient material for further biological testing. Conditions for selective oxidation, or oxidation/halogenations of dialkoxyisoquinolines were also described. Structure assignments were in full agreement with the literature (Table 1). X-ray diffraction and 2D-NMR data unequivocally prove the regiochemistry of isoquinoline-5,8-diones aminolyses.

EXPERIMENTAL SECTION

General Methods. Flash column chromatography was performed as described by Still et al.[18] employing silica gel 60 (spherical), 40–100 μm. Analytical thin-layer chromatography (TLC) was performed on analytical plates precoated with silica gel 60 F254 (0.25 mm thick). TLC plates were visualized by exposure to ultraviolet light (UV) and/or stained with iodine vapor. Preparative thin-layer chromatography (PLC) was performed on precoated glass plates (20 × 20 cm) with silica gel 60 F254 (1 mm thick). Tribromoisocyanuric acid (TBCA) was prepared according to the literature.[19] Other reagents were obtained from commercial sources and used without previous purifications. Tetrahydrofuran was distilled from sodium/benzophenone under argon, and methanol was distilled from calcium hydride. Melting points were obtained in open capillary tubes and are uncorrected. Chemical shifts for ^{1}H NMR were reported in parts per million (δ scale) downfield from tetramethylsilane as the internal standard, and coupling constants are reported in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were reported in parts per million (δ scale) relative to the tetramethylsilane signal. High resolution mass spectrometry (HRMS) analyses were obtained by ESI/TOF at positive mode, and low-resolution MS data were obtained using EI at 70 eV.

***N*-(2,5-Dimethoxybenzyl)-2,2-dimethoxyethanamine (6).** To a stirred solution of 2,5-dimethoxybenzaldehyde (**5**, 216.0 mg; 1.3 mmol) in 5 mL of dry toluene was added 1.0 mmol (105.0 mg) of 2,2-dimethoxyethanamine. The solution was boiled under reflux in a Dean–Stark apparatus until no further water was evolved (4 h). The removal of solvent under vacuum gave the required Schiff's base in a virtually quantitative yield. The isolated benzylideneamino acetal was used without further purification in the following step. Thus, the isolated intermediate (253.0 mg, 1.0 mmol) was dissolved in 5 mL of methanol, and 189.0 mg (5.0 mmol) of sodium borohydride was added to the mixture at room temperature. The mixture was stirred at room temperature for 3 h, and after this period the organic solvent was evaporated in vacuum. Addition of saturated $NaHCO_3$ solution and CH_2Cl_2 followed by separation, drying, and evaporation of the organic phase under reduced pressure gave a yellow oil. The residue obtained was purified by column chromatography in silica gel with AcOEt/MeOH (90:10, R_f = 0.44) as eluent to yield **6** (95%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm), *J* (Hz): 6.81 (d, *J* = 1.6, 1H); 6.73 (m, 2H); 4.48 (t, *J* = 5.3, 1H); 3.78 (s, 3H); 3.76 (s, 2H) 3.75 (s, 3H); 3.34 (s, 6H); 2.72 (d, *J* = 5.3, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ(ppm): 153.4; 151.8; 128.7; 116.1; 112.4; 111.1; 103.7; 55.8; 55.7; 53.8; 50.1; 49.2. MS (EI, 70 eV) (*m*/*z*, relative abundance): 255 (7); 180 (30); 151 (100).

***N*-(2,5-Dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide (7).** To 8.0 mL of a dichloromethane solution of **6** (255.0 mg; 1.0 mmol) were added an aqueous solution of sodium carbonate (10%, 5.0 mL) and 215.0 mg (0.97 mmol) of 2-nitrobenzenesulfonyl chloride. The resulting emulsion was stirred at room temperature for 6 h. Hereafter, the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated. The residue obtained was purified by column chromatography in silica gel using hexane/AcOEt (70:30, R_f = 0.33) as eluent to yield **7** (>99%) as a yellowish oil. ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm), *J* (Hz): 7.87 (d, *J* = 7.6, 1H); 7.66–7.49 (m, 3H); 6.87–6.79 (m, 1H); 6.74–6.65 (m, 2H); 4.65 (s, 2H); 4.47 (t, *J* = 5.4, 1H); 3.68 (s, 3H); 3.67 (s, 3H); 3.45 (d, *J* = 5.4, 2H); 3.31 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 153.7; 151.8; 148.0; 134.5; 133.1; 131.5; 130.8; 124.4; 123.9; 115.5; 114.0; 111.3; 103.9; 55.7; 54.9; 53.5, 49.4; 47.5; 41.9. HRMS: found 479.0891, calcd for $[C_{19}H_{25}N_2O_8S + K]^+$ 479.0917; also found 463.1151, calcd for $[C_{19}H_{25}N_2O_8S + Na]^+$ 463.1172.

5,8-Dimethoxyisoquinoline (8, from 7). A stirred solution of **7** (440.0 mg; 1.0 mmol) in 25 mL of dioxane/HCl 6 M (4:1), in the dark and under argon atmosphere, was kept under reflux in a round-bottom flask for 7 h. After completion of the reaction as indicated by

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TLC, the pH of the reaction mixture was adjusted to 8 with Na_2CO_3 and extracted with 3 × 50 mL of dichloromethane. The combined extracts were dried over $MgSO_4$, filtered, and evaporated to yield brownish oil. Purification of this oil by column chromatography in silica gel with hexane/AcOEt (60:40, R_f = 0.33) as eluent furnished 5,8-dimethoxyisoquinoline (**8**) in 88% yield as a pale brown solid. Mp: 59−61 °C (lit.[8] mp 56.5−57.0 °C). ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm), J (Hz): 9.57 (s, 1H); 8.56 (d, J = 5.6, 1H); 7.92 (d, J = 5.6, 1H); 6.86 (d, J = 9.0, 1H); 6.74 (d, J = 9.0, 1H); 3.97 (s, 3H); 3.94 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 150.0; 148.1; 147.2; 143.4; 129.1; 121.0; 114.5; 107.5; 104.3; 55.8; 55.7. HRMS: found 190.0877, calcd for $[C_{11}H_{11}NO_2 + H]^+$ 190.0868.

***N*-(2,5-Dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (9).** To 9.0 mL of a dichloromethane/ether (3:1) solution of **6** (255.3 mg; 1.0 mmol) were added an aqueous solution of sodium carbonate (10%, 5.0 mL) and 228.8 mg (1.2 mmol) of *p*-toluenesulfonyl chloride. The resulting emulsion was stirred at room temperature for 2 h. Hereafter, the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated. The residue obtained was purified by column chromatography in silica gel using hexane/AcOEt (70:30, R_f = 0.50) as eluent to yield **7** (>99%) as a yellowish oil. ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm), J (Hz): 7.65 (d, J = 8.5, 2H); 7.23 (d, J = 8.5, 2H); 6.86 (d, J = 2.6, 1H); 6.74−6.65 (m, 2H); 4.46 (s, 2H); 4.42 (t, J = 5.4, 1H); 3.68 (s, 3H); 3.64 (s, 3H); 3.29 (d, J = 5.4, 2H); 3.24 (s, 6H); 2.38 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 157.6; 151.4; 143.0; 137.5; 129.4; 127.2; 125.5; 113.5; 111.2; 103.7; 77.3; 55.7; 54.4; 49.9; 47.6; 21.5. HRMS: found 410.1663, calcd for $[C_{20}H_{28}NO_6S + H]^+$ 410.1637.

5,8-Dimethoxy-3-methyl-2-tosyl-1,2-dihydroisoquinoline (10). A stirred suspension of **9** (409.5 mg; 1.0 mmol) in 10 mL of dioxane/HCl 6 M (4:1), in the dark and under argon atmosphere, was kept under reflux in a round-bottom flask for 7 h. After completion of the reaction as indicated by TLC, the pH of the reaction mixture was adjusted to 8 with Na_2CO_3 and extracted with 3 × 50 mL of dichloromethane. The combined extracts were dried over $MgSO_4$, filtered, and evaporated to yield brownish oil. Purification of this oil by column chromatography in silica gel with hexane/AcOEt (60:40, R_f = 0.50) as eluent furnished 5,8-dimethoxy-3-methyl-2-tosyl-1,2-dihydroisoquinoline (**10**) in 62% yield as a yellow solid. Mp: 128−130 °C dec; (lit.[8] mp 130−133 °C). ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm), J (Hz): 7.71 (d, J = 8.5, 2H); 7.26 (d, J = 8.5, 2H); 6.75 (d, J = 8.0, 1H); 6.65−6.54 (m, 2H); 6.11 (d, J = 8.0, 1H); 4.59 (s, 2H); 3.73 (s, 6H); 2.38 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ(ppm): 149.4; 148.2; 144.1; 134.9; 129.9; 127.4; 126.0; 120.8; 117.1; 110.3; 109.8; 104.1; 56.3; 55.9; 41.9; 21.7. HRMS: found 346.1139, calcd for $[C_{18}H_{19}NO_4S + H]^+$ 346.1113.

5,8-Dimethoxyisoquinoline (8, from 10). To a solution of **10** (345.4 mg; 1.0 mmol) in 3.5 mL of *t*-BuOH was added *t*-BuOK (224.4 mg; 2.0 mmol), and the mixture was stirred and kept at 80 °C in a round-bottom flask for 30 min. After completion of the reaction as indicated by TLC, H_2O (10 mL) was added, and the reaction mixture was extracted with 3 × 10 mL of AcOEt. The combined extracts were dried over $MgSO_4$, filtered, and evaporated to furnish 5,8-dimethoxyisoquinoline (**8**) in 60% yield as a pale brown solid without purification. Mp: 59−61 °C (lit.[8] mp 56.5−57.0 °C). ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm), J (Hz): 9.57 (s, 1H); 8.56 (d, J = 5.6, 1H); 7.92 (d, J = 5.6, 1H); 6.86 (d, J = 9.0, 1H); 6.74 (d, J = 9.0, 1H); 3.97 (s, 3H); 3.94 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 150.0; 148.1; 147.2; 143.4; 129.1; 121.0; 114.5; 107.5; 104.3; 55.8; 55.7. HRMS: found 190.0877, calcd for $[C_{11}H_{11}NO_2 + H]^+$ 190.0868.

Caulibugulone A (1). 5,8-Dimethoxyisoquinoline (**8**, 189.0 mg, 1.0 mmol) was added to a well-stirred mixture of NBS (196.0 mg, 1.1 mmol) in a solution of THF (15 mL), water (5 mL), and sulfuric acid (0.05 mL) at room temperature. The reaction mixture was stirred for 48 h, 493.0 mg of $CeCl_3$ (2 mmol) and 346.0 μL of 40% aqueous methylamine (4 mmol) were added, and the mixture was stirred for an additional 20 h at room temperature. Then the suspension was concentrated under reduced pressure, and the crude residue was diluted with EtOAc (50 mL) and washed with brine (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by column chromatography in silica gel with AcOEt/hexane (80:20, R_f = 0.37) as eluent to yield a mixture of caulibugulone A (**1**) and its regioisomer (69%, ∼4:1 ratio by ^{1}H NMR). Further purification in PLC silica gel plate (CH_2Cl_2/MeOH 199:1, R_f = 0.03) gave caulibugulone A (**1**) as red needles. Ten consecutive runs were necessary to separate the regioisomers. The spectroscopic data obtained for this compound were consistent with those reported in the literature.[1−3] Mp: 218−220 °C dec (lit.[2] mp 228 230 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm), J (Hz): 9.19 (s, 1H), 8.94 (d, J = 5.0 Hz, 1H), 7.85 (d, J = 5 Hz, 1H), 6.05 (br s, 1H), 5.75 (s, 1H), 2.90 (d, J = 5.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 181.2, 180.9, 156.3, 148.5, 147.9, 139.3, 124.3, 119.0, 101.2, 29.3. HRMS: found 189.0667, calcd for $[C_{10}H_9N_2O_2 + H]^+$ 189.0664.

Caulibugulone B (2). 5,8-Dimethoxyisoquinoline (**8**, 189.0 mg, 1.0 mmol) was solubilized in HBr 8.84 M (22 mL). After the mixture was cooled in an ice bath (0 °C), TBCA (475.4 mg, 1.3 mmol) was added. The reaction mixture was stirred for 48 h at room temperature; after this time, a liquid−liquid extraction was performed by addition of aqueous sodium carbonate (97 mmol in 20 mL of water) and three portions if CH_2Cl_2 (20 mL). The organic phase was dried with anhydrous $MgSO_4$, and the solvent was removed on a rotary evaporator. To the flask containing a solution of 6,7-dibromoisoquinolino-5,8-dione (**12**) in ethanol (10 mL) a second solution of 86.7 μL of 40% aqueous methylamine (1.0 mmol) in ethanol (5.0 mL) was added and the resulting mixture was stirred for additional 24 h at room temperature. Then the reaction was concentrated under reduced pressure, and the residue obtained was purified by column chromatography in silica gel with AcOEt (R_f = 0.66) as eluent to yield a mixture of caulibugulone B (**2**) and its regioisomer (44%, ∼4:1 ratio by ^{1}H NMR). After eight consecutive elutions in a PLC silica gel plate (CH_2Cl_2/MeOH 199:1, R_f = 0.06) caulibugulone B (**2**) was isolated as dark red needles. The spectroscopic data obtained for this compound were consistent with those reported in the literature.[1−3] Mp: 198 200 °C dec (lit.[2] mp 182 184 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm), J (Hz): 9.19 (s, 1H), 8.93 (d, 1H, J = 5.0 Hz), 7.89 (d, 1H, J = 5.0 Hz), 6.21 (br s, 1H), 3.42 (d, 3H, J = 5.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 179.6, 174.9, 156.3, 148.5, 146.8, 138.2, 124.0, 119.5, 33,3. HRMS: found 266.9754, calcd for $[C_{10}H_9N_2O_2 + H]^+$ 266.9769.

Caulibugulone C (3). 5,8-Dimethoxyisoquinoline (**8**, 189.0 mg, 1.0 mmol) was solubilized in HCl 12 M (17 mL). After the mixture was cooled in an ice bath (0 °C), TCCA (302.0 mg, 1.3 mmol) was added. The reaction mixture was stirred for 3 h at room temperature; after this time, a liquid−liquid extraction was performed by addition of aqueous sodium carbonate (97 mmol in 20 mL of water) and three portions of CH_2Cl_2 (20 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was removed on a rotary evaporator. To the flask containing a solution of extracted 6,7-dichloroisoquinolino-5,8-dione (**13**) in ethanol (10 mL) was added a second solution of 86.7 μL of 40% aqueous methylamine (1.0 mmol) in ethanol (5.0 mL), and the resulting mixture was stirred for additional 24 h at room temperature. Then the suspension was concentrated under reduced pressure. The residue obtained was purified by column chromatography in silica gel with AcOEt (R_f = 0.64) as eluent to yield a mixture of caulibugulone C (**3**) and its regioisomer (85%, ∼4:1 ratio by ^{1}H NMR). After eight consecutive elutions in a PLC silica gel plate (CH_2Cl_2/MeOH 199:1, R_f = 0.05) caulibugulone C (**3**) was isolated as dark red needles. The spectroscopic data obtained for this compound were consistent with those reported in the literature.[1−3] Mp: 225−227 °C dec (lit.[2] mp 219 221 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm), J (Hz): 9.18 (s, 1H), 8.94 (d, 1H, J = 5.0 Hz), 7.89 (d, 1H, J = 5.0 Hz), 6.15 (br s, 1H), 3.41 (d, 3H, J = 5.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 180.0, 175.3, 156.5, 148.4, 144.9, 138.4, 123.5, 119.3, 32.7 HRMS: found 223.0257, calcd for $[C_{10}H_9N_2O_2 + H]^+$ 223.0274.

Caulibugulone D (4). 5,8-Dimethoxyisoquinoline (**8**, 189.0 mg, 1.0 mmol) was added to a well-stirred mixture of NBS (196.0 mg, 1.1 mmol) in a solution of THF (15 mL), water (5 mL), and sulfuric acid (0.05 mL) at room temperature. The reaction mixture was stirred for

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48 h, 493.0 mg of $CeCl_3$ (2 mmol) and 241.0 μL of ethanolamine (4 mmol) were added, and the mixture was stirred for an additional 20 h at room temperature. The suspension was concentrated under reduced pressure, and the crude residue was diluted with EtOAc (50 mL) and washed with brine (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel with AcOEt/MeOH (95:05, R_f = 0.42) as eluent to yield a mixture of caulibugulone D (**4**) and its regioisomer (36%, ∼4:1 ratio by ^{1}H NMR). After eight sequential elutions in a PLC silica gel plate ($CHCl_3$/MeOH 97:3, R_f = 0.07) caulibugulone D (**4**) was isolated as a dark orange solid. The spectroscopic data obtained for this compound were consistent with those reported in the literature.[1−3] Mp: 180−182 °C dec (lit.[2] mp 189−191 °C). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm), *J* (Hz): 9.20 (s, 1H), 8.94 (d, 1H, *J* = 5.0 Hz), 7.84 (d, 1H, *J* = 5.0 Hz), 6.28 (br s, 1H), 5.80 (s, 1H), 3.88 (m, 2H), 3.32 (q, 2H, *J* = 5.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 181.2, 156.5, 148.1, 139.3, 124.4, 119.1, 101.7, 60.1, 44.5. HRMS: found 219.0768, calcd for $[C_{10}H_9N_2O_2 + H]^+$ 219.0770.

■ ASSOCIATED CONTENT

Supporting Information

Additional analytical and spectroscopic data of all compounds and X-ray crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Milanowski, D. J.; Gustafson, K. R.; Kelley, J. A.; McMahon, J. B. *J. Nat. Prod.* **2004**, *67*, 70.

(2) Wipf, P.; Joo, B.; Nguyen, T.; Lazo, J. S. *Org. Biomol. Chem.* **2004**, *2*, 2173.

(3) Alagille, D.; Baldwin, R. M.; Tamagnan, G. D. *Tetrahedron Lett.* **2004**, *45*, 6179.

(4) Brisson, M.; Foster, C.; Wipf, P.; Joo, B.; Tomko, R. J., Jr.; Nguyen, T.; Lazo, J. S. *Mol. Pharmacol.* **2007**, *71*, 184.

(5) Vintonyak, V. V.; Antonchick, A. P.; Rauh, D.; Waldmann, H. *Curr. Opin. Chem. Biol.* **2009**, *13*, 272.

(6) Contour-Galcera, M. O.; Sidhu, A.; Prévost, G.; Bigg, D.; Ducommun, B. *Pharmacol. Therapeut.* **2007**, *115*, 1.

(7) Konakahara, T.; Kiran, Y. B.; Okuno, Y.; Ikeda, R.; Sakai, N. *Tetrahedron Lett.* **2010**, *51*, 2335.

(8) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185.

(9) Song, Y.; Shao, Z.; Dexheimer, T. S.; Scher, E. S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2010**, *53*, 1979.

(10) Bracca, A. B. J.; Kaufman, T. S. *Eur. J. Org. Chem.* **2007**, 5284.

(11) Silveira, C. C.; Bernardi, C. R.; Braga, A. L.; Kaufman, T. S. *Synlett* **2002**, 907.

(12) Aizawa, K.; Nakagawa, H.; Matsuo, K.; Kawai, K.; Ieda, N.; Suzuki, T.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2340.

(13) Kim, D. W.; Choi, H. Y.; Lee, K. J.; Chi, D. Y. *Org. Lett.* **2001**, *3*, 445.

(14) Tozetti, S. D. F.; Almeida, L. S.; Esteves, P. M.; Mattos, M. C. S. *J. Braz. Chem. Soc.* **2007**, *18*, 675.

(15) Almeida, L. S.; Esteves, P. M.; Mattos, M. C. S. *Synthesis* **2006**, 221.

(16) See the Supporting Information for further details.

(17) Lisboa, C. D.; Santos, V. G.; Vaz, B. G.; Lucas, N. C.; Eberlin, M. N.; Garden, S. J. *J. Org. Chem.* **2011**, *76*, 5264.

(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(19) Almeida, L. S.; Esteves, P. M.; Mattos, M. C. S. *Synlett* **2006**, *10*, 1515.