Synthesis of a Fully Functionalized 7-Methoxyaziridinomitosene

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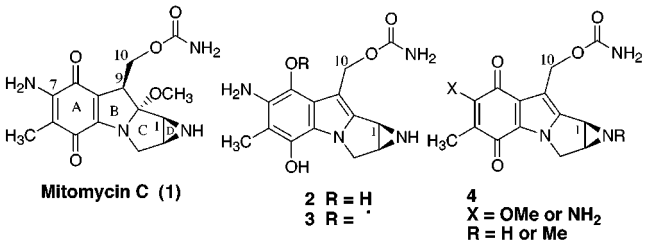
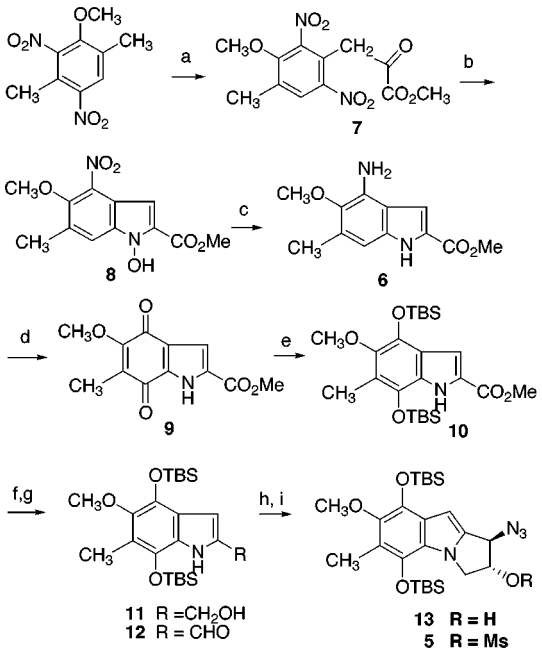
Mitomycin C (**1**) is a potent antitumor agent whose mode of action requires activation by either enzymatic or chemical reduction[1] or mild acidic treatment.[2] The active intermediate generated by reduction of mitomycin C is believed to be either 7-aminoleucoaziridinomitosene[3] (**2**) or the corresponding semiquinone **3**.[1b] This active intermediate binds to the minor groove of DNA[4] where alkylation of the 2-amino group of guanine results in the formation of both monoalkylated adducts and DNA cross-links.[5] Several 7-substituted 1,2-aziridinomitosenes **4** have shown activity comparable to mitomycin C against various tumor model systems.[6]



A number of aziridinomitosenes (**4**) have been prepared by careful reduction of natural mitomycins, followed by reoxidation of the intermediate hydroquinone.[7] Synthetic approaches have resulted in mitosenes with various leaving groups at C-1 and C-10[8] and in cyclopropamitosenes.[9] An efficient synthesis of an aziridinomitosene with an ester group at C-9 has been recently reported.[10] This paper describes the preparation of a fully functionalized aziridinomitosene with a carbamate side chain at C-9 in 16 steps (3.4% overall yield) from 2,5-dimethylanisole.

Scheme 1



(a) Dimethyl oxalate, $KOC(CH_3)_3$, ether, 63%. (b) $SnCl_2$, MeOH, 63%. (c) H_2/Pd-C, EtOH. (d) Fremy's salt, 0.2 M NaH_2PO_4, acetone. (e) H_2/Pd-C, then TBSCl, imidazole, CH_2Cl_2, 78% from **8**. (f) DIBAL, THF. (g) MnO_2, CH_2Cl_2. (h) Diisopropylvinylsulfonium triflate, NaH, THF, 0°C; then NaN_3, acetone-water, 72%. (i) MsCl/NEt_3, CH_2Cl_2, 90%.

To synthesize significant quantities of the azido mesylate **5**, it was necessary to improve our earlier synthesis of the intermediate 4-aminoindole **6** (Scheme 1). This compound had been previously prepared in a single operation (47% yield) from 3,6-dimethyl-2,4-dinitroanisole.[11] However, the yields fell dramatically when this reaction was attempted on more than a 0.5 g scale. Also our previous preparation of 3,6-dimethyl-2,4-dinitroanisole on a multigram scale became prohibitively expensive using nitronium tetrafluoroborate as the nitrating agent.[11] An improved procedure was developed in which 2,5-dimethylanisole could be nitrated on a 50 g scale with sodium nitrite in trifluoroacetic acid (Scheme 1).[12] The α-keto ester **7** was prepared in a 63% yield from 3,6-dimethyl-2,4-dinitroanisole and dimethyl oxalate in the presence of potassium *tert*-butoxide.[13] Reaction of **7** with 3 equiv of stannous chloride in methanol resulted in a 60% yield of the hydroxyindole **8**.[14] Catalytic hydrogena-

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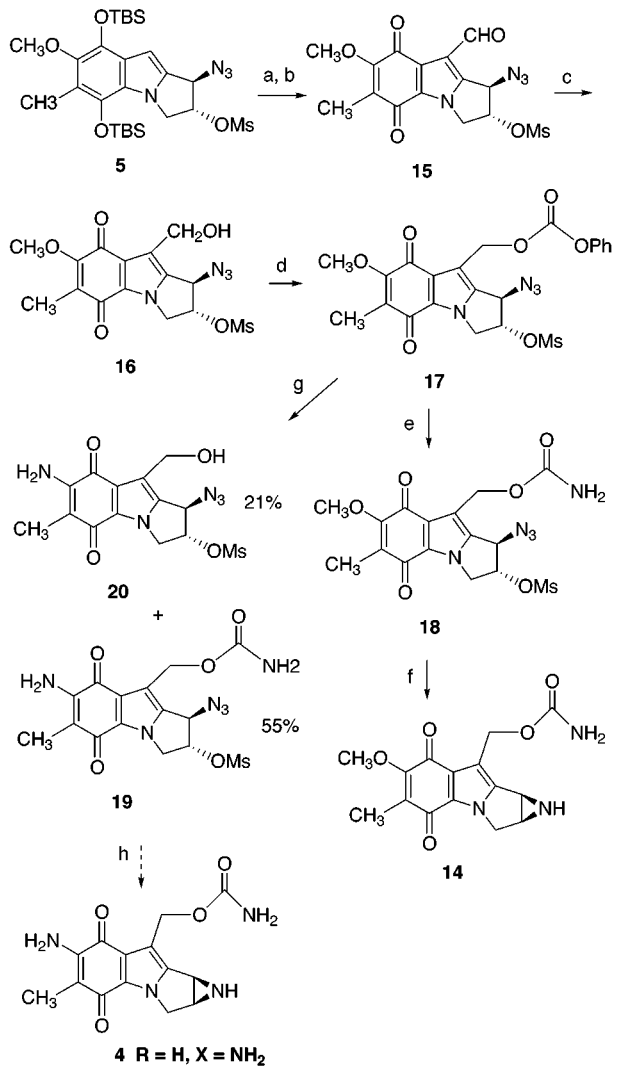
Scheme 2



(a) $POCl_3$, DMF. (b) PCC, CH_2Cl_2, 78% from **5**. (c) 1) $NaBH_4$, MeOH 5 min, 2) O_2, 74%. (d) phenyl chloroformate, pyridine, 90%. (e) NH_3(g) CH_2Cl_2, 77%. (f) PPh_3, NEt_3, THF/H_2O, 70%. (g) 2M NH_3, MeOH, 2 days, rt. (h) PPh_3, NEt_3, THF/H_2O.

tion gave a quantitative yield of **6**. This three-step procedure allowed the synthesis of **6** on a multigram scale in a 38% overall yield from 3,6-dimethyl-2,4-dinitroanisole. Oxidation of **6** with potassium nitrosodisulfonate (Fremy's salt) gave the corresponding quinone **9**, which was used without further purification to give the protected hydroquinone **10** by catalytic hydrogenation, followed by treatment with 4 equiv of *tert*-butyldimethylsilyl chloride and imidazole.[15] The overall yield from **8** was 78%. Reduction with DIBAL gave an 89% yield of the alcohol **11**, which was converted to the corresponding aldehyde **12** with MnO_2 in 85% yield. An improved yield (72%) of the azido alcohol **13** was obtained by reacting **12** with diisopropylvinylsulfonium triflate[16] in the presence of sodium hydride, followed by the addition of sodium azide. Use of dimethylvinylsulfonium iodide as previously reported[11] led to *N*-methylation of **12** among other sideproducts. The mesylate **5** is obtained in a 90% yield from **13**.

The fully functionalized mitosene **14** has been synthesized from the azido mesylate **5** (Scheme 2). The aldehyde **15** was obtained from **5** by Vilsmeier−Haack formylation (96%), followed by oxidative cleavage of the TBS groups with PCC (81%).[17] Treatment of **15** with $NaBH_4$ in methanol for 5 min, followed by bubbling air through the reaction solution (to reoxidize the hydroquinone) resulted in a 74% yield of the alcohol **16**. This was then converted into the phenyl carbonate **17** by reaction with phenyl chloroformate.[8a] Bubbling ammonia through a solution of **17** dissolved in dichloromethane gave a 77% yield of **18**, which was transformed into the mitosene **14** (70%) in the presence of triphenylphosphine. Stirring **17** in 2 M ammonia in methanol for 2 days at room temperature gave **19** (55%) plus a 21% yield of the alcohol **20**. Reaction of **19** with triphenylphosphine in the presence of triethylamine did not result in the isolation of the mitosene **4** (R = H, X = NH_2), although **19** was consumed. Mitosene **4** (R = H, X = NH_2) appears to be quite labile under our reaction conditions. These results are similar to those reported earlier for optically pure **4** (R = H, X = NH_2) prepared from mitomycin C by electrolysis in MeOH, in which HPLC analysis produced only the ring-opened byproducts.[7c]

The synthesis of a fully functionalized mitosene **14** has been achieved. Although this compound lacks the element of methanol across the C9−9a double bond, it has the two alkylating moieties, the carbamoyloxymethyl side chain and the aziridine ring, necessary to form a DNA−mitosene cross-link upon reduction of the quinone ring. Such compounds have exhibited potent activity against various tumor model systems.[6]

Experimental Section

General. Elemental analyses were processed by Quantitative Technologies, Inc, Whitehouse, NJ. Mass spectra were processed by the University of California Mass Spectroscopy Facility, Riverside, CA, and the Center for Advanced Food Technology, Rutgers University, New Brunswick, NJ.

Dichloromethane and tetrahydrofuran were distilled from calcium hydride. Anhydrous methanol, toluene, ethyl ether, and 1.0 M hydrogen chloride in ethyl ether were obtained from Aldrich Chemical Co.

3,6-Dimethyl-2,4-dinitroanisole. In a 2-L round-bottomed flask, 52.0 g (382 mmol) of 2,5-dimethylanisole was dissolved into 1.0 L of trifluoroacetic acid (TFA). The solution was cooled to −10 °C (acetone/ice bath) and stirred vigorously. A total of 158 g (2.29 mol) of $NaNO_2$ was added into the solution in portions (about 1 h). After this addition, another 430 mL of TFA was added. The reaction temperature was raised slowly to room temperature, and the solution was stirred for 24 h and then poured into 1.0 L of ice−water. The mixture was extracted by CH_2Cl_2 (4 × 500 mL), and the combined organic layer was washed with 1 N $NaHCO_3$ (2 × 500 mL) and brine (1 × 500 mL) and then dried over $MgSO_4$. Filtration, followed by evaporation under reduced pressure, gave a brown solid. This crude product was recrystallized from 95% EtOH, and 63.9 g of white crystals was obtained. The mother liquid was concentrated, and the residue was purified by flash chromatography (1:1 CH_2Cl_2/petroleum ether), yielding another 8.5 g of light yellow solid. A total of 72.4 g was obtained (84%). Mp 63−64 °C. ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H), 2.44 (s, 3H), 3.91 (s, 3H), 7.95 (s, 1H). MS (EI): *m/z* 226 (M^+). Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.38. Found: C, 47.75; H, 4.43; N, 12.41.

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Methyl 3-(3-Methoxy-4-methyl-2,6-dinitrophenyl)-2-oxopropanoate (7). A total of 36.2 g (307 mmol) of 95% *t*-BuOK was added into a 2-L three-necked round-bottomed flask with 500 mL of anhydrous ether under a N_2 atmosphere at 0 °C. A total of 50 mL of MeOH was added dropwise which turned the heterogeneous mixture to a clear solution. Then 36.2 g (307 mmol) of dimethyl oxalate was added in one portion. After the mixture was stirred for 15 min, a total of 63.0 g (279 mmol) of 3,6-dimethyl-2,4-dinitroanisole in 350 mL of anhydrous ether was added dropwise into the solution at 0 °C. The reddish suspension was stirred at room temperature for 2 days and filtered to collect a reddish solid. A total of 10.0 g (14%) of unreacted 3,6-dimethyl-2,4-dinitroanisole was recovered from the filtrate. The reddish solid was dissolved in 1 N HCl in ether to obtain a clear yellow solution which was washed twice with water and dried over $MgSO_4$. Filtration, followed by evaporation of ether, gave a brown residue. The brown residue was passed through a short silica gel column (1:2 ethyl acetate/petroleum ether) to remove more polar material. Recrystallization with ethyl acetate/petroleum ether gave 54.6 g of a yellow solid (63%). Mp 86−88 °C. ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H), 3.94 (s, 6H), 4.44 (s, 2H), 8.19 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 16.2, 38.8, 53.3, 62.5, 121.0, 129.6, 134.3, 143.5, 147.5, 154.0, 159.9, 186.6. Anal. Calcd for $C_{12}H_{12}N_2O_8$: C, 46.15; H, 3.85; N, 8.97. Found: C, 46.26; H, 3.67; N, 8.88.

1-Hydroxy -5-methoxy-2-(methoxycarbonyl)-6-methyl-4-nitroindole (8). Under a N_2 atmosphere, a total of 33.5 g (107 mmol) of **7** and 62.0 g (321 mmol) of anhydrous $SnCl_2$ was dissolved into 500 mL of methanol. The mixture was refluxed for 1.5 h and then poured onto ice. The aqueous emulsion was extracted with CH_2Cl_2 (4 × 500 mL), and the combined organic layer was dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography (1:1 ethyl acetate/petroleum ether), gave 18.1 g of a yellow solid (60%). Mp 142−144 °C. ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 3H), 3.96 (s, 3H), 4.02 (s, 3H), 7.25 (s, 1H), 7.60 (s, 1H), 10.4−10.6 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 17.2, 52.7, 62.2, 102.2, 113.7, 115.8, 122.8, 130.0, 132.4, 135.8, 149.1, 163.9. MS (EI): *m*/*z* 280 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.29; N, 10.00. Found: C, 51.56; H, 4.29; N, 9.80.

4-Amino-5-methoxy-2-(methoxycarbonyl)-6-methylindole (6). At 0 °C, a total of 4.89 g (18.5 mmol) of **8** was dissolved into 200 mL of absolute ethanol in a 500-mL round-bottomed flask. A total of 250 mg of 10% palladium on activated carbon was then added. The suspension was stirred under a hydrogen atmosphere at ambient temperature for 24 h, it was filtered through a Celite pad, and the filtrate was evaporated in vacuo. A total of 4.09 g of **6** was obtained (100%). The product appeared pure by TLC and ^{1}H NMR and was carried on to the next step without further purification. For the purpose of characterization, a 200 mg sample was purified by flash chromatography (1:2 ethyl acetate/petroleum ether, with 1% diethylamine). Mp 125−126 °C. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 3.75 (s, 3H), 3.90 (s, 3H), 4.12 (br s, 2H), 6.58 (s, 1H), 7.12 (d, 1H, J = 1.2 Hz), 8.80−9.00 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 17.0, 51.8, 59.6, 102.2, 105.8, 116.8, 125.5, 131.1, 132.5, 134.6, 138.2, 162.2. MS (EI): *m*/*z* 234 (M^+). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.15; H, 6.02; N, 11.95. Found: C, 61.17; H, 6.12; N, 11.98.

5-Methoxy-2-(methoxycarbonyl)-6-methylindole-4,7-dione (9). In a 2-L three-necked round-bottomed flask, a total of 12.1 g (44.0 mmol) of potassium nitrosodisulfonate (Fremy's salt) was dissolved into 900 mL of 0.2 M NaH_2PO_4 at 0 °C. Then 4.40 g (18.8 mmol) of **6** in 200 mL of acetone was added into the flask. The reaction mixture was stirred for 10 h at ambient temperature and then extracted by CH_2Cl_2 (3 × 500 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. A total of 3.65 g of **9** was obtained (78%). The product appeared pure by TLC and ^{1}H NMR and was carried on to the next step without further purification. For the purpose of characterization, a 200 mg sample was purified by flash chromatography (2:5 ethyl acetate/petroleum ether). Mp 225−226 °C. ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 3H), 3.92 (s, 3H), 4.07 (s, 3H), 7.16 (s, 1H), 9.70−10.20 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 8.7, 52.5, 61.4, 112.4, 123.6, 127.4, 128.8, 132.9, 158.3, 160.5, 178.1, 178.7. MS (EI): *m*/*z* 249 (M^+). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.80; H, 4.42; N, 5.50.

4,7-Bis[(1,1-dimethylethyl)dimethylsilyloxy]-5-methoxy-2-(methoxycarbonyl)-6-methylindole (10). At room temperature, a solution of 500 mg (2.01 mmol) of **9** in 10 mL of CH_2Cl_2 was stirred with 50 mg of 10% palladium on activated carbon in a 50-mL round-bottomed flask under a H_2 atmosphere for about 0.5 h, at which point the yellow solution had turned colorless. A total of 545 mg (8.00 mmol) of imidazole and 1.23 g (8.00 mmol) of *tert*-butyldimethylsilyl chloride was added into the flask. The mixture was stirred for 12 h at room temperature and then filtered through a Celite pad. Concentration and purification of the filtrate by column chromatography (6:1 petroleum ether/ether) gave 958 mg of a colorless solid (100%). Mp 96−98 °C. ^{1}H NMR ($CDCl_3$): δ 0.16 (s, 6H), 0.17 (s, 6H), 1.06 (s, 9H), 1.09 (s, 9H), 2.22 (s, 3H), 3.68 (s, 3H), 3.90 (s, 3H), 7.14 (d, 1H, J = 2.3 Hz), 8.40−8.60 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ −4.5, −3.8, 10.9, 18.4, 25.9, 51.9, 60.1, 107.0, 120.2, 121.4, 125.5, 128.5, 133.1, 136.3, 142.9, 162.2. MS (EI): *m*/*z* 479 (M^+). Anal. Calcd for $C_{24}H_{41}NO_5Si_2$: C, 60.08; H, 8.61; N, 2.92. Found: C, 59.88; H, 8.51; N, 2.85.

4,7-Bis[(1,1-dimethylethyl)dimethylsilyoxy]-2-(hydroxymethyl)-5-methoxy-6-methylindole (11). In a 250 mL round-bottomed flask, a total of 3.31 g (6.91 mmol) of **10** was dissolved into 65 mL of dry THF under a N_2 atmosphere. The solution was cooled to −20 °C (ice/salt bath) and 35.0 mL (35.0 mmol) of 1.0 M DIBAL in THF was added dropwise with stirring (∼10 min). The reaction temperature was raised from −20 °C to −5 °C over a period of 1 h. Then the mixture was quenched with saturated potassium sodium tartrate, allowed to warm to room temperature and then extracted by CH_2Cl_2 (4 × 80 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography (1:6 ethyl acetate/petroleum ether) gave 210 mg (6.3%) of unreacted **10** and 2.79 g of a white solid **11** (89%). Mp 123−124 °C. ^{1}H NMR ($CDCl_3$): δ 0.18 (s, 6H), 0.19 (s, 6H), 1.08 (s, 9H), 1.10 (s, 9H), 1.60−1.75 (br s, 1H), 2.23 (s, 3H), 3.70 (s, 3H), 4.78 (s, 2H), 6.36 (d, 1H, J = 2.3 Hz), 7.90−8.00 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ −4.5, −3.7, 10.7, 18.5, 26.0, 58.8, 60.1, 98.9, 116.4, 121.2, 127.5, 132.8, 135.3, 135.7, 142.5. Anal. Calcd for $C_{23}H_{41}NO_4Si_2$: C, 61.20; H, 9.09; N, 3.10. Found: C, 61.25; H, 9.27; N, 2.93.

4,7-Bis[(1,1-dimethylethyl)dimethylsilyloxy]-2-formyl-5-methoxy-6-methylindole (12). Under a N_2 atmosphere, 1.96 g (4.34 mmol) of **11** was dissolved into 145 mL of dry CH_2Cl_2 in a 250-mL round-bottomed flask. A total of 3.78 g (43.4 mmol) of freshly activated MnO_2 (MnO_2 was heated at 110 °C in an oven for 24 h) was added to the solution during the first 4 h (2 equiv/h). After the solution was stirred for another 8 h at room temperature (monitored by TLC), it was filtered through a Celite pad and concentrated. Flash chromatography (1:14 ether/petroleum ether) gave 1.65 g of a yellow solid (85%). Mp 108−110 °C. ^{1}H NMR ($CDCl_3$): δ 0.18, (s, 12H), 1.07, (s, 9H), 1.08, (s, 9H), 2.23, (s, 3H), 3.69 (s, 3H), 7.20 (d, 1H, J = 2.3 Hz), 8.50−8.65 (br s, 1H), 9.73 (s, 1H). ^{13}C NMR ($CDCl_3$): δ −4.5, −3.7, 11.1, 18.5, 25.9, 60.2, 113.0, 121.6, 122.6, 129.6, 133.3, 134.7, 136.9, 143.1, 181.2. MS (EI): *m*/*z* 449 (M^+). Anal. Calcd for $C_{23}H_{39}NO_4Si_2$: C, 61.43; H, 8.74; N, 3.11. Found: C, 61.73; H, 8.63; N, 2.95.

1-Azido-5,8-bis[(1,1-dimethylethyl)dimethylsilyloxy]-2,3-dihydro-2-hydroxy-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole (13). In a 100-mL round-bottomed flask, a total of 350 mg (0.78 mmol) of **12** and 47.4 mg (1.56 mmol) of NaH (80% dispersion in mineral oil) was stirred in 10 mL of dry THF under N_2 at 0 °C. After 20 min, a total of 439 mg (1.17 mmol) of diisopropylvinylsulfonium triflate in 10 mL of dry THF was added slowly into the flask. Then the reaction mixture was stirred about 14 h at ambient temperature. A total of 507 mg (7.8 mmol) of NaN_3 in 5.0 mL of 1:1 acetone−water was added to the mixture, and the reaction mixture was stirred at room temperature for 12 h. A total of 25 mL of water was added, and the aqueous solution was extracted by CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (7:2:1 petroleum ether:CH_2Cl_2:ether). A total of 20 mg of unreacted **12** and 290 mg of **13** as a colorless oil was obtained (72%). IR: 2099 (N_3), 3439 (broad, OH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.16 (s, 6H), 0.17 (s, 6H), 1.02 (s, 9H), 1.05 (s, 9H), 2.19 (s, 3H), 3.68 (s, 3H), 4.17 (dd, 1H, J_1 = 2.0 Hz, J_2

= 11.6 Hz), 4.46 (dd, 1H, J_1 = 4.8 Hz, J_2 = 11.6 Hz), 4.65−4.70 (br m, 1H), 4.72 (d, 1H, J = 3.0 Hz), 6.50 (s, 1H). ^{13}C NMR ($CDCl_3$): δ −4.4, −3.1, 11.0, 18.6, 26.0, 53.1, 60.0, 64.0, 80.3, 95.8, 117.1, 125.2, 126.0, 133.6, 135.7, 136.2, 142.7. Anal. Calcd for $C_{25}H_{42}N_4O_4Si_2$: C, 57.88; H, 8.16. Found: C, 58.14; H, 7.99.

1-Azido-9-formyl-2,3-dihydro-2-(methanesulfonyloxy)-7-methoxy-6-methyl-5,8-bis[(1,1-dimethylethyl)dimethylsilyloxy]-1*H*-pyrrolo[1,2-*a*]indole. In a 50-mL round-bottomed flask, a total of 378 μL (4.20 mmol) of $POCl_3$ was added dropwise to 2.5 mL of anhydrous DMF under N_2 at 0 °C. After the mixture was stirred for 45 min, a total of 313 mg (0.525 mmol) of **5** in 20.0 mL of dry THF was added slowly (∼20 min). The solution was stirred at ambient temperature for 20 h. Then, 10 mL of water was added, and the mixture was stirred at room temperature for 4 h. This aqueous solution was extracted by CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4. Filtration, evaporation, and flash chromatography (1:4 ethyl acetate/petroleum ether) gave 315 mg of a white solid (96%). Mp 138−140 °C. IR: 2111 (N_3), 1654 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.21 (s, 6H), 0.22 (s, 6H), 1.01 (s, 9H), 1.04 (s, 9H), 2.22 (s, 3H), 3.10 (s, 3H), 3.72 (s, 3H), 4.61 (m, 2H), 5.41 (d, 1H, J = 3.2 Hz), 5.50 (s, 1H), 10.47 (s, 1H). ^{13}C NMR ($CDCl_3$): δ −3.8, −3.7, −3.0, −2.8, 11.6, 18.6, 18.7, 25.9, 26.1, 38.6, 52.7, 60.3, 61.9, 84.2, 113.4, 119.1, 123.3, 124.4, 134.7, 136.9, 141.6, 145.8, 186.7. Anal. Calcd for $C_{27}H_{44}N_4O_7SSi_2$: C, 51.92; H, 7.05; N, 8.97. Found: C, 52.10; H, 6.84; N, 8.84.

1-Azido-9-formyl-2,3-dihydro-2-(methanesulfonyloxy)-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (15). In a 50-mL round-bottomed flask, a total of 100 mg (0.16 mmol) of the preceding aldehyde was dissolved into 10 mL of dry CH_2Cl_2 under N_2 at room temperature. A total of 70.5 mg (0.32 mmol) of pyridinium chlorochromate (PCC) was added. After the reaction mixture was stirred for 5 h, it was concentrated under reduced pressure, and the product was purified by flash chromatography (2:3 ethyl acetate/petroleum ether). A total of 51 mg of an orange solid **15** was obtained (81%). Mp decomposed > 150 °C. IR: 2116 (N_3), 1650 (CHO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H), 3.12 (s, 3H), 4.10 (s, 3H), 4.61 (s, 1H), 4.62 (s, 1H), 5.45 (s, 2H), 10.42 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 8.5, 38.7, 52.6, 61.4, 61.8, 83.9, 118.2, 125.4, 127.7, 128.4, 140.4, 157.6, 178.7 (merged), 186.1. Anal. Calcd for $C_{15}H_{14}N_4O_7S$: C, 45.68; H, 3.55; N, 14.21. Found: C, 45.78; H, 3.51; N, 14.04.

1-Azido-2,3-dihydro-9-(hydroxymethyl)-2-(methanesulfonyloxy)-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (16). A total of 127 mg (0.32 mmol) of **15** was partially dissolved into 10 mL of methanol at room temperature. Then 61 mg (1.6 mmol) of $NaBH_4$ was added. Bubbles could be seen immediately, and the yellow color of the solution turned colorless in 5 min. Air was then bubbled through the solution. The air was stopped when a yellow solid appeared in the methanol solution. A total of 10 mL of water was added, and the aqueous solution was extracted by CH_2Cl_2 (3 × 10 mL). The combined yellow organic layer was dried over Na_2SO_4. Filtration, evaporation of the solvent under reduced pressure, and flash chromatography (3:2 ethyl acetate/petroleum ether) gave 94 mg of a yellow solid (74%). Mp decomposed > 150 °C. IR: 2109 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.45−1.75 (br s, 1H), 1.98 (s, 3H), 3.12 (s, 3H), 4.04 (s, 3H), 4.55 (s, 1H), 4.56 (d, 1H, J = 5.9 Hz), 4.82 (d, 2H, J = 4.2 Hz), 5.20 (d, 1H, J = 1.6 Hz), 5.46 (m, 1H). Anal. Calcd for $C_{15}H_{16}N_4OS$: C, 45.45; H, 4.04; N, 14.14. Found: C, 45.69; H, 3.95; N, 13.89.

1-Azido-2,3-dihydro-2-(methanesulfonyloxy)-7-methoxy-6-methyl-9-[(phenoxy- carbonyloxy)methyl]-1*H*-pyrrolo-[1,2-*a*]indole-5,8-dione (17). In a 100-mL round-bottomed flask, a total of 94 mg (0.24 mmol) of **16** was partially dissolved into 20 mL of dry CH_2Cl_2 under N_2 at 0 °C. Then, 313 μL (1.20 mmol) of pyridine and 313 μL (1.20 mmol) of phenyl chloroformate were added via syringe. The solution was stirred at ambient temperature for 5 h. Then it was washed with 1 N $NaHCO_3$ (3 × 10 mL), 1 N HCl (3 × 10 mL), and brine (3 × 10 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure, followed by flash chromatography (2:3 ethyl acetate/petroleum ether), gave 110 mg of a yellow oil (90%). IR: 2110 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H), 3.07 (s, 3H), 4.06 (s, 3H), 4.48−4.68 (m, 2H), 5.27−5.31 (m, 1H), 5.42−5.50 (m, 1H), 5.53 (d, 2H, J = 2.6 Hz), 7.14−7.31 (m, 3H), 7.33−7.45 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 8.5, 38.7, 51.7, 61.3, 61.8, 62.0, 84.2, 114.5, 121.0, 124.2, 126.2, 127.5, 128.2, 129.5, 136.0, 151.0, 153.5, 157.5, 178.6, 178.8. Anal. Calcd for $C_{22}H_{20}N_4O_9S$: C, 51.16; H, 3.88; N, 10.85. Found: C, 51.18; H, 3.85; N, 10.46.

9-[(Aminocarbonyloxy)methyl]-1-azido-2,3-dihydro-2-(methanesulfonyloxy)-7-methoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (18). In a 100 mL round-bottomed flask, a total of 35 mg (0.068 mmol) of **17** was dissolved into 10 mL of dry CH_2Cl_2 under N_2 at −78 °C (dry ice/acetone bath). Then ammonia gas was bubbled through the solution for 30 min. After the ammonia was stopped, the temperature of the green-yellow solution was raised from −78 °C to room temperature slowly (∼3 h). The solution was concentrated and purified by flash chromatography (3:2 ethyl acetate/petroleum ether). A total of 23 mg of a yellow oil was obtained (77%). IR: 2107 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.96 (s, 3H), 3.12 (s, 3H), 4.05 (s, 3H), 4.45−4.66 (m, 2H), 4.83 (br s, 2H), 5.27 (d, 1H, J = 1.5 Hz), 5.36 (s, 2H), 5.41−5.51 (m, 1H). ^{13}C NMR (acetone-d_6): δ 8.5, 38.4, 52.6, 58.6, 61.4, 63.1, 86.4, 117.4, 124.7, 128.0, 128.6, 136.7, 157.2, 158.3, 179.0, 179.5. HRMS, m/z (M^+, $C_{16}H_{17}N_5O_8S$) calcd 439.0798, obsd 439.0798.

8-[(Aminocarbonyloxy)methyl]-1,1a,2,8b-tetrahydro-6-methoxy-5-methylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione (14). In a 25-mL round-bottomed flask, a total of 18 mg (0.041 mmol) of **18** was dissolved into 2.2 mL of 10:1 THF/H_2O. Then, 40 μL of NEt_3 was added, followed by 16.2 mg (0.060 mmol) of PPh_3. The mixture was stirred at room-temperature overnight. A total of 10 mL of water was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 portions were dried over Na_2SO_4. Filtration, evaporation of the solvent under reduced pressure, and flash chromatography (5:95 methanol/ethyl acetate) gave 9 mg of an orange solid (70%). Mp decomposed > 200 °C. ^{1}H NMR: because **14** exists as a mixture of invertomers (isomers by inversion at the aziridine center) and the isomerization is very slow at room temperature, some shoulder peaks could be seen. This is more obvious in $CDCl_3$ than in pyridine-d_5. ($CDCl_3$): δ 1.93 (s, 3H), 1.96 (s, minor isomer's peak), 3.49 (t, 1H, J = 3.8 Hz, with a small side peak at 3.44), 3.62 (br s, 1H), 4.02 (s, 3H, with a small shoulder peak), 4.22−4.44 (m, 2H, with small side peaks at 4.05−4.20), 4.67 (br s, 2H), 5.27 (d, J = 12.9 Hz, 1H), 5.36 (d, J = 12.9 Hz, 1H). (C_5D_5N): δ 1.97 (s, 3H), 3.35 (t, 1H, J = 3.7 Hz), 3.76−3.84 (m, 1H), 3.97−4.16 (m, 1H), 4.00 (s, 3H), 4.38 (d, 1H, J = 14.1 Hz), 5.72 (d, 2H, J = 0.92 Hz), 7.74 (br s, 2H). MS (EI): m/z 317 (M^+). HRMS, m/z (M^+, $C_{15}H_{15}N_3O_5$) calcd 317.1012, obsd 317.1010.

7-Amino-9-[(aminocarbonyloxy)methyl]-1-azido-2,3-dihydro-2-(methanesulfonyl- oxy)-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (19) and 7-amino-1-azido-2,3-dihydro-9-(hydroxylmethyl)-2-(methanesulfonyloxy)-6-methyl-1*H*-pyrrolo[1,2-*a*] indole-5,8-dione (20). In a 25-mL round-bottomed flask, a total of 33 mg (0.064 mmol) of **17** was dissolved into 3.0 mL of 2.0 M ammonia in methanol under N_2. The mixture was stirred at room temperature for 24 h. The original yellow-colored solution had turned red and a black precipitate was formed. The solvent was removed under reduced pressure and acetone was used to rinse out the products except the black precipitate. The red acetone solution was concentrated and purified by flash chromatography (3:2 ethyl acetate/petroleum ether). A total of 15 mg of a red oil of **19** (55%) and 5 mg of **20** (21%) was obtained. For **19**: IR: 2111 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 3H), 3.12 (s, 3H), 4.54−4.59 (m, 2H), 4.76−4.82 (br s, 2H), 5.00 (br s, 2H), 5.23 (d, 1H, J = 1.6 Hz), 5.35 (s, 2H), 5.43−5.49 (m, 1H). ^{13}C NMR (acetone-d_6): δ 8.3, 38.5, 52.5, 58.8, 63.0, 86.6, 107.0, 116.9, 122.6, 130.3, 134.5, 147.8, 157.3, 177.3, 179.2. For **20**: ^{1}H NMR ($CDCl_3$): δ 1.87 (s, 3H), 3.11 (s, 3H), 4.56 (d, 2H, J = 3.1 Hz), 4.78−4.84 (m, 2H), 4.99 (br s, 2H), 5.17 (d, 1H, J = 1.1 Hz), 5.41−5.48 (m, 1H). MS (EI): m/z 381 (M^+). HRMS, m/z (M^+, $C_{14}H_{15}N_5O_6S$) calcd 381.0743, obsd 381.0743.

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