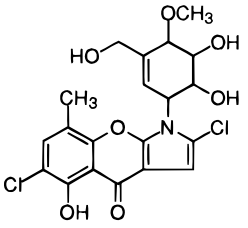
Total Synthesis of the Pyralomicinones

T. Ross Kelly* and Rimma L. Moiseyeva

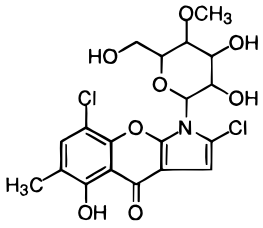
Department of Chemistry, E. F. Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02167

Received December 31, 1997

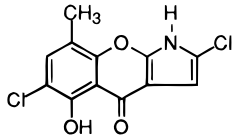
The structures of the pyralomicins, typified by **1** and **2**, were recently reported.[1] These heterocycles, which were isolated from the microorganism *Microtetraspora spiralis*, exhibit antimicrobial and antitumor activities.[1] Because of their unusual benzopyranopyrrole ring system[2] and our continuing interest in the synthesis of heterocyclic natural products,[3] we undertook the synthesis of pyralomicinones **3** and **4**, which are the "aglycones" of the pyralomicins. We now report the first synthesis of the pyralomicinones.



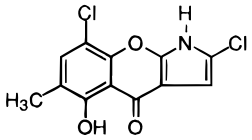
1



2

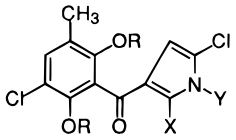


3



4

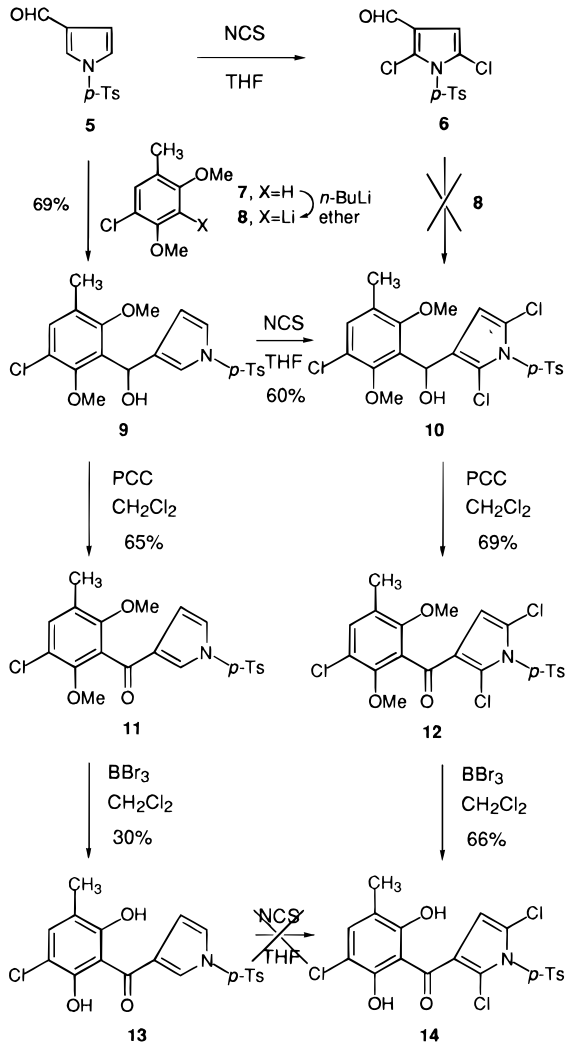
In planning the syntheses of **3** and **4**, we envisioned preparing them from a common intermediate already containing the pyrrole and benzene rings, as in **I**, and



≡ **I**

forming the pyranone ring in the final major constructive step. Intermediate **I**, in turn, was expected to be assembled from suitably protected phenyl and pyrrolyl precursors. To that end, the tosylated pyrrole aldehyde **5** (Scheme 1) was prepared from commercially available pyrrole in four steps according to the procedure of Demopoulos.[4a−c] It was necessary to protect the pyrrole NH for the coupling reaction with **8** due to the former's acidity. Chloride **7** was made in one step from commercially available 2,4-dimethoxytoluene by chlorinating it with *N*-chlorosuccinimide (NCS). Addition of the lithium anion **8** derived from **7** to aldehyde **5** produced **9**. Unexpectedly, reaction of chlorinated aldehyde **6** with **8** failed to form alcohol **10** under an analogous procedure. Alcohol **9** was then oxidized to ketone **11** with pyridinium chlorochromate (PCC) and deprotected with BBr_3 to afford ketone **13**. To our surprise, attempts to chlorinate ketone **13** with NCS or SO_2Cl_2[5] were unsuccessful, even though we had previously chlorinated pyrrole-3-carboxaldehyde[6] and **5** using NCS. Therefore, we chlorinated alcohol **9** with NCS and oxidized the resulting **10** to **12**

Scheme 1



(1) (a) Kawamura, N.; Sawa, R.; Takahashi, Y.; Isshiki, T.; Sawa, T.; Kinoshita, N.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 435. (b) Kawamura, N.; Sawa, R.; Takahashi, Y.; Isshiki, T.; Sawa, T.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 651. (c) Kawamura, N.; Sawa, R.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 657. (d) Kawamura, N.; Kinoshita, N.; Sawa, R.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 706. (e) Kawamura, N.; Nakamura, H.; Sawa, R.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 147.

(2) The benzopyranopyrrole ring system has also been reported recently in TAN-876A: Funabashi, Y.; Takizawa, M.; Tsubotani, S.; Tanida, S.; Harada, S. *Takeda Kenkyushoho* **1992**, *51*, 73; *Chem. Abstr.* **1992**, *118*, 55722. (b) For a very recent synthesis of the ring system (by a different route) see Alberola, A.; Álvaro, R.; Ortega, A. G.; Sañudo, C. *Tetrahedron* **1997**, *53*, 16185.

(3) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623 and earlier work cited therein.

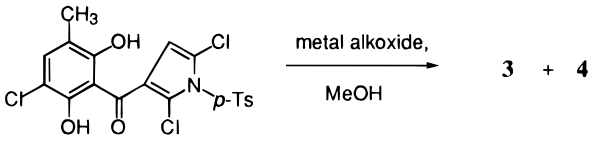
(4) (a) Demopoulos, V. J. *J. Heterocycl. Chem.* **1988**, *25*, 635. (b) Demopoulos, V. J. *Org. Prep. Proced. Int.* **1986**, *18*, 278. (c) Demopoulos, B. J.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.*, **1983**, *61*, 2415.

(5) Artico, M. In *Pyrroles*; Jones, R. A., Ed.; Wiley: New York, 1990; Part 1, pp 349−371.

(6) Unpublished results of R. L. Moiseyeva and T. R. Kelly.

S0022-3263(97)02340-2 CCC: $15.00
Published on Web 04/04/1998

Scheme 2



14

Table 1

conditions	ratio **3:4**
LiOMe, MeOH	1:1
NaOMe, MeOH	**1:2.5**
TlOEt, EtOH	1:2
$Mg(OMe)_2$, MeOH	**3:1**
$Sr(Oi\text{-}Pr)_2$, MeOH	1:1
$Ba(Oi\text{-}Pr)_2$, MeOH	1:2
$Al(Oi\text{-}Pr)_3$, MeOH	2:1
$Sm(Oi\text{-}Pr)_3$, MeOH	1:1

with PCC. Deprotection of ketone **12** with BBr_3 furnished the pyralomicinones' anticipated precursor **14**.

Now what remained were to form the tricyclic system by an intramolecular, base-promoted, nucleophilic aromatic substitution and to remove the tosyl protecting group. 2-Halopyrroles are usually inert to nucleophilic aromatic substitution,[7] but we believed that the presence on the pyrrole of two strongly electron-withdrawing groups, and the use of an intramolecular reaction, nonetheless augured well for success. Since the two possible regioisomers that might be produced in the cyclization were both desired products, we had chosen to avoid the complication of a protecting-group or other strategy to form an individual regioisomer separate from the other one. Rather, we anticipated that different reaction conditions might be developed to favor production of first one and then the other regioisomer. That expectation proved justified, as use of a variety of metal alkoxides for the base-induced cyclizations resulted in different regioselectivities (Scheme 2; Table 1). Moreover, cleavage of the tosyl group also occurred during the reaction to give the desired **3** and **4** directly. The variation in regiochemistry may be due to different associations of the metal ions between the carbonyl and one of the phenolic oxygens. The best regioselectivities (Table 1) were obtained with magnesium and sodium methoxides. Finally, the mixtures of **3** and **4** were separated using preparative reverse phase HPLC to afford the pure pyralomicinones.

Assignment of which regioisomer was which was initially tentatively made by comparing the ^1H and ^{13}C NMR spectra of **3** and **4** with spectra of the regioisomeric chromophores of **1** and **2** (see Table 2), but a rigorous assignment was achieved by $^1H-^1H$ NOESY 2D NMR experiments (see Supporting Information for spectra) on derivatives of **3** and **4**. Accordingly, pyralomicinones **3** and **4** were separately methylated with iodomethane to afford the two dimethylated derivatives **15** and **16**, respectively, and the expected crossover peaks were observed (Scheme 3). In particular, in **3**-derived **15** the aromatic CH_3 group displayed a crossover peak with the aromatic hydrogen, but not with the methoxy group; in contrast, in **4**-derived **16** the aromatic CH_3 group exhibited crossover peaks with both the aromatic hydrogen and the methoxy group. Authentic samples of naturally derived aglycones **3** and **4** were not available (the pyralomicins have not been hydrolyzed to their aglycones[8]), but the spectra of the synthetic aglycones are in excellent agreement with the spectra for the corresponding components of the natural products (Table 2).

Scheme 3

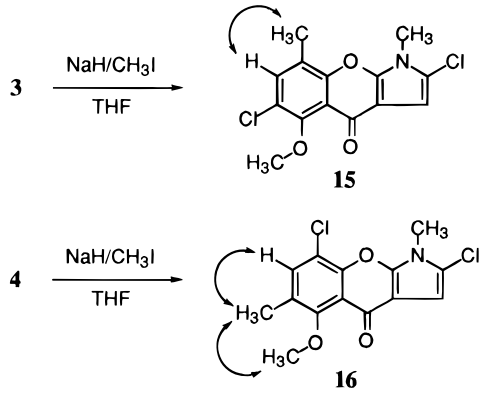


Table 2

1	**3**	**2**	4
	^1H NMR (δ)		
2.38	2.38	2.27	2.25
6.74	6.55	6.80	6.57
7.71	7.64	7.77	7.69
13.81	14.04	13.40	13.82
	^{13}C NMR (δ)		
14.8	14.7	14.4	14.7
99.7	99.8	100.8	100.7
105.2	105.8	105.6	106.3
110.1	110.3	109.9	109.9
114.2	114.0	109.9	110.5
117.8	117.5	119.0	116.6
119.8	117.6	122.2	122.4
135.6	135.4	136.0	136.1
150.2	151.6	148.3	148.8
151.4	151.7	149.9	150.9
155.5	155.8	158.8	159.6
177.5	177.7	177.8	178.3

Conclusion

In summary, the first synthesis of the two tricyclic aglycones (**3** and **4**) of the pyralomicins has been achieved. The spectra of **3** and **4** strongly support the structures assigned to the chromophore units of the natural products.

Experimental Section[9]

1-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3-carboxaldehyde (5). This compound was prepared as a light beige solid in four steps from pyrrole (Acros) according to the procedure of Demopoulos:[4a-c] mp 53−55 °C (lit.[4a] mp 61−62 °C); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 6.64 (dd, 1H, J = 3.2, 1.6 Hz), 7.13−7.15 (m, 1H), 7.29 (d, 2H, J = 8.4 Hz), 7.76−7.78 (m, 3H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 110.8, 122.3, 127.3, 128.2, 129.5, 130.4, 134.7, 146.3, 185.2; IR ($CDCl_3$) ν 3125, 1677 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.64; H, 4.28; N, 5.38.

2,5-Dichloro-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carboxaldehyde (6). Aldehyde **5** (5.15 g, 20.7 mmol) was placed with *N*-chlorosuccinimide (13.8 g, 103 mmol, 5.0 equiv) in a 250 mL round-bottomed flask under a nitrogen atmosphere. Anhydrous THF (150 mL) was added all at once, and the solution was refluxed with stirring overnight. After cooling to room temperature, the solution was poured into a saturated aqueous solution of NaCl (200 mL) and extracted with diethyl ether (3

(7) (a) Dennis, N. In *Pyrroles*; Jones, R. A., Ed.; Wiley: New York, 1990; Part 1, pp 537−548. (b) Joule, J. A.; Smith, G. F. *Heterocyclic Chemistry*; Van Nostrand Reinhold: London, 1972; p 211.

(8) Personal communication from Dr. T. Takeuchi.[1]

(9) For general experimental procedures, see ref 3.

× 100 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo to afford a brown oil. Flash chromatography on a 6 × 25 cm SiO_2 column eluting with 50:50 diethyl ether/petroleum ether afforded **6** (2.17 g, 33%) as a light yellow solid. Recrystallization from ether/petroleum ether produced a white solid: mp 105−106.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.44 (s, 1H), 7.33 (d, 2H, J = 8.4 Hz), 7.87 (d, 2H, J = 8.4 Hz), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 109.8, 119.9, 123.3, 125.5, 127.8, 130.4, 134.3, 147.1, 182.8; IR ($CDCl_3$) ν 1681 cm^{-1}. Anal. Calcd for $C_{12}H_9Cl_2NO_3S$: C, 45.30; H, 2.85; N, 4.40. Found: C, 45.05; H, 2.78; N, 4.33.

1-Chloro-2,4-dimethoxy-5-methylbenzene (7).[10] 2,4-Dimethoxytoluene (Aldrich, 4.98 g, 32.8 mmol) was placed with *N*-chlorosuccinimide (6.56 g, 49.2 mmol, 1.5 equiv) in a 100 mL round-bottomed flask under a nitrogen atmosphere. Anhydrous DMF (50 mL) was added, and the solution was refluxed with stirring for 2 h. After cooling to room temperature, the solution was poured into a saturated aqueous solution of NaCl (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with a saturated solution of NaCl (2 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting brown-orange oil was purified using flash column chromatography (6 × 20 cm SiO_2 column, CH_2Cl_2) to afford **7** (4.67 g, 76%) as a white fluffy solid: mp 89−90 °C (lit.[10] mp 74−75 °C); ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 6.42 (s, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.2, 55.7, 56.4, 96.5, 112.7, 119.5, 131.1, 153.7, 157.1; IR ($CDCl_3$) ν 1604, 1504, 1302, 1210, 1168, 1035, 808 cm^{-1}. Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94. Found: C, 57.68; H, 5.73.

α-(3-Chloro-2,6-dimethoxy-5-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-methanol (9). Chlorodimethoxytoluene **7** (2.11 g, 11.3 mmol) was dissolved in 100 mL of anhydrous diethyl ether in a 250 mL round-bottomed flask under a nitrogen atmosphere, and *n*-butyllithium (6.36 mL of a 2.31 M solution in hexanes, 14.7 mmol, 1.3 equiv) was added at room temperature all at once. After 40 min of stirring at room temperature, the resulting yellow suspension was cooled in an ice bath and added dropwise over 30 min via cannula to a vigorously stirred solution of aldehyde **5** (2.81 g, 11.3 mmol) in 100 mL of anhydrous diethyl ether in a 500 mL round-bottomed flask cooled in an ice/salt bath. The cooling bath was removed, and the mixture was stirred for an additional 10 min. The solvent was evaporated to afford a brown oil, which was dissolved in a minimum amount of methanol (∼ 20 mL), and mixed with SiO_2 (∼2 g); volatiles were removed in vacuo, and the solid residue was applied to the top of a 6 × 20 cm SiO_2 column. Elution with 30:70 ethyl acetate/petroleum ether afforded **9** (3.39 g, 69%) as a pale pink glass: mp 87−89 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H), 2.40 (s, 3H), 3.43 (s, 3H), 3.49 (s, 3H), 4.13 (d, 1H, J = 11.0 Hz), 5.95 (d, 1H, J = 11.0 Hz), 6.16 (dd, 1H, J = 3.2, 1.6 Hz), 6.98−6.99 (m, 1H), 7.11−7.12 (m, 1H), 7.15 (s, 1H), 7.27 (d, 2H, J = 8.4 Hz), 7.73 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.7, 21.5, 60.9, 61.0, 65.0, 112.7, 116.6, 121.2, 122.6, 126.8, 128.4, 129.9, 131.2, 131.6, 134.8, 135.9, 145.1, 152.2, 155.3; IR ($CDCl_3$) ν 3534, 2936, 1472, 1372, 1174 cm^{-1}. An analytical sample was obtained as large, pale-pink crystals, mp 94−96 °C, after recrystallization from CH_2Cl_2/petroleum ether. Anal. Calcd for $C_{21}H_{22}ClNO_5S$: C, 57.86; H, 5.09; N, 3.21. Found: C, 58.04; H, 5.23; N, 3.27.

α-(3-Chloro-2,6-dimethoxy-5-methylphenyl)-2,5-dichloro-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-methanol (10). Alcohol **9** (3.75 g, 8.6 mmol) was placed with *N*-chlorosuccinimide (2.87 g, 21.5 mmol, 2.5 equiv) in a 250 mL round-bottomed flask under a nitrogen atmosphere. Anhydrous THF (150 mL) was added, and the resulting solution was heated at reflux overnight with stirring. After cooling to room temperature, the solution was poured into a saturated aqueous solution of NaCl (200 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (200 mL), dried over Na_2SO_4, and concentrated in vacuo to afford a dark yellow oil. Flash chromatography on a 6 × 25 cm SiO_2 column, eluting with 10:40:50 ethyl acetate/petroleum ether/CH_2Cl_2, afforded **10** (2.60 g, 60%) as a beige oil: ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.40 (s, 3H), 3.28 (br s, 1H), 3.53 (s, 3H), 3.62 (s, 3H), 5.97 (s, 1H), 6.27 (s, 1H), 7.12 (s, 1H), 7.29 (d, 2H, J = 8.4 Hz), 7.84 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 16.0, 21.8, 61.1, 61.3, 63.7, 112.9, 113.7, 117.3, 122.7, 127.7, 128.3, 128.4, 129.5, 130.1, 132.2, 135.4, 146.1, 152.3, 155.5; IR ($CDCl_3$) ν 3471, 2942, 1469, 1394 cm^{-1}. An analytical sample was obtained as beige plates, mp 150−152 °C, after crystallization from CH_2Cl_2/petroleum ether. Anal. Calcd for $C_{21}H_{20}Cl_3NO_5S$: C, 49.97; H, 3.99; N, 2.77. Found: C, 49.89; H, 3.80; N, 2.65.

3-Chloro-2,6-dimethoxy-5-methylphenyl 1-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl Ketone (11). Ketone **11** (65%) was prepared as off-white prisms, mp 130−132 °C, in a manner analogous to the preparation of ketone **12**: ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.41 (s, 3H), 3.61 (s, 3H), 3.69 (s, 3H), 6.69 (dd, 1H, J = 3.2, 1.6 Hz), 7.12−7.14 (m, 1H), 7.27 (s, 1H), 7.32 (d, 2H, J = 8.4 Hz), 7.50−7.51 (m, 1H), 7.77 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.6, 21.8, 62.1, 62.4, 112.8, 121.8, 122.6, 126.9, 127.4, 128.8, 129.6, 130.1, 130.4, 132.9, 134.9, 146.2, 151.3, 154.4, 188.1; IR ($CDCl_3$) ν 1659, 1469, 1377, 1173 cm^{-1}. Anal. Calcd for $C_{21}H_{20}ClNO_5S$: C, 58.13; H, 4.65; N, 3.23. Found: C, 57.95; H, 4.55; N, 3.05.

3-Chloro-2,6-dimethoxy-5-methylphenyl 2,5-Dichloro-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl Ketone (12). Alcohol **10** (2.15 g, 4.26 mmol) was placed with PCC (2.76 g, 12.8 mmol, 3.0 equiv) in a 250 mL round-bottomed flask under a nitrogen atmosphere. Anhydrous CH_2Cl_2 (150 mL) was added, and the mixture was stirred at room temperature overnight. The solvent was evaporated, and the black residue was extracted (30:70 ethyl acetate/petroleum ether, 3 × 100 mL) and filtered off in order to eliminate the insoluble impurities. The combined filtrates were concentrated in vacuo, and the resulting yellow oil was purified using flash column chromatography (3 × 25 cm SiO_2 column, 30:70 ethyl acetate/petroleum ether) to afford ketone **12** (1.48 g, 69%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H), 2.46 (s, 3H), 3.62 (s, 3H), 3.71 (s, 3H), 6.39 (s, 1H), 7.25 (s, 1H), 7.38 (d, 2H, J = 8.4 Hz), 7.93 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.7, 22.0, 62.1, 62.3, 113.1, 118.8, 121.9, 122.7, 123.8, 128.2, 128.9, 130.2, 130.4, 133.2, 134.8, 147.0, 151.1, 154.2, 186.7; IR ($CDCl_3$) ν 2942, 1662, 1475 cm^{-1}. Anal. Calcd for $C_{21}H_{18}Cl_3NO_5S$: C, 50.17; H, 3.61; N, 2.79. Found: C, 49.98; H, 3.43; N, 2.68.

3-Chloro-2,6-dihydroxy-5-methylphenyl 1-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl Ketone (13). Ketone **13** (30%) was prepared as a bright yellow oil in a manner analogous to the preparation of ketone **14**: ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.43 (s, 3H), 6.16 (br s, 1H), 6.71 (dd, 1H, J = 3.2, 1.6 Hz), 7.11−7.13 (m, 1H), 7.24 (s, 1H), 7.34 (d, 2H, J = 8.4 Hz), 7.76−7.80 (m, 3H), 10.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 21.9, 110.3, 111.5, 114.0, 119.9, 120.9, 126.7, 127.5, 129.2, 130.6, 134.5, 135.3, 146.2, 149.1, 157.8, 191.5; IR ($CDCl_3$) ν 3427, 2923, 1643, 1614, 1453, 1338, 1170 cm^{-1}. Anal. Calcd for $C_{19}H_{16}ClNO_5S$: C, 56.23; H, 3.97; N, 3.45. Found: C, 55.93; H, 3.79; N, 3.24.

3-Chloro-2,6-dihydroxy-5-methylphenyl 2,5-Dichloro-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl Ketone (14). Ketone **12** (0.25 g, 0.50 mmol) was dissolved in 15 mL of anhydrous CH_2Cl_2 under a nitrogen atmosphere. BBr_3 (3.0 mL of a 1.0 M solution in heptanes, 3.0 mmol, 6.0 equiv) was added dropwise at room temperature over 1 min, and the resulting brown-orange solution was stirred at room temperature for 24 h. The solution was washed with water (3 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo to afford a brown oil, which was purified by preparative TLC (Analtech, catalog no. 81013, SiO_2 UNIPLATE-T Taper Plate, 10:90 ethyl acetate/petroleum ether) to give **14** (0.156 g, 66%) as a bright yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.46 (s, 3H), 5.98 (s, 1H), 6.38 (s, 1H), 7.25 (s, 1H), 7.38 (d, 2H, J = 8.4 Hz), 7.93 (d, 2H, J = 8.4 Hz), 10.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.2, 22.0, 109.8, 111.0, 113.2, 118.2, 119.5, 119.8, 125.8, 128.1, 130.4, 135.1, 136.0, 146.8, 149.9, 158.9, 191.1; IR ($CDCl_3$) ν 3502, 1612, 1480, 1403 cm^{-1}. Anal. Calcd for $C_{19}H_{14}Cl_3NO_5S$: C, 48.07; H, 2.97; N, 2.95. Found: C, 48.45; H, 2.81; N, 2.97.

2,6-Dichloro-5-hydroxy-8-methyl-[1]benzopyrano[2,3-*b*]-pyrrol-4(1*H*)-one (3) and 2,8-Dichloro-5-hydroxy-6-methyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (4). Method A. To a stirred solution of **14** (60 mg, 0.13 mmol) at room temperature in anhydrous methanol (5 mL) under a nitrogen atmosphere was added 7.4% methanolic $Mg(OCH_3)_2$ (Aldrich, 0.30 mL, 2.0 equiv). After 3 h the mixture was acidified with 2 M HCl to pH 2, and the precipitate was collected by vacuum filtration to afford a

light yellow solid (25 mg, 70%), which was approximately (^{1}H NMR) a 3:1 mixture of **3** and **4**, respectively.

Method B. To a stirred solution of **14** (60 mg, 0.13 mmol) at room temperature in anhydrous methanol (7 mL) under a nitrogen atmosphere was added 4.6 M methanolic $NaOCH_3$ (Aldrich, 82 μL, 3.0 equiv). After 3 h the mixture was acidified with 2 M HCl to pH 2, and the precipitate was collected by vacuum filtration to afford a light yellow solid (28.6 mg, 80%), which was approximately (^{1}H NMR) a 1:2.5 mixture of **3** and **4**, respectively.

The mixtures were separated using preparative reverse phase HPLC (Rainin Microsorb (8 μm particle size) C18 column: 21.4 mm × 250 mm, on a Rainin HPXL HPLC, equipped with a model UV-D Dynamax absorbance detector) with a 60:40 acetone/water mixture as the mobile phase at 21 mL/min flow rate. Retention times: ~ 12.4 min for **3** and 16.9 min for **4**.

3: mp 330−332 °C (dec); UV−vis (DMF)[11] 274 (4.07), 306 (4.07), 368 (4.19) nm; ^{1}H NMR (DMF-d_7) δ 2.38 (s, 3H), 6.55 (s, 1H), 7.64 (s, 1H), 14.04 (s, 1H); ^{13}C NMR (DMF-d_7) δ 14.7, 99.8, 105.8, 110.3, 114.0, 117.5, 117.6, 135.4, 151.6, 151.7, 155.8, 177.7; HRMS (MH^+) calcd for $C_{12}H_7Cl_2NO_3$ 283.9882, found 283.9879; IR (KBr) ν 3443, 3048, 2917, 1633, 1602, 1260 cm^{-1}. Anal. Calcd for $C_{12}H_7Cl_2NO_3$: C, 50.73; H, 2.48; N, 4.93. Found: C, 50.62; H, 2.40; N, 4.85.

4: mp 334−336 °C (dec); UV−vis (DMF)[11] 272 (4.05), 306 (4.04), 368 (4.10) nm; ^{1}H NMR (DMF-d_7) δ 2.25 (s, 3H), 6.57 (s, 1H), 7.69 (s, 1H), 13.82 (s, 1H); ^{13}C NMR (DMF-d_7) δ 14.7, 100.7, 106.3, 109.9, 110.5, 116.6, 122.4, 136.1, 148.8, 150.9, 159.6, 178.3; HRMS (MH^+) calcd for $C_{12}H_7Cl_2NO_3$ 283.9882, found 283.9876; IR ($CDCl_3$) ν 3437, 3043, 2913, 1609, 1299 cm^{-1}. Anal. Calcd for $C_{12}H_7Cl_2NO_3$: C, 50.73; H, 2.48; N, 4.93. Found: C, 50.50; H, 2.52; N, 4.92.

(10) For another procedure, see Bergquist, K.-E.; Nilsson, A.; Ronlan, A. *Acta Chem. Scand. Ser. B* **1982**, *B36* (10), 675.

(11) Unlike the natural products, the pyralomicinones are not soluble in methanol, which is why the UV−vis spectra are recorded in DMF, not methanol.

2,6-Dichloro-5-methoxy-1,8-dimethyl-[1]benzopyrano-[2,3-*b*]pyrrol-4(1*H*)-one (15) and 2,8-Dichloro-5-methoxy-1,6-dimethyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (16). Pyralomicinone **3** (8.0 mg, 0.028 mmol) was placed with NaH (7.0 mg of a 60% dispersion in mineral oil, 0.17 mmol, 6.0 equiv) under a nitrogen atmosphere. Anhydrous THF (5 mL) and CH_3I (178 μL, 2.8 mmol, 100 equiv) were added, and the mixture was refluxed[12] with stirring for 20 h. The solution was concentrated in vacuo to afford a yellow solid, which was purified by preparative TLC (Analtech, catalog no. 81013, SiO_2 UNI-PLATE-T Taper Plate, CH_2Cl_2) to give **15** (5.0 mg, 57%) as a white solid: mp 202−204 °C; ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.68 (s, 3H), 3.96 (s, 3H), 6.57 (s, 1H), 7.49 (s, 1H); HRMS (MH^+) calcd for $C_{14}H_{11}Cl_2NO_3$ 312.0195, found 312.0195.

Compound **16** was prepared from pyralomicinone **4** in an analogous manner: mp 210−211 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.70 (s, 3H), 3.89 (s, 3H), 6.57 (s, 1H), 7.52 (s, 1H); HRMS (MH^+) calcd for $C_{14}H_{11}Cl_2NO_3$ 312.0195, found 312.0196.

Acknowledgment. We thank Dr. Tomio Takeuchi[1] for valuable exchange of information, Dr. Richard J. Mears for helpful discussions, Dr. John Boylan for help with NMR experiments, and Mr. Jeffrey T. Sieglen for assistance in the preparation of some intermediates.

Supporting Information Available: ^{1}H−^{1}H NOESY 2D NMR spectra of compounds **15** and **16** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO972340H

(12) Stirring at room temperature affords methylation on nitrogen only.