Total Synthesis of (+)- and (−)-Neopyrrolomycins, Chlorinated Phenylpyrrole Antibiotics

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The first total synthesis of (+)- and (−)-neopyrrolomycins (**11a** and **11b**) is detailed based on regioselective chlorinations of 3,5-dichloroanisole (**2**) and 1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid (**8**) with isocyanuric trichloride, followed by optical resolution of racemic neopyrrolomycin (**11**) with *N*-(*p*-tolylsulfonyl)-L-phenylalanyl chloride. Several analogs (**21**—**25**) have been prepared from the intermediates, and the structure-activity relationships are also discussed.

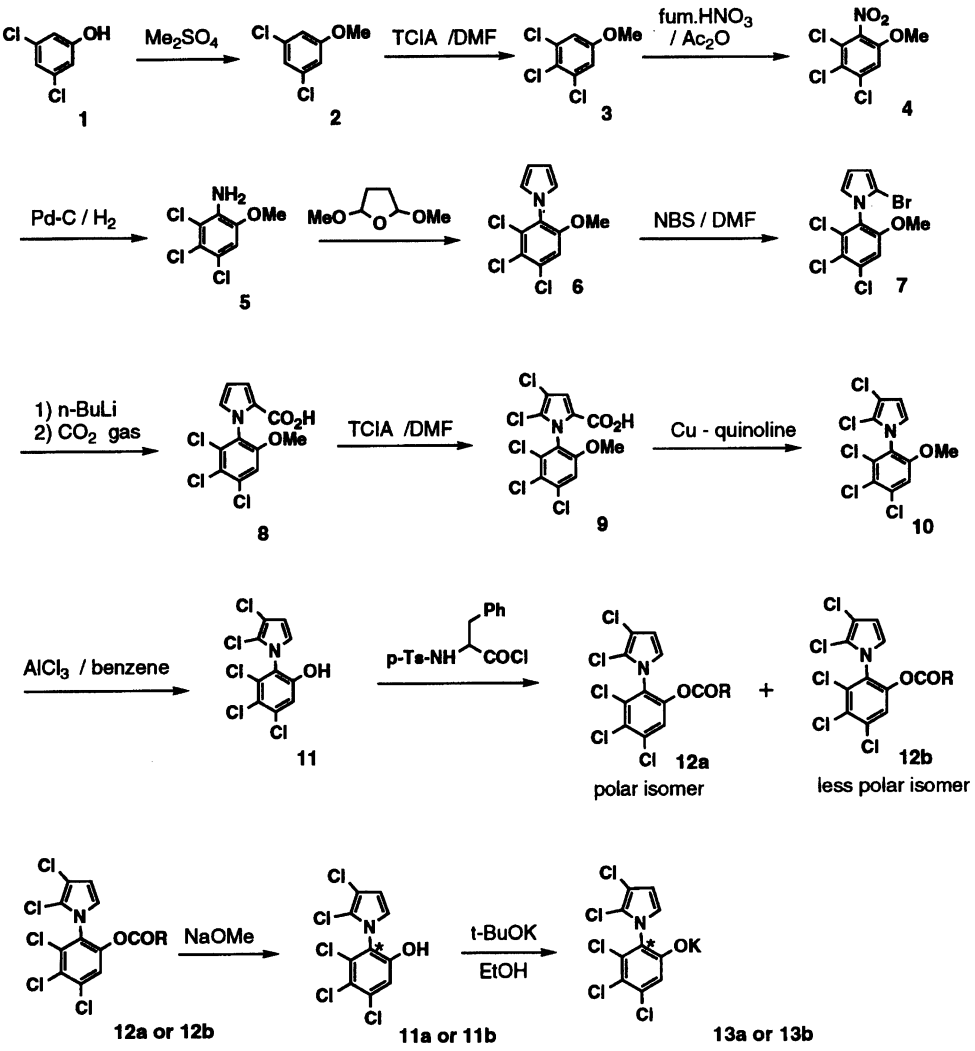
(+)-Neopyrrolomycin (**11a**), a novel optically active phenylpyrrole antibiotic, was isolated as a metabolite of *Streptomyces* sp. and unambiguously identified by single-crystal X-ray analysis by Takeuchi and co-workers in 1990.[1] (+)-Neopyrrolomycin (**11a**) and its analogs[2,3] showed significant activity as broad-spectrum antibiotics against Gram positive and negative bacteria and fungi. Structurally, **11a** has an atropisomerism due to the twisted state found in the direct linkage between benzene and pyrrole rings to be endowed with an optical activity, while usual phenylpyrrole antibiotics possess a methylene bridge between both rings.[4] This has renewed interest in the synthesis and biological evaluation of the other atrope isomer (**11b**) and analogs of natural neopyrrolomycin (**11a**) as well as their isomerization.[2,3]

Herein we provide full details of the first total synthesis of (+)- and (−)-neopyrrolomycins (**11a** and **11b**) based on the regioselective chlorinations of the benzene and pyrrole rings with isocyanuric trichloride (ICTC).

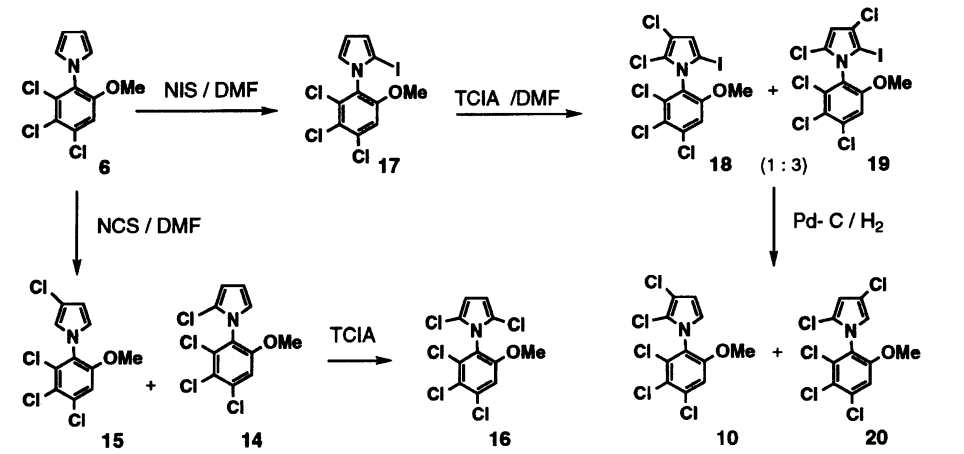
Results and Discussion

The starting 3,5-dichlorophenol (**1**) was methylated with dimethyl sulfate to give quantitatively 3,5-dichloroanisole (**2**) (Scheme 1). The regioselective chlorination was assayed by several conditions using ICTC, *N*-chlorosuccinimide (NCS), and sulfuryl chloride. The best result was obtained by chlorination with ICTC to give 3,4,5-trichloroanisole (**3**) in 87% yield, while NCS afforded **3** in 61%. Nitration of **3** with fum. HNO_3 in acetic anhydride afforded 3,4,5-trichloro-2-nitroanisole (**4**) in 87% yield, which was subjected to the catalytic reduction on Pd–C to 2,3,4-trichloro-6-methoxyaniline (**5**) in 76% yield, whereas usual reduction procedure of the nitro compound with zinc in acetic acid gave **5** only in 57% yield. Reaction of **5** with 2,5-dimethoxytetrahydrofuran gave 1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (**6**) in 91% yield.[5] Direct chlorination of **6** with NCS provided a mixture of monochloropyrrole derivatives **14** and **15** as described later. Although **6** was regiospecifically brominated with *N*-bromosuccinimide[6] to give exclusively 2-bromo-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (**7**) in 92% yield, this compound **7** was also not regioselectively chlorinated with the aforesaid reagents. Even the iodo derivative, 1-(2,3,4-trichloro-6-methoxyphenyl)-2-iodo-1*H*-pyrrole (**17**), having a bulky iodine atom at the C-2 position of the pyrrole ring afforded a 1 : 3 mixture of 2,3-dichloro- and 2,4-dichloropyrrole derivatives (**18** and **19**) by chlorination with ICTC. The presence of the iodine atom effected little steric hindrance for the chlorination. Then, the bromo compound **7** was converted into 1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid (**8**) in 81% yield by lithiation with *n*-BuLi followed by bubbling CO_2 gas. The regiospecific chlorination of **8** was realized by ICTC in DMF to give exclusively the desired 4,5-dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid (**9**) in almost quantitative yield, while NCS gave **9** in 83% yield. Decarboxylation of **9** on heating with Cu powder in quinoline at 210 °C produced 2,3-dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (**10**) in 66% yield, which was submitted to de-O-methylation with $AlCl_3$ to give racemic neopyrrolomycin, 2-(2,3-dichloro-1*H*-pyrrol-1-yl)-3,4,5-trichlorophenol (**11**) in 91% yield. Remarkably, both atropisomers (**11a** and **11b**) were effectively resolved by acylation with *N*-(*p*-tolylsulfonyl)-L-phenylalanyl chloride[7] to yield, after silica-gel column chromatography, the polar isomer **12a** (R_f=0.10 with 1 : 9 EtOAc–hexane) and the less polar isomer **12b** (R_f=0.18) in 40 and 38% yield, respectively. Methanolysis of **12a** and **12b** with sodium methoxide followed by acidification gave the target molecules, (+)- and (−)-neopyrrolomycins (**11a** and **11b**) in 86% and 87% yields, respectively. The (+)-atropisomer **11a** was identical with the authentic sample of natural neopyrrolomycin in all respects,[8] completing the first total synthesis. Further, both (+)- and (−)-neopyrrolomycins were led to the corresponding potassium salts, (−)-**13a** and (+)-**13b**, respectively, with the striking reverse change of their optical rotations. Naturally, (−)-**13a** was identical with the potassium salt of natural neopyrrolomycin in all respects including the antibacterial and antifungal activities.[8] These findings also suggested that the energy barrier for isomerization of the atrope isomers was too high to make them isomerize.

Several racemic analogs of neopyrrolomycin (**11**) were prepared from the aforesaid intermediates (Scheme 2). Monochloropyrrole derivatives, 2-chloro- and 3-chloro-1-



Scheme 1.



Scheme 2.

(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrroles (**14** and **15**) were obtained from **6** with NCS in 55 and 9% yield, respectively, and **14** was further chlorinated with ICTC to 2,5-dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (**16**) in 53% yield. A mixture of other dichloropyrrole derivatives, 2,3-dichloro- and 2,4-dichloro-5-iodo-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrroles (**18** and **19**), which were prepared from **17** by chlorination with ICTC, was converted into the aforesaid dichlorocompound **10** and 2,4-dichloro-1-(2,3,4-trichloro-6-

Fig. 1.

methoxyphenyl)-1*H*-pyrrole (**20**) by catalytic reduction on Pd–C. These derivatives **6**, **7**, **14**, **15**, and **20** were de-O-methylated with $AlCl_3$ to give the corresponding phenols, 2-(1*H*-pyrrol-1-yl)-3,4,5-trichlorophenol (**21**), and 2-(2-bromo-1*H*-pyrrol-1-yl)-, 2-(2-chloro-1*H*-pyrrol-1-yl)-, 2-(3-chloro-1*H*-pyrrol-1-yl)-, and 2-(2,4-dichloro-1*H*-pyrrol-1-yl)-3,4,5-trichlorophenols (**22**, **23**, **24**, and **25**) (Fig. 1). To our surprise, de-O-methylation of 2, 5-dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (**16**) with $AlCl_3$ gave exclusively the aforesaid 2, 4-dichloropyrrole analog **25** in 92% yield through the unexpected migration of the chlorine atom.

The antibacterial and antifungal activities of the synthesized analogs (**6**—**10**, **14**—**16**, and **20**—**25**) as well as potassium salts (**13** and **13a** and **b**) of neopyrrolomycin are shown in Table 1.

Both enantiomers of neopyrrolomycin (K salts: **13a** and **13b**) and the racemate showed almost the same activities, although the activity of the potassium salt of the natural antibiotic (−)-**13a** against Gram negative bacteria was slightly weaker than that of the unnatural (+)-**13**. The O-methyl derivatives (**6**—**10**, **14**—**16**, and **20**) showed no significant activities. Remarkably, the dechlorinated pyrrole analog **21** showed fairly good activities against most of bacteria and fungi, suggesting that chlorine atoms on the pyrrole ring are not required for the appearance of the biological activities.

Experimental

The melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-370 photoelectric polarimeter. Mass spectra were recorded on a JEOL JMX-DX303 mass spectrometer, IR spectra were on a JASCO FT/IR-5M spectrometer with KBr unless otherwise noted, and ^{1}H NMR spectra were on a JEOL GSX270 spectrometer or a Varian EM390 spectrometer in $CDCl_3$ using TMS as internal standard unless otherwise noted. Silica-gel TLC and column chromatography were performed on a Merck TLC 60F-254 and a Merck Kieselgel 60 or a Fuji-Davison BW-820MH, respectively. Air- and/or moisture sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, the organic solvents were purified and dried by appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

3,5-Dichloroanisole (2). To a stirred and ice-cooled suspension of 3,5-dichlorophenol (**1**: 5.0 g, 30 mmol) and K_2CO_3 (4.2 g, 30 mmol) in acetone (30 ml) was added dropwise dimethyl sulfate (2.8 ml, 30 mmol), and the reaction mixture was stirred at room temperature for 3 h. After addition of 1 M NaOH (100 ml) (1 M=1 mol dm^{-3}), the mixture was stirred for 1 h, and extracted with ether. The extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to give **2** (5.30 g, 100%), which was used for the next reaction. Recrystallization from hexane afforded colorless crystals: R_f=0.40 (hexane); mp 36—38 °C; IR 1596, 1570, 1455, 1415, 1259, 1106, 1045, 832, and 798 cm^{-1}; ^{1}H NMR δ=3.79 (3H, s, Me), 6.78 (2H, d, J=2 Hz, H-2 and 6), and 6.94 (1H, t, J=2 Hz, H-4).

3,4,5-Trichloroanisole (3). To a stirred and ice-cooled solution of **2** (200 mg, 1.1 mmol) in DMF (1.0 ml) was added ICTC (88 mg, 0.38 mmol), and the reaction mixture was stirred at room temperature for 1 h. After dilution with ether, the mixture was washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (10 g) with hexane to afford **3** (208 mg, 87%) as colorless needles: R_f=0.35 (hexane); mp 62—63 °C; IR 1590, 1557, 1452, 1424, 1291, 1145, 1058, 854, 836, 807, and 651 cm^{-1}; ^{1}H NMR δ=3.79 (3H, s, Me) and 6.94 (2H, s, H-2 and 6).

2-Nitro-3,4,5-trichloroanisole (4). Fum. HNO_3 (5.2 ml) and a few drops of concentrated H_2SO_4 were added to acetic anhydride below 0 °C under cooling with ice and NaCl. To the solution was added portionwise **3** (9.0 g, 35.1 mmol), and the reaction mixture was stirred at 0 °C for 30 min. After stirring with 10% NaOH (200 ml) below 10 °C for 1 h, the mixture was extracted with EtOAc, and the extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to give **4** (9.50 g, 87%). Recrystallization from hexane gave **4** as colorless crystals: R_f=0.45 (1 : 2 benzene–hexane); mp 133—135 °C; MS (M^+) 255, 257, 259, and 261 (1 : 0.96 : 0.31 : 0.03); IR 1592, 1546, 1431, 1381, 1366, 1293, 1050, and 691 cm^{-1}; ^{1}H NMR δ=3.94 (3H, s, Me) and 7.13 (1H, s, H-6). Found: C, 33.03; H, 1.44; N, 5.28%. Calcd for $C_7H_4NO_3Cl_3$: C, 32.78; H, 1.57; N, 5.46%.

2,3,4-Trichloro-6-methoxyaniline (5). A solution of **4** (2.0 g, 7.8 mmol) in a mixture of DMF (10 ml) and EtOH (20 ml) was stirred with Pd–C (200 mg) under atmospheric pressure of hydrogen at room temperature for 4 h. After filtration, the filtrates were evaporated to a residue, which was partitioned between ether and water. The ethereal extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (100 g) with 1 : 2 benzene–hexane to give **5** as pale-yellow needles (1.33 g, 76%). Recrystallization from hexane gave an analytical sample: R_f=0.38 (1 : 2 benzene–hexane); mp 83—85 °C; MS (M^+) 225, 227, 229, and 231 (1 : 0.96 : 0.32 : 0.02); IR 3439, 3320, 1625, 1578, 1485, 1435, 1388, 1227, 1049, and 840 cm^{-1}; ^{1}H NMR δ=3.86 (3H, s, Me), 4.30 (2H, br, s, NH_2), and 6.81 (1H, s, H-5). Found: C, 37.20; H, 2.58; N, 5.88%. Calcd for $C_7H_6NOCl_3$: C, 37.12; H, 2.67; N, 6.18%.

1-(2,3,4-Trichloro-6-methoxyphenyl)-1*H*-pyrrole

Table 1. Antibacterial and Antifungal Activities of Neopyrrolomycin Analogs[a)]

Test organism	MIC/ μg ml^{-1}																			
	13a	**13b**	**13**	**6**	**7**	**8**	**9**	**10**	**14**	**15**	**16**	**20**	**21**	**22**	**23**	**24**	**25**
Streptococcus epidermidis IFO 13889	0.39	0.39	0.39	>100	>100	>100	25	>100	>100	>50	>50	>50	3.13	3.13	1.56	0.39	0.39
Enterococcus faecalis IFO 12964	0.78	0.39	0.78	>100	>100	>100	>100	>100	>100	>50	>50	>50	12.5	6.25	3.13	0.78	0.78
Enterococcus faecium IFO 12367	0.20	0.20	0.39	>100	>100	>100	>100	>100	>100	>50	>50	>50	3.13	1.56	1.56	0.39	0.20
Staphylococcus aureus IFO 12732	0.20	0.20	0.39	>100	>100	>100	>100	>100	>100	>50	50	>50	0.78	1.56	1.56	0.39	0.20
Methicillin-resistant *S. aureus* 4[b)]	0.20	0.20	0.20	>100	>100	>100	>100	100	>100	>50	>50	>50	0.78	1.56	1.56	0.20	0.10
Methicillin-resistant *S. aureus* 69[b)]	0.20	0.20	0.39	>100	>100	>100	100	25	>100	>50	50	>50	1.56	1.56	1.56	0.39	0.20
Citrobacter freundii IFO 12681	50	50	50	>100	>100	>100	>100	>100	>100	>50	>50	>50	>100	>100	>50	>25	50
Enterobacter cloacae IFO 12935	25	6.25	12.5	>100	>100	>100	>100	>100	>100	>50	>50	>50	1.56	12.5	6.25	6.25	25
Escherichia coli NIHJ JC-2	50	6.25	12.5	>100	>100	>100	>100	>100	>100	>50	>50	>50	1.56	12.5	12.5	6.25	25
Klebsiella pneumoniae IFO 3317	12.5	1.56	3.13	>100	>100	>100	>100	>100	>100	>50	>50	>50	0.20	3.13	1.56	1.56	12.5
Proteus vulgaris GN 5298	25	1.56	3.13	>100	>100	>100	>100	>100	>100	>50	>50	>50	1.56	6.25	3.13	1.56	12.5
Pseudomonas aeruginosa IFO 3445	50	50	50	>100	>100	>100	>100	>100	>100	>50	>50	>50	>100	>100	>50	>25	50
Serratia marcescens 3759	50	50	50	>100	>100	>100	>100	>100	>100	>50	>50	>50	100	>100	>50	25	50
Candida albicans IFO 1269	3.13	3.13	3.13	>100	>100	>100	>100	>100	>100	>50	>50	>50	12.5	12.5	12.5	3.13	6.25
Candida albicans IFM 40009	6.25	6.25	6.25	>100	>100	>100	>100	>100	>100	>50	>50	>50	12.5	12.5	12.5	3.13	6.25
Cryptococcus neoformans TIMM 0354	0.39	0.39	0.39	>100	>100	>100	>100	>100	>100	50	>50	25	1.56	0.78	0.78	≤0.20	≤0.20
Cryptococcus neoformans TIMM 0362	≤0.20	≤0.20	≤0.20	>100	50	>100	>100	6.25	6.25	3.13	>50	6.25	1.56	0.78	0.78	0.39	≤0.20
Aspergillus fumigatus TIMM 0063[c)]	6.25	6.25	6.25	>100	>100	>100	>100	>100	>100	>50	>50	>50	6.25	6.25	6.25	3.13	6.25
Aspergillus fumigatus IMF 4942[c)]	6.25	6.25	6.25	>100	>100	>100	>100	>100	>100	>50	>50	>50	6.25	12.5	12.5	6.25	6.25

a) MIC values were determined by an agar dilution method using mueller Hinton agar for antibacterial tests with incubation at 37 °C for 18 h and a Sabouraud Dextrose agar for antifungal tests with incubation at 30 °C for 24 h. b) Clinical isolate. c) Incubation: 48 h.

(6). A solution of **5** (1.65 g, 7.28 mmol) and 2,5-dimethoxytetrahydrofuran (0.94 ml, 7.28 mmol) in acetic acid (15 ml) was stirred at 70—80 °C for 1 h, and then evaporated to a residue, which was chromatographed on silica gel (25 g) with 1:9 EtOAc–hexane, followed by recrystallization from hexane to give **6** (1.83 g, 91%): R_f=0.16 (1:9 benzene–hexane); mp 115—117 °C; MS (M^+) 275, 277, 279, and 281 (1:0.96:0.32:0.03); IR 1494, 1454, 1312, 1072, 1049, 948, 725, and 709 cm^{-1}; ^{1}H NMR δ=3.76 (3H, s, Me), 6.35 (2H, t, J=2.5 Hz, H-3 and 4 of pyrrole), 6.66 (2H, t, J=2.5 Hz, H-2 and 5 of pyrrole), and 7.09 (1H, s, H-5 of Ph). Found: C, 47.87; H, 2.79; N, 4.66%. Calcd for $C_{11}H_8NOCl_3$: C, 47.78; H, 2.91; N, 5.06%.

2-Bromo-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (7). To a stirred solution of **6** (2.77 g, 10 mmol) in DMF (15 ml) cooled with ice and NaCl was added dropwise a solution of NBS (1.87 g, 10.5 mmol) in DMF (5 ml). After stirring for 1 h, the reaction mixture was poured into ice-water, and extracted with EtOAc. The extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (100 g) with 1:9 benzene–hexane to give colorless crystals of **7** (3.26 g, 92%). Recrystallization from hexane gave an analytical sample: R_f=0.24 (1:9 benzene–hexane); mp 69—70 °C; MS (M^+) 353, 355, 357, 359, and 361 (1:1.90:1.25:0.32:0.01); IR 1581, 1558, 1481, 1454, 1370, 1048, and 704 cm^{-1}; ^{1}H NMR δ=3.76 (3H, s, Me), 6.35 (2H, m, H-3 and 4 of pyrrole), 6.66 (1H, m, H-5 of pyrrole), and 7.10 (1H, s, H-5 of Ph). Found: C, 37.45; H, 1.98; N, 3.62%. Calcd for $C_{11}H_7NOCl_3Br$: C, 37.17; H, 1.98; N, 3.94%.

1-(2,3,4-Trichloro-6-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid (8). To a stirred solution of **7** (3.0 g, 8.44 mmol) in dry THF (30 ml) was added at −78 °C 1.61 M *n*-BuLi in hexane (5.3 ml, 8.44 mmol) during 5 min. After stirring for 10 min, CO_2 gas was bubbled for 15 min, and then the reaction temperature was gradually raised to room temperature. The reaction mixture was diluted with ether, and extracted with 1 M aqueous NaOH. The aqueous extracts were acidified to pH 5 with concentrated HCl, and again extracted with EtOAc. The organic extracts were washed with saturated aqueous NaCl, dried, and evaporated to a residue, which was washed with ether to give colorless crystals of **8** (2.18 g, 81%). Recrystallization from methanol gave an analytical sample: R_f=0.41 (9:1 $CHCl_3$–MeOH); mp 244—246 °C; MS (M^+) 319, 321, and 323 (1:0.94:0.28); IR 1660, 1481, 1433, 1376, 1291, 1268, 1139, 1044, 745, and 713 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=3.76 (3H, s, Me), 6.31 and 6.91 (1H and 2H, respectively, m, pyrrole protons), and 7.53 (1H, s, H-5 of Ph). Found: C, 45.20; H, 2.41; N, 4.03%. Calcd for $C_{12}H_8NO_3Cl_3$: C, 44.96; H, 2.51; N, 4.37%.

4,5-Dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid (9). To a stirred and ice-cooled solution of **8** (2.00 g, 6.24 mmol) in DMF (20 ml) was added portionwise ICTC (0.97 g, 4.16 mmol) during 30 min, and the reaction mixture was stirred at room temperature for 1 h. After further addition of ICTC (30 mg, 0.13 mmol), the mixture was stirred for 1 h, and then poured into ice-water. The resulting mixture was extracted with EtOAc, and the extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was washed with hexane to give **9** as colorless crystals (2.30 g, 95%). Recrystallization from ethanol gave an analytical sample:

R_f=0.27 (9:1 $CHCl_3$–MeOH); mp 231—233 °C; MS (M^+) 387, 389, 391, 393, and 395 (1:2.05:1.08:0.32:0.05); IR 1680, 1477, 1447, 1374, 1288, 1269, 1174, 1049, and 838 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.79 (3H, s, Me), 7.13 (1H, s, H-3 of pyrrole), and 7.64 (1H, s, H-5 of Ph). Found: C, 37.02; H, 1.42; N, 3.26%. Calcd for $C_{12}H_6NO_3Cl_5$: C, 37.01; H, 1.55; N, 3.60%.

2,3-Dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (10). A suspension of **9** (190 mg, 0.49 mmol) and Cu powder (60 mg) in quinoline (3.5 ml) was heated at 210 °C for 7 min. After cooling, ether was added. The resulting mixture was washed with 1 M aqueous HCl and saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (5 g) with 1:9 benzene–hexane to give colorless crystals of **10** (110 mg, 66%). Recrystallization from hexane gave an analytical sample: R_f=0.31 (1:9 benzene–hexane); mp 112—113 °C; MS (M^+) 343, 345, 347, 349, and 351 (1:1.61:1.02:0.32:0.05); IR 1490, 1458, 1436, 1395, 1372, 1304, 1052, 949, and 720 cm^{-1}; ^1H NMR δ=3.79 (3H, s, Me), 6.31 (1H, d, J=4 Hz, H-4 of pyrrole), 6.50 (1H, d, J=4 Hz, H-5 of pyrrole), and 7.09 (1H, s, H-5 of Ph). Found: C, 38.23; H, 1.64; N, 3.77%. Calcd for $C_{11}H_6NOCl_5$: C, 38.25; H, 1.75; N, 4.05%.

(±)-Neopyrrolomycin: 2-(2,3-Dichloro-1*H*-pyrrol-1-yl)-3,4,5-trichlorophenol (11). To a solution of **10** (410 mg, 1.19 mmol) in benzene (60 ml) was added $AlCl_3$ (800 mg, 6.0 mmol), and the mixture was stirred at room temperature for 14 h. After addition of ice-water, the resulting mixture was washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (25 g) with 1:9 EtOAc–hexane to give a syrup of **11** (358 mg, 91%) used for the next step. Recrystallization from hexane gave an analytical sample as prisms: R_f=0.36 (1:9 EtOAc–hexane); mp 89—91 °C; MS (M^+) 329, 331, 333, 335, and 337 (1:1.59:1.02:0.29:0.02); IR 3495, 3453, 3401, 1558, 1479, 1449, 1338, 1292, 1217, and 712 cm^{-1}; ^1H NMR δ=5.38 (1H, br s, OH), 6.37 (1H, d, J=4 Hz, H-4 of pyrrole), 6.56 (1H, d, J=4 Hz, H-5 of pyrrole), and 7.18 (1H, s, H-6 of Ph). Found: C, 36.18; H, 1.39; N, 3.97%. Calcd for $C_{10}H_4NOCl_5$: C, 36.24; H, 1.22; N, 4.23%.

(+)-Neopyrrolomycin (11a). An ice-cold solution of **12a** (145 mg, 0.23 mmol) and sodium methoxide (66 mg, 0.35 mmol) in methanol (3 ml) was stirred for 30 min. After addition of 0.1 M HCl (10 ml), the resulting mixture was extracted with EtOAc. The extracts were washed with saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (5 g) with 1:9 EtOAc–hexane to afford **11a** as a pale-yellow syrup (65 mg, 86%): R_f=0.36 (1:9 EtOAc–hexane); $[\alpha]_D^{22}$+31.0° (*c* 0.60, $CHCl_3$); $[\alpha]_D^{22}$+41° (*c* 0.07, $CHCl_3$); $[\alpha]_D^{22}$+6.4° (*c* 0.07, MeOH); MS (M^+) 329, 331, 333, 335, and 337 (1:1.59:1.03:0.29:0.02); IR (neat) 3518, 1481, 1450, 1384, 1339, 1206, 1155, 974, 832, and 709 cm^{-1}; ^1H NMR δ=5.38 (1H, br s, OH), 6.37 (1H, d, J=4 Hz, H-4 of pyrrole), 6.56 (1H, d, J=4 Hz, H-5 of pyrrole), and 7.18 (1H, s, H-6 of Ph). The authentic sample of the natural product[8] showed the identical data including the optical rotations: $[\alpha]_D^{22}$+40° (*c* 0.06, $CHCl_3$); $[\alpha]_D^{22}$+6.7° (*c* 0.06, MeOH).

(−)-Neopyrrolomycin (11b). A sample of **12b** (150 mg, 0.24 mmol) was treated with methanolic sodium methoxide and purified by the same manner as described above for the preparation of **11a** to give a pale-yellow syrup of **11b** (68 mg, 87%): R_f=0.36 (1:9 EtOAc–hexane); $[\alpha]_D^{22}$−30.8° (*c* 0.60, $CHCl_3$); $[\alpha]_D^{22}$−41° (*c* 0.07, $CHCl_3$); MS (M^+) 329, 331, 333, 335, and 337 (1:1.59:1.04:0.28:0.02); IR (neat) 3518, 1481, 1450, 1384, 1339, 1206, 1155, 974, 832, and 709 cm^{-1}; ^1H NMR δ=5.38 (1H, br s, OH), 6.37 (1H, d, J=4 Hz, H-4 of pyrrole), 6.56 (1H, d, J=4 Hz, H-5 of pyrrole), and 7.18 (1H, s, H-6 of Ph).

***O*-[*N*-(*p*-Tolylsulfonyl)-L-phenylalanyl]neopyrrolomycins (12a and 12b).** To a stirred and ice-cooled solution of **11** (250 mg, 0.75 mmol) and pyridine (0.081 ml, 1.0 mmol) in CH_2Cl_2 (5 ml) was added dropwise a solution of *N*-(*p*-tolylsulfonyl)-L-phenylalanyl chloride (338 mg, 1.0 mmol) in CH_2Cl_2, and the reaction mixture was stirred at 5 °C for 30 min and at room temperature for 30 min. After dilution with CH_2Cl_2, the mixture was washed with water, dried, and evaporated to a residue, which was chromatographed on silica gel (50 g) with 1:9→3:17 EtOAc–hexane to give polar isomer **12a** (191 mg, 40%) and less polar isomer **12b** (181 mg, 38%) as pale-yellow foams.

12a: R_f=0.10 (1:9 EtOAc–hexane); $[\alpha]_D^{22}$−14.2° (*c* 1.00, MeOH); MS (M^+−1) 629, 631, 633, and 635 (1:1.77:1.19:0.38); IR 1780, 1483, 1450, 1328, 1161, 1132, 1090, 702, and 665 cm^{-1}; ^1H NMR δ=2.36 (3H, s, Me), 2.59 (2H, m, CH_2), 4.10 (1H, m, CH), 4.83 (1H, d, J=9 Hz, NH), 6.29 (1H, d, J=4 Hz, H-4 of pyrrole), 6.48 (1H, d, J=4 Hz, H-5 of pyrrole), 6.94 (2H, m, Phe), 7.10 (1H, s, H-6 of Ph), 7.23 (5H, m, Phe and Ts), and 7.54 (2H, d, J=9 Hz, Ts).

12b: R_f=0.18 (1:9 EtOAc–hexane); $[\alpha]_D^{22}$−32.7° (*c* 1.00, MeOH); MS (M^+−1) 629, 631, 633, and 635 (1:1.73:1.18:0.36); IR 1780, 1484, 1450, 1340, 1161, 1132, 1089, 702, 664, and 552 cm^{-1}; ^1H NMR δ=2.43 (3H, s, Me), 2.73 (2H, m, CH_2), 4.13 (1H, m, CH), 4.83 (1H, d, J=10 Hz, NH), 6.25 (1H, d, J=4 Hz, H-4 of pyrrole), 6.44 (1H, d, J=4 Hz, H-5 of pyrrole), 6.96 (2H, m, Phe), 7.03 (1H, s, H-6 of Ph), 7.25 (5H, m, Phe and Ts), and 7.57 (2H, d, J=8 Hz, Ts).

(−)-Potassium Salt of Neopyrrolomycin (13a). To a stirred and ice-cooled solution of **11a** (55 mg, 0.166 mmol) in ethanol (0.6 ml) was added 0.5 M ethanolic *t*-BuOK (0.33 ml, 0.165 mmol). After 5 min, the reaction mixture was evaporated to a residue, which was crystallized from $CHCl_3$–hexane. The formed crystals were filtered off, and washed with hexane to give **13a** as a very hydroscopic dihydrate (56 mg, 84%): $[\alpha]_D^{22}$−45.4° (*c* 0.50, $CHCl_3$); $[\alpha]_D^{22}$−31.5° (*c* 0.12, MeOH); IR 3600—3000, 1639, 1567, 1517, 1482, 1445, 1402, 978, and 721 cm^{-1}; ^1H NMR δ=6.31 (1H, d, J=4 Hz, H-4 of pyrrole), 6.53 (1H, d, J=4 Hz, H-5 of pyrrole), and 6.61 (1H, s, H-6 of Ph). Found: C, 29.76; H, 1.99; N, 3.11%. Calcd for $C_{10}H_3NOCl_5K\cdot 2H_2O$: C, 29.62; H, 1.74; N, 3.45%.

The authentic sample of the natural product[8] showed the identical data including the optical rotation: $[\alpha]_D^{22}$−30° (*c* 0.08, MeOH).

(+)-Potassium Salt of Neopyrrolomycin (13b). A sample of **11b** (60 mg, 0.181 mmol) was treated by the same manner, as described above for the preparation of **13a**, to give **13b** as a very hygroscopic dihydrate (61 mg, 83%): $[\alpha]_D^{22}$+44.3° (*c* 0.49, $CHCl_3$); $[\alpha]_D^{22}$+31.3° (*c* 0.12, MeOH); IR 3600—3000, 1637, 1565, 1511, 1482, 1446, 1403, 978, and 732 cm^{-1}; ^1H NMR δ=6.31 (1H, d, J=4 Hz, H-4 of pyrrole), 6.53 (1H, d, J=4 Hz, H-5 of pyrrole), and 6.61 (1H, s, H-6 of Ph). Found: C, 29.92; H, 2.03; N, 3.14%. Calcd for

$C_{10}H_3NOCl_5K \cdot 2H_2O$: C, 29.62; H, 1.74; N, 3.45%.

(±)-Potassium Salt of Neopyrrolomycin (13). A sample (30 mg, 0.09 mmol) of racemic neopyrrolomycin (**11**) was treated by the same manner as described above for the preparation of **13a** to give the racemic salt of **13** as a dihydrate (31 mg, 84%): Mp 74—77 °C; IR 3590, 1638, 1525, 1484, 1448, 1315, 975, 935, 736, and 717 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.33 (1H, d, J=4 Hz, H-4 of pyrrole), 6.81 (1H, d, J=4 Hz, H-5 of pyrrole), and 6.84 (1H, s, H-6 of Ph). Found: C, 29.88; H, 1.80; N, 3.07%. Calcd for $C_{10}H_3NOCl_5K \cdot 2H_2O$: C, 29.62; H, 1.74; N, 3.45%.

2-Chloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (14) and 3-Chloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (15). To a stirred and ice-cooled solution of **6** (700 mg, 2.53 mmol) in DMF (15 ml) was added NCS (355 mg, 2.66 mmol). The reaction mixture was stirred at room temperature for 14 h, poured into ice-water, and then extracted EtOAc. The extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (40 g) with 1 : 9 benzene–hexane to give crystals of **14** (428 mg, 55%) and **15** (65 mg, 9%), after recrystallization from hexane.

14: R_f=0.26 (1 : 9 benzene–hexane); mp 70—72 °C; MS (M^+) 309, 311, 313, and 315 (1 : 1.27 : 0.62 : 0.13); IR 1485, 1459, 1370, 1311, 1052, and 704 cm^{-1}; ^1H NMR δ=3.84 (3H, s, Me), 6.30 (2H, m, H-3 and 4 of pyrrole), 6.58 (1H, m, H-5 of pyrrole), and 7.13 (1H, s, H-5 of Ph).

15: R_f=0.24 (1 : 9 benzene–hexane); mp 96—98 °C; MS (M^+) 309, 311, 313, and 315 (1 : 1.27 : 0.61 : 0.11); IR 1497, 1462, 1437, 1388, 1321, 1048, 766, and 715 cm^{-1}; ^1H NMR δ=3.80 (3H, s, Me), 6.28 (1H, m, H-4 of pyrrole), 6.60 (2H, m, H-2 and 5 of pyrrole), and 7.08 (1H, s, H-5 of Ph).

2,5-Dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (16). To a stirred and ice-cooled solution of **14** (200 mg, 0.64 mmol) in DMF (2 ml) was added ICTC (50 mg, 0.22 mmol). The reaction mixture was stirred at the same temperature for 2 h, poured into ice-water, and then extracted with EtOAc. The extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was purified by column chromatography on silica gel (15 g) with 1 : 19 benzene–hexane and recrystallization from hexane to give crystals of **16** (116 mg, 53%): R_f=0.41 (1 : 9 benzene–hexane); mp 67—69 °C; MS (M^+) 343, 345, 347, 349, and 351 (1 : 1.64 : 1.03 : 0.31 : 0.03); IR 1477, 1447, 1393, 1365, 1307, 1276, 1050, 766, and 720 cm^{-1}; ^1H NMR δ=3.82 (3H, s, Me), 6.20 (2H, s, H-3 and 4 of pyrrole), and 7.13 (1H, s, H-5 of Ph).

1-(2,3,4-Trichloro-6-methoxyphenyl)-2-iodo-1*H*-pyrrole (17). To a stirred and ice-cooled solution of **6** (500 mg, 1.81 mmol) in DMF (2 ml) was added NIS (407 mg, 1.81 mmol). The reaction mixture was stirred under ice-cooling for 1 h and at room temperature overnight, poured into ice-water, and extracted with EtOAc. The extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was purified by column chromatography on silica gel (10 g) with 1 : 9 benzene–hexane and recrystallization from hexane to give crystals of **17** (555 mg, 76%): R_f=0.22 (1 : 9 benzene–hexane); mp 93—96 °C; IR 1580, 1556, 1484, 1439, 1383, 1368, 1315, 1274, 1050, 825, and 714 cm^{-1}; ^1H NMR δ=3.80 (3H, s, Me), 6.33, 6.54 and 6.77 (each 1H, m, H-3, 4 and 5 of pyrrole), and 7.08 (1H, s, H-5 of Ph).

2,3-Dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (10) and 2,4-Dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-1*H*-pyrrole (20) through a Mixture of 2,3-Dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-5-iodo-1*H*-pyrrole (18) and 3,4-Dichloro-1-(2,3,4-trichloro-6-methoxyphenyl)-5-iodo-1*H*-pyrrole (19). To a stirred and ice-cooled solution of **17** (71 mg, 0.176 mmol) in DMF (0.5 ml) was added ICTC (27.3 mg, 0.117 mmol), and the reaction mixture was stirred under ice-cooling for 1 h and at room temperature for 1 h. After further addition of ICTC (3 mg, 0.013 mmol), the mixture was stirred for 30 min, poured into ice-water, and extracted with EtOAc. The extracts were washed with water and saturated aqueous NaCl, dried, and evaporated to a residue, which was chromatographed on silica gel (10 g) with 1 : 19 benzene–hexane to give a 1 : 3 oily mixture (40 mg) of **18** and **19**: R_f=0.45 (1 : 9 benzene–hexane); ^1H NMR δ=3.84 (3H, s, Me), 6.33 (3/4H, s, H-3 of pyrrole), 6.54 (1/4, s, H-4 of pyrrole), and 7.10 (1H, s, H-5 of Ph).

A mixture of **18** and **19** (40 mg) in ethanol (1 ml) was stirred for 5 h with K_2CO_3 (20 mg) and 10% Pd–C (4 mg) under atmospheric pressure of hydrogen. After filtration, the filtrates were evaporated to a residue, which was chromatographed on silica gel (8 g) with 1 : 2 benzene–hexane to give crystals of **10** (3 mg, 10%) and **20** (13 mg, 58%). Compound **10** was identical with a sample obtained from **9**.

20: R_f=0.38 (1 : 9 benzene–hexane); mp 66—67 °C; MS (M^+) 343, 345, 347, and 349 (1 : 1.68 : 1.04 : 0.21); IR 1491, 1435, 1389, 1368, 1318, 1275, 1050, 830, 764, and 603 cm^{-1}; ^1H NMR δ=3.83 (3H, s, Me), 6.20 (1H, d, J=2 Hz, H-3 of pyrrole), 6.53 (1H, d, J=2 Hz, H-5 of pyrrole), and 7.10 (1H, s, H-5 of Ph).

2-(1*H*-Pyrrol-1-yl)-3,4,5-trichlorophenol (21). A sample of **6** (125 mg, 0.45 mmol) was treated by the same manner as described above for the preparation of **11** from **10**, followed by recrystallization from hexane to give **21** (107 mg, 91%): R_f=0.36 (1 : 9 EtOAc–hexane); mp 83—84 °C; MS (M^+) 261, 263, 265, and 267 (1 : 0.96 : 0.32 : 0.03); IR 3402, 1561, 1491, 1445, 1340, 1287, 1206, 1158, and 718 cm^{-1}; ^1H NMR δ=6.46 (2H, t, J=2 Hz, H-3 and 4 of pyrrole), 6.70 (2H, t, J=2 Hz, H-2 and 5 of pyrrole), and 7.17 (1H, s, H-6 of Ph).

2-(2-Bromo-1*H*-pyrrol-1-yl)-3,4,5-trichlorophenol (22). A sample of **7** (110 mg, 0.31 mmol) was treated by the same manner as described above for the preparation of **11** from **10**, followed by recrystallization from hexane to give **22** (93 mg, 88%): R_f=0.36 (1 : 9 EtOAc–hexane); mp 78 °C (decomp); MS (M^+) 339, 341, 343, and 345 (1 : 2.00 : 1.29 : 0.31); IR 3413, 1566, 1469, 1336, 1291, 1213, 1156, and 709 cm^{-1}; ^1H NMR δ=6.43 (2H, m, H-3 and 4 of pyrrole), 6.72 (1H, m, H-5 of pyrrole), and 7.19 (1H, s, H-6 of Ph).

2-(2-Chloro-1*H*-pyrrol-1-yl)-3,4,5-trichlorophenol (23). A sample of **14** (31 mg, 0.10 mmol) was treated by the same manner as described above for the preparation of **11** from **10**, followed by recrystallization from hexane to give **23** (20 mg, 68%): R_f=0.36 (1 : 9 EtOAc–hexane); mp 119—121 °C; MS (M^+) 295, 297, 299, and 301 (1 : 1.29 : 0.55 : 0.04); IR 3409, 1565, 1473, 1393, 1336, 1294, 1215, 1157, 834, and 710 cm^{-1}; ^1H NMR δ=5.20 (1H, s, OH), 6.40 (2H, m, H-3 and 4 of pyrrole), 6.62 (1H, m, H-5 of pyrrole), and 7.30 (1H, s, H-6 of Ph).

2-(3-Chloro-1*H*-pyrrol-1-yl)-3,4,5-trichlorophenol (24). A sample of **15** (45 mg, 0.14 mmol) was treated by the same manner as described above for the preparation of **11** from **10** to give **24** as a syrup (35 mg, 82%): R_f = 0.36 (1 : 9 EtOAc–hexane); MS (M^+) 295, 297, 299, and 301 (1 : 1.32 : 0.56: 0.03); IR 3510, 1563, 1493, 1449, 1341, 1200, 1153, 766, and 727 cm^{-1}; ^1H NMR δ=5.37 (1H, s, OH); 6.40 (1H, m, H-4 of pyrrole), 6.63 (2H, m, H-2 and 5 of pyrrole), 7.17 (1H, s, H-6 of Ph).

2-(2,4-Dichloro-1*H*-pyrrol-1-yl)-3,4,5-trichlorophenol (25). A) From 20: A sample of **20** (89 mg, 0.26 mmol) was treated by the same manner as described above for the preparation of **11** from **10** to give **25** as a syrup (76 mg, 89%): R_f=0.36 (1 : 9 EtOAc–hexane); MS (M^+) 329, 331, 333, and 335 (1 : 1.68 : 1.05: 0.27); IR 3140, 1585, 1562, 1480, 1384, 1335, 1266, 1206, 1154, 965, and 837 cm^{-1}; ^1H NMR δ=5.87 (1H, s, OH), 6.30 (1H, d, J=2 Hz, H-3 of pyrrole), 6.60 (1H, d, J=2 Hz, H-5 of pyrrole), and 7.20 (1H, s, H-6 of Ph).

B) From 16: A sample of **16** (97 mg, 0.28 mmol) was treated by the same manner as described above for the preparation of **11** from **10** to give **25** as a syrup (86 mg, 92%), which was identical with the authentic sample obtained from **20** in all respects.

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