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

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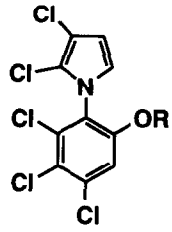
Abstract: (+)- and (-)-Neopyrrolomycins have been synthesized from 3,5-dichlorophenol through regioselective halogenations and optical resolution.

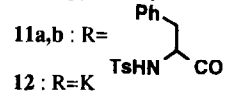
(+)-Neopyrrolomycin [(+)-**1**] is a novel antibiotic isolated from cultured broth of *Streptomyces* sp. with potent antibacterial and antifungal activities.[1] The unusual structure was established by X-ray crystallographic analysis to have an atrope isomerism due to the twisted state found in the linkage between benzene and pyrrole rings.[1] Herein we report the first synthesis of (+)- and (-)-neopyrrolomycins [(+)- and (-)-**1**] through the optical resolution of the atrope isomers.

Our synthetic plan takes advantage of the ready availability of 3,5-dichlorophenol and the regioselective chlorination of its O-methyl derivative **2** to 3,4,5-trichloroanisole (**3**).

O-Methylation of 3,5-dichlorophenol (Me_2SO_4/K_2CO_3/acetone, 3h) gave **2**[2](quant., mp38°C), which was chlorinated by trichloroisocyanuric acid (TCIA) in DMF (1h) to **3**[2](87%; mp63°C). Chlorination by NCS in AcOH gave **3** in 61% yield. Nitration of **3** (fum.$HNO_3/H_2SO_4/Ac_2O$, 0°C, 0.5h) to give the mono-nitro compound **4**[2](87%; mp135°C) was followed by reduction (H_2/Pd-C/DMF-EtOH, 4h) to afford the corresponding amino compound **5**[2](76%; mp85°C). Reduction by Zn and AcOH provided the lower yield (57%) of **5**. Reaction of **5** with 2,5-dimethoxytetrahydrofuran (AcOH, 70-80°C, 1h)[3] produced the pyrrole **6**[2](91%; mp117°C), which was regioselectively brominated (NBS/DMF, -5°C, 1h)[4] to give the 2-bromopyrrole **7**[2](92%; mp70°C). Lithiation of **7** (n-BuLi/THF, -78°C, 10min) followed by treatment with CO_2 gas (-78°C→rt., after blowing for 15min) generated the corresponding carboxylic acid **8**[2][81%; mp246°C (MeOH)], the carboxyl group of which effectively controlled the regioselectivity for the next chlorination. The carboxylic acid **8** was chlorinated by TCIA (DMF, 2h) to give exclusively the 4,5-dichloropyrrole **9**[2] [95%; mp233°C(EtOH)], while chlorination of **6** and **7** could not selectively give the desired dichloro compound. Upon heating in quinoline with Cu powder (210°C, 7min), **9** was converted into **10**[2] with decarboxylation (65%; mp113°C), which was submitted to de-O-methylation ($AlCl_3$/PhH, 14h)[5] to give a mixture of atrope isomers of neopyrrolomycin [**1**: 91%; mp91°C(pale yellow prisms)]. Remarkably, both isomers were resolved by acylation with N-(*p*-toluenesulfonyl)-L-phenylalanyl chloride [6](Py/CH_2Cl_2, 1h) to yield, after silica-gel column chromatography (EtOAc-hexane, 1:9→3:17), the polar isomer **11a**[2] [40%; foam, $[\alpha]_D$-15°(*c* 1.0, MeOH), TLC(EtOAc-hexane, 1:9): Rf 0.10; **11b**: Rf 0.18] and less polar isomer **11b**[2][38%; foam, $[\alpha]_D$-33°(*c* 1.0, MeOH)]. The polar isomer **11a** was saponified by 1N KOH (5°C, 1h) followed by acidification with 0.1N HCl to give (+)-neopyrrolomycin [(+)-**1**[2]: 82%; pale yellow oil, $[\alpha]_D$+41°(*c* 0.07, $CHCl_3$), $[\alpha]_D$+6.4°(*c* 0.07, MeOH)], which was identical with the natural antibiotic[7] in all respects. The other isomer **11b** was

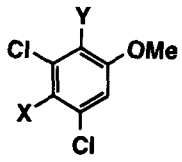


1 : R=H
(Neopyrrolomycin)

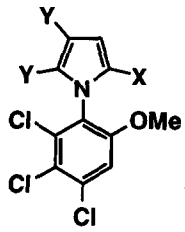


11a,b : R=

12 : R=K



2 : X=Y=H
3 : X=Cl,Y=H
4 : X=Cl,Y=NO_2
5 : X=Cl,Y=NH_2



6 : X=Y=H
7 : X=Br,Y=H
8 : X=COOH,Y=H
9 : X=COOH,Y=Cl
10 : X=H,Y=Cl

similarly hydrolyzed to (-)-neopyrrolomycin [(-)-**1**[2]: 85%; pale yellow oil, $[\alpha]_D$-41°(*c* 0.07, $CHCl_3$), $[\alpha]_D$-6.7°(*c* 0.07, MeOH)]. Finally, by treatment with t-BuOK (EtOH, 5°C, 5min), (+)- and (-)-neopyrrolomycins [(+)- and (-)-**1**] were led to the corresponding hygroscopic potassium salts, (-)- and (+)-**12**, respectively, with the striking reverse change of the signs of their optical rotations: (-)-**12**[2]: 92%; $[\alpha]_D$-46°(*c* 0.5, $CHCl_3$), $[\alpha]_D$-32°(*c* 0.12, MeOH); identical with the K salt of natural neopyrrolomycin[7] in all respects (^{1}H-NMR, IR, $[\alpha]_D$, TLC and biological activities). (+)-**12**[2]: 84%; $[\alpha]_D$+45°(*c* 0.49, CHCl3), $[\alpha]_D$+32°(*c* 0.12, MeOH). Both K salts (-)- and (+)-**12** were reasonably returned to the corresponding (+)- and (-)-**1** by neutralization with dil HCl.

The K salts, (-)- and (+)-**12** showed almost the same antibacterial and antifungal activities, and the details will be reported elsewhere with the biological evaluation of other synthesized analogs.

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REFERENCES AND NOTES

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2. All compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means. Compounds were recrystallized from hexane unless otherwise noted in the text. Optical lotations were measured using a 1dm tube at 22°C. Significant ^{1}H-NMR spectral data (90MHz, $CDCl_3$, δ: TMS=0, unless otherwise noted) are the following. (+)- and (-)-**1**, and (±)- **1** : δ 5.38(1H,br.s), 6.37(1H,d,J=4Hz), 6.56(1H,d,J=4Hz), 7.18(1H,s). **2** : δ 3.79(3H,s), 6.78(2H,d), 6.94(1H,t). **3** : δ 3.79(3H,s), 6.94(2H,s). **4** : δ 3.94(3H,s), 7.13(1H,s). **5** : δ 3.86(3H,s), 4.30(2H,br.s), 6.81(1H,s). **6** : δ 3.76(3H,s), 6.35(2H,t), 6.66(2H,t), 7.09(1H,s). **7** : δ 3.76(3H,s), 6.35(2H,m), 6.66(1H,m), 7.10(1H,s) **8** (DMSO-*d*6) : δ 3.76(3H,s), 6.31(1H,m), 6.91(2H,m), 7.53(1H,s). **9** (DMSO-*d*6): δ 3.79(3H,s), 7.13 (1H,s), 7.64(1H,s). **10** : δ 3.79(3H,s), 6.31(1H,d), 6.50(1H,d), 7.09(1H,s). **11a** : δ 2.36(3H,s), 2.59 (2H,m), 4.10(1H,m), 4.83 (1H,d), 6.29(1H,d), 6.48(1H,d), 6.94(2H,m), 7.10(1H,s), 7.23(5H,m), 7.54(2H,d). **11b** : δ 2.43(3H,s), 2.73(2H,m), 4.13(1H,m), 4.83(1H,d), 6.25(1H,d), 6.44(1H,d), 6.96 (2H,m), 7.03(1H,s), 7.25(5H,m), 7.57(2H,d). (-)- and (+)-**12** : δ 6.31(1H,d,J=4Hz), 6.53(1H,d,J=4Hz) 6.61(1H,s).
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6. Hashimoto, S.; Kase, S.; Suzuki, A.; Yanagiya, Y.; Ikegami, S. *Synth. Commun.*, **21**, 833 (1991).
7. The authentic sample of natural pyrrolomycin was kindly provided by Dr. H. Naganawa.[1] Natural pyrrolomycin showed $[\alpha]_D$+40°(*c* 0.06, $CHCl_3$) and $[\alpha]_D$+6.7°(*c* 0.08, MeOH), and its potassium salt $[\alpha]_D$-46°(*c*.0.5, $CHCl_3$) and $[\alpha]_D$-30°(*c* 0.08, MeOH).

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