was warmed to 25 °C, stirred overnight, and filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate, and the solution was washed with 5% $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo to afford *N*-[(2*RS*)-3-(morpholinocarbonyl)-2-(1-naphthylmethyl)propionyl]-L-histidine methyl ester (3.5 kg, 83%). The mixture of the isomers (3.5 kg, 7.31 mol) and salicylic acid (1.01 kg, 7.31 mol) was crystallized from ethyl acetate three times to give pure **3** salicylic acid salt (1.0 kg, 36.2%) as white crystals: mp 142–143 °C; $[\alpha]^{24.5}_D$ +38.10° (*c* 1.29, methanol); IR (KBr) 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.28 (dd, 1 H, J_1 = 16.2, J_2 = 5.5 Hz), 2.60 (dd, 1 H, J_1 = 16.2, J_2 = 6.6 Hz), 2.87 (dd, 1 H, J_1 = 14.8, J_2 = 8.8 Hz), 3.00 (dd, 1 H, J_1 = 14.8, J_2 = 5.5 Hz), 3.1–3.45 (m, 11 H), 3.53 (s, 3 H), 4.54 (dd, 1 H, J_1 = 13.7, J_2 = 8.2 Hz), 6.7–6.85 (m, 2 H), 7.25–7.45 (m, 3 H), 7.45–7.6 (m, 2 H), 7.7–7.85 (m, 2 H), 7.91 (d, 1 H, J = 7.7 Hz), 8.20 (s, 1 H), 8.27 (d, 1 H, J = 8.2 Hz), and 8.36 (d, 1 H, J = 7.7 Hz).

To **3** salicylic acid salt was added chloroform, and the solution was washed with 5% $NaHCO_3$ and saturated NaCl and dried over $MgSO_4$. The solution was concentrated in vacuo and then crystallized from benzene to afford **3** (780 g, quant) as white crystals: mp 92–96 °C; $[\alpha]^{23}_D$ +35.7° (*c* 2.2, MeOH); IR (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3–2.5 (m, 1 H), 3.0–3.75 (m, 14 H), 4.55–4.65 (m, 1 H), 6.19 (d, 1 H, J = 6.6 Hz), 6.66 (s, 1 H), 7.25–7.6 (m, 7 H), 7.74 (d, 1 H, J = 8.2 Hz), 7.85 (d, 1 H, J = 7.7 Hz), 7.99 (d, 1 H, J = 8.2 Hz); HPLC >99.9% (column, Cosmosil $5C_{18}$ 4.6 × 100 mm; eluent, acetonitrile/0.05 M NH_4OAc (aqueous) (3/7); flow rate, 1 mL/min; elution time, 8.0 min); FABMS *m/z* 479 (M + 1). Anal. Calcd for $C_{26}H_{30}N_4O_5 \cdot C_6H_6$: C, 69.05; H, 6.52; N, 10.06. Found: C, 69.28; H, 6.58; N, 9.74.

Alternatively, **3** was obtained by the condensation of (−)-**2** and L-histidine methyl ester. To a stirred solution of (−)-**2** (0.33 g, 1 mmol) and L-histidine methyl ester (dihydrochloride, 0.24 g, 1 mmol) in acetonitrile (2 mL) were added triethylamine (0.28 mL, 2 mmol), HONB (0.18 g, 1 mmol), and DCC (0.21 g, 1 mmol) at 0 °C sequentially. After 2 h the mixture was warmed to ambient temperature gradually, stirred overnight, filtered, and evaporated in vacuo. The residue was dissolved in ethyl acetate, and the solution was washed with 5% $NaHCO_3$ and saturated NaCl and dried over $MgSO_4$. The solution was concentrated in vacuo and then crystallized from benzene to afford **3** (0.38 g, 82%) as white crystals: physical and spectral characteristics were identical with those of **3** obtained above.

(2*R*)-3-(Morpholinocarbonyl)-2-(1-naphthylmethyl)-propionyl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (*R*,*R*-6). To a stirred 0 °C solution of (−)-**2** (0.1 g, 0.31 mmol) in dry THF were added triethylamine (0.047 mL, 0.34 mmol) and ethyl chloroformate (0.032 mL, 0.34 mmol) sequentially. After 1 h the reaction mixture was filtered, and the filtrate was added to a stirred 0 °C solution of $NaBH_4$ (0.058 g, 1.55 mmol) in water (0.3 mL). After 1 h the mixture was warmed to 25 °C for 15 min and evaporated in vacuo. The residue was dissolved in ethyl acetate, and the solution was washed with 1 N HCl, 5% $NaHCO_3$, and saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo to afford (2*R*)-3-(morpholinocarbonyl)-2-(1-naphthylmethyl)propyl alcohol (0.05 g, 52%). To the alcohol (0.01 g, 0.032 mmol) in dry $CHCl_3$ (1 mL, washed with water, then dried over $MgSO_4$) at 0–5 °C (ice bath) were added triethylamine (0.06 mL, 0.038 mmol), DMAP (0.4 mg, 3.3 × 10^{-2} mmol), and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.01 g, 0.038 mmol) sequentially. After 2 h the mixture was warmed to 25 °C and stirred overnight. The mixture was washed with 5% $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (silica gel plates; solvent, $CHCl_3$) to give *R*,*R*-**6** (15.8 mg, 93%) as colorless oil: $[\alpha]^{23}_D$ + 32.07° (*c* 6.61 chloroform); IR (neat) 1745 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25–2.45 (m, 2 H), 2.75–2.9 (m, 1 H), 3.02 (dd, 1 H, J_1 = 13.7, J_2 = 8.2 Hz), 3.1–3.2 (m, 2 H), 3.27 (dd, 1 H, J_1 = 13.7, J_2 = 7.2 Hz), 3.56 (s, 3 H), 3.4–3.7 (m, 4 H), 4.25–4.4 (m, 2 H), 7.18 (d, 1 H, J = 7.1 Hz), 7.25–7.6 (m, 8 H), 7.74 (d, 1 H, J = 8.2 Hz), 8.85 (dd, 1 H, J_1 = 6.6, J_2 = 2.2 Hz), and 8.14 (d, 1 H, J = 9.9 Hz); FABMS *m/z* 530 (M + 1). The lanthanide-induced shift of the methoxy proton resonance vs molar ratio of $Eu(fod)_3$ for *R*,*R*-**6** was 0.72 ppm.

(2*R*)-3-(Morpholinocarbonyl)-2-(1-naphthylmethyl)-propionyl (*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (*R*,*S*-6). The synthesis of *R*,*S*-**6** was carried out as described above for *R*,*R*-**6** with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. *R*,*S*-**6** (94% yield) as a white powder: mp 86–88 °C; $[\alpha]^{23}_D$ +5.34° (*c* 0.72, chloroform); IR (KBr) 1750 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2–2.4 (m, 2 H), 2.75–2.9 (m, 1 H), 3.03 (dd, 1 H, J_1 = 13.7, J_2 = 8.2 Hz), 3.1–3.3 (m, 3 H), 3.49 (t, 1 H, J = 4.6 Hz), 3.56 (s, 3 H), 3.6–3.7 (m, 2 H), 4.19 (dd, 1 H, J_1 = 11.0, J_2 = 4.4 Hz), 4.44 (dd, 1 H, J_1 = 11.0, J_2 = 4.4 Hz), 7.19 (d, 1 H, J = 7.2 Hz), 7.36–7.6 (m, 8 H, 7.74 (d, 1 H, J = 8.3 Hz), 7.85 (d, 1 H, J = 9.3 Hz), and 8.13 nd, 1 H, J = 9.3 Hz); FABMS *m/z* 530 (M + 1). The lanthanide-induced shift of the methoxy proton resonance vs molar ratio of $Eu(fod)_3$ for *R*,*S*-**6** was 0.64 ppm.

Acknowledgment. We thank Dr. S. Urano of Tokyo Metropolitan Institute of Gerontology for advice about NMR analysis.

Mutactin, a Novel Polyketide from *Streptomyces coelicolor*. Structure and Biosynthetic Relationshp to Actinorhodin

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Received January 16, 1990

In 1979 Rudd and Hopwood[1] reported the isolation of 75 mutants of *Streptomyces coelicolor* A 3(2) which were unable to synthesize the pigment antibiotic, actinorhodin (1). These were grouped into seven classes based on various phenotypic characteristics, particularly their ability to engage in cosynthesis of 1.[1] Subsequent chemical analysis, based on a modification of the cosynthesis assay, led to the isolation of several intermediates of 1 biosynthesis accumulated by these mutants.[2-4] The biosynthetic intermediate in extracts of mutant B_{40}, a member of class VII, the earliest class of mutants acting as secretors in the cosynthesis assay,[1] proved too unstable for isolation. However, another less polar material was uniquely prominent in chromatograms of these extracts, was identified as a novel 16-carbon polyketide, and was called mutactin.

Mutactin was purified from cultures of *S. coelicolor* mutant B_{40}[1] grown in CM medium[5] by extraction of the broth at pH 3.0 with EtOAc, chromatography on LH-20 (methanol), or partitioning between aqueous MeOH and organic solvents, followed by either preparative TLC or crystallization. The material, mp 192–193 °C, had UV absorptions at 222 (ε 24 300), 265 (ε 16 900), and 290 nm (sh, ε 9600) and showed no antibiotic activity (MIC > 100 μg/mL) against 19 strains of bacteria, fungi, and yeasts.

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0022-3263/90/1955-1682$02.50/0

Table I. NMR Data for Mutactin (3)[a]

position	$\delta^{13}C$, ppm, mult[b]	$\delta^{1}H$, mult (J, Hz)
1	164.4, s	-
2	90.8, d	5.45, d (2.16)
3	170.0, s	-
4	105.1, d	6.15, d (2.16)
5	161.2, s	-
6	124.6, s	-
7	142.6, s	-
8	36.6, t	50%: 8_{ax}, 2.90, ddd (16.7, 6.63, 1.27), 8_{eq}, 3.13, ddd (16.7, 3.67, 0.85) 50%: 8_{ax}, dd (16.7, 6.63), 8_{eq}, dd (16.6, 3.67)
9	65.9, d	4.40, cplx m (7.14, 6.63, 3.67)
10	46.9, t	10_{ax}, 2.74, ddd (16.9, 7.14, 1.27), 10_{eq}, 2.96, ddd (16.9, 3.67, 0.83)
11	204.7, s	-
12	115.7, s	-
13	163.9, s	-
14	117.2, d	6.74, q (0.64)
15	147.5, s	-
16	20.5, q	2.20, d (0.64)
13-OH		12.70, sharp singlet

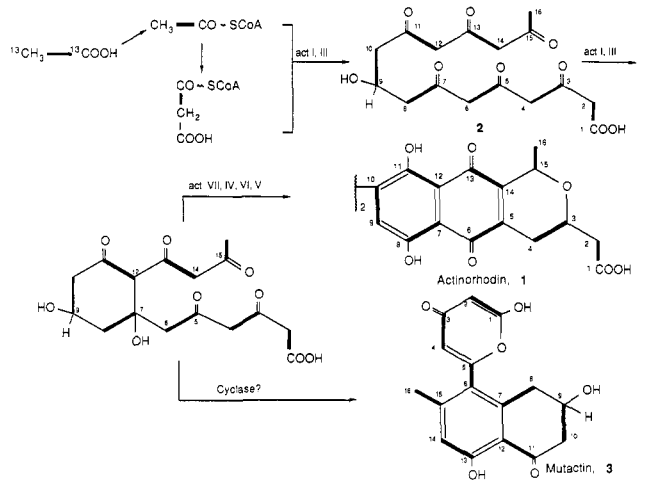
[a] Spectra acquired in acetone-d_6 at 7.1 T, referenced internally to acetone. [b] q = quartet, d = doublet, t = triplet, s = singlet, m = multiplet.

High-resolution MS and elemental analysis gave a molecular formula $C_{16}H_{14}O_6$. Although an X-ray structure analysis indicated a disordered structure, it did point to the presence of a novel ring system combining a tetralone and a pyrone moiety. Following this lead, the structure of mutactin was then deduced from ^1H and ^{13}C NMR data[6] (Table I) as **3**.

Proton NMR spectroscopy (7.1 Tesla, δ in ppm) on a sample of mutactin in acetone-d_6 was entirely consistent with the tetralone/pyrone system revealed by X-ray analysis. In the upfield region of the spectrum were proton resonances indicative of a 5-proton spin system of two methylene groups surrounding a central carbinol methine proton. Based on a Karplus-type analysis of the coupling constants, the C-9 hydroxyl group was assigned to equatorial configuration. Interestingly, proton multiplets for H-8 revealed conformational flexibility, demonstrating 50% ddd as well as 50% dd patterns, in which the 4-bond diaxial and diequatorial couplings with H-10 were lost. A single methyl group resonance was present in the proton spectrum at δ 2.20, which demonstrated a 0.64-Hz coupling to the proton at δ 6.74. Proton steady-state NOE (nuclear Overhauser enhancement) difference experiments revealed, upon irradiation of the methyl resonance, 18.5% and 5.6% NOE to protons at δ 6.74 and 6.15 ppm, respectively, revealing their close proximity to the methyl group. The signal at δ 6.15 ppm was coupled to another resonance at δ 5.45. These signals were consistent with a pyrone system. A sharp singlet at δ 12.70 was assigned to an aromatic, probably hydrogen-bonded hydroxyl group in peri disposition to a carbonyl group.

Carbon-13 DEPT[7] analysis of the sample confirmed the presence of 16 carbon atoms, including 9 singlets, 4 doublets, 2 triplets, and 1 quartet. Unequivocal assignment of all carbon signals was possible through their one- and multiple-bond couplings to protons. These data were obtained from inverse heteronuclear multiple quantum correlation (HMQC)[8] and inverse heteronuclear multiple bond correlation (HMBC).[9] The data were in accord with the structure suggested by the X-ray analysis. Because the carbonyl resonance at δ 170 was coupled via $^2J_{CH}$ with equal intensity to both H-2 (δ 5.45) and H-4 (δ 6.15), and the enolic carbon at C-2 demonstrated coupling to only H-2, we assigned the $\Delta_{1,2}$, $\Delta_{4,5}$ arrangement of double bonds to the pyrone moiety.

Scheme I



Mutactin represents a novel ring system not encountered in Nature before, although the corresponding tetralone without the pyrone substituent has been reported.[10] Notably, neither the crystalline sample of **3** nor material purified entirely by chromatography gave any CD signal, suggesting that either its molar ellipticity is exceedingly small or the compound is present as the racemate. However, attempts to further probe this issue by derivatization with an optically active auxiliary or NMR analysis in the presence of a chiral shift reagent have so far been unsuccessful.

Presumably, **3** arises by an alternate cyclization of the same precursor polyketide (**2**) which gives rise to actinorhodin (**1**). In support of this notion, feeding of sodium [1,2-$^{13}C_2$]acetate to *S. coelicolor* B_{40} gave **3**, which displayed a single ^{13}C–^{13}C coupling pattern corresponding entirely to that determined earlier for **1**[11] (Scheme I). HPLC analysis of the extracts of several other *S. coelicolor* strains revealed that **3** was also present in the wild-type, albeit in 100 times lower concentration than in mutant B_{40}, but was not produced by *act I* [polyketide synthase (PKS)-negative] or *act III* [polyketide reductase (PKR)-negative] mutants. This shows that **3** is a natural metabolite of *S. coelicolor* and that its biosynthesis shares the first two enzymes, PKS and PKR, with the actinorhodin biosynthetic pathway. Also common to both pathways is the first cyclization step, C–C bond formation between C-7 and C-12, which therefore is probably also catalyzed by the PKS–PKR complex. Blockage of the next step on the pathway to **1** (*act VII* mutation) channels more substrate

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into the branch leading to 3. Whether the remaining steps required to produce 3, C-6/C-15 bond formation, enolization, and pyrone ring closure, occur spontaneously or require additional enzyme(s) is not yet clear. The fact that neither the granaticin producer, *S. violaceoruber* Tü 22,[12] nor a transformant of the daunomycin producer, *S. galilaeus* ATCC 31133 bearing plasmid pANT 12 carrying the *act I, III, IV,* and *VII* genes,[13] synthesized 3 favors the secondary possibility.

Experimental Section

General Procedures and Materials. NMR spectra were acquired at 303 K on acetate-d_6 solutions of mutactin with an IBM AF-300 FT-NMR spectrometer operating at a field strength of 7.1 T. FT mass spectra were obtained on a Nicolet FT-MS-1000 spectrometer operating at a field strength of 3.0 T using laser desorption. UV spectra were recorded on a Varian DMS-90 double-beam UV-vis spectrophotometer, and CD spectra on a JASCO J-500A spectropolarimeter, using methanol as solvent. HPLC separations and quantitations were carried out on an Alltech C-18 reverse-phase column connected to a Waters 590 solvent delivery system and a Waters R401 refractive index detector, using methanol–water–acetic acid (50:50:0.01) as solvent. Peak areas were integrated on a Hitachi D-2000 integrator. Elemental analyses were obtained from Midwest Microlab, Indianapolis, IN, and antimicrobial testing was carried out at Huashang Hospital, Shanghai, China.

Cultures of *S. coelicolor* B_{1190} (wild type), B_{40} (*act VII* mutant), B_{17} (*act I* mutant, lacking PKS), and B_{41} (*act III* mutant, lacking PKR) were obtained from Prof. D. A. Hopwood, Norwich, and were maintained on slants of CM medium[5] containing 1.5% Bacto-agar (Difco). *S. violaceoruber* Tü 22 was obtained from Prof. H. Zähner, Tübingen, and maintained as previously described,[12,14] and *S. galilaeus* ATCC 31133 {pANT 12}[13] was provided by Prof. W. R. Strohl, The Ohio State University. Sodium [1,2-$^{13}C_2$]acetate (99% ^{13}C) was obtained from Cambridge Isotopes, Inc.

Fermentation. Seed cultures were grown in 500-mL Erlenmeyer flasks containing 150 mL of CM medium inoculated with 2–5 mL of spore suspension from a well-sporulated slant of *S. coelicolor* B_{40}. The flasks were incubated for 36 h at 30 °C on a New Brunswick Controlled Environment gyratory shaker (300 rpm), and 25 mL of seed culture were then used to inoculate each production culture containing 150 mL of CM medium in a 500-mL Erlenmeyer flask. These were incubated with shaking as described above and harvested 5 days later. To produce larger quantities of 3, a 14-L New Brunswick Microferm fermentor containing 8 L of CM medium was inoculated with 4 seed cultures (600 mL). The fermentation was conducted for 5 days at 30 °C with agitation at 250 rpm and aeration at 1000 mL/min.

Fermentations of the other cultures were conducted in shake flasks using the same protocol. For the biosynthetic feeding experiment, 1 g of sodium [1,2-$^{13}C_2$]acetate was dissolved in 20 mL of water and added in equal portions to 12 36 h old production flasks. The cultures were harvested 84 h later; workup gave 80 mg of ^{13}C-labeled 3 with an average enrichment of about 1.2–1.5% per carbon.

Isolation of 3. The 5 day old cultures of *S. coelicolor* B_{40} were filtered first through Whatman 3MM filter paper and then through Celite, and the pH of the clear filtrate was adjusted to 3.0 with 1 N HCl. This solution was then extracted three times with equal volumes of ethyl acetate; the combined extracts were dried and evaporated to a syrup on a rotary evaporator at a bath temperature up to 50 °C. The residue was loaded onto a column of Sephadex LH-20, which was developed with methanol. Fractions containing 3 were located by analytical TLC (silica gel, $CHCl_3/CH_3OH$, 4:1, R_f 0.35), and the material was further purified by preparative layer chromatography in the same system.

Alternatively, the residue from the ethyl acetate extract was dissolved in CH_3OH, an equal volume of water was added, and the pH was adjusted to 7–8. This solution was extracted successively with $CHCl_3$ and with EtOAc, and the extracts were discarded. The aqueous methanol solution was then adjusted to pH 2–3 and extracted twice with ethyl acetate. The extract was treated with activated charcoal (0.5–1.0%), filtered, and taken to dryness on a rotary evaporator. The residue was dissolved in a small volume of acetone and kept in the refrigerator until crystals deposited. Yield: about 40–50 mg/L. Mp: 192–193 °C. Molecular formula $C_{16}H_{14}O_6$ (MS: MH^+ calc 303.08687, obsd 303.08270). Anal. Obsd: C, 63.57; H, 4.72. Calc for $C_{16}H_{14}O_6 \cdot H_2O$: C, 63.58; H, 4.64. UV (λ, ϵ: 222 nm, 24300 mM^{-1} cm^{-1}; 265, 16900; 290, 9600 (sh). CD: no signal at 6.4 mg/mL in methanol over range of 250–600 nm. NMR: see Table I. Antimicrobial activity: at 100 μg/mL no inhibitory activity against *S. aureus* (3 strains), *E. coli* (3 strains), *P. aeruginosa* (2 strains), *K. pneumoniae* (2 strains), *Citrobacter* (2 strains), *Saccharomyces sake* (2 strains), *Candida albicans*, *Rhizopus nigricans*, *Aspergillus niger*, *A. oryzae*, *Penicillium citrinum*.

Acknowledgment. We are indebted to Prof. D. A. Hopwood and Dr. B. A. M. Rudd, Norwich, for providing the *S. coelicolor* mutants, to The Ohio State Campus Chemical Instrument Center for mass spectral analyses, to Huashang Hospital, Shanghai, for assistance with the antibiotic testing, and to Prof. W. R. Strohl, Columbus, OH, for providing *S. galilaeus* ATCC 31133 {pANT 12} and for stimulating discussions and collaboration. Financial support by the NIH (AI 20264) and the NSF (DMB 8607619) is gratefully acknowledged.

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Synthesis of (*S*,*S*)- and (*R*,*R*)-2-Alkyl-2,5-diazabicyclo[2.2.1]heptanes

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Received November 8, 1989

Danofloxacin (1)[1] is a member of a growing family of the totally synthetic antibacterials known as the quinolones,[2] the synthesis of which is accomplished by the nucleophilic introduction of (*S*,*S*)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (2) to the nucleus moiety 3.[3] This paper describes a new efficient synthesis of 2 and its enantiomer (see Scheme I).

The synthesis of 2 has been reported previously,[4] from *trans*-4-hydroxy-L-proline (see Scheme II). In this synthesis, the tritosyl intermediate 4 was prepared from 4-hydroxy-L-proline by N-tosylation, esterification, and reduction with $LiBH_4$ followed by ditosylation of the resulting diol. Intermediate 4 was then cyclized with benzylamine, and the sulfonamide was cleaved with HI.[5] The

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