SYNTHESIS OF ISOPENTABROMOPSEUDILIN

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Pentabromopseudilin (1), an antibiotic isolated from the marine bacteria Pseudomonas bromoulitis, Chromobacteria and Alteromonas luteoviolaceus [R. H. Thomson, H. Laatsch, J. Chem. Soc., Perkin Trans. 2, 1331 (1984)] shows very high antibacterial activity. 1 has a phenyl group at the alpha position, whereas the antifungal agent pyrrolinitrin (2) has the phenyl group at the beta position of the pyrrole ring. To obtain information on the importance of the position of the phenyl group, we synthesised the 3 phenyl isomer of 1, isopentabromopseudilin (3).

3,5-Dibromo-2-methoxy-benzaldehyde was transformed in an one-pot-reaction with isocyanoaetic acid methyl ester to the 2,4-diester-3-phenyl-pyrrole (4) [M. Suzuki, M. Miyoshi, K. Matsumoto, J. Org. Chem. 39, 1980 (1974)]. After saponification and decarboxylation the pyrrole ring was brominated with pyridinium hydrobromide perbromide. Subsequent deprotection with BBr3 released the unstable target molecule 3.

Compound 3 was tested against a variety of microorganisms and showed no biological activity.
Synthesis of Isopentabromopseudulin

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Received March 14, 1991

Key Words: Antibiotics, marine / Isopentabromopseudulin / Pseudulin, isopentabromo- / Pyrrole, 3-phenyl

Isopentabromopseudulin (4) and the analogous compounds 12g, 12h have been synthesized by base-catalyzed cyclization of substituted benzaldehydes with isocynoacetic acid methyl ester (6). In contrast to the highly antibiotic and cytotoxic active natural product 1, compounds 4, 12g and 12h have been shown to be inactive.

The marine bacterium Alteromonas luteoviolacea produces the highly antibiotic, phytotoxic and antitumoral active pentabromopseudulin (1). 1 and several 2-phenylpyrrole derivatives thereof have been synthesized for structure-activity studies. All are in vitro bacteriotoxic or highly cytotoxic, but hardly fungitoxic and in vivo inactive. In opposition to cytotoxicity, the phenolic hydroxy group is essential for the antibiotic activity, and higher bromination usually enhances it. Most derivatives are less active than 1.

In contrast, the fungitoxic pyrrolinitrin (2) is also in vivo active and used as a drug against trichophytosis. As the 3-connected bromonitrins (3) are highly active, too, it has seemed a challenging task to synthesize isopentabromopseudulin (4) with the phenyl group in position 3 of the pyrrole ring, thus trying to unite the positive aspects of 1 and 2 and to gain further information on structure-activity correlations.

3-Phenylpyrroles are synthesized usually indirectly via higher substituted pyrroles. Of several syntheses, we have chosen a way using the diesters 9a-d. The intermediate (E/Z)-formamidoinoacetic acid esters 7a-d are obtained in good yield by condensation of isocynoacetic acid methyl ester (6, ICA) with the benzaldehydes 5a-d. Subsequent dehydration of 7a with triphenylphosphine, carbon tetra-

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\begin{align*}
\text{Ar}^-\text{CHO} + \text{N} = \text{Cl} & \longrightarrow \text{Ar}^-\text{CH} = \text{C} = \text{NHCHO} \\
5a-d & \underset{\text{BuOK}}{\longrightarrow} \text{Ar}^-\text{CH} = \text{C} = \text{N=Cl} \\
6 & \underset{n\text{-BuLi}}{\longrightarrow} 7a-d \\
7a-d & \overset{2) \text{Cu/\Delta}}{\longrightarrow} 11a-c \\
8a & \\
9a-d & : R = \text{Me} \\
10a-c & : R = \text{H} \\
11a-c & \\
12a,b,c & \\
12d, f, g, h & \\
\begin{array}{llllllll}
a & b & c & d & e & f & g & h \\
\text{R}^1 & \text{OMe} & \text{H} & \text{H} & \text{Br} & \text{Br} & \text{OH} & \text{H} & \text{Br} \\
\text{R}^2 & \text{Br} & \text{Br} & \text{OMe} & \text{OMe} & \text{OMe} & \text{Br} & \text{OH} & \text{Br} \\
\text{R}^3 & \text{H} & \text{OMe} & \text{H} & \text{Br} & \text{Br} & \text{OH} & \text{Br} \\
\text{R}^4 & \text{Br} & \text{Br} & \text{OMe} & \text{H} & \text{OMe} & \text{Br} & \text{Br} & \text{OH} \\
\text{R}^5 & \text{H} & \text{H} & \text{H} & \text{Br} & \text{H} & \text{H} & \text{H} \\
\end{array}
\end{align*}
\]
chloride and triethylamine in chloroform affords only a poor yield of 8a, whilst treatment with phosphoryl chloride and triethylamine in dichloromethane gives 8a in 80% yield. The Michael reaction of ICA (6) with 8a (n-butyllithium as a base), followed by cyclization and elimination of the isocyano group furnishes 9a in 37% yield.

Similar results as for the sequence 5a → 7a → 8a → 9a are obtained far more easily, in a one-pot reaction. The condensation of 5a → 7a → 8a → 9a is followed by a Michael reaction of a second molecule ICA (6), ring closure and elimination of the formamido instead of the isocyano group as in step 8a → 9a, gives 9a → 8a in up to 38% yield, when the most successful of a variety of reaction conditions is applied.

Although yields, especially those of 9a and 9d, are poor, the synthesis has been carried out in this way, as the pyrrole ring is built up in a simple one-pot procedure, and the starting compounds are easily to obtain in large quantities.

The 3-phenylpyrrole 2,4-diesters 9a–c are saponified with potassium hydroxide in methanol/water (1:1) within four days (reflux). Decarboxylation of the resulting acids 10a–c in quinoline with copper powder at 190°C (1 h) yielded the less stable 3-phenylpyrroles 11a–c in 25–40% yield. The pyrrole ring of 11a and 11b is easily brominated with pyridinium hydrobromide perbromide. 11c is also brominated in two positions of the phenyl ring. Demethylation occurs on treatment with boron tribromide in dichloromethane. The pentabromides 12a, 12b and 12e and the phenols 12f are sensitive to light and heat.

The synthesis was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

**Experimental**

Material and methods as reported in ref. 1.

Biological Tests: The tests were carried out on agar plates seeded with Streptomyces viridochromogenes, Candida albicans, Mucor miehei, Escherichia coli and Bacillus subtilis. No biological activity has been observed with any of the compounds, apart from 4, 12g and 12h, which show a low activity towards Bacillus subtilis in synthetic medium.

The results suggest that the position of the pyrrole-phenyl connection must be essential for the activity of 2-(hydroxyphenyl)pyrroles like 1. The degree of bromination seems to be less important for biological activity. Obviously pentabromopseuduin (1) and pyrrolotrim (2) act in a different way.

Acid Methyl Ester (7b): According to the procedure used for the preparation of 7a, from 58.8 g (0.2 mol) of Sb 52.2 g (67%) of 7b was obtained; crystallization from ethyl acetate afforded a colorless, amorphous powder; m. p. 165°C. — 18 NMR (CDCl₃, 80 MHz): δ = 8.27 (s; 1H, CHO), 7.57 (s; 2H, 2', 6'-H), 7.25 (s; 1H, 2-H), 7.13 (s; 1H, NH, exchange with D₂O), 3.90 (8.72 (s; 2H, 2', 6'-H) OCH₃). — MS (70 eV): m/z (%) = 395, 393, 391, 384, 50, 50 [M⁺], 376, 365, 365 (8, 18, 10) [M⁺ + CO], 338, 336, 334 (12, 30, 24), 308, 306, 304 (34, 70, 38), 289 (26), 183 (18).

3-(3',5'-Dibromo-4'-methoxyphenyl)-2-formamido-2-propenoic Acid Butyl Ester (7d): To a solution of 0.99 g (0.010 mol) of ICA (6) in 20 ml of THF at 60°C was added dropwise to a solution of 22.4 g (0.2 mol) of potassium tert-butoxide in 300 ml of THF. Then within 15 min, 58.8 g (0.2 mol) of 5a in 100 ml of THF was added. After stirring at room temp. for 12 h, 7a began to crystallize. The reaction mixture was concentrated in vacuo and the residue dissolved in 12 g (0.2 mol) of acetic acid and 200 ml of water. The solution was extracted with CH₂Cl₂. After concentration of the dried (Na₂SO₄) extracts the residue was recrystallized from ethyl acetate to afford 43.2 g (55%) of 7a as a colorless solid; m. p. 148°C. — 18 NMR (CDCl₃, 80 MHz): δ = 8.16 (s; 1H, CHO), 7.63, 7.23 (2 d, J₂₆ = 2.5 Hz each 1H, 4', 6'-H), 7.60 (s; br., 1H, NH, exchange with D₂O), 7.41 (s; 1H, 3'-H), 3.90, 3.81 (2 s; 6 H, 2 OCH₃). — MS (70 eV): m/z (%) = 395, 393, 391, 384, 50, 50 [M⁺], 376, 365, 363 (8, 18, 10) [M⁺ + CO], 338, 336, 334 (12, 30, 24), 308, 306, 304 (34, 70, 38), 289 (26), 183 (18).

**References**

D_{2}O), 7.15 (s; 1H, 3-H), 4.25 (t, 3J_{2,1} = 7 Hz; 2H, OCH_{2}CH_{2}CH_{2}CH_{2}), 3.91 (s; 3 H, OCH_{3}), 1.58 (m; 4 H, CH_{2}CH_{2}), 0.97 (t, 4J_{2,1} = 7 Hz; 3H, CH_{2}CH_{2}CH_{2}CH_{2}). MS (70 eV; m/z (%)) = 437, 433, 433 (1, 12, 24, 12, 24) [M^{+} - H], 409, 407, 405 (45, 100, 41) [M^{+} - CHO], 373, 351, 349 (26, 50, 30), 338, 336, 334 (20, 44, 26), 292, 290 (88, 20, 44, 18).

C_{12}H_{22}Br_{3}NO_{5} (435.1). Calc. C 41.40 H 3.94 Br 36.73 N 3.22 Found C 41.58 H 4.05 Br 36.54 N 3.27

3-(3',5'-Dibromo-2'-methoxyphenyl)-2-isocyano-2-propenoic Acid Methyl Ester (8a). Method A: 29.1 g (0.075 mol) of 7a, 23.6 g (0.090 mol) of triethylphosphine, 11.54 g (0.075 mol) of triethylamine in 100 ml of CHCl_{3} were heated for 3 h at 60°C. The reaction mixture was concentrated in vacuo and the residue dissolved at 0°C in petroleum ether/CHCl_{3} (4:1). After 30 min the precipitate was filtered off and washed with petroleum ether. The solvents of the filtrate and washings were evaporated, and the residue was chromatographed on alumina (ether) to afford 3.65 g (13%) of 8a as pale yellow needles; m. p. 141°C (dec.).

Method B: 3.93 g (0.01 mol) of 7a and 3.00 g (0.03 mol) of triethylamine were dissolved in 50 ml of CHCl_{3} and a solution of 1.53 g (0.01 mol) of phosphonol chloride in 20 ml of CHCl_{3} was added dropwise. After stirring for 3 h at room temp., a solution of 2.5 g of Na_{2}CO_{3} in 20 ml of water was carefully added at 0°C and stirring was continued for further 15 min. The organic layer was dried (K_{2}CO_{3}), filtered, and concentrated in vacuo. The residue was chromatographed on alumina (ether) to afford 2.98 g (80%) of 8a as pale yellow needles; m. p. 142°C (dec.). — 1H NMR (CDCl_{3}, 80 MHz): δ = 8.12, 7.75 (2 d, 3J_{2,1} = 2.5 Hz; 2H, 3′-, 5′-H), 7.82 (s; 1H, 3-H), 3.93, 3.82 (s; 2H, OCH_{3}). MS (70 eV; m/z (%)) = 377, 375, 373 (36, 73, 38) [M^{+}], 344, 343, 342, (60, 68, 30), 316 (24), 302 (24), 289 (25), 236 (16), 194, 192 (26, 32), 156 (18).

C_{12}H_{22}Br_{3}NO_{5}  (375.0). Calc. C 38.43 H 2.42 Br 42.61 N 3.74 Found C 38.54 H 2.45 Br 42.47 N 3.75

3-(3',5'-Dibromo-2'-methoxyphenyl)-1H-pyrrrole-2,4-dicarboxylic Acid Dimethyl Ester (9a) via 8a: At −60°C, 2.5 ml of 1.6 n-butyllithium (solution in pentane, 0.004 mol) was added dropwise to a solution of 0.42 g (0.004 mol) of ICA (6) in 20 ml of THF. Within 15 min, 1.40 g (0.004 mol) of 8a in 20 ml of THF was added. The reaction mixture was stirred at room temp. for 1 h, the solvent evaporated, the residue dissolved in 0.24 g (0.004 mol) of acetic acid and 20 ml of water, and the solution was extracted with ether. After drying (Na_{2}SO_{4}) the extract and evaporation of the solvent the residual was chromatographed on silica gel (petroleum ether/tert-butyl methyl ether, 1:1) to afford 0.65 g (37%) of 9a as a pale yellow solid; m. p. 156°C. — 1H NMR (CDCl_{3}, 80 MHz): δ = 9.55 (s; 3Br, 1H, NH, exchange with D_{2}O), 7.53 (d, 3J_{2,1} = 3 Hz; each 1H, 3′-, 5′-H), 7.62, 7.23 (2d, 3J_{2,1} = 2Hz; each 1H, 3′-, 5′-H), 3.46, 3.68, 3.66 (3 s; 9H, 3 OCH_{3}). MS (70 eV; m/z (%)) = 449, 447, 445 (2.5, 2.7) [M^{+}], 418, 416, 414 (2, 2, 5) [M^{+} - OMe], 386, 384, 382 (2, 3, 2), 196 (16).

3-Phenyl-1H-pyrrrole-2,4-dicarboxylic Acid Dimethyl Esters 9a – d. General Procedure: Within 15 min, a 0.4 mol solution of 1 equiv. of 5a, b, c or d in THF was added to a 0.7 mol solution of 2 equiv. of ICA (6) and 2 equiv. of DUB in THF. After stirring for 8 h at 50°C, the cooled reaction mixture was neutralized with 2 equiv. of acetic acid and the solvent evaporated. The residue was dissolved in ethyl acetate, the solution washed with diluted HCl and water and dried with Na_{2}SO_{4}. The solvent was evaporated and the residue chromatographed on silica gel (petroleum ether/tert-butyl methyl ether, 1:2).
Decarboxylation of Acids 10 — General Procedure: Under a continuous nitrogen gas flow, a well stirred mixture of 2.0 g of acid 10 and 2.0 g of Cu powder was heated in 100 ml of quinoline to 180–190°C until the outflowing gas did not contain any CO2 (ca. 1 h). The cold mixture was dissolved in ether, the solution extracted with diluted HCI and washed neutral. After drying (Na2SO4), the solvent was evaporated and the residue chromatographed on silica gel (petroleum ether/tert-butyl methyl ether, 1:2).

3-(3′,5′)-Dibromo-2-methoxyphenyl)-1-H-pyrole (11a): According to the general procedure 2.0 g of 10a gave 0.42 g (26%) of 11a as a colorless solid; m. p. 87–89°C. — 1H NMR (CDCl3, 200 MHz): δ = 8.39 (s, br.; 1H, NH; very slow exchange with D2O), 7.60, 7.56 (2 d, J4a,J6 = 2.5 Hz, 2H, 4′, 6′-H), 7.36 (dd, J4a,3,2 = 2.8 Hz, J4a,3 = 1.8 Hz, 1H, 4′-H), 6.83 (dd, J3,2 = 2.8 Hz, J3,2 = 2.5 Hz, 1H, 2′-H, 5′-H), 6.57 (dd, J3,2 = 2.8 Hz, J3,2 = 1.8 Hz, 1H, 5′-H) 6.76 (s, br.; 2H, 2′, 6′-H), 3.84 (s, br.; 1H, NH, very slow exchange with D2O). — MS (70 eV): m/z (%) = 333, 331, 329 (48, 100, 50) [M+], 317, 315, 314 (12, 30, 16) [M+ − CH3].

C8H8Br2NO Calcd. 280, 278, 276 (7, 14, 6), 237, 235 (24, 24), 170 (8), 156 (20), 142 (24), 128 (38).

C8H8Br2NO Calcd. 328.90508 Found 328.90506 (MS)

3-(3′,5′)-Dibromo-4-methoxyphenyl)-1H-pyrole (11b): According to the general procedure 2.0 g of 10b gave 0.38 g (24%) of 11b as a colorless solid; m. p. 94°C. — 1H NMR (CDCl3, 200 MHz): δ = 3.88 (s, 3H, OCH3), 6.44 (dd, J4a,3 = 2.8 Hz, J4a,3 = 1.8 Hz, 1H, 4′-H), 6.83 (dd, J3,2 = 2.8 Hz, J3,2 = 2.8 Hz, 1H, 2′-H, 5′-H), 6.57 (dd, J3,2 = 2.8 Hz, J3,2 = 1.8 Hz, 1H, 5′-H) 6.76 (s, br.; 2H, 2′, 6′-H), 3.84 (s, br.; 1H, NH, very slow exchange with D2O). — MS (70 eV): m/z (%) = 333, 331, 329 (8, 16, 8) [M+], 318, 316, 314 (8, 20, 10) [M+ − CH2].

C11H8Br2NO2 Calcd. C 39.92 H 2.74 N 4.23 Found C 40.07 H 2.80 N 4.20

3-(3′,5′)-Dimethoxyphenyl)-1H-pyrole (11c): According to the general procedure 2.0 g (6.87 mmol) of 10c gave 0.56 g (41%) of 11c as a colorless solid; m. p. 59°C. — 1H NMR (CDCl3, 200 MHz): δ = 8.28 (s, br.; 1H, NH; very slow exchange with D2O), 7.08 (dd, J3,2 = 2.8 Hz, J4a,3 = 2.8 Hz, 1H, 2′-H, 5′-H), 6.70 (s, br.; 3H, OCH3). — MS (70 eV): m/z (%) = 203 (5.5) [M+], 174 (2), 142, 141, (14, 10), 73 (80), 45 (100).

C11H8Br2NO3 (203.2) Calcd. C 70.92 H 6.54 N 6.89 Found C 70.78 H 6.55 N 6.77

2,3,5-Trisubstituted-1H-pyrole (12a): A solution of 180 mg (0.55 mmol) of 11a in 20 ml of abs. ethanol was stirred for 30 min with 504 mg (1.65 mmol) of pyridinium hydrobromide perbromide and then concentrated. The residue was chromatographed on silica gel (petroleum ether/tert-butyl methyl ether, 1:1) to yield 180 mg (58%) of 12a as a colorless oil. — 1H NMR (CDCl3, 80 MHz): δ = 8.45 (s, br.; 1H, NH, exchange with D2O), 7.69, 7.25 (2 d, J4a,J6 = 2.5 Hz each 1H, 4′, 6′-H), 3.55 (s, 3H, OCH3). — MS (70 eV): m/z (%) = 573, 571, 569, 567, 565, 563 (0.2, 1, 2.5, 2.4, 1.4, 0.3) [M+], 411, 409, 407, 405, 403 (2, 7, 3, 2) [M+ − 2 Br].

C11H8Br2NO4 Calcd. 562.636614 Found 562.63665 (MS)

2,3,5-Trisubstituted-1H-pyrole (12b): A solution of 310 mg (0.94 mmol) of 11b in 20 ml of abs. ethanol was stirred for 30 min with 948 mg (3.10 mmol) of pyridinium hydrobromide perbromide and then concentrated. The residue was chromatographed on silica gel (petroleum ether/tert-butyl methyl ether, 1:1) to yield 352 mg (66%) of 12b as a colorless solid; m. p. 96°C (dec.). — 1H NMR (CDCl3, 80 MHz): δ = 8.45 (s, br.; 1H, NH, exchange with D2O), 7.53 (s, 2H, 2′, 6′-H), 3.92 (s, 3H, OCH3). — MS (70 eV): m/z (%) = 573, 571, 569, 567, 565, 563 (4, 44, 100, 90, 48, 10) [M+] 555, 553, 551, 549 (30, 58, 55, 30) [M+ − CH3].

C11H8Br2NO Calcd. 562.63661 Found 562.63658 (MS)

Demethylation of 12a, b, c. — General Procedure: 4 equiv. of a 0.01 m solution of BF3 in CH2Cl2 per methoxy group were slowly added at −78°C to a 0.01 m solution of the ethers 12a, b, c in CH2Cl2. After stirring for 5 d at room temp., the reaction mixture was poured on ice/diluted HBr, then extracted with CH2Cl2 and the extract washed with water until neutral. The dried solution (Na2SO4) was concentrated and the residue chromatographed on silica gel (CH2Cl2).

2,3,5-Trisubstituted-1H-pyrole (12d): According to the general procedure 120 mg (0.211 mmol) of 12a gave 51 mg (44%) of 12d as a colorless oil, which quickly turned dark. — 1H NMR (CDCl3, 80 MHz): δ = 8.50 (s, br.; 1H, NH, exchange with D2O), 7.60, 7.20 (2 d, J4a,J6 ≈ 2.5 Hz; each 1H, 4′, 6′-H), 5.00 (s, br.; 1H, OH, exchange with D2O). — MS (70 eV): m/z (%) = 557, 555, 553, 551 (2, 4, 8, 5, 2.5) [M+] 476, 474, 472 (3.5, 5, 3) [M+ − Br].

C11H8Br2NO Calcd. 548.62096 Found 548.62099 (MS)

CAS Registry Numbers


12. When n-BuLi was used as a base instead of DBU, 7b gives the corresponding butyl ester and no pyrrole; with t-BuOK, only poor yields are obtained.

[61/91]