Synthesis of Two Naphthoquinone Antibiotics Pentalongin and Psychorubrin

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Abstract: The synthesis of two naturally occurring pyranonaphthoquinone antibiotics, pentalongin (**1**) and psychorubrin (**2**), is reported.

Key words: pyranonaphthoquinone, Pentas longiflora, 1*H*-naphtho[2,3-c]pyran-5,10-dione, pentalongin, psychorubrin

Pentalongin (**1**) (1*H*-naphtho[2,3-*c*]pyran-5,10-dione) has been isolated from *Pentas longiflora* Oliv. (Rubiaceae).[1] The dry powder from the roots of *P. longiflora* is used as a folk remedy (Rwanda) to treat pityriasis versicolor, a fungal infection disease of the skin.[2] In a bioassay-guided phytochemical study of the roots, pentalongin was identified as the physiologically active compound, responsible for the antimycotic activity of the dry plant material.[2] Pentalongin was obtained before by acid-catalysed dehydration of psychorubrin (**2**), another naturally occurring pyranonaphthoquinone with significant antitumor activity, isolated from *Psychotria rubra*.[3]

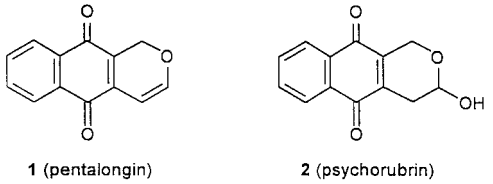
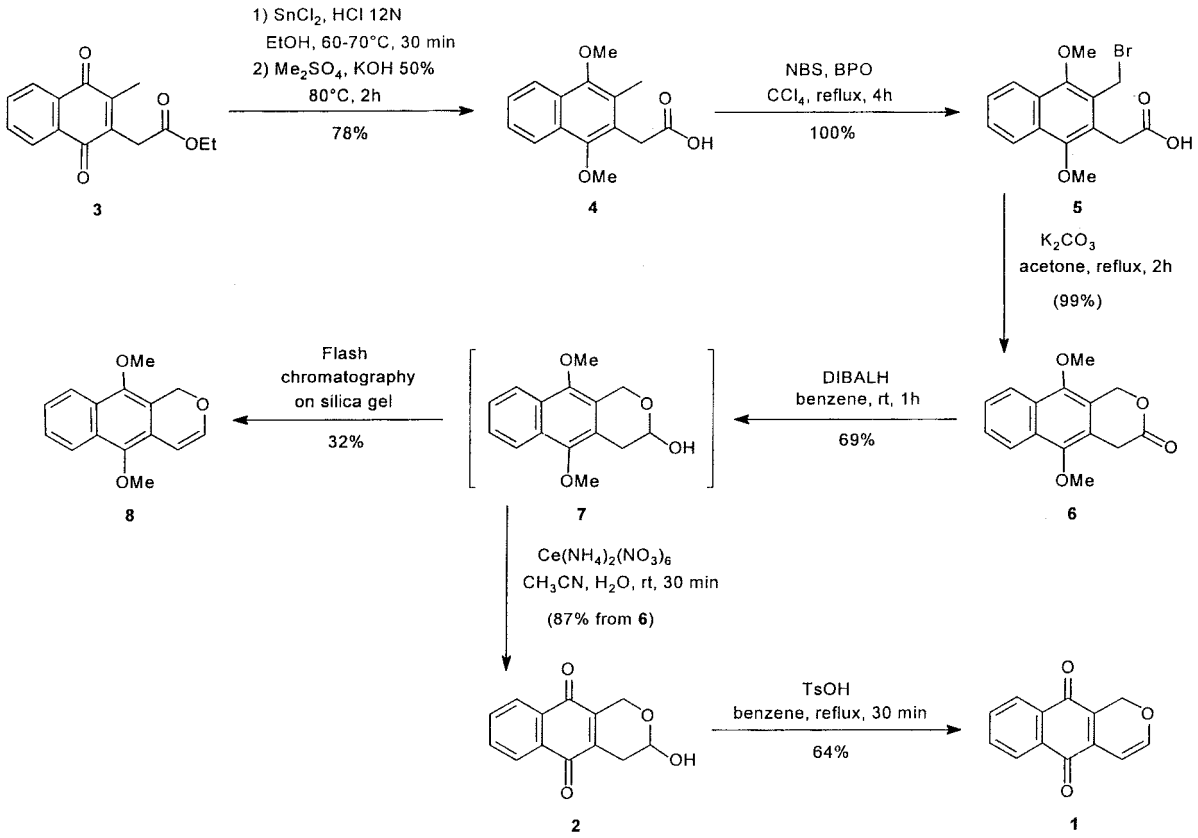


Figure 1

Pentalongin (**1**) and psychorubrin (**2**) are both so-called pyranonaphthoquinone antibiotics. This particular group of microbial and plant metabolites with a characteristic 1H-naphtho[2,3-*c*]pyran-5,10-dione nucleus which includes examples such as nanaomycin A,[4] frenolycin B[5] and eleutherin,[6] is known to possess a variety of physiological activities. Several synthetic efforts have been made toward their synthesis.[7] Never before has much attention been paid to the synthesis of those pyranonaphthoquinones, such as pentalongin, having a double bond in the pyran ring.[8] In a previous paper we already described a strategy that allows the introduction of this C(3)-C(4) double bond in the pyranonaphthoquinone ring-system.[9] Unfortunately, this methodology allowed pentalongin only to be obtained in an overall yield of 14%.[9] Therefore, in this paper, we present the total synthesis of pentalongin (**1**) as well as its closely related pyranonaphthoquinone antibiotic psychorubrin (**2**), using a new, improved and straightforward synthetic approach.

The synthesis of pentalongin (**1**) and psychorubrin (**2**) is presented in Scheme 1, using ethyl 3-methyl-1,4-dioxo-2-naphthylacetate (**3**)[10] as starting material. Reduction of the naphthoquinone ester **3** with tin(II) chloride in concentrated hydrochloric acid and subsequent methylation of the intermediate hydroquinone ester with dimethyl sulfate in the presence of excess potassium hydroxide gave the naphthylacetic acid (**4**) in 78% yield. Upon treatment of the acid **4** with *N*-bromosuccinimide (NBS) and a catalytic amount of benzoyl peroxide in carbon tetrachloride, radical bromination occurred selectively and quantitatively at the methyl group. The bromomethylnaphthylacetic acid (**5**) thus obtained, was then cyclised to lactone **6** in virtually quantitative yield using potassium carbonate in acetone under reflux. Partial reduction of lactone **6** using 1 equivalent of diisobutylaluminium hydride in benzene gave the hemi-acetal **7** which was found to spontaneously eliminate water in anhydrous solvents such as chloroform. An attempted flash chromatography on silica gel using 5% ethyl acetate in hexane as eluent also led to the isolation of elimination product **8** as the sole product. Curiously, in an attempt to oxidize this naphthopyran **8** to pentalongin (**1**), using the common oxidizing agents cerium(IV) ammonium nitrate or silver(II) oxide, only complex reaction mixtures were obtained. Therefore, in an alternative approach, pentalongin (**1**) was synthesized by oxidation of the crude lactol **7** and subsequent acid catalyzed elimination of water. Thus, psychorubrin (**2**) was prepared by treatment of the crude lactol **7** with cerium(IV) ammonium nitrate in aqueous acetonitrile, in an overall yield of 87% from lactone **6**. Dehydration of psychorubrin (**2**) with *p*-toluenesulfonic acid in benzene under reflux gave pentalongin (**1**) in a yield of 64% after flash chromatography. After recrystallisation from methanol, pentalongin (**1**) was obtained as red needles with physical and spectral data in complete accordance with those reported for the natural product.[1,2] In this way, pentalongin (**1**) was synthesized in an overall yield of 43% from ethyl 3-methyl-1,4-dioxo-2-naphthylacetate (**3**).

^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were run with a Jeol JNM-EX 270 NMR spectro-meter. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra and HETCOR spectra. IR spectra were obtained from a Perkin Elmer model 1310 spectrophotometer while mass spectra were measured with a Varian MAT 112 spectrometer (70 eV). Melting points were measured with a Büchi 535 apparatus. Flash chromatography was carried out using a glass column with



Scheme 1

Acros silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm).

1,4-Dimethoxy-3-methyl-2-naphthylacetic Acid (4)

To a solution of ethyl 3-methyl-1,4-dioxo-2-naphthylacetate (**3**)[10] (40 mmol, 10.3 g) in 95% EtOH (200 mL) was added dropwise a solution of $SnCl_2$ (140 mmol, 26.6 g) in concentrated HCl (25 mL). Stirring was continued for 0.5 h and the reaction mixture was concentrated in vacuo until most of the EtOH was evaporated. Upon the addition of cold H_2O (500 mL) to the resulting mixture, a white solid precipitated and after 30 min the precipitate was isolated by filtration and mixed together with dimethyl sulfate (800 mmol, 100.8 g). Then a solution of KOH (1.6 mol, 89.6 g) in H_2O (200 mL) was added at 0 °C over a period of 1 h. Stirring was continued for 2 h at 70–80 °C and then the mixture was poured in ice-water (800 mL). The aqueous solution was acidified with concentrated HCl until precipitation of the naphthylacetic acid derivative was completed. The precipitate was obtained by filtration and dissolved in acetone (150 mL), dried ($MgSO_4$) and evaporated in vacuo to give 1,4-dimethoxy-3-methyl-2-naphthylacetic acid (**4**) (8.12 g, 78%). The crude product (purity about 98%) was used without further purification in the next step. An analytical sample was purified by means of flash chromatography on silica gel with 2% MeOH in $CHCl_3$ as eluent, mp 124–125 °C.

IR (KBr): ν_{max} = 1695 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.37 (3H, s, CH_3), 3.87 (3H, s, MeO), 3.91 (3H, s, MeO), 3.95 (2H, s, CH_2), 7.46–7.50 (2H, m, H-6 and H-7), 8.01–8.08 (2H, m, H-5 and H-8), 10.8 (1H, broad s, COOH).

^{13}C NMR ($CDCl_3$): δ = 12.70 (CH_3), 32.72 (CH_2), 61.47 (MeO), 62.35 (MeO), 122.32 and 122.46 (=CH-5 and =CH-8), 123.25 (=C_{quat}), 125.62 and 126.22 (=CH-6 and =CH-7), 126.47 (=C_{quat}), 126.97 (=C_{quat}), 128.46 (=C_{quat}), 150.26 (=C-OMe), 150.82 (=C-OMe), 177.25 (C=O).

EIMS *m/z* (%): 260 (M^+, 100), 245(18), 213(30), 201(48), 199(13), 185(22), 157(22), 141(11), 129(12), 128(18), 115(12).

Anal. calcd. for $C_{15}H_{16}O_4$: C 69.22%, H 6.20%, found C 69.20%, H 6.05%.

3-Bromomethyl-1,4-dimethoxy-2-naphthylacetic Acid (5)

A stirred mixture of 1,4-dimethoxy-3-methyl-2-naphthylacetic acid (**4**) (8 mmol, 2.08 g), NBS (8.4 mmol, 1.5 g) and benzoyl peroxide (0.8 mmol, 0.2 g) in CCl_4 (100 mL) was heated under reflux for 2 h. The mixture was allowed to cool to r.t. and, after filtration of succinimide and evaporation of the solvent in vacuo, 3-bromomethyl-1,4-dimethoxy-2-naphthylacetic acid (**5**) (2.7 g, 100%) was obtained as an orange solid, mp 133–134 °C. This compound was used as such in the next reaction step (purity > 96%).

IR (KBr) ν_{max} = 2900 (OH), 1700 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.93 (3H, s, MeO), 4.06 (3H, s, MeO), 4.13 (2H, s, CH_2-COOH), 4.84 (2H, s, CH_2Br), 7.50–7.57 (2H, m, H-6 and H-7), 8.02–8.10 (2H, m, H-5 and H-8), 11.20 (1H, br s, COOH).

^{13}C NMR ($CDCl_3$): δ = 26.80 (CH_2COOH), 31.72 (CH_2Br), 62.30 (MeO), 62.53 (MeO), 122.23 (=C_{quat}), 122.71 and 123.05 (=CH-5 and =CH-8), 126.18 (=C_{quat}), 126.65 and 127.11 (=CH-6 and =CH-7), 128.23 (=C_{quat}), 128.82 (=C_{quat}), 151.55 (=C-OMe), 151.71 (=C-OMe), 177.55 (C=O).

EIMS *m/z* (%): 338/40 (M^+, 12), 259 (100), 258 (44), 243(11), 231(38), 215(17), 214(12), 213(29), 201(40), 200(28), 199(47), 186(38), 185(23), 183(18), 171(21), 163(16), 157(19), 143(17), 141(34), 139(21), 129(17), 128(43), 127(23), 115(39), 105(21), 104(16), 82(15), 80(16), 77(29), 76(31), 51(22), 43(19).

Anal. Calcd. for $C_{15}H_{15}BrO_4$: C 53.12%, H 4.46%; found C 53.37%, H 4.34%.

3,4-Dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-one (6)

To a solution of 3-bromomethyl-1,4-dimethoxy-2-naphthylacetic acid (**5**) (2 mmol, 0.68 g) in acetone (50 mL) was added K_2CO_3 (10 mmol, 1.38 g) and the mixture was heated under reflux for 2 h. Then the precipitate was removed by filtration and evaporation of the filtrate in vacuo gave pure 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-one (**6**) (0.51 g, 99%). An analytical sample was obtained after recrystallization from MeOH, mp 126 °C.

IR (KBr): ν_{max} = 1745 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.90 (2H, s, CH_2C=O), 3.92 (3H, s, MeO), 3.93 (3H, s, MeO), 5.53 (2H, s, CH_2O), 7.54–7.58 (2H, m, H-7 and H-8), 8.08–8.12 (2H, m, H-6 and H-9).

^{13}C NMR ($CDCl_3$): δ = 30.80 (CH_2C=O), 62.43 (MeO), 63.02 (MeO), 65.28 (CH_2O), 119.55 (=C_{quat}), 120.57 (=C_{quat}), 122.39 and 122.57 (=CH-6 and =CH-9), 126.63 and 126.92 (=CH-7 and =CH-8), 127.78 (=C_{quat}), 128.89 (=C_{quat}), 148.23 (=C-OMe), 148.91 (=C-OMe), 170.51 (C=O).

EIMS m/z (%):258(M^+, 100), 243(18), 215(15), 199(26), 171(11), 141(12), 128(17), 115(16).

Anal. calcd. for $C_{15}H_{14}O_4$: C 69.76%, H 5.46%; found C 69.52%, H 5.36%.

3,4-Dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-ol (7) and 5,10-Dimethoxy-1*H*-naphtho[2,3-*c*]pyran (8)

Under N_2, a solution of 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-one (**6**) (0.39 mmol, 100 mg) in benzene (5 mL), was treated with a solution of 1 M DIBALH in hexane (0.47 mmol, 0.47 mL) and after stirring for 1 h the mixture was poured in 2 M HCl. The organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-ol (**7**) (70 mg, 69%) together with traces of the elimination product **8**.

IR (NaCl): ν_{max} = 3390 (OH), 1590, 1450, 1355, 1265, 1068 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 2.97 (1H, dd, *J* = 16.8 Hz, 5.3 Hz, ArCH_aH_b), 3.29 (1H, dd, *J* = 16.8 Hz, 4.0 Hz, ArCH_aH_b), 3.89 (3H, s, MeO), 3.90 (3H, s, MeO), 4.99 and 5.19 (each 1H, each d, *J* = 15.5 Hz, CH_2-O), 5.42 (1H, dd, *J* = 5.3 Hz, 4.0 Hz, CH-OH), 7.45-7.51 (2H, m, H-7 and H-8), 8.01-8.08 (2H, m, H-6 and H-9).

This compound was found to eliminate H_2O rapidly when dissolved in anhyd solvents ($CDCl_3$). Flash chromatography of the crude lactol **7** on silica gel with 5% EtOAc in hexane as eluent gave 5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran (**8**) (30 mg, 32%) as an oil.

^{1}H NMR ($CDCl_3$): δ = 3.89 (3H, s, MeO), 3.90 (3H, s, MeO), 5.29 (2H, s, CH_2O), 6.19 (1H, d, *J* = 5.9 Hz, CH = CH-O), 6.70 (1H, d, *J* = 5.9 Hz, CH = CH-O), 7.41-7.51 (2H, m, H-7 and H-8), 8.00–8.06 (2H, m, H-6 and H-9).

^{13}C NMR ($CDCl_3$): δ = 62.17 (MeO), 63.25 (MeO), 99.98 (CH=CH-O), 119.15 (=C_{quat}), 119.50 (=C_{quat}), 122.28 and 122.32 (=CH-6 and =CH-9), 125.44 and 126.31 (=CH-7 and =CH-8), 128.08 (=C_{quat}), 128.84 (=C_{quat}), 144.74 (=C-OMe), 146.57 (=C-OMe), 146.99 (CH=CH-O).

EIMS *m/z* (%): 242 (M^+, 67), 228(16), 227(100), 212(48), 184(11), 139(11), 128(17).

Anal. calcd. for $C_{15}H_{14}O_3$: C 74.36%, H 5.82%; found C 73.98%, H 5.72%.

Psychorubrin (2)

Under N_2, a solution of 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-one (**6**) (1.7 mmol, 430 mg) in benzene (10 mL), was treated with a solution of 1 M DIBALH in hexane (2 mmol, 2 mL). After stirring for 1 h, the mixture was poured in 4 M HCl. The organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic extracts were washed with aq $NaHCO_3$, evaporated in vacuo and dissolved again in MeCN (10 mL). Then, a solution of $Ce(NH_4)_2(NO_3)_6$ (5.1 mmol, 2.76 g) in water (10 mL) was added at 0 °C and the reaction was allowed to warm to r.t. for 30 min. The mixture was poured in H_2O, extracted with EtOAc, washed with brine, dried and evaporated in vacuo. Flash chromatography on silica gel with EtOAc/hexane 1:1 as eluent gave psychorubrin (**2**) (340 mg, 87%) as a pale yellow solid, mp 149 °C (lit.,[3] mp 150–152 °C).

Pentalongin (1)

A solution of psychorubrin (**2**) (330 mg, 1.4 mmol) in benzene (20 mL) was heated under reflux for 30 min with a catalytic amount of *p*-HOTs. The mixture was cooled to r.t., dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography (eluent 10% EtOAc in hexane) afforded pentalongin (**1**) (190 mg, 64%) as a red powder, mp 160–161 °C (MeOH) (lit.,[1] mp 160–161 °C).

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