SYNTHESES OF CORIOLIN, 1-DEOXY-1-KETOCORIOLIN AND 1,8-DIDEOXY-1,8-DIKETOCORIOLIN FROM CORIOLIN B*

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Hydrolysis of 5,8-di-O-tetrahydropyranyl-5-deoxo-5-hydroxycoriolin which was prepared from coriolin B, followed by oxidation of the hydroxy groups at C-5, or C-1 and C-5, or C-1, C-5 and C-8 afforded coriolin (2), 1-deoxy-1-ketocoriolin (3) and 1,8-dideoxy-1,8-diketocoriolin (4). All three ketones were found to have antitumor activity, whereas antibacterial activity was observed in 2 and 3 but not in 4.

Coriolins\(^1\) are tricyclic sesquiterpenoid antitumor antibiotics produced by Coriolus consors. As reported previously\(^2\) 5-keto-8\(\alpha\)-methylcoriolin B, 8-deoxy-5-keto-8\(\beta\)-methylcoriolin B and 5-keto-8-methylene coriolin B which were chemically derived from coriolin B were found to be more stable in alkaline and acidic media than diketocoriolin B and to show antitumor and antibacterial activities similar to the latter. We have also reported previously\(^3\) the syntheses of a number of 1-O-acyl and alkyl analogs of diketocoriolin B which all showed antitumor and antibacterial actions.

As reported previously, coriolin\(^1\) which lacks the fatty acid moiety exhibits antitumor and antibacterial activity similar to that of diketocoriolin B\(^3\). Since a sufficient amount of coriolin was not obtained by fermentation, we had to develop a chemical method to prepare coriolin from coriolin B which was easily obtained by fermentation. In the present paper, we report on the syntheses of coriolin and its analogs from 5,8-di-O-tetrahydropyranyl-5-deoxo-5-hydroxycoriolin\(^3\) which is easily prepared in three steps from coriolin B.

5,8-di-O-tetrahydropyranyl-5-deoxo-5-hydroxycoriolin\(^3\) was hydrolyzed with acetic acid to give 5-deoxo-5-hydroxycoriolin (1) in 68\% yield. Selective oxidation of 1 with anhydrous chromic acid in pyridine gave coriolin (2) in 40\% yield. Oxidation of coriolin (2) with anhydrous chromic acid in acetic acid gave a mixture of 1-deoxy-1-ketocoriolin (3) and 1,8-dideoxy-1,8-diketocoriolin (4) in 36\% and 31\% yield respectively.

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Antibacterial activities of coriolin (2), 1-deoxy-1-ketocoriolin (3) and 1,8-dideoxy-1,8-diketo-coriolin (4) were tested by the agar streak method and the results are shown in Table 1. Antitumor activity was tested by the methods previously described and the results are shown in Table 2.

Experimental

Infrared spectra (IR) were recorded with a HITACHI Grating Infrared Spectrophotometer 285. Nuclear magnetic resonance (nmr) spectra were recorded with a Varian S-100XL spectrometer. Tetra-
methylsilane was used as the internal standard. Thin-layer chromatography (tlc) was performed on silica gel and the spots were visualized with sulfuric acid.

5-Deoxo-5-hydroxycoriolin (1):
A solution of 5,8-di-O-tetrahydropyranyl-5-deoxo-5-hydroxycoriolin (280 mg) in 70% acetic acid (6 ml) was allowed to stand for 4 hours at room temperature. On tlc with benzene-acetone (2:1), the starting material of Rf 0.82 disappeared and the products of Rf 0.80 and 0.33 appeared. The solution was evaporated to give a colorless solid (170 mg). Recrystallization from a mixture of ethanol - ether (5:1) gave colorless crystals of 5-deoxo-5-hydroxycoriolin (1), 120 mg (68%): mp 196~197°C (brown melt); [a]D 71° (c 1.5, acetone); IR (KBr) 3400, 2950, 2900, 1480, 1460, 1400, 1370, 1340, 1310, 1295, 1290, 1260, 1220, 1200, 1145, 1120, 1095, 1090, 1035, 1000, 970, 965, 920, 885, 865, 850, 815, 775, 755, 715, 670, 625, 615, 550, 525, 460 cm⁻¹; nmr (Py-d5 containing a small amount of D2O) δ 1.20 (6H s., CH3), 1.53 (3H s., CH3), 1.0-3.4 (4H m., C2-H, C6-H, C10-H and C10'-H), 2.88 and 3.15 (2H ABq., JAB 6 Hz, an exocyclic ethyleneoxide), 3.82 (1H d., J6,0 2 Hz, C6-H), 4.10 (1H d., J1,2 8 Hz, C1-H), 4.21 (1H d., J8,0 6 Hz, C8-H).

Anal. Calcd. for C15H22O5: C 63.81; H 7.85
Found: C 63.53; H 7.68%

Coriolin (2):
To a solution of 5-deoxo-5-hydroxycoriolin (1, 1.67 g) in dry pyridine (25 ml) was added dropwise a solution of anhydrous chromic acid (1.61 g) in dry pyridine (18 ml) at room temperature over 1.5 hours, and the mixture was stirred for 3 hours. Anhydrous chromic acid (850 mg) was further added and the reaction was continued for another 2 hours. On tlc with benzene - acetone (3:1), the mixture showed 2 spots of Rf 0.17 (the starting material) and 0.51. The mixture was poured into cold water (400 ml), and the aqueous layer was extracted with six 200 ml portions of ethyl acetate. The ethyl acetate extracts were combined, washed with water, dried (Na2SO4) and evaporated. The resulting syrup (1.19 g) was chromatographed on a column (26 x 360 mm) of silica gel (Wako Gel, 95 g) with benzene - acetone (5:1), and the fraction of 340~470 ml containing the product was evaporated to give a colorless solid of 2 (700 mg). Recrystallization from n-hexane gave colorless needles of 2 (658 mg, 40%); mp 167~168°C; [a]D 71° (c 1.0, chloroform); IR (KBr) 3450, 3400, 3010, 2970, 2950, 2880, 1755 (ketone), 1600, 1470, 1390, 1370, 1345, 1330, 1290, 1280, 1250, 1220, 1180, 1140, 1100, 1050, 1040, 1020, 970, 940, 930, 910, 900, 890, 850, 830, 820, 790, 760, 730, 665, 620 cm⁻¹; nmr (CDCl3) δ 0.93, 1.09 and 1.22 (3H s. each, CH3), 1.86 (1H q., J9,10 11 Hz, and J10,10' 13 Hz, C10'-H), 2.38 (1H q., J9,10 10 Hz, and J10,10' 13 Hz, C10-H), 2.97 and 3.13 (2H ABq., JAB 7 Hz, an exocyclic ethyleneoxide), 3.56 (1H s., CO-H), 3.75 (1H d., J3,10 9 Hz, C3-H) and 4.03 (1H d., J8,9 6 Hz, C8-H).

Anal. Calcd. for C15H22O5: C 64.27; H 7.19
Found: C 64.05; H 6.94%

1-Deoxy-1-ketocoriolin (3) and 1,8-dideoxy-1,8-diketocoriolin (4):
To a solution of coriolin (600 mg) in dry acetone (18 ml) cooled at −20°C, a solution of anhydrous chromic acid (347 mg) in glacial acetic acid (5.4 ml) was added, and the mixture was stirred for 17 hours at −20°C. On tlc with benzene - acetone (5:1), the mixture showed three spots of Rf 0.27 (the starting material), 0.32 (3) and 0.46 (4). The mixture was poured into cold water (100 ml), and the aqueous layer was extracted with five 150 ml portions of ethyl acetate. The ethyl acetate extracts were combined, washed with water, dried (Na2SO4) and evaporated to give a dark green syrup (800 mg). The syrup was chromatographed on a column (16 x 740 mm) of silica gel (Wako Gel, 360 g) with benzene - acetone (5:1) and the fractions of 700~1,040 ml and 1,070~1,300 ml were evaporated to give colorless solids of 4 (184 mg, 31%) and 3 (212 mg, 36%), respectively. Each solid was crystallized from n-hexane to give colorless crystals.

3: mp 135~136°C; [a]D 72° (c 0.98, acetone); IR (KBr) 3500, 2970, 2940, 2880, 1760 and 1735 (ketone), 1470, 1390, 1370, 1300, 1225, 1200, 1180, 1160, 1120, 1090, 1040, 1010, 970, 940, 920, 890, 860, 820, 790, 770, 730, 680 cm⁻¹; nmr (CDCl3) δ 1.03, 1.10 and 1.15 (3H s. each, CH3), 1.88 (1H q. with a very small additional coupling, J9,10 9 Hz, and J10,10' 13 Hz, C10'-H), 2.38 (1H q., J9,10 11 Hz
and J_{10,10'} 13 Hz, C_{10'-H}), 2.82 (1H d. with a very small additional coupling, J_{2,9} 11 Hz, C_{2'-H}), 3.0~
3.5 (1H m., C_{9}-H), 3.15 and 3.33 (2H ABq., J_{AB} 7 Hz, an exocyclic ethyleneoxide), 3.68 (1H s., C_{6}-
H) and 4.45 (1H d., J_{8,9} 8 Hz, C_{6}-H).

Anal. Calcd. for C_{15}H_{18}O_{5}: C 64.73; H 6.52
Found: C 64.89; H 6.67%

4: mp 128~129°C; [\alpha]_{D}^{25} = -89.5° (c 0.58, acetone); IR (KBr) 2980, 2940, 2880, 1770 and 1740
(ketone), 1620, 1470, 1460, 1390, 1370, 1285, 1230, 1135, 1110, 1090, 1010, 940, 900, 865, 740, 680,
640 cm^{-1}; nmr (CDCl_{3}) δ 0.97, 1.09 and 1.15 (3H s. each, CH_{3}), 1.84 (1H q., J_{9,10} 11 Hz and J_{10,10'}
13 Hz, C_{10'-H}), 2.42 (1H q. with a very small coupling, J_{8,10'} 9 Hz and J_{10,10'} 13 Hz, C_{10}-H), 3.22 and
3.42 (2H ABq., J_{AB} 7 Hz, an exocyclic ethyleneoxide) and 3.88 (1H s., C_{6}-H).

Anal. Calcd. for C_{15}H_{16}O_{5}: C 65.21; H 5.84
Found: C 65.16; H 5.92%

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