CHEMICAL MODIFICATION OF THE ESTER GROUP OF DIKETOCORIOLIN B*

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5,8-Di-O-tetrahydropyranylcoriolin B (**2**) was synthesized and its two epoxide groups were found to be resistant to alkaline hydrolysis to give di-O-tetrahydropyranyldihydrocoriolin (**3**). Acylation or alkylation of the free hydroxyl group at C-1 of **3** followed by hydrolysis of the tetrahydropyranylether groups and oxidation of the hydroxyl groups at C-5 and C-8 afforded a number of 1-O-acyl or alkyl analogs of diketocoriolin B. All of them showed antibacterial and antitumor activities.

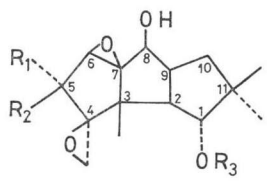
Coriolins[1] are a group of sesquiterpene antitumor antibiotics produced by *Coriolus consors*. As reported previously[2], 5-keto-8α-methylcoriolin B, 8-deoxy-5-keto-8β-methylcoriolin B and 5-keto-8-methylenecoriolin B which can be chemically derived from coriolin B have been found to be more stable in alkaline and acidic media than diketocoriolin B[3] and to show similar antitumor and antibacterial activities to the latter.

Among known coriolins, 5-ketocoriolin B and coriolin C have different ester groups[4,5] at C-1, while the hydroxyl group of coriolin is free. These coriolins are different in biological activity, suggesting a possible role of the acyl group in their activities. Therefore, we undertook to study variation in the nature of the substituent at C-1. We have successfully developed a method for removal of the C-1 octanoyl group of coriolin B without breaking its two epoxide groups which are essential for the biological activities. We have found that 5,8-di-O-tetrahydropyranylation of coriolin B makes the neighbouring epoxides resistant to alkaline hydrolysis. The present paper deals with the preparation of 5,8-di-O-tetrahydropyranyldihydrocoriolin (**3**) and syntheses of a number of 1-O-acyl and 1-O-alkyl derivatives of diketocoriolin B.

Synthesis

The two hydroxyl groups of coriolin B (**1**) were protected as tetrahydropyranyl ethers to give 5,8-di-O-tetrahydropyranylcoriolin B (**2**) in 91% yield. Hydrolysis of the ester group at C-1 without breaking the epoxide groups was successfully effected with 0.08 N sodium methoxide in anhydrous methanol at room tem-

Fig. 1.



Coriolin : $R_1,R_2=O,R_3=H$
Coriolin B: $R_1=H,R_2=OH,R_3=CO(CH_2)_6CH_3$
Coriolin C: $R_1,R_2=O,R_3=COCH(OH)(CH_2)_5CH_3$

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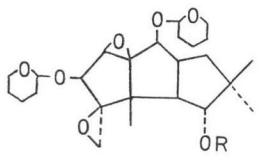
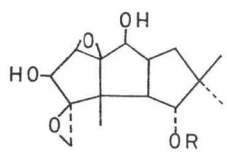
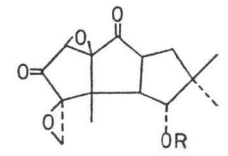
Fig. 2.



4a: R=$COCH_3$
5a: R=$COCH_2CH_3$
6a: R=$CO(CH_2)_4CH_3$
7a: R=$CO(CH_2)_5CH_3$
8a: R=$CO(CH_2)_{13}CH_3$
9a: R=COC_6H_5
10a: R=$COCH_2CH{=}CH_2$
11a: R=$COCH{=}CH(CH_2)_4CH_3$
12a: R=$COCH{=}CH(CH_2)_5CH_3$
13a: R=$COCH{=}CH(CH_2)_{12}CH_3$
14a: R=$COCH(CH_3)_2$
15a: R=$COCH(CH_3)CH_2CH_3$
16a: R=$COCH(CH_3)CH_2CH_2CH_3$
17a: R=CH_3
18a: R=$(CH_2)_3CH_3$
19a: R=$(CH_2)_7CH_3$



4b: R=$COCH_3$
5b: R=$COCH_2CH_3$
6b: R=$CO(CH_2)_4CH_3$
7b: R=$CO(CH_2)_5CH_3$
8b: R=$CO(CH_2)_{13}CH_3$
9b: R=COC_6H_5
10b: R=$COCH_2CH{=}CH_2$
11b: R=$COCH{=}CH(CH_2)_4CH_3$
12b: R=$COCH{=}CH(CH_2)_5CH_3$
13b: R=$COCH{=}CH(CH_2)_{12}CH_3$
14b: R=$COCH(CH_3)_2$
15b: R=$COCH(CH_3)CH_2CH_3$
16b: R=$COCH(CH_3)CH_2CH_2CH_3$
17b: R=CH_3
18b: R=$(CH_2)_3CH_3$
19b: R=$(CH_2)_7CH_3$



4c: R=$COCH_3$
5c: R=$COCH_2CH_3$
6c: R=$CO(CH_2)_4CH_3$
DKCB: R=$CO(CH_2)_6CH_3$
7c: R=$CO(CH_2)_5CH_3$
8c: R=$CO(CH_2)_{13}CH_3$
9c: R=COC_6H_5
10c: R=$COCH_2CH{=}CH_2$
11c: R=$COCH{=}CH(CH_2)_4CH_3$
12c: R=$COCH{=}CH(CH_2)_5CH_3$
13c: R=$COCH{=}CH(CH_2)_{12}CH_3$
14c: R=$COCH(CH_3)_2$
15c: R=$COCH(CH_3)CH_2CH_3$
16c: R=$COCH(CH_3)CH_2CH_2CH_3$
17c: R=CH_3
18c: R=$(CH_2)_3CH_3$
19c: R=$(CH_2)_7CH_3$

perature to give 5,8-di-O-tetrahydropyranyldihydrocoriolin (**3**) in 35% yield. Treatment of **3** with acid anhydrides in pyridine (method A) or with acids in the presence of dicyclohexylcarbodiimide in dichloromethane and pyridine (method B) gave acyl derivatives (**4a**~**16a**) of 5,8-di-O-tetrahydropyranyldihydrocoriolin (**3**) in excellent yields.

Treatment of **3** with alkyl halides in the presence of sodium hydride in dimethylformamide gave alkyl derivatives (**17a**~**19a**) of **3** in good yield.

Treatment of each 1-O-acyl or 1-O-alkyl derivative of **3** with 70% aqueous acetic acid removed the tetrahydropyranyl groups and gave the corresponding 1-O-acyl or 1-O-alkyl derivative of dihydrocoriolin (**4b**~**19b**), which were subsequently converted into their 5,8-diketo derivatives (**4c**~**19c**) by oxidation with anhydrous chromic acid in acetic acid.

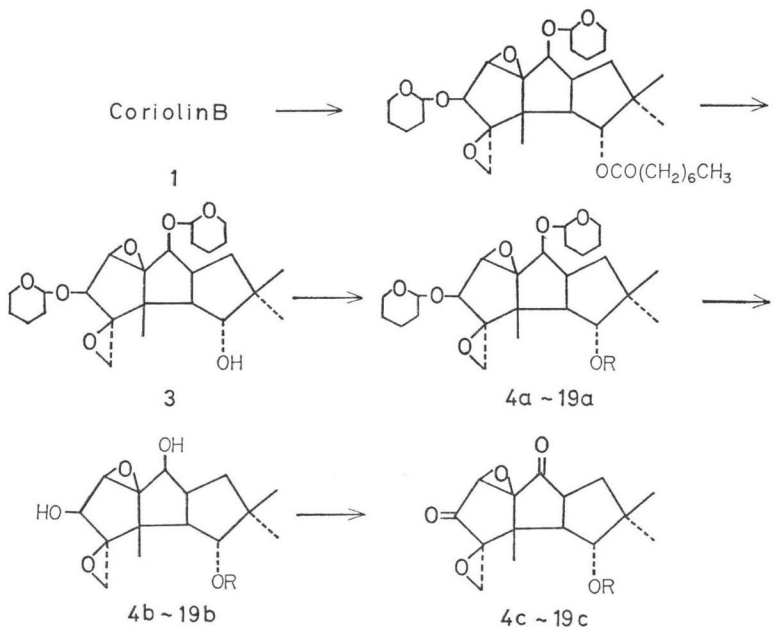
Antibacterial and Antitumor Activity

The antibacterial activity of acyl and alkyl derivatives of 8-ketocoriolin was tested by the agar streak method and the results are shown in Table 1.

In the 1-ester series, the saturated ester **7c** (R=$CO(CH_2)_5CH_3$) and diketocoriolin B itself (R=$CO(CH_2)_6CH_3$) showed the highest antibacterial activity. The α,β-unsaturated ester **11c** (R=$COCH{=}CH(CH_2)_4CH_3$) showed a lower activity than the corresponding saturated ester (diketocoriolin B). The straight-chain ester **6c** (R=$CO(CH_2)_4CH_3$) showed an activity similar to the α-methyl analog **16c** (R=$COCH(CH_3)CH_2CH_2CH_3$). The alkyl derivative **19c** (R=$(CH_2)_7CH_3$) showed an activity similar to diketocoriolin B.

Antitumor activity was tested by the method previously described[6] and the results are shown in Table 2. The saturated esters, **7c**, **8c** (R=$CO(CH_2)_{13}CH_3$), diketocoriolin B and the α,β-unsaturated

Fig. 3.



ester **11c** were most active. The α-methylvaleryl ester, **16c**, showed an activity lower than the straight-chain ester, **6c**. The activity of the alkyl derivative **19c** was lower than that of diketocoriolin B.

Experimental

5,8-Di-O-tetrahydropyranylcoriolin B (**2**)

To a solution of coriolin B (**1**) (5 g) in anhydrous dioxane (100 ml) was added fused-dried *p*-toluenesulfonic acid (210 mg) and 2,3-dihydropyran (6 ml), and the reaction mixture was stirred for 1 hour at room temperature. On TLC with benzene - acetone (7: 1), the mixture showed 4 spots of Rf 0.68 (**2**, major), 0.42 (minor), 0.36 (minor) and 0.14 (**1**, minor). The reaction mixture was poured into 1% sodium bicarbonate solution, and the resulting syrup was separated. The syrup was dissolved in chloroform (800 ml), and the solution was washed with 2 portions of water (50 ml), dried (Na_2SO_4), filtered, and the filtrate was evaporated to give a syrup (7.1 g). The syrup was chromatographed on a column (45×350 mm) of silica gel (Wako Gel, 300 g) with benzene - acetone (7: 1), and the fraction of 350~580 ml containing the product of Rf 0.68 was evaporated to give a syrup of **2**, 6.38 g (91%): $[\alpha]_D^{20}$ +1.0° (*c* 1.5, $CHCl_3$); IR (KBr) 2925, 2870, 1730 (ester), 1460, 1435, 1385, 1370, 1350, 1340, 1320, 1280, 1255, 1200, 1175, 1150, 1125, 1110, 1075, 1030, 1020, 980, 940, 900, 865, 810, 750, 660, 630, 550 cm^{-1}; NMR (60 MHz, in $CDCl_3$) δ 0.88 (3H t., J 6 Hz, CH_3), 0.97 (3H s., CH_3), 1.03 (6H s., CH_3), 5.0~2.0 (39H m., 18H of THP, C_2-H, C_5-H, $CO(CH_2)_6$-, C_6-H, C_8-H, C_9-H, C_{10}-H, $C_{10'}$-H, and an exocyclic ethyleneoxide), 5.10 (1H d., $J_{1,2}$ 8 Hz, C_1-H).

Anal. Calcd. for $C_{33}H_{52}O_8$: C 68.72; H 9.09%
Found: C 68.34; H 9.11%

5,8-Di-O-tetrahydropyranyldihydrocoriolin (**3**)

To a solution of **2** (5.7 g) in anhydrous methanol (130 ml), 2 N sodium methoxide in methanol (5.8 ml) was added, and the mixture was allowed to stand at room temperature for 6 days. On silica gel TLC with benzene - acetone (7: 1), the mixture showed 3 spots of Rf 0.62 (starting material), 0.30 and 0.23 (**3**). The mixture was neutralized with Dowex 50W ×8 (H^+) to pH 7 and filtered, and the

Table 1. Antibacterial activities of coriolin derivatives.

Test organisms	Minimal inhibitory concentration mcg/ml																
	4c	5c	6c	DKCB	7c	8c	9c	10c	11c	12c	13c	14c	15c	16c	17c	18c	19c
Staphylococcus aureus FDA 209P	>100	100	50	12.5	12.5	100	100	>100	25	50	100	100	100	50	100	100	12.5
Staphylococcus aureus Terajima	>100	100	50	12.5	50	>50	100	>100	12.5	100	>50	100	100	50	>100	100	25
Staphylococcus aureus Smith	100	50	50	12.5	25	>50	50	100	25	50	>50	50	50	50	50	100	12.5
Bacillus subtilis NRRL B-558	>100	>100	50	25	12.5	100	100	>100	25	50	100	100	100	50	100	100	12.5
Bacillus subtilis anthracis	100	50	25	12.5	6.25	50	12.5	50	6.25	50	>50	25	25	25	50	50	6.25
Sarcina lutea PCI 1001	>100	100	50	12.5	6.25	>50	100	100	25	50	>50	100	100	50	100	100	25
Micrococcus flavus FDA 16	100	50	25	12.5	50	>50	25	>100	25	50	>50	25	25	25	100	50	12.5

Nutrient agar, 37°C, 17 hours.

Table 2. Activity of coriolin derivatives prolonging the survival period of mice inoculated with L-1210.

Dose mcg/mouse/day×10	Anti-L-1210 (T/C[a])×100)																
	4c	5c	6c	DKCB	7c	8c	9c	10c	11c	12c	13c	14c	15c	16c	17c	18c	19c
200	TOX[b]	TOX	TOX	TOX	—	—	TOX	130	—	—	—	TOX	TOX	TOX	129	123	TOX
100	135	132	TOX	156	TOX	146	125	130	TOX	127	146	TOX	TOX	111	129	123	132
50	135	132	145	144	146	158	132	123	152	127	146	123	130	100	129	99	158
25	128	132	132	138	158	146	118	111	133	139	120	123	123	111	118	105	125
12.5	109	118	132	138	146	146	111	111	127	133	120	117	123	111	105	93	118
6.25	103	111	125	125	127	120	—	105	127	127	114	123	123	109	94	93	105
3.00	—	—	—	—	127	114	—	—	108	120	—	—	—	—	—	—	—

a) The T/C values are the percentage ratios of the mean survival of 5 treated mice to the mean survival of the control group. 10^6 L-1210 cells were inoculated peritoneally and the treatment was started on day 1 and continued for 10 days.

b) Mice were killed by toxicity of compound.

filtrate was evaporated to give a syrup (4.6 g). The syrup was chromatographed on a column (35×550 mm) of silica gel (Wako Gel, 250 g), and the fraction of 1,420~2,790 ml containing the product of Rf 0.23 was evaporated to give a syrup of **3**, 1.55 g (34%): $[\alpha]_D^{20}$ +86.8° (*c* 1.1, $CHCl_3$); IR (KBr) 3500, 2940, 2875, 2240, 1485, 1465, 1450, 1440, 1380, 1350, 1340, 1320, 1285, 1260, 1200, 1185, 1130, 1120, 1080, 1030, 1020, 990, 950, 910, 890, 870, 809, 770, 730, 680, 650, 630, 550, 460, 430 cm^{-1}; NMR (60 MHz, in $CDCl_3$) δ 0.94, 1.07 and 1.08 (3H s., each CH_3), 1.0~2.0 (14H m., 12H of THP, C_{10}-H and $C_{10'}$-H), 2.0~4.3 (12H m., 6H of THP, C_2-H, C_9-H, an exocyclic ethyleneoxide, C_1-H and OH), 4.42 (1H d., $J_{5,6}$ 2 Hz, C_6-H), 4.58 (1H d., $J_{5,6}$ 2 Hz, C_5-H) and 4.93 (1H d., $J_{8,9}$ 6 Hz, C_8-H).

Anal. Calcd. for $C_{25}H_{38}O_7$: C 66.64; H 8.50%
Found: C 66.30; H 8.36%

1-O-Acylation of **3**

The method A or the method B was used. The detail of the method A is described below for preparation of **4a** and the detail of the method B is described below for preparation of **8a**. Benzoylation was effected with benzoyl chloride in pyridine.

[1] Method A. 1-O-Acetyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**4a**): A solution of **3** (1 g) in anhydrous pyridine (20 ml) and acetic anhydride (4 ml) was allowed to stand at room temperature overnight. On TLC in benzene - acetone (7: 1), the starting material of Rf 0.23 disappeared and the product of Rf 0.61 appeared. The mixture was poured into 1% sodium bicarbonate solution, and the resulting syrup was dissolved in chloroform (200 ml). The solution was washed with water to pH 7, dried (Na_2SO_4), filtered, and the filtrate was evaporated to give a syrup of **4a**, 950 mg (89%): $[\alpha]_D^{20}$ +56° (*c* 1.74, CH_3COCH_3); IR (KBr) 1740 cm^{-1} (ester); NMR (60 MHz, in $CDCl_3$) δ 0.95, 1.01 and 1.16 (3H s., each CH_3), 1.2~2.0 (14H m., 12H of THP, C_{10}-H and $C_{10'}$-H), 2.03 (3H s., $COCH_3$), 2.1~4.3 (11H m., 6H of THP, C_2-H, C_8-H, C_9-H and an exocyclic ethyleneoxide), 3.57 (1H d., $J_{5,6}$ 2 Hz, C_6-H), 4.48 (1H q., $J_{5,6}$ 2 Hz, and J 10 Hz, C_5-H) and 5.04 (1H d., $J_{1,2}$ 9 Hz, C_1-H).

Anal. Calcd. for $C_{27}H_{40}O_8$: C 65.83; H 8.19%
Found: C 65.64; H 8.06%

1-O-Propionyl-5,8-di-O-teteahydropyranyldihydrocoriolin (**5a**)

A sample of **3** was acylated with propionic anhydride by method A, yielding **5a** (syrup, 93%): $[\alpha]_D^{20}$ +49° (*c* 1.2, $CHCl_3$); IR (KBr) 1740 (ester) cm^{-1}.

Anal. Calcd. for $C_{29}H_{42}O_8$: C 66.38; H 8.36%
Found: C 66.70; H 8.11%

1-O-Caproyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**6a**)

A sample of **3** was acylated with *n*-caproic anhydride by method A, yielding **6a**, (syrup, 90%): $[\alpha]_D^{20}$ +45.8° (*c* 1.1, $CHCl_3$); IR 1730 (ester) cm^{-1}.

Anal. Calcd. for $C_{31}H_{48}O_8$: C 67.85; H 8.82%
Found: C 67.68; H 8.82%

1-O-Capryl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**7a**)

A sample of **3** was acylated with *n*-capric anhydride by method A, yielding **7a** (syrup, 99%): $[\alpha]_D^{20}$ +31° (*c* 1.0, CH_3COCH_3); IR (KBr) 1730 cm^{-1}.

Anal. Calcd. for $C_{35}H_{56}O_8$: C 69.50; H 9.33%
Found: C 69.40; H 9.44%

1-O-Isobutyryl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**14a**)

A sample of **3** was acylated with isobutyric anhydride by method A, yielding **14a** (92%): $[\alpha]_D^{20}$ +54.7° (*c* 0.79, $CHCl_3$); IR (KBr) 1720 (ester) cm^{-1}.

Anal. Calcd. for $C_{29}H_{44}O_8$: C 66.90; H 8.52%
Found: C 66.70; H 8.35%

[2] Method B. 1-O-Pentadecanoyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**8a**): To a solution of pentadecanoic acid (6.27 g) in anhydrous dichloromethane (23 ml) was added dropwise a solution of dicyclohexylcarbodiimide (3.19 g) in anhydrous dichloromethane (10 ml) at 0°C. The mixture was stirred at 0°C for 1 hour. The resulting precipitate was filtered off, and the filtrate was evaporated to give a syrup. A solution of the syrup was added to **3** (700 mg) in anhydrous pyridine

(15 ml) and allowed to stand for 26 hours at 70°C. On TLC with benzene - acetone (7: 1), the starting material of Rf 0.21 disappeared and the product of Rf 0.67 appeared. The mixture was evaporated to give a light brown syrup. The syrup was subjected to column (27×170 mm) chromatography on silica gel (Wako Gel, 40 g). The dicyclohexylurea and unreacted pentadecanoic acid were eluted out with benzene (1.5 liters). Thereafter, elution (98~140 ml) with benzene - acetone (10: 1) followed by evaporation gave a syrup of **8a**, 821 mg (78%): $[\alpha]_D^{20}$ +45.6° (*c* 1.73, $CHCl_3$); IR (KBr) 1730 cm^{-1} (ester); NMR (60 MHz, in $CDCl_3$) δ 0.8~3.3 (55H m., 12H of THP, $(CH_2)_{13}$, 4 CH_3, an exocyclic ethyleneoxide, C_2-H, C_{10}-H, $C_{10'}$-H), 3.3~4.5 (8H m., 6H of THP, C_8-H and C_9-H), 3.60 (1H d., $J_{5,6}$ 2 Hz, C_6-H), 4.60 (1H d., $J_{5,6}$ 2 Hz, C_5-H) and 5.13 (1H d., $J_{1,2}$ 8 Hz, C_1-H).

Anal. Calcd. for $C_{40}H_{66}O_8$: C 71.18; H 9.86%
Found: C 71.10; H 9.76%

1-O-Vinylacetyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**10a**)

A sample of **3** was acylated with vinylacetic acid by method B, yielding **10a** (syrup, 81%); $[\alpha]_D^{20}$ +26.5° (*c* 0.98, CH_3COCH_3); IR (KBr) 1735 (ester), 1645 (–CH=CH_2) cm^{-1}.

Anal. Calcd. for $C_{29}H_{42}O_8$: C 67.16; H 8.16%
Found: C 67.19; H 8.14%

1-O-(2-Octenoyl)-5,8-di-O-tetrahydropyranyldihydrocoriolin (**11a**)

A sample of **3** was acylated with 2-octenoic acid by method B, yielding **11a** (98%): $[\alpha]_D^{20}$ +50.2° (*c* 1.38, $CHCl_3$); IR (KBr) 1730 (ester), 1660 (–CH=CH–) cm^{-1}.

Anal. Calcd. for $C_{32}H_{50}O_8$: C 68.30; H 8.96%
Found: C 68.56; H 8.75%

1-O-(2-Dodecenoyl)-5,8-di-O-tetrahydropyranyldihydrocoriolin (**12a**)

A sample of **3** was acylated with 2-dodecenoic acid by method B, yielding **12a** (96%): $[\alpha]_D^{20}$ +38.2° (*c* 1.047, $CHCl_3$); IR (KBr) 1735 (ester), 1650 (CH=CH) cm^{-1}.

Anal. Calcd. for $C_{36}H_{58}O_8$: C 69.87; H 9.45%
Found: C 70.11; H 9.28%

1-O-(2-Hexadecenoyl)-5,8-di-O-tetrahydropyranyldihydrocoriolin (**13a**)

A sample of **3** was acylated with 2-hexadecenoic acid by method B, yielding **13a** (97%): $[\alpha]_D^{20}$ +32.3° (*c* 1.36, $CHCl_3$); IR (KBr) 1720 (sh., ester), 1660 (CH=CH) cm^{-1}.

Anal. Calcd. for $C_{40}H_{66}O_8$: C 71.18; H 9.86%
Found: C 70.98; H 9.61%

1-O-(2-Methylbutyryl)-5,8-di-O-tetrahydropyranyldihydrocoriolin (**15a**)

A sample of **3** was acylated with 2-methylbutyric acid by method B, yielding **15a** (98%): $[\alpha]_D^{20}$ +46.2° (*c* 1.6, $CHCl_3$); IR (KBr) 1730 (ester) cm^{-1}.

Anal. Calcd. for $C_{30}H_{46}O_8$: C 67.39; H 8.67%
Found: C 67.51; H 8.95%

1-O-(2-(R and S)-methylvaleryl)-5,8-di-O-tetrahydropyranyldihydrocoriolin (**16a**)

A sample of **3** was acylated with 2-methyl-*n*-valeric acid by method B, yielding **16a** (99%): $[\alpha]_D^{20}$ +52.5° (*c* 1.0, $CHCl_3$); IR (KBr) 1730 (ester) cm^{-1}.

Anal. Calcd. for $C_{31}H_{48}O_8$: C 67.85; H 8.82%
Found: C 67.31; H 8.95%

1-O-Benzoyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**9a**)

To a solution of **3** (450 mg) in anhydrous pyridine (9 ml) was added benzoyl chloride (0.5 ml). The reaction mixture was allowed to stand at room temperature for 2 hours. On TLC with benzene - acetone (7: 1), the starting material of Rf 0.23 disappeared and the product of Rf 0.67 appeared. The mixture was poured into 1% sodium bicarbonate solution, and the resulting syrup was separated. The syrup was dissolved in chloroform (200 ml), and the solution was washed with water to pH 7, dried (Na_2SO_4), and filtered. The filtrate was evaporated and the resulting syrup was purified by a short column chromatography to give a colorless syrup of **9a**, 480 mg (86%): $[\alpha]_D^{20}$ +5.3° (*c* 0.94, $CHCl_3$); IR (KBr) 1730 cm^{-1} (ester); NMR (60 MHz, in $CDCl_3$) δ 1.10 (9H s., CH_3), 1.2~3.0 (17H m., 12H of THP, an exocyclic ethyleneoxide, C_2-H, C_{10}-H, $C_{10'}$-H), 3.0~5.2 (10H m., 6H of THP, C_5-H, C_6-H,

C_8-H, C_9-H), 5.3 (1H d., $J_{1,2}$ 8 Hz, C_1-H) and 7.2~8.2 (5H m., C_6H_5).

Anal. Calcd. for $C_{32}H_{42}O_8$: C 69.29; H 7.63%
Found: C 69.51; H 7.34%

1-O-Methyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**17a**)

To a solution of **3** (1 g) in dry DMF (10 ml) cooled at 0°C, 50% oily sodium hydride (845 mg) was added under nitrogen and the mixture was stirred for 1.5 hours. To the mixture was added methyl iodide (1.1 ml) and the solution was stirred in the dark at room temperature for 1.5 hours. On TLC with benzene - ether (2: 7), the starting material of Rf 0.34 disappeared and products of Rf 0.75 (minor), 0.57 (major) and 0.45 (minor) appeared. The solution was evaporated and the resulting syrup was dissolved in chloroform. The solution was washed with water, dried (Na_2SO_4), filtered, and the filtrate was evaporated to give a syrup, which was chromatographed on a column (38×260 mm) of silica gel (Wako Gel, 140 g) with benzene - acetone (10: 1). The fraction of 270~460 ml containing the product of Rf 0.57 was evaporated to give a syrup of **17a**, 710 mg (69%): $[\alpha]_D^{20}$ +10° (*c* 1.0, CH_3COCH_3); NMR (60 MHz, in $CDCl_3$) δ 0.92, 1.10 and 1.16 (3H s., each CH_3), 3.37 (3H s., OCH_3), 3.92 (1H d., $J_{8,9}$ 6 Hz, C_8-H), 4.53 (1H d., $J_{5,6}$ 2 Hz, C_5-H).

Anal. Calcd. for $C_{26}H_{40}O_7$: C 67.21; H 8.68%
Found: C 67.29; H 8.51%

1-O-Butyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**18a**)

A sample of **3** was alkylated with butyl bromide in the same manner as described for **17a**, yielding **18a** (59%): $[\alpha]_D^{20}$ +6.9° (*c* 1.16, $CHCl_3$).

Anal. Calcd. for $C_{29}H_{46}O_7$: C 68.74; H 9.15%
Found: C 68.76; H 8.97%

1-O-Octyl-5,8-di-O-tetrahydropyranyldihydrocoriolin (**19a**)

A sample of **3** was alkylated with *n*-octyl bromide in the same manner as described for **17a**, yielding **19a** (syrup, 40%): $[\alpha]_D^{20}$ +62.6° (*c* 1.23, CH_3COCH_3).

Anal. Calcd. for $C_{33}H_{54}O_7$: C 70.43; H 9.67%
Found: C 70.26; H 9.47%

De-tetrahydropyranylation

A solution of each 1-O-acyl or 1-O-alkyl-5,8-di-O-tetrahydropyranyl compound (700 mg) in 70% aqueous acetic acid (20 ml) was allowed to stand for 5 hours at 60°C. The reaction mixture was poured into water (70 ml) to give a solid. Recrystallization from methanol gave each de-tetrahydropyranylated derivative.

1-O-Acetyldihydrocoriolin (**4b**)

Yield 76% from **4a**; mp 248~250°C; $[\alpha]_D^{20}$ +28.8° (*c* 0.73, DMF); IR (KBr) 1730 (ester) cm^{-1}; NMR (60 MHz, in Py-d_5) δ 1.05, 1.09 and 1.40 (3H s., each CH_3), 1.0~3.0 (4H m., C_2-H, C_9-H, C_{10}-H and $C_{10'}$-H), 2.03 (3H s., $COCH_3$), 2.51 and 2.68 (2H ABq., J 6 Hz, an exocyclic ethyleneoxide), 3.64 (1H d., $J_{5,6}$ 2 Hz, C_6-H), 4.11 (1H d., $J_{8,9}$ 6 Hz, C_8-H), 4.66 (1H d., $J_{5,6}$ 2 Hz, C_5-H), 5.36 (1H d., $J_{1,2}$ 8 Hz, C_1-H).

Anal. Calcd. for $C_{17}H_{24}O_6$: C 62.95; H 7.46%
Found: C 63.04; H 7.39%

1-O-Propionyldihydrocoriolin (**5b**)

Yield 93% from **5a**; mp 242~244°C; $[\alpha]_D^{20}$ +21.2° (*c* 0.8, DMF); IR (KBr) 1730 (ester) cm^{-1}.

Anal. Calcd. for $C_{18}H_{26}O_6$: C 63.88; H 7.74%
Found: C 63.62; H 7.70%

1-O-Caproyldihydrocoriolin (**6b**)

Yield 86% from **6a**; mp 227~228°C; $[\alpha]_D^{20}$ +23.3° (*c* 1.4, DMF); IR (KBr) 1730 (ester) cm^{-1}.

Anal. Calcd. for $C_{21}H_{36}O_6$: C 66.30; H 8.48%
Found: C 66.10; H 8.41%

1-O-Capryldihydrocoriolin (**7b**)

Yield 74% from **7a**; mp 295.5~296°C; $[\alpha]_D^{20}$ +19° (*c* 1.0, DMF); IR (KBr) 1730 (ester) cm^{-1}.

Anal. Calcd. for $C_{25}H_{40}O_6$: C 68.88; H 9.24%
Found: C 68.95; H 9.14%

1-O-Pentadecanoyldihydrocoriolin (**8b**)

Yield 87% from **8a**; mp 201~202°C; $[\alpha]_D^{20}$ +18° (*c* 0.67, DMF); IR (KBr) 1725 (ester) cm^{-1}.
Anal. Calcd. for $C_{30}H_{50}O_6$: C 71.11; H 9.95%
Found: C 70.85; H 9.78%

1-O-Benzoyldihydrocoriolin (**9b**)

Yield 96% from **9a**; mp 244~245°C; $[\alpha]_D^{20}$ +43.4° (*c* 1.2, DMF); IR (KBr) 1725 (ester) cm^{-1}.
Anal. Calcd. for $C_{22}H_{26}O_6$: C 68.38; H 6.78%
Found: C 68.59; H 6.77%

1-O-Vinylacetyldihydrocoriolin (**10b**)

Yield 76% from **10a**; mp 206~207°C; $[\alpha]_D^{20}$ +27.9° (*c* 0.90, CH_3COCH_3); IR (KBr) 1730 (ester), 1645 (–CH=CH_2) cm^{-1}.
Anal. Calcd. for $C_{19}H_{26}O_6$: C 65.12; H 7.48%
Found: C 64.83; H 7.23%

1-O-(2-Octenoyl)dihydrocoriolin (**11b**)

Yield 86% from **11a**; mp 198~199°C; $[\alpha]_D^{20}$ +22.0° (*c* 0.73, DMF); IR (KBr) 1730 and 1710 (ester), 1660 (CH=CH) cm^{-1}.
Anal. Calcd. for $C_{22}H_{34}O_6$; C 66.98; H 8.69%
Found: C 67.02; H 8.48%

1-O-(2-Dodecenoyl)dihydrocoriolin (**12b**)

Yield 89% from **12a**; mp 191~192°C; $[\alpha]_D^{20}$ +20° (*c* 0.8, DMF); IR (KBr) 1735 and 1710 (ester), 1650 (CH=CH) cm^{-1}.
Anal. Calcd. for $C_{26}H_{42}O_6$: C 69.30; H 9.40%
Found: C 69.90; H 9.31%

1-O-(2-Hexadecenoyl)dihydrocoriolin (**13b**)

Yield 91% from **13a**; mp 189~191°C; $[\alpha]_D^{20}$ +17.6° (*c* 0.73, DMF); IR (KBr) 1730 and 1710 (ester), 1650 (CH=CH) cm^{-1}.
Anal. Calcd. for $C_{30}H_{50}O_6$: C 71.11; H 9.95%
Found: C 71.40; H 9.62%

1-O-Isobutyryldihydrocoriolin (**14b**)

Yield 67% from **14a**; mp 209~210°C; $[\alpha]_D^{20}$ +18.7° (*c* 0.86, DMF); IR (KBr) 1725 (ester) cm^{-1}.
Anal. Calcd. for $C_{19}H_{28}O_6$: C 64.75; H 8.01%
Found: C 64.64; H 7.94%

1-O-(2-Methylbutyryl)dihydrocoriolin (**15b**)

Yield 63% from **15a**; mp 189~190°C; $[\alpha]_D^{20}$ +17.2° (*c* 0.76, DMF); IR (KBr) 1720 (ester) cm^{-1}.
Anal. Calcd. for $C_{20}H_{30}O_6$: C 65.55; H 8.25%
Found: C 65.30; H 8.21%

1-O-(2-Methylvaleryl)dihydrocoriolin (**16b**)

Yield 63% from **16a**; mp 187~188°C; $[\alpha]_D^{20}$ +17.3° (*c* 0.87, DMF); IR (KBr) 1720 (ester) cm^{-1}.
Anal. Calcd. for $C_{21}H_{32}O_6$: C 66.30; H 8.48%
Found: C 66.17; H 8.35%

1-O-Methyldihydrocoriolin (**17b**)

Yield 81% from **17a**; mp 197~198°C; $[\alpha]_D^{20}$ +65.7° (*c* 0.93, DMF); NMR (60 MHz, in Py-d_5 containing a small amount of D_2O) δ 1.10, 1.20 and 1.40 (3H s., each CH_3), 1.5~3.5 (6H m., C_{10}-H and $C_{10'}$-H, C_2-H, C_9-H and an exocyclic ethyleneoxide), 3.40 (3H s., OCH_3), 3.78 (1H d., $J_{5,6}$ 2 Hz, C_6-H), 3.52 (1H d., $J_{1,2}$ 7 Hz, C_1-H), 4.15 (1H d., $J_{8,9}$ 6 Hz, C_8-H) and 4.81 (1H d., $J_{5,6}$ 2 Hz, C_5-H), 4.90 and 5.70 (1H broad s., each OH).
Anal. Calcd. for $C_{16}H_{24}O_5$: C 64.84; H 8.16%
Found: C 65.05; H 8.12%

1-O-Butyldihydrocoriolin (**18b**)

Yield 97% from **18a**; mp 188~189°C; $[\alpha]_D^{20}$ +67.3° (*c* 1.06, $CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_5$: C 67.43; H 8.94%
Found: C 67.25; H 8.81%

1-O-Octyldihydrocoriolin (**19b**)

Yield 93% from **19a**; mp 160~161.5°C; $[\alpha]_D^{20}$ +65.4° (*c* 0.92, CH_3COCH_3).

Anal. Calcd. for $C_{23}H_{38}O_5$: C 70.01; H 9.71%
Found: C 70.18; H 9.59%

Oxidation of 1-O-acyl or 1-O-alkyldihydrocoriolin derivative

To a suspension of each 1-O-acyl or 1-O-alkyldihydrocoriolin derivative in acetic acid (40 fold) was added anhydrous chromic acid (2.5 eq.) and the reaction mixture was stirred at room temperature for 1 hour. The mixture was poured into ice water, and the solution was extracted with ethyl acetate. The extracts were washed with 0.2 N sodium hydroxide to pH 4, and then washed with water, dried (Na_2SO_4) and filtered. The filtrate was evaporated. The dark green syrup was purified by column chromatography on silica gel. The solid obtained was crystallized from *n*-hexane - acetone (10: 1) to give crystals of each 8-ketocoriolin derivative.

1-O-Acetyl-8-ketocoriolin (**4c**)

Yield 27% from **4b**; mp 177~178°C; $[\alpha]_D^{20}$ −52° (*c* 0.77, $CHCl_3$); IR (KBr) 1750 (ketone), 1720 (ester) cm^{-1}; NMR (100 MHz, in $CDCl_3$) δ 1.03, 1.13 and 1.21 (3H s., each CH_3), 1.62 (1H t., J 12 Hz, $C_{10'}$-H), 2.07 (1H q., $J_{9,10}$ 8 Hz and $J_{10,10'}$ 12 Hz, C_{10}-H), 2.16 (3H s., $COCH_3$), 2.27 and 3.22 (2H ABq., J 7 Hz, an exocyclic ethyleneoxide), 2.86 (1H q., $J_{1,2}$ 7 Hz and $J_{2,9}$ 12 Hz, C_2-H), 3.22 (1H sextet, $J_{2,9}$ and $J_{9,10'}$ 12 Hz, $J_{9,10}$ 8 Hz, C_9-H), 3.87 (1H s., C_6-H) and 5.27 (1H d., $J_{1,2}$ 7 Hz, C_1-H).

Anal. Calcd. for $C_{17}H_{20}O_6$: C 63.74; H 6.29%
Found: C 63.39; H 6.62%

1-O-Propionyl-8-ketocoriolin (**5c**)

Yield 25% from **5b**; mp 151~152°C; $[\alpha]_D^{20}$ −58.8° (*c* 1.4, $CHCl_3$); IR (KBr) 1755 (ketone), 1725 (ester) cm^{-1}.

Anal. Calcd. for $C_{18}H_{22}O_6$: C 64.65; H 6.63%
Found: C 64.52; H 6.82%

1-O-Caproyl-8-ketocoriolin (**6c**)

Yield 21% from **6b**; mp 134~135°C; $[\alpha]_D^{20}$ −51.1° (*c* 1.4, $CHCl_3$); IR (KBr) 1760 and 1745 (ketone), 1725 (ester) cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}O_6$: C 67.00; H 7.50%
Found: C 66.96; H 7.55%

1-O-Capryl-8-ketocoriolin (**7c**)

Yield 31% from **7b**; mp 114~115°C; $[\alpha]_D^{20}$ −49° (*c* 1.0, $CHCl_3$); IR (KBr) 1750 (ketone), 1725 (ester) cm^{-1}.

Anal. Calcd. for $C_{25}H_{36}O_6$: C 69.42; H 8.39%
Found: C 69.11; H 8.43%

1-O-Pentadecanoyl-8-ketocoriolin (**8c**)

Yield 41% from **8b**; mp 103~104°C; $[\alpha]_D^{20}$ −37.4° (*c* 1.0, $CHCl_3$); IR (KBr) 1750 (ketone), 1720 (ester) cm^{-1}.

Anal. Calcd. for $C_{30}H_{46}O_6$: C 71.68; H 9.22%
Found: C 71.55; H 9.34%

1-O-Benzoyl-8-ketocoriolin (**9c**)

Yield 28% (syrup) from **9b**; $[\alpha]_D^{20}$ −14.8° (*c* 1.0, $CHCl_3$); IR (KBr) 1760 (ketone), 1720 (ester) cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}O_6$: C 69.10; H 5.80%
Found: C 69.34; H 6.06%

1-O-Vinylacetyl-8-ketocoriolin (**10c**)

Yield 27% from **10b**; mp 131.5~132°C; $[\alpha]_D^{20}$ −53° (*c* 0.57, $CHCl_3$); IR (KBr) 1750 (ketone), 1730 (ester), 1645 (–CH=CH_2) cm^{-1}.

Anal. Calcd. for $C_{19}H_{22}O_6$: C 65.88; H 6.40%
Found: C 66.05; H 6.61%

1-O-(2-Octenoyl)-8-ketocoriolin (**11c**)

Yield 20% from **11b**; mp 122.5~123.5°C; $[\alpha]_D^{20}$ −52.5° (*c* 1.6, $CHCl_3$); IR (KBr) 1750 (ketone), 1720 and 1700 (ester), 1660 (CH=CH) cm^{-1}.

Anal. Calcd. for $C_{22}H_{30}O_6$: C 67.67; H 7.74%
Found: C 67.51; H 7.95%

1-O-(2-Dodecenoyl)-8-ketocoriolin (**12c**)

Yield 20% from **12b**; mp 127~128°C; $[\alpha]_D^{20}$ −43.98° (*c* 1.6, $CHCl_3$); IR (KBr) 1750 (ketone), 1725 and 1700 (ester), 1650 (CH=CH) cm^{-1}.

Anal. Calcd. for $C_{26}H_{38}O_6$: C 69.93; H 8.58%
Found: C 69.87; H 8.64%

1-O-(2-Hexadecenoyl)-8-ketocoriolin (**13c**)

Yield 20% from **13b**; mp 88~89°C; $[\alpha]_D^{20}$ −37.5° (*c* 1.6, $CHCl_3$); IR (KBr) 1750 (ketone), 1720 and 1700 (ester), 1650 (CH=CH) cm^{-1}.

Anal. Calcd. for $C_{30}H_{46}O_6$: C 71.68; H 9.22%
Found: C 72.08; H 9.10%

1-O-Isobutyryl-8-ketocoriolin (**14c**)

Yield 24% from **14b**; mp 147~148°C; $[\alpha]_D^{20}$ −58.8° (*c* 0.71, $CHCl_3$); IR (KBr) 1750 (ketone), 1720 (ester) cm^{-1}.

Anal. Calcd. for $C_{19}H_{24}O_6$: C 65.50; H 6.94%
Found: C 65.12; H 7.22%

1-O-(2-Methylbutyryl)-8-ketocoriolin (**15c**)

Yield 33% from **15b**; mp 122.5~123.5°C; $[\alpha]_D^{20}$ −50.5° (*c* 0.87, $CHCl_3$); IR (KBr) 1760 (ketone), 1720 (ester) cm^{-1}.

Anal. Calcd. for $C_{20}H_{26}O_6$: C 66.28; H 7.23%
Found: C 65.66; H 7.48%

1-O-(2-Methylvaleryl)-8-ketocoriolin (**16c**)

Yield 26% from **16b**; mp 103~104°C; $[\alpha]_D^{20}$ −53.7° (*c* 0.8, $CHCl_3$); IR (KBr) 1750 (ketone), 1720 (ester) cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}O_6$: C 67.00; H 7.50%
Found: C 67.01; H 7.50%

1-O-Methyl-8-ketocoriolin (**17c**)

Yield 37% from **17b**; mp 159~161°C; $[\alpha]_D^{20}$ −25.5° (*c* 0.71, $CHCl_3$); IR (KBr) 1765 and 1750 (ketone) cm^{-1}; NMR (100 MHz, in $CDCl_3$) δ 0.98, 1.11 and 1.23 (3H s., each CH_3), 1.45 (1H t., $J_{9,10'}$ and $J_{10,10'}$ 12 Hz, $C_{10'}$-H), 1.89 (1H q., $J_{9,10}$ 9 Hz, $J_{10,10'}$ 12 Hz, C_{10}-H), 2.69 (1H q., $J_{1,2}$ 7 Hz, $J_{2,9}$ 12 Hz, C_2-H), 3.11 (1H sextet, $J_{2,9}$ and $J_{9,10'}$ 12 Hz, $J_{9,10}$ 9 Hz, C_9-H), 3.04 and 3.16 (2H ABq., J 7 Hz, an exocyclic ethyleneoxide), 3.43 (3H s., OCH_3), 3.46 (1H d., $J_{1,2}$ 7 Hz, C_1-H) and 3.82 (1H s., C_6-H).

Anal. Calcd. for $C_{16}H_{20}O_5$: C 65.74; H 6.90%
Found: C 65.50; H 6.76%

1-O-Butyl-8-ketocoriolin (**18c**)

Yield 23% (syrup) from **18b**; $[\alpha]_D^{20}$ −23.6° (*c* 0.25, $CHCl_3$); IR (KBr) 1760 (ketone) cm^{-1}.

Anal. Calcd. for $C_{19}H_{26}O_5$: C 68.24; H 7.84%
Found: C 67.86; H 7.77%

1-O-Octyl-8-ketocoriolin (**19c**)

Yield 23% (syrup) from **19b**; $[\alpha]_D^{20}$ −30.0° (*c* 0.36, $CHCl_3$); IR (KBr) 1760 (ketone) cm^{-1}.

Anal. Calcd. for $C_{23}H_{34}O_5$: C 70.74; H 8.78%
Found: C 70.79; H 8.61%

References

1) TAKEUCHI, T.; H. IINUMA, J. IWANAGA, S. TAKAHASHI, T. TAKITA & H. UMEZAWA: Coriolin, a new basidiomycetes antibiotic. J. Antibiotics 22: 215~217, 1969
2) NISHIMURA, Y.; Y. KOYAMA, S. UMEZAWA, T. TAKEUCHI, M. ISHIZUKA & H. UMEZAWA: Chemical modification of coriolin B. J. Antibiotics 30: 59~65, 1977
3) TAKEUCHI, T.; S. TAKAHASHI, H. IINUMA & H. UMEZAWA: Diketocoriolin B, an active derivative of coriolin B by *Coriolus consors*. J. Antibiotics 24: 631~635, 1971
4) TAKAHASHI, S.; H. NAGANAWA, H. IINUMA, T. TAKITA, K. MAEDA & H. UMEZAWA: Revised structures and stereochemistry of coriolins. Tetrahedron Lett. 1971: 1955~1958, 1971
5) NAKAMURA, T.; T. TAKITA, H. UMEZAWA, M. KUNISHIMA, Y. NAKAYAMA & Y. IITAKA: Absolute configuration of coriolin, a sesquiterpene antibiotic from *Coriolus consors*. J. Antibiotics 27: 301~302, 1974
6) KUNIMOTO, T.; M. HORI & H. UMEZAWA: Mechanism of action of diketocoriolin B. Biochim. Biophys. Acta 298: 513~525, 1973