Synthesis of Bicyclic Coriolin Models†

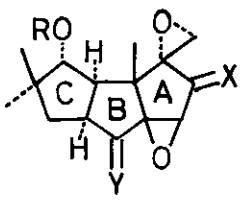
Hisanobu Hashimoto, Toshio Ito, Haruhisa Shirahama, and Takeshi Matsumoto*

Department of Chemistry, Faculty of Science

Hokkaido University, Sapporo, 060 JAPAN

Abstract ——Bicyclic coriolin models 10a and 13 have been obtained in a stereoselective manner from 3, through methylenation at C-4, epoxidation at the C-1 double bond, borohydride reduction and subsequent epoxidation at the methylene group. Similar transformation of 16b, obtained from the enol acetate of 3 through oxidation (mCPBA), afforded dihydroxydiepoxide 23, Jones oxidation of which gave a bicyclic diketocoriolin B model 26.

The highly oxygenated hirsutanoids, coriolins (1), isolated from Coriolus consors and studied by H. Umezawa et al.[1], have attracted attention as anticancer agents. A characteristic structural feature of coriolins is the presence of a densely oxygenated cyclopentanone ring bearing two epoxide groups (ring A). Previously we reported a total synthesis[2] of a simpler hirsutanoid hirsutic acid (2), which contains the same skeleton as coriolins. We should like to report here stereoselective synthesis of properly functionalized A-B ring models of coriolins, starting from 5-methylbicyclo[3.3.0]oct-1-en-3-one (3)[3].

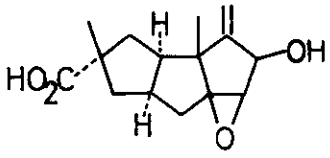


1a coriolin A ; R=H, X=O, Y=

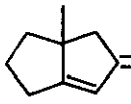
1b coriolin B ; R=COC_7H_{15}, X=, Y=

1c coriolin C ; R=$CO(OH)C_6H_{13}$, X=O, Y=

1d diketocoriolin B ; R=COC_7H_{15}, X=O, Y=O

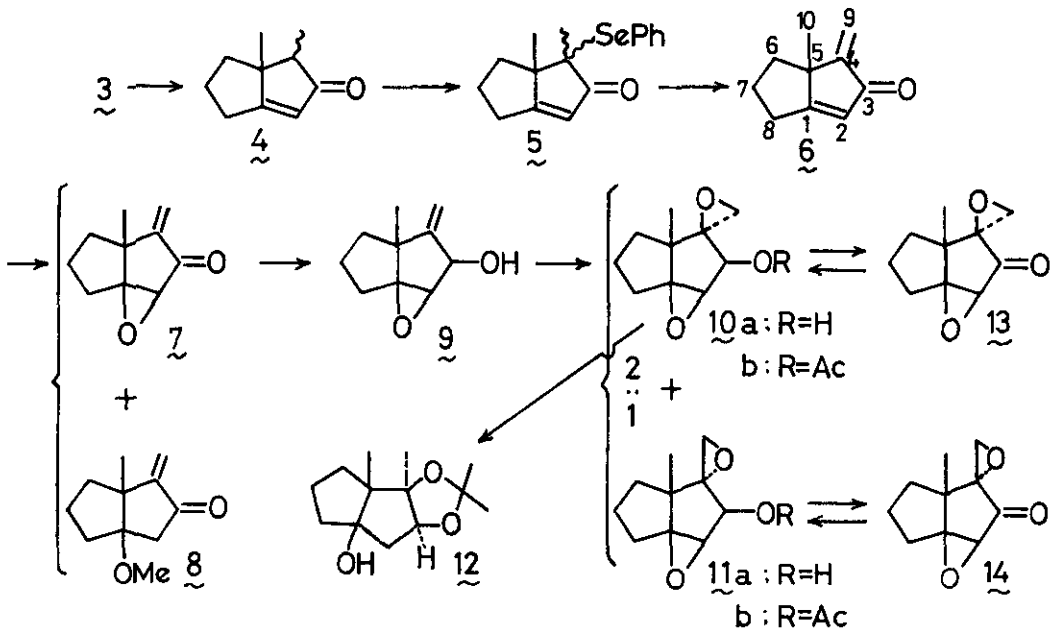


2 hirsutic acid



3

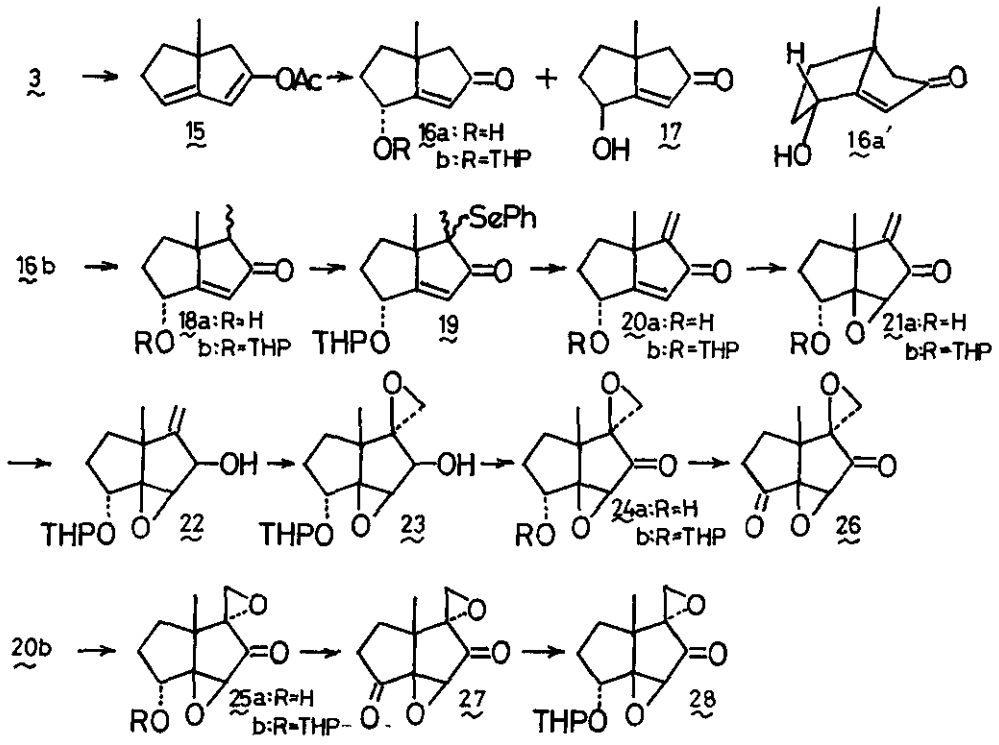
† This article is dedicated to Professor Hamao Umezawa on the occasion of the celebration of his 65th birthday.



First, regioselective introduction of a C_1 unit at the C-4 position of 3 was attempted. However, usual treatments such as methylation with MeI/t-BuOK/t-BuOH, hydroxymethylation with HCHO/base, formylation with HCO_2Et/base etc. resulted in the main reaction at C-2. Preliminary deuterium exchange experiments (MeOD-MeONa, in an nmr sample tube) revealed that the enone 3 was readily converted to a pentadeuterio compound and the deuteration occurred most rapidly at C-4. Methylation of 3 was therefore carried out under kinetically controlled conditions (LDA/THF/CH_3I/0°C/25 min) to give 4 in 98% yield [$C_{10}H_{14}O$[4]; ν($CHCl_3$) 1690, 1630 cm^{-1}; δ[5] 1.04[6] (3H, d, J=7, 9Me), 1.16 (3H, s, 10Me), 2.27 (1H, q, J=7, C_4-H), 5.69 (1H, t, J=1.2, C_2-H)]. Phenyl selenenylation[7] of the products 4 (LDA/THF/ SeBr/0°~ rt/30 min, y=76%) followed by oxidation (30% H_2O_2/THF-AcOH/0°C/40 min, quant.) afforded exomethylene ketone 6 in 74% overall yield [$C_{10}H_{12}O$; ν(neat) 1690, 1640, 1625 cm^{-1}; δ 1.25 (3H, s, 10Me), 5.25 (1H, s[8], C_9(E)-H), 5.90 (1H, s, C_9(Z)-H), 5.96 (1H, m, C_2-H)]. On treatment with alkaline H_2O_2 (30% H_2O_2/1N-NaOH/MeOH/-35°/40 min) 6 was converted to 7 (53%) and 8 (11%)[7: $C_{10}H_{12}O_2$; ν($CHCl_3$) 1730, 1640 cm^{-1}; δ 1.27 (3H, s, 10Me), 3.40 (1H, s, C_2-H), 5.37 (1H, s, C_9(E)-H), 6.10 (1H, s, C_9(Z)-H). 8: ν($CHCl_3$) 1730, 1630, 1090 cm^{-1}, δ 1.19 (3H, s, 10Me), 2.50 and 2.61 (2H, ABq, J=12, (C_2-H_2), 3.24 (3H, s, MeO-), 5.23 (1H, s, C_9(E)-H), 6.03 (1H, s, C_9(Z)-H)]. Configuration of the epoxide ring of 7 as well as that of the methoxyl group of 8 was deduced to be β from the analogy of the similar oxidation reaction of 3[3] and related hirsutic acid intermediates[2], which afforded invariably β-epoxides and β-methoxy derivatives. Reduction of the ketone 7 ($NaBH_4$/EtOH/0°C) gave quantitatively

β-alcohol 9 [ν(neat) 3400, 3060, 1665, 1115, 1090, 1060, 1015, 915, 895, 845 cm^{-1}; δ 1.13 (3H, s, 10Me), 3.44 (1H, d, J=2.1[9], C_2-H), 4.58 (1H, m, C_3-H), 5.10 (1H, d, J=2.4, C_9(E)-H), 5.31 (1H, d, J=2.2, C_9(Z)-H); 3,5-dinitrobenzoate, mp 124~5°, $C_{17}H_{16}N_2O_7$]. On epoxidation of the exomethylene group of 9 (mCPBA[10]/CH_2Cl_2/rt), two isomeric diepoxides, 10a and 11a were obtained in a ratio of 2:1 in 74% yield. They were separated by chromatography as acetates and the major diepoxide acetate 10b was treated successively with $LiAlH_4$/THF and acetone dimethylacetal/pTsOH/DMF to give acetonide 12, whose formation showed the configuration of the spiro epoxide group to be β-oriented [$C_{13}H_{22}O_3$; ν($CHCl_3$) 3480, 1380, 1095, 1028, 950 cm^{-1}; δ 1.04 (3H, s, 10Me), 1.37 (6H, s, $Me_2C<^{O}_{O}$), 1.48 (3H, s, 4Me), 1.98 (2H, d, J=3.0, C_2-H_2), 4.38 (1H, t, J=3.0, C_3-H) . The two isomeric alcohols 10a and 11a were obtained pure through oxidation (CrO_3/An/rt, good yield) of the mixture, chromatographic separation of the resultant ketones 13 and 14 [13: ν(neat) 1760 cm^{-1}; δ 1.02 (3H, s, 10Me), 2.76 and 3.07 (2H, ABq, J=6.3, C_9-H_2), 3.45 (1H, s, C_2-H). 14: ν(neat) 1760 cm^{-1}, δ 1.13 (3H, s, 10Me), 2.84 (2H, s, C_9-H_2), 3.39 (1H, s, C_2-H)] and reduction ($NaBH_4$/EtOH/0°C, each in 90% yield) [10a: ν($CHCl_3$), 3440, 1115, 1090, 1068, 943, 905, 870, 840 cm^{-1}; δ 0.85 (3H, s, 10Me), 2.64 (2H, s, C_9-H_2), 3.45 (1H, d, J=1.5, C_2-H), 4.38 (1H, d, J=1.5, C_3-H); 3,5-dinitrobenzoate, mp 128~9°, $C_{17}H_{16}N_2O_8 \cdot H_2O$. 11a : mp 93~5°; ν($CHCl_3$) 3460, 1115, 1085, 1050, 1020, 990, 945, 835 cm^{-1}; δ 1.00 (3H, s, 10Me), 2.63 and 2.93 (2H, ABq, J=5.0, C_9-H_2), 3.51 (1H, d, J=2.5, C_2-H), 4.18 (1H, d, J=2.5, C_3-H)].

Next, introduction of a hydroxyl group to ring B was attempted. For this purpose enol acetate 15 was prepared by distilling off the formed acetone from a solution of 3 in isopropenyl acetate in the presence of pTsOH (30 hr, Ar atmosphere, 83% yield)[ν(neat) 3060, 1770, 1605, 1585, 1370, 1210, 1190, 1135, 1010, 900, 875, 855 cm^{-1}; δ(CCl_4) 1.04 (3H, s, 10Me), 2.12 (3H, s, AcO-), 1.70 and 2.30 (2H, ABq, J=15.6, C_4-H_2), 5.19 (1H, t, J=2.5, C_2-H), 5.95 (1H, m, C_8-H)]. Oxidation followed by hydrolysis (1. mCPBA/THF/$NaHCO_3$/0°→ rt, 2. Na_2CO_3aq/reflux/20 hr) accomplished introduction of a γ-hydroxyl group in the enone 3. A mixture of 16a and 17 was obtained in 70% yield (ratio=3/1). They were separated through chromatography [16a : ν($CHCl_3$) 3450, 1710, 1635 cm^{-1}; δ 1.19 (3H, s, 10Me), 2.35 (2H, s, C_4-H_2), 5.05 (1H, m, C_8-H), 5.95 (1H, d, J=1.7, C_2-H). 17: ν($CHCl_3$) 3480, 1710, 1635 cm^{-1}; δ 1.37 (3H, s, 10Me), 2.35 (2H, s, C_4-H_2), 5.05 (1H, m, C_8-H), 5.89 (1H, s, C_2-H); analyzed as acetate, bp 95 100°/3 mmHg, $C_{11}H_{14}O_3$]. Configuration of the hydroxyl group was determined by the following observations in the nmr spectra. 1) The signal due to C_2-H of 16a showed the allylic coupling, while that of 17 did not. 2) Decoupling experiments showed that the peak due to C_8-H of 16a coupled with C_7-H_2 with J=9.3 and 4.1 Hz. These coupling constants are well explained by assuming that C_8-H takes an axial-like orientation and that the stereostructure of 16a is expressed by 16á. 3) The Me-signal of 17



appeared at a field lower by 0.18 ppm than that of 16a.

Introduction of an exomethylene group at C_4 of 16 was carried out in a similar manner to that described above, using a THP-blocked alcohol 16b. Compounds 18b, 19 and 20b were obtained in 79%, 57% and 77% yield respectively [18a: ν(neat) 3380, 1690, 1635 cm^{-1}; δ 1.07[6] (3H, d, J=7.0, 9Me), 1.19 (3H, s, 10Me), 5.10 (1H, m, C_8-H), 5.94 (1H, d, J=1.7, C_2-H 3.5-dinitrobenzoate, mp 131~2°, $C_{17}H_{16}N_2O_7$. 20b: ν(neat) 3080, 1705, 1650, 1628, 1125, 1075, 1025, 885, 875, 815 cm^{-1}, 1.29 (3H, s, 10Me), 5.10 (1H, m, C_8-H), 5.28 (1H, s, C_9(E)-H), 5.92 (1H, s, C_9(Z)-H), 6.10 and 6.25 (total 1H[11], each d, J=1.9, C_2-H); 20a: 3,5-dinitrobenzoate, mp 128~9°, $C_{12}H_{14}N_2O_7$]. The dienone 20b gave a monoepoxide 21b in 60% yield on oxidation (30% H_2O_2/1N-NaOH/EtOH/-30°/1h). Alcohol 22 [ν(neat) 3440, 3060, 1665, 1125, 1080, 1023, 985, 945 cm^{-1}; δ 1.17 (3H, s, 10Me), 3.69 and 3.83 (total 1H[11], each d, J=2.5, C_2-H), 4.47 (1H, m, C_3-H), 5.08 (1H, d, J=2.6, C_9(E)-H), 5.31 (1H, d, J=2.0, C_9(Z)-H)] was obtained from 21b by $NaBH_4$ reduction (quantitative). Configuration of the newly formed hydroxyl group was determined by the analogy to the case of 9 (see above). Stereoselective epoxidation of 22 (t-BuOOH/VO(acac)$_2$/C_6H_6/reflux) gave a diepoxide 23 in 74% yield as a sole product [ν($CHCl_3$) 3540, 1125, 1085, 1020, 980, 940, 895, 860 cm^{-1}; δ 0.86 (3H, s, 10Me), 2.61 (2H, s, C_9-H_2), 3.70 and 3.82 (total 1H[11], each d, J=2.2, C_2-H), 4.40

Table Chemical Shifts of 10-Me, C_9-H_2, and C_2-H

		3-keto compound				3-hydroxyl compound	
		13/14	24a/25a	24b/25a	26/27	10a/11a	23/28
A	a	1.02	1.03	1.04	1.14	0.85	0.86
	b	1.13	1.13	1.12	1.26	1.00	1.02
B	a	2.76, 3.07 AB	2.77, 3.09 AB	2.78, 3.09 AB	2.92, 3.16 AB	2.61 A_2	2.61 A_2
	b	2.84 A_2	2.85, 2.92 A_2like AB	2.84, 2.92 A_2like AB	2.96, 3.02 A_2like AB	2.75, 3.06 AB	2.75, 3.06 AB
C	a	3.45	3.75	—	3.83	3.45(d, 1.5)	—
	b	3.39	3.71	—	3.74	3.51(d, 2.5)	—

A Chemical shift of 10-Me

B Chemical shifts (and equivalency) of C_9-H_2

C Chemical shift of C_2-H

a 4β,9-Epoxy compounds, 13, 24a, 24b, 10a, 23, and 26

b 4α,9-Epoxy compounds, 14, 25a, 25b, 11a, 38, and 27

(1H, m, C_3-H)]. Stereochemical control of the epoxidation of allyl alcohols catalysed by vanadyl acetylacetonate[12] is well known and comparison of the nmr spectrum with those of 10a and 11a clearly indicated the spiro β-epoxide structure of 23 (Table). Collins oxidation of 23 afforded ketodiepoxide 24b (72% yield) which was demasked to give 24a in 84% yield [ν($CHCl_3$) 3400, 1760, 1110, 915 cm^{-1}; δ 1.03 (3H, s, 10Me), 2.77 and 3.09 (2H, ABq, J=6.3, C_9-H_2), 3.75 (1H, s, C_2-H), 4.65 (1H, dd, J=8.5 and 4.4, C_8-H); 3.5-dinitrobenzoate, mp 93~4°, $C_{17}H_{14}N_2O_9$]. Finally the A,B ring model of diketocoriolin B[13], 26, was quantitatively obtained by Jones oxidation of 24a [26: ν($CHCl_3$) 1765, 1100, 1080, 915, 890, 840 cm^{-1}; δ 1.14 (3H, s, 10Me), 2.92 and 3.16 (2H, ABq, J= 6.5, C_9-H_2), 3.83 (1H, s, C_2-H)]. Isomeric diketodiepoxide 27 was prepared by the same sequence from diepoxide 25b which in turn was furnished by hydrogen peroxide treatment (30% H_2O_2/Na_2CO_3/ aqTHF/ rt/1 hr) of 20b as a mixture of 24b and 25b (60% yield, ratio, 1:1) [27: mp 91~93°; ν($CHCl_3$) 1760, 1105, 1085, 915, 905 cm^{-1}; δ 1.26 (3H, s, 10Me), 2.96 and 3.02 (2H, ABq, J=6.0, C_9-H_2), 3.74 (1H, s, C_2-H)]. Comparison of the nmr data indicates that here also the 10-methyl group of 26 resonates at a higher field than that of 27 by 0.12 ppm. This difference in chemical shifts invariably appeared in all pairs of stereoisomeric 4,9-epoxides so far examined (Table) and is very useful for determination of the stereochemistry of the epoxide group. The nmr splitting pattern of the methylene protons of the 4,9-spiro-epoxide ring is a typical AB quartet in 26. However, that in 27 is approximately A_2 (60 MHz). These characteristics are similar to those of 13 and 14. The above data support the stereostructures of the final products 26 and 27. These and other useful empirical correlations between the nmr data and stereochemistry of the 4,9-

epoxide ring are summarized in Table.

References and Notes

1) a) T. Takeuchi, H. Iinuma, J. Iwanaga, S. Takahashi, T. Takita, H. Umezawa, J. Antibiotics, 22, 215 (1969), b) T. Takeuchi, S. Takahashi, H. Iinuma, H. Umezawa, ibid, 24, 631 (1971), c) H. Nakamura, T. Takita, H. Umezawa, M. Kunishima, Y. Nakayama, Y. Iitaka, ibid, 27, 301 (1974).

2) H. Hashimoto, K. Tsuzuki, F. Sakan, H. Shirahama, T. Matsumoto, Tetrahedron Lett., 3745 (1974).

3) K. Tsuzuki, H. Hashimoto, H. Shirahama, T. Matsumoto, Chem. Lett., 1469 (1977). This compound was prepared from 2-methylcyclopentanone through the following successive treatments in 30% over all yield; 1)Methallyl chloride/t-BuOK/t-BuOH, 2)O_3/CH_2Cl_2/pyr/-78°C, 3)Zn/AcOH, 4)50% KOH/MeOH.

4) Satisfactory elementary analytical data were obtained for the compound for which the molecular formula was indicated.

5) Unless otherwise noted, all nmr spectra were measured in $CDCl_3$.

6) For typical chemical shift values for Me-groups of α-methylcyclopentanones, see L. M. Jackman, and S. Sternhell, " Applications of NMR Spectroscopy in Org. Chem. " 2nd ed., p.168, Pergamon Press, London, 1969.

7) P. A. Grieco, M. Miyashita, J. Org. Chem., 39, 120 (1974).

8) This signal coupled with that at δ 5.96 with a small coupling constant.

9) A similar coupling constant (2.1 Hz) between C_2-H and C_3-H has been observed for coriolin B, hirsutic acid and their derivatives containing 1β,2β-epoxy and 3β-hydroxyl groups.

10) Effect of a neighboring hydroxyl group on the steric course of the epoxidation. H. B. Henbest, Proc. Chem. Soc., 159 (1963).

11) Separate appearance of the two signals is due to the presence of a chiral center in the THP group.

12) K. B. Sharpless, R. C. Michaelson, J. Amer. Chem. Soc., 95, 6136 (1973), B. M. Trost, T. N. Salzmann, J. C. S. Chem. Comm., 571 (1975).

13) For the antitumoric activity, see ref. 1b.

Received, 20th September, 1979