Tetrahedron Vol. 37, No. 25, pp. 4365 to 4369, 1981
Printed in Great Britain.

0040-4020/81/254365-05$02.00/0

THE TOTAL SYNTHESIS OF (±)-CORIOLIN

KUNIAKI TATSUTA,* KOHJI AKIMOTO and MITSUHIRO KINOSHITA
Department of Applied Chemistry, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama, 223, Japan

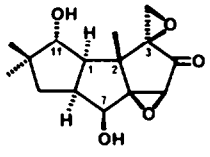
(*Received in USA 5 January* 1981)

Abstract—The first total synthesis of (±)-coriolin from the tricyclo 6–4–5-fused ring photo-adduct through the key tricyclo 5–5–5-fused ring intermediate, 7,8,11 - trihydroxy - 1,4,4 - trimethyltricyclo[6.3.0.0^{2,6}]undecan - 3 - one, is described.

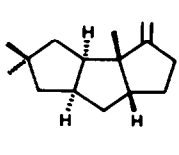
In 1969, Umezawa[1] isolated coriolin **1** from fermentation broths of the Basidiomycete *Coriolus consors*, and demonstrated that this new metabolite increased the number of antibody-forming cells in mouse spleen. As the cell immunity is decreased in cancer patients, it is thought that compounds enhancing cell immunity could enhance the effect of any cancer treatment.[2] Therefore, their strong activity rapidly won for the coriolin group antibiotics an important place in antitumor antibiotics. The structure of coriolin **1** was established in 1971 through chemical studies,[3] followed by X-ray crystallographic studies in 1974.[4] Thus, it was early clear that coriolin **1** was a member of the hirsutanoid sesquiterpene group,[5] of which hirsutic acid[6] and hirsutene **2**[7,8] were also known. Both the unusual biological activity and the unique tricyclo 5–5–5-fused ring, cis,anti,cis - tricyclo[6.3.0.0^{2,6}]undecane system, have attracted widespread interest. Indeed, coriolin **1** is a challenging synthetic target owing to the presence of eight asymmetric centres of a compact carbon skeleton. Consequently, it was our intention to successfully develop a general method of entry into the tricyclo 5–5–5-fused ring system by our own strategy. In this connection, we achieved a stereocontrolled total synthesis[8] of hirsutene **2**, a biogenetic precursor of coriolin **1**.[7] The key step was a unique skeletal-rearrangement of a tricyclo 6–4–5-fused ring derivative **7** to a tricyclo 5–5–5-fused ring derivative **8**. Subsequently, as an extension of the strategy, we achieved the first[9] total synthesis of coriolin **1**. This accomplishment was followed by the elegant syntheses of Danishefsky,[10] and Shibasaki and Ikegami *et al.*[11]

Herein we describe in detail, our first total synthesis of coriolin **1** from the above-mentioned key intermediate **8**.

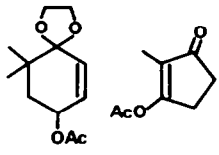
Compound **8** contains already felicitously placed functional groups, an epoxide group of potential value for the introduction of oxygen atoms at appropriate positions, and five asymmetric carbon atoms properly oriented. The synthesis[8] of **8** was initiated from the tricyclo 6–4–5-fused ring derivative **5**, which was



1: Coriolin



2 Hirsutene

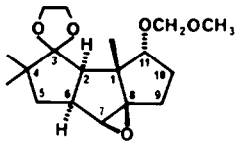


3 4

5: $R^1=R^3=Ac$, $R^2=H$

6: $R^1=R^3=H$, $R^2=CH_2OCH_3$

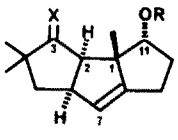
7: $R^1=H$, $R^2=CH_2OCH_3$, $R^3=Ts$



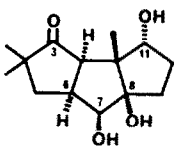
8

obtained from 4 - acetoxy - 6,6 - dimethylcyclohex - 2 - enone ethylene acetal **3**[8] and 3 - acetoxy - 2 - methylcyclopent - 2 - enone **4**[12] by photocycloaddition and subsequent reduction, through the formation of the diol **6** and the skeletal-rearrangement of the tosylate **7**, as described in detail in the Experimental section. The structural assignments of **5–8** have been already verified by the successful transformation to (±)-hirsutene **2** as well as the X-ray analyses of their derivatives.[8]

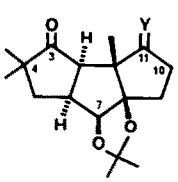
We now came to grips with the problem of treating the 7,8-epoxide ring of **8**. The cleavage of the epoxide ring by hydrolytic reagents would be expected to lead to a trans diol having an undesired α-hydroxy group at C-7.[8] On the other hand, the deoxygenation of **8** with NaI and Zn dust afforded the olefin **9**. Though we suffered a loss of valuable asymmetry at C-7 and C-8 in this process, it was clear that **9** could be a useful intermediate provided that a cis-dihydroxylation could be achieved at the less hindered convex side. Then, **9** was hydrolyzed with 2% H_2SO_4 to the ketoalcohol **10**, which was submitted to a catalytic OsO_4 cis-dihydroxylation[13] to give the key triol **11** in a high yield. The latter was readily converted to the corresponding acetonide **12** by treatment with 2,2-dimethoxypropane and TsOH for 10 min. The stereochemistry of the newly introduced hydroxyl groups at C-7 and C-8 positions was assigned as depicted by **11** on the following basis: (i) formation of a cis 5–5-fused bicyclic ring is thermodynamically favored over that of a trans fused ring;[8,14] (ii) attack upon the olefin group is initiated at the convex face by OsO_4; (iii) therefore, the most readily accessible transition state is one which gives the desired stereochemistry fixed in cis configurations relative to the angular methyl group. The fact is



9: R = CH_2OCH_3, X = O,O

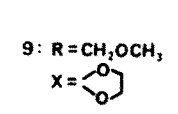


11



12: Y = H, OH

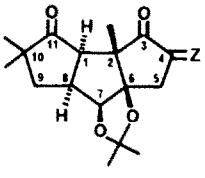
13: Y = O



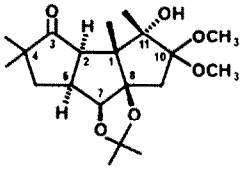
10: R = H, X = O

completely confirmed by the completion of the synthesis by the methods shown below.

Oxidation of **12** with pyridinium chlorochromate smoothly afforded the corresponding ketone **13**, which was the key intermediate for further functionalization. Bis-sulfenylation[15] of **13** with NaH and methyl 2-nitrophenyl disulfide readily gave the thioacetal **14**, which was treated with thallium(III) trinitrate in MeOH to give the corresponding dimethyl acetal **15**. Thus, the desired introduction of the oxygen atom to C-10 of **12** was accomplished and then the stage was set for the next introduction of a carbon atom to C-3 of **15** in order to advance the synthesis to completion. The latter introduction was realized by preferential attack of MeLi on the less hindered carbonyl group of **15** to give the tertiary alcohol **16**. Subsequently, the other relatively hindered carbonyl group of **16** was subjected to be reduced by a variety of methods. Reduction with Li and liquid NH_3 predominantly gave the desired α-alcohol **17**, while hydride reductions predominantly gave the corresponding β-epimer. Conclusive evidence for the stereochemical assignments at the C-3 and C-11 positions was provided by transformation of **17** to the unsaturated ketone **20** which was identical with the naturally derived product as described later on. Thus, deprotection of **17** with 90% trifluoroacetic acid to give the tetraol **18**, followed by selective acetylation gave the diacetate **19**. Elimination of the hydroxyl groups of **19** with methanesulfonyl chloride and (N,N-dimethyl) 4-aminopyridine in pyridine afforded the unsaturated ketone **20** in moderate yield. An authentic sample of **20** is derived from coriolin B,[3] which

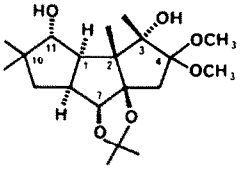


14: Z = $C(SCH_3)_2$

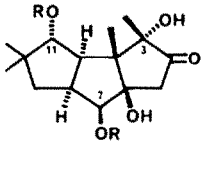


16

15: Z = $C(OCH_3)_2$

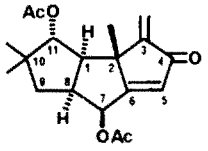


17

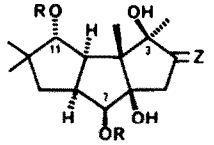


18 R = H

19: R = Ac



20



21: R = H, Z = OH, H

22: R = H, Z = O

23: R = Ac, Z = O

is known to be a biogenetic analogue of coriolin **1**, as follows.

Coriolin B was treated with $LiAlH_4$ to give the hexahydrocoriolin **21**,[3] which was selectively oxidized with anhydrous CrO_3 in pyridine to yield the monoketone **22**. Selective acetylation of **22** gave the diacetate **23**, which was converted to the unsaturated ketone **20** in the manner described above. While, in regard to the spectral data and tlc behavior, **22** and **23** were not identical with **18** and **19** respectively, the synthetic **20** was identical with the naturally derived product. This fact showed that **18** and **19** differed from **22** and **23** only in their relative configurations at C-3.

Finally, deacetylation of the synthetic **20** with LiOH, followed by epoxidation[5] with excess of alkaline hydrogen peroxide completed the synthesis. It seemed reasonable to assume that possible isomers other than coriolin **1** were also produced.[10] The desired (±)-coriolin **1**, however, was isolated as a biologically active product by using bioautography with *Bacillus subtilis*. The racemic coriolin **1** thus obtained was identical both spectroscopically and chromatographically with an authentic sample of the natural product.

EXPERIMENTAL

M.ps were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. IR, UV and MS spectra were recorded on a Hitachi Perkin-Elmer 225, JASCO UV IDEC-1 and Hitachi RMU-7M FD/EI M991 spectrometers, respectively, and NMR spectra in $CDCl_3$ with TMS as internal standard on a Varian A60D (60 MHz), a Varian EM-390 (90 MHz) or a Varian XL 100 spectrometer (100 MHz) unless otherwise mentioned. Optical rotations were measured on a Carl Zeiss photoelectric polarimeter. Silica gel (SiO_2) tlc and column chromatography were performed on Merck tlc 60 F-254 and Kieselgel 100, respectively. In general, evaporation was carried out under reduced pressure below 30°C.

(1SR,2SR,5RS,6RS,7RS,11SR) - 2,11 - *Diacetoxy* - 5 - *hydroxy* - 6,9,9 - *trimethyltricyclo*[5.4.0.$0^{2,6}$]*undecan* - 8 - *one ethylene acetal* **5**

The starting 4 - acetoxy - 6,6 - dimethylcyclohex - 2 - enone ethylene acetal **3** was prepared by the procedure developed in

these laboratories.[8] The product had b.p. ~57°/0.005 mm; NMR (60 MHz) peaks at δ 1.02 and 1.08 (each 3H, s, Me X 2), and 2.08 (3H, s, OAc); λ_{max} (cyclohexane) 219 nm (ε 266). 3 - Acetoxy - 2 - methylcyclopent - 2 - enone **4** was prepared according to the method of de Mayo[12] and had NMR (60 MHz) peaks at δ 1.61 (3H, t, Me) and 2.29 (3H, s, OAc); λ_{max} (cyclohexane) 227 nm (ε 10500).

A soln of the acetal **3** (21.0 g) in dry cyclohexane (31.2 ml) was flushed with argon for 30 min. The acetate **4** (1.73 g) was added and the mixture irradiated through a Pyrex-filter with a 400W high-pressure mercury arc (Nikko Sekiei UV-HT) in a water-cooled immersion well for 60 h under argon. The solvent was removed and the resultant oil was chromatographed on SiO_2 (500 g) with n-hexane–methyl ethyl ketone (3:1). The excess acetal **3** having R_f 0.64 on tlc (hexane–EtOAc 2:1) was recovered (18.9 g) and the crude photo-adduct having R_f 0.23–0.28 obtained (2.05 g).

To a stirred soln of the photo-adduct in MeOH (41 ml) was added $NaBH_4$ (142 mg) by portions within 15 min. The reaction mixture was then stirred for 30 min and neutralized with 10% AcOH, and the solvent removed to give the residue. This was partitioned between $CHCl_3$ and water and the combined $CHCl_3$ layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to give an oil, which was chromatographed on SiO_2 (100 g) with n-hexane–EtOAc (4:3). The fractions containing **5** were combined and the solvent was evaporated to a solid, which was recrystallized from ether–n-hexane to give 1.15 g (26.8% from **4**) of crystalline **5**: R_f 0.33 (n-hexane–EtOAc 1:1); m.p. 167–169°; δ (100 MHz) 0.87, 1.15, 1.24 (each 3H, s, Me X 3), 1.96, 2.03 (each 3H, s, OAc X 2), 3.8–4.0 (4H, m, ethylene acetal), 5.16 (1H, dt, $J_{1,11} = J_{10,11} = 10$ Hz, $J_{10',11} = 6$ Hz, H-11). Found: C, 63.09; H, 7.95. Calc. for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91%.

(1SR,2SR,5RS,6RS,7RS,11SR) - 2,11 - *Dihydroxy* - 5 - *methoxymethoxy* - 6,9,9 - *trimethyltricyclo*[5,4,0,$0^{2,6}$]*undecan* - 8 - *one ethylene acetal* **6**

N,N-Di-isopropylethylamine (1.25 ml) and methoxymethyl chloride (0.72 ml) were added to a soln of **5** (915 mg) in $CHCl_3$ (9.15 ml) and the mixture was stirred at room temp for 5 hr. After addition of water (10 ml), the mixture was extracted with $CHCl_3$ and the combined $CHCl_3$ layer was successively washed with $NaHCO_3$ aq and NaCl aq, dried (Na_2SO_4) and evaporated to give a crude oil of the methoxymethoxy derivative (1.12 g).

To a soln of the oil in MeOH (20.5 ml) was added MeONa (64.9 mg) and the mixture was left to stand overnight at room temp. The mixture was neutralized with Amberlite CG-50 (H-type) resin, filtered and evaporated, leaving a residue, which was chromatographed over SiO_2 (60 g) with $CHCl_3$–MeOH (10:1) to give 603 mg (73.5% from **5**) of **6** as a viscous syrup: R_f 0.41 ($CHCl_3$–MeOH 10:1); δ (60 MHz) 0.87, 1.11, 1.24 (each 3H, s, Me X 3), 3.37 (3H, s, OCH_3), 4.63 (2H, s, CH_2 of MM). Found: C, 62.86; H, 8.60. Calc. for $C_{22}H_{34}O_8$: C, 63.13; H, 8.83%.

(1SR,2SR,5RS,6RS,7RS,11SR) - 2 - *Hydroxy* - 5 - *methoxymethoxy* - 6,9,9 - *trimethyl* - 11 - *p* - *toluenesulfonyloxytricyclo*[5.4.0.$0^{2,6}$]*undecan* - 8 - *one ethylene acetal* **7**

To a stirred and ice-cooled soln of **6** (401 mg) in pyridine (4 ml) was added p-toluenesulfonyl chloride (894 mg), and the mixture was stirred at 5° for 1 hr and then at 19° for 3 hr. After addition of water (0.084 ml), the mixture was evaporated to give a residue, which was partitioned between $CHCl_3$ and water. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give quantitatively solid (590 mg) of **7**, which was used for the next step without further purification. Purification by column chromatography on Sephadex LH-20 column with n-hexane–methyl ethyl ketone (2:1) gave an analytical sample of **7** as cubics: R_f 0.40 (n-hexane–EtOAc 1:1); m.p. 104–105.5°; δ (100 MHz) 0.83, 1.07, 1.23 (each 3H, s, Me X 3), 2.01 (1H, d, $J_{1,7} = 14$ Hz, H-7), 2.44 (3H, s, Me of Ts), 2.60 (1H, dd, $J_{1,11} = 10$ Hz, H-1), 3.34 (3H, s, OCH_3), 4.68 (1H, dt, $J_{10,11} = 10$ Hz, $J_{10',11} = 5.5$ Hz, H-11). (Found: C, 60.62; H, 7.25; S, 6.69. Calc. for $C_{25}H_{36}O_8S$: C, 60.46, H, 7.31; S, 6.46%); MS: *m/e* 496 (M^+).

(1RS,2RS,6SR,7SR,8RS,11RS) - 7,8 - *Epoxy* - 11 - *methoxymethoxy* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 3 - *one ethylene acetal* **8**

To a soln of the crude **7** (113 mg) in 60% aq acetone (3.8 ml) was added $KHCO_3$ (22.8 mg), and the mixture was stirred at 86° for 1 day and concentrated to give a residue, which was extracted with ether. The ether soln was washed with water, dried (Na_2SO_4) and evaporated, leaving a residue. This was chromatographed on SiO_2 with n-hexane–$CHCl_3$–acetone (8:1:1) to give 66 mg (90% from **6**) of **8** as a syrup: R_f 0.30 (n-hexane–$CHCl_3$–acetone 8:1:1); δ (100 MHz) 0.96, 0.99, 1.10 (each 3H, s, Me X 3), 1.44, 1.76 (each 1H, dd, $J_{5,5'} = 12.5$ Hz, $J_{5,6} = J_{5',6} = 9$ Hz, H-5 and 5'), 2.66 (1H, ddt, $J_{2,6} = 11.5$ Hz, $J_{6,7} = 2.5$ Hz, H-6), 3.10 (1H, d, H-2), 3.19 (1H, d, H-7), 3.37 (3H, s, OCH_3), 3.61 (1H, d, $J_{10',11} = 5$ Hz, H-11), 4.57, 4.69 (2H in total, AB-q, J = 7 Hz, CH_2 of MM). Found: C, 66.70; H, 8.65. Calc. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70%.

(1SR,2RS,6RS,11RS) - 11 - *Methoxymethoxy* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undec* - 7 - *en* - 3 - *one ethylene acetal* **9**

To a soln of **8** (205 ml) in 97% aq DMF (4.2 ml) was added a mixture of NaI (947 mg) and Zn dust (413 mg), and the suspension was stirred at 130° for 1 day. After further addition of NaI (473 mg) and Zn dust (207 mg), the suspension was stirred at 130° for 2 days and then cooled to room temp. The suspension was extracted with n-hexane and the organic layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to give a residue, which was chromatographed on SiO_2 with n-hexane–EtOAc (5:1) to give 158 mg (81%) of **9** as a syrup: R_f 0.69 (n-hexane–EtOAc 2:1); δ (60 MHz) 1.00, 1.05, 1.13 (each 3H, s, Me X 3), 3.38 (3H, s, OCH_3), 3.6 (1H, m, H-11), 4.62 (2H, AB-q, J = 6 Hz, CH_2 of MM), 5.3 (1H, m, H-7). Found: C, 70.12; H, 9.07. Calc. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15%.

(1SR,2RS,6RS,11RS) - 11 - *Hydroxy* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undec* - 7 - *en* - 3 - *one* **10**

A sample of **9** (107 mg) was dissolved in a mixture of acetone (2.7 ml) and 2.5% aq H_2SO_4 (4 ml) and the mixture was stirred at 50° for 1 day. The resulting mixture was partitioned between EtOAc and $NaHCO_3$ aq and the combined organic layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to a residue. This was chromatographed on SiO_2 (5 g) with n-hexane–EtOAc (2:1) to give a solid, which was recrystallized from EtOAc–n-hexane to afford 72 mg (94%) of **10** as crystals: R_f 0.33 (n-hexane–EtOAc 2:1); m.p. 82.5–83.5°; δ (100 MHz) 0.93, 1.06, 1.07 (each 3H, s, Me X 3), 1.59 (1H, dd, $J_{5,6} = 10$ Hz, $J_{5,5'} = 13$ Hz, H-5), 3.74 (1H, broad t, $J_{10,11} = 4$ Hz, H-11), 5.47 (1H, m, H-7). Found: C, 76.09; H, 9.03. Calc. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

(1RS,2RS,6SR,7SR,8RS,11RS) - 7,8,11 - *Trihydroxy* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 3 - *one* **11**

A soln of **10** (95.3 mg) in acetone (0.95 ml) was added to a soln of N - methylmorpholine - N - oxide monohydrate[13] (563 mg) and OsO_4 (11 mg) in a mixture of acetone (0.95 ml), t-butanol (0.19 ml) and water (0.95 ml), and the mixture was stirred at room temp for 40 hr. To the mixture was added $NaHSO_3$ (135 mg), and the mixture was neutralized to pH 7 with 4N HCl, diluted with NaCl aq and extracted with EtOAc. The combined organic layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (5 g) with $CHCl_3$–MeOH (15:1) and recrystallized from EtOAc–n-hexane to give 94 mg (86%) of **11** as crystals: R_f 0.39 ($CHCl_3$–MeOH 8:1); m.p. 108–109.5°; δ (acetone-d_6, 90 MHz) 1.01 (3H, s, Me), 1.04 (6H, s, Me X 2), 3.07 (1H, d, $J_{2,6} = 9$ Hz, H-2), 3.95 (1H, dd, $J_{6,7} = 5.5$ Hz, $J_{7,OH} = 5.0$ Hz, H-7), 4.26 (1H, d, OH-7). Found: C, 65.96; H, 8.46. Calc. for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72%.

(1RS,2RS,6SR,7SR,8RS,11RS) - 7,8,11 - *Trihydroxy* - 7,8 - O - *isopropylidene* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 3 - *one* **12**

To a soln of **11** (97 mg) in acetone (1.95 ml) containing TsOH (4.4 mg) was added 2,2-dimethoxypropane (0.97 ml), and the mixture was left to stand at room temp for 10 min. After addition of triethylamine, the mixture was diluted with EtOAc and water

and the organic layer was separated. The aq layer was extracted with EtOAc and the combined organic layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to give a residue. This was recrystallized from ether–n-hexane to give 110 mg (98%) of **12** as cubics: R_f 0.65 ($CHCl_3$–MeOH 10:1); m.p. 164.5–166°; δ (100 MHz) 1.04, 1.07, 1.11 (each 3H, s, Me X 3), 1.35, 1.46 (each 3H, s, acetonide), 2.47 (1H, m, OH-11), 3.24 (1H, d, $J_{2,6}$ = 10 Hz, H-2), 4.49 (1H, d, $J_{6,7}$ = 6.5 Hz, H-7). Found: C, 69.40; H, 8.88. Calc. for $C_{14}H_{22}O_4$: C, 69.36; H, 8.90%.

(1SR,2RS,6SR,7SR,8RS) - 7,8 - *Dihydroxy* - 7,8 - O - *isopropylidene* - 1,4,4 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undecane* - 3,11 - *dione* **13**

To a stirred and ice-cooled soln of **12** (10 mg) in CH_2Cl_2 (0.2 ml) was added pyridinium chlorochromate (18.5 mg), and the mixture was stirred at room temp for 1 hr. The resulting mixture was extracted with EtOAc and the combined organic layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to a residue. This was chromatographed on SiO_2 (1.0 g) with n-hexane–EtOAc (3:1) and recrystallized from ether–n-hexane to give 9.0 mg (89%) of **13** as cubics: R_f 0.49 (n-hexane–EtOAc 2:1); m.p. 163.5–165°; δ (60 MHz) 1.09, 1,16 (each 3H, s, Me X 2), 1.38 (9H, s, Me and acetonide), 3.00 (1H, d, $J_{2,6}$ = 9.0 Hz, H-2), 4.38 (1H, d, $J_{6,7}$ = 5.0 Hz, H-7). Found: C, 69.79; H, 8.37. Calc. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%.

(1RS,2SR,6RS,7SR,8SR) - 6,7 - *Dihydroxy* - 6,7 - O - *isopropylidene* - 2,10,10 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undecane* - 3,4,11 - *trione* 4 - *dimethyl dithioacetal* **14**

To a stirred and ice-cooled soln of **13** (20 mg) in THF (0.40 ml) was added 55% NaH (72 mg) and the mixture was stirred at room temp for 15 min. Methyl 2-nitrophenyl disulfide[15] (33 mg, yellow needles, m.p. 57.5–58.5°) was then added to the mixture. After stirring for 13 min, the mixture was diluted with water and ether, the ether layer was separated and the aq layer was extracted with ether. The combined ether layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to a residue. This was purified by preparative tlc (n-hexane–EtOAc 3:1) and recrystallized from ether–n-hexane to give 21 mg (80%) of **14** as cubics: R_f 0.67 (n-hexane–EtOAc 3:1); m.p. 162.5–163.5°; δ (60 MHz) 1.09, 1.15, 1.50 (each 3H, s, Me X 3), 2.14 (6H, s, SMe X 2), 2.65 (2H, AB-q, CH_2-5), 4.43 (1H, d, $J_{7,8}$ = 5 Hz, H-7). Found: C, 59.29; H, 7.35. Calc. for $C_{19}H_{28}O_4S_2$: C, 59.34; H, 7.34%.

(1RS,2SR,6RS,7SR,8SR) - 6,7 - *Dihydroxy* - 6,7 - O - *isopropylidene* - 2,10,10 - *trimethyltricyclo*[6.3.0.$0^{2,6}$]*undecane* - 3,4,11 - *trione* 4 - *dimethyl acetal* **15**

To a soln of **14** (40 mg) in MeOH (2.0 ml) was added a soln of thallium(III) trinitrate (105 mg) in MeOH (0.80 ml), and the mixture was stirred at room temp for 5 min. The resulting precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was partitioned between CH_2Cl_2 and water, and the combined CH_2Cl_2 layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to give a residue. This was purified by preparative tlc (n-hexane–EtOAc 3:1 containing a trace of MeOH) and recrystallization from ether–n-hexane to give 25 mg (68%) of **15** as crystals; R_f 0.48 (n-hexane–EtOAc 3:1); m.p. 131.5–132.5°; δ (60 MHz) 1.08, 1.15, 1.44 (each 3H, s, Me X 3), 2.96 (1H, d, $J_{1,8}$ = 9 Hz, H-1), 3.25, 3.37 (each 3H, s, OMe X 2), 4.40 (1H, d, $J_{7,8}$ = 4.5 Hz, H-7). Found: C, 64.63; H, 8.14. Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01%.

(1RS,2RS,6SR,7SR,8RS,11SR) - 7,8,11 - *Trihydroxy* - 7,8 - O - *isopropylidene* - 1,4,4,11 - *tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undecane* - 3,10 - *dione* 10 - *dimethyl acetal* **16**

To a stirred and cooled (−70°) soln of **15** (17 mg) in ether (0.34 ml) was injected 1.2M ethereal MeLi soln (0.485 ml) under argon, and the mixture was stirred at −70° for 15 min and gradually warmed to 0° for 1 hr. The mixture was diluted with NH_4Cl aq, the organic layer was separated and the aq layer was extracted with ether. The combined ether layer was washed with NaCl aq, dried (Na_2SO_4) and evaporated to a residue. This was chromatographed on SiO_2 with n-hexane–EtOAc (5:3) containing a trace of MeOH and recrystallized from ether–n-hexane to give 10.7 mg (60%) of **16** as needles: R_f 0.30 (n-hexane–EtOAc 3:1); m.p. 186–187°; δ (100 MHz) 1.04, 1.05, 1.10, 1.19, 1.32, 1.41 (each 3H, s, Me X 4 and acetonide), 2.29 (2H, AB-q, J = 15 Hz, CH_2-9), 3.05 (1H, m, H-6), 3.34 (6H, s, OMe X 2), 3.56 (1H, d, $J_{2,6}$ = 10.5 Hz, H-2), 4.40 (1H, d, $J_{6,7}$ = 6 Hz, H-7). Found: C, 65.19; H, 8.87. Calc. for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75%.

(1RS,2RS,3SR,6RS,7SR,8SR,11RS) - 3,6,7,11 - *Tetrahydroxy* - 6,7 - O - *isopropylidene* - 2,3,10,10 - *tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 4 - *one dimethyl acetal* **17**

To a stirred slurry of **16** (17 mg) in THF (0.1 ml), liquid NH_3 (2 ml) was added and then Li (15 mg) added all at once. The mixture was stirred at −30° for 5 min. After quenching with NH_4Cl, the mixture was extracted with EtOAc and the combined EtOAc solution was evaporated to a residue. This was chromatographed on SiO_2 (8 g) with n-hexane–EtOAc (2:1) containing a trace of MeOH to give 13 mg (75%) of crystalline **17**: R_f 0.29 (n-hexane–EtOAc 2:1; compared with R_f 0.53 for the C-11 epimer); m.p. 183.5–185.5°; δ (100 MHz) 0.92, 1.04, 1.17, 1.20, 1.32, 1.49 (each 3H, s, Me X 4 and acetonide), 2.55 (1H, m, H-1), 3.34 (6H, s, OMe X 2), 3.68 (1H, dull dd, $J_{1,11}$ = 9.5 Hz, $J_{11,OH}$ = ~3 Hz, H-11), 4.14 (1H, d, $J_{7,8}$ = 6 Hz, H-7). Found: C, 64.67; H, 9.29. Calc. for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25%. A trace of the C-11 epimer of **17** was detected on tlc.

(1RS,2RS,3SR,6RS,7SR,8SR,11RS) - 3,6,7,11 - *Tetrahydroxy* - 2,3,10,10 - *tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 4 - *one* **18**

A soln of **17** (42 mg) in 90% trifluoroacetic acid (0.69 ml) was stirred at room temp for 12 min and evaporated to a residue. This was chromatographed on SiO_2 (8 g) with benzene–EtOAc (1:2) and recrystallized from ether–n-hexane to give 30 mg (93%) of crystalline **18**: R_f 0.35 ($CHCl_3$–MeOH 8:1; compared with R_f 0.31 for the C-3 epimer **22**); m.p. 140–142°; δ (acetone-d_6 with a drop of D_2O, 90 MHz) 0.90, 1.04, 1.17, 1.26 (each 3H, s, Me X 4), 3.66 (1H, d, $J_{1,11}$ = 8.5 Hz, H-11), 3.84 (1H, d, $J_{7,8}$ = 6.5 Hz, H-7). Found: C, 63.17; H, 8.62. Calc. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%.

(1RS,2RS,3SR,6RS,7SR,8SR,11RS) - 7,11 - *Diacetoxy* - 3,6 - *dihydroxy* - 2,3,10,10 - *tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 4 - *one* **19**

To a soln of **18** (19 mg) in pyridine (0.57 ml) was added Ac_2O (0.285 ml), and the mixture was stirred overnight at 30°. The reaction was quenched with EtOH and the mixture was evaporated to a residue, which was chromatographed on SiO_2 (5 g) with n-hexane–EtOAc (1:1) to give 20 mg (78%) of crystalline **19**: R_f 0.78 ($CHCl_3$–MeOH 8:1) or 0.40 (benzene–acetone 3:1; compared with R_f 0.35 for the C-3 epimer **23**); m.p. 170–171.5°; δ (100 MHz) 0.93, 1.00, 1.21, 1.29 (each 3H, s, Me X 4), 2.02, 2.18 (each 3H, s, OAc X 2), 4.97 (1H, d, $J_{7,8}$ = 7 Hz, H-7), 5.08 (1H, d, $J_{1,11}$ = 8 Hz, H-11). Found: C, 62.10; H, 7.68. Calc. for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66%.

(1RS,2RS,7SR,8SR,11RS) - 7,11 - *Diacetoxy* - 2,10,10 - *trimethyl* - 3 - *methylenetricyclo*[6.3.0.$0^{2,6}$]*undec* - 5 - *en* - 4 - *one, racemic* **20**

To a soln of **19** (9 mg) in pyridine (0.18 ml) were added methanesulfonyl chloride (8.4 mg) and (N,N-dimethyl) 4-aminopyridine (3 mg), and the mixture was stirred overnight at 40°. Then, the aforesaid amounts of pyridine, methanesulfonyl chloride and (N,N-dimethyl) 4-aminopyridine were further added and the mixture was stirred at 60° for 6 hr and then at 80° for 15 hr. After quenching with water, the mixture was evaporated to a residue, which was partitioned between EtOAc and water. The EtOAc layer was evaporated to dryness. The residue was chromatographed on SiO_2 with n-hexane–EtOAc (3:1) and further purified by preparative tlc (benzene–ether 3:1) to give 4 mg (46%) of crystalline **20**: R_f 0.57 (benzene–EtOAc 3:1); m.p. 73–76°; δ (100 MHz) 1.00, 1.09, 1.47 (each 3H, s, Me X 3), ~1.6 (2H, m, CH_2-9), 2.13 (6H, s, OAc X 2), 2.38 (1H, dd, $J_{1,11}$ = 8 Hz, $J_{1,8}$ = 12 Hz, H-1), 3.05 (1H, m, H-8), 5.17 (1H, s, H-5), 5.27 (1H, d, H-11), 5.63 (1H, d, $J_{7,8}$ = 7 Hz, H-7), 5.95, 6.18 (*each* 1H, s, CH_2 = C); λ_{max} (MeOH) 248 nm (ϵ 12900); ν_{max} (CCl_4) 1735, 1703, 1630, 875 cm^{-1}. Found: C, 68.47; H, 7.40. Calc. for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28%.

(±)-Coriolin **1**

To a soln of **20** (59 mg) in THF (0.77 ml) was added 1 m LiOH (0.53 ml), and the mixture was stirred at 30° for 2 hr. The mixture was neutralized with Amberlite CG-50 (H-type) resin, filtered and evaporated to give a crude syrup of the de - O - acetate (60 mg). To a soln of the syrup in 65% aq THF (0.54 ml), a powder of $NaHCO_3$ (60 mg) was added and then 30% H_2O_2 (0.20 ml) added, and the mixture was stirred at room temp for 1 hr. The mixture was neutralized with Amberlite CG-50 (H-type) resin and the solvent was removed yielding a residue, which was chromatographed on preparative tlc with benzene–ether (1:1). The band having the same R_f-value as that of natural coriolin was collected and eluted with EtOAc. The eluates were evaporated to a residue, which was further purified by preparative tlc (benzene–acetone 3:1). The band centered at R_f 0.47, which showed an antibacterial activity against *Bacillus subtilis* PCI 219 on bioautography, was collected and eluted with EtOAc. The eluates were evaporated to a residue, which was recrystallized from EtOAc–$CHCl_3$–n-hexane to give 6 mg (12%) of racemic coriolin **1** as crystals: R_f 0.41 (benzene–EtOAc 3:2) or R_f 0.47 (benzene–acetone 3:1); m.p. 180–183°; δ (100 MHz) 0.93, 1.09, 1.23 (each 3H, s, Me X 3), 2.32 (1H, dd, $J_{1,11}$ = 9 Hz, $J_{1,8}$ = 12 Hz, H-1), 2.75 (1H, m, H-8), 2.98, 3.14 (2H in total, AB-q, J = 6.5 Hz, exo-cyclic ethylene oxide), 3.56 (1H, s, H-5), 3.77 (1H, d, H-11), 4.05 (1H, d, $J_{7,8}$ = 6 Hz, H-7); ν_{max} ($CHCl_3$) 2940 (m), 1760 (s), 1200 (s), 1190 (s) cm^{-1}; MS: *m/e* 280 (M^+). Found: C, 64.42; H, 7.22. Calc. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19%. Its IR, NMR and MS spectra and tlc behavior were identical with those of an authentic sample of the natural product.

(1R,2R,3R,4S,6R,7S,8S,11R) - 2,3,10,10 - *Tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undecane* - 3,4,6,7,11 - *pentaol* **21**

To a soln of coriolin B[3] (1.00 g) in THF (30 ml) was added $LiAlH_4$ (922 mg), and the mixture was refluxed for 1 hr. After cooling, a powder of $Na_2SO_4 \cdot 10H_2O$ (8.0 g) was gradually added and the mixture was filtered through Celite and washed with EtOAc. The combined organic solution was evaporated to a residue, which was purified by chromatography on SiO_2 (100 g) with CH_2Cl_2–MeOH (6:1) and recrystallization from EtOAc–n-hexane to give 675 mg (96%) of **21** as needles: R_f 0.07 (benzene–acetone 2:1); m.p. 188.5–189.5° (lit.[3] m.p. 189°); $[\alpha]_D^{18}$ +41.5° (c 1.0, MeOH). Found: C, 62.70; H, 8.99. Calc. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15%.

(1R,2R,3R,6R,7S,8S,11R) - 3,6,7,11 - *Tetrahydroxy* - 2,3,10,10 - *tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 4 - *one* **22**

To a stirred and ice-cooled soln of **21** (323 mg) in pyridine (6.4 ml) was added pulverized CrO_3 (643 mg), and the mixture was stirred at room temp for 3 hr and then extracted with EtOAc. The extracts were washed with NaCl aq, dried (Na_2SO_4) and evaporated to a residue, which was chromatographed on SiO_2 (32 g) with CH_2Cl–MeOH (14:1). The fractions containing **22** were combined and the solvent was evaporated, leaving a solid, which was recrystallized from EtOAc–n-hexane to give 49 mg (15%) of crystalline **22**: R_f 0.31 ($CHCl_3$–MeOH 8:1) compared with R_f 0.35 for the C-3 epimer **18**; m.p. 191–193°; $[\alpha]_D^{15}$ +48° (c 1.0, MeOH); δ (acetone-d_6 with a drop of D_2O, 90 MHz) 0.88, 1.03, 1.18, 1.30 (each 3H, s, Me X 4), 3.76 (1H, d, $J_{1,11}$ = 9 Hz, H-11), 3.80 (1H, d, $J_{7,8}$ = 5.5 Hz, H-7). Found: C, 63.09; H, 8.27. Calc. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%.

(1R,2R,3R,6R,7S,8S,11R) - 7,11 - *Diacetoxy* - 3,6 - *dihydroxy* - 2,3,10,10 - *tetramethyltricyclo*[6.3.0.$0^{2,6}$]*undecan* - 4 - *one* **23**

This was prepared in the similar manner as described for **19**, starting from **22** (157 mg). Recrystallization of the crude product from EtOAc–n-hexane gave 138 mg (68%) of **23** as needles: R_f 0.67 ($CHCl_3$–MeOH 8:1) or R_f 0.35 (benzene–acetone 3:1; compared with R_f 0.40 for the C-3 epimer **19**); m.p. 186–187.5°; $[\alpha]_D^{20}$ +86° (c 1.0, MeOH); δ (100 MHz) 0.91, 1.02, 1.08, 1.26 (each 3H, s, Me X 4), 1.90 (1H, dd, $J_{1,11}$ = 8 Hz, $J_{1,8}$ = 12 Hz, H-1), 2.04, 2.18 (each 3H, s, OAc X 2), 2.83 (1H, m, H-8), 5.04 (1H, d, $J_{7,8}$ = 6.5 Hz, H-7), 5.17 (1H, d, H-11). Found: C, 62.18; H, 7.55. Calc. for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66%.

(1R,2R,7S,8S,11R) - 7,11 - *Diacetoxy* - 2,10,10 - *trimethyl* - 3 - *methylenetricyclo*[6.3.0.$0^{2,6}$]*undec* - 5 - *en* - 4 - *one* **24**

This was prepared in the similar manner as described for the racemic **20**, starting from **23** (22 mg) to give 4.0 mg (20%) of crystalline **24**: m.p. 109–111°; $[\alpha]_D^{19}$ −51° (c 1.0, MeOH). Found: C, 68.45; H, 7.44. Calc. for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28%. Its IR and NMR spectra and tlc behavior were identical with those of the racemic **20**.

Acknowledgements—We are grateful to Prof. Sumio Umezawa, Institute of Bioorganic Chemistry, and Prof. Hamao Umezawa, Institute of Microbial Chemistry, for their generous support of our program. We are also indebted to Mr. H. Kikuchi and Mr. T. Ando for their skilful technical assistance and Dr. T. Takeuchi, Institute of Microbial Chemistry, for generous gifts of coriolins. Thanks are due to Dr. H. Naganawa for NMR and MS spectral analyses and Mr. S. Nakada for elemental analyses.

REFERENCES

[1]T. Takeuchi, H. Iinuma, J. Iwanaga, S. Takahashi, T. Takita and H. Umezawa, *J. Antibiotics* **22**, 215 (1969).
[2]H. Umezawa, *Heterocycles, Special Issue* **13**, 23 (1979).
[3]S. Takahashi, H. Naganawa, H. Iinuma, T. Takita, K. Maeda and H. Umezawa, *Tetrahedron Letters* 1955 (1971).
[4]H. Nakamura, T. Takita, H. Umezawa, M. Kunishima, Y. Nakayama and Y. Iitaka, *J. Antibiotics* **27**, 301 (1974).
[5]H. Hashimoto, T. Ito, H. Shirahama and T. Matsumoto, *Heterocycles, Special Issue* **13**, 151 (1979).
[6]F. W. Comer and J. Trotter, *J. Chem. Soc. B* 11 (1966); F. W. Comer, F. McCapra, I. H. Qureshi and A. I. Scott, *Tetrahedron* **23**, 4761 (1967). Total synthesis: H. Hashimoto, K. Tsuzuki, F. Sakan, H. Shirahama and T. Matsumoto, *Tetrahedron Letters* 3745 (1974); B. M. Trost, C. D. Shuey and F. DiNinno, *J. Am. Chem. Soc.* **101**, 1284 (1979).
[7]S. Nozoe, J. Furukawa, U. Sankawa and S. Shibata, *Tetrahedron Letters* 195 (1976).
[8]K. Tatsuta, K. Akimoto and M. Kinoshita, *J. Am. Chem. Soc.* **101**, 6116 (1979).
[9]Preliminary communication: K. Tatsuta, K. Akimoto and M. Kinoshita, *J. Antibiotics* **33**, 100 (1980).
[10]S. Danishefsky, R. Zamboni, M. Kahn and S. J. Etheredge, *J. Am. Chem. Soc.* **102**, 2097 (1980); S. Danishefsky and R. Zamboni, *Tetrahedron Letters* **21**, 3439 (1980).
[11]M. Shibasaki, K. Iseki and S. Ikegami, *Tetrahedron Letters* **21**, 3587 (1980).
[12]B. D. Challand, G. Kornis, G. L. Lange and P. de Mayo, *Chem. Commun.* 704 (1967); B. D. Challand, H. Hikino, G. Kornis, G. Lange and P. de Mayo, *J. Org. Chem.* **34**, 794 (1969).
[13]V. van Rheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Letters* 1973 (1976).
[14]S. Chang, D. McNally, S. Shary-Tehrany, S. M. J. Hickey and R. H. Boyd, *J. Am. Chem. Soc.* **92**, 3109 (1970).
[15]Y. Nagao, K. Kaneko, K. Kawabata and E. Fujita, *Tetrahedron Letters* 5021 (1978).