THE TOTAL SYNTHESIS OF (±)-CORIOLIN*

Sir:

Coriolin (**1**), a metabolite of the Basidiomycete, *Coriolus consors*, was isolated by H. UMEZAWA and coworkers in 1969[1] and its structure was established in 1971 through chemical studies,[2] followed by X-ray crystallographic studies in 1974[3]. The unusual antitumor activity and the unique tricyclo 5-5-5- fused ring system have attracted widespread interest. We have already reported a stereocontrolled total synthesis of hirsutene (**2**)[4], a biogenetic precursor of coriolin[5], by using a unique skeletal-rearrangement of a tricyclo 6-4-5- fused ring derivative (**3**) to a tricyclo 5-5-5- fused ring derivative (**4**).

We now wish to record the first total synthesis of (±)-coriolin (**1**).

The key epoxide **4**, upon treatment with NaI and zinc in 97% aq.DMF (130°C, 2 days), afforded the olefin **5**[4], which was hydrolized with 1% sulfuric acid in aq.acetone (50°C, 1 day) to the ketoalcohol **6** (72% overall yield from **4**); mp 82.5~83.5°C. A catalytic OsO_4 *cis*-dihydroxylation[6] of **6** (0.1 eq. OsO_4, 8.5 eq. N-methylmorpholine-N-oxide, room temp., 40 hours) to give the triol **7**; mp 108~109.5°C, PMR (acetone-d_6) δ 1.01 (3H, s, Me), 1.04 (6H, s, Me ×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), followed by treatment with 2,2-dimethoxypropane and TsOH (room temp., 10 minutes) gave the acetonide **8** as cubic crystals; mp 164.5~166°C (85% overall yield). The stereochemistry of the newly introduced hydroxyl groups at C-7 and C-8 positions was controlled by that of the C-1-methyl group because of the difficulty in forming a *trans* 5-5-fused ring[7] and consequently fixed in *cis* configurations relative to the angular methyl group. Compound **8** was oxidized with pyridinium chlorochromate (room temp., 1 hour) to give the ketone **9** in a nearly quantitative yield; mp 163.5~165°C, PMR ($CDCl_3$) δ 1.09 and 1.16 (each 3H, s, Me ×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); which was the key intermediate for the following functionalization. Bis-sulfenylation[8] of **9** with NaH (2.4 eq.) and methyl 2-nitrophenyl disulfide (mp 58~59°C, 2.4 eq.) in THF (room temp., 13 minutes) gave the thioketal **10**; mp 162.5~163.5°C, pmr ($CDCl_3$) δ 1.09, 1.15 and 1.50 (each 3H, s, Me ×3), 1.34 (6H, s, acetonide), 2.14 (6H, s, SMe ×2),

* Dedicated to Professor SUMIO UMEZAWA on his 70th birthday.

Chart 1.

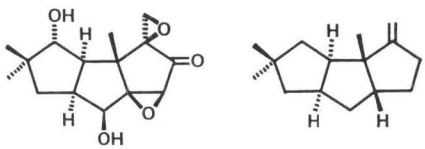
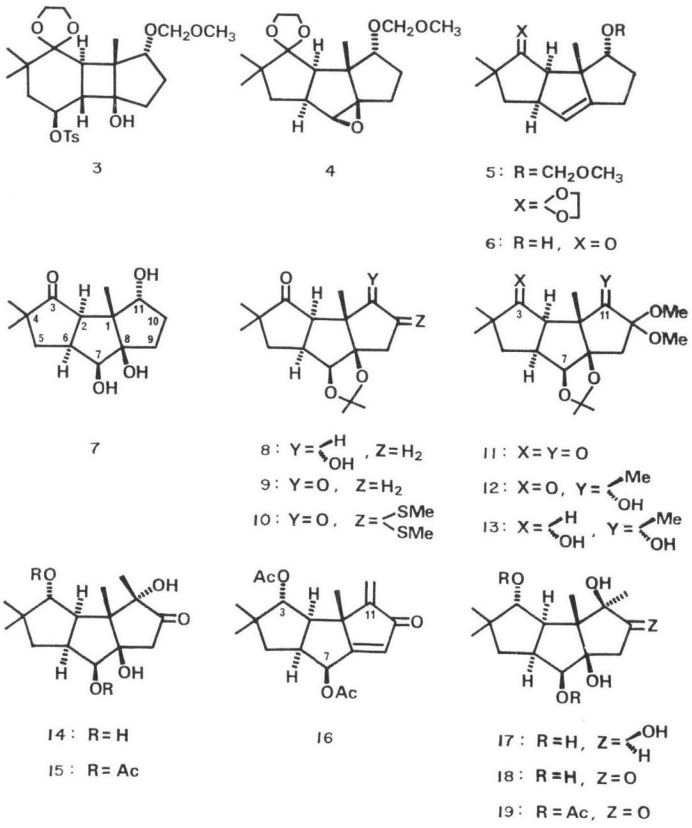


Chart 2.



2.65 (2H, AB-q, CH_2-9), 4.43 (1H, d, $J_{6,7}=5$ Hz, H-7); which was treated with thallium (III) trinitrate (2.2 eq.) in MeOH (room temp., 5 minutes) to give the corresponding dimethylketal **11** (54% overall yield); mp 131.5~132.5°C, PMR ($CDCl_3$) δ 1.08, 1.15 and 1.44 (each 3H, s, Me ×3), 1.35 (6H, s, acetonide), 2.96 (1H, d, $J_{2,6}=9$ Hz, H-2), 3.25 and 3.37 (each 3H, s, OMe ×2), 4.40 (1H, d, $J_{6,7}=5$ Hz, H-7). The latter was transformed by treatment with excess methyl lithium in ether (−70°C to 0°C, 1 hour) to the tertiary alcohol **12** (60% yield); mp 186~187°C, PMR ($CDCl_3$) δ 1.04, 1.05, 1.10, 1.19, 1.32 and 1.41 (each 3H, s, Me ×4 and acetonide), 2.0 (2H, m, CH_2-5), 2.29 (2H, AB-q, J=15 Hz, CH_2-9), 3.05 (1H, m, H-6), 3.34 (6H, s, OMe ×2), 3.56 (1H, d, $J_{2,6}=10.5$ Hz, H-2), 4.40 (1H, d, $J_{6,7}=6$ Hz, H-7); which was reduced in a small amount of THF by excess Li and liquid ammonia (−30 °C, 5 minutes) to give the desired α-alcohol **13** (78% yield); mp 183.5~185.5°C, PMR ($CDCl_3$) δ 0.92, 1.04, 1.17, 1.20, 1.32 and 1.49 (each 3H, s, Me×4 and acetonide), 2.55 (1H, m, H-2), 3.34 (6H, s, OMe ×2), 3.68 (1H, dull dd, $J_{2,3}=9.5$ Hz, $J_{3,OH}=\sim 3$ Hz, H-3), 4.14 (1H, d, $J_{6,7}=6$ Hz, H-7). Conclusive evidence for the stereochemical assignments at the C-3 and C-11 positions was provided by transformation of **13** to the unsaturated ketone **16** which was identical with the naturally derived product as described later on. Reduction of **12** with $LiAlH_4$ in THF gave a mixture (approximately 1:7) of **13** and the β-epimer **13'**; TLC (hexane - EtOAc, 2:1; Rf 0.42 (**12**), 0.29 (**13**) and 0.53 (**13'**)]; the latter was not convertible to the desired product **16**. Thus, deprotection of **13** with 90% trifluoroacetic acid (room temp., 12 minutes) to give the tetraol **14**, followed by selective acetylation (Ac_2O, pyridine, 30°C, overnight) gave the diacetate **15** (68% overall yield); mp 171~172°C, PMR ($CDCl_3$) δ 0.93, 1.00, 1.21 and 1.29 (each 3H, s, Me ×4), 2.02 and 2.18 (each 3H, s, OAc ×2), 2.34 and 2.74 (each 1H, AB-q, J=20 Hz, CH_2-9), 4.97 (1H, d, $J_{6,7}=7$ Hz, H-7), 5.08 (1H, d, $J_{2,3}=8$ Hz, H-3). Elimination of the hydroxyl groups of **15** with methanesulfonyl chloride (3 eq.) and 4-dimethylaminopyridine (1 eq.) in pyridine (50~80°C, 2 days) afforded the unsaturated ketone **16** (46% yield); IR ($CHCl_3$) 1735, 1703, 1630 and 875 cm^{-1}, UV λ_{Max}^{MeOH} 248 nm (ε 12,900), PMR ($CDCl_3$) δ 1.00, 1.09 and 1.47 (each 3H, s, Me ×3), 1.6 (2H, m, CH_2-5), 2.13 (6H, s, OAc ×2), 2.38 (1H, dd, $J_{2,3}=8$ Hz, $J_{2,6}=12$ Hz, H-2), 3.05 (1H, m, H-6), 5.17 (1H, s, H-9), 5.27 (1H, d, H-3), 5.63 (1H, d, $J_{6,7}=7$ Hz, H-7), 5.95 and 6.18 (each 1H, s, $C=CH_2$).

Coriolin B[2], which is known to be a biogenetic analogue of coriolin (**1**), was treated with $LiAlH_4$ to give the hexahydrocoriolin **17**; mp 188.5~189.5°C (lit.[2] mp 189°C); which was selectively oxidized[2] with anhydrous CrO_3 in pyridine to yield the ketone **18**; PMR (acetone-d_6 + D_2O) δ 0.88, 1.03, 1.18 and 1.30 (each 3H, s, Me ×4), 3.76 (1H, d, $J_{2,3}=9$ Hz, H-3), 3.80 (1H, d, $J_{6,7}=5.5$ Hz, H-7), TLC [$CHCl_3$ - MeOH, 8:1] Rf 0.31 compared with 0.35 for **14**. Selective acetylation of **18** gave the diacetate **19**; mp 186~187.5°C, PMR ($CDCl_3$) δ 0.91, 1.02, 1.08 and 1.26 (each 3H, s, Me ×4), 1.90 (1H, dd, $J_{2,3}=8$ Hz, $J_{2,6}=12$ Hz, H-2), 2.04 and 2.18 (each 3H, s, OAc ×2), 2.32 and 2.90 (each 1H, AB-q, J=20 Hz, CH_2-9), 2.83 (1H, m, H-6), 5.04 (1H, d, $J_{6,7}=6.5$ Hz, H-7), 5.17 (1H, d, H-3), TLC (benzene - acetone, 3:1) Rf 0.35 (compared with 0.40 for **15**); which was converted to the unsaturated ketone in the manner described above. The spectral data were in total agreement with the aforementioned product **16**, showing that **14** and **15** differed from **18** and **19** only at the C-11 position with respect to the relative configuration.

Finally, deacetylation of **16** in aq.THF with 1 N LiOH (room temp, 1 day), followed by epoxidation[9] with excess of alkaline hydrogen peroxide (30% H_2O_2, $NaHCO_3$, aq. THF, 0°C to room temp., 6 hours), completed the synthesis, giving (±)-coriolin (**1**) in 6% overall yield; mp 181~183°C (from EtOAc - $CHCl_3$ - hexane), PMR ($CDCl_3$) δ 0.93, 1.09 and 1.23 (each 3H, s, Me ×3), 1.49 and 1.86 (each 1H, m, CH_2-5), 2.32 (1H, dd, $J_{2,3}=9$ Hz, $J_{2,6}=12$ Hz, H-2), 2.75 (1H, m, H-6), 2.98 and 3.14 (2H, AB-q, J=6.5 Hz, exocyclic ethylene oxide), 3.56 (1H, s, H-9), 3.77 (1H, d, H-3), 4.05 (1H, d, $J_{6,7}=6$ Hz, H-7); which was identical both spectroscopically (IR, PMR and mass spectra) and chromatographically (TLC detected by stain with H_2SO_4 and by bioautography using *Bacillus subtilis* PCI 219) with an authentic sample of the natural product.

Acknowledgement

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 skillful technical assistance and Dr. T. TAKEUCHI, Institute of Microbial Chemistry, for generous gifts of coriolins. Thanks are due to Dr. H. NAGANAWA for PMR and mass spectral analyses.

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(Received November 19, 1979)

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