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A TOTAL SYNTHESIS OF *dl*-CORIOLIN

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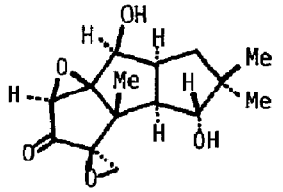
Summary: *A total synthesis of dl-coriolin has been accomplished starting from 1,3-cyclooctadiene, in which a rational and efficient introduction of various functional groups to the synthetic intermediate, 7-endo-t-butyldimethylsilyloxybicyclo[3.3.0]-oct-8-en-2-one, is involved.*

Coriolin (1), a metabolite of the Basidiomycete, *Coriolus consors*, was isolated by H.Umezawa and coworkers in 1969[2] and its structure was determined in 1971.[3] The interesting antibacterial and antitumor activities and the fascinating chemical structure consisted of the highly functionalized *cis,anti,cis*-tricyclo[6.3.0.$0^{2,6}$]undecanoid have stirred considerable interest into synthesis of such a class of sesquiterpenes. Very recently, two elegant total syntheses of coriolin (1) were reported independently by Tatsuta et al.[4a] and Danishefsky et al.[4b]

As a part of our synthetic program of biologically active substances, synthetic studies on coriolin (1) and the related substances were undertaken. In this communication, we wish to report a total synthesis of *dl*-coriolin (1) starting from 1,3-cyclooctadiene.

A stereo and regiospecific synthetic route to the enone (2) which is an attractive intermediate for the total synthesis of coriolin (1) was established by our recent efforts in *ca.* 35% overall yield.[5,7] In an introduction of the various functionalities to 2, we, first of all, undertook methylation by the conjugate addition. The reaction of 2 with lithium dimethylcopper (1.4 equiv, ether, -78°) gave the methyl-ketone (3)[6a][PMR($CDCl_3$,TMS) δ0.98(d,J=7Hz,3H,CH_3); IR(neat) 1740 cm-1], whose stereoconfiguration was tentatively assigned as 3, in 95% yield. Then, the methyl-ketone (3) was subjected again to dimethylation in THF using 2.2 equiv of potassium *t*-butoxide and 10 equiv of methyl iodide (-78~0°) to provide the dimethylated ketone (4)[6a] [PMR($CDCl_3$,TMS) δ1.02(d,J=7Hz,3H,CH_3), 1.03(s,3H,CH_3), 1.06(s,3H,CH_3); MS(EI) 239(M^+)] regiospecifically in 77% yield. None of the products methylated at the angular carbon could be detected by either the PMR spectrum or the careful TLC analysis. Reduction of 4 (Li, NH_3, a small amount of THF) afforded the desired alcohol (5)[6a] along with its epimer (6)[6a] in a ratio of *ca.* 5:2 [*Rf* 0.26(5), 0.43(4) (silica gel, ether-petr.ether(1:4)]. The configuration of the alcohol functionality of 5 is well-established by considering the reduction mechanism and by being successfully converted to coriolin (1). Various attempts to invert the useless alcohol



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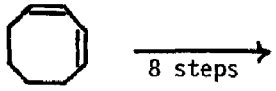

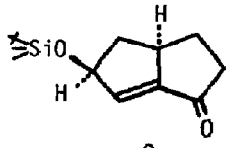

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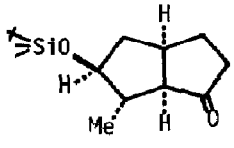

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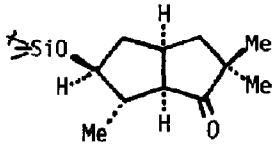

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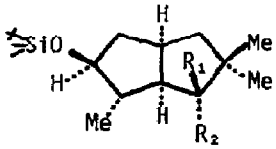
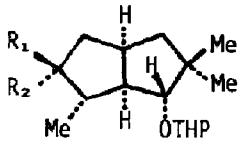
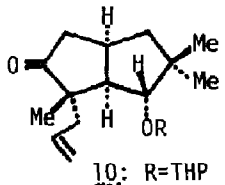


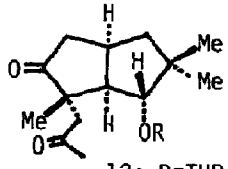
5: R_1=H, R_2=OH
6: R_1=OH, R_2=H



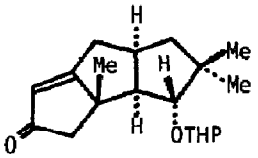
7: R_1=OSi≡, R_2=H
8: R_1=OH, R_2=H
9: R_1-R_2=O



10: R=THP
11: R=H



12: R=THP
13: R=H



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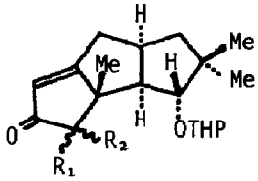
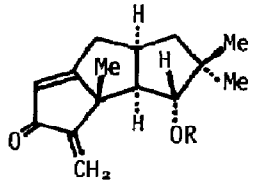
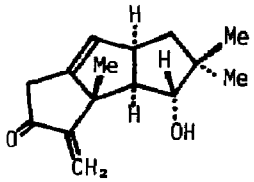


15: R_1=Me, R_2=H
16: R_1=Me, R_2=SePh



17: R=THP
18: R=H



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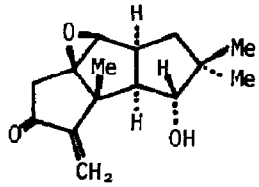

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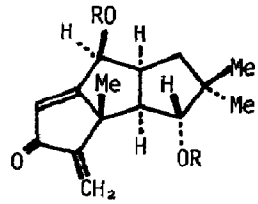

21: R=H
22: R=Ac

(6) to 5 resulted in failure, probably due to sterically crowded environment around the alcoho group. However, the alcohol (6) was able to be recycled to the parent ketone (4) by oxidation with PDC in DMF (r.t., 10 hr) in 70-75% yield. Protection of the alcohol (5) as a THP ether, followed by desilylation with a fluoride ion in THF, gave the THP-alcohol (8)[6a] [MS(EI) 268(M^+ in nearly quantitative yield. Subsequent oxidation of the THP-alcohol (8) with PCC in the presence of sodium acetate afforded the ketone (9)[6b] [IR($CHCl_3$) 1740 cm-1] in 90% yield.

The stereo and regiocontrolled introduction of an acetonyl fragment to the ketone (9), on of the most crucial steps in our synthesis, was easily achieved as follows. Thus, treatment of 9 with sodium hydride (1.2 equiv) in DME at room temperature for 2 hr, followed by addition of an excess of allyl bromide (10 equiv) and continued stirring under the same condition for *ca.* 10 hr,[8] afforded, stereo and regiospecifically, the desired product (10)[6a] [MS(EI) 306(M^+)] in 81% yield (94% yield when based on the recovered starting material). The critical stereo an regiochemistry of 10 was characterized by the following facts; that is, (1) 10 could be succes fully transformed into coriolin (1) and (2) the PMR spectrum of the deprotected allyl-ketone (11) displayed clean three singlets (δ0.94, 1.02, 1.16) for the three methyl groups. In order to convert the allyl group of 10 to an acetonyl group, the allyl-ketone (10) was subject to react with palladium chloride (0.4 equiv) and cuprous chloride (2 equiv) in DMF-H_2O(10:1.2) under oxygen atmosphere at room temperature for 24 hr, providing the desired methyl ketone (12)[6a,9] [IR(neat) 1739, 1715 cm-1; MS(EI) 322(M^+)] in 77% yield. Further confirmation concerning the stereo and regiochemistry of the allyl-ketone (10) was obtained from the PMR spectrum of the deprotected methyl-ketone (13) observing clean four singlets (δ0.94, 1.07, 1.15, 2.11) assignable to the four different methyl groups.

The methyl-ketone (12) was then cyclized by treatment with 0.5 equiv of potassium *t*-butoxide in *t*-butanol at 35° for 10 min to give the tricyclic enone (14)[6a] [IR(neat) 1703, 1640 cm-1; PMR($CDCl_3$,TMS) δ5.70(olefinic proton); MS(EI) 304(M^+)] in 83% yield.

Introduction of α-methylene functionality to the cyclopentenone system (14) succeeded in the following method.[4c] The enone (14) was methylated in THF using 2.2 equiv of LDA and 10 equiv of methyl iodide (-78~0°) to give the methyl-ketone (15)[6a] [MS(EI) 318(M^+)] as a mixtu of stereoisomers in 90% yield. The methyl-ketone (15) was further treated with 2.2 equiv of LDA at -78° for 0.5 hr, followed by addition of 3 equiv of phenylselenenyl bromide (-78~0°), t provide the selenide (16), which was directly oxidized with 30% hydrogen peroxide and a small amount of acetic acid in THF at 0° for 0.5 hr, yielding the α-methylene-enone (17). Without purification, the α-methylene-enone (17) was deprotected with AcOH-H_2O-THF (3:1:1) at room temperature to furnish the hydroxy-enone (18)[6a] [PMR($CDCl_3$,TMS) δ5.94(s,2H,olefinic protons), 5.37(s,1H,olefinic proton); IR(neat) 3430, 1690, 1621 cm-1; MS(EI) 232(M^+)] in *ca.* 50% overal yield from 15.

The formation of a hydroxy group on the B ring was accomplished by the essentially same method as Danishefsky et al. utilized.[4b,10] Thus, the enone (18) was treated with 10 equiv of potassium *t*-butoxide in DME at room temperature for 1 hr, followed by rapid quenching with 10% acetic acid to result in the formation of the deconjugated ketone (19) and the starting enone (18) in a ratio of *ca.* 2:1, both of which were then reacted with MCPBA in methylene chloride a room temperature for 0.5 hr to afford the β-epoxide (20).[11] Direct treatment of the epoxide

(20) with 2 equiv of DBU in benzene at 10° for 5 min provided the dihydroxy-enone (21)[6a] [PMR($CDCl_3$,TMS) δ0.94 (s,3H,CH_3), 1.13(s,3H,CH_3), 1.16(s,3H,CH_3), 3.90(d,J=7Hz,1H,=CHOH), 4.69(d,J=6Hz,1H,=CHOH), 5.38(s,1H,olefinic proton), 5.96(s,1H,olefinic proton), 6.06(s,1H, olefinic proton); IR(neat) 3400, 1690, 1620 cm-1; MS(EI) 248(M^+), 230(M^+-H_2O)] in 21% overall yield from 18 (60% yield when based on the 67% recovery[10] of the conjugated ketone (18)).

Since the diol (21) was already converted to *dl*-coriolin (1) by Tatsuta et al.[4a] and Danishefsky et al.,[4b] we finished a total synthesis of coriolin. Finally, the diol (21) was transformed into the diacetate (22) and its structure was confirmed by direct identification with an authentic material kindly supplied by Prof. Tatsuta.

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References and Notes

1) Visiting scientist from Mitsubishi Pharmaceutical Co. Ltd., Ibaragi 300-03.

2) T.Takeuchi, H.Iinuma, J.Iwanaga, S.Takahashi, T.Takita and H.Umezawa, *J. Antibiotics*, 22, 215(1969).

3) S.Takahashi, H.Naganawa, H.Iinuma, T.Takita, K.Maeda, and H.Umezawa, *Tetrahedron Lett.*, 1955(1971); For the X-ray crystallographic study, see H.Nakamura, T.Takita, H.Umezawa, M.Kunishima, Y.Nakayama, and Y.Iitaka, *J. Antibiotics*, 27, 301(1974).

4) a, K.Tatsuta, K.Akimoto, and M.Kinoshita, *J. Antibiotics*, 33, 100(1980); b, S.Danishefsky R.Zamboni, M.Kahn, and S.J.Etheredge, *J. Am. Chem. Soc.*, 102, 2097(1980); c, For the synthetic approach to coriolin, see H.Hashimoto, T.Ito, H.Shirahama, and T.Matsumoto, *Heterocycles*, 13, 151(1979).

5) M.Shibasaki, K.Iseki, and S.Ikegami, *Synth. Commun.*, in press.

6) a, An oily product was obtained. b, A product was a crystalline solid, whose melting point was not measured because of the presence of a diastereoisomer caused by a THP group.

7) Lithium dimethylcopper should attack at a less hindered side. For alkylation with similar reagents, see M.Shibasaki, K.Iseki, and S.Ikegami, *Chem. Lett.*, 1299(1979).

8) S.Nozoe, J.Furukawa, U.Sankawa, and S,Shibata, *Tetrahedron Lett.*, 195(1976).

9) J.Tsuji, I.Shimizu, and K.Yamamoto, *Tetrahedron Lett.*, 2975(1976); Since a part of the product was hydrolyzed in a reaction medium and/or at the work-up stage, the crude reaction products were again protected as a THP ether before purification.

10) J.Ringold and S.K.Malhotra, *Tetrahedron Lett.*, 669(1962); It was found that the deconjugated ketone (19) isomerized gradually to the conjugated ketone (18) during its working-up.

11) The stereochemistry of the epoxide (20) could be primarily predicted from the consideration that the undesired α-epoxide must be in the unacceptable *trans*-fusion between the A and B rings. The conjugated ketone (18) remained intact under these reaction conditions.

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