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ISOLATION, STRUCTURE AND SYNTHESIS OF HIRSUTENE, A PRECURSOR HYDROCARBON OF CORIOLIN BIOSYNTHESIS

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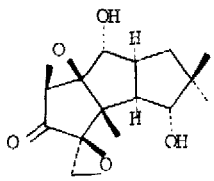
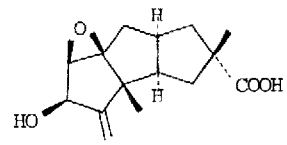
Coriolin is a sesquiterpene antibiotic isolated from *Coriolus consors* by H. Umezawa *et.al.*[1] Coriolin 1 and its congeneric substances possess the structure containing a same carbon skeleton with those of hirsutic acid 2[2] and complicatic acid 3[3], which were isolated from *Stereum hirsutum* and *Stereum complicatum* respectively. All these compounds are assumed to be derived biogenetically from the parent hydrocarbon having the structure 4, described in the literature as a hypothetical precursor[5]. Biogenesis involving a complex rearrangement process leading to this hydrocarbon from farnesyl precursor was proposed and was demonstrated by the biosynthetic studies using carbon-13 nmr spectroscopy [4,5].



(1)



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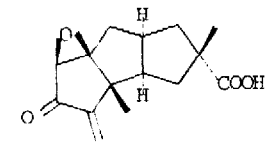

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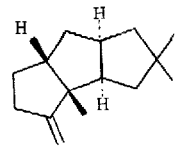

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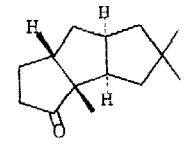
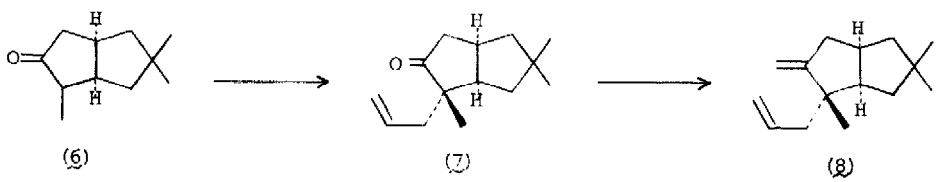


(5)

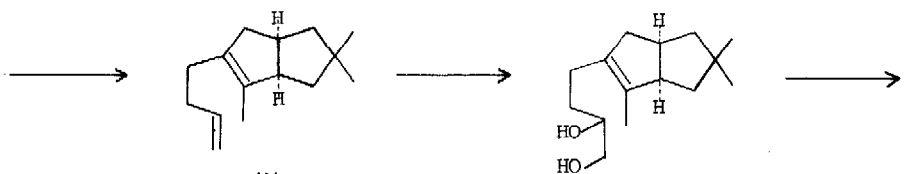
In the course of investigations on the sesquiterpenoids produced by Basidiomycetes, we have recognized the presence of the hydrocarbon actually possessing the structure 4 in the hydrocarbon fraction obtained from the extract of *Coriolus consors*. In the present paper,

we wish to report the isolation and total synthesis of the hydrocarbon 4, for which the name of hirsutene was proposed[6]. We also confirmed the presence of humulene and caryophyllene, albeit in a trace amount, in this hydrocarbon mixture.

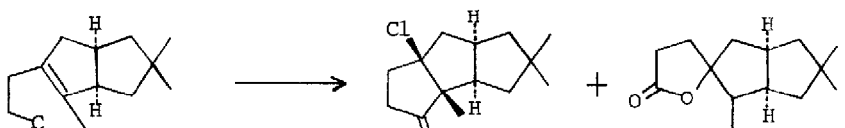
Sesquiterpene hydrocarbon fraction (0.05~0.1 % of the total extract) was obtained from the crude extract of the fermented micellium of *Coriolus consors* by silica gel chromatography, followed by preparative glc separation of the n-hexane eluate. Gc-ms analysis of the hydrocarbon[7] revealed the presence of several sesquiterpenes, all of which exhibited molecular ion peak at m/e 204. Two minor components corresponding to the peaks whose retention time are 8.2 and 10.2 min. were found to be caryophyllene and humulene respectively, and this was confirmed by a comparison of their mass spectra with those of authentic specimens. Co-occurence of hirsutene and humulene strongly supports the biogenetical hypothesis involving eleven-membered-cation intermediate[5]. Main component (retention time, 5.9 min.; 40 % of the total C_{15}-hydrocarbon), ms,204 (M^+, $C_{15}H_{24}$), 94 (base peak), exhibites nmr signals[8] at 1.05 (s, 3H), 0.92 (s, 6H) and 4.72 (2H, exo-methylene protons),indicating the compound is tricyclic Oxidative cleavage of this compound with OsO_4-$NaIO_4$ in aqueous THF afforded the nor-ketone 5, ms, 206 (M^+, $C_{14}H_{22}O$); nmr, 0.91, 0.95 and 1.07 (s, 3H each) exhibites ir absorption band at 1740 cm^{-1}due to a five membered ring ketone. The mass fragmentation patterns of 4 and 5 also support the assigned structures.



(6) (7) (8)



(9) (10)



(11) R=H
(12) R=OH
(13) R=OCH_3
(14) R=Cl

(15) (16)

In order to confirm the structure of the hydrocarbon and to prepare the labelled substrate for the biosynthetic study, the total synthesis of (±)-hirsutene 4 has been carried out by a route involving the nor-ketone intermediate 5 [9]. The starting material for the synthesis was the bicyclic ketone 6 which was prepared by the procedure similar to that employed by T. Matsumoto *et. al.*[10]. Treatment of the enolate anion of 6 generated with one equivalent of NaH in DME with allyl chloride led to selective formation of the alkylated product 7[12], ms, 206 (M^+, $C_{14}H_{22}O$); ir (film), 1745 cm^{-1}; nmr, 0.88, 0.97, 1.06 (s, 3H each), 5.30~6.00 (m, 1H), and 4.8~5.1 (m, 2H), in 71 % yield. Methylenation of the ketone 7 under the usual Wittig condition afforded the hydrocarbon 8[12], ms, 204 (M^+, $C_{15}H_{24}$); nmr, 0.95 (s, 6H), 1.01 (s, 3H), 4.4~6.0 (5H). The dienic hydrocarbon 8 underwent Cope rearrangement by heating to 240° under an atomosphere of argon to give the isomeric diene 9[12], ms, 204 (M^+,$C_{15}H_{24}$); nmr, 0.96, 1.00 (s, 3H each), 1.50 (bs, 3H, methyl group on a double bond), 2.02 (4H, methylene protons), 5.6 (m, 1H), and 4.8~5.0 (m, 2H), in 83 % yield from 7. The fragmentation pattern of the mass spectrum in 9 is virtually identical with that in 8 except intensity of molecular ion peak. The diene 9 was then converted into the aldehyde 11 by treatment with OsO_4 in a mixture of ether and pyridine (2 : 1) at -78°, followed by oxidation of the resulting diol 10, ms, 238 (M^+, $C_{15}H_{26}O_2$); nmr, 0.99, 1.04, 1.55, and 3.45, with $NaIO_4$ in aqueous THF (50 % yield). The aldehyde 11 showed nmr signals at 0.94, 1.00 (s, 3H each), 1.53 (bs, 3H, methyl group on a double bond), 2.33 (4H, methylene protons), and 9.69 (t, 1H, aldehydic proton) and M^+-ion peak at m/e 206 ($C_{14}H_{22}O$). Oxidation of the aldehyde 11 with Ag_2O-NaOH in aqueous THF at 25° yielded the carboxylic acid 12, which was led to the corresponding methyl ester 13, ms, 236 (M^+, ($C_{15}H_{24}O_2$); ir (film) 1745 cm^{-1}; nmr, 0.96, 1.05 (s, 3H each), 1.52 (bs, 3H, methyl group on a double bond), 3.58 (s, 3H, ester-methyl), and 2.23 (4H, methylene protons), in 80 % yield.

Intramolecular acylation of the tetra-substituted double bond[11] was achieved by the treatment of the acid chloride 14, obtained from 12 with oxalyl chloride in benzene containing a trace amount of pyridine, with $SnCl_4$ in carbon disulfide at 30°. The reaction products were found to be a mixture of the desired ketone 15[12] and the spiro-lactone 16 in a ratio of ca. 1 : 1. The crystalline chloro-ketone 15, obtained in 20 % yield, m.p. 87°, ms, 240 and 242 (M^+, $C_{14}H_{21}O$ Cl); nmr, 0.93, 1.03, 1.09 (s, 3H each), showed ir absorption band at 1745 cm^{-1} due to a five membered ring ketone. The spiro-lactone 16, obtained in 20 % yield, ms,222 (M^+, $C_{14}H_{22}O_2$); nmr, 0.91(d,3H),0.93,1.04(s,3H each),showed ir absorption at 1775 cm^{-1} due to a γ-lactone moiety. Treatment of the chloro-ketone 15 with lithium metal in liquid ammonia and ether containing t-BuOH, followed by oxidation of the reduced ketone with Collins reagent afforded the nor-ketone 5 in 60 % yield. The synthetic nor-ketone exhibited ir, nmr, and mass spectra identical to those of an authentic sample derived from natural product. The nor-ketone 5 was converted into hirsutene 4 by treatment with large excess of Wittig reagent in DMSO (70 % yield). The synthetic 4 showed ir, nmr, and mass spectrum identical to those of natural hydrocarbon.

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6. Exact specific rotation of the hydrocarbon could not be determined due to shortage of the pure specimen, however, positive plain curve ($\alpha_{500}\sim36°$;$\alpha_{400}\sim72°$;$\alpha_{300}\sim220°$) was observed in ord measurement.
7. Gc-ms analysis was on 2m of 1.5% OV-17 columun using Shimadzu-LKB 9000.
8. Nmr was determined in CCl_4 at 100MHz.
9. For total synthesis of hirsutic acid, see H.Hashimoto, K.Tsuzuki, F.Sakan, H.Shirahama, and T.Matsumoto, Tetrahedron Lett., 3745 (1974); and for synthesis of hirsutane skeletone see F.Sakan, H.Hashimoto, A.Ichihara, H.Shirahama and T.Matsumoto, Tetrahedron Lett., 3703 (1971);P.T.Lansbury, N.Y.Wang and J.E.Rhodes, Tetrahedron Lett., 1829 (1971),2053 (1972); P.T.Lunsbury and N.Nazarenko, Tetrahedron Lett., 1833 (1971).
10. S.Kagawa, S.Matsumoto, S.Nishida, S.Yu, J. Morita, A.Ichihara, H.Shirahama and T.Matsumoto, Tetrahedron Lett., 3913 (1969).
11. Cf. H.O.House: Modern Synthetic Reactions, p.786; W.A.Benjamin Inc.,1972.
12. Satisfactory analytical data were obtained for this compound.