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SYNTHESIS OF (±)-CORONAFACIC ACID

Akitami Ichihara*, Ryoji Kimura, Koichi Moriyasu, and Sadao Sakamura

Department of Agricultural Chemistry, Faculty of Agriculture

Hokkaido University, Sapporo 060, Japan

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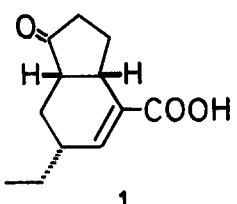
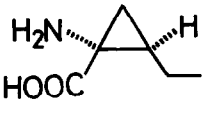
Coronafacic acid (1) is one of the components of coronatine[1] (3), a phytotoxin produced by phytopathogenic bacteria of Italian ryegrass[2,3], and also isolated directly from the culture broth. Since the partial synthesis of coronatine from natural coronafacic acid and optically active coronamic acid (2) which was obtained by stereoselective synthesis and subsequent optical resolution, has been completed[4], the synthesis of (±)-coronafacic acid means the total synthesis of coronatine in formal sense except optical resolution. In this communication we wish to disclose the first synthesis of (±)-coronafacic acid.



1



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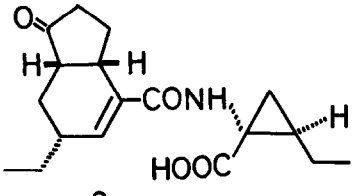
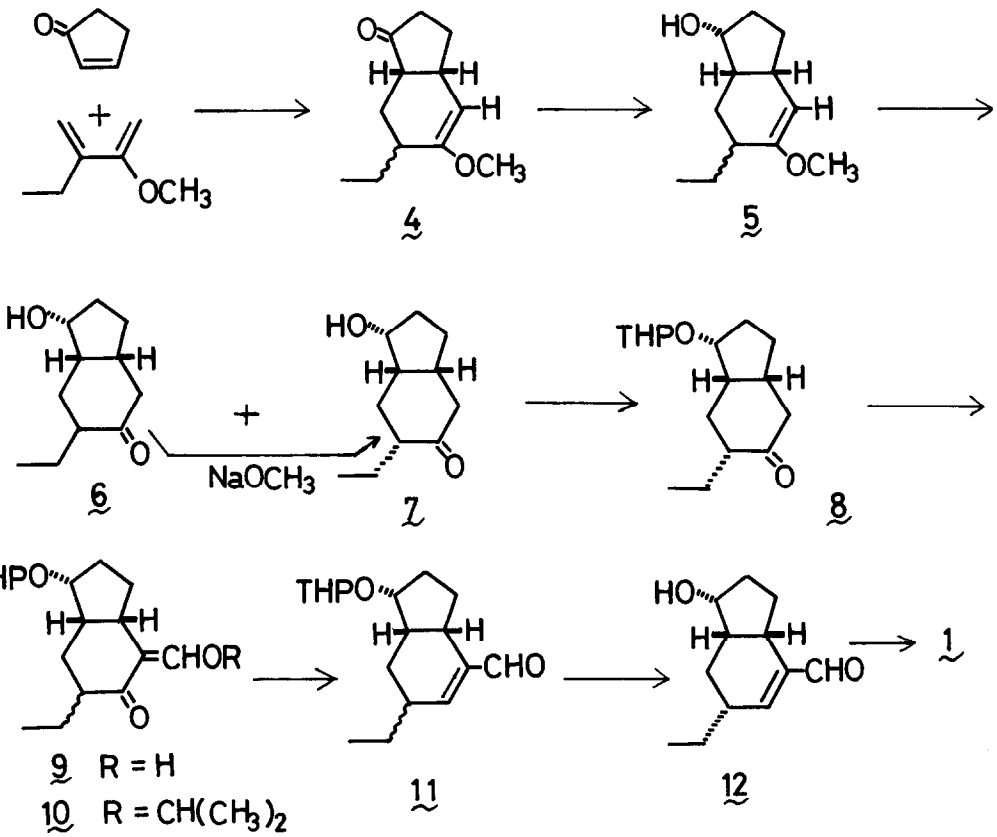


3

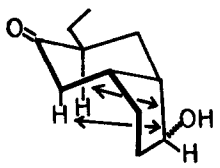
Diels-Alder reaction of 2-ethyl-3-methoxybutadiene with cyclopentenone, heated at ca. 200°C for 27 hr in xylene afforded, accompanied migration of double bond, a stereoisomeric mixture 4, m/e 194 (M^+); ν_{max}^{film} 1740, 1660 cm^{-1}, related to ethyl group in 38% yield. The migrated feature was confirmed by the NMR spec-

trum, in which two signals due to vinylic protons were observed at δ 4.50 (J= 3Hz) and δ 4.62 (J=4Hz) in a ratio of ca. 1 : 1. cis-Configuration at ring jucture protons in 4 was deduced from the NMR spectrum which indicates one proton multiplet at δ 3.00 ascribable to α-keto methine of cis-1-hydrindanone[5]. The adducts 4 were converted to alcohols 5, m/e 196 (M^+), ν_{max}^{film} 3350, 1660 cm^{-1} with $NaBH_4$ reduction in tetrahydrofuran. Treatment of the alcohol 5 with 1.2N-HCl yielded two ketols 6, ν_{max}^{film} 3450, 1700 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.95 (3H, t, J=7Hz,

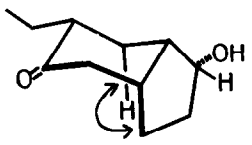


CH_3), 1.15~2.60 (14H), 4.40 (1H, m, CH-O) and 7, mp 62~63°C, $C_{11}H_{18}O_2$, m/e 182 (M^+), ν_{max}^{KBr} 3350, 1705 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.95 (3H, t, J=7Hz, CH_3), 1.10~2.60 (14H), 4.40 (1H, m, CH-O). The stereochemistry of the hydroxyl group in 6 was deduced from the observation that under conditions of formylation using sodium hydride in benzene, easy dehydration of the hydroxyl group with vicinal 7a-H involved.

This fact indicates that these occupy trans disposition each other. On the stability of these isomers, the ketol 7 is more stable isomer than 6, since alkaline treatment ($NaOCH_3$) of 6 afforded isomer 7 predominantly. The stereochemistry of each isomer was deduced from molecular model, in which stable isomer 7 has one 1,3-diaxial interaction (7a) but less stable isomer 6 has two (6a).



6a



7a

The ketol 7 was converted to a pyranyl ether 8, m/e 266 (M^+), ν_{max}^{film} 1700 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.90 (3H, t, J=7Hz, CH_3), 3.55, 3.90 (each 1H, m, CH_2-O), 4.30 (1H, m, CH-O), 4.70 (1H, m, $-CH\langle_{O}^{O}$). The pyranyl ether 8 was treated with ethyl formate and sodium hydride in diglyme to formylated compounds 9, m/e 294 (M^+), ν_{max}^{film} 1640, 1590 cm^{-1}, which were shown to be a stereoisomeric mixture arising from C-6 ethyl group, since in the NMR spectrum a pair of signals for each proton of 9 was observed. The results indicate that under the conditions of sequence of reaction, new equilibration with the configuration at C-6 ethyl group was attained and the ratio of these isomers[6] was elucidated to be 3 : 1. The formyl compounds 9 were protected with isopropyl iodide to give an isopropyl ether 10, m/e 336 (M^+), ν_{max}^{film} 1680, 1590 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.90 (3H, t, J=7Hz, CH_3), 1.20 (6H, d, J=6Hz, $CH-CH_3$), 3.00 (1H, m, $-\overset{O}{\overset{\|}{C}}-CH-$), 4.20 (1H, septet, J=6Hz, $CH(CH_3)_2$), 4.60 (1H, m, $HC\langle_{O}^{O}$), 7.20 (1H, d, J=1Hz, $=\!\!\swarrow^{H}$). Reduction of 10 with $LiAlH_4$ in tetrahydrofuran and subsequent treatment with acetic acid afforded a stereoisomeric mixture of α,β-unsaturated aldehyde 11[7], m/e 278 (M^+), ν_{max}^{film} 2700, 1690, 1640 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.70 (2/3H, br.s, $=\!\!\swarrow^{H}$), 6.80 (1/3H, d, J=4Hz,

$\rightleftharpoons^{H}$). After removal of the protecting group of 11, the products were separated by silica gel column to yield a pure aldehyde, 12, m/e 194 (M^+), ν_{max}^{film} 3400, 2700, 1690, 1640 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.05 (3H, t, J=7Hz, CH_3), 4.45 (1H, m, >CHOH), 6.65 (1H, br.s, $\rightleftharpoons^{H}$), 9.05 (1H, s, -CHO). Jones oxidation of the aldehyde 12 gave (±)-coronafacic acid, mp 117~119°C, $C_{12}H_{16}O_3$, which was identical in spectral data and behavior on TLC with anthentic sample.

References and footnotes

1) A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaki, T. Matsumoto, J. Am. Chem. Soc., 99, 636 (1977)

2) K. Nishiyama, R. Sakai, A. Ezuka, A. Ichihara, K. Shiraishi, M. Ogasawara, H. Sato, S. Sakamura, Am. Phytopath. Soc. Japan, 42, 613 (1976)

3) K. Nishiyama, R. Sakai, A. Ezuka, A. Ichihara, K. Shiraishi and S. Sakamura, ibid., 43, 219 (1977)

4) A. Ichihara, K. Shiraishi, S. Sakamura, K. Nishiyama, R. Sakai, Tetrahedron Lett., 269 (1977)

5) The signals due to the keto methines in coronatine (3) and coronafacic acid (1) appeared at δ3.15 (in CD_3COCD_3) and δ3.15 (in $CDCl_3$) respectively.

6) The same mixture (9) in a ratio of 3 : 1 was obtained by the formylation of the pyranyl ether derived from a mixture of 6 and 7.

7) The configuration at C-6 of major isomer in 11 was deduced to be the same with that of coronafacic acid 1 (δ 7.28, br.s.) from the coupling pattern.