Tetrahedron Letters No. 3, pp 269 - 272, 1977. Pergamon Press. Printed in Great Britain.

# PARTIAL SYNTHESIS AND STEREOCHEMISTRY OF CORONATINE

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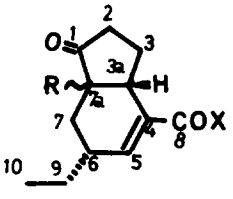
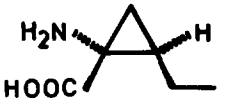
(Received in Japan 22 November 1976; received in UK for publication 7 December 1976)

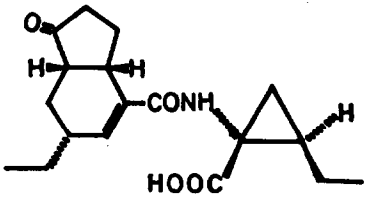
In the preceding paper[1], we reported the structural determination of coronatine[2] (3) on the basis of spectral data and X-ray analysis. In this communication we would like to report the partial synthesis of coronatine (3) from natural coronafacic acid (1) and optically active coronamic acid (2a) which was obtained by the synthesis and subsequent optical resolution. The partial synthesis and ORD measurement of coronafacic acid (1a) have been clarified the stereochemistry of coronatine as 3.




1a X = OH, R = —H
1b X = OH, R = ···H
1c X = Cl , R = —H




2a
2b (antipode of 2a)




3

The relative configuration of 1a was settled by X-ray crystallography of the isomer 1b, which was easily convertible to 1a. The absolute configuration of 1a has been confirmed by ORD measurement, which exhibited a positive Cotton

effect ( $[\phi]_{290}$ + 1400, C 0.01, MeOH). Thus, since the octant projection of 1a indicates that carbon atoms, C-5, C-6, C-7, C-9 and C-10, lie in positive octants[3] (Fig. 1), the absolute configuration must be depicted as 1a.

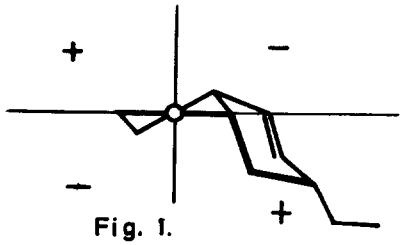
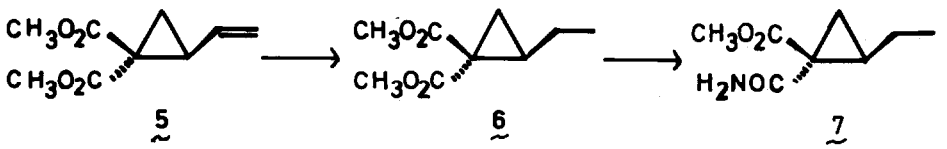
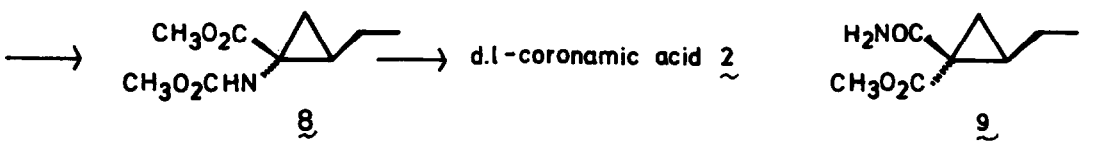


Fig. 1.

The synthesis of coronamic acid 2a was carried out starting from dimethyl 2-vinylcyclopropane-1, 1-dicarboxylate (5), which was prepared by condensation of trans-1, 4-dibromo-2-butene and methyl malonate according to known procedure.[4] Reduction of vinyl double bond in 5 was accomplished by tosyl hydrazide[5] in diglyme to give a saturated compound 6 in 53% yield.[6] Treatment of 6 with methanolic ammonia afforded a monoamide 7 m.p. 75.5~77.5°, $C_8H_{13}O_3N$, $\nu_{max}^{KBr}$ 3425,




3200, 1710, 1680 $cm^{-1}$; $\delta_{TMS}^{CDCl_3}$ 0.98 (3H, t; J=7Hz, $CH_3$), 1.60 (4H, br. m), 3.78 (3H, s, $OCH_3$), 6.05, 8.10 (each 1H, br. s, $NH_2$) in 75.3% yield. In this reaction sterically less hindered ester group was selectively ammonolized to give the amide 7. The stereochemistry of 7 was supported by the fact that owing to nearby ethyl group[7], methyl signal ( $\delta$3.78) of ester group in 7 is more deshielded than that of 9, m.p. 81~85°, ( $\delta$3.68), a stereoisomer of 7, which was derived from condensation product of trans-1, 4-dibromo-2-butene and methyl cyanoacetate. Hofmann degradation[8] of 7 with bromine and sodium hydroxide in methanol and subsequent hydrolysis of resultant carbamate ester 8, $\nu_{max}^{film}$ 3340,

1730 $cm^{-1}$; $\delta^{CDCl_3}_{TMS}$ 0.96 (3H, t, J=7Hz, $CH_3$), 3.72, 3.75 (each 3H, s, $2\times OCH_3$), afforded dl-coronamic acid 2, $C_6H_{11}O_2N$, $\nu^{KBr}_{max}$ 3400, 3100~3200, 2075, 1640~1520, 1390 $cm^{-1}$; $\delta^{D_2O}_{MeOH}$ 0.94 (3H, t, J=6Hz, $CH_3$), whose Rf value (0.45, BAW 4 : 1 : 5) on paper chromatography and retention time (4.29 hr) on amino acid analyser are identical with those of natural coronamic acid 2a.[9] Optical resolution of 2 was carried out with quinine salts of N-formyl coronamic acid and after several fractional recrystallization, resultant two crystalline materials were hydrolized to yield optically active 2a, $[\alpha]_D^{20}$ + 14.7 (c 1.67, $H_2O$) and 2b, $[\alpha]_D^{23}$ -14.2 (c 1.67, $H_2O$) respectively. Enzymatic resolution of dl-N-acetylcoronamic acid using L-acylase also gave directly 2a, and recovered 2b acetate was hydrolysed to 2b. Application of sector rule[10] to 2a and 2b demonstrated that the absolute configuration of these amino acids must be shown as 2a and 2b respectively. (In the case of 2a, see Fig. 2 and 3)

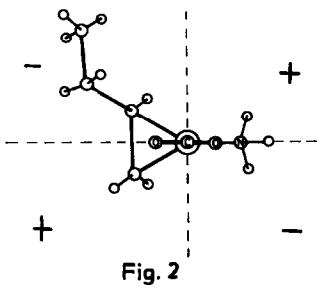


Fig. 2

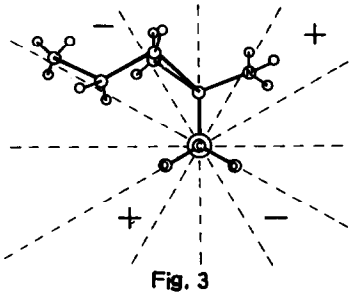


Fig. 3

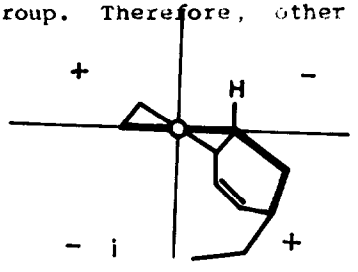
The partial synthesis of coronatine from 2a and the acid chloride, 10, which was obtained by chlorination with thionyl chloride afforded synthetic coronatine, 3 m.p. 158~160°. The synthetic coronatine is identical with natural sample in spectral data and in biological activity. On the other hand, diastereomeric coronatine synthesized from 2b and 10 exhibited different NMR and IR spectra but the same biological activity on potato slice compared with natural coronatine.

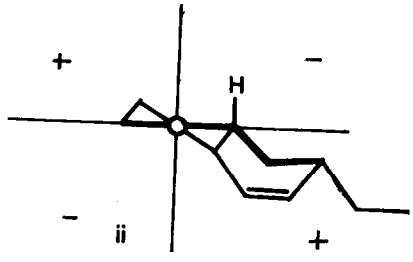
## References and footnotes

1) A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaki, T. Matsumoto, J. Am. Chem. Soc., in press.

2) For physiological activities of coronatine, see K. Nishiyama, R. Sakai, A. Ichihara, K. Shiraishi, M. Ogasawara, H. Sato, S. Sakamura, Ann. Phytopath. Soc. Japan. in press.

3) The conformation of 1a was supported by the findings that in the NMR spectrum the signal ( $\delta$3.15) due to 7a-H is deshielded by the coplaner C-1 carbonyl group. Therefore, other possible conformations i or ii were excluded.




4) K. C. Murdock and R. B. Angier, J. Org. Chem., 27, 2395 (1962).

5) R. S. Dewey and E. E. van Tamelen, J. Am. Chem. Soc., 83, 3729 (1961).

6) Catalytic reduction of 5 with Pd-C involved a cleavage of cyclopropane ring. cf S. Danishefsky, G. Rovnyak, J. Org. Chem., 40, 114 (1975).

7) R. M. Silverstein and G. C. Bassler "Spectrometric Identification of Organic Compounds" 2nd. ed. John Wiley and Sons, Inc. N. Y. (1967), p. 117.

8) This reaction proceeds with complete retention of configuration: M. S. Newman "Steric Effects in Organic Chemistry", John Wiley and Sons, Inc. N. Y. (1956), p. 250.

9) The other diastereomer ($NH_2/CH_2CH_3$ cis) of 2 showed different Rf value (0.39 BAW 4 : 1 : 5) on paper chromatography and retention time (4.44 hr) on amino acid analyser.

10) E. C. Jorgensen, Tetrahedron Letters, 863 (1971).