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TOTAL SYNTHESIS OF (±)-CORONAFACIC ACID

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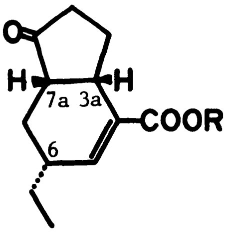
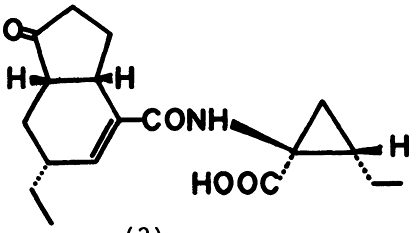
Coronafacic acid, the acidic component of coronatine, was synthesized *via* the stereospecific alkylation of the tricyclo-[4,3,0,$0^{1.5}$]nonane derivative, followed by the fission of cyclopropane ring.

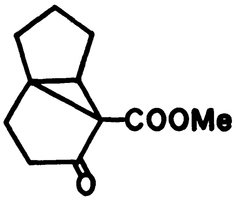
Coronafacic acid (1) is the acidic component of coronatine (2), a phytotoxic amide, which is produced by *Pseudomonas coronafacience var. atropurpurea.*1) The total synthesis of (±)-1 has been achieved by two groups *via* the stereospecific or nonstereospecific route.2) As C_{7a}-epimer of 1 is easily convertible to 1, the major problem in the synthesis of 1 is the stereocontrolled introduction of C_6-ethyl group trans to C_{3a}-proton. We describe here the stereocontrolled synthesis of 1 utilizing the tricyclo[4,3,0,$0^{1.5}$]nonane derivative (3) as a key intermediate.



(1) R=H
(10) R=Me



(2)

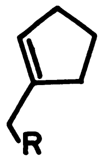


(3)

The tricyclo derivative (3) was obtained in 40% overall yield from cyclopenten-1-aldehyde. Reduction with lithium aluminium hydride of the aldehyde, followed by the treatment with p-toluenesulfonyl chloride under the phase-transfer catalysed conditions (30% aq. NaOH, benzene, BTEA, rt, 7 h)3) gave the corresponding p-toluenesulfonate (4),4) whose exposure to the dianion of methyl acetoacetate in tetrahydrofuran (-10°C to rt, 8 h),5) afforded β-keto ester (5). The thermal decomposition of the azide, prepared from 5 (TsN_3, Et_3N, CH_3CN, rt, 12 h), in the presence of CuI-$(MeO)_3P$ complex, yielded the desired cycloadduct (3).6)

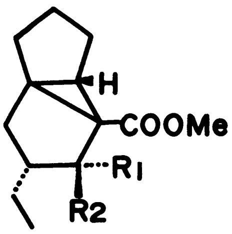
Alkylation of 3 with excess ethyl iodide (LDA 1.2 eq. and HMPA 4 eq. in THF, and EtI 5 eq., 0°C, 10 h) gave monoethyl derivative (6)7) in 53% yield. The by-product of this reaction was only dialkylated one, and the stereoisomer of 6 was not obtained. It was presumable that the stereochemistry of 6 is proper, because C_6-epimer of 6 must have two 1,3-diaxial interactions between the ethyl group and two bonds of the cyclopropane ring. The structure of 6 was finally confirmed by X-ray diffraction analysis.8)

The ethyl ketone (6) was converted to the alcohol (7) ($NaBH_4$, MeOH, rt, 1 h) in 66% yield as an epimeric mixture.9) Treatment of 7 with p-toluenesulfonyl chloride (pyridine, rt, overnight) afforded a 1:1 unseparable mixture of 8 and 9 in 76% yield.10) Hydroboration of the mixture ($NaBH_4$, Me_2SO_4, THF, 0°C, 1 h),11) followed by the treatment with basic hydrogen peroxide and subsequent pyridinium chlorochromate oxidation gave only cis-fused coronafacic acid methyl ester (10) in about 20% yield from 8.12) 10 was hydrolyzed with aq. hydrochloric acid (2.4M, reflux, 3 h) to 1 in 80% yield.13) The spectral data of synthetic (±)-1 were identical with those of the authentic sample.14) Thus, the synthesis of (±)-1 was accomplished by an eleven-step process.



(4) R=OTs

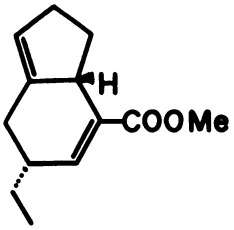
(5) $R=CH_2COCH_2COOMe$



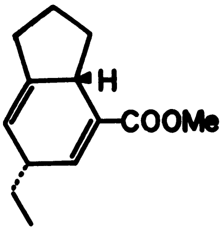
(6) $R_1=R_2=O$

(7) a $R_1=H,R_2=OH$

b $R_1=OH,R_1=H$



(8)



(9)

References and Notes

1) A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaki, and T. Matsumoto, J. Am. Chem. Soc., 99, 636 (1977); A. Ichihara, K. Shiraishi, S. Sakamura, A. Furusaki, N. Hashiba, and T. Matsumoto, Tetrahedron Lett., 1979, 365.

2) A. Ichihara, R. Kimura, K. Moriyasu, and S. Sakamura, Tetrahedron Lett., 1977, 4331; M. E. Jung and J. P. Hudspeth, J. Am. Chem. Soc., 102, 2463 (1980); A. Ichihara, R. Kimura, S. Yamada, and S. Sakamura, Ibid., 102, 6353 (1980).

3) W. Szeja, Synthesis, 1979, 822.

4) Satisfactory spectral and analytical data were obtained for all new compounds.

5) S. N. Huckin and L. Weiler, J. Am. Chem. Soc., 96, 1032 (1974).

6) 3: mp 68.5-69.5°C; m/z 194(M^+); IR(CCl_4) 1745, 1725 cm^{-1}.

7) 6: mp 71.5-73.0°C; m/z 222(M^+); IR(CCl_4) 1745, 1725 cm^{-1}; ^1H-NMR(CCl_4) δ 0.88 (3H, t, J=7.0 Hz), 3.70 (3H, s).

8) We thank Dr. H. Nozaki, Hiroshima University, for the X-ray analysis. Details will be reported elsewhere.

9) Each epimer of 7 was separated by preparative TLC (7a, major product: ^1H-NMR (CCl_4) δ 4.11 (d, J=6.5 Hz); 7b, minor product: ^1H-NMR(CCl_4) δ 4.06 (d, J=3.5 Hz)).

10) ^1H-NMR(CCl_4) δ: 8, 5.17(bs); 9, 5.40(bs). Treatment of 7a and/or 7b with TsCl in pyridine gave the same reaction products.

11) H. M. Bell, C. W. Vanderslice, and A. Spehar, J. Org. Chem., 34, 3923 (1969).

12) 9 resisted the hydroboration at 0°C and was recovered after PCC oxidation, accompanied with the aromatized product.

13) (±)-1: mp 122-125°C (after preparative TLC) (lit. (+)-1: mp 125-126°C1); (±)-1: mp 115-127°C2))

14) We thank Dr. A. Ichihara for kindly providing us with an authentic sample of natural coronafacic acid and the spectral data of both the natural and their synthetic material.

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