

The Synthesis of (\pm)-Coronafacic Acid by a Tandem Wessely Oxidation–Diels–Alder Reaction Sequence

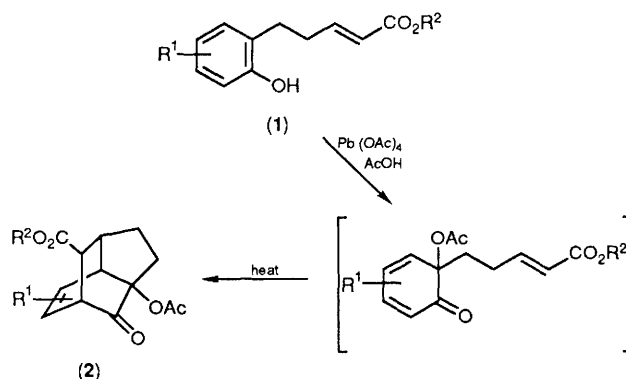
N. K. Bhamare, Thierry Granger, T. S. Macas, and Peter Yates*

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

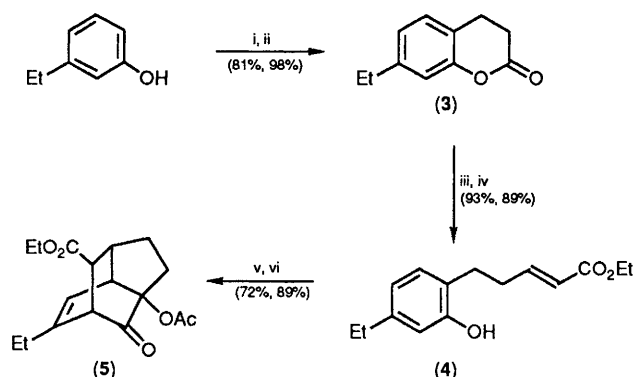
(\pm)-Coronafacic acid (**9**) has been synthesized from ethyl 5-(4-ethyl-2-hydroxyphenyl)pent-2-enoate (**4**) via a tandem Wessely oxidation–Diels–Alder reaction sequence.

It was reported earlier from these laboratories that isotwistanone derivatives of type (**2**) could be synthesized from 5-(2-hydroxyphenyl)pent-2-enoic acid derivatives of type (**1**) by a tandem Wessely oxidation–intramolecular Diels–Alder reaction sequence (Scheme 1).¹ This approach differs from other syntheses of related tricyclic ketones *via* intramolecular Diels–Alder reactions² in that an α -acetoxy ketone function is present in the product. This serves to broaden the scope of these reactions by introducing an oxygen substituent and by providing a facile route for oxidative bond cleavage under mild conditions.

We now report the application of the latter to the synthesis of (\pm)-coronafacic acid (**9**), whose (+)-enantiomer constitutes the acid component of the naturally occurring phytotoxic amide, coronatine (**10**) (Scheme 3).³



Scheme 1

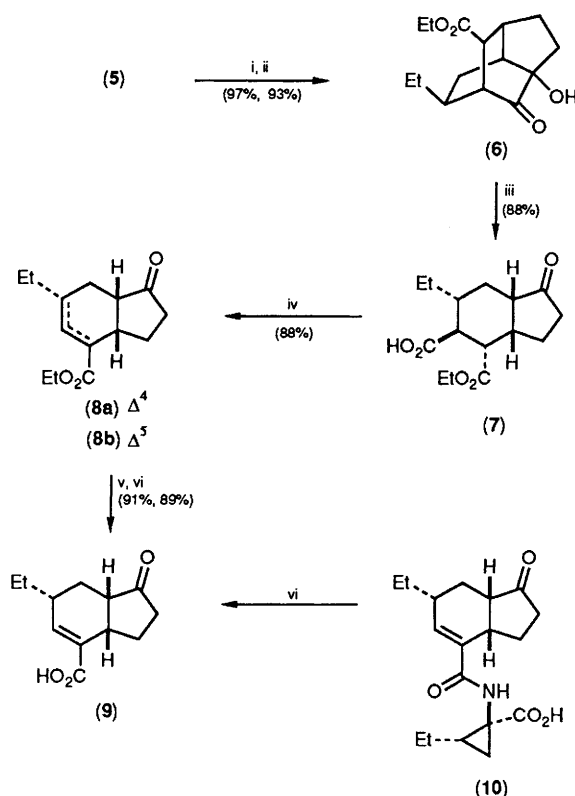


Scheme 2. Reagents and conditions: i, $\text{HO}_2\text{CCH}(\text{OH})\text{CH}_2\text{CO}_2\text{H}$, H_2SO_4 ; ii, H_2 , Pd/C ; iii, BuLiAlH ; iv, $\text{Ph}_3\text{P=CHCO}_2\text{Et}$; v, $\text{Pb}(\text{OAc})_4$, AcOH ; vi, 140°C .

7-Ethyl-3,4-dihydrocoumarin (3),[†] prepared from condensation of *m*-ethylphenol with malic acid, followed by hydrogenation of the resulting coumarin, was converted to the phenol (4) of type (1) by BuLiAlH (Dibal) reduction followed by a Wittig reaction. This was subjected to Wessely oxidation with lead tetra-acetate followed by an intramolecular Diels–Alder reaction in boiling xylenes to give the isotwistanone derivative (5) of type (2) (Scheme 2), which was obtained as a colourless oil after purification; b.p. $94\text{--}98^\circ\text{C}$ (0.3 Torr); λ_{max} 5.70 and 5.77 μm , δ_{H} 1.01 (t, J 8 Hz, 3H), 1.25 (t, J 7 Hz, 3H), 1.7–2.7 (m, 8H), 2.02 (s, 3H), 3.40 (m, 2H), 4.09 (q, J 7 Hz, 2H), and 5.78 (m, 1H). The Wittig product was largely the (*E*)-isomer (4); this was accompanied by a small amount of the corresponding (*Z*)-isomer, which gave a Diels–Alder product epimeric with (5) at C-4.

Hydrogenation of (5) followed by mild alkaline hydrolysis gave the α -ketol (6), m.p. $71\text{--}72^\circ\text{C}$. This was oxidized with sodium periodate to give the keto acid (7), m.p. $151\text{--}152^\circ\text{C}$, λ_{max} 2.90, 5.78, and 5.88 μm , δ_{H} 0.93 (m, 3H), 1.26 (t, J 7 Hz, 3H), 0.9–3.0 (m, 13H), 4.22 (q, J 7 Hz, 2H), and 8.44 (br s, 1H, absent after D_2O treatment). Oxidative decarboxylation of the acid (7) gave a mixture of the Δ^4 and Δ^5 esters (8a) and (8b), respectively (Scheme 3), which gave a mixture rich in isomer (8a) on treatment with ethanolic sodium ethoxide. Hydrolysis of this with hydrochloric acid³ gave coronafacic acid (9), which after recrystallization from di-isopropyl ether had m.p. $122\text{--}123^\circ\text{C}$, undepressed on admixture with an authentic sample. Its spectra were identical with those of the authentic sample.

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Scheme 3. Reagents and conditions: i, H_2 , Pd/C ; ii, $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ / EtOH ; iii, $\text{NaIO}_4/\text{H}_2\text{O}$; iv, $\text{Pb}(\text{OAc})_4$, $\text{Cu}(\text{OAc})_2$, $\text{C}_5\text{H}_5\text{N}$; v, EtONa / EtOH ; vi, $\text{HCl}/\text{H}_2\text{O}$.

(Hokkaido University) for authentic samples and/or spectra of (\pm)-coronafacic acid.

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References

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- 2 Cf., e.g., H. Greuter and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 2382.
- 3 For previous syntheses of coronafacic acid, see: A. Ichihara, R. Kimura, K. Moriyasu, and S. Sakamura, *Tetrahedron Lett.*, 1977, 4331; M. E. Jung and J. P. Hudspeth, *J. Am. Chem. Soc.*, 1980, **102**, 2463; A. Ichihara, R. Kimura, S. Yamada, and S. Sakamura, *ibid.*, 1980, **102**, 6353; M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, 1981, **22**, 2735; M. Nakayama, S. Ohira, Y. Okamura, and S. Soga, *Chem. Lett.*, 1981, 731; J. Tsuji, *Pure Appl. Chem.*, 1981, **53**, 2371; H.-J. Liu and M. Llinas-Brunet, *Can. J. Chem.*, 1984, **62**, 1747; S. Ohira, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 1902.

[†] The elemental composition of all new compounds was established by combustion or mass spectrometric analysis.