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

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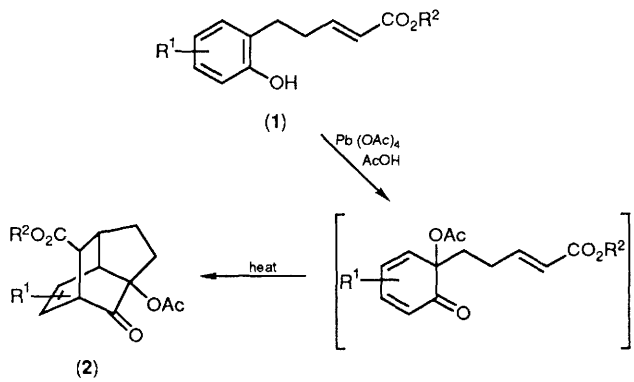
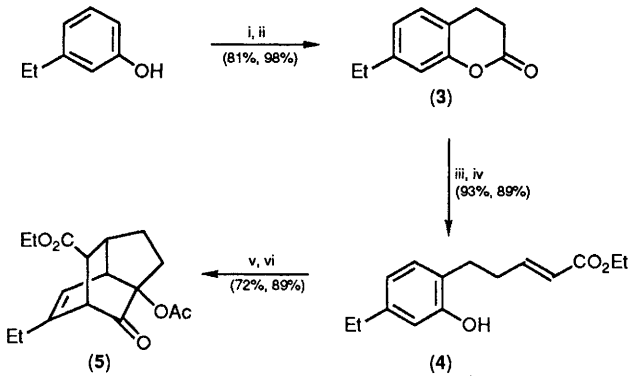
(±)-Coronafacic acid (**9**) has been synthesized from ethyl 5-(4-ethyl-2-hydroxyphenyl)pent-2-enoate (**4**) *via* a tandem Wessely oxidation–Diels–Alder reaction sequence.

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 reactions[2] 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 (±)-coronafacic acid (**9**), whose (+)-enantiomer constitutes the acid component of the naturally occurring phytotoxic amide, coronatine (**10**) (Scheme 3).[3]



Scheme 1



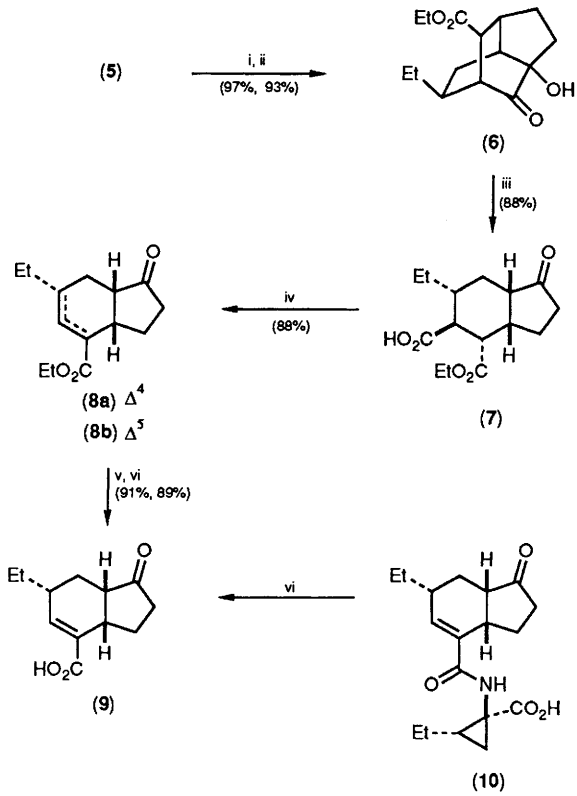
Scheme 2. *Reagents and conditions*: i, $HO_2CCH(OH)CH_2CO_2H$, H_2SO_4; ii, H_2, Pd/C; iii, Bu^i_2AlH; iv, $Ph_3P{=}CHCO_2Et$; v, $Pb(OAc)_4$, AcOH; vi, 140 °C.

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 Bu^i_2AlH (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—98 °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—72 °C. This was oxidized with sodium periodate to give the keto acid (**7**), m.p. 151—152 °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 acid[3] gave coronafacic acid (**9**), which after recrystallization from di-isopropyl ether had m.p. 122—123 °C, undepressed on admixture with an authentic sample. Its spectra were identical with those of the authentic sample.

We thank the Natural Sciences and Engineering Research Council of Canada for support and are greatly indebted to Professors M. E. Jung (University of California, Los Angeles), H.-J. Liu (University of Alberta), and A. Ichihara (Hokkaido University) for authentic samples and/or spectra of (±)-coronafacic acid.

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



Scheme 3. *Reagents and conditions*: i, H_2, Pd/C; ii, $Ba(OH)_2{\cdot}8H_2O$/EtOH; iii, $NaIO_4/H_2O$; iv, $Pb(OAc)_4$, $Cu(OAc)_2$, C_5H_5N; v, EtONa/EtOH; vi, HCl/H_2O.

Received, 3rd January 1990; Com. 0/00050G

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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.