

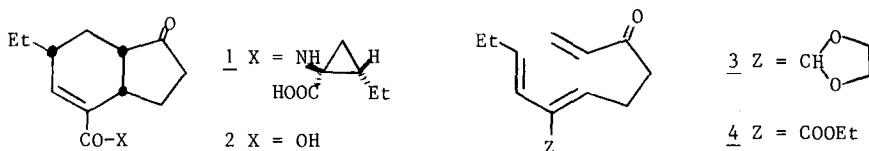
INTRAMOLECULAR LEWIS-ACID PROMOTED (2+2) CYCLOADDITIONS: AN EFFICIENT
TOTAL SYNTHESIS OF (+)-CORONAFACIC ACID VIA AN INTERNAL DIELS-ALDER REACTION.¹

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Internal (2+2) cycloaddition of the ester 7 gave the cyclobutene 8 in fair yield; cyclization of the readily derived trienone 4 and hydrolysis produced coronafacic acid in 7% overall yield.

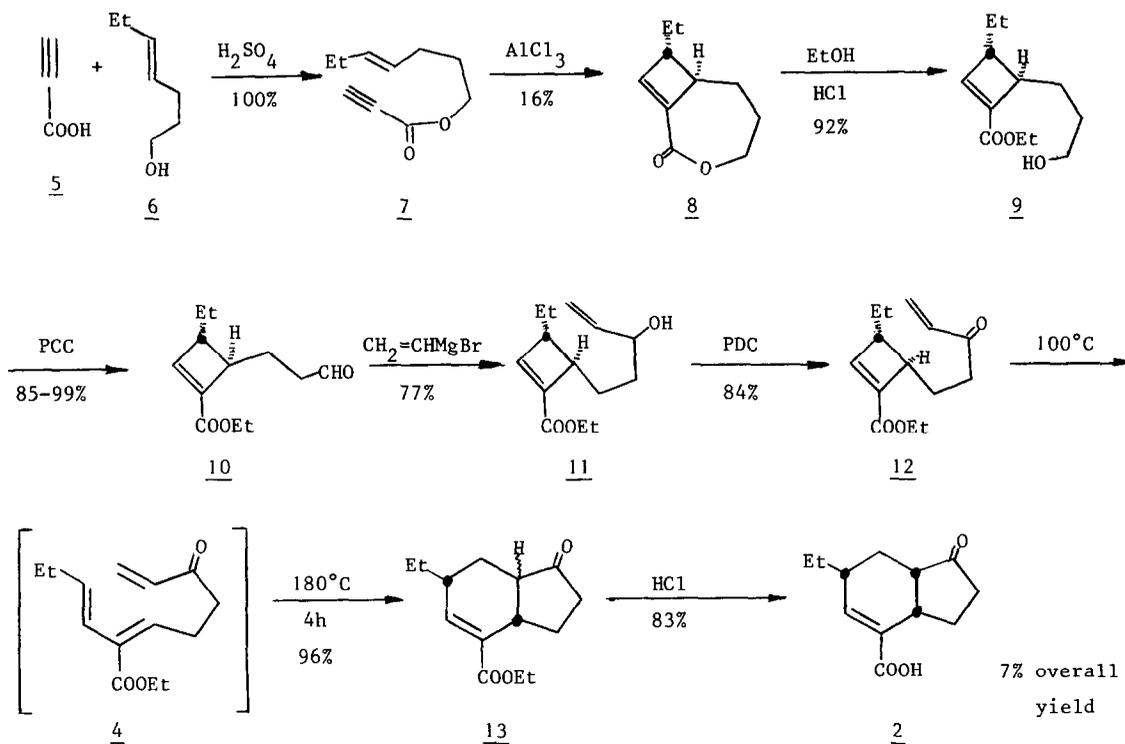
The phytotoxin, coronatine 1, isolated from the culture broth of Pseudomonas coronafaciens, promotes the expansion of potato cells at very low concentrations and induces chlorosis on the leaves of Italian rye grass.⁴ The acid component of this amide, coronafacic acid 2, has also been isolated directly from cultures of this phytopathogenic bacterium. Two very different synthetic approaches to 2 have been successfully completed, namely via an initial Diels-Alder reaction of cyclopentenone with a substituted diene⁵ and via an anionic oxy-Cope rearrangement of a benzofuryl norbornenol.⁶ Very recently, Ichihara has reported the synthesis of 2 in 0.4% overall yield by a route in which the key step is an intramolecular Diels-Alder reaction of the trienone 3, itself prepared by a retro-Diels-Alder process.⁷ This recent report prompts us to describe our own results in this area, namely a very similar synthesis of 2 via the trienone 4 prepared by a completely different route in which the key cyclobutene formation step was effected by an intramolecular (2+2) cycloaddition.



Of the many routes to substituted cyclobutenes, the condensation of an enamine with an unsaturated ester followed by quarternization and elimination was chosen by Ichihara; the necessary 3,4-trans stereochemistry is presumably produced either in the addition step or, more likely by equilibration in the elimination step.⁸ We decided upon a much more general approach, namely an intramolecular (2+2) cycloaddition of an olefinic propiolate, a reaction in which the

stereochemistry at C3 and C4 in the cyclobutenecarboxylate would be necessarily controlled by the stereochemistry of the starting olefin. (The trans stereochemistry is required so that the thermal conrotatory opening of the cyclobutene will produce the desired trienone 4.) The intermolecular version of this reaction has been thoroughly investigated by Snider,⁹ who has shown that the olefin geometry is retained in the cyclobutene product. However, there were serious questions about the feasibility of the intramolecular process.¹⁰ Nevertheless, the ease of preparation of the desired substrate 7 convinced us to test the possibility of the reaction.

The synthesis of coronafacic acid 2 is shown in the Scheme. Esterification of propiolic acid 5 with the known alcohol 6¹¹ afforded the propiolate 7 in quantitative yield.¹² The internal (2+2) cyclization was attempted under many conditions using various Lewis acids (AlCl₃, EtAlCl₂) in several solvents (CH₂Cl₂, toluene, benzene) at different temperatures. The best initial results were obtained as follows: stirring a 0.02M solution of 7 in CH₂Cl₂ with 0.9 equiv of AlCl₃ at 25°C for 8h afforded an isolated, purified yield of 16% of the cyclobutene 8. In addition a fair amount of starting material was recovered¹³ along with small quantities of several other products. Lactone 8 was expected to be a very useful intermediate for the synthesis of 2 since it lacked only two carbon atoms of the skeleton of 2 and had the correct stereochemistry and necessary functionality for its facile conversion into 4 and thence 2. Opening of the lactone in acidic ethanol¹⁴ produced in good yield the hydroxy ester 9 which was oxidized to the aldehyde 10 in quantitative yield. Addition of vinylmagnesium bromide to 10 at 0°C afforded the alcohol 11 in which the more reactive aldehyde has been attacked in preference to the ester. A second oxidation converted 11 into the enone 12 in good yield. Upon heating to 100°C, the cyclobutene was cleanly opened to the desired trienone 4 which was stable to cycloaddition at this temperature.¹⁵ However, heating a solution of 4 in toluene in a sealed tube at 180°C for 4h afforded a 96% yield of the crude mixture of isomeric esters 13. The ratio of these esters could not be directly determined but could be estimated by careful integration of the 200 MHz ¹H NMR spectrum. The methine proton α to the ketone in the cis isomer absorbs at 2.75 δ and integrates for approximately 60% of a proton vs the other clearly resolved protons. Unfortunately the analogous proton in the trans isomer cannot be clearly identified and thus we can only estimate the cis:trans ratio as ~60:40.¹⁶ However, this isomerism is of no consequence to the synthesis since hydrolysis of the ester 13 is accompanied by equilibration of the ring juncture to produce crystalline coronafacic acid 2 (mp 116-8°C) in 83% yield. The identity of



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the synthetic material was established by comparison with our earlier synthetic material⁵ and with an authentic sample.¹⁷ Having isolated and characterized each of the intermediates of this synthesis, we have found it preferable to carry out the conversion of the lactone 8 directly to the desired ester 2 without the purification of any intermediates, thereby producing 2 in 7% overall yield from 5 and 6.

Further use of intramolecular cycloadditions of this type is currently under investigation and will be reported in due course.

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12. All new compounds possessed spectroscopic data (NMR, IR, mass spectra) in complete accord with the structures assigned.
13. Based on the amount of starting material consumed, the yield is consistently 20-25%.
14. In basic alcohol a fair proportion of Michael addition of alkoxide to the unsaturated lactone (ester) is observed, a side reaction which is minimized under acidic conditions.
15. This is in stark contrast to compounds with one additional methylene group between the diene and enone units, which normally cyclize at below room temperature. Examination of molecular models indicates that the carbonyl group in compounds such as 4 can not overlap with the olefin in the transition state for internal cycloaddition, while the opposite is true for the homologated compounds mentioned above. For examples, see: Taber, D.F.; Gunn, B.P. J. Am. Chem. Soc. 1979, 101, 3992; Gras, J.-L.; Bertrand, M. Tetrahedron Lett. 1979, 4549; Vig, O.P.; Trehan, I.R.; Kumar, R. Indian J. Chem. Sect B. 1977, 15B, 319.
16. When compound 3 is cyclized, only the compound with a trans ring juncture is produced presumably due to destabilization of the endo transition state by the steric interference of the large acetal function and the methylene group α to the ketone.⁷ In the case of 4, this interaction is presumably weaker due to the smaller size of an ethyl ester vs an acetal.
17. We thank Professor Ichihara for an authentic sample of natural coronafacic acid and spectra of both the natural and synthetic material.