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(6) The kinetic evaluation is given in ref 3b.

(7) The details of this measurement as well as the synthesis carried out by Dr. A. M. Braun in our laboratory will be published in a forthcoming full paper.

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(10) 3-Carboxyamidpyridinium surfactants show a similarly low affinity for cationic micelles: C. A. Bunton, private communication.

(11) The back-reaction is accelerated by increasing the ionic strength. For example, addition of 10^{-2} M NaCl produces ~30% augmentation of k_3.

(12) Owing to low frequency noise interference with measurements on relatively long time scales, only an upper limit for the rate constant can be given.

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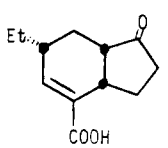
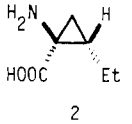
Total Synthesis of (±)-Coronafacic Acid: Use of Anionic Oxy-Cope Rearrangements on Aromatic Substrates in Synthesis

Sir:

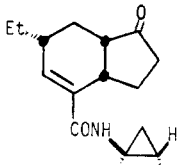
Coronafacic acid (**1**) has been isolated directly from the culture broth of *Pseudomonas coronafacience* var. atropurpurea.[1] The amide of coronafacic acid (**1**) with coronamic acid (**2**) is also produced by the same phytopathogenic bacterium.[1]



1



2

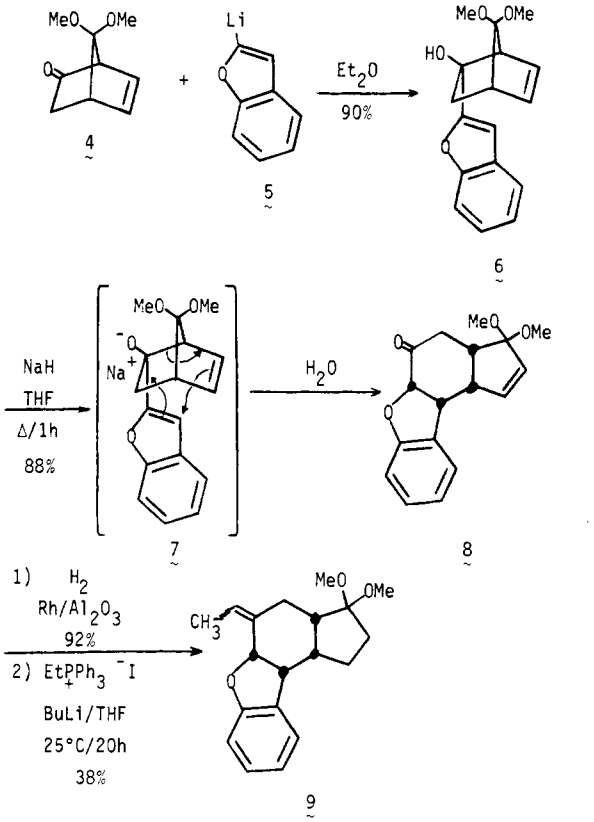


3

This natural phytotoxin, coronatine (**3**), induces chlorosis on the leaves of Italian rye grass and promotes the expansion of potato cells at very low concentrations.[2] Herein is reported an efficient total synthesis of coronafacic acid which employs as a key step an anionic oxy-Cope rearrangement on an aromatic substrate, a synthetic process developed recently in our laboratory.[3] In addition, a novel silicon-based alternative to an ethylidene Wittig reaction is described.

The only known total synthesis of coronafacic acid utilized a Diels–Alder reaction between cyclopentenone and a substituted butadiene to construct the 1-hydrindanone skeleton.[4] It was envisioned that the anionic oxy-Cope rearrangement of a suitably substituted norbornenyl alcohol would produce a hydrindan intermediate which could be easily transformed into the desired natural product (Scheme I). To this end, the highly

Scheme I



functionalized enone **4**[5] was treated with 2-lithiobenzofuran (**5**, prepared from benzofuran[6] by treatment with *n*-butyllithium) to furnish a 90% yield of the crystalline exo alcohol **6**[7] (mp 116–117 °C, IR 3500 cm^{-1}).[8] The stereochemistry of the product was assigned both by analogy to our earlier work in these norbornenyl systems[3] and by the effect of the shift reagent, $Eu(fod)_3$, on the chemical shifts of the various protons in the molecule, especially those of the *syn*-7-methoxy group, which undergo a very large downfield shift.

Refluxing a solution of **6** and sodium hydride in tetrahydrofuran (THF) for 1 h afforded the crystalline rearranged product **8** in 88% yield (mp 146–147 °C; IR 1735, 1600, 1460 cm^{-1}). This reaction proceeds by the presumed intermediacy of the anion **7** which would be expected to undergo facile oxy-Cope rearrangement.[3,9] The stereochemistry of the four asymmetric centers in **8** are assumed to be all cis based both on analogy to our previous work[3] and on the similarity of the chemical shifts and coupling constants of the protons in **8** and those of **12**, the structure of which was proven unambiguously by an X-ray analysis. Although catalytic hydrogenation of **8** proceeded in high yield, the subsequent Wittig reaction gave only a fair yield of the ethylidene mixture **9**[7] under all conditions tried. A large amount of starting ketone is recovered so that enolization of the ketone by the very basic ylide is the probable source of difficulty. The use of other solvents, e.g., DME or Me_2SO, for the production of the ylide did not significantly improve the reaction. Since the highest yield for this process was only 38% (68% on unrecovered ketone), we sought alternatives to the Wittig route.

Encouraged by the widely reported successes of the silyl-Wittig reaction of Peterson[10] for methylene formation, we attempted to extend this approach to the formation of an ethylidene unit. Reaction of the Grignard reagent formed from commercially available α-chloroethyltrimethylsilane with the ketone **8** afforded simple reduction of the carbonyl in 85% yield with no evidence for addition. This result is not due to the steric bulk of the carbonyl in **8** since both benzophenone and cyclohexanone also give nearly quantitative yields of the corre-

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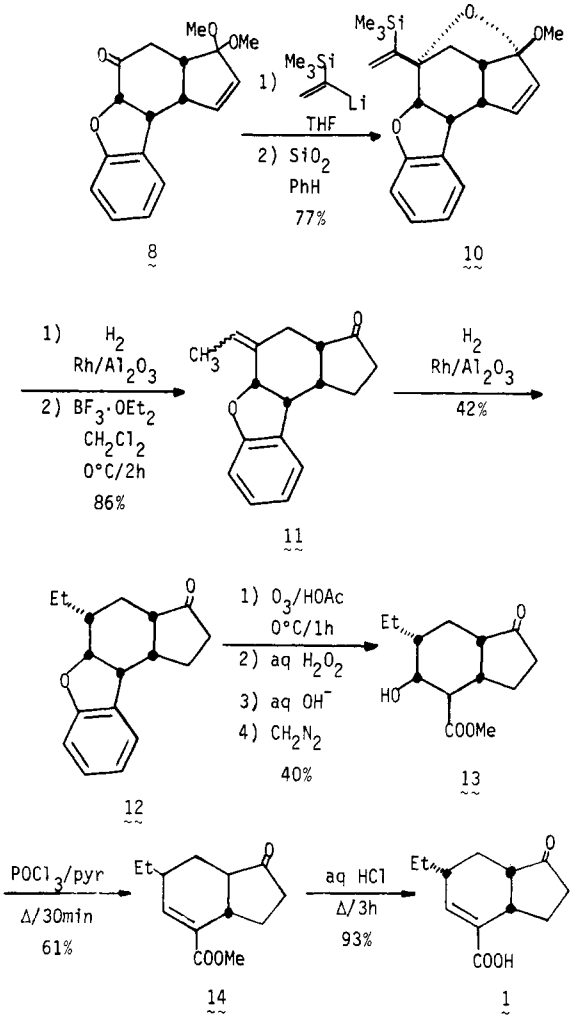
Scheme II



sponding alcohols under these conditions. It is presumably the great steric bulk of the Grignard reagent which causes elimination of hydride from the β position[11] to be preferred over simple addition.[12]

Since a vinyllithium should not undergo facile β-elimination–reduction, the use of the α-trimethylsilylvinyllithium offered another alternative to the Wittig process (Scheme II). Reaction of this organometallic reagent[13,14] with the ketone **8** followed by stirring in benzene over silica gel afforded the internal ketal **10**[7] in good yield. Catalytic hydrogenation produced the tetrahydro compound which now underwent clean desilylative olefin formation upon treatment with boron trifluoride to give the mixture of keto olefins **11**[7] in excellent yield.[15] This three-step alternative for ethylidene formation should be generally useful. Catalytic hydrogenation of **11** produced a mixture of products from which the major product **12**[7] could be purified without chromatography by direct crystallization from the reaction mixture (mp 140–141 °C). The desired product **12** corresponds to reduction of the olefin from the less hindered convex face of the molecule. The stereochemistry of all centers in **12** was determined by a single-crystal X-ray diffraction.[16]

Having served as the protected form of the carboxylate function, the aromatic ring in **12** was now converted into the ester **13** by ozonolysis in acid, oxidation, hydrolysis, and esterification in 40% yield. The final conversion to coronafacic acid (**1**) was effected in 57% overall yield by elimination of the β-hydroxy function with phosphorus oxychloride–pyridine to give the ester **14**[17] which was hydrolyzed in acid to afford **1**.[18] The synthetic product was thus produced by a nine-step process in an overall yield of 5%. It was identical in all respects with an authentic sample.[19] Since coronafacic acid (**1**) has been coupled with coronamic acid (**2**),[4] this report also constitutes a formal total synthesis of coronatine (**3**).

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(7) All new compounds had spectral properties (NMR, IR, mass spectra) in complete accord with the assigned structures. Also satisfactory elemental analyses were obtained for all crystalline compounds.
(8) We also attempted to use the simple analogous dihydrofuryl system corresponding to **8** which we had prepared earlier[3] for the preparation of **1**. However when selective hydrogenation of the cyclopentene double bond could not be effected, this approach was abandoned.
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(11) Reductions of this type are well known. For a discussion of the mechanism, see M. S. Singer, R. M. Salinger, and H. S. Mosher, *J. Org. Chem.*, **32**, 3821 (1967).
(12) Attempts to prepare the α-lithiosilane, which should be less prone to cause reductions, from the chloride failed.
(13) Prepared from α-bromovinyltrimethylsilane[14] by reaction with *n*-butyllithium in THF.
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(15) These isomers could be separated by chromatography to give a crystalline (mp 145–146 °C) isomer and an oil. However, since hydrogenation of the purified isomers offered no advantages the mixture was used in the subsequent step.
(16) This study was carried out by Professor Charles Strouse and Mr. Larry Goldsmith in our department and will be described in detail in the full paper.
(17) The ester **14** is a mixture of two major compounds in the approximate ratio of 4:1 (NMR integration). This mixture was not separated but rather used directly in the next step.
(18) We assume that coronafacic acid has the structure indicated by **1** as proposed by Ichihara. His evidence for this structure is very strong, although two alternative structures with the ethyl group having the β-stereochemistry cannot be absolutely eliminated since there is the possibility of epimerization of the hydrogen γ to the α,β-unsaturated carboxylate in the final acidic ester hydrolysis.
(19) We thank Professor Ichihara for kindly providing us with an authentic sample of natural coronafacic acid and the spectral data for both the natural and their synthetic material.
(20) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; Alfred P. Sloan Foundation Fellow, 1979–1981.
(21) Recipient of the Winstein Dissertation Award.

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Secondary Deuterium Isotope Effects on Epoxide Methanolysis Reactions

Sir:

Secondary kinetic deuterium isotope effects have recently come into widespread use as probes of reaction mechanism and transition state structure.[1-7] They are particularly useful for detailed comparison of transition states for enzymatic and chemical model reactions because isotopic substitution, in contrast to introduction of chemical substituent groups, does not change the potential energy surface of the reaction pathway. These effects are presumed to arise by one of two major

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