(7) Bartlett, P. D.; Nelsen, S. F. *J. Am. Chem. Soc.* **1966**, *88*, 137–143.
(8) Migirdicyan, E.; Baudet, J. *J. Am. Chem. Soc.* **1975**, *97*, 7400–7404.
(9) Tseng, K. L.; Michl, J. *J. Am. Chem. Soc.* **1977**, *99*, 4840–4842.
(10) Vögtle, F.; Neumann, P. *Synthesis* **1973**, 85–103. Givens, R. S.; Wylie, P. L. *Tetrahedron Lett.*, **1978**, 865–868, and references contained therein.
(11) Pellegrin, M. *Recl. Trav. Chim. Pays-Bas.* **1899**, *18*, 457–465. Baker, W.; McOmie, J. F. W.; Norman, J. M. *J. Chem. Soc.* **1951**, 1114–1118.
(12) Rule, M.; Matlin, A. R.; Hilinski, E. F.; Dougherty, D. A.; Berson, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 5098–5099.

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Total Synthesis of *dl*-Coriolin

Sir:

Coriolin (**1**), a metabolite of *Coriolus consor* is a member of a larger class of microbially derived cis,anti,cis-tricyclo[6.3.0.$0^{2,6}$] undecanoid sesquiterpenes known as the hirsutanes.[1] The novel ring system of the hirsutanes, embroidered by varied pendant functionality, poses an intrinsic synthetic challenge. Adding to the incentives for the successful realization of this goal are the promising antibacterial and antitumor properties which have been asserted on behalf of several of these compounds.[2] Early and substantive synthetic contributions to this area were provided by Lansbury.[3,4] A major milestone was the total synthesis of hirsutic acid, achieved by Matsumoto[5] and by Trost.[6]

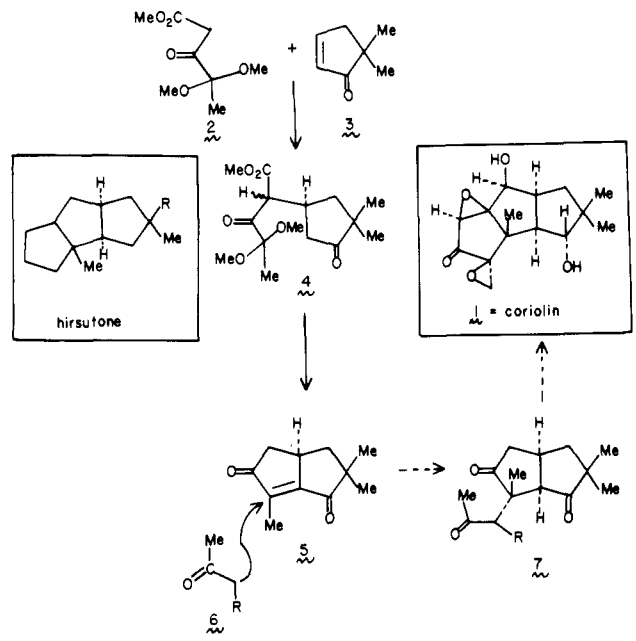
The densely oxygenated coriolin[7] is a particularly attractive target for total synthesis. Its eight centers of chirality arrayed about its six units of unsaturation underscore the need for an orderly approach. Moreover, coriolin and several of its congeners have received rather detailed biological scrutiny vis-à-vis antitumor and antibiotic activity. Indeed, a novel mode of antitumor action, involving the inhibition of uptake of amino acids and potassium ions into tumor cells, has been ascribed to these compounds.[8,9]

Concise and pleasing approaches to the coriolin branch of the hirsutane family have been provided by Tatsuta[10] and by Little.[21] However, for the moment, no fully comprehensive solution has yet been recorded. Below we describe the total synthesis of *dl*-coriolin.

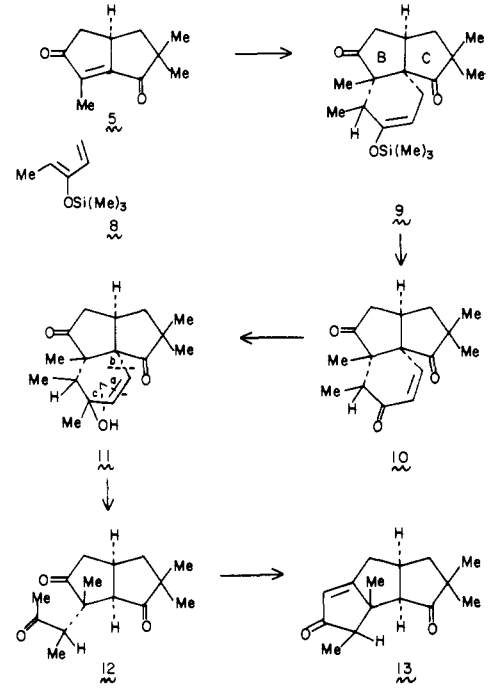
A practical route to enedione **5** was our first subgoal. Michael addition of β-keto ester **2**[11] to cyclopentenone **3**[12] (0.25 equiv of sodium methoxide, methanol, room temperature, 3 days) gave the epimers **4**.[13a] Reaction of **4** with *p*-TsOH in toluene containing 0.2% water, under reflux, provides a 60–65% yield of **5**[13] (Scheme I), mp 54–55 °C, from **4**. We next addressed what we defined to be the central problem of the undertaking, i.e., finding a means for the delivery of an acetonyl fragment **6** (R = H or R = alkyl) to enedione **5** with positional[14] and stereochemical control. The latter issue was complicated by the sheet-like nature of the bicyclic system. Prognoses as to the likely stereochemical sense (α or β) of attack of external reagents at the desired carbon of such an enedione were not convincing.

A more securely based approach is implicit in Scheme II. *It could be predicted that cycloaddition to the double bond would occur in the required α sense, since the alternative and undesired β mode would result, even at the level of the transition state, in an unacceptable trans fusion of the bicyclic BC system.* Reaction of **5** + **8**[15] (3 equiv of **8**, xylene, 120 °C, 11 h) afforded apparently a single product, **9**.[16,17] Treatment of **9** with phenylselenenyl chloride,[15b] followed by oxidation according to Reich and Sharpless,[18] gave the highly crystalline enone **10**, mp 168–169 °C,[13] in 50% overall yield from **5**.

Scheme I



Scheme II



Treatment of **10** with methyllithium (2.5 equiv of MeLi, THF, −78 °C, 1 h) afforded **11**[13,16,19] in 82% yield. The acetonyl group was retrieved from **11** as follows. Ozonolysis followed by Jones oxidation gave, presumably,[20] a hydroxy diacid (cleavage a). Decarboxylation (aqueous barium hydroxide, reflux, 3 h) of the now extraneous bridgehead β-keto acid gave, presumably,[20] a hydroxy monoacid (cleavage b). The next treatment (lead tetraacetate, PhH, room temperature, cleavage c) exposed the required 2-butanon-3-yl residue in the form of the crystalline trione **12**,[13] mp 66–67.5 °C, in 58% yield from **11**. Aldolization–dehydration, according to Stork and Clarke,[21] afforded (70%) **13**.[13,22]

The adjustments of functionality were achieved as shown in Scheme III. Deconjugation, according to Ringold[23] of **13**

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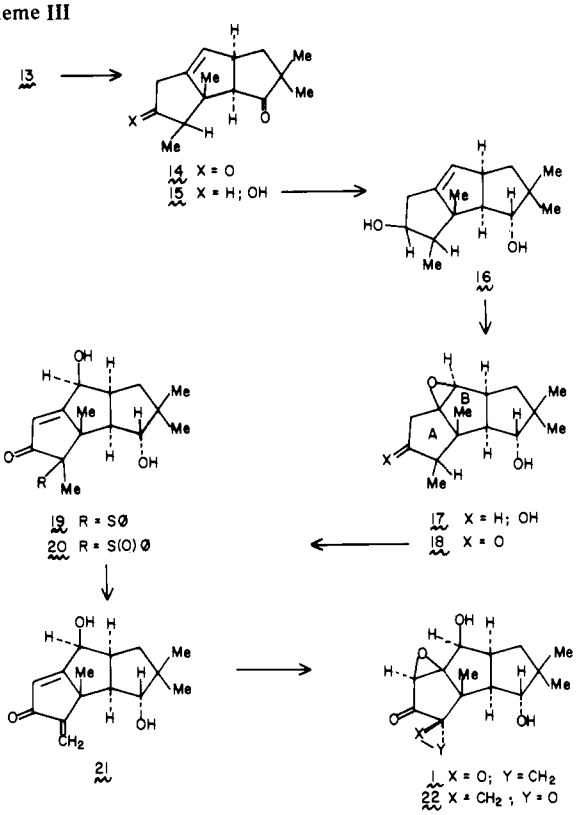
Scheme III



afforded (70%) **14**[13,22] which gave, after reduction with 3 equiv of Dibah (THF, −78 °C, 2 h), the homoallylic alcohol epimers **15**[24] in 85% yield. The latter, upon further reduction (Li, NH_3, and methanol) affords quantitatively **16**,[24] bearing the more stable α alcohol in the A ring. Epoxidation of **16** (MCPBA, methylene chloride, room temperature, 10 min) clearly provides **17**.[24] *The desired β sense of this epoxidation could be predicted with confidence since the alternate and undesired α mode would result in an energetically unacceptable trans fusion of the A and B rings.*

Selective oxidation of the more accessible alcohol according to Corey and Suggs[25] affords **18**.[13,24] Treatment of **18** with (4 mmol, i.e., 1.3 equiv) of lithium diisopropylamide from −30 → 0 °C, followed by quenching at 0 °C with phenylthiophenylsulfonate,[26] affords **19**[13] in 40% yield. This key transformation was shown to first proceed through β elimination of the epoxide. This is then followed by in situ enolization of the enone dialkoxide in the α' sense.[27] In this way, no protecting groups are employed in the entire synthesis. Oxidation of **19** (MCPBA, methylene chloride, −78 °C) gave **20** which suffers smooth elimination (ethyl acetate, reflux, 30 min)[27] to afford **21**.[13] Finally, treatment of **21** with alkaline hydrogen peroxide affords *dl*-coriolin (**1**), along with its spiroepoxide epimer **22**[13a] in an ~7:5 ratio. These were readily separated by preparative LC to provide *dl*-coriolin, mp 151–154 °C, whose chromatographic mobility and infrared and NMR (600 MHz) spectra were identical with those of a specimen of natural coriolin kindly furnished by Drs. Umezawa and Takita.

Experiments addressed to improving the yields of this 19-step total synthesis, attainment of stereospecificity in the creation of the spiroexpoxide, and suitable modifications to embrace several active coriolin congeners are well in progress and their outcome will be disclosed in due course.

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References and Notes

(1) For an excellent compilation of these and related sesquiterpenes see: Little, R. D.; Bukhari, A.; Venegas, M. G. *Tetrahedron Lett.* **1979**, 305.
(2) For a compilation of pertinent references including citations to the biological literature see: Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 7129.
(3) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1971** 1829. Lansbury, P. T.; Nazareno, N. *Ibid.* **1971**, 1833.
(4) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1972**, 2053.
(5) Hashimoto, H.; Tsuzuki, T.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1974**, 3745.
(6) Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284.
(7) For pertinent structure and stereochemical information on coriolin see: (a) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955. (b) Nakamura, H.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y.; Iitaka, Y. *J. Antibiot.* **1974**, *27*, 301.
(8) Ishizaka, M.; Inuma, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 320.
(9) Umezawa, H.; Kumimoto, T. *Biochem. Biophys. Acta* **1973**, *318*, 78.
(10) Tatsuta, K.; Akimoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 6116.
(11) The preparation of the diethoxy ketal methyl ester version of **2**, for another purpose, had been described by J. Quick, Thesis, University of Pittsburgh, 1973.
(12) Agosta, W. C.; Smith, A. B., III *J. Am. Chem. Soc.* **1971**, *93*, 5513.
(13) (a) The structure of this compound is in accord with its infrared, NMR, and (b) mass spectra.
(14) In fact several Michael reactions to enedione **7** resulted, exclusively, in angular entry of nucleophile: M. Kahn, unpublished results.
(15) (a) Mock, G. A.; Holmes, A. B.; Raphael, R. A. *Tetrahedron Lett.* **1977**, 4539. (b) Danishefsky, S.; Yan, C. F. *Synth. Commun.* **1978**, *8*, No. 4, 211.
(16) The stereochemistry of the secondary methyl group can not be rigorously assigned.
(17) The issue of the directionality of Diels–Alder reactions of enedione **5** with various dienes has been studied in some detail. The results will be discussed in a separate publication.
(18) (a) Reich, H. J.; Renga, J.; Reich, I. L. *J. Am. Chem. Soc.* **1973**, *95*, 5813. (b) Sharpless, K. B.; Lauer, R.; Teranishi, A. Y. *Ibid.* **1973**, *95*, 6137. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *Ibid.* **1975**, *97*, 5434.
(19) Although the reaction is regiospecific as shown, there appears to be produced a 9:1 ratio of epimers in this addition. These are carried on together.
(20) The intermediates in this degredative sequence have not been characterized.
(21) Stork, G.; Clarke, F. H., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 3114.
(22) This reaction results in epimerization of the secondary methyl group to varying extents. The two epimers are not separated for subsequent reactions.
(23) Ringold, J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, 669.
(24) Three epimers **15a–c** in an isolated yield ratio of 55:20:10 were obtained in pure form from this reduction. Each was carried forth separately in the sequence shown. The secondary alcohol epimers **15a** and **15c** converge at the stage of compound **18a**. Epimer **15b** leads to compound **18b**. Epimers **18a** and **18b** converge at sulfide **19** of undetermined configuration at the thiophenyl center. We now believe that the sequence from **15** → **19** could be carried out on the mixture. However, this has not been fully demonstrated.
(25) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(26) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.
(27) Lee, R. A.; McAndrews, C.; Patel, K. M.; Reusch, W. *Tetrahedron Lett.* **1973**, 965.
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Reactions of Arc Generated Carbon Atoms with Benzene

Sir:

The reaction of atomic carbon with benzene is of interest in that it provides a potential entry onto the interesting C_7H_6 energy surface. Two possible pathways for this reaction are C–H insertion to generate phenylcarbene (**1**) and addition to

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