Stereospecific Total Syntheses of *dl*-Coriolin and *dl*-Coriolin B

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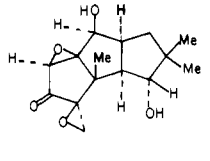
Received August 21, 1980

Abstract: The total syntheses of the title compounds are described. The starting materials were the enedione **6** and the siloxy diene **27**. Cycloaddition of these compounds afforded **28**, which was converted to **30**. Degradation of enone **30** gave methyl ketone **32**, which upon cyclization afforded tricyclic enone **33**. After suitable manipulation, this was converted to cross-conjugated dienone **4**. This was transformed to dihydrocoriolin (**44**) and thence to the title compounds.

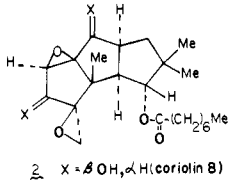
Background

The sesquiterpene coriolin (**1**) was first isolated from a cultured broth of a Bacidomycetes, *Coriolus consors*, by the Umezawa group.[1] Its structure was originally perceived in terms of an illudane skeleton.[2] More extensive chemical investigations by the same group led to a reformulation of its structure as a hirsutane derivative.[3] In addition, a related compound, coriolin B, whose structure was shown to be **2**,[3,4] was isolated from the same microorganism.

As part of the chemical investigation of compound **2**, it was oxidized in a Jones-like fashion to afford diketocoriolin B, formulated as **3**. While coriolin B (**2**) itself has antitumor and antibiotic activity, its derivative **3** exhibits the more promising biological profile (vide infra).[5] The chemically based structural assignments **1-3**, were subsequently verified through X-ray crystallographic means.[6]



1 (coriolin)



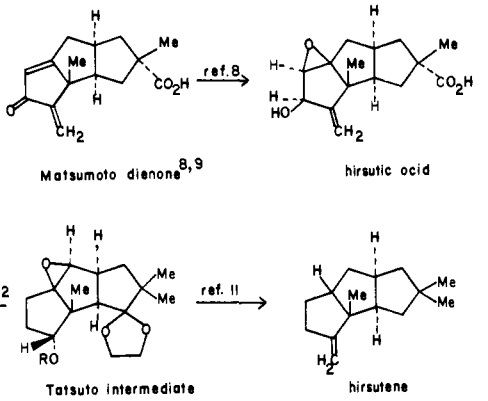
2 X = β OH, α H (coriolin B)
3 X = O (diketocoriolin B)

The defenses of the coriolins against the incursions of total synthesis would appear to be robust. One is immediately struck by an elaborate network of oxygens which embroiders their interesting tricyclo[6.3.0.$0^{2,6}$] ring system. In the case of the "parent" compound coriolin (**1**), eight chiral centers are arrayed about its six units of unsaturation. Additional complications, from a synthetic standpoint, are seen in coriolin B (**2**), which contains nine chiral centers and a triol arrangement, in which one of three secondary alcohols appears in acylated (octanoylated) form. A total synthesis would clearly be challenging.

Additional incentives for synthetic exploration in this area are the promising antitumor and antibiotic properties of compound **3**. Indeed a novel mode of antitumor action, involving the inhibition of uptake of amino acids and potassium ions into tumorous cells, has been found for this derivative.[5] Thus our main objective was coriolin B (**2**), from which **3** is obtained. However, it seemed tactically prudent to concentrate, at first, on the somewhat less forbidding "parent" compound, coriolin (**1**).

At the time of our investigations, there had been described no total syntheses of the coriolins. Of course, the early and fruitful investigations of Lansbury into the construction of the related hirsutic acid provide an ever-present backdrop in this area.[7] The first total synthesis of hirsutic acid, accomplished by the Matsumoto group, is also a landmark in this field.[8] The terminal steps of the Matsumoto synthesis eventually became of some relevance to our effort (vide infra). More recently, the total synthesis of hirsutic acid was also formally achieved by Trost,[9] who reached the Matsumoto dienone by a highly novel approach.

Scheme I



Concise and pleasing approaches to the coriolin system, of particular note, are seen in the work of Little[10] and Tatsuta.[11] Tatsuta had described the conversion of his intermediate to the naturally occurring hirsutene. By a rather indirect sequence, Tatsuta has in fact achieved the conversion of his intermediate, which was well directed for a synthesis of hirsutene, into a synthesis of coriolin (**1**).[12] Interestingly, the Tatsuta route passes through an intermediate, **4**, which appears in our[13,14] synthesis.

* To whom correspondence should be addressed at Yale University.

(1) (a) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (b) Takeuchi, T.; Iinuma, H.; Takahashi, S.; Umezawa, H. *Ibid.* **1971**, *24*, 631.
(2) Takahashi, S.; Iinuma, H.; Tomohisa, S.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1969**, 4663.
(3) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955.
(4) In addition, coriolin C was isolated. This compound contains an additional center of chirality in the octanoyl chain.
(5) (a) Kunimota, T.; Umezawa, H. *Biochim. Biophys. Acta* **1974**, *298*, 513. (b) Ishizaka, M.; Inuma, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 320.
(6) Nakamura, N.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y.; Iitaka, Y. I. *J. Antibiot.* **1974**, *27*, 301.
(7) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1971**, 1829. Lansbury, P. T.; Nazarenko, N. *Ibid.* **1971**, 1833. Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Ibid.* **1972**, 2053.
(8) Hashimoto, H.; Tsuzuki, T.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1974**, 3745.
(9) Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284.
(10) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 7129.
(11) Tatsuta, K.; Akimoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 6116.
(12) Tatsuta, K.; Akimoto, K.; Kimoshita, M. *J. Antibiot.* **1980**, *33*, 100.
(13) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097. For a preliminary account of the synthesis of coriolin B see: Danishefsky, S.; Zamboni, R. *Tetrahedron Lett.* **1980**, 3439. Our results were first disclosed in a plenary lecture at the International Congress of Antibiotic Compounds in Boston on Oct 2, 1979.
(14) We also note that, by a series of transformations remarkably similar to those which we reported,[13] another Japanese group has achieved the synthesis of coriolin from a bicyclic intermediate. See: (a) Shibasaki, M.; Iseki, K.; Ikegami, S. *Synth. Commun.* 1980 *10*, 551. (b) *Tetrahedron Lett.* **1980**, 3587.

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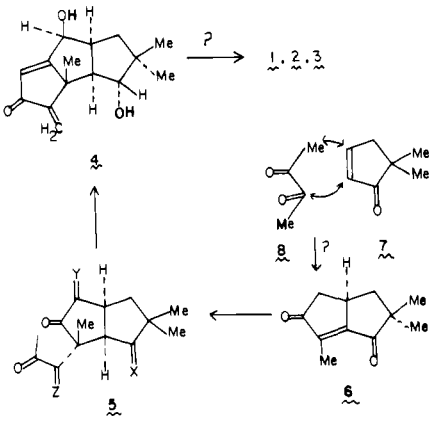
Scheme II



Below, we describe the regio- and stereospecific total synthesis of coriolin (**1**) and coriolin B (**2**).

Synthetic Planning

It seemed reasonable to define as a major subgoal the cross-conjugated dienone **4**—a system which contains the potentialities for construction of the two epoxides vital for any of the coriolins. One could project with some confidence[8] that oxidation of the trisubstituted double bond would give rise to the needed β epoxide in which the A and B rings could be cis fused. No comparably convincing arguments could be asserted to predict the outcome of epoxidation of the exocyclic methylene group. The feasibility of stereospecificity in such a process would have to be ascertained strictly by experiment. As will be seen, the attainment of stereospecificity in the spiroepoxidation proved to be a troublesome but solvable matter.

A more immediate goal would then become system **5**, whose conversion to **4** would involve intramolecular aldolization. It was hoped that in this precursor, the pattern Y = H_2 would suffice. If our plans (vide infra) for introduction of a ring-B hydroxyl group by exploiting its γ relationship to the ring-A enone of **4** were frustrated in practice, it would then be necessary to seek more elaborate permutations of Y at the stage of **5**. Similarly, the nature of Z in **5** was left unspecified. Certainly one could consider the obvious possibility of Z = H_2. Other permutations which offer more advanced provision for the eventual exocyclic methylene group of **4** could also be entertained. However, it did seem clear that X in **5** must correspond to some state of oxygenation, since the prospects for a de novo introduction of the ring-C oxygen in **4**, from a deoxy precursor, seemed none too promising.

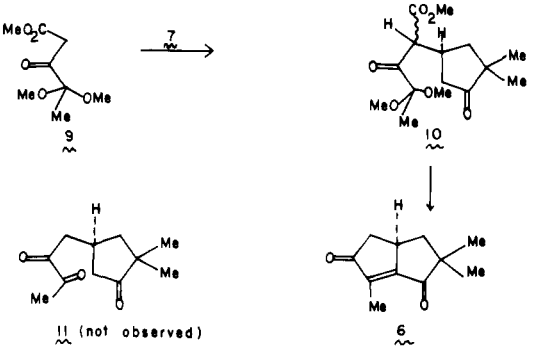
Given these considerations, the enedione **6** presented itself as an early target for synthesis. With this compound in hand, one would then confront the central problem of the program, i.e., the attachment of an acetonyl (cf. Z = H_2 in **5**) residue, or its equivalent, to the required carbon of the enedione **6** in the required stereochemical sense.

Before we could launch the several schemes we had in mind in this connection, we required comfortable access to this enedione. Surprisingly, the construction of such systems by annelation of a ketone had not been systematically investigated.[15] Upon inspection, it is quickly perceived that compound **6** is, in principle, derivable from the condensation of biacetyl **8** with 5,5-dimethylcyclopent-2-en-1-one (**7**), a known[16] compound. The translation of this obvious formalism to the more exacting realm of laboratory practice became our first concern.

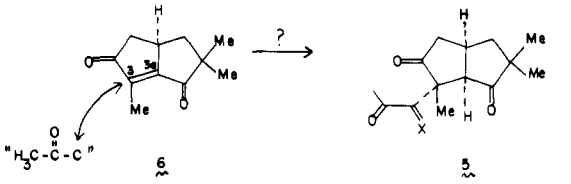
Discussion of Results

(i) Preparation of Enedione 6. The biacetyl equivalent **9** was readily prepared by the carbomethoxylation of the known 3,3-dimethoxy-2-butanone.[17,18] A Michael reaction between **9** and

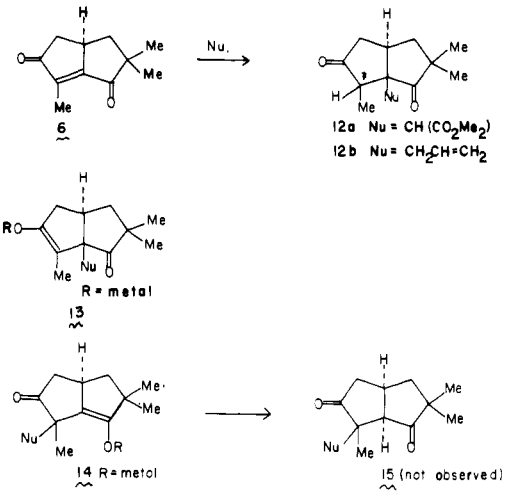
Scheme III



Scheme IV



Scheme V



7, under the influence of 0.2 equiv of sodium methoxide in methanol at room temperature for 3 days, afforded **10**, presumably as a mixture of diastereomers. Reaction of **10** with *p*-toluenesulfonic acid in toluene under reflux brought about the desired decarbomethoxylation and cyclization, affording the enedione **6**, mp 54–55 °C (in ca. 45–50% yield from **7**). The scope and limitations of this annulation will be described elsewhere.[19] For the moment it is interesting to note that we were unable to isolate, or observe, compound **11**. Its intermediacy in the annelation is, accordingly, not established.

(ii) Preparation of Enone 30. Our next objective was the synthesis of a system of the type **5**. Here we faced the critical issue of the introduction of an "acetonyl" residue, or its equivalent. Such a transformation requires a solution to the problem of alkylating a particular carbon, 3 or 3a in the case at hand, of an "enedione" system.[20] An even more interesting challenge is that of stereochemical control. Given the sheetlike nature of **6** and the absence of sterically demanding substituents which might sharply differentiate its α and β faces, predictions as to the likely sense of attack at the required C_3 were unconvincing.

(15) For a related annulation see: Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Ito, N.; Hisamitsu, T.; Kamada, T.; Sakan, F.; Nishida, S. *Tetrahedron Lett.* **1968**, 1925.

(16) Agosta, W. C.; Smith, A. B., III *J. Am. Chem. Soc.* **1971**, *93*, 5513.

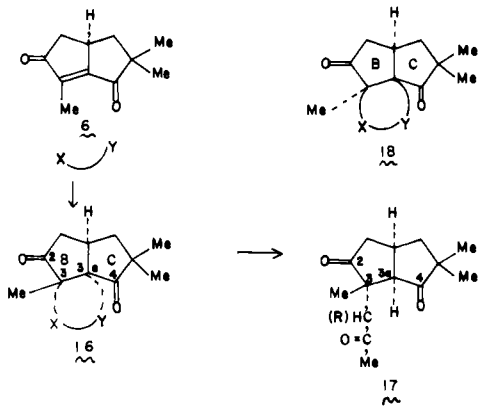
(17) Braude, E. A.; Timmons, C. *J. Chem. Soc.* **1953**, 3131.

(18) The preparation of the diethoxy ketal methyl ester version of **9** had been described: Quick, J. Thesis, University of Pittsburgh.

(19) Etheredge, S. J., unpublished results.

(20) For an interesting solution to this type of problem in a different context see: Stork, G.; Logusch, E. W. *J. Am. Chem. Soc.* **1980**, *102*, 1218.

Scheme VI



With no particular rationale to guide us, we investigated the outcome of Michael reactions on compound **6**. A variety of such attempts led to the introduction of the nucleophile at the undesired angular position. Two examples are the efficient preparation of compounds **12a** and **12b** from the reactions of **6** with dimethyl sodiomalonate in methanol and allyltrimethylsilane (catalyzed by titanium tetrachloride) in methylene chloride. We have investigated such reactions in some detail and our results will be described elsewhere.[21] For the moment, suffice it to say that the direct "Michael" technology, in our hands, failed to produce any of the desired products of type **15**.

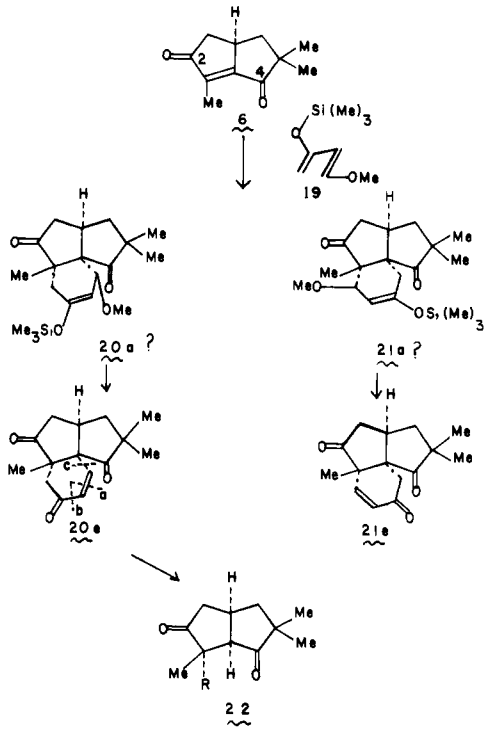
Armed with the facts, one can argue that the results are not surprising. Thus, formation of the observed products **12** involves the intermediacy of enol derivatives of type **13**. Enol derivatives of the structure **14** would have been required to produce the desired products **15**. *Early rehybridization of the bridgehead carbon from the sp^2 to the sp^3 state would be expected to be energetically favorable.* This postulated effect, which nicely rationalizes the results of the Michael reaction, was destined to be of rather general predictive value at several points in the investigation.

To simultaneously address the regiochemical and stereochemical issues implicit in the required transformation, we came to explore the possibilities inherent in a cycloaddition approach. The overall plan is set forth in Scheme VI. Cycloaddition of **6** with the hypothetical XY would be expected to produce a product of type **16**, rather than **18**, since in the latter structure, the five-membered B and C rings must emerge in the very unstable trans-fused form. In the expected **16**, these rings are cis fused.

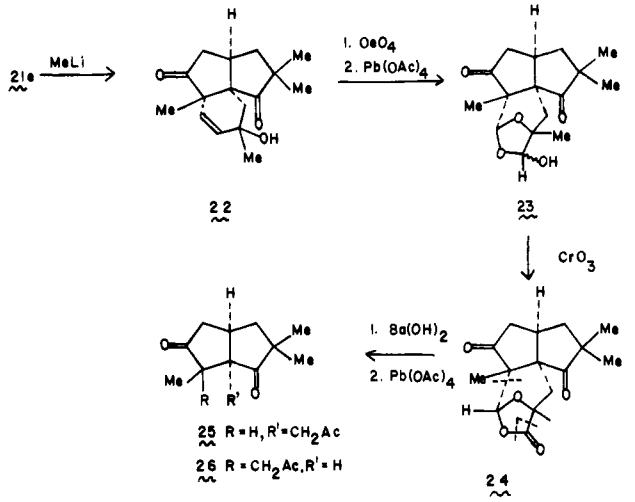
While this prediction seemed securely based, its pertinence to the problem at hand rested on the feasibility of replacing the junction substituent (at C_{3a}) by a hydrogen atom and retrieving an acetonyl group or its equivalent as part of this degradation. It will be noted that in going from **6** to **17** a new chiral center is created at the fusion of the two five-membered rings (i.e., C_{3a}). However, here one could be very confident of a favorable outcome since, minimally, this center is subject to thermodynamic control via enolization of the C_4 ketone. Thus the α configuration at this center would be ensured. The notable feature of the scheme, in stereochemical terms, is that it provides a rational kinetic basis to ensure the α configuration of the acetonyl group in structure **17**. In summary, we sought to link the uncertain mode of stereochemical attack at C_3 to the predictable α mode of attack at C_{3a}. Once the "linkage" were ensured at the kinetic level, we would rely on thermodynamic stability to ensure the result at C_{3a}. Since C_3 is not subject to equilibration by enolization, the α configuration of the acetonyl residue must persist.

As our first inquiry into the feasibility of such a strategy, we studied the Diels–Alder reaction of **6** with compound **19**,[22] a diene which had served us well on other occasions.[23]

Scheme VII



Scheme VIII

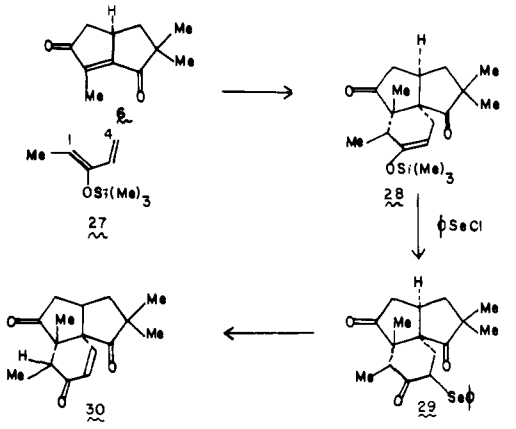


The hope was that cycloaddition of **6** with **19** would afford adduct **20a**, which would suffer transformation in the usual way[22,23] to enone **20e**. This enone would be susceptible to oxidative degradation (see dotted bonds a and b) and decarboxylation (see dotted bond c) to afford a product of type **22** (R = acetonyl). It will be recognized that adduct **20a** would be the one in which the s-cis ketone (i.e., the C_4 ketone) controls the dienophilicity of the tetrasubstituted double bond.[24]

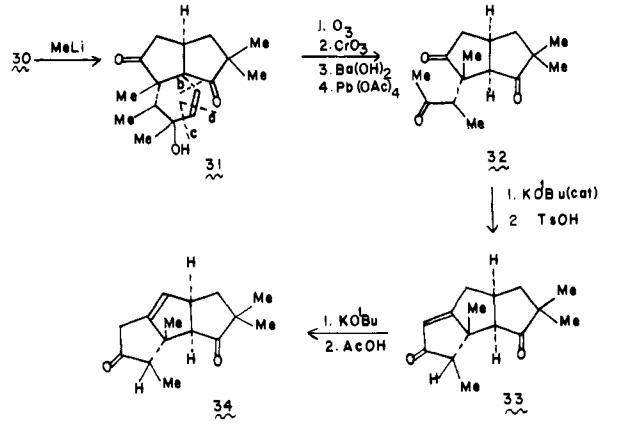
Cycloaddition of **6** with **19** occurred in toluene under reflux. Unfortunately, for our purposes, the product was the undesired adduct **21a**, as seen by its transformation to the undesired enone **21e** on treatment with dilute acid. The structure of **21e** was established by the degradative steps shown in Scheme VIII.[25] These steps were carried out under the mistaken[26] impression that

(21) Kahn, M., unpublished results.
(22) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.
(23) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1979**, *101*, 7020.
(24) This expectation was based on the enhanced dienophilicity of alkylidenecycloalkanones relative to that of cycloalkenones.
(25) On the basis of a different degradation which did not produce a pure product, the structure of the enone was first formulated as **20e**. This result was privately reported to Professor S. F. Martin and unfortunately appears in his review. Martin, S. F. *Tetrahedron* **1980**, *36*, 419.
(26) Kahn, M., unpublished results which will be described elsewhere.

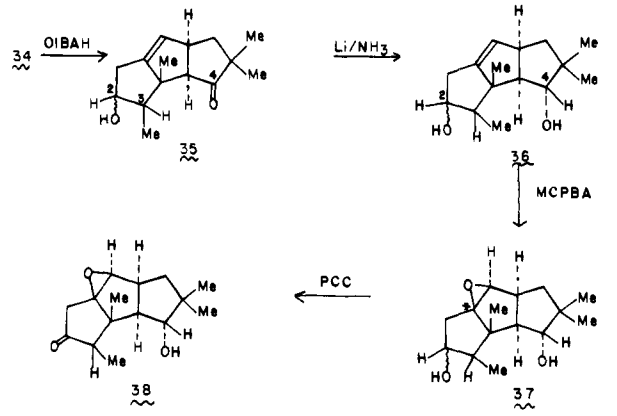
Scheme IX



Scheme X



Scheme XI



the adduct was actually **20a**. The enone would thus have been **20e** and its degradation product would have been **26**. However, NMR analysis at the stage of the final triketone revealed it to be **25** rather than **26**. Although this result was surely disappointing in terms of the coriolin project, it was not without some positive learning consequences. First, enedione **6** had been shown to be a viable dienophile. Given its highly hindered double bond, this could hardly have been assumed in advance. Second, a degradative protocol by which the required acetonyl group could be obtained was achieved. Finally, at least an apparent consistency had emerged between the Michael (vide supra) and Diels–Alder results.

As noted above, the results of Michael reactions were interpretable in terms of a preferred rehybridization of C_{3a}, presumably leading to a corresponding decrease in the serious strain at this bridgehead center. In the Diels–Alder reaction of **6** with **19**, though admittedly in a much more subtle sense, the same tendency seems to predominate.

With these considerations now firmly in mind, we studied the reaction of **6** with diene **27**.[27,28a] With quinones as the dienophiles, there could be found in the literature precedent for believing that the "initial" bonding to dienes of type **27** occurs at C_4. Thus with finely balanced dienophiles, the C_1 methyl group appears to be of greater orienting power than a C_2 alkoxy function.[29] If this analogy[30] would govern the cycloaddition of **6** with **27**, the formation of adduct **28** would be expected.

In practice, the reaction was carried out in xylene at 120 °C. The crude adduct **28** was subjected to the action of phenylselenyl chloride[28b] and the crude phenylselenyl ketone **29** was subjected to oxidation in the usual way.[31] There was thus obtained, in 55–60% yields, the crystalline enetrione **30**, mp 168–169 °C.

The structural assignment for **30** was only tentative at this point but was rigorously demonstrated by virtue of its conversion to the required **32** (vide infra). We leave unspecified the stereochemistry of the secondary methyl group in this compound. For subsequent reactions we used only the crystalline enone **30**. The mother liquors from which this material was obtained were not carried forward and may well contain some of the secondary methyl diastereomer of **30**. The major byproduct in the formation of **30** appeared to be its dihydro derivative (i.e., the cyclohexanone rather than cyclohexenone), arising from inefficient selenenylation of the crude adduct **28**. To the best of our knowledge, orientational isomer **28** is the only one produced from the reaction—an observation which is well consistent with relevent precedents.[29]

(iii) Preparation of Dienone 4. For the conversion **30** → **32** a simpler degradation was developed than that used for **21e** → **25**. It is shown in Scheme X. Selective addition of methyllithium to the cyclohexenone carbonyl group was readily accomplished. Only the crystalline tertiary allylic alcohol **31** (stereochemistry unassigned) was carried forward. Ozonolytic cleavage of the double bond was followed by Jones oxidation. The hydroxy diacid thus presumably generated (see cleavage of bond a) was subjected to the action of barium hydroxide to effect decarboxylation of the β-keto acid (see cleavage of bond b). Oxidation of the resultant α-hydroxy acid (see cleavage of bond c) afforded crystalline triketone **32**, mp 65.0–66.5 °C in 46–58% yield.

Aldolization–dehydration of **32**, using the conditions of Stork and Clarke,[32] provided **33** in 70% yield. Both epimers, of unassigned stereochemistry at the secondary methyl center, were obtained in homogeneous form. However, it was found that the mixture of epimers could be carried forward effectively.

Deconjugation of **33** according to Ringold[33] gave rise to **34** (60–70%) along with recovered **33** (10–15%), which was not recycled. Again, both secondary methyl epimers of **34** were isolated in a homogeneous state, though the stereochemistry at this center was not assigned. The mixture was carried forward.

Selective reduction of the unhindered ring A cyclopentanone was readily achieved. Varying ratios of **35** were produced. The outcome depended on the nature of the epimeric mixture of starting **34**. The crude mixture of stereoisomers **35** was subjected to the action of lithium in ammonia containing ethanol. The

(27) Mock, G. A.; Holmes, A. B.; Raphael, R. A. *Tetrahedron Lett.* **1977**, 4539.

(28) (a) Danishefsky, S.; Yan, C. F. *Synth. Commun.* **1978**, *8* (4), 211. (b) Danishefsky, S.; Yan, C. F.; McCurry, P. M. *J. Org. Chem.* **1977**, *42*, 1819.

(29) Schmidt, C.; Sabnis, S. D.; Schmidt, E.; Taylor, D. K. *Can. J. Chem.* **1971**, *49*, 371. Yamakawa, K.; Satah, T. *Chem. Pharm. Bull.* **1979**, *27*, 1747. Yamakawa, K.; Satah, T.; Ohba, N.; Sakaguchi, R. *Chem. Lett.* **1979**, 763.

(30) For two contrary precedents where the C_2 alkoxyl appers to predominate in its orienting power over the C_1-alkyl group see ref 27 and: Beyer, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 1397. However, these "contrary" precedents involve dienophiles which are electronically unbalanced and thus would be more likely to be more responsive to the greater donating power of the alkoxyl group.

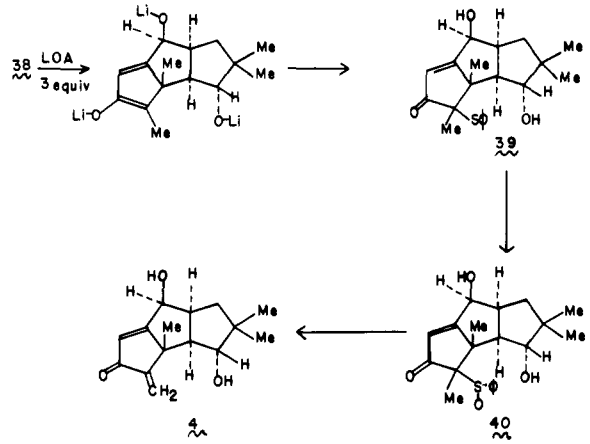
(31) (a) Reich, H. J.; Renga, J.; Reich, I. L. *J. Am. Chem. Soc.* **1973**, *95*, 5813. (b) Sharpless, K. B.; Lauer, R.; Teranishi, A. Y. *Ibid.* **1973**, *95*, 6137. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *Ibid.* **1975**, *97*, 5435.

(32) Stork, G.; Clarke, F. H., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 3114.

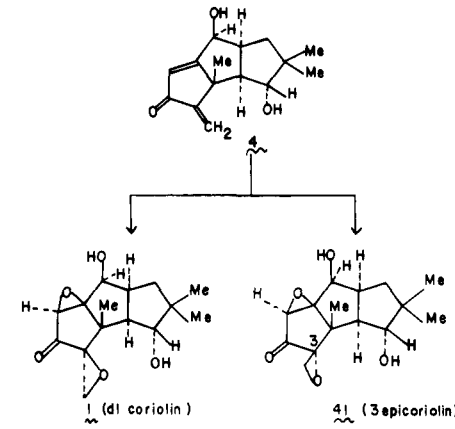
(33) Ringold, J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, 669.

(34) The numbering system in the Discussion is based on the IUC method and corresponds to that used in the Experimental Section.

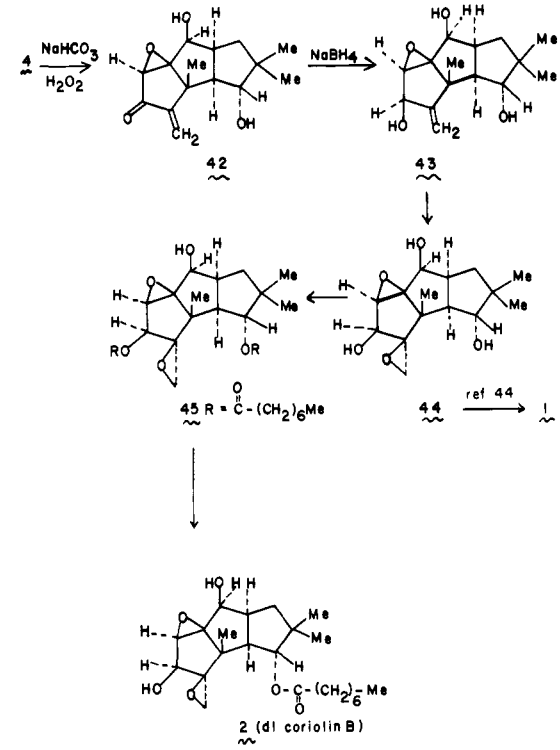
Scheme XII



Scheme XIII



Scheme XIV



resultant diol **36** suffered very rapid epoxidation with *m*-chloroperoxybenzoic acid, leading to **37**. The secondary alcohol of the A ring was selectively oxidized (pyridinium chlorochromate)[35] to afford **38**, which was now obtained as a two-component mixture of epimers. Again, the individual stereoisomers were readily obtained in pure form and fully characterized.

Though for preparative purposes it was most expedient to group the secondary methyl epimers till their point of convergence at the stage of compound **39** (vide infra), we did carry three of the individual components of **35** forward. In this way we could demonstrate that the reduction of any individual epimer of **35**, with lithium in ammonia, affords a single stereoisomeric diol **36** bearing an α hydroxyl at C_4. Thus, as expected, the metal–ammonia reduction of the C-ring ketone under these conditions is responsive to the thermodynamic stability of the product, leading to the convex-oriented alcohol.[37] Moreover, action of MCPBA on homogeneous **36**, affords, in each case a single (β) epoxide. This result was also expected, since only in this fashion would the A and B rings emerge in a cis fusion.

Although the bridgehead (see asterisk in **37**) chirality is destined to be eliminated in its conversion to **39**, the stereochemistry at this center is introduced to control the chirality of its neighboring center. In this sense, the stereochemical logic used in the sequence **6** → **30** → **32** and that used in the sequence **36** → **37** → **38** → **39** have a common rationale. They use the principle of product development control in defining the junction stereochemistry such that cis-fused bicyclo[3.3.0] rings are produced. A ring structure (i.e., an epoxide in the case of **37** or a cyclohexene in the case of **30**) is used to impart predictability to the adjacent center. This crucial chirality is preserved even when its connection to the junction chirality is severed.

The least efficient stage of the sequence was the oxidation of **37** to **38**, which could not be carried to completion without incurring unacceptable overoxidiation of the A-ring alcohol.

Treatment of **38** with 4 equiv of lithium diisopropylamide from −30 to 0 °C and quenching at 0 °C with excess phenyl (thiophenyl)sulfonate,[38] afforded the sulfide **39** as a single[39] product. Though this transformation was achieved in only a modest 40% yield, it accomplished a great deal. We also note that this remarkable process, which presumably involves the intermediacy of trianion **38***a*, allows (vide infra) for the provision for all the oxygens of coriolin *without recourse to any explicit protection–deprotection maneuvers*. While the technology of protecting groups is certainly fluorishing and their utility is widespread, the esthetic advantages of directness need hardly be emphasized.[40]

Treatment of **39** with *m*-chloroperoxybenozic acid afforded sulfoxide **40**, which upon thermolysis in ethyl acetate under reflux afforded the long-awaited dienone **4** in 64% yield from **39**. The critical introduction of the two epoxides could now be investigated.

(iv) Completion of the Total Syntheses. We first examined the direct bis epoxidation of **4** with alkaline hydrogen peroxide. Under all conditions we obtained a mixture of *dl*-coriolin (**1**) and *dl*-epicoriolin (**41**). These were separated by preparative high performance LC (LC). The chromatographic properties and infrared, NMR (60 MHz), and mass spectra of the *dl*-coriolin, mp 154–155 °C, were identical with those obtained from a specimen of the natural product, kindly furnished by Professor H. Umezawa. The more polar component, mp 204–205 °C, while similar to coriolin, was unmistakably different in its NMR and infrared spectral properties (see Experimental Section).

Surprisingly, Tatsuta[11] failed to note the formation of **41** from this reaction. In our hands, all attempts to achieve stereospecificity

(35) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(36) Cf.: Grieco, P. A.; Burke, S.; Metz, W.; Nishizawa, M. *J. Org. Chem.* **1979**, *44*, 152.
(37) $LiAlH_4$ reduction of ring-C alcohol afforded a 1:7 mixture of alcohols, with the undesired β epimer predominating.
(38) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.
(39) Although **40** appears to be a single compound, the stereochemistry at C_3 was left undetermined.
(40) We have investigated the opening of epoxy ketone **38** with LDA in some detail. We found that treatment of either epimer of epoxy ketone **38** with LDA at −78 °C, followed by quenching with AcOH at −78 °C, afforded a single enone. When we raised the temperature to ~40 °C, we obtained a mixture of enones. This clearly indicated that at temperatures >−40 °C, deprotonation occurs at C_3.

in the direct epoxidation of **4** were unmistakably unsuccessful. The "best" isolated ratio of **1**:**41** was 7:5.[41] With the total synthesis of **1** accomplished, the attainment of complete stereospecificity became our next objective.

In monitoring the progress of the reaction of **4** with alkaline hydrogen peroxide, we found that the endocyclic double bond is attacked first. When the reaction was carried out at 0 °C for 2 h in aqueous tetrahydrofuran, monoepoxide **42** was obtained in very high yield.[42] That the endocyclic double bond reacts first is fully consistent with previous trends which had emerged in our investigations of enedione **6**, wherein the principal chemical tendency seemed to be that of rehybridization of the sp^2 bridgehead carbon toward the sp^3 sense. That the β epoxide should be the sole product was, by now, also fully expected. The alternative α epoxide would result in an apparently energetically unacceptable trans fusion of the A and B rings. Reduction of **42** with sodium borohydride afforded **43**. This result follows a precedent laid down by Matsumoto[8] in his total synthesis of hirsutic acid.

We could now use the β-oriented allylic alcohol of **43** to "direct" the stereochemistry of the spiroepoxidation in the desired β sense. This was experimentally accomplished by the methodology developed by Sharpless.[43]

There was thus obtained crystalline *dl*-dihydrocoriolin (**44**), mp 183–185 °C, whose chromatographic mobility and infrared and NMR (270 MHz) spectra were identical with those of a sample prepared from authentic coriolin B using methodology described by Umezawa.[44] Since Umezawa had also described the selective oxidation of **44** to coriolin (**1**),[44] in a technical sense, a fully stereospecific solution to the synthesis of coriolin has thus been achieved.

Of greater interest to us was the actual total synthesis of *dl*-coriolin B, in a fully stereospecific manner. In investigating the behavior of **44** toward octanoylation, we found that the ring-A alcohol reacts more rapidly than the hydroxyl in the C ring, while the ring-B alcohol was not affected. Thus, reaction of **44** with octanoyl chloride, in the presence of 4-(dimethylamino)pyridine,[45] led to the acylation of the A- and C-ring hydroxyl groups, thereby affording **45**. Happily, reaction of **45** with potassium carbonate in methanol resulted in the selective deoctanoylation of the A-ring ester and the formation of crystalline *dl*-coriolin B (**2**) (56% yield from **44**, 36% from **4**). The chromatographic properties and infrared, NMR (270 MHz), and mass spectra of fully synthetic *dl*-coriolin B, mp 183–185 °C, were identical with those of an authentic sample, kindly provided by Professor H. Umezawa. The total synthesis of coriolin B in a manner which, to the best of our knowledge, is stereospecific in the construction of each of its nine chiral centers and regiospecific throughout all reactions is thus complete. Given the known oxidation of coriolin B (**2**) to diketocoriolin B (**3**), the synthesis of the latter is technically accomplished, though we have not repeated this reaction on our fully synthetic **2**.

Conclusions

The total synthesis of coriolin B is thus achieved in 24 steps[46] in 0.2% yield. Given the efficiency of the fermentation process, this synthesis cannot be represented as making a contribution to the availability of the target system. However, it is our expectation that several demonstrations of some importance have been achieved. First we note the new annelation reaction leading to **6**. Second, we note the use of Diels–Alder chemistry to achieve a consequence generally perceived to be in the domain of "carbanion" chemistry (cf. **6** → **32**). Finally, we would hope that some of the stereochemical principles which served us well here will find wider application in the total synthesis of other natural products. Research addressed to the implementation of such strategies is a continuing activity of our laboratory.

Experimental Section[47]

Methyl 4,4-Dimethoxy-3-oxopentanoate (9). The monoketal 3,3-dimethoxybutan-2-one[17] (23 g, 174 mmol) was added dropwise over 3 h to a refluxing suspension of NaH (9.5 g, 445 mmol) in benzene (600 mL) and dimethyl carbonate (35 g, 389 mmol). After 2 h of stirring at reflux, the green suspension was cooled in an ice bath and carefully quenched with a solution of acetic acid (25 mL) in ether (500 mL). The reaction mixture was washed with water (500 mL), dried (Na_2SO_4), and evaporated in vacuo. Vacuum distillation of the residue afforded 21 g (63%) of ester **9**: bp 69–73 °C (0.35 mm); ν_{max} (film) 3050, 1770, 1750, 1690, 1052 cm^{-1}; δ ($CDCl_3$) 1.35 (s), 1.45 (s), 3.10 (s), 3.15 (s), 3.20 (s), 3.60 (s), 3.70 (s), 3.75 (s), 5.8 (s).

Preparation of the Michael Adduct 10. To a solution of 5,5-dimethyl-2-cyclopenten-1-one (**7**) (6.7 g, 62 mmol) and methyl 4,4-dimethoxy-3-oxopentanoate (**9**) (13 g, 69 mmol) in 60 mL of methanol at 0 °C was added a solution of sodium methoxide (22 mmol) in methanol (20 mL). The yellow solution was allowed to warm to room temperature and stirred for 3 days. The contents were poured into a mixture of water (1 L), acetic acid (10 mL), and ether (600 mL). The aqueous phase was reextracted with ether (2 × 600 mL). The combined ether layers were washed with saturated NaCl solution (100 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue on 300 g of SiO_2 first with 2 L of 9% ethyl acetate in hexane, followed by 2 L of 16% ethyl acetate in hexane, afforded 15.5 g (85%) of Michael adduct **10** as a mixture of epimers: ν_{max} (film) 3600, 3450, 2950, 1740–1750 cm^{-1}; δ ($CDCl_3$) 1.05 (s), 1.1 (s), 1.15 (s), 1.35 (s), 1.4–3.0 (m), 3.20 (s), 3.25 (s), 3.7 (s), 3.85 (s), 7.2 (br s).

1,5,6a,6b-Tetrahydro-3,5,5-trimethylpentalene-2,4-dione (6). A solution of the Michael adduct **10** (20 g, 67 mmol), TsOH (5 g, 26 mmol), and H_2O (6 mL, 333 mM) in toluene (4 L) was refluxed for 18 h. After being cooled to room temperature, the solution was washed with 5% $NaHCO_3$ (2 × 300 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue on 300 g of SiO_2, using 15% ethyl acetate in hexane as eluent, afforded 6 g (51%) of enedione **6**: mp 54–55 °C; ν_{max} ($CHCl_3$) 3025, 2964, 2866, 1705, 1650 cm^{-1}; δ ($CDCl_3$) 1.10 (s, 3), 1.15 (s, 3), 1.4 (t, J = 10 Hz, 1), 1.95 (d, J = 6 Hz, 3), 2–2.6 (m, 2), 2.8 (dd, J_1 = 6 Hz, J_2 = 17 Hz, 1), 3.2 (m, 1); m/e 178 (M^+).

(3aα,5a*S*,6ϵ,9a*S)-3,3a-Dihydro-2,2,5a,6a-tetramethylcyclopenta[3,3a]-2*H*-indene-1,5,7-trione (30).** A solution of enedione **6** (6.3 g, 35 mmol) and diene **27** (18 g, 137 mmol) in 80 mL of xylene under N_2 was heated at 120 °C for 12 h. Xylene and excess diene were removed by using a rotary evaporator at 50 °C. The residue was further evaporated under high vacuum at 40 °C until ^1H NMR analysis indicated that all the excess diene had been removed. The residue was dissolved in ether (250 mL) and cooled to −78 °C. A solution of PhSeCl (8 g) in ether (200 mL) was added dropwise over 30 min until the orange-red color persisted (~160 mL). The reaction mixture was stirred for 15 min at −78 °C and then quenched with saturated $NaHCO_3$ (200 mL). After the reaction mixture was allowed to warm to room temperature, the ether layer was washed with $NaHCO_3$ (2 × 100 mL), dried, and evaporated in vacuo. The yellow solid residue was dissolved in CH_2Cl_2 (200 mL) and pyridine (8 mL). To this solution was added carefully H_2O_2 (80 mL of 15% aqueous solution) over 30 min. The delayed exothermic reaction was moderated with a cold H_2O bath. After 2 h of stirring at room temperature, the reaction mixture was poured onto a mixture of saturated Na_2CO_3 (200 mL) and ether (500 mL). The ether layer was washed with Na_2CO_3 (2 × 100 mL), dried (Na_2SO_4), and evaporated in vacuo to afford 7.2 g of crude enone. Trituration with 17% ethyl acetate in hexane (2 × 10 mL) afforded 5.2 g (57%) of enone **30**: mp 168–169 °C; ν_{max} ($CHCl_3$) 3019, 2962, 2874, 1736, 1690 cm^{-1}; δ ($CDCl_3$, 270 MHz) 1.20 (s, 6), 1.23 (s, 3), 1.35 (d, J = 7 Hz, 3), 1.80 (dd, J_{AB} = 13 Hz, J_{BX} = 11 Hz, 1), 2.40 (dd, J_{AB} = 13 Hz, J_{AX} = 5.5 Hz, 1), 2.54 (m, 2), 2.8 (m, 1), 2.86 (q, J = 7 Hz, 1), 6.08 (d, J_{CD} = 10 Hz, 1), 6.33 (d, J_{CD} = 10 Hz, 1); m/e 260.1414 (calcd for $C_{16}H_{20}O_3$, m/e 260.1412 (parent)).

Formation of 31. To 2.6 g (10 mmol) of enone **30** in THF (250 mL) at −78 °C was added dropwise over 30 min a solution of methyllithium (20 mL of 1.4 M (28 mmols) in ether (20 mL). The orange solution was

(41) Tatsuta also described the double epoxidation of dienone **4**. However, he makes no mention of the formation of spiroepoxide epimer **41**. In our hands, this epoxidation was unmistakably and uniformly nonspecific under all conditions, including those descirbed by Tatsuta et al.[12]

(42) Crude monoepoxide was essentially pure by ^1H NMR.

(43) Yamamoto, H.; Nazaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254.

(44) Takeuchi, T.; Ishizuka, M.; Umezawa, H.; Nishimura, Y.; Koyama, Y.; Umezawa, S. *J. Antibiot.* **1980**, *33*, 404.

(45) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.

(46) Though the synthesis involves 24 chemical steps, purification was only necessary at 12 stages.

(47) Melting points were uncorrected. Infrared spectra were measured with Perkin-Elmer 137, Perkin-Elmer 247, and Nicolet Series 7000 FT-IR spectrometers. Low-resolution mass spectra were measured on an LKB-9000 system or on a Hewlett-Packard 5985 GC/MS system. High-resolution measurements were obtained from an AEI MS30 system. Unless otherwise indicated, NMR spectra were measured at 90 MHz in $CDCl_3$ solution with tetramethylsilane as internal standard.

allowed to stir for 1 h at −78 °C and then quenched with saturated NH_4Cl (50 mL). The reaction mixture was extracted with ether (2 × 500 mL), dried (Na_2SO_4), and evaporated in vacuo to afford 2.6 g of crude adduct. Trituration with 3:1 ether/hexane (10 mL) afforded 2.0 g (73%) of adduct **31** as a mixture of epimers: ν_{max} ($CHCl_3$) 3597, 3499, 3011, 2968, 1728, 1087 cm^{-1}; δ ($CDCl_3$) 1.1 (s), 1.2 (s), 1.25 (d, J = 8 Hz), 1.30 (s), 1.35 (s), 1.5–3.0 (m), 5.4 (d, J = 10 Hz), 5.9 (d, J = 10 Hz), 6.15 (d, J = 10 Hz); m/e 276 (M^+).

(3*R,3aα,6aα)-1,5a,6,6a-Tetrahydro-2-(1-methylacetonyl)-3,5,5-trimethylpentalene-2,4-dione (32).** Ozone was bubbled into a solution of alcohol **31** (1.8 g, 6.6 mmol) in acetone at −78 °C for 15 min. The solution turned a deep blue. After excess ozone was purged with a stream of nitrogen (15 min), Jones reagent (55 mL of 1.23 M) was added dropwise over 10 min. The resulting orange solution was stirred at −78 °C (30 min). After the solution was allowed to warm up −5 °C, H_2O (200 mL) and ethyl acetate (200 mL) were added. Solid $NaHSO_3$ was added until the layers separated and the organic layer became clear and colorless. The organic volatiles were removed on a rotary evaporator and the resulting dark green aqueous solution was extracted with ethyl acetate (3 × 300 mL). The combined organic phases were washed with saturated NaCl, dried, and evaporated to afford 2.35 g of crude diacid. The diacid, in water (100 mL), and $Ba(OH)_2$ (4 g, 12.7 mmol) were refluxed for 4 h under N_2. After the light brown suspension was cooled in and ice–water bath, concentrated HCl (4 mL) was added dropwise. The mixture was extracted with ethyl acetate (3 × 200 mL). The combined ethyl acetate layers were washed with saturated NaCl, dried (Na_2SO_4), and evaporated to give 1.75 g (91%) of residue. This solution of the hydroxy acid (1.75 g) was dissolved in benzene (200 mL) and treated with $Pb(OAc)_4$ (4 g, 9 mmol) at room temperature for 16 h. Benzene was removed in vacuo and the residue was treated with ether (100 mL) and H_2O (5 mL). The brown mixture was filtered through Celite. The clear yellow filtrate was washed with saturated $NaHCO_3$ (2 × 100 mL) and saturated NaCl (50 mL), dried (Na_2SO_4), and evaporated to give 1.45 g of crude methyl ketone **32**. Flash chromatography, using 14% ethyl acetate in hexane as eluent, afforded 0.75 g (46%) of methyl ketone **32**: mp 65–66.5 °C; ν_{max} ($CHCl_3$) 3019, 2964, 2868, 1728, 1706, 1462 cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.95 (s, 3), 1.05 (s, 6), 1.32 (d, J = 7.3 Hz, 3), 1.47 (t, J = 12 Hz, 1), 2.15 (m, 1), 2.18 (s, 3), 2.27 (d, J = 7 Hz, 1), 2.8 (d, J = 10 Hz, 1), 2.9–3.1 (m, 3); m/e 250.1411 (calcd for $C_{15}H_{22}O_3$, m/e 250. 1569 (parent)).

(3aβ,3bα,6aα)-3a,3b,5,6,6a,7-Hexahydro-3,3a,5,5-tetramethylcyclopenta[4,5]pentalene-2,4-dione (33). To methyl ketone **32** (1.65 g, 6.6 mmol) in dry *tert*-butyl alcohol (25 mL) was added potassium *tert*-butoxide (130 mg, 1.2 mmol). The suspension was stirred for 45 min at room temperature. The clear orange solution was partitioned between ethyl ether (100 mL) and water (100 mL). The ether layer was washed with water (3 × 50 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was dissolved in a solution of benzene and *p*-toluenesulfonic acid (10 mg), refluxed for 45 min, washed with saturated $NaHCO_3$, dried, and evaporated. Flash chromatography of the residue, using 25% ethyl acetate in hexane as eluent, afforded 1.09 g (71%) of enone **33** as a 2:1 mixture of epimers: m/e 232.1461 (calcd for $C_{15}H_{20}O_2$, m/e 232.1464 (parent)). These two epimers were separated by LC on a Waters μ-Porasil column, using 20% ethyl acetate in hexane as eluent. Minor epimer: mp 73–75 °C; ν_{max} ($CHCl_3$) 3027, 2965, 2869, 1732, 1697, 1636 cm^{-1}; δ ($CDCl_3$, 270 MHz) 1.09 (s, 3), 1.1 (s, 6), 1.17 (d, J = 7.7 Hz, 1), 1.74 (dd, J_{BX} = 10 Hz, J_{AB} = 14 Hz, 1), 2.30 (q, J = 7.7 Hz, 1), 2.40 (q, J_{AB} = 14 Hz, J_{AX} = 7 Hz, 1), 2.56 (m, 1), 2.9 (d, J = 12 Hz, 1), 3.0–3.16 (m, 2), 5.7 (d, J = 1.8 Hz, 1); m/e 232 (M^+). Major epimer: mp 93–95 °C; ν_{max} 3026, 2964, 2872, 1733, 1702, 1637 cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.9 (s, 3), 1.09 (s, 3), 1.10 (s, 3), 1.18 (d, J = 7.5 Hz, 3), 1.69 (dd, J_{AB} = 14 Hz, J_{BX} = 10 Hz, 1), 2.38 (q, J = 7.5 Hz, 1), 2.38 (dd, J_{AB} = 14 Hz, J_{AX} = 10 Hz, 1), 2.58 (br d, 1), 2.75 (d, J = 11 Hz, 1), 3.0–3.3 (m, 2), 5.81 (d, J = 1.8 Hz, 1); m/e 232 (M^+).

(3aβ,3bα,6aα)-3,3a,3b,5,6,6a-Hexahydro-3,3a,5,5-tetramethylcyclopenta[4,5]pentalene-2,4-dione (34). To a solution of enone **33** (366 mg, 1.6 mmol) was added potassium *tert*-butoxide (2 g, 19 mmol). The suspension was stirred for 80 min. After the mixture was quenched with a solution of acetic acid (5 mL) in H_2O (5 mL), it was partitioned between ether (200 mL) and saturated $NaHCO_3$ (150 mL). The aqueous phase was reextracted with ether (2 × 100 mL). The combined ether layers were washed with saturated NaCl solution, dried, and evaporated. The residue was flash chromatographed on 20 g of SiO_2. Elution with 12% ethyl acetate in hexane afforded 230 mg (63%) of deconjugated enone **34** as a 2:1 mixture of epimers: m/e 232.1477 (calcd for $C_{15}H_{20}O_2$, m/e 232.1464 (parent)). The epimers were separated by LC on a Waters μ-Porasil column, using 9% ethyl acetate in hexane as eluent. Major epimer: mp 113–114 °C; ν_{max} 3028, 2963, 2934, 1741, 1676, 1462 cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.96 (d, J = 8 Hz, 3), 1.02 (s, 3), 1.09 (s, 6), 1.62 (t, J = 13 Hz, 1), 2.16 (dd, J_1 = 13 Hz, J_2 = 8 Hz, 1), 2.27 (q, J = 8 Hz, 1), 2.86 (m, 2), 3.16 (d, J = 10 Hz, 1), 3.48 (br q, 1), 5.64 (m, 1); m/e 232 (M^+). Minor epimer: mp 104–105 °C; ν_{max} 3030, 2960, 2934, 1738, 1733, 1673, 1461 cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.85 (s, 3), 1.09 (s, 6), 1.10 (d, J = 8 Hz, 3), 1.65 (t, J = 12 Hz, 1), 2.17 (m, 2), 2.86 (m, 2), 3.09 (d, J = 10 Hz, 1), 3.53 (br q, 1), 5.6 (m, 1); m/e 232 (M^+).

(4aβ,4bα,5α,7aα,7bα)-4,4a,4b,5,6,7,7a,7b-Octahydro-4,4a,6,6-tetramethyl-5-hydroxycyclopenta[4,5]pentaleno[6,6a-*b*]oxiren-3-one (38). DibaH (4.6 mL, 7.0 mmol) was added dropwise over 2 h to a solution of diketone **34** (420 mg, 1.7 mmol) in tetrahydrofuran (40 mL) at −78 °C. The solution was stirred for 15 more min and quenched at −78 °C with H_2O. The reaction mixture was then partitioned between 1:1 saturated NaCl/2% HCl and ethyl acetate (300 mL). The aqueous phase was further extracted with ethyl acetate (2 × 150 mL). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo to give crude keto alcohol **35** as a mixture of three epimers in approximately a 15:50:10 ratio: ν_{max} ($CHCl_3$) 3550, 3300, 1730 cm^{-1}; m/e 234 (M^+). To the crude keto alcohol in a solution of liquid ammonia (30 mL), MeOH (2.5 mL), and THF (6 mL) was added 3 cm of lithium wire (3-mm diameter). The white suspension was stirred for 10 min and then quenched with solid NH_4Cl. After the ammonia had evaporated, the residue was partitioned between ethyl acetate (100 mL) and saturated NH_4Cl, dried (Na_2SO_4), and evaporated to give 420 mg of crude diol **36**: ν_{max} ($CHCl_3$) 3600, 3450, 2960, 2930, 1234, 1048, 1026 cm^{-1}; m/e 236 (M^+). To a solution of the diol (420 mg, 1.7 mmol) in CH_2Cl_2 (15 mL) was added MCPBA (550 mg, 2.7 mmol). After stirring 1 h at room temperature, the solution was partitioned between CH_2Cl_2 (100 mL) and saturated Na_2CO_3 solution (100 mL). The organic phase was washed with saturated Na_2CO_3 solution (2 × 100 mL), dried (Na_2SO_4), and evaporated to give 460 mg of crude epoxy diol **37** as a colorless foam: ν_{max} ($CHCl_3$) 3690, 3680, 3457, 2959, 2932, 1045 cm^{-1}; m/e 252 (M^+).

To a solution of the crude **37** (460 mg) in CH_2Cl_2 (20 mL) was added NaOAc (360 mg, 4.4 mmol) and PCC (360 mg, 1.7 mmol). After 2 h of stirring at room temperature, an additional 60 mg of PCC[35] and NaOAc were added. After ~1 h, the reaction was quenched by the addition of ether (100 mL). The reaction mixture was filtered through a silica gel plug and evporated in vacuo. The residue was flash chromatographed on 30 g of SiO_2. Elution with 40% ethyl acetate in hexane afforded compound **38**, 170 mg (38%). Elution with 60% ethyl acetate in hexane afforded 190 mg of recovered **37**. Retreatment of **37** with PCC[35] (150 mg) and NaOAc (150 mg) in the same way afforded 60 mg of **38** and 70 mg of **37**. Oxidation of the recovered **37** afforded a further 20 mg of **38**. This gave a combined yield of 250 mg (55%) of epoxy ketone **38** as a 2:1 mixture of epimers: m/e 250.1590 (calcd for $C_{15}H_{22}O_3$, m/e 250.1569 (parent)). These epimers could be separated by LC on a Waters μ-Porasil column, using 30% ethyl acetate in hexane as eluent. Major epimer: ν_{max} ($CHCl_3$) 3605, 3400, 2962, 1743, 1460 cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.89 (s, 3), 1.04 (s, 3), 1.07 (d, J = 8 Hz, 3), 1.26 (s, 3), 1.67 (m, 2), 2.3 (q, J = 8 Hz, 1), 2.43 (t, J = 10 Hz, 1), 2.45 (d, J = 15 Hz, 1), 2.64 (m, 1), 2.75 (dd, J_1 = 1.5 Hz, J_2 = 15 Hz, 1), 3.40 (d, J = 1.5 Hz, 1), 3.61 (dd, J_1 = 5 Hz, J_2 = 10 Hz, 1); m/e 232 (M^+ − 18). Minor epimer: mp 146–148 °C; ν_{max} ($CHCl_3$) 3611, 3444, 3023, 2961, 2934, 1743 cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.88 (s, 3), 1.04 (s, 3), 1.07 (d, J = 7 Hz, 3), 1.07 (s, 3), 1.66 (m, 2), 2.17 (q, J = 7 Hz, 1), 2.30 (t, J = 10 Hz, 1), 2.42 (d, J_{AB} = 20 Hz, 1), 2.65 (d, J_{AB} = 20 Hz, 1), 2.77 (m, 1), 3.38 (d, J = 2 Hz, 1), 3.55 (q, J_1 = 10 Hz, J_2 = 6 Hz, 1); m/e 232 (M^+ − 18).

(3ε,3aβ,3ba,4α,6aα,7β)-3a,3b,5,6,6a,7-Hexahydro-3a,5,5-trimethyl-4,7-dihydroxy-3-(phenylthio)-4*H*-cyclopenta[4,5]pentalen-2-one (39). To a solution of *n*-butyllithium (0.91 mL, 1.5 mmol) in tetrahydrofuran (6 mL) at 0 °C was added diisopropylamine (210 μL, 1.5 mmol). The solution was stirred for 10 min at 0 °C. After the mixture was cooled to −35 °C, a solution of **38** (92 mg, 137 mmol) in 3 mL of tetrahydrofuran was added dropwise over 10 min. The yellow cloudy solution was stirred for 30 min at −35° and then for 15 min at 0 °C. Phenyl (thiophenyl)sulfonate (370 mg, 1.5 mmol) in tetrahydrofuran (1 mL) was then added in one batch. The reaction mixture was stirred at 0 °C for 40 min and then for 5 min at room temperature. The resulting green solution was quenched with saturated $NaHCO_3$ (5 mL), partitioned between $NaHCO_3$ (saturated) and ethyl acetate, dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography of the residue on 10 g of SiO_2, using 35% ethyl acetate in hexane as eluent, afforded 52 mg (40%) of sulfide **39**: ν_{max} ($CHCl_3$) 3602, 3419, 1703, 1645, 1076, 1068 cm^{-1}; δ ($CDCl_3$) 1.1 (s, 3), 1.17 (s, 3), 1.32 (s, 3), 1.4 (s, 3), 1.6 (m, 1), 1.8 (m, 2), 2.7 (m, 1), 3.15 (dd, J_1 = 10 Hz, J_2 = 12 Hz, 1), 3.8 (m, 1), 4.6 (br d, J = 6 Hz, 1), 6.0 (s, 1), 7.45 (br s, 5); m/e 360 (M^+ + 2), 358 (M^+).

(3aβ,3bα,4α,6aα,7β)-3a,3b,5,6,6a,7-Hexahydro-3a,5,5-trimethyl-4,7-dihydroxy-3-methylene-4*H*-cyclopenta[4,5]pentalen-2-one (4). To sulfide **39** (52 mg, 15 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added a solution

of *m*-chloroperoxybenzoic acid (64 mg in 2 mL of CH_2Cl_2). The solution was stirred for 1 h at −78 °C and then quenched with saturated Na_2CO_3 (10 mL). The reaction mixture was extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with saturated Na_2CO_3 (3 × 50 mL), dried (Na_2SO_4), and evaporated in vacuo to afford 52 mg of crude **40**. The sulfoxide was heated for 20 min in refluxing ethyl acetate (10 mL) and then evaporated in vacuo. Flash chromatography of the residue, using 35% ethyl acetate in hexane, afforded 23 mg (64%) of α-methylene enone **4**: ν_{max} ($CHCl_3$) 3600, 3400, 2950, 1690, 1650, 1610, 1045 cm^{-1}; δ ($CDCl_3$) 0.91 (s, 3), 1.14 (s, 3), 1.5 (s, 3), 1.5–1.9 (m, 4), 2.2 (dd, J_1 = 9 Hz, J_2 = 12 Hz, 1), 2.6 (m, 1), 3.9 (d, J = 9 Hz, 1), 4.7 (d, J = 6 Hz, 1), 5.4 (s, 1), 5.95 (s, 1), 6.1 (s, 1); *m/e* 248.1428 (calcd for $C_{15}H_{20}O_3$, *m/e* 248.1412 (parent)).

(1aα,3aβ,3bα,4aα,6aα,7β,7aS)-3,3a,3b,4,5,6a,7,7a-Octahydro-3a,5,5-trimethyl-4,7-dihydroxy-3-methylenecyclopenta[4,5]pentaleno-[1,6a-*b*]oxiren-2(1a*H*)-one (42). To compound **4** (19 mg, 0.07 mmol) in tetrahydrofuran (3 mL) at 0 °C was added a solution of $NaHCO_3$ (100 mg, 1.2 mmol) and 30% H_2O_2 (60 μL, 15 mmol). The suspension was stirred for 2 h at 0 °C. The reaction mixture was then partitioned between ethyl acetate (20 mL) and saturated NH_4Cl, dried (Na_2SO_4), and evaporated to afford 20 mg (100%) of essentially pure monoepoxide **42**: ν_{max} 3607, 3438, 2950, 1723, 1632, cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.91 (s, 3), 1.11 (s, 3), 1.35 (d, J = 6.5 Hz, 1), 1.50 (m, 4), 1.86 (dd, J_1 = 10 Hz, J_2 = 13 Hz, 1), 2.0 (d, J = 2 Hz, 1), 2.26 (dd, J_1 = 9 Hz, J_2 = 12 Hz, 1), 2.74 (m, 1), 3.54 (s, 1), 3.90 (dd, J_1 = 9 Hz, J_2 = 6.5 Hz, 1), 3.98 (dd, J_1 = 2 Hz, J_2 = 6 Hz, 1), 5.51 (s, 1), 6.16 (s, 1); *m/e* 264 (M^+).

(1aα,3*R,3aβ,3bα,4α,6aα,7β,7a*S**)-3,4,5,6a,6,7-Hexahydro-3a,5,5-trimethyl-4,7-dihydroxyspiro[cyclopenta[4,5]pentaleno[1,6a-*b*]oxiren-3-(3a*H*),2′-oxiran]-2(1a*H*)-one (1) and (1aα,3*S**,3aβ,3bα,4α,6aα,7β,-7a*S**)-3,4,5,6,6a,7-Hexahydro-3a,5,5-trimethyl-4,7-dihydroxyspiro[cyclopenta[4,5]pentaleno[1,6a-*b*]oxiren-3-(3a*H*),2′-oxiran]-2(1a*H*)-one (41).**[49] To compound **4** (17 mg, 0.07 mmol) in THF (2 mL) at 0 °C were added $NaHCO_3$ (100 mg) in H_2O (2 mL) and 30% H_2O_2 (60 μL). The reaction mixture was allowed to warm to room temperature and stirred for 7 h. After the mixture was quenched with saturated NH_4Cl (5 mL), it was partitioned between saturated NH_4Cl (15 mL) and ethyl acetate (50 mL). The aqueous phase was reextracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate layers were dried and evaporated in vacuo. LC of the residue on a Waters μ-Porasil column, using 30% ethyl acetate in hexane as eluent, afforded 5 mg (26%) of coriolin (**1**) and impure epicoriolin (5 mg). Resubmission of the impure epicoriolin to LC afforded 4 mg (21%) of epicoriolin **41** and 0.5 mg (2.6%) of coriolin. Coriolin:[50] mp 155–156 °C (ether–hexane); ν_{max} ($CHCl_3$) 3600, 3400, 2950, 1744, 1080 cm^{-1}; δ ($CDCl_3$, 600 MHz) 0.93 (s, 3), 1.09 (s, 3), 1.23 (s, 3), 1.40 (d, J = 5.6 Hz, 1), 1.50 (dd, J_1 = 9 Hz, J_2 = 13 Hz, 1), 1.86 (dd, J_1 = 10 Hz, J_2 = 13 Hz, 1), 1.99 (br s, 1), 2.33 (dd, J_1 = 9 Hz, J_2 = 12 Hz, 1), 2.81 (m, 1), 3.0 (d, J = 6.9 Hz, 1), 3.14 (d, J = 6.9 Hz, 1), 3.58 (s, 1), 3.77 (dd, J_1 = 4.5 Hz, J_2 = 9 Hz, 1), 4.06 (d, J = 6 Hz, 1); *m/e* 280 (M^+). Epicoriolin: mp 204–205 °C (ether, ethyl acetate); ν_{max} ($CHCl_3$) 3691, 3600, 3026, 2997, 2955, 1755 cm^{-1}; δ ($CDCl_3$, 270 MHz) 0.94 (s, 3), 1.11 (s, 3), 1.39 (s, 3), 1.49 (dd, J_1 = 9 Hz, J_2 = 13 Hz, 1), 1.81 (t, J = 10 Hz, 1), 2.03 (br s, 1), 2.44 (dd, J_1 = 9 Hz, J_2 = 12 Hz, 1), 2.83 (m, 1), 2.98 (q, J_{AB} = 6 Hz, 2), 3.52 (s, 1), 3.67 (d, J = 9 Hz, 1), 4.06 (d, J = 6 Hz, 1); *m/e* 280 (M^+).

(1aα,2β,3aβ,3bα,4α,6aα,7β,7a*S)-1a,2,3,3a,3b,4,5,6,6a,7-Decahydro-3a,5,5-trimethyl-2,4,7-trihydroxy-3-methylenecyclopenta[4,5]pentaleno[1,6a-*b*]oxirene (43).** To a solution of monoepoxide **42** (20 mg, 0.08 mmol) in ethanol (2 mL) at 0 °C was added $NaBH_4$ (262 μL, 1% solution in EtOH). The solution was stirred 15 min at 0 °C. After being quenched with saturated NH_4Cl (5 mL), the solution was partitioned between water (20 mL) and ethyl acetate (50 mL), dried (Na_2SO_4), and evaporated in vacuo to afford compound **43** (20 mg): ν_{max} 3700, 3660, 3450, 2950, 1602, 1082 cm^{-1}; δ ($CDCl_3$, CD_3COCD_3) 0.93 (s, 3), 1.15 (s, 3), 1.40 (m, 4), 1.85 (dd, J_1 = 10 Hz, J_2 = 13 Hz, 1), 2.2 (m, 1), 2.7 (m, 1), 3.5 (d, J = 1.5 Hz, 1), 3.8 (d, J = 9 Hz, 1), 3.9 (d, J = 6 Hz, 1), 4.6 (m, 1), 5.15 (d, J = 2 Hz, 1), 5.25 (d, J = 2 Hz, 1).

(1aα,2β,3aβ,3*R,3bα,4α,6aα,7β,7a*S**)-1a,2,3,4,5,6a,6,7-Octahydro-3,a,5,5-trimethyl-2,4,7-trihydroxyspiro[cyclopenta[4,5]pentaleno[1,6a-*b*]-oxiren-3(3a*H*),2′-oxirane] (44).** To a refluxing solution of crude **43** (20 mg, 0.08 mmol) in benzene (5 mL) was added V(acac)$_2$ (1 mg) and *tert*-butyl hydroperoxide (30 μL, 0.21 mmol).[43] The reaction mixture was refluxed for 20 min and cooled to room temperature. The solution was concentrated to 0.5 mL and acetone (0.5 mL) was added to dissolve the precipitated solid. Flash chromatography, using 25% benzene in acetone as eluent, afforded 14 mg (65%) of triol **44**:[51] mp 183–185 °C; ν_{max} (film) 3414, 2951, 1106, 1084 cm^{-1}; δ ($CDCl_3$, CD_3COCD_3, drop of D_2O, 270 MHz) 0.90 (s, 3), 1.01 (s, 6), 1.43 (dd, J_1 = 9 Hz, J_2 = 13 Hz, 1), 1.77 (dd, J_1 = 13 Hz, J_2 = 11 Hz, 1), 2.34 (dd, J_1 = 9 Hz, J_2 = 12 Hz, 1), 2.56 (d, J_{AB} = 5 Hz, 1), 2.75 (m, 1), 2.75 (d, J_{AB} = 5 Hz, 1), 3.43 (d, J = 2 Hz, 1), 3.68 (d, J = 9 Hz, 1), 3.88 (d, J = 6 Hz, 1), 4.40 (d, J = 2 Hz, 1); *m/e* 249 (M^+ − 33).

(1aα,2β,3aβ,3*R,3bα,4α,6aα,7β,7a*S**)-1a,2,3,4,5,6a,6,7-Octahydro-3a,5,5-trimethyl-2,7-dihydroxy-3-spiro[cyclopenta[4,5]pentaleno[1,6a-*b*]-oxiren-3(3a*H*),2′-oxiran-4-yl] Octanoate[52] (2).** To triol **44** (7 mg, 0.037 mmol) in THF (200 μL) and methylene chloride (100 μL) were added pyridine (30 μL, 137 mmol), DMAP (2 mg), and octanoyl chloride (30 μL, 122 mmol). The resulting suspension was stirred for 2 h at room temperature. The reaction mixture was partitioned between methylene chloride and water, dried, and evaporated in vacuo. The residue[45] was dissolved in mehtanol (2 mL), and K_2CO_3 (~1 g) was added. After 45 min of stirring at room temperature, the suspension was partitioned between saturated NH_4Cl and CH_2Cl_2. The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated in vacuo. Flash chromatography of the residue, using 20% benzene in acetone as eluent, afforded 6 mg (59%) of synthetic coriolin B[53] (**2**): mp 183–185 °C; ν_{max} 3700, 3596, 3519, 2962, 1730, 1100, 1050 cm^{-1}; δ ($CDCl_3$, D_2O) 0.90 (br t, 3), 0.98 (s, 3), 1.04 (s, 3), 1.08 (s, 3), 1.3 (br m, 8), 1.48 (dd, J_1 = 8 Hz, J_2 = 13 Hz, 1), 1.6 (br m, 2), 1.94 (t, J = 12 Hz, 1), 2.30 (m, 2), 2.43 (dd, J_1 = 8 Hz, J_2 = 12 Hz, 1), 2.47 (d, J_{AB} = 5 Hz, 1), 2.58 (d, J_{AB} = 5 Hz, 1), 2.91 (m, 1), 3.55 (d, J = 2 Hz, 1), 3.99 (d, J = 6 Hz, 1), 4.39 (d, J = 2 Hz, 1), 5.13 (d, J = 8 Hz, 1); *m/e* 408 (M^+).

Acknowledgment. This research was supported by PHS Grants CA12107-15 and CA12107-16 and by a grant from Merck Co. A National Research Council (Canada) Fellowship to Robert Zamboni, and a Centers of Excellence Fellowship from the University of Pittsburgh to Michael Kahn are also gratefully acknowledged. NMR measurements at 600 MHz were obtained on facilities housed at the Mellon Institute and supported by Grant RR-00292-14 for the Mellon, Pitt, Carnegie (MPC) Corp. The measurements at 270 MHz were obtained from the Northeast Regional NSF/NMR Facility at Yale University supported by NSF Chemistry Division Grant CHE7916210. We also thank Professors H. Umezawa and T. Takita of the Institute of Microbial Chemistry (Tokyo) for samples of coriolin and coriolin B and for providing us with an experimental procedure for the preparation of dihydrocoriolin (**44**) prior to its publication.[44]

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(49) This experiment was carried out four times with identical results.
(50) The infrared, mass, and ^{1}H NMR spectra were identical with those of an authentic sample of coriolin.
(51) The infrared, mass, and ^{1}H NMR spectra were identical with those of an authentic sample of dihydrocoriolin.
(52) This experiment was repeated four times with essentially identical results.
(53) The infrared, mass, and ^{1}H NMR spectra were identical with those of an authentic sample of coriolin B.