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STEREOSPECIFIC SYNTHESES OF CORIOLIN, CORIOLIN B AND DIKETOCORIOLIN B

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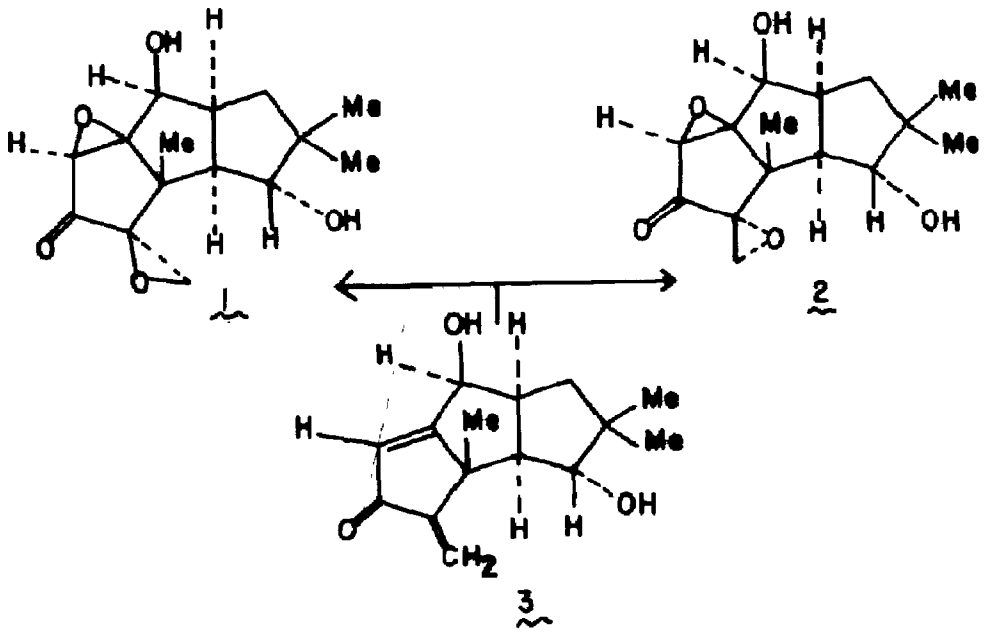
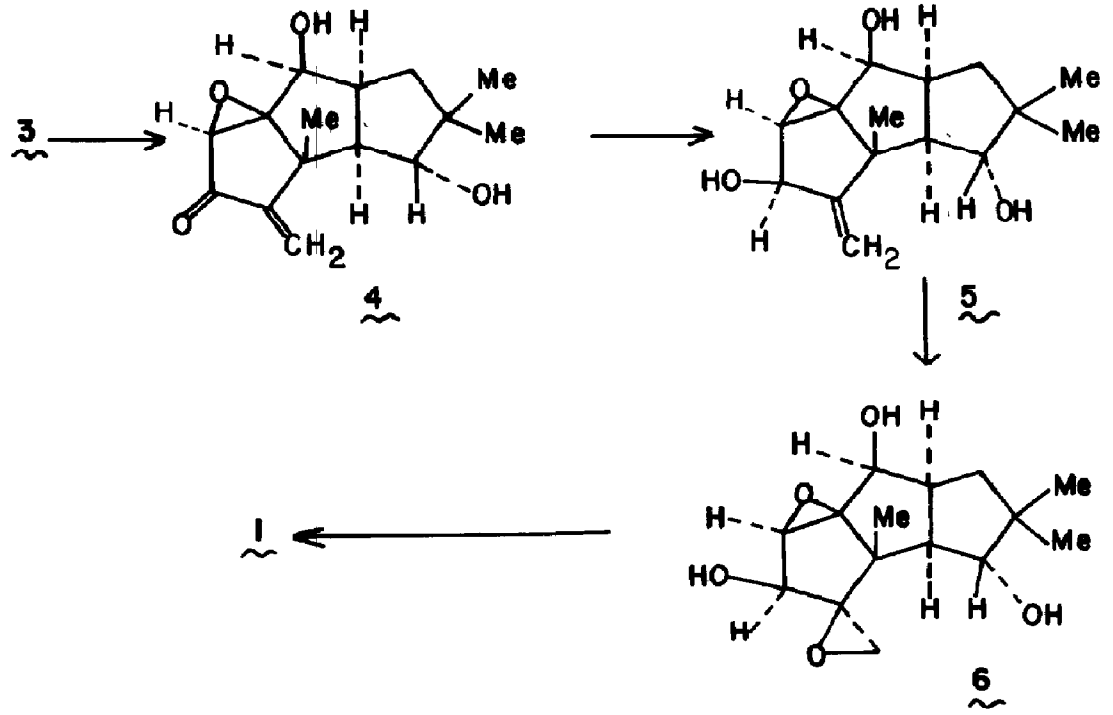
Summary: Routes to the title compounds via a fully stereospecific total synthesis of dihydrocoriolin are reported.

Recently [1] we described the total synthesis of dl coriolin (1) via the intermediate cross conjugated dienone 3, whose synthesis was stereospecific. Unfortunately, the epoxidation of 3, using alkaline hydrogen peroxide, was not endowed with comparable specificity.[2,3] In our hands, such reactions produced a mixture of spiroepoxide epimers 1 and 2 in, at best, a 7:5 ratio. Below we describe fully stereospecific routes to 1 and its congeners, coriolin B (8) and diketocoriolin B (9). The key intermediate in this regard became dihydrocoriolin, 6.

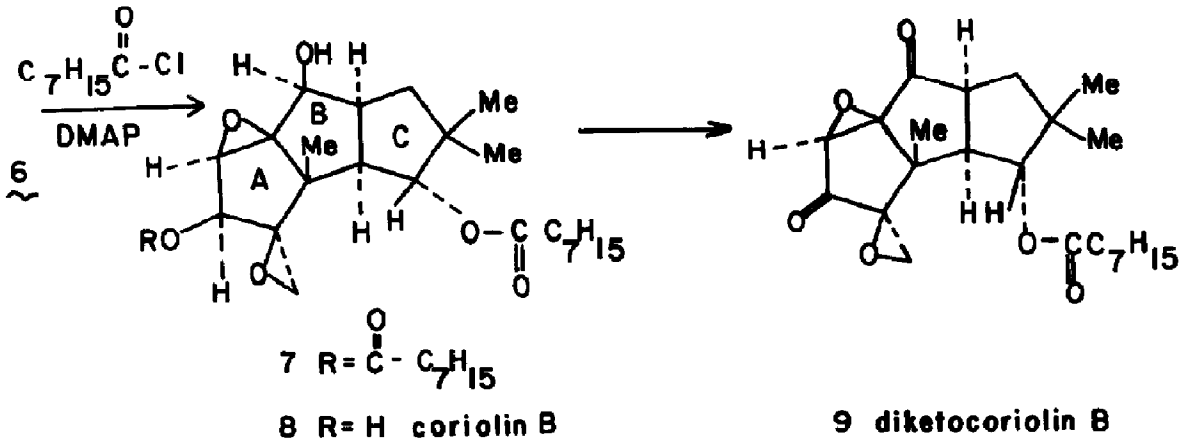


In studying the behavior of 3 with respect to alkaline epoxidation, it became apparent that the endocyclic double bond was substantially more reactive.[4,5] We speculate that the origin of this reactivity difference may well lie in the energy-lowering effect of rehybridizing the bridgehead carbon toward the sp^3 level, as it is attacked by hydroperoxide anion. Whatever the reason, the fact is that compound 3 can be converted (H_2O_2(ca.10 eq.); $NaHCO_3$ (ca. 10 eq.); 1:1 THF/H_2O; 3 hr.;0°) to 4 in very high yield.[6] Reduction of this epoxyketone with sodium borohydride[5] affords the hydroxyepoxide 5[6] as, apparently, the only product. The allylic alcohol grouping was now used to cleanly direct the epoxidation of the exocyclic double bond. Thus, reaction of 5[7] (tert-butyl hydroperoxide; $VO(acac)_2$; 1:1 ØH/dichloroethane; reflux; 15 min.) afforded the desired 6. The latter is a known[8] transformation product of coriolin B, and the selective reoxidation of 6 to coriolin (1) using Sarret's reagent has been reported.[8] The chromatographic mobility, nmr, infrared and mass spectra of the synthetic 6 are identical with those of an authentic sample which was prepared from coriolin B.[9] A fully stereospecific route to coriolin (1) is thus in hand.



We have also achieved the conversion of 6 to coriolin B (8). The reaction of 6 with 3 eq. of octanoyl chloride in the presence of 4-dimethylaminopyridine, gave the bis-octanoylated product, 7.[10] Treatment of crude 7 with potassium carbonate in methanol at room temperature leads to the selective cleavage of the A-ring ester with the clean formation of 8. Thus, a fully stereospecific and regiospecific route to coriolin B, bearing 9 contiguous centers of chirality has been achieved. Finally, given the known [11] conversion of coriolin B (8) to diketocoriolin B (9), the total synthesis of this biologically promising compound[12] is, therefore, formally accomplished.

A full report on these findings will be submitted.



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References:

1. S. Danishefsky, R. Zamboni, M. Kahn and S.J. Etheredge, J. Amer. Chem. Soc. 102, 2097 (1980).
2. Concurrently with our own report, a synthesis of 1 from hirsutene intermediates was described.[3] The Japanese workers also described the double epoxidation of dienone 3. However, they make no mention of the formation of the spiroepoxide epimer, 2. In our hands, this epoxidation was unmistakably and uniformly non-specific under all conditions including those described by Tatsuta et.al.[3]
3. K. Tatsuta, K. Akimota, and M. Kimoshita, J. Antibiot., 33, 100 (1980).
4. This trend was also observed by Matsumoto and co-workers in their total synthesis of hirsutic acid[5] with a related dienone.

5. H. Hashimoto, T. Tsuzuki, F. Sakan, H. Shirahama and T. Matsumoto, Tetrahedron Lett. 3745 (1974).
6. This intermediate was carried through to 6 without purification. Its nmr spectrum indicated it to be essentially homogeneous.
7. cf. H. Yamamoto, H. Nozaki, K.B. Sharpless, R.C. Michaelson, and J.D. Cutting, J. Amer. Chem. Soc., 96, 5254 (1974).
8. Y. Nishimura, Y. Koyama, S. Umezawa, T. Takeuchi, M. Ishizuka, and H. Umezawa, J. Antibiot. Chem. 33, 404 (1980).
9. We thank Professor H. Umezawa of the Institute of Microbial Chemistry, for the procedure for preparing 6 from coriolin B, and for a generous gift of coriolin B from which we carried out this preparation. We also acknowledge Prof. Umezawa for the procedure for converting 6→1, though this has not yet been done by us on fully synthetic material.
10. In studying the course of this reaction, it is clear that the first acylation occurs at the ring A hydroxyl. However, double octanoylation and mono hydrolysis is clearly the simplest method to convert 6→8.
11. T. Takeuchi, S. Takahashi, H. Iinuma and H. Umezawa, J. Antibiot., 24, 631 (1972).
12. For an account of these properties see K. Maeda and M. Ohno, Heterocycles, Special Issue, 13, 49 (1979).

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