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CYCLOEUDESMOL, AN ANTIBIOTIC CYCLOPROPANE CONTAINING SESQUITERPENE FROM THE MARINE ALGA, CHONDRIA OPPOSITICLADA DAWSON

William Fenical*
Institute of Marine Resources
Scripps Institution of Oceanography
La Jolla, California 92037

and

James J. Sims
Department of Plant Pathology
University of California
Riverside, California 92502

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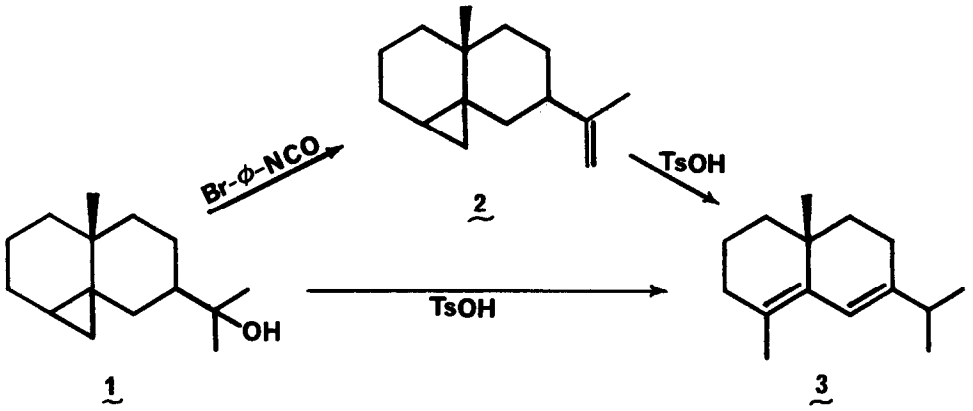
As part of a study of the occurrence of halogenated compounds from marine sources, we have been investigating the marine algae of the Sea of Cortez. In an earlier paper[1] we described a halogenated non-terpene, chondriol, from Chondria oppositiclada Dawson, an abundant alga in the vicinity of Puerto Peñasco, Mexico. We wish to report here that this plant also produces a cyclopropane containing sesquiterpene alcohol, cycloeudesmol, 1. Cycloeudesmol is related to γ-eudesmol[2] by cyclopropane bond formation and was found to be strongly antibiotic toward Staphylococcus aureus and Candida albicans.

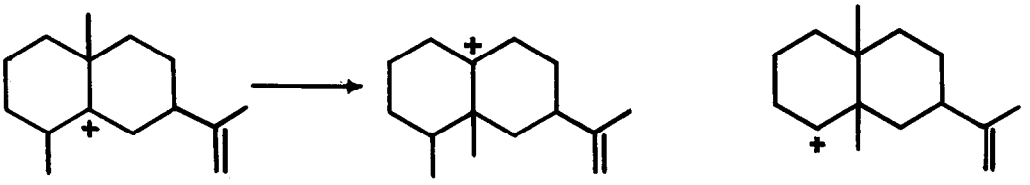
Repeated chromatography of the methylene chloride extract of C. oppositiclada (collected Puerto Peñasco, Sonora, Mexico, October, 1971) resulted in the isolation of cycloeudesmol, m.p. 94-95°, as colorless needles purified by crystallization from hexane (0.021% dry weight). Cycloeudesmol, $[\alpha]_D^{25}$ -41.1° c 0.32, MeOH, showed a molecular ion in the mass spectrum of 222 and analyzed for $C_{15}H_{26}O$. An intense M^+-18 fragment, coupled with its failure to form an acetate at room temperature (Ac_2O/py), indicated that 1 was a tertiary alcohol. This was confirmed by absorption in the infrared at 3680 and 3550 cm^{-1} and by an



ultimate dehydration reaction. The infrared spectrum also indicated the strained ring hydrogen of the cyclopropyl group by a weak band at 3095 cm^{-1}. The cyclopropane ring in 1 was also obvious in the NMR spectrum by very high field resonance at 0.35 and 0.47 δ. These bands were observed as two doublets, J = 5Hz (taken at 220 MHz, CCl_4). Other bands in the NMR spectrum, which indicated its isoprenoid nature, were a singlet at 1.00 δ (3H), assigned to the angular methyl, two singlets at 1.25 and 1.33 δ (3H each), assigned to the methyls of the isopropyl group, and multiple bands from 1.0-2.3 δ for the remaining fourteen methylene ring protons.

Treatment of 1 with p-bromophenylisocyanate in warm benzene resulted in quantitative dehydration to cycloeudesmene, (2), rather than the expected urethane formation. The isopropenyl group (terminal olefin) and cyclopropane ring in 2 gave rise to absorption at 3090, 1620 and 890 cm^{-1} in its infrared spectrum. The NMR spectrum of this hydrocarbon confirmed these structural features. The terminal olefin protons were observed at 4.78 and 4.62 δ, each as broadened bands indicating allylic coupling. The isopropenyl methyl appeared at 1.85 δ and was also broadened by allylic coupling. The angular methyl was observed as a singlet at 1.07 δ, and the cyclopropyl protons appeared as doublets (J = 5Hz) at 0.37 and 0.60 δ. The highest field cyclopropyl proton also showed very small (~1Hz) additional coupling, which indicates an ABX system with JAB = 5Hz, JAX approximately 1Hz and JBX non-existent or very small.

These data require a bicyclic sesquiterpene which contains an isopropyl alcohol group, a bridgehead methyl, and a cyclopropane ring bonded as part of a bridgehead. Only two terpenoid carbon ring systems can meet these requirements, the selinane system and the pseudoguaiane type (perhydroazulene) skeleton found in the lactones mexicanin A[3] and brevilin A[4], among others. The assignment of cycloeudesmol to the selinane ring system was made based on the facile conversion of either 1 or 2 to (+)-δ-selinene[5]. Treatment of either 1 or 2 with traces of p-toluenesulfonic acid in hot benzene gave the conjugated diene in nearly quantitative yield. The product, (3), $[\alpha]_D^{25}$ +120° c 1.56, hexane, had UV, IR, and NMR bands identical to those reported for (+)-δ-selinene[5]. The low molecular rotation of the diene (literature value + 265°) indicates that ca. 70% optically pure (+) isomer was obtained. The optical center in δ-selinene is the methyl substituted quaternary carbon, and the configuration of the methyl group is known to be β. Since this center should not be epimerized during any of the above transformations, its stereochemistry in 1 and 3 must be identical.



4 5 6

The cation, (4), has long been considered as a participant in the biosynthesis of eremophilane sesquiterpenes. A recent chemical conversion of this nature, (4) to (5), gives proof that reactions analogous to the biosynthetic speculation can be carried out in the laboratory[6]. Acid treatment of cycloeudesmol would be expected to generate cation 4. A careful search was made for products containing a rearranged methyl group; however, none were found.

Cycloeudesmol may also be considered to be related to the valeranone group[7] of sesquiterpenes. Cleavage of the cyclopropane ring to give cation 6 would generate this skeleton.

Acknowledgements

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References

1. W. Fenical, J. Sims, P. Radlick, Tetrahedron Letters, 4, 313 (1973).

2. R. Bates, E. Hendrickson, Chem. and Ind., 1759 (1962).

3. W. Herz, M. Lakshmikantham, R. Mirrington, Tetrahedron, 22, 1709 (1966).

4. W. Herz, G. Gast, P. Subramaniam, J. Am. Chem. Soc., 81, 1481 (1959).

5. M. Maheshwari, T. Jain, R. Bates, S. Bhattacharyya, Tetrahedron, 19, 1079 (1963).

6. I. Kitagawa, Y. Yamazoe, R. Takeda, I. Yosioka, Tetrahedron Letters, 4483 (1972) and references contained therein.

7. H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, T. Takemoto, Chem. Pharm. Bull., 13, 1408 (1965).