

CHEMICAL STUDIES OF MARINE INVERTEBRATES. X.
LOBOPHYTOLIDE, A NEW CEMBRANOLIDE DITERPENE FROM THE SOFT CORAL
LOBOPHYTUM CRISTAGALLI (Coelenterata, Octocorallia, Alcyonacea) ⁽¹⁾.

B. TURSCH, J.C. BRAEKMAN^x, D. DALOZE, M. HERIN, R. KARLSSON^{xx}.

Collectif de Bio-écologie
Université Libre de Bruxelles
Bruxelles Belgique.

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In the course of our continuing search for terpenoids from marine invertebrates, we have isolated a new cembranolide diterpene, lobophytolide (I), from the soft coral *Lobophytum cristagalli* Von Marenzeller, 1886.

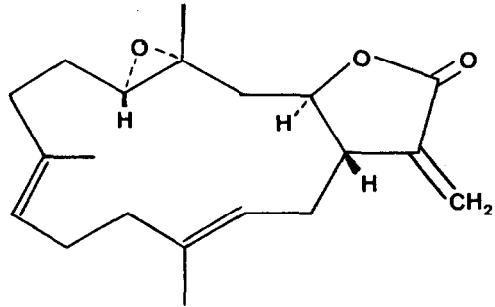
The dichloromethane extract of the sun-dried animals, collected off Serwaru, Leti Island, Indonesia ⁽²⁾, was chromatographed on silica gel. Elution with hexane/acetone (8:2) afforded crystalline lobophytolide (I; 1% on the basis of dry starting material; m.p. 137-8°; $[\alpha]_{\text{D}}^{\text{CHCl}_3} = 7^\circ$ (c = 0.42); M = 316; C₂₀H₂₈O₃). The IR ($\nu_{\text{C=O}}$ at 1755 cm⁻¹ and $\nu_{\text{C=C}}$ at 1670 cm⁻¹), UV ($\lambda_{\text{max}}^{\text{MeOH}}$ 209 nm, $\epsilon = 9080$) and NMR spectra (two 1H doublets at 6.22 (J = 2.5 Hz) and 5.58 ppm (J = 2 Hz) respectively) of I strongly suggest the presence of a γ -lactone conjugated to an exomethylene group ^(3,4).

This was further confirmed by NaBH₄ treatment of I (MeOH - room temperature - 3 min) which, on selective reduction of the conjugated exomethylene group ⁽⁵⁾, led to a mixture of two epimeric dihydroderivatives (II; M = 318; $\nu_{\text{C=O}}$ at 1775 cm⁻¹; NMR ⁽⁶⁾; no signals beyond 5.5 ppm but presence of two doublets (J = 7 Hz) of 1.5 H each at 1.18 and 1.25 ppm respectively).

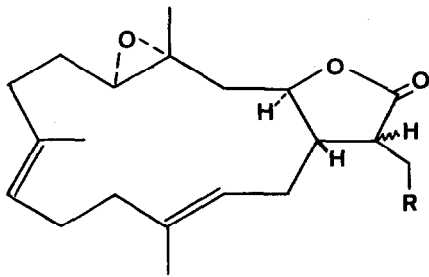
Moreover treatment of lobophytolide with a 1% solution of NaOH in methanol yielded compound III (m.p. 104-5°; M = 348; $\nu_{\text{C=O}}$ at 1780 cm⁻¹; NMR ⁽⁶⁾; 2H doublet at 3.7 ppm and 3H singlet at 3.4 ppm (CH₂-OCH₃) resulting from the addition of methanol to the exomethylene group ⁽⁷⁾. The five membered ring nature of the conjugated lactone was demonstrated by NMR decoupling experiments. Indeed, the 1H multiplet at 2.66 ppm in the spectrum of I and attributed to H₁, was found to be coupled with both the lactonic proton appearing

^x Chercheur qualifié du Fonds National de la Recherche Scientifique.

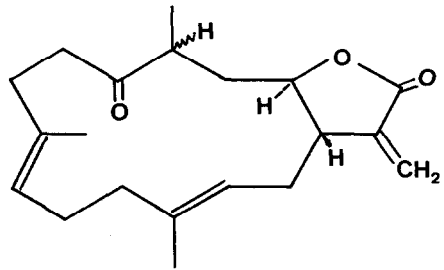
^{xx} Arrhenius Laboratory, University of Stockholm, Sweden.



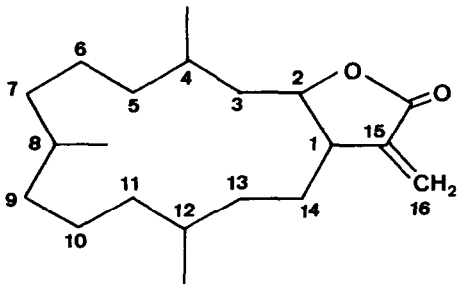
I Lobophytolide



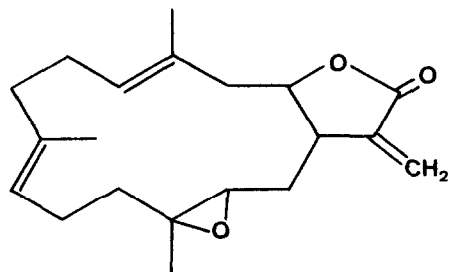
II R = H

III R = OCH₃

IV



V



VI

as a quadruplet at 3.94 ppm ($J_{H_1H_2} = 5$ Hz) and the exomethylenic protons ($J_{H_1H_{16cis}} = 2$ Hz; $J_{H_1H_{16trans}} = 2.5$ Hz).

Since lobophytolide is devoid of either hydroxyl or further carbonyl group, the third oxygen atom of the molecule must be implied in an ether. This ether function is an epoxide since I readily reacts with p-toluenesulfonic acid to give a mixture from which the ketone (IV) could be isolated ($M = 316$; $\nu_{C=O}$ at 1765 and 1705 cm^{-1} and $\nu_{C=C}$ at 1665 cm^{-1} ; NMR ⁽³⁾; 3H doublet ($J = 7$ Hz) at 1.22 ppm ($\text{CH}_3\text{-CH=C=O}$). Moreover, the presence in the NMR spectrum ⁽³⁾ of I, of a 3H singlet at 1.29 ppm and a triplet of 1H ($J = 6$ Hz) at 2.80 ppm implies the sequence $\text{CH}_3\text{-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-CH-CH}_2\text{-}$.

In addition to the characteristic signals previously discussed, the 270 MHz NMR spectrum of I also shows a 2H multiplet at 5.02 ppm and two 3H broad singlets at 1.66 and 1.56 ppm respectively, assignable to two CH=C-CH_3 groups. The presence of these two double bonds was further proved by the obtention of a tetrahydroderivative ($M = 352$; $\nu_{C=O}$ at 1775 cm^{-1} ; NMR ⁽⁶⁾: complex 6H signal at 1.00 ppm) on hydrogenation of III over platinum oxide.

The existence of a γ -lactone conjugated to an exomethylene, two double bonds and an epoxide, accounts for 6 of the 7 saturations required by formula $\text{C}_{20}\text{H}_{28}\text{O}_3$ of I and implies that lobophytolide is monocarbocyclic ⁽⁸⁾. By analogy with other diterpenes isolated from Coelenterates ^(11,12) it appeared thus logical to admit that lobophytolide possesses the cembranolide skeleton (V) in which two of the three methyl groups are located on a double bond, the last one bearing the epoxide. The number of possible arrangements of these functions (initially 24) could be rapidly reduced to two - (I) and (VI) - since:

- microozonolysis ⁽⁹⁾ of I yields levulinaldehyde.
- decoupling experiments on I ⁽³⁾ show that there is no coupling between the lactonic proton at 3.94 ppm (H_2), the ether proton at 2.82 ppm (H_5) and the olefinic protons at 5.01 ppm (H_9 and H_{13}).
- the NMR spectrum ⁽³⁾ of the ketone IV does not show any signal beyond 3 ppm, attributable to a methylene group located between a keto group and a double bond.

Of the two remaining structures, I was the most probable, since on irradiation at 2.66 ppm (proton H_1) one observes small modifications of the shape of the complex signal of 8H centered at 2.2 ppm and attributed to the CH_2 adjacent to sp^2 carbon atoms.

Independent X-ray diffraction analysis ⁽¹⁰⁾ established the structure and relative configuration of lobophytolide as I, in full agreement with the hypothesis derived from chemical and spectroscopic methods. Crystal data: lobophytolide crystallized in the orthorhombic system; space group $\text{P2}_1\text{2}_1\text{2}_1$ with $a = 22.29$ Å, $b = 13.84$ Å, $c = 6.00$ Å.

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