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Havellockate, A Novel Seco and Spiro Lactone Diterpenoid from the Indian Ocean Soft Coral *Sinularia granosa*

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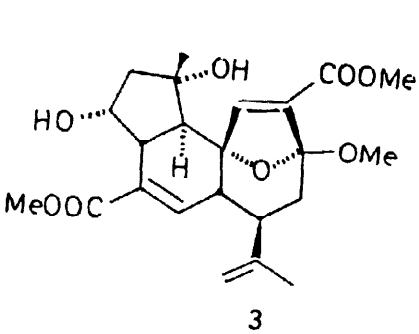
Abstract : The isolation of a novel seco and spiro lactone diterpenoid, havellockate (**1**) from the Indian ocean soft coral *Sinularia granosa* and its structure elucidation using all spectral data including X-ray analysis is presented.

In our continuing interest on the bio-active secondary metabolites of the Indian ocean soft corals,[1] we have examined the species *Sinularia granosa* collected from the Havellock Island of the Andaman and Nicobar group of Islands of the Indian Ocean and present herein the isolation and structure elucidation of a novel seco and spiro lactone diterpenoid, havellockate (**1**), by a study of its spectral data including X-ray analysis.

Chemical examination of this species was not reported earlier. The ethyl acetate extract of the organism on column chromatography over silica gel furnished **1**,[2] $C_{21}H_{26}O_8$, colourless needles, m.p. 212-13°C, $[\alpha]_D$ + 23.7.



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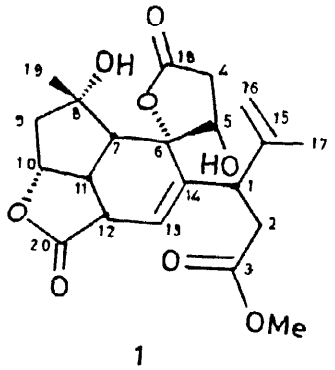

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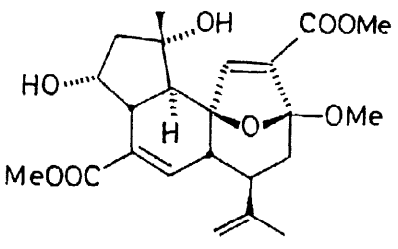

2

The presence of two hydroxyls (3510, 3435 cm^{-1}) and three carbonyl groups (1770, 1750, 1710 cm^{-1}), two of γ-lactones and one of a methyl ester was evident from its IR spectrum. Its UV spectrum was transparent above 200 nm indicating the absence of conjugation. Its ^{13}C NMR spectrum taken in d_5-pyridine showed 21 carbons and the DEPT spectrum indicated their nature (3 methyls, 4 methylenes, 7 methines and 7 quaternary). All the three carbonyl functionalities were indicated at δ 176.0, 175.0 and 175.3, two of which were lactones and one a methyl ester which was supported by the presence of a three proton signal at δ 3.50. In addition, the spectrum showed four olefinic carbons, two of an exocyclic methylene [δ 147.9 (s) and 112.9 (t)] and two of a trisubstituted double bond [δ 138.3 (s) and

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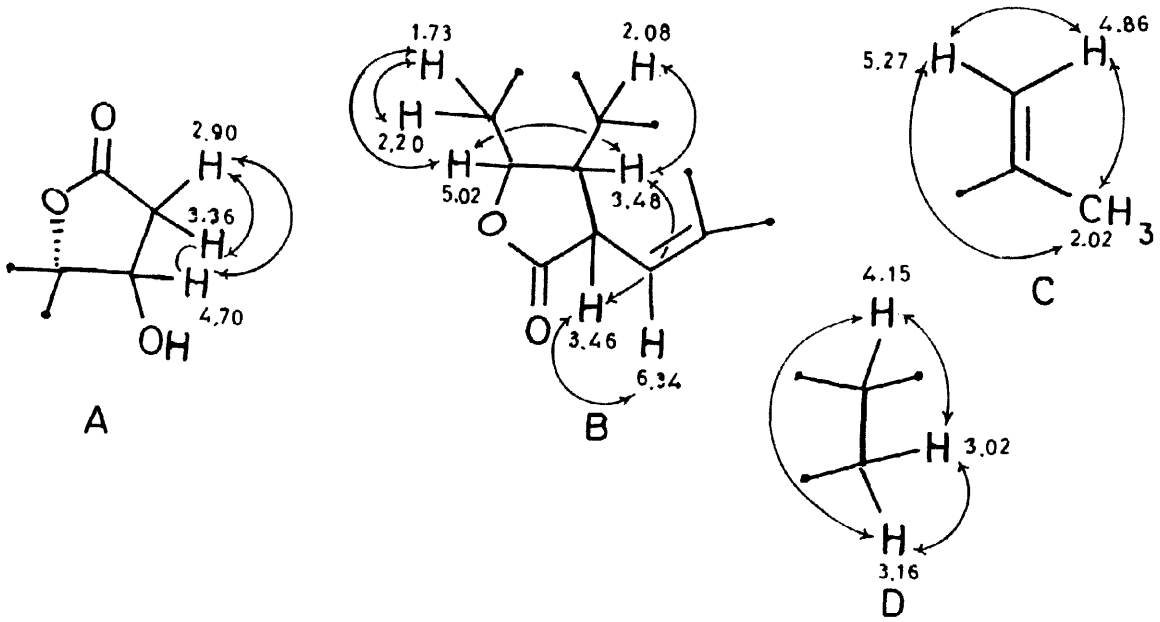
123.1 (d)]. These were supported by the respective exocyclic methylene protons (5.27 and 4.86, each s) and an olefinic proton at δ 6.34. Five oxygenated carbons including that of COOMe group were noticed in the spectrum. Two of these happened to be quaternary carbons and two tertiary carbons. One of the quaternary carbons appeared very much deshielded at δ 91.6 reminiscent of a spiro lactone system. In view of the functional groups discussed above, the molecule must be a tetracyclic diterpenoid.

From the partial connectivities noticed in its ^{1}H-^{1}H COSY spectrum the following part structural units could be determined. A proton appearing at δ 4.70 assignable to a carbinolic methine proton showed connectivity to two protons at δ 2.90 and δ 3.36 assignable to an α-methylene group to a carbonyl functionality. This formed an isolated system **A** which might be assigned to a spiro lactone unit.

A proton appearing at δ 5.02 assignable again to a carbinolic methine proton over a lactonic oxygen was coupled to two methylene protons appearing at δ 1.73 and 2.26 which were mutually coupled. By a study of their coupling constants the latter two protons were regarded to be geminal. The same carbinolic proton at δ 5.02 also showed connectivity to a proton at δ 3.48 which was in turn connected to two protons at δ 2.08 and δ 3.46. Since the latter two protons were not mutually coupled they were regarded as being on two different carbons. The proton at δ 2.08 was not coupled any further while the proton at δ 3.46 showed connectivity to an olefinic proton at δ 6.34. This set of connectivities led to the part structure **B**.



The third set of connectivities noticed between the protons of a terminal methylene group at δ 5.27 and δ 4.86 and a methyl signal at δ 2.02 correspond to the unit C. A proton at δ 4.15 showed connectivity to two protons at δ 3.02 and δ 3.16 which were only mutually coupled giving rise to part structure **D**.

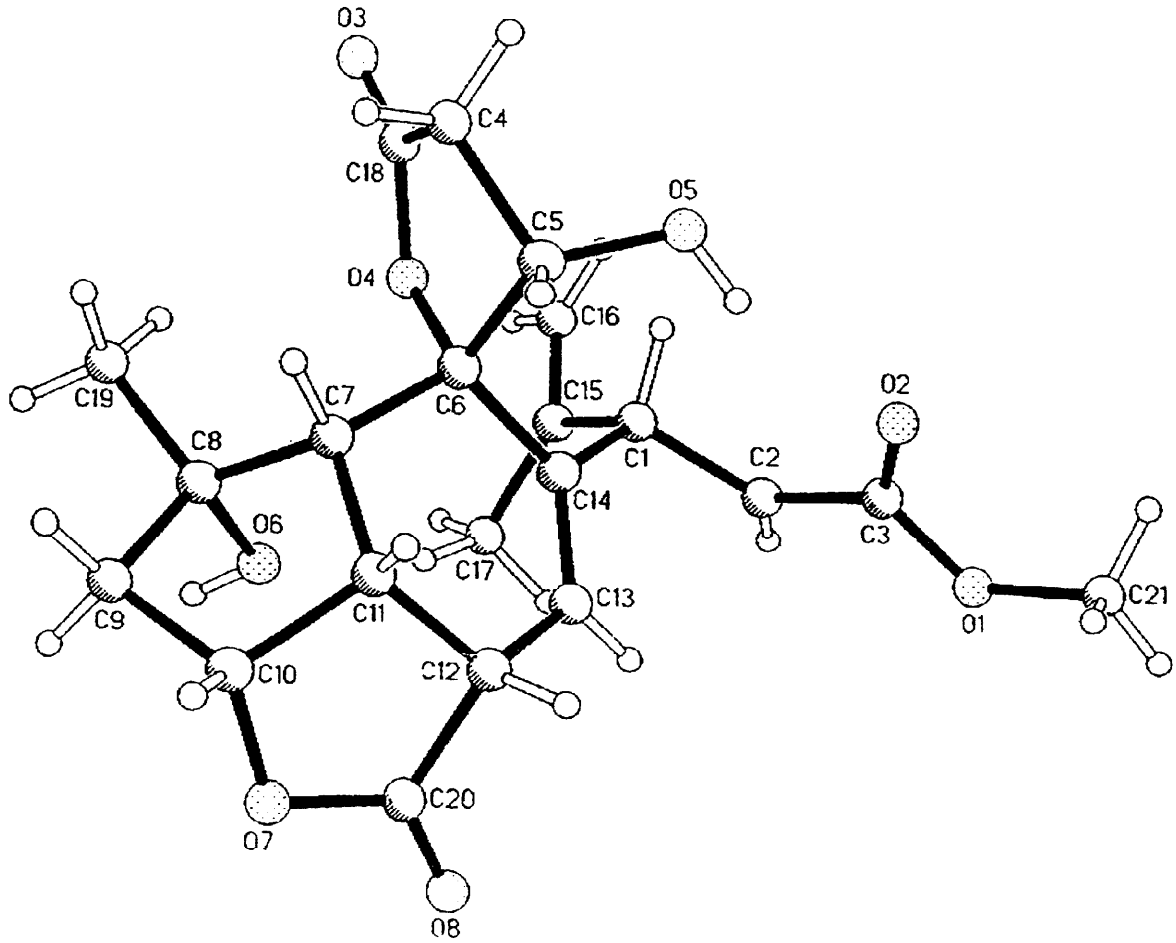
The other missing units, a tertiary methyl connected to oxygenated carbon in the form of hydroxyl could fit into part structure **B** and carbomethoxyl could fit into part structure **D**. Keeping the tetracyclic nature in view the partial structures could be pieced together to give the total structure (**1**).

^{1}H-^{1}H COSY data of havellockate (400 MHz spectrum in d_5-pyridine)

Chemical Shift	Assignment	Chemical Shift	Assignment
1.73 - 2.20	9-H_a and 9-H_b	3.02 - 3.16	2-H_a and 2-H_b
1.73 - 5.02	9-H_a and 10-H	4.70 - 2.90	5-H and 4-H_a
5.02 - 3.48	10-H and 11-H	4.70 - 3.36	5-H and 4-H_b
3.48 - 3.46	11-H and 12-H	2.90 - 3.36	4-H_a and 4-H_b
3.46 - 6.34	12-H and 13-H	5.27 - 2.02	16-H_a and 17-CH_3
3.48 - 2.08	11-H and 7-H	4.86 - 2.02	16-H_b and 17-CH_3
4.15 - 3.02	1-H and 2-H_a	5.27 - 4.86	16-H_a and 16-H_b
4.15 - 3.16	1-H and 2-H_b		

A careful examination of the above structural features revealed that it might have been derived from the fourteen membered carbocyclic cembrane nucleus. The molecule also finds similarity with the recently isolated tetracyclic diterpenoids mandapamate (**2**) from *Sinularia dissecta*[3] and isomandapamate (**3**) from *Sinularia maxima*.[1] Going by the numbering of the cembrane unit the molecule could be regarded as a 3,4-seco derivative with carbons 4 and 18 (in its oxidised form) forming a spiro lactone with carbon 6.

In view of only a small quantity of the compound being available no further 2D NMR spectral data (HETCOR, NOESY, COLOC) could be obtained to decide its total stereochemistry. X-ray analytical data was obtained for the molecule which not only confirmed the gross structure of the molecule but also gave its probable absolute configuration as shown in the X-ray picture. A few pertinent details of the X-ray analysis are given below.



Single crystal X-ray analysis of (1). Data were acquired with a Siemens R3m/V diffractometer Cu K_α radiation (λ = 1.5418 A), graphite monochromator. $C_{21}H_{26}O_8$ (405.41), crystal size 0.25 x 0.20 x 0.15 mm, triclinic, space group P1, 293 K, a = 7.544(2), b = 8.672(2), c = 8.934(2) Å, V = 498.3(2) Å^3, D_c = 1.376 g/cm^3, Z = 1, F(000) = 215 μ = 0.886 mm^{-1}. A total of 1396 reflections were collected in the $3^\circ < 2\theta < 110^\circ$ range using variable speed (2-29°/m) $\omega/2\theta$-scans. 1389 reflections were assumed as observed ($F > 4\sigma(F)$). Lorentz and polarization but not absorption corrections were applied. Three standard reflections monitored every 97 reflections indicated no significant intensity variation.

The structure was solved by direct methods (SHELXS-86 [1]). Hydrogen atoms were set in calculated positions. The structure was refined by full-matrix least-squares on F^2 (SHELXL-9 : [2]) using anisotropic thermal parameters for all non-hydrogen atoms and riding hydrogens. The refinement converged to R_1 = 3.3%, wR_2 = 10.0%, GOF = 0.982 and a final difference map revealed no peaks greater than 0.32 e/Å^3.

Complete details of the structure investigation are available at request from the Cambridge Crystal Data Centre, 12 Union Road, Cambridge CB2 1EZ, England.

[1] G.M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, 46, 467.

[2] G.M. Sheldrick, University of Gottingen, 1993.

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References and notes

1a. Anjaneyulu, A.S.R.; Sagar, K.S.; Venugopal, M.J.R.V.; *Tetrahedron*, **1995**, 51, 10997-11110 and references cited therein.

b. Anjaneyulu, A.S.R.; Krishna Murthy, M.V.R.; Rao, G.V., *Tetrahedron*, 1997, 1997, **53**, 9301-12 and the references cited therein.

2. Havellockate (**1**), $C_{21}H_{26}O_8$, m.p. 212-13°C, $[\alpha]_D^{25}$ + 23.70 (c, 0.43, C_5H_5N), ^{1}H NMR (400 MHz, d_5-pyridine) δ : 1.53 (3H, s, 19-Me), 1.73 (1H, dd, J = 13.3, 6.5, 9-H_a); 2.02 (3H, s, 17-Me); 2.08 (1H, d, J = 8.2, 7-H); 2.20 (1H, d, J = 13.3, 9-H_b); 2.90 (1H, d, J = 16.3, 4-H_a); 3.02 (1H, dd, J = 13.8, 2-H_a); 3.16 (1H, dd, J = 13.4, 2-H_b); 3.36 (1H, dd, J = 19.5, 6.5, 4-H_b); 3.46 (1H, d, J = 3, 12-H); 3.48 (1H, m, 11-H); 3.50 (3H, s, -OMe); 4.15 (1H, dd, J = 8.3, 1-H); 4.70 (1H, , d, J = 6, 5-H); 4.72 (1H, brs, -OH); 4.86 (1H, brs, 16-H_a); 5.02 (1H, m, 10-H); 5.27 (1H, brs, 16-H_b); 6.34 (1H, d, J = 3, 13-H); 7.48 (1H, br, -OH); ^{13}C NMR (22.5 MHz, d_5-pyridine) δ : 20.7 (q, C-17); 28.1 (q, C-19); 38.2 (t); 39.1 (t); 40.3 (d); 40.4 (d); 44.8 (d); 49.0 (d); 5.10 (t, C-9); 51.3 (q, -OMe); 76.0 (d); 80.2 (d); 81.8 (s, C-8); 91.7 (s, C-6); 112.9 (t, C-16); 123.1 (d, C-13); 138.3 (s, C-14); 147.9 (s, C-15); 173.1 (s, C-3); 175.8 (s, C-18); 176.4 (s, C-20).

3. Venkateswarlu, Y.; Farooq Biabani, M.A.; Venkata Rami Reddy, M.; Prabhakar Rao, T.; Kunwar, A.C.; Faulkner, D.J.; *Tetrahedron Lett.*, **1994**, 2249-2252.