



Pergamon

Tetrahedron Letters 39 (1998) 8217–8220

TETRAHEDRON  
LETTERS

## Rameswaralide, A Novel Diterpenoid from the Soft Coral *Sinularia dissecta*<sup>#</sup>

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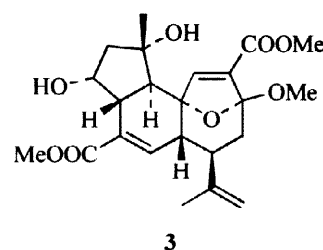
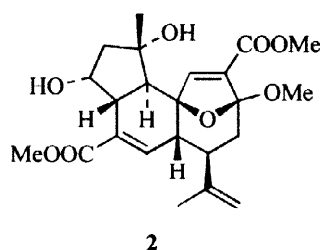
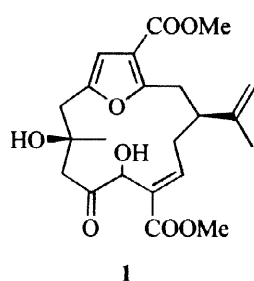
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Received 20 August 1998; accepted 28 August 1998

**Abstract:** Rameswaralide (**4**), a novel diterpene having a 5-7-6 tricyclic skeleton has been isolated along with known terpenes, africanene, 4,5-*seco*-african-4,5-dione,  $\beta$ -elemene and isomandapamate (**3**) from the soft coral *Sinularia dissecta* from the Mandapam coast, South India. The structure and stereochemistry of rameswaralide (**4**) were determined using spectroscopic methods and confirmed by selective reduction of the unusually stable enol group of **4** to form dihydrorameswaralide (**5**).  
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Soft corals are a rich source of terpenoids with diverse structures and various biological activities.<sup>1,2</sup>

Prior studies have shown that members of the genus *Sinularia* produce unusual sesquiterpenes, cembrane diterpenes and sterols.<sup>3</sup> We have previously reported two new diterpenes, furanocembrane diester (**1**) and mandapamate (**2**) from a 1991 collection of the soft coral *Sinularia dissecta*.<sup>4,5</sup> We now report the structural elucidation of rameswaralide (**4**), a diterpene with an unusual carbon skeleton, along with some known compounds,  $\Delta^{9(15)}$ -africanene,<sup>6</sup> 4,5-*seco*-african-4,5-dione,<sup>7</sup>  $\beta$ -elemene,<sup>8</sup> and isomandapamate<sup>9</sup> (**3**) from a 1996 collection.

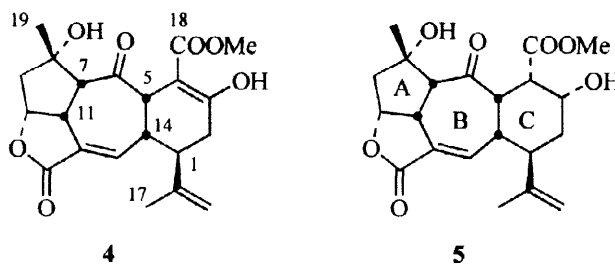


<sup>#</sup> IICT Contribution No. 4098.

**Table 1.** <sup>1</sup>H (300 MHz, CDCl<sub>3</sub>) and <sup>13</sup>C (100 MHz, CDCl<sub>3</sub>) NMR data for rameswaralide (4) and dihydrorameswaralide (5).<sup>a</sup>

rameswaralide (4)					dihydrorameswaralide (5)				
C#	δ <sub>C</sub>	δ <sub>H</sub>	mult., J (Hz)	HMBC	NOESY	δ <sub>C</sub>	δ <sub>H</sub>	mult., J (Hz)	NOESY
1	41.7	2.58	m	C2, C14, C15, C16, C17	H2, H13, H16a, H17	39.1	2.38	dt, 13, 3.5	H2, H13, H16a, H17
2	34.2	2.39	dd, 18.5, 10	C1, C3, C4, C14, C15	H1, H14, H16a, H17	39.7	1.68	dd, 14, 3.5	H1, H4, H14, H16a, H17
3	173.8	2.45	dd, 18.5, 6.5	C1, C3, C4, C14, C15	H1, H14, H16a, H17		2.07	dt, 14, 3.5	H1, H16a, H17
4	95.5					65.1	4.45	m	H2a, H2b, H4
5	46.0	4.35	d, 6	C1, C3, C4, C6, C14, C18	H7, H11, H14	49.7	3.01	dd, 5.5, 4.5	H2a, H3, H14
6	210.5					47.4	4.19	br t, 6	H4, H7, H11, H14
7	68.3	3.32	d, 9	C6, C8, C11, C12, C19	H5, H9a, H11, H19	211.0			
8	78.3					69.0	3.75	d, 9	H5, H9a, H11, H19
9	46.2	1.84	dd, 15.5, 7	C19	H7, H9b, H10, H19	78.7			
		2.28	d, 15.5	C6, C7, C8, C10, C11	H9a, H10, H19	46.5	1.91	dd, 15.5, 7	H7, H9b, H10, H19
10	79.3	5.05	t, 7	C7, C8, C20	H9a, H9b, H11		2.39	d, 15.5	H9a, H10, H19
11	41.8	4.21	m	C7, C8, C9, C12, C13, C20	H7, H10	79.4	5.10	t, 7	H9a, H11
12	131.8					42.2	4.22	m	H7, H10
13	135.2	6.54	br s	C1, C5, C20	H1, H14, H16a, H17	131.5			
14	40.1	2.89	m	C1, C5, C6, C12, C13	H2, H5, H13, H16a, H17	135.8	6.63	br s	H1, H4, H14, H16a, H17
15	143.0					42.1	2.86	m	H2a, H5, H13, H16a, H17
16	115.6	4.86	br s	C1, C15, C17	H1, H2, H13, H14	145.2			
		4.95	br s	C1, C15, C17	H17	114.7	4.89	br s	H1, H2, H13, H14
17	18.1	1.66	s, 3 H	C1, C15, C16	H1, H2, H13, H14, H16b		5.00	br s	H17
18	170.8					19.0	1.73	s, 3 H	H1, H2, H13, H14, H16b
19	26.6	1.42	s, 3 H	C7, C8, C9	H7, H9a, H9b	170.0			
20	169.8					26.6	1.57	s, 3 H	H7, H9a, H9b
21	51.2	3.71	s, 3 H	C18		169.5			
3-OH		12.15	br s			52.6	3.78	s, 3 H	
							5.38	br d, 11	H1, H3

<sup>a</sup> <sup>1</sup>H-<sup>13</sup>C correlations were determined by HMQC.



The 1:1 dichloromethane-methanol extract of the soft coral *Sinularia dissecta* was chromatographed on Sephadex LH-20 using 1:1 dichloromethane-methanol as eluant, followed by silica gel chromatography to afford  $\Delta^{9(15)}$ -africanene (0.05 % dry wt.), 4,5-*seco*-african-4,5-dione (0.0005 % dry wt),  $\beta$ -elemene (0.0005 % dry wt.), isomandapamate (**3**, 0.0025 % dry wt.) and a novel cembrane diterpene, rameswaralide (**4**, 0.003 % dry wt.), which was purified by HPLC on silica gel using 1:3 hexane/ethylacetate as eluant. The known compounds were identified from literature data.<sup>6-9</sup> The structure of the novel compound, rameswaralide (**4**) was determined by extensive 1D and 2D NMR experiments and confirmed by selective reduction of the enolic group with sodium borohydride to form dihydrorameswaralide (**5**).

Rameswaralide (**4**)<sup>10</sup> was obtained as a white solid, m.p. 169-171 °C,  $[\alpha]_D -20.5$  ( $c = 0.22$ ,  $\text{CHCl}_3$ ). The molecular formula  $\text{C}_{21}\text{H}_{24}\text{O}_7$ , which was derived from HREIMS ( $m/z$  388.1523) and  $^{13}\text{C}$  NMR data, requires 10 degrees of unsaturation. The IR spectrum contained bands at 3500, 1752, 1715, 1670  $\text{cm}^{-1}$ , from which the presence of a hydroxyl and three different carbonyl groups was inferred. The UV spectrum showed absorptions at 250 nm (sh,  $\epsilon$  11, 700), 229 (sh, 15,500), 222 (15,700), 205 (14,700), which underwent reversible bathochromic shifts on addition of base, indicating the presence of an enolisable  $\beta$ -keto ester as well as an  $\alpha,\beta$ -unsaturated carboxylic ester in the molecule. The  $^{13}\text{C}$  NMR spectrum (Table 1) contained 21 signals that include a ketone signal at  $\delta$  210.5, methyl ester signals at 170.8 and 51.2,  $\gamma$ -lactone carbonyl signals at 169.8 and 79.3 and six olefinic carbon signals at 173.8, 143.0, 135.2, 131.8, 115.6 and 95.5. The carbonyl and olefinic carbons account for six degrees of unsaturation; hence the compound is tetracyclic. The  $^1\text{H}$  NMR spectrum contained signals corresponding to an isopropylidene group at  $\delta$  1.66 (s, 3 H), 4.86 (br s, 1 H), 4.95 (br s, 1 H), a conjugated trisubstituted olefinic proton at 6.54 (br s, 1 H), a methine proton bearing oxygen at 5.05 (t, 1 H,  $J = 7$  Hz), four low field methine protons at 4.35 (d, 1 H,  $J = 6$  Hz), 4.21 (m, 1 H), 3.32 (d, 1 H,  $J = 9$  Hz), 2.89 (m, 1H), a quaternary methyl at 1.42 (s, 3 H) and an exchangeable proton at 12.15 ppm. The COSY spectrum revealed some similarities with mandapamate (**2**), which was obtained from the same specimen.<sup>5</sup> The spectral data for ring A and ring C were assigned from COSY and HMBC data and the presence of allylic coupling between H-11 and H-13 established the connection between rings A and C. The chemical shifts of H-7 and H-5 and their HMBC correlations to the ketone signal at  $\delta$  210.5 completed the 7-membered ring B. An HMBC correlation between H-10 and C-20 established the presence of the  $\gamma$ -lactone and a correlation between Me-17 and C-1 indicated that the isopropyl group was located at

C-1, as expected. The fully enolised  $\beta$ -keto ester moiety that completes ring C was defined by the HMBC correlations from H-5 to the three carbon signals at 173.8 (C-3), 95.5 (C-4) and 170.8 (C-18) and from H-2 to C-3 and C-4. The structure of rameswaralide (4) was further confirmed by selective reduction of enolic group with  $\text{NaBH}_4$  to form exclusively single isomer, dihydrorameswaralide (5).

The stereochemistry of rameswaralide (4) was determined by analysis of  $^1\text{H}$  NMR coupling constants and NOESY correlations. The coupling constants  $J_{5,14} = 6$  Hz and  $J_{7,11} = 9$  Hz and a NOESY correlation between H-5, H-7 and H-11 suggested that rings A and C are *cis* fused to ring B. The NOESY correlations between H-10 and H-11 and Me-19 and H-7, together with  $J_{10,11} = 7$  Hz, showed that Me-19, H-10, H-7 and H-11 were all on the same side of ring A. The NOESY data (Table 1) for dihydrorameswaralide (5) showed that the H-14, H-4 and H-2a are axial and that H-5, H-3 and the isopropylidene group are equatorial with respect to ring C and also showed that rings A and B were the same as in rameswaralide (4).

The carbon skeleton of rameswaralide (4) is related to that of isomandapamate (3) by opening of the furan ring with a concomitant migration of the C-14 bond from C-6 to C-5.<sup>11</sup>

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10. The soft coral was collected on the Mandapam coast near Rameswaram, which is one of the mythological and historical sites in India.
11. We thank Dr. V. Jayasree for identifying the soft coral. We thank the Director, IICT and Dr. J.S. Yadav for their encouragement of this research. This research was supported by the Department of Ocean Development, New Dehli, India, the National Institutes of Health (CA 49084), and by fellowships from UGC (to P.R.) and CSIR (to N.S.R.).