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Mandapamate, a Diterpenoid from the Soft Coral *Sinularia dissecta*[#]

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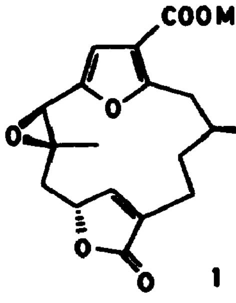
Abstract: Mandapamate (3) is a diterpene with an unusual carbon skeleton from the soft coral *Sinularia dissecta*. The structure of mandapamate(3) was elucidated by interpretation of spectral data, particularly extensive NMR experiments, and was supported by a mechanistic hypothesis for its formation and molecular modelling.

Marine organisms, especially soft corals, provide many secondary metabolites that exhibit varying degrees of biological activity[1]. Coelenterates of the genus *Sinularia* are rich source of diterpenoids,[2] and it was from *S. abrupta* that the furanocembranoid pukalide (1) was first reported in 1975[3]. Since that time, several related compounds, such as 11β,12β-epoxypukalide[4], 13α-acetoxypukalide and 13α-acetoxy-11β,12β-epoxypukalide,[5] lophotoxin(2)[6] and related compounds[7], the bipinnatins[8] and coralloidolides[9] have been described. Although mandapamate (3) is clearly related to this series of compounds, it has a more complex tetracyclic carbon skeleton that is thought to be the result of an internal Diels-Alder cyclization reaction.



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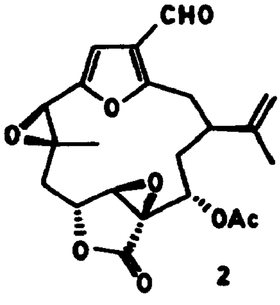

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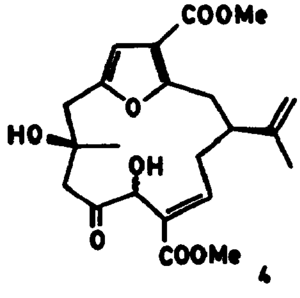

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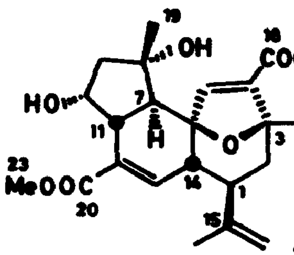
We have previously reported the isolation of pukalide (1) and the cembranoid diester (4) from a specimen *Sinularia dissecta* from Mandapam on the Gulf of Mannar, India[10]. Further investigation of a 1:1 dichloromethane-methanol extract[10] of this specimen revealed the presence of the related diterpenoid, mandapamate (3, 0.0037% wet wt.), which was eluted from silica gel with ethyl acetate-hexane (7:3).

Mandapamate (3), $[\alpha]_D$ +147 (c=0.25, $CHCl_3$), was obtained as a clear viscous oil of molecular formula $C_{23}H_{30}O_8$, which corresponds to nine degrees of unsaturation. The infrared spectrum contained bands at 3480, 1720, and 1640 cm^{-1} that were appropriate for hydroxy and unsaturated ester functionalities. The characterization of 3 was based on interpretation of NMR experiments (DEPT, HETCOR, DQF-COSY, NOEDS, NOESY, and COLOC - see Table 1)[11], assisted by molecular modelling. Due to overlap of signals, the NMR experiments were performed in both $CDCl_3$ and C_6D_6 solutions to obtain unambiguous assignments, although only the $CDCl_3$ data are reported in Table1.

The ^{13}C NMR spectrum of 3 contained 23 signals, three of which were assigned to methoxy groups and two to ester carbonyls. The olefinic region contained 6 signals that were attributed to olefins, both of which were assigned to α,β-unsaturated esters, and a 1,1-disubstituted olefin. A key signal at δ 111.1 (s) was assigned to a ketal carbon, to which one of the methoxy signal must be attached. Assuming that mandapamate (3) had been derived from a compound in the pukalide (1) series, the ketal carbon could be located at either C-3 or C-6. While studying the chemistry of lophotoxin (2), Bandurraga and Fenical[12] had observed addition of ethanol at C-3 with concomitant opening of the epoxide ring to obtain a ketal analogous to the C-3 to C-8 region in intermediates 5 and 6. Molecular models of the hypothetical precursors 5 and 6 generated using PC Model (Serena Software) revealed that the 11, 13-diene is ideally situated to react with a 6,7-olefin in a Diels-Alder reaction to obtain the proposed tetracyclic skeleton of 3. The ^1H and ^{13}C NMR data could be assigned as shown in Table 1.



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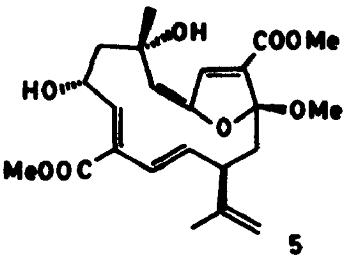

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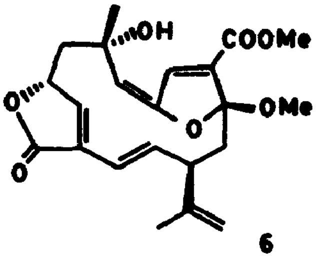

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The stereochemistry of 3 was determined by analysis of ^1H NMR coupling constants and NOESY data. Coupling constants of $J_{1,14}$ = 11.6 Hz and $J_{7,11}$ = 13.1 Hz indicated that H-1, H-7, H-11, and H-14 were all axial with respect to the six-membered rings and the *cis* relationship between H-11 and H-14 was defined by the observation of a strong crosspeak in the NOESY spectrum. The stereochemistry of the oxygen bridge between C-3 and C-6 was defined by nOe correlations from H-5 to H-1 and H-7. The stereochemistry of the substituents on the five-membered ring was defined by nOe correlations from H-11 to CH_3-19 and H-10. All other crosspeaks in the NOEDS spectrum are consistent with the stereochemistry proposed.

Table 1 ^{13}C [100 MHz: δ in ppm (mult.)] and ^{1}H [400 MHz: δ in ppm (mult., J in Hz)] NMR data for mandepamate (3) in $CDCl_3$ solution, with double quantum filtered COSY correlations, selected nuclear Overhauser enhancements, and long-range C-H correlations (some NOESY and COLOC data recorded in C_6D_6 solution).

C no.	δ_C	δ_H	DQF.COSY	NOESY	COLOC
1	43.2 (d) (44.69*)	2.16 (ddd,11.6, 11, 5.2)	H2α, H2β, H14	H2β, H5, H13, H14, H16a	H2α, H16b,
2	33.4 (t)	1.94 (dd, 13.1, 11, Hα) 1.65 (dd, 13.1, 5.2, Hβ)	H1, H2β H1, H2α	H2β H2α, H14	
3	111.1 (s)				H5
4	134.8 (s)				H5
5	154.4 (d)	6.68 (s)		H1, H7	H7
6	84.7 (s)				H5
7	52.6 (d)	2.72 (d, 13.1)	H11	H5, H9α	Me19
9	51.3 (t)	2.01 (br d, 14.9, Hα) 2.22 (dd, 14.9, 6, Hβ)	H9β H9α, H10	H7, H9β, H9α, H10, Me19	H7,Me19
10	67.6 (d)	4.62 (ddd, 6, 3.4, 1.1)	H9α, H9β, H11	H9β, H11	H9α
11	46.9 (d)	2.49 (m, 13.1, 3.4, 3, 1.6)	H7, H10, H13, H14	H10, H14, Me19	H13
12	133.5 (s)				H11, H13
13	143.2 (d)	6.67 (dd, 3.4, 3)	H11, H14	H1, H14, H16a	H1, H11
14	43.2 (d) (44.65*)	2.23 (ddd, 11.6, 3.4, 1.6)	H1, H11, H13	H2β, H11, H16a	
15	144.2 (s)				Me17
16	113.4 (t)	4.76 (br s, Ha) 4.85 (br s, Hb)	Me17 Me17	H1, H13, H14, H16b H16a, Me17	
17	19.6 (d)	1.66 (br s, 3H)	H16a, H16b	H16	H16a, H16b
18	162.5 (s)		H15		
19	26.8 (q)	1.56 (s, 3H)	H9β, H11	H9β	
20	166.6 (s)		H13		
21	51.8 (q)	3.37 (s, 3H)			
22	52.0 (q)	3.78 (s, 3H)			
23	52.3 (q)	3.74 (s, 3H)			

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* Values observed in C_6D_6.

Since the studies of Bandurraga and Fenical[12] suggest that mandapamate (3) might be an artifact resulting from methanol addition during extraction, we have searched for the possible precursors to 5 and 6 but without success[13].

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\# IICT communication No. 3312

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