

82. Coralloidolide F, the First Example of a 2,6-Cyclized Cembranolide: Isolation from the Mediterranean Alcyonacean Coral *Alcyonium coralloides*¹⁾

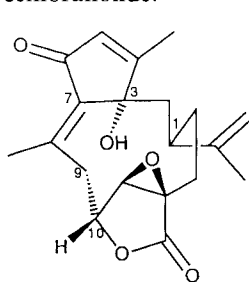
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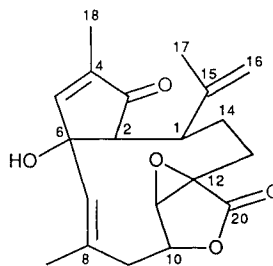
(16. II. 90)

The Mediterranean alcyonacean *Alcyonium* (= *Parerythropodium*) *coralloides* (Pallas, 1766) is shown here to contain coralloidolide F (= (+)-(3a*R**,7*R**,8*R**,9*R**,12*S**,12a*S**)-8,9-epoxy-1,3a,6,7,8,9,10,11,12,12a-decahydro-3a-hydroxy-12-isopropenyl-2,5-dimethyl-1-oxocyclopentacycloundecene-9,7-carbolactone; (+)-**2**), the first example of a 2,6-cyclized cembranolide. Structural assignments are mainly based on 1D and 2D NMR and MS data.

1. Introduction. – We have recently reported on various novel cembranolides [1] and a 3,7-cyclized cembranolide, coralloidolide C((+)-**1**) [1b], from the Mediterranean alcyonacean *Alcyonium* (= *Parerythropodium*) *coralloides* [1]. Continuing to examine *A. coralloides* extracts, we have now isolated and report here on a diterpenoid of novel skeleton, coralloidolide F ((+)-**2**), which can be considered as the first example of a 2,6-cyclized cembranolide.



(+)-**1**¹⁾



(+)-**2**¹⁾

2. Results and Discussion. – The composition $C_{20}H_{24}O_5$ for the new terpenoid (+)-**2** isolated from *A. coralloides* derives from high-resolution MS and ^{13}C -NMR data. The latter, obtained in both $CDCl_3$ and $(CD_3)_2CO$ (Table) in order to overcome problems of overlapping signals in either solvent, reveal 20 resonances for 3 Me, 3 CH_2 , 2 sp^3 CH at a heteroatom, 2 sp^3 CH not at a heteroatom, 2 olefinic CH, 1 olefinic CH_2 , 2 trisubstituted C at a heteroatom, 3 disubstituted olefinic C, 1 ester $C=O$, and 1 ketonic $C=O$. This suggests a tetracyclic diterpene two cycles of which are accounted for by an epoxidized butenolide, as in the case of coralloidolide C ((+)-**1**) [1b] and other coralloidolides [1].

¹⁾ Throughout this paper, we use the cembrene numbering for the structural formulae and spectroscopic data; IUPAC nomenclature and numbering are given in the *Exper. Part*.

Table. ^{13}C - and ^1H -NMR Data (CDCl_3) for Coralloidolide F((+)-2)

Atom	^{13}C -NMR	^1H -NMR
1	43.02 (<i>d</i>)	2.10 (br. <i>ddd</i> , $J(1,14\text{a}) = 12.5$, $J(1,2) = 1.8$, $J(1,14\text{b}) = 1.5$, $J(1,16\text{a}) = 0.9$, $J(1,17)$ small)
2	59.11 (<i>d</i>)	2.68 (<i>d</i> , $J(2,1) = 1.8$)
3	206.44 (<i>s</i>)	
4	138.05 (<i>s</i>)	
5	158.27 (<i>s</i>)	7.06 (<i>q</i> , $J(5,18) = 1.5$)
6	80.06 (<i>s</i>)	
7	129.82 (<i>d</i>)	5.48 (br. <i>q</i> , $J(7,19) = 1.2$, $J(7,9\text{b}) = 0.9$)
8	141.41 (<i>s</i>)	
9	40.62 (<i>t</i>)	2.75 (<i>dd</i> , $J_{\text{gem}} = 14.4$, $J(9\text{a},10) = 5.4$, H_a); 2.52 (<i>ddd</i> , $J_{\text{gem}} = 14.4$, $J(9\text{b},10) = 1.5$, $J(9\text{b},7) = 0.9$, H_b)
10	oversh. ^a)	4.74 (<i>ddd</i> , $J(10,9\text{a}) = 5.4$, $J(10,9\text{b}) = 1.5$, $J(10,13\text{a}) = 0.6$)
11	61.26 (<i>d</i>)	3.84 (<i>s</i>)
12	60.44 (<i>s</i>)	
13	22.22 (<i>t</i>) ^b)	2.62 (<i>dddd</i> , $J_{\text{gem}} = 14.7$, $J(13\text{a},14\text{b}) = 13.0$, $J(13\text{a},14\text{a}) = 2.1$, $J(13\text{a},10) = 0.6$, H_a); 1.42 (<i>ddd</i> , $J_{\text{gem}} = 14.7$, $J(13\text{b},14\text{a}) = 5.1$, $J(13\text{b},14\text{b}) = 2.7$, H_b)
14	25.97 (<i>t</i>)	1.83 (<i>dddd</i> , $J_{\text{gem}} = 14.5$, $J(14\text{a},1) = 12.5$, $J(14\text{a},13\text{b}) = 5.1$, $J(14\text{a},13\text{a}) = 2.1$, H_a); 0.89 (<i>dddd</i> , $J_{\text{gem}} = 14.5$, $J(14\text{b},13\text{a}) = 13.0$, $J(14\text{b},13\text{b}) = 2.7$, $J(14\text{b},1) = 1.5$, H_b)
15	142.64 (<i>s</i>)	
16	112.62 (<i>t</i>)	5.12 (br. <i>dq</i> , $J_{\text{gem}} = 1.8$, $J(16\text{a},1) = 0.9$, $J(16\text{a},17)$ small, H_a); 4.93 (<i>dq</i> , $J_{\text{gem}} = 1.8$, $J(16\text{b},17) = 1.8$, H_b)
17	22.22 (<i>q</i>) ^c)	1.88 (br. <i>dd</i> , $J(17,16\text{b}) = 1.8$, $J(17,16\text{a}) = J(17,1)$ small)
18	9.78 (<i>q</i>)	1.77 (<i>d</i> , $J(18,5) = 1.5$)
19	22.22 (<i>q</i>) ^d)	2.07 (<i>d</i> , $J(19,7) = 1.2$)
20	172.01 (<i>s</i>)	

^a) In $(\text{CD}_3)_2\text{CO}$, 78.84 (*d*). ^b) In $(\text{CD}_3)_2\text{CO}$, 23.07. ^c) In $(\text{CD}_3)_2\text{CO}$, 22.38. ^d) In $(\text{CD}_3)_2\text{CO}$, 22.19.

The epoxybutenolide moiety is supported by the chemical-shift values of one of the trisubstituted C at a heteroatom (60.44 ppm), one of the sp^3 CH at a heteroatom (61.26 ppm), and a *s* at 3.84 ppm in the ^1H -NMR. Comparison of the ^1H -NMR data (Table) with those of (+)-1 support the presence of a molecular fragment C(9)–C(10) to C(1)–C(15)(C(17))C(16) identical to that in (+)-1. The spectral differences between (+)-1 and (+)-2 suggest that the two remaining cycles of (+)-2 neither involves C(3) nor C(7). Indeed, the CH_2 group adjacent to H–C(1) in (+)-1 is absent in (+)-2; instead, the above mentioned sp^3 CH (not at a heteroatom) is coupled to H–C(1), indicating cyclization at C(2). Moreover, the olefinic CH group of (+)-2 which is not present in (+)-1 is coupled with H_b –C(9), thus extending the connectivity from C(9) to C(7) and suggesting C(6) to be the other center of cyclization.

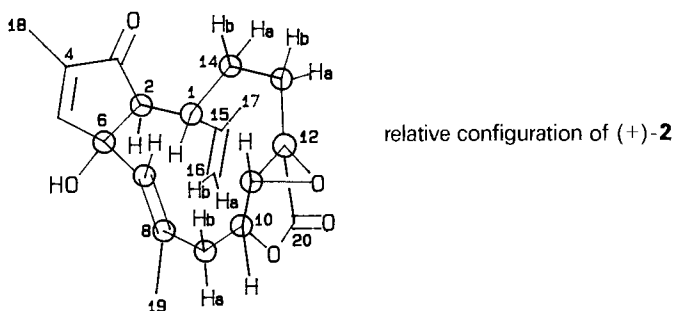
This analysis implies that one of the trisubstituted C at a heteroatom is C(12); that the other one (80.06 ppm), is C(6), is based on the identification of the C(5)–C(4)(C(18))–C(3) fragment from NMR (Table) and UV data (Exper. Part). This fragment defines a five-membered carbocycle with the configuration shown in (+)-2 as indicated by a NOE between H–C(5) and H–C(7) (see below). That the substituent at C(6) must be OH rests on the observation of only 23 C-bound protons (Table) and a M^+ at m/z 345 after exchange with CD_3OD .

Having defined the constitution of coralloidolide F((+)-2), some suggestions concerning its relative configuration can be made using NMR data and NOE results.

Thus, the (*E*)-configuration at C(7)=C(8) of (+)-2 rests on *i*) the relatively low field δ of C(9) (40.62 ppm²), *ii*) the high-field δ of $2\text{H}-\text{C}(9)^3$ as compared with (+)-1 [1b], and *iii*) the fact that on irradiation at Me(19), a

²) In this case, the δ of Me(19) can not be taken as a criterion for the configuration at the double bond, because Me(19) is deshielded by the OH group (*q* at 22.22 instead of the expected 17–18 ppm in the absence of OH).

³) Should the configuration at C(7)=C(8) be (*Z*), H_b –C(9) would be deshielded by the OH group, like in the case of (+)-1 [1b].



4% NOE enhancement at H_a -C(9) is observed whereas H-C(7) is unaffected. The configuration at C(6) with respect to both the olefinic system and the epoxyactone unit derives from the observation of NOE enhancements of 6% at H-C(5), 7% at H-C(11), and 5% at H_b -C(9) on irradiation at H-C(7). The spatial position of H-C(1), bearing in mind that H_a -C(14) and H-C(1) are in a *trans* diaxial relationship, is derived from NOESY experiments which show that H_b -C(14) is spatially close to both H-C(7) and H-C(11). Finally, the configuration at C(2) rests on a NOESY relationship and a differential NOE of H-C(2) with only H-C(1). In accordance, the close proximity of H-C(2) to Me(17) is supported by a +3% NOE at H-C(2) on irradiation at MeC(17).

Owing to the presence of cembranolides in *A. coralloides* [1], it can be assumed that coralloidolide F((+)-2) derives from a cembranoid by 2,6-cyclization. This is not an isolated case: several other diterpenes from marine animals and terrestrial plants are known which may be thought to derive biogenetically from cembranoids. Marine examples thought to originate from cembranoids by ring opening and reclosure comprise three cases. One is coralloidolide C((+)-1) which involves 3,7-cyclization and was isolated from the same coral as (+)-2 [1b]. Another case is represented by eunicellin and the sarcodictyins which involve 2,11-cyclization and were isolated from the Mediterranean gorgonian *Eunicella stricta* [2] and the Mediterranean stolonifer *Sarcodictyon roseum* [3], respectively. Finally, there are the briareins and verecynarmins which involve 3,8-cyclization and were isolated from the Caribbean gorgonian *Briareum asbestinum* [4a]⁴⁾ and the octocoral *Veretillum cynomorium* [4b], respectively. Examples from terrestrial plants are the taxanes such as verticillol, isolated from *Sciadopitys verticillata* (Taxodiaceae) [5]. Finally, besides the asbestinins referred to above, other irregular diterpenoids such as the cubitanes (isolated from both termite soldiers [6] and the Caribbean gorgonian *Eunicea calyculata* [7]) are also thought to originate from cembranoids by ring opening and reclosure.

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⁴⁾ Together with the asbestinins which are thought to derive biogenetically from a eunicellin-type compound by migration of a Me group from C(12) to C(13) [4].

Experimental Part

1. *General.* All evaporations were carried out at reduced pressure. HPLC: *Merck-LiChrosorb Si-60* (7 μm) or *Merck-LiChrosorb CN* (7 μm). Reverse-phase HPLC: *Merck-LiChrosorb RP18* (7 μm) column. All HPLC columns were 25 \times 1 cm. Polarimetric data: *JASCO-DP-181* polarimeter. UV (λ_{max} in nm, ϵ in $\text{mol}^{-1} \cdot \text{l} \cdot \text{cm}^{-1}$): *Perkin-Elmer-Lambda-3* spectrophotometer. IR ($\tilde{\nu}_{\text{max}}$ in cm^{-1}): *Pye-Unicom-SP3-200S* spectrometer. NMR: *Varian-XL-300* (^{13}C -NMR at 75.43 MHz, ^1H -NMR at 300 MHz); δ 's (ppm) relative to internal Me_4Si (= 0 ppm) and J 's in Hz ('small' means $J < 0.5$). EI-MS (m/z (%)): *VG-70-70* spectrometer.

2. *Isolation.* The fraction at t_{R} 6.5 min from reverse-phase HPLC of the AcOEt extract [1b] was subjected to HPLC (*CN*, hexane/EtOH 84:16) collecting two fractions at t_{R} 17.8 and 20.1 min which proved to contain pure coralloidolide E [1b]⁵ (11.8 mg) and coralloidolide F [(+)-2; 1.1 mg).

3. *Coralloidolide F* (= (+)-*(3aR*,7R*,8R*,9R*,12S*,12aS*)-8,9-Epoxy-1,3a,6,7,8,9,10,11,12,12a-decahydro-3a-hydroxy-12-isopropenyl-2,5-dimethyl-1-oxocyclopentacycloundecene-9,7-carbolactone*; (+)-2). $[\alpha]_{\text{D}}^{20} = +76$ ($c = 0.05$, EtOH). UV (EtOH): 224 (6000). Differential NOE's (CDCl_3 ; irradiated proton \rightarrow NOE on the observed proton(s) (%)): 3 H-C(17) \rightarrow H_a-C(16) (4%), H-C(2) (3%); 3 H-C(18) \rightarrow H-C(5) (4%); 3 H-C(19) \rightarrow H_a-C(9) (4%); H-C(2) \rightarrow H-C(1) (4%); H-C(5) \rightarrow H-C(7) (6%); H-C(7) \rightarrow H-C(11) (7%), H-C(5) (6%), H_b-C(9) (5%). Significant NOESY: H-C(7)/H_b-C(14); H-C(11)/H_b-C(14), H-C(10), H_b-C(9); H-C(10)/H_b-C(9); H-C(2)/H-C(1). HR-MS: 344.16286 ± 0.004 ($\text{C}_{20}\text{H}_{24}\text{O}_5$, calc. 344.16237). MS: 344 (100, M^+), 329 (11), 307 (7), 293 (15), 279 (10), 255 (6), 193 (7), 167 (24), 149 (94). Linked scans (B/E) [8]: working on M^+ , a peak was observed at 329 ($[M - \text{CH}_3]^+$).

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⁵) In a previous paper [1b], we have inadvertently inverted t_{R} for coralloidolide D and E.