Six New Cembranolides from the Hainan Soft Coral *Lobophytum* sp.

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Six new cembrane diterpenes, lobophytolides A–F (**1**–**6**, resp.), along with six known related cembranoids, **7**–**12**, were isolated from the Hainan soft coral *Lobophytum* sp. Their structures, including their relative configuration, were elucidated by extensive analyses of the spectroscopic data and by comparison with related known compounds.

Introduction. – A large number of highly functionalized cembranoid diterpenes, sterols, and other related metabolites have been isolated and identified from marine soft corals, especially from the genera *Lobophytum*, *Sarcophyton*, and *Sinularia*. All of which belong to the family Alcyoniidae within the order of Alcyonacea [1][2]. *Lobophytum* sp. is a common soft-coral species widespread in Indo-Pacific reefs [3]. This species has been reported to contain cembranoid diterpenes [4–7], eudesmane-type diterpenoids [7], polyhydroxylated sterols [2][8], and various related compounds [9].

As part of our ongoing research with the purpose of discovering bioactive substances from Chinese marine invertebrates [10–13], we recently made a collection of the soft coral *Lobophytum* sp. off the Lingshui Bay, Hainan Province, China. Chemical investigation of the Et_2O-soluble fraction from an acetone extract of this soft coral led to the isolation of six new cembrane diterpenes, lobophytolides A–F (**1**–**6**, resp.), all containing an α-methylidene-γ-lactone moiety, together with six known related analogues (**7**–**12**). The present work deals with the isolation and structural elucidation of these new compounds.

Results and Discussion. – A freshly collected sample of *Lobophytum* sp. was immediately chilled to $-20°$ and kept frozen until used. A specimen of this soft coral was extracted exhaustively with acetone. This extract was then partitioned between Et_2O and H_2O. The Et_2O-soluble portion was repeatedly fractionated by SiO_2 and *Sephadex LH-20* column chromatography, followed by reversed-phase HPLC purification. This procedure led to the isolation of twelve α-methylene-γ-lactone-containing cembranoids, of which six (the lobophytolides A–F[1]), **1**–**6**) are reported for the first time. The known compounds were identified as (3*E*,7*E*,11*E*)-cembra-3,7,11,15-tetraen-

[1]) For systematic names, see *Exper. Part*.

16,14-olide (**7**) [14], sinularolides B, C, and E (**8**–**10**, resp.) [15], (7*E*,11*E*)-18-acetoxy-3,4-epoxy-13α-hydroxy-7,11,15(17)-cembratrien-16,14-olide (**11**) [5][16] and (7*E*,11*E*)-18-acetoxy-3,4-epoxy-13β-hydroxy-7,11,15(17)-cembratrien-16,14-olide (**12**) [5][16], respectively (*Fig. 1*) by analysis of their NMR spectra and by comparison with the pertinent data reported in the literature.

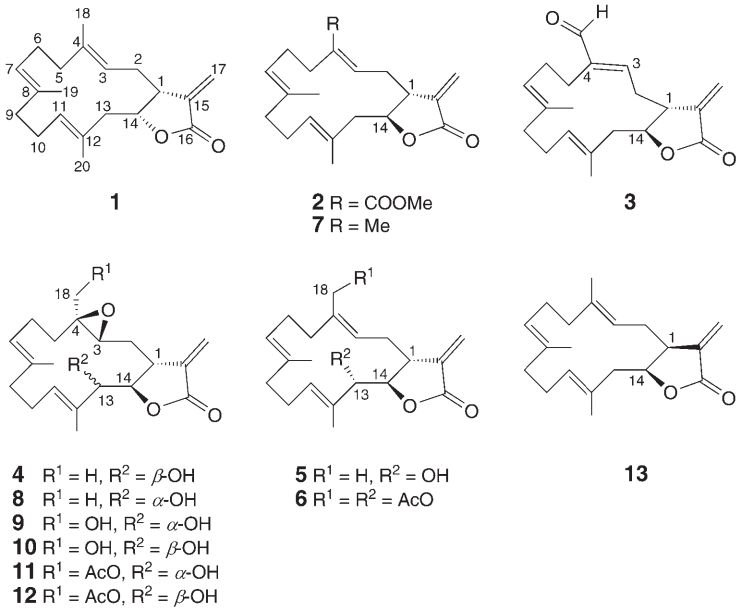

Fig. 1. *Structure of compounds* **1**–**13**

Lobophytolide A (**1**) was obtained as a colorless oil. The molecular formula, $C_{20}H_{28}O_2$, consistent with seven degrees of unsaturation, was determined by HR-ESI-MS ($[M+Na]^+$ at *m*/*z* 323.1992). Analysis of 1D- and 2D- (^{1}H,^{1}H-COSY, HMQC, HMBC, and ROESY) NMR spectra pointed to a typical cembrane structure with three trisubstituted double bonds, namely C(3)=C(4), C(7)=C(8), and C(11)=C(12), and to a *cis*-fused α-methylidene-γ-butanolide moiety at C(1)/C(14) as depicted in *Fig. 1*. The NMR data of **1** (*Tables 1* and *2*) were almost identical with those of model compound **13**, which was obtained earlier during a synthetic and a SAR study of some gorgonian cembranolides [17]. In fact, **1** differs from **13** only by the sign of the optical rotation ($[\alpha]_D^{25} = -65$ ($c = 0.08$, $CHCl_3$) for **1** and $+31.4$ ($c = 8.5$, $CHCl_3$) for **13** [17]). As a consequence, the structure of lobophytolide A was determined as (1*R*,3*E*,7*E*,11*E*,14*R*)-3,7,11,15-tetraen-16,14-olide[1]) (**1**), *i.e.*, the optical antipode of **13**. We wish to point out that the proposed absolute configuration of **1** is well consistent with the general empirical rule reported in [18], namely that all cembrane diterpenes of known absolute configuration at C(1) reported from the order Alcyonacea belong to the α series, while all cembranoids isolated from the order Gorgonacea belong to the β series [19].

Table 1. *^{1}H-NMR Data*[a]) *for Compounds* **1**–**6**. Measured in $CDCl_3$; δ in ppm, J in Hz.

	1	**2**	**3**	**4**	**5**	**6**
H−C(1)	3.07–3.10 (*m*)	2.82–2.83 (*m*)	2.27–2.31 (*m*)	3.28–2.33 (*m*)	2.73–2.75 (*m*)	2.74–2.78 (*m*)
H_a−C(2)	2.21–2.23 (*m*)	2.54–2.56 (*m*)	2.52–2.56 (*m*)	1.40–1.44 (*m*)	2.20–2.25 (*m*)	2.28–2.31 (*m*)
H_b−C(2)	2.20–2.23 (*m*)	2.55–2.58 (*m*)	2.60–2.64 (*m*)	1.74–1.76 (*m*)	2.25–2.30 (*m*)	2.36–2.39 (*m*)
H−C(3)	4.90 (*dd*, *J* = 6.5, 6.5)	5.70 (*dd*, *J* = 7.7, 7.7)	6.49 (*dd*, *J* = 7.3, 7.3)	2.75 (*dd*, *J* = 3.0, 14.6)	4.99 (*dd*, *J* = 7.3, 7.3)	5.27 (*dd*, *J* = 6.7, 6.7)
H_a−C(5)	1.95–1.98 (*m*)	2.25–2.28 (*m*)	2.08–2.10 (*m*)	1.24–1.27 (*m*)	2.12–2.16 (*m*)	2.22–2.25 (*m*)
H_b−C(5)	2.12–2.15 (*m*)	2.51–2.55 (*m*)	2.28–2.32 (*m*)	2.01–2.05 (*m*)	2.12–2.16 (*m*)	2.22–2.25 (*m*)
H_a−C(6)	2.10–2.14 (*m*)	2.13–2.16 (*m*)	2.19–2.22 (*m*)	2.08–2.01 (*m*)	2.13–2.18 (*m*)	2.14–2.17 (*m*)
H_b−C(6)	2.11–2.13 (*m*)	2.25–2.27 (*m*)	2.40–2.43 (*m*)	2.17–2.21 (*m*)	2.27–2.30 (*m*)	2.26–2.28 (*m*)
H−C(7)	4.83 (*dd*, *J* = 6.0, 6.0)	4.89 (*dd*, *J* = 5.9, 5.9)	4.92 (*dd*, *J* = 6.6, 6.6)	5.00–5.03 (*m*)	4.87 (*dd*, *J* = 3.9, 7.8)	4.89–4.92 (*m*)
H_a−C(9)	2.13–2.15 (*m*)	2.06–2.09 (*m*)	1.93–1.95 (*m*)	2.16–2.18 (*m*)	2.09–2.12 (*m*)	2.10–2.14 (*m*)
H_b−C(9)	2.13–2.16 (*m*)	2.06–2.09 (*m*)	2.14–2.16 (*m*)	2.30–2.34 (*m*)	2.10–2.14 (*m*)	2.10–2.14 (*m*)
H_a−C(10)	2.11–2.12 (*m*)	2.07–2.10 (*m*)	2.18–2.22 (*m*)	2.50–2.53 (*m*)	2.10–2.14 (*m*)	2.14–2.17 (*m*)
H_b−C(10)	2.11–2.12 (*m*)	2.25–2.27 (*m*)	2.18–2.22 (*m*)	2.50–2.53 (*m*)	2.31–2.35 (*m*)	2.25–2.28 (*m*)
H−C(11)	4.99 (*dd*, *J* = 6.6, 6.6)	5.06–5.09 (*m*)	5.02 (*dd*, *J* = 7.2, 7.2)	5.59–5.62 (*m*)	5.31 (*d*, *J* = 7.9, 7.9)	5.36–5.39 (*m*)
H_α−C(13)	2.23–2.26 (*m*)	2.08–2.11 (*m*)	2.16–2.19 (*m*)	4.40 (*s*)	3.74 (*d*, *J* = 7.2)	4.93 (*d*, *J* = 6.9)
H_β−C(13)	2.33–2.35 (*m*)	2.42–2.46 (*m*)	2.54–2.57 (*m*)	–	–	–
H−C(14)	4.67 (*dt*, *J* = 4.2, 7.0)	4.41 (*dt*, *J* = 9.2, 3.0)	4.41 (*dt*, *J* = 9.9, 3.8)	4.18 (*dd*, *J* = 1.8, 7.2)	4.17 (*dd*, *J* = 2.7, 7.2)	4.28 (*dd*, *J* = 2.2, 6.9)
H_a−C(17)	5.53 (*d*, *J* = 2.6)	5.69 (*d*, *J* = 2.1)	5.69 (*d*, *J* = 2.2)	6.00 (*d*, *J* = 2.8)	5.66 (*d*, *J* = 1.8)	5.69 (*d*, *J* = 1.5)
H_b−C(17)	6.18 (*d*, *J* = 2.6)	6.27 (*d*, *J* = 2.1)	6.37 (*d*, *J* = 2.6)	6.25 (*d*, *J* = 3.5)	6.27 (*d*, *J* = 2.1)	6.30 (*d*, *J* = 1.6)
Me(18), H−C(18), or CH_2(18)	1.67 (*s*)	–	9.40 (*s*)	1.21 (*s*)	1.57 (*s*)	4.55 (*s*)
H−C(19)	1.56 (*s*)	1.54 (*s*)	1.52 (*s*)	1.59 (*s*)	1.58 (*s*)	1.60 (*s*)
H−C(20)	1.59 (*s*)	1.64 (*s*)	1.63 (*s*)	1.70 (*s*)	1.69 (*s*)	1.71 (*s*)
MeO	–	3.75 (*s*)	–	–	–	–
AcO	–	–	–	–	–	2.06 (*s*)[b])
AcO	–	–	–	–	–	2.07(*s*)[b])

[a]) *Bruker DRX-400* NMR spectrometer; assignments made with the aid of HMQC and HMBC experiments. [b]) Interchangeable assignments.

Table 2. *^{13}C-NMR Data*[a]) *for Compounds* **1**–**7**. Measured in $CDCl_3$; δ in ppm, J in Hz.

	1	**2**	**3**	**4**	**5**	**6**	**7**
C(1)	45.1 (*d*)	44.1 (*d*)	42.4 (*d*)	37.2 (*d*)	42.3 (*d*)	42.0 (*d*)	44.8 (*d*)
C(2)	27.8 (*t*)	34.8 (*t*)	32.2 (*t*)	33.5 (*t*)	33.9 (*t*)	33.5 (*t*)	33.7 (*t*)
C(3)	126.4 (*d*)	139.2 (*d*)	139.2 (*d*)	63.4 (*d*)	120.2 (*d*)	126.3 (*d*)	120.4 (*d*)
C(4)	133.3 (*s*)	133.7 (*s*)	144.5 (*s*)	60.6 (*s*)	137.6 (*s*)	136.2 (*s*)	137.1 (*s*)
C(5)	38.8 (*t*)	33.9 (*t*)	24.3 (*t*)	37.9 (*t*)	38.6 (*t*)	34.7 (*t*)	38.6 (*t*)
C(6)	24.3 (*t*)	25.0 (*t*)	24.7 (*t*)	24.3 (*t*)	24.4 (*t*)	24.2 (*t*)	24.3 (*t*)
C(7)	124.9 (*d*)	123.0 (*d*)	123.2 (*d*)	124.4 (*d*)	123.9 (*d*)	123.8 (*d*)	124.1 (*d*)
C(8)	136.2 (*s*)	134.7 (*s*)	135.77 (*s*)	134.5 (*s*)	133.4 (*s*)	133.7 (*s*)	133.4 (*s*)
C(9)	39.1 (*t*)	38.0 (*t*)	39.2 (*t*)	38.7 (*t*)	37.9 (*t*)	37.7 (*t*)	38.1 (*t*)
C(10)	24.5 (*t*)	24.4 (*t*)	25.3 (*t*)	24.5 (*t*)	24.2 (*t*)	23.8 (*t*)	24.4 (*t*)
C(11)	121.5 (*d*)	128.6 (*d*)	129.4 (*d*)	127.7 (*d*)	130.8 (*d*)	131.6 (*d*)	128.1 (*d*)
C(12)	130.5 (*s*)	129.3 (*s*)	129.3 (*s*)	131.1 (*s*)	132.4 (*s*)	130.3 (*s*)	129.5 (*s*)
C(13)	39.3 (*t*)	44.8 (*t*)	44.6 (*t*)	73.5 (*d*)	79.1 (*d*)	78.7 (*d*)	44.9 (*t*)
C(14)	80.6 (*d*)	81.3 (*d*)	81.0 (*d*)	82.1 (*d*)	84.4 (*d*)	81.5 (*d*)	81.8 (*d*)
C(15)	140.4 (*s*)	136.2 (*s*)	138.3 (*s*)	139.9 (*s*)	138.9 (*s*)	138.0 (*s*)	139.6 (*s*)
C(16)	170.3 (*s*)	170.0 (*s*)	169.8 (*s*)	170.0 (*s*)	170.0 (*s*)	169.3 (*s*)	170.4 (*s*)
C(17)	120.0 (*t*)	122.8 (*t*)	123.3 (*t*)	123.2 (*t*)	122.7 (*t*)	122.7 (*t*)	122.3 (*t*)
C(18)	16.5 (*q*)	167.9 (*s*)	194.7 (*d*)	16.8 (*q*)	15.9 (*q*)	61.3 (*t*)	17.4 (*q*)
C(19)	15.8 (*q*)	16.5 (*q*)	15.7 (*q*)	15.5 (*q*)	16.6 (*q*)	16.2 (*q*)	16.5 (*q*)
C(20)	15.5 (*q*)	17.3 (*q*)	17.0 (*q*)	15.3 (*q*)	13.1 (*q*)	13.7 (*q*)	17.4 (*q*)
MeO	–	51.4 (*q*)	–	–	–	–	–
MeCO_2	–	–	–	–	–	20.7 (*q*)[b])	–
MeCO_2	–	–	–	–	–	20.8 (*q*)[b])	–
Me*C*O_2	–	–	–	–	–	170.6 (*s*)[b])	–
Me*C*O_2	–	–	–	–	–	170.0 (*s*)[b])	–

[a]) *Bruker DRX-400* NMR spectrometer; assignments made by HMQC and HMBC experiments.
[b]) Interchangeable assignments.

Lobophytolide B (**2**) was also obtained as colorless oil. The HR-ESI-MS of **2** indicated the molecular formula $C_{21}H_{28}O_4$, 44 mass units more than that of **1** and of the co-occurring compound **7**. Comparison of the ^{13}C-NMR data (*Table 2*) of compounds **2** and **7** showed that **2** possesses the same α-methylidene-γ-lactone-containing cembrane-type diterpenoid framework as **7**, with the exception of signals assigned to C(3)–C(5), C(15), and C(18). The presence of a COOMe group in **2** was evident as deduced by the diagnostic NMR signals (δ(C) 167.9 (*s*, C(18)); 51.4 (*q*, C(21)); δ(H) 3.75 (*s*, Me(21)). Further, a HMBC correlation from H–C(3) (δ(H) 5.70 (*dd*, J = 7.7, 7.7 Hz, 1 H) to C(18) led to the placement of the COOMe group at C(4). The substitution of Me(18) by a COOMe group significantly deshielded (+18.8 ppm) the ^{13}C-NMR signal of C(3), while C(4) was shifted slightly upfield (– 3.4 ppm) relative to the ^{13}C-NMR data of **7**. The relative configuration of **2** at C(1) and C(14) was tentatively assigned to be the same as in **7**, based mainly on the comparison of the ^{13}C-NMR chemical shifts of C(1), C(2), C(13), and C(14) (*Table 2*), showing almost identical δ values in **2** and **7** but clearly distinct from those of lobophytolide A (**1**). In particular, the diagnostic downfield shift of C(2) (+ 7.0 ppm) due to absence of the γ-gauche effect was observed in **2**, compared to **1**. Thus, the lactone ring at C(1) and C(14) [18] was *trans*-fused and

the α absolute configuration at C(1) was suggested according to the empirical rule for cembranolides from Alcyonacea (see above) [19].

Lobophytolide C (**3**) has the molecular formula $C_{20}H_{26}O_3$ determined by HR-ESI-MS ($[M+Na]^+$ at m/z 337.1783). The IR, and ^{1}H- and ^{13}C-NMR spectra of **3** were closely related to those of **2**, suggesting an α-methylidene- and γ-lactone-containing cembranolide structure. In fact, **3** differs from **2** concerning the substituent at C(4), where the COOMe group in **2** is replaced by an aldehyde function (δ(C) 194.7 (*s*, C(18)); δ(H) 9.40 (*s*, H–C(18)), in agreement with the 30 mass unit difference between them. Detailed analysis of HMBC spectrum allowed an unambiguous definition of the relative configuration of **3**. In particular, HMBC correlations between H–C(18) (δ(H) 9.40) and C(4) (δ(C) 144.5), C(5) (δ(C) 24.3), and between H_a–C(5) (δ(H) 2.08–2.10) and C(18) (δ(C) 194.7) are consistent with the location of the aldehyde group at C(4).

In analogy to **2**, the ^{13}C-NMR chemical shifts of Me(19) and Me(20) (<20 ppm) [20] delineated an (*E*)-configuration to C(7)=C(8), and C(11)=C(12). The (*E*)-geometry for C(3)=C(4) was determined by a positive ROESY correlation between H–C(3) and C(18)HO. The relative configuration at C(1) and C(14) was established to be the same as that of **2** by comparison of the relevant ^{13}C-NMR data. In fact, the ^{13}C-NMR chemical shifts of **2** and **3** are very similar, and, in particular, C(2) and C(13) displayed the same diagnostic downfield shifts.

Lobophytolide D (**4**) was obtained as a colorless oil. Its molecular formula, $C_{20}H_{28}O_4$, was identical with that of the co-occurring compound **8** as indicated by HR-ESI-MS ($[M+Na]^+$ at m/z 355.1889). The IR, ^{1}H-, ^{13}C-NMR, and DEPT data of **4** were also comparable with those of **8** [15], with the exception of the ^{13}C-NMR chemical shift of C(13) in **4**, which resonated at δ 73.5 in contrast to that in **8** (δ(C) 81.6), and the ^{1}H-NMR chemical shifts of H–C(1) (δ(H) 3.28–2.33 in **4**; δ(H) 2.32 in **8**), and H–C(13) (δ(H) 4.40), which appeared as a broad *singlet* instead of a *doublet* as observed for **8**. The remaining NMR data of **4** were almost identical to those of **8**, indicating the same relative configurations at C(1), C(3), C(4), and C(14), respectively, for both compounds. The observed differences can be rationalized if the two compounds are C(13)-epimers. Since the OH group at C(13) of **8** was α-oriented, the opposite configuration at this center is therefore tentatively suggested for lobophytolide D (**4**). Analogous stereochemical relationships were recently [15] described for compounds **9** and **10**. It is interesting to point out that compound **9**, named sinularolide B by *Lin* and co-workers [15], was suggested to be an epimer at C(3) of deacetyl-13-hydroxylobolide, a cembranoid previously isolated [16] from Red Sea *L. crassum*. Interestingly, when we carefully compared their NMR data, we found that the two compounds are actually identical and a complete correspondence of the ^{13}C-NMR data is obtained inverting the assignments for C(3) (δ(C) 63.2) and C(18) (δ(C) 61.8). Obviously, the structure of sinularolide B, which was declared as a new compound by *Lin* and co-workers, should be revised as depicted for lobolide (**9**).

Lobophytolide E (**5**) yielded an HR-ESI-MS peak at m/z 339.1932, 16 mass units more than that of **7**, indicating that **5** is a hydroxylated derivative of **7**. Comparison of the ^{13}C-NMR spectra of **5** and **7**, in combination with COSY, HMQC, and HMBC data, allowed us to locate the additional OH group at C(13). In fact, the ^{1}H,^{1}H-COSY clearly correlated H–C(13) (δ(H) 3.74 (*d*, J = 7.2 Hz)) to H–C(14) (δ(H) 4.17 (*dd*, J = 2.7, 7.2

Hz)), whereas HMBC cross-peaks were observed between H–C(13) and C(14) (δ(C) 84.4) and C(12) (δ(C) 132.4). As in the case of **2** and **3**, the γ-lactone is *trans*-fused to the 14-membered carbocycle on the basis of the diagnostic chemical shift of C(2) and by analysis of the ROESY spectrum in which H–C(1) (δ(H) 2.73–2.75) correlated with H–C(13), and H_b–C(2) (δ(H) 2.25–2.30) is correlated with H–C(14) (*Fig. 2*). Contrary to compound **4**, the OH group at C(13) is α-oriented on the basis of the coupling pattern of H–C(13) (*d*, $J = 7.2$ Hz), the downfield ^{13}C-NMR resonance of C(13) (δ(C) 79.1), and the chemical shift of H–C(1) (δ(H) 2.73–2.75). It is worthwhile to note that the ^{13}C-NMR chemical shift of C(13), the coupling pattern of H–C(13), and the ^{1}H-NMR chemical shift of H–C(1) are quite diagnostic and can be used to determine the relative configuration at C(13). For example, in case of compounds **5**, **8**, **9**, and **11**, all having an α-oriented OH group at C(13), the ^{1}H-NMR signal of H–C(13) appeared as a *doublet*, the ^{13}C-NMR chemical shift of C(13) resonates at δ *ca.* 80 ppm, and the H–C(1) δ value is always smaller than 3 ppm; while in the case of β-orientation of HO–C(13) (*e.g.*, compounds **10** and **12**), the H–C(13) signal appears as a broad *singlet*, and the C(13) δ value shows up at *ca.* 73 ppm, and H–C(1) δ value is at *ca.* 3.30 ppm.

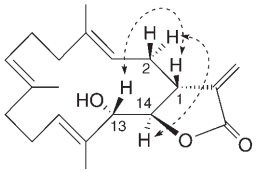

Fig. 2. *Selected ROESY correlations in compound* **5**

Lobophytolide F (**6**) was shown to be an acetylated and acetoxylated derivative of **5**. The HR-ESI-MS of **6** established the molecular formula $C_{24}H_{32}O_6$ through the presence of the pseudo-molecular ion $[M + Na]^+$ at *m*/*z* 439.2083. Analysis of the ^{1}H- and ^{13}C-NMR data of **6** (*Tables 1* and *2*) established a great similarity to those of **5**, deviating only at C(4) and C(13), where two AcO groups were attached. Acetylation of HO–C(13) deshields H–C(13) from δ(H) 3.74 in **5** to 4.93 in **6**, while the presence of an AcO bearing CH_2 group at C(4) was supported by both the downfield ^{1}H-NMR signal at δ(H) 4.55 (*s*, CH_2(18)) and by HMBC correlations between CH_2(18) and C(4) (δ(C) 136.2), and the ester CO group resonating at δ 170.6. These data (*Tables 1* and *2*) confirm structure **6** for lobophytolide F.

In conclusion, α-methylene-γ-lactone-containing cembranoids represent a characteristic structural group among the constituents of soft corals, and the number of this kind of diterpenes is increasing rapidly. However, it should be noted that to correctly determine the fusion pattern of C(1)/C(14) by NOE technique or H-atom coupling constant still represents a challenge, and sometimes the derived conclusion can be ambiguous due to the conformational flexibility of the macrocycle. Our present study provided some helpful information to delineate the *cis*- or *trans*-junction of the lactone ring and to determine whether the OH group at C(13) is α- or β-oriented. Moreover, the case of lobophytolide A (**1**) confirms the validity of the empirical rule for the prediction of the absolute configuration at C(1) of cembranes, suggested almost thirty

years ago [19]. Further studies should be conducted to understand the biological/ecological role of these metabolites in the life cycle of the soft coral, as well as to screen their cytotoxic and anti-inflammatory activities.

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Experimental Part

General. Column chromatography (CC): commercial SiO_2 (*Qing Dao Hai Yang Chemical Group Co.*; 200–300 mesh), and *Sephadex LH-20* (*Amersham Biosciences*). TLC: precoated SiO_2 plates (*Yan Tai Zi Fu Chemical Group Co.*; *G60*, *F-254*). M.p.: *X-5* apparatus, uncorrected. Optical rotation: *Perkin-Elmer 341* polarimeter. UV Spectra: *756 CRT* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet Magna FT-IR 750* spectrophotometer; ν_{max} in cm^{-1}. ^{1}H- and ^{13}C-NMR: *Varian Mercury 400* (400 MHz for ^{1}H, and 100 MHz for ^{13}C) spectrometer; chemical shifts δ in ppm, with residual $CHCl_3$ (δ(H) 7.26, δ(C) 77.0) or CD_3OD (δ(H) 3.30, δ(C) 49.5) as internal standard, coupling constant *J* in Hz. HR-ESI-MS: *Q-TOF Micro* LC/MS/MS spectrometer in *m*/*z*.

Animal Material. Specimen of the soft coral *Lobophytum* sp. were collected off the Lingshui Bay, Hainan Province, China, in July 2004, at 20 m below sea level, and were frozen immediately after collection. The specimen was subsequently identified by Associate Prof. *H. Huang* of South China Sea Institute of Oceanology, Chinese Academy of Sciences. A voucher specimen is available for inspection at the Institute of Materia Medica, SIBS-CAS.

Extraction and Isolation. The frozen animals (431 g dry weight) were cut into small pieces and exhaustively extracted with acetone at r.t. (3×3 l). The org. extract was evaporated to give a residue, which was partitioned between Et_2O and H_2O. The Et_2O soln. was concentrated under reduced pressure to give a dark brown residue (18.5 g), which was fractioned by gradient SiO_2 CC (0–100% acetone in light petroleum ether (PE)), yielding five fractions (*A*–*E*). *Fr. B* eluted with PE/Me_2CO 98:2 was further purified by a second SiO_2 CC eluting with PE/Et_2O 97:3 to afford **7** (22.8 mg). *Fr. C* eluted with PE/acetone 9:1 was further chromatographed by SiO_2 CC eluting with PE/Me_2CO 95:5, and successively further purified by RP-HPLC (semi-prep. *OSD-HG-5* (5 μm, 250×10 mm)) to yield **1** (1.7 mg), **2** (21.8 mg), **3** (0.7 mg), **4** (11.2 mg), **5** (6.3 mg), and **6** (42.2 mg), resp. *Fr. E* eluted with PE/acetone 3:2 was treated in the same way as that for *Fr. C* by further eluting with PE/acetone from 9:1 to 5:5 to give **8** (5.5 mg), **9** (153.0 mg), **10** (65.3 mg), **11** (5.4 mg), and **12** (43.2 mg), resp.

Lobophytolide A (=*(3a*R,*5*E,*9*E,*13*E,*15a*R*)-3a,4,7,8,11,12,15,15a-Octahydro-6,10,14-trimethyl-3-methylidenecyclotetradeca[*b*]furan-2(3*H*)-one*; **1**). Colorless oil. $[\alpha]_D^{25} = -65$ ($c = 0.08$, $CHCl_3$). UV (MeOH): 204 (2.12). IR (KBr): 3419, 1759, 1659, 960. ^{1}H-NMR and ^{13}C-NMR: see *Tables 1* and *2*. HR-ESI-MS: 323.1992 ($[M+Na]^+$; calc. 323.1987).

Lobophytolide B (=*Methyl (3a*R,*5*Z,*9*E,*13*E,*15a*S*)-2,3,3a,4,7,8,11,12,15,15a-Decahydro-10,14-dimethyl-3-methylidene-2-oxocyclotetradeca[*b*]furan-6-carboxylate*; **2**). Colorless oil. $[\alpha]_D^{25} = +44$ ($c =$ 0.78, $CHCl_3$). UV (MeOH): 202 (1.95). IR (KBr): 3386, 2917, 2850, 1762, 1714, 1652, 1436, 1382, 1216, 1126, 957. ^{1}H-NMR and ^{13}C-NMR: see *Tables 1* and *2*. HR-ESI-MS: 367.1865 ($[M+Na]^+$; calc. 367.1885).

Lobophytolide C (=*(3a*R,*5*E,*9*E,*13*E,*15a*S*)-2,3,3a,4,7,8,11,12,15,15a-Decahydro-10,14-dimethyl-3-methylidene-2-oxocyclotetradeca[*b*]furan-6-carbaldehyde*; **3**). Colorless oil. $[\alpha]_D^{25} = -15$ ($c = 0.12$, $CHCl_3$). UV (MeOH): 202 (2.43). IR (KBr): 3397, 1740, 1692, 1596, 975. ^{1}H-NMR and ^{13}C-NMR: see *Tables 1* and *2*. HR-ESI-MS: 337.1783 ($[M+Na]^+$; calc. 337.1780).

Lobophytolide D (=*(1a*R,*4*E,*8*E,*10*R,*10a*R,*13a*R,*14a*R*)-2,3,6,7,10,10a,13,13a,14,14a-Decahydro-10-hydroxy-1a,5,9-trimethyl-13-methylideneoxireno[4,5]cyclotetradeca[1,2-*b*]furan-12(1a*H*)-one*; **4**). Colorless oil. $[\alpha]_D^{25} = -81$ ($c = 0.60$, $CHCl_3$). UV (MeOH): 206 (2.07). IR (KBr): 3402, 1758, 960. ^{1}H-NMR and ^{13}C-NMR: see *Tables 1* and *2*. HR-ESI-MS: 355.1889 ($[M+Na]^+$; calc. 355.1885).

Lobophytolide E (=*(3a*R,5E,*9*E,*13*E,*15*S,*15a*R*)-3a,4,7,8,11,12,15,15a-Octahydro-15-hydroxy-6,10,14-trimethyl-3-methylidenecyclotetradeca[*b*]*furan-2(3*H*)-one*; **5**). Colorless oil. $[\alpha]_D^{25} = +12$ ($c =$ 0.18, $CHCl_3$). UV (MeOH): 203 (2.52). IR (KBr): 3384, 1747, 1685, 976. ^{1}H-NMR and ^{13}C-NMR: see *Tables 1* and *2*. HR-ESI-MS: 339.1932 ($[M + Na]^+$; calc. 339.1936).

Lobophytolide F (=*(3a*R,*5Z,9*E,*13*E,*15*S,*15a*R*)-15-(Acetyloxy)-6-[(acetyloxy)methyl]-3a,4,7,8,11,12,15,15a-octahydro-10,14-dimethyl-3-methylidenecyclotetradeca[*b*]*furan-2(3*H*)-one*; **6**). Colorless oil. $[\alpha]_D^{25} = +14$ ($c = 0.14$, $CHCl_3$). UV (MeOH): 207 (2.70). IR (KBr): 3429, 1760, 1742, 1739, 1645, 968. ^{1}H-NMR and ^{13}C-NMR: *see Tables 1* and *2*. HR-ESI-MS: 439.2083 ($[M + Na]^+$; calc. 439.2097).

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