Further New Cembranoid Diterpenes from the Hainan Soft Coral *Sarcophyton latum*

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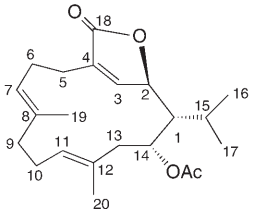
Four new cembranoid diterpenes, sarcophytonolides I–L (**1**–**4**), were isolated from the Hainan soft coral *Sarcophyton latum*. Their structures were established by detailed analysis of 1D and 2D NMR spectra and by comparison with related model compounds.

Introduction. – Cembranoid diterpenes are characteristic secondary metabolites of the genus *Sarcophyton* (Family Alcyoniidae). Ecologically, these compounds play functional roles in the survival of octocorals such as defensive, competitive, reproductive, and possibly pheromonal roles [1]. Bioassay screening of cembranoids has demonstrated some of them to have cytotoxic, ichthytoxic, and anti-inflammatory activities [2]. In particular, the recent discovery of the potent inhibitor of Ras farnesyl transferase, which is a cembranoid diterpene, has further enhanced the interest in these metabolites [3].

The soft coral of the genus *Sarcophyton* are prolific in the South China Sea. In our previous studies on the Hainan soft corals of the genus *Sacrophyton* [4][5], eight new cembranoids, sarcophytonolides A–H, have been isolated and structurally characterized. Recently, during our continuing studies on bioactive substances from Hainan marine organisms [6], we made another collection of *Sacrophyton latum* off the coast of Monkey Island, Lingshui, China. Chemical investigation of the Et_2O-soluble fraction from the acetone extract of the animal resulted in the isolation of four new cembranoid diterpenes, sarcophytonolides I–L (**1**–**4**). Interestingly, compounds **1**–**4** are structurally related to the previously reported sacrophytonolides C–H, exemplified by sacrophytonolide D (**5**), in that all contain an α,β-unsaturated butenolactone moiety. This paper describes the isolation and structural determination of these new compounds.

Results and Discussion. – Specimens of *S. latum* were collected off Monkey Island, Hainan Province, China, in December 2001, and kept frozen prior to extraction. The workup for the extraction and isolation of the cembranolides was basically performed as previously reported [4][5]. This common procedure yielded four new compounds, named sacrophytonolides I (**1**; 3.2 mg), J (**2**; 8.9 mg), K (**3**; 1.2 mg), and L (**4**; 2.3 mg).

Sarcophytonolide I (**1**) was obtained as colorless oil. Its molecular formula $C_{22}H_{32}O_4$ was deduced from its HR-EI-MS (M^+ at m/z 360.2289). Thus, seven degrees of



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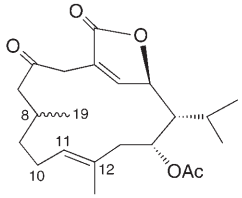

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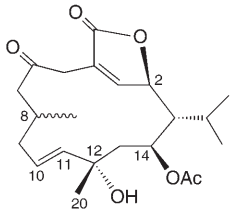

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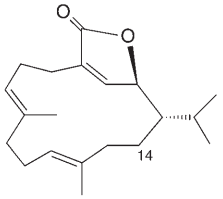

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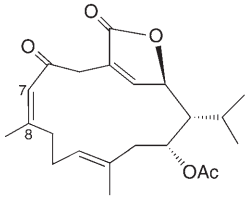

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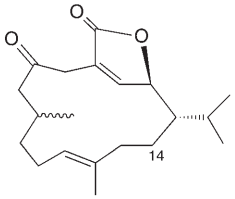

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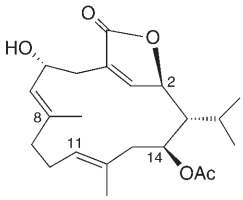

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unsaturation were determined for **1**. Compound **1** exhibited IR absorptions indicative of the presence of lactone and ester carbonyl moieties ($\tilde{\nu}_{max}$ 1759 and 1736 cm^{-1}). A strong UV absorption at λ_{max} 235 nm (log ε 4.22) suggested the presence of an α,β-unsaturated γ-lactone moiety. A comparison of the ^{1}H- and ^{13}C-NMR data of **1** (*Tables 1* and *2*) with those of sarcophytonolide D (**5**), previously isolated from the Hainan soft coral *S. tortuosum* [4], revealed great similarities. The spectral data allowed to determine the structure of sarcophytonolide I as **1**[1]).

The ^{1}H- and ^{13}C-NMR and DEPT spectra of **1** revealed the presence of five Me, five sp^3 CH_2, four sp^3 CH, and three sp^2 CH groups, and of five sp^2 quaternary C-atoms. The presence of an isopropyl group was deduced from the following NMR data: δ(H) 1.08 (*d*, J = 7.3 Hz, 3 H) and 1.09 (*d*, J = 7.3 Hz, 3 H), and δ(C) 18.8 (*q*), 25.2 (*q*), and 25.8 (*d*). Two isolated Me-bearing trisubstituted C=C bonds were disclosed by the NMR data: δ(H) 4.89–4.91 (*m*, H–C(7)) and 1.46 (*s*, Me(19)), and δ(C) 123.8 (*d*, C(7)), 136.0 (*s*, C(8)), and 15.3 (*q*, C(19)); δ(H) 4.95–4.97 (*m*, H–C(11)) and 1.63 (*s*, Me(20), and δ(C) 125.9 (*d*, C(11)), 133.0 (*s*, C(12)), and 18.9 (*q*, C(20))[1]). Three C=C bonds and two ester C=O accounted for five degrees of unsaturation. As a consequence, the remaining two degrees of unsaturation were

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

Table 1. *^{1}H-NMR Data*[a]) (500 MHz) *of Compounds* **1**–**4**[1]). δ in ppm, J in Hz.

	1	**2**	**3**	**4**
H–C(1)	1.44–1.46 (*m*)	1.65–1.67 (*m*)	1.76–1.80 (*m*)	1.29–1.32 (*m*)
H–C(2)	4.88 (*d*, *J* = 11.3)	5.06 (*d*, *J* = 11.7)	5.08–5.10 (*m*)	4.65 (*d*, *J* = 10.0)
H–C(3)	7.34 (*s*)	7.61 (*s*)	7.50 (*s*)	7.11 (*s*)
H_a–C(5)	2.22–2.26 (*m*)	3.50 (*d*, *J* = 14.8)	3.38 (*d*, *J* = 15.0)	2.43–2.46 (*m*)
H_b–C(5)	2.43–2.47 (*m*)	3.23 (*d*, *J* = 14.8)	3.28 (*d*, *J* = 15.0)	2.55–2.59 (*m*)
H_a–C(6)	2.11–2.14 (*m*)	–	–	2.09–2.12 (*m*)
H_b–C(6)	2.19–2.23 (*m*)	–	–	2.09–2.12 (*m*)
H_a–C(7)	4.89–4.91 (*m*)	2.47 (*dd*, *J* = 12.2, 6.6)	2.80 (*dd*, *J* = 16.0, 4.8)	4.96–4.98 (*m*)
H_b–C(7)	–	2.19–2.21 (*m*)	2.08–2.11 (*m*)	–
H–C(8)	–	1.54–1.57 (*m*)	1.91–1.95 (*m*)	–
H_a–C(9)	2.13–2.17 (*m*)	1.25–1.29 (*m*)	2.06–2.10 (*m*)	2.10–2.14 (*m*)
H_b–C(9)	2.13–2.17 (*m*)	1.44–1.47 (*m*)	2.07–2.10 (*m*)	2.10–2.14 (*m*)
H_a–C(10)	2.50–2.53 (*m*)	2.00–2.04 (*m*)	5.56 (*ddd*, *J* = 16.0, 8.7, 6.2)	2.21–2.25 (*m*)
H_b–C(10)	2.58–2.62 (*m*)	2.00–2.04 (*m*)	–	2.21–2.25 (*m*)
H–C(11)	4.95–4.97 (*m*)	5.00–5.03 (*m*)	5.29 (*d*, *J* = 16.0)	4.95–4.97 (*m*)
H_a–C(13)	2.22–2.26 (*m*)	2.19–2.24 (*m*)	2.23 (*dd*, *J* = 15.3, 6.3)	2.05–2.09 (*m*)
H_b–C(13)	2.22–2.26 (*m*)	2.19–2.24 (*m*)	1.72 (*dd*, *J* = 15.3, 5.1)	2.05–2.09 (*m*)
H_a–C(14)	5.19–5.22 (*m*)	4.98–5.01 (*m*)	5.05–5.07 (*m*)	1.58–1.61 (*m*)
H_b–C(14)	–	–	–	1.22–1.26 (*m*)
H–C(15)	2.19–2.24 (*m*)	2.19–2.23 (*m*)	2.09–2.12 (*m*)	2.10–2.13 (*m*)
Me(16)	1.08 (*d*, *J* = 7.3)	1.11 (*d*, *J* = 7.1)	1.12 (*d*, *J* = 7.3)	0.96 (*d*, *J* = 6.8)
Me(17)	1.09 (*d*, *J* = 7.3)	1.14 (*d*, *J* = 7.1)	1.16 (*d*, *J* = 7.3)	0.95 (*d*, *J* = 6.8)
Me(19)	1.46 (*s*)	0.87 (*d*, *J* = 6.6)	0.97 (*d*, *J* = 6.4)	1.48 (*s*)
Me(20)	1.63 (*s*)	1.66 (*s*)	1.35 (*s*)	1.56 (*s*)
AcO	2.08 (*s*)	2.09 (*s*)	2.12 (*s*)	–

[a]) In $CDCl_3$, referred to the residual $CHCl_3$ (δ(H) 7.26).

attributed to a bicyclic ring system in compound **1**. Comparison of the NMR data of **1** and **5** established closely related structures possessing the same α,β-unsaturated γ-lactone system (C(2) to C(4) and C(18)), an acetyloxy group at C(14), and an isopropyl group at C(1). The former differed from the latter by the lack of the carbonyl group at C(6) and by the different geometry of the olefinic C(7)=C(8) bond. Due to the missing C=O group at C(6), the vicinal olefinic H–C(7) was significantly shifted upfield (from δ(H) 6.01 in **5** to δ(H) 4.89–4.91 in **1**). On the other hand, an upfield shift for the ^{13}C-NMR chemical shift of C(8) (from δ(C) 158.8 in **5** to δ(C) 136.0 in **1**) was also observed, in agreement with the lack of the C(6)=O group in **1**. The (*E*)-configuration of the C(7)=C(8) bond was determined by the upfield shifted ^{13}C-NMR resonance of Me(19) (from δ(C) 23.1 in **5** to δ(C) 15.3 in **1**) [7] and supported by the strong NOE correlations between H–C(7) and CH_2(9). The relative configurations at C(1), C(2), and C(14) were assigned to be the same as those in **5** by comparison of the ^{13}C-NMR data of **1** with those of **5** [4], showing almost identical chemical shift values for C(1), C(2), and C(14), and by interpretation of the NOESY plot of **1**.

Compound **2**, had the molecular formula $C_{22}H_{32}O_5$, established by HR-EI-MS and indicating two mass units more than the one of **5**. Analysis of the ^{1}H- and ^{13}C-NMR spectra of **2** (*Table 1* and *2*) revealed a close relationship with both **5** and sarcophytonolide C (**6**) [4][5] and allowed to assign the structure of sarcophytonolide J[1]) (**2**).

Table 2. *^{13}C-NMR Data*[a]) (125 MHz) *of Compounds* **1**–**4**. δ in ppm.

	1	**2**	**3**	**4**
CH(1)	50.3 (*d*)	50.1 (*d*)	50.8 (*d*)	45.4 (*d*)
CH(2)	80.7 (*d*)	81.4 (*d*)	81.4 (*d*)	83.3 (*d*)
CH(3)	150.3 (*d*)	152.0 (*d*)	150.5 (*d*)	149.9 (*d*)
C(4)	130.7 (*s*)	128.0 (*s*)	129.4 (*s*)	132.0 (*s*)
CH_2(5)	25.5 (*t*)	41.3 (*t*)	40.6 (*t*)	25.5 (*t*)
CH_2(6) or C(6)	24.0 (*t*)	205.2 (*s*)	204.6 (*s*)	24.2 (*t*)
CH(7) or CH_2(7)	123.8 (*d*)	49.8 (*d*)	46.2 (*t*)	123.3 (*d*)
C(8) or CH(8)	136.0 (*s*)	29.4 (*d*)	28.7 (*d*)	135.6 (*s*)
CH_2(9)	38.2 (*t*)	35.4 (*t*)	39.3 (*t*)	38.6 (*t*)
CH_2(10) or CH(10)	25.0 (*t*)	24.1 (*t*)	128.1 (*d*)	25.4 (*t*)
CH(11)	125.9 (*d*)	128.7 (*d*)	133.2 (*d*)	125.6 (*d*)
C(12)	133.0 (*s*)	131.4 (*s*)	83.0 (*s*)	132.8 (*s*)
CH_2(13)	40.9 (*t*)	42.0 (*t*)	42.2 (*t*)	37.4 (*t*)
CH(14) or CH_2(14)	73.3 (*d*)	72.6 (*d*)	70.7 (*d*)	23.2 (*t*)
CH(15)	25.8 (*d*)	25.7 (*d*)	26.3 (*d*)	29.0 (*d*)
Me(16)	18.8 (*q*)	18.6 (*q*)	19.4 (*q*)	18.0 (*q*)
Me(17)	25.2 (*q*)	24.9 (*q*)	24.6 (*q*)	20.1 (*q*)
C(18)	173.3 (*s*)	172.2 (*s*)	173.3 (*s*)	173.4 (*s*)
Me(19)	15.3 (*q*)	19.8 (*q*)	20.1 (*q*)	15.6 (*q*)
Me(20)	18.9 (*q*)	17.9 (*q*)	25.1 (*q*)	16.2 (*q*)
*Me*CO	21.2 (*q*)	21.1 (*q*)	21.4 (*q*)	
Me*C*O	170.9 (*s*)	171.1 (*s*)	171.1 (*s*)	

[a]) In $CDCl_3$, referred to $CDCl_3$ (δ(C) 77.0).

The presence in **2** of the same functional groups at C(2)–C(4)[1]) (α,β-unsaturated butenolactone moiety) and C(6) (ketone group) as in **5** and **6** was evident. In particular, the ^{13}C-NMR spectrum of **2** displayed four olefinic C-signals assignable to C(3)=C(4) (δ(C) 152.0 and 128.0) and C(11)=C(12) (δ(C) 128.7 and 131.4), but the lack of the diagnostic signals for C(7)=C(8) (δ(C) 125.2 and 158.8 in **5**) indicated that this conjugated C=C bond was absent in **2**. The downfield-shifted ^{13}C-NMR resonance of C(6) (from δ(C) 196.1 in **5** to 205.2 in **2**) further supported structure **2**. In analogy to **1**, the relative configuration of the three chiral centers at C(1), C(2), and C(14) was elucidated to be the same as those of **1** by a NOESY experiment, as well as by analysis of the coupling constants, splitting pattern of H–C(1), H–C(2), and H–C(14). The configuration of the C(11)=C(12) bond was inferred to be (*E*) by the ^{13}C-NMR chemical shifts of Me(20) [7] and by an NOE correlation between CH_2(10) and Me(20). Unfortunately, due to the flexibility of the 14-membered macrocycle, the configuration at C(8) could not be unambiguously determined by the NOE technique.

Sarcophytonolide K (**3**), a colorless oil, had the molecular formula $C_{22}H_{32}O_6$ according to the HR-ESI-MS $[M+Na]^+$ at *m*/*z* 415.2076). Interpretation of the ^{1}H- and ^{13}C-NMR spectra of **3** (*Tables 1* and *2*) in comparison with those of **2** led to identify three partial structures: **a** (from C(1) to C(8)), **b** (from C(1) to C(14)), and **c** (from C(1) to C(15)) (*Fig.*), identical to the corresponding parts in **2**. In fact, **3** differed from **2** mainly in the substitution pattern at C(10)–C(12). 2D-NMR Data confirmed the proposed structure of sarcophytonolide K[1]) (**3**).

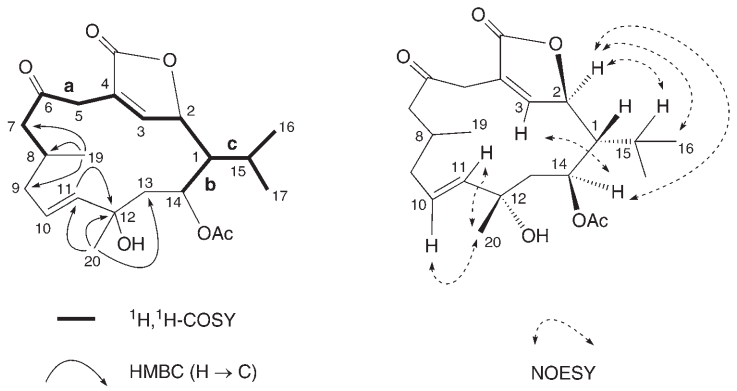

Figure. *Selected 2D-NMR correlations of compound* **3**

The presence in **3**, of an endocyclic disubstituted C(10)=C(11) bond was evidenced by NMR data (δ(H) 5.56 (*ddd*, J = 16.0, 8.7, 6.2 Hz) and 5.29 (*d*, J = 16.0 Hz), and δ(C) 128.1 (*d*) and 133.2 (*d*)) and confirmed by the HMBC correlations Me(20)/C(11) and H–C(11)/C(12) and C(20). The hydroxylation at C(12) accompanying the double-bond migration from C(11)=C(12) to C(10)=C(11) and the upfield shifted Me(20) (from δ(H) 1.66 in **2** to 1.35 in **3**) further supported structure **3**. The (*E*) configuration of C(10)=C(11) was determined by the large coupling constant of H–C(10) and H–C(11) (J = 16.0 Hz). Analogously to **2**, the relative configuration of the chiral centers of **3** was elucidated by a NOESY experiment (*Fig.*). Thus, the NOE correlations H–C(2)/H–C(14), H–C(2)/H–C(15), H–C(2)/Me(16), and H–C(3)/H–C(14) were observed, suggesting that both H–C(14) and H–C(2) were α oriented, opposite to H–C(1). No NOE correlation Me(20)/H–C(14) but a strong correlation Me(20)/H–C(11) and a moderate correlation Me(20)/H–C(10) suggested that both OH–C(12) and H–C(14) are oriented α. The configuration at C(8) could not be determined.

Sarcophytonolide L (**4**) was isolated as colorless oil. Its HR-EI-MS suggested the molecular formula $C_{20}H_{30}O_2$ (*m*/*z* 302.2227). The NMR data of **4** were reminiscent of those of the co-occurring compound **1**. In fact, the main differences appeared in the ^{13}C-NMR spectrum of **4**, where the acetyloxy group of **1** was missing, and a new CH_2 signal (δ(C) 23.2) was visible, suggesting the loss of the acetyloxy group at C(14) of **4**, in agreement with the molecular-mass difference of 58 mass units between **4** and **1**. ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments allowed an unambiguous definition of the structure of sarcophytonolide L[1]) (**4**), which is a 14-(deacetyloxy) derivative of **1**.

The absolute configuration of compounds **1**–**4** remains to be determined, the scarcity of material preventing so far a reliable determination. However, considering the fact that these compounds are closely related to the co-occurring sarcophytonolide H (**7**) [5], of which the absolute configuration has been determined by *Mosher*'s method, and bearing in mind the already elaborated relative configuration at all chiral centers of compounds **1**–**4**, the absolute configurations of sarcophytonolides I–L are tentatively assigned as shown in the formulas **1**–**4**.

The bioassay screening such as for antibacterial, anti-inflammatory, *etc.*, activity to evaluate the biological properties of compounds **1**–**4** are currently ongoing.

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Experimental Part

General. Column chromatography (CC): commercial silica gel (*Qing Dao Hai Yang Chemical Group Co.*; 200–300 mesh) and *Sephadex LH-20* (*Amersham Biosciences*). TLC: precoated silica gel plates (*Yan Tai Zi Fu Chemical Group Co.*; *G60*, *F-254*). Optical rotation: *Perkin-Elmer-341* polarimeter. UV Spectra: *Varian-Cary-300-Bio* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet-Magna-FT-IR-750* spectrophotometer; $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AV500* (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer; chemical shifts δ in ppm, with residual $CHCl_3$ (δ(H) 7.26; δ(C) 77.0) or C_5D_5N (δ(H) 7.20, 7.57, 8.73; δ(C) 123.6, 135.8, 150.0) as internal standard, coupling constant *J* in Hz. EI-MS and HR-EI-MS: *Finnigan-MAT-95* mass spectrometer; in *m*/*z*. ESI-MS and HR-ESI-MS: *Q-TOF-Micro* LC-MS-MS spectrometer, in *m*/*z*.

Biological Material. The specimen of *S. latum*, identified by Prof. *R.-L. Zhou* of the South China Sea Institute of Oceanology, Chinese Academy of Sciences, were collected off the Monkey Island, Lingshui, Hainan Province, China, in December 2001, at a depth of −20 m, and were frozen immediately after collection. A voucher specimen (HN-103) is available for inspection at the Herbarium of the Shanghai Institute of Materia Medica, CAS.

Extraction and Isolation. The frozen soft coral (dry weight 68 g) was extracted with acetone at r.t. The acetone extract was concentrated and the resulting residue partitioned between H_2O and Et_2O. The Et_2O extract (3.2 g) was subjected to CC (silica gel, eluent of increasing polarity from light petroleum ether to Et_2O, MeOH). The fraction eluted with 5% Et_2O/petroleum ether was further purified by CC (*LH-20*, petroleum ether/$CHCl_3$/MeOH 2:1:1): **4** (2.3 mg). The fraction eluted with 10% Et_2O/petroleum ether was further purified by CC (*LH-20*, petroleum ether/$CHCl_3$/MeOH 2:1:1): **1** (3.2 mg). The fractions eluted with 15%, 17%, and 20% Et_2O/petroleum ether were further purified by CC (*LH-20*, petroleum ether/$CHCl_3$/MeOH 2:1:1): **2** (8.9 mg) and **3** (1.2 mg).

Sacrophytonolide I (= *(4*E*,8*E*,11*R*,12*R*,13*R*)-11-(Acetyloxy)-5,9-dimethyl-12-(1-methylethyl)-14-oxabicyclo[11.2.1]hexadeca-1(16),4,8-trien-15-one*; **1**): Colorless oil. $[\alpha]_D^{20} = +71$ ($c = 0.58$, $CHCl_3$). UV (MeOH): 235 (4.22). IR (film): 2919.7, 1758.8, 1735.6, 1686.0, 1436.7, 1375.0, 1234.2, 1022.6, 968.1, 732.8. ^{1}H-NMR: *Table 1*. ^{13}C-NMR: *Table 2*. EI-MS: 360 (M^+), 300, 257, 204, 161, 135. HR-EI-MS: 360.2289 (M^+, $C_{22}H_{32}O_4^+$; calc. 360.2301).

Sacrophytonolide J (= *(8*E*,11*R*,12*R*,13*R*)-11-(Acetyloxy)-5,9-dimethyl-12-(1-methylethyl)-14-oxabicyclo[11.2.1]hexadeca-1(16),8-diene-3,15-dione*; **2**): Colorless oil. $[\alpha]_D^{20} = +32$ ($c = 1.08$, $CHCl_3$). UV (MeOH): 233 (3.76). IR (film): 2919.7, 1760.7, 1736.0, 1686.0, 1456.0, 1376.9, 1234.2, 1083.8, 1024.0, 972.0, 757.9. ^{1}H-NMR: *Table 1*. ^{13}C-NMR: *Table 2*. EI-MS: 376 (M^+), 316, 298, 273, 255, 177, 163, 135. HR-EI-MS: 376.2230 (M^+, $C_{22}H_{32}O_5^+$; calc. 374.2249).

Sacrophytonolide K (= *(7*E*,9*S*,11*S*,12*R*,13*R*)-11-(Acetyloxy)-9-hydroxy-5,9-dimethyl-12-(1-methylethyl)-14-oxabicyclo[11.2.1]hexadeca-1(16),7-diene-3,15-dione*; **3**): Colorless oil. $[\alpha]_D^{20} = +90$ ($c = 0.20$, $CHCl_3$). UV (MeOH): 239 (4.02). IR (film): 3390.3, 2917.8, 1756.9, 1734.8, 1686.0, 1471.4, 1375.0, 1238.1, 1087.7, 1026.0, 757.9. ^{1}H-NMR: *Table 1*. ^{13}C-NMR: *Table 2*. ESI-MS: 415 ($[M + Na]^+$). HR-ESI-MS: 415.2076 ($[M + Na]^+$, $C_{22}H_{32}NaO_6^+$; calc. 415.2097).

Sacrophytonolide L (= *(4E,8*E*,12*S*,13*S*)-5,9-Dimethyl-12-(1-methylethyl)-14-oxabicyclo[11.2.1]hexadeca-1(16),4,8-trien-15-one;* **4**): Colorless oil. $[\alpha]_D^{20} = +82$ ($c = 1.0$, $CHCl_3$). UV (MeOH): 241 (3.96). IR (film): 2956.4, 1751.1, 1436.7, 1369.2, 1043.3, 854.3, 754.0. ^{1}H-NMR: *Table 1*. ^{13}C-NMR: *Table 2*. EI-MS: 302 (M^+), 284, 269, 159, 145, 133, 119. HR-EI-MS: 302.2227 (M^+, $C_{20}H_{30}O_2^+$, calc. 302.2245).

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