New Cembrane Diterpenes from Taiwanese Soft Coral *Sinularia flexibilis*

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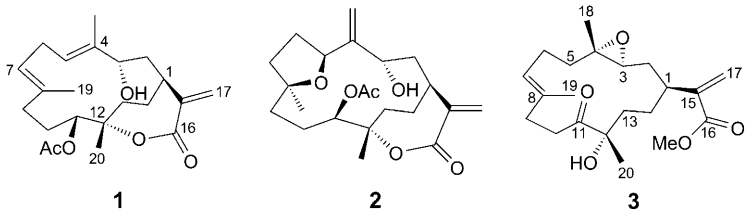
A chemical investigation of the Taiwanese soft coral *Sinularia flexibilis* has resulted in the isolation of three new cembrane diterpenes designated sinuladiterpenes G–I (**1**–**3**, resp.). The structures of **1**–**3** were determined on the basis of spectroscopic analyses, especially 2D-NMR and HR-ESI-MS.

Introduction. – For the past decades, soft corals have been investigated extensively, and many natural products with interesting biological activities have been discovered [1][2]. Nevertheless, due to long-term adaptation in different environments, many soft corals have developed unique chemical defense systems to protect themselves. Recently, several 14-membered monocyclic rings, usually called cembrane diterpenes, were isolated from western pacific *Sinularia* [3–6]. These novel metabolites, produced also by other soft corals and gorgonians, are assumed to be involved in a defense mechanism against predators such as molluscs, fish, and other vertebrates, and against settlement of microorganisms [7]. Cembrane diterpenes have been shown to possess interesting biological and pharmacological activities, such as cytotoxic [8–10], anti-HIV [11], and calcium-antagonism [12]. Here, we report the isolation and identification of three new cembrane diterpenes, sinuladiterpenes G–I (**1**–**3**, resp.), from *Sinularia flexibilis*, a Taiwanese marine soft coral. Their structures were determined by spectroscopic methods, especially 2D-NMR and HR-ESI-MS.

Results and Discussion. – Extensive fractionation of CH_2Cl_2/MeOH extracts by using normal-phase chromatography afforded sinuladiterpenes G–I (**1**–**3**, resp.) from *Sinularia flexibilis*.



1 **2** **3**

The molecular formula of **1** was determined as $C_{22}H_{32}O_5$ by HR-ESI-MS (*m*/*z* 399.2151 $[M+Na]^+$) and NMR data. The IR absorption bands indicated the presence

of OH (3445 cm^{-1}), ester (1742 and 1710 cm^{-1}), and C=C bond (1642 cm^{-1}) functionalities. The ^{1}H- and ^{13}C-NMR-spectroscopic data (*Tables 1* and *2*) revealed the presence of a methylidene (δ(H) 6.20, 5.51; δ(C) 124.4) and an ester C=O (δ(C) 169.0) group, and of two trisubstituted C=C bonds (δ(H) 5.74, 5.21; δ(C) 129.6 (*s*), 129.5 (*d*), 127.9 (*d*), 134.6 (*s*)). One AcO moiety was detected by the signals at δ(H) 2.10, and δ(C) 170.7 and 21.0. These functionalities accounted for five degrees of unsaturation, implying the presence of two rings. Spectroscopic analysis of **1** suggested the presence of a 14-membered cembrane ring with one OH and one AcO group, and two C=C bonds. The cembrane structure was confirmed by detailed analysis of the COSY correlations (H−C(1)/CH_2(2)/H−C(3), H−C(5)/CH_2(6)/H−C(7), and CH_2(9)/CH_2(10)/H−C(11)) depicted in *Fig. 1* [13]. The downfield-shifted signal of a quaternary O-bearing C-atom at δ(C) 86.1 was assigned to C(12), suggesting 16,12-lactonization, thus forming a seven-membered ε-lactone ring [14]. This was evidenced from HMBCs (*Fig. 1*) of the exocyclic CH_2 H-atoms (CH_2(17)) to the CH group (δ(C) 31.8 (C(1)) and 169.0 (C(15))), and between the Me group (δ(H) 1.32; assigned to Me(20)) and C(12). The O-bearing CH group H-atom signal at δ(H) 4.68 was assigned to H−C(3) due to its correlation to C(2), and correlations to C(1) and C(18), as well as an olefinic CH group (δ(C) 129.5, C(5)). The latter was attached to a H-atom (δ(H) 5.74) that was correlated to C(18) and to C(6), thereby establishing 4,5-unsaturation. The vinylic Me *singlet* at δ(H) 1.69 (Me(19)) correlated with the signal for the olefinic CH group (δ(C) 127.9 (C(7))) and a CH_2 group (δ(C) 34.6 (C(9))) pointed to a 7,8-unsaturation. The chemical shifts of both C(18) (δ(C) 16.0) and C(19) (δ(C) 16.7) implied (*E*)-configuration of the C(4)=C(5) and C(7)=C(8) bonds, respectively. The O-bearing CH group (δ(H) 5.46 (H−C(11))) exhibited HMBCs with C(10), C(12), C(13), C(20), as well as the AcO CO group (δ(C) 170.7), establishing the location of the AcO group at C(11). The NOESY correlations H−C(1)/H−C(11), along with absence of any correlation between H−C(1) and either H−C(3) or Me(20), indicated an α-orientation of H−C(11) and HO−C(3), and β-orientation of H−C(3) and Me(20). Thus, the structure of **1** (sinuladiterpene G) was assigned as shown.

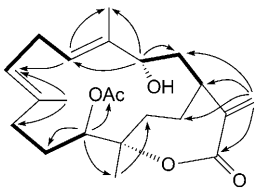


Fig. 1. *Key COSY* (bold line) *and HMBC* (arrow) *correlations of* **1**

The HR-ESI-MS of **2** exhibited a molecular-ion peak at *m*/*z* 415.2093 ($[M+Na]^+$), corresponding to a molecular formula $C_{22}H_{32}O_6$, which indicates seven degrees of unsaturation. The NMR data (*Tables 1* and *2*) disclosed the presence of two Me, seven CH_2, two exocyclic CH_2, three O-bearing CH groups, and one AcO group. The Me(20) group (δ(H) 1.32) showed HMBCs with the characteristic O-bearing quaternary C-atom C(12) (δ(C) 87.4) and an O-bearing CH(11) group (δ(C) 74.4), whereas H−C(11) (δ(H) 6.30) correlated with C(12), C(20), and the ester C=O (δ(C) 170.8), indicating AcO substitution at C(11). The exocyclic CH_2 H-atom *singlet*s at δ(H) 6.28

Table 1. *^{1}H-NMR Data* ($CDCl_3$, 300 MHz) *of Compounds* **1**–**3**[a])

	1	**2**[b])	**3**
H–C(1)	2.46–2.51 (*m*)	3.45–3.50 (*m*)	2.65–2.70 (*m*)
CH_2(2)	2.05–2.11 (*m*),	2.44–2.49 (*m*),	1.34–1.40 (*m*),
	1.60–1.65 (*m*)	1.30–1.36 (*m*)	1.92–1.98 (*m*)
H–C(3)	4.68 (*dd*, *J* = 11.5, 2.7)	3.70 (*dd*, *J* = 9.5, 3.7)	2.78 (*dd*, *J* = 9.0, 3.6)
H–C(5) or CH_2(5)	5.74 (*dd*, *J* = 10.7, 6.2)	4.36 (*t*, *J* = 6.6)	1.75 (*m*), 1.50 (*m*)
CH_2(6)	3.16–3.22 (*m*),	2.40–2.46 (*m*),	2.07–2.13 (*m*),
	2.52–2.58 (*m*)	1.92–1.98 (*m*)	2.02–2.08 (*m*)
H–C(7)	5.21 (*d*, *J* = 9.3)	1.77–1.83 (*m*)	5.12 (*t*, *J* = 5.5)
CH_2(9)	2.03–2.09 (*m*),	1.87–1.93 (*m*),	2.48–2.54 (*m*),
	1.87–1.93 (*m*)	1.82–1.87 (*m*)	2.20–2.26 (*m*)
CH_2(10)	1.58–1.63 (*m*),	1.92–1.98 (*m*),	2.72–2.78 (*m*),
	1.40–1.45 (*m*)	1.87–1.93 (*m*)	2.62–2.67 (*m*)
H–C(11)	5.46 (*d*, *J* = 9.6)	6.30 (*d*, *J* = 9.0)	
CH_2(13)	1.98–2.02 (*m*),	1.97–2.02 (*m*),	2.57–2.63 (*m*),
	1.80–1.84 (*m*)	1.82–1.87 (*m*)	2.12–2.18 (*m*)
CH_2(14)	1.94–2.00 (*m*),	1.95–2.00 (*m*),	1.90–1.95 (*m*),
	1.20–1.25 (*m*)	1.84–1.90 (*m*)	1.57–1.63 (*m*)
CH_2(17)	6.20 (*s*), 5.51 (*s*)	6.28 (*s*), 5.47 (*s*)	6.30 (*s*), 5.48 (*s*)
Me(18)	1.66 (*s*)	5.17 (*s*), 5.01 (*s*)	1.26 (*s*)
Me(19)	1.69 (*s*)	1.25 (*s*)	1.65 (*s*)
Me(20)	1.32 (*s*)	1.32 (*s*)	1.33 (*s*)
MeO–C(16)			3.75 (*s*)
Ac	2.10 (*s*)	2.11 (*s*)	

[a]) *J* Values in Hz are given in parentheses. [b]) Recorded at 500 MHz.

and 5.47 were assigned to CH_2(17) based on their HMBCs to C(1) (δ(C) 32.0) and C(16) (δ(C) 169.2). The relatively upfield-shifted exocyclic CH_2 H-atoms resonating at δ(H) 5.17 and 5.01 correlated with a quaternary olefin C-atom at δ(C) 150.5 (C(4)), and with two O-bearing CH groups at δ(C) 74.1 (C(3)) and δ(C) 81.3 (C(5)), establishing the presence of a C(4)=C(18) bond. The HMQC spectrum indicated that H–C(3), resonating at δ(H) 3.70, correlated to C(4) as well as to C(1) and C(5). The Me(19) group (δ(H) 1.25) correlated with a quaternary O-bearing C-atom (δ(C) 86.1 (C(8))) and with two CH_2 groups (δ(C) 38.0 (C(7)) and 37.6 (C(9))). The downfield shift of both C(5) and C(8), together with consideration of seven degrees of unsaturation, required the presence of an ether linkage between C(5) and C(8). The proposed 2,2,5-trisubstituted tetrahydrofuran unit was substantiated by HMBCs between H–C(5)/C(6), C(7), and, most significantly between H–C(5) and C(8). The NOESY correlations H–C(11)/H–C(1), H–C(5); H–C(5)/Me(19); and H–C(3)/H_β–C(2) evidenced the α-orientation of H–C(5), H–C(11), and Me(19), as well as β-orientation of H–C(3) (*Fig. 2*). Thus, the structure of **2**, sinuladiterpene H, was unambiguously elucidated as shown.

The molecular formula $C_{21}H_{32}O_5$ was established for **3** by HR-ESI-MS, which showed a pseudo-molecular-ion peak at *m*/*z* 387.2150 ($[M+Na]^+$). The IR spectrum displayed absorption bands for OH (3421 cm^{-1}), conjugated ester (1711 cm^{-1}), and C=C (1634 cm^{-1}) functionalities. The ^{1}H-NMR spectroscopic data (*Tables 1* and *2*)

Table 2. *^{13}C-NMR Data* ($CDCl_3$, 75 MHz) *of Compounds* **1**–**3**[a])

	1	**2**[b])	**3**
C(1)	31.8 (*d*)	32.0 (*d*)	36.5 (*d*)
C(2)	39.1 (*t*)	29.2 (*t*)	25.2 (*t*)
C(3)	66.2 (*d*)	74.1 (*d*)	59.5 (*d*)
C(4)	129.6 (*s*)	150.5 (*s*)	60.7 (*s*)
C(5)	129.5 (*d*)	81.3 (*d*)	36.1 (*t*)
C(6)	26.8 (*t*)	31.7 (*t*)	22.9 (*t*)
C(7)	127.9 (*d*)	38.0 (*t*)	126.3 (*d*)
C(8)	134.6 (*s*)	86.1 (*s*)	134.6 (*s*)
C(9)	34.6 (*t*)	37.6 (*t*)	31.6 (*t*)
C(10)	27.5 (*t*)	28.6 (*t*)	34.3 (*t*)
C(11)	71.4 (*d*)	74.4 (*d*)	213.7 (*s*)
C(12)	86.1 (*s*)	87.4 (*s*)	78.8 (*s*)
C(13)	33.0 (*t*)	33.8 (*t*)	31.6 (*t*)
C(14)	29.3 (*t*)	33.3 (*t*)	36.9 (*t*)
C(15)	145.0 (*s*)	144.7 (*s*)	142.3 (*s*)
C(16)	169.0 (*s*)	169.2 (*s*)	167.5 (*s*)
C(17)	124.4 (*t*)	123.7 (*t*)	124.5 (*t*)
C(18)	16.0 (*q*)	114.6 (*t*)	18.2 (*q*)
C(19)	16.7 (*q*)	17.9 (*q*)	17.2 (*q*)
C(20)	23.7 (*q*)	23.8 (*q*)	25.7 (*q*)
*Me*O–C(16)			52.1 (*q*)
Ac	170.7 (*s*)	170.8 (*s*)	
	21.0 (*q*)	21.1 (*q*)	

[a]) Assignments were supported by DEPT, HMQC, and HMBC data. [b]) Recorded at 125 MHz.

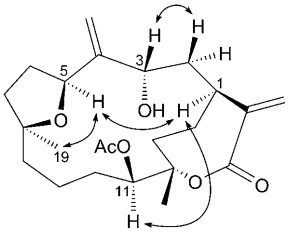


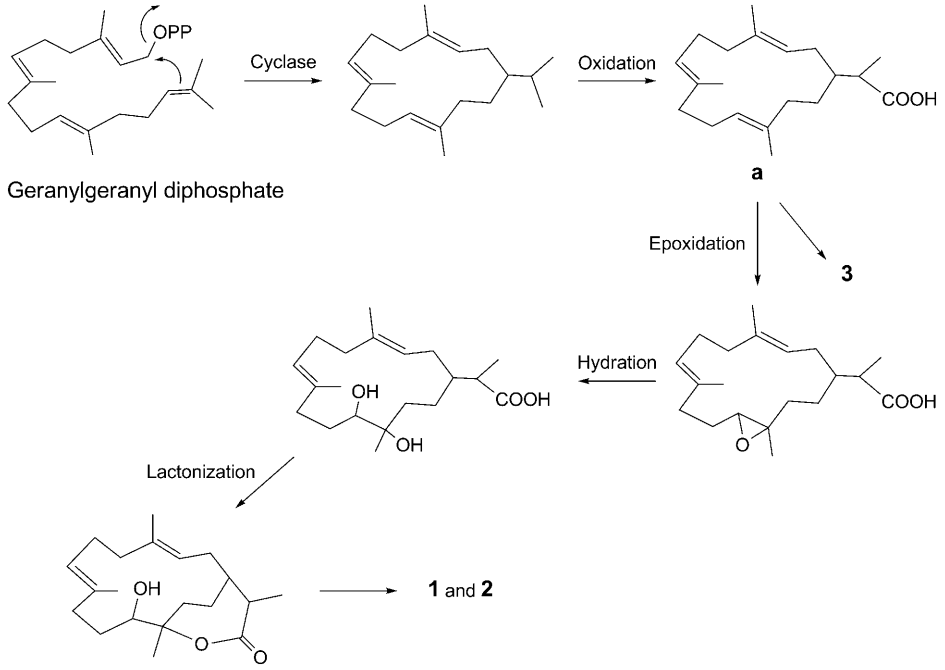
Fig. 2. *Key NOESY correlations of* **2**

indicated the presence of a trisubstituted C=C bond (δ(H) 5.12, H–C(7)), of a terminal CH_2 group (δ(H) 6.30, 5.48 (CH_2(17))), three Me groups (δ(H) 1.26, 1.33; one olefinic at δ(H) 1.65), and one MeO group (δ(H) 3.75). The ^{13}C-NMR revealed the presence of a ketone C=O (δ(C) 213.7), and α,β-unsaturated ester C=O group (δ(C) 167.5), a C=C bond (δ(C) 134.6, 126.3), a terminal CH_2 group (δ(C) 124.5), three Me groups (δ(C) 17.2, 18.2, 25.7), and a MeO group (δ(C) 52.1). The O-bearing quaternary C-atom (δ(C) 60.7 (C(4))) and O-bearing CH group (δ(C) 59.5) pointed to an oxirane ring, which was further supported by the signal of an O-bearing CH group H-atom (δ(H) 2.78 (H–C(3))). The two C=O groups, one C=C bond, terminal CH_2 group, and the epoxy ring accounted for only five degrees of unsaturation, implying the

necessity for an additional ring. In the HMBC, the terminal CH_2 H-atoms correlated with C(1) and the ester C=O, whereas the Me(20) group (δ(H) 1.33) correlated with a C=O (δ(C) 213.7 (C(11))), CH_2 (δ(C) 31.6 (C(13))) as well as with an O-bearing quaternary C-atom (δ(C) 78.8 (C(12))), establishing 11-oxo substitution. The Me group (δ(H) 1.26) correlated with an epoxy CH C-atom (δ(C) 59.5 (C(3))), CH_2 (δ(C) 36.1 (C(5))), and epoxy C-atom (δ(C) 60.7 (C(4))), indicating 3,4-epoxy ring. The third Me group (δ(H) 1.65), assigned as Me(19), correlated to the two olefinic C-atoms (δ(C) 134.6, 126.3 (C(8) and C(7))) and a CH_2 group (δ(C) 31.6 (C(9))), pointing to a 7,8-unsaturation. The COSY correlations H–C(1)/CH_2(2)/H–C(3) and CH_2(6)/H–C(7), along with EI-MS fragment ion at *m*/*z* 280 ([*M* – side chain]$^+$) and *m*/*z* 85 ($[C_4H_5O_2]^+$), confirmed the proposed structure. The terminal CH_2 group was assigned to C(17) on the basis of an HMBC CH_2(17)/C(1), whereas correlation of both CH_2(17) and MeO (δ(H) 3.75) to the ester C=O (δ(C) 167.5 (C(16))) allowed the location of the methyl ester group at C(15). The relative configuration of **1** was deduced from NOESY correlations and biosynthetic considerations [15]. The NOESY correlations H–C(3)/Me(18), along with absence of mutual NOE interactions H–C(1)/H–C(3) and H–C(1)/Me(20), were in agreement with the β-orientation of H–C(3), Me(18), and Me(20), as well as with an α-orientation of the oxirane ring, and of the OH group at C(12). Based on these findings, the structure of **3**, sinuladiterpene I, was established as shown.

A plausible biogenetic pathway for these new compounds is proposed as displayed in the *Scheme*. Geranylgeranyl diphosphate (GGPP) most likely serves as precursor of

Scheme. *Proposed Biogenetic Pathway for Compounds* **1**–**3**



cembranoids **1**–**3**. Cyclization of GGPP, followed by oxidation, yields an acid derivative **a**, which may lead to compound **1**. Epoxidation of acid **a**, followed by hydration, lactonization, and acylation, could furnish compounds **2** and **3**.

Experimental Part

General. Column chromatography (CC): silica gel *60* (SiO_2; *Merck*). Prep. TLC: pre-coated silica gel plates (*Kieselgel 60 F-254*, 1 mm, *Merck*). *Sephadex LH-20* (*Amersham Pharmacia Biotech AB*, Uppsala, Sweden) was used for separation. *LiChrospher®* Si *60* (5 μm, *250-10*, *Merck*) was used for NP-HPLC (*Hitachi*). Optical rotations: *JASCO DIP-1000* polarimeter. IR and UV spectra: *Hitachi T-2001* and *Hitachi U-3210* spectrophotometers, resp. ^{1}H- and ^{13}C-NMR, COSY, HMQC, HMBC, and NOESY spectra: *Bruker FT-300* spectrometer or on a *Varian Unity INOVA 500* FT-NMR at 500 MHz for ^{1}H and 125 MHz for ^{13}C, using TMS as internal standard; the chemical shifts are given in δ values [ppm] and coupling constants in Hz. EI-MS and FAB-MS: *VG Quattro 5022* mass spectrometer. HR-ESI-MS: *JEOL JMS-SX 102* spectrometer.

Animal Material. The soft coral *Sinularia flexibilis* was collected at Green Island, Taiwan, in April 2004, at a depth of 10–15 m and immediately stored in a freezer until extraction. A voucher specimen (GSC-II-10) was deposited with the School of Pharmacy, National Taiwan University, Taipei, Taiwan.

Extraction and Isolation. The wet organism (4 kg) was sliced and extracted with CH_2Cl_2/MeOH 1:1 three times using a stirrer, and the combined extracts were evaporated *in vacuo*. The resulting crude extract (32 g) was separated by flash chromatography (SiO_2; hexane/AcOEt/MeOH 100:0:0 to 0:3:1) to furnish 15 fractions, *Frs. 1–15*. *Fr. 12* (1.8 g) was separated on a *Sephadex* column with CH_2Cl_2/MeOH 1:1 into three fractions, *Frs. 12-A–12-C*. Crystallization of *Fr. 12-A* gave 11-episinulariolide acetate (990 mg). *Fr. 12-B* (220 mg) was chromatographed on a SiO_2 column with a gradient of hexane/AcOEt (20:1 to 2:1) to produce eight fractions, *Frs. 12-B-1–12-B-8*. *Fr. 12-B-3* yielded 11-dehydrosinulariolide (2 mg). *Fr. 12-B-4* was further separated by NP-HPLC using hexane/CH_2Cl_2/MeOH 25:15:1 to yield **3** (14 mg). *Fr. 13* (1.2 g) was similarly separated on a *Sephadex* column using CH_2Cl_2/MeOH 1:1 to give three fractions, *Frs. 13-A–13-C*. *Fr. 13-C* (300 mg) was chromatographed on a SiO_2 column with a gradient of hexane/AcOEt/MeOH (100:0:0 to 0:5:1) to yield eleven fractions, *Frs. 13-C-1–13-C-11*. *F13-C-10* (58 mg) was repeatedly subjected to NP-HPLC with hexane/CH_2Cl_2/MeOH (15:15:1, then 25:20:10) to furnish **1** (8 mg) and **2** (4 mg).

Sinuladiterpene G (=(*1*S*,*3*S*,*4*E,*7*E,*11*R*,*12*S*)*-3-Hydroxy-4,8,12-trimethyl-15-methylidene-14-oxo-13-oxabicyclo[10.3.2]heptadeca-4,7-dien-11-yl Acetate*; **1**). Colorless amorphous solid. $[\alpha]_D^{24} = -13.5$ ($c = 0.1$, MeOH). IR (CH_2Cl_2): 3445 (OH), 2930 (CH), 1742 (ester), 1710 (C=O), 1642 (C=C), 1239, 1020, 759. ^{1}H- and ^{13}C-NMR ($CDCl_3$): see *Tables 1* and *2*, resp. HR-EI-MS: 399.2151 ($C_{22}H_{32}NaO_5^+$; calc. 399.2147).

Sinuladiterpene H (=(*1*S*,*3*S*,*5*S*,*8*R*,*11*R*,*12*S*)*-3-Hydroxy-8,12-dimethyl-4,15-dimethylidene-14-oxo-13,18-dioxatricyclo[10.3.2.1^{5,8}]octadec-11-yl Acetate*; **2**). Colorless amorphous solid. $[\alpha]_D^{24} = -15.6$ ($c = 0.1$, MeOH). IR (CH_2Cl_2): 3443 (OH), 2950 (CH), 1736 (ester), 1709 (C=O), 1640 (C=C). ^{1}H- and ^{13}C- NMR ($CDCl_3$): see *Tables 1* and *2*, resp. HR-EI-MS: 415.2093 ($C_{22}H_{32}NaO_6^+$; calc. 415.2093).

Sinuladiterpene I (= *Methyl 2-[(1*S*,3*S*,6*S*,10*E,*14*S*)-6-Hydroxy-6,10,14-trimethyl-7-oxo-15-oxabicyclo[12.1.0]pentadec-10-en-3-yl]prop-2-enoate*; **3**). Colorless amorphous solid. $[\alpha]_D^{24} = +68.3$ ($c = 0.1$, MeOH). IR (CH_2Cl_2): 3421 (OH), 2926 (CH), 1711 (C=O), 1634 (C=C), 1236 (C–O), 1022, 756. ^{1}H- and ^{13}C-NMR ($CDCl_3$): see *Tables 1* and *2*, resp. HR-ESI-MS: 387.2150 ($C_{21}H_{32}NaO_5^+$; calc. 387.2147).

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