New Briaranes from the Taiwanese Gorgonian *Junceella juncea*

Ya-Ching Shen,* Yu-Chi Lin, Chin-Lien Ko, and Li-Tang Wang

Institute of Marine Resources, National Sun Yat-sen University, 70 Lien-Hai Road, Kaohsiung, Taiwan, Republic of China

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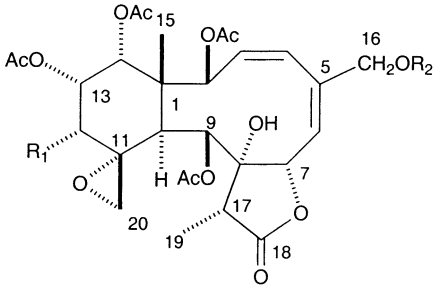
In addition to the known junceelolide C (**4**), three new briaranes, juncenolides B (**1**), C (**2**), and D (**3**), have been isolated from the acetone extract of a red Gorgonian *Junceella juncea* collected in Taiwan. The structures of **1**−**3** were elucidated on the basis of FABMS and 2D NMR techniques including COSY, HMQC, HMBC, and NOESY experiments. Among them, compound **2** exhibited mild cytotoxicity against human liver carcinoma (HEPA 59T/VGH) and oral epidermoid (KB) carcinoma cells.

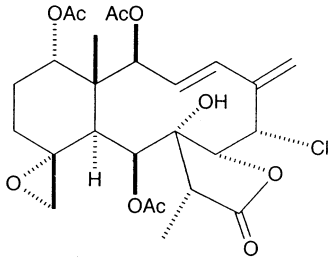
Briaranes are a group of diterpenoid γ-lactones of a highly oxidized bicyclo[8.4.0] system.[1] Briaranes continue to intrigue natural product chemists because their structures are novel and they possess interesting biological properties such as cytotoxic,[2,3] antiinflammatory,[4,5] antiviral,[6] insecticidal,[7] and antifouling activity.[8] Although *Junceella juncea* (Pallas) (Ellisellidae) is a gorgonian distributed in the coral reef worldwide, its chemistry is relatively complex and diverse. The constituents of *J. juncea* were found to be diverse from different geographical locations. For example, juncins A−F were found in *J. juncea* from the Red Sea.[9] The same species collected in the Indian Ocean contains juncins G and H.[10] During the course of searching for bioactive natural products from marine resources, we have surveyed a series of crude extracts of marine invertebrates using cytotoxicity tests. Among them, a lipophilic extract of a red sea whip *J. juncea* collected in the southern tip of Taiwan was found to possess significant cytotoxicity against human gastric (NUGC) and mouth epidermoid (HONE-1) carcinoma cells (12% and 3%, respectively). Previously, a new briarane, juncenolide A (**5**), was isolated from this gorgonian, and its structure was confirmed by X-ray analysis.[11] Continued investigation of the more polar fractions has resulted in the isolation of three additional new briaranes, juncenolides B (**1**), C (**2**), and D (**3**), along with the known compound junceellolide C (**4**) from *J. juncea*. [12] In this note we wish to report the isolation and structural elucidation of compounds **1**−**3**.

The residue from the acetone extract of *J. juncea* was partitioned between EtOAc and H_2O. Extensive Si gel column and preparative thin-layer chromatography using different solvent combinations yielded compounds **1**−**4** from the EtOAc-soluble fraction. Compound **4** was identified as junceellolide C by comparison of its spectral data (^{1}H and ^{13}C NMR, MS, and optical rotation) with literature values.[12] The structures of **1**−**3** are described below.

Juncenolide B (**1**), $[\alpha]_D$ −12.4° (MeOH), had a molecular formula of $C_{28}H_{36}O_{13}$ as derived from quasi-molecular ions at *m*/*z* 581 ($[M + H]^+$) and 603 ($[M + Na]^+$) in the FABMS and from DEPT ^{13}C NMR spectra. Its UV and IR bands indicated the presence of hydroxyls (3482 cm^{-1}), γ-lactone (1778 cm^{-1}), and esters (1743 cm^{-1}) and a conjugated diene system (275 nm). The ^{1}H NMR data of **1** (Table 1) showed four acetyl singlets (δ 2.18, 2.13, 1.99, 1.96), a methyl doublet (δ 1.39, J = 7.3 Hz) and a methyl singlet (δ 1.10), an exocyclic 11(20)-epoxide at δ 2.74 and 3.57, a methine doublet at δ 3.08 (H-10), a trisubstituted olefin (δ 5.58, 6.33, and 5.80), a hydroxymethylene group (δ 4.45, H-16), and five oxygenated methine protons (δ 5.52, H-2; 4.95, H-7; 4.70, H-9; 4.98, H-13; 5.24, H-14). To assign the proton relationships of **1**, COSY was used to reveal that the four acetoxyl groups were located at C-2, C-9, C-13, and C-14, in addition to the connectivities of H-2/H-3/H-4, H-6/H-7, H-9/H-10, H-12/H-13/H-14, and H-17/H-19. Detailed analysis of the ^{1}H and ^{13}C NMR data and comparison with those



1 $R_1 = R_2 = H$
2 $R_1 =$ OAc, $R_2 = H$
3 $R_1 =$ OAc, $R_2 = CH_3$



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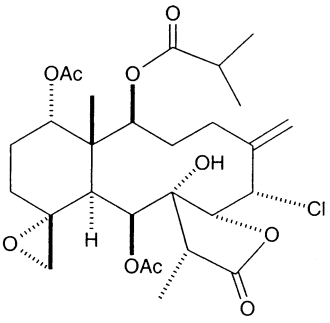

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* To whom correspondence should be addressed. Tel: (886) 7-525-2000, ext 5058. Fax: (886) 7-525-5020. E-mail: ycshen@mail.nsysu.edu.tw.

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Table 1. ^{1}H and ^{13}C NMR ($CDCl_3$) Spectral Data of Juncenolide B (**1**)

position	^{13}C[a]	^{1}H[b]	COSY	HMBC
1	46.4 s			H-2, H-10, H-14, Me-15
2	75.8 d	5.52 (d, 10.0)	H-3	H-10, H-14, Me-15
3	131.1 d	5.58 (t, 10.0)	H-2, H-4	H-2
4	129.4 d	6.33 (d, 10.0)	H-3	H-2, H-6, H-16
5	144.1 s			H-3, H-7, H-16
6	123.9 d	5.80 (dd, 8.8, 1.5)	H-7, H-16	H-4, H-7, H-16
7	78.5 d	4.95 (d, 8.8)	H-6	H-6, H-9
8	80.8 s			H-9, H-10, H-17, Me-19
9	64.3 d	4.70 (d, 5.3)	H-10	H-10
10	37.4 d	3.08 (d, 5.3)	H-9	H-9, H-14
11	58.3 s			H-9, H-10, H-12
12	34.3 t	2.51 (d, 13.0)	H-13, H-20	H-14
		1.34 (dd, 2.5, 10.0)		
13	67.6 d	4.98 (ddd, 13, 4, 2.5)	H-12, H-14	H-12, H-14
14	73.8 d	5.24 (brs)	H-13	H-2, H-12
15	14.5 q	1.10 s		H-2, H-10, H-14
16	64.0 t	4.45 (brs)	H-6	H-6
17	43.9 d	2.26 (q, 7.3)	Me-19	H-19, Me-9
18	175.4 s			H-19, Me-17
19	6.6 q	1.39 (d, 7.3)	H-17	H-17
20A	50.1 t	2.74 (d, 2.5)	H-12, H-20B	H-10
20B		3.57 (brs)	H-12, H-20A	
2-OAc	171.0 s	1.99 s		H-2
	21.4 q			
9-OAc	170.2 s	2.13 s[c]		H-9
	20.9 q			
13-OAc	170.2 s	2.18 s		
	21.5 q			
14-OAc	170.3 s	1.96 s[c]		H-14
	20.8 q			
OH		2.82 (brs)		

[a] Assignments made using the HMQC and HMBC techniques. [b] Multiplicities and coupling constants in Hz in parentheses. [c] Data interchangeable.

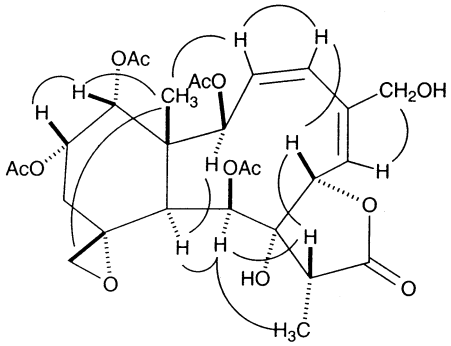

Figure 1. Selective NOESY correlation of **1**.

from the literature suggested that **1** is similar to the structure of gemmacolide F and nui-inoalide B.[1b,13] The ^{13}C NMR and DEPT spectra of **1** exhibited signals for three methylene carbons (34.3, 64.0, 50.1) and five ester carbons (δ 170.0, 170.2, 170.2, 170.3, 175.4). HMBC correlations of **1** (Table 1) revealed the connectivities of C-1/H-2, H-10, H-14, Me-15; C-5/H-3, H-16, C-8/H-9, H-10, H-17, Me-19; C-11/H-9, H-10, H-12; and C-15/H-2, H-10, H-14. The four acetoxyl groups were confirmed at C-2, C-9, C-13, and C-14 because their carbonyl carbons were correlated with the corresponding methine protons in the HMBC of **1**. The relative stereochemistry of **1** was determined from NOESY. NOESY-detected correlations between Me-15/H-3, H-7/H-17, H-20/Me-15, H-13/H-14, and H-14/Me-15 in **1** suggested that H-7, H-17, H-20, H-13, H-14, and Me-15 were all in the assigned arbitrarily β-face orientation. Correlations of H-2/H-10, H-9/H-10, and H-9/Me-19 indicated that H-2, H-9, H-10, and Me-19 were all in the α-orientation (Figure 1). Thus, the structure of juncenolide B (**1**) was determined as (1*S**,2*S**,3*Z*,5*E*,7*R**,8*R**,9*S**,10*S**,11*R**,-13*S**,14*R**,17*R**)-11,20-epoxy-2,9,13,14-tetraacetoxy-8-hydroxybriaran-3(4),5(6)-dien-18,7-olide.

Juncenolide C (**2**), $[\alpha]_D$ −24.4° (CH_2Cl_2), had a molecular formula $C_{30}H_{38}O_{15}$ as deduced from FABMS and NMR data. The IR and UV spectra of **2** showed absorbances similar to those for **1**, including hydroxyl (3483 cm^{-1}), γ-lactone (1770 cm^{-1}), esters (1749 cm^{-1}), and a conjugated diene (276 nm), suggesting that it was an analogue of **1**. The ^{1}H NMR spectrum (Table 2) of **2** revealed the presence of six oxymethine protons at δ 5.63, 4.96, 4.74, 4.88, 5.07, and 5.22. A hydroxymethylene group (δ 4.46, H-16), three olefinic protons (δ 5.62, 6.34, 5.82), a terminal epoxide group (δ 2.92, 3.63), and associated carbon resonances at δ 63.9 (C-16), 131.1 (C-3), 129.6 (C-4), 144.5 (C-5), 123.8 (C-6), and 49.0 (C-20) were also observed. A comparison of the ^{1}H and ^{13}C NMR spectra of **2** with those of juncenolide B (**1**) revealed that they were almost identical. The only difference between them was that **2** had an additional acetoxyl group at the C-12 position. This finding was supported by a COSY spectrum of **2**, which showed cross-peaks of H-12/H-13, H-13/H-12, and H-13/H-14. Compound **2** was assigned the same relative stereochemistry as in **1** because, except for H-12, the chemical shifts and proton coupling constants were essentially identical and most of the same NOESY correlations (Table 2) were observed for the two compounds. NOESY cross-peaks of H-12/H-13 and H-12/H20 indicated that the acetoxyl group at C-12 was also α.

Juncenolide D (**3**), $[\alpha]_D$ −10.3° (CH_2Cl_2), had a molecular formula $C_{31}H_{40}O_{15}$ (14 amu greater than **2**) as derived FABMS peaks observed at *m*/*z* 653 ($[M + H]^+$) and 675 ($[M + Na]^+$). The UV, IR, and ^{1}H NMR spectra of **3** displayed absorptions and signals similar to those of **2**, suggesting that it was a close analogue. The ^{1}H NMR spectrum (Table 3) of **3** exhibited six oxymethine protons at δ 5.56, 4.99, 4.70, 4.87, 5.06, and 5.20, three olefinic protons (δ 5.57, 6.29, 5.88), a terminal epoxide group (δ 2.91, 3.60), and corresponding carbon resonances at δ 131.2 (C-3), 128.6

Table 2. ^1H and ^{13}C NMR ($CDCl_3$) Spectral Data of Juncenolide C (**2**)

position	^{13}C[a]	^1H[b]	COSY	NOESY
1	46.4 s			
2	75.6 d	5.63 (d, 9.2)	H-3	H-10
3	131.1 d	5.62 (t, 9.2, 8.7)	H-2, H-4	H-4, Me-15
4	129.6 d	6.34 (d, 8.7)	H-3, H-6, H-16	H-3
5	144.5 s			
6	123.8 d	5.82 (d, 8.6)	H-4, H-7, H-16	H-16
7	78.7 d	4.96 (d, 8.6)	H-6	H-17
8	81.1 s			
9	64.7 d	4.74 (d, 4.8)	H-10	H-10, Me19
10	32.6 d	3.65 (overlap)	H-9	H-2, H-9
11	58.3 s			
12	73.2 d	4.88 (d, 2.5)	H-13	H-13, H-20
13	66.5 d	5.07 (t, 2.5)	H-12, H-14	H-12, Me-15
14	73.8 d	5.22 (d, 2.5)	H-13	Me-15
15	14.4 q	1.36 s		H-3, H-13, H-14, H-20
16	63.9 t	4.46 (brs)	H-4, H-6	H-6
17	44.1 d	2.29 (q, 7.2)	Me-19	H-7, Me-19
18	175.2 s			
19	6.3 q	1.45 (d, 7.2)	H-17	H-9, H-17
20A	49.0 t	2.92 (d, 2.4)	H-20B	H-12, H-20B
20B		3.63 (brs)	H-20A	Me-20A
2-OAc	169.7 s	1.94 s		
	20.5 q			
9-OAc	169.7 s	2.16 s[c]		
	20.9 q			
12-OAc	170.1 s	2.21 s		
	21.4 q			
13-OAc	170.9 s	1.98 s		
	21.5 q			
14-OAc	170.1 s	2.10 s[c]		
	20.7 q			

[a] Assignments made using the HMQC and HMBC techniques. [b] Multiplicities and coupling constants in Hz in parentheses.

(C-4), 141.5 (C-5), 122.7 (C-6), and 49.0 (C-20). A comparison of the ^1H and ^{13}C NMR spectra of **3** with those of juncenolide C (**2**) revealed that they were almost identical. The only difference between **3** and **2** was that **3** had a methoxyl group (δ 3.45, 58.4) at the C-16 (δ 72.2) position, leading to signal splitting of H_2-16 (δ 4.23, d, J = 14.6 Hz; δ 4.50, d, J = 14.6 Hz). Indeed, an HMBC correlation between C-16 and the OMe signal further supported this finding. The relative stereochemistry of **3** was determined by comparisons of proton coupling constants between **3** and **2** and the NOESY data shown in Figure 2. NOESY correlations of Me-15/H-3, H-7/H-17, H-20/Me-15, H-12/H-13, H-13/H-14, and H-14/Me-15 in **3** indicated that H-7, H-17, H-20, H-12, H-13, H-14, and Me-15 were all in the β-orientation. Correlations of H-2/H-10, H-9/H-10, and H-9/Me-19 indicated an α-configuration for H-2, H-9, H-10, and Me-19.

Juncenolide C (**2**) exhibited mild cytotoxicity against human hepa adenocarcinoma (HEPA 59T/VGH) and oral epidermoid carcinoma (KB-16) cells at a concentrations of 6.6 and 7.8 μg/mL, respectively. However, compounds **1**, **3**, and **4** were inactive toward these cell lines.

Experimental Section

General Experimental Procedures. Optical rotation was measured on a JASCO DIP-1000 polarimeter. IR spectra were recorded with a HORIBA FT-720 spectrophotometer. ^1H and ^{13}C NMR, COSY, HMQC, HMBC, and NOESY spectra were recorded using a Bruker FT-300 (AVANCE) or a Varian FT-500 (INOVA) NMR instrument. EIMS and FABMS were measured with VG Quattro 5022 and JEOL JMS-SX 102 mass spectrometers.

Animal Material. *Junceella juncea* (Pallas) was collected in Nan-wan in February 2000. A voucher specimen (WSG-4) was deposited in the Institute of Marine Resources, National Sun Yat-sen University, Kaohsiung, Taiwan.

Table 3. ^1H and ^{13}C NMR ($CDCl_3$) Spectral Data of Juncenolide D (**3**)

position	^{13}C[a]	^1H[b]	COSY	HMBC
1	47.3 s			Me-15
2	74.0 d	5.56 (overlap)	H-3	H-15, Me-4
3	131.2 d	5.57 (overlap)	H-2, H-4	H-4
4	128.6 d	6.29 (d, 8.7)	H-3	H-6
5	141.5 s			H-3, H-6, H-16
6	122.7 d	5.88 (d, 8.5)	H-7, H-16	H-16
7	78.9 d	4.99 (d, 8.5)	H-6	
8	81.0 s			Me-19
9	63.7 d	4.70 (d, 4.8)	H-10	
10	32.6 d	3.61 (overlap)	H-9	Me-15
11	58.2 s			H-10, H-12, H-20
12	73.2 d	4.87 (d, 2.4)	H-13	H-13
13	66.5 d	5.06 (t, 3.2)	H-12, H-14	H-12, H-14
14	73.8 d	5.20 (d, 2.4)	H-13	
15	14.4 q	1.13 s		
16	72.2 t	4.23 (d, 14.6)	H-6	OMe
		4.50 (d, 14.6)		
17	44.1 d	2.30 (q, 7.2)	Me-19	Me-19
18	175.3 s			H-17, Me-19
19	6.3 q	1.14 (d, 7.2)	H-17	
20A	49.0 t	2.91 (d, 2.4)	H-20B	
20B		3.60 (overlap)	H-20A	
2-OAc	170.1 s	1.95 s		
	21.1 q			
9-OAc	169.7 s	2.15 s[c]		
	20.9 q			
12-OAc	170.2 s	2.19 s		
	21.3 q			
13-OAc	169.6 s	1.95 s		
	20.5 q			
14-OAc	170.2 s	2.06 s[c]		
	20.8 q			
OMe	58.4 q	3.45 s		H-16

[a] Assignments made using the HMQC and HMBC techniques. [b] Multiplicities and coupling constants in Hz in parentheses. [c] Data interchangeable.

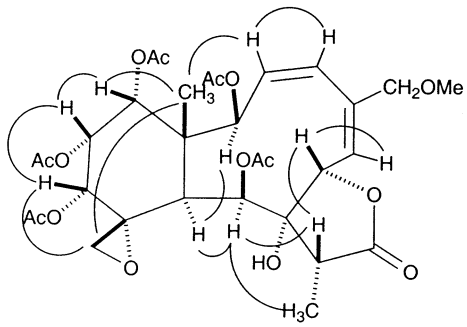

Figure 2. Key NOESY correlation of compound **3**.

Extraction and Isolation. The outer red layer of *J. juncea* (wet, 0.8 kg) was extracted with acetone, and the acetone extract was partition between EtOAc and H_2O (each 300 mL). The EtOAc-soluble residue (3.24 g) was chromatographed as previously described to afford five fractions: A (570 mg), B (244 mg), C (201 mg), D (0.84 g), and E (0.2 g). Part (0.5 g) of fraction D was chromatographed on a Si gel (20 g) column and eluted with *n*-hexane/CH_2Cl_2/MeOH (15:15:1) to give a residue (69 mg), which was applied on a preparative TLC plate (Si gel) developed with *n*-hexane/CH_2Cl_2/MeOH/ (12:12:1) to yield junceellolide C (**4**, 5.7 mg). Part (0.3 g) of fraction D was applied on preparative TLC plates and developed with *n*-hexane/CH_2Cl_2/EtOAc (30:30:1) to give a residue (40 mg), which was further purified by a PTLC plate (Si gel, *n*-hexane/CH_2Cl_2/EtOAc, 5:5:1) to afford juncenolide D (**3**, 2 mg). Fraction E was chromatographed on a Si gel (3 g) column eluted with *n*-hexane/CH_2Cl_2/MeOH in the following ratios and volumes (200:200:1, 100:100:1, 90:90:1, 80:80:1 to 10:10:1, each 100 mL) to give two fractions, I (76 mg) and II (67 mg). Fraction I was

applied on a preparative TLC plate (Si gel, 1 mm thickness) and developed with CH_2Cl_2/EtOAc (1:1) to give a residue (15 mg). This residue was reapplied to a TLC plate (Si gel, 0.2 mm thickness) using *n*-hexane/CH_2Cl_2/EtOAc (1:1:1) as solvent to afford juncenolide B (**1**, 4 mg). Fraction II was applied on a preparative TLC plate (Si gel, 1 mm), developed with CH_2Cl_2/EtOAc (3:1), to yield a residue (12 mg), which was reapplied to a TLC plate (Si gel, 0.2 mm thickness) using *n*-hexane/CH_2Cl_2/EtOAc (1:2:1) as the developing solvent to give juncenolide C (**2**, 1 mg).

Juncenolide B (1): amorphous solid; $[\alpha]^{25}_D$ −12.4° (*c* 0.4, MeOH); UV (MeOH) λ_{max} (log ϵ) 275 nm (2.52); IR (neat) ν_{max} 3566, 3482, 1778, 1743, 1335, 1047 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 1; FABMS *m*/*z* 603 $[M + Na]^+$, 581 $[M + H]^+$; EIMS (30 eV) *m*/*z* 175 (2), 159 (3), 149 (5), 135 (9), 121 (12), 111 (14), 95 (16), 91 (11), 83 (14), 74 (16), 69 (17), 60 (100), 55 (47).

Juncenolide C (2): amorphous solid; $[\alpha]^{25}_D$ −24.4° (*c* 0.05, CH_2Cl_2); UV λ_{max} (log ϵ) 276 nm (2.50); IR (neat) ν_{max} 3565, 3483, 1770, 1749, 1645, 1627, 1461, 737 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 2; EIMS (30 eV) *m*/*z* 239 (1), 225 (3), 207 (2), 191 (2), 175 (3), 163 (4), 149 (7), 135 (7), 121 (9), 105 (7), 95 (9), 81 (11), 69 (17), 60 (100), 55 (38).

Juncenolide D (3): amorphous solid; $[\alpha]^{25}_D$ −10.3° (*c* 0.2, CH_2Cl_2); UV λ_{max} (log ϵ) 274 nm (2.54); IR (neat) ν_{max} 3566, 3482, 1778, 1743, 984, 736 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see Table 3; FABMS *m*/*z* 675 $[M + Na]^+$, 653 $[M + H]^+$; EIMS (30 eV) *m*/*z* 322 (4), 281 (4), 265 (6), 249 (6), 235 (7), 211 (8), 181 (7), 159 (8), 143 (11), 133 (13), 121 (17), 105 (17), 95 (20), 85 (76), 83 (20), 60 (100).

Cytotoxicity Assay. A bioassay against KB (oral epidermoid carcinoma) and Hepa 59T/VGH (human liver carcinoma) tumor cells was based on reported procedures.[14,15] The cytotoxicity assay utilizes binding of methylene blue to fixed monolayers of cells at pH 8.5. The monolayer is washed and the dye released by lowering the pH value. The 96-well plate was dipped into a 0.01 M borate-buffer solution four times to remove the dye. Then 100 μL/well ethanol−0.1 M HCl (1:1) was added as a dye-eluting solvent, and the absorbance was measured on a microtiter plate reader (Dynatech, MR 7000) at a wavelength of 650 nm. The IC_{50} value was defined, by a comparison with the untreated cells, as the concentration of test sample resulting in a 50% reduction of absorbance. Mitomycin was used as a standard compound and gave an IC_{50} value of 0.25 μg/mL under the above conditions.

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