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## New Briarane Stecholidide Diterpenes from the Indonesian Gorgonian *Briareum* sp.<sup>†</sup>

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The Indonesian gorgonian *Briareum* sp. has afforded two new briarane stecholidide diterpenes: 2,9-diacetyl-2-debutyrylstecholide H (**1**) and 13-dehydroxystecholide J (**2**), the semisynthetic 2 $\beta$ -acetoxy-2-(debutyryloxy)stecholide E acetate (**3**), which was isolated as a natural product for the first time, along with the known compounds stecholides I–M (**4–8**), stecholide A acetate (**9**), and stecholide C acetate (**10**). The structures of the new compounds were deduced by extensive NMR studies (<sup>1</sup>H, <sup>13</sup>C, <sup>1</sup>H–<sup>1</sup>H COSY, NOESY, HMQC, and HMBC) and FABMS data (HR and LR). Cytotoxic activity was found for the first time in stecholide L (**7**).

Terpenoid chemistry predominates across the Octocorallia class (phylum Cnidaria). Sesquiterpenes and mainly diterpenes are the most common terpenes isolated from its major groups, the Gorgonacea and Alcyonacea orders.<sup>1</sup> *Briareum* gorgonians (syn: *Solenopodium*, Briareidae family),<sup>2</sup> which were both taxonomically and chemically placed between those orders,<sup>3</sup> have been subjected to numerous chemical investigations yielding a wide variety of diterpenoids belonging to the skeletal class of briaranes, diterpenoid  $\gamma$ -lactones with a highly substituted bicyclo [8.4.0] system.<sup>4</sup> Among these molecules, the stecholides and briareolides are the common names given to the briaranes distinguished by the presence of an  $\alpha,\beta$ -epoxide group in the lactone ring. More than 45 of these compounds have been isolated so far, almost all of them from species belonging to the *Briareum* (*Solenopodium*) genus.<sup>5</sup>

As part of our continuing search for bioactive compounds from marine organisms, specially from gorgonians,<sup>6</sup> we have studied an Indonesian gorgonian iden-

tified as *Briareum* sp., selected because of the cytotoxic activity found in its extracts. In this paper, we describe the isolation and structure elucidation of 10 briaranes belonging to the stecholide/briareolide family: two new compounds (**1–2**), one briarane isolated for the first time as a natural product (**3**), and seven metabolites (**4–10**) reported previously (Chart 1).

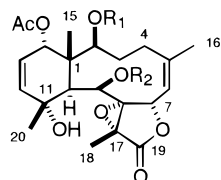
The gorgonian *Briareum* sp., collected in October 1995 along the coast of the Togian Islands (Indonesia), was extracted with MeOH to afford a crude extract that was submitted to our standard partition procedure. The CH<sub>2</sub>Cl<sub>2</sub> partition fraction gave a diterpene mixture that was subjected to several chromatographic separations including SiO<sub>2</sub> flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub> with MeOH) and HPLC (normal phase with EtOAc–hexane mixtures and reversed-phase C<sub>18</sub> with MeOH–H<sub>2</sub>O 6:4) to give pure compounds **1–10**.

Compound **1** was isolated as a white powder. The FABMS (positive mode) displayed two pseudomolecular ions at  $m/z$  529 [M + Na]<sup>+</sup> and  $m/z$  507 [M + H]<sup>+</sup> suggesting a molecular formula of C<sub>26</sub>H<sub>34</sub>O<sub>10</sub> (10 degrees of unsaturation), which was confirmed by HRFABMS. The <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>, 500 MHz) indicated the presence of seven methyl groups, three of them corre-

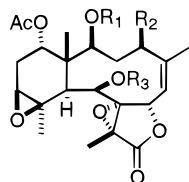
\* To whom correspondence should be addressed. Phone: 34-81-167000. Fax: 34-81-167065.

<sup>†</sup> Dedicated to the memory of Professor Luigi Minale, a pioneer in the Chemistry of Marine Natural Products.

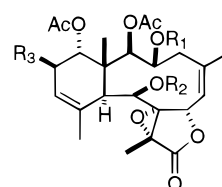
## Chart 1



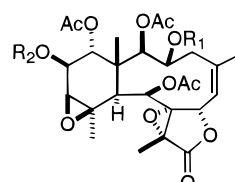
1  $R_1=R_2=Ac$ , 2, 9-Diacetyl-2-debutyrylstecholide H  
11  $R_1=COC_3H_7$ ,  $R_2=H$ , Stecholide H



3  $R_1=R_3=Ac$ ,  $R_2=H$ , 2β-Acetoxy-2-(debutyryloxy)stecholide E acetate  
9  $R_1=COC_3H_7$ ,  $R_2=OAc$ ,  $R_3=Ac$ , Stecholide A acetate  
10  $R_1=R_3=Ac$ ,  $R_2=OAc$ , Stecholide C acetate  
13  $R_1=Ac$ ,  $R_2=R_3=H$



2  $R_1=R_2=Ac$ ,  $R_3=H$ , 13-Dehydroxystecholide J  
4  $R_1=COC_3H_7$ ,  $R_2=Ac$ ,  $R_3=OH$ , Stecholide I  
5  $R_1=R_2=Ac$ ,  $R_3=OH$ , Stecholide J  
12  $R_1=Ac$ ,  $R_2=R_3=H$



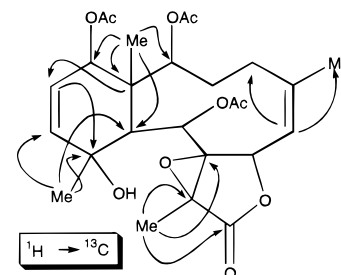
6  $R_1=R_2=Ac$ , Stecholide K  
7  $R_1=Ac$ ,  $R_2=H$ , Stecholide L  
8  $R_1=COC_3H_7$ ,  $R_2=H$ , Stecholide M

**Table 1.**  $^1H$ - (500 MHz) and  $^{13}C$ - (125 MHz) NMR Chemical Shift Data for Compounds **1** and **2** in  $CDCl_3$

2,9-diacetyl-2-debutyrylstecholide H ( <b>1</b> )			13-dehydroxystecholide J ( <b>2</b> )	
no.	$\delta_H$ mult. $J$	$\delta_C$ mult.	$\delta_H$ mult. $J$	$\delta_C$ mult.
1		46.0 s		43.9 s
2	4.92 br s	72.9 d	5.52 d 2.3	72.6 d
3/3'	2.55 m/1.71 m	24.1 t	4.78 br d	72.5 d
4/4'	1.89 m/2.55 m	25.5 t	3.24 dd 15.5 3.5/2.09 m	33.8 t
5		145.5 s		142.5 s
6	5.41 br s	119.5 d	5.40 br d 9.1	121.6 d
7	5.41 br s	73.1 d	5.61 d 9.1	73.5 d
8	-	68.9 s	-	73.9 d
9	5.66 br s	74.3 d	5.56 br s	72.6 s
10	3.00 br s	40.3 d	3.10 br s	44.0 d
11		72.1 s		135.1 s
12	5.40 d 10	120.7 d	5.49 br s	122.1 d
13	5.81 br d 10	141.2 d	2.38 m/2.22 m	28.2 t
14	4.86 br s	79.3 d	4.81 dd 8.7 6.6	76.0 d
15	1.24 s	21.1 q	1.52 s	17.0 q
16	1.85 br s	25.6 q	1.86 br s	23.5 q
17		62.4 q		62.2 s
18	1.57 s	10.1 q	1.62 s	10.5 q
19		171.5 s		171.3 s
20	1.42 s	27.6 q	1.78 br s	20.7 q
OCOCH <sub>3</sub>		169.9 s		169.3, 169.6, 169.9, 170.2 s
OCOCH <sub>3</sub>	2.07 s (6H)/2.20 s	21.2q/21.8 q	2.23, 2.13, 1.99, 1.98 s	20.7, 20.9, 21.7, 23.5 q

sponding to acetate groups at  $\delta_H$  2.07 (s, 6H) and  $\delta_H$  2.20 (s); three methyls attached to  $sp^3$  quaternary carbons at  $\delta_H$  1.57 (s), 1.42 (s), and 1.24 (s); and last, one vinylic methyl at  $\delta_H$  1.85 (br s). The existence of trisubstituted and disubstituted double bonds in **1** was deduced by the signals at lowfield in the  $^1H$ -NMR spectrum corresponding to three vinylic protons [ $\delta_H$  5.81 (br d,  $J = 10$  Hz), 5.40 (d,  $J = 10$  Hz), and 5.41 (br s), 1H each] and four olefinic carbon signals in the  $^{13}C$ - and DEPT-135 NMR spectra at  $\delta_C$  119.5 (d), 120.7 (d), 141.2 (d), and 145.5 (s). The former NMR experiments also showed singlet peaks at  $\delta_C$  169.9 and 171.5, indicating the presence of carbonyl groups corresponding to acetate groups and a  $\gamma$ -lactone moiety, respectively.

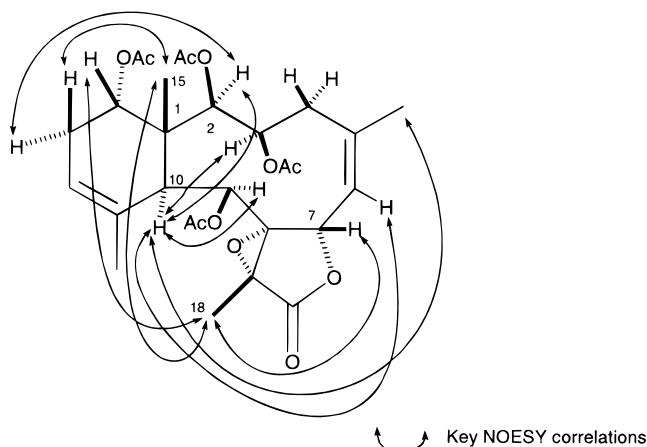
The gross structure of **1** was determined by a detailed analysis of 1D and 2D NMR spectra. The HMQC experiment allowed us to assign all the protons to the corresponding carbon atoms (Table 1) and the  $^1H$ - $^1H$  NMR COSY spectrum to identify three different spin



**Figure 1.** HMBC correlations observed in **1**.

units, which were assembled with the help of a HMBC experiment (see Figure 1).

The comparison of these spectral data to those of other briarane diterpenes reported in the literature indicated that **1** had the same skeleton as stecholide H (**11**)<sup>7</sup> but with different substitutions at C-2 and C-9. The lack of signals in the  $^1H$ - and  $^{13}C$ -NMR spectra of **1** (Table 1) corresponding to the butyrate group in **11** indicated



**Figure 2.** Key NOESY correlations of **2**.

that the butyrate group at C-2 in **11** was substituted by an acetate group in **1**. On the other hand, the resonance at  $\delta$  74.3 assigned to C-9 in the  $^{13}\text{C}$ -NMR spectrum of **1** is shifted upfield by  $\delta$  5.9 ppm in relation to that in **11**, while the C-8 ( $\delta$  68.9) and C-10 ( $\delta$  40.3) resonances are shifted upfield by 2.6 and 0.6 ppm, respectively, in relation to those in **11**. These changes are characteristic for  $\alpha$ - and  $\beta$ - effects of an acetyl group and indicated that the hydroxy group in **11** is acetylated in **1**.

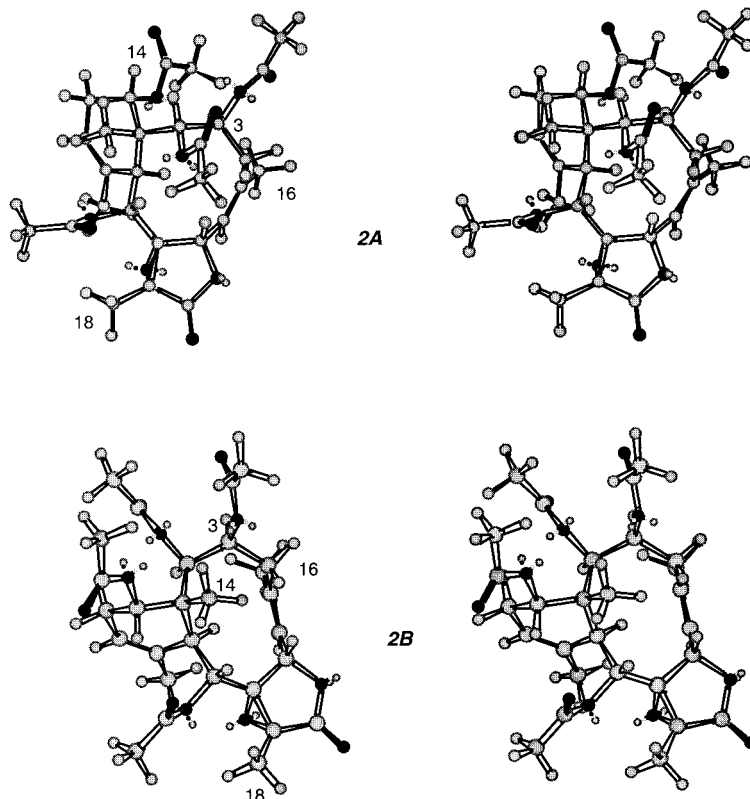
The relative stereochemistry of **1** was shown to be the same as in **11** by analysis of proton–proton coupling constants in the  $^1\text{H}$ -NMR spectrum of **1** and by comparison of its NMR data with those of stecholide H. Thus, the  $\alpha$ -configuration of the quaternary hydroxy group at C-20 and of the 8,17-epoxide group in the lactone ring in **1** was confirmed by the C-20 chemical shift at  $\delta_{\text{C}}$  27.6 of the methyl group and by the C-8, C-17,

and C-18 chemical shifts ( $\delta_{\text{C}}$  68.9, 62.4, and 10.1, respectively), which are virtually identical with those of related 8,17  $\alpha$ -epoxybriaranes.<sup>8</sup> So, we named compound **1** as 2,9-diacetyl-2-debutyrylstecholide H.

The new briarane diterpene **2** was isolated as a colorless powder. Its molecular formula of  $\text{C}_{28}\text{H}_{36}\text{O}_{11}$  was deduced from the pseudomolecular ion at  $m/z$  549  $[\text{M} + \text{H}]^+$  in its HRFABMS. The  $^{13}\text{C}$ - and DEPT-135 NMR data showed the presence in **2** of 10 quaternary, 8 methine (6  $\text{sp}^3$  and 2  $\text{sp}^2$ ), 2 methylene carbons, and 8 methyl groups that account for a diterpene structure bearing four acetate groups. This was corroborated by the four signal singlets in the  $^1\text{H}$  NMR at  $\delta_{\text{H}}$  2.23, 2.13, 1.99, and 1.98 (3H each) corresponding to four methyl groups of the acetate moieties. Also, consistent with these NMR data is the presence in **2** of two trisubstituted double bonds by the carbon chemical shifts at  $\delta_{\text{C}}$  142.5 (s), 121.6 (d), 135.1 (s), 122.1 (d), and by the two olefinic protons at  $\delta_{\text{H}}$  5.40 (br d, 1H) and 5.49 (br s, 1H) in the  $^1\text{H}$  NMR of **2**.

Following the same procedure as in **1**, HMQC and  $^1\text{H}$ – $^1\text{H}$  COSY experiments allowed us to assign all the protons to the corresponding carbons as shown in Table 1. Key HMBC correlations between Me-15 to C-10 and C-2, H-7 to C-5 and C-19, Me-18 to C-17 and C-19, Me-16 to C-4, and Me-20 to C-10 permitted the connectivity of the isolated spin systems.

Comparison of the spectral data found for **2** with those of other briarane diterpenes reported in the literature indicated that this compound is the acetate derivative of 2,3,14-triacetoxy-8,17-epoxy-9-hydroxybriara-5,11-dien-19-one (**12**) isolated from *Briareum* sp.<sup>8</sup> Due to the instability of that compound, the authors could not get all the NMR experiments to confirm the relative stereochemistry of **12**, and we thus obtained a NOESY



**Figure 3.** Stereoview of the MMX low-energy conformers of **2**.

**Table 2.** Selected Coupling Constants of the Calculated Conformers **2A** and **2B** vs Experimental

	<b>2A</b>			<b>2B</b>	
	$J_{\text{exptl}}$	$J_{\text{calcd}}$	dihedral angle ( $\phi$ )	$J_{\text{calcd}}$	dihedral angle ( $\phi$ )
<b>H2–H3</b>	1.1	1.1	–96	3.9	45
<b>H6–H7</b>	11.6	11.3	170	11.2	168
<b>H9–H10</b>	0.5	1.0	96	1.7	104

experiment of our stable compound **2** (Figure 2). NOE-SY correlations between H-10 to H-2, H-3, and H-9 indicated these protons are on the  $\alpha$ -side of the cyclo-decene ring. In a similar way, NOE cross peaks between Me-18 and H-7 and H-14 and between the axial H-13 $\beta$  and Me-15 indicated a  $\beta$ -configuration for these protons.

Energy minimization calculations using the MMX molecular mechanic program<sup>9</sup> followed by molecular dynamics studies of **2** showed two low-energy conformers with different three-dimensional shapes. Overall, the conformational analysis of **2** showed the cyclo-decene–cyclohexene bicyclic system has two different low-energy regions with C9–C10–C1–C2 angles of 73.7° (conformer **2A**, the lowest energy conformer) and 143.5° (conformer **2B**, with a 1.7 kcal/mol higher steric energy). In both conformers the  $\Delta^5$  is nearby the cyclohexene ring (see Figure 3). This unusual folding explained the NOE cross peaks H-2/H-13 $\alpha$  ( $\delta_{\text{H}}$  5.52/2.22), and H-6/H-10 ( $\delta_{\text{H}}$  5.61/3.10) in the NOESY spectrum of **2** (see Figure 2), and confirmed the proximity between  $\Delta^5$  and H10. Furthermore, the orthogonal (torsional angle around 90°) arrangement of H-2 and H-3 protons in both conformers can be corroborated by the presence of a very small coupling ( $J = 2.3$  Hz) in the  $^1\text{H}$ -NMR spectrum of **2** (see Table 2).

These results are very similar to those obtained for related briarane derivatives, such as the stecholides I–N isolated from *Solenopodium* (*Briareum*) *excavatum*<sup>10</sup> and the briareolides isolated by Bowden *et al.*,<sup>8</sup> which are characterized by an uncommon conformation. Compound **2** can be envisioned as another example where 2 $\beta$ ,3 $\beta$  disubstitution is critical for this unusual conformation. The lack of a  $\beta$ -OH at C-13 in **2** demonstrates this substitution is not necessary for adoption of such a conformation, although its presence would operate in favor the mentioned 3D shape. To keep some order in the nomenclature of briaranes, we named compound **2** as a member of the stecholide family as 13-dehydroxystecholide J.<sup>10</sup>

The  $\text{C}_{26}\text{H}_{34}\text{O}_{10}$  molecular formula for compound **3** was established from its FABMS spectrum (positive ion), which showed the pseudomolecular ion peaks at  $m/z$  507  $[\text{M} + \text{H}]^+$  (HRFABMS) and at  $m/z$  529  $[\text{M} + \text{Na}]^+$ . Comparison of the spectral data ( $^1\text{H}$  NMR, MS, and optical rotation) found for **3** with those of other briarane diterpenes reported in the literature indicated that this compound is the acetate derivative of 2 $\beta$ -acetoxy-2-debutyryloxystecholide E (**13**) isolated from a Formosan gorgonian *Briareum* sp. and obtained by acetylation of **13** in the same work.<sup>11</sup> Thus, this is the first time that **3** [2 $\beta$ -acetoxy-2-(debutyryloxy)stecholide E acetate] was isolated from a natural source.

Spectral data ( $^1\text{H}$  and  $^{13}\text{C}$  NMR, MS,  $[\alpha]^{20}_{\text{D}}$ ) of briarane stecholides **4–8** were identical with those

reported by Schimtz *et al.* from the gorgonian *Solenopodium excavatum* collected in New Guinea for stecholides I (**4**), J (**5**), K (**6**), L (**7**), and M (**8**),<sup>10</sup> while the data for briarane stecholides **9** and **10** matched those reported also by Schimtz *et al.* from the Australian gorgonian *Solenopodium stechei* for stecholide A acetate (**9**) and stecholide C acetate (**10**).<sup>7</sup> Stecholide L (**7**) showed mild cytotoxic activity against tumor cells P-388 ( $\text{IC}_{50}$  10  $\mu\text{g}/\text{mL}$ ), A-549 ( $\text{IC}_{50}$  2.5  $\mu\text{g}/\text{mL}$ ), HT-29 ( $\text{IC}_{50}$  5  $\mu\text{g}/\text{mL}$ ), and MEL-28 ( $\text{IC}_{50}$  5  $\mu\text{g}/\text{mL}$ ).

*Briareum* is one of the most widely studied genera of the Gorgonacea order, yielding a great variety of briarane diterpenes. This work is another demonstration of the high capability of these organisms to biosynthesize new metabolites. On the other hand, 2,9-diacetyl-2-debutyrylstecholide H (**1**) is the second example reported in the literature of a briarane diterpene having a  $\Delta^{12}$  double bond. The conformational analysis of compound **2** explained the uncommon conformation adopted. Although compound **3** was previously obtained by acetylation of 2 $\beta$ -acetoxy-2-(debutyryloxy)stecholide E (**13**), this is the first time it was isolated as a natural product. Compounds **1–6**, **9** and **10** were devoid of cytotoxic activity against tumor cells P-388, A-549, HT-29, and MEL-28 ( $\text{IC}_{50} > 10$ ), although compound **3** was reported to exhibit significant activity against the growth of P-388 cells ( $\text{EC}_{50}$  1.59  $\mu\text{g}/\text{mL}$ ).<sup>11</sup> Finally, this is the first time that mild cytotoxic activity is found for the known compound **7**.

## Experimental Section

**General Experimental Procedures.** NMR spectra were recorded at 500/100 MHz ( $^1\text{H}/^{13}\text{C}$ ) Varian Unity Plus, AMX-Bruker; 200/50 MHz ( $^1\text{H}/^{13}\text{C}$ ), Bruker AC-200 NMR spectrometer in  $\text{CDCl}_3$ . Carbon multiplicities were determined using DEPT-135 and DEPT-90 sequences. Atom connectivities were determined using HMQC, HMBC, and COSY data. NOESY experiments were carried out using a mixing time of 0.8 s. LR-FABMS and HRFABMS were measured on a VG-Quattro and FISIONS VG AUTOSPEC M, respectively. Optical rotations were determined on a JASCO DIP-1000 with Hg lamp at 590 nm. Preparative HPLC was performed using an  $\mu$ -Porasil and  $\mu$ -Bondapak  $\text{C}_{18}$  columns (250  $\times$  10 mm) with IR detection.

**Animal Material.** The gorgonian *Briareum* sp. (phylum Cnidaria, subphylum Anthozoa, class Octocorallia, order Gorgonacea, family Briareidae) was collected by hand using scuba equipment at 10–15 m depths off Togian Island (Indonesia). A voucher specimen (JR 9524) was deposited at the Departamento de Química Fundamental e Industrial, Universidade da Coruña. A picture can be obtained from the authors. The specimen grows in a digitated colony with retracted polyps and well-developed calyx. Coenenchyme was divided into an outlet or cortical layer and an inner or medullar layer. The medulla was penetrated by solenia but not separated by longitudinal boundary canals. Sclerites from cortex are coarse white spindles. Sclerites from medulla are coarse purple spindles with some isolated tripods.

**Extraction and Isolation.** The gorgonian (0.2 kg, dry wt) gave an aqueous MeOH extract that was processed according to our standard procedure.<sup>12</sup> The

CH<sub>2</sub>Cl<sub>2</sub> fraction (7.4 g) was flash chromatographed on Si gel (CH<sub>2</sub>Cl<sub>2</sub>–MeOH) yielding 11 fractions. Fractions 4 and 6 (eluted with CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 95:5) were purified by HPLC (normal phase, hexanes–EtOAc, 45:55) and (reversed phase, 40% aqueous MeOH) affording compounds **1** (6 mg), **2** (7 mg), **3** (4 mg), **4** (14 mg), **5** (100 mg), **6** (6 mg), **7** (36 mg), **8** (10 mg), **9** (10 mg), and **10** (14 mg).

**2,9-Diacetyl-2-debutyrylstecholide H (1):** white powder; [α]<sub>D</sub> –69.8° (c 0.05, CH<sub>2</sub>Cl<sub>2</sub>); UV (MeOH) λ<sub>max</sub> 228 nm; <sup>1</sup>H and <sup>13</sup>C NMR, see Table 1; FABMS *m/z* (rel int): 529 (10 [M + Na]<sup>+</sup>); 507 (7 [M + H]<sup>+</sup>); HRFABMS *m/z* 507.2219 (calcd. for C<sub>26</sub>H<sub>35</sub>O<sub>10</sub>, 507.2230).

**13-Dehydroxystecholide J (2):** white powder; [α]<sub>D</sub> –19.2° (CH<sub>2</sub>Cl<sub>2</sub>, c 0.05); UV (MeOH) λ<sub>max</sub> 230 nm; <sup>1</sup>H and <sup>13</sup>C NMR, see Table 1; FABMS *m/z* (rel int) 571 (19 [M + Na]<sup>+</sup>); 549 (9 [M + H]<sup>+</sup>), 507 (7 [M – Ac]<sup>+</sup>), 489 (13 [M – HOAc]<sup>+</sup>); HRFABMS *m/z* 549.2340 (calcd. for C<sub>29</sub>H<sub>37</sub>O<sub>11</sub>, 549.2336).

**2β-Acetoxy-2-(debutyryloxy)stecholide E acetate (3):** white powder; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) 4.89 (d, *J* = 6.4 Hz, H-2); 2.59–1.70 (m, 1H each, H-3/3'); 2.54 (m, 2H, H-4/4'); 5.30 (s, H-6); 5.38 (s, H-7); 5.74 (d, *J* = 3.5 Hz, H-9); 2.45 (1H d, *J* = 3.5 Hz, H-10); 3.03 (1H, br s, H-12); 2.04–2.14 (1H each, m, H-13/13'); 4.71 (1H, br s, H-14); 1.00 (3H, s, H-15); 2.06 (3H, s, H-16); 1.68 (3H, s, H-18); 1.43 (3H, s, H-20); 2.01–2.03–2.04 (3H each, s, OAc); FABMS *m/z* (rel int) 529 (11 [M + Na]<sup>+</sup>); 507 (11 [M + H]<sup>+</sup>); HRFABMS *m/z* 507.2215 (calcd. for C<sub>26</sub>H<sub>34</sub>O<sub>10</sub>, 507.2230).

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10301A97) and CICYT (MAR95-1933 CO2-O2). Taxonomic information was generously provided by Dr. Francisco Ramil (Universidad de Vigo, Spain). We appreciate assistance in the collection of gorgonians by Prof. Phillip Crews (University of Santa Cruz, California) and for providing logistical support. We are grateful to BIOMAR S.A. for the pharmacological assays.

## References and Notes

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- (2) After a long debate about the phylogenetic position of the genus *Briareum* in relation to the *Solenopodium*, both genera have been merged. See: Bayer, F. M. *Proc. Biol. Soc. Wash.* **1981**, *94*, 902–947.
- (3) Although *Briareum* soft corals are taxonomically placed within the Gorgonacea, their growth form and appearance is more typically Alcyonacea. See ref 2.
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