

## Scalarane-Based Sesterterpenoid RCE-Protease Inhibitors Isolated from the Indonesian Marine Sponge *Carteriospongia foliascens*

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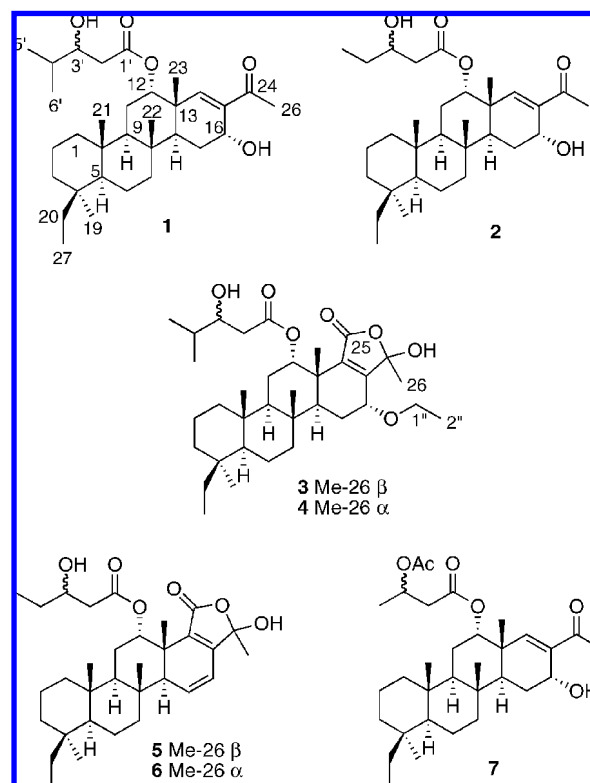
Two new 20,24-bishomo-25-norscalaranes, compounds **1** and **2**, and two new and two known 20,24-bishomoscalaranes, compounds **3–6**, have been isolated from the Indonesian marine sponge *Carteriospongia foliascens*. The structures of **1–6** were determined by spectroscopic analysis. Compounds **1** and **3–6** inhibit RCE-protease activity.

The Ras signaling pathway has been identified as an important target for the development of anticancer drugs.<sup>1–3</sup> Ras proteolysis represents one promising target for disrupting Ras signaling. The characterization of hRCE1 (human Ras-covering enzyme),<sup>2</sup> which is responsible for proteolytic processing of Ras, led to the development of an assay to screen for RCE-protease inhibitors.<sup>3</sup> In 2002 we published the structures of the sesterterpene barangca-dioic acid A and the norsesterterpenes rhopaloic acids D to G. These terpenoids, isolated from an Indonesian sponge, represented the first reported natural product inhibitors of the RCE-protease.<sup>4</sup> Sponges continue to be the single richest marine source of structurally novel secondary metabolites.<sup>5</sup> Crude extracts of the Indonesian sponge *Carteriospongia foliascens* (order Dictyoceratida, family Thorectidae) showed promising activity in the RCE protease assay. Sponges of the order Dictyoceratida and particularly the family Thorectidae are known sources of scalarane-based sesterterpenes, and many 20,24-bishomoscalarane and 20,24-bishomo-25-norscalarane derivatives have been isolated from members of the genus *Phyllospongia* (syn. *Carteriospongia*).<sup>5,6</sup> Bioassay-guided fractionation of the extracts of *C. foliascens* led to the identification of the two new bishomonorscalaranes **1** and **2** and two new and two known bishomoscalaranes, **3–6**. Details of the isolation, structure elucidation, and biological activities of the terpenoids **1–6** are presented below.

### Results and Discussion

*C. foliascens* (order Dictyoceratida, family Thorectidae) was harvested by hand using scuba on reefs off Palau Barang Lompo near Makassar, Indonesia. Freshly collected sponge was repeatedly extracted with EtOH. The EtOH extracts were combined, concentrated *in vacuo*, and then partitioned between H<sub>2</sub>O and EtOAc. Repeated fractionation of the EtOAc-soluble materials via Sephadex LH-20 and flash silica gel column chromatography, followed by repetitive reversed-phase HPLC, gave pure samples of the two new 20,24-bishomo-25-norscalaranes **1** and **2**, inseparable mixtures of the new epimeric 20,24-bishomoscalarane ketals **3** and **4**, and the recently reported epimeric 20,24-bishomoscalarane ketals **5** and **6**.<sup>7</sup>

Compound **1** was obtained as a clear oil that gave a [M + Na]<sup>+</sup> ion in the HRESIMS at *m/z* 539.3708, appropriate for a molecular formula of C<sub>32</sub>H<sub>52</sub>O<sub>5</sub>, requiring seven sites of unsaturation. The <sup>1</sup>H



NMR spectrum of **1** contained five methyl singlets ( $\delta$  0.78, 0.83, 0.86, 1.04, 2.24), two methyl doublets ( $\delta$  0.89 ( $J = 6.8$  Hz), 0.91 ( $J = 6.7$  Hz)), and one methyl triplet ( $\delta$  0.72 ( $J = 7.4$  Hz)). A search of the literature using the MarineLit<sup>8</sup> database with methyl number criteria rapidly identified 20,24-bishomoscalaranes and 20,24-bishomo-25-norscalaranes as likely candidates for a carbon skeleton template. The <sup>1</sup>H/<sup>13</sup>C/COSY/HSQC/HMBC NMR data obtained for **1** (Table 1) identified resonances that could be assigned to 32 carbon atoms, which was consistent with the HRESIMS data. In addition to the eight methyls, the presence of a conjugated trisubstituted olefin ( $\delta$  138.1 (C-17); 6.58 s (H-18), 151.4 (C-18)), a conjugated methyl ketone ( $\delta$  201.4 (C-24); 2.24 s (H-26), 25.3 (C-26)), two carbinol methines ( $\delta$  4.54 (H-16), 63.3 (C-16); 3.68 (H-3'), 73.1 (C-3')), and an ester ( $\delta$  5.08 (H-12), 76.7 (C-12); 172.5 (C-1')) was apparent in the NMR data and accounted for three of the seven required sites of unsaturation. These structural features and the chemical shifts of the remaining <sup>13</sup>C resonances are markedly similar to the structural components of phyllofenone C

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**Table 1.** NMR Data for Compounds **1** and **2** (600 MHz, CDCl<sub>3</sub>)

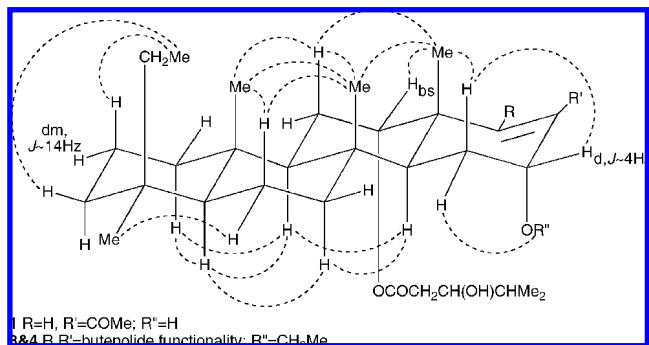
atom # <sup>a</sup>	<b>1</b>		<b>2</b>	
	$\delta_C^b$	$\delta_H$ (J in Hz)	$\delta_C^b$	$\delta_H$ (J in Hz)
1 <sub>ax</sub>	39.9	0.66, td (12.5, 3.4)	40.1	0.65, bt (12.2)
1 <sub>eq</sub>		1.54, nd <sup>c</sup>		1.54, nd
2 <sub>ax</sub>	18.1	1.47, nd	18.2	1.46, nd
2 <sub>eq</sub>		1.35, m		1.34, m
3 <sub>ax</sub>	36.4	0.83, nd	36.6	0.82, nd
3 <sub>eq</sub>		1.64		63, nd
4	35.8		36.2	
5	58.3	0.93, nd	58.5	0.93, nd
6	17.9	1.44, nd	17.9	1.44, nd
		1.56, nd		1.56, nd
7 <sub>ax</sub>	40.8	1.09, nd	41.1	1.09, nd
7 <sub>eq</sub>		1.80, dm (12.6)		1.80, dm (12.9)
8	36.8		37.0	
9	53.3	1.35, m	53.5	1.35, m
10	36.8		37.0	
11	22.1	1.76, nd	22.3	1.76, nd
		1.76, nd		1.76, nd
12	76.7	5.08, bs	76.7	5.08, bs
13	41.3		41.6	
14	43.5	1.87, dm (11.2)	43.6	1.86, dm (12.2)
15	25.0	1.55–1.58, nd	25.1	1.58, nd
		1.85, dm (10.8)		1.85, dm (14.2)
16	63.3	4.54, d (4.1)	63.2	4.54, d (4.1)
17	138.1		138.2	
18	151.4	6.58, s	151.6	6.58, s
19	28.3	0.78, s	28.5	0.78, s
20	24.3	1.16, dq (14.4, 7.2)	24.5	1.16, dq (14.0, 7.0)
		1.50, nd		1.51, nd
21	17.0	0.83, s	16.9	0.83, s
22	17.0	0.86, s	17.1	0.86, s
23	19.6	1.04, s	19.7	1.05, s
24	201.4		201.5	
26	25.3	2.24, s	25.6	2.24, s
27	8.5	0.72, t (7.2)	8.7	0.72, t (6.8)
1'	172.5		172.4	
2'	39.3	2.38, dd (15.7, 9.6)	41.8	2.38, dd (15.7, 9.2)
		2.47, dd (15.7, 3.1)		2.49, dd (15.7, 3.4)
3'	73.1	3.68, m	69.6	3.85, m
4'	33.0	1.67, nd	29.6	1.49, nd
				1.49, nd
5'	17.4	0.91, d (6.7)	10.0	0.93, t (7.4)
6'	18.4	0.89, d (6.8)		

<sup>a</sup> Numbering system follows that proposed by Kazlauskas et al.<sup>6</sup>

<sup>b</sup> Values obtained from HSQC and HMBC correlations. <sup>c</sup> Multiplicity not determined due to overlapping signals/chemical shifts determined from 2D data.

(**7**) isolated from the closely related Indonesian sponge *Strepsichordia aliena* (family Thorectidae).<sup>9</sup> The NMR assignments for the sesterterpene portion of **1** were almost identical to those assigned to **7**, and COSY and HMBC NMR data showed that **1** contained a 3-hydroxy-4-methylpentanoate ester in place of the 3-acetoxybutanoate ester found in **7**. HMBC correlations were observed from H-12 ( $\delta$  5.08) and both of the methylene H-2' protons ( $\delta$  2.38 and 2.47) to the C-1' ester carbonyl resonance at  $\delta$  172.5, demonstrating that the pentanoate moiety was attached at C-12 of the sesterterpene fragment of **1**. Analysis of 2D NOESY and  $J$  coupling values (Figure 1) demonstrated that the relative configuration of the substituents on the sesterterpene core of **1** was the same as that observed in **7**.

Compound **2** gave a  $[M + Na]^+$  ion in the HRESIMS at  $m/z$  525.3557, appropriate for a molecular formula of C<sub>31</sub>H<sub>50</sub>O<sub>5</sub>, which differed from the molecular formula of **1** simply by the loss of CH<sub>2</sub>. The <sup>1</sup>H NMR spectrum of **2** was remarkably similar to that of **1**, the major difference being the absence of the two methyl doublets assigned to the isopropyl group of the 3-hydroxy-4-methylpentanoyl moiety in **1**. Instead, the <sup>1</sup>H NMR spectrum of **2** contained a new methyl triplet at  $\delta$  0.93 ( $J = 7.4$  Hz), and analysis of the 2D NMR data (Table 1) demonstrated that the 3-hydroxy-

**Figure 1.** Summary of the significant NOESY correlations (dashed) and  $J$  coupling values used to assign the relative stereochemistry of compounds **1**, **3**, and **4**.

4-methylpentanoyl unit in **1** had been replaced by a 3-hydroxy-pentanoyl moiety in **2**. All other structural features of **1** and **2** were identical.

Compounds **3** and **4** were isolated as an inseparable mixture of C-24 epimers that gave a  $[M + Na]^+$  ion at  $m/z$  611.3925 in the HRESIMS appropriate for a molecular formula of C<sub>35</sub>H<sub>56</sub>O<sub>7</sub>. Two sets of signals with partial overlap were observed in the <sup>1</sup>H and <sup>13</sup>C NMR of this mixture, and the <sup>1</sup>H NMR integrals indicated that the two compounds were present in a 4:1 ratio. Analysis of the <sup>1</sup>H/<sup>13</sup>C/COSY/HSQC/HMBC NMR data (Tables 2 and 3, Figure 2) obtained for the mixture indicated that compounds **3** and **4** were closely related to **1** and **2**, with the same methyl substitution pattern on the A, B, and C rings, a 3-hydroxy-4-methylpentanoyl moiety at C-12, and an oxymethine at C-16 ( $\delta$  69.0 and 68.5). The presence of additional structural components (chemical shifts quoted for the major isomer **3**) including a conjugated tetrasubstituted olefin ( $\delta$  156.8 (C-17), 137.6 (C-18)), an ester ( $\delta$  168.1 (C-25)), a ketal carbon ( $\delta$  104.5 (C-24)), a carbinol methine ( $\delta$  3.68 (H-3'), 73.1 (C-3')), a methyl singlet ( $\delta$  1.60 (H-26), 23.5 (C-26)), and an oxethyl group ( $\delta$  3.56/3.69 (dq,  $J = 16.1, 7.1$  Hz) (H'-1), 65.5 (C-1''); 1.23 (t,  $J = 7.1$  Hz) (H-2''), 15.6 (C-2'')) was also apparent in the NMR data for **3** and **4**. HMBC correlations observed between C-18 ( $\delta$  137.6) and Me-23 ( $\delta$  1.15), H-16 ( $\delta$  4.08), and H-14 ( $\delta$  1.95) and between C-17 ( $\delta$  156.8) and both H-15<sub>eq</sub> ( $\delta$  2.03) and H-16 ( $\delta$  4.08) indicated that an  $\alpha,\beta$ -unsaturated- $\gamma$ -lactone was fused to ring D. In addition, a methyl substituent at the ketal carbon C-24 satisfied the observed HMBC correlations between Me-26 ( $\delta$  1.60) and both C-17 ( $\delta$  156.8) and C-24 ( $\delta$  104.5). The butenolide functionality in the position proposed for **3** and **4** is commonly seen in the 20,24-bishomoscleranes found in the Phyllospongiae subfamily of sponges.<sup>10</sup> HMBC cross-peaks observed between H-16 ( $\delta$  4.08) and C-1'' ( $\delta$  65.5) and between H-1'' ( $\delta$  3.56/3.69) and C-16 ( $\delta$  69.0) demonstrated that the ethoxy fragment was attached at C-16. The NMR data indicated clearly that compounds **3** and **4** are epimers at the ketal C-24. Analysis of 2D NOESY and  $J$  coupling values demonstrated that the relative configuration of the substituents on the sesterterpene portion of **3** and **4** was the same as that observed in **1** and **2** (Figure 1). In the major isomer **3**, a 2D NOESY correlation between H-16 and Me-26 indicated that Me-26 is in the  $\beta$ -configuration. The presence of an ethoxide functionality at C-16 in **3** and **4** is unusual. The sponge tissue was worked up in EtOH, so it is possible that compounds **3** and **4** are artifacts of the isolation procedure.

Compounds **5** and **6** were also isolated as an inseparable mixture that gave a  $[M + Na]^+$  ion in the HRESIMS at  $m/z$  551.3351, appropriate for a molecular formula of C<sub>32</sub>H<sub>48</sub>O<sub>6</sub>. The <sup>1</sup>H NMR indicated that the two compounds were in a 1:1 ratio and were closely related to compounds **1–4**. Analysis of the <sup>1</sup>H/<sup>13</sup>C/COSY/HSQC/HMBC NMR data (Tables 2 and 3) obtained for the mixture indicated that the oxygen substituent at C-16 found in **1–4** was replaced with a  $\Delta^{15-16}$  double bond. Hence, **5** and **6** were found to

**Table 2.**  $^1\text{H}$  NMR Data for Compounds **3**, **4**, **5**, and **6** (600 MHz,  $\text{CDCl}_3$ )

atom # <sup>a</sup>	<b>3</b> $\delta_{\text{H}}$ (J in Hz)	<b>4</b> $\delta_{\text{H}}$ (J in Hz)	<b>5</b> and <b>6</b> $\delta_{\text{H}}$ (J in Hz)
1 <sub>ax</sub>	0.60, td (12.5, 3.6)	0.60, td (12.5, 3.6)	0.61, tm (12.4)
1 <sub>eq</sub>	1.57, nd <sup>b</sup>	1.57, nd	1.58, nd
2 <sub>ax</sub>	1.46, nd	1.46, nd	1.47, nd
2 <sub>eq</sub>	1.33, dm (14.2)	1.33, dm (14.2)	1.34, nd
3 <sub>ax</sub>	0.82, nd	0.82, nd	0.83, nd
3 <sub>eq</sub>	1.66, nd	1.66, nd	1.62, nd
5	0.91, nd	0.91, nd	0.88, nd
6	1.48, nd	1.48, nd	1.47, nd
	1.57, nd	1.57, nd	1.53, nd
7 <sub>ax</sub>	0.98, td (12.5, 3.5)	0.98, td (12.5, 3.5)	1.00, nd
7 <sub>eq</sub>	1.77, dm (12.5)	1.77, dm (12.5)	1.91 and 1.93, nd
9	1.24, m	1.24, nd	1.22, nd
11	1.69, nd	1.67, nd	1.63, nd
	1.96, nd	2.01, nd	2.05, nd
12	5.66, bs	5.55, bs	5.51/5.56, bs
14	1.95, dm (13.2)	1.81, dm (13.6)	2.63/2.67, bs
15	1.44, tm (13.2)	1.47, nd	6.39/6.40, dd (9.6/9.8, 2.7/2.8)
	2.03, nd $J = 13.2$ Hz	2.03, nd	
16	4.08, d (4.0)	4.16, d (4.0)	6.24/6.28, dd (9.6/9.8, 2.7/2.8)
19	0.81, s	0.77, s	0.78/0.79, s
20	1.16, nd	1.16, nd	1.15, nd
	1.52, nd	1.52, nd	1.50, nd
21	0.83, s	0.82, s	0.83, s
22	0.89, s	0.89, s	1.01, s
23	1.15, s	1.13, s	1.04/1.06, s
26	1.60, s	1.69, s	1.62/1.65, s
27	0.73, t (7.4)	0.72, nd	0.73, t (7.4)
2'	2.37, dd (16.1, 9.9)	2.32, nd	2.32–2.57, nd
	2.45, dd (16.1, 2.3)	2.45, nd	
3'	3.74, m	3.64, m	3.86/3.90, m
4'	1.64, nd	1.66, nd	1.49, nd
			1.49, nd
5'	0.90, d (6.8)	0.90, nd	0.94, t (7.4)
6'	0.89, nd	0.89, nd	
1''	3.56, m	3.48, m	
	3.69 m	3.70, nd	
2''	1.23, t (7.1)	1.24, t (7.1)	

<sup>a</sup> Numbering system follows that proposed by Kazlauskas et al.<sup>6, b</sup> Multiplicity not determined due to overlapping signals/chemical shifts determined from 2D data.

be the C-12 epimers of the known metabolites phylloctones D and E, isolated from *Phyllospongia foliascens*.<sup>11</sup> Compounds **5** and **6** have previously been isolated from the sponge *Phyllospongia papyracea* collected in the South China Sea.<sup>7</sup>

Compound **1** and the mixtures of **3/4** and **5/6** all had  $\text{IC}_{50}$  values of 4.2–38.0  $\mu\text{g}/\text{mL}$  in the RCE-protease assay (Table 4), which utilizes a fluorescent-labeled peptide from the carboxy terminal of farnesylated K-Ras as substrate and is analyzed by reversed-phase HPLC as described previously.<sup>3</sup> Additionally, the compounds were tested against four tumor cell lines for inhibition of cell growth. The LoVo colon cell line has a mutated K-Ras and activated Ras pathway, and consequently it is quite sensitive to Ras pathway inhibitors. CACO-2 is a colon tumor cell line that has normal Ras and is generally resistant to Ras pathway inhibitors. PC-3 is a prostate tumor line and MDA-468 is a breast cancer cell line (both with mutated PTEN and p53 but not RAS) that were not expected to be particularly sensitive to Ras pathway inhibition. The compounds do not appear to exhibit a significant trend of stronger activity against the LoVo cell line compared to CACO-2 (or for the other two cell lines), the expected trend for RCE-protease inhibitors. The mixtures of **3/4** and **5/6** have similar activities in both the cell-based assays and the enzyme assays, which might suggest that the cytotoxic effect of these compounds results from modulating a target outside of the Ras pathway. A compound that inhibits only a RAS pathway target would be expected to be selective for LoVo over CACO-2 and also would be expected to inhibit cell growth at concentrations higher than that needed to inhibit the enzyme target *in vitro*. Furthermore compound **1** is even more active in the cell-based assays than in the enzyme assay, which suggests that the cytotoxic effect of **1** results from hitting more

than one molecular target or at least a different target than the others. The assay results for the mixtures of **3/4** and **5/6** are further complicated since the individual components may have different physical properties (such as permeability and solubility at the  $\mu\text{M}$  levels needed) and/or different target activities.

## Experimental Section

**General Experimental Procedures.** Optical rotations were recorded on a Jasco P1010 polarimeter, and UV spectra were recorded on a Waters 2487 UV detector.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a 600 MHz spectrometer with a 5 mm inverse probe or a 5 mm inverse cryoprobe.  $^1\text{H}$  chemical shifts are referenced to the residual  $\text{CDCl}_3$  signal ( $\delta$  7.24 ppm), and  $^{13}\text{C}$  chemical shifts are referenced to the  $\text{CDCl}_3$  solvent peak ( $\delta$  77.0 ppm).

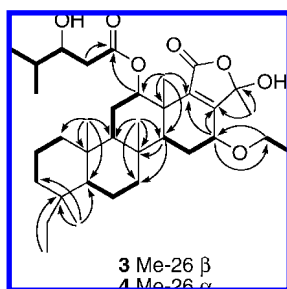
**Sponge Material.** Specimens of *Carteriospongia foliascens* (Pallas, 1766) were collected by hand using scuba at a depth of 10 m near Palau Barang Lompo, Makassar, Sulawesi, Indonesia, in October 1997 (S 5°02.52', E 119°19.48'). A voucher sample has been deposited at the Zoological Museum of Amsterdam (ZMA POR. 19109).

**Extraction of *Carteriospongia foliascens* and Isolation of Compounds 1–6.** Freshly collected sponge (110 g) was cut into small pieces and immersed in and subsequently extracted repeatedly with EtOH (3  $\times$  300 mL). The combined ethanolic extracts were concentrated *in vacuo*, and the resultant oil was shipped to Vancouver. The extract was then partitioned between EtOAc (3  $\times$  5 mL) and  $\text{H}_2\text{O}$  (15 mL). The combined EtOAc extract was evaporated to dryness, and the resulting oil was chromatographed on Sephadex LH-20. First 4:1 MeOH/ $\text{CH}_2\text{Cl}_2$  and second 20:5:2 EtOAc/MeOH/ $\text{H}_2\text{O}$  was used as eluent to give early eluting bioactive fractions from both columns, which exhibited a multitude of  $^1\text{H}$  NMR signals between 3.5 and 6.7 ppm. This material was further fractionated using silica gel flash chromatography, employing a step gradient from 19:1 hexanes/EtOAc to

**Table 3.**  $^{13}\text{C}$  NMR Data for Compounds **3**, **4**, **5**, and **6** (150 MHz,  $\text{CDCl}_3$ )

atom # <sup>a</sup>	<b>3</b> <sup>b</sup>	<b>4</b> <sup>b</sup>	<b>5</b> and <b>6</b> <sup>c</sup>
1	40.1	40.1	40.0
2	18.2	18.2	18.2
3	36.6	36.6	36.6
4	36.1	36.1	36.1
5	58.7	58.5	58.6
6	17.9	17.9	17.8
7	41.5	41.3	41.0
8	37.1	36.9 <sup>d</sup>	37.2
9	53.7	53.1	52.5
10	37.1	37.0 <sup>d</sup>	36.8
11	21.3	21.0	21.3
12	74.2	74.3	73.1
13	39.5	39.0	40.0
14	45.1	45.8	53.9
15	22.9	22.9	138.8
16	69.0	68.5	118.1
17	156.7	158.1	156.4/157.2
18	137.6	137.6	131.1
19	28.5	28.5	28.5
20	24.5	24.5	24.5
21	16.8	16.7	16.7
22	17.5	17.5	18.9
23	18.7	18.6	17.0
24	104.5	104.5	103.2
25	168.1	168.1	unassigned
26	23.5	25.8	23.4/24.5
27	8.6	8.6	8.64
1'	170.1	171.8	171.1/171.3
2'	40.1	39.0	41.8
3'	73.2	72.8	69.7
4'	33.2	33.2	29.5
5'	18.9	19.3	9.9
6'	17.2	17.2	
1''	65.5	65.2	
2''	15.6	15.5	

<sup>a</sup> Numbering system follows that proposed by Kazlauskas et al.<sup>6</sup>  
<sup>b</sup> Values obtained from  $^{13}\text{C}$  NMR spectrum. <sup>c</sup> Values obtained from HSQC and HMBC correlations. <sup>d</sup> Assignments within a column are interchangeable.

**Figure 2.** Summary of the significant COSY (bold bonds) and HMBC (arrow) correlations used to assign the structure of compounds **3** and **4**.

$\text{EtOAc}$ . A RCE-protease inhibitory fraction, eluting with 19:1–3:1 hexanes/ $\text{EtOAc}$ , exhibited interesting  $^1\text{H}$  NMR signals. Mixtures of compounds **1–6** were obtained from this fraction via  $\text{C}_{18}$  reversed-phase HPLC using a CSC-Inertsil 150A/ODS2, 5  $\mu\text{m}$  25  $\times$  0.94 cm column, with 17:3 MeCN/ $\text{H}_2\text{O}$  as eluent. From these mixtures after fractionation with a second  $\text{C}_{18}$  reversed-phase HPLC, using the same

**Table 4.** Inhibition of Both RCE-Protease and Cell Proliferation<sup>a</sup> of Four Tumor Cell Lines

compound	enzyme (RCE) assay $\text{IC}_{50}$ ( $\mu\text{g}/\text{mL}$ )	cell line assays $\text{IC}_{50}$ ( $\mu\text{g}/\text{mL}$ )			
		PC3	LoVo	CACO-2	MDA468
<b>1</b>	38	3.8	7.6	3.4	9.5
<b>2</b>	>100	>10	>10	>10	>10
<b>3/4</b>	4.2	3.2	2.9	4.2	4.4
<b>5/6</b>	9.0	3.7	3.4	6.2	>10

<sup>a</sup> Three-day treatment.

column but with 9:1 MeOH/ $\text{H}_2\text{O}$  as eluent, compounds **1** (0.3 mg), **2** (0.1 mg), a mixture of **3** and **4** (0.8 mg), and a mixture of **5** and **6** (0.3 mg) were obtained all as clear oils.

**Compound 1:** clear oil;  $[\alpha]_D^{25}$  0.0 (*c* 0.20,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 232 (3.3) nm;  $^1\text{H}$  NMR, see Table 1;  $^{13}\text{C}$  NMR, see Table 1; (+)-HRESIMS  $[\text{M} + \text{Na}]^+ m/z$  539.3708 (calcd for  $\text{C}_{32}\text{H}_{52}\text{O}_5\text{Na}$ , 539.3712).

**Compound 2:** clear oil;  $[\alpha]_D^{25}$  0.0 (*c* 0.13,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 229 (3.3) nm;  $^1\text{H}$  NMR, see Table 1;  $^{13}\text{C}$  NMR, see Table 1; (+)-HRESIMS  $[\text{M} + \text{Na}]^+ m/z$  525.3557 (calcd for  $\text{C}_{31}\text{H}_{50}\text{O}_5\text{Na}$ , 525.3556).

**Compounds 3 and 4:** clear oil;  $[\alpha]_D^{25}$  +26.0 (*c* 0.53,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  204 nm;  $^1\text{H}$  NMR, see Table 2;  $^{13}\text{C}$  NMR, see Table 3; (+)-HRESIMS  $[\text{M} + \text{Na}]^+ m/z$  611.3925 (calcd for  $\text{C}_{35}\text{H}_{56}\text{O}_7\text{Na}$ , 611.3924).

**Compounds 5 and 6:** clear oil;  $[\alpha]_D^{25}$  +30.0 (*c* 0.20,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 202 (3.76), 290 (3.77) nm;  $^1\text{H}$  NMR, see Table 2;  $^{13}\text{C}$  NMR, see Table 3; (+)-HRESIMS  $[\text{M} + \text{Na}]^+ m/z$  551.3351 (calcd for  $\text{C}_{32}\text{H}_{48}\text{O}_6\text{Na}$ , 551.3349).

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**Supporting Information Available:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compounds **1**, **2**, and **3/4**; and HSQC and HMBC spectra for **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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