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## Thorectandrols C, D, and E, New Sesterterpenes from the Marine Sponge *Thorectandra* sp.

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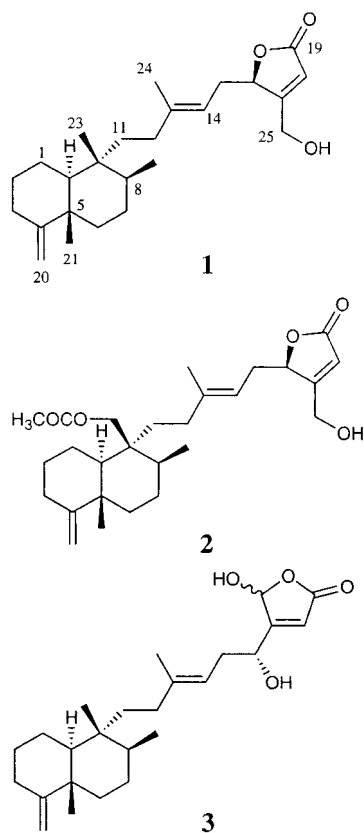
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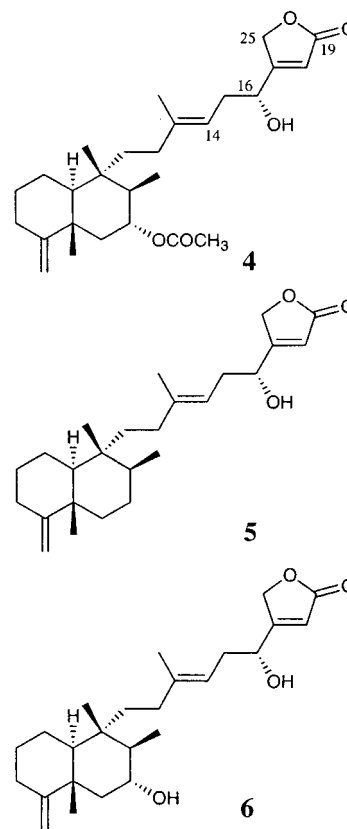
Extracts of the marine sponge *Thorectandra* sp. have been found to contain three new sesterterpenes, thorectandrols C (**4**), D (**5**), and E (**6**), together with the known compounds luffarin R (**7**), luffarin V (**8**), and palauolide (**9**). The structures were determined by extensive NMR spectral data analysis. Their relative stereochemistry was defined using NOE correlations and coupling constants, while CD data were used to suggest their absolute stereochemistry. Cytotoxicity data for compounds **4–9** as well as the previously reported compounds thorectandrols A and B and palauolol (**1–3**) against six or more human tumor cell lines are also reported.

Natural products isolated from sponges of the family Thorectidae have been widely reported;<sup>1</sup> however there are only a few reports of secondary metabolites isolated from sponges of the genus *Thorectandra*. Examples include terpene-derived metabolites such as manoalide acetate,<sup>2</sup> two furanoditerpenes,<sup>3</sup> and a terpene lactone.<sup>4</sup> From a Palauan collection of a *Thorectandra* sp. we have reported two sesterterpenes, thorectandrols A (**1**) and B (**2**),<sup>5</sup> along with the known compound palauolol (**3**).<sup>6</sup> During a continu-

E (**6**) together with the known compounds luffarin R (**7**),<sup>7</sup> luffarin V (**8**),<sup>7</sup> and palauolide (**9**).<sup>8</sup>



ing investigation of *Thorectandra* sp. we identified three more new sesterterpenes, thorectandrols C (**4**), D (**5**), and



### Results and Discussion

The crude organic extract of the frozen sponge showed antiproliferative activity in the human melanoma and breast cancer cell lines and therefore was subjected to bioassay-guided fractionation, which began with solvent–solvent partitioning.<sup>9</sup> The active methyl *tert*-butyl ether partition was further separated by reversed-phase HPLC (CH<sub>3</sub>CN/H<sub>2</sub>O) to give thorectandrol C (**4**, 2.8 mg), thorectandrol D (**5**, 1.3 mg), and thorectandrol E (**6**, 1.4 mg) and the

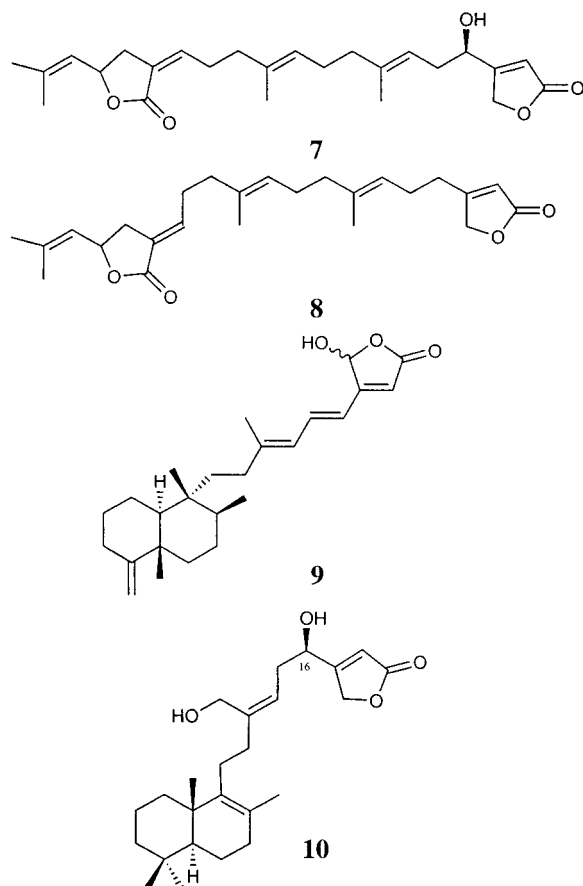
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**Table 1.**  $^1\text{H}$ ,  $^{13}\text{C}$  NMR Spectral Data for Thorectandrol C (**4**) in Methanol- $d_4$ 

position	$\delta^{13}\text{C}$	$\delta^1\text{H}$ (mult., $J = \text{Hz}$ )	COSY <sup>a</sup>	HMBC
1	22.9	a 1.50 (m) b 1.58 (m)	H10 H10	C2, C5, C9, C10 C5, C9, C10
2	29.6	a 1.28 (m) b 1.91 (m)	H1a, H2b, H3a H2a, H3b	C3 C10
3	33.6	a 2.11 (m) b 2.32 (dt, 14.0, 4.9)	H2a, H3b H2b, H3a	C1, C4, C5, C20 C2, C4, C20
4	160.4			
5	41.6			
6	44.1	a 1.48 (m) b 1.91 (m)	H6b, H7 H6a, H7	C4, C5, C7, C8, C21 C5, C7, C10, C21
7	75.3	4.96 (dt, 11.3, 4.0)	H6, H8	C8, C22, C26
8	42.8	1.58 (m)	H7, H22	C6, C7, C9, C10, C11, C22, C23
9	41.9			
10	49.7	1.20 (dd, 12.0, 2.6)		C2, C5, C23
11	38.3	1.40 (m, 2H)	H12	C8, C9, C10, C12, C13, C23
12	34.1	a 1.77 (m) b 1.85 (m)	H11 H11	C11, C13, C14, C24 C11, C13, C14, C24
13	140.3			
14	119.8	5.21 (t, 7.0)	H15, H24	C12, C15, C16, C24
15	36.0	2.40 (t, 6.6, 2H)	H16, H24	C13, C14, C16, C17
16	69.4	4.61 (t, 6.3)	H15	C14, C17, C18
17	176.3 <sup>b</sup>			
18	115.1	5.93 (br s)	H16, H25	C19
19	176.4 <sup>b</sup>			
20	103.5	a 4.48 (bs) b 4.51 (bs)	H3 (w) H3	C3, C5 C4, C5
21	22.2	1.17 (s, 3H)		C4, C5, C6, C10
22	11.0	0.85 (d, 6.7, 3H)	H8	C7, C8
23	19.7	0.83 (s, 3H)		C10, C11
24	16.6	1.61 (bs, 3H)		C12, C13, C14
25	73.0	4.90 (s, 2H)		C17, C19
26	172.8			
27	21.0	2.05 (s, 3H)		C26

<sup>a</sup> a and b denote upfield and downfield resonances, respectively, for a geminal pair. <sup>b</sup> Assignments can be interchanged.

known compounds luffarin R (**7**, 1.2 mg), luffarin V (**8**, 0.7 mg), and palauolide (**9**, 2.5 mg).



Thorectandrol C (**4**) was obtained as an optically active, light yellow oil. The molecular formula  $\text{C}_{27}\text{H}_{40}\text{O}_5$  was established by HRFABMS ( $m/z$  445.2938 [ $\text{M} + \text{H}$ ]<sup>+</sup>, calcd  $m/z$  for  $\text{C}_{27}\text{H}_{41}\text{O}_5$  445.2914), indicating eight degrees of unsaturation. The  $^{13}\text{C}$  NMR spectrum of **4** contained resonances for all 27 carbons, while a DEPT experiment indicated 20 of these carbons were protonated with five methyls, nine methylenes, six methines, and seven quaternary carbons. A broad infrared absorption band centered at  $3500\text{ cm}^{-1}$  suggested the presence of an OH group.

The molecular formula indicated that thorectandrol C (**4**) was isomeric with thorectandrol B (**2**); however, the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Table 1) indicated that thorectandrol C (**4**) had an additional methyl group and one less methylene group than **2**.  $^1\text{H}$  and  $^{13}\text{C}$  data together with a standard series of 2D NMR data indicated that C23 ( $\delta_{\text{C}}$  67.7,  $\delta_{\text{H}}$  4.16), the methylene bearing the acetate group in thorectandrol B (**2**), was now replaced by a methyl group ( $\delta_{\text{C}}$  11.0,  $\delta_{\text{H}}$  0.85) in thorectandrol C (**4**). In addition, a new oxymethine proton [ $\delta_{\text{C}}$  75.3;  $\delta_{\text{H}}$  4.96 (dt, 11.3, 4.0)] appeared with COSY correlations to the resonances at H6b ( $\delta$  1.91) and to two multiplets  $\delta$  1.48 (H6a and H1a) and 1.58 (H1b and H8). The oxymethine proton also showed HMBC correlations to C8 ( $\delta$  42.8) and C22 ( $\delta$  11.0) and the ester carbonyl resonance at  $\delta$  172.8 (C26), indicating attachment at C7. Additional HMBC correlations from a methyl singlet at  $\delta$  2.05 to the C26 ester carbonyl supported the presence of an acetate functionality at C7 in thorectandrol C (**4**). Further support for this was provided by the HMBC connectivities of H6b to C5 and C7 and H22 to C7 and C8. Another notable difference in the  $^1\text{H}$  NMR of **4** when compared to thorectandrols A (**1**) and B (**2**) was the absence of the AB resonance characteristic of the oxymethylene substituent on C17 in **1** and **2**. This resonance, which appeared at 4.39 ppm in thorectandrols A (**1**) and B (**2**),

was now replaced by a two-proton singlet at  $\delta$  4.90 (H25) in thorectandrol C (**4**). This methylene was correlated in an HSQC experiment to a resonance at  $\delta$  73.0, which was significantly downfield from the corresponding resonance in **1** and **2**, where it appeared at about 59 ppm. HMBC data showed that H25 ( $\delta$  4.90) was correlated to C17 ( $\delta$  176.3) and H18 ( $\delta$  5.93) was correlated to both C17 and the C19 carbonyl ( $\delta$  176.4), supporting the presence of the  $\alpha,\beta$ -unsaturated butenolide moiety as shown in **4**.

The C11 to C14 region of thorectandrol C (**4**) was very similar to the corresponding data for thorectandrols A (**1**) and B (**2**). H14 ( $\delta$  5.21) showed COSY correlations to H15 ( $\delta$  2.40), and H15, in turn, was coupled to a triplet at  $\delta$  4.61 (H16). HMBC correlations from H14 to C15 and C16, H15 to C14 and C16, and H16 to C14 supported the connectivities C14 to C16. In addition, H16 showed HMBC correlations to C17 and C18, allowing attachment of the butenolide moiety at C16–C17. Unlike thorectandrols A (**1**) and B (**2**), C16 of thorectandrol C (**4**) was linked to the  $\beta$  position of the  $\alpha,\beta$ -unsaturated butenolide. This type of linkage was also present in palauolol (**3**),<sup>6</sup> palaulide (**9**),<sup>7</sup> and luffarin I (**10**).<sup>8</sup> The *E* configuration of the  $\Delta^{13}$  double bond was inferred<sup>10</sup> from the upfield  $^{13}\text{C}$  resonance at  $\delta$  16.6 assigned to C24 and confirmed by NOE enhancements of the H15 protons on irradiation of C24 methyl protons. Correlations from a series of one-dimensional gNOESY<sup>11</sup> experiments showed the spatial proximity of H7 and the methyl protons at C21, C22, and C23, indicating a *cis* relationship between these protons, thus suggesting that the acetate group was *trans* to the methyl groups and allowing the assignment of the relative stereochemistry of the bicyclic ring in **4**.

The HRFABMS of thorectandrol D (**5**) gave a molecular formula of  $\text{C}_{25}\text{H}_{38}\text{O}_3$  ( $m/z$  387.2879 [ $\text{M} + \text{H}$ ]<sup>+</sup>, calcd for  $\text{C}_{25}\text{H}_{39}\text{O}_3$  387.2899), indicating that **5** was isomeric with thorectandrol A (**1**). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of the C1–C10 fragment for thorectandrol D (**5**) (Table 2) were very similar to those for thorectandrol A (**1**), indicating an intact bicyclic unit (C1–C10). The remaining  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (C11–C25) for thorectandrol D (**5**) were identical to that for thorectandrol C (**4**). A standard series of 2D NMR data confirmed the assignment of the structure of thorectandrol D (**5**). The *E* geometry of the  $\Delta^{13}$  double bond and the relative stereochemistry of the bicyclic ring were established from  $^{13}\text{C}$  chemical shift and NOE correlations and were identical to the stereochemistry observed in **1–3**.

The HRFABMS of thorectandrol E (**6**) gave a molecular formula of  $\text{C}_{25}\text{H}_{38}\text{O}_4$  ( $m/z$  403.2855 [ $\text{M} + \text{H}$ ]<sup>+</sup>, calcd for  $\text{C}_{25}\text{H}_{39}\text{O}_4$  403.2848), indicating that **6** had one more oxygen than thorectandrol D (**5**). Close inspection of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data indicated that the C1–C10 unit in thorectandrol E (**6**) was similar to that found in thorectandrol C (**4**) except at position 7. The  $^1\text{H}$  and  $^{13}\text{C}$  resonances for C7 ( $\delta_{\text{H}}$  3.57;  $\delta_{\text{C}}$  70.8) indicated the presence of a hydroxyl group in thorectandrol E (**6**) instead of an acetate group found in **4** ( $\delta_{\text{H}}$  4.96;  $\delta_{\text{C}}$  75.3). Thorectandrol E (**6**) had the same C11–C25 unit as found in thorectandrols C (**4**) and D (**5**). These structural features were confirmed by 2D NMR data to give the structure shown in **6**. The *E* geometry of the  $\Delta^{13}$  double bond and the relative stereochemistry of the bicyclic ring in **6** were identical to thorectandrol C (**4**), according to the same methods applied in **4**.

An attempt to assign the absolute configuration at C16 in thorectandrol C (**4**) using Mosher's ester methodology<sup>12,13</sup> did not yield conclusive results. However, a comparison of the CD data of **4–6** with that of luffarin I (**10**)<sup>7</sup> suggested the absolute stereochemistry at C16 in **4–6**. Compounds

**Table 2.**  $^1\text{H}$ ,  $^{13}\text{C}$  NMR Spectral Data for Thorectandrol D (**5**) and Thorectandrol E (**6**) Recorded in Methanol- $d_4$

position	thorectandrol D ( <b>5</b> )		thorectandrol E ( <b>6</b> )	
	$\delta$ $^{13}\text{C}$	$\delta$ $^1\text{H}$ (mult., $J = \text{Hz}$ )	$\delta$ $^{13}\text{C}$	$\delta$ $^1\text{H}$ (mult., $J = \text{Hz}$ )
1	22.8	1.48 (m) 1.56 (m)	23.0	1.49 (m) 1.56 (m)
2	29.8	1.25 (m) 1.88 (m)	29.7	1.28 (m) 1.90 (m)
3	34.1	2.10 (m) 2.31 (dt, 13.7, 4.9)	33.7	2.10 (m) 2.31 (dt, 13.7, 5.1)
4	161.7		160.9	
5	42.2		41.8	
6	38.7	1.57 (m, 2H)	47.9	1.44 (m) 1.93 (m)
7	28.6	1.45 (m) 1.52 (m)	70.8	3.57 (dt, 10.8, 3.6)
8	38.0	1.45 (m)	45.5	1.32 (m)
9	40.3		41.4	
10	50.0	1.11 (dd, 12.2, 2.4)	49.7	1.15 (dd, 12.1, 2.9)
11	38.3	1.32 (m, 2H)	38.5	1.38 (m, 2H)
12	34.2	1.73 (m) 1.85 (m)	34.2	1.74 (m) 1.85 (m)
13	140.7		140.5	
14	119.5	5.17 (t, 7.0)	119.7	5.20 (t, 6.9)
15	36.0	2.38 (m, 2H)	36.0	2.40 (m, 2H)
16	69.4	4.59 (t, 6.4)	69.4	4.59 (t, 6.4)
17	176.2		176.1	
18	115.1	5.93 (d, 1.5)	115.1	5.94 (d, 1.5)
19	176.3		176.3	
20	103.2	4.48 (s) 4.49 (s)	103.4	4.52 (s) 4.53 (s)
21	21.4	1.05 (s, 3H)	22.3	1.11 (s, 3H)
22	16.6	0.81 (d, 6.1, 3H)	11.2	0.97 (d, 6.7, 3H)
23	18.7	0.75 (s, 3H)	19.8	0.78 (s, 3H)
24	16.4	1.61 (s, 3H)	16.6	1.61 (s, 3H)
25	73.0	4.89 (t, 2.3)	72.6	4.88 (t, 2.3)

**Table 3.** Cytotoxicity Data for Compounds **1–3** and **9** against 12 Human Tumor Cell Lines

cell line <sup>a</sup>	compound (IC50 $\mu\text{g/mL}$ )			
	thorectandrol A ( <b>1</b> )	thorectandrol B ( <b>2</b> )	palauolol ( <b>3</b> )	palaulide ( <b>9</b> )
MCF-7	40.0	30.0	7.0	>100.0 <sup>b</sup>
SNB-19	40.0	35.0	2.1	52.1
COLO-205	37.0	>100.0 <sup>b</sup>	1.1	23.6
KM12	40.0	94.0	1.8	14.4
MOLT-4	32.0	19.0	0.6	43.5
H460	35.0	96.0	1.3	10.1
A549	35.0	35.0	>100.0 <sup>b</sup>	30.0
LOX	35.0	>100.0 <sup>b</sup>	2.4	51.2
MALME-3M	40.0	30.0	0.5	37.0
OVCAR-3	35.0	70.0	2.2	30.0
IGROV1	31.0	>100.0 <sup>b</sup>	1.5	7.7
786-O	30.0	35.0	1.4	53.0

<sup>a</sup> Cell lines: MCF-7 (breast), SNB-19 (central nervous system), COLO-205 and KM12 (colon), MOLT-4 (leukemia), H460 and A549 (non small lung cancer), LOX and MALME-3M (melanoma), OVCAR-3 and IGROV1 (ovarian), and 786-O (renal) human tumor cell lines. <sup>b</sup> Maximum dose tested.

**4–6** displayed a negative Cotton effect at  $\lambda_{\text{max}}$  216  $\pm$  1 nm, a result similar to that reported for luffarin I (**10**), suggesting an *R* stereochemistry for C16 in **4**, **5**, and **6**. Compounds **7**, **8**, and **9** were identified as luffarin R,<sup>7</sup> luffarin V,<sup>7</sup> and palaulide<sup>8</sup> respectively, by comparison of their NMR data with that of published data.

When adequate sample was available, the purified compounds were tested for antiproliferative and cytotoxic activity against 12 human tumor cell lines (Table 3): MCF-7 (breast cancer), SNB-19 (CNS), COLO-205 and KM12 (colon), MOLT-4 (leukemia), H460 and A549 (non small lung cancer), LOX and MALME-3 (melanoma),



OVCAR-3 and IGROV1 (ovarian), and 786 O (renal).<sup>14</sup> The known compound palauolol (**3**) was active in all the cell lines except A549, with IC<sub>50</sub>'s in the range 0.5–7.0  $\mu\text{g/mL}$  (Table 3), while the closely related compound palauolide (**9**) showed a decrease in activity in all the cell lines. Thorectandrol A (**1**) was weakly active in all the cell lines, with IC<sub>50</sub>'s in the range 30–40  $\mu\text{g/mL}$ , while thorectandrol B (**2**) showed similar activity but was inactive in the COLO-205, LOX, and IGROV1 cell lines. Due to limited supply, compounds **4**–**8** were tested against fewer cell lines (generally six to ten, depending on availability). Thorectandrol C (**4**) showed weak activity (IC<sub>50</sub>'s 30–40  $\mu\text{g/mL}$ ) in A549, 786-O, and MALME-3M; however it was not active in MCF-7, LOX, and OVCAR-3. Thorectandrol D (**5**) on the other hand showed only weak activity in the OVCAR-3, COLO-205, and H460 cell lines. Thorectandrol E (**6**), luffarin V (**7**), and luffarin R (**8**) were not cytotoxic to any of the cell lines at the maximum dose tested (100  $\mu\text{g/mL}$ ). While it is difficult to draw firm conclusions from these data on structural requirements for activity, it appears that the hemiacetal lactone functional group present in palauolol (**3**) enhances the cytotoxicity and the 16-hydroxyl group results in an increase of activity compared to the presence of an alkene at C-15 as in palauolide (**9**).

## Experimental Section

**General Experimental Procedures.** Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in MeOH. CD spectra were recorded on a JASCO 720 spectrophotometer; UV spectra on a Beckman DU-64 spectrophotometer and FTIR spectra were obtained on a Perkin-Elmer 267 spectrophotometer. All 1D and 2D NMR spectra were recorded on a Varian Unity Inova spectrometer at 500 and 125 MHz for <sup>1</sup>H and <sup>13</sup>C, respectively, and referenced to the residual solvent signal. The number of attached protons for <sup>13</sup>C resonances was determined from a DEPT experiment. Proton-detected heteronuclear correlations were measured using HSQC (optimized for <sup>1</sup>J<sub>C-H</sub> = 140 Hz) and HMBC (optimized for <sup>n</sup>J<sub>C-H</sub> = 8.3 Hz) pulse sequences. The selective 1D TOCSY experiments were carried out with a total of 256 transients using mixing time of 80 ms. For the gNOESY experiments, a mixing time of 300 ms was used. Mass spectra were recorded on a JEOL SX102 spectrometer.

**Sponge Material.** The sponge was collected in 1991 from Palau by P. Colin from the Coral Reef Research Foundation, under contract to the National Cancer Institute. The sponge was collected at a depth of 10 m and was described as 5–15 cm in diameter, with dark rusty red color both inside and outside, and a convoluted, easily torn, surface. A voucher specimen (OCDN5079) from this collection is maintained at the Smithsonian Institution. The sponge was identified by Michelle Kelly (National Institute of Water and Atmosphere).

**Extraction and Purification.** The frozen sponge material was ground to a coarse powder (327 g) and sequentially extracted with water followed by MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:1). The organic extract was evaporated *in vacuo* and dried to give a maroon solid (4.89 g). A 1.08 g portion of the cytotoxic crude extract was subjected to solvent–solvent partitioning.<sup>9</sup> A portion (245 mg) of the methyl *tert*-butyl ether fraction was purified by reversed-phase HPLC (RPHPLC, 1.0  $\times$  25 cm; C<sub>18</sub>; 60 Å; Dynamax) using 90% (by volume) of acetonitrile in water. A fraction eluting at 18 min was further purified by RPHPLC (1.0  $\times$  10 cm; C<sub>18</sub>; 60 Å; Dynamax) using 80% (by volume) of

acetonitrile in water to give thorectandrol C (**4**, 2.8 mg, 1.15% extract) and luffarin V (**8**, 1.2 mg, 0.49%). Two later eluting sesterterpene fractions were further purified by RPHPLC (1.0  $\times$  10 cm; C<sub>18</sub>; 60 Å; Dynamax) using 90% acetonitrile in water to give thorectandrol D (**5**, 1.3 mg, 0.53%) and palauolide (**9**, 2.5 mg, 1.02%). A second fraction from the original HPLC fractionation eluting at 14 min was likewise further purified by RPHPLC using 60% (by volume) of acetonitrile in water to give thorectandrol E (**6**, 1.4 mg, 0.57%) and luffarin R (**7**, 1.2 mg, 0.49%). Elution of the individual components was monitored using a photodiode array detector (Waters 990).

**Thorectandrol C (4):** light yellow oil; 2.8 mg, 1.15% extract, [ $\alpha$ <sub>D</sub>] –29.0° (c 0.27, MeOH); CD (MeOH)  $\lambda_{\text{max}}$  (log  $\Delta\epsilon$ ) 241 (+3.2), 215 (–3.1), 197 (+4.5) nm; UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 218 (3.6) nm; IR (film)  $\nu_{\text{max}}$  3500 (OH), 1737 (C=O), 1645 (C=C) cm<sup>–1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data, see Table 1; HRFABMS *m/z* 445.2938 [M + H]<sup>+</sup>, calcd for C<sub>27</sub>H<sub>41</sub>O<sub>5</sub> 445.2914.

**Thorectandrol D (5):** light yellow oil; 1.3 mg, 0.53% extract, [ $\alpha$ <sub>D</sub>] –12.4° (c 0.13, MeOH); CD (MeOH)  $\lambda_{\text{max}}$  (log  $\Delta\epsilon$ ) 238 (+2.9), 217 (–3.4), 191 (+4.9) nm; UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 213 (3.8) nm; IR (film)  $\nu_{\text{max}}$  3500 (OH), 1737 (C=O), 1645 (C=C) cm<sup>–1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data, see Table 2; HRFABMS *m/z* 387.2879 [M + H]<sup>+</sup>, calcd for C<sub>25</sub>H<sub>39</sub>O<sub>3</sub> 387.2899.

**Thorectandrol E (6):** light yellow oil; 1.4 mg, 0.57% extract, [ $\alpha$ <sub>D</sub>] –2.14° (c 0.14, MeOH); CD (MeOH)  $\lambda_{\text{max}}$  (log  $\Delta\epsilon$ ) 241 (+3.3), 216 (–3.6), 191 (+4.9) nm; UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 206 (3.6) nm; IR (film)  $\nu_{\text{max}}$  3500 (OH), 1737 (C=O), 1645 (C=C) cm<sup>–1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data, see Table 2; HRFABMS *m/z* 403.2855 [M + H]<sup>+</sup>, calcd for C<sub>25</sub>H<sub>39</sub>O<sub>4</sub> 403.2848.

**Cytotoxicity Assays.** Cytotoxicity assays using MCF-7 (breast cancer), SNB-19 (central nervous system), COLO-205 and KM12 (colon), MOLT-4 (leukemia), H460 and A549 (non small lung cancer), LOX and MALME-3 (melanoma), OVCAR-3 and IGROV1 (ovarian), and 786 O (renal) cancer cell lines were performed as previously described.<sup>14</sup>

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