Three New Scalarane Sesterterpenoids from the Okinawan Sponge *Hyrtios erectus*

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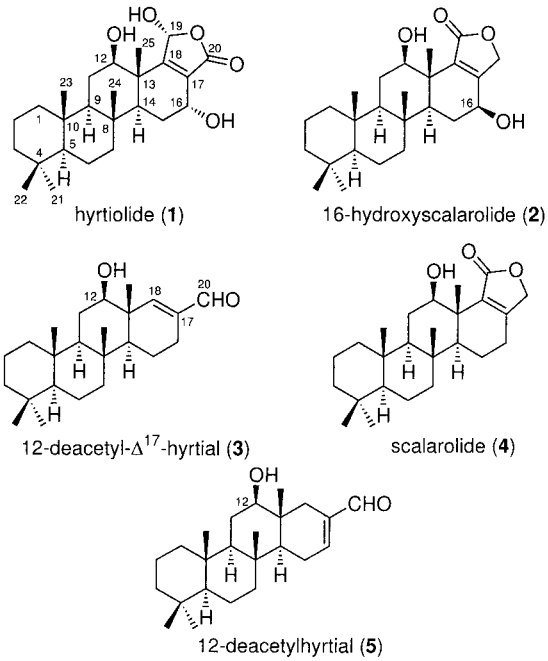
Three new scalarane sesterterpenoids—hyrtiolide (**1**), 16-hydroxyscalarolide (**2**), and 12-deacetyl-Δ^{17}-hyrtial (**3**), were isolated from Okinawan sponge *Hyrtios erectus*, along with scalarolide (**4**) and 12-deacetylhyrtial (**5**). The structures of new compounds **1**−**3** were determined by spectroscopic analysis and chemical conversions. Compounds **3** and **5** showed antiproliferative activity toward KB cells.

Many scalarane sesterterpenoids have been isolated from marine sponges since the time scalarin was obtained from the marine sponge, *Cacospongia scalaris*,[1] and many of these are of considerable interest from the standpoint of biological activities such as cytotoxicity,[2−8] antiinflammatory,[9−11] antimicrobial,[12−14] ichthyotoxicity,[15] platelet-aggregation inhibitory,[13,16] and nerve growth factor (NGF) enhancement.[17] In studies on chemical constituents of Okinawan marine invertebrates,[18] the authors isolated the cytotoxic sesterterpenoid hyrtiosal from the marine sponge *Hyrtios erectus* (Keller, 1891).[19] In the search for additional biologically active constituents from the same sponge, three new scalarane sesterterpenoids hyrtiolide (**1**), 16-hydroxyscalarolide (**2**) and 12-deacetyl-Δ^{17}-hyrtial (**3**), were found along with known compounds, scalarolide (**4**)[20] and 12-deacetylhyrtial (**5**).[14] The isolation and structure determination of these compounds are herein discussed.



Results and Discussion

Specimens of *H. erectus* (wet wt 9.5 kg), obtained from the coral reef of Ishigaki Island, Okinawa, Japan, in November 1994, were immersed in MeOH, and the extracts were partitioned between H_2O and hexane and then EtOAc. The hexane-soluble portion (25.8 g) was purified to give 12-deacetyl-Δ^{17}-hyrtial (**3**) (16 mg), scalarolide (**4**) (53 mg), and 12-deacetylhyrtial (**5**) (10 mg). The EtOAc-soluble portion (10.8 g) was purified to give hyrtiolide (**1**) (18 mg) and 16-hydroxyscalarolide (**2**) (20 mg).

Hyrtiolide (**1**) was found to have the molecular formula $C_{25}H_{38}O_5$ based on high-resolution mass measurement. The IR spectrum of **1** showed absorption at 3402 cm^{-1} due to a hydroxyl group. An α,β-unsaturated carbonyl group was recognized by IR absorption at 1697 and 1650 cm^{-1} and UV absorption (λ_{max} 212 nm). All 25 carbons in the ^{13}C NMR and DEPT spectra indicated the presence of five methyls, seven methylenes, six sp^3 methines, four sp^3 quaternary carbons, and three sp^2 quaternary carbons. ^1H and ^{13}C NMR correlations were indicated by the HMQC spectrum. ^1H and ^{13}C NMR indicated one α,β-disubstituted-γ-hydroxy-α,β-unsaturated-γ-lactone [δ_H 6.34 (1H, br s), δ_C 173.0 (C), 129.5 (C), 171.3 (C), 101.7 (CH)] and two secondary hydroxy groups [δ_H 3.64 (1H, dd, J = 4.3, 11.1 Hz), 4.42 (1H, br d, J = 2.9 Hz), δ_C 75.8 (CH), 61.0 (CH)]. The presence of three secondary hydroxy groups was confirmed by acetylation. Treatment of **1** with acetic anhydride in pyridine at 50 °C gave a triacetate [δ_H 6.94 (1H, d, J = 1.5 Hz), 5.63 (1H, d, J = 4.7 Hz), 4.87 (1H, dd, J = 11.1, 4.6 Hz), 2.11 (3H, s), 2.09 (3H, s), 1.99 (3H, s)]. Interpretation of COSY cross-peaks indicated the following four partial structures: C-1 to C-3, C-5 to C-7, C-9 to C-12, and C-14 to C-16. These partial structures and the above γ-hydroxy-α,β-unsaturated-γ-lactone (C-17−C-20) were found to be connected through quaternary carbons based on HMBC data; also observed were the cross-peak: Me-21/C-3, C-5, C-22; Me-22/C-3, C-5, C-21; Me-23/C-1, C-5, C-9; Me-24/C-7, C-9, C-14; Me-25/C-12, C-14, C-18, and H-16/C-14, C-17, C-18, so that the tetracarbocyclic scalarane skeleton could be constructed. The planar structure of **1** was thus determined. All trans junctures of the tetracyclic rings (A, B, C, and D) were demonstrated from ^{13}C NMR chemical shifts of methyl groups (δ_C 14.4, 16.7, 18.3, 21.7, and 33.8).[11] The trans juncture of any of these rings was clearly indicated by the NOESY spectrum and coupling constant in ^1H NMR. The H-12 signal at δ_H 3.46 (dd, J = 4.3, 11.1 Hz) suggested H-12 to be axial, and the H-16 signal at δ_H 4.42 (br d, J = 2.9 Hz) suggested H-16 to be equatorial. The α-configuration of the hydroxyl group at C-19 was indicated by NOESY correlation between H-19 (δ_H 6.34) and Me-25 (δ_H 1.16). The structure of **1** was thus determined to be that shown in **1**.

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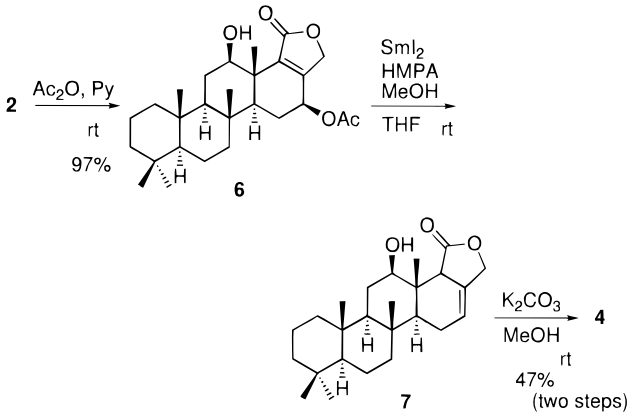
Scheme 1



16-Hydroxyscalarolide (**2**) had the molecular formula $C_{25}H_{38}O_4$ based on HRMS. The IR spectrum of **2** showed absorption at 3392 cm^{-1} due to a hydroxy group. An α,β-unsaturated carbonyl group was indicated by IR absorption at 1697 and 1650 cm^{-1} and UV absorption (λ_{max} 208 nm). All 25 carbons in the ^{13}C NMR and DEPT spectra indicated the presence of five methyls, eight methylenes, five sp^3 methines, four sp^3 quaternary carbons, and three sp^2 quaternary carbons. ^1H and ^{13}C NMR correlations were evident from the HMQC spectrum. ^1H and ^{13}C NMR data indicated two secondary hydroxy groups [δ_H 3.64 (1H, dd, J = 4.4, 10.9 Hz), 4.50 (1H, m), δ_C 75.5 (CH), 67.9 (CH)] and one α,β-disubstituted-α,β-unsaturated-γ-lactone [δ_H 4.81 (1H, d, J = 17.8 Hz), 4.99 (1H, d, J = 17.8 Hz), δ_C 175.6 (C), 136.3 (C), 162.3 (C), 70.7 (CH_2)]. The presence of two secondary hydroxy groups was confirmed by acetylation. Treatment of **2** with acetic anhydride in pyridine in the presence of a catalytic amount of DMAP at 50 °C afforded a diacetate [δ_H 4.93 (1H, dd, J = 4.7, 11.2 Hz), 5.49 (1H, dd, J = 6.9, 10.3 Hz), 2.10 (3H, s), 2.10 (3H, s)]. The NMR spectra of **2** were closely related to those of known scalarane sesterterpenoid scalarolide (**4**)[20] except for the presence of a hydroxyl group that was one more than those of salarolide (**4**), suggesting the structure of 16-hydroxyscalarolide to possibly be **2**. The planar structure of **2** was supported by COSY, HMQC, and HMBC spectra, and its relative configuration was determined from the NOESY spectrum. The absolute configuration of **2** was determined by chemical conversion of **2** to scalarolide (**4**) (Scheme 1). Acetylation of 16-hydroxyscalarolide (**2**) with acetic anhydride in pyridine at room temperature gave mono acetate **6**, whose treatment with SmI_2 in the presence of HMPA and MeOH[21] provided Δ^{16}-scalarolide (**7**). Isomerization of the double bond in **7** was carried out by treatment with K_2CO_3 in MeOH to give scalarolide (**4**), $[\alpha]^{25}_D$ +25.3° (*c* 0.087, $CHCl_3$), {lit.[20] $[\alpha]_D$ +24.9° (*c* 1.35, $CHCl_3$)}. The absolute configuration was thus confirmed to be **2**.

The molecular formula of 12-deacetyl-Δ^{17}-hyrtial (**3**) was shown to be $C_{24}H_{38}O_2$ based on high-resolution mass measurement. The IR spectrum of **3** indicated absorption at 3350 cm^{-1} due to a hydroxy group. An α,β-unsaturated carbonyl group was shown to be present from IR absorption at 1686 and 1641 cm^{-1} and UV absorption (λ_{max} 234 nm). All 24 carbons in the ^{13}C NMR and DEPT spectra indicated the presence of five methyls, eight methylenes, four sp^3 methines, two sp^2 methines, four sp^3 quaternary carbons, and one sp^2 quaternary carbon. ^1H and ^{13}C NMR correlations were demonstrated by the HMQC spectrum. ^1H and ^{13}C NMR data indicated one α,β-unsaturated aldehyde [δ_H 6.93 (1H, t, J = 1.0 Hz), 9.42 (1H, s), δ_C 138.0 (C), 158.3 (CH), 195.1 (CH)] and one secondary hydroxy group [δ_H 3.46 (1H, dd, J = 4.3, 11.1 Hz), δ_C 76.8 (CH), 67.9]. A secondary hydroxy group was shown to be present by acetylation. Treatment of **3** with acetic anhydride in pyridine at room temperature afforded an acetate [δ_H 4.69 (1H, dd, J = 11.3, 4.4 Hz), 2.10 (3H, s)]. The NMR spectra of **3** were closely related to those of the known scalarane sesterterpenoid 12-deacetylhyrtial (**5**),[14] except for the double-bond position, thus indicating **3** to be the regioisomer of **5**. The planar structure of **3** was supported by COSY, HMQC, and HMBC spectra, and the relative configuration of **3** was determined from the NOESY spectrum. The gross structure of compound **3** was thus determined.

12-Deacetyl-Δ^{17}-hyrtial (**3**) and 12-deacetylhyrtial (**5**) showed antiproliferative activity toward KB cells at IC_{50} values of 2.82 and 10.0 μg/mL, respectively.

Experimental Section

General Experimental Procedures. Optical rotation was measured with a JASCO DIP-360 polarimeter. IR spectra were recorded with a Perkin-Elmer FT-IR 1710 spectrometer; UV spectra, with a Hitachi 124 spectrophotometer or JASCO V-550; and ^1H and ^{13}C NMR spectra, with a Bruker AM-400, or a Bruker AM-500. EIMS and HREIMS were obtained with a VG Auto Spec spectrometer.

Animal Material. The sponge, *Hyrtios erectus*, was collected from the coral reef of Ishigaki Island (Okinawa, Japan) in November 1994, at a depth of 10−20 m. by hand using scuba. This sponge was previously identified by Professor R. W. M. van Soest, University of Amsterdam.[19] A voucher specimen (S-94−1) is presently deposited at this laboratory, School of Pharmacy, Tokyo University of Pharmacy and Life Science (Tokyo, Japan).

Extraction and Isolation. Wet specimens (9.5 kg) were cut into small pieces and extracted with MeOH (14 L × 5). The combined MeOH extracts were concentrated and partitioned between hexane (1.0 L × 3) and water (1.0 L) to give the hexane-soluble portion (25.8 g). The aqueous layer was extracted with EtOAc (1.0 L × 3) to give the EtOAc-soluble portion (10.8 g).

The hexane-soluble portion was chromatographed on Si gel using a hexane−EtOAc (10:1) to EtOAc gradient and MeOH as eluent to give fractions 1 (7.3 g), 2 (8.7 g), and 3 (8.7 g). Fraction 2 was subjected to repeated flash Si gel column chromatography [elution with hexanes−EtOAc (5:1 to 1:1)] to give fractions 2-1−2-6. On fraction 2-1, flash Si gel column chromatography was conducted with hexane−EtOAc (2:1) to give scalarolide (**4**) (53 mg), and on fraction 2-2, repeated flash Si gel column chromatography [elution with hexane−acetone (4:1), $CHCl_3$−acetone (90:1), MeOH−H_2O (30:1)(ODS) and $CHCl_3$−acetone (60:1)] to gave fractions 2-2-1 and 2-2-2. Fraction 2-2-1 was subjected to flash Si gel column chromatography [elution with hexanes−EtOAc (4:1)] to give 12-deacetyl-Δ^{17}-hyrtial (**3**) (16 mg). Fraction 2-2-2 was subjected to flash Si gel column chromatography [elution with hexane-acetone (8:1)] to afford 12-deacetylhyrtial (**5**) (10 mg).

The EtOAc-soluble portion was chromatographed on Si gel using a hexane−EtOAc (1:1) to EtOAc gradient and MeOH as eluate to give fractions 4 (3.6 g), 5 (425 mg), and 6 (5.2 g). Fraction 4 was subjected to repeated flash Si gel column chromatography [elution with hexane−EtOAc (3:2 to 1:1)] to give fractions 4-1 and 4-2. and fraction 4-1 was gel-filtered on Sephadex LH-20 with $CHCl_3$−MeOH (1:1) to give 16-hydroxyscalarolide (**2**) (20 mg). Fraction 4−2 underwent repeated flash Si gel column chromatography [elution with hexane−EtOAc (4:3) and hexane−acetone (5:2)] to give a fraction that was subsequently gel-filtered on Sephadex LH-20 with $CHCl_3$−MeOH (1:1) and chromatographed on ODS with MeOH−H_2O (5:1) to give hyrtiolide (**1**) (18 mg).

Hyrtiolide (1): colorless, amorphous solid; $[\alpha]^{25}_D$ +6.0° (*c* 0.43, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 212 (3.76) nm; IR (KBr) ν_{max} 3402, 1751 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table 1; HMBC correlation, see text; NOESY correlation, see text;

Table 1. NMR Data for **1** and **2**

	1		**2**	
no.	^{13}C NMR[a]	^{1}H NMR[b]	^{13}C NMR[c]	^{1}H NMR[d]
1	41.0 (CH_2)	0.87 (1H, m) 1.73 (1H, m)	39.7 (CH_2)	0.78 (1H, m) 1.72 (1H, br d, 13.0)
2	19.3 (CH_2)	1.48 (1H, m) 1.61 (1H, m)	18.2 (CH_2)	1.42 (1H, m) 1.62 (1H, m)
3	43.3 (CH_2)	1.20 (1H, m) 1.40 (1H, m)	42.0 (CH_2)	1.09 (1H, m) 1.38 (1H, m)
4	34.2 (C)		33.3 (C)	
5	58.0 (CH)	0.85 (1H, m)	56.7 (CH)	0.75 (1H, m)
6	19.6 (CH_2)	1.48 (1H, m) 1.61 (1H, m)	18.6 (CH_2)	1.40 (1H, m) 1.58 (1H, m)
7	42.5 (CH_2)	0.98 (1H, m) 1.83 (1H, m)	41.7 (CH_2)	0.92 (1H, m) 1.80 (1H, td, 3.3, 12.4)
8	38.1 (C)		37.0 (C)	
9	60.1 (CH)	1.00 (1H, m)	58.0 (CH)	0.88 (1H, m)
10	38.6 (C)		37.4 (C)	
11	27.6 (C)	1.62 (1H, m) 1.82 (1H, m)	25.7 (CH_2)	1.49 (1H, dd, 2.1, 13.2) 1.88 (1H, m)
12	75.8 (CH)	3.64 (1H, dd, 4.3, 11.1)	75.5(CH)	3.64 (1H, dd, 4.5, 10.9)
13	45.9 (C)		42.8 (C)	
14	50.4 (CH)	1.51 (1H, m)	54.3 (CH)	1.14 (1H, m)
15	28.0 (CH_2)	1.82 (1H, m) 1.88 (1H, m)	28.2 (CH_2)	1.66 (1H, dd, 2.1, 12.4) 2.23 (1H, dd, 6.7, 12.5)
16	61.0 (CH)	4.42 (1H, br d, 2.9)	67.9 (CH)	4.50 (1H, m)
17	129.5 (C)		162.3 (C)	
18	171.3 (C)		136.3 (C)	
19	101.7 (CH)	6.34 (1H, br s)	175.6 (C)	
20	173.0 (C)		70.7 (CH_2)	4.81 (1H, d, 17.8) 4.99 (1H, d, 17.8)
21	33.8 (CH_3)	0.87 (3H, s)	33.3 (CH_3)	0.84 (3H, s)
22	21.7 (CH_3)	0.85 (3H, s)	21.3 (CH_3)	0.81 (3H, s)
23	16.7 (CH_3)	0.91 (3H, s)	15.9 (CH_3)	0.84 (3H, s)
24	18.3 (CH_3)	0.94 (3H, s)	17.4 (CH_3)	0.90 (3H, s)
25	14.4 (CH_3)	1.16 (3H, s)	16.7 (CH_3)	1.19 (3H, s)

[a] 100 MHz, CD_3OD. [b] 400 MHz, CD_3OD. [c] 100 MHz, $CDCl_3$. [d] 400 MHz, $CDCl_3$.

EIMS *m*/*z* 418 $[M]^+$ (1), 400 (10), 382 (3); HREIMS *m*/*z* 418.2732 (calcd for $C_{25}H_{38}O_5$, 418.2719).

16-Hydroxyscalarolide (2): colorless needles; mp 300−303 °C; $[\alpha]^{25}_D$ −25.0° (*c* 0.16, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 208 (3.85) nm; IR (KBr) ν_{max} 3392, 1697, 1650 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table 1; HMBC correlation (H/C) H-5/C-21, C-23; H-9/C-8, C-24; H-11/C-9, C-12; H-14/C-8, C-13, C-15, C-24, C-25; H-15a/C-14, C-16; H-15b/C-13, C-14, C-16, C-17; H-20/C-17, C-18; Me-21/C-3, C-5, C-22; Me-22/C-3, C-5, C-21; Me-23/C-1, C-5, C-9, C-10; Me-24/C-7, C-8, C-9, C-14; Me-25/C-12, C-13, C-14, C-18; NOESY correlation (H/H) 5/9, 9/14, 12/14, 14/16, 23/24, 24/25; EIMS *m*/*z* 402 $[M]^+$ (27), 387 (32), 369 (4); HREIMS *m*/*z* 402.2782 (calcd for $C_{25}H_{38}O_4$, 402.2770).

12-Deacetyl-Δ^{17}-hyrtial (3): colorless amorphous solid; $[\alpha]^{25}_D$ +22.3° (*c* 0.44, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 234 (4.00) nm; IR (KBr) ν_{max} 3350, 1686, 1641 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table 2; HMBC correlation (H/C) H-1/C-3, C-5; H-11/C-9, C-12; H-14/C-8, C-13, C-15, C-16; H-16/C-14, C-17, C-18; H-18/C-12, C-14, C-16, C-20; H-20/C-16, C-17, Me-21/C-3, C-5, C-22; Me-22/C-3, C-5, C-21; Me-23/C-1, C-9, C-10, Me-24/C-7, C-9, C-14, Me-25/C-12, C-13, C-14, C-18; NOESY correlation (H/H) 5/9, 5/21, 9/12, 12/14, 12/18, 18/20, 22/23, 23/24, 24/25; EIMS *m*/*z* 358 $[M]^+$ (16), 343 (40), 325 (11); HREIMS *m*/*z* 358.2888 (calcd for $C_{24}H_{38}O_2$, 358.2872).

Acetylation of Hyrtiolide (1). To a solution of hyrtiolide (**1**) (1.0 mg, 2.39 μmol) in pyridine (100 μL) was added acetic anhydride (50 μL). The mixture was stirred at room temperature for 3 h and then at 50 °C for 10 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by Si gel column chromatography [elution with hexane−acetone (5:1)] to give triacetate (1.3 mg, 96% yield) as a colorless amorphous solid: $[\alpha]^{25}_D$ −27.2° (*c* 0.125, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 212 (3.86) nm; IR (KBr) ν_{max} 1768, 1741, 1234 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.94 (1H, d, J = 1.5 Hz), 5.63 (1H, d, J = 4.7 Hz), 4.87 (1H, dd, J = 11.1, 4.6 Hz), 2.17 (1H, d, J = 1.9 Hz), 2.13 (1H, m), 2.11 (3H, s), 2.09 (3H, s), 1.99 (3H, s), 1.93 (1H, m), 1.77 (1H, dt, J = 12.5, 2.7 Hz), 1.67−1.57 (6H, m), 1.46−1.36 (4H, m), 1.22 (3H, s), 0.92 (3H, s), 0.88−0.84 (2H, m), 0.86 (3H, s), 0.83 (3H, s), 0.81 (3H, s);

Table 2. NMR Data for **3**

	3	
no.	^{13}C NMR[a]	^{1}H NMR[b]
1	40.0 (CH_2)	0.81 (1H, m) 1.67 (1H, m)
2	18.2 (CH_2)	1.42 (1H, m) 1.58 (1H, m)
3	42.1 (CH_2)	1.12 (1H, dt, 3.8, 13.8) 1.38 (1H, br d, 13.8)
4	33.3 (C)	
5	56.7 (CH)	0.80 (1H, m)
6	18.6 (CH_2)	1.42 (1H, m) 1.58 (1H, m)
7	41.2 (CH_2)	0.91 (1H, m) 1.81 (1H, m)
8	37.6 (C)	
9	58.8 (CH)	0.92 (1H, m)
10	37.5 (C)	
11	27.2 (CH_2)	1.50 (1H, m) 1.81 (1H, m)
12	76.8 (CH)	3.46 (1H, dd, 4.3, 11.1)
13	42.5 (C)	
14	54.0 (CH)	1.00 (1H, dd, 1.8, 12.5)
15	16.1 (CH_2)	1.46 (1H, m) 1.82 (1H, m)
16	23.1 (CH_2)	2.02 (1H, dddd, 2.2, 7.2, 11.3, 18.2) 2.41 (1H, dd, 6.1, 18.2)
17	138.0 (C)	
18	158.3 (CH)	6.93 (1H, t, 1.0)
19		
20	195.1 (CH)	9.42 (1H, s)
21	33.3 (CH_3)	0.84 (3H, s)
22	21.3 (CH_3)	0.81 (3H, s)
23	16.2 (CH_3)	0.85 (3H, s)
24	17.6 (CH_3)	0.88 (3H, s)
25	15.6 (CH_3)	1.03 (3H, s)

[a] 125 MHz, $CDCl_3$. [b] 500 MHz, $CDCl_3$.

EIMS *m*/*z* 484 $[M - HOAc]^+$ (1), 442 (100); HREIMS *m*/*z* 484.2806 (calcd for $C_{29}H_{40}O_6$, 484.2825).

Acetylation of 16-Hydroxyscalarolide (2). To a solution of 16-hydroxyscalarolide (**2**) (2.0 mg, 4.98 μmol) in pyridine

(200 μL) were added acetic anhydride (100 μL) and DMAP (0.1 mg). The mixture was stirred at 50 °C for 13 h and then concentrated under reduced pressure. The residue was purified by Si gel column chromatography [elution with hexane−EtOAc (5:1)] to provide diacetate (0.88 mg, 37% yield) as a colorless amorphous solid: $[\alpha]^{25}_D$ −11.4° (*c* 0.088, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 218 (3.54) nm; IR (KBr) ν_{max} 1741, 1237 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.49 (1H, dd, J = 10.3, 6.9 Hz), 4.93 (1H, dd, J = 11.2, 4.7 Hz), 4.57 (2H, br s), 2.34 (1H, m), 2.25 (1H, ddd, J = 12.5, 6.9, 1.1 Hz), 2.17 (1H, m), 2.13 (3H, s), 2.10 (3H, s), 1.79 (2H, m), 1.63 (6H, m), 1.39 (2H, m), 1.13 (2H, dt, J = 4.0, 13.0 Hz), 0.93 (3H, s), 0.85 (3H, s), 0.83 (3H, s), 0.81 (3H, s), 1.06−0.77 (5H, m); EIMS *m*/*z* 487 $[M]^+$ (4), 426 $[M - HOAc]^+$ (84); HREIMS *m*/*z* 426.2781 (calcd for $C_{24}H_{38}O_2$, 426.2770).

Conversion of 16-Hydroxyscalarolide (2) to Scalarolide (4). To a solution of 16-hydroxyscalarolide (**2**) (3.0 mg, 7.46 μmol) in pyridine (600 μL) was added acetic anhydride (300 μL) followed by stirring at room temperature for 1 h and concentrating under reduced pressure. The residue was purified by Si gel column chromatography [elution with hexane−EtOAc (3:1)] to give 16-acetoxyscalarolide (3.2 mg, 97% yield) as a colorless amorphous solid: $[\alpha]^{25}_D$ −38.1° (*c* 0.32, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 212 (3.89) nm; IR (KBr) ν_{max} 3393, 1729, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.74 (1H, d, J = 1.1 Hz), 5.51 (1H, dd, J = 10.1, 7.2 Hz), 4.77 (1H, dd, J = 17.9, 1.4 Hz), 4.70 (1H, d, J = 17.9 Hz), 3.66 (1H, ddd, J = 10.8, 4.4, 1.1 Hz), 2.26 (1H, ddd, J = 12.7, 7.1, 1.2 Hz), 2.12 (3H, s), 1.88 (1H, ddd, J = 13.4, 4.4, 2.1 Hz), 1.77 (2H, m), 1.60 (2H, m), 1.50 (1H, dd, J = 13.1, 2.1 Hz), 1.42 (4H, m), 1.23 (2H, m), 1.20 (3H, s); EIMS *m*/*z* 444 $[M]^+$ (19), 384 (79); HREIMS *m*/*z* 444.2879 (calcd for $C_{27}H_{40}O_5$, 444.2876).

To the solution of the above acetate (3.2 mg, 7.20 μmol) in THF (100 μL), HMPA (12 μL), and MeOH (6 μL) was added SmI_2 (360 μL, 36.0 μmol, 0.1 M in THF). The mixture was stirred at room temperature for 10 min followed by dilution with Et_2O and filtration through Si gel. The filtrate was concentrated under reduced pressure to give a crude compound for subsequent use in the reaction below without purification.

To a solution of the above crude compound in MeOH (500 μL) was added K_2CO_3 (10 mg). The mixture was stirred at room temperature for 2 h, diluted with EtOAc, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by Si gel column chromatography [elution with hexane−EtOAc (4:1)] to give scalarolide (**4**)[20] (1.3 mg, 47% yield, two steps) as a colorless amorphous solid: $[\alpha]^{25}_D$ +25.3° (*c* 0.087, $CHCl_3$), [lit.[20] $[\alpha]_D$ +24.9° (*c* 1.35, $CHCl_3$)].

Acetylation of 12-Deacetyl-Δ[17]-hyrtial (3). To a solution of 12-deacetyl-Δ17-hyrtial (**3**) (2.0 mg, 5.60 μmol) in pyridine (400 μL) was added acetic anhydride (200 μL). The mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was purified by Si gel column chromatography [elution with hexane−EtOAc (6:1)] to give acetate (2.3 mg, 97% yield) as a colorless amorphous solid: $[\alpha]^{25}_D$ +7.82° (*c* 0.23, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 229 (4.04) nm; IR (KBr) ν_{max} 1738, 1687, 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.38 (1H, s), 6.49 (1H, d, J = 0.9 Hz), 4.69 (1H, dd, J = 11.3, 4.4 Hz), 2.10 (3H, s), 2.09−1.99 (2H, m), 1.87 (1H, ddd, J = 12.7, 4.4, 2.2 Hz), 1.81 (2H, m), 1.64−1.50 (6H, m), 1.48−1.35 (6H, m), 1.17−1.09 (3H, m), 1.10 (3H, s); EIMS *m*/*z* 400 $[M]^+$ (14), 340 (100), 325 (41); HREIMS *m*/*z* 400.2974 (calcd for $C_{26}H_{40}O_3$, 400.2977).

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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