Sesterterpenoids from the Marine Sponge *Hyrtios erectus*

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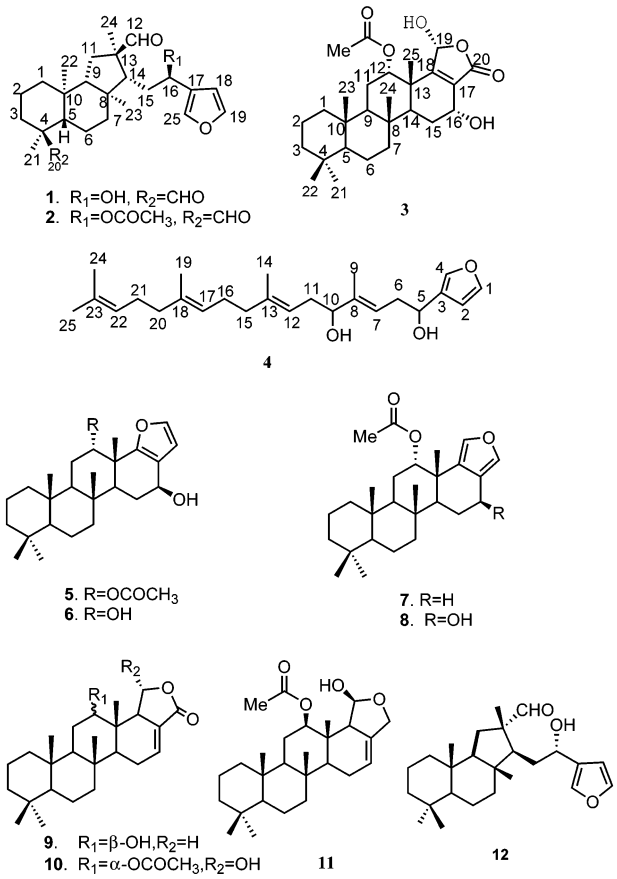
Four new sesterterpenes, namely, (+)-20-formylhyrtiosal (**1**), (+)-16-*O*-acetyl-20-formylhyrtiosal (**2**), 12-α-*O*-acetylhyrtiolide (**3**), and 5,10-dihydroxyfurospinulosine-1 (**4**), together with seven known sesterterpenes (**5**−**11**) were isolated from the marine sponge *Hyrtios erectus* collected at Hainan, China. The structures were elucidated on the basis of extensive spectroscopic analysis involving mainly one- and two-dimensional NMR as well as mass spectroscopy.

Sponges from the genus *Hyrtios* occur frequently in tropical and subtropical waters and often form dominant life forms on coral reefs. Previous chemical investigations of different *Hyrtios* spp. and their associated microorganisms have revealed the presence of numerous structurally unique natural products including scalarane sesterterpenoids,[1−14] acyclic triterpenoids,[15] indole alkaloids,[16−19] macrolides,[20−23] and steroids.[24] Many of these compounds possess important biological activities. The secondary metabolites of the sponge *Hyrtios erectus* (also called *H. erecta*), collected from Okinawa (Japan) and from Indonesia, have been investigated extensively.[1−30] However, this sponge when collected from Chinese waters has not been investigated before. In our ongoing research program on bioactive secondary metabolites from marine organisms, *H. erectus* was collected using scuba on the inner reef (15 m depth) at Hainan Island, South China Sea. Repeated chromatographic separation using silica gel column chromatography followed by reversed-phase HPLC of the CH_2Cl_2 fraction obtained from a MeOH extract of the sponge gave 11 pure compounds (**1**−**11**), of which **1**−**4** were determined as new sesterterpenoids. The structure elucidation of the new compounds mainly employing one- and two-dimensional NMR spectroscopy as well as mass spectroscopy is discussed.

From the 11 natural products isolated from *H. erectus*, compounds **5** and **6** were identical to the known tetracyclic sesterterpenoids furoscalarol and its corresponding deacetyl derivative 12-*O*-desacetylfuroscalarol, previously reported from the sponge *Cacospongia mollior*,[31] and the latter two compounds were also isolated from the sponge *Hyrtios* sp.[14] The structures of compounds **7** and **8** were in agreement with the scalarane sesterterpenoids 16-deacetyl-12-*epi*-scalarafuran acetate and isoscalarafuran A, respectively, of which the former had been originally isolated from *Spongia officinalis*,[32] whereas the latter had been obtained from *S. hispida*.[33] Compounds **9**−**11** were identical to scalarane type sesterterpenoids, namely, 12-*O*-deacetyl-19-deoxyscalarin (**9**),[34] scalarin (**10**),[31,34] and 12-epideoxoscalarin (**11**),[35,36] respectively. All of the known compounds were readily identified by comparison of their spectral data with those reported in the literature.

Compound **1** was obtained as a white amorphous powder, and its molecular formula was determined as $C_{25}H_{36}O_4$ by HRFABMS. The ^1H and ^{13}C NMR spectral features of **1** resembled those of hyrtiosal, a unique rearranged tricyclic sesterterpenoid.[3] In the ^1H NMR spectrum of **1**, three downfield protons at δ 7.40 (dd, J = 1.6, 1.5 Hz, H-19), 7.39 (dd, J = 1.5, 0.8 Hz, H-25), and 6.39 (dd, J = 0.8, 1.6 Hz, H-18) were characteristic of a monosubstituted furan moiety, and a small *w*-bond coupling between H-19 and H-25 through an oxygen bridge was observed. Four methyl singlets at δ 1.23 (3H, s, H-24), 1.09 (3H, s, H-21), 0.95 (3H, s, H-22), and 0.89 (3H, s, H-23) as well as two formyl protons at δ 9.51 (s) and 9.22 (s) indicated that in **1** one of the five methyl groups present in hyrtiosal was replaced by a formyl group instead. The DEPT spectrum of **1** exhibited two methine carbons at δ 206.28 (d) and 205.37 (d), thus supporting the presence of two formyl groups in the molecule. HMBC correlations between δ 9.51 (s, H-12)



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and 19.20 (q, C-24) and between δ 9.22 (s, H-20) and 13.51 (q, C-21) indicated that the second formyl group was positioned at C-4.

The stereochemistry of **1** was assumed to be in agreement with those of (+)-hyrtiosal due to the similar optical rotations between **1** ($[\alpha]_D^{20}$ +60°) and (+)-hyrtiosal ($[\alpha]^{20}_D$ +64.2°),[37] whereas the optical rotation of (−)-hyrtiosal (**12**) is $[\alpha]^{20}_D$ −72.1°.[3] Moreover, the NOE correlations of aldehydic proton H-12 (δ 9.51, s) to H-14 (δ 2.07, dd, J = 5.2, 9.4 Hz) and H-24 (δ 1.23, 3H, s), and of H-24 to H-23 (δ 0.89, 3H, s) and H-16 (δ 4.45, dd, J = 5.2, 8.1 Hz), as well as between pairs H-21 (δ 1.09, 3H, s)/H-22 (δ 0.95, 3H, s), H-22/H-23 in the NOESY spectrum, supported the designated configurations of chiral centers at positions C-4, C-10, C-8, C-13, C-14, and C-16. Additionally, compounds related to the (−)-hyrtiosal skeleton featuring a carbonyl group attached to C-4 in β-configuration had been shown to shift the signal of the methyl group at C-4 to more than 24 ppm;[38] the chemical shift of C-21 (δ 13.51, q) in **1** also implied a α-configuration for Me-21. Therefore, the structure of the new natural product **1** was determined as a 4-β-formyl-substituted hyrtiosal, named (+)-20-formylhyrtiosal.

Compound **2** was isolated as a minor component, and its molecular formula $C_{27}H_{38}O_5$ was afforded by HR-FABMS, 42 amu higher than that of **1**. IR absorptions suggested the presence of two carbonyl groups (1726, 1721 cm^{-1}) and the absence of a hydroxyl group. The ^1H and ^{13}C NMR spectra of compound **2** closely resembled those of **1**, with the exception of an additional acetyl group that appeared at δ_H 2.07 (s, 3H) and δ_C 21.54 (q), 171.24 (s). The acetoxyl group was assigned to a position at C-16 due to the observed downfield shift of H-16 to δ 5.64 (dd, J = 6.0, 7.5 Hz), whereas H-16 of **1** resonated at δ 4.45 (dd, J = 5.2, 8.1 Hz) in comparison. The relative stereochemistry of compound **2** was assumed to be identical to that of **1** due to the similar optical rotation between **1** and **2** ($[\alpha]_D$ +65°), as well as the NOE correlations between H-12 (δ 9.40, s) and the acetyl proton at δ_H 2.07 (3H, s) and between pairs H-24 (δ 1.18, 3H, s)/H-16, H-21 (δ 1.08, 3H, s)/H-22 (δ 0.94, 3H, s), H-22/H-23 (δ 0.92, 3H, s), and H-23/H24 in the NOESY spectrum. Accordingly, compound **2** was identified as (+)-16-*O*-acetyl-20-formylhyrtiosal.

Compound **3** was isolated as colorless needles. The HRFABMS gave the molecular formula $C_{27}H_{40}O_6$. IR absorptions suggested the presence of hydroxyl (3421 cm^{-1}), unsaturated δ-lactone (1753, 1632 cm^{-1}), and ester (1716 cm^{-1}) groups. The ^1H NMR spectrum exhibited six methyl groups [δ 0.80 (3H, s), 0.81 (6H, s), 0.94 (3H, s), 1.55 (3H, s), and 1.97 (3H, s)] and three protons in the vicinity of the oxygen-bearing substituents [δ 6.60 (s), 5.69 (br s), and 4.94 (d, J = 3.0 Hz)]. The ^{13}C NMR and DEPT spectra exhibited 27 carbons, six of which were methyls, seven methylenes, six methines, and eight quaternary carbons (four sp^3 and four sp^2). The ^1H and ^{13}C spectral data were compatible to a large degree with those of the known scalarane sesterterpenoid hyrtiolide, [5] with the exception of an additional acetyl group [δ_H 1.97 (3H, s); δ_C 21.02 (q), 170.45 (s)] present in compound **3**. The acetyl substituent was assigned to C-12 on the basis of the correlation of H-12 (δ_H 5.69, br) with the acetyl carbon at δ_C 171.12 (s) in the HMBC spectrum. The relative configurations of H-12, H-16, and H-19 were determined by their coupling constants and by interpreting the NOESY spectrum. The NOE correlations of Me-22 (δ 0.80, s)/Me-23 (δ 0.81,s), Me-23/Me-24 (δ 0.94, s), and Me-24/Me-25 (δ 1.55, s) in the NOESY in association with ^{13}C NMR chemical shifts of the methyl groups [5] indicated *trans* junctures of the rings A−D, identical to those of hyrtiolide. The broad signals of H-12 (δ 5.69, br s) and H-16 (δ 4.94, br d, J = 3.0 Hz) suggested that H-12 and H-16 are in equatorial positions. The NOE correlations between H-12/Me-25 (δ_H 1.55, s), Me-25/H-15-(δ_H 2.12(d), and H-15/H-16 in the NOESY spectrum further confirmed the β-configurations for H-12 and H-16. The α-configuration of the hydroxyl group at C-19 was deduced by NOE correlations between H-19 (δ 6.60, br) and H-12 and between H-19 and Me-25. Thus, compound **3** was identified as 12-α-*O*-acetylhyrtiolide.

Compound **4** was isolated as a white oil, and its molecular formula, $C_{25}H_{38}O_3$, was established on the basis of the HRFABMS spectrum. The ^{13}C NMR and DEPT spectra exhibited five methyl groups [δ 26.55 (q, C-25), 17.70 (q, C-24), 16.02 (q, C-19), 16.33 (q, C-14), 12.20 (q, C-9)], six methylene carbons [δ 25.71 (t, C-21), 39.73 (t, C-20), 26.76 (t, C-16), 39.85 (t, C-15), 34.13 (t, C-11), 36.30 (t, C-6)], nine methines [δ 124.35 (d, C-22), 123.96 (d, C-17), 119.69 (d, C-12), 120.95 (d, C-7), 139.04 (d, C-4), 108.58 (d, C-2), 143.29 (d, C-1), 77.02 (d, C-10), 66.66 (d, C-5)], and five quaternary carbons [δ 140.53 (s, C-8), 138.90 (s, C-13), 131.34 (s, C-23), 135.31 (s, C-18), 128.62 (s, C-3)], of which four (C-1 to C-4) were attributed to a β-substituted furan moiety. In ^1H NMR spectrum, three proton signals at δ 7.41 (d, J = 1.0 Hz, H-1), 7.41 (br s, H-4), and 6.44 (br s, H-2) were assigned for the β-substituted furan moiety. The proton signals at δ 5.47 (dd, J = 7.0, 7.0 Hz, 1H, H-7) and 5.11−5.08 (m, 3H, H-12, H-17, H-22) were due to four olefinic protons. Additionally, there were five methyl singlets at δ 1.70 (3H, s, H-25), 1.68 (3H, s, H-9), 1.66 (3H, s, H-14), and 1.62 (6H, s, H-19, H-24). ^{13}C NMR data indicated the presence of four trisubstituted olefinic bonds in addition to the β-substituted furan ring [δ 108.58 (d, C-2), 128.62 (s, C-3), 139.04 (d, C-4), 143.29 (d, C-1)]. Since the seven sites of unsaturation that had been revealed by interpretation of the mass spectrum could be accounted for by the four double bonds and the furan ring, compound **4** was identified as a linear sesterterpene. The HMQC and HMBC spectral analysis enabled us to establish the gross structure, which is closely related to a known linear sesterterpene, furospinulosin-1.[36] The new natural product **4** differed from the known furospinulosin-1 by the presence of two additional hydroxyl groups, which were assigned to C-5 and C-10, respectively, on the basis of HMBC correlations observed between H-4 (δ 7.41, br) and C-5 (δ 66.66, d) and between Me-9 and C-10, and Me-9 was further correlated with the olefinic carbons C-8 and C-7. The geometry of the double bonds was determined to be all *E* on the basis of the chemical shifts of the methyl groups at high field (<18 ppm) and a downfield methyl signal at δ 26.50 (q, C-25) being *cis* to the olefinic proton H-22.[36,39] Accordingly, the structure of **4** was determined to be 5,-10-dihydroxylfurospinulosine-1.

Experimental Section

General Experimental Procedures. Melting points were measured by a XT-4A micromelting point apparatus without correction. The IR spectra were determined on a Thermo Nicolet Nexus 470 FT-IR spectrometer. ^1H NMR and ^{13}C NMR as well as 2D NMR spectra were recorded on an AVANCE-500 FT 500 MHz NMR spectrometer using TMS as internal standard. EIMS spectra were performed with a Bruker APEX II mass spectrometer. Column chromatography was performed with silica gel (200−300 mesh). HF254 silica gel for TLC was provided by Sigma Co. Ltd. Sephadex LH-20 (18−110 μm) was obtained from Pharmacia Co.

Sponge Material. The specimen of *Hyrtios erectus* was collected from Hainan Island, South China Sea, in July 2002. The species was identified by Dr. R. van Soest (Institute of

Table 1. ^{13}C and ^{1}H NMR Data of Compounds **1**, **2**, and Hyrtiosal (**12**)[a]

	1		**2**		**12**[3]	
no.	δ_C	δ_H (*J* Hz)	δ_C	δ_H (*J* Hz)	δ_C	δ_H (*J* Hz)
1	39.20 CH_2	1.01 m 1.53 m	39.53 CH_2	1.03 m 1.53 m	40.2 CH_2	
2	16.54 CH_2	1.61 m 1.72 m	17.10 CH_2	1.55 m 1.69 m	18.8 CH_2	
3	32.49 CH_2	1.25, 1.28 m	30.02 CH_2	1.28 m	42.4 CH_2	
4	49.30 qC		50.44 qC		33.1 qC	
5	49.58 CH	1.43 m	49.71 CH	1.41 m	57.4 CH	0.85 m
6	21.49 CH_2	0.98 m 1.42 m	21.62 CH_2	1.02 m 1.49 m	18.3 CH_2	1.40 m 1.60 m
7	39.62 CH_2	1.19 m 1.72 m	40.44 CH_2	1.13 m 1.78 m	40.3 CH_2	1.13 m 1.72 td (*3.2*, *12.5*)
8	44.79 qC		42.56 qC		44.5 qC	
9	60.05 CH	1.18 dd (*7.0*)	60.13 CH	1.16 d (*7.9*)	60.4 CH	1.07 dd (*6.2*, *13.8*)
10	35.72 qC		36.21 qC		36.8 qC	
11	33.64 CH_2	1.69 m 1.97 dd (*6.0*, *11.2*)	33.55 CH_2	1.35 m 1.91 dd (*6.2*, *13.0*)	33.68 CH_2	1.40 m 1.89 dd (*6.3*, *13.1*)
12	206.28 CH	9.51 s	204.98 CH	9.40 s	205.7 CH	9.45 s
13	52.69 qC		53.36 qC		52.8 qC	
14	48.13 CH	2.07 dd (*5.2*, *9.4*)	49.12 CH	1.78 m	48.1 CH	1.98 dd (*6.6*, *7.9*)
15	33.49 CH_2	1.47 m 1.56 m	33.86 CH_2	1.43 m 1.55 m	33.69 CH_2	1.62 m
16	64.25 CH	4.45 dd (*5.2*, *8.1*)	66.97 CH	5.64 dd (*6.0*, *7.5*)	64.2 CH	4.42 dd (*6.0*, *7.4*)
17	129.19 qC		124.5 qC		129.2 qC	
18	108.44 CH	6.39 dd (*0.8*, *1.6*)	109.13 CH	6.37 br s	109.5 CH	6.37 t (*1.1*)
19	143.29 CH	7.40 dd (*1.6*, *1.5*)	143.65 CH	7.40 d (*1.6*)	143.2 CH	7.36 br s
20	205.37 CH	9.22 s	208.22 CH	9.23 s	33.5 CH	0.845 s
21	13.51 CH_3	1.09 s	13.89 CH_3	1.08 s	21.2 CH_3	0.82 s
22	15.74 CH_3	0.95 s	16.14 CH_3	0.94 s	15.7 CH_3	0.86 s
23	16.54 CH_3	0.89 s	16.50 CH_3	0.92 s	16.5 CH_3	0.851 s
24	19.20 CH_3	1.23 s	19.61 CH_3	1.18 s	19.1 CH_3	1.18 s
25	138.80 CH	7.39 dd (*1.5*, *0.8*)	143.71 CH	7.42 br s	139.8 CH	7.36 br s
Ac			21.54 CH_3 171.24 qC	2.07 s		

[a] The ^{1}H and ^{13}C NMR spectra are measured in $CDCl_3$.

Systematic Population Biology, Amsterdam University, The Netherlands). A voucher specimen (HS-17) is deposited at the State Key Laboratory of Natural and Biomimetic Drugs, Peking University.

Extraction and Isolation. The sponge (2.3 kg, wet wt) was homogenized and then extracted with MeOH and $CHCl_3$ successively. The concentrated total extract was partitioned between petroleum ether and 90% MeOH to remove lipids, and then the 90% aqueous MeOH was concentrated under reduced pressure to afford a degreased extract, which was partitioned between H_2O and CH_2Cl_2. CH_2Cl_2 extract was subjected to silica gel column chromatography eluted with an equivalent petroleum ether−ethyl acetate stepwise gradient to obtain 10 fractions. Fraction 3 (petroleum ether−EtOAc, 3:1) was subjected to a Sephadex LH-20 column and eluted with 85% aqueous MeOH to get fractions 2-1 to 2-7. Fraction 2-1 was chromatographed on silica gel eluting with petroleum ether−EtOAc (2:1) to yield compounds **1** (7.8 mg), **2** (2.3 mg), **5** (1263 mg), **7** (4.3 mg), **8** (158 mg), and **11** (28.0 mg). Fractions 2-3 to 2-5 were combined and subjected to a Sephadex LH-20 column and eluted with 80% MeOH to collect 10 fractions, which were monitored by TLC and ^{1}H NMR spectra. Terpenoid-containing fractions were combined and separated by silica gel column chromatography using petroleum ether−acetone (2:1) as eluting solvent to give compounds **3** (5.2 mg), **4** (11.4 mg), **6** (87 mg), **9** (2.1 mg), and **10** (821 mg).

Compound (1): white amorphous; $[\alpha]^{25}_D$ +60° (*c* 0.245, MeOH); IR (Nujol) ν_{max} 3432 (br), 2927, 2870, 1718, 1502, 1455, 1386, 1159, 1054, 1023, 874, 796, 730, 601 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$, 500 MHz), see Table 1; ESIMS *m/z* (positive mode) 401 $[M + H]^+$, 383 $[M - OH]^+$, 367, 337, 273; HR-FABMS *m/z* 423.24972 (calcd for $C_{25}H_{36}O_4Na$, 423.25113).

Compound (2): white oil, $[\alpha]^{25}_D$ +65° (*c* 0.2, MeOH); IR (Nujol) ν_{max} 2929, 2869, 1725, 1721, 1504, 1459, 1372, 1239, 1161, 1023, 971, 874, 796, 729, 602 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; FABMS *m/z* (positive mode) 443 $[M + 1]^+$, 383 $[M - OAc]^+$, 399 $[M - Ac]^+$; HRFABMS *m/z* 465.26058 (calcd for $C_{27}H_{38}O_5Na$, 465.26169).

Table 2. ^{13}C and ^{1}H NMR Data of **4** and **3**

	4[a]		**3**[b]	
no.	δ_C	δ_H (*J* Hz)	δ_C	δ_H (*J* Hz)
1	143.29 CH	7.41 d (*1.0*)	40.07 CH_2	1.57, 0.75 m
2	108.58 CH	6.44 br s	18.32 CH_2	1.47, m
3	128.62 qC		42.27 CH_2	1.34,1.08 m
4	139.04 CH	7.41 br s	33.38 qC	
5	66.66 CH	4.73 dd (*6.8*, *7.1*)	56.60 CH	0.82 m
6	36.30 CH_2	2.51, 2.55 m	18.83 CH_2	1.42, 1.33 m
7	120.95 CH	5.47 dd (*7.0*, *7.0*)	41.50 CH_2	1.84, 1.20 m
8	140.53 qC		37.73 qC	
9	12.20 CH_3	1.68 s	53.21 CH	1.54 m
10	77.02 CH	4.04 dd (*6.1*, *6.8*)	37.22 qC	
11	34.13 CH_2	2.26, 2.30 m	21.99 CH_2	2.09, 1.84 m
12	119.69 CH	5.10 m	75.49 CH	5.69 br s
13	138.90 qC		42.12 qC	
14	16.33 CH_3	1.66 s	45.93 CH	2.51 dd (*12.5*)
15	39.85 CH_2	2.03 m	28.18 CH_2	2.13 d (*14.0*) 1.90 ddd (*14.0*, *4.0*)
16	26.76 CH_2	2.06 m	59.53 CH	4.94 d (*3.0*)
17	123.96 CH	5.10 m	131.42 qC	
18	135.31 qC		168.10 qC	
19	16.02 CH_3	1.62 s	98.27 CH	6.60 s
20	39.73 CH_2	2.11 m	171.12 qC	
21	25.71 CH_2	1.99 m	33.25 CH_3	0.81 s
22	124.35 CH	5.10 m	21.48 CH_3	0.80 s
23	131.34 qC		17.57 CH_3	0.81 s
24	17.70 CH_3	1.62 s	16.12 CH_3	0.94 s
25	26.55 CH_3	1.70 s	19.22 CH_3	1.55 s
Ac			21.02 CH_3 170.45 qC	1.97 s

[a] The ^{1}H and ^{13}C NMR spectra are measured in pyridine-d_5. [b] The ^{1}H and ^{13}C NMR spectra are measured in $CDCl_3$.

Compound (3): colorless needles, mp 220−222 °C, $[\alpha]^{25}_D$ +81.46° (*c* 0.205, MeOH); IR (Nujol) 3421(br), 2931, 1753, 1716, 1632, 1463, 1376, 1238 cm^{-1}; ^{1}H and ^{13}C data, see Table 2, ESIMS *m/z*: 460 $[M]^+$, 920 $2M^+$; HRFABMS *m/z* 483.27315 (calcd for $C_{27}H_{40}O_6Na$, 483.27226).

Compound (4): colorless oil, $[\alpha]^{25}_D$ +32.52° (*c* 0.12, MeOH); IR (Nujol) 3383 (br), 2925, 1453, 1378, 1026, 974, 875, 842

cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; ESIMS *m*/*z* 404 $[M + NH_4]^+$, 369 $[M - OH]^+$, 351 $[M - 2OH]^+$; HRFABMS *m*/*z* 385.27441 (calcd for $C_{25}H_{37}O_3$, 385.27427).

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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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