# Two New Sesquiterpenes from the Marine Fungus *Eutypella scoparia* FS26 from the South China Sea

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A new monocyclofarnesane-type sesquiterpene, 3,7,10-trihydroxy-6,11-cyclofarnes-1-ene (**1**), and a new acorane-type sesquiterpene, 8-(hydroxymethyl)-1-(2-hydroxy-1-methylethyl)-4-methylspiro[4.5]-dec-8-en-7-ol (**2**), were isolated from the culture of *Eutypella scoparia* FS26 from the South China Sea, along with three known terpenes, **3**–**5**. The structures of these compounds were determined by extensive analysis of their spectroscopic data as well as by comparison with literature reports. The isolated compounds **1**–**5** were evaluated for their cytotoxic activities against the SF-268, MCF-7, and NCI-H460 tumor cell lines.

**Introduction.** – Marine fungi living in diverse environments such as high-pressure, high-salt, oxygen deficiency, and low nutrition have evolved specific physiological and biochemical pathways to produce structurally novel and biologically active metabolites [1–5]. *Eutypella scoparia* is a ubiquitous fungus which has been reported from many environments ranging from soil in Antarctica to tropical forests of Australia and Thailand, and also from marine sources [6]. In recent years, some new metabolites, including pimarane diterpenes, cytochalasin derivatives, $\gamma$-lactones, *ent*-eudesmane sesquiterpenes, and cytosporin-related compounds have been reported from the genus *Eutypella*, together with several known benzopyran derivatives and cyclic dipeptide metabolites [6–8]. In our previous study, a marine fungus, *E. scoparia* FS26, from the South China Sea was shown to produce several secondary metabolites. The peculiarity of the marine biotope and the chemical diversity of this genus attracted our attention and prompted us to investigate the extract from this fungus strain. Here, we describe the isolation, structure elucidation, and cytotoxic activities of two new sesquiterpenes.

**Results and Discussion.** – 1. *Isolation and Structure Elucidation*. The culture of *E. scoparia* FS26 (100 l) was centrifuged to separate broth and mycelia, and then both were exhaustively extracted with AcOEt. The concentrated extracts were further purified by various chromatographic methods, including silica gel, reversed-phase silica gel $C_{18}$, and *Sephadex LH-20*, to yield one new monocyclofarnesane-type sesquiterpene, 3,7,10-trihydroxy-6,11-cyclofarnes-1-ene (**1**), and one new acorane-type sesqui-

terpene, 8-(hydroxymethyl)-1-(1-hydroxy-1-methylethyl)-4-methylspiro[4.5]dec-8-en-7-ol (**2**), as well as the three known terpenes **3**–**5** (*Fig. 1*). The three known terpenes, (3*S*,3a*R*,7a*S*)-3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one (**3**) [9], *rel*-(3*S*,6*S*,7*R*,10*R*)-7,10-epoxy-3,7,11-trimethyldodec-1-ene-3,6,11-triol (**4**) [10][11], and euphorbol (**5**) [12], were identified by comparison of their spectroscopic data ($^1$H- and $^{13}$C-NMR, and MS) with those reported in the literature. All known compounds, **3**–**5**, were isolated from this genus for the first time.

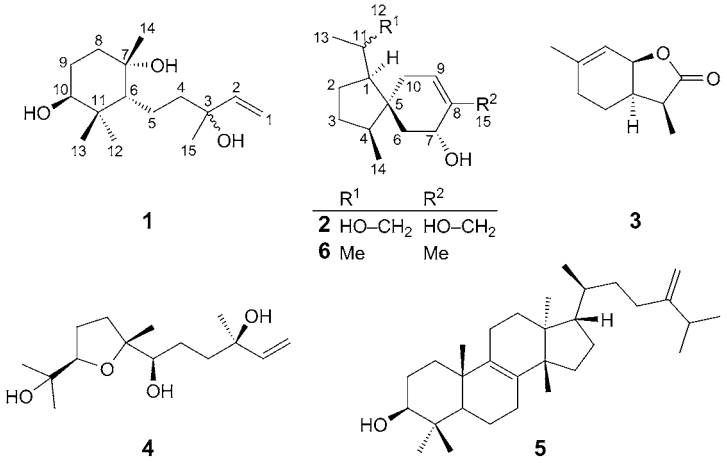
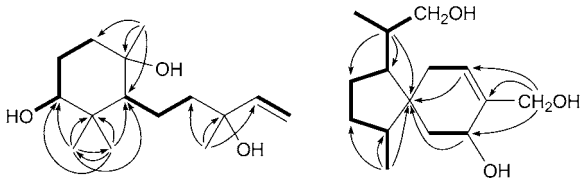



Fig. 1. *Stuctures of compounds* **1**–**6** *isolated from* Eutypella scoparia

Compound **1** was obtained as colorless oil. The IR spectrum of **1** showed absorption bands of OH (3383 cm$^{-1}$), and C=C (1642 cm$^{-1}$). The molecular formula, $C_{15}H_{28}O_3$, consistent with two degrees of unsaturation, was determined by HR-EI-MS (*m*/*z* 279.1947 ([*M* + Na]$^+$, $C_{15}H_{28}NaO_3^+$; calc. 279.1936)). The $^1$H-NMR spectrum (*Table*) of **1** exhibited signals characteristic of terminal vinylic H-atoms at $\delta$(H) 5.21 (*dd*, *J* = 17.4, 1.6, $H_a$–C(1)), 5.03 (*dd*, *J* = 10.8, 1.6, $H_b$–C(1)), and 5.94 (*dd*, *J* = 17.4, 10.8, H–C(2)), four tertiary Me signals at $\delta$(H) 1.01 (Me(12)), 0.78 (Me(13)), 1.14 (Me(14)), and 1.26 (Me(15)), in addition to one O-bearing CH group signal at $\delta$(H) 3.23 (*dd*, *J* = 10.9, 4.2, H–C(10)). Analyses of $^{13}$C-NMR, DEPT-135, and HSQC data revealed that **1** contains 15 C-atoms (*Table*), including four *singlet* Me, five $CH_2$ (one sp$^2$ and four sp$^3$), three CH groups (one sp$^2$, one O-bearing sp$^3$, and one sp$^3$), and three quaternary C-atoms (two O-bearing sp$^3$ and one sp$^3$). To account for the molecular formula of compound **1**, the presence of three OH groups was suggested. The chemical shifts of C(3), C(7), and C(10) indicated that the three OH groups were attached to them, respectively. $^1$H,$^1$H-COSY Spectrum of **1** revealed correlations between H–C(1) and H–C(2), as well as partial structures H–C(4) to H–C(6) *via* H–C(5), and H–C(8) to H–C(10) *via* H–C(9) (*Fig. 2*). In the HMBC spectrum (*Fig. 2*), correlations observed from Me(12) to C(6), C(10), C(11), and C(13), and from Me(13) to C(6), C(10), C(11), and C(12) indicated the connection of CH(6)–C(11)(Me(12),Me(13))–CH(10)OH. HMBC Cross-peaks observed from Me(14) to C(6), C(7), and C(8) indicated the subunits of CH(6)–C(7)OH(Me(14))–$CH_2$(8), and hence the six-

Table. *$^1$H- and $^{13}$C-NMR Data* (500 and 125 MHz, resp.; $CD_3OD$) *of* **1** *and* **2**. Assignments were corroborated by $^1$H,$^1$H-COSY, HSQC, and HMBC experiments.

| | **1** | | **2** | |
|---|---|---|---|---|
| | $\delta$(H) (*J* in Hz) | $\delta$(C) | $\delta$(H) (*J* in Hz) | $\delta$(C) |
| $CH_2$(1) or H–C(1) | 5.03 (*dd*, *J* = 10.8, 1.6), 5.21 (*dd*, *J* = 17.4, 1.6) | 111.3 (*t*) | 1.43 – 1.52 (*m*) | 56.6 (*d*) |
| H–C(2) or $CH_2$(2) | 5.94 (*dd*, *J* = 17.4, 10.8) | 146.2 (*d*) | 1.43 – 1.52, 1.82 – 1.87 (2*m*) | 26.3 (*t*) |
| C(3) or $CH_2$(3) | | 73.9 (*s*) | 1.21 (*ddd*, *J* = 11.8, 6.3, 3.2), 1.70 – 1.82 (*m*) | 29.4 (*t*) |
| $CH_2$(4) or H–C(4) | 1.56 – 1.60, 1.77 – 1.84 (2*m*) | 45.8 (*t*) | 1.58 – 1.64 (*m*) | 47.1 (*d*) |
| $CH_2$(5) or C(5) | 1.41 (*ddd*, *J* = 13.4, 8.3, 4.0), 1.46 – 1.56 (*m*) | 20.8 (*t*) | | 46.2 (*s*) |
| H–C(6) or $CH_2$(6) | 1.12 (*dd*, *J* = 8.3, 4.0) | 56.4 (*d*) | 1.35 (*dd*, *J* = 13.4, 10.2), 1.82 – 1.87 (*m*) | 32.4 (*t*) |
| C(7) or H–C(7) | | 74.0 (*s*) | 4.47 (br. *s*) | 66.7 (*d*) |
| $CH_2$(8) or C(8) | 1.47 – 1.54, 1.69 – 1.73 (2*m*) | 41.2 (*t*) | | 140.3 (*s*) |
| $CH_2$(9) or H–C(9) | 1.53 – 1.56, 1.64 – 1.68 (2*m*) | 29.2 (*t*) | 5.77 (*dd*, *J* = 3.4, 2.1) | 125.7 (*d*) |
| H–C(10) or $CH_2$(10) | 3.23 (*dd*, *J* = 10.9, 4.2) | 78.6 (*d*) | 1.93 (*d*, *J* = 19.0), 2.23 (*d*, *J* = 19.0) | 35.3 (*t*) |
| C(11) or H–C(11) | | 41.2 (*s*) | 1.66 (*dd*, *J* = 10.1, 7.0) | 38.5 (*d*) |
| Me(12) or $CH_2$(12) | 1.01 (*s*) | 28.3 (*q*) | 3.28 (*dd*, *J* = 10.6, 7.0), 3.61 (*dd*, *J* = 10.6, 3.2) | 67.4 (*t*) |
| Me(13) | 0.78 (*s*) | 15.0 (*q*) | 1.04 (*d*, *J* = 7.0) | 17.0 (*q*) |
| Me(14) | 1.14 (*s*) | 22.5 (*q*) | 0.88 (*d*, *J* = 6.8) | 13.9 (*q*) |
| Me(15) or $CH_2$(15) | 1.26 (*s*) | 27.0 (*q*) | 4.14 (*d*, *J* = 13.5), 4.22 (*d*, *J* = 13.5) | 63.5 (*t*) |




**1** **2**

Fig. 2. *$^1$H,$^1$H-COSY* (—) *and key HMBC* (→) *correlations of* **1** *and* **2**

membered ring (C(6)–C(7)–C(8)–C(9)–C(10)–C(11)) within **1** was evidenced. Similarly, HMBCs from Me(15) to C(2), C(3), and C(4) revealed partial structures of CH(2)–C(3)OH(Me(15))–$CH_2$(4), and hence the nature of the six-C-atom side-chain was established. Thus, the molecular formula of **1** was established. The relative configuration of **1** was assigned by the analysis of H-atom coupling constants and a NOESY spectrum (*Fig. 3*). The large vicinal coupling constant of H–C(10) ($J$ = 10.9 Hz) indicated the characteristic *trans*-diaxial relationship, evidencing the axial orientation of H–C(10). NOE Correlation between H–C(10) and Me(12) indicated their *cis*-orientation, while Me(13) showed NOE correlations with Me(14) and

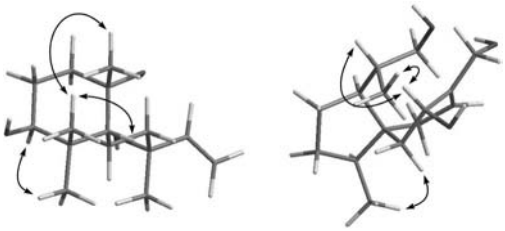


Fig. 3. *Key NOESY correlations for* **1** *and* **2**

H–C(6), the *cis*-orientation for the latter. The above spectral evidence established the relative configurations at C(6), C(7), and C(10). The relative configuration at C(3) and the absolute configuration of **1** remain to be determined. Based on the above spectral evidences, the structure of **1** was elucidated as 3,7,10-trihydroxy-6,11-cyclofarnes-1-ene.

Compound **2** was obtained as colorless oil. The IR spectrum of **2** showed absorption bands of OH group (3374 $cm^{-1}$) and C=C bond (1677 $cm^{-1}$). The molecular formula was determined as $C_{15}H_{26}O_3$ (three degrees of unsaturation) by HR-EI-MS (*m/z* 277.1797 $[M+Na]^+$, $C_{15}H_{26}NaO_3^+$; calc. 277.1780)). The $^1$H-NMR spectrum (*Table*) of **2** showed signals due to an $sp^2$-CH group at $\delta$(H) 5.77 (*dd*, $J=3.4$, 2.1, H–C(9)), two pairs of O-bearing $CH_2$ groups at $\delta$(H) 3.61 (*dd*, $J=10.6$, 3.2, $H_a$–C(12)) and 3.28 (*dd*, $J=10.6$, 7.0, $H_b$–C(12)), and 4.22 (*d*, $J=13.5$, $H_a$–C(15)) and 4.14 (*d*, $J=13.5$, $H_b$–C(15)), one O-bearing $sp^3$-CH group at $\delta$(H) 4.47 (br. *s*, H–C(7), and two secondary Me groups at $\delta$(H) 1.04 (*d*, $J=7.0$, Me(13)) and 0.88 (*d*, $J=6.8$, Me(14)). Analyses of $^{13}$C-NMR, DEPT-135, and HSQC data revealed that **2** contained 15 C-atoms, including two Me, six $CH_2$ (two O-bearing $sp^3$ and four $sp^3$), five CH groups (one $sp^2$ and one O-bearing $sp^3$, and three $sp^3$), and two quaternary C-atoms (one $sp^2$ and one $sp^3$). The $^1$H- and $^{13}$C-NMR spectra of **2** were similar to those of the reported acorane-type sesquiterpene trichoacorenol (**6**) which had been isolated from *Trichoderma koningii* [13], except that signals for one secondary Me group ($\delta$(H) 0.86 (*d*, $J=6.8$); $\delta$(C) 23.8) and one olefinic tertiary Me group ($\delta$(H) 1.73; $\delta$(C) 20.0) were absent, and instead those of two new OH-bearing $CH_2$ groups ($\delta$(H) 3.61, 3.28; $\delta$(C) 67.4; $\delta$(H) 4.22, 4.14; $\delta$(C) 63.5) were observed. The $^1$H,$^1$H-COSY cross-peaks indicated the presence of three independent spin systems shown by bold lines in *Fig. 2*, and the observed HMBCs from $CH_2$(15) to C(7), C(8), and C(9), and $^3J$ HMBC cross-peaks observed from H–C(7), H–C(9), H–C(11), and Me(14) to quaternary C-atom C(5) further confirmed the formula for **2** (*Fig. 2*). The relative configuration of **2** was identical to that in trichoacorenol **6** on the basis of the H-atom coupling constants and NOESY spectrum (*Fig. 3*). The coupling constants of H–C(6) (*dd*, $J=13.4$, 10.2) revealed characteristic geminal and *trans*-diaxial relationships, indicating the axial orientiation of H–C(6) ($\delta$(H) 1.35) and H–C(7). The H–C(7) showed NOE correlations with H–C(11) and Me(13), and Me(14) exhibited NOE correlation with $H_{ax}$–C(6), indicating an $\alpha$-oriented OH group at C(7). Based on the above spectral evidences, the structure of **2** was established as 8-(hydroxymethyl)-1-(1-hydroxy-1-methylethyl)-4-methylspiro[4.5]dec-8-en-7-ol with a yet undetermined absolute configuration and relative configuration at C(11).

2. *Cytotoxic Activity.* The cytotoxicity of compounds **1**–**5** were evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) method [14]. As a result, compounds **1** and **2** exhibited weak inhibition activities against MCF-7 cell line (30.6 and 47.8% inhibition rates, resp., at the concentration of 100 μM) and no cytotoxicities against the SF-268 and NCI-H460 cell lines. The compound **5** showed moderate inhibitory activities against the SF-268 and MCF-7 cell lines, and weak cytotoxicity against the NCI-H460 cell line with 90.3, 93.6, and 41.1% inhibition rates, respectively, at the same concentration. However, compounds **3** and **4** did not exhibit any cytotoxicity against all the three cell lines. Cisplatin as a positive control had 95.0, 97.4, and 97.6% inhibition rates against the SF-268, MCF-7, and NCI-H460 lines, respectively, at the same concentration.

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## Experimental Part

*General.* Column chromatography (CC): commercial silica gel ($SiO_2$; 200–300 mesh; *Qingdao Haiyang Chemical Group Co.*, Qingdao, P. R. China), *Chromatorex ODS* (40–75 μm; *Fuji Silysia*), and *Sephadex LH-20* (*Amersham Biosciences*). TLC: Precoated silica gel plates *GF-254* (*Qingdao Haiyang Chemical Group Co.,* Qingdao, P. R. China). M.p.: *Netzsch DSC 204* apparatus. Optical rotation: *Perkin-Elmer 341* polarimeter. UV Spectra: *Biochrom Ultrospec 6300pro* UV/VIS spectrophotometer; $\lambda_{max}$ (log $\varepsilon$) in nm. IR Spectra: *Bruker EQUINOX 55* spectrophotometer; KBr pellets; in $cm^{-1}$. $^1H$- and $^{13}C$-NMR Spectra: *Bruker Avance-500* spectrometer; at 500 and 125 MHz, resp.; $\delta$ in ppm, *J* in Hz. EI-MS: *Thermo DSQ* mass spectrometer and/or *Thermo MAT95XP* mass spectrometer; in *m*/*z*. HR-EI-MS: *Thermo MAT95XP* mass spectrometer; in *m*/*z*.

*Fungal Material.* Marine fungus *E. scoparia* FS26 was isolated from a marine sediment sample, which was collected (–139 m) in the South China Sea (18° 42.878′ N, 111° 2.797′ E) in August 2008. The strain was indentified by sequence analysis of rDNA ITS (internal transcribed spacer) region. The sequence of ITS region of marine fungus *E. scoparia* FS26 has been submitted to GenBank (Accession No. HM989831). By using BLAST (nucleotide sequence comparison program) to search the GenBank database, *E. scoparia* FS26 revealed 100% similarity to *Eutypella scoparia* (Accession No. EU702431). The strain is preserved at the Guangdong Provincial Key Laboratory of Microbiol Culture Collection and Application, Guangdong Institute of Microbiology.

*Extraction and Isolation. E. scoparia* FS26 was cultured in potato dextrose broth, which was prepared in 50% (*v*/*v*) seawater instead of distilled $H_2O$. The fungus *E. scoparia* FS26 was maintained on 50% (*v*/*v*) seawater potato dextrose agar medium at 28° for 5 d, and then three pieces ($0.5 \times 0.5$ $cm^2$) of mycelial agar plugs were inoculated into $20 \times 500$ ml *Erlenmeyer* flasks, each containing 250 ml 50% (*v*/*v*) of seawater potato dextrose broth. After 6 d of incubation at 28° on a rotary shaker at 130 rpm, 25 ml of liquid culture were aseptically transferred into each of a total of 200 flasks (1000 ml) containing 500 ml of 50% (*v*/*v*) seawater potato dextrose broth. The liquid cultivation that followed was kept for 7 d at 28° and 130 rpm on a rotary shaker. The culture (100 l) was centrifuged to give the broth and mycelia. The broth was extracted with AcOEt four times, then the AcOEt layers were combined and evaporated under reduced pressure at a temp. not exceeding 40° to yield a dark brown gum (24.8 g). Fungal mycelia was thoroughly extracted with AcOEt four times, and then the extracts were combined and concentrated under reduced pressure to give a mycelial crude extract (132.4 g). Both crude AcOEt extracts were separated by column chromatography ($SiO_2$; 200–300 mesh) with a gradient system of increasing polarity (petroleum ether (PE)/AcOEt/MeOH) to afford *Fractions A*–*V* for the liquid culture and *Fractions 1*–*20* for the mycelia. *Fr. H* eluted with PE/AcOEt 90:10 was subjected to CC (*Sephadex LH-*

*20*; $CHCl_3$/MeOH 1:1), followed by CC (reversed-phase (RP) silica gel $C_{18}$; MeOH/$H_2O$ 60:40) to yield compound **3** (7.5 mg). *Fr.Q* eluted with PE/AcOEt 30:70 was subjected to CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1), then followed by CC (RP silica gel $C_{18}$; MeOH/$H_2O$ 45:55) to yield three subfractions, *Frs. Q-1 – Q-3*. *Fr. Q-1* (25 mg) was subjected to CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1) to yield compound **4** (18 mg). *Fr. R* eluted with PE/AcOEt 10:90 was further fractionated by CC (*Sephadex LH-20*; MeOH), followed by CC (RP silica gel $C_{18}$; MeOH/$H_2O$ 50:50) to yield five subfractions, *Frs. R-1 – R-5*. Compound **1** (6 mg) was isolated from *Fr. R-2* (20 mg) by CC ($SiO_2$; $CHCl_3$/MeOH 40:1). *Fr. T* eluted with AcOEt was subjected to CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1), followed by CC (RP silica gel $C_{18}$; MeOH/$H_2O$ 70:30) to yield two subfractions, *Frs. T-1* and *T-2*. Compound **2** (4 mg) was isolated from *Fr. T-2* (10 mg) by CC ($SiO_2$; $CHCl_3$/MeOH 20:1). *Fr. 5* eluted with PE/AcOEt 90:10 was subjected to CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1), and then purified by repeated CC ($SiO_2$; PE/AcOEt 20:1) to furnish compound **5** (28 mg).

*3,7,10-Trihydroxy-6,11-cyclofarnes-1-ene* (*=2-(3-Hydroxy-3-methylpent-4-en-1-yl)-1,3,3-trimethylcyclohexane-1,4-diol*; **1**). Colorless oil. $[\alpha]_D^{20} = -15.2$ ($c = 0.33$, MeOH). IR (KBr): 3383, 3087, 2968, 2936, 2871, 1718, 1642, 1461, 1412, 1380, 1337, 1170, 1082, 1040, 1021, 998, 917, 853, 646, 436. $^1$H- and $^{13}$C-NMR: see *Table*. HR-EI-MS: 279.1947 ($[M+Na]^+$, $C_{15}H_{28}NaO_3^+$; calc. 279.1936).

*8-(Hydroxymethyl)-1-(2-hydroxy-1-methylethyl)-4-methylspiro[4.5]dec-8-en-7-ol* (**2**).Colorless oil. $[\alpha]_D^{20} = +6.7$ ($c = 0.33$, MeOH). IR (KBr): 3374, 2953, 2873, 1707, 1677, 1461, 1378, 1332, 1274, 1181, 1032, 749, 610. $^1$H- and $^{13}$C-NMR: see *Table*. HR-EI-MS: 277.1797 ($[M+Na]^+$, $C_{15}H_{28}NaO_3^+$; calc. 277.1780).

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