# Terpenoids from the Stems of *Drypetes congestiflora*

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Two new eremophilane-type sesquiterpenoids, 1$\alpha$-hydroxyeremophila-6,9,11-trien-8-one (**1**), 4$\alpha$-hydroxyeremophila-1,9-diene-3,8-dione (**2**), and a new friedelane-type triterpenoid, friedelane-3$\alpha$,16$\beta$-diol (**4**), along with six known terpenoids, **3** and **5**–**9**, have been isolated from the stems of *Drypetes congestiflora*. Their structures and relative configurations were elucidated on the basis of detailed spectroscopic analyses and by comparison of their NMR data with those reported in the literature. All of the compounds, **1**–**9**, were isolated for the first time from this species. Compound **3** exhibited moderate cytotoxic activities against the A549 and B16F10 cell lines.

**Introduction.** – The genus *Drypetes* (Euphorbiaceae) with over 200 species worldwide is widely used in West and Central Africa for diverse therapeutic purposes, such as the treatment of sinusitis, swellings, boils, gonorrhoea, and dysentery [1–3]. Previous phytochemical studies revealed the presence of characteristic pentacyclic triterpenoids, mainly friedelane, oleanane, and lupane types [4–7], podocarpane diterpenes [8][9], eremophilane-type sesquiterpenoids [10][11], flavonoids [7][12], sterols, and other phenoids [13] with antimicrobial [5][6], antileishmanial [10], antifungal [14], anti-inflammatory and analgesic activities [11].

As part of our ongoing search for compounds with structural and biological diversity from tropical plants in Hainan, we carried out a study of *Drypetes congestiflora*, an evergreen tree widely distributed in Guangdong, Guangxi, Hainan, and Yunnan provinces in China, for which no phytochemistry or biological activity have been reported. Our study resulted in the isolation of two new eremophilane-type sesquiterpenoids, **1** and **2**, and of a new friedelane-type triterpenoid, **4**, along with six known terpenoids with diverse structures, including one eremophilane sesquiterpene, **3**, one friedelane triterpenoid, **5**, one 30-norlupane triterpenoid **6**, two lupane triterpenoids, **7** and **8**, and one oleanane triterpenoid, **9** (*Fig. 1*). The cytotoxic activities of compounds **3**, **4**, and **7** against a panel of cancer cell lines (A549 and B16F10) have been evaluated by MTS (= 5-[3-carboxymethoxy)phenyl]-2-(4,5-dimethyl-1,3-thiazol-2-yl)-3-(4-sulfophenyl)-2,3-dihydro-1*H*-tetrazol-1-ium) assay.

**Results and Discussion.** – *Structure Elucidation.* Compound **1** was obtained as colorless oil. Its molecular formula, $C_{15}H_{20}O_2$, was deduced from the HR-ESI-MS (*m*/*z* 255.1355 ([$M$ + Na]$^+$)), indicating six degrees of unsaturation. The UV spectrum showed an absorption maximum at 242 nm, suggesting the presence of a conjugated

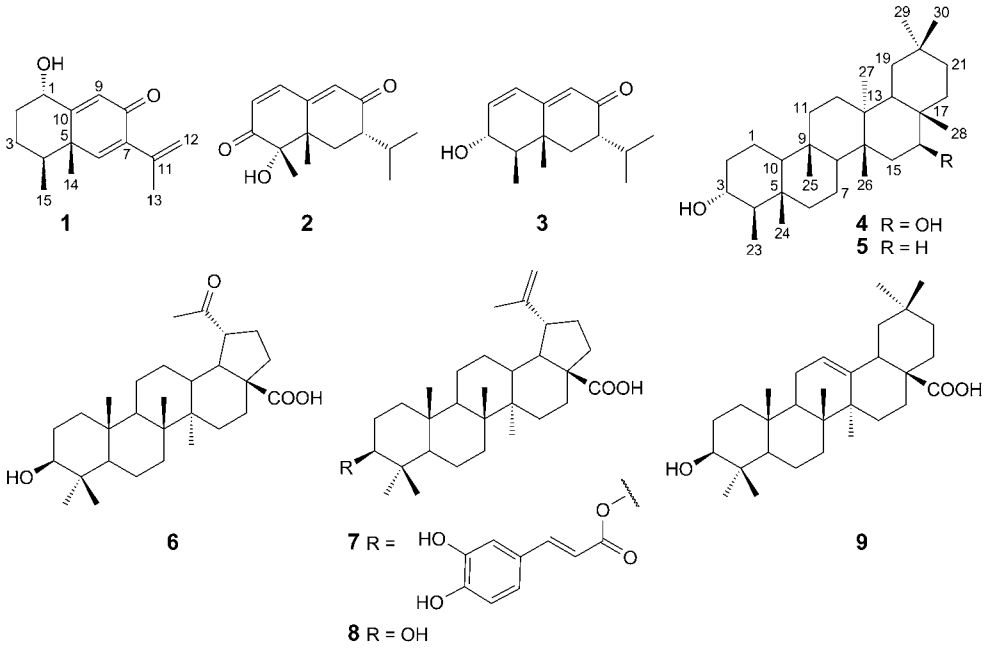


Fig. 1. *Structures of compounds* **1**–**9**

chromophore. The IR spectrum indicated the presence of OH (3433 $cm^{-1}$) and $\alpha,\beta,\alpha',\beta'$-unsaturated C=O (1636 $cm^{-1}$) functionalities.

The $^{13}$C-NMR spectrum of **1** exhibited signals for 15 C-atoms (*Table*), specifically three Me, three $CH_2$ (one exocyclic methylidene group), four CH, and five quaternary C-atoms, as determined from DEPT experiment. Among them, there were evidently one C=O group ($\delta$(C) 185.9), six olefinic C-atoms (one $CH_2$ ($\delta$(C) 116.2), two CH ($\delta$(C) 126.8, 152.7), and three quarternary C-atom ($\delta$(C) 138.5, 141.3, 164.3), and a more shielded quaternary C-atom ($\delta$(C) 43.4). Since the C=O and C=C groups accounted for four of the six degrees of unsaturation, the skeleton of **1** was determined to be bicyclic. The structural elements revealed by the $^1$H-NMR spectrum included three Me groups, two at quaternary ($\delta$(H) 1.35, 1.97) and one at CH ($\delta$(H) 1.12) C-atoms, one HO–CH ($\delta$(H) 4.54), and two olefinic H-atoms stemming from an exocyclic methylidene group ($\delta$(H) 5.10, 5.23) and two further olefinic H-atoms ($\delta$(H) 6.16, 6.92) belonging to the $\alpha,\beta,\alpha',\beta'$-unsaturated C=O moiety. One of the three Me groups (*singlet*) was part of an isopropenyl moiety, as revealed from the correlations of C(7) ($\delta$(C) 138.5) and C(11) ($\delta$(C) 141.3) with both C*H*$_2$(12) ($\delta$(H) 5.10, 5.23) and Me(13) ($\delta$(H) 1.97) in the HMBC spectrum (*Fig. 2*). The above information, in conjunction with further correlations provided by HSQC, HMBC, and COSY experiments, suggested an eremophilane skeleton with a $\alpha,\beta,\alpha',\beta'$-unsaturated C=O and a HO–CH groups [15–17]. The correlations of H–C(6) ($\delta$(H) 6.92) with C(4) ($\delta$(C) 41.3), C(8) ($\delta$(C) 185.9), C(10) ($\delta$(C) 164.3), and C(11) positioned the $\alpha,\beta,\alpha',\beta'$-unsaturated C(8)=O group, and the C(6)=C(7), C(9)=C(10), C(11)=C(12) bonds, whereas the correlations of H–C(1) ($\delta$(H) 4.54) with C(3) ($\delta$(C) 25.0), C(5) ($\delta$(C)

Table. *$^1$H- and $^{13}$C-NMR* (400 and 100 MHz, resp., $CDCl_3$) *Data of* **1** *and* **2**[a]). $\delta$ in ppm, $J$ in Hz. Arbitrary atom numberings as indicated in *Fig. 1*.

| Position | **1** | | **2** | |
|---|---|---|---|---|
| | $\delta$(H) | $\delta$(C) | $\delta$(H) | $\delta$(C) |
| 1 | 4.54 (*s*) | 73.7 | 7.05 (*d*, *J* = 10.0) | 129.2 |
| 2 | 1.64 (*t*, *J* = 14.0, $H_\beta$), 2.07 (*d*, *J* = 14.0, $H_\alpha$) | 34.4 | 6.22 (*d*, *J* = 10.0) | 142.8 |
| 3 | 1.48 (*d*, *J* = 13.6, $H_\alpha$), 1.92 (*t*, *J* = 13.6, $H_\beta$) | 25.0 | – | 196.7 |
| 4 | 1.52–1.57 (*m*) | 41.3 | – | 77.9 |
| 5 | – | 43.4 | – | 43.7 |
| 6 | 6.92 (*s*) | 152.7 | 1.75 (*d*, *J* = 7.6, $H_\alpha$), 2.40–2.42 (*m*, $H_\beta$)[b]) | 27.2 |
| 7 | – | 138.5 | 2.40–2.42 (*m*)[b]) | 46.6 |
| 8 | – | 185.9 | – | 199.8 |
| 9 | 6.16 (*s*) | 126.8 | 6.12 (*s*) | 131.8 |
| 10 | – | 164.3 | – | 155.7 |
| 11 | – | 141.3 | 2.61–2.67 (*m*) | 26.0 |
| 12 | 5.10 (*s*), 5.23 (*s*) | 116.2 | 0.88 (*d*, *J* = 6.8) | 17.6 |
| 13 | 1.97 (*s*) | 22.4 | 1.01 (*d*, *J* = 6.8) | 20.2 |
| 14 | 1.35 (*s*) | 19.0 | 1.22 (*s*) | 21.1 |
| 15 | 1.12 (*d*, *J* = 6.8) | 16.1 | 1.40 (*s*) | 16.0 |

[a]) Assignments were confirmed by DEPT-135, HSQC, HMBC, $^1$H,$^1$H-COSY, and NOESY experiments.
[b]) Overlapped signals.

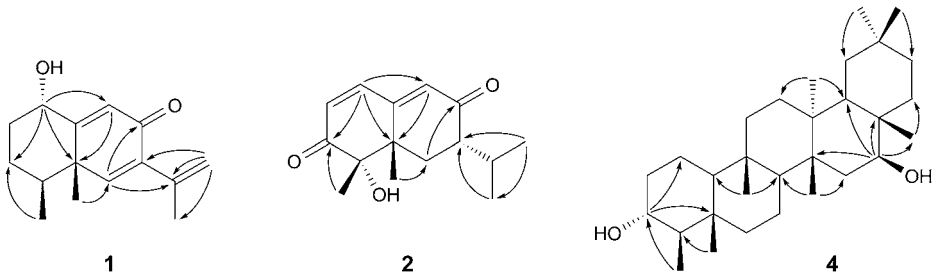


Fig. 2. *Key HMBCs* (H → C) *of* **1**, **2**, *and* **4**

43.4), and C(9) ($\delta$(C) 126.8) placed the OH group at C(1). The relative configuration of **1** was determined through interpretation of the NOESY spectrum (*Fig. 3*). The NOESY correlations of $H_\beta$–C(3) ($\delta$(H) 1.93) with H–C(1), Me(14) ($\delta$(H) 1.35), and Me(15) ($\delta$(H) 1.12) implied the $\alpha$-orientation of HO–C(1), since, on biogenetic grounds, the Me groups at C(14) and C(15) are $\beta$-oriented. Therefore, the structure of compound **1** was deduced as 1$\alpha$-hydroxyeremophila-6,9,11-trien-8-one.

Compound **2** was obtained as pale-yellow gum. Its HR-ESI-MS provided the molecular formula $C_{15}H_{20}O_3$, with one O-atom more than the known eremophilane derivative, pleodendione [15]. The UV maximum at 294 nm, as well as its $^1$H- and

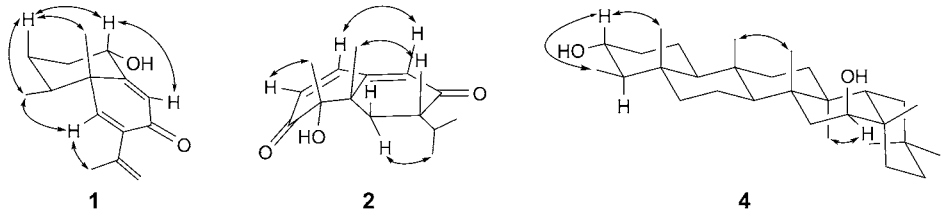


Fig. 3. *Key NOESY* (H ↔ H) *correlations of* **1**, **2**, *and* **4**

$^{13}$C-NMR spectra (*Table*), together with DEPT, $^{1}$H,$^{1}$H-COSY, HSQC, and HMBC experiments, suggested that the structure was closely related to pleodendione. The most notable differences between **2** and pleodendione were the presence of an additional oxygenated quaternary C-atom ($\delta$(C) 77.9), and the Me *doublet* ($\delta$(H) 1.14) in the $^{1}$H-NMR spectrum of pleodendione disappeared and replaced by a Me *singlet* ($\delta$(H) 1.40) in **2**. These findings implied that a OH group was located at C(4), as deduced from the correlations from H–C(2) ($\delta$(H) 6.22), Me(14) ($\delta$(H) 1.22), and Me(15) ($\delta$(H) 1.40) to C(4) ($\delta$(C) 77.9) in the HMBC spectrum (*Fig. 2*). The relative configuration of **2** was established using information from NOESY correlations, by comparing the data with those of the known eremophilane sesquiterpene **3**, named hoaensieremone, recently isolated from another *Drypetes* species [17]. On the basis of biogenetic considerations, Me(14) and Me(15) were assigned $\beta$-orientations, as well as based on the strong NOESY correlations of $H_{\beta}$–C(6)/H–C(7) ($\delta$(H) 2.41) with Me(14) and Me(15) in the NOESY spectrum (*Fig. 3*). The remaining stereogenic center C(7) in **2** has the same configuration as in **3**, which could be deduced from the similar $^{1}$H chemical shifts and the NOESY correlations of $H_{\alpha}$–C(6) ($\delta$(H) 1.75) with Me(12) ($\delta$(H) 0.88) and Me(13) ($\delta$(H) 1.01). Thus, the structure of compound **2** was established as 4$\alpha$-hydroxyeremophila-1,9-diene-3,8-dione.

Compound **4**, obtained as white amorphous powder, showed a pseudomolecular-ion peak at *m*/*z* 467.3858 ($[M + Na]^{+}$) in the HR-ESI-MS, in agreement with the molecular formula $C_{30}H_{32}O_2$. The IR spectrum of **4** displayed a strong absorption band at 3412 cm$^{-1}$ for OH groups. The $^{1}$H-NMR spectrum of **4** (*Table*) was highly informative and exhibited signals of eight Me groups (seven *singlet*s at $\delta$(H) 0.77, 0.82, 0.96 (2 ×), 1.02, 1.06, 1.17, and one *doublet* at $\delta$(H) 0.90) and of two CH–O H-atoms ($\delta$(H) 3.34 and 4.00). The $^{13}$C-NMR spectrum (*Table*) displayed 30 C-atom resonances ascribable to eight Me, ten $CH_2$, and six CH (two of which were oxygenated $\delta$(C) 72.2, 75.6) groups, and six quaternary C-atoms (*Table*). The NMR data were found to be analogous to those of the known compound 3$\alpha$-friedelinol (**5**) [18], except for an additional CH–O ($\delta$(C) 75.6, $\delta$(H) 4.00) instead of the $CH_2$ group at C(16) ($\delta$(C) 35.9) in **5**. The HMBC spectrum (*Fig. 2*) showed correlations between H–C(3) ($\delta$(H) 3.34) and C(4) ($\delta$(C) 53.1), C(5) ($\delta$(C) 38.2) and C(23) ($\delta$(C) 9.9), between H–C(16) ($\delta$(H) 4.00) and C(14) ($\delta$(C) 39.2), C(18) ($\delta$(C) 44.7), C(22) ($\delta$(C) 30.8), and C(28) ($\delta$(C) 24.9). These data confirmed the position of the OH groups at C(3) and C(16), respectively. The NOESY spectrum of **4** (*Fig. 3*) showed interactions between H–C(16) and Me(27) ($\delta$(H) 0.96), together with the NOESY cross-peaks from H–C(3) to Me(23) ($\delta$(H) 0.90) and Me(24) ($\delta$(H) 0.77); in addition, the coupling

constants of H–C(3) (*dt*, $J = 10.0, 4.0$) [18] and H–C(16) (*t*, $J = 8.8$) [19] confirmed the $\alpha$-equatorial orientation of OH at C(3) and consequently the $\beta$-axial orientation of the OH group at C(16), in agreement with reported data. The structure of **4** was thus deduced as friedelane-3$\alpha$,16$\beta$-diol.

The structures of six known terpenoids were identified as hoaensieremone (**3**) [17], friedelin-3$\alpha$-ol (**5**) [18], platanic acid (**6**) [20], betulinic acid 3$\beta$-caffeate (**7**) [21], betulinic acid (**8**) [22], and oleanolic acid (**9**) [23] by comparision of their spectroscopic data with those reported in the literature. Although eremophilane-type sesquiterpenoids were widely present in several genera (such as *Ligularia*, *Senecio*, *Cacalia*, *Petasites*) of Asteraceae, there have only been three eremophilane-type sesquiterpenoids identified in the genus *Drypetes* (Euphorbiaceae), namely 1-oxofuranoeremophil-13-oic acid [9], hoaensieremone, and hoaensifuranonal, and a nor-eremophilane sesquiterpene, hoaensieremodione [10]. Therefore, this is the third report of eremophilane-type sesquiterpenoids from the *Drypetes* genus. The occurrence of friedelane-, oleanane-, and lupane-type triterpenoids, **4**, **5**, and **7**–**9**, respectively, in *D. congestiflora* is in agreement with triterpenoid constitution previously reported in other *Drypetes* species [4–7]. Thus, terpenoids **1**–**9** isolated from *Drypetes* species could be chemotaxonomic markers for the genus *Drypetes*.

*Antitumor Activity.* Compounds **3**, **4**, and **7** were evaluated for their cytotoxic activities against a panel of cancer cell lines (A549 and B16F10) by standard MTS assay. Only **3** exhibited moderate cytotoxic activities against the A549 and B16F10 cell lines, with $IC_{50}$ values of 27.5 and 41.3 μM, respectively.

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## Experimental Part

*General*. TLC: Precoated $SiO_2$ *GF-254* (10–40 μm) plates (*Qingdao Haiyang Chemical Group Co.*). Column chromatography (CC): silica gel ($SiO_2$, 200–300 mesh; *Qingdao Haiyang Chemical Group Co.*) and *Sephadex LH-20* (*Pharmacia*). Optical rotations: *PolAAr 3005* polarimeter (*Optical Activity Ltd.*, Cambridgeshire). UV Spectra: *Hitachi U-3900* (*Hitachi*); $\lambda_{max}$ (log $\varepsilon$) in nm. IR Spectra: *Thermo Nicolet 6700* (KBr disks) spectrophotometer (*Thermo Scientific*, Madison); $\tilde{\nu}$ in $cm^{-1}$. NMR Spectra: *Bruker AV 400* spectrometer (400 ($^1H$) and 100 MHz ($^{13}C$)); $\delta$ in ppm rel. to $Me_4Si$ as internal standard, *J* in Hz. ESI-MS: *Bruker Esquire 6000* ion-trap mass spectrometer; in *m*/*z*. HR-ESI-MS: *Bruker Daltonics Apex-Ultra 7.0 T* mass spectrometer; in *m*/*z*.

*Plant Material*. The stems of *D. congestiflora* were collected from Changjiang County, Hainan Province, P. R. China, in August 2011, and identified by Prof. *Qiong-Xin Zhong*, School of Life Science, Hainan Normal University. A voucher specimen (No. 20110010) was deposited with the Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education, Hainan Normal University.

*Extraction and Isolation*. The air-dried stems of *D. congestiflora* (20.0 kg) were powdered and exhaustively extracted with 95% EtOH/$H_2O$ at r.t. The extract was concentrated, and the residue was suspended in $H_2O$ and then partitioned successively with petroleum ether (PE), $CHCl_3$, AcOEt, and BuOH. The $CHCl_3$-soluble fraction (115 g) was subjected to CC ($SiO_2$; step gradient-elution technique, $CHCl_3$/AcOEt (25:1–0:1), to afford eight fractions, *Fr. 1* (25:1), *Fr. 2* (20:1), *Fr. 3* (15:1), *Fr. 4* (10:1), *Fr. 5* (6:1), *Fr. 6* (3:1), *Fr. 7* (2:1), *Fr. 8* (0:1), according to TLC analysis. *Fr. 2* (5.3 g) was further purified by CC ($SiO_2$; PE/acetone 25:1) to give *Frs. 2–1* and *2–2*. Compound **5** (3.6 mg) was obtained

from *Fr. 2–1* (0.8 g) by CC ($SiO_2$; $CHCl_3$/AcOEt 20:1). and compound **2** (1.0 mg) from *Fr. 2–2* (0.2 g) by CC ($SiO_2$; PE/acetone 15:1). *Fr. 3* (5.6 g) was submitted to CC ($SiO_2$; $CHCl_3$/AcOEt 15:1 → 10:1 → 5:1) to afford four major subfractions, *Frs. 3–1–3–4*. *Fr. 3–1* (1.8 g) was further separated by CC ($SiO_2$; $CHCl_3$/AcOEt 10:1; *Sephadex LH-20*; $CHCl_3$/MeOH 1:1) to furnish **3** (21.5 mg) and **4** (4.7 mg). *Fr. 3–2* (0.9 g) was purified by CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1; $SiO_2$, $CHCl_3$/AcOEt, 10:1) to provide compounds **9** (3.6 mg), **7** (12.4 mg), while compounds **6** (8.7 mg), and **8** (17.2 mg) were isolated from the *Fr. 3–3* (1.2 g) by CC ($SiO_2$; $CHCl_3$/AcOEt 8:1; $SiO_2$; PE/AcOEt 5:1). Compound **1** (7.3 mg) was obtained from *Fr. 3–3* (0.7 g) by CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1).

*1α-Hydroxyeremophila-6,9,11-trien-8-one* (*=(4a*S*,5*S*,8*S*)-5,6,7,8-Tetrahydro-8-hydroxy-4a,5-dimethyl-3-(1-methylethenyl)naphthalen-2(4a*H*)-one*; **1**). Colorless oil. $[\alpha]_D^{30} = +50$ ($c = 0.2$, MeOH). UV (MeOH): 204 (3.75), 242 (2.90). IR (KBr): 3433, 3160, 1636, 1398, 1030. $^1$H- and $^{13}$C-NMR: see the *Table*. HR-ESI-MS: 255.1355 ($[M+Na]^+$, $C_{15}H_{20}NaO_2^+$; calc. 255.1356).

*4α-Hydroxyeremophila-1,9-diene-3,8-dione* (*=(1*S*,7*S*,8a*S*)-1,7,8,8a-Tetrahydro-1-hydroxy-1,8a-dimethyl-7-(1-methylethyl)naphthalene-2,6-dione*; **2**). Pale-yellow gum. $[\alpha]_D^{30} = -178$ ($c = 0.06$, MeOH). UV (MeOH): 294 (4.18). IR (KBr): 3444, 3181, 1649, 1398, 1086. $^1$H- and $^{13}$C-NMR: see the *Table*. HR-ESI-MS: 271.1306 ($[M+Na]^+$, $C_{15}H_{20}NaO_3^+$; calc. 271.1305).

*Friedelane-3α,16β-diol* (*=(3*R*,4*R*,4a*S*,6b*R*,8*S*,8a*S*,12b*S*,14a*S*)-Docosahydro-4,4a,6b,8a,11,11,12-b,14a-octamethylpicene-3,8-diol*; **4**). White amorphous powder. $[\alpha]_D^{30} = +163$ ($c = 0.11$, $CHCl_3$/MeOH 1:1). IR (KBr): 3433, 1398, 1030. $^1$H-NMR ($CDCl_3$, 100 MHz): 0.77 (*s*, Me(24)); 0.82 (*s*, Me(25)); 0.90 (*d*, $J = 6.8$, Me(23)); 0.96 (*s*, Me(27), Me(29)); 1.02 (*s*, Me(30)); 1.06 (*s*, Me(26)); 1.17 (*s*, Me(28)); 3.34 (*dt*, $J = 10.0$, 4.4, H–C(3)); 4.00 (*t*, $J = 8.8$, H–C(16)). $^{13}$C-NMR ($CDCl_3$, 100 MHz): 9.9 (C(23)); 14.6 (C(24)); 18.1 (C(7)); 18.3 (C(25)); 19.6 (C(1)); 20.3 (C(27)); 21.3 (C(26)); 24.9 (C(28)); 28.0 (C(20)); 30.7 (C(30)); 30.8 (C(22)); 31.9 (C(12)); 35.4 (C(29)); 35.6 (C(19/21)); 37.7 (C(17)); 35.9 (C(11)); 36.6 (C(2)); 37.1 (C(9)); 38.2 (C(5)); 39.2 (C(14)); 40.1 (C(13)); 41.3 (C(6)); 44.2 (C(15)); 44.7 (C(18)); 53.1 (C(4)); 53.2 (C(8)); 60.1 (C(10)); 72.2 (C(3)); 75.6 (C(16)). ESI-MS: 467 ($[M+Na]^+$). HR-ESI-MS: 467.3858 ($[M+Na]^+$, $C_{30}H_{52}NaO_2^+$; calc. 467.3865).

*Antitumor Activity.* The cytotoxicities of compounds **3**, **4**, and **7** against A549, and B16F10 cell lines were determined by standard MTS assay as described in [24]. Untreated cells in medium were used as control. Corresponding groups without cells were used as blanks. All experiments were carried out with four replicates.

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