Artemyrianosins A–J, cytotoxic germacrane-type sesquiterpene lactones from *Artemisia myriantha*

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**Abstract**

Ten new germacrane-type sesquiterpenoids, artemyrianosins A–J (1–10), were isolated from the aerial parts of *Artemisia myriantha*. Their structures were elucidated by spectral analyses including UV, IR, HRESIMS, 1D and 2D NMR, ECD and the absolute configurations of compounds 1 and 7–9 were characterized using X-ray crystallography. All isolates were tested their cytotoxicity against three human hepatoma cell lines (HepG2, Huh7, and SK-Hep-1), and compounds 1–3, 7, and 10 showed cytotoxicity with IC₅₀ values ranging from 43.7 to 89.3 μM. Among them, the most active compound 3 exhibited activity against three human hepatoma cell lines with IC₅₀ values of 43.7 μM (HepG2), 47.9 μM (Huh7), and 44.9 μM (SK-Hep-1).

**Keywords:** *Artemisia myriantha*, Artemyrianosins A–J, Germacrane-type sesquiterpenoids, Cytotoxicity

**1 Introduction**

Hepatocellular carcinoma (HCC) as one of the most serious and common type of liver cancer is mainly caused by HBV or HCV infection, and heavy alcohol intake [1, 2]. HCC has resulted in nearly 0.83 million deaths worldwide in the year 2020 [3, 4], and suffered more than 1
million people will be affected by 2025 [5]. Clinically, four synthetic ones (sorafenib, regorafenib, lenvatinib and cabozantinib) and three monoclonal antibody ones (nivolumab, pembrolizumab and ramucirumab) are used to treat HCC [6, 7]. Although these drugs have obtained significant achievements, there are still some inevitable drawbacks, such as the low objective response rate, high incidence of adverse reactions, and drug resistance [8]. Therefore, new drugs with different targets for treating HCC are urgently needed (Fig. 1).

Artemisia, one of the dominant genus within Asteraceae family, contains nearly 380 species globally with 186 species being dispersed in China [9]. Many Artemisia plants, such as A. annua, A. argyi, A. capillaris, and A. scoparia, have been recorded for the treatment of malaria, inflammation, hepatitis, cancer in the traditional Chinese medicine system [9–12]. Phytochemical investigation revealed that Artemisia genus are rich in sesquiterpenoids with antimalarial, anti-inflammatory, antitumor, cytotoxic, antibacterial, and antihelminthic activities [13]. For example, artemisinin, a sesquiterpenoid lactone with an unusual peroxide bridge, which was obtained from A. annua by the Chinese scientist You-You Tu in 1972, showed antimalarial, anticancer and anti-inflammatory activities [14]. Dihydroartemisinin, artemether, and artesunate which were chemically modified from artemisinin also exhibited antimalarial, antiviral, antifungal, anticancer, and antiinflammatory properties [15]. Arglabin, a guaiane-type sesquiterpenolide from A. glabella, inhibited of farnesyltransferase and its dimethyl-amino hydrochloride has been successfully developed into an anticancer drug in Kazakhstan for the treatment of colon, breast, ovarian, lung and liver cancers [16]. Arteminolides A–D from A. argyi were potential inhibitors of farnesyl protein transferase (FPTase) with IC50 values less than 1.0 μM in vitro, of which arteminolide C could prevent the development of lung tumor and human colon xenograft without causing weight loss in nude mice [17].

Our ongoing efforts to investigate bioactive sesquiterpenoids from the Artemisia plants, bioassay-guided isolation of A. atrovirens let to 26 guaiane dimers ([4 + 2] Diels–Alder cyclization) [18, 19], six rotundane-guaiane dimers ([4 + 2] Diels–Alder cyclization or containing a methylene-bridge) [19, 20], two guaiane-rotundane-guaiane trimers (containing a methylene-bridge) [20], two novel cagelike sesquiterpenoids (formed by intramolecular Diels–Alder cycloaddition) [21], and 16 undescribed guaiane sesquiterpenoids [9]. Among them, four guaiane-guaiane dimers (lavandiolide H and artematrolides A, J, and K) possessed significant cytotoxicity against HepG2, SMMC-7721, and Huh7 cell lines with IC50 values.

![Fig. 1 Chemical structures of compounds 1–10](image-url)
ranging from 3.8 to 9.6 μM, and lavandiolide H could induce G2/M cell cycle arrest and apoptosis in HepG2 cells via upregulating cleaved-PARP-1 and downregulating BCL-2 and PARP-1 [18]. Furthermore, artematrolide A was shown to activate the ROS/ERK/mTOR signaling pathway and promote metabolic shift in cervical cancer cells [22]. And the biomimetic synthesis via Diels–Alder reaction of the guaianolide dimers (artematrolide F and lavandiolides H, I, and K) and a battery of analogues were also achieved [23].

*A. myriantha* Wall. ex Bess. is commonly used for treating menorrhagia and inflammatory diseases in traditional Chinese medicine [24]. Phytochemical investigation on this species revealed the presence of sesquiterpenoids, flavonoids, and essential oils [25]. Among them, some sesquiterpenoids showed cytotoxicity against human colon cancer HCT-8, human gastric cancer BGC-823, and human liver cancer Bel-7402 cells [26, 27]. Our previous investigation reported 23 undescribed sesquiterpenolides with cytotoxicity against HepG2, SMMC-7721, and Huh7 from *A. myriantha*, classifying as germacranolide, guaianolide, and eudesmanolide, and revealed that artemyrianolide H displayed promising cytotoxicity against HepG2, SMMC-7721, and Huh7 with IC₅₀ values of 4.9, 3.1, and 4.3 μM, respectively [25]. During our continuous search for antihepatic sesquiterpenoids from *A. myriantha*, 10 undescribed germacranolides (1‒10) were discovered (Fig. 1). Hence their isolation, structural identification, and cytotoxicity were discussed in this study.

### 2 Results and discussion

Artemyrianosin A (1) showed a molecular formula of C₁₅H₂₀O₄ based on the analysis of the (+)-HRESIMS ion at m/z 287.1254 [M+Na]⁺ (calcd for C₁₅H₂₀O₄Na, 287.1254) with six degrees of unsaturation. Its IR spectrum exhibited the presence of hydroxy (3414 cm⁻¹), carbonyl (1757 cm⁻¹), and double-bond (1643 and 1570 cm⁻¹) groups. The ¹H and ¹³C NMR data (Tables 1 and 2) resembled those of artemyrianolide M [25], except for the only difference being that a ketone group at C-3 in artemyrianolide M was replaced by one oxygenated methine [δ_H 4.11 (1H, dd, J = 12.7, 5.1 Hz, H-3), δ_C 73.3 (C-3)]. This deduction was confirmed by the HMBC correlations from H-3 to C-15 (δ_C 117.2) and C-4 (δ_C 144.2) as well as the correlations of H-1/H₂-2/H-3 in the ¹H-¹H COSY spectrum (Fig. 2). To determine its relative configuration, a ROESY experiment was carried out. The cross-peaks of H-3/H-7 and H-7/H-9 in the ROESY spectrum (Fig. 3) indicated that these protons were cofacial and β-oriented. However, the correlations of H-6/H-9 or H-6/H-3 were not observed in the ROESY spectrum, suggesting that H-6 was α-oriented. The absolute configuration of 1 was unambiguously verified to be (3R,6S,7R,9R) by Cu Kα X-ray crystallographic analysis.

### Table 1 ¹H NMR data for compounds 1‒5 (600 MHz, CD₃OD, δ in ppm, J in Hz)

| No  | 1   | 2   | 3   | 4   | 5   |
|-----|-----|-----|-----|-----|-----|
| 1a  | 2.13, m | 2.24, m | 2.27, m | 2.30, m | 2.31, m |
| 1b  | 1.97, m | 2.06, m |
| 2a  | 2.10, m | 2.14, m | 2.16, m | 2.18, m | 2.04, m |
| 2b  | 1.95, m | 1.92, m | 1.90, m | 1.90, m | 1.91, m |
| 3   | 4.11, dd (10.9, 3.1) | 4.18, dd (10.6, 4.4) | 4.35, dd (9.2, 5.3) | 4.04, dd (8.8, 4.1) | 4.23, dd (10.2, 4.0) |
| 5a  | 3.05, dd (12.7, 5.1) | 3.02, dd (13.0, 4.7) | 2.58, m | 2.37, m | 2.37, m |
| 5b  | 2.07, m | 2.06, m | 2.45, dd (15.5, 10.7) |
| 6   | 4.30, m | 4.37, ddd (11.0, 6.2, 4.8) | 4.93, ddd (10.6, 7.5, 3.2) | 4.90, m | 5.35, td (8.0, 2.4) |
| 7   | 2.58, m | 2.93, m | 3.51, m | 2.38, m | 3.67, m |
| 8a  | 1.94, m | 2.03, m | 2.38, m | 2.07, m | 2.27, m |
| 8b  | 1.83, m | 1.93, m | 2.00, m | 1.79, m | 1.91, m |
| 9   | 4.28, m | 4.23, m | 4.17, d (3.6) | 4.16, dd (7.8, 6.1) | 4.36, dd (6.3, 2.6) |
| 11  | 6.15, d (3.4) | 6.20, dd (3.0, 0.6) | 6.19, d (3.1) | 1.19, d (6.4) | 6.30, s |
| 13a | 5.75, d (3.4) | 6.11, dd (3.0, 0.6) | 5.69, d (3.1) | 5.12, s | 5.13, s |
| 14a | 5.26, s | 5.34, d (1.4) | 5.44, s | 5.08, s | 5.04, s |
| 14b | 5.20, s | 5.16, s | 5.20, s | 5.37, s | 5.22, s |
| 15a | 5.37, s | 5.33, s | 5.20, s | 5.18, s | 5.19, s |
| 15b | 5.33, s | 5.23, s | 5.15, s |
| 2'  | OMe | | | | 1.98, s |
| OMe| | | | | 3.75, s |
Table 2: $^{13}$C NMR data for compounds 1–10 (150 MHz, CD$_3$OD, δ in ppm)

| No | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|----|----|----|----|----|----|----|----|----|----|----|
| 1  | 23.4, CH$_2$ | 28.0, CH$_2$ | 29.9, CH$_2$ | 26.6, CH$_2$ | 31.6, CH$_2$ | 243, CH$_2$ | 23.7, CH$_2$ | 43.5, CH$_2$ | 43.0, CH$_2$ | 43.1, CH$_2$ |
| 2  | 32.5, CH$_3$ | 32.6, CH$_2$ | 31.6, CH$_2$ | 34.1, CH$_2$ | 31.6, CH$_2$ | 34.4, CH$_2$ | 28.6, CH$_2$ | 70.8, CH$_2$ | 70.4, CH$_2$ | 70.4, CH$_2$ |
| 3  | 73.3, CH$_3$ | 74.4, CH$_3$ | 70.4, CH$_3$ | 75.7, CH$_3$ | 77.2, CH$_3$ | 76.4, CH$_3$ | 66.8, CH$_3$ | 132.5, CH$_3$ | 132.6, CH$_3$ | 132.0, CH$_3$ |
| 4  | 144.2, C   | 145.3, C   | 147.8, C   | 151.6, C   | 146.8, C   | 147.6, C   | 143.8, C   | 133.5, C   | 132.9, C   | 133.0, C   |
| 5  | 41.3, CH$_2$ | 40.8, CH$_2$ | 37.0, CH$_2$ | 34.1, CH$_2$ | 33.0, CH$_2$ | 35.7, CH$_2$ | 123.8, C   | 41.1, CH$_2$ | 43.0, CH$_2$ | 42.8, CH$_2$ |
| 6  | 85.2, CH$_3$ | 85.0, CH$_3$ | 81.8, CH$_3$ | 83.9, CH$_3$ | 74.4, CH$_3$ | 74.7, CH$_3$ | 78.5, CH$_3$ | 82.8, CH$_3$ | 83.3, CH$_3$ | 83.4, CH$_3$ |
| 7  | 41.0, CH$_3$ | 40.3, CH$_3$ | 39.0, CH$_3$ | 39.9, CH$_3$ | 35.5, CH$_3$ | 37.5, CH$_3$ | 42.5, CH$_3$ | 38.0, CH$_3$ | 43.7, CH$_3$ | 39.9, CH$_3$ |
| 8  | 40.5, CH$_3$ | 40.2, CH$_3$ | 32.6, CH$_3$ | 36.3, CH$_3$ | 32.8, CH$_3$ | 31.6, CH$_3$ | 33.5, CH$_3$ | 31.2, CH$_3$ | 38.7, CH$_3$ | 41.2, CH$_3$ |
| 9  | 77.6, CH$_3$ | 72.3, CH$_3$ | 72.2, CH$_3$ | 76.6, CH$_3$ | 72.1, CH$_3$ | 77.2, CH$_3$ | 78.8, CH$_3$ | 74.2, CH$_3$ | 73.4, CH$_3$ | 73.3, CH$_3$ |
| 10 | 149.9, C   | 150.7, C   | 150.3, C   | 151.5, C   | 149.1, C   | 150.8, C   | 149.6, C   | 147.0, C   | 147.8, C   | 146.8, C   |
| 11 | 143.4, C   | 142.6, C   | 141.8, C   | 46.3, CH$_3$ | 144.3, C   | 142.2, C   | 139.8, C   | 38.6, CH$_3$ | 44.2, CH$_3$ | 141.8, C   |
| 12 | 171.5, C   | 172.2, C   | 172.2, C   | 181.2, C   | 169.3, C   | 169.0, C   | 172.3, C   | 182.6, C   | 182.2, C   | 172.2, C   |
| 13 | 121.4, CH$_3$ | 124.6, CH$_3$ | 121.3, CH$_3$ | 13.5, CH$_3$ | 126.4, CH$_3$ | 126.2, CH$_3$ | 121.6, CH$_3$ | 10.9, CH$_3$ | 16.4, CH$_3$ | 124.7, CH$_3$ |
| 14 | 115.0, CH$_3$ | 112.2, CH$_3$ | 111.7, CH$_3$ | 113.4, CH$_3$ | 114.0, CH$_3$ | 116.1, CH$_3$ | 113.4, CH$_3$ | 114.1, CH$_3$ | 113.7, CH$_3$ | 113.6, CH$_3$ |
| 15 | 117.2, CH$_3$ | 118.1, CH$_3$ | 116.2, CH$_3$ | 112.4, CH$_3$ | 117.2, CH$_3$ | 115.3, CH$_3$ | 16.7, CH$_3$ | 20.8, CH$_3$ | 21.0, CH$_3$ | 22.1, CH$_3$ |
| 1$'$| 172.2, C   | 172.3, C   | 121.0, CH$_3$ | 20.9, CH$_3$ | 524.3, CH$_3$ | 525.3, CH$_3$ | 524.3, CH$_3$ | 525.3, CH$_3$ |
Therefore, the structure of compound 1 was defined as \((3R,6S,7R,9R)\)-3,9-dihydroxygermacra-4(15),10(14),11(13)-trien-12,6-olide.

Artemyrianosin B (2) was deduced with the same molecular formula of \(C_{15}H_{20}O_{4}\) as 1 by the HRESIMS at \(m/z\) 265.1427 [M + H]+ (calcd for \(C_{15}H_{21}O_{4}\), 265.1434). The \(^1H\) and \(^{13}C\) NMR data (Tables 1 and 2) of compound 2 were closely related to those of 1, and further analyses of 2D NMR spectra implied that they possessed the same planar structure. Their only difference was the chemical shift changes of H-9 (\(\delta_H 4.23\) vs 4.28) and C-9 (\(\delta_C 72.3\) vs 77.6) and those surrounding the C-9 position (Tables 1 and 2), which might be caused by the different configurations at C-9. In the ROESY spectrum (Fig. 3), the correlations of H-3/H-7 and H-6/H-9 revealed \(\beta\)-orientations of H-3 and H-7; whereas \(\alpha\)-orientations of H-6 and H-9. Its absolute configuration was assigned to be \(3R,6S,7R,9S\) by comparison of its experimental ECD spectrum with the calculated one (Fig. 5). Therefore, the structure of compound 2...
was established as (3R,6S,7R,9S)-3,9-dihydroxygermacra-4 (15), 10 (14), 11 (13)-trien-12,6-olide (Fig. 5).

Artemyrianosin C (3) was assigned to have the same molecular formula C_{12}H_{20}O_{4} with compounds 1 and 2 from the HRESIMS at m/z 265.1431 [M + H]^{+} (calcld for C_{12}H_{21}O_{4} 265.1434). Compound 3 had the identical 2D structure as 1 and 2 based on their 1D and 2D NMR data (Tables 1 and 2, Fig. 2). The ROESY correlations of H-3/H-6, H-3/H-7, and H-7/H-9 revealed that these protons were β-oriented. Its absolute configuration was concluded to be 3R,6R,7R,9R by comparison of its experimental ECD spectrum with the calculated one (Fig. 5). Thus, the structure of compound 3 was established to be (3R,6R,7R,9R)-3,9-dihydroxygermacra-4 (15), 10 (14), 11 (13)-trien-12,6-olide.

Artemyrianosin D (4) had a molecular formula C_{12}H_{22}O_{4} according to the HRESIMS data at m/z 267.1579 [M + H]^{+} (calcld for C_{12}H_{23}O_{4} 267.1591), suggesting five degrees of unsaturation. The similarity of 1H and 13C NMR data (Tables 1 and 2) between compounds 4 and 1 indicated that they were structural analogs, and the main difference was that the exocyclic double bond between C-11 and C-13 in compound 1 was disappeared, and a doublet methyl [δ_{H} 1.19 (3H, d, J = 6.4 Hz, H-13), δ_{C} 13.5 (C-13)] and a methine [δ_{H} 2.36 (1H, m, H-11), δ_{C} 46.3 (C-11)] signals were appeared in compound 4. This deduction was confirmed by the 1H-1H COSY interactions of H-7/H-11/H-13 and the HMBC correlations from H_{3}-13 to C-7, C-11, and C-12. Its absolute stereochemistry was defined to be (3R,6S,7R,9R,11R) by the ROESY correlations of H-3/H-7, H-7/H-9, H-7/H-13, and H-6/H-11 and the similarity between the experimental and calculated ECD spectra. Consequently, the structure of compound 4 was assigned as (3R,6S,7R,9R,11R)-3,9-dihydroxygermacra-4 (15), 10 (14)-dien-12,6-olide.

Artemyrianosin E (5) was determined to possess a molecular formula C_{18}H_{26}O_{6} with six indices of hydrogen deficiency by its HRESIMS ion at m/z 339.1792 [M + H]^{+} (calcld for C_{18}H_{27}O_{6} 339.1802). The IR spectrum of 5 showed the characteristic absorptions for hydroxy (3428 cm^{-1}), carbonyl (1718 cm^{-1}), and olefinic (1631 cm^{-1}) functionalities. The 1H NMR spectrum (Table 1) of 5 displayed a methyl at δ_{H} 1.98 (3H, s), a methoxy δ_{H} 3.75 (3H, s), three oxygenated methine protons at δ_{H} 5.35 (1H, td, J = 8.0, 2.4 Hz, H-6), 4.36 (1H, dd, J = 6.3, 2.6 Hz, H-9), and 4.23 (1H, dd, J = 10.2, 4.0 Hz, H-3), and three pairs of olefinic methylene protons [δ_{H} 6.30 (1H, s, H-13a), 5.73 (1H, s, H-13b); 5.13 (1H, s, H-14a), 5.04 (1H, s, 14b); 5.22 (1H, s, 15a), 5.19 (1H, s, 15b)]. The 13C NMR spectrum (Table 2) showed the existence of 18 carbons, including two methyl groups, seven methylenes (three terminal double bonds, and four aliphatic methylenes), four methines (three oxygenated and an aliphatic methine), and five quaternary carbons (two ester carbonyl and three olefinic carbons). The above characteristic signals indicated that compound 5

![Fig. 5 The experimental and calculated ECD spectra of compounds 2–6, and 10](image-url)
was a germacranolide-type sesquiterpenoid with acetoxy and methoxy groups. The above inference was supported by two proton spin systems of H<sub>2</sub>-1/H<sub>2</sub>-2/H-3 and H<sub>2</sub>-5/H-6/H-7/H<sub>2</sub>-8/H-9 in the 1H-1H COSY spectrum, as well as the HMBC correlations from H<sub>2</sub>-14 to C-1, C-9 and C-10 and from H<sub>2</sub>-15 to C-3, C-4 and C-5. In addition, the correlation from H-6 to C-1 in the HMBC spectrum implied that the acetoxy group (δ<sub>H</sub> 1.98; δ<sub>C</sub> 172.2 and 21.0) was linked at C-6; the HMBC correlation of OMe to C-12 suggested that the methoxy group was pointed at C-12. In the ROESY spectrum (Fig. 3), the cross peaks of H-3/H-6, H-3/H-7, and H-7/H-9 determined its relative configuration. The absolute configuration of 5 was defined as (3<sup>R</sup>,6<sup>R</sup>,7<sup>R</sup>,9<sup>R</sup>) by the similarity between the experimental and calculated ECD curves. Therefore, the structure of compound 5 was established as (3<sup>R</sup>,6<sup>R</sup>,7<sup>R</sup>,9<sup>R</sup>)-6-acetoxy-3,9-dihydroxygermacra-4(15),10(14),11(13)-trien-12-oic acid methyl ester.

Artemyrianosin F (6) was assigned to have the same molecular formula C<sub>18</sub>H<sub>26</sub>O<sub>6</sub> with compound 5 from the HRESIMS data at m/z 339.1785 [M+H]<sup>+</sup> (calcd for C<sub>18</sub>H<sub>27</sub>O<sub>6</sub>, 339.1802). The 1H and 13C NMR data (Tables 2 and 3) of compound 6 were very similar to those of 5, indicating that both were architecturally semblable. Further analyses of their 2D NMR spectra indicated that the planar structure of compound 6 was identical with that of compound 5. In the ROESY spectrum, the correlations of H-3/H-9 and H-7/H-9 indicated the homolateral orientation of H-3, H-7, and H-9. However, no correlation of H-6 with the former three protons was observed, but the correlation of H-6/H<sub>2</sub>-8 was obviously appeared in the ROESY spectrum, suggesting that H-6 was on the opposite side. Hence, the absolute stereochemistry of compound 6 was elucidated and named as (3<sup>R</sup>,6<sup>S</sup>,7<sup>R</sup>,9<sup>R</sup>)-6-acetoxy-3,9-dihydroxygermacra-4(15),10(14),11(13)-trien-12-oic acid methyl ester by comparing the calculated and experimental ECD curves.

Artemyrianosin G (7) was determined to have a molecular formula of C<sub>15</sub>H<sub>20</sub>O<sub>4</sub> based on the HRESIMS data at m/z 265.1423 [M+H]<sup>+</sup> (calcd for C<sub>15</sub>H<sub>21</sub>O<sub>4</sub>, 265.1434). The 1H and 13C NMR data (Tables 2 and 3) of compound 7 resembled to those of 1, the main difference was that the exocyclic double bond between C-4 and C-15 in 1 was absent and replaced by a trisubstituent double bond [δ<sub>H</sub> 4.98 (1H, d, J = 10.6 Hz, H-5); δ<sub>C</sub> 143.8 (C-4) and 123.8 (C-5)] and a singlet methyl [δ<sub>H</sub> 1.75 (3H, d, J = 1.3 Hz, H-15); δ<sub>C</sub> 16.7 (C-15)] in 7. This deduction was supported by the proton spin systems of H-5/H-6/H<sub>2</sub>-8/H-9 in the 1H-1H COSY spectrum and the HMBC correlations from H<sub>3</sub>-15 to C-3/C-4/C-5. Its relative configuration was proposed by the ROESY correlations of H-3/H-6 and H-7/H-9. In addition, the ROESY correlation of H-5 with H<sub>3</sub>-15 manifested that Δ<sup>4,5</sup>-double bond was Z-configuration. The absolute configuration of H-3/H-9 and H-7/H-9 indicated the homolateral orientation of H-3, H-7, and H-9. However, no correlation of H-6 with the former three protons was observed, but the correlation of H-6/H<sub>2</sub>-8 was obviously appeared in the ROESY spectrum, suggesting that H-6 was on the opposite side. Hence, the absolute stereochemistry of compound 6 was elucidated and named as (3<sup>R</sup>,6<sup>S</sup>,7<sup>R</sup>,9<sup>R</sup>)-6-acetoxy-3,9-dihydroxygermacra-4(15),10(14),11(13)-trien-12-oic acid methyl ester by comparing the calculated and experimental ECD curves.

**Table 3** 1H NMR data for compounds 6–10 (600 MHz, CD<sub>3</sub>OD, δ in ppm, J in Hz)

| No  | 6     | 7     | 8     | 9     | 10    |
|-----|-------|-------|-------|-------|-------|
| 1a  | 2.34, m | 2.12, m | 2.73, m | 2.70, dd (12.7, 5.9) | 2.76, dd (12.5, 6.5) |
| 1b  | 2.19, m | 1.70, m | 1.93, m | 1.98, m | 1.99, m |
| 2a  | 2.29, m | 2.20, m | 4.54, td (10.1, 5.9) | 4.54, td (10.3, 6.0) | 4.60, m |
| 2b  | 1.89, m | 1.72, m |  |  |  |
| 3   | 3.99, dd (8.9, 2.9) | 4.79, dd (10.7, 5.8) | 5.27, d (9.7) | 5.34, d (8.1) | 5.34, d (9.6) |
| 5a  | 2.63, m | 4.98, d (10.6) | 2.77, m | 2.89, dd (13.2, 6.3) | 2.98, dd (13.6, 6.3) |
| 5b  | 2.16, m |  | 2.05, dd (13.7, 8.0) | 1.94, m | 1.71, m |
| 6   | 5.34, ddd (10.1, 5.5, 1.9) | 5.50, dd (10.9, 8.2) | 4.44, q (6.8) | 4.42, m | 4.56, m |
| 7   | 3.29, m | 3.11, m | 2.27, m | 1.86, m | 2.68, m |
| 8a  | 2.04, m | 2.04, m | 1.82, m | 1.88, m | 2.03, m |
| 8b  | 1.81, m | 1.83, m | 1.61, m |  | 1.91, m |
| 9   | 3.88, dd (11.7, 4.2) | 4.16, dd (11.1, 4.4) | 4.10, dd (8.8, 2.9) | 4.09, t (5.0) | 4.05, dd (9.6, 3.1) |
| 11  | 2.85, m |  | 2.40, m |  |  |
| 13a | 6.35, s | 6.24, d (3.7) | 1.18, d (7.6) | 1.32, d (7.3) | 6.24, d (2.8) |
| 13b | 5.84, s | 5.67, d (3.7) |  |  | 5.98, d (2.8) |
| 14a | 5.01, s | 5.33, d (2.7) | 5.16, s | 5.22, s | 5.27, s |
| 14b | 4.84, s | 5.07, d (2.7) | 5.12, s | 5.09, s | 5.10, s |
| 15a | 5.43, s | 1.75, d (1.3) | 1.74, s | 1.78, s | 1.73, s |
| 15b | 5.22, s | 2′ 1.97, s |  |  |  |
| OMe| 3.76, s |  |  |  |  |
configuration of 7 was defined as 3R,6R,7R,9R by a single crystal X-ray crystallographic diffraction experiment with Cu Kα radiation (Fig. 4). Therefore, the structure of 7 was identified as (3R,6R,7R,9R,4Z)-3,9-dihydroxygermacra-4,10(14),11(13)-trien-12,6-olide.

Artemyrianosin H (8) was deduced to have a molecular formula of C_{15}H_{22}O_{4} with five indices of hydrogen deficiency by its HRESIMS at m/z 267.1585 [M + H]^+ (calcd for C_{15}H_{23}O_{4}, 267.1591). The similarity of 1H and 13C NMR data (Tables 2 and 3) of 8 and 4 implied structurally closely related, but the major differences were that the oxygenated methine at C-3 and terminal double bond between C-4 and C-15 in compound 4 were absent, meanwhile, a trisubstituent double bond [δ_{H} 5.27 (1H, d, J = 9.7 Hz, H-3); δ_{C} 132.5 (C-3) and 133.5 (C-4)], a singlet methyl [δ_{H} 1.74 (3H, s, H-15); δ_{C} 20.8 (C-15)], and an oxygenated methine [δ_{H} 4.54 (1H, td, J = 10.3, 6.0 Hz, H-2); δ_{C} 70.8 (C-2)] were appeared in 8. The spin coupling of H_{2}-1/H-2/H-3 in the 1H-1H COSY spectrum, together with the HMBC correlations from H_{3}-15 to C-3/C-4/C-5 and from H_{2}-5 to C-3/C-4/C-6/C-7/C-15 verified the above inference. In the ROESY spectrum (Fig. 3), the cross-peak of H-2/H-7 indicated that H-2 and H-7 were β-oriented, while the cross-peaks of H-6/H_{13}-13 and H-6/H-9 supported their α-orientation. In addition, the correlation of H-2/H_{15}-15 was clearly observed in the ROESY spectrum, indicating Δ^{3}-double bond was E-configuration. Ultimately, the structure of compound 8 was elucidated as (2R,6S,7R,9S,11S,3E)-2,9-dihydroxygermacra-3,10(14)-dien-12,6-olide by a single-crystal X-ray crystallographic analysis with Cu Kα radiation (Fig. 4).

Artemyrianosin I (9) shared the same molecular formula C_{15}H_{22}O_{4} with 8 according to the HRESIMS at m/z 267.1576 [M + H]^+ (calcd for C_{15}H_{23}O_{4}, 267.1591). Its 1H and 13C NMR data (Tables 2 and 3) were similar to those of 8, and detailed interpretation of the 1H-1H COSY and HMBC spectra revealed the same planar structures. The relative configuration was established through the ROESY cross-peaks of H-2/H-7, H-7/H-13, and H-6/H-9. Likely, the ROESY correlation of H-2/H_{15}-15 implied Δ^{3}-double bond was E-configuration. Subsequently, the structure of compound 9 was assigned as (2R,6S,7R,9S,11R,3E)-2,9-dihydroxygermacra-3,10 (14)-dien-12,6-olide by Cu Kα radiation X-ray crystallographic analysis (Fig. 4).

Artemyrianosin J (10) had a molecular formula of C_{15}H_{20}O_{4} as defined by the HRESIMS at m/z 265.1423 [M + H]^+, which indicated two hydrogen atoms less than compound 9. The 1H and 13C NMR data of compound 10 were closely similar to those of 9, and the main differences were that a doublet methyl at C-13 and a methine at C-11 in compound 9 were replaced by an pair of exocyclic double bond between C-11 and C-13 [δ_{C} 141.8 (C-11), 124.7 (C-13); δ_{H} 6.24 (1H, d, J = 2.8 Hz, H-13a), 5.98 (1H, d, J = 2.8 Hz, H-13b)] in compound 10. This deduction was verified by the spin coupling of H-7/H-11/H-13 in 1H-1H COSY spectrum and the correlations from H_{3}-13 to C-7/C-11/C-12 in the HMBC spectrum. In the ROESY spectrum, the correlation of H-9 with H-2/H-6/H-7 allowed these β-orientation. The additional ROESY correlation of H-2/H_{15}-15 implied Δ^{3}-double bond was E-configuration. Therefore, the structure of compound 10 was assigned as (2R,6R,7R,9R,3E)-2,9-dihydroxygermacra-3,10(14),11(13)-trien-12,6-olide based on the similar experimental and calculated ECD curves (Fig. 5).

The cytotoxicity of all isolates against three human hepatoma cell lines (HepG2, Huh7, and SK-Hep-1) was evaluated at the concentration of 100 μM with sorafenib as the positive control. As shown in Fig. 6,
compounds 1–3, 7, and 10 containing an α-exomethylene γ-butyrolactone group showed activity on HepG2, Huh7, and SK-Hep-1 with inhibitory ratios higher than 50%. The dose–response curves of the active compounds were further investigated to yield their respective IC₅₀ values. As shown in Table 4, compounds 1–3 exhibited cytotoxicity against HepG2 cells with IC₅₀ values of 43.7–46.5 μM, while compounds 7 and 10 showed weaker cytotoxicity (IC₅₀: 55.1 and 66.1 μM). Meanwhile, compounds 1–3 and 7 also displayed cytotoxicity against Huh7 cells with IC₅₀ values ranging from 44.3 to 48.9 μM, but compound 10 showed weaker cytotoxicity with an IC₅₀ value of 71.0 μM. For SK-Hep-1 cells, only compound 3 manifested cytotoxicity against HepG2 cells with IC₅₀ values of 71.7 μM. Interestingly, compound 3 showed weak cytotoxicity with an IC₅₀ value of 44.9 μM, while other compounds (1, 2, 7 and 10) showed weaker cytotoxicity (IC₅₀: 55.1 and 66.1 μM). Meanwhile, compounds 1–3 and 7 also displayed cytotoxicity against Huh7 cells with IC₅₀ values ranging from 44.3 to 48.9 μM; only compound 3 showed weaker cytotoxicity with an IC₅₀ value of 44.9 μM, while other compounds (1, 2, 7 and 10) showed weaker cytotoxicity with IC₅₀ values of 43.7 (HepG2), 47.9 (Huh7), and 44.9 (SK-Hep-1) μM, respectively. This investigation provided valuable information for the understanding of antihepatoma parts of *A. myriantha* and germacrane-type sesquiterpenoids as the active constituents.

### 3 Conclusion

In this study, 10 new germacrane-type sesquiterpenoids (1–10) were isolated and identified from *A. myriantha*. Their structures were elucidated by extensive analyses of spectral data, X-ray analyses, and ECD spectra. Compounds 1–3 showed cytotoxicity against HepG2 cells with IC₅₀ values of 43.7–46.5 μM; compounds 1–3 and 7 had cytotoxicity against Huh7 cell lines with IC₅₀ values ranging from 44.3 to 48.9 μM; only compound 3 exhibited cytotoxicity against SK-Hep-1 cells with IC₅₀ value of 44.9 μM. Interestingly, compound 3 displayed cytotoxicity against three human hepatoma cell lines with IC₅₀ values of 43.7 (HepG2), 47.9 (Huh7), and 44.9 (SK-Hep-1) μM, respectively. This investigation provided valuable information for the understanding of antihepatoma parts of *A. myriantha*.

### 4 Materials and methods

General experimental procedures, the ECD calculation, and cytotoxicity assays were provided in Additional file 1.

#### 4.1 Plant materials

*A. myriantha* was collected from Lijiang, Yunnan province, China in September 2018, and identified by Dr. Zhuo Zhou (Kunming Institute of Botany, Chinese Academy of Sciences). A voucher specimen (No. 201809AM) was deposited in the laboratory of Antivirus and Natural Medicinal Chemistry, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, China.

### 4.2 Extraction and isolation

In connection with our previous paper [25], Fr. E (165 g) was chromatographed on a silica gel column (1.6 kg, 10 × 90 cm, MeOH–CHCl₃, 2.98–10.90, v/v) to obtain fractions E1–E4 (25, 30, 46 and 55 g). Fraction E2 was subjected to MCI gel CHP 20P column (490 g, 5.0 × 50 cm) and eluted with an H₂O–MeOH gradient (70:30, 50:50, 30:70, 0:100) to yield four subfractions E2.1–E2.4. Fraction E2.2 (18 g) was applied to Si CC (200 g, 5.0 cm × 25 cm) and eluted with an EtOAc–CHCl₃ gradient (70:30, 50:50, 30:70, 0:100) to produce four subfractions E2.2.1–E2.2.4. The obtained fraction E2.2.2 (2.2 g) was separated by preparative HPLC (H₂O–MeCN, 76:24, 10.0 mL/min) to afford three fractions (E2.2.2.1–E2.2.2.3). Fraction E2.2.2.1 (218 mg) was purified by semipreparative HPLC (H₂O–MeOH, 72:28, 3.0 mL/min) to yield compounds 7 (22 mg, tᵣ = 28.3 min), 2 (13 mg, tᵣ = 26.5 min), and 3 (25 mg, tᵣ = 30.6 min). Fraction E2.2.3 (1.9 g) was isolated by repeated silica gel CC (50 g, 2.5 × 20 cm, EtOAc–CHCl₃, 10:90–30:70) and semipreparative HPLC (H₂O–MeCN, 75:25) to get compounds 4 (14 mg, tᵣ = 27.8 min) and 8 (8 mg, tᵣ = 29.3 min). Fraction E3 (46 g) was fractionated by MPLC on an MCI gel CHP 20P column (490 g, 5 cm × 50 cm) with a gradient solvent system of H₂O–MeOH (80:20, 60:40, 40:60, 0:100) to provide four subfractions E3.1–E3.4 (16, 6.5, 8.9, and 18 g). Fraction E3.2 (6.5 g) was fractionated with Si CC (80 g, 3.5 × 35 cm) using EtOAc–CHCl₃ gradient (70:30, 50:50, 30:70, 0:100) to yield four subfractions E3.2.1–E3.2.3 (2.5, 1.6 and 1.8 g). The obtained fraction E3.2.2 (1.6 g) was further isolated by Sephadex LH-20 CC (120 g, 2.5 × 150 cm, MeOH) and semipreparative HPLC (H₂O–MeCN, 82:18, 3.0 mL/min) to provide compounds 7 (18 mg, tᵣ = 24.3 min), 9 (6 mg, tᵣ = 21.2 min), and 10 (5 mg, tᵣ = 22.8 min). Fraction E3.3 (8.9 g) was chromatographed over a silica gel column (110 g, 4.5 × 20 cm) eluted with an EtOAc–CHCl₃.

### Table 4 Cytotoxicity of compounds 1–3, 7, and 10

| No | IC₅₀ (μM)ᵃ | HepG2 | Huh7 | SK-Hep-1 |
|----|------------|-------|------|----------|
| 1  | 465 ± 0.9  | 44.3 ± 6.0 | 89.3 ± 0.7 |
| 2  | 45.9 ± 3.2 | 48.9 ± 4.0 | 71.7 ± 0.4 |
| 3  | 43.7 ± 2.8 | 47.9 ± 4.6 | 44.9 ± 2.8 |
| 7  | 55.1 ± 2.5 | 44.9 ± 3.0 | 87.0 ± 1.7 |
| 10 | 66.1 ± 4.9 | 71.0 ± 2.8 | 74.8 ± 1.2 |
| Sorafenibᵇ | 13.5 ± 2.2 | 20.7 ± 1.1 | 11.8 ± 0.6 |

ᵃ Data were expressed as means ± SD (n = 3)
ᵇ Sorafenib was used as a positive control
3.3 Spectroscopic data of compounds 1–10

3.3.1 Artemyrianosin A (1)

Colorless monoclinic crystals (MeOH–CHCl₃, 95:5); mp 153.8–155.2 °C; [α]D₂₀ +12.5 (c 0.11, MeOH); ECD (MeOH) λmax (Δε) 199 (− 0.4), 218 (+3.4), 250 (+1.3) nm; IR νmax 3414, 1757, 1643, 1570, 1457, 1414, 1384, 1276, 1155, 1016, 994 cm⁻¹; ¹H and ¹³C NMR data see Tables 1 and 2; (+)-HRESIMS m/z 287.1254 [M + Na]⁺ (calcd for C₁₅H₂₀O₄Na, 287.1254).

3.3.2 Artemyrianosin B (2)

White amorphous powder; [α]D₂₀ +37.9 (c 0.11, MeOH); ECD (MeOH) λmax (Δε) 196 (− 0.8), 220 (+4.6) nm; IR νmax 3430, 1742, 1644, 1449, 1384, 1276, 1160, 1001, 908 cm⁻¹; ¹H and ¹³C NMR data see Tables 1 and 2; (+)-HRESIMS m/z 265.1427 [M + H]⁺ (calcd for C₁₅H₂₁O₄, 265.1434).

3.3.3 Artemyrianosin C (3)

White amorphous powder; [α]D₂₀ +31.2 (c 0.11, MeOH); ECD (MeOH) λmax (Δε) 197 (+1.4), 212 (+3.4) nm; IR νmax 3424, 3388, 1767, 1648, 1632, 1426, 1384, 1323, 1286, 1116, 989 cm⁻¹; ¹H and ¹³C NMR data see Tables 1 and 2; (+)-HRESIMS m/z 265.1431 [M + H]⁺ (calcd for C₁₅H₂₁O₄, 265.1434).

3.3.4 Artemyrianosin D (4)

White amorphous powder; [α]D₂₀ +46.4 (c 0.11, MeOH); ECD (MeOH) λmax (Δε) 201 (− 3.6), 244 (+0.2) nm; IR νmax 3427, 1759, 1634, 1459, 1384, 1346, 1186, 1039, 991, 908 cm⁻¹; ¹H and ¹³C NMR data see Tables 1 and 2; (+)-HRESIMS m/z 267.1579 [M + H]⁺ (calcd for C₁₅H₂₃O₄, 267.1591).

3.3.5 Artemyrianosin E (5)

Colorless oil; [α]D₂⁰ +3.9 (c 0.10, MeOH); ECD (MeOH) λmax (Δε) 197 (− 5.7), 224 (+1.0) nm; IR νmax 3428, 1718, 1631, 1439, 1384, 1245, 1150, 1020, 909 cm⁻¹; ¹H and ¹³C NMR data see Tables 1 and 2; (+)-HRESIMS m/z 339.1792 [M + H]⁺ (calcd for C₁₈H₂⁵O₆, 339.1802).

3.3.6 Artemyrianosin F (6)

Colorless oil; [α]D₂⁰ +17.6 (c 0.12, MeOH); ECD (MeOH) λmax (Δε) 202 (− 10.3), 224 (+1.7) nm; IR νmax 3423, 1719, 1629, 1439, 1382, 1246, 1152, 1027, 908 cm⁻¹; ¹H and ¹³C NMR data see Tables 2 and 3; (+)-HRESIMS m/z 339.1785 [M + H]⁺ (calcd for C₁₈H₂⁵O₆, 339.1802).

4.3.7 Artemyrianosin G (7)

Colorless monoclinic crystals (MeOH–CHCl₃, 95:5); mp 154.2–156.1 °C; [α]D₂⁰ +66.8 (c 0.14, MeOH); ECD (MeOH) λmax (Δε) 203 (+8.5), 220 (+3.2) nm; IR νmax 3467, 3435, 1749, 1664, 1643, 1632, 1445, 1410, 1381, 1314, 1263, 1129, 1027 cm⁻¹; ¹H and ¹³C NMR data see Tables 2 and 3; (+)-HRESIMS m/z 265.1423 [M + H]⁺ (calcd for C₁₅H₂₁O₄, 265.1434).

4.3.8 Artemyrianosin H (8)

Colorless monoclinic crystals (MeOH–CHCl₃, 95:5); mp 151.2–153.1 °C; [α]D₂⁰ +83.8 (c 0.13, MeOH); ECD (MeOH) λmax (Δε) 202 (−27.1), 227 (+0.5) nm; IR νmax 3500, 3367, 1751, 1667, 1650, 1452, 1384, 1195, 1184, 1021, 1010 cm⁻¹; ¹H and ¹³C NMR data see Tables 2 and 3; (+)-HRESIMS m/z 267.1585 [M + H]⁺ (calcd for C₁₅H₂₃O₄, 267.1591).

4.3.9 Artemyrianosin I (9)

Colorless tetragonal crystals (MeOH–CHCl₃, 95:5); mp 150.8–152.3 °C; [α]D₂⁰ −6.5 (c 0.12, MeOH); ECD (MeOH) λmax (Δε) 202 (−3.9), 229 (+0.2) nm; IR νmax 3391, 3308, 1751, 1632, 1564, 1384, 1064 cm⁻¹; ¹H and ¹³C NMR data see Tables 2 and 3; (+)-HRESIMS m/z 267.1576 [M + H]⁺ (calcd for C₁₅H₂₃O₄, 267.1591).

4.3.10 Artemyrianosin J (10)

White amorphous powder; [α]D₂⁰ −11.4 (c 0.13, MeOH); ECD (MeOH) λmax (Δε) 201 (+4.0), 222 (+0.8) nm; IR νmax 3391, 1754, 1631, 1594, 1567, 1384, 1073 cm⁻¹; ¹H and ¹³C NMR data see Tables 2 and 3; (+)-HRESIMS m/z 265.1423 [M + H]⁺ (calcd for C₁₅H₂₁O₄, 265.1434).

4.4 X-ray crystallographic analysis of compounds 1 and 7–9

Compounds 1 and 7–9 were afforded by recrystallization in a mixture of MeOH–CHCl₃ (95:5). X-ray diffraction analyses were performed on a Bruker D8 QUEST instrument using Cu Kα radiation and the intensity data were collected at 100 (2) K. The crystal structures were solved by using SHELXS-97 and difference Fourier techniques, and refinements were performed through the program and refined by full-matrix least-squares calculations on F². All non-hydrogen atoms were anisotropically refined, and the positions of hydrogens bonded to carbons were initially determined through geometry and refined using a riding model. The crystallographic data for compounds 1 and 7–9 in standard CIF format were deposited in the Cambridge Crystallographic Data Centre. The data can be accessed free of charge at http://www.ccdc.cam.ac.uk/.
Crystal data for compound 1: C_{15}H_{26}O_{5}, M = 264.31, a = 8.1236 (3) Å, b = 10.9775 (5) Å, c = 15.0127 (6) Å, α = 90°, β = 95.6520 (10)°, γ = 90°, V = 1332.28 (9) Å³, T = 100°. (1) K, space group P1211, Z = 4, μ (Cu Kα) = 0.774 mm⁻¹, 33,394 measured reflections, 5199 independent reflections (R_{int} = 0.0763). The final R1 values were 0.0397 [I > 2σ(I)]. The final wR (I²) values were 0.1190 [I > 2σ(I)]. The final R1 values were 0.0447 (all data). The final wR (I²) values were 0.1207 (all data). The goodness of fit on F² was 1.115. Flack parameter = 0.11 (6). CCDC 2,142,473.

Crystal data for compound 7: C_{15}H_{20}O_{4}, M = 264.31, a = 5.6882 (2) Å, b = 15.5718 (4) Å, c = 7.6450 (2) Å, α = 90°, β = 93.2180 (10)°, γ = 90°, V = 676.09 (3) Å³, T = 100°. (2) K, space group P1211, Z = 2, μ (Cu Kα) = 0.762 mm⁻¹, 14,454 measured reflections, 2570 independent reflections (R_{int} = 0.0451). The final R1 values were 0.0379 [I > 2σ(I)]. The final wR (I²) values were 0.0984 [I > 2σ(I)]. The final R1 values were 0.0379 (all data). The final wR (I²) values were 0.0985 (all data). The goodness of fit on F² was 1.070. Flack parameter = 0.04 (8). CCDC 2,142,472.

Crystal data for compound 8: C_{15}H_{20}O_{4}·2 (H₂O), M = 302.36, a = 10.1051 (5) Å, b = 5.9207 (3) Å, c = 13.4788 (6) Å, α = 90°, β = 96.4640 (10)°, γ = 90°, V = 801.30 (7) Å³, T = 100°. (2) K, space group P1211, Z = 2, μ (Cu Kα) = 0.776 mm⁻¹, 13,564 measured reflections, 3137 independent reflections (R_{int} = 0.0336). The final R1 values were 0.0292 [I > 2σ(I)]. The final wR (I²) values were 0.0752 [I > 2σ(I)]. The final R1 values were 0.0294 (all data). The final wR (I²) values were 0.0755 (all data). The goodness of fit on F² was 1.081. Flack parameter = 0.06 (4). CCDC 2,142,471.

Crystal data for compound 9: C_{15}H_{22}O_{4}, M = 266.32, a = 8.2909 (4) Å, b = 8.2909 (4) Å, c = 40.8360 (19) Å, α = 90°, β = 90°, γ = 90°, V = 2807.0 (3) Å³, T = 100°. (2) K, space group P41212, Z = 8, μ (Cu Kα) = 0.735 mm⁻¹, 44,745 measured reflections, 2766 independent reflections (R_{int} = 0.0520). The final R1 values were 0.0723 [I > 2σ(I)]. The final wR (I²) values were 0.0705 [I > 2σ(I)]. The final R1 values were 0.0723 (all data). The final wR (I²) values were 0.0706 (all data). The goodness of fit on F² was 1.091. Flack parameter = 0.05 (2). CCDC 2,142,474.

Supplementary Information
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Additional file 1. Supporting information.

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Author contributions
All authors read and approved the final manuscript.

Declarations
Competing interests
The authors declare that there is no conflict of interest.

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