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•Original article•

Anti-inflammatory sesquiterpene polyol esters from the stem and branch of *Tripterygium wilfordii*

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[ABSTRACT] The stem and branch extract of *Tripterygium wilfordii* (Celastraceae) afforded seven new dihydroagarofuran sesquiterpene polyesters [tripterysines A–G (**1**–**7**)] and eight known ones (**8**–**15**). The chemical structures of these new compounds were established based on combinational analysis of HR-ESI-MS and NMR techniques. The absolute configurations of tripterysines A–C (**1**–**3**) and E–G (**5**–**7**) were determined by X-ray crystallographic analysis and circular dichroism spectra. All the compounds were screened for their inhibitory effect on inflammation through determining their inhibitory effect on nitric oxide production in LPS-induced RAW 264.7 cells and the secretion of inflammatory cytokines TNF-*α* and IL-6 in LPS-induced BV2 macrophages. Compound **9** exhibited significant inhibitory activity on NO production with an IC_{50} value of 8.77 μmol·L^{-1}. Moreover, compound **7** showed the strongest inhibitory effect with the secretion of IL-6 at 27.36%.

[KEY WORDS] *Tripterygium wilfordii*; Sesquiterpene polyester; Tripterysine; Anti-inflammation.
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Introduction

Tripterygium Hook. f. (Celastraceae) is a genus comprised of three species of plants, namely *T. hypoglaucum*, *T. regelii* and *T. wilfordii* in China [1]. The roots of *Tripterygium* plants have been widely used for several hundred years as traditional herbal medicines with anticancer, immunosuppressive and anti-inflammatory effects [2-3]. In particular, *T. wilfordii* can be used for the treatment of lupus erythematosus and rheumatoid arthritis [4-8]. The remarkable bioactivities and therapeutic effects encouraged organic chemists and natural product researchers to further investigate the potential bioactive constituents of this species. Consequently, hundreds of effective chemical compositions including sesqui-, tri-, and diterpenoids, alkaloids, and lignans have been obtained, and exhibit a wide range of biological effects, such as cytotoxic, anti-HIV and insecticidal activities [9-24]. The typical and widespread metabolites that attract the most attention are dihydro-*β*-agarofuran sesquiterpenes, which are a large class of poly-esters with tricyclic scaffolds based on a core C15 sesquiterpenoid skeleton. This skeleton contains rings A and B in the form of *trans*-decalin. In addition, Me_2C-O bridge forms the C ring of tetrahydrofuranyl. Previous investigations about *T. wilfordii* indicated that dihydro-*β*-agarofurans are the main type of secondary metabolites [20-24], which prompts us to search for more bioactive constituents of *T. wilfordii*. In the current study, seven new dihydroagarofuran sesquiterpene poly esters, together with eight known ones were isolated and identified from the stem and branch of the titled plant. Furthermore, all compounds **1**–**15** (Fig. 1) were tested for their ability to inhibit NO production in LPS-induced RAW 264.7 cells, and two inflammatory cytokines TNF-*α* and IL-6 in LSP-induced BV2 macrophages.

Results and Discussion

The HR-ESI-MS $[M + Na]^+$ data (*m/z* 671.1931) of tripterysine A (**1**) was consistent with the molecular formula $C_{31}H_{36}O_{15}$ (Calcd. for $C_{31}H_{36}NaO_{15}$, 671.1946). The ^1H

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These authors have no conflict of interest to declare.

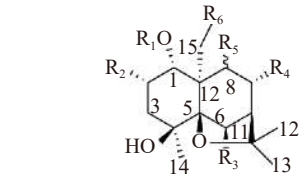
NMR data (Table 1) revealed the presence of six olefinic protons [δ_H 7.85 (dd, J = 1.6, 0.8 Hz, 1H), 7.60 (dd, J = 1.6, 0.8 Hz, 1H), 7.29 (t, J = 1.6 Hz, 1H), 7.14 (t, J = 1.6 Hz, 1H), 6.45 (dd, J = 1.6, 0.8 Hz, 1H), 6.38 (dd, J = 1.6, 0.8 Hz, 1H)], three acetoxy groups [δ_H 2.31, 2.12, 2.09 (s, each 3H)], three methyl groups [δ_H 1.57, 1.57, 1.50 (s, each 3H)], an oxymethylene group [δ_H 5.03 and 4.91 (d, J = 13.4 Hz, each 1H)], and five oxymethine protons (δ_H 6.80, 5.71, 5.53, 5.34, 4.39). The ^{13}C NMR spectrum provided 31 carbon signals. According to the 1D-NMR and HSQC spectra, the signals at δ_C 161.4, 161.2, 148.3, 147.9, 144.0, 143.5, 118.6, 118.3, 109.3, 109.3 were assigned to two furoyloxy groups, whereas the signals at δ_C 170.3, 169.9, 169.3, 21.7, 21.4, 21.2 were attributed to three acetoxy groups. There were remaining 15 carbons displayed for the skeleton in the ^{13}C NMR spectrum, which comprised of three methyls (δ_C 29.5, 24.6, 24.3), one aliphatic methylene (δ_C 42.1), one aliphatic methine (δ_C 56.0) and one aliphatic quaternary one (δ_C 54.3), and nine oxygenated ones including three quaternary ones (δ_C 92.0, 83.0, 69.7), five methine (δ_C 75.2, 74.6, 74.2, 68.6, 68.5) and one methylene (δ_C 60.4) from the combinational analysis of its DEPT and HSQC spectra. The ^{1}H-^{1}H COSY experiments (Fig. 2) of **1** showed two separated spin-spin coupling systems of H-1/H-2/H-3 and H-7/H-8/H-9, which formed two six-membered rings and connected by C-5 and C-10, deduced from the HMBC correlations (Fig. 2) of H-1 (δ_H 5.71), H-9 (δ_H 5.53) and H-2 (δ_H 5.34)/C-10 (δ_C 54.3), H-6 (δ_H 6.80) and H-3 (δ_H 2.01)/C-5 (δ_C 92.0), and H-1 (δ_H 5.71)/C-9 (δ_C 74.6). The HMBC cross-peaks (Fig. 2) of H-6 (δ_H 6.80)/C-11 (δ_C 83.0), Me-13(δ_H 1.57)/C-12 (δ_C 29.5), and Me-12 (δ_H 1.57) and Me-13 (δ_H 1.57)/C-7 (δ_C 56.0), along with the chemical shift values of C-5 (δ_C 92.0) and C-11 (δ_C 83.0) suggested that C-5 and C-11 were oxygenated quaternary carbons attached by an ether bond and a *gem*-dimethyl group was located at C-11. The remaining methyl was attached to C-4, supported by the HMBC correlations (Fig. 2) of Me-14 (δ_H 1.50)/C-5 (δ_C 92.0) and C-3 (δ_C 42.1). Furthermore, the HMBC cross-peaks (Fig. 2) of H-1 (δ_H 5.71)/C-15 (δ_C 60.4), and H-15 (δ_H 5.03)/C-5 (δ_C 92.0) and C-9 (δ_C 74.6) suggested that C-15 was connected to C-10. The above information indicated that compound **1** was a dihydroagarofuran sesquiterpenoid, substituted with three acetoxy and two furoyloxy groups.

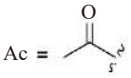
The locations of the ester and hydroxyl groups were determined through the HMBC spectrum. The HMBC cross-peaks (Fig. 2) of H-2 (δ_H 5.34), H-6 (δ_H 6.80), and H_2-15 (δ_H 5.03, 4.91) correspondingly with three carbonyl carbons from acetyl groups (δ_C 169.3, 169.9, 170.3) suggested that these acetoxy groups were attached to C-2, C-6, and C-15, respectively. Furthermore, two -OFu moieties were located at C-1 and C-9 according to the HMBC signals of H-1 (δ_H 5.71) and H-9 (δ_H 5.53) with carbonyl carbons in two -OFus (δ_C 161.4, 161.2), respectively. In addition, the chemical shift values of C-4 (δ_C 69.7) and C-8 (δ_C 68.5) suggested that two hydroxyl groups were assigned to C-4 and C-8. Thus, the planar structure of **1** was deduced as shown.

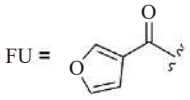
The relative configuration of **1** was established by analysis of ^{1}H-^{1}H coupling constant values and NOESY spectrum. One the one hand, the NOESY interactions of Me-14/H-15 (δ_H 5.03), H-6/H-15 (δ_H 5.03), H-6/8-OH, H-6/H-7, and H-6/Me-14 suggested that these protons and the hydroxyl group of C-8 were on the same face of the molecule. On the other hand, the NOESY correlations (Fig. 2) of H-1/H-2, H-8/Me-13, H-9/H-1, H-9/H-2, H-9/H-8, H-9/Me-13, H-3 (δ_H 2.18)/H-1, and H-3 (δ_H 2.18)/H-2 revealed that H-1, H-2, H-8, H-9 and Me-13 were on the other side. Meanwhile, the small coupling constant values between H-2 and H_2-3 ($J_{1,2}$ = 4.0, 2.7 Hz) indicated that H-2 was equatorially oriented, and on the same side with Me-13 and 4-OH [25]. Moreover, a single-crystal X-ray diffraction experiment using Cu Kα radiation was applied to define the absolute configuration of **1** (Fig. 3). So the structure of **1** was assigned as shown in Fig. 1.

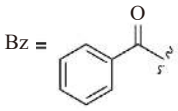
Tripterysine B (**2**) and tripterysine C (**3**) were obtained as amorphous powder and possessed the molecular formulas of $C_{34}H_{36}O_{16}$ and $C_{36}H_{38}O_{17}$ based on their HR-ESI-MS at *m/z* 723.1884 (Calcd. for $C_{34}H_{36}NaO_{16}$, 723.1896) and 765.1986 (Calcd. for $C_{36}H_{38}NaO_{17}$, 765.2001), respectively. The 1D NMR data of **2** and **3** indicated that their molecular skeletons were consistent with that of **1**. The HMBC correlation between H-6 (δ_H 7.29) and ester carbonyl carbon in -OFu (δ_C 163.5) suggested that the -OFu moiety was located at C-6 in **2**, different from the acetoxy group attached in **1**. For compound **3**, the proton signal at δ_H 5.61 (H-8) was correlated with the carbon one at δ_C 162.4 (-OFu) in HMBC, which suggested that **3** possessed a -OFu group at C-8 rather than a hydroxyl group in compound **1**. The relative configurations of **2** and **3** were determined to be identical to that of **1** through their nearly identical NOESY correlations of Me-13/H-9, Me-13/H-8, H-1/H-9, H-1/H-2, H-6/H_2-15, and H-6/Me-14. The small coupling constant values ($J_{2,3}$ = 4.5, 2.5 Hz) between H-2 and H_2-3 of both compounds **2** and **3**, along with the NOESY correlations of H-3 (δ_H 2.34/2.26)/H-1 and H-2 indicated that the H-2 was equatorially oriented and both H-1 and H-2 were β-oriented [25]. In addition, the similarity of ECD spectra (Fig. S34) of compounds **1**–**3** suggested that their key asymmetric carbons showed identical absolute configurations. Finally, the chemical structures of **2** and **3** were elucidated as shown in Fig. 1.

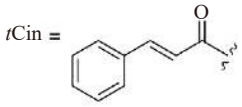
Tripterysines D (**4**) and E (**5**) were assigned the molecular formulas of $C_{36}H_{38}O_{17}$ and $C_{30}H_{38}O_{13}$ through analysis of their HR-ESI-MS $[M + Na]^+$ ions at *m/z* 765.1968 (Calcd. for $C_{36}H_{38}NaO_{17}$, 765.2001) and 629.2200 (Calcd. for $C_{30}H_{38}NaO_{13}$, 629.2205), respectively. By comparison of the NMR data of **4** with those of **3**, the proton signal at δ_H 5.63 (H-2) was correlated with the carbon one at δ_C 163.3 (-OFu), and the proton signal at δ_H 5.62 (H-9) with the carbonyl one at δ_C 171.2 (-OAc), which suggested that 2-OAc and 9-OFu in **3** had transposition in **4**. Moreover, the relative configuration of **4** was determined to be the same as those of **1**–**3** due to the similarity of coupling constant values and NOESY spectra. There were differences in substituents and

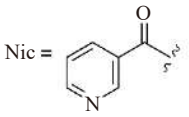


Ac = 

FU = 

Bz = 

*t*Cin = 

Nic = 

	R_1	R_2	R_3	R_4	R_5	R_6
1	FU	OAc	OAc	OH	*α*-OFu	OAc
2	FU	OAc	OFU	OH	*α*-OFu	OAc
3	FU	OAc	OAc	OFU	*α*-OFu	OAc
4	FU	OFU	OAc	OFU	*α*-OAc	OAc
5	Ac	OAc	OAc	OH	*β*-OBz	OAc
6	Ac	H	OAc	OFU	*α*-OBz	OAc
7	FU	H	OAc	OFU	*α*-OBz	OAc
8	Bz	H	H	H	*β*-O*t*Cin	H
9	FU	H	ONic	H	*β*-O*t*Cin	H
10	Bz	H	ONic	H	*β*-O*t*Cin	H
11	Bz	H	ONic	H	*β*-OBz	H
12	Bz	H	OH	H	*β*-O*t*Cin	H
13	FU	H	ONic	H	*β*-OBz	H
14	Nic	H	OH	H	*β*-OBz	H
15	*t*Cin	H	OAc	H	*β*-O*t*Cin	H

Fig. 1 Chemical structures of compounds 1–15 (1–7 are new)

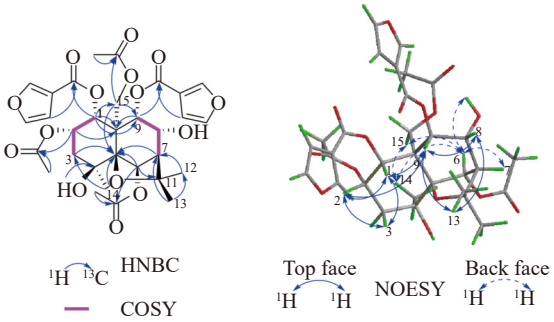


Fig. 2 Key 2D NMR correlations of 1

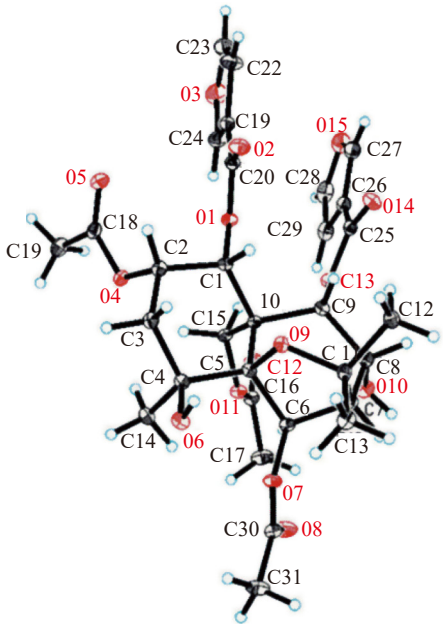


Fig. 3 X-ray crystallographic structure of 1

relative configuration at C-9 between **5** and **3**. The main difference was that 1-OFu, 9-OFu, and 8-OFu in **3** were replaced by an acetoxy group at C-1, an benzoyloxy group at C-9 and an hydroxy group at C-8 in **5**, repectively, which was deduced from the HMBC correlations (Fig. S57) of the proton signal at δ_H 5.60 (H-1) with the carbonyl one at δ_C 171.2 of acetyl group, the signal at δ_H 5.54 (H-9) with the carbon one at δ_C 166.2 of benzoyloxy group, and the chemical shift value of H-8 (δ_H 4.25) due to non-esterization of a vicinal hydroxyl group. The key NOESY signal (Fig. S57) of H-9/H_2-15 suggested that 9-benzoyloxy group was *β*-oriented, whereas the NOESY interaction (Fig. S57) between H-8 and Me-13 showed the *β*-orientation of H-8. In addition, no obvious coupling splitting of H-8 and H-9 indicated a dihedral angle close to 90° between H-8 and H-9, which further confirmed the relative configuration of C-8 and C-9 [25-26]. The key NOESY cross-peaks (Fig. S57) of H-6/Me-14, and H-3 (δ_H 2.32)/H-1 and H-2, along with the coupling constant values between H-2 and H_2-3 suggested that the other relative configurations was identical to those in **3** [25]. Compound **5** possessed identical absolute configuration to tripfordisinine I due to their similar ECD spectra and chromophores [27] and the same biogenesis in the plant. Accordingly, the chemical structures of **4** and **5** were identified as shown.

Tripterysines F (**6**) and G (**7**) were isolated as amorphous powder and assigned the molecular formulas of $C_{33}H_{38}O_{13}$ and $C_{36}H_{38}O_{14}$ through analysis of HR-ESI-MS ion peaks at *m/z* 643.2384 $[M + H]^+$ (Calcd. for $C_{33}H_{39}O_{13}$, 643.2385) and 717.2148 $[M + Na]^+$ (Calcd. for $C_{36}H_{38}NaO_{14}$, 717.2154), respectively. The ^1H NMR data revealed that **6** and **7** were similar to the above compounds in structure, possessing the skeleton of dihydroagarofuran sesquiterpenoid except for the variety of types and the number of substituted moieties. In the HMBC spectrum of **6**, the correlations of pro-

tons at δ_H 5.35 (H-1), 6.80 (H-6) and 4.82 (H_2-15) with three carbonyl carbons at δ_C 170.1, 170.1 and 170.9 (all -OAc) suggested that three acetoxy groups were located at C-1, C-6 and C-15, respectively. A benzoyloxy moiety was located at C-9 by the HMBC cross-peak between H-9 (δ_H 5.76) and ester carbonyl carbon in benzoyloxy moiety (δ_C 165.0). There was a -OFu group at C-8 in **6** based on the chemical shift value of C-8 (δ_C 70.9), although there was no direct HMBC cross-peak to be observed between H-8 (δ_H 5.68) and carbonyl carbon in -OFu (δ_C 162.2). The NOESY cross-peaks of H-1/H-9, Me-13/H-9, Me-13/H-8 suggested that these protons were on the same side of the molecule plane, while the correlations of H_2-15/H-6, H_2-15/Me-14, H-6/H-7, H-6/Me-14 indicated that these protons were on the other side in **6**. Meanwhile, the coupling constant values ($J_{1,2}$ = 11.6, 4.4 Hz) between H-1 and H_2-2 suggested that H-1 was axially oriented and on the same side with 4-OH [25, 28-29]. The 1D NMR spectra of **7** resembled those of **6** except that an furoyloxy group (δ_H 7.39, 6.94, 6.27; δ_C 162.1, 147.8, 143.2, 118.6, 109.3) replaced the acetoxy group of **6**, which was confirmed by the key HMBC cross-peak between H-1 (δ_H 5.61) and carbonyl carbon in -OFu group (δ_C 162.1). In addition, the nearly identical NOESY signals including the key cross-peaks of H-9/H-1, H-9/Me-13, Me-13/H-8, H-6/H_2-15, H-6/Me-14, H_2-15/Me-14, along with coupling constants analysis suggested that **7** and **6** as a whole had identical relative configuration. Their ECD spectra of **6** [Fig. S60] and **7** [Fig. S71] showed the negative Cotton effect at 242 nm ($\Delta\varepsilon$ –3.5)/239 nm ($\Delta\varepsilon$ –5.8) and the positive Cotton effect at 223 nm ($\Delta\varepsilon$ 0.0)/219 nm ($\Delta\varepsilon$ –1.7), respectively, originated from the coupling of α-OFu at C-8 and α-OBz at C-9, which allowed the determination of their absolute configurations [28]. All these data above established the structures of **6** and **7** as shown.

The eight known compounds were identified as triptofordin A (**8**) [30], 9α-cinnamoyloxy-1β-furoyloxy-4-hydroxy-6α-nicotinoyloxy-β-dihydroagarofuran (**9**) [31], 9-O-*trans*-cinnamoyl-9-debenzoylregelidine (**10**) [32], regilidine (**11**) [33], 1β-benzoyl-8α-cinnamoyl-4α,5α-dihydroxydihydroagarofuran (**12**) [34], triptregeline I (**13**) [35], tripterygiumine R (**14**) [22] and 5α-acetyl-1β,8α-bis-cinnamoyl-4α-hydroxydihydroagarofuran (**15**) [36] by comparison of their NMR data with those previously reported.

With respect to the potential anti-inflammatory activity of dihydroagarofuran sesquiterpene polyester [4, 21, 23, 31], the activities of compounds **1**-**15** against nitric oxide (NO) production in LPS-induced RAW 264.7 cells and inflammatory cytokines TNF-α and IL-6 in LPS-induced BV2 macrophages were assessed. The results were showed in Tables 2 and 3. Compounds **8**, **9** and **13** exhibited inhibitory effect on NO production with IC_{50} values of 42.28, 8.77 and 46.50 $\mu mol \cdot L^{-1}$, respectively. Furthermore, compounds **2**, **6** and **7** inhibited inflammatory response with the secretion of TNF-α and IL-6 ranging from 27.36% to 46.94%.

Experimental

General experimental procedures

CD spectra were recorded in MeOH on a Jasco J-810 spectrometer (Japan). UV spectra and optical rotation values were measured by a Jasco V-550 UV/VIS spectrometer and a Jasco digital polarimeter (Japan), respectively. IR spectra were measured on a Jasco Nicolet Impact 410-FTIR spectrometer (Japan) using KBr discs. HRESIMS data were acquired on an Agilent 6210 LC/MS time-of-flight (TOF) mass spectrometer (USA). Column chromatography (CC) was performed on Silica gel (200–300 mesh, Haiyang Chemical Group Corporation, China), RP-C_{18} (50 μm, YMC, Japan) and Sephadex LH-20 (25–100 μm, Pharmacia, Sweden). NMR experiments were carried out using Bruker 400 and 600 MHz spectrometers (Bruker Instrument, Inc., Switzerland). HPLC data were obtained on an Agilent 1200 HPLC system (USA) consisting of two pumps and a diode array detector. Column A (Ultimate XB-C_{18}, 4.6 mm × 250 mm, 5 μm, Welch, Potamac, USA) and column B (Ultimate XB-C_{18}, 10 mm × 250 mm, 5 μm, Welch, Potamac, USA) were used for HPLC analysis and semi-preparative purification, respectively.

Plant material

The stem and branch parts of *Tripterygium wilfordii* HooK. f. were collected in Jiekanling Mountain of Jixi County, Anhui Province, China, in August 2017. A voucher specimen (No. J201708) was deposited at the Teaching and Research Office of Pharmacognosy, Jinan University, China. The species were identified by ZHOU Guangxiong at College of Pharmacy, Jinan University, China.

Extract and isolation

A total of 40 L of 95% ethanol was added to the air-dried and powdered stem and branch of *T. wilfordii* HooK. f. (22.0 kg). The powder was soaked at room temperature for 2 d by percolation method. The procedure was repeated three more times. After evaporation of EtOH *in vacuum*, a crude residue (1.8 kg) was suspended in H_2O (10 L) and then partitioned with PE (10 L × 3), CH_2Cl_2 (10 L × 3), and EtOAc (10 L × 3) successively. The CH_2Cl_2 soluble part (184 g) was fractionated by CC (silica gel) using a gradient solvent system of PE/EtOAc (10 ∶ 1 to 1 ∶ 10, *V*/*V*), to obtain ten fractions (Frs. A–J). Fr. F (22.1 g) was subjected to silica gel and eluted with CH_2Cl_2/EtOAc (100 ∶ 1 to 0 ∶ 1, *V*/*V*) to produce nine subfractions (Frs. F1–9). Fr. F3 (3.5 g) was separated on an ODS column using MeOH/H_2O in a gradient mixed solution (20 ∶ 80 to 100 ∶ 0, *V*/*V*) as mobile phase to afford Frs. F3a–i. Frs. F3a–d were purified with RP-semi-preparative HPLC using aquatic solution (3 $mL \cdot min^{-1}$) of 60%, 70%, 77% and 78% MeOH as eluting solvent to afford compounds **3** (2.8 mg), **4** (2.2 mg), **11** (10.8 mg) and **15** (3.5 mg). Fr. F3e (75 mg) was separated by RP-semi-preparative HPLC, with 82% MeOH in H_2O as mobile phase, to afford compounds **9** (11.8 mg) and **10** (15.2 mg). Separation of Frs. F3f–i through RP-semi-preparative HPLC with 64%, 59%, 61%, and 45%

MeCN in H_2O (3 mL·min^{-1}) as mobile phase yielded compounds **8** (5.8 mg), **12** (8.0 mg), **13** (3.2 mg) and **14** (1.5 mg), respectively. Fr. H (21.9 g) was separated by CC and eluted with CH_2Cl_2/EtOAc (100 ∶ 1 to 0 ∶ 1, *V*/*V*) to give nine fractions (Frs. H1-9). Fraction 5 (1.8 g) was subjected to a Sephadex LH-20 chromatography column with CH_2Cl_2/MeOH (1 ∶ 1, *V*/*V*) to yield Frs. H5a–j. Frs. H5c–g were separated by RP-semi-preparative HPLC using 64%, 65%, 52%, 53%, and 48% MeOH in H_2O (3 mL·min^{-1}) as isocratic elution to obtain compounds **6** (1.2 mg), **7** (1.8 mg), **1** (5.0 mg), **5** (6.4 mg) and **2** (3.3 mg), respectively.

Tripterysine A (**1**): white amorphous powder; $[\alpha]_D^{27}$ –16.9 (*c* 0.36, MeOH); UV (MeOH) λ_{max} (log ε) 205 (4.07), 239 (3.60) nm; ECD (MeOH, $\Delta\varepsilon$) 229 (+0.062), 251 (−0.899) nm; IR (KBr) ν_{max}: 3470, 3145, 2935, 1736, 1372, 1308, 1233, 1163, 1075, 956, 873, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: OFu-1 [7.60 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.14 (t, *J* = 1.6 Hz, 1H), 6.38 (dd, *J* = 1.6, 0.8 Hz, 1H)], OAc-2 [2.09 (s, 3H)], OAc-6 [2.12 (s, 3H)], OFu-9 [7.85 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.29 (t, *J* = 1.6 Hz, 1H), 6.45 (dd, *J* = 1.6, 0.8 Hz, 1H)], OAc-15 [2.31 (s, 3H)], and other ^{1}H NMR data, see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: OFu-1 (161.4, 147.9, 143.5, 118.3, 109.3), OAc-2 (169.3, 21.2), OAc-6 (169.9, 21.7), OFu-9 (161.2, 148.3, 144.0, 118.6, 109.3), OAc-15 (170.3, 21.4), and other ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 671.1931 $[M + Na]^+$ (Calcd. for $C_{31}H_{36}NaO_{15}$, 671.1946).

Tripterysine B (**2**): white amorphous powder; $[\alpha]_D^{27}$ –6.77 (*c* 0.47, MeOH); UV (MeOH) λ_{max} (log ε) 205 (3.93), 236 (3.39) nm; ECD (MeOH, $\Delta\varepsilon$) 232 (+0.520), 258 (−0.562) nm; IR (KBr) ν_{max}: 3439, 2925, 1727, 1625, 1382, 1309, 1236, 1149, 1075, 963, 871, 754 cm^{-1}; ^{1}H NMR (MeOH-d_4, 600 MHz) δ: OFu-1 [8.09 (m, 1H), 7.42 (t, *J* = 1.8 Hz, 1H), 6.54 (d, *J* = 1.8 Hz, 1H)], OAc-2 [2.07 (s, 3H)], OFu-6 [8.23 (m, 1H), 7.61 (t, *J* = 1.8 Hz, 1H), 6.85 (d, *J* = 1.8 Hz, 1H)], OFu-9 [7.77 (m, 1H), 7.32 (t, *J* = 1.8 Hz, 1H), 6.44 (d, *J* = 1.8 Hz, 1H)], OAc-15 [2.30 (s, 3H)], and other ^{1}H NMR data, see Table 1; ^{13}C NMR (MeOH-d_4, 100 MHz) δ: OFu-1 (163.5, 150.2, 145.1, 120.2, 110.4), OAc-2 (171.2, 21.0), OFu-6 (163.5, 150.3, 145.6, 120.9, 110.7), OFu-9 (163.1, 149.7, 145.1, 119.5, 110.1), OAc-15 (172.7, 21.7), and other ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 723.1884 $[M + Na]^+$ (Calcd. for $C_{34}H_{36}NaO_{16}$, 723.1896).

Tripterysine C (**3**): white amorphous powder; $[\alpha]_D^{27}$ –28.0 (*c* 0.47, MeOH); UV (MeOH) λ_{max} (log ε) 205 (4.04), 239 (3.69) nm; ECD (MeOH, $\Delta\varepsilon$) 221 (−1.349), 234 (−2.303) nm; IR (KBr) ν_{max}: 3437, 2930, 1740, 1375, 1310, 1235, 1163, 1080, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: OFu-1 [7.59 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.16 (t, *J* = 1.7 Hz, 1H), 6.41 (dd, *J* = 1.7, 0.8 Hz, 1H)], OAc-2 [2.06 (s, 3H)], OAc-6 [2.17 (s, 3H)], OFu-8 [8.15 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.43 (t, *J* = 1.7 Hz, 1H), 6.76 (dd, *J* = 1.7, 0.8 Hz, 1H)], OFu-9 [7.69 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.27 (t, *J* = 1.7 Hz, 1H), 6.36 (dd, *J* = 1.7, 0.8 Hz, 1H)], OAc-15 [2.09 (s, 3H)], and other ^{1}H NMR data, see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: OFu-1 (161.5, 147.9, 143.5, 118.4, 109.5), OAc-2 (169.4, 21.2), OAc-6 (169.9, 21.7), OFu-8 (162.4, 148.6, 144.1, 119.0, 110.1), OFu-9 (161.1, 147.9, 143.8, 118.8, 109.3), OAc-15 (170.8, 21.7), and other ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 765.1986 $[M + Na]^+$ (Calcd. for $C_{36}H_{38}NaO_{17}$, 765.2001).

Tripterysine D (**4**): white amorphous powder; $[\alpha]_D^{27}$ –93.2 (*c* 0.41, MeOH); UV (MeOH) λ_{max} (log ε) 205 (4.05), 238 (3.65) nm; ECD (MeOH, $\Delta\varepsilon$) 234 (−0.880), 255 (−0.095) nm; IR (KBr) ν_{max}: 3437, 2924, 1735, 1580, 1507, 1375, 1309, 1239, 1157, 1078, 965, 873, 757, 599 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz) δ: OFu-1 [8.05 (s, 1H), 7.58 (s, 1H), 6.64 (s, 1H)], OFu-2 [8.42 (s, 1H), 7.67 (s, 1H), 6.94 (s, 1H)], OAc-6 [2.21 (s, 3H)], OFu-8 [8.41 (s, 1H), 7.65 (s, 1H), 6.88 (s, 1H)], OAc-9 [1.65 (s, 3H)], OAc-15 [2.08 (s, 3H)], and other ^{1}H NMR data, see Table 1; ^{13}C NMR (MeOH-d_4, 100 MHz) δ: OFu-1 (162.9, 149.7, 145.8, 120.0, 110.4), OFu-2 (163.3, 150.3, 145.7, 120.4, 110.9), OAc-6 (171.9, 21.4), OFu-8 (164.0, 150.0, 145.9, 119.9, 110.6), OAc-9 (171.2, 20.6), OAc-15 (172.7, 21.4), and other ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 765.1968 $[M + Na]^+$ (Calcd. for $C_{36}H_{38}NaO_{17}$, 765.2001).

Tripterysine E (**5**): white amorphous powder; $[\alpha]_D^{27}$ –17.6 (*c* 0.41, MeOH); UV (MeOH) λ_{max} (log ε) 203 (3.83), 232 (3.92), 276 (2.74) nm; ECD (MeOH, $\Delta\varepsilon$) 210 (−1.510), 215 (−1.339), 228 (−1.611), 279 (+0.187) nm; IR (KBr) ν_{max}: 3444, 2924, 1742, 1636, 1373, 1240, 1147, 1095, 713 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz) δ: OAc-1 [1.50 (s, 3H)], OAc-2 [2.08 (s, 3H)], OAc-6 [2.13 (s, 3H)], OBz-9 [8.01 (m, 2H), 7.63 (m, 1H), 7.48 (m, 2H)], OAc-15 [2.23 (s, 3H)], and other ^{1}H NMR data, see Table 1; ^{13}C NMR (MeOH-d_4, 100 MHz) δ: OAc-1 (171.2, 20.6), OAc-2 (171.5, 21.0), OAc-6 (171.7, 21.6), OBz-9 (166.2, 134.8, 131.2 × 2, 130.3, 129.5 × 2), OAc-15 (172.7, 21.3), and other ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 629.2200 $[M + Na]^+$ (Calcd. for $C_{30}H_{38}NaO_{13}$, 629.2205).

Tripterysine F (**6**): white amorphous powder; $[\alpha]_D^{27}$ –34.5 (*c* 0.44, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.05), 231 (3.95), 278 (2.83) nm; ECD (MeOH, $\Delta\varepsilon$) 223 (−0.047), 242 (−3.477) nm; IR (KBr) ν_{max}: 3444, 2925, 1733, 1627, 1455, 1373, 1312, 1268, 1233, 1146, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: OAc-1 [1.47 (s, 3H)], OAc-6 [2.15 (s, 3H)], OFu-8 [8.12 (s, 1H), 7.42 (s, 1H), 6.74 (s, 1H)], OBz-9 [7.96 (d, *J* = 7.8 Hz, 2H), 7.53 (m, 1H), 7.40 (m, 2H)], OAc-15 [2.11 (s, 3H)], and other ^{1}H NMR data, see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: OAc-1 (170.1, 20.9), OAc-6 (170.1, 21.7), OFu-8 (162.2, 148.5, 144.1, 119.0, 110.0), OBz-9 (165.0, 133.5, 129.8 × 2, 129.4, 128.7 × 2), OAc-15 (170.9, 21.5), and other ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 643.2384 $[M + H]^+$ (Calcd. for $C_{33}H_{39}O_{13}$, 643.2385).

Tripterysine G (**7**): white amorphous powder; $[\alpha]_D^{27}$ –33.3 (*c* 0.53, MeOH); UV (MeOH) λ_{max} (log ε) 205 (4.21), 232 (4.03), 278 (2.97) nm; ECD (MeOH, $\Delta\varepsilon$) 204 (+1.721), 212 (−2.553), 219 (−1.665), 239 (−5.800) nm; IR (KBr) ν_{max}: 3441, 2928, 1729, 1626, 1380, 1309, 1243, 1147, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: OFu-1 [7.39 (s, 1H), 6.94 (s, 1H), 6.27 (s ,1H)], OAc-6 [2.15 (s, 3H)], OFu-8 [8.13

Table 1 ^{1}H and ^{13}C NMR data for compounds **1**–**7** (*J* in hz)

No.	**1**[a, d]		**2**[b, e]		**3**[b, d]		**4**[a, e]		**5**[a, e]		**6**[a, d]		**7**[c, d]	
	δ_H (mult; *J*)	δ_C	δ_H (mult; *J*)	δ_C	δ_H (mult; *J*)	δ_C	δ_H (mult; *J*)	δ_C	δ_H (mult; *J*)	δ_C	δ_H (mult; *J*)	δ_C	δ_H (mult; *J*)	δ_C
1	5.71, d (4.0)	75.2	5.68, d (4.0)	77.2	5.73, d (4.5)	75.8	5.83, d (3.9)	77.2	5.60, d (3.8)	72.6	5.35, dd (11.6, 4.4)	78.2	5.61, dd (10.7, 5.8)	77.8
2	5.34, td (4.0, 2.7)	68.6	5.36, m	69.7	5.42, td (4.5, 2.5)	68.4	5.63, o	69.7	5.52, td (3.8, 3.2)	69.4	1.83, m	25.2	1.87, m	25.6
											1.70, m		1.87, m	
3	2.18, dd (15.6, 4.0)	42.1	2.34, dd (15.2, 4.5)	43.0	2.26, dd (15.3, 4.5)	42.2	2.48, dd (15.4, 4.6)	42.6	2.32, dd (15.3, 3.8)	42.4	1.97, m	38.0	2.04, m	38.0
	2.01, m		1.96, dd (15.2, 2.5)		2.01, dd (15.3, 2.5)		2.07, m		1.93, dd (15.3, 3.2)		1.71, m		1.75, m	
4		69.7		71.0		69.9		70.9		71.2		70.7		70.8
5		92.0		93.4		91.8		92.6		92.8		92.0		92.2
6	6.80, s	74.2	7.29, s	76.4	6.98, s	75.5	7.05, s	76.7	6.70, s	76.6	6.80, s	75.3	6.78. s	75.3
7	2.37, d (3.9)	56.0	2.43, d (3.9)	57.7	2.52, d (3.8)	54.1	2.58, d (3.2)	55.4	2.26, d (3.0)	57.8	2.51, d (3.9)	53.7	2.52, d (4.1)	53.6
8	4.39, q (5.2)	68.5	4.35, dd (5.5, 3.9)	69.1	5.61, dd (6.1, 3.8)	70.8	5.59, o	71.7	4.25, d (3.0)	75.6	5.68, dd (5.7; 3.9)	70.9	5.67, dd (5.5; 4.1)	70.9
9	5.53, d (5.9)	74.6	5.49, d (5.5)	76.3	5.71, d (6.1)	71.7	5.62, o	73.6	5.54, s	77.0	5.76, d (5.7)	73.1	5.85, d (5.5)	73.2
10		54.3		55.7		53.4		54.2		56.1		52.3		52.6
11		83.0		83.9		82.7		83.8		84.5		82.8		83.0
12	1.57, s	29.5	1.63, s	29.8	1.59, s	29.4	1.65, s	29.3	1.62, s	29.9	1.58, s	29.5	1.60, s	29.5
13	1.57, s	24.3	1.59, s	24.3	1.67, s	24.6	1.66, s	24.4	1.57, s	25.9	1.69, s	24.5	1.72, s	24.3
14	1.50, s	24.6	1.53, s	24.8	1.51, s	24.4	1.54, s	25.2	1.51, s	25.3	1.37, s	22.7	1.40, s	22.5
15	5.03, d (13.4)	60.4	5.37, m	60.4	5.16, d (13.5)	60.7	5.62, o	62.5	4.87, m	66.1	4.82, m	61.2	5.00, d (13.4)	61.2
	4.91, d (13.4)		4.85, o		4.87, d (13.5)		4.53, d (13.5)		4.87, m		4.82, m		4.85, d (13.4)	
4-OH	2.76, s				2.75, br s						2.68, s		2.71, br s	
8-OH	2.83, d (6.0)													

[o] Overlapped; [a] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data of compounds; [b] ^{1}H (600 MHz) and ^{13}C (100 MHz) NMR data of compounds; [c] ^{1}H (400 MHz) and ^{13}C (150 MHz) NMR data of compound; [d] In $CDCl_3$; [e] In MeOH-d_4.

Table 2 Inhibition of NO production in LPS-induced RAW 264.7 cells and cytotoxicity against RAW 264.7 cells of some compounds[a] (means ± SD, *n* = 3)

Compounds	IC_{50} (μmol·L^{-1})	TC_0 (μmol·L^{-1})
8	42.28 ± 1.42	>50
9	8.77 ± 0.49	20.94 ± 0.81
13	46.50 ± 1.13	>50
Dexamethasone[b]	11.94 ± 0.38	>50

[a] Inactive compounds are omitted; [b] Positive control

Table 3 Inhibition of inflammatory cytokines in LPS-induced BV2 cells[a, b] (means ± SD, *n* = 3)

Group	TNF-*α* (%)	IL-6 (%)
Blank	1.78 ± 2.40	1.62 ± 2.62
LPS	100 ± 2.59	100 ± 3.20
Dexamethasone	49.00 ± 2.21	17.01 ± 2.54
2	40.46 ± 2.01	46.94 ± 3.52
6	34.53 ± 2.14	42.60 ± 2.68
7	42.03 ± 3.15	27.36 ± 3.00

[a] No obvious cytotoxicities on BV2 cells; [b] The compounds with no obvious anti-inflammatory activities are omitted.

(s, 1H), 7.43 (s, 1H), 6.74 (s, 1H)], OBz-9 [7.67 (d, *J* = 7.8 Hz, 2H), 7.44 (m, 1H), 7.23 (m, 2H)], OAc-15 [2.14 (s, 3H)], and other ^{1}H NMR data, see Table 1; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: OFu-1 (162.1, 147.8, 143.2, 118.6, 109.3), OAc-6 (170.1, 21.7), OFu-8 (162.0, 148.5, 144.1, 119.0, 110.0), OBz-9 (164.8, 133.2, 129.4 × 2, 129.3, 128.3 × 2), OAc-15 (170.8, 21.6), and other ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 717.2148 $[M + Na]^+$ (Calcd. for $C_{36}H_{38}NaO_{14}$, 717.2154).

Inhibitory effect on NO production in LPS-induced RAW 264.7 cells

The cytotoxicities were evaluated by MTT assay and the inhibitory activities against LPS-activated RAW 264.7 macrophages were tested based on the production of NO as previously described [37].

Inhibitory effect on inflammatory cytokines TNF-α and IL-6 in LPS-induced BV2 cells

All compounds **1**–**15** were investigated for their inhibitory effect against the secretion of inflammatory cytokines TNF-*α* and IL-6 in LPS-induced BV2 macrophages. All the compounds were assessed for their toxicity to BV2 cells by MTT assay. In this study, BV2 cells (4×10^5 cells per well) were seeded onto 24-well plates at 37 °C overnight. The secretion of inflammatory mediators including TNF-*α* and IL-6 were measured by ELISA as previously described [38].

Supporting Information

HR-ESI-MS, 1D and 2D NMR spectra of compounds **1**–**7** can be requested by sending E-mail to the corresponding author.

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