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Ligusaginoids A–D, four eremophilane-type sesquiterpenoid dimers and trimers from *Ligularia sagitta*

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ABSTRACT

Four novel highly oxygenated eremophilane-type sesquiterpenoid dimers and trimers with the unique 6/6/5/5 polycyclic skeleton, designated as ligusaginoids A–D (**1**–**4**), were isolated from the aerial parts of *Ligularia sagitta*. Their structures with absolute configurations were determined by a combined method. Moreover, a plausible biosynthetic pathway of **1**–**4** was also proposed. These compounds showed weak antibacterial activities.

Introduction

Ligularia sagitta, belonging to the genus *Ligularia* of the family Compositae, is a traditional herbal medicine in China. It has been used to treat inflammation, eliminate phlegm, suppress cough, relieve pain, and stimulate blood flow [1]. Phytochemical investigations suggested that *L. sagitta* contained high level eremophilane-type sesquiterpenoids [2–4], which exhibit diverse biological activities, such as anticancer, anti-inflammatory, antiviral, antibacterial, antidiabetic and phytogrowth-inhibitory activities [5–10].

Our research on chemical constituents of *L. sagitta* collected from Gansu Province in China has led to the isolation of a series of eremophilane-type sesquiterpenoids with a novel carbon skeleton [11]. Motivated by a search for natural products of new structures and biological activities, the aerial parts of *L. sagitta* collected from Sichuan Province were targeted and afforded four unprecedented highly oxygenated eremophilane-type sesquiterpenoid dimers (**1** and **2**) and trimers (**3** and **4**) (Fig. 1) characterized with the 6/6/5/5 polycyclic skeleton. Here, we report the isolation, structural elucidation, and biological evaluation of these compounds.

Results and discussion

The air-dried aerial parts of *L. sagitta* were extracted with MeOH to give a crude extract, which was suspended in H_2O and successively partitioned with EtOAc and *n*-BuOH. The EtOAc extract was subjected to the column chromatography (CC) over silica gel, sephadex LH-20, and semi-preparative HPLC to afford ligusaginoids A–D (**1**–**4**).

Ligusaginoid A (**1**) was obtained as optically active colorless crystals (CH_3OH). Its molecular formula of $C_{43}H_{56}O_{13}$ was determined by the HRESIMS ion at *m*/*z* 803.3630 $[M+Na]^+$ (calcd for $C_{43}H_{56}O_{13}Na$, 803.3613), which required sixteen degrees of unsaturation. Its IR spectrum exhibited absorptions at 3418 and 1705 cm^{-1}, assignable to hydroxyl and carbonyl groups, respectively. The ^1H NMR spectrum showed the presence of a trisubstituted olefinic proton signal at δ_H 6.32 (q, J = 7.6 Hz) and seven methyl signals at δ_H 1.98 (d, J = 7.6 Hz), 1.88 (s), 1.53 (d, J = 1.6 Hz), 1.05 (d, J = 6.4 Hz), 1.04 (s), 0.87 (s), and 0.82 (d, J = 6.8 Hz). The ^{13}C NMR spectrum of **1** exhibited 43 carbon signals, including three ester carbonyl carbons, three pairs of double bond carbons, four quaternary carbons, four oxygenated tertiary carbons, eight methines (six oxygenated ones), eleven methylenes (three oxygenated ones), seven methyls. Moreover, deducting six degrees of unsaturation accounted for three ester carbonyl groups and three pairs of double bonds, the remaining ten indices of hydrogen deficiency indicated that ten rings should be present in **1**.

The ^1H–^1H COSY spectrum revealed two spin-coupling systems as drawn with bold bonds in Fig. 2. A further analysis of the 1D NMR spectra and ^1H–^1H COSY spectrum indicated that compound **1** contained parts I and II. In part I (in black in Fig. 1), the A, B, and C ring systems were established by the HMBC correlations of H-1 with C-5, of H_3-15 with C-5, of H-4 with C-5 and C-10, of H_3-14 with C-4, C-5, C-6, and C-10, of H-6 with C-4, C-5, C-7, and C-11,

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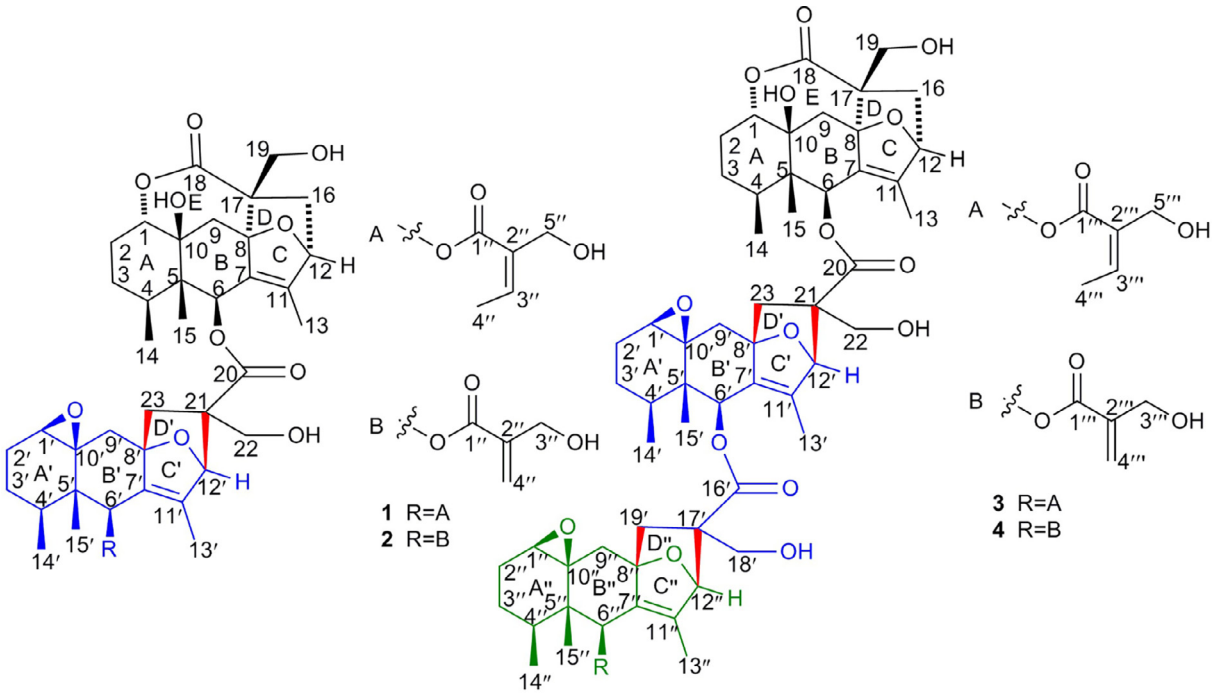

Fig. 1. Structures of ligusaginoids A–D (**1**–**4**).

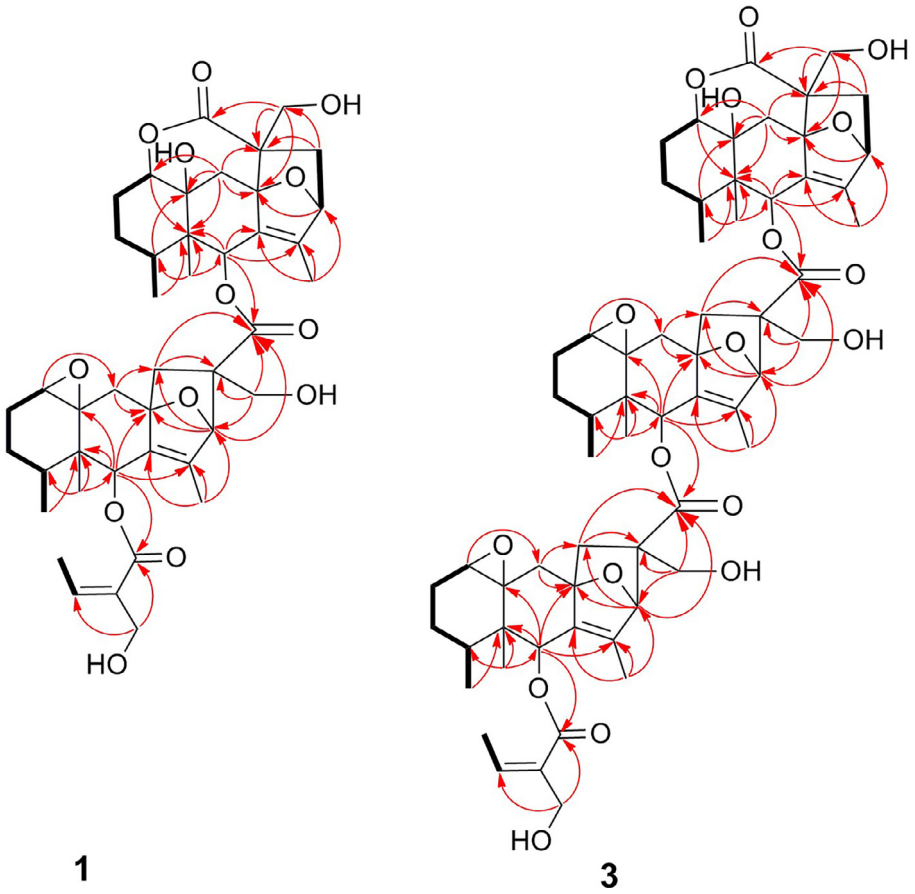

Fig. 2. ^{1}H–^{1}H COSY (bold) and HMBC (arrows) correlations of **1** and **3**.