



Caesalpinone A, a new type of gorgonane sesquiterpenoid containing an unprecedented 1,15-bridge, from the pods of *Caesalpinia spinosa* Kuntze



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ABSTRACT

Caesalpinone A (**1**), a new type of gorgonane sesquiterpenoid containing an unprecedented 1,15-bridge, along with ten known sesquiterpenoids (**2**–**11**) were isolated from the pods of *Caesalpinia spinosa* Kuntze (Tara). The structure of caesalpinone A was elucidated based on its 1D and 2D NMR spectra. The absolute configuration of **1** was assigned by the comparison of the experimental and calculated electronic circular dichroism spectra. Compound **1** was evaluated for the inhibitory activities against five human tumor cell lines. The sesquiterpenoids of isodaucane skeleton and caryolane skeleton were isolated from *Caesalpinia* genus for the first time. Compounds **5**–**9** were firstly reported from Tara.

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1. Introduction

Caesalpinia spinosa Kuntze, commonly known as Tara, is a small Leguminous tree or thorny shrub native to Peru. It has been introduced and cultured in the drier parts of Yunnan Province as a source of tannins rich in the fruit pods. The pods also have medical uses in Peru for inflamed tonsils, fever, cold and stomachaches [1]. The cassane diterpenoids and homoisoflavonoids are the characteristic components of *Caesalpinia* plants. Sesquiterpenoids are rare in *Caesalpinia* species. To date, there have been only fourteen sesquiterpenoids reported belonging to nine structural subtypes of eudesmane, oplopanane, clovane, oppositane, tricyclohumulane, cadinane, guaiane, caryophyllane, aromadendrane from four *Caesalpinia* species [2,3,4,5,6]. As our continuous research on *Caesalpinia* plants in Yunnan Province, a new type of gorgonane sesquiterpenoid containing an unprecedented 1,15-bridge, caesalpinone A (**1**) (Fig. 1), together with ten known sesquiterpenoids, 9 α -hydroxy-1 β -ethoxycaryolanol (**2**) [7], clovane-2 β ,9 α -diol (**3**) [8], tricyclohumuladiol (**4**) [9], aromadendrane-4 β ,10 α -diol (**5**) [10], (+)-aphanamol I (**6**) [11], 10-hydroxy-6,10- epoxy-7(14)-isodaucane (**7**) [12], artabotrol (**8**) [13], 4(14)-eudesmene-6 α ,11-diol (**9**) [14], 4(15)-eudesmene-1 β ,6 α -diol (**10**) [15], and oplopanone (**11**) [16] were isolated from the pods of this plant. The sesquiterpenoids of isodaucane skeleton (**6**, **7** and **8**) and caryolane skeleton (**2**) (Fig. 1) were isolated from

Caesalpinia genus for the first time. Compounds **5**–**9** were firstly reported from Tara.

2. Experimental

2.1. General experimental procedures

Optical rotations were measured with a JASCO P-1020 digital polarimeter. UV spectra were recorded on Shimadzu UV-2401 PC spectrophotometer. IR Spectra were obtained on a Bruker Tensor 27 FT-IR polarimeter with KBr pellets. ECD spectra were obtained using a JASCO J-815 spectropolarimeter. NMR spectra were acquired on Bruker DRX-500 and Bruker Avance 600 MHz spectrometer with TMS as the internal standard. EIMS and HREIMS data were obtained using Autospec Premier P776 spectrometers. Fractions were monitored by TLC on silica gel plates (Pre-coated silica gel GF₂₅₄, Qingdao Haiyang Chemical Co., Ltd., Qingdao, China) sprayed with 10% H₂SO₄ in ethanol, followed by heating. Column chromatography (CC) was performed on silica gel (100–200 mesh or 200–300 mesh; Qingdao Haiyang Chemical Co., Ltd., Qingdao, China), Sephadex LH-20 (GE Healthcare) and MCI gel (75–150 mm, Mitsubishi Chemical Corporation, Tokyo, Japan).

2.2. Plant material

The materials were collected by the corresponding author from Yimen County, Yunnan Province, P. R. China, in April 2013, and the voucher specimen was collected in August 2014 by the corresponding

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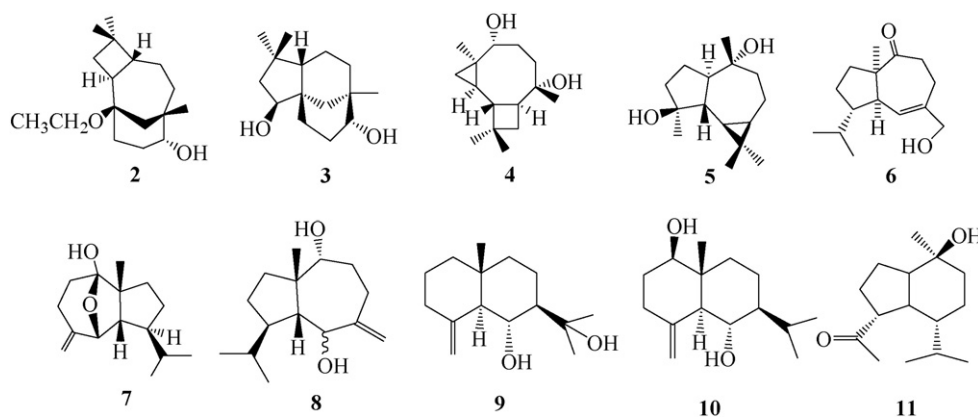


Fig. 1. The structures of the known sesquiterpenoids (2–11) from the pods of Tara.

author and identified by Dr. Haiying Ma (Yunnan University). A voucher specimen (Ma H.Y. 2014290) was deposited at Herbarium of Yunnan University, Kunming, China.

2.3. Extraction and isolation

The air-dried and powdered pods (15.0 kg) of Tara were extracted with 55 L 85% EtOH (4 times) at room temperature, which afforded a dark residue (8.4 kg) after evaporation under reduced pressure. The residue was dissolved in H₂O and extracted by CHCl₃. The CHCl₃ extract (192 g) was subjected to column chromatography (CC) (SiO₂, 100–200 mesh; petroleum ether/EtOAc 40:1, 20:1, 10:1, 7:1, 5:1, 3:1, 1:1, 0:1) to gain twelve fractions (Fr. S₁–S₁₂). Fr.S₇ (15 g) was subjected to SiO₂ CC (petroleum ether/EtOAc 10:1–1:1) to gain seven subfractions (S_{7a}–S_{7g}). Fr.S_{7a} (3.9 g) was repeatedly subjected to CC (SiO₂ petroleum ether/EtOAc 100:1–0:1; CHCl₃/EtOAc 30:1; CHCl₃/CH₃OH 100:1; Sephadex LH-20, CHCl₃/CH₃OH 1:1) to provide compound **7** (14 mg). Fr.S_{7b} (640 mg) was subjected to CC (SiO₂ petroleum ether/CHCl₃ 100:1–0:1; MCl, MeOH/H₂O 4:6–1:0; CHCl₃/CH₃COCH₃ 30:1) to provide compound **2** (10 mg). Fr.S_{7d} (2.4 g) was subjected to CC (SiO₂ CHCl₃/CH₃OH 100:1–0:1; petroleum ether/EtOAc 4:1; MCl, MeOH/H₂O 4:6–1:0; petroleum ether/CH₃COCH₃ 5:1) to provide compounds **10** (15 mg), **9** (10 mg) and **8** (10 mg). Fr.S₈ (5.22 g) was subjected to CC (SiO₂, CHCl₃/CH₃OH 100:1–20:1) to obtain seven subfractions (S_{8a}–S_{8g}). S_{8c} (948 mg) was subjected repeatedly to CC (petroleum ether/EtOAc 8:1; CHCl₃/EtOAc 16:1; CHCl₃/CH₃OH 60:1; Sephadex LH-20, CHCl₃/CH₃OH 1:1) to provide compounds **1** (5.5 mg) and **11** (9 mg); S_{8d} (1.0 g) was resubjected to CC (petroleum ether/EtOAc 6:1–4:1; Sephadex LH-20, CHCl₃/CH₃OH 1:1) to provide compound **6** (9 mg). Fr.S₁₀ (26.1 g) was subjected to CC (SiO₂, petroleum ether/CH₃COCH₃ 6:1–3:1) to obtain four subfractions (S_{10a}–S_{10d}). S_{10b} (5.6 g) was subjected to CC (petroleum ether/EtOAc 3:1–1:1; CHCl₃/CH₃COCH₃ 20:1) to get compound **5** (67 mg). S_{10c} (8.3 g) was subjected to CC (petroleum ether/EtOAc 3:1–0:1; CHCl₃/CH₃OH 30:1; CHCl₃/CH₃COCH₃ 20:1–2:1; petroleum ether/CH₃COCH₃ 5:1) to get compounds **3** (6 mg) and **4** (16 mg).

3. Results and discussion

Caesalpinone A (**1**), was obtained as colorless oil with the molecular formula C₁₅H₂₂O₂ (five degrees of unsaturation), which was deduced by HREIMS at *m/z* 234.1618 ([M]⁺, calcd. 234.1620). The 1D and 2D NMR spectra also showed 15 carbon atoms due to three methyls (δ_c 19.2, 19.6 and 30.0), four methylenes (δ_c 22.9, 24.7, 32.8 and 41.7), five methines (δ_c 27.9, 30.0, 31.0, 34.5 and 46.4), three quaternary carbons (δ_c 41.7; two ketones at δ_c 214.4 and 208.9). The absorption at 1719 cm⁻¹ in the IR spectrum of **1** further verified the existence of the carbonyl group. The MS and NMR suggested that compound **1**

could be a sesquiterpenoid. Apart from two degrees of unsaturation occupied by two ketonic groups, the remaining three degrees of unsaturation indicated that **1** should possess a tricyclic system. The HMBC correlations (Fig. 2) from H-6 (δ_H 0.68) to C-11 (δ_c 31.0), C-12/13 (δ_c 19.2/19.6), C-7 (δ_c 24.7) and C-8 (δ_c 41.7), from H-8 (δ_H 2.55, 2.50) to C-6 (δ_c 46.4), C-7 (δ_c 24.7) and C-9 (δ_c 208.9), from one of H-7 (δ_H 1.74) to C-9 (δ_c 208.9), from H-11 (δ_H 1.78) to C-6 (δ_c 46.4), C-7 (δ_c 24.7) and C-12/13 (δ_c 19.2/19.6) showed the existence of fragment A (Fig. 2), which was verified by the 1H–1H COSY cross-peaks between H-6/H-7, H-7/H-8, H-6/H-11, H-11/H-12, and H-11/13. The HMBC correlations (Fig. 2) from H-4 (δ_H 1.87) to C-15 (δ_c 22.9), C-2 (δ_c 32.8), C-3 (δ_c 214.4) and C-6 (δ_c 46.4), from H-5 (δ_H 1.04) to C-3 (δ_c 214.4), C-4 (δ_c 27.9), C-15 (δ_c 22.9), C-7 (δ_c 24.7) and C-11 (δ_c 31.0), showed the existence of fragment B (Fig. 2), which was confirmed by the 1H–1H COSY cross-peaks between H-15/H-4, H-4/H-5. The HMBC correlations (Fig. 3) from H-14 (δ_H 2.18, s, 3H) to C-9 (δ_c 208.9) and C-10 (δ_c 41.7) showed it must be assigned a Me group at the ring-fusion site, and must be attached to C-10 (δ_c 41.7). Thus, the tricyclic system should be the connection of fragment A and B by C-10 (δ_c 41.7) and the last remaining methine (C-1, δ_c 34.5). The connection of fragment A and B was also supported by the HMBC correlations from H-2 (δ_H 2.07) to C-15 (δ_c 22.9), and from one of H-15 (δ_H 2.15) to C-2 (δ_c 32.8) (Fig. 3). As a result, the planar structure of compound **1** was decided, which was a new type of gorgonane sesquiterpenoid with an unprecedented bridge between C-1 and C-15 (Fig. 3).

The relative configuration of **1** was established by analysis of the ROESY spectra. The correlations of H-14 (δ_H 2.18) with H-5 (δ_H 1.04), of H-5 (δ_H 1.04) with one of H-15 (δ_H 2.15), showed the *cis* fusion between the two six-membered ring and the co-facial orientation of the H-15 with H-14. Therefore, there were four possible candidate stereoisomers, **1a** (1*R*,4*S*,5*S*,6*S*,10*R*-) and its enantiomers **1b** (1*S*,4*R*,5*R*,6*R*,10*S*-), **1c** (1*S*,4*R*,5*R*,6*S*,10*S*-) and its enantiomers **1d** (1*R*,4*S*,5*S*,6*R*,10*R*-).

The absolute configuration of **1** was determined by comparison of the experimentally obtained-, and simulated-, electronic circular dichroism (ECD) spectra. Since the ECD spectra calculated for **1a** would

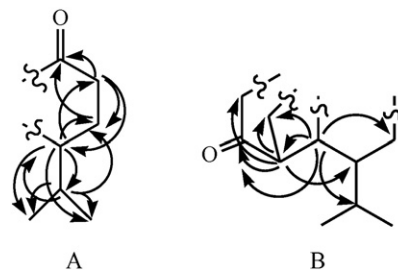


Fig. 2. The structures of fragments A and B, and the HMBC correlations.

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