PERGAMON

Phytochemistry 59 (2002) 845–849

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

Guaiane- and aristolane-type sesquiterpenoids of *Nardostachys chinensis* roots

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Received 4 April 2001; received in revised form 3 October 2001

Abstract

Two guaiane-type compounds, nardoguaianone J and K (**1** and **2**) and two aristolane-type compounds, kanshone F and G (**3** and **4**), were isolated from *Nardostachys chinensis* roots. The structures including the absolute configurations were elucidated by spectral means and by comparison of their CD spectra.

Keywords: *Nardostachys chinensis* Batalin; Valerianaceae; Sesquiterpenoid; Guaiane; Aristolane; Nardoguaianone J; Nardoguaianone K; Kanshone F; Kanshone G

1. Introduction

The roots of *Nardostachys chinensis* Batalin (Japanese crude drug name "Kanshoko"), a Valerianaceous plant, are used as a sedative and an analgesic in Oriental medicines. In previous work, guaiane, aristolane and nardosinane-type sesquiterpenoids were isolated from this plant (Bagchi et al., 1988a,b,c; Takaya et al., 1998, 2000a,b), and some of the compounds bearing an endoperoxide moiety showed antimalarial activity (Takaya et al., 1998, 2000b). Our continuous phytochemical investigation focusing on the sesquiterpenoids of the plant led to the isolation of four novel sesquiterpenoids named nardoguaianone J (**1**), K (**2**), kanshone F (**3**) and G (**4**), none of which had antimalarial properties.

2. Results and discussion

2.1. Structure of nardoguaianone J and K

Nardoguaianone J (**1**) has its molecular formula $C_{15}H_{22}O_2$ (HREI–MS: m/z 234.1623 $[M]^+$). Its ^{13}C NMR spectrum demonstrated the presence of four methyl carbons, three methylene carbons, two methine carbons, one oxygen-attached quaternary carbon, four olefinic carbons and one carbonyl carbon. Two of the olefinic carbons (δ 141.0 and 167.5) and carbonyl carbon (δ 210.2) showed characteristic chemical shifts for an α,β-unsaturated carbonyl group in a five-membered ring, and the UV absorption band at 295.5 nm indicated the presence of a dienone moiety in the molecule. Its ^1H–^1H COSY spectrum suggested three partial structures: (i) $–CH_2–CH_2–$, (ii) $–CH_2–CH(CH_3)–$ and (iii) $–CH(CH_3)_2$. The chemical bonds of C-2–C-3, C-4–C-5, C-7–C-8, C-7–C-11 and C-9–C-10–C-1 were unambiguously deduced by analysis of the HMBC spectrum (Fig. 1). The structure for nardoguaianone J (**1**) was thus determined to be 10-hydroxyguaia-1(5),6-dien-2-one.

The ^1H and ^{13}C NMR spectra of nardoguaianone K (**2**), which bears the same molecular formula as that of **1**, were very similar to those of **1**. In addition, HMBC spectrum of **2** exhibited the same cross peaks as those of **1**. These spectral features indicated that **2** is a stereoisomer of **1**.

Biogenetic consideration that all the guaianoids isolated from the plant bear a 4α-methyl group implies that **1** and **2** also have the *R*-configuration at C-4. The CD spectra of **1** and **2** resembled those of nardoguaianone H and I (**5** and **6**), respectively (Takaya et al., 2000a). The absolute configurations of **1** and **2** were therefore confirmed to be 4*R*,10*R* and 4*R*,10*S* (Fig. 2).

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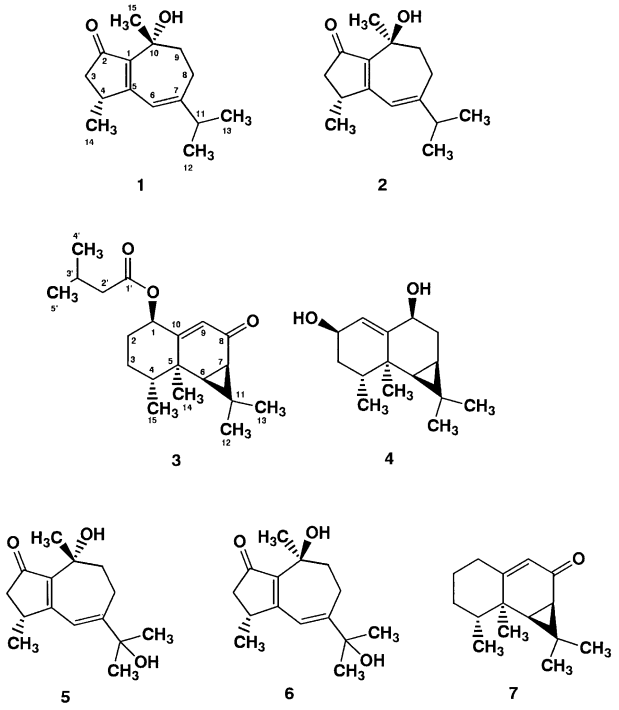
PII: S0031-9422(01)00469-1



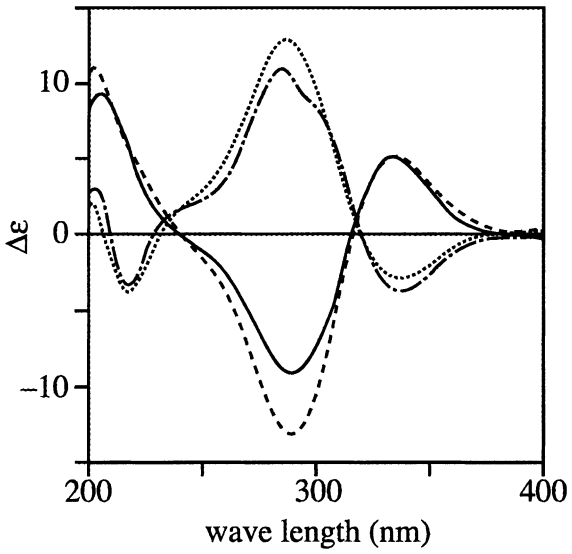


Fig. 2. CD spectra of nardoguaianone J (**1**), K (**2**), H (**5**) and I (**6**). **1** (—) **2** (— · —) **5** (– – – –) **6** (· · · · ·).

2.2. Structure of kanshone F

Kanshone F (**3**), $C_{20}H_{30}O_3$ (HREI–MS: *m*/*z* 319.2301 $[M+H]^+$), had six methyl carbons, three methylene carbons, four methine carbons, one oxygen-attached methine carbon, two quaternary carbons, two olefinic carbons and two carbonyl carbons in its ^{13}C NMR spectrum. Its ^1H–^1H COSY spectrum suggested three partial structures: (i) –CH–CH–, (ii) –O–CH–CH_2–CH_2–CH(CH_3)– and (iii) –CH_2–CH(CH_3)$_2$. The partial structure (iii) was expanded to an isovaleryloxy group on the basis of cross peaks of C-1′–H-3′, C-1′–H-2′ and C-1′–H-1 in the HMBC spectrum and a fragment ion peak at *m*/*z* 84 on EI–MS, and thus the partial structure (ii) was combined with this isovaleryloxy group. The chemical shift of the olefinic proton at δ 5.93 was assigned to the α-carbon of the α,β-unsaturated ketone. The HMBC spectrum showed cross-peaks of C-14–H-6, C-5–H-15, C-5–H-9, C-11–H-7, C-12–H-6, C-10–H-1, C-10–H-6, C-8–H-6 and C-9–H-7 (Fig. 3). These findings revealed this compound (**3**) to be an aristolane sesquiterpene with an enone moiety in its molecule as shown in Fig. 3. NOE's of H-1–H14, H-6–H-7, H-6–H-14, H-6–H-15 and H-7–H-15 clearly showed that these protons were oriented in the same direction. A comparative study of the Cotton effect of **3** [322.0 nm ($\Delta\varepsilon$ 0.13) and 251.4 nm ($\Delta\varepsilon$ −0.36)] with that of aristolone (**7**) (Krepinsky et al., 1970) deduced the absolute configuration of **3** to be 1*R*, 4*R*, 5*R*, 6*S*, 7*R* (Fig. 4).

2.3. Structure of kanshone G

HREI–MS of kanshone G (**4**) at *m*/*z* 236.1781 ($[M]^+$) indicated the molecular formula to be $C_{15}H_{24}O_2$. The ^1H–^1H COSY spectrum suggested two partial structures: (i) –CH(OH)–CH_2–CH–CH– and (ii) =CH–CH(OH)–CH_2–CH(CH_3)–. These structures along with HMBC spectrum demonstrated that **4** was also an aristolane-type compound as shown in Fig. 5. Relative configurations of **4** were determined with NOESY experiment. NOEs of H-3α–H-14, H-3α–H-15, H-6–H-14, H-7–H-14 and H-4–H-13 indicated that two methyl groups at C-4

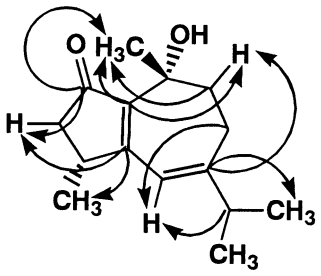


Fig. 1. HMBC signals of nardoguaianone J (**1**). The arrows indicate the correlations.

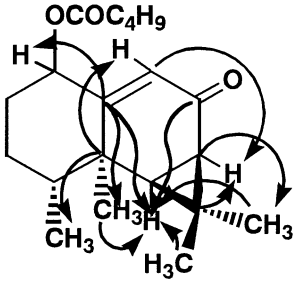


Fig. 3. HMBC signals of kanshone F (**3**). The arrows indicate the correlations.

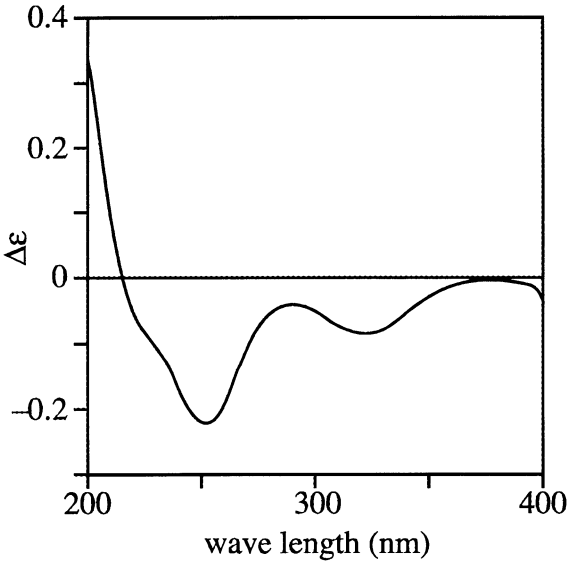


Fig. 4. CD spectrum of kanshone F (**3**).

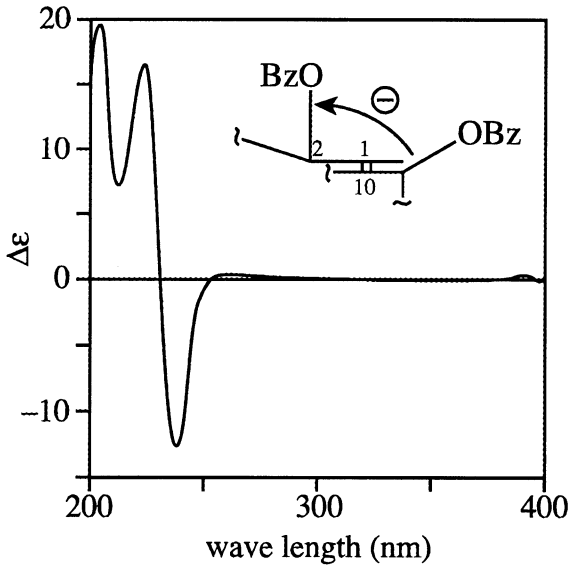


Fig. 6. CD spectrum of benzoylated kanshone G (**4a**).

and C-5 and the cyclopropane ring were directed to the opposite side. Furthermore, the NOE between H-9 and H-14 and the coupling constant between protons at H-2 and H-3 ($J_{\text{H-2–H-3}\alpha}=4.6$ Hz and $J_{\text{H-2-H-3}\beta}=1.5$ Hz) indicated that the two hydroxyl groups at C-2 and C-9 and the cyclopropane ring are in the same plane. The absolute structure of **4** was deduced with exciton chirality method using 2,9-di-*O*-benzoylated derivative (**4a**). **4a** showed a negative first Cotton effect at 237.8 nm ($\Delta\varepsilon$ −13.3) and a positive second Cotton effect at 222.8 nm ($\Delta\varepsilon$ +16.8). From this result, the absolute configuration was established to be 2*R*, 4*R*, 5*R*, 6*S*, 7*R* and 9*S* (Fig. 6).

The parent 1-epimeric alcohol corresponding to **3** was isolated from *Aristolochia debilis* and the 9-epimer of **4** was obtained by biotransformation of calarene (Rucker et al., 1984, Abraham et al., 1992). Recently, *ent*-aristolane-type sesquiterpenoids were isolated from mushroom and liverwort (Vidari et al., 1998; Toyota et al., 1999). It is of value to mention that the genus *Nardostachys* contains only the "normal type" of aristolane compounds.

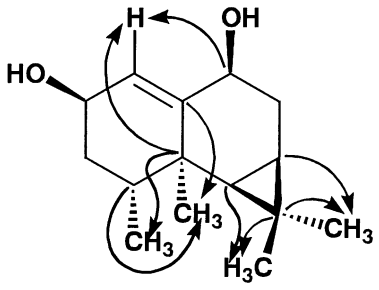


Fig. 5. HMBC signals of kanshone G (**4**). The arrows indicate the correlations.

2.4. Antimalarial activities of nardoguaianone J, K and kanshone F

Our previous papers showed that the endoperoxide moiety of the *N. chinensis* sesquiterpenoids has an important role in their antimalarial activities (Takaya et al., 1998, 2000b), while no data were reported concerning the antimalarial activities of the guaianoids bearing α,β,γ,δ-unsaturated carbonyl moiety and the aristolane-type sesquiterpenoids. Antimalarial activities of nardoguaianone J, K and kanshone F were thus examined. Unfortunately, they showed no promising activities in vitro against *Plasmodium falciparum* in the concentration of 4.0×10^{-5} M.

3. Experimental

3.1. General

UV and IR spectra were recorded on Hitachi U-3200 and JASCO FT/IR-5300 spectrometers, respectively. Optical rotations and CD spectra were measured with a JASCO DIP-370 polarimeter and a JASCO J-720 circular dichroism spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Jeol JNM GSX-500 (^{1}H: 500 MHz and ^{13}C: 125 MHz) and Varian Gemini 2000 (^{1}H: 300 MHz and ^{13}C: 75 MHz) spectrometers. ^{13}C multiplicities were determined by DEPT techniques. Solvents for NMR spectral measurements were $CDCl_3$ for **1**–**3** and methanol-d_4 for **4**. Chemical shifts for ^{1}H and ^{13}C NMR spectra are given in parts per million (δ) relative to tetramethylsilane (δ_H 0.00) and $CDCl_3$ (δ_C 77.1) or CD_3OD (δ_C 49.8) as internal standards, respectively. LR and HR EI–MS were obtained with Jeol JMS DX-303

and AX-500 mass spectrometers. Analytical TLC was performed on silica gel 60 F254 (Merck). Column chromatography was carried out on silica gel 60 (70–230 mesh, Merck) and Cosmosil 75C18-OPN (Nacalai Tesque, Kyoto). Preparative HPLC was performed using Tosoh TSKgel ODS-120A (2.54 cm i.d. × 30 cm).

3.2. Plant material

N. chinensis was collected in Sichuan Province, the People's Republic of China and identified by the late Professor H. Hikino (our University). The voucher specimen was deposited at the Graduate School of Pharmaceutical Sciences, Tohoku University.

3.3. Extraction and isolation

Dried roots (3 kg) of *N. chinensis* were extracted with MeOH (4 l×3) at room temperature. The MeOH solutions were combined and concentrated under reduced pressure to give the extract (345 g). The extract was suspended with H_2O (3 l) and extracted with EtOAc (3 l). The EtOAc extract was evaporated under reduced pressure giving a brown solid (214 g), which was subjected to silica gel column chromatography. The column was eluted with *n*-hexane, *n*-hexane–EtOAc (8:2, 6:4, 4:6, 2:8) and EtOAc (6 l each) to give fractions 1–11. Fraction 3 [*n*-hexane–EtOAc (8:2) eluate (17.5 g)] was subjected to silica gel column chromatography. The $CHCl_3$–MeOH (99:1)-eluting fraction (790 mg) was applied to a ODS column eluted with (CH_3CN–H_2O (4:6, 5:5, 6:4, 7:3) and CH_3CN, respectively; further preparative HPLC of the CH_3CN–H_2O (6:4)-eluting fraction (330 mg) (solvent: CH_3CN–H_2O (6:4); flow rate: 5 ml/min) gave nardoguaianone J (**1**), K (**2**) and kanshone F (**3**) (1.9, 10.4 and 5.6 mg, retention time: 68.4, 69.8 and 85.2 min, respectively).

Fraction 5 (*n*-hexane–EtOAc (6:4) eluate (8.3 g) of the chromatography of the EtOAc extract) was applied to silica gel and the column was eluted with $CHCl_3$–MeOH (97:3). The fraction (115 mg) was further purified by preparative HPLC (solvent: CH_3CN–H_2O (6:4); flow rate: 5 ml/min) to give kanshone G (**4**) (7.0 mg).

3.4. Nardoguaianone J ((4R, 10R)-10-hydroxyguaia-1(5),6-dien-2-one) (*1*)

Colorless oil, $[\alpha]_D^{26}$ −34.1° (MeOH; *c* 0.26). UV λ_{max}^{MeOH} nm (log ε): 295.5 (4.10). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1667, 1593. CD λ (MeOH) (nm ($\Delta\varepsilon$)) 333.0 (+5.01), 287.8 (−8.52). ^1H NMR spectral data (500 MHz, $CDCl_3$): δ 5.89 (1H, *s*, H-6), 4.93 (1H, *s*,−OH), 2.77 (1H, *d·quint*, *J* = 1.7, 6.9 Hz, H-4), 2.64 (1H, *dd*, *J* = 18.7, 6.9 Hz, H-3), 2.48 (1H, *sept*, *J* = 6.9 Hz, H-11), 2.38 (1H, *ddd*, *J* = 17.1, 7.9, 1.8 Hz, H-8), 2.30 (1H, *ddd*, *J* = 17.1, 10.4, 2.8 Hz, H-8), 2.02 (1H, *dd*, *J* = 18.7, 1.7 Hz, H-3), 1.98 (1H, *ddd*, *J* = 13.7, 10.4, 1.8 Hz, H-9), 1.76 (1H, *ddd*, *J* = 13.7, 7.9, 2.8 Hz, H-9), 1.43 (3H, *s*, H-15), 1.21 (3H, *d*, *J* = 6.9 Hz; H-14), 1.10 (6H, *d*, *J* = 6.9 Hz, H-12 and H-13). ^{13}C NMR spectral data (125 MHz, $CDCl_3$): δ 210.2 (*s*, C-2), 167.5 (*s*, C-5), 166.1 (*s*, C-7), 141.0 (*s*, C-1), 117.4 (*d*, C-6), 72.3 (*s*, C-10), 43.3 (*t*, C-3), 38.9 (*t*, C-9), 38.6 (*d*, C-11), 36.8 (*d*, C-4), 28.8 (*q*, C-15), 27.3 (*t*, C-8), 21.3 (*q*, C-12), 21.0 (*q*, C-13), 20.4 (*q*, C-14). HREI–MS: *m*/*z* 234.1623 $[M]^+$, $C_{15}H_{22}O_2$ requires 234.1618.

3.5. Nardoguaianone K ((4R,10S)-10-hydroxyguaia-1(5),6-dien-2-one) (*2*)

Colorless oil, $[\alpha]_D^{26}$ +210.3° (MeOH; *c* 0.53). UV λ_{max}^{MeOH} nm (log ε): 295 (3.21). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1667, 1595. CD λ (MeOH) (nm ($\Delta\varepsilon$)) 336.4 (−3.47), 284.4 (+11.2). ^1H NMR spectral data (500 MHz, $CDCl_3$): δ 5.86 (1H, *s*, H-6), 5.06 (1H, *s*, −OH), 2.79 (1H, *d·quint*, *J* = 1.4, 6.8 Hz, H-4), 2.65 (1H, *dd*, *J* = 18.8, 6.8 Hz, H-3), 2.47 (1H, *sept*, *J* = 6.9 Hz, H-11), 2.37 (2H, *m*, H-8), 2.03 (1H, *dd*, *J* = 18.8, 1.4 Hz, H-3), 2.01 (1H, *ddd*, *J* = 13.7, 10.4, 2.5 Hz, H-9), 1.75 (1H, *ddd*, *J* = 13.7, 6.4, 2.5 Hz, H-9), 1.41 (3H, *s*, H-15), 1.19 (3H, *d*, *J* = 6.9 Hz, H-14), 1.11 (6H, *d*, *J* = 6.9 Hz, H-12 and H-13). ^{13}C NMR spectral data (125 MHz, $CDCl_3$): δ 210.0 (*s*, C-2), 167.5 (*s*, C-5), 166.0 (*s*, C-7), 141.2 (*s*, C-1), 117.6 (*d*, C-6), 71.9 (*s*, C-10), 43.3 (*t*, C-3), 38.7 (*t*, C-9), 38.5 (*d*, C-11), 36.8 (*d*, C-4), 27.9 (*q*, C-15), 27.8 (*t*, C-8), 21.6 (*q*, C-12), 21.1 (*q*, C-13), 20.2 (*q*, C-14). HREI–MS: *m*/*z* 234.1617 $[M]^+$, $C_{15}H_{22}O_2$ requires 234.1618.

3.6. Kanshone F ((1R, 4R, 5S, 6S, 7R)-1-isovaleryl oxyaristol-9-en-8-one) (*3*)

Colorless oil, $[\alpha]_D^{27}$ −8.3° (MeOH; *c* 0.50). UV λ_{max}^{MeOH} nm (log ε): 240 (4.75). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 1730, 1643. CD λ (MeOH) (nm ($\Delta\varepsilon$)) 322.0 (−0.13), 251.4 (−0.36). ^1H NMR spectral data (500 MHz, $CDCl_3$): δ 5.93 (1H, *dd*, *J* = 2.2, 0.9 Hz, H-9), 5.55 (1H, *ddd*, *J* = 12.4, 5.5, 2.2 Hz, H-1), 2.25 (2H, *d*, *J* = 7.0 Hz, H-2′), 2.13 (1H, *m*, H-2), 2.13 (1H, *m*, H-3′), 1.88 (1H, *m*, H-4), 1.77 (1H, *dd*, *J* = 8.0, 0.9 Hz, H-7), 1.57 (1H, *dq*, *J* = 3.9, 12.4 Hz, H-3), 1.47 (1H, *dq*, *J* = 3.0, 12.4 Hz, H-3), 1.43 (1H, *dq*, *J* = 3.9, 12.4 Hz, H-2), 1.33 (1H, *d*, *J* = 8.0 Hz, H-6), 1.26 (3H, *s*, H-13), 1.24 (3H, *s*, H-14), 1.22 (3H, *s*, H-12), 1.09 (3H, *d*, *J* = 6.9 Hz, H-15), 0.98 (3H, *d*, *J* = 7.0 Hz, H-5′), 0.97 (3H, *d*, *J* = 7.0 Hz, H-4′). ^{13}C NMR spectral data (125 MHz, $CDCl_3$): δ 195.9 (*s*, C-8), 171.9 (*s*, C-1′), 163.0 (*s*, C-10), 120.8 (*d*, C-9), 70.1 (*d*, C-1), 43.4 (*t*, C-2′), 39.9 (*s*, C-5), 39.5 (*d*, C-6), 38.4 (*d*, C-4), 35.0 (*d*, C-7), 32.2 (*t*, C-2), 29.7 (*q*, C-12), 28.1 (*t*, C-3), 25.7 (*d*, C-3′), 24.4 (*s*, C-11), 23.2 (*q*, C-14), 22.4 (*q*, C-5′), 22.3 (*q*, C-4′), 16.6 (*q*, C-13), 15.9 (*t*, C-15). HREI–MS: *m*/*z* 319.2301 $[M+H]^+$, $C_{20}H_{31}O_3$ requires 319.2273.

3.7. Kanshone G ((2R, 4R, 5R, 6S, 7R, 9S)- 1(10)-aristolen-2,9-diol) (**4**)

Colorless amorphous solid, $[\alpha]_D^{31}$ +149.6° (EtOH; *c* 0.52). ^{1}H NMR spectral data (500 MHz, methanol-d_4): δ 5.76 (1H, *br. d*, *J* = 4.6 Hz, H-1), 4.29 (1H, *ddt*, *J* = 7.0, 11.9, 1.5 Hz, H-9), 4.15 (1H, *tt*, *J* = 1.5, 4.6 Hz, H-2), 2.35 (1H, *ddd*, *J* = 13.4, 9.2, 7.0 Hz, H-8α), 2.20 (1H, *ddq*, *J* = 14.3, 3.1, 7.0 Hz, H-4), 1.65 (1H, *dt*, *J* = 4.6, 14.3 Hz, H-3α), 1.56 (1H, *ddt*, *J* = 14.3, 3.1, 1.5 Hz, H-3β), 1.37 (1H, *ddd*, *J* = 13.4, 11.9, 4.0 Hz, H-8β), 1.10 (3H, *s*, H-14), 1.09 (3H, *s*, H-13), 1.04 (3H, *s*, H-12), 1.04 (3H, *d*, *J* = 7.0 Hz, H-15), 0.86 (1H, *dt*, *J* = 4.0, 9.2 Hz, H-7), 0.63 (1H, *d*, *J* = 9.2 Hz, H-6). ^{13}C NMR spectral data (125 MHz, methanol-d_4): δ 152.0 (*s*, C-10), 118.8 (*d*, C-1), 67.6 (*d*, C-9), 64.5 (*d*, C-2), 40.3 (*s*, C-5), 36.6 (*t*, C-3), 33.9 (*t*, C-6), 32.4 (*d*, C-4), 30.9 (*t*, C-8), 30.0 (*q*, C-12), 22.9 (*q*, C-14), 19.8 (*s*, C-11), 19.4 (*d*, C-7), 17.6 (*q*, C-13), 15.9 (*q*, C-15). HREI–MS: *m*/*z* 236.1781 $[M]^+$, $C_{15}H_{24}O_2$ requires 236.1777.

3.8. Benzoylation of kanshone G (**4**)

Kanshone G (**4**) (3.0 mg) was dissolved in dry pyridine (0.5 ml), to which was added benzoyl chloride (100 μl) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h, then poured into H_2O (3 ml) and extracted twice with EtOAc (3 ml). The organic layer was combined, washed with H_2O and brine, dried (anhydrous $MgSO_4$), and evaporated to dryness under reduced pressure. The residue was separated by silica gel column chromatography to give dibenzoylated kanshone G (**4a**) (4.1 mg). Colorless amorphous solid, CD λ (EtOH) (nm ($\Delta\varepsilon$)) 237.8 (−1.33), 222.8 (+1.68). ^{1}H NMR spectral data (500 MHz, $CDCl_3$): δ 5.78 (1H, *d*, *J* = 5.2 Hz, H-1), 5.73 (1H, *dd*, *J* = 13.1 7.0 Hz, H-9), 5.46 (1H, *dd*, *J* = 5.2, 2.6 Hz, H-2), 2.53 (1H, *ddd*, *J* = 13.1, 11.3, 7.0 Hz, H-8α), 2.32 (1H, *m*, H-4), 1.75 (1H, *d*, *J* = 2.6 Hz, H-3α), 1.56 (1H, *d*, *J* = 4.0 Hz, H-3β), 1.63 (1H, *dt*, *J* = 3.8 11.3 Hz, H-8β), 1.25 (3H, *s*, H-14), 1.24 (3H, *s*, H-13), 1.07 (3H, *s*, H-12), 1.06 (3H, *d*, *J* = 6.7 Hz, H-15), 0.95 (1H, *dt*, *J* = 3.8 9.2 Hz, H-7), 0.75 (1H, *d*, *J* = 9.2 Hz, H-6). HREI–MS: *m*/*z* 444.2312 $[M]^+$, $C_{29}H_{32}O_4$ requires 444.2300.

3.9. Antimalarial activity

Antimalarial activity of the compounds was measured by the method described in the paper (Takaya et al., 1999).

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