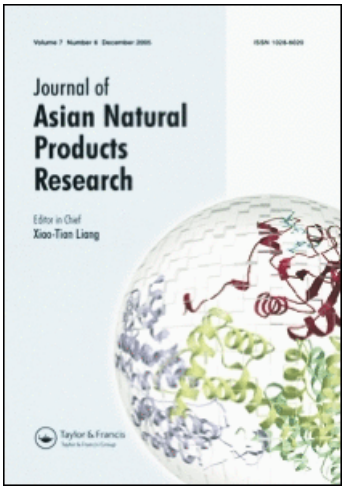

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CHEMICAL CONSTITUENTS OF *ISODON MELISSOIDES*

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Four new diterpenoids, melissoidesin E (**1**), F (**2**), G (**4**) and H (**5**), together with one known diterpenoid and two lignan glycosides, were isolated from aerial parts of *Isodon melissoides*. Their structures were established by spectral analysis and comparison with related compounds. The lignan glycosides (compounds **7** and **8**) were the first examples to be isolated from the genus *Isodon* plants.

Keywords: *Isodon melissoides*; Labiatae; *ent*-Kaurane diterpenoids; Melissoidesin E–H

INTRODUCTION

In the previous study of chemical constituents of *Isodon melissoides*, we have reported on the isolation of four new diterpenoids, melissoidesin A–D [1]. Further investigation on the chemical constituents of the same plant led to the isolation of four new diterpenoids (melissoidesin E–H), in addition to one known diterpenoid and two lignan glycosides. This paper describes the structure elucidiation of these compounds.

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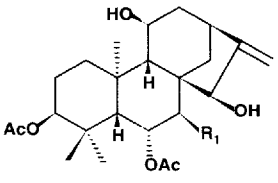
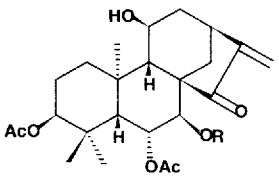
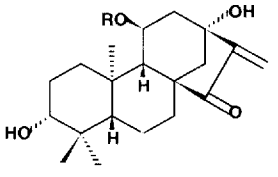


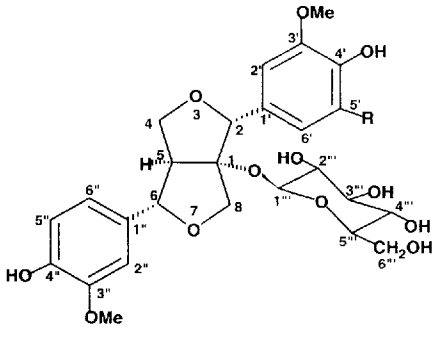
1 R_1=OH
2 R_1=H



3 R=Ac
4 R=H



5 R=H
6 R=Ac



7 R=H
8 R=OMe

RESULTS AND DISCUSSION

Melissoidesin E (**1**), has a molecular formula $C_{24}H_{36}O_7$ deduced from the MS and NMR spectrometry, and exhibited the signals of two acetoxyl groups, three methyl groups, five methylenes (including one exo-methylene group) and eight methines (including five oxygenated methines) in its ^1H and ^{13}CNMR spectra. Considering the structures of the compounds isolated so far from *Isodon* genus plants [2], melissoidesin E (**1**) was suggested to possess an *ent*-kaurene skeleton. This conclusion was verified by 2D NMR experiments (the principal results of COLOC experiment to be shown by the arrows in Fig. 1). According to the cross peaks in COLOC spectrum, two acetoxyl groups in **1** are obviously located at C-3 and C-6, respectively. Meanwhile, observation of signals from the ^{13}CNMR and DEPT spectra indicated that three hydroxyl groups should be located at C-7 (δ 77.3, d), C-11 (δ 65.1, d) and C-15 (δ 82.5, d), respectively. The β-orientation for OAc at C-3 based on the coupling constant of H-3α (δ 4.82, t, $J = 2.9$ Hz) as well as the upfield shift of C-18 (δ 28.1) due to the γ-steric compression effect between 3β-OAc and Me-18. On the other hand, the segment of H-7α

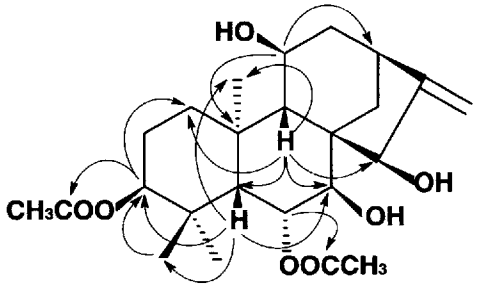


FIGURE 1 The $^{1}H-^{13}C$ long-range COSY of **1**.

(δ 3.82, d, $J=3.2$ Hz) → H-6β (δ 5.63, dd, $J=3.2$, 1.7 Hz) → H-5β (δ 2.60, br s) suggested by $^{1}H-^{1}H$ COSY spectrum revealed that the substituents at C-6 and C-7 should possess the orientation of C-6α and C-7β. The hydroxyl group at C-11 should be β-orientation due to the coupling constant of H-11 (δ 4.18, $J=4.4$ Hz). The configuration of 15β-OH was established according to the abnormal upfield shift of C-9 (δ 52.2) due to γ-steric compression between 15β-OH and C-9 [3]. Therefore, melissoidesin E (**1**) was elucidated as 3β, 6α-diacetoxy-7β, 11β, 15β-trihydroxy-*ent*-kaur-16-ene.

Melissoidesin F (**2**), $C_{24}H_{36}O_6$ ($[M]^+ m/z$ 420), showed the absence of the α, β-unsaturated ketonic group absorption in its UV and IR spectrum. The ^{1}H and ^{13}CNMR spectral data of **2** were similar to those of **1** except for the B-ring signals, which suggested that **2** possessed the same substitution pattern as **1** apart from ring B. The signal at δ 49.0 (t, C-7) indicated that there was no oxygenated substituent at C-7, which was confirmed by the downfield shift of C-5 from δ 42.2 (d) in **1** to δ 49.0 (d) in **2**. The signal at δ 70.3 (d, C-6) showed the existence of 6α-OAc, which was quite similar to the case of gesneroidin A [4]. Thus, melissoidesin F (**2**) should be 3β,6α-diacetoxy-11β, 15β-dihydroxy-*ent*-kaur-16-ene.

Compound (**3**), $C_{26}H_{36}O_8$ ($[M]^+$ m/z 476), was obtained as colorless crystals. Its IR, UV, MS, ^{1}H and ^{13}CNMR spectral data were identical with those of dawoensin A [5].

Melissoidesin G (**4**), $C_{24}H_{34}O_7$ ($[M]^+$ m/z 434), was isolated for the first time as a natural product from plants and its IR, UV, MS, ^{1}H and ^{13}CNMR spectral data were identical with those of the 3-acetyl derivative of xindongnin B [6–8].

Melissoidesin H (**5**), $C_{20}H_{30}O_4$ ($[M]^+$ m/z 334), differed from the known compound, isodopharicin A [9], only by the loss of one acetyl group. The upfield shift of C-11 signal from δ 69.1 (d) in isodopharicin A to δ 66.3 (d) in **5** revealed that the acetoxyl group at C-11 in isodopharicin A had been

replaced by a hydroxyl group in **5**. The coupling constants of the H-3 (δ 3.36, dd, $J=10.7, 4.1$ Hz) and H-11 (δ 4.48, d, $J=3.7$ Hz) clearly indicated that the two hydroxyl groups should possess α and β-orientation, respectively. Therefore, melissoidesin H (**5**) was determined as $3\alpha, 11\beta, 13\alpha$-trihydroxy-*ent*-kaur-16-en-15-one.

(+)-Hydroxypinorresinnol-1-β-D-glycoside (**7**), $C_{26}H_{32}O_{12}$ (FABMS $[M+H]^+$ m/z 537), was obtained as an amorphous powder from this plant. The IR, UV, FABMS, ^1H and ^{13}CNMR spectral data of **7** were identical with those reported previously [10,11]. It has been found in the bark of *Olea europaea* L. and the bark of *Olea africana* Mill. However, **7** was a compound to be isolated from the plants of genus *Isodon* for the first time.

(+)-Fraxiresinol-1-β-D-glycoside (**8**), $C_{27}H_{34}O_{13}$ (FABMS $[M+H]^+$ m/z 567), an amorphous powder, was identified by comparison of the IR, UV, FABMS, ^1H and ^{13}CNMR spectral data with those reported previously [10,11].

EXPERIMENTAL SECTION

General Experimental Procedures All mps were obtained on a Kofler apparatus and are uncorrected. IR spectral data were measured on a Perkin–Elmer 577 spectrometer as KBr pellets. NMR spectra were recorded on a Bruker AM-400 instrument with TMS as internal standard and pyridine-d_5 as solvent. ^{1}HNMR and $^1H-^1H$ COSY spectra were recorded at 400.13 MHz; ^{13}CNMR and DEPT spectra were recorded at 100.6 MHz. ^{13}CNMR assignments were determined by $^{13}C-^1H$ COSY and COLOC spectra. The EIMS data were obtained on a VG Autospec-3000 Spectrometer.

Plant Material Plant material was collected in Dali county, Yunnan province, China, in Sept. 1993, and identified as *I. melissoides* (Benth.) Hara by Prof. Xi-Wen Li. A voucher specimen is deposited in the herbarium of the Department of Taxonomy, Kunming Institute of Botany.

Extraction and Isolation Dried aerial parts (5.9 kg) of *I. melissoides* were extracted with ethanol (20 l × 3) under reflux. The combined EtOH extract was concentrated *in vacuo* to give a residue (500 g) which was dissolved in 90% EtOH (2000 ml) and the solution was partitioned with petroleum ether. The 90% EtOH layer was concentrated *in vacuo*. The residue was suspended in water (2000 ml) and the suspension was extracted with EtOAc (1000 ml × 3). After being washed with H_2O, the EtOAc extract was evaporated *in vacuo* to give a residue (200 g) which was chromatographed over

silica gel column chromatography (200–300 mesh, 1.5 kg). The column was eluted with $CHCl_3$, $CHCl_3$–Me_2CO (9.5:0.5, 9:1, 8:2, 7:3, 6:4) and Me_2CO. The elutes were collected as 500 ml fractions. All components were further purified by column chromatography (including column chromatography on Sephadex LH-20, RP-8, RP-18, MCI CHP-20 gel) and recrystallization, yielding compound **1** (200 mg), **2** (170 mg), **3** (120 mg), **4** (1.08 g), **5** (80 mg), **7** (300 mg), **8** (120 mg).

Melissoidesin E (**1**) $C_{24}H_{36}O_7$, an amorphous powder, $[\alpha]_D^{22}$: +19.3 ($CHCl_3$, $c=0.46$); UV (MeOH) end absorption; IR (KBr) ν_{max}: 3480, 2910, 1725, 1372, 1235, 1025 cm^{-1}; ^{1}HNMR (pyridine-d_5) δ: 1.70 (1H, m, H-1β), 2.00 (1H, overlapped, H-1α), 2.05 (1H, m, H-2α), 1.69 (1H, m, H-2β), 4.82 (1H, t, $J=2.9$ Hz, H-3α), 2.60 (1H, br s, H-5β), 5.63 (1H, dd, $J=$ 3.2, 1.7 Hz, H-6β), 3.82 (1H, d, $J=3.2$ Hz, H-7α), 4.18 (1H, d, $J=4.4$ Hz, H-11α), 2.16 (1H, m, H-12α), 2.08 (1H, m, H-12β), 2.64 (1H, br s, H-13α), 2.60 (1H, d, $J=12.1$ Hz, H-14α), 4.54 (1H, br s, H-15), 5.63 (1H, br s, H-17a), 5.20 (1H, br s, H-17b), 1.05 (1H, m, H-14β), 1.03 (3H, s, Me-18), 1.05 (3H, s, Me-19), 1.32 (3H, s, Me-20), 2.07, 1.94 (each 3H, s, 2 × Ac); ^{13}CNMR (DEPT) see Table I. EIMS *m/z* (rel. int.): 436[M]$^+$(10), 358 [M–AcOH–H_2O]$^+$(27), 340[M–HOAc–2 × H_2O]$^+$(20), 298[M-2 × AcOH–H_2O]$^+$(35), 283[M-2 × AcOH–Me–H_2O]$^+$(100), 265[M–Me-2 × HOAc-2 × H_2O]$^+$(65).

Melissoidesin F (**2**) $C_{24}H_{36}O_6$, an amorphous powder, $[\alpha]_D^{22}$: +17.7 ($CHCl_3$, $c=0.47$); UV (MeOH) λ_{max}: end absorption; IR (KBr) ν_{max}: 3440, 2910, 1725, 1365, 1230, 1030 cm^{-1}; ^{1}HNMR (pyridine-d_5) δ: 4.56 (1H, t, $J=3.0$ Hz, H-3α), 5.07 (1H, m, H-6β), 4.20 (1H, br d, $J=4.0$ Hz, H-11α), 2.60 (1H, br s, H-13α), 2.17 (1H, d, $J=12.3$ Hz, H-14α), 0.96 (3H, s, Me-18), 1.02 (3H, s, Me-19), 1.42 (3H, s, Me-20), 2.03, 1.94 (each 3H, s, 2 × Ac); ^{13}CNMR (DEPT) see Table I. EIMS *m/z* (rel. int.): 420[M]$^+$(8), 402 [M–H_2O]$^+$(13), 342[M–AcOH–H_2O]$^+$(50), 282[M-2 × AcOH–H_2O]$^+$(38), 267[M-2 × AcOH–Me–H_2O]$^+$(100).

Dawoensin A (**3**) $C_{26}H_{36}O_8$, an amorphous powder, $[\alpha]_D^{22}$: −49.6 (MeOH, $c=0.56$); UV (MeOH) λ_{max} (log ε): 239 (3.78) nm; IR (KBr) ν_{max}: 3475, 1730, 1650, 1375, 1249, 1030 cm^{-1}; ^{1}HNMR (pyridine-d_5) δ: 4.76 (1H, t, $J=$ 3.2 Hz, H-3α), 5.39 (1H, dd, $J=3.5$, 1.6 Hz, H-6β), 5.53 (1H, d, $J=$ 3.5 Hz, H-7α), 4.34 (1H, br d, $J=4.0$ Hz, H-11α), 3.00 (1H, br s, H-13α), 2.70 (1H, d, $J=12.0$ Hz, H-14α), 0.98 (3H, s, Me-18), 1.00 (3H, s, Me-19), 1.40 (3H, s, Me-20), 2.01, 1.95 (each 3H, s, 2 × Ac); ^{13}CNMR (DEPT) see Table I. EIMS *m/z* (rel. int.): 476[M]$^+$(5), 416[M–AcOH]$^+$(5), 374[M–AcOH–$COCH_2$]$^+$(52), 356[M-2 × AcOH]$^+$(30), 341[M-2 × HOAc–Me]$^+$(25), 314[M-2 × AcOH– $COCH_2$]$^+$(100).

TABLE I ^{13}CNMR (DEPT) data of compounds **1–5** (pyridine-d_5)

C	**1**	**2**	**3**	**4**	**5**	**6***
1	43.2t	42.8t	41.0t	41.2t	34.2t	32.8t
2	23.2t	22.7t	22.8t	23.6t	28.0t	26.9t
3	78.7d	78.6d	78.4d	78.3d	77.9d	78.3d
4	37.7s	37.4s	38.3s	38.1s	38.3s	38.5s
5	42.2d	49.0d	43.7d	41.9d	55.0d	54.2d
6	73.5d	70.3d	70.4d	71.4d	18.9t	18.2t
7	77.3d	49.0t	71.6d	72.9d	39.5t	37.8t
8	46.3s	54.1s	48.6s	49.5s	53.4s	53.1s
9	52.2d	54.1d	59.4d	58.6d	63.3d	58.7d
10	37.2s	37.3s	37.1s	37.3s	38.7s	38.9s
11	65.1d	66.3d	64.9d	65.8d	66.3d	69.1d
12	36.3t	36.4t	35.8t	35.5t	50.0t	44.7t
13	40.4d	39.3d	37.5d	37.7d	75.5s	75.2s
14	34.7t	35.8t	35.6t	34.8t	45.9t	45.4t
15	82.5d	82.5d	205.0s	213.1s	208.2s	207.0s
16	156.7s	157.0s	151.3s	149.6s	155.2s	152.1s
17	106.3t	106.2t	111.1t	113.9t	111.3t	113.5t
18	28.1q	28.0q	28.1q	27.9q	28.9q	28.3q
19	23.8q	23.0q	23.3q	23.5q	17.9q	17.8q
20	19.1q	18.6q	19.3q	19.3q	16.4q	15.5q
Ac	170.2s	170.6s	170.0s	170.6s		
	170.1s	170.1s	169.6s	169.3s		
	21.2q	21.7q	169.5s	21.6q		
	21.0q	21.2q	21.3q	21.4q		
			21.2q			
			21.0q			

*The data were obtained in $CDCl_3$ [9].

Melissoidesin G (**4**) $C_{24}H_{34}O_7$, an amorphous powder, $[\alpha]_D^{22}$: −35.3 ($CHCl_3$, $c = 0.52$); UV (MeOH) λ_{max} (log ε): 242.5 (3.84) nm; IR (KBr) ν_{max}: 3485, 1700, 1650, 1375, 1250, 1030 cm^{-1}; ^{1}HNMR (pyridine-d_5) δ: 4.59 (1H, t, $J = 3.2$ Hz, H-3α), 5.20 (1H, dd, $J = 3.4, 1.8$ Hz, H-6β), 3.77 (1H, d, $J = 3.4$ Hz, H-7α), 4.12 (1H, br d, $J = 4.2$ Hz, H-11α), 3.05 (1H, br s, H-13α), 2.57 (1H, d, $J = 12.3$ Hz, H-14α), 0.93 (3H, s, Me-18), 0.99 (3H, s, Me-19), 1.30 (3H, s, Me-20), 2.01, 1.99 (each 3H, s, 2 × Ac) ; ^{13}CNMR (DEPT) see Table I. EIMS *m/z* (rel. int.): 434[M]$^+$(3), 374[M−AcOH]$^+$(8), 314[M-2 × AcOH]$^+$(92), 299[M-2 × AcOH−Me]$^+$(100).

Melissoidesin H (**5**) $C_{20}H_{30}O_4$, an amorphous powder, $[\alpha]_D^{22}$: −133.9 (MeOH, $c = 0.41$); UV (MeOH) λ_{max} (log ε): 240 (3.32) nm; IR (KBr) ν_{max}: 3450, 2910, 1710, 1650, 1430, 1070 cm^{-1}; ^{1}HNMR (pyridine-d_5) δ: 3.36 (1H, dd, $J = 10.7, 4.1$ Hz, H-3β), 4.48 (1H, br d, $J = 3.7$ Hz, H-11α), 3.69 (1H, d, $J = 11.2$ Hz, H-14α), 1.00 (3H, s, Me-18), 1.05 (3H, s, Me-19), 1.17 (3H, s, Me-20); ^{13}CNMR (DEPT) see Table I. EIMS *m/z* (rel. int.): 334[M]$^+$(12), 316[M−H_2O]$^+$(25), 298[M-2 × H_2O]$^+$(50), 283[M-2 × H_2O−Me]$^+$(100).

TABLE II ^{13}CNMR data of compounds **7–8** (pyridine-d_5)

C	7	8
1	98.7s	98.7s
2	88.3d	88.3d
4	70.9t	71.0t
5	60.0d	60.0d
6	87.4d	87.5d
8	74.6t	74.5t
1′, 1″	128.5, 132.6 (s)	127.4, 132.6 (s)
2′, 2″	114.3, 111.0 (d)	107.9, 111.1 (d)
3′, 3″	148.2, 149.1 (s)	148.7, 149.2 (s)
4′, 4″	148.0, 148.1 (s)	137.5, 148.1 (s)
5′, 5″	115.7, 116.5 (d)	148.7 s, 116.5 d
6′, 6″	122.2, 120.1 (d)	107.9, 120.1 (d)
OMe	56.2, 56.0 (q)	56.6, 56.6, 56.2 (q)
1‴	100.4d	100.4d
2‴	75.0d	75.1d
3‴	79.0d	79.0d
4‴	71.1d	71.7d
5‴	78.6d	78.6d
6‴	62.8t	62.9t

(+)-*1-Hydroxypinoresinol-1-β-D-glucoside* (**6**) $C_{26}H_{32}O_{12}$, an amorphous powder, $[\alpha]_D^{22}$: −17.1 (MeOH, $c=0.50$); UV (MeOH) λ_{max}: 245, 290 nm; IR (KBr) ν_{max}: 3400, 1610, 1520 cm^{-1}; ^{1}HNMR (pyridine-d_5) δ: 5.39 (1H, d, $J=7.8$ Hz, H-1‴α), 5.14 (1H, s, H-2), 3.45–4.20 (2H, m, H-4), 3.00–3.32 (1H, m, H-5), 5.03 (1H, d, $J=5.8$ Hz, H-6), 5.18 (1H, AB d, $J=10.2$ Hz, H-8), 4.43 (1H, AB d, $J=10.2$ Hz, H-8), 7.18–7.61 (6H, m, arom. H), 3.69 (3H, s, OMe), 3.80 (3H, s, OMe); ^{13}CNMR (DEPT) see Table II. FABMS m/z 537[M+H]$^+$.

(+)-*Fraxiresinol-1-β-D-glucoside* (**7**) $C_{27}H_{34}O_{13}$, an amorphous powder, $[\alpha]_D^{22}$: −12.5 (MeOH, $c=0.50$); UV (MeOH) λ_{max}: 250, 285 nm; IR (KBr) ν_{max}: 3400, 1610, 1515 cm^{-1}; ^{1}HNMR (pyridine-d_5) δ: 5.39 (1H, d, $J=$ 7.7 Hz, H-1‴α), 5.16 (1H, s, H-2), 3.50–4.21 (2H, m, H-4), 3.10–3.2 (1H, m, H-5), 5.06 (1H, d, $J=6.4$ Hz, H-6), 5.20 (1H, AB d, $J=10.2$ Hz, H-8), 4.44 (1H, AB d, $J=10.2$ Hz, H-8), 7.20–7.57 (5H, m, arom. H), 3.73 (3H, s, OMe), 3.73 (3H, s, OMe), 3.94 (3H, s, OMe); ^{13}CNMR (DEPT) see Table II. FABMS m/z: 567[M+H]$^+$.

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