Pergamon

Tetrahedron 58 (2002) 6691–6695

TETRAHEDRON

Three new apo-tirucallols with six-membered hemiacetal from Meliaceae

Xiao-Dong Luo,* Shao-Hua Wu, Da-Gang Wu, Yun-Bao Ma and Shu-Hua Qi

State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, The Chinese Academy of Sciences, 650204 Kunming, Yunnan, People's Republic of China

Received 21 March 2002; revised 23 May 2002; accepted 20 June 2002

Abstract—Three new apo-tirucallols, 1α,7α-diacetoxyl-17α-20*S*-21,24-epoxy-apotirucall-14-ene-3α,23*R*,24*S*,25-tetraol (**1**), 7α-acetoxyl-17α-20*S*-21,24-epoxy-apotirucall-14-ene-3α,23*R*,24*S*,25-tetraol (**2**), 7α-acetoxyl-17α-20*S*-21,24-epoxy-apotirucall-14-en-3-one-23*R*,24*S*,25-triol (**3**) were obtained from the plants of the family Meliaceae. Their configurations were elucidated on the basis of extensive 1D and 2D NMR techniques in CD_3OD solution. The equilibrium of the six-membered ring hemiacetal at side chain is also discussed. Finally, the stereochemistry of compound **1** was demonstrated by X-ray crystallography.

1. Introduction

Apo-tirucallane derivatives are always isolated together with teranortriterpenoids from the family Meliaceae, and both of them have been considered to be chemotaxonomic markers.[1] Usually, the side chains of apo-tirucallane derivatives are long chains or cyclize to form five-membered rings.[2–8] The basic tetranortriterpenoid skeleton is bio-synthesized form apo-tirucallane with a five-membered ring, and the 17β-furan ring is formed by the loss of four carbons from the side chain.[9] However, the hemiacetal side chain at C-17 depicted in these three compounds is not common and was first reported in spicatin, a prolimonoid obtained from *Entandrophragma spicatum*.[10] Since then, only two others has been published,[11,12] of which meliavolin[11] was analysed as Mosher ester derivative and by X-ray crystallographic analysis of meliavolin diacetate. In this paper, we deal with the isolation and elucidation of three analogues from Meliaceae. Their structures were elucidated on the basis of 1D and 2D NMR experiments, and stereochemistry of compound **1** was supported by X-ray crystallography. Compound **1** was isolated from the seed kernel of *Azadirachta indica*, and compounds **2** and **3** were obtained from the bark of *Dysoxylum hainanensis*.

2. Results and discussion

Three compounds showed similar ^1H and ^{13}C NMR spectra and an interesting phenomenon was observed in each. The signals appeared as mixtures in their ^1H and ^{13}C NMR spectra, in the proportion of 5:2, when they were measured in $CDCl_3$ solution, but appeared almost pure, when they were measured in CD_3OD. This finding suggested that an equilibrium system might exist in solution. Inspection of the 1D and 2D NMR spectra of three compounds in CD_3OD, the same six-membered ring hemiacetals were indicated, and the following equilibrium system was proposed (Fig. 1). **I** is more stable than **II** because the 2-hydroxyisopropyl attached to C-24 is a larger substituent than hydroxyl. To avoid steric hindrance from 21-Ha and 22-Ha, 2-hydroxyisopropyl is equatorial and the hydroxyl at axial.

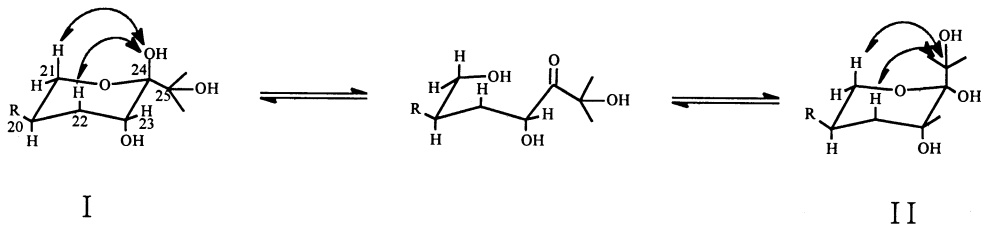


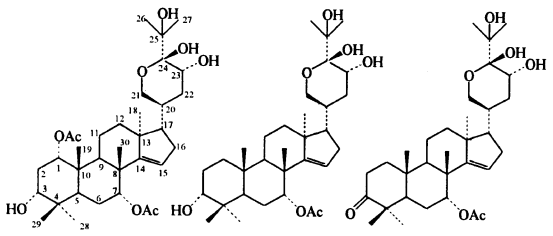
Figure 1. Equilibrium system of the side chain in three compounds.

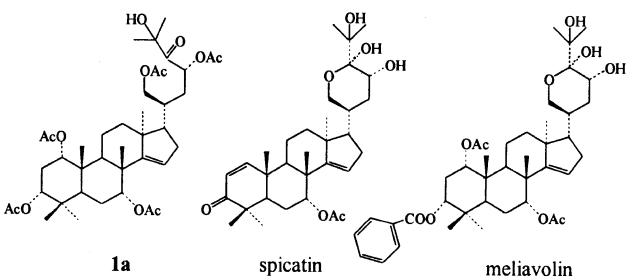
Keywords: *Azadirachta indica*; *Dysoxylum hainanensis*; Meliaceae; apo-tirucallols; X-ray analysis.

* Corresponding author. Tel.: +86-871-5223421; fax: +86-871-5150227; e-mail: x_dluo@hotmail.com

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00679-8

Compound **1** was found to possess a molecular formula of $C_{34}H_{54}O_9$ as determined by negative-ion HRFABMS, which was confirmed from the ^{13}C and DEPT NMR spectra. Its IR spectrum revealed absorption bands for hydroxyls (3491 and 3422 cm^{-1}), carbonyl groups (1728 and 1711 cm^{-1}), and a double bond (1637 cm^{-1}). The ^1H and ^{13}C NMR spectra showed the presence of seven tertiary methyls, seven methylenes, one of which was oxygenated, eight methines, four of which were oxygenated, one trisubstituted double bond and two acetates. The ^{13}C NMR spectrum of **1** also showed four quaternary carbon signals, one hydroxytertiary carbon signal and one hemiacetal carbon signal. These data suggested that **1** belonged to an apo-tirucallol (euphol) skeleton.





Three oxymethine protons at δ_H 4.63 (t, J=2.8 Hz), 3.39 (t, J=2.8 Hz) and 5.11 (brs) were placed at the C-1, C-3 and C-7 positions by the COLOC spectrum, with cross peaks between C-1 to H-19, C-3 to H-28, H-29 and C-7 to H-30 (Table 3). Small or undetectable coupling constants of three protons suggested substitution at C-1, C-3 and C-7 all possessed α orientation, which was confirmed by the NOESY spectrum of **1**. C-1 and C-7 were assumed to be acetylated from the chemical shift values of H-1 (δ_H 4.63) and H-7 (δ_H 5.11). The assumption was supported by the cross signal between δ_C 172.2 (s) to H-1 (δ_H 4.63) and δ_C 172.4 to H-7 (δ_H 5.11) in the COLOC spectrum. The chemical shift values of C-14 (δ_C 161.0) and C-15 (δ_C 120.1) suggested a double bond between C-14 and C-15,[2–6] which was supported by cross peaks between C-14 to H-18 and C-15 to H-16 in the COLOC spectrum. All data suggested that **1** is 1α,7α-diacetoxy-3α-hydroxy-apoeuphol (tirucallol)-14-ene with a 17α side chain.

In the COLOC spectrum, cross signals between the oxymethylene protons (δ_H 3.78 and 3.56 (H-21)) and a hemiacetal carbon (δ_C 96.4 (C-24)), indicated that there is an ether bridge across the oxymethylene and hemiacetal. Two methyl group protons H-26 (δ_H 1.31 (s)) and H-27 (δ_H 1.21 (s)) also showed cross peaks to the hemiacetal carbon (C-24) in the COLOC spectrum, and this suggested that the 2-hydroxyisopropyl group (C-25, C-26, C-27) is connected to the hemiacetal. In addition, acetylation of **1** afforded **1a**, which showed the presence of three new acetate groups and a downfield shift of H-21 in its ^1H NMR spectrum. Its ^{13}C NMR spectrum lacked the hemiacetal carbon and displayed instead a carbonyl at δ_C 211.3. A downfield shift for C-23 to δ_C 73.5 was also observed. These data indicated the cleavage of side chain by the acetylation, which supported the presence of the equilibrium system (Fig. 1). Thus, the side chain was determined as 21,24-epoxy-23,24,25-triol.

The oxymethylene protons at δ_H 3.56 and 3.78 (H-21) showed a large coupling constant (J=11.2 Hz) and a small coupling constant (J=3.6 Hz), respectively, which revealed axial orientations for H-20 and H-21a. NOE interactions between δ_H 3.78 (1H, dd, J=11.2, 3.6 Hz, H-21α) with 1.12 (3H, s, H-18), and δ_H 3.56 (1H, dd, J=11.2, 11.2 Hz, H-21β) with 1.35 (1H, m, H-17) in the NOESY spectrum, indicated that **1** prefer C-20*S* configuration to C-20*R* configuration at side chain by a molecular model. In other words, **1** was an apo-tirucallol. The hydroxyl at C-23 was placed axially since H-23 appeared as triplet with a small J (δ_H 3.86 (t, J=3.1 Hz)). So the structure of **1** was determined as 1α,7α-diacetoxyl-17α-20*S*-21,24-epoxy-apotirucall-14-ene-3α,23*R*,24*S*,25-tetraol.

Fortunately, compound **1** was obtained as a prismatic crystal from CH_3OH-H_2O, and was subjected to X-ray diffraction. It is interesting that only the stable configuration was present in crystal, rather than a pair of anomers. Finally, the stable structure of **1** was demonstrated unambiguously by X-ray crystallographic analysis, which confirmed its proposed configuration, the results of which are shown in Fig. 2.

The molecular formula of **2** was determined as $C_{32}H_{52}O_7$ by negative-ion HRFABMS. The ^1H and ^{13}C NMR of **2** were very similar to those of **1**, except for one acetoxyl group less. The acetoxyl group was absent at C-1 in **2**, as determined by the HMBC spectrum, with cross signals between δ_H 5.10 (brs, H-7) and δ_C 43.5 (s, C-8), and δ_C 172.3 (s, OAc). The other moieties of **2** were identical to those of **1**, as supported by its ^1H, ^{13}C NMR, $^1H-^1H$ COSY,

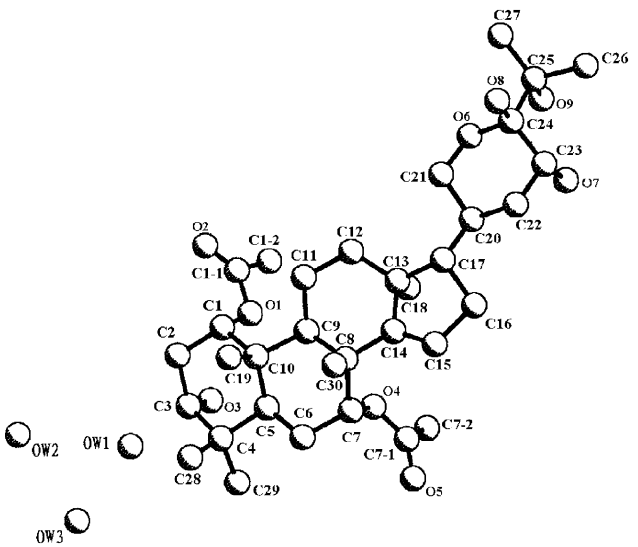


Figure 2. The crystal structure of compound **1**.

HMQC, HMBC, and NOESY spectra. Thus, **2** was elucidated as 7α-acetoxyl-17α-20*S*-21,24-epoxy-apotirucall-14-ene-3α,23*R*,24*S*,25-tetraol.

Compound **3** possessed a molecular formula $C_{32}H_{50}O_7$ as determined by negative-ion HRFABMS, which revealed that the molecular formula of **3** comprised two hydrogens less than that of **2**. Comparison of ^1H and ^{13}C NMR spectra of **3** with those of **2** indicated that instead of three oxymethine groups in **2**, two oxymethine groups and a ketone were presented in **3**. The ketone carbonyl was attributed to the C-3, since chemical shift values of C-4 and C-5 shifted downfield significantly in the ^{13}C NMR of **3**. The assignment was further confirmed by cross peaks between two methyl protons δ_H 1.04 (3H, s, H-29) and 1.09 (3H, s, H-28) to δ_C 219.2 (s, C-3) in the HMBC spectrum. Therefore, **3** was determined to be 7α-acetoxyl-17α-20*S*-21,24-epoxy-apotirucall-14-en-3-one-23*R*,24*S*,25-triol.

3. Experimental

3.1. General procedure

Melting points were obtained on an XRC-1 micromelting apparatus and are uncorrected. Optical rotations were taken with a Horiba SEAP-300 spectropolarimeter. IR spectra (KBr) were obtained on a Bio-Rad FTS-135 infrared spectrophotometer. ^1H, ^{13}C NMR and 2D NMR spectra were recorded on a Bruker AM-400 and a DRX-500 NMR spectrometer with TMS as internal standard. MS data were obtained on a VG Autospec-3000 spectrometer, at 70 eV for EI. Si gel (200–300 mesh) for column chromatography and GF_{254} for TLC were obtained from the Qindao Marine Chemical Factory, Qindao, People's Republic of China.

3.2. Plant material

Seeds of *A. indica* were collected in Mandalay, Myanmar in August 1994, where the plant is cultivated. The plant material was identified by Professor Tianlu Ming, Kunming Institute of Botany, Acedemia Sinica, Kunming, Yunnan, People's Republic of China. The bark of *D. hainanense* Merr. was collected from Xishuangbanna, Yunnan province, People's Republic of China, in December 1996. The plant was identified by Professor G.-D. Tao, Xishuangbanna Botany Garden, Academia Sinica. A voucher specimen (No. 7188) was deposited in the herbarium of Taxonomy Department, Kunming Institute of Botany, Academia Sinica, Kunming, People's Republic of China.

3.3. Extraction and isolation

The dehulled and air-dried neem seed kernels (1.3 kg) were extracted with petroleum ether three times at room temperature, then the defatted kernels were extracted with methanol six times at room temperature. The combined extracts were evaporated in vacuo. The residue was suspended in H_2O, and then extracted with petroleum

Table 1. ^{13}C NMR spectral data of compounds **1**–**3**

C	1	2	3	1a
1	75.1 d	36.5 t	39.9 t	72.5 d
2	29.1 t	26.2 t	36.8 t	25.6 t
3	76.0 d	76.7 d	219.2 s	76.7 d
4	37.9 s	38.0 s	48.0 s	36.0 s
5	37.4 d	44.7 d	49.4 d	37.2 d
6	24.1 t	24.2 t	25.3 t	22.9 t
7	77.2 d	77.6 d	76.9 d	76.2 d
8	43.3 s	43.5 s	43.2 s	42.2 s
9	36.7 d	43.0 d	44.2 d	35.3 d
10	41.4 s	38.6 s	38.2 s	40.2 s
11	17.2 t	17.6 t	17.8 t	16.1 t
12	36.2 t	34.9 t	34.9 t	34.8 t
13	47.7 s	47.9 s	47.9 s	46.6 s
14	161.0 s	161.6 s	160.9 s	159.5 s
15	120.1 d	119.3 d	119.9 d	119.2 d
16	34.2 t	33.9 t	34.3 t	34.3 t
17	58.5 d	58.6 d	58.7 d	55.4 d
18	20.5 q	19.7 q	20.0 q	20.5 q
19	16.6 q	16.0 q	15.6 q	15.9 q
20	30.9 d	31.0 d	31.0 d	36.6 d
21	66.2 t	66.3 t	66.3 t	65.6 t
22	34.8 t	33.9 t	34.9 t	31.3 t
23	69.0 d	69.1 d	69.1 d	73.5 d
24	96.4 s	96.4 s	96.4 s	211.3 s
25	77.3 s	77.4 s	77.4 s	77.0 s
26	25.3 q	25.2 q	25.3 q	27.1 q
27	23.5 q	23.5 q	23.5 q	27.4 q
28	28.6 q	28.7 q	26.5 q	27.4 q
29	22.6 q	22.5 q	21.5 q	21.2 q
30	27.6 q	28.0 q	27.4 q	27.7 q
CH_3COO	21.7, 21.3 q	21.3 q	21.2 q	22.9, 21.7, 21.7, 20.9, 20.5 q
CH_3*C*OO	172.4, 172.2 s	172.3 s	171.9 s	171.0, 170.7, 170.2, 169.9, 169.8 s

Compounds **1** and **1a** were measured on a Bruker AM-400, while **2** and **3** on a DRX-500 spectrometer with TMS as internal standard; **1**–**3** were measured in CD_3OD, while **1a** in $CDCl_3$; chemical shifts are in ppm.

ether, EtOAc, and *n*-BuOH, respectively. The EtOAc layer was concentrated in vacuo to give 32 g of residue. The EtOAc extract was repeatedly chromatographed over silica gel. The column was eluted with $CHCl_3$–Me_2CO (9:1–3:1) to give 30 fractions. Fraction 22 was purified on reversed-phase C_{18} silica gel columns using CH_3OH–H_2O (3:2) as eluent to yield **1** (44 mg). Dried and powdered bark (4.2 kg) of *D. hainanense* was extracted with EtOH under reflux three times, the solvent was evaporated in vacuo, and the residue was suspended in H_2O and partitioned with EtOAc. The EtOAc layer was concentrated in vacuo to give 72 g of residue, which was subjected to column chromatography (silica gel), using $CHCl_3$–Me_2CO (from $CHCl_3$ to $CHCl_3$–Me_2CO 1:1) as eluent. Combined the fractions with TLC monitoring. Then, fraction 7 was further purified on silica gel CC to afford **2** (59 mg) and **3** (48 mg).

3.3.1. Compound 1. Colorless prisms (MeOH and H_2O); mp 146–148°C; $[\alpha]_D^{23}=-61.4$ (*c* 3.15, MeOH); IR (KBr) ν_{max} 3491, 3422, 1728, 1711, 1637, 1461, 1375, 1266, 1046 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; EIMS *m/z* 588 $[M-H_2O]^+$ (13), 570 (20), 530 (12), 486 (67), 468 (43), 453 (15), 430 (35), 409 (100), 379 (54), 349 (26), 311 (22), 293 (55), 277 (23), 199 (23), 185 (30), 145 (46), 133 (42), 105 (53), 81 (47), 59 (77); HRFABMS *m/z* 605.3690 $[M-H]^-$ (calcd for $C_{34}H_{53}O_9$, 605.3690).

3.3.2. Compound 2. White powder; mp 115–117°C; $[\alpha]_D^{19}=-50.5$ (*c* 0.61, CH_3OH); IR (KBr) ν_{max} 3449, 2943, 2874, 1715, 1652, 1560, 1509, 1379, 1268, 1213, 1157, 1096, 1028, 991, 939, 893, 864, 776 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; EIMS *m/z* 548 $[M]^+$ (2) 530 (20), 512 (25), 472 (22), 452 (10), 429 (27), 411 (50), 372 (48), 351 (10), 325 (13), 312 (30), 299 (25), 275 (23), 259 (33), 231 (43), 187 (55), 173 (39), 161 (62), 145 (55), 135 (77), 119 (58), 105 (65), 95 (63), 81 (66), 69 (100); HRFABMS *m/z* 547.3659 $[M-H]^-$ (calcd for $C_{32}H_{51}O_7$, 547.3635, error: 4.5 ppm).

3.3.3. Compound 3. White powder; mp 111–113°C; $[\alpha]_D^{20}=-46.3$ (*c* 0.71, CH_3OH); IR (KBr) ν_{max} 3445, 2941, 2875, 1734, 1709, 1458, 1379, 1248, 1213, 1095, 1033, 952, 893 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; EIMS *m/z* 528 $[M-H_2O]^+$ (5), 510 (37), 470 (20), 450 (15), 427 (22), 414 (19), 396 (22), 370 (12), 311 (25), 259 (22), 231 (15), 159 (25), 119 (28), 101 (79), 83 (66), 69 (61), 59 (100); HRFABMS *m/z* 545.3508 $[M-H]^-$ (calcd for $C_{32}H_{49}O_7$, 545.3478, error: 5.5 ppm).

3.3.4. Preparation of 1a. Compound **1** (20 mg) was acetylated by Ac_2O–pyridine, 36 h, room temperature, and the mixture was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ extract was subject to column chromatography on silica gel with petroleum ether–acetone (8:1) as eluent to give **1a** (10 mg). ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; EIMS *m/z* 714 $[M-H_2O]^+$ (2), 672 (20), 654 (13), 614 (97), 597 (22), 572 (14), 552 (100), 526 (43), 494 (41), 466 (70), 451 (68), 435 (44), 406 (59), 293 (66), 145 (56), 119 (58), 59 (91).

3.4. X-Ray crystal structure analysis of 1[13]

Crystal data: $C_{34}H_{54}O_9$, MW=606.80; orthorhombic, space group $P2_12_12_1$; a=10.880(1), b=13.845(1), c=24.101(1) Å. V=3630.4(5) $Å^3$, Z=4, D_{calc}=1.165 g/cm^3, Mo Kα (λ=0.71069 Å). The data were collected on a MAC DIP-2030K diffractometer, with graphite-monochromater, Mo Kα radiation using a colorless crystal of dimensions of

Table 2. ^1H NMR spectral data of compounds **1**–**3**

H	1	2	3	1a
1	4.63 (t, 2.8)	1.80 (m)	1.98, 1.54 (m)	4.67 (brs)
2	2.28 (dt, 13.2, 2.8)	1.98 (m)	2.62 (m)	2.22 (dt, 13.2, 2.8)
	1.90 (dt, 13.4, 2.8)	1.54 (m)	1.92 (m)	1.92 (dt, 13.4, 2.8)
3	3.39 (t, 2.8)	3.32 (brs)		4.58 (t, 2.6)
5	2.28 (m)	1.88 (m)	1.95 (m)	2.28 (m)
6	1.88, 1.72 (m)	1.78, 1.62 (m)	1.90, 1.68 (m)	1.88, 1.72 (m)
7	5.11 (brs)	5.10 (brs)	5.17 (brs)	5.11 (d, 3.0)
9	2.58 (dd, 12.0, 4.2)	2.12 (dd, 12.0, 4.2)	2.10 (m)	2.58 (dd, 12.0, 4.2)
11	1.27, 1.45 (m)	1.68 (m)	1.81 (m)	1.27, 1.45 (m)
12	1.40, 1.67 (m)	1.32, 1.67 (m)	1.32, 1.70 (m)	1.40, 1.67 (m)
15	5.25 (t, 2.0)	5.19 (brs)	5.23 (brs)	5.27 (t, 2.0)
16	2.16, 1.92 (m)	2.18, 1.95 (m)	2.20, 1.95 (m)	2.14, 1.92 (m)
17	1.35 (m)	1.32 (m)	1.39 (m)	1.35 (m)
18	1.12 (s)	1.09 (s)	1.02 (s)	1.22 (s)
19	0.97 (s)	0.92 (s)	0.98 (s)	0.91 (s)
20	2.18 (m)	2.14 (m)	2.12 (m)	2.18 (m)
21	3.78 (dd, 11.2, 3.6)	3.82 (dd, 14.5, 4.2)	3.82 (dd, 14.5, 4.2)	4.24 (dd, 11.4, 3.0)
	3.56 (dd, 11.2, 11.2)	3.55 (dd, 14.5, 13.0)	3.56 (dd, 14.5, 13.0)	3.87 (dd, 11.4, 5.2)
22	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)
23	3.86 (t, 3.1)	3.85 (brs)	3.85 (brs)	5.57 (dd, 9.2, 3.0)
26	1.31 (s)	1.30 (s)	1.30 (s)	1.39 (s)
27	1.20 (s)	1.20 (s)	1.19 (s)	1.36 (s)
28	0.90 (s)	0.81 (s)	1.09 (s)	0.88 (s)
29	0.87 (s)	0.82 (s)	1.04 (s)	1.00 (s)
30	1.14 (s)	1.10 (s)	1.15 (s)	1.09 (s)
CH_3COO	2.10, 1.99 (s)	1.91 (s)	1.91 (s)	2.04, 2.03, 2.02, 1.96, 1.95 (s)

Compounds **1** and **1a** were measured on a Bruker AM-400, while **2** and **3** on a DRX-500 spectrometer with TMS as internal standard; **1**–**3** were measured in CD_3OD, while **1a** in $CDCl_3$; chemical shifts are in ppm and coupling constants in Hz.

Table 3. HMBC correlation data of compounds **1**–**3**

C	**1** (COLOC)	**2**	**3**
1	H-2, 3, 19	H-19	H-2, 19
2	H-3		
3	H-28	H-28, 29	H-5, 28, 29
4	H-3, 28, 29	H-3, 28, 29	H-5, 28, 29
5	H-3, 7, 19, 28, 29	H-3, 7, 19, 28, 29	H-7, 19, 28, 29
6	H-5	H-5	H-5
7	H-30	H-30	H-30
8	H-30	H-7, 30	H-30
9	H-7, 19	H-19	H-7, 19
10	H-19	H-19	H-19
11	H-9		H-9
12	H-18	H-18	H-18
13	H-15, 18	H-15, 18	H-15, 18
14	H-18	H-18	H-16, 18
15		H-16	H-16
16	H-15	H-15	H-15
17	H-15, 18	H-15	H-15, 18
19	H-5	H-5, 9	H-5, 9
20	H-22, 23	H-23	H-23
22		H-23	H-23
24	H-26, 27	H-23, 26, 27	H-23, 26, 27
25	H-26, 27	H-26, 27	H-26, 27
26	H-27	H-27	H-27
27	H-26	H-26	H-26
28	H-29	H-29	H-29
29	H-28	H-28	H-28
30		H-9	H-9
CH_3COO	H-1, 7, CH_3COO	H-7, CH_3COO	H-7, CH_3COO

$0.25\times0.30\times0.50$ mm^3, maximum 2θ value of 50.0°, independent reflections: 3360, observed number of reflections: 3274 [$|F|^2 \geq 8\sigma(|F|^2)$]. The structure was solved by the direct method SHELX-86[14] and expanded using difference Fourier techniques, refined by the program and method NOMCSDP[15] and full-matrix least-squares calculations. Hydrogen atoms were fixed at calculated positions. The final indices were R=0.080, R_w=0.077. The CCDC deposit number is 185431.

Acknowledgments

The authors are grateful to the National Natural Science Foundation of China (Project No. C30000213), Yunnan Committee of Science and Technology (Project No. 2000C0021Q, 2000YP23) and The Chinese Academy of Sciences (XiBuZhiGuang Project) for financial support, and members of the analytical group in the Laboratory of Phytochemistry, Kunming Institute of Botany, for the spectral measurements. We also thank Professor Qitai, Zheng and Yang Lu (Institute of Material Medica, The Chinese Academy of Medical Sciences) for X-ray diffraction.

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