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DITERPENOIDS FROM *ISODON ERIOCALYX* VAR. *LAXIFLORA*

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Key Word Index—*Isodon eriocalyx* var. *laxiflora*; Labiatae; diterpenoids; laxiflorins A, B and C; eriocalyxin B; maoecrystal A, B; oridonin; biological evaluation.

Abstract—Three new, *seco-ent*-kaurane diterpenoids, laxiflorins A, B and C, together with four known diterpenoids eriocalyxin B, oriodonin, and maeocrystals A and B, were isolated from the leaves of *Isodon eriocalyx* var. *laxiflora*. Their structures were assigned by a combination of one- and two-dimensional NMR techniques and computer modeling calculations. Laxiflorin C displayed weak cytotoxic activity.

INTRODUCTION

In a previous paper [1], we have reported on four diterpenoids isolated from *Isodon eriocalyx* var. *laxiflora* C.-Y. Wu *et* H.-W. Li, a perennial herb of the Labiatae family, which is distributed in the southern area of Yunnan Province, P.R. China, and is used as an anti-inflammatory and antibacterial agent in local folk medicine [2]. Our recent study of this plant, collected from a different district, led to the isolation of three additional new diterpenoids, laxiflorins A (**1**), B (**2**) and C (**3**), together with four known diterpenoids, eriocalyxin B (**4**), maoecrystals A (**5**) and B (**6**), and oridonin (**7**) [1]. In this report, we present the isolation, structure determination and NMR assignments of the new compounds by a combination of one- and two-dimensional NMR techniques, including COSY, phase-sensitive ROESY [3–5], HETCOR, FLOCK [6] and selective INEPT [7, 8] NMR techniques, and computer modelling calculations, together with an evaluation of the biological activity.

RESULTS AND DISCUSSION

The ethereal extract of the leaves of *I. eriocalyx* var. *laxiflora* was subjected to repeated chromatography to yield laxiflorins A (**1**), B (**2**) and C (**3**), eriocalyxin B (**4**), maoecrystals A (**5**) and B (**6**) and oridonin (**7**). Laxiflorin A (**1**), $C_{20}H_{26}O_5$ (HRFAB-MS), was shown to contain primary and secondary hydroxyl groups [ν_{max} 3440–3260 cm^{-1}; δ58.6 (*t*) and 82.7 (*d*)], an α,β-unsaturated ketone [ν_{max} 1665 cm^{-1}; δ124.8 (*d*), 159.2 (*d*) and 201.8 (*s*)], a δ-lactone [(ν_{max} 1705 cm^{-1}; δ175.9 (*s*)] and an exocyclic methylene moiety [ν_{max} 1655 cm^{-1}; δ109.0 (*t*) and 160.7 (*s*)] by examination of its IR and ^{13}CNMR (Table 1) spectra. Direct comparison of its NMR data with those of eriocalyxin A (**8**) [9] and rabdosichuanin A (**9**) [10] suggested that laxiflorin A (**1**) had a B-seco-ent-kaurane skeleton. The COSY, ROESY, HETCOR, FLOCK and selective INEPT spectra (Table 2) indicated that **1** had a B-seco-ent-kaurane skeleton with a primary hydroxyl group at C-6, a secondary hydroxyl group at C-15 and a δ-lactone ring at C-7(20); its unambiguous ^1H and ^{13}CNMR data should be as shown in Tables 3 and 1, respectively.

The principal results (Table 2) from the ROESY experiment [3–5] suggested that this isolate had the stereochemistry shown in Fig. 1. Based on information from the ^1H, COSY, and ROESY NMR spectra, a computer-assisted three-dimensional structure (Fig. 2) was obtained by the molecular modelling program PCMODEL 386 V 4.0, using MMX force-field calculations for energy minimization. This structure shows that its six-membered ring (A-ring) with the C-2/C-3 inner double bond, and another six membered ring (C-ring) are in a deformed boat conformation, while the six-membered lactone ring (B-ring) is in a chair conformation. The calculated distances between H-20a and H-6, H-6 and H-9β, H-5β and H-11β, as well as H-20b and the H_3-19 protons, are 2.17, 2.64, 2.12 and 2.72 Å, respectively, consistent with the strong ROESY correlations between each of these pairs, and thereby, confirming the A-, B- and C-rings to be in a boat, a chair and a boat conformation, respectively. This is the first time that a B-seco-ent-kauranoid with an α,β-unsaturated ketone in its A-ring has been shown to possess a boat A-ring and a chair δ-lactone ring conformation. The NOE effect between the

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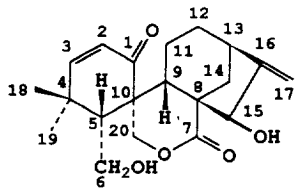

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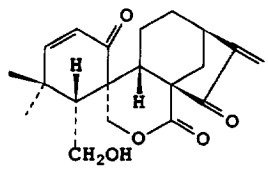

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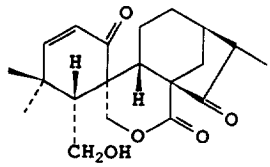

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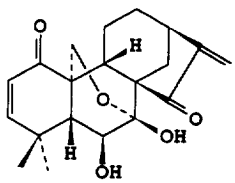

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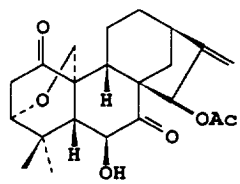

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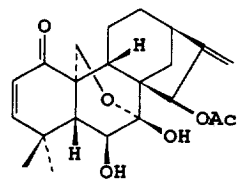

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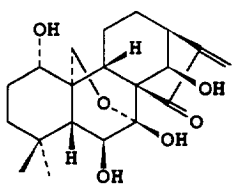

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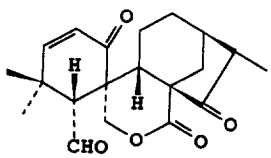

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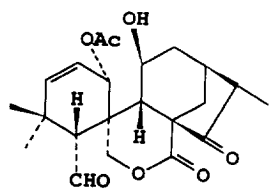

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Table 1. ^{13}C NMR spectral data of laxiflorins A–C (**1**–**3**) (in pyridine-d_5, δ values in ppm from TMS, 125.8 MHz)

C	1	2	3
1	201.8	201.0	201.0
2	124.8	124.4	124.5
3	159.2	158.9	158.9
4	36.7	36.8	36.7
5	48.1	47.4	47.4
6	58.6	58.0	58.2
7	175.9	170.4	175.5
8	58.3	59.3	59.5
9	35.6	42.1	41.8
10	52.1	52.9	52.3
11	17.5	18.4	20.2
12	33.6	30.5	17.9
13	36.7	35.5	32.6
14	31.6	30.7	32.7
15	82.7	203.2	217.5
16	160.7	151.8	48.8
17	109.0	118.3	11.8
18	32.4	31.8	31.7
19	24.2	23.7	23.8
20	70.2	70.9	70.8

H-15 and one (H-14β) of the C-14 methylene protons (with a calculated distance of 2.48 Å from the computer modelling), which lay in the rear of the plane of the structure, led to the assignment of H-15 in an α-configuration. Thus, OH-15 should be in a β-configuration as shown in the computer-generated structure. Similarly, the CH_2OH group was suggested to be connected to C-5 in an α-configuration by the NOE effects of H-5β with H-11β (2.12 Å), H-9β (2.55 Å) and the β-H-18 methyl (2.27 Å), as well as the NOE effects of the C-6 methylene with the α-H-20 methylene (2.17 Å) and the α-H-19 methyl (2.72 Å). Thus, all of the results (Table 2) from the above experiments identified laxiflorin A (**1**) as 6,15β-dihydroxy-1-oxo-6,7-seco-ent-kaura-2,16-dien-7,20-olide, with a conformation as shown in Fig. 2.

Molecular dynamics simulation also afforded information about the average dihedral angles and the corresponding J values between each of the vicinal proton pairs, and was used to check the J values from the NMR measurements, in order to assign the complex coupling patterns, and to determine the stereochemistry of the functional groups. One of the H-11 protons of **1**, which appeared in front of the plane, should be H-11β, having J values of about 4.5 Hz (dihedral angle of about 57°) with H-9β, 6.9 Hz (40°) with the H-12 proton in the

Table 2. Principal results from the ROESY, FLOCK and selective INEPT spectra of laxiflorin A (1)*†

H	ROESY (H)	FLOCK (C)	Selective INEPT (C)
2	3	4, 10	4, 10
3	2, 18	1, (4), 5	1, (4), 5, 18
5β	6, 11β, 18	(6), (10), 20	1, (4), (6), 9, (10), 18, 19, 20
6	5β, 9β, 18, 20a	10	4, (5), 10
9β	6, 11β, 20a	(11)	1, 5, 7, (8), (10), (11), 12, 14, 15
11α	11β, 12α, 14α, 20a	n.o.	8, (9), 10, (12)
11β	5β, 11α, 12β	n.o.	8
12α	11α, 12β, 13α	14	(13), 14, 16
12β	11β, 12α, 13α	n.o.	9, (11), (13), 16
13α	12α, 12β	n.o.	8, 11, (12), (14), 15, (16), 17
14α	11α, 13a	(8), 15, 16	(8), 9, 12, (13), 15, 16
14β	15α	n.o.	7, (8), 9, (13), 15
15α	14β	(16), 17	7, (8), 9, (16), 17
17a	17b	13, 15	15, (16)
17b	17a	13, 15	13, 15, (16)
18	3, 5β, 6	3, (4), 5, 19	3, (4), 5, 19
19	6, 20b	3, (4), 5, 18	3, (4), 5
20a	6, 9β	1, (10)	1, 9, (10)
20b	19	7, 9, (10)	1, 7, 9, (10)

*ROESY experiment was performed at 500.1 MHz with a spin-lock time of 300 msec, and a spin-lock field strength of 5 kHz [17, 18].

†FLOCK and HMBC experiments were performed at 500.1/125.8 MHz with $J = 6$ Hz [17, 18]; two-bond correlations are in parentheses; n.o. indicates no clear FLOCK contours with this proton.

Table 3. ^{1}H NMR spectral data of laxiflorins A–C (**1**–**3**) (in pyridine-d_5, δ values in ppm from TMS, 500.1 MHz)

H	1	2	3
2	5.89 (*d*, 10.5)	5.88 (*d*, 10.0)	5.87 (*d*, 10.0)
3	6.45 (*d*, 10.5)	6.44 (*d*, 10.0)	6.44 (*d*, 10.0)
5β	2.34 (*dd*, 3.5, 3.5)	2.18 (*dd*, 4.0, 4.0)	2.21 (*dd*, 4.5, 4.5)
6a	4.25 (*dd*, 11.5, 3.5)	3.99 (*dd*, 12.5, 4.0)	3.98 (*dd*, 12.0, 4.5)
6b	4.04 (*dd*, 11.5, 3.5)	3.94 (*dd*, 12.5, 4.0)	3.96 (*dd*, 12.0, 4.5)
9β	3.35 (*dd*, 12.5, 4.5)	2.97 (*dd*, 13.0, 4.5)	2.79 (*dd*, 13.0, 5.0)
11α	1.61 (*dddd*, 13.5, 12.5, 11.0, 7.6)	1.77 (*dddd*, 14.0, 13.0, 11.2, 7.0)	1.59 (*m*)
11β	1.56 (*ddd*, 13.5, 6.9, 4.5)	1.61 (*ddd*, 14.0, 6.6, 4.5)	1.43 (*m*)
12α	1.44 (*ddd*, 13.0, 7.6, 6.5)	1.33 (*ddd*, 13.5, 7.0, 4.5)	1.64 (*m*)
12β	1.98 (*ddd*, 13.0, 11.0, 6.9)	2.02 (*ddd*, 13.5, 11.2, 6.6)	1.56 (*m*)
13α	2.66 (*dd*, 6.5, 6.5)	2.66 (*dd*, 12.0, 4.5)	2.36 (*m*)
14α	2.54 (*d*, 12.0)	2.92 (*d*, 13.0)	2.97 (*d*, 12.0)
14β	2.38 (*dd*, 12.0, 6.5)	2.66 (*dd*, 13.0, 4.5)	2.63 (*dd*, 12.0, 4.5)
15α	4.96 (*s*)	—	—
16α	—	—	2.46 (*qd*, 7.0, 7.0)
17a	5.41 (*s*)	5.86 (*s*)	1.00 (*d*, 7.0)
17b	5.16 (*s*)	5.27 (*s*)	—
18	1.22 (*s*)	1.11 (*s*)	1.09 (*s*)
19	1.16 (*s*)	1.07 (*s*)	1.09 (*s*)
20a	5.38 (*d*, 11.0)	5.28 (*d*, 11.5)	5.25 (*d*, 11.5)
20b	4.65 (*d*, 11.0)	4.83 (*d*, 11.5)	4.77 (*d*, 11.7)

*Signal multiplicity and coupling constants (Hz) are shown in parentheses.

front (H-12β), and distances of 2.12 Å with H-5β, and of 2.41 Å with H-9β. In practice, the H-11 proton signal appeared at δ1.56 as a clear double doublet with J = 4.5 Hz with H-9β, J = 6.9 Hz with H-12β, and J = 13.5 Hz with its geminal proton; thus, it should be assigned to H-11β. Similarly, the computer modelling calculations indicated that H-11α had J values of 12.5 Hz with H-9β, 7.6 Hz, with H-12α, and 11.0 Hz with H-12β,

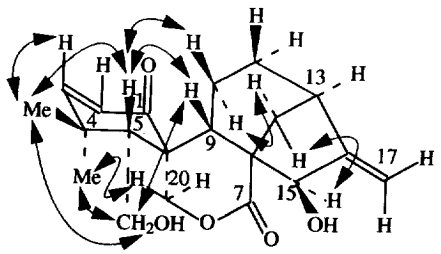

Fig. 1. Expression of the major ROESY correlations in laxiflorin A (**1**).

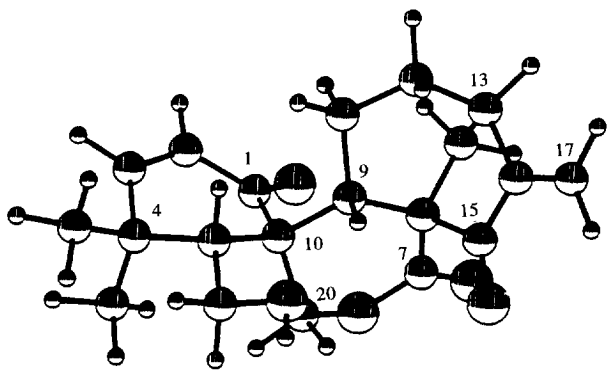

Fig. 2. Stereoview of laxiflorin A (**1**) generated from computer modelling.

which is consistent with the signal at δ1.61 (*dddd*, J = 13.5, 12.5, 11.0, 7.6 Hz); thus, this signal was assigned to H-11α. Continuing in the same manner, all of the remaining coupled vicinal protons could be assigned stereochemically as shown in Table 3.

Laxiflorin B (**2**), mp 171–173°, was obtained as needles, and its mass spectrum showed a molecular ion two amu less than that of **1**. The ^{1}H and ^{13}C DEPT NMR spectra showed that **2** had one more carbonyl than that of **1**, and one hydroxyl group and one methine carbon less. Inspection of the COSY, HETCOR and FLOCK spectra indicated that **2** had a carbonyl function at the C-15 position, and led to an unambiguous assignment of the ^{13}C and ^{1}H NMR data as shown in Tables 1 and 3. Therefore, **2** is 1,15-dioxo-6-hydroxy-6,7-seco-ent-kaura-2,16-dien-7,20-olide.

Laxiflorin C (**3**), mp 178–180°, $C_{20}H_{26}O_5$ (HRMS), was shown to contain an α-methyl cyclopentanone group [ν_{max} 1745 cm^{-1}; δ217.5 (*s*)], a δ-lactone [ν_{max} 1715 cm^{-1}; δ175.5 (*s*)], an α,β-unsaturated ketone [ν_{max} 1665 cm^{-1}; δ124.5 (*d*), 158.9 (*d*) and 201.0 (*s*)] and a primary hydroxyl [ν_{max} 3530 cm^{-1}; δ58.2 (*t*)] group in its IR and ^{13}C NMR spectra. Comparison of the ^{1}H and ^{13}C NMR data of **3** with those of **2**, indicated that the only difference between them was that the α-exocyclic methylene at C-16 of **2** was replaced by a methyl group in **3**. The stereochemistry of the Me-16 was suggested as a β-orientation from its chemical shift around δ1.00 (*d*, J = 7.0 Hz), and by consideration of the mechanism of the hydrogenation of the C-16 double bond [10–12]. This assignment was confirmed by the NOE effects between H-12β and the C-16 methyl, and the unique upfield shift of C-12 (δ17.9) owing to the γ effect of Me-16β. The ^{1}H and ^{13}C NMR data of **3** were unambiguously assigned by the use of COSY, ROESY, HETCOR and FLOCK techniques, and are shown in Tables 1 and 3. Accordingly, the structure of laxiflorin C (**3**) can be represented as 1,15-dioxo-6-hydroxy-6,7-seco-ent-kaur-2-en-7,20-olide.

Table 4. Evaluation of the cytotoxic activity of laxiflorins A and C (**1** and **3**)*

	ED_{50} (μg ml^{-1})	
Cell lines	**1**	**3**
Lu-1	> 20	4.7
KB	> 20	4.0
KB-V (+ VLB)	> 20	9.2
KB-V (– VLB)	> 20	18.8
LNCaP	> 20	1.8
ZR-75-1	> 20	4.2
ASK†	—	—

*Lu-1 = human lung cancer, KB = human oral epidermoid carcinoma, KB-V = vinblastine-resistant KB, LNCaP = hormone-dependent human prostatic cancer, ZR-75-1 = hormone-dependent human breast cancer, ASK = human astrocytoma.
†'—', no activity in ASK test.

Among over 40 B-seco-ent-kaurenoids, only eriocalyxin A (**8**) and laxiflorins A (**1**), B (**2**) and C (**3**) have an A ring with an α,β-unsaturated ketone. An extensive NMR study with computer modelling calculation such as that carried out on laxiflorins A, B and C is particularly helpful in assigning the NMR data for this kind of diterpene.

Compounds **1** and **3** were subjected to anticancer, antimalarial and HIV reverse transcriptase inhibitory tests [13–16], and **3** showed weak cytotoxic activity (Table 4), but neither compound showed any antimalarial or HIV RT inhibitory activity.

EXPERIMENTAL

General. Mps: uncorr. IR spectra: KBr pellets. ^{1}H, ^{13}C, DEPT, COSY, DQF-COSY, ROESY, HETCOR, and FLOCK spectra were taken on a GE Omega 500 instrument operating at 500.1 MHz for ^{1}H and homonuclear 2D NMR spectra, 125.8 MHz for ^{13}C and DEPT spectra, and 500.1/125.8 MHz for heteronuclear 2D spectra with a long-range coupling constant of J = 6 Hz, using standard GE programs in pyridine-d_5 soln, and have been described in detail previously [17, 18]. Selective INEPT spectra were taken on a Nicolet NT-360 instrument operating at 90.8 MHz, with J = 6 Hz for aliphatic protons.

Plant material. The plant material of *Isodon eriocalyx* var. *laxiflora* was collected from Xishungbanna, Yunnan

Province, P.R. China, in 1990, and identified by Prof. H.-W. Li. A voucher specimen is deposited in the Herbarium of the Department of Taxonomy, Kunming Institute of Botany, Academia Sinica, Kunming, P.R. China.

Extraction and isolation. The powdered air-dried leaves (2.44 kg) of *I. eriocalyx* var. *laxiflora* were extracted with Et_2O and the solvent removed under vacuum. The residue was dissolved in MeOH, and decolorized with activated charcoal. The MeOH was evapd and the residue (94 g) was subjected to CC on silica gel, eluted with $CHCl_3$, and $CHCl_3$–Me_2CO mixtures with an increasing proportion of Me_2CO. Frs were collected, and combined by monitoring with TLC, followed by recrystallization to yield laxiflorin A (**1**, 240 mg, 0.0098%), laxiflorin B (**2**, 15 mg, 0.00061%), laxiflorin C (**3**, 347 mg, 0.014%), eriocalyxin B (**4**, 2.12 g, 0.086%), maoecrystal A (**5**, 170 mg, 0.0070%), maoecrystal B (**6**, 210 mg, 0.0061%) and oridonin (**7**, 183 mg, 0.0075%). All of the known compounds were identified by direct comparison of their mp, mmp, TLC, IR and ^{1}H NMR data with the respective authentic samples.

Laxiflorin A (**1**). Obtained as crystals from MeOH; mp 165–167°; $[\alpha]_D$ + 71.3° (MeOH; *c* 0.06); UV λ_{max}^{MeOH} (log ε) nm: 227.5 (4.02); IR ν_{max}^{KBr} cm^{-1}: 3440–3260, 1705, 1665, 1230, 1103 and 895; ^{1}H NMR data: see Table 3; ^{13}C NMR data: see Table 1; EIMS *m/z* (100%): 346 $[M]^+$ (100), 328 (13), 318 (30), 316 (30), 315 (11), 298 (13), 297 (28), 288 (14) and 285 (11); HRMS: obsd 346.1772 for $C_{20}H_{26}O_5$, calc. 346.1780.

Laxiflorin B (**2**). Obtained as needles from MeOH, mp 171–173°; $[\alpha]_D$ + 75.3° (MeOH; *c* 0.09); UV λ_{max}^{MeOH} (log ε) nm: 231.5 (4.02); IR ν_{max}^{KBr} cm^{-1}: 3570, 3468, 1743, 1718, 1666, 1388, 1263, 1217, 1130, 1198 and 1050; ^{1}H NMR data: see Table 3; ^{13}C NMR data: see Table 1; EIMS *m/z* (100%): 344 (59), 317 (21), 316 (85), 286 (23), 285 (39), 283 (22), 255 (46), 233 (21), 185 (37), 167 (43), 151 (24), 150 (30), 149 (26), 137 (30), 136 (51), 135 (100), 133 (39), 121 (20) and 105 (53); HRMS: obsd 344.1630 for $C_{20}H_{24}O_5$, calc. 344.1624.

Laxiflorin C (**3**). Obtained as crystals from MeOH, mp 178–180°; $[\alpha]_D$ + 95.9° (MeOH; *c* 0.14); UV λ_{max}^{MeOH} (log ε) nm: 228.5 (4.32); IR ν_{max}^{KBr} cm^{-1}: 3530, 1745, 1715, 1665, 1251, 1218, 1135, 918 and 835; ^{1}H NMR data: see Table 3; ^{13}C NMR data: see Table 1; EIMS *m/z* (100%); 346 $[M]^+$ (18), 318 (71), 287 (41), 185 (32), 167 (33), 165 (87), 149 (37), 147 (38), 137 (53), 136 (51), 135 (100), 123 (51), 111 (67), 109 (68), 107 (52) and 105 (550; HR-MS: obsd 346.1781 for $C_{20}H_{26}O_5$, calc. 346.1780.

Cytotoxicity, antimalarial and HIV-1 RT inhibitory assays. The biological evaluations for cytotoxic, antimalarial, and HIV-1 RT inhibitory activities of **1** and **3** were carried out according to established protocols [15–18], and the cytotoxicity data are summarized in Table 4.

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