



DITERPENOIDS FROM *ISODON ERIOCALYX* VAR. *LAXIFLORA*

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(Received in revised form 29 September 1994)

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, oridonin, and maoecrystals 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 al.* 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} ; δ 58.6 (t) and 82.7 (d)], an α,β -unsaturated ketone [ν_{\max} 1665 cm^{-1} ; δ 124.8 (d), 159.2 (d) and 201.8 (s)], a δ -lactone [ν_{\max} 1705 cm^{-1} ; δ 175.9 (s)]

and an exocyclic methylene moiety [ν_{\max} 1655 cm^{-1} ; δ 109.0 (t) and 160.7 (s)] by examination of its IR and ^{13}C NMR (Table 1) spectra. Direct comparison of its NMR data with those of eriocalyxin A (8) [9] and rabdosischuanin 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}C NMR 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-9 β , H-5 β and H-11 β , as well as H-20b and the H₃-19 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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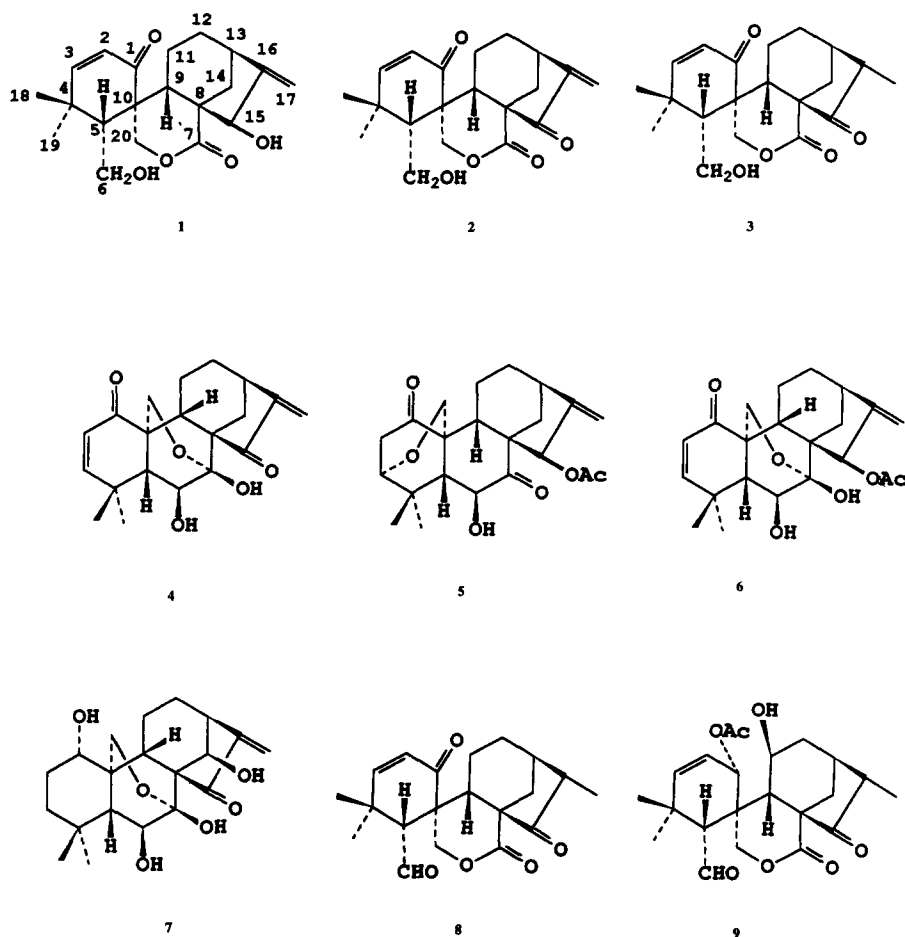


Table 1. ^{13}C NMR spectral data of laxiflorins A–C (1–3) (in pyridine- d_5 , δ values in ppm from TMS, 125.8 MHz)

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-14 β) 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-5 β with H-11 β (2.12 Å), H-9 β (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 6,15 β -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-11 β , having J values of about 4.5 Hz (dihedral angle of about 57°) with H-9 β , 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
5 β	6, 11 β , 18	(6), (10), 20	1, (4), (6), 9, (10), 18, 19, 20
6	5 β , 9 β , 18, 20a	10	4, (5), 10
9 β	6, 11 β , 20a	(11)	1, 5, 7, (8), (10), (11), 12, 14, 15
11 α	11 β , 12 α , 14 α , 20a	n.o.	8, (9), 10, (12)
11 β	5 β , 11 α , 12 β	n.o.	8
12 α	11 α , 12 β , 13 α	14	(13), 14, 16
12 β	11 β , 12 α , 13 α	n.o.	9, (11), (13), 16
13 α	12 α , 12 β	n.o.	8, 11, (12), (14), 15, (16), 17
14 α	11 α , 13a	(8), 15, 16	(8), 9, 12, (13), 15, 16
14 β	15 α	n.o.	7, (8), 9, (13), 15
15 α	14 β	(16), 17	7, (8), 9, (16), 17
17a	17b	13, 15	15, (16)
17b	17a	13, 15	13, 15, (16)
18	3, 5 β , 6	3, (4), 5, 19	3, (4), 5, 19
19	6, 20b	3, (4), 5, 18	3, (4), 5
20a	6, 9 β	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. ^1H 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 (<i>d</i> , 10.5)	5.88 (<i>d</i> , 10.0)	5.87 (<i>d</i> , 10.0)
3	6.45 (<i>d</i> , 10.5)	6.44 (<i>d</i> , 10.0)	6.44 (<i>d</i> , 10.0)
5 β	2.34 (<i>dd</i> , 3.5, 3.5)	2.18 (<i>dd</i> , 4.0, 4.0)	2.21 (<i>dd</i> , 4.5, 4.5)
6a	4.25 (<i>dd</i> , 11.5, 3.5)	3.99 (<i>dd</i> , 12.5, 4.0)	3.98 (<i>dd</i> , 12.0, 4.5)
6b	4.04 (<i>dd</i> , 11.5, 3.5)	3.94 (<i>dd</i> , 12.5, 4.0)	3.96 (<i>dd</i> , 12.0, 4.5)
9 β	3.35 (<i>dd</i> , 12.5, 4.5)	2.97 (<i>dd</i> , 13.0, 4.5)	2.79 (<i>dd</i> , 13.0, 5.0)
11 α	1.61 (<i>dddd</i> , 13.5, 12.5, 11.0, 7.6)	1.77 (<i>dddd</i> , 14.0, 13.0, 11.2, 7.0)	1.59 (<i>m</i>)
11 β	1.56 (<i>ddd</i> , 13.5, 6.9, 4.5)	1.61 (<i>ddd</i> , 14.0, 6.6, 4.5)	1.43 (<i>m</i>)
12 α	1.44 (<i>ddd</i> , 13.0, 7.6, 6.5)	1.33 (<i>ddd</i> , 13.5, 7.0, 4.5)	1.64 (<i>m</i>)
12 β	1.98 (<i>ddd</i> , 13.0, 11.0, 6.9)	2.02 (<i>ddd</i> , 13.5, 11.2, 6.6)	1.56 (<i>m</i>)
13 α	2.66 (<i>dd</i> , 6.5, 6.5)	2.66 (<i>dd</i> , 12.0, 4.5)	2.36 (<i>m</i>)
14 α	2.54 (<i>d</i> , 12.0)	2.92 (<i>d</i> , 13.0)	2.97 (<i>d</i> , 12.0)
14 β	2.38 (<i>dd</i> , 12.0, 6.5)	2.66 (<i>dd</i> , 13.0, 4.5)	2.63 (<i>dd</i> , 12.0, 4.5)
15 α	4.96 (<i>s</i>)	—	—
16 α	—	—	2.46 (<i>qd</i> , 7.0, 7.0)
17a	5.41 (<i>s</i>)	5.86 (<i>s</i>)	1.00 (<i>d</i> , 7.0)
17b	5.16 (<i>s</i>)	5.27 (<i>s</i>)	—
18	1.22 (<i>s</i>)	1.11 (<i>s</i>)	1.09 (<i>s</i>)
19	1.16 (<i>s</i>)	1.07 (<i>s</i>)	1.09 (<i>s</i>)
20a	5.38 (<i>d</i> , 11.0)	5.28 (<i>d</i> , 11.5)	5.25 (<i>d</i> , 11.5)
20b	4.65 (<i>d</i> , 11.0)	4.83 (<i>d</i> , 11.5)	4.77 (<i>d</i> , 11.7)

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

front (H-12 β), and distances of 2.12 Å with H-5 β , and of 2.41 Å with H-9 β . In practice, the H-11 proton signal appeared at δ 1.56 as a clear double doublet with $J = 4.5$ Hz with H-9 β , $J = 6.9$ Hz with H-12 β , and $J = 13.5$ Hz with its geminal proton; thus, it should be assigned to H-11 β . Similarly, the computer modelling calculations indicated that H-11 α had J values of 12.5 Hz with H-9 β , 7.6 Hz, with H-12 α , and 11.0 Hz with H-12 β ,

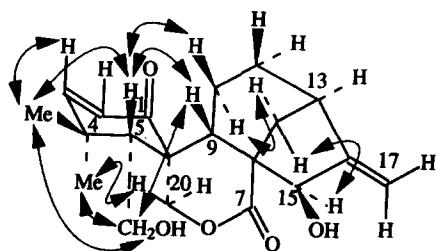


Fig. 1. Expression of the major ROESY correlations in laxiflorin A (1).

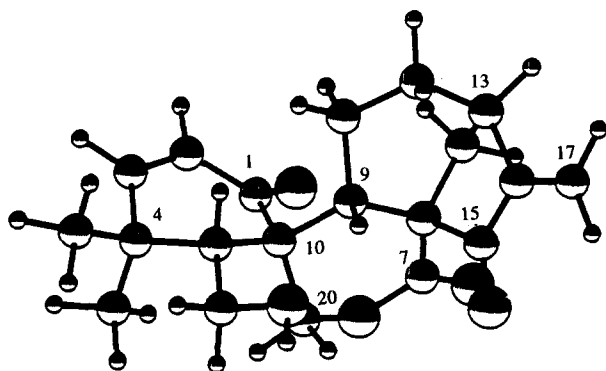


Fig. 2. Stereoview of laxiflorin A (1) generated from computer modelling.

which is consistent with the signal at δ 1.61 (*dddd*, J = 13.5, 12.5, 11.0, 7.6 Hz); thus, this signal was assigned to H-11 α . 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 ^1H 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 ^1H 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°, $\text{C}_{20}\text{H}_{26}\text{O}_5$ (HRMS), was shown to contain an α -methyl cyclopentanone group [ν_{max} 1745 cm^{-1} ; δ 217.5 (*s*)], a δ -lactone [ν_{max} 1715 cm^{-1} ; δ 175.5 (*s*)], an α,β -unsaturated ketone [ν_{max} 1665 cm^{-1} ; δ 124.5 (*d*), 158.9 (*d*) and 201.0 (*s*)] and a primary hydroxyl [ν_{max} 3530 cm^{-1} ; δ 58.2 (*t*)] group in its IR and ^{13}C NMR spectra. Comparison of the ^1H 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 δ 1.00 (*d*, J = 7.0 Hz), and by consideration of the mechanism of the

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

Cell lines	ED ₅₀ ($\mu\text{g ml}^{-1}$)	
	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.

hydrogenation of the C-16 double bond [10–12]. This assignment was confirmed by the NOE effects between H-12 β and the C-16 methyl, and the unique upfield shift of C-12 (δ 17.9) owing to the γ effect of Me-16 β . The ^1H 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.

Among over 40 B-seco-ent-kaurenoids, only ericalexyn 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. ^1H , ^{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 ^1H 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 Et₂O 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 CHCl₃, and CHCl₃–Me₂CO mixtures with an increasing proportion of Me₂CO. 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 ¹H NMR data with the respective authentic samples.

Laxiflorin A (1). Obtained as crystals from MeOH; mp 165–167°; [α]_D + 71.3° (MeOH; *c* 0.06); UV $\lambda_{\max}^{\text{MeOH}}$ (log ϵ) nm: 227.5 (4.02); IR ν_{\max}^{KBr} cm⁻¹: 3440–3260, 1705, 1665, 1230, 1103 and 895; ¹H NMR data: see Table 3; ¹³C 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 C₂₀H₂₆O₅, calc. 346.1780.

Laxiflorin B (2). Obtained as needles from MeOH, mp 171–173°; [α]_D + 75.3° (MeOH; *c* 0.09); UV $\lambda_{\max}^{\text{MeOH}}$ (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; ¹H NMR data: see Table 3; ¹³C 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 C₂₀H₂₄O₅, calc. 344.1624.

Laxiflorin C (3). Obtained as crystals from MeOH, mp 178–180°; [α]_D + 95.9° (MeOH; *c* 0.14); UV $\lambda_{\max}^{\text{MeOH}}$ (log ϵ) nm: 228.5 (4.32); IR ν_{\max}^{KBr} cm⁻¹: 3530, 1745, 1715, 1665, 1251, 1218, 1135, 918 and 835; ¹H NMR data: see Table 3; ¹³C 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 C₂₀H₂₆O₅, 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.

Acknowledgements—This work was supported, in part, by grants from the Laboratory of Phytochemistry, Kun-

ming Institute of Botany, Academia Sinica, P.R. China, to the Chinese research group, and by a grant from the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, U.S.A., to the U.S.A. research group. The authors thank Prof. H.-W. Li for the identification of the plant material, Mr R. Dvorak for MS, Dr J. M. Pezzuto, Dr C. K. Angerhofer, Dr H. Chai, Ms T. Pengsuparp, Ms M. You and Ms E. Pisha for the biological tests, and the Research Resources Center of the University of Illinois at Chicago for the provision of NMR spectroscopic facilities.

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