Apotirucallane and Tirucallane Triterpenoids from *Luvunga sarmentosa*

Christine Kamperdick,[†] Trinh Phuong Lien,[†] Guenter Adam,[‡] and Tran Van Sung*,[†]

Institute of Chemistry, National Center for Natural Science and Technology of Vietnam, Hoang Quoc Viet Road, Cau Giay, Hanoi, Vietnam, and Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle/Saale, Germany

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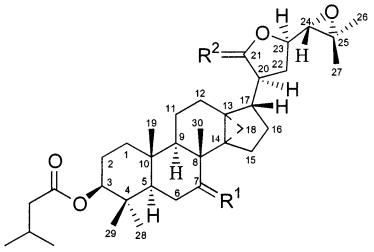
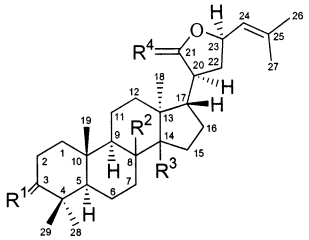
The leaves of *Luvunga sarmentosa* yielded two new apotirucallane triterpenoids, 3-*epi*-skimmiarepin A (**1**) and 21,23-epoxy-7α,21-dihydroxyapotirucalla-14,24-dien-3-one (**2**), and a new tirucallane triterpene, 3-*epi*-flindissol (**3**). Because of a hemiacetal functionality at C-21, all compounds occurred as mixtures of 21-epimers. 3-*epi*-Skimmiarepin A (**1**) and 3-*epi*-flindissol (**3**) were oxidized to the corresponding γ-lactones. The structures have been elucidated on the basis of mass and NMR spectroscopic methods.

Luvunga sarmentosa (Bl.) Kurz (*Triphasia sarmentosa* Bl., *L. eleutherandra* Dalz.) is a shrub growing in the rainforests of Vietnam.[1] It is used in traditional medicine to treat toothache, pain in the limbs, and rheumatism.[2] From the stem bark of *L. sarmentosa* some triterpenes, coumarins, and acridone alkaloids have been isolated.[3] Recently, we reported the new apotirucallane triterpenes luvungins A−G and acetoxyluvungin A from the leaves of this plant.[4] Characteristic of luvungins A−G were a seven-membered lactone ring for ring A, an α-hydroxy or α-acetyloxy group at C-7, and a five-, six-, or seven-membered ring with an oxygen bridge in the side chain. In a continuation of this work we now describe the structure elucidation of three further new triterpenes (**1**−**3**) with a six-membered ring A from this same plant.



	R^1	R^2
1	α-OH, β-H	OH, H
1a	O	O



		R^1	R^2	R^3	R^4
2	Δ^{14}	O	β-CH_3	-	OH, H
3	Δ^7	β-OH, α-H	-	β-CH_3	OH, H
3a	Δ^7	O	-	β-CH_3	O

3-*epi*-Skimmiarepin A (**1**) was obtained as needles. The molecular weight of 572 was determined from the $[M + Na]^+$ peak at *m*/*z* 595 in the ESIMS. Like luvungin C,[4] compound **1** was an epimeric mixture due to the hemiacetal functionality at C-21 (δ_C 98.2/102.1). The content of the major component was determined by integration of the proton signals as 60−67%. Besides this hemiacetal group, the NMR spectra did not show similarities to the other luvungins obtained.[4] To simplify the spectra, **1** was oxidized and yielded **1a**, which showed a molecular ion in the EIMS at *m*/*z* 568. From this derivative, the HRESITOFMS gave the base peak at *m*/*z* 569.3810 for the $[M + H]^+$ ion, resulting in the molecular formulas $C_{35}H_{52}O_6$ for **1a** and $C_{35}H_{56}O_6$ for **1**. The NMR spectra of **1a** exhibited the characteristic ^1H signals of a cyclopropane methylene group at δ 0.35 and 0.56 (each 1H, d, J = 5.8 Hz) and the ^{13}C signals for an ester group at δ_C 172.9, a newly introduced γ-lactone group (δ_C 178.1), and one keto group at δ_C 214.6, originating from a secondary hydroxyl group of **1**. Furthermore, the NMR spectra showed characteristic signals and the corresponding correlations for an isovaleroyl ester and a 1,1-dimethylepoxy group in the side chain (δ_C 64.3, δ_H 2.81 and δ_C 57.3). Analysis of the 2D NMR spectra (HSQC, HMBC) confirmed the expected attachment of the epoxide to the γ-lactone ring by correlations from H_3-26 and H_3-27 to C-23 (weak)/C-24/C-25, from H-24 to C-23, from H-23 to C-24, from H-22a to C-23/C-20, and from H-22b to C-20/C-21. The proton signal at δ 4.48 was identified as H-3 on the basis of its long-range correlation to C-4 (δ 38.1) in the HMBC experiment. Its axial configuration was deduced from the coupling constants (dd, J = 11.5 and 4.9 Hz). One known compound with all these features, except that H-3 is equatorial, is the oxidation product of skimmiarepin A.[5] Full analysis of the 2D NMR spectra of **1a** (HSQC, HMBC, HH-COSY, NOESY) led to unambiguous ^1H and ^{13}C NMR assignments and confirmed **1a** to be the 3-epimer of the oxidation product of skimmiarepin A. Thus, **1** was established as the new 3-*epi*-skimmiarepin A (21,23:24,25-diepoxy-3-*O*-isovaleroyl-14,18-cycloapotirucalla-3β,7α,21-triol). Confirmation of this constitution and relative configuration was obtained by analysis of the HSQC, HMBC, HH-COSY, and NOESY experiments on **1**. The ^{13}C NMR shifts were nearly identical to those of skimmiarepin A, except for C-1 ($\Delta\delta$ +4.1), C-2 ($\Delta\delta$ −3.1), C-3 ($\Delta\delta$ +2.7), C-5 ($\Delta\delta$ + 4.5), C-10 ($\Delta\delta$ +0.7), C-12 ($\Delta\delta$ +2.4), and C-29 ($\Delta\delta$ −5.5), which reflected the influence of the different configuration at C-3.

Compound **2** was isolated as an amorphous powder. The molecular formula was determined as $C_{30}H_{46}O_6$ from the

* To whom correspondence should be addressed. Tel: +844-7564794. Fax: +844-8361283. E-mail: tvs@ich.ncst.ac.vn.
[†] National Center for Natural Science and Technology, Hanoi.
[‡] Institute of Plant Biochemistry, Halle/Saale.

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Table 1. ^{13}C NMR Data of Compounds **1**−**3**, **1a**, and **3a** (75 MHz, $CDCl_3$, shifts of the minor component in brackets)

position	1	1a	2	3	3a
1	38.19 [38.09]	38.4	38.44 [38.48]	37.12	38.5
2	23.50	23.3	33.91	27.60	34.9
3	80.43 [80.40]	79.7	217.52	79.16 [79.18]	216.9
4	37.19	38.1	46.94[a] [46.91[b]]	38.92	47.9
5	45.98 [46.05]	54.8	46.46 [46.53]	50.64 [50.70]	52.4
6	24.10	35.6	24.73	23.92	24.4
7	74.31 [74.18]	214.6	71.95	118.13 [118.04]	118.2
8	38.75 [38.82]	49.9	44.01	145.45 [145.68]	145.5
9	44.09 [43.91]	51.4	40.97 [40.94]	48.75 [48.78]	48.4
10	37.08 [37.14]	36.9	37.13	34.97	35.1
11	16.29 [16.13]	17.1	16.21 [16.26]	17.51	17.6
12	25.50	26.9	32.52 [32.94]	31.65 [31.46]	33.9[a]
13	28.88 [28.47]	28.6	46.88[a] [46.57[b]]	43.70 [43.54]	43.7
14	36.80 [35.91]	33.6	161.91 [161.60]	50.91 [50.72]	50.5
15	26.26 [25.85[a]]	28.2	119.42 [119.91]	33.78 [34.19]	34.7[a]
16	27.43 [25.88[a]]	21.2	34.68 [35.07]	27. 35 [27.32]	31.0
17	44.73 [48.14]	44.7	57.85 [52.74]	50.54 [45.08]	41.4
18	13.68 [13.49]	15.1	19.40 [19.88]	22.50 [23.15]	21.5
19	15.91 [15.78]	16.2	14.93 [14.90]	13.01	12.7
20	49.28 [50.59]	40.7	48.21 [45.98]	50.13 [47.67]	46.9
21	98.18 [102.10]	178.1	101.97 [97.04]	101.38 [97.27]	178.6
22	30.75 [32.74]	26.3	39.12 [35.29]	39.61 [35.48]	23.9
23	78.39 [77.29]	78.5	74.15 [75.63]	73.93 [75.70]	75.2
24	67.61 [65.29]	64.3	124.54 [127.65]	124.80 [127.96]	123.1
25	58.00 [57.21]	57.3	137.11 [135.83]	136.84 [135.49]	139.7
26	24.96 [24.88]	24.8	25.76	25.78	25.7
27	19.15 [19.34[b]]	19.4	18.28 [17.91]	18.27 [17.89]	18.4
28	27.66	27.4	26.21 [26.15]	27.56	24.5
29	16.68	16.0	21.12	14.67	23.4
30	19.46 [19.38[b]]	18.8	27.05 [27.09]	27.07 [27.27]	27.5
1′	172.88	172.9			
2′	43.95	43.8			
3′	25.73	25.7			
4′	22.45	22.4			
5′	22.34	22.3			

[a,b] Exchangeable signals within the same vertical column.

HRESITOFMS (*m*/*z* 553.3329 $[M + H - H_2O]^+$). The NMR spectra indicated the presence of an epimeric mixture and were similar to those of luvungin C,[4] but instead of the lactone group at C-3, the signal of a keto group at δ 217.5 was observed. The proton and carbon shifts of ring D and the side chain were identical to those of luvungin C.[4] Rings B and C had some slight differences (maximum 0.4 ppm), suggesting the closely related structures of luvungin C and compound **2** except for one missing oxygen atom in ring A. The structure of ring A was established by the C−H long-range correlations of C-3 with H-2a/H-2b/H-1b/H_3-28/H_3-29 and of C-1 with H-2a/H-2b/H-9/H_3-19. The proposed structure of **2** was confirmed by analysis of the 2D NMR spectra (HSQC, HMBC, HH-COSY, NOESY). The α-configuration of the 7-hydroxy group was deduced from the coupling constants of H-7, which appeared as a broad singlet because of its equatorial configuration. Thus, compound **2** was established as the new compound 21,23-epoxy-7α,21-dihydroxyapotirucalla-14,24-dien-3-one. The 7β-hydroxy isomer of compound **2** was described as a constituent of *Melia azadirachta* in 1969.[6]

3-*epi*-Flindissol (**3**) was obtained as an amorphous powder. The molecular weight was deduced from its $[M]^+$ peak at *m*/*z* 456 in the EIMS and the elemental composition $C_{30}H_{48}O_3$ from the $[M + H - H_2O]^+$ peak at *m*/*z* 439.3572 in the HRESITOFMS. Again, the NMR spectra indicated the presence of an epimeric mixture with a content of the main compound of roughly 60%, determined by the integrals of the very close ^1H NMR signals. Comparison with the NMR data of luvungin C[4] showed a very good correspondence for the signals of the side chain with the five-membered hemiacetal ring and the Δ^{24} double bond. To simplify its spectra, **3** was oxidized to give **3a**, which showed a $[M]^+$ peak at *m*/*z* 452 ($\Delta m/z = 4$ amu) and new signals for the γ-lactone group at C-21 (δ_C 178.6) and for a keto group at C-3 (δ_C 216.9) originating from a secondary alcohol group at δ 79.16/79.18 in **3**. Comparison of the ^1H and ^{13}C NMR data with flindissol lactone[7] showed good correspondence of the chemical shifts for the rings C and D and for the side chain, whereas the remaining signals for the rings A and B were very close to those of the tirucallane triterpene hispidone from *Eurycoma longifolia*[8] with a 3-keto group and with the rings A−D identical to compound **3a**. This resulted in the structure of 3,21-dioxotirucalla-7,24-dien-21,23-oxide being proposed for **3a**. Thus, compound **3** was assigned as the corresponding 3,-21-diol. The coupling constants of H-3 (δ 3.24, dd, $J = 11.2$ and 3.9 Hz) revealed the axial α-configuration of H-3 and the β-configuration of the hydroxyl group. The 3α-hydroxy isomer is known as flindissol from *Aucoumea kleineana*,[7] but no carbon shifts were available in the literature. Analysis of the 2D NMR spectra (HSQC, HMBC, HH-COSY) confirmed the constitution and gave the full assignment of the signals for the two epimers. The NOESY experiment of **3** gave the relative configuration of the tetracyclic moiety by the NOE enhancements from H-3 to H-1α (δ 1.13), H-2α (δ 1.64), and H_3-28 (δ 0.97), from H-5 (δ 1.31) to H-1α (δ 1.13), H-3 (δ 3.24), H-9 (δ 2.22−2.24), and H_3-28 (δ 0.97), from H-9 (δ 2.22−2.24) to H-1α (δ 1.13), H-5 (δ 1.31), and H_3-18 (δ 0.90), and from H_3-19 (δ 0.75) to H-6β (δ 1.97), H_3-29 (δ 0.86), and H_3-30 (δ 0.98). The relative configuration of C-17 and C-20 for both components was proved by the NOE interactions between H-17 (δ 1.79/2.05) and H_3-30 (δ 0.98/1.00) and between H_3-18 (δ 0.90/0.85) and H-20 (δ 2.20/2.03). For H-23 only NOE enhancements to H_3-27 but no interactions with other protons of

Table 2. ^{1}H NMR Data of Compounds **1**−**3**, **1a**, and **2a** ($CDCl_3$, δ ppm, J in Hz, shifts of the minor components in brackets[a])

position	**1**[b]	**1a**[c]	**2**[b]	**3**[b]	**3a**[c]
1	1.61; 1.04	1.77; 1.00	1.86; 1.52	α 1.13; β 1.66	
2	1.67; 1.61	1.73; 1.68	2.53; 2.44	α 1.64; β 1.60	b: 2.00 ddd (13.3, 5.4, 3.1)[e]
3	4.54 dd (11.4, 4.7)	4.48 dd (11.5, 4.9)		3.24 dd (11.2, 3.9)	
5	1.59	1.21 dd (14.4, 2.2)	2.08	1.31	
6	1.73; 1.59	2.60 dd (14.4, 13.2); 2.24 dd (13.2, 2.2)	1.84; 1.79	α 2.14; β 1.97	
7	3.77 m		3.96	5.27	5.32 td (3.3, 3.0)
9	1.23 [1.26]	1.04 d (ca 11.5)	2.03	2.24−2.22	
11	1.28−1.33	1.39; 1.32	1.72; 1.58	1.54; 1.50	
12	2.10;[d] 1.77	1.90; 1.59	2.00; 1.48 [1.83; 1.56]	1.74; 1.72 [1.98; 1.42]	
15	1.92; 1.55 [n.d.]	1.99 dd (12.6, 8.2); 1.89	5.48 [5.50]	1.54; 1.48 [1.54; 1.50]	
16	1.67; 0.89 [n.d.]	1.53; 0.96	2.20−2.10	1.88; 1.30	
17	2.20 [2.04]	2.47 ddd (11.3, 7.1, 4.2)	1.74 [2.01]	1.79 [2.05]	
18	0.66 d (4.3); 0.47 d (4.9) [0.74 d (5.2); 0.49 d (5.2)]	0.56 d (5.8); 0.35 d (5.8)	1.10 [1.03]	0.90 s [0.85 s]	0.82 s
19	0.90 s	1.09 s	1.01 s	0.75 s	1.12 s
20	1.88 [2.15]	2.92 ddd (12.5, 8.6, 4.2)	2.37 [2.20]	2.20 [2.03]	2.71 m
21	5.43 d (3.7) [5.43 d (3.7)]		5.30 [5.33]	5.30 d (3.3) [5.27 d (3.0)]	
22	1.99; 1.69 [2.07; 1.41[d]]	2.23; 1.90	2.10; 1.30 [2.00; 1.60]	2.12; 1.26 [2.00; 1.58]	b: 2.77 dt (14.6, 5.5)
23	3.89 dt (9.7, 7.2) [3.96 ddd (10.5, 7.6, 5.2)]	4.17 ddd (10.8, 7.5, 5.9)	4.84 [4.74]	4.81 ddd (10.4, 8.6, 4.6) [4.70 td (9.4, 5.9)]	a: 5.03 ddd (10.2, 8.8, 5.8) b: overlapped
24	2.81 d (7.3) [2.70 d (7.6)]	2.81 d (7.5)	5.13 [5.23]	5.14 dm (7.3, 1.2) [5.24]	5.20 dm (8.5, 1.4)
26	1.32 s [1.34 s]	1.39 s	1.74 s	1.73 s	1.77 (d (0.8)
27	1.31 s	1.36 s	1.72 s [1.70 s]	1.70 s [1.69 s]	1.74 d (1.4)
28	0.87 s	0.86 s	1.10 s	0.97 s	1.07[f] s
29	0.85 s	0.89 s	1.05 s	0.86 s	1.05[f] s
30	1.04 s [1.03 s]	1.31 s	1.10 s	0.98 s [1.00 s]	1.02 s
2′	2.18 d (6.7)	2.19 d (6.6)			
3′	2.10 m	2.10 qq (6.7, 6.6)			
4′/5′	0.96 d (6.7)	0.96 d (6.6)			

[a] When different from the main component. [b] Run at 500 MHz. [c] Run at 300 MHz. [d] Chemical shift obtained from ^{1}H−^{1}H COSY spectrum. [e] Assignment not confirmed. [f] Exchangeable.

the tetrahydropyran ring were observed. The relative configuration of C-23 was assumed to be identical with that of luvungin C[4] because of the very close correspondence of the chemical shifts. Thus, compound **3** was assigned as 3-*epi*-flindissol (21,23-epoxy-tirucalla-7,24-dien-3β,21-diol). The major isomers of compounds **2** and **3** were established as the 21α-hydroxy epimers by comparison of the carbon shifts with luvungin C[4] with an identical side chain.

Experimental Section

General Experimental Procedures. Melting points were uncorrected. The optical rotations $[\alpha]_D$ were recorded on a JASCO DIP 1000 polarimeter. IR spectra were measured on a Bruker IFS 28 spectrometer. ^{1}H and 2D spectra were acquired on a Varian Unity 500 spectrometer at 499.83 MHz. ^{13}C and APT spectra were recorded on a Varian Gemini 300 spectrometer at 75.5 MHz. EIMS was measured with 70 eV on a AMD 402 (AMD Intectra GmbH) mass spectrometer. ESIMS were recorded on a TSQ 7000 (Finnigan) mass spectrometer with positive ion mode, electrospray voltage of 4.5 kV, and a syringe pump. HRESITOFMS were measured on a QStar Pulsar spectrometer (Applied Biosystems).

Plant Material. Leaves and branches of *L. sarmentosa* (Bl.) Kurz were collected near the village of Lap Thach, Vinh Phuc Province, North Vietnam, in August 1997. The sample was identified by Mr. Ngo Van Trai, Institute of Materia Medica, Hanoi. A voucher specimen (No. 2-27-8-97) was deposited in the herbarium of this same institute.

Extraction and Isolation. The plant material (820 g) of *L. sarmentosa* was dried at room temperature, ground, and extracted three times for 12 h with 95% MeOH. The solvent was evaporated in vacuo, and the aqueous solution was extracted with *n*-hexane, followed by EtOAc and *n*-BuOH (each 3×). The solvents were evaporated in vacuo. The *n*-hexane extract (8 g) was fractionated on silica gel with *n*-hexane−EtOAc (2:8), increasing the amount of EtOAc to 100% (19 fractions). Fractions 13 and 14 were chromatographed on silica gel using *n*-hexane−acetone (8:2) to afford 3-*epi*-skimmiarepin A (**1**, 40 mg). The EtOAc extract (13 g) was chromatographed over silica gel with *n*-hexane−acetone (7:3), increasing the ratio of acetone to 100% (11 fractions). Fractions 4 and 5 were purified by column chromatography on silica gel ($CHCl_3$−acetone, 9:1) followed by reversed-phase chromatography (RP-8), giving 21,23-epoxy-7α,21-dihydroxyapotirucalla-14,24-dien-3-one (**2**, 25 mg) and 3-*epi*-flindissol (**3**, 20 mg).

3-*epi*-Skimmiarepin A (1): needles, mp 115−117 °C (acetone−*n*-hexane); R_f 0.26 (chloroform−acetone, 9:1); $[\alpha]^{22}_D$ +11.0° (*c* 1.00, EtOH); IR ($CHCl_3$) ν_{max} 3587 (OH), 3450−3370 (OH), 2961, 2872, 1718 (ester), 1465, 1389, 1295, 1264, 1169, 1120, 1026, 997, 945 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 572 $[M]^+$ (0.5), 554 $[M - H_2O]^+$ (2), 536 $[M - 2H_2O]^+$ (2), 523 (2), 508 (2), 381 (12), 304 (29), 203 (43), 202 (43), 85 (62), 57 (100); ESIMS *m*/*z* 595 $[M + Na]^+$.

Oxidation of 1. To a suspension of pyridinium chlorochromate (50 mg) in dichloromethane (0.5 mL) was added a solution of **1** (30 mg) in dichloromethane (0.5 mL). The mixture was stirred for 6 h at room temperature and then worked up in the usual manner. The product was subjected to chromatography over silica gel. Elution with 20% acetone in *n*-hexane gave a keto lactone **1a** (20 mg): amorphous; $[\alpha]^{28}_D$ −59.1° (*c* 0.77, $CHCl_3$); ^{1}H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 568 $[M]^+$ (5), 413 $[M - C_8H_{11}O_3]^+$ (cleavage between C-17 and C-20) (100), 383 (3), 311 (15), 293 (8), 175 (13); HRESITOFMS *m*/*z* 569.3810 $[M + H]^+$, calcd for $C_{35}H_{53}O_6$ 569.3836.

21,23-Epoxy-7α,21-dihydroxyapotirucalla-14,24-dien-3-one (2): amorphous; R_f 0.44 (chloroform−acetone, 9:1); $[\alpha]^{24}_D$ −28.0° (*c* 1.00, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS *m*/*z* 453.3329 $[M + H - H_2O]^+$, calcd for $C_{30}H_{45}O_3$ 453.3369.

3-*epi*-Flindissol (3): amorphous; R_f 0.31 (chloroform−acetone, 9:1); $[\alpha]^{25}_D$ −20.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3599 (OH), 3415 (broad), 2952, 2869, 1706, 1445, 1385, 1377, 1024, 983 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 456 $[M]^+$ (2), 438 $[M - H_2O]^+$ (8), 423 $[M - H_2O - CH_3]^+$ (6), 405 (4), 314 (26), 229 (11), 187 (17), 175 (44), 123 (49), 91 (70), 84 (100), 69 (33); HRESITOFMS *m*/*z* 439.3572 $[M + H - H_2O]^+$, calcd for $C_{30}H_{47}O_2$ 439.3576.

Oxidation of 3. Compound **3a** (5 mg) was prepared by the same procedure as described for **1a**: $[\alpha]^{28}_D$ −119.3° (*c* 0.35, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m*/*z* 452 $[M]^+$ (45), 437 (100), 419 (5), 391 (9), 311 (16), 295 (18), 285 (11).

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