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TRITERPENOID SAPONINS FROM THE LEAVES OF *ILEX LATIFOLIA*

MING-AN OUYANG, HAN-QING WANG, YU-QING LIU† and CHONG-REN YANG†*

Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China;
† Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, People's Republic of China

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Key Word Index—*Ilex latifolia*; Aquifoliaceae; triterpene; saponins; latifoloside A–E; pomolic acid; siaresinolic acid; ilexgenin B.

Abstract—Five new triterpenoid saponins latifolosides A–E were isolated from the leaves of *Ilex latifolia*, along with a known compound. Their chemical structures have been elucidated on the basis of the chemical and spectral methods.

INTRODUCTION

Ilex latifolia Thunb, one of the species in the *Ilex* genus used in the tea Ku-Ding Cha [1], has been used in China as a diuretic and remedy for sore throat, weight loss and hypertension [2, 3]. In a previous paper [4, 5], we reported the identity of the triterpenoid glycosides from *I. kudincha*. As a part of our continuing phytochemical research on plants in the genus of *Ilex*, this paper deals with the isolation and structural elucidation of five new triterpenoid saponins, latifoloside A(**1**), B(**2**), C(**3**), D(**4**) and E(**5**), along with a known compound (**6**) from the leaves of *I. latifolia*.

RESULTS AND DISCUSSION

The butanol soluble fraction of the methanol extract of the leaves of *I. latifolia* was repeatedly chromatographed on silica gel to yield six saponins **1**–**6**. By comparing of the ^{1}H and ^{13}C NMR signals with reported data, compound (**6**) was identified as kudinoside G, isolated from *I. kudincha* [4]. Three compounds **1**, **2**, **4** and the other three compounds **3**, **5**, **6** were isomers, respectively. Their IR spectra showed ester group absorption (1730 cm^{-1}) together with strong hydroxyl absorption (3650–3100 cm^{-1}) and a C=C double bond (1640 cm^{-1}).

Compound **1** was a colourless powder and its molecular formula was determined as $C_{47}H_{76}O_{17}$ by the negative FAB-mass spectrum together with its NMR spectrum (DEPT). Cellulase treatment of **1** gave an aglycone (**7**), which was identified as pomolic acid by comparison of its spectral properties with reference data [6]. The ^{1}H, ^{13}C NMR spectra of **1** indicated the presence of three anomeric signals; one α-arabinopyranosyl unit [H-1: δ 4.88 (*d*, *J* = 5.2 Hz), C-1: δ 104.8], one α-rhamnopyranosyl unit [H-1: δ 6.11, *br s*, C-1: δ 101.9], and one β-glucopyranosyl unit [H-1: δ 6.28 (*d*, *J* = 8.0 Hz), C-1: δ 96.0]. Compound **1** afforded L-arabinose, D-glucose, and L-rhamnose (1:1:1) (by HPLC) on acid hydrolysis. For the aglycone moiety, a glycosylation shift was observed for C-3 signal (+10.7 ppm, from δ 78.4 to δ 89.1). In the ^{13}C NMR spectrum, the anomeric carbon of the glucose group at δ 96.0 suggested that **1** had a 28-*O*-glycosidic linkage, which was proved by the ^{13}C NMR signal at δ 177.2 (C-28), alkaline hydrolysis and the HMBC spectrum (see Fig. 1). Alkaline hydrolysis of **1** gave compound (**8**) and D-glucose. The ^{1}H NMR and ^{13}C NMR spectra of **8** indicated the presence of one α-arabinopyranosyl unit [H-1: δ 4.87 (*d*, *J* = 5.3 Hz), C-1: δ 104.9] and one α-rhamnopyranosyl unit [H-1: δ 6.20, *br s*, C-1: δ 102.0]. Comparison of the ^{13}C NMR spectrum of **8** with that of ziyuglucoside **9** [7] showed a glycosylating shift for the C-2 signal of the arabinopyranosyl moiety, demonstrating that an α-rhamnopyranosyl group is located at the C-2 hydroxyl of arabinose. In the HMBC spectrum of **1**, there were three characteristic cross-peaks between C-3 of the aglycone and the anomeric proton of arabinose, between the C-2 of arabinose and the anomeric proton of rhamnose, and between the quaternary carbon C-28 and the anomeric proton of glucose. Thus, compound **1** was identified as 3-*O*-[α-L-rhamnopyranosyl (1-2)]-α-L-arabinopyranosyl pomolic acid 28-*O*-β-D-glucopyranoside, and named as latifoloside A.

* Author to whom correspondence should be addressed.

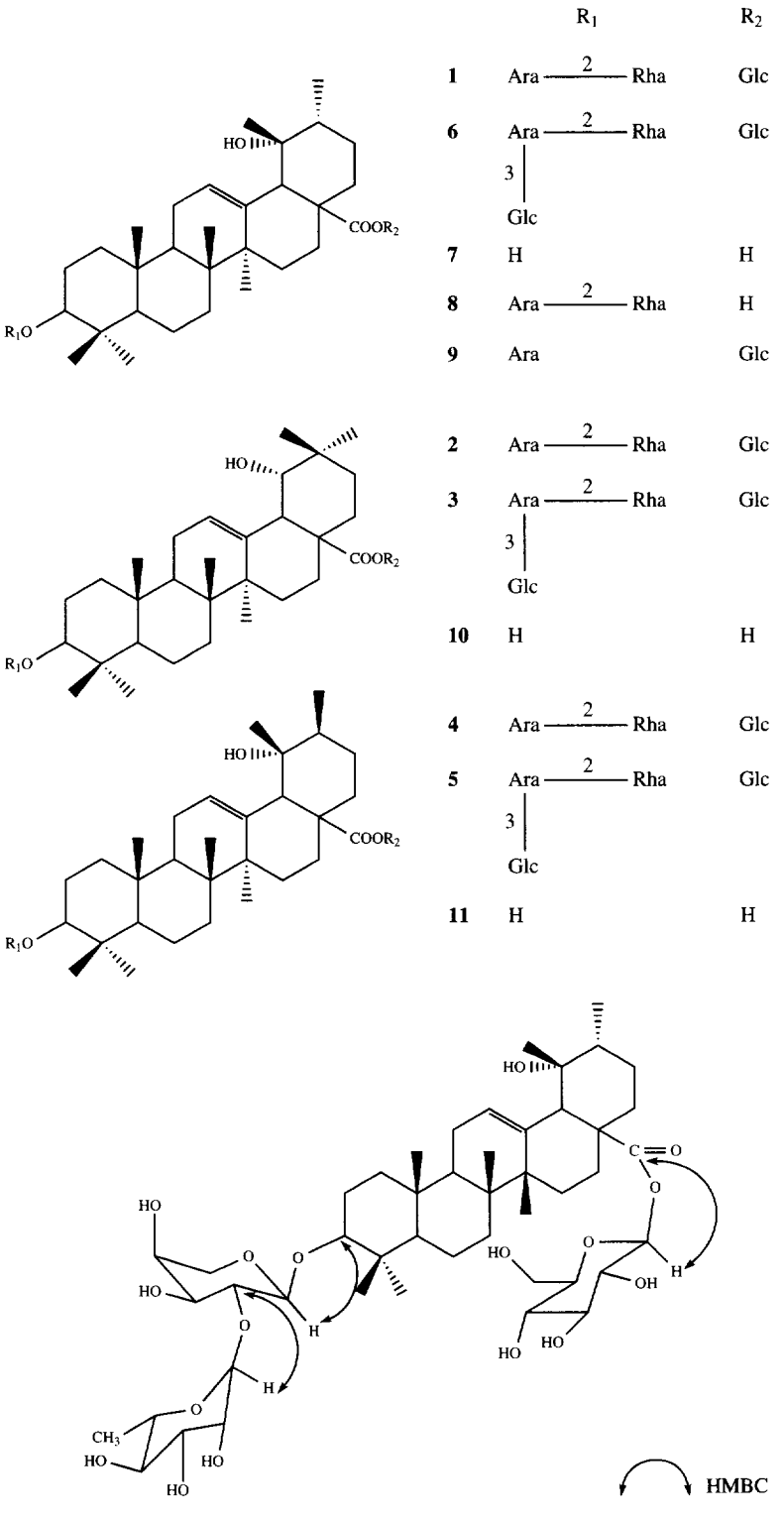

Fig. 1.

Compound **2** gave a quasi-molecular ion peak $[M-H]^-$ at *m/z* 911, which corresponded to $C_{47}H_{76}O_{17}$ in the negative FAB-mass spectrum and ^{13}C NMR (DEPT). Cellulase treatment of **2** provided an aglycone (**10**), which was identical with siaresinolic acid, and a mixture of L-arabinose, D-glucose and L-rhamnose (1:1:1) as determined by HPLC analysis. The IR spectrum of **2** showed a similar absorption pattern to that of latifoloside A. Comparison of the ^{13}C NMR data for **2** with that of the sugar moiety of **1** showed

that **2** and **1** were the same sugar chain. Thus, B(**2**) was concluded to the 3-*O*-[α-L-rhamnopyranosyl(1-2)]-α-L-arabinopyranosyl siaresinolic acid 28-*O*-β-D-glucopyranoside (^{13}C NMR Table 1).

The element composition of compound **3** was proved to be $C_{53}H_{86}O_{22}$ by the negative FAB-mass spectrum and ^{13}C NMR (DEPT). Treatment of **3** with cellulase afforded siaresinolic acid by comparing the ^{13}C NMR data, and a mixture of L-arabinose, D-glucose and L-rhamnose (1:2:1). Comparison of the NMR data for **3** with that for **6** showed that **3** contained the same oligosaccharic sequence as **6** (Table 1). Consequently, latifoloside C (**3**) was identified as 3-*O*-[α-L-rhamnopyranosyl(1-2)]-[β-D-glucopyranosyl (1-3)]-α-L-arabinopyranosyl siaresinolic acid 28-*O*-β-D-glucopyranoside.

The negative fast atom bombardment mass spectrum of compound **4** gave a quasi-molecular ion peak *m/z* 911 $[M-1]^+$, corresponding to $C_{47}H_{76}O_{17}$. Cellulase treatment of **4** furnished an aglycone (**11**) and a mixture of L-arabinose, D-glucose and L-rhamnose (1:1:1) by HPLC. In the ^{1}H NMR spectrum of **4** and **11**, one methyl δ 0.98 (3H, *d*, *J* = 6.6 Hz) was observed, which showed that the methyl connected with the carbon of methine. The NOESY experiment on the aglycone (**11**) exhibited two characteristic cross peaks between the signal assignable to the methine proton at C-18 (δ 3.16) and the signal assignable to the methyl proton at C-29 (δ 1.40), and the signal of the methyl proton at C-30 (δ 0.96). Comparison of the NMR data for **11** with that for **7** showed that resonances of the D- and E-ring carbons were significantly different (Table 1). The chemical shifts (**7** vs **11**) of signals due to C-18 (−7.2 ppm), C-22 (−4.2 ppm) and C-29 (+2.7 ppm) revealed the C-30 methyl group to be β (axial) in place of the α-(equatorial) methyl in **7**. Hence, the aglycone of **4** was formulated as 30(*s*)-3β,19α-dihydroxyurs-12-en-28-oic acid, which has the same aglycone as the triterpene ilexgenin B [6, 8]. As latifolosides A, B, D were isomers, latifoloside D (**4**) was formulated as 3-*O*-[α-L-rhamnopyranosyl (1-2)]-α-L-arabinopyranosyl ilexgenin B 28-*O*-β-glucopyranoside.

By the same deduction, compounds **3**, **5**, **6** were isomers and **5** and **4** have the same aglycone (ilexgenin B). Thus, **5** was determined to be 3-*O*-[α-L-rhamnopyranosyl(1-2)]-[β-D-glucopyranosyl(1-3)-]-α-L-arabinopyranosyl ilexgenin B 28-*O*-β-D-glucopyranoside (^{13}C NMR Table 1).

Table 1. ^{13}C NMR spectral data for latifoloside A–E (400 MHz, pyridine-d_5)

Carbon	A	(**6**)	B	C	D	E
1	39.1	39.3	39.0	39.0	39.2	39.3
2	26.8	26.8	26.7	26.7	27.0	27.0
3	89.1	88.4	89.2	88.3	89.1	88.4
4	39.6	39.7	39.7	39.7	39.7	39.8
5	56.1	56.2	56.2	56.2	56.2	56.2
6	18.9	18.8	18.9	18.8	18.9	18.9
7	33.6	33.6	33.1	33.1	32.1	32.0
8	40.7	40.7	40.2	40.3	40.6	40.6
9	47.9	47.9	48.4	48.4	48.0	48.0
10	37.1	37.1	37.3	37.3	37.2	37.2
11	24.2	24.2	24.2	24.2	24.2	24.2
12	128.5	128.6	123.7	123.6	127.8	127.8
13	139.4	139.4	144.4	144.4	139.0	138.9
14	42.2	42.2	42.2	42.2	42.3	42.3
15	29.4	29.4	29.2	29.2	29.4	29.4
16	26.2	26.3	28.1	28.1	24.9	24.8
17	48.8	48.8	46.6	46.6	48.6	48.5
18	54.6	54.6	44.7	44.7	47.4	47.4
19	72.8	72.8	81.1	81.1	73.6	73.6
20	42.2	42.2	35.7	35.7	42.9	42.9
21	26.7	26.8	29.0	29.0	26.8	26.8
22	37.9	37.9	33.3	33.3	33.7	33.6
23	28.3	28.3	28.2	28.2	28.3	28.3
24	16.8	16.9	17.0	17.1	17.2	17.2
25	15.8	15.9	15.7	15.7	15.9	15.9
26	17.5	17.5	17.6	17.7	17.7	17.6
27	24.7	24.7	24.8	24.2	242.5	24.5
28	177.2	177.3	177.5	177.5	177.5	177.3
29	27.2	27.2	28.7	28.8	29.9	29.8
30	17.1	17.2	25.0	25.0	16.3	16.2
Sugar						
3-*O*-Ara						
1	104.8	104.8	104.9	104.9	104.9	104.8
2	76.1	74.7	76.1	74.7	76.2	74.7
3	74.2	82.1	74.2	82.3	74.2	82.1
4	68.6	68.2	68.7	68.3	68.8	68.2
5	64.5	64.9	64.7	64.6	64.7	64.8
Rha						
1	101.9	102.0	101.9	102.0	101.9	102.0
2	72.7	72.5	72.4	72.6	72.5	72.5
3	72.8	72.6	72.6	72.5	72.5	72.6
4	74.1	74.2	74.1	74.2	74.1	74.2
5	70.0	70.2	70.1	70.1	70.1	70.2
6	18.7	18.7	18.7	18.7	18.8	18.7
Glc						
1		104.7		104.7		104.7
2		75.1		75.1		75.1
3		78.3		78.3		78.3
4		71.3		71.5		71.6
5		78.8		78.6		78.7
6		62.6		62.6		62.6
28-*O*-Glc						
1	96.0	96.0	96.0	96.0	96.0	96.0
2	73.7	74.0	73.7	74.0	73.8	74.0
3	79.0	79.0	79.0	79.0	79.0	79.0
4	71.4	71.5	71.3	71.2	71.2	71.2
5	79.3	79.4	79.3	79.4	79.4	79.4
6	62.5	62.4	62.2	62.2	62.3	62.3

EXPERIMENTAL

All mps were determined on a Beijing Micromelting apparatus and are uncorr. IR were run with a Perkin–Elmer 683 spectrometer. ^{1}H, ^{13}C NMR and 2D NMR were measured by Bruker AM 400 Hz spectromers with pyridine-d_5 as a solvent and TMS as an int. standard. FAB-MS were taken on a ZAM-HB system spectrometer. CC and TLC were performed on silica

gel, RP-8 and RP-18 using the following solvent systems: *a*) $CHCl_3$–MeOH–H_2O (7:3:0.5), $CHCl_3$–MeOH–H_2O (65:35:9) and MeOH–H_2O (6:4–7:3) for saponins; *b*) $CHCl_3$–MeOH–H_2O (7:3:1) lower-layer 9 ml + 1 ml HOAc for sugars. Detection: for saponins, spraying with 5% H_2SO_4 following by heating for 5 min at 105°, for sugar, aniline-phthalate reagent.

Plant material. Ilex latifolia plants were collected in the Hunan Province of China in the Summer of 1993 and identified by Prof. Chong-Ren Yang. A voucher specimen is deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Science.

Extraction and isolation of saponins. The dry leaves (800 g) were extracted x 3 with MeOH at 50° for 8 hr, and the solvent was removed under red. pres. The combined extract (100 g) was suspended in H_2O and the aq. suspension was extracted with $CHCl_3$ and *n*-BuOH, respectively. The *n*-BuOH layer was evapd to dryness to give a residue (50 g) which was chromatographed on silica gel (1.5 kg, 200–300 mesh) with $CHCl_3$–MeOH–H_2O (7:3:0.5) to give 20 fr. Fr. 10 and fr. 14 were sepd on HPLC [ODS, eluting with MeOH–H_2O (8:2–6:4). Flow rate: 5 ml min^{-1}; Injection: 0.4 ml (10 mg ml^{-1})] to afford latifoloside A (**1**, 80 mg), B (**2**, 50 mg), C (**3**, 75 mg), D (**4**, 80 mg), E (**5**, 140 mg) and F (**6**, 125 mg).

Latifoloside A (**1**). Colourless powder, mp (207–210°, $C_{47}H_{76}O_{17}$ IR ν_{max}^{KBr} cm^{-1}: 3433 (OH), 2933 (C-H), 1734 (C=O), 1647 (C=C), 1458, 1386, 1074, 1028. FAB-MS *m/z*: 911 $[M-H]^-$, 749 $[M-H-162]^-$, 603 $[M-H-162-146]^-$, 471 $[M-H-162-146-132]^-$, 453 $[M-H-162-146-132-H_2O]^-$. ^1H NMR: δ 0.89 (*s*, 3-H), 1.05 (*d*, J = 6.4 Hz, 3H), 1.07 (*s*, 3H), 1.39 (*s*, 3H), 1.75 (*s*, 3H), 2.92 (1H, *br s*, 18β-H), 3.23 (1H, *dd*, J = 11.3, 4.2 Hz, 3α-H), 5.55 (1H, *br s*, 12-H), 4.88 (1H, *d*, J = 5.2 Hz, C-1-H of Ara), 6.11 (1H, *br s*, C-1-H of Rha), 1.61 (3H, *d*, J = 6.2 Hz, C-6-H of Rha), 6.28 (1H, *d*, J = 8.0 Hz, C-1-H of Glc). ^{13}C NMR data see Table 1.

Latifoloside B (**2**). Colourless powder, mp 225–228°, $C_{47}H_{76}O_{17}$; IR ν_{max}^{KBr} cm^{-1}: 3404 (OH), 2935 (C-H), 1730 (C=O), 1643 (C=C), 1450, 1380, 1072, 1030. FAB-MS *m/z*: 911 $[M-H]^-$, 749 $[M-H-162]^-$, 603 $[M-H-164-146]^-$, 453 $[M-H-162-146-132]^-$. ^1H NMR: δ 0.87 (*s*, 3H), 0.97 (*s*, 3H), 1.10 (*s*, 3H), 1.12 (*s*, 3H), 1.14 (*s*, 3H), 1.19 (*s*, 3H), 1.64 (*s*, 3H), 3.29 (*dd*, J = 11.2, 4.5 Hz, 3α-H), 5.50 (*br s*, 12-H), 3.54 (*t*-like), 3.50 (*br s*, 18α-H), 4.86 (1H, *d*, J = 5.5 Hz, C-1-H of Ara), 6.11 (1H, *br s*, C-1-H of Rha), 1.61 (3H, *d*, J = 6.2 Hz, C-6-H of Rha), 6.30 (1H, *d*, J = 7.9 Hz, C-1-H of Glc); ^{13}C NMR data see Table 1.

Latifoloside C (**3**). Colourless powder, mp 231–234°, $C_{53}H_{86}O_{22}$, IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 2930 (C-H), 1731 (C=O), 1637 (C=C), 1454, 1386, 1070, 1026. FAB-MS *m/z*: 1073 $[M-1]^-$, 911 $[M-1-162]^-$, 749 $[M-1-2-162]^-$, 765 $[M-1-162-146]^-$, 603 $[M-1-146-2\times162]^-$, 453 $[M-1-146-2\times162-132-H_2O]^-$. ^1H NMR: δ 0.87 (*s*, 3H), 0.97 (*s*, 3H), 1.10 (*s*, 3H), 1.12 (*s*, 3H), 1.14 (*s*, 3H), 1.19 (*s*, 3H), 1.64 (*s*, 3H), 3.30 (1H, *dd*, J = 11.3, 4.3 Hz, 3α-H), 3.51 (*br s*, 18α-H), 5.50 (*br s*, 12-H), 4.86 (1H, *d*, J = 5.7 Hz, C-1-H of Ara), 5.09 (1H, *d*, J = 8.1 Hz, C-1-H of Glc), 6.16 (1H, *br s*, C-1-H of Rha), 1.62 (*d*, J = 6.8 Hz, C-6-H of Rha), 6.36 (1H, *d*, J = 7.5 Hz, C-1-H of Glc); ^{13}C NMR data see Table 1.

Latifoloside D (**4**). Colourless powder, mp 212–215°, $C_{47}H_{76}O_{17}$, IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 2930 (C-H), 1733 (C=O), 1641 (C=C), 1450, 1387, 1074, 1026. FAB-MS *m/z*: 911 $[M-1]^-$, 749 $[M-1-162]^-$, 603 $[M-1-162-146]^-$, 471 $[M-1-162-146-132]^-$, 453 $[M-1-162-146-132-H_2O]^-$. ^1H NMR: δ 0.88 (*s*, 3H), 0.96 (*dd*, J = 6.6 Hz, 3H), 1.06 (*s*, 3H), 1.13 (*s*, 3H), 1.16 (*s*, 3H), 1.40 (*s*, 3H), 1.71 (*s*, 3H), 3.18 (*dd*, J = 11.4, 4.4 Hz, 3α-H), 3.16 (*s*, 18α-H), 5.49 (*br s*, 12-H), 5.27 (*s*, 19β-OH), 4.88 (1H, J = 5.1 Hz, C-1-H of Ara), 6.30 (1H, *d*, J = 7.9 Hz, C-1-H of Glc), 6.11 (1H, *br s*, C-1-H of Rha), 1.60 (3H, *d*, J = 5.7 Hz, C-6-H of Rha). ^{13}C NMR data: see Table 1.

Latifoloside E (**5**). Colourless powder, mp 228–230°, $C_{53}H_{86}O_{22}$, IR ν_{max}^{KBr} cm^{-1}: 3430 (OH), 2932 (C-H), 1730 (C=O), 1454, 1388, 1072. FAB-MS *m/z*: 1073 $[M-1]^-$, 911 $[M-1-162]^-$, 765 $[M-1-162-146]^-$, 749 $[M-1-2\times162]^-$, 603 $[M-1-146-2\times162]^-$, 471 $[M-1-146-2\times162-132]^-$, 453 $[M-1-146-2\times162-132-H_2O]^-$. ^1H NMR: δ 0.87 (*s*, 3H), 0.96 (*dd*, J = 7.0 Hz, 3H), 1.12 (*s*, 3H), 1.16 (*s*, 3H), 1.17 (*s*, 3H), 1.39 (*s*, 3H), 1.71 (*s*, 3H), 3.27 (*dd*, J = 11.2 Hz, 4.3 Hz, 3a-H), 3.16 (*s*, 18α-H), 5.22 (*s*, 19β-OH), 5.50 (*br s*, 12-H), 4.85 (1H, *d*, J = 5.3 Hz, C-1-H of Ara), 5.08 (1H, *d*, J = 7.6 Hz, C-1-H of Glc), 6.13 (1H, *br s*, C-1-H of Rha), 1.61 (3H, *d*, J = 6.1 Hz, C-6-H of Rha), 6.31 (1H, *d*, J = 8.0 Hz, C-1-H of Glc). ^{13}C NMR data: see Table 1.

Compound (**6**). Colourless powder, mp 228–230°, $C_{53}H_{86}O_{22}$, IR ν_{max}^{KBr} cm^{-1}: 3428 (OH), 2932 (C-H), 1734 (C=O), 1638 (C=C), 1454, 1389, 1073, 1026. FAB-MS *m/z*: 1073 $[M-1]^-$, 911 $[M-1-162]^-$, 765 $[M-1-162-146]^-$, 749 $[M-1-2\times162]^-$, 603 $[M-1-146-2\times162]^-$, 453 $[M-1-146-2\times162-132-H_2O]^-$. ^1H NMR: δ 0.87 (*s*, 3H), 1.06 (*d*, J = 6.4 Hz, 3H), 1.12 (*s*, 3H), 1.16 (*s*, 3H), 1.18 (*s*, 3H), 1.39 (*s*, 3H), 1.70 (*s*, 3H), 1.61 (3H, *d*, J = 6.0 Hz, C-6-H of Rha), 4.85 (1H, *d*, J = 5.4 Hz, C-1-H of Ara), 3.27 (1H, *dd*, J = 11.4, 4.5 Hz, 3α-H), 5.54 (1H, *br s*, 12-H), 5.08 (1H, *d*, J = 7.7 Hz, C-1-H of Glc), 6.14 (1H, *br s*, C-1-H of Rha), 6.28 (1H, *d*, J = 8.0 Hz, C-1-H of Glc).

Alkaline hydrolysis of latifoloside A (**1**). LiOH (6 mg) was added to a soln of latifoloside A (**1**, 24 mg) in H_2O (3.0 ml). The reaction mixt. was heated with stirring at 40° for 10 hr, then cooled to ambient temp. and the solvent was removed on a rotary evaporator to give **8** (18 mg). Compound **8** was purified by CC (silica gel, 3 g, CH_2Cl_2–MeOH, 3:1) to afford a hydrolysate (15 mg) and D-glucose.

Acid hydrolysis of latifoloside A–E. A soln of each compound (10 mg) in 5% H_2SO_4 in 50% EtOH was

heated at 100° for 10 hr. The reaction mixt. was diluted with H_2O, neutralized with 2% NaOH and evapd *in vacuo* to dryness. The mole ratio and D/L of each sugar was determined using RI detection (Waters 410) and chiral detection (Shodex OR-1), respectively, in HPLC (Shodex RS pak DC-613, MeCN–H_2O, 3:1, 1 ml min^{-1}, 70°) by comparison with authentic sugars (10 mM each of L-Ara, D-Glc and L-Rha). Each sugar gave a peak as follows: L-Ara, 6.0 min; D-Glc, 7.4 min and L-Rha, 4.8 min.

Enzymatic hydrolysis of latifoloside A (**1**). Latifoloside A (**1**) (35 mg) was taken in EtOH–H_2O (1:9) and 0.01 M NaH_2PO_4 buffer (pH 4.0), 5 ml of each, incubated with crude cellulase (50 mg, Sigma) for two weeks at 37° and worked-up as usual. The crude genin was chromatographed on a silica gel column with $CHCl_3$–MeOH–H_2O (250:40:1) giving pomolic acid (**7**, 12 mg) which was identical with an authentic sample of pomolic acid based on comparison of ^1H and ^{13}C NMR data.

Enzymatic hydrolysis of latifoloside B (**2**) *and C* (**3**). Enzymatic hydrolysis of latifoloside B (**2**) (25 mg) or C (**3**) (30 mg) was carried out in the same way as for **1** to give siaresindic acid (**9**, 8 mg), which had the same NMR data as an authentic sample.

Enzymatic hydrolysis of latifoloside D (**4**) *and E* (**5**). Latifoloside D (**4**) (20 mg), or E (**5**) (30 mg), was hydrolysed in the same way as for **1** to give ilexgenin B (**10**, 8 mg), which had the same NMR data as an authentic sample.

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