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Sesquiterpene Lactones from *Ixeris tamagawaensis* KITAM. II[1)]

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Three new guaianolide glucosides, ixerins D, E and F, and a new melampolide glucoside, ixerin G, have been isolated from the polar fraction of *Ixeris tamagawaensis* KITAM. Their structures were elucidated on the basis of spectral data and several chemical transformations.

Keywords——*Ixeris tamagawaensis*; Compositae; sesquiterpene lactone; glycoside; ixerin D; ixerin E; ixerin F

This study is a continuation of our work on the constituents of *Ixeris tamagawaensis* KITAM. (Compositae), which produces cytotoxic and antitumor sesquiterpene lactones, and from which we have previously isolated four sesquiterpenes, ixerins A, B and C and 8-desoxyurospermal A.[1)] In the present paper, we describe the isolation of four new sesquiterpene lactones, obtained in rather small quantities. One of these is a melampolide, ixerin G. The other three substances are guaianolides, ixerins D, E and F.

We will discuss first the structure elucidation of ixerin D (I), which has the molecular formula $C_{21}H_{30}O_9$, mp 230—231 °C. Its infrared (IR) spectrum showed absorptions at 3450 cm^{-1} (hydroxyl) and 1773 cm^{-1} (lactone), and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed two doublet signals [δ 5.35 (J=3.0 Hz), δ 6.20 (J=3.1 Hz)] which are characteristic of the exocyclic methylene protons of an α-methylene-γ-lactone group. Decoupling experiments showed that the olefinic protons at δ 5.42 and δ 5.72 were coupled with H-3 and H-5, respectively. In the ^{1}H-NMR spectrum, the anomeric proton appeared as a doublet centered at δ 5.10 (J=7 Hz). On the other hand, in the ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectrum, in addition to the signals of glucopyranose attached to secondary alcohol, fifteen signals were assignable to the aglycone. Thus, we deduced that this compound is a sesquiterpene glucoside having the structure I. The application of circular dichroism (CD) spectroscopy has been of great value in the determination of the stereochemistry of many sesquiterpene lactones.[2)] The CD spectral data of I led us to the conclusion that the 6,7-fused lactone was *trans*, and this was confirmed by the coupling constant.[3)]

Acetylation of I with acetic anhydride in pyridine at room temperature afforded the tetraacetate (II), and dehydration with $POCl_3$ gave III, which was identical with glucozaluzanin C tetraacetate.[4)]

The stereochemistry of the C-10 hydroxyl group was determined as follows. The enzymatic hydrolysis of ixerin D gave the aglycone (IV). The acetylation of IV with acetic anhydride in pyridine at room temperature afforded the monoacetate (V) and at 100 °C gave the diacetate (VI). When the ^{1}H-NMR spectra of V and VI were compared, it became apparent that the chemical shifts of H-5 and H-7 of VI exhibited upfield shifts of 0.06 and 0.25 ppm, respectively. This kind of effect is observed only when the hydroxyl group is close to H-5 and H-7, so that the C-10 hydroxyl group must be α-oriented. Acid hydrolysis of ixerin D gave glucose.

Ixerin E (VII) has the molecular formula $C_{21}H_{32}O_9$, mp 214.5—216 °C. The IR and ^{1}H-

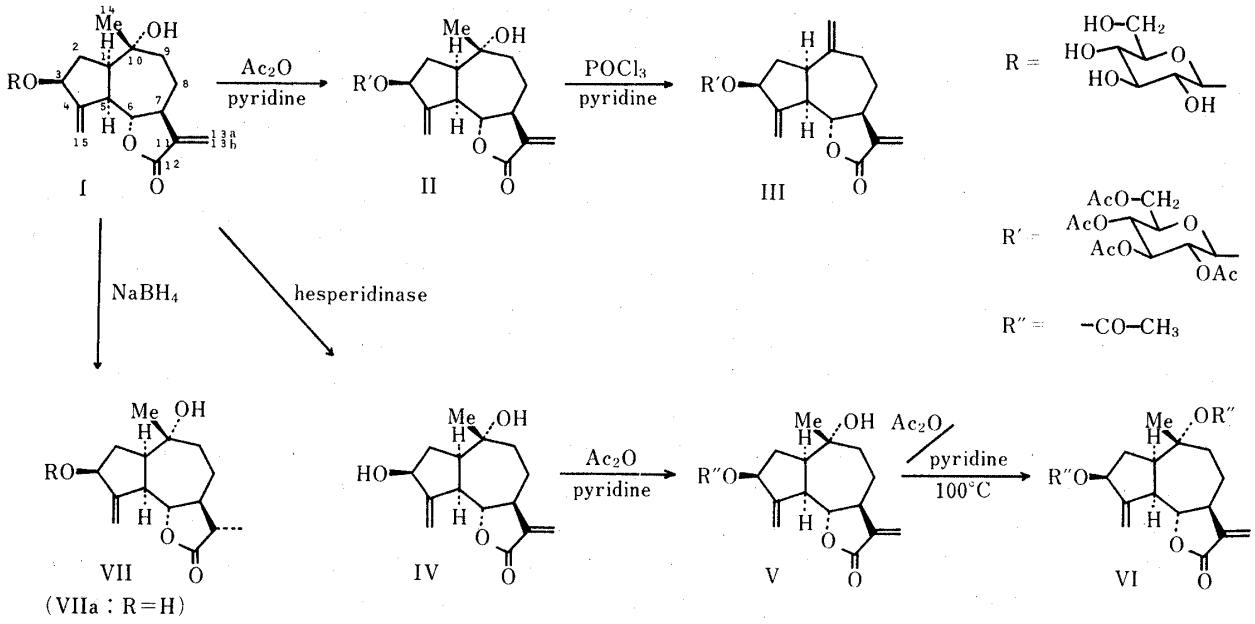


Chart 1

TABLE I. ^{1}H-NMR Data for IV, V, VI in $CDCl_3$ (400 MHz)

	IV	V	VI
1	2.23 (m)	2.25 (m)	2.44 (m)
2	1.96 (m) 2.32 (m)	2.25 (m) 2.42 (m)	2.44 (m) 2.71 (m)
3	4.55 (br t, J=6.5 Hz)	5.53 (br t, J=6.8 Hz)	5.53 (br t, J=7.5 Hz)
5	2.84 (br t, J=9.3 Hz)	2.86 (br t, J=9.2 Hz)	2.80 (t, J=9.0 Hz)
6	4.24 (t, J=10.1 Hz)	4.15 (t, J=10.1 Hz)	4.13 (dd, J=9.5, 9.6 Hz)
7	3.15 (m)	3.21 (m)	2.96 (m)
8	1.45—1.75 (m)	1.50—1.95 (m)	1.53—1.65 (m)
9	1.45—1.75 (m)	1.50—1.95 (m)	1.53—1.65 (m)
13a	5.45 (d, J=3.3 Hz)	5.46 (d, J=3.2 Hz)	5.45 (d, J=3.4 Hz)
13b	6.18 (d, J=3.8 Hz)	6.18 (d, J=3.5 Hz)	6.19 (d, J=3.5 Hz)
14	1.24 (s)	1.24 (s)	1.52 (s)
15	5.28 (br s) 5.35 (br s)	5.29 (br s) 5.41 (br s)	5.36 (br s) 5.44 (br s)
Ac		2.08 (s)	2.04, 2.07 (s)

NMR spectra were similar to those of ixerin D, but there was a methyl doublet at δ 1.18 (J= 7 Hz) instead of the usual two doublets, and the γ-lactone carbonyl resonated at δ 178.4 in the ^{13}C-NMR spectrum, indicating an 11,13-dihydro lactone. Thus, we considered the structure to be VII. The reduction of ixerin D (I) with $NaBH_4$ afforded only one product (VII), which was identical with ixerin E based on a comparison of the IR and ^{1}H-NMR spectra.

When an α-methylene-γ-lactone is reduced with $NaBH_4$, the reduction product generally has an α-oriented methyl group.[4,5] The methyl group of VIIa exhibited an upfield shift of 0.22 ppm in benzene-d_6 relative to chloroform-d_1 solution, and from Narayanan's rule the methyl group should be α-oriented.[6] Acid hydrolysis of ixerin E gave glucose.

Ixerin F (VIII) has the molecular formula $C_{21}H_{30}O_9 \cdot 1/2H_2O$. The IR spectrum of ixerin F showed strong absorptions at 3380 cm^{-1} (hydroxyl) and 1750 cm^{-1} (lactone). Enzymatic hydrolysis of ixerin F (VIII) afforded an aglycone (IX) and its ^{1}H-NMR spectrum showed a

doublet methyl signal at δ 1.10 (J=7 Hz) instead of the two doublets characteristic of an exocyclic methylene in a γ-lactone group. The remaining part of the structure was evident from spin-decoupling experiments on IX. The H-15 olefinic proton signals were seen as triplets (J=1 Hz) at δ 5.32 and δ 5.40 showing long-range coupling with H-3 [δ 4.65 (m)] and H-5 [δ 2.90 (tt, J=9.5, 1 Hz)]. An olefinic proton signal at δ 5.10 (2H, br s) was assigned to H-14 and also had long-range coupling with H-1 (δ 3.30 m). Irradiation at this proton converted the H-5 triple triplet to a double triplet in addition to sharpening the H-14 singlet signal. Further, a triplet at δ 4.00 (J=9 Hz) is characteristic of a guaianolide with a 6,7-fused lactone. The signals in the region of δ 4.60 to δ 4.70 corresponded to 2H; one of these hydrogens was unambiguously H-3, while the other proton is attached to the α-carbon carrying a secondary alcohol. Acetylation of IX supported the presence of two hydroxyl groups. One hydroxyl group was attached to C-3, but the possibility of 2,3-diol system was ruled out by spin-decoupling experiments, so that the other hydroxyl group must be attached to C-9 or C-8. On the basis of a comparison of the ^{13}C-NMR spectrum of VIII with that of 11,13α-dihydroglucozaluzanin C, which was previously prepared in our laboratory, the remaining hydroxyl group was attached to C-9. That is to say, the C-9 carbon signal at δ 72.9 in ixerin F showed a downfield shift of 36.9 ppm and the β-carbons, C-10 and C-8, exhibited downfield shifts of 3.9 and 8.4 ppm, respectively. Furthermore, the γ-carbons C-1, C-7 and C-14 displayed upfield shifts of 2.4, 5.7 and 2.4 ppm, respectively. The above conclusion was confirmed by the existence of allylic coupling between H-9 and H-14. Irradiation at the H-9 signal converted the broad singlet of H-14 into a sharp singlet. Subsequently, in order to determine the stereochemistry of the C-9 hydroxyl group we compared the ^{1}H-NMR spectrum of IX with that of X. The signals of H-1 and H-7 of X showed upfield shifts of 0.2 and 0.1 ppm, respectively. These shifts require that the hydroxyl group has the same spatial direction as H-7 and H-1. If it is assumed that all naturally occurring sesquiterpene lactones have α-oriented H-7 on the basis of biosynthetic considerations, the C-9 hydroxyl group and H-1 are α-oriented in ixerin F (VIII). The configuration of C-5 was determined as follows. The ^{1}H-NMR chemical shift of H-14a (Chart 3) showed an upfield shift in XI, obtained by oxidation with CrO_3, compared with that of IX and no upfield shift was observed in the actylated derivative X. Thus, H-14a is more shielded than in other guaianolides.This is due to the anisotropy of the carbonyl group in the five-membered ring. The H-14a olefinic proton is

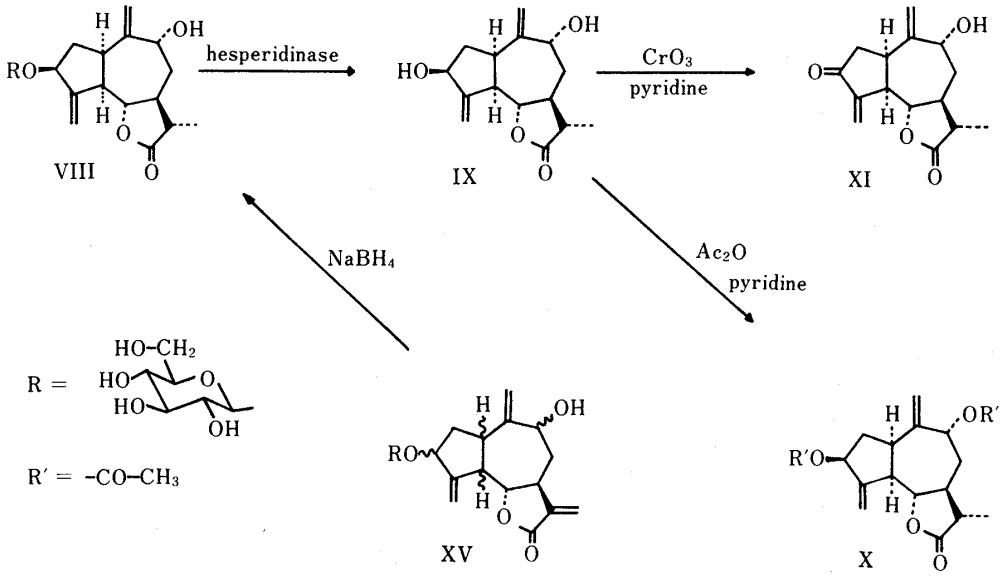
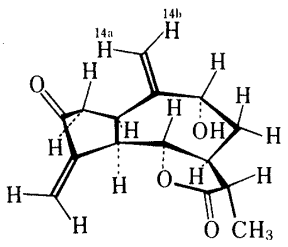
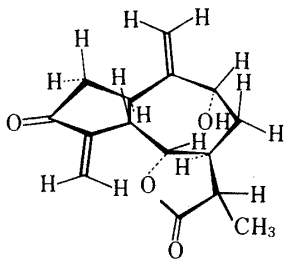


Chart 2



XI (1-5, *cis*)



XI (1-5, *trans*)

Chart 3

TABLE II. ^{1}H-NMR Data for IX, X, XI in $CDCl_3$ (90 MHz)

	IX	X	XI
1	3.30 (m)	3.10 (m)	3.80 (m)
2	1.5—2.6 (m)	1.6—2.6 (m)	1.5—2.9 (m)
3	4.65 (m)	5.59 (br t, J=6.5 Hz)	—
5	2.90 (tt, J=9.5, 1 Hz)	2.83 (tt, J=9.5, 1 Hz)	3.18 (tt, J=9.5, 1 Hz)
6	4.00 (t, J=9 Hz)	3.98 (t, J=9 Hz)	3.95 (t, J=9 Hz)
7	1.5—2.6 (m)	1.6—2.6 (m)	1.5—2.9 (m)
8	1.5—2.6 (m)	1.6—2.6 (m)	1.5—2.9 (m)
9	4.65 (m)	5.55 (br t, J=4 Hz)	4.60 (br s)
11	1.5—2.6 (m)	1.6—2.6 (m)	1.5—2.9 (m)
13	1.30 (d, J=7 Hz)	1.23 (d, J=7 Hz)	1.30 (d, J=7 Hz)
14	5.10 (s)	5.10 (br s) 5.18 (br s)	4.62 (br s) 5.05 (br s)
15	5.32 (t, J=1 Hz) 5.40 (t, J=1 Hz)	5.29 (t, J=1 Hz) 5.42 (t, J=1 Hz)	5.75 (d, J=3 Hz) 6.25 (d, J=3 Hz)
Ac		2.10×2 (s)	

right above the C=O double bond plane. However, in a 1,5-*trans* fused guaianolide, the H-14a proton cannot adopt such a position. The most probable conformation of ixerin F, deduced from these data and from analysis of the Dreiding stereomodel, is shown in Chart 3. The stereochemistry of C-13 and the γ-lactone ring was determined from the results described below. The $NaBH_4$ reduction of XV, which was previously isolated in our laboratory and has a 6,7-*trans* fused lactone ring (J_{7-13a}=3.3 Hz, J_{7-13b}=3.1 Hz), gave dihydro derivative, which was identified as ixerin F (VIII) (^{1}H-NMR and IR). The stereochemistry of C-3 is still unknown. However, the chemical shifts of C-2, C-3, C-4 and C-5 were nearly the same as those of other guaianolides with a β-oriented hydroxyl group, so the hydroxyl group of ixerin F (VIII) may be β-oriented. Acid hydrolysis of ixerin F gave glucose.

Ixerin G (XII) has the molecular formula $C_{29}H_{34}O_{11}\cdot 1/2H_2O$ and its ultraviolet (UV) spectrum showed maximum absorptions at 227.5 and 277.5 nm. Its IR spectrum showed absorptions at 3420 cm^{-1} (hydroxyl), 1750 cm^{-1} (lactone) and 1742 cm^{-1} (aldehyde). The ^{1}H-NMR spectrum was nearly the same as that of ixerin C (XIII), which had previously been isolated from this plant in our laboratory.[1)]

Saponification with alkali gave *p*-hydroxyphenylacetic acid and ixerin B (XIV), which had also been isolated previously, so that ixerin G has *p*-hydroxyphenylacetic acid esterified at the glucose moiety of ixerin B. In order to determine the structure, we compared the ^{13}C-NMR spectrum with that of ixerin B. The signals due to glucose exhibited upfield shifts of 3.2 ppm at C-3 and 3.3 ppm at C-1, but a downfield shift of 1.1 ppm at C-2. From these results, we concluded that the *p*-hydroxyphenylacetic acid moiety is bound at C-2 of the

TABLE III. ^{13}C-NMR Data for I, VII, VIII, 11,13-Dihydroglucozaluzanin C

	I	VII	VIII	11,13-Dihydro-glucozaluzanin C
Aglycone moiety				
1	50.3[a)]	48.7[c)]	41.8	44.2[f)]
2	35.4[b)]	35.3[d)]	37.3	37.8
3	79.8	79.9	80.6	80.5
4	150.7	151.5	151.2	150.7[h)]
5	50.7[a)]	49.7[c)]	49.4	50.2[g)]
6	81.9	82.6	83.9	83.4
7	44.5	39.0	36.5	42.2[f)]
8	24.9	26.4	40.7	32.3
9	35.5[b)]	35.2[d)]	72.9	36.0
10	73.4	73.6	153.5	149.6[h)]
11	142.8	43.2	45.3	50.0[g)]
12	170.1	178.5	178.4	178.2
13	118.2	13.3	13.2	13.3
14	30.3	28.1	110.8[e)]	113.2
15	112.9	110.6	111.6[e)]	112.0
Glucose moiety				
1	103.6	104.0	104.3	104.1
2	75.2	75.3	75.2	75.2
3	78.4	78.5	78.4	78.5
4	71.9	72.0	71.8	71.8
5	78.1	78.2	78.0	78.1
6	63.0	63.0	62.9	63.0

a—*h*) May be interchanged in each column (measured in pyridine-d_5).

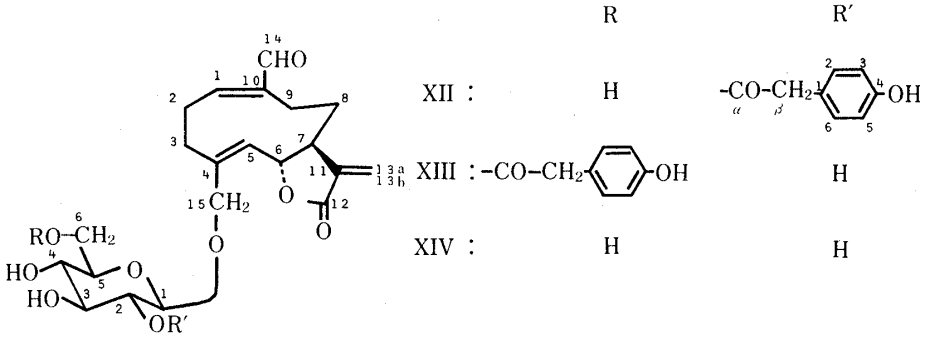


Chart 4

glucose moiety of ixerin B. Acid hydrolysis of ixerin G afforded glucose.

Experimental

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 digital polarimeter and CD was determined with a JASCO J-400 X spectropolarimeter. IR spectra were run on a JASCO A 202 grating infrared spectrophotometer, UV spectra on a Shimadzu UV-360 recording spectrophotometer and mass spectra (MS) on a JEOL JMS-D/100 mass spectrometer. NMR spectra were recorded on JEOL JNM GX-400 and JEOL FX-90 Q spectrometers (^{1}H-NMR: 399.65 and 89.55 MHz, ^{13}C-NMR: 22.5 MHz); chemical shifts were given in ppm with tetramethylsilane as an internal standard. Field desorption (FD)-MS were measured on a JEOL JMS-D/300, with an MS-FD/03 ion source.

Isolation——Whole plants of *Ixeris tamagawaensis* (7.2 kg) were extracted with methanol under reflux. The

TABLE IV. ^{13}C-NMR Data for XII, XIV in Pyridine-d_5

	XII	XIV
Aglycone moiety		
1	153.3	153.4
2	27.3	27.1
3	33.3	33.5
4	138.1	138.4
5	129.7	129.7
6	79.5	79.4
7	46.2	46.1
8	22.2	22.1
9	24.3	24.1
10	145.0	145.0
11	140.6	140.5
12	170.1	170.1
13	118.2	118.2
14	195.9	196.1
15	67.4	67.8
Glucose moiety		
1	101.7	105.0
2	76.1	75.0
3	75.3	78.5
4	71.9	71.6
5	78.7	78.5
6	62.6	62.8
p-Hydroxyphenylacetic acid moiety		
α	171.2	
β	40.9	
1	125.2	
2	116.3	
3	131.0	
4	157.9	
5	131.0	
6	116.3	

extract was concentrated *in vacuo* and the residue was suspended in water. This suspension was extracted with ethyl acetate and with *n*-butanol to give gums (106 and 46 g, respectively). The *n*-butanol extract was chromatographed repeatedly on a silica gel column to give sesquiterpenes.

Ixerin D (I)——Colorless needles (30 mg), mp 230—231 °C (MeOH). $[\alpha]_D^{19}$: −32.7° (c=0.51, MeOH). *Anal.* Calcd for $C_{21}H_{30}O_9$: C, 59.14; H, 7.09. Found: C, 58.89; H, 7.20. IR ν_{max}^{KBr} cm^{-1}: 3450, 3300, 1773. ^{1}H-NMR (pyridine-d_5) δ: 1.32 (3H, s, H-14), 2.95 (1H, br t, J=8.5 Hz, H-5), 3.35 (1H, m, H-7), 4.89 (1H, br t, J=7 Hz, H-3), 5.10 (1H, d, J=7 Hz, anomeric), 5.35 (1H, d, J=3.0 Hz, H-13a), 5.42 (1H, br s, H-15), 5.72 (1H, br s, H-15), 6.20 (1H, d, J=3.1 Hz, H-13b). CD (c=3.14×10^{-4}, MeOH) [θ] (nm): −4500 (255). FD-MS m/z: 427 (M+H)$^+$.

Ixerin E (VII)——Colorless needles (11 mg) mp 214.5—216 °C (MeOH–C_6H_6). $[\alpha]_D^{19}$: −12.3° (c=0.16, MeOH). *Anal.* Calcd for $C_{21}H_{32}O_9$: C, 58.87; H, 7.52. Found: C, 58.78; H, 7.26. IR ν_{max}^{KBr} cm^{-1}: 3500, 3460, 1775. ^{1}H-NMR (pyridine-d_5) δ: 1.25 (3H, s, H-14), 1.18 (3H, d, J=7 Hz, H-13), 2.82 (1H, br t, J=8.5 Hz, H-5), 4.82 (1H, br t, J=7 Hz, H-3), 4.99 (1H, d, J=7 Hz, anomeric-H), 5.34, 5.72 (each 1H, br s, H-15). FD-MS: m/z: 429 (M+H)$^+$.

Ixerin F (VIII)——Amorphous powder (700 mg). $[\alpha]_D^{19}$: +1.0° (c=0.48, MeOH). *Anal.* Calcd for $C_{21}H_{30}O_9 \cdot 1/2H_2O$: C, 57.92; H, 7.20. Found: C, 57.66; H, 7.04. IR ν_{max}^{KBr} cm^{-1}: 3380, 1750. ^{1}H-NMR (pyridine-d_5) δ: 1.10 (3H, d, J=7 Hz, CH_3), 2.89 (1H, br t, J=8.5 Hz, H-5), 4.95 (1H, d, J=7.5 Hz, anomeric-H), 5.08 (2H, br s, H-14), 6.45, 6.85 (each 1H, br s, H-15). FD-MS m/z: 427 (M+H)$^+$.

Ixerin G (XII)——Amorphous powder (5 mg). $[\alpha]_D^{22}$: −15.1° (c=0.11, MeOH). *Anal.* Calcd for $C_{29}H_{34}O_{11} \cdot 1/2H_2O$: C, 61.38; H, 6.22. Found: C, 61.55; H, 6.15. IR ν_{max}^{KBr} cm^{-1}: 3420, 1750, 1742. UV λ_{max}^{MeOH} nm (log ε): 227.5 (4.19), 277.5 (3.37). ^{1}H-NMR (pyridine-d_5) δ: 3.85 (2H, s, Ar-CH_2), 5.01 (1H, d, J=8 Hz, anomeric-H), 5.39 (1H, d, J=3.3 Hz, H-13a), 5.61 (1H, t, J=9.5 Hz, H-2 of glucose moiety), 6.38 (1H, br t, J=8 Hz, H-1), 6.81 (1H, d, J=3.3 Hz, H-13b), 7.06 (2H, d, J=9 Hz, H-2,6 of ester), 7.44 (2H, d, J=9 Hz, H-3, 5 of ester), 9.53 (1H, br s, H-14). FD-MS m/z: 559 (M+H)$^+$.

Dehydration of I——Ixerin D (15 mg) was dissolved in acetic anhydride and pyridine (0.5 ml each) and the solution was left for 30 min at room temperature. The mixture was evaporated *in vacuo*, and 0.5 ml of pyridine and 5 drops of $POCl_3$ were added to the residue. The mixture was left to stand for 4 h at room temperature, then excess H_2O was added in order to destroy the reagent. The aqueous solution was extracted with ethyl acetate 3 times. The residue (19 mg) from the extract was purified by silica gel column to afford colorless needles (III) (recrystallized from methanol). This product was identical with authentic glucozaluzanin C tetraacetate [mp, ^{1}H-NMR, IR] mp 159.5—161 °C (lit. 159—160 °C). IR ν_{max}^{KBr} cm^{-1}: 1770, 1746.

Enzymatic Hydrolysis of I——Ixerin D (100 mg) was dissolved in water (3 ml) and treated with hesperidinase for 3 h at 35 °C with stirring. The solution was extracted with ethyl acetate 3 times and purified on a silica gel column to give an aglycone (IV) (amorphous powder 45 mg). ^{1}H-NMR: Table I.

Acetylation of IV——IV (20 mg) was dissolved in acetic anhydride and pyridine (2 ml each). The solution was left for 12 h, then concentrated *in vacuo* to give the monoacetate (V) (25 mg). V (10 mg) was dissolved in acetic anhydride and pyridine (1 ml each), and the solution was heated at 100 °C in a water bath for 10 h to give the diacetate (VI). These compounds were purified by silica gel column chromatography (amorphous powders, 8 and 5 mg, respectively). ^{1}H-NMR: Table I.

Reduction of I——Ixerin D (I) (50 mg) was dissolved in methanol (5 ml) and stirred with $NaBH_4$ (20 mg) for 1 h at room temperature. A small amount of acetic acid and excess water were added, the methanol was evaporated off *in vacuo*, and the residual solution was extracted with *n*-butanol 5 times. Recrystallization from benzene–methanol gave colorless needles (VII) (45 mg) (mp 214.5—216 °C). This product was identical with ixerin E [^{1}H-NMR, IR, mixed mp]. ^{1}H-NMR, ^{13}C-NMR: ixerin E.

Enzymaic Hydrolysis of VIII——Ixerin F (VIII) (240 mg) and hesperidinase (120 mg) were dissolved in water and the solution was stirred for 12 h at 35 °C, then extracted with ethyl acetate 3 times. The residue from the extract was purified by silica gel column chromatography to give the aglycone (IX) (amorphous powder 90 mg). ^{1}H-NMR: Table II.

Oxidation of IX——IX (20 mg) was dissolved in pyridine and treated with CrO_3–pyridine complex. The mixture was stirred for 8 h at room temperature. After being diluted with water, the reaction mixture was passed through an Amberlite XAD-2 column, which was washed with water. The methanol eluate was purified on a silica gel column chromatography to give the monoketone (XI) (amorphous powder 3 mg). ^{1}H-NMR: Table II.

Acetylation of IX——IX (5 mg) was dissolved in pyridine and acetic anhydride (1 ml each) and the solution was left for 12 h. The solution was concentrated *in vacuo* to give a residue, which was purified by silica gel column to provide 5 mg of pure X (amorphous powder). ^{1}H-NMR: Table II.

Saponification of XII——A solution of ixerin F (XII) (2 mg) in aqueous 2% NaOH was stirred for 3 h at room temperature under a nitrogen atmosphere. The solution was acidified with diluted HCl and extracted with ethyl acetate and *n*-butanol 3 times. The ethyl acetate extract was concentrated to give *p*-hydroxyphenylacetic acid, which was detected by high performance liquid chromatography (HPLC) in comparison with a standard sample. The *n*-butanol extract was concentrated to give ixerin B (XIV), which was identified by thin layer chromatography (TLC). HPLC conditions: Lichrosorb RP-8 column, 4 mm × 25 cm; eluent, H_2O–CH_3CN (75 : 25); UV detector at 240 nm.

Acid Hydrolysis of Glycosides——A solution of a glycoside (*ca.* 1 mg) in 10% H_2SO_4 (1 ml) was heated in a boiling water bath for 30 min. The solution was passed through an Amberlite IR-45 column and concentrated to give a residue, which was reduced with $NaBH_4$ (*ca.* 3 mg) for 1 h. The reaction mixture was passed through an Amberlite IR-120 column and concentrated to dryness. Boric acid was removed by distillation with methanol and the residue was acetylated with acetic anhydride (1 drop) and pyridine (1 drop) at 100 °C for 1 h. The reagents were evaporated off *in vacuo*. Glucitol acetate was detected by gas chromatography from each glycoside. Conditions: 1.5% OV-17 column, 3 mm × 1 m; column temperature, 230 °C; carrier gas, N_2; t_R, 3.8 min.

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References and Notes

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