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A TRITERPENOID SAPONIN FROM *THLADIANTHA HOOKERI* VAR. *PENTADACTYLA*

RUI-LIN NIE, TAKAHIRO TANAKA,* MASAZUMI MIYAKOSHI,* RYOJI KASAI,* TOSHINOBU MORITA,* JUN ZHOU and OSAMU TANAKA*,†

Kunming Institute of Botany, Chinese Academy of Science, Kunming Yunnan, China; *Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan

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Key Word Index—*Thladiantha hookeri* var. *pentadactyla*; Cucurbitaceae; Wu-ye-chi-pa; saponin; Chinese folk medicine; gypsogenin.

Abstract—A new triterpenoid saponin was isolated from the tubers of *Thladiantha hookeri* C. B. Clarke var. *pentadactyla* in a high yield (9.7%). On the basis of chemical and spectral evidence, the structure was determined as β-xylopyranosyl-(1→3)-β-xylopyranosyl-(1→4)-α-rhamnopyranosyl-(1→2)-β-xylopyranosyl ester of 3-*O*-β-galactopyranosyl-(1→2)-β-glucuronopyranosyl-gypsogenin. The solubilizing effect of this saponin is also described.

INTRODUCTION

In continuation of studies on Chinese cucurbitaceous folk medicine, the present paper reports the isolation and structural determination of a new saponin named thladioside-H1 (**1**) from tubers of *Thladiantha hookeri* C. B. Clarke var. *pentadactyla* Cogn. (Chinese name: Wu-ye-chi-pa).

RESULTS AND DISCUSSION

An ethanolic extract of the tubers was separated as described in the Experimental, affording a new saponin named thladioside-H1 (**1**) in a surprisingly high yield (9.7%).

Compound **1** was hydrolysed with acid to yield glucuronic acid(GlcUA), galactose(Gal), xylose(Xyl) and rhamnose(Rha) as sugar components. On enzymatic hydrolysis with crude hesperidinase [1], compound **1** gave gypsogenin (**2**) [2, 3] as an aglycone. The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) of compound **1** showed the presence of six monosaccharide units. On comparison of the ^{13}C NMR spectrum of compound **1** with that of compound **2**, the glycosylation shifts [4] were observed for C-2, C-3, C-23 and C-28, indicating that **1** was a bisdesmoside of **2** with glycosyl linkages at both the 3-hydroxyl and 28-carboxyl groups.

Since the aldehyde group would perturb the structure elucidation, compound **1** was converted into a relatively stable saponin (**3**) of hederagenin (**4**) [2, 5] by reduction of the aldehyde group to a primary alcohol with sodium borohydride in water.

On selective cleavage of the ester glycoside linkage at C-28 with LiI-2,6-lutidine in methanol [6], compound **3** gave a monodesomoside (**5**) and a methyl tetrasaccharide (**6**), the former of which was purified as a monomethyl ester (**7**) by mild treatment with methanolic hydrogen chloride. Acid hydrolysis of compound **7** yielded GlcUA and Gal. Anomeric configurations of both the glycosyl linkages were assigned as β by the coupling constant of the anomeric proton signals. The location of the methyl

Table 1. ^{13}C NMR chemical shifts of aglycone moieties in C_5D_5N

C	1	2	7	8	9	10	11
1	38.0	38.4	38.5	38.8	38.6	38.7	38.6
2	25.1	27.0	25.9	25 8	27.0	27.1	27.0
3	82.0	71.6	82.3	82.3	71.5	71.7	71 6
4	54.9	56.2	42.0[c]	42.3	56.2	56.3	56.3
5	48.6[a]	48.0[a]	48.0[a]	48.2[a]	48.0[a]	48.0	48.0
6	20.6	21.0	18.1	18.2	21.1	21.3	21.2
7	32.5	32.5	32.8	32.9	32.4[b]	32.5	32.5[a]
8	40.1	40.0	39 7	39.8	40.2	40.2	40.2
9	47.8[a]	47.7[a]	47.6[a]	47.8[a]	47.8[a]	48.0	48.0
10	36.2	36.2	36.8	37.0	36.1	36.2	36.2
11	23.6	23 8	23.8	23.8	23.6	23.7	23.6
12	122.5	122.2	122.5	122.6	122.4	122.6	122.5
13	144.0	144.8	144.5	144.8	144.2	144.2	144 1
14	42 2	42.2	42 1	42.3	42.4	42.4	42.4
15	28.4	28.2	28.3	28 5	28.7	28.5	28.5
16	23.6	23.8	23.8	23.9	23.2	23.4	23.2
17	47.2	46.6[b]	46.6[b]	46.8	47.2	47.3	47.2
18	41.9	41 9	42.1[c]	42 3	41.9	42.0	41.9
19	46.7	46.5[b]	46 4[b]	46.8	46.4	46.5	46.3
20	30.7	30.9	30.9	31.0	30.7	30.8	30.8
21	34.1	34.2	34.2	34.3	34.1	34.2	34.0
22	32.5	33.1	33.2	33.3	32.5[b]	32.5	32.7[a]
23	210.0	207.1	64.1	64.5	207.1	207 3	207.8
24	10.0	9.6	13.5	13 7	9.6	9.8	9.7
25	15.7	15.7	16.0	16.1	15.7	15.9	15.8
26	17.3	17 3	17.4	17.6	17.3	17.4	17.4
27	25.8	26.1	26.2	26.3	25.8	25.9	25.9
28	176.4	180.0	180 2	180.2	176.4	176.5	176.4
29	33 1	33.2	33.2	33.3	33.1	33.1	33.1
30	23.6	23.8	23.8	23.9	23.6	23.7	23.6

[a, b, c] Assignments may be interchanged in each column.

†Author to whom correspondence should be addressed.

Table 2. ^{13}C NMR chemical shifts of sugar moieties in C_5D_5N

	1	7		8	9	10	11
3-O-GlcUA-1	103 4	104.2	3-O-Glc-1	103 9			
2	83 8	83 3	2	83 9			
3	77 4	77 0[a]	3	78 0			
4	72 8	72 7	4	71 0			
5	77 4	76 7[a]	5	78 5			
6	172 3	170 4	6	62.7			
Gal-1	106.0	106.6	Gal-1	105 1			
2	74 2	74.4	2	74.4			
3	75 0	75 0	3	75 0			
4	70.0	69 6	4	71 0			
5	77 4	77 5	5	77 0			
6	62 0	61 4	6	61 5			
28-O-Xyl-1	95 1				95 3	95 2	95 2
2	78 0				78 3	78.6	78 0
3	75 8				75 4	75.9[a]	75.9[a]
4	70 7				70 8	70 9	70 8
5	67 2				67 2	67 2[b]	66 9[b]
Rha-1	101 2				101 4	101 3	101 2
2	72 5				72 1	72 5	72 5
3	71 5				72 5	71 3	71 6
4	84 9				73 7	85 1	84 8
5	68 1				69.8	68 4	68 2
6	18 5				18.7	18 6	18 5
Xyl-1	105 7					107 6	105 7
2	75 0[a]					76 2[a]	75 1[a]
3	87 0					77 7	87 1
4	68 8					70 9	68.9
5	67 2					67 5[b]	66 7[b]
Xyl-1	106 8						106.2
2	74 8[a]						75 1[a]
3	77 4						77.5
4	70 7						70 8
5	67 2						67 3

[a,b,c] Assignments may be interchanged in each column

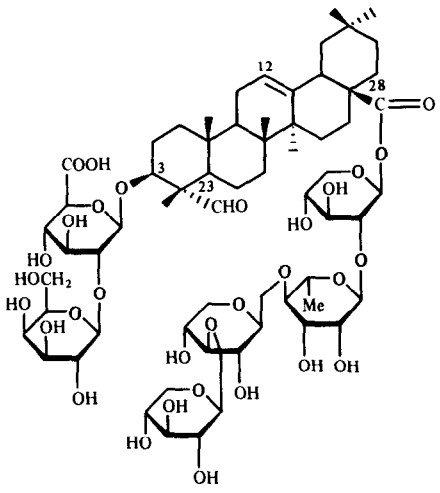
ester group of compound **7** at the GlcUA unit was confirmed by the ^{13}C NMR spectrum (Table 1) Compound **7** was reduced with sodium borohydride or sodium borodeuteride in ethanol [7], whereby the GlcUA unit was converted into a corresponding neutral hexose unit or deuterated neutral hexose unit, affording **8** and **8**-$^2H_2$, respectively. The methylation-analysis [8] of compound **8**-$^2H_2$, afforded 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methylhexitol and 1,2,5-tri-*O*-acetyl-6-dideutero-3,4,6-tri-*O*-methylhexitol, which were proved to be associated with terminal galactopyranosyl and 2-linked glucopyranosyl-d_2 residues, respectively, by GC-MS The coupling constant of both the anomeric proton signals indicated the β-anomeric configuration It follows that the structure of **5** was assigned as the 3-*O*-β-galactopyranosyl-(1→2)-β-glucuronopyranoside of compound **4** and this structure was supported by the ^{13}C NMR spectrum

Compound **1** was treated with β-glucuronidase and the resulting neutral prosapogenin mixture was separated by CC to give three compounds (**9**–**11**). The FD mass spectra of compounds **9**–**11** exhibited molecular ion peaks as a cationized cluster ion at *m/z* 771 $[M+Na]^+$ [M=**2**−(Xyl-Rha)], 903$[M+Na]^+$ [M=**2**-(2Xyl-Rha)], 1035 $[M+Na]^+$ [M=**2**-(3Xyl-Rha)], respectively, so that compound **11** was assigned as 3-desglyco-prosapogenin of **1**.

The EI-mass spectrum of a peracetate of compound **9** exhibited fragment ions at *m/z* 273 $[(Rha)Ac_3]^+$ and 489 $[(Rha\text{-}Xyl)Ac_5]$, which, coupled with the ^1H(anomeric proton) and ^{13}C NMR signals due to the sugar moiety, led to the formulation of **9** as the α-rhamnopyranosyl-(1→2)-β-xylopyranosyl ester of compound **2**

The EI-mass spectrum of a peracetate of compound **10** showed fragment ions at *m/z* 259$[(Xyl)Ac_3]$. 489$[(Xyl\text{-}Rha)Ac_5]$ and 705$[(Xyl\text{-}Rha\text{-}Xyl)Ac_7]$ Compound **10** was treated with LiI-2,6-lutidine in methanol, yielding a methyl trisaccharide (**12**). The methylation analysis of compound **12** revealed the presence of terminal xylopyranosyl and 2-linked xylopyranosyl and 4-linked rhamnopyranosyl residues. This evidence coupled with the formulation of compound **9** led to the structure of compound **10** as shown in Chart 1 The anomeric configuration of each glycosyl linkage of **10** was substantiated by the ^1H and ^{13}C NMR spectra

The methylation analysis of compound **6** obtained from **3** (*vide supra*) proved the presence of terminal, 2-



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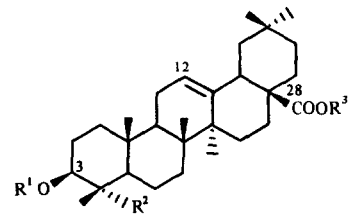

	R^1	R^2	R^3
2	—H	—CHO	—H
3	β-GlcUA-(β-^{2})-Gal	—CH_2OH	β-Xyl-(α-^{2})-Rha-(β-^{4})-Xyl-(β-^{3})-Xyl
4	—H	—CH_2OH	—H
5	β-GlcUA-(β-^{2})-Gal	—CH_2OH	—H
7	β-GlcUA(^{6}COOMe)-(β-^{2})-Gal	—CH_2OH	—H
8	β-Glc-(β-^{2})-Gal	—CH_2OH	—H
9	—H	—CHO	β-Xyl-(α-^{2})-Rha
10	—H	—CHO	β-Xyl-(α-^{2})-Rha-(β-^{4})-Xyl
11	—H	—CHO	β-Xyl-(α-^{2})-Rha-(β-^{4})-Xyl-(β-^{3})-Xyl

linked, 3-linked xylopyranosyl and 4-linked rhamnopyranosyl residues. Based on this evidence and the formulation of **9** and **10** together with the elucidation of the anomeric configuration by the ^1H and ^{13}C NMR spectra, the structure was assigned to compound **11**.

Accordingly, the structure of compound **1** was established as 28-*O*-β-xylopyranosyl-(1→3)-β-xylopyranosyl-(1→4)-α-rhamnopyranosyl-(1→2)-β-xylopyranosyl ester of 3-*O*-β-galactopyranosyl-(1→2)-β-glucuronopyranosyl-gypsogenin.

In our serial studies on surfactive properties of natural oligo-glycosides, we have disclosed that glucuronide saponins such as ginsenoside-Ro (oleanolic acid saponin of Ginseng root) [9] and glycyrrhizin [10] strongly increase the water solubility of saikosaponins, active principles of *Bupleuri radix*. The essential role of the glucuronide moiety in this solubilizing effect was also revealed. In the present study, this specific solubilizing effect was observed with **1**, the saponin with a glucuronide unit (Table 3). Compound **1** also solubilized Yellow OB (a water insoluble synthetic dye) and increased the water solubility of saponin A from pericarps of *Sapindus mukurossi* which is sparingly soluble in water (Tables 4, 5).

EXPERIMENTAL

NMR spectra were measured in C_5D_5N–TMS, ^1H NMR at 100 or 270 MHz and ^{13}C NMR at 25 and 67.8 MHz. The solvents used for spectral determination were; MeOH($[\alpha]_D$); Nujol(IR), unless otherwise stated. Acid hydrolysis of saponins followed by identification of the resulting monosaccharides and the methylation analysis of sugar moiety by GC-MS were carried out as described in the previous paper [8]. For CC, silica gel 60 was used. The solvent systems for CC was all homogeneous.

Plant material. Thladiantha hookeri C. B. Clarke var. *pentadactyla* Cogn. was collected at Lufeng (Yunnan), China in June 1970 and identified by Emeritus Professor C.-Y. Wu (Kunming Institute of Botany, Chinese Academy of Science). A voucher specimen has been deposited in the Herbarium of this Institute.

Extraction and separation The dried and powdered tubers (2 kg) were extracted with hot EtOH. After removal of the solvent by evapn, the residue was separated into H_2O-soluble and insoluble portions by treatment with H_2O and an aq. soln of the water-soluble portion was extracted with Et_2O and then with *n*-BuOH satd with H_2O. After removal of solvents by evapn, the *n*-BuOH extract (210 g) was proved to consist of an almost homogeneous saponin, compound **1** by TLC on silica gel ($CHCl_3$–MeOH–H_2O, 13.7 2, lower layer), visualized by spraying with 10% ethanolic H_2SO_4 followed by heating at 110° and on a reverse phase plate, HPTLC RP-3 Merck [solvent 70% MeOH, visualized in the same way as above] This fraction

Table 3. Solubilizing effect on saikosaponin-a in water at 37°

Compound (1 mg/ml)	Solubility of saikosaponin-a (mg/ml)
None	0.1
Ginsenoside Ro	3.4
Glycyrrhizin	5.0
Thladioside H1 (**1**)	5 1

Table 4. Solubilizing effects on Yellow OB in buffer at 37°

Compound (1 mM)	Solubility of Yellow OB
None	Insoluble
Ginsenoside Ro	25.9 μM
Thladioside H1 (**1**)	39 2 μM

M/80 phosphate buffer (pH 6 5 ionic strength 0.02).

Table 5 Solubilizing effects on saponin A in water at 37°

Compound (1 mg/ml)	Amount of saponin A (mg/ml)	Solubility of saponin A (mg/ml)	M/M*
None	1.6	0 017	—
Ginsenoside Ro	30	11	13
Thladioside H1 (1)	30	2 14	3 28

* Molar ratio of solubilized saponin A to bisdesmosides

was further purified by CC on silica gel ($CHCl_3$–MeOH–H_2O, 6 4:1) to give **1** in a yield of 9.7%.

Compound **1** a white powder, $[\alpha]_D^{22}$ +3 8° (H_2O, *c* 0.89), IR ν_{max} cm^{-1} 3300 (OH), 1740, 1720 (Found C, 54.32; H, 7.22. $C_{63}H_{38}O_{31}$ $2H_2O$ requires C, 54.53; H, 7.41%), ^1H NMR (270 MHz) δ 1 79 (3H, *d*, *J* = 5.9 Hz, H-6 of Rha), 4.92 (1H, *d*, *J* = 7 3 Hz, anomeric proton), 5 09 (1H, *d*, *J* = 7 0 Hz, anomeric proton), 5 24 (1H, *d*, *J* = 7 3 Hz, anomeric proton), 5 27 (1H, *d*, *J* = 8 4 Hz, anomeric proton), 5.42 (1H, *t*-like, H-12), 6.19 (1H, *d*, *J* = 6.6 Hz, anomeric proton of Xyl ester), 6.37 (1H, *s*, anomeric proton of Rha), 10 0 (1H, *s*, –CHO).

Enzymatic hydrolysis of compound **1** *with crude hesperidinase.* A soln of compound **1** (1 g) and crude hesperidinase (1 g, Tanabe Pharm. Co., Ltd, Osaka, Japan) in H_2O (120 ml) was incubated for 8 days at 37°. After cooling, the reaction mixture was concd to dryness. The residue was chromatographed on silica gel ($CHCl_3$–MeOH, 49:1) to give the aglycone **2** (= gypsogenin) as colourless needles from aq. MeOH, mp 265–267° (uncorr.), $[\alpha]_D^{26}$ +94.9° (EtOH, *c* 0.99) which was identified by comparison of the melting point, optical rotation and ^{13}C NMR spectrum with those of the reported data [2].

Preparation of compound **3** *from compound* **1**. $NaBH_4$ (1 1 g) was added to a soln of compound **1** (2.0 g) in H_2O (80 ml) and the mixture was stirred for 18 hr at room temp. Me_2CO (5 ml) was added to the reaction mixture and the solvent was evapn to dryness. The residue was passed through a highly porous polymer, DIAION HP-20 (Mitsubishi Chem. Ind. Tokyo, Japan) column (solvent. H_2O and MeOH successively). The MeOH eluate was evapd to dryness to give compound **3** (1 8 g) as a white powder, $[\alpha]_D^{22}$ −13 2° (H_2O, *c* 0.97), IR ν_{max} cm^{-1} 3300 (–OH), 1750 (ester), the ^1H NMR spectrum showed no –CHO signal (Found: C, 55 00, H, 7 42 requires $C_{63}H_{100}O_{31} \cdot H_2O$ C, 55 17 H, 7 50%).

Selective cleavage of the ester glycoside linkage of **3**. A soln of **3** (250 mg) and LiI (dried at 150° for 3 hr, 650 mg) and dry 2,6-lutidine (10 ml) in dry MeOH (10 ml) was refluxed for 83 hr under Ar atmosphere. After cooling, the reaction mixture was diluted with 50% aq. MeOH (3 ml), deionized with Amberlite MB-3 (H^+, OH^- form) and evapd to dryness. The residue was dissolved in H_2O and extd with *n*-BuOH. The H_2O layer was chromatographed on silica gel ($CHCl_3$–MeOH–H_2O, 10:5.1) to give **6** (64 mg) as a white powder which was subjected to the methylation analysis (2-linked, 3-linked and terminal xylopyranose residue and a 4-linked rhamnopyranose residue). The *n*-BuOH extract was chromatographed on silica gel ($CHCl_3$–MeOH–H_2O, 10.5 1 and then 6·4.1) to give compound **5** (81 mg). A soln of **5** (28 mg) in 2% HCl–MeOH (10 ml) was stirred for 2 hr at room temp. After neutralization with Amberlite MB-3, the solvent was evapd to dryness to give compound **7** as a white powder, $[\alpha]_D^{21}$ +19 6° (*c* = 0.75), IR ν_{max} cm^{-1} 3300 (OH), 1725 (ester), 1680 (COOH), ^1H NMR (100 MHz) δ 3 67 (3H, *s*, –COOMe of GlcUA), 5.12 (1H, *d*, *J* = 5 Hz, anomeric proton), 5 26 (1H, *d*, *J* = 8 Hz, anomeric proton). (Found: C, 58 90, H, 8 23. $C_{43}H_{68}O_{15}$ $3H_2O$ requires: C, 58.75, H, 8.49%).

Preparation of compound **8** *and* **8**-$^2H_2$ *from compound* **7**. A soln of **7** (42 mg) and $NaBH_4$ (39 mg) in EtOH (3 ml) was stirred for 20 min at room temp. After decomposition of the excess of the reagent with Me_2CO (2 ml), the reaction mixture was deionized with Amberlite MB-3 and concd *in vacuo* to give compound **8** (29 mg) as a white powder, $[\alpha]_D^{21}$ +32.0° (*c* 1.10), IR ν_{max} cm^{-1} 3250 (OH), 1680 (COOH), ^1H NMR (100 MHz) δ 5.00 (1H, *d*, *J* = 6 Hz, anomeric proton), 5 24 (1H, *d*, *J* = 8 Hz, anomeric proton). (Found: C, 60 84, H, 8 66. $C_{42}H_{68}O_{14}$ $2H_2O$ requires C, 60 55, H, 8 71%). The deuterated compound, **8**-$^2H_2$ was prepared with NaB^2H_4 in the same way. The methylation analysis of **8**-$^2H_2$ indicated the presence of a 2-linked 6-dideuteroglucopyranosyl and a terminal galactopyranosyl residue.

Enzymatic hydrolysis with β-glucuronidase of compound **1**. A soln of compound **1** (500 mg) and β-glucuronidase (3 ml, Sigma Co., from *Helix pomatia*) in H_2O (30 ml) was incubated for 44 hr at 37°. After cooling, the reaction mixture was chromatographed on DIAION HP-20 (H_2O and MeOH, successively). The MeOH eluate (294 mg) was chromatographed on silica gel ($CHCl_3$–MeOH–H_2O, 40·10 1 and then 30 10 1) to give compounds **9** (73 mg), **10** (40 mg) and **11** (41 mg) together with a mixture of **10** and **11** (70 mg).

Compound **9**. A white powder, $[\alpha]_D^{22}$ +10.3° (*c* 0.80). IR ν_{max} cm^{-1} 3300 (OH), 1750, 1720 (ester), ^1H NMR (100 MHz) δ 1 75 (3H, *d*, *J* = 6 Hz, H-6 of Rha), 6 12 (1H, *d*, *J* = 8 Hz, anomeric proton of Xyl ester), 6 50 (1H, *s*, anomeric proton of Rha), 9 60 (1H, *s*, –CHO). (Found: C, 62 82; H, 8 66. $C_{41}H_{64}O_{12} \cdot 2H_2O$ requires C, 62 73; H, 8 73%).

Compound **10**. A white powder, $[\alpha]_D^{22}$ +10 9° (*c* 0 65). IR ν_{max} cm^{-1} 3300 (OH), 1750, 1720 (ester), ^1H NMR (100 MHz). δ 1 83 (3H, *d*, *J* = 5 Hz, H-6 of Rha), 5 06 (1H, virtual coupling, anomeric proton of terminal Xyl), 6 16 (1H, *d*, *J* = 6 Hz, anomeric proton of Xyl ester), 6 38 (1H, *s*, anomeric proton of Rha), 9.60 (1H, *s*, –CHO). (Found: C, 60 44, H, 8.33. $C_{46}H_{72}O_{16}$ $2H_2O$ requires C, 60.24, H, 8 35%).

Compound **11**. A white powder, $[\alpha]_D^{22}$ −4.89° (*c* 0.47). IR ν_{max} cm^{-1} 3300 (OH), 1750, 1720 (ester), ^1H NMR (100 MHz) δ 1.83 (3H, *d*, *J* = 5 Hz, H-6 of Rha), 5 06 (1H, virtual coupling, anomeric proton of terminal Xyl), 5 21 (1H, *d*, *J* = 6 Hz, anomeric proton of inner Xyl), 6 16 (1H, *d*, *J* = 6 Hz, anomeric proton of Xyl ester), 6.35 (1H, *s*, H-1 of Rha), 9.70 (1H, *s*, –CHO). (Found: C, 58.13, H, 8 18. $C_{51}H_{80}O_{20}$ $2H_2O$ requires C, 58 38, H, 8.07%).

Selective cleavage of the ester glycoside linkage of compound **10**. A soln of compound **10** (75 mg), dry LiI (102 mg) and dry 2,6-lutidine (3 ml) in dry MeOH (3 ml) was refluxed for 18 hr under Ar atmosphere. After cooling, the reaction mixture was diluted with 50% aq. MeOH (2 ml), deionized with Amberlite MB-3 (H^+, OH^- form) and evapn to dryness. The residue was chromatographed on silica gel ($CHCl_3$–MeOH–H_2O 30 10 1) to give **11** (16 mg) as a white powder, which was subjected to

methylation analysis (2-linked and terminal xylopyranose units and 4-linked rhamnopyranose unit).

Solubilizing effect of compound **1** *on saikosaponin-a, Yellow OB and saponin A.* The effects were determined by the same procedure reported previously [11, 12]

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