



## A New Steroidal Glycoside from *Allium macrostemon* Bunge

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**Abstract** – A phytochemical investigation of *Allium macrostemon* Bunge (Liliaceae) afforded the new pregnane steroidal glycoside, named allimacroside F (**1**), along with three known glycosides, benzyl-*O*- $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranoside (**2**), phenylethyl-*O*- $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranoside (**3**), (*Z*)-3-hexenyl-*O*- $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranoside (**4**). The identification and structural elucidation of a new compound (**1**) was carried out based on spectral data analyses ( $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ ,  $^1\text{H-}^1\text{H COSY}$ , HSQC, HMBC, and NOESY) and HR-FAB-MS.

**Keywords** – *Allium macrostemon*, Liliaceae, Steroidal glycoside, Allimacroside F.

### Introduction

*Allium macrostemon* Bunge (Liliaceae), known as wild onion, is widely distributed in East Asian countries.<sup>1</sup> Its dried bulbs have been known as a traditional Chinese medicine “Xiebai”, and used for treatment of heart diseases such as thoracic pain, stenocardia, and heart asthma.<sup>2</sup> Various steroidal glycosides with medicinal properties have been reported from the genus *Allium*,<sup>3</sup> and previous phytochemical investigations on *A. macrostemon* demonstrated the presence of steroidal glycosides, including macrostemonosides A-S.<sup>4-8</sup> In the course of our search for the new steroidal glycosides from this plant, we reported the isolation of allimacrosides A–E.<sup>9</sup> In continuing study of this source, we isolated further a new pregnane-type steroidal glycoside, namely allimacroside F (**1**), together with three known compounds (**2** - **4**).

### Experimental

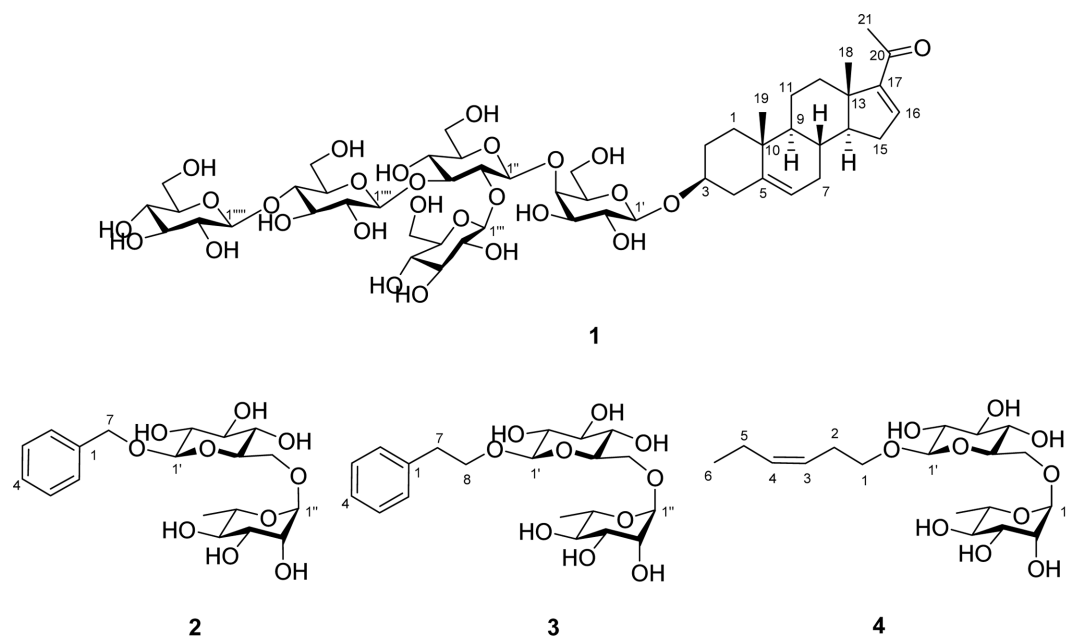
**General experimental procedures** – Optical rotations were measured on a Jasco P-1020 polarimeter in MeOH. IR spectra were recorded on a Bruker IFS-66/S FT-IR spectrometer. UV spectra were recorded using a Shimadzu UV-1601 UV-visible spectrophotometer. High resolution (HR)-fast atom bombardment (FAB) mass spectra were obtained on a JEOL JMS700 mass spectrometer. NMR spectra, including  $^1\text{H-}^1\text{H}$  correlated spectroscopy (COSY),

distortionless enhancement by polarization transfer (DEPT), heteronuclear single quantum correlation (HSQC), heteronuclear multiple bond correlation (HMBC) and nuclear overhauser effect spectroscopy (NOESY) experiments, were recorded on a Varian UNITY INOVA 700 NMR spectrometer operating at 700 MHz ( $^1\text{H}$ ) and 175 MHz ( $^{13}\text{C}$ ) with chemical shifts given in ppm ( $\delta$ ). Preparative HPLC was conducted using a Gilson 306 pump with Shodex refractive index detector and Econosil RP-C<sub>18</sub> 10  $\mu\text{m}$  column (250  $\times$  10 mm). Silica gel 60 (Merck, 70 - 230 mesh and 230 - 400 mesh) and RP-C<sub>18</sub> silica gel (YMC GEL ODS-A, 12 nm, S-75  $\mu\text{m}$ ) were used for column chromatography. TLC was performed using percolated Silica gel F<sub>254</sub> plates and RP-18 F<sub>254s</sub> plates (Merck). Spots were detected by TLC under UV light or by heating after spraying with 10% H<sub>2</sub>SO<sub>4</sub> in C<sub>2</sub>H<sub>5</sub>OH (v/v). A Hewlett-Packard (HP) GC system 6890 Series equipped with a 5973 Mass Selective Detector (MSD) system was controlled by the Enhanced ChemStation Version B.01.00 software. The capillary column used for GC was an Agilent J&W HP-5MS UI (30.0 m  $\times$  0.25 mm i.d., 0.25  $\mu\text{m}$  film thickness coated 5% diphenyl 95% dimethylpolysiloxane).

**Plant materials** – *A. macrostemon* was collected in Taebak, Gangwon province, Korea in April, 2010, and the plant was identified by one of the authors (K. R. Lee). A voucher specimen (SKKU-NPL 1202) was deposited in the herbarium of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

**Extraction and isolation** – Dried whole plants of *A. macrostemon* (1.5 kg) were extracted with 80% MeOH three times at room temperature and evaporated under

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**Fig. 1.** The structures of **1** - **4** isolated from *A. macrostemon*.

reduced pressure to give a residue (210.0 g), which was dissolved in water (800 ml) and partitioned with solvents to give *n*-hexane (10.0 g),  $\text{CHCl}_3$  (5.5 g), EtOAc (1.9 g), and *n*-BuOH (12.2 g) soluble layers. The *n*-BuOH-soluble layer (12.2 g) was chromatographed on a silica gel column (diameter  $\times$  height: 5.5  $\times$  35.0 cm, 300.0 g) with a  $\text{CHCl}_3$ -MeOH- $\text{H}_2\text{O}$  (20:10:1 to 2:3:1) to give 10 fractions (B1-B10) based on a TLC analysis. Fraction B4 (1.3 g) was separated on a RP-C<sub>18</sub> open column (2.5  $\times$  30.0 cm, 60.0 g), eluting with 50% aqueous MeOH to give nine subfractions (B41-B49). Subfraction B42 (43 mg) was purified by an RP-C<sub>18</sub> semi-prep. HPLC (2 mL/min, 35% aqueous MeOH) to afford **2** (7 mg,  $t_R$  = 17.8 min). Subfraction B44 (27 mg) was purified by an RP-C<sub>18</sub> semi-prep. HPLC (2 mL/min, 35% aqueous MeOH) to afford **3** (6 mg,  $t_R$  = 33.7 min). Subfraction B45 (30 mg) was purified by an RP-C<sub>18</sub> semi-prep. HPLC (2 mL/min, 40% aqueous MeOH) to afford **4** (8 mg,  $t_R$  = 21.3 min). Fraction B7 (2.6 g) was separately chromatographed on a Diaion HP-20 column (2.5  $\times$  35.0 cm, 80.0 g) eluting with a gradient solvent system of 100%  $\text{H}_2\text{O}$  and 100% MeOH, yielding subfractions B71 and B72. Subfraction B72 (1.5 g) separated on a RP-C<sub>18</sub> silica gel open column (2.5  $\times$  30.0 cm, 60 g), eluting with 40% aqueous MeOH to give six subfractions (B721-B726). Subfraction 726 (22 mg) was purified by an RP-C<sub>18</sub> semi-prep. HPLC (2 mL/min, 36% aqueous MeCN) to afford **1** (3 mg,  $t_R$  = 15.2 min).

**Allimacroside F (1)** – White amorphous powder;  $[\alpha]_D^{25}$  -59.3 (MeOH); UV (MeOH)  $\lambda_{\text{max}}$ : 239 nm; IR

(KBr)  $\nu_{\text{max}}$ : 3385, 2925, 1664, 1370, 1160, 1070  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (Pyridine- $d_5$ , 700 MHz) and  $^{13}\text{C-NMR}$  (Pyridine- $d_5$ , 175 MHz) see Table 1; HR-FAB-MS  $m/z$  1147.4785 [ $\text{M} + \text{Na}$ ] $^+$  (calcd. for  $\text{C}_{51}\text{H}_{80}\text{NaO}_{27}$ : 1147.4785).

**Benzyl-*O*- $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranoside (2)** – Colorless gum; IR (KBr)  $\nu_{\text{max}}$ : 3385, 2923, 1049  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (700 MHz, Pyridine- $d_5$ ):  $\delta$  7.53 (2H, d,  $J$  = 7.3 Hz, H-2, 6), 7.27 (2H, m, H-3, 5), 7.22 (1H, m, H-4), 5.16 (1H, d,  $J$  = 11.8 Hz, H-7a), 5.56 (1H, d,  $J$  = 1.2 Hz, H-1''), 4.91 (1H, d,  $J$  = 7.8 Hz, H-1'), 4.83 (1H, d,  $J$  = 11.8 Hz, H-7b), 1.63 (3H, d,  $J$  = 6.2 Hz, H-6'');  $^{13}\text{C-NMR}$  (175 MHz, Pyridine- $d_5$ ):  $\delta$  138.5 (C-1), 128.4 (C-2, 6), 128.4 (C-3, 5), 127.6 (C-4), 103.5 (C-1'), 102.4 (C-1''), 78.3 (C-5'), 77.0 (C-3'), 74.9 (C-2'), 73.9 (C-4''), 72.6 (C-3''), 72.1 (C-2''), 71.7 (C-4'), 70.7 (C-1), 69.6 (C-5''), 68.2 (C-6'), 18.5 (C-6''); FAB-MS (positive mode)  $m/z$  = 417.23 [ $\text{M} + \text{H}$ ] $^+$ .

**Phenylethyl-*O*- $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranoside (3)** – Colorless gum; UV (MeOH)  $\lambda_{\text{max}}$ : 254, 212 nm; IR (KBr)  $\nu_{\text{max}}$ : 3385, 2925, 1047  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (700 MHz, Pyridine- $d_5$ ):  $\delta$  7.30 (2H, d,  $J$  = 7.1 Hz, H-2, 6), 7.25 (2H, dd,  $J$  = 7.1, 7.4 Hz, H-3, 5), 7.19 (1H, dd,  $J$  = 7.4, 1.3 Hz, H-4), 5.52 (1H, d,  $J$  = 0.8 Hz, H-1''), 4.84 (1H, d,  $J$  = 7.8 Hz, H-1'), 4.18 (1H, m, H-8a), 3.93 (1H, dt,  $J$  = 9.8, 7.4 Hz, H-8b), 2.98 (2H, dd,  $J$  = 7.2, 7.2 Hz, H-7), 1.62 (3H, d,  $J$  = 6.2 Hz, H-6'');  $^{13}\text{C-NMR}$  (175 MHz, Pyridine- $d_5$ ):  $\delta$  140.7 (C-1), 130.7 (C-3, 5), 130.0 (C-2, 6), 127.7 (C-4), 106.0 (C-1'), 103.8 (C-1''), 79.8 (C-3'), 78.4 (C-5'), 76.3 (C-2'), 75.3 (C-4''), 74.1 (C-3''), 73.6

(C-2''), 73.1 (C-8), 71.8 (C-4'), 71.1 (C-5''), 69.6 (C-6'), 37.9 (C-7), 20.0 (C-6''); FAB-MS (positive mode)  $m/z = 431.26 [M+H]^+$ .

**(Z)-3-Hexenyl-O- $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  6)- $\beta$ -D-glucopyranoside (4)** – Colorless gum; IR (KBr)  $\nu_{\max}$ : 3385, 2933, 1048  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (700 MHz, Pyridine- $d_5$ ):  $\delta$  5.51 (1H, d,  $J = 0.8$  Hz, H-1''), 5.46 (1H, dt,  $J = 10.8, 7.3, 1.5$  Hz, H-3), 5.38 (1H, dt,  $J = 10.8, 7.3, 1.5$  Hz, H-4), 4.81 (1H, d,  $J = 7.7$  Hz, H-1'), 4.12 (1H, dt,  $J = 9.5, 7.1$  Hz, H-1a), 3.71 (1H, dt,  $J = 9.4, 7.1$  Hz, H-1b), 2.41 (2H, q,  $J = 6.9$  Hz, H-2), 1.92 (2H, quin,  $J = 7.2$  Hz, H-5), 1.63 (3H, d,  $J = 6.2$  Hz, H-6''), 0.82 (3H, t,

$J = 7.5$  Hz, H-6);  $^{13}\text{C-NMR}$  (175 MHz, Pyridine- $d_5$ ):  $\delta$  133.2 (C-4), 125.4 (C-3), 104.4 (C-1'), 102.4 (C-1''), 78.3 (C-3'), 76.9 (C-5'), 74.9 (C-2'), 73.8 (C-4''), 72.6 (C-3''), 72.1 (C-2''), 71.6 (C-4'), 69.6 (C-5''), 69.2 (C-1), 68.1 (C-6'), 28.1 (C-2), 20.6 (C-5), 18.4 (C-6''), 14.1 (C-6); FAB-MS (positive mode)  $m/z = 431.25 [M+Na]^+$ .

**Acid hydrolysis of 1 and sugar determination – 1** (2.0 mg) was dissolved in 2 mL of 15% HCl. The solution was heated at 80 °C for 2 h. The hydrolysate was extracted with  $\text{CH}_2\text{Cl}_2$ , and the aqueous layer was neutralized using an Amberlite IRA-67 column to yield the sugars. The sugar acquired from the hydrolysis was dissolved in

**Table 1.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of **1** in Pyridine- $d_5$ . ( $\delta$  in ppm, 700 MHz for  $^1\text{H}$  and 175 MHz for  $^{13}\text{C}$ )<sup>a</sup>

Position	1		Position	1	
	$\delta_{\text{H}}$	$\delta_{\text{C}}$		$\delta_{\text{H}}$	$\delta_{\text{C}}$
1	1.59 m, 0.90 m	38.6	Gal 1'	4.87 d (7.7)	104.0
2	2.06 m, 1.66 m	31.4	2'	4.41 m	74.5
3	3.85 m	79.4	3'	4.07 m	76.4
4	2.65 dd (13.3, 2.4), 2.40 t-like (12.2)	40.5	4'	4.57 m	81.4
5	-	142.8	5'	3.94 m	76.6
6	5.29 br d (5.2)	122.6	6'	4.65 m, 4.15 m	61.8
7	1.83 m, 1.52 m	33.0	Glc 1''	5.12 d (7.8)	106.4
8	1.49 m	31.6	2''	4.37 m	82.7
9	0.89 m	52.0	3''	4.13 m	89.2
10	-	38.3	4''	3.77 m	72.0
11	1.45 m, 1.45 m	22.2	5''	3.82 m	78.8
12	2.58 m, 1.34 m	36.4	6''	4.45 m, 3.98 m	64.3
13	-	47.5	Glc 1'''	5.55 d (7.7)	106.2
14	1.26 m	57.7	2'''	4.03 m	77.5
15	2.12 ddd (16.9, 6.5, 3.3) 1.85 m	33.6	3'''	4.18 m	79.5
16	6.58 dd (2.9, 1.8)	146.0	4'''	4.13 m	72.9
17	-	156.5	5'''	3.82 m	79.8
18	0.90 s	17.2	6'''	4.55 m, 4.27 m	63.8
19	0.86 s	20.5	Glc 1''''	5.25 d (7.7)	105.3
20	-	197.6	2''''	4.02 m	76.0
21	2.23 s	28.4	3''''	4.18 m	78.0
			4''''	4.21 m	82.7
			5''''	3.99 m	77.9
			6''''	4.51 m, 4.22 m	63.0
			Glc 1'''''	5.11 d, (7.5)	106.3
			2'''''	4.04 m	76.1
			3'''''	3.89 m	80.0
			4'''''	4.22 m	72.2
			5'''''	4.10 m	79.1
			6'''''	4.55 m, 4.36 m	63.7

<sup>a</sup> $J$  values are in parentheses and reported in Hz; the assignments were based on  $^1\text{H}$ - $^1\text{H}$  COSY, HMQC, and HMBC experiments.

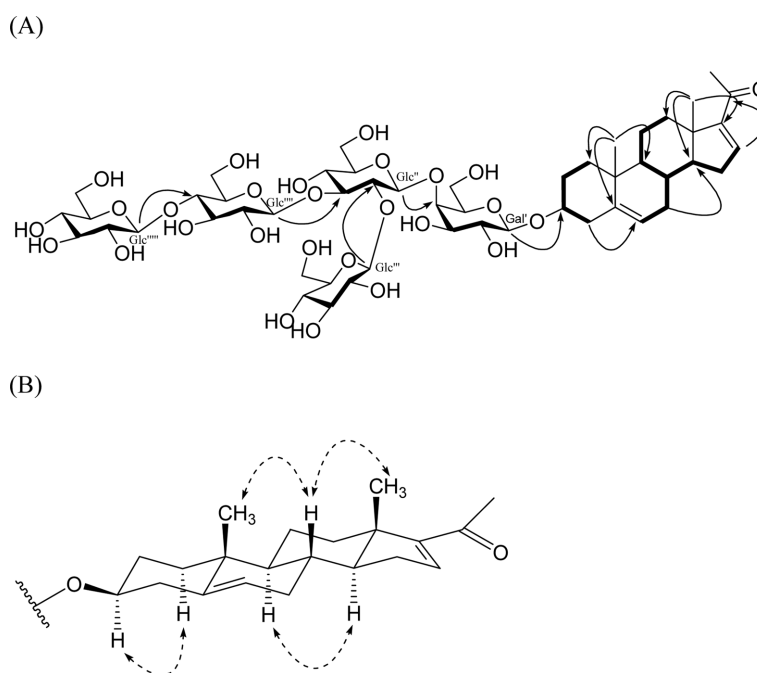
anhydrous pyridine (0.1 mL), and 2.0 mg of L-cysteine methyl ester hydrochloride was added. The mixture was stirred at 60 °C for 1.5 h and trimethylsilylated through adding 0.1 mL of 1-trimethylsilylimidazole for 2 h. The mixture was partitioned with *n*-hexane and H<sub>2</sub>O (0.3 mL each), and the *n*-hexane layer (1.0 μL) was analyzed through GC/MS. Identification of D-galactose (20.093 min) and D-glucose (22.103 min) were detected in each case by co-injection of the hydrolysate with standard silylated sugars.

## Result and Discussion

Structures of **2**–**4** were identified by comparing <sup>1</sup>H-, <sup>13</sup>C-NMR, and MS spectral data with those in the literatures to be benzyl-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**2**),<sup>10</sup> phenylethyl-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**3**),<sup>11,12</sup> (*Z*)-3-hexenyl-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**4**).<sup>13</sup> Compounds **2**–**4** were isolated from this source for the first time.

Compound **1** was isolated as a white amorphous powder. The molecular formula was determined to be C<sub>51</sub>H<sub>80</sub>O<sub>27</sub> from the molecular ion peak [M+Na]<sup>+</sup> at *m/z* 1147.4785 (calcd. for C<sub>51</sub>H<sub>80</sub>NaO<sub>27</sub> : 1147.4785) in the positive-ion HR-FAB-MS. The IR spectrum showed characteristic absorptions for α,β-unsaturated ketone (1664 cm<sup>-1</sup>), hydroxyl (3385 cm<sup>-1</sup>), and glycosidic linkage (1000–1160 cm<sup>-1</sup>).<sup>14</sup> The <sup>1</sup>H-NMR spectrum of **1** (Table 1)

displayed the signals of two olefinic protons at δ<sub>H</sub> 6.58 (dd, *J* = 2.9, 1.8 Hz, H-16) and 5.29 (br d, *J* = 5.2 Hz, H-6), an oxygenated methine proton at δ<sub>H</sub> 3.85 (m, H-3), and three methyl singlet signals at δ<sub>H</sub> 2.23 (s, H-21), 0.90 (s, H-18), and 0.86 (s, H-19) of aglycone, and five anomeric protons at 4.87 (d, *J* = 7.7 Hz, H-1'), 5.12 (d, *J* = 7.8 Hz, H-1''), 5.55 (d, *J* = 7.7 Hz, H-1'''), 5.25 (d, *J* = 7.7 Hz, H-1''''), and 5.11 (d, *J* = 7.5 Hz, H-1''''') of five sugar moieties. The <sup>13</sup>C-NMR spectrum (Table 1) showed a total of 51 carbon signals, of which 21 carbons were assigned to the aglycone and the remaining 30 carbons to five hexoses. The <sup>13</sup>C-NMR and DEPT spectra displayed 21 signals for the aglycone, which are composed of one ketone carbon at δ<sub>C</sub> 197.6, four olefinic carbons at δ<sub>C</sub> 156.5, 146.0, 142.8 and 122.6, one oxygenated methine carbon at δ<sub>C</sub> 79.4, two quaternary carbons at δ<sub>C</sub> 47.5 and 38.3, three methine carbons at δ<sub>C</sub> 57.7, 52.0, and 31.6, seven methylene carbons at δ<sub>C</sub> 40.5, 38.6, 36.4, 33.6, 33.0, 31.4 and 22.2, and three methyl carbons at δ<sub>C</sub> 28.4, 20.5 and 17.2. A comparison of the NMR spectral findings of **1** with literature data revealed that the aglycone pair of **1** was identical to that of allimacroside A.<sup>9</sup> Detailed comparison of <sup>13</sup>C-NMR, <sup>1</sup>H–<sup>1</sup>H COSY, HSQC, and HMBC spectra of **1** with those of allimacroside A suggested that the sugar moiety of **1** was similar to that of allimacroside A with the exception of presence of an additional glucopyranose [δ<sub>H</sub> 5.11 (d, *J* = 7.5, H-1''''') and δ<sub>C</sub> 106.3, 76.1, 80.0, 72.2, 79.1, and 63.7]. In the HMBC



**Fig. 2.** Key HMBC (HC), <sup>1</sup>H–<sup>1</sup>H COSY (—) correlations **1** (A), and NOESY (←-→) correlations of **1** (B).

spectrum, the key correlations from  $\delta_{\text{H}}$  4.87 (H-1') to  $\delta_{\text{C}}$  79.4 (C-3), from  $\delta_{\text{H}}$  5.12 (H-1'') to  $\delta_{\text{C}}$  81.4 (C-4'), from  $\delta_{\text{H}}$  5.55 (H-1''') to  $\delta_{\text{C}}$  82.7 (C-2''), from  $\delta_{\text{H}}$  5.25 (H-1''') to  $\delta_{\text{C}}$  89.2 (C-3'') and  $\delta_{\text{H}}$  5.11 (H-1''''') to  $\delta_{\text{C}}$  82.7 (C-4''') suggested that the sequence of sugar moieties and the linkage position between the sugar unit and aglycone was the C-3 hydroxyl group (Fig. 2 A). Large coupling constants ( $^3J_{\text{H}_1, \text{H}_2} \geq 7.5$  Hz) for anomeric protons revealed the  $\beta$ -configuration of all sugars. The relative stereochemistry of the aglycone was corroborated by NOESY cross-peaks of H<sub>ax</sub>-1/H-3, H-19/H-8/H-18, and H-9/H-14 (Fig. 2 B). On acid hydrolysis, **1** yielded D-galactose and D-glucose in a ratio of 1:4 by GC analysis after derivatization.<sup>15</sup> Thus, the structure of **1** was established as pregna-5,16-dien-3 $\beta$ -ol-20-one 3-O- $\beta$ -D-glucopyranosyl (1 $\rightarrow$ 4)- $\beta$ -D-glucopyranosyl (1 $\rightarrow$ 3)-[ $\beta$ -D-glucopyranosyl (1 $\rightarrow$ 2)]- $\beta$ -D-glucopyranosyl (1 $\rightarrow$ 4)- $\beta$ -D-galactopyranoside, named allimacroside F.

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