

## Pregnane glycosides from *Gymnema sylvestre*

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### Abstract

Three pregnane glycosides, gymnepregoside F (1), 12-*O*-(*E*)-cinnamoylgymnepregoside F (2), and stephanoside I (3) were isolated from the leaves of *Gymnema sylvestre* (Retz.) R.Br. ex Schult. Their structures were identified on the basis of spectroscopic evidences and in comparison with those reported in the literature. All these compounds were reported from this genus *Gymnema* for the first time.

**Keywords.** *Gymnema sylvestre*, pregnane glycoside.

### 1. INTRODUCTION

*Gymnema sylvestre* (Asclepiadaceae) is a large woody climber plant and distributed in India, tropical Africa, Australia, and Vietnam. This plant is well known for the treatment of diabetes in India. The chemical components of *G. sylvestre* have been confirmed the presence of pregnane glycosides,<sup>[1]</sup> gymnemic acid glycosides,<sup>[2]</sup> and oleanane saponins.<sup>[3,4]</sup> Herein, we reported the isolation and structural elucidation of three pregane-*type* triterpene glycosides from the leaves of *G. sylvestre* (figure 1).

### 2. MATERIALS AND METHODS

#### 2.1. Plant materials

The leaves of *Gymnema sylvestre* (Retz.) R.Br. ex Schult. were collected in Hai Loc, Hai Hau, Nam Dinh in November, 2015, and identified by Dr. Nguyen The Cuong, Institute of Ecology and Biological Resources. A voucher specimen (NCCT-P20) was deposited at the Herbarium Institute of Marine Biochemistry, VAST.

#### 2.2. General experimental procedures

Optical rotations were determined on a Jasco DIP-370 automatic polarimeter. NMR spectra were recorded on an Agilent 400-MR-NMR spectrometer, operated at 400 and 100 MHz for <sup>1</sup>H and <sup>13</sup>C, respectively.

Data processing was carried out with the MestReNova ver.6.0.2 program. HR-ESI mass spectra were obtained using an AGILENT 6550 iFunnel Q-TOF LC/MS system. Column chromatography was performed using silica-gel (Kieselgel 60, 230-400 mesh, Merck) or RP-18 resins (30-50 μm, Fujisilisa Chemical Ltd.), and thin layer chromatography (TLC) was performed using a precoated silica gel 60 F<sub>254</sub> (0.25 mm, Merck) and RP-18 F<sub>254S</sub> plates (0.25 mm, Merck).

#### 2.3. Extraction and isolation

The dried powders of *G. sylvestre* leaves (4.0 kg) were sonicated with hot methanol (3 times × 10 L, each 3 h) to give 450 g extract after evaporation of the solvent. This extract was suspended in H<sub>2</sub>O and successively partitioned with *n*-hexane, CH<sub>2</sub>Cl<sub>2</sub> and EtOAc to obtain the *n*-hexane (GS1, 47.0 g), CH<sub>2</sub>Cl<sub>2</sub> (GS2, 60.0 g), EtOAc extracts (GS3, 27.0 g) and H<sub>2</sub>O layer (GS4). GS2 was chromatographed on a silica gel column eluting with gradient solvent of *n*-hexane/acetone (40/1, 20/1, 10/1, 5/1, 1/1, and 0/1, v/v) to give seven smaller fractions, GS2A-GS2G. GS2F was chromatographed on a silica gel column eluting with CHCl<sub>3</sub>/MeOH (11/1, v/v) to give four fractions, GS2F1-GS2F4. GS2F1 was chromatographed on a RP-18 column using MeOH/H<sub>2</sub>O (4/1, v/v) as solvent to give five fractions, GS2F1A-GS2F1D. Compounds 2 (10.0 mg) and 3 (12.0 mg) were yielded from GS2F1A

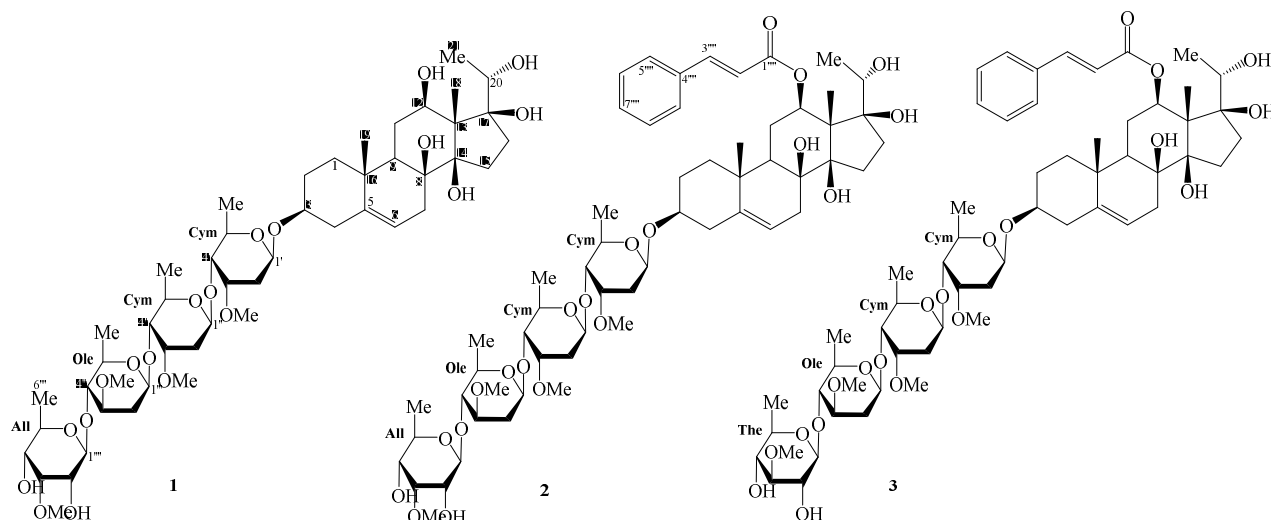


Figure 1: The chemical structures of compounds 1-3

fraction using HPLC system: J'sphere H-80 column (150 × 20 mm), solvent condition of 40 % acetonitrile, and a flow rate of 3 mL/min). Compound **1** (72.0 mg) was obtained from GS2F1C using HPLC system: J'sphere H-80 column (150 × 20 mm), solvent condition of 35 % acetonitrile, and a flow rate of 3 mL/min).

**Gymnepregoside F (1):** White amorphous powder;  $[\alpha]_D^{25} +12.0$  (*c* 0.1, MeOH); HR-ESI-MS *m/z*: 997.5318  $[M+Na]^+$  (Calcd. for  $[C_{49}H_{82}O_{19}Na]^+$ , 997.5343).  $^1H$ - and  $^{13}C$ -NMR ( $CD_3OD$ ), see table 1.

**12-O-(E)-Cinnamoylgymnepregoside F (2):** White amorphous powder;  $[\alpha]_D^{25} +15.0.0$  (*c* 0.1, MeOH); HR-ESI-MS *m/z*: 1127.5766  $[M+Na]^+$  (Calcd. for  $[C_{58}H_{88}O_{20}Na]^+$ , 1127.5761).  $^1H$ - and  $^{13}C$ -NMR ( $CD_3OD$ ), see table 1.

**Stephanoside I (3):** White amorphous powder;  $[\alpha]_D^{25} +30.0$  (*c* 0.1, MeOH); HR-ESI-MS *m/z*: 1127.5771  $[M+Na]^+$  (Calcd. for  $[C_{58}H_{88}O_{20}Na]^+$ , 1127.5761).  $^1H$ - and  $^{13}C$ -NMR ( $CD_3OD$ ), see table 1.

### 3. RESULTS AND DISCUSSION

Compound **1** was isolated as a white amorphous powder. The HR-ESI-MS of **1** showed a pseudo-molecular ion peak at *m/z* 997.5318  $[M+Na]^+$  (Calcd. for  $[C_{49}H_{82}O_{19}Na]^+$ , 997.5343), corresponding to a molecular formula of  $C_{49}H_{82}O_{19}$ . The  $^1H$ -NMR spectrum of **1** (table 1) exhibited the following proton signals: one olefinic proton at  $\delta_H$  5.31 (br s), one secondary methyl group at  $\delta_H$  1.14 (d, *J* = 7.0 Hz), and two tertiary methyl groups at  $\delta_H$  1.16 and 1.31 (each 3H, s) assigned to a pregame aglycone. In addition, four anomeric protons at  $\delta_H$  4.56 (br d, *J* = 10.0 Hz),

4.70 (d, *J* = 8.4 Hz), 4.77 (br d, *J* = 8.8 Hz), 4.83 (overlapped signal), four secondary methyl groups at  $\delta_H$  1.16 (d, *J* = 6.0 Hz), 1.20 (d, *J* = 6.0 Hz), 1.21 (d, *J* = 6.0 Hz), and 1.35 (d, *J* = 6.4 Hz), together with four methoxy groups at  $\delta_H$  3.39, 3.41 × 2, and 3.58 (each 3H, s) suggested the presence of four sugar moieties. The  $^{13}C$ -NMR and DEPT spectra of **1** displayed signals of 49 carbons, including six non-protonated carbons, twenty two methines, ten methylenes, and eleven methyl carbons. The positions of functional groups and sugar moieties were assigned using analysis of HSQC and HMBC. The HMBC correlations (figure 2) between H-19 ( $\delta_H$  1.16) to C-1 ( $\delta_C$  39.8)/C-5 ( $\delta_C$  140.1)/C-9 ( $\delta_C$  45.1)/C-10 ( $\delta_C$  38.0) confirmed the position of double bond at C-5/C-6. The HMBC correlations from H-1 ( $\delta_H$  1.07 and 1.86)/H-4 ( $\delta_H$  2.20 and 2.33) to C-3 ( $\delta_C$  79.3); from H-6 ( $\delta_H$  5.31) to C-4 ( $\delta_C$  39.8)/C-8 ( $\delta_C$  74.7); from H-18 ( $\delta_H$  1.31) to C-12 ( $\delta_C$  73.7)/C-13 ( $\delta_C$  59.0)/C-14 ( $\delta_C$  89.1)/C-17 ( $\delta_C$  89.5); from H-21 ( $\delta_H$  1.14) to C-17 ( $\delta_C$  89.5)/C-20 ( $\delta_C$  71.4) proved the positions of five hydroxyl groups at C-8/C-12/C-14/C-17/C-20. Thus, the aglycone was elucidated as pregn-5-en-3,8,12,14,17,20-hexaol.<sup>[5]</sup> Moreover, the four  $^{13}C$ -NMR data sets ( $\delta_C$  97.2, 36.6, 78.4, 83.8, 69.9, 18.6, and 58.6; 101.2, 36.4, 78.5, 83.8, 69.8, 18.7, and 58.6; 102.6, 37.5, 80.3, 83.7, 72.5, 18.9, and 57.4; and 102.2, 73.5, 83.7, 75.0, 71.2, 18.7, and 62.5) and the multiplicities of four anomeric protons in the  $^1H$ -NMR ( $\delta_H$  4.56 (br d, *J* = 10.0 Hz), 4.70 (d, *J* = 8.4 Hz), 4.77 (br d, *J* = 8.8 Hz), 4.83 (overlapped signal) confirmed the presence of sugar moieties to be two  $\beta$ -D-cymaropyranosyls, one  $\beta$ -D-oleadropyranosyl, and one  $\beta$ -D-allomethylpyranosyl. The HMBC correlations between All H-1'''' ( $\delta_H$  4.70) and Ole C-4'''' ( $\delta_C$  83.7); Ole H-1'''' ( $\delta_H$  4.56) and Cym C-4'''' ( $\delta_C$  83.8); Cym H-1'' ( $\delta_H$  4.77) and Cym C-4' ( $\delta_C$  83.8)

Table 1: The <sup>1</sup>H- and <sup>13</sup>C-NMR data for compounds **1-3** and reference compounds

C	<b>1</b>			<b>2</b>			<b>3</b>		
	$\delta_C^{\#}$	$\delta_C^a$	$\delta_H^a$ (mult., <i>J</i> in Hz)	$\delta_C^{\S}$	$\delta_C^a$	$\delta_H^a$ (mult., <i>J</i> in Hz)	$\delta_C^{\&}$	$\delta_C^a$	$\delta_H^a$ (mult., <i>J</i> in Hz)
1	38.6	39.8	1.07 (m)/1.86 (m)	38.8	39.8	1.10 (m)/1.82 (m)	39.0	39.8	1.11 (m)/1.82 (m)
2	29.8	30.2	1.59 (m)/1.85 (m)	29.8	30.2	1.58 (m)/1.84 (m)	30.0	30.2	1.58 (m)/1.84 (m)
3	78.0	79.3	3.49 (m)	77.7	79.3	3.50 (m)	77.8	79.3	3.50 (m)
4	39.3	39.8	2.20 (m)/2.33 (m)	39.2	39.8	2.20 (m)/2.34 (m)	39.4	39.8	2.19 (m)/2.35 (m)
5	139.2	140.1	-	139.1	140.0	-	139.2	140.1	-
6	119.8	119.9	5.31 (br s)	119.6	119.9	5.33 (br s)	119.7	119.9	5.33 (br s)
7	34.8	35.4	2.08 (m)	35.0	35.2	2.13 (m)	35.2	35.2	2.14 (m)
8	74.3	74.7	-	74.1	75.0	-	74.3	74.9	-
9	44.7	45.1	1.40 (m)	44.1	44.8	1.53 (m)	44.2	44.9	1.54 (m)
10	37.6	38.0	-	37.2	38.0	-	37.4	38.0	-
11	29.3	29.1	1.59 (m)/2.00 (m)	25.6	26.0	1.72 (m)/2.05 (m)	25.7	26.0	1.72 (m)/2.05 (m)
12	73.4	73.7	3.94 (d, 7.0)	74.8	75.5	4.75 (m)	74.9	75.5	4.74 (m)
13	58.8	59.0	-	56.9	57.5	-	57.0	58.4	-
14	89.1	89.1	-	88.8	89.3	-	89.0	89.3	-
15	32.4	34.2	1.81 (m)	32.8	33.6	1.78 (m)	33.0	33.6	1.77 (m)
16	34.4	34.5	1.79 (m)/2.08 (m)	34.2	34.3	1.83 (m)/1.91 (m)	34.4	34.4	1.82 (m)/1.93 (m)
17	89.0	89.5	-	88.6	89.1	-	88.7	89.1	-
18	11.7	10.7	1.31 (s)	11.6	11.2	1.57 (s)	11.9	11.2	1.57 (s)
19	18.0	18.6	1.16 (s)	18.1	18.6	1.14 (s)	18.3	18.5	1.14 (s)
20	71.1	71.4	3.56 (m)	70.9	71.7	3.53 (m)	71.1	71.8	3.53 (m)
21	19.1	17.0	1.14 (d, 7.0)	19.2	18.8	1.07 (d, 6.8)	19.5	18.8	1.07 (d, 6.4)
<b>3-OCym</b>									
1'	96.5	97.2	4.83 (*)	96.4	97.2	4.84 (*)	96.4	97.2	4.84 (*)
2'	37.4	36.6	1.56 (m)/2.09 (m)	37.2	36.4	1.54 (m)/2.07 (m)	37.2	36.6	1.53 (m)/2.06 (m)
3'	78.2	78.4	3.82 (m)	78.0	78.5	3.82 (m)	78.1	78.5	3.82 (m)
4'	83.2	83.8	3.18 (m)	83.1	83.8	3.18 (m)	83.4	83.8	3.20 (m)
5'	69.2	69.9	3.79 (m)	69.0	69.8	3.80 (m)	69.1	69.9	3.78 (m)
6'	18.7	18.6	1.16 (d, 6.0)	18.5	18.6	1.15 (d, 6.8)	18.6	18.6	1.19 (d, 6.4)
3'-OMe	59.0	58.6	3.41 (s)	58.8	58.5	3.41 (s)	58.9	58.5	3.41 (s)
<b>4'-OCym</b>									
1''	100.5	101.2	4.77 (br d, 8.8)	100.4	101.2	4.77 (br d, 8.8)	100.5	101.2	4.77 (br d, 8.8)
2''	37.2	36.4	1.56 (m)/2.09 (m)	36.9	36.6	1.54 (m)/2.07 (m)	37.0	36.4	1.53 (m)/2.06 (m)
3''	78.0	78.5	3.82 (m)	77.7	78.6	3.82 (m)	77.8	78.6	3.82 (m)
4''	83.5	83.8	3.18 (m)	83.8	83.8	3.18 (m)	83.4	83.8	3.20 (m)
5''	69.1	69.8	3.79 (m)	68.6	70.0	3.80 (m)	69.0	70.0	3.78 (m)
6''	18.8	18.7	1.20 (d, 6.0)	18.5	18.5	1.19 (d, 6.0)	18.6	18.5	1.20 (d, 6.0)
3''-OMe	59.1	58.6	3.41 (s)	58.8	58.4	3.41 (s)	59.0	58.4	3.41 (s)
<b>4''-OOle</b>									
1'''	102.0	102.6	4.56 (br d, 10.0)	101.8	102.6	4.56 (br d, 10.0)	101.9	102.6	4.57 (br d, 10.0)
2'''	37.7	37.5	1.40 (m)/2.30 (m)	37.4	37.5	1.39 (m)/2.30 (m)	37.6	37.6	1.40 (m)/2.30 (m)
3'''	79.4	80.3	3.36 (m)	79.7	80.4	3.36 (m)	79.3	80.2	3.36 (m)
4'''	83.0	83.7	3.23 (m)	82.8	83.7	3.23 (m)	83.2	84.1	3.62 (m)
5'''	72.2	72.5	3.35 (m)	72.0	72.5	3.34 (m)	72.1	72.5	3.36 (m)
6'''	18.8	18.9	1.35 (d, 6.4)	18.8	19.0	1.35 (d, 6.0)	18.9	18.9	1.35 (d, 6.0)
3'''-OMe	57.4	57.4	3.39 (s)	57.1	57.4	3.39 (s)	57.3	57.6	3.40 (s)

	4'''-OAll			4'''-OAll			4'''-OThe		
1''''	102.1	102.2	4.70 (d, 8.4)	101.9	102.2	4.70 (d, 8.0)	104.2	104.3	4.41 (d, 8.8)
2''''	73.3	73.5	3.30 (m)	73.2	73.5	3.28 (m)	75.3	75.6	3.19 (m)
3''''	84.1	83.7	3.60 (m)	83.9	83.9	3.60 (m)	88.2	87.7	3.00 (m)
4''''	74.7	75.0	3.15 (m)	74.5	75.0	3.15 (m)	76.1	76.7	3.00 (m)
5''''	71.0	71.2	3.63 (m)	70.9	71.2	3.63 (m)	72.9	73.2	3.25 (m)
6''''	18.6	18.7	1.21 (d, 6.0)	18.4	18.2	1.22 (d, 6.0)	18.6	18.1	1.25 (d, 6.4)
3''''-OMe	62.3	62.5	3.58 (s)	62.0	62.5	3.58 (s)	61.0	61.1	3.60 (s)
<b>12-OCin</b>									
1''''				167.0	168.4	-	167.1	168.4	-
2''''				119.6	119.2	6.62 (d, 16.0)	119.7	119.3	6.62 (d, 15.6)
3''''				145.3	146.8	7.76 (d, 16.0)	145.4	146.8	7.76 (d, 15.6)
4''''				135.1	135.8	-	135.1	135.8	-
5'''' , 9''''				128.6	129.4	7.60 (d, 7.6)	128.8	129.4	7.60 (d, 7.6)
6'''' , 8''''				129.2	129.9	7.38 (m)	129.3	129.9	7.38 (m)
7''''				130.6	131.5	7.38 (m)	130.6	131.5	7.38 (m)

<sup>a)</sup>recorded in CD<sub>3</sub>OD, <sup>#</sup> $\delta_C$  of gymnepregoside F, <sup>[5]</sup>  $\delta_C$  of 12-*O*-(*E*)-cinnamoylgymnepregoside F<sup>[5]</sup>, &<sup>8</sup> $\delta_C$  of stephanoside I<sup>[6]</sup>, Cym,  $\beta$ -D-cymaropyranosyl, Ole,  $\beta$ -D-oleadropyranosyl, All,  $\beta$ -D-allomethylpyranosyl, The,  $\beta$ -D-thevetopyranosyl, Cin, cinnamoyl.

proved the sugar linkage as  $\beta$ -D-allomethylpyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleadropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl.

Moreover, the sugar linkage position at C-3 of aglycone was confirmed by HMBC correlations between Cym H-1' ( $\delta_H$  4.83) and C-3 ( $\delta_C$  79.3). Based on the above evidence, the structure of **1** was elucidated as gymnepregoside F, the compound was previously reported from *G. alternifolium*.<sup>[5]</sup>

The molecular formula of **2** established as C<sub>58</sub>H<sub>88</sub>O<sub>20</sub> from the HR-ESI-MS pseudo-molecular ion at  $m/z$  1127.5766 [M+H]<sup>+</sup> (Calcd. for [C<sub>58</sub>H<sub>88</sub>O<sub>20</sub>Na]<sup>+</sup>, 1127.5761). The molecular formula of **2** (C<sub>58</sub>H<sub>88</sub>O<sub>20</sub>) was compared to those of **1** (C<sub>49</sub>H<sub>82</sub>O<sub>19</sub>) indicated the structure of **2** with the addition of a cinnamoyl moiety (C<sub>9</sub>H<sub>6</sub>O). These were also proved by analysis of the <sup>1</sup>H- and <sup>13</sup>C-NMR data of **2** for cinnamoyl moiety: C-1'''' ( $\delta_C$  168.4), H/C-2'''' [( $\delta_H$  6.62 (d,  $J$  = 16.0 Hz),  $\delta_C$  119.2), H/C-3'''' [( $\delta_H$  7.76 (d,  $J$  = 16.0 Hz),  $\delta_C$  146.8), C-4'''' ( $\delta_C$  135.8), H/C-5'''' (9''''') [( $\delta_H$  7.60 (d,  $J$  = 7.6 Hz),  $\delta_C$  129.4), H/C-6'''' (8''''') [( $\delta_H$  7.38 (m),  $\delta_C$  129.9), and H/C-7'''' [( $\delta_H$  7.38 (m),  $\delta_C$  131.5)]. The position of cinnamoyl moiety at C-12 was confirmed by the shift to high-field of oxygenated methine (H/C-12:  $\delta_H$  4.75 (m),  $\delta_C$  75.5) comparing to those of **1** (H/C-12:  $\delta_H$  3.94 (m),  $\delta_C$  73.7) as well as HMBC correlations from H-12 ( $\delta_H$  3.94) to Cin C-1'''' ( $\delta_C$  168.4). In addition, the NMR data of **2** were found to be similar to those of 12-*O*-(*E*)-cinnamoylgymnepregoside F (**2**). The important HMBC correlations of **2** were shown in figure 2. Thus, the compound **2** were elucidated to be 12-*O*-(*E*)-cinnamoylgymnepregoside F, the compound was previously reported from *G. alternifolium*.<sup>[5]</sup>

Compound **3** was isolated as a white amorphous powder. The molecular formula of **3** was determined as C<sub>49</sub>H<sub>82</sub>O<sub>19</sub> by a pseudo-molecular ion peak at  $m/z$  1127.5771 [M+Na]<sup>+</sup> in the HR-ESI-MS (Calcd. for [C<sub>58</sub>H<sub>88</sub>O<sub>20</sub>Na]<sup>+</sup>, 1127.5761), similar to those of **2**. The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra of **3** exhibited the signals of one pregnane aglycone, one cinnamoyl, and four sugar moieties. The structure of pregame aglycone was identical to those of **1** and **2**. The location of cinnamoyl moiety at C-12 was confirmed by HMBC correlations between H-12 ( $\delta_H$  3.94) and Cin C-1'''' ( $\delta_C$  168.4). The <sup>13</sup>C-NMR data of sugar moieties ( $\delta_C$  97.2, 36.6, 78.5, 83.8, 69.9, 18.6, and 58.5; 101.2, 36.4, 78.6, 83.8, 70.0, 18.5, and 58.4; 102.6, 37.6, 80.2, 84.1, 72.5, 18.9, and 57.6; 104.3, 75.6, 87.7, 76.7, 73.2, 18.1, and 61.1) and the multiplicities of four anomeric protons in the <sup>1</sup>H-NMR ( $\delta_H$  4.41 (br d,  $J$  = 8.8 Hz), 4.57 (d,  $J$  = 10.0 Hz), 4.77 (br d,  $J$  = 8.8 Hz), 4.84 (overlapped signal)) were found to be identical to those of stephanoside I indicated the sugar moieties to be two  $\beta$ -D-cymaropyranosyls, one  $\beta$ -D-oleadropyranosyl, and one  $\beta$ -D-thevetopyranosyl. The HMBC correlations from The H-1'''' ( $\delta_H$  4.41) to Ole C-4'''' ( $\delta_C$  84.1); Ole H-1'''' ( $\delta_H$  4.57) and Cym C-4'''' ( $\delta_C$  83.8); Cym H-1'''' ( $\delta_H$  4.77) and Cym C-4'''' ( $\delta_C$  83.8); and between Cym H-1' and C-3 ( $\delta_C$  79.3) proved the sugar linkage as  $\beta$ -D-thevetopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-oleadropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl and at C-3 of pregnane aglycone. This sugar linkage was reported as the glycoside part from *Gymnema* genus.<sup>[7]</sup> Consequently, the structure of **3** was elucidated as stephanoside I,<sup>[6]</sup> the compound was reported from *G. alternifolium*.<sup>[5]</sup>

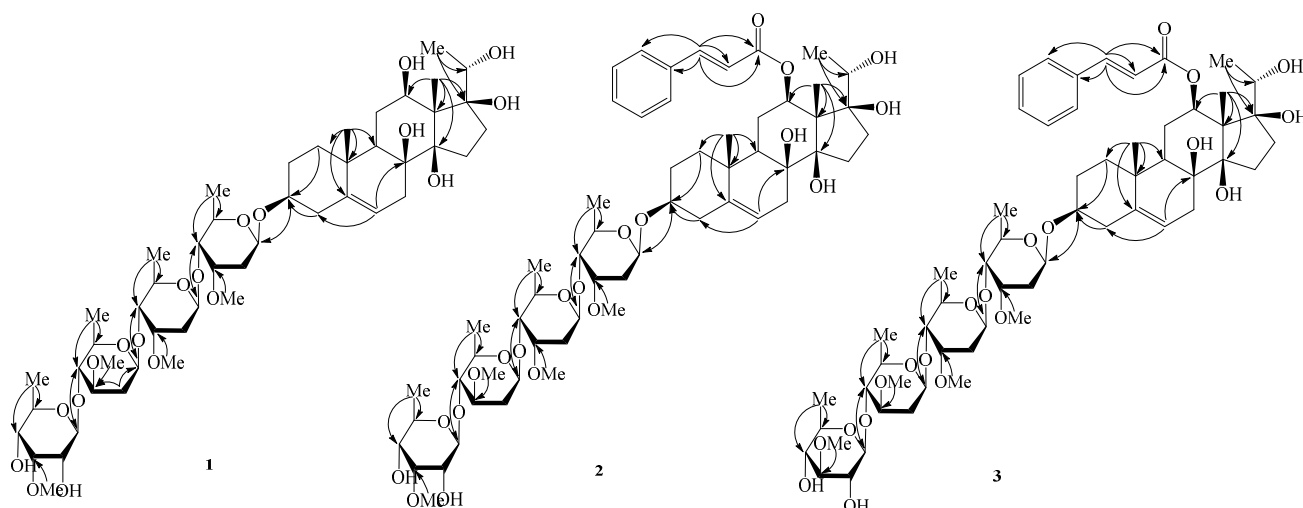


Figure 2: The key HMBC correlations of compounds 1-3

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