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Argeloside A and B, two novel 14,15-secopregnane glycosides from *Solenostemma argel*

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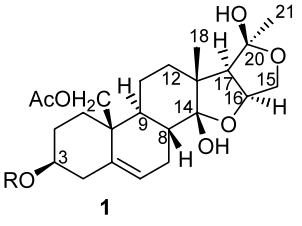
Abstract—Argeloside A and B, two novel 14,15-secopregnane glycosides characterized by the presence of two hemiketal functions involved in two five-membered rings, were isolated from *Solenostemma argel* fruits. Their structures have been established by ESIMS and NMR experiments. In particular the relative configuration of the molecules has been defined by combining the available NMR data with quantum chemical calculations of the geometries and ^{13}C chemical shifts.

Plants belonging to the family Asclepiadaceae are frequently used in traditional medicine and have been reported to be rich in steroidal glycosides.[1,2] Studies have shown that pregnanes and their glycosides possess antitumor and cytotoxic activities.[3–5] *Solenostemma argel* Hayne (Asclepiadaceae) is an Egyptian wild perennial erect shrub[6] whose leaves are commonly used as a purgative, antipyretic, expectorant, antispasmodic and in cases of bile congestion.[7] Previous studies have reported the presence of monoterpenes,[8] pregnane glycosides[9,10] and acylated phenolic glycosides in the leaves.[11]



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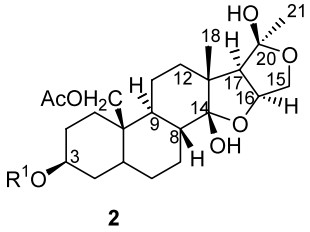

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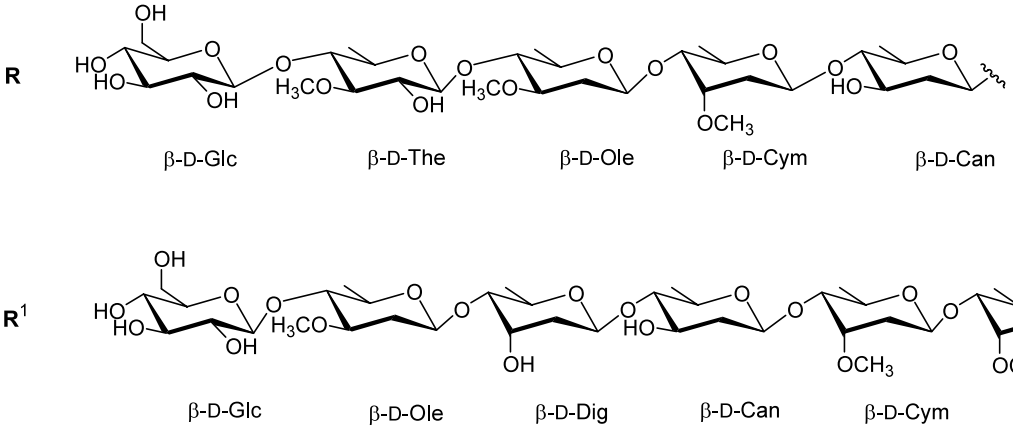

Keywords: *Solenostemma argel*; 14,15-secopregnane glycosides; NMR; GIAO; DFT calculations.
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Here we report the occurrence of two novel pregnane glycosides namely argeloside A (**1**) and B (**2**) from the pericarps of *S. argel*. Compounds **1** and **2** showed a novel unusual secopregnane skeleton characterized by the opening of ring D between C-14 and C-15, and the presence of two hemiketal functions on C-14 and C-20 generating two five-membered rings with oxygenated functions in positions 16 and 15, respectively. The structures of these compounds were elucidated by extensive spectroscopic methods including 1D- (^{1}H and ^{13}C) and 2D-NMR experiments (DQF-COSY, HSQC, HMBC, HOHAHA and ROESY) as well as ESIMS analysis. In particular, the relative configuration of compound **1** has been defined combining the NMR data with quantum chemical calculations of the geometries and ^{13}C chemical shifts.

Collection and isolation. Fresh samples of *S. argel* pericarps were collected at Allaqi (South–East of Aswan, Egypt) in May 2002 and identified by one of the authors (A.I.H.) The dried pericarps (1.5 kg) were extracted with EtOH 80% yielding 50 g of extract. Part of this extract (2.3 g) was fractionated on Sephadex LH-20 (100×5 cm) using MeOH as the mobile phase. Ninety-five fractions (8 mL) were obtained. The fractions containing pregnane glycosides (fractions 18–39, 450 mg) were chromatographed by HPLC (Refractive index detector), on a Waters (XTerra Prep MSC_{18}) column (300×7.8 mm) using MeOH–H_2O 13:7 and 73:27 as mobile phases (flow rate 2.5 mL/h) to yield compound **1** (2.5 mg) and **2** (4.0 mg), respectively.

Structure elucidation. Compound **1** showed a quasi-molecular ion peak at m/z 1163 $[M+H]^+$ and significant fragments at m/z 1103 $[M+H-60]^+$, m/z 941 $[M+H-60-162]^+$, m/z 781 $[M+H-60-162-160]^+$ and m/z 637 $[M+H-60-162-160-144]^+$ in the positive ESIMS. The molecular formula was unequivocally established to be $C_{56}H_{90}O_{25}$ by HREIMS (1162.5765 found, 1162.5771 calcd). Data from the ^{13}C NMR spectrum suggested a glycoside structure. The ^{1}H NMR spectrum of the aglycone portion showed signals for two methyl groups at δ 1.21 (3H, s) and 1.65 (3H, s), an acetyl methyl signal at δ 2.04 (3H, s), one olefinic proton at δ 5.68 (1H, br d, $J=4.6$ Hz), two signals at δ 4.60 (1H, d, $J=11.8$ Hz) and 4.00 (1H, d, $J=11.8$ Hz) corresponding to a primary oxygenated carbon and one signal at δ 4.56 (1H, br m) corresponding to a secondary oxygenated carbon. The ^{13}C NMR spectrum showed for the aglycone moiety 23 signals, two of them corresponding to an acetyl group, suggesting the presence of an acetylated pregnane skeleton. The ^{13}C NMR chemical shifts of all the hydrogenated carbons could be assigned unambiguously by the HSQC spectrum. In particular the analysis of the ^{13}C NMR spectrum on the basis of the HSQC correlations clearly showed the occurrence of one olefinic quaternary carbon (δ 136.0), one olefinic methine (δ 126.6), two secondary oxygenated carbons (δ 78.8 and 78.3), two primary oxygenated carbons (δ 72.0 and 65.0) and two hemiketal functions (δ 110.4 and 114.6). The complete elucidation of the aglycone structure of argeloside A **1** was achieved by the HMBC experiment. The HMBC correlations between the proton signals at δ 1.65 (Me-21) and the carbon resonances at δ 58.5 (C-17) and δ 114.6 (C-20); the proton at δ 1.21 (Me-18) and the carbon resonances at δ 31.2 (C-12), δ 50.1 (C-13), δ 110.4 (C-14) and δ 58.5 (C-17); the proton at δ 4.56 (H-16) and the carbon resonances at δ 78.3 (C-15), δ 58.5 (C-17) and δ 114.6 (C-20); and the proton at δ 3.86 (H-15) and the carbon resonances at δ 78.3 (C-16) and δ 114.6 (C-20) (Fig. 1), allowed us to deduce that the pregnane skeleton of **1** was characterized by the opening of ring D between C-14 and C-15, and the presence of two hemiketal functions at C-14 and C-20. This generates two five-membered rings with oxygenated functions in positions 16 and 15, respectively.

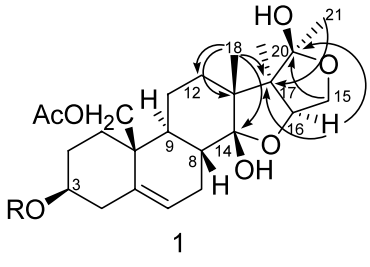

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Figure 1. Diagnostic HMBC correlations for argeloside A (**1**).

Moreover, the sugar portion showed in the ^{1}H NMR spectrum signals corresponding to four doublet methyls at δ 1.40 (6H, d, $J=6.2$ Hz) and 1.27 (6H, d, 6.2 Hz), three methoxy groups at δ 3.66 (3H, s), 3.48 (3H, s) and 3.45 (3H, s), as well as signals for five anomeric protons at δ 4.81 (1H, dd, $J=9.5$, 2.0 Hz), 4.72 (1H, dd, $J=9.2$, 1.6 Hz), 4.64 (1H, dd, $J=9.0$, 2.0 Hz), 4.46 (1H, d, $J=7.5$ Hz) and 4.44 (1H, d, $J=7.5$ Hz). All these data indicated that **1** had five sugars, three of them being 2,6-dideoxy sugars and one of them being a 6-deoxy-sugar. ESIMS, 2D-HOHAHA, DQF-COSY and HSQC experiments showed the presence of one β-D-cymaropyranosyl unit (δ 4.81), one β-D-canaropyranosyl unit (δ 4.72), one β-D-oleandropyranosyl unit (δ 4.64), one β-D-thevetopyranosyl unit (δ 4.46) and one β-D-glucopyranosyl (δ 4.44) unit. An unambiguous determination of the sequence and linkage sites was obtained from the HMBC correlations which allowed the deduction of the sugar sequence as 3-*O*-β-D-glucopyranosyl-(1→4)-β-D-thevetopyranosyl-(1→4)-β-D-oleandropyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-canaropyranoside.

Due to the presence of nine stereogenic centers in the molecule, the assignment of the relative configuration was not an easy task to accomplish. Therefore we have carried out an approach based on the combination of the analysis of 2D-NMR data with ^{13}C GIAO (gauge including atomic orbitals)—DFT (density functional theory) calculations of the chemical shifts.

On the basis of the known biosynthetic pathways, and from a preliminary analysis of the 2D-ROESY spectra, we selected 18 (**1a**–**s**) of the possible 2^8 relative stereoisomers, taking into consideration only the agly-

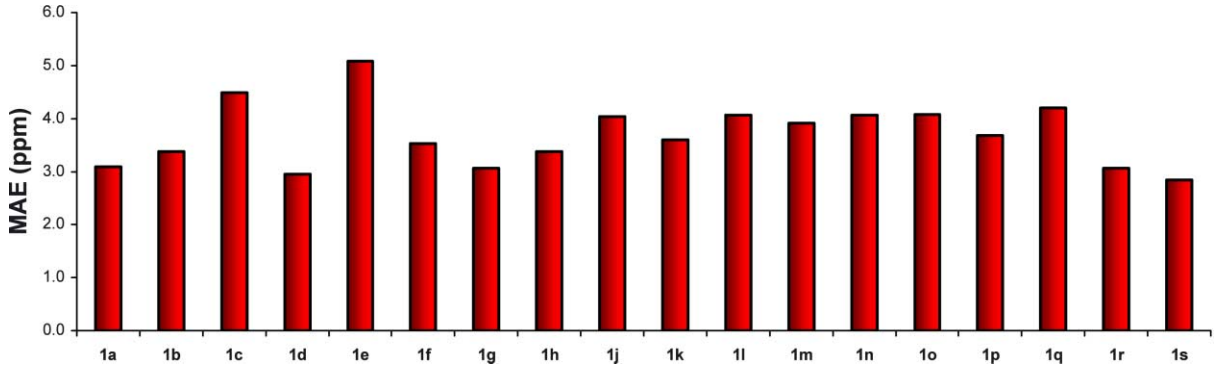


Figure 2. Mean absolute error (MAE) found for the ^{13}C NMR calculated chemical shifts of compounds **1a**–**s** versus the ^{13}C experimental values. $MAE = \Sigma[|(\delta_{exp} - \delta_{calcd})|]/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and calculated ^{13}C chemical shifts), normalized to the number of carbon atoms considered.

cone moiety and replacing the sugar portion, clearly irrelevant for our analysis, with a methyl group.

A preliminary molecular mechanics and dynamics study of the 18 stereoisomers afforded 18 minimum energy conformers that have been further refined by a DFT geometry optimization, using the mPW1PW91[12] functional and the 6-31G(d) basis set (Gaussian 98W[13] software package). Following a procedure recently proposed by one of the authors,[14] ^{13}C GIAO chemical shift (c.s.) calculations at mPW1PW91/6-31G(d,p) on the optimized structures were subsequently performed; the obtained calculated c.s. were then compared with the experimental (Fig. 2) in order to obtain clear indications of the stereostructure of **1**. While it was straightforward to exclude most of the stereoisomers on the basis of their large mean absolute error (MAE) values, obtained by subtracting the experimental from the calculated c.s. values, it was difficult to distinguish between compounds **1a**, **1d**, **1g**, **1r** and **1s**. This was probably due to the neglecting of the solvent effect for both the geometry optimization and the ^{13}C c.s. calculation steps, and/or to the replacement of the sugar moiety with a methyl group.

Analysis of the 2D-ROESY data, focused on the five stereoisomers suggested from the above considerations, confirmed the indications coming from the ^{13}C GIAO c.s calculations, and allowed the elucidation of the relative stereochemistry. In particular, the minimum energy conformers for **1a**–**1s** were examined in order to select the stereoisomer fitting all the available experimental data collected in the 2D-ROESY (Fig. 3). A ROESY correlation between H-16 and H-17, and between H-17 and Me-21, indicated a relative stereochemistry for the ring E as shown in compounds **1a**, **1c**, **1d**, **1e**, **1f**, **1m**, **1n** and **1r**, thus ruling out stereoisomers **1b**, **1g**, **1h**, **1j**, **1k**, **1l**, **1o**, **1p**, **1q** and **1s**. The relative orientation of Me-18 with respect to centers 16 and 17 was suggested by the lack of a ROESY correlation between Me-18 and H-16, which was compatible with stereoisomers **1a**, **1c**, **1m**, **1n** and **1r**, thus ruling out stereoisomers **1d**, **1e** and **1f**. This arrangement was confirmed by a strong correlation relative to H-16 and H-12α, which was also in contrast to the *anti* disposition of Me-18 and OH-14, thus ruling out stereoisomer **1r**. A strong ROE correlation between H-8 and Me-18 eliminated the candidate **1m**, and a correlation between H-8 and H-19b (δ 4.60) ruled out **1n**. Stereoisomers **1a** and **1c** were both compatible with the relative arrangement of ring A, suggested by dipolar correlations between H-3α and H-1α, and H-1β and H-19a (δ 4.00). Nevertheless the lack of a correlation between H-8 and H-9, and the observation of a dipolar effect for H-9 and H-1α suggested the exclusion of stereoisomer **1c**, and indicated the correct relative configuration of the molecule as in **1a**.

Compound **2** showed a quasimolecular ion peak at m/z 1279 $[M+H]^+$ and significant fragments at m/z 1219 $[M+H-60]^+$, m/z 1057 $[M+H-60-162]^+$, m/z 913 $[M+H-60-162-144]^+$, m/z 783 $[M+H-60-162-144-130]^+$, m/z 653 $[M+H-60-162-144-130-130]^+$ and m/z 365 $[M+H-60-162-144-130-130-288]^+$ in the positive ESIMS. The molecular formula was unequivocally established to be $C_{62}H_{102}O_{27}$ by HREIMS (1278.6601 found, 1278.6609 calcd), which was confirmed by data from the ^{13}C NMR spectrum. ^1H and ^{13}C NMR data of **2** in comparison to those of **1** clearly suggested that the aglycone moiety of **2** differed from that of **1** only by the absence of the double bond. Additionally for **2**, resonances for the anomeric protons were observed in the

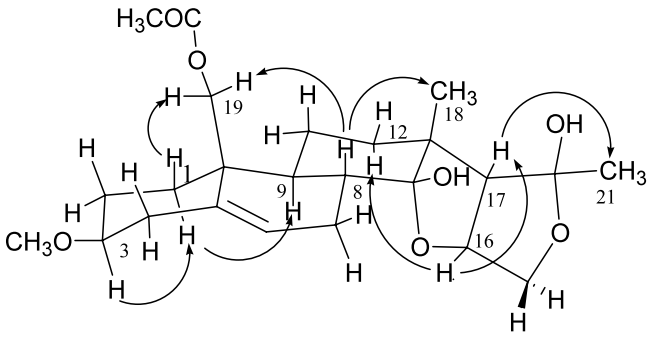
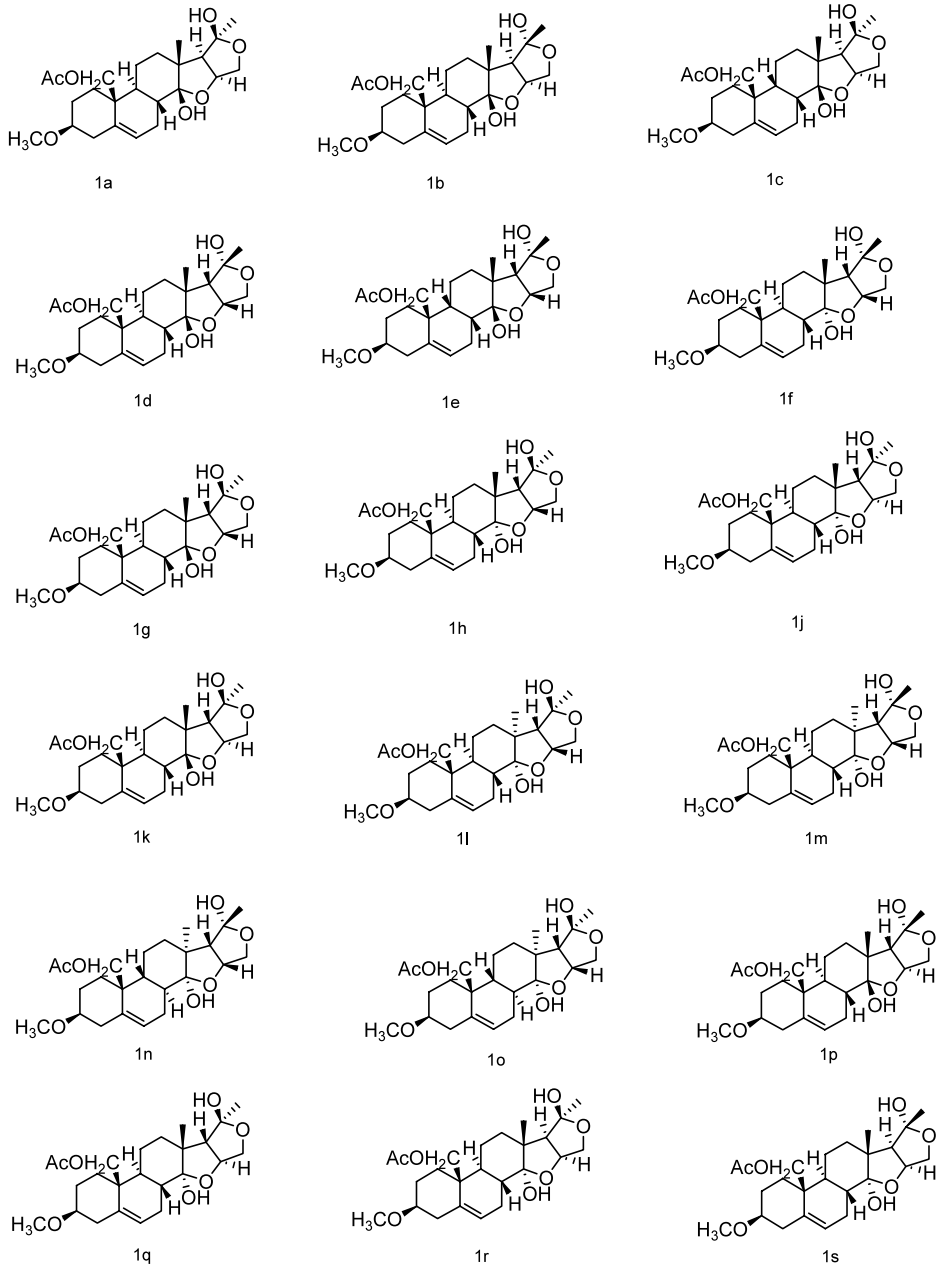


Figure 3. Diagnostic 2D-ROESY correlations for argeloside A (**1**).



1H NMR spectra at δ 4.90 (1H, dd, $J=9.2$, 2.0 Hz), 4.89 (1H, dd, $J=9.5$, 2.0 Hz), 4.81 (1H, dd, $J=9.0$, 1.5 Hz), 4.70 (1H, dd, $J=9.5$, 2.0 Hz), 4.65 (1H, dd, $J=9.5$, 2.0 Hz) and 4.47 (1H, d, $J=7.0$ Hz). Complete assignments of the ^{1}H and ^{13}C NMR signals of the sugar portion were accomplished by HSQC, HMBC, DQF-COSY and 2D-HOHAHA experiments and allowed the identification of the sugars as a terminal β-D-glucopyranosyl (δ 4.47) as well as inner units of β-D-oleandropyranosyl (δ 4.70), β-D-digitoxopyranosyl (δ 4.89) and β-D-canaropyranosyl (δ 4.65 H-1), and two inner units of β-D-cymaropyranosyl (δ 4.90 and 4.81). Direct evidence for the sugar sequence and their linkage sites was obtained from the HMBC correlations which led to the determination of the sugar sequence as 3-*O*-β-D-glucopyranosyl-(1→4)-β-D-oleandropyranosyl-(1→4)-β-D-digitoxopyranosyl-(1→4)-β-D-canaropyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranoside.

Argeloside A, 0.0025 g; ESIMS m/z 1163 $[M+H]^+$, 1103 $[M+H-60]^+$, 941 $[M+H-60-162]^+$, 781 $[M+H-60-162-160]^+$, 637 $[M+H-60-162-160-144]^+$; HREIMS (1162.5765 found, 1162.5771 calcd).^{1}H NMR (CD_3OD, 600 MHz) aglycone moiety δ 5.68 (1H, br d, $J=4.6$ Hz, H-6), 4.60 (1H, d, $J=11.8$ Hz, H-19b), 4.56 (1H, br m, H-16), 4.00 (1H, d, $J=11.8$ Hz, H-19a), 2.04 (3H, s, CO<u>Me</u>), 1.65 (3H, s, Me-21), 1.21 (3H, s, Me-18); β-D-can: δ 4.72 (1H, dd, $J=9.2$, 1.6 Hz, H-1), 1.46 (1H, ddd, $J=13.0$, 4.0, 1.6 Hz, H-2a), 2.14 (1H, ddd, $J=13.0$, 9.2, 9.0 Hz, H-2b), 3.36 (1H, ddd, $J=9.5$, 9.0, 4.0 Hz, H-3), 2.97 (1H, dd, $J=9.5$, 9.5 Hz, H-4), 3.60 (1H, dq, $J=9.5$, 6.0 Hz, H-5), 1.27 (3H, d, $J=6.0$ Hz, Me-6); β-D-cym: δ 4.81 (1H, dd, $J=9.5$, 2.0 Hz, H-1), 1.65

(1H, m, H-2a), 2.21 (1H, m, H-2b), 3.89 (1H, br m, H-3), 3.36 (1H, dd, $J=9.5$, 3.0 Hz, H-4), 3.95 (1H, dq, $J=9.5$, 6.0, H-5), 1.27 (3H, d, $J=6.0$ Hz, Me-6), 3.48 (3H, s, OMe); β-D-ole: δ 4.64 (1H, dd, $J=9.0$, 2.0 Hz, H-1), 2.36 (1H, ddd, $J=13.0$, 4.0, 2.0 Hz, H-2a), 1.45 (1H, ddd, $J=13.0$, 9.0, 9.0, H-2b), 3.41 (1H, ddd, $J=9.5$, 9.0, 4.0 Hz, H-3), 3.24 (1H, dd, $J=9.5$, 9.5 Hz, H-4), 3.41 (1H, dq, $J=9.5$, 6.2, H-5), 1.40 (3H, d, $J=6.2$ Hz, Me-6), 3.45 (3H, s, OMe); β-D-the: δ 4.46 (1H, d, $J=7.5$ Hz, H-1), 3.26 (1H, dd, $J=9.5$, 7.5 Hz, H-2), 3.21 (1H, dd, $J=9.5$, 9.5 Hz, H-3), 3.38 (1H, dd, $J=9.5$, 9.5, H-4), 3.46 (1H, m, H-5), 1.40 (3H, d, $J=6.2$, Me-6), 3.66 (3H, s, OMe); β-D-glc: δ 4.44 (1H, d, $J=7.5$ Hz, H-1), 3.20 (1H, dd, $J=7.5$, 9.0 Hz, H-2), 3.37 (1H, dd, $J=9.0$, 9.0 Hz, H-3), 3.24 (1H, dd, $J=9.0$, 9.0 Hz, H-4), 3.28 (1H, ddd, $J=2.0$, 4.5, 9.0 Hz, H-5), 3.66 (1H, dd, 4.5, 12.0 Hz, H-6a), 3.89 (1H, dd, $J=12.0$, 2.0 Hz, H-6b); ^{13}C NMR (CD_3OD, 150 MHz) aglycone moiety δ 34.8 (C-1), 30.6 (C-2), 78.8 (C-3), 39.5 (C-4), 136.0 (C-5), 126.6 (C-6), 25.3 (C-7), 33.2 (C-8), 46.4 (C-9), 46.4 (C-10), 21.1 (C-11), 31.2 (C-12), 50.1 (C-13), 110.4 (C-14), 72.0 (C-15), 78.3 (C-16), 58.5 (C-17), 15.5 (C-18), 65.0 (C-19), 114.6 (C-20), 23.4 (C-21), 172.0 (COMe), 20.7 (COMe); β-D-can: δ 98.9 (C-1), 39.7 (C-2), 71.6 (C-3), 88.8 (C-4), 70.6 (C-5), 37.5 (C-6); β-D-cym: δ 100.7 (C-1), 36.1 (C-2), 78.2 (C-3), 83.3 (C-4), 70.3 (C-5), 37.5 (C-6), 58.6 (OMe); β-D-ole: δ 102.4 (C-1), 37.6 (C-2), 80.2 (C-3), 84.2 (C-4), 72.3 (C-5), 18.5 (C-6), 57.7 (OMe); β-D-the: δ 104.4 (C-1), 75.2 (C-2), 86.4 (C-3), 82.8 (C-4), 72.5 (C-5), 18.5 (C-6), 61.1 (OMe); β-D-glc: δ 104.4 (C-1), 75.5 (C-2), 78.0 (C-3), 71.6 (C-4), 78.2 (C-5), 62.8 (C-6).

Argeloside B, 0.004 g; ESIMS m/z 1279 $[M+H]^+$, 1219 $[M+H-60]^+$, 1057 $[M+H-60-162]^+$, 913 $[M+H-60-162-144]^+$, 783 $[M+H-60-162-144-130]^+$, 653 $[M+H-60-162-144-130-130]^+$, 365 $[M+H-60-162-144-130-130-288]^+$; HREIMS (1278.6601 found, 1278.6609 calcd);^{1}H NMR (CD_3OD, 600 MHz) aglycone moiety δ 4.56 (1H, br m, H-16), 4.41 (1H, d, $J=11.8$ Hz, H-19b), 4.21 (1H, d, $J=11.8$ Hz, H-19a), 2.09 (3H, s, COMe), 1.63 (3H, s, Me-21), 1.15 (3H, s, Me-18); β-D-cymI: δ 4.90 (1H, dd, $J=9.2$, 2.0 Hz, H-1), 1.56 (1H, m, H-2a), 2.08 (1H, m, H-2b), 3.86 (1H, br m, H-3), 3.25 (1H, dd, $J=9.5$, 3.0 Hz, H-4), 3.33 (1H, dq, $J=9.5$, 6.2 Hz, H-5), 1.21 (3H, d, $J=6.2$ Hz, Me-6), 3.45 (3H, s, OMe); β-D-cymII: δ 4.81 (1H, dd, $J=9.0$, 1.5 Hz, H-1), 1.62 (1H, m, H-2a), 2.17 (1H, m, H-2b), 3.87 (1H, br m, H-3), 3.30 (1H, dd, $J=9.5$, 3.0 Hz, H-4), 3.86 (1H, dq, $J=9.5$, 6.2, H-5), 1.24 (3H, d, $J=6.2$ Hz, Me-6), 3.45 (3H, s, OMe); β-D-can: δ 4.65 (1H, dd, $J=9.5$, 2.0 Hz, H-1), 2.22 (1H, ddd, $J=13.0$, 4.0, 2.0 Hz, H-2a), 1.52 (1H, ddd, $J=13.0$, 9.5, 9.0, H-2b), 3.60 (1H, ddd, $J=9.5$, 9.0, 4.0 Hz, H-3), 3.00 (1H, dd, $J=9.5$, 9.5 Hz, H-4), 3.38 (1H, dq, $J=9.5$, 6.2, H-5), 1.29 (3H, d, $J=6.2$ Hz, Me-6); β-D-dig: δ 4.89 (1H, dd, $J=9.5$, 2.0 Hz, H-1), 1.75 (1H, m, H-2a), 2.09 (1H, m, H-2b), 4.28 (1H, br m, H-3), 3.33 (1H, dd, $J=9.5$, 3.0 Hz, H-4), 3.96 (1H, dq, $J=9.5$, 6.2, H-5), 1.28 (3H, d, $J=6.2$ Hz, Me-6); β-D-ole: δ 4.70 (1H, dd, $J=9.5$, 2.0 Hz, H-1), 2.37 (1H, ddd, $J=13.0$, 4.0, 2.0 Hz, H-2a), 1.53 (1H, ddd, $J=13.0$, 9.5, 9.0, H-2b), 3.45 (1H, ddd, $J=9.5$, 9.0, 4.0 Hz, H-3), 3.33 (1H, dd, $J=9.5$, 9.5 Hz, H-4), 3.45 (1H, dq, $J=9.5$, 6.2, H-5), 1.40 (3H, d, $J=6.2$ Hz, Me-6), 3.50 (3H, s, OMe); β-D-glc: δ 4.47 (1H, d, $J=7.5$ Hz, H-1), 3.19 (1H, dd, $J=7.5$, 9.0 Hz, H-2), 3.38 (1H, dd, $J=9.0$, 9.0 Hz, H-3), 3.28 (1H, dd, $J=9.0$, 9.0 Hz, H-4), 3.28 (1H, ddd, $J=2.5$, 4.5, 9.0 Hz, H-5), 3.67 (1H, dd, 4.5, 12.0 Hz, H-6a), 3.89 (1H, dd, $J=2.5$, 12.0 Hz, H-6b); ^{13}C NMR (CD_3OD, 150 MHz) aglycone moiety δ 32.9 (C-1), 30.3 (C-2), 77.8 (C-3), 35.7 (C-4), 45.3 (C-5), 28.6 (C-6), 35.7 (C-7), 36.2 (C-8), 39.4 (C-9), 49.6 (C-10), 21.7 (C-11), 31.6 (C-12), 50.2 (C-13), 111.0 (C-14), 71.8 (C-15), 78.3 (C-16), 58.7 (C-17), 16.0 (C-18), 69.2 (C-19), 115.0 (C-20), 23.5 (C-21), 172.5 (COMe), 20.8 (COMe); β-D-cymI: δ 97.2 (C-1), 36.4 (C-2), 78.4 (C-3), 83.8 (C-4), 69.8 (C-5), 18.3 (C-6), 58.3 (OMe); β-D-cymII: δ 101.2 (C-1), 36.2 (C-2), 78.4 (C-3), 83.9 (C-4), 69.7 (C-5), 18.3 (C-6), 58.3 (OMe); β-D-can: δ 102.5 (C-1), 39.5 (C-2), 70.5 (C-3), 88.8 (C-4), 71.5 (C-5), 18.0 (C-6); β-D-dig: δ 100.5 (C-1), 38.3 (C-2), 68.0 (C-3), 83.3 (C-4), 69.6 (C-5), 18.0 (C-6); Ole: δ 102.2 (C-1), 37.5 (C-2), 80.0 (C-3), 83.5 (C-4), 72.7 (C-5), 18.3 (C-6), 58.1 (OMe); β-D-glc: δ 104.0 (C-1), 75.5 (C-2), 77.9 (C-3), 71.6 (C-4), 78.1 (C-5), 62.7 (C-6).

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