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Chemical constituents and absolute configuration of megastigmanes' isolated from *Sedum sarmentosum* Bunge

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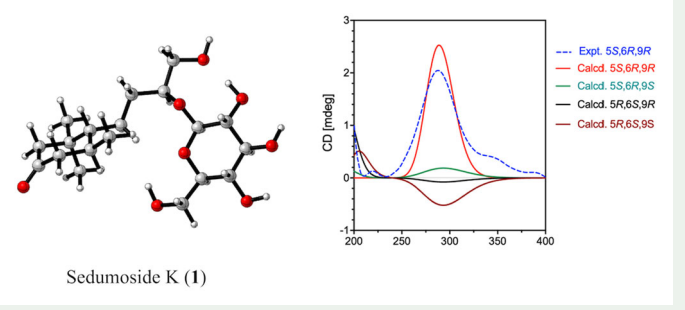
ABSTRACT

Phytochemical investigation of a methanolic extract of *Sedum sarmentosum* collected from Vietnam resulted in the isolation of a new megastigmane glucoside, named sedumoside K (**1**), together with 17 previously reported compounds (**2–18**). Structural elucidation of the new compound was achieved by HRFABMS, NMR spectroscopic analysis, acid hydrolysis and quantum ECD calculations. The absolute configuration of compounds **2–6** has been revised. The major isolates were tested for cytotoxic activity against HeLa human cervical cancer cells, and all showed moderate activities.



Sedumoside K (**1**)

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KEYWORDS
Megastigmane; *Sedum sarmentosum*; ECD calculation; absolute configuration

1. Introduction

Sedum sarmentosum Bunge (Crassulaceae) is a herbaceous plant traditionally used to treat burns, hepatitis, dysentery, snake bites, scabies, pimples and sore throat (Vv,

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2012). Phytochemical investigation of *S. sarmentosum* resulted in the discovery of many megastigmanes, flavonoids, alkaloids, and terpenoids with a wide range of biological activities (Bai et al., 2016; Cho et al., 2017; He et al., 1998; Ma et al., 2017; Morikawa et al., 2012; Muraoka et al., 2009; Zhang et al., 2007). Chemical composition of Vietnamese *S. sarmentosum has* been never investigated. In the present study, phytochemical investigation *S. sarmentosum*, collected from Vietnam, was carried out for the first time, which led the isolation of a new megastigmane-type sesquiterpene (**1**), together with 17 known compounds. The isolated compounds can be classified as six megastigmanes, five flavonoids, six phenolics and a lignan. The previously reported compounds were identified as sedumoside C (**2**) (Yoshikawa et al., 2007), myrsinionoside A (**3**) (Otsuka et al., 2001), simplicifloranoside (**4**) (Yean et al., 2014), sedumoside I (**5**) (Yoshikawa et al., 2007), sarmentol A (**6**) (Yoshikawa et al., 2007), luteolin (**7**) (Lin et al., 2015), isorhamnetin-3,7-*O*-di-*β*-D-glucoside (**8**) (Mskhiladze et al., 2016), quercetin-3-*O*-*β*-D-glucopyranose (**9**) (Zhang et al., 2014), 3′-methoxyluteolin-7-*O*-*β*-D-glucopyranoside (**10**) (Harput et al., 2006), 3′-methoxy-3,5,4′-trihydroxyflavone-7-neohesperidoside (**11**) (Umehara et al., 1988), 2-phenylethyl-D-rutinoside (**12**) (Umehara et al., 1988), ferulic acid (**13**) (Van et al., 2004), *trans-p*-coumaric acid (**14**) (Ren et al., 2013), *p*-hydroxybenzoic acid (**15**) (Chen et al., 2010), 4-hydroxyphenylethyl

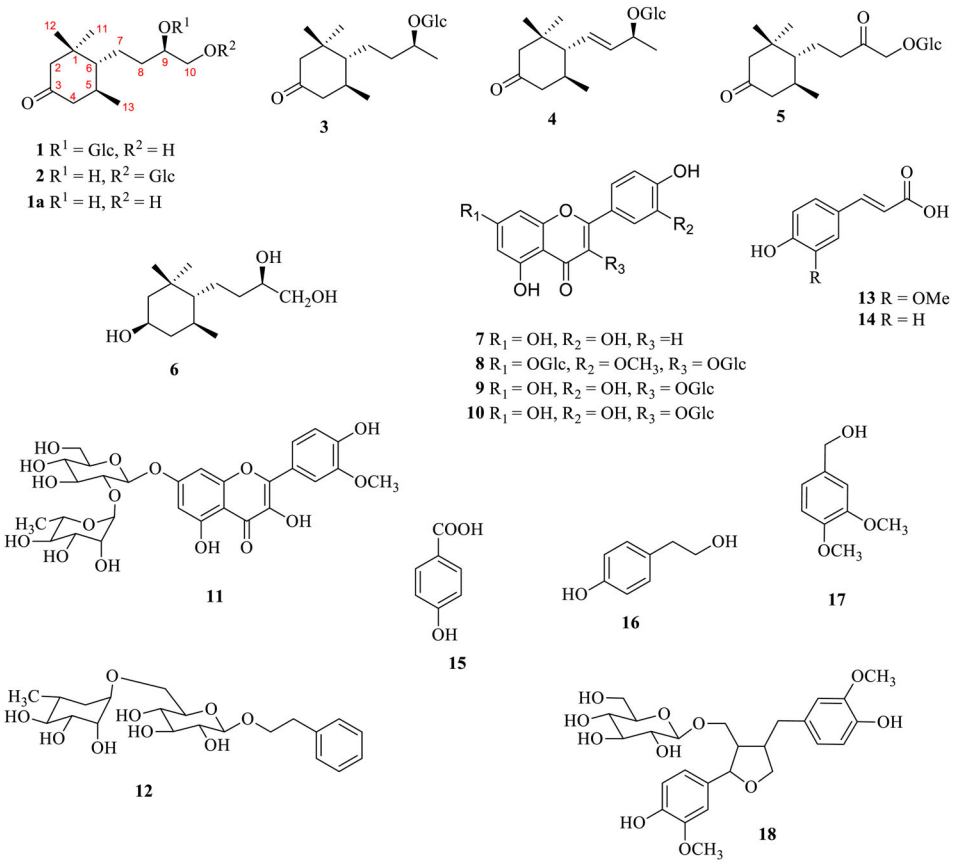

Figure 1. Structures of compounds **1**–**18** isolated from *S. sarmentosum*.

alcohol (**16**) (Capasso et al., 1992), 3,4-dimethoxybenzyl alcohol (**17**) (Kanho et al., 2005) and lariciresinol-9-*O*-β-D-glucopyranoside (**18**) (Cho et al., 2014) (Figure 1). Herein, we report the isolation and structural elucidation of the new compound **1** and the absolute configuration revision of compounds **2–6**.

2. Results and discussion

Sedumoside K (**1**) was isolated as a pale-yellow oil. Its molecular formula was deduced by HRMS as $C_{19}H_{34}O_8$ [*m/z* 425.1940 $(M+Cl)^-$]. The IR spectrum of **1** showed absorption bands of hydroxy (3449 cm^{-1}) and carbonyl (1652 cm^{-1}) groups. The ^{1}H NMR spectrum of **1** displayed the presence of signals corresponding to three methyl groups [δ_H 0.81 (s, H-11), 1.12 (s, H-12) and 1.14 (d, $J = 6.5$ Hz, H-13)], four methylenes [δ_H 2.43 (d, $J = 13.0$ Hz, H-2a), 2.25 (m, H-4a), 2.20 (m, H-4b), 2.01 (dd, $J = 13.0$, 2.0 Hz, H-2b), 1.80 (m, H-7a), 1.79 (m, H-8a), 1.69 (m, H-8b) and 1.25 (m, H-7b),] in addition to two methines [δ_H 1.83 (m, H-5) and 1.20 (m, H-6)]. Moreover, ^{1}H NMR spectrum showed the presence of two oxymethylene groups [δ_H 3.59 (dd, $J = 12.0$, 6.0 Hz, 10b), 3.71 (m, H-10a and H-6'b) and 3.91 (dd, $J = 12.0$, 2.0 Hz, H-6'a)] and five oxymethines [δ_H 3.79 (m, H-9), 3.62 (m, , H-2′), 3.42 (m, H-3′) 3.35 (m, H-4′) and 3.33 (m, H-5′)]. ^{1}H NMR spectrum of **1** also showed the presence of an anomeric proton [δ_H 4.48 (d, $J = 7.5$ Hz, H-1′′)] which is characteristic for one sugar unit. The ^{13}C NMR spectrum of **1** exhibited signals of 19 carbons corresponding to three methyls (δ_C 21.1, 21.5, 30.3), four methylenes (δ_C 26.0, 34.9, 50.9, 57.1), two methines (δ_C 37.6, 53.7), two oxymethylene groups (δ_C 62.9, 64.8), five oxymethines (δ_C 71.7, 75.5, 77.9, 78.0, 82.3), an anomeric carbon (δ_C 103.9), a quaternary carbon (δ_C 40.4) and a carbonyl group (δ_C 214.6). Part of these data suggested the presence of sarmentol C (δ_C 21.1, 21.5, 26.0, 30.3, 34.9, 37.6, 40.4, 50.9, 53.7, 57.1, 64.8, 82.3, 214.6) which was confirmed from the COSY, HMQC and HMBC spectra of **1** (Figure S1, Supporting Information) (Yoshikawa et al., 2007). Remaining ^{1}H and ^{13}C NMR signals suggested the presence of a β-glucose unit (δ_C 103.9, 75.5, 78.0, 71.7, 77.9, 62.9). The HMBC correlation from H-1′ to C-9 confirmed the location of the β-glucose at C-9 of sarmentol C unit (Figure S1, Supporting Information). Thus, the planar structure of **1** was deduced to be 6-(3-β-D-glucopyranosyl-4-hydroxy-*n*-butyl)-3,3,5-trimethylcyclohexanone. The relative configuration of **1** was assigned by analyzing the coupling constants and NOESY data (Figure S2, Supporting Information). The large coupling constant ($J_{1',2'} = 7.5$ Hz) suggested the *trans*-disposition of H-1′ (α) and H-2′ (β). The presence of NOESY correlations H-1′/H-3′ and H-1′/H-5′ suggested their α-axial orientation, while correlations between H-2′ and H-4′ suggested their β-axial orientation (Figure S2, Supporting Information). For the present study, conformational analysis at MM2 (Cho et al., 1989), followed by geometry optimization using DFT at CAM-B3LYP/6-31G* level (Dewar and O'Connor 1987, Yanai et al., 2004), which gave the most stable conformer as depicted in figure S2. Theoretical ECD calculation on the optimized geometry was carried out at the same level of theory. The calculated ECD data for 5*R*,6*S*,9*R* and 5*R*,6*S*,9*S* gave negative cotton effects at 280 nm. Since the observed ECD is positive, the new compound should possess 5*S*,6*R* absolute configuration (Figure S3, Supporting Information). Furthermore, the rotatory strength of

the cotton effect was found to be in close agreement with the experimental data of 5*S*,6*R*,9*R*. In order to confirm absolute configuration of the sugar unit, we further carried out acid hydrolysis of **1**, which yielded a sugar with positive optical rotation value of $[\alpha]^{22}_{D}$ +13.2 (*c* 0.2, H_2O), similar to the value reported for D-glucose $[\alpha]^{25}_{D}$ +52 (*c* 0.02, H_2O) (Kim et al., 2015). Therefore, the sugar unit in **1** was confirmed as D-glucose. The aglycone **1a**, obtained from acid hydrolysis of **1**, showed specific optical rotation, $[\alpha]^{22}_{D}$ −11.3 (*c* 0.22, MeOH), opposite to that reported for sarmentol C, $[\alpha]^{23}_{D}$ +11.9 (*c* 0.22, MeOH), having a 5*R*,6*S* configuration (Yoshikawa et al., 2007). Furthermore, specific optical rotation calculation of the optimized geometry of an aglycone (**1a)** was carried out and compared with the experimental data. The sign of calculated specific optical rotation (−38.76) was found to be in close agreement with experimental data (Figure S4, Supporting Information). This data further suggested that the aglycone **1a** should have a 5*S*,6*R* configuration. In addition, computational ECD calculation for **1a** was carried out. The experimental ECD spectrum of **1a** was found to match closely with the theoretical ECD spectrum calculated for the 5*S*,6*R*,9*R* configuration, confirming the absolute configuration of **1a** as 5*S*,6*R*,9*R* (Figure S4, Supporting Information). All these evidences unequivocally conclude the 5*S*,6*R*,9*R* absolute configuration of compound **1**.

Since the new compound **1** possessed 5*S*,6*R* configuration, which was found to be opposite to those previously reported for **2–6**, we further studied their chiroptical properties. Compounds **2–6** displayed negative optical rotations and were comparable with those reported in the literature (Otsuka et al., 2001; Yean et al., 2014; Yoshikawa et al., 2007). Furthermore, compounds **1–5** displayed positive cotton effects at 280 − 290 nm (Figure S5, Supporting Information), suggesting that the absolute configuration of C-5 and C-6 in **2–6** should be the same as **1**. Therefore, reported absolute configuration of **2–5** should be re-assigned as 5*S*,6*R* (Figure 1).

The major isolates (**1–6**, **8**, **10**, **13–16**) were tested for their cytotoxic activity against HeLa human cervical cancer cells. All the compounds showed moderate cytotoxic activity (Figure S14, Supporting Information).

3. Experimental

3.1. General experimental procedures

Optical rotations, UV, ECD, and IR spectra were recorded on A JASCO P-2100 digital polarimeter, a Hitachi U-5100 UV − Visible ratio-beam spectrophotometer, a JASCO J-805 spectropolarimeter and a JASCO FT/IR-460 Plus spectrophotometer, respectively. NMR spectra were recorded using a Bruker 500 MHz spectrometer, using $CDCl_3$ as solvent and TMS as internal standard, and chemical shifts are expressed in δ values. An Agilent 6550 iFunnel Q-TOF LC/MS system was used for HRESIMS measurement. Column chromatography was performed using adsorbents silica gel (70–230 mesh) or reverse phase C-18 (RP-18) resins (150 μm). Thin layer chromatography (TLC) was carried out using pre-coated silica gel 60 F254 and RP-18 F_{254S} plates.

3.2. Plant material

Whole plant parts of *S. sarmentosum* Bunge were collected at Sa Pa, Lao Cai province, Vietnam in June 2015, and voucher specimens (DL-300615) have been deposited in Herbarium of Military Institute of Traditional Medicine and Herbarium of National Institute of Medicinal Materials.

3.3. Extraction and isolation procedures

Air dried *Sedum sarmentosum* Bunge (9 kg) was ground to a fine powder then extracted with methanol (3 × 15 L) to give a methanol extract (400 g). The extract (400 g) was suspended in hot water and partitioned successively with *n*-hexane, CH_2Cl_2 and EtOAc to obtain *n*-hexane (162 g), dichloromethane (41 g), EtOAc (14 g) and H_2O (155 g) soluble fractions. The EtOAc fraction (14 g) was subjected to silica gel column chromatography using a CH_2Cl_2–MeOH (20:1) mixture to obtained 5 fractions (fr. 1 to 5). Fraction 1 (0.4 g) was further chromatographed separated on a RP-silica gel using an acetone–water (2:1) mixture to give 3,4-dimethoxybenzyl alcohol (**17**, 3.0 mg). Fraction 2 (3.4 g) was chromatographed on RP-silica gel using MeOH–water (1:2) mixture to afford 3 subfractions, (fr. 2-1 to 2-3). Subfraction 2-1 (500 mg) was separated using silica gel column eluted with a CH_2Cl_2–acetone–water (5:1:0.1) mixture to give *p*-hydroxybenzoic acid (**15**, 20 mg) and 4-hydroxyphenylethyl alcohol (**16**, 30 mg). Subfraction 2-2 (200 mg) was further purified on a Shephadex LH-20 column, eluted with MeOH–water (1:1) to yield ferulic acid (**13**, 60 mg). Subfraction 2-3 (250 mg) was purified using silica gel column eluted with a CH_2Cl_2–MeOH (20:1) mixture to give *trans-p*-coumaric acid (**14**, 20.0 mg). Fraction 3 (2.9 g) was subjected to RP-silic gel column chromatography column using MeOH–water (1:2) mixture to yield 4 fractions (fr. 3-1 to 3-4). Subfraction 3-1 (300 mg) was further purified on a Shephadex LH-20 column, eluted with MeOH–water (1:1) mixture to yield luteolin (**7**, 10 mg). Subfraction 3-2 (900 mg) was separated using silica gel column eluted with CH_2Cl_2–acetone–water (5:1:0.1) to give sarmentol A (**6**, 15 mg) and myrsinionoside A (**3**, 50 mg). Subfraction 3-3 (150 mg) was further separated on a Shephadex LH-20 column, eluting with MeOH–water (1:1) mixture to yield simplicifloranoside (**4**, 20 mg). Subfraction 3-4 (200 mg) was further purified on a Sephadex LH-20 column, eluting with MeOH–water (1:1) mixture to yield sedumoside I (**5**, 15 mg). Fraction 4 (3.7 mg) was further purified using RP-silica gel column chromatography using a MeOH–water (1:2) mixture to yield 2 fractions. Subfraction 4-1 (900 mg) was purified using silica gel column chromatography eluted with a CH_2Cl_2–MeOH–water (6:1:0.05) mixture to give 3′-methoxyluteolin-7-*O*-β-D-glucopyranoside (**10**, 12 mg). The H_2O soluble fraction (155 g) was further purified on a Sephadex LH-20 column eluted with MeOH–water (25:75) mixture to obtained 4 fractions, (fr. 1 to 4). Fraction 3 (13.7 g) was subjected to silica gel column chromatography using a CH_2Cl_2–MeOH (20:1) mixture to afford 5 subfractions, (fr. 3-1 to 3-5). Subfraction 3-1 (2.1 g) was further purified using a RP-silica gel column chromatography eluted with a MeOH–water (1:2) mixture to afford quecertin-3-*O*-β-D-glucopyranose (**9**, 5 mg). Subfraction 3-4 (1.5 g) was separated on a RP-18 column eluted with MeOH–water (1:2.5) to afford 5 subfractions, (fr.3-4-1 to 3-4-5). Subfractions 3-4-1 (200 mg) and 3-4-3 (250 mg) were subjected to a silica gel column chromatography

using a CH_2Cl_2–acetone-water (1:2:0.1) mixture to afford sedumoside K (**1**, 41 mg), sedumoside C (**2**, 10 mg), isorhamnetin-3,7-*O*-di-β-D-glucoside (**8**, 12 mg), 3′-methoxy-3,5,4′-trihydroxyflavone-7-neohesperidoside (**11**, 15 mg), 2-phenylethyl-D-rutinoside (**12**, 15 mg) and lariciresinol-9-*O*-β-D-glucopyranoside (**18**, 4 mg).

*Sedumoside K (**1**)*: pale-yellow oil, $[\alpha]^{23}_{D}$ +26.6 (*c* 0.03, MeOH); UV (MeOH) λ_{max} (log ε) 208 (3.0) nm; IR (KBr) ν_{max} 3417, 2924, 2855, 2365, 1654, 1438, 1410, 1317, 1022, 954, 709,674 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ_H 4.48 (1H, d, J = 7.5 Hz, H-1′), 3.91 (1H, dd, J = 12.0, 2.0 Hz, H-6′a), 3.79 (1H, m, H-9), 3.71 (2H, m, H-10a, H-6′b), 3.62, (1H, m, H-2′), 3.59, (dd, J = 13.0, 6.0 Hz, H-10b), 3.42 (1H, m, H-3′), 3.35 (1H, m, H-4′), 3.33 (1H, m, H-5′), 2.43 (1H, d, J = 13.0 Hz, H-2a), 2.25 (1H, m, H-4a), 2.20 (1H, m, H-4b), 2.01 (1H, m, H-2b), 1.83 (1H, m, H-5), 1.80 (1H, m, H-7a), 1.79 (1H, m, H-8a), 1.69 (1H, m, H-8b), 1.25 (1H, m, H-7b), 1.20 (1H, m, H-6), 1.14 (1H, d, J = 6.5 Hz, H-13), 1.12 (1H, s, H-12), 0.81 (1H, s, H-11). ^{13}C NMR (100 MHz, CD_3OD): 214.6 (C-3), 103.9 (C-1′), 82.3 (C-9), 78.0 (C-3′), 77.9 (C-5′), 75.5 (C-2′), 71.7 (C-4′), 64.8 (C-10), 62.9 (C-6′), 57.1 (C-2), 53.7 (C-6), 50.9 (C-4), 40.4 (C-1), 37.6 (C-5), 34.9 (C-8), 30.3 (C-12), 26.0 (C-7), 21.5 (C-13), 21.1 (C-11). HRMS *m/z* 425.1940 $[M + Cl]^-$ (calcd for $C_{19}H_{34}O_8$, 425.1942).

3.4. Cytotoxicity assay

The cytotoxicity assay against HeLa cancer cell line was carried out as described previously (Lombe et al., 2018).

3.5. Computational ECD calculations

The ECD calculations were performed as previously reported (Omar et al., 2019; Omar et al. 2020). The conformational search was performed on Spartan'16 (Wave function, Inc., Irvine, CA, U.S.A.) by using MM2 molecular force field (Cho et al., 1989). All possible conformers with Boltzmann distribution > 1% were reoptimized using DFT at the CAM-B3LYP/6-31G* level in the gas phase (Dewar and O'Connor 1987, Yanai et al., 2004). The theoretical ECD calculations on these optimized geometries were carried out at the same level of theory in PCM solvation model for EtOH Using Gaussian 09 (Frisch et al. 2009). The output files were summed to obtain Boltzmann weighed spectra and compared with the experimental spectra by using SpecDis v. 1.71.2 (Bruhn et al., 2017) with respect to the experimental data employing the default σ (0.16 eV) and without applying any UV correction.

Conclusions

In conclusion, phytochemical investigation of *Sedum sarmentosum* resulted in the isolation of a new megastigmane glucoside (**1**) together with 17 previously reported compounds. The absolute configuration of **1** was deduced through computational ECD calculation and acid hydrolysis. The absolute configuration of compounds **2–6** was revised. The major isolates were tested for cytotoxic activity against HeLa human cervical cancer cells, and all showed moderate activities.

Disclosure statement

No potential conflict of interest was reported by the authors.

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