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Constituents of the Rhizomes of *Sansevieria cylindrica*

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A new sappanin-type 3-benzyl chroman-4-one (homoisoflavanone), (3*S*)-3-(4Ninethoxybenzyl)-3,5-dihydroxy-7-methoxy-6-methyl chroman-4-one (**1**), together with known congeners (3*S*)-3-(4Ninethoxybenzyl)-3,5-dihydroxy-7-methoxy chroman-4-one (**2**), (3*S*)-3-(4Nihydroxybenzyl)-3,5-dihydroxy-7-methoxy-6-methyl chroman-4-one (**3**), (3*S*)-3-(4Nihydroxybenzyl)-3,5-dihydroxy-7-methoxy chroman-4-one (**4**), 3-(3ô,4ô-methyledioxybenzyl)-7-hydroxy-8-methoxy chroman-4-one (**5**), and stigmasterol and ergosterol peroxide have been isolated from the rhizomes of *Sansevieria cylindrica*, collected in Myanmar. Moreover, the first isolation of the (-)-enantiomer of the dihydrochalcone trifasciatine C (**7**) from nature is described. The structures of the compounds have been established by extensive spectroscopic analysis. Compounds **4** and **7** showed no significant cytotoxicity against HeLa cells. Compounds **1**-**4** and **7** exhibited weak radical scavenging activity (DPPH). A new biosynthetic pathway has been proposed for the formation of homoisoflavanone **5** and dihydrochalcone **7**.

Keywords: *Sansevieria cylindrica*, Dracaenaceae, 3-Benzyl chroman-4-ones, Dihydrochalcone, Biosynthesis, Myanmar medicinal plant.

The genus *Sansevieria* (family Dracaenaceae) comprises about 70 species of flowering plants with a distribution ranging from Africa through Asia, including Myanmar and the islands of the Indian Ocean [1]. *S. cylindrica* Bojer ex Hook is native to the subtropical African regions, and it is cultivated in Myanmar for ornamental purposes. Moreover, the whole plant is used in Myanmar traditional medicine for treating cuts, sprains and broken bones, whereas the roots are used to cure snakebites. *Sansevieri*a species have been reported to be rich in steroidal sapogenins and saponins. Previous phytochemical investigations of leaves and aerial parts of *S. cylindrica* led to the isolation of steroidal saponins [2-4], one of which demonstrated inhibition of capillary permeability activity [2], whereas others exhibited moderate cytotoxicities *in vitro* [4]. In addition, (+)-trifasciatine B (**6**), with antioxidant activity [3], and dihydrochalcone (+)-**7** [4a], named trifasciatine C [4b], showing a moderate cytotoxicity against MCF7 cells, were reported from the same source.

As a part of our investigations of the secondary metabolites from medicinal plants used in Myanmar [5], we have studied, for the first time, the constituents of *S. cylindrica* rhizomes. We describe the isolation and characterization of a new sappanin-type 3-benzyl-chroman-4-one (homoisoflavanone) (**1**), together with four known congeners (**2**-**5**), dihydrochalcone **7**, stigmasterol, and ergosterol peroxide.

Compound **1**, [Ŭ]$_D^{20}$ +22.9 (*c* 0.004, CH_2Cl_2), had the molecular formula $C_{19}H_{20}O_6$ as determined by the ESI-MS, which exhibited two pseudo-molecular ion peaks at *m/z* 367.11 and *m/z* 345.47, corresponding to $[M+Na]^+$ and $[M+H]^+$, respectively. Moreover, the hydrogen and carbon numbers were deduced from the ^{1}H and

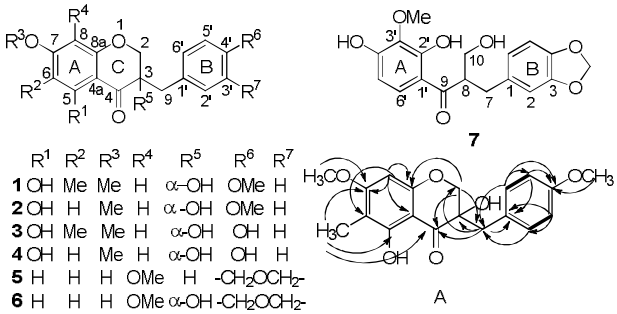

Figure 1: Structures of compounds **1**-**7** and (A) ^{1}HŸ ^{13}C HMBC correlations of homoisoflavanone **1**.

^{13}C-NMR spectra, respectively. The IR spectrum exhibited absorption bands at 3448 cm^{-1} and 1634 cm^{-1}, indicating the presence of hydroxyl and conjugated carbonyl groups. The structure of **1** was inferred by 1D, 2D NMR, UV and CD experiments.

The ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1** showed the typical splitting pattern of a 3-hydroxy-substituted 3-benzylchroman-4-one (homoisoflavanone), with two pairs of germinal coupled proton resonances at ŭ 4.20 and 4.05 (ABq , *J* = 11.0 Hz, H_2-2) and at ŭ 2.96 and 2.93 (ABq, *J* = 14.1 Hz, H_2-9). The pattern of a 1,4-disubstituted ring B was elucidated as an AA'BB' system at ŭ 7.12 (2H, d, *J* = 8.6 Hz, H-2Ni and H-6Ni) and ŭ 6.85 (2H, d, *J* = 8.6 Hz, H-3Ni and H-5Ni). The ^{1}H NMR spectrum of compound **1** also showed two singlets for a chelated OH at ŭ 12.1 (*H*O-5), an isolated aromatic proton at δ 6.07 (H-8), and a singlet of an aromatic methyl group at δ 2.02 (Me-6).

Furthermore, two three-proton singlets located at ŭ 3.88 and 3.79, corresponding to aromatic carbon resonances at ŭC 55.9 and 55.2, respectively, indicated the presence of two methoxy groups, which were placed at the available positions C-7 and C-4Ń respectively. The ^{13}C NMR spectrum displayed 19 signals: thirteen were assignable to sp^2 carbons, including a *C*O and twelve aromatic carbons, four of which were oxygenated; the remaining signals were attributable to six sp^3 carbons, including two methylenes, three methyls and one quaternary oxygenated carbon. These data suggested the basic skeleton of a 3-hydroxy-3-benzylchroman-4-one [6], which was confirmed by the HMBC correlations between H$_2$-2 and C-3 and C-4, and between H$_2$-9 and C-2, C-4, and C-1Ń The HMBC correlations between the resonances of H-8 (ŭ 6.07) and C-7 (ŭ 166.4), C-8a (ŭ 161.1), C-6 (ŭ 106.5) and C-4a (ŭ 100.2), and between 6-Me (ŭ 2.02) and C-5 (ŭ 160.2), C-6 (ŭ 106.5) and C-7 (ŭ 166.4) provided definitive evidence for the A ring structure. The position of the two methoxy groups was confirmed by the NOESY cross peaks between the methoxy protons at ŭ 3.79 (MeO-4Ń and the H-3Ńl-5Ń resonances, and by the HMBC correlations between the methoxy protons at ŭ 3.88 (MeO-7) and the oxygenated carbon C-7 (ŭ 166.4), and between the methoxy protons at ŭ 3.79 (MeO-4Ń and the oxygenated carbon C-4Ń ŭ 158.8), respectively.

In addition to the new compound **1**, comparison of the spectral data with the literature allowed for the identification of (3*S*)-3-(4Ń methoxybenzyl)-3,5-dihydroxy-7-methoxy chroman-4-one (**2**), [(-)-7-*O*-methyleucomol] [7], (3*S*)-3-(4Ń hydroxybenzyl)-3,5-dihydroxy-7-methoxy-6-methyl chroman-4-one (**3**) [8], (3*S*)-3-(4Ń hydroxybenzyl)-3,5-dihydroxy-7-methoxy chroman-4-one (**4**) [9], 3-(3Ń 4Ń methyledioxybenzyl)-7-hydroxy-8-methoxy chroman-4-one (**5**) [10], 2Ń 4Ń dihydroxy-3Ń methoxy-3,4-methylenedioxy-8-hydroxymethylene dihydrochalcone (**7**) [4], stigmasterol, and ergosterol peroxide. Compounds **1-4** have been isolated for the first time from the genus *Sansevieria* [6], while the structure of compound **5** corresponded to (*R*)-(-)-trifasciatine A, recently isolated from the aerial parts of *S. trifasciata* [10]. However, the configuration of the two samples could not be compared, because an unambiguous measurement of the optical activity of compound **5** isolated from *S. cylindrica* was hampered by the minute amounts in our hands. As regards dihydrochalcone **7**, the specific rotation, $[\alpha]_D^{25}$ -130 (*c* 0.028, MeOH), measured for the sample isolated from the rhizomes of *S. cylindrica*, was much higher in absolute value and opposite in sign to the specific rotation, $[\alpha]_D^{25}$ +1.4 (*c* 0.0013, MeOH), reported for a compound with the same structure isolated from the aerial parts of the same plant [4a]. The specific rotation is also higher and opposite to the value, $[\alpha]_D^{25}$ +20 (*c* 0.3, MeOH), reported for (+)-trifasciatine C, isolated from the aerial parts of *S. trifasciata*, to which the same structure **7** has been assigned, and the (8*S*)-configuration has been tentatively attributed [4b]. Thus, this is the first isolation of (-)-trifasciatine C from nature. This finding suggests that different scalemic compositions of compound **7** may exist in the aerial parts of different *Sansevieria* species or even in different organs of the same species. Alternatively, the compound may suffer severe racemization during isolation. Trifasciatine C (**7**) adds to the numerous known examples of the occurrence of both enantiomers or the formation of enantiomeric congeners of opposite antipodal series in the same plant or in different species [11]. Among homoisoflavanones, a recent example of biosynthetic enantiodivergence is given by trifasciatine B (**6**), which occurs as the (3*S*)-enantiomer in *S. cylindrica* [3], while the (3*R*)-antipode has been isolated from *S. trifasciata* [10].

The configuration at C-3 of compounds **1-4** was determined by comparison of the electronic circular dichroism (ECD) spectra with those of previously reported homoisoflavonoids [6,9,12]. The negative πŸ π* strong Cotton effect in the 287-295 nm region and the positive nŸ π* weak Cotton effect at about 315 nm indicated the *S* configuration for all these compounds.

Compounds **4** and **7** showed no cytotoxicity (IC_{50} > 80 μM) on Hela cells in a standard MTT test [13], while **1**-**3** could not be tested due to their insolubility in the saline solution containing 10% DMSO. In addition, compounds **1-4** and **7** displayed low radical scavenging activity, having EC_{50} values > 100 μM in the DPPH test [14].

Biosynthetic considerations: The co-occurrence in the same plant, e.g. *S. trifasciata* [4b, 10] and *S. cylindrica* [this paper] of dihydrocalcone **7** and sappanin-type 3-benzyl chroman-4-ones (homoisoflavanones [15]) **5** (and **6**), showing the same substituent patterns in rings A and B, have suggested a plausible biogenetic relationship between these compounds. On the basis of early experiments with radioactive precursors on the biosynthesis of the 3-benzylchroman-4-one eucomin (**8**) in *Eucomis bicolor* [15], it has been proposed that the sappanin skeleton of eucomin **8**, as well as trifasciatine A (**5**) and B (**6**), derives from a chalcone-like precursor **9**, whose methoxy group is used to create the C(2)-C(3) bond of

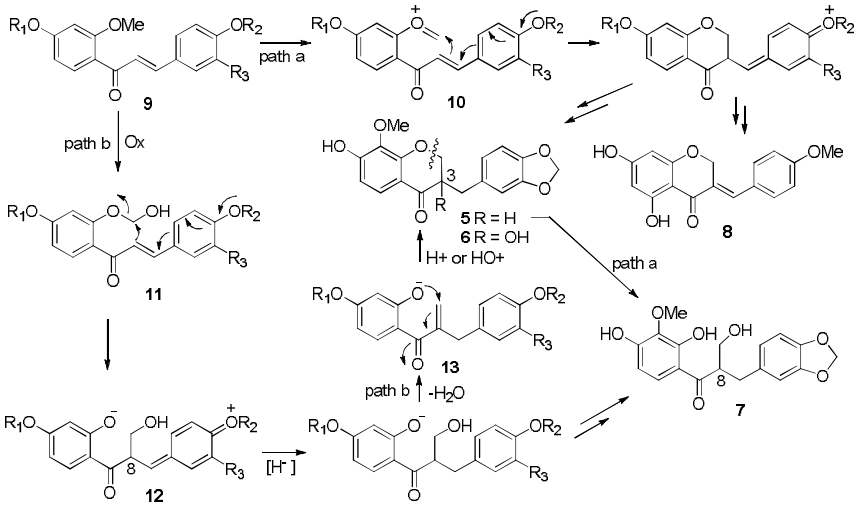

Figure 2: Proposed biosynthetic pathways to the formation of compounds **5-8** from chalcone **9**.

homoisoflavanones [10]. The proposed biosynthetic mechanism would involve the formation of the oxonium ion **10**, which is then intercepted intramolecularly by the styryl double bond (Figure 2). Trifasciatine C (**7**) could then be formed from trifasciatine A (**5**) by enzymatic cleavage of its C-ring through breakage of the ether bond (path a in Figure 2) [4b]. In our opinion, however, this hypothesis does not take into consideration that a) etherase enzymes capable of breaking ether bonds are produced by some bacteria [16], while, to our knowledge, their presence in the biochemical machinery of higher plants is still unknown; b) the ether bond scission in compound **5** to give **7** should be stereospecific, i.e. with preservation of the stereochemical integrity of the stereogenic center C(3). In striking contrast, instead, opposite configurations have been attributed to trifasciatine A, (*R*)-**5** [10], and trifasciatine C, (*S*)-**7** [4b], isolated from the same plant, *S. trifasciata*. Based on these observations, we tentatively propose an alternative biosynthetic pathway (path b in Figure 2), which also takes into account the enantiodivergent formation of the same homoisoflavonoid in the same or in different species. Therefore, according to our suggested mechanism, the stereocenters C(3) of trifasciatine A (**5**) and B(**6**), and C(8) of trifasciatine C (**7**) would be formed from different achiral precursors, i.e. **11** and **13**, and thus a different stereochemistry might ensue.

Experimental

General experimental procedures: Optical rotation was measured with a Perkin-Elmer 241 polarimeter, and infrared spectra recorded on NaCl disks on an FT IR Perkin Elmer Paragon 100 PC spectrometer; ν in cm^{-1}. NMR experiments were performed on either a Bruker AV 300 spectrometer, at 300 MHz (^{1}H) and 75 MHz (^{13}C) without TMS or a Bruker 600 MHz (^{1}H) and 150 MHz (^{13}C) with TMS. NMR chemical shifts (δ) are reported in ppm and solvent peaks were used as the internal standards; coupling constants (*J*) are in Hz. UV/ Vis absorption spectra were recorded in MeOH on a JASCO V-560. CD spectra were measured in MeOH on a JASCO J-710 spectrophotometer. ESIMS data were recorded on a Thermo TSQ mass spectrometer, by flow injection analysis (FIA), with an electron spray ionization source (ESI), High resolution mass spectra were measured on a FT-ICR Bruker Daltonics Apex II mass spectrometer. For silica gel and reversed phase column chromatography, Merck Kieselgel 60 (40-63 μm) and Merck LiChroprep RP-18 (25-40 μm) were employed, respectively; for direct phase and reversed phase TLC, 0.25 mm silica gel 60 (GF_{254}, Merck) or RP-18 (F_{254S}, Merck), aluminum-supported plates were used. Medium Pressure Liquid Chromatography (MPLC) separations were performed on an *Isolera* instrument using home-made silica gel and RP-18 gel filled cartridges and a UV detector. Reagent grade solvents, purchased from either Carlo Erba (Milano, Italy) or from Aldrich, were used for extraction and chromatographic separations.

Plant material: *Sansevieria cylindrica* Bojer ex Hook (Dracaenaceae) was collected in August 2012 at Thazi Township, Mandalay Region, Myanmar. The plant was identified by Professor Dr Soe Myint Aye, Department of Botany, Mandalay University, Myanmar. A voucher specimen (N-11) has been deposited at the Department of Chemistry, Mandalay University, Myanmar.

Extraction and isolation: The rhizomes (800.0 g) of *S. cylindrica* were soaked in MeOH (3 L) for 2 weeks. The whole mixture was then filtered through filter paper and the filtrate was evaporated *in vacuo* at room temperature to provide a gummy residue (7.0 g), which was partitioned between EtOAc and H_2O. The 2 extracts were filtered through a cotton plug and then evaporated *in vacuo* to provide an EtOAc extract (3.0 g) and an aqueous MeOH extract (4.0 g). The EtOAc extract (3.0 g) was partitioned between *n*-hexane and MeCN at room temperature which, by evaporation *in vacuo* afforded residue A (1.2 g) and B (1.7 g), respectively. Residue A (1.0 g) was separated by MPLC (Buchi R 605 column, 30 cm x 5 cm; fraction collector Buchi 684) on a silica gel column. Elution with a *n*-hexane-EtOAc gradient gave 19 fractions. Separation of fraction 7 on a silica gel column using a gradient of CH_2Cl_2-EtOAc (19:1, 9:1 → EtOAc 100 %), followed by preparative TLC on silica gel plates eluted with *n*-hexane-EtOAc, 4:1, afforded compound **4** (1.8 mg). Separation of fraction 10 (118.3 mg) on a silica gel column eluted by *n*-hexane-EtOAc (19:1→4:1), afforded stigmasterol (42 mg). Separation of residue B (1.0 g) by MPLC on an RP-18 column (eluent: MeCN: H_2O, from 3:7 to 100% MeCN) gave 24 fractions. Separation of fraction 8 on silica gel using mixtures of CH_2Cl_2-EtOAc as eluent (from 19:1 to 100 % EtOAc), followed by preparative TLC on silica gel plates eluted with *n*-hexane-EtOAc, 19:1, gave compounds **3** (3.3 mg) and **5** (0.5 mg). Separation of fraction 9 on a silica gel column using a gradient of CH_2Cl_2-EtOAc (from 19:1 to 100 % EtOAc), followed by preparative TLC on silica gel plates eluted with *n*-hexane-EtOAc, 4:1, gave compound **2** (3.4 mg). Separation of fraction 12 on a silica gel column eluted by a *n*-hexane-EtOAc gradient (from 19:1 to 4:1) afforded compound **1** (8.2 mg). HPLC separation of fraction 10 (224.1 mg) on a reversed phase (C-30) column using a gradient mixture of MeOH–H_2O (2:98) and MeOH, from 9:1 to 3:7 as a mobile phase, afforded compound **7** (5.8 mg). Separation of fraction 23 on a silica gel column eluted by CH_2Cl_2-EtOAc mixtures (19:1, 9:1, and 4:1) gave ergosterol peroxide (2.4 mg).

Bioactivity tests: The cytotoxicity of compounds **4** and **7** was measured by a standard MTT test [13]. The free radical scavenging activity (FRS) of compounds **1**-**4** and **7** was determined by the 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) test [14].

(3*S*)-3-(4′-methoxybenzyl)-5-hydroxy-7-methoxy-6-methyl chroman-4-one (1)

Colorless oil.
$[\alpha]_D^{20}$: +22.9 (*c* 0.004, CH_2Cl_2).
IR (NaCl) ν: 3448, 1634, 1579, 1077 cm^1.
UV: λ_{max}: 273.5 nm (*c* 0.001 mM, MeOH).
CD [mdeg (nm)]: +1.89 (260.7), -3.35 (290.6), (*c* 0.031 mM, MeOH).
^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.02 (3H, s, 6-Me), 2.96 (2H, ABq, H_2-9), 3.79 (3H, s, 4′-OMe), 3.88 (3H, s, 7-OMe), 4.05 (1H, d, *J* =11.0 Hz, H-2a), 4.20 (1H, d, *J* = 11.0 Hz, H-2b), 6.07 (1H, s, H-8), 6.85 (2H, d, *J* =8.6 Hz, H-3′, 5′), 7.12 (2H, d, *J* =8.6 Hz, H-2′, 6′), 12.1 (1H, s, *H*O-5).
^{13}C NMR (150 MHz, $CDCl_3$)*: δ_C 6.9 (3, 6-Me), 40.8 (2, C-9), 55.2 (3, 4′-OMe), 55.9 (3, 7-OMe), 71.9 (2, C-2), 72.2 (0, C-3), 90.9 (1, C-8), 100.2 (0, C-4a), 106.5 (0, C-6), 113.8 (1, C-3′), 113.8 (1, C-5′),126.2 (0, C-1′), 131.6 (1, C-2′), 131.6 (1, C-6′), 158.9 (0, C-4′), 160.2 (0, C-5), 161.1 (0, C-8a), 166.4 (0, C-7), 198.2 (0, C-4).
*The numbers in parentheses are the protons attached to each carbon, as determined by DEPT experiments.
ESIMS $[M+H]^+$ *m/z* 345.47 for $C_{19}H_{20}O_6$.

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