Secoiridoid Glycosides from the Pitcher Plant *Sarracenia alata*

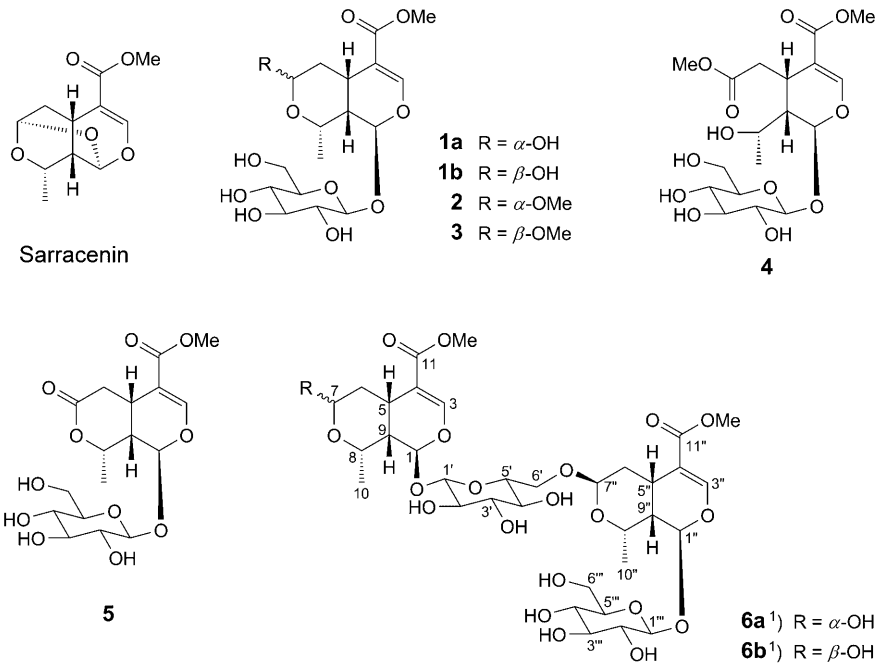
by **Jin-Feng Hu***, **Courtney M. Starks**, **Russell B. Williams**, **Stephanie M. Rice**, **Vanessa L. Norman**, **Krista M. Olson**, **Grayson W. Hough**, **Matt G. Goering**, **Mark O'Neil-Johnson**, and **Gary R. Eldridge**

Lead Discovery and Rapid Structure Elucidation Group, *Sequoia Sciences*, *Inc.*, 1912 Innerbelt Business Center Drive, St. Louis, Missouri 63114, USA
(phone: +1-314-3735181; fax: +1-314-3735186; e-mail: jhu@sequoiasciences.com)

The new secoiridoid glycoside alatenoside (**6**) was isolated along with the known secoiridoid glycosides morroniside (**1**), (7α)-7-*O*-methylmorroniside (**2**), (7β)-7-*O*-methylmorroniside (**3**), alpigenoside (**4**), and kingiside (**5**). Complete NMR data for **2**, **3**, and **4** are presented here for the first time. The structure elucidation and de-replication of the isolates were performed by utilizing a capillary-scale NMR probe and HR-ESI-MS data. Alatenoside (**6**) represents the first naturally occurring morroniside dimer.

Introduction. – The pitcher plant family Sarraceniaceae consists of only three genera, *Sarracenia*, *Heliamphora*, and *Darlingtonia*. All members of the Sarraceniaceae are carnivorous, and all eight species of *Sarracenia* are endemic in North America [1][2]. The typical *Sarracenia* bog is very acidic, and available nitrogen is limited. The captured insects provide a nitrogen source. All members of the family possess leaves that form a pitcher with an apical hood that presumably keeps rain out and aids in capturing the insects. The pitchers have a wide variety of colorations and scents used to attract prey. Once inside the pitcher, the fluids and downward pointing hairs trap insects. The insects are eventually digested by enzymes secreted from the pitcher [1][3]. *S. alata* WOOD (common name: yellow trumpet) is one of the Southeastern American pitcher plants. The word 'alata' in Latin means 'winged' and this narrow wing on the front of the pitcher gives the plant its name. This plant can be found mostly in the open bogs and savannas along the West Gulf Coastal Plain [2][4]. The leaves of *S. flava* were previously found to show antitumor and insect-paralyzing activity [5], and afforded the highly oxygenated sarracenin [6], the first secoiridoid isolated from the genus *Sarracenia*. This compound was also detected by GC/MS from the CH_2Cl_2 extract of the cultivated plant *S. alata* [7]. To the best of our knowledge, compounds have not been previously isolated from *S. alata*. As part of our high-throughput natural-products program [8] directed toward the discovery of naturally occurring compounds with diverse skeletons and broad biological properties from American and African plants [9], one new (see **6**[1])) and five known (see **1**–**5**) secoiridoid glycosides were obtained from *S. alata*.

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*



Results and Discussion. – The AcOEt/MeOH 7:3 fraction from silica gel flash chromatography [8b][9j] of the organic extract of *S. alata* was generated, and was further fractionated by prep. reversed-phase HPLC (C_{18}). Fractions containing secoiridoid glycosides were pooled and subjected to semi-prep. HPLC to isolate compounds **1**–**6**[2]) (*Fig. 1*).

Compound **1** was identified as morroniside by spectral analysis [10][11]. It was isolated as a mixture of 7α-OH (**1a**) and 7β-OH (**1b**) epimers (**1a**/**1b** 2:1, estimated from the relative intensities of the H-atom signals) attributed to the hemiacetal at C(7)[1]). Compounds **2** and **3** (7α)-7-*O*-methylmorroniside and (7β)-7-*O*-methylmorroniside, resp.) had been obtained previously as a mixture [12][13], but were successfully separated here. The NMR data for **2** and **3** are listed in *Tables 1* and *2*.

Alpigenoside (**4**) and kingiside (**5**) were isolated as well-resolved HPLC peaks (t_R 14.9 and 10.6 min, resp.). The structure of **5** was readily established by using MS and 1D- and 2D-NMR spectroscopy, and was confirmed by comparison to literature data [10][14]. The NMR data for **4**, however, indicated a mixture of two compounds in a 1:1 ratio. One of these components was **5**, and the other was identified as **4** by examination of the NMR data (*Tables 1* and *2*). LC/MS Analysis of the material collected from the dried NMR sample, indicated the presence of **5** only. We therefore hypothesized that **4** and **5** are readily separated by HPLC but that **4** cyclizes to **5** during drying or storage.

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[2]) HPLC *Fractions 8–12* containing secoiridoid glycosides inhibited the formation of bacterial biofilms in *Escherichia coli* UTI89; however, purified compounds **1**–**6** from these HPLC fractions were found inactive in the same bioassay.

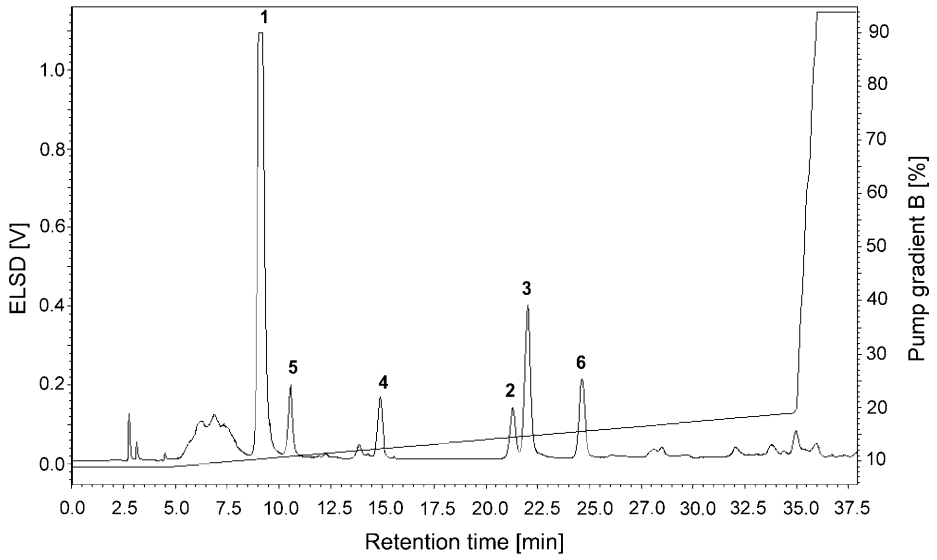

Fig. 1. *Representative ELSD chromatogram for the semiprep. HPLC purification of the secoiridoid glycosides* **1**–**6**

Table 1. *^{1}H-NMR Data* (CD_3OD, 600 MHz) *of* **2**–**4**[1])[a]). δ in ppm, J in Hz.

	2	**3**	**4**
H–C(1)	5.80 (*d*, *J* = 9.4)	5.89 (*d*, *J* = 9.1)	5.71 (*d*, *J* = 8.8)
H–C(3)	7.52 (br. *s*)	7.51 (br. *s*)	7.49 (br. *s*)
H–C(5)	2.83 (*dt*, *J* = 12.9, 4.7)	3.05 (*dt*, *J* = 12.9, 4.6)	3.24 (*dt*, overlapped)
CH_2(6)	1.17 (*td*, *J* = 12.9, 10.0),	1.52 (*td*, *J* = 12.9, 3.5),	2.40 (*dd*, *J* = 14.7, 7.6),
	2.01 (*ddd*, *J* = 12.9, 4.1, 2.1)	1.92 (*ddd*, *J* = 12.9, 4.6)	2.77 (*dd*, *J* = 14.7, 5.9)
H–C(7)	4.49 (*dd*, *J* = 10.0, 2.1)	4.75 (br. *d*, *J* = 3.5)	
MeO-C(7)	3.50 (*s*)	3.35 (*s*)	3.64 (*s*)
H–C(8)	3.95 (*dq*, *J* = 6.8, 2.1)	4.29 (*dq*, *J* = 6.9, 2.1)	4.07 (*dq*, *J* = 6.5, 4.7)
H–C(9)	1.80 (*ddd*, *J* = 10.0, 4.7, 2.1)	1.80–1.84 (*m*)	1.91 (*ddd*, *J* = 8.8, 4.7, 4.1)
Me(10)	1.41 (*d*, *J* = 6.8)	1.35 (*d*, *J* = 6.9)	1.37 (*d*, *J* = 6.5)
MeO–C(11)	3.70 (*s*)	3.69 (*s*)	3.67 (*s*)
H–C(1′)	4.79 (7.9)	4.79 (7.9)	4.78 (7.8)
H–C(2′)	3.22 (*dd*, *J* = 9.5, 7.9)	3.22 (*dd*, *J* = 9.4, 7.9)	3.23 (*dd*, overlapped)
H–C(3′)	3.38 (*t*, *J* = 9.5)	3.38 (*t*, *J* = 9.4)	3.38 (*t*, *J* = 9.4)
H–C(4′)	3.25 (*t*, *J* = 9.5)	3.28 (*t*, *J* = 9.4)	3.27 (*t*, *J* = 9.4)
H–C(5′)	3.28–3.32 (*m*)	3.27–3.33 (*m*)	3.28–3.34 (*m*)
CH_2(6′)	3.67 (*dd*, *J* = 12.2, 6.3),	3.66 (*dd*, *J* = 12.1, 6.2),	3.67 (*dd*, *J* = 12.1, 6.2),
	3.89 (*dd*, *J* = 12.2, 1.8)	3.89 (*dd*, *J* = 12.1, 1.8)	3.88 (*dd*, *J* = 12.1, 1.8)

[a]) Assignments were made by a combination of 1D- and 2D-NMR (COSY, HSQC, and HMBC) experiments.

Table 2. *^{13}C-NMR Data* (CD_3OD, 150 MHz) *of* **2**–**4**[1])[a]). δ in ppm.

	2	**3**	**4**
C(1)	95.7	95.5	97.6
C(3)	154.5	154.1	153.9
C(4)	111.1	111.7	112.7
C(5)	31.6	28.5	31.4
C(6)	35.2	33.1	36.6
C(7)	104.3	99.8	174.4
*Me*O–C(7)	56.3	54.7	51.8
C(8)	74.0	66.1	67.5
C(9)	40.1	40.5	45.8
C(10)	19.2	18.9	22.3
C(11)	169.1	168.5	169.3
*Me*O–C(11)	51.4	51.4	51.4
C(1′)	99.7	99.9	100.8
C(2′)	74.9	74.8	74.7
C(3′)	78.0	78.0	78.0
C(4′)	71.5	71.1	71.3
C(5′)	78.4	78.5	78.3
C(6′)	62.5	62.5	62.4

[a]) Assignments were made by a combination of 1D- and 2D-NMR (COSY, HSQC, and HMBC) experiments.

To further explore this hypothesis, we recorded NMR data from the corresponding two peaks from an HPLC collection made with the same method but on a different day. Both peaks gave NMR signals corresponding to compound **5** only, rather than to a mixture of **4** and **5**. This suggests that the degree of conversion of **4** to **5** is sensitive to subtle differences in drying and storage conditions.

The molecular formula of alatenoside (**6**) was established as $C_{34}H_{50}O_{21}$ by the negative-mode HR-ESI-MS which showed an ion peak at *m*/*z* 793.2766 ($[M-H]^-$). The ^{1}H-NMR spectrum (*Table 3*) resembles that of morroniside (**1**) but is more complex. Whereas the ^{1}H-NMR spectrum of **1** shows two sets of signals, corresponding to the 7α- and 7β-epimers, the spectrum of **6** shows four sets of related signals. Examination of the chemical shifts, particularly those of CH_2(6), H–C(7), and H–C(8), with comparison to the corresponding signals in compound **1**, suggested that one set of signals corresponds to a 7α-epimer moiety, while three sets correspond to 7β-epimer moieties. This distribution of signals is consistent with a dimeric structure, in which one of the monomers is 'locked' in the 7β-configuration by formation of an acetal upon dimerization, while the other monomer remains a hemiacetal that can epimerize in solution. The linkage position in the dimer was established by the HMBC cross-peaks CH_2(6′)/C(7″) and ROESY correlations CH_2(6′)/H–C(7″) (*Fig. 2*). This substitution shifts the signal of C(6′) to δ(C) 67.7, compared with δ(C) 62.5 for C(6‴), and the signal of H–C(5′) to δ(H) 3.48, compared with δ(H) 3.29–3.31 for H–C(5‴). Chemical shifts for the connecting sugar molecule are very similar in the 7α- and 7β-form **6a** and **6b**, respectively, thereby making it difficult to assign resonances in

Table 3. *^{1}H- and ^{13}C-NMR* (CD_3OD, 600 and 150 MHz, resp.) *Data of* **6**[1])[a]). δ in ppm, J in Hz.

	6a		**6b**	
	δ(H)	δ(C)	δ(H)	δ(C)
H–C(1)	5.80 (*d*, *J* = 9.1)	96.1	5.85 (*d*, *J* = 9.7)	95.5
H–C(3)	7.51(br. *s*)[b])	155.1	7.50 (br. *s*)[b])	155.1
H–C(4)		111.8		111.8
H–C(5)	2.79 (*dt*, *J* = 12.8, 4.7)	32.0	3.12 (*dt*, overlapped)	27.6
CH_2(6)	1.09 (*td*, *J* = 12.8, 10.0), 1.97 (*ddd*, overlapped)	37.3	1.39 (*td*, *J* = 12.9, 3.3), 1.84 (*ddd*, overlapped)	33.9
H–C(7)	4.75 (*dd*, overlapped)	97.0	5.16 (br. *d*, *J* = 3.3)	91.9
H–C(8)	3.88 (*dq*, overlapped)	74.0	4.48 (*dq*, *J* = 6.9, 2.0)	65.6
H–C(9)	1.73–1.77 (*m*)	40.6	1.78–1.81 (*m*)	40.6
Me(10)	1.36 (*d*, *J* = 6.8)	19.9	1.28 (*d*, *J* = 6.9)	19.9
C(11)		168.9		168.9
*Me*O–C(11)	3.70 (*s*)[c])	51.5	3.69 (*s*)[c])	51.5
H–C(1′)	4.80 (*J* = 7.9)	100.0	4.80 (*d*, *J* = 7.9)	100.0
H–C(2′)	3.26 (*dd*, *J* = 9.5, 7.9)	74.8	3.26 (*dd*, *J* = 9.5, 7.9)	74.8
H–C(3′)	3.30 (*t*, overlapped)	70.7	3.30 (*t*, overlapped)	70.7
H–C(4′)	3.35 (*t*, overlapped)	71.0	3.35 (*t*, overlapped)	71.0
H–C(5′)	3.48 (*m*, overlapped)	77.5	3.46–3.50 (*m*, overlapped)	77.5
H–CH_2(6′)	3.65 (*dd*, overlapped), 3.97 (*dd*, overlapped)	67.7	3.63 (*dd*, overlapped), 3.98 (*dd*, *J* = 12.3, 1.8	67.7
H–C(1″)	5.87 (*d*, *J* = 9.1)	95.8	5.90 (*d*, *J* = 9.7)	95.0
H–C(3″)	7.52 (br. *s*, overlapped)[b])	155.1	7.52 (br. *s*, overlapped)[b])	155.1
C(4″)		111.8		111.8
H–C(5″)	3.10 (*dt*, overlapped)	27.6	3.09 (*dt*, overlapped)	27.6
CH_2(6″)	1.63 (*dt*, *J* = 13.0, 3.3), 1.95 (*ddd*, overlapped)	33.5	1.49 (*dt*, *J* = 13.1, 3.3), 1.97 (*ddd*, overlapped)	33.7
H–C(7″)	5.01 (br. *d*, *J* = 3.5)	99.2	4.95 (br. *d*, *J* = 3.5)	99.1
H–C(8″)	4.41 (*dq*, overlapped)	66.4	4.43 (*dq*, overlapped)	66.5
H–C(9″)	1.85–1.89 (*m*, overlapped)	40.2	1.85 (overlapped)	40.2
Me(10″)	1.36 (*d*, *J* = 7.0)	19.9	1.34 (*d*, *J* = 7.0, overlapped)	19.6
C(11″)		168.9		168.9
*Me*O–C(11″)	3.67 (*s*)[c])	51.5	3.68 (*s*)[c])	51.5
H–C(1‴)	4.77 (*d*, *J* = 7.9)	100.0	4.78 (*d*, *J* = 7.9)	100.0
H–C(2‴)	3.21 (*dd*, overlapped)	74.8	3.23 (*dd*, overlapped)	74.8
H–C(3‴)	3.38 (*t*, *J* = 9.5, overlapped)	77.9	3.38 (*t*, *J* = 9.5, overlapped)	77.9
H–C(4‴)	3.25 (*t*, overlapped)	71.2	3.25 (*t*, overlapped)	71.2
H–C(5‴)	3.29–3.31 (*m*, overlapped)	78.2	3.29–3.31 (*m*, overlapped)	78.2
CH_2(6‴)	3.65 (*dd*, overlapped), 3.89 (*dd*, overlapped)	62.5	3.65 (overlapped), 3.89 (overlapped)	62.5

[a]) Assignments were made by a combination of 1D- and 2D-NMR (COSY, HSQC, and HMBC) experiments. [b])[c]) Resonances may be interchanged.

the terminal monomer to the correct set of signals in the other monomer. However, differences in integration for the two dimers **6a** and **6b** allowed the connection of the correct sets of signals for the two monomer halves; the 7α-form **6a** of the dimer is slightly more abundant than the 7β-form **6b**.

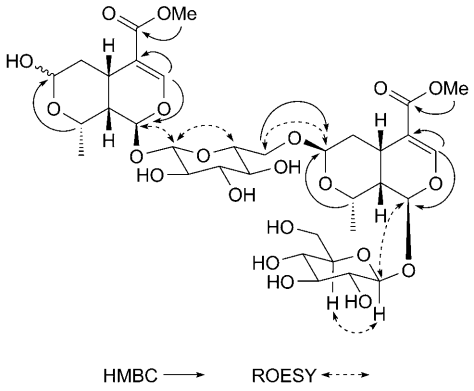

Fig. 2. *Key ROESY correlations and HMBC of* **6**

Secoiridoids represent only a small fraction of the naturally occurring iridoids [15]. Sarracenin-type secoiridoids have been previously found from a few plants such as *Lonicera morrowii* [16], *Cornus officinalis* [12], *Lonicera alpigena* [10], *Gallium mollugo* [17], *Sambucus ebulus* [11], *Isertia haenkeana* [13], *Gentiana rhodentha* [14], *Gentiana pyrenaica* [18], *Jasminum odoratissimum* [19], *Tripterospermum japonicum* [20], and *Hydrangea macrophylla* [21]. Dimeric secoiridoids were isolated from plants such as *Lonicera japonica* and *Adina racemosa* [15][22]; however, compound **6** is the first sarracenin-type secoiridoid dimer.

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Experimental Part

General. For instrumentation and general methods, see [8b][9j]. UV/VIS: λ_{max} in nm. NMR Spectra: *Bruker Avance* 600 MHz spectrometer (*Bruker Instruments*, Rheinstetten, Germany), equipped with a 5 µl capillary-scale NMR probe (*CapNMR*™ probe; *MRM*/*Protasis*, Savoy, IL), having a 1.5 µl active volume; purified secoiridoid glycoside was dissolved in 6.5 µl of CD_3OD and loaded manually into the probe. MS: in *m*/*z*.

Plant Material. The whole plant of *S. alata* was collected from the Big Thicket National Preserve, Southeast Texas, in the spring of 2000. Plant samples were shipped frozen to *Sequoia Sciences* where they were processed. The plant was identified by *John Stone* (Missouri Botanical Garden Herbarium, St. Louis, MO). A voucher specimen (No. 502) was deposited with the Herbarium of Missouri Botanical Garden.

Extraction and Isolation. The dried plant (109 g) was extracted with EtOH/AcOEt 1:1 (2 × 500 ml) followed by MeOH (2 × 500 ml) to obtain 9.9 g and 4.2 g dry extracts, resp. Extractions were done with shaking at r.t. for 4 h for the first portion of solvent, and overnight for the second portion. The EtOH/AcOEt extract was fractionated in 1 g portions on the *Flash Master II* automated chromatographic

system with our standard elution gradient to generate the flash fractions [8b][9j]. *Flash fraction 4* (AcOEt/MeOH 75:25) from two flash runs yielded 570 mg. This material was further fractionated in 70 mg portions by prep. reversed-phase HPLC (*Aquasil C_{18}* column (*Thermo Scientific*, 21.2 × 100 mm; 5 μm); eluent $A = 0.05\%$ CF_3COOH in H_2O and eluent $B = 0.05\%$ CF_3COOH in MeCN; 2 min isocratic with 5% *B*/*A*, followed by a 10 min gradient to 10% *B*/*A*, a 24 min gradient to 40% *B*/*A*, and then a flush with 85% *B*/*A*; flow 20 ml/min; fractions (one min each) were collected from 2–42 min). The secoiridoid glycosides were isolated from pooled *Fractions 8–12* by HPLC (semiprep. *Fluophase-PFP* column (*Thermo Scientific*, 7.7 × 250 mm; 5 μm); eluent $A = H_2O$ and eluent $B =$ MeCN; 5 min of isocratic elution in 10% *B*/*A*, followed by a gradient to 20% *B*/*A* over 30 min, and a flush with 95% *B*/*A*; flow 1.5 ml/min). The corresponding ELSD (evaporative light-scattering detection) peaks (*Fig. 1*) from six collections were combined to afford compounds **1** (500 μg, t_R 9.2 min), **2** (80 μg, t_R 21.3 min), **3** (180 μg, t_R 22.0 min), **4** (100 μg, t_R 14.9 min), **5** (100 μg, t_R 10.6 min), and **6** (130 μg, t_R 24.6 min). The quantity was estimated by HPLC/ELSD methods described previously [8b]. Additional material was prepared similarly.

*(7α)-7-*O*-Methylmorroniside* (= *(1*S*,3*S*,4a*S*,8*S*,8a*S*)-8-(β-*D*-Glucopyranosyloxy)-4,4a,8,8a-tetrahydro-3-methoxy-1-methyl-1*H*,3*H*-pyrano[3,1-*c*]pyran-5-carboxylic Acid Methyl Ester*; **2**): Colorless gum. $[\alpha]_D^{20} = -24$ ($c = 0.050$, MeOH). ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 465 ($[M + HCOO^-]^-$), 443 ($[M + Na]^+$). HR-ESI-MS: 443.1502 ($[M + Na]^+$, $C_{18}H_{28}O_{11}Na^+$; calc. 443.1529).

*(7β)-7-*O*-Methylmorroniside* (= *1*S*,3*R*,4a*S*,8*S*,8a*S*)-8-(β-*D*-Glucopyranosyloxy)-4,4a,8,8a-tetrahydro-3-methoxy-1-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-5-carboxylic Acid Methyl Ester*; **3**): Colorless gum. $[\alpha]_D^{20} = -125$ ($c = 0.083$, MeOH). ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 465 ($[M + HCOO^-]^-$), 479 ($[M + CH_3COO^-]^-$), 438 ($[M + NH_4]^+$), 443 ($[M + Na]^+$). HR-ESI-MS: 443.1506 ($[M + Na]^+$, $C_{18}H_{28}O_{11}Na^+$; calc. 443.1529).

Alpigenoside (= *(2*S*,3*S*,4*S*)-2-(β-*D*-Glucopyranosyloxy)-3,4-dihydro-3-[(*1S*)-1-hydroxyethyl]-5-(methoxycarbonyl)-2*H*-pyran-4-acetic Acid Methyl Ester*; **4**): Colorless gum. $[\alpha]_D^{20} = -12$ ($c = 0.207$, MeOH; likely as a mixture with **5**). ^{1}H- and ^{13}C-NMR: *Tables 1 and 2*.

Alatenoside (= *(1*S*,4a*S*,8*S*,8a*S*)-8-{[6-*O*-[(1*S*,3*R*,4a*S*,8*S*,8a*S*)-8-(β-*D*-Glucopyranosyloxy)-4,4a,8,8a-tetrahydro-5-(methoxycarbonyl)-1-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-3-yl]-β-*D*-glucopyranosyl}oxy}-4,4a,8,8a-tetrahydro-2-methoxy-1-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-5-carboxylic Acid Methyl Ester*; **6**): Colorless gum. $[\alpha]_D^{20} = +8.2$ ($c = 0.560$, MeOH). UV (HPLC diode array, MeCN/H_2O): 241. ^{1}H- and ^{13}C-NMR: *Table 3*. ESI-MS: 793 ($[M - H]^-$), 839 ($[M + HCOO^-]^-$). HR-ESI-MS: 793.2766 ($[M - H]^-$, $C_{34}H_{49}O_{21}^-$; calc. 793.2766).

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