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STEROIDAL ALKALOIDS FROM *SOLANUM SYCOPHANTA*

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Key Word Index—*Solanum sycophanta*; Solanaceae; fruits; glycoalkaloids; sycophantine; 22,25-diepisycophantine; 21-hydroxysycophantine; solasonine; solamargine.

Abstract—Reinvestigation of the fruits of *Solanum sycophanta* yielded sycophantine as the major glycoalkaloid besides 22,25-diepisycophantine and 21-hydroxysycophantine and the already known glycoalkaloids, solasonine and solamargine. The structures were established by spectroscopic methods, mainly by 2D NMR.

INTRODUCTION

Steroidal alkaloids with an unaltered cholestane carbon skeleton, which generally occur as glycosides, have been isolated from numerous species of the Solanaceae and Liliaceae [1–3]. Among these alkaloids spirosolane-type structures prevail but compounds with other heterocyclic structures have also been found [1, 4]. Previous studies centred their attention on the isolation of steroidal alkaloids of the spirosolane-type as starting materials in the industrial production of hormonal steroids, in the search for steroidal alkaloids of novel structure, as well as in the biological activity of these natural products [1, 5, 6]. More recently, the inactivation of *Herpes simplex* virus and the inhibition of fungal growth by *Solanum* glycoalkaloids has been demonstrated [7, 8]. On the other hand, some studies report that solasodine glycosides are clinically and histologically effective in the treatment of skin tumours [9, 10].

Solanum sycophanta [11] grows as a tree up to 30 m high in the Northern Andes from Nariño (Southern Colombia) to Merida (Venezuela) at altitudes ranging from 1400 to 2200 m above sea level [12]. Local people refer to it as caname, tuno and 'árbol de la papa' [12]. Some years ago, solasodine and solasodiene were reported from unripe fruits of this tree [13]. The bitter taste and foaming activity of the pale green berries of *S. sycophanta* prompted us to examine their more polar constituents. These investigations resulted in the isolation of five steroid alkaloid glycosides which were revealed as solasonine (**1**) [1, 14] and solamargine (**2**) [1, 14, 15] and the hitherto unknown spirosolane glycosides, **3**–**5**. A preliminary report on **3** has been published [16].

RESULTS AND DISCUSSION

Following known methods [17], the basic constituents of *S. sycophanta* were enriched. Separation of this alkaloidal fraction was achieved by HPLC and afforded **3** as the major glycoside (*ca* 90% of total alkaloidal fraction), together with **1** and **2** as minor, and **4** and **5** as very minor components.

The structures of solasonine (**1**) and solamargine (**2**) were established by their spectroscopic and other physicochemical data [14, 15] and, in addition, by comparison with authentic samples obtained from *S. americanum* [18].

Compound **3** was identified as a solasodine tetraoside by comparison of its ^{1}H and ^{13}C NMR data with those of **1** and **2** (Tables 1 and 2) and by its M_r 999, determined by FAB mass spectrometry. Two rhamnose, one glucose and one xylose units were ascertained as building blocks of the sugar moiety, from NMR studies using TOCSY, HMQC and HMBC spectra (Fig. 1). These experiments also revealed the connections of the basic sugar units, which were further corroborated by NOE measurements (Fig. 2). For the new tetrasaccharide moiety we propose the name β-sycophantetraose and for **3** the name sycophantine.

The spectroscopic properties of **4** closely resembled those of **3**. In particular, the same M_r was determined and all ^{1}H and ^{13}C NMR resonances, which were attributable to the carbons and protons of the sugar part, as well as of rings A to C of the aglycone, appeared with almost the same chemical shifts and with identical multiplicity in both compounds. Major

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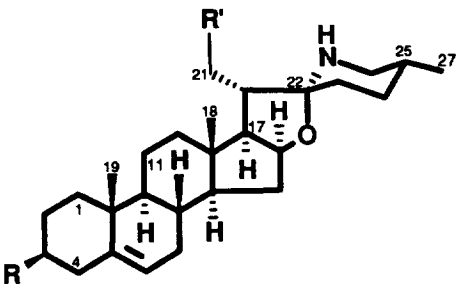
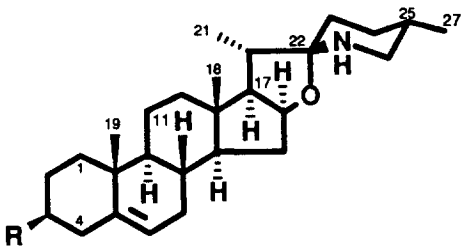


1 R: O-β-D-Gal(3→β-D-Glu, 2→α-L-Rha) R': H

2 R: O-β-D-Glu(4→α-L-Rha, 2→α-L-Rha) R': H

3 R: O-β-D-Glu(4→α-L-Rha(2→β-D-Xyl), 2→α-L-Rha) R': H

5 R: O-β-D-Glu(4→α-L-Rha(2→β-D-Xyl), 2→α-L-Rha) R': OH



4 R: O-β-D-Glu(4→α-L-Rha(2→β-D-Xyl), 2→α-L-Rha)

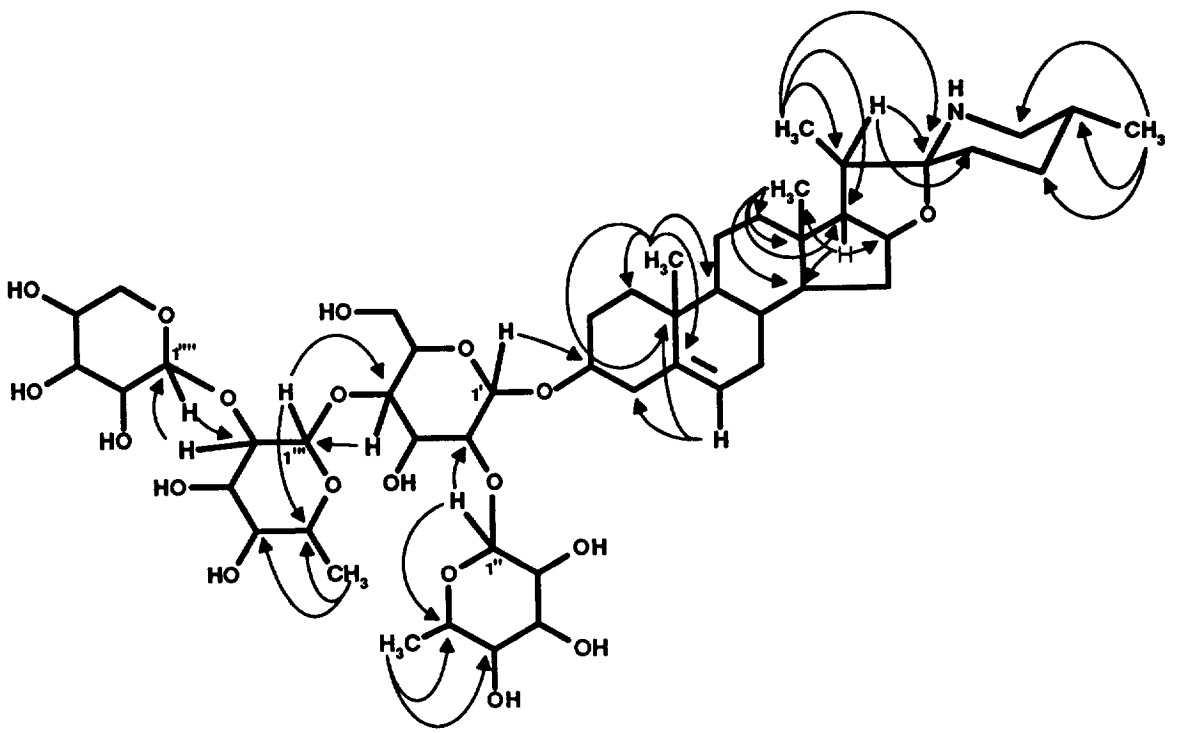


Fig. 1. Important long-range correlations observed in the HMBC of compound **3**.

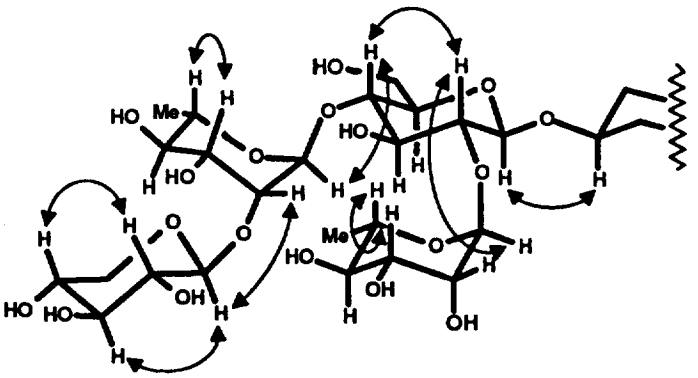


Fig. 2. Rotating frame NOE correlations within the sugar part of compound **3** (obtained from a ROESY experiment).

differences, however, were observed only for the signals of the protons and carbons in the vicinity of C-22 suggesting a different stereochemistry at this carbon and at C-25 and, therefore, the presence of the 3-*O*-β-sycophantetraoside of tomatidenol (25*S*)-22β*N*-spirosol-5-en-3β-ol, which we named 22,25-diepi-sycophantine. These considerations were corroborated by HMQC and HMBC experiments, as well as by comparison of the ^{13}C NMR data of **4** with those of tomatine [19].

The M_r of **5** was measured 16 mu higher than that of **3** and **4**, and comparison of the NMR data demonstrated that the sugar part of **5** was identical with that of **3** and **4**. However, the NMR spectra (DEPT) revealed the presence of only three methyl groups in the aglycone of **5**. On the other hand, an 'additional' methylene resonance appeared at δ 62.6. The corresponding protons gave signals at δ 4.02 (1H, *dd*, $J_1 = 10.5, J_2 = 7.5$ Hz) and δ 4.2 (overlapped by other signals) in the ^{1}H NMR. These observations suggested the presence of a hydroxyl group at C-21. The HMQC and HMBC spectra corroborated the structure as 21-hydroxy-sycophantine (**5**).

Solasonine (**1**) and solamargine (**2**) have to be regarded as the common glycoalkaloidal constituents of *Solanum* species [1–3]. However, in *S. sycophanta* they are only minor constituents; sycophantine (**3**) is the major component (*ca* 90% of alkaloidal fraction). Structurally, **3** contains the aglycone solasodine, which is encountered in solasonine (**1**) and solamargine (**2**), and also in other glycoalkaloids from the Solanaceae [1–3]. However, the tetrasaccharidic sugar part of **3**, the β-sycophantetraose, has not been described previously in this plant family. Its characteristic structural feature is a terminal xylose unit connected to the 2-OH of the 4-*O*-rhamnosyl unit in the sugar part of **2**. Therefore, sycophantine (**3**) can be regarded as xylosyl-solamargine. Treatment of **3** with 10% acetic acid (for 10 days at 70°) afforded **2** as the main decomposition product (*ca* 2%). The spirosolane glycoside **4** represents the 22,25-diepi-isomer of the major component **3** and, thus, can be regarded as xylosyl-β-solamarine.* The structure of 21-hydroxy-sycophantine (**5**) and also of its aglycone, 21-hydroxy-solasodine, has not been described previously in the literature.

Glycoalkaloids might be produced by plants as protective agents with antifungal and antifeedant properties. Solamargine (**2**) exhibited high activity against viruses and *Trypanosoma* species [21]. Solasonine (**1**) alone is considerably less active but mixing it with **2** increases its activity. As the mode of action for these biological effects, a disruption of cell membranes has been proposed [22, 23]. In these tests, sycophantine (**3**), as far as we have tested it, is not as effective as solamargine (**2**) but it obviously protects the plant against pests, because fruits and leaves do not show any signs of attack by insects, fungi or viruses [21].

EXPERIMENTAL

General. Mp uncorr. TLC on ready-made plates (nano-plates SIL-20 UV_{254}, Macherey-Nagel) using $CHCl_3$–MeOH–1%NH_3 (14:6:1); detection by anisaldehyde reagent [24]. CC on basic Al_2O_3 and Sephadex LH 20 using MeOH as eluant. HPLC on Eurospher RP-18, 7 μ (Knauer). IR: KBr. $[\alpha]_D$ in MeOH at 21°, unless otherwise stated. ^{1}H and ^{13}C NMR in pyridine-d_5 at 360 MHz and 90 MHz, respectively; int. standard: TMS for ^{1}H; highfield solvent signal δ 123.5 for ^{13}C. Positive FABMS with Xe at 8 kV from glycerol matrix.

Plant material. Semi-ripe fruits of *S. sycophanta* Dunal et DC. (6.4 kg) were collected in October 1992, 13 km from Merida, along the road from Merida to Jaji and identified by Dr Carmen Benitez de Rojas (Universidad Central de Venezuela, Maracay). A

*After submission of this article to *Phytochemistry*, Ripperger *et al.* [20] have reported the isolation and structural elucidation of glycosides **3** and **4** from *Solanum coccineum* Jacq.

Table 1. ^{1}H NMR data of compounds **1**–**5**

Proton	**1**	**2**	**3**	**4**	**5**
1	1.72[a]	1.73[a]	1.73[a]	1.74[a]	1.72[a]
	0.98 *ddd*	1.00 *ddd*	1.01 *ddd*	0.99[a]	1.02[a]
	14, 14, 4	14, 14, 4	14, 14, 4		
2	2.10[a]	2.07[a]	2.12[a]	2.11 *m*	2.10[a]
	1.85[a]	1.85[a]	1.87[a]	1.87[a]	1.85[a]
3	3.97[a]	3.89 *dddd*	3.93 *dddd*	3.93 *dddd*	3.91 *dddd*
		11, 11, 5, 5	11, 11, 5, 5	11, 11, 5, 5	11, 11, 5, 5
4	2.83[a]	2.77[a]	2.86 *brdd*	2.84 *brdd*	2.82[a]
			12, 3.5	14, 4	
	2.74 *brdd*	2.77[a]	2.71 *brdd*	2.72 *brdd*	2.73 *m*
	12, 11		12, 11	14, 12	
6	5.37 *brd*	5.32 *brd*	5.37 *brd*	5.38 *brd*	5.35 *brd*
	4.5	4.5	4.5	4.5	4.5
7	1.90[a]	1.85[a]	1.89[a]	1.87[a]	1.88[a]
	1.54[a]	1.50[a]	1.51[a]	1.35–1.55[a]	1.55[a]
8	1.54[a]	1.50[a]	1.51[a]	1.35–1.55[a]	1.55[a]
9	0.90[a]	0.90[a]	0.89[a]	0.91[a]	0.90 *ddd*
					11, 11, 4.5
11	1.45[a]	1.45[a]	1.45[a]	1.35–1.55[a]	1.43[a]
	1.45[a]	1.45[a]	1.45[a]	1.35–1.55[a]	1.43[a]
12	1.70[a]	1.73[a]	1.73[a]	1.69 *m*	1.93[a]
	1.10[a]	1.12[a]	1.13[a]	1.16[a]	1.15[a]
14	1.10[a]	1.07[a]	1.08[a]	1.05[a]	1.15[a]
15	2.10[a]	2.07[a]	2.09[a]	2.07 *ddd*	2.10[a]
				12, 7, 5.5	
	1.54[a]	1.50[a]	1.51[a]	1.35–1.55[a]	1.60[a]
16	4.51 *ddd*	4.38[a]	4.52 *ddd*	4.10–4.25[a]	4.65 *ddd*
	7.5, 7.5, 7.5		8, 7.5, 7		8, 7.5, 7
17	1.83[a]	1.85[a]	1.87[a]	1.61 *dd*	2.10[a]
				8, 7	
18	0.88 *s*	0.88 *s*	0.88 *s*	0.88 *s*	0.97 *s*
19	1.06 *s*	1.04 *s*	1.04 *s*	1.04 *s*	1.03 *s*
20	2.01 *dq*	1.98 *dq*	2.01 *dq*	1.91 *dq*	2.45 *ddd*
	7, 7	7, 7	7, 7	7, 7	7.5, 7, 6.5
21	1.17 *d*	1.09 *d*	1.19 *d*	1.14 *d*	4.10–4.25[a]
	7	7	7	7	
					4.02 *dd*
					10.5, 7.5
23	1.70[a]	1.73[a]	1.73[a]	1.74[a]	2.10[a]
	1.70[a]	1.73[a]	1.73[a]	1.35–1.55[a]	1.93[a]
24	1.65[a]	1.63[a]	1.65[a]	1.35–1.55[a]	1.65[a]
	1.65[a]	1.63[a]	1.65[a]	1.35–1.55[a]	1.65[a]
25	1.48[a]	1.50[a]	1.51[a]	1.78[a]	1.65[a]
26	2.83[a]	2.77[a]	2.82[a]	2.95 *dd*	2.80[a]
				10.5, 10	
	2.83[a]	2.77[a]	2.82[a]	2.90 *dd*	2.80[a]
				10, 4.5	
27	0.81 *d*	0.82 *d*	0.81 *d*	0.81 *d*	0.80 *m*
	6	6	6	6.5	
1′	4.93 *d*	4.95[a]	4.95 *m*	4.97 *d*	4.96 *m*
	8			7.5	
2′	3.97[a]	4.22[a]	4.15[a]	4.10–4.25[a]	4.10–4.25[a]
3′	4.34[a]	4.22[a]	4.15[a]	4.10–4.25[a]	4.10–4.25[a]
4′	4.90[a]	4.38[a]	4.33[a]	4.35[a]	4.34[a]
5′	4.12[a]	3.65 *ddd*	3.74 *m*	3.75 *m*	3.74 *m*
		9, 3, 2			
6′	4.34[a]	4.38[a]	4.33[a]	4.35[a]	4.34[a]
	4.24[a]	4.10 *dd*	4.15[a]	4.10–4.25[a]	4.10–4.25[a]
		13, 3			
1″	6.23 *brs*	6.39 *brs*	6.29 *brs*	6.31 *brs*	6.32 *brs*
2″	4.90[a]	4.84 *dd*	4.84 *dd*	4.85 *dd*	4.84 *dd*
		3.5, 1.5	3.5, 1.5	3.5, 1.5	3.5, 1.5

continued

Table 1—*Continued*

Proton	1	2	3	4	5
3″	4.60 *dd* 9.5, 3.5	4.63 *dd* 9.5, 3.5	4.62 *dd* 9.5, 3.5	4.63 *dd* 9.5, 3.5	4.63 *dd* 9.5, 3.5
4″	4.34[a]	4.38[a]	4.38 *dd* 9.5, 9.5	4.38 *dd* 9.5, 9.5	4.38 *dd* 9.5, 9.5
5″	4.90[a]	4.95[a]	4.92 *dq* 9.5, 6	4.93 *dq* 9.5, 6	4.94 *dq* 9.5, 6
6″	1.69 *d* 6	1.77 *d* 6	1.76 *d* 6	1.76 *d* 6	1.76 *d* 6
1‴	5.15 *d* 8	5.85 *brs*	5.90 *brs*	5.92 *brs*	5.93 *brs*
2‴	4.67 *dd* 9, 8	4.69 *dd* 3.5, 1.5	4.59[a]	4.61[a]	4.61[a]
3‴	4.24[a]	4.54 *dd* 9.5, 3.5	4.56 *dd* 9.5, 3.5	4.57 *dd* 9.5, 3.5	4.56 *dd* 9.5, 3.5
4‴	4.09 *dd* 9, 9	4.22[a]	4.26 *dd* 9.5, 9.5	4.27 *dd* 9.5, 9.5	4.27 *dd* 9.5, 9.5
5‴	3.97[a]	4.95[a]	4.86 *dq* 9.5, 6	4.88 *dq* 9.5, 6	4.89 *dq* 9.5, 6
6‴	4.49[a] 4.34[a]	1.63 *d* 6	1.54 *d* 6	1.55 *d* 6	1.55 *d* 6
1⁗	—	—	5.14 *d* 7.5	5.16 *d* 7.5	5.17 *d* 7.5
2⁗	—	—	4.06 *m*	4.06 *m*	4.06 *m*
3⁗	—	—	4.15[a]	4.10–4.25[a]	4.10–4.25[a]
4⁗	—	—	4.15[a]	4.10–4.25[a]	4.10–4.25[a]
5⁗	—	—	4.33[a] 3.69 *m*	4.35[a] 3.70 *m*	4.34[a] 3.69 *m*

δ, J (Hz), in pyridine-d_5 containing *ca* 2% D_2O.
[a] Overlapped signals.

voucher specimen is kept under No. 'D. Diaz-Miranda and A. Usubillaga, 1946' at the Herbarium of the Faculty of Pharmacy at Merida (MERF).

Extraction and isolation. Extraction was performed according to ref. [17]. Freshly sliced berries were treated with the equal vol. of boiling H_2O. After cooling, 5% HOAc was added and the mixt. allowed to stand at room temp. for 24 hr. Plant material was filtered and then treated once more with 5% HOAc for 24 hr. The combined acid extracts were centrifuged, warmed to 70° and made alkaline with conc. NH_4OH. After cooling, the ppt. was filtered, washed with H_2O and dried at 50°. The dry ppt. was ground and extracted with MeOH under reflux, the MeOH extract treated with charcoal, filtered and dried *in vacuo*. Finally, this glycoalkaloid-containing fr. was dissolved in 2% HOAc and precipitated with NH_4OH at 70°. On drying, 14.1 g of crude glycoalkaloid mixt. was obtained. CC on basic Al_2O_3 using EtOAc–MeOH (1:1) afforded 7.8 g of a glycoalkaloid fr. which was further separated into frs A to C by prep. HPLC using MeOH–1% aq. NH_3 (9:1). From fr. A, after purification by CC on Sephadex® LH 20 and subsequent HPLC (0.5% aq. NH_3–MeCN (3:2)), compound **5** (8 mg) was isolated. Fr. B afforded compounds **3** (1.35 g) and **4** (15 mg), together with **1** and **2** (50 mg each) by repeated HPLC [0.5% aq. NH_3–MeCN (31:19)].

Solasonine, (25R)-3β-{O-α-L-*rhamnopyranosyl*-(1 → 2)-[O-β-D-*glucopyranosyl*-(1 → 3)]-β-D-*galactopyranosyloxy*}-22αN-*spirosol*-5-*ene* (**1**). Crystals from MeOH, mp 296–298° (dec), (ref. [14] mp 301° (dec.)). $[\alpha]_D$ −68° (*c* 1.0) (ref. [14] $[\alpha]_D^{25}$ −73°). Identical with an authentic sample isolated from *S. americanum* [18].

Solamargine, (25R)-3β-{O-α-L-*rhamnopyranosyl*-(1 → 2)-[O-α-L-*rhamnopyranosyl*-(1 → 4)]-β-D-*glucopyranosyloxy*}-22αN-*spirosol*-5-*ene* (**2**). Crystals from MeOH, mp 304–306° (dec.), (ref. [14] mp 310° (dec.)). $[\alpha]_D$ −94° (pyridine, *c* 0.5) (ref. [15] $[\alpha]_D^{23}$ −109° (pyridine)). Identical with an authentic sample isolated from *S. americanum* [18].

Sycophantine, (25R)-3β-{O-α-L-*rhamnopyranosyl*-(1 → 2)-[O-β-D-*xylopyranosyl*-(1 → 2)-O-α-L-*rhamnopyranosyl*-(1 → 4)]-β-D-*glucopyranosyloxy*}-22αN-*spirosol*-5-*ene* (**3**). Crystals from MeOH, mp 269–271° (dec.). $[\alpha]_D$ −90° (*c* 0.6). TLC: R_f = 0.19, anisaldehyde: green. IR ν_{max} cm^{-1}: 3400, 2932, 1639, 1127, 1044. FABMS *m/z*: 1000 $[M+H]^+$, 868, 850 $[M-xylose]^+$, 722, 704 $[M-xylose-rhamnose]^+$, 558, 442, 414 $[aglycone+H]^+$, 396 $[aglycone-H_2O+H]^+$. ^1H NMR: Table 1. ^{13}C NMR: Table 2.

22-*epi*-*Sycophantine*, (25S)-3β-{O-α-L-*rhamnopyranosyl*-(1 → 2)-[*O*-β-D-*xylopyranosyl*-(1 → 2)-*O*-α-L-*rhamnopyranosyl*-(1 → 4)]-β-D-*glucopyranosyloxy*}-

Table 2. ^{13}C NMR shifts of compounds **1–5**

Carbon	1	2	3	4	5
1	37.0	37.5	37.2	36.9	37.3
2	29.6	30.2	29.8	29.5	29.9
3	77.6	78.1	77.9	77.6	78.0
4	38.3	39.0	38.6	38.3	38.7
5	140.4	140.8	140.5	140.3	140.6
6	121.3	121.8	121.6	121.3	121.6
7	31.8	32.4	32.0	31.8	32.1
8	31.2	31.7	31.3	31.0	31.7
9	49.8	50.4	50.0	49.8	50.2
10	36.6	37.2	36.8	36.6	36.9
11	20.6	21.2	20.8	20.6	20.8
12	39.6	40.1	39.7	39.5	39.4
13	40.1	40.6	40.3	40.2	40.7
14	56.1	56.7	56.3	56.5	56.6
15	32.0	32.6	32.2	32.4	32.6
16	78.5	78.8	78.7	78.2	79.7
17	62.9	63.6	63.0	61.7	59.9
18	16.0	16.5	16.2	16.3	16.3
19	18.9	19.4	19.1	18.8	19.2
20	41.2	41.6	41.4	42.3	49.6
21	15.2	15.7	15.4	15.6	62.6
22	98.0	98.3	98.2	98.9	97.4
23	34.0	34.7	34.1	26.4	36.0
24	30.4	31.0	30.6	28.5	30.8
25	30.8	31.6	30.9	30.5	31.2
26	47.3	48.1	47.4	49.8	47.7
27	19.2	19.8	19.4	19.2	19.5
1′	99.9	100.3	99.9	99.6	100.0
2′	75.6	77.8	77.2	77.0	77.4
3′	84.6	78.0	77.6	77.4	77.8
4′	69.3	78.7	77.9	77.6	78.0
5′	74.3	76.9	76.7	76.4	76.8
6′	61.9	61.3	60.9	60.7	61.1
1″	101.5	102.0	101.8	101.5	101.8
2″	71.7	72.5	71.9	71.6	72.0
3″	72.0	72.7	72.2	72.0	72.4
4″	73.4	73.9	73.4	73.2	73.6
5″	68.9	69.5	69.2	69.0	69.3
6″	18.0	18.6	18.2	18.2	18.4
1‴	105.1	102.9	101.1	100.8	101.2
2‴	74.2	72.8	81.3	81.1	81.5
3‴	77.6	72.5	71.9	71.6	72.1
4‴	70.9	74.1	73.4	73.2	73.7
5‴	77.3	70.4	69.7	69.4	69.8
6‴	61.5	18.5	17.9	17.9	18.1
1⁗	—	—	106.9	106.7	107.1
2⁗	—	—	74.9	74.6	75.1
3⁗	—	—	77.6	77.4	77.8
4⁗	—	—	70.4	70.2	70.6
5⁗	—	—	66.7	66.5	66.9

δ, in pyridine-d_5.

22βN-*spirosol*-5-*ene* (**4**). Crystals from MeOH, mp 268–272° (dec.). $[\alpha]_D - 52°$ (*c* 0.6). TLC: $R_f = 0.22$, anisaldehyde: green. IR ν_{max} cm^{-1}: 3400, 2932, 1665, 1131, 1045. FABMS *m/z*: 1000, 868, 850, 722, 704, 442, 414, 396, 378. ^1H NMR: Table 1. ^{13}C NMR: Table 2.

21-*Hydroxysycophantine*, (25R)-3β-{O-α-L-*rhamnopyranosyl*-(1 → 2)-[O-β-D-*xylopyranosyl*-(1 → 2)-*O*-α-L-*rhamnopyranosyl*-(1 → 4)]-β-D-*glucopyranosyloxy*}-22αN-*spirosol*-5-*ene* (**5**). Powder from MeOH, mp 256–258° (dec.). $[\alpha]_D - 78°$ (*c* 0.9). TLC: $R_f = 0.16$, anisaldehyde: green. IR ν_{max} cm^{-1}: 3400, 2932, 1664, 1129, 1045. FABMS *m/z*: 1016 $[M+H]^+$, 998, 866 $[M-\text{xylose}]^+$, 852 $[M-\text{rhamnose}]^+$, 720 $[M-\text{xylose}-\text{rhamnose}]^+$, 702, 556, 412, 394. ^1H NMR: Table 1. ^{13}C NMR: Table 2.

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