Two New Nor-triterpene Glycosides from Peruvian "Uña de Gato" (*Uncaria tomentosa*)

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Received August 30, 2002

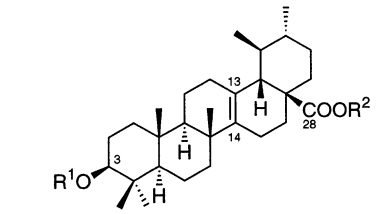
Two new 27-nor-triterpene glycosides, tomentosides A (**1**) and B (**2**), were isolated from Peruvian "Uña de Gato" (cat's claw, plant of origin: *Uncaria tomentosa)*, a traditional herbal medicine in Peru. Their structures were determined by spectroscopic analysis and chemical interconversions. This is the first report of naturally occurring pyroquinovic acid glycosides.

"Uña de Gato" (cat's claw)[1] is a Peruvian traditional herbal medicine used for treating various ailments. Recently, some bioactivities of this herbal medicine, including antiinflammatory activity,[2] have been reported. The plants of origin of "Uña de Gato" are *Uncaria tomentosa* (Willd.) D. C. and *U. guianensis* (Aubl.) Gmel. (Rubiaceae), which are distributed in the South American continent. From these plants, various kinds of secondary metabolites, i.e., oxindole and indole alkaloids,[3−7] quinovic acid glycosides,[6,8] polyoxygenated triterpenes,[8] catechins,[9] and sterols,[10] have been isolated. We have also reported the isolation and identification of new triterpenes[11] and alkaloids[12,13] from Peruvian "Uña de Gato" (plant of origin: *Uncaria tomentosa*).

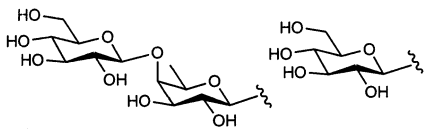
Further study of the chemical constituents led us to the discovery of two new 27-nor-triterpene glycosides (**1** and **2**) from Peruvian "Uña de Gato", which we describe herein.

The MeOH extract of *U. tomentosa* was dissolved in 30% MeOH−H_2O. After filtration, the filtrate was extracted with $CHCl_3$ and then *n*-BuOH to give a $CHCl_3$ extract and a *n*-BuOH extract, respectively. The *n*-BuOH extract was subjected to column chromatography to give two new 27-nor-triterpene glycosides (**1** and **2**) together with quinovic acid glycosides and cincholic acid glycosides.

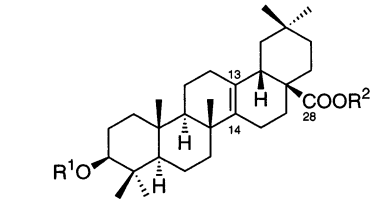
The HRFABMS of tomentoside A (**1**) measured in the positive-ion mode gave a sodiated molecular ion peak at *m/z* 935.4930 ($[M + Na]^+$) corresponding to the molecular formula $C_{47}H_{76}O_{17}Na$ (*m/z* 935.4980). The ^1H NMR spectrum showed four singlets at δ 1.02, 0.90, 0.86, and 0.82 and two doublets at δ 0.93 and 0.92 (overlapped), due to five methyl groups of the triterpene aglycon, but no signals indicating the presence of any olefinic protons. The ^{13}C NMR spectrum showed six methyl carbons of the terpene aglycon at δ 28.4, 20.4, 19.9, 18.2, 17.1, and 16.8 and one ester carbon at δ 177.7. Two sp^2 carbons of a tetrasubstituted olefin (δ 140.7, 132.5) were observed in place of two sp^2 carbons of a trisubstituted olefin and one extra carboxyl carbon, which are characteristic signals of normal quinovic acid derivatives. Therefore, the aglycon of **1** was deduced to be a 27-nor-triterpene, pyroquinovic acid (**3**),[14,15] which represents the rearrangement of the double bond at C-12/C-13 to C-13/C-14 and the simultaneous decarboxylation of the C-27 carboxylic acid of quinovic acid. Three doublets



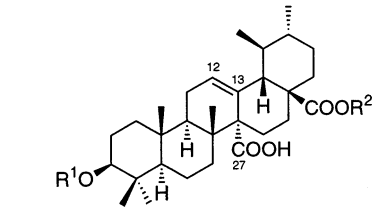
1 : R^1=β-D-Fuc^4-β-D-^{1}Glc, R^2=β-D-Glc



3 : R^1=R^2=H



2 : R^1=β-D-Fuc^4-β-D-^{1}Glc, R^2=β-D-Glc
6 : R^1=R^2=H



4 : R^1=β-D-Fuc^4-β-D-^{1}Glc, R^2=β-D-Glc

with a large coupling constant due to anomeric protons at δ 5.32 (J = 8.1 Hz, H-1‴), 4.54 (J = 7.8 Hz, H-1″), and 4.24 (J = 7.3 Hz, H-1′) in the ^1H NMR spectrum and three anomeric carbons at δ 107.1 (C-1′), 105.9 (C-1″), and 95.6 (C-1‴) in the ^{13}C NMR spectrum revealed that **1** possesses two β-linked sugar units attached through an ether linkage and one β-linked sugar attached through an ester linkage. The presence of two glucoses and one fucose in **1** and their linkages were deduced from ^{13}C NMR and HMBC data and by comparison with the ^{13}C NMR chemical shift of the sugar part of the known quinovic acid glycoside **4**,[16] as follows. From the HMBC correlation between H-1‴ of glucose at δ 5.32 and the ester carbonyl carbon at δ 177.7,

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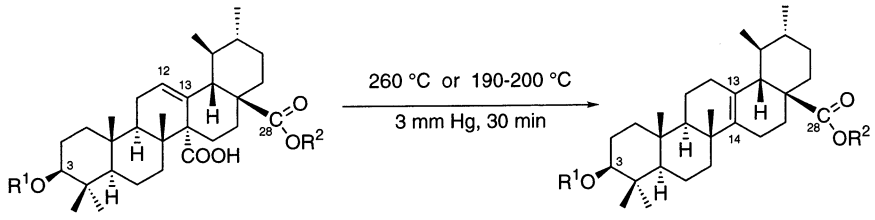
10.1021/np0203741 CCC: $25.00
Published on Web 01/24/2003

Scheme 1



4 : R^1=β-D-Fuc^4-β-D-^{1}Glc, R^2=β-D-Glc

1 : R^1=β-D-Fuc^4-β-D-^{1}Glc, R^2=β-D-Glc
3 : R^1=R^2=H
5 : R^1=β-D-Fuc^4-β-D-^{1}Glc, R^2=H

one glucose was found to be attached at C-27. The HMBC correlation between H-1′ of fucose at δ 4.24 and C-3 of the aglycon at δ 91.0 revealed that fucose was attached at C-3 of the aglycon. The HMBC correlation between both H-1″ of glucose at δ 4.54 and methyl protons (H_3-6′) of fucose at δ 1.29 and C-4′ of fucose at δ 82.4 revealed that a terminal glucose was attached at C-4′ of an inner fucose. From the above data, **1** was deduced to be pyroquinovic acid 3*β*-*O*-*β*-glucopyranosyl-(1→4)-*β*-fucopyranosyl-28-*O*-*β*-glucopyranosyl ester, which corresponds to a 27-nor-type compound derived from **4**. Next, we attempted the chemical conversion of **4**[16] to the new nor-triterpene **1** to establish its structure including its absolute configuration. First, **4** was heated at 260 °C under 3 mmHg for 30 min according to the literature[14] to give pyroquinovic acid (**3**) in 45% yield. ^{13}C NMR data of the semisynthetic compound, including the chemical shifts of the tetrasubstituted olefinic carbons (δ 130.9 and 139.4), were identical with those of reported data.[14,15] To prevent the cleavage of the sugar units, the reaction was carried out at a low temperature. Heating **4** at 190−200 °C under 3 mmHg for 30 min gave the expected **1** in 21% yield. The synthetic compound **1** was identical with the natural product **1** (TLC, ^{1}H and ^{13}C NMR, mass spectra, and optical rotation). Therefore, the structure of **1** was pyroquinovic acid 3*β*-*O*-*β*-D-glucopyranosyl-(1→4)-*β*-D-fucopyranosyl-28-*O*-*β*-D-glucopyranosyl ester. During these reactions, **5** was also obtained (yield 34%). The ^{13}C NMR spectrum of **5** showed tetrasubstituted olefinic carbons at δ 140.6 (C-14) and 132.5 (C-13) and an ester carbonyl carbon at δ 181.7 (C-28). The existence of two sugar units attached at C-3 was revealed by the two anomeric proton signals at δ 4.54 (H-1″) and 4.25 (H-1′) in the ^{1}H NMR spectrum and the two anomeric carbon signals at δ 107.1 (C-1′) and 105.9 (C-1″) in the ^{13}C NMR spectrum.

The second new 27-nor-triterpene glycoside, **2**, named tomentoside B, gave a sodiated molecular ion peak at *m*/*z* 935.4972 ([M + Na]$^+$) in the HRFABMS, revealing the molecular formula $C_{47}H_{76}O_{17}Na$ (*m*/*z* 935.4980). Acid hydrolysis of **2** gave pyrocincholic acid (**6**),[14,17] D-glucose, and D-fucose. In the ^{1}H NMR spectrum, six singlet methyl signals of the triterpene aglycon at δ 1.03, 0.93, 0.92, 0.91, 0.86, and 0.83, a doublet methyl signal of fucose at δ 1.30, and three anomeric protons at δ 5.38, 4.54, and 4.24 were observed. In addition, the ^{13}C NMR spectrum showed two tetrasubstituted olefinic carbons at δ 137.9 and 131.2 as well as six methyl carbons of the triterpene aglycon at δ 33.0, 28.4, 25.1, 21.1, 17.1, and 16.8, one methyl carbon of fucose at δ 17.4, three anomeric carbons at δ 107.1, 105.9, and 95.7, and one ester carbon at δ 178.2. The ^{13}C NMR chemical shifts of the sugar part of **2**, which were consistent with those of **1**, and the HMBC correlations revealed that **2** has the same sugar chain as that of **1**. Therefore, the structure of **2** was confirmed to be pyrocincholic acid 3*β*-*O*-*β*-D-glucopyranosyl-(1→4)-*β*-D-fucopyranosyl-28-*O*-*β*-D-glucopyranosyl ester.

Although some nor-type pyrocincholic acid glycosides were isolated from *Isertia haenkeana*[14,18,19] and *Adina rubella*[20−22] (Rubiaceae), to the best of our knowledge, the isolation of pyroquinovic acid glycoside from nature has not been reported so far.

Experimental Section

General Experimental Procedures. Optical rotation: JASCO DIP-140. IR: JASCO FT/IR-230. ^{1}H and ^{13}C NMR spectra: at 500 (^{1}H NMR) and 125.65 (^{13}C NMR) MHz, respectively, JEOL JNM A-500. FABMS and HRFABMS: JEOL JMS-HX110. TLC: precoated silica gel 60 F_{254} plates (Merck, 0.25 mm thick). Column chromatography: silica gel 60 [Merck, 230−400 mesh (for flash column chromatography)], DIAION HP20 (Mitsubishikasei, Tokyo, Japan). MPLC: C.I.G. prepacked column CPS-HS-221-05 (SiO_2) and CPO-HS-221-20 (ODS) (Kusano Kagakukikai, Tokyo, Japan). HPLC: Shodex RSpak DC-613 (Showa Denko, Tokyo, Japan). Compound **4** was isolated from Peruvian "Uña de Gato" used in this study. Its structure and purity were confirmed by comparison of the ^{1}H and ^{13}C NMR spectra with those in the literature.[16]

Plant Material. "Uña de Gato" used in this study was imported from Peru through Coperunix Japan, Inc. (Tokyo, Japan) in 1996. The plant of origin was confirmed to be *Uncaria tomentosa* (stem and stem bark) by the company. A voucher specimen was deposited at the Herbarium of Research Center of Medicinal Resources, Graduate School of Pharmaceutical Sciences, Chiba University.

Extraction and Isolation. The plant material (835 g dry weight) was extracted with hot MeOH six times (1 L × 6) to give the MeOH extract (total 95 g). A portion (40 g) of the MeOH extract was dissolved in 30% MeOH−H_2O. After filtration, the filtrate was extracted with $CHCl_3$ (× 3) and then *n*-BuOH (× 3) to give the $CHCl_3$ extract (3.4 g) and the *n*-BuOH extract (25 g), respectively. The *n*-BuOH extract was subjected to column chromatography on DIAION HP20 (2.5 cm × 90 cm) to give six fractions (1 L each): fr. G, MeOH−H_2O, 3:7, 11.85 g, fr. H, MeOH−H_2O, 1:1, 2.46 g, fr. I, MeOH−H_2O, 7:3, 5.24 g, fr. J, MeOH, 9.50 g, fr. K, MeOH−acetone, 1:1, 0.02 g, and fr. L, acetone, 0.08 g. Fraction J (9.50 g) was purified by SiO_2 gel flash column chromatography (7 cm × 16 cm), eluting with a stepwise gradient mixture of MeOH−$CHCl_3$ ($CHCl_3$, 10%, 15%, 20%, 30%, 40%, 60%, 80%, MeOH; 800 mL each). Purification of the 40% MeOH−$CHCl_3$ eluate (136 mg) by MPLC (SiO_2, 25% MeOH−$CHCl_3$) gave two fractions. Fraction 2 (35.5 mg) was separated by SiO_2 gel flash column chromatography (1 cm × 15 cm), eluting with a stepwise gradient mixture of MeOH−$CHCl_3$ ($CHCl_3$, 90 mL; 5%, 90 mL; 10%, 180 mL; 15%, 180 mL; 50%, 90 mL; MeOH, 90 mL; 30 mL each). The 15% MeOH−$CHCl_3$ eluate (fr. 14−16, 19.2 mg) was finally purified by MPLC (ODS, H_2O−MeOH, 1:3) to give the nor-triterpene glycosides **1** (3.0 mg) and **2** (10.5 mg). Compound **2** (13.1 mg) was also obtained from the 60% MeOH−$CHCl_3$ eluate of SiO_2 gel flash column chromatography of fr. J. The 60% MeOH−$CHCl_3$ eluate was subjected to SiO_2

Table 1. ^{13}C NMR Data of **1** and **2** in CD_3OD (125 MHz)

position	1	2	position	1	2
1	39.5	39.5	Fuc-1′	107.1	107.1
2	27.2	27.2	2′	73.5	73.5
3	91.0	90.9	3′	75.8	75.8
4	40.3	40.3	4′	82.4	82.4
5	57.2	57.1	5′	71.2	71.2
6	19.4	19.5	6′	17.4	17.4
7	40.2	40.7	Glc-1″	105.9	105.9
8	39.3	38.9	2″	76.0	75.9
9	58.0	57.8	3″	78.1[a]	78.1[a]
10	38.1	38.2	4″	71.6[b]	71.6[b]
11	19.0	18.9	5″	78.2[a]	78.3[a]
12	36.7	32.8	6″	62.9	62.9
13	132.5	131.2	Glc-1‴	95.6	95.7
14	140.7	137.9	2‴	74.1	74.0
15	20.6	21.5	3‴	78.3[a]	78.7[a]
16	23.9	24.3	4‴	71.5[b]	71.2[b]
17	*c*	46.6	5‴	78.4[a]	78.4[a]
18	51.1	40.2	6‴	62.8	62.5
19	41.3	42.4			
20	39.7	31.4			
21	31.6	35.1			
22	34.9	32.0			
23	28.4	28.4			
24	16.8	16.8			
25	17.1	17.1			
26	19.9	21.1			
28	177.7	178.2			
29	18.2	33.0			
30	20.4	25.1			

[a,b] Interchangeable. [c] Under CD_3OD signals.

gel flash column chromatography (2.6 cm × 15.5 cm), eluting with a gradient mixture of MeOH−$CHCl_3$ ($CHCl_3$, 160 mL; 15%, 720 mL; 20%, 720 mL; 30%, 480 mL; 50%, 240 mL; MeOH, 240 mL; 80 mL each). The 15−20% MeOH−$CHCl_3$ eluate (fr. 11−13, 138 mg) was further purified by MPLC (ODS, H_2O−MeOH, 1:3) to give **2** (13.1, mg).

Tomentoside A (1): amorphous powder; $[\alpha]^{23}_D$ −37.3° (*c* 0.13, MeOH); IR (KBr) ν_{max}, 3416, 2921, 1633, 1428, 1074 cm^{-1}; selected ^1H NMR (CD_3OD, 500 MHz) data δ 5.32 (1H, d, J = 8.1 Hz, Glc-H-1‴), 4.54 (1H, d, J = 7.8 Hz, Glc-H-1″), 4.24 (1H, d-like, J = 7.3 Hz, Fuc-H-1′), 3.84 (1H, dd, J = 11.8, 2.3 Hz, Glc-H-6″), 3.81 (1H, br s, Fuc-H-4′), 3.79 (1H, dd, J = 11.7, 2.6 Hz, Glc-H-6‴), 3.70 (1H, dd, J = 11.7, 4.3 Hz, Glc-H-6‴), 3.65 (1H, dd, J = 11.8, 5.4 Hz, Glc-H-6″), 3.12 (1H, dd, J = 11.2 Hz, H-3), 2.22 (2H, overlapped, H-12, H-15), 1.29 (3H, d, J = 6.3 Hz, Fuc-H_3-6′), 1.02 (3H, s, H_3-23), 0.98 (1H, br d, J = 11.5 Hz, H-9), 0.93 and 0.92 (overlapped, H_3-29 and H_3-30), 0.90 (3H, s, H_3-26), 0.86 (3H, s, H_3-25), 0.82 (3H, s, H_3-24), 0.78 (1H, br d, J = 12.0 Hz, H-5); for ^{13}C NMR data, see Table 1; FABMS (positive, NBA) *m/z* 935 $[M + Na]^+$; HRFABMS *m/z* 935.4930 $[M + Na]^+$ (calcd for $C_{47}H_{76}O_{17}Na$, 935.4980).

Tomentoside B (2): amorphous powder; $[\alpha]^{26}_D$ −23.9° (*c* 0.56, MeOH); IR (KBr) ν_{max} 3425, 2942, 1734, 1647, 1072 cm^{-1}; selected ^1H NMR (CD_3OD, 500 MHz) data δ 5.38 (1H, d, J = 8.3 Hz, Glc-H-1‴), 4.54 (1H, d, J = 7.8 Hz, Glc-H-1″), 4.24 (1H, d-like, J = 7.6 Hz, Fuc-H-1′), 3.84 (1H, dd, J = 11.8, 2.1 Hz, Glc-H-6″), 3.82 (1H, br s, Fuc-H-4′), 3.80 (1H, overlapped, Glc-H-6‴), 3.11 (1H, dd, J = 11.7, 4.4 Hz, H-3), 2.41 (1H, dd, J = 12.1, 4.0 Hz, H-18), 2.20 (2H, overlapped, H-12, H-15), 1.30 (3H, d, J = 6.4 Hz, Fuc-H_3-6′), 1.03 (3H, s, H_3-23), 0.97 (1H, d, J = 12.7 Hz, H-9), 0.93 (3H, s, H_3-30), 0.92 (3H, s, H_3-26), 0.91 (3H, s, H_3-29), 0.86 (3H, s, H_3-25), 0.83 (3H, s, H_3-24), 0.78 (1H, d, J = 11.5 Hz, H-5); for ^{13}C NMR data, see Table 1; FABMS (positive, NBA) *m/z* 935 $[M + Na]^+$; HRFABMS *m/z* 935.4972 $[M + Na]^+$ (calcd for $C_{47}H_{76}O_{17}Na$, 935.4980).

Rearrangement of Double Bond and Decarboxylation of 4. Procedure A. Compound **4** (21.5 mg, 0.225 mmol), which was isolated from "Uña de Gato", was heated at 260 °C under 3 mmHg for 30 min. The residue was purified by silica gel column chromatography (15% MeOH−$CHCl_3$) to give pyroquinovic acid (**3**, 4.5 mg, yield 45%). **3**: $[\alpha]^{21}_D$ −50.7° (*c* 0.141, EtOH); selected ^1H NMR ($CDCl_3$, 500 MHz) data δ 3.20 (1H, dd, J = 11.4, 4.8 Hz, H-3), 0.96 (3H, s, H_3-23), 0.90 (1H, d, J = 6.1 Hz, H_3-30), 0.89 (1H, d, J = 6.4 Hz, H_3-29), 0.86 (3H, s, H_3-26), 0.81 (3H, s, H_3-25), 0.77 (3H, s, H_3-24); ^{13}C NMR data of the synthetic compound were identical with reported data;[14,15] FABMS (negative, NBA) *m/z* 441 $[M - H]^-$.

Procedure B. Compound **4** (106.6 mg, 0.111 mmol) was heated at 190−200 °C under 3 mmHg for 30 min. The residue was purified by silica gel column chromatography (10% and 15% MeOH−$CHCl_3$) to give **1** (21.7 mg, yield 21%) and **5** (28.6 mg, yield 34%) (recovery of **4**, 19%). **5**: amorphous powder; $[\alpha]^{27}_D$ −57.8° (*c* 0.50, MeOH); IR (KBr) ν_{max}, 3458, 2925, 1696, 1647, 1071 cm^{-1}; selected ^1H NMR ($CDCl_3$, 500 MHz) data δ 4.54 (1H, d, J = 7.9 Hz, H-1″), 4.25 (1H, br d, J = 7.6 Hz, H-1′), 3.12 (1H, dd, J = 11.8, 4.4 Hz, H-3), 3.82 (1H, br s, H-4″), 1.29 (1H, d, J = 6.4 Hz, H_3-6′), 1.03 (3H, s, H_3-23), 0.91 (overlapped, H_3-26, 29, 30), 0.85 (3H, s, H_3-25), 0.83 (3H, s, H_3-24); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.7 (C-28), 140.6 (C-14), 132.5 (C-13), 107.1 (C-1′), 105.9 (C-1″), 90.9 (C-3), 82.4 (C-4′), 78.3, 78.1, 76.0, 75.8, 73.5, 71.6, 71.2, 62.9, 57.9, 57.2, 51.7, 48.6, 41.3, 40.3, 40.2, 39.9, 39.5, 39.1, 38.1, 36.6, 35.5, 31.7, 28.4 (C-23), 27.1, 23.7, 20.8, 20.5 (C-30), 19.7 (C-26), 19.4, 19.1, 18.3 (C-29), 17.4, 17.0 (C-25), 16.8 (C-24); FABMS (negative, glycerol) *m/z* 749 $[M - H]^-$; HRFABMS (negative, NBA) *m/z* 749.4479 $[M - H]^-$ (calcd for $C_{41}H_{65}O_{12}$, 749.4476).

Acid Hydrolysis of 2. A solution of **2** (4.5 mg) in 5% aqueous H_2SO_4 (0.25 mL) and 1,4-dioxane (0.25 mL) was heated at 115 °C for 3 h under Ar. Water was added to the reaction mixture, and the entire mixture was extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (2% MeOH−$CHCl_3$) to afford pyrocincholic acid (**6**, 2 mg); $[\alpha]^{21}_D$ −26.7° (*c* 0.104, EtOH). The aqueous layer was neutralized by passage through Amberlite IRA-93 eluting with H_2O. This was followed by evaporation in vacuo to give a sugar fraction. The identification and configuration of the sugars were determined by HPLC analysis by comparison with authentic D-(+)-glucose (t_R, 11.4 min) and D-(+)-fucose (t_R, 8.7 min). HPLC conditions: column, Shodex RSpak DC-613 (6.0 × 150 mm i.d.); solvent, CH_3CN−H_2O, 7:3 (v/v); flow rate, 0.5 mL/min; temperature, 70 °C; RI detection, Shodex RI-72; and chiral detection, JASCO OR-1590. The sugar fraction gave corresponding peaks of D-(+)-glucose (t_R, 11.4 min) and D-(+)-fucose (t_R, 8.7 min).

Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1** and **2**. This information is available free of charge via the Internet at http://pubs.acs.org.

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NP0203741