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STARFISH SAPONINS, PART 44.[1] STEROIDAL GLYCOSIDES FROM THE STARFISH *PISASTER GIGANTEUS*

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ABSTRACT.—Three novel steroidal monoglycoside sulfates, pisasterosides D [**2**], E [**3**], and F [**4**], have been isolated from the starfish *Pisaster giganteus*. These compounds occur with one known steroidal monglycoside sulfate, pycnopodioside B [**1**], and two known asterosaponins, thornasteroside A and versicoside A; these asterosaponins have been also found as constituents of two previously investigated *Pisaster* species.

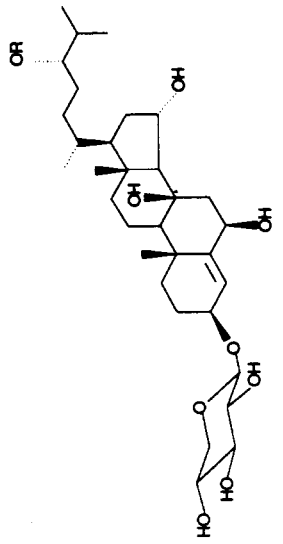
In a previous paper of this series (1) we have described the steroidal glycoside compounds from two species of starfishes of the genus *Pisaster* (family Asteriidae), collected off the Gulf of California. In addition to major amounts of two known asterosaponin steroidal penta- and hexaglycoside sulfates, thornasteroside A (2) and versicoside A (3), *Pisaster ochraceus* and *Pisaster brevispinus* were shown to contain minor amounts of three novel steroidal monoglycoside sulfates: pisasteroside A, (24*R*)-28-*O*-[β-D-glucopyranosyl-6′-sulfate]-24-methyl-5α-cholesta-3β,6α,8,15β,16β,28-hexaol, from both species; pisasteroside B, (24*S*)-3-*O*-(β-D-xylopyranosyl)-5α-cholesta-3β,6β,8,15α,24-pentaol 24-sulfate from *P. brevispinus*; and pisasteroside C, (24*Z*)-29-*O*-(β-D-xylopyranosyl-4′-sulfate)-24-ethyl-5α-cholest-24(28)-ene-3β,6α,8,15β,16β,29-hexaol from *P. ochraceus*. We now report the glycoside constituents of a third *Pisaster* species, *Pisaster giganteus* (Brandt), collected off the Gulf of California. In addition to thornasteroside A (2) and versicoside A (3), which are in common with the previously investigated *Pisaster* species, the extracts of *P. giganteus* also contained four steroidal monoglycoside sulfates, the known pycopodioside B [**1**] (4) and the novel pisasterosides D [**2**], E [**3**], and F [**4**].

The fabms (negative ion mode) of Pisasteroside D [**2**] showed a molecular anion peak at *m/z* 661. On solvolysis in dioxane/pyridine (5) the steroid afforded a desulfated derivative **2a**, fabms (negative ion mode) *m/z* 581 $[M-H]^-$ and 449 (loss of a pentasaccharide unit). Examination of the spectral properties (Experimental and Table 1) indicated that **2** contains a β-xylopyranosyl unit, as confirmed by acid methanolysis affording methyl xylosides. In addition to the sugar moiety, the ^{1}H-nmr spectrum showed signals for the steroid aglycone protons at δ 5.70 (1H, br s, H-4) and 4.25 (1H, m, H-3), coupled to each other, and at δ 4.33 (m, H-6α) and 1.38 (3H, s, H_3-19) already observed in the spectra of echinasterosides A and B (6) from *Echinaster sepositus*, which are characterized by a Δ^4,3β,6β,8-hydroxylation pattern in the steroidal nucleus. Two additional >CH-O- signals in the ^{1}H-nmr spectrum of **2** were seen at δ 4.33 (overlapping with H-6α) and 4.14 (q, $J=6.5$ Hz) and were assigned to 15α-hydroxyl (7,8) and 24-sulfoxyl groups (9), respectively. The location of the sulfoxyl group at C-24 was supported by the upfield shift of the H-24 signal to δ 3.27 in the spectrum of the desulfated derivative **2a**.

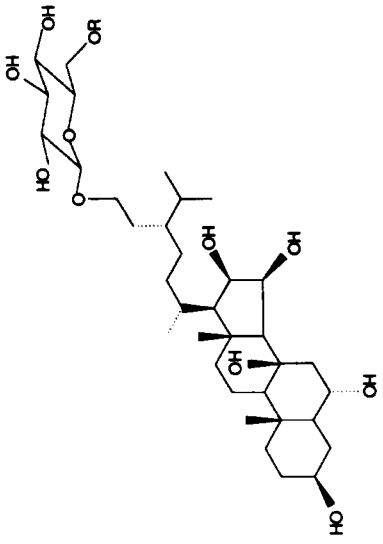
Analysis of the ^{13}C-nmr spectra (Table 1) of **2** and **2a** and comparison with those of the echinasterosides (6) established that the sugar unit was located at C-3 and confirmed the formulation **2** for pisasteroside D.

The fabms (negative ion mode) of Pisasteroside E [**3**] showed a molecular

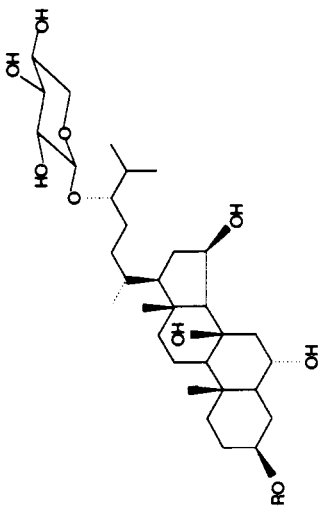
[1]For Part 43, see I. Bruno, L. Minale and R. Riccio, *J. Nat. Prod.*, **53**, 366 (1990).



2 R=$SO_3^-Na^+$
2a R=H



4 R=$SO_3^-Na^+$
4a R=H



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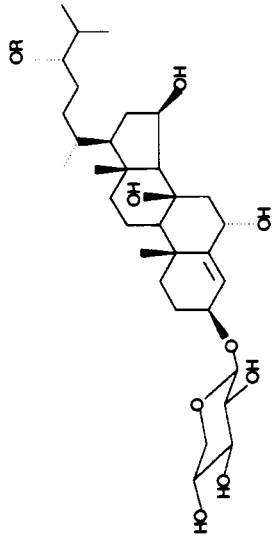
1a R=H



3 R=$SO_3^-Na^+$
3a R=H

TABLE 1. ^{13}C nmr Shifts (62.9 MHz, CD_3OD) of the Glycosides **1–4** and their Desulfated Analogues **1a–4a**.

Carbon	Compound							
	1	**1a**	**2**	**2a**	**3**	**3a**	**4**	**4a**
C-1	39.5	39.4	39.7	39.7	39.4	39.4	39.5	39.5
C-2	30.1	31.5	27.7	27.7	27.7	27.7	31.5	31.5
C-3	80.1	72.2	77.0	77.0	77.3	77.3	72.3	72.3
C-4	29.1	32.4	126.9	126.9	118.0	118.0	32.4	32.4
C-5	54.1	53.9	148.6	148.6	151.8	151.8	54.0	54.0
C-6	67.7	67.6	76.5	76.4	66.9	66.9	67.8	67.8
C-7	[a]	49.4	44.7	44.5	[a]	[a]	49.6	49.6
C-8	77.5	77.3	76.5	76.4	76.9	76.9	77.3	77.3
C-9	57.5	57.5	57.9	57.8	57.9	57.9	57.6	57.6
C-10	37.9	38.0	37.7	37.7	38.4	38.4	38.0	38.0
C-11	19.7	19.7	19.7	19.7	19.6	19.6	19.4	19.4
C-12	43.5	43.4	42.7	42.7	43.3	43.3	43.7	43.7
C-13	44.5	44.6	45.4	45.4	44.4	44.4	44.6	44.6
C-14	62.8	62.7	66.7	66.5	62.4	62.4	61.3	61.3
C-15	71.4	71.4	70.2	70.1	71.3	71.3	71.8	71.8
C-16	42.4	42.2	41.4	41.5	42.4	42.4	73.0	73.0
C-17	58.1	58.0	55.8	55.9	58.1	58.1	63.1	63.1
C-18	16.5	16.5	15.3	15.3	16.5	16.5	17.9	17.9
C-19	13.9	14.2	22.6	22.6	21.1	21.1	14.0	14.0
C-20	36.2	36.3	36.1	36.2	36.3	36.3	31.4	31.4
C-21	19.0	18.9	19.0	19.0	19.0	19.0	18.5	18.5
C-22	32.8	32.7	32.2	33.3	32.3	32.3	35.0	35.0
C-23	29.1	28.7	28.4	31.6	28.4	28.4	28.9	28.9
C-24	86.4	86.3	86.0	78.1	85.9	78.1	42.8	42.8
C-25	32.1	31.9	31.9	34.5	31.9	34.5	31.1	31.1
C-26	18.2	18.3	18.5	17.5	18.5	17.5	19.3	19.3
C-27	18.4	18.3	17.9	19.4	18.0	19.4	19.9	19.9
C-28							32.1	32.1
C-29							70.2	70.2
C-1′	104.9	104.9	104.2	104.2	104.0	104.0	104.5	104.5
C-2′	75.3	75.4	75.0	75.0	75.0	75.0	75.3	75.3
C-3′	77.9	78.0	77.9	77.9	77.9	77.9	78.0	78.0
C-4′	71.3	71.1	71.3	71.2	71.3	71.3	71.4	71.4
C-5′	66.7	66.8	66.7	66.8	66.7	66.7	76.2	76.2
C-6′							68.4	62.7

[a]Under solvent signal.

anion peak at *m/z* 661 and indicated it to be isomeric with pisasteroside D. It differs from **2** in the stereochemistry at C-6 and C-15, which in **3** is 6α-OH and 15β-OH. The ^1H-nmr spectrum showed a broad doublet at δ 4.60 (H-6β) with *J* of 12.5 and 5 Hz, characteristic of an axially oriented proton, which was transformed into a sharp double doublet on irradiation at δ 5.82 (br singlet, H-4) and into a broad doublet ($J = 12.5$ Hz) on irradiation at δ 2.45 (m, H-7β). In agreement with the presence of a 6α-OH, the Me-19 proton signal was observed to be shifted upfield to δ 1.21 (δ 1.38 in **2**). Appearance of one hydroxymethine signal at δ 4.45 (m, partially overlapped with the anomeric proton signal of the xylosyl residue) along with one methyl singlet signal at δ 1.31 in place of those at 4.33/1.00 ppm in **2** (H-15 and H_3-18) indicated the presence of a 15β-OH in **3**. The ^{13}C-nmr spectrum (Table 1) and comparison with **2** confirmed the formulation **3** for pisasteroside E.

The fabms (negative ion mode) of

Pisasteroside F [**4**] showed a molecular anion peak at *m/z* 737. On solvolysis in dioxane/pyridine mixture (5), compound **4** afforded a desulfated derivative **4a**, fabms (negative ion mode) *m/z* 657 $[M-H]^-$ and 495 (loss of an hexasaccharide unit). Acid methanolysis afforded methyl glucosides. Examination of the spectral properties (Experimental and Table 1) indicated that **4** contains the (24*R*)-24-ethyl-5α-cholesta-3β,6α,8,15β,16β,29-hexaol aglycone already encountered in halityloside B (10) and showed the presence of the β-D-glycopyranosyl 6′-sulfate unit instead of the 2-*O*-methyl-β-D-xylosyl-(1↦2)-β-D-xylosyl disaccharide moiety in halityloside B. We note that the β-D-glycopyranosyl-6′-sulfate residue has been recently found in pisasteroside A from both *P. ochraceus* and *P. brevispinus* (1). The location of the sugar moiety at C-29 of the aglycone in **4** was readily derived from the ^{13}C-nmr data (Table 1) and comparison with those of halityloside B (10) and 24-(β-hydroxyethyl) model steroids (11). The 24*R* configuration to **4** was assigned on the basis of ^1H- and ^{13}C-nmr spectral data and comparison with those of (24*R*)- and (24*S*)-29-hydroxylated model steroids (11). Particularly diagnostic in this respect are the differences in chemical shifts of the isopropyl methyl protons (Δδ 0.03, 24*R*; Δδ 0.01, 24*S*; δ 0.88 and 0.91 ppm in **4**) as well as the difference in the chemical shifts in the isopropyl methyl carbons (Δδ 1.1, 24*R*; Δδ 0.1, 24*S*; δC 19.3 and 19.9 ppm in **4**).

EXPERIMENTAL

INSTRUMENTATION.—For instruments used see Zollo *et al.* (12).

EXTRACTION AND ISOLATION.—The animals (*P. giganteus*, 3.8 kg) were collected in 1985 off the Gulf of California and identified by the zoologists of the Scripps Institution of Oceanography, La Jolla, California; a voucher specimen is preserved at the Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli. The animals were chopped and extracted with distilled H_2O (3 liters) for 3 h at room temperature. The extraction was repeated twice.

The aqueous extracts were passed through a column of Amberlite XAD-2 (1 kg). This column was washed with H_2O and then MeOH. The MeOH eluates were dried on a rotary evaporator to give 3.9 g of a glassy material that was then chromatographed on a column of Sephadex LH-60 (80 cm × 4 cm i.d., 100 g) using MeOH-H_2O (2:1) as eluent. The flow rate was 30 ml/h. The eluents were collected in 10-ml fractions and monitored by tlc on silica precoated glass sheets (Merck) with *n*-BuOH–HOAc–H_2O (12:3:5); detection with ceric sulfate/H_2SO_4.

The asterosaponins were eluted in the first fractions to give 0.7 g of material, whereas the subsequent fractions contained the steroidal monoglycoside sulfates (0.9 g). Fractionation of the asterosaponins was continued by dccc with *n*-BuOH–Me_2CO–H_2O (45:15:75) (descending mode, the upper phase was the stationary phase, flow 24 ml/h; 6-ml fractions were collected and monitored by tlc) to give two main fractions: 76–95 (65 mg) contained mainly thornasteroside A (2) and smaller amounts of versicoside A (3); 96–125 (24 mg) contained only thornasteroside A. These fractions were then separated by hplc on C-18 μ-Bondapak column (30 cm × 7.8 mm i.d.) with MeOH-H_2O (9:11). The flow rate was 5 ml/min. The total yield of each saponin was: thornasteroside A, 46 mg; versicoside A, 8 mg. Fractionation of the monoglycoside sulfates was continued by dccc with *n*-BuOH–Me_2CO–H_2O (45:15:75) [ascending mode; the lower phase was the stationary phase; flow 24 ml/h; 6-ml fractions were collected and monitored by tlc on silica with *n*-BuOH–HOAc–H_2O (12:3:5)] to give the following fractions: 118–129, 39 mg, **1**; 130–143, 57 mg, **1**+**4**; 144–156, 68 mg, **1**+**4**+**3**; 157–170, 57 mg, **1**+**4**+**3**+**2**; 171–192, 50 mg, **2**.

Each of the fractions was then submitted to hplc on a C-18 μ-Bondapak column (30 cm × 7.8 mm i.d.) with MeOH-H_2O (1:1) (flow rate 5 ml/min) to give single compounds.

Compound **1**.—Pycnopodioside B [(24*S*)-24-*O*-(β-D-xylopyranosyl)-5α-cholesta-3β,6α,8,15β,24-pentaol, 3-sulfate] [**1**]: 30 mg; Rt in hplc 13.6 min; $[\alpha]_D$ −6.29° (*c* = 1, MeOH); negative ion fabms *m/z* $[M]^-$ 663 (100%), $[M-132]^-$ 531 (50%); ^1H nmr (CD_3OD) δ (aglycone) 0.95 (3H, d, *J* = 6.5 Hz, H_3-26 or H_3-27), 0.97 (3H, d, *J* = 6.5 Hz, H_3-27 or H-26), 0.98 (3H, d, *J* = 6.5 Hz, H_3-21), 1.02 (3H, s, H_3-19), 1.29 (3H, s, H_3-18), 2.43 (3H, m, H-16, H-7, and H-4), 3.30 (1H under solvent signal, H-24), 3.73 (1H, dt, *J* = 3, 10 Hz, H-6β), 4.22 (1H, m, H-3α), 4.44 (1H, m, H-15α); δ (sugar) 3.17 (1H, dd, *J* = 7, 9 Hz, H-2′), 3.20 (1H, dd, *J* = 9, 11 Hz, Hax-5′), 3.35 (1H under solvent signal, H-3′), 3.50 (1H, m, H-4′), 3.86 (1H, dd, *J* = 5, 11 Hz, Heq-5′), 4.27 (1H, d, *J* = 7.0 Hz, H-1′); ^{13}C nmr see Table 1.

Compound **2**.—Pisasteroside D [3-*O*-(β-xylopyranosyl)-5α-cholest-4-ene-3β,6β,8,15α,24-pentaol 24-sulfate] [**2**]: 16 mg; Rt in hplc 19.2 min; [α]D 0° (*c* = 1, MeOH); negative ion fabms *m/z* $[M]^-$ 661 (100%), $[M-132]^-$ 529 (20%); ^{1}H nmr (CD_3OD) δ (aglycone) 0.95 (3H, d, *J* = 6.5 Hz, H_3-26 or H_3-27), 0.96 (3H, d, *J* = 6.5 Hz, H_3-27 or H_3-26), 0.98 (3H, d, *J* = 6.5 Hz, H_3-21), 1.00 (3H, s, H_3-18), 1.38 (3H, s, H_3-19), 2.43 (1H, m, H-16), 2.56 (1H, dd, *J* = 5, 12 Hz, H-7β), 4.14 (1H, q, *J* = 6.5 Hz, H-24), 4.25 (1H, m, H-3α), 4.33 (2H, m, H-15β and H-6α), 5.70 (1H, br s, H-4); δ (sugar) 3.17 (1H, dd, *J* = 7, 9 Hz, H-2′), 3.20 (1H, dd, *J* = 9, 11 Hz, Hax-5′), 3.35 (1H under solvent signal, H-3′), 3.50 (1H, m, H-4′), 3.87 (1H, dd, *J* = 5, 11 Hz, Heq-5′), 4.40 (1H, d, *J* = 7.0 Hz, H-1′); ^{13}C nmr see Table 1.

Compound **3**.—Pisasteroside E [3-*O*-(β-D-xylopyranosyl)-5α-cholest-4-ene-3β,6α,8,15β,24-pentaol 24-sulfate] [**3**]: 5.7 mg, Rt in hplc 14 min; [α]D 0° (*c* = 1, MeOH); negative ion fabms *m/z* $[M]^-$ 661 (100%), $[M-132]^-$ 529 (20%); ^{1}H nmr (CD_3OD) δ (aglycone) 0.96 (3H, d, *J* = 6.5 Hz, H_3-26), 0.97 (3H, d, *J* = 6.5 Hz, H_3-27), 0.98 (3H, d, *J* = 6.5 Hz, H_3-21), 1.21 (3H, s, H_3-19), 1.31 (3H, s, H_3-18), 2.43 (2H, m, H-7β, H-16), 4.14 (1H, q, *J* = 6.5 Hz, H-24), 4.27 (1H, m, H-3α), 4.44 (1H, m, H-15α), 4.60 (1H, br dd, *J* = 12.5, 5 Hz, H-6β), 5.82 (1H, br s, H-4); δ (sugar) 3.17 (1H, dd, *J* = 7, 9 Hz, H-2′), 3.20 (1H, dd, *J* = 9, 11 Hz, Hax-5′), 3.35 (1H under solvent signal, H-3′), 3.50 (1H, m, H-4′), 3.87 (1H, dd, *J* = 5, 11 Hz, Heq-5′), 4.43 (1H, d, *J* = 7.0 Hz, H-1′); ^{13}C nmr see Table 1.

Compound **4**.—Pisasteroside F [(24*R*)-29-*O*-(β-D-glucopyranosyl-6′-sulfate)-24-ethyl-5α-cholesta-3β,6α,8,15β,16β,29-hexaol] [**4**]: 7 mg; Rt in hplc 15.2 min; [α]D + 10° (*c* = 1, MeOH); negative ion fabms *m/z* $[M]^-$ 737 (100%); ^{1}H nmr (CD_3OD) δ (aglycone) 0.88 (3H, d, *J* = 6.5 Hz, H_3-26 or H_3-27), 0.91 (3H, d, *J* = 6.5 Hz, H_3-27 or H_3-26), 0.98 (3H, d, *J* = 6.5 Hz, H_3-21), 1.02 (3H, s, H_3-19), 1.28 (3H, s, H_3-18), 1.95 (1H, m, H-20), 2.24 (2H, m, H-4), 2.43 (1H, dd, *J* = 5, 12.5 Hz, H-7β), 3.50 (1H, m, H-3α), 3.75 (1H, dt, *J* = 5, 10.5 Hz, H-6β), 4.27 (1H, t, *J* = 6.5 Hz, H-16α), 4.43 (1H, dd, *J* = 5.6, 6.7 Hz, H-15α); δ (sugar) 3.20 (1H, dd, *J* = 7, 9 Hz, H-2′), 3.48 (2H, m, H-4′ and H-5′), 4.18 (1H, dd, *J* = 5, 12 Hz, H-6′), 4.29 (1H, d, *J* = 7 Hz, H-1′), 4.35 (1H, dd, *J* = 2.5, 12 Hz, H-6′); ^{13}C nmr see Table 1.

SOLVOLYSIS OF SULFATED COMPOUNDS **1**–**4**.—A solution of each of the above compounds (from 2 to 4 mg) in dioxane (0.25 ml) and pyrioline (0.25 ml) was heated at 130° for 2 h in a stoppered reaction vial. After the solution had cooled, H_2O (1 ml) was added and the solution was extracted with *n*-BuOH (3 × 0.5 ml). The combined extracts were washed with H_2O and evaporated to dryness under reduced pressure. The residues were submitted to fabms and 250 MHz ^{1}H-nmr (CD_3OD) measurements, without purification. Spectral data for desulfated compounds are given below.

Compound **1a**.—Negative ion fabms *m/z* $[M-H]^-$ 583 (100%), $[M-H-132]^-$ 451 (40%); ^{1}H nmr δ (aglycone) 0.95 (3H, d, *J* = 6.5 Hz, H_3-26 or H_3-27), 0.97 (3H, d, *J* = 6.5 Hz, H_3-27 or H_3-26), 0.98 (3H, d, *J* = 6.5 Hz, H_3-21), 1.02 (3H, s, H_3-19), 1.29 (3H, s, H_3-18), 2.22 (1H, m, H-4), 2.41 (1H, m, H-16β), 2.43 (1H, dd, *J* = 12, 5 Hz, H-7β), 3.50 (1H, m, H-3α), 3.73 (1H, dt, *J* = 5, 10 Hz, H-6β), 4.44 (1H, m, H-15α); δ (sugar) signals virtually identical with those of **1**.

Compound **2a**.—Negative ion fabms *m/z* $[M-H]^-$ 581 (100%), $[M-H-132]^-$ 449 (40%); ^{1}H nmr δ (aglycone) 0.92 (3H, *J* = 6.5 Hz, H_3-26 or H_3-27), 0.94 (3H, *J* = 6.5 Hz, H_3-27 or H_3-26), 0.95 (3H, d, *J* = 6.5 Hz, H_3-21), 1.01 (3H, s, H_3-18), 1.39 (3H, s, H_3-19), 2.43 (1H, m, H-16), 2.56 (1H, dd, *J* = 2.5, 12 Hz, H-7β), 3.24 (1H, m, H-24), 4.24 (1H, m, H-3α), 4.30 (1H, td, *J* = 3, 10 Hz, H-15β), 4.34 (1H, t, *J* = 2 Hz, H-6α), 5.71 (1H, br s, H-4); δ (sugar) signals virtually identical with those of **2**.

Compound **3a**.—Negative ion fabms *m/z* $[M-H]^-$ 581 (100%), $[M-H-132]^-$ 449 (40%); ^{1}H nmr δ (aglycone) 0.92 (3H, d, *J* = 6.5 Hz, H_3-26 or H_3-27), 0.94 (3H, d, *J* = 6.5 Hz, H_3-27 or H_3-26), 0.98 (3H, d, *J* = 6.5 Hz, H_3-21), 1.20 (3H, s, H_3-19), 1.30 (3H, s, H_3-18), 2.45 (2H, m, H-7β and H-16β), 3.24 (1H, m, H-24), 4.27 (1H, m, H-3α), 4.43 (1H, m, H-15α), 4.60 (1H, br dd, *J* = 12.5, 5 Hz, H-6β), 5.82 (1H, br s, H-4); δ (sugar) signals virtually identical with those of **3**.

Compound **4a**.—Negative ion fabms *m/z* $[M-H]^-$ 657 (100%), $[M-H-162]^-$ 495 (40%); ^{1}H nmr δ (aglycone) signals virtually identical with those of **4**: δ (sugar) 3.20 (1H, dd, *J* = 7, 9 Hz, H-2′), 3.48 (1H, t, *J* = 9 Hz, H-4′), 3.50 (1H, ddd, *J* = 2.5, 5, 9 Hz, H-5′), 3.71 (1H, dd, *J* = 2.5, 12 Hz, H-6′), 3.90 (1H, dd, *J* = 5, 12 Hz, H-6′), 4.30 (1H, d, *J* = 7 Hz, H-1′).

METHANOLYSIS AND SUGAR ANALYSIS.—A solution of each glycoside (1 mg) in anhydrous 2 M HCl was heated at 80° in a stoppered reaction vial for 8 h. After being cooled the reaction mixture was neutralized with Ag_2CO_3 and centrifuged, and the supernatant was evaporated to dryness under N_2. The residue was dissolved in TRISIL Z [0.1 ml, *N*-(-trimethylsilyl)-imidazole in pyridine, Pierce Chemical,], left at room temperature for 15 min, and analyzed by glc (140°, SE-30, 25 m).

Glc peaks in the silylated hydrolysate coeluted with those in silylated standards (methylxylosides and methylglucosides).

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