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NEW NORCUCURBITACIN AND HEPTANORCUCURBITACIN GLUCOSIDES FROM *FEVILLEA TRILOBATA*

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ABSTRACT.—From the MeOH extract of the seeds of *Fevillea trilobata* (Cucurbitaceae) were isolated fevicordin A glucoside [**1**], cayaponoside B [**2**], cayaponoside D [**3**], a new norcucurbitacin glucoside, and a new heptanorcucurbitacin glucoside. The structure of the new norcucurbitacin glucoside, andirobicin A glucoside, was established as 29-nor-1,2,3,4,5,10-dehydro-25-methoxy-2-*O*-β-D-glucopyranosyl-3,16α,20*R*,22ξ-tetrahydroxy-11-oxocucurbit-23-ene [**4**], and that of the novel heptanorcucurbitacin glucoside, andirobicin B glucoside, as 22,23,24,25,26,27,29-heptanor-1,2,3,4,5,10-dehydro-2-*O*-β-D-glucopyranosyl-3,16α-dihydroxycucurbita-11,20-dione [**5**].

Fevillea trilobata L. (Cucurbitaceae), known in Brazil mainly as andiroba, nhandiroba, or gendiroba, is a climbing plant growing in most parts of Brazil and in other countries in northern South America. A tea prepared from its seeds has been used in folk medicine against fever and also as an emetic, and the seed oil has been used for illumination and also topically in some skin diseases and against snake bites (1). A preliminary bioassay of the seed oil has shown antimicrobial activity (2). In the only chemical study reported (3), the seeds of *F. trilobata* were found to contain unsaturated conjugated acids similar to the seed oils of other *Fevillea* species (4). In the present study we have investigated a MeOH extract of the seeds of *F. trilobata* which led to the isolation of fevicordin A glucoside [**1**], cayaponoside B [**2**], cayaponoside D [**3**], the glucoside **4** of a new norcucurbitacin which we have named as andirobicin A, and the glucoside **5** of a new heptanorcucurbitacin, andirobicin B. This paper deals with the structure elucidation of these compounds.

RESULTS AND DISCUSSION

The hot MeOH extract of the seeds of *F. trilobata* was partitioned between hexane and 80% aqueous MeOH. H_2O was added to the latter fraction to dilute it to 60% aqueous MeOH, and this fraction was extracted with $CHCl_3$. The $CHCl_3$ fraction was further fractionated by Si gel cc and reversed-phase hplc to give five pure compounds.

Compound **1** had a molecular formula $C_{37}H_{52}O_{13}$, as determined by hrfabms. Its ^1H- and ^{13}C-nmr spectra indicated the presence of a pentasubstituted aromatic ring (methine δ_C 113.24, δ_H 6.66s, 1H; quaternary carbons δ_C 124.85, 129.90, 131.25, 144.70, 144.80), eight quaternary methyl groups [δ_H 0.89 s, 0.99 s, 1.29 s, 1.36 s, 1.56 s (2H), 1.97 s and 2.07 s], a disubstituted double bond [coupling constants (Hz) are cited in parentheses] [δ_H 6.79 d, 1H (15.9) and 6.96 d, 1H (15.9)], three carbonyl carbons (δ_C 171.87, 205.38, and 217.19), and a sugar moiety [δ_H 4.56 d, 1H (7.6); 3.83 dd, 1H

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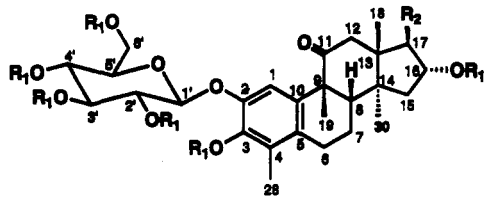
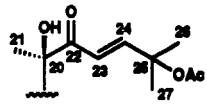
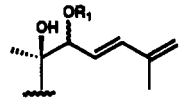
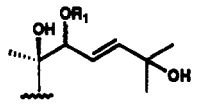
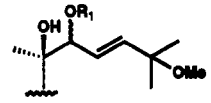


Compound	R_1	R_2
1	H	
2	H	
3	H	
7	Ac	
4	H	
8	Ac	
5	H	

(11.0, 4.0); 3.96 dd, 1H (11.0, 2.3)], suggesting a norcucurbitacin glucoside structure (5–7). Complete nmr spectral analysis, including COSY and HETCOR spectral correlations, while allowing the complete assignment of its ^{1}H- and ^{13}C-nmr spectra (Table 1), permitted the identification of **1** as fevicordin A glucoside (H. Achenbach, personal communication), a compound previously isolated from *Fevillea cordifolia* (5).

Compound **2** had a molecular formula $C_{35}H_{50}O_{11}$ as determined by hrfabms. The ^{1}H- and ^{13}C-nmr spectra of **2** showed signals characteristic of a norcucurbitacin skeleton with a β-D-glucose moiety attached, and both spectra had chemical shifts essentially identical to those of compound **1** for carbons and protons of the ring system and of the β-D-glucose moiety. The spectra differed only in respect to the side chain at C-17, with those for **2** showing the presence of four olefinic protons [δ 5.79 dd (15.9, 5.8), 1H; 6.34 d (15.9, 1.2), 1H; 4.94 s, 2H], one vinyl methyl singlet at δ 1.82, only one quaternary methyl group, and a methine at δ_C 81.39, δ_H 4.08 dd, 1H (5.8, 1.2). The multiplicity [dd (15.9, 5.8)] of the olefinic proton at δ 5.79 suggested that it must be coupled with another proton besides that at δ 6.34 d (15.9, 1.2), and the COSY spectrum indicated this to be the proton at δ 4.08 dd (5.8, 1.2), suggesting the presence of an allylic hydroxy group. Complete analysis of the ^{1}H- and ^{13}C-nmr spectra with the aid of COSY, HETCOR, and COLOC techniques suggested the identity of **2** with cayaponoside B, a norcucurbitacin glucoside recently encountered in *Cayaponia tayuya* (7). Enzymatic hydrolysis of **2** with cellulase afforded the aglycone. The structure **6** proposed for this aglycone was based on its ^{1}H- and ^{13}C-nmr spectral data and the ms fragmentations (Figure 1).

TABLE 1. ^{13}C- (100.57 MHz) and ^{1}H- (400 MHz) nmr Data of Compounds **1**, **4**, and **5**.[a]

Position	δC			δH		
	1	**4**	**5**	**1**	**4**	**5**
1	113.24	113.30	113.34	6.66 s	6.63 s	6.66 s
2	144.70[b]	144.80	144.78[b]			
3	144.80[b]	144.80	145.01[b]			
4	124.85	124.90	124.98			
5	131.25	131.20	131.22			
6β	24.80	24.83	24.72	2.58–2.69 m	2.55–2.70 m	2.60–2.72 m
α				2.77–2.94 m	2.79–2.92 m	2.70–2.92 m
7β	20.09	20.23	20.32	1.90–1.97 m	1.90–1.94 m	1.92–2.05 m
α				2.19–2.35 m	2.17–2.34 m	2.12–2.36 m
8	44.15	43.96	44.25	2.11 bd (6.8)	2.15 bd (6.0)	2.01–2.05[g]
9	52.19	51.94[b]	52.47			
10	129.90	129.98	129.71			
11	217.19	217.22	215.31			
12β	51.80	52.11	50.12	2.61 d (13.9)	2.58 d (13.9)	2.48 d (14.0)
α				2.87 d (13.9)	2.75 d[g]	2.99 dd (14.0, 0.8)
13	s.o.[f]	51.91[b]	50.47[c]			
14	51.30	51.91[b]	50.99[c]			
15β	46.35	45.51	45.87	1.49 d[g]	1.59 d (13.6)	1.59 d (13.4)
α				1.90–1.97 m	1.90–1.94 m	1.90–2.07 m
16	71.80	72.20	72.39	4.53 bt (7.6)	4.62 bt (7.5)	4.84–4.88[h]
17	60.45	56.78	68.13	2.48 d (6.8)	2.34 d (6.7)	3.17 d (6.7)
18	20.06[c]	19.83[c]	20.05	0.89 s	0.97[b] s	0.68 s
19	29.22	29.14	29.11	1.29 s	1.30 s	1.31 s
20	80.24[d]	76.99	210.77			
21	25.50	23.74	31.73	1.36 s	1.20 s	2.04 s
22	205.38	81.17			4.01 d (4.4)	
23	122.61	130.0		6.79 d (15.9)	5.75 dd (15.6, 4.7)	
24	151.58	138.04		6.96 d (15.9)	5.67 (15.6)	
25	81.04[d]	76.40				
26	26.74[e]	26.11[d]		1.52 s	1.24 s	
27	26.60[e]	26.58[d]		1.52 s	1.24 s	
28	11.50	11.50	11.48	2.07 s	2.09 s	2.09 s
30	20.67[c]	20.20[c]	20.05	0.99 s	0.99[b] s	1.03 s
1′	105.17	105.17	105.21	4.56 d (7.5)	4.53 d (7.2)	4.58 d (7.5)
2′	74.78	74.80	74.82	3.39–3.54 m	3.40–3.54 m	3.43–3.56 m
3′	77.70	77.71	77.74	3.39–3.54 m	3.40–3.54 m	3.43–3.56 m
4′	70.85	70.80	70.87	3.39–3.54 m	3.40–3.54 m	3.43–3.56 m
5′	78.09	78.15	78.17	3.29–3.34 m[h]	3.26–3.36[h]	3.34–3.36[h]
6′	62.05	62.02	62.02	3.83 dd (11.0, 4.0)	3.78–3.87 m	3.84 dd (12.6, 4.1)
				3.96 dd (11.0, 2.3)	3.90–3.98 m	3.97 dd (12.5, 2.4)
OMe		50.81			3.23 s	
OCOMe	171.87					
$OCOCH_3$	21.87					

[a]Coupling constants (Hz) in parentheses; spectra recorded in CD_3OD.
[b–e]Signals interchangeable in the same column.
[f]Signal totally obscured by solvent signal.
[h]Signal partially obscured by a solvent signal.
[g]Signal partially obscured by other signals.

Compounds **3** and **4** had molecular formulae $C_{35}H_{52}O_{12}$ and $C_{36}H_{54}O_{12}$, respectively, as determined by their hrfabms. Their ^{1}H- and ^{13}C-nmr spectra showed the same characteristic signals of a norcucurbitacin glucoside skeleton as for compounds **1** and **2**. Other similarities were also observed. For example, signals for two olefinic protons [**3** δ 5.67 d (15.6), 5.75 dd (15.6, 4.7); **4** δ 5.69 dd (15.7, 5.2), 5.77 d (15.8)] similar to the olefinic pattern of compound **2**, suggested the presence of an allylic hydroxy system in compounds **3** and **4** at C-22, -23, and -24. This was confirmed by COSY correlations and by analysis of ^{1}H-nmr and COSY spectra of the acetylated derivatives **7** and **8**, which

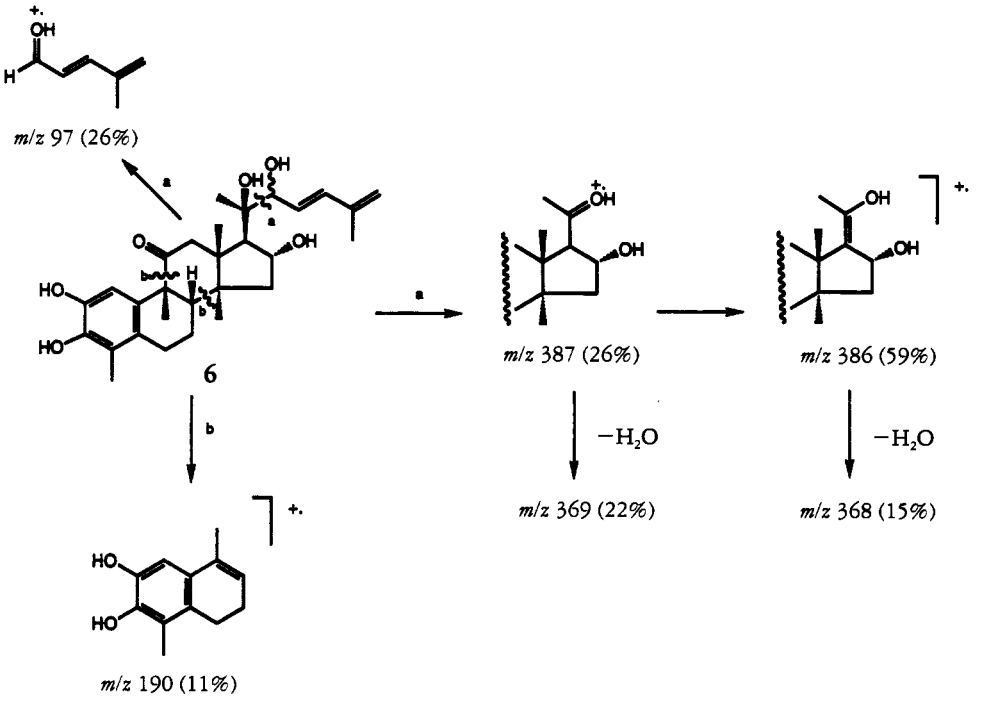


FIGURE 1. Ms fragmentation of **6**.

showed a downfield shift of the proton coupled with the olefinic proton. The ^{1}H- and ^{13}C-nmr spectra of compound **3** also showed the presence of an MeO group at δ_H 3.23 (3H) and δ_C 50.81, suggesting that this was attached to a quaternary carbon (8). Analysis of the chemical shifts of the two oxygenated quaternary carbons in compounds **3**, **4**, **7**, and **8** and comparison with some cucurbitacin models from the literature (9) permitted the identification of compound **3** as cayaponoside D, also recently isolated from *C. tayuya* (7), and established the structure of compound **4** as the new norcucurbitacin glucoside 29-nor-1,2,3,4,5,10-dehydro-25-methoxy-2-*O*-β-D-glucopyranosyl-3,16α,20*R*,22ξ-tetrahydroxy-11-oxocucurbit-23-ene.

Compound **5** had a molecular formula $C_{29}H_{40}O_{10}$ as determined by hrfabms. Its ^{1}H-nmr and ^{13}C-nmr spectra were again very similar to the spectra of compounds **1–4** for the basic ring system (excluding C-17) and the β-D-glucose moiety. The major difference between the spectra of **5** and those of **1–4** was that the spectra of **5** contained signals for only two additional carbons: a carbonyl group at δ 210.77 and a methyl group at δ_C 31.73 and δ_H 2.04 (correlated by HMQC). In addition, the signal for C-17 was shifted downfield to δ 68.13. These data indicated the compound **5** lacks the normal side chain, presumably due to a biogenetic oxidative cleavage of the C-20, C-22 bond. Comparison of the nmr data of ring D and C-20 and C-21 of compound **5** with those of hexanorcucurbitacins from the literature (9–11) confirmed the structure of **5** as 22,23,24,25,26,27,29-heptanor-1,2,3,4,5,10-dehydro-2-*O*-β-D-glucopyranosyl-3,16α-dihydroxycucurbita-11,20-dione, the first heptanorcucurbitacin, to our knowledge, so far described in the literature.

Several attempts were made at establishing the stereochemistry of the OH group at C-22 in compounds **2–4**, both by chemical transformation and by nmr analysis. Regrettably these efforts did not prove fruitful due to decomposition of the compounds on attempted chemical transformation and to ambiguities in the nmr analyses. We were

unable to obtain suitable crystals for X-ray analysis, and efforts to determine the stereochemistry at C-22 by chemical methods are thus continuing. The chemical composition of the aqueous MeOH fraction from the liquid-liquid partition is also being investigated.

Since several cucurbitacins are known to have cytotoxic and antitumor activity (12), compounds **1**, **2**, and **4** were tested against DNA repair deficient mutants of *Saccharomyces cerevisieae* (13) and for cytotoxicity against Vero cells, but showed either no or only very weak activity.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv spectra were taken in MeOH on a Beckman DU-50 spectrophotometer. Optical rotations were obtained in MeOH on a Perkin-Elmer Model 241 polarimeter. The nmr spectra (δ ppm, *J* in Hz) were obtained on a Varian Unity 400 spectrometer (400 MHz) using CD_3OD for compounds **1–5** and $CDCl_3$ for compounds **7** and **8** [TMS or solvent (CD_3OD) as internal standard]. Cc employed Si gel 60 (230–400 mesh). Tlc and preparative tlc analyses were performed by using precoated Si gel 60 F_{254} and Si gel GF 1000 μm plates, respectively, and detection was accomplished by uv_{254} irradiation and by spraying with 25% anisaldehyde in alcoholic H_2SO_4/HOAc followed by heating. Hplc separations were carried out on a Waters Nova-Pak C_{18} Cartridge column using MeOH/H_2O mixtures with a Waters 990 Series photodiode array detector at 230 nm.

PLANT MATERIAL.—Seeds of *F. trilobata* were obtained in Caruaru, Pernambuco, Brazil, in September 1990; a voucher specimen is deposited at the Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, R.J. Brazil. The kernels were separated manually from the shells and then ground.

EXTRACTION AND ISOLATION.—The ground kernel (2180 g) was extracted using a Soxhlet apparatus with hexane (yielding 1310 g of oil) and then MeOH (yielding 229 g of extract). Part of the MeOH extract (118.5 g) was partitioned between hexane and 80% aqueous MeOH, H_2O was added to give 60% aqueous MeOH, and this fraction was extracted thoroughly with $CHCl_3$ to yield 6.50 g of a $CHCl_3$ fraction and 97.3 g of an MeOH fraction. Part of the $CHCl_3$ fraction (3.82 g) was subjected to flash chromatography on a Si gel column [$CHCl_3$-MeOH (4:1) to MeOH] yielding 37 fractions. Fractions 18 (155.0 mg), 22 (184.6 mg) 27–28 (58.0 mg), and 33–37 (567.6 mg), which contained the major compounds (monitored by tlc), were further purified by hplc. Compound **1** (152.0 mg) was obtained from fraction 18 [MeOH-H_2O (60:40)], compound **2** (181.0 mg) from fraction 22 [MeOH-H_2O (60:40)], compound **3** (8.7 mg) and **5** (5.8 mg) from fractions 27–28 [MeOH-H_2O (55:45)], and compound **4** (556.0 mg) from fractions 33–37 [MeOH-H_2O (60:40)].

Fevicordin A glucoside [**1**].—White amorphous powder: uv λ max (MeOH) nm (log ε) 220 (4.24), 284 (3.36); $[\alpha]_D$ −19° (*c*=3.2); ^1H and ^{13}C nmr see Table 1; hrfabms *m/z* $[M+Na]^+$ 727.3303 ($C_{37}H_{52}O_{13}Na$ requires 727.3306).

Cayaponoside B [**2**].—Chromatographically homogeneous material was further purified by precipitation from MeOH (freezer) to yield a white amorphous powder: uv λ max (MeOH) nm (log ε) 231 (4.32), 284 (3.35); $[\alpha]_D$ −9° (*c*=1.1); ^1H nmr (*interchangeable signals) δ 0.99* (s, H_3-18), 1.00* (s, H_3-30), 1.19 (s, H_3-21), 1.30 (s, H_3-19), 1.82 (s, H_3-27), 2.09 (s, H_3-28), 2.14 (bd, *J*=7.1 Hz, H-8), 2.35 (d, *J*=6.7 Hz, H-17), 3.29–3.34 (m, H-5′); 3.41–3.54 (m, H-2′, -3′, -4′); 3.83 (dd, *J*=12.2, 4.1 Hz, H_a-6′), 3.94 (dd, *J*=12.2, 2.2 Hz, H_b-6′), 4.08 (dd, *J*=5.8, 1.2 Hz, H-22), 4.56 (d, *J*=7.5, H-1′), 4.62 (bt, *J*=7.5, H-16), 4.94 (s, H_2-26), 5.79 (dd, *J*=15.9, 5.8 Hz, H-23), 6.34 (d, *J*=15.9, 1.2 Hz, H-24), 6.65 (s, H-1); ^{13}C nmr δ 11.55 (C-28), 18.80 (C-27), 52.09 (C-12), 61.96 (C-6′), 70.76 (C-4′), 72.11 (C-16), 74.70 (C-2′), 77.11 (C-20), 77.58 (C-3′), 78.01 (C-5′), 81.39 (C-22), 105.03 (C-1′), 113.17 (C-1), 116.77 (C-26), 124.83 (C-23), 131.22 (C-5), 135.67 (C-24), 217.29 (C-11); hrfabms *m/z* $[M+Na]^+$ 669.3230 ($C_{35}H_{50}O_{11}Na$ requires 669.3251).

ENZYMATIC HYDROLYSIS OF **2**.—The glucoside **2** (12.5 mg) in MeOH (0.5 ml) was added to a solution of cellulase (70 mg) in H_2O (2 ml), and the mixture was incubated with shaking at 37° under an inert atmosphere for 84 h. After evaporation of MeOH, the solution was extracted with EtOAc, dried (Na_2SO_4), and evaporated. The residue was purified on a Si gel column [$CHCl_3$-MeOH (10:1)] to yielded **6** (4.6 mg): ^1H nmr (*interchangeable signals) δ 0.98* (s, H_3-18), 0.99* (s, H_3-30), 1.17 (s, H_3-21), 1.28 (s, H_3-19), 1.81 (s, H_3-27), 2.05 (s, H_3-28), 2.11 (bd, *J*=7.0 Hz, H-8), 4.08 (dd, *J*=5.7, 1.0 Hz, H-22), 4.93 (bs, H_2-26), 6.19 (s, H-1); ^{13}C nmr δ 11.52 (C-28), 18.79 (C-27), 44.08 (C-8), 45.67 (C-15), 52.12 (C-12), 72.20 (C-16), 77.21 (C-20), 81.23 (C-22), 110.26 (C-1), 116.69 (C-26), 126.91 (C-5), 129.48 (C-23), 135.63 (C-24),

142.98 (C-25), 143.00, 143.92 (C-3, -4); eims *m/z* (rel. int.) $[M-3H_2O]^+$ 430 (11), 387 (26), 386 (59), 369 (22), 368 (15), 351 (15), 190 (11), 189 (11), 97 (26), 57 (100).

Cayaponoside D [**3**].—White amorphous powder: uv λ max (MeOH) nm (log ε) 207 (4.61), 284 (3.64); $[\alpha]_D$ −17° (*c*=1.7); ^{1}H nmr (*interchangeable signals) δ 0.94* (s, H_3-18), 0.95* (s, H_3-30), 1.16 (s, H_3-21), 1.20 (s, H_3-26, H_3-27), 1.25 (s, H_3-20), 2.04 (s, H_3-28), 2.10 (d, *J*=7.0 Hz, H-8), 3.22–3.29 (m, H-5′), 3.34–3.49 (m, H-2′, -3′, -4′); 3.77 (dd, *J*=12.3, 4.1 Hz, H_a-6′), 3.89 (dd, *J*=12.2, 2.4 Hz, H_b-6′), 3.91 (bd, *J*=5.2 Hz, H-22), 4.57 (bt, *J*=7.4 Hz, H-16), 5.69 (dd, *J*=15.7, 5.2 Hz, H-23), 5.71 (d, *J*=15.8 Hz, H-24); ^{13}C nmr δ 11.50 (C-28), 52.07 (C-12), 62.01 (C-6′), 70.83 (C-4′), 71.23 (C-25), 72.21 (C-16), 74.78 (C-2′), 77.68 (C-3′), 78.13 (C-5′), 81.76 (C-22), 105.11 (C-1′), 113.21 (C-1), 126.17 (C-23), 141.48 (C-24), 217.49 (C-11); hrfabms *m/z* $[M+Na]^+$ 687.3356 ($C_{35}H_{52}O_{12}$ requires 687.3359).

ACETYLATION OF **3**.—Compound **3** (6.1 mg) was stirred with Ac_2O/pyridine overnight at room temperature. Purification of the crude product by Si gel cc [$CHCl_3$-MeOH (12:1)] under inert atmosphere yielded compound **7** (3.0 mg): ^{1}H nmr δ 2.61 (bd, *J*=6.1 Hz, H-17), 3.84–3.92 (m, H-5′), 4.24 (dd, *J*=10.0, 2.0 Hz, H_a-6′), 4.34 (dd, *J*=10.5, 4.6 Hz, H_b-6′), 4.81 (d, *J*=7.2, Hz, H-22), 4.93 (d, *J*=7.2 Hz, H-1′), 5.48 (bt, *J*=7.3 Hz, H-16), 5.62 (dd, *J*=15.3, 7.3 Hz, H-23), 5.90 (d, *J*=15.7 Hz, H-24); ^{13}C nmr δ 43.76 (C-15), 52.57 (C-17), 61.74 (C-6′), 67.98 (C-4′), 70.42 (C-2′), 72.17 (C-5′), 72.72 (C-3′), 74.36 (C-20), 74.61 (C-16), 98.43 (C-1′), 120.02 (C-23), 136.81 (C-3), 145.43 (C-24), 146.15 (C-2), 214.16 (C-11).

Andirobicin A glucoside [**4**].—White amorphous powder: uv λ (MeOH) nm (log ε) 208 (3.74), 285 (3.21); $[\alpha]_D$ −9° (*c*=4.0); ^{1}H and ^{13}C nmr see Table 1; hrfabms *m/z* $[M+Na]^+$ 701.3522 ($C_{36}H_{54}O_{12}Na$ requires 701.3513).

ACETYLATION OF **4**.—A mixture (15.4 mg) containing about 50% of compound **4**, as judged by hplc, was acetylated under the same conditions described for compound **3**. Purification by preparative tlc [hexane-EtOAc (1:3)] yielded compound **8** (8.0 mg): ^{1}H nmr δ 3.24 (s, OMe), 3.89 (ddd, *J*=9.3, 4.5, 2.1 Hz, H-5′), 4.27 (dd, *J*=12.3, 2.0 Hz, H_a-6′), 4.33 (dd, *J*=12.2, 4.7 Hz, H_b-6′), 4.83 (bd, *J*=6.3 Hz, H-22), 4.93 (d, *J*=7.3 Hz, H-1′), 5.12–5.18 (m, H-4′), 5.24–5.33 (m, H-2′ and -3′), 5.48 (t, *J*=7.2 Hz, H-16); ^{13}C nmr (*interchangeable signals) δ 43.77 (C-15), 50.57 (OMe), 52.58 (C-17), 61.73 (C-6′), 67.99 (C-4′), 70.40, C-2′), 72.18 (C-5′), 72.72 (C-3′), 74.42 (C-25), 74.60* (C-22), 74.62* (C-16), 98.40 (C-1′), 109.00 (C-1), 122.80 (C-23), 129.10 (C-4), 136.80 (C-3), 142.86 (C-24), 146.16 (C-2), 214.13 (C-11).

Andirobicin B glucoside [**5**].—White amorphous powder: uv λ max (MeOH) nm (log ε) 209 (4.37), 285 (3.50); $[\alpha]_D$ +31° (*c*=1.7); ^{1}H and ^{13}C nmr see Table 1; hrfabms *m/z* $[M+Na]^+$ 571.2529 ($C_{29}H_{40}O_{10}Na$ requires 571.2519).

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