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ACETOGENINS FROM THE BARK OF *UVARIA PAUCI-OVULATA**

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Key Word Index—*Uvaria pauci-ovulata*; Annonaceae; bark; cytotoxicity; acetogenins; espelicin; uvariasolins I and II; narumicins I and II; panalicin; squamocin.

Abstract—Three new 5-hydroxy acetogenins, espelicin and uvariasolins I and II, were isolated from extract of bark of *Uvaria pauci-ovulata*, in addition to the known acetogenins narumicins I and II (separated here for the first time), panalicin and squamocin. © 1997 Elsevier Science Ltd

INTRODUCTION

Uvaria pauci-ovulata Hook. is a liana with simple and alternate leaves which grows in Malaysia [1]. Annonaceae are commonly used in traditional medicine for various purposes. In recent years, many acetogenins have been isolated from this family. This interest in acetogenins is based on their potential cytotoxic, antitumour or pesticidal activities [2]. As cytotoxic activity had been observed with a bark extract of title plant [unpublished work], a systematic investigation of the chemical content of the plant has been undertaken. This has resulted in the isolation of seven acetogenins. Three of them are new: espelicin (**1**), uvariasolin I (**2**) and uvariasolin II (**3**). The four others, narumicin I (**4**), narumicin II (**5**), panalicin (**6**) and squamocin (**7**) are known acetogenins, but, previously, narumicins I and II had only been obtained as an equimolecular mixture of two diasteroisomers [3]. Products **1** to **6** are hydroxylated at C-5, which seems to be a feature of acetogenins from *Uvaria* species [3–6]. In addition to the acetogenins, two other known compounds were isolated, i.e. benzyl benzoate and taraxerol.

RESULTS AND DISCUSSION

An ethanolic extract of the bark of *U. pauci-ovulata* was partitioned between H_2O and CH_2Cl_2 in slightly acid conditions to prevent opening of lactone rings and eliminate alkaloïdal constituents; the CH_2Cl_2 extract was subjected to chromatographic purification on silica gel columns. Acetogenins **1**–**7** were separated by repeated chromatography and purified by semi-preparative HPLC.

Espelicin (**1**) was assigned the molecular formula $C_{37}H_{66}O_8$ (FAB-Li MS m/z = 645 $[M+Li]^+$). The ^1H and ^{13}C NMR spectra (Tables 1 and 2) showed, in agreement with a positive Kedde reaction, characteristic signals of a γ-methyl α,β-unsaturated γ-lactone moiety: δ_H 7.03 (H-35), 5.00 (H-36), 2.39 (H-3) and 1.40 (H-37) and δ_c 177.1 (C-1), 149.5 (C-35), 133.0 (C-2), 77.5 (C-36) and 19.1 (C-37). The chemical shifts of H-35, H-3 and H-4 (δ 1.70) suggested the presence of a hydroxyl group in position 5 [7], in accord with a correlation, in the HMQC spectrum, between a carbon at δ 70.8 (C-5) and a proton at δ 3.59 (H-5). The NMR spectra of **1** exhibited other typical signals of an acetogenin [2] with an adjacent bis-THF moiety (type B: four carbons between δ 81 and 83 and five protons between δ 3.83 and 3.94), a long aliphatic chain and three other hydroxyl groups (three carbons at δ 74.0, 71.3 and 71.8 correlated with proton signals at δ 3.39, 3.87 and 3.59, respectively).

The NMR spectra of **1** were very close to those of panalicin (**6**) [4], except the chemical shift of the terminal methyl group (δ 0.87 for **6** and 0.90 for **1**), which indicated a different position of a hydroxyl group on the aliphatic chain [8].

The location of the hydroxyl groups was established by MS/MS, due to remote charge fragmentations (RCF) of aliphatic chain. Collision induced dissociation (CID) of the $[M+Li]^+$ ion showed two fragments series (Fig. 1), respectively, starting from the

* Part 54 in the series Acetogenins of Annonaceae. For part 53, see Duret, P., Waechter, A. I., Figadère, B., Hocquemiller, R., Cavé A., Piérard, C. and Pérès, M., *Tetrahedron Letters*, 1996, **37**, 7043.

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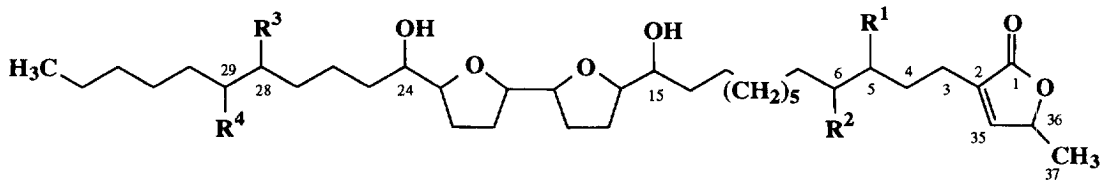

	R1	R2	R3	R4	Relative stereochemistry
1	OH	H	H	OH	*threo/trans/threo/trans/erythro*
2	OH	OH	H	H	*threo/trans/threo/trans/threo*
3	OH	OH	H	H	*threo/trans/threo/trans/erythro*
4	OH	H	H	H	*threo/trans/threo/trans/threo*
5	OH	H	H	H	*threo/trans/threo/trans/erythro*
6	OH	H	OH	H	*threo/trans/threo/trans/erythro*
7	H	H	OH	H	*threo/trans/threo/trans/erythro*

Table 1. ^{1}H NMR data of compounds **1**–**5** (400 MHz, $CDCl_2$)

H	1	2	3	4	5
3	2.39 *m*	2.49 *m*	2.44 *m*	2.40 *m*	2.40 *m*
4	1.70 *m*	1.70 *m*	1.71 *m*	1.63 *m*	1.63 *m*
5	3.59 *m*	3.38 *m*	3.40 *m*	3.60 *m*	3.60 *m*
6	1.45 *m*	3.38 *m*	3.40 *m*	1.40 *m*	1.40 *m*
7	1.25 *m*	1.38 *m*	1.39 *m*	1.25 *m*	1.26 *m*
8	1.25 *m*	1.25 *m*	1.27 *m*	1.25 *m*	1.26 *m*
9–13	1.25 *m*	1.25 *m*	1.27 *m*	1.25 *m*	1.26 *m*
14	1.35 *m*	1.35 *m*	1.35 *m*	1.35 *m*	1.35 *m*
15	3.39 *m*	3.38 *m*	3.40 *m*	3.40 *m*	3.39 *m*
16	3.83–3.94 *m*	3.82–3.94 *m*	3.85–3.95 *m*	3.82–3.93 *m*	3.82–3.93 *m*
17–18	1.50–2.00 *m*	1.50–2.00 *m*	1.50–2.00 *m*	1.50–2.00 *m*	1.50–2.00 *m*
19–20	3.83–3.94 *m*	3.82–3.94 *m*	3.85–3.95 *m*	3.82–3.93 *m*	3.82–2.93 *m*
21–22	1.50–2.00 *m*	1.50–2.00 *m*	1.50–2.00 *m*	1.50–2.00 *m*	1.50–2.00 *m*
23	3.83–3.94 *m*	3.82–3.94 *m*	3.85–3.95 *m*	3.82–3.93 *m*	3.82–3.93 *m*
24	3.87 *m*	3.38 *m*	3.85–3.95 *m*	3.40 *m*	3.82–3.93 *m*
25	1.35 *m*	1.25 *m*	1.27 *m*	1.35–1.40 *m*	1.35–1.40 *m*
26	1.35 *m*	1.25 *m*	1.27 *m*	1.26 *m*	1.26 *m*
27	1.35 *m*	1.25 *m*	1.27 *m*	1.26 *m*	1.26 *m*
28	1.35 *m*	1.25 *m*	1.27 *m*	1.26 *m*	1.26 *m*
29	3.59 *m*	1.25 *m*	1.27 *m*	1.26 *m*	1.26 *m*
30	1.35 *m*	1.25 *m*	1.27 *m*	1.26 *m*	1.26 *m*
31–33	1.25 *m*	1.25 *m*	1.27 *m*	1.26 *m*	1.26 *m*
34	0.90 *t* (6.9)	0.87 *t* (6.9)	0.87 *t* (6.8)	0.87 *t* (6.8)	0.87 *t* (6.7)
35	7.03 *d* (1.5)	7.07 *d* (1.4)	7.07 *d* (1.3)	7.03 *d* (1.5)	7.03 *d* (1.5)
36	5.00 *qd* (6.8, 1.5)	5.03 *qd* (6.8, 1.4)	5.02 *qd* (6.8, 1.3)	5.01 *qd* (6.9, 1.5)	5.01 *qd* (6.8, 1.5)
37	1.40 *d* (6.8)	1.41 *d* (6.8)	1.41 *d* (6.8)	1.42 *d* (6.9)	1.42 *d* (6.8)

Table 2. ^{13}C NMR data of compounds **1–5** (50 MHz, $CDCl_3$)

C	1	2	3	4	5
1	177.1	176.9	176.0	176.7	176.9
2	133.0	134.0	134.0	133.9	134.0
3	21.4	21.4	21.4	21.4	21.5
4	35.3	31.9	32.3	35.3	35.3
5	70.8	74.4[a]	74.4[a]	70.8	70.8
6	37.4	73.2[a]	73.2[a]	37.5	37.5
7	25.6	33.4	33.5	25.6	25.6
8–12	29.6	29.3–29.7	29.3–29.6	29.3–29.6	29.3–29.6
13	25.5	25.5	25.5	25.6	25.7
14	33.4	33.4	33.4	33.4	33.3
15	74.0	74.0[a]	74.0	74.0	74.0
16	83.2	83.2	83.2	83.1	83.2
17	28.8[b]	28.9[b]	28.9[b]	28.9[b]	28.9[b]
18	28.3[b]	28.4[b]	28.3[b]	28.3[b]	28.3[b]
19	82.5	81.8	82.5	81.8	82.5
20	82.2	81.8	82.3	81.8	82.3
21	24.6	28.4[b]	28.3[b]	28.3[b]	24.5[b]
22	28.8[b]	28.9[b]	28.9[b]	28.9[b]	28.9[b]
23	82.8	83.2	82.8	83.1	82.8
24	71.3	74.0[a]	71.3	74.0	71.3
25	32.3	31.8	32.3	33.4	32.4
26	22.6	22.7	24.5	25.6	25.6
27	29.6	29.3–29.7	29.3–29.7	29.3–29.7	29.3–29.7
28	37.2	29.3–29.7	29.3–29.7	29.3–29.7	29.3–29.7
29	71.8	29.3–29.7	29.3–29.7	29.3–29.7	29.3–29.7
30	37.4	29.3–29.7	29.3–29.7	29.3–29.7	29.3–29.7
31	26.1	29.3–29.7	29.3–29.7	29.3–29.7	29.3–29.7
32	31.8	31.8	31.9	31.9	31.8
33	22.7	22.7	24.5	22.7	22.7
34	14.1	14.1	14.1	14.1	14.1
35	149.5	149.8	149.6	149.5	149.4
36	77.5	77.1	77.2	77.5	77.5
37	19.1	19.1	19.1	19.1	19.1

[a,b] May be reversed within column.

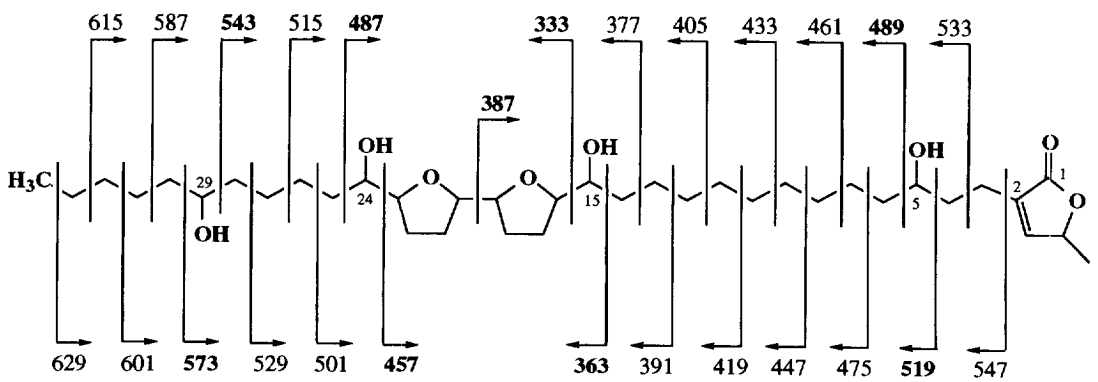

Fig. 1. MS/MS spectrum of the $[M+Li]^+$ ion (*m/z* 645) generated by FAB from **1** (FAB matrix *m*-NBA + LiCl).

terminal methyl side and from the γ-lactone side. Fragments at *m/z* 519 and 489 confirmed the presence of a C-5 hydroxyl, and fragments at *m/z* 363 and 333, 457 and 487, 543 and 573 clearly indicated the position of three other hydroxyl groups at C-15, C-24 and C-29. Peaks at *m/z* 457, 387 and 333 placed the adjacent bis-THF moiety between C-16 and C-23.

The relative configuration in the bis-THF part was assigned as *threo/trans/threo/trans/erythro* by comparison with the literature [9]. Indeed, in the ^{13}C NMR

spectrum of **1**, oxygenated carbons of the α,α′-dihydroxylated adjacent bis-THF moiety appeared as six distinct signals at δ 74.0 (C-15), 83.2 (C-16), 82.5 (C-19), 82.2 (C-20), 82.8 (C-23), 71.3 (C-24) and in the ^{1}H NMR spectrum of **1**, H-15 appeared at δ 3.39 and H-24 at *ca* δ 3.87, together with the oxymethine protons of the THF rings.

The 2D HOHAHA spectrum showed a correlation between H-29 (δ 3.59) and H-24 (δ 3.83–3.94) characteristic of an *erythro* configuration [10]. Consequently, the relative configuration of the bis-THF moiety was determined as *threo/trans/threo/trans/erythro* from C-15 to C-24.

Due to the minute amount isolated, Mosher esters could not be prepared. So the absolute configuration of the carbinolic carbons remains unknown. This new acetogenin only differs from panalicin (**6**), previously isolated from *Uvaria narum* [4], by the position of the sub-terminal OH group at C-29.

Uvariasolins I (**2**) and II (**3**) had very close R_fs on analytical HPLC, but could be separated by semi-prep. HPLC. Uvariasolin I (**2**) showed a $[M+Li]^+$ ion at *m/z* 645 in the FAB-Li mass spectrum corresponding to a molecular formula $C_{37}H_{66}O_8$. The ^{1}H NMR and ^{13}C NMR spectra were characteristic of a tetrahydroxylated acetogenin of type B, sub-type Ia (γ-methyl α,β-unsaturated γ-lactone). The location of the four hydroxyl groups was established by fragmentations of the $[M+Li]^+$ ion of **2** on FABMS. The successive fragment ions at *m/z* 519, 489 and 459 clearly indicated the position of two hydroxyl groups at C-5 and C-6 (Fig. 2).

The ^{1}H and ^{13}C NMR spectra were in agreement with the presence of two vicinal OH groups. The two protons geminated with hydroxyl groups appeared at δ 3.38 which is characteristic of a vicinal diol with a *threo* configuration [11, 12]. Because of the very small amount of **2** isolated, the acetonide derivative could be not prepared. By comparison with the other 5-OH acetogenins [3–6], the olefinic proton of the lactone was slightly deshielded in **2** (δ 7.07 instead of *ca* 7.03). Until now, acetogenins with a vicinal diol at C-5, C-6 had never been reported.

The *pseudo*-symmetric stereochemistry of the adjacent bis-THF moiety (*threo/trans/threo/trans/threo*) was deduced from the observation of only two signals at δ_c 83.2 (C-16, C-23) and 81.8 (C-19, C-20) and a single resonance at δ 74.0 for both C-15 and C-24; in the ^{1}H NMR spectrum, H-15 and H-24 appeared at δ 3.38.

Compound **3** (uvariasolin II), was found to have the same molecular formula, $C_{37}H_{66}O_8$, and a very similar FAB-Li mass spectrum to those of **2**. The NMR spectral data showed that **3** differed from **2** only in the relative stereochemistry of the bis-THF pattern. The ^{13}C NMR spectrum showed six distinct signals for C-15, C-16, C-19, C-20, C-23 and C-24, indicative of a *threo/trans/threo/trans/erythro* relationship for the THF rings and confirmed by signals at δ 3.40 and *ca* 3.90 in the ^{1}H NMR spectrum, corresponding to the vicinal hydroxy methine groups.

Narumicins I (**4**) and II (**5**) are two acetogenins of type B, sub-type Ia. They have been previously isolated from root bark of *Uvaria narum* and described as an equimolecular mixture [3]. In this work, we describe the first separation of these two isomers by semi-preparative HPLC.

The spectral data of **4** were similar to those reported in [3]. The ^{1}H and ^{13}C NMR spectra confirmed the relative stereochemistry of the adjacent bis-THF moiety. Indeed, C-16, C-19, C-20 and C-23 showed two signals at δ_c 83.1 (C-16, C-23) and δ_c 81.8 (C-19, C-20), and C-15 and C-24 appeared as a single peak at δ_c 74.0. In the ^{1}H NMR spectrum, H-15 and H-24 appeared at δ 3.40. These data are characteristic of a symmetric relative stereochemistry *threo/trans/threo/trans/threo* [9].

In the same way, the asymmetric relative stereochemistry *threo/trans/threo/trans/erythro*, from C-15 to C-24 or the converse, was confirmed for the bis-THF moiety of **5**: C-16, C-19, C-20, C-23 showed four distinct signals in the ^{13}C NMR spectrum and the

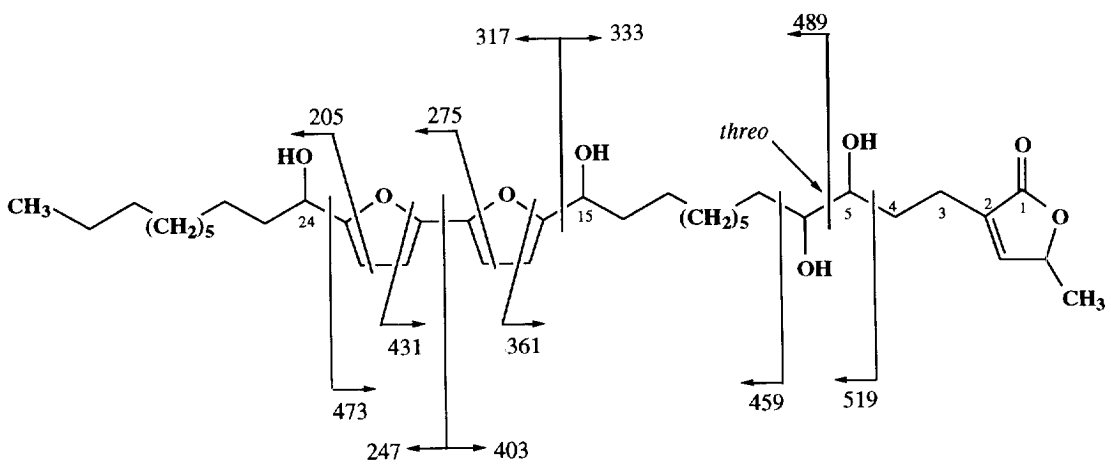

Fig. 2. Diagnostic fragment ions in the FAB-Li mass spectrum of uvariasolins I and II (**2** and **3**).

carbinol methine carbons C-15 and C-24 showed two signals at δ 74.0 and 71.3. These configurations were confirmed by the presence of only one proton at δ 3.39 in the ^{1}H NMR spectrum. In addition to these acetogenins, the known compounds benzyl benzoate and taraxerol [3] were isolated and their structure were elicited by comparison of their spectral data with those of the literature.

Until now, only eight 5-OH acetogenins have been described, principally in the *Uvaria* genus [3–6, 13]. In this work, three new 5-OH acetogenins were isolated from *U. pauci-ovulata*. Espelicin (**1**) is an isomer of panalicin (**6**) and uvariasolins I (**2**) and II (**3**) are the first examples of 5,6-dihydroxyacetogenins of Annonaceae.

EXPERIMENTAL

General experimental procedures. ^{1}H and ^{13}C NMR: 400 and 50 MHz, respectively, $CDCl_3$; EIMS and CIMS (NH_4^+): Nermag R 10-10 C spectrometer; FABMS (matrix: *m*-NBA + LiCl): Kratos NS 80 RF double focusing mass spectrometer under conventional conditions; CID-MIKE and MS/MS: ZabSpec-T five-sector tandem mass spectrometer (Fisons Instruments, VG organic, Manchester, U.K.). The first analyser (MS1) comprises a ZabSpec triple sector ($E_1B_1E_2$) instrument and the second mass spectrometer (MS2) consists of a double sector instrument (B_2E_3) of reverse Mattausch–Herzog geometry focusing the ion beam on a focal plane. $[M+Li]^+$ precursor ions were generated by caesium ion bombardment at 30 keV (matrix: *m*-NBA + LiCl). The MIKE experiments were performed by setting E_1 and B_1 at fixed values corresponding to the chosen precursor ion accelerated at 8 keV. The fragmentations of the selected precursor ion occurring in the third field free region can be recorded by scanning E_2. The precursor ions submitted to MS/MS experiments were selected by MS1, set at appropriate E and B values and then focused in a collision cell located in the fourth field-free region (between E_2 and B_2). Helium was introduced at a pres. leading to an attenuation of the precursor ion beam of almost 70%. The collision cell was floated at 4 kV so as to attain a collision energy of 4 keV. Fragment ions detection was achieved by use of the MCAD detector operating with a mass ratio of 1.225:1.0 at an angle of 30° with regard to the ion beam. For each MS/MS acquisition, the mass scale comprised between the precursor ion peak and the lowest mass end (*m/z* 50) was covered by successive overlapping exposures of 0.5 s. HPLC: Waters 590 pump system and a Millipore Waters 484 (Milford, MA), spectrophotometer.

Plant material. Bark of *Uvaria pauci-ovulata* was collected in July 1994, in Kedah (north Malaysia). Herbarium specimens are deposited at Forest Research Institute, Kepong, Malaysia, and at Laboratoire de Phanérogamie, Museum National d'Histoire Naturelle de Paris, under the reference KL 4388.

Extraction and isolation. The dried and ground bark (4.8 kg) was extracted with EtOH in Malaysia. 100 g of this EtOH extract (145 g overall) were partitioned between 0.1 M HCl–MeOH (9:1) and CH_2Cl_2, to yield 11.54 g of CH_2Cl_2 extract. Of this extract, 10 g were submitted to CC (silica gel, 70–230 mesh) eluting with CH_2Cl_2–EtOAc (100:0 to 0:100) then EtOAc–MeOH (100:0 to 17:3) gradients, which yielded 75 frs. Frs 37–41 (532 mg) were further sepd by CC (silica gel 60H) with CH_2Cl_2–MeOH (19:1) and furnished a fr. containing **4** and **5** (229 mg). **4** and **5** were sepd and purified by semi-prep. HPLC using a μBondapack C18 prepacked column [10 μm, 25 × 100 mm], eluted with MeOH–H_2O (21:4), flow rate 10 ml min^{-1}, UV detection 214 nm. 6.7 mg of **4** and 16 mg of **5** were obtained. Frs 44–49 (326 mg) were chromatographed on a column of silica gel 60H eluting with CH_2Cl_2–EtOAc–MeOH (10:9:1) and yielded a partially purified fr. containing **7**. HPLC purifications (MeOH–H_2O 87:13) afforded **7** (63.6 mg). Frs 51 (144 mg) was chromatographed on a silica gel 60H column eluting with CH_2Cl_2–EtOAc–MeOH (6:13:1) and yielded a fr. (20 mg) containing **1**, **2** and **3**. HPLC sepn and purification (MeOH–H_2O, 41:9) furnished **1** (3 mg), **2** (1.5 mg) and **3** (1.5 mg). Frs. 53–56 (278 mg) were submitted to chromatography on a column of silica gel 60H eluting with CH_2Cl_2–EtOAc–MeOH (2:17:1) which furnished a partially purified fr. containing **6** (120 mg), which was finally purified by HPLC (MeOH–H_2O, 41:9). From frs 2 and 7, benzyl benzoate and taraxerol, respectively, were isolated.

Espelicin (**1**). White waxy solid (3 mg); ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; FAB-MS (*m*-NBA + LiCl), *m/z*: 645 $[M+Li]^+$ (100%), 627 $[M+Li-H_2O]^+$, 519, 489, 487, 457, 415, 387, 363, 345, 333, 317, 291, 221, 161, 160, 154, 137, 136, 121, 107; MS/MS: remote charge fragmentations, Fig. 1.

Uvariasolin I (**2**). White waxy solid (1.5 mg); ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; FAB-MS (*m*-NBA + LiCl): Fig. 2.

Uvariasolin II (**3**). White waxy solid (1.5 mg); ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; FAB-MS (*m*-NBA + LiCl): Fig. 2.

Narumicin I (**4**). White waxy solid (6.7 mg); ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; CIMS (NH_4^+), *m/z*: 640 $[M+NH_4]^+$ (100%), 623 $[M+H]^+$ (9%), 605 $[MH-H_2O]^+$, 587 $[MH-2H_2O]^+$, 569 $[MH-3H_2O]^+$, 528, 470, 415, 363, 327, 311, 293; EIMS 70 eV, *m/z*: 452, 415, 397, 363, 345, 327, 311, 293, 275, 267, 241, 197, 169, 141.

Narumicin II (**5**). White waxy solid (16 mg); ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; CIMS (NH_4^+), *m/z*: 640 $[M+NH_4]^+$ (100%) 623 $[M+H]^+$ (18%), 605 $[MH-H_2O]^+$, 587 $[MH-2H_2O]^-$, 569 $[MH-3H_2O]^+$, 529, 470, 416, 363, 328, 311, 293. EIMS 70 eV, *m/z*, 415, 397, 363, 345, 327, 311, 293, 275, 267, 241, 169, 155, 141, 126.

Panalicin (**6**). White waxy solid (36.5 mg), $[\alpha]_D^{25}$ +24° ($CHCl_3$, *c* 1.9); ^{1}H and ^{13}C NMR: see ref. [4]; CIMS (NH_4^+), *m/z*: 657 $[M+NH_4]^-$ (100%), 639

$[M+H]^+$, 620 $[MH-H_2O]^+$, 602 $[MH-2H_2O]^+$, 584 $[MH-3H_2O]^+$, 566 $[MH-4H_2O]^+$, 522, 469, 434, 398, 328, 306, 239, 204, 186; EIMS 40 eV, *m/z*, 397, 363, 345, 311, 293, 276, 239, 221, 169, 155, 151, 137; MS/MS (remote charge fragmentations)—Series A, from the terminal methyl side: 645, 629, 615, 601, 587, 573, 559, 529, 515, 501, 487, 457. Series B, from the lactone side: 645, 547, 533, 519, 489, 475, 461, 447, 433, 419, 405, 391, 377, 363, 333.

Squamocin (**7**). White waxy solid (63.6 mg): data were in agreement with those described in refs [4, 14].

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