Three New Sesquiterpene Pyridine Alkaloids from *Euonymus fortunei*

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Three new macrocyclic β-dihydroagarofuran-type sesquiterpene pyridine alkaloids, fortuneines A (**1**), B (**2**), and C (**3**), together with the four known alkaloids wilfornine E (**4**), aquifoliunine E-I (**5**), euoverrine B (**6**), and euojaponine I (**7**), were isolated from the aerial parts of *Euonymus fortunei*. Their structures were elucidated by spectroscopic methods, including HR-ESI-MS, ^{1}H- and ^{13}C-NMR, DEPT, ^{1}H,^{1}H-COSY, HSQC, HMBC, and ROESY. This is the first isolation of the above sesquiterpene pyridine alkaloids from this plant, except for compound **6**.

Introduction. – The genus *Euonymus* (Celastraceae) has been used as traditional Chinese medicine for hundreds of years. Modern pharmacologic researches found that *Euonymus* plants have immunosuppressive, antitumor-promoting and cytotoxic, antiviral, and anti-inflammatory properties [1]. *Euonymus fortunei*, as a plant of *Euonymus*, has been widely used for various diseases in the nationalities area, such as hemorrhage (stanching bleeding), bruises, and strain of lumber muscles [2]. In the last 20 years, many dihydroagarofuran sesquiterpene alkaloids have been isolated from Celastraceae plants; however, just twelve sesquiterpene alkaloids have been obtained from the genus *Euonymus* [3–8]. Some of these sesquiterpene pyridine alkaloids have been of interest because of their cytotoxicity against several human-tumor cell lines [9] and insect antifeedant and insecticidal activities [10]. Previous chemical investigations on the *fortunei* species demonstrated the presence of triterpenes [11–12], lignans [13], and dihydroagarofuran polyesters [14].

In the present study, three new β-dihydroagarofuran sesquiterpene pyridine alkaloids, fortuneines A[1]) (**1**), B[1]) (**2**), and C[1]) (**3**), along with four known compounds, wilfornine E (**4**), aquifoliunine E-I (**5**), euoverrine B (**6**), and euojaponine I (**7**), were isolated by repeated column chromatography from the $CHCl_3$ partitioning of the EtOH extract of the aerial parts of *E. fortunei* (*Fig. 1*) (β-dihydroagarofuran = (3*R*,5a*S*,9-*R*,9a*S*)-octahydro-2,2,5a,9-tetramethyl-2*H*-3,9a-methano-1-benzoxepin). Their structures were elucidated by spectroscopic methods, especially 2D-NMR techniques. This article mainly describes the isolation and structure elucidation of these new compounds.

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[1]) Arbitrary atom numbering; for systematic names, see *Exper. Part*.

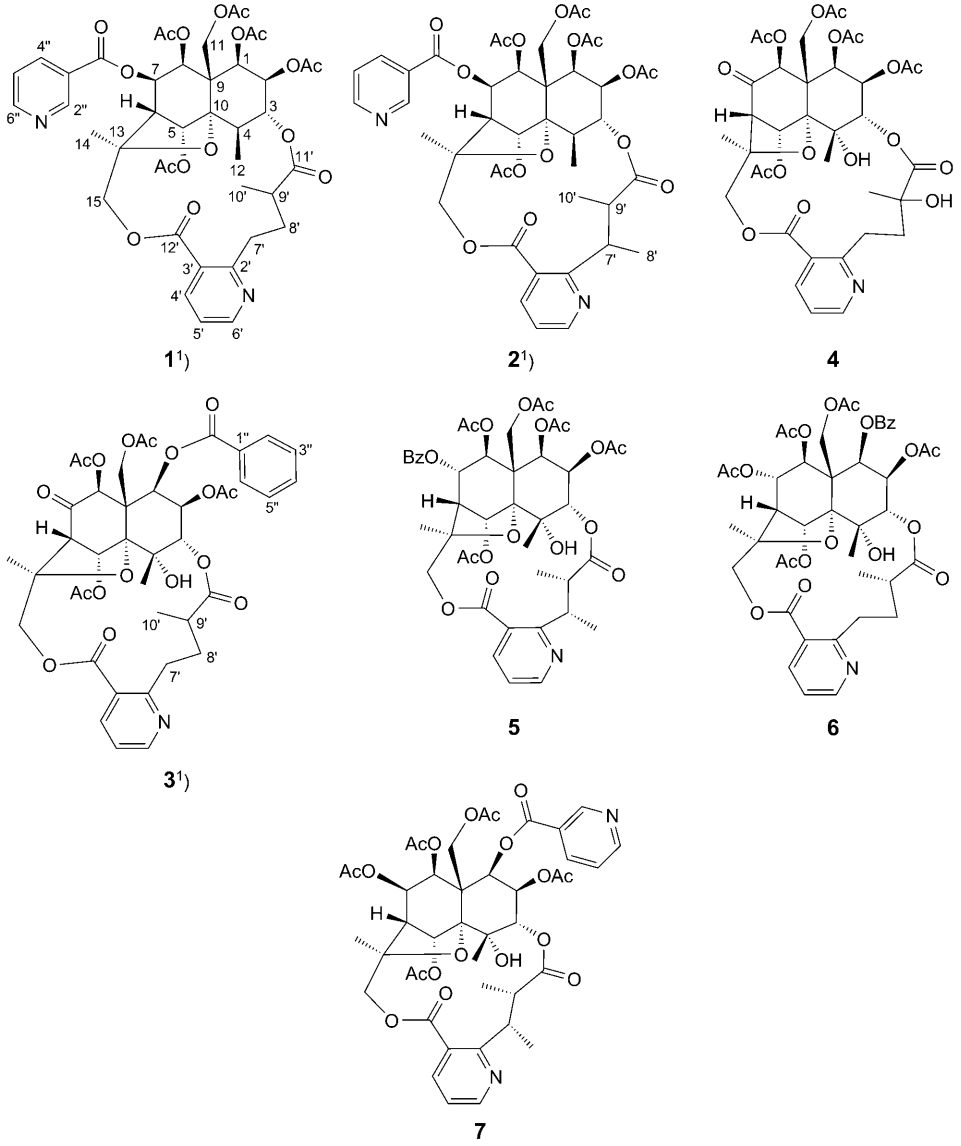

Fig. 1. *Compounds* **1**–**7** *isolated from* Euonymus fortunei

Results and Discussion. – Compound **1**, obtained as white powder, gave a molecular-ion peak $[M+\mathrm{Na}]^+$ at *m/z* 875.2825 in its high-resolution (HR) ESI-MS, corresponding to the molecular formula $C_{42}H_{48}N_2O_{17}$. Its ^{1}H-NMR spectrum (*Table*) showed the presence of five Ac groups (δ(H) 1.86, 2.13, 1.94, 2.18, and 2.21 (5*s*)), three Me groups (δ(H) 1.10 (*d*, $J=7.0$ Hz), 1.29 (*d*, $J=8.0$ Hz), and 1.62 (*s*)), two O-acylated CH_2 groups (δ(H) 3.60 and 5.80 (2*d*, $J=11.5$ Hz, each 1 H); 4.33 and 5.47 (2*d*, $J=$

13.0 Hz, each 1 H)), two other CH_2 groups (δ(H) 1.95 (*m*) and 2.23–2.26 (*m*); 3.80–3.86 (*m*) and 3.98–4.02 (2*m*)), a 2′,3′-disubstituted pyridine ring (δ(H) 7.41 (*dd*, J = 8.0, 2.0 Hz), 8.40 (*dd*, J = 8.0, 5.0 Hz), and 8.68 (*dd*, J = 5.0, 2.0 Hz)), a 3″-disubstituted pyridine (Nic) ring (δ(H) 7.61 (*dd*, J = 4.5, 8.0 Hz), 8.47 (*ddd*, J = 8.0, 2.0, 2.0 Hz), 8.79 (*dd*, J = 4.5, 2.0 Hz), and 9.17 (*s*)), three CH groups (δ(H) 2.62 (*d*, J = 4.0 Hz), 2.74–2.77 (*m*) and 2.72–2.79 (*m*)), and six O-bearing CH groups (δ(H) 5.03 (br. *s*), 5.39 (*d*, J = 6.0 Hz), 5.51 (*dd*, J = 4.0, 2.0 Hz), 5.57 (*dd*, J = 4.0, 6.0 Hz), 5.78 (*d*, J = 4.0 Hz), and 6.68 (*s*)). The ^{13}C-NMR data (*Table*) revealed the presence of eight Me, four CH_2, and 17 CH groups, and 14 quaternary C-atoms including eight C=O groups. These data suggested that the compound might be a macrocyclic β-dihydroagarofuran-type sesquiterpene dipyridine alkaloid which has a nicotinoyl group, as reported for aquifoliunine E-IV [15]. The nicotinoyl group was located at C(7) since the HMBC spectrum (*Fig. 2*) showed a long-range correlation between the H-atom at δ(H) 5.57 (H–C(7)) and the ester C=O at δ(C) 165.1 as well as between the signals at δ(H) 8.47 (H–C(4″)) and 9.17 (H–C(2″)) and the same C=O group. In addition, the H-atoms at δ(H) 5.78 (H–C(1)), 5.51 (H–C(2)), 6.68 (H–C(5)), 5.39 (H–C(8)), and 4.33 and 5.47 (CH_2(11)) showed long-range correlations with the C=O groups of the Ac groups at δ(C) 171.0, 171.1, 171.3, 171.9, and 171.8, respectively. Furthermore, the HMBC spectrum of **1** showed the cross-peaks H–C(3) (δ(H) 5.03)/C(11′) (δ(C) 176.6) and H–C(15) (δ(H) 5.80)/C(12′) (δ(C) 166.6), indicating that the 2-(3-carboxybutyl)nicotinic acid moiety should be connected at C(3) and C(15) on the β-dihydroagarofuran skeleton. The relative orientations of the Ac groups at the β-dihydroagarofuran skeleton of **1** were determined by analysis of the ROESY data (*Fig. 2*). The following NOEs were observed: H–C(8)/H–C(1) and Me(14), Me(12)/H–C(3), H–C(5), and H–C(11) (δ 5.47), and H–C(6)/H–C(5). These spectral data and the coupling constants of the H-atoms of the β-dihydroagarofuran skeleton suggested that the relative orientation of the Ac groups could be assigned as (1α,2α,3β,5β,7α,8α). Hence, the structure of **1** was confirmed as shown in *Fig. 1*.

The ROESY data of the new alkaloids **2** and **3** showed that the relative configuration on the β-dihydroagarofuran moiety was the same as that of **1**.

Compound **2** had an $[M+Na]^+$ ion peak at *m*/*z* 875.2825 in its HR-ESI-MS, corresponding to the molecular formula $C_{42}H_{48}N_2O_{17}$. The spectral data were similar to those of **1**, except for the presence of signals of a CH group at δ(H) 4.18 (H–C(7′)) and δ(C) 37.7 (C(7′)) and the addition of a *d* at δ(H) 1.43 (H–C(9′)). The HMBC spectrum of **2** exhibited the cross-peaks δ(H) 4.18 (H–C(7′))/δ(C) 127.9 (C(3′)), 176.0 (C(11′)), and 13.3 (C(9′)), and δ(H) 1.43 (H–C(9′))/δ(C) 37.7 (C(7′)). These correlations indicated that one H–C(7′) of **1** is replaced by a Me group in **2**. Thus, the structure of **2** was determined as shown in *Fig. 1*.

Compound **3** had an $[M+Na]^+$ ion peak at *m*/*z* 846.2581 in its HR-ESI-MS, corresponding to the molecular formula $C_{41}H_{45}NO_{17}$. The spectral data were similar to those of **1**, except for the existence of signals of a C=O group (δ(C) 197.5), one Bz group (δ(H) 7.38 (*dd*, J = 7.5, 8.0 Hz), 7.50 (*dd*, J = 8.0, 8.0 Hz), and 8.26 (*d*, J = 7.5 Hz)), and an OH group δ(H) 5.43 (*s*). The HMBC spectrum of **3** exhibited the correlations between the H-atoms at δ(H) 3.67 (H–C(6)) and 6.18 (H–C(8)) and the ketone C-atom at δ(C) 197.5, and between the H-atoms at δ(H) 6.16 (H–C(1)) and the ester C=O group at δ(C) 165.7, the latter being correlated with the H-atoms at δ(H)

Table. *^{1}H- and ^{13}C-NMR Data of Compounds* **1**–**3**[1]). δ in ppm, J in Hz.

	1[a])		**2**[b])		**3**[b])	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
H–C(1)	5.78 (*d*, *J* = 4.0)	72.1	5.82 (*d*, *J* = 4.0)	71.6	6.16 (*d*, *J* = 3.3)	73.6
H–C(2)	5.51 (*dd*, *J* = 4.0, 2.0)	70.1	5.52 (*dd*, *J* = 4.0, 2.0)	69.7	5.81 (*dd*, *J* = 3.3, 3.2)	70.8
H–C(3)	5.03 (br. *s*)	75.8	4.92 (br. *s*)	74.9	5.58 (*d*, *J* = 3.2)	76.1
H–C(4)	2.74–2.77 (*m*)	38.1	2.80 (*q*, *J* = 7.6)	36.8	–	70.6
H–C(5)	6.68 (*s*)	74.8	6.74 (*s*)	74.8	7.05 (*s*)	74.9
H–C(6)	2.62 (*d*, *J* = 4.0)	51.4	2.21 (*d*, *J* = 3.6)	50.8	3.67 (*s*)	62.9
H–C(7)	5.57 (*dd*, *J* = 4.0, 6.0)	75.0	5.63 (*dd*, *J* = 3.6, 6.0)	74.7	–	197.5
H–C(8)	5.39 (*d*, *J* = 6.0)	72.3	5.37 (*d*, *J* = 6.0)	71.6	6.18 (*s*)	80.4
C(9)	–	51.7	–	51.4	–	54.2
C(10)	–	91.9	–	91.5	–	95.6
CH_2(11)	4.33, 5.47 (2*d*, *J* = 13.0)	61.6	4.34, 5.36 (2*d*, *J* = 13.2)	60.9	4.96, 5.65 (2*d*, *J* = 13.1)	60.9
Me(12)	1.29 (*d*, *J* = 8.0)	15.6	1.29 (*d*, *J* = 7.2)	15.0	1.67 (*s*)	24.5
C(13)	–	84.4	–	83.4	–	87.1
Me(14)	1.62 (*s*)	18.2	1.53 (*s*)	18.4	1.51 (*s*)	18.8
CH_2(15)	3.60, 5.80 (2*d*, *J* = 11.5)	70.2	3.93, 5.24 (2*d*, *J* = 11.2)	70.2	4.26, 6.04 (2*d*, *J* = 11.7)	71.0
C(2′)	–	164.0	–	164.3	–	163.6
C(3′)	–	127.4	–	127.9	–	125.6
H–C(4′)	8.40 (*dd*, *J* = 8.0, 2.0)	140.4	8.02 (*dd*, *J* = 8.0, 1.8)	138.6	8.27 (*dd*, *J* = 7.9, 1.8)	139.3
H–C(5′)	7.41 (*dd*, *J* = 8.0, 5.0)	122.8	7.27 (*dd*, *J* = 7.8, 4.8)	122.0	7.27 (*dd*, *J* = 7.9, 4.8)	121.6
H–C(6′)	8.68 (*dd*, *J* = 5.0, 2.0)	153.4	8.70 (*dd*, *J* = 4.8, 1.8)	151.7	8.83 (*dd*, *J* = 4.8, 1.8)	153.6
CH_2(7′) or H–C(7′)	3.98–4.02, 3.80–3.86 (2*m*)	34.4	4.18 (*q*, *J* = 7.0)	37.7d	3.20–3.25, 4.07–4.12 (2*m*)	34.4
CH_2(8′) or Me(8′)	2.23–2.26 (*m*)	32.7	2.75 (*q*, *J* = 7.3)	44.4	2.34–2.41 (*m*)	34.0
H–C(9′)	2.72–2.79 (*m*)	38.1	1.43 (*d*, *J* = 7.0)	13.3	2.74–2.79 (*m*)	39.6
Me(10′)	1.10 (*d*, *J* = 7.0)	19.5	1.25 (*d*, *J* = 7.3)	10.6	1.22 (*d*, *J* = 7.0)	18.8
C(11′)	–	176.6	–	176.0	–	175.7
C(12′)	–	166.6	–	168.3	–	169.4
C(1″)	–	–	–	–	–	129.9
H–C(2″)	9.17 (*s*)	151.4	9.30 (*d*, *J* = 2.0)	151.9	8.26 (*d*, *J* = 7.5)	129.5
C(3″) or H–C(3″)	–	126.8	–	125.4	7.38 (*dd*, *J* = 7.5, 8.0)	130.4

Table (cont.)

	1[a])		**2**[b])		**3**[b])	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
H–C(4″)	8.47 (*ddd*, *J* = 8.0, 2.0, 2.0)	139.2	8.41 (*dd*, *J* = 8.0, 2.0)	137.9	7.50 (*dd*, *J* = 8.0, 8.0)	134.5
H–C(5″)	7.61 (*dd*, *J* = 4.5, 8.0)	125.4	7.50 (*dd*, *J* = 4.8, 8.0)	123.6	7.38 (*dd*, *J* = 7.5, 8.0)	130.4
H–C(6″)	8.79 (*dd*, *J* = 4.5, 2.0)	154.6	8.84 (*dd*, *J* = 4.8, 2.0)	154.9	8.26 (*dd*, *J* = 7.5)	129.5
*Ac*O–C(1)	1.86 (*s*)	20.6, 171.0	1.83 (*s*)	20.8, 170.1	–	–
*Ac*O–C(2)	2.13 (*s*)	20.7, 171.1	2.15 (*s*)	20.9, 170.2	2.17 (*s*)	20.9
*Ac*O–C(5)	1.94 (*s*)	21.1, 171.3	1.93 (*s*)	21.3, 170.3	2.21 (*s*)	21.5, 171.3
*Ac*O–C(8)	2.18 (*s*)	21.2, 171.9	2.20 (*s*)	21.6, 171.0	1.55 (*s*)	20.1, 170.4
*Ac*O–C(11)	2.21 (*s*)	21.2, 171.8	2.21 (*s*)	21.4, 170.8	1.99 (*s*)	20.9, 171.2
Nic*C*OO–C(7)	–	165.1	–	164.5	–	–
Ph*C*OO–C(1)	–	–	–	–	–	165.7
OH–C(4)	–	–	–	–	5.43 (*s*)	–

[a]) In CD_3OD at 500 (^1H) and 125 MHz (^{13}C). [b]) In C_5D_5N at 400 (^1H) and 100 MHz (^{13}C).

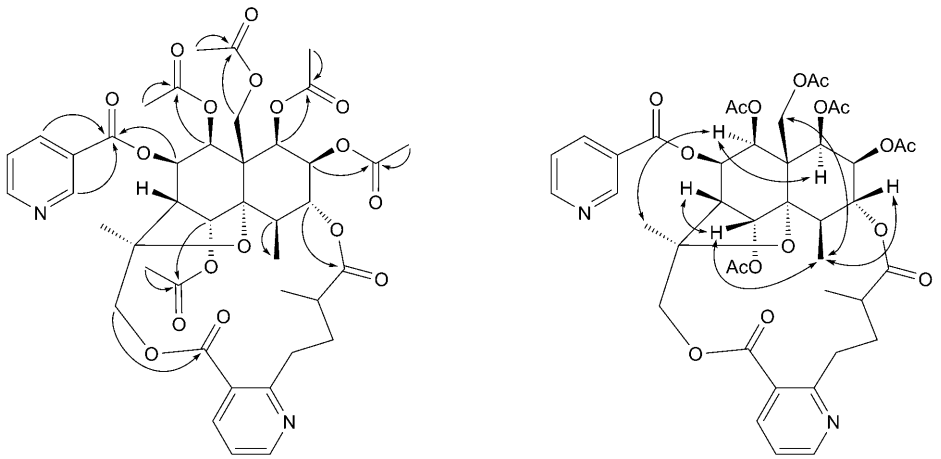

Fig. 2. *Significant HMBC* (H → C) *and ROESY* (H ↔ H) *features of compound* **1**

8.26 (H–C(2″,6″)) of to the Bz group. These correlations indicated that the CH(7)–O group of **1** is replaced by a C=O group in **3**, and that the Bz group should be located at C(1). As a result, the structure of **3** was confirmed as shown in *Fig. 1*.

Upon comparison with values reported in the literature, several known compounds were identified by their spectral data as wilfornine E (**4**) [16], aquifoliunine E-I (**5**) [17], euoverrine B (**6**) [18], and euojaponine I (**7**) [5]. According to the reports, aquifoliunine E-I (**5**) exhibited weak but selective activity in a mechanism-based DNA-modifying yeast assay, indicating that they might be responsible for the slight DNA-damaging activity of the plant [19]. The insecticidal activity of euoverrine B (**6**) against *Mythimna separata* was KD_{50} 21.6 μg g^{-1} [4].

We gratefully acknowledge financial support of this work by the *Guangxi Natural Science Foundation of China* (No. 0991006).

Experimental Part

General. TLC: silica gel GF_{254} plates precoated (SiO_2; *Qingdao Haiyang Chemical Co., Ltd.*, P. R. China). Column chromatography (CC): SiO_2 (200–300 mesh; *Qingdao Haiyang Chemical Co., Ltd.*, P. R. China) and C_{18} reversed-phase SiO_2 (*YMC Co., Ltd.*, Japan). HPLC: *Ultimate-3000* HPLC system; *Ultimate-3000* pump; *Ultimate-3000* variable-wavelength detector; column *Waters* $5C_{18}$*-MS-II* (10 × 250 mm). UV Spectra: *SP-2102UVPC* spectrometer; λ_{max} in nm. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AM-400* instrument, *Bruker-AM-500* instrument; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI- and HR-ESI-MS: *VG-Auto-Spec-3000* and *Waters*/*Micromass-Q-Tof-Ultima* spectrometers, resp., in m/z (rel. %).

Plant Material. The plant material was collected from the Guangxi Zhuang Autonomous Region, P. R. China, and identified by Prof. *Dingrong Wan*, College of Pharmacy, South-Central University for Nationalities, P. R. China, wherein the voucher specimen (0708) is deposited.

Extraction and Isolation. The milled, air-dried aerial parts of *Euonymus fortunei* (7.5 kg) were powered and then extracted three times with 95% EtOH at r.t. The dried EtOH extract (490 g) was suspended in 90% MeOH/H_2O and then partitioned with petroleum ether (3 × 4.0 l), $CHCl_3$ (3 × 4.0 l), and BuOH (3 × 4.0 l). The $CHCl_3$ extract (149 g) was applied to CC (SiO_2, cyclohexane/AcOEt 9 : 1, 8 : 2,

7:3, 1:1, 3:7, and 0:1): *Fractions 1–12*. *Fr. 9* (3.0 g) was subjected to CC (*ODS*, H_2O/EtOH 9:1 → 7:3): *Frs. 9.1–9.10*. *Fr. 9.6* (255.6 mg) was subjected to CC (*ODS*, H_2O/EtOH 7:3 → 0:1) and then further purified by semi-prep. HPLC (MeOH/H_2O 75:25): **5** (35.3 mg, 2.2 ml/min). *Fr. 10* (4.8 g) was subjected to CC (SiO_2, $CHCl_3$/MeOH 95:5 → 0:1): *Frs. 10.1–10.6*. *Fr. 10.1* (595.2 mg) was subjected to CC (*ODS*, H_2O/EtOH 7:3 → 0:1): *Frs. 10.1.1–10.1.3*. *Fr. 10.1.2* (62.8 mg) was subjected to CC (*ODS*, H_2O/EtOH 9:1 → 7:3) and then further purified by semi-prep. HPLC (MeOH/H_2O 60:40): **2** (3.6 mg, 2.3 ml/min), **3** (12.8 mg, 2.3 ml/min), **4** (8.0 mg, 2.3 ml/min), and **6** (6.7 mg, 2.3 ml/min). *Fr. 10.5* (663.7 mg) was subjected to CC (*ODS*, H_2O/EtOH 8:2 → 4:6): *Frs. 10.5.1–10.5.9*. *Fr. 10.5.1* (62.8 mg) was applied to semi-prep. HPLC (MeOH/H_2O 10:90): **1** (5.2 mg, 3 ml/min) and **7** (5.0 mg, 3 ml/min).

Fortuneine A (= rel-*(8*R*,9*R*,10*R*,11*S*,12*R*,13*R*,14*S*,15*R*,21*R*,22*S*,23*R*)-10,13,14,22-Tetrakis(acetyloxy)-12-[(acetyloxy)methyl]-7,8,9,10,12,13,14,15,17,18,19,20-dodecahydro-8,18,21-trimethyl-5,17-dioxo-8,11-epoxy-9,12-ethano-11,15-methano-5*H,11*H-[1,9]dioxacyclooctadecino[4,3-b]pyridin-23-yl Pyridine-3-carboxylate*; **1**): White powder. $[\alpha]_D^{20} = +13$ ($c = 0.26$ MeOH). UV (MeOH): 233, 269. ^{1}H- and ^{13}C-NMR: *Table*. HR-ESI-MS: 852.2825 ($[M+Na]^+$, $C_{42}H_{48}N_2O_{17}Na^+$; calc. 875.2851).

Fortuneine B (= rel-*(8*R*,9*R*,10*R*,11*S*,12*R*,13*R*,14*S*,15*R*,20*R*,21*S*,22*R*)-10,13,14,21-Tetrakis(acetyloxy)-12-[(acetyloxy)methyl]-5,7,8,9,10,12,13,14,15,17,18,19-dodecahydro-8,18,19,20-tetramethyl-5,17-dioxo-8,11-epoxy-9,12-ethano-11,15-methano-11*H-[1,8]dioxacycloheptadecino[4,3-b]pyridin-22-yl Pyridine-3-carboxylate*; **2**): White powder. $[\alpha]_D^{20} = +6$ ($c = 0.18$ MeOH). UV (MeOH): 236, 270. ^{1}H- and ^{13}C-NMR: *Table*. HR-ESI-MS: 852.2825 ($[M+Na]^+$, $C_{42}H_{48}N_2O_{17}Na^+$; calc. 875.2851).

Fortuneine C (= rel-*(8*R*,9*R*,10*R*,11*S*,12*S*,13*R*,14*R*,15*S*,21*S*,22*S*)-10,14,22-Tris(acetyloxy)-12-[(acetyloxy)methyl]-13-(benzoyloxy)-7,8,9,10,12,13,14,15,19,20-decahydro-21-hydroxy-5,18,21-trimethyl-8,11-epoxy-9,12-ethano-11,15-methano-5*H,11*H-[1,9]dioxacyclooctadecino[4,4-b]pyridine-5,17,23(18*H)-trione*; **3**): White powder. $[\alpha]_D^{20} = +30$ ($c = 0.45$ MeOH). UV (MeOH): 291. ^{1}H- and ^{13}C-NMR: *Table*. HR-ESI-MS: 846.2581 ($[M+Na]^+$, $C_{41}H_{45}NO_{17}Na^+$; calc. 846.2585).

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Received November 8, 2010