Chemical and Cytotoxic Constituents from the Stem of *Machilus zuihoensis*

by **Ming-Jen Cheng**[a]), **Bolleddula Jayaprakasam**[a]), **Tsutomu Ishikawa**[b]), **Hiroko Seki**[c]), **Ian-Lih Tsai**[a]), **Jeh-Jeng Wang**[d]), and **Ih-Sheng Chen***[a])

[a]) Graduate Institute of Pharmaceutical Sciences, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.

[b]) Faculty of Pharmaceutical Sciences, Chiba University, 1–33 Yayoi, Inage, Chiba 263-8522, Japan

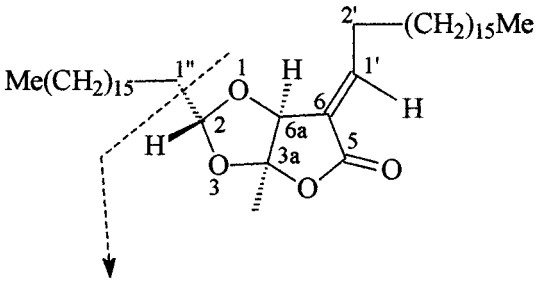
[c]) Analytical Center, Chiba University, 1–33 Yaoyi, Inage, Chiba 263-8522, Japan

[d]) School of Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.

Five new compounds, including a novel lactone, machilactone (= *rel*-(2*R*,3a*R*,6*E*,6a*S*)-2-heptadecyl-3a-methyl-6-octadecylidene-6,6a-dihydrofuro[2,3-*d*][1,3]dioxol-5(3a*H*)-one; **1**), a new sesquiterpene, 3,4-dihydroxy-β-bisabolol (= *rel*-(1*R*,2*S*,4*R*)-1-[(1*R*)-1,5-dimethylhex-4-enyl]-1-methylcyclohexane-1,2,4-triol; **2**), a new secobutyrolactone, methyl (2*E*)-2-(1-hydroxy-2-oxopropyl)eicos-2-enoate (**3**), two new butyrolactones, machicolide A (**4**) and machicolide B (**5**) (= 3*E*,4*R*,5*R*)- and (3*Z*,4*R*,5*R*)-4,5-dihydro-4-hydroxy-5-methoxy-5-methyl-3-octadecylidenefuran-2(3*H*)-one, resp.) as a mixture, together with known caryophyllene oxide (=4,12,12-trimethyl-9-methylene-5-oxatricyclo[8.2.0.0^{4,6}]dodecane), hexacosane, tetracosanoic acid, isomahubanolide-23 (=(3*E*,4*R*)-4,5-dihydro-4-hydroxy-5-methylidene-3-octadecylidenefuran-2(3*H*)-one), and β-bisabolol (=(1*S*)-1-[(1*S*)-1,5-dimethylhex-4-enyl]-4-methylcyclohex-3-en-1-ol) were isolated from the stem wood of *Machilus zuihoensis*. The structures of these compounds were established by spectroscopic studies. The eicos-2-enoate (**3**) and β-bisabolol exhibited marginal cytotoxicity against NUGC and HONE-1 cancer cell lines *in vitro*.

Introduction. – Recently, studies on Lauraceous plants of chemical interest have gradually brought cytotoxic constituents into focus [1–7]. *Machilus zuihoensis* HAYATA (Lauraceae), an endemic species in Taiwan, is an evergreen medium-sized tree found widely throughout the island from the lowlands up to 1500 m [8]. Its bark is an incense material for joss sticks. Earlier investigations have established the presence of the two alkaloids: (−)-L-*N*-norarmepavine and (±)-*N*-norarmepavine in the stem [9], and of four neolignans in the bark of this plant [10]. Of this plant, only the stem wood showed significant cytotoxicity on high-throughput screening against NUGC-3 and HONE-1 cancer cell lines *in vitro*. Examination of the hexane-soluble part of the stem wood led to the isolation of five new compounds: machilactone (**1**), 3,4-dihydroxy-β-bisabolol (**2**), methyl (2*E*)-2-(1-hydroxy-2-oxopropyl)eicos-2-enoate (**3**), and the mixture of machicolide A (**4**) and machicolide B (**5**). We now report the isolation and characterization of **1**–**5** by spectral analyses and the cytotoxicity of the isolates.

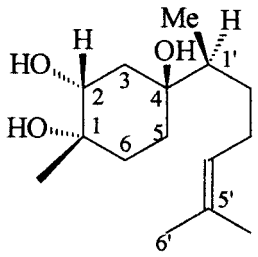
Results and Discussion. The optically active machilactone (**1**), obtained as colorless needles, was analyzed for $C_{41}H_{76}O_4$ from its FAB-HR-MS (633.5803 ($[M+H]^+$)). The UV spectrum (243 nm) and IR data (1763 and 1677 cm^{-1}) indicated the presence of an α-alkylidene-substituted γ-lactone skeleton and the ^{1}H- and ^{13}C-NMR spectra suggested the presence of a γ-butyrolactone moiety [4] connected to another aliphatic chain by an acetal linkage.



m/z 393

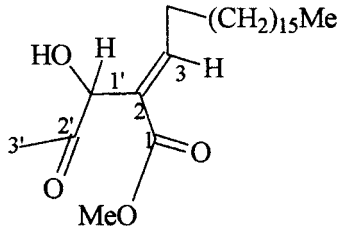
1

NOE: H-C(6a)/Me-C(3a)
H-C(6a)/C*H*$_2$CH=C(6)
H-C(6a)/C*H*$_2$-C(2)
HMBC: Me-C(3a)/C(3a), C(6a)
H-C(6a)/C(5), C(2)
C*H*=C(6)/C(5), C(6a)
C*H*$_2$CH=C(6)/C(6)



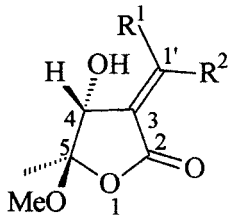
2

NOE: Me-C(1)/H-C(2)
H-C(2)/CH$_2$(2')
CH$_2$(3)/Me-C(1')
Me-C(1')/H$_b$-C(2'),H$_b$-C(3)
Me-C(5')/Me(6')
HMBC: Me-C(1)/C(1), C(2)
Me-C(1')/C(1')
H-C(1')/C(4)
Me-C(5')/C(5'), C(4')
Me-(6')/C(5'), C(4')

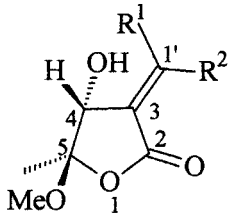


3

NOE: CH$_2$(4)/H-C(1')
H-C(1')/Me(3')



NOE (**4**): H-C(4)/CH$_2$(2'), MeO
NOE (**5**): H-C(4)/H-C(1'), MeO



4 $R^1 = Me(CH_2)_{16}$, $R^2 = H$
5 $R^1 = H$, $R^2 = Me(CH_2)_{16}$

6 $R^1 = Me(CH_2)_{14}$, $R^2 = H$
7 $R^1 = H$, $R^2 = Me(CH_2)_{14}$

The ^{1}H-NMR signals of **1** at δ 7.09 and 2.40 were assignable to C*H*=C(6) and CH_2CH=C(6) based on HMQC and ^{1}H,^{1}H-COSY experiments. Comparison with available butyrolactones of this kind and a significant fragment at *m/z* 393 in the FAB-MS suggested the presence of an octadecylidene side chain at C(6). The geometry of the alkylidene moiety was determined to be (*E*) based on the chemical shifts of C*H*=C(6) (δ 7.09) and CH_2CH=C(6) (δ 2.40) [4]. This was also confirmed by the NOE difference spectrum, which showed the correlation H–C(6a)/CH_2CH=C(6). The ^{1}H-NMR signal at δ 5.01 was assigned to H–C(2) as this proton correlated with the dioxygenated aliphatic C(2) signal at δ 103.9 in the HMQC and with the neighboring C*H*–C(2) (δ 1.68) in the COSY plot. From the ^{1}H,^{1}H-COSY experiment and the molecular formula of **1**, the length of the saturated aliphatic side-chain portion connected to the exocyclic C=C bond was deduced to be C_{17}. A Me group at δ 1.71 was placed at C(3a), as these protons showed ^2J correlation with C(3a) (δ 109.8) and ^3J correlation with C(6a) (δ 78.4) in its HMBC plot. The connection of the alipathic hydrocarbon chain to the γ-butyrolactone moiety by a O–C–O linkage was confirmed by the ^{13}C-NMR signals of two aliphatic dioxygenated C-atoms at δ 103.9 (C(2)), 109.8 (C(3a)) and the correlation observed between H–C(6a) (δ 4.89) and C(2) in the HMBC plot.

According to HMQC, COSY, NOE, and HMBC data, the structure of **1** was elucidated as 2-heptadecyl-3a-methyl-6-octadecylidene-6,6a-dihydrofuro[2,3-*d*][1,3]dioxol-5-(3a*H*)-one was attributed to **1**, with the relative *cis* configuration of H–C(6a)/Me–C(3a) and H–C(6a)/CH_2–C(2) and (6*E*)-configuration.

Compound **2**, obtained as colorless needles, has the molecular formula $C_{15}H_{28}O_3$, as determined by FAB-HR-MS. According to the IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY, NOE, HMQC, and HMBC studies, the structure of **2** was elucidated as 3,4-dihydroxy-β-bisabolol, *i.e.* as *rel*-(1*R*,2*S*-4*R*)-1-[(1*R*)-1,5-dimethylhex-4-enyl]-1-methylcyclohexane-1,2,4-triol.

A strong IR absorption band at 3322 cm^{-1} indicated the presence of OH groups in **2**. The ^{13}C-NMR and DEPT experiments showed the 15 C resonances for 4 Me, 5 CH_2, 3 CH, and 3 quarternary C-atoms, suggesting that **2** could be a sesquiterpene of the α- or β-bisabolene type. The presence of a Me at δ 0.93 (J = 6.6, Me–C(1′)) supported that **2** was of the latter type. A close comparison of ^{13}C-NMR data with β-bisabolol [11], also isolated in this study (see below), the missing signal for the C=C bond, and the presence of further two oxygenated C-atoms at δ 71.7 and 74.9 suggested that **2** could be 3,4-dihydroxy-β-bisabolol. The ^{1}H-NMR showed signals for two Me groups at δ 1.60 and 1.68, assigned to Me–C(6′) and Me–C(5′), respectively, as they showed the correlation with each other as well as ^2J correlation with C(5′) and ^3J correlation with C(4′) in its HMBC plot. The third Me group at δ 0.93 (*d*, J = 6.6) was attributed to Me–C(1′), and the remaining Me signal at δ 1.33 to Me–C(1) based on HMBC studies. An olefinic proton at δ 5.09 was placed at C(4′) and another proton with a br. *s* at δ 3.52 was assigned to H–C(2). Three OH groups were recognized in the ^{1}H-NMR at δ 1.10, 1.90, and 3.80 by addition of D_2O. The strong NOE difference correlation between Me–C(1) and H–C(2) supported the relative *cis* configuration of the dihydroxy groups at C(1) and C(2) (axial position), which was also evidenced by the Me–C(1) signal at δ(C) 27.7 [12][13]. The NOE difference spectrum also showed correlation between the H–C(2) and CH_2(2′), supporting the equatorial position of OH–C(4). Other NOE correlations between Me–C(1′) and H_b–C(3) and H_b–C(2′) were also found.

Compound **3** was obtained as colorless oil. The molecular formula was deduced to be $C_{24}H_{44}O_4$ by FAB-HR-MS as it showed the $[M+H]^+$ ion at *m/z* 397.3318. From the spectral studies, the structure of **3** was elucidated as methyl (2*E*)-2-(1-hydroxy-2-oxopropyl)eicos-2-enoate (**3**), which was further substantiated by COSY, NOESY, and HMQC experiments. The zero $[\alpha]_D^{20}$ value of **3** suggested that it was considerably racemized.

The IR spectrum of **3** showed absorption bands due to the presence of OH (3462 cm^{-1}) and C=O (1726 cm^{-1}) groups. The ^{1}H-NMR spectrum exhibited the signals for an olefinic proton at δ 7.08 (*t*, J = 8.0), an oxymethine proton at δ 4.90 (br. *s*), an OH group at δ 4.02 (br. *s*) (D_2O exchangeable), a MeO group at δ 3.73

(*s*), an Ac group at δ 2.15 (*s*), CH_2 groups at δ 2.35 (*q*), 1.51 (*m*), and 1.26 (br. *s*), and a terminal Me group at δ 0.88 (*t*, $J = 6.8$), similar to that of the methanolysis product of isolineranolide E [14]. The geometry of the alkene chain of **3** was determined to be the (*E*) form based on the chemical shifts of H–C(3) (δ 7.08) and H–C(4) (δ 2.35) [14].

The optically active mixture of machicolide A (**4**; (*E*); 65%) and machicolide B (**5**; (*Z*); 35%) was obtained as a colorless oil. The molecular formula was deduced to be $C_{24}H_{44}O_4$ from FAB-HR-MS (397.3308, $[M+H]^+$). The UV spectrum exhibited the absorption maxima at 216 nm, and the IR absorptions inferred the presence of an OH group (3420 cm^{-1}) and an α,β-unsaturated γ-lactone (1746 and 1683 cm^{-1}). The data suggested the structure of (3*E*)- and (3*Z*)-4,5-dihydro-4-hydroxy-5-methoxy-5-methyl-3-octadecylidenefuran-2(3*H*)-one for **4** and **5**, respectively.

The ^{1}H-NMR spectrum of **4** showed signals for an olefinic proton (δ 6.99 (*td*, $J = 8.0, 1.6$)), an oxymethine proton (δ 4.54 (br. *s*)), a MeO group (δ 3.39 (*s*)), a Me group (δ 1.60 (*s*)) and CH_2 groups (δ 2.38 (*m*); 1.50 (*m*); 1.26 (br. *s*)), and a striking resemblance to those of litseakolide F (**6**) [7]. The side chain at the γ-lactone of **4** was found to be an octadecylidene group from its molecular formula. The ^{1}H-NMR spectrum of **5** showed high similarity to that of litseakolide G (**7**) except for an octadecylidene group in **5**.

The configuration at C(4) in both compounds was reasonably determined to be (4*R*) [6][9][15], and the NOESY data supported (5*R*) configuration.

The NOESY of **4/5** showed correlations between the H–C(4) and MeO–C(5) signals, like in the case of **6** and **7**, supporting the (5*R*) configuration [7].

Besides **1**–**5**, the known caryophyllene oxide (=4,12,12-trimethyl-9-methylene-5-oxatricyclo[8.2.0.0^{4,6}]dodecane), hexacosane, tetracosanoic acid, isomahubanolide-23 (=(3*E*),4*R*)-4,5-dihydro-4-hydroxy-5-methylidene-3-octadecylidenefuran-2(3*H*)-one), and β-bisabolol (=(1*S*)-1-[(1*S*)-1,5-dimethylhex-4-enyl]-4-methylcyclohex-3-en-1-ol) were also isolated from the stem wood of *Machilus zuihoensis*.

The cytotoxicity activity of all isolates were tested *in vitro* against NUGC-3 and HONE-1 cancer cell lines. The eicos-2-enoate **3** showed marginal activity, with ED_{50} values of 6.33 and 6.44 μg ml^{-1}, respectively, as did β-bisabolol with ED_{50} values of 6.68 and 6.73 μg ml^{-1}, respectively.

Experimental Part

General. TLC: silica gel *60 F_{254}* precoated plates (*Merck*). Column chromatography (CC): silica gel *60* (*Merck* 70–230 mesh, 230–400 mesh, ASTM). M.p.: Uncorrected. Optical rotation: *Jasco DIP-370* polarimeter; in $CHCl_3$. UV Spectra: *Jasco UV-240* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Perkin-Elmer 2000* FT-IR spectrophotometer; ν in cm^{-1}, ^{1}H-,^{13}C- and 2D-NMR: *Varian Unity-Plus-400* and *Jeol GSX-600* spectrometers; δ in ppm, *J* in Hz. EI-MS Spectra: *VG-Biotech Quatro-5022* spectrometer; *m*/*z* (rel. %). FAB-HR-MS: *Jeol SX102A* mass spectrometer.

Plant Material. The stem wood of *M. zuihoensis* was collected at Mutan, Pingtung County, Taiwan, in January 2000. A voucher specimen (No. Chen 2280) was deposited in the Herbarium of the School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.

Extraction and Isolation. Shade-dried and powered plant material (23 kg) was extracted with MeOH. The extract (2 kg) was partitioned into hexane (500 g), AcOEt (87 g), and MeOH-soluble (500 g) parts. The hexane fraction (81 g) was submitted to CC (silica gel, hexane/AcOEt step gradients): *Fractions 1–7. Fr. 1* (AcOEt/hexane 1:4, 5 g) was subjected to CC (silica gel; AcOEt/hexane) to give tetracosanoic acid (5 mg). Repeated

purification of *Fr. 3* (AcOEt//hexane 2:3; 4 g) by CC (silica gel; AcOEt/hexane) gave **1** (15 mg), **2** (10 mg), hexacosane (30 mg), isomahubanolide-23 (100 mg), and β-bisabolol (10 mg). *Fr. 4* (AcOEt/hexane 1:1; 100 mg) was subjected to prep. TLC ($AcOEt/CH_2Cl_2$ 1:4) to furnish **3** (15 mg) and caryophyllene oxide (20 mg). *Fr. 6* (AcOEt/hexane 4:1; 20 mg) was purified by prep. TLC ($Me_2CO/CHCl_3$ 1:1): **4**/**5** (3 mg).

rel-*(2*R*,3a*R*,6*E*,6a*S*)-2-Heptadecyl-3a-methyl-6-octadecylidene-6,6a-dihydrofuro[2,3-*d*][1,3]dioxol-5(3a*H*)-one* (= *Machilactone A*; **1**). Colorless needles. M.p. 58–60°. $[\alpha]_D^{20} = +20.95$ ($c = 0.082$, $CHCl_3$). UV ($CHCl_3$): 243 (4.36). IR (KBr): 2917, 2846, 1763, 1677, 1468, 1389, 1266, 1116, 1057. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.88 (*t*, *J* = 7.2, Me(18′), Me(17″)); 1.26 (br. *s*, 29 CH_2); 1.50 (*m*, CH_2(3′)); 1.68 (*m*, CH_2(1″)); 1.71 (*s*, Me–C(3a)); 2.40 (*m*, CH_2(2′)); 4.89 (*d*, *J* = 1.2, H–C(6a)); 5.01 (*t*, *J* = 4.8, H–C(2)); 7.09 (*td*, *J* = 7.8, 1.8, H–C(1′)). ^{13}C-NMR ($CDCl_3$, 150 MHz): 14.1 (C(18′), C(17″)); 22.7 (Me–C(3a)); 22.4, 23.6, 26.9, 27.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.0 (29 C, CH_2); 28.2 (C(3′)); 30.2 (C(2′)); 32.7 (C(1″)); 78.4 (C(6a)); 103.9 (C(2)); 109.8 (C(3a)); 126.3 (C(6)); 150.8 (C(1′)); 168.1 (C(5)). FAB-MS: 633 (26, $[M+H]^+$), 569 (12), 525 (20), 481 (16), 437 (20), 393 (28), 365 (71), 242 (47), 205 (100). FAB-HR-MS: 633.5803 ($C_{41}H_{77}O_4^+$; calc. 633.5822).

rel-*(1*R*,2*S*,4*R*)-1-[(1*R*)-1,5-Dimethylhex-4-enyl]-1-methylcyclohexane-1,2,4-triol* (= *3,4-Dihydroxy-β-bisabolol*; **2**). Colorless needles. M.p. 138–140°. $[\alpha]_D^{20} = -14.9$ ($c = 0.112$, $CHCl_3$). UV ($CHCl_3$): 243 (3.57). IR (KBr): 3322 (OH), 2961, 2925, 2360, 1455, 1375, 1204, 1066, 1029, 914, 850. ^{1}H-NMR ($CDCl_3$, 600 MHz): 0.93 (*d*, *J* = 6.6, Me–C(1′)); 1.06 (*m*, H_b–C(6)); 1.10 (br. *s*, OH); 1.33 (*s*, Me–C(1)); 1.36 (*m*, H–C(1′)); 1.41 (*m*, H_b–C(3)); 1.43 (*m*, H_b–C(5)); 1.60 (*s*, Me(6′)); 1.61 (*m*, H_a–C(6)); 1.68 (*s*, Me–C(5′)); 1.72 (*m*, H_b–C(2′)); 1.86 (*m*, H_a–C(3)); 1.90 (br. *s*, OH); 1.91 (*m*, H_b–C(3′)); 1.96 (*m*, H_a–C(2′)); 2.02 (*m*, H_a–C(5)); 2.10 (*m*, H_a–C(3′)); 3.52 (br. *s*, H–C(2)); 3.80 (br. *s*, OH); 5.09 (*t*, *J* = 8.2, H–C(4′)). ^{13}C-NMR ($CDCl_3$, 150 MHz): 13.5 (Me–C(1′)); 17.7 (C(6′)); 25.7 (Me–C(5′)); 26.5 (C(3′)); 27.7 (Me–C(1)); 29.1 (C(5)); 29.8 (C(3)); 30.8 (C(6)); 34.0 (C(2′)); 43.6 (C(1′)); 71.7 (C(1)); 74.9 (C(2)); 75.8 (C(4)); 124.4 (C(4′)); 131.8 (C(5′)). FAB-MS: 257 (16, $[M+H]^+$), 239 (63, $[M+H-H_2O]^+$), 221 (61), 203 (50), 69 (100). FAB-HR-MS: 257.2128 ($C_{15}H_{29}O_3^+$; calc. 257.2116).

*Methyl (2*E*)-2-(1-hydroxy-2-oxopropyl)eicos-2-enoate* (**3**). $[\alpha]_D^{20} = 0$ ($c = 0.376$, $CHCl_3$). UV (MeOH): 213 (4.13). IR (KBr): 3462 (OH), 2922, 2853, 1726, 1646, 1466, 1357, 1275, 1152, 1071. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.88 (*t*, *J* = 6.8, Me(20)); 1.26 (br. *s*, 14 CH_2); 1.51 (*m*, CH_2(5)); 2.15 (*s*, MeCOO); 2.35 (*q*, *J* = 7.61, CH_2(4)); 3.73 (*s*, MeO); 4.02 (br. *s*, OH–C(1′)); 4.90 (br. *s*, H–C(1′)); 7.08 (*t*, *J* = 8.0, H–C(3)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.0 (C(20)); 27.1 (C(3′)); 22.6, 24.7, 29.2, 29.3, 29.4, 29.5, 29.7 (14 C, CH_2); 28.6 (C(5)); 31.9 (C(4)); 51.9 (MeO); 73.3 (C(1′)); 129.6 (C(2)); 149.1 (C(3)); 166.5 (C(1)); 206.3 (C(2′)). EI-MS: 397 (4, $[M+H]^+$), 365 (2), 353 (21), 321 (14), 293 (10), 284 (5), 275 (3), 241 (3), 115 (38). FAB-HR-MS: 397.3318 ($C_{24}H_{45}O_4^+$; calc. 397.3318).

Mixture **4**/**5**. Colorless oil. $[\alpha]_D^{20} = +70.28$ ($c = 0.044$, $CHCl_3$). UV (MeOH): 216 sh (4.13). IR (KBr): 3420 (OH), 2921, 2851, 1746, 1683, 1466, 1384, 1283, 1199, 1079, 1021. EI-MS: 397 (42, $[M+H]^+$), 396 (5, M^+), 365 (24), 347 (3), 322 (4), 304 (3), 275 (2), 205 (2), 164 (13), 153 (77), 140 (100). FAB-HR-MS: 397.3308 ($C_{24}H_{45}O_4^+$; calc. 397.3319).

*(3*E*,4*R*,5*R*)-4,5-Dihydro-4-hydroxy-5-methoxy-5-methyl-3-octadecylidenefuran-2(3*H*)-one* (= *Machicolide A*; **4**). ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.88 (*t*, *J* = 7.0, Me(18′)); 1.26 (br. *s*, 14 CH_2); 1.50 (*m*, CH_2(3′)); 1.60 (*s*, Me–C(5)); 2.38 (*m*, CH_2(2′)); 3.39 (*s*, MeO); 4.54 (br. *s*, H–C(4)); 6.99 (*td*, *J* = 8.0, 1.6, H–C(1′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.1 (Me(18′)); 16.1 (Me–C(5)); 22.4, 27.2, 28.8, 29.3, 29.4, 29.5, 29.6, 29.8 (14 C, CH_2); 29.2 (C(3′)); 31.9 (C(2′)); 50.3 (MeO); 72.6 (C(4)); 109.3 (C(5)); 130.0 (C(2)); 148.4 (C(1′)); 168.0 (C(2)).

*(3*Z*,4*R*,5*R*)-4,5-Dihydro-4-hydroxy-5-methoxy-5-methyl-3-octadecylidenefuran-2(3*H*)-one* (= *Machicolide B*; **5**). ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.88 (*t*, *J* = 7.0, Me(18′)); 1.26 (br. *s*, 14 CH_2); 1.51 (*m*, CH_2(3′)); 1.55 (*s*, Me–C(5)); 2.76 (*m*, CH_2(2′)); 3.40 (*s*, MeO); 4.40 (br. *s*, H–C(4)); 6.57 (*td*, *J* = 8.0, 1.6, H–C(1′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.1 (C(18′)); 16.3 (Me–C(5)); 22.7, 26.9, 28.4, 29.4, 29.4, 29.5, 29.6, 29.7 (14 C, CH_2); 29.3 (C(3′)); 33.3 (C(2′)); 50.5 (MeO); 75.8 (C(4); 108.8 (C(5)); 129.8 (C(3)); 150.3 (C(1′)); 167.8 (C(2)).

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