Alkaloids from the Twigs and Leaves of *Daphniphyllum macropodum*

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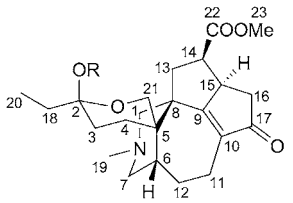
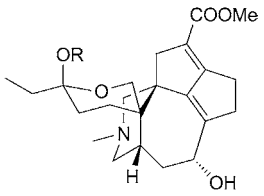
Three new alkaloids, macrodumines A – C (**1** – **3**, resp.), along with ten known analogs, were isolated from the twigs and leaves of *Daphniphyllum macropodum*. Their structures were elucidated on the basis of spectroscopic methods. The 11-OH configuration of the known alkaloid hydroxydaphgraciline (**4**) was assigned as α for the first time by comparing the NMR data with those of macrodumine C (**3**).

Introduction. – *Daphniphyllum* alkaloids from the plants of the *Daphniphyllum* genus constitute a class of diverse and structurally complex heterocyclic natural compounds, which have been attracting interest in natural-product and synthetic chemistry for decades [1]. *D. macropodum* MIQ. is native to Southern China [2], previous studies on which have resulted in the isolation of a number of novel *Daphniphyllum* alkaloids, some of which exhibited cytotoxic activities against several tumor cell lines [3]. In a continuing phytochemical study of this plant, the twigs and leaves of *D. macropodum* were examined, and three new *Daphniphyllum* alkaloids, macrodumines A – C (**1** – **3**, resp.), along with ten known analogs, were isolated. Their structures were elucidated on the basis of spectroscopic methods. The 11-OH configuration of a known compound, hydroxydaphgraciline (**4**) [4], was assigned as α for the first time by comparing the NMR data with those of **3**. We report herein the isolation and structure elucidation of these alkaloids.



1 R = H
2 R = Me



3 R = Me
4 R = H

Results and Discussion. – Macrodumine A (**1**) was obtained as a white amorphous powder, whose molecular formula, $C_{23}H_{33}NO_5$, was determined by HR-EI-MS (*m*/*z* 403.2358 (M^+; calc. 403.2359)), indicating eight degrees of unsaturation. The UV absorption band at 246 nm (log ε 4.05), and IR absorptions at 1699 and 1657 cm^{-1} were characteristic for an α,β-unsaturated keto group. The IR absorption bands at 3433 and

1734 cm^{-1} revealed the presence of OH and ester C=O groups, respectively. The NMR data (*Table*) displayed 23 C-atom resonances, including those for three Me (those resonating at δ(C) 52.4 and 46.9 being linked with a N- or O-atom), ten CH_2 (those resonating at δ(C) 64.2, 63.9, and 57.1 being linked with a N- or O-atom), three CH groups, and seven quaternary C-atoms (two olefinic C-atoms (δ(C) 188.5, 139.4), one ester C=O C-atom (δ(C) 175.9), one ketone C=O C-atom (δ(C) 212.9), and one O-bearing C-atom (δ(C) 97.9)). Further analysis of the NMR data of **1** (*Table*) revealed the presence of an O-bearing CH_2 (δ(C) 64.2, δ(H) 3.76 (*d*, $J = 12.3$) and 3.48 (*dd*, $J =$ 12.3, 2.5, CH_2(21))), an Et group (δ(C) 36.7; δ(H) 1.54–1.60 (*m*, CH_2(18); and δ(C) 8.8; δ(H) 0.91 (*t*, $J = 7.5$, Me(20))), and a MeN group (δ(C) 46.9; δ(H) 2.17 (*s*, MeN), and a quaternary hemiketal C-atom (δ(C) 97.9 (C(2))), which are the characteristic features of a yuzurine-type *Daphniphyllum* alkaloid [5]. The constitution of **1** was determined by using a combination of 2D-NMR spectra (^{1}H,^{1}H-COSY, HSQC, and HMBC; *Fig. 1*). The presence of a C(9)=C(10) bond was confirmed by the HMBCs CH_2(1)/C(9), CH_2(11)/C(9), CH_2(13)/C(9), H–C(14)/C(9), CH_2(16)/C(9), CH_2(11)/C(10), CH_2(12)/C(10), and CH_2(16)/C(10). The keto C-atom was attributed to C(17) by the HMBC features of CH_2(11)/C(17) and CH_2(16)/C(17). The Me(23)O was attached to C(22) on the basis of the HMBC Me(23)/C(22). The relative configuration of **1** was also determined as the same as the yuzurine-type *Daphniphyllum* alkaloid by the ROESY spectrum (*Fig. 1*), in which the typical key ROESY correlations of a yuzurine-type *Daphniphyllum* alkaloid were observed.

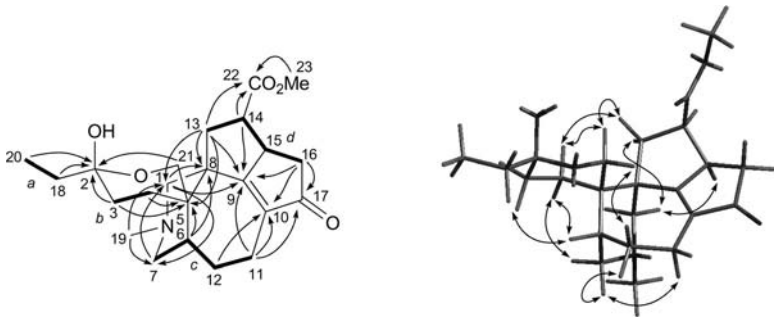


Fig. 1. *^{1}H,^{1}H-COSY* (—), *Selected HMB* (H → C) *and ROESY* (H ↔ H) *correlations of* **1**

Macrodumine B (**2**) possessed the molecular formula $C_{24}H_{35}NO_5$ as deduced from its HR-EI-MS (*m*/*z* 417.2513 (M^+; calc. 417.2515)), which indicated 14 mass units more than that of **1**, suggesting that compound **2** is likely a methylated analog of **1**. The ^{1}H- and ^{13}C-NMR data (*Table*) of **2** closely resembled those of **1** except for the presence of signals for an additional MeO group, which was determined to be at C(2) on the basis the key HMBC (*Fig. 2*) of MeO (δ(H) 3.15 (*s*, 3 H); δ(C) 48.2)/C(2) (δ(C) 101.2). The structure and relative configuration of **2** were further confirmed by its HSQC, HMBC, and ROESY spectra (*Fig. 2*).

Macrodumine C (**3**) had the molecular formula of $C_{24}H_{35}NO_5$ on the basis of HR-EI-MS (*m*/*z* 417.2505 (M^+; calc. 417.2515)), indicating eight degrees of unsaturation. The UV absorption band at 294 nm (log ε 4.18), and IR absorptions at 1703, 1657, and

Table. *^{1}H- and ^{13}C-NMR* (at 400 and 100 MHz, resp.) *Data of* **1**–**4** *in CD_3OD.* Arbitrary atom numbering as indicated in the *Formulae*; δ in ppm, J in Hz.

Position	**1**		**2**		**3**		**4**
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(C)
1	2.50 (br. *s*)	63.9	2.53–3.59 (*m*, H_a)[a]), 2.44–2.46 (*m*, H_b)[a])	62.3	2.43 (*d*, J = 11.7), 2.32 (br. *d*, 11.7)	59.9	59.2
2		97.9		101.2		101.0	97.8
3	1.68–1.72 (*m*, H_a)[a]), 1.50–1.54 (*m*, H_b)[a])	29.1	1.52–1.64 (*m*)[a])	28.8	1.63 (br. *s*)	28.7	29.0
4	2.05–2.09 (*m*, H_a)[a]), 1.62–1.66 (*m*, H_b)	24.4	2.09–2.16 (*m*)[a])	22.9	1.96–2.02 (*m*, H_a)[a]), 1.57–1.68 (*m*, H_b)[a])	22.9	23.2
5		39.0		37.1		36.1	36.2
6	2.36–2.40 (*m*)[a])	34.6	2.39–2.43 (*m*)[a])	34.5	2.49 (br. *s*)	35.2	34.7
7	2.70–2.82 (*m*, H_a), 2.63–2.72 (*m*, H_b)[a])	57.1	2.78–2.82 (*m*, H_a), 2.67–2.73 (*m*, H_b)[a])	56.9	2.69–2.75 (*m*, H_a)[a]), 2.62–2.68 (*m*, H_b)[a])	56.0	56.0
8		52.0		51.7		47.8	47.7
9		188.5		188.2		154.9	154.7
10		139.4		140.9		150.4	150.2
11	2.36–2.48 (*m*)[a])	22.6	2.78–2.82 (*m*, H_a)[a]), 2.22–2.30 (*m*, H_b)[a])	23.2	4.11 (*t*-like, J = 3.3)	67.7	67.5
12	2.09–2.13 (*m*, H_a)[a]), 1.70–1.80 (*m*, H_b)[a])	27.8	2.01–2.09 (*m*, H_a)[a]), 1.81–1.87 (*m*, H_b)[a])	29.0	2.32–2.38 (*m*, H_a)[a]), 1.91–1.99 (*m*, H_b)[a])	36.0	35.7
13	2.58–2.62 (*m*, H_a)[a]), 1.87–1.93 (*m*, H_b)	39.8	2.22–2.30 (*m*, H_a)[a]), 1.73–1.80 (*m*, H_b)[a])	39.9	3.09–3.15 (*m*, H_a)[a]), 2.31–2.35 (*m*, H_b)[a])	45.2	45.1
14	3.09–3.14 (*m*)	43.8	2.64–2.68 (*m*)[a])	47.1		120.5	120.8
15	3.28–3.32 (*m*)	46.4	2.96–3.00 (*m*)	52.1		170.3	170.1
16	2.62–2.72 (*m*, H_a)[a]), 2.36–2.44 (*m*, H_b)[a])	39.4	2.54–2.60 (*m*, H_a)[a]), 2.22–2.30 (*m*, H_b)[a])	43.2	2.66–2.72 (*m*)[a])	27.1	27.0
17		212.9		211.4	3.08–3.12 (*m*, H_a)[a]), 2.87–2.93 (*m*, H_b)	41.1	41.2
18	1.54–1.60 (*m*)[a])	36.7	1.71–1.77 (*m*, H_a)[a]), 1.39–1.49 (*m*, H_b)	30.0	1.68–1.77 (*m*, H_a), 1.38–1.47 (*m*, H_b)	30.0	36.6
19	2.17 (*s*)	46.9	2.18 (*s*)	46.3	2.28 (*s*)	45.6	45.3
20	0.91 (*t*, J = 7.5)	8.8	0.85 (*t*, J = 7.5)	8.4	0.84 (*t*, J = 7.6)	8.5	8.7
21	3.76 (*d*, J = 12.3, H_a), 3.48 (*dd*, J = 12.3, 2.5, H_b)	64.2	3.70–3.74 (*m*, H_a)[a]), 3.62 (*dd*, J = 14.7, 2.8, H_b)	63.5	3.40 (*d*, J = 11.8, H_a), 3.36 *dd*, J = 11.8, 2.8, H)	63.9	63.4
22		175.9		176.3		168.6	168.4
23	3.64 (*s*)	52.4	3.71 (*s*)	53.0	3.71 (*s*)	52.2	52.2
*Me*O			3.15 (*s*)	48.2	3.11 (*s*)	48.2	

[a]) Overlapped signals.

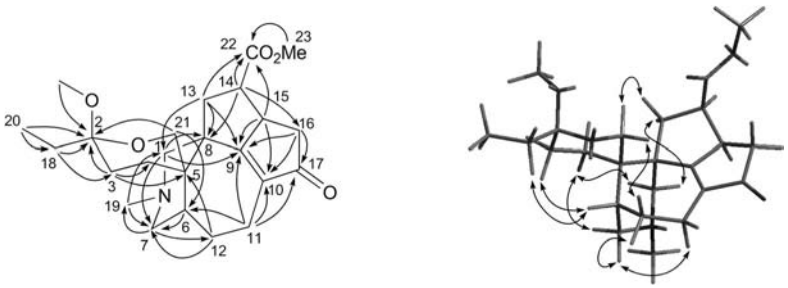


Fig. 2. *Selected HMB* (H → C) *and ROESY* (H ↔ H) *correlations of* **2**

1628 cm^{-1} were typical features of an ester C=O conjugated with two C=C bonds. The IR absorption bands at 3427 cm^{-1} revealed the presence of a OH group. The NMR data (*Table*) displayed 24 C-atom resonances, including those for four Me (those resonating at δ(C) 52.2, 48.2, and 45.6 being linked with a N- or O-atom), ten CH_2 (those resonating at δ(C) 63.9, 59.9, and 56.0 being linked with a N- or O-atom), two CH groups (one O-bearing C-atom (δ(C) 67.7)), and eight quaternary C-atoms (four olefinic C-atoms (δ(C) 170.3, 154.9, 150.4, and 120.5), one ester C=O C-atom (δ(C) 168.6), and one ketal C-atom (δ(C) 101.0)). These data suggested that compound **3** was also a yuzurine-type *Daphniphyllum* alkaloid [5]. The structure of **3** was finally elucidated by the 2D-NMR spectra (HSQC, HMBC, and ROESY; *Fig. 3*). The presence of conjugated of C(9)=C(10) and C(14)=C(15) bonds was established by the multiple HMBCs CH_2(1)/C(9), H–C(11)/C(9), H–C(11)/C(10), CH_2(12)/C(10), CH_2(13)/C(9), CH_2(13)/C(14), CH_2(13)/C(15), CH_2(16)/C(15), CH_2(17)/C(9), CH_2(11)/C(10), and CH_2(17)/C(15). Two MeO groups were at C(2) and C(22), respectively, on the basis of the key HMBCs MeO–C(2)/C(2) and Me(23)/C(22). The only OH group was located at C(11), due to the HMBCs of CH_2(12)/C(11), and H–C(11)/C(6), C(9), C(10), and C(17). The small coupling constants between H–C(11) (δ(H) 4.11 (*t*-like, $J = 3.3$), H_a–C(12) (δ(H) 2.32 – 2.38 (*m*)), and H_b–C(12) (δ(H) 1.91 – 1.99 (*m*)) suggested that H–C(11) was likely β-orientated, which was confirmed by the key ROESY correlation H–C(11)/CH_2(17) (δ(H) 3.08 – 3.12, 2.87 – 2.93 (*m*, each 1 H)). Thus, the structure of compound **3** was elucidated as shown.

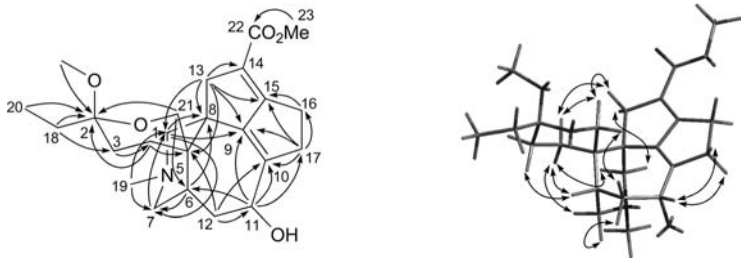


Fig. 3. *Selected HMB* (H → C) *and ROESY* (H ↔ H) *correlations of* **3**

Compound **4** was identified as the known alkaloid hydroxydaphgraciline [4], whose previously unassigned orientation of H–C(11) was established as β by comparing the NMR data (*Table*) with those of **3**.

Ten known *Daphniphyllum* alkaloids, hydroxydaphgraciline (**4**) [4], yuzurine [5b][6], deoxycalyciphylline B [1e], deoxyisocalyciphylline B [1e], methyl homosecodaphniphyllate [7], longistylumphylline A [8], daphniyunnine B [9], daphnilongamine E [10], codaphniphylline [11], and dehydroxymacropodumine A [12], were identified on the basis of their ^{1}H- and ^{13}C-NMR, and EI-MS data, some of which were also confirmed by co-TLC with authentic samples.

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Experimental Part

General. All solvents used were of anal. grade (*Shanghai Chemical Plant*, Shanghai, P. R. China). TLC: Pre-coated silica-gel GF_{254} plates (SiO_2; *Qingdao Haiyang Chemical Plant*, Qingdao, P. R. China). Column chromatography (CC): silica gel (SiO_2; 200–300 mesh), SiO_2 *H60*, *Sephadex LH-20* (*Amersham Biosciences*). Optical rotations: *Perkin-Elmer 341* polarimeter. UV Spectra: *Shimadzu UV-2550* UV/VIS spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Perkin-Elmer 577* spectrometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker AM-400* spectrometer; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI (70 eV) and ESI-MS: *Finnigan MAT 95* mass spectrometer and *Finnigan LCQ-DECA* instruments, resp.; in *m*/*z* (rel. %).

Plant Material. Twigs and leaves of *Daphniphyllum macropodum* were collected in June 2006, in Guilin of Guangxi Province, P. R. China, and authenticated by Prof. *Shao-Qing Tang* at Guangxi Normal University. A voucher specimen has been deposited with the Shanghai Institute of Materia Medica, Chinese Academy of Sciences (accession No. 2006-DM-2Y1).

Extraction and Isolation. The powdered dried twigs and leaves (6 kg) of *D. macropodum* were extracted with 95% EtOH at r.t. three times. After removal of the solvent under reduced pressure, the crude extract (1500 g) was dissolved in 2 l of H_2O to form a suspension and adjusted with 2N H_2SO_4 to pH of *ca.* 4. The acidic mixture was defatted with AcOEt (800 ml × 3), and the aq. phase was basified with 30% Na_2CO_3 in H_2O to pH of *ca.* 10 and extracted with $CHCl_3$ (500 ml × 4) to obtain 3.4 g of crude alkaloids. This was then subjected to CC (SiO_2; $CHCl_3$/MeOH 200 : 1 to 5 : 1), to give five major fractions, *Frs. 1–5*. *Fr. 1* (1.9 g) was submitted to CC (SiO_2; petroleum ether (Pe)/Et_2NH; 100 : 1 to 20 : 1), to afford three further fractions, *Frs. 1a–1c*. *Fr. 1a* was purified by CC (*Sephadex LH-20*; MeOH), to yield deoxycalyciphylline B (15 mg) and methyl homosecodaphniphyllate (9 mg). *Fr. 1b* was separated by CC (SiO_2; $CHCl_3$/MeOH 100 : 1) to furnish three major components, and each was then purified by CC (*Sephadex LH-20*; MeOH), to yield **1** (18 mg), **2** (8 mg), codaphniphylline (7 mg). *Fr. 1c* was subjected to CC (SiO_2; $CHCl_3$/MeOH 100 : 1, 150 : 1) to yield **3** (5 mg), **4** (7 mg). *Fr. 2* was purified by CC (SiO_2; PE/Et_2NH 50 : 1) to afford deoxyisocalyciphylline B (26 mg). *Fr. 3* was subjected to CC (SiO_2; PE/Et_2NH 30 : 1 to yield yuzurine (5 mg) and longistylumphylline A (9 mg). *Fr. 4* was separated by CC (SiO_2; PE/Et_2NH 6 : 1) to yield daphnilongamine E (3 mg) and dehydroxymacropodumine A (17 mg). *Fr. 5* was subjected to CC (*Sephadex LH-20*; MeOH) and then purified by CC (SiO_2; $CHCl_3$/MeOH 50 : 1) to yield daphniyunnine B (5 mg).

Macrodumine A (= *Methyl (4*S*,6′*S*,8a*R*,9*R*,10a*R*,11*S*)-6′-Ethyl-2,3,4,5,5′,6,6′,7,8,8a,9,10-dodecahydro-6′-hydroxy-2-methyl-7-oxo-1*H*,4′*H*-spiro[4,10a-methanopentaleno[1,6-*cd*]azonine-11,3′-pyran]-9-carboxylate*; **1**). White amorphous powder. $[\alpha]_D^{20} = +7.0$ ($c = 0.75$, $CHCl_3$). UV (MeOH): 246 (4.05). IR (film): 3433, 2937, 2883, 2785, 1734, 1699, 1657, 1460, 1377, 1284, 1202, 1042, 1024, 928. ^{1}H- and ^{13}C-NMR: see the *Table*. EI-MS: 403 (38, M^+), 372 (24), 342 (6), 318 (10), 301 (15), 285 (5), 245 (4), 155 (6), 129 (8), 84 (23), 70 (7), 58 (100). HR-EI-MS: 403.2358 (M^+, $C_{23}H_{33}NO_5^+$; calc. 403.2359).

Macrodumine B (= *Methyl (4*S*,6′*S*,8a*R*,9*R*,10a*R*,11*S*)-6′-Ethyl-2,3,4,5,5′,6,6′,7,8,8a,9,10-dodecahydro-6′-methoxy-2-methyl-7-oxo-1*H*,4′*H*-spiro[4,10a-methanopentaleno[1,6-*cd*]azonine-11,3′-pyran]-9-carboxylate*; **2**). White amorphous powder. $[\alpha]_D^{20} = +30.0$ ($c = 0.28$, $CHCl_3$). UV (MeOH): 248 (4.05). IR (KBr): 3431, 2937, 2850, 2789, 1736, 1705, 1662, 1460, 1377, 1200, 1038. ^{1}H- and ^{13}C-NMR: see the *Table.* EI-MS: 417 (2, M^+), 420 (24), 385 (32), 374 (7), 328 (7), 301 (23), 288 (4), 258 (1), 237 (3), 179 (7), 165 (7), 149 (51), 84 (34), 58 (100). HR-EI-MS: 417.2513 (M^+, $C_{24}H_{35}NO_5^+$; calc. 417.2515).

Macrodumine C (= *Methyl (4*S*,6*R*,6′*S*,10a*R*,11*S*)-6′-Ethyl-2,3,4,5,5′,6,6′,7,8,10-decahydro-6,6′-dihydroxy-2-methyl-1*H*,4′*H*-spiro[4,10a-methanopentaleno[1,6-*cd*]azonine-11,3′-pyran]-9-carboxylate*; **3**). White amorphous powder. $[\alpha]_D^{20} = +6.0$ ($c = 0.155$, $CHCl_3$). UV (MeOH): 294 (4.18). IR (KBr): 3427, 2920, 2852, 2804, 1703, 1657, 1628, 1437, 1355, 1256, 1113, 1041. ^{1}H- and ^{13}C-NMR: see the *Table.* EI-MS: 417 (49, M^+), 402 (16), 388 (66), 385 (100), 367 (23), 356 (53), 328 (5), 301 (8), 283 (13), 268 (4), 227 (6), 202 (5), 165 (7), 115 (6), 74 (87), 58 (56). HR-EI-MS: 417.2505 (M^+, $C_{24}H_{35}NO_5^+$; calc. 417.2515).

Hydroxydaphgraciline (= *Methyl (4*S*,6*R*,6′*S*,10a*R*,11*S*)-6′-Ethyl-2,3,4,5,5′,6,6′,7,8,10-decahydro-6-hydroxy-6′-methoxy-2-methyl-1*H*,4′*H*-spiro[4,10a-methanopentaleno[1,6-*cd*]azonine-11,3′-pyran]-9-carboxylate*; **4**). White amorphous powder. ^{13}C-NMR: see the *Table.*

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