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Alkaloids from the Twigs of *Daphniphyllum calycinum*

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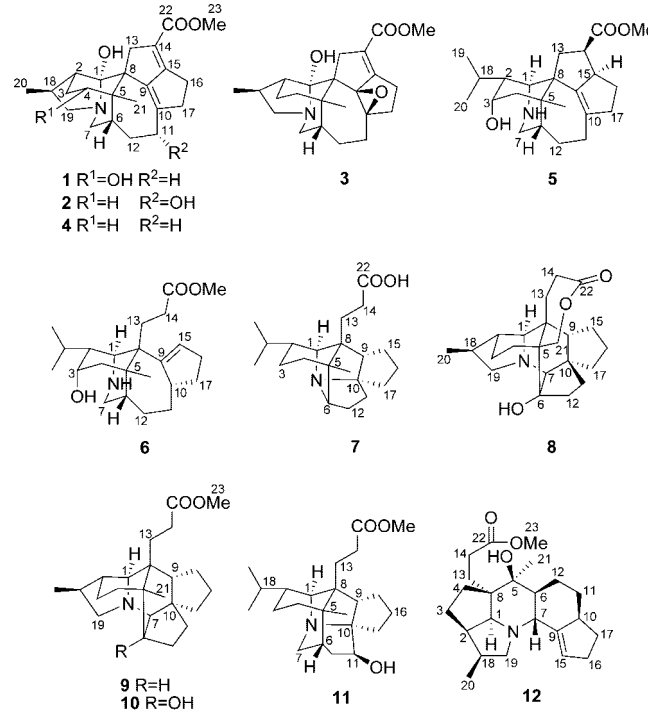
Twelve new alkaloids, caldaphnidines G−R (**1**−**12**), along with 24 known ones, were isolated from the twigs of *Daphniphyllum calycinum*. Their structures were elucidated by spectroscopic methods, especially two-dimensional NMR techniques.

Plants in the genus of *Daphniphyllum* are well known for containing structurally diverse *Daphniphyllum* alkaloids with highly complex polycyclic skeletons, which have been attractive subjects for natural products and organic chemists.[1] In recent years, quite a number of *Daphniphyllum* alkaloids have been isolated, some of which exhibited cytotoxic activity against several tumor cell lines.[2] *Daphniphyllum calycinum* benth. (Daphniphyllaceae) is an evergreen tree that grows mainly in southern China, and its leaves and seeds have been applied in traditional Chinese medicine to treat fever, inflammation, and influenza.[3] Our previous studies on different parts of *D. calycinum* collected from several locations (caldaphnidines A−F were isolated from the leaves and seeds) and other research groups have resulted in the isolation of a series of alkaloids[2b,e,4−6] and a few flavonoid glycosides.[7] In further study, 12 new *Daphniphyllum* alkaloids, caldaphnidines G−R (**1**−**12**), along with 24 known ones, were isolated from an ethanolic extract of *D. calycinum* twigs. We report herein the isolation and structural elucidation of these alkaloids.



Results and Discussion

Caldaphnidine G (**1**), a white amorphous powder, possessed the molecular formula $C_{23}H_{31}NO_4$ as determined by HREIMS, *m*/*z* 385.2246 $[M]^+$ (calcd 385.2253), with 9 degrees of unsaturation. The UV absorption band at 300 nm (log ε 3.88) and IR absorptions at 1666, 1643, and 1624 cm^{-1} were features typical of an ester carbonyl conjugated with two double bands,[8] the same as in the cases of calycinine A and caldaphnidine A.[4,6] The ^{13}C NMR data (Table 1) displayed 23 carbon resonances, including three methyls (one oxygenated at δ_C 50.9), eight methylenes (with those at δ_C 64.0 and 58.7 being linked with the N atom), four methines (one oxygenated at δ_C 75.1), and eight quaternary carbons (four olefinic

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Table 1. ^{13}C NMR Data of **1**−**12**

carbon	**1**[a]	**2**[b]	**3**[b]	**4**[b]	**5**[b]	**6**[b]	**7**[b]	**8**[b]	**9**[b]	**10**[b]	**11**[b]	**12**[b]
1	96.5	98.3	100.3	69.6	56.8	58.7	69.4	63.3	62.9	63.0	64.9	70.2
2	42.3	43.2	45.3 c	39.7	46.0	45.4	39.6	38.9	39.4	39.2	39.9	52.7
3	31.9	23.1	22.9	24.1	64.6	65.3	24.7	20.2	19.2	20.7	28.3	25.4
4	75.1	36.6	37.3	38.8	49.6	50.4	34.8	26.7	37.3	33.6	37.9	34.8
5	42.6	38.6	42.1	35.7	36.8	37.7	44.4	44.6	38.2	43.4	38.7	75.4
6	35.0	45.9	43.2	45.0	42.8	42.1	70.2	84.7	42.7	85.8	43.9	54.6
7	58.7	59.0	59.4	59.6	44.0	41.4		71.4	69.0	70.6	47.7	57.2
8	52.5	54.1	50.3	48.0	52.0	44.6	53.2	39.1	37.6	39.3	50.2	54.7
9	151.7	154.2	85.4	153.8	147.7	152.0	52.3	50.0	55.1	53.8	47.9	150.0
10	150.5	150.8	75.1	152.1	136.9	47.2	84.6	52.0	52.6	52.4	78.5	43.0
11	25.9	68.1	27.7	27.0	28.8	32.0	34.8	36.4	41.1	37.3	70.8	37.3
12	29.3	38.1	29.6	30.6	30.3	29.6	23.6	32.9	24.5	35.4	34.1	27.9
13	41.7	44.5	42.8	44.8	38.7	30.2	23.1	26.7	29.8	30.2	27.8	32.8
14	118.6	122.0	127.8	117.8	44.1	30.4	34.8	29.7	32.0	32.0	33.7	31.7
15	169.8	172.8	161.9	171.2	55.5	130.5	30.1	28.6	30.5	30.2	30.4	124.7
16	25.1	26.6	23.5	26.8	27.6	30.6	27.2	27.1	27.8	27.5	28.1	32.5
17	42.5	41.7	35.8	43.6	44.2	34.4	37.4	38.0	37.7	38.6	41.4	32.0
18	34.5	36.9	34.6	38.5	27.1	26.6	33.6	39.1	38.6	39.2	32.4	35.9
19	64.0	63.4	65.4	66.1	22.1	21.3	21.7	58.1	59.1	58.1	21.9	61.5
20	15.3	16.7	14.4	15.7	22.4	21.2	21.6	12.4	12.4	12.3	22.4	14.0
21	21.4	25.1	24.4	25.2	27.4	26.7	19.5	71.7	22.6	23.3	26.5	26.4
22	166.7	168.8	166.4	169.2	177.4	175.9	181.8	179.0	177.0	176.9	176.5	176.8
23	50.9	52.1	52.6	52.1	52.0	52.8			52.6	52.6	52.7	52.6

[a] Data measured in $CDCl_3$ at 100 MHz. [b] Data measured in CD_3OD at 100 MHz.

at δ_C 169.8, 151.7, 150.5, and 118.6 and one ester carbonyl at δ_C 166.7). The NMR data of **1** showed high similarity to those of calycinine A,[4] except that the C-4 methylene in calycinine A was replaced by an oxygenated methine at δ_C 75.1 in **1**. This assignment was confirmed by $^1H-^1H$ COSY and HMBC spectra (see Supporting Information), especially by the HMBC correlations from Me-21 (δ_H 0.99, s, 3H) and H_2-3 (δ_H 1.88 and 1.60, each 1H, m) to C-4 and from H-4 (δ_H 3.86, dd, J = 11.4, 7.4 Hz) to C-5 (δ_C 42.6), C-6 (δ_C 35.0), and C-8 (δ_C 52.5). Therefore, the C-3 (δ_C 31.9) and C-5 (δ_C 42.6) were respectively shifted downfield ca. $\Delta\delta$ +9.7 and $\Delta\delta$ +4.0 as compared with those of calycinine A due to the presence of 4-OH, and the C-6 (δ_C 35.0) was shifted upfield ca. $\Delta\delta$ +7.2, attributable to the γ-gauche effect of the 4-OH. The β-configuration of H-4 was assigned on the basis of the ROESY (Supporting Information) correlation of H-4/H_2-13 (δ_H 3.03, brs, 2H).

Caldaphnidine H (**2**) had the same molecular formula of $C_{23}H_{31}NO_4$ as that of **1**. The ^{13}C and ^1H NMR data (Tables 1 and 2) showed that alkaloid **2** was an analogue of **1** and of calycinine A,[4] and the only difference was the presence of an OH group at C-11 (δ_C 68.1) in **2**, as judged by the HMBC (Supporting Information) correlations from H-11 (δ_H 4.02, t-like, J = 3.2 Hz) to C-6 (δ_C 45.9), C-9 (δ_C 154.2), C-10 (δ_C 150.8), and C-17 (δ_C 41.7) and from H_2-12 (δ_H 2.17 and 1.83, each 1H, m) to C-11. The small coupling constants among H-11, H-12a (δ_H 2.17, m), and H-12b (δ_H 1.83, m) implied that H-11 likely had a β-orientation, which was confirmed by the ROESY (Supporting Information) correlations of H-11/H_2-17 (δ_H 3.16 and 2.89, each 1H, m).

Caldaphnidine I (**3**) had a molecular formula of $C_{23}H_{31}NO_4$ as determined by HREIMS. The strong IR absorptions at 3435 and 1713 cm^{-1} indicated the presence of OH and carbonyl groups. The ^{13}C (Table 1) and ^1H (Table 2) NMR data suggested that **3** was also an analogue of calycinine A.[4] Two oxygenated quaternary carbons at δ_C 85.4 and 75.1 were respectively assigned to C-9 and C-10, which formed an epoxide, as in the case daphmanidin F,[9] by the mutual HMBC correlations from H_2-11 (δ_H 2.30 and 2.19, each 1H, m), H_2-16 (δ_H 2.30 and 2.21, each 1H, m), and H_2-17 (δ_H 2.71 and 2.08, each 1H, m) to C-9 (δ_C 85.4) and C-10 (δ_C 75.1), from H-13b (δ_H 3.14, m) to C-9, and from H_2-12 (δ_H 2.21 and 1.44, each 1H, m) to C-10 (Supporting Information). The epoxide was assigned a β-orientation from the ROESY (Supporting Information) correlations between H-11a (δ_H 2.30, m) and H-17b (δ_H 2.08, m) and between H-11b (δ_H 2.19, m) and H-17a (δ_H 2.71, m). The structure of **3** was confirmed by $^1H-^1H$ COSY, HMBC, and ROESY data.

Caldaphnidine J (**4**) gave the molecular formula $C_{23}H_{31}NO_2$ by HREIMS, one oxygen (16 mass units) less than that of calycinine A.[4] As compared with calycinine A, the ^{13}C NMR data (Table 1) of **4** showed the presence of one nitrogenated methine at δ_C 69.6, suggesting that **4** was likely the deoxy product of calycinine A. HMBC correlations of H_2-13 (δ_H 3.09, brd, J = 15.6 Hz and δ_H 2.72, m)/C-1 confirmed this assignment. The relative configuration of **4** was further verified by ROESY data (see Supporting Information).

Caldaphnidine K (**5**) showed a molecular ion at m/z 373 in the HREIMS, consistent with the molecular formula $C_{23}H_{35}NO_3$, and one more oxygen atom than caldaphnidine B.[7] Comparison of the NMR data of **5** (Tables 1 and 2) with those of caldaphnidine B indicated that **5** was an analogue of caldaphnidine B, and the only difference was the presence of an OH group in **5**. The sole OH group was attached to the C-3 methine (δ_C 64.6; δ_H 4.07, t-like, J = 5.8 Hz), as indicated by the mutual HMBC (Supporting Information) correlations from H-3 to C-1 (δ_C 56.8), C-2 (δ_C 46.0), C-4 (δ_C 49.6), and C-5 (δ_C 36.8) or from C-3 to H-1 (δ_H 2.66, d, J = 4.1 Hz), H-2 (δ_H 1.52, m), and H_2-4 (δ_H 1.82, dd, J = 15.3, 5.8 Hz and δ_H 1.56, brd, J = 15.3 Hz). This was supported by the downfield shifts of C-2 (ca. $\Delta\delta$ +3.6) and C-4 (ca. $\Delta\delta$ +8.8) as compared with those of caldaphnidine B due to the presence of 3-OH. The small coupling constant of H-3 (δ_H 4.07, t-like, J = 5.8 Hz) clearly indicated that it occupied the equatorial bond and was β-configured. The structure of **5** was thus elucidated.

Caldaphnidine L (**6**) gave a molecular formula of $C_{23}H_{37}NO_3$ as determined by HREIMS at m/z 375.2752 $[M]^+$ (calcd. 375.2773). Comparison of the ^{13}C NMR data of **6** with those of calyciphylline K[5i] isolated in the current study indicated that both compounds shared the same alkaloid backbone, and the only difference was that **6** had an OH group at C-3 (δ_C 65.3), as judged from their similar NMR patterns (Tables 1 and 2) and 2D NMR spectra of **6**. This deduction was supported by the molecular formula of **6**, which had one more oxygen atom than that of calyciphylline K. In the HMBC (Supporting Information), the mutual correlations from H-3 (δ_H 4.16, brs) to C-1 (δ_C 58.7) and C-5 (δ_C 37.7) and from H-1 (δ_H 3.79, brs) and H_2-4 (δ_H 2.20 and 1.70, each 1H, m) to C-3 confirmed the presence of an OH group at C-3, which was consistent with the expectation of the downfield shifted C-2 (ca. $\Delta\delta$ +4.4) and C-4 (ca. $\Delta\delta$ +9.4) as compared with those of calyciphylline K. The broad singlet of H-3 at δ_H 4.16 (1H, brs) indicated that it adopted an equatorial bond, suggesting that the 3-OH was α-oriented.

Table 2. ^{1}H NMR Data of **1**−**6**

proton	**1** (*J* in Hz)[a]	**2** (*J* in Hz)[b]	**3** (*J* in Hz)[b]	**4** (*J* in Hz)[b]	**5** (*J* in Hz)[b]	**6** (*J* in Hz)[b]
1				2.96 (m)	2.66 (d, 4.1)	3.79 (brs)
2	2.38 (m)	2.36 (m)	2.32 (m)	2.44 (m)	1.52 (m)	1.45 (m)
3a	1.88 (m)	2.02 (m)	1.88 (m)	1.79 (m)	4.07 (t-like, 5.8)	4.16 (brs)
3b	1.60 (m)	1.64 (m)	1.74 (m)	1.65 (m)		
4a	3.86 (dd, 11.4, 7.4)	1.78 (m)	1.98 (m)	1.69 (m)	1.82 (dd, 15.3, 5.8)	2.20 (m)
4b		1.51 (m)	1.55 (m)	1.63 (m)	1.56 (brd, 15.3)	1.70 (m)
6	2.34 (m)	1.91 (m)	2.13 (m)	2.07 (m)	1.62 (dd, 7.1, 5.9)	2.27 (m)
7a	3.21 (m, 2H)	3.45 (dd, 13.2, 6.2)	3.73 (m)	3.41 (m)	4.51 (dd, 14.5, 7.1)	3.92 (dd, 13.6, 10.1)
7b		3.10 (m)	3.45 (brd, 14.7)	3.34 (m)	2.58 (brd, 14.5)	3.01 (dd, 13.6, 5.4)
10						3.17 (m)
11a	2.82 (m)	4.02 (t-like, 3.2)	2.30 (m)	2.69 (m)	1.87 (m)	1.70 (m, 2H)
11b	2.07 (m)		2.19 (m)	2.16 (m)	1.44 (m)	
12a	1.83 (m)	2.17 (m)	2.21 (m)	2.05 (m)	2.21 (m)	2.08 (m)
12b	1.53 (m)	1.83 (m)	1.44 (m)	1.54 (m)	1.50 (m)	1.47 (m)
13a	3.03 (brs, 2H)	3.08 (brs, 2H)	3.26 (m)	3.09 (brd,15.6)	2.47 (dd, 14.5, 4.1)	1.87 (m)
13b			3.14 (m)	2.72 (m)	1.96 (dd, 14.5, 10.0)	1.73 (m)
14a					2.89 (ddd, 14.0, 10.0, 4.1)	2.32 (m)
14b						2.15 (m)
15					3.44 (m)	5.75 (brs)
16a	2.71 (m)	2.68 (m, 2H)	2.30 (m)	2.69 (m)	2.38 (m)	2.52 (m)
16b	2.61 (m)		2.21 (m)	2.60 (m)	2.20 (m)	2.27 (m)
17a	2.93 (m)	3.16 (m)	2.71 (m)	2.89 (m)	2.68 (m)	2.09 (m)
17b	2.88 (m)	2.89 (m)	2.08 (m)	2.83 (m)	2.40 (m)	1.64 (m)
18	2.78 (m)	2.81 (m)	3.05 (m)	2.44 (m)	2.01 (m)	2.05 (m)
19a	3.59 (dd, 11.9, 10.6)	3.56 (dd, 11.6, 10.1)	4.05 (dd, 11.9, 10.7)	3.49 (m)	1.05 (d, 6.5, 3H)	1.11 (d, 6.5, 3H)
19b	2.21 (dd, 11.9, 6.0)	2.29 (dd, 11.6, 5.1)	2.80 (dd, 11.9, 6.5)	2.52 (m)		
20	1.08 (d, 7.4, 3H)	1.16 (d, 7.6, 3H)	1.15 (d, 7.4, 3H)	1.11 (d, 6.1, 3H)	0.93 (d, 6.5, 3H)	1.07 (d, 6.5, 3H)
21	0.99 (s, 3H)	0.86 (s, 3H)	1.02 (s, 3H)	0.92 (s, 3H)	1.04 (s, 3H)	1.26 (s, 3H)
23	3.68 (s, 3H))	3.70 (s, 3H)	3.75 (s, 3H)	3.68 (s, 3H)	3.61 (s, 3H)	3.64 (s, 3H)

[a] Data measured in $CDCl_3$ at 400 MHz. [b] Data measured in CD_3OD at 400 MHz. Chemical shifts (δ) are in ppm from TMS.

Table 3. ^{1}H NMR Data of **7**−**12**[a]

proton	**7** (*J* in Hz)	**8** (*J* in Hz)	**9** (*J* in Hz)	**10** (*J* in Hz)	**11** (*J* in Hz)	**12** (*J* in Hz)
1	3.55 (brs)	2.95 (m)	2.91 (d, 4.0)	2.99 (d, 2.7)	2.94 (d, 4.4)	3.30 (m)
2	1.48 (m)	1.90 (m)	1.85 (m)	1.85 (m)	1.47 (m)	2.49 (m)
3a	1.97 (m)	1.46 (m, 2H)	1.44 (m,2H)	1.85 (m)	1.89 (m)	1.46 (m, 2H)
3b	1.40 (m)			1.30 (m)	1.61 (m)	
4a	1.96 (m)	1.65 (m)	1.74 (m)	1.71 (m)	1.98 (m)	1.85 (m)
4b	1.46 (m)	1.44 (m)	1.24 (m)	1.55 (m)	1.48 (m)	1.43 (m)
6	4.09 (dd, 6.2, 4.0)		2.14 (m)		1.55 (m)	1.46 (m)
7a		2.49 (brs)	2.41 (m)	2.47 (m)	3.27 (m)	3.72 (d, 2.5)
7b					2.75 (brd, 14.5)	
9	2.33 (m)	2.25 (m)	1.78 (m)	1.76 (m)	2.65 (m)	
10						2.72 (m)
11a	2.30 (m)	1.70 (m)	1.73 (m)	1.66 (m)	4.01 (t-like, 8.0)	2.03 (m)
11b	2.09 (m)	1.53 (m)	1.60 (m)	1.40 (m)		0.91 (m)
12a	2.11 (m, 2H)	1.89 (m)	1.69 (m)	1.98 (m)	2.06 (m)	1.73 (m)
12b		1.49 (m)	1.32 (m)	1.42 (m)	1.60 (m)	1.52 (m)
13a	2.02 (m)	1.85 (m)	1.81 (m)	1.84 (m)	2.08 (m)	1.66 (m)
13b	1.68 (m)	1.42 (m)	1.64 (m)	1.60 (m)	1.36 (m)	1.60 (m)
14a	2.22 (m)	2.93 (m)	2.43 (m)	2.38 (m)	2.56 (m)	2.39 (m, 2H)
14b	2.00 (m)	2.31 (m)	2.36 (m)	2.32 (m)	2.51 (m)	
15a	2.04 (m)	1.57 (m)	1.66 (m)	1.58 (m)	1.82 (m)	5.41 (brd, 1.7)
15b	1.61 (m)	1.49 (m)	1.56 (m)	1.49 (m)	1.47 (m)	
16a	1.90 (m)	1.71 (m)	1.75 (m)	1.67 (m)	1.69 (m, 2H)	2.28 (m, 2H)
16b	1.55 (m)	1.48 (m)	1.45 (m)	1.37 (m)		
17a	2.10 (m)	2.01 (m)	1.92 (m)	1.88 (m)	2.16 (m)	2.12 (m)
17b	1.83 (m)	1.48 (m)	1.55 (m)	1.43 (m)	1.38 (m)	1.34 (m)
18	1.48 (m)	2.15 (m)	2.16 (m)	2.11 (m)	1.60 (m)	2.25 (m)
19a	1.01 (d, 5.9, 3H)	3.09 (dd, 11.6, 9.3)	2.99 (dd, 11.5, 7.5)	3.13 (dd, 11.0, 8.7)	1.01 (d, 6.3, 3H)	2.95 (m)
19b		3.00 (m)	2.64 (dd, 11.5, 9.9)	2.93 (m)		2.22 (m)
20	0.98 (d, 5.9, 3H)	0.95 (d, 7.2, 3H)	0.97 (d, 6.7, 3H)	0.93 (d, 6.4, 3H)	0.94 (d, 6.3, 3H)	0.97 (d, 6.7, 3H)
21	1.06 (s, 3H)	4.57 (d, 12.6)	0.84 (s, 3H)	0.91 (s, 3H)	0.95 (s, 3H)	1.25 (s, 3H)
		3.96 (d, 12.6)				
23			3.64 (s, 3H)	3.64 (s, 3H)	3.66 (s, 3 h)	3.64 (s, 3H)

[a] Data measured in CD_3OD at 400 MHz. Chemical shifts (δ) are in ppm from TMS.

Caldaphnidine M (**7**) was isolated as a white, amorphous powder having the molecular formula $C_{21}H_{33}NO_2$ (HREIMS). Comparison of the ^{1}H (Table 3) and ^{13}C NMR (Table 1) data of **7** with those of calyciphylline F[5g] showed that the data of the polycyclic alkaloid core in both alkaloids matched very well, and only the chemical shifts of C-13, C-14, and C-22 changed slightly. No methoxy group was observed in **7**, indicating that alkaloid **7** was the free acid of calyciphylline F. This was supported by its IR absorption bands at 3425−2500 and 1633 cm^{-1}, and it had 14-mass units less than calyciphylline F. This

structure of **7** was confirmed by the interpretation of its $^1H-^1H$ COSY, HSQC, HMBC, and ROESY spectra.

Caldaphnidine N (**8**), a colorless oil, possessed a molecular formula of $C_{22}H_{31}NO_3$. The IR spectrum showed strong absorptions at 3427, 1732, and 1716 cm^{-1} assignable to OH and carbonyl groups. The ^{13}C NMR (Table 1) and DEPT spectra displayed 22 carbon resonances, and these were distinguished as one methyl, 11 methylenes (one oxygenated at δ_C 71.7 and one nitrogenated at δ_C 58.1), five methines (two nitrogenated at δ_C 63.3 and 71.4), and five quaternary carbons (one oxygenated at δ_C 84.7 and one ester carbonyl at δ_C 179.0). Comparison of the NMR data of **8** with those of bukittinggine[10] showed high similarity, the major difference being that the C-6 methine in bukittinggine was oxygenated to a quaternary carbon (δ_C 84.7) bearing an OH group in **8**. This assignment was confirmed by HMBC correlations from H_2-4, H-7, H_2-11, and H_2-12 to C-6. The structure of **8** was further verified by a combination analysis of the HSQC, HMBC, and ROESY spectra.

The molecular formula of caldaphnidine O (**9**) was determined as $C_{23}H_{35}NO_2$ by HREIMS. There were 23 carbon resonances in the ^{13}C NMR (Table 1), and these were distinguished as three methyls, 10 methylenes, six methines, and four quaternary carbons (including an ester carbonyl at δ_C 177.0). The NMR data of **9** showed high similarity to those of bukittinggine,[10] except for the presence of a tertiary methyl (C-21) and a methoxy in **9** and the absence of the oxygenated C-21 methylene in bukittinggine, suggesting that the six-membered lactone of bukittinggine was absent in **9**. The only methoxy group was attached to C-22, as indicated by the HMBC (Supporting Information) correlation between O*Me* (δ_H 3.64, s, 3H) and C-22 (δ_C 177.0). The relative configurations of all the chiral centers of **9** were assigned to be the same as in bukittinggine by the ROESY spectrum (Supporting Information).

Caldaphnidine P (**10**) possessed a molecular formula of $C_{23}H_{35}NO_3$ as determined by HREIMS, 16 mass units more than that of caldaphnidine O (**9**). The ^1H (Table 3) and ^{13}C NMR (Table 1) spectra indicated that the structure of **10** was closely related to that of **9**. The only difference was that the C-6 methine of **9** was oxygenated to a quaternary carbon (δ_C 85.8) bearing an OH in **10**. This was confirmed by the HMBC correlations from H_2-4, H-7, H_2-11, and H_2-12 to C-6. As compared with **9**, this assignment was consistent with the expectation of downfield chemical shifts of C-5 (ca. $\Delta\delta$ +5.2) and C-12 (ca. $\Delta\delta$ +8.9) due to the 6-OH and the upfield chemical shifts of of C-4 (ca. $\Delta\delta$ −3.7) and C-11 (ca. $\Delta\delta$ −3.8) due to γ-gauche effects. The relative configuration of **10** was determined to be the same as **9** by a ROESY experiment.

Caldaphnidine Q (**11**) had the same molecular formula ($C_{23}H_{37}NO_3$) as methyl 17-hydroxhomodaphniphyllate.[11] Comparison of the ^1H (Table 3) and ^{13}C NMR (Table 1) data of **11** with those of methyl 17-hydroxhomodaphniphyllate indicated that they were analogues, and the only difference was the location of the OH. The HMBC placed it at C-11, as revealed by correlations from H-11 (δ_H 4.01, t-like, J = 8.0 Hz) to C-6 (δ_C 43.9), C-9 (δ_C 47.9), and C-10 (δ_C 78.5) and from H_2-12 (δ_H 2.06 and 1.60, each 1H, m) to C-11 (δ_C 70.8). The H-11 was assigned a α-configuration on the basis of the ROESY correlation between H-11 and H-7a (δ_H 2.75, brd, J = 14.5 Hz).

Caldaphnidine R (**12**), a colorless oil, possessed a molecular formula of $C_{23}H_{35}NO_3$. The IR spectrum showed strong absorption bands at 3425 and 1737 cm^{-1}, which were assignable to OH and carbonyl groups, respectively. Comparing the ^1H (Table 3) and ^{13}C NMR (Table 1) data of **12** with those of deoxyisocalyciphylline B[2f] implied that their structures were closely related. The OCH_3 group was located at C-22 by the HMBC correlation between O*Me* (δ_H 3.64, s, 3H) and C-22 (δ_C 176.8), suggesting that alkaloid **12** was the methanolysis product of deoxyisocalyciphylline B. The quaternary carbon resonance at δ_C 75.4 was assigned to C-5, bearing an OH by the mutual HMBC correlations from Me-21, CH_2-4, and CH_2-13 to C-5. The relative configuration of **12** was established by comparison of NMR data with those of deoxyisocalyciphylline B and was further supported by the ROESY spectrum.

Twenty-four known compounds were identified as calycinine A,[4] paxdaphnine B,[12] daphnicyclidin A,[13] deoxycalyciphylline B,[2f] calyciphylline B,[2f] daphnezomine L,[14] daphnicyclidin D,[14] deoxyisocalyciphylline B,[2f] daphnilongeridine,[15] calyciphylline D,[5a] daphniyunnine A,[16] daphnilongeranin D,[17] codaphniphylline,[15,18] calyciphylline K,[5i] methyl homosecodaphniphyllate,[19] daphnezomine B,[20] calyciphylline F,[5g] secodaphniphylline,[19] caldaphnidine B,[6] daphniteijsmine,[21] daphnilongeranin A,[17] longistylumphylline A,[2i] methyl homodaphniphyllate,[19a,22] and daphnezomine M[14] on the basis of their ^1H NMR, ^{13}C NMR, and EIMS data and confirmed by co-TLC with authentic samples. It was notable that 11 alkaloids, paxdaphnine B, daphnilongeridine, daphniyunnine A, daphnilongeranin D, codaphniphylline, daphnezomine B, secodaphniphylline, daphniteijsmine, daphnilongeranin A, longistylumphylline A, and methyl homodaphniphyllate, were isolated from *D. calycinum* for the first time.

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Perkin-Elmer 577 spectrometer (KBr disk). UV spectra were measured on a Shimadzu UV-2550 UV−visible spectrophotometer. Optical rotations were made on a Perkin-Elmer 341 polarimeter at room temperature. NMR spectra were measured on a Bruker AM-400 spectrometer with TMS as internal standard. EIMS (70 eV) was carried out on a Finnigan MAT 95 mass spectrometer instrument. All solvents used were of analytical grade (Shanghai Chemical Plant, Shanghai, People's Republic of China). Silica gel (200−300 mesh), silica gel H60, and Sephadex LH-20 (Amersham Biosciences) were used for column chromatography, and precoated Si gel GF_{254} plates (Qingdao Haiyang Chemical Plant, Qingdao, People's Republic of China) were used for TLC.

Plant Material. Twigs of *D. calycinum* were collected from Guangxi Province of China and authenticated by Professor Shao-Qing Tang of Guangxi Normal University, People's Republic of China. A voucher specimen (2004-DC-2Y) has been deposited in Shanghai Institute of Materia Medica.

Extraction and Isolation. The powder of dried twigs (3 kg) of *D. calycinum* was extracted with 95% ethanol at room temperature three times. After removal of the solvent under reduced pressure, the crude extract (600 g) was dissolved in 2 L of H_2O to form a suspension and adjusted with 2 N H_2SO_4 to pH ≈ 4. The acidic mixture was immediately defatted with EtOAc (800 mL × 4), and the aqueous phase was basified with 30% Na_2CO_3 in water to pH ≈ 10 and extracted with $CHCl_3$ (500 mL × 5) to obtain 15.4 g of crude alkaloids. This was then subjected to a silica gel column eluted with $CHCl_3/CH_3OH/Et_2NH$ (200:1:0.1 to 5:1:0.1) to give three major fractions, 1−3. Fraction 1 (7.9 g) was chromatographed on silica gel eluted with petroleum/EtOAc/Et_2NH (from 8:1:0.1 to 4:1:0.1) in gradient to afford six fractions (F1a−F1f). F1a was chromatographed on a silica gel column eluted with hexane/EtOAc/Et_2NH (from 20:1:0.1 to 10:1:0.1) to afford three fractions (F1a1−F1a3). F1a1 was chromatographed with $CHCl_3/Et_2NH$ (300:0.1 to 50:0.1) in gradient to afford six fractions (F1a1a−F1a1f). F1a1b and F1a1c were purified on a silica gel column eluted with petroleum/EtOAc/Et_2NH (8:1:0.01) to yield calyciphylline K (33 mg) and methyl homosecodaphniphyllate (30 mg), respectively. F1a1f was chromatographed, eluted with EtOAc/CH_3OH/Et_2NH (300:1:0.1), to yield **9** (7 mg). F1a2 was chromatographed on silica gel, eluted with $CHCl_3/Et_2NH$ (300:0.1 to 50:0.1), to afford five fractions (F1a2a−F1a2e). F1a2a was purified by silica gel CC eluted with petroleum/EtOAc/Et_2NH (4:1:0.01) to yield **12** (7 mg). F1a2b was separated on a silica gel column eluted with petroleum/EtOAc/Et_2NH (5:1:0.01) to yield secodaphniphylline (10 mg) and caldaphnidine B (15 mg). F1a2d was purified by silica gel CC eluted with EtOAc/CH_3OH/Et_2NH (200:1:0.1) to give calycinine A (35 mg). F1a2e was chromatographed using EtOAc/CH_3OH/Et_2NH (200:1:0.1) to give **10** (11 mg), daphnezomine B (5 mg), and calyciphylline F (13 mg). F1a3 was purified on a Sephadex LH-20 column eluted with CH_3OH to yield deoxycalyciphylline B (38 mg). F1b was separated by silica gel CC eluted with $CHCl_3/CH_3OH$ (200:1) to give six fractions (F1b1−F1b6). F1b4 was chromatographed eluting with EtOAc/CH_3OH/Et_2NH (300:1:0.1) to yield daphniteijsmine (14 mg) and methyl homodaphniphyllate (6 mg). F1b5 was purified on a Sephadex LH-20 gel column eluted with CH_3OH to yield **4** (5 mg). F1c was purified on a Sephadex LH-20 gel column (CH_3OH) to yield **2** (11 mg). F1d was chromatographed over silica gel eluted with $CHCl_3/CH_3OH/Et_2NH$ (100:

1:0.1) to give longistylumphylline A (10 mg). F1e was separated by silica silica gel CC eluted with $CHCl_3/CH_3OH/Et_2NH$ (100:1:0.1) to give **8** (6 mg) and daphnilongeranin A (8 mg). Fraction 2 (4.1 g) was chromatographed on silica gel eluted with petroleum/EtOAc/Et_2NH (from 6:1:0.1 to 4:1:0.1) in gradient to afford seven fractions (F2a−F2g). F2a was chromatographed on silica gel eluted with EtOAc/CH_3OH/Et_2NH (100:1:0.1) to afford **3** (5 mg) and codaphniphylline (18 mg). F2b was first chromatographed on silica gel, and each major fraction was then purified using a Sephadex LH-20 column (CH_3OH) to yield **5** (8 mg), **6** (5 mg), and daphnilongeranin D (86 mg). F2c was chromatographed on silica gel eluted with EtOAc/CH_3OH/Et_2NH (100:1:0.1) to afford deoxyisocalyciphylline B (13 mg), daphnilongeridine (6 mg), and daphniyunnine A (15 mg). F2d was recrystallized from petroleum/EtOAc to yield **1** (19 mg). F2f and F2g were purified by silica gel CC to yield **11** (7 mg) and calyciphylline D (3 mg), respectively. Fraction 3 (3.4 g) was subjected to a MCI gel column eluted with MeOH/H_2O (3:7 to 7:3) to give four subfractions (F3a−F3d). F3a was first chromatographed on silica gel, and each major fraction was then purified by silica gel CC eluted with $CHCl_3/CH_3OH/Et_2NH$ (30:1:0.1) to yield daphnicyclidin D (4 mg), **7** (16 mg), paxdaphnine B (8 mg), and daphnicyclidin A (17 mg), respectively. F3b was separated on silica gel eluted with $CHCl_3/CH_3OH$ (30:1) to yield calyciphylline B (87 mg) and daphnezomine L (5 mg). F3c was chromatographed on silica gel eluted with EtOAc/CH_3OH/Et_2NH (2:1:0.1) to give daphnezomine M (25 mg).

Caldaphnidine G (1): white, amorphous powder; $[\alpha]^{20}_D$ +23.0 (*c* 0.435, MeOH); UV (MeOH) λ_{max} (log ε) 300 (3.88) nm; IR (KBr) ν_{max} 3535, 3514, 2951, 2864, 1666, 1643, 1624, 1443, 1352, 1257, 1118, 1043 cm^{-1}; for ^1H NMR data, see Table 2; for ^{13}C NMR data, see Table 1; EIMS *m/z* 385 $[M]^+$ (38), 367 (39), 352 (31), 338 (12), 324 (47), 280 (12), 261 (13), 183 (12), 165 (14), 153 (16), 115 (17), 91 (19), 85 (66), 83 (100); HREIMS *m/z* 385.2246 $[M]^+$ (calcd for $C_{23}H_{31}NO_4$ 385.2253).

Caldaphnidine H (2): colorless oil; $[\alpha]^{20}_D$ +37.6 (*c* 0.380, MeOH); UV (MeOH) λ_{max} (log ε) 296 (3.94) nm; IR (KBr) ν_{max} 3400, 2954, 2928, 1701, 1600, 1635, 1460, 1435, 1350, 1246, 1117, 1071, 1030, 760 cm^{-1}; for ^1H NMR data, see Table 2; for ^{13}C NMR data, see Table 1; EIMS *m/z* 385 $[M]^+$ (13), 367 (46), 351 (31), 340 (100), 324 (24), 280 (17), 227 (17), 181 (15), 165 (22), 128 (19), 115 (21), 94 (22); HREIMS *m/z* 385.2245 $[M]^+$ (calcd for $C_{23}H_{31}NO_4$ 385.2253).

Caldaphnidine I (3): colorless oil; $[\alpha]^{20}_D$ +44.0 (*c* 0.085, MeOH); UV (MeOH) λ_{max} (log ε) 236 (3.81) nm; IR (film) ν_{max} 3435, 2924, 2852, 1713, 1626, 1500, 1466, 1444, 1379, 1257, 1232, 1128 cm^{-1}; for ^1H NMR data, see Table 2; for ^{13}C NMR data, see Table 1; EIMS *m/z* 385 $[M]^+$ (13), 367 (43), 351 (34), 326 (53), 308 (21), 299 (28), 280 (21), 264 (12), 236 (16), 218 (14), 167 (14), 123 (34), 124 (16), 97 (63), 71 (67), 57 (100); HREIMS *m/z* 385.2237 $[M]^+$ (calcd for $C_{23}H_{31}NO_4$ 385.2253).

Caldaphnidine J (4): colorless oil; $[\alpha]^{20}_D$ +57.0 (*c* 0.200, MeOH); UV (MeOH) λ_{max} (log ε) 296 (3.91) nm; IR (KBr) ν_{max} 3427, 2924, 2854, 1701, 1630, 1649, 1437, 1350, 1263, 1240, 1115 cm^{-1}; for ^1H NMR data, see Table 2; for ^{13}C NMR data, see Table 1; EIMS *m/z* 353 $[M]^+$ (100), 339 (28), 324 (19), 310 (16), 294 (25), 280 (9), 252 (6), 227 (6), 181 (8), 167 (10), 149 (18), 115 (9), 96 (26), 57 (37); HREIMS *m/z* 353.2364 $[M]^+$ (calcd for $C_{23}H_{31}NO_2$ 353.2355).

Caldaphnidine K (5): colorless oil; $[\alpha]^{20}_D$ −17.4 (*c* 0.530, MeOH); IR (film) ν_{max} 3370, 2951, 1734, 1653, 1566, 1437, 1381, 1169, 1034, 754 cm^{-1}; for ^1H NMR data, see Table 2; for ^{13}C NMR data, see Table 1; EIMS *m/z* 373 $[M]^+$ (100), 356 (16), 342 (8), 330 (8), 314 (6), 286 (8), 274 (20), 258 (13), 229 (9), 171 (10), 143 (9), 129 (10), 98 (28); HREIMS *m/z* 373.2630 $[M]^+$ (calcd for $C_{23}H_{35}NO_3$ 373.2617).

Caldaphnidine L (6): colorless oil; $[\alpha]^{20}_D$ −41.0 (*c* 0.140, MeOH); IR (KBr) ν_{max} 3410, 2952, 2854, 1738, 1574, 1458, 1373, 1261, 1174, 1037, 802 cm^{-1}; for ^1H NMR data, see Table 2; for ^{13}C NMR data, see Table 1; EIMS *m/z* 375 $[M]^+$ (42), 358 (39), 344 (24), 332 (17), 302 (55), 288 (31), 274 (100), 260 (15), 246 (10), 208 (9), 188 (10), 147 (19), 136 (22), 98 (40); HREIMS *m/z* 375.2752 $[M]^+$ (calcd for $C_{23}H_{37}NO_3$ 375.2773).

Caldaphnidine M (7): white, amorphous powder; $[\alpha]^{20}_D$ −43.0 (*c* 0.265, MeOH); IR (KBr) ν_{max} 3600−2500 (broadband), 1633, 1456, 1383, 1167, 1065 cm^{-1}; for ^1H NMR data, see Table 3; for ^{13}C NMR data, see Table 1; EIMS *m/z* 331 $[M]^+$ (84), 315 (25), 302 (25), 288 (77), 272 (73), 258 (100), 246 (13), 230 (14), 216 (61), 209 (37), 153 (35), 147 (31), 123 (64), 105 (23), 93 (21), 58 (68); HREIMS *m/z* 331.2515 $[M]^+$ (calcd for $C_{21}H_{33}NO_2$ 331.2511).

Caldaphnidine N (8): colorless oil; $[\alpha]^{20}_D$ −65.0 (*c* 0.155, MeOH); IR (KBr) ν_{max} 3427, 2937, 2852, 1732, 1716, 1630, 1466, 1377, 1261, 1073 cm^{-1}; for ^1H NMR data, see Table 3; for ^{13}C NMR data, see Table 1; EIMS *m/z* 357 $[M]^+$ (100), 342 (2), 340 (2), 328 (3), 314 (4), 302 (14), 298 (17), 270 (28), 243 (10), 215 (20), 125 (16), 111 (25), 97 (37), 85 (44), 57 (74); HREIMS *m/z* 357.2296 $[M]^+$ (calcd for $C_{22}H_{31}NO_3$ 357.2304).

Caldaphnidine O (9): colorless oil; $[\alpha]^{20}_D$ −42.0 (*c* 0.190, MeOH); IR (film) ν_{max} 2935, 1737, 1460, 1377, 1309, 1198, 1090 cm^{-1}; for ^1H NMR data, see Table 3; for ^{13}C NMR data, see Table 1; EIMS *m/z* 357 $[M]^+$ (27), 343 (6), 326 (10), 298 (20), 284 (100), 270 (60), 256 (26), 224 (41), 202 (7), 143 (37), 99 (41), 56 (94); HREIMS *m/z* 357.2655 $[M]^+$ (calcd for $C_{23}H_{35}NO_2$ 357.2668).

Caldaphnidine P (10): colorless oil; $[\alpha]^{20}_D$ −49.9 (*c* 0.465, MeOH); IR (film) ν_{max} 3408, 2947, 2870, 1732, 1651, 1450, 1381, 1313, 1198, 1090, 756 cm^{-1}; for ^1H NMR data, see Table 3; for ^{13}C NMR data, see Table 1; EIMS *m/z* 373 $[M]^+$ (29), 359 (15), 342 (10), 317 (8), 300 (100), 286 (52), 272 (8), 258 (9), 216 (9), 209 (5), 97 (8), 57 (15); HREIMS *m/z* 373.2619 $[M]^+$ (calcd for $C_{23}H_{35}NO_3$ 373.2617).

Caldaphnidine Q (11): colorless oil; $[\alpha]^{20}_D$ −1.0 (*c* 0.150, MeOH); IR (KBr) ν_{max} 3421, 2925, 2872, 1736, 1630, 1458, 1381, 1196, 1084 cm^{-1}; for ^1H NMR data, see Table 3; for ^{13}C NMR data, see Table 1; EIMS *m/z* 375 $[M]^+$ (87), 360 (100), 344 (18), 332 (27), 302 (29), 288 (56), 274 (16), 246 (23), 208 (37), 182 (32), 149 (16), 97 (43), 85 (55), 71 (72), 57 (95); HREIMS *m/z* 375.2769 $[M]^+$ (calcd for $C_{23}H_{37}NO_3$ 375.2773).

Caldaphnidine R (12): colorless oil; $[\alpha]^{20}_D$ −60.6 (*c* 0.335, MeOH); IR (film) ν_{max} 3425, 2924, 2850, 1737, 1456, 1377, 1261, 1092, 1020, 800, 756 cm^{-1}; for ^1H NMR data, see Table 3; for ^{13}C NMR data, see Table 1; EIMS *m/z* 373 $[M]^+$ (100), 358 (24), 345 (35), 342 (27), 330 (13), 300 (28), 286 (14), 270 (24), 254 (15), 220 (8), 216 (15), 192 (22), 166 (13), 120 (22), 96 (51), 91 (33), 79 (26); HREIMS *m/z* 373.2616 $[M]^+$ (calcd for $C_{23}H_{35}NO_3$ 373.2617).

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Supporting Information Available: Key HMBC and ROESY correlations of **1**−**12** (figures) and selected IR, MS, 1D and 2D NMR spectra of **1**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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