Hasubanan Type Alkaloids from *Stephania longa*

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Thirteen new hasubanan type alkaloids, stephalonines **A**−**I** (**1**−**9**), norprostephabyssine (**15**), isoprostephabyssine (**16**), isolonganone (**18**), and isostephaboline (**21**), as well as nine known ones, were isolated from the whole plants of *Stephania longa*, a well-known traditional Chinese medicine. Their structures were elucidated on the basis of spectroscopic data and chemical methods.

The genus *Stephania*, belonging to the Menispermaceae family, comprises about 60 species distributed mainly in the tropical and subtropical areas of Asia and Africa. Thirty-nine species and one variant occur in China, with most species found in the south of China, especially in Yunnan and Guangxi Provinces.[1] Many plants of the *Stephania* genus growing in China have a series of applications in Traditional Chinese Medicine (TCM) or folklore herbs.[2,3] The alkaloids from this genus are classified into six major categories: hasubanan, aporphine, proaporphine, protoberberine, bisbenzylisoquinoline, and morphinandienone types.[3] More than 150 alkaloids have been isolated from plants of the *Stephania* genus,[3] and some show important biological activities such as antitumor activity and emetine type activity.[4,5] *Stephania longa* Lour. is a perennial herbaceous liana, and both its roots and the whole plants are applied in TCM to treat fever, inflammation, and dysentery.[2] There are several reports relevant to the isolation of eight alkaloids and five nonalkaloids from this plant.[6] Recently, an extensive chemical study in our laboratory has led to the isolation of 22 hasubanan type alkaloids from the whole plants of *S. longa*. Among them, 13 alkaloids, stephalonines **A**−**I** (**1**−**9**), norprostephabyssine (**15**), isoprostephabyssine (**16**), isolonganone (**18**), and isostephaboline (**21**), are new compounds. This paper describes the isolation and structural elucidation of these new alkaloids.

Results and Discussion

Stephalonine **A** (**1**) was obtained as a white powder. A molecular formula of $C_{25}H_{35}NO_7$ was assigned to **1** on the basis of HREIMS at *m/z* 461.2411 $[M]^+$ (calcd 461.2414), indicating the presence of nine degrees of unsaturation. Its IR spectrum showed the absorption bands of hydroxyl and ester carbonyl groups at 3385 and 1732 cm^{-1}, respectively.[7] The NMR data (Tables 1 and 2) showed the presence of an ester carbonyl (δ_C 177.0), six aromatic carbons (four quaternary ones at δ_C 146.7, 143.5, 134.4, and 128.0 and two aromatic methines at δ_C 115.9 and 106.5), three oxygenated methines at δ_C 81.6, 77.0, and 67.0, three *O*-methyls at δ_C 57.1, 55.7, and 51.6, an *N*-methyl at δ_C 38.6, and two aliphatic methyls at δ_C 15.2 and 11.1 in **1**. The aromatic ring and the carbonyl accounted for five degrees of unsaturation, and the remaining four degrees of unsaturation were attributed to the existence of four more rings in **1**.

The aforementioned spectroscopic data and the typical EIMS fragmentation ions at *m/z* 360, 231, 230, and 229 suggested that **1** was a hasubanan type alkaloid.[8] Comparison of its NMR data (Tables 1 and 2) with those (Tables 1 and 3) of the known alkaloid *N*-methylstephuline (**11**)[9] showed that they were analogues possessing a hemiacetal ether bridge between C-8 and C-10. The only difference was the presence of a 2-methylbutyryl ester group at C-6 in **1**. Compared with compound **11**, the deshielded proton at δ_H 5.31 (1H, m, H-6) of **1** caused by acylation effect supported the location of the 2-methylbutyryl moiety at C-6. Methanolysis of **1** with NaOMe−MeOH gave *N*-methylstephuline (**11**). The 2*S* absolute configuration of the 2-methylbutyryl moiety was determined by comparing the retention time of methyl 2-methylbutyrate obtained from the methanolysis of **1** with those of authentic samples (*S*-configuration and a racemic mixture) on chiral GC analysis. Thus, the structure of stephalonine A (**1**) was elucidated as (6*β*,7*β*,8*β*,-10*β*)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxy-17-methylhasubanan 6-((2*S*)-methylbutyrate) and was confirmed by HSQC, HMBC, and $^1H-^1H$ COSY spectra.

Stephalonine B (**2**) had the molecular formula $C_{29}H_{33}NO_7$ as determined by HREIMS. It was also a hasubanan type alkaloid as compared with the spectroscopic data of stephalonine A (**1**). The only difference between alkaloids **1** and **2** was the ester moiety at C-6. The ester group of **2** was determined to be a cinnamoyl group as judged by the ^1H and ^{13}C NMR data (Tables 1 and 2). The structure of **2** and the assignments for the ^1H and ^{13}C NMR data were confirmed by HMQC, HMBC, and $^1H-^1H$ COSY spectra. Stephalonine B (**2**) was therefore identified as (6*β*,7*β*,8*β*,-10*β*)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxy-17-methylhasubanan 6-cinnamate.

Stephalonines C (**3**) and D (**4**) gave the same molecular formula of $C_{28}H_{31}NO_7$ as determined by HREIMS, which was 14 mass units less than that of stephalonine B (**2**). Comparison of the ^1H and ^{13}C NMR spectra (Tables 1 and 2) of **3** with those of **2** showed that compound **3** was the *N*-demethyl product of **2**, as judged by the absence of the typical *N*-methyl group in both the ^1H and ^{13}C NMR spectra. The structure of stephalonine C (**3**) was thereby established as (6*β*,7*β*,8*β*,10*β*)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxyhasubanan 6-cinnamate. Similarly, the ^1H and ^{13}C NMR spectra (Tables 1 and 2) of **4** showed one *O*-methyl less than compound **2**, and the C-8 carbon signal of **4** was shielded ca. $\Delta\delta_C$ 2 ppm, suggesting the existence of a hemiacetal group at C-8. Furthermore, comparison of the NMR data of **4** with those (Tables 1 and 3) of longanine **12** indicated that compound **4** was a C-6 cinnamic ester of **12**. Stephalonine D (**4**) was thus elucidated to be (6*β*,7*β*,8*β*,-10*β*)-8,10-epoxy-4,6,8-trihydroxy-3,7-dimethoxy-17-methylhasubanan 6-cinnamate.

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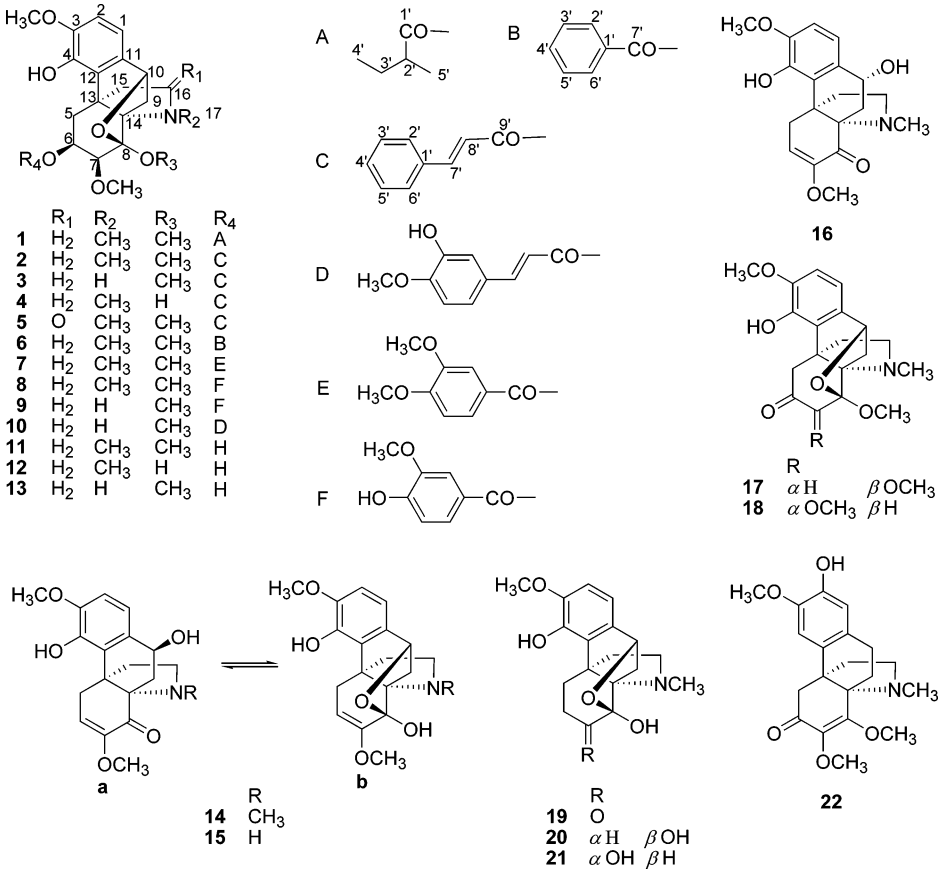
Chart 1



	R_1	R_2	R_3	R_4
1	H_2	CH_3	CH_3	A
2	H_2	CH_3	CH_3	C
3	H_2	H	CH_3	C
4	H_2	CH_3	H	C
5	O	CH_3	CH_3	C
6	H_2	CH_3	CH_3	B
7	H_2	CH_3	CH_3	E
8	H_2	CH_3	CH_3	F
9	H_2	H	CH_3	F
10	H_2	H	CH_3	D
11	H_2	CH_3	CH_3	H
12	H_2	CH_3	H	H
13	H_2	H	CH_3	H

Stephalonine E (**5**) showed a molecular formula of $C_{29}H_{31}NO_8$ as deduced from HREIMS. The ^1H and ^{13}C NMR data (Tables 1 and 2) of **5**, closely related to those of stephalonine B (**2**), showed the presence of a carbonyl at C-16 (δ_C 174.4) replacing the C-16 methylene group in **2** to form an amide functionality, which was confirmed by the HMBC correlations of C-16 to the *N*-methyl protons and H_2-15 at δ_H 3.07 (1H, d, J = 17.1 Hz) and 2.46 (1H, d, J = 17.1 Hz), respectively. Comparing with compound **2**, the deshielded *N*-methyl protons at δ_H 3.06 (3H, s, H-17) and the shielded carbon at δ_C 28.3 (C-17) were caused by the effects of the C-16 amido group. Hence, the structure of stephalonine E (**5**) was established as (6β,7β,8β,10β)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxy-17-methyl-16-oxohasubanan 6-cinnamate.

Stephalonine F (**6**) had the molecular formula $C_{27}H_{31}NO_7$ as determined by HREIMS. Analyses of the ^1H and ^{13}C NMR spectra (Tables 1 and 2) revealed that **6** was an analogue of stephalonines A (**1**) and B (**2**), with the only difference being the C-6 acyl group, which was defined as a benzoyl group by the ^1H and ^{13}C NMR data (Tables 1 and 2). This was confirmed in the HMBC spectrum, in which the H-6 at δ_H 5.61 (1H, m) correlated with C-7′ at δ_C 166.3 to locate the benzoyl group. Therefore, stephalonine F (**6**) was unambiguously assigned as (6β,7β,8β,10β)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxy-17-methylhasubanan 6-benzoate.

Stephalonine G (**7**) had a molecular formula of $C_{29}H_{35}NO_9$ as established by HREIMS. Comparison of the ^1H and ^{13}C NMR data (Tables 1 and 2) with those of stephalonine F (**6**) revealed that there were two additional *O*-methyl groups in **7**, and the proton chemical shifts (δ_H 3.85 and 3.86) indicated that they were attached to the aromatic ring of the acyl group. The acyl moiety was identified as a 3,4-dimethoxybenzoyl group on the basis of ^1H and ^{13}C NMR data (Tables 1 and 2). Thus, the structure of stephalonine G (**7**) was elucidated as (6β,7β,8β,10β)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxy-17-methylhasubanan 6-(3,4-dimethoxybenzoate). The structure of **7** and the assignments of the proton and carbon signals were also confirmed by HMQC and HMBC experiments.

Stephalonine H (**8**) was determined by HREIMS to have a molecular formula of $C_{28}H_{33}NO_9$, 14 mass units less than that of **7**. From the ^1H and ^{13}C NMR data (Tables 1 and 2), it was clear that stephalonine H (**8**) was a derivative of **7** by the loss of one methyl group in the acyl moiety, which was identified as a 4-hydroxy-3-methoxybenzoyl group (vanilloyl) in **8**. The structure of stephalonine H (**8**) was elucidated as (6β,7β,8β,10β)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxy-17-methylhasubanan 6-vanillate. The structure of **8** and the assignments for the proton and carbon signals were also confirmed by HMQC and HMBC spectra.

Stephalonine I (**9**) exhibited a molecular formula of $C_{27}H_{31}NO_9$ as established by HREIMS at *m/z* 513.1996, which was 14 mass units less than stephalonine H (**8**). The ^1H and ^{13}C NMR data (Tables 1 and 2) clearly indicated that compounds **8** and **9** were similar, and the only difference was the absence of the typical *N*-methyl group in **9**, suggesting that stephalonine I (**9**) was an *N*-demethyl compound of **8**. The structure of stephalonine I (**9**) was thus established as (6β,7β,8β,10β)-8,10-epoxy-4,6-dihydroxy-3,7,8-trimethoxyhasubanan 6-vanillate and was confirmed by the HMBC spectrum.

Norprostephabyssine (**15**), isolated as white powder with optical rotation $[\alpha]^{20}_D$ = −80.4°, showed a molecular formula of $C_{18}H_{21}NO_5$ as assigned by HREIMS at *m/z* 331.1409 (calcd 331.1420). The most notable feature of its ^1H and ^{13}C NMR spectra (Tables 1 and 3) was that all the proton and carbon signals were resolved in pairs as in the case of prostephabyssine (**14**),[6c] suggesting that compound

Table 1. ^{1}H NMR Data of Alkaloids **1**−**9**, **15**, **16**, **18**, and **21**

	1[b] (multi, *J* (Hz))	**2**[b] (multi, *J* (Hz))	**3**[c] (multi, *J* (Hz))	**4**[b] (multi, *J* (Hz))	**5**[b] (multi, *J* (Hz))	**6**[b] (multi, *J* (Hz))	**16**[b] (multi, *J* (Hz))
1	6.60 (d, 8.2)	6.67 (d, 8.0)	6.59 (d, 8.0)	6.63 (d, 8.1)	6.70 (d, 8.1)	6.65 (d, 7.9)	6.94 (d, 8.3)
2	6.56 (d, 8.2)	6.34 (d, 8.0)	6.42 (d, 8.0)	6.31 (d, 8.1)	6.39 (d, 8.1)	6.36 (d, 7.9)	6.84 (d, 8.3)
5	3.00 (dd, 15.2, 3.4)	3.18 (dd, 15.2, 3.8)	3.22 (dd, 15.4, 3.8)	3.21 (dd, 15.2, 3.6)	3.25 (m)	3.16 (dd, 15.4, 3.4)	3.54 (dd, 17.8, 7.1)
	2.12 (dd, 15.2, 3.0)	2.13 (dd, 15.2, 2.5)	1.84 (dd, 15.4, 2.4)	2.13 (dd, 15.2, 2.5)	1.84 (dd, 15.5, 2.6)	2.25 (dd, 15.4, 2.7)	2.47 (m)
6	5.31 (m)	5.39 (m)	5.36 (m)	5.43 (m)	5.37 (m)	5.61 (m)	5.77 (dd, 7.1, 2.8)
7	3.68 (d, 4.5)	3.78 (d, 4.4)	3.83 (d, 4.6)	3.75 (d, 4.0)	3.59 (d, 4.2)	3.89 (d, 3.7)	
9	2.65 (dd, 10.7, 6.2)	2.68 (dd, 10.7, 6.2)	2.42 (dd, 10.7, 5.9)	2.91 (m)	2.93 (dd, 10.9, 6.1)	2.72 (dd, 10.7, 6.3)	2.57 (dd, 14.9, 2.8)
	1.48 (d, 10.7)	1.54 (d, 10.7)	1.90 (d, 10.7)	1.59 (d, 10.7)	1.68 (d, 10.9)	1.56 (d, 10.7)	1.88 (dd, 14.9, 4.0)
10	4.87 (d, 6.2)	4.96 (d, 6.2)	4.88 (d, 5.9)	4.96 (d, 6.4)	5.00 (d, 6.1)	4.96 (d, 6.3)	4.60 (dd, 4.0, 2.8)
15	2.45 (m)	2.44 (m)	2.63 (m)	2.47 (m),	3.07 (d, 17.1)	2.47 (m)	2.76 (m)
	1.84 (m)	1.84 (m)	1.98 (m)	1.90 (ddd, 13.4, 11.4, 7.2)	2.46 (d, 17.1)	1.84 (m)	2.42[a]
16	3.38 (m), 2.51 (m)	3.39 (m), 2.51 (m)	3.06 (2H, m)	3.40 (m), 2.54 (m)		3.47 (m), 2.54 (m)	2.98 (m), 2.42[a]
17	2.56 (s)	2.58 (s)		2.62 (s)	3.06 (s)	2.61 (s)	2.56 (s)
2′	1.58 (m)	7.33−7.38 (5H)	7.38−7.44 (5H)	7.31−7.37 (5H)	7.33−7.40 (5H)	7.26 (dd, 8.3, 1.4)	
3′	1.32 (m), 1.13 (m)					7.14 (dd, 8.3, 7.4)	
4′	0.71 (t, 7.4)					7.36 (tt, 7.4, 1.4)	
5′	0.62 (d, 7.0)						
7′		7.18 (d, 16.1)	7.09 (d, 16.2)	7.09 (d, 16.0)	7.20 (d, 16.0)		
8′		5.48 (d, 16.1)	5.58 (d, 16.2)	5.55 (d, 16.0)	5.49 (d, 16.0)		
4-OH	5.77 (br s)	5.69 (br s)					6.15 (br s)
3-OMe	3.83 (s)	3.23 (s)	3.33 (s)	3.30 (s)	3.26 (s)	3.47 (s)	3.92 (s)
7-OMe	3.34 (s)	3.40 (s)	3.37 (s)	3.43 (s)	3.43 (s)	3.41 (s)	3.64 (s)
8-OMe	3.52 (s)	3.57 (s)	3.51 (s)		3.63 (s)	3.55 (s)	

	7[b] (multi, *J* (Hz))	**8**[d] (multi, *J* (Hz))	**9**[b] (multi, *J* (Hz))	**15a**[b] (multi, *J* (Hz))	**15b**[b] (multi, *J* (Hz))	**18**[b] (multi, *J* (Hz))	**21**[e] (multi, *J* (Hz))
1	6.60 (d, 8.0)	6.84 (d, 8.0)	6.61 (d, 8.0)	7.17 (dd, 8.5, 0.9)	6.61 (d, 8.1)	6.54 (d, 8.1)	6.59 (d, 8.1)
2	6.32 (d, 8.0)	6.65 (d, 8.0)	6.38 (d, 8.0)	6.84 (d, 8.5)	6.64 (d, 8.1)	6.59 (d, 8.1)	6.67 (d, 8.1)
5	3.15 (dd, 15.3, 3.5)	3.84 (dd, 15.0, 3.3)	3.12 (m)	3.63 (dd, 19.5, 6.6)	3.20[a]	3.57 (d, 12.1)	2.43 (dt, 14.3, 3.2)
	2.20 (dd, 15.3, 2.9)	2.51 (dd, 15.0, 3.0)	2.14 (dd, 15.2, 2.5)	2.59 (m)	2.60 (m)	3.11 (d, 12.1)	2.11[a]
6	5.55 (m)	6.02 (m)	5.58 (m)	5.76 (dd, 6.6, 2.9)	4.49 (dd, 6.2, 2.1)		1.61 (m), 1.45 (m)
7	3.80 (d, 4.5)	4.14 (d, 4.2)	3.80 (d, 4.5)			3.54 (s)	3.80 (br s)
9	2.68 (dd, 10.7, 6.3)	2.81 (dd, 10.6, 6.3)	2.39 (dd, 10.4, 5.9)	2.17 (dd, 12.7, 6.2)	2.41 (dd, 10.7, 5.4)	2.83 (dd, 10.7, 6.3)	2.90 (dd, 10.6, 6.2)
	1.51 (d, 10.7)	1.68 (d, 10.6)	1.88 (d, 10.4)	1.75 (dd, 12.7, 10.5)	2.02 (d, 10.7)	1.57 (d, 10.7)	1.65 (d, 10.6)
10	4.93 (d, 6.3)	5.12 (d, 6.3)	4.88 (d, 5.9)	5.12 (ddd, 10.5, 6.2, 0.9)	4.84 (d, 5.4)	4.75 (d, 6.3)	4.87 (d, 6.2)
15	2.42 (m)	2.87 (m)	2.57 (ddd, 13.0, 8.3, 3.9)	2.81 (m)	2.66 (m)	2.53 (m)	2.68 (ddd, 13.2, 8.6, 3.4)
	1.80 (m)	2.07 (m)	1.96 (ddd, 13.0, 10.7, 7.9)	2.10 (m)	2.08 (m)	2.03 (m)	2.11[a]
16	3.37 (m)	3.47 (m)	3.18 (2H, m)	2.79 (m)	3.30 (m)	3.45 (m), 2.57 (m)	3.78 (m)
	2.49 (m)	2.57 (ddd, 11.4, 9.8, 4.0)		2.58 (m)	3.20[a]		2.75 (td, 10.9, 3.4)
17	2.56 (s)	2.77 (s)				2.63 (s)	2.81 (s)
2′	7.26 (d, 1.8)	7.64 (d, 1.9)	7.27 (br s)				
5′	6.49 (d, 8.5)	7.08 (d, 8.3)	6.58 (d, 8.1)				
6′	6.54 (dd, 8.5, 1.8)	7.15 (dd, 8.3, 1.9)	6.45 (br d, 8.1)				
4-OH						6.03 (s)	
3-OMe	3.48 (s)	3.49 (s)	3.52 (s)	3.91 (s)	3.88 (s)	3.84 (s)	3.88 (s)
7-OMe	3.39 (s)	3.54 (s)	3.41 (s)	3.66 (s)	3.52 (s)	3.35 (s)	
8-OMe	3.53 (s)	3.76 (s)	3.56 (s)			3.33 (s)	
3′-OMe	3.85 (s)	3.69 (s)	3.87 (s)				
4′-OMe	3.86 (s)						

[a] Data completely overlapped in the same column. [b] In $CDCl_3$. [c] In CD_3OD. [d] In pyridine-d_5. [e] In $CDCl_3$−CD_3OD (5:1).

Table 2. ^{13}C NMR Data of Alkaloids **1**−**11**

	1[a]	**2**[a]	**3**[b]	**4**[a]	**5**[a]	**6**[a]	**7**[a]	**8**[c]	**9**[a]	**10**[a]	**11**[a]
1	115.9	115.9	116.5	115.7	116.3	115.9	115.9	115.7	116.5	116.6	115.7
2	106.5	106.2	109.1	106.7	107.2	107.2	107.0	108.6	107.3	106.6	107.1
3	146.7	146.8	150.8	146.9	147.2	147.0	147.1	149.4	147.1	147.0	147.3
4	143.5	143.3	148.2	143.4	143.7	143.8	144.0	146.3	144.2	143.7	144.1
5	32.1	31.5	32.3	32.0	31.5	31.8	32.1	33.2	31.8	31.2	34.9
6	67.0	68.0	69.7	66.5	66.6	67.9	68.2	68.9	67.7	67.6	67.5
7	81.6	81.6	83.0	80.3	82.0	81.7	82.1	83.3	81.7	81.3	82.1
8	103.2	103.3	103.6	101.7	101.4	103.2	103.5	104.4	101.8	101.7	104.0
9	29.0	28.9	39.5	28.7	33.0	29.2	28.9	28.9	38.4	38.3	28.9
10	77.0	77.3	80.0	76.3	76.3	77.2	77.4	78.0	77.6	77.5	77.5
11	134.4	134.0	135.3	134.4	133.7	134.2	134.7	135.2	134.6	134.2	132.8
12	128.0	128.0	129.5	127.9	124.4	127.6	128.1	129.9	127.4	127.5	128.2
13	48.7	48.9	48.9	48.8	42.7	48.8	49.1	50.3	46.3	46.3	49.0
14	76.1	76.3	76.3	74.4	74.6	76.4	76.4	77.0	74.4	74.3	76.6
15	34.7	34.4	38.5	34.8	43.5	34.5	34.8	35.7	36.9	36.6	35.5
16	54.3	54.3	42.9	54.3	174.4	54.2	54.4	54.6	41.5	41.5	54.4
17	38.6	38.6		38.0	28.3	38.7	38.5	38.5			38.5
1′	177.0	134.7	136.5	134.7	134.6	129.8	124.7	122.4	122.0	128.4	
2′	40.0	128.0	129.7	128.0	128.0	129.9	112.3	113.9	111.8	113.2	
3′	26.2	128.6	130.4	128.6	128.7	127.3	148.1	147.7	145.7	145.6	
4′	11.1	129.7	131.7	129.8	129.9	132.0	152.6	152.5	149.8	148.1	
5′	15.2	128.6	130.4	128.6	128.7	127.3	109.6	115.5	113.2	110.3	
6′		128.0	129.7	128.0	128.0	129.9	128.1	125.7	125.3	121.5	
7′		142.6	145.3	143.0	143.2	166.3	166.4	166.7	166.3	142.5	
8′		118.6	119.5	118.4	118.2					116.7	
9′		167.0	168.7	166.7	166.7					167.2	
3-OMe	55.7	55.1	56.3	55.5	55.4	55.8	55.9	55.9	55.9	55.4	55.7
7-OMe	57.1	57.1	58.0	57.6	57.4	57.6	57.7	58.1	57.4	56.9	56.8
8-OMe	51.6	51.6	52.6		52.0	51.6	51.5	51.7	51.8	51.9	51.8
3′-OMe							56.1	56.0	56.2		
4′-OMe							56.2			55.9	

[a] In $CDCl_3$. [b] In CD_3OD. [c] In C_5D_5N.

Table 3. ^{13}C NMR Data of Alkaloids **12**−**21**

	12[a]	**13**[a]	**14a**[a]	**14b**[a]	**15a**[a]	**15b**[a]	**16**[a]	**17**[a]	**18**[a]	**19**[a]	**20**[b]	**21**[b]
1	115.3	116.5	117.1	116.9	117.9	117.4	121.1	116.1	115.5	116.4	115.4	115.6
2	107.0	107.3	108.6	107.6	109.1	107.9	109.2	107.6	107.6	107.9	107.5	107.8
3	147.4	147.4	145.8	146.9	145.8	147.1	146.3	147.0	147.0	147.2	147.3	147.5
4	144.0	144.3	142.9	143.8	143.0	144.3	142.9	143.8	143.9	144.0	143.6	143.8
5	35.2	34.9	32.3	29.6	29.6	29.6	28.8	44.6	41.9	31.1	27.8	23.1
6	66.0	67.2	113.5	92.1	114.4	92.3	113.5	204.2	207.4	33.0	28.7	25.8
7	79.9	81.9	151.4	151.3	148.6	151.4	151.6	88.6	81.6	207.3	71.7	69.7
8	102.4	102.4	196.6	98.3	199.7	97.1	193.4	107.0	105.4	98.5	102.3	99.8
9	28.8	38.3	29.2	29.3	35.7	38.7	28.8	29.0	29.3	30.4	29.9	30.6
10	76.4	77.6	65.7	75.9	66.2	76.7	67.7	77.1	76.2	77.6	75.3	76.1
11	133.0	132.8	131.8	133.7	132.1	134.0	130.8	134.0	134.0	134.3	134.0	133.5
12	128.2	127.8	129.5	126.2	128.1	126.2	128.1	124.3	125.0	125.1	125.8	125.3
13	48.7	46.4	48.2	48.7	46.6	46.5	48.4	52.3	52.2	50.4	50.6	50.0
14	74.2	74.5	70.6	73.0	70.8	71.4	71.3	76.9	74.2	79.2	74.6	74.4
15	36.0	36.9	32.9	34.1	32.3	36.4	33.2	34.7	35.3	33.6	33.6	33.3
16	54.4	42.0	51.4	54.6	41.6	41.9	53.1	54.3	54.1	54.4	54.4	54.7
17	38.0		36.0	38.9			37.4	38.6	38.2	38.3	38.7	39.3
3-OMe	55.7	55.8	56.1	55.9	56.2	56.0	56.1	55.8	55.8	56.0	55.6	55.7
7-OMe	56.7	56.5	55.0	54.4	55.1	54.5	55.1	59.4	58.6			
8-OMe		52.1						51.8	47.6			

[a] In $CDCl_3$. [b] In $CDCl_3$−CD_3OD (5:1).

15 existed as two isomers in an equilibrium (**a**:**b** = ca. 3:2) in $CDCl_3$. The only difference between the two alkaloids **14** and **15** observed in their ^1H and ^{13}C NMR spectra was the absence of *N*-methyl signals in **15**. Accordingly, norprostephabyssine (**15**) was established as (10β)-6,7-didehydro-4,10-dihydroxy-3,7-dimethoxy-8-oxohasubanan (**15a**) or (8β,10β)-6,7-didehydro-8,10-epoxy-4,8-dihydroxy-3,7-dimethoxyhasubanan (**15b**). The structure of norprostephabyssine (**15**) and the assignments for the proton and carbon signals were confirmed by HMQC and HMBC experiments.

Isoprostephabyssine (**16**) had the molecular formula $C_{19}H_{23}NO_5$ as determined by HREIMS, which was identical with the molecular formula of prostephabyssine (**14**). The spectroscopic analyses, especially the HMBC correlations, implied that **16** had the same planar structure as **14a**. Comparison of the ^1H and ^{13}C NMR data (Tables 1 and 3) of the two alkaloids **14a** and **16** showed that the major differences were at C-10, suggesting that **16** was likely a C-10 stereoisomer of **14a**. The chemical shifts and coupling constants of H-10 at δ_H 4.60 (1H, dd, J = 4.0, 2.8 Hz) and H-9 at δ_H 2.57 (1H, dd, J = 14.9, 2.8 Hz) and 1.88 (1H, dd, J = 14.9, 4.0 Hz) in **16** were significantly different from that of **14a**, indicating that the 10-OH was α-oriented in **16**. The NOESY (Figure 1) experiments for both compounds **14** and **16** were performed to verify the configuration, in which the H-10 correlated with the *N*-methyl in **14a**, while no such correlation was observed in **16**. The 3D structures (Figure 1) of **14a** and **16** were generated by computer modeling with the molecular modeling program CS Chem3D Ultra 8.0 (MM2 force field calculation was applied for

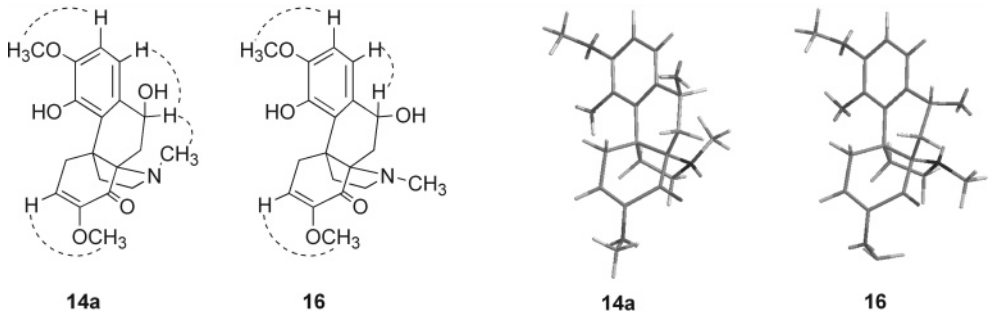


Figure 1. Key NOESY correlations (dashed) and stereoviews generated from computer modeling of **14a** and **16**.

energy minimization). The relative configuration and preferred conformation of **14a** and **16** were consistent with those of **14a** and **16** assigned by NOESY experiments. Consequently, isoprostephabyssine (**16**) was identified as (10α)-6,7-didehydro-4,10-dihydroxy-3,7-dimethoxy-17-methyl-8-oxohasubanan. This is the first report of a hasubanan type alkaloid with a 10α-OH.

Isolonganone (**18**) had a molecular formula of $C_{20}H_{25}NO_6$ as determined by HREIMS, which is identical with that of longanone (**17**).[6b] An extensive comparison of the ^1H and ^{13}C NMR data (Tables 1 and 3) of the two alkaloids revealed that they were stereoisomers at C-7. Alkaloid **17** is known to have a C-7-β-OCH_3; therefore alkaloid **18** was assigned with a C-7-α-OCH_3. Comparison of the IR absorption bands for the C-6 carbonyls of **17** (1732 cm^{-1}) and **18** (1720 cm^{-1}) also verified the configurational assignments for both alkaloids, with a similar change reported in the case of two C-7 isomers of hasubanan alkaloids.[10] The structure of isolonganone (**18**) was therefore elucidated as (7α,8β,10β)-8,10-epoxy-4-hydroxy-3,7,8-trimethoxy-17-methyl-6-oxohasubanan.

Isostephaboline (**21**) had the same molecular formula of $C_{18}H_{23}NO_5$ as that of stephaboline (**20**),[6c] as determined by HREIMS. Its ^1H and ^{13}C NMR data (Tables 1 and 3) were very similar to those of **20**, except for some minor chemical shift differences for the carbons and protons around C-7. This suggested that two compounds had the same planar structure, and the only difference was the configuration at C-7, which was confirmed by a $^1H-^1H$ COSY spectrum. Alkaloid **20** possesses a C-7-β-OH; therefore compound **21** was assigned as a new isomer bearing a C-7-α-OH group. Reduction of stephabyssine (**19**)[6c] with $NaBH_4$ gave a mixture of the alkaloids **20** and **21** (identified by ESIMS, ^1H and ^{13}C NMR spectra), which supported the structural assignment. The structure of isostephaboline (**21**) was thus established as (7α,8β,10β)-8,10-epoxy-4,7,8-trihydroxy-3-methoxy-17-methylhasubanan.

The known alkaloids were identified as stephisoferuline (**10**),[9] *N*-methylstephuline (**11**),[9] longanine (**12**),[6a] stephuline (**13**),[9] prostephabyssine (**14**),[6c] longanone (**17**),[6b] stephabyssine (**19**),[6c] stephaboline (**20**),[6c] and cephatonine (**22**)[11] on the basis of ESIMS and ^1H and ^{13}C NMR spectra. Except for **22**, the ^{13}C NMR data (Tables 2 and 3) of other known compounds have been reported for the first time.

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Perkin-Elmer 577 spectrometer. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. NMR spectra were measured on Bruker AM-400 (or 500) or Varian Mercury-400 spectrometers. EIMS (70 eV) was carried out on a Finnigan MAT 95 mass spectrometer. Chiral GC was performed on a Perkin-Elmer Autosystem XL instrument with a column of Rt-βDEXcst (30 m × 0.25 mm). All solvents used were of analytical grade (Shanghai Chemical Company, Ltd.). Silica gel H and neutral alumina (200−300 mesh) were used for column chromatography, and precoated silica gel GF254 plates (Qingdao Haiyang Chemical Company, Ltd.) were used for TLC. Sephadex LH-20 (Amersham Biosciences), amino silica gel (20−45 μm, Fuji Silysia Chemical Ltd.), RP-18 silica gel (150−200 mesh, Merck), and MCI gel CHP20P (75−150 μm, Mitsubishi Chemical Industries, Ltd.) were also used for column chromatography.

Plant Material. The plant material of *S. longa* was collected from Guangxi Province of People's Republic of China in the summer of 2002 and was identified by Prof. Su-Hua Shi of the Institute of Botany, School of Life Sciences, Zhongshan University. A voucher specimen was deposited in Shanghai Institute of Materia Medica (accession number: SL-2002-1Y).

Extraction and Isolation. The powder of the whole plants (5.0 kg) of *S. longa* was extracted with 95% EtOH at room temperature (× 3, each for 5 days). After removal of the solvent under reduced pressure, the residue (280 g) was suspended in 2.0 L of acidic water (adjusted with 2.0 mol/L H_2SO_4 to pH ca. 1−2). The acidified suspension was partitioned with EtOAc to remove the nonalkaloids. The acidic solution was then basified with 5% Na_2CO_3 to pH 6−7 and extracted with $CHCl_3$ (3 × 1.0 L) to obtain the A1 alkaloids. The aqueous phase was further adjusted with 5% Na_2CO_3 to pH 9−10 and extracted with $CHCl_3$ (3 × 1.0 L) again to give A2 alkaloids. TLC monitoring showed that the A1 and A2 alkaloids did not differ significantly and were thus combined to give 37.0 g of crude alkaloids.

The crude alkaloids (37.0 g) were chromatographed on a neutral alumina column (ϕ 6 × 45 cm, about 800 g) eluted with gradient mixtures of Et_2O−MeOH (from 100:1 to 1:1) to give six major fractions (F1−F6). F1 (8.27 g) was subjected to a silica gel column eluted with $CHCl_3$−MeOH (100:1 to 40:1) to afford three major subfractions, F1a−F1c. F1a was extensively chromatographed on a silica gel column ($CHCl_3$−MeOH, 70:1) to obtain **1** (50 mg), **2** (155 mg), and **6** (18 mg). F1b was purified on a silica gel column (petroleum ether−EtOAc−Et_2-NH, 7:1:0.3) and then preparative TLC ($CHCl_3$−MeOH, 50:1) to give **3** (86 mg). F1c was subjected to a silica gel column (petroleum ether−EtOAc−Et_2NH, 5:1:0.3) and then purified on an amino silica gel column eluted with $CHCl_3$ to get **7** (13 mg). F3 (6.02 g) was subjected to a silica gel column eluted with a solvent mixture of petroleum ether−EtOAc−Et_2NH (10:1:0.3 to 2:1:0.3) to give three major fractions, F3a to F3c. F3a was separated on a silica gel column eluted with $CHCl_3$−MeOH (50:1 to 20:1) to afford **14** (207 mg) and two major parts; part 1 was purified by preparative TLC to give **16** (16 mg), and part 2 was further separated on a RP-18 silica gel column eluted with MeOH−H_2O (1:1) to obtain **17** (41 mg) and **18** (18 mg). F3b was subjected to extensive silica gel column chromatography and eluted with $CHCl_3$−MeOH (40:1 to 20:1) to yield **4** (22 mg), **11** (20 mg), and **13** (15 mg). F3c was chromatographed on a silica gel column eluted with $CHCl_3$−MeOH (30:1) to give **12** (102 mg) and **19**, which was further purified by preparative TLC (developed with $CHCl_3$−MeOH, 20:1) to finally give 29 mg of **19**. F5 (3.03 g) was chromatographed on an MCI gel column eluted with MeOH−H_2O (3:7 to 6:4) to obtain fractions F5a−F5d. F5a was chromatographed

on a silica gel column eluting with petroleum ether−EtOAc−Et_2NH (3:1:0.3) to give **15** (30 mg) and **8** (26 mg). F5b was chromatographed on a silica gel column ($CHCl_3$−MeOH, 15:1) to obtain a mixture of two major alkaloids, which were then separated on an amino silica gel column ($CHCl_3$−MeOH, 50:1 and 2:1) to give **10** (50 mg) and **9** (27 mg). F5d was purified by TLC preparation (developed by $CHCl_3$−MeOH, 20:1) to obtain alkaloid **22** (43 mg). F6 (2.63 g) was first chromatographed on an MCI gel column eluted with MeOH−H_2O (3:7 to 6:4) to enrich the alkaloids and was then separated on a silica gel column eluted with petroleum ether−EtOAc−Et_2NH (2:1:0.3) to afford **20** (94 mg), **21** (10 mg), and **5**, which was further purified by preparative TLC ($CHCl_3$−MeOH, 40:1) to obtain 5 mg.

Methanolysis of 1. To about 2 mL of MeOH solution containing 8.0 mg of stephalonine A (**1**) was added a small amount of NaOMe. The reaction was stirred overnight at about 40 °C. The reaction was quenched by addition of 2.0 mL of 0.1 N HCl and then partitioned with 2.0 mL of ether. The organic phase, containing the methyl ester of 2-methylbutanoic acid, was washed with 5% $NaHCO_3$ and saturated NaCl solution in turn and then dried with anhydrous Na_2SO_4 for the chiral GC analysis. After basification and chloroform partition, the aqueous phase gave 5 mg of *N*-methylstephuline (**11**).

Preparation of Authentic Samples. Methyl esters of racemic 2-methylbutanoic acid and (*S*)-2-methylbutanoic acid were prepared by methylation of the free acids with freshly prepared CH_2N_2 in Et_2O.

Chiral GC Analysis. GC analysis showed that the retention time (11.675 min) of the methyl ester of 2-methylbutanoic acid prepared from **1** was consistent with that (11.668 min) of the authentic sample methyl ester of (*S*)-2-methylbutanoic acid (see Supporting Information: Figures S 80, S 81, and S 82).

Stephalonine A (1): white powder; $[\alpha]_D^{20}$ +102.8° (*c* 0.68, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 225 (3.69), 285 (2.97) nm; IR (KBr) ν_{max} 3385, 2958, 2939, 1732, 1616, 1487, 1464, 1441, 1275, 1196, 1101, 1047, 920, 814 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 461 $[M]^+$ (7), 446 (4), 360 (7), 231 (100), 230 (48), 229 (55), 198 (12), 196 (10); HREIMS *m/z* 461.2411 (calcd for $C_{25}H_{35}NO_7$, 461.2414).

Stephalonine B (2): white powder; $[\alpha]_D^{20}$ +7.7° (*c* 0.77, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 277 (4.25) nm; IR (KBr) ν_{max} 3406, 3012, 2941, 2837, 1713, 1641, 1489, 1441, 1371, 1313, 1273, 1178, 1097, 1043, 978, 920, 746 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 507 $[M]^+$ (4), 492 (2), 360-(4), 231 (52), 230 (42), 229 (100), 198 (13), 196 (16); HREIMS *m/z* 507.2239 (calcd for $C_{29}H_{33}NO_7$, 507.2257).

Stephalonine C (3): white powder; $[\alpha]_D^{20}$ −4.2° (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ) 277 (4.21) nm; IR (KBr) ν_{max} 3464, 2941, 2833, 1705, 1639, 1487, 1443, 1313, 1275, 1182, 1063, 928 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 493 $[M]^+$ (4), 270 (12), 231 (22), 229 (15), 216 (33), 215 (100), 184 (9), 182 (15); HREIMS *m/z* 493.2098 (calcd for $C_{28}H_{31}NO_7$, 493.2101).

Stephalonine D (4): white powder; $[\alpha]_D^{20}$ −17.9° (*c* 0.28, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 277 (4.26) nm; IR (KBr) ν_{max} 3431, 2937, 2839, 1703, 1639, 1487, 1450, 1313, 1277, 1178, 1067, 770 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 493 $[M]^+$ (5), 345 (11), 259 (59), 247 (34), 231 (41), 230 (44), 229 (100), 198 (19), 196 (34); HREIMS *m/z* 493.2104 (calcd for $C_{28}H_{31}NO_7$, 493.2101).

Stephalonine E (5): white powder; $[\alpha]_D^{20}$ +49.6° (*c* 0.115, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 279 (4.25) nm; IR (KBr) ν_{max} 3388, 3010, 2941, 2831, 1701, 1639, 1489, 1444, 1383, 1315, 1279, 1186, 1103, 1047, 952, 885, 812, 739 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 521 $[M]^+$ (2), 390 (4), 243 (100), 242 (35), 212 (10); HREIMS *m/z* 521.2044 (calcd for $C_{29}H_{31}NO_8$, 521.2050).

Stephalonine F (6): white powder; $[\alpha]_D^{20}$ −11.9° (*c* 0.21, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 282 (3.39) nm; IR (KBr) ν_{max} 3419, 2939, 2835, 1709, 1487, 1452, 1281, 1122, 1059, 1045, 710 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS 481 $[M]^+$ (5), 360 (5), 231 (59), 230 (39), 229 (100), 198 (11), 196 (17); HREIMS *m/z* 481.2094 (calcd for $C_{27}H_{31}NO_7$, 481.2100).

Stephalonine G (7): white powder; $[\alpha]_D^{20}$ −26.9° (*c* 0.29, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 262 (3.92), 287 (3.68) nm; IR (KBr) ν_{max} 3431, 2937, 2837, 1703, 1603, 1512, 1464, 1269, 1225, 1045, 764 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS 541 $[M]^+$ (2), 360 (4), 231 (65), 230 (49), 229 (100), 198 (17), 196 (27); HIEIMS *m/z* 541.2312 (calcd for $C_{29}H_{35}NO_9$, 541.2312).

Stephalonine H (8): white powder; $[\alpha]_D^{20}$ −100.7° (*c* 0.15, C_5H_5N); UV (MeOH) λ_{max} (log ϵ) 264 (3.90), 288 (3.73) nm; IR (KBr) ν_{max} 3346, 2926, 2850, 1701, 1597, 1514, 1487, 1452, 1427, 1284, 1223, 1109, 1061, 881, 816, 764 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 527 $[M]^+$ (5), 360 (6), 231 (76), 230 (58), 229 (100), 198 (14), 196 (20); HREIMS *m/z* 527.2139 (calcd for $C_{28}H_{33}NO_9$, 527.2156).

Stephalonine I (9): white powder; $[\alpha]_D^{20}$ −18.3° (*c* 0.115, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 263 (3.91), 287 (3.74) nm; IR (KBr) ν_{max} 3361, 2951, 2868, 1699, 1597, 1510, 1489, 1448, 1421, 1369, 1279, 1219, 1182, 1117, 1057, 1034, 920, 766 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 513 $[M]^+$ (2), 270 (3), 243 (4), 217 (18), 216 (37), 215 (100), 182 (15); HREIMS *m/z* 513.1996 (calcd for $C_{27}H_{31}NO_9$, 513.1998).

Norprostephabyssine (15): white powder; $[\alpha]_D^{20}$ −80.4° (*c* 0.52, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 276 (3.45) nm; IR (KBr) ν_{max} 3425, 2937, 1674, 1639, 1487, 1441, 1277, 1225, 1138, 1080, 1053, 874, 812 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 3; EIMS *m/z* 331 $[M]^+$ (33), 316 (17), 287 (20), 270 (13), 259 (83), 233 (47), 216 (35), 215 (100), 184 (39), 182 (45); HREIMS *m/z* 331.1409 (calcd for $C_{18}H_{21}NO_5$, 331.1420).

Isoprostephabyssine (16): white powder; $[\alpha]_D^{20}$ −242.4° (*c* 0.32, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 276 (3.68) nm; IR (KBr) ν_{max} 3423, 2935, 2839, 1672, 1641, 1489, 1452, 1279, 1225, 1097, 1059, 1032, 905, 810 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 3; EIMS *m/z* 345 $[M]^+$ (9), 327 (3), 317 (66), 302 (47), 299 (30), 284 (18), 247 (100), 229 (51), 214 (14), 196 (43), 168 (22); HREIMS *m/z* 345.1581 (calcd for $C_{19}H_{23}NO_5$, 345.1576).

Isolonganone (18): white powder; $[\alpha]_D^{20}$ +57.5° (*c* 0.57, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 284 (3.31) nm; IR (KBr) ν_{max} 3564, 3433, 2943, 2827, 1720, 1620, 1491, 1460, 1441, 1286, 1232, 1090, 1040, 968, 818 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 3; EIMS *m/z* 375 $[M]^+$ (4), 231 (19), 230 (31), 229 (100), 198 (18), 196 (14); HREIMS *m/z* 375.1684 (calcd for $C_{20}H_{25}NO_6$, 375.1682).

Isostephaboline (21): white powder; $[\alpha]_D^{20}$ +26.7° (*c* 0.30, MeOH); UV (MeOH) λ_{max} (log ϵ) 226 (3.63), 285 (3.23) nm; IR (KBr) ν_{max} 3412, 3284, 3105, 2972, 1662, 1491, 1446, 1390, 1283, 1223, 1121, 1063, 1020, 982, 820, 619 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 3; EIMS *m/z* 333 $[M]^+$ (11), 258 (8), 231 (100), 230 (35), 229, (20), 198 (37), 196 (18); HREIMS *m/z* 333.1578 (calcd for $C_{18}H_{23}NO_5$, 333.1576).

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Supporting Information Available: 1D and 2D NMR, EIMS, and IR spectra of all the new alkaloids; chiral GC analyses of methyl ester of 2-methylbutanoic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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