New Bisindole Alkaloids from *Tabernaemontana corymbosa*

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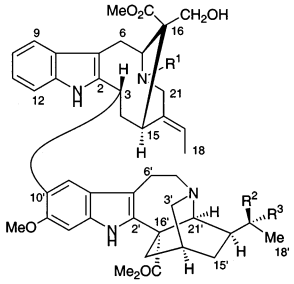
Ten new bisindole alkaloids of the vobasinyl-ibogan type, viz., conodiparines A−F (**1**−**6**), conodutarines A and B (**7**, **8**), and cononitarines A and B (**9**, **10**), were obtained from the leaf extract of the Malayan species *Tabernaemontana corymbosa*. The structures were determined using NMR and MS analysis.

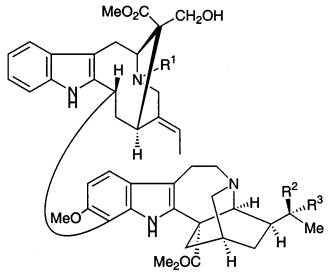
The genus *Tabernaemontana* (Apocynaceae) incorporates a large number of species that are distributed mainly over tropical America, Africa, and Asia.[1] Plants belonging to this genus are notable for producing a wide variety of indole alkaloids, including many with intriguing carbon skeletons as well as novel biological activity.[2−4] Several new indole alkaloids, some possessing novel carbon skeletons, have been previously reported by us from the Malayan species *T. corymbosa* Roxb. Ex Wall.[5−8] We have also recently reported the presence of several new iboga derivatives, as well as the biological activity of conodiparine A (**1**), a new vobasinyl-ibogan bisindole from the same plant, which was found to reverse multidrug-resistance (MDR) in vincristine-resistant KB cells.[9,10] We now wish to report the structures of 10 new bisindole alkaloids obtained from the leaf extract of this species.



1 R^1 = Me, R^2 = OH, R^3 = H

3 R^1 = Me, R^2, R^3 = O

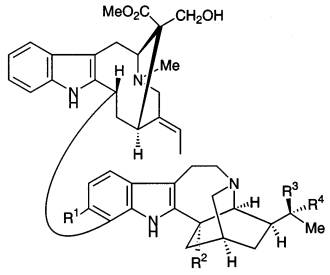
5 R^1 = H, R^2 = OH, R^3, = H



2 R^1 = Me, R^2 = OH, R^3 = H

4 R^1 = Me, R^2, R^3 = O

6 R^1 = H, R^2 = OH, R^3, = H



7 R^1 = OMe, R^2 = H, R^3 = OH, R^4 = H

8 R^1 = OMe, R^2 = H, R^3, R^4 = O

9 R^1 = OH, R^2 = CO_2Me, R^3 = OH, R^4 = H

10 R^1 = OH, R^2 = CO_2Me, R^3 = H, R^4 = H

Results and Discussion

Of the 10 bisindoles (**1**−**10**), conodiparine A (**1**), represents the most abundant alkaloid obtained. All 10 compounds were isolated from the leaf extract, and all showed UV spectra characteristic of an indole chromophore (see Experimental Section, e.g., conodiparine A, λ_{max} 227, 286, 296 nm). The EI-mass spectra of cononiparines A−F (**1**−**6**) showed fragments at *m*/*z* 180, 136, 124, and 122, which are characteristic of vobasine-iboga bisindoles.[11,12] In addition, the fragment at *m*/*z* 367 due to an intact vobasinyl fragment was common in the mass spectra of conodiparines A−D (**1**−**4**), suggesting that they share a common vobasinyl moiety, while the demethyl compounds, conodiparines E and F (**5**, **6**), showed the corresponding fragment at *m*/*z* 353. Conodiparine A (**1**) was obtained as an amorphous powder, $[\alpha]_D$ −34° (*c* 0.05, $CHCl_3$). The IR spectrum showed bands due to NH/OH (3388 cm^{-1}) and ester (1722 cm^{-1}) functions. The EIMS of **1** showed a molecular ion at *m*/*z* 750 with a peak due to loss of H_2O observed at *m*/*z* 732. HRMS measurements gave the molecular formula $C_{44}H_{55}N_4O_7$. The ^{13}C NMR spectrum showed a total of 44 separate resonances, in agreement with the formula derived from the HRMS. Examination of the ^1H and ^{13}C NMR spectra with the aid of COSY, HMQC, and HMBC confirmed the presence of vobasinyl and ibogan units. Thus the ^1H NMR spectrum of **1** (Table 1) showed the presence of two indole NH, an unsubstituted indole ring (vobasinyl), another indole ring substituted at C(10′) and C(11′) (iboga), one aromatic methoxy group (iboga), two ester carbomethoxy groups, one *N*-Me (vobasinyl), an ethylidene (vobasinyl), a hydroxymethyl (vobasinyl), and a hydroxyethyl group (iboga). The ester methyl associated with the vobasinyl unit is unusually shielded (δ 2.38), which is in agreement with the configuration of C(16), which places the ester function in the shielding zone of the aromatic ring. The H(3) resonance of the vobasinyl unit was observed as a broad one-proton doublet at δ 5.14 (*J* 13 Hz), and the attachment of this carbon (3) to the aromatic C(10′) is confirmed by the observed two- and three-bond correlations from C(10′) to H(3) and C(3) to H(9′), respectively, in the HMBC spectrum. The placement of the methoxy substituent at C(11′) of the iboga unit is supported by comparison of the aromatic carbon resonances with that of those in related vobasine-iboga bisindoles with similar substitution and branching such as conoduramine. The hydrogens of the iboga unit were observed as two singlets, indicating substitution of the aromatic moiety at positions 10′ and 11′. The signal due to H(12′) is characteristically at higher field (δ_H 6.81, δ_C 92.7), which is also confirmed by the observed NOE interaction between NH′ and H(12′). The upfield carbon shift of H(12′) is a characteristic of adjacent C(11′)

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Table 1. ^{1}H NMR Spectral Data for **1**−**5** (400 MHz, $CDCl_3$)[a]

H	1	2	3	4	5
3	5.14 br d (13)	5.32 dd (13, 3)	5.14 br d (13)	5.32 dd (13, 3)	5.16 br d (13)
5	3.92 t (9)	3.94 m	3.95 m	3.96 m	4.00 t (9)
6	3.28 m	3.49 m	3.28 dd (15, 8)	3.44 m	3.38 dd (14, 9)
	3.61 m	3.49 m	3.56 m	3.44 m	3.78 m
9	7.55 d (7)	7.68 dd (7.4, 1)	7.55 d (6.9)	7.67 br d (7.7)	7.57 br d (7.5)
10	7.05 m	7.14 td (7.4, 1)	7.06 m	7.13 td (7.7, 1)	7.06 m
11	7.05 m	7.08 td (7.4, 1)	7.06 m	7.08 td (7.7, 1)	7.06 m
12	7.05 m	7.02 dd (7.4, 1)	7.06 m	7.02 br d (7.7)	7.06 m
14	2.00 m	1.95 ddd (15, 7, 3)	2.02 m	1.97 m	2.03 m
	2.63 m	2.68 m	2.59 m	2.70 m	2.76 m
15	3.52 m	3.59 dd (11, 7)	3.50 m	3.59 m	3.54 m
17	ca. 3.70	ca. 3.75	ca. 3.72	ca. 3.75	3.61 d (10.5)
	ca. 3.70	ca. 3.75	ca. 3.72	ca. 3.75	3.81 d (10.5)
18	1.65 d (6)	1.66 dd (6.8, 1.6)	1.64 d (6)	1.66 dd (6.6, 1)	1.61 d (6.6)
19	5.37 q (6)	5.37 q (6.8)	5.38 q (6)	5.37 q (6.6)	5.31 q (6.6)
21	2.96 d (14)	2.95 d (10)	2.98 d(14)	2.96 d (14)	3.11 d (15)
	3.59 d (14)	3.51 dd (10, 1.6)	3.62 d (14)	3.53 br d (14)	4.02 br d (15)
NH	7.59 br s	7.69 br s	7.60 br s	7.77 br s	7.81 br s
CO_2Me	2.38 s	2.46 s	2.38 s	2.45 s	2.38 s
NMe	2.56 s	2.59 s	2.58 s	2.60 s	
3′	2.73 br d (9)	2.43 m	2.72 m	2.42 br d (8)	2.76 m
	2.91 m	2.75 ddd (9, 4, 2)	2.91 m	2.74 dt (8, 3)	2.91 m
5′	2.91 m	2.97 m	2.91 m	2.97 m	2.99 m
	3.28 m	3.31 m	3.20 m	3.25 m	3.27 dt (13.5, 7)
6′	2.80 m	2.97 m	2.72 m	2.97 m	2.99 m
	3.02 m	2.97 m	2.91 m	2.97 m	2.99 m
9′	6.85 s	7.25 d (8.7)	6.86 s	7.25 d (8.8)	6.88 s
10′		6.83 d (8.7)		6.83 d (8.8)	
12′	6.81 s		6.82 s		6.81 s
14′	1.98 m	1.57 m	1.97 m	1.57 m	1.97 m
15′	1.51 m	1.30 m	1.54 m	1.37 dddd (14, 10, 4, 2)	1.51 m
	1.87 m	1.72 m	2.20 m	1.97 m	1.87 m
17′	1.87 m	0.69 ddd (14, 4, 2)	1.87 dt (13, 3)	0.77 dt (14, 3)	1.87 m
	2.52 m	1.72 m	2.57 m	1.76 dt (14, 2)	2.55 br d (13.5)
18′	1.06 d (6)	1.00 d (6)	2.19 s	2.15 s	1.06 d (6)
19′	4.10 br q (6)	4.04 qd (6, 1)			4.10 q (6)
20′	1.40 m	1.24 m	2.42 m	2.23 ddd (10, 6.5, 1)	1.40 m
21′	3.73 br s	3.65 br s	4.14 d (1)	4.07 d (1)	3.73 br s
NH′	7.72 br s	7.50 br s	7.72 br s	7.51 br s	7.96 br s
11′-OMe	3.96 s	3.97 s	3.96 s	3.97 s	3.95 s
CO_2Me′	3.68 s	3.71 s	3.75 s	3.74 s	3.68 s
19′-OH					6.45 br s

[a] Assignments based on COSY, HMQC, and NOE.

oxygenation and supports placement of the aromatic methoxy substituent at C(11′).[13] Further proof of this is provided by the observed correlation from C(11′) to H(9′) and OMe′ in the HMBC spectrum. The NMR spectral data in fact resemble that of the bisindole 19′(*R*)-hydroxyconoduramine,[13] recently isolated from *Tabernaemontana subglobosa*, which has a similar mode of branching of the monomeric entities [C(3) to C(10′) connection], except for the presence of a hydroxymethyl function at C(16) of the vobasinyl unit in **1**. The configuration of C(19′) is readily determined to be *S* from examination of the carbon shifts of C(15′) and C(21′), which correspond to that of the monomeric iboga alkaloid, heyneanine, exemplifying the 19(*S*) series in iboga alkaloids with a hydroxyethyl side chain [versus that of 19-*epi*-heyneanine, exemplifying the 19(*R*) series]. The 19(*S*) compounds have the chemical shift of C(15) at ca. δ 23, which is shifted downfield by about 6.7 ppm compared to those in the 19(*R*) compounds, for which the C(21) resonances are shifted upfield by about 5 ppm to ca. δ 54.7 compared to the 19(*S*) epimers.[14] The stereochemistry at C(3) can be determined from a combination of two observations. First, the signal for H(3) is a doublet with *J* 13 Hz, requiring H(3) and one of the H(14) to be *trans*-diaxial. Furthermore, irradiation of H(3) results in NOE enhancement of NH and vice versa, requiring these two hydrogens to be in mutual proximity. These two observations are satisfied only in the case where H(3) has β stereochemistry, since in the alternative arrangement in which the stereochemistry of H(3) is α, the conformation adopted by the central 10-membered ring, in order that one H(14) is *trans* to H(3), would result in H(3) pointing into the concave face of the middle ring and therefore away from NH, in which case NOE between NH and H(3) would have been impossible.

Conodiparine B (**2**), $[\alpha]_D$ −64° (*c* 0.93, $CHCl_3$), is isomeric with conodiparine A (**1**), as shown by its mass spectrum (M^+ *m*/*z* 750). The UV, IR, and ^{1}H and ^{13}C NMR spectra are very similar to those of **1**, except for a few changes. The main difference from **1** is in the mode of branching of the monomeric units, which in **2** is from C(3) of the vobasinyl unit to C(12′) of the iboga unit, as in the related compound 19′(*R*)-hydroxyconodurine.[13] This is clearly shown by the aromatic-H resonances of the iboga unit which were observed as a pair of AB doublets at δ 7.25 H(9′) and 6.83 H(10′). Further proof of the C(3)−C(12′) connection is provided by the observed correlation from C(12′) to H(3) in the HMBC spectrum. The change in the mode of branching has also resulted in a noticeable upfield shift of both the C(17′) hydrogens from δ 1.87 and 2.52 to 0.69 and 1.72, respectively. This pattern appears to be quite general and was also observed in the spectra of the other bisindoles, **4** and **6**−**10** (Tables 1 and 2), which also possess the same C(3)−C(12′) connection. As in the previous compound, the observed J_{3-14} coupling of 13 Hz and the NOE interaction

Table 2. ^{1}H NMR Spectral Data for **6**−**10** (400 MHz, $CDCl_3$)[a]

H	6	7	8	9	10
3	5.34 dd (13, 3)	5.31 dd (13, 3)	5.33 dd (13, 3)	5.29 dd (13, 3)	5.29 dd (13, 3)
5	4.16 t (9)	3.94 m	3.99 m	3.97 t (9)	3.98 t (9)
6	3.62 m	3.36 m	3.39 dd (15, 8)	3.51 m	3.54 m
	3.76 m	3.59 m	3.63 m	3.51 m	3.54 m
9	7.73 br d (7.4)	7.60 br d (7.8)	7.62 br d (7.8)	7.69 br d (7.7)	7.69 br d (7.5)
10	7.15 td (7.4, 1)	7.11 m	7.11 m	7.14 td (7.7, 1)	7.14 td (7.5, 1)
11	7.10 td (7.4, 1)	7.11 m	7.11 m	7.09 td (7.7, 1)	7.08 td (7.5, 1)
12	7.03 br d (7.4)	7.04 br d (7.8)	7.07 br d (7.8)	7.03 br d (7.7)	7.02 br d (7.5)
14	2.01 ddd (15, 7, 3)	2.02 ddd (15, 7, 3)	2.02 ddd (15, 7, 3)	2.04 ddd (15, 7, 3)	2.01 ddd (15, 7, 3)
	2.81 m	2.69 m	2.74 m	2.68 m	2.73 m
15	3.62 m	3.59 m	3.63 m	3.65 m	3.62 dd (11.5, 7)
17	ca. 3.72	ca. 3.75	ca. 3.76	ca. 3.79	ca. 3.76
	3.89 d (11.5)	ca. 3.75	ca. 3.76	ca. 3.79	ca. 3.76
18	1.65 d (6.5)	1.67 dd (6.8, 1.5)	1.68 dd (6.8, 1.6)	1.63 dd (6.7, 1.5)	1.61 dd (6.8, 1.5)
19	5.39 q (6.5)	5.38 q (6.8)	5.39 q (6.8)	5.38 q (6.7)	5.38 q (6.8)
21	3.23 d (15)	2.97 d (11)	2.97 d (13.6)	2.96 d (13)	2.97 dd (11.8, 1.5)
	3.98 m	3.57 d (11)	3.59 dd (13.6, 1.6)	3.53 dd (13, 1.5)	3.50 d (11.8)
NH	7.74 br s	7.59 br s	7.60 br s	7.89 br s	7.91 br s
CO_2Me	2.49 s	2.44 s	2.43 s	2.48 s	2.48 s
NMe		2.57 s	2.59 s	2.60 s	2.61 s
3′	2.44 br d (9)	2.42 m	2.45 m	2.46 br d (9.8)	2.46 m
	2.75 m	2.81 dt (8, 3)	2.84 dt (9, 2.5)	2.75 m	2.67 m
5′	2.95 m	3.11 m	3.06 m	2.91 m	3.09 m
	3.31 m	3.21 m	3.15 m	3.30 dt (14, 7)	3.24 dt (14, 7.5)
6′	2.95 m	2.61 m	2.53 m	2.99 m	2.83 m
	2.95 m	3.11 m	3.06 m	2.99 m	3.09 m
9′	7.25 d (8.7)	7.23 d (8.6)	7.24 d (8.7)	7.13 d (8.4)	7.13 d (8.5)
10′	6.84 d (8.7)	6.82 d (8.6)	6.83 d (8.7)	6.67 d (8.4)	6.66 d (8.5)
12′					
14′	1.55 m	1.69 m	1.71 m	1.58 m	1.51 m
15′	1.30 m	1.37 m	1.37 m	1.31 m	0.93 m
	1.69 m	1.80 br dd (13, 6)	2.24 m	1.73 m	1.45 m
16′		2.37 m	2.48 m		
17′	0.68 br d (14)	0.84 br d (14)	0.99 br d (14)	0.71 br d (13.5)	0.68 br d (14)
	1.69 m	1.13 m	1.26 m	1.70 m	1.75 br d (14)
18′	0.99 d (6)	1.04 d (6.3)	2.15 s	1.01 d (6.3)	0.81 t (7)
19′	4.04 qd (6, 1)	4.07 qd (6.3, 1.3)		4.06 qd (6.3, 2)	1.34 m; 1.45 m
20′	1.24 m	1.49 br dd (11, 6)	2.48 m	1.24 m	1.10 m
21′	3.64 br s	2.95 br s	3.44 t (2)	3.76 br s	3.34 br s
NH′	7.43 br s	7.82 br s	7.79 br s	7.52 br s	7.52 br s
11′-OMe	3.98 s	3.96 s	3.97 s		
CO_2Me′	3.70 s			3.72 s	3.70 s

[a] Assignments based on COSY, HMQC, and NOE.

between NH and H(3) confirm the α attachment of the iboga moiety at C(3).

Conodiparine C (**3**) was obtained as a light yellow amorphous powder with $[\alpha]_D$ −27° (*c* 0.50, $CHCl_3$). The EI-mass spectrum of **3** showed a molecular ion peak at *m*/*z* 748, which analyzed for $C_{44}H_{52}N_4O_7$, with other major fragments at *m*/*z* 705 (M − COMe) and 689 (M − CO_2Me). The IR spectrum of conodiparine C (**3**) was virtually identical to that of conodiparine A (**1**), except for the presence of an additional carbonyl band at 1714 cm^{-1} due to a ketonic function. The presence of the ketone function was confirmed by the carbon resonance at δ 208.0, which was observed in place of the oxymethine resonance in the ^{13}C NMR spectrum (Table 3). The ^{1}H NMR spectrum of **3** was generally similar to that of **1**, except for the signals of the hydroxyethyl group, which were absent. Instead a 3H signal due to an acetyl group was observed at δ 2.19 (Table 1). As in the case of conodiparine A (**1**), the dimer is branched from C(3) of the vobasine unit to C(10′) of the iboga unit, as shown by the presence of the two aromatic singlets due to H(9′) and H(12′) and consistent with the observed C(10′) to H(3) and C(3) to H(9′) correlations in the HMBC spectrum.

Conodiparine D (**4**) was also obtained in amorphous form, with $[\alpha]_D$ −42° (*c* 0.90, $CHCl_3$). The EI-mass spectrum of **4** showed a molecular ion peak at *m*/*z* 748, indicating that it is an isomer of **3**. In common with compound **3**, the mass-spectrum of **4** also lacked the (M − H_2O) fragment, which was observed in the mass-spectra of **1** and **2**. As in **3**, the IR spectrum of **4** showed the presence of a ketone absorption band at 1714 cm^{-1}, which was supported by the carbonyl resonance at δ 208.2 in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum was essentially similar to that of conodiparine B (**2**), indicating a similar C(3) to C(12′) connection in the dimer, except for the replacement of the hydroxyethyl group by an acetyl group (δ 2.15). Conodiparine D (**4**) is therefore the C(19′) oxo-analogue of conodiparine B (**2**).

Conodiparine E (**5**), $[\alpha]_D$ −101° (*c* 0.07, $CHCl_3$), had UV and IR spectra that were very similar to those of conodiparine A (**1**). The expected molecular ion at *m*/*z* 736 ($C_{43}H_{52}N_4O_7$) was too weak to be detected in both the EI- and the FAB-mass spectra. The highest mass fragment was observed at *m*/*z* 718, which analyzed for $C_{43}H_{50}N_4O_6$ and which corresponds to the loss of H_2O. The MH^+ ion could however be detected by API-MS at *m*/*z* 737. The ^{1}H and ^{13}C NMR spectral data are generally similar to that of conodiparine A (**1**), except for the conspicuous absence of the peak due to *N*Me of the vobasinyl unit. The connection of the monomeric units is from C(3) to C(10′) as in **1**, from the observed aromatic resonances of H(9′) and H(12′), and from the HMBC spectrum, which showed C(10′) to H(3) and C(3) to H(9′) correlations. Conodiparine E (**5**) is therefore the *N*(4)-demethyl analogue of **1**.

Table 3. ^{13}C NMR Spectral Data for **1**−**10** (100 MHz, $CDCl_3$)[a]

C	1	2	3	4	5	6	7	8	9	10
2	137.8	136.2	137.9	136.9	137.8	137.0	136.2	136.2	136.3	136.3
3	36.8	35.0	36.8	35.0	37.0	35.3	35.4	35.3	35.2	35.2
5	60.1	59.9	60.1	60.0	53.5	53.4	59.9	59.9	60.1	60.2
6	17.3	17.5	17.4	17.5	24.8	25.0	17.3	17.4	17.6	17.5
7	110.5	109.4	110.4	108.9	110.0	110.3	107.1	108.2	109.7	109.3
8	130.0	129.5	130.0	129.5	129.8	129.4	129.1	129.1	129.5	129.5
9	117.4	118.0	117.5	117.9	117.6	118.3	117.6	117.6	118.0	118.1
10	118.7	119.4	118.8	119.4	118.7	119.7	119.5	119.4	119.4	119.4
11	121.5	122.2	121.6	122.3	121.5	122.4	122.5	122.5	122.4	122.3
12	109.5	109.8	109.9	109.9	109.7	109.8	110.1	110.2	109.9	109.9
13	136.0	136.1	136.1	136.2	134.8	136.2	136.1	135.9	136.3	136.0
14	36.7	33.6	36.7	33.7	36.8	33.8	34.1	34.1	33.5	33.5
15	35.8	35.5	35.9	35.6	36.0	35.9	35.7	35.7	36.7	35.5
16	52.8	52.1	51.9	52.1	51.5	51.6	52.1	52.1	52.3	52.3
17	70.5	70.2	70.5	70.4	68.9	69.0	70.4	70.3	70.4	70.5
18	12.0	12.1	12.1	12.1	11.7	11.9	12.1	12.1	12.2	12.2
19	119.6	120.2	120.4	120.2	118.9	120.0	120.3	120.4	120.5	120.5
20	136.7	136.9	136.7	136.9	136.0	136.9	137.4	137.4	136.6	136.5
21	51.9	51.8	52.1	51.9	43.1	43.0	51.9	51.9	52.0	51.9
CO_2Me	50.0	50.2	50.1	50.3	50.0	50.4	50.3	50.3	50.5	50.5
CO_2Me	174.1	174.1	173.8	174.0	174.8	174.3	174.1	174.0	174.1	174.8
NMe	41.9	42.0	42.0	42.1			42.0	42.0	42.1	42.1
2′	134.4	135.2	134.8	135.0	134.4	135.3	139.8	140.1	135.3	135.3
3′	51.1	50.9	50.8	51.0	51.1	51.2	48.9	48.9	50.8	50.0
5′	52.0	51.9	53.1	52.9	52.2	52.0	52.6	53.8	51.9	52.9
6′	21.4	21.3	21.6	21.7	21.4	21.3	20.3	20.3	21.3	22.1
7′	109.8	108.6	110.4	109.3	109.5	108.6	107.1	108.2	108.8	109.3
8′	122.1	124.0	122.4	124.2	122.1	124.1	125.1	125.2	123.4	124.0
9′	117.8	117.1	117.9	117.1	117.9	117.2	116.6	116.6	117.4	117.4
10′	127.6	105.2	127.5	105.2	127.5	105.2	105.0	105.1	105.2	109.4
11′	153.4	152.1	153.4	152.1	153.3	152.2	152.0	151.9	148.6	148.1
12′	92.7	114.5	92.7	114.5	92.7	114.4	114.2	114.3	112.7	112.5
13′	134.7	135.0	134.6	135.2	134.4	135.2	134.4	134.1	135.3	135.2
14′	26.7	26.4	26.7	26.5	26.6	26.5	25.7	25.7	26.5	27.0
15′	22.8	22.7	24.6	24.8	22.8	22.7	22.7	24.2	22.7	31.9
16′	53.9	53.4	53.9	53.5	53.9	53.5	39.9	39.5	53.5	54.5
17′	36.7	35.0	37.1	35.2	36.8	35.1	32.9	33.3	35.4	34.7
18′	20.2	20.2	27.7	27.6	20.2	20.2	20.1	27.7	20.2	11.6
19′	71.2	71.2	208.0	208.2	71.2	71.3	71.4	209.1	71.3	26.5
20′	39.4	39.2	50.8	50.6	39.4	39.2	41.7	53.3	39.2	39.0
21′	59.6	59.4	56.0	55.4	59.6	59.4	60.6	56.3	59.6	57.6
CO_2Me'	52.8	52.6	52.8	52.6	52.7	52.8			52.7	52.3
CO_2Me'	174.9	174.1	174.9	174.1	173.9	173.9			174.1	174.8
11′-OMe	55.8	56.8	55.8	56.8	55.8	56.8	56.8	56.8		

[a] Assignments based on HMQC and HMBC.

Similarly conodiparine F (**6**), $[\alpha]_D$ −73° (*c* 0.32, $CHCl_3$), can be readily shown to be the *N*(4)-demethyl analogue of **2**. The UV and IR spectra were similar to that of **2**. The FABMS gave an MH^+ peak at *m*/*z* 737, which analyzed for $C_{43}H_{53}N_4O_7$, differing from **2** by loss of 14 mass units, consistent with replacement of a methyl group by H. As in the previous compound **5**, the NMR spectral data are notable for the conspicuous absence of the *N*Me resonance. In addition, the absence of the *N*Me group has apparently caused the upfield shift of C(5) and C(21) from δ 59.9 and 51.8 in **2** to δ 53.4 and 43.0 in **6**, respectively (Table 3). A similar effect was also observed in the case of conodiparine E (**5**) (see Table 3). As in **2**, the dimer is branched from C(3) to C(12′), from the observed aromatic coupling pattern, as well as the C(12′) to H(3) correlation in the HMBC spectrum.

Conodutarine A (**7**), $[\alpha]_D$ −51° (*c* 0.18, $CHCl_3$), was obtained as a light yellowish oil. The UV spectrum was typical of an indole chromophore, and the IR spectrum showed NH/OH and ester carbonyl bands. The FAB-mass spectrum showed the MH^+ peak at *m*/*z* 693, which analyzed for $C_{42}H_{53}N_4O_5$, differing from conodiparine B (**2**) by 58 mass units, suggesting replacement of a methyl ester (CO_2-Me) group with H. This is further supported by both the ^1H and ^{13}C NMR spectral data, which showed a close correspondence with **2**, except for the absence of peaks associated with the C(16′)-CO_2Me group. The H(16′) signal in **7** (as well as **8**) is seen as a multiplet at δ 2.37, while the C(16′) signal has undergone an upfield shift to ca. δ 39 from ca. δ 53 in the other compounds with an intact C(16′) methyl ester substituent (Table 3). The aromatic coupling pattern and the observed C(12′) to H(3) correlation in the HMBC spectrum confirm the C(3) to H(12′) connection.

Conodutarine B (**8**), $[\alpha]_D$ −45° (*c* 0.14, $CHCl_3$), is similarly shown to be the C(16′)-decarbomethoxy analogue of conodiparine D (**4**). The FABMS gave an MH^+ peak at *m*/*z* 691, which analyzed for $C_{42}H_{51}N_4O_5$, differing from **4** by 58 mass units, and comparison of the ^1H and ^{13}C NMR with that of **4** again showed a general similarity, except for the replacement of the C(16′)-CO_2Me function with H, which was observed as a multiplet at δ 2.48.

Cononitarine A (**9**) was obtained as a light yellowish oil with $[\alpha]_D$ −52° (*c* 0.11, $CHCl_3$). The UV spectrum showed typical indole absorptions at 223, 285, and 294 nm. Upon basification, the spectrum showed a bathochromic shift (see Experimental Section), suggesting the presence of a phenolic group. The IR spectrum showed the presence of NH/OH and ester functions. The FABMS showed a MH^+ peak at 737, which analyzed for $C_{43}H_{53}N_4O_7$. The molecular formula for **9** indicates that it differs from conodiparine B

(**2**) by 14 mass units, suggesting replacement of a methyl group by H. The NMR spectral data of **9** were generally identical with that of **2**, except for the absence of the 11′-methoxy substituent on the iboga indole moiety in **9**, which is replaced by an OH group {δ C(11′) 148.6}. The dimer is branched from C(3) to C(12′) as in **2**, from the aromatic resonances of H(9′) and H(10′), which were observed as a pair of AB doublets. In contrast to the previous 11′-methoxy-substituted bisindoles (**1**−**8**), which showed the characteristic C(11′) shift at ca. δ 152−153, the C(11′) resonances in cononitarines A (**9**) and B (**10**) are shifted slightly upfield to ca. δ 148, consistent with the change in the C(11′) aromatic substitution from OMe to OH.[15]

Cononitarine B (**10**) was obtained as a light yellowish oil, with $[\alpha]_D$ −43° (*c* 0.10, $CHCl_3$). The UV and IR spectra were similar to that of **9**. The UV spectrum also showed a bathochromic shift on addition of a base, suggesting the presence of a phenolic function, which is deduced to be at C(11′) from the observed C(11′) shift at δ 148.1. The FABMS showed an MH^+ peak at *m/z* 721, differing from **9** by 16 mass units. HRFABMS measuerments yielded the molecular formula $C_{43}H_{52}N_4O_6$, indicating that **10** differs from **9** by loss of an oxygen atom. Comparison of the ^{1}H NMR spectrum of **10** with that of **9** revealed that the structure of **10** is closely related to **9** except for the hydroxyethyl side chain at C(20′), which is replaced by an ethyl side chain in **10**. This is confirmed by the observation of a triplet due to the methyl (CH_3-18′) at δ 0.81 (*J* 7 Hz) and two multiplets due to the two H(19′) at δ 1.34 and 1.45 in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed the presence of an additional methylene carbon resonance at δ 26.5 {C(19′)} in place of the oxymethine signal at δ 71.3 when compared to the spectrum of **9**. As in compound **9**, the pattern of the aromatic-H signals and the observed C(12′) to H(3) correlation in the HMBC spectrum confirm a similar C(3) to C(12′) branching of the dimer.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrophotometer. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-LA 400 spectrometer at 400 and 100 MHz, respectively. API-MS were obtained on a Perkin-Elmer API 100 instrument. EIMS, HREIMS, and FABMS were obtained at The Research School of Chemistry, Australian National University, Canberra (compounds **1**−**6**), and at The Kitasato Institute, Tokyo (compounds **7**−**10**), courtesy of Dr. K. Komiyama.

Plant Material. Plant material was collected in Perak, Malaysia (May, 1996), and was identified by Dr. A. J. M. Leeuwenberg, Laboratory of Plant Taxonomy and Plant Geography, Agricultural University, Wageningen, The Netherlands. Herbarium voucher specimens (GK 604) are deposited at the Herbarium of the Department of Chemistry, University of Malaya, Malaysia, and at Wageningen.

Extraction and Isolation. Extraction of the ground leaf material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as has been described in detail elsewhere.[16,17] In the first extraction using 3.3 kg of material only compounds **1**−**6** were obtained. In a second study using 6.8 kg of material, compounds **7**−**10** were isolated in addition to compounds **1**−**6**. The alkaloids were isolated by initial column chromatography on silica gel using $CHCl_3$ with increasing proportions of MeOH followed by rechromatography of appropriate partially resolved fractions using centrifugal TLC. Solvent systems used for centrifugal TLC were EtOAc/cyclohexane (1:1; NH_3), MeOH/$CHCl_3$ (60:1; NH_3), and Et_2O/MeOH (20:1). The yields (g kg^{-1}) of the alkaloids from the first extraction were as follows: **1** (0.107), **2** (0.065), **3** (0.015), **4** (0.049), **5** (0.002), and **6** (0.016). The yields from the second extraction were as follows: **1** (0.581), **2** (1.68), **3** (0.012), **4** (0.028), **5** (0.022), **6** (0.089), **7** (0.007), **8** (0.008), **9** (0.002), and **10** (0.001).

Conodiparine A (1): light yellow amorphous powder; $[\alpha]_D$ −34° (*c* 0.71, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (4.92), 286 (4.32), 296 (4.35) nm; IR (dry film) ν_{max} 3388, 1722 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 3; EIMS *m/z* 750 $[M]^+$ (9), 732 (5), 719 (5), 509 (5), 367 (11), 204 (100), 180 (41), 149 (56), 136 (42), 124 (22), 122 (31); HREIMS *m/z* 750.3991 (calcd for $C_{44}H_{54}N_4O_7$, 750.3993).

Conodiparine B (2): light yellow amorphous powder; $[\alpha]_D$ −64° (*c* 0.93, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 224 (4.90), 286 (4.32), 293 (4.30) nm; IR (dry film) ν_{max} 3374, 1727 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 3; EIMS *m/z* 750 $[M]^+$ (11), 732 (6), 719 (5), 509 (6), 367 (10), 204 (100), 180 (43), 149 (52), 136 (40), 124 (20), 122 (34); HREIMS *m/z* 750.3981 (calcd for $C_{44}H_{54}N_4O_7$, 750.3993).

Conodiparine C (3): light yellow amorphous powder; $[\alpha]_D$ −27° (*c* 0.50, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (4.63), 286 (4.02), 296 (4.05) nm; IR (dry film) ν_{max} 3372, 1728, 1714 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 3; EIMS *m/z* 748 $[M]^+$ (7), 717 (8), 705 (10), 689 (15), 507 (5), 367 (38), 180 (60), 149 (100), 136 (40), 124 (35), 122 (38); HREIMS *m/z* 748.3827 (calcd for $C_{44}H_{52}N_4O_7$, 748.3836).

Conodiparine D (4): light yellow amorphous powder; $[\alpha]_D$ −42° (*c* 0.90, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 224 (4.17), 286 (4.13), 296 (4.12) nm; IR (dry film) ν_{max} 3375, 1724, 1714 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 3; EIMS *m/z* 748 $[M]^+$ (7), 717 (9), 705 (8), 685 (15), 507 (5), 367 (40), 180 (58), 149 (100), 136 (39), 124 (33), 122 (35); HREIMS *m/z* 748.3842 (calcd for $C_{44}H_{52}N_4O_7$, 748.3836).

Conodiparine E (5): light yellow amorphous powder; $[\alpha]_D$ −101° (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 223 (4.23), 285 (3.64), 294 (3.66) nm; IR (dry film) ν_{max} 3380, 1727 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 3; EIMS *m/z* 718 $[M - H_2O]^+$ (15), 705 (15), 509 (18), 353 (24), 180 (100), 136 (60), 124 (20), 122 (75); HREIMS *m/z* 718.3706 (calcd for $C_{43}H_{50}N_4O_6$, 718.3730); API-MS *m/z* 737 $[MH]^+$.

Conodiparine F (6): light yellow amorphous powder; $[\alpha]_D$ −73° (*c* 0.32, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 224 (4.86), 286 (4.29), 294 (4.28) nm; IR (dry film) ν_{max} 3378, 1724 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 3; EIMS *m/z* 736 $[M]^+$ (11), 718 (23), 705 (25), 509 (33), 353 (18), 180 (100), 136 (65), 124 (22), 122 (82); FABMS *m/z* 737 $[MH]^+$; HRFABMS *m/z* 737.3979 (calcd for $C_{43}H_{53}N_4O_7$, 737.3914).

Conodutarine A (7): light yellowish oil; $[\alpha]_D$ −51° (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (4.85), 285 (4.26), 293 (4.25) nm; IR (dry film) ν_{max} 3390, 1721 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 3; FABMS *m/z* 693 $[MH]^+$ (27), 675 (3), 661 (4), 621 (5), 531 (6), 367 (2), 180 (16), 136 (100), 124 (24), 122 (10); HRFABMS *m/z* 693.4026 (calcd for $C_{42}H_{53}N_4O_5$, 693.4016).

Conodutarine B (8): light yellowish oil; $[\alpha]_D$ −45° (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (4.87), 285 (4.31), 293 (4.28) nm; IR (dry film) ν_{max} 3385, 1720, 1709 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 3; FABMS *m/z* 691 $[MH]^+$ (25), 659 (4), 621 (4), 460 (7), 367 (4), 180 (24), 136 (100), 124 (6), 122 (12); HRFABMS *m/z* 691.3853 (calcd for $C_{42}H_{51}N_4O_5$, 691.3859).

Cononitarine A (9): light yellowish oil; $[\alpha]_D$ −52° (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 223 (4.78), 285 (4.19), 294 (4.25) nm; UV (EtOH/NaOH) λ_{max} (log ϵ) 280 (4.15), 295 (4.09), 314 (3.99) nm; IR (dry film) ν_{max} 3375, 1726 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 3; FABMS *m/z* 737 $[MH]^+$ (60), 719 (8), 367 (6), 180 (100), 136 (75), 124 (11), 122 (14); HRFABMS *m/z* 737.3924 (calcd for $C_{43}H_{53}N_4O_7$, 737.3914).

Cononitarine B (10): light yellowish oil; $[\alpha]_D$ −43° (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 223 (4.52), 285 (3.92), 294 (3.89) nm; UV (EtOH/NaOH) λ_{max} (log ϵ) 280 (4.15), 295 (4.08), 315 (4.00) nm; IR (dry film) ν_{max} 3380, 1724 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 3; FABMS *m/z* 721 $[MH]^+$ (61), 689 (7), 367 (6), 180 (49), 136 (100), 124 (35), 122 (15); HRFABMS *m/z* 721.3965 (calcd for $C_{43}H_{53}N_4O_6$, 721.3965).

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