Leucoridines A−D, Cytotoxic *Strychnos*−*Strychnos* Bisindole Alkaloids from *Leuconotis*

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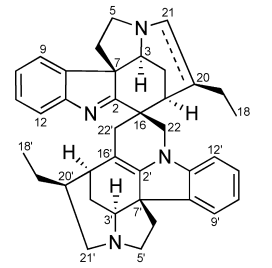
Four new bisindole alkaloids of the *Strychnos*−*Strychnos* type, leucoridines A−D (**1**−**4**), were isolated from the stem-bark extract of *Leuconotis griffithii*. Alkaloids **1**−**4** showed moderate cytotoxicity against drug-sensitive and vincristine-resistant human KB cells.

Plants of the genus *Leuconotis* (Apocynaceae) are usually woody climbers and occur in Indonesia and Peninsular Malaysia.[1−4] Previous studies of the Malayan *L. griffithii* and *L. eugenifolia* have provided, in addition to the ring-opened alkaloids, leuconolam and rhazinilam and their derivatives, various strychnan, kopsan, and eburnan derivatives,[5,6] while several yohimbines and the pentacyclic diazaspiro alkaloid leuconoxine were subsequently reported from *L. eugenifolia* occurring in Indonesia.[7] In continuation of our studies of biologically active alkaloids from Malaysian Apocynaceae,[8−29] we undertook an investigation of the alkaloids of *Leuconotis* including *L. griffithii* and *L. maingayi* (the latter species has not been previously investigated) and reported the isolation of new oxindole, strychnan, and eburnan alkaloids and a novel cytotoxic bisindole alkaloid from *L. griffithii* and *L. maingayi*.[27−29] We now report the isolation, structure, and biological activity of four new cytotoxic bisindole alkaloids of the *Strychnos*−*Strychnos* type (**1**−**4**) from the stem-bark extract of *L. griffithii*.

Results and Discussion

Leucoridine A (**1**) was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ −29 ($CHCl_3$, *c* 0.26). The UV spectrum showed absorption maxima at 213 and 267 nm, characteristic of an indolenine chromophore.[30] The ESIMS of **1** showed an $[M + H]^+$ peak at *m*/*z* 557, and HRESIMS measurements yielded the molecular formula $C_{38}H_{44}N_4$ (19 double-bond equivalents, or DBE). The ^{13}C NMR spectrum (Table 1) accounted for 38 carbon resonances, comprising two methyl, 12 methylene, 14 methine, and 10 quaternary carbons. The presence of the imine function was supported by the observed carbon resonance at δ 188.0, while the presence of a tetrasubstituted double bond associated with an enamine function was seen at δ 110.2 and 147.8. The ^1H NMR spectrum (Table 2) showed the presence of eight aromatic hydrogens corresponding to two disubstituted aromatic moieties (δ 7.30, dd, J = 7.3, 1 Hz, H-9; 7.17, td, J = 7.3, 1 Hz, H-10; 7.26, td, J = 7.3, 1 Hz, H-11; 7.36, dd, J = 7.3, 1 Hz, H-12; 7.08, dd, J = 7.3, 1 Hz, H-9′; 6.83, td, J = 7.3, 1 Hz, H-10′; 7.11, td, J = 7.3, 1 Hz, H-11′; 6.68, dd, J = 7.3, 1 Hz, H-12′), two ethyl side chains (δ 1.00, t, J = 7.3 Hz, H-18; 1.57, m, H-19; 0.99, t, J = 7.3 Hz, H-18′; 1.75, m, H-19′), and two isolated methylenes (δ 3.01, d, J = 10 Hz, H-22; 4.59, d, J = 10 Hz, H-22; 2.03, m, H-22′; 2.91, d, J = 13 Hz, H-22′). The COSY and HSQC data disclosed the presence of the following partial structures: two NCH_2CH_2, two $NCHCH_2CH$, and one $NCH_2CHCH_2CH_3$. Another $NCH_2CHCH_2CH_3$ fragment could not be discerned from the COSY spectrum alone but was deduced with the aid of HMBC data (three-bond correlations from H-18 to C-20 and from H-19 to C-21).



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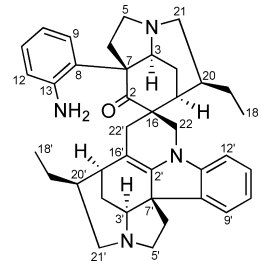

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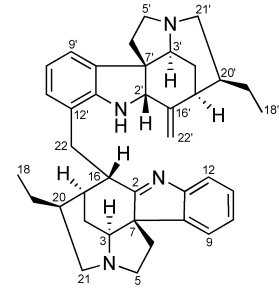

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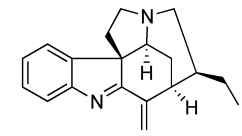

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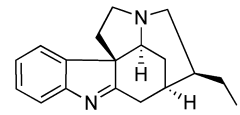

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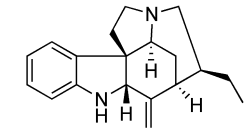

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The ^1H and ^{13}C NMR shifts indicated that the two sets of partial structures correspond to the presence of two strychnan units constituting the bisindole. The chemical shifts of one of these units (the indolenine-containing half) showed a close correspondence to those of the known *Strychnos* alkaloid tubifoline (**5**),[31] except for the distinct change involving C-16, which is a quaternary center in **1** instead of a methylene in **5**. This provided an early indication that branching of the bisindole from this indolenine unit is from C-16, since there was no evidence of substitution at the other carbons of the tubifoline-like unit.

Examination of the remaining fragments that correspond to those constituting the other strychnan unit revealed a similar ring system to **5**, except for the presence of an enamine double bond instead of an indolenine. This left two isolated methylene groups, one each attached to the indolic nitrogen N-1′ and to C-16′ of the second strychnan unit. This is consistent with the observed shifts of these methylenes (δ 3.01, 4.59, NCH_2; δ 2.03, 2.91, CCH_2) as well as the HMBC data (Figure 1). Both of these methylenes are linked to C-16 of the first or tubifoline-like unit to forge a tetrahydropyridine ring incorporating C-16 as a spirocyclic center. This was supported

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Table 1. ^{13}C NMR Data (δ) of **1**−**4** (100 MHz, $CDCl_3$)[a]

C	1	2	3	4
2	188.0	187.9	215.7	192.7
3	69.5	66.6	64.7	70.9
5	58.0	55.0	52.7	57.6
6	35.0	40.5	36.5	33.0
7	65.6	65.7	60.6	66.4
8	146.5	147.0	124.8	145.2
9	120.4	120.2	125.1	121.0
10	125.6	125.8	118.1	125.4
11	127.4	127.6	128.5	127.6
12	119.8	120.3	117.6	119.5
13	153.7	154.7	147.5	153.7
14	30.1	27.1	28.0	28.5
15	42.4	42.3	47.7	41.8
16	47.7	47.5	52.4	40.5
18	12.9	13.0	14.2	11.4
19	27.4	29.4	27.5	24.8
20	44.6	124.1	46.1	42.4
21	53.6	131.9	51.8	51.5
22	49.4	50.3	50.5	35.0
2′	147.8	148.2	149.4	71.1
3′	61.5	61.7	61.8	67.1
5′	53.6	53.9	53.7	55.2
6′	40.0	31.8	40.7	41.2
7′	50.6	51.1	51.3	53.9
8′	136.9	137.1	135.3	137.7
9′	119.9	119.7	119.7	120.1
10′	120.4	120.4	119.9	118.9
11′	126.8	126.9	127.5	128.6
12′	108.9	108.8	108.1	122.4
13′	150.0	150.2	148.8	149.4
14′	31.5	37.5	32.0	26.9
15′	34.1	34.8	34.7	33.7
16′	110.2	108.8	101.7	146.9
18′	11.8	12.0	12.8	11.7
19′	25.3	25.6	24.6	24.1
20′	39.7	40.0	39.0	43.3
21′	51.5	51.9	52.0	50.7
22′	46.3	45.4	40.0	115.7

[a] Assignments are based on HMQC, HSQC, HETCOR, and HMBC.

Table 2. ^{1}H NMR Data (δ) for **1**−**4** (400 MHz, $CDCl_3$)[a]

H	1	2	3	4
3	3.74 br s	3.79 br s	3.75 br s	3.69 br s
5	2.98 m	3.43 td (12, 5)	2.84 td (13, 3)	3.15 m
	3.32 m	3.54 dd (12, 6.5)	2.84 td (13, 3)	3.15 m
6	2.13 dd (13, 4)	1.57 m	2.13 m	1.86 m
	3.05 m	2.65 td (13, 5.6)	3.44 dt (14, 9)	2.64 td (12, 7)
9	7.30 dd (7.3, 1)	7.30 d (7.6)	7.19 d (8)	7.30 dd (7.6, 1)
10	7.17 td (7.3, 1)	7.19 t (7.6)	6.65 t (7.7)	7.19 td (7.6, 1)
11	7.26 td (7.3, 1)	7.31 t (7.6)	6.96 t (7.7)	7.32 td (7.6, 1)
12	7.36 dd (7.3, 1)	7.39 d (7.6)	6.56 d (7)	7.54 dd (7.6, 1)
14	1.32 br d (14)	1.60 m	2.33 dt (14, 3)	1.56 m
	1.70 br d (14)	1.95 m	2.98 m	1.56 m
15	2.00 m	2.16 m	2.00 m	2.04 m
16				2.97 m
18	1.00 t (7.3)	1.03 t (7.3)	1.00 t (7)	1.03 t (7.3)
19	1.57 m	1.95 m	1.48 m	1.43 m
	1.57 m	2.08 dq (14, 7.3)	1.64 m	1.56 m
20	2.00 m		1.93 m	1.77 m
21	2.78 t (12)	5.85 s	2.18 t (13)	2.54 m
	3.41 dd (12, 5.6)		2.92 dd (13, 3)	3.21 m
22b	3.01 d (10)	3.00 m	2.48 d (11)	2.50 m
22a	4.59 d (10)	4.21 d (11)	4.11 d (9)	3.40 dd (13, 11)
NH			4.85 br s	
2′				4.12 d (5)
3′	3.80 br s	3.76 br s	3.72 br s	3.02 br s
5′	2.78 dd (12, 7.6)	2.80 m	2.76 dd (12, 8)	2.92 m
	2.98 m	3.05 m	3.01 m	3.09 m
6′	1.50 m	1.49 m	1.82 m	2.26 m
	2.57 td (12, 5)	2.01 m	2.62 dd (13, 4)	2.26 m
9′	7.08 dd (7.3, 1)	7.08 d (7.6)	7.02 d (7)	6.90 d (7.6)
10′	6.83 td (7.3, 1)	6.80 t (7.6)	6.77 t (7.7)	6.70 t (7.6)
11′	7.11 td (7.3, 1)	7.09 t (7.6)	7.10 t (7.7)	6.92 d (7.6)
12′	6.68 dd (7.3, 1)	6.64 d (7.6)	6.54 d (7.2)	
14′	1.50 m	2.04 m	1.28 dt (12, 3)	1.86 m
	2.03 m	2.67 m	1.85 m	2.35 dt (13, 3)
15′	2.33 br s	2.32 br s	1.93 m	2.82 m
18′	0.99 t (7.3)	1.00 t (7.3)	0.53 t (7)	1.00 t (7.3)
19′	1.75 m	1.63 m	−0.13 m	1.26 m
	1.75 m	1.68 m	−0.11 m	1.43 m
20′	1.77 m	1.78 m	1.41 m	1.72 m
21′	2.62 t (12)	2.57 t (12)	1.72 t (12)	2.13 t (12)
	3.01 m	3.00 m	2.69 dd (12, 4)	2.70 dd (12, 4)
22′b	2.03 m	1.97 m	1.98 d (14)	5.06 s
22′a	2.91 d (13)	2.93 d (12)	2.52 d (16)	5.40 s
NH′				6.85 d (5)

[a] Assignments are based on COSY, HMQC, HSQC, and HETCOR.

by the observed ^{2}J and ^{3}J correlations from H-22 to C-16 and from H-22′ to C-2, respectively, as seen in the HMBC spectrum. The proposed structure is entirely consistent with the full HMBC data (Figure 1).

The relative configurations at the various stereogenic centers in the strychnan moieties were established from NOEs (Figure 2) and analysis of the vicinal coupling constants, in the same manner as that carried out previously for the monomeric strychnan alkaloids isolated from this plant.[28] This leaves the configuration at the spirocyclic C-16 to be determined. The two alternative 16*S* and 16*R* stereoisomers are shown in Figure 3. The H-6/H-22 NOE, previously used to establish the relative configuration (16*S*) in the related *Aspidosperma*−*Aspidosperma* bisindole anhydrohazuntiphyllidine,[32] could not be applied in the present instance due to the overlap of the H-6 and H-22 signals, although the presence of the alternative H-15/H-22′a and H-15′/H-22′a, respectively NOESY cross-peaks was suggestive of the 16*S* epimer. Additional support for the 16*S* configuration was deduced from the following evidence. In the case of the 16*S* epimer, examination of models revealed that the two indole units are situated in approximately the same plane, with the aromatic rings located at opposite ends and pointing in opposite directions (H-12 and H-12′ pointing in opposite directions), whereas in the 16*R* epimer, folding of the second indole unit results in H-12 of the tubifoline-like unit pointing into the aromatic ring of the second unit (Figure 3). This would result in clear anisotropy experienced by H-12, which would cause the H-12 resonance to be shifted significantly upfield compared with H-12′ in the ^{1}H NMR spectrum, an effect previously observed in the bisindole conophylline (H-9 in conophylline seen at δ 5.55).[33] In the present case, the chemical shifts of H-12 and H-12′ were seen at δ 7.36 and 6.68, respectively; the H-12 resonance was in fact slightly downfield compared to H-12′, with no evidence of any upfield shift as a result of anisotropy caused by the other aromatic ring. On the basis of the above lines of evidence, the relative configuration of the spirocyclic C-16 was assigned as *S*.

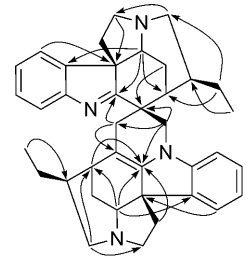


Figure 1. Selected HMBCs of **1**.

Leucoridine B (**2**) was isolated as a light yellowish oil, $[\alpha]^{25}_{D}$ +56 ($CHCl_3$, *c* 0.29). The UV spectrum showed absorption maxima at 215, 268, and 329 nm, consistent with the presence of indolenine and methyleneindoline chromophores, while the IR spectrum was similar to that of **1**. The ESIMS of **2** showed a quasi molecular ion at *m*/*z* 555, and HRESIMS measurements established the molecular formula as $C_{38}H_{42}N_4$ (DBE 20), i.e., two mass units less than that of **1**. The ^{1}H and ^{13}C NMR data of **2** (Tables 2 and 1, respectively) were generally similar to those of **1**. However, the ^{13}C NMR spectrum of **2** indicated the presence of an additional double bond from the resonances at δ 124.1 and 131.9, corresponding to olefinic quaternary and methine carbons, respectively. Comparison of the ^{13}C NMR spectrum with that of **1** showed that while the chemical

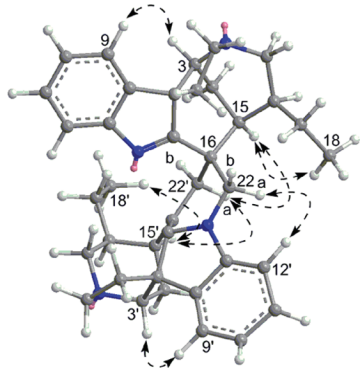


Figure 2. Selected NOEs of **1**.

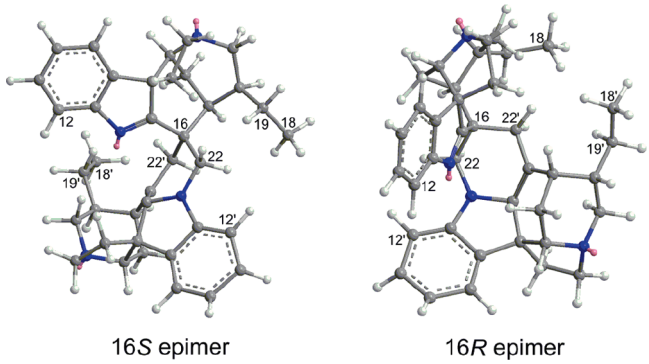


Figure 3. The 16*S* and 16*R* stereoisomers of **1**.

shifts of the other carbons were essentially unchanged, those of C-20 and C-21 (of the tubifoline-like half) have undergone substantial shifts to the lower field sp^2 region, indicating that these carbons correspond to the site of the unsaturation. This was also supported by the observed two-bond correlation from H-21 to C-20 and the three-bond correlations from H-3 and H-15 to C-21 in the HMBC spectrum. The signal due to H-20, seen in the ^{1}H NMR spectrum of **1** (δ 2.00), was absent in that of **2**. Instead, a new olefinic H signal corresponding to H-21, was observed as a singlet at δ 5.85 in the ^{1}H NMR spectrum of **2**, in place of the two C-21 methylene signals previously seen for **1** at δ 2.78 and 3.41. Corresponding changes also occurred in the signals due to H-19, which in **2** were seen at δ 1.95 as a multiplet and at δ 2.08 as a doublet of quartets (J = 14, 7.3 Hz). These features are all consistent with the presence of a double bond across C-20 and C-21.

Leucoridine C (**3**) was isolated as a light yellowish oil, $[\alpha]^{25}_D$ −61 ($CHCl_3$, *c* 0.26). The UV spectrum was different from those of **1** and **2**, showing absorption maxima at 206, 250, and 275 nm, while the IR spectrum indicated the presence of primary amine (3414, 3358 cm^{-1}) and ketone (1686 cm^{-1}) functionalities. The ESIMS of **3** showed a quasi molecular ion at *m*/*z* 575, and HRESIMS measurements established the molecular formula as $C_{38}H_{46}N_4O$ (DBE 18). Comparison of the ^{13}C NMR data of **3** (Table 1) with those of **1** showed that the imine function in **1** (δ 188.0, C-2) has been replaced by a ketone function (δ 215.7, C-2). Similarly, comparison of the ^{1}H NMR spectrum of **3** with that of **1** indicated that the major difference was the appearance of two exchangeable hydrogens as a broad peak at δ 4.85, which was attributed to the presence of a primary amine (NH_2) group, which was also detected in the IR spectrum. Other changes in the ^{13}C NMR spectrum involved the shifts of C-7 (δ 60.6) and C-16 (δ 52.4), which are α to C-2, and C-13 (δ 147.5), to which the amino group is attached in compound **3**. These changes are consistent with hydrolytic cleavage of the N-1−C-2 imine linkage of **1** to yield a primary amine and a ketone function. The ready detection of the NH_2 signal in the ^{1}H NMR spectrum is probably due to intramolecular H-bonding of the amine hydrogens with the proximate ketone function at C-2. Another significant change involved the ethyl hydrogens of the other strychnan moiety. These hydrogens have been significantly shifted upfield, in particular the methylene hydrogens, H-19′ (δ −0.11, −0.13). This is likely the result of anisotropy due to the carbonyl function at C-2, as a consequence of the new conformation adopted in the seco compound **3**.

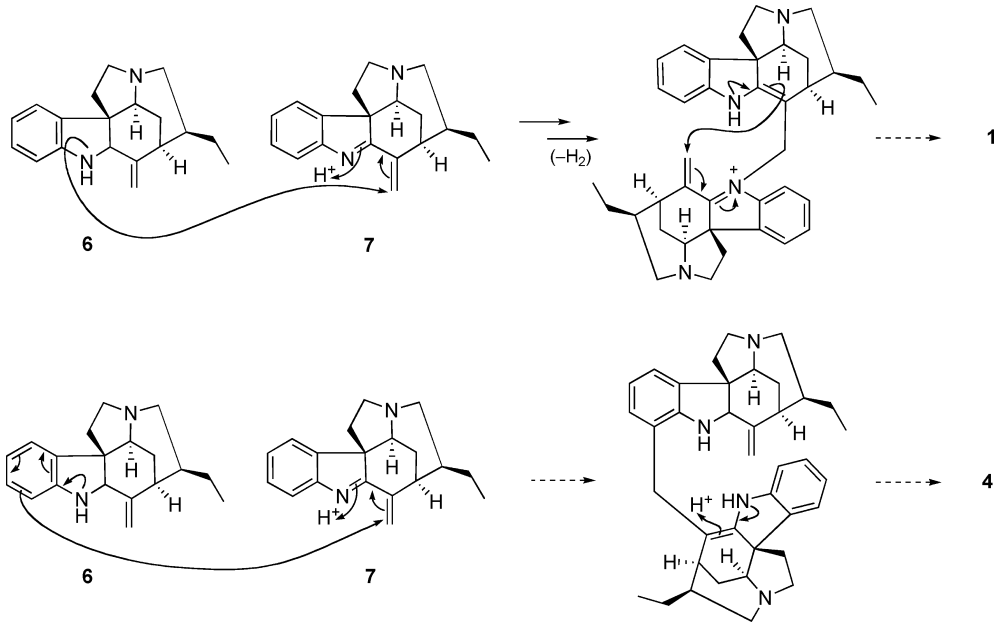
The configurations at the spirocyclic C-16 in compounds **2** and **3** were deduced to be similar, i.e., 16*S*, to that in compound **1** for the same reasons that were discussed in the case of **1** (vide supra). In the case of compound **3**, however, the observed anisotropic shielding of the ethyl hydrogens provide further support for the 16*S* configuration of the spirocyclic C-16, since if the C-16 configuration is *R*, the ethyl side chain of the second strychnan moiety would be directed away, and therefore too far removed from the tubifoline unit (Figure 3) to experience anisotropic effects.

A possible origin of the basic ring system of the bisindoles **1**−**3**, which are characterized by branching of one unit from a common spirocyclic carbon (C-16), is shown in Scheme 1, involving conjugate addition via the indolic nitrogen of anhydropereirine (**6**) (vide infra) onto the dihydrovalparicine[34] derivative **7**, to effect the N-1′ to C-16 link, followed by a subsequent conjugate addition of an enamine to forge the spirocyclic ring system.

Leucoridine D (**4**) was isolated as a light yellowish oil, $[\alpha]^{25}_D$ +6 ($CHCl_3$, *c* 0.40). The UV spectrum showed absorption maxima at 213, 253, and 299 nm, indicating the presence of indolenine and dihydroindole chromophores, while the IR spectrum indicated the presence of an indolic NH (3246 cm^{-1}). The ESIMS of **4** showed a quasi molecular ion at *m*/*z* 559, and HRESIMS measurements established the molecular formula as $C_{38}H_{46}N_4$ (DBE 18). The ^{13}C NMR spectrum (Table 1) accounted for 38 carbon resonances, comprising two methyl, 12 methylene, 15 methine, and nine quaternary carbons. The presence of the imine function was supported by the observed carbon resonance at δ 192.7, while the presence of a gem-disubstituted double bond was indicated by the signals seen at δ 115.7 and 146.9. Aside from these, the 12 remaining low-field sp^2 carbon resonances can be attributed to the presence of two aromatic rings associated with two indole moieties. The ^{1}H NMR spectrum showed the presence of seven aromatic hydrogens (δ 7.30, dd, J = 7.6, 1 Hz, H-9; 7.19, td, J = 7.6, 1 Hz, H-10; 7.32, td, J = 7.6, 1 Hz, H-11; 7.54, dd, J = 7.6, 1 Hz, H-12; 6.90, d, J = 7.6 Hz, H-9′; 6.70, t, J = 7.6 Hz, H-10′; 6.92, d, J = 7.6 Hz, H-11′), one indolic NH as a doublet at δ 6.85 (J = 5 Hz), two ethyl side chains (δ 1.03, t, J = 7.3 Hz, H-18; 1.43, m, H-19; 1.56, m, H-19; 1.00, t, J = 7.3 Hz, H-18′; 1.26, m, H-19′; 1.43, m, H-19′), and two singlets at δ 5.06 and 5.40 due to the geminal hydrogens of an exocyclic double bond. Since only seven aromatic hydrogens are present, branching of the bisindole must be from one of the aromatic carbons.

The NMR shifts showed that one unit of the bisindole corresponds to the same tubifoline-like unit as in the previous three alkaloids, except that in compound **4** C-16 was a methine and not a quaternary center as in the previous three alkaloids. In addition, examination of the NMR data of the other monomeric unit yielded a structure that corresponded to the strychnan compound anhydropereirine (or anhydrogeissoschizoline) (**6**),[35] previously obtained as a dehydration product of pereirine (or geissoschizoline).[35,36] All four aromatic shifts of the tubifoline-like unit were seen, while only three contiguous aromatic hydrogens of the anhydropereirine-like unit were present. These were assigned to the C-9′−C-10′−C-11′ fragment from the observed NOE between H-9′ and H-3′ of the anhydropereirine unit. Branching of the bisindole is therefore from C-16 of the tubifoline-like unit to C-12′ of the anhydrogeissoschizoline unit. The 2-D NMR data (COSY, HSQC, and HMBC) revealed all the partial structures associated with the two strychnan halves constituting the bisindole, except for the presence of an additional methylene (δ_C 35.0, δ_H 2.50, 3.40), which is attributed

Scheme 1. Possible Biogenetic Pathways to **1** and **4**



to the methylene bridge linking the two halves from C-12′ of the anhydropereirine unit to C-16 of the tubifoline-like unit. This assignment is consistent with the observed ^3J and ^2J correlations from H-22 to C-11′ and C-13′ and from H-22 to C-16, respectively, in the HMBC spectrum.

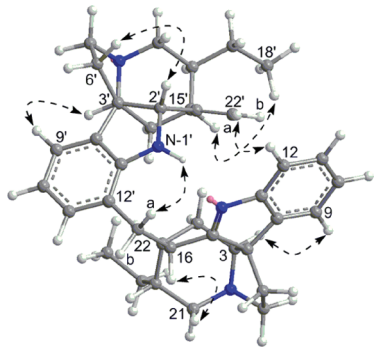


Figure 4. Selected NOEs of **4**.

The relative configurations of the stereogenic centers in the two strychnan halves were shown by NOE to correspond to those in the constituent monomers, tubifoline and anhydropereirine/geissoschizoline (Figure 4). The relative configuration at the branching point, C-16, was demonstrated by NOE (Figure 4) as follows. First, the observed reciprocal NOEs between H-16 and H-21β are only possible if H-16 is β (16*S*), since, if H-16 is α, the two hydrogens will be located on opposite faces of the molecule and too far removed for NOEs to be observed. Similarly, the observed reciprocal NOEs between H-22a and N(1′)-H, and between H-12 and H-22′a, are only possible if H-16 is β. A possible biogenetic origin of **4** is shown in Scheme 1, involving the same coupling partners as in the proposed biogenetic route to the bisindoles **1**−**3** (vide supra). In the case of **4**, the sequence is initiated by conjugate addition of the nucleophilic *ortho* carbon of the anhydropereirine unit **6** onto the dihydrovalparicine moiety **7**.

Alkaloids **1**−**4** showed moderate cytotoxicity toward drug-sensitive and vincristine-resistant (KB/VJ300) human KB cells (IC_{50} 0.57−13.29 μg/mL, see Experimental Section), with **1** manifesting the highest potency (IC_{50} 0.57 and 2.39 μg/mL, respectively, against KB and KB/VJ300 cells).

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a Perkin-Elmer RX1 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 JEOL JNM-LA 400 and JNM-ECA 400 spectrometers at 400 and 100 MHz, respectively. ESIMS and HRESIMS were obtained on an Agilent 6530 Q-TOF mass spectrometer.

Plant Material. Plant material was collected in Pahang, Malaysia, and identification was confirmed by Dr. Richard C. K. Chung, Forest Research Institute, Malaysia. Herbarium voucher specimens (K672) are deposited at the Herbarium, University of Malaya.

Extraction and Isolation. Extraction of the ground bark material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid, as has been described in detail elsewhere.[37] The alkaloids were isolated by initial column chromatography on silica gel using $CHCl_3$ with increasing proportions of MeOH followed by rechromatography of the appropriate partially resolved fractions using centrifugal TLC. Solvent systems used for centrifugal preparative TLC were Et_2O−hexanes (2:1), Et_2O, Et_2O−MeOH (20:1), Et_2O−MeOH (10:1), $CHCl_3$, $CHCl_3$−MeOH (100:3), and $CHCl_3$−MeOH (10:1). The yields (mg kg^{-1}) of the alkaloids were as follows: **1** (0.4), **2** (0.4), **3** (0.3), and **4** (0.6).

Leucoridine A (1): light yellowish oil; $[\alpha]^{25}_D$ −29 (*c* 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 213 (3.89), 267 (3.52) nm; ^{1}H NMR and ^{13}C NMR data, Tables 2 and 1, respectively; ESIMS *m*/*z* 557 $[M + H]^+$; HRESIMS *m*/*z* 557.3643 (calcd for $C_{38}H_{44}N_4$ + H, 557.3644).

Leucoridine B (2): light yellowish oil; $[\alpha]^{25}_D$ +56 (*c* 0.29, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 215 (4.45), 268 (4.06), 329 (3.50) nm; ^{1}H NMR and ^{13}C NMR data, Tables 2 and 1, respectively; ESIMS *m*/*z* 555 $[M + H]^+$; HRESIMS *m*/*z* 555.3487 (calcd for $C_{38}H_{42}N_4$ + H, 555.3488).

Leucoridine C (3): light yellowish oil; $[\alpha]^{25}_D$ −61 (*c* 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 206 (4.58), 250 (4.04), 275 (4.02) nm; IR (dry film) ν_{max} 3414, 3358, 1686 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, Tables 2 and 1, respectively; ESIMS *m*/*z* 575 $[M + H]^+$; HRESIMS *m*/*z* 575.3751 (calcd for $C_{38}H_{46}N_4O$ + H, 575.3750).

Leucoridine D (4): light yellowish oil; $[\alpha]^{25}_D$ +6 (*c* 0.40, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 213 (3.70), 253 (3.20), 299 (2.84) nm; IR (dry film) ν_{max} 3246 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, Tables 2 and 1, respectively; ESIMS *m*/*z* 559 $[M + H]^+$; HRESIMS *m*/*z* 559.3794 (calcd for $C_{38}H_{46}N_4$ + H, 559.3795).

Cytotoxicity Assays. Cytotoxicity assays were carried out following the procedure that has been described previously.[38,39] The IC_{50} values for compounds **1**−**4** are 0.57, 11.59, 10.91, and 12.53 μg/mL,

respectively, against KB cells and 2.39, 12.05, 11.80, and 13.29 μg/mL, respectively, against vincristine-resistant (KB/VJ300) KB cells.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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