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Perhentidines A–C: Macroline–Macroline Bisindoles from *Alstonia* and the Absolute Configuration of Perhentinine and Macralstonine

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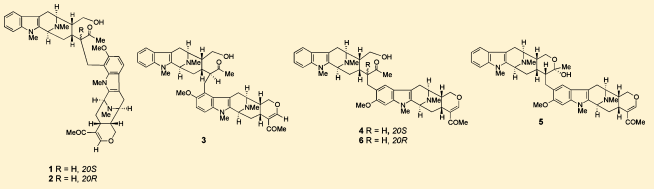
Supporting Information

ABSTRACT: Three new bisindole alkaloids of the macroline–macroline type, perhentidines A–C (**1**–**3**), were isolated from the stem-bark extract of *Alstonia macrophylla* and *Alstonia angustifolia*. The structures of these alkaloids were established on the basis of NMR and MS analyses. The absolute configurations of perhentinine (**4**) and macralstonine (**5**) were established by X-ray diffraction analyses, which facilitated assignment of the configuration at C-20 in the regioisomeric bisindole alkaloids perhentidines A–C (**1**–**3**). A potentially useful method for the determination of the configuration at C-20 based on comparison of the NMR chemical shifts of the bisindoles and their acetate derivatives, in these and related bisindoles with similar constitution and branching of the monomeric units, is also presented.



The genus *Alstonia* (Apocynaceae), which is widely distributed in Southeast Asia,[1−3] is rich in alkaloids.[4−24] We previously reported the structure of perhentinine (**4**), a bisindole alkaloid constituted from the union of two macroline moieties from *Alstonia macrophylla*.[14] The structure was elucidated on the basis of the analysis of the NMR and MS data, which were however insufficient to assign the configuration at C-20. In continuation of our ongoing studies of Malaysian *Alstonia* species,[12−21] we have isolated three additional bisindole alkaloids related to perhentinine from two Malayan *Alstonia* species, perhentidines A (**1**) and B (**2**) from *A. macrophylla* Wall and perhentidines A (**1**) and C (**3**) from *A. angustifolia* Wall.

Perhentidine A (**1**) was obtained as a light yellowish oil with $[\alpha]^{25}_{D}$ −77 (*c* 0.40, $CHCl_3$). The IR spectrum showed bands at 3400, 1702, 1648, and 1617 cm^{-1}, due to the presence of OH, ketocarbonyl, and an α,β-unsaturated carbonyl group, respectively, while the UV spectrum showed absorption maxima at 231 and 286 nm, consistent with the presence of indole chromophores. The ESIMS of **1** showed a pseudomolecular ion $[M + H]^+$ at *m*/*z* 705, which analyzed for $C_{43}H_{52}N_4O_5$ + H. The ^{13}C NMR spectrum (Table 1) showed a total of 43 resonances, comprising seven methyl, seven methylene, 16 methine, and 13 quaternary carbon atoms, in agreement with the molecular formula. The quaternary carbon resonance at δ_C 212.9 is consistent with the presence of a ketocarbonyl, while the other quaternary carbon resonance at δ_C 195.2 and the associated olefinic carbon signals at δ_C 121.0 and 157.2, are consistent with the presence of an α,β-unsaturated carbonyl group. The unusual deshielding of the β-carbon at δ_C 157.2 indicated oxygen substitution. In addition, two oxymethylene carbons were observed at δ_C 66.8 and 67.6, the former due to a hydroxymethyl group, as shown by acetylation, which yielded an *O*-acetyl derivative (**1a**).

The ^1H NMR data (Table 2) showed the presence of four aromatic hydrogens (δ_H 7.16–7.56) associated with an unsubstituted indole moiety, a pair of AB doublets at δ_H 6.75 and 7.22 associated with another indole moiety substituted at positions 11′ and 12′, a vinylic singlet at δ_H 7.49 associated with a trisubstituted double bond, and a total of seven methyl singlets, corresponding to two N1-Me (δ_H 3.58, 3.69), two N4-Me (δ_H 2.36, 2.37), two acetyl methyls (δ_H 1.55, 2.06), and an aromatic methoxy substituent (δ_H 3.83, 11′-OMe). Since only six aromatic hydrogens were observed and both indolic nitrogens are substituted, it is reasonable to conclude that the bisindole is branched from one of the aromatic carbon atoms of one monomer, with the adjacent position occupied by the methoxy substituent. The aromatic doublet at δ_H 7.22 was assigned to H-9′ from its NOE with H-6′, while the placement of the methoxy substituent at C-11′ was confirmed by the observed NOE between H-10′ (δ_H 6.75) and 11′-OMe (δ_H 3.83). These assignments were further supported by the observed three-bond correlations from H-9′ to C-7′ and C-13′ and from H-9′ and 11′-OMe to C-11′ in the HMBC spectrum (Figure 1). These observations indicated C-12′ as the site of branching of the bisindole from this monomeric unit.

The remaining part of this macroline half was assembled via the 2-D NMR data. The COSY spectrum revealed an $NCHCH_2CHCHCH_2O$ fragment, which corresponds to the N-4′–C-3′–C-14′–C-15′–C-16′–C-17′–O unit of the lower macroline half. The observed three-bond correlations from the

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Table 1. ^{13}C NMR Data (δ) for 1−6[a]

C	1[b]	2[b]	3[b]	4[b]	5[c]	6[c]
2	132.8	132.9	133.1	132.9	133.3	132.6
3	53.2	53.2	53.3	53.1	54.0	53.1
5	59.5	59.6	59.3	59.2	55.5	59.6
6	22.1	22.5	22.1	22.6	22.7	22.4
7	106.1	106.1	106.2	105.9	106.5	105.9
8	126.4	126.5	126.5	126.3	126.45	126.36
9	118.4	118.2	118.3	118.2	117.9	118.0
10	118.9	118.9	118.8	119.0	118.4	118.9
11	121.0	121.1	120.8	120.9	120.2[f]	121.0
12	108.8	109.2	108.8	108.7	108.5	109.0
13	137.1	137.4	137.1	137.0	136.8	137.2
14	32.2	32.7	32.0	32.3	26.9	33.0
15	31.5	32.4	31.7	31.5	25.9	32.3
16	42.6	42.2	42.7	43.1	44.0	42.1
17	66.8	66.1	66.7	66.5	61.4	66.2
18	31.8	34.4	32.6	31.1	29.5	33.9
19	212.9	214.7	213.3	213.2	99.0	214.5
20	55.5	52.7	53.9	54.5	45.6	53.8[j]
21	26.0	26.3	28.8	32.0	28.8	32.49[k]
N_1Me	29.1	29.1	28.9[e]	29.0	29.07	29.14
N_4Me	41.3[d]	41.4	41.3	41.7	41.69	41.4
2′	133.5	133.7	133.9	131.3	131.2	131.5
3′	53.9	53.9	53.9	53.7	53.76	53.8[j]
5′	54.6	54.7	54.4	54.7	54.7[g]	54.7[g]
6′	22.5	22.77	25.2	22.0	22.5	22.8
7′	105.8	105.3	105.3	105.4	105.1	105.6
8′	122.9	123.3	126.2	120.1	119.7	119.1
9′	116.0	115.9	118.0	118.7	118.8	119.5
10′	104.8	104.3	151.2	119.1	120.1	120.2[f]
11′	153.6	153.9	106.4	153.6	153.9	153.8
12′	110.9	110.2	107.1	91.3	91.4	91.2
13′	136.3	136.2	133.0	136.5	136.1	136.6
14′	32.2	32.1	32.3	32.4	32.4	32.47[k]
15′	22.7	22.85	22.7	22.8	22.9[h]	22.9[h]
16′	38.4	38.6	38.3	38.3	38.5	38.4
17′	67.6	67.8	67.6	67.7	67.87	67.85
18′	24.9	25.1	25.0	24.9	25.0	25.1
19′	195.2	195.6	195.5	195.4	195.5	195.8
20′	121.0	121.2	121.0	120.8	121.2[i]	121.2[i]
21′	157.2	157.5	157.5	157.4	157.4	157.7
N_1Me'	32.3	32.5	29.0[e]	28.9	28.7	29.04
N_4Me'	41.9[d]	41.8	41.6	41.2	41.77	41.74
10′-OMe			56.9			
11′-OMe	56.7	56.7		55.5	55.3	55.6

[a]Assignments are based on COSY, HSQC, and HMBC. [b]100 MHz, $CDCl_3$. [c]150 MHz, $CDCl_3$. [d−k]Assignments are interchangeable.

vinylic H-21′ (which is associated with the acetyl group forming the α,β-unsaturated carbonyl chromophore) to C-17′ and C-15′ in the HMBC spectrum indicated that the lower macroline half corresponds to a type-B macroline[12] [a 12′-substituted alstophylline (**7**)],[8,12,22] which was in agreement with the NMR data.

The other unit of the bisindole, after discounting the signals due to the substituted alstophylline (**7**) half, corresponded to that of another macroline derivative with an unsubstituted indole moiety. The oxymethylene C-17 hydrogens were observed as two doublets of doublets at δ_H 3.88 and 3.91 (δ_C 66.8). This oxymethylene constitutes part of a primary alcohol function, as shown by acetylation (δ_H 4.15 and 4.53; δ_C 63.7). The 18-methyl (acetyl) singlet was observed at δ_H 1.55 with the C-19 ketocarbonyl observed at δ_C 212.9. An additional methine corresponding to C-20 was observed at δ_C 55.5 (δ_H 3.26), which was linked to C-19 from the observed three-bond correlations from 18-Me to C-20. These features are suggestive of a *seco*-macroline (with an opened ring E) such as alstomicine (**8**),[15] which was also in agreement with the COSY spectrum, which showed the presence of an $NCHCH_2CH(CHCH_2)$-$CHCH_2O$ partial structure. The branching of the bisindole from this upper *seco*-macroline unit must be from this methine C-20. Connection from C-20 of the upper macroline unit to C-12′ of the lower half was mediated via a methylene bridge (C-21), as shown by the observed H-21 to C-11′, C-13′, and C-19 three-bond correlations in the HMBC spectrum (Figure 1). The structure of perhentidine A (**1**) indicated that it is a regioisomer of the previously encountered *Alstonia* bisindole, perhentinine (**4**).[14]

Perhentidine B (**2**) was isolated as a light yellowish oil with $[\alpha]^{25}_D$ −38 (*c* 0.52, $CHCl_3$). The UV (234 and 286 nm) and IR (3392, 1707, 1653, and 1618 cm^{-1}) spectra were similar to those of **1**, suggesting the presence of similar functionalities. The ESIMS of **2** showed a pseudomolecular ion $[M + H]^+$ at *m/z* 705, which also analyzed for $C_{43}H_{52}N_4O_5$ + H, indicating that **2** and **1** are isomers.

Inspection of the ^{1}H and ^{13}C NMR data (Tables 2 and 1) of **2** indicated a general similarity with those of **1**, showing the presence of an unsubstituted indole moiety (δ_H 7.14−7.56), another indole moiety substituted at C-11′ and C-12′ (a pair of AB doublets at δ_H 6.76 and 7.20; NOE: H-9′/H-6′, H-10′/11′-OMe), a vinylic singlet at δ_H 7.48 associated with a trisubstituted double bond, an α,β-unsaturated carbonyl moiety (δ_C 195.6, 121.2, and 157.9; δ_H 2.05), a ketocarbonyl (δ_C 214.7), a hydroxylmethyl group (δ_C 66.1; δ_H 4.09 and 4.49; acetylation yielded an acetate derivative **2a**), and seven methyl singlets, corresponding to two N1-Me, two N4-Me, two acetyl methyls, and an aromatic methoxy group. The ^{1}H and ^{13}C NMR data of **2** are generally similar to those of **1** except for differences in the chemical shifts of C-15, C-18, C-19, and C-20 in the ^{13}C NMR spectrum and H-14β, H-17, and H-20, in the ^{1}H NMR spectrum. The NMR data therefore indicated that **2** was also a bisindole of the macroline−macroline type incorporating the same two constituent halves as in **1**.

The COSY and HSQC data of **2** disclosed the same partial fragments as in **1**. In addition, the HMBC data of **2** (Figure 2) showed the same key three-bond correlations (H-21 to C-11′, C-13′, and C-19) as those of **1**, indicating similar branching of the bisindole from C-12′ of the lower macroline half to C-20 of the upper half, the C-20 connection being mediated by the C-21 methylene bridge. On the basis of the above observations, perhentidine B (**2**) is the C-20 epimer of perhentidine A (**1**).

The remaining issue concerns the assignment of the relative configuration of C-20 in **1** and **2**. Examination of the ^{1}H NMR data of perhentidines A (**1**) and B (**2**) showed that the signals of H-20 in both compounds were observed as multiplets (Table 2). Furthermore the signal of one of the C-21 hydrogens in perhentidine A (**1**) and of both the C-21 hydrogens in perhentidine B (**2**) were also observed as multiplets. In the case of the *O*-acetyl derivatives of both compounds (**1a** and **2a**) however, the signals for H-20 and H-21 were clearly resolved. The H-20 signal in *O*-acetylperhentidine A (**1a**) was seen as a triplet of doublets at δ_H 2.99 with *J* = 10.7 and 3.8 Hz (i.e., $J_{20-21a} = J_{15-20}$ = 10.7, J_{20-21b} = 3.8 Hz). The signal of one of the C-21 hydrogens was observed as a doublet of doublets at

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Table 2. ^{1}H NMR Data (δ) for 1–6[a]

H	1[b]	2[b]	3[b]	4[b]	5[c]	6[c]
3	4.14 m	3.98 m	4.14 m	4.09 dd (4, 2)	3.95 m	4.00 m
5	3.48 d (7.6)	3.63 m	3.45 m	3.46 d (7)	2.93 d (6)	3.59 m
6β	2.57 d (17)	2.58 d (17)	2.56 d (17)	2.54 m	2.13 m (*a*)	2.56 d (17) (*a*)
6α	3.29 m	3.37 dd (17, 7)	3.29 dd (17, 7)	3.32 m	2.63 dd (*b*) (17, 10)	3.35 dd (*b*) (17, 7.5)
9	7.56 d (7.5)	7.56 d (8)	7.56 d (7.5)	7.52 d (8)	7.33 (7.5)	7.51 d (7.5)
10	7.16 t (7.5)	7.14 m	7.16 t (7.5)	7.13 td (8, 1)	7.00 m	7.12 t (7.5)
11	7.26 m	7.22 m	7.24 m	7.22 td (8, 1)	7.09 m	7.21 t (7.5)
12	7.36 d (7.5)	7.32 d (8)	7.34 d (7.5)	7.32 d (8)	7.09 m	7.30 d (7.5)
14β	2.01 m	1.48 m	2.04 m	1.98 m	1.87 m (*a*)	1.44 d (12) (*a*)
14α	2.46 m	2.26 m	2.50 m	2.41 m	2.86 td (13, 3.5) (*b*)	2.35 m (*b*)
15	2.27 m	2.11 m	2.21 m	2.14 m	1.77 m	2.01 m
16	1.66 m	1.88 m	1.60 m	1.57 m	1.77 m	1.90 m
17a	3.88 dd (11, 2)	4.09 m	3.83 dd (11, 2)	3.95 dd (11, 3)	3.49 m	4.12 dd (12, 3)
17b	3.91 dd (11, 2)	4.49 d (12)	3.90 m	4.01 dd (11, 2)	4.52 t (11.5)	4.43 d (12)
18	1.55 s	1.40 s	1.30 s	1.72 s	1.51 s	1.68 s
20	3.26 m	3.55 m	3.42 m	3.32 m	1.91 m	3.39 td (11, 4)
21a	2.92 dd (13, 10.5)	3.05 m	2.60 t (12)	2.41 m	2.43 m	2.39 m
21b	3.26 m	3.17 m	3.23 dd (12, 4)	3.08 m	3.06 dd (14, 3.5)	3.00 m
N_1*Me*	3.69 s	3.57 s	3.69 s	3.65 s	3.47 s	3.56 s
N_4*Me*	2.36[d] s	2.36 s	2.37 s	2.34 s	2.28 s	2.38 s
3′	3.80 m	3.72 m	3.77 m	3.79 t (3)	3.75 m	3.79 m
5′	3.05 d (7)	3.01 m	2.87 d (7)	2.99 d (7)	3.00 m	3.00 m
6′α	2.40 m	2.34 m	2.26 d (17)	2.28 m	2.33 m (*a*)	2.35 m (*a*)
6′β	3.23 dd (17, 7)	3.20 m	3.18 dd (17, 7)	3.08 m	3.00 m (*b*)	3.17 dd (16.5, 7) (*b*)
9′	7.22 d (8.6)	7.20 d (8.6)		6.90 s	6.74 s	6.90 s
10′	6.75 d (8.6)	6.76 d (8.6)				
11′			6.83 d (9)			
12′			7.07 d (9)	6.69 s	6.40 s	6.69 s
14′α	1.75 td (12, 4)	1.70 td (12.5, 3.5)	1.75 m	1.75 td (12, 3)	1.76 m (*a*)	1.77 m (*a*)
14′β	2.01 m	1.99 m	2.04 m	2.04 m	2.01 m (*b*)	2.01 m (*b*)
15′	2.50 m	2.51 m	2.50 m	2.54 m	2.60 m	2.60 m
16′	1.84 m	1.82 m	1.75 m	1.84 dt (11, 4)	1.87 m	1.87 m
17′β	4.14 m	4.12 m	4.08 dd (11, 4)	4.13 ddd (11, 4, 1)	4.19 dd (11, 3) (*a*)	4.14 dd (12, 3) (*a*)
17′α	4.39 t (11)	4.37 t (11)	4.32 t (11)	4.37 t (11)	4.38 m (*b*)	4.38 t (12) (*b*)
18′	2.06 s	2.05 s	2.06 s	2.05 s	2.07 s	2.09 s
21′	7.49 s	7.48 s	7.49 s	7.51 s	7.52 s	7.53 s
N_1*Me*′	3.58 s	3.53 s	3.53 s	3.55 s	3.50 s	3.59 s
N_4*Me*′	2.37[d] s	2.24 s	2.24 s	2.25 s	2.13 s	2.24 s
10′-OMe			3.89 s			
11′-OMe	3.83 s	3.94 s		3.87 s	3.92 s	3.65 s

[a]Assignments are based on COSY, HSQC, and HMBC. [b]400 MHz, $CDCl_3$. [c]600 MHz, $CDCl_3$. [d]Assignments are interchangeable.

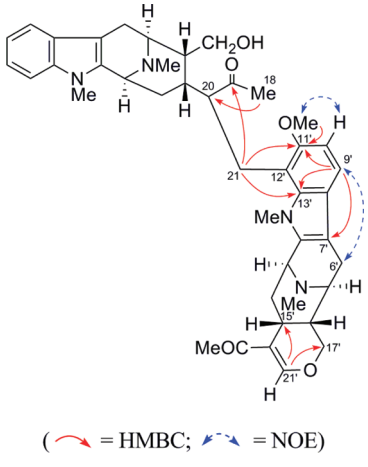

Figure 1. Selected HMBCs and NOEs of **1**.

δ_H 2.83 ($J_{21a\text{-}21b}$ = 14 Hz, J_{20-21a} = 10.7 Hz). The large coupling constant of 10.7 Hz due to the coupling between H-20 and H-21a suggested that the conformation adopted about the C-21–C-20 bond was one that places the two vicinal hydrogens at C-21 and C-20 *anti* to one another. The preferred *anti* conformation was likely due to the presence of three bulky groups, two on C-20 and one on C-21, which resulted in steric hindrance to free rotation about the C-20–C-21 bond. The observation that H-20 is *anti* to H-21a, coupled with the observed NOE interactions between H-21a and H-15; H-20 and H-14, H-21b; H-21b and H-14; and 18-Me and H-17, H-20 (Figure 3), allowed the configuration at C-20 in the *O*-acetyl derivative **1a**, and therefore in perhentidine A (**1**) as well, to be assigned as *S*.

In the case of *O*-acetylperhentidine B (**2a**), the signal due to H-20 was also seen as a triplet of doublets at δ_H 3.23 with J = 11 and 5 Hz. The observed H-20–H-21a coupling of 11 Hz indicated an *anti* disposition of the two hydrogens as before in

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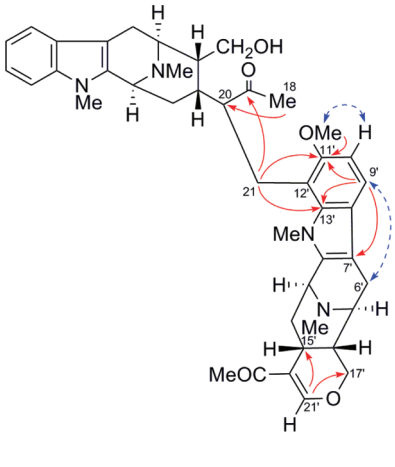


(= HMBC; = NOE)

Figure 2. Selected HMBCs and NOEs of **2**.

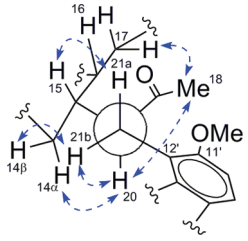


Figure 3. Selected NOEs of **1a**.

the case of *O*-acetylperhentidine A (**1a**). In this instance however, the definitive NOEs, which allowed the assignment of the configuration at C-20, were different from those observed in **1a**. Thus, in the case of *O*-acetylperhentidine B (**2a**), NOEs were observed between H-20 and H-14, H-21b; H-21a and H-15; H-21b and H-16, H-17; and H-18 and H-14, H-15, H-20 (Figure 4). These NOEs are consistent with the assignment of the C-20 configuration in **2a** (and **2**) as *R*.

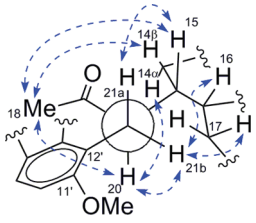
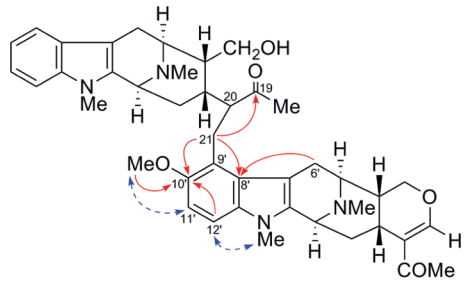


Figure 4. Selected NOES of **2a**.

Perhentidine C (**3**) was obtained as a colorless oil, $[\alpha]_D$ −73 (*c* 0.50, $CHCl_3$). The IR (3387, 1703, 1651, 1615 cm^{-1}) and UV (230 and 285 nm) data were essentially similar to those of **1** and **2**. The expected molecular ion at *m/z* 704 ($C_{43}H_{52}N_4O_5$) was too weak to be detected in the EIMS. The highest mass fragment was observed at *m/z* 686 ($C_{43}H_{50}N_4O_4$), which corresponded to the loss of H_2O from the parent ion. The $[M + H]^+$ ion could however be detected by LSIMS at *m/z* 705, and HRLSIMS measurements (*m/z* 705.4029) gave the molecular formula $C_{43}H_{52}N_4O_5$. Perhentidine C (**3**) is therefore an isomer of perhentidines A (**1**) and B (**2**).

The NMR data (Tables 1 and 2) of **3** showed some similarities with those of **1** and **2**, such as the presence of an unsubstituted indole moiety (δ_H 7.16−7.56), a disubstituted indole moiety (a pair of AB doublets at δ_H 6.83 and 7.07), a vinylic singlet at δ_H 7.49 associated with a trisubstituted double bond, an α,β-unsaturated carbonyl moiety (δ_C 195.5, 121.0, and 157.5; δ_H 2.06), a ketocarbonyl (δ_C 213.3), a hydroxymethyl group (δ_C 66.7; δ_H 3.83 and 3.90; acetylation gave the *O*-acetyl derivative **3a**), and seven methyl singlets, corresponding to two N1-Me, two N4-Me, two acetyl methyls, and an aromatic methoxy group. The observed NOE between the N1′-methyl signal (δ_H 3.53) and the aromatic resonance at δ_H 7.07 of the disubstituted indole unit allowed assignment of the aromatic AB doublets at δ_H 6.83 and 7.07 to H-11′ and H-12′, respectively. The placement of the methoxy substituent at C-10′ was confirmed by the observed NOE between H-11′ and 10′-OMe, which was further supported by the observed three-bond correlations from H-12′ and 10′-OMe to C-10′ in the HMBC spectrum (Figure 5). This indicated C-9′ as the site of branching of the bisindole from this lower unit.



(= HMBC; = NOE)

Figure 5. Selected HMBCs and NOEs of **3**.

Examination of the NMR data indicated that while the bisindoles **1** and **2** are constituted from a *seco*-macroline or alstomicine (**8**) (upper half) and a 12′-substituted alstophylline (**7**) (lower half), perhentidine C (**3**) differs in that while the upper unit is the same *seco*-macroline indole, alstomicine (**8**), the lower half entity is now a 9′-substituted-10′-methoxyalstonerine (**9**).[12,13,22] The mode of branching in **3** is therefore from C-9′ of the lower 10′-methoxyalstonerine unit to C-20 of the alstomicine unit, the connection to the upper alstomicine unit being mediated by the C-21 methylene bridge. This was supported by the observed three-bond correlations from H-21 to C-19, C-8′, and C-10′ in the HMBC spectrum (Figure 5) of **3**.

As in the previous two bisindoles **1** and **2**, the relative configuration of C-20 in **3** can be deduced from analysis of the coupling constants and the observed NOEs. In the case of **3** (unlike **1** and **2**), the H-21 resonances were well resolved in the ^1H NMR spectrum, whereas the resonances of H-20 and H-21 were multiplets in the *O*-acetyl derivative **3a**. As before, the signal due to one of the hydrogens on C-21 was observed as a triplet at δ_H 2.60 ($J_{21a\text{-}21b}$ = $J_{21a\text{-}20}$ = 12 Hz), indicating a preferred conformation about the C-20−C-21 bond that places the two vicinal hydrogens *anti* to one another due to steric hindrance caused by the presence of three bulky groups. This, coupled with the observed NOE interactions between H-21a and H-15, H-6′β; H-21b and H-14β; and 18-Me and H-16, H-17, H-20 (Figure 6), allowed the configuration at C-20 to be assigned as *S* (NOE between H-21a and H-15 is impossible for 20*R* or H-20 is β-oriented).

Perhentidines A (**1**), B (**2**), and C (**3**) are therefore regiosomers of the previously isolated *Alstonia* bisindole, perhentinine

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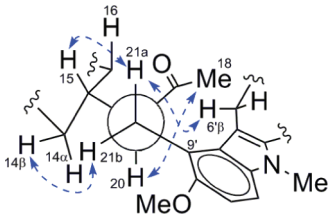

Figure 6. Selected NOEs of **3**.

(**4**). Repeated attempts to obtain crystals of perhentinine as well as perhentidines A, B, and C were singularly unsuccessful. Eventually it was found that in the case of perhentinine (**4**) treatment with excess MeI gave suitable crystals for X-ray diffraction analysis, which revealed formation of the dimethyl diiodide salt of the ring-E cyclized (hemiketal) product (**4b**) (Figure 7), from which the absolute configuration at C-20 of the

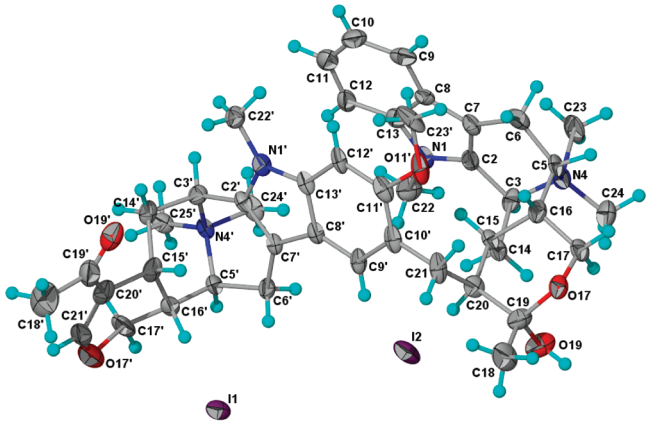

Figure 7. X-ray crystal structure of **4b**. Flack parameter x = −0.04(0.03).

precursor *E-seco*-compound, perhentinine, could be established as *S*. This was also in agreement with the results of analysis of the coupling constants (J_{20-21a} = 11.0, J_{20-21b} = 3.5 Hz) and NOEs (H-21a/H-15; H-21b/H-14, H-20; 18-Me/H-17, H-20) of perhentinine acetate (**4a**), carried out in a similar manner to that described for perhentidines A–C (**1**–**3**) (*vide supra*).

Since we have secured firm confirmation of the C-20 configuration of perhentinine by X-ray diffraction analysis of its cyclized or hemiketal derivative (in the form of its dimethyl diiodide salt, **4b**), it would be advantageous if the X-ray structure of a corresponding 20*R* bisindole alkaloid was also available to serve as a model compound for comparison. In the present series, perhentidine B (**2**) would constitute such a candidate. However, as mentioned previously, repeated attempts at crystallization (including treatment with MeI) proved fruitless. Another relevant bisindole candidate available from *A. macrophylla* is macralstonine (**5**),[10,12,24] which has been previously investigated by Hesse and Schmid.[23] It has been observed that macralstonine exists as an equilibrium mixture of acyclic (ketone, **6**) and cyclized (hemiketal, **5**) forms in $CHCl_3$ solution.[23] We have confirmed this by analysis of high-field NMR data (600 MHz) of macralstonine. Thus, in $CDCl_3$ solution, the ratio of acyclic to cyclized form was 2.32:1, while in CD_2Cl_2, it was 1.14:1, and in THF-d_8, it was virtually detected as the cyclized hemiketal form (**5**), albeit with poor solubility in this solvent. With the help of 2-D methods, the NMR data of the two forms could be distinguished (Tables 1 and 2).[25] The *E-seco*-macralstonine (**6**) could be trapped by conversion to its *O*-acetyl derivative **6a**,[23] in which case the NMR data of the pure *O*-acetyl-*E-seco*-macralstonine could be determined (Tables 3 and 4).

Table 3. ^{13}C NMR Data (δ) for 1a–4a and 6a[a]

C	1a[b]	2a[b]	3a[c]	4a[b]	6a[b]
2	133.6	133.6	133.1	133.8	133.4
3	53.5	53.2	53.7	53.5	53.2
5	54.6	53.3	55.0[e]	54.2	53.6
6	21.7	22.1	21.8	21.8	22.1
7	107.0	106.7	107.1	106.8	106.6
8	126.7	126.7	126.8	126.6	126.5
9	118.4	118.0	118.5	118.3	118.0
10	118.8	118.6	118.7	118.7	118.7
11	120.7	120.7	120.7	120.7	120.8
12	108.8	109.1	108.9	108.8	109.0
13	137.0	137.2	137.2	137.0	137.2
14	30.3	31.3	30.1	30.3	31.46
15	30.8	31.6	31.2	31.3	31.55
16	43.0	42.0	43.3	43.6	41.9
17	63.7	62.6	64.0	63.5	62.6
18	32.2[d]	34.1	32.9	31.7	32.7
19	212.8	214.1	213.1	213.1	213.9
20	54.8	52.4	53.2[e]	54.1	53.9
21	26.2	25.6	29.0	33.2	31.8
N_1*Me*	29.1	28.9	29.1[f]	29.2	29.1
N_4*Me*	41.9	41.9	41.6[g]	42.1	42.1
OCO*Me*	21.2	21.3	21.2	21.1	21.3
OCOMe	171.3	171.6	171.2	171.4	171.4
2′	133.8	133.6	133.8	131.5	131.3
3′	53.9	53.8	54.0	53.8	53.9
5′	54.6	54.6	54.4	54.7	54.7
6′	22.5	22.7	25.3	22.8	22.9
7′	105.8	105.2	105.3	105.6	105.5
8′	122.9	123.2	126.3	119.2	120.1
9′	116.1	115.8	118.0	119.4	119.4
10′	104.7	104.5	151.2	118.7	119.0
11′	153.5	153.8	106.5	153.7	153.9
12′	110.9	110.0	107.3	91.4	91.3
13′	136.3	136.1	133.1	136.7	136.7
14′	32.2[d]	32.0	32.2	32.4	32.4
15′	22.7	22.8	22.8	22.9	22.8
16′	38.4	38.5	38.5	38.4	38.4
17′	67.7	67.7	67.5	67.8	67.8
18′	25.0	25.0	25.1	25.4	25.1
19′	195.3	195.5	195.7	195.6	195.7
20′	121.0	121.1	120.9	121.1	121.1
21′	157.2	157.4	157.8	157.7	157.6
N_1*Me*′	32.2[d]	32.4	29.2[f]	29.0	29.0
N_4*Me*′	42.1	41.7	42.2[g]	41.9	41.7
10′-OMe			56.9		
11′-OMe	56.6	56.6		55.6	55.5

[a]Assignments are based on COSY, HSQC, and HMBC. [b]150 MHz, $CDCl_3$. [c]100 MHz, $CDCl_3$. [d–g]Assignments are interchangeable.

The relative configuration at C-20 in the *O*-methyl congener of macralstonine isolated from the Thai *A. macrophylla* was established as *R* on the basis of its NOESY spectrum.[10,24] In the case of macralstonine, however, NOE was not feasible due to the observation of H-20 and H-21 as multiplets. In the case of the *O*-acetyl-*E-seco*-macralstonine derivative **6a**, H-20 was clearly seen as a triplet of doublets (J_{20-21a} = 11.0, J_{20-21b} = 4.0 Hz),

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Table 4. ^{1}H NMR Data (δ) for 1a−4a and 6a[a]

H	1a[b]	2a[b]	3a[c]	4a[b]	6a[b]
3	4.03 m	3.88 m	4.07 m	4.00 m	3.90 m
5	3.25 m	3.44 m	3.25 m	3.26 m	3.43 d (6)
6β	2.50 m	2.52 m	2.48 m	2.44 d (17)	2.49 d (16.5)
6α	3.25 m	3.35 dd (17, 8)	3.25 m	3.14 dd (17, 7)	3.33 dd (16.5, 7)
9	7.57 d (8)	7.58 d (7.5)	7.58 br d (7.5)	7.54 br d (7.5)	7.53 d (7.5)
10	7.15 t (8)	7.14 t (7.5)	7.16 td (7.5, 1)	7.13 td (7.5, 1)	7.12 td (7.5, 1)
11	7.23 t (8)	7.22 t (7.5)	7.23 td (7.5, 1)	7.22 td (7.5, 1)	7.19 td (7.5, 1)
12	7.34 d (8)	7.31 d (7.5)	7.33 br d (7.5)	7.32 br d (7.5)	7.29 d (7.5)
14β	1.94 m	1.32 m	1.94 m	1.86 m	1.28 d (12)
14α	1.94 m	1.81 m	1.94 m	1.86 m	1.89 m
15	2.25 m	2.14 m	2.21 m	2.14 m	2.03 m
16	1.94 m	2.21 m	1.87 m	1.88 m	2.23 m
17a	4.15 dd (11, 3.5)	4.63 m	4.22 dd (11, 4)	4.28 dd (11, 3.5)	4.59 m
17b	4.53 dd (11, 9)	4.63 m	4.49 dd (11, 9)	4.58 t (11)	4.59 m
18	1.59 s	1.30 s	1.34 s	1.71 s	1.59 s
20	2.99 td (10.7, 3.8)	3.23 td (11, 5)	3.15 m	3.08 td (11, 3.5)	3.06 td (11, 4)
21a	2.83 dd (14, 10.7)	3.04 m	2.48 m	2.31 m	2.37 m
21b	3.17 dd (14, 3.8)	3.32 dd (14, 5)	3.15 m	2.97 dd (13.5, 3.5)	3.15 m
N_1Me	3.66 s	3.55 s	3.67 s	3.64 s	3.55 s
N_4Me	2.35 s	2.28 s	2.37 s	2.28 s	2.31 s
OCO*Me*	2.03 s	2.16 s	1.99 s	2.06 s	2.15 s
3′	3.79 m	3.72 m	3.81 m	3.80 br s	3.81 m
5′	3.05 m	3.01 m	2.81 d (7)	3.02 d (7)	3.03 m
6′α	2.40 d (16)	2.35 d (16)	2.26 d (16)	2.54 m	2.39 m
6′β	3.23 m	3.18 dd (16, 7)	3.11 m	3.14 dd (16.5, 7)	3.17 m
9′	7.23 d (8.5)	7.19 d (8.5)		6.87 s	6.90 s
10′	6.76 d (8.5)	6.77 d (8.5)			
11′			6.83 d (8.7)		
12′			7.07 d (8.7)	6.69 s	6.69 s
14′α	1.74 m	1.71 td (12, 3.5)	1.75 m	1.75 m	1.78 m
14′β	1.98 m	1.99 m	2.08 m	2.06 m	2.07 m
15′	2.48 m	2.50 m	2.48 m	2.53 dt (11.5, 6)	2.59 m
16′	1.84 m	1.82 m	1.69 m	1.88 m	1.89 m
17′β	4.13 dd (11.5, 3.5)	4.12 dd (11, 3)	4.09 m	4.14 dd (11, 2)	4.14 d (10.5)
17′α	4.39 t (11.5)	4.37 t (11)	4.31 t (11)	4.41 t (11)	4.39 t (10.5)
18′	2.06 s	2.06 s	2.06 s	2.07 s	2.09 s
21′	7.49 s	7.50 s	7.50 s	7.51 s	7.53 s
N_1Me'	3.48 s	3.52 s	3.53 s	3.57 s	3.57 s
N_4Me'	2.27 s	2.24 s	2.31 s	2.30 s	2.26 s
10′-OMe			3.88 s		
11′-OMe	3.85	3.92 s		3.88 s	3.91 s

[a]Assignments are based on COSY, HSQC, and HMBC. [b]600 MHz, $CDCl_3$. [c]400 MHz, $CDCl_3$.

and this, coupled with the observed NOEs (H-21a/H-15, H-9′; H-21b/H-16, H-17, H-9′), allowed assignment of the C-20 configuration as *R*. In the event, macralstonine crystallized wholly as the cyclized hemiketal form (**5**) from a CH_2Cl_2/MeOH solution. X-ray analysis was therefore carried out and confirmed the 20*R* absolute configuration (Figure 8).

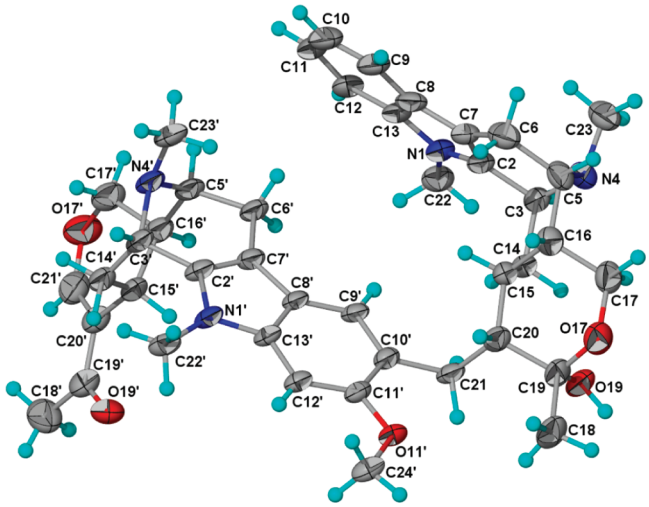

Figure 8. X-ray crystal structure of **5**. Flack parameter x = −0.1(0.4); Hooft parameter y = −0.30(0.14).

Since we now have two bisindole alkaloids, viz., perhentinine (**4**) (and its cyclized hemiketal derivative in the form of its dimethyl diiodide salt, **4b**) and macralstonine (**5**) (and its acyclic form as its *O*-acetyl derivative, **6a**), which possesses opposite C-20 configuration and for which we have obtained X-ray crystal structure data, these two alkaloids can therefore serve as model compounds for comparison of the perhentidines.

In the NMR spectra of the parent bisindoles (**1**−**4**, **6**), the signals of the C-17 oxymethylene hydrogens are well separated in the case of the 20*R* bisindoles, **2** and **6** ($\Delta\delta = \delta_{17b} - \delta_{17a} \approx$ 0.3−0.4), whereas these signals are close in the 20*S* compounds, **1**, **3**, and **4** ($\Delta\delta = \delta_{17b} - \delta_{17a} \approx$ 0.02−0.07). In the case of the *O*-acetyl derivatives (**1a**−**4a**, **6a**) however, this trend is reversed, and a clear distinction could be observed between the 20*S* and 20*R* series. Thus the signals due to the C-17 oxymethylene hydrogens in the *O*-acetyl derivatives of the 20*S* series (**1a**, **3a**, **4a**) were observed as clearly separated AX doublets of doublets ($\Delta\delta = \delta_{17b} - \delta_{17a} \approx$ 0.3−0.4), while those in the *O*-acetyl derivatives of the 20*R* series (**2a**, **6a**) were invariably observed as overlapped multiplets ($\Delta\delta = \delta_{17b} - \delta_{17a} \approx$ 0) (Figure 9). This not only provided additional strong support for the assignment of the C-20 configurations in compounds **1**−**6** based on analysis of the NMR coupling constant and NOE data (*vide infra*) but in addition could serve as a potentially general method for the determination of the configuration at C-20 in related bisindoles with similar constitution and branching of the monomeric units.

In conclusion we have established complete and firm structure assignment of the new macroline−macroline bisindoles perhentidines A (**1**), B (**2**), and C (**3**), including determination of the configuration at C-20. We have also obtained X-ray confirmation of the structures (absolute configuration) of the previously isolated bisindoles, perhentinine (**4**) (via its dimethyl diiodide salt **4b**) and macralstonine (**5**), which has also facilitated assignment of the structures of perhentidines A−C (**1**−**3**).

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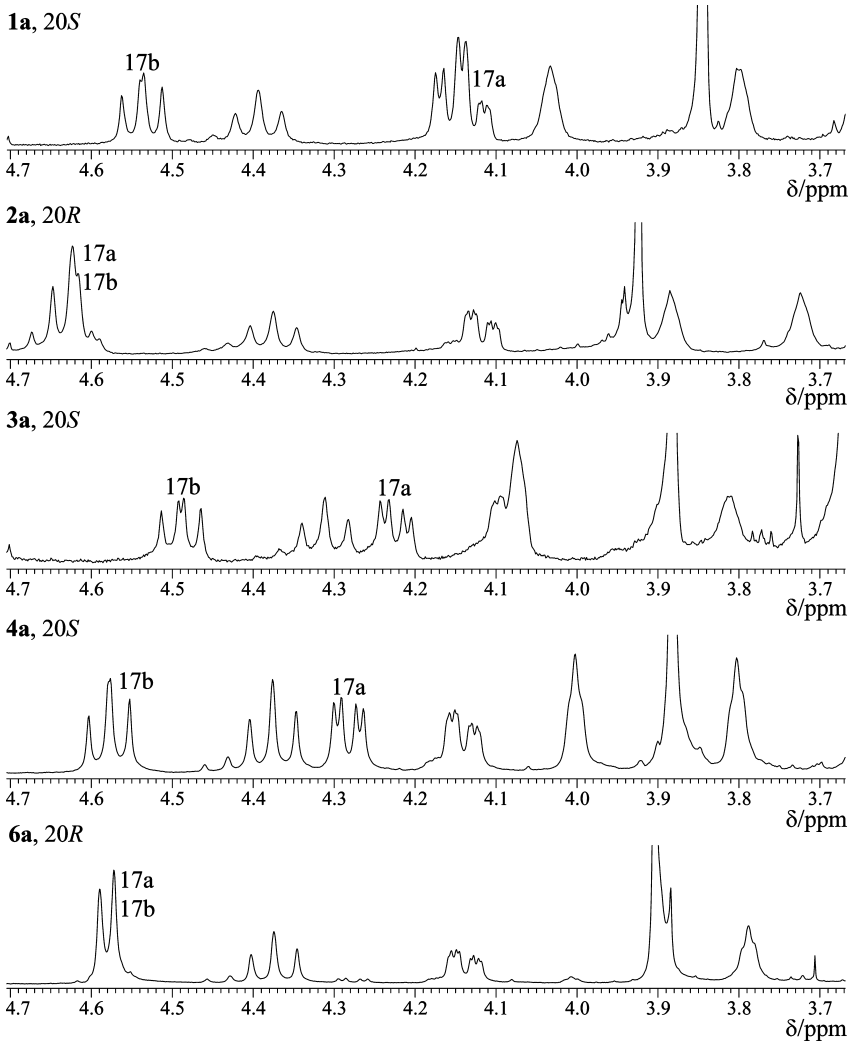


Figure 9. Partial ^{1}H NMR spectrum (400 MHz) of acetates **1a**−**4a** and **6a**.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were determined on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a Perkin-Elmer Spectrum 400 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, JNM-ECA 400, or Bruker Avance III 400 spectrometer, at 400 and 100 MHz, respectively, or on a Bruker Avance III 600 spectrometer at 600 and 150 MHz, respectively. ESIMS and HRESIMS were obtained on an Agilent 6530 Q-TOF mass spectrometer. EIMS and HRLSIMS were obtained at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia. X-ray diffraction analysis was carried out on a Bruker SMART APEX II CCD area detector system equipped with a graphite monochromator and using Mo Kα radiation (λ = 0.71073 Å) or on an Agilent Technologies SuperNova Dual CCD area detector system equipped with mirror monochromator and using Cu Kα radiation (λ = 1.54184 Å), at 100 K. All reactions were carried out under N_2 in oven-dried glassware. CH_2Cl_2 and pyridine were distilled from CaH_2 under N_2. Ac_2O and CH_3I were distilled under N_2 prior to use.

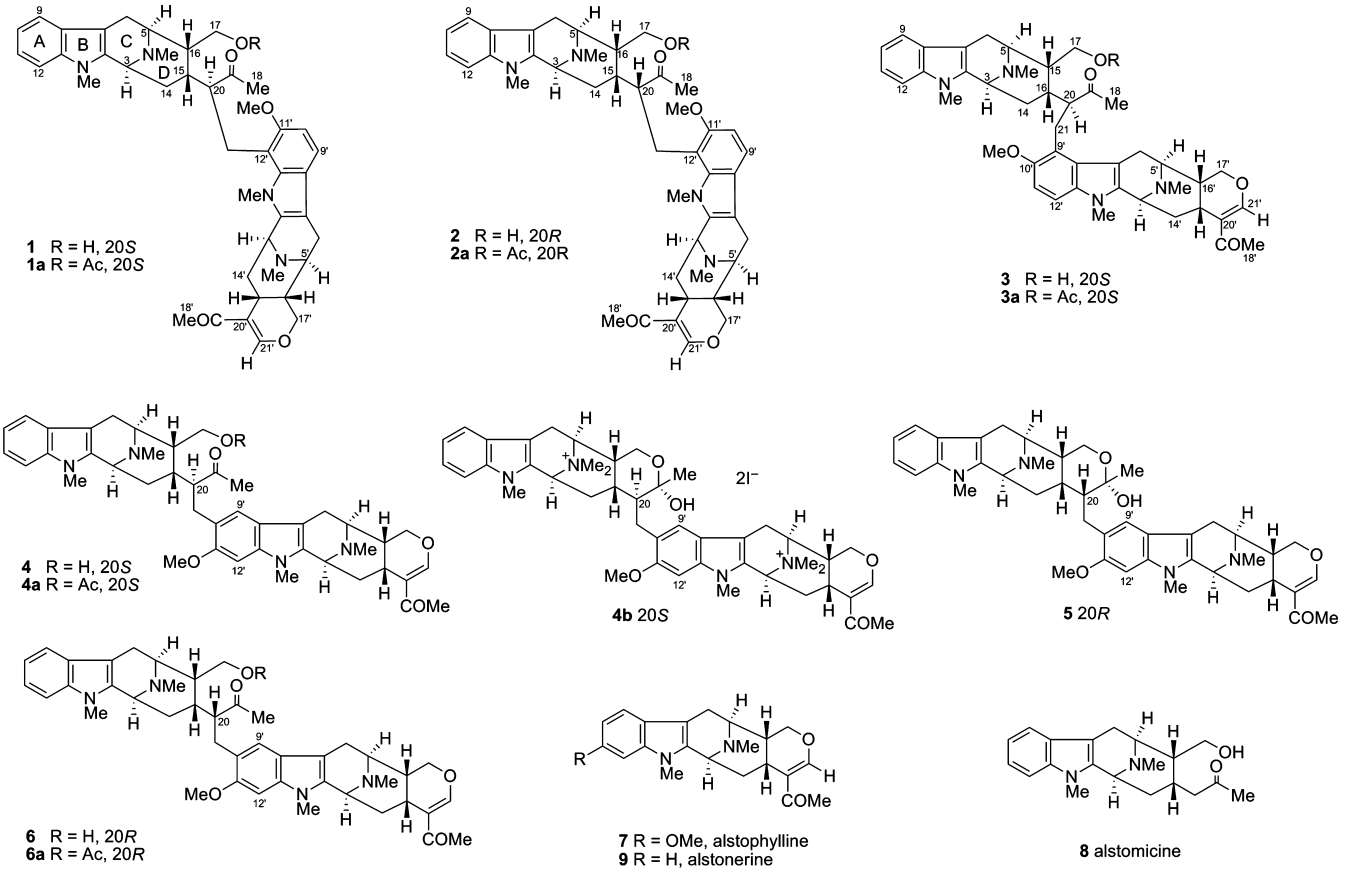
Plant Material. *A. macrophylla* was collected in Perak, Malaysia, while *A. angustifolia* was collected in Johor, Malaysia. Identification of both plants was confirmed by Dr. Richard C. K. Chung, Forest Research Institute, Malaysia. Herbarium voucher specimens (*A. macrophylla*, K671; *A. angustifolia*, K665) were deposited at the Herbarium, University of Malaya.

Extraction and Isolation. The bark material was extracted with EtOH, and the concentrated EtOH extract was then partitioned with dilute tartaric acid. 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 preparative TLC. For the bark extract of *A. angustifolia*, solvent systems used for centrifugal preparative TLC were $CHCl_3$/hexanes (2:1; NH_3-saturated) and Et_2O/MeOH (30:1; NH_3-saturated). The yields (g kg^{-1}) of the alkaloids from the bark extract of *A. angustifolia* were as follows: **1** (0.0009), **3** (0.0011), and **4** (0.0050). For the bark extract of *A. macrophylla*, the solvent systems used for centrifugal preparative TLC were Et_2O/MeOH (30:1; NH_3-saturated), EtOAc/MeOH (100:1; NH_3-saturated), and $CHCl_3$/MeOH (100:1; NH_3-saturated). The yields (g kg^{-1}) of the alkaloids from the bark extract of *A. macrophylla* were as follows: **1** (0.0141), **2** (0.0156), **4** (0.0459), and **5** (0.0335).

Perhentidine A (1): light yellowish oil; $[\alpha]^{25}_D$ −77 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (4.35), 286 (3.69) nm; IR (dry film) ν_{max} 3400, 1702, 1648, 1617 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 2 and 1, respectively; ESIMS *m*/*z* 705 $[MH]^+$; HRESIMS *m*/*z* 705.4010 $[M + H]^+$ (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4013).

Perhentidine B (2): light yellowish oil; $[\alpha]^{25}_D$ −38 (*c* 0.52, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 234 (4.49), 286 (3.81) nm; IR (dry film) ν_{max} 3392, 1707, 1653, 1618 cm^{-1}; ^{1}H NMR and ^{13}C NMR data,

Chart 1



see Tables 2 and 1, respectively; ESIMS *m/z* 705 $[M + H]^+$; HRESIMS *m/z* 705.3993 (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4013).

Perhentidine C (3): light yellowish oil; $[\alpha]^{25}_D$ −73 (*c* 0.5, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.53), 285 (3.93) nm; IR (dry film) ν_{max} 3387, 1703, 1651, 1615 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2 and 1, respectively; EIMS *m/z* 686 $[M - H_2O]^+$ (100), 616 (6), 547 (5), 486 (42), 379 (27), 343 (12), 307 (15), 277 (5), 251 (19), 197 (99), 170 (21), 70 (8); HRLSIMS *m/z* 705.4029 $[M + H]^+$ (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4013).

Macralstonine (5): colorless rectangular rod crystals from CH_2Cl_2/MeOH; mp 260−263 °C (lit.[23] mp 279−282 °C); $[\alpha]^{25}_D$ +22 (*c* 0.5, $CHCl_3$){lit.[23] $[\alpha]^{25}_D$ +22 (*c* 2.0, $CHCl_3$)}; ^1H NMR and ^{13}C NMR data, see Tables 2 and 1, respectively. The ^1H and ^{13}C NMR spectra recorded in CD_2Cl_2 and THF-d_8 are provided in the Supporting Information.

General Procedure for the Acetylation of Alkaloids 1−6. To a solution of the appropriate alkaloid (1.0 mmol), pyridine (3 equiv), and CH_2Cl_2 was added Ac_2O (1.5 equiv), and the mixture was stirred at rt. The progress of the reaction was monitored with TLC and stopped at ca. 95% completion by addition of 5% Na_2CO_3 solution. The organic layer was washed with H_2O, dried with Na_2SO_4, and concentrated *in vacuo*, and the product was purified by centrifugal preparative TLC (SiO_2, 100:5 $CHCl_3$/MeOH, NH_3-saturated) to give the corresponding *O*-acetyl derivatives.

*O-Acetylperhentidine A (**1a**).* Reaction of **1** (18.3 mg, 0.026 mmol) with Ac_2O (3.7 μL, 0.039 mmol) in pyridine (6.3 μL, 0.079 mmol) and CH_2Cl_2 (2 mL) gave **1a** (9.1 mg, 47%): light yellowish oil; $[\alpha]^{25}_D$ −111 (*c* 0.45, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.99), 285 (4.30) nm; IR (dry film) ν_{max} 1732, 1703, 1652, 1620 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 4 and 3, respectively; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4122 $[M + H]^+$ (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119).

*O-Acetylperhentidine B (**2a**).* Reaction of **2** (18.8 mg, 0.027 mmol) with Ac_2O (3.9 μL, 0.04 mmol) in pyridine (6.4 μL, 0.081) and CH_2Cl_2 (2 mL) gave **2a** (8.5 mg, 43%): light yellowish oil; $[\alpha]^{25}_D$ −42 (*c* 0.43, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.01), 288 (4.32) nm; IR (dry film) ν_{max} 1734, 1709, 1654, 1619 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 4 and 3, respectively; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4109 $[M + H]^+$ (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119).

*O-Acetylperhentidine C (**3a**).* Reaction of **3** (2.8 mg, 0.004 mmol) with Ac_2O (0.6 μL, 0.006 mmol) in pyridine (1 μL, 0.012) and CH_2Cl_2 (1 mL) gave **3a** (2.2 mg, 74%): colorless oil; $[\alpha]_D$ −105 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.70), 285 (4.07) nm; IR (dry film) ν_{max} 1737, 1706, 1650, 1618 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 4 and 3, respectively; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4118 $[M + H]^+$ (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119).

*O-Acetylperhentinine (**4a**).* Reaction of **4** (15.1 mg, 0.021 mmol) with Ac_2O (3 μL, 0.032 mmol) in pyridine (5 μL, 0.063 mmol) and CH_2Cl_2 (2 mL) gave **4a** (8.2 mg, 52%): light yellowish oil; $[\alpha]^{25}_D$ −103 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.15), 295 (4.41) nm; IR (dry film) ν_{max} 1736, 1706, 1651, 1618 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 4 and 3, respectively; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4123 $[M + H]^+$ (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119).

*O-Acetyl-E-seco-macralstonine (**6a**).* Reaction of **6** (16.8 mg, 0.024 mmol) with Ac_2O (3.4 μL, 0.036 mmol) in pyridine (5.8 μL, 0.071 mmol) and CH_2Cl_2 (2 mL) gave **6a** (11 mg, 62%): light yellowish oil; $[\alpha]^{25}_D$ +34 (*c* 1.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.00), 297 (4.21) nm; IR (dry film) ν_{max} 1732, 1715, 1651, 1614 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 4 and 3, respectively; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4119 $[M + H]^+$ (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119).

Conversion of Perhentinine (4) to Its Dimethyl Diiodide Salt 4b. Iodomethane (0.5 mL, 8 mmol) was added to perhentinine (**4**) (16 mg, 0.02 mmol), and the mixture allowed to stand for 24 h at rt. Excess iodomethane was then removed under reduced pressure to

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furnish a yellowish residue, which on recrystallization from hot MeOH gave the corresponding dimethyl diiodide salt **4b** (14 mg, 62%): light yellowish block crystals; mp 228−230 °C; $[\alpha]^{25}_{D}$ −55 (*c* 0.05, MeOH); UV (EtOH) λ_{max} (log ε) 221 (5.83), 295 (4.97) nm; ESIMS *m*/*z* 367 $[M]^{2+}$; HRESIMS *m*/*z* 367.2207 $[M]^{2+}$ (calcd for $C_{45}H_{58}N_4O_5$, 734.4396).

X-ray Crystallographic Analysis of 4b and 5. Crystal data of **4b** were collected on a Bruker SMART APEX II CCD, while the crystal data of **5** were collected on an Agilent Technologies SuperNova Dual CCD diffractometer. The structures were solved by direct methods (SHELXS-97) and refined with full-matrix least-squares on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed in idealized positions and refined as riding atoms with the relative isotropic parameters. The absolute structures were determined by refinement of the Flack parameter[26] and computation of the Hooft parameter.[27] Crystallographic data for **4c** and **5** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223-336033, or e-mail: deposit@ccdc.cam.ac.uk).

Crystallographic data of ***4b****:* $C_{45}H_{58}N_4O_5^{2+}2I^-$, M_r = 988.77, orthorhombic, space group $P2_12_12_1$, *a* = 14.5059(2) Å, *b* = 14.8002(2) Å, *c* = 22.4594(3) Å, *V* = 4821.81(11) Å^3, *T* = 100 K, *Z* = 4, D_{calcd} = 1.307 g cm^{-3}, crystal size 0.16 × 0.19 × 0.21 mm^3, *F*(000) = 1920. The final R_1 value is 0.0634 (wR_2 = 0.1921) for 8480 reflections [$I > 2\sigma(I)$]. The absolute configuration of **4b** was determined on the basis of the Flack parameter [*x* = 0.04(0.03)] and corroborated by the Hooft parameter [*y* = 0.022(0.07)]. CCDC number: 865674

Crystallographic data of ***5****:* $C_{43}H_{52}N_4O_5$, M_r = 704.89, monoclinic, space group C_2, *a* = 11.73280(10) Å, *b* = 13.07670(10) Å, *c* = 19.2454(2) Å, $\alpha = \gamma = 90°$, β = 108.475°(3), *V* = 3632.9(7) Å^3, *T* = 100 K, *Z* = 4, D_{calcd} = 1.289 g cm^{-3}, crystal size 0.02 × 0.10 × 0.20 mm^3, *F*(000) = 1512. The final R_1 value is 0.0720 (wR_2 = 0.1869) for 6280 reflections [$I > 2\sigma(I)$]. The absolute configuration of compound **5** was determined on the basis of the Flack parameter [*x* = −0.1(0.4)] in conjunction with the Hooft parameter [*y* = −0.30(0.14)] obtained from a statistical analysis of the Bijvoet pairs. CCDC number: 865675

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Notes

The authors declare no competing financial interest.

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