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Seco-tabersonine alkaloids from *Tabernaemontana corymbosa*

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ABSTRACT

Two *seco*-tabersonine alkaloids, jerantiphyllines A and B, in addition to a tabersonine hydroxyindolenine, jerantinine H, and a recently reported vincamine alkaloid **7**, were isolated from the leaf extract of the Malayan *Tabernaemontana corymbosa* and the structures were established using NMR and MS analysis. Biomimetic conversion of jerantinines A and E to their respective vincamine and 16-*epi*vincamine derivatives were also carried out.

1. Introduction

Plants of the genus *Tabernaemontana* comprising about 110 species and widely distributed in the pantropical regions are rich in alkaloids (Leeuwenberg, 1991; Van Beek et al., 1984; Danieli and Palmisano, 1986; Kam, 1999). In our systematic study of the Malaysian representatives of this genus, we have reported many examples of new alkaloids which are distinguished by their structural novelty, as well as useful bioactivity (Kam et al., 2004a,b, 2003a,b, 2001, 2000, 1999, 1998, 1993; Kam and Sim, 2003a,b, 2002a). The Malayan *T. corymbosa* Roxb. ex Wall for instance provided several new alkaloids which are characterized by novel molecular skeletons such as the hexacyclic alkaloid, tronoharine (Kam et al., 1999), the pentacyclic indole tronocarpine (Kam et al., 2000), and the quinolinic alkaloid, voastrictine (Kam et al., 2001). The same plant also yielded a number of new indole and bisindole alkaloids (Kam et al., 2003b; Kam and Sim, 2003a,b, 2002a,b,c; Zhang et al., 2007; Zèches et al., 1994), including several vobasinyl-iboga bisindoles which reverse multidrug-resistance in vincristine resistant KB cells (Kam et al., 1998). In continuation of our studies of biologically active alkaloids from Malaysian *Tabernaemontana* (Kam et al., 2004a,b, 2003a,b, 2001, 2000, 1999, 1998, 1993, 1992; Kam and Sim, 2003a,b, 2002a,b,c, 2001, 1999), we recently reported the isolation of several new cytotoxic *Aspidosperma*-type alkaloids, jerantinines A–G, from the leaf extract of the same species, but involving plant material collected from a different location (Lim et al., 2008). We now wish to report the further isolation of additional new alkaloids from the leaf extract of the same plant.

2. Results and discussion

Jerantiphylline A (**1**) was obtained from the leaf extract of *T. corymbosa* as a colorless oil, with $[\alpha]_D$ −214 (*c* 0.08, $CHCl_3$). The EIMS of **1** showed a molecular ion at *m*/*z* 414, which analyzed for $C_{22}H_{26}N_2O_6$, requiring 11° of unsaturation, while the fragment ion observed at *m*/*z* 382 is due to loss of MeOH. The UV spectrum showed absorption maxima at 247, 318 and 342 nm (log ε 3.89, 4.11 and 4.01, respectively), consistent with a β-anilinoacrylate chromophore and reminiscent of tabersonine alkaloids. In addition to the absorption band due to the presence of the β-anilinoacrylate chromophore (1606 cm^{-1}), the IR spectrum showed bands at 3529, 3377, 1710, 1660 and 1624 cm^{-1} due to OH, NH, aldehyde, conjugated ester and amide functions, respectively. The ^{13}C NMR spectrum (Table 1) showed a total of 22 separate carbon resonances (four methyls, four methylenes, four methines and ten quaternary carbons), in agreement with the molecular formula established from HREIMS measurements. The presence of the β-anilinoacrylate chromophore was also indicated by the ^{13}C NMR spectrum which showed the characteristic carbon resonances for C-2 at δ 168.5, C-16 at δ 89.3 and CO_2Me at δ 168.5 and 51.2. In addition to the conjugated methyl ester carbonyl resonance, two other carbonyl resonances observed at δ 205.3 and 170.6 were assigned to aldehyde and amide functions, respectively. The ^1H NMR spectrum of **1** (Table 1) showed the presence of an isolated aldehyde group, two methoxy groups (one aromatic methoxy and one belonging to an ester CO_2Me group), two isolated aromatic hydrogens, an isolated methyl, methylene and methine, an ethyl side chain, a phenolic OH and an indolic NH. The aromatic methoxy substituent and phenolic OH were deduced to be at C-10 and C-11, respectively, from examination of the aromatic carbon resonances and from the HMBC data (three bond correlations from OH to C-9, C-11

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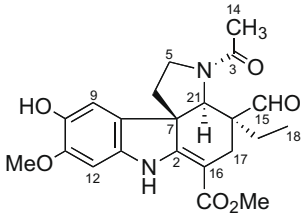
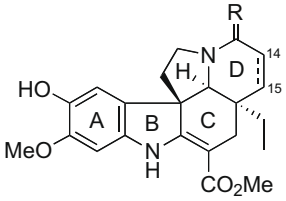
and from 11-OMe to C-11). The COSY and HMQC data revealed the presence of an NCH_2CH_2 fragment which corresponds to NC(5)–C(6).

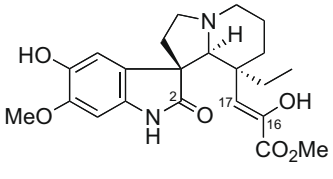
The ^1H and ^{13}C NMR data of **1** are somewhat similar to those of tabersonine alkaloids, particularly jerantinines A–E (Lim et al., 2008). However, the N(4)–C(3)–C(14)–C(15) fragment usually present in the tabersonine/*Aspidosperma* alkaloids was conspicuously absent in **1**, being replaced instead by an *N*-acetyl and an isolated aldehyde group. Since the structural elements associated with rings A, B, C and E of **1** remained intact when compared with those of jerantinines A–E (Lim et al., 2008), the *N*-acetyl and aldehyde groups in **1** must be associated with an altered ring-D. Furthermore, since the degree of unsaturation for **1** is 11, a tetracyclic carbon skeleton with the lost of ring-D was indicated. Further clues to the structure of **1** were provided by the observed heteronuclear correlations from the HMBC spectrum (Fig. 1). The observed correlation from H-21 to the acetyl carbonyl indicated attachment of the acetyl group to N-4, while correlations from the aldehyde hydrogen to C-17 and C-19, as well as from H-17 and H-19 to the aldehyde carbon, indicated that the aldehyde group is branched from the quaternary C-20. The structure deduced is entirely consistent with the rest of the HMBC data (Fig. 1) as well as with the NOESY/DNOE data (Fig. 1). The latter also revealed the relative stereochemistry at all the stereogenic centers in **1**. Thus, irradiation of H-21 caused enhancement of H-9 and H-19, indicating that the orientation of the aldehyde group at C-20 is β. Irradiation of H-9 on the other hand resulted in enhancement of H-5, the acetyl CH_3 and H-21. These observations allowed the orientation of the N-4 lone pair to be assigned as β. Irradiation of H-12 resulted in enhancement of NH and 11-OMe, providing additional confirmation for the substitution pattern of the aromatic ring. Jerantiphylline A (**1**) represents the first example of a ring-D-*seco*-tabersonine alkaloid. A possible origin of this ring-opened alkaloid is from a 3-oxo-tabersonine derivative such as jerantinine C (**2**), *via* a retro-Aldol reaction.



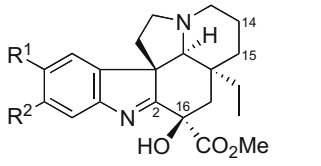
1



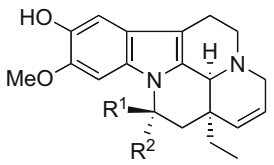
2 R = O, $\Delta^{14,15}$
4 R = H_2
9 R = H_2, $\Delta^{14,15}$



3



5 R^1 = OH, R^2 = OMe
6 R^1 = R^2 = H, 14,15-α-epoxide



7 R^1 = OH, R^2 = CO_2Me
8 R^1 = CO_2Me, R^2 = OH

Jerantiphylline B (**3**) was isolated as a colorless oil, with $[\alpha]_D$ −182 (*c* 0.07, $CHCl_3$). The UV spectrum was characteristic of an oxindole chromophore with absorption maxima at 213, 267 and 303 nm, while the IR spectrum showed bands at 3538, 3281 and 1706 cm^{-1} due to OH, NH and carbonyl functions, respectively. The ^1H NMR spectrum of **3** (Table 1) revealed some similarities with those of the jerantinines. Firstly, the aromatic substitution pattern in **3** is similar to that in the jerantinine alkaloids (Lim et al., 2008). In addition, **3** resembles jerantinine E (**4**) in having in common, an unfunctionalized piperidine ring-D. The presence of the oxindole moiety, which was also indicated in the ^{13}C NMR spectrum (δ 184.1, Table 1), suggested that the main change in **3** when compared to **4**, is the loss of ring C, giving rise to a 2,16-*seco*-tabersonine alkaloid. The ^1H, ^{13}C and 2D NMR data indicated the presence of a trisubstituted double bond at C-16 and C-17, with the latter being an olefinic methine from the observed three-bond correlations from H-17 to C-15, C-19, C-21 and CO_2Me in the HMBC spectrum. The molecular formula of **3** (*m*/*z* 416, $C_{22}H_{28}N_2O_6$) differs from that of jerantinine E (**4**) by 32 mass units, suggesting that **3** possesses two additional oxygen atoms compared to jerantinine E (**4**). Since the oxindole moiety accounted for one of the additional oxygen atoms, the other is due to an OH group which is in turn linked to the ester bearing, olefinic C-16. This is consistent with the observed carbon resonance of C-16 at δ_C 143.4, as well as the HMBC data, which showed a three-bond correlation from the downfield enol OH signal at δ_H 15.1 to the carbonyl carbon of the methyl ester group. The unusual deshielding experienced by the enol OH is likely due to intramolecular hydrogen bonding between the enol hydrogen and the proximate ester carbonyl oxygen. The occurrence of such intramolecular hydrogen bonding probably accounts for the stability of the enol moiety in **3**. Jerantiphylline B (**3**) is therefore the 2,16-*seco*-derivative of jerantinine E (**4**) and is characterized by the presence of an unusually stable enol moiety. Only one example (vincatine) with a similar carbon skeleton is known as a natural product (Dopke et al., 1969), while several 2,16-*seco*-derivatives similar to **3** and incorporating a similar enol function, have been obtained in some instances on further oxidation of various vincadifformine 16-hydroxindolenine derivatives (Danieli et al., 1981; Calabi et al., 1982; Hugel et al., 1981).

Jerantinine H (**5**) was isolated as a colorless oil, with $[\alpha]_D$ −156 (*c* 0.07, $CHCl_3$). The UV spectrum showed the presence of an indolenine chromophore (210, 235 and 305 nm), which was further supported by the presence of the characteristic imine carbon resonance at δ 185.7 in the ^{13}C NMR spectrum (Table 1). The ^1H NMR spectrum of **5** (Table 1) was however generally similar to that of jerantinine E (**4**) (Lim et al., 2008), except for H-12, which was shifted downfield. This observation is consistent with the change from an indole to an indolenine chromophore in **5**. HREIMS measurements gave the formula $C_{22}H_{28}N_2O_5$ (*m*/*z* 400.1986, calcd for 400.2000), differing from jerantinine E (**4**) by 16 mass units, suggesting the presence of an additional oxygen atom. Since the β-anilinoacrylate chromophore present in **4** was replaced by an imine chromophore in **5**, the additional oxygen atom is readily deduced to be associated with an OH group. The notable change in the chemical shift of the methyl ester bearing C-16 from δ_C 92.1 in **4** to δ_C 77.7 in **5** indicated that C-16 is the site of oxygenation. Jerantinine H (**5**) is therefore the 16-hydroxyindolenine derivative of jerantinine E (**4**). The configuration at C-16 was assumed to be the same as that found in the semisynthetic derivative, 1-dehydro-16-hydroxyvincadifformine (**6**) (Calabi et al., 1982) based on the similarity of the ^1H and ^{13}C NMR data for the non-indolic portion of both the alkaloids (**5** and **6**).

The lone vincamine alkaloid isolated, **7**, was readily identified as 14,15-didehydro-10-hydroxy-11-methoxyvincamine by comparison of its spectroscopic data with those of the same alkaloid

Table 1
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectroscopic data in $CDCl_3$ for compounds **1**, **3** and **5**[a]

Position	**1**		**3**		**5**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	–	168.5	–	184.1	–	185.7
3	–	170.6	2.31 *td* (13, 3) 3.35 *m*	53.8	2.20 *td* (11, 3) 3.23 *m*	52.0
5	3.72 *m* 3.72 *m*	45.9	2.65 *ddd* (11.3, 9.5, 7.6) 3.31 *m*	53.4	2.54 *dt* (10.5, 8) 3.23 *m*	53.5
6	1.92 *m* 2.54 *m*	36.8	2.16 *m* 2.16 *m*	36.4	1.87 *dd* (13.5, 8) 2.78 *ddd* (13.5, 11, 8)	33.7
7	–	55.2	–	55.6	–	62.2
8	–	127.0	–	122.0	–	137.5
9	6.60 *s*	108.8	7.15 *s*	114.5	6.88 *s*	107.3
10	–	140.7	–	141.3	–	146.0
11	–	146.9	–	146.8	–	146.2
12	6.49 *s*	94.6	6.42 *s*	94.1	7.20 *s*	105.2
13	–	136.2	–	133.0	–	144.7
14	2.13 s	22.8	1.60 *m* 1.85 qt (13, 4)	21.4	1.70 br d (13.5) 1.93 *m*	21.3
15	9.72 *s*	205.3	1.24 *td* (13, 4) 1.62 *m*	36.9	1.09 *td* (13.5, 4.4) 1.51 *br d* (13.5)	33.1
16	–	89.3	–	143.4	–	77.7
17	2.55 *d* (16.1) (β) 2.73 *d* (16.1) (α)	22.8	5.25 *s* –	111.7	2.23 *d* (15) 2.71 *d* (15)	45.0
18	0.78 *t* (7.6)	9.0	0.69 *t* (7)	7.2	0.55 *m*	7.1
19	1.34 *dq* (14, 7.5) 1.93 *dq* (14, 7.5)	27.6	0.95 *dq* (15, 7) 1.01 *dq* (15, 7)	29.5	0.57 *m* 0.57 *m*	31.8
20	–	55.2	–	43.3	–	36.3
21	4.04 *s*	69.0	2.75 *s*	77.8	2.52 *s*	78.1
11-OMe	3.89 *s*	56.5	3.82 *s*	56.1	3.90 *s*	56.1
10-OH	5.50 *br s*	–	5.42 *br s*	–	5.74 *br s*	–
16-OH	–	–	15.1 *br s*	–	8.13 *br s*	–
NH	8.91 *br s*	–	8.64 *br s*	–	–	–
CO_2Me	3.77 *s*	51.2	3.78 *s*	52.3	3.94 *s*	53.0
CO_2Me	–	168.5	–	166.7	–	171.2

[a] Assignments based on COSY, HMQC, HMBC and NOESY/DNOE.

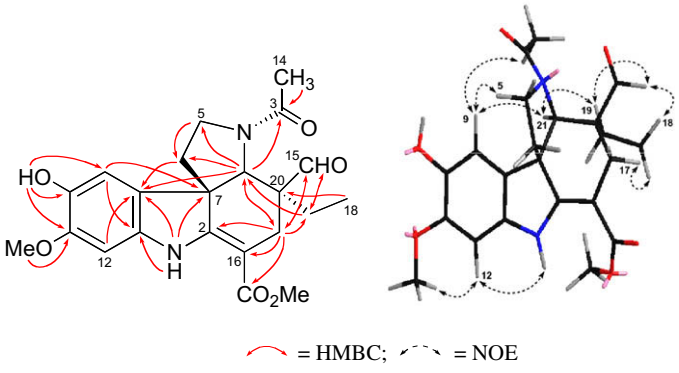


Fig. 1. Selected HMBCs and NOEs of **1**.

recently isolated together with its C(16)-epimer **8**, from *Ervatamia divaricata* occurring in China (Zhang et al., 2007).

Scrutiny of the structures of jerantinines A (**9**) and E (**4**), jerantinine H (**5**), and the vincamine alkaloid **7**, indicated that they correspond to the precursors, oxidized intermediate and final products, respectively, of the *Aspidosperma*→eburnea transformation, originally proposed by Wenkert to account for the origin of the eburnane/vincamine alkaloids (Wenkert and Wickberg, 1965). Accordingly, such a transformation was attempted as shown in Scheme 1 (Hugel et al., 1972). Protection of the labile phenolic OH of both **4** and **9** as the acetates **10** and **11**, respectively, were first carried out to prevent conversion of these alkaloids into their respective iminoquinones. Peracid oxidation of the acetates (**10** and **11**) followed by an unexpected OH deprotection with 10% Na_2SO_3 solution, gave the 16-hydroxyindolenine N-oxides, **12** and **13**, respectively. Treatment of the N-oxide **12** with triphenylphosphine in the absence of acid yielded the 16-hydroxyindolenine, jerantinine H (**5**), while attempted further oxidation of **12** with *m*-CPBA did not lead to any ring-opened products (Hugel et al., 1981). Treatment of the N-oxide **13** with triphenylphosphine in the presence of aqueous HOAc, on the other hand, yielded 14, 15-didehydro-10-hydroxy-11-methoxyvincamine (**7**) and its C(16)-epimer **8**. Similar treatment of the N-oxide **12** gave the two epimeric vincamines, **14** and **15**.

Although 16-hydroxindolenines similar to **5** and 2,16-*seco*-derivatives similar to **3** have been obtained in studies related to the *Aspidosperma*→eburnea transformation, these compounds have not been previously isolated from any natural source, except for a 16-hydroxyindolenine **6** isolated from the seeds of *Amsonia elliptica* (Aimi et al., 1978). The authors then noted that the possibility that **6** was an artifact of the isolation procedure cannot be ruled out. In the present study, it was observed that the solutions of jerantinine E (**4**) in dichloromethane when stored over long periods, resulted in decomposition yielding a complex mixture of compounds, from which the 2,16-*seco*-compound, jerantiphylline B (**3**), and the 16-hydroxyindolenine, jerantinine H (**5**), were isolated in trace amounts. In the light of this observation, as well as from the results of the oxidative transformations carried out on **4** and **9** above, the possibility that **3** and **5** may also be artifacts derived from jerantinine E (**4**) cannot be completely discounted.

In contrast to jerantinines A–E which were previously found to display pronounced cytotoxicity towards both drug-sensitive as well as vincristine-resistant KB cells (Lim et al., 2008), the alkaloids **3**, **5** and **7** were found to be ineffective. In the case of **3** and **5**, it would appear that a drastic departure from the vincadifformine

structure (loss of ring C or the anilinoacrylate chromophore) abolished the biological activity altogether.

A comparison of the present results (plant material collected from Tekam Forest, Pahang, Malaysia) with those of the previous one based on samples collected from a different location (plant material collected from Chenderiang, Perak, Malaysia), revealed a variation in the alkaloidal composition. The leaf material from the present study (this report and Lim et al., 2008) yielded only alkaloids of the *Aspidosperma*-type with the exception of one vincamine alkaloid, while leaf samples from the previous study gave predominantly ibogan alkaloids and iboga-vobasinyl bisindoles (Kam et al., 2003b, 1992; Kam and Loh, 1993; Kam and Sim, 2003a,b, 2002a,b, 2001, 1999).

3. Experimental

3.1. General

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 a JEOL JNM-LA 400 spectrometer at 400 and 100 MHz, respectively. EIMS and HREIMS and HR-FT-APCIMS were obtained at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia.

3.2. Plant material

Plant material was collected in Pahang, Malaysia, and identification was confirmed by Dr. K. M. Wong, Institute of Biological Sciences, University of Malaya, Kuala Lumpur, Malaysia. Herbarium voucher specimens (K 667) are deposited at the Herbarium, University of Malaya.

3.3. 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 (Kam and Tan, 1990) to provide a basic fraction (Lim et al., 2008). The alkaloids were isolated by initial column chromatography of the basic fraction on silica gel using CH_2Cl_2 with increasing proportions of MeOH, followed by rechromatography of the appropriate partially resolved fractions using centrifugal TLC. Solvent systems used for centrifugal TLC were Et_2O/hexane (2:1), Et_2O/MeOH (50:1), EtOAc/hexane (1:6), EtOAc/hexane (1:3), EtOAc/hexane (1:2), EtOAc/hexane (1:1), CH_2Cl_2/hexane (2:1), CH_2Cl_2/hexane (5:1), CH_2Cl_2/hexane (6:1), CH_2Cl_2, CH_2Cl_2/MeOH (100:1) and $CHCl_3$/MeOH (50:1). The yields (g Kg^{-1}) of the alkaloids were as follows: jerantiphylline A (**1**) (0.0008), jerantiphylline B (**3**) (0.002), jerantinine H (**5**) (0.001) and 14,15-didehydro-10-hydroxy-11-methoxy-vincamine (**7**) (0.010).

3.4. Characterization data

3.4.1. Jerantiphylline A (*1*)

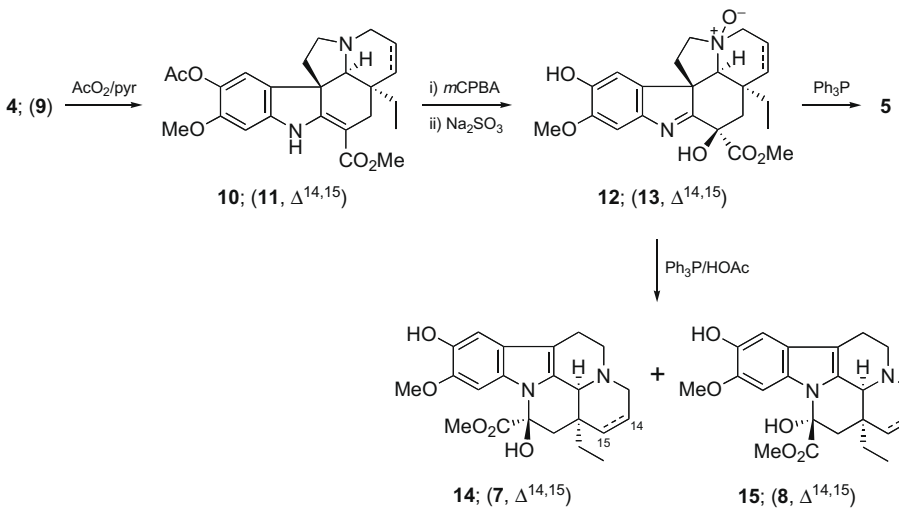
Colorless oil; $[\alpha]_D$ −214 (*c* 0.08, $CHCl_3$); UV (EtOH), λ_{max} (log ε): 247 (3.89), 318 (4.11), 342 (4.01) nm; IR (dry film) ν_{max}: 3529, 3377, 1710, 1660, 1624, 1606 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS (probe) 70 eV, *m/z* (rel. int.): 414 $[M]^+$ (70), 382 $[M-MeOH]^+$ (21), 354 (18), 325 (8), 300 (17), 260 (55), 241 (100), 228 (25), 213 (10), 200 (30), 185 (9), 111 (10), 97 (14), 85 (19), 71 (24), 57 (28), 43 (19); HREIMS *m/z*: 414.1791 (calcd for $C_{22}H_{26}N_2O_5$, 414.1791).

3.4.2. Jerantiphylline B (*3*)

Colorless oil; $[\alpha]_D$ −182 (*c* 0.07, $CHCl_3$); UV (EtOH), λ_{max} (log ε): 213 (4.33), 267 (3.86), 303 (3.49) nm; IR (dry film) ν_{max}: 3538, 3281, 1706 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS (probe) 70 eV, *m/z* (rel. int.): 416 $[M]^+$ (53), 401 $[M-Me]^+$ (29), 357 $[M-CO_2Me]^+$ (11), 329 (15), 299 (8), 247 (9), 225 (14), 196 (24), 176 (9), 162 (6), 124 (100), 109 (8); HREIMS *m/z*: 416.1939 (calcd for $C_{22}H_{28}N_2O_6$, 416.1947).

3.4.3. Jerantinine H (*5*)

Colorless oil; $[\alpha]_D$−156 (*c* 0.07, $CHCl_3$); UV (EtOH), λ_{max} (log ε): 210 (4.33), 235 (4.32), 305 (3.87) nm; IR (dry film) ν_{max}: 3534, 3391, 1745, 1596 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS (probe) 70 eV, *m/z* (rel. int.): 400 $[M]^+$ (11), 382 $[M-H_2O]^+$ (32), 353 $[M-H_2O-CH_2CH_3]^+$ (100), 339 (25), 312 (86), 297 (26), 283 (11), 254 (10); HREIMS *m/z*: 400.1986 (calcd for $C_{22}H_{28}N_2O_5$, 400.2000).



Scheme 1. Biomimetic conversion of **4** and **9** to their respective vincamine and 16-*epi*vincamine derivatives.

3.5. General procedure for the preparation of **10** and **11**

Alkaloid **4** or **9** (20 mg, 0.05 mmol) was dissolved in a mixture of Ac_2O (1 mL) and pyridine (1 mL) and stirred for 20 min. Water (10 mL) was then added and the mixture was basified to pH 9.0 using 10% Na_2CO_3 solution, followed by extraction with CH_2Cl_2. Concentration of the dried CH_2Cl_2 extract and centrifugal TLC (Et_2O/hexane 1:1) afforded the corresponding acetates.

3.5.1. Jerantinine E acetate (**10**)

Yield 86%; Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.58 (3H, *t*, *J* = 7.3 Hz, Me-18), 0.63 (1H, *m*, H-19a), 0.98 (1H, *dq*, *J* = 14.7 and 7.3 Hz, H-19b), 1.24 (1H, *m*, H-15a), 1.53 (1H, *m*, H-14a), 1.75 (1H, *dd*, *J* = 11.5 and 4.1 Hz, H-6a), 1.80 (2H, *m*, H-14b and H-15b), 2.04 (1H, *td*, *J* = 11.5 and 6.6 Hz, H-6b), 2.26 (1H, *dd*, *J* = 15.1 and 1.7 Hz, H-17a), 2.29 (3H, *s*, COMe), 2.41 (2H, *m*, H-3a and H-21), 2.54 (1H, *m*, H-5a), 2.68 (1H, *d*, *J* = 15.1 Hz, H-17b), 2.91 (1H, *t*, *J* = 7.0 Hz, H-5b), 3.10 (1H, *br d*, *J* = 10.8 Hz, H-3b), 3.76 (3H, *s*, CO_2Me), 3.80 (3H, *s*, 11-OMe), 6.48 (1H, *s*, H-12), 6.90 (1H, *s*, H-9), 8.89 (1H, *br s*, NH); EIMS (probe) 70 eV, *m/z* (rel. int.): 426 $[M]^+$ (20), 124 (100); HREIMS *m/z*: 426.2149 (calcd for $C_{24}H_{30}N_2O_5$, 426.2155).

3.5.2. Jerantinine A acetate (**11**)

Yield 87%; Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.64 (3H, *t*, *J* = 7.3 Hz, Me-18), 0.87 (1H, *dq*, *J* = 15 and 7.3 Hz, H-19a), 1.00 (1H, *dq*, *J* = 15 and 7.3 Hz, H-19b), 1.84 (1H, *dd*, *J* = 11.5 and 4.9 Hz, H-6a), 2.06 (1H, *td*, *J* = 11.5 and 7 Hz, H-6b), 2.30 (3H, *s*, COMe), 2.39 (1H, *d*, *J* = 15.1 Hz, H-17a), 2.54 (1H, *dd*, *J* = 15.1 and 1.5 Hz, H-17b), 2.63 (1H, *br s*, H-21), 2.67 (1H, *m*, H-5a), 3.03 (1H, *t*, *J* = 7 Hz, H-5b), 3.17 (1H, *d*, *J* = 15.9 Hz, H-3a), 3.43 (1H, *dd*, *J* = 15.9 and 4.6 Hz, H-3b), 3.77 (3H, *s*, CO_2Me), 3.81 (3H, *s*, 11-OMe), 5.70 (1H, *d*, *J* = 10 Hz, H-15), 5.78 (1H, *ddd*, *J* = 10, 4.6 and 1.5 Hz, H-14), 6.51 (1H, *s*, H-12), 6.93 (1H, *s*, H-9), 8.97 (1H, *br s*, NH); EIMS (probe) 70 eV, *m/z* (rel. int.): 424 $[M]^+$ (49), 393 $[M-OMe]^+$ (5), 317 (19), 275 (55), 260 (7), 242 (21), 216 (14), 200 (13), 135 (100), 122 (34), 107 (57), 93 (25), 81 (7); HREIMS *m/z*: 424.1994 (calcd for $C_{24}H_{28}N_2O_5$, 424.1998).

3.6. General procedure for the oxidation of **10** and **11** to their respective 16-hydroxyindolenine N-oxides

m-Chloroperbenzoic acid (24 mg, 0.137 mmol) was added over a 5 min period to a stirred solution of **10** or **11** (27 mg, 0.064 mmol) in dry toluene (2 mL) under a nitrogen atmosphere. After 10 min of continuous stirring at room temperature, 10% Na_2SO_3 solution (10 mL) was added to the reaction mixture and was left stirring for another 5 min. The solution was then extracted with Et_2O followed by with $CHCl_3$. The $CHCl_3$ extract was dried, concentrated under reduced pressure and subjected to centrifugal TLC ($CHCl_3$/MeOH, 9:1) to give the corresponding 16-hydroxyindolenine N-oxides.

3.6.1. 16-Hydroxyindolenine N-oxide **12**

Yield 75%; Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.70 (3H, *t*, *J* = 7.1 Hz, Me-18), 0.90 (1H, *dq*, *J* = 14.4 and 7.1 Hz, H-19a), 1.10 (1H, *dq*, *J* = 14.4 and 7.1 Hz, H-19b), 1.45 (1H, *td*, *J* = 13.5 and 3.2 Hz, H-15a), 1.56 (1H, *d*, *J* = 13.5 Hz, H-15b), 1.82 (1H, *m*, H-14a), 1.92 (1H, *m*, H-14b), 2.30 (1H, *d*, *J* = 16 Hz, H-17a), 2.45 (1H, *d*, *J* = 16 Hz, H-17b), 2.66 (1H, *dd*, *J* = 12.2 and 6.1 Hz, H-6a), 3.10 (1H, *td*, *J* = 12.2 and 7.1 Hz, H-6b), 3.73 (2H, *m*, H-3a and H-5a), 3.86 (1H, *br s*, H-21), 3.88 (3H, *s*, 11-OMe), 3.91 (3H, *s*, CO_2Me), 4.10 (1H, *m*, H-5b), 4.19 (1H, *d*, *J* = 12.9 Hz, H-3b), 7.07 (1H, *s*, H-12), 7.58 (1H, *s*, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.7 (C-18), 18.1 (C-14), 31.4 (C-15), 32.5 (C-19), 35.0 (C-6), 37.7 (C-20), 40.2 (C-17), 53.3 (CO_2Me), 55.8 (11-OMe), 59.0 (C-7), 64.9 (C-3), 65.0 (C-5), 73.4 (C-16), 88.7 (C-21), 104.8 (C-12), 111.1 (C-9), 137.0 (C-8), 143.4 (C-13), 148.0 (C-10), 148.4 (C-11), 174.0 (CO_2Me), 177.6 (C-2); FT-APCI-MS: *m/z* 417 $[M+H]^+$; HR-FT-APCI-MS *m/z*: 417.2020 (calcd for $C_{22}H_{28}N_2O_6$ + H, 417.2026).

3.6.2. 16-Hydroxyindolenine N-oxide **13**

Yield 79%; Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.72 (3H, *t*, *J* = 7.1 Hz, Me-18), 1.25 (1H, *dq*, *J* = 14.4 and 7.1 Hz, H-19a), 1.40 (1H, *dq*, *J* = 14.4 and 7.1 Hz, H-19b), 2.26 (1H, *d*, *J* = 15.8 Hz, H-17a), 2.52 (1H, *dd*, *J* = 15.8 Hz, H-17b), 2.92 (1H, *dd*, *J* = 12.4 and 6.6 Hz, H-6a), 3.04 (1H, *td*, *J* = 12.4 and 7.8 Hz, H-6b), 3.91 (3H, *s*, CO_2Me), 3.94 (3H, *s*, 11-OMe), 3.96 (1H, *br s*, H-21), 4.00 (2H, *m*, H-5a and H-5b), 4.43 (1H, *dt*, *J* = 17.8 and 2 Hz, H-3a), 4.61 (1H, *dd*, *J* = 17.8 and 4.4 Hz, H-3b), 5.59 (1H, *d*, *J* = 10.5 and 2 Hz, H-15), 5.69 (1H, *ddd*, *J* = 10.5, 4.4 and 2 Hz, H-14), 7.13 (1H, *s*, H-12), 7.87 (1H, *s*, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.5 (C-18), 32.8 (C-19), 33.0 (C-6), 40.9 (C-20), 45.8 (C-17), 53.3 (CO_2Me), 55.9 (11-OMe), 59.7 (C-7), 62.8 (C-3), 66.7 (C-5), 73.0 (C-16), 84.0 (C-21), 104.8 (C-12), 112.9 (C-9), 117.7 (C-14), 132.2 (C-15), 137.2 (C-8), 144.3 (C-13), 147.7 (C-10), 148.0 (C-11), 173.3 (CO_2Me), 177.2 (C-2); FT-APCI-MS: *m/z* 415 $[M+H]^+$; HR-FT-APCI-MS *m/z*: 415.1864 (calcd for $C_{22}H_{26}N_2O_6$ + H, 415.1869).

3.7. Reduction of **12** to jerantinine H (**5**)

A stirred solution of N-oxide **12** (12 mg, 0.029 mmol) in CH_2Cl_2 (3 mL) was treated with excess Ph_3P (82 mg, 0.31 mg) at room temperature in the dark. Stirring was continued for 46 h under nitrogen atmosphere. The reaction mixture was then subjected to centrifugal TLC (Et_2O) to give **5** (8.5 mg, 74%).

3.8. General procedure for the conversion of **12** and **13** to their respective vincamine and 16-epivincamine alkaloids

A solution of N-oxide **12** or **13** (20 mg, 0.048 mmol) and Ph_3P (60 mg, 0.23 mmol) in aqueous AcOH (1 mL) was stirred at room temperature for 1 h. The solution was washed with 10% Na_2CO_3, extracted with $CHCl_3$, concentrated under reduced pressure and subjected to centrifugal TLC (Et_2O, NH_3 saturated) to afford the corresponding vincamines and 16-*epi*vincamines.

3.8.1. 14,15-Didehydro-10-hydroxy-11-methoxyvincamine (**7**) and its 16-epimer **8**

Compound **7**: Yield 19%; Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.99 (3H, *t*, *J* = 7.6 Hz, Me-18), 1.61 (1H, *dq*, *J* = 14 and 7.6 Hz, H-19a), 1.94 (1H, *dq*, *J* = 14 and 7.6 Hz, H-19b), 2.31 (1H, *d*, *J* = 14.1 Hz, H-17a), 2.37 (1H, *d*, *J* = 14.1 Hz, H-17b), 2.50 (1H, *ddd*, *J* = 16.4, 6 and 1.7 Hz, H-6a), 3.00 (1H, *br d*, *J* = 17 Hz, H-3a), 3.01 (1H, *m*, H-6b), 3.09 (1H, *ddd*, *J* = 17, 4 and 2.0 Hz, H-3b), 3.32 (1H, *ddd*, *J* = 14.0, 10.6 and 6 Hz, H-5a), 3.37 (1H, *td*, *J* = 14.0 and 7.1 Hz, H-5b), 3.84 (3H, *s*, 11-OMe), 3.86 (3H, *s*, CO_2Me), 4.05 (1H, *br s*, H-21), 5.59 (1H, *ddd*, *J* = 10, 4 and 2.3 Hz, H-14), 5.74 (1H, *d*, *J* = 10 Hz, H-15), 6.57 (1H, *s*, H-12), 6.95 (1H, *s*, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.4 (C-18), 16.6 (C-6), 34.7 (C-19), 36.7 (C-20), 43.5 (C-17), 43.7 (C-3), 49.5 (C-5), 53.9 (CO_2Me), 56.3 (11-OMe), 57.4 (C-21), 82.1 (C-16), 93.8 (C-12), 102.8 (C-9), 105.8 (C-7), 122.6 (C-8), 125.7 (C-14), 127.9 (C-13), 128.0 (C-15), 130.1 (C-2), 141.4 (C-10), 143.9 (C-11), 173.1 (CO_2Me); EIMS *m/z* 398 $[M]^+$ (34), 380 $[M-H_2O]^+$ (40), 365 (16), 351 (100), 312 (58), 295 (18), 264 (10), 249 (7), 216 (23), 190 (7), 145 (5), 121 (7), 99 (24), 83 (10), 57 (7), 40 (20); HREIMS *m/z*: 398.1835 (calcd for $C_{22}H_{26}N_2O_5$, 398.1842).

Compound **8**: Yield 37%; Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95 (3H, *t*, *J* = 7.5 Hz, Me-18), 1.51 (1H, *dq*, *J* = 15 and 7.5 Hz, H-19a), 1.84 (1H, *dq*, *J* = 15 and 7.5 Hz, H-19b), 2.12 (1H, *d*, *J* = 14.1 Hz, H-17a), 2.48 (1H, *ddd*, *J* = 16.3, 6.4 and 1.7 Hz,

H-6a), 2.61 (1H, *d*, *J* = 14.1 Hz, H-17b), 3.05 (3H, *m*, H-3a, H-3b and H-6b), 3.25 (1H, *m*, H-5a), 3.38 (1H, *dd*, *J* = 13.9 and 6.8 Hz, H-5b), 3.49 (3H, *s*, CO_2Me), 3.85 (3H, *s*, 11-OMe), 3.94 (1H, *br s*, H-21), 5.27 (1H, *br d*, *J* = 10.2, H-15), 5.50 (1H, *dt*, *J* = 10.2 and 3.2 Hz, H-14), 6.94 (1H, *s*, H-9), 7.02 (1H, *s*, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.3 (C-18), 16.6 (C-6), 35.2 (C-19), 38.4 (C-20), 45.9 (C-17), 43.6 (C-3), 49.8 (C-5), 52.5 (CO_2Me), 56.4 (11-OMe), 57.1 (C-21), 84.1(C-16), 96.0 (C-12), 102.3 (C-9), 106.2 (C-7), 122.4 (C-8), 125.8 (C-14), 130.8 (C-13), 126.6 (C-15), 131.4 (C-2), 141.1 (C-10), 143.6 (C-11), 172.0 (CO_2Me); EIMS (probe) 70 eV, *m/z* (rel. int.): *m/z* 398 $[M]^+$ (100), 380 $[M-H_2O]^+$ (12), 369 $[M-CH_2CH_3]^+$ (32), 351 $[M-CH_2CH_3-H_2O]^+$ (34), 330 (49), 295 (65), 281 (25), 267 (14), 216 (22), 190 (16), 121 (16); HREIMS *m/z*: 398.1833 (calcd for $C_{22}H_{26}N_2O_5$, 398.1842).

*3.8.2. 10-Hydroxy-11-methoxyvincamine (**14**) and its 16-epimer **15***

Compound **14**: Yield 42%; Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (3H, *t*, *J* = 7.8 Hz, Me-18), 1.43 (4H, *m*, H-14a, H-15a, H-15b and H-19a), 1.69 (2H, *m*, H-14b and H-19b), 2.10 (1H, *d*, *J* = 14.1, H-17a), 2.21 (1H, *d*, *J* = 14.1, H-17b), 2.23 (1H, *m*, H-3a), 2.48 (1H, *m*, H-6a), 2.59 (1H, *m*, H-3b), 2.90 (1H, *m*, H-6b), 3.27 (2H, *m*, H-5a and H-5b), 3.82 (3H, *s*, 11-OMe), 3.86 (3H, *s*, CO_2Me), 3.88 (1H, *s*, H-21), 4.65 (1H, *br s*, 16-OH), 6.60 (1H, *s*, H-12), 6.97 (1H, *s*, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.7 (C-18), 17.0 (C-6), 20.8 (C-14), 25.1 (C-15), 28.9 (C-19), 35.2 (C-20), 44.4 (C-3), 44.6 (C-17), 51.0 (C-5), 54.4 (CO_2Me), 56.5 (11-OMe), 59.3 (C-21), 82.0 (C-16), 93.8 (C-12), 103.1 (C-9), 105.5 (C-7), 122.6 (C-8), 127.9 (C-13), 130.0 (C-2), 141.5 (C-10), 144.1 (C-11), 174.8 (CO_2Me); EIMS *m/z* 400 $[M]^+$ (100), 382 $[M-H_2O]^+$ (9), 353 $[M-H_2O-CH_2CH_3]^+$ (33), 339 (33), 313 (50), 298 (62), 283 (25), 270 (27), 255 (14), 243 (24), 230 (7), 216 (8); HREIMS *m/z*: 400.1991 (calcd for $C_{22}H_{28}N_2O_5$, 400.1998).

Compound **15**: Yield 8%; Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (3H, *t*, *J* = 7.8 Hz, Me-18), 1.24 (2H, *m*, H-14a and H-15a), 1.36 (3H, *m*, H-15b, H-14b and H-19a), 1.71 (1H, *m*, H-19b), 2.04 (1H, *d*, *J* = 15.1, H-17a), 2.12 (1H, *m*, H-3a), 2.45 (1H, *dd*, *J* = 16 and 5 Hz, H-6a), 2.58 (1H, *m*, H-3b), 2.63 (1H, *d*, *J* = 15.1 Hz, H-17b), 2.91 (1H, *m*, H-6b), 3.16 (1H, *td*, *J* = 13 and 5.9 Hz, H-5a), 3.27 (1H, *dd*, *J* = 13, 6.4 Hz, H-5b), 3.73 (3H, *s*, CO_2Me), 3.84 (3H, *s*, 11-OMe), 3.82 (1H, *s*, H-21), 6.87 (1H, *s*, H-9), 6.96 (1H, *s*, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.6 (C-18), 16.7 (C-6), 20.7 (C-14), 24.2 (C-15), 29.0 (C-19), 36.6 (C-20), 44.7 (C-3), 47.2 (C-17), 51.2 (C-5), 53.5 (CO_2Me), 56.5 (11-OMe), 59.1 (C-21), 83.1 (C-16), 95.6 (C-12), 102.6 (C-9), 105.9 (C-7), 122.1 (C-8), 128.5 (C-13), 129.6 (C-2), 141.3 (C-10), 143.9 (C-11), 172.6 (CO_2Me); EIMS *m/z* 400 $[M]^+$ (75), 382 $[M-H_2O]^+$ (11), 353 $[M-H_2O-CH_2CH_3]^+$ (41), 339 (32), 312 (34), 298 (100), 283 (27), 270 (16), 255 (8); HREIMS *m/z*: 400.1991 (calcd for $C_{22}H_{28}N_2O_5$, 400.1998).

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