Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6677–6680

Mersinaline and mersirachine, novel quinolinic alkaloids of the mersinine group from *Kopsia*

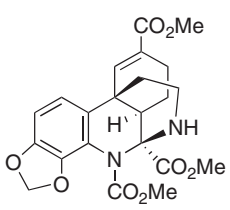
G. Subramaniam[†] and Toh-Seok Kam[*]

Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia

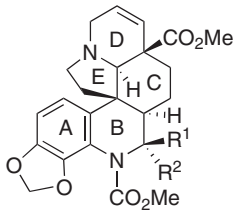
Received 6 June 2007; revised 2 July 2007; accepted 19 July 2007
Available online 27 July 2007

Abstract—Two quinolinic alkaloids belonging to the novel mersinine subclass were isolated from *Kopsia singapurensis*. The structures of these alkaloids were established by spectroscopic methods and possible biogenetic relationships between these and the mersinine alkaloids are presented.

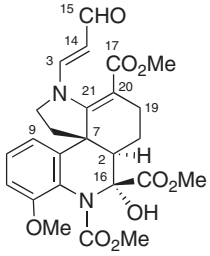
Plants of the genus *Kopsia*[1] (Apocynaceae) are well known as prodigious sources of structurally novel as well as biologically active alkaloids.[2–21] Recent examples of unusual alkaloids from *Kopsia*, which are notable for possessing novel ring systems and which were postulated to derive from known monoterpenoid indole precursors through pathways involving deep-seated rearrangements and/or loss of key fragments, include, inter alia, the cage indole arbophylline,[4] the three-nitrogen pentacyclic indole arboflorine,[5] the tetracyclic indole mersicarpine,[7] the tetracyclic quinolinic alkaloid, mersilongine (**1**),[8] and a pair of intriguing regioisomeric tetracyclic indoles, arboricine and arboricinine.[2] We also recently reported the isolation and structure elucidation of several alkaloids belonging to the novel mersinine subclass, as exemplified by mersinines A and B (**2**, **3**), which are characterized by a novel pentacyclic skeleton incorporating a quinolinic chromophore.[11,22] We now report the isolation and structure determination of two novel alkaloids **4** and **5**, bearing a biogenetic relationship to the mersinines, which were isolated from the same plant.[23]



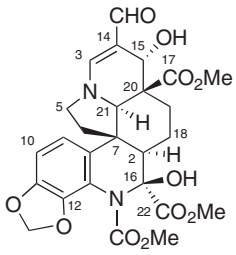
1



2 $R^1 = CO_2Me$, $R^2 = OH$
3 $R^1 = OH$, $R^2 = CO_2Me$



4



5

The *seco*-mersinine alkaloid, mersirachine (**4**) was obtained as a colorless oil, with $[\alpha]_D$ −50 ($CHCl_3$, *c* 0.05). The UV spectrum (EtOH) showed bands at 207, 235 (sh), 255 (sh), 284, and 334 nm, which were somewhat similar to that of mersinaline (**5**) (vide infra). The IR spectrum showed bands at 3458, 1746, and 1709 cm^{-1}, due to OH, ester, and conjugated carbonyl/carbamate functionalities, respectively. The EIMS showed a M^+ ion at *m*/*z* 500, which analyzed for $C_{25}H_{28}N_2O_9$.[24] The ^{13}C NMR spectral data (Table 1) showed the presence of 25 carbon resonances (four

Keywords: Quinolinic alkaloids; NMR; *Kopsia*; Apocynaceae.
* Corresponding author. Tel.: +60 3 79674266; fax: +60 3 79674193; e-mail: tskam@um.edu.my
† Present address: MerLion Pharmaceuticals, 1 Science Park Road, The Capricorn 05-01, Singapore Science Park II, Singapore 117528, Singapore.

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.122

Table 1. ^{1}H and ^{13}C NMR spectral data of **4** and **5**[a]

Position	4		5	
	δ_C	δ_H	δ_C	δ_H
2	50.9	2.40 dd (13.5, 2.5)	49.2	2.12 br d (13)
3	153.5	7.67 d (13.3)	153.7	7.27 s
5	47.3	3.20 td (12, 6)	51.2	3.76 m
5′		3.62 m		3.64 m
6	34.6	2.25 m	32.5	1.78 (12.5, 6.5)
6′		2.63 dd (12, 6)		3.14 m
7	50.2	—	44.6	—
8	136.0	—	135.2	—
9	117.7	6.34 dd (8, 1)	114.1	6.53 d (8.2)
10	126.6	7.11 t (8)	104.2	6.62 d (8.2)
11	111.5	6.89 dd (8, 1)	147.5	—
12	153.3	—	139.8	—
13	123.9	—	118.5	—
14	108.5	5.47 dd (13.3, 8)	115.5	—
15	190.7	9.36 d (8)	64.2	4.87 s
16	85.2	—	86.2	—
17	167.0		172.3	—
18α	19.7	2.01 br dd (13.5, 6)	20.0	1.44 m
18β		0.88 m		1.51 m
19α	26.4	2.25 m	26.5	1.59 br t (13)
19β		2.56 dd (18.3, 6)		2.29 br d (13)
20	108.0	—	50.4	—
21	150.8	—	61.4	3.98 s
22	172.4	—	172.1	—
CHO	—	—	187.5	9.01 s
12-OMe	56.2	3.84 s	—	—
17-OMe	51.7	3.77 s	52.2	3.60 s
22-OMe	53.8	3.90 s	53.4	3.82 s
$N$$CO_2$Me	53.4	3.75 s	53.7	3.82 s
$N$$CO_2$Me	156.6	—	153.7	—
OCH_2O	—	—	101.4	5.96 br s; 6.00 br s
16-OH	—	4.31 s	—	5.10 br s

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC and HMBC.

methyls, four methylenes, seven methines, and 10 quaternary carbons). In addition to the carbamate and methyl ester functions indicated by the carbon resonances at δ 156.6 and 172.4, respectively, two other carbonyl signals were observed, one due to a conjugated ester at δ 167.0, and the other due to a conjugated aldehyde at δ 190.7. Furthermore, two double bonds were indicated, a 1,2-disubstituted double bond (δ 108.5, 153.5) and a tetrasubstituted double bond (δ 108.0, 150.8). The characteristic quaternary C-16, associated with substitution by an OH and a methyl ester group was observed at δ 85.2.[11] The ^{1}H NMR spectrum (Table 1) indicated an aromatic moiety substituted by a methoxy group at C-12 (δ 3.84; NOE between OMe and H-11), a carbamate function (δ 3.75), a trans-double bond (δ 5.47, 7.67, $J = 13.3$ Hz; NOE between H-15 and H-3, H-14), an α,β-unsaturated aldehyde (δ 9.36), a C(16)–OH (δ 4.31), a methyl ester group (δ 3.90; linked to C-16), and a conjugated methyl ester (δ 3.77). The relative configuration at C-16 was deduced to be *R*, as indicated by the characteristic C(16)–OH and C-2 chemical shifts at δ_H 4.31 and δ_C 50.9, respectively.[11] The COSY spectrum showed the presence of NCH_2CH_2, $CHCH_2CH_2$ and NCH=CHCHO partial structures, while the isolated aminomethine normally associated with C-21 was not observed. These NMR data suggested that the A, B, C, and E rings of the mersinine-type skeleton were intact, with a double bond from C-20 to C-21 constituting part of the α,β-unsaturated methyl ester moiety. The α,β-unsaturated aldehyde fragment is therefore linked to *N*(4), constituting a vinylogous amide unit. These conclusions are supported by the HMBC data (H-5/C-7; H-6/C-2, C-21; H-18/C-20; H-19/C-2; H-3/C-15).

Mersinaline (**5**) was obtained as a light yellowish oil, with $[\alpha]_D$ +98 ($CHCl_3$, *c* 0.15). The UV spectrum (EtOH) showed bands at 205, 215, 225 (sh), 240 (sh), and 300 nm, suggestive of additional conjugation compared to the mersinines.[11] The IR spectrum showed bands due to OH (3455, 3329 cm^{-1}), ester carbonyl (1736 cm^{-1}, broad), and carbamate and/or α,β-unsaturated aldehyde (1714 cm^{-1}) functionalities. The EIMS showed a M^+ ion at *m*/*z* 544, which analyzed for $C_{26}H_{28}N_2O_{11}$.[25] The ^{13}C NMR spectral data showed the presence of 26 carbon resonances (three methyls, five methylenes, seven methines, and 11 quaternary carbons). Two methyl ester functions were indicated by the resonances at δ 172.3 and 172.1, a carbamate by the resonance at δ 153.7, a conjugated aldehyde from the resonance at δ 187.5, and the characteristic quaternary C-16 resonance at δ 86.2, associated with substitution by an OH and a methyl ester group.[11] The ^{1}H NMR spectrum indicated an aromatic moiety substituted by a methylenedioxy function at C-11 and C-12

(δ_H 5.96, 6.00; δ_C 101.4), in addition to two methoxy signals associated with the methyl ester and carbamate groups (one ester and the carbamate methyl signals were overlapped at δ 3.82, the other ester methyl signal was observed at δ 3.60). A trisubstituted double bond was indicated from the lone vinylic signal at δ 7.27 (signal overlapped with residual $CHCl_3$, δ_C 153.7); the other quaternary olefinic resonance was observed at δ 115.5. An aldehyde-H signal was observed at δ 9.01 (δ_C 187.5), the upfield shift of both the ^1H and ^{13}C resonances suggesting conjugation with the trisubstituted olefinic moiety. The presence of an isolated oxymethine was indicated by the observed resonance at δ 64.2 (δ_H 4.87, s), although the OH signal itself was not observed.

The COSY and HMQC data indicated the presence of two fragments, namely, NCH_2CH_2, $CHCH_2CH_2$, in addition to an isolated aminomethine corresponding to C-21, an isolated oxymethine, and a vinylogous amide unit incorporating a trisubstituted double bond (*N*CH=C(CHO)–). The former two fragments correspond to the usual C(5)–C(6) and C(2)–C(18)–C(19) fragments present in the mersinine-type compounds, and together with the NMR data suggested that while rings A, B, C and E were intact, the piperidine ring D had undergone substantial changes.

The presence of the vinylogous amide unit associated with *N*(4) was clearly indicated by the three-bond

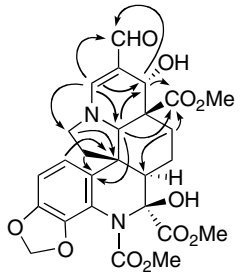


Figure 1. Selected HMBCs of **5**.

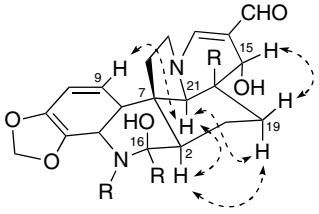
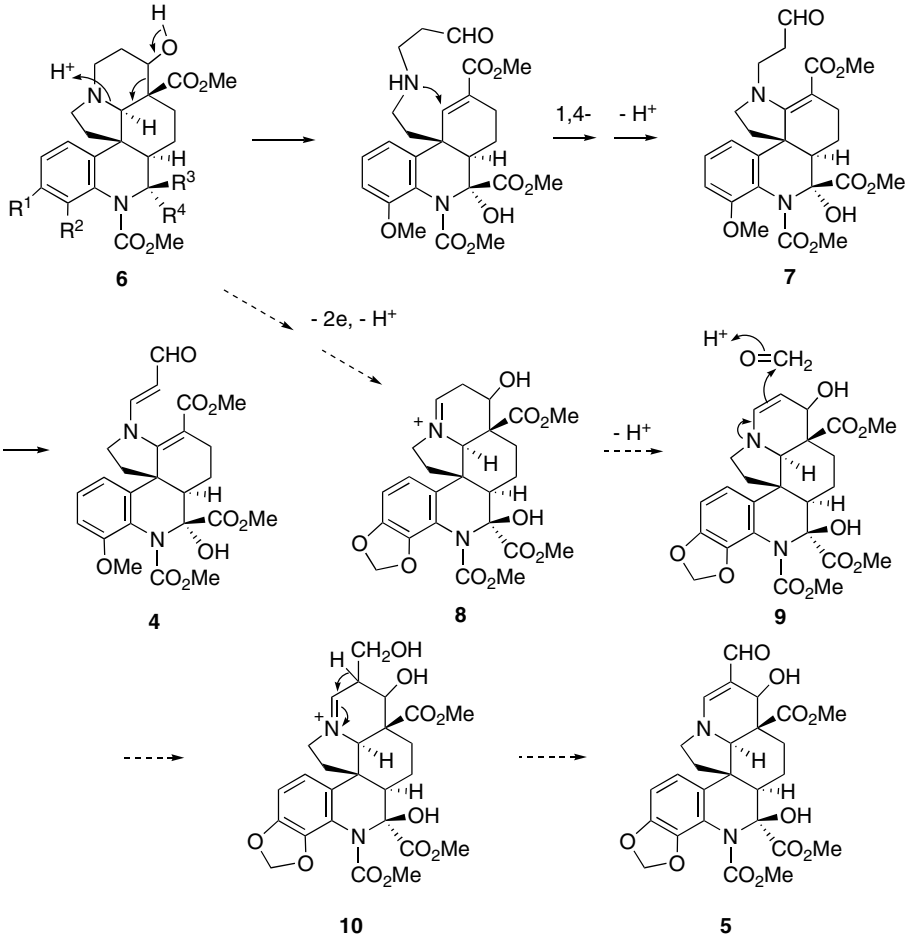


Figure 2. Selected NOEs of **5** (R = CO_2Me).



Scheme 1.

correlations from the vinylic H-3 to C-5 and C-21, and the observed CHO/H-3 NOE, while the H-3 to the oxymethine C-15, and H-15 to the aldehyde carbonyl correlations, indicated that the oxymethine C-15 was linked to the olefinic C-14. Attachment of the oxymethine C-15 to the quaternary C-20 (from the H-21/C-15, H-19/C-17 HMBCs) completes the assembly of the molecule, which is in accord with the full HMBC data (Fig. 1). The observed H-9/H-21, H-2/H-21, H-2/H-19α, and H-21/H-19α reciprocal NOEs (Fig. 2) established the relative configurations at C-7, C-21, C-2, and C-20, while the 16*S* configuration was defined by the characteristic C(16)–OH and C-2 chemical shifts at δ_H 5.10 and δ_C 49.2, respectively.[11]

The stereochemistry of the C(15)–OH was deduced to be α from the observed NOE between H-15 and H-19β. Mersinaline represents a new variation in the mersinine series having incorporated an additional carbon in the form of a formyl group, constituting part of a vinylogous amide unit associated with *N*(4).

We previously proposed that the novel tetracyclic indole mersilongine (**1**), isolated from the same plant is derived from a mersinine-type precursor, which on successive Grob fragmentation, followed by retro-Michael elimination of acrolein, followed in turn by an intramolecular primary amine-iminium ion reaction, leads to **1**.[8] In the present case, we propose that both mersirachine and mersinaline are derived from a similar mersinine-type precursor, **6** (Scheme 1). Thus, the product of the Grob fragmentation, instead of undergoing protonation followed by elimination of acrolein in a retro-Michael reaction en route to mersilongine, undergoes instead, intramolecular conjugate addition to the α,β-unsaturated ester moiety, leading to the tetracyclic amino aldehyde **7**, which on subsequent oxidation or dehydrogenation yields the *seco*-mersinine compound, the *E*-vinylogous amide **4**, corresponding to mersirachine. Alternatively, oxidation of **6** leads to the iminium ion intermediate **8**, which on deprotonation yields enamine **9**.[19] An intermolecular enamine-formaldehyde reaction then follows to provide the pentacyclic imino 1,3-diol **10**, which on subsequent deprotonation, followed by oxidation yields mersinaline (**5**). The present isolation of mersinaline (**5**) and the *seco*-compound mersirachine (**4**), as well as the previous isolation of the novel alkaloid mersilongine (**1**),[8] provide firm support for the proposed biogenetic origin of these compounds from a common mersinine-type precursor **6**.

Acknowledgments

We would like to thank the University of Malaya and MOSTI Malaysia (ScienceFund) for financial support and Dr. David Middleton, Herbarium, Royal Botanic Garden, Edinburgh, 20A Inverleith Row, EH3 5LR Scotland, for identification of plant material. Mass spectral measurements were carried out at OIC Organic Mass Spectrometry, University of Tasmania, Tasmania, Australia.

References and notes

1. Middleton, D. J. *Harvard Pap. Bot.* **2004**, *9*, 89–142.
2. Lim, K. H.; Komiyama, K.; Kam, T. S. *Tetrahedron Lett.* **2007**, *48*, 1143–1145.
3. Lim, K. H.; Kam, T. S. *Helv. Chim. Acta* **2007**, *90*, 31–35.
4. Lim, K. H.; Kam, T. S. *Tetrahedron Lett.* **2006**, *47*, 8653–8655.
5. Lim, K. H.; Kam, T. S. *Org. Lett.* **2006**, *8*, 1733.
6. Lim, K. H.; Low, Y. Y.; Kam, T. S. *Tetrahedron Lett.* **2006**, *47*, 5037–5039.
7. Kam, T. S.; Subramaniam, G.; Lim, K. H.; Choo, Y. M. *Tetrahedron Lett.* **2004**, *45*, 5995.
8. Kam, T. S.; Subramaniam, G. *Tetrahedron Lett.* **2004**, *45*, 3521.
9. Kam, T. S.; Choo, Y. M. *Helv. Chim. Acta* **2004**, *87*, 991.
10. Kam, T. S.; Choo, Y. M. *Tetrahedron Lett.* **2003**, *44*, 1317.
11. Kam, T. S.; Subramaniam, G.; Lim, T. M. *Tetrahedron Lett.* **2001**, *42*, 5977.
12. Kam, T. S.; Lim, T. M.; Choo, Y. M. *Tetrahedron* **1999**, *55*, 1457.
13. Kam, T. S.; Subramaniam, G.; Sim, K. M.; Yoganathan, K.; Koyano, T.; Toyoshima, M.; Rho, M. C.; Hayashi, M.; Komiyama, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2769.
14. Kam, T. S.; Yoganathan, K.; Chen, W. *Tetrahedron Lett.* **1996**, *37*, 3603.
15. Kam, T. S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765.
16. Kam, T. S.; Yoganathan, K.; Chuah, C. H. *Tetrahedron Lett.* **1995**, *36*, 759.
17. Kam, T. S.; Yoganathan, K.; Chuah, C. H. *Tetrahedron Lett.* **1994**, *35*, 4457.
18. Kam, T. S.; Yoganathan, K.; Chuah, C. H. *Tetrahedron Lett.* **1993**, *34*, 1819.
19. Kam, T. S.; Lim, T. M.; Tan, G. H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1594.
20. Uzir, S.; Mustapha, A. M.; Hadi, A. H. A.; Awang, K.; Wiart, C.; Gallard, J. F.; Pais, M. *Tetrahedron Lett.* **1997**, *38*, 1571.
21. Awang, K.; Sevenet, T.; Hadi, A. H. A.; David, B.; Pais, M. *Tetrahedron Lett.* **1992**, *33*, 2493.
22. From a biogenetic viewpoint, these compounds may be envisaged to have arisen from an aspidofractinine precursor via cleavage and ring opening of an aziridinium intermediate.
23. The plant was in the first instance tentatively identified as *K. fruticosa* by Dr. D. Middleton but was subsequently amended to *K. singapurensis* on completion of his review on *Kopsia*.[1]
24. HREIMS found *m*/*z* 500.1794 (calcd for $C_{25}H_{28}N_2O_9$, 500.1795).
25. HREIMS found *m*/*z* 544.1686 (calcd for $C_{26}H_{28}N_2O_{11}$, 544.1693).