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Methyl chanofruticosinate alkaloids from *Kopsia arborea*

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Abstract

Six alkaloids belonging to the methyl chanofruticosinate group, viz., prunifolines A–F, in addition to six other known methyl chanofruticosinate alkaloids, were isolated from the leaf extract of *Kopsia arborea*. The structures were determined using NMR and MS analysis and comparison with known related compounds.

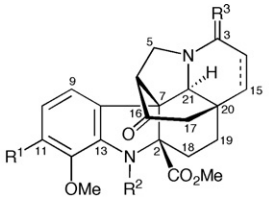
Keywords: *Kopsia* species; Apocynaceae; Indole alkaloids

1. Introduction

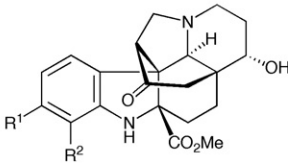
We have previously reported the presence of four methyl chanofruticosinate alkaloids from the leaf extract of *Kopsia arborea* Blume (Kam et al., 1993), one of about 16 species that occur in Malaysia (Middleton, 2004). The bark extract of this species has yielded a number of interesting alkaloids with intriguing carbon skeletons (Lim et al., 2006, 2007; Lim and Kam, 2007, 2006; Kam et al., 2004). We now wish to report the isolation of additional new alkaloids of the methyl chanofruticosinate type from a second study of the leaf extract of the same species, but involving a different collection of plant material.

2. Results and discussion

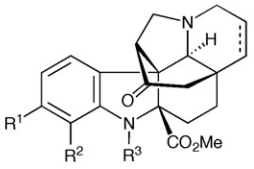
A total of 12 methyl chanofruticosinate type alkaloids, including six new derivatives (**1–6**), were obtained in the present study. To avoid the cumbersome naming system previously adopted based on methyl chanofruticosinate as the base name (Kam et al., 1993; Husain et al., 2001, 2003; Zhou et al., 2006; Chen et al., 1981), we designate the six new alkaloids, **1–6**, prunifolines A–F, respectively. In addition, six other known alkaloids (**7–12**) were also obtained.



1 R^1 = H, R^2 = CO_2Me, R^3 = O
2 R^1 = OMe, R^2 = CO_2Me, R^3 = H_2, $\Delta^{14,15}$
3 R^1 = R^2 = H, R^3 = H_2, $\Delta^{14,15}$



4 R^1 = R^2 = H
5 R^1, R^2 = OCH_2O
6 R^1 = H, R^2 = OMe



7 R^1 = H, R^2 = OMe, R^3 = CO_2Me
8 R^1 = R^2 = OMe, R^3 = CO_2Me
9 R^1 = R^2 = R^3 = H
10 R^1, R^2 = OCH_2O, R^3 = CO_2Me
11 R^1, R^2 = OCH_2O, R^3 = H
12 R^1, R^2 = OCH_2O, R^3 = H, $\Delta^{14,15}$
13 R^1, R^3 = H, R^2 = OMe

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Table 1
^{1}H NMR spectral data for **1**–**6** (400 MHz, $CDCl_3$)[a]

H	1	2	3	4	5	6
3	–	3.27 *dt* (16, 3)	3.39 *dt* (19, 3)	2.84 *dd* (15, 5)	2.83 *dd* (14, 5)	2.84 *dd* (15, 5)
3′	–	3.38 *dt* (16, 3)	3.84 *ddd* (19, 3, 2)	3.28 *td* (15, 3)	3.30 *m*	3.29 *td* (15, 3)
5α	4.26 *dd* (13.1, 5)	4.16 *dd* (11, 6)	4.16 *dd* (11, 6)	3.80 *dd* (11, 6)	3.72 *dd* (11, 6)	3.79 *dd* (11, 6)
5β	3.95 *d* (13.1)	2.86 *d* (11)	2.85 *d* (11)	2.94 *d* (11)	2.92 *d* (11)	2.94 *d* (11)
6	3.33 *d* (5)	3.11 *d* (6)	3.32 *d* (6)	3.34 *d* (6)	3.29 *m*	3.36 *d* (6)
9	6.97 *dd* (8, 1)	6.95 *d* (8)	6.86 *dd* (8, 1)	7.10 br *d* (8)	6.61 *d* (8)	6.77 *m*
10	7.05 *t* (8)	6.58 *d* (8)	6.79 *t* (8)	6.79 *td* (8, 1)	6.32 *d* (8)	6.78 *m*
11	6.92 *dd* (8,1)	–	6.72 *dd* (8, 1)	7.08 *td* (8, 1)	–	6.71 *m*
12	–	–	–	6.73 br *d* (8)	–	–
14α	2.42 *m*	5.61 *dt* (10, 3)	5.60 *dt* (10, 3)	1.41 *dt* (15, 3)	1.40 *dt* (14, 3)	1.41 *dt* (15, 3)
14β	2.42 *m*	–	–	2.26 *tdd* (15, 5, 3)	2.27 *tdd* (14, 5, 3)	2.30 *tdd* (15, 5, 3)
15	1.67 *m*	5.97 *dt* (10, 3)	5.97 *ddd* (10, 3, 2)	3.66 br *t* (3)	3.67 br *t* (3)	3.66 br *s*
15′	1.76 *dd* (11, 2)	–	–	–	–	–
17α	2.06 *d* (18)	2.36 *d* (18)	2.33 *d* (18)	2.09 *d* (19)	2.07 *d* (19)	2.09 *d* (19)
17β	2.23 *d* (18)	2.50 *d* (18)	2.48 *d* (18)	2.58 *d* (19)	2.60 *d* (19)	2.59 *d* (19)
18α	3.24 *dt* (16.5, 3.5)	1.63 *m*	1.98 *ddd* (13, 4, 2)	1.99 *ddd* (15, 5, 2)	2.00 *ddd* (15, 5, 2)	2.05 *ddd* (15, 5, 2)
18β	1.93 *ddd* (16.5, 14, 4)	1.44 *td* (13, 4)	1.83 *m*	1.83 *ddd* (15, 13, 5)	1.84 *ddd* (15, 13, 5)	1.84 *ddd* (15, 13, 5)
19α	1.43 *td* (14, 4)	1.92 *ddd* (16, 13, 4)	1.94 *dd d* (16, 13, 4)	1.18 *ddd* (13, 5, 2)	1.18 *ddd* (13, 5, 2)	1.19 *ddd* (13, 5, 2)
19β	1.84 *dt* (14, 3.5)	1.63 *m*	1.56 *ddd* (12, 4, 2)	2.17 *td* (13, 5)	2.19 *td* (13, 5)	2.22 *td* (13, 5)
21	3.37 *s*	2.61 *s*	2.65 *s*	3.03 *s*	3.00 *s*	3.06 *s*
*N*H	–	–	4.64 br *s*	4.53 br *s*	4.52 br *s*	4.64 br *s*
11-OMe	–	3.80 *s*	–	–	–	–
12-OMe	3.89 *s*	3.77 *s*	3.84 *s*	–	–	3.84 *s*
CO_2Me	3.60 *s*	3.57 *s*	3.62 *s*	3.60 *s*	3.63 *s*	3.61 *s*
NCO_2Me	3.86 *s*	3.83 *s*	–	–	–	–
OCH_2O	–	–	–	–	5.87 *d* (1.4)	–
	–	–	–	–	5.92 *d* (1.4)	–

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

Table 2
^{13}C NMR spectral data for **1**–**6** (100 MHz, $CDCl_3$)[a]

C	1	2	3	4	5	6
2	76.4	78.2	74.2	73.6	74.4	74.2
3	175.2	51.0	50.4	41.2	40.3	41.2
5	50.8	59.4	59.5	52.2	52.2	52.3
6	52.5	53.5	54.5	55.3	55.5	55.4
7	58.6	60.2	58.5	58.1	58.0	58.7
8	134.8	[b]	133.7	132.8	130.0	134.1
9	114.6	118.5	119.8	123.8	116.5	116.4
10	124.8	107.7	116.0	119.7	100.2	120.3
11	112.8	153.2	110.0	128.1	148.1	110.0
12	148.6	138.4	145.5	110.1	131.6	145.4
13	130.6	134.8	137.0	147.7	129.0	136.7
14	29.0	125.0	126.1	24.9	24.7	24.7
15	32.4	135.9	136.1	70.9	71.2	71.2
16	204.9	205.4	207.8	208.0	207.9	208.0
17	46.2	47.0	47.0	43.2	43.2	43.3
18	22.6	23.2	27.3	27.3	27.5	27.5
19	32.3	32.8	32.0	30.3	30.2	30.3
20	38.7	36.7	37.1	40.1	40.3	40.2
21	66.9	66.9	65.8	61.8	61.7	61.9
11-OMe	–	56.0	–	–	–	–
12-OMe	55.9	60.1	54.5	–	–	55.5
CO_2Me	52.4	52.7	52.3	52.2	52.3	52.3
CO_2Me	170.5	171.3	175.0	174.8	174.6	174.8
NCO_2Me	52.6	53.2	–	–	–	–
NCO_2Me	152.5	153.8	–	–	–	–
OCH_2O	–	–	–	–	101.0	–

[a] Assignments based on HMQC and HMBC.
[b] Not observed.

Prunifoline A (**1**) was obtained as a colourless oil, $[\alpha]_D + 230°$ ($CHCl_3$, *c* 0.15). The UV spectrum showed absorption maxima at 214, 250 and 290 nm, characteristic of a dihydroindole chromophore, while the IR spectrum indicated the presence of ketone (1740 cm^{-1}), ester/carbamate (1717 cm^{-1}) and lactam (1670 cm^{-1}) functions. The mass spectrum showed a molecular ion at *m/z* 454, while the base peak was observed at *m/z* 395, which corresponds to loss of CO_2Me, indicating the presence of a methyl ester group. HREIMS measurements established the molecular formula as $C_{24}H_{26}N_2O_7$. The NMR data of **1** (Tables 1 and 2) was generally similar to that of methyl-12-methoxychanofruticosinate (**7**) (Husain et al., 2001), except that the usual C(3)–C(14)–C(15) fragment is now replaced by a CH_2CH_2 fragment corresponding to C(14)–C(15). Moreover, the H(14) resonance (δ 2.42) indicated that C(14) is adjacent to a carbonyl function. These observations coupled with the presence of a lactam carbonyl function (δ_C 175.2) from the ^{13}C NMR spectrum (Table 2), suggested that **1** is the 3-oxo derivative of **7**. This is in accord with the HMBC data (three-bond correlations from H(5) and H(21) to C(3)), as well as from the observed anisotropic effect of the carbonyl function on the C(5) hydrogens, which have been shifted downfield (Husain et al., 2003).

Prunifoline B (**2**) was obtained in small amount as a colourless oil, $[\alpha]_D + 51°$ ($CHCl_3$, *c* 0.07). The UV spectrum showed absorption maxima at 220, 247 and 280 nm, while the IR spectrum showed absorption bands at 1741 and

1716 cm^{-1} due to ketone and ester/carbamate functions, respectively. The mass spectrum showed a molecular ion at *m/z* 468 ($C_{25}H_{28}N_2O_7$), which is two mass units less than that of methyl-11,12-dimethoxychanofruticosinate (**8**) (Husain et al., 2001). Other major fragments were observed at *m/z* 440 ($M-CH_2CH_2$) and 409 ($M-CO_2Me$). Compound **2** is readily deduced to be the 14,15-dehydro derivative of **8** from examination of the ^1H and ^{13}C NMR spectra (Tables 1 and 2) which indicated the presence of a 14,15-double bond (δ_H 5.61, 5.97; δ_C 125.0, 135.9) as the main change when compared with **8**. Apart from these differences, the NMR spectral data of **2** (Tables 1 and 2) are essentially similar to those of **8**.

Prunifoline C (**3**) was obtained as a colourless oil, $[\alpha]_D + 226°$ ($CHCl_3$, *c* 0.51). The UV spectrum showed absorption maxima at 206, 235 and 292 nm, while the IR spectrum showed absorption bands at 3353, 1720 and 1715 cm^{-1} due to *N*H, ketone and ester functions, respectively. The mass spectrum showed a molecular ion at *m/z* 380 ($C_{22}H_{24}N_2O_4$), which is two mass units less than that of methyl-12-methoxy-*N*(1)-decarbomethoxychanofruticosinate (**13**). The NMR data of **3** (Tables 1 and 2) was generally similar to that of **13** (Husain et al., 2001), except for the presence of signals due to the 14,15-double bond. Prunifoline C (**3**), is therefore the 14,15-dehydro derivative of **13**.

Three alkaloids prunifolines D–F (**4–6**) are distinguished by the presence of an OH substituent at C(15), representing the first instance of such functionalization in the piperidine ring in compounds of this group. Prunifoline D (**4**) was obtained as a colourless oil, $[\alpha]_D + 214°$ ($CHCl_3$, *c* 0.30). The UV spectrum (205, 236 and 293 nm) was similar to that of methyl-*N*(1)-decarbomethoxychanofruticosinate (**9**) (Kam et al., 1993) showing absorptions characteristic of a dihydroindole chromophore. The IR spectrum showed absorption bands at 3445, 3353, 1722 and 1713 cm^{-1} due to OH, *N*H, ketone and ester functions, respectively. The EIMS of **4** showed a molecular ion at *m/z* 368 which analyzed for $C_{21}H_{24}N_2O_4$, differing from **9** by addition of 16 mass units, consistent with replacement of a hydrogen by an OH group. This was further supported by the ^1H and ^{13}C NMR spectral data (Tables 1 and 2) which showed a close correspondence with those of **9** (Kam et al., 1993) except for some notable differences. For instance the H(21) signal (Table 1) has undergone a significant downfield shift from δ 2.50 to 3.03. The same was true of the C(15) signal (Table 2) which has been shifted downfield from δ 34.9 to 70.9. This is due to the presence of an OH group at C(15) which accounts for the observed carbon shift. The α-stereochemistry of the C(15)–OH is supported by the observed paramagnetic deshielding of the spatially proximate H(21) (Kam et al., 2001; Bisset et al., 1973). Further confirmation of the configuration at C(15) was provided by the reciprocal NOEs observed between H(15) and H(17β), requiring H(15) to be β.

Prunifoline E (**5**), $[\alpha]_D + 166°$ ($CHCl_3$, *c* 0.33), was readily identified as the 11,12-methylenedioxy-substituted derivative of **4** from the NMR spectral data (Tables 1 and 2). The mass spectrum yielded a M^+ at *m/z* 412 (HRMS *m/z* 412.1634), which analyzed for $C_{22}H_{24}N_2O_6$. The NMR spectral data (Tables 1 and 2) are similar in all respects to those of **3** except for the aromatic region, which indicated the presence of a methylenedioxy substituent at C(11) and C(12).

Similarly prunifoline F (**6**), $[\alpha]_D + 261°$ ($CHCl_3$, *c* 0.12) is readily shown to be the 12-methoxy derivative of **4**. The mass spectrum showed a M^+ at *m/z* 398 which analyzed for $C_{22}H_{26}N_2O_5$, differing from **4** by the substitution of a hydrogen with a methoxy group. The ^1H and ^{13}C NMR spectral data (Tables 1 and 2) of **6** are essentially similar to those of **4**, except for the replacement of an aromatic hydrogen with an additional methoxy function. Comparison of the aromatic carbon shifts with those of the appropriate dihydroindole derivatives, such as **7** (Husain et al., 2001), allows the placement of the methoxy function to be at C(12).

3. Experimental

3.1. General

Optical rotations were determined on a JASCO P-1020 digital polarimeter or an Atago Polax-D polarimeter. IR spectra were recorded on a Perkin–Elmer RX1 FT-IR spectrophotometer. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. ^1H 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. ESI-MS were obtained on a Perkin Elmer API 100 instrument. EIMS and HREIMS were obtained at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia.

3.2. Plant material

Plant material was collected in Petaling Jaya, Malaysia, and identification was confirmed by Dr. David Middleton, Herbarium, Royal Botanic Garden, Edinburgh, 20A Inverleith Row, EH3 5LR. Scotland. Herbarium voucher specimens (K 668) are deposited at the Herbarium, University of Malaya, Kuala Lumpur, Malaysia, and at Edinburgh.

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). Extraction of 8 kg of leaves gave about 20 g of basic mixture. The alkaloids were isolated by initial column chromatography on silica gel using $CHCl_3$ with increasing proportions of MeOH followed by rechromatography of appropriate partially resolved fractions using centrifugal TLC. Solvent systems used for

centrifugal TLC were Et_2O (NH_3-saturated), Et_2O/hexane (1:1, NH_3-saturated), Et_2O/hexane (3:1, NH_3-saturated), Et_2O/hexane (5:1, NH_3-saturated), EtOAc/hexane (1:1, NH_3-saturated), EtOAc/hexane (1:3, NH_3-saturated), EtOAc/hexane (2:3, NH_3-saturated) and EtOAc/hexane (3:2, NH_3-saturated). The yields ($g\,kg^{-1}$) of the alkaloids were as follows: **1** (0.003), **2** (0.0009), **3** (0.005), **4** (0.003), **5** (0.001), **6** (0.003), methyl-12-methoxychanofruticosinate (**7**) (0.027), methyl-11,12-dimethoxychanofruticosinate (**8**) (0.002) (Husain et al., 2001), methyl-*N*(1)-decarbomethoxychanofruticosinate (**9**) (0.103), methyl-11,12-methylenedioxychanofruticosinate (**10**) (0.077), methyl-11,12-methylenedioxy-*N*(1)-decarbomethoxychanofruticosinate (**11**) (0.166) and methyl-11,12-methylenedioxy-*N*(1)-decarbomethoxy-$\Delta^{14,15}$-chanofruticosinate (**12**) (0.020) (Kam et al., 1993).

Prunifoline A (**1**), colourless oil, $[\alpha]_D = +230°$ ($CHCl_3$, *c* 0.15); UV (EtOH), λ_{max} (log ε): 214 (4.77), 250 (4.13), 290 (3.53) nm; IR (dry film) ν_{max} 1740, 1717, 1670 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 454 $[M]^+$, (31), 395 $[M-CO_2Me]^+$ (100), 363 (16), 335 (59), 307 (9), 266 (4), 224 (6); HREIMS *m/z* 454.1747 (calc. for $C_{24}H_{26}N_2O_7$, 454.1740).

Prunifoline B (**2**), colourless oil, $[\alpha]_D + 51°$ ($CHCl_3$, *c* 0.07); UV (EtOH), λ_{max} (log ε): 220 (4.45), 247 (3.93), 280 (3.22) nm; IR (dry film) ν_{max} 1741, 1716 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 468 $[M]^+$ (3), 440 $[M-CH_2CH_2]^+$ (24), 409 $[M-CO_2Me]^+$ (13), 381 (100), 349 (16), 321 (30), 293 (12); HREIMS *m/z* 468.1899 (calc. for $C_{25}H_{28}N_2O_7$, 468.1897).

Prunifoline C (**3**), colourless oil, $[\alpha]_D + 226°$ ($CHCl_3$, *c* 0.51); UV (EtOH), λ_{max} (log ε): 206 (4.48), 235 (3.88), 292 (3.39) nm; IR (dry film) ν_{max} 3353, 1720, 1715 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 380 $[M]^+$ (8), 321 $[M-CO_2Me]^+$ (100), 291 (42), 236 (13); HREIMS *m/z* 380.1739 (calc. for $C_{22}H_{24}N_2O_4$, 380.1736).

Prunifoline D (**4**), colourless oil, $[\alpha]_D + 214°$ ($CHCl_3$, *c* 0.30); UV (EtOH), λ_{max} (log ε): 205 (4.40), 236 (3.80), 293 (3.43) nm; IR (dry film) ν_{max} 3445, 3353, 1722, 1713 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 368 $[M]^+$ (7), 339 (7), 309 $[M-CO_2Me]^+$ (100), 291 (2), 265 (9), 222 (4), 210 (8), 195 (5), 182 (16), 168 (8); HREIMS *m/z* 368.1732 (calc. for $C_{21}H_{24}N_2O_4$, 368.1736).

Prunifoline E (**5**), colourless oil, $[\alpha]_D = +166°$ ($CHCl_3$, *c* 0.33); UV (EtOH), λ_{max} (log ε): 219 (4.16), 239 (3.93), 285 (3.00) nm; IR (dry film) ν_{max} 3443, 3347, 1723, 1712 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 412 $[M]^+$ (13), 353 $[M-CO_2Me]^+$ (100), 309 (22), 254 (10), 226 (17), 212 (5), 182 (7), 154 (8), 140 (4); HREIMS *m/z* 412.1635 (calc. for $C_{22}H_{24}N_2O_6$, 412.1634).

Prunifoline F (**6**), colourless oil, $[\alpha]_D = +261°$ ($CHCl_3$, *c* 0.12); UV (EtOH), λ_{max} (log ε): 208 (4.38), 238 (3.68), 293 (3.19) nm; IR (dry film) ν_{max} 3446, 3356, 1723, 1716 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2, respectively; EIMS *m/z* 398 $[M]^+$ (10), 339 $[M-CO_2Me]^+$ (100), 321 (2), 309 (8), 252 (4), 240 (9), 225 (4), 212 (19), 198 (9); HREIMS *m/z* 398.1842 (calc. for $C_{22}H_{26}N_2O_5$, 398.1842).

Acknowledgments

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