Cytotoxic Xanthones from *Garcinia penangiana* Pierre

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Z. Naturforsch. **62 c**, 786–792 (2007); received April 17/May 25, 2007

Two new xanthones, characterized as 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**) and penangianaxanthone (**2**), with three known xanthones, cudratricusxanthone H (**3**), macluraxanthone C (**4**) and gerontoxanthone C (**5**), as well as friedelin and stigmasterol were isolated from the leaves of *Garcinia penangiana*. Their structures were elucidated by analysis of spectroscopic data and comparison of the NMR data with the literature ones. Significant cytotoxicity against DU-145, MCF-7 and NCI-H460 cancer cell lines was demonstrated by compounds **1**–**5**, with IC_{50} values ranging from 3.5 to 72.8 μM.

Key words: Garcinia penangiana, Cytotoxic Activity, Xanthones

Introduction

The medicinal properties of the species *Garcinia* (family Guttiferae) are well documented, both on their traditional use as well as the scientific basis for their biological activities (Burkill, 1966; Cao *et al*., 1998; Chomnawang *et al.*, 2005; Grosvenor *et al.*, 1995; Tona *et al.*, 1999). Isolation of xanthones, benzophenones, triterpenes and biflavonoids has been reported (Ali *et al.*, 2000; Matsumoto *et al.*, 2003a; Peres *et al.*, 2000; Waterman and Hussain, 1983). The constituents isolated from *Garcinia* exhibit various bioactivities, such as antitumour, anti-inflammatory (Lin *et al.*, 1997; Nakatani *et al.*, 2002) and antibacterial (Permana *et al.*, 2001; Rukachaisirikul *et al.,* 2003). Xanthones are especially noted as potential antitumour and chemopreventive agents (Chiang *et al.*, 2003; Ito *et al.*, 2003; Mackeen *et al.*, 2000; Matsumoto *et al.*, 2003b; Thoison *et al.*, 2000). In this report, the isolation of two new cytotoxic prenylated xanthones, 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**) and the furanoxanthone penangianaxanthone (**2**), is described. Three known xanthones, including cudratricusxanthone H (**3**), macluraxanthone C (**4**) and gerontoxanthone C (**5**), along with friedelin and stigmasterol were also isolated.

Results and Discussion

Compound **1** was isolated as a yellow amorphous solid with a melting point of 220–222 °C. The EIMS spectrum exhibited the HREIMS molecular ion peak ([M^+]) at *m/z* 328.3269 corresponding to the molecular formula $C_{18}H_{16}O_6$. The UV spectrum showed typical absorptions of the xanthone chromophore at 226, 256, 281 and 325 nm (Govindachari *et al.*, 1971). The absorption bands at 3392, 2922, 1585, and 1031 cm^{-1} in the IR spectrum indicated the presence of hydroxy, alkyl, carbonyl, and allyl groups, respectively.

The ^{1}H NMR spectrum contained nine signals representing two chelated hydroxy groups [δ_H 12.26, 1H (s) and δ_H 11.18, 1H (s)], two *ortho*-coupled protons (δ_H 7.32, d , J = 9.0 Hz, H-6 and δ_H 6.64, d, J = 9.0 Hz, H-7), a set of four signals of the 1,1-dimethylallyl group [δ_H 6.58 (dd, J = 17.0, 10.0 Hz, H-2′), δ_H 5.11 (dd, J = 17.0, 1.5 Hz, H_{trans}-3′), δ_H 4.95 (dd, J = 10.0, 1.5 Hz, H_{cis}-3′) and δ_H 1.76 ($2CH_3$, s, H-4′ and H-5′)], and one aromatic proton (δ_H 6.38, s, H-2).

The ^{13}C NMR spectrum revealed the presence of 18 carbon atoms including one carbonyl carbon atom by a signal at δ_C 185.2 (C-9). Further inspection on the ^{13}C NMR and HSQC spectra indicated

the presence of two aromatic rings with six oxygenated carbon atoms, corresponding to a tetrahydroxylated xanthone and one dimethylallyl group. In the HMBC spectrum, correlations were observed between the dimethyl signals (δ_H 1.76, CH_3-4′/CH_3-5′) with the carbon signal of C-4 (δ_C 112.5), thus allowing us to assign the connectivity of a dimethylallyl moiety at C-4.

The assignment of a hydroxy group at C-1 was based on the HMBC correlation of the chelated hydroxy signal at δ_H 12.26 with the carbon signals at δ_C 161.3 (C-1), δ_C 99.8 (C-2) and δ_C 102.2 (C-9a). The correlation of the proton signal at δ_H 6.38 with the carbon signals at δ_C 161.3 (C-1), δ_C 165.5 (C-3), δ_C 112.5 (C-4) and δ_C 102.2 (C-9a) confirmed the assignment of an aromatic methine carbon atom of C-2. The chelated hydroxy group at δ_H 11.18 correlated with the carbon signals at δ_C 153.1 (C-8), δ_C 107.4 (C-8a) and δ_C 109.3 (C-7) in the HMBC spectrum, thus suggesting that the OH group was located at C-8. The assignment of the *ortho*-coupled H-6 proton (δ_H 7.32) was based on its correlations with the carbon signals at δ_C 153.1 (C-8), δ_C 137.6 (C-5) and δ_C 144.0 (C-10a), whereas, the assignment of the H-7 proton (δ_H 6.64) was based on its correlations with the signals at δ_C 153.1 (C-8), δ_C 107.4 (C-8a) and δ_C 137.6 (C-5). Based on these observations, the compound was concluded to be 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**, Fig. 1). The ^{1}H NMR, ^{13}C NMR and HMBC data for **1** are summarized in Table I.

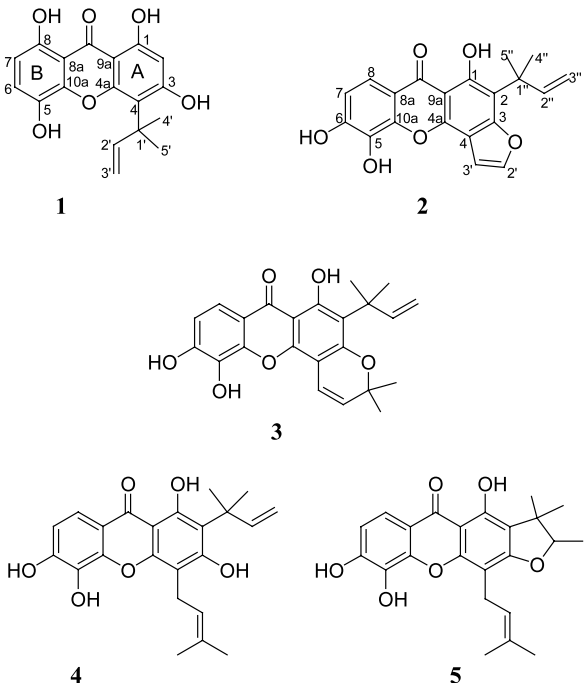

Fig. 1. Compounds isolated from *G. penangiana* leaves: 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**), penangianaxanthone (**2**), cudratricusxanthone H (**3**), macluraxanthone C (**4**), and gerontoxanthone C (**5**).

Penangianaxanthone (**2**) was isolated as yellow fluffy crystals with a melting point of 216–218 °C. The HREI mass spectrum of this compound showed the molecular ion peak at *m/z* 352.0960,

Table I. NMR spectroscopic data (^{13}C at 125 MHz and ^{1}H at 500 MHz, acetone-d_6) of compound **1**.

C	^{13}C chemical shift (ppm)	^{1}H chemical shift (integration of proton, multiplicity, *J* in Hz)	HMBC correlations (H to C)
C-1	161.3	12.26 (1H, s, OH-1)	C-1, C-2, C-9a
C-2	99.8	6.38 (1H, s)	C-1, C-3, C-4, C-9a
C-3	165.5		
C-4	112.5	155.0	
C-5	137.6		
C-6	123.3	7.32 (1H, d, *J* = 9.0)	C-8, C-5, C-10a
C-7	109.3	6.64 (1H, d, *J* = 9.0)	C-8a, C-5
C-8	153.1	11.18 (1H, s, OH-8)	C-7, C-8, C-8a
C-8a	107.4		
C-9	185.2		
C-9a	102.2		
C-10a	144.0		
C-1′	41.3		
C-2′	151.6	6.58 (1H, dd, *J* = 17.0, 10.0)	C-4, C-1′, C-2′, C-5′
C-3′	107.4	5.11 (1H, dd, *J* = 17.0, 1.5)	C-4, C-1′, C-2′, C-4′
		4.95 (1H, dd, *J* = 10.0, 1.5)	C-1′, C-4′, C-5′
C-4′	28.8	1.76 (3H, s)	C-1′, C-2′
C-5′	28.8	1.76 (3H, s)	C-1′

corresponding to the molecular formula $C_{20}H_{16}O_6$. The UV spectral data is consistent with the xanthone chromophore with absorption maxima at 258, 280, 326 and 381 nm. The IR spectrum showed the presence of carbonyl and OH functionalities by absorption bands at 1582 and 3427 cm^{-1}, respectively.

In the ^1H NMR spectrum, the presence of a 1,1-dimethylallyl group was noted by the presence of proton signals at δ_H 6.48 (dd, J = 17.0, 10.0 Hz, H-2″), δ_H 5.03 (d, 17.0 Hz, H_{trans}-3″), δ_H 4.95 (d, J = 10.0 Hz, H_{cis}-3″) and two overlapping methyl peaks at δ_H 1.77. In the ^1H-^1H COSY experiment (Table II) the proton signal at δ_H 6.48 (H-2″) was correlated with proton signals at δ_H 5.03 (H-3″$_{trans}$) and δ_H 4.95 (H-3″$_{cis}$), which further supported the presence of an allylic system. The HSQC spectrum showed the correlation between the allylic methine proton signal at δ_H 6.48 with the carbon signal at δ_C 148.1 (C-2″), while terminal allylic methylene proton signals at δ_H 5.03 and δ_H 4.95 correlated with a carbon signal at δ_C 109.1 (C-3″). The HMBC spectrum further showed the correlation of a dimethyl proton signal at δ_H 1.77 (H-4″ and H-5″) with the allylic carbon atom (δ_C 148.1, C-2″). Correlation of dimethyl allyl proton signals at δ_H 1.77 (CH_3-4″ and CH_3-5″) with the carbon signal at δ_C 113.5 (C-2) suggested the connectivity of the 1,1-dimethylallyl moiety to the xanthone skeleton through C-2. In the ^1H NMR low field region, a chelated hydroxy proton signal at δ_H 13.94 (OH-1), which correlated with the carbon signals at δ_C 158.3 (C-1), δ_C 113.5 (C-2) and δ_C 104.9 (C-9a), was observed in the HMBC spectrum, thus confirming the position of the chelated hydroxy group at C-1.

The presence of two methine protons in the fused furan ring was noted from the ^1H NMR spectrum by the signals at δ_H 7.38 (d, J = 2.0 Hz, H-3′) and δ_H 7.86 (d, J = 2.0 Hz, H-2′), which mutually correlated in the ^1H-^1H COSY spectrum. The HSQC spectrum further allowed the assignment of the furanyl carbon signals at δ_C 103.9 and δ_C 144.1 to C-3′ and C-2′, respectively. The connectivity of the fused furan ring to the xanthone skeleton was further determined by the HMBC spectrum. The correlations between H-3′ (δ_H 7.38) with the carbon signals at δ_C 148.7 (C-4a), δ_C 158.7 (C-3) and δ_C 144.1 (C-2′) and the other methine proton, H-2′ (δ_H 7.86), with the carbon signals at δ_C 158.7 (C-3), δ_C 109.3 (C-4) and δ_C 103.9 (C-3′) suggested that the connection of the fused furan ring was at C-4 and C-3 of the xanthone skeleton.

In the ^1H NMR spectrum, two *ortho*-coupled aromatic proton signals (AB system) at δ_H 7.77 (d, J = 8.5 Hz) and δ_H 7.09 (d, J = 8.5 Hz) were observed. The former was assigned to H-8 due to its HMBC correlation with the carbon signals at δ_C

Table II. NMR spectroscopic data (^{13}C at 125 MHz and ^1H at 500 MHz, acetone-d_6) of compound **2**.

C	^{13}C chemical shift (ppm)	^1H chemical shifts (integration of proton, multiplicity, J in Hz)	COSY	HMBC correlations (H to C)
C-1	158.3	13.94 (1H, s, OH-1)		C-1, C-2, C-9a
C-2	113.5			
C-3	158.7			
C-4	109.3			
C4a	148.7			
C-5	132.6			
C-6	146.0			
C-7	113.7	7.09 (1H, d, J = 8.5)	H-8	C-8a, C-5
C-8	117.1	7.77 (1H, d, J = 8.5)	H-7	C-9, C-6, C-10a, C-8a
C-8a	114.4			
C-9	182.0			
C-9a	104.9			
	152.0			
C-1″	40.9			
C-2″	148.1	6.48 (1H, dd, J = 17.0, 10.0)	H-3″$_{cis}$, H-3″$_{trans}$	C-2, C-1″, C-4″, C-5″
C-3″	109.1	5.03 (1H, d, J = 17.0)	H-2″	C-2″, C-1″
		4.95 (1H, d, J = 10.0)	H-2″	C-1″
C-4″	28.1	1.77 (3H, s)		C-2, C-2″, C-1″, C-4″, C-5″
C-5″	28.1	1.77 (3H, s)		C-2, C-2″, C-1″, C-4″, C-5″
C-2′	144.1	7.86 (1H, d, J = 2.0)	3′	C-3′, C-4, C-3
C-3′	103.9	7.38 (1H, d, J = 2.0)	2′	C-4a, C-3, C-2′

182.0 (C-9), δ_C 146.0 (C-6) and δ_C 152.0 (C-10a), while the latter was assigned to H-7 due to its HMBC correlation signals at δ_C 114.4 (C-8a) and δ_C 132.6 (C-5). Comparison of respective data for proton and carbon signals in previously isolated xanthone compounds, containing a fused furanyl system in subelliptenone C and D (Iinuma *et al.*, 1995, 1996), supported the assignments. Based on these observations (see Table II), compound **2** was assigned as penangianaxanthone or 1,5,6-trihydroxy-2-(1′,1′-dimethylallyl)furano(4′,5′:3,4)xanthone (Fig. 1).

From the biogenetic point of view, compounds **2**, **3** and **5** may have the common origin of compound **4**. Intramolecular cyclization of 3-OH with the 2-prenyl moiety led to compound **5**, while cyclization of 3-OH with an epoxidized 4-prenyl moiety led to pyranoxanthone **3** or a furanoxanthone intermediate which underwent further elimination of the isopropyl moiety to penangianaxanthone (**2**).

The cytotoxic activity test of the isolates against three cell lines, MCF-7 (hormone-dependent breast cancer), NCI-H460 (non-small lung cancer) and DU-145 (non-hormone-dependent prostate cancer), was conducted and the results are presented in Table III. All compounds except for friedelin and stigmasterol showed strong to weak activity towards MCF-7 cell lines. Xanthones **2**–**5** showed strong cytotoxic activity towards MCF-7, NCI-H460 and DU-145 cell lines, with IC_{50} values ranging between 3.5 to 16.4 μM, while **1** showed only weak activity towards MCF-7 and NCI-H460, with IC_{50} values of 72.8 μM and 40.8 μM, respectively. Compound **4** seemed to be the most cytotoxic among the isolates.

Table III. Cytotoxic activity of compounds isolated from *G. penangiana.*

Compound	IC_{50} [μM][a]		
	MCF-7	NCI-H460	DU-145
1	72.8 ± 2.6	40.8 ± 1.1	nd
2	16.4 ± 1.2	12.7 ± 1.4	12.2 ± 0.4
3	9.8 ± 0.8	12.6 ± 1.2	11.7 ± 0.2
4	7.8 ± 0.1	3.5 ± 0.9	6.6 ± 0.6
5	7.6 ± 0.2	5.0 ± 0.7	7.6 ± 0.4
Friedelin	na	nd	nd
Stigmasterol	na	nd	nd

[a] Results are expressed as IC_{50} values ± SD of three experiments performed in four replicates; MCF-7, human breast cancer (Re+); NCI-H460, non-small human lung cancer; DU-145, human prostate cancer; na, not active; nd, not determined.

The most obvious structural difference between compounds **1** and **2**–**5** is the location of two hydroxy groups in ring B. While compound **1** has two hydroxy groups located *para* to each other (C-5 and C-8), the hydroxy groups in compounds **2**–**5** are located *ortho* (C-5 and C-6) to each other. This factor may therefore be responsible for the cytotoxic activity of these compounds. The presence of *ortho*-dihydroxy groups in the aromatic system of antioxidative compounds such as curcuminoids, cinnamonoids and feruloids has been emphasized in previous reports (Cai *et al.*, 2006; Kanski *et al.,* 2002; Mansouri *et al.*, 2005; Notarbartolo *et al.*, 2005; Sen *et al.*, 2005). The principle of antioxidative compounds in expressing cytotoxic activity has also been proposed for example in the case of curcumin (Notarbartolo *et al.*, 2005; Sen *et al.*, 2005). The presence of one or two prenyl moieties in ring A, either cyclized into furanyl or pyranyl rings, did not seem to affect the cytotoxic activity.

Experimental

General experimental procedures

NMR spectra were recorded on a Varian Unity 500 spectrometer using CD_3OD, $CDCl_3$ and acetone-d_6 as solvents. Chemical shifts are recorded in δ (ppm) with tetramethylsilane (TMS) as an internal reference. All mass spectra were taken under EI condition, using a PolarisQ mass spectrometer and a Finnigan MAT95XL-T HREIMS instrument. UV spectra were recorded on a CARY Conc 100 spectrometer in MeOH and IR spectra on an FTIR Perkin Elmer spectrometer 1650 in KBr disc.

Plant material

The plant material was collected from the Fraser Hill Forest Reserve (elevation: 1100 m above the sea level) in Pahang, Malaysia, and was classified by Mr. Shamsul Khamis, a resident botanist of the Institute of Bioscience, University Putra Malaysia. The sample (SK 95/01) was deposited in the herbarium of the Institute of Bioscience, University Putra Malaysia.

Extraction

The air-dried (1.5 kg) leaves of *G. penangiana* were ground to powder and soaked in methanol

(MeOH) for 2 d at room temperature and the extract was filtered. The solvent was removed under reduced pressure. The extraction was repeated for 3 times and the combined MeOH extract (77 g) was partitioned into hexane, DCM, EA and butanol to yield 4.2 g, 12.3 g, 5.2 g and 35.9 g, respectively, of the dried fractionated extracts.

*Isolation of compounds **1**, **2**, **3**, **4** and **5***

Approx. 4.2 g of the hexane-fractionated extract was subjected to gel permeation chromatography (Sephadex LH-20, 2.5 cm $\phi \times 40$ cm) with methanol/chloroform (1:1) as an eluant, to give eight (20 ml) fractions. Fractions 1–3 were combined and further purified to yield 10 mg of friedelin and 2 mg of stigmasterol. The combined fractions 4–8 (1.8 g) were subjected to silica gel column chromatography (2 cm $\phi \times 40$ cm) and eluted with hexane/EA/MeOH mixtures, in ascending polarity manner, to give 30 (10 ml) fractions. The fractions were combined into 4 fractions based on their TLC profile. Fraction 3 (96.9 mg) was subjected to further silica gel column chromatography (1 cm $\phi \times 30$ cm) eluting with hexane/EA (8:2) to yield 4 mg of **1**. Fraction 4 (41.5 mg) was subjected onto a C-18 reverse phase silica column and eluted with MeOH/water mixtures to give **3** (8.3 mg).

The DCM fraction (12.3 g) was subjected to a silica gel column (10 cm $\phi \times 30$ cm) and eluted in ascending polarity manner with hexane/DCM/EA/MeOH mixtures to give 9 combined fractions (A–I) based on their TLC pattern. Fraction E (6.8 g) was subjected to gel permeation column chromatography (Sephadex LH-20, 2.5 cm $\phi \times 30$ cm) with a methanol/chloroform (1:1) mixture as eluant to give fifteen (20 ml) fractions. The combined fractions 9–15 (408 mg) were subjected to C-18 reverse phase column chromatography (2.5 cm $\phi \times 30$ cm) using MeOH/water as eluant to afford 20.4 mg of compound **2**. The combined fractions 4–8 (4 g) were subjected to reverse phase column chromatography (4.0 cm $\phi \times 30$ cm) and eluted with a MeOH/water mixture in descending manner to afford compounds **2** (40 mg) and **5** (80 mg). Fraction D (1.7 g) was also subjected to C-18 reverse phase column chromatography (2 cm $\phi \times 30$ cm) and eluted with MeOH/water to afford 67.7 mg of the yellow amorphous solid of compound **4**.

*4-(1,1-Dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**):* Yellow amorphous solid, m.p. 220–222 °C. – IR (KBr): ν_{max} = 3392 (OH stretching), 2922 (CH stretching), 2848 (sp^3 CH stretching), 1585 (carbonyl stretching), 1031 cm^{-1} (out of plane bending of alkene). – UV (MeOH): λ_{max} (log ε) = 226 (3.88), 256 (3.94), 281 (3.76), 325 nm (3.59). – HREIMS: *m/z* = 328.3269 (calcd. for $C_{18}H_{16}O_6$: 328.3246). – MS: *m/z* = 328 [M^+] (32), 313 [M^+-methyl] (100), 285 (46), 273 (26), 257 (38), 244 (18), 149 (24), 129 (22), 105 (18), 91 (36), 83 (68), 76 (28), 56 (24), 46 (34), 44 (79). – ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz): see Table I.

*Penangianaxanthone (**2**):* Yellow fluffy crystals, m.p. 216–218 °C. – IR (KBr): ν_{max} = 3427 (OH stretching), 2900 (CH stretching), 2830 (CH stretching), 1582 (carbonyl stretching), 1414, 1332, 1314, 1284, 1239, 1215, 1174, 1132, 1095 cm^{-1}. – UV (MeOH): λ_{max} (log ε) = 258 (4.25), 280 (4.05), 326 (3.82), 381 (3.55). – HREIMS: *m/z* = 352.0960 (calcd. for $C_{20}H_{16}O_6$: 352.0946). – MS: *m/z* = 352 [M^+] (42), 336 [352-methyl-H] (100), 318 [336-H_2O] (56), 297 (90), 280 (26), 253 (6), 189 (6), 153 (6), 147 (10), 97 (16), 81 (22), 57 (24). – ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz): see Table II.

*Cudratricusxanthone H (**3**):* Yellow needles, m.p. 174–176 °C (lit. m.p. 175 °C (Kanski *et al.*, 2002)]. – MS, ^{1}H NMR, ^{13}C NMR data are consistent with cudratricusxanthone H (Zou *et al.*, 2004).

*Macluraxanthone C (**4**):* Yellow amorphous solid, m.p. 204 °C (lit. m.p. is not available). – MS, ^{1}H NMR, ^{13}C NMR data are consistent with macluraxanthone C (Groweiss and Boyd, 2000).

*Gerontoxanthone C (**5**):* Yellow amorphous solid, m.p. 205–207 °C (lit. m.p. 204–206 °C). – MS, ^{1}H NMR, ^{13}C NMR data are consistent with gerontoxanthone C (Chang *et al.*, 1989).

Friedelin: White needles, m.p. 260–262 °C (lit. m.p. 262–265 °C). – MS, ^{1}H NMR, ^{13}C NMR data are consistent with friedelin (Queiroga *et al.*, 2000).

Stigmasterol: White needles, m.p. 168–170 °C (lit. m.p. 170 °C) (Forgo and Kover, 2004).

In vitro test for cytotoxic activity (MTT assay)

Three types of human tumour cell lines, DU-145, MCF-7 and NCI-H460, were used in the cytotoxicity study. Crude extracts or compounds were tested at 0.1 μg/ml, 1 μg/ml, 10 μg/ml and 100 μg/ml concentrations and each concentration was performed in 4 replicates. The assay was conducted according to the previously described protocol (Stanslas *et al*., 2000).

Acknowledgement

The authors are grateful to the Ministry of Science, Technology and the Environment, Malaysia for its financial support and the IRPA-EAR research grant No. 09-02-04-0313. M. L. J. is grateful to the Malaysian Agriculture Research and Development Institute (MARDI) for the scholarship provided to complete his Master of Science Programme.

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