

## TWO NEW PRENYLATED CHALCONES FROM THE LEAVES OF *ARTOCARPUS LOWII* KING

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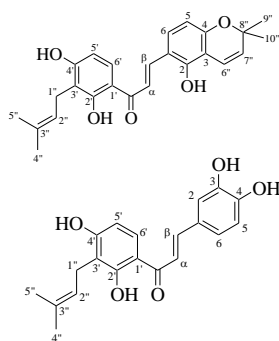
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### Graphical abstract



### Abstract

Two minor prenylated chalcones were isolated for the first time from the leaves of *Artocarpus lowii* King. These prenylated chalcones were identified as 2-hydroxyparatocarpin C (**1**) and 2',3,4',4-tetrahydroxy-3'-prenylchalcone (**2**). The structures of these prenylated chalcone were elucidated by utilizing the data values obtained from <sup>1</sup>H NMR, <sup>13</sup>C NMR, DEPT, COSY, IR, UV and MS, as well as by comparison with literature values.

**Keywords:** *Artocarpus lowii*, prenylated chalcones

### Abstrak

Dua chalcon terprenil minor berjaya diasingkan untuk pertama kali daripada bahagian daun *Artocarpus lowii* King. Chalkon terprenil ini dikenalpasti sebagai 2-hidroksiparatokarpin C (**1**) dan 2',3,4',4-tetrahidroksi-3'-prenilchalkon (**2**). Struktur chalkon terprenil ini telah dikenalpasti dengan menggunakan data yang diperolehi daripada RMN <sup>1</sup>H, RMN <sup>13</sup>C, DEPT, COSY, IM, UL dan SJ, juga melalui perbandingan nilai literatur.

**Kata kunci:** *Artocarpus lowii*, chalkon terprenil

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## 1.0 INTRODUCTION

*Artocarpus* is the most commonly encountered genus, representatives of the Moraceae in the lowland forest of the tropical Southeast Asia, apart from *Ficus*. There are 47 species of *Artocarpus* in which only 20 species including the cultivated plants could be found in Malaysia. This genus is known world wide for its edible fruits like the jackfruit, *A. heterophyllus* locally known as 'nangka', bread fruit, *A. communis* ('sukun') and 'cempedak', *A. integer*. These species are widely cultivated in Malaysia as villagers and traders commercially sell their fruits in local market. The lightwood known locally as 'terap' and the medium hardwood known as 'keledang' constitute valuable timber resources [1-2]. Some of

Malaysia's *Artocarpus* species are rare including *Artocarpus lowii*, *A. anisophyllus*, *A. bracteata*, *A. fulvicortex*, *A. hispidus*, *A. kemando*, *A. nitidus* and *A. odoratissima* [1]. The earlier work on the phytochemical investigation of *Artocarpus* species started long ago in 1895 where morin and cyanomaclurin were isolated from *A. heterophyllus*. It was only in 1963 that a study of the NMR spectrum of the acetate of cyanomaclurin trimethyl ether led to the structure of cyanomaclurin [3]. Two more prenylflavonoids were isolated in very minute quantities from the same species and identified as cycloheterophyllin and heterophyllin [4]. Since then, many types of new prenylated and pyranoflavonoids were isolated from *Artocarpus* species. Our continuous research on Malaysia's rare species

especially on *A. lowii*, *A. fulvicortex* and *A. anisophyllus* had successfully identified several new compounds together with known flavonoids. 2',4'-Dihydroxy-4-methoxy-3'-prenyldihydrochalcone was isolated from the leaves of *A. lowii* King [5]; 5-hydroxy-(6:7,3':4')-di(2,2-dimethylpyrano)flavone was isolated from the leaves of *A. fulvicortex* FM Jarret [6] and 4',5'-dihydroxy-6,7-(2,2-dimethylchromeno)-2'-methoxy-8- $\gamma,\gamma$ -dimethylallylflavone was obtained from the heartwoods of *A. anisophyllus* Miq [7] as novel compounds. A thorough literature search revealed that not many phytochemicals and bioactivity studies had been conducted on Malaysia's rare species. It is very interesting to conduct these studies on rare *Artocarpus* species in order to search for new flavonoids with different substituents pattern. Flavonoids with hydroxyl, prenyl and/or pyrano moieties might show significant bioactivities towards several bioassays including antioxidant, antimicrobial, anti-inflammatory, antiproliferative and tyrosinase inhibitory activity [8-11].

In continuation of phytochemical studies on Malaysia's *Artocarpus* plants, we reinvestigated the petroleum ether and ethyl acetate crude extracts of the leaves of *A. lowii*. Herein, we report on the isolation and identification of two new prenylated chalcones namely 2-hydroxyparatocarpin C (**1**) and 2',3,4',4-tetrahydroxy-3'-prenylchalcone (**2**).

## 2.0 EXPERIMENTAL

### 2.1 General Experimental Procedures

Ultraviolet (UV) spectra were recorded on Shimadzu UV 1601PC spectrophotometer. Infrared (IR) spectra were recorded on Perkin Elmer 1650 FTIR spectrometer with chloroform as solvent. Mass spectral data were obtained from Kent Mass Spectrometry Service, UK.  $^1\text{H}$ ,  $^{13}\text{C}$  and DEPT NMR and 2D NMR spectra were recorded on a Bruker Avance 300 Spectrometer (300 MHz and 75 MHz respectively), Universiti Teknologi Malaysia. Deuterated chloroform ( $\text{CDCl}_3$ ) and acetone ( $\text{CD}_3\text{COCD}_3$ ) were used as solvents. Vacuum liquid chromatography (VLC) was performed using silica gel (Merck, 230-400 mesh), while gravity column chromatography was performed using either silica gel (Merck, 70-230 mesh) or Sephadex LH-20 (Sigma). Thin layer chromatography (TLC, aluminium sheets precoated with silica gel 60 F254, 0.20 mm thickness) was used to detect or monitor the presence of chemical components in the crude extracts or fractions. The spots were visualized under UV light at wavelength 254 nm or 365 nm, incooperated with acidic anisaldehyde solution or ethanolic ferric chloride solution.

### 2.2 Plant Material

The leaves of *A. lowii* (UKMB03995) were collected from Gombak Forest, Selangor in May 2003. The

sample was authenticated by Mr Ahmad Zainuddin bin Ibrahim and the voucher specimen was deposited at the Herbarium of Department of Biology, Universiti Kebangsaan Malaysia, Bangi, Selangor.

### 2.3 Extraction and Isolation

Sequential cold extraction of the powdered leaves of *A. lowii* (2 kg) were carried out using 5 L each of petroleum ether (PE), dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) and ethyl acetate (EtOAc) for 48 hours. The extracts were filtered and concentrated to dryness to afford PE crude extract (20 g),  $\text{CH}_2\text{Cl}_2$  crude extract (28 g) and EtOAc crude extract (23 g). The PE crude extract (18 g) was subjected to silica gel VLC (200 g) and eluted with *n*-hexane, *n*-hexane- $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_2\text{Cl}_2$ -EtOAc, EtOAc, in the order of increasing polarity to give twelve fractions. Each fraction was subjected to TLC analysis. Fractions with similar pattern on TLC were combined to give four major fractions: ALLPE 1 (10.7 g), ALLPE 2 (1.7 g), ALLPE 3 (2.5 g) and ALLPE 4 (1.6 g). Fraction ALLPE 4 (1.6 g) was subjected to Si gel column chromatography (80 g, column size: 3.0  $\times$  75.0 cm, solvent system: *n*-hexane-EtOAc), followed by Sephadex LH-20 column chromatography (15 g, column size: 2.5  $\times$  50.0 cm, MeOH) to give 2-hydroxyparatocarpin C (**1**) (2.2 mg) as yellow gums. The EtOAc crude extract (20 g) was also subjected to Si gel VLC (220 g) and eluted by *n*-hexane, *n*-hexane- $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_2\text{Cl}_2$ -EtOAc, EtOAc in order of increasing polarity to afford fourteen fractions. Each fraction was subjected to TLC analysis. Fractions with similar pattern on TLC were combined to give ALLE 1 (2.4 g), ALLE 2 (6.7 g) and ALLE 3 (3.5 g). Fraction ALLE 3 (3.0 g) was purified by column chromatography over silica gel (120 g, column size: 3.0  $\times$  75.0 cm, solvent system: *n*-hexane-EtOAc) to yield 2',3,4',4-tetrahydroxy-3'-prenylchalcone (**2**) (6.2 mg) as an orange gums.

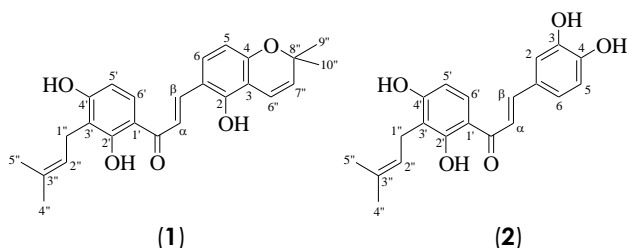
2-Hydroxyparatocarpin C (**1**) (2.2 mg) as yellow gums;  $R_f$  = 0.38 (*n*-hexane:EtOAc = 4:1);  $\text{FeCl}_3$  test: positive (dark grey); IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3317 (OH), 1625 (chelated C=O); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) nm: 372 (3.90), 284 (3.77); UV (MeOH + NaOMe)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) nm: 401 (3.88), 268 (3.78);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  13.80 (s, 2'-OH), 7.85 (1H, d,  $J$  = 15.3 Hz, H- $\beta$ ), 7.73 (1H, d,  $J$  = 9.0 Hz, H-6'), 7.58 (1H, d,  $J$  = 8.7 Hz, H-6), 7.46 (1H, d,  $J$  = 15.3 Hz, H- $\alpha$ ), 6.90 (1H, d,  $J$  = 8.7 Hz, H-5), 6.77 (1H, d,  $J$  = 10.1 Hz, H-6''), 6.39 (1H, d,  $J$  = 9.0 Hz, H-5'), 5.61 (1H, d,  $J$  = 10.1 Hz, H-7''), 5.34 (1H, t,  $J$  = 6.0 Hz, H-2''), 3.40 (2H, d,  $J$  = 6.0 Hz, H-1''), 1.82 (3H, s, H-5''), 1.64 (3H, s, H-4''), 1.49 (6H, s, H-9'' and H-10'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ , 75 MHz):  $\delta$  192.0 (C=O), 160.9 (C, C-2'), 159.7 (C, C-4'), 158.0 (C, C-4), 156.2 (C, C-2), 144.0 (CH, C- $\beta$ ), 135.5 (C, C-3''), 132.4 (CH, C-7''), 130.6 (2  $\times$  CH, C-6 and C-6'), 128.8 (CH, C-6''), 128.1 (CH, C-2''), 127.9 (C, C-1), 121.4 (C, C-3), 117.9 (CH, C-5), 115.9 (C, C-3'), 116.0 (CH, C- $\alpha$ ), 114.1 (C, C-1'), 108.2 (CH, C-5'), 80.1 (C, C-8''), 29.6 ( $\text{CH}_2$ , C-1''), 28.4 (2  $\times$   $\text{CH}_3$ , C-9'' and C-10''), 25.8 ( $\text{CH}_3$ , C-4''), 17.9 ( $\text{CH}_3$ , C-5''); EIMS  $m/z$  (rel. int.): 406 (20) [ $\text{M}^+$ ,  $\text{C}_{25}\text{H}_{26}\text{O}_5$ ], 391 (45), 375 (8),

337 (8), 323 (70), 307 (100), 281 (6), 203 (4), 187 (80), 149 (30).

2',3,4',4'-Tetrahydroxy-3'-prenylchalcone (**2**) (6.2 mg) as an orange gums;  $R_f = 0.64$  (*n*-hexane:EtOAc = 2:3);  $\text{FeCl}_3$  test: positive (dark grey); IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3313 (OH), 1624  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) nm: 379 (3.84), 265 (3.62); UV (MeOH +  $\text{AlCl}_3$ )  $\lambda_{\text{max}}$  (log  $\epsilon$ ) nm: 419 (3.36), 284 (3.33); UV (MeOH +  $\text{AlCl}_3$  + HCl)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) nm: 379 (3.44), 265 (3.20); UV (MeOH + NaOMe)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) nm: 408 (3.83), 343 (3.72), 274 (3.66);  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ , 300 MHz)  $\delta$  14.00 (s, 2'-OH), 7.98 (1H, d,  $J = 9.0$  Hz, H-6'), 7.78 (1H, d,  $J = 15.0$  Hz, H- $\beta$ ), 7.68 (1H, d,  $J = 15.0$  Hz, H- $\alpha$ ), 7.35 (1H, d,  $J = 2.1$  Hz, H-2), 7.23 (1H, dd,  $J = 8.1$  Hz and 2.1 Hz, H-6), 6.92 (1H, d,  $J = 8.1$  Hz, H-5), 6.54 (1H, d,  $J = 9.0$  Hz, H-5'), 5.30 (1H, t,  $J = 7.3$  Hz, H-2''), 3.38 (2H, d,  $J = 7.3$  Hz, H-1''), 1.79 (3H, s, H-5''), 1.66 (3H, s, H-4'');  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{COCD}_3$ , 75 MHz):  $\delta$  192.1 (C=O), 164.8 (C, C-2'), 164.2 (C, C-4'), 162.7 (C, C-4), 162.0 (C, C-3), 144.6 (CH, C- $\beta$ ), 130.6 (C, C-3''), 130.3 (CH, C-2), 129.9 (CH, C-6), 129.4 (CH, C-6'), 127.3 (C, C-1), 122.5 (CH, C-2''), 117.6 (CH, C- $\alpha$ ), 115.5 (CH, C-5), 113.4 (C, C-1'), 113.3 (C, C-3'), 107.2 (CH, C-5'), 25.0 ( $\text{CH}_3$ , C-4''), 21.4 ( $\text{CH}_2$ , C-1''), 17.0 ( $\text{CH}_3$ , C-5''); EIMS  $m/z$  (rel. int.): 340 (58) [ $\text{M}^+$ ,  $\text{C}_{20}\text{H}_{20}\text{O}_5$ ], 322 (20), 307 (50), 297 (40), 270 (20), 256 (6), 221 (10), 203 (15), 187 (75), 176 (15), 161 (30), 149 (100), 135 (30).

### 3.0 RESULTS AND DISCUSSION

Purification of the PE and EtOAc crude extracts of the leaves of *Artocarpus lowii* have resulted in the isolation of two new prenylated chalcones, 2-hydroxyparatocarpin C (**1**) and 2',3,4',4'-tetrahydroxy-3'-prenylchalcone (**2**) (Figure 1).



**Figure 1** Structure of 2-hydroxyparatocarpin C (**1**) and 2',3,4',4'-tetrahydroxy-3'-prenylchalcone (**2**)

Compound (**1**) (2.2 mg) was isolated as yellow gum from the PE crude extract. This compound was found to be easily decomposed. The TLC spot gave a dark grey colour when reacted with an ethanolic ferric chloride solution, indicating the presence of polyhydroxyl groups. The molecular formula was determined to be  $\text{C}_{25}\text{H}_{26}\text{O}_5$  from its EIMS with molecular ion peak, [ $\text{M}^+$ ] at  $m/z$  406. The IR spectrum showed absorption bands for hydroxyl and chelated carbonyl groups at 3317  $\text{cm}^{-1}$  and 1625  $\text{cm}^{-1}$ , respectively. The UV spectrum exhibited maximum absorptions at 372 and 284 nm in MeOH which

indicated 2',4',4'-trioxygenated chalcone derivatives [12]. The  $^1\text{H}$  NMR spectrum of (**1**) showed characteristic signals for protons of a 2,2-dimethylpyran ring at  $\delta$  1.49 (6H, s, H-9'' and H-10''),  $\delta$  5.61 and  $\delta$  6.77 (1H each, d,  $J = 10.1$  Hz each, H-7'' and H-6''). Signals for a prenyl substituent were observed at  $\delta$  1.64 and  $\delta$  1.82 (3H each, s, H-4'' and H-5''),  $\delta$  3.40 (2H, d,  $J = 6.0$  Hz, H-1'') and  $\delta$  5.34 (1H, t,  $J = 6.0$  Hz, H-2''). Two sets of an *ortho*-coupled signals were observed at  $\delta$  6.39,  $\delta$  7.73 (1H each, d,  $J = 9.0$  Hz, H-5' and H-6') and at  $\delta$  6.90,  $\delta$  7.58 (1H each, d,  $J = 8.7$  Hz, H-5 and H-6). Two other doublets at  $\delta$  7.46 and  $\delta$  7.85 ( $J = 15.3$  Hz each) were attributable to the *trans*-olefinic protons, H- $\alpha$  and H- $\beta$  respectively. Finally, a singlet observed at  $\delta$  13.80 was assigned to the chelated hydroxyl group, 2'-OH. The  $^1\text{H}$ - $^1\text{H}$  correlations were supported by the  $^1\text{H}$ - $^1\text{H}$  COSY. Analysis of the  $^{13}\text{C}$  NMR and DEPT spectra of (**1**) showed the presence of four methyl carbons at  $\delta$  17.9 (C-4''), 25.8 (C-5'') and 28.4 (C-9'' and C-10''); a methylene carbon at  $\delta$  29.6 (C-1''); nine methine carbons at  $\delta$  108.2 (C-5'), 116.0 (C- $\alpha$ ), 117.9 (C-5), 128.1 (C-2''), 128.8 (C-6''), 130.6 (C-6 and C-6'), 132.4 (C-7''), and 144.0 (C- $\beta$ ); and a carbonyl group at  $\delta$  192.0. Signals for quaternary carbons were also observed at  $\delta$  80.1 (C-8''), 114.1 (C-1'), 115.9 (C-3'), 121.4 (C-3), 127.9 (C-1), 135.5 (C-3''), 156.2 (C-2), 158.0 (C-4), 159.7 (C-4') and 160.9 (C-2'). The structural assignment of compound (**1**) was aided by spectral data of paratocarpin C, a prenylchalcone isolated from *Paratocarpus venenosa* [13]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of paratocarpin C and (**1**) showed similarity, except for an ABX type spin system at B-ring in paratocarpin C was observed as an AB type spin system or *ortho*-coupled aromatic protons in (**1**). So, it was suggested that there is an additional of hydroxyl group at position C-2 in compound (**1**). This was confirmed by the UV spectrum where a shift was observed upon addition of NaOMe, indicating the presence of free hydroxyl groups at C-2 and C-4' [12]. Based on these spectral analyses, compound (**1**) was identified as 2-hydroxyparatocarpin C.

Compound (**2**) (6.2 mg) was isolated as an unstable orange gum from the EtOAc crude extract. This compound was also easily decomposed. It gave a dark grey colour with an ethanolic ferric chloride solution. The EIMS spectrum of (**2**) showed a molecular ion peak, [ $\text{M}^+$ ] at  $m/z$  340 which corresponded to molecular formula  $\text{C}_{20}\text{H}_{20}\text{O}_5$ . The IR spectrum showed absorption bands for hydroxyl and chelated carbonyl at 3313  $\text{cm}^{-1}$  and 1624  $\text{cm}^{-1}$ , respectively. The UV spectrum exhibited maximum absorptions at 379 and 265 nm in MeOH, characteristic of a chalcone skeleton [12]. The bathochromic shift induced by NaOMe indicated the occurrence of free hydroxyl group at C-2 and C-4' while a shift induced by  $\text{AlCl}_3$  indicated the presence of an *ortho*-hydroxyl group located at B-ring [12]. Comparison of the  $^1\text{H}$  NMR spectrum of compound (**2**) with those of isobavachalcone [14] showed that compound (**2**) has the same chalconoid skeleton. Instead of an AA'BB' spin system presence at B-ring of

isobavachalcone, compound (**2**) has an ABX spin system in the structure. The ABX signals were observed at  $\delta$  7.23 (1H, dd,  $J = 8.1$  Hz and 2.1 Hz, H-6),  $\delta$  6.92 (1H, d,  $J = 8.1$  Hz, H-5) and  $\delta$  7.35 (1H, d,  $J = 2.1$  Hz, H-2). These signals gave clear evidences for the presence of an *ortho*-dihydroxy group at C-3 and C-4 of the B-ring. The  $^1\text{H}$  NMR also exhibited a set of signals for a prenyl substituent at  $\delta$  1.66 and 1.79 (3H each, s, H-4" and H-5"),  $\delta$  3.38 (2H, d,  $J = 7.3$  Hz, H-1") and  $\delta$  5.30 (1H,  $J = 7.3$  Hz, H-2"). Signals observed at  $\delta$  7.68 and 7.78 (1H each,  $J = 15.0$  Hz) was characteristic for *trans*-olefinic protons, H- $\alpha$  and H- $\beta$  in chalcone skeleton. A set of doublet at  $\delta$  6.54 and 7.98 (1H each, d,  $J = 9.0$  Hz) was attributable to *ortho*-coupled aromatic protons at A-ring, H-5' and H-6'. A downfield signal which appeared at  $\delta$  14.00 was attributable to the hydrogen-bonded hydroxyl group, 2'-OH. The connectivities between protons in the structure were further supported by the  $^1\text{H}$ - $^1\text{H}$  COSY. Analysis of the  $^{13}\text{C}$  NMR and DEPT spectra of (**2**) supported the presence of two methyl carbons at  $\delta$  17.0 (C-5") and 25.0 (C-4"); a methylene carbon at  $\delta$  21.4 (C-1"); eight methine carbons at  $\delta$  107.2 (C-5'), 115.5 (C-5), 117.6 (C- $\alpha$ ), 122.5 (C-2'), 129.4 (C-6'), 129.9 (C-6), 130.3 (C-2), and 144.6 (C- $\beta$ ); and a carbonyl at  $\delta$  192.1. Thus, compound (**2**) was identified as 2',3,4',4-tetrahydroxy-3'-prenylchalcone. To the best of our knowledge, these two prenylated chalcones have never been reported elsewhere.

#### 4.0 CONCLUSION

Purification of the PE and EtOAc crude extracts of the leaves of *A. lowii* King had afforded two new prenylated chalcones named as 2-hydroxyparatocarpin C (**1**) and 2',3,4',4-tetrahydroxy-3'-prenylchalcone (**2**).

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