PERGAMON

Phytochemistry 59 (2002) 99–104

PHYTOCHEMISTRY

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β-Methoxy-γ-methylene-α,β-unsaturated-γ-butyrolactones from *Artabotrys hexapetalus*

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Received 18 June 2001; received in revised form 5 October 2001

Abstract

The dichloromethane extract of the aerial parts of *Artabotrys hexapetalus* afforded three β-methoxy-γ-methylene-α,β-unsaturated-γ-butyrolactones, which are proposed to be derived from a C_{18} unsaturated fatty acid by a biosynthetic route similar to that proposed for the Annonaceous acetogenins. The structure of the unique β-methoxy-γ-methylene-substituted, α,β-unsaturated-γ-butyrolactone ring of artapetalins A–C (**1**–**3**) was determined by 2D-NMR spectroscopic analyses. Two unusual simple butyrolactones, (+)-tulipalin B and (2*R*,3*R*)- 3-hydroxy-2-methylbutyrolactone were also isolated from this species. © 2002 Published by Elsevier Science Ltd.

Keywords: *Artabotrys hexapetalus*; Annonaceae; β-Methoxy-γ-methylene-α,β-unsaturated-γ-butyrolactones; Artapetalins A–C, (+)-Tulipalin B; Unsaturated fatty acid derivative; Biosynthesis; 2D NMR

1. Introduction

Artabotrys hexapetalus [(L.f.) Bhandari] (Annonaceae) is widely distributed in the southern part of China, and is used in traditional Chinese medicine for the treatment of malaria and scrofula (Li et al., 1997; Li and Yu, 1998). The phytochemistry of the genus *Artabotrys* includes compounds classified as bisabolane (Liang et al., 1979a,b; Zhang et al., 1988; Boukouvalos et al., 1995) and guaiane sesquiterpenes (Fleischer et al., 1997), steroids (Hasan et al., 1987), aporphine (Eloumi-Ropivia et al., 1985; Wu et al., 1989; Guinaudeau et al., 1994; Wijeratne et al., 1995, 1996; Hsieh et al., 1999) and tetrahydroberberine (Cave et al., 1986) alkaloids, and long chain hydrocarbons (Jain et al., 1998). Previous phytochemical studies of *A. hexapetalus* have yielded several flavonoid glycosides (Li and Yu, 1997, 1998; Li et al., 1997). We now report the isolation and characterization of three novel β-methoxy-γ-methylene-α,β-unsaturated-γ-butyrolactones, artapetalins A–C, together with the unusual butyrolactones (+)-tulipalin B and (2*R*,3*R*)-(+)-3-hydroxy-2-methylbutyrolactone.

2. Results and discussion

The dichloromethane extract of the aerial parts of *A. hexapetalus* yielded three novel compounds **1**–**3** after separation by CC and HPLC (Fig. 1).

The mass spectrum of artapetalin A (**1**) contained a peak for the molecular ion at *m*/*z* 344, which corresponded to the molecular formula $C_{22}H_{32}O_3$ in HREIMS, indicating seven double bond equivalents (unsaturation number) in the structure of **1**. The ^1H and ^{13}C NMR spectra of **1** (Table 1) revealed that five of these equivalents were present as carbon-carbon double bonds [δ_C 161.3 C, 149.9 C, 132.0 CH, 130.1 CH, 128.3 CH, 128.2 CH, 127.8 CH, 127.1 CH, 105.9 C, 91.2 CH_2 ppm; δ_H 5.36 (6H, *m*), 4.96 (1H, *d*, *J* = 2.5 Hz), 4.94 (1H, *d*, *J* = 2.5 Hz) ppm] and that one was present as a carbon-oxygen double bond (δ_C 170.3 C ppm), thereby requiring that the structure of **1** contains a single ring in order to satisfy the number of double bond equivalents. 2D NMR spectral analysis of **1** [HSQC (Table 1), HMBC and ^1H–^1H COSY (Fig. 2)] allowed the assignment of three of these carbon-carbon double bonds to the C_{16} unsaturated hydrocarbon portion of **1**. These three double bonds were shown to be present as "skipped dienes" [double bonds separated by a single methylene (CH_2) unit] and the ^{13}C chemical shifts observed for the saturated carbons inside and adjacent (C-11, 14, 17 and

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0031-9422/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0031-9422(01)00433-2

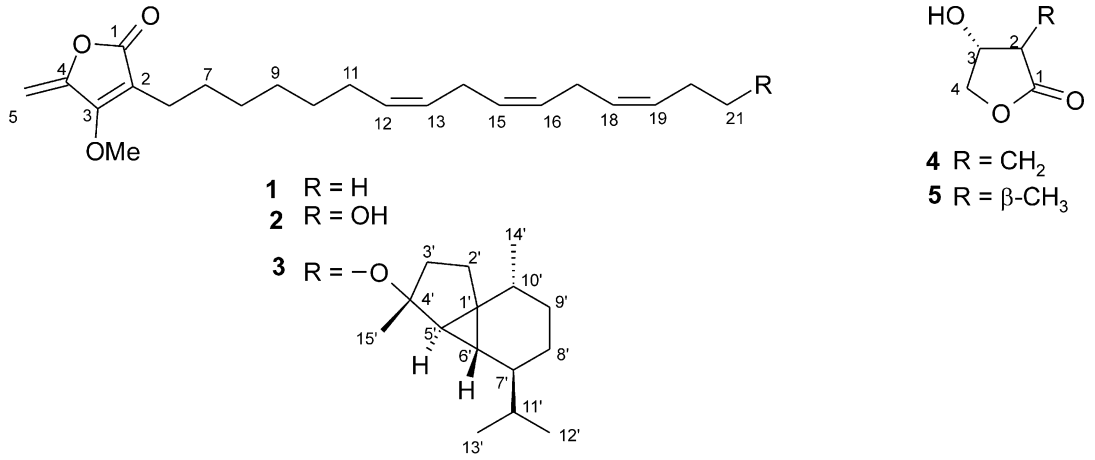

Fig. 1. Unusual butyrolactones isolated from *Artabotrys hexapetalus* (relative stereochemistry only shown for the 4-*epi*-cubebol moiety in compound **3**).

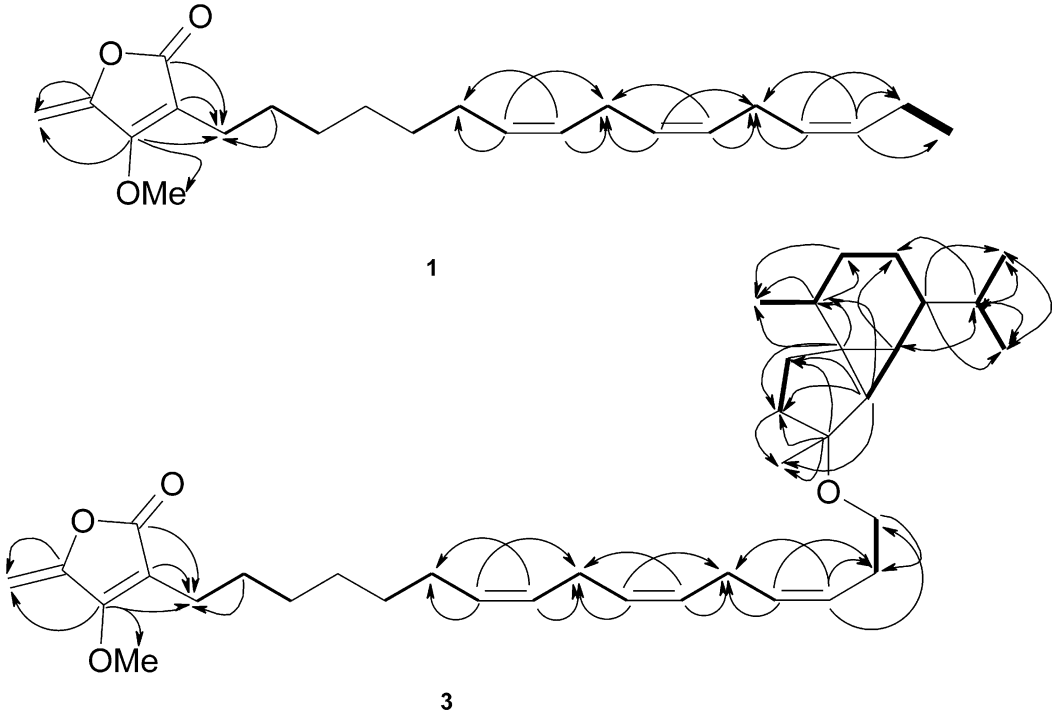

Fig. 2. HMBC correlations used in establishing the structures of compounds **1** and **3** are indicated by arrows from ^{13}C to ^{1}H. ^{1}H–^{1}H COSY correlations are indicated by bold lines in the structure.

20; δ_C 27.2, 25.5, 25.6 and 20.5 ppm, respectively) to these "skipped diene" double bonds (Δ^{12}, Δ^{15} and Δ^{18}) indicated that all three were present as their *cis* geometric isomers (Gunstone et al., 1977) as found in α-linolenic acid (Sandri and Viala, 1995). The ^{13}C chemical resonances at these positions are expected to be shifted upfield by about 5 ppm (Rakoff and Emken, 1982) when the two alkyl substituents are present on the same side of the double bond, as the result of a strong steric interaction, the so-called "γ-effect", which is absent for the corresponding *trans* isomer.

The remaining two carbon–carbon double bonds, the carbon–oxygen double bond and the ring identified in compound **1** were assigned as being part of a β-methoxy-γ-methylene-substituted α,β-unsaturated-γ-butyrolactone functional group on the basis of correlations observed in the HMBC spectrum (Fig. 2). The unusually upfield signal for the C-2 alkene resonance (δ_C 105.9 ppm) in the butyrolactone ring and the correspondingly downfield signal for its partner (δ_C 161.3 ppm, C-3) in the ^{13}C NMR spectrum of **1** were consistent with the electron-withdrawing effect of the carbonyl substituent at C-2 and the electron-donating effect of the methoxyl group at the C-3 position (3-OMe) acting in concert to produce a large separation in chemical shift across the $\Delta^{2,3}$ double bond. The other

Table 1
^{13}C and ^{1}H NMR spectroscopic assignments for compounds **1**–**3**

	δ ^{13}C[a,b]			δ ^{1}H[a,c]		
Assignment[e]	**1**	**2**	**3**	**1**	**2**	**3**
1 (C)	170.3	170.4	170.4	–	–	–
2 (C)	105.9	105.9	105.9	–	–	–
3 (C)	161.3	161.4	161.4	–	–	–
4 (C)	149.9	149.8	149.4	–	–	–
5a (CH_2)	91.2	91.3	91.6	4.96 (*d* 2.5)	4.97 (*d* 2.5)	4.96 (*d* 2.3)
5b				4.94 (*d* 2.5)	4.94 (*d* 2.5)	4.94 (*d* 2.3)
6 (CH_2)	23.2	23.2	23.3	2.45 (2H *t* 7.9)	2.45 (2H *t* 7.9)	2.45 (2H *t* 7.8)
7 (CH_2)	30.3	30.3	30.3	1.58 (2H)	1.54 (2H)	1.53 (2H)
8 (CH_2)	29.5	29.5	29.6	1.35 (2H)	1.35 (2H)	1.35 (2H)
9 (CH_2)	29.4	29.4	29.5	1.35 (2H)	1.35 (2H)	1.35 (2H)
10 (CH_2)	29.0	29.0	29.1	1.35 (2H)	1.35 (2H)	1.35 (2H)
11 (CH_2)	27.2	27.2	27.2	2.04 (2H)	2.05 (2H *dt* 6.5, 6.5)	2.05 (2H)
12 (CH)	130.1	130.2	130.3	5.36	5.39	5.38
13 (CH)	127.8	127.8[d]	128.4	5.36	5.37	5.36
14 (CH_2)	25.5	25.7	25.7	2.80 (2H *br*)	2.80 (2H *dd* 6.5, 6.5)	2.80 (2H *dd* 6.5, 6.5)
15 (CH)	128.3[d]	128.6[d]	128.2 [d]	5.36	5.37	5.36
16 (CH)	128.2[d]	127.7[d]	127.9[d]	5.36	5.37	5.36
17 (CH_2)	25.6	25.8	25.8	2.80 (2H *br*)	2.85 (2H *dd* 6.7, 6.7)	2.82 (2H *dd* 6.5, 6.5)
18 (CH)	127.1	131.1	129.3	5.36	5.52 (*dt* 10.6, 6.7)	5.41
19 (CH)	132.0	125.6	126.7	5.36	5.42 (*dt* 10.6, 6.7)	5.42
20a (CH_2)	20.5	30.8	29.0	2.06 (2H)	2.36 (2H *ddd* 6.7, 6.7, 6.7)	2.28 (2H)
20b						
21a (CH_3)	14.3	62.2 (CH_2)	61.5 (CH_2)	0.97 (3H *t* 7.5)	3.66 (2H *t* 6.7)	3.41
21b						3.35
3-OMe (CH_3)	58.8	58.9	58.9	4.11 (3H *s*)	4.11 (3H *s*)	4.11 (3H *s*)
1′ (C)			34.8			–
2α′ (CH_2)			30.5			2.05
2β′						1.40
3α′ (CH_2)			33.7			1.62
3β′						1.11
4′ (C)			85.4			–
5′ (CH)			36.7			0.96
6′ (CH)			24.5			0.37 (*dd* 3.2, 3.2)
7′ (CH)			44.9			0.97
8α′ (CH_2)			27.3			1.40
8β′						0.80
9α′ (CH_2)			32.0			0.54 (*ddd* 13.3, 13.3, 13.3)
9β′						1.59
10′ (CH)			30.7			1.73
11′ (CH)			33.8			1.52
12′[d](CH_3)			20.2			0.88 (3H *d* 6.4)
13′[d](CH_3)			20.0			0.93 (3H *d* 7.1)
14′ (CH_3)			19.1			0.97 (3H *d* 6.2)
15′ (CH_3)			21.5			1.27 (3H *s*)

[a] ^{13}C directly attached to ^{1}H determined by HSQC.
[b] Multiplicity determined by DEPT indicated in parentheses.
[c] Multiplicity and coupling constant(s) (in Hz), when resolved in 1D NMR, indicated in parentheses; integrals which are not shown correspond to [1H].
[d] Signals interchangeable.
[e] α And β assignments for the 4-*epi*-cubebol moiety of compound **3** refer to the relative stereochemistry shown for this compound in Fig. 1.

(terminal) double bond at C-4 of the butyrolactone ring showed a slightly less marked difference in chemical shifts for the two alkene carbons (δ_C 91.2 ppm for C-5 and δ_C 149.9 ppm for C-4) which was again consistent with substitution by oxygen in the ring of the lactone at the C-4 position of this double bond. A strong absorbance at 1767 cm^{-1} in the IR spectrum of **1** was consistent with the presence of the γ-butyrolactone ring.

Artapetalins B (**2**) and C (**3**) were identified as the 21-hydroxyl and 21-(4-*epi*-cubebol) derivatives of compound **1** by 2D NMR (unambiguous assignments of most of the resonances in the ^{1}H and ^{13}C NMR spectra

of these compounds are given in Table 1). NMR spectroscopic analysis of compound **2** gave essentially the same chemical shifts and correlations as were observed for compound **1**, with the exception of the 21-position, which is substituted by a primary hydroxyl group, resulting in strongly downfield ^{1}H and ^{13}C chemical shifts for this position as compared with **1**. The proximity of this substituent to the $\Delta^{18,19}$ double bond also resulted in a sufficiently large perturbation to the chemical shifts of the H-18 and H-19 alkene protons that it became possible to measure the coupling constant ($^{3}J_{HH} = 10.6$ Hz) across the $\Delta^{18,19}$ double bond, leaving little doubt that the stereochemistry at this position was *cis*, as had already been deduced for compound **1** from the evidence of ^{13}C chemical shifts at C-11, 14, 17 and 20. The IR spectrum of artapetalin B contained an additional broad absorption at 3530 cm^{-1}, which confirmed the presence of a hydroxyl group.

For compound **3**, two distinct spin systems were observed by 2D NMR spectroscopic analysis, with an unfortunate absence of any correlations in ^{1}H–^{1}H COSY and HMBC spectra to connect the two. (In our experience the absence of 3-bond correlations in HMBC spectra about nuclei which are connected by a freely rotating ether linkage is not unusual.) One of these spin systems was nearly identical with that of compound **2**, except for a slightly upfield shift in the signals at H-21 and C-21 for **3** as compared with **2** (Table 1). The second spin system was deduced to be due to a 4-*epi*-cubebol unit by correlations observed in the 2D NMR spectrum (Fig. 2) and by comparison of ^{1}H and ^{13}C chemical shifts for the 4-*epi*-cubebol moiety in **3** with fully assigned spectra for 4-*epi*-cubebol and its 4-OH derivatives reported in the literature (Pizza and de Tommasi, 1987; de Rosa et al., 1994; Hieda et al., 1996). Our proposal for an ether functionality linking the two independent spin systems between C-21 and C-4′ was confirmed by analysis of the NOESY spectrum of **3** which showed correlations between H-21 (δ_H 3.41, 3.35 ppm) of the butyrolactone/fatty acid spin system and H-5′ (δ_H 0.96 ppm) and H-15′ (δ_H 1.27 ppm) of the 4-*epi*-cubebol moiety. NOESY correlations within the 4-*epi*-cubebol moiety confirmed the relative stereochemistry shown in Fig. 1, although the absolute stereochemistry of this derivative remains uncertain.

Many secondary metabolites are now known to contain butyrolactone rings. However, to the best of our knowledge, the β-methoxy-γ-methylene-substituted α,β-unsaturated-γ-butyrolactone functional group which is found in compounds **1**–**3** has not been reported previously as part of the structure of any natural product. The closest relatives we have been able to find to compounds **1**–**3** are the acyl esters of variabilin, a β-methyl-γ-methoxy-α,β-unsaturated-γ-butyrolactone, which are described in the fatty acid literature (Lie Ken Jie and Pasha, 1998). We propose that the biogenesis of this unusual structural feature arises by the condensation of α-linolenic acid (18:3 [9*Z*, 12*Z*, 15*Z*]) with pyruvic acid (C_3), and the final tautomerization of a ketone to an enol, which is methylated by *S*-adenosylmethionine (SAM), as shown in Fig. 3. This proposal is based on the biosynthesis of the Annonaceous acetogenins, which are now commonly reported from the Annonaceae, from C_{32} or C_{34} long chain fatty acids which are combined with a propan-2-ol unit at C-2 to form an α,β-unsaturated-γ-methyl-γ-butyrolactone ring (Zeng et al., 1996). We therefore propose that the novel structural class of β-methoxy-γ-methylene-substituted α,β-unsaturated-γ-butyrolactone be tentatively assigned within the broader class of the Annonaceous acetogenins, pending the results of future biosynthetic studies.

Two further known simple butyrolactones, (+)-tulipalin B (**4**) and (2*R*,3*R*)-3-hydroxy-2-methylbutyrolactone (**5**) were also isolated from *A. hexapetalus*. The structures

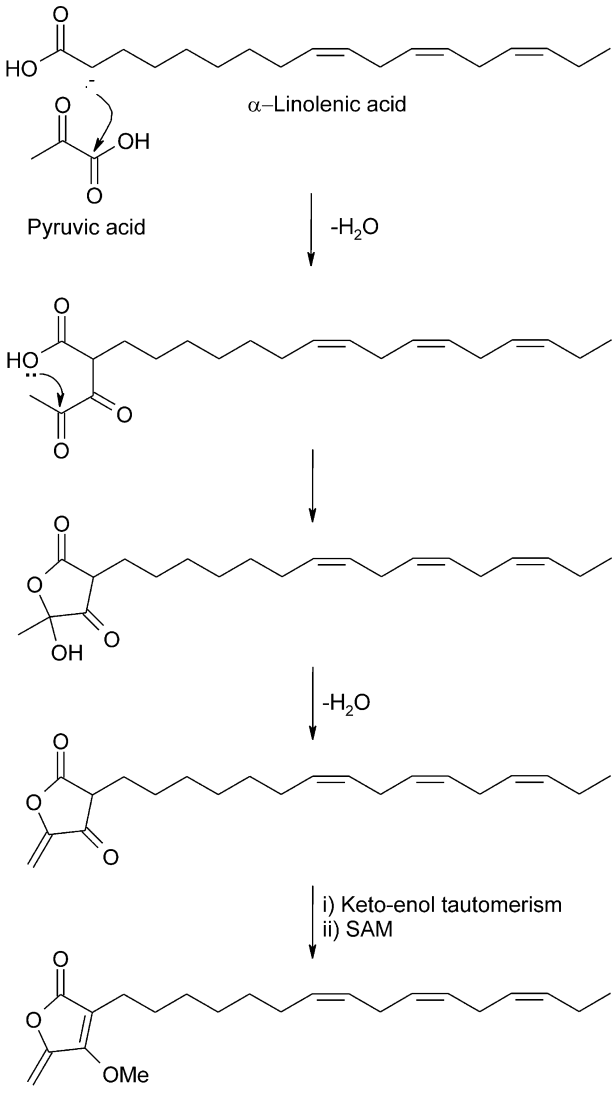

Fig. 3. Possible biogenesis of compound **1** from a C_{18} unsaturated fatty acid precursor.

of these unusual lactones were determined by 2D NMR spectroscopic analyses and confirmed by comparison of their ^{1}H NMR spectra and specific optical rotations with the literature (Wyss et al., 1981; Jaime et al., 1986; Cardona et al., 1994; Christensen, 1999). Although these two butyrolactones are rare as natural products, synthetic methods for the preparation of both compounds have been reported (Larchevêque and Henrot, 1990; Papageorgiou and Benezra, 1985). In addition to the novel or unusual butyrolactones **1**–**5**, significant amounts of the common terpenoids humulene (5.7 mg), caryophyllene (37.5 mg), caryophyllene oxide (9.5 mg) and lutein (xanthophyll, β,ε-carotene-3,3′-diol) (9.6 mg) were also isolated from the aerial parts of *A. hexapetalus*.

3. Experimental

Chemical shifts are expressed in ppm (δ) relative to TMS as internal standard. All NMR experiments were run on a Bruker DRX 500 instrument. Two-dimensional spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. HREMIS were recorded at 70 eV on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in $CHCl_3$ on a Shimadzu FTIR-8201 PC spectrometer. TLC plates were developed using *p*-anisaldehyde. Column chromatography was performed using silica gel 60–200 μm (Merck). HPLC separations were preformed using a Varian chromatograph equipped with RI star 9040 and UV 9050 detectors and an Intersil PREP–SIL column (20 mm×25 cm), operating isocratically with EtOAc/*n*-hexane mixtures at a flow rate of 8 ml/min.

3.1. Plant material

The aerial parts of *A. hexapetalus* were collected from a cultivated specimen grown at the Kadoorie farm and botanic garden, Lam Kam Road, Tai Po, New Territories, Hong Kong in November 1999 and was taxonomically identified by Dr. Lawrence Chau of the Kadoorie farm. Taxonomically verified specimens are held at the Kadoorie farm and botanic garden.

3.2. Extraction and isolation

The aerial parts of *A. hexapetalus* (358 g) were pulverized to a fine powder under liq. N_2 and repeatedly extracted with CH_2Cl_2. The combined solvent extracts were dried ($MgSO_4$) and solvent was removed under reduced pressure to yield a dark brown gum (4.17 g; 1.2% w/w) which was subjected to gradient CC (20×1.5 cm) [developing solvents 100% *n*-hexane (100 ml)→20% EtOAc/80% *n*-hexane (200 ml)→40% EtOAc/60% *n*-hexane (200 ml)→60% EtOAc/40% *n*-hexane (200 ml)→80% EtOAc/20% *n*-hexane (400 ml)→100% EtOAc (250 ml)→50% MeOH/50% EtOAc (200 ml)→100% MeOH (300 ml)]. Fractions from CC were further purified by HPLC yielding: **1** (29.2 mg, R_t 16.0 min in 10% EtOAc/*n*-hexane); **2** (22.8 mg, R_t 26.1 min in 36% EtOAc/*n*-hexane); **3** (2.1 mg, R_t 15.0 min in 10% EtOAc/*n*-hexane); **4** (43.3 mg, R_t 57.3 min in 46% EtOAc/*n*-hexane/4% CH_3COOH); and **5** (3.3 mg, R_t 51.9 min in 46% EtOAc/*n*-hexane/ 4% CH_3COOH).

3.3. Artapetalin A (*1*)

Gum. IR ($CHCl_3$) ν_{max} 3013, 2932, 2858, 1767, 1670, 1636, 1456 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table 1; HREIMS: *m*/*z* (rel. int.) 344.2353 (M^+, calc. for $C_{22}H_{32}O_3$ requires 344.2351) (25), 329 (3), 315 (12), 301 (8), 252 (22), 153 (68), 139 (100).

3.4. Artapetalin B (*2*)

Gum. IR ($CHCl_3$) ν_{max} 3530 (*br*), 3013, 2932, 2858, 1763, 1670, 1634, 1456 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table 1; HREIMS: *m*/*z* (rel. int.) 360.2309 (M^+, calc. for $C_{22}H_{32}O_4$ requires 360.2301).

3.5. Artapetalin C (*3*)

Gum. $[\alpha]_D$ −7.4 (*c* = 0.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3028, 2930, 2856, 1765, 1634, 1458 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table 1; HREIMS: *m*/*z* (rel. int.) 204.1881 (calc. for $C_{15}H_{24}$ from fragmentation of the 4-epi-cubebol moiety requires 204.1878) (32), 189 (12), 161 (100).

3.6. (+)-Tulipalin B (*4*)

Gum. $[\alpha]_D$ +76.0 (*c* = 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3430 (*br*), 3013, 2930, 2858, 1742, 1466 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ ppm): 6.41 (1H, *d*, *J* = 1.7 Hz, 2 = CH_2), 6.05 (1H, *d*, *J* = 1.7 Hz, 2 = CH_2), 4.96 (1H, *m*, H-3), 4.51 (1H, *dd*, *J* = 10.1, 6.6 Hz, H-4), 4.19 (1H, *dd*, *J* = 10.1, 3.7 Hz, H-4), 3.92 (1H, *br s*, OH); ^{13}C NMR (δ, $CDCl_3$ ppm): 170.0 C (C-1), 137.6 C (C-2), 126.9 CH_2 (2 = CH_2), 73.7 CH_2 (C-4), 67.4 CH (C-3); HREIMS: *m*/*z* (rel. int.) 115.0405 ($M^+ + 1$, calc. for $C_5H_7O_3$ requires 115.0395).

3.7. (2R,3R)-3-Hydroxy-2-methylbutyrolactone (*5*)

Gum. $[\alpha]_D$ +10.8 (c = 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3422 (*br*), 3024, 2930, 1774, 1458 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ ppm): 4.46 (1H, *dd* *J* = 10.5, 5.9 Hz, H-4), 4.28 (1H, *ddd*, *J* = 5.9, 5.6, 5.3 Hz, H-3), 4.06 (1H, *dd*, *J* = 10.5, 5.3 Hz, H-4), 2.56 (1H, *dq*, J = 5.6, 7.4 Hz, H-2), 2.28 (1H, *br s*, −OH), 1.31 (3H, *d*, *J* = 7.4 Hz, 2-Me); ^{13}C NMR (δ, $CDCl_3$ ppm): 177.8 C (C-1), 74.1 CH (C-3), 72.3 CH_2 (C-4), 43.3 CH (C-2), 12.9 CH_3 (2-Me);

HREIMS: m/z (rel. int.) 116.0473 (M^+, calc. for $C_5H_8O_3$ requires 116.0473).

Acknowledgements

We thank Dr. Lawrence Chau of the Kadoorie farm and botanic garden for kindly supplying a sample of *A. hexapetalus*, and Dr. Richard Saunders of the Ecology and Biodiversity Department of The University of Hong Kong for his help in procuring the sample. The Chemistry Department of The University of Hong Kong provided a postgraduate studentship to H.-F.W. This work was supported by a grant from the CRCG.

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