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Cyclobutanes from *Combretum albopunctatum*

David R. Katerere[a,1], Alexander I. Gray[a], Alan R. Kennedy[b], Robert J. Nash[c], Roger D. Waigh[a,*]

[a]*Department of Pharmaceutical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, UK*
[b]*Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, UK*
[c]*MolecularNature Ltd, IGER, Plas Goggerdan, Aberystwyth, Dyfed SY23 3EB, UK*

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Abstract

A dichloromethane extract of the aerial parts of *Combretum albopunctatum* Suesseng afforded five phenolic compounds—three known flavonoids and two novel cyclobutane chalcone dimers. The chemical structures were determined by standard spectroscopic techniques and the structure and relative stereochemistry of one chalcone dimer, *rel*-(1α,2β)-di-(2,6-dimethoxy-4-hydroxy)-benzoyl-*rel*-(3α,4β)-diphenylcyclobutane, were confirmed by single crystal X-ray diffraction.

Keywords: *Combretum albopunctatum*; Combretaceae; Flavonoids; Chalcones; Flavanones Chalcone dimer

1. Introduction

In our continuing phytochemical survey of the African Combretaceae, we report here the first phytochemical and pharmacological screening of the aerial parts of *Combretum albopunctatum* Suesseng, which occurs as a thicket-forming shrub or small tree up to 3 m high with a tendency to climb. It is found in hot dry areas on grits and sandstones or in alluvial or riverine thickets. It was collected on the Zambezi Escarpment, a hot, sandy and dry low-lying area in Northern Zimbabwe. Three flavonoids, alpinetin **3**, its chalcone derivative **5** and pinocembrin **4**, a flavanone, were isolated and identified. These are common phenolics but have only been recently reported to occur in the Combretaceae (Katerere, 2001). Two chalcone dimers, both based on the cyclobutane ring, are reported here for the first time.

2. Results and discussion

Compound **1** was isolated by HPLC. The ^{1}H NMR showed three methoxy groups, one at δ_H 3.26, δ_C 56.8, and two which were equivalent at δ_H 3.53, δ_C 57.4. The most striking feature of the ^{1}H NMR spectrum was four sets of well-resolved triplets between *ca.* δ_H 4.20 (δ_C 45) and δ_H 5.40 (δ_C 55), each one due to a single methine proton and with a coupling constant of 9 Hz. The aromatic protons were located at δ_H 6.11, ($J=2$, δ_C 94.1), δ_H 6.48, ($J=2$, δ_C 98.8), a singlet of two protons at δ_H 6.38, δ_C 95.0 and a complex pattern of merging chemical shifts ca. δ_H 7.20–7.70 (δ_C 130). Having tried several solvents, there was better resolution of this area in pyridine, which indicated the presence of two unsubstituted phenyl rings. Use of pyridine as solvent also revealed three phenolic protons, at δ 11.9, 13.1 and 14.57, the latter being strongly H-bonded.

HR-FAB-MS gave the quasi-molecular ion, $M+H^+$, which was also the base peak at 555.2002, corresponding to a molecular formula of $C_{33}H_{30}O_8$. There were also prominent peaks at 401.1 (20.7%) $[M–C_8H_9O_3]^+$, 347.1 (21.3%) $[M–C_{11}H_{11}O_4]^+$, 285.1 (99.9%) $[M–C_{13}H_{13}O_6]^+$ 277.2 (29.9%) $[M–C_{17}H_9O_4]^+$, 271.1 (21.6%) $[M–C_{17}H_{15}O_7]^+$, 246.1 (24.8%) $[M–C_{19}H_{16}O_4]^+$ and 207.1 (30.3%) $[M–C_{19}H_{21}O_6]^+$.

The structural connectivities were established, in part, from ^{1}H–^{1}H COSY. It was found that the most downfield triplet, a methine designated H-1 at δ_H 5.31, δ_C 55.1 was connected to H-2, at δ_H 4.81, δ_C 55.6 which in turn was connected to H-3 at δ_H 4.22, δ_C 50.5 and then to a fourth methine at H-4, δ_H 4.50, δ_C 48.4 which in turn

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* Corresponding author.

[1] Present address: Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, PO Box 2034, Pretoria 0001, Republic of South Africa

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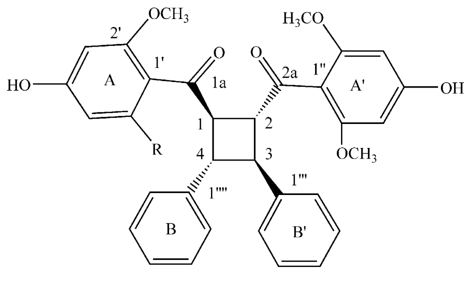
was connected to the most downfield proton, H-1. Thus, the presence of a cyclobutane ring was established. The chemical shifts are in total agreement with those of similar structures in the literature (Montaudo et al., 1974; Toda et al., 1998). HMBC supported this conclusion, showing all the expected ^2J and ^3J correlations.

The aromatic protons attached to the oxygenated rings occurred at higher field than the unsubstituted rings with the protons at δ_H 6.11, δ_C 94.1, δ_H 6.48, δ_C 98.8 being *meta*-coupled. A singlet at δ_H 6.38, δ_C 95.0 integrated for two protons, located on another ring.

The NMR and FABMS point to a dimer based on two different chalcone monomers. Two structures were proposed for **1**, either α-truxillic (head-to-tail) or β-truxinic (head-to-head), with two similar unsubstituted benzene rings, a symmetrically substituted aromatic ring (hence two equivalent protons) and a fourth ring with non-equivalent protons. The truxillic (head-to-tail) orientation could be eliminated by HMBC as the correlations seen between the protons in the cyclobutane ring and the phenyl attachments are not possible in this arrangement. Both H-3 at δ_H 4.22 (δ_C 50.5) and H-4 at δ_H 4.50 (δ_C 48.4) were placed next to the benzene rings because they showed ^2J coupling to C-1'''' (145.5) and C-1''' (145.7) as well as ^3J to C-2'''/6''' (129.9) and C-2''''/6'''' (129.0). These two cyclobutyl protons showed coupling to separate carbonyl signals, H-3 with C-1'a (δ_C 204.0) and H-4 with C-1'' a (δ_C 205.4). H-1 correlated to C-1' a, which is on the other monomer, while H-2 correlated to C-1'' a.

The important NOESY interactions were between H-1 and H-3 and between H-2 and H-4, so that **1** was identified as *rel*-1β-(4,6-dihydroxy-2-methoxy)-benzoyl-*rel*-2α-(2,6-dimethoxy-4-hydroxy)-benzoyl-*rel*-(3β,4α)-diphenylcyclobutane. This compound is reported here for the first time. Despite repeated attempts, we were unable to grow single crystals of **1** suitable for analysis by X-ray crystallography. Compound **1** is chiral and showed an optical rotation of 19.3°, which would be consistent with a biosynthetic origin. Previous workers have tended to favour a purely photochemical mechanism for the synthesis of related cyclobutanes from plants (Seidel et al., 2000), in accord with the usual method of preparation in synthetic organic chemistry. It is worth noting that laboratory photodimerisation of chalcones in the molten state also gives *anti*-head-to-head products, which are of course racemic (Toda et al., 1998). While photochemical assistance is not ruled out, it would appear that the plant may constrain the precursor in a pre-chiral conformation prior to dimerisation.



1, R = OH, **2**, R = OCH$_3$

Fig. 1. Structures of **1** and **2**.

Compound **2** was isolated using a column of Sephadex LH-20 eluted with 50% MeOH/CHCl$_3$ and was also isolated from the leaves of *C. apiculatum* (Katerere, 2001). The IR spectra of **1** and **2** were similar, showing the presence of hydroxyl (ca. 3295, 1340, 1130 cm^{-1}), methoxyl (ca. 2845, 1130 cm^{-1}), α,β-unsaturated carbonyl (ca. 1590 cm^{-1}), and benzenoid (ca. 815, 750, 715 cm^{-1}). Compound **2** (Fig. 1) had an optical rotation of 17.5°.

The 1D NMR of **2** showed four methoxy groups at δ_H 3.44, δ_C 55.9, two multiplets, each integrating for two protons, at δ_H 4.39 δ_C 46.4 and δ_H 4.57 δ_C 55.2, a singlet at δ_H 6.32 integrating for four protons, and a complex set of multiplets at ca. δ_H 7.19–7.51 (δ_C 127–130) indicating two mono-substituted phenyl rings.

HR-FAB-MS gave M + 1 at *m*/*z* 569.2175 which requires the molecular ion to be $C_{34}H_{32}O_8$. Prominent peaks were also seen at *m*/*z* 506 (6.5%) $[M–C_2H_6O_2]^+$, 415 (20%) $[M–C_{12}H_8]^+$, 284 (54%) $[M–C_{17}H_{16}O_4]^+$, 181 (100%) $[M–C_{25}H_{23}O_4]^+$and 166 (62%) $[M–C_8H_6O_4]^+$ (Fig. 2). This suggested that **2** was another chalcone dimer. ^1H ^1H COSY showed coupling between

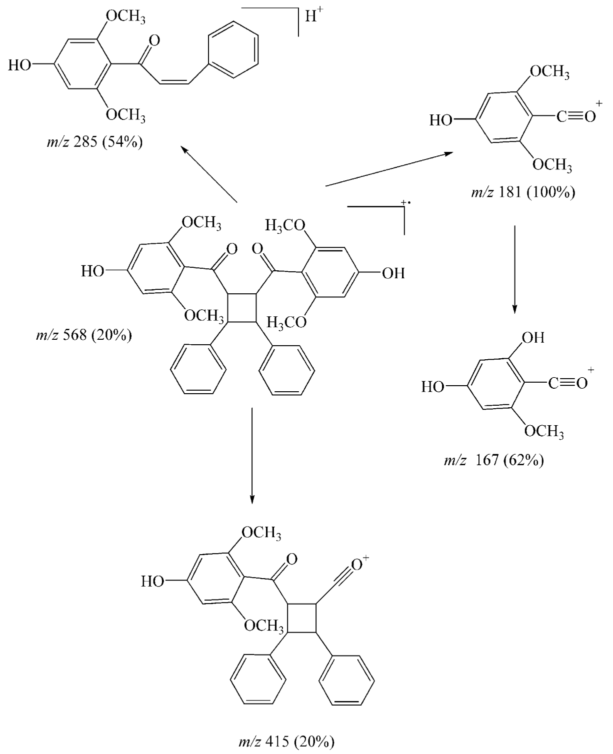


Fig. 2. Suggested electron impact mass spectral fragmentation pattern for compound **2**.

the multiplets at δ_H 4.57 and 4.39 and HMBC showed both 1- and 3- bond correlations to the carbons to which they were attached. This pattern suggested that the protons were arranged in a symmetrically-substituted cyclobutane ring. Both multiplets showed strong ^3J correlations to the carbonyl and aromatic carbons at δ_C 202.9 and δ_C 144.4 ppm, respectively, the points of attachment of the substituents to the cyclobutane ring.

The four methoxy groups at δ_H 3.44 ppm, δ_C 55.9 ppm, were attached to carbons resonating at δ_C 159.9 ppm, indicating symmetrical substitution in both rings. These carbons were designated C-2′ and C-6′. They showed strong correlations to the protons on C-3′ and C-5′ which were also superimposed at δ_H 6.32.

The methoxys showed NOESY cross-peaks with the cyclobutane ring protons, evidence that the oxygenated rings had phloroglucinol (rather than pyrogallol) substitution patterns. Two basic structures were proposed, both dimers of 4-hydroxy-2,6-dimethoxychalcone, with the head-to-head (α-truxinic) or head-to-tail (β-truxillic) arrangements, but neither these nor the relative configuration could be differentiated by NOESY or HMBC, owing to the overall symmetry of the molecule.

Single crystals of **2** were obtained by slow evaporation of a methanol–ethanol solution. This allowed the structure to be determined by X-ray diffraction, which confirmed that compound **2** was *rel* (1α,2β)-di-(2,6-dimethoxy-4-hydroxy)-benzoyl-*rel* (3α,4β)-diphenylcyclobutane (or 2,6-dimethoxy-4-hydroxychalcone dimer), and allowed an unambiguous assignment of the NMR data.

The crystal structure showed two molecules of **2** to be linked by intermolecular hydrogen bonding between the ketone and hydroxy groups. There was also a third weaker hydrogen bond to the O atom of a methoxy group. Small amounts of solvent (both water and ethanol) were incorporated into the crystal. The crystallographic data for **2** confirm it to be the α-truxinic, head to head isomer with alternate α and β protons around the cyclobutane ring (Fig. 3). The bond lengths and angles are normal for such a strained system (Allen et al., 1999) and are in good agreement with those found for the simpler analogue 1,2-dibenzoyl-3,4-diphenylcyclobutane (Caccamese et al., 1978; Toda et al., 1998). The cyclobutane ring shows a degree of puckering (average magnitude of internal torsion angles = 14.3°) which reduces the strain in the ring-system by minimising the extent to which adjacent substituents are eclipsed (C5-C1-C2-C14 −109.4(2), C14-C2-C3-C23 104.6(2), C23-C3-C4-C29 −101.4(3) and C5-C1-C4-C29 101.0(2)°).

The relative stereochemistry of **1** and **2** is the same as that generated from molten precursors when irradiated with UV light (Toda et al., 1998), but the observation of optical rotation for both compounds tends to suggest that they are true natural products. It is possible that **1** is derived from **2** by demethylation, which would be consistent with further biochemical processing. Biosynthesis of **1** from two different monomers appears unlikely to occur randomly, particularly since the third possible dimer, formed from two molecules of **5** (see below), has not been found.

Compound **3** was identified as alpinetin (7-hydroxy-5-methoxyflavanone) which has been previously isolated from *Chrysothamnus nauseosus, Helichrysum herbaceum*, *Dalea scandens*, *Alnus, Alpinia*, *Kaempferia, Eucalyptus* and *Piper* species (Burke and Nair, 1986) and recently from the related species, *C. apiculatum* (Katerere, 2001).

Compound **4** was identified as 5,7-dihydroxyflavanone, or pinocembrin. This commonly occurring flavanone was isolated from the Combretaceae for the first time recently (Katerere, 2001). It has been previously reported from a variety of sources including *Alpinia*, *Alnus, Eucalyptus*, *Pinus*, and *Populus* species (Itokawa et al., 1981).

Compound **5** was identified as 4′,6′-dihydroxy-2′-methoxychalcone or cardamomin. It crystallised from a Sephadex LH-20 fraction obtained by eluting with 100% TCM. It has been previously isolated from *Boesebergia pandura, Pityrogramma chrysophylla,* and species of *Alpinia, Piper and Populus* (Itokawa et al., 1981).

3. Experimental

3.1. General

NMR spectra were recorded with either a Brüker DRX500 NMR spectrometer equipped with an autotune probe and using the automation mode aided by the Brüker programme, Icon-NMR, or Brüker AMX 400 MHz NMR instruments. Infra-red spectra were recorded as KBr discs or drying trichloromethane dissolved samples on NaCl windows by a Matson Genesis series FT-IR spectrophotometer. Melting point (Mp) (unadjusted) measurements were done using the Reichert Apparatus (Austria). HREIMS were run on a Jeol JMS-AX505HA double focusing instrument at 70 eV. FABMS were also run on this instrument using glycerol as the matrix.

In all cases the preparative HPLC method used was a gradient of water/acetonitrile with 0.1% trifluoroacetic acid (TFA) (90%/10% to 0%/100%) for 20–30 min on Waters LC with UV detector. PrepLC column 40 mm (i.d.) and 100 mm long were used with Merck Anal reagents as eluents.

3.2. Plant material

The leaves and fruit of *Combretum albopunctatum* were collected at Guruve, Zambezi Valley in Northern

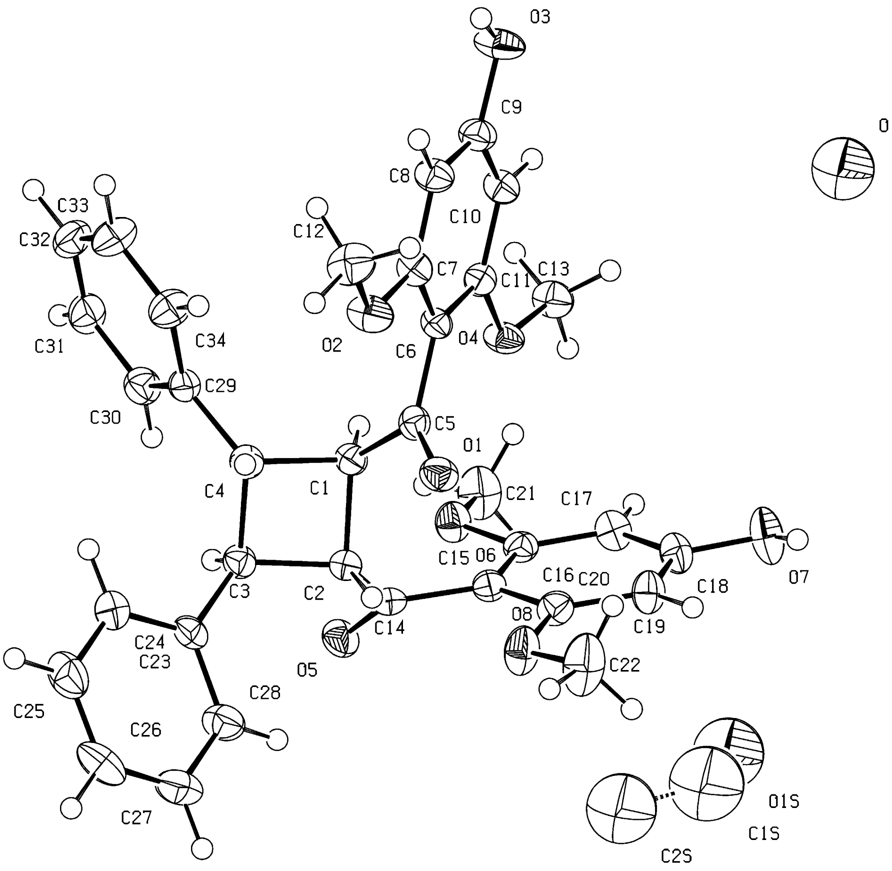


Fig. 3. ORTEP plot of **2** solvate. Non-H atoms are drawn as 50% probability ellipsoids. Selected geometric parameters (Å, °); C1-C2 1.546(3), C2-C3 1.539(3), C3-C4 1.557(3), C1-C4 1.586(3), C4-C1-C2 87.9(2), C1-C2-C3 90.7(2), C2-C3-C4 89.2(2), C3-C4-C1 88.6(2).

Zimbabwe in May 1999. A voucher specimen, SRGH-DRK-5/99-cal, has been deposited at the herbarium of the Harare Botanical Gardens, Zimbabwe.

3.3. *Extraction and isolation*

Dry leaf and fruit of *C. albopunctatum* (419.3 g) was ground, of which 157.0 g was defatted with *n*-hexane and extracted with CH_2Cl_2 at room temperature by maceration. A yield of 4.2 g was obtained from CH_2Cl_2. The extract was dried using a rotary evaporator and then fractionated by gel filtration on Sephadex LH-20 using 100% $CHCl_3$ and then gradually increasing polarity by mixing with MeOH, starting with 1% MeOH, then 2, 5 and 10%. Compounds **3**, **4** and **5** were obtained from eluting with 100% $CHCl_3$, while **1** and **2** co-eluted at 10%MeOH/$CHCl_3$. This last fraction was put through preparative HPLC to separate the two components.

3.3.1. *rel-1β-(4,6-Dihydroxy-2-methoxy)-benzoyl-rel-2α-(2,6-dimethoxy-4-hydroxy)-benzoyl-rel-(3β,4α)-diphenylcyclobutane (**1**)*

Yellowish amorphous solid, 5.6 mg, mp 210 °C $t_R = 7.35$, $[\alpha]_D^{21}$ +19.3° (*c* 0.1 MeOH). IR ν_{max} film cm^{-1} 3290, 3010, 2940, 2840,1616, 1466, 1429, 1235, 1168, 1131, 698. Found [M+1] 555.2002 (C_{33} $H_{31}O_8$ requires 555.2021). HRFABMS *m/z* (rel. int.%): 401.1 (20.7), 347.1 (21.3), 285.1 (99.9), 277.2 (29.9), 271.1 (21.6), 246.1 (24.8), 207.1 (30.3). ^{1}H and ^{13}C NMR: Table 1.

3.3.2. *rel-(1α,2β)-Di-(2,6-dimethoxy-4-hydroxy)-benzoyl-rel-(3α,4β)-diphenylcyclobutane (**2**)*

White crystalline solid, 6.5 mg, mp 213 °C $t_R = 17$min, $[\alpha]_D^{21}$ +17.5° (*c* 0.5 MeOH). IR ν_{max} film cm^{-1} 3292, 3012, 2940, 2844, 1591, 1472, 1429, 1340, 1213, 1132, 1080, 996, 813, 754, 714. Found [M+1] 569.2175 ($C_{34}H_{33}O_8$ requires 569.2177) HRFABMS *m/z* (rel. int.%) 506 (6.5), 415 (20), 284 (54), 181 (100), 166 (62). ^{1}H and ^{13}C NMR: Table 2.

3.3.3. *5-Hydroxy-7-methoxyflavanone (alpinetin) (**3**)*

White crystalline solid, 5 mg. IR ν_{max} film cm^{-1} 3030, 1605 cm^{-1} (OH), 830 cm^{-1} (aryl), 1630 cm^{-1} 2850 cm^{-1} (OCH_3). Found [M$^+$] 270.0891 ($C_{16}H_{14}O_4$ requires 270.0892). HREIMS *m/z* (rel. int.%): 270 (13), 256 (100), 255 (57), 179 (70), 152 (71), 124 (50). NMR data were in accord with those reported by Burke and Nair (1986).

Table 1
^{1}H (500 MHz), ^{13}C (125 MHz) and HMBC data for **1**

Position	δ_H	δ_C	2*J*	3*J*
1	5.31 (*t*, *J* = 9)	55.1	55.6 (C-2), 50.5 (C-4)	204.0 (C-1a)
2	4.81 (*t*, *J* = 9)	55.6	55.1 (C-1), 48.4 (C-3)	205.4 (C-2a), 145.7 (C-1&‴)
3	4.22 (*t*, *J* = 9)	50.5	55.1 (C-1), 48.4 (C-4)	205.4 (C-2a) 129.9 (C-2‴/6‴)
4	4.50 (*t*, *J* = 9)	48.4	55.6 (C-2), 50.5 (C-3), 145.7 (C-1‴), 145.5 (C-1⁗)	204.0 (C-1a) 129.0 (C-2⁗/6⁗)
1a	–	204.0	–	–
1′	–	108.0	–	–
2′	–	165.0	–	–
3′	6.11 (*d*, *J* = 2)	94.1	–	108.0 (C-1′), 98.8 (C-5′)
4′	–	170.2	–	–
5′	6.48 (*d*, *J* = 2)	98.8	–	94.1 (C-3′), 108.0 (C-1′)
6′	–	169.1	–	–
2′-OCH_3	3.26 (*s*)	56.8	–	165.0 (C-2′)
2a	–	205.4	–	–
1″	–	114.0	–	–
2″/6″	–	161.3	–	–
3″/5″	6.38 (*s*)	95.0	161.3 (C-2″), 164.3 (C-4″)	114.0 (C-1″) 95.0 (C-5″)
4″	–	164.3	–	–
2″/6″-OCH_3	3.53 (*s*)	57.4	–	161.3 (C-2″/6″)
1‴	–	145.7	–	–
2‴/6‴	7.54 (*m*)	129.9	130.8 (C-3/5‴)	129.5 (C-4‴), 50.5 (C-3)
3‴/5‴	7.31 (*m*)	130.8	–	145.7 (C-1‴) 130.8 (C-5‴/3‴)
4‴	7.21 (*m*)	129.5	130.8 (C-3/5‴)	129.9 (C-2‴/6‴)
1⁗	–	145.5	–	–
2⁗/6⁗	7.58 (*m*)	129.0	130.8 (C-3/5⁗)	48.4 (C-4), 128.8 (C-4⁗)
3‴/5‴	7.31 (*m*)	130.8	129.0 (C-2/6⁗)	145.5 (C-1⁗)
4⁗	7.21 (*m*)	128.8	130.8 (C-3/5⁗)	129.0 (C-2⁗/6⁗)

Data obtained in C_5D_5N.

Table 2
^{1}H (400MHz), ^{13}C (100MHz) and HMBC data for **2**

Position	δ_H	δ_C	^{2}J	^{3}J
1,2	4.57 (*m*)	55.2	46.4 (C-3), 202.9 (C-1′a)	144.4 (C-1′,1″)
3,4	4.39 (*m*)	46.4	55.2 (C-1), 144.4 (C-1″)	202.9 (C-1a,2a), 128.3 (Ph,2/6)
1a,2a	–	202.9	–	–
1′,1″	–	112.3	–	–
2′/6′,2″,6″	–	159.9	–	–
3′/5′,3″/5″	6.32 (*s*)	93.1	159.9 (C-2′/6′), 162.6 (C-4′)	112.2 (C-1′)
4′,4″	–	162.6	–	–
4xOCH_3	3.44	55.9	–	159.9 (C-2′/6′)
2xPh,1	–	144.4	–	–
2xPh,2/6	7.51 (*m*)	128.3	129.3 (Ph,3/5)	127.4 (Ph,4), 128.3 (Ph,2/6)
2xPh,3/5	7.28 (*m*)	129.3	127.4 (Ph,4)	129.3 (Ph,3/5), 144.4 (Ph,1)
2xPh,4	7.19 (*m*)	127.4	–	128.3 (Ph,3/5)

Data obtained in C_5D_5N.

3.3.4. 5,7-Dihydroxyflavanone (pinocembrin) (**4**)

Cream crystalline solid, 4.5 mg. IR ν_{max} film cm^{-1} 3235, 3070, 1630, 1600, 1495, 1275, 1160, 1090, 830, 765, 700. Found [M^+] 256.0740 ($C_{15}H_{12}O_4$ requires 256.0736). HREIMS *m/z* (rel. int.%): 256 (100), 255 (44), 179 (63), 124 (41), 104 (18). NMR data were in accord with those reported by Itokawa et al. (1981).

3.3.5. 4′,6′-Dihydroxy-2′-methoxychalcone (cardamomin) (**5**)

Yellow crystalline solid, 4.8 mg. IR ν_{max} film cm^{-1} 3130, 2925, 111625, 1450, 1340, 1210, 1115, 970, 745. Found [M^+] 270.0893 ($C_{16}H_{14}O_4$ requires 270.0892). HREIMS *m/z* (rel. int.%): 270 (70), 256 (82), 226 (44), 191 (100), 189 (54), 166 (44), 151 (42), 131 (10), 124 (28), 77 (28). NMR data were in accord with those reported by Itokawa et al. (1981).

3.4. Crystallography

Diffraction data were collected on a partially solvated (ethanol and water) crystal of **2** at 150 K on a Nonius Kappa CCD diffractometer using monochromated MoK_α radiation ($\lambda = 0.71073$ Å). Found triclinic, space group P $\bar{1}$, $a = 9.5521(3)$, $b = 11.3163(3)$, $c = 15.9182(6)$ Å, $\alpha = 77.579(1)$, $\beta = 72.926(1)$, $\gamma = 74.768(1)°$, $V = 1569.20(9)$ Å^3, $Z = 2$. The structure was solved by direct methods using the program SIR-97 (Altomare et al., 1997) with atomic positions and displacement parameters refined using SHELXL-97 (Sheldrick, 1997). The final refinement to convergence was against F^2 with 5271 unique reflections and 401 parameters to give a final *R*-factor of 0.0507 and wR = 0.1140. The non-H atoms of **2** were treated anisotropically and the H atoms placed in idealised geometries. The partially present ethanol and water moieties were treated isotropically (occupancy set at 0.2 after several trial calculations) and their H atoms were not included in the model.

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