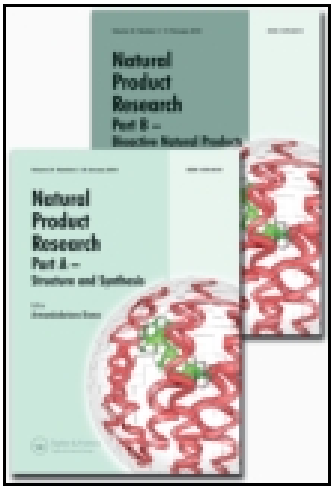

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New methylethers of cordatolides from Calophyllum cordato-oblongum and their synthesis

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New methylethers of cordatolides from *Calophyllum cordato-oblongum* and their synthesis

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Twigs of *Calophyllum cordato-oblongum* Thw. have been shown to contain cordatolide A–OMe, cordatolide B–OMe, cordatolide C–OMe, cordatolide A, cordatolide B, oblongulide, cordatooblongic acid, friedelin, canophyllol, and sitosterol. Methylation of cordatolide B and the attempted methylation of cordatolide A under acidic conditions gave cordatolide B–OMe and 11,12-anhydrocordatolide. Cordatolide A–OMe, cordatolide C–OMe and 11,12-anhydrocordatolide are new compounds.

Keywords: *Calophyllum cordato-oblongum*; Clusiaceae; twigs; cordatolide A–OMe; cordatolide B–OMe; cordatolide C–OMe; 11,12-anhydrocordatolide; methylation

1. Introduction

Calophyllum species are well known for their anti HIV-1 RT active pyranocoumarins (Kashman et al., 1992) (see Figure 1). In recent times, we have shown the anti HIV-1 RT activity of two of pyranocoumarins, cordatolide A (**1**) and cordatolide B (**2**), isolated from *Calophyllum cordato-oblongum* Thw. (Dharmaratne, Wanigasekera, Mata-Greenwood, & Pezzuto, 1998b). Prompted by the above activities and as a part of our continuing study on the *Calophyllum* species (Bandara, Dharmaratne, Sotheeswaran, & Balasubramaniam, 1986; Dharmaratne, Sajeevani, Marasinghe, & Ekanayake, 1998a; Dharmaratne, Sotheeswaran, & Balasubramaniam, 1984; Dharmaratne, Sotheeswaran, Balasubramaniam, & Waight, 1985; Dharmaratne & Wanigasekera, 1996; Dharmaratne, Wanigasekera, & Amarasekera, 1996), the extracts of different parts of *C. cordato-oblongum* were investigated. *Calophyllum cordato-oblongum* (local name Kalu Keena) of the family Clusiaceae (Guttiferae) is a rare endemic plant that grows in the lowland evergreen wet zone forests of Sri Lanka. Previous chemical investigations on this plant gave xanthones, coumarins, chromene acids and triterpenoids (Dharmaratne et al., 1985, 1996, 1998a; Dharmaratne & Wanigasekera, 1997; Gunasekera, Jayatilaka, Selliah, & Sultanbawa, 1977). In this communication, we report the isolation of two new methyl derivatives 12-methylethers of cordatolide A (**3**) and cordatolide C (**4**). So far, cordatolide

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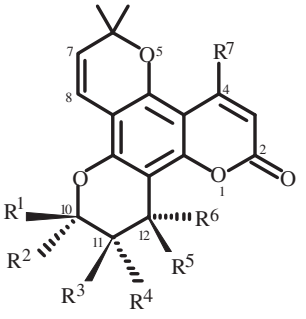

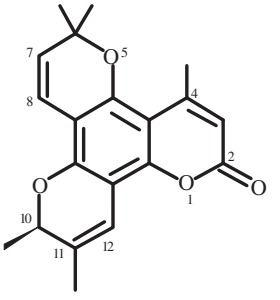

11, 12-anhydrocordatolide **(6)**

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7
Cordatolide A **(1)**	CH_3	H	H	CH_3	OH	H	CH_3
Cordatolide B **(2)**	CH_3	H	H	CH_3	H	OH	CH_3
Cordatolide A–OMe **(3)**	CH_3	H	H	CH_3	OCH_3	H	CH_3
Cordatolide C–OMe **(4)**	CH_3	H	CH_3	H	H	OCH_3	CH_3
Cordatolide B–OMe **(5)**	CH_3	H	H	CH_3	H	OCH_3	CH_3
Calanolide A **(7)**	CH_3	H	H	CH_3	OH	H	CH_2 CH_2 CH_3
Calanolide F **(8)**	H	CH_3	H	CH_3	OH	H	CH_2 CH_2 CH_3
Inophyllum D **(9)**	CH_3	H	CH_3	H	H	OH	Ph
Calanolide F–OMe **(10)**	H	CH_3	H	CH_3	OCH_3	H	CH_2 CH_2 CH_3
Calanolide A–OMe **(11)**	CH_3	H	H	CH_3	OCH_3	H	CH_2 CH_2 CH_3

Figure 1. Pyranocoumarins from *Calophyllum* species and their derivatives.

C has not been reported either as a natural product or as a synthetic product. During the attempted synthesis of cordatolide A–OMe (**3**) from cordatolide A, cordatolide B–OMe (**5**) and a new compound, 11,12-anhydrocordatolide (**6**), were obtained. The same reaction was carried out with cordatolide B (**2**) and again **5** and **6** were obtained. Synthetic implications of the above reactions are also discussed.

2. Results and discussion

Twigs of *C. cordato-oblongum* were processed and extracted (Dharmaratne et al., 1998a) with hot hexane. The hexane extract was subjected to medium-pressure silica gel column chromatography (MPLC) to give cordatolide A (**1**), cordatolide B (**2**), cordatolide B–OMe (**5**), oblongulide, cordatooblongic acid, friedelin, canophyllol, sitosterol (Dharmaratne et al., 1998b) and an unidentified UV active product (***M***), which showed a single spot on TLC plates. The EIMS of ***M*** showed M^+ at m/z 356 with the base peak at m/z 341, which is identical to the EIMS of cordatolide B–OMe (**5**) (Dharmaratne et al., 1998b). The IR spectra of ***M*** showed the presence of carbonyl (coumarin) and olefinic groups. The ^1H

NMR spectrum of ***M*** showed two singlets at δ 3.58 and 3.54, due to two methoxy groups. Further, the ^{1}H NMR spectrum of ***M*** showed two sets of AB quartets and two methyl signals integrated for two olefinic and six alkyl protons for each set, respectively. The above two sets of signals can be assigned to four methyl groups and four olefinic protons of the two 2,2-dimethylpyran ring systems. Comparison of the ^{1}H NMR and EIMS data of ***M*** and **5** indicated ***M*** to be a mixture of the methyl ethers of probably two enantiomers of cordatolides. ^{1}H NMR signals due to all the protons from two diasteroisomers of cordatolides were observed in the spectrum of ***M***. So far, only two cordatolides (A and B) have been reported from *C. cordato-oblongum* (Dharmaratne et al., 1985), and TLC comparisons showed that the R_f value of ***M*** is different from **5**. Therefore, ***M*** should be a mixture of methyl ethers of two different cordatolides other than **5**. Careful examination of the ^{1}H NMR spectrum of ***M*** showed the presence of all the signals due to the protons of cordatolide A–OMe (**3**) (Table 1). However, significant differences were observed amongst some of the ^{1}H NMR signals of chromanol ring substituents of cordatolide A (**1**) and 12-*O*-methylcordatolide **A** (**3**). In addition to the vicinal coupling of J_{10-11} (3.3 Hz) and J_{11-12} (3.6 Hz), a *W* coupling of 1.2 Hz was observed between H-10 and H-12 in compound **3**. The *W* coupling required a pseudo-equatorial configuration for the H-10 and H-12. The same phenomena have been observed in the case of calanolide A (7) and 12-*O*-metylcalanolide A (**11**) (Kashman et al., 1992). Therefore, it appeared that in 12-*O*-methylcordatolide A (**3**), the preferred conformation of the chromanol ring should be inverted relative to cordatolide A (**1**). However, in **1** and **3**, protons H-10, H-11 and H-12 are oriented to α, β, α, respectively. Consequently, in cordatolide A (**1**), protons H-10, H-11 and H-12 should be axial, and in 12-*O*-methylcordatolide A (**3**) they should be equatorial. The remaining signals of ***M*** clearly represented a set of signals due to a new methyl ether (**4**) from a different cordatolide other than **1** and **2**. From the remaining ^{1}H NMR signals of ***M***, the two 1H doublets at δ 5.51 and 6.63 with 9.9 Hz coupling constants and the 6H singlet at δ 1.48 indicated the presence of another 2,2-dimethylpyran ring system in **4**. The singlet at δ 2.55 integrating for six protons should be due to two methyl groups attached to double bonds at C-4 in **3** and **4**. The singlet at δ 5.93 confirmed the presence of an olefinic proton (H-3), as in the case of cordatolide **A** and **B**. The 1H multiplet at δ 4.5 (J = 6.6 and 2.1 Hz) and the 3H doublet at δ 1.42 (J = 6.6 Hz) could be assigned for the 10-H and 10-Me, respectively. The 1H multiplet at δ 2.07 (J = 7.2, 2.1 and 2.1 Hz) and the 3H doublet at δ 0.76 (J = 7.2 Hz) could be assigned for the H-11 and Me-11 of **4**, respectively, and the coupling constants of 2.1 Hz should be due to the coupling of 11-H with 10 and 12-H. Therefore, the coupling constant of 2.1 Hz should be due to the coupling between 10 and 11-H, which revealed that these two protons had an equatorial–axial or an equatorial–equatorial relationship. The doublet at δ 4.39 (J = 2.1 Hz) can be assigned to benzylic proton H-12. In both cases, the coupling constants $J_{10\text{-}11}$ and $J_{11\text{-}12}$ are 2.1 Hz. The above-mentioned low coupling constants (2.1 Hz) among 10-H, 11-H and 12-H indicated the unavailability of trans–diaxial relationships between the neighbouring protons. This is the same relative stereochemistry reported for calanolide F (**8**) (McKee et al., 1996) and inophyllum D (**9**) (Patil et al., 1993). Though **8** and **9** pose an axial–equatorial–equatorial relationship among H-10, H-11 and H-12, calanolide F (**8**) is reported to have Me-10α, Me-11α and OH-12β, whereas in inophyllum D (**9**), it is Me-10β, Me-11β and OH-12α. The coupling constants of calanolide F (**8**) and inophyllum D (**9**) are well in agreement with cordatolide C–OMe (**4**). Therefore, the above two structures are possible for the ring D of 12-*O*-methylcordatolide C. The remaining signals of the ^{13}C NMR spectrum of ***M*** were assigned to the new compound 12-*O*-methylcordatolide C (**4**) in

Table 1. ^{1}H NMR data of dipyranocoumarins ($CDCl_3$).

Proton No.	Calanolide A–OMe (**11**)	Cordatolide A–OMe (**3**)	Cordatolide B–OMe (**5**)	Cordatolide C–OMe (**4**)	Calanolide F–OMe (**10**)	Inophyllum D (**9**)
H-3	5.94, t (1.0)	5.942, s	5.93, s	5.93, s	5.95, t	5.98, s
H-7	5.50, d (10.0)	5.51, d (9.9)	0.52, d (9.9)	5.51, d (9.9)	5.54, d (10.5)	5.36, d (10.2)
H-8	6.61, d (10.0)	6.62, d (9.9)	6.62, d (9.9)	6.63, d (9.9)	6.65, d (10.5)	6.59, d (10.2)
H-10	4.26, ddq (6.5, 3.5, 1.3)	4.27, ddq (1.2, 6.9, 3.3)	4.30, dq (6.3, 12.6)	4.50, dq (6.6, 2.1)	4.50, dq (6.8, 2.0)	4.59, m (6.7, 2.0)
H-11	2.23, ddq (7.5, 3.5, 3.7)	2.24, m (7.5, 3.6, 3.3)	1.9, ddq (2.7, 6.8, 9.9)	2.07, tq (7.2, 2.1, 2.1)	2.03, m	1.99, m (7.2, 2.0, 2.0)
H-12	4.31, dd (3.7, 1.3)	4.33, dd (3.6, 1.2)	4.56, d (2.4)	4.39, d (2.1)	4.86, d (2.0)	4.95, d (2.0)
Me-6	1.45, s 1.47, s	1.45, s	1.47, s 1.49, s	1.48, s	1.48, s 1.49, s	0.95, s
Me-10	1.45, d (7.0)	–	1.41, d (6.29)	1.42, d (6.6)	1.43, d (6.8)	1.45, d (6.7)
Me-11	1.00, d (7.5)	1.10, d (7.5)	1.15, d (6.9)	0.76, d (7.2)	0.79, d (7.5)	0.83, d (7.2)
Me, Pr or Ph-4	2.80, ddd 2.92, ddd 1.63, m 1.01, t (7.5)	2.54, s	2.57, s	2.55, s	2.88, s 1.65, sext (7.7) 1.03, t (7.7)	7.3, m
OMe	3.59, s	3.54, s	3.59, s	3.58, s		2.67, br. s

Note: Coupling constants (Hz) are given in parentheses.

Table 2. ^{13}C NMR data for 12-OMe cordatolides.

Carbon No.	Cordatolide A–OMe (**3**)	Cordatolide B–OMe (**5**)	Cordatolide C–OMe (**4**)
2	160.7	160.5	160.7
3	111.2	110.7	111.2
4	151.9	151.9	151.9
4a	104.4	104.4	104.4
4b	154.7	154.6	154.7
6	77.5*	77.9	77.5*
7	116.5	116.4	116.5
8	126.8	126.6	126.8
8a	105.9*	106.1	106.4*
8b	151.7	152.9	151.7
10	73.3*	73.3	73.8*
11	33.8*	38.6	35.2*
12	70.8	70.6	70.8
12a	101.8*	104	102.6*
12b	154.3	153	154.3
13	24.3	24.8	24.3
14	29.6*	27.8	27.8
15	27.9*	27.9	27.6*
16	16.9	19.5	19.5*
17	17.7	13.6	
12–OMe		59.2	57.5*

Note: *Interchangeable due to close electronic and steric environment.

the mixture ***M***. In the ^{13}C NMR spectrum of ***M***, except the signals assigned to the C-17 of **3** and **4**, the other assigned signals may be interchangeable due to their close electronic environment (Table 2). However, further studies suggested that the remaining signal at δ 9.0 must be due to the C-17 of **4**, which is a β carbon (Patil et al., 1993). Thus **4** should have a structure with a C-17β. Hence, the structure related to inophyllum D (**9**) must be the correct structure for **4**, with the Me-10β, Me-11β and OMe-12α orientation. As discussed above, studies on the EIMS, ^{1}H NMR and the ^{13}C NMR spectra of ***M*** lead us to conclude it as a mixture of cordatolide A–OMe (**3**) and cordatolide C–OMe (**4**), which are new natural products. So far, cordatolide C has not been reported from either a plant or a synthetic source. Attempts were made to synthesise **3** and **5** to confirm their proposed structures. Cordatolide A (**1**) was treated with MeOH under acidic conditions at reflux temperature for 30 min, with the objective of obtaining the methyl ether **3**. This reaction gave two products and the comparison of the ^{1}H NMR spectra of the major product (50%) with the methyl ethers **5** indicated it to be cordatolide B–OMe (**5**). TLC and HPLC comparisons further confirmed our observation. Formation of cordatolide B–OMe (**5**) as the major product in the attempted methylation of cordatolide A, indicated a change of stereochemistry during the methylation process. In the above reaction, the protonation of the 12-OH group under the acidic condition followed by the elimination of a water molecule leads to give a planer carbonium ion. The lone pair of electrons in the oxygen atom of the MeOH can attack the planer carbonium ion from either side of the molecule, which could lead to methyl ethers **3** or **5**. According to the reaction products, the attack

from below the plane seems to be favourable, and it has paved the way to the formation of 12-αOMe product **5**. The absence of a signal due to an OMe group in the ^{1}H NMR spectrum of the minor product **6** (12%) from the attempted methylation of **1** clearly indicated it to be a non-methoxyl derivative. The above observation clearly showed that the attempted methylation of **1** under acidic conditions is not giving the expected methyl ether **3**, but **5** as the major product. The same reaction was carried out with **2**, and cordatolide B–OMe (**4**) was obtained as a minor product (16%), while compound **6** was isolated as the major product (62%). The above results indicated compound **5** to be more stable from the methyl ethers **3** and **5**. In both of the above reactions, **6** was obtained as a product. The IR spectrum of **6** showed the presence of carbonyl (coumarin) and olefinic groups. The ^{1}H NMR spectrum of **6** showed the presence of a 2,2-dimethylpyran ring system, the allylic methyl group at C-4 and the olefinic proton at the C-3 as in the starting materials **1** and **2**. However, we have observed that the signals due to the protons at ring D of the cordatolides were replaced by a new set of signals. This observation indicated that during the reaction, instead of methylation, some other changes had occurred in the D-ring of the pyranocoumarin substrate, while the rings B and C were intact. The two doublets due to the 12-H and 11-Me of the starting material appeared at δ 4.92 and 1.13, respectively, were not observed in the ^{1}H NMR spectrum of product **6**, while a new 1H singlet due to an olefinic proton and a 3H singlet due to an allylic methyl group were observed at δ 6.61 and 1.84, respectively. However, the multiplet due to the 10-H of the starting material at δ 4.24 was replaced by a 1H quartet at δ 4.88 with a shift towards the low-field region. The above observations indicated the presence of a new double bond in **6**, with an olefinic proton and an allylic methyl group probably at the 11 and 12 positions. During the attempted methylation process, after the formation of the carbonium ion, the proton at C-11 can leave as a H^+ after donating the electron pair of the C–H bond to the carbonium ion at C-12. This process paves the way to the formation of **6** with 11,12 double bond. After the elimination of the C-11 proton, the multiplicity of the proton at C-10 has been reduced to a quartet. According to the above spectral analysis, the structure 11,12-anhydrocordatolide (**6**) is proposed to the by-product of methylation of cordatolides A and B. As the stereochemistry at C-10 and C-11 of cordatolide A (**1**) and B (**2**) are the same (Dharmaratne et al., 1998a), the stereochemistry of the 11,12-anhydrocordatolide (**6**) should have the same 10β-Me configuration. The EIMS and ^{13}C NMR spectrum of compound **6** are well in agreement with the proposed structure.

3. Experimental

3.1. *General procedure*

Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian (300 MHz for ^{1}H NMR and 75.45 MHz for ^{13}C NMR) and Varian Unity (300 MHz for ^{1}H NMR and 75.6 MHz for ^{13}C NMR) for solutions in $CDCl_3$ and are reported in δ (ppm) values relative to TMS as internal standard. IR spectra were recorded on a Shimadzu IR 460 spectrometer; UV spectra were run in a Shimadzu 160 A UV-Vis spectrophotometer and mass spectra (EIMS) were recorded on a Shimadzu QP-5000 GCMS. HPLC was performed on a Shimadzu Liquid Chromatograph LC-6A equipped with an SPD-6AV UV-Vis spectrophotometric detector, using an ODS analitycal column (25 cm $\times$ 10 mm).

3.2. *Plant material*

Calophyllum cordato-oblongum was identified and collected by Mr Shantha Ekanayake of the Institute of Fundamental Studies in June 1996, from the Kanneliya forest in the Southern Province of Sri Lanka, and the plant specimens were compared with the herbarium specimens (Specimen No. 24771) at the Royal Botanic Gardens, Peradeniya, Sri Lanka.

3.2.1. *Extraction and isolation*

A portion (20 g) of the hexane extract of the twigs was separated on a column of silica gel (300 g, Merck Art 7734.1) with hexane and EtOAc as eluants. Further purification of the column fractions by preparative TLC, Merck Kieselgel 60 F_{254} and flash and medium pressure CC, Merck Kieselgel 60 (230–300 mesh ASTM) with hexane, CH_2Cl_2, and EtOAc as solvents gave cordatolide A (**1**) (1.722 g, 0.025%), cordatolide B (**2**) (1.303 g, 0.19%), oblongulide (1.055 g, 0.15%), cordatolide B–OMe (**5**) (87 mg, 0. 013%), friedelin (1.08g, 0.16%), canophyllol (12 mg, 0.043%), sitosterol (146 mg, 0.02%) and a (1:1) mixture of cordatolide A–OMe (**3**) and cordatolide C–OMe (**4**) (30 mg, 0.01%).

Mixture (***M***): Yellow semi-solid, UV λ_{max} (MeOH) nm: (log ε) 322(3.32), 282(3.57) and 228(3.59); IRν_{max} (KBr) cm^{-1}: 3456, 3000, 1715, 1686, 1635, 1580, 1456, 1382, 1212, 1136, 1094, 758 and 668.

Methylation: Cordatolide A (**1**) and cordatolide B (**2**) were separately dissolved in methanol, and 2N HCl was added. Then the reaction mixture was refluxed for 30 min. After the usual workup, the crude product was subjected to PTLC separation to give 11,12-anhydrocordatolide (**6**) and cordatolide B–OMe (**5**).

11,12-Anhydrocordatolide (**6**): Light yellow semi solid; UV λ_{max} (MeOH) nm (log ε): 295(3.74), 247(3.73) and 208(3.57); IRν_{max} (KBr) cm^{-1}: 2928, 1731, 1580, 1360, 1136 and 1094; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (1H, s, H-12), 6.59 (1H, d, $J = 9.9$ Hz, H-8), 5.89 (1H, d, $J = 0.9$ Hz, H-3), 5.53 (1H, d, $J = 9.9$ Hz, H-7), 4.88 (1H, q, $J = 6.5$ Hz, H-10), 2.55 (3H, d, $J = 0.9$ Hz, Me-4), 1.85 (3H, s, Me-11), 1.49,1.46 (6H, 2s, Me_2-6), 1.38 (3H, d, $J = 6.5$ Hz, Me-10). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9 (C-2), 154.5 (C-4b), 154.1 (C-12b), 151.1 (C-8b), 150.0 (C-4), 132.2 (C-11), 127.4 (C-8), 116.2 (C-7), 111.9 (C-12), 111.1 (C-3), 106.4 (C-8a), 104.4 (C-4a), 103.7 (C-12a), 77.6 (C-6), 75.9 (C-10), 27.9 (C-14), 27.5 (C-15), 24.4 (C-13), 19.3 (C-16) and 19.2 (C-17).

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