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A 6-substituted-5,6-dihydro-2-pyrone from *Cryptocarya strictifolia*

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Abstract

The structure and absolute configuration of an α-pyrone isolated from *Cryptocarya strictifolia* was elucidated as 6*R*-(4′*R*,6′*R*-dihydroxy-8′-phenyloct-1′-enyl)-5,6-dihydro-2*H*-pyran-2-one. Pinocembrin and lysicamine were also isolated. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *Cryptocarya strictifolia*; Lauraceae; 6-Substituted-5,6-dihydro-2-pyrone; Strictifolione; Absolute configuration; Pinocembrin; Lysicamine

1. Introduction

Cryptocarya strictifolia belongs to the family Lauraceae and grows in the Indonesian tropical rainforests. Plants of this genus are known to contain 6-substituted-5,6-dihydro-2-pyrones (Davies-Coleman and Rivett, 1989; Collet et al., 1998) in addition to other types of compounds, such as flavonoids, alkaloids and terpenoids. *C. strictifolia* Kosterm. is a large tree (25 m tall and 35 cm in diameter) which grows in the forests of West Kalimantan, at ca. 100 m altitude, and which has hitherto not been chemically studied. This contribution describes the structure elucidation of one new α-pyrone, strictifolione (**1**), and two known compounds.

2. Results and discussion

Strictifolione (**1**) was obtained as colorless needles mp 119–121°C, whose molecular formula, $C_{19}H_{24}O_4$, was established by elemental analysis and mass spectrometry. The presence of an α,β-unsaturated-δ-lactone ring was shown by UV [λ_{max} 206 nm (log ε 4.36) and 252 nm (log ε 3.06)] and IR (υ_{max} 1723 cm^{-1}) data. An absorption at υ_{max} 3325 cm^{-1} from a hydroxyl group was present in the IR spectrum. The ^{13}C-NMR spectrum showed the presence of 17 carbon signals, and the DEPT spectrum indicated that 5 methylene, 10 methyne, and 2 quaternary carbons were present. The presence of a monosubstituted benzene group was indicated by the ^{1}H-NMR signals at δ 7.17–7.21 (3H, *m*) and 7.27–7.29 (2H, *m*) and confirmed by resonances at δ 125.92, 128.38, 128.46, and 141.80 in the ^{13}C-NMR spectrum. The ^{1}H-NMR spectrum also exhibited signals at δ 6.05 (H-3) and 6.88 (H-4) due to Hα and Hβ of an α,β-unsaturated lactone. The coupling constant of ca. 15 Hz for the olefinic protons (δ 5.68 and 5.86) indicated the presence of a *trans* double bond in the side chain of **1**. The signals at δ 2.36 and 2.52, which were exchangeable on the addition of D_2O, indicated the presence of two hydroxyl groups. The two oxymethine protons (δ 3.99 and 4.03) were both coupled to a methylene at δ 1.65, suggesting that the latter was located between the methine groups.

Cross peaks observed in the HMBC spectrum

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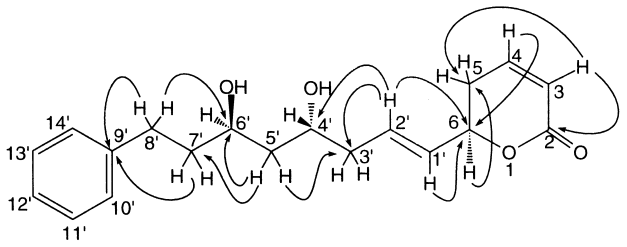


Fig. 1. Selected HMBC correlations.

(Fig. 1) showed that the proton at δ 5.68 (H-1′) correlated with δ 77.73 (C-6) and 29.74 (C-5), while the proton at δ 5.86 (H-2′) correlated only with C-6. These data demonstrated that the *trans* olefin was attached at C-6 of an α-pyrone ring. The carbon-bearing hydroxy groups (δ 68.29 and 68.82) were placed at C-4′ and C-6′, respectively, because of the connectivity of H-2′ to C-3′ (δ 40.34) and C-4′ (δ 68.29). This was confirmed by the correlation of H-5′ (δ 1.65) and H-8′ (δ 2.68 and 2.79) to δ 68.82. The connectivity of H-5′ to C-7′ (δ 38.97) established that the oxymethine of C-6′ was adjacent to C-7′. The proton at H-8′ having connectivity with C-9′ (δ 141.80) demonstrated that the monosubstituted benzene ring was attached to C-8′. Moreover, the collapse of the broad doublet hydroxy signal at δ 2.52 to a singlet on irradiation of δ 4.03 (H-4′) served to locate the hydroxy peaks of δ 2.52 and 2.36 at C-4′ and C-6′, respectively. Other HMBC data supported the correlation between the protons and carbons as shown in structure **1**).

A positive Cotton effect due to the carbonyl $n\rightarrow\pi^*$ transition of an α,β-unsaturated-δ-lactone was observed at λ_{max} 257 nm ($\Delta\varepsilon + 2.63$) in the CD spectrum of **1**. This observation indicated that the absolute configuration at C-6 was (*R*) on the basis of the rule first proposed by Snatzke (1968) and later modified by Beecham (1972). The validity of this rule is well supported in the literature (Davies-Coleman and Rivett, 1989).

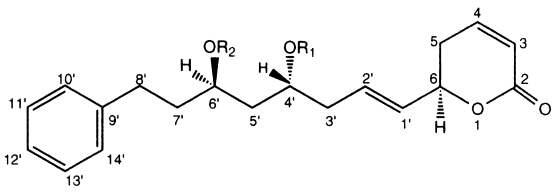
The relative and absolute configurations at C-4′ and C-6′ were clarified as follows. First, acetonide (**2**) was prepared from **1** through treatment with dimethoxypropane in the presence of *p*-TsOH. The 1,3-*anti* relationship of the two secondary hydroxyl groups in **1** was evident from the carbon chemical shifts of the two methyl groups of the acetonide ring of **2**; both methyl carbons resonated at almost the same positions, δ 24.83 and 24.85, indicating that the acetonide ring possessed a twist-boat conformation, exposing these two methyl groups to nearly the same magnetic environment. This indicates that the two alcohol groups are in a 1,3-*anti* orientation (Evans et al., 1990; Rychovsky and Skalitzky, 1990). At this point the structure of strictifolione can be depicted either as **1** or **1′**.

The absolute configurations of both hydroxyl-bearing carbons were determined by the modified Mosher's method using the (*S*) and (*R*)-MTPA [α-methoxy-α-(trifluoromethyl)phenylacetyl] esters of **1** (Dale and Mosher, 1973; Ohtani et al., 1991). Reaction of **1** with an equivalent amount of (*S*)-MTPA chloride in pyridine afforded two esters, **3** (15.6%) and **4** (5.7%). The same reaction of **1** with (*R*)-MTPA chloride gave **5** (13.8%) and **6** (8.5%). The structure of compound **3**, esterified at C-4′ with (*S*)-MTPA, was determined by comparison of the NMR spectral data with those of **1**. The peak at δ 3.48 in the ^{1}H-NMR spectrum and at δ 55.48 in the ^{13}C-NMR spectrum indicated the presence of only one methoxyl group proving **3** to be a monoester. The signal of H-4′ in **3** shifted downfield to δ 5.39 compared to that in **1**. The HMBC spectrum clearly showed correlations between H-4′ (δ 5.39) and the carbonyl carbon of the MTPA group (δ 166.97) and between H-4′ and C-2′ (δ 128.89), confirming that the (*S*)-MTPA was located at C-4′. In the same way, structures **4**, **5** and **6** were also rigorously proved with respect to the positions of esterification.

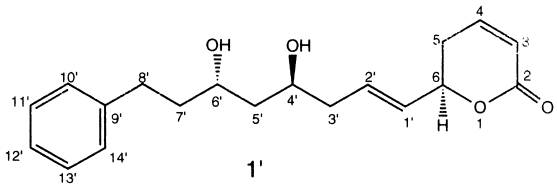
Application of Mosher's method to the four MTPA esters led to the structures in Fig. 1. In the case of the C-4′ esters **3** and **5**, the $\Delta\delta$ values of the ^{1}H-chemical shifts ($\delta_{(S)-MTPA} - \delta_{(R)-MTPA}$) for H-2′ and H-3′ were +0.16 and +0.08, respectively, while for H-5′ and H-6′ they were −0.01 and −0.13 ppm. The above observation indicated that the absolute configuration is (*R*) at the C-4′ chiral center and supported structure **1** instead of **1′**. This assignment was supported by similar examination of the C-6′ esters, **4** and **6**. The $\Delta\delta$ values ($\delta_{(S)\text{-}MTPA} - \delta_{(R)\text{-}MTPA}$) were −0.14 (H-4′), −0.03 and −0.07 (H-5′), +0.03 and +0.05 (H-7′) and +1.0 (H-8′) ppm. This observation confirmed that the absolute configuration of C-6′ is (*R*), as in structure **1**. Accordingly, strictifolione (**1**) is 6*R*-(4′*R*,6′*R*-dihydroxy-8′-phenyloct-1′-enyl)-5,6-dihydro-2-pyrone.

Strictifolione is closely related to cryptofolione obtained from *C. latifolia*, *C. myrtifolia* and *C. liebertiana* (Sehlapelo et al., 1994; Drewes et al., 1995, 1997) for which structure **7** has been proposed. The absolute stereochemistry of the hydroxyl groups in **7** was proved by ^{1}H-NMR analysis of the acetonide derivative (Collet et al., 1998) but, because the CD spectrum was not recorded, the absolute stereochemistry at C-6 is unproven although it is almost certainly (*R*).

We also isolated pinocembrin (**8**) (Wagner et al., 1976) and the oxoaporphine alkaloid, lysicamine (**9**) (Guinadeau, 1983), the latter for the first time from the genus *Cryptocarya*, from *C. strictifolia*. Pinocembrin has also been obtained from *C. ferrea* and *C. cariaefolia* (Achmad, unpublished results).



1 $R_1 = R_2 = H$
2 $R_1 + R_2 = -C(CH_3)_2$
3 $R_1 = (S)$-MTPA, $R_2 = H$
4 $R_1 = H$, $R_2 = (S)$-MTPA
5 $R_1 = (R)$-MTPA, $R_2 = H$
6 $R_1 = H$, $R_2 = (R)$-MTPA
7 $R_1 = R_2 = H$, $\Delta = 7,8$



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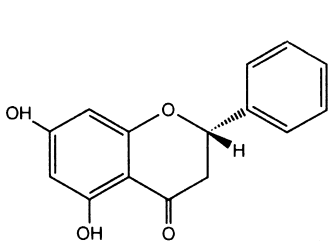

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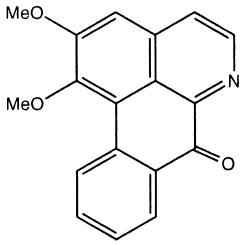

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3. Experimental

3.1. General

^1H and ^{13}C-NMR spectra were recorded on a JEOL JNM GSX400A or a JEOL JNM GSX500A. Proton spectra were measured at 400 or 500 MHz and carbon spectra at 125 MHz (TMS as an internal standard). UV spectra were recorded on a JASCO V-560 model UV spectrometer. IR spectra were measured on a JASCO FT/IR-230 IR spectrometer. Mass spectra were obtained by use of a JEOL JMS-AM20 (EIMS) or a JEOL JMS-HX-110A (FABMS, HR-FABMS) mass spectrometer. Elemental analysis was carried out using a Perkin-Elmer 240 Analyzer. Optical rotation was measured by a JASCO DIP-140 polarimeter. CD spectra were measured by a JASCO J-720WI instrument. For liquid chromatography a silica gel prepacked column (Kusano CPS-HS-221-5) or a YMC packed column (SH-043-5 S-5 120A SIL) were used. Column chromatography was carried out by use of Merck Silica gel 60 [70–230 mesh (for open chromatography) or 230–400 mesh (for flash chromatography)]. For TLC, Merck Silica gel 60 F_{254} plates (0.25 mm thick) were used.

3.2. Plant material

Stem bark of *C. strictifolia* was collected in September 1997 from the National Garden of Palung Mountain, West Kalimantan, Indonesia. A herbarium specimen has been deposited at the Herbarium Bogorienses, Center of Biological Research and Development, National Institute of Science, Bogor, Indonesia (No. GP.01).

3.3. Extraction and isolation

The milled stem bark of *C. strictifolia* (2.2 kg) was extracted with *n*-hexane at room temperature. The residue was refluxed with MeOH to give the crude extract (89.3 g) which was then partitioned by use of $CHCl_3$ to afford a $CHCl_3$ extract (38 g). Next, the $CHCl_3$ extract was subject to chromatography on silica gel and eluted successively with *n*-hexane, *n*-hexane/EtOAc and EtOAc/MeOH in the order of increasing polarity. The EtOAc fraction gave a white powder (583.2 mg) showing a single spot on TLC. Crystals of strictifolione (**1**) were obtained from $CHCl_3$–*n*-hexane. The fraction eluted with 20% of EtOAc–*n*-hexane gave a greenish powder (26.1 g). Further purification with silica gel column chromatography gave pinocembrin

(**8**) (17.5 g). The fraction eluted with 10% MeOH–EtOAc was submitted to flash column chromatography, then to MPLC and finally to silica gel column chromatography to give lysicamine (**9**) (4.5 mg).

3.4. Strictifolione (*1*)

Recrystallization from $CHCl_3$–*n*-hexane gave fine colorless needles, mp. 119–121°. Found: C, 72.16; H, 7.63. $C_{19}H_{24}O_4$ requires: C, 72.12, H, 7.65%, R_f value 0.62 (SiO_2, solvent system: 20% MeOH/EtOAc), $[\alpha]_D^{24}$ +81.5° ($CHCl_3$; *c* 0.52), UV λ_{max}^{MeOH} nm (log ε): 206 (4.36) and 252 (3.06), IR υ_{max}^{KBr} cm^{-1}: 1048, 1239, 1380, 1437, 1723 (α,β-unsaturated-δ-lactone), 2932, and 3325 (OH), CD (MeOH: *c* 0.021) nm (Δε): 203 (+9.48), 236 (+1.82), 257 (+2.63), and 311 (+0.02), FABMS (NBA) *m/z*: 317 $(M + H)^+$; ^{1}H-NMR spectral data (500 MHz, $CDCl_3$): δ 1.65 (2H, *dd*, *J* = 5.2 and 6.1 Hz, H-5′), 1.78 (1H, *m*, H-7′), 1.87 (1H, *m*, H-7′), 2.28 (2H, *dd*, *J* = 6.7 and 7.0 Hz, H_2-3′), 2.36 (1H, *d*, *J* = 4.6 Hz, OH-6′), 2.43 (2H, *m*, H_2-5), 2.52 (1H, *d*, *J* = 3.9 Hz, OH-4′), 2.68 (1H, *m*, H-8′), 2.79 (1H, *m*, H-8′), 3.99 (1H, *m*, H-6′), 4.03 (1H, *m*, H-4′), 4.89 (1H, *ddd*, *J* = 6.0, 6.0, and 9.4 Hz, H-6), 5.68 (1H, *ddd*, *J* = 1.2, 6.4, and 15.6 Hz, H-1′), 5.86 (1H, *dddd*, *J* = 1.2, 7.5, 7.5, and 15.4 Hz, H-2′), 6.05 (1H, *ddd*, *J* = 1.7, 2.1, and 9.6 Hz, H-3), 6.88 (1H, *ddd*, *J* = 3.6, 4.9, and 9.7 Hz, H-4), 7.17–7.21 (3H, *m*, H-10, H-12′, and H-14′), 7.27–7.29 (2H, *m*, H-11′, H-13′); ^{13}C-NMR spectral data (125 MHz, $CDCl_3$): δ 29.74 (C-5), 32.17 (C-8′), 38.97 (C-7′), 40.34 (C-3′), 42.09 (C-5′), 68.29 (C-4′), 68.82 (C-6′), 77.73 (C-6), 121.56 (C-3), 125.92 (C-12′), 128.38[1](C-11′, C-13′), 128.46[1] (C-10′, C-14′), 130.0 (C-1′), 131.07 (C-2′), 141.80 (C-9′), 144.64 (C-4), 163.96 (C-2).

3.5. Acetonide *2*

The acetonide reaction of **1** (20 mg) was prepared in the usual way to give **2** as a yellow oil (18.9 mg). EIMS *m/z*: 356.91 (base peak), FABMS (NBA) *m/z*: 357 $(M + H)^+$; HR-EIMS (NBA) *m/z*: 356.1981 $[M]^+$(calcd. for $C_{22}H_{28}O_4$, 356.1988); ^{1}H-NMR spectral data (400 MHz, $CDCl_3$): δ 1.33 (3H, *s*, CH_3), 1.35 (3H, *s*, CH_3), 1.58 (2H, *dd*, *J* = 7.6 and 7.8 Hz, H_2-5′), 1.73 (1H, *m*, H-7′), 1.84 (1H, *m*, H-7′), 2.24 (2H, *m*, H_2-3′), 2.41 (2H, *m*, H_2-5), 2.61 (1H, *m*, H-8′), 2.76 (1H, *m*, H-8′), 3.75 (1H, *m*, H-6′), 3.85 (1H, *m*, H-4′), 4.88 (1H, *m*, H-6), 5.65 (1H, *dd*, *J* = 6.6 and 15.6 Hz, H-1′), 5.79 (1H, *ddd*, *J* = 7.3, 7.3, and 15.5 Hz, H-2′), 6.03 (1H, *ddd*, *J* = 1.8, 2.4, and 10.3 Hz, H-3), 6.86 (1H, *ddd*, *J* = 4.1, 4.1, and 9.7 Hz, H-4), 7.15–7.19 (3H, *m*, H-10′, H-12′, H-14′), 7.26 (2H, *t*, *J* = 7.6, H-11′, H-13′), ^{13}C-NMR spectral data (125 MHz, $CDCl_3$): δ 24.83 (C of Me), 24.85 (C of Me), 29.73 (C-5), 31.58 (C-8′), 37.37 (C-7′), 38.10 (C-5′), 38.43 (C-3′), 65.67 (C-6′), 65.94 (C-4′), 77.97 (C-6), 100.36 (C of ketal), 121.55 (C-3), 125.73 (C-12′), 128.27 (C-11′, C-13′), 128.43 (C-10′, C-14′), 129.11 (C-1′), 130.92 (C-2′), 141.90 (C-9′), 144.59 (C-4), 163.99 (C-2).

3.6. Esterification of *1* by (*S*) and (*R*)-MTPA chloride

Compound **1** (30 mg) was esterified with (*S*)-MTPA chloride following the usual procedure (Ohtani et al., 1991). The residue was subjected to MPLC and then HPLC to give the oily (*S*)-MTPA esters, **3** (7.9 mg, 15.6%) and **4** (2.9 mg, 5.7%).

By the same procedure, two colorless oily (*R*)-MTPA esters of **1**, **5** (7 mg, 13.8%) and **6** (4.3 mg, 8.5%) were also obtained.

3.7. Selected spectral data of 4′-(*S*)-MTPA ester (*3*)

FABMS (NBA) *m/z*: 533 $(M + H)^+$; ^{1}H-NMR spectral data (500 MHz, $CDCl_3$): δ 1.67 (2H, *m*, H_2-5′), 2.09 (1H, *d*, *J* = 4.9 Hz, OH-6′), 3.38 (1H, *br s*, H-6′), 3.48 (3H, *s*, OMe of MTPA), 5.39 (1H, *m*, H-4′); ^{13}C-NMR spectral data (125 MHz, $CDCl_3$): δ 41.70 (C-5′), 55.48 (OMe of MTPA), 66.64 (C-6′), 73.57 (C-4′), 166.97 (C═O of MTPA).

3.8. Selected spectral data of 6′-(*S*)-MTPA ester (*4*)

FABMS (NBA) *m/z*: 533 $(M + H)^+$; ^{1}H-NMR spectral data (500 MHz, $CDCl_3$): δ 1.63 (1H, *m*, H-5′), 1.73 (1H, *m*, H-5′), 2.19 (1H, *d*, *J* = 4.3 Hz OH-4′), 3.45 (1H, *m*, H-4′), 3.56 (3H, *s*, OMe of MTPA), 5.36 (1H, *m*, H-6′); ^{13}C-NMR spectral data (125 MHz, $CDCl_3$): δ 41.37 (C-5′), 55.46 (OMe of MTPA), 66.40 (C-4′), 74.25 (C-6′), 167.12 (C═O of MTPA).

3.9. Selected spectral data of 4′-(*R*)-MTPA ester (*5*)

FABMS (NBA) *m/z*: 533 $(M + H)^+$; ^{1}H-NMR spectral data (500 MHz, $CDCl_3$): δ 1.68 (2H, *m*, H_2-5′), 3.41 (3H, *s*, OMe), 3.51 (1H, *m*, H-6′), 5.34 (1H, *m*, H-4′); ^{13}C NMR spectral data (125 MHz, $CDCl_3$): δ 41.90 (C-5′), 55.38 (OMe of MTPA), 66.44 (C-6′), 73.74 (C-4′), 167.09 (C═O of MTPA).

3.10. Selected spectral data of 6′-(*R*)-MTPA ester (*6*)

FABMS (NBA) *m/z*: 533 $(M + H)^+$; ^{1}H-NMR spectral data (500 MHz, $CDCl_3$): δ 1.66 (1H, *m*, H-5′), 1.80 (1H, *m*, H-5′), 3.56 (3H, *s*, OMe), 3.59 (1H, *m*, H-4′), 5.32 (1H, *m*, H-6′); ^{13}C-NMR spectral data (125 MHz, $CDCl_3$): δ 41.74 (C-5′), 55.47 (OMe of MTPA), 66.64 (C-4′), 74.42 (C-6′), 167.30 (C═O of MTPA).

[1] May be interchanged.

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