

Studies on the Constituents of *Picrodendron baccatum* Growing in Indonesia. II. Structures of Two New Sesquiterpene Lactones, Picrodendrins C and D

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Two new picrotoxane-type sesquiterpene lactones, picrodendrins C and D, together with a known compound, isohyenananchin, were isolated from the barks of Indonesian *Picrodendron baccatum*. The structures were elucidated on the basis of spectroscopic data and X-ray structure analysis.

Keywords *Picrodendron baccatum*; Simaroubaceae; picrodendrin C; picrodendrin D; isohyenananchin; picrotoxane-type sesquiterpene lactone; X-ray structure analysis

Furthering our research into the chemical compositions of Simaroubaceae plants, we investigated *Picrodendron baccatum* (L.) KLUG *et* URBAN growing in Indonesia. The isolation and structure elucidation of a picrotoxane-type nor-diterpene lactone, picrodendrin A, from the bark of this plant were reported previously.¹⁾ In a continuation of our studies on the bark of this plant, we isolated two new picrotoxane-type sesquiterpene lactones, named picrodendrins C and D, together with a known compound, isohyenananchin. The present paper deals with the isolation and structure elucidation of these compounds on the basis of spectral data and X-ray diffraction analysis.

The terpene fractions of the chloroform extract of the bark of *P. baccatum* collected in Indonesia were repeatedly column-chromatographed on silica gel to give isohyenananchin (**1**) and two new sesquiterpene lactones, picrodendrins C (**2**) and D (**3**).

Isohyenananchin (**1**) is a crystalline compound isolated by Jommi and co-workers²⁾ from *Hyenanche globosa* LAMB. (*Toxicodendrum capense* THUMB.). Although the proton nuclear magnetic resonance (¹H-NMR) spectra favor the structure of isohyenananchin, other structures could not be definitively eliminated and the stereochemistry was not revealed (e.g., the conformations of the cyclohexane, cyclopentane, γ -lactone and two epoxide rings, and the stereochemistry of the methyl group at C-1, the hydroxyisopropyl group at C-4 and the two hydroxyl groups at C-2 and C-6). In order to establish a definitive structure, an X-ray diffraction analysis of a single crystal was carried out. An ORTEP³⁾ drawing of the X-ray model of isohyenananchin (**1**) is presented in Fig. 1. The present study showed the presence of five fused rings; cyclohexane, cyclopentane, γ -

lactone and two epoxide rings. A characteristic feature of this compound is the γ -lactone ring coming across the cyclohexane ring from C-3 to C-5. The cyclohexane ring has a quasi-chair conformation with an α -equatorial methyl group at C-1, β -equatorial hydroxyl group at C-2, α -axial

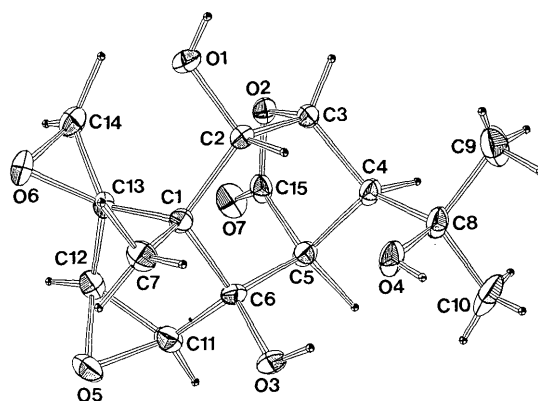


Fig. 1. ORTEP Drawing of Compound **1** with 50% Probability Ellipsoids

TABLE I. Final Positional Parameters ($\times 10^4$) and Equivalent Isotropic Thermal Parameters with Estimated Standard Deviations in Parentheses for Compound **1**

Atom	x	y	z	B_{eq} (\AA^2)
C-1	2522 (3)	2368 (3)	-920 (8)	1.9
C-2	3300 (2)	2290 (3)	-2440 (8)	2.0
C-3	4248 (3)	2495 (3)	-1650 (8)	2.0
C-4	4336 (3)	3508 (4)	-808 (9)	2.2
C-5	3753 (3)	3353 (4)	1019 (9)	2.2
C-6	2711 (3)	3202 (3)	612 (8)	2.0
C-7	1635 (4)	2526 (4)	-2065 (9)	2.7
C-8	4237 (4)	4394 (4)	-2108 (10)	2.8
C-9	4389 (5)	5273 (4)	-881 (13)	4.6
C-10	4905 (4)	4353 (5)	-3770 (12)	4.3
C-11	2289 (3)	2887 (4)	2511 (9)	2.6
C-12	2107 (3)	1859 (4)	2450 (9)	2.6
C-13	2388 (3)	1500 (4)	474 (8)	2.1
C-14	2812 (4)	550 (4)	371 (10)	3.2
C-15	4144 (3)	2380 (4)	1676 (9)	2.4
O-1	3256 (3)	1370 (3)	-3329 (6)	2.7
O-2	4427 (2)	1908 (2)	79 (6)	2.2
O-3	2323 (3)	4092 (2)	63 (7)	2.6
O-4	3327 (3)	4414 (3)	-2924 (7)	2.9
O-5	1370 (2)	2551 (3)	2319 (7)	3.1
O-6	21879 (3)	690 (3)	-211 (7)	3.3
O-7	4218 (3)	2069 (3)	3291 (7)	3.4

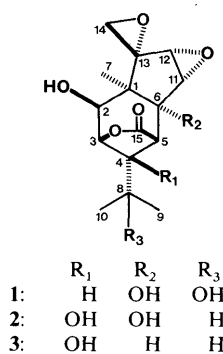


Chart 1

hydroxyisopropyl group at C-4 and α -equatorial hydroxyl group at C-6. The cyclopentane ring has a flattened envelope conformation which carries a *cis*-fused α -epoxide between C-11 and C-12. Another epoxide ring, spiro-fused at C-13, is perpendicular to that of the cyclopentane ring. The cyclohexane and the cyclopentane rings are *cis*-fused by β -axial bonds between C-1 and C-6. Therefore the compound is isohyenchin, in agreement with the conclusion based on spectral studies in the preceding paper.²⁾ The information gained by the X-ray study, completely resolved, the relative stereochemistry.

Picrodendrin C (**2**), colorless prisms, mp 234 °C, $[\alpha]_D^{25} +1.2^\circ$, showed the absorption bands of hydroxyl (ν_{\max} 3550 cm^{-1}) and γ -lactone (ν_{\max} 1740 cm^{-1}) groups in the infrared (IR) spectrum. From the elementary analysis, **2** had the same molecular formula, $\text{C}_{15}\text{H}_{20}\text{O}_7$ as determined for **1**. The ^1H -NMR spectrum (Table II) of **2** showed an isopropyl group [δ 1.11 and 1.46 (each 3H, d, $J=6.6$ Hz, H-9 and H-10) and 2.96 (1H, septet, $J=6.6$ Hz, H-8)] and one tertiary methyl group at δ 2.06 (3H, s, 1- CH_3). The ^1H spin decoupling NMR experiments on **2** showed AX-type vicinal protons at δ 4.24 and 3.63 (each 1H, d, $J=2.9$ Hz, H-11 and H-12) of the 11,12-epoxide group and the nonequivalent methylene protons at δ 3.11 and 4.85 (each 1H, d, $J=6.2$ Hz, H-14) of the 13,14-epoxide group. The two-dimensional ^1H - ^1H correlation (2D ^1H - ^1H COSY) spectrum of **2** showed that a signal at δ 4.44 (1H, d, $J=5.5$ Hz, H-2) was coupled with a methine signal at δ 5.13 (1H, d, $J=1.1$ Hz, H-3). Irradiation of the signal at δ 4.44 caused sharpening of the methine signal at δ 5.13 indicating vicinal coupling. When the signal at δ 5.13 was irradiated, the change observed was collapse of the doublet at δ 3.50 (1H, d, $J=1.1$ Hz, H-5) into a singlet, indicating W-type long-range coupling. From a comparison of the chemical shift of the carbon-13 nuclear magnetic resonance (^{13}C -NMR) signals (Table III) of **2** with that of **1**, the hydroxyl group was linked to C-4 (δ 82.04) and exerted the β -effect on C-3 (δ 90.04) and C-5 (δ 58.34). The signals of C-8, C-9 and C-10 were, in turn, shifted upfield by replacing the hydroxyl group at C-8 of the hydroxyisopropyl group with the hydrogen. The relative stereochemistry of **2** was ascertained from the ^1H nuclear Overhauser effect (NOE) difference spectra of **2** (Fig. 2). On irradiation of the signal of 1- CH_3 , NOE's were observed at the signals of H-2 (2%), H-3 (2%), 6-OH (4%) and H-8 (2%). Irradiation of 6-OH gave NOE's at the signals of 1- CH_3 (14%), H-3 (4%), H-5 (7%) and H-11 (3%). Irradiation of H-11 gave NOE's at the signals of H-5 (5%), 6-OH (3%) and H-12 (9%). Irradiation of H-12 gave NOE's at the signals of H-11 (9%) and H_a-14 (6%). These NOE experiments allowed us to establish (i) the orientation of the 1- CH_3 , 2-OH, 4-OH and 6-OH groups of the cyclohexane ring; (ii) *cis*-fusion between the cyclohexane and the cyclopentane rings; (iii) the orientation of two 11,12- and 13,14-epoxide groups; (iv) location of the γ -lactone ring perpendicular to the cyclohexane ring. Thus, the structure of picrodendrin C was concluded to be **2**.

Picrodendrin D (**3**), colorless prisms, mp higher than 300 °C, $[\alpha]_D^{25} -72.3^\circ$, showed the absorption bands of hydroxyl (ν_{\max} 3550 cm^{-1}) and γ -lactone (ν_{\max} 1780 cm^{-1}) groups in the IR spectrum. From the elementary analysis, the molecular formula was concluded to be $\text{C}_{15}\text{H}_{20}\text{O}_6$, sug-

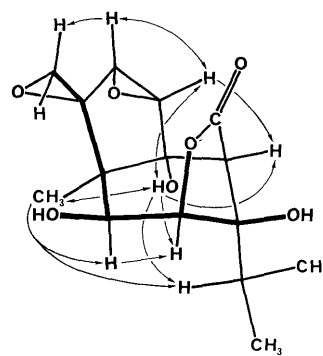


Fig. 2. NOEs Observed in NOE Difference Spectra of Picrodendrin C (**2**)

TABLE II. ^1H -NMR Spectral Data^{a)} for Compounds **1**, **2**, and **3**

Proton	1	2	3
H-2	5.15 (1H, d, 4.8)	4.44 (1H, d, 5.5)	4.20 (1H, d, 4.4)
H-3	5.17 (1H, dd, 4.4, 1.1)	5.13 (1H, d, 1.1)	5.00 (1H, d, 1.1)
H-4	2.75 (1H, t, 4.4)		
H-5	3.43 (1H, dd, 4.4, 1.1)	3.50 (1H, d, 1.1)	3.12 (1H, dd, 3.1, 1.1)
H-6			2.69 (1H, d, 3.1)
H-8		2.96 (1H, sep, 6.6)	2.04 (1H, sep, 6.8)
H-9	1.39 (3H, s)	1.11 (3H, d, 6.6)	1.08 (3H, d, 6.8)
H-10	1.55 (3H, s)	1.46 (3H, d, 6.6)	1.18 (3H, d, 6.8)
H-11	4.26 (1H, d, 2.9)	4.24 (1H, d, 2.9)	4.07 (1H, d, 2.9)
H-12	3.59 (1H, d, 2.9)	3.63 (1H, d, 2.9)	3.56 (1H, d, 2.9)
H _a -14	3.11 (1H, d, 6.2)	3.11 (1H, d, 6.2)	3.11 (1H, d, 6.2)
H _b -14	4.85 (1H, d, 6.2)	4.85 (1H, d, 6.2)	4.80 (1H, d, 6.2)
1- CH_3	1.97 (3H, s)	2.06 (3H, s)	1.89 (3H, s)
2-OH	7.27 (1H, d, 4.8) ^{b)}	7.53 (1H, d, 5.5) ^{b)}	7.43 (1H, d, 4.4) ^{b)}
4-OH		7.32 (1H, d, 1.8) ^{b)}	7.34 (1H, s) ^{b)}
6-OH	9.14 (1H, s) ^{b)}	8.26 (1H, d, 1.8) ^{b)}	
8-OH	7.45 (1H, s) ^{b)}		

a) The spectra were measured in pyridine- d_5 . s=singlet, d=doublet, dd=doublet of doublets, sep=septet. b) Disappeared with the addition of D_2O .

TABLE III. ^{13}C -NMR Spectral Data^{a)} for Compounds **1**, **2**, and **3**

Carbon	1	2	3
C-1	46.26	45.53	40.83
C-2	73.06	75.35	76.22
C-3	84.81	90.04	89.44
C-4	54.54	82.04	80.94
C-5	50.25	58.34	51.48
C-6	77.34	78.52	45.16
C-7	21.42	21.75	27.70
C-8	68.35	30.91	29.57
C-9	28.53	15.44	15.27
C-10	30.53	18.32	16.52
C-11	61.11	61.82	57.18
C-12	60.33	60.95	60.83
C-13	66.97	66.90	67.28
C-14	52.25	52.35	52.04
C-15	175.55	176.45	177.63

a) The spectra were measured in pyridine- d_5 . The signal assignment was based on analyses of the ^1H - ^{13}C and long-range ^1H - ^{13}C shift correlation spectra.

gesting that it has one less hydroxyl group than **2**. The ^1H -NMR spectrum (Table II) of **3** was similar to that of **2** but revealed a signal at δ 2.69 (1H, d, $J=3.1$ Hz) due to H-6, instead of the hydroxyl group at C-6 in **2**, and the doublet of the methine proton at H-5 in **2** was transformed into a doublet of doublets in **3**. In the 2D ^1H - ^1H COSY spectrum

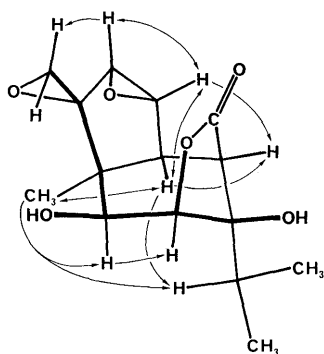


Fig. 3. NOEs Observed in NOE Difference Spectra of Picrodendrin D (3)

of **3**, a signal at δ 4.20 (1H, d, $J=4.4$ Hz, H-2) was coupled with a signal at δ 5.00 (1H, d, $J=1.1$ Hz, H-3) indicating a vicinal coupling. The proton at δ 2.69 was coupled to a proton at δ 4.07 (1H, d, $J=2.9$ Hz, H-11). Irradiation of the signal at δ 2.69 caused sharpening of the signal at δ 4.07, indicating vicinal coupling. When the signal at δ 5.00 was irradiated, the change observed was a collapse of the doublet at δ 3.12 (1H, dd, $J=3.1, 1.1$ Hz, H-5) into a singlet, indicating W-type long-range coupling. In a comparison of the chemical shifts of the ^{13}C -NMR signals (Table III) assigned to C-1, C-5, C-6, C-7 and C-11 in compound **3** with the corresponding signals of **2**, upfield-shifted C-1 (δ 40.83), C-5 (δ 51.48), C-6 (δ 45.16) and C-11 (δ 57.18) and downfield-shifted C-7 (δ 27.70) were observed. The relative stereochemistry of **3** was ascertained by analysis of the ^1H NOE difference spectrum of **3** (Fig. 3). Irradiation of the signal for 1- CH_3 gave NOE's at the signals of H-2 (8%), H-6 (10%) and H-8 (2%). Irradiation of H-6 gave NOE's at the signals of 1- CH_3 (9%), H-8 (9%), H-5 (9%) and H-11 (7%). Irradiation of H-11 gave NOE's at the signals of H-5 (9%), H-6 (3%) and H-12 (10%). Irradiation of H-12 gave NOE's at the signals of H-11 (8%) and H_a-14 (6%). These observations indicated that all chiral centers were compatible with those of isohyenchin (1) and picrodendrin C (2). The coupling constants $J_{\text{H2}, \text{H3}}$ and $J_{\text{H6}, \text{H11}}$ were very small (each $J=ca. 0$ Hz) which indicated that both dihedral angles were *ca.* 90 degrees. Thus, the structure of picrodendrin D was concluded to be **3**.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were recorded with a Hitachi 260-30 spectrophotometer. The ^1H - and ^{13}C -NMR spectra were recorded with a JEOL JNM GX-400 (^1H -NMR at 400 MHz and ^{13}C -NMR at 100 MHz) spectrometer. Chemical shifts are given on the δ scale (ppm) with tetramethylsilane as an internal standard and coupling constants (J) are given in hertz (Hz). Electron ionization mass spectra (EI-MS) were measured with a JEOL JMS D-300 mass spectrometer. Optical rotations were determined on a JASCO DIP-4 digital polarimeter. Column chromatography was carried out on silica gel (BW-820MH, Fuji Davison).

Extraction and Isolation Dried bark (1.5 kg) of *P. baccatum* collected at Kebun Raya Bogor, Indonesia, in July 1986 was extracted successively with *n*-hexane, chloroform and methanol. The chloroform-soluble fraction (18 g) was subjected to column chromatography on silica gel (200 g) (chloroform, then 1, 2, 5, 10, 20 and 50% methanol in chloroform, and finally methanol). The fraction (2.5 g) eluted with 10 and 20% methanol in chloroform was further purified by column chromatography on silica gel to give isohyenchin (**1**, 143 mg), picrodendrin C (**2**, 21 mg) and picrodendrin D (**3**, 132 mg).

Isohyenchin (1) Colorless prisms (methanol), mp $>300^\circ\text{C}$, $[\alpha]_{\text{D}}^{24} -15.4^\circ$ ($c=2.0$, pyridine), $[\text{lit.}]^2$ mp 298°C , $[\alpha]_{\text{D}}^{20} -61.2^\circ$ ($c=0.2$, H_2O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3520, 3250, 2980, 1760, 1300, 1160, 950. MS m/z (%): 294 $[(\text{M}-\text{H}_2\text{O})^+, 2]$, 261 (3), 249 (3), 235 (3), 207 (8), 191 (10), 177 (22), 161 (21), 151 (12), 141 (33), 125 (36), 108 (28), 95 (33), 71 (23), 59 (100), 43 (79). ^1H - and ^{13}C -NMR data are given in Tables I and II, respectively. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_7$: C, 57.69; H, 6.45. Found: C, 57.50; H, 6.52.

X-Ray Crystal Structure Analysis of Isohyenchin (1) Suitable crystals of **1** were grown from methanol as colorless prisms. Crystals were orthorhombic, space group $P2_1P2_1P2_1$, $a=14.754$ (3), $b=14.056$ (3), $c=6.857$ (1) (\AA); $V=1422.08$ \AA^3 , $Z=4$, $D_{\text{calcd}}=1.459$ $\text{g}\cdot\text{cm}^{-3}$. All unique diffraction maxima with $2\theta < 120^\circ$ were collected with a Rigaku AFC-6 four-circle automatic diffractometer using the ω - 2θ scanning method at a speed of $4^\circ/\text{min}$ with graphite-monochromated CuK_α radiation. Of the 1661 unique reflections, 1369 had $|F_o| > 3\sigma(F_o)$ and were judged as observed. The structure was solved by the direct method using the structure determination program package MULTAN 80⁴⁾ provided with the diffractometer. The structure was refined by the block-diagonal least-squares methods to an R value of 0.0505. The final positional parameters are given in Table I.

Picrodendrin C (2) Colorless prisms (methanol), mp 234°C , $[\alpha]_{\text{D}}^{24} +1.2^\circ$ ($c=1.9$, pyridine). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3550, 3460, 2880, 1740, 1660, 1360, 1145, 920. MS m/z (%): 294 $[(\text{M}-\text{H}_2\text{O})^+, 2]$, 265 (2), 241 (19), 211 (17), 193 (21), 166 (26), 149 (55), 141 (100), 125 (79), 113 (57), 95 (45), 85 (24), 77 (15), 71 (57), 55 (24), 43 (81). ^1H - and ^{13}C -NMR data are given in Tables I and II, respectively. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_7$: C, 57.69; H, 6.45. Found: C, 57.47; H, 6.49.

Picrodendrin D (3) Colorless prisms (methanol), mp $>300^\circ\text{C}$, $[\alpha]_{\text{D}}^{24} -72.3^\circ$ ($c=2.4$, pyridine). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3550, 3410, 2990, 1780, 1480, 1385, 1280, 1160, 1000. MS m/z (%): 296 (M^+ , 1), 278 (1), 235 (3), 223 (5), 205 (9), 195 (13), 177 (24), 155 (48), 137 (57), 125 (53), 111 (82), 95 (39), 77 (22), 71 (100), 55 (27), 43 (82). ^1H - and ^{13}C -NMR data are given in Tables I and II, respectively. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_6$: C, 60.80; H, 6.80. Found: C, 60.56; H, 6.84.

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References and Notes

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