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Studies on the Constituents of *Picrodendron baccatum* Growing in Indonesia: Structure of a Nor-diterpene Lactone, Picrodendrin A

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A new nor-diterpene lactone, picrodendrin A, was isolated from the bark of Indonesian *Picrodendron baccatum* (Simaroubaceae), and its structure was established on the basis of spectroscopic data and an X-ray crystal structure analysis.

Keywords picrodendrin A; nor-diterpene lactone; *Picrodendron baccatum*; Simaroubaceae; X-ray crystal structure analysis

Furthering our research into the chemical compositions of Simaroubaceae plants,[1)] we investigated *Picrodendron baccatum* (L.) Klug & Urban growing in Indonesia.[2)] *P. baccatum* belongs to one of the endemic taxa of the West Indies and Indonesia which has not been subjected to chemical investigation up to now. We report here the isolation and structure elucidation of a novel picrotoxin-group nor-diterpene lactone from the bark of *P. baccatum*.

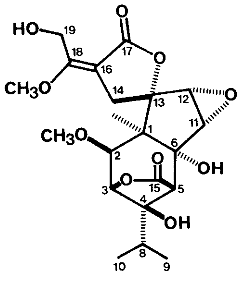

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Chart 1

Results and Discussion

The terpene fraction obtained from the bark of *P. baccatum* collected in Indonesia was repeatedly column-chromatographed on silica gel to give a novel nor-diterpene lactone named picrodendrin A (**1**). Its high-resolution mass spectrum (HRMS) indicated the formula $C_{21}H_{28}O_{10}$. The infrared (IR) and ultraviolet (UV) spectra of **1** showed the presence of hydroxyl (ν_{max} 3340 cm^{-1}) and saturated and unsaturated γ-lactone (ν_{max} 1785, 1725 cm^{-1} and λ_{max} 258 nm) groups. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** showed an isopropyl group [δ 1.21, 1.48 (each 3H, d, $J=6.2$ Hz) and 2.74 (1H, septet, $J=6.2$ Hz)], a tertiary methyl group [δ 1.89 (3H, s)], and two methoxyl groups [δ 3.31 and 3.96 (each 3H, s)]. Selective proton decoupling nuclear magnetic resonance (NMR) experiments on **1** showed two isolated nonequivalent methylene protons at δ 3.44 and 4.74 (each 1H, d, $J=17.2$ Hz) and δ 5.29 and 5.37 (each 1H, dd, $J=13.2$ and 4.0 Hz) and the methine proton at 5.15 (d, $J=1.1$ Hz) showed *W*-type long-range coupling with the methine proton at δ 3.47 (d, $J=1.1$ Hz). By exchanging the hydrogen of the hydroxyl group at δ 7.35 (br d, $J=4.0$ Hz) with D_2O, each doublet of doublets of the methylene protons of the hydroxymethyl group at δ 5.29 and 5.37 was transformed into a doublet ($J=13.2$ Hz). The ^{13}C-NMR spectrum (Table I) of **1** confirmed the presence of 21 carbons [$5\times CH_3$, $2\times CH_2$, $6\times CH$, $8\times C$ as determined from the ^{1}H–^{13}C correlation spectroscopy (COSY) spectrum] including two γ-lactone carbons (δ 170.09 and 175.83), two olefinic carbons (δ 104.27 and 166.34), and ten oxygen-bearing carbons (δ 55.75, 53.63, 59.08, 62.85, 63.17, 78.17, 82.21, 83.15, 87.89, and 89.33). Of the ten oxygen-bearing carbons, seven were proton-coupled carbons [$2\times CH_3$ (δ 55.75 and 59.08), $1\times CH_2$ (δ 166.34) and $4\times CH$ (δ 83.15, 87.89, 62.85, 63.17)], while the remaining three (δ 78.17, 82.21, and 89.33) were quaternary in nature. Three of ten oxygens in **1** were hydroxyl groups [δ 7.35 (br d, $J=4.0$ Hz), 7.41 (s), and 8.09 (s) as determined from the ^{1}H-NMR; each signal disappeared with the addition of D_2O], and one oxygen was shown to be an epoxide ring from the chemical shifts of two methines [δ ^{13}C, 62.85, δ ^{1}H, 4.18 [1H, d, $J=2.9$ Hz) and δ ^{13}C, 63.17, δ ^{1}H, 3.66 (1H, d,

Table I. ^{13}C- and ^{1}H-NMR Spectral Data for Picrodendrin A (**1**)$^{a,b)}$

Position	C	H (J/Hz)
1	52.99	
2	87.89	3.70 (1H, s)
3	83.15	5.15 (1H, d, $J=1.1$)
4	82.21	
5	57.82	3.47 (1H, d, $J=1.1$)
6	78.17	
7	25.12	1.89 (3H, s)
8	31.03	2.74 (1H, sep, $J=6.2$)
9	15.63	1.21 (3H, d, $J=6.2$)
10	18.24	1.48 (3H, d, $J=6.2$)
11	62.85	4.18 (1H, d, $J=2.9$)
12	63.17	3.66 (1H, d, $J=2.9$)
13	89.33	
14	34.25	3.44, 4.74 (each 1H, d, $J=17.2$)
15	175.83	
16	104.27	
17	170.09	
18	166.34	
19	53.63	5.29, 5.37 (each 1H, dd, $J=13.2$, $4.0^{c)}$)
2-OCH$_3$	59.08	3.96 (3H, s)
18-OCH$_3$	55.75	3.31 (3H, s)
4-OH		7.41 (1H, s)$^{c,d)}$
6-OH		8.09 (1H, s)$^{c,d)}$
19-OH		7.35 (1H, br d, $J=4.0^{c)}$)

a) The spectra were measured in pyridine-d_5. *b*) Abbreviations: s = singlet, d = doublet, dd = doublet of doublets, sep = septet, br d = broad doublet. *c*) Disappeared with the addition of D_2O. *d*) May be exchangeable.

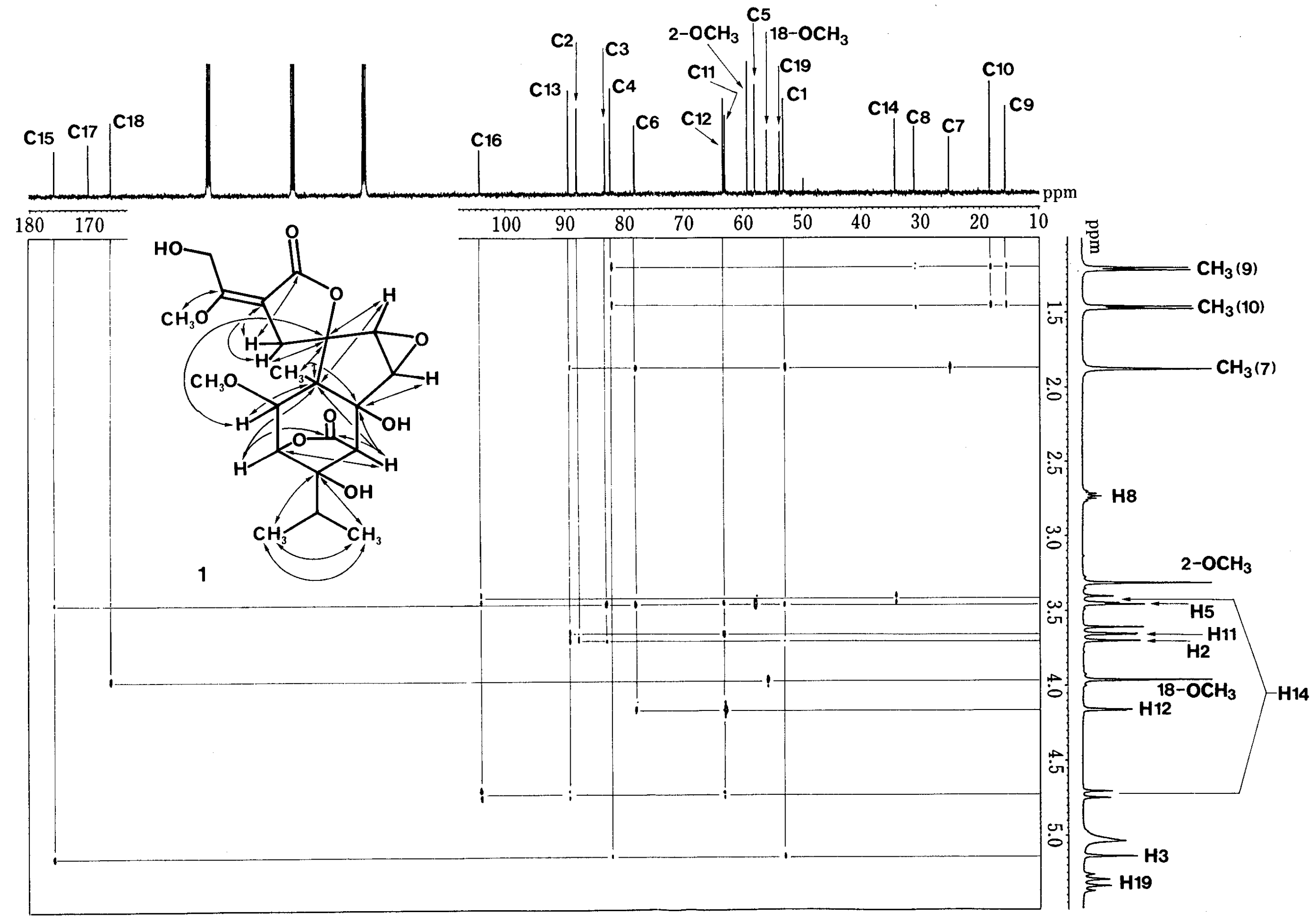

Fig. 1. ^{1}H–^{13}C Long-Range 2D COSY Spectrum and Two- and Three-Bond Correlations of Picrodendrin A (**1**)

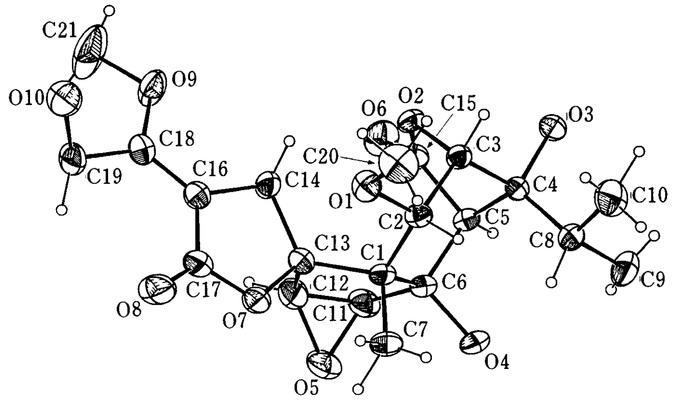

Fig. 2. ORTEP Drawing of Picrodendrin A (**1**) with 50% Probability Ellipsoids

$J=2.9$ Hz)], while the other six must be two γ-lactones and two methoxyl groups. Next, a long-range ^{1}H–^{13}C COSY experiment on **1** was carried out to clarify the sequence of the carbon atoms. The significant ^{1}H–^{13}C long-range correlations are indicated by arrows in the formula in Fig. 1. These observations suggested that the structure of picrodendrin A is as presented by formula **1**. In order to determine the exact structure of picrodendrin A (**1**), an X-ray crystal structure analysis was undertaken. Recrystallization of **1** from methanol furnished colorless prisms of mp 223 °C suitable for X-ray analysis. Figure 2 shows a perspective ORTEP drawing of the final X-ray model for picrodendrin A (**1**) showing the relative stereochemistry of the molecule. This is the first report on the isolation and structure determination of a picrotoxin-group nor-diterpene lactone from *Picrodendron* species.

Experimental

The melting point was determined on a Yanagimoto micromelting point apparatus and is uncorrected. The UV and IR spectra were recorded with Hitachi 340 and Hitachi 260-30 spectrophotometers, respectively. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a JEOL JNM GX-400 (^{1}H-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 ionizatin mass spectrom (EI-MS), and HRMS were measured with a JEOL JMS DX-303 mass spectrometer. Optical rotation was determined on a JASCO DIP-4 digital polarimeter. Column chromatography was carried out on silica gel (BW-820MH, Fuji Davison).

Extraction and Isolation Dried barks (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 solution was dried over Na_2SO_4 and concentrated to give a chloroform-soluble fraction (18 g), which was subjected to column chromatography on silica gel (200 g) (chloroform, 1, 2, 5, 10, 20 and 50% methanol in chloroform, and methanol). The fraction (1.3 g) eluted with 10% methanol in chloroform was further purified by column chromatography on silica gel to give picrodendrin A (**1**, 132 mg).

Picrodendrin A (1) Colorless prisms, mp 223 °C, $[\alpha]_D^{25}$ $-25.0°$ ($c=1.3$, pyridine). UV λ_{max}^{MeOH} nm (log ε): 258 (4.23). IR ν_{max}^{KBr} cm^{-1}: 3340, 2960, 1785, 1725, 1660, 1470, 1290, 1255, 1160, 1090, 1015. ^{1}H-NMR and ^{13}C-NMR: Table I. MS m/z (%): 440 (M$^+$, 8), 422 (8), 320 (9), 260 (8), 250 (100), 235 (18), 181 (67), 153 (46), 127 (42), 113 (33), 99 (50), 85 (24), 77 (13), 71 (68), 55 (25), 43 (97). HRMS Calcd for $C_{21}H_{28}O_{10}$. m/z: 440.1682. Found m/z: 440.1669.

X-Ray Crystal Structure Analysis of Picrodendrin A (1) Suitable

Table II. Final Positional Parameters ($\times 10^4$) and Equivalent Isotropic Thermal Parameters with Estimated Standard Deviations in Parentheses for Picrodendrin A (**1**)

Atom	x	y	z	B_{eq} (Å^2)
C(1)	8335 (2)	6850 (5)	9608 (7)	1.88 (9)
C(2)	8938 (2)	6714 (5)	10810 (7)	1.83 (9)
C(3)	9299 (2)	5930 (5)	10040 (7)	1.79 (9)
C(4)	9047 (2)	4774 (5)	9714 (7)	1.82 (9)
C(5)	8576 (2)	5046 (5)	7941 (7)	1.79 (9)
C(6)	8117 (2)	5765 (5)	8379 (7)	1.9 (1)
C(7)	8003 (2)	7059 (6)	11078 (8)	2.7 (1)
C(8)	8915 (2)	4234 (5)	11424 (8)	2.3 (1)
C(9)	9424 (3)	4122 (7)	13054 (9)	3.5 (1)
C(10)	8643 (3)	3110 (6)	10950 (1)	3.4 (1)
C(11)	7742 (2)	6201 (6)	6551 (8)	2.6 (1)
C(12)	7775 (2)	7407 (6)	6471 (9)	2.8 (1)
C(13)	8219 (2)	7822 (5)	8113 (8)	2.2 (1)
C(14)	8673 (2)	8319 (5)	7281 (8)	2.2 (1)
C(15)	8891 (2)	5742 (5)	6861 (7)	2.1 (1)
C(16)	8583 (2)	9540 (5)	7398 (8)	2.2 (1)
C(17)	8221 (2)	9729 (5)	8619 (9)	2.7 (1)
C(18)	8787 (2)	10320 (5)	6474 (8)	2.4 (1)
C(19)	8709 (3)	11541 (5)	6653 (9)	2.8 (1)
C(20)	9581 (3)	7804 (7)	12976 (9)	3.6 (1)
C(21)	9169 (4)	10664 (8)	386 (1)	6.6 (2)
O(1)	9179 (2)	7779 (4)	11187 (5)	2.44 (8)
O(2)	9308 (1)	6272 (3)	8131 (5)	1.99 (7)
O(3)	9429 (2)	4099 (4)	9042 (5)	2.33 (7)
O(4)	7821 (2)	5019 (4)	9239 (6)	2.67 (8)
O(5)	7320 (2)	6881 (5)	6983 (7)	3.3 (1)
O(6)	8807 (2)	5880	5203 (5)	3.24 (9)
O(7)	8015 (2)	8760 (4)	8984 (6)	2.79 (8)
O(8)	8092 (2)	10568 (4)	9285 (7)	4.1 (1)
O(9)	9111 (2)	9959 (4)	5389 (6)	3.43 (9)
O(10)	9244 (2)	12042 (4)	7420 (7)	3.6 (1)

Table III. Bond Lengths (Å) with Standard Deviations in Parentheses for Picrodendrin A (**1**)

Atom 1 Atom 2	Distance (Å)	Atom 1 Atom 2	Distance (Å)
C(1) –C(2)	1.562 (6)	C(16)–C(18)	1.348 (9)
C(1) –C(7)	1.558 (9)	C(18)–C(19)	1.507 (9)
C(1) –C(13)	1.588 (9)	O(1) –C(2)	1.427 (8)
C(2) –C(3)	1.529 (8)	O(1) –C(20)	1.437 (7)
C(3) –C(4)	1.534 (8)	O(2) –C(3)	1.471 (7)
C(4) –C(5)	1.555 (6)	O(2) –C(15)	1.373 (6)
C(4) –C(8)	1.532 (8)	O(3) –C(4)	1.453 (7)
C(5) –C(6)	1.558 (8)	O(4) –C(6)	1.426 (7)
C(5) –C(15)	1.522 (8)	O(5) –C(11)	1.454 (8)
C(6) –C(1)	1.610 (8)	O(5) –C(12)	1.456 (8)
C(6) –C(11)	1.524 (7)	O(6) –C(15)	1.195 (7)
C(8) –C(9)	1.520 (8)	O(7) –C(13)	1.467 (8)
C(8) –C(10)	1.528 (9)	O(7) –C(17)	1.345 (8)
C(11)–C(12)	1.47 (1)	O(8) –C(17)	1.211 (8)
C(12)–C(13)	1.506 (8)	O(9) –C(18)	1.362 (8)
C(13)–C(14)	1.560 (9)	C(9) –C(21)	1.45 (2)
C(14)–C(16)	1.566 (8)	C(10)–C(19)	1.458 (7)
C(16)–C(17)	1.461 (9)		

Table IV. Bond Angles (°) with Standard Deviations in Parentheses for Picrodendrin A (**1**)

Atom 1 Atom 2 Atom 3	Angle (°)	Atom 1 Atom 2 Atom 3	Angle (°)
C(2)–C(1) –C(6)	111.9 (4)	C(5)–C(11)–C(6)	109.2 (5)
C(2)–C(1) –C(7)	104.7 (4)	O(5) –C(11)–C(12)	59.7 (4)
C(2)–C(1) –C(13)	116.6 (4)	C(11)–C(12)–C(13)	109.9 (5)
C(6)–C(1) –C(7)	110.7 (5)	O(5) –C(12)–C(11)	59.6 (4)
C(6)–C(1) –C(13)	104.2 (4)	O(5) –C(12)–C(13)	114.7 (5)
C(7)–C(1) –C(13)	108.9 (5)	C(12)–C(13)–C(14)	106.8 (5)
C(1)–C(2) –C(3)	116.7 (4)	C(1) –C(13)–C(12)	105.8 (5)
O(1)–C(2) –C(1)	108.7 (4)	C(1) –C(13)–C(14)	122.6 (4)
O(1)–C(2) –C(3)	111.5 (4)	O(7) –C(13)–C(1)	107.3 (4)
C(1)–C(3) –C(2)	111.2 (5)	O(7) –C(13)–C(12)	109.4 (4)
O(2)–C(3) –C(2)	109.9 (4)	O(7) –C(13)–C(14)	104.7 (5)
O(2)–C(3) –C(4)	102.7 (4)	C(13)–C(14)–C(16)	102.7 (5)
C(3)–C(4) –C(5)	97.7 (5)	O(2) –C(15)–C(5)	108.7 (4)
C(3)–C(4) –C(8)	115.8 (5)	O(6) –C(15)–O(2)	121.9 (5)
C(5)–C(4) –C(8)	119.6 (4)	O(6) –C(15)–C(5)	129.4 (5)
O(3)–C(4) –C(3)	106.3 (4)	C(14)–C(16)–C(17)	108.6 (5)
O(3)–C(4) –C(5)	105.6 (4)	C(14)–C(16)–C(18)	125.4 (6)
O(3)–C(4) –C(8)	110.5 (4)	C(17)–C(16)–C(18)	126.0 (6)
C(4)–C(5) –C(6)	113.5 (4)	O(7) –C(17)–O(8)	119.5 (6)
C(4)–C(5) –C(15)	99.4 (4)	O(7) –C(17)–C(16)	109.1 (5)
C(6)–C(5) –C(15)	108.8 (5)	O(8) –C(17)–C(16)	131.5 (6)
C(5)–C(6) –C(1)	114.0 (4)	C(17)–C(18)–C(19)	124.8 (6)
C(5)–C(6) –C(11)	109.9 (5)	O(9) –C(18)–C(16)	116.3 (6)
C(1)–C(6) –C(11)	104.8 (5)	O(9) –C(18)–C(19)	118.8 (6)
O(4)–C(6) –C(1)	114.4 (5)	O(10)–C(19)–C(18)	108.3 (5)
O(4)–C(6) –C(5)	104.3 (5)	C(2) –O(1) –C(20)	111.2 (5)
O(4)–C(6) –C(11)	109.5 (4)	C(3) –O(2) –C(15)	108.3 (4)
C(4)–C(8) –C(9)	111.2 (5)	C(11)–O(5) –C(12)	60.6 (4)
C(4)–C(8) –C(10)	112.1 (5)	C(13)–O(7) –C(17)	112.9 (5)
C(9)–C(8) –C(10)	110.0 (5)	C(18)–O(9) –C(21)	117.6 (6)
C(6)–C(11)–C(12)	110.6 (5)		

crystals of **1** were grown from methanol as colorless prisms. Crystal data: $C_{21}H_{28}O_{10} \cdot 1/2$ MeOH, space group $C2$, $a=25.396$ (7), $b=12.136$ (3), $c=7.359$ (2) Å; $\beta=105.24$ (2) Å, $V=2187.7$ Å^3, $Z=4$, $D_{calcd}=1.386\,g \cdot cm^{-3}$ $D_{obs}=1.392\,g \cdot cm^{-3}$. Intensity data were measured on an Enraf-Nonius CAD-4 diffractometer using monochromated Cu $K\alpha$ radiation. In total, 2357 independent structure factors with $I_0 > 3\sigma(I_0)$ within $4 \leqq 2\theta \leqq 150°$ were obtained in the 2θ–ω scanning mode. The structure was solved by the direct method using the structure determination package SDP. The structure was refined by the full-matrix least-squares method to the final R factor of 0.058. The final parameters are listed in Table II, and bond lengths and bond angles are listed in Tables III and IV, respectively, along with their standard deviations.

References and Notes

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