Bioactive Constituents of the Roots of *Polyalthia cerasoides*

Somdej Kanokmedhakul,* Kwanjai Kanokmedhakul, and Ratsami Lekphrom

Department of Chemistry, Applied Taxonomic Research Center, Faculty of Science, Khon Kaen University, Khon Kaen 40002, Thailand

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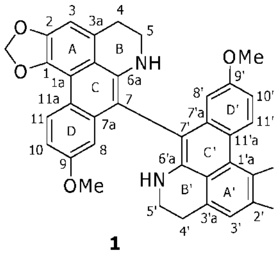
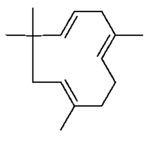
A new dimeric aporphine alkaloid, bidebiline E (**1**), and a new natural product, octadeca-9,11,13-triynoic acid (**2**), along with three known sesquiterpenes, α-humulene (**3**), caryophyllene oxide (**4**), and (−)-α-cadinol (**5**), and four known isoquinoline alkaloids, laudanosine (**6**), codamine (**7**), laudanidine (**8**), and reticuline (**9**), were isolated from the roots of *Polyalthia cerasoides*. The structures of compounds **1** and **2** were established on the basis of their 1D and 2D NMR spectroscopic data. Among these isolates, **1**, **2**, **4**, **7**, and **8** exhibited antimalarial activity against *Plasmodium falciparum*, while **1–3** showed antimycobacterial activity against *Mycobacterium tuberculosis* using in vitro assays.

Polyalthia cerasoides (Roxb.) Benth. ex Bedd (Annonaceae) is a tree, 5–15 m in height, growing widely in Thailand.[1] Its local names are "Sai den", "Ka chian", "Mod dong", and "Kha sam sik", and a water decoction of the roots is used traditionally as a tonic and a febrifuge.[2] Previous phytochemical investigations on *P. cerasoides* have resulted in the isolation of various types of compounds such as sterols from the leaves and stems,[3] sesquiterpene benzopyrans from the stem bark,[4–6] and protoberberine alkaloids,[7] aporphine alkaloids,[8] benzophenones, a xanthone, and flavanone glucosides from the leaves and branches.[9] However, there have not been any previous studies of extracts from the roots of this plant. As part of our search for bioactive constituents from Thai plants, hexane, EtOAc, and MeOH extracts of air-dried roots of *P. cerasoides* were shown to be active against *Plasmodium falciparum* (IC_{50} range 0.1–9.0 μg/mL). We report herein the isolation, characterization, and bioactivity of two new compounds, **1** and **2**, together with seven known compounds, **3–9**, from the roots of *P. cerasoides.*

The structures of the known compounds were identified by physical and spectroscopic data measurement ($[\alpha]_D$, ^{1}H and ^{13}C NMR, 2D NMR, and MS) and by comparing the data obtained with published values, as α-humulene (**3**),[10] caryophyllene oxide (**4**),[11] (−)-α-cadinol (**5**),[12] laudanosine (**6**),[13] codamine (**7**),[14] laudanidine (**8**),[15] and reticuline (**9**).[16] It should be noted that this is the first report of compounds **3–9** from *P. cerasoides.*



1



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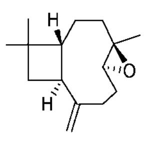

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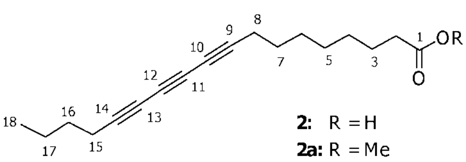
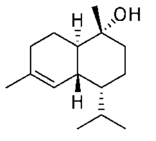


2: R = H
2a: R = Me



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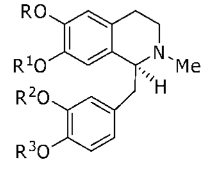

	R	R¹	R²	R³
6:	Me	Me	Me	Me
7:	Me	H	Me	Me
8:	Me	Me	H	Me
9:	Me	H	H	Me

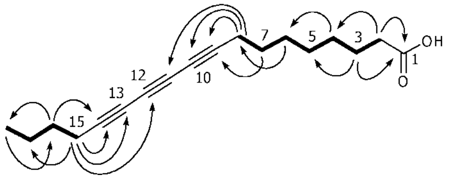

Figure 1. COSY (bold line) and HMBC (arrow, ^{1}H → ^{13}C) of **2**.

Bidebiline E (**1**) was obtained as a pale yellow, amorphous solid, and its molecular formula, $C_{36}H_{28}N_2O_6$, was deduced from the HRESITOFMS (observed *m/z* 585.2003 $[M + H]^+$). The ESITOFMS showed an intense fragmentation ion at *m/z* 293 $C_{18}H_{15}NO_3$ for $[M/2 + H]^+$, indicating that **1** readily fragmented into two identical halves, and this observation suggested that **1** is a dimer. The IR spectrum of **1** showed characteristic N–H (3375 cm^{-1}) and aromatic ring (1610 and 1538 cm^{-1}) bands. The ^{1}H and ^{13}C NMR spectra of **1** were similar to that of bis-7,7′-dehydro-10,10′-dimethoxyanonaine, bidebiline D, reported from *P. debilis*,[17] except that the methoxy groups at rings D and D′ were located on the C-9 and C-9′ positions. The monomeric units of rings A and A′ exhibited a singlet signal at δ 6.97 (H-3, H-3′), while three protons in rings D and D′ showed a spin pattern of methoxy substitutions on C-9 and C-9′ at δ 8.97 (d, $J = 8.8$ Hz, H-11, H-11′), 6.98 (dd, $J = 8.8$, 2.7 Hz, H-10, H-10′), and 6.58 (d, $J = 2.7$ Hz, H-8, H-8′). The assignments were confirmed by COSY and HMBC techniques. The COSY spectrum showed correlations between H-4 and H-5, and H-10 and H-11. The HMBC spectrum exhibited correlations of H-3 to C-1 and C-2; H-4 to C-3a; H-5 to C-3a; H-8 to C-7, C-9, and C-10; H-10 to C-9; H-11 to C-9 and C-1a; methoxy protons to C-9; and methylenedioxy protons to C-1 and C-2. On the basis of the above data, the structure of **1** was elucidated as bis-7,7′-dehydro-9,9′-dimethoxyanonaine and was named bidebiline E.

Octadeca-9,11,13-triynoic acid (**2**) was obtained as white plates, and it was assigned the molecular formula $C_{18}H_{24}O_2$ from the HRESITOFMS (observed *m/z* 273.1748 $[M + H]^+$). The IR spectrum showed the presence of carboxylic acid (3400–2500 and 1695 cm^{-1}) and acetylene (2217 cm^{-1}) bands. Esterification of **2** with MeOH in the presence of $SOCl_2$ yielded the methyl ester **2a** [δ_H 3.62, δ_C 51.3, 174.2 (CO_2CH_3)], supporting the presence of a carboxylic acid in **2**. The ^{13}C NMR and DEPT spectra of **2** indicated one carbonyl, six acetylenic carbons, 10 methylenes, and one methyl group. The methylene group next to carbonylic acid showed a triplet

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* To whom correspondence should be addressed. Tel: +66-43-202222-41, ext. 12243, 12370-4. Fax: +66-43-202373. E-mail: somdej@kku.ac.th.

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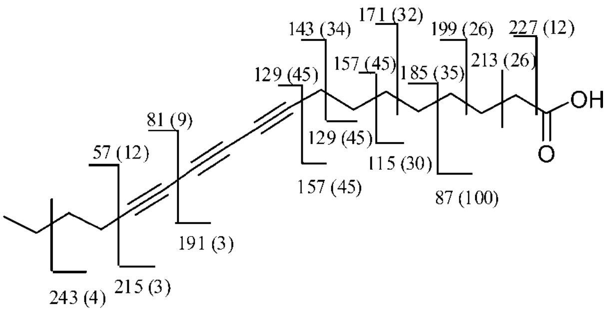

Figure 2. EIMS fragmentation (*m/z*) of **2** with relative intensity values in parentheses.

at δ 2.34 (2H, $J = 7.4$ Hz). Two triplet signals at δ 2.24 (2H, $J = 7.4$ Hz) and 2.22 (2H, $J = 7.4$ Hz) were consistent with two methylene groups on both sides of the triple-bond system, which were also coupled to a methylene chain. The COSY spectrum indicated the partial structures of a methylene chain, $-CH_2(CH_2)_6COOH$, and a butyl unit, $-CH_2CH_2CH_2CH_3$ (Figure 1). The conjugated acetylenic carbons were observed as six signals at δ 79.3, 79.1, 65.7, 65.6, 60.4, and 60.3, suggesting the symmetry of these three pairs of acetylenic units, which is comparable to those reported for a related compound, 17-octadecene-9,11,13-triynoic acid.[18] The HMBC correlations of H-2 to C-1 (δ 179.3) and C-4; H-3 to C-1 and C-5; H-4 to C-2; H-6 to C-8; H-7 to C-8 and C-9 (δ 79.3); H-8 to C-9, C-10 (65.7), and C-11 (60.4); H-15 to C-12 (60.3), C-13 (65.6), C-14 (79.1), and C-17; H-16 to C-14 and C-18; and H-18 to C-16 revealed the two partial structures of C-1–C-8 and C-15–C-18 connected through the conjugated acetylenic unit, C-9–C-14 (Figure 1). The complete structure of **2** was further established by the intensive examination of EIMS fragmentation (Figure 2). The fragment at *m/z* 227 $[M - COOH]^+$ confirmed the presence of a carboxylic group. The conjugated acetylene unit located between C-8 and C-15 was also confirmed by the ion peaks at *m/z* 129, 81, and 57. Thus, the structure of **2** was established as octadeca-9,11,13-triynoic acid. Compound **2** has been previously reported as a synthesis product in 1966 by Kraevskii et al.[19] However, this is the first report of compound **2** isolated from a natural source.

Compounds **1**, **2**, **4**, **7**, and **8** exhibited antimalarial activity in vitro against *P. falciparum* with IC_{50} values of 4.2, 5.0, 2.8, 4.2, and 7.0 μg/mL, respectively. Compounds **1**, **2**, and **3** showed antimycobacterial activity against *M. tuberculosis* with MIC values of 6.25 μg/mL (for all). None of these compounds were cytotoxic when evaluated against KB, BC1, and NCI-H187 cancer cell lines ($IC_{50} > 5$ μg/mL).

Experimental Section

General Experimental Procedures. Optical rotations were obtained using a JASCO DIP-1000 digital polarimeter. IR spectra were taken using a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 400 spectrometer, using residual $CHCl_3$ as an internal standard. HRESITOFMS were obtained using a Micromass LCT mass spectrometer, and the lock mass calibration was applied for the determination of accurate masses. EIMS were measured on a Thermo Finnigan GC-MS.

Plant Material. The roots of *P. cerasoides* were collected on the campus of Khon Kaen University in March 2005 and identified by Prof. Pranom Chantaranothai, Department of Biology, Khon Kaen University. A voucher specimen of the whole plant (S. Kanokmedhakul 6) was deposited at the herbarium of the Department of Biology, Khon Kaen University, Khon Kaen, Thailand.

Extraction and Isolation. The air-dried roots (3.7 kg) of *P. cerasoides* were ground into a powder and extracted successively with hexane, EtOAc, and MeOH (3 × 4 L). Removal of solvents from each extract under reduced pressure gave crude hexane (81.0 g), EtOAc (40.2 g), and MeOH (149.0 g) extracts, respectively.

The hexane extract (20.0 g) was subjected to silica gel flash column chromatography and eluted with increasing concentrations of EtOAc in hexane. Each fraction (200 mL) was monitored by TLC, with fractions having similar TLC patterns combined to yield seven further fractions (HF_1–HF_7). Fraction HF_2 (10% EtOAc–hexane) was further purified by silica gel column chromatography and gradually eluted with a gradient of hexane–EtOAc to give seven subfractions, $HF_{1.1}$–$HF_{1.7}$. Subfraction $HF_{2.2}$ afforded a colorless oil of **3** (8.0 mg). Subfraction $HF_{2.3}$ was further purified by preparative TLC using 20% EtOAc–hexane as an eluent to yield a yellow oil of **4** (24.3 mg). Fraction HF_4 (20–30% EtOAc–hexane) was rechromatographed and eluted with a gradient system of 20% EtOAc–hexane, to yield white plates of **2** (1.2 g). Fraction HF_5 (40–50% EtOAc–hexane) was rechromatographed and eluted with a gradient system of 30% EtOAc–hexane, to afford an additional amount of **2** (460.3 mg).

The EtOAc extract (20.0 g) was subjected initially to silica gel flash column chromatography eluted with the same gradient system as the hexane extract above to give eight fractions, EF_1–EF_8. Fraction EF_1 (10–20% EtOAc–hexane) was chromatographed on a silica gel column, eluted with a gradient system of CH_2Cl_2–hexane, to give an additional amount of **3** (1.3 g). Fraction EF_3 (40% EtOAc–hexane) was separated by column chromatography, eluted with a gradient system of hexane–EtOAc, to yield a light yellow oil of **5** (10.3 mg). Fraction EF_6 (70–90% EtOAc–hexane) was further purified by column chromatography, eluted with a gradient system of hexane–CH_2Cl_2 and MeOH–CH_2Cl_2, to give a pale yellow solid of **1** (53.2 mg).

The MeOH extract (40.0 g) was subjected to silica gel flash column chromatography, eluted with a gradient system of hexane–EtOAc and CH_2Cl_2–MeOH to give eight fractions, MF_1–MF_8. Fraction MF_2 (20% EtOAc–hexane) was chromatographed on a silica gel column, eluted with a gradient system of hexane–CH_2Cl_2, to give an additional amount of **1** (36.8 mg). Fraction MF_7 (50% MeOH–CH_2Cl_2) was rechromatographed and eluted with a gradient system of CH_2Cl_2–MeOH–H_2O (30:3:1−6:4:1), to yield 10 subfractions designated as $MF_{7.1}$–$MF_{7.10}$. Subfraction $MF_{7.4}$ was separated by column chromatography, eluted with CH_2Cl_2–MeOH–H_2O (50:3:1) and finally with MeOH, to give six combined fractions, $MF_{7.4.1}$–$MF_{7.4.6}$. Fraction $MF_{7.4.4}$ was further purified by preparative TLC, using MeOH–CH_2Cl_2–NH_4OH (94:5:1) as eluent, to yield **6** as a brown-yellow, amorphous solid (11.2 mg). Subfraction $MF_{7.7}$ was separated by preparative TLC, using MeOH–CH_2Cl_2–NH_4OH (94:5:1) as eluent (developed × 5) to yield **7** as a brown-yellow, amorphous solid (19.6 mg) as well as **8** (15.8 mg). Fraction MF_8 was

Table 1. Biological Activities of the Isolated Compounds

compound	antimalarial (IC_{50}, μg/mL)	anti-TB (MIC, μg/mL)	cytotoxicity (IC_{50}, μg/mL) KB[a]	BC1[b]	NCI-H187[c]
1	4.2	6.25	nd[d]	nd	nd
2	5.0	6.25	inactive	13.0	inactive
3	inactive	6.25	inactive	inactive	inactive
4	2.8	inactive	inactive	inactive	19.5
7	4.2	inactive	inactive	inactive	inactive
8	7.0	inactive	inactive	inactive	inactive
artemisinin	0.001				
isoniazid		0.05			
kanamycin sulfate		2.5			
ellipticine			0.36	0.26	0.32

[a] Human epidermoid carcinoma in the mouth. [b] Human breast cancer cell. [c] Human small cell lung cancer. [d] nd = not determined.

chromatographed, using a gradient system of CH_2Cl_2–MeOH–H_2O (30:3:1–6:4:1), to give six subfractions, $MF_{8.1}$–$MF_{8.6}$. Subfraction $MF_{8.2}$ was purified by preparative TLC, using MeOH–CH_2Cl_2–NH_4OH (93:6:1) as eluent (developed × 3), to yield **9** as a brown-yellow, amorphous solid (55.3 mg).

Bidebiline E (1): pale yellow solid; dec 250 °C; $[\alpha]^{29}_{D}$ −42.8 (*c* 0.20, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 272 (4.7), 343 (4.0); IR (KBr) ν_{max} 3375, 1610, 1538, 1219, 1458, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (2H, d, J = 8.8 Hz, H-11, H-11′), 6.98 (2H, dd, J = 8.8, 2.7 Hz, H-10, H-10′), 6.97 (2H, s, H-3, H-3′), 6.58 (2H, d, J = 2.70 Hz, H-8, H-8′), 3.55 (6H, s, OMe-9, OMe-9′), 3.37–3.25 (4H, m, H-5, H-5′), 3.16–3.10 m (4H, m, H-4, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (C-9, C-9′), 145.6 (C-2, C-2′), 141.3 (C-1, C-1′), 140.5 (C-6a, C-6a′), 134.6 (C-7a, C-7a′), 128.9 (C-11, C-11′), 128.3 (C-3a, C-3a′), 118.4 (C-11a, C11a′), 117.8 (C-1a, C1-a′), 117.2 (C-1b, C1-b′), 111.5 (C-10, C-10′), 107.0 (C-3, C-3′), 105.8 (C-7, C-7′), 105.0 (C-8, C-8′), 100.9 (OCH_2O-1, OCH_2O-1′), 55.0 (OCH_3-9, OCH_3-9′), 41.4 (C-5, C-5′), 30.5 (C-4, C-4′); HRESITOFMS *m/z* 585.2003 $[M + H]^+$ (calcd for $C_{36}H_{28}N_2O_6$ + H, 585.1947).

Octadeca-9,11,13-triynoic acid (2): white plates; mp 60–63 °C; UV (MeOH) λ_{max} (log ε) 247 (3.9), 270 (3.6), 286 (3.6); IR (KBr) ν_{max} 3447, 2955, 2932, 2867, 2217, 1695, 1465, 1434, 1411, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (2H, t, J = 7.2 Hz, H-2), 2.24 (2H, t, J = 7.2 Hz, H-8), 2.22 (2H, t, J = 7.2 Hz, H-15), 1.63 (2H, quint., J = 7.0 Hz, H-3), 1.52 (4H, m, H-7 and H-16), 1.42 (2H, m, H-17), 1.40–1.35 (4H, m, H-5 and H-6), 1.34 (2H, m, H-4), 0.90 (3H, t, J = 7.4 Hz, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3 (C-1), 79.3 (C-9), 79.1 (C-14), 65.7 (C-10), 65.6 (C-13), 60.4 (C-11), 60.3 (C-12), 33.8 (C-2), 30.1(C-16), 28.8 (C-4), 28.6 (C-5), 28.5 (C-6), 27.9 (C-7), 24.6 (C-3), 21.8 (C-17), 19.3 (C-8), 19.0 (C-15), 13.4 (C-18); HRESITOFMS *m/z* 273.1748 $[M + H]^+$ (calcd for $C_{18}H_{24}N_2$ + H, 273.1776).

Preparation of Ester 2a. To a solution of **2** (100 mg) in absolute MeOH (3 mL) were added a few drops of $SOCl_2$. The reaction mixture was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The product was purified by preparative TLC (EtOAc–hexane, 20:80) to give a yellow oil of **2a** (83 mg, 79%): IR (neat) 2926, 2855, 2202, 1737, 1465, 1462, 1436, 1435, 1094 cm^{-1}. The ^1H and ^{13}C NMR spectroscopic data of **2a** were similar to those of **2** except for the presence of a methyl ester group [δ_H 3.62, δ_C 51.3, 174.2 (CO_2CH_3)]; EIMS *m/z* 286 $[M]^+$ (2), 255(10), 227 (2), 213 (3), 199 (4), 185 (9), 171 (15), 157 (27), 143 (43), 129 (100), 105 (10), 81 (6), 57 (3).

Caryophyllene oxide (4): $[\alpha]^{29}_{D}$ −16.2 (*c* 0.20, $CHCl_3$) [lit.[11] −46.4 (*c* 5.60, $CHCl_3$)].

(−)-α-Cadinol (5): $[\alpha]^{29}_{D}$ −67.2 (*c* 0.20, $CHCl_3$) [lit.[12] −98.0 (*c* 0.20, $CHCl_3$)].

Laudanosine (6): mp 85–87 °C (lit.[13,20] 87–88 °C); $[\alpha]^{29}_{D}$ +54.4 (*c* 0.20, $CHCl_3$) [lit.[20] +51.6 (*c* 0.50, $CHCl_3$)].

Codamine (7): mp 124–125 °C (lit.[14] 126–127 °C); $[\alpha]^{29}_{D}$ +50.7 (*c* 0.20, $CHCl_3$).

Laudanidine (8): mp 175–177 °C (lit.[15] 176–178 °C); $[\alpha]^{29}_{D}$ +41.3 (*c* 0.20, $CHCl_3$) [lit.[15] +90.0 (*c* 0.20, $CHCl_3$)].

Reticuline (9): mp 72–73 °C (lit.[16] 71–74 °C); $[\alpha]^{29}_{D}$ +39.5 (*c* 0.20, $CHCl_3$) [lit.[16] +112.0 (*c* 0.22, $CHCl_3$)].

Antimalarial Assay. Antimalarial activity was evaluated against the parasite *Plasmodium falciparum* (K1, multidrug-resistant strain), using the method of Trager and Jensen.[20] Quantitative assessment of malarial activity in vitro was determined by means of the microculture radioisotope technique based upon the method described by Desjardins et al.[21] The inhibitory concentration (IC_{50}) represents the concentration that causes 50% reduction in parasite growth as indicated by the in vitro uptake of [^{3}H]-hypoxanthine by *P. falciparum*. The standard compound was artemisinin (Table 1).

Antimycobacterial Assay. Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H37Ra using the microplate Alamar Blue assay (MABA).[22] The standard drugs isoniazid and kanamycin sulfate were used as the reference compounds (Table 1).

Cytotoxicity Assay. Cytotoxic assays against human epidermoid carcinoma (KB), human breast cancer (BC1), and human small cell lung cancer (NCI-H187) cell lines were performed employing the colorimetric method as described by Skehan and co-workers.[23] The reference substance was ellipticine (Table 1).

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