Structure and Synthesis of a New Monoterpenoidal Carboxamide from the Seeds of the Thai Medicinal Plant *Acacia concinna*

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A new monoterpenoidal carboxamide, concinnamide (1), has been isolated from the seeds of a Thai medicinal plant, *Acacia concinna* DC. (Leguminosae). Its structure has been revised to (*E*)-2,6-dimethyl-6-hydroxy-2,7-octadienamide by detailed spectroscopic and synthetic studies, though it had been preliminarily assigned as a seven-membered lactam derivative by our previous work. (−)-Concinnamide, (−)-1, was synthesized from (−)-linalool (2) by stepwise oxidation, followed by amidation to confirm the structure. The inhibitory effects of 1 and related compounds on the arachidonate 5-lipoxygenase of RBL-1 cells are also described.

Key words concinnamide; monoterpene; *Acacia concinna*; Leguminosae; Thai medicinal plant; (*E*)-2,6-dimethyl-6-hydroxy-2,7-octadienamide

Acacia concinna DC. is a leguminous plant which grows in Asian tropical areas. Its seeds have been used as a folk medicine for skin diseases. As a continuation of our phytochemical studies on the biologically active constituents of medicinal plants and crude drugs,[1–5] a new monoterpenoidal amide (**1**) has been isolated from these seeds. We describe here the revision of the structure and synthesis of (−)-**1** which was incorrectly assigned in a previous communication.[1]

Results and Discussion

Compound **1**, a colorless oil, $[\alpha]_D$ +4.3°, was isolated from 75% EtOH extracts of the seeds by repeated column chromatography, as described in the experimental section. It gave bands at 1670 cm^{-1} (C=O) and at 3100—3600 cm^{-1} (OH+NH_2) in the IR spectrum. A *quasi*-molecular ion $[M+H]^+$ at *m/z* 184.1341 in the high-resolution (HR) fast ion bombardment mass spectrum (FAB-MS) established the molecular formula as $C_{10}H_{17}NO_2$ (Calcd as $C_{10}H_{18}NO_2$, 184.1337). This was also confirmed by the appearance of a dominant *pseudo*-molecular ion at *m/z* 206 $[M+Na]^+$ and the disappearance of a $[M+H]^+$ ion in the spectrum of **1** on the addition of sodium chloride.

The ^{13}C-NMR spectrum of **1** exhibited ten signals, suggesting the presence of an aliphatic monoterpene skeleton. Thus, signals of two sets of double bonds [δ 144.6 (C-7), 137.7 (C-3), 129.9 (C-2), 112.2 (C-8)], a carbonyl [δ 171.5 (C-1)], two methylene [δ 40.8 (C-5), 23.2 (C-4)], and two methyl groups [δ 28.0 (C-10), 12.7 (C-9)] were observed, together with a comparatively deshielded quaternary carbon signal at δ 73.0 (C-6), indicating that an OH group is attached to one of the allylic positions (Table 1).

Table 1. ^{13}C-NMR Data for **1**, (−)-**1**, **2**, **3a**, **3b**, **4**, and **5** in $CDCl_3$ (ppm from Tetramethylsilane)

	1	(−)-1	2	3a	3b	4	5
C-1	171.5	171.8	25.7	68.5	26.7[a)]	195.4	173.1
C-2	129.9	129.7	124.3	134.9	48.5	139.1	127.1
C-3	137.7	137.7	131.9	125.7	85.9	155.0	144.7
C-4	23.2	23.1	22.8	22.3	27.9	23.8	23.6
C-5	40.8	40.7	42.0	41.6	37.3	40.2	40.4
C-6	73.0	72.8	73.5	73.3	83.2	72.8	73.2
C-7	144.6	144.5	145.0	144.8	143.6	144.3	144.3
C-8	112.2	112.0	111.7	111.8	111.2	112.3	112.3
C-9	12.7	12.5	17.7	13.6	26.6[a)]	9.0	11.9
C-10	28.0	27.8	27.9	27.7	26.3	28.0	27.9

a) Assignment may be reversed.

The ^{1}H-NMR spectrum of **1** revealed an isolated vinyl group (δ 5.91, 5.24, 5.10, each 1H, dd, H-7, H-8, H-8′), an additional olefinic hydrogen (δ 6.43, 1H, ddq, H-3), two methylene groups (δ 2.25, 1.65, each 2H, m, H-4, H-5) and two *tert*-methyl groups (δ 1.31, 3H, s, H-10; δ 1.85, 3H, dt, H-9). Furthermore, a well-dried sample of **1** gave two additional broad peaks at δ 5.56 and 1.53, which were integrated for two and one hydrogens, respectively, in its ^{1}H-NMR spectrum. Chemical shifts of these two peaks varied remarkably with sample concentration, and these peaks disappeared on the addition of D_2O, consistent with the presence of primary $CONH_2$ and OH groups in **1**.

On the basis of the above spectral data, **1** was reconsidered as a new monoterpenoidal carboxamide (Fig. 1). The two dimensional (2D)-NMR analysis of **1** also supported the deduced structure; for example, an amide carbonyl carbon (C-1) showed a three-bond correlation to an olefinic hydrogen (H-3) in the ^{1}H detected heteronuclear multiple bond connectivity (HMBC) spectrum (8 Hz). Other important cross peaks were observed

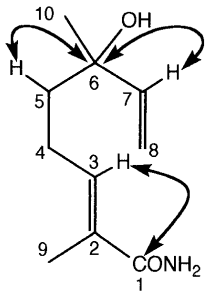

Fig. 1. Structure and Significant Carbon–Hydrogen Multiple-Bond Correlation Observed in the HMBC Spectrum of **1**

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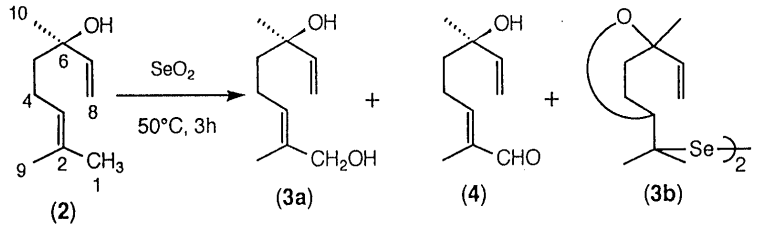

Chart 1

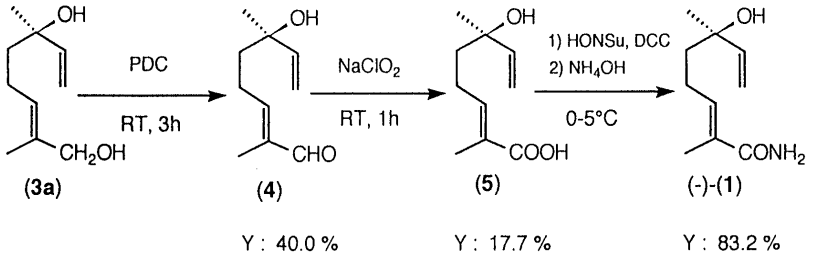

Chart 2

between a quaternary carbon (C-6) and a vinylic hydrogen (H-7) and also with one of the methylene hydrogens (H-5) (Fig. 1).

In order to confirm the structure proposed by the spectroscopic analysis, (−)-**1** was synthesized from natural (−)-linalool (**2**) by stepwise oxidation and subsequent amidation.

(−)-Linalool (**2**) was oxidized by SeO_2[6,7] in EtOH at 50 °C to afford several oxidative products (**3a**, **b**, **4**) (Chart 1). The hydroxymethylene carbon and hydrogens in **3a** resonated at δ 68.5 and 3.92 in the ^{13}C- and ^{1}H-NMR spectra, respectively, consistent with the structure of **3a**. Under this reaction condition, a 1-hydroxyl form (**3a**) became a major product together with minor products, a 1-aldehyde form (**4**) and a dimeric by-product (**3b**), whereas the reaction products became miscellaneous when the reaction was performed at a higher temperature. Compound **3b** possesses a symmetric dimer structure with two selenium atoms in the molecule. The validity of the structure of **3b** was confirmed by the analyses of FAB-MS (*m/z* 465 $[M+H]^+$) and HMBC spectra which showed a three bond correlation between H-3 and C-6. Chromatographic purification of **4** was unsuccessful, however it was identified from the following oxidation reaction.

The 1-hydroxyl derivative (**3a**) was rapidly oxidized by pyridinium dichromate (PDC)[8] in CH_2Cl_2 at room temperature to give a 1-aldehyde form (**4**) as a sole product in a yield of 40.0% (Chart 2). An attempt of the similar oxidation of **3a** with pyridinium chlorochromate (PCC)[9] resulted in the formation of **4** in a poorer yield. The aldehydic hydrogen (H-1) in **4** resonated characteristically at δ 9.31 as a singlet in the ^{1}H-NMR spectrum. A diagnostic cross peak was observed between the aldehydic hydrogen (H-1) and the olefinic hydrogen (H-3) in the nuclear Overhauser effect correlation spectrum (NOESY). Therefore, the stereochemistry of the double bond system between C-2 and C-3 in **4** was confirmed to be an *E*-form. Compound **4** was further treated by $NaClO_2$[10] in *tert*-BuOH–H_2O at room temperature to yield a 1-carboxylic acid form (**5**) (Chart 2). The carboxylic carbon (C-1) in **5** resonated at δ 173.1 in the ^{13}C-NMR spectrum (Table 1).

The desired (−)-**1** was efficiently obtained by the condensation of **5** with ammonia in a good yield by an usual DCC–HONSu (dicyclohexylcarbodiimide–*N*-hydroxysuccinimide) method[11] (Chart 2). The overall yield of (−)-**1** was 3.0% from (−)-linalool.

The spectral data and chromatographic behavior of synthesized (−)-**1** are completely identical to those of natural **1** (Fig. 2). Therefore, the planar structure of **1** was confirmed as (*E*)-2,6-dimethyl-6-hydroxy-2,7-octadienamide. The sign and absolute value of the optical rotation of (−)-**1** (−25.6°) synthesized from the naturally occurring (−)-6(*R*)-linalool does not coincide with those of the isolated **1** (+4.3°), thereby showing that **1** isolated in this study may be a mixture of the 6(*R*)- and 6(*S*)-form. We have previously reported the isolation and structural elucidation of a new compound named (+)-acacialactam from *A. concinna*.[1] However, reexamination of the spectral data, especially by employing FAB-MS measurement and also the synthetic study described here, led to the revision of the structure previously reported to the new monoterpenoidal compound (**1**), which was tentatively proposed by Fox *et al.*[12] Consequently, we here renamed the new structure (**1**) concinnamide. As for the constituents of *A. concinna*, several triterpenoids,[13,14] saponins,[15] and alkaloids[16] were isolated. This is the first report of **1**, whereas 1-carboxylic acid[17] and its derivatives as esteric[18−21] forms have often been found in several plants.

Finally, the biological activity of **1** and related compounds was studied. Among the samples (**1**—**5**) prepared during the synthetic study, **2** and **3b** exhibited moderate inhibitory effects on the arachidonate 5-lipoxygenase[22] of rat basophilic leukemia (RBL-1) cells. The inhibition values (%) of **2** and **3b** for 5-lipoxygenase were 75.2 and 66.0% at a concentration of 100 mM, respectively, while **1** had no inhibitory effect. Interestingly, linalool derivatives (**1**, **3a**, **b**, **4**, **5**), except for (−)-linalool (**2**), which is re-

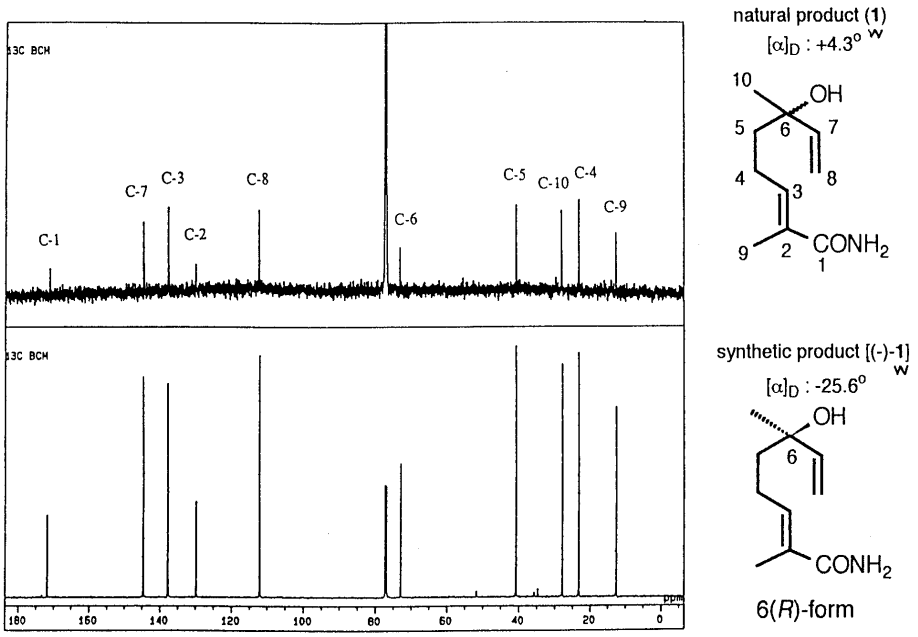

Fig. 2. ^{13}C-NMR Spectra of Natural **1** and Synthetic (−)-**1**

ported to possess an antimicrobial activity often anticipated for general essential oils,[2,3] show no antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, *Aspergillus niger*, and *Trichophyton mentagrophytes*, indicating that the 1-methyl group of linalool may be essential for the activity.

Experimental

Details have been reported previously.[1,2]

Plant Materials The seeds of *A. concinna* were collected in Chiang Mai (Thailand). Voucher specimens are deposited in the herbarium of the Faculty of Pharmaceutical Sciences, Chiba University.

Extraction and Isolation of Concinnamide (1) The seeds of *A. concinna* (200 g) were extracted with 75% EtOH. The basic fraction obtained in the usual manner was subjected to silica gel column chromatography using CH_2Cl_2–MeOH–conc.NH_4OH gradient system (90 : 1 : 0.2—90 : 20 : 1). Fractions rich in **1** were combined and subjected to prep. TLC (silica gel) with EtOAc–MeOH–conc.NH_4OH (150 : 9 : 1) as a developing solvent to afford **1** (32 mg): colorless oil, $[\alpha]_D$ +4.3° (MeOH, c=0.16). UV λ_{max}^{MeOH} [ε] nm: 210 [15700]. IR ν_{max}^{film} cm^{-1}: 3600—3100 (NH_2+OH), 2960, 2920, 1670, 1580. HR-FAB-MS (positive mode) [*m*-nitrobenzylalcohol (NBA)] *m/z*: 184.1341 $[M+H]^+$, (Calcd for $C_{10}H_{18}NO_2$: 184.1337). FAB-MS [NBA] *m/z*: 184 $[M+H]^+$, 166 $[M-H_2O+H]^+$, [NBA+NaCl] *m/z*: 206 $[M+Na]^+$, [NBA+KI] *m/z*: 222 $[M+K]^+$. ^{1}H-NMR ($CDCl_3$): 6.43 (1H, ddq, J=7.4, 7.4, 1.2 Hz, H-3), 5.91 (1H, dd, J=17.3, 10.7 Hz, H-7), 5.56 (2H, br s, $CONH_2$), 5.24 (1H, dd, J=17.3, 1.2 Hz, H-8), 5.10 (1H, dd, J=10.7, 1.2 Hz, H-8), 2.25 (2H, m, H-4), 1.85 (3H, dt, J=1.2, 1.0 Hz, H-9), 1.65 (2H, m, H-5), 1.53 (1H, br s, C_6-OH), 1.31 (3H, s, H-10). ^{13}C-NMR : See Table 1.

Reaction of (−)-Linalool (2) with Selenium Dioxide Crushed SeO_2 (8.62 g) was added to a solution of **2** (10 g) in EtOH (400 ml) with stirring at 50 °C. After being stirred for 3 h, the reaction mixture was concentrated *in vacuo*. The residue was extracted with ethyl acetate and water. The ethyl acetate layer was washed with a small amount of water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography. Elution with $CHCl_3$–MeOH (10 : 0—95 : 5) gave **3b** (270 mg), a 4-rich fraction (1.0 g) and **3a** (2.77 g) in order of elution. **3a**: colorless oil. UV λ_{max}^{MeOH} [log ε] nm: 202.1 [3.76]. IR ν_{max}^{film} cm^{-1}: 3350 (OH), 2970, 2920, 2860, 1010 (C-O), 920. Positive ion FAB-MS (glycerol) *m/z*: 171 $[M+H]^+$, 153 $[M+H-H_2O]^+$, 135 $[M+H-2\times H_2O]^+$. ^{1}H-NMR ($CDCl_3$): 5.86 (1H, dd, J=17.7, 10.4 Hz, H-7), 5.36 (1H, dd, J=7.0, 7.0 Hz, H-3), 5.17 (1H, d, J=17.7 Hz, H-8), 5.02 (1H, d, J=10.4 Hz, H-8), 3.92 (2H, s, H-1), 2.17 (1H, br s, C_6-OH), 2.03 (2H, m, H-4), 1.96 (1H, br s, C_1-OH), 1.60 (3H, s, H-9), 1.52 (2H, m, H-5), 1.24 (3H, s, H-10). ^{13}C-NMR: See Table 1.

3b: yellow oil, UV λ_{max}^{MeOH}: end absorption. IR ν_{max}^{film} cm^{-1}: 3100, 2950, 2920, 2860, 1475, 1385, 1370, 1120, 1025 (C-O), 935, 760. Positive ion FAB-MS [NBA] *m/z*: 469, 468, 467, 466, 465 $[M+H]^+$, 464, 463, 462, 461, 311, 233, 231, 153 (base peak), 135, 125, 81, 71, 69, 55. ^{1}H-NMR ($CDCl_3$): 5.81 (1H×2, dd, J=17.1, 10.4 Hz, H-7), 5.15 (1H×2, dd, J=17.1, 1.5 Hz, H-8), 4.94 (1H×2, dd, J=10.4, 1.5 Hz, H-8), 3.91 (1H×2, m, H-3), 1.87 (1H×2, m, H-4), 1.87 (2H×2, m, H-5), 1.69 (1H×2, m, H-4), 1.39 (3H×2, d, J=0.7 Hz, H-1), 1.38 (3H×2, d, J=1.9 Hz, H-9), 1.29 (3H×2, s, H-10). ^{13}C-NMR: See Table 1.

Reaction of 3a with PDC PDC (3.58 g) was added to a solution of **3a** (810 mg) in CH_2Cl_2 (40 ml) at room temperature with vigorous stirring. After being stirred for 3 h, the reaction mixture was filtered. The filtrate was evaporated *in vacuo* to dryness. The residue was dissolved in ether. The ether solution was filtered and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel column chromatography [$CHCl_3$–MeOH (10 : 0—95 : 5) as an eluent] to give **4** (320 mg). **4**: colorless oil. UV λ_{max}^{MeOH} [log ε] nm: 229.1 [4.01]. IR ν_{max}^{film} cm^{-1}: 3430 (OH), 2980, 2940, 1680 (C=O), 1645 (C=C), 1000 (C-O), 925. Positive ion FAB-MS (NBA) *m/z*: 169 $[M+H]^+$, 151 $[M+H-H_2O]^+$, (NBA+KI) *m/z*: 207 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): 9.31 (1H, s, H-1), 6.45 (1H, ddd, J=7.3, 7.3, 1.2 Hz, H-3), 5.86 (1H, dd, J=17.7, 10.4 Hz, H-7), 5.20 (1H, dd, J=17.7, 1.2 Hz, H-8), 5.05 (1H, dd, J=10.4, 1.2 Hz, H-8), 2.35 (2H, m, H-4), 2.18 (1H, br s, C_6-OH), 1.67 (3H, s, H-9), 1.65 (2H, m, H-5), 1.28 (3H, s, H-10). ^{13}C-NMR: See Table 1.

Reaction of 4 with $NaClO_2$ $NaClO_2$ (1.5 g) was slowly added to a solution of **4** (750 mg), NaH_2PO_4 (695 mg) and 2-methyl-2-butene (1.25 g) in *tert*-BuOH–H_2O (31.8+8.5 ml). After being stirred for 1 h at room temperature, the reaction mixture was acidified with 5% HCl and extracted with CH_2Cl_2 (75 ml×3), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, then eluted with $CHCl_3$–EtOH (10 : 0—95 : 5) to give **5** (300 mg). **5**: colorless oil. UV λ_{max}^{MeOH} [log ε] nm: 213.9 [4.09]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (OH), 3020, 2980, 1695 (C=O), 1650 (C=C), 1295, 935. Positive ion FAB-MS (NBA) *m/z*: 185 $[M+H]^+$, 167 $[M+H-H_2O]^+$, (NBA+KI) *m/z*: 223 $[M+K]^+$. ^{1}H-NMR ($CDCl_3$): 6.86 (1H, ddd, J=7.5, 7.5, 1.2 Hz, H-3), 5.88 (1H, dd, J=17.7, 11.0 Hz, H-7), 5.21 (1H, d, J=17.7, 1.2 Hz, H-8), 5.07 (1H, d, J=11.0, 1.2 Hz, H-8), 2.21 (2H, m, H-4), 1.79 (3H, s, H-9), 1.63 (2H, m, H-5), 1.29 (3H, s, H-10). ^{13}C-NMR: See Table 1.

Amidation of 5 with Ammonia by DCC and HONSu To the cold mixture (*ca.* 5 °C) of **5** (290 mg) and HONSu (181 mg) in acetonitrile–CH_2Cl_2 (10+1 ml), DCC (390 mg) was added with stirring. After the reaction mixture was allowed to stand at 5 °C overnight, 2.9% NH_4OH (0.93 ml) was added, and after being stirred at 5 °C, the precipitated dicyclohexylurea was filtered off. The filtrate was evaporated *in vacuo* to dryness. The residue was subjected to silica gel column chromatography. Elution with $CHCl_3$–MeOH (10 : 0—95 : 5) gave (−)-**1** (240 mg).

(−)-**1**: colorless oil, $[\alpha]_D$ −25.6° (MeOH, $c=0.55$). UV λ_{max}^{MeOH} [ε] nm: 206.4 [14800]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (NH_2+OH), 3000, 1680 (C=O), 1645, 1580, 1375, 930, 910. ^{1}H-NMR ($CDCl_3$): 6.36 (1H, dd, $J=7.3$, 7.3 Hz, H-3), 6.07 (2H, br s, $CONH_2$), 5.83 (1H, dd, $J=17.4$, 10.4 Hz, H-7), 5.16 (1H, d, $J=17.4$ Hz, H-8), 5.01 (1H, d, $J=10.4$ Hz, H-8), 2.13 (2H, m, H-4), 1.8 (1H, br s, C_6-OH), 1.76 (3H, s, H-9), 1.57 (2H, m, H-5), 1.23 (3H, s, H-10). ^{13}C-NMR: See Table 1.

Inhibitory Effects of Linalool Derivatives on Arachidonate 5-Lipoxygenase The inhibitory effects of linalool derivatives on arachidonate 5-lipoxygenase of RBL-1 cells were measured as reported previously.[3] The inhibition value (%) of caffeic acid as a positive control was 49.2% at 100 mM.

Antimicrobial Activity Tests of Linalool Derivatives Antimicrobial activities of **1**—**5** were evaluated by a micro broth dilution method as reported previously.[5] Only natural **2** showed antimicrobial activity with minimum inhibitory concentration (MIC) values of 25 and 100 μg/ml against *Staphylococcus aureus* and *Candida albicans*, respectively.

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