TRICYCLOILLICINONE, A NOVEL PRENYLATED C_6-C_3 COMPOUND INCREASING CHOLINE ACETYLTRANSFERASE (ChAT) ACTIVITY, ISOLATED FROM *ILLICIUM TASHIROI*

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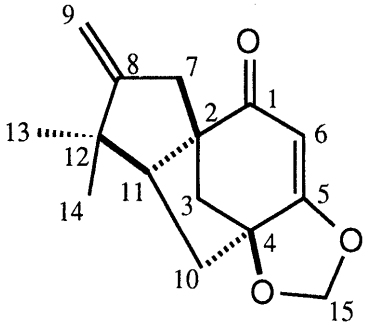
Tricycloillicinone (**1**), a novel tricyclic prenylated C_6-C_3 compound, has been isolated as a neurotrophic substance from the woods of *Illicium tashiroi* and its structure has been elucidated by spectroscopic analyses. Compound **1** could increase ChAT activity in culture of P10 rat septal neurons.

KEY WORDS *Illicium tashiroi*; Magnoliaceae; tricycloillicinone; prenylated C_6-C_3 compound; choline acetyltransferase activity; neurotrophic substance

In preceding papers, [1,2] we reported the isolation and structural elucidation of isodunnianin and 2(*R*)-12-chloro-2,3-dihydroillicinone E (**2**), which increased ChAT activity in culture of fetal rat cerebral hemisphere and in culture of P10 rat septal neurons, respectively. These neurotrophic substances were found in the methanol extract of *Illicium tashiroi* collected in Ishigaki island. Our continuing effort to search for more potent neurotrophic substances in the title plant has resulted in the isolation of a novel tricyclic prenylated C_6-C_3 compound **1**,[3] designated tricycloillicinone. In this communication, we wish to report the structure and biological activity of this new compound.

Tricycloillicinone (**1**)[4] had the molecular formula $C_{15}H_{18}O_3$ established by high–resolution FABMS, indicating seven degrees of unsaturation. The spectral data of **1** revealed the presence of an α, β-unsaturated ketone substituted with an oxy-function at the β position [5] (242 nm; 1667 cm^{-1}; δ_H 5.44; δ_C 198.3, 177.0, 95.3) and an exomethylene moiety, and thereby **1** turns out to be



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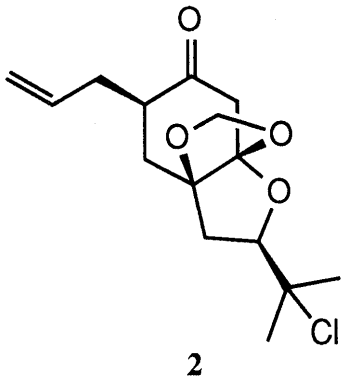

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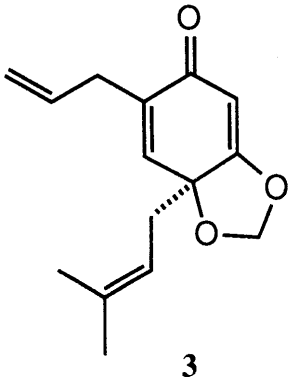

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made up of a tetracyclic framework. In addition to two tertiary methyl groups (δ_H 0.80, 0.94), a methylenedioxy group (δ_H 4.71, 4.92: δ_C 98.9), and a CH_2(10)-CH(11) unit, compound **1** had two isolated methylenes at δ_H 1.64 (dd, 10.7, 1.9 Hz) and 1.84 (d, 10.7 Hz) and at δ_H 1.91 (dd, 15.0, 1.0 Hz) and 3.62 (dd, 15.0, 1.0 Hz), which showed long-range couplings to the one [δ_H 1.41 (ddd, 12.2, 8.3, 1.9 Hz) of the H_2-10 signals and the exomethylene resonances, respectively. Taking its tetracyclic system into consideration, HMBC correlations between the proton signals of the above structural fragments and six quaternary carbon signals including three sp^3 carbons at δ_C 42.8, 57.0, and 87.7 could assemble the plane structure, as shown in Fig. 1.

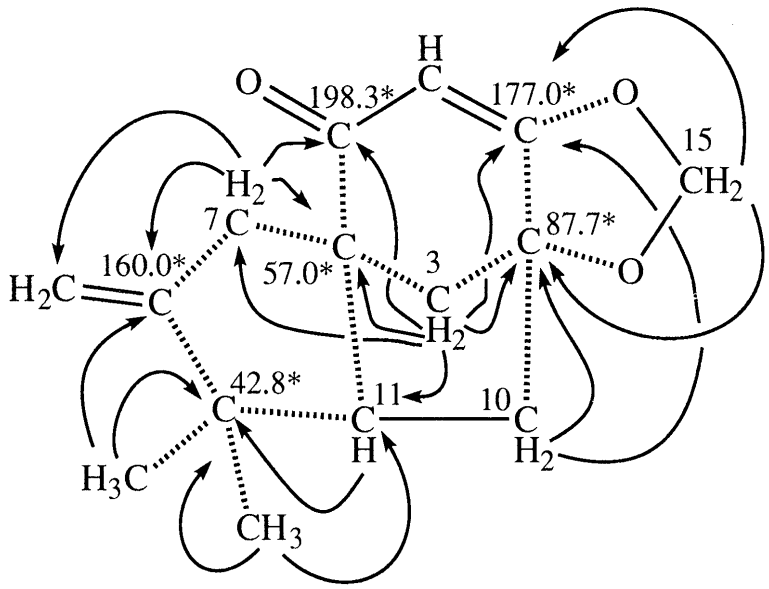

Fig. 1. Dotted Lines Indicate the Connectivities of the Partial Structures Arrows denote the HMBC (J_{C-H} = 8.1 Hz) correlation between the proton (tail) and carbons (head). Asterisks show δ_C vaules for the quaternary carbons.

Molecular models disclosed that, by the formation of a bicyclo[3,2,1]octane framework, the tetracyclic system itself set up the relative configurations at the chiral centers of C-2 and C-4. Therefore, the relative stereochemistry of the remaining chiral carbon at C-11 should be proved. Upon irradiation of 14-CH_3 resonated at δ_H 0.80, NOEs were observed for each (δ_H 1.84 and 1.48) of the H-3 and H-10 methylene signals, indicating the proximity of 14-CH_3 only to these protons of H-3 and H-10, whereas the 13-CH_3 signal at δ_H 0.94 showed NOE interactions with the H-11 signal and one (δ_H 3.62) of the H-7 signals. These NOE results as shown in Fig. 2 suggest that the five–membered ring bearing the exomethylene moiety must be fused cis at the C-2 and C-11 positions. Hence, the above spectral data corroborated the structure **1** for tricycloillicinone.

The structure **1** causes no conflicts, not only in explaining a W-shaped long-range coupling with 1.9 Hz between H-3 (δ_H 1.64) and H-10 (δ_H 1.41), a methylene proton having no NOE to 14-CH_3,

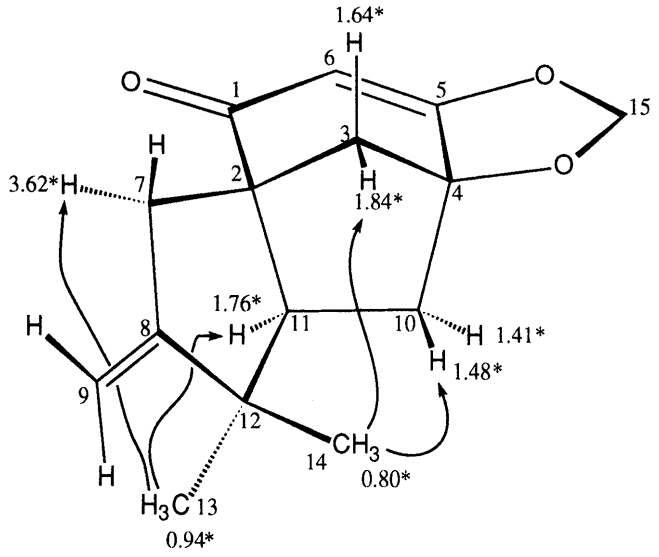

Fig. 2. Relative Configuration Based on NOEs Indicated by Arrows
Asterisks show δ_H values.

but also in rationalizing an abnormal δ_H value (δ_H 3.62) for the exo proton on C-7 as being due to the diamagnetic deshielding effect of the neighboring carbonyl group.

Tricycloillicinone (**1**) is presumably biosynthesized from illicinone A (**3**),[6] main component in the same plant, by sequential cyclization of the prenyl group on **3**.

To our knowledge, **1** is the first example of a polycyclic prenylated C_6-C_3 compound. Tricycloillicinone could increase ChAT activity to 143 % at 30 μM in culture of P10 rat septal neurons,[7] but its potency was not as strong as the previously reported compound **2**.[2]

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4) **1** (17 mg) was isolated from the EtOAc extract (117 g). Colorless needles: mp 78-79°C; $[\alpha]_D^{20}$ –5.56 (c 1.15, EtOH); HR-FABMS *m/z*: 247.1309 $[M+H]^+$ (Cacld for $C_{15}H_{19}O_3$: 247.1334); IR (FT) cm^{-1}: 3077 (=CH_2), 1667 (conj. C=O); λ_{max}^{EtOH}nm: 242 (ε 9600); ^{1}H-NMR (400 MHz, C_6D_6) δ: 0.80 (s, 3H, 14-CH_3), 0.94 (s, 3H, 13-CH_3), 1.41 (ddd, 1H, *J* = 12.2, 8.3, 1.9 Hz, 10-H), 1.48 (dd, 1H, *J* = 12.2, 8.3 Hz, 10-H), 1.64 (dd, 1H, *J* = 10.7, 1.9 Hz, 3-H), 1.76 (dd, 1H, *J* = 8.3, 8.3 Hz, 11-H), 1.84 (d, 1H, *J* = 10.7 Hz, 3-H), 1.91 (dd, 1H, *J* = 15.0, 1.0 Hz, 7-H), 3.62 (dd, 1H, *J* = 15.0, 1.0 Hz, 7-H), 4.70 (dt, 1H, *J* = 2.2, 1.0 Hz, 9-H), 4.71 (s, 1H, 15-H), 4.78 (dt, 1H, *J* = 2.2, 1.0 Hz, 9-H), 4.92 (s, 1H, 15-H), 5.44 (s, 1H, 6-H). ^{13}C NMR (100 MHz, C_6D_6) δ: 24.5 (C-14), 30.8 (C-10), 31.4 (C-13), 35.4 (C-7), 42.8 (C-12), 44.9 (C-3), 53.9 (C-11), 57.0 (C-2), 87.7 (C-4), 95.3 (C-6), 98.9 (C-15), 105.1 (C-9), 160.0 (C-8), 177.0 (C-5), 198.3 (C-1).
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