# New phenanthrenes from Trigonostemon lii Y.T. Chang 

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#### Abstract

Three new phenanthrenes, thrigonosomone $\mathrm{A}(\mathbf{1}), 6,9$-O-dedimethyltrigonostemone (2), and thrigonosomone B(3) were isolated from Trigonostemon lii. Their structures were elucidated by spectroscopic methods. Thrigonosomone A (1) possessed a novel seven-membered cyclic anhydride moiety, and its relative configuration was determined by chemical computation and ROESY experiment. The cytotoxicity of compounds 1-3 was also evaluated.


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The genus Trigonostemon belongs to Euphorbiaceae comprising about 50 species, mainly distributed in tropical and subtropical Asia. ${ }^{1}$ Previous studies on the chemical constituents and their activities from two species of this genus have led to the isolation of several classes of compounds including diterpenoid, ${ }^{2-6}$ phenanthrenone, ${ }^{7}$ and flavonoidal indole alkaloid. ${ }^{8}$ Among them, Daphnane diterpenoids have been found to possess potent activity against fleas.

Trigonostemon lii Y. T. Chang is a shrub or small tree endemic to South China. So far, there has been no report on the chemical constitute from this species. In our continuing investigation on novel and potentially bioactive secondary metabolites from Euphorbiaceae, ${ }^{9-11}$ three new phenanthrenes, thrigonosomone $A(\mathbf{1}), 6,9-0-$ dedimethyltrigonostemone (2), and thrigonosomone B (3) were isolated from the roots and stems of T. lii. Compound 1, featuring an unusually seven-membered cyclic anhydride moiety, is the first of naturally occurring highly oxygenated and seven-membered O heterocycle. Herein we describe the isolation and structure elucidation and cytotoxic activities of three new compounds.

Roots and stems of $T$. lii, collected in Xishuangbanna of Yunnan Province, PR China, were extracted with $95 \% \mathrm{EtOH}$, and the extract was suspended in $\mathrm{H}_{2} \mathrm{O}$ and then partitioned successively with petroleum ether, EtOAc, and n-BuOH. The EtOAc extract ( 100 g ) was further separated by a series of column chromatography including silica gel, sephadex LH-20, and reversed-phase silica gel columns to afford compounds $\mathbf{1}(4.6 \mathrm{mg}), \mathbf{2}(60 \mathrm{mg})$, and $\mathbf{3}$ ( 4.2 mg ).

Compound 1 was obtained as a yellow solid, $\alpha_{D}^{24}-50.79$ (c 0.11, $\mathrm{CHCl}_{3}$ ), and was analyzed for a molecular formula of $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{O}_{6}$ by HRESIMS ([M+Na] at $m / z 353.1009$, calcd 353.1001), correspond-

[^0]ing to 10 degrees of unsaturation. The IR absorption spectrum suggested the presence of hydroxyl $\left(3423 \mathrm{~cm}^{-1}\right)$, aromatic (1636, $1433 \mathrm{~cm}^{-1}$ ), and ester carbonyl ( $1748 \mathrm{~cm}^{-1}$ ) groups. The 1D and 2D NMR spectra (Table 1) displayed 18 carbon signals consisting of one $O$-methyl group, three methyl groups, four methines, eight quaternary carbons, and two ester carbonyls ( $\delta_{\mathrm{C}} 177.9,170.7$ ). Among them, three aromatic methines ( $\delta_{\mathrm{C}} 105.2, \delta_{\mathrm{H}} 7.28 ; \delta_{\mathrm{C}}$ $124.5, \delta_{\mathrm{H}} 7.95$, and $\delta_{\mathrm{C}} 102.8, \delta_{\mathrm{H}} 6.59$ ) and seven aromatic quaternary carbons composed of a five-substituted naphthyl moiety (Fig. 1). Since two ester carbonyl groups and the naphthyl accounted for 9 of 10 unsaturations, compound 1 was inferred to possess the other ring. The other ring was deduced as a sevenmembered O-heterocycle fragment based on the HMBC correlations (Fig. 2) from a gem-dimethyl group $\mathrm{C}-1-\mathrm{Me}_{2}\left(\delta_{\mathrm{H}} 1.68,1.63\right)$ to $\mathrm{C}-10 \mathrm{a}\left(\delta_{\mathrm{C}} 138.4\right), \mathrm{C}-2\left(\delta_{\mathrm{C}} 177.9\right)$ and $\mathrm{C}-1\left(\delta_{\mathrm{C}} 41.6\right)$, and from $\mathrm{H}-$ $4\left(\delta_{\mathrm{H}} 6.41\right)$ to $\mathrm{C}-2\left(\delta_{\mathrm{C}} 177.9\right), \mathrm{C}-3\left(\delta_{\mathrm{C}} 170.7\right)$ and $\mathrm{C}-10 \mathrm{a}\left(\delta_{\mathrm{C}} 138.4\right)$. The connectivity of the seven-membered ring to naphthyl was furnished by HMBC correlations from $\mathrm{H}-4$ to $\mathrm{C}-5 \mathrm{a}$, and from $\mathrm{H}-10$ to $\mathrm{C}-4 \mathrm{a}$ and $\mathrm{C}-1$. The HMBC correlation between $O$-methyl group and $\mathrm{C}-4$, and ROESY correlation between $\mathrm{H}-4$ and $\mathrm{H}-5$ indicated that the $O$-methyl group was placed at $\mathrm{C}-4$. The substituents of naphthyl were assigned by the HMBC and ROESY experiments. The aromatic methyl group was placed at C-7 by its HMBC correlations with C-6, C-7, and C-8 and ROESY correlation with H-8. The ${ }^{1} \mathrm{H}$ NMR spectrum contained only 16 proton resonances, and two remaining protons in the molecule were attributed to the exchangeable protons of two OH groups. Accordingly, the two hydroxy groups were placed at C-6 and C-9, which were supported by the HMBC correlations of $\mathrm{H}-8 / \mathrm{C}-9, \mathrm{H}-10 / \mathrm{C}-9$, and $\mathrm{H}-8 / \mathrm{C}-6$, and ROE correlation of $\mathrm{H}-4 / \mathrm{H}-5$. Finally, the planar structure of 1 was established as shown in Figure 2.

To further determine relative configuration of C-4 on the sevenmembered ring of compound $\mathbf{1}$, ROESY experiment and computer-

Table 1
${ }^{1} \mathrm{H}\left[\delta_{\mathrm{H}}(\mathrm{J}, \mathrm{Hz})\right] \mathrm{NMR}$ data at 400 MHz and ${ }^{13} \mathrm{C}\left[\delta_{\mathrm{C}}\right] \mathrm{NMR}$ data at 100 MHz of thrigonosomone $\mathrm{A}(\mathbf{1})$ at 300 K

| No. | ${ }^{13} \mathrm{C}\left(\delta_{\mathrm{C}}\right)^{\mathrm{a}}$ | ${ }^{1} \mathrm{H}\left(\delta_{\mathrm{H}}\right)^{\mathrm{a}}$ |
| :--- | :--- | :--- |
| 1 | 41.6 s |  |
| 2 | 177.9 s |  |
| 3 | 170.7 s |  |
| 4 | 76.8 d | $6.41, \mathrm{~s}$ |
| 4 a | 110.7 s |  |
| 5 | 105.2 d | $7.28, \mathrm{~s}$ |
| 5 a | 130.9 s |  |
| 6 | 156.4 s |  |
| 7 | 127.0 s |  |
| 8 | 124.5 d |  |
| 8 a | 119.2 s | $6.59, \mathrm{~s}$ |
| 9 | 155.0 s |  |
| 10 | 102.8 d | $1.68, \mathrm{~s}$ |
| 10 a | 138.4 s | $1.63, \mathrm{~s}$ |
| $1-\mathrm{Me}$ | 29.7 q | $2.36, \mathrm{~s}$ |
| 1-Me | 29.3 q | $3.68, \mathrm{~s}$ |
| $7-\mathrm{Me}$ | 16.8 q |  |
| OMe | 53.2 q |  |

${ }^{\text {a }}$ Measured in $\mathrm{CDCl}_{3}-\mathrm{CD}_{3} \mathrm{OD}(1: 2)$.


Figure 1. Structures of compounds 1-3.


Figure 2. Key HMBC and ROESY correlations of $\mathbf{1}$.
generated molecular modeling using DFT calculations at the B3LYP/6-31G+(d) level (Gaussian 03, D01) were employed. ${ }^{12}$ Ester carbonyl group at C-3 was arbitrarily assigned downside of plane of naphthalene moiety. The calculation showed two low-energy isomers of $\mathbf{1}$ (Fig. 3) which were distinguished as $r$ and $s$ according to orientation difference of $\mathrm{OCH}_{3}$ at $\mathrm{C}-4$. The calculated distance between $\mathrm{H}-4$ and $\mathrm{H}-5$ is $3.72 \AA$ in $r$-isomer and is $1.85 \AA$ in $s$-isomer, respectively. With consideration of well-defined interaction observed for this pair of protons in ROESY spectrum, relative configuration of $\mathbf{1}$ was assigned to be $s$-isomer as shown in Figure 1.

Compound 2 was isolated as deep yellow needles, mp 164$165{ }^{\circ} \mathrm{C}$, and the molecular formula was established as $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{O}_{4}$, as determined by positive HRESIMS ( $[\mathrm{M}+\mathrm{H}]^{+}$at $\mathrm{m} / \mathrm{z} 299.1287$, calcd 299.1283), indicating $10^{\circ}$ of unsaturation. The IR absorption spectrum suggested the presence of hydroxyl ( $3395 \mathrm{~cm}^{-1}$ ), aromatic (1630, $1460 \mathrm{~cm}^{-1}$ ), and $\alpha, \beta$-unsaturated ketone ( $1670 \mathrm{~cm}^{-1}$ ) groups. The ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data of 2 (Table 2) were closely related to those of trigonostemone, ${ }^{7}$ except for the loss of two $O$-methyl group signals. The hydroxyl groups are assigned at C-6 and C-9, respectively, due to HMBC correlations of $\mathrm{H}-5 / \mathrm{C}-6, \mathrm{CH}_{3}-\mathrm{C}-7 / \mathrm{C}-6$, $\mathrm{H}-8 / \mathrm{C}-6, \mathrm{H}-8 / \mathrm{C}-9$, and $\mathrm{H}-10 / \mathrm{C}-9$, and ROE correlation of $\mathrm{H}-4 / \mathrm{H}-$


Figure 3. DFT-calculated two isomers ( $s$-isomer and $r$-isomer) were found for $\mathbf{1}$. Relative energies in kcal/mol of the two isomers are given in parentheses. Distance between H 4 and H 5 (in italic) is also given.

Table 2
${ }^{1} \mathrm{H}\left[\delta_{\mathrm{H}}(\mathrm{J}, \mathrm{Hz})\right]$ NMR data at 400 MHz and ${ }^{13} \mathrm{C}\left[\delta_{\mathrm{C}}\right]$ NMR data at 100 MHz of compounds 2 and $\mathbf{3}$ at 300 K

| No. | $2^{\text {a }}$ |  | $3{ }^{\text {b }}$ |  |
| :---: | :---: | :---: | :---: | :---: |
|  | ${ }^{13} \mathrm{C}\left(\delta_{\mathrm{C}}\right)$ | ${ }^{1} \mathrm{H}\left(\delta_{\mathrm{H}}\right)$ | ${ }^{13} \mathrm{C}\left(\delta_{\mathrm{C}}\right)$ | ${ }^{1} \mathrm{H}\left(\delta_{\mathrm{H}}\right)$ |
| 1 | 49.6 s |  | 123.7 s |  |
| 2 | 201.3 s |  | 145.2 s |  |
| 3 | 147.3 s |  | 144.6 s |  |
| 4 | 114.6 d | 7.39, s | 105.3 d | 7.81, s |
| 4a | 113.8 s |  | 126.1 s |  |
| 5 | 104.2 d | 7.41, s | 106.6 d | 7.78, s |
| 5a | 132.5 s |  | 129.0 s |  |
| 6 | 156.3 s |  | 155.0 s |  |
| 7 | 126.5 s |  | 126.1 s |  |
| 8 | 124.7 d | 7.95, s | 124.0 d | 7.81, s |
| 8a | 119.3 s |  | 122.3 s |  |
| 9 | 154.4 s |  | 145.0 s |  |
| 10 | 104.9 d | 6.74, s | 145.6 s |  |
| 10a | 144.0 s |  | 118.7 s |  |
| 1-Me | 28.6 q | 1.46, s | 13.7 q | 2.78, s |
| 1-Me | 28.6 q | 1.46 , s |  |  |
| 7-Me | 16.8 q | 2.36, s | 16.7 q | 2.38, s |
| OMe | 55.6 q | 3.85, s | 60.8 q | 3.96, s (C-9) |
| OMe |  |  | 60.8 q | 3.84, s (C-10) |

a Measured in $\mathrm{CDCl}_{3}-\mathrm{CD}_{3} \mathrm{OD}$ (1:2).
${ }^{b}$ Measured in $\left(\mathrm{CD}_{3}\right)_{2} \mathrm{CO}$.

5(Fig. 4A). Therefore, compound 2 was assigned as 6,9-0dedimethyltrigonostemone.

Compound 3 was isolated as a yellow solid, which gave a $[\mathrm{M}+\mathrm{H}]^{+}$ion at $m / z 315.1139$ in HRESIMS consistent with a molecular formula $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{O}_{5}$ (calcd 315.1133 for $\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{O}_{5}$ ), requiring 10 sites of unsaturation. The UV spectrum of $\mathbf{3}$ showed absorption at 202, 243, and 267 nm , indicating the presence of a conjugated system. The IR spectrum showed the presence of hydroxyl ( $3395 \mathrm{~cm}^{-1}$ ) and aromatic ( $1636,1460 \mathrm{~cm}^{-1}$ ) groups. Analysis of ${ }^{13}$ C NMR, DEPT, and HSQC data revealed that $\mathbf{3}$ contains eleven aromatic quaternary carbons (including six olefinic and five oxygenated), three olefinic methines, and four methyl groups (including


A


B

$$
\underset{\text { RMBC }}{\text { ROESY }}
$$

Figure 4. Key HMBC and ROESY correlations of compounds 2 and 3.


Scheme 1. Biogenetic pathway proposed for compounds 1 and 2.
two O-methyl groups). Apart from seven double bonds, the remaining elements of unsaturation in $\mathbf{3}$ were assumed to be a tricyclic skeleton. A phenanthrene skeleton was, therefore, deduced for compound $\mathbf{3}$ and its spectral parameters were consistent with those of similar phenanthrenes that were previously reported. ${ }^{13}$ The relative positions of substituents on the phenanthrene nucleus were determined by a detailed analysis of 1D, 2D-NMR data (Fig. 4B). The ${ }^{1} \mathrm{H}$ NMR spectrum (Table 1) exhibited 15 proton signals for two methyl groups ( $\delta_{\mathrm{H}} 2.78$ and 2.38 ), two 0 -methyl groups ( $\delta_{\mathrm{H}} 3.96$ and 3.84 ), and three isolated olefinic proton signals ( $\delta_{\mathrm{H}} 7.81,7.81$, and 7.78 ), and the three remaining protons in the molecule were attributed to the exchangeable protons of three OH groups. In the HMBC spectrum, the proton signal of an aromatic methyl group ( $\delta_{\mathrm{H}} 2.78, \mathrm{~s}$ ) showed correlation with C-10a, C-1, and $\mathrm{C}-2$, and ROESY correlations were observed between the methyl and $O$-methyl group ( $\delta_{\mathrm{H}} 3.84, \mathrm{~s}$ ) groups, indicating that the methyl group should be placed at C-1. Similarly, the HMBC correlations of another aromatic methyl group ( $\delta_{\mathrm{H}} 2.38, \mathrm{~s}$ ) with C-6, C-7, and C-8, and the ROESY correlations were observed between methyl ( $\delta_{\mathrm{H}}$ $2.38, \mathrm{~s}$ ) and H-8, indicating that this methyl group ( $\delta_{\mathrm{H}} 2.38$ ) should be at C-7. The HMBC correlations from the proton signals of 0 methyl groups at $\delta_{\mathrm{H}} 3.96,3.84$ showed correlation with C-9 and C-10, respectively, and ROESY correlations were observed between $O$-methyl group ( $\delta_{\mathrm{H}} 3.96, \mathrm{~s}$ ) and $\mathrm{H}-8$, thus 0 -methyls ( $\delta_{\mathrm{H}} 3.96$ ) should be placed at C-9, and $O$-methyl group ( $\delta_{\mathrm{H}} 3.84$ ) should be placed at C-10, respectively. Finally, ROE correlation between H-4 and $\mathrm{H}-5$ indicated that three hydroxyl groups were placed at $\mathrm{C}-2$, C-3, and C-6. Thus, the structure of $\mathbf{3}$ was assigned as shown.

We proposed a possible biosynthetic pathway for compounds 1 and 2, as shown in Scheme 1, in which 4 should be a common biogenetic precursor. From 4, compound $\mathbf{1}$ is proposed to undergo oxidation and methylation, to construct intermediate 6. Subsequent isomerization and oxidation would result in a ring-expended heptacyclic anhydride.

The cytotoxicity of compounds 1-3 against human leukemia HL-60 and human lung adenocarcinoma A549 cell lines was evaluated with MTT ${ }^{14}$ and SRB ${ }^{15}$ methods. Only compound 3 showed weak activity against HL-60 cells ( $\mathrm{IC}_{50}=17 \mu \mathrm{M}$; positive control compound etoposide, $\mathrm{IC}_{50}=0.16 \mu \mathrm{M}$ ).

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.186.

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