THE STRUCTURE OF CYCLOOCTATIN, A NEW INHIBITOR OF LYSPHOSPHOLIPASE

Sir:

In the preceding paper\textsuperscript{1}, we have described the taxonomy, isolation, physico-chemical properties and biological activities of cyclooctatin (Fig. 1), a novel inhibitor of lysophospholipase (Lyso-PL). In this paper, we describe the structure determination of cyclooctatin.

The molecular weight and formula of cyclooctatin were elucidated as \( \text{C}_{20}\text{H}_{34}\text{O}_{3} \) (MW 322.49) by the FD-MS peak at \( m/z \) 322 (M\(^{+}\)), elemental analysis (found: C 74.09, H 10.63; calcd for \( \text{C}_{20}\text{H}_{34}\text{O}_{3} \): C 74.45, H 10.63) and \( ^{1}\text{H} \) and \( ^{13}\text{C} \) NMR spectra (Table 1). UV spectrum showed the end absorption in EtOH. IR spectrum (KBr) showed the presence of hydroxy group (3430 cm\(^{-1}\)). \( ^{13}\text{C} \) NMR spectrum revealed two signals of \( sp^{2} \) carbon (\( \delta_{c} \) 119.1 and 154.5 ppm) and eighteen signals of \( sp^{3} \) carbon in which three signals (C-3, C-4 and C-11) appeared in lower field (\( \delta_{c} \) 75.7, 78.4 and 63.4 ppm) indicating the oxygen-bearing carbons.

In the \((^{1}\text{H})-^{1}\text{H} \) COSY spectrum and proton decoupling NMR experiments, a \( vicinal\)-spin spin coupling between the signals at \( \delta_{\text{H}} \) 1.91, 2.74 (5-H\(_{3}\)) ppm and the signal at \( \delta_{\text{H}} \) 5.28 (6-H) ppm was observed, and \( vicinal\)-spin spin couplings between the signals at \( \delta_{\text{H}} \) 1.42, 1.59 (9-H\(_{2}\)) ppm and the signals at \( \delta_{\text{H}} \) 1.38, 1.56 (8-H\(_{2}\)) ppm, \( \delta_{\text{H}} \) 1.38, 1.56 (8-H\(_{2}\)) and 2.30 (7-H) ppm, \( \delta_{\text{H}} \) 2.30 (7-H) and 1.83 (13-H) ppm, \( \delta_{\text{H}} \) 1.83 (13-H) and 0.79 (15-H\(_{3}\)) ppm, \( \delta_{\text{H}} \) 1.83 (13-H) and 0.96 (16-H\(_{3}\)) ppm were also observed. Furthermore, \( vicinal\)-spin spin couplings indicated the linkage of C-10 to C-11 in the same fashion as described above. From the above results, the presence of three partial structures (Fig. 2A, B and C) were revealed.

As shown in Fig. 3, in the HMBC (heteronuclear multiple bond connectivity) spectrum, partial structures A, B and C could be connected as follows. The olefinic proton at \( \delta_{\text{H}} \) 5.28 (6-H) ppm coupled to two carbons at \( \delta_{c} \) 55.1 (C-7) and 45.9 (C-9a) ppm, and the methine proton at \( \delta_{\text{H}} \) 2.30 (7-H) ppm coupled to the carbon at \( \delta_{c} \) 154.5 (C-6a) ppm, indicating the connectivity of partial structures A and B. The methyl protons at \( \delta_{\text{H}} \) 1.25 (14-H\(_{3}\)) ppm correlated with four carbons at \( \delta_{c} \) 154.5 (C-6a), 46.6 (C-9), 45.9 (C-9a) and 45.6 (C-10) showing the connectivity of partial structures B and C. The methyl protons at \( \delta_{\text{H}} \) 1.33 (12-H\(_{3}\)) ppm showed cross peaks with the carbon signals at \( \delta_{c} \) 58.0 (C-3a), 78.4 (C-4) and 42.2 (C-5) ppm indicating the connectivity of partial structures A and C. Correlation between the methylene protons at \( \delta_{\text{H}} \) 3.55, 3.66 (11-H\(_{2}\)) ppm and the carbon at \( \delta_{c} \) 35.8 (C-10a) ppm were also observed.

From the above results, the structure of cyclooctatin was determined to be 1,2,3,3a,4,5,7,8,9,9a,10,10a-dodecahydro-3,4-dihydroxy-1-hydroxy-

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig1.png}
\caption{Structure of cyclooctatin.}
\end{figure}

\begin{table}[h]
\centering
\caption{\( ^{13}\text{C} \) and \( ^{1}\text{H} \) NMR data of cyclooctatin in CD\(_{3}\)OD.}
\begin{tabular}{llll}
\hline
Carbon & \( \delta_{c} \) ppm (100 MHz) & \( \delta_{\text{H}} \) ppm (J in Hz, 400 MHz) \\
\hline
1 & 44.9 (d) & 2.61 (m) \\
2 & 39.7 (t) & 1.38 (dt, 3.4, 12.6), 1.71 (br dd, 12.6, 5.0) \\
3 & 75.7 (d) & 4.44 (br dd, 3.4, 5.0) \\
3a & 58.0 (d) & 1.97 (t, 5.0) \\
4 & 78.4 (s) & \\
5 & 42.2 (t) & 1.91 (dd, 12.8, 7.4), 2.74 (br t, 11.6) \\
6 & 119.1 (d) & 5.28 (ddd, 10.8, 7.4, 2.2) \\
6a & 154.5 (s) & \\
7 & 55.1 (d) & 2.30 (m) \\
8 & 24.3 (t) & 1.38 (m), 1.56 (m) \\
9 & 46.6 (t) & 1.42 (m), 1.59 (m) \\
9a & 45.9 (s) & \\
10 & 45.6 (t) & 1.20 (t, 12.8), 1.68 (br d, 12.8) \\
10a & 35.8 (d) & 2.56 (m) \\
11 & 63.4 (t) & 3.55 (dd, 10.8, 6.8), 3.66 (dd, 10.8, 7.4) \\
12 & 26.7 (q) & 1.33 (br s) \\
13 & 30.2 (d) & 1.83 (m) \\
14 & 25.2 (q) & 1.25 (s) \\
15 & 17.8 (q) & 0.79 (d, 6.6) \\
16 & 22.5 (q) & 0.96 (d, 6.6) \\
\hline
\end{tabular}
\end{table}
Cyclooctatin is closely related to ophiobolins (A, B, C, D, F, G and H)\(^2\) and fusicoccin A\(^3\). Although these metabolites belong to the class of sesterterpenoid, only cyclooctatin is a diterpenoid compound. Moreover, cyclooctatin is produced by actinomycetes and the others are produced by fungi. Terpentecin\(^4\), a diterpenoid antibiotic from actinomycetes, is not so similar to cyclooctatin.

Fig. 2. Partial structures of cyclooctatin.

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\begin{align*}
\text{A} & \quad -\text{CH}_2-\text{CH}=\text{C}- \\
\delta_H & \quad 1.91 \quad 5.28 \quad 2.74 \\
\delta_C & \quad 42.2 \quad 119.1 \quad 154.5 \\
\text{B} & \quad -\text{CH}_2-8\text{CH}_2-\text{CH}=\text{C}-\text{CH} \quad \text{CH}_3 \\
\delta_H & \quad 1.42 \quad 1.38 \quad 2.30 \quad 1.83 \quad 0.79 \\
\delta_C & \quad 46.6 \quad 24.3 \quad 55.1 \quad 30.2 \quad 17.8 \\
\text{C} & \quad -\text{CH}_2-\text{CH}=\text{C}-\text{CH} \quad \text{CH} \quad \text{CH}_2 \quad -\text{CH}=\text{C}-\text{CH} \\
\delta_H & \quad 1.20 \quad 2.56 \quad 1.97 \quad 4.44 \quad 1.38 \quad 2.61 \quad 3.55 \\
\delta_C & \quad 45.6 \quad 35.8 \quad 58.0 \quad 75.7 \quad 39.7 \quad 44.9 \quad 63.4 \\
\end{align*}
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Fig. 3. The key \(^1\)H-\(^{13}\)C correlation by HMBC experiment.

1704 THE JOURNAL OF ANTIBIOTICS OCT. 1992

References


