THE STRUCTURE OF CYCLOOCTATIN, A NEW INHIBITOR OF LYSOPHOSPHOLIPASE

Sir:

In the preceding paper[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 $C_{20}H_{34}O_3$ (MW 322.49) by the FD-MS peak at m/z 322 (M^+), elemental analysis (found: C 74.09, H 10.63; calcd for $C_{20}H_{34}O_3$: C 74.45, H 10.63) and ^1H and ^{13}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}C NMR spectrum revealed two signals of sp^2 carbon (δ_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 (δ_C 75.7, 78.4 and 63.4 ppm) indicating the oxygen-bearing carbons.

In the ^1H-^1H COSY spectrum and proton decoupling NMR experiments, a *vicinal*-spin spin coupling between the signals at δ_H 1.91, 2.74 (5-H_2) ppm and the signal at δ_H 5.28 (6-H) ppm was observed, and *vicinal*-spin spin couplings between the signals at δ_H 1.42, 1.59 (9-H_2) ppm and the signals at δ_H 1.38, 1.56 (8-H_2) ppm, δ_H 1.38, 1.56 (8-H_2) and 2.30 (7-H) ppm, δ_H 2.30 (7-H) and 1.83 (13-H) ppm, δ_H 1.83 (13-H) and 0.79 (15-H_3) ppm, δ_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 δ_H 5.28 (6-H) ppm coupled to two carbons at δ_C 55.1 (C-7) and 45.9 (C-9a) ppm, and the methine proton at δ_H 2.30 (7-H) ppm coupled to the carbon at δ_C 154.5 (C-6a) ppm, indicating the connectivity of partial structures A and B. The methyl protons at δ_H 1.25 (14-H_3) ppm correlated with four carbons at δ_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 δ_H 1.33 (12-H_3) ppm showed cross peaks with the carbon signals at δ_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 δ_H 3.55, 3.66 (11-H_2) ppm and the carbon at δ_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-

Fig. 1. Structure of cyclooctatin.

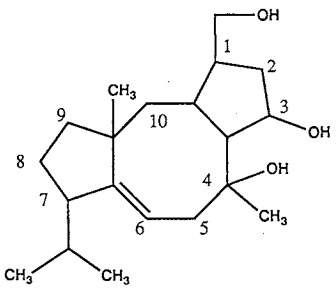


Table 1. ^{13}C and ^1H NMR data of cyclooctatin in CD_3OD.

Carbon	δ_C ppm (100 MHz)	δ_H ppm (J in Hz, 400 MHz)
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)

Fig. 2. Partial structures of cyclooctatin.

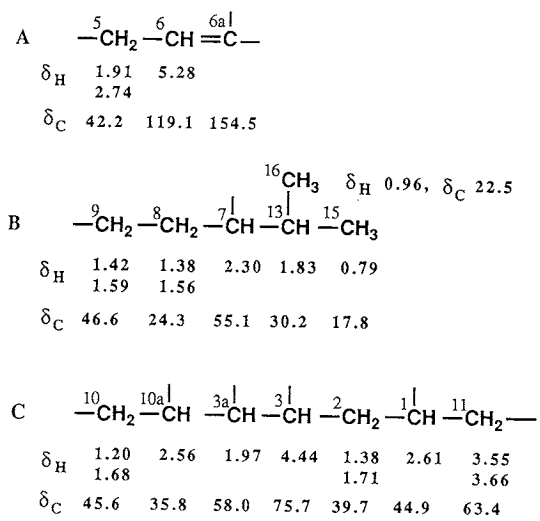
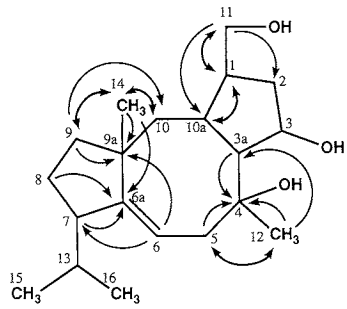


Fig. 3. The key ^{1}H-^{13}C correlation by HMBC experiment.



methyl-4,9a-dimethyl-7-(1-methylethyl)-dicyclopenta[*a,d*]cyclooctene. The absolute configuration remains to be determined.

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.

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