

Structure Revision of FD-891, a 16-Membered Macrolide Antibiotic

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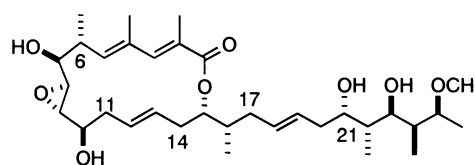
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FD-891 was isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890 in 1994, and was shown to have a cytotoxic activity *in vitro* against several tumor cell lines¹⁾. The structure of FD-891 was first proposed to be an 18-membered macrolactone by spectroscopic means²⁾, and recently, the stereochemistry of

each chiral center of FD-891 was determined through synthetic studies of relevant fragments as well as X-ray diffraction of degradative derivatives as shown in Fig. 1³⁾. During our synthetic studies of FD-891 and its related compound, FD-892, we noticed the synthesized fragments including the C12-C15 conjugated double bond moiety showed a quite different signal pattern in ¹H NMR, especially the chemical shifts of the double bonds compared to those reported in natural FD-891 and FD-892.

Table 1. ¹H and ¹³C NMR data of FD-891 in pyridine-*d*₅.



Carbon No.	δ_C	δ_H (multiplicity, <i>J</i> in Hz)
1	169.4	
2	124.0	
3	145.5	7.62 (s)
4	135.2	
5	144.4	5.88 (d, 5.2)
6	38.0	3.12 (m)
7	71.3	4.27 (d, 3.6)
8	56.1	3.23 (s)
9	57.8	3.79 (s)
10	72.8	3.78 (m)
11	39.0	2.76 (m)
12	131.0	5.90 (m)
13	127.5	5.73 (ddd, 4.8, 9.6, 14.8)
14	35.1	2.36 (brd, 13.6), 2.15 (m)
15	77.0	4.96 (dt, 6.4, 3.2)
16	35.1	1.90 (m)
17	36.5	2.15 (m), 1.90 (m)
18	129.1	5.48 (dt, 15.2, 7.2)
19	130.9	5.64 (dt, 15.2, 6.8)
20	39.0	2.49 (dt, 13.6, 7.2) 2.25 (dt, 13.6, 6.8)
21	71.4	4.46 (t, 6.0)
22	40.4	1.90 (m)
23	74.8	4.04 (dd, 3.2, 8.0)
24	41.5	1.74 (m)
25	80.8	3.39 (quintet, 6.4)
26	8.9	1.08 (d, 6.0)
2-CH ₃	14.0	2.01 (s)
4-CH ₃	15.8	1.95 (s)
6-CH ₃	17.1	1.02 (d, 6.8)
16-CH ₃	10.8	0.91 (d, 6.4)
22-CH ₃	16.7	0.96 (d, 6.8)
24-CH ₃	16.6	1.09 (d, 6.8)
25-OCH ₃	56.2	3.11 (s)

Fig. 1. Proposed structures of FD-891.

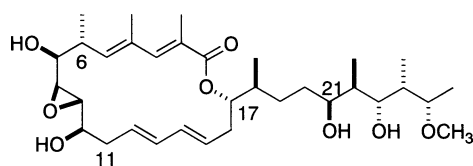
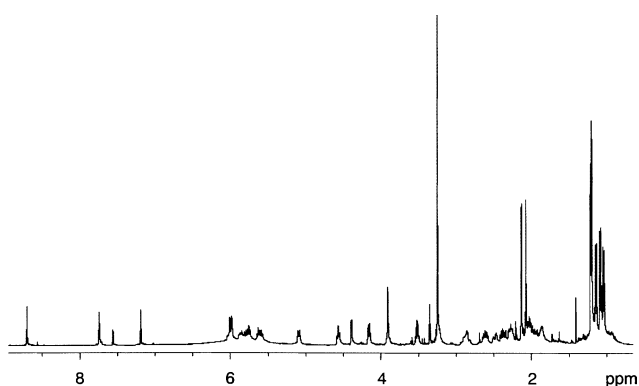
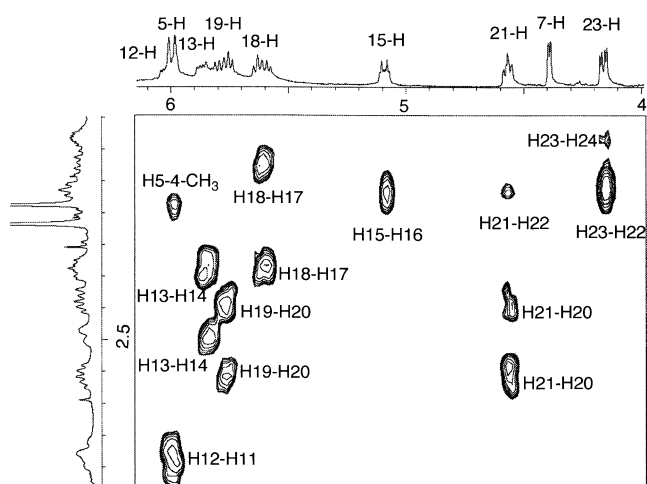


Fig. 2. ¹H-NMR spectrum of FD-891 in pyridine-*d*₅ (400 MHz).



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Fig. 3. ^1H - ^1H COSY spectrum of FD-891 in pyridine- d_5 .



The numbering is according to Table 1.

Therefore, we undertook re-investigation of the structure of FD-891.

In order to clarify the position of the double bonds, we attempted several different solvents for ^1H NMR studies, since the original description suggested complex signal overlaps in CDCl_3 .²⁾ As a result, moderate spectral resolution was observed in pyridine- d_5 as shown in Fig. 2. Under these conditions, we examined several NMR spectra including COSY and HMBC spectra. The resulting ^1H and ^{13}C NMR data are summarized in Table 1. As shown in ^1H - ^1H COSY spectrum (Fig. 3), the connectivities of each double bond to the neighboring protons were clearly observed. These results clearly indicated that two disubstituted *E*-double bonds must be in isolated environments, but not in conjugated to each other. Based on these results, the plain structure of FD-891 has now been finalized to be a 16-membered macrolactone as shown in Fig. 4. This plain structure turned out to be the same as BE-45653⁴⁾ reported in 1997. Previously, we encountered certain difficulty in explaining the results of ozonolysis studies, however, the present revised structure of FD-891 is quite consistent with our degradation studies³⁾. The absolute structure of FD-891 is now depicted as shown in Fig. 5.

Fig. 4. ^1H - ^1H COSY and HMBC correlations of FD-891.

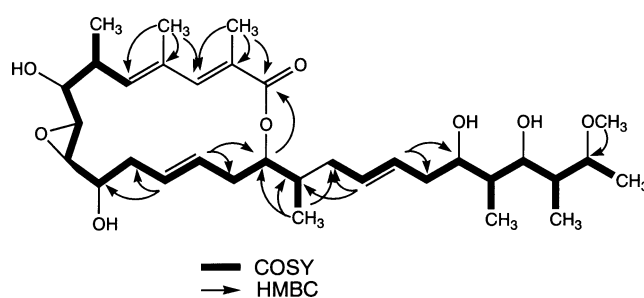
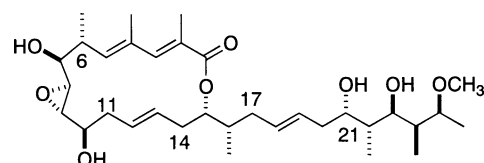


Fig. 5. Revised structure of FD-891.



Although we cannot confirm the structure of FD-892, analog of FD-891, because the organism does not produce FD-892 any more, it seems likely that FD-892 also has the same carbon skeleton.

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