Communications to the Editor

Mer-WF3010, A NEW MEMBER OF THE PAPULACANDIN FAMILY

II. STRUCTURE DETERMINATION

Sir:

In a previous paper[1], we have reported the fermentation, isolation and biological and physicochemical properties of Mer-WF3010 (**1**), a new antifungal antibiotic which was produced by *Phialophora cyclaminis*. This communication describes the structural elucidation of **1**.

The structure of **1** has been established by means of spectral analyses of **1** and some of its hydrolysis products in comparison with papulacandins.

Mer-WF3010 (**1**): mp 163~166°C (dec.); $[\alpha]_D^{24}$ +36.2° (*c* 1.0, CH_3OH); IR (KBr) cm^{-1} 3400 (br), 1700, 1640, 1615, 1370, 1240 (br), 1130; UV $\lambda_{max}^{CH_3OH}$ nm 232 (ε 29,700), 239 (ε 29,600), 266 (ε 33,100), 297 (sh, ε 23,300); FAB-MS (matrix: mNBA) *m/z* positive 857 $(M+H)^+$, negative 855 $(M-H)^-$; high resolution FAB-MS calcd for $(M+H)^+$: 857.3942, found: 857.3944, indicating the molecular formula $C_{45}H_{60}O_{16}$; ^1H NMR and ^{13}C NMR spectra are shown in Table 1.

Mer-WF3010 (**1**) is similar to the papulacandins in physico-chemical properties as shown by the above data, but is different in the molecular formula from the papulacandin family of compounds; papulacandins A, B, C, D[2,3], chaetiacandin[4,5] and L-687,781[6,7].

Alkaline hydrolysis (0.5 N NaOH, CH_3OH-H_2O (1:1), 2.5 hours, room temperature) of Mer-WF3010 (**1**) gave two unsaturated fatty acids **2** and **3** together with the spirocyclic diglycoside **4** (Scheme 1).

Acids **2** and **3** were esterified with diazomethane to provide methyl esters **5** and **6**, respectively.

Otherwise, selective alkaline hydrolysis of **1** (0.05 M K_2CO_3, CH_3OH-H_2O (1:1), 1.5 hours, room temperature) afforded an unsaturated fatty acid which was identified with the shorter acid **2** given by the above hydrolysis, and two products **7** and **8** (Scheme 1).

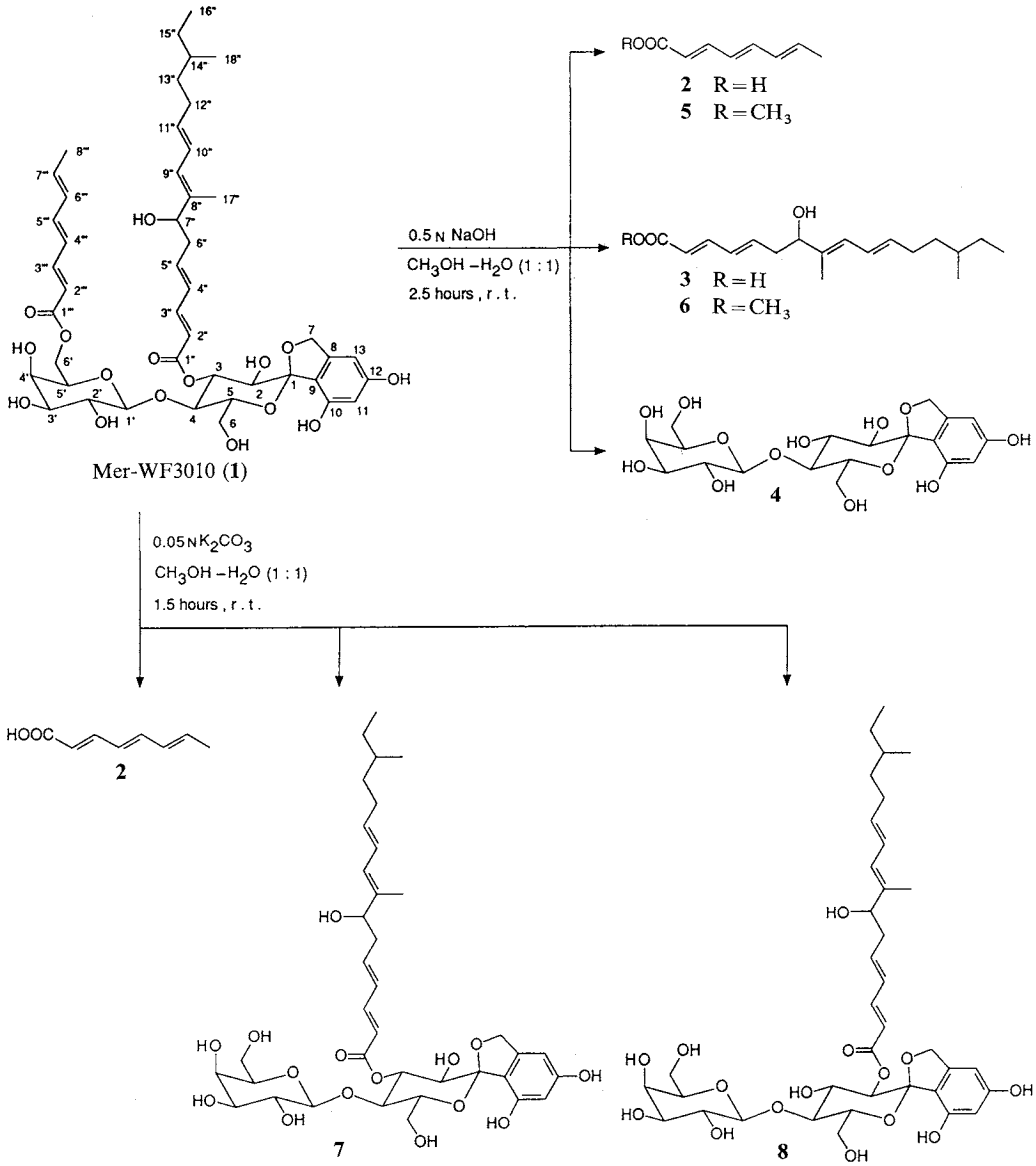
The spirocyclic diglycoside **4**, the two products **7** and **8** obtained from the selective hydrolysis, and the longer fatty acid methyl ester **6** were identified with those obtained from the hydrolysis of

Table 1. ^1H NMR and ^{13}C NMR spectra of Mer-WF3010.

Carbon	^1H NMR	^{13}C NMR	Carbon	^1H NMR	^{13}C NMR
1		111.9	4″	6.26 (m)	131.5
2	4.37 (d, *J*=10.3 Hz)	71.9	5″	6.09 (dd, *J*=14.7, 7.3 Hz)	141.7
3	5.43 (t, *J*=9.5 Hz)	76.3	6″	2.40 (br t, 2H, *J*=6.6 Hz)	40.0
4	3.99 (m)	74.7	7″	4.04 (dd, *J*=13.9, 6.6 Hz)	77.6
5	3.96 (m)	77.8	8″		137.6
6	3.78 (m), 4.02 (m)	61.5	9″	5.97 (d, *J*=12.5 Hz)	127.1
7	5.03 (2H, AB, *J*=13.2 Hz)	73.9	10″	6.25 (m)	127.0
8		145.4	11″	5.65 (m)	136.1
9		116.5	12″	2.11 (2H, m)	31.6
10		161.5	13″	1.17 (m), 1.40 (m)	37.5
11	6.20 (s)	100.1	14″	1.31 (m)	35.2
12	6.21 (s)	154.5	15″	1.17 (m), 1.34 (m)	30.4
13		103.0	16″	0.88 (3H, t, *J*=6.6 Hz)	11.7
1′	4.35 (m)	105.4	17″	1.71 (3H, s)	12.2
2′	3.47 (br d, *J*=4.4 Hz)	72.5	18″	0.88 (3H, d, *J*=6.6 Hz)	19.5
3′	3.47 (br d, *J*=4.4 Hz)	74.6	1‴		168.6
4′	3.76 (m)	70.2	2‴	5.94 (d, *J*=15.4 Hz)	120.3
5′	3.67 (t, *J*=6.6 Hz)	73.9	3‴	7.38 (dd, *J*=15.4, 11.7 Hz)	147.1
6′	4.12 (dd, *J*=11.0, 6.6 Hz), 4.23 (dd, *J*=11.0, 5.1 Hz)	64.6	4‴	6.30 (dd, *J*=15.4, 11.7 Hz)	128.6
			5‴	6.64 (dd, *J*=15.4, 11.0 Hz)	143.3
1″		169.1	6‴	6.21 (m)	132.5
2″	5.89 (d, *J*=15.4 Hz)	121.5	7‴	6.02 (q, *J*=7.3 Hz)	136.7
3″	7.25 (dd, *J*=15.4, 11.0 Hz)	146.1	8‴	6.02 (q, *J*=7.3 Hz)	18.7

δ in ppm downfield from internal TMS. CD_3OD was used as solvent. s: singlet, d: doublet, t: triplet, q: quartet.

Scheme 1.



papulacandin B by comparisons of the physicochemical and spectral properties[2,3].

The structure of the shorter fatty acid methyl ester **5** was determined on the basis of spectral analysis and by comparison with UV and mp data reported[8]. That is, **5** was *E,E,E*-octatrienoic acid methyl ester. mp 73~76°C (colorless needles, *n*-pentane) [lit.[8] 74~75°C (colorless needles, *n*-pentane)], UV (CH_3OH); 299.1 (28,200) [lit.[8] EtOH; 301 (37,700)], IR ($CHCl_3$); 1700, 1615, 1430, 1340, 1265, 1135, 1000, ^1H NMR ($CDCl_3$); 1.83 (3H, dd, J=7.0, 1.1 Hz, C(8‴)), 3.74 (3H, s, $CO_2\underline{CH_3}$), 5.84 (1H, d, J=15.4 Hz, C(2″)), 5.94 (1H, dq, J=15.0, 7.0 Hz, C(7‴)), 6.16 (1H, ddd, J=15.0, 10.6, 1.8 Hz, C(6‴)), 6.20 (1H, dd, J=14.7, 11.4 Hz, C(4‴)), 6.52 (1H, dd, J=14.7, 10.6 Hz, C(5‴)), 7.30 (1H, dd, J=15.0, 11.0 Hz, C(3‴)), ^{13}C NMR ($CDCl_3$); 18.53 (s, $CO_2\underline{CH_3}$), 51.43 (s, C(8‴)), 119.52 (t, C(2‴)), 127.51 (t, C(4‴)), 131.19 (t, C(6‴)), 135.17 (t, C(7‴)), 141.19 (t, C(5‴)), 145.07 (t, C(3‴)), 167.64 (q, C(1‴)), EI-MS; *m/z* 152 (M^+).

From these findings and the 2D NMR experiments of the intact Mer-WF3010, we concluded that Mer-WF3010 has the structure **1** as shown

in Scheme 1.

Papulacandins A, B, C and D were first reported by TRAXLER *et al.*[2,3]. Secondly chaetiacandin was reported by KOMORI *et al.*[4,5]. Recently L-687,781 has been reported by VANMIDDLESWORTH *et al.*[6,7]. Thus, Mer-WF3010 is the seventh member of the papulacandin family to be isolated from natural sources.

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References

1) KANETO, R.; H. CHIBA, H. AGEMATU, N. SHIBAMOTO, T. YOSHIOKA, H. NISHIDA & R. OKAMOTO: Mer-WF3010, a new member of the papulacandin family. I. Fermentation, isolation and characterization. J. Antibiotics 46: 247~250, 1993
2) TRAXLER, P.; J. GRUNER & J. A. L. AUDEN: Papulacandins, a new family of antibiotics with antifungal activity. I. Fermentation, isolation, chemical and biological characterization of papulacandins A, B, C, D and E. J. Antibiotics 30: 289~296, 1977
3) TRAXLER, P.; H. FRITZ, H. FUHRER & W. J. RICHTER: Papulacandins, a new family of antibiotics with antifungal activity. Structures of papulacandins A, B, C and D. J. Antibiotics 33: 967~978, 1980
4) KOMORI, T.; M. YAMASHITA, Y. TSURUMI & M. KOHSAKA: Chaetiacandin, a novel papulacandin. I. Fermentation, isolation and characterization. J. Antibiotics 38: 455~459, 1985
5) KOMORI, T. & Y. ITOH: Chaetiacandin, a novel papulacandin. II. Structure determination. J. Antibiotics 38: 544~546, 1985
6) VANMIDDLESWORTH, F.; M. N. OMSTEAD, D. SCHMATZ, K. BARTIZAL, R. FROMTLING, G. BILLS, K. NOLLSTADT, S. HONEYCUTT, M. ZWEERINK, G. GARRITY & K. WILSON: L-687,781, a new member of the papulacandin family of β-1,3-D-glucan synthesis inhibitors. I. Fermentation, isolation, and biological activity. J. Antibiotics 44: 45~51, 1991
7) VANMIDDLESWORTH, F.; C. DUFRESNE, J. SMITH & K. E. WILSON: Structure elucidation of L-687,781, a new β-1,3-D-glucan synthesis inhibitor. Tetrahedron 47: 7563~7568, 1991
8) BÜCHI, G. & E. M. BURGESS: Photochemical reactions. X. Experiments with 1,3,5-cycloöctatrien-7-one and cycloöctatetraene epoxide. J. Am. Chem. Soc. 84: 3104~3109, 1962