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Theopederins F-J: Five New Antifungal and Cytotoxic Metabolites from the Marine Sponge, *Theonella swinhoei*[1]

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Abstract: Five new bioactive metabolites, theopederins F-J, have been isolated from the marine sponge, *Theonella swinhoei*. Their structures are derivatives of theopederins on the basis of spectral data. Theopederin F was antifungal against *Saccharomyces cerevisiae* at 1 μg/disk and cytotoxic against P388 murine leukemia cells with an IC_{50} value of 0.15 ng/mL.

Keywords: Sponges; marine metabolites; polyketides; antifungals.

Classical antimicrobial and cytotoxic assays have long been employed to discover antimicrobial/cytotoxic substances. However, the substances discovered by these assays are in most cases non-specific toxins. Therefore, more selective assay systems are desirable. A mechanism-based bioassay using genetic-deficient mutants of the budding yeast *Saccharomyces cerevisiae* should result in the discovery of selective bioactive agents. In search for such metabolites from Japanese marine invertebrates, we found that the lipophilic extract of the Okinawan marine sponge *Theonella swinhoei* inhibited an *erg6* mutant which lacks (*S*)-adenosylmethionine:Δ^{24}-methyltransferase[2] involved in synthesis of ergosterol, a main sterol in cytoplasmic membrane of fungi. Bioassay-guided fractionation resulted in the isolation of five new antifungal metabolites, theopederins F-J along with the known theopederins A-C and E.[3] This paper describes the isolation, structural elucidation, and biological activities of these new compounds.

The frozen sponge (70 kg) collected off the Kerama Islands, the Ryukyu Archipelago (26°13' N, 127°23' E) was extracted with EtOH and $CHCl_3$/MeOH (1:1); the combined extracts were partitioned between H_2O and $CHCl_3$. The $CHCl_3$ solubles were partitioned between 80 % EtOH and *n*-hexane. The aqueous layer was repeatedly purified by a combination of column chromatography on Sephadex LH-20, ODS, silica gel, and ODS HPLC to afford new antifungal compounds, theopederins F (**1**, 4.0 mg), G (**2**, 1.5 mg), H (**3**, 1.5 mg), I (**4**, 0.3 mg), and J (**5**, 0.5 mg).

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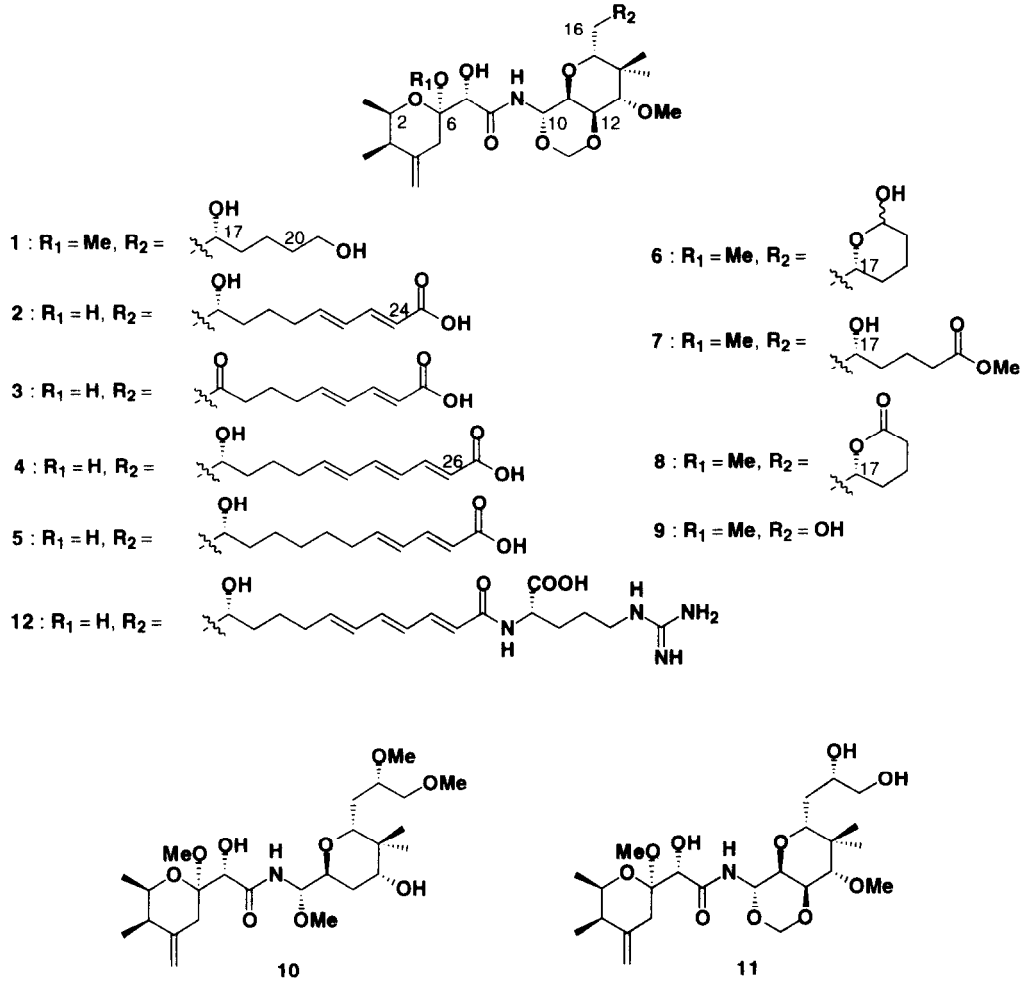

Theopederin F (**1**) had a molecular formula of $C_{27}H_{47}NO_{10}$ as established by HRFABMS, differing from theopederin B (**7**) by the elements of CO. The ^1H and ^{13}C NMR spectra of **1** were almost superimposable on those of **7** except for signals assignable to a terminal hydroxy methyl group [δ_H 3.62 (2H, m, H_2-21); δ_C 62.9 (C21)] in **1** instead of a methyl ester group in **7**, which was supported by HMBC cross peaks, δ 1.46 (H-19) and 1.56 (2H, m, H_2-20)/δ 62.9 (C21). The structure of **1** was further confirmed by chemical transformation from theopederin A (**6**); **6** was treated with sodium borohydride to afford **1**, which confirmed the structure of **1** including its stereochemistry.

Theopederins G-J (**2**-**5**) were isolated from the more polar fraction which contained theopederins A-C (**6**-**8**), E (**9**), and F (**1**). Theopederin G (**2**) had a molecular formula of $C_{30}H_{47}NO_{11}$. The ^1H NMR spectrum was very similar to that of **1** except for the lack of a methoxy group at C-6 and the presence of a butadiene system conjugated with a carboxylic acid. In fact, the COSY and HMBC spectra together with UV absorption at 260 nm (ε 17000) implied that the terminal hydroxy methyl moiety in **1** was replaced by a 2,4-

pentadienoate moiety in **2** [δ_H 6.20 (H-21), 6.29 (H-22), 7.25 (H-23), and 5.80 (H-24) (Table 1); δ_C 146.7 (C-21), 130.6 (C-22), 147.8 (C-23), 121.2 (C-24), and 170.6 (C-25)]; an all *trans*-diene unit was suggested by coupling constants of the vinyl protons. The stereochemistry of all chiral carbons in **2** was assumed to be identical with that of **1** as judged from the magnitude of the coupling constants; hence the structure of **2** was as shown.

Theopederin H (**3**) was smaller than theopederin G (**2**) by two hydrogen atoms. Two sets of methylene protons in **3** resonated at lower field [δ 2.43/2.48 (H_2-16) and 2.43 (2H, H_2-18) vs. δ 1.50 (2H, H_2-16) and 1.28/1.48 (H_2-18) in **2**] based on the COSY spectrum; and the absence of the H-17 proton signal in the ^{1}H NMR spectrum of **3** implied the 17-oxo structure. Analysis of the COSY spectrum indicated that the remaining portion of **3** was identical to that of **2** including relative stereochemistry. Hence, **3** is 17-oxotheopederin G.

Theopederin I (**4**) had a molecular formula of $C_{32}H_{49}NO_{11}$, a C_2H_2 unit larger than **2**. The ^{1}H NMR spectrum of **4** was almost superimposable on that of **2** except for the presence of an additional *trans* double bond [δ 6.00 (dt, J = 16.2, 7.2 Hz, H-21) and 6.24 (dd, J = 16.2, 10.8 Hz, H-22)] (Table 1), thereby implying to a 2,4,6-heptatrienoate moiety, which was further supported by a characteristic UV absorption at 300 nm (ε 24000). Therefore, the structure of **4** was established.

Theopederin J (**5**) possessed a molecular formula of $C_{32}H_{51}NO_{11}$, larger by two hydrogen atoms than **4**, indicating that one double bond in **4** was saturated. In fact, the COSY spectrum showed that Δ^{21} double bond in **4** was reduced to two methylenes in **5**. Thus, the structure of **5** was established.

Table 1. Selected ^{1}H NMR Data for **2**-**5**[a, b]

	2	**3**	**4**	**5**
15	3.43 t 6.6	3.88 m	3.43 t 6.6	3.45 dd 9.6,2.0
16	1.50 m	2.48 m	1.51 m	1.50 m
	1.50 m	2.43 m	1.51 m	1.50 m
17	3.63 m		3.63 m	3.62 m
18	1.48 m	2.43 m	1.47 m	1.44 m
	1.28 m	2.43 m	1.28 m	1.28 m
19	1.58 m	1.64 m	1.57 m	1.46 m
	1.44 m	1.63 m	1.42 m	1.32 m
20	2.23 m	2.13 m	2.19 m	1.37 m
	2.18 m	2.13 m	2.15 m	1.32 m
21	6.20 dt 15.6,8.4	5.98 dt 15.0,7.8	6.00 dt 16.2,7.2	1.58 m
				1.47 m
22	6.29 dd 15.6,10.8	6.18 dd 15.0,10.2	6.24 dd 16.2,10.8	2.20 m
				2.20 m
23	7.25 dd 15.0,10.2	7.04 dd 15.0,10.2	6.61 dd 14.4,10.8	6.17 dt 15.6,8.4
24	5.80 d 15.0	5.82 d 15.0	6.31 dd 14.4,11.4	6.24 dd 15.6,10.8
25			7.28 dd 15.0,11.4	7.21 dd 15.0,10.8
26			5.82 d 15.0	5.78 d 15.0

[a] Data recorded in CD_3OD. [b] Coupling constants in Hz are given.

Theopederin F (**1**) exhibited a 12 mm of growth inhibitory zone against the *erg6* mutant at 1 μg/disk (φ6 mm), while it showed an 11 mm inhibitory zone against the wild type at 10 μg/disk. It was also cytotoxic against P388 leukemia cells with an IC_{50} value of 0.15 ng/mL. Theopederins G-J (**2**-**5**) exhibited similar

activities.[4] Pederin (**10**),[5-7] isolated from the blister beatle *Paederus fuscipes*, and mycalamides A (**11**) and B,[8, 9] from a New Zealand *Mycale* sponge, have been reported to disrupt protein synthesis;[10, 11] the latter compounds showed potent antitumor activity as well.[11] It is known that the *erg6* mutant lacks ergosterol which alters membrane fluidity and permeability.[12] Obviously the high sensitivity of the mutant towards theopederins is due to its membrane properties.

In an earlier paper,[13] we reported the isolation of onnamide[14] derivatives, e.g. pseudoonnamide A (**12**), from another *Theonella* sponge. They share common structural features with theopederins G-J except for L-arginine moiety linked to the terminal carboxylic acid. Theopederins may be precursors of onnamide derivatives.

Experimental Section

Antimicrobial assay. This assay was performed as previously described.[15] The *Saccharomyces cerevisiae* strains used in this study are the *erg6* strain YAT2285 (*MATα leu2 his3 trp1 ura3 ade2 can1 erg6::URA3*) and its wild type W303-1B (*MATα leu2 his3 trp1 ura3 ade2 can1*).

Isolation. The sponge (70 kg) was collected by scuba at a depth of 15 m off the Kerama Islands, Okinawa. The frozen sponge was extracted with EtOH and $CHCl_3$-MeOH (1:1, 3 times). The combined extract was concentrated under reduced pressure and extracted with $CHCl_3$. After evaporation of $CHCl_3$, the residue was partitioned between 80 % EtOH and *n*-hexane. The aqueous fraction which was antifungal against the *erg6* mutant was purified by gel-filtration on Sephadex LH-20 with $CHCl_3$-MeOH (1:1), followed by flash column chromatography on ODS with MeOH-H_2O. A fraction (1.11 g) which eluted with 80 % MeOH-H_2O was subjected to silica gel column chromatography with MeOH/$CHCl_3$. An active 2.5 % MeOH-$CHCl_3$ fraction (112.5 mg) was purified by silica gel column chromatography with hexane-AcOEt (1:3) to afford theopederin B (**7**, 14.9 mg, 2.1 x 10^{-5} % wet weight), a mixture of theopederins A and B (**6** and **7**, 21.9 mg), and theopederin C (**8**, 19.6 mg, 2.8 x 10^{-5} %): An active 5 % MeOH-$CHCl_3$ fraction (98.3 mg) was subjected to silica gel column chromatography with hexane-AcOEt (1:3), AcOEt, and hexane-acetone (1:1) to afford a mixture of **6** and **7** (21.4 mg, 3.0 x 10^{-5} %), **8** (3.8 mg, 5.4 x 10^{-6} %), theopederin E (**9**, 11.2 mg, 1.6 x 10^{-5} %), and theopederin F (**1**, 4.0 mg, 5.7 x 10^{-6} %). A more polar active fraction (68.3 mg) eluted with $CHCl_3$-MeOH-H_2O (7:3:0.5) was separated by ODS HPLC with 44 % CH_3CN-H_2O (0.05 % TFA) and 70 % MeOH-H_2O to afford theopederins G (**2**, 1.5 mg, 2.1 x 10^{-6} %), H (**3**, 0.3 mg, 4.3 x 10^{-7} %), I (**4**, 1.0 mg, 1.4 x 10^{-6} %), and J (**5**, 0.5 mg, 7.1 x 10^{-7} %).

CAUTION! Theopederin-rich samples cause adverse reactions.

Theopederin F (**1**): $[\alpha]_D^{24}$ +32° (*c* 0.30, MeOH). ^1H NMR ($CDCl_3$) δ 0.86 (3H, s, 14-Me_{ax}), 0.96 (3H, s, 14-Me_{eq}), 0.98 (3H, d, *J* = 6.6 Hz, 3-Me), 1.18 (3H, d, *J* = 6.6 Hz, 2-Me), 1.38 (3H, m, H_2-18 and H-19), 1.42 (1H, m, H-16), 1.46 (1H, m, H-19), 1.51 (1H, dt, *J* = 14.4, 2.0 Hz, H-16), 1.56 (2H, m, H_2-20), 2.23 (1H, dq, *J* = 2.4, 6.6 Hz, H-3), 2.35 (1H, d, *J* = 13.8 Hz, H-5), 2.39 (1H, d, *J* = 13.8 Hz, H-5), 3.29 (3H, s, 6-OMe), 3.46 (1H, d, *J* = 10.2 Hz, H-13), 3.55 (3H, s, 13-OMe), 3.62 (1H, m, H-15), 3.62 (2H, m, H_2-21), 3.63 (1H, m, H-17), 3.85 (1H, dd, *J* = 10.2, 6.6 Hz, H-11), 3.98 (1H, dd, *J* = 6.6, 2.4 Hz, H-2), 4.22 (1H, dd, *J* = 10.2, 6.6 Hz, H-12), 4.30 (1H, s, H-7), 4.72 (1H, s, 4-CH), 4.83 (1H, s, 4-CH), 4.86 (1H, d, *J* = 6.6 Hz, 10-OCH), 5.14 (1H, d, *J* = 6.6 Hz, 10-OCH), 5.89 (1H, t, *J* = 10.2 Hz, H-10), and 7.48 (1H, d, *J* = 9.6 Hz, NH). ^{13}C NMR ($CDCl_3$) δ 12.1 (q, 3-Me), 13.6 (q, 14-Me_{ax}), 18.0 (q, 2-Me), 21.3 (t, C19), 23.1 (q, 14-Me_{eq}), 32.3 (t, C20), 33.8 (t, C5), 35.8 (t, C16), 36.5 (t, C18), 41.5 (d,

C3), 41.8 (s, C14), 48.9 (q, 6-OMe), 61.8 (q, 13-OMe), 62.9 (t, C21), 69.9 (d, C2), 71.2 (d, C17), 71.3 (d, C11), 72.8 (d, C7), 73.8 (d, C10), 74.6 (d, C12), 79.2 (d, C13), 80.3 (d, C15), 87.0 (t, 10-OCH_2), 110.6 (t, 4-CH_2), 145.6 (s, C4), and 172.1 (s, C8). FABMS (positive, glycerol matrix) *m/z* 546 $(M + H)^+$ and 514 $(546 - MeOH)^+$. HRFABMS (positive, glycerol + PEG600 in NBA matrix) *m/z* 514.3030 (calcd for $C_{26}H_{44}NO_9$, 514.3016).

Theopederin G (**2**): $[\alpha]_D^{24}$ +45° (*c* 0.12, MeOH). UV λ_{max} (MeOH) 260 nm (ε 17000). ^1H NMR (MeOH-*d*4) δ 0.85 (3H, s, 14-Me_{ax}), 0.99 (3H, s, 14-Me_{eq}), 1.00 (3H, d, *J* = 7.2 Hz, 3-Me), 1.07 (3H, d, *J* = 6.6 Hz, 2-Me), 2.10 (1H, d, *J* = 13.8 Hz, H-5), 2.19 (1H, m, H-3), 2.72 (1H, d, *J* = 13.8 Hz, H-5), 3.56 (3H, s, 13-OMe), 3.67 (1H, d, *J* = 10.2 Hz, H-13), 3.94 (1H, s, H-7), 3.97 (1H, dd, *J* = 9.6, 7.2 Hz, H-11), 4.16 (1H, m, H-2), 4.17 (1H, dd, *J* = 10.2, 7.2 Hz, H-12), 4.68 (2H, br s, 4-CH_2), 4.78 (1H, d, *J* = 7.2 Hz, 10-OCH), 5.22 (1H, d, *J* = 7.2 Hz, 10-OCH), amd 5.80 (1H, d, *J* = 9.6 Hz, H-10). ^1H chemical shifts for H-15 - H-24 are shown in Table 1. ^{13}C NMR (MeOH-*d*4) δ 12.0 (q, 3-Me), 14.0 (q, 14-Me_{ax}), 18.2 (q, 2-Me), 23.1 (q, 14-Me_{eq}), 25.7 (t, C16), 34.0 (t, C20), 36.6 (t, C5), 36.7 (t, C18), 37.1 (t, C19), 42.4 (s, C14), 43.1 (d, C3), 62.1 (q, 13-OMe), 71.1 (2C, d, C2 and C11), 71.3 (d, C17), 75.5 (d, C10), 76.0 (d, C12), 77.1 (d, C7), 78.9 (d, C15), 80.7 (d, C13), 88.2 (t, 10-OCH_2), 99.1 (s, C6), 110.6 (t, 4-CH_2), 121.2 (d, C24), 130.6 (d, C22), 146.7 (d, C21), 147.8 (d, C23), 148.5 (s, C4), 170.6 (s, C25), and 175.2 (s, C8). FABMS (positive, glycerol matrix) *m/z* 580 $(M + H - H_2O)^+$. HRFABMS (positive, glycerol + PEG600 in NBA matrix) *m/z* 580.3124 (calcd for $C_{30}H_{46}NO_{10}$, 580.3122).

Theopederin H (**3**): $[\alpha]_D^{24}$ +60° (*c* 0.023, MeOH). UV λ_{max} (MeOH) 260 nm (ε 21000). ^1H NMR (MeOH-*d*4) δ 0.89 (3H, s, 14-Me_{ax}), 1.00 (3H, d, *J* = 6.6 Hz, 3-Me), 1.00 (3H, s, 14-Me_{eq}), 1.08 (3H, d, *J* = 6.6 Hz, 2-Me), 2.12 (1H, d, *J* = 13.8 Hz, H-5), 2.19 (1H, dq, *J* = 2.0, 6.6 Hz, H-3), 2.72 (1H, d, *J* = 13.8 Hz, H-5), 3.56 (3H, s, 13-OMe), 3.68 (1H, d, *J* = 10.8 Hz, H-13), 3.90 (1H, m, H-11), 4.01 (1H, s, H-7), 4.14 (1H, m, H-12), 4.16 (1H, m, H-2), 4.69 (2H, br s, 4-CH_2), 4.78 (1H, d, *J* = 6.6 Hz, 10-OCH), 5.20 (1H, d, *J* = 6.6 Hz, 10-OCH), and 5.74 (1H, d, *J* = 9.0 Hz, H-10). ^1H chemical shifts for H-15 - H-24 shown in Table 1. FABMS (positive, glycerol matrix) *m/z* 578 $(M + H - H_2O)^+$. HRFABMS (positive, glycerol + PEG600 in NBA matrix) *m/z* 578.2961 (calcd for $C_{30}H_{44}NO_{10}$, 578.2965).

Theopederin I (**4**): $[\alpha]_D^{24}$ +54° (*c* 0.077, MeOH). UV λ_{max} (MeOH) 300 nm (ε 24000). ^1H NMR (MeOH-*d*4) δ 0.85 (3H, s, 14-Me_{ax}), 0.99 (3H, s, 14-Me_{eq}), 1.00 (3H, d, *J* = 6.6 Hz, 3-Me), 1.07 (3H, d, *J* = 6.6 Hz, 2-Me), 2.10 (1H, d, *J* = 13.8 Hz, H-5), 2.19 (1H, m, H-3), 2.72 (1H, d, *J* = 13.8 Hz, H-5), 3.56 (3H, s, 13-OMe), 3.67 (1H, d, *J* = 10.2 Hz, H-13), 3.95 (1H, s, H-7), 3.97 (1H, dd, *J* = 9.6, 7.2 Hz, H-11), 4.16 (1H, dd, *J* = 10.2, 7.2 Hz, H-12), 4.16 (1H, m, H-2), 4.67 (2H, br s, 4-CH_2), 4.78 (1H, d, *J* = 7.2 Hz, 10-OCH), 5.22 (1H, d, *J* = 7.2 Hz, 10-OCH), and 5.80 (1H, d, *J* = 9.6 Hz, H-10). ^1H chemical shifts for H-15 - H-26 shown in Table 1. FABMS (positive, glycerol matrix) *m/z* 606 $(M + H - H_2O)^+$. HRFABMS (positive, glycerol + PEG600 in NBA matrix) *m/z* 606.3276 (calcd for $C_{32}H_{48}NO_{10}$, 606.3278).

Theopederin J (**5**): $[\alpha]_D^{24}$ +48° (*c* 0.038, MeOH). UV λ_{max} (MeOH) 260 nm (ε 22000). ^1H NMR (MeOH-*d*4) δ 0.88 (3H, s, 14-Me_{ax}), 0.99 (3H, s, 14-Me_{eq}), 1.01 (3H, d, *J* = 6.6 Hz, 3-Me), 1.08 (3H, d, *J* = 6.6 Hz, 2-Me), 2.20 (1H, m, H-3), 2.11 (1H, d, *J* = 13.8 Hz, H-5), 2.73 (1H, d, *J* = 13.8 Hz, H-5), 3.56 (3H, s, 13-OMe), 3.68 (1H, d, *J* = 10.8 Hz, H-13), 3.95 (1H, s, H-7), 3.97 (1H, dd, *J* = 10.2, 7.2 Hz, H-11), 4.16 (1H, m, H-2), 4.17 (1H, dd, *J* = 10.8, 7.2 Hz, H-12), 4.68 (2H, br s, 4-CH_2), 4.78 (1H, d, *J* = 7.2 Hz, 10-OCH), 5.23 (1H, d, *J* = 7.2 Hz, 10-OCH), and 5.80 (1H, d, *J* = 10.2 Hz, H-10). ^1H chemical

shifts for H-15 - H-26 shown in Table 1. FABMS (positive, glycerol matrix) *m/z* 608 $(M + H - H_2O)^+$. HRFABMS (positive, glycerol + PEG600 in NBA matrix) *m/z* 608.3436 (calcd for $C_{32}H_{50}NO_{10}$, 608.3435).

Preparation of 1 from 6. To **6** (1.0 mg) in MeOH (1.0 mL) was added $NaBH_4$ (35.2 mg); the mixture was stirred at room temperature for 10 min. After addition of water (2 mL), the reaction mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4 followed by in a stream of N_2. The residue was purified by silica gel column chromatography with 15 % MeOH-$CHCl_3$ to afford **1** (0.8 mg), whose ^1H NMR spectrum and FABMS were identical with those of the natural product.

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