Antifungal Cyclic Depsipeptide, Eujavanicin A, Isolated from *Eupenicillium javanicum*

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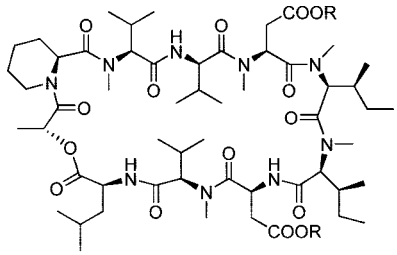
In the course of searching for new antifungal agents, a new cyclic depsipeptide, eujavanicin A (**1**), was isolated from *Eupenicillium javanicum* as an antifungal agent against the human pathogenic filamentous fungus *Aspergillus fumigatus*. The structure of **1** was established by spectroscopic and chemical investigations. The absolute stereochemistry was elucidated by Marfey's method and by chiral HPLC analysis.

Our group has been searching for fungal metabolites that show antifungal activity against the pathogenic filamentous fungi *Aspergillus fumigatus* and *Aspergillus niger* and/or the pathogenic yeasts *Candida albicans* and *Cryptococcus neoformans*. During previous research for antifungal substances from fungal sources,[1] it was found that an organic extract of *Eupenicillium javanicum* IFM 54704 showed a potent antifungal activity against *A. fumigatus*. In this paper, we report the isolation and structure determination of a new cyclic depsipeptide, designated eujavanicin A (**1**), which is responsible for the anti-*A. fumigatus* activity.



1 R = H
2 R = Me

The molecular formula of eujavanicin A (**1**) was established as $C_{55}H_{93}N_9O_{15}$ by HRFABMS. Compound **1** showed no reaction against ninhydrin reagent on TLC. However, **1** showed a positive coloration (purple) with ninhydrin reagent on TLC when it was treated with dilute HCl and then heated on a hot plate. The absorption bands at 1734 and 1639 cm^{-1} in the IR spectrum of **1** suggested the presence of ester and amide groups, respectively. Hence, **1** could be assigned as a cyclic depsipeptide. The structural fragment of **1** shown by bold lines in Figure 1 was established from its ^1H-^1H COSY and 1D and 2D TOCSY NMR spectra. These results and analysis of the HSQC and HMBC NMR spectra of **1** revealed the presence of units of lactic acid (Lac), pipecolic acid (Pip), valine (Val), leucine (Leu), two *N*-methylvalines (*N*-MeVal), two *N*-methylisoleucines (*N*-MeIle), and two amino acids having a carbonyl group at the β-position. Methylation of **1** with CH_2N_2 provided a dimethyl ester (**2**),[2] indicating the presence of aspartic acid (Asp) and *N*-methylaspartic acid (*N*-MeAsp) in **1**. From the HMBC correlations of *N*-methyl protons of *N*-MeIle (δ_H 2.91) with C-1 of *N*-MeAsp (δ_C 169.7), of *N*-methyl protons of *N*-MeAsp (δ_H 2.88) with C-1 of Val (δ_C 170.4), of the NH proton of Val (δ_H 6.90) with C-1 of *N*-MeVal (δ_C 168.0), of *N*-methyl protons of *N*-MeVal (δ_H 2.77) with C-1 of Pip (δ_C 172.0), and of H-2 in Pip (δ_H 5.58) with C-1 of Lac (δ_C 173.2), **1** was assigned a sequence determined as Lac-Pip-*N*-MeVal-Val-*N*-MeAsp-*N*-MeIle (I). Further HMBC correlations of the NH proton of Leu (δ_H 7.47) with C-1 of the other *N*-MeVal (δ_C 169.3) and of *N*-methyl protons of the *N*-MeVal (δ_H 3.08) with C-1 of Asp (δ_C 171.0) indicated that **1** has one more sequence of Asp-*N*-MeVal-*N*-Meleu (II). As it was not possible to distinguish among cross-peaks derived from five of the carbonyl resonances (for the two *N*-MeIle and Leu units and the side-chain carboxyl groups in *N*-MeAsp and Asp) observed in the region from δ_C 171.3 to 171.5, the HMBC spectra of **1** consequently led to the proposal of three fragments, one independent *N*-MeIle and two sequences, I and II, as shown in Figure 1.

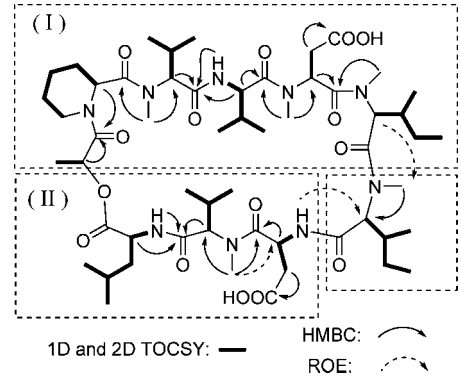


Figure 1. 1D and 2D TOCSY, HMBC, and ROE NMR correlations for eujavanicin A (**1**).

In order to connect the above three fragments, a ROE NMR experiment was carried out. Irradiation of the resonance for the H-2 (δ 5.28) of *N*-MeIle in sequence I brought about enhancement of the resonance for the *N*-methyl protons (δ 3.39) of the independent *N*-MeIle. When the NH proton (δ 7.88) of Asp in the sequence II was irradiated, enhancement of the H-2 (δ 3.13) of the independent *N*-MeIle was observed. The above results suggest that eujavanicin A (**1**) is the structure, as shown in Figure 1. To confirm the amino acid sequence of **1**, the ring-opened methyl ester (**3**) was prepared by methanolysis. Detailed examination of the data from the FABMS of **3** established the sequence shown in Figure 2.

The absolute configuration of the lactic acid constituent in **1** was elucidated by comparative HPLC analysis on a chiral column using standards of D- and L-lactic acids after complete hydrolysis of **1**. The lactic acid derived from **1** was identified with D-Lac. The absolute configuration of the amino acid constituents in **1** was

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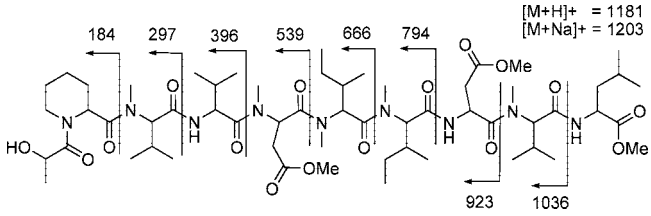

Figure 2. FABMS-MS fragmentation (*m*/*z* values) of the trimethyl ester (**3**).

established by acid hydrolysis followed by derivatization with Marfey's reagent [1-fluoro-2,4-dinitrophenyl-5-L-alanine amide (L-FDAA)][3] and subsequent HPLC analysis, on comparing the chromatograms with those of derivatives of amino acids and *N*-methyl amino acids. From the above result, all amino acid constituents in **1** have the L-configuration.

Antimicrobial activity was determined by the paper disk method, as described in a previous paper.[4] The active compound derived from *Eupenicillium javanicum* IFM 54704, eujavanicin A (**1**), showed strong growth inhibition against *A. fumigatus* (23 mm inhibition zone at 6.25 μg/disk), whereas **1** showed no antimicrobial activity against *A. niger*, *C. albicans*, and *C. neoformans* at 50 μg/disk. The dimethyl ester (**2**) of **1** showed no antifungal activity against all of the above fungi and yeasts. We therefore conclude that the carboxyl groups in **1** are necessary in order to show the anti-*A. fumigatus* activity. Antibacterial tests against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli*, and *Salmonella enteritidis* were performed by the paper disk method. Compounds **1** and **2** also showed no antibacterial activity at 100 μg/disk.

Previously, we found that the organic extract of *E. javanicum* IFM 52670 showed characteristic and strong antifungal activity against *A. fumigatus*, and one active compound was the acyclic form of the lactone in compactin.[4] In this paper, we report that a new cyclic depsipeptide, eujavanicin A (**1**), having potent anti-*A. fumigatus* activity, was isolated from the organic extract of another strain, IFM 54704, identified as *E. javanicum*. However, compactin and related compounds were not found in this extract derived from the strain IFM 54704. As mentioned above, strains of *E. javanicum* might be divided into two chemotypes based on antifungal substance profile. The species of *E. javanicum* are commonly occurring and widely distributed. It is interesting that strains having the ability to produce a different type of compound for antifungal activity exist in the same species.

Experimental Section

General Experimental Procedures. Most of the general experimental procedures used were described in the previous paper.[5] FABMS was taken with a JMS-MS700V spectrometer. Analytical HPLC were performed with a JASCO pump PU-2089, equipped with a JASCO UV-2075 detector and a JASCO CO-2067 temperature control unit. Detection of materials on TLC was carried out as follows; a TLC plate soaked with 6 M HCl was heated on a hot plate, followed by spraying with 1 M KH_2PO_4 solution and heated again, and then treated by ninhydrin reagent. D-*N*-MeIle, L-*N*-MeIle, D-*N*-Me-*allo*-Ile, and L-*N*-Me-*allo*-Ile were prepared in a typical procedure.[6,7] L-Pip using HPLC analysis was purchased from MP Biomedicals, D-Pip from Aldrich, DL-*N*-MeAsp and *allo*-Ile from Sigma, and the other amino acids and D- and L-lactic acids from Nakalai Tesque (Kyoto, Japan).

Fungal Material. The examined strain was isolated from a cultivated soil in Chiba, Japan, identified as *Eupenicillium javanicum* based on morphology (by T.Y.), and deposited at the Research Center for Pathogenic Fungi and Microbial Toxicoses, Chiba University, under the accession number IFM 54704. The strain IFM 54704 was cultured at 25 °C for 21 days in 23 Roux flasks containing 160 g of moist rice in each flask.

Extraction and Isolation. The fermented rice was extracted with CH_2Cl_2−MeOH (3:2), and the organic layer was evaporated in vacuo. The resultant extract was suspended in H_2O and extracted with EtOAc, and then the organic layer was evaporated in vacuo. The EtOAc extract (53 g), which showed strong antifungal activity against *A. fumigatus*, was separated by column chromatography on silica gel (800 g) into six fractions eluted with CH_2Cl_2 (22.2 g), CH_2Cl_2−EtOH (20:1) (6.8 g), CH_2Cl_2−EtOH (10:1) (15.4 g), CH_2Cl_2−EtOH (5:1) (2.2 g), and EtOH (4.4 g). The third [CH_2Cl_2−EtOH (10:1)] and fourth [CH_2Cl_2−EtOH (5:1)] fractions showed anti-*A. fumigatus* activity. The third fraction was further separated by low-pressure liquid chromatography (LPLC) on silica gel with $CHCl_3$−acetone (3:1) and then using cyclohexane−acetone (3:1) to give an antifungal active fraction (107 mg). The active fraction was further purified with HPLC on a silica gel column eluting with cyclohexane−acetone (3:2) to give eujavanicin A (**1**) (80 mg).

Eujavanicin A (1): colorless cubes; mp 243.2−243.5 °C (from hexane−EtOAc); $[\alpha]^{23}_D$ −194.9 (*c* 0.8, MeOH); UV λ_{max} (MeOH) end absorption; IR ν_{max} 1734 (−COO−), 1683 (CO), 1639 (−CON<) cm^{-1}; ^{1}H and ^{13}C NMR signal assignments, see in Table 1; HRFABMS *m*/*z* 1120.6855 [M + H]$^+$ (calcd for $C_{55}H_{94}N_9O_{15}$, 1120.6869).

Methylation of Eujavanicin A (1) with CH_2N_2. An excess ethereal solution of diazomethane was added to a solution of eujavanicin A (**1**) (10.2 mg) in MeOH (1 mL), and the solution was allowed to stand for 5 min at 25 °C followed by evaporation to give a colorless solid. The residue was purified with HPLC on a silica gel column eluting cycohexane−acetone (2:1) to give a dimethyl ester (**2**) (9.3 mg).

Dimethyl ester (2) of 1: colorless, amorphous solid; UV λ_{max} (MeOH) end absorption; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (NH, d, J = 10.3 Hz, Leu) [7.95 (d J = 9.8 Hz)], 8.00 (NH, d, J = 10.4 Hz, Val) [8.12 (d, J = 9.7 Hz)], 6.61 (NH, d, J = 7.4 Hz, Asp) [8.09 (d, J = 8.6 Hz)], 6.58 (1H, dd, J = 10.6, 4.9 Hz, *N*-Me-Asp-2) [6.19 (dd, J = 9.2, 5.7 Hz)], 5.52 (1H, d, J = 6.9 Hz, Lac-2) [5.38 (ov)], 5.35 (1H, m, Pip-2), 5.13 (1H, m, Asp-2) [5.19 (m)], 5.12 (1H, d, J = 10.8 Hz, *N*-Me-Ile-2 [I]) [5.24 (d, J = 11.5 Hz)], 4.85 (1H, m, Leu-2) [4.91 (m)], 4.60 (1H, m, Val-2) [4.62 (m)], 4.39 (1H, d, J = 11.5 Hz, *N*-Me-Val-2 [II]) [4.70 (d, J = 10.9 Hz)], 4.27 (1H, d, J = 10.9 Hz, *N*-Me-Val-2 [I]) [4.23 (d, J = 10.3 Hz)], 4.11 (1H, m, Pip-6), 3.73 (1H, d, J = 10.3 Hz, *N*-Me-Ile-2) [3.08 (d, J = 11.7 Hz)], 3.69 (3H, s, COOMe) [3.70 (s)], 3.59 (1H, m, Pip-6), 3.48 (3H, s, COOMe) [3.52 (s)], 3.18 (3H, s, *N*-Me-Val [II]) [3.20 (s)], 3.05 (3H, s, *N*-Me-Ile [I]) [3.05 (s)], 3.01 (3H, s, *N*-Me-Asp) [2.98 (s)], 2.88 (1H, m, *N*-Me-Asp-3) [2.86 (m)], 2.76 (3H, s, *N*-Me-Val [I]), 2.74 (3H, s, *N*-Me-Ile) [3.15 (s)], 2.62 (1H, dd, J = 13.6, 3.2 Hz, Asp-3) [2.53 (1H, dd, J = 15.8, 3.2 Hz)], 2.45 (1H, m, *N*-Me-Val-3 [I]), 2.29 (1H, m, *N*-Me-Val-3 [II]), 2.29 (1H, m, *N*-Me-Ile-3 [I]) [2.20 (m)], 2.26 (1H, m, Asp-3) [2.36 (m)], 2.20 (1H, m, *N*-Me-Asp-3) [2.43 (m)], 2.12 (1H, m, Pip-4), 2.03 (1H, m, *N*-Me-Ile-3) [2.86 (m)], 1.96 (1H, m, Val-3) [1.97 (m)], 1.85 (2H, m, Pip-3 and 5), 1.70 (1H, m, Pip-3), 1.62 (1H, m, Pip-4), 1.61 (1H, m, Leu-3) [1.67 (m)], 1.53 (1H, m, Leu-3) [1.57 (m)], 1.48 (1H, m, Pip-5), 1.44 (1H, m, Leu-4) [1.42 (m)], 1.41 (1H, d, J = 6.9 Hz, Lac-3) [1.38 (d, J = 6.9 Hz)], 1.34 (1H, m, *N*-Me-Ile-4) [1.48 (m)], 1.20 (1H, m, *N*-Me-Ile-4 [I]) [1.29 (m)], 1.05 (Me, d, J = 6.3, *N*-Me-Val [II]) [1.1 (d, J = 6.9 Hz)], 1.03 (1H, m, *N*-Me-Ile-4) [1.01 (m)],1.01 (1H, m, *N*-Me-Ile-4 [I]) [1.07 (m)], 0.96 (Me, ov, *N*-Me-Val [I]), 0.93 (2Me, ov, *N*-Me-Ile) [0.90 (ov)], 0.89 (Me, ov, *N*-Me-Val [I]) [0.88 (ov)], 0.87 (2Me, ov, *N*-Me-Ile [I]) [0.90 (ov)], 0.84 (Me, ov, Val) [0.82 (ov)], 0.81 (2Me, ov, Leu) [0.82 (ov)], 0.74 (Me, d, J = 6.9 Hz, *N*-Me-Val [II]) [0.88 (ov)], 0.74 (Me, d, J = 6.9 Hz, Val) [0.75 (d, 6.3)] (ov = overlapped by other signals) (values in brackets are for minor conformers and are not shown when resonances of the two conformers are the same); FABMS *m*/*z* 1149 [M + H]$^+$, 1171 [M + Na]$^+$.

Methanolysis of 2 by NaOMe. Dimethyl ester **2** (9.3 mg) and NaOMe (10 mg) were dissolved in MeOH (2 mL), and the mixture was kept for 3 h at rt. After the addition of iced water, the reaction mixture was extracted with EtOAc. The EtOAc layer was evaporated. The residue was purified with HPLC on a silica gel column eluting with cyclohexane−acetone (2:1) to give a trimethyl ester (**3**) (3.3 mg).

Trimethyl ester 3: FABMS *m*/*z* 1203 (1.8) [M + Na]$^+$, 1181 (1.6) [M + H]$^+$, 1036 (2.5) [M − Leu(OMe)]$^+$, 923 (1) [M − (*N*-MeVal-Leu(OMe))]$^+$, 794 (32) [M − (Asp(OMe)-*N*-MeVal-Leu(OMe))]$^+$, 666 (18) [M − (*N*-MeIle-Asp(OMe)-*N*-MeVal-Leu(OMe))]$^+$, 539 (24) [M − (*N*-MeIle-*N*-MeIle-Asp(OMe)-*N*-MeVal-Leu(OMe))]$^+$, 396 (5) [(Lac-Pip-*N*-MeVal-Val) − OH]$^+$, 297 (89) [(Lac-Pip-*N*-MeVal) − OH]$^+$, 184 (100) [(Lac-Pip) − OH]$^+$.

Acid Hydrolysis of 1. A tube containing **1** (1.2 mg) and 6 M HCl (1 mL) was sealed under vacuum after being flushed with argon, and kept at 110 °C for 21 h. This solution was evaporated to dryness under vacuum to give the hydrolysate.

Absolute Configuration of Lactic Acid in 1. The hydrolysate was dissolved in 1 mL of water, with 16 μL of this solution used for one

Table 1. Correlated ^{1}H and ^{13}C Spectroscopic Data ($CDCl_3$) for Eujavanicin A (**1**)

		δ	
amino acid	residue no.	^{13}C, mult.	^{1}H (mult., *J* (Hz))
lactic acid	1	173.2, qC	
	2	67.0, CH	5.47 (q, 7.0)
	3	18.1, CH_3	1.39 (d, 7.0)
L-Pip	1	172.0, qC	
	2	46.7, CH	5.59 (d, 6.0)
	3	27.6, CH_2	1.76 (m)
			1.88 (m)
	4	18.8, CH_2	1.66 (m)
			2.18 (m)
	5	25.0, CH_2	1.48 (m)
			1.91 (m)
	6	43.4, CH_2	3.64 (d, 13.4)
			4.23 (dt, 13.4, 3.0)
L-*N*-MeVal	1	168.0, qC	
	2	66.9, CH	4.34 (d, 10.4)
	3	26.0, CH	2.44 (m)
	4	19.2, CH_3	0.87 (d, 7.0)
	5	19.6, CH_3	1.04 (d, 6.5)
	NCH_3	28.8, CH_3	2.77 (s)
L-Val	1	170.4, qC	
	2	54.6, CH	4.51 (t, 10.4)
	3	29.1, CH	1.98 (m)
	4	20.0, CH_3	0.78 (d, 7.0)
	5	18.1, CH_3	0.79 (d, 6.5)
	NH		6.90 (d, 10.4)
L-*N*-MeAsp	1	169.7, qC	
	2	52.0, CH	6.40 (dd, 11.9, 5.5)
	3	35.5, CH_2	2.75 (m)
			3.09 (m)
	4	171.49[a], qC	
	NCH_3	30.5, CH_3	2.87 (s)
L-*N*-MeIle	1	171.4[a], qC	
	2	57.1, CH	5.26 (d, 10.9)
	3	32.6, CH	2.18 (m)
	4	24.5, CH_2	1.07 (m)
			1.31 (m)
	5	15.1, CH_3	0.92 ov
	6	10.0, CH_3	0.91 ov
	NCH_3	29.72, CH_3	2.91 (s)
L-*N*-MeIle	1	171.43[a], qC	
	2	75.0, CH	3.12 (d, 10.0)
	3	33.8, CH	2.71 (m)
	4	25.8, CH_2	1.03 (m)
			1.51 (m)
	5	17.0, CH_3	0.99 (d, 6,5)
	6	10.8, CH_3	0.89 ov
	NCH_3	41.4, CH_3	3.39 (s)
L-Asp	1	171.0, qC	
	2	47.6, CH	4.92 (m)
	3	37.8, CH_2	2.44 (dd, 16.3, 3.0)
			2.56 (dd, 16.3, 8.0)
	4	171.38[a], qC	
	NH		7.88 (d, 6.9)
L-*N*-MeVal	1	169.3, qC	
	2	62.5, CH	4.84 (d, 11.4)
	3	26.0, CH	2.33 (m)
	4	18.6, CH_3	0.81 ov
	5	18.6, CH_3	0.96 (d, 6.5)
	NCH_3	29.69 CH_3	3.07 (s)
L-Leu	1	171.34[a], qC	
	2	49.3, CH	4.93 (m)
	3	37.5, CH_2	1.63 (m)
			2.15 (m)
	4	25.1, CH	1.51 (m)
	5	21.1, CH_3	0.86 (d, 6.5)
	6	23.1, CH_3	0.83 (d, 6.9)
	NH		7.46 (d, 9.9)

[a] Assignments for these carbon atoms may be interchanged.

analysis. HPLC analysis was performed on a ligand exchange type chiral column, 5 μm, 4.6 × 150 mm (Sumichiral OA-5000); UV 254 nm. The solvent of HPLC analysis was eluted with 1 mM copper(II) sulfate in water, 25 °C, flow rate 1.0 mL/min. The configuration was determined by co-injection with L-lactic acid (t_R 21.8min) and D-lactic acid (t_R 28.4min).

Preparation and Analysis of Marfey Derivatives.[3] To the remaining hydrolysate solution, or to a solution of the reference amino acid, was added a solution of FDAA (1-fluoro-2,4-dinitrophenyl-5-alanine amide) in acetone. After addition of 1 M $NaHCO_3$, each mixture was kept at 40 °C for 1 h. After addition of 2 M HCl at rt, the solvents were evaporated to dryness, and the residue was redissolved in MeOH−H_2O (1 mL; 1:1). A part of the solution (10 μL) was analyzed by HPLC (YMC-Pack ODS, 250 × 4.6 mm, 5 μm, flow rate of 1.0 mL min^{-1}) using a linear gradient of 30−60% CH_3CN−H_2O containing 0.05% TFA in 80 min at 25 °C. Retention times (min) of the amino acid derivatives were as follows: D-Pip (19.9), L-Val (20.3), L-Pip (22.7), L-*N*-MeVal (25.9), D-Val (27.7), L-Leu (28.7), D-*N*-MeVal (30.4), L-*N*-MeIle (32.6), L-*N*-Me-*allo*-Ile (33.4), D-Leu (37.0), D-*N*-MeIle (38.0), and D-*N*-Me-*allo*-Ile (38.9). For the separation of the other amino acids, a different HPLC condition was used as mobile phase and temperature (linear gradient of 15−45% CH_3CN−H_2O containing 0.05% TFA in 80 min at 30 °C). These retention times were as follows: D-*N*-MeAsp (29.1), L-Asp (32.1), L-*N*-MeAsp (33.1), and D-Asp (34.2).

Antimicrobial Activity. The antifungal assay was performed by the same method as in the previous paper.[4] The antibacterial assay was performed by the paper disk method against *S. aureus* MBRC12732, *B. subtilis* NBRC3134, *E. coli* NBRC 14237, and *S. enteritidis* NBRC 3313. At 50 μg/disk, it showed no inhibition zone against the above bacteria.

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(2) The dimethyl ester exists as an equilibrium mixture of two stable conformers. The methyl ester showed two peaks (t_R 8.5 and 9.0 min) on a chart by HPLC on a silica gel columun [Kanto Mightysil Si-60 (5 μm) 250 × 10 mm] eluting with cyclohexane−acetone (3:2) and a flow rate of 4 mL/min. Each fraction displayed the same two peaks on a chart by HPLC analysis. ^{1}H NMR spectrum in $CDCl_3$ also showed the presence of two conformers in the ratio of 3 to 2. The ^{1}H and ^{13}C NMR assignments of dimethyl ester **2** were determined by ^{1}H-^{1}H COSY, 1D and 2D TOCSY, HSQC, and HMBC NMR spectra.

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