VOL. 56 NO. 4, APR. 2003 THE JOURNAL OF ANTIBIOTICS pp. 351 — 357

Terreulactones A, B, C, and D: Novel Acetylcholinesterase Inhibitors Produced by *Aspergillus terreus*

II. Physico-chemical Properties and Structure Determination

WON-GON KIM[†,*], KYUNG-MI CHO[†,††], CHONG-KIL LEE[††] and ICK-DONG YOO[†]

[†] Korea Research Institute of Bioscience and Biotechnology,
P. O. Box 115, Yusong, Daejeon, 305-600, Korea
[††] Department of Pharmacy, Chung-Buk National University,
Cheong-Ju 361-763, Korea

(Received for publication December 2, 2002)

Terreulactones A, B, C, and D, new meroterpenoid compounds with potent anti-acetylcholinesterase activity, were determined to be mixed polyketides-terpenoid structures by spectroscopic studies.

In the course of our screening for selective inhibitors of acetylcholinesterase from microbial metabolites, we isolated four new meroterpenoid compounds named terreulactones A (**1**), B (**2**), C (**3**), and D (**4**) from the solid state fermentation of *Aspergillus terreus* Fb000501 (Fig. 1)[1,2]. Terreulactones A (**1**), B (**2**), C (**3**), and D (**4**) are structurally related to arisugacins[3~6] and territrems[7,8] which were reported as acetylcholinesterase inhibitors and tremorgenic mycotoxins from *Penicillium* sp. and *Aspergillus terreus*, respectively. Arisugacins and territrems, however, were not detected in this study. Terreulactones showed a potent and selective inhibitory activity on acetylcholinesterase compared with butyrylcholinesterase. In the proceeding paper we described the taxonomy of the producing strain, fermentation, isolation, and biological activities of these compounds. And, the structure of terreulactones A (**1**) was previously reported[9]. We report here physico-chemical properties and structure determination of terreulactones B (**2**), C (**3**), and D (**4**).

Physico-chemical Properties of Terreulactones B (2), C (3), and D (4)

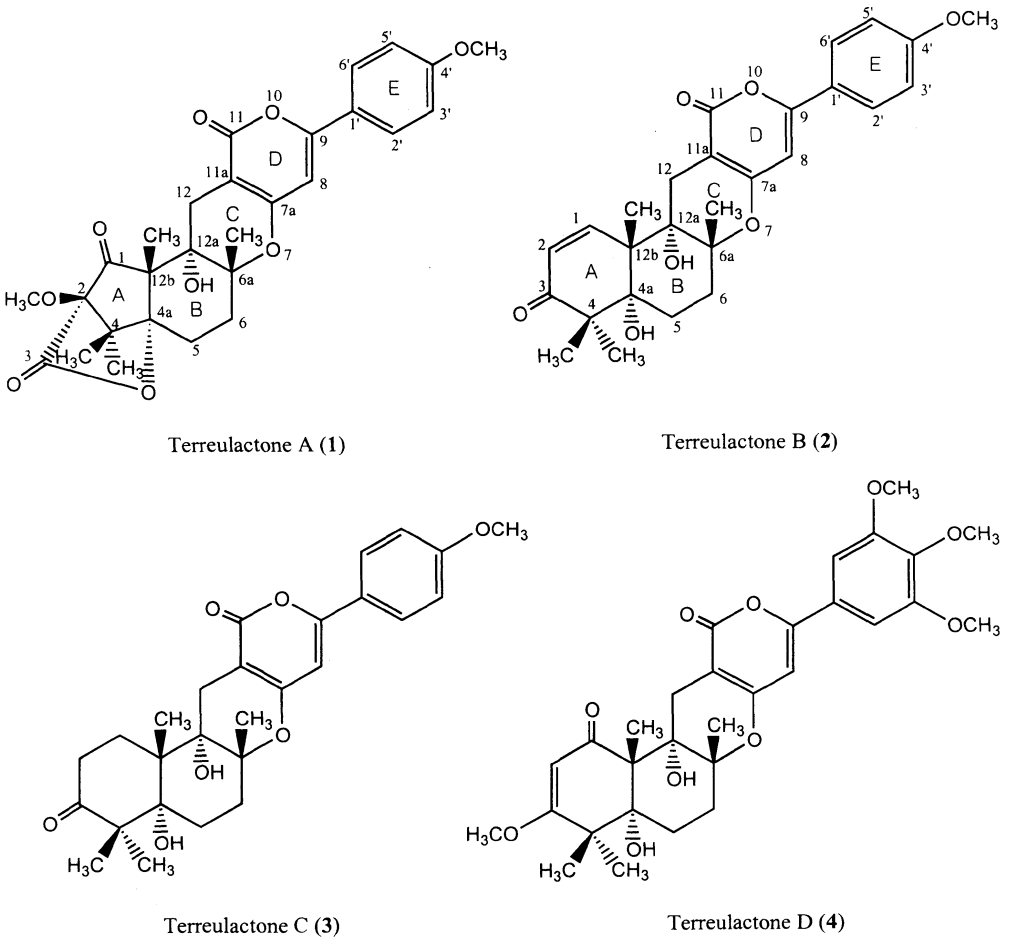
The compounds were obtained as white powders as shown in Table 1. They are soluble in methanol, dimethlylsulfoxide and $CHCl_3$, and insoluble in water, ether and *n*-hexane. Their UV absorption spectra showed the absorption maxima at 208~213, 247~252, and 330~331 which are similar to those of terreulactone A. Also, their IR spectra revealed similar absorption bands to those of terreulactone A which were attributable to a γ-lactone (1671~1702 cm^{-1}) and a hydroxyl (3403~3432 cm^{-1}) moiety. Chemical shifts in the ^1H and ^{13}C NMR of **2**~**4** are shown together with those of terreulactone A in Table 2 and 3, respectively.

Structure of Terreulactone B (2)

The molecular formula of **2** was determined to be $C_{27}H_{30}O_7$ on the basis of high resolution ESI-MS [$(M+H)^+$, 467.2070 *m/z* (+0.1 mmu error)] in combination with ^1H and ^{13}C NMR data. The ^1H and ^{13}C NMR spectral data (Tables 2 and 3) of **2** with ^1H-^1H COSY, HMQC and DEPT spectral data revealed the presence of an 1,4-disubstituted benzene ring, a *cis*-disubstituted ethene, an isolated olefinic methine (δ_H 6.12, 1H, s; δ_C 96.4), an methoxy (δ_H 3.87, 3H, s; δ_C 55.4), $-CH_2-CH_2-$, an isolated methylene (δ_H 2.78, 1H, d, J=16.6; δ_H 2.86, 1H, d, J=16.6; δ_C 25.8), four isolated methyls, one carbonyl

* Corresponding author: wgkim@kribb.re.kr

Fig. 1. Relative structures of terreulactones A (**1**), B (**2**), C (**3**) and D (**4**).



Terreulactone A (**1**)

Terreulactone B (**2**)

Terreulactone C (**3**)

Terreulactone D (**4**)

Table 1. Physico-chemical property of terreulactones A (**1**), B (**2**), C (**3**) and D (**4**).

	1	**2**	**3**	**4**
Appearance	white powder	white powder	white powder	white powder
$[\alpha]_D$	+60 (*c* 0.1, $CHCl_3$)	+110 (*c* 0.1, MeOH)	+132.5 (*c* 0.023, MeOH)	+111.0 (*c* 0.073, $CHCl_3$)
ESI-MS (*m/z*)	511 $(M+H)^+$	465 $(M-H)^-$	469 $(M+H)^+$	579 $(M+Na)^+$
HRESI-MS (*m/z*)				
found	511.1964 $(M+H)^+$	467.2070 $(M+H)^+$	469.2220 $(M+H)^+$	557.2387 $(M+H)^+$
calcd.	511.1968	467.2069	469.2226	557.2386
Molecular formula	$C_{28}H_{30}O_9$	$C_{27}H_{30}O_7$	$C_{27}H_{32}O_7$	$C_{30}H_{36}O_{10}$
UV λ_{max} nm (ε)(MeOH)	214 (85,459), 253 (10969), 331(11275)	208 (41365), 247 (21234), 331(22884)	210 (29700), 252 (14400) 330 (18800)	213 (39300), 252 (17000) 331 (15200)
IR (KBr) γcm^{-1}	3437, 2924, 1800, 1754, 1704, 1572,1259, 1178	3432, 2926, 1671, 1569, 1514, 1260, 1180	3403, 2938, 1702, 1673, 1569, 1514, 1260, 1182	3430, 2944, 1688, 1610, 1583,1505, 1199, 1126
HPLC (R_t)[a] (minute)	7.6	5.4	6.6	9.0

[a] Column, Cosmosil C_{18} (4.6 x 150 mm); solvent, CH_3CN-H_2O (50:50); flow rate, 0.9 ml/min; UV absorbance at 330 nm.

Table 2. The ^{1}H NMR data of terreulactones A (**1**) , B (**2**), C (**3**) and D (**4**).

	1	2	3	4
1		7.29 (1H, d, 10.2)	1.70 (1H, m) 2.82 (1H, m)	
2		6.10 (1H, d, 10.2)	2.53 (1H, m) 2.93 (1H, m)	5.22 (1H, s)
2-OMe	3.73 (3H, s)			
3-OMe				3.73 (3H, s)
4α-Me	1.21 (3H, s)	1.26 (3H, s)	1.18 (3H, s)	1.27 (3H, s)
4β-Me	1.23 (3H, s)	1.33 (3H, s)	1.22 (3H, s)	1.34 (3H, s)
4α-OH		6.40 (1H, brs)[b]	6.46 (1H, brs)	5.98 (1H, brs)
5-Hα	1.96 (1H, d, 14.0)[a]	1.93 (1H, ddd, 3.6, 4.1, 13.9)	1.88 (1H, ddd, 2.8, 3.4, 14.2)	1.96 (1H, ddd, 3.1, 3.2, 13.9)
-Hβ	2.23 (1H, ddd, 14.0, 13.6, 3.7)	2.00 (1H, ddd, 3.5, 13.8, 13.9)	1.91 (1H, ddd, 3.3, 14.0, 14.2)	1.88 (1H, ddd, 3.3, 13.7, 13.9)
6-Hα	1.75 (1H, d, 12.8)	1.84 (1H, ddd, 3.5, 3.6, 13.4)	1.78 (1H, ddd, 2.8, 3.3, 12.8)	1.82 (1H, ddd, 3.2, 3.3, 13.1)
-Hβ	2.45 (1H, ddd, 13.6, 12.8, 3.7)	2.56 (1H, ddd, 4.1, 13.4, 13.8)	2.60 (1H, ddd, 3.4, 12.8, 14.0)	2.48 (1H, ddd, 3.1, 13.1, 13.7)
6a-Me	1.42 (3H, s)	1.49 (3H, s)	1.42 (3H, s)	1.47 (3H, s)
8	6.73 (1H, s)	6.12 (1H, s)	5.75 (1H, s)	6.40 (1H, s)
12-Hα	2.53 (1H, d, 17.0)	2.78 (1H, d, 16.6)	2.64 (1H, d, 16.9)	3.51 (1H, d, 17.8)
-Hβ	2.97 (1H, d, 17.0)	2.86 (1H, d, 16.6)	2.70 (1H, d, 16.9)	2.87 (1H, d, 17.8)
12a-OH	4.80 (1H, brs)	6.78 (1H, brs)[b]	5.51 (1H, brs)	4.20 (1H, brs)
12b-Me	1.38 (3H, s)	1.44 (3H, s)	1.19 (3H, s)	1.52 (3H, s)
2'	7.81 (1H, d, 8.9)	7.60 (1H, d, 8.8)	7.44 (1H, d, 8.6)	7.00 (1H, s)
3'	7.03 (1H, d, 8.9)	6.91 (1H, d, 8.8)	6.87 (1H, d, 8.6)	
3'-OMe				3.91 (3H, s)
4'-OMe	3.81 (3H, s)	3.87 (3H, s)	3.88 (3H, s)	3.90 (3H, s)
5'	7.03 (1H, d, 8.9)	6.91 (1H, d, 8.8)	6.87 (1H, d, 8.6)	
5'-OMe				3.91 (3H, s)
6'	7.81 (1H, d, 8.9)	7.60 (1H, d, 8.8)	7.44 (1H, d, 8.6)	7.00 (1H, s)

The ^{1}H NMR spectra of **1** and **2 - 4** were recorded at 600 MHz in DMSO-d_6 and CD_3Cl, respectively. [a]Proton resonance multiplicity and coupling constant (J = Hz) are in parenthesis. [b]The signals were detected in DMSO-d_6. The assignments were aided by ^{1}H-^{1}H COSY, DEPT, NOESY, HMQC, and HMBC.

carbon (δ 203.1), one carboxylic carbon (δ 165.2), five sp^2 quaternary carbons and five sp^3 quaternary carbons. These ^{1}H and ^{13}C spectral data indicated the presence of the rings B, C, D and E which are the same as those of terreulactone A. The structure of the ring A was determined by HMBC experiments. The ^{1}H and ^{13}C chemical shift of the *cis*-disubstituted ethene (δ_H 6.10, 1H, d, J=10.2; δ_C 128.0; δ_H 7.29, 1H, d, J=10.2; δ_C 151.5) suggested the presence of α,β-unsaturated carbonyl in the ring A. In the HMBC spectrum (Fig. 2), one olefinic proton at δ 7.29 (H-1) of the *cis*-disubstituted ethene was long-range coupled to the carbonyl carbon at δ 203.1 (C-3) and three sp^3 quaternary carbons at δ 79.6 (C-4a), δ 75.9 (C-12a), and δ 48.0 (C-12b). The other olefinic proton at δ 6.10 (H-2) was long-range coupled to two sp^3 quaternary carbons at δ 51.7 (C-4) and δ 48.0 (C-12b) and a methyl carbon at δ 26.7 (12b-Me). Also, long-range couplings were observed between methyl protons at δ 1.26 (4α-Me) and δ 1.33 (4β-Me) and the carbons at C-3, C-4, and C-4a and between methyl protons at δ 1.44 (12b-Me) and the carbons at C-1, C-4a, C-12b and C-12a. These HMBC data indicated that the ring A should be 6-membered containing α,β-unsaturated carbonyl as shown in Fig. 1. Thus, the planar structure of **1** was determined as shown in Fig. 2.

The relative stereochemistry of **2** was examined by NOESY spectrum in DMSO-d_6 in which two exchangeable protons at δ 6.40 (4a-OH) and δ 6.78 (12a-OH) were detected. As shown in Fig. 2, NOEs were observed among the protons at δ 1.10 (4α-Me), δ 6.40 (4a-OH), δ 6.78 (12a-OH) and δ 2.32 (6-Hβ). Also NOEs among the protons at δ 1.17 (4β-Me), δ 2.1 (5-Hβ), δ 1.44 (6a-Me), δ 2.76 (12-Hβ), and δ 1.36 (12b-Me) were observed. Thus, the relative stereochemistry of C-4a, C-6a, C-12a, and C-12b was determined to be R^*, R^*, S^*, S^*, respectively.

Table 3. The ^{13}C NMR data of terreulactones A (**1**) , B (**2**), C (**3**) and D (**4**).

	1	**2**	**3**	**4**
C-1	208.4 C	151.5 CH	27.6 CH_2	203.9 C
C-2	98.4 C	128.0 CH	33.5 CH_2	97.2 CH
2-OMe	54.8 CH_3			
C-3	166.9 C	203.1 C	216.7 C	177.9 C
3-OMe				56.1 CH_3
C-4	56.8 C	51.7 C	52.9 C	45.9 C
4α-Me	18.9 CH_3	25.0 CH_3	23.6 CH_3	22.7 CH_3
4β-Me	21.3 CH_3	23.2 CH_3	22.5 CH_3	23.2 CH_3
C-4a	92.2 C	79.6 C	79.9 C	78.3 C
C-5	19.9 CH_2	25.4 CH_2	26.9 CH_2	25.1 CH_2
C-6	29.6 CH_2	28.9 CH_2	28.9 CH_2	28.5 CH_2
C-6a	80.8 C	81.4 C	82.0 C	80.0 C
6a-Me	24.5 CH_3	24.4 CH_3	23.7 CH_3	23.9 CH_3
C-7a	162.8 C	164.0 C	164.3 C	162.8 C
C-8	96.7 CH	96.4 CH	96.3 CH	97.5 CH
C-9	157.1 C	158.8 C	158.5 C	158.5 C
C-11	163.5 C	165.2 C	165.6 C	164.4 C
C-11a	97.3 C	96.2 C	95.6 C	97.6 C
C-12	27.8 CH_2	25.8 CH_2	24.7 CH_2	28.1 CH_2
C-12a	74.0 C	75.9 C	76.4 C	76.3 CH_3
C-12b	51.9 C	48.0 C	43.7 C	56.0 C
12b-Me	21.1 CH_3	26.7 CH_3	21.8 CH_3	22.8 CH_3
C-1'	123.4 C	123.5 C	123.1 C	126.8 C
C-2'	126.8 CH	127.2 CH	127.0 CH	102.8 CH
C-3'	114.5 CH	114.2 CH	113.9 CH	153.5 C
3'-OMe				56.3 CH_3
C-4'	161.1 C	161.7 C	161.7 C	140.3 C
4'-OMe	55.4 CH_3	55.4 CH_3	55.4 CH_3	61.0 CH_3
C-5'	114.5 CH	114.2 CH	113.9 CH	153.5 C
5'-OMe				56.3 CH_3
C-6'	123.4 CH	127.2 CH	127.0 CH	102.8 CH

The ^{13}C NMR spectra of **1** and **2** - **4** were recorded at 125 MHz in DMSO-d_6 and CD_3Cl, respectively. The assignments were aided by ^1H-^1H COSY, DEPT, NOESY, HMQC, and HMBC.

Structure of Terreulactone C (**3**)

The molecular formula of **3** was determined to be $C_{27}H_{32}O_7$ on the basis of high resolution ESI-MS [$(M+H)^+$, 469.2220 *m/z* (−0.6 mmu error)] in combination with ^1H and ^{13}C NMR data. The ^1H and ^{13}C NMR spectral data (Table 2) of **3** were similar to those of **2**. The major differences between **2** and **3** in ^1H and ^{13}C NMR spectra with ^1H-^1H COSY and HMQC data were that the signals (δ_H 1.70, 1H, m; δ_H 2.82, 1H, m; δ_C 27.6; δ_H 2.53, 1H, m; δ_H 2.93, 1H, m; δ_C 33.5) corresponding to $-CH_2-CH_2-$ were newly observed in **3** instead of disappearance of the *cis*-disubstituted ethene signals of **2**. In addition, the sp^3 quaternary carbon of C-12b was upfield-shifted from δ 48.0 to δ 43.7 and the carbonyl carbon of C-3 was downfield-shifted from δ 203.1 to δ 216.7 in **3**. These spectral data suggested that the *cis*-disubstituted ethene of **2** could be hydrogenated in **3**. The hydrogenation of the ethene group of **2** in **3** was determined by HMBC experiments (Fig. 3). The methylene protons at δ 1.70 (Hβ-1) and δ 2.82 (Hα-1) were long-range coupled to the carbonyl carbon at δ 216.7 (C-3) and two sp^3 quaternary carbons at δ 79.9 (C-4a) and δ 43.7 (C-12b). The other methylene protons at δ 2.53 (Hβ-2) and δ 2.93 (Hα-2) were long-range coupled to two sp^3 quaternary carbons at δ 52.9 (C-4) and δ 43.7 (C-12b). Also, long-range couplings were observed from the methyl protons at δ 1.19 (12b-Me)

Fig. 2. ^{1}H-^{1}H COSY, HMBC and NOE data of **2**.

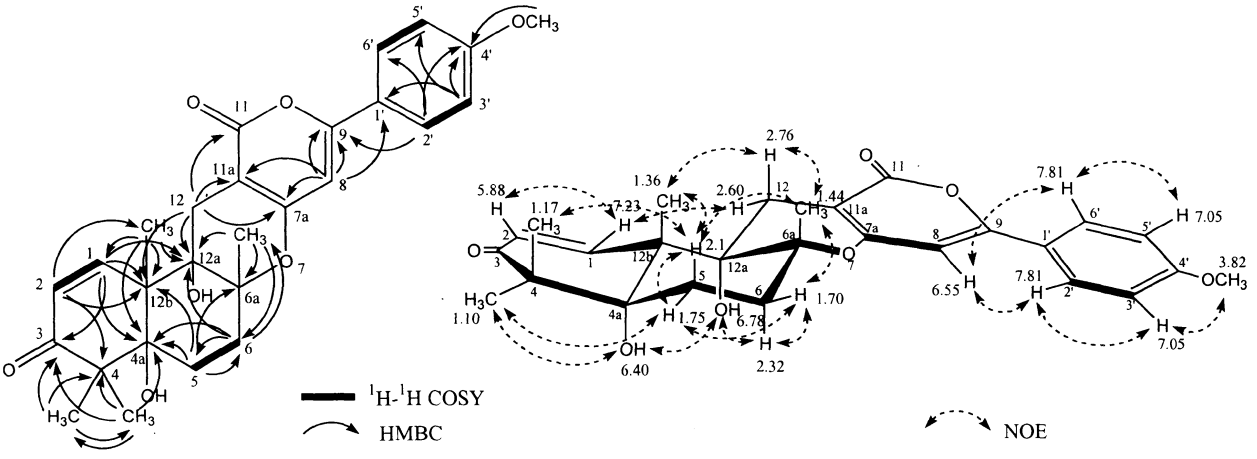
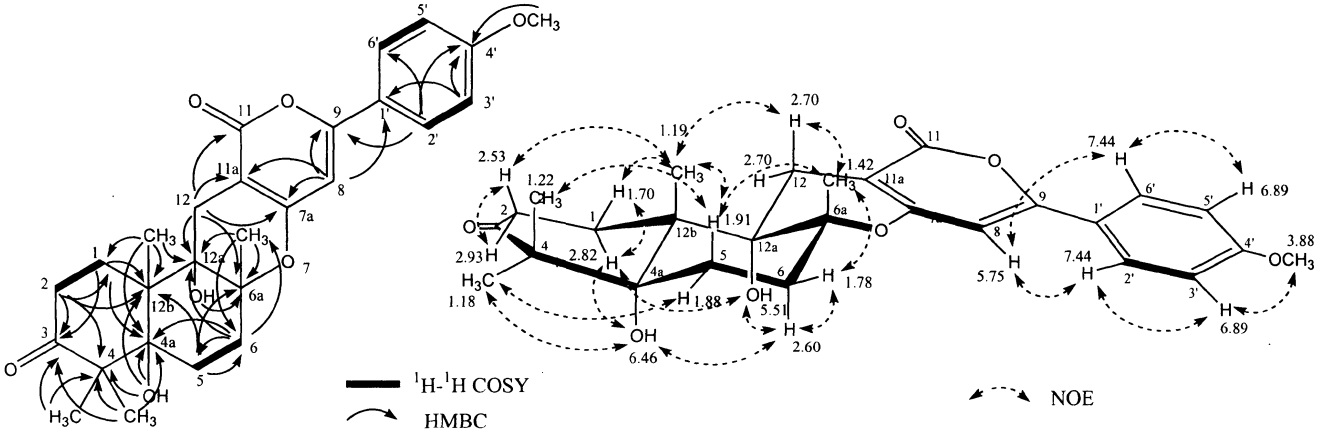


Fig. 3. ^{1}H-^{1}H COSY, HMBC and NOE data of **3**.



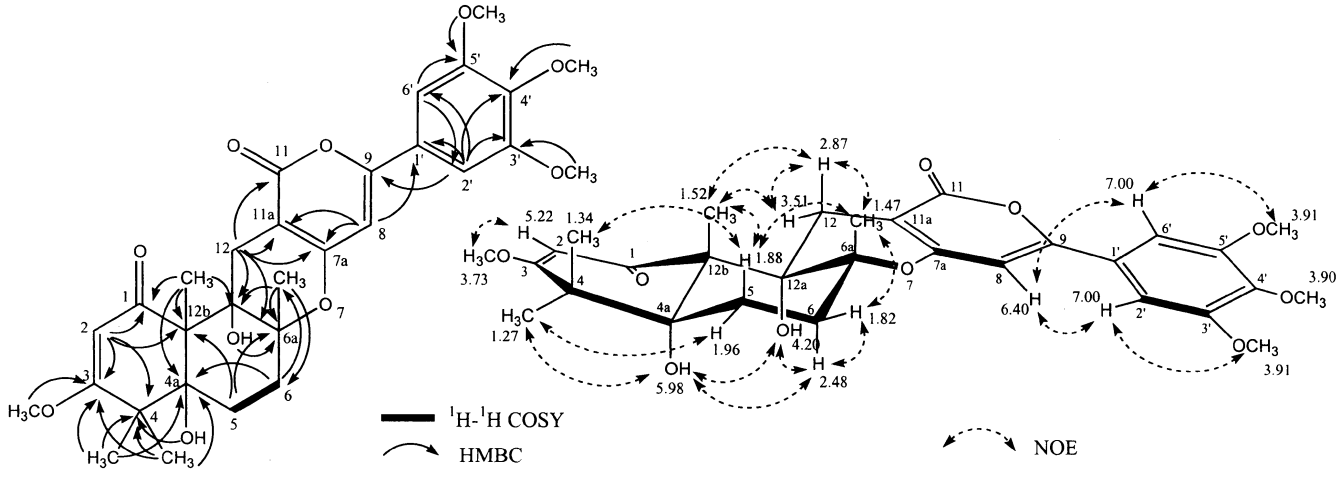
to the methylene carbon at δ 27.6 (C-1) and three sp^3 quaternary carbons at C-4a, C-12b and C-12a. These HMBC data indicated that the *cis*-disubstituted ethene of **2** should be hydrogenated in **3**. The remaining structure was also confirmed by HMBC and ^{1}H-^{1}H COSY spectral data in Fig. 3. Thus, the planar structure of **3** was determined as shown in Fig. 1.

The relative stereochemistry of **2** was examined by NOESY spectrum in $CDCl_3$. As shown in Fig. 3, NOEs were observed among the protons at δ 1.18 (4α-Me), δ 6.46 (4a-OH), δ 5.51 (12a-OH) and δ 2.60 (6-Hβ). Also, NOEs among the protons at 4$_\beta$-Me (δ 1.22), 5-Hβ (δ 1.91), 6a-Me (δ 1.42), 12-Hβ (δ 2.70), and 12b-Me (δ 1.19) were observed. Thus, the relative stereochemistry of C-4a, C-6a, C-12a, and C-12b was determined to be *R**, *R**, *S**, *S**, respectively.

Structure of Terreulactone D (**4**)

The molecular formula of **4** was determined to be $C_{30}H_{36}O_{10}$ on the basis of high resolution ESI-MS [$(M+H)^+$, 557.2387 *m/z* (+0.1 mmu error)] in combination with ^{1}H and ^{13}C NMR data. The ^{1}H and ^{13}C NMR spectral data (Tables 2 and 3) of **4** were quite different in two major parts from those of **3**. The first different part between **3** and **4** in ^{1}H and ^{13}C NMR spectra with ^{1}H-^{1}H COSY and

Fig. 4. ^{1}H-^{1}H COSY, HMBC and NOE data of **4**.



HMQC data was that two equivalent methoxys (δ_H 3.91, 6H, s; δ_C 56.3), two equivalent olefinic methines (δ_H 7.00, 2H, s; δ_C 102.8), and two equivalent sp^2 quaternary carbons (δ 153.5) newly appeared in **4** instead of disappearance of the aromatic methines of **3**, suggesting that the two equivalent methoxys could be substituted to C-2′/C-6′ or C-3′/C-5′ of the benzene ring of **3** in **4**. The substitution position of the two methoxys was determined by HMBC experiments (Fig. 4). The two equivalent olefinic methine protons (δ_H 7.00, 2H, s, 2′-H/6′-H) were long-range coupled to their own carbons at δ 102.8 (C-2′/C-6′) and four sp^2 quaternary carbons at δ 158.5 (C-9), δ 126.8 (C-1′), δ 153.5 (C-3′/C-5′), and δ 140.3 (C-4′). Also, the two equivalent methoxy protons (δ_H 3.91, 6H, s, 3′-OMe/5′-OMe) were long-range coupled to sp^2 quaternary carbons at δ 153.5 (C-3′/C-5′). These HMBC data indicated that the two methoxys should be substituted to C-2′ and C-6′, which was confirmed by NOEs effect between the protons at δ 7.00 (2′-H) and δ 6.40 (H-8) (Fig. 4). The second different part between **3** and **4** in ^{1}H and ^{13}C NMR spectra was that a methoxy (δ_H 3.73, 3H, s; δ_C 56.1), an isolated olefinic methine (δ_H 5.22, 1H, s; δ_C 97.2), and an sp^2 quaternary carbon (δ 177.9) were newly observed in **4** instead of disappearance of $-CH_2-CH_2-$ of **3**, suggesting that $-CH_2-CH_2-$ group of **3** could be replaced with $-CH=C(OCH_3)-$ in **4**. In the HMBC spectrum (Fig. 4), the isolated olefinic methine proton at δ 5.22 (H-2) was long-range coupled to a carbonyl carbon at δ 203.9 (C-1), the sp^2 quaternary carbon at δ 177.9 (C-3), and two sp^3 quaternary carbons at δ 45.9 (C-4) and δ 56.0 (C-12b). Long-range couplings were observed from a methyl protons at δ 1.52 (12b-Me) to the carbonyl carbon at δ 203.9 and three sp^3 quaternary carbons at C-4a, C-12b and C-12a. These data indicated that the carbonyl carbon should located at C-1 in the ring A. Also, the methoxy protons at δ 3.73 (3-OMe) were long-range coupled to the sp^2 quaternary carbon at δ 177.9 (C-3) which was in turn long-range coupled with methyl protons at δ 1.27 (4α-Me) and δ 1.34 (4β-Me). These spectral data indicated that the olefinic methine of $-CH=C(OCH_3)-$ should be connected to the carbonyl carbon of C-1. The remaining rings of B, C and D were also confirmed by HMBC and ^{1}H-^{1}H COSY spectral data in Fig. 4. Thus, the planar structure of **4** was determined as shown in Fig. 1.

The relative stereochemistry of **4** was examined by NOESY spectrum in $CDCl_3$. As shown in Fig. 4, NOEs were observed among the protons at δ 1.27 (4α-Me), δ 5.98 (4a-OH), δ 4.20 (12a-OH) and δ 2.48 (6-Hβ). Also NOEs among the protons at δ 1.34 (4β-Me), δ 1.88 (5-Hβ), δ 1.47 (6a-Me), δ 2.87 (12-Hβ), and δ 1.52 (12b-Me) were observed. Thus, the relative stereochemistry of C-4a, C-6a, C-12a, and C-12b was determined to be *R**, *R**, *S**, *S**, respectively.

Discussion

Like terreulactones A, terreulactones B, C and D are meroterpenoid type compounds that have mixed polyketide-terpenoid structures, which are not common in microbial metabolites. Terreulactones B and C was structurally related to arisugacin C which were isolated

from the mutant strain *Penicillum* sp. FO-4259-11 selected from UV-light treatment of the spores suspension of the parent *Penicillum* sp. FO-4259, an arisugacins A and B producing strain[6]. Terreulactone B was new 1,2-dehydro-12_a-hydroxy derivative of arisugacin C. Terreulactone C was new 12_a-hydroxy derivative of arisugacin C. Terreulactone D was new 3-methoxy derivative of territrem B which was isolated from *Aspergillus terreus*, a territrems A~C producing strain[8]. Interestingly, arisugacins and territrems compounds were not detected in this study. So far a few meroterpenoid such as arisugacins A~H[3~6], territrems A~C[7,8], pyripyropene[10] and oxalicine[11] were isolated from microbial metabolites. The absolute stereochemistry of arisugacin F and territrem B has been reported[12]. The biosynthetic origin of pyripyropene A and territrem B has been studied[13,14]. The benzene ring of territrem B is biosynthesized from shikimate and the nonaromatic moiety is derived *via* the mevalonate pathway. Since the structures of terreulactones A~D including stereochemistry are similar to those of arisugacins and territrems, terreulactones compounds seems to be biogenetically related to arisugacins.

Acknowledgment

We express our thanks to Ms. EUN-HEE KIM at Korea Basic Science Institute for NMR (DMX 600 and DRX 300, Bruker, Karlsruhe, Germany) measurements. This work was supported in part by National Research Laboratory grants (to I.-D. Y.) and the 21C Frontier Microbial Genomics and Application Center Program (to W.-G. K.) from the Korean Ministry of Science and Technology.

References

1) KIM, W.-G.; N.-K. SONG & I.-D. YOO: Quinolactacins A1 and A2, New acetylcholinesterase inhibitors from *Penicillium citrinum*. J. Antibiotics 54: 831~835, 2001
2) CHO, K.-M.; W.-G. KIM, C.-K. LEE & I.-D. YOO: Terreulactones A, B, C and D: Novel acetylcholinesterase inhibitors produced by *Aspergillus terreus*. I. Taxonomy, fermentation, isolation, and biological activities. J. Antibiotics 56: 344~350, 2003
3) KUNO, F.; K. OTAGURO, K. SHIOMI, Y. IWAI & S. ŌMURA: Arisugacins A and B, novel and selective acetylcholinesterase inhibitors from *Penicillium* sp. FO-4259. I. Screening, taxonomy, fermentation, isolation and biological activity. J. Antibiotics 49: 742~747, 1996
4) KUNO, F.; K. SHIOMI, K. OTAGURO, T. SUNAZUKA & S. ŌMURA: Arisugacin A and B, novel and selective acetylcholinesterase inhibitors from *Penicillium* sp. FO-4259. II. Structure elucidation. J. Antibiotics 49: 748~751, 1996
5) OTAGURO, K.; F. KUNO & S. ŌMURA: Arisugacins, selective acetylcholinesterase inhibitors of microbial origin. Pharmacol. Ther. 76: 45~54, 1997
6) OTAGURO, K.; K. SHIOMI, Y. YAMAGUCHI, N. ARAI, T. SUNAZUKA, R. MASUMA, Y. IWAI & S. ŌMURA: Arisugacins C and D, novel acetylcholinesterase inhibitors and their related novel metabolites produced by *Penicillium.* sp. FO-4259. J. Antibiotics 53: 50~57, 2000
7) LING, K. H.; H.-H. LIOU, C.-M. YANG & C.-K. YANG: Territrems, tremorgenic mycotoxin of *Aspergillus terreus*. Appl. Environ. Microbiol. 47: 98~100, 1984
8) PENG, F.-C.: Acetylcholinesterase inhibition by territrem B derivatives. J. Nat. Prod. 58: 857~862, 1995
9) KIM, W.-G.; K.-M. CHO, C.-K. LEE & I.-D. YOO: Terreulactone A, a new meroterpenoid with anti-acetylcholinesterase activity from *Aspergillus terreus*, Tetrahedron Letters 43: 3197~3198, 2002
10) ŌMURA, S.; H. TOMODA, Y. K. KIM & H. NISHIDA: Pyripyropenes, highly potent inhibitors of acyl-CoA cholesterol acyltransferase produced by *Aspergillus fumigatus*. J. Antibiotics 46: 1168~1169, 1993
11) UBILLAS, R.; C. L. BARNES, H. GRACZ, G. E. ROTTINGHAUS & M. S. TEMPESTA: X-ray crystal structure of oxalicine A, a novel alkaloid from *Penicillium cyclopium*. J. Chem. Soc. Chem. Commun. 1618~1619, 1989
12) HANDA, M.; T. SUNAZUKA, K. NAGAI, R. KIMURA, K. OTOGURO, Y. HARIGAYA & S. ŌMURA: Determination of absolute stereochemistries of arisugacin F and territrem B, novel acetylcholinesterase inhibitors. J. Antibiotics 54: 386~391, 2001
13) TOMODA, H.; N. TABATA, Y. NAKATA, H. NISHIDA, T. KANEKO, R. OBATA, T. SUNAZUKA & S. ŌMURA: Biosynthesis of pyripyropene A. J. Org. Chem. 61: 882~886, 1994
14) LING, K. H. & Y. W. PENG: Biosynthesis of territrems by *Aspergillus terreus*. Appl. Environ. Microbiol. 54: 585~587, 1988