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ACETYLCHOLINESTERASE INHIBITION BY TERRITREM B DERIVATIVES

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ABSTRACT.—Five derivatives of territrem B [**2**], a potent acetylcholinesterase inhibitor isolated from a rice culture of *Aspergillus terreus*, were prepared from **2** as well as from its major metabolite, 4β-hydroxymethyl-4β-demethylterritrem B [**4**]. The inhibitory activities of these derivatives against electric eel acetylcholinesterase (E.C. 3.1.1.7) were tested and it was concluded that the enone and the pyrone groups present in **2** may play an important biological role.

Three tremorgenic mycotoxins, territrems A [**1**], B [**2**], and C [**3**] (Figure 1), have been isolated previously from rice cultures of *Aspergillus terreus* (Hyphomycetes) (1–3). These compounds differ only in the substituents on their aromatic moieties (Figure 1) (1–4) and the structure of **2**, the major product, was ultimately determined by X-ray crystallography (5). The ^{1}H- and ^{13}C-nmr data of territrems A–C [**1–3**] and **4**, the major metabolite of **2** produced by treatment with the S-9 fraction of rat liver (6), were recently assigned (7). It has been demonstrated that **2** is 20 times more potent than neostigmine in inhibiting acetylcholinesterase (AChE) activity in human red blood corpuscles (8). Territrems A–C [**1–3**] are also potent inhibitors of insect head AChE, making them comparable to paraoxon (9), and have shown similar inhibitory effects on electric eel AChE. This implies that the aromatic substituents of these compounds have little effect in mediating their anti-AChE activity (8). Therefore, the aim of this investigation was to modify other structural features of **2**, including the enone, pyrone, and C-4 methyl moieties and to compare their relative inhibitory potencies on electric eel AChE.

RESULTS AND DISCUSSION

Compound **5** was prepared from **2** by treatment with *t*-butyl hydroperoxide in the presence of triton B (10). The ^{1}H-nmr spectrum of **5** showed an additional AB system in the aliphatic region, δ 3.52 and 3.29 (J=3.3 Hz), but lacked the pyrone double bond resonances at δ_{H-2} 5.90 and δ_{H-3} 6.29 (J=10.0 Hz) (6), when compared to the ^{1}H-nmr spectrum of **2** (Table 1). The hrfabms of **5** revealed a molecular ion at *m/z* 542.2136, assignable to an elemental formula of $C_{29}H_{34}O_{10}$. These data supported the structure of **5** as the 2,3-epoxy derivative of **2**. The NOESY nmr spectrum revealed the nOe relationship of Me-12b (δ 1.40, s) to H-2 (δ 3.52, d), Me-4β (δ 1.29, s), H-5β (δ 1.81), Me-6a (δ 1.39, s), and H-12β (δ 2.74, d), and established the presence of a 2,3-α-epoxy function in **5**. Thus, the epoxidation occurred at the expected less-hindered site.

Catalytic hydrogenation of **2** with H_2 over Pd/C (11) yielded compounds **6** and **7**. The ^{13}C-nmr signals of C-2 (δ 124.0, d) and C-3 (δ 153.1, d) in **2** (6) were shifted to δ 37.4 (t) and 35.4 (t) in **6**, indicating **6** to be the 2,3-dihydro derivative of **2** (6). The molecular formula of **6**, $C_{29}H_{36}O_9$, deduced from hrfabms, was consistent with this proposed structure. Compound **7** showed a uv absorption maximum at 255 nm, which is different from **2**, where the uv absorption maxima occurred at 331 and 219 nm. The ^{13}C-nmr spectrum of **7** displayed signals for two additional methylenes at δ 33.0 and 34.0, but the signals at δ 158.5 (C-9, s) and 97.4 (C-8, d) in **6** were absent. In addition, the lactone carbon C-11 in **6** shifted from δ 164.9 to 168.0. The hrfabms data of **7** showed a molecular ion at *m/z* 532.2680, suggesting a molecular formula of $C_{29}H_{40}O_9$. These data taken together established **7** as the 2,3,8,9-tetrahydro-9,10-seco derivative of **2**.

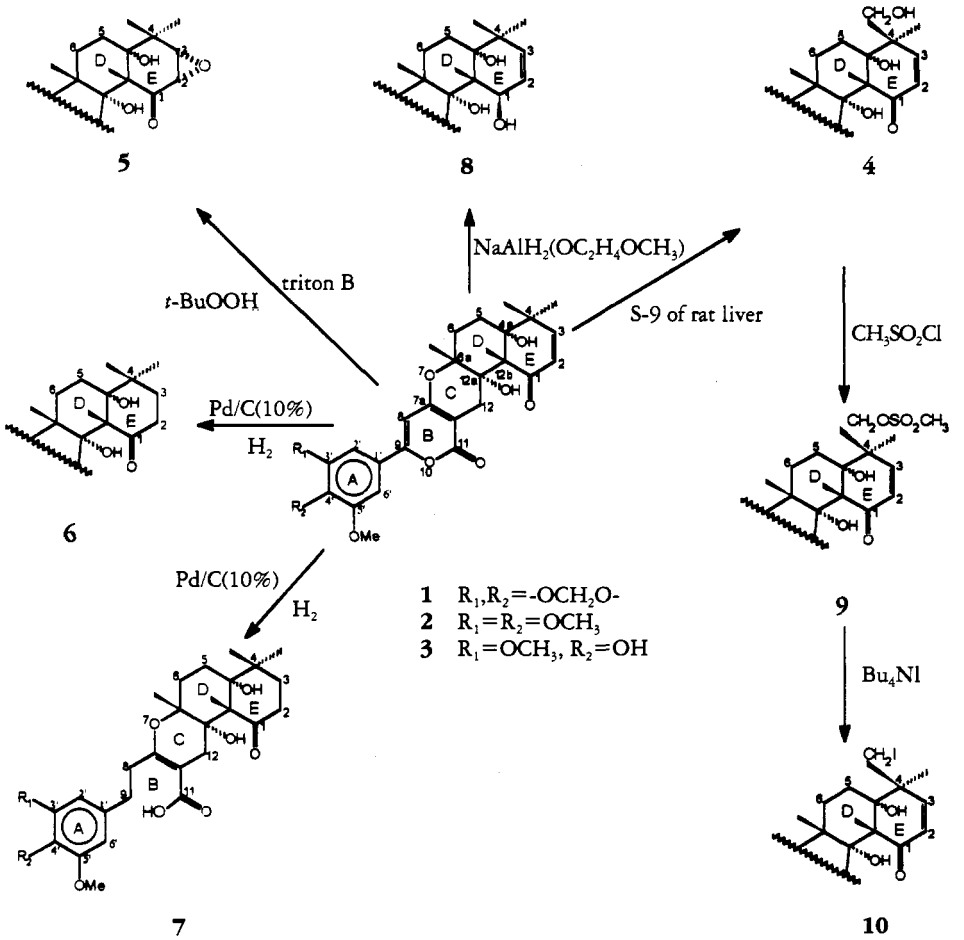

FIGURE 1. Preparation of derivatives of territrem B [**2**].

Compound **8** was prepared from **2** by selective reduction of the enone with *bis*-(2-methoxyethoxy) aluminum hydride (12). In their ^{1}H-nmr spectra, the AB system for H-2 and H-3 in **2** became for **3** part of an ABX system composed of H-1, H-2, and H-3 at δ 5.07, 5.25, and 5.40, respectively, with $J_{2,3}$=10.3 Hz, $J_{1,2}$=2.0 Hz, and $J_{1,3}$=1.6 Hz, as determined from a COSY-45 nmr spectrum. The ^{13}C-nmr spectrum of **8** showed evidence of a hydroxylated methine carbon (C-1) at δ 68.7 (d) while a signal for a carbonyl carbon of an enone (δ 202.1 in **2**) was absent. The molecular formula, $C_{29}H_{36}O_9$, as deduced from fabms, was consistent with **8** being the 1-dihydro derivative of **2**. The NOESY nmr spectrum revealed nOes of Me-12b (δ 1.23) to Me-4β (δ 1.11, s), H-5β (δ 1.98, ddd, J=3.5, 13.3, and 14.3 Hz), Me-6a (δ 1.47, s) and H-12β (δ 2.74, d, J=18.0 Hz), thereby helping to establish that H-1 is α-oriented and **8** is therefore the (1*R*)-1-dihydro derivative of **2**.

Treatment of **4** with mesyl chloride in pyridine (13) yielded **9**. The ^{1}H-nmr spectrum of **9** showed a characteristic methyl signal of the mesyl group at δ 3.08 and the signals for CH_2-4β shifted downfield to δ 4.28 and 4.48 (J=10.0 Hz) from δ 3.97 and 3.62 (J=9.0 Hz) compared with analogous data for **4**. Its ^{13}C-nmr spectrum also revealed an additional methyl signal at δ 37.7 (q) for the methyl carbon of the mesyl group. The iodinated compound **10** was prepared from **9** by reaction with tetra-*n*-

TABLE 1. ^{1}H-Nmr Data of Territrem B [**2**] Derivatives (δ in ppm, *J* in Hz).[a]

Proton	Compound					
	5	**6**	**7**	**8**	**9**	**10**
H-1				5.27 m 5.25 dd (10.0, 12.0)		
H-2	3.52 d (3.3)			5.40 dd (10.0, 12.0)	5.94 d (10.4)	5.87 d (10.4)
H-3	3.52 s (3.3)			1.87 dt (14.3, 3.5, 3.5)	6.35 d (10.0) 1.82 dt (13.8, 3.3, 3.3)	6.50 d (10.4)
H-5α	1.90 s			1.82 dt (14.3, 13.5, 3.5)	1.97 dt (13.8, 13.8, 3.3)	1.88 m
H-5β	1.81 m			2.42 dt (13.3, 13.5, 3.5)	2.46 dt (13.8, 13.8, 3.3)	1.92 m
H-6α	2.41 m			1.69 dt (13.3, 3.5, 3.5)	1.79 dt (13.8, 3.3, 3.30)	2.45 m
H-6β		1.90 m				1.80 m
H-8	6.33 s	6.34 s		6.58 s	6.33 s	6.33 s
H-12α	3.47 d (17.4)	3.24 d (17.6)		3.15 d (18.0)	3.39 d (17.8)	3.40 d (18.0)
H-12β	2.47 d (17.4)	2.79 d (17.6)		2.74 d (18.0)	2.83 d (17.8)	2.82 d (18.0)
Me-4α	1.33 s	1.24 s	1.19 s	1.09 s	1.54 s	1.50 s
Me-4β	1.29 s	1.05 s	1.04 s	1.11 s		
CH_2-4β					4.28 d (9.8) 4.48 d (9.8)	3.24 d (10.0) 3.74 d (10.0)
-OSO_2CH_3					3.08 s	
Me-6a	1.40 s	1.48 s	1.39 s	1.47 s	1.43 s	1.44 s
Me-12b	1.39 s	1.41 s	1.24 s	1.23 s	1.31 s	1.31 s
H-2′,6′	6.97 s	6.97 s	6.47 s	7.17 s	6.96 s	6.98 s
OCH_3-4′	3.86 s	3.86 s	3.79 s	3.78 s	3.88 s	3.88 s
OCH_3-3′,5′	3.88 s	3.88 s	3.81 s	3.92 s	3.87 s	3.87 s

[a]Compounds **6** and **7** were measured in 80 MHz and **5**, **8–10** were measured in 400 MHz; except for **8** in Me_2CO-d_6, all compounds were recorded in $CDCl_3$.

butylammonium iodide in refluxing Me_2CO (13). The hrfabms spectrum of **10** showed a $[M+H]^+$ at *m/z* 653.1216 and is consistent with the calculated value for the elemental formula, $C_{29}H_{35}O_9I$. Its ^{1}H-nmr spectrum displayed the iodomethylene protons at δ 3.74 and 3.24 (J=10.0 Hz). The ^{13}C-nmr spectrum also revealed the characteristic upfield shifted signal (δ 71.0 to δ 13.7) for CH_2-4β caused by the replacement of the mesyl group with iodide. These data are consistent with **10** being the 4β-iodomethyl-4β-demethyl derivative of **2**.

The inhibitory activity of the above-described territrem B [**2**] derivatives on electric eel AChE was evaluated by the colorimetric method (14). The results (Table 2) indicated that either saturation of the C-2 double bond or reduction of C-1 carbonyl of **2** causes a loss of more than 90% of the anti-AChE activity. Epoxidation of the C-2 double bond or conversion of 4β-CH_2OH into the more hydrophobic and bulky 4β-CH_2I has little effect on anti-AChE activity. In addition, it was found that the intact pyrone moiety may be essential to anti-AChE activity since **7** is inactive. This study indicates that both the enone and the pyrone moieties of territrem B [**2**] play important roles in inhibitory activity on electric eel AChE.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were measured on a hot-stage melting point apparatus (Shimatzu Seisakusho Ltd.) and are uncorrected. Ir spectra were recorded using a Perkin-Elmer 1760X or P839 infrared Fourier transform spectrophotometer. Mass spectra were recorded using a JEOL JMS-HX 110 mass spectrometer. ^{1}H- and ^{13}C-nmr spectra were recorded in $CDCl_3$ or Me_2CO-d_6, on a Bruker AC 80 or

TABLE 2. Inhibition of Electric Eel Acetylcholinesterase by Territrem B [2] Derivatives.

Compound	In vitro I_{50} (M)[a]
2	2.6×10^{-7}
5	1.7×10^{-7}
6	2.2×10^{-6}
7	N.I.[b]
8	7.9×10^{-5}
10	2.9×10^{-7}

[a]I_{50} values were calculated by probit analysis from responses obtained from eight doses of inhibitor, each differing by an order of magnitude.
[b]N.I.=not inhibitory.

a Bruker AMX 400 spectrometer using solvent peaks as the reference standard. NOESY spectra were recorded using Bruker's standard pulse program.

EXTRACTION AND ISOLATION.—Compound **2** was isolated from a rice culture of *Aspergillus terreus* according to previously published procedures (1–3).

PREPARATION OF **5**.—A mixture of **2** (96 mg, 0.18 mM), *t*-BuOOH (100 ml, 1 mM), triton B (10 ml) and C_6H_6 (100 ml) was stirred at room temperature for 10 min (10). The reaction mixture was washed with brine solution (100 ml×3), dried over Na_2SO_4, and evaporated to give 97 mg of residue, from which **5** (32.8 mg, 34.2%) was separated via prep. tlc [C_6H_6-EtOAc (1:1)].

2,3-Epoxyterritrem B [**5**].—Mp 250–252° (from MeOH); ir (KBr) ν max 3400 (OH), 2941–2844 (CH, aromatic and aliphatic), 1718 (C=O, ester), 1688 (C=O, ketone), 1641, 1586, 1505, 1129 (C-O-C, ether) cm^{-1}; ^{1}H-nmr data, see Table 1; ^{13}C nmr ($CDCl_3$, 100.61 MHz) δ 202.2 (s, C-1), 54.5 (d, C-2), 63.2 (d, C-3), 38.1 (s, C-4), 79.2 (s, C-4a), 25.5 (t, C-5), 28.0 (t, C-6), 80.2 (s, C-6a), 162.5 (s, C-7a), 97.7 (d, C-8), 158.3 (s, C-9), 164.2 (s, C-11), 97.9 (s, C-11a), 27.5 (t, C-12), 75.4 (s, C-12a), 59.0 (s, C-12b), 25.5, 23.7, 23.6 (q, Me-4α, Me-4β, Me-6a), 20.1 (q, Me-12b), 126.9 (s, C-1′), 102.8 (d, C-2′), 153.5 (s, C-3′), 140.0 (s, C-4′), 153.5 (s, C-5′), 102.8 (d, C-6′), 56.3 (q, OMe-3′), 61.0 (q, OMe-4′), 56.3 (q, OMe-5′); fabms *m/z* $[M+Na]^+$ 565 (8), $[M+H]^+$ 543 (56), $[M]^+$ 542 (40), 524 (95), 520 (39), 507 (66), 480 (37), 412 (24), 307 (38), 292 (38), 291 (21), 278 (43), 210 (100), 204 (23), 195 (99); hrfabms *m/z* $[M]^+$ 542.2136 (calcd for $C_{29}H_{34}O_{10}$, 542.2152).

PREPARATION OF **6** AND **7**.—Catalytic hydrogenation of **2** (97 mg) in MeOH (80 ml) with H_2 (1 atmosphere over Pd/C) (10%) (60 mg) at room temperature for 10 h (11), yielded a residue (105 mg) after workup. The products **6** (82.4 mg, 82.9%) and **7** (3.1 mg, 3.1%) were separated from the residue via prep. tlc [C_6H_6-EtOAc (1:1)] and purified by ODS hplc with elution using MeCN-H_2O (6:4).

2,3-Dihydroterritrem B [**6**].—Mp 248–250° ($CHCl_3$); ir (KBr) ν max 3388 (OH), 2942 (CH, aromatic and aliphatic), 1708 (C=O, ester), 1685 (C=O, ketone), 1641, 1585, 1505, 1128 (C-O-C, ether) cm^{-1}; ^{1}H-nmr data, see Table 1; ^{13}C nmr ($CDCl_3$, 100.61 MHz) δ 215.6 (s, C-1), 37.4 (t, C-2), 35.4 (t, C-3), 38.7 (s, C-4), 80.0 (s, C-4_a), 27.1 (t, C-5), 29.8 (t, C-6), 81.7 (s, C-6_a), 163.0 (s, C-7a), 97.4 (d, C-8), 158.5 (s, C-9), 164.9 (s, C-11), 97.4 (s, C-11_a), 27.0 (t, C-12), 77.0 (s, C-12_a), 57.0 (s, C-12_b), 26.4, 25.0 (q, Me×4), 24.0 (q, Me-6a), 19.5 (q, Me-12b), 126.8 (s, C-1′), 103.2 (d, C-2′), 153.6 (s, C-3′), 141.1 (s, C-4′), 153.6 (s, C-5′), 103.2 (d, C-6′), 56.4 (q, OMe-3′), 60.9 (q, OMe-4′), 56.4 (q, OMe-5′); eims (70 eV) *m/z* 529 (35), $[M]^+$ 528 (100), 510 (34), 495 (3), 359 (2), 345 (5), 291 (5), 210 (3), 191 (3); hrfabms *m/z* $[M]^+$ 528.2360 (calcd for $C_{29}H_{36}O_9$, 528.2359).

2,3,8,9-Tetrahydro-9,10-seco-territrem B [**7**].—Mp 77–79° ($CHCl_3$); uv (MeOH) λ max (log ε) 255 (0.8) nm; ir ν max (KBr) 3375 (OH), 2940–2839 (CH, aromatic and aliphatic), 1693 (C=O, ketone), 1679 (C=O, acid), 1591, 1549, 1510, 1240, 1129 (C-O-C, ether) cm^{-1}; ^{1}H-nmr data, see Table 1; ^{13}C nmr ($CDCl_3$, 20.13 MHz) δ 215.6 (s, C-1), 35.4 (t, C-2), 37.4 (t, C-3), 38.5 (s, C-4), 78.3 (s, C-4a), 25.8 (t, C-5), 29.7 (t, C-6), 81.4 (s, C-6a), 158.1 (s, C-7a), 33.0 (t, C-8), 34.0 (t, C-9), 168.0 (s, COOH-11), 109.1 (s, C-11a), 29.9 (t, C-12), 76.3 (s, C-12a), 57.9 (s, C-12b), 27.0, 26.5 (q, Me×4), 23.6 (q, Me-6a), 19.1 (q, Me-12a), 136.5 (s, C-1′), 105.8 (d, C-2′), 153.2 (s, C-3′), 137.2 (s, C-4′), 153.2 (s, C-5′), 105.8 (d, C-6′), 56.0 (q, OMe-3′), 60.6 (q, OMe-4′), 56.0 (q, OMe-5′); fabms *m/z* $[M+Na]^+$ 555 (21), $[M+H]^+$ 533 (30),

$[M]^+$ 532 (19), 486 (61), 488 (100), 470 (35), 452 (66), 318 (6), 191 (18), 181 (73); hrfabms *m/z* $[M]^+$ 532.2680 (calcd for $C_{29}H_{40}O_9$, 532.2672).

PREPARATION OF **8**.—A reaction mixture of **2** (100 mg, 0.19 mM) and $NaAlH_2(OC_2H_4OCH_3)_2$ (100 mg) in C_6H_6 (100 ml) was stirred at 0° for 5.5 h, then stopped with 0.1 N HCl (100 ml) (12). The C_6H_6 layer was washed with H_2O (100 ml×3), dried over Na_2SO_4, and then evaporated under reduced pressure to give 105 mg of an amorphous powder which yielded **8** (33.7 mg, 37%) after purification by prep. tlc [C_6H_6-EtOAc (1:1)].

1-Dihydroterritrem B [**8**].—Mp 309.5–310° (MeOH); ir (KBr) ν max 3396 (OH), 2942–2841 (CH, aromatic and aliphatic), 1685 (C=O, ketone), 1641, 1585, 1505, 1127 (C-O-C, ether) cm^{-1}; ^{1}H-nmr data, see Table 1; ^{13}C nmr (Me_2CO-d_6, 20.13 MHz) δ 68.7 (d, C-1), 129.1 (t, C-2), 135.4 (t, C-3), 42.0 (s, C-4), 80.2 (s, C-4a), 26.9 (t, C-5), 30.2 (t, C-6), 82.5 (s, C-6a), 163.4 (s, C-7a), 98.7 (d, C-8), 158.3 (s, C-9), 163.4 (s, C-11), 99.7 (s, C-11a), 29.0 (t, C-12), 77.0 (s, C-12a), 49.2 (s, C-12b), 26.3, 25.5 (q, Me×4), 24.2 (q, Me-6a), 17.4 (q, Me-12b), 128.1 (s, C-1′), 103.7 (d, C-2′), 154.7 (s, C-3′), 141.3 (s, C-4′), 154.7 (s, C-5′), 103.7 (d, C-6′), 56.7 (q, OMe-3′), 60.7 (q, OMe-4′), 56.7 (q, OMe-5′); eims (70 eV) *m/z* 529 (36), $[M]^+$ 528 (100), 514 (23), 496 (12), 361 (12), 319 (2), 291 (4), 210 (33), 195 (27); hrfabms *m/z* $[M]^+$ 528.2352 (calcd for $C_{29}H_{36}O_9$, 528.2359).

PREPARATION OF **9**.—The reaction mixture of **4** (6.5 mg, 1.2 mM) and mesyl chloride (0.2 ml) in dried pyridine (1 ml) was stirred 30 min at 0° and 1 h at room temperature (13). The reaction was stopped by adding pyridine-H_2O (2:1, 4 ml) and the mixture was extracted with Et_2O (10 ml×3). The organic layer was evaporated to give 8.2 mg of amorphous residue which yielded **9** (6.9 mg, 94.5%) via prep. tlc purification [C_6H_6-EtOAc (1:1)].

Mesylate of **4** [**9**].—Mp 203–204° (from $CHCl_3$); ^{1}H-nmr data, see Table 1; ^{13}C nmr ($CDCl_3$, 100.61 MHz) δ 203.1 (s, C-1), 125.8 (d, C-2), 146.5 (d, C-3), 46.0 (s, C-4), 78.5 (s, C-4a), 25.9 (t, C-5), 28.2 (t, C-6), 79.6 (s, C-6a), 162.8 (s, C-7a), 97.5 (d, C-8), 158.7 (s, C-9), 164.2 (s, C-11), 97.0 (q, Me-4α), 71.0 (t, CH_2-4β), 37.7 (q, OSO_2CH_3), 23.8 (q, Me-6a), 21.4 (q, Me-12b), 126.6 (s, C-1), 102.8 (d, C-2′), 153.5 (s, C-3′), 140.4 (s, C-4′), 153.5 (s, C-5′), 102.8 (d, C-6′), 56.3 (q, OMe-3′), 61.0 (q, OMe-4′), 56.3 (q, OMe-5′); fabms *m/z* $[M+Na]^+$ 644 (13), $[M+H]^+$ 621 (42), 620 (6), 291 (8), 289 (11), 217 (41), 195 (34), 181 (41), 147 (25), 109 (23), 91 (100).

PREPARATION OF **10**.—The reaction mixture of **9** (6.9 mg, 0.01 mM), $Bu_4N^+I^-$ (21.7 mg, 0.06 mM) in dried Me_2CO (1 ml) was refluxed at 97° in a degassed sealed tube for 58 h (13). The reaction mixture was evaporated to dryness using N_2 gas to give 9 mg of an amorphous powder which yielded **10** (3.3 mg, 44.5%) via prep. tlc separation [C_6H_6-EtOAc (1:1)].

4β-Iodomethyl-4β-demethyl territrem B [**10**].—Mp 218–219° ($CHCl_3$); ir (KBr) ν max 3443 (OH), 2941 (CH, aromatic and aliphatic), 1677 (C=O, ketone), 1580, 1126 (C-O-C, ether); ^{1}H-nmr data, see Table 1; ^{13}C nmr ($CDCl_3$, 100.61 MHz) δ 203.3 (s, C-1), 124.6 (d, C-2), 152.0 (d, C-3), 43.9 (s, C-4), 79.7 (s, C-4a), 26.1 (t, C-5), 28.3 (t, C-6), 79.7 (t, C-6a), 162.8 (s, C-7a), 97.5 (d, C-8), 158.6 (s, C-9), 164.2 (s, C-11), 97.0 (s, C-11a), 27.9 (t, C-12), 75.9 (s, C-12a), 56.1 (s, C-12b), 21.8 (q, Me-4α), 13.7 (t, CH_2-4β), 23.8 (q, Me-6a), 22.8 (q, Me-12b), 126.7 (s, C-1′), 102.8 (d, C-2′), 153.5 (s, C-3′), 140.4 (s, C-4′), 153.5 (s, C-5′), 102.8 (d, C-6′), 56.3 (q, OMe-3′), 61.0 (q, OMe-4′), 56.3 (q, OMe-5′); fabms *m/z* $[M+Na]^+$ 657 (4), $[M+H]^+$ 653 (100), 652 (13), 528 (14), 147 (11), 91 (32); hrfabms *m/z* $[M+H]^+$ 653.1216 (calcd for $C_{29}H_{34}O_9I$, 653.1248).

ACETYLCHOLINESTERASE ASSAYS.—The acetylcholinesterase activity was determined by the method of Ellman *et al.* (14). In a usual run, aliquots of 20–40 μl of the working enzyme solution or of the inhibited specimen were added to 1 ml of the assay system containing 4.8×10^{-4} M acetylcholine and 3.2×10^{-4}M DTNB in a 0.1 M phosphate buffer, pH 8.0. The initial rate of substrate hydrolysis was determined at 412 nm using a Beckman spectrophotometer at room temperature. The mole of activity per site of acetylcholinesterase was calculated as mole of substrate hydrolyzed per min per site, divided by 5.9×10^5 according to Gordon *et al.* (15).

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