Notes

TERRECYCLIC ACID A, A NEW ANTIBIOTIC FROM *ASPERGILLUS TERREUS* IV. ABSOLUTE STEREOCHEMISTRY OF TERRECYCLIC ACID A

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Terrecyclic acid A (**I**), $C_{15}H_{20}O_3$, is a sesquiterpene antibiotic from *Aspergillus terreus* Thom No. 14[1,2] and has the same novel carbon skeleton as that of quadrone (**II**), an antitumor substance from *A. terreus*.[3,4] *A. terreus* No. 14 also produced several sesquiterpenes structurally related to **I**.[5,6] The carbon skeleton of such substances is very unique from the viewpoint of sesquiterpene biosynthesis and the studies on the biosynthesis of **I** and **II** have already been reported by our group[7,8] and two other groups.[9,10]

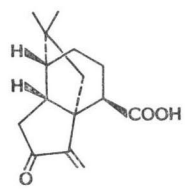
The relative stereochemistry of **I** and **II** were first reported by RANIERI and CALTON[4]; this received support from our studies by the nuclear Overhauser effect (NOE) experiment[5] to lead to stereostructure **I** with a conformation as depicted in Fig. 1 or its mirror image.

Recently, study of the absolute stereochemistry of **I** and **II** by organic synthesis has been reported.[11,12] We describe here a determination of the absolute stereochemistry of **I** by means of the CD allylic benzoate method.[13]

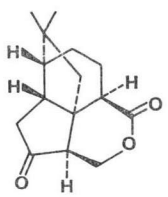
To elucidate the absolute stereostructure by the CD exciton chirality method **I** was transformed to a derivative suitable for the method. **I** was reduced with sodium borohydride to give a crystalline substance (**III**), which has already been characterized except for the stereochemistry.[5] Treatment of **III** with ethereal diazomethane yielded the methyl ester (**IV**), mp 134~135.5°C, $C_{16}H_{24}O_3$, as a crystalline compound. The 400 MHz ^1H NMR spectrum of **IV** is shown in Fig. 2 and the assignments of protons on the basis of their chemical shifts, coupling constants and the comparison with the ^1H NMR spectra of **III** and other related substances: 2-H δ 2.57 (dd), one of 3-H_2 δ 2.19 (dt), 4-H δ 4.50 (m), 4-OH δ 1.59 (br s). The relative stereochemistry of the asymmetric carbon C-4 with the hydroxyl group was determined by the NOE method. In the ^1H NMR measurement of **IV**, on irradiation at δ 4.50, the signals at δ 2.57 and at δ 2.19 were enhanced. Accordingly, the hydroxyl group in **IV** is situated on the same side as the dimethyl-ethyleno bridge as depicted in Fig. 1.

Treating **IV** with benzoyl chloride in pyridine the benzoate (**V**) was obtained. The CD spectrum of **V** showed a negative Cotton effect ($\Delta\varepsilon$ −5.6) at 226 nm in ethanol. This value indicated that the relationship between the

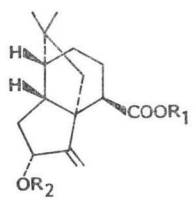
Fig. 1. Structures of I, II, III, IV and V.



I



II



III $R_1=H$, $R_2=H$
IV $R_1=CH_3$, $R_2=H$
V $R_1=CH_3$, $R_2=COC_6H_5$

Fig. 2. ^{1}H NMR spectrum (A) and differential NOE spectrum irradiated at δ 4.50 (B) of **IV** (400 MHz, $CDCl_3$).

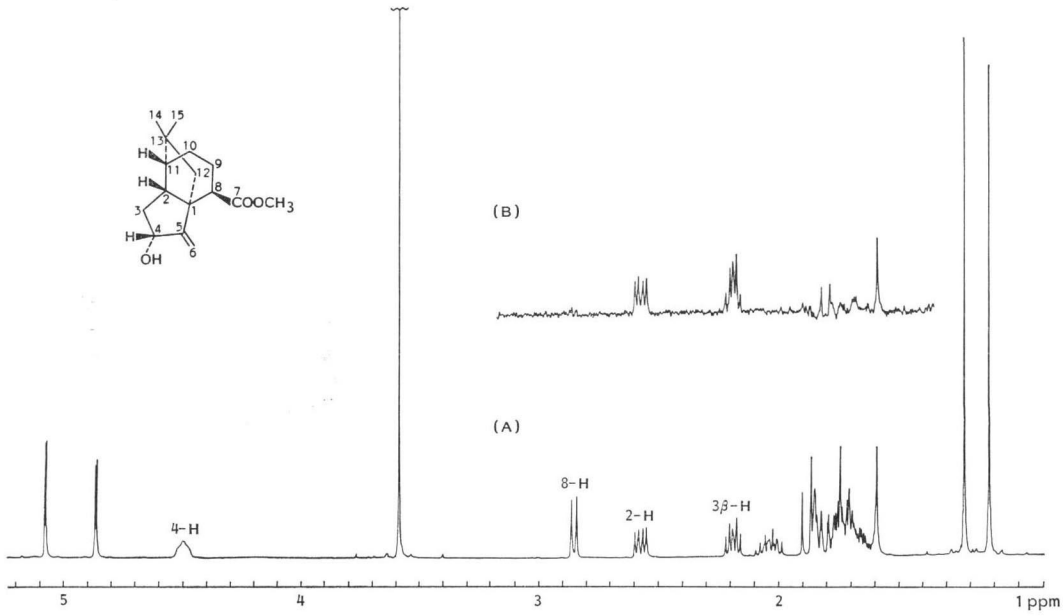
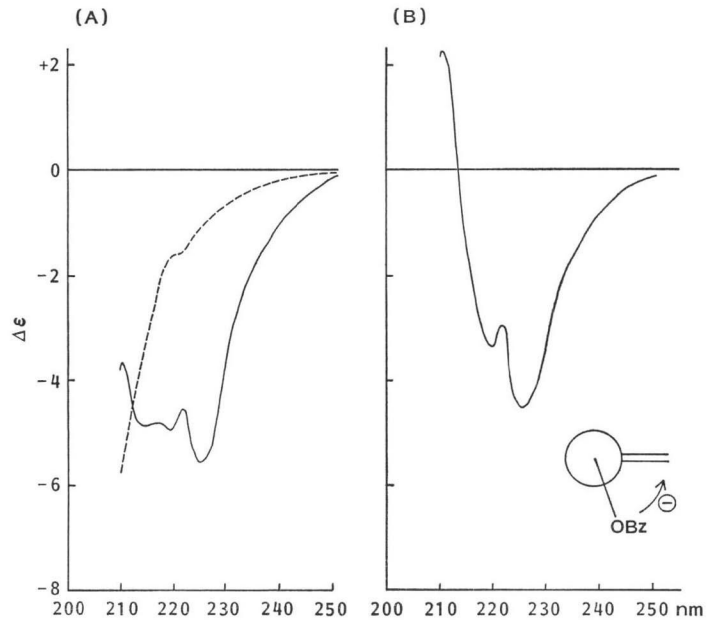


Fig. 3.
(A) CD spectra of **IV** (------) and **V** (——), (EtOH).
(B) CD difference spectrum (**V** minus **IV**), (EtOH).



exocyclic double bond and the benzoate chromophore was anti-clockwise.[13] Therefore, the absolute stereostructure of **I** was established to be, as shown in Fig. 1, in accordance with the results obtained by the synthetic method.[11,12]

Experimental

Melting points were determined on a microscope hot plate (Yanagimoto Co.) and are uncorrected. IR spectra were measured with

Jasco IRA-2 and Hitachi 260-30 infrared spectrometers and the CD spectra were recorded on a Jasco model J-20. The 400 MHz ^{1}H NMR, 90 MHz ^{1}H NMR and 25 MHz ^{13}C NMR spectra were measured with Jeol JNM-GX-400, Varian EM-390 and Jeol JMN-FX-100 spectrometers, respectively. Mass spectra were obtained with a Jeol JMS-D-300 mass spectrometer and the UV spectrum was recorded on a Hitachi 340 spectrometer.

Reduction of **I** with Sodium Borohydride

Terrecyclic acid A (**I**) (50 mg) was treated with sodium borohydride (20 mg) in 2-PrOH (5 ml) at room temperature for 30 minutes. Water (5 ml) was then added. After standing for 30 minutes, the reaction mixture was concentrated *in vacuo* and the residue was extracted after acidification (pH 3) with EtOAc. The extract gave the crude **III**, which was recrystallized from EtOAc to afford needles (40 mg): mp 187°C; MS M^+ *m/z* 250.1562 (Calcd for $C_{15}H_{22}O_3$ 250.1567), *m/z* (relative abundance) 250 (M^+, 1.2), 235 (1.2), 232 (0.4), 193 (100), 149 (9.2), 147 (9.7); IR_{max}^{KBr} cm^{-1} 3420 (OH), 3360 (OH), 2950 (CH), 1730 (sh), 1690 (C=O), 1650 (sh, C=C), 1450 (CH), 1210 (C–O), 1080 (C–O), 880 (=CH); ^{1}H NMR (400 MHz, pyridine-d_5, ppm) δ 1.05 (3H, s), 1.13 (3H, s), 1.71 (1H, m), 1.73 (1H, d), 1.79 (1H, br t), 1.82 (1H, m), 1.96 (1H, d), 2.07 (1H, d), 2.08 (1H, m), 2.18 (1H, ddd), 2.33 (1H, ddd), 3.05 (1H, dd), 3.17 (1H, d), 5.18 (1H, m), 5.22 (1H, br s), 5.64 (1H, br s); ^{13}C NMR (25 MHz, pyridine-d_5, ppm) δ 23.37 (t), 27.32 (q), 29.75 (t), 35.10 (q), 39.31 (s), 39.31 (t), 48.00 (d), 49.17 (d), 50.14 (d), 55.40 (t), 55.99 (s), 76.75 (d), 104.48 (t), 163.57 (s), 177.61 (s).

Methyl Ester (**IV**)

The hydroxyl acid (**III**) (65 mg) was treated with large excess of ethereal diazomethane and the methyl ester of **III** was obtained in almost quantitative yield (68 mg): mp 134~135.5°C; MS M^+ *m/z* 264.1761 (Calcd for $C_{16}H_{24}O_3$ 264.1726), *m/z* (relative abundance) 264 (M^+, 4.2), 249 (2.5), 208 (15), 207 (100), 205 (10), 149 (14), 147 (31); IR_{max}^{KBr} cm^{-1} 3450 (OH), 2950 (CH), 1720 (C=O), 1640 (C=C), 1455 (CH), 1430 (CH), 1200 (C–O), 1170 (C–O), 1090 (C–O), 890 (=CH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.12 (3H, s), 1.23 (3H, s), 1.59 (1H, s), 1.6~1.82 (4H, m), 1.72 (1H, d), 1.85 (1H, br s), 1.88 (1H, d), 2.04 (1H, ddd), 2.19 (1H, ddd), 2.57 (1H, dd), 2.85 (1H, d), 3.59 (3H, s), 4.50 (1H, br s), 4.86 (1H, d), 5.08 (1H, d); ^{13}C NMR (25 MHz, $CDCl_3$, ppm) δ 22.54 (t), 27.30 (q), 29.23 (t), 35.10 (q), 38.71 (t), 39.44 (s), 47.75 (d), 48.78 (d), 49.51 (d), 51.09 (q), 55.45 (t), 55.55 (s), 76.60 (d), 105.37 (t), 161.49 (s), 175.7 1(s); CD (EtOH) λ_{ext} 222 nm ($\Delta\varepsilon$ −1.6).

Benzoate (**V**)

A mixture of **IV** (10 mg) and benzoyl chloride (*ca.* 0.1 ml) in pyridine (2 ml) was stirred overnight at room temperature. After addition of crushed ice-water, the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was worked up as usual to afford a crude benzoate, which was purified by silica gel (2.5 g) column chromatography. Elution with benzene afforded a crystalline compound (**V**; 9 mg): mp 78.5~79.5°C; MS M^+ *m/z* 368.2025 (Calcd for $C_{23}H_{28}O_4$ 368.1987), *m/z* (relative abundance) 368 (M^+, 5), 336 (3), 311 (6), 246 (16), 105 (100); IR_{max}^{KBr} cm^{-1} 2960 (CH), 1735 (C=O), 1720 (C=O), 1640 (C=C), 1600 (benzene ring), 1455 (CH), 1440 (CH), 1280 (C–O), 1170 (C–O), 1120 (C–O), 905 (=CH); ^{1}H NMR (90 MHz, $CDCl_3$, ppm) δ 1.15 (3H, s), 1.26 (3H, s), 1.5~3.0 (11H, m), 3.63 (3H, s), 4.90 (1H, d), 5.07 (1H, d), 5.72 (1H, t-like), *ca.* 7.5 (3H, m), 8.07 (2H, m); UV_{max}^{EtOH} (ε) 229.5 (13,400); CD (EtOH) λ_{ext} 226 nm ($\Delta\varepsilon$ −5.6).

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