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Terpenoids. XXI.(1) The Structure and Stereochemistry of Isodotricin, a Diterpenoid of *Isodon trichocarpus* and *I. japonicus*

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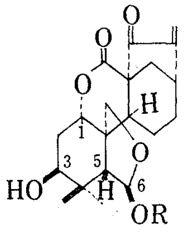
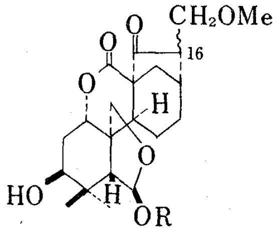
The structure of isodotricin, a diterpenoid of *Isodon trichocarpus* and *I. japonicus*, was determined to be **4** by a chemical conversion from enmein (**1**). The more detailed investigation on the stereochemistry of C-16 led to a conclusion for the S-configuration, *i.e.*, the structure and absolute configuration of isodotricin was established as shown in formula **21**.

Isodotricin is a diterpenoid isolated from the leaves of *Isodon trichocarpus* Kudo and *I. japonicus* Hara and shows mp 240—245° and $[\alpha]_D^{17}$ −114°.(3) Its molecular formula has been determined as $C_{21}H_{30}O_7$.(3)

The presence of a cyclopentanone and a δ-lactone in the molecule was suggested by the absorption bands at 1755 and 1705 cm^{-1} in its infrared (IR) spectrum. The same environment as hemiacetal moiety in enmein (**1**)(4) was expected because of the observation of a singlet signal at δ 5.89, which corresponded to the C-6 proton signal of enmein (**1**), in its nuclear magnetic resonance (NMR) spectrum.



1 : R=H
2 : R=Me



3 : R=Me
4 : R=H

Another secondary alcoholic hydroxy group was shown to be present by the IR and NMR spectra. The diterpenoid on acetylation gave a diacetate, mp 110–120°, $C_{25}H_{34}O_9$. The spectroscopic data did not shown the presence of the exocyclic methylene group, but suggested a methoxyethylidene group, *i.e.*, the NMR spectrum showed three protons singlet signal at δ 3.15 and two proton multiplet signal at δ 3.58. Thus, all of the oxygens were characterized.

A combined consideration of the foregoing data and an enmein-frame led to an assumption that isodotricin might have a structure in which a methoxymethyl group was attached to C-16 instead of the exocyclic methylene in enmein (**1**). Hence, enmein (**1**) in methanol was allowed to reflux in the presence of conc. sulfuric acid to give a monomethyl ether **2**, mp 235—239°, and a dimethyl ether (**3**), mp 200—203°. The latter was hydrolyzed with dil. acetic acid to give another monomethyl ether (**4**), which proved to be identical with the natural compound, isodotricin. In the preliminary communication,(3) the β-orientation was assigned to the stereochemistry of the C-16 substituent, under the consideration of the more stable stereochemistry(5) but without any evidence. This assignment, however, was proved to be incorrect by the following experiments.

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1) Part XX: E. Fujita and M. Taoka, *Chem. Pharm. Bull.* (Tokyo), **20**, 1752 (1972).
2) Location: *Uji, Kyoto-Fu, 611, Japan.*
3) E. Fujita, T. Fujita, and M. Shibuya, *Tetrahedron Letters*, **1966**, **3153**.
4) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, H. Irie, A. Numata, T. Fujita, and T. Suzuki, *Tetrahedron*, **22**, 1659 (1966).
5) C.A. Hendrick and P.R. Jefferies, *Austral. J. Chem.*, **17**, 915 (1964).

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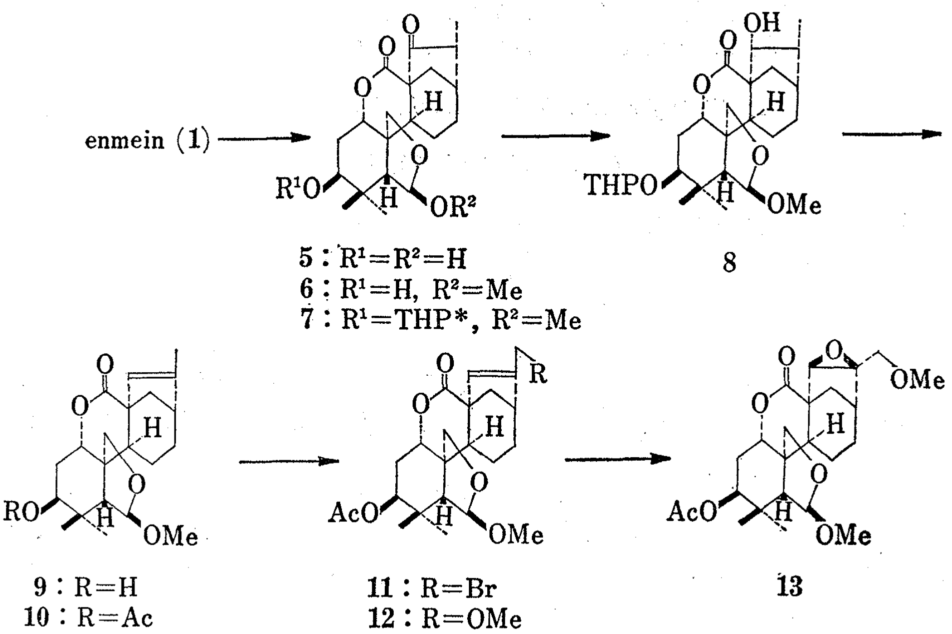
Methylation[4] of the 6-hydroxy group followed by tetrahydropyranylation of the 3-hydroxy group of dihydroenmein (**5**)[4,6] gave the desired protected derivative **7**. Reduction of the 15-carbonyl group of **7** with sodium borohydride in methanol afforded the 15α-alcohol (**8**) in high yield, under a stereoselective hydride attack from the less hindered β-side.



5 : R^1=R^2=H
6 : R^1=H, R^2=Me
7 : R^1=THP*, R^2=Me

8

9 : R=H
10 : R=Ac

11 : R=Br
12 : R=OMe

13

* THP=tetrahydropyranyl

Chart 1

The alcohol (**8**) on dehydration with phosphoryl chloride and pyridine[7] gave 15-ene derivative (**9**) in 45% yield. The tetrahydropyranyl group was hydrolyzed during the treatment after reaction. After protection of 3-hydroxy group by acetylation, allylic bromination with N-bromosuccinimide and dibenzoylperoxide in benzene yielded *via* **10** the desired 17-bromo-derivative (**11**) as the major crystalline product of mp 181—183° in 60% yield, accompanied by a minor product, the 15-bromo-16-ene-derivative. The 17-bromo-compound (**11**) was easily converted into 17-methoxy-derivative (**12**), mp 147—149°, by its treatment with silver carbonate in absolute methanol. The subsequent epoxidation of **12** with *m*-chloroperbenzoic acid in chloroform gave stereoselectively the β-epoxide (**13**), mp 126—129°, in a good yield.

The attempted transformation of this epoxide (**13**) into **14** by its treatment with borontrifluoride resulted in failure. The hydrogenolysis of **13** under 100° temperature and 80 atm pressure over Adams catalyst in methanol in the presence of sulfuric acid, however, gave an alcohol (**15**), mp 187—189°, in 54% yield. In its NMR spectrum, the 15-proton signal appeared at δ 3.84 as a broad singlet. The NMR spectrum of its acetate (**16**), mp 213—215°, revealed the 15-proton signal as a doublet with the coupling constant of 3.0 Hz at δ 4.71. These data showed that the 15-hydroxy or acetoxy group and the 16-methoxymethyl group were *trans* to each other. The stereochemistry of the 15-hydroxy or acetoxy group was clarified to have the β-orientation, on the basis of the following reasons. (i) The starting material was β-epoxide (**13**). (ii) A hydrogen bonding was recongized between the 15-hydroxy group and the δ-lactone carbonyl group. Thus, the IR spectrum of the alcohol showed an absorption of the lactone carbonyl at 1697 cm^{-1}, while that of the acetate revealed the corresponding

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6) Y. Iitaka and M. Natsume, *Acta Cryst.*, **20**, 197 (1966).
7) W.G. Dauben and G.A. Boswell, *J. Am. Chem. Soc.*, **83**, 5003 (1961).

absorption at 1735 cm^{-1}. Similarly, the NMR spectrum of the alcohol showed the hydroxy proton signal at δ 5.93, while that of the epimeric alcohol (**18**) showed the corresponding signal at δ 3.09. (iii) When the NMR spectra were compared, the 15-proton signal of the acetate (**19**) appeared at the much lower magnetic field (δ 5.93) than the 15-proton signal of the acetate (**16**) (δ 4.71). An investigation of the stereomodel recognized that only the 15β-proton was subject to the anisotropic effect of the 7-carbonyl.

Thus, the α-stereochemistry of the 16-methoxymethyl group of **15** and **16** was established. It was probably due to the twisted conformation of the ring D because of the strong hydrogen bonding that the 15-proton signal of alcohol (**15**) appeared as a broad singlet.

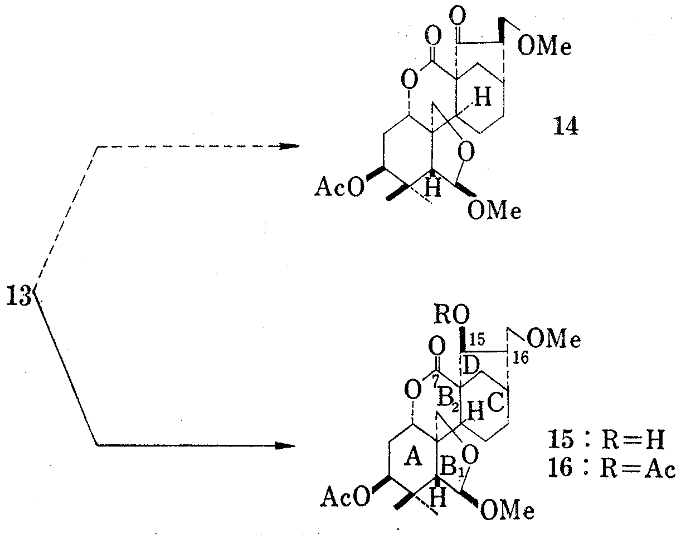
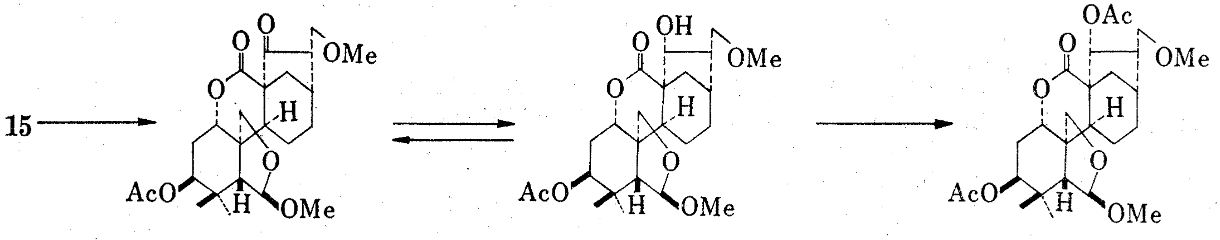


Chart 2

Alcohol (**15**) on oxidation with Sarett reagent gave ketone (**17**), mp 176—179°. The sodium borohydride reduction of this ketone in methanol yielded alcohol (**18**). In the NMR spectrum of its acetate (**19**), mp 223—225°, the 15-proton signal appeared at δ 5.93 as a doublet splitted with the coupling constant of 10.5 Hz. This fact indicated the *cis*-relationship between the 15-substituent and the 16-methoxymethyl group. The stereochemistry of the 15-hydroxy or acetoxy group was shown to have α-configuration, because of the following data. (i) In this series of compounds, sodium borohydride reduction in methanol usually gives α-alcohol by the hydride attack from the less hindered β-side. (ii) No hydrogen bonding was recognized between the 15-hydroxy group and the 7-carbonyl group; in the IR spectrum of alcohol (**18**), an absorption at 1730 cm^{-1} attributed to the δ-lactone carbonyl group was observed. The data of the NMR spectra of **18** and **15** also gave an evidence as mentioned above. (iii) The comparison between the 15-proton chemical shifts of the acetates (**16** and **19**) described above.

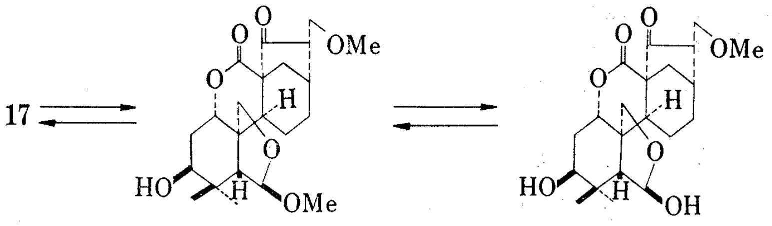
Therefore, the α-configuration of the 16-methoxymethyl group was again confirmed. The Sarett oxidation of **18** regenerated the ketone **17**.



17 **18** **19**

Chart 3

The hydrolyses of 3-acetoxy group by dil. sodium carbonate solution and of 6-acetal by dil. acetic acid from the ketone (**17**) gave rise to isodotricin (**21**) *via* **20**. Following the opposite course, 6-methylation followed by 3-acetylation of isodotricin regenerated the ketone (**17**). Thus, the possibility for enolation and epimerization of C-16 during the hydrolyses was excluded. Consequently, the absolute configuration, especially the S-configuration of C-16, of isodotricin was unequivocally established, which was shown in formula **21**.



20 21

Chart 4

Experimental

Melting points were determined on a Yanagimoto micro mp apparatus and uncorrected. The IR spectra were taken on a Hitachi model EPI-S2 spectrophotometer, and NMR spectra on a Varian T-60 spectrometer using TMS as an internal standard. Specific rotations were measured by Jasco DIP-180 Automatic Polarimeter. Mallinokrodt Silicic Acid and Kieselgel 0.05—0.2 mm (Merck) were used for column chromatography, and Kieselgel G nach Stahl (Merck) for thin-layer chromatography.

Isolation of Isodotricin from the Plants——A hundred kg of the dried leaves of *Isodon trichocarpus* KUDO were extracted by 3000 liter of MeOH under reflux for 4 hr. The extract was concentrated to 100 liter under the reduced pressure, and allowed to stand at room temperature for 2 weeks to precipitate 600 g of the crystals of enmein. To the filtrate (500 ml) from enmein, 500 ml of MeOH were added, and the mixture was heated with 20 g of charcoal under reflux for 1 hr. After filtration from the charcoal, the same precedure was repeated for 3 times. The color of the liquid changed to yellow from green. Evaporation of MeOH left 200 g of residue, which was dissolved in ethyl acetate and washed with 0.5% aq. Na_2CO_3 and then 0.1N HCl. After washing with water and drying, the solvent was distilled off to give 100 g of a syrupy residue, 20 g of which was chromatographed on 800 g of silica gel. Elution with a mixture of acetone–$CHCl_3$ (1: 4) separated isodotricin, besides isodocarpin, nodosin, trichodonin, and trichodin. The yield of isodotricin was 430 mg per 1 kg of dried leaves. A similar treatment of the dried leaves of *Isodon japonicus* HARA yielded isodotricin, besides isodocarpin, nodosin, and ponicidin.

The crude crystals of isodotricin were recrystallized from MeOH to afford colorless pure crystals, mp 240—245°. $[\alpha]^{17}_{D}$ $-114°$ ($c=1$, pyridine). *Anal.* Calcd. for $C_{21}H_{30}O_7$: C, 63.94; H, 7.66. Found: C, 63.83; H, 7.88. IR ν^{KBr}_{max} cm^{-1}: 3400, 1755, 1705. NMR δ_{ppm} (pyridine): 1.06, 1.34 (each 3H, s), 3.15 (3H, s, OMe), 3.58 (2H, m), 3.82 (1H, br. m, C-3-H), 4.52, 4.38 (each 1H, AB type, $J=8.5$ Hz, C-20 H_2), 5.39 (1H, q, $J=7.5$, 10.0 Hz, C-1-H), 5.89 (1H, s, C-6-H).

Isodotricin Diacetate——A solution of 45 mg of isodotricin in each 1 ml of pyridine and acetic anhydride was allowed to stand overnight, and then warmed on a water-bath for 30 minutes. Evaporation of the reaction mixture to dryness and chromatography of the residue on a silica gel column gave a crystalline fraction by elution with $CHCl_3$. It was recrystallized from MeOH to give isodotricin diacetate as 23 mg of pure crystals, mp 110—120°. *Anal.* Calcd. for $C_{25}H_{34}O_9$: C, 62.75; H, 7.16. Found: C, 62.82; H, 7.33. IR ν^{KBr}_{max} cm^{-1}: 1755, 1740. NMR δ_{ppm} ($CDCl_3$): 3.36 (3H, s, OMe), 4.08 (2H, s, C-20 H_2), 4.93 (1H, q, $J=2.0$, 4.0 Hz, C-1-H), 6.19 (1H, s, C-6-H).

Chemical Conversion of Enmein into 6-Methyl Ether (2) and Dimethyl Ether (3) (=20)——A solution of 120 mg of enmein (1) in 10 ml of MeOH was refluxed under addition of 0.4 ml of conc. H_2SO_4 for 6 hr. After concentration of 5 ml under reduced pressure, it was poured into aq. Na_2CO_3 under cooling with ice. Extraction with $CHCl_3$, washing, drying, and evaporation of the solvent left 124 mg of a residue, which was chromatographed on silica gel column with elution by $CHCl_3$ to yield enmein-6-methyl ether (2) and dimethyl ether (3) as crystals. The former was recrystallized from MeOH to afford 24 mg of the pure compound 2, mp 235—239°. *Anal.* Calcd. for $C_{21}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 66.18; H, 7.98. IR ν^{KBr}_{max} cm^{-1}: 1760, 1715. UV λ^{EtOH}_{max} nm: 233 (ε 7500). NMR δ_{ppm} ($CDCl_3$): 3.69 (1H, br, C-3-H), 4.83 (1H, s, C-6-H), 6.05, 5.50 (each 1H, s, C-17 H_2), 3.26 (3H, s, -OMe). The latter was recrystallized from MeOH to afford 17 mg of the pure compound 3, mp 200—203°. *Anal.* Calcd. for $C_{22}H_{32}O_7$: C, 64.68; H, 7.90. Found: C, 64.97; H, 7.93. IR ν^{KBr}_{max} cm^{-1}: 3450, 1750, 1715. NMR δ_{ppm} ($CDCl_3$): 3.7 (1H, br, C-3-H), 4.82 (1H, s, C-6-H), 3.27, 3.55 (each 3H, s, -OMe).

Acid Hydrolysis of Dimethylether 3——To a mixture of each 2 ml of acetic acid and water was added 30 mg of dimethylether 3, and the mixture was heated at reflux for 3 hr. After cooling, it was extracted with ethyl acetate, and the extract was washed with aq. Na_2CO_3 and then water. After drying, the solvent was distilled off to leave 18 mg of crystalline residue, which was recrystallized from MeOH to yield a pure crystalline compound, mp 240—243°. $[\alpha]_D^{25}$ $-111°$ ($c=0.05$, pyridine). This compound was proved to be identical with isodotricin (TLC, mp, IR).

Tetrahydropyranylation of Acetal (6)——To a solution of 31 g of acetal (**6**) in 150 ml of dried (P_2O_5) $CHCl_3$, 10.5 g of dihydropyrane was slowly added. The reaction mixture was stirred at room temperature for 1 hr and poured into dil. aq. Na_2CO_3. Extraction with CH_2Cl_2, washing of the extract with water, drying over Na_2SO_4, and evaporation of the solvent gave 35 g of the crude crystalline product, which was recrystallized from ether to give pure sample of **7**, mp 234—236°. $[\alpha]_D^{20}$ $-92°$ ($c=0.4$, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{38}O_7$: C, 67.58; H, 8.58. Found: C, 67.51; H, 8.28. IR ν_{max}^{KBr} cm^{-1}: 1758, 1723. NMR δ_{ppm} ($CDCl_3$): 3.27 (3H, s, OCH_3), 3.65 (1H, m, C-3-H), 3.92, 4.08 (each 1H, AB type, $J=9.0$ Hz, C-20 H_2), 4.62 (1H, quartet-like, C-1-H), 4.80 (1H, m, THP acetal H), 4.82 (1H, s, C-6-H).

Sodium Borohydride Reduction of 7——To a solution of 30 g of **7** in 1.5 liter of MeOH, 35 g of $NaBH_4$ was added little by little and the mixture was stirred at room temperature for 3 hr. After neutralization with 5% acetic acid, MeOH was evaporated off under reduced pressure. The remaining residue was extracted with ethyl acetate and the extract was treated as usual to give 29 g of the crude alcohol **8**, which was purified by recrystallization from ether–hexane to give pure sample, mp 223—225°. $[\alpha]_D^{20}$ $-100°$ ($c=0.2$, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{40}O_7$: C, 67.47; H, 8.86. Found: C, 67.21; H, 8.68. IR ν_{max}^{KBr} cm^{-1}: 3525, 1715. NMR δ_{ppm} ($CDCl_3$): 3.32 (3H, s, OCH_3), 3.91 (2H, s, C-20 H_2), 4.60 (1H, m, THP acetal H), 4.80 (1H, s, C-6-H), 4.90 (1H, quartet-like, C-1-H).

Dehydration of Alcohol (8)——To a solution of 6.0 g of alcohol (**8**) in 50 ml of pyridine, 21.1 g of $POCl_3$ was added and the mixture was heated at 60° for 12 hr. Pyridine was evaporated off and, after addition of a small amount of water, extracted with ethyl acetate. A usual treatment of the extract gave an oily product, which was chromatographed on silica gel column by elution with 2% acetone–CH_2Cl_2 to give 0.6 g of a syrupy fraction and 2.1 g of crystalline unsaturated alcohol (**9**). The latter was recrystallized from ether to give a pure sample, mp 200—203°, $[\alpha]_D^{20}$ $-147°$ ($c=0.58$, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.33; H, 8.44. IR ν_{max}^{KBr} cm^{-1}: 3425, 1715. NMR δ_{ppm} ($CDCl_3$): 0.95, 1.10 (each 3H, s), 1.75 (3H, d, $J=2.0$ Hz, C-17-CH_3), 3.30 (3H, s, OCH_3), 3.63 (1H, m, C-3-H), 3.60. 4.06 (each 1H, AB type, $J=9.0$ Hz, C-20 H_2), 4.89 (1H, s, C-6-H), 5.02 (1H, q, $J=8.0$, 10.5 Hz, C-1-H), 5.67 (1H, br. s, C-15-H).

Acetate (10)——A solution of 1.01 g of **9** in a mixture of each 8 ml of acetic anhydride and pyridine was allowed to stand overnight. Evaporation *in vacuo* left a residue, to which a small amount of water was added. After extraction of the mixture with CH_2Cl_2, the organic layer was treated as usual to give a syrupy crude product. Chromatography on silica gel column under elution with 1% acetone–CH_2Cl_2 gave a crystalline substance, which was recrystallized from ether-isopropyl ether to afford 1.01 g of acetate **10**, mp 136—138°. $[\alpha]_D^{20}$ $-84°$ ($c=0.32$, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.01; H, 8.07. IR ν_{max}^{KBr} cm^{-1}: 1733. NMR δ_{ppm} ($CDCl_3$): 2.12 (3H, s, -$OCOCH_3$), 4.90 (1H, m, C-3-H).

Allylic Bromination of (10)——A solution of 1.45 g of acetate (**10**) in 75 ml of the dried benzene was heated under equipment of a water separator to distil 10 ml of benzene for removing water further. To this anhydrous solution was added 650 mg of N-bromo-succinimide and 10 mg of dibenzoylperoxide, and the mixture was heated for 45 minutes under mild reflux. After cooling, the reaction mixture was poured into dil. aq. Na_2CO_3, and extracted with ethyl acetate. After washing with water and drying over Na_2SO_4 of the extract, evaporation of the solvent left a crystalline residue. The chromatography of the residue on a silica gel column using 1% acetone–CH_2Cl_2 for elution afforded 250 mg of syrupy substance and 1.04 g of the desired 17-bromo-derivative as crystals. The former syrupy substance was shown to be 15-bromo-16(17)-ene derivative. NMR δ_{ppm} ($CDCl_3$): 5.21—5.58 (2H, m, C-17 H_2). The latter crystals were recrystallized from ether–isopropyl ether to yield a pure sample of **11**, mp 181—183°. $[\alpha]_D^{20}$ $-111°$ ($c=0.34$, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{31}O_6Br$: C, 57.14; H, 6.48. Found: C, 57.20; H, 6.53. IR ν_{max}^{KBr} cm^{-1}: 1735. NMR δ_{ppm} ($CDCl_3$): 0.98, 1.03 (each 3H, s), 2.15 (3H, s), 3.32 (3H, s), 3.60, 4.04 (each 1H, AB type, $J=10.0$ Hz, C-20 H_2), 4.09 (2H, s, C-17 H_2), 4.77 (1H, q, $J=8.0$, 10.5 Hz, C-1-H), 4.80 (1H, s, C-6-H), 4.92 (1H, m, C-3-H), 6.13 (1H, br. s, C-15-H).

Methoxylation of Bromo-derivative 11——To a suspension of 1.87 g of **11** in 150 ml of absolute MeOH was added 3.0 g of Ag_2CO_3, and the mixture was heated under mild reflux for 1.5 hr. After filtration the solvent was distilled off to leave a crystalline residue, which was purified by chromatography on a silica gel column under elution with 5% acetone–CH_2Cl_2. Further purification by recrystallization from ether–petroleum ether yielded 1.14 g of the pure sample of **12**, mp 147—149°, $[\alpha]_D^{20}$ $-92°$ ($c=0.28$, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.35; H, 7.95. IR ν_{max}^{KBr} cm^{-1}: 1735. NMR δ_{ppm} ($CDCl_3$): 1.00. 1.03 (each 3H, s), 2.13 (3H, s), 3.30, 3.34 (each 3H, s, -OCH_3), 3.60, 4.07 (each 1H, AB type, $J=10.0$ Hz, C-20 H_2), 4.03 (2H, s, C-17 H_2), 4.87 (1H, s, C-6-H), 5.98 (1H, br. s, C-15-H).

Epoxidation of 12——To a solution of 900 mg of **10** in 40 ml of $CHCl_3$, 500 mg of *m*-chloroperbenzoic acid was added. The mixture was allowed to stand at room temperature in a dark room overnight. The reaction mixture was poured into dil. aq. Na_2CO_3, and extracted with CH_2Cl_2. A usual work-up of the extract gave a crystalline product, which was chromatographed on a silica gel column using 5% acetone–CH_2Cl_2 for elution and then recrystallized from ether–petroleum ether to yield 815 mg of pure crystals of epoxide **13**, mp 126—129°, $[\alpha]_D^{20}$ $-41°$ ($c=0.22$, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{34}O_8 \cdot H_2O$: C, 61.52; H, 7.75.

Found: C, 61.24; H, 7.93. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3570, 3470, 1730, 1725. NMR δ_{ppm} ($CDCl_3$): 0.98, 1.02 (each 3H, s), 2.12 (3H, s), 3.35, 3.42 (each 3H, s), 4.68 (1H, q, J=8.0, 11.0 Hz, C-1-H), 4.84 (1H, s, C-6-H), 4.90 (1H, m, C-3-H).

Hydrogenolysis of Epoxide (13)——To a solution of 390 mg of epoxide (**13**) in 60 ml of absolute MeOH, 10 drops of conc. H_2SO_4 and 250 mg of PtO_2 were added, and the mixture was hydrogenated for 2 days at 100° and 80 atm. in an autoclave. The catalyst was filtered off and the filtrate was concentrated to 10 ml, then neutralized with dil. aq. Na_2CO_3. Extraction with CH_2Cl_2 and a usual work-up of the extract gave a syrupy crude product, which was purified by chromatography on a silica gel column using 5% acetone–CH_2Cl_2 for elution to afford 215 mg of crystalline alcohol **15**. Recrystallization from ether gave an analytical sample, mp 187—189°. $[\alpha]_D^{20}$ $-75°$ (c=0.34, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{36}O_8$: C, 63.70; H, 8.02. Found: C, 63.64; H, 8.03. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3420, 1739, 1697. NMR δ_{ppm} ($CDCl_3$): 1.00, 1.03 (each 3H, s), 2.11 (3H, s), 3.33, 3.40 (each 3H, s), 3.50 (2H, d, J=8.0 Hz, C-17 H_2), 3.72, 4.04 (each 1H, AB type, J=9.0 Hz, C-20 H_2), 3.84 (1H, br. s, C-15-H), 4.75 (1H, q, J=7.0, 12.0 Hz, C-1-H), 4.82 (1H, s, C-6-H), 4.90 (1H, m, C-3-H), 5.93 (1H, s, -OH).

Acetylation of Alcohol (15)——A solution of 65 mg of alcohol (**15**) in a mixture of each 1 ml of acetic anhydride and pyridine was allowed to stand at room temperature for 2 days. Concentration of the reaction mixture gave a syrupy residue, which was subjected to silica gel column chromatography using 5% acetone–CH_2Cl_2 for elution, and then to recrystallization from ether to yield 41 mg of the crystals of pure acetate (**16**), mp 213—215°. $[\alpha]_D^{20}$ $-78°$ (c=0.12, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{38}O_9$: C, 63.14; H, 7.75. Found: C, 63.03; H, 7.63. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1735. NMR[8] δ_{ppm} ($CDCl_3$): 2.04 2.09 (each 3H, s), 4.71 (1H, d, J=3.0 Hz, C-15-H).

Oxidation of Alcohol (15)——To a solution of 73 mg of alcohol (**15**) in 2 ml of pyridine, CrO_3 (200 mg)–pyridine (1 ml) complex was added, and the mixture was stirred at room temperature for 2 days. After addition of a small amount of water, the mixture was extracted with CH_2Cl_2. The extract on a usual work-up gave a syrupy product, which was chromatographed on silica gel column using 5% acetone-CH_2Cl_2 for elution to afford a crystalline substance. Its recrystallization from ether-petroleum ether yielded 26 mg of ketone **17**, mp 176—179°, $[\alpha]_D^{20}$ $-116°$ (c=0.22, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 63.89; H, 7.43. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1763, 1730. NMR δ_{ppm} ($CDCl_3$): 0.99, 1.04 (each 3H, s), 2.12 (3H, s), 3.25, 3.37 (each 3H, s), 3.90, 4.31 (each 1H, AB type, J=9.0 Hz, C-20 H_2), 4.63 (1H, q, J=8.0, 11.0 Hz, C-1-H), 4.89 (1H, s, C-6-H), 4.97 (1H, m, C-3-H).

Sodium Borohydride Reduction of Ketone (17)——To a solution of 125 mg of ketone (**17**) in 25 ml of MeOH, 150 mg of $NaBH_4$ was added, and the mixture was stirred at room temperature for 1 hr. After neutralization by addition of 5% acetic acid and evaporation of MeOH under reduced pressure, extraction with CH_2Cl_2 and a usual work-up of the extract gave a syrupy product, which was purified by silica gel column chromatography using 5% acetone–CH_2Cl_2 for elution to give 95 mg of syrupy alcohol **18**. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3450, 1730. NMR δ_{ppm} ($CDCl_3$): 1.00, 1.03 (each 3H, s), 2.10 (3H, s), 3.09 (1H, d, J=4.0 Hz, -OH), 3.33, 3.35 (each 3H, s), 3.96 (2H, s, C-20 H_2), 4.69 (1H, q, J=7.0, 10.5 Hz, C-1-H), 4.82 (1H, s, C-6-H).

Acetylation of Alcohol (18)——A solution of 82 mg of alcohol (**18**) in a mixture of each 1 ml of acetic anhydride and pyridine was allowed to stand at room temperature for 3 days. Evaporation of the solvent and the reagent left a syrupy residue, which was purified by silica gel column chromatography (5% acetone–CH_2Cl_2) to afford a crystalline substance. Its recrystallization from ether–petroleum ether yielded 49 mg of crystals of acetate **19**, mp 223—225°. $[\alpha]_D^{20}$ $-88°$ (C=0.14, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{38}O_9$: C, 63.14; H, 7.75. Found: C, 62.94; H, 7.81. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1749, 1735. NMR δ_{ppm} ($CDCl_3$): 1.01, 1.05 (each 3H, s), 2.09, 2.14 (each 3H, s), 3.33, 3,37 (each 3H, s), 3.76, 3.97 (each 1H, AB type, J=9.0 Hz, C-20 H_2), 4.70 (1H, q, J=7.0, 11.0 Hz, C-1-H), 4.89 (1H, s, C-6-H), 5.93 (1H, d, J=10.5 Hz, C-15-H).

Oxidation of Alcohol (18)——To a solution of 152 mg of alcohol (**18**) in 2 ml of pyridine, CrO_3 (300 mg)–pyridine (2 ml) complex was added, and the mixture was stirred for 2 days. Then, 10 ml of water was added and the mixture was extracted with CH_2Cl_2. A usual work-up of the extract gave a crystalline product, which was chromatographed on silica gel column (5% acetone–CH_2Cl_2) and then recrystallized from ether to yield 82 mg of pure crystal. It was proved to be identical with the ketone (**17**) (TLC, mp, NMR, IR).

Alkaline Hydrolysis of Acetate (17)——Five ml of 3% aq. Na_2CO_3 was added to a solution of 80 mg of acetate (**17**) in 25 ml of MeOH, and the mixture was stirred at room temperature for 1 day. After distillation of MeOH, addition of a small amount of water, and extraction with CH_2Cl_2, a usual treatment of the extract gave a syrupy product, which was chromatographed on silica gel column (8% acetone–CH_2Cl_2) to afford a crystalline substance. Its recrystallization from ether yielded C-3-ol **20** as crystals, mp 198—200°. *Anal.* Calcd. for $C_{22}H_{32}O_7$: C, 64.68; H, 7.90. Found: C, 64.97; H, 7.93. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3440, 1755, 1714. NMR δ_{ppm} ($CDCl_3$): 0.95, 1.07 (each 3H, s), 3.28, 3.38 (each 3H, s), 4.90 (1H, s, C-6-H).

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[8] This NMR spectrum was taken on Hitachi R 22 NMR spectrometer. We express our thanks to Dr. Enoki, Kyoto Univ. for the spectrum.

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Acid Hydrolysis of Acetal (20)——Thirty mg of acetal (**20**) was added to a mixture of 0.2 ml of acetic acid and 2 ml of water, and the mixture was heated at reflux for 3 hr. After cooling, the mixture was extracted with ethyl acetate. After washing with dil. aq. Na_2CO_3 and then water and drying over Na_2SO_4, the solvent was evaporated off to give 18 mg of a crystalline residue. The purified crystal obtained after recrystallization from MeOH was proved to be identical with isodotricin (TLC, mp, IR).

Acetalization of Isodotricin——One drop of conc. H_2SO_4 was added to a solution of 15 mg of isodotricin in 3 ml of absolute MeOH, and the mixture was heated at 70° for 1 hr. After concentration of the mixture to 1 ml, it was poured into dil. aq. Na_2CO_3 and extracted with CH_2Cl_2. A usual work-up of the extract and purification of the crude crystalline product by recrystallization from ether yielded a pure crystalline product, which was proved to be identical with acetal (**20**) (TLC, mp, IR).

Acetylation of Alcohol (20)——A solution of 820 mg of **20** in a mixture of each 8 ml of pyridine and acetic anhydride was allowed to stand at room temperature overnight. Evaporation of the solvent and the reagent left a syrupy residue, which was crystallized by silica gel column chromatography (5% acetone–CH_2Cl_2). Recrystallization from ether-petroleum ether yielded 790 mg of pure substance, which was proved to be identical with **17** (TLC, mp, IR, NMR).

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