Reduction and Stereochemistry of Terrecyclic Acid A and Its Derivatives

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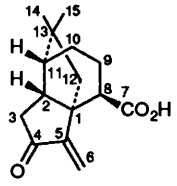
Two kinds of hydride (sodium borohydride and diisobutylaluminium hydride) and catalytic hydrogenation have been used to reduce terrecyclic acid A **1** and several derivatives **5**, **6**, **7** and **15**. Some interesting stereochemical results were obtained.

Terrecyclic acid A **1**, a sesquiterpene antibiotic produced by *Aspergillus terreus* Thom No. 14,[1] possesses the same carbon skeleton as quadrone **2**.[2]† Recently, the absolute configurations of both compounds have been determined by total syntheses of optically active forms of **1**[3] and **2**.[4] We have also confirmed the absolute stereochemistry of **1** by applying the CD allylic benzoate rule to the benzoate **3**, a derivative of the natural compound **1**.[5] During the chemical derivatization of the ketone **1** into the benzoate **3** and other correlated compounds, several



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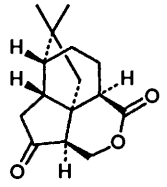

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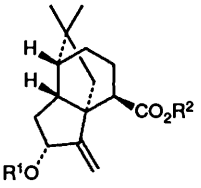


3 R^1 = Bz, R^2 = Me
4 R^1 = R^2 = H
5 R^1 = H, R^2 = Me

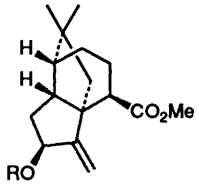
interesting stereochemicl results were obtained, especially with the reductions. Here, we report the results of these reductions and the stereochemistry of several derivatives of terrecyclic acid A **1**.

Results and Discussion

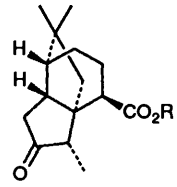
Hydride Reduction.—Reduction of terrecyclic acid A, **1**, with sodium borohydride in propan-2-ol gave the hydroxy acid **4** as the sole product in almost 80% yield.[5,6] Treatment of the reaction mixture directly with diazomethane and column chromatography of the product gave the known compound **5** (80%) together with **6** (5%) and **7** (15%). The yield of the hydroxy acid **5** was raised to 96% when cerium(III) chloride was added during the borohydride reduction.

In contrast reduction of compound **1** with diisobutylaluminium hydride (DIBAL) in tetrahydrofuran (THF) followed by diazomethane treatment, gave different yields of the same products: (**5**, 9; **6**, 62; and **7**, 29%).

Two of these compounds **5** and **7** were identical with the methyl esters obtained by diazomethane treatment of the known carboxylic acids.[6] The remaining methyl ester **6** was established as a C-4 epimer of **5** on the basis of spectral evidence. Thus, irradiation of 4-H [δ 4.46 (br s, $W_{\frac{1}{2}}$ *ca.* 11 Hz)] gave NOE enhancements at both 3α-H (strong) and 3β-H (weak) whilst irradiation of 4-OH [δ 3.75 (br s)] resulted in strong NOE enhancement at 2β-H and weak enhancement at 3β-H. From these NMR results, compound **6** appeared to have



6 R = H
8 R = Bz



7 R = Me
9 R = H

a 4β-hydroxy group in the axial rather than the equatorial orientation. However the hydroxy group of compound **5** was confirmed as having an α-equatorial orientation from the half-width value for 4-H ($W_{\frac{1}{2}}$ *ca.* 21 Hz) and NOE enhancement at 2β- and 3β-H on irradiation of 4 β-H. These results suggest that the conformation of the hydroxy group-bearing cyclopentane ring in compound **6** is almost the same as that in compound **5**. These results show good correlation with the result of a molecular mechanics calculation using the MM2 force field which shows that the β-axial-hydroxy conformer (see Fig. 1) of compound **6** is *ca.* 1.5 kcal mol^{-1} more stable than the β-equatorial-hydroxy conformer.[7]

Several explanations present themselves as to why the major product was compound **5** on $NaBH_4$ reduction and compound **6** on DIBAL reduction. One explanation is as follows. Since the dimethylethano bridge presents no steric hindrance to carbonyl reduction, $NaBH_4$ reduction gave compound **5** *via* a product-like transition state. In contrast, on reduction with DIBAL, the latter might interact with the C-8 carboxy group to afford compound **6** as a major product.

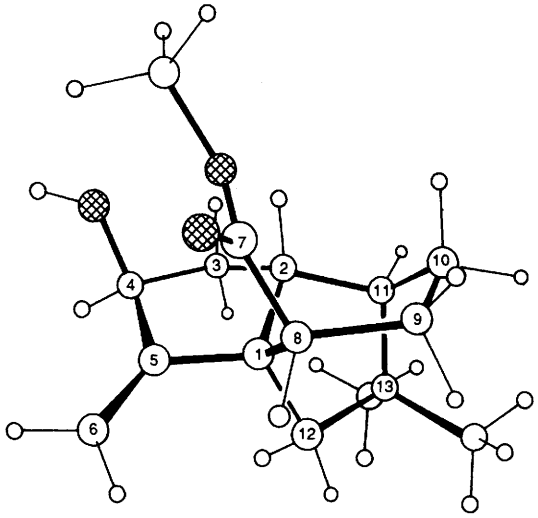
The β-hydroxy compound **6** was converted into the benzoate

† Numberings of compounds described in this text are adopted from those of quadrone **2** shown in ref. 2.

Table 1 Catalytic hydrogenation reactions of several derivatives of terrecyclic acid A **1**[a]

Run	Starting materials	Products (yields)
1	**1**	**9** (quant.)
2	**5**	**10** (85%); **11** (15%)
3	**6**	**12** (50%); **13** (<5%); **14** (35%)
4	**15**	**7** (quant.)
5	**16**	**16** (no change)

[a] All the reactions were carried out under the identical conditions over 10% palladium–carbon with methanol as a solvent for 1 h at room temperature under atmospheric pressure.



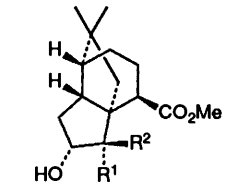
○ , carbon ⊗ , oxygen O , hydrogen

Fig. 1 The most stable conformation of compound **6** by molecular mechanics calculation using the MM2 force field

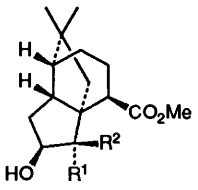
8, the CD spectrum of which showed a positive Cotton effect ($\Delta\varepsilon_{230}$ +7.1). From the CD allylic benzoate chirality rule,[8] this large positive value confirmed the correctness of the absolute stereostructures described herein.

Catalytic Hydrogenation over 10% Pd–C *in Methanol.*—As we reported earlier,[6] the ketone **9** with an α-oriented methyl group was the sole product on catalytic hydrogenation of terrecyclic acid A **1** over Pd–C. At that time, we thought that the steric hindrance resulting from the dimethylethano bridge to the α-side of terrecyclic acid A **1** would lead to hydrogen attack from the less hindered β-side to afford the ketone **9** stereospecifically.

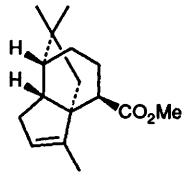
Table 1 shows the results of the catalytic hydrogenation (10% palladium–carbon with methanol as a solvent) of several derivatives of terrecyclic acid A **1** under identical conditions. The structures of the new products **10**–**14** were deduced from the spectral data. The stereochemistries of the saturated alcohols **10**–**13** were confirmed by the preparation of two authentic compounds, **11** and **13**, by hydride reduction of the ketone **7**; that is, sodium borohydride reduction of **7** afforded the α-hydroxy ester **11** (85%) and the β-hydroxy ester **13** (12%). The methyl ester **15** of terrecyclic acid A **1** was prepared by heating a mixture of compound **1**, methyl iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile. The ketone **16** with a β-methyl group, obtained by oxidation of compound **12**, was completely transformed into the more stable ketone **7** with an α-methyl group by treatment with methanolic hydrogen chloride.



10 R^1 = H, R^2 = Me
11 R^1 = Me, R^2 = H



12 R^1 = H, R^2 = Me
13 R^1 = Me, R^2 = H



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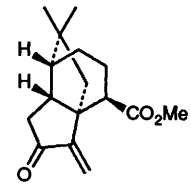

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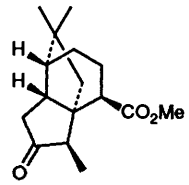

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Since the major hydrogenation products **10** and **12** of the allylic alcohols **5** and **6**, respectively, arose by hydrogen attack from the α-side, clearly there was no steric hindrance from the dimethylethano bridge in either case. The result of run 4 indicates that the carboxy group cannot act as an acid catalyst for the hydrogenation of **1** under these conditions. Similarly, the result of run 5 indicates that no isomerization (epimerization) took place under the hydrogenation conditions.

From these results, we propose that the hydrogenation pathway of **1** and **15** is as follows: there is no 1,2-addition of hydrogen, but hydrogen might make a 1,4-addition to the α,β-unsaturated ketone to afford enol-type intermediate, which isomerized into the thermodynamically more stable ketones **9** and **7**, respectively, stereospecifically.

Experimental

General Procedures.—All m.p.s were measured on a Meltemp capillary melting-point apparatus (Laboratory Devices) and are uncorrected. UV, IR and CD spectra were measured on a Hitachi 340, a Hitachi 260-30 and a Jasco J-20 spectrometers, respectively. ^{1}H NMR spectra were taken using a Varian EM-390 (90 MHz), a JEOL FX-90Q (90 MHz), a JEOL GX-270 (270 MHz) and a JEOL GX-400 (400 MHz) spectrometers at ambient temperature. ^{13}C NMR spectra were measured on JEOL FX-90Q (22.5 MHz) and JEOL GX-270 (67.5 MHz) spectrometers. Deuteriochloroform was used as the NMR solvent. Chemical shifts were expressed in δ(ppm) downfield from tetramethylsilane as an internal standard and coupling constants in Hz. Mass spectra were run on a JEOL D-300 mass spectrometer operating at 70 eV. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 GF_{254} coated to 0.25 mm thickness. Wakogel C-200 (Wako) was used for silica-gel column chromatography.

Sodium Borohydride Reduction Followed by Diazomethane Treatment of Terrecyclic Acid A **1**.—To a solution of terrecyclic acid A **1** (52 mg) in propan-2-ol (10 ml) was added sodium borohydride (27 mg) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The solution was extracted with ether and the extract was washed successively with dilute hydrochloric acid and brine, dried ($MgSO_4$) and filtered. A large excess of an ethereal solution of diazomethane was added to the solution, and the reaction mixture was set aside overnight. After the removal of ether, the reaction mixture was charged onto a silica gel (15 g) column and eluted with benzene–acetone (10:1) to afford three esters, **7** (8 mg), **6** (3 mg) and **5** (44 mg), successively.

Compound **5**: m.p. 134–135.5 °C (benzene); ν_{max}(KBr)/cm^{-1} 3250, 1720, 1640, 1215, 1200, 1165, 1085, 1050 and 890; δ_H(400 MHz) 1.12 (3 H, s), 1.23 (3 H, s), 2.19 (1 H, ddd, *J* 11.5, 6.5 and 6.5, 3β-H), 2.57 (1 H, dd, *J* 13 and 6, 2β-H), 2.85 (1 H, d, *J* 8.5, 8α-H), 3.59 (3 H, s), 4.50 (1 H, br s, $W_{\frac{1}{2}}$ *ca.* 21, 4β-H), 4.86 (1 H, d, *J* 2.5, 6-H) and 5.08 (1 H, d, *J* 2.5, 6-H); δ_C(22.5 MHz): 22.54 (CH_2), 27.30 (CH_3), 29.23 (CH_2), 35.10 (CH_3), 38.71 (CH_2), 39.44 C, 47.75 (CH), 48.78 (CH), 49.51 (CH), 51.09 (CH_3), 55.45 (CH_2), 55.55 C, 76.60 (CH), 105.37 (CH_2), 161.49 C and 175.71 C; *m*/*z* 264 (5), 249 (3), 207 (100), 205 (10) and 147 (35%) (Found: M, 264.1761. Calc. for $C_{16}H_{24}O_3$: M, 264.1725).

Compound **6**: an oil; ν_{max}(neat)/cm^{-1} 3500, 1725, 1660, 1265, 1220, 1200, 1180, 1140, 1055, 1010 and 900; δ_H(400 MHz) 1.12 (3 H, s), 1.18 (3 H, s), 1.52 (1 H, dddd, *J* 13.5, 13.5, 6.5 and 3, 10β-H), 1.63 (1 H, d, *J* 14, 12-H), 1.66 (1 H, d, *J* 14, 12-H), 1.77 (1 H, dddd, *J* 13.5, 6.5, 3.5 and 1, 10α-H), 1.85 (1 H, ddd, *J* 15.5, 6.5 and 1, 9β-H), 1.86 (1 H, dd, *J* 3.5 and 3, 11-H), 1.91 (1 H, ddd, *J* 13, 6.5 and 1, 3β-H), 1.99 (1 H, ddd, *J* 13, 13 and 5, 3α-H), 2.17 (1 H, dddd, *J* 15.5, 13.5, 9 and 6.5, 9α-H), 2.79 (1 H, dd, *J* 13 and 6.5, 2β-H), 2.92 (1 H, d, *J* 9, 8α-H), 3.63 (3 H, s), 3.76 (1 H, br s, OH), 4.46 (1 H, br s, $W_{\frac{1}{2}}$ *ca.* 11, 4α-H), 4.86 (1 H, br s, 6-H) and 5.22 (1 H, br s, 6-H); δ_C(22.5 MHz) 23.02 (CH_2), 27.38 (CH_3), 29.33 (CH_2), 34.81 (CH_3), 38.90 (CH_2), 39.93 C, 48.78 (CH), 49.22 (CH), 51.36 (CH_3), 51.57 (CH), 54.53 (CH_2), 76.76 (CH), 108.75 (CH_2), 161.52 C and 176.74 C; *m*/*z* 264 (19), 249 (13), 246 (27), 232 (24), 207 (38), 204 (33), 190 (39), 187 (25) and 131 (100%) (Found: M, 264.1702. Calc. for $C_{16}H_{24}O_3$: M, 264.1725).

Compound **7**: m.p. 44–45.5 °C (ether–hexane); ν_{max}(KBr)/cm^{-1} 2950, 1740, 1200 and 1175; δ_H(270 MHz) 0.98 (3 H, d, *J* 7, 6-Me), 1.11 (3 H, s), 1.15 (3 H, s), 1.38 (2 H, s, 12-H_2), 1.7–2.0 (5 H, m), 2.21 (1 H, qd, *J* 7 and 2, 5-H), 2.33 (1 H, dd, *J* 19 and 8, 3-H), 2.47 (1 H, ddd, *J* 19, 12.5 and 2, 3-H), 2.75 (1 H, m, 8-H), 2.79 (1 H, dd, *J* 13 and 8, 2-H) and 3.67 (3 H, s); δ_C(67.5 MHz) 8.52 (CH_3), 22.35 (CH_2), 27.23 (CH_3), 28.99 (CH_2), 34.26 (CH_3), 39.57 C, 40.37 (CH_2), 44.96 (CH), 47.64 (CH_2), 48.09 (CH), 49.40 (CH), 51.25 (CH_3), 51.58 (CH), 55.18 C, 175.52 C and 218.19 C; *m*/*z* 264 (28), 249 (5), 207 (100), 205 (11) and 163 (13%) (Found: M, 264.1717. Calc. for $C_{16}H_{24}O_3$: M, 264.1725).

When cerium(III) chloride (*ca.* 300 mg) was added to the sodium borohydride reduction, compound **5** was obtained as the sole isolable product in 96.5% yield, after the same treatments as above.

Diisobutylaluminium Hydride (DIBAL) *Reduction followed by Diazomethane Treatment of Terrecyclic Acid* A **1**.—To a solution of terrecyclic acid A **1** (43 mg) in toluene (4 ml) was added a hexane solution of diisobutylaluminium hydride (1 mol dm^{-3}; 1 ml) under a nitrogen atmosphere at −78 °C. The mixture was stirred for 2 h at the same temperature after which it was diluted with water and the toluene evaporated. The mixture was then acidified with hydrochloric acid and extracted with ether. The ether solution was washed with saturated brine, dried ($MgSO_4$) and filtered. To the filtered ether solution was added a large excess of an ether solution of diazomethane. After the mixture had been set aside overnight, it was evaporated and the residue subjected to column chromatography by silica gel (16 g) [benzene–acetone (50:1)] to afford **7** (13.5 mg), **6** (28.5 mg) and **5** (4 mg), successively.

Benzoylation of 4β*-Hydroxy Ester* **6**.—A mixture of **6** (7 mg) and benzoyl chloride (*ca.* 0.1 ml) in pyridine was stirred overnight at room temperature. It was then diluted with cold water, and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and saturated brine, dried ($MgSO_4$) and evaporated. The crude benzoate was purified by column chromatography on silica gel with benzene as eluant to afford the crystalline benzoate **8** (9 mg), m.p. 111.5–112.5 °C (recrystallized from benzene–acetone); λ_{max}(EtOH)/nm 229.5 (ε 12 900 dm^3 mol^{-1} cm^{-1}); CD (*c* 0.002 68, EtOH) $[\theta]_{300}$ 0, $[\theta]_{280}$ 2050, $[\theta]_{255}$ 670, $[\theta]_{230}$ 23 400 and $[\theta]_{215}$ 0; ν_{max}(KBr)/cm^{-1} 1735, 1715, 1640, 1275, 1265, 1170, 1115, 920 and 880; δ_H(90 MHz) 1.14 (3 H, s), 1.24 (3 H, s), 3.36 (3 H, s), 5.09 (1 H, br s), 5.40 (1 H, br s), 5.82 (1 H, br d, *J* 5), 7.42 (3 H, m) and 8.06 (2 H, m); *m*/*z* 368 (11), 226 (7), 311 (5), 246 (29), 131 (39) and 105 (100%) (Found: M, 368.2006. Calc. for $C_{23}H_{28}O_4$: M, 368.1988).

Catalytic Hydrogenation of the 4α*-Hydroxy Ester* **5**.—A mixture of **5** (13 mg) and a catalytic amount of 10% Pd–C in methanol (2 ml) was stirred under hydrogen atmosphere at room temperature for 1 h. After filtration and evaporation, the reaction mixture was separated by silica gel (7 g) column chromatography. Elution with benzene–acetone (20:1) afforded the 5α-methyl alcohol **11** (2 mg) as a less polar product and 5β-methyl alcohol **10** (11 mg) as a more polar product.

Compound **10**: m.p. 124–125.5 °C (benzene–acetone); ν_{max}(KBr)/cm^{-1} 3550–3100br, 1730, 1195, 1165, 1090, 1070 and 1030; δ_H(90 MHz) 0.90 (3 H, d, *J* 7), 1.06 (3 H, s), 1.25 (3 H, s), 2.51 (1 H, br d, *J* 7.5, 8α-H), 3.08 (1 H, dd, *J* 13 and 6.5, 2β-H), 3.64 (3 H, s) and 3.81 (1 H, ddd, *J* 9.5, 9 and 6, 4β-H); δ_C(22.5 MHz) 13.43 (CH_3), 24.54 (CH_2), 27.14 (CH_3), 29.06 (CH_2), 35.13 (CH_3), 39.30 (CH_2), 39.38 C, 46.45 (CH), 48.35 (CH), 49.14 (CH), 51.19 (CH_3), 53.17 (CH), 54.80 C, 59.92 (CH_2), 82.29 (CH), 174.44 C; *m*/*z* 266 (2), 248 (76), 233 (100) and 192 (38%) (Found: *m*/*z* 266.1903. Calc. for $C_{16}H_{26}O_3$: M, 266.1881).

Compound **11**: m.p. 84.5–85.5 °C (recrystallized from benzene); ν_{max}(KBr)/cm^{-1} 3550, 1700, 1205, 1155, 1050, 1000 and 945; δ_H(90 MHz) 1.02 (3 H, d, *J* 7), 1.08 (3 H, s), 1.28 (3 H, s), 3.61 (3 H, s) and 4.20 (1 H, ddd, *J* 6.5, 6.5 and 1.5); δ_C(22.5 MHz) 9.24 (CH_3), 22.08 (CH_2), 27.66 (CH_3), 29.69 (CH_2), 34.27 (CH_3), 38.27 (CH_2), 40.01 C, 45.23 (CH), 46.56 (CH_2), 49.68 (CH), 50.22 (CH), 50.54 (CH), 50.90 (CH_3), 57.75 C, 76.98 (CH) and 176.39 C; *m*/*z* 266 (2.5), 248 (87), 233 (100), 192 (42) and 131 (60%) (Found: *m*/*z* 266.1872. Calc. for $C_{16}H_{26}O_3$: M, 266.1881).

Catalytic Hydrogenation of the 4β*-Hydroxy Ester* **6**.—A mixture of **6** (25 mg) and a catalytic amount of 10% Pd–C in methanol (2 ml) was stirred under a hydrogen atmosphere at room temperature for 1 h. After filtration and evaporation, the reaction mixture was separated by silica gel (5 g) column chromatography. Elution with benzene–acetone (20:1) afforded the dehydro ester **14** (8.5 mg), the 5β-methyl alcohol **12** (12.5 mg) and the 5α-methyl alcohol **13** (*ca.* 1 mg).

Compound **12** (less polar alcohol): an oil; ν_{max}(neat)/cm^{-1} 3600–3100br, 1735, 1200, 1160 and 1070; δ_H(90 MHz) 0.84 (3 H, d, *J* 7), 1.07 (3 H, s), 1.19 (3 H, s), 2.57 (1 H, d, *J* 8), 3.06 (1 H, t, *J* 9), 3.67 (3 H, s), 4.15 (1 H, br, $W_{\frac{1}{2}}$ *ca.* 10); δ_C(22.5 MHz) 9.89 (CH_3), 24.81 (CH_2), 27.06 (CH_3), 29.36 (CH_2), 34.37 (CH_3), 39.38 (CH_2), 39.84 C, 46.51 (CH), 49.54 (CH), 49.60 (CH), 50.11 (CH), 51.71 (CH_3), 55.85 C, 59.05 (CH_2), 77.71 (CH) and 179.04 C; *m*/*z* 266 (4), 248 (82), 233 (100), 192 (50), 147 (47) and 133 (55%) (Found: M, 266.1906. Calc. for $C_{16}H_{26}O_3$: M, 266.1881).

Compound **13** (more polar alcohol): m.p. 125–126 °C (recrystallized from benzene–acetone); ν_{max}(KBr)/cm^{-1} 3500–3100br, 1730, 1200, 1175, 1160 and 1075; δ_H(90 MHz) 0.99 (3 H, d, *J* 6.5), 1.07 (3 H, s), 1.12 (3 H, s), 3.66 (3 H, s) and 3.94 (1 H, ddd, *J* 8.5, 8.5 and 8.5); δ_C(22.5 MHz) 11.43 (CH_3), 22.10 (CH_2), 26.90 (CH_3), 29.47 (CH_2), 32.72 (CH_3), 37.92 (CH_2), 40.06 C, 47.59 (CH), 47.59 (CH), 47.67 (CH_2), 49.00 (CH), 50.71 (CH), 51.06 (CH_3), 56.75 C, 78.58 (CH) and 175.87 C; *m*/*z* 266 (1.5), 248 (74), 233 (100), 191 (48) and 131 (90%) (Found: M, 266.1896. Calc. for $C_{16}H_{26}O_3$: M, 266.1881).

Compound **14**: an oil; ν_{max}(neat)/cm^{-1} 1730, 1640, 1210 and 1150; δ_H(270 MHz) 1.07 (3 H, s), 1.16 (3 H, s), 1.46 (1 H, d, *J* 13.5), 1.56 (1 H, d, *J* 13.5), 1.56 (3 H, s), 2.83 (1 H, d, *J* 5), 3.59 (3 H, s) and 5.08 (1 H, br s); *m*/*z* 248 (21), 233 (18), 191 (33) and 131 (100%) (Found: M, 248.1756. Calc. for $C_{16}H_{24}O$: M, 248.1774).

Methyl Esterification of Terrecyclic Acid A **1**.—Methyl iodide (0.6 ml) was added dropwise to a solution of terrecyclic acid A **1** (105 mg) in acetonitrile (10 ml) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (2 ml), and the mixture was stirred for 6.5 h at *ca.* 40–50 °C. After evaporation, the reaction mixture was extracted with ethyl acetate, washed with brine and dried ($MgSO_4$). Purification of the residue by column chromatography on silica gel (3 g) (eluted with benzene) afforded the methyl ester **15** (103 mg) as a colourless oil, ν_{max}(neat)/cm^{-1} 1730, 1640, 1155, 935 and 910; δ_H(90 MHz) 1.15 (3 H, s), 1.20 (3 H, s), 3.53 (3 H, s), 5.13 (1 H, s) and 5.90 (1 H, s); δ_C(22.5 MHz) 22.59 (CH_2), 27.36 (CH_3), 28.96 (CH_2), 34.81 (CH_3), 40.49 C, 41.42 (CH_2), 46.35 (CH), 47.92 (CH), 49.00 (CH), 51.19 (CH_3), 54.09 (CH_2), 55.18 C, 115.31 (CH), 150.95 C, 175.03 C and 206.81 C; *m*/*z* 262 (100), 247 (87), 230 (95), 221 (38), 207 (74), 202 (62), 187 (60), 147 (62) and 91 (53%) (Found: M, 262.1592. Calc. for $C_{16}H_{22}O_3$: M, 262.1569).

Catalytic Hydrogenation of Terrecyclic Acid A Methyl Ester **15**.—A mixture of compound **15** (10 mg) and a catalytic amount of 10% Pd–C in methanol (2 ml) was stirred under a hydrogen atmosphere at room temperature for 1 h. It was then filtered and evaporated to give the saturated keto ester **7** (10 mg) as the sole product. Neither ^{1}H NMR spectroscopy nor TLC detected other isomers.

Oxidation of the 3β-*Hydroxy*-4β-*methyl Ester* **12**.—A few drops of Jones reagent were added to a solution of **12** (6 mg) in acetone (2 ml) at 0–10 °C and the mixture was stirred for 5 min at that temperature. Aqueous sodium hydrogen sulphite and aqueous sodium hydrogen carbonate were then added and the product was extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and evaporated to give the ketone **16** as the sole product as a colourless oil; ν_{max}(neat)/cm^{-1} 1735, 1195 and 1160; δ_H(270 MHz) 0.97 (3 H, d, *J* 7.5, 6-Me), 1.13 (3 H, s), 1.16 (3 H, s), 1.43 (1 H, d, *J* 14.7, 12-H), 1.54 (1 H, dd, *J* 13.5 and 5.7, 9-H), 1.75 (1 H, d, *J* 14.7, 12-H), 1.80–1.95 (3 H, m), 2.08 (1 H, m, 9-H), 2.29 (1 H, q, *J* 7.5, 5-H), 2.41 (1 H, dd, *J* 20 and 7.7, 3-H), 2.50 (1 H, dd, *J* 20 and 11.1, 3-H), 3.63 (3 H, s) and 3.64 (1 H, dd, *J* 11.1 and 7,7, 2-H); δ_C(67.5 MHz) 13.09 (CH_3), 24.64 (CH_2), 26.91 (CH_3), 28.23 (CH_2), 34.21 (CH_3), 39.11 C, 40.45 (CH_2), 43.03 (CH_2), 45.88 (CH), 50.11 (CH), 51.36 (CH_3), 54.13 (CH), 55.41 (CH_2), 55.65 C, 177.09 C and 222.30 C; *m*/*z* 264 (71), 249 (31), 246 (21), 221 (20), 207 (100) and 163 (52%) (Found: M, 264.1727. Calc. for $C_{16}H_{24}O_3$: M, 264.1725).

A mixture of **16** (5 mg) and a catalytic amount of 10% Pd–C in methanol (2 ml) was stirred under hydrogen atmosphere at room temperature for 1 h. After filtration and evaporation, only the starting material **16** could be recovered no isomerization having occurred (^{1}H NMR).

Isomerization of the 4β-*Methyl Ketone* **16** *into the* 4α-*Methyl Ketone* **7**.—3% Methanolic hydrogen chloride (3 ml; prepared by adding 0.15 ml of acetyl chloride to 3 ml of methanol) was added to the 4β-methyl ketone **16** (*ca.* 3 mg), and the mixture was stirred for 0.5 h at room temperature. After addition of saturated aqueous sodium hydrogen carbonate and evaporation of methanol, the mixture was extracted with ether. The ether layer was washed with brine and dried ($MgSO_4$), and evaporated to give the 4α-methyl ketone **7** (*ca.* 3 mg) was obtained as the sole product.

Sodium Borohydride Reduction of the Ketone **7**.—A mixture of **7** (63 mg) and sodium borohydride (12 mg) in methanol (5 ml) was stirred for *ca.* 0.5 h at room temperature. Acetone and dilute hydrochloric acid were added and the mixture was extracted with ethyl acetate. The extract was washed, dried and evaporated to give a residue which was subjected to column chromatography on silica gel (15 g). Elution with benzene–acetone (10 : 1) afforded the 5α-methyl 4α-alcohol **11** (55 mg) as a less polar compound and the 5α-methyl 4β-alcohol **13** (7.5 mg) as a more polar alcohol.

Acknowledgements

We thank Dr. Kazuo Furihata (The Institute of Applied Microbiology, The University of Tokyo) for the measurements of 400 MHz ^{1}H NMR spectra, including NOE experiments. We also express thanks to Emeritus Professor Michio Shiota (Department of Chemistry, Ochanomizu University) for his valuable discussions on catalytic hydrogenations.

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Paper 0/03197F
Received 16*th July* 1990
Accepted 10*th August* 1990