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Marine Terpenes and Terpenoids. V.[1] Oxidation of Sarcophytol A, a Potent Anti-tumor-Promoter from the Soft Coral *Sarcophyton glaucum*

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Sarcophytol A (**1a**), a potent anti-tumor-promotor cembranoid from the soft coral *Sarcophyton glaucum*, was subjected to various oxidation reactions. *m*-Chloroperbenzoic acid oxidation of **1a** gave two epoxides (**2a**, **2b**) which were converted to the corresponding diols **6b**, **11b**, **12b**, **12'b** and triols **4b**, **9b**. Lithium aluminum deuteride reduction of **2a** gave a C-7 monodeuterated diol; this was used as a model experiment for the tritiation of **1a**. Chromic acid oxidation of **1a** gave seco-cembranoids **13b**—**18**, a dienone **19**, and a dihydrofuran derivative **20a**. Sarcophytol A acetate (**1b**) was less reactive in chromic acid oxidation and afforded a seco-aldehyde **22a** and a dihydroxy derivative **23a** in low yield. Hydrolysis of **22a** followed by acid treatment afforded the furan **18**. Hydrolysis of **23a** gave a triol, which, on further oxidation, gave the aldehyde **16**, the major product of the chromic acid oxidation of **1a**.

Keywords——soft coral; *Sarcophyton glaucum*; cembranoid; seco-cembranoid; sarcophytol A; oxidation

Sarcophytol A (**1a**) is a simple monohydroxy cembratetraene which we previously isolated from *Sarcophyton glaucum*, a common soft coral found in the coral reefs of Indo-Pacific coastal waters.[2] Recently, Fujiki and co-workers found that sarcophytol A efficiently inhibits the activity of the powerful tumor promoter teleocidin,[3a] in a two-stage carcinogenesis experiment on the mouse dorsal skin using dimethylbenzanthracene as an initiator.[3b,4] The effects on the growth and average numbers of tumors were observed even with an equimolar amount of **1a** with respect to teleocidin, and its potency is almost equal to those of known anti-tumor-promoter retinoic acid derivatives. Usually retinoids simultaneously cause severe hypervitaminosis A syndrome when applied to test animals,[5] which limits the prospects of clinical use of retinoids in the future. The potency of sarcophytol A is also unparalleled when compared with known natural anti-tumor-promoters such as pentagalloylglucose,[6] flavonoids,[7] or cembranoids from tobacco leaves,[8] since they invariably exert their activity only when amounts more than thousand times that of the promoters are applied.

There are several reasons that led us to examine the derivatization of sarcophytol A. In the first place its tritium labeling is indispensable for biochemical and physiological experiments. Secondly, unsaturated cembranoids are generally susceptible to oxidation and the structures and properties of the possible oxidative products should be taken into account. Also, the lipophilic nature of **1a** sometimes made it difficult to dissolve at the required concentrations in aqueous media, so that more hydrophilic derivatives of **1a** were desirable as possible substitutes for **1a**. For these reasons we prepared several oxidized derivatives of **1a** and also examined its stability to autoxidation.

S. glaucum is one of the most intensively studied soft corals as regards its chemical components but the major cembranoids varied according the localities where the coral was

collected.[9] *S. glaucum* collected at Ishigaki Island, Okinawa, contains mainly **1a** (about a quarter of the total lipids) with its dihydroxy derivatives.[2,13] The geometry at the C-1 double bond and the absolute configuration at C-14 of **1a** remained unsettled. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1a** showed 1,2-*Z* geometry since there are significant nuclear Overhauser effects (NOEs) between the protons at C-14 (δ 4.99, dd, J= 10.0, 4.0 Hz) and at C-3 (δ 5.99, br d, J= 11.5 Hz), and also between the protons at C-2 (δ 6.15, d, J= 11.5 Hz) and C-16, 17, and C-18 (δ 1.74, d, J= 1.0 Hz). The absolute configuration at C-14 was shown to be *S* by Horeau's method.[10,11]

Epoxidation of the acetate **1b** gave two monoepoxides **2a** and **2b**. The lack of NOEs between the methyl group and the vicinal oxymethine proton of the epoxide rings indicated that both **2a** and **2b** are *E*-epoxides. Treatment of **2a** with *p*-toluenesulfonic acid in benzene gave a mixture of allyl alcohols from which the major product **3a** was isolated. Similar treatment of **2b** gave an allyl alcohol **8a** as the predominant product. The products from **2a** were complex and a small amount of **8a** was also obtained. The ^{1}H-NMR and ultraviolet (UV) spectra of **3a** and **8a** (Experimental) indicated that their conjugated diene moieties were unaffected by epoxidation and acid treatment. Since the coupling patterns of C-14 acetoxy methine protons in **3a** and **8a** were unchanged (**3a**, δ 5.82, dd, J= 11.4, 3.3 Hz; **8a**, δ 5.73, dd, J= 10.3, 4.2 Hz), as compared with that of **1b** (δ 6.03, dd, J=9.5, 4.5 Hz), both **2a** and **2b** are 7,8-epoxides. Formation of **8a** from **2a** was assumed to be due to the acid-catalyzed isomerization from **3a**, or to the partial conversion of **2a** to **2b** by hydrolysis of the epoxide ring, giving **4a** or **9a**, followed by recyclization. The absolute configurations at C-7 of **3a** and **8a** were shown by Horeau's method to be *R* and *S*, respectively, and hence the configuration of the epoxide group of **2a** is 7*R*,8*R* and that of **2b** is 7*S*,8*S*.

Treatment of **2a** with dilute perchloric acid in acetone gave a glycol **4a**. The ring-opening occurred at C-8 since dehydration of the diacetate **4c** with thionyl chloride in pyridine followed by hydrolysis gave **3b**. Similarly, **2b** gave the glycol **9a** which on acetylation, dehydration, and hydrolysis afforded **8b**. The major product was the terminal olefin (**5** from **4c** and **10** from **9c**) in both cases. Lithium aluminum hydride reduction of **2a** gave a diol **6b** as the major product. In contrast, the reduction of **2b** gave the 8,14-diol **11b** and significant amounts of 7,14-diols **12b** and **12'b**, whose configurations at C-8 are unknown at present. These ten di- and trihydroxycembranoids (**3b**, **4b**, **5**, **6b**, **8b**, **9b**, **10**, **11b**, **12b**, **12'b**) retain the 1,3-diene and 14-hydroxy moieties of **1a**. However, their diverse specific rotations and the chemical shifts of the protons at C-2 and C-3, and C-14 to C-18 (Experimental) indicate that there are significant conformational variations among these compounds. Hydrolysis of one acetoxyl group sometimes caused large differences; for example, the triol monoacetate **9a** ($[\alpha]_D$ +118°) on hydrolysis gave the triol **9b**, $[\alpha]_D$ −105°.

For the tritiation of **1a**, a model experiment was carried out using deuterium. Dehydration of the monoacetate **6a** with phosphoryl chloride or thionyl chloride in pyridine gave sarcophytol A acetate (**1b**) as the major product, with smaller amounts of isomeric olefins. The by-products were easily removable on silver nitrate-impregnated silica gel chromatography. Pyrolysis of the diacetate of **6b** led to similar results but in poor overall yield. Lithium aluminum deuteride reduction and acetylation of **2b** gave **6c** in which the C-7 pro-(*S*) hydrogen was replaced by deuterium. The introduced deuterium would not be simply antiperiplanar with respect to the C-8 hydroxyl group, unlike acyclic compounds, but the *anti*-elimination reaction was supposed to give an olefin in which the deuterium at C-7 was mostly lost. Indeed, treatment of **6c** with phosphoryl chloride or thionyl chloride in pyridine and subsequent purification afforded **1b** which retained only 25% or 37% of deuterium respectively, as judged from the intensity of C-7 olefinic proton signal (δ 4.98, br t, J=7.0 Hz) in the ^{1}H-NMR spectra. However, treatment of **6c** with thionyl chloride in refluxing benzene, which was proposed to be a *syn*-elimination reaction,[12] was quite efficient and the purified

Chart 1

product **7** showed nearly complete loss of the signal at δ 4.98. One of the olefinic methyl signals (δ 1.47) of **7** was heightened as compared with that of **1b**, showing it to be that of the C-19 protons. These three dehydration methods are however equally applicable for the tritiation of **1a** to a sufficient specific activity for ordinary use.

Compound **1a** was next subjected to several oxidative conditions. Manganese dioxide oxidation gave only a low yield of the dienone **19**.[13] After several attempts, chromic acid oxidation of **1a** using Jones' reagent was studied in detail since it gave a variety of products, some of which are products of autoxidation of **1a**. A solution of **1a** in ether was stirred briefly with excess Jones' reagent and the product was separated to yield a minor acidic fraction, which gave **13b**—**15b** after methylation, and a major neutral fraction, which gave **16**—**19** and **20a**. Compounds **13b**—**15b** were found to be the seco-acid derivatives formed by oxidative cleavage at C-1,14 (**13b**, **14b**), and C-1,14 and C-3,4 (**15b**). Compound **13b** was an α,β-unsaturated ketone [UV, 222 nm (ε, 12000)] and its ^{1}H-NMR spectrum showed the signals of two olefinic methyls (δ 1.59, 3H, s; 1.68, 3H, br d, J=0.7 Hz), an isopropyl (δ 1.13, 6H, d, J=6.8 Hz), one tertiary methyl which is adjacent to oxygen (δ 1.34, 3H, s), two olefinic protons linked to isolated double bonds (δ 5.14 and 5.26, each 1H, br t, J=7.0 Hz), and olefinic protons of an α,β-conjugated ketone (δ 6.41, 1H, d, J=15.6 Hz; 6.88, 1H, d, J=15.6 Hz). Its infrared (IR) spectrum showed absorptions due to hydroxyl (3450 cm^{-1}), ester (1735 cm^{-1}), and α,β-unsaturated ketone (1690, 1668, 1625 cm^{-1}) moieties. All these data support the view that oxidative cleavage occurred at C-1,14 and the conjugated diene moiety in **1a** was converted to a γ-hydroxy-α,β-unsaturated ketone in **13b**. Compound **14b** was a conjugated enol dihydrofuran derivative of **13a**, and showed signals of the olefinic protons of a conjugated diene at δ 5.91 (d, J=5.9 Hz) and 6.26 (d, J=5.9 Hz) in the ^{1}H-NMR spectrum. The carbon-13 NMR (^{13}C-NMR) spectrum showed characteristic signals of the enol moiety at δ 153.6 (C-1) and 98.5 (C-15) ppm. Compound **15b** was the methylketone derivative (^{1}H-NMR δ: 2.14, 3H, s) formed by cleavage at two sites (C-1,14 and C-3,4).

The neutral fraction was composed of seco-cembranoid (**16**—**18**) and cembranoid (**19**, **20a**) derivatives. The major product was the ketoaldehyde **16** and its ^{1}H-NMR signals were essentially the same (Experimental) as those of **13b** except that the signal of the methoxyl group was replaced with that of an aldehyde (δ 9.96, 1H, t, J=2.5 Hz). Compound **17** was a 1 : 1 mixture of α,β-unsaturated *Z*- and *E*-aldehyde [^{1}H-NMR δ: 9.99 and 9.92, each d, J=8.1 Hz]. Alkaline treatment of **16** gave **17** and a 1 : 1 mixture of conjugated dihydrofuran (**21**). It is interesting to note that compounds **13a**—**17** are related to retinoids both in their gross molecular weight and partial structure involving C-6 to C-14, and C-19 and C-20. Compound **18** was a seco-cembranoid having a furan ring formed by cleavage at C-3,4, followed by cyclization. Its ^{1}H-NMR spectrum showed the signals of a 2,3-disubstituted furan ring at δ 6.25 (1H, d, J=2.0 Hz) and 7.23 (1H, d, J=2.0 Hz), and the signal of a methylketo group at δ 2.13. Compound **19** was obtained in low yield and was identical with the dienone obtained by manganese dioxide oxidation of **1a**.[13] Compound **20a** was also a cembranoid derivative of **1a** having one extra oxygen atom. The IR spectrum showed the presence of a hydroxyl group which was not acetylated under the usual conditions (Ac_2O–pyridine). The UV absorption of the diene was lost and the ^{1}H-NMR showed the signals of the protons on a 2,3,5-trisubstituted dihydrofuran ring (δ 4.70, 1H, dq, J=5.5, 1.0 Hz, 3-H; δ 4.86, 1H, br t, J=5.5 Hz, 14-H; δ 5.41, 1H, q, J=1.0 Hz, 2-H). These assignments were based on the presence of coupling of 14-H with one of the 13-H (δ 2.46, dd, J=13.6, 5.5 Hz) and also with 3-H, the latter being characteristic of such dihydrofuran ring systems, as found in deoxosarcophine or sarcophytonin A.[2,14] The acetate **20b**, prepared by acetic anhydride–triethylamine–dimethylaminopyridine medium, showed little change in the signals of these protons (Experimental).

Sarcophytol A acetate (**1b**) was resistant to Jones' reagent and after prolonged stirring

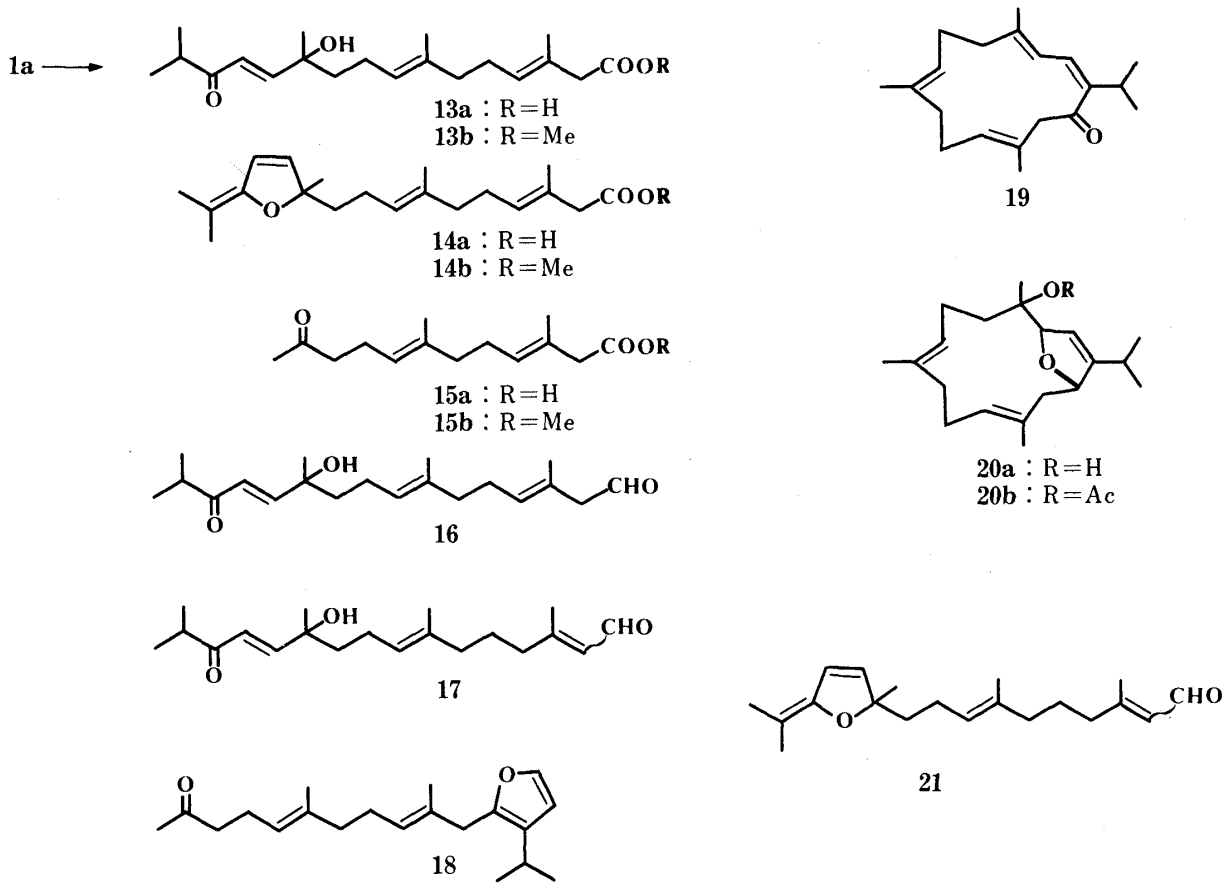

Chart 2

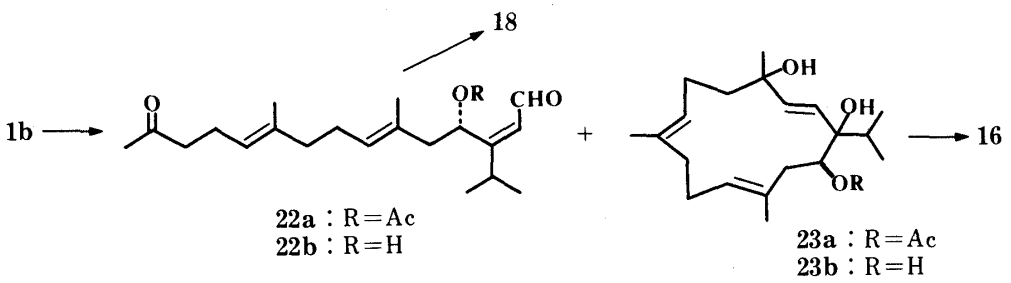

Chart 3

(22 h), it afforded small amounts of **22a** and **23a** (Chart 3). Compound **22a** was an α,β-unsaturated aldehyde formed by the oxidative cleavage of the C-3,4 bond [UV: 234 nm (ε, 16000). ^{1}H-NMR δ: 2.04, 3H, s, Ac; 2.14, 3H, s, 18-H; 5.90, 1H, d, J=7.8 Hz, 2-H; 5.98, 1H, dd, J=7.8, 5.6 Hz, 14-H; 10.19, 1H, d, J=7.8 Hz, 3-H]. Compound **23a** was the 1,4-dihydroxy derivative with an *E*-double bond at C-2,3 (^{1}H-NMR δ: 5.74, 1H, d, J=16.1 Hz; 6.11, 1H, d, J=16.1 Hz). The structures of **22a** and **23a** were confirmed by correlating to **18** and **16**, respectively. Alkaline hydrolysis of **22a** gave an alcohol which on brief treatment with dilute acid was converted to **18** in 85% yield. Alkaline hydrolysis of **23a** gave a triol **23b**, which, on brief treatment with Jones' reagent, afforded **16** in 60% yield. These results suggest that the primary product of the chromic acid oxidation of **1a** is probably the 3,4-epoxide **24**, and **20a** is an its internal cyclization product. Conversion of **24** to the glycol **25**, or to the glycol **23b** with double bond migration, and subsequent oxidation would afford compounds **13a**, **15a**, **16**, and **22b**. Probably the strongly acidic Jones' reagent catalyzed the cyclization of **13a** and **22b** into

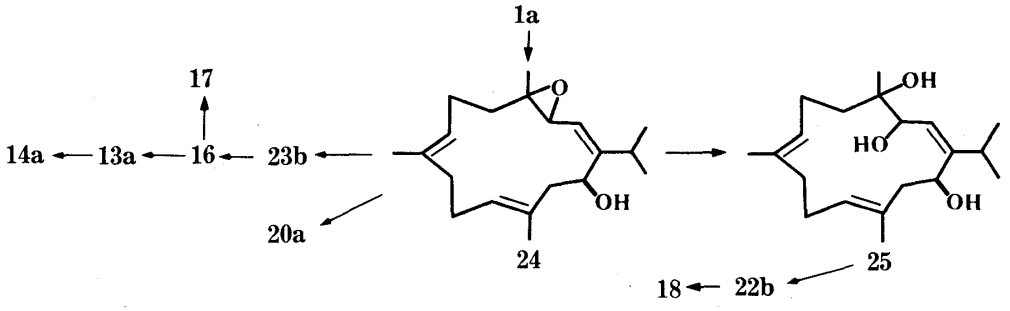

Chart 4

14a and **18**, respectively (Chart 4).

Examination of the complex autoxidation products of **1a** showed that compound **20a** was one of the major components. Compound **18** was also a minor component but the presence of other synthetic compounds, described above, were not confirmed. When **1a** was kept in air at room temperature, it afforded mainly two more polar compounds, supposed to be **24** and a derivative. They are quite labile and after separation soon changed to mixtures, of which compound **20a** was the major product. Similar but much slower conversion was observed when **1a** was kept in dilute solution in benzene or hexane–ethyl acetate (8 : 2). Facile decomposition of **1a** was observed when **1a** was kept in chloroform. A yellow color developed gradually and decomposition was complete in a week. Probably the trace of hydrochloric acid in chloroform accelerated the decomposition. In contrast, **1a** was stable in ethanol solution and showed virtually no change on standing at room temperature for 7 d.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-4 digital polarimeter. ^{1}H-NMR spectra were determined in $CDCl_3$ solution with tetramethylsilane as an internal standard, on a JNM GX-270 spectrometer at 270 MHz unless otherwise specified. ^{13}C-NMR spectra were determined in $CDCl_3$ solution on a JNM FX-90Q spectrometer at 22.5 MHz. Mass spectra (MS) were determined on a JEOL JMS D300 spectrometer. IR spectra were taken on a JASCO A 102 spectrometer. UV spectra were determined on a Hitachi EPS-3T spectrometer. Chromatography was carried out on a column of silica gel by the flash chromatography method.[15]

Configuration at C-14 of 1a——Compound **1a** (288 mg, 1 mmol) was esterified with 620 mg (2 mmol) of α-phenylbutyric anhydride in pyridine for 1 h. Thin-layer chromatography (TLC) of the mixture showed about 80% of **1a** was esterified. The mixture was worked up according the standard method.[10] The resultant benzene solution (5 ml) showed rotation of $-0.28°$ and, accordingly, 14*S* configuration.

Epoxidation of 1b——Compound **1b** (11.5 g) in 120 ml of $CHCl_3$ was treated dropwise with a solution of *m*-chloroperbenzoic acid (9.24 g) in 120 ml of $CHCl_3$ at 0 °C over a period of 1 h. The mixture was washed with 10% Na_2SO_3 solution (200 ml), H_2O, and saturated NaCl solution, then the solvent was evaporated off. Column chromatography of the residue in portions over silica gel with ethyl acetate–hexane (1 : 9 and 1 : 1) afforded a mixture (0.6 g) which consisted of unreacted **1b** and unidentified compounds, **2a** (4.4 g), **2b** (2.9 g), and a mixture of more polar compounds which did not show any strong UV absorption. **2a**, oil, $[\alpha]_D$ +150° (c=1.02, $CHCl_3$). ^{1}H-NMR δ: 1.06, 1.16 (each 3H, d, J=7.0 Hz, 16,17-H), 1.30 (3H, s, 19-H), 1.52 (3H, s, 20-H), 1.79 (3H, s, 18-H), 2.05 (3H, s), 2.54 (1H, sept, J=7 Hz, 15-H), 2.79 (1H, t, J=6.0 Hz, 7-H), 5.19 (1H, br t, J=6.0 Hz, 11-H), 5.92 (1H, dd, J=9.5, 4.0 Hz, 14-H), 6.08 (1H, br d, J=11.5 Hz, 3-H), 6.23 (1H, d, J=11.5 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 251 (15000). IR ν_{max}^{neat} cm^{-1}: 1735, 1650, 1605. MS *m/z*: 346 (M^+), 331, 286, 243, 137, 109. High-resolution MS [Found (Calcd)] *m/z*: $C_{22}H_{34}O_3$ (M^+), 346.25063 (346.25073). **2b**, oil, $[\alpha]_D$ +110° (c=1.18, $CHCl_3$). ^{1}H-NMR δ: 1.05, and 1.08 (each 3H, d, J=7.0 Hz, 16,17-H), 1.18 (3H, s, 19-H), 1.63 (3H, s, 20-H), 1.71 (3H, s, 18-H), 2.06 (3H, s), 2.49 (1H, sept, J=7.0 Hz, 15-H), 2.76 (1H, dd, J=8.5, 3.5 Hz, 7-H), 5.03 (1H, tq, J=7.0, 1.5 Hz, 11-H), 6.00 (1H, dd, J=7.8, 6.2 Hz, 14-H), 6.18 (1H, d, J=11.0 Hz, 2-H), 6.24 (1H, br d, J=11.0 Hz, 3-H). UV λ_{max}^{EtOH} nm (ε): 250 (17400). IR ν_{max}^{neat} cm^{-1}: 1735, 1650, 1610. MS *m/z*: 346 (M^+), 331, 286, 243, 137, 109. High-resolution MS [Found (Calcd)] *m/z*: $C_{22}H_{34}O_3$ (M^+), 346.24956 (346.25073).

Conversion of 2a to 3a and 3b——A mixture of **2a** (200 mg) and *p*-toluenesulfonic acid (17 mg) in benzene (40 ml) was stirred at 55 °C for 15 min then washed with H_2O, saturated $NaHCO_3$ solution, H_2O, and saturated NaCl

solution, then the solvent was evaporated off. Repeated column chromatography of the residue over silica gel with ethyl acetate–hexane (1 : 3) afforded **3a** (32 mg) and **8a** (10 mg). **3a**, oil. ^{1}H-NMR δ: 1.07 and 1.16 (each 3H, d, J= 7.0 Hz, 16,17-H), 1.62 (3H, t, J=1.0 Hz), 1.68 (3H, s), 1.72 (3H, s), 2.02 (3H, s), 2.55 (1H, sept, J=7.0 Hz, 15-H), 2.87 (1H, ddd, J=13.7, 11.5, 8.5 Hz, 10-H), 3.85 (1H, dd, J=11.0, 4.8 Hz, 7-H), 5.01 (1H, ddd, J=11.5, 4.0, 1.0 Hz), 5.33 (1H, t, J=8.4 Hz), 5.76 (1H, br d, J=11.7 Hz, 3-H), 5.82 (1H, dd, J=11.4, 3.3 Hz, 14-H), 6.18 (1H, d, J=11.7 Hz, 2-H). ^{13}C-NMR δ: C-1 (141.9), C-2, C-3 (121.6, 123.9), C-4 (135.2), C-5, C-6 (26.7, 29.4), C-7 (77.9), C-8, C-12 (130.8, 132.3), C-9,11 (127.9, 125.3), C-10 (36.5), C-13 (42.3), C-14 (73.3), C-15 (28.0), C-16, C-17 (24.4, 25.4), C-18 (14.3), C-19 (9.4), C-20 (18.1), OAc (21.4, 170.3). Assignments were based on the structural similarity and dissimilarity with **1b**. UV λ_{max}^{EtOH} nm (ε): 254 (16500). IR ν_{max}^{neat} cm^{-1}: 3400, 1730. MS m/z: 346 (M$^+$), 286, 243, 225, 203, 137, 109. Compound **8a** was identical with the compound obtained from **2b** in several TLC systems. Compound **3a** (10 mg) was treated with α-phenylbutyric anhydride as shown for **1a**. The resultant excess acid in 1 ml of benzene showed the rotation of +0.05° and hence 7*R* configuration of **3a**.[10] The blank test showed rotation of less than ±0.01°. Hydrolysis of **3a** by 2.5% KOH in MeOH followed by the usual work-up gave **3b**. Oil, $[\alpha]_D$ +100° (c=0.65, $CHCl_3$). ^{1}H-NMR δ: 1.12 and 1.15 (each 3H, d, J=7.0 Hz, 16,17-H), 1.66 and 1.63 (each 3H, s, 19,20-H), 1.72 (3H, s, 18-H), 2.62 (1H, sept, J= 7.0 Hz, 15-H), 2.85 (1H, ddd, J=13.6, 11.4, 8.4 Hz, 10-H), 3.86 (1H, dd, J=11.0, 5.0 Hz, 7-H), 4.82 (1H, dd, J=11.0, 3.2 Hz, 14-H), 5.01 (1H, br dd, J=11.5, 3.5 Hz), 5.26 (1H, br t, J=8.4 Hz), 5.70 (1H, br d, J=11.7 Hz, 3-H), 6.14 (1H, d, J=11.7 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 254 (23000). MS (m/z): 304 (M$^+$), 286, 271, 261, 243, 235, 217, 137.

Conversion of 2b to 8a and 8b——A solution of **2b** (310 mg) in benzene (40 ml) was treated with *p*-toluenesulfonic acid (23 mg) at 55 °C for 15 min and then the mixture was worked up as above. Silica gel column chromatography of the mixture with ethyl acetate–hexane (1 : 3) gave 210 mg of **8a** as an oil. ^{1}H-NMR δ: 1.05 and 1.15 (each 3H, d, J= 6.8 Hz, 16,17-H), 1.48 (3H, s), 1.64 (3H, t, J=1.0 Hz), 1.72 (3H, br s, 18-H), 2.04 (3H, s), 2.90 (1H, dt, J=13.7, 9.6 Hz, 10-H), 3.95 (1H, br t, J=7.3 Hz, 7-H), 5.2—5.5 (2H, m), 5.73 (1H, dd, J=10.3, 4.2 Hz, 14-H), 5.89 (1H, br d, J= 11.7 Hz, 3-H), 6.16 (1H, d, J=11.7 Hz, 2-H). ^{13}C-NMR δ: C-1 (141.8), C-2,3 (121.8, 123.1), C-4 (134.9), C-5,6 (27.3, 29.8), C-7 (80.0), C-8 (136.5), C-9,11 (125.3, 125.8), C-10 (36.6), C-12 (130.0), C-13 (42.1), C-14 (74.3), C-15 (28.8), C-16,17 (23.8, 25.2), C-18 (15.1), C-19 (10.5), C-20 (19.0). UV λ_{max}^{EtOH} nm (ε): 254 (15500). IR ν_{max}^{neat} cm^{-1}: 3400, 1735. MS m/z: 346 (M$^+$), 328, 286, 271, 243, 225, 137, 109. Compound **8a** (10 mg) was treated with α-phenylbutyric anhydride as described for **1a**. The resultant excess acid in 1 ml of benzene showed the rotation of −0.07°, and hence 7*S* configuration of **8a**.[10] The blank test showed rotation of less than ±0.01°. Hydrolysis of **8a** by 2.5% KOH in MeOH followed by usual work-up gave **8b**, $[\alpha]_D$ −15° (c=0.95, $CHCl_3$). ^{1}H-NMR δ: 1.11 and 1.15 (each 3H, d, J=7.0 Hz, 16,17-H), 1.49, 1.64, 1.73 (each 3H, s), 2.53 (1H, sept, J=7.0 Hz, 15-H), 2.89 (1H, dt, J=13.5, 9.5 Hz, 10-H), 3.96 (1H, dd, J=9.5, 4.0 Hz, 7-H), 4.76 (1H, br dd, J=10.0, 3.5 Hz, 14-H), 5.24 (1H, br dd, J=9.0, 6.5 Hz), 5.36 (1H, br dd, J=9.5, 7.5 Hz), 5.88 (1H, br d, J=11.5 Hz, 3-H), 6.12 (1H, d, J=11.5 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 254 (18000). MS m/z: 304 (M$^+$), 286, 271, 261, 243, 235, 217, 137.

Glycolation of 2a and 2b——(a) A solution of **2a** (250 mg) in 4 ml of acetone was treated for 5 min at room temperature with 0.6 ml of $HClO_4$ solution made from 0.15 ml of 70% perchloric acid and 5 ml of H_2O. The mixture was diluted with Et_2O and washed with H_2O and saturated NaCl solution, then the solvent was evaporated off. Column chromatography of the residue with Et_2O–$CHCl_3$ (15 : 85) gave **4a** (200 mg) as an oil, $[\alpha]_D$ +160° (c=0.81, $CHCl_3$). ^{1}H-NMR δ: 1.07 and 1.19 (each 3H, d, J=7.0 Hz, 16,17-H), 1.13 (3H, s, 19-H), 1.55 (3H, s, 20-H), 1.77 (3H, s, 18-H), 2.03 (3H, s), 2.57 (1H, sept, J=7.0 Hz, 15-H), 3.54 (1H, br t, J=7.0 Hz, 7-H), 5.56 (1H, br dd, J=9.8, 3.0 Hz, 11-H), 5.73 (1H, dd, J=9.8, 2.8 Hz, 14-H), 6.07 (1H, br d, J=11.2 Hz, 3-H), 6.27 (1H, d, J=11.2 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 251 (16000). IR ν_{max}^{neat} cm^{-1}: 3500, 1720. Hydrolysis of **4a** with 2.5% KOH in MeOH gave **4b** (180 mg). Oil, $[\alpha]_D$ +140° (c=1.0, $CHCl_3$). ^{1}H-NMR δ: 1.13, 1.18 (each 3H, d, J=7.0 Hz, 16,17-H), 1.12 (3H, s, 19-H), 1.56 (3H, s, 20-H), 1.77 (3H, s, 18-H), 2.64 (1H, sept, J=7.0 Hz, 15-H), 3.49 (1H, m, 7-H), 4.74 (1H, br d, J=9.2 Hz, 14-H), 5.47 (1H, br dd, J=9.5, 4.0 Hz, 11-H), 6.02 (1H, br d, J=11.2 Hz, 3-H), 6.24 (1H, d, J=11.2 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 251 (15500). IR ν_{max}^{neat} cm^{-1}: 3350. MS m/z: 322 (M$^+$), 304, 289, 137, 109. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{34}O_3$ (M$^+$), 322.25206 (322.25076).

(b) Compound **2b** (200 mg) was treated in the same way as shown in (a) and gave 173 mg of **9a**. Oil, $[\alpha]_D$ +118° (c=0.80, $CHCl_3$). ^{1}H-NMR δ: 1.09 and 1.18 (each 3H, d, J=7.0 Hz, 16,17-H), 1.13 (3H, s, 19-H), 1.58 (3H, s, 20-H), 1.70 (3H, s, 18-H), 2.07 (3H, s), 2.45 (1H, sept, J=7.0 Hz, 15-H), 3.45 (1H, dd, J=10.3, 1.8 Hz, 7-H), 5.41 (1H, br t, J=7.0 Hz, 11-H), 5.64 (1H, dd, J=7.7, 4.8 Hz, 14-H), 6.19 (2H, s, 2,3-H). UV λ_{max}^{EtOH} nm (ε): 251 (15000). IR ν_{max}^{neat} cm^{-1}: 3500, 1720. Hydrolysis of **9a** as in (a) gave the triol **9b** quantitatively. Oil, $[\alpha]_D$ −105° (c=1.24, $CHCl_3$). ^{1}H-NMR δ: 1.10, 1.14 (each 3H, d, J=7.0 Hz, 16,17-H), 1.09 (3H, s, 19-H), 1.57 (3H, s, 20-H), 1.71 (3H, s, 18-H), 3.60 (1H, dd, J=10.0, 3.0 Hz, 7-H), 4.48 (1H, m, 14-H), 5.43 (1H, br dd, J=9.0, 4.5 Hz, 11-H), 6.16 (1H, d, J= 11.0 Hz, 2-H), 6.45 (1H, br d, J=11.0 Hz, 3-H). UV λ_{max}^{EtOH} nm (ε): 250 (16000). MS m/z: 322 (M$^+$), 304, 289, 286, 261, 243, 235, 222, 137, 109.

Dehydration of 4c and 9c——(a) Compound **4c** was prepared from **4a** in a usual way (Ac_2O–pyridine). A solution of **4c** (74.3 mg) in 0.5 ml of pyridine was treated with 40 μl of thionyl chloride at room temperature for 1 h. After addition of H_2O, the mixture was extracted with Et_2O. The extract was washed with H_2O, 5% HCl solution, saturated $NaHCO_3$ solution, H_2O, and saturated NaCl solution, then the solvent was evaporated off. The residue was hydrolyzed with 2.5% KOH in MeOH (30 min at room temperature) and the mixture was worked up as usual. Silica

gel column chromatography of the residue with ethyl acetate–hexane (1 : 4) gave **3b** (20 mg) and **5** (20 mg). **5**, $[\alpha]_D$ +200° (c=1.50, $CHCl_3$). ^{1}H-NMR δ: 1.11 and 1.14 (each 3H, d, J=7.0 Hz, 16,17-H), 1.53 (3H, s, 20-H), 1.77 (3H, s, 18-H), 2.62 (1H, sept, J=7.0 Hz, 15-H), 3.87 (1H, br t, J=6.0 Hz, 7-H), 4.87 (1H, dd, J=10.0, 4.0 Hz, 14-H), 4.99 and 5.06 (each 1H, s, 19-H), 5.19 (1H, br t, J=6.0 Hz, 11-H), 5.89 (1H, br d, J=11.3 Hz, 3-H), 6.19 (1H, d, J=11.3 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 250 (22000). IR ν_{max}^{neat} cm^{-1}: 3350, 1005, 910. MS m/z: 304 (M^+), 286, 271, 261, 243, 235, 137, 109. Compound **3b** ($[\alpha]_D$ +95°) was identical with that obtained from **2a** as judged from UV, ^{1}H-NMR and mass spectra, and in several TLC systems.

(b) Compound **9c** was prepared in a usual way (Ac_2O–pyridine) from 200 mg of **9a**. It was dissolved in 2 ml of pyridine and 150 μl of thionyl chloride was added with cooling. After standing at room temperature for 1 h, the mixture was worked up as in (a). Silica gel column chromatography of the hydrolysis product as shown in (a) gave **8b** (40 mg) and **10** (105 mg). Compound **8b**, $[\alpha]_D$ −16.1° (c=0.62, $CHCl_3$), was identical with that obtained from **2b** as judged from UV, ^{1}H-NMR, and mass spectra, and in several TLC systems. **10**, oil, $[\alpha]_D$ +150° (c=0.71, $CHCl_3$). ^{1}H-NMR δ: 1.13 and 1.15 (each 3H, d, J=7.0, 16,17-H), 1.56 (3H, s, 20-H), 1.70 (3H, s, 18-H), 2.55 (1H, sept, J=7.0 Hz, 15-H), 4.04 (1H, br t, J=6.5 Hz, 7-H), 4.78 (1H, dd, J=9.0, 4.0 Hz, 14-H), 4.92 and 5.04 (each 1H, s, 19-H), 5.32 (1H, t, J=7.0 Hz, 11-H), 6.07 (1H, br d, J=10.5 Hz, 3-H), 6.13 (1H, d, J=10.5 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 250 (15000). MS m/z: 304 (M^+), 286, 271, 261, 243, 235, 217, 137, 109.

Lithium Aluminum Hydride Reduction of 2a and 2b——(a) $LiAlH_4$ (300 mg) was added in portions to a solution of **2a** (1 g) in dry Et_2O (10 ml). After 3 h, excess reagent was decomposed with moist Et_2O and the Et_2O layer was washed with H_2O, 5% HCl, H_2O, and saturated NaCl solution, then the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (1 : 9) gave **6b** (300 mg). Oil, $[\alpha]_D$ −30° (c=0.64, $CHCl_3$). ^{1}H-NMR δ: 1.12 and 1.13 (each 3H, d, J=7.0 Hz, 16,17-H), 1.14 (3H, s, 19-H), 1.58 (3H, s, 20-H), 1.69 (3H, s, 18-H), 4.60 (1H, m, 14-H), 5.35 (1H, br t, J=7.0 Hz, 11-H), 6.16 (1H, d, J=11.2 Hz, 2-H), 6.29 (1H, br d, J=11.2 Hz, 3-H). UV λ_{max}^{EtOH} nm (ε): 251 (17700). IR ν_{max}^{neat} cm^{-1}: 3400. MS m/z: 306 (M^+), 288, 273, 270, 255, 245, 137. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{34}O_2$ (M^+), 306.25717 (306.25587). Acetylation of **6b** under usual conditions (Ac_2O–pyridine) gave **6a**. ^{1}H-NMR δ: 1.07 and 1.17 (each 3H, d, J=7.0 Hz, 16,17-H), 1.17 (3H, s, 19-H), 1.57 (3H, d, J=1.0 Hz, 20-H), 1.69 (3H, s, 18-H), 2.07 (3H, s), 2.48 (1H, sept, J=7.0 Hz, 15-H), 5.31 (1H, br t, J=7.0 Hz, 11-H), 5.75 (1H, dd, J=8.8, 4.0 Hz, 14-H), 6.07 (1H, br d, J=10.6 Hz, 3-H), 6.19 (1H, d, J=10.6 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 251 (15000). IR ν_{max}^{neat} cm^{-1}: 3500, 1730, 1650, 1605, 1240. MS m/z: 348 (M^+), 288, 270, 255, 245, 227, 137.

(b) A solution of **2b** (300 mg) in tetrahydrofuran (10 ml) was treated with lithium aluminum hydride (100 mg) at room temperature for 1 h. Excess reagent was decomposed by adding moist Et_2O and the mixture was worked up as in (a). Separation of the residue was difficult, so the whole residue was acetylated. Silica gel column chromatography of the acetate mixture with ethyl acetate–hexane (1 : 4) gave **12a**, **12'a** and **11a** in that order, as oils. **11a**, ^{1}H-NMR δ: 1.06 and 1.19 (each 3H, d, J=7.0 Hz, 16,17-H), 1.12 (3H, s, 19-H), 1.53 (3H, s, 20-H), 1.69 (3H, s, 18-H), 2.03 (3H, s), 2.56 (1H, sept, J=7.0 Hz, 15-H), 5.39 (1H, br t, J=7.0 Hz, 11-H), 5.81 (1H, dd, J=10.0, 3.7 Hz, 14-H), 6.07 (1H, br d, J=11.0 Hz, 3-H), 6.22 (1H, d, J=11.0 Hz, 2-H). MS m/z: 348 (M^+), 330, 288, 255, 245, 227, 137. **12a**, ^{1}H-NMR δ: 0.92 (3H, d, J=6.6 Hz, 19-H), 1.04 and 1.18 (each 3H, d, J=7.0 Hz, 16,17-H), 1.58 (3H, s, 20-H), 1.78 (3H, s, 18-H), 2.01 and 2.04 (each 3H, s), 2.57 (1H, sept, J=7.0 Hz, 15-H), 4.68 (1H, dq, J=10.5, 2.5 Hz, 7-H), 5.17 (1H, t, J=7.0 Hz, 11-H), 5.91 (1H, dd, J=11.0, 3.3 Hz, 14-H), 6.07 (1H, br d, J=11.4 Hz, 3-H), 6.24 (1H, d, J=11.4 Hz, 2-H). MS m/z: 390 (M^+), 330, 270, 255, 227, 137. **12'a**, ^{1}H-NMR δ: 0.82 (3H, d, J=6.6 Hz, 19-H), 1.07 and 1.16 (each 3H, d, J=7.0 Hz, 16,17-H), 1.65 (3H, s, 20-H), 1.72 (3H, s, 18-H), 2.01 and 2.04 (each 3H, s), 2.48 (1H, sept, J=7.0 Hz, 15-H), 4.78 (1H, dq, J=9.8, 2.0 Hz, 7-H), 5.07 (1H, br t, J=7.2 Hz, 11-H), 5.73 (1H, t, J=6.5 Hz, 14-H), 6.17 (2H, s, 2,3-H). MS m/z: 390 (M^+), 330, 270, 255, 227, 137. They were hydrolyzed with 2.5% KOH in MeOH, giving **11b**, **12b** and **12'b**. **11b**, mp 102—104 °C, $[\alpha]_D$ +240° (c=0.67, $CHCl_3$). ^{1}H-NMR δ: 1.13 and 1.19 (each 3H, d, J=7.0 Hz, 16,17-H), 1.13 (3H, s, 19-H), 1.54 (3H, s, 20-H), 1.69 (3H, s, 18-H), 2.65 (1H, sept, J=7.0 Hz, 15-H), 4.82 (1H, dd, J=9.8, 3.0 Hz, 14-H), 5.37 (1H, br dd, J=9.0, 4.8 Hz, 11-H), 5.97 (1H, br d, J=11.0 Hz, 3-H), 6.19 (1H, d, J=11.0 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 251 (17000). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1650, 1605, 1100, 1005, 920. MS m/z: 306 (M^+), 288, 273, 270, 255, 245, 227, 137. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{34}O_2$ (M^+), 306.25527 (306.25577). **12b**, mp 77—78 °C, $[\alpha]_D$ +140° (c=0.42, $CHCl_3$). ^{1}H-NMR δ: 0.84 (3H, d, J=7.0 Hz, 19-H), 1.13 and 1.17 (each 3H, d, J=7.0 Hz, 16,17-H), 1.53 (3H, s, 20-H), 1.76 (3H, s, 18-H), 2.64 (1H, sept, J=7.0 Hz, 15-H), 3.49 (1H, m, 7-H), 4.91 (1H, br d, J=11.0 Hz, 14-H), 5.16 (1H, br t, J=7.0 Hz, 11-H), 5.95 (1H, br d, J=11.2 Hz, 3-H), 6.19 (1H, d, J=11.2 Hz, 2-H). UV λ_{max}^{EtOH} nm (ε): 252 (15600). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1005, 930, 840. MS m/z: 306 (M^+), 291, 288, 273, 237, 224, 137, 109. **12'b**, oil, $[\alpha]_D$ +49° (c=0.70, $CHCl_3$). ^{1}H-NMR δ: 0.77 (3H, d, J=7.0 Hz, 19-H), 1.13 and 1.15 (each 3H, d, J=7.0 Hz, 16,17-H), 1.56 (3H, s, 20-H), 1.71 (3H, s, 18-H), 2.46 (1H, sept, J=7.0 Hz, 15-H), 3.58 (1H, br t, J=6.0 Hz, 7-H), 4.71 (1H, br d, J=7.8 Hz, 14-H), 5.14 (1H, br t, J=7.0 Hz, 11-H), 6.15 (1H, d, J=11.4 Hz, 2-H), 6.18 (1H, br d, J=11.4 Hz, 3-H). UV λ_{max}^{EtOH} nm (ε): 252 (19500). IR ν_{max}^{neat} cm^{-1}: 3400, 1005, 975, 900. MS m/z: 306 (M^+), 291, 288, 273, 237, 224, 137, 109.

Lithium Aluminum Deuteride Reduction of 2a——Compound **2a** (1 g) was treated with lithium aluminum deuteride (300 mg) as described above and the product was acetylated in the usual way, giving 250 mg of **6c**.

Dehydration of 6a and 6c——(a) Phosphoryl chloride (200 μl) was added to a solution of **6a** (190 mg) in pyridine

(3 ml) with cooling and the mixture was kept at room temperature. After 1.5 h, the excess reagent was decomposed with a small amount of H_2O and the reaction mixture was diluted with Et_2O. The Et_2O solution was washed with 5% HCl, H_2O, and saturated NaCl solution, then the solvent was evaporated off to give 170 mg of **1b** with about 90% purity. A portion of this was purified over a column of 10% silver nitrate-impregnated silica gel with ethyl acetate–hexane (1 : 19) giving **1b**, which was identical with natural **1b** based on comparisons of IR and ^{1}H-NMR spectra, and also in several TLC systems. ^{1}H-NMR δ: 1.04 and 1.07 (each 3H, d, J=7.0 Hz, 16,17-H), 1.47 (3H, s, 19-H), 1.57 (3H, s, 20-H), 1.73 (3H, d, J=1.0 Hz, 18-H), 2.50 (1H, sept, J=7.0 Hz, 15-H), 4.98 (1H, br t, J=7.0 Hz, 7-H), 5.07 (1H, br t, J=7.0 Hz, 11-H), 6.03 (1H, dd, J=9.5, 4.4 Hz, 14-H), 6.10 (1H, br d, J=11.5 Hz, 3-H), 6.18 (1H, d, J=11.5 Hz, 2-H). The experiment was repeated on a reduced scale with 50 mg of **6c**, giving **1b** with 25% deuterium incorporation at C-7.

(b) Compound **6a** (50 mg) in 0.5 ml of pyridine was treated with 30 μl of thionyl chloride with cooling. After 1 h, the mixture was worked up as in (a). TLC (ethyl acetate–hexane, 1 : 19) of the crude product showed virtually the same pattern as in (a) and **1b** was the predominant product. The experiment was repeated on a reduced scale with 50 mg of **6c**, giving **1b** with 38% deuterium incorporation at C-7.

(c) A solution of **6c** (50 mg) in 5 ml of benzene was evaporated to *ca.* 3 ml to remove moisture. Thionyl chloride (40 μl) was added to the refluxing solution and the mixture was cooled immediately. Usual work-up followed by purification as in (a) gave 25 mg of **7**. The ^{1}H-NMR spectrum was identical with that of **1b**, except for the lack of a signal at δ 4.98.

Chromic Acid Oxidation of 1a——In a typical run, Jones' reagent (40 ml) was added slowly to a solution of **1a** (5 g) in Et_2O (75 ml) with cooling. The mixture was stirred for 5 min, then the Et_2O layer was separated. It was washed with H_2O, then with 1 N NaOH solution (10 ml × 3), H_2O, and saturated NaCl solution. Evaporation of the solvent gave 3.48 g of the neutral fraction. The 1 N NaOH extract was acidified with concentrated HCl and extracted with Et_2O. It was washed with H_2O, and saturated NaCl solution, then the solvent was evaporated off to give 0.67 g of the carboxylic acid mixture. A portion (1.67 g) of the carboxylic acid mixture was treated briefly with ethereal diazomethane solution and then the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (1 : 19 to 1 : 4) gave **15a** (53 mg), **14a** (38 mg), and **13a** (450 mg), in order of elution. Column chromatography of a portion (2.0 g) of the neutral fraction with ethyl acetate–hexane (1 : 19 to 1 : 4) gave **19** (50 mg), **18** (95 mg), **20a** (98 mg), **16** (1.0 g) and **17** (34 mg) in order of elution.

Compound 13b——Oil, $[\alpha]_D$ +3.6° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.13 (6H, d, J=6.8 Hz, 16,17-H), 1.34 (3H, s, 18-H), 1.59 (3H, br s), 1.68 (3H, br d, J=0.7 Hz), 2.81 (1H, sept, J=6.8 Hz, 15-H), 3.00 (2H, s, 13-H), 3.67 (3H, s), 5.14 and 5.26 (each 1H, br t, J=7.0 Hz), 6.41 (1H, d, J=15.6 Hz, 2-H), 6.88 (1H, d, J=15.6 Hz, 3-H). UV λ_{max}^{EtOH} nm (ε): 222 (12000). IR ν_{max}^{neat} cm^{-1}: 3450, 1735, 1690, 1668, 1625, 984. MS m/z: 350 (M^+), 335, 332, 317, 301, 289, 261. High-resolution MS [Found (Calcd)] m/z: $C_{21}H_{34}O_4$ (M^+), 350.2438 (350.2457).

Compound 14b——Oil, $[\alpha]_D$ 0° (c=0.70, $CHCl_3$). ^{1}H-NMR δ: 1.32 (3H, s, 18-H), 1.58 (3H, br s), 1.68 (6H, br s), 1.70 (3H, s), 2.98 (2H, br s, 13-H), 3.67 (3H, s), 5.15 (1H, br t, J=7.0 Hz), 5.28 (1H, br t, J=7.0 Hz), 5.91 (1H, d, J=5.9 Hz, 2-H), 6.26 (1H, d, J=5.9 Hz, 3-H). ^{13}C-NMR δ: C-1 (153.6), C-2,3 (121.7, 136.4), C-4 (90.8), C-5,9 (39.3, 40.6), C-6 (22.8), C-7 (124.7), C-8 (134.6), C-10 (26.8), C-11 (129.2), C-12 (128.1), C-13 (44.9), C-14 (172.6), C-15 (98.5), C-18 (26.1), C-16,17,19,20 (15.9, 16.3, 17.0, 18.9). UV λ_{max}^{EtOH} nm (ε): 276 (10000). IR ν_{max}^{neat} cm^{-1}: 1736, 1680, 1580, 1157, 847. MS m/z: 332 (M^+), 317, 314, 301, 123. High-resolution MS [Found (Calcd)] m/z: $C_{21}H_{32}O_3$ (M^+), 332.2333 (332.2351).

Compound 15b——Oil. ^{1}H-NMR δ: 1.64 and 1.71 (each 3H, br s), 2.14 (3H, s, 18-H), 2.99 (2H, s, 13-H), 3.67 (3H, s), 5.09 and 5.24 (each 1H, br t, J=7.0 Hz). IR ν_{max}^{neat} cm^{-1}: 1736, 1715, 1158. MS m/z: 252 (M^+), 194, 178, 151, 135, 125, 107. High-resolution MS [Found (Calcd)] m/z: $C_{15}H_{24}O_3$ (M^+), 252.1717 (252.1725).

Compound 16——Oil, $[\alpha]_D$ −3.0° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.13 (6H, d, J=6.8 Hz, 16,17-H), 1.34 (3H, s, 18-H), 1.60 (3H, br s), 1.67 (3H, br d, J=0.7 Hz), 2.82 (1H, sept, J=6.8 Hz, 15-H), 3.03 (2H, br d, J=2.5 Hz, 13-H), 5.14 (1H, br t, J=6.8 Hz), 5.28 (1H, br t, J=7.1 Hz), 6.40 (1H, d, J=15.6 Hz, 2-H), 6.88 (1H, d, J=15.6 Hz, 3-H), 9.96 (1H, t, J=2.5 Hz, 14-H). ^{13}C-NMR δ: C-1 (204.0), C-2 (130.4), C-3 (152.0), C-4 (73.3), C-5 (41.9), C-6 (22.7), C-7,11 (124.7, 124.3), C-8 (135.3), C-9 (39.2), C-10 (26.6), C-12 (126.4), C-13 (54.2), C-14 (200.6), C-15 (39.2), C-16,17 (18.3), C-18 (27.9), C-19,20 (16.0, 16.9). UV λ_{max}^{EtOH} nm (ε): 227 (10000). IR ν_{max}^{neat} cm^{-1}: 3450, 1725, 1694, 1667, 1630, 985. MS m/z: 320 (M^+), 305, 302, 259, 231, 205, 165. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_3$ (M^+), 320.2347 (320.2351).

Compound 17——Oil, $[\alpha]_D$ 0° (c=1.0, $CHCl_3$). ^{1}H-NMR δ: 1.13 (6H, d, J=6.8 Hz, 16,17-H), 1.35 (3H, s, 18-H), 1.59 (3H, br s, 19-H), 1.97 and 2.17 (total 1H, br d, J=1.2 Hz, 20-H), 2.81 (1H, sept, J=6.8 Hz, 15-H), 5.15 (1H, br t, J=7.3 Hz, 11-H), 5.88 (1H, br d, J=8.1 Hz, 13-H), 6.40 (1H, d, J=15.6 Hz, 2-H), 6.88 (1H, d, J=15.6 Hz, 3-H), 9.99 and 9.92 (total 1H, d, J=8.1 Hz, 14-H). ^{13}C-NMR δ: C-1 (203.9), C-2 (130.8), C-3 (151.8), C-4 (73.2), C-5 (41.9), C-6 (22.6), C-7 (124.7), C-8 (134.9, 132.4), C-9 (39.0, 39.3), C-10 (26.8), C-11 (40.0, 25.2), C-12 (164.2, 164.7), C-13 (124.7, 128.8), C-14 (190.7, 191.2), C-15 (39.3), C-16,17 (18.3), C-18 (28.0), C-19 (15.9), C-20 (17.5, 24.9). UV λ_{max}^{EtOH} nm (ε): 234 (12000). IR ν_{max}^{neat} cm^{-1}: 3350, 1670, 1630, 982. MS m/z: 320 (M^+), 302, 259, 231, 207. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_3$ (M^+), 320.2346 (320.2351).

Compound 18——Oil. ^{1}H-NMR δ: 1.13 (6H, d, J=6.8 Hz, 16,17-H), 1.57 and 1.61 (each 3H, s, 19,20-H), 2.13

(3H, s, 18-H), 2.80 (1H, sept, J=6.8 Hz, 15-H), 3.25 (2H, br s, 13-H), 4.9—5.2 (2H, m, 7,11-H), 6.25 (1H, d, J=2.0 Hz, 2-H), 7.23 (1H, d, J=2.0 Hz, 3-H). ^{13}C-NMR δ: C-1 (126.6), C-2 (108.6), C-3 (140.1), C-4 (208.5), C-5 (43.7), C-6,10 (22.5, 26.6), C-7,11 (122.7, 125.6), C-8 (136.0), C-9 (39.4), C-12 (132.2), C-13 (36.2), C-14 (147.4), C-15 (24.4), C-16,17 (23.8), C-18 (29.9), C-19,20 (16.0). UV λ_{max}^{EtOH} nm (ε): 214 (7000). IR ν_{max}^{neat} cm^{-1}: 1715, 1672, 1605. MS m/z: 302 (M^+), 223, 205, 189, 177, 176, 149. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O_2$ (M^+), 302.2228 (302.2225).

Compound 19——Oil. ^{1}H-NMR and IR spectra were identical with those described in our previous report.[13]

Compound 20a——Oil, $[\alpha]_D$ −133° (c=0.63, $CHCl_3$). ^{1}H-NMR δ: 1.02 (3H, s, 18-H), 1.03 and 1.17 (each 3H, d, J=6.8 Hz, 16,17-H), 1.56 and 1.58 (each 3H, t, J=1.5 Hz, 19,20-H), 2.46 (1H, dd, J=13.6, 5.5 Hz, 13-H), 4.70 (1H, dq, J=5.5, 1.0 Hz, 3-H), 4.86 (1H, br t, J=5.5 Hz, 14-H), 5.12 (1H, br d, J=9.2 Hz), 5.28 (1H, br d, J=10.3 Hz), 5.41 (1H, q, J=1.0 Hz, 2-H). ^{13}C-NMR δ: C-1 (151.0), C-2 (131.2), C-3 (87.2), C-4 (74.7), C-5,9 (38.6, 39.8), C-6,10 (22.1, 25.4), C-7,11 (128.5, 119.4), C-8 (132.4), C-12 (129.8), C-13 (43.1), C-14 (84.5), C-15 (26.6), C-16,17 (21.0, 22.1), C-18 (23.8), C-19,20 (15.7, 17.7). IR ν_{max}^{neat} cm^{-1}: 3460, 1085, 975, 955. MS m/z: 304 (M^+), 286. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_2$ (M^+), 304.2402 (304.2416).

Compound 20b——A mixture of **20a** (61.5 mg), dimethylaminopyridine (3 mg), and triethylamine (0.1 ml) was treated with Ac_2O (0.1 ml) at 110 °C for 1.5 h, then extracted with Et_2O and worked up as usual. Silica gel column chromatography of the crude product with ethyl acetate–hexane (1 : 40) gave 29.2 mg of **20b**, mp 62—63 °C, $[\alpha]_D$ −97° (c=0.76, $CHCl_3$). ^{1}H-NMR δ: 1.03 and 1.19 (each 3H, d, J=7.0 Hz, 16,17-H), 1.27 (3H, s, 18-H), 1.55 and 1.56 (each 3H, s, 19,20-H), 2.30 (1H, br sept, J=7.0 Hz, 15-H), 4.75 (1H, br d, J=5.3 Hz, 3-H), 4.85 (1H, br t, J=5.5 Hz, 14-H), 5.15 (1H, br d, J=8.4 Hz), 5.31 (1H, m), 5.32 (1H, br s, 2-H). IR ν_{max}^{neat} cm^{-1}: 1735, 1245, 1087, 847, 822. MS m/z: 346 (M^+), 303, 286, 243, 218, 150.

Compound 21——A solution of **16** (150 mg) in 0.5% KOH in MeOH (3 ml) was kept at room temperature for 1 h. Extraction with Et_2O followed by usual work-up gave a mixture, which, on silica gel column chromatography (Et_2O–$CHCl_3$, 1 : 4), gave 50 mg of **17**. It was further treated at room temperature with 0.5% KOH in MeOH for 2 h. Extraction with Et_2O, usual work-up, and chromatography in the same way as above gave **21** as an oil, $[\alpha]_D$ +3° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.33 (3H, s, 18-H), 1.57, 1.68, 1.70 (each 3H, s, 16,17,19-H), 2.16 and 1.97 (total 3H, d, J=1.2 Hz, 20-H), 5.13 (1H, br t, J=7.0 Hz, 7-H), 5.88 (1H, br d, J=8.2 Hz, 13-H), 5.91 and 6.27 (each 1H, d, J=6.0 Hz, 2,3-H), 9.93 and 9.99 (total 1H, J=8.2 Hz, 14-H). ^{13}C-NMR δ: C-1 (153.4), C-2,3 (121.7, 136.2), C-4 (90.6), C-5 (40.5), C-6 (22.7), C-7 (125.3), C-8 (133.6, 133.9), C-9 (39.0, 39.2), C-10 (26.8), C-11 (25.3, 40.0), C-12 (164.0, 164.5), C-13 (127.3, 128.5), C-14 (190.6, 191.1), C-15 (98.5), C-16,17,19 (15.7, 17.0, 18.8), C-18 (26.1), C-20 (17.5, 25.5). UV λ_{max}^{EtOH} nm (ε): 240 (12000), 276 (8000). IR ν_{max}^{neat} cm^{-1}: 1715, 1672, 1627, 1580, 950, 845. MS m/z: 302 (M^+), 287, 273, 205, 137, 123. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O_2$ (M^+), 302.2247 (302.2225).

Chromic Acid Oxidation of 1b——Jones' reagent (8 ml) was added slowly to a solution of **1b** (2 g) in 30 ml of Et_2O and the mixture was stirred at room temperature for 22 h. The Et_2O layer was separated, washed with H_2O, 2 N NaOH solution (5 ml × 3), H_2O, and saturated NaCl solution. Evaporation of the solvent gave 1.6 g of neutral fraction. Acidification of the NaOH extract followed by extraction with Et_2O gave 64 mg of acid mixture. Silica gel column chromatography of the neutral fraction with Et_2O–$CHCl_3$ (1 : 9) gave first unreacted **1b** (0.78 g), then **22a** (50 mg), an unidentified material (70 mg), and **23a** (290 mg) in order of elution.

Compound 22a——Oil, $[\alpha]_D$ +6° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.09 and 1.16 (each 3H, d, J=7.0 Hz, 16,17-H), 1.61 and 1.66 (each 3H, br s), 2.05 (3H, s), 2.14 (3H, s, 18-H), 4.92—5.28 (2H, m), 5.90 (1H, d, J=7.8 Hz, 2-H), 5.99 (1H, dd, J=7.8, 5.6 Hz, 14-H), 10.19 (1H, d, J=7.8 Hz, 3-H). UV λ_{max}^{EtOH} nm (ε): 234 (16000). IR ν_{max}^{neat} cm^{-1}: 1740, 1714, 1668. MS m/z: 302 (M^+ − AcOH), 284, 259. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O_2$ (M^+ − AcOH), 302.2261 (302.2245).

Compound 23a——Oil, $[\alpha]_D$ −33° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 0.81 and 0.91 (each 3H, d, J=6.8 Hz, 16,17-H), 1.44 (3H, s, 18-H), 1.62 and 1.77 (each 3H, br s), 2.06 (3H, s), 5.14 (1H, dd, J=9.0, 6.2 Hz, 14-H), 5.26 (1H, br t, J=7.0 Hz), 5.34 (1H, br t, J=8.0 Hz), 5.74 and 6.11 (each 1H, d, J=16.1 Hz, 2,3-H). ^{13}C-NMR δ: C-1 (79.2), C-2,7,11 (128.4, 128.6, 129.0), C-3 (137.1), C-4 (72.2), C-5,13 (43.7, 42.4), C-6,10 (22.4, 23.7), C-8,12 (132.6, 132.7), C-9 (39.0), C-14 (71.5), C-15 (32.9), C-16,17 (16.2, 16.7), C-18 (27.9), C-19,20 (14.8, 15.4), OAc (21.9, 169.8). IR ν_{max}^{neat} cm^{-1}: 3500, 1730, 1720, 980. MS m/z: 364 (M^+), 346, 286, 261, 243. High-resolution MS [Found (Calcd)] m/z: $C_{22}H_{34}O_3$ ($M^+ - H_2O$), 346.2518 (346.2508).

Conversion of 22a to 18——A solution of **22a** (20 mg) in 0.5% KOH in MeOH solution (2 ml) was kept at 40 °C for 30 min and then poured into water. The mixture was extracted with Et_2O, the extract was worked up as usual, and the solvent was evaporated off to give 15 mg of residue. The residue (10 mg) was dissolved in 0.1 N HCl in MeOH and kept at room temperature for 30 min. It was extracted with Et_2O, and worked up as usual. Silica gel column chromatography of the evaporation residue with ethyl acetate–hexane mixture gave 8 mg of oil which was shown to be identical with **18** by comparisons of IR and ^{1}H-NMR spectra, and by TLC.

Conversion of 23a to 16——A solution of **23a** (30 mg) in 0.5% KOH in MeOH solution (2 ml) was kept at 40 °C for 30 min and then poured into H_2O. The mixture was extracted with Et_2O, the extract was worked up as usual, and the solvent was evaporated off to give 20 mg of **23b**. ^{1}H-NMR δ: 0.77 and 0.96 (each 3H, d, J=6.6 Hz, 16,17-H), 1.35 (3H, s, 18-H), 1.54 and 1.64 (each 3H, br s), 3.98 (1H, dd, J=9.0, 5.9 Hz, 14-H), 5.0—5.4 (2H, m), 5.69 and 6.01 (each 1H, d, J=16.1 Hz, 2,3-H). Jones' reagent (1 ml) was added slowly to a solution of **23b** (10 mg) in Et_2O (2 ml) and the

mixture was stirred at room temperature for 10 min. The mixture was diluted with Et_2O, and the Et_2O layer was washed with H_2O, and saturated NaCl solution, then the solvent was evaporated off. Silica gel column chromatography of the residue with ethyl acetate–hexane mixture gave 6 mg of oil, shown to be identical with **16** by comparisons of IR and ^{1}H-NMR spectra, and by TLC.

References and Notes

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