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Marine Terpenes and Terpenoids. VIII.[1] Transannular Cyclization of 3,4-Epoxy-1,7,11-cembratriene Systems

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The major cembranoid, sarcophytol A (1a), from the soft coral *Sarcophyton glaucum* was found to be converted to a bicyclo[9.3.0]tetradecene derivative (3a), on standing in $CHCl_3$ solution at room temperature. Two unstable epoxides (7a and 8), obtained by autoxidation of 1a, were shown to afford 3a on further storage in $CHCl_3$. The acetate 7b, in contrast, is stable under the same conditions and gave the dihydrofuran (9) and triol monoacetate (11) derivatives on mild alkaline and acid treatments, respectively. Five minor cembranoids of *S. glaucum*, having the 1,3-diene system, were examined for the cyclization reaction by dissolving them in $CHCl_3$. The 1,3,7,11-tetraenes (2, 14, 16) gave similar bicyclotetradecene derivatives (12, 15, 17), while the 7-hydroxy 1,3,8(19),11-tetraenes (18, 20) gave the 3,7-oxide derivatives (19, 21) in low yields.

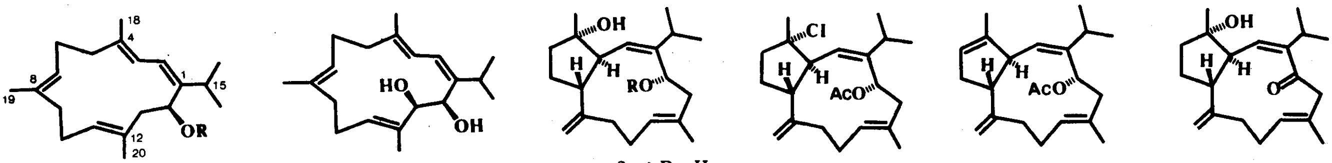
Keywords *Sarcophyton glaucum*; soft coral; transannular cyclization; cembranoid; bicyclo[9.3.0]tetradecene; 3,7-epoxycembrane; 4,7-epoxycembrane

The common soft coral *Sarcophyton glaucum*, collected in Ishigaki Island, contains a variety of cembranoid diterpenes.[2] The predominant component is sarcophytol A (**1a**) which, together with its dihydroxy derivative sarcophytol B (**2**), has attracted considerable attention because of its unparalleled inhibitory effect against the action of the powerful tumor-promoter teleocidin,[3] in a two-stage carcinogenesis experiment on mouse dorsal skin.[4,5] In relation to this unique activity of **1a** and **2**, we investigated the minor components of *S. glaucum* and also the behavior of **1a** in oxidation reactions.[1,6]

In the course of these experiments we noticed that on storage, purified **1a** gradually affords several autoxidation products. The major component, having the largest polarity, was found to be identical with an unknown compound which had previously been isolated from *S. glaucum* and had been designated sarcophytol L (**3a**). Sarcophytol L was thus shown to be an artifact derived from **1a** but its formation process is noteworthy, since it involves unusual transannular cyclization of a fourteen-membered epoxycembranoid system, in contrast to those well-known in ten-membered sesquiterpene derivatives. The present work deals with the structure elucidation of **3a**, its formation process from **1a**, and the behavior of other minor cembranoids of *S. glaucum* when treated under the same conditions.

Sarcophytol L (**3a**), $C_{20}H_{32}O_2$, was first isolated by column chromatography from the polar lipid fraction of *S. glaucum* extract, but the same compound was found to occur in stored samples of less polar fractions which contained **1a**. Its ultraviolet (UV) and proton nuclear magnetic resonance (^{1}H-NMR) spectra indicated that the conjugated 1,3-diene moiety and one of the two trisubstituted double bonds of **1a** were lost in the transformation to **3a**. The normal and two-dimensional ^{1}H-NMR spectra of **3a** showed that its H-2 (δ 4.99, d, J=9.5 Hz) is coupled with H-3 (2.48, dd, J=11.0, 9.5 Hz), and H-3 is, in turn, coupled with a methine proton at δ 2.38 (dt, J=11.0, 8.0 Hz). Newly appearing signals are those of terminal methylene (δ 4.78 and 4.84, br s) and a methyl which is adjacent to an oxygen atom (δ 1.11, s, H-18). These spectroscopic changes indicated that **3a** is a bicyclic compound formed by the internal cyclization of 3,4-epoxysarcophytol A or its derivative. Two doublet signals of sp^3 carbons (δ 50.2 and 54.9) in the carbon-13 NMR (^{13}C-NMR) spectrum of **3a** correspond to C-3 and C-7. Treatment of the acetate **3b** with $SOCl_2$ in pyridine gave a chloride **4**, and an olefin **5** whose H-5 signal appeared as a broad singlet, as found in cyclopentene. Pyridinium chlorochromate (PCC) oxidation of **3a** gave an α,β-unsaturated ketone **6**. The nuclear Overhauser effect (NOE) differential spectrum of **6** showed the proximity of one of the H-13 methylene protons (δ 3.31, d, J=11.0 Hz) with the unchanged olefinic proton (δ 5.34, br t, J=7.5 Hz) and indicated that C-3 is linked to C-7 and not to C-11. A ^{1}H-NMR experiment with **6** indicated the bicyclic system to be *trans*-fused and showed marked NOE between H-2 and H-7 (δ 2.47, dt, J=10.5, 8.5 Hz) but none between H-2 and H-3. Weak NOE was observed between H-2 and H-18 and between H-2 and the isopropyl methyl group. The weakness of the UV absorption of **6** (236 nm, ε 4400) indicated that the coplanarity of the carbonyl group and its conjugated double bond is significantly obstructed.

When purified **1a** was ketp in $CHCl_3$ at room temperature, it was converted to **3a** (42%) after 9 d. When kept similarly in benzene or ethyl acetate–hexane (1 : 4) mixture, it was partly converted to two major products (**7a** and **8**) and **9**, and a very small amount of **10**, but at this stage the



1a : R=H
1b : R=Ac

2

3a : R=H
3b : R=Ac

4

5

6

Chart 1

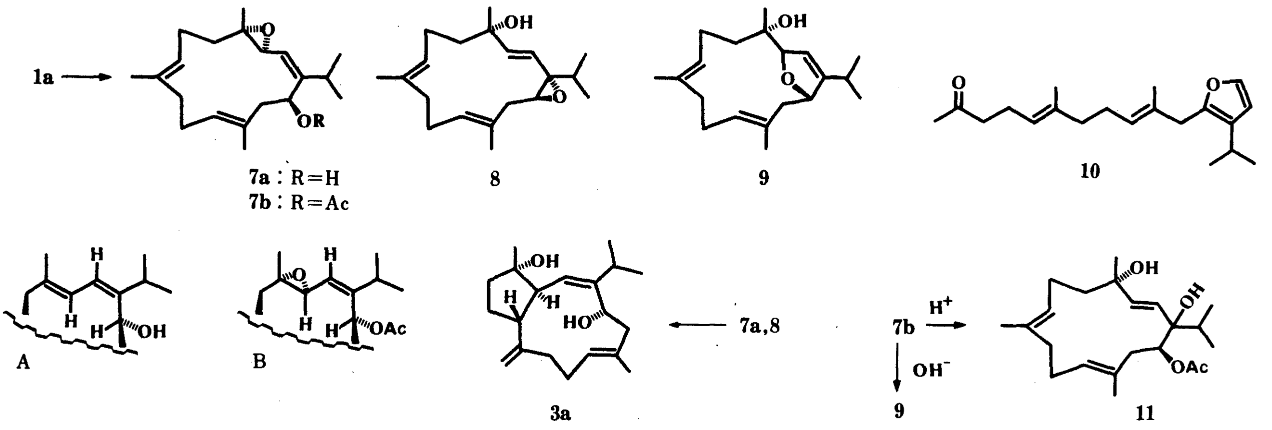


Chart 2

formation of **3a** was minimal. Both **9** and **10** were previously obtained by Jones oxidation of **1a**.[6)] Direct exposure of **1a** to air caused a similar but more facile conversion. The two major products **7a** and **8** were unstable after purification; their ^{1}H-NMR spectra indicated that one component (**7a**) is the expected 3,4-epoxide (δ 3.44, 5.16, each d, $J=8.0$ Hz) and the other one (**8**) is the 4-hydroxy-1,14-epoxide (δ 3.31, dd, $J=10.0$, 3.0 Hz; 5.88 and 6.20, each d, $J=16.5$ Hz). The geometry of the C-2 double bond of **8** is *E*, from the coupling constants of H-2 and H-3, while the NOEs observed between H-14 and one of the doublet olefinic protons (δ 6.20) but not between H-14 and H-15,16,17, indicated **8** to be a 1,14*E*-epoxide. Compound **8** is the diastereomer of the known compound sarcophytol C, whose stereochemistry remains unsettled.[2b)] These results indicated that the primary reaction in the autoxidation of **1a** is the epoxidation at the C-3 double bond. In the previous work, epoxidation of **1a** by *m*-chloroperbenzoic acid gave predominantly two 7,8*E*-epoxides.[6)] When purified **7a** and **8** were kept in $CHCl_3$ at room temperature, they were gradually converted to mixtures containing **3a**, during several days. Possibly a trace of residual hydrochloric acid in $CHCl_3$ catalyzed the cyclization reaction. Thin-layer chromatography (TLC) examination of the mixture showed that the epoxide **7a** was first converted to **8** and **9**, and eventually to a mixture composed of mainly **9** and **3a**.

The absolute configuration at C-3,4,7, shown in **3a**, was correlated with that of C-14 (*S*), on the basis of the NOE experiments described above, and the following reasoning. ^{1}H-NMR experiments on **1a** and its derivatives (**2**, **14**, **16**, **18**, **20**) having the same 1*Z*,3*E*-diene,[1,6)] showed a common feature as regards the relation between H-14 and the 1,3-diene with *s-trans* conformation, indicating that H-14 lies nearly in the plane which involves C-14 and the 1,3-diene system and which is perpendicular, due to the steric repulsion, to the average plane of the fourteen-membered ring (Chart 2, A). The large NOE enhancements (13—17%) observed between H-14 and H-3 are the result of this arrangment; this forces H-14 to be exposed in the deshielding region of the magnetic field induced by the 1,3-diene. As a result, the signals of the protons at C-14 of these systems occur at unusually low field (δ 4.7—5.1)[1)] for allylic hydroxymethine protons, whose usual position is around δ 3.6—4.1 in the cembranoids we isolated.[1,6)] A similar arrangement could be expected in the 3,4-epoxide **7a** and its acetate **7b**. The ^{1}H-NMR spectrum of the stable acetate **7b**, which was obtained as a minor product by epoxidation of **1b** with *m*-chloroperbenzoic acid,[1,6)] showed the presence of NOE between H-2 and H-16,17 (7.5%) and between H-2 and H-18 (6.5%). The largest NOE (17%) was observed between H-3 and H-14 (Chart 2, B). These results are in fact exactly the same pattern as found in **1a**.[6)] Such a spatial arrangement of C-14 and C-1 to C-4, and the absolute configuration at C-14 (*S*) define the direction of the cembrane ring in **1a**, namely C-6 and C-13 are located on the same side with respect to the 1,3-diene (Chart 2, A). The π-orbital of the diene system is directed horizontally with respect to the average plane of the strained medium-sized ring, and only outside attack is possible. When the epoxidation of **1a** occur at the C-3 double bond from the outside of the ring, it would afford the epoxide **7a** with 3*S*,4*S* configuration.

This is the first demonstration of the transannular cyclization of an epoxy cembrane system, though a similar reaction has been found in germacrane-type sesquiterpenes having a trisubstituted epoxide and trisubstituted double bonds separated by two methylene groups.[7)] On acid treatment, they transform mainly into *trans*- or *cis*-fused bicyclo[5.3.0]decane derivatives, according to the parallel or crossed spatial arrangement of the two functional groups. However, in our case the acetate **7b** was stable in $CHCl_3$ solution and the cyclization did not take place even on prolonged storage (one month). Treatment of **7b** with 2.5% KOH in MeOH at room temperature for 1 h caused cyclization, giving **9** (70%) together with trace amount of **3a**. Treatment of **7b** with dilute acid (0.05% H_2SO_4 in dioxane–H_2O (4 : 1)) also caused epoxide ring opening but no trace of **3a** was detected. The major product (76%) was the triol monoacetate **11**. Compound **11** had previously been obtained by Jones oxidation of **1b**.[6)] In contrast to the case of **7a**, the acid-catalyzed epoxide ring opening of **7b** is followed by migration of the C-1 double bond and nucleophilic attack at C-1. This is a markedly different behavior as compared with those of the reported sesquiterpene epoxides in which the epoxide rings are not contiguous to double bonds.

To examine further examples, three minor cembranoids of *S. glaucum*, sarcophytol B (**2**), sarcophytol E (**14**) and sarcophytol G (**16**), having a 1,3,7,11-cembratetraene system, were tested for autoxidation by keeping them in

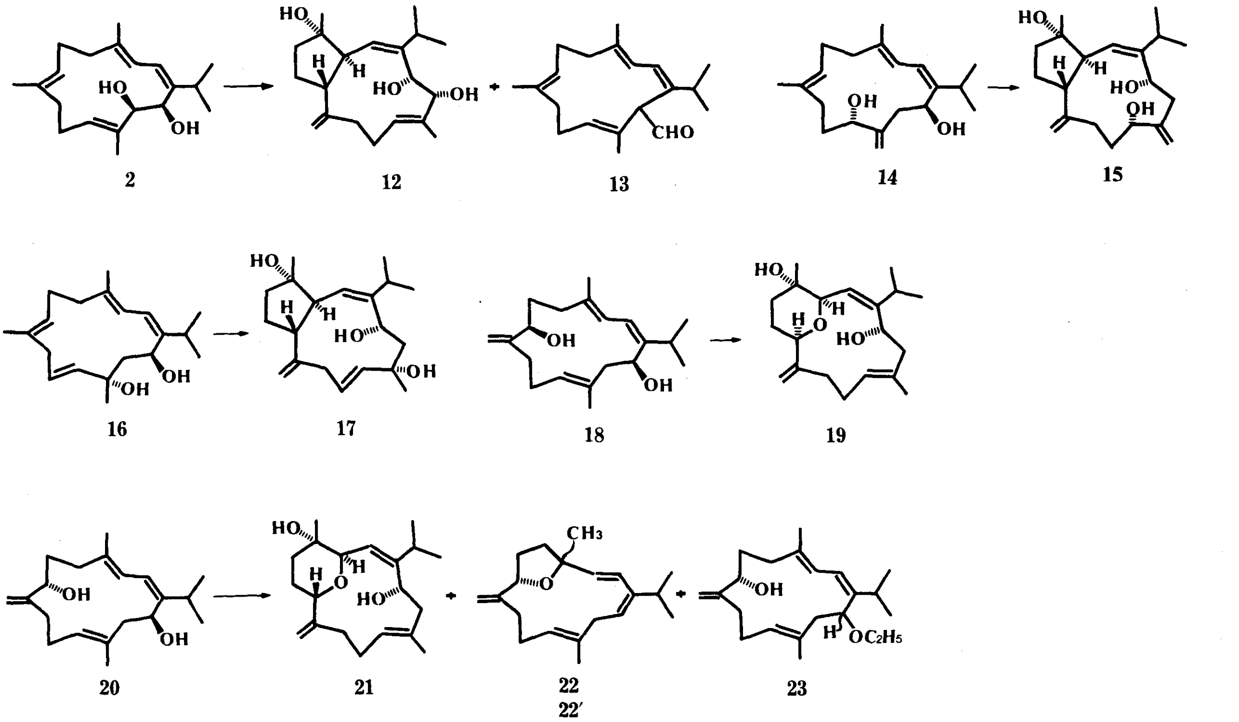


Chart 3

$CHCl_3$ for 7—20 d (Chart 3). In each case the bicyclic derivative was the major product (**12**, 32%; **15**, 12%; **17**, 26%). Their ring-fusion is *E*, as in **3a**, as confirmed by the NOE observed between H-2 and H-7,16,17,18 but not between H-2 and H-3. Compound **2** gave a small amount of ring-contracted aldehyde (**13**, 6%), which is the major product of treatment of **2** with *p*-toluenesulfonic acid (TsOH) in benzene.[1] Treatment of sarcophytol H (**18**) and sarcophytol O (**20**) in $CHCl_3$ showed that the primary reaction is also epoxidation at the C-3 double bond, giving the 3,7-oxide **19** (18%) from **18**, and **21** (8%) from **20**. Sarcophytol O (**20**) simultaneously gave an epimeric pair of 4,7-oxides **22** (7%) and **22′** (6.5%), and the ethyl ether **23** (24%) which was derived by the reaction with the stabilizer ethanol in $CHCl_3$. Both **19** and **21** showed NOEs between H-2 and H-16,17,18 but not between H-3 and H-2,16,17,18. Sarcophytol A (**1a**) is known to give a high yield of the 2,4(18),7,11,14(1)-pentaene on acid treatment.[1] The 4,7-oxides **22** and **22′** are the products derived by participation of the C-7 hydroxyl group in a similar acid-catalyzed dehydration of **20**, supposedly existing as two different conformers, as in the case of **1b** (*vide infra*). Their geometry at C-2 is *E* from the coupling constants of H-2 and H-3 (**22**, 16.0 Hz; **22′**, 15.5 Hz), but the geometry at C-14 is unknown. These observations, especially the failure of **7b** to give cyclization products, could be interpreted as indicating that the reaction occurred through the intermediate **8**, namely, the free 14-hydroxyl group is necessary. This seems to be consistent with the results of the $CHCl_3$ treatment of **2**, **14** and **16**. The highly flexible nature of the cembrane rings permits a variety of conformers. For instance, from the results of the epoxidation reaction, **1b** was supposed to take at least two major conformers (4.5 : 3), having their C-19 methyl groups oriented in opposite directions with respect to the average plane of the fourteen-membered ring.[1] The preferred conformers and their ratios in **7a** and **7b** are unknown, but the closely related ^{1}H-NMR chemical shifts of H-16,17,18 (**7a**, δ 1.03, 1.11, each 3H, d, $J=7.0$ Hz, 1.28, 3H, s; **7b**, δ 1.06, 1.07, each 3H, d, $J=7.0$ Hz, 1.28, 3H, s) and the coupling constants of H-14 (**7a**, 7.0, 6.0 Hz; **7b**, 7.5, 6.0 Hz) indicate that conformational discrepancy between **7a** and **7b** is minimal. In contrast, the structural variations in compounds **2**, **14** and **16** would allow their 3,4-epoxy derivatives to take different conformations as compared with that of **7a**. These discrepancies should be greater than that expected between **7a** and **7b** but nevertheless do not prevent the compounds from undergoing transannular cyclization.

This cyclization reaction is also a biogenetically possible process, as shown by a natural product **24**, isolated from an Australian soft coral, *Cespitularia* sp.[8] Discovery of similar bicyclic systems might be expected from soft corals and other lower marine invertebrates. However, the present study shows that if the rather common 1,3,7-triunsaturated cembranoids occurred simultaneously, there could be confusion as to their true origins. Lactiflorenol (**25**),[9] isolated as an antiasthmatic sesquiterpene from *Artemisia lactiflora*, and its racemate in a soft coral *Nephthea chabrolii*,[10] are the natural sesquiterpene analogs of **3a**. In the latter case, germacrene C (**26**) was isolated simultaneously. Whether the racemate could arise from germacrene C 4,5-epoxide by transannular cyclization is not known. Also, there are many cases where diterpenes occur alongside each other as the

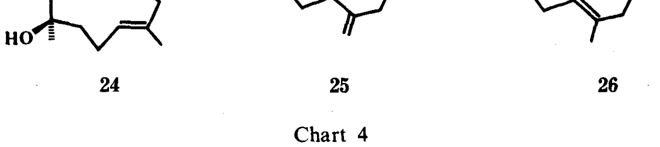


Chart 4

two enantiomeric ring fusion derivatives in the same plant species.

Experimental

Melting points were determined on a Kofler hot-stage melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a JASCO A 102 spectrometer. UV spectra were determined on a Hitachi EPS-3T spectrometer. Optical rotations were determined in $CHCl_3$ on a JASCO DIP-4 digital polarimeter. NMR spectra were determined in $CDCl_3$ on a JEOL GX-270 spectrometer at 270 MHz (^{1}H) and on a JEOL JNM FX-90Q spectrometer at 22.5 MHz (^{13}C) with tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a JEOL JMS D300 mass spectrometer. Chromatography was done by flash column chromatography using silica gel (Wako gel C-300, 200—300 mesh, Wako Pure Chemical Industries).

Isolation of 3a Chromatography fractions 95—120, described in the preceding report,[1)] were used as the source meterial. They were complex mixtures containing **3a** and large amounts of batyl alcohol. Most of the batyl alcohol was removed by crystallization from acetone and filtration. A portion (4 g) of the mixture obtained from the mother liquor was submitted to repeated chromatography with ethyl acetate–hexane (6:4) and MeOH–$CHCl_3$ (1:40) to give **3a** (150 mg), mp 125—127 °C, $[\alpha]_D$ $-54°$ ($c=2.56$). ^{1}H-NMR δ: 1.07, 1.13 (each 3H, d, $J=7.0$ Hz, H-16,17), 1.11 (3H, s, H-18), 1.69 (3H, s, H-20), 2.09 (1H, dd, $J=12.0$, 10.5 Hz, H-13), 2.38 (1H, dt, $J=11.0$, 8.0 Hz, H-7), 2.48 (1H, dd, $J=11.0$, 9.5 Hz, H-3), 2.52 (1H, sept, $J=7.0$ Hz, H-15), 4.60 (1H, dd, $J=10.5$, 3.5 Hz, H-14), 4.78, 4.84 (each 1H, br s, H-19), 4.99 (1H, d, $J=9.5$ Hz, H-2), 5.15 (1H, br t, $J=7.5$ Hz, H-11). ^{13}C-NMR δ: C-1,8 (148.8, 149.3), C-2,11 (125.2, 126.6), C-3,7 (50.2, 54.9), C-4 (81.4), C-5,6 (27.4, 28.0), C-9 (40.3), C-10 (25.5), C-12 (131.1), C-13 (44.3), C-14 (71.1), C-15 (26.7), C-16,17 (23.4, 24.9), C-18 (26.5), C-19 (111.5), C-20 (18.1). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1635, 900, 890, 870. MS m/z: 304 (M^+), 289, 286, 271, 261, 243, 217, 203, 193. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_2$ (M^+), 304.23929 (304.24024). Acetylation of **3a** (50 mg) in the usual way (Ac_2O–pyridine) followed by chromatography with ethyl acetate–hexane (1:9) gave 28.2 mg of **3b**, oil, $[\alpha]_D$ $-71°$ ($c=2.80$). ^{1}H-NMR δ: 0.97, 1.07 (each 3H, d, $J=7.0$ Hz), 1.13 (3H, s, H-18), 1.70 (3H, d, $J=1.0$ Hz, H-20), 2.05 (3H, s), 2.52 (1H, dd, $J=10.5$, 9.5 Hz, H-3), 4.79, 4.86 (each 1H, br s, H-19), 5.14 (1H, d, $J=9.5$ Hz, H-2), 5.21 (1H, br t, $J=7.5$ Hz, H-11), 5.39 (1H, dd, $J=10.0$, 4.5 Hz, H-14). IR ν_{max}^{neat} cm^{-1}: 3520 1735, 1640, 907, 890, 875. MS m/z: 286 ($M^+ -$ AcOH), 271, 258, 243, 185.

$SOCl_2$ Treatment of 3b A solution of **3b** (28 mg) in pyridine (0.2 ml) was treated with $SOCl_2$ (18 μl) at room temperature for 1.5 h. The mixture was diluted with Et_2O, and washed with 5% HCl solution, H_2O, and saturated NaCl solution, then the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (1:99) gave **5** (5.2 mg) and **4** (5.4 mg), in that order, as an oil. **4**, $[\alpha]_D$ $-190°$ ($c=0.54$). ^{1}H-NMR δ: 1.12 (6H, d, $J=7.0$ Hz), 1.51 (3H, s), 1.65 (3H, d, $J=1.0$ Hz), 2.04 (3H, s), 2.34 (1H, dd, $J=10.5$, 9.5 Hz, H-3), 2.52 (1H, sept, $J=7.0$ Hz), 2.92 (1H, dt, $J=7.0$, 10.5 Hz, H-7), 4.83, 4.95 (1H, br s, H-19), 5.22 (1H, br t, $J=7.5$ Hz, H-11), 5.26 (1H, d, $J=9.5$ Hz, H-2), 5.54 (1H, dd, $J=11.0$, 3.5 Hz, H-14). MS m/z: 366 (M^+), 364 (M^+), 328, 306, 304, 269, 261, 236, 201. High-resolution MS [Found (Calcd)] m/z: $C_{22}H_{33}O_2Cl$ (M^+), 364.21798 (364.21688). **5**, $[\alpha]_D$ $-230°$ ($c=0.52$). ^{1}H-NMR δ: 1.05, 1.10 (each 3H, d, $J=7.0$ Hz), 1.55 (3H, br s), 1.64 (3H, d, $J=1.0$ Hz), 2.05 (3H, s), 2.49 (1H, sept, $J=7.0$ Hz), 2.66 (1H, dt, $J=9.2$, 8.5 Hz, H-7), 3.31 (1H, br dd, $J=10.5$, 9.2 Hz, H-3), 4.85, 4.94 (each 1H, s, H-19), 5.04 (1H, d, $J=10.5$ Hz, H-2), 5.27 (1H, br t, $J=7.5$ Hz, H-11), 5.31 (1H, br s, H-5), 5.76 (1H, dd, $J=11.0$, 3.0 Hz, H-14). MS m/z: 328 (M^+), 268, 253, 225, 200, 185.

PCC Oxidation of 3a A solution of **3a** (93 mg) in CH_2Cl_2 (5 ml) was stirred with PCC (150 mg) at room temperature for 25 min, then the mixture was diluted with H_2O and extracted with Et_2O. The Et_2O solution was washed with 5% HCl solution, saturated $NaHCO_3$ solution, and saturated NaCl solution, then the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (1:9) gave 30 mg of **6**, mp 104.5—105 °C, $[\alpha]_D$ $-315°$ ($c=0.54$). ^{1}H-NMR δ: 1.00, 1.14 (each 3H, d, $J=7.0$ Hz), 1.10 (3H, s, H-18), 1.71 (3H, d, $J=1.5$ Hz), 1.88 (1H, t, $J=10.5$ Hz, H-3), 2.47 (1H, dt, $J=10.5$, 8.5 Hz, H-7), 2.59 (1H, d sept, $J=1.5$, 7.0 Hz, H-15), 2.81, 3.31 (each 1H, d, $J=11.0$ Hz, H-13), 4.83, 4.89 (each 1H, br s, H-19), 5.12 (1H, dd, $J=10.5$, 1.5 Hz, H-2), 5.34 (1H, br t, $J=7.5$ Hz, H-11). ^{13}C-NMR δ: C-1,8 (149.2, 149.7), C-2,11 (129.0, 130.8), C-3,7 (54.0, 55.4), C-4 (79.3), C-5,6,10 (26.5, 27.6, 28.3), C-9 (40.9), C-12 (126.5), C-13 (50.3), C-14 (205.7), C-15 (30.1), C-16,17,18 (20.5, 23.1, 25.3), C-19 (111.7), C-20 (17.4). UV λ_{max}^{EtOH} nm (ε): 236 (4400), 310 (520). IR ν_{max}^{Nujol} cm^{-1}: 3470, 1665, 1630, 888. MS m/z: 302 (M^+), 287, 284, 269, 260, 259, 138.

$CHCl_3$ Treatment of 1a, 2, 14, 16, 18 and 20 a) Compound **1a** (470 mg) was dissolved in 20 ml of $CHCl_3$ and kept at room temperature for 9 d. After evaporation of the solvent, the residue was submitted to column chromatography with MeOH–$CHCl_3$ (1:40) to give 210 mg of **3a**, $[\alpha]_D$ $-57°$ ($c=0.60$).

b) A solution of **2** (100 mg) in 15 ml of $CHCl_3$ was kept for 10 d. The evaporation residue was separated by column chromatography, first with ethyl acetate–hexane (1:30), giving 5.5 mg of **13**, and then with MeOH–$CHCl_3$ (1:30), giving 33.8 mg of **12**. Compound **13** was identical with an authentic specimen prepared previously,[1)] by comparison of their ^{1}H-NMR spectra, and their behavior in several TLC systems. **12**, mp 120—122 °C, $[\alpha]_D$ $-75°$ ($c=1.69$). ^{1}H-NMR δ: 1.03, 1.13 (each 3H, d, $J=7.0$ Hz), 1.08 (3H, s, H-18), 1.66 (3H, s), 3.80 (1H, d, $J=9.5$ Hz, H-13), 4.48 (1H, d, $J=9.5$ Hz, H-14), 4.78, 4.81 (each 1H, s, H-19), 5.01 (1H, d, $J=10.0$ Hz, H-2), 5.45 (1H, br t, $J=7.5$ Hz, H-11). ^{13}C-NMR δ: C-1,8 (146.8, 149.5), C-2,11 (127.0, 127.3), C-3,7 (50.6, 54.4), C-4 (81.5), C-5,6 (27.5, 27.7), C-9 (40.5), C-10 (25.5), C-12 (134.5), C-13,14 (74.1, 76.7), C-15 (27.7), C-16,17 (23.0, 24.3), C-18 (26.5), C-19 (111.7), C-20 (15.0). MS m/z: 320 (M^+), 302, 287, 284, 259, 241. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_3$ (M^+), 320.2343 (320.2351).

c) A solution of **14** (220 mg) in $CHCl_3$ (10 ml) was kept for 20 d and separated as in a) to give 28.7 mg of **15**, oil, $[\alpha]_D$ $-58°$ ($c=2.87$). ^{1}H-NMR δ: 1.06, 1.13 (each 3H, d, $J=7.0$ Hz), 1.17 (3H, s, H-18), 2.5—2.7 (3H, m, H-3,7,15), 4.02 (1H br t, $J=6.0$ Hz, H-11), 4.87 (1H, dd, $J=8.5$, 6.5 Hz, H-14), 4.91, 5.04, 5.05, 5.14 (each 1H, s, H-19,20), 5.17 (1H, d, $J=11.5$ Hz, H-2). ^{13}C-NMR δ: C-1,8 (148.2, 148.3), C-2 (126.9), C-3,7 (51.5, 56.0), C-4 (82.5), C-5 (32.7), C-6 (28.9), C-9,13 (41.0, 41.3), C-10 (30.5), C-11,14 (68.8, 70.4), C-12 (153.1), C-15 (26.9), C-16, 17 (23.0, 24.3), C-18 (27.0), C-19 (114.8), C-20 (108.0). MS m/z: 320 (M^+), 302, 287, 284, 269, 259, 241, 213. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_3$ (M^+), 320.2352 (320.2352).

d) A solution of **16** (100 mg) in $CHCl_3$ (10 ml) was kept for 7 d and separated as in a) with MeOH–$CHCl_3$ (1:40) to give 27.6 mg of **17**, oil, $[\alpha]_D$ $-56.3°$ ($c=1.60$). ^{1}H-NMR δ: 1.02 (3H, s, H-18), 1.09, 1.12 (each 3H, d, $J=7.0$ Hz), 1.24 (3H, s, H-20), 2.19 (1H, dd, $J=15.0$, 7.5 Hz, H-13), 2.40 (1H, dt, $J=11.0$, 8.5 Hz, H-7), 2.51 (1H, sept, $J=7.0$ Hz, H-15), 2.68 (1H, br d, $J=15.0$ Hz, H-9), 2.80 (1H, dd, $J=15.0$, 8.0 Hz, H-9), 2.97 (1H, dd, $J=11.0$, 10.5 Hz, H-3), 4.60, 4.75 (each 1H, d, $J=2.0$ Hz, H-19), 4.66 (1H, d, $J=7.5$ Hz, H-14), 4.90 (1H, d, $J=10.5$ Hz, H-2), 5.46 (1H, br d, $J=16.0$ Hz, H-11), 5.73 (1H, ddd, $J=16.0$, 8.0, 3.5 Hz, H-10). ^{13}C-NMR δ: C-1,8 (148.2, 150.9), C-2 (125.8), C-3,7 (52.9, 54.2), C-4 (81.2), C-5 (33.5), C-6 (26.7), C-9 (40.5), C-10 (123.8), C-11 (137.3), C-12 (74.0), C-13 (50.7), C-14 (67.4), C-15 (27.7), C-16,17,18 (22.4, 25.7, 26.2), C-19 (113.9), C-20 (30.5). MS m/z: 302 ($M^+ - H_2O$), 284, 259, 241, 213, 201. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O_2$ ($M^+ - H_2O$), 302.2253 (302.2246).

e) A solution of **18** (100 mg) in $CHCl_3$ (10 ml) was kept for 7 d and separated as in a) with MeOH–$CHCl_3$ (1:65) to give 18.6 mg of **19** as an oil, $[\alpha]_D$ $-1.0°$ ($c=2.08$). ^{1}H-NMR δ: 1.13, 1.14 (each 3H, d, $J=7.0$ Hz), 1.26 (3H, s, H-18), 1.73 (3H, s, H-20), 2.69 (1H, br sept, $J=7.0$ Hz, H-15), 3.55 (1H, d, $J=10.0$ Hz, H-3), 3.63 (1H, br d, $J=9.0$ Hz, H-7), 4.73, 4.84 (each 1H, br s, H-19), 4.80 (1H, m, H-14, overlapped with a signal at 4.84), 5.08 (1H, m, H-11), 5.37 (1H, d, $J=10.0$ Hz, H-2). ^{13}C-NMR δ: C-1 (150.4), C-2 (130.8), C-3,7 (77.3, 80.0), C-4 (70.1), C-5 (34.5), C-6,10 (27.5, 27.8), C-8 (155.5), C-9 (39.6), C-11 (118.4), C-12 (127.1), C-13 (46.0), C-14 (70.1), C-15 (27.2), C-16,17,18 (20.9, 24.6, 25.9), C-19 (109.9), C-20 (17.7). MS m/z: 320 (M^+), 302, 287, 210, 193, 175, 135. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_3$ (M^+), 320.2347 (320.2352).

f) A solution of **20** (61 mg) in $CHCl_3$ (1.5 ml) was kept for 10 d and the solvent was evaporated off. Column chromatography of the residue gave **22** (4.2 mg) and **22′** (3.8 mg) on elution with hexane–$CHCl_3$ (9:1), **23** (16.2 mg) with hexane–$CHCl_3$ (1:1), and **21** (5.0 mg) with MeOH–$CHCl_3$ (1:65).

21, $[\alpha]_D$ $-10°$ ($c=1.00$). ^{1}H-NMR δ: 1.12 (3H, s, H-18), 1.12, 1.20 (each 3H, d, $J=7.0$ Hz), 1.67 (3H, s), 2.64 (1H, sept, $J=7.0$ Hz, H-15), 3.86 (1H, m, H-7), 4.06 (1H, d, $J=8.0$ Hz, H-3), 4.80 (1H, dd, $J=10.5$, 3.0 Hz, H-14), 5.14 (2H, s, H-19), 5.22 (1H, m, H-11), 5.36 (1H, d, $J=8.0$ Hz, H-2). MS m/z: 320 (M^+), 302, 287, 277, 259, 233, 217, 203, 193. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O_2$ ($M^+ - H_2O$), 302.2235 (302.2245).

22, oil, $[\alpha]_D$ $+110°$ ($c=0.84$). ^{1}H-NMR δ: 1.04, 1.08 (each 3H, d, $J=7.0$ Hz), 1.39 (3H, s, H-18), 1.51 (3H, s, H-20), 2.59 (1H, sept, $J=7.0$ Hz), 2.70 (1H, dd, $J=15.0$, 8.0 Hz, H-13), 3.04 (1H, dd, $J=15.0$, 6.0 Hz, H-13), 4.16 (1H, dd, $J=9.0$, 6.0 Hz, H-7), 4.94, 5.02 (each 1H, s, H-19), 5.43 (1H, d, $J=16.0$ Hz, H-3), 5.50 (1H, m, H-11), 5.52 (1H, dd, $J=8.0$, 6.0 Hz, H-14), 7.01 (1H, d, $J=16.0$ Hz, H-2). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 246 (8200). MS m/z: 286 (M^+), 271, 268, 243, 225, 201, 187. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O$ (M^+), 286.2300 (286.2297).

22′, oil, $[\alpha]_D$ $-76°$ ($c=0.76$). ^{1}H-NMR δ: 1.04 (6H, d, $J=7.0$ Hz), 1.31 (3H, s, H-18), 1.51 (3H, s, H-20), 2.56 (1H, sept, $J=7.0$ Hz, H-15), 2.68 (1H, dd, $J=14.0$, 8.5 Hz, H-13), 2.96 (1H, dd, $J=14.0$, 6.0 Hz, H-13), 4.53 (1H, dd, $J=7.0$, 6.0 Hz, H-7), 5.00, 5.11 (each 1H, s, H-19), 5.50 (1H, dd, $J=8.5$, 6.0 Hz, H-14), 5.50 (1H, m, H-11), 5.61 (1H, d, $J=15.5$ Hz, H-3), 7.06 (1H, d, $J=15.5$ Hz, H-2). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 245 (7900). MS m/z: 286 (M^+), 271, 268, 253, 243, 225. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O$ (M^+), 286.2289 (286.2297).

23, oil, $[\alpha]_D$ $+120°$ ($c=1.60$). ^{1}H-NMR δ: 1.08, 1.13 (each 3H, d, $J=7.0$ Hz), 1.17 (3H, t, $J=7.0$ Hz), 1.57 (3H, s, H-20), 1.70 (3H, s, H-18), 2.39 (1H, dd, $J=13.5$, 4.0 Hz, H-13), 2.53 (1H, sept, $J=7.0$ Hz), 3.33, 3.43 (each 1H, dq, $J=10.0$, 7.0 Hz), 4.06 (1H, m, H-7), 4.31 (1H, dd, $J=8.5$, 4.0 Hz, H-14), 4.91, 5.04 (each 1H, s, H-19), 5.27 (1H, br t, $J=7.0$ Hz, H-11), 6.06 (1H, br d, $J=10.0$ Hz, H-3), 6.21 (1H, d, $J=10.0$ Hz, H-2). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 250 (13000). MS m/z: 332 (M^+), 218, 203, 193, 175, 156, 137. High-resolution MS [Found (Calcd)] m/z: $C_{22}H_{36}O_2$ (M^+), 332.2731 (332.2716).

Autoxidation of 1a Compound **1a** (300 mg) was put on the surface of an evaporating dish and exposed to the air at room temperature. After 4 d, about half of **1a** was consumed. Column chromatography of the mixture with ethyl acetate–hexane (1 : 7) gave a mixture of **1a**, **9** and **10**, and then **7a** (21 mg) and **8** (35 mg). **7a**, ^{1}H-NMR δ: 1.03, 1.11 (each 3H, d, $J=7.0$ Hz), 1.28 (3H, s, H-18), 1.59, 1.66 (each 3H, s), 2.47 (1H, sept, $J=7.0$ Hz), 3.44 (1H, d, $J=8.0$ Hz, H-3), 4.72 (1H, m), 4.99 (1H, dd, $J=7.0$, 6.0 Hz, H-14), 5.05 (1H, m), 5.16 (1H, d, $J=8.0$ Hz, H-2). **8**, ^{1}H-NMR (100 MHz) δ: 0.87, 1.07 (each 3H, d, $J=7.0$ Hz), 1.38 (3H, s, H-18), 1.61, 1.66 (each 3H, s), 3.31 (1H, dd, $J=10.0$, 3.0 Hz, H-14), 5.0—5.3 (2H, m), 5.88, 6.20 (each 1H, d, $J=16.5$ Hz, H-2,3). MS m/z: 304 (M^+), 286, 271, 261, 243, 193. Compounds **7a** and **8** were unstable and were found to decompose in $CHCl_3$, gradually giving mixtures having a similar composition. Compound **7a** (20 mg) was dissolved in $CHCl_3$ (5 ml) and kept at room temperature for 1 d. Most of **7a** was converted mainly to **8**, with small amounts of **3a**, **9** and **10**, as shown by TLC. The mixture was kept another 2 d and the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (1 : 1) gave 3 mg of **3a** which was identical with an authentic specimen, by comparison of their ^{1}H-NMR spectra.

Alkaline Hydrolysis of 7b Isolation of **7b** from the epoxidation product of **1b** was described in our previous report,[1] but the physical constants and spectral properties were not recorded. **7b**, $[\alpha]_D$ $-11°$ ($c=1.09$). ^{1}H-NMR δ: 1.06, 1.07 (each 3H, d, $J=7.0$ Hz), 1.28 (3H, s, H-18), 1.60, 1.65 (each 3H, s), 2.36 (2H, br d, $J=6.5$ Hz, H-13), 2.52 (1H, sept, $J=7.0$ Hz, H-15), 3.54 (1H, d, $J=9.0$ Hz, H-3), 5.00 (1H, br t, $J=7.0$ Hz), 5.07 (1H, m), 5.20 (1H, d, $J=9.0$ Hz, H-2), 5.89 (1H, dd, $J=7.5$, 6.0 Hz, H-14). ^{13}C-NMR δ: C-1 (150.9), C-2,7,11 (123.0, 123.2, 127.6), C-3 (59.3), C-4 (62.0), C-5,9 (38.4 (2C)), C-6,10 (23.8, 24.6), C-8 (134.5), C-12 (130.1), C-13 (41.7), C-14 (72.4), C-15 (28.3), C-16,17 (24.2, 24.7), C-18,19,20 (16.6, 17.2, 17.7), Ac (21.4, 169.8). MS m/z: 346 (M^+), 286, 271, 243. High-resolution MS [Found (Calcd)] m/z: $C_{22}H_{34}O_3$ (M^+), 346.2518 (346.2508). A solution of **7b** (18.5 mg) in 2.5% KOH in MeOH (1 ml) was kept at room temperature for 1 h. The mixture was diluted with H_2O and extracted with Et_2O. After the usual work-up, the solvent was evaporated off. Column chromatography of the residue with $CHCl_3$–hexane (2 : 1) gave 11.5 mg of **9** which was identical with an authentic specimen[6] by comparison of their ^{1}H-NMR spectra. The more polar fraction contained a very small amount of **3a**, which was not isolated. The identification was made only by comparison with an authentic specimen in several TLC systems.

TsOH Treatment of 7b A mixture of **7b** (50 mg) in 0.05% H_2SO_4 in dioxane–H_2O (4 : 1, 1 ml) was kept at room temperature for 20 min. The mixture was diluted with H_2O and extracted with Et_2O. After the usual work-up, the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (1 : 6) gave 40.1 mg of **11**. It was identical with an authentic specimen previously prepared from **1b**,[6] based on a comparison of their ^{1}H-NMR spectra.

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