Marine Terpenes and Terpenoids. XI.[1] Structures of New Dihydrofuranocembranoids Isolated from a *Sarcophyton* sp. Soft Coral of Okinawa

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The cembranoids of a *Sarcophyton* sp. soft coral, collected in Okinawa, were found to be composed predominantly of dihydrofuranocembranoid derivatives (2, 3, 5a, 6 and 7) together with a hydrocarbon cembrene C (1) and a lactonic cembranoid, sarcophytonin B (4). The major constituents sarcophytonin A (2), deoxosarcophine (5a), and sarcophytonin C (6) were shown to be mixtures having similar enantiomeric ratios. The structures of the new compounds (3, 4, 6 and 7) were derived on the basis of spectroscopic studies and chemical correlations. Compounds 3 and 7 were supposed to be artefacts derived from 5a or 6 (3), and from 5a (7) respectively.

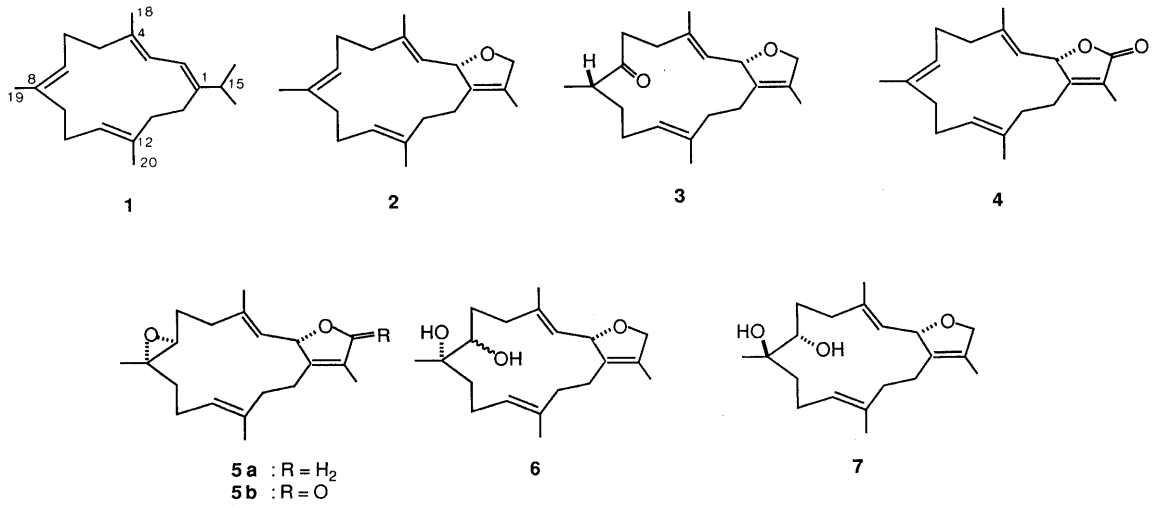
Keywords soft coral; *Sarcophyton* sp.; cembranoid; dihydrofuranocembranoid; sarcophytonin B; sarcophytonin C

Cembranoids are the characteristic chemical components of soft coral lipids. The majority of them are lactonic compounds due to the oxidized isopropyl side chain.[2] The cembranoids having a dihydrofurano-type moiety are less common. Deoxosarcophine (**5a**) is a typical example of this group. It was first isolated from a soft coral *Sarcophyton glaucum* in the Red Sea, in quite high yield.[3] In our earlier work we studied the cembranoids of *S. glaucum*, collected in Ishigaki Island, Okinawa, and isolated more than 20 cembranoids (sarcophytols).[4] Interestingly, all but one compound, sarcophytonin A (7,8-deepoxydeoxosarcophine, **2**),[4a] were derivatives having an intact isopropyl side chain. Sarcophytonin A accounted for 5—10% of the total lipids in the material collected in June 1977 but it was not found in the material which was collected in the same place in September 1978, and in subsequent years. These facts illustrate well the complexity of the production of such metabolites in marine organisms, influenced by their habitats and other as yet unknown factors.

Recently, we collected several soft coral samples in Chatan, Okinawa (26°19′N, 127°46′E), a district which is some 400 km northeast of Ishigaki Island. One of them was identified at the genus level as a *Sarcophyton* sp., by courtesy of Mr. Y. Imahara, Fisheries Promotion Division, Wakayama Prefectural Office, Japan. Most of its cembranoids were found to be dihydrofurano-type derivatives, including sarcophytonin A (**2**). The present paper deals with the analyses of the cembranoids of this material and the structures of four new sarcophytonin A derivatives (**3**, **4**, **6** and **7**).

Repeated flash column chromatography of the lipid extract gave three major (**2**, **5a** and **6**) and four minor cembranoids (**1**, **3**, **4** and **7**). Of these, compounds **1** (cembrene C),[5] **2**, [4a] and **5a**[3,6] are known, and were identified by comparisons of their proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra, mass (MS) spectrum and other spectral properties (see Experimental) with those in the literature.

A prominent feature of these dihydrofuranocembranoids, unlike other types of cembranoids, is that they occur as enantiomeric mixtures. The specific rotation of **2** (+120°), obtained in the present study, was different from that (−90°) of sarcophytonin A which we obtained from *S. glaucum* of Ishigaki Island, although the two products were spectroscopically identical.[4a] Sarcophytonin A was later synthesized by deoxygenation of the corresponding epoxides,[6,7] which also seem to be enantiomeric mixtures. In these reports, the specific rotation of **2** varied in both sign and magnitude (+239° to −210°). The specific rotation of **5a** obtained in the present work was +129° while the recorded values are diverse (+157° to −191°).[6] The absolute configuration of (+)-deoxosarcophine (**5a**) was established by X-ray crystallography of **5a**[8] and **5b** (sarcophine),[9] the circular dichroism (CD) study of **5b**[10]



1 2 3 4

5a : R = H_2
5b : R = O

6 7

Chart 1

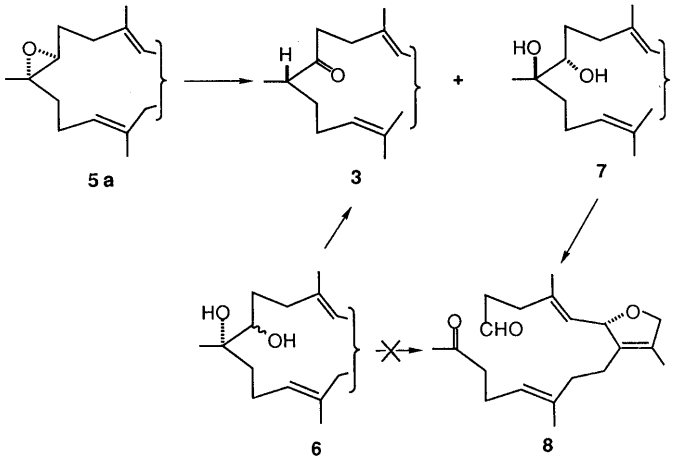


Chart 2

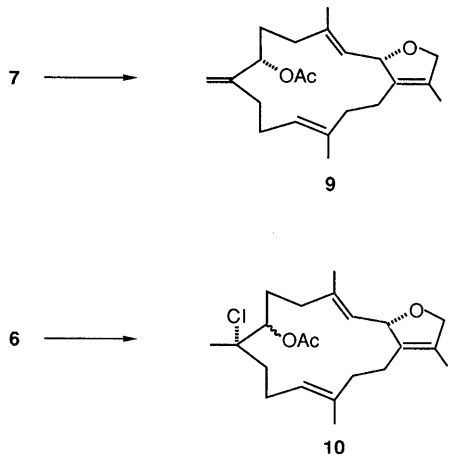


Chart 3

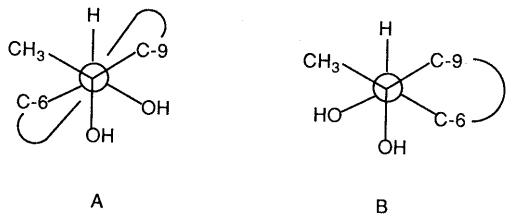


Chart 4

and the chemical conversion of **5a** to **5b**.[11] The positive specific rotations of **2** and **5a** in the present work indicated that they are composed mainly of the (+)-2*S* isomer (**2**) and (+)-2*S*,7*S*,8*S* isomer (**5a**).[6]

Compound **4** (sarcophytonin B) was found to be the 16-oxo derivative of **2** (infrared (IR) spectrum, 1755 cm^{-1}). Compounds **2** and **4** showed common ^{13}C-NMR chemical shifts due to C-5 to C-12; the maximum deviation was less than 0.6 ppm. The carbon signals of the γ-lactone moiety (C-1, δ 163.0, C-2, 79.2, C-3, 120.0, C-15, 122.4, C-16, 175.0, C-17, 9.0) showed close analogy with those reported for sarcophine (**5b**, δ 162.3, 78.8, 120.7, 122.9, 173.0, 8.9).[12] The absolute configuration of **4** at C-2 was concluded to be *S* from the CD spectrum, which showed the same negative Cotton curve (247 nm, $\Delta\varepsilon$ −3.3) due to the chiral butenolide ring as reported for 2*S*-**5b** (246 nm, $\Delta\varepsilon$ −6.5).[10] From the biosynthetic viewpoint, it is noteworthy that **4** represents both a plausible precursor and metabolite of sarcophytonin A (**2**) in the soft coral.

When treated with a trace of perchloric acid in acetone, **5a** gave two major products, a glycol **7** ($[\alpha]_D$ +135°) and a ketone **3** ($[\alpha]_D$ +113°). Compounds **3** and **7** were found to be identical with those isolated from the soft coral lipids (**3**, $[\alpha]_D$ +110°; **7**, $[\alpha]_D$ +140°). The coincidcnce of the specific rotations indicates closely similar enantiomeric ratios of the synthetic and natural **3** and **7**. This suggests, though does not prove, that **3** and **7** obtained from this *Sarcophyton* sp. soft coral were derived from **5a** during the extraction and isolation processes.

Compound **6** (sarcophytonin C) is a dihydroxy derivative of **2** (^{13}C-NMR, δ 72.7 (d), 78.8 (s); ^1H-NMR, δ 3.71, br d, J = 11.0 Hz). Since β-hydroxy substituent effects were not observed in the ^{13}C-NMR chemical shifts of double bonds (Experimental), and since the hydroxymethine proton signal indicated coupling with two protons, the possibility is that **6** bears a glycol, at C-7, 8 or C-11, 12 on biogenetic grounds. In order to determine the position of the glycol group, we tried to convert **5a** and **6** to keto-aldehyde derivatives. Sodium metaperiodate oxidation of **7**, derived from **5a**, smoothly gave the secoaldehyde **8**. In contrast, compound **6** was resistant to periodate oxidation. Most of the starting material was recovered but one product, formed in very small amounts, showed the same mobility as **3** on thin-layer chromatography (TLC). When **6** was treated with a trace of perchloric acid in MeOH–H_2O (2 : 1), it gave the ketone **3** ($[\alpha]_D$ + 110°) in 22% yield. This confirmed that compound **6** bears the glycol group at C-7 and C-8, as in **7**. Compound **3** was the sole product from **6** and the rearrangement should have occurred in a concerted manner, like that of epoxides.[13] Similar rearrangement of the glycol was observed previously on acid-treatment of sarcophytol B, a cembranoid of *S. glaucum*, having a 13,14-glycol moiety.[4c] In the transition state of the reaction, the C-8 hydroxyl group and H-7 should take an antiperiplanar arrangement, resulting in inversion of the configuration at C-8. Formation of **3** indicates that the configuration of **6** at C-8 is *S*. The specific rotation of **3** derived from **6** is identical with those of **3** isolated from the soft coral and **3** prepared from **5a**. This indicates that **6** is an enantiomeric mixture, like **5a** and **3**. It means at the same time that there is a possibility that **3** obtained from the soft coral was derived artificially from **6**.

Dehydration of the 7-monoacetate of **7** gave the allylic alcohol **9**. If the same or a different exocyclic olefin was derived from **6**, its configuration at C-7 could be determined as 7*S* or 7*R*. However, treatment of the acetate of **6** with thionyl chloride and phosphoryl chloride gave not the desired olefin but a C-8 chloro derivative (**10**). Attempted dehydrochlorination of **10** using several bases was unsuccessful. Although the configuration at C-7 of **6** was not derived by correlation to known compounds, it was possible to speculate on the basis of conformational considerations. If compound **6** takes an antiperiplanar disposition regarding the H-7 and C-8 hydroxyl group, as mentioned above, partial conformations about the C-7, 8 bond could be assumed for the 7*S* (A) and 7*R* (B) isomers as shown in Chart 4. In the 7*S*, 8*S* isomer the C-7 hydroxyl group or H-7 would have to be directed to the inner side of the cembrane ring, and this is sterically unlikely (A). In

contrast, the *7R,8S* configuration does not suffer such hindrance (B), and seems to be the more probable one.

Experimental

Melting points were determined on a Kofler hot stage and are uncorrected. Optical rotations were determined in $CHCl_3$ on a JASCO DIP-370 digital polarimeter. NMR spectra were determined in $CDCl_3$ solution on a JEOL JNM GX-270 spectrometer at 270 MHz (^1H) and on a JEOL JNM FX-90Q spectrometer at 22.5 MHz (^{13}C) with tetramethylsilane as an internal standard. MS spectra were determined on a JEOL JMS D300 mass spectrometer. Chromatography was done by flash column chromatography[14] using silica gel (Wako gel C-300, 200—300 mesh, Wako Pure Chemical Industries).

Materials The material (1.9 kg) of the *Sarcophyton* sp. collected in October 1986 in Chatan, Okinawa, was extracted with MeOH and MeOH–$CHCl_3$ (1 : 1). The combined extract contained significant amounts of inorganic salts. The evaporation residue was dissolved in $CHCl_3$ and the insoluble materials were removed by filtration. Evaporation of the $CHCl_3$ soluble extract gave 20.9 g of dark oily residue. It was subjected, in portions, to repeated chromatography over a column of silica gel. Compounds **2**, **5a** and **6** were predominant, but only portions of them, sufficient for the structural study, were isolated. The amounts of the compounds purified, their order of elution, and the solvent mixtures used are as follows: **1** (84 mg, hexane), **2** (183 mg, ethyl acetate–hexane, 1 : 19), **5a** (500 mg, ethyl acetate–hexane, 7 : 93), **6** (90 mg, ethyl acetate–hexane, 13 : 87), **7** (151.5 mg, ethyl acetate–hexane, 55 : 45). Compounds **3** and **4** eluted as a mixture immediately before **5a**. The mixture was subjected to 7% silver nitrate-impregnated silica gel column chromatography with ethyl acetate–hexane (15 : 85), giving first **3** (68.3 mg) and then **4** (31 mg). Compound **1** (cermbrene C) and **2** (sarcophytonin A) were identified by comparisons of their ^1H- and ^{13}C-NMR and MS spectra with those of the authentic specimens isolated previously.

Compound 3 Oil, $[\alpha]_D^{20}$ +110° (c=0.92). ^1H-NMR δ: 1.08 (3H, d, J=7.5 Hz, H-19), 1.58, 1.64 (each 3H, s, H-17,20), 1.86 (3H, d, J=1.5 Hz, H-18), 2.54 (1H, ddd, J=18.0, 10.0, 3.0 Hz, H-6), 2.76 (1H, ddd, J=18.0, 8.0, 3.0 Hz, H-6), 4.48 (2H, br s, H-16), 4.83 (1H, br dd, J=12.0, 6.5 Hz, H-11), 5.18 (1H, dq, J=10.0, 1.0 Hz, H-3), 5.43 (1H, m, H-2). ^{13}C-NMR δ: C-1 (133.8), C-2 (84.2), C-3 (126.0), C-4 (140.4), C-5 (39.6), C-6,9 (32.1, 32.5), C-7 (213.7), C-8 (46.4), C-10 (24.1), C-11 (123.1), C-12 (136.5), C-13 (36.7), C-14 (26.0), C-15 (127.6), C-16 (78.2), C-17 (10.1), C-18, 19, 20 (15.7, 17.6, 18.9). MS m/z: 302 (M^+), 287, 231, 218, 203, 189, 175, 163. IR ν_{max}^{Neat} cm^{-1}: 1710. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O_2$ (M^+), 302.2274 (302.2245).

Compound 4 Oil, $[\alpha]_D^{21}$ +160° (c=0.97). ^1H-NMR δ: 1.59, 1.63 (each 3H, s, H-19, 20), 1.78, 1.83 (each 3H, s, H-17, 18), 4.86 (1H, br d, J=10.0 Hz, H-3), 4.81—4.89 (1H, overlapped by the signal at δ 4.86), 5.01 (1H, br dd, J=7.0, 6.5 Hz), 5.52 (1H, dd, J=10.0, 1.5 Hz, H-2), ^{13}C-NMR δ: C-1 (163.0), C-2 (79.2), C-3 (120.0), C-4 (144.7), C-5, 9 (38.9, 39.8), C-6, 10 (23.6, 24.6), C-7, 11 (124.6, 125.2), C-8, 12 (133.9, 133.9), C-13 (36.4), C-14 (27.0), C-15 (122.4), C-16 (175.0), C-17 (9.0), C-18, 19, 20 (15.3, 15.9, 15.9). MS m/z: 300 (M^+). IR ν_{max}^{Neat} cm^{-1}: 1755, 1680. UV ν_{max}^{EtOH} nm (ε): 207 (7700). High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{28}O_2$ (M^+), 300.2074 (300.2090).

Compound 5a Oil, $[\alpha]_D^{26}$ +129° (c=1.02). ^1H-NMR δ: 1.27 (3H, s, H-19), 1.60, 1.65 (each 3H, s, H-17, 20), 1.83 (3H, d, J=1.5 Hz, H-18), 2.72 (1H, dd, J=4.0, 4.5 Hz, H-7), 4.50 (2H, m, H-16), 5.10 (1H, br dd, J=10.0, 4.5 Hz, H-11), 5.23 (1H, dq, J=10.0, 1.0 Hz, H-3), 5.54 (1H, m, H-2). ^{13}C-NMR δ: C-1 (133.2), C-2 (83.7), C-3 (126.3), C-4 (139.2), C-5 (37.7), C-6 (25.4), C-7 (61.9), C-8 (59.9), C-9 (39.8), C-10 (23.6), C-11 (123.6), C-12 (136.8), C-13 (36.6), C-14 (26.1), C-15 (127.9), C-16 (78.4), C-17 (10.4), C-18, 20 (15.3, 15.7), C-19 (17.1). MS m/z: 302 (M^+), 231, 203, 175, 163.

Compound 6 Oil, $[\alpha]_D^{27}$ +90.0° (c=1.09). ^1H-NMR δ: 1.55 (3H, s, H-19), 1.64 (6H, br s, H-17, 20), 1.82 (3H, br s, H-18), 3.71 (1H, br d, J=11.0 Hz, H-7), 4.50 (2H, m, H-16), 5.02 (1H, br t, J=6.5 Hz, H-11), 5.17 (1H, br d, J=10.0 Hz, H-3), 5.53 (1H, m, H-2). ^{13}C-NMR δ: C-1 (133.4), C-2 (84.0), C-3 (127.3), C-4 (138.8), C-5, 13 (35.6, 36.5), C-6 (28.0), C-7 (72.7), C-8 (78.8), C-9 (39.5), C-10, 14 (24.6, 24.9), C-11 (123.0), C-12 (136.3), C-15 (128.0), C-16 (78.5), C-17 (10.3), C-18, 20 (15.6, 15.9), C-19 (26.6). MS m/z: 302 ($M^+ - H_2O$), 287, 233, 218, 163. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{30}O_2$ ($M^+ - H_2O$), 302.2274 (302.2245).

Compound 7 mp 93—95 °C, $[\alpha]_D^{21}$ +140° (c=0.48). ^1H-NMR δ: 1.20 (3H, s, H-19), 1.64 (6H, br s, H-17, 20), 1.85 (3H, br s, H-18), 3.57 (1H, br d, J=10.5 Hz, H-7), 4.50 (2H, br s, H-16), 4.92 (1H, br dd, J=10.0, 4.0 Hz, H-11), 5.14 (1H, d, J=10.0 Hz, H-3), 5.54 (1H, m, H-2). ^{13}C-NMR δ: C-1 (133.4), C-2 (83.9), C-3 (126.6), C-4 (139.1), C-5, 9, 13 (35.5, 36.6, 36.9), C-6, 10, 14 (23.6, 25.2, 26.6), C-7 (72.8), C-8 (75.5), C-11 (124.2), C-12 (135.6), C-15 (127.5), C-16 (78.2), C-17 (10.1), C-18, 20 (15.2, 15.8), C-19 (24.2). MS m/z: 320 (M^+), 305, 302, 276, 263, 203, 175, 163. High-resolution MS [Found (Calcd)] m/z: $C_{20}H_{32}O_3$ (M^+), 320.2369 (320.2352).

Perchloric Acid Treatment of 5a A solution of **5a** (130 mg) in 3 ml of acetone was treated for 1 h at room temperature with 4 drops of $HClO_4$ solution made from 0.15 ml of 70% perchloric acid and 5 ml of H_2O. The mixture was diluted with H_2O and Et_2O and the Et_2O layer was washed with H_2O and saturated NaCl solution, then the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (15 : 85) gave 20 mg of **3** as an oil, $[\alpha]_D^{19}$ +113° (c=1.08). Further elution with ethyl acetate–hexane (6 : 4) gave 47 mg of **7**, mp 97—98 °C, $[\alpha]_D^{22}$ +135° (c=0.65). It was identical with **7** isolated from the soft coral material, by comparisons of their ^1H-, ^{13}C-NMR and MS spectra, and their behavior in several TLC systems.

Perchloric Acid Treatment of 6 A solution of **6** (7.5 mg) in MeOH–H_2O (2 : 1, 1.5 ml) was treated overnight at room temperature with 4 drops of $HClO_4$ solution prepared above. The mixture was diluted with H_2O and Et_2O and the Et_2O layer was washed with H_2O and saturated NaCl solution, then the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (1 : 9) gave 1.6 mg of **3** as an oil, $[\alpha]_D^{19}$ +110 (c=0.31). It was identical with **3** isolated from the soft coral material, by comparisons of their ^1H-NMR and MS spectra, and their behavior in several TLC systems.

Sodium Periodate Treatment of 7 A solution of **7** (33 mg) prepared from **5a** was added to 10 ml of MeOH–H_2O (1 : 1) and the mixture was stirred at room temperature with $NaIO_4$ (29 mg) for 20 h, then concentrated *in vacuo* and diluted with H_2O and Et_2O. The Et_2O layer was washed with H_2O and saturated NaCl solution and the solvent was evaporated off. Column chromatography of the residue with ethyl acetate–hexane (2 : 8) gave 16.3 mg of **8** as an oil, $[\alpha]_D^{21}$ +46° (c=1.19). ^1H-NMR δ: 1.61 (3H, s), 1.62 (3H, s), 1.78 (3H, d, J=1.5 Hz), 2.14 (3H, s, H-19), 4.43 (1H, br d, J=11.5 Hz, H-16), 4.53 (1H, dd, J=11.5, 5.5 Hz, H-16), 5.06 (1H, t, J=7.0 Hz, H-11), 5.10 (1H, dq, J=9.5, 1.0 Hz, H-3), 5.40 (1H, m, H-2), 9.77 (1H, dd, J=2.0, 1.5 Hz, H-7). ^{13}C-NMR δ: C-1 (133.1), C-2 (84.3), C-3 (126.1), C-4 (137.4), C-5 (31.8), C-6 (41.9), C-7,8 (201.8, 201.8), C-9 (43.6), C-10,14 (22.5, 23.7), C-11 (123.3), C-12 (135.9), C-13 (38.0), C-15 (128.4), C-16 (78.2), C-17 (10.0), C-18,20 (15.9, 16.7), C-19 (29.9). MS m/z: 318 (M^+), 303, 279, 274, 261, 247, 233, 219, 192, 164, 149.

Conversion of 7 to 9 Compound **7** was acetylated in a usual way (Ac_2O–pyridine). A solution of the acetate (30 mg) in pyridine (0.3 ml) was treated at 0°C with $SOCl_2$ (20 μl) for 10 min. The mixture was diluted with H_2O and extracted with Et_2O. The Et_2O layer was 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 : 9) gave 13.4 mg of **9** as an oil, $[\alpha]_D^{20}$ +86° (c=2.68). ^1H-NMR δ: 1.64 (6H, s), 1.84 (3H, d, J=1.5 Hz, H-18), 2.08 (3H, s, OAc), 4.48 (2H, m, H-16), 4.85 (1H, br s, H-19), 4.87 (1H, t, J=1.5 Hz, H-19), 5.03 (1H, br d, J=10.2 Hz, H-3), 5.09 (1H, br t, J=7.5 Hz, H-11), 5.28 (1H, br d, J=11.0 Hz, H-7), 5.55 (1H, m, H-2). MS m/z: 344 (M^+), 329, 301, 285, 269.

Conversion of 6 to 10 Compound **6** was acetylated and the acetate (35 mg) was treated with $SOCl_2$ in the same way as above. Column chromatography of the reaction mixture with ethyl acetate–hexane (1 : 9) gave 11.8 mg of **10** as an oil, $[\alpha]_D^{20}$ +42° (c=2.36). ^1H-NMR δ: 1.47 (3H, s, H-19), 1.64 (6H, s), 1.85 (3H, s, H-18), 2.12 (3H, s, OAc), 2.56 (1H, ddd, J=14.0, 11.5, 8.0 Hz), 4.48 (2H, m, H-16), 4.87 (1H, br d, J=10.5 Hz, H-11), 5.00 (1H, br d, J=10.0 Hz, H-3), 5.18 (1H, dd, J=8.0, 4.5 Hz, H-7), 5.52 (1H, m, H-2). MS m/z: 382 (M^+), 380 (M^+), 345 ($M^+ - Cl$), 285 ($M^+ - Cl$, AcOH).

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