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Bioactive Marine Diterpenoids from Japanese Soft Coral of *Clavularia* sp.

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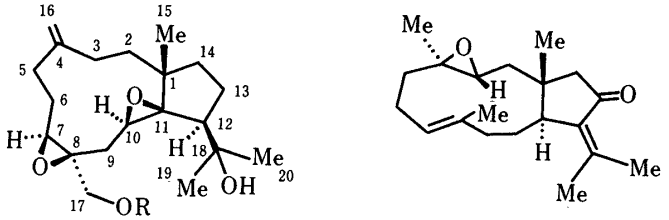
Three new bioactive marine diterpenoids, stolonidiol (**1**), stolonidiol monoacetate (**2**), and claenone (**3**), were isolated from Japanese soft coral of the genus *Clavularia*. The structures of these diterpenoids were elucidated on the basis of spectroscopic data including two-dimensional nuclear magnetic resonance, chemical reactions, and/or X-ray crystallographic analysis. Compounds **1** and **2** showed a strong cytotoxic activity against P388 leukemia cells, and **3** was inhibitory in the fertilized sea urchin egg assay.

Keywords——marine diterpenoid; stolonidiol; stolonidiol monoacetate; claenone; *Clavularia* sp.; Stolonifera; soft coral; cytotoxic activity; sea urchin egg development-inhibitory activity

Previously we reported the isolation and structural elucidation of a new type of antitumor marine prostanoids, clavulones and their halogenated congeners, from the Japanese soft coral *Clavularia viridis*.[1] During our continuing investigation on *Clavularia* spp., we have found that a new collection of *Clavularia* sp., which was also identified as *C. viridis*,[2] differed remarkably in chemical constituents from the *C. viridis* studied previously. No marine prostanoid (such as clavulones) was detected in the new collection by a preliminary thin layer chromatographic (TLC) analysis of its crude extract. This unexpected finding prompted us to investigate the chemical constituents of this soft coral, resulting in the isolation of three bioactive diterpenoids, stolonidiol (**1**), stolonidiol monoacetate (**2**), and the related major diterpenoid claenone (**3**). Compounds **1** and **2** showed potent cytotoxic activity against P388 leukemia cells *in vitro* (IC_{50} value of each; 0.015 μg/ml), and an ichthyotoxic activity toward killifish *Oryzias latipes* (minimum lethal concentration: 10 μg/ml for **1** and 17 μg/ml for **2**). Although **3** did not show these activities, **3** inhibited cell division in fertilized sea urchin eggs (*Pseudocentrotus depressus*) at a concentration of 2 μg/ml. This paper describes the details of the isolation and structures of these diterpenoids.[3]

Extraction and Isolation

The freeze-dried specimens (1 kg) of *Clavularia* sp., collected on the coral reef of Ishigaki Island (Okinawa, Japan), were extracted with ethyl acetate. The extract (73 g), which showed an ichthyotoxic activity, was chromatographed on a silica gel column by stepwise elution with hexane–ethyl acetate mixture (20:1, 4:1, 3:2, 1:1, 2:3, and 1:4), to give six fractions. Fractions 4 and 5 with the ichthyotoxic activity were further purified by using flash chromatography to give stolonidiol (**1**) (1.5 g, 0.15% yield based on the freeze-dried organisms, colorless oil, $C_{20}H_{32}O_4$, $[\alpha]_D$ $-31.6°$) from fraction 5, and stolonidiol monoacetate (**2**) (2.3 g, 0.23% yield based on the freeze-dried organisms, colorless oil, $C_{22}H_{34}O_5$, $[\alpha]_D$ $-26.8°$) from fraction 4. Similar purification of fraction 2, which did not show the ichthyotoxic activity, gave claenone (**3**) (14.0 g, 1.4% yield based on the freeze-dried



1 : R=H
2 : R=Ac

3

Chart 1

organisms, colorless needles, mp 124—126 °C, $C_{20}H_{30}O_2$, $[\alpha]_D$ −50.9 °) as the most abundant terpenoid of the soft coral.

Structures of Stolonidiol (1) and Stolonidiol Monoacetate (2)

The infrared (IR) spectrum of **1** showed the presence of hydroxyl group (3430 cm^{-1}) and *exo*-methylene group (1645, 910 cm^{-1}) absorptions. The proton nuclear magnetic resonance (^{1}H-NMR) (400 MHz, $CDCl_3$) and carbon 13 nuclear magnetic resonance (^{13}C-NMR) (100 MHz, $CDCl_3$) spectra of **1** showed the signals due to two trisubstituted epoxides [δ_H 3.12 (1H, dd, J=2.0, 8.0 Hz), 3.16 (1H, dd, J=6.4, 7.5 Hz); δ_C 56.6 (d), 58.0 (d), 63.7 (s), 75.9 (s)], a hydroxymethyl [δ_H 3.62 (1H, d, J=12.4 Hz), 3.77 (1H, d, J=12.4 Hz); δ_C 65.5 (t)], an *exo*-methylene [δ_H 4.72 (1H, br s), 4.81 (1H, br s); δ_C 111.3 (t), 148.7 (s)], and three methyls [δ_H 0.85 (3H, s), 1.19 (3H, s), 1.29 (3H, s)]. These spectral data and the degree of unsaturation (five) suggest that **1** is a bicarbocyclic diterpenoid with two epoxide moieties. Acetylation of **1** with acetic anhydride in pyridine at room temperature gave the monoacetate **2**, which was identical to the natural stolonidiol monoacetate. The IR spectrum of **2** showed an absorption at 3450 cm^{-1}, suggesting the presence of a tertiary hydroxy group in **1** in addition to the primary hydroxy group. The following chemical reactions of **1** and **2** (Chart 2) extended the partial structures. Treatment of **1** with methanolic potassium hydroxide under

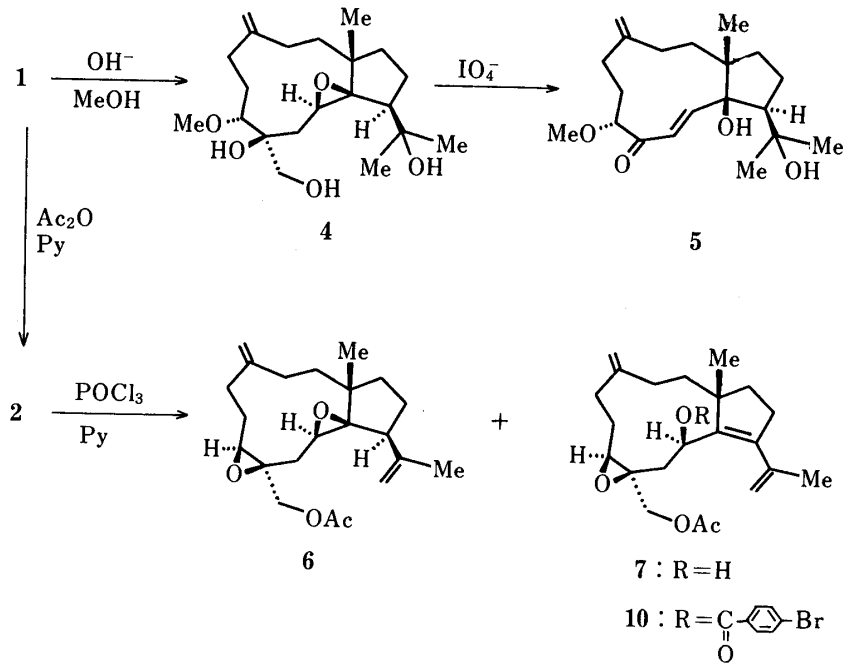


Chart 2

reflux gave a triol **4**, which was then oxidized with sodium metaperiodate in methanol to give a conjugated enone **5** [IR 3500, 1700, 1630 cm^{-1}; ultraviolet (UV) absorption 238 nm (ε 6470); δ_H 6.68 (1H, d, J = 15.2 Hz), 6.70 (1H, d, J = 15.2 Hz)]. This finding showed the presence of the partial structure $-CH_2-\underset{\backslash O /}{CH}-C(CH_2OH)-CH_2-\underset{\backslash O /}{CH}-C<$ in **1**. Treatment of **2** with phosphorus oxychloride in pyridine gave **6** [δ_H 1.76 (3H, d, J = 0.6 Hz)] and **7** (IR 3300 cm^{-1}; UV 226 nm (ε 6900); δ_H 1.90 (3H, s)], showing the presence of the partial structure $-\underset{\backslash O /}{CH}-\underset{|}{C}-CH-C(OH)<\begin{matrix}CH_3\\CH_3\end{matrix}$. Since the epoxide moiety in the right part of the former partial structure is common with the epoxide of the latter one, these two partial structures can be extended to the partial structure $-CH_2-\underset{\backslash O /}{CH}-C(CH_2OH)-CH_2-\underset{\backslash O /}{CH}-\underset{|}{C}-\underset{|}{CH}-\underset{|}{C}(OH)<\begin{matrix}CH_3\\CH_3\end{matrix}$.

The results of the following two-dimensional NMR (2D NMR) measurements of **1**, coupled with the above-mentioned findings, led to the plane structures of **1** and **2**. Firstly, the chemical shifts and the coupling patterns of the overlapped ^1H signals of **1** were clarified by the analysis of the ^1H J-resolved spectrum as summarized in Table I. Then the ^1H signals and the ^{13}C signals were fully correlated by the measurement of the ^{13}C–^1H heteronuclear shift correlation 2D spectrum (CH-COSY) as summarized in Table I. The ^1H–^{13}C long-range coupling correlation 2D spectrum (COLOC) of **1** clarified the relations between the protons and carbons as summarized in Table II, giving the two extended partial structures shown

TABLE I. ^{13}C- and ^1H-NMR Data for **1** in $CDCl_3$

Carbon	δ_C ppm	δ_H ppm (J in Hz)
1	44.5 (s)	—
2	37.9 (t)	1.29 (br dd, 8.8, 14.6)
		1.54 (ddd, 8.8, 10.0, 14.6)
3	29.3 (t)	1.92 (dd, 10.0, 16.2)
		2.16 (td, 8.8, 16.2)
4	148.7 (s)	—
5	31.4 (t)	2.26 (dtd, 1.4, 8.4, 14.1)
		2.47 (br ddd, 6.4, 7.7, 14.1)
6	24.8 (t)	1.65 (tdd, 6.4, 8.4, 16.4)
		1.76 (m)
7	58.0 (d)	3.16 (dd, 6.4, 7.5)
8	63.7 (s)	—
9	26.9 (t)	2.13 (dd, 2.0, 15.9)
		2.48 (dd, 8.0, 15.9)
10	56.6 (d)	3.12 (dd, 2.0, 8.0)
11	75.9 (s)	—
12	48.3 (d)	2.29 (dd, 3.8, 9.8)
13	27.2 (t)	1.61 (m)
		1.95 (m)
14	36.9 (t)	1.68 (m)
		1.70 (m)
15	23.5 (q)	0.85 (s)
16	111.3 (t)	4.72 (br s)
		4.81 (br s)
17	65.5 (t)	3.62 (d, 12.4)
		3.77 (d, 12.4)
18	74.6 (s)	—
19	29.6 (q)	1.19 (s)
20	26.1 (q)	1.29 (s)

TABLE II. Long-Range Correlated ^{13}C and ^{1}H Signals in the COLOC Spectrum ($CDCl_3$) of **1**

^{13}C signals (δ ppm)	Correlated ^{1}H signals[a] (δ ppm)
C-1 (44.5)	H-2a (1.29)
	H-15 (0.85)
C-2 (37.9)	H-5
C-3 (29.3)	H-16a (4.72)
	H-16b (4.81)
C-4 (148.7)	H-3a (1.92)
	H-5b (2.47)
C-5 (31.4)	H-16a, H-16b
C-7 (58.0)	H-9a (2.13)
C-8 (63.7)	H-7 (3.16)
	H-9a
	H-9b (2.48)
	H-17b (3.77)
C-9 (26.9)	H-10 (3.12)
C-10 (56.6)	H-9a, H-9b
C-11 (75.9)	H-9a, H-9b, H-15
C-12 (48.3)	H-13b (1.95)
	H-19 (1.19)
	H-20 (1.29)
C-14 (36.9)	H-15
C-15 (23.5)	H-14a (1.68)
C-17 (65.5)	H-9a
C-18 (74.6)	H-12 (2.29)
	H-19, H-20
C-19 (29.6)	H-20
C-20 (26.1)	H-19

a) H_a corresponds to the high-field proton of the methylene protons and H_b to the low-field proton.

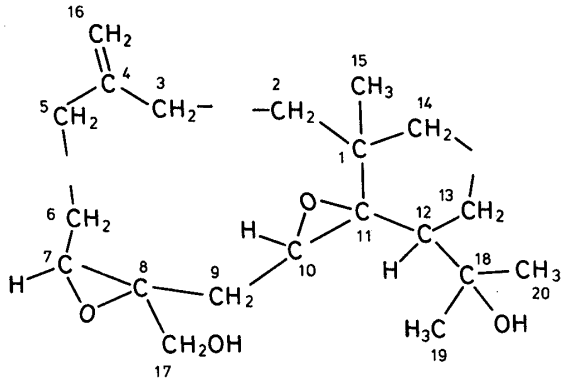


Chart 3

in Chart 3. Measurement of the ^{13}C–^{13}C homonuclear shift correlation 2D spectrum (INADEQUATE) confirmed the presence of these two partial structures, and further elucidated the connections between C-2 and C-3, C-5 and C-6, and C-13 and C-14, respectively. The INADEQUATE spectrum showed the cross peaks of twenty-one pairs of carbons as shown in Fig. 1. Connection of each carbon pair clarified the sequence of carbon atoms, giving the plane structures of stolonidiol (**1**) and thus stolonidiol monoacetate (**2**).

The relative and absolute configurations of **1** and **2** were determined by an X-ray analysis on a single crystal of the *p*-bromobenzoate **9**, which was obtained as a crystalline product

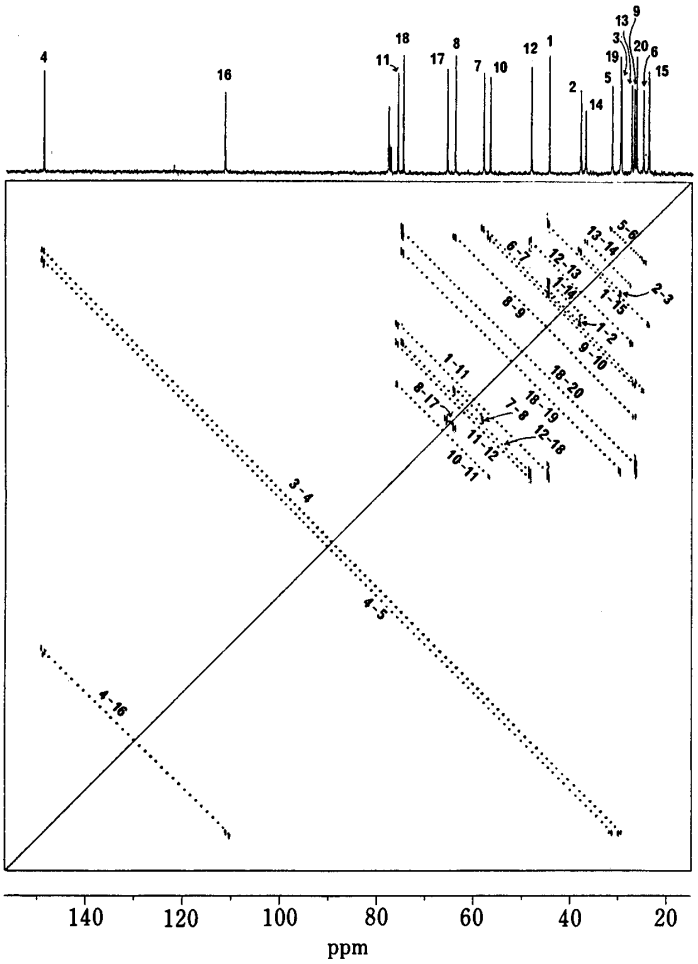
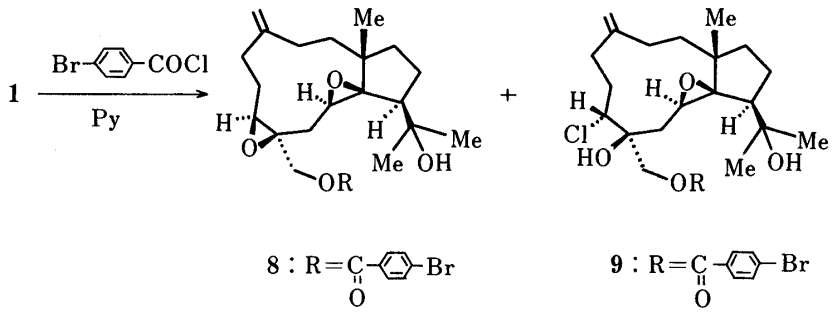


Fig. 1. ^{13}C–^{13}C Homonuclear Shift Correlation 2D NMR Spectrum (INADEQUATE, 100 MHz, $CDCl_3$) of **1**



8 : R=C(=O)-C6H4-Br 9 : R=C(=O)-C6H4-Br

Chart 4

together with non-crystalline **8** in the reaction of **1** with *p*-bromobenzoyl chloride in pyridine, as shown in Chart 4. Compound **9** was regenerated to stolonidiol (**1**) by treatment with methanolic potassium carbonate, showing the retention of the same configuration at C-8 in **9** as that in **1**. The result of the X-ray analysis of **9** is shown in Fig. 2. Thus, the absolute configurations of six chiral centers in **1** and **2** were elucidated as 1*S*, 7*S*, 8*S*, 10*R*, 11*R*, and 12*S*. The absolute configuration at C-10 of **1** and **2** was also supported by the circular dichroism (CD) measurement of the *p*-bromobenzoate **10** derived from the allylic alcohol **7**. The CD spectrum (in ethanol) of **10** [UV 243 nm (ε 10700)] showed a positive Cotton effect at 247 nm ($\Delta\varepsilon$ + 10.8), indicating positive chirality between the two chromophores (the diene and the *p*-bromobenzoyl group) according to the exciton chirality rule.[4] This CD result revealed the *R* configuration at C-10 in **10**, and thus the 10*R* configuration in **1** and **2**.

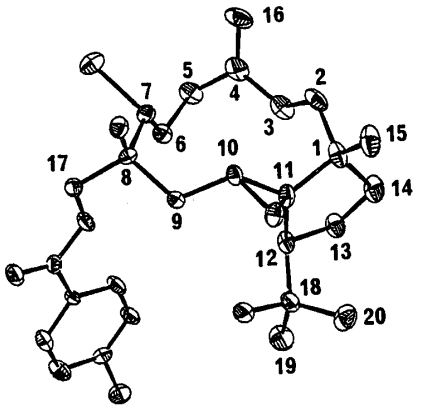


Fig. 2. Perspective View (ORTEP) of the Molecule of **9**

TABLE III. ^{1}H-Decoupling Data for **3**

Irradiated proton (δ ppm)	Observed protons and changes
H-2a (1.31)	H-2b [1.71 (dd)]→br s
	H-3 [2.98 (dd)]→changed
H-3 (2.98)	H-2a [1.31 (dd)]→d (J=13.7 Hz)
	H-2b [1.71 (dd)]→br s
H-6 (2.09)[a)]	H-5 [1.14 (dt)][a)]→changed
	H-7 [4.84 (br d)][a)]→br s
H-11 (2.93)	H-10a [1.53 (dddd)]→ddd (J=1.7, 6.2, 15.1 Hz)
	H-10b [1.68 (m)]→changed
	H-14a [2.13 (dd)]→d (J=18.3 Hz)
H-14a (2.13)	H-14b [2.40 (d)]→s

a) These signals were observed in C_6D_6. The signals of 1.14 (dt, J=5.5, 12.6 Hz) and 4.84 (br d, J=11.1 Hz) in C_6D_6 could correspond to the signals of 1.27 (dt, J=5.7, 13.2 Hz) and 5.12 (br d, J=11.0 Hz) in $CDCl_3$, respectively, because of the similarity of the chemical shifts and coupling constants.

TABLE IV. Long-Range Correlated ^{13}C and ^{1}H Signals in COLOC Spectrum ($CDCl_3$) of **3**

^{13}C signal (δ ppm)	Correlated ^{1}H signals (δ ppm)
C-1 (37.5)	H-2a (1.31)
	H-2b (1.71)
	H-10a (1.53)
	H-14b (2.40)
	H-15 (1.40)
C-3 (63.8)	H-2b
	H-5 (1.27)
	H-16 (1.14)
C-4 (61.3)	H-2a, H-16
C-8 (133.0)	H-10b (1.68)
	H-17 (1.73)
C-11 (42.3)	H-10b
	H-14a (2.13)
	H-15
C-12 (137.2)	H-11 (2.93)
	H-14a
	H-19 (1.83)
	H-20 (2.18)
C-13 (206.0)	H-11, H-14a, H-14b
C-18 (146.8)	H-19, H-20

The structures of **1** and **2** are characterized by a new skeleton having *cis* geometry between the methyl group at C-1 and the alkyl group at C-12, which differs from that of the known dolabellane-type diterpenoids.[5)]

Structure of Claenone (3)

The IR (1690, 1620 cm^{-1}) and UV [256 nm (ε 9060)] spectra of **3** showed the presence of an α,β-unsaturated ketone moiety. The ^{1}H- and ^{13}C-NMR spectra showed the signals due to a trisubstituted epoxide [δ_H 2.98 (1H, dd, J=2.9, 11.0 Hz); δ_C 61.3 (s), 63.8 (d)], a non-conjugated trisubstituted olefin [δ_H 5.12 (1H, br d, J=11.0 Hz); δ_C 128.3 (d)], two methyls [δ_H 1.14 (3H, s), 1.40 (3H, s)], and three olefinic methyls [δ_H 1.73 (3H, s), 1.83 (3H, s), 2.18 (3H, s)]

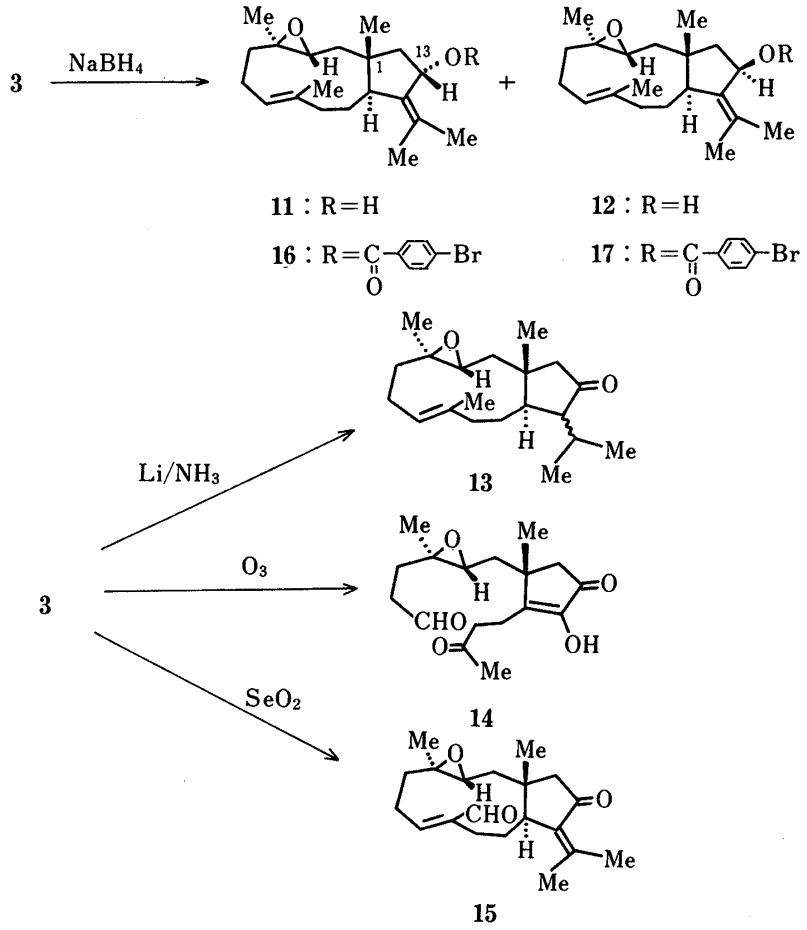


Chart 5

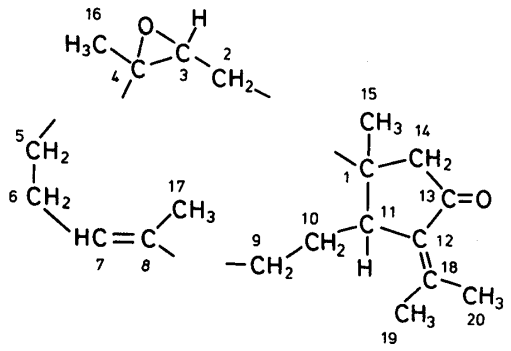


Chart 6

in addition to the above-mentioned α,β-unsaturated ketone [δ_C 206.0 (s)]. The ^{1}H-NMR decoupling experiments as summarized in Table III revealed the presence of the partial structures $-CH_2-CO-$, $-CH_2-CH_2-CH=\dot{C}-CH_3$, $-\dot{C}(O)-CH-CH_2-$, and $-CH_2-CH_2-CH<$. The following chemical reactions (Chart 5) showed that the α,β-unsaturated ketone is an α-isopropylidene cyclopentanone. Reduction of **3** with sodium borohydride gave the epimeric alcohols **11** and **12**. Reduction of **3** with lithium in liquid ammonia gave a cyclopentanone **13** (IR 1730 cm^{-1}). Ozonolysis of **3** afforded a diosphenol **14**. The presence of the trisubstituted olefin was confirmed by the formation of an α,β-unsaturated aldehyde **15** [δ_H 10.23 (1H, br s)] in the reaction of **3** with selenium dioxide. These findings led to the three extended partial structures shown in Chart 6. These partial structures were connected by measurement of COLOC of **3** as summarized in Table IV, leading to the plane structure of **3**.

The relative stereochemistry of **3** was elucidated as follows. The *E* configurations of the olefin at C-7 and the epoxide moiety were shown by the ^{13}C chemical shifts[6] of the olefinic methyl carbon (C-17, δ_C 16.6 ppm)[7] and the methyl carbon on the epoxide (C-16, 15.5 ppm),[8] respectively. The *trans* ring juncture was shown by the presence of the W-type long-range coupling (J=0.8 Hz) between H-11 (2.93 ppm) and H-14a (2.13 ppm).[9] The nuclear Overhauser effect (NOE) correlation 2D NMR spectrum (NOESY) of **3** (Fig. 3) showed the NOE correlations between the protons (H-3 and H-15, and H-11 and H-16) as indicated by the arrows in the structure in Fig. 3. These NOE correlations revealed the relative configurations between the angular positions (C-1 and C-11) and the positions bearing the epoxide (C-3 and C-4).

The absolute stereochemistry of **3** was elucidated by CD analysis of the *p*-bromobenzoates of the epimeric allylic alcohols **11** and **12**. The relative stereochemistries between the angular methyl and the hydroxy group at C-13 in **11** and **12** were determined from the ^{1}H shifts of the angular methyl signals induced by Eu(FOD)$_3$ in the ^{1}H-NMR spectrum. The lanthanide-induced ^{1}H shift of the methyl signal in **12** (0.35 ppm) was greater

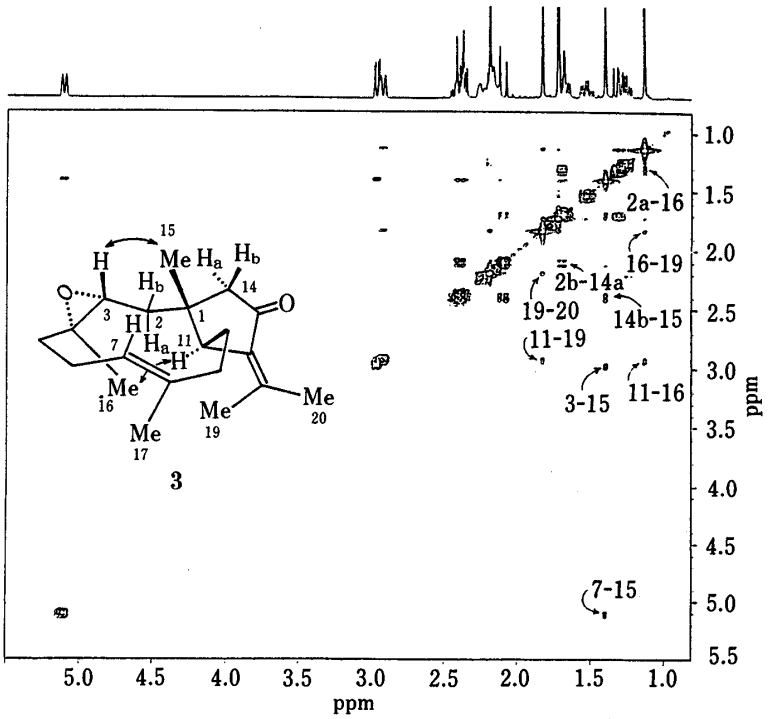
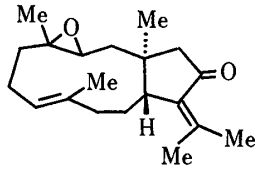


Fig. 3. Nuclear Overhauser Effect Correlation 2D NMR Spectrum (NOESY, 400 MHz, $CDCl_3$) of **3**



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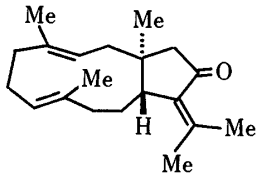

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Chart 7

than that in **11** (0.23 ppm) at the molar ratio [Eu(FOD)$_3$]/[allylic alcohol] = 0.1, indicating the *cis* configuration in **12** and the *trans* configuration in **11**. The CD spectra (in ethanol) of the corresponding *p*-bromobenzoates **16** and **17** showed a positive Cotton effect at 235 nm ($\Delta\varepsilon$ +6.2) in the case of **16** and a negative Cotton effect at 240 nm ($\Delta\varepsilon$ −4.3) for **17**. On the basis of the exciton chirality rule, these CD data indicated positive chirality between the chromophores (the *p*-bromobenzoyl and olefin groups) in **16** and negative chirality in **17**, showing the absolute configuration at C-13 to be as depicted. These findings revealed the 1*R*, 3*R*, 4*R*, and 11*S* configuration in **3**.

The physical data of claenone (**3**) were found to be identical with those of the epoxide **18** which was chemically derived from the dolabellane-type diterpenoid **19** isolated from the Caribbean gorgonian *Eunicea calyculata* by Look and Fenical.[10] The structures only differ in the absolute configurations of the angular positions (C-1 and C-11). Our CD data for the *p*-bromobenzoates **16** and **17** seem inconsistent with the absolute configuration at C-1 of the structure **18**. Furthermore no usual dolabellane-type diterpenoid was found in the present soft coral.

We currently assume that the present soft coral is a variant of *Clavularia viridis*. The remarkable difference of the chemical constituents between *C. viridis* studied previously and the present *Clavularia* sp. is particularly interesting in the taxonomy of stoloniferan soft corals.

Experimental

Melting points were measured on a Kofler block and are uncorrected. The optical rotations were measured with a JASCO DIP-360 automatic polarimeter. The IR spectra were recorded with a Hitachi 215 spectrometer, and the UV spectra with a Hitachi 124 spectrometer. The ^{1}H-NMR spectra were recorded with a Bruker AM-400 (400 MHz) spectrometer. The ^{13}C-NMR spectra were obtained either with a Bruker AM-400 (100 MHz) or with a JEOL FX-270 (67.8 MHz) spectrometer. Chemical shifts are given on a δ (ppm) scale with tetramethylsilane as an internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). The mass spectra (MS) were taken with a Hitachi M-80 spectrometer. The CD spectra were taken with a JASCO J-500 spectropolarimeter. Column chromatography was carried out on Merck silica gel 60 (70—230 mesh), and flash chromatography[11] was carried out on Merck silica gel 60 (230—400 mesh). Preparative thin layer chromatography (PTLC) was carried out on Silica gel F_{254} (Merck) TLC plates.

Extraction and Isolation——The freeze-dried specimens of *Clavularia* sp., collected on the coral reef of Ishigaki Island in May, 1986, were ground to powder, which was extracted three times with ethyl acetate (each 6 l) to give an ethyl acetate extract (73 g). The extract showed an ichthyotoxic activity toward killifish, *Oryzias latipes*. A half of the extract was chromatographed on a silica gel column (70—230 mesh, 700 g). Stepwise elution with hexane–ethyl acetate mixtures (20 : 1, 4 : 1, 3 : 2, 1 : 1, 2 : 3, and 1 : 4; each 2 l) gave six fractions. The remaining extract was also chromatographed similarly to give six fractions, which were combined with the corresponding fractions obtained initially. Purification of fraction 5 by repeated flash chromatography (silica gel 230—400 mesh, hexane–ethyl acetate as an eluent) gave stolonidiol (**1**) (1.5 g). Similar purification of fraction 4 by flash chromatography gave stolonidiol monoacetate (**2**) (2.3 g).

Flash chromatography (hexane–ethyl acetate as an eluent) of fraction 2 (34 g) gave a crystalline substance, which was recrystallized from hexane–ethyl acetate mixture to give claenone (**3**) (14.0 g).

Stolonidiol (**1**): Colorless viscous oil. $[\alpha]_D$ −31.6° (c = 1.4, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1645, 910. In-beam CIMS m/z: 337 ($M^+ + H$), 318 ($M^+ - H_2O$). High-resolution MS Calcd for $C_{20}H_{30}O_3$ ($M^+ - H_2O$): 318.2192. Found:

318.2164. The ^{1}H- and ^{13}C-NMR data are summarized in Table I.

Stolonidiol monoacetate (**2**): Colorless viscous oil. $[\alpha]_D$ −26.8° (c=0.38, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1730, 1640, 1240, 905. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, s), 1.18 (3H, s), 1.29 (3H, s), 2.11 (3H, s), 2.46 (1H, dd, J=7.3, 14.4 Hz), 2.53 (1H, dd, J=7.9, 16.1 Hz), 3.01 (1H, t, J=7.0 Hz), 3.14 (1H, dd, J=1.5, 7.9 Hz), 3.91 (1H, d, J=12.2 Hz), 4.28 (1H, d, J=12.2 Hz), 4.72 (1H, br s), 4.80 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.8 (q), 23.5 (q), 24.6 (t), 26.1 (q), 26.6 (t), 27.4 (t), 29.4 (t), 29.6 (q), 31.1 (t), 37.1 (t), 38.9 (t), 44.5 (s), 48.5 (d), 56.3 (d), 58.6 (d), 60.9 (s), 67.9 (t), 74.5 (s), 76.2 (s), 110.2 (t), 148.2 (s), 170.5 (s). In-beam CIMS m/z: 379 (M^++H), 361 (M^++H−H_2O). High-resolution MS Calcd for $C_{22}H_{33}O_4$ (M^++H−H_2O): 361.2343. Found: 361.2358.

Claenone (**3**): Colorless needles. $[\alpha]_D$ −50.9° (c=1.25, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1620. UV λ_{max}^{EtOH} nm (ε): 256 (9060). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.27 (1H, dt, J=5.7, 13.2 Hz), 1.31 (1H, dd, J=11.1, 13.7 Hz), 1.40 (3H, s), 1.53 (1H, dddd, J=1.7, 6.2, 13.5, 15.1 Hz), 1.68 (1H, m), 1.71 (1H, dd, J=2.8, 13.7 Hz), 1.73 (3H, s), 1.83 (3H, s), 2.13 (1H, dd, J=0.8, 18.3 Hz), 2.18 (3H, s), 2.40 (1H, d, J=18.3 Hz), 2.93 (1H, br d, J=12.0 Hz), 2.98 (1H, dd, J=2.9, 11.0 Hz), 5.12 (1H, br d, J=11.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.5 (q), 16.6 (q), 21.3 (q), 23.3 (q), 24.4 (t), 24.5 (q), 27.4 (t), 37.2 (s), 37.5 (s), 38.5 (t), 40.9 (t), 42.3 (d), 55.5 (t), 61.3 (s), 63.8 (d), 128.3 (d), 133.0 (s), 137.2 (s), 148.6 (s), 206.0 (s). EIMS m/z: 302 (M^+). High-resolution MS Calcd for $C_{20}H_{30}O_2$ (M^+): 302.2235. Found: 302.2245. *Anal.* Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.73; H, 10.11.

Acetylation of 1——A mixture of **1** (20 mg), acetic anhydride (0.5 ml), and pyridine (1 ml) was stirred at room temperature for 20 h. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The extract was washed successively with saturated $CuSO_4$ solution, water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column using hexane–ethyl acetate (3 : 2) as an eluent to give a colorless oil (17 mg), whose spectral data and optical rotation coincided with those of **2**.

Treatment of 1 with Alkali——A mixture of **1** (64 mg) and 5% methanolic KOH solution (5 ml) was refluxed for 3 h. After neutralization with 3% HCl, the reaction mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crystalline residue was recrystallized from hexane–ethyl acetate to give **4** (37 mg).

Compound **4**: Colorless needles. mp 88—90 °C. $[\alpha]_D$ −0.9° (c=0.67, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, s), 1.19 (3H, s), 1.26 (3H, s), 3.02 (1H, dd, J=1.3, 6.4 Hz), 3.20 (1H, br s), 3.35 (1H, d, J=11.8 Hz), 3.59 (3H, s), 3.85 (1H, d, J=11.8 Hz), 4.86 (1H, br s), 4.94 (1H, br s). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 24.0 (q), 25.3 (t), 26.1 (q), 27.7 (t), 28.3 (t), 29.6 (q), 34.6 (t), 35.1 (t), 38.6 (t), 42.4 (t), 44.6 (s), 50.0 (d), 54.8 (d), 61.8 (q), 67.2 (t), 74.9 (s), 75.9 (s), 76.2 (s), 84.0 (d), 113.1 (t), 149.9 (s). CIMS m/z: 369 (M^++H). *Anal.* Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.11; H, 9.88.

Oxidation of 4 with Sodium Metaperiodate——A solution of sodium metaperiodate (40 mg) in water (0.5 ml) was added to a mixture of **4** (37 mg) in methanol (2 ml) and 5% $NaHCO_3$ solution (0.1 ml). The reaction mixture was stirred at room temperature for 20 min, then poured into a mixture of ethyl acetate and water. The ethyl acetate extract was washed successively with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column using hexane–ethyl acetate (6 : 4) as an eluent to give a crystalline compound. Recrystallization from hexane–ethyl acetate gave **5** (15 mg).

Compound **5**: Colorless needles. mp 146—148 °C. $[\alpha]_D$ −52.4° (c=0.58, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1700, 1630, 900. UV λ_{max}^{EtOH} nm (ε): 238 (6470). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, s), 1.26 (3H, s), 1.34 (3H, s), 3.49 (3H, s), 4.11 (1H, t, J=3.6 Hz), 4.55 (1H, br s), 4.62 (2H, br s), 6.68 (1H, d, J=15.2 Hz), 6.70 (1H, d, J=15.2 Hz). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 20.0 (q), 25.2 (t), 27.7 (t), 27.9 (t), 29.1 (t), 29.6 (q), 29.7 (q), 37.3 (t), 39.1 (t), 50.3 (s), 56.8 (d), 58.3 (q), 74.4 (s), 83.8 (s), 85.8 (d), 111.7 (t), 121.9 (d), 149.0 (s), 151.9 (d), 201.2 (s). EIMS m/z: 336 (M^+). *Anal.* Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.63.

Dehydration of 2 with Phosphorus Oxychloride——Phosphorus oxychloride (0.2 ml) was added to a solution of **2** (120 mg) in pyridine (1.0 ml), and the mixture was stirred at 30 °C for 3 h. The reaction mixture was poured into ice-water and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column using hexane–ethyl acetate (8 : 2) as an eluent to give **6** (53 mg) and **7** (11 mg) in order of increasing polarity.

Compound **6**: Colorless oil. $[\alpha]_D$ −6.0° (c=0.2, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1644, 1230, 897. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s), 1.76 (3H, d, J=0.6 Hz), 2.08 (3H, s), 2.98 (1H, br t, J=8.3 Hz), 3.02 (1H, dd, J=5.6, 8.8 Hz), 3.12 (1H, dd, J=1.8, 7.3 Hz), 3.95 (1H, d, J=12.1 Hz), 4.18 (1H, d, J=12.1 Hz), 4.66 (1H, d, J=2.2 Hz), 4.71 (2H, m), 4.78 (1H, br s). EIMS m/z: 360 (M^+). High-resolution MS Calcd for $C_{20}H_{29}O_2$ (M^+−AcO): 301.2165. Found: 301.2151.

Compound **7**: Colorless oil. $[\alpha]_D$ +22.2° (c=0.09, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1735, 1635, 1615, 1240. UV λ_{max}^{EtOH} nm (ε): 226 (6900). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, s), 1.90 (3H, s), 2.10 (3H, s), 3.10 (1H, dd, J=6.0, 7.7 Hz), 4.06 (1H, d, J=12.0 Hz), 4.30 (1H, d, J=12.0 Hz), 4.30 (1H, m), 4.68 (1H, br s), 4.73 (1H, br s), 5.00 (1H, q, J=1.5 Hz), 5.06 (1H, q, J=0.8 Hz). CIMS m/z: 361 (M^++H), 360 (M^+). High-resolution MS Calcd for $C_{20}H_{29}O_2$ (M^+−AcO): 301.2165. Found: 301.2142.

***p*-Bromobenzoylation of 1**——A mixture of **1** (10 mg), *p*-bromobenzoyl chloride (30 mg), and pyridine (0.5 ml) was stirred at room temperature for 20 h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed successively with saturated $CuSO_4$ solution, water, 5% $NaHCO_3$ solution, water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash chromatography (hexane–ethyl acetate (3:7) as an eluent) to give **8** (6 mg) and **9** (6 mg) in order of increasing polarity.

Compound **8**: Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1640, 1590, 1265, 900. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, s), 1.14 (3H, s), 1.29 (3H, s), 4.17 (1H, d, J=12.2 Hz), 4.53 (1H, d, J=12.2 Hz), 4.72 (1H, br s), 4.81 (1H, br s), 7.59 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.6 Hz). CIMS m/z: 519, 521 (M^++H).

Compound **9**: Colorless rods. mp 163—164 °C. $[\alpha]_D$ +35.9° (c=0.44, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1644, 1592, 1240, 908. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, s), 1.21 (3H, s), 1.27 (3H, s), 2.98 (1H, dd, J=3.1, 4.7 Hz), 3.98 (1H, d, J=11.6 Hz), 4.25 (1H, d, J=11.7 Hz), 4.70 (1H, d, J=11.7 Hz), 4.86 (1H, br s), 5.03 (1H, br s), 7.59 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.6 Hz). EIMS m/z: 554, 556, 558 (3:4:1, M^+). *Anal.* Calcd for $C_{27}H_{36}BrClO_5$: C, 58.33; H, 6.53. Found: C, 57.98; H, 6.57.

Treatment of 9 with Potassium Carbonate——Potassium carbonate (2 mg) was added to a solution of **9** (2.5 mg) in methanol (0.2 ml), and the mixture was stirred at room temperature for 35 min. The reaction mixture was diluted with ether. The ethereal solution was washed with water and then brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PTLC to give **1** (2 mg).

X-Ray Analysis of 9——The crystal data are as follows: $C_{27}H_{36}BrClO_5$, F.W. 555.93, D_m=1.33 g/cm^3, orthorhombic, space group $P2_12_12_1$, a=12.780(3), b=18.724(3), c=11.351(4) Å, and Z=4. The intensities were measured on a Rigaku AFC-5 diffractometer with graphite-monochromated Mo $K\alpha$ radiation up to 2θ=55°. The structure was solved by a heavy atom method and refined by the full-matrix least-squares procedure[12] using 1625 independent structure factors with $|F_O| \geq 3\sigma(F_O)$. Measurement of 30 Bijvoet pairs of S value, $[|F_C(hkl)| - |F_C(-h-k-l)|]/\sigma(F_O)$, larger than ±4.9 determined the absolute stereochemistry. The final refinement with anisotropic temperature factors for all non-hydrogen atoms under fixed geometries and B_{iso}'s of hydrogens except those of the hydroxyls converged the R factor to 0.045. All crystallographic calculations were done on a FACOM M-380 computer at the Science Information Processing Center, University of Tsukuba. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

***p*-Bromobenzoylation of 7**——A mixture of **7** (2 mg), *p*-bromobenzoyl chloride (10 mg), *N*,*N*-dimethylaminopyridine (5 mg), and pyridine (0.3 ml) was stirred at 65 °C for 9 h. The reaction mixture was diluted with ether, and the ethereal solution was successively washed with saturated $NaHCO_3$ solution, water, saturated $CuSO_4$ solution, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PTLC to give **10** (2.2 mg).

Compound **10**: Colorless crystals. $[\alpha]_D$ +77.3° (c=0.44, $CHCl_3$). UV λ_{max}^{EtOH} nm (ε): 243 (10700). ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, s), 1.88 (3H, br s), 1.94 (3H, s), 3.03 (1H, dd, J=4.9, 8.8 Hz), 4.08 (1H, d, J=11.9 Hz), 4.73 (1H, br s), 4.77 (1H, br s), 5.03 (1H, br s), 5.21 (1H, br s), 5.74 (1H, t, J=4.3 Hz), 7.58 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.6 Hz).

Reduction of 3 with Sodium Borohydride——Sodium borohydride (70 mg) was added to a solution of **3** (200 mg) in methanol (5 ml), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether, and the ethereal solution was washed with water and then brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane–ethyl acetate (2:3) as an eluent) to give **12** (70 mg) and **11** (70 mg) in order of increasing polarity.

Compound **11**: Colorless oil. $[\alpha]_D$ −153.6° (c=0.64, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.29 (3H, s), 1.69 (3H, s), 1.73 (3H, s), 1.80 (3H, s), 2.72 (1H, br d, J=10.7 Hz), 2.96 (1H, dd, J=3.3, 11.0 Hz), 4.62 (1H, br d, J=6.7 Hz), 5.08 (1H, br d, J=10.7 Hz). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 15.5 (q), 16.7 (q), 21.8 (q), 22.0 (q), 23.6 (q), 24.5 (t), 27.5 (t), 37.2 (t), 38.8 (t), 41.3 (t), 43.5 (d), 43.8 (s), 51.3 (t), 61.6 (s), 64.7 (d), 71.2 (d), 127.8 (d), 130.4 (s), 133.3 (s), 147.1 (s). EIMS m/z: 304 (M^+). High-resolution MS Calcd for $C_{20}H_{32}O_2$ (M^+): 304.2399. Found: 304.2359.

Compound **12**: Colorless needles. mp 138—140 °C. $[\alpha]_D$ −203.7° (c=1.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, s), 1.35 (3H, s), 1.67 (3H, s), 1.72 (3H, s), 1.77 (3H, s), 2.55 (1H, br d, J=11.9 Hz), 2.93 (1H, dd, J=2.8, 11.2 Hz), 4.60 (1H, br t, J=6.8 Hz), 5.07 (1H, br d, J=11.4 Hz). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 15.5 (q), 16.5 (q), 20.8 (q), 21.8 (l), 24.0 (q), 24.5 (t), 28.2 (t), 37.5 (t), 38.7 (t), 41.3 (t), 42.5 (s), 43.0 (d), 52.6 (t), 61.7 (s), 64.4 (d), 71.3 (d), 127.7 (d), 129.9 (s), 133.4 (s), 144.6 (s). EIMS m/z: 304 (M^+). *Anal.* Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.74; H, 10.54.

Lithium-Liquid Ammonia Reduction of 3——A solution of **3** (50 mg) in tetrahydrofuran (5 ml) was added to a solution of lithium (30 mg) in liquid ammonia (5 ml), and the mixture was refluxed for 20 min. After addition of excess ammonium chloride, the reaction mixture was added to a mixture of ether and water. The ether extract was washed successively with saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane–ethyl acetate (7:3) as an

eluent) to give **13** (20 mg).

Compound **13**: Colorless amorphous substance. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J= 6.9 Hz), 1.13 (3H, d, J=6.9 Hz), 1.15 (3H, s), 1.25 (3H, s), 1.77 (3H, s), 2.91 (1H, dd, J=1.6, 8.4 Hz), 5.16 (1H, br d, J=10.8 Hz). EIMS m/z: 304 (M^+). High-resolution MS Calcd for $C_{20}H_{32}O_2$ (M^+): 304.2399. Found: 304.2417.

Ozonolysis of 3——Ozone was passed through a solution of **3** (100 mg) in methanol (5 ml) at −78 °C for 15 min. After addition of excess dimethyl sulfide, the temperature of the mixture was raised to room temperature and the mixture was stirred for 30 min. The reaction mixture was diluted with ethyl acetate. The solution was washed successively with water, saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane–ethyl acetate (4 : 1) as an eluent) to give **14** (40 mg).

Compound **14**: Unstable colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1735, 1715, 1665. UV λ_{max}^{EtOH} nm (ε): 263 (7200). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, s), 1.28 (3H, s), 2.20 (3H, s), 6.33 (1H, br s), 9.75 (1H, t, J=1.2 Hz). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 17.0 (q), 19.5 (q), 26.2 (q), 29.8 (q), 30.2 (t), 37.5 (t), 39.0 (t), 40.0 (t), 40.4 (s), 45.2 (t), 59.3 (s), 59.7 (d), 148.8 (s), 150.6 (s), 200.8 (s), 201.1 (d), 208.0 (s).

Oxidation of 3 with Selenium Dioxide——Selenium dioxide (500 mg) was added to a solution of **3** (400 mg) in ethanol (7 ml), and the mixture was refluxed for 90 min. The reaction mixture was filtered, and the filtrate was diluted with ethyl acetate. The ethyl acetate solution was washed with 5% $NaHCO_3$ solution and then brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane–ethyl acetate (1 : 1) as an eluent) to give **15** (138 mg).

Compound **15**: Colorless oil. $[\alpha]_D$ +18.6° (c=1.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1675, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, s), 1.41 (3H, s), 1.60 (3H, s), 2.16 (3H, s), 6.49 (1H, dd, J=2.4, 12.2 Hz), 10.23 (1H, br s). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 15.3 (q), 21.2 (q), 23.1 (q), 23.6 (t), 25.1 (q), 27.6 (t), 30.0 (t), 37.6 (s), 38.2 (t), 40.5 (t), 42.7 (d), 55.3 (t), 60.7 (s), 63.4 (d), 136.4 (s), 138.7 (s), 149.7 (s), 151.8 (d), 190.1 (d), 205.4 (s). EIMS m/z: 316 (M^+). High-resolution MS Calcd for $C_{20}H_{28}O_3$ (M^+): 316.2036. Found: 316.2004.

***p*-Bromobenzoylation of 11**——*p*-Bromobenzoyl chloride (90 mg) and *N*,*N*-dimethylaminopyridine (10 mg) were successively added to a solution of **11** (30 mg) in pyridine (1.5 ml), and the mixture was stirred at room temperature for 2 d. The reaction mixture was diluted with ether. The ethereal solution was washed successively with saturated $CuSO_4$ solution, water, saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crystalline residue was purified by PTLC and recrystallized from methanol to give **16** (20 mg).

Compound **16**: Colorless leaflets. mp 135—136 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1714, 1590. UV λ_{max}^{EtOH} nm (ε): 244 (13600). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, s), 1.32 (3H, s), 1.58 (3H, s), 1.75 (3H, s), 1.76 (3H, s), 2.82 (1H, m), 2.97 (1H, dd, J=4.1, 10.0 Hz), 5.10 (1H, br d, J=10.9 Hz), 5.85 (1H, d, J=6.7 Hz), 7.55 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.6 Hz). EIMS m/z: 486, 488 (M^+). *Anal.* Calcd for $C_{27}H_{35}BrO_3$: C, 66.53; H, 7.24. Found: C, 66.29; H, 7.24.

***p*-Bromobenzoylation of 12**——A mixture of **12** (10 mg), *p*-bromobenzoyl chloride (20 mg), and pyridine (0.5 ml) was stirred at room temperature for 16 h. The reaction mixture was diluted with ether. The ethereal solution was washed successively with water, saturated $CuSO_4$ solution, water, saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crystalline residue was purified by PTLC and recrystallized from methanol to give **17** (10 mg).

Compound **17**: Colorless rods. mp 130—131 °C. $[\alpha]_D$ −171.7° (c=0.12, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1590. UV λ_{max}^{EtOH} nm (ε): 244 (15300). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.36 (3H, s), 1.64 (3H, s), 1.73 (3H, s), 1.75 (3H, s), 2.65 (1H, br d, J=11.3 Hz), 2.95 (1H, dd, J=2.7, 11.1 Hz), 5.10 (1H, br d, J=11.2 Hz), 5.75 (1H, t, J=6.5 Hz), 7.57 (2H, d, J=8.6 Hz), 7.86 (2H, d, J=8.6 Hz). EIMS m/z: 486, 488 (M^+). *Anal.* Calcd for $C_{27}H_{35}BrO_3$: C, 66.53; H, 7.24. Found: C, 66.29; H, 7.26.

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8) The assignment of the signal (15.5 ppm) was done on the basis of the COLOC data of **3**.
9) The assignment of the methylene protons at C-14 was performed on the basis of the NOE correlation. An NOE correlation between the angular methyl proton (1.40 ppm) and H-14b (2.40 ppm, β-oriented) was observed, while no NOE was observed between the angular methyl proton and H-14a (2.13 ppm, α-oriented). The assignment of the angular methyl proton (1.40 ppm) and the methyl proton on the epoxide (1.14 ppm) was done on the basis of the COLOC data. The remarkable shifts of these methyl protons are due to the anisotropy effect of the carbon–carbon double bond at C-7.
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