Structures of Crenulacetals A, B, C, and D. The New Diterpenoids from the Brown Algae of Dictyotaceae

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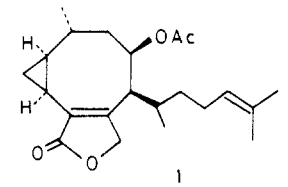
New diterpenoid acetals which possess a bicyclo[6.1.0]nonane skeleton were isolated from the brown algae of the Dictyotaceae family, and their structures have been elucidated on the basis of spectral analyses and chemical transformations. Conformational mobility of these compounds has been discussed by means of ^1H and ^{13}C NMR spectroscopies.

Brown algae belonging to the Dictyotaceae family are rich resources of diterpenoids, the structures of which are quite different from those of terrestrial plants.[2] Among the diterpenes found from the Dictyotaceae seaweeds, crenulides are one of the most unique groups, because they have a novel skeleton composed of a cyclooctane ring fused with a cyclopropane ring, as exemplified by acetoxycrenulide (**1**)[3] and pachylactone (**2**).[4] The crenulide **1** has



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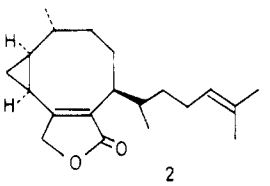

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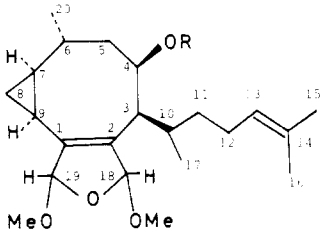

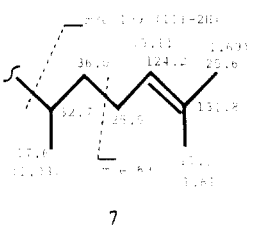

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3: 18β,19β-OMe; R = H
4: 18β,19α-OMe; R = H
5: 18α,19α-OMe; R = Ac
6: 18α,19β-OMe; R = Ac

a piscicidal activity and may serve as a fish antifeedant.[3] Despite their biological and structural interest, only a few crenulides have been isolated thus far.[3-6] In the course of our study on the ingredients of Dictyotaceae algae, we have isolated new crenulides designated as crenulacetals A (**3**), B (**4**), C (**5**), and D (**6**), and this report deals with the structures and chemical behaviors of them.

Results

Crenulacetal A (**3**), $C_{22}H_{36}O_4$, $[\alpha]_D$ +5.1° (*c* 0.4, $CHCl_3$), was isolated from *Dictyota dichotoma*.[7] It shows the IR bands ascribable to hydroxy (3460 cm^{-1}) and ether (1090 and 1075 cm^{-1}) groups. The mass spectrum gave the fragments at *m/e* 109 and 69, which appear in the spectra of the diterpenoids possessing side chain 7.[4,8] The presence of moiety **7** in crenulacetal A is supported by the ^1H and ^{13}C NMR signals denoted in partial structure **7**. The ^{13}C NMR spectrum (Table I) reveals the existence of one other olefinic group (δ 140.5 and 140.7), which confirms crenulacetal A to be tricyclic. The ^1H NMR signals at δ 0.53 and 0.61 imply the occurrence of a cyclopropane ring, and four singlets at δ 3.41, 3.54 (each OMe), 5.44, and 5.25 (each OCHO) are suggestive of a 2,5-dimethoxy-2,5-dihydrofuran moiety. These properties are reminiscent of crenulides, and the structure **3** (without stereochemistry) was assumed for crenulacetal A. The structure was verified by analysis of the 360-MHz ^1H NMR spectrum (Table I), and the relative stereochemistry was fully assigned as shown in **3** on the basis of COSY and NOEDS experiments; the cyclopropane ring is disubstituted [only one cyclopropane methylene group: ^{13}C NMR δ 5.6 (t)] and has to be adjacent to a double bond, because one of the cyclopropane methine protons resonates at the downfield region (δ 1.32; 9-H). This proton is coupled with another cyclopropane methine proton (δ 0.83; 7-H), the coupling constant (J = 9 Hz) indicating that the cyclopropane ring is fused with another ring in a cis manner.[4] Connectivity of the other side of the cyclopropane ring with a tertiary carbon bearing a methyl group was deduced from the coupling (J = 9 Hz) of the cyclopropane methine proton (δ 0.83) with a proton appearing at δ 1.55 (6-H) as a multiplet, which exhibits an intense cross peak to the secondary methyl signal (δ 1.01, d, J = 7 Hz) in the COSY spectrum. Location of the side chain **7** on the allylic carbon (3-C) was deduced by the coupling (J = 9 Hz) of a methine proton (δ 1.7; 10-H; also coupled to a methyl group) of the side chain with a markedly deshielded proton at δ 2.88 (3-H). This latter signal is a sharp doublet (J = 9 Hz), suggesting that the proton is not adjacent to methylene protons but rather to a carbinyl proton (δ 4.07; 4-H) since there is no sp^3-quaternary carbon in this compound. The null coupling between 4-H and 3-H is characteristic with crenulides.[4] The coupling pattern of the protons discussed above and shown in Table I indicates that the conformation of crenulacetal A is the same as proposed for pachylactone (**2**)[4] and isoacetoxycrenulatin (4-acetoxy-**2**),[4,6] and from the consideration of the conformation and the coupling constants of the protons the relative configurations of the substituents at the 3-, 4-, 6-, 7-, and 9-positions are assignable as illustrated in **8** (= **3**).

The stereochemistry of the two methoxy groups at the 18- and 19-carbons was determined by NOEDS experiments (see **9**); the cis relation of the methoxy groups was confirmed by the presence of significant NOE (3%) between two acetal protons. The β-configuration of the 19-methoxy group was deduced from the downfield chemical

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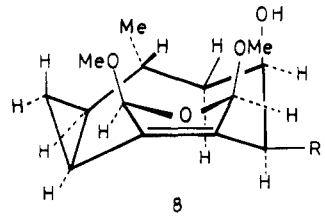

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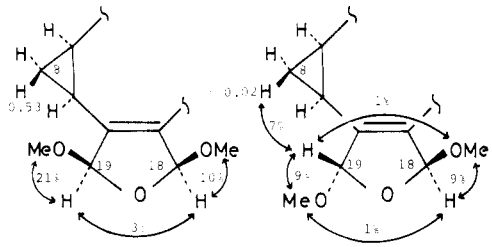


9 (=3) 10 (=4)

shift (δ 0.53) of the 8β-H, which is deshielded by the methoxy group (cf. analogous proton in **2**, δ 0.11).

Crenulacetal B (**4**), $C_{22}H_{36}O_4$, $[\alpha]_D$ +69.9° (*c* 0.33, $CHCl_3$), was isolated from *D. spinulosa*[7] along with **3**. It showed NMR spectral properties (Table I) similar to those of crenulacetal A. Structure of **4** for crenulacetal B was deduced in an analogous manner as described for **3**. Presence of NOEs (see **10**) between 18-H and 19-OMe suggests the trans relation of the two methoxy groups. The upfield chemical shift (δ 0.02) of 8β-H as well as a distinct NOE (7%) between 8β-H and 19-H led to assignment of α-configuration of 19-methoxy group, and this necessitates the 18β-methoxy group.

Crenulacetals C (**5**), $[\alpha]_D$ −6.15° (*c* 0.65, $CHCl_3$), and D (**6**), $[\alpha]_D$ +14.1° (*c* 1.70, $CHCl_3$), isolated from an unidentified species of Dictyotaceae, have the same molecular formula, $C_{24}H_{38}O_5$, corresponding to that of an acetate of crenulacetals A and B. In fact, each shows an IR band at 1720 cm^{-1} and also a ^1H NMR signal at δ 2.00 (3 H, s), which indicates the presence of an acetoxy group. The ^1H NMR features of these are, on the whole, similar to those of crenulacetals A and B, except for the fact that some signals appear in very broad and ambiguous shapes. Acetylation (acetic anhydride/(dimethylamino)-pyridine/triethylamine) of **3** and **4** afforded the respective acetates, whose ^1H NMR spectra are different from those of **5** and **6** not only in chemical shifts of the signals but also in that the acetates of **3** and **4** exhibit sharp and well-defined ^1H NMR signals. The same problem was encountered in the ^{13}C NMR spectra of the former pair of acetals **5** and **6**; they showed broadened signals besides several sharp ones assignable as the carbons of the side chains and acetyl groups. These properties imply that the conformations of the ring systems of both the compounds are "mobile" at the applied temperature (24 °C). When the ^1H NMR spectrum of **5** was measured at −50 °C, two sets of sharp signals appeared in the integral ratio of 2:1 (Figure 1). Evidently, crenulacetal C exists in two slowly interconverting conformations at this low temperature. However, it was not feasible to deduce the structure of crenulacetal C by analyzing the spectrum because of the serious overlapping of the aliphatic proton signals. Treatment of **5** and **6** with oxalic acid in methanol in the attempt to epimerize at the 18- and 19-positions only resulted in the recovery of the starting materials. However, when the reaction was carried out in methanol containing concentrated hydrochloric acid, two unexpected products were obtained. They were identical with acetoxycrenulide (**1**)[3] and hydroxycrenulide (deacetyl-**1**)[5] by comparison of

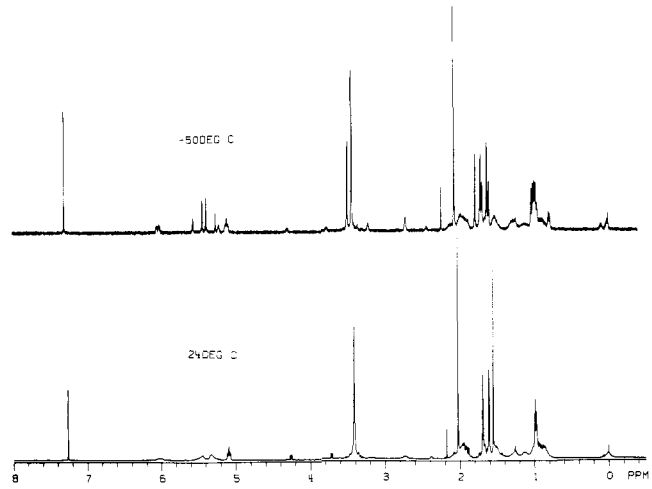
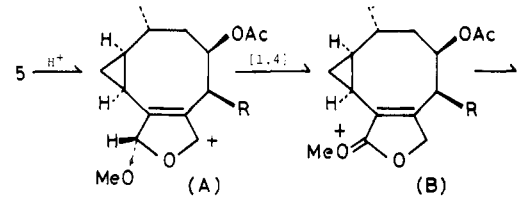


Figure 1. ^1H NMR (360-MHz) spectra of crenulacetal C (**5**) taken at 24 °C (lower) and −50 °C (upper).

their spectral data and chromatographic behaviors with those of authentic samples. These findings allowed us to assign the relative configurations at C-3, -4, -6, -7, and -9 of crenulacetals C and D as seen in the structures **5** and **6**. These stereochemical features are identical with those of crenulacetals A and B. Since crenulacetals A and B have 18β-methoxy groups and the acetates of them show the spectral properties different from those of crenulacetals C and D, 18-methoxy groups of the latter compounds have to have an α-configuration. The configurations of the 19-methoxy groups of **5** and **6** were assigned as α and β, respectively, on the same ground as discussed for **3** and **4**; the ^1H NMR signal of 8β-H (a cyclopropane proton) of **5** appears more upfield (δ 0.04) than that of **6** (δ 0.40).

Discussion

Whereas crenulacetals A (**3**) and B (**4**) take the fixed



(A) (B)

conformation (**8**), the same one as reported for other crenulides,[3] crenulacetals C (**5**) and D (**6**) take more than two conformations which invert one another at ambient temperature. Inspection of molecular models reveals that, in **5** (and **6**), 18α-methoxy group is located close to the side chain at C-3 and destabilizes the "ordinary" conformation **5a**. On the basis of the coupling constants of the protons determined from the NMR spectrum (−50 °C), it was deduced that crenulacetal C takes two conformations **5a** and **5b** (1:2). Noteworthy is the fact that the ^1H NMR signal

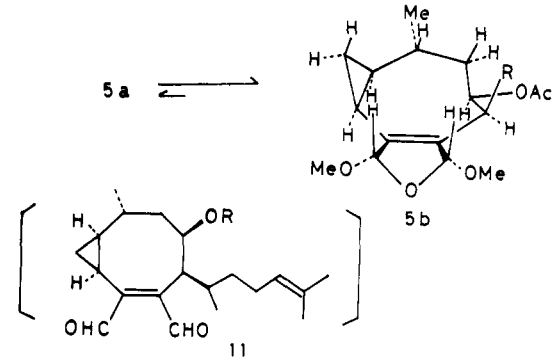


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Table I. ^1H and ^{13}C NMR ($CDCl_3$) Chemical Shifts and Coupling Constants of Crenulacetals A (3) and B (4)[a]

	3		4	
positn no.	^1H NMR[i]	^{13}C NMR[i]	^1H NMR[i]	^{13}C NMR[i]
1		140.7 (s)[b]		141.7 (s)[f]
2		140.5 (s)[b]		141.2 (s)[f]
3	2.88 (br d, 9)	47.7 (d)	2.86 (d, 10)	48.0 (d)
4	4.07 (br d, 3)	68.6 (d)	4.08 (m)	68.8 (d)
5	1.66 (dd, 15, 3)	47.5 (t)	1.70 (dd, 15, 5)	47.3 (t)
	1.80 (dd, 15, 5)		1.79 (dd, 15, 3)	
6	1.55 (qdd, 7, 9, 5)	28.2 (d)	e	28.6 (d)
7	0.83 (qd, 9, 6)	25.4 (d)	0.94 (qd, 9, 6)	26.7 (d)
8	0.53 (td, 6, 5)	5.6 (t)	0.02 (td, 6, 5)	7.3 (t)
	0.61 (td, 9, 5)		0.80 (td, 9, 5)	
9	1.32 (tdd, 9, 6, 2)	11.9 (d)	1.35 (tdd, 9, 6, 2)	11.5 (d)
10	1.7 (m)	32.7 (d)	1.75 (m)	32.4 (d)
11	1.08 (m)	36.0 (t)	e	36.1 (t)
	1.32 (m)		e	
12	1.97 (m)	25.5 (t)	2.0 (m)	25.6 (t)
	2.05 (m)		2.0 (m)	
13	5.11 (br t, 7)	124.2 (d)	5.16 (br t, 8)	124.3 (d)
14		131.8 (s)		132.0 (s)
15	1.69 (br s)	25.6 (q)	1.70 (br s)	25.8 (q)
16	1.61 (br s)	17.0 (q)[c]	1.60 (br s)	17.1 (q)[g]
17	1.03 (d, 7)	17.6 (q)[c]	1.03 (d, 7)	17.7 (q)[g]
18	5.25 (d, 2)	109.1 (d)[d]	5.58 (dd, 2, 3.5)	109.9 (d)[h]
19	5.44 (br s)	106.5 (d)[d]	5.63 (d, 3.5)	108.7 (d)[h]
20	1.01 (d, 7)	23.5 (q)	1.03 (d, 7)	23.5 (q)
OMe	3.41 (s)	54.6 (q)	3.35 (s)	53.0 (q)
	3.54 (s)	56.2 (q)	3.52 (s)	56.4 (q)

[a] ^1H and ^{13}C NMR spectra were recorded at 360 and 22.5 MHz, respectively. ^1H and ^{13}C chemical shifts are from Me_4Si signal. Multiplicity of the carbon signals were determined by INEPT experiments. Assignments of the carbon signals were done by comparison of their chemical shifts with those of the known crenulides such as 1 and 2. [b-d,f-h] These assignments can be interchanged. [e] Chemical shifts could not be determined. [i] Chemical shifts are reported as δ values and J values are given in hertz in parentheses.

due to 3-H in either conformation appears as a singlet, which indicates that the dihedral angle formed by 3-H and 10-H as well as 3-H and 4-H is 90°. This is in contrast to the fact that in the crenulides hitherto isolated the signal of 3-H appears as a doublet (J = 9 Hz), since the side chain takes a conformation in which the dihedral angle between 3-H and 10-H comes close to 0° (or 180°).[4]

Formation of acetoxycrenulide (1)[3] and hydroxycrenulide[5] by acid treatment of the crenulacetals is worth noting. When the reaction was done by using deuteriohydrochloric acid in deuteriomethanol, no deuterium was incorporated in 1. Considering this finding, we propose the following reaction pathway including intramolecular [1,4] hydride shift in the intermediate A. The selective removal of the 18-methoxy group is reasonably interpreted by participation of the cyclopropane ring in stabilizing the cation at C-18 of A by linear conjugation. For a cation at C-19, the cyclopropane would not be in a position to contribute for resonance stabilization.

The crenulacetals reported herein seem to be derived from the dialdehyde 11, which has not been isolated so far.

Experimental Section

Infrared spectra were determined on a Hitachi 360 spectrometer. NMR spectra were taken on JEOL FX-90Q and Nicolet NT-360 spectrometers. Mass spectra were obtained on Hitachi RMU-6M and JEOL JMS-DX 300 spectrometers.

Materials. *Dictyota dichotoma* (25 kg) and *Dictyota spinulosa* (25 kg) were collected at Yagachi, Okinawa, in June 1983, and the unidentified species of Dictyotaceae (3 kg) was obtained at Izu-Shirahama, Shimoda, in June 1983. The seaweeds were soaked in MeOH immediately after the collection and allowed to stand for 2 days. The MeOH was decanted, and the residual material was again extracted with fresh MeOH for 1 week. The combined MeOH extracts were concentrated on a rotary evaporator, and the residue was successively washed with hexane, CH_2Cl_2, and ethyl acetate (EtAc).

Crenulacetal A (3). The hexane extract of *D. dichotoma* was concentrated, and the residue (100 g) was fractionally separated by chromatography on silica gel (Wakogel C-300; 1 kg). Elution with gradient proportions of hexane and EtAc yielded crude 3 (100 mg), which was purified by preparative TLC (Merck, Kieselgel 60, GF_{254}; CH_2Cl_2/EtAc, 95:5) to give 3 (80 mg) as a colorless oil: IR ($CHCl_3$) 3460, 1450, 1380, 1090, 1075 cm^{-1}; high resolution mass spectrum, $C_{21}H_{32}O_3$ (M^+ - MeOH) obsd m/e 332.2375, calcd 332.2353; other ions at low resolution (direct inlet) mass spectrum, m/e (relative intensity) 364 (M^+, 0.1), 300 (19), 199 (10), 109 (30), 69 (68). From the hexane extract, four other diterpenes were isolated: hydroxycrenulide (40 mg),[5] hydroxyacetyldictyolal (40 mg),[9a,b] dictytriol (1000 mg),[10] and 4-hydroxydictyolactone (40 mg).[9b]

Crenulacetal B (4). The hexane extract of *D. spinulosa* was concentrated, and the residue was fractionated in a similar manner as described above to produce 4 (70 mg) as a colorless oil: IR ($CHCl_3$) 3475, 1085, 1050, 1030 cm^{-1}; high resolution mass spectrum, $C_{22}H_{36}O_4$ (M^+) obsd m/e 364.2622, calcd 364.2615; other ions at low resolution (direct inlet) mass spectrum, m/e (relative intensity) 333 (31), 332 (100), 315 (10), 301 (8), 109 (46), 69 (50). Other diterpenes isolated from this extract were pachydictyol A (320 mg),[11] dictytriol (52 mg),[10] neodictyolactone (12 mg),[12] 19α- and 19β-methoxyisodictyoacetals (20 mg),[15] isodictyoacetal (44 mg),[12] and dictyodial (50 mg).[13]

Crenulacetals C (5) and D (6). The hexane extract from the unidentified species of Dictyotaceae was concentrated, and the residue (39 g) was fractionated as described above to give 5 (30 mg) and 6 (50 mg). Crenulacetal C (5): colorless oil; IR ($CHCl_3$) 1720, 1080, 1000 cm^{-1}; high resolution mass spectrum, $C_{24}H_{38}O_5$ (M^+) m/e obsd 406.2735, calcd 406.2720; other ions at low resolution mass spectrum (GC/MS) m/e 374 (5), 342 (16), 314 (9), 259 (13), 203 (100), 109 (28), 69 (84); ^1H NMR ($CDCl_3$, 24 °C)

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δ 0.04 (br d, 1 H), 0.95 (br d, 6 H), 1.58 (s, 3 H), 1.68 (s, 3 H), 2.00 (s, 3 H), 3.38 (s, 6 H), 5.05 (br t, 1 H), 5.28 (s, 1 H), 5.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 24 °C) δ 8.1 (t), 12.6 (d), 17.7 (q), 21.5 (q), 25.7 (q), 26.6 (t), 32.1 (d), 35.4 (t), 45.9 (d), 53.5 (q), 54.5 (q), 73.6 (d), 109.3 (d), 124.5 (d), 131.5 (s), 169.8 (s). The others were unobserved possibly due to broadening. Crenulacetal D (6): colorless oil; IR ($CHCl_3$) 1720, 1080, 1000 cm^{-1}; high resolution mass spectrum, $C_{24}H_{38}O_5$ (M^+) *m/e* obsd 406.2717, calcd 406.2720; ^1H NMR ($CDCl_3$, 24 °C) δ 0.40 (m, 1 H), 0.96 (br d, 6 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 2.00 (s, 3 H), 2.82 (m, 1 H), 3.34 (s, 6 H), 5.06 (br t, 1 H), 5.66 (s, 2 H). This extract was extremely rich in terpenoids, and the following ten other diterpenes were isolated: dictyoxide (17 mg),[14] pachydictyol A (150 mg),[11] isodictyoacetal (92 mg),[12] 19α- and 19β-methoxyisodictyoacetals (50 mg),[15] acetyldictyolal (4 mg),[9a,15] dictyolactone (2 mg),[13] acetylsanadaol (3 mg),[16] dictyone (10 mg),[10] and 18-hydroxy-2,7-dolabelladiene (18 mg).[17]

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Acid Hydrolysis of Crenulacetal C (5). A solution of **5** (15 mg) in MeOH (0.75 mL) was treated with 0.08 mL of 35% hydrochloric acid, and the mixture was allowed to stand at room temperature for 21 h. The mixture was neutralized with an aqueous saturated solution of sodium bicarbonate, and the product was taken up in CH_2Cl_2. After being dried over sodium sulfate, the CH_2Cl_2 solution was concentrated into an oily residue (11.8 mg), which was separated by preparative TLC (Merck, Kieselgel 60, GF_{254}; hexane/acetone, 9:1) to give **1** (4.6 mg) and hydroxycrenulide (1.5 mg). The products were identified by comparison of their ^1H and ^{13}C NMR data as well as R_f values of TLC with those of authentic samples. Crenulacetals A (**3**), B (**4**), and D (**6**) also afforded the same products under the same reaction conditions. In another experiment, a solution of **5** (10 mg) in tetradeuteriomethanol (0.5 mL) was treated with deuteriochloric acid (12 M; 0.06 mL), and after 10 h, the mixture was neutralized with a sodium bicarbonate solution in D_2O. Workup as described above afforded **1** (5 mg), whose ^1H NMR spectrum exhibited a broad singlet due to 18-CH_2 (δ 4.82). The intensity of this signal corresponded to exactly two protons.

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Hydration of Diacetylene Compounds. Synthesis of a Marine Natural Product: (±)-1-(2,6,6-Trimethyl-4-hydroxycyclohexenyl)-1,3-butanedione

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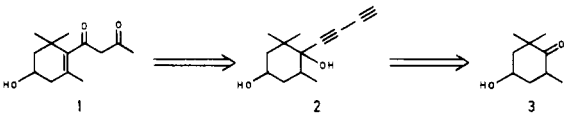
The marine natural product (±)-1-(2,6,6-trimethyl-4-hydroxycyclohexenyl)-1,3-butanedione (**1**) was synthesized from the known keto alcohol **3** and 1,4-dichlorobut-2-yne. The synthetic sequence involves dehydration of the diyne tertiary alcohol **2** and hydration of the diyne system to give the β-diketone moiety. This reaction was accomplished in excellent yield by using 85% formic acid as also demonstrated with a simple model substrate.

In the course of our studies on the synthesis of biologically active natural products structurally related to carotenoids, we became interested in the recently described marine natural product **1**, 1-(2,6,6-trimethyl-4-hydroxycyclohexenyl)-1,3-butanedione, isolated from cultures of the dinoflagellate *Prorocentrum minimum* by Andersen, Le Blanc, and Sum.[1] They pointed out the structural relation between **1** and compounds believed to be degradation products of carotenoids, suggesting that zeaxanthin could be a precursor of **1**. These authors showed also that compound **1** has in vitro antibiotic activity against *Staphylococcus aureus*.

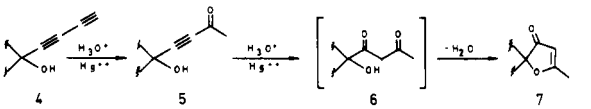
In our preliminary communication[2] on the synthesis of (±)-**1**, the retrosynthetic planning depicted in Scheme I drew our attention to the problem of hydration of diacetylene alcohols.

Diacetylene alcohols such as **2** are relatively unstable compounds; however, they can be satisfactorily stored in solution at low temperatures. The hydration of these compounds in the presence of mercury salts and acid results, through a stepwise addition of water, in hydroxylated β-diketone **6**, which gives, by cyclization and water elimination, a furanone **7** (Schene II).[3] To obtain an unsaturated β-diketone such as **1** it would seem necessary to eliminate the tertiary hydroxyl group of compound **2** before hydration of the diacetylene.

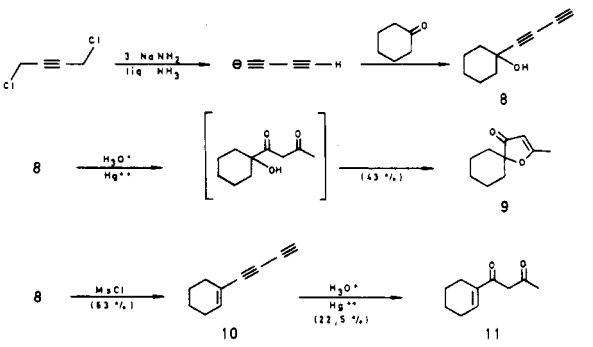
Scheme I



Scheme II



Scheme III



† FFCLRP-USP.
‡ IQ-USP.

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