min. The resulting maroon solution was stirred at 0 °C for 1 h and at rt for 1 h. The solution was then poured into 150 mL of 1 M HCl, washed with Et_2O, made basic with 65 mL of 2 M NaOH, and extracted with Et_2O 2X. The Et_2O extracts were combined, dried (Na_2SO_4), and concd on a rotary evaporator to yield 8.0 g (94%) of **9a** as an oil that was pure by TLC (SiO_2 eluted with MeO–*t*-Bu:hexane:IPA = 30:67:3) and was converted to 4.75 g (50%) of **9a** as the monohydrochloride salt: mp 182.0–2.5 °C; IR 3240, 2960–2800 br, 2085, 1640, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.3 (s, 9), 5.95 (s, 1), 7.28–7.58 (m, 8), 7.71 (d, 1, J = 8), 8.05 (s, 1), 9.28 (s, 3). Anal. Calcd for $C_{18}H_{24}N_2O$·HCl: C, 67.80; H, 7.21; N, 8.79. Found: C, 67.80; H, 7.30; N, 8.72.

2-(Aminophenylmethyl)-*N*-methylbenzamide (9b) and 2,3-Dihydro-3-phenyl-1*H*-isoindol-1-one (10). A solution of 0.68 g (5.0 mmol) of *N*-methylbenzamide in 18 mL of THF was stirred at −10 °C while 4.4 mL (11 mmol) of 2.5 M *n*-butyllithium in hexanes was added in 5 min. The reaction mixture was stirred at 0 ± 2 °C for 1 h, and then 0.97 g (5.5 mmol) of *N*-(trimethylsilyl)benzalimine[4] was added in 3 min. After being stirred another 1 h at 0 °C and at rt for 1 h, the mixture was poured into ice–water containing 15 mL of 1 M HCl and washed with Et_2O 2X. The aqueous solution was then made basic with 2 M NaOH and extracted 2X with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and ethereal HCl was added. The resulting precipitate was crystallized from $CHCl_3$ and gave 0.50 g (36%) of **9b** as the HCl salt: mp 210–2 °C; IR 3250, 3150, 2900, 1625, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.72 (d, 3, J = 4), 6.02 (s, 1), 7.26–7.75 (m, 9), 8.52 (d, 1, J = 4), 9.25 (s, 3). Crystals formed in the aqueous basic solution and were collected to give 0.36 g (34%) of **10**: mp 222–4 °C (lit.[11] mp 218–20 °C).

Registry No. **1a**, 134389-96-1; **1b**, 134389-97-2; **1c**, 134389-98-3; **1d**, 134389-99-4; **1e**, 134390-00-4; **1f**, 134390-01-5; **1g**, 134390-02-6; **1h**·HCl, 134390-03-7; **1i**·2HCl, 134390-04-8; **1j**, 134390-06-0; **1k**, 134390-07-1; **1l**, 134390-08-2; **4a**, 49572-99-8; **4b**, 4725-83-1; **4c**, 134389-93-8; **4d**, 51107-08-5; **4e**, 134389-94-9; **4f**, 3306-73-8; **4g**, 134389-95-0; **4h**, 5004-45-5; **4i**, 134418-61-4; **5a**, 134390-09-3; **5b**, 134390-05-9; **6**, 134390-10-6; **8a**, 5894-65-5; **9a**·HCl, 134390-12-8; **9b**·HCl, 134390-13-9; **10**, 835-18-7; phenyllithium, 591-51-5; (2-methyl-1-naphthalenyl)phenylmethanone, 4919-69-1; methylhydrazine, 60-34-4; 2-benzoylbenzaldehyde, 16780-82-8; benzylhydrazine dihydrochloride, 20570-96-1; 1-phenyl-1,2,3,4-tetrahydrophthalazine monohydrochloride, 134390-11-7; *N*-(trimethylsilyl)benzalimine, 17599-61-0; *N*-methylbenzamide, 613-93-4; 2-(1-naphthoyl)benzoic acid, 5018-87-1; 2-phenylacetylbenzoic acid, 33148-55-9; 2-(4-methoxybenzoyl)benzoic acid, 1151-15-1; 2-benzoylbenzoic acid, 85-52-9; *tert*-butylhydrazine hydrochloride, 7400-27-3.

Supplementary Material Available: Experimental details and spectroscopic and analytical data for compounds **4c–e**, **4g**, **4i**, **1a–g**, and **1j–l** (5 pages). Ordering information is given on any current masthead page.

Amphidinolides G and H: New Potent Cytotoxic Macrolides from the Cultured Symbiotic Dinoflagellate *Amphidinium* sp.

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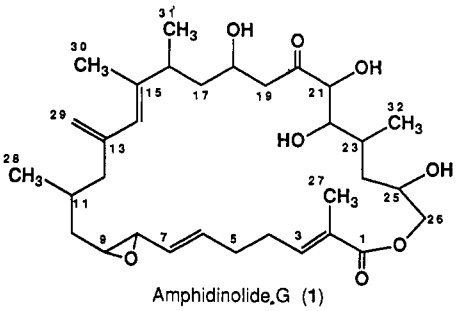
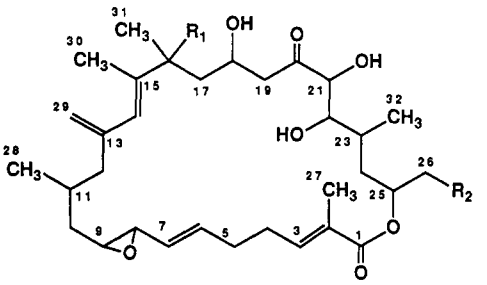
Marine microorganisms have proven to be a new valuable source of compounds with interesting pharmacological activities.[2] During our studies on bioactive substances from Okinawan marine organisms,[3] we have investigated symbiotic microalgae associated with marine invertebrates and previously isolated five novel cytotoxic macrolides, amphidinolides A–E, from the cultured dinoflagellates.[4] Our continuing search for more pharmacologically useful substances from cultured dinoflagellates of the genus *Amphidinium* has now led to the isolation of two new cytotoxic macrolides, amphidinolides G (1) and H (2), possessing extremely potent cytotoxic activity. This paper describes the isolation and structure elucidation of 1 and 2.



Amphidinolide G (1)



R_1=H, R_2=OH Amphidinolide H (2)
R_1=OH, R_2=H Amphidinolide B (3)

The dinoflagellate *Amphidinium* sp.[5] was isolated from the Okinawan flatworm *Amphiscolops breviviridis* and grown unialgally in a sea-water medium enriched with 1% Provasoli's ES supplement at 25 °C for 2 weeks.[4c] The harvested cells (70 g from ca. 160 L of culture) were extracted with methanol–toluene (3:1), and the extracts were partitioned between toluene and 1 M aqueous NaCl. The toluene-soluble fraction was chromatographed on a silica

(1) (a) Hokkaido University. (b) University of the Ryukyus. (c) The University of Tokyo. (d) Kanazawa University.
(2) Kobayashi, J. *J. Nat. Prod.* **1989**, *52*, 225–238.
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(4) (a) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Sasaki, T.; Hirata, Y. *Tetrahedron Lett.* **1986**, *27*, 5755–5788. (b) Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1127–1129. (c) Kobayashi, J.; Ishibashi, M.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490–494. (d) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *J. Nat. Prod.* **1989**, *52*, 1036–1041. (e) Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421–3423.
(5) This species of *Amphidinium* is different from those reported previously.[4]

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Table I. ^1H and ^{13}C NMR Data of Amphidinolide G (1)[a]

position	H		J (Hz)	C		H coupled with C[b]
1				167.7	s	H_3-27
2				128.3	s	
3	6.70	br t	6.4	141.1	d	H_3-27
4a	2.36	m		30.9	t	
4b	2.21	m				
5a	2.34	m		27.0	t	H-7
5b	2.20	m				
6	5.81	ddd	15.4, 8.9, 4.6	135.7	d	
7	5.18	dd	15.4, 8.4	128.8	d	H-8
8	3.03	dd	8.4, 2.2	59.8	d	
9	2.91	dt	8.6, 2.2	59.3	d	
10a	1.46	m		39.8	t	H_3-28
10b	1.18	m				
11	1.60	m		29.3	d	H-10b, H_3-28
12a	2.20	m		46.8	t	H_3-28, H-29a, H-29b
12b	1.86	m				
13				143.9	s	H_3-30, H-14
14	5.50	s		125.8	d	H-29a, H-29b, H_3-30
15				141.6	s	H_3-30, H_3-31
16	2.18	m		40.7	d	H_3-31, H-14, H-17a
17a	1.79	m		40.5	t	H_3-31, H-14
17b	1.41	m				
18	3.94	m		66.6	d	H-19a, H-19b
19a	2.68	dd	16.3, 8.3	44.1	t	
19b	2.64	dd	16.3, 3.1			
20				211.5	s	H-19a, H-19b, H-21
21	4.33	br s		77.8	d	
22	3.92	m		74.3	d	H_3-32
23	2.08	m		36.0	d	H_3-32
24a	1.99	m		36.9	t	H_3-32
24b	1.32	m				
25	3.89	m		69.0	d	
26a	4.20	dd	11.4, 3.3	68.7	t	
26b	4.11	dd	11.4, 3.1			
27	1.81 (3 H)	s		12.8	q	
28	0.87 (3 H)	d	6.4	18.3	q	
29a	4.97	s		114.9	t	
29b	4.80	s				
30	1.71 (3 H)	s		12.7	q	H-14
31	1.04 (3 H)	d	6.7	20.6	q	
32	1.09 (3 H)	d	6.8	17.7	q	

[a] Recorded in $CDCl_3$. [b] HMBC correlations.

gel column with $CHCl_3$–MeOH (95:5) followed by reversed-phase HPLC on ODS with MeOH–H_2O (88:12) to give amphidinolides G (1, 0.0020%, wet weight) and H (2, 0.0017%).

Amphidinolide G (1) was obtained as a colorless amorphous powder. The molecular formula, $C_{32}H_{50}O_8$, of 1 was determined by HRFABMS (m/z 668.4377 (M + diethanolamine (DEA) + H)$^+$, Δ +0.3 mmu, $C_{36}H_{62}NO_{10}$). The IR spectrum suggested the presence of hydroxyl(s) (3400 cm^{-1}) and unsaturated lactone (1705 cm^{-1}) groups, and the UV absorption maximum at 222 nm was indicative of the presence of an α,β-unsaturated ester moiety. The ^1H and ^{13}C NMR spectra (Table I) revealed that 1 possessed four double bonds: an *exo*-methylene, a disubstituted, and two trisubstituted double bonds, both of which bore methyl groups and were *E* since the ^{13}C signals for the olefinic methyl groups were located at high fields (δ_C 12.7 and 12.8). The presence of another carbonyl group was shown by the ^{13}C NMR spectrum of 1, the chemical shift of which (δ_C 211.5) implied that the carbonyl was not conjugated. The assignments of all protonated carbons were established by the ^1H-detected multiple quantum coherence (HMQC)[6] spectrum.

The analyses of the ^1H–^1H COSY[7] spectrum of 1 allowed assignment of all protons and established the proton connectivities of the following three segments: C-2–C-15, C-16–C-19, and C-21–C-26. The signal for Me-27 showed cross-peaks due to allylic couplings to H-3 and methylene protons on C-4. The *exo*-methylene protons (H-29a and H-29b) showed cross-peaks with one of the C-12 methylene protons and H-14. Other vicinal couplings were easily obtained.[7] The *E* configuration of the $\Delta^{6(7)}$ double bond and the trans configuration of the 8,9-oxirane ring were suggested by the coupling constants ($J_{6,7}$ = 15.4 Hz and $J_{8,9}$ = 2.2 Hz) and confirmed by the NOESY[8] spectrum (cross-peaks H-6 and H-8; H-7 and H-9). The NOESY spectrum also revealed the (s)-cis conformation of Δ^{13} and $\Delta^{14(15)}$ double bonds (cross-peak H-29a,29b and Me-30). The ester oxygen on C-1 was connected with the terminal oxymethylene (C-26), which was implied by the ^1H chemical shifts (δ_H 4.20 and 4.11; H_2-26). The proton connectivities of two segments, C-16–C-19 and C-21–C-26, were also elucidated by the ^1H–^1H COSY spectrum of 1.[7] The connection from C-15 to C-16 was revealed by the NOESY (cross-peaks Me-30 and Me-31; H-14 and H-16) and the

(6) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565–569.

(7) The ^1H–^1H COSY spectrum of 1 clearly showed the following connectivities (H–H): Me(27)–3, 3–4a, 3–4b, 5a–6, 5b–6, 6–7, 7–8, 8–9, 9–10a, 9–10b, 10a–10b, 10a–11, Me(28)–11, 11–12b, 12a–12b, 12b–29a, 12b–29b, 29a–29b, 29b–14, 14–Me(30), Me(31)–16, 16–17a, 16–17b, 17a–17b, 17b–18, 18–19a, 18–19b, 21–22, 22–23, 23–Me(32), 24a–24b, 24a–25, 25–26a, 25–26b, and 26a–26b.

(8) The NOESY spectrum of 1 afforded the following correlations (H–H): 3–4a, 3–5a, 5a–6, 5b–6, 6–7, 6–8, 7–8, 7–9, 8–10b, 9–10a, 9–Me(28), 12a–12b, 12a–14, 29a–29b, 29b–Me(30), 14–16, Me(30)–Me(31), Me(31)–16, 21–Me(32), 22–23, Me(32)–24b, 25–26a, and 26a–26b.

Table II. ^1H and ^{13}C NMR Data of Amphidinolide H (2)[a]

position	H		J (Hz)	C		H coupled with C[b]
1				168.7	s	H_3-27, H-3
2				27.8	s	H_3-27
3	6.81	t	7.2	141.0	d	H_3-27, H-5a
4a	2.43	m		30.9	t	
4b	2.24	m				
5a	2.34	m		26.9	t	H-7
5b	2.08	m				
6	5.88	ddd	15.5, 9.0, 4.7	135.8	d	H-4a
7	5.13	dd	15.5, 8.2	128.6	d	H-8
8	3.12	dd	8.2, 2.3	60.3	d	H-6
9	2.94	dt	9.7, 2.3	59.5	d	
10a	1.48	m		39.7	t	H-9
10b	1.16	m				
11	1.56	m		29.0	d	H-10a, H-12a, H-12b, H_3-28
12a	2.12	dd	8.2, 4.8	47.1	t	H_3-28, H-29a
12b	1.84	m				
13				144.1	s	H-12a, H-12b
14	5.57	s		126.1	d	H-29a, H-29b, H_3-30
15				141.7	s	H_3-30, H_3-31, H-17b
16	2.23	m		40.7	d	H_3-31, H_3-30, H-14
17a	1.79	m		40.8	t	H_3-31, H_3-30, H-14
17b	1.42	m	8.8, 16.6			
18	3.92	m		67.5	d	H-19a, H-19b
19a	2.73	dd	15.8, 8.6	45.2	t	
19b	2.61	dd	15.8, 1.6			
20				212.1	s	H-18, H-19a, H-19b, H-21
21	4.30	m		77.7	d	
22	3.72	m		75.4	d	
23	1.85	m		32.9	d	
24a	2.02	m		33.4	t	
24b	1.26	m				
25	5.07	ddd	11.4, 5.7, 3.0	73.4	d	H-26b
26a	3.73	m		66.1	t	
26b	3.65	dd	11.4, 5.7			
27	1.82 (3 H)	s		12.5	q	H-3
28	0.84 (3 H)	d	6.4	17.9	q	H-12a
29a	4.97	s		114.7	t	H-12a, H-14
29b	4.80	s				
30	1.71 (3 H)	s		13.1	q	
31	1.05 (3 H)	d	6.7	20.2	q	
32	1.00 (3 H)	d	6.7	15.5	q	

[a] Recorded in $CDCl_3$. [b] HMBC correlations.

^1H-detected heteronuclear multiple-bond correlation (HMBC)[9] spectra (cross-peaks Me-30 and C-16; Me-31 and C-15; H-14 and C-16). The connection from C-19 to C-21, therefore, remained to be elucidated. These two carbons were suggested to be connected through the isolated ketone (δ_C 211.5), since the chemical shift of the C-19 methylene protons (δ_H 2.67 and 2.14) indicated that this methylene carbon was located at the α-position to the carbonyl group. The connection from C-19 to C-21 through the carbonyl (C-20) was further verified by the HMBC spectrum of 1 (cross-peaks H-19 and C-20; H-21 and C-20). Thus, the structure of amphidinolide G was concluded to be 1.[10]

Amphidinolide H (2) was obtained as a colorless amorphous powder. The molecular formula, $C_{32}H_{50}O_8$, of 2 was determined by HRFABMS (m/z 668.4407 (M + DEA + H)$^+$, Δ+3.3 mmu, $C_{36}H_{62}NO_{10}$). This molecular formula of 2 was the same as that of amphidinolide G (1). The UV and IR absorptions of 2 were also analogous to those of 1. All protons were assigned on the basis of the ^1H–^1H COSY[11] spectrum, and the ^{13}C signals were assigned by comparison with those of 1 along with the DEPT,[12] HMQC, and HMBC spectra of 2 (Table II). The proton–proton and long-range C–H connectivities obtained by the ^1H–^1H COSY, NOESY,[13] and HMBC spectra indicated the similar location of functional groups between 1 and 2. The ^1H–^1H coupling constants and the ^{13}C chemical shifts of the olefinic methyl groups showed that the geometries of the double bonds and the epoxide were also identical with each other. The structural difference between 1 and 2 was found only in the location of the lactone linkage. The lactone terminal position of amphidinolide H (2) was shown to be at the C-25 position by comparison with the ^1H chemical shifts of H-25 (δ_H 5.07) and H_2-26 (δ_H 3.73 and 3.65) with those of 1 (H-25 δ_H 3.89; H_2-26 δ_H 4.20 and 4.11). The structure of amphidinolide H was, therefore, concluded to be 2. Amphidinolide H (2) possesses a primary hydroxyl group at C-26 position, while amphidinolide G (1) has a secondary hydroxyl group on C-25. The structures of amphidinolides G (1) and H (2)[10] have proven to be related to that of amphidinolide B (3), previously isolated from the different species of the di-

(9) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093–2094.

(10) The stereochemistry of all chiral centers remains undefined.

(11) The ^1H–^1H COSY spectrum of 2 afforded the following connectivities (H–H): Me(27)–3, 3–4a, 3–4b, 4a–4b, 4–5a, 4–5b, 5a–5b, 5a–6, 5b–6, 6–7, 7–8, 8–9, 9–10a, 9–10b, 10a–10b, Me(28)–10b, Me(28)–11, Me(28)–12a, 11–12a, 11–12b, 12a–12b, 12b–29a, 29a–29b, 14–29b, 29b–Me(30), Me(30)–14, Me(31)–16, Me(31)–17a, 16–17a, 16–17b, 17a–18, 17b–18, 18–19a, 18–19b, 21–22, 22–23, Me(32)–23, 23–24b, 24a–24b, 24a–25, 24b–25, 25–26a, 25–26b, and 26a–26b.

(12) Bendall, M. R.; Pegg, D. T.; Doddrell, D. M.; Williams, D. H. *J. Org. Chem.* **1982**, *47*, 3021–3023.

(13) The NOESY spectrum of 2 afford the following correlations (H–H): 3–4b, 3–6, 3–7, 4a–4b, 4b–6, 5a–5b, 5a–6, 5a–7, 6–7, 6–8, 7–8, 7–9, 8–9, 8–10a, 9–Me(28), 10a–10b, 11–29a, 12a–14, 29a–29b, 29b–Me(30), Me(30)–Me(31), 14–16, Me(31)–16, 16–17a, 16–18, 16–19b, 17a–17b, 18–19b, 19a–19b, 19a–21, 19a–22, 21–22, 21–24, 21–Me(32), 22–Me(32), Me(32)–23, Me(32)–25, 25–26a, 25–26b, and 26a–26b.

noflagellate of the genus *Amphidinium*.[4b] Amphidinolide B (3) possesses the tertiary methyl and tertiary hydroxyl groups at C-16, and the C-26 position is not oxygenated (methyl group), whereas amphidinolides G (1) and H (2) have the secondary methyl group at C-16 and the oxygenated methylene group on C-26.

Amphidinolide G (1) is a new cytotoxic 27-membered macrolide, while amphidinolide H (2) is a 26-membered macrolide bearing the similar molecular constitution and substitution pattern of 1.[14] These two compounds, especially 2, exhibited extremely strong cytotoxic activities against L1210 murine leukemia cells in vitro with the IC_{50} (50% inhibitory concentration) values of 0.0054 and 0.000 48 μg/mL[15] and KB human epidermoid carcinoma cells in vitro with IC_{50} values of 0.0059 and 0.000 52 μg/mL, respectively.[16]

Experimental Section

General Procedure. The 7.26 ppm resonance of residual $CHCl_3$ and 77.0 ppm resonance of $CDCl_3$ were used as internal references for ^1H and ^{13}C chemical shifts, respectively. FABMS were obtained using glycerol or diethanolamine as a matrix.

Isolation. The procedure for the algal cultivation has been previously described.[4c] The harvested cells (70 g, wet weight) from 160 L of culture were extracted with toluene–methanol (1:3, 200 mL × 3). After addition of 1 M NaCl (300 mL), the mixture was extracted with toluene (200 mL × 3). The toluene-soluble fraction was evaporated under reduced pressure to give a residue (1.0 g), which was subjected to silica gel column chromatography (Wako gel C-300, Wako Chemical, 2.2 × 37 cm) eluted with chloroform–methanol (95:5, 540 mL). The fraction (10 mg) eluting from 160 to 210 mL was further separated by SEP-PAK C_{18} cartridges (Waters, 10 × 12 mm) eluted with MeOH–H_2O (80:20, 20 mL). The eluate (6.9 mg) was then purified by HPLC (Develosil ODS-5, Nomura Chemical, 10 × 250 mm; flow rate 2.5 mL/min; UV detection at 254 nm; eluent MeOH–H_2O (88:12)) to afford compound 1 (1.4 mg, t_R 12.2 min) and compound 2 (1.2 mg, t_R 10.6 min).

Amphidinolide G (1): colorless amorphous powder; $[\alpha]^{22}_D$ −60.1° (*c* 0.15, $CHCl_3$); UV (MeOH) 222 nm (ϵ 11 000); IR (film) 3400, 1705, 1280, 1260, and 1120 cm^{-1}; ^1H and ^{13}C NMR (Table I); FABMS (positive ion, glycerol matrix) *m/z* 563 $(M + H)^+$, 545 $(M - H_2O + H)^+$, 527 $(M - 2H_2O + H)^+$, and 509 $(M - 3H_2O + H)^+$; FABMS (positive ion, diethanolamine (DEA) matrix) *m/z* 668 $(M + DEA + H)^+$ and 585 $(M + Na)^+$; HRFABMS *m/z* 668.4377 (M + DEA + H), calcd for $C_{36}H_{62}NO_{10}$ 668.4374.

Amphidinolide H (2): colorless amorphous powder; $[\alpha]^{18}_D$ −32.3° (*c* 0.2, $CHCl_3$); UV (MeOH) 222 nm (ϵ 10 000); IR (film) 3400, 1700, 1255, and 1130 cm^{-1}; ^1H and ^{13}C NMR (Table II); FABMS (positive ion, diethanolamine matrix) *m/z* 668 (M + DEA + H)$^+$, 650 $(M + DEA - H_2O + H)^+$; HRFABMS *m/z* 668.4407 (M + DEA + H), calcd for $C_{36}H_{62}NO_{10}$ 668.4374.

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Supplementary Material Available: ^1H–^1H COSY, ^{13}C NMR, NOESY, HMQC, HMBC, FABMS, HRFABMS, IR, and UV spectra of 1 and 2 (18 pages). Ordering information is given on any current masthead page.

(14) No interconversion between the two compounds (1 and 2) was observed.

(15) The cytotoxicity of amphidinolide H (2) is almost as potent as that of amphidinolide B (3, IC_{50} 0.000 14 μg/mL against L1210 cells).[4b]

(16) Before the cytotoxicity test, compounds 1 and 2 were further purified by HPLC (Develosil ODS-5, 10 × 250 mm) with MeOH–H_2O (88:12) to remove the impurities contained in the samples of the NMR experiments (see supplementary material).

Regioselective Synthesis of 1-Formylcyclohexenes by One-Carbon Homologation

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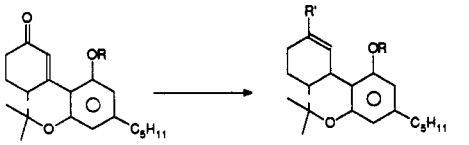
As one aspect of our general synthetic program directed toward the regio- and stereoselective synthesis of cannabinoids, we sought a method for the conversion of enone 1 to 11-oxocannabinoid 2.[1] Aldehyde 2 was to be a pre-



1 R = Me or MOM

2 R = Me or MOM, R' = CHO
3 R = Me or MOM, R' = CO_2H

cursor to 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol 3, a human metabolite of Δ^9-tetrahydrocannabinol, the major active component of marijuana. Although a number of procedures have been described for the preparation of unsaturated aldehydes by one-carbon homologation,[2] only two appeared attractive for the synthesis of 2. One of these, developed by Denmark,[2a] proceeds by conjugate reduction of an enone, trapping the derived enolate as the trimethylsilyl ether, and Rubottom oxidation to the TMS ether of an α-hydroxy ketone.[3] The TMS ether is cleaved, the hydroxyl group reprotected as the *tert*-butyldimethylsilyl ether; Horner–Emmons reaction,[4] followed by hydrolysis, provides the unsaturated aldehyde.[2a] The second procedure for regioselective synthesis of cyclohexenals entails palladium-catalyzed reaction of a vinyl triflate with carbon monoxide–tributytin hydride.[2b]

The attempted conversion of 1 to aldehyde 2 by both these procedures was unsuccessful, and in response to this problem, we developed a new synthetic procedure for the regioselective elaboration of cyclohexanones or cyclohexenones to 1-formylcyclohexenes. This procedure has been applied to the preparation of several unsaturated aldehydes in yields comparable to those reported by Denmark.[2a] In addition, the synthetic procedure is significantly shorter than Denmark's and does not require the isolation of sensitive silyl enol ethers.

This procedure, which is outlined in Scheme I, proceeds in three steps from an enone or saturated ketone, by formation of an α-phenylthio ketone, Wittig reaction with (methoxymethylene)triphenylphosphorane, or Warren's variation of the Horner–Emmons reaction.[4] Mercuric ion assisted acid hydrolysis provides directly the unsaturated aldehyde. This sequence has been applied to six substi-

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