Gino Sasso of the NMR Laboratory (under the direction of Dr. T. Williams) for their assistance in obtaining 100-MHz NMR spectra and carrying out numerous decoupling experiments. The skilled assistance of Mr. Jack Lin in preparing compound i[5] and isolating some of the initial quantities of **11** is gratefully acknowledged. We also thank Dr. J. F. Blount for the X-ray analysis confirming the structure of compound i.

**Registry No.**—**1a,** 1695-77-8; **6,** 56782-21-9; **7,** 58515-30-3; **8,** 67421-50-5; **9,** 67421-51-6; **10,** 67421-52-7; **11,** 67462-78-6; **11** 7-*O*-acetyl derivative, 67421-53-8; **14,** 67462-79-7; **15,** 67462-80-0; **17a,** 67421-54-9; **17b,** 67421-55-0; **18a,** 67421-56-1; **18b,** 67421-57-2; **19,** 67421-58-3; **20,** 67421-59-4; **21a,** 67462-81-1; **21b** 9-benzoate, 67421-62-9; **21b,** 67421-60-7; **22a,** 67462-82-2; **22b,** 67421-61-8; 2,2-dimethoxypropane, 77-76-9.

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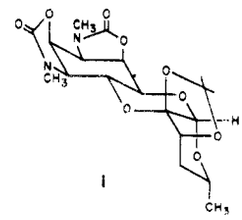
(5) An X-ray analysis carried out on the bis(carbamate) i, prepared in a series of steps from the acetonide **7,** confirmed its structure as well as that of **7** (J. Lin, unpublished results).



i

(6) For recent discussions of the "anomeric effect" see, Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969,** *4,* 73–7. David, S.; Einstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R. *J. Am. Chem. Soc.,* **1973,** *95,* 3806–7. Bailey, W. F.; Eliel, E. L. *ibid.* **1974,** *96,* 1798–1806.
(7) The numbering system used in this paper is that of the 2*H*-pyrano[2,3-*b*][1,4]benzodioxin ring system. This numbering system also corresponds to the one used for spectinomycin.
(8) Details of the spin decoupling experiments may be found in the Experimental Section.
(9) The narrow line width of the triplet, $J = 2.5–3$ Hz, observed for H-4 indicates that the actinospectose ring exists in the boat conformation. Examination of Dreiding models reveals that the chair conformation would result in considerable steric interaction between the C-2 methyl group and the oxygen atom of the 1,4-benzodioxin ring.
(10) The unlikely possibility that the keto alcohol **13** represents the most stable form of this molecule may be discounted since the 4(*S*)-dihydrospectinomycin **1c** or its derivatives do not rearrange under conditions used for preparing the acetonides or on treatment with mild base (unpublished results).
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# Malyngamides D and E, Two *trans*-7-Methoxy-9-methylhexadec-4-enamides from a Deep Water Variety of the Marine Cyanophyte *Lyngbya majuscula*

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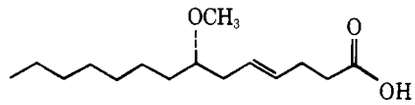
Malyngamides D and E are two *trans*-7-methoxy-9-methylhexadec-4-enamides that have been isolated from the lipid extract of a deep water variety of the marine blue-green alga *Lyngbya majuscula*. Detailed spectral analysis, mostly NMR, and chemical degradation show that malyngamides D and E have the gross structures **2** and **3**, respectively. Malyngamides D and E produce the same diacetate on acetylation. The ring stereochemistry of **2** and **3** has been defined from NMR and chemical reactivity data.

Malyngamides A, B, and C are chlorine-containing *trans*-7(*S*)-methoxytetradec-4-enamides that are present in shallow-water varieties of the marine blue-green alga *Lyngbya majuscula*.[1,2] Free *trans*-7(*S*)-methoxytetradec-4-enoic acid (**1**) is also a lipophilic constituent of the shallow-water strains.[1]

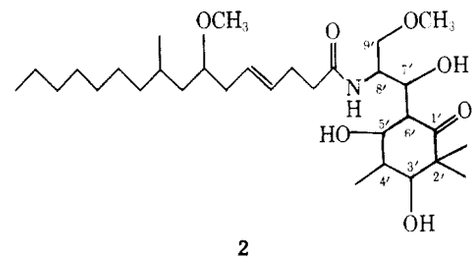


1

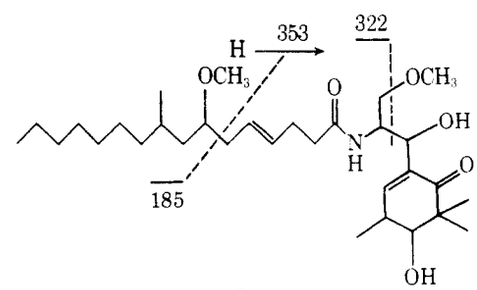
Neither **1** nor amides of **1** have been found in a toxic, deep-water variety of *L. majuscula* from Enewetak.[3,4] Instead two closely related *trans*-7-methoxy-9-methylhexadec-4-enamides, malyngamides D (**2**) and E (**3**),[5] are present in this alga. This paper describes the gross structure elucidations of malyngamides D and E.

## Structure Determination

Mass spectral analysis showed that amides **2,** $[\alpha]_D$ −33.0° in $CHCl_3$, and **3,** $[\alpha]_D$ +24.2° in $CHCl_3$, differed in molecular composition by the elements of $H_2O$. Except for a small $M^+$ ion at *m/e* 555 for **2,** the mass spectra of **2** and **3** were essentially identical, with compound **3** showing a $M^+$ ion at *m/e* 537.40235 for $C_{31}H_{55}NO_6$ (calcd 537.40295). The



2



3

molecular formula of **2** was therefore $C_{31}H_{57}NO_7$ and this agreed with the formula determined from $^{13}C$ NMR (5 $CH_3$ bonded to carbon, 2

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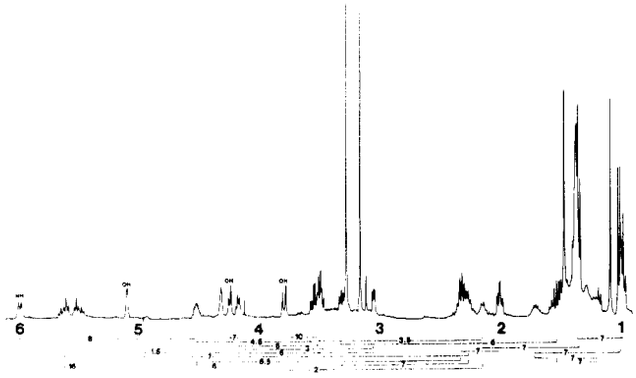


**Figure 1.** The 360-MHz $^1H$ NMR spectrum of malyngamide D (**2**) in benzene-$d_6$ at 54 °C. The chemical shift scale is in $\delta$ (ppm) units. Connecting lines denote coupled (in Hz) proton signals that have been determined by homonuclear decoupling and deuterium exchange (addition of $D_2O$) experiments. The sample contains a small amount of malyngamide E (**3**).

$OCH_3$, 11 $CH_2$, 10 CH, 1 C bonded to carbon only, 2 C=O) and $^1H$ NMR (3 OH, 1 NH) spectral data.

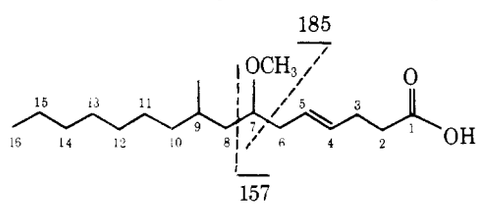
The $^{13}C$ NMR spectrum of **2** (Table I) exhibited only four unsaturated carbon signals, i.e., $\delta$ 217.04 (ketone C=O), 172.48 (amide C=O), and 131.00 and 127.2 (-CH=CH-) in benzene-$d_6$; **2** was therefore monocyclic. The $^{13}C$ NMR spectrum also indicated that, in addition to two methoxyl carbons ($\delta$ 58.64, 56.00), five other carbon atoms were singly bonded to oxygen, one methylene ($\delta$ 70.57) and four methines ($\delta$ 84.76, 79.37, 79.02, 72.53). In the $^1H$ NMR spectrum of **2** in benzene-$d_6$ (Figure 1), three hydroxyl signals appeared as doublets at $\delta$ 5.11 (partially resolved, $J$ = 1.5 Hz), 4.26 ($J$ = 7 Hz), and 3.81 ($J$ = 10 Hz) and an amide NH signal was observed as a doublet at $\delta$ 6.00 ($J$ = 8 Hz); on addition of $D_2O$ all four of these signals disappeared. The IR spectrum of **2** supported the presence of ketone (1700 $cm^{-1}$) and amide (1660 $cm^{-1}$) functionalities and furthermore indicated that the disubstituted double bond was trans (975 $cm^{-1}$). All seven oxygens and the single nitrogen could therefore be accounted for by a ketone, a secondary amide, two methoxyl (one attached to $CH_2$ and the other to CH), and three secondary alcohol functionalities.

The $^{13}C$ NMR spectrum of **3** (Table I) differed from the $^{13}C$ NMR spectrum of **2** in two ways. First it had absorptions at $\delta$ 136.08 (singlet) and 145.68 (doublet) in $CDCl_3$ for an additional double bond which was trisubstituted and conjugated with the ketone carbonyl as shown in a. The UV spectrum, $\lambda_{max}$ 235 nm ($\epsilon$ 6400), was consistent with this interpretation.

a b

Second it lacked two saturated methine absorptions, one for a methine attached to carbon only and the other for a methine bonded to an oxygen and to a carbon, and this suggested that **2** was the corresponding $\beta$-hydroxy ketone of partial structure b.

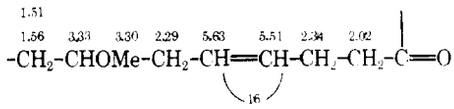
Acid hydrolysis of **3** yielded *trans*-7-methoxy-9-methylhexadec-4-enoic acid (**4**). The $^1H$ NMR spectrum of **4** showed signals for the



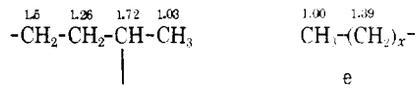
**4**

C-2, C-3, C-4, C-5, and C-6 protons that were superimposable on those of 1;[1] the C-7 methine signal, however, was at slightly lower field (in $CDCl_3$ $\delta$ 3.25 compared with $\delta$ 3.15 for **1**). The mass spectrum of **4** showed fragmentation that was compatible with the molecular formula $C_{18}H_{34}O_3$ and the placement of the methoxyl substituent on C-7. The $^1H$ NMR spectrum also indicated that **4** contained a secondary methyl group (broad doublet at $\delta$ 0.88, $J$ = 7 Hz).

The presence of the *trans*-7-methoxy-9-methylhexadec-4-enoyl unit in **2** and **3** was demonstrated by high-frequency $^1H$-NMR experiments. Successive homonuclear decoupling experiments on **2** (Figure 1) and **3** established partial structures c, d, and e. Since the

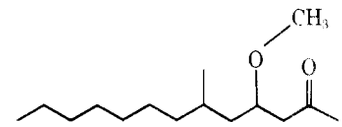


c



d e

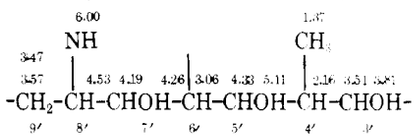
nonequivalent C-8 methylene proton signals ($\delta$ 1.51 and 1.57 for **2**) were sharp, we felt that the methyl group had to be attached to either C-9 or C-10. The proton decoupling studies favored the C-9 position since the C-8 absorptions appeared to be doublets ($J_{gem}$ = −12 to −14 Hz) of triplets ($J$ = 6–7 Hz) which collapsed to doublets of doublets on irradiation of the C-7 methine ($\delta$ 3.33). Since another methylene (C-11) resonated at $\delta$ 1.5 (broad signal), however, we were not able to make a definite decision. The $^{13}C$ NMR data of **2** and **3**, however, were only consistent with the placement of the methyl substituent on C-9 (Table I). Calculated carbon-13 chemical shifts agreed with the observed values when the methyl group was on C-9 and not on C-10. The assignment was confirmed by a lanthanide induced shift (LIS) study of **5** (from ozonolysis of **2** and **3**) which clearly showed that a single methylene separated the methoxyl and methyl bearing methines. In the presence of 6.25 equiv of Eu(fod)$_3$ in $CDCl_3$ the C-4 methylene signal of **5** was observed as a well-defined triplet at $\delta$ 4.37 which col-



**5**

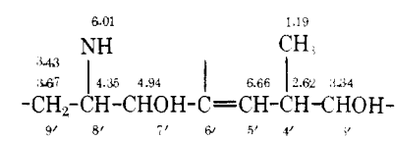
lapsed to a doublet when the quintet for the C-3 methine was irradiated ($\delta$ 9.1).

Additional proton spin–spin decoupling experiments on **2** (Figure 1) established the sequence f in **2**. Addition of $D_2O$ led to changes in



f

the signals at $\delta$ 4.53, 4.19, 4.33, and 3.51, in agreement with the decoupling results. Since **4** was furnished on hydrolysis the fatty acyl group had to be attached to the NH. The ketone carbonyl therefore was connected to C-6′, since only this position had an OH $\beta$ to the C=O as in b. The other $OCH_3$ ($\delta$ 3.18) group had to be on C-9′ from NMR evidence. The remaining *gem*-dimethyl carbon [$^{13}C$ $\delta$ 52.59; $^1H$ $\delta$ 1.10 (3 H, s) and 1.49 (3 H, s)] was then placed between the ketone carbonyl and C-3′ to form a cyclohexanone ring. In support of these structural conclusions, proton spin–spin decoupling studies of **3** led to the related partial structure g. Unlike the $^1H$ NMR spectrum of **2**, however, the C-3′ and C-7′ proton signals of **3** did not show coupling to hydroxyl protons and the two OH signals could not be observed. The attachment of OH groups at C-3′ and C-7′ in **3** was verified by acetylation (see below).



g

## Stereochemistry

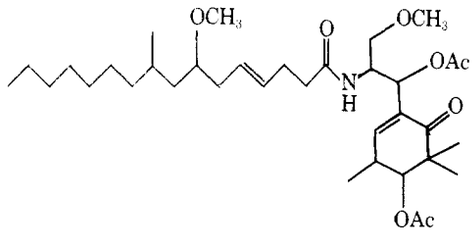
Malyngamide D was recovered unchanged when treated with acetic anhydride and pyridine at room temperature;

**Table I. Carbon-13 NMR Data for Malyngamides D (2) and E (3)**

| Chemical shift[a] | | | | |
|---|---|---|---|---|
| 2 | | 3 | | |
| $CDCl_3$ | $C_6D_6$ | $CDCl_3$ | $C_6D_6$ | Assignment[b] |
| 216.75 | 217.04 (s) | 202.21 (s) | 202.5 | 1′ |
| 172.27 | 172.48 (s) | 173.07 (s) | 173.09 | 1 |
| | | 145.68 (d) | 145.97 | 5′ |
| | | 136.08 (s) | 136.90 | 6′ |
| 130.35 | 131.00 (d) | 130.62 (d) | 131.17 | 4 |
| 127.27 | 127.2 (d) | 127.18 (d) | 127.2 | 5 |
| 84.56 | 84.76 (d) | 79.63 (d) | 79.74 | 3′[c] |
| 79.63 | 79.37 (d) | | | 5′[c] |
| 78.66 | 79.02 (d) | 78.84 (d) | 79.21 | 7[c] (75.5) |
| 72.32 | 72.53 (d) | 69.06 (d) | 69.00 | 7′[c,d] |
| 70.03 | 70.57 (t) | 71.70 (t) | 71.99 | 9′ |
| 58.85 | 58.64 (q) | 58.93 (q) | 58.96 | $OCH_3$ on 9′ |
| 56.07 | 56.00 (q) | 56.20 (q) | 56.32 | $OCH_3$ on 7 |
| 52.24 | 52.59 (d) | | | 6′[c] |
| 51.45 | 52.59 (s) | 48.10 (s) | 48.48 | 2′ |
| 49.86 | 50.01 (d) | 53.21 (d) | 54.03 | 8′[c,d] |
| 41.06 | 41.54 (t) | 41.14 (t) | 41.70 | 8[c] (40.9) |
| 36.83 | 37.36 (t) | 36.83 (t) | 37.47 | 10[c] (37.2) |
| 36.21 | 36.80 (t) | 36.39 (t) | 36.94 | 6[c] |
| 36.21 | 36.15 (t) | 36.2 (t) | 36.41 | 2[c] |
| 34.45 | 34.84 (d) | 32.95 (d) | 33.42 (d) | 4′[c,d] |
| 31.81 | 32.26 (t) | 31.81 | 32.36 (t) | 14 (32.4) |
| 29.74 | 30.33 (t) | 30.0 | 30.43 (t) | 12 (30.2) |
| 29.34 | 29.87 (d) | 29.43 | 29.90 (d) | 9[c] (29.5) |
| 29.34 | 29.74 (t) | 29.43 (t) | 29.90 | 13 (29.7) |
| 28.46 | 28.84 (t) | 28.37 (t) | 28.84 | 3 |
| 26.79 | 27.33 (t) | 26.79 (t) | 27.43 | 11 (27.3) |
| 25.47 | 25.49 (q) | 23.27 (q) | 23.56 | $CH_3$ on 4′[e] |
| 22.56 | 23.03 (t) | 22.65 (t) | 23.21 | 15 (22.7) |
| 20.63 | 21.32 (q) | 21.24 | 21.80 (q) | eq $CH_3$ on 2′[c] |
| 20.10 | 20.46 (q) | 20.10 (q) | 20.56 | $CH_3$ on 9[c] (20.1) |
| 14.20 | 14.72 (q) | 16.84 (q) | 17.22 | ax $CH_3$ on 2′[e] |
| 14.02 | 14.28 (q) | 14.11 (q) | 14.57 | 16[c] (13.9) |

[a] Reported in $\delta$ units relative to the solvent peak, i.e., benzene-$d_6$ ($\delta$ 128.0) or chloroform-$d$ ($\delta$ 76.9), as an internal standard. [b] Numbers in parentheses are calculated chemical shifts [G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972, pp 41 and 47]. [c] Based on proton single frequency off-resonance decoupling (sford) experiments on **2** in $C_6D_6$ at 90 MHz. [d] Based on proton sford experiments on **3** in $CDCl_3$. [e] Tentative assignments; removal of OH from C-5′ should result in an upfield shift of the Me on C-4′ and the removal of axial proton from C-6′ should shift the signal for the axial Me on C-2′ downfield.

however, **2** did react slowly at 55 °C to form a diacetate which was spectrally and optically identical with malyngamide E diacetate (**6**), obtained by a similar acetylation of **3** at 55 °C.

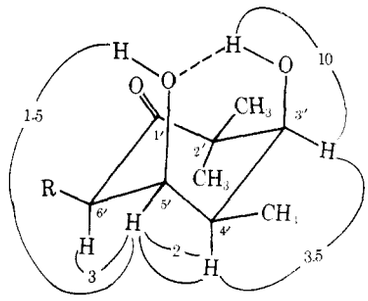



**6**

The $^1H$ NMR spectrum of **6** in $CDCl_3$ exhibited sharp singlets at $\delta$ 1.98 and 2.04 for the two acetoxyl groups. As expected the C-3′ and C-7′ protons of **6** resonated at much lower field, $\delta$ 5.16 and 5.62, than the C-3′ and C-7′ protons of **3**, $\delta$ 3.53 and 4.71, respectively.

The resistance of **2** to acetylation suggested that the hydroxyl groups on C-3′ and C-5′ are axially disposed. Furthermore the facile $\beta$ elimination of the C-5′ hydroxyl during the acetylation of **2** suggested that the C-6′ proton is axial and therefore trans to the C-5′ hydroxyl group. The small proton–proton coupling constants for $J_{3',4'}$, $J_{4',5'}$, and $J_{5',6'}$ agree with these stereochemical conclusions.

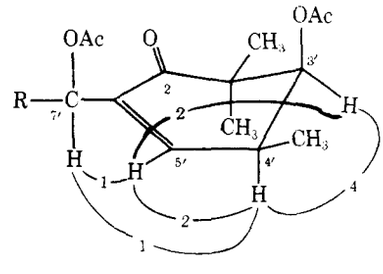
In the $^1H$ NMR spectrum of **2** in benzene-$d_6$ at 54 °C the signals for the three hydroxyl protons appear as well-resolved doublets, reflecting coupling to the adjacent methine protons. In the $^1H$ NMR spectrum of **3** in benzene-$d_6$ at 54 °C, however, the signals for the two hydroxyl protons cannot be seen. Moreover, the C-3′ and C-7′ proton signals of **3** do not show any coupling to OH protons. Obviously the proton exchange rate is much slower in **2** than it is in **3**. When the C-3′ and C-5′ OH groups are axial, intramolecular hydrogen bonding is allowed, not only between the C-3′ and C-5′ OH groups, but also between the C-5′ and C-7′ OH groups of **2**. Since the C-5′ OH is missing in **3**, intramolecular hydrogen bonding is not possible between the C-3′ and C-7′ OH groups. In **2** the magnitudes of $J_{CHOH}$ for the OH signals at $\delta$ 3.81 (10 Hz) and 5.11 (1.5 Hz) indicate dihedral angles of approximately 180 and 60°, respectively.[6] At C-3′ the OH proton must therefore be trans to the C-3′ methine proton and at C-5′ the OH proton must be gauche to the C-5′ methine proton as shown in h. The




h

stereochemistry at C-7′, however, as well as at the other chiral centers in the side chain, cannot be deduced from the NMR data.

In the $^1H$ NMR spectra of **3** and **6**, W coupling (2 Hz) is observed between the C-3′ and C-5′ protons, requiring that the C-3′ proton in **3** and **6** be equatorial as it is in **2**. The methyl group on C-4′ must therefore be in an equatorial position. If the C-3′ and C-4′ substituents of **3** and **6** were trans, it would be impossible to have both groups axial in the preferred conformer. The C-4′ methyl group in **2** is then also equatorially oriented. Small (1 Hz) but significant homoallylic coupling can be detected between the C-4′ and C-7′ protons of **3** and **6**. From Dreiding models of **3** and **6** the dihedral angle between the C-4′ and C-5′ protons appears to be close to 90° which is consistent with the observed homoallylic coupling.[7] The proposed stereochemistry of the ring in **6** (absolute configuration not implied) is depicted in i.




i

## Experimental Section

$^1$H- and $^{13}$C-NMR spectra were obtained on a Varian XL-100 spectrometer equipped with a Digilab Fourier transform system. High-frequency $^1$H- and $^{13}$C-NMR studies were performed on the HXS-360 instrument at the Stanford Magnetic Resonance Laboratory. Proton chemical shifts are reported in $\delta$ units relative to the benzene-$d_5$ peak ($\delta$ 7.24) when benzene-$d_6$ was used as the solvent or to $(CH_3)_4Si$ ($\delta$ 0) as an internal standard when chloroform-$d$ was used as the solvent; $J$ values are given in hertz. Electron impact mass spectra were determined at 70 eV on a Varian MAT 311 high-resolution mass spectrometer. Optical rotations were measured on a ETL-NPL (Ericsson Telephone Unlimited) automatic polarimeter. Elemental analyses were performed by the Chemical Analytical Services, University of California, Berkeley.

**Isolation.** Wet *Lyngbya majuscula*[3] (3 kg), collected from Reefer 8 pinnacle (80–100 ft), Enewetak lagoon in September, 1975, was extracted with chloroform–methanol (1:2). Water was added to the extract and the chloroform layer was evaporated to give 22 g of a dark brown oil. Chromatography on a column of Florisil (40 cm × 4.7 cm) gave a toxic fraction[4] which was eluted with chloroform–methanol (9:1). Gel filtration of the toxic oil (1.9 g) on a column (1.15 m × 1.5 cm) of Sephadex LH-20 with chloroform-methanol (1:1) gave 580 mg of a fraction which was then rechromatographed on a column (1 cm × 24 cm) of silica gel PF254 with ethyl acetate. The resulting mixture of malyngamides (341 mg) was finally separated by preparative TLC on plates of silica gel PF254 with two developments of chloroform–methanol (19:1) into 71 mg of malyngamide D and 190 mg of malyngamide E.

Malyngamide D (**2**) had the following properties: $[\alpha]^{25}_D$ −33.0° ($CHCl_3$, $c$ 0.53); IR ($CCl_4$) $\nu_{max}$ 1700 (s), 1660 (s), 975 cm$^{-1}$ (s); $^1$H NMR (benzene-$d_6$, 54°, 360 MHz) $\delta$ 6.00 (br d, $J$ = 8, amide NH), 5.63 (dt, $J_{5,4}$ = 16, $J_{5,6}$ = 7, C-5 -CH=), 5.51 (dt, $J_{4,5}$ = 16 and $J_{4,3}$ = 6.5, C-4 =CH–), 5.11 (br d, $J_{OH,5'}$ = 1.5, OH on C-5′), 4.53 (br dq, $J_{8',NH}$ = 8, $J_{8',9'}$ = 4.5 and 6, $J_{8',7'}$ = 6, C-8′ H), 4.33 (br m, $J_{5',OH}$ = 1.5, $J_{5',6'}$ = 3, $J_{5',4'}$ = 2, C-5′ H), 4.26 (d, $J_{OH,7'}$ = 7, OH on C-7′), 4.19 (quartet, $J_{7',OH}$ = 7, $J_{7',8'}$ = $J_{7',6'}$ = 6, C-7′ H), 3.81 (d, $J_{OH,3'}$ = 10, OH on C-3′ H), 3.57 (dd, $J_{gem}$ = −10, $J_{9',8'}$ = 4.5, C-9′ proton), 3.51 (m, obscured by dd at 3.47 ppm, C-3′ H), 3.47 (dd, C-9′ proton), 3.33 (quintet, $J_{7,8}$ = 6, $J_{7,6}$ = 7, C-7 H), 3.30 (s, OMe on C-7), 3.18 (s, OMe on C-9′), 3.06 (dd, $J_{6',5'}$ = 3, $J_{6',7'}$ = 6, C-6′ H), 2.34 (quartet, $J_{3,4}$ = 6.5, $J_{3,2}$ = 7, C-3 methylene), 2.29 (m, C-6 methylene), 2.16 (m, C-4′), 2.02 (m, $J_{gem}$ = −14, C-2 methylene), 1.72 (br m, C-9), 1.57 (dt, C-8 proton), 1.51 (dt, C-8 proton), 1.5 (br m under dt at 1.51, C-11 methylene), 1.49 (s, Me on C-2′), 1.39 (br m, C-12, C-13, C-14, C-15 methylenes), 1.37 (d, J = 7, Me on 4′), 1.26 (m, C-10 methylene), 1.10 (s, Me on C-2′), 1.03 (d, $J$ = 7, Me on C-9), 1.00 (br t, $J$ = 7, C-16 methyl); MS m/e (rel intensity) 555 (0.1, M$^+$), 537 (1, M − $H_2O$), 522 (1), 519 (2), 505 (1), 460 (3), 442 (2), 354 (28), 353 (25), 335 (22), 323 (22), 322 (64), 299 (13), 281 (35), 267 (12), 199 (15), 185 (91), 139 (51), 116 (68), 111 (49), 97 (100), 85 (67), 83 (100).

Malyngamide E (**3**) had the following properties: $[\alpha]^{24}_D$ + 24.2° ($CHCl_3$, $c$ 0.6); UV (MeOH) $\lambda_{max}$ 235 nm ($\epsilon$ 6400); IR ($CCl_4$) $\nu_{max}$ 1675 (s, broad), 985 cm$^{-1}$ (m); $^1$H NMR (benzene-$d_6$, 54°, 360 MHz) $\delta$ 6.66 (br, $J_{5',4'} \sim J_{5',3'} \sim J_{5',7'} \sim 1$, C-5′), 6.01 (br d, $J_{NH,8'}$ = 8, amide NH), 5.63 (dt, $J_{5,4}$ = 16, $J_{5,6}$ = 6.5, C-5 -CH=), 5.54 (dt, $J_{4,5}$ = 16, $J_{4,3}$ = 6.5, C-4 =CH–), 4.94 (br d, $J_{7',8'}$ = 6, $J_{7',4'} \sim 2$, $J_{7',5'} \sim 1$, C-7′), 4.35 (br m, $J_{8',NH}$ = 8, $J_{8',7'}$ = 6, $J_{8',9'}$ = 3 and 5, C-8′ H), 3.67 (dd, $J_{gem}$ = −10, $J_{9',8'}$ = 3, C-9′ proton), 3.43 (dd, $J_{gem}$ = −10, $J_{9',8'}$ = 5, C-9′ proton), 3.34 (m, C-7 H), 3.34 (m, C-3′ H), 3.29 (s, OMe on C-7), 3.12 (s, OMe on C-9′), 2.62 (m, C-4′ H), 2.40 (quartet, $J_{3,4}$ = 6.5, $J_{3,2}$ = 7, C-3 methylene), 2.29 (br m, C-6 methylene), 2.13 (dt, $J_{gem}$ = −14.5, $J_{2,3}$ = 7, C-2 proton), 2.06 (dt, $J_{gem}$ = −14.5, $J_{2,3}$ = 7, C-2 proton), 1.72 (br m, C-9 H), 1.55 (m, C-8 proton), 1.50 (m, C-8 proton), 1.5 (br m, C-11 methylene), 1.42 (s, Me on C-2′), 1.39 (br, C-12, C-13, C-14, C-15 methylenes), 1.24 (m, C-10 methylene), 1.19 (d, $J$ = 7, Me on C-4′), 1.03 (d, $J$ = 7, Me on C-9), 1.01 (s, Me on C-2′), 1.01 (br t, $J$ = 7, C-16 methyl); $^1$H NMR ($CDCl_3$, 360 MHz), $\delta$ 6.58 (br, C-5′ H → t, $J$ = 2 on irr at 4.71), 6.14 (br d, $J$ = 8, NH), 5.48 (m, C-5 H), 5.44 (m, C-4 H), 4.71 (br d, $J$ = 6, C-7′ H → dd, $J$ = 6 and 2 on irr at 6.58), 4.16 (m, C-8′ H), 3.60 (dd, $J$ = −11 and 3.5, C-9′ proton), 3.53 (t, $J$ = 2, C-3′ H), 3.42 (dd, $J$ = −11 and 5.5, C-9′ proton), 3.29 (s, OMe), 3.27 (s, OMe), 3.22 (quintet, C-7 H), 2.93 (m, C-4′ H), 2.27 (m, $CH_2$), 2.20 (m, $CH_2$), 2.10 (m, $CH_2$), 1.47 (m, C-9 H), 1.24 (d, $J$ = 7, Me on C-4′), 1.23 (br m, C-8, C-10, C-11, C-12, C-13, C-14, C-15 methylenes), 1.19 (s, Me on C-2′), 1.07 (s, Me on C-2′), 0.85 (br t, C-16 methyl), 0.83 (d, $J$ = 7, Me on C-9); MS m/e (rel intensity) 537 (3, M$^+$), 522 (2, M − $CH_3$), 519 (2.5, M − $H_2O$), 505 (5, M − $CH_3OH$), 460 (5), 354 (44), 353 (40), 335 (33), 323 (34), 322 (64), 299 (12), 281 (26), 199 (12), 185 (89), 139 (32), 113 (51), 111 (78), 97 (100), 85 (90), 83 (94); high resolution MS m/e 537.40235 (calcd for $C_{31}H_{55}NO_6$, 537.40295), 353.22585 (calcd for $C_{19}H_{31}NO_5$, 353.22023), 322.27208 (calcd for $C_{20}H_{36}NO_2$, 322.27461), 185.19049 (calcd for $C_{12}H_{25}O$, 185.19055).

Anal. Calcd for $C_{31}H_{55}NO_6 \cdot H_2O$: C, 67.0; H, 10.3; N, 2.5. Found: C, 66.7; H, 9.9; N, 2.6.

**Acid Hydrolysis of Malyngamide E.** A solution of 9.8 mg of **3** in 5 mL of aqueous 2NHCl and 5 mL of methanol was heated at 50 °C for 19 h. The mixture was diluted with water and extracted with chloroform. Gel filtration of the extract on a 1.4 m × 1.5 cm column of Sephadex LH-20 with chloroform–methanol (1:1) gave three fractions, A (108–125 mL, 3.5 mg), B (125–138 mL, 3.5 mg), and C (138–159 mL, 1.7 mg). Fraction A was unreacted **3**. Fraction B was *trans*-7-methoxy-9-methylhexadec-4-enoic acid (**4**): $^1$H NMR ($CDCl_3$) $\delta$ 5.51 (br m, 2 H, C-4 and C-5 methines), 3.33 (s, $OCH_3$ on C-7), 3.25 (m, 1 H, C-7 methine), 2.40 (br s, 4 H, C-2 and C-3 methylenes), 2.14 (br m, 2 H, C-6 methylene), 1.26 (br s with low field sh, 15 H), 0.89 (br t, $J$ = 7, 3 H), 0.88 (br d, $J$ = 7, 3 H), chemical shift of $CO_2H$ proton not determined; MS m/e (rel intensity) 213 (3), 185 (50), 157 (6), 111 (26), 97 (100), 85 (49), 83 (63), 71 (76), 69 (48); high resolution MS m/e 185.19103 (calcd for $C_{12}H_{25}O$, 185.19055), 157.08658 (calcd for $C_8H_{13}O_3$, 157.08647). Fraction C was methyl *trans*-7-methoxy-9-methylhexadec-4-enoate: $^1$H NMR ($CDCl_3$) $\delta$ 5.49 (br m, 2 H, C-4 and C-5 methines), 3.68 (s, ester $OCH_3$), 3.32 (s, $OCH_3$ on C-7), 3.24 (m, 1 H, C-7 methine), 2.38 (br s, 4 H, C-2 and C-3 methylenes), 2.18 (m, 2 H, C-6 methylene), 1.27 (br s with low field sh, 15 H), 0.90 (br t, $J$ = 7, 3 H), 0.88 (br d, $J$ = 7 Hz, 3 H); MS m/e (rel intensity) 312 (0.2, M$^+$), 281 (0.7, M − $OCH_3$), 185 (100), 171 (3), 111 (19), 97 (73), 85 (44), 83 (43), 71 (43), 69 (26); high resolution MS m/e 185.19121 (calcd for $C_{12}H_{25}O$, 185.19055), 111.11853 (calcd for $C_8H_{15}$, 111.11738).

**Ozonolysis of Malyngamides D and E.** A solution of 27 mg of **3** in 5 mL of methanol was cooled to −77 °C and treated with excess ozone. When TLC analysis indicated that **3** had been consumed, the excess ozone was removed in a stream of nitrogen and 1 mL of dimethyl sulfide was added. The mixture was allowed to warm to room temperature and then evaporated in vacuo. Gel filtration on a 117 × 1.75 cm column of Sephadex LH-20 with chloroform-methanol (1:1) gave a fraction (119.0–122.5 mL) that contained an almost quantitative yield of crude 3-methoxy-5-methyldodecanal (**5**): $^1$H NMR ($CDCl_3$) $\delta$ 9.83 (t, $J$ = 2, C-1), 3.76 (quintet, $J$ = 6, C-3 methine), 3.34 (s, OMe on C-3), 2.55 (dd, $J$ = 6 and 2, C-2 methylene), 1.4 (m), 1.25 (br m), 0.89 (d, $J$ = 7, Me on C-5), 0.87 (br, t, $J$ = 7, C-12 methyl); $^1$H NMR ($CDCl_3$ + 6.25 equiv of Eu(fod)$_3$) $\delta$ 9.1 (m, C-3 H), 4.37 (t, $J$ = 6-7, C-4 methylene); MS m/e (rel intensity) 185 (7), 149 (6), 111 (16), 97 (27), 87 (54), 85 (34), 71 (53), 69 (34), 59 (84), 57 (67), 55 (50), 43 (100).

3-Methoxy-5-methyldodecanal was also produced by a similar ozonolysis of **2**.

Jones oxidation of **5** gave 3-methoxy-5-methyldodecanoic acid: $^1$H NMR ($CDCl_3$) 3.73 (quintet, $J$ = 6, C-3 H), 3.42 (s, OMe), 2.56 (d, $J$ = 6, C-2 $CH_2$), 1.80–1.20 (br multiplets), 0.93 (d, $J$ = 7, Me on C-5), 0.90 (br t, $J$ = 7, C-12 Me); MS m/e (rel intensity) 244 (0.1, M$^+$), 243 (0.5), 229 (4), 212 (4), 185 (8), 174 (11), 128 (18, loss of OH and $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ from M$^+$), 103 (100), 97 (23), 85 (20), 83 (20), 71 (28), 69 (26), 61 (77); high resolution MS m/e 212.17922 (calcd for $C_{13}H_{24}O_2$, 212.17764), 185.19049 (calcd for $C_{12}H_{25}O$, 185.19055), 128.08432 (calcd for $C_7H_{12}O_2$, 128.08373), 103. 03972 (calcd for $C_4H_7O_3$, 103.03952).

**Acetylation of Malyngamides D and E.** A solution of 10 mg of **2** in 1 mL of pyridine and 0.5 mL of acetic anhydride was heated (55 °C) under nitrogen for 1.5 h. The mixture was evaporated in vacuo and the residual oil was subjected to LC on a 3/8 in. × 4 ft column of Porasil A (37–75 μm) using $CH_3CN$–$CHCl_3$ (1:9) to give 1.1 mg of malyngamide E diacetate (**6**): $[\alpha]^{25}_D$ +37.5° ($CHCl_3$, 0.12); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 6.46 (br t, $J_{5',4'} = J_{5',3'} = 2.5$, $J_{5',7'} \sim 1$, C-5′ H), 6.04 (d, $J_{NH,8'}$ = 9, amide NH), 5.62 (dt, $J_{7',8'}$ = 9, $J_{7',5'} \sim J_{7',4'} \sim 1$, C-7′ H), 5.46 (dt, $J_{5,4}$ = 15, $J_{5,6}$ = 6, C-5 H), 5.43 (dt, $J_{4,5}$ = 15, $J_{4,3}$ = 6, C-4 H), 5.16 (dd, $J_{3',4'}$ = 5, $J_{3',5'}$ = 2.5, C-3′ H), 4.31 (tt, $J_{8',NH} = J_{8',7'}$ = 9, $J_{8',9'}$ = 3, C-8′ H), 3.49 (dd, $J_{gem}$ = −10, $J_{9',8'}$ = 3, C-9′ proton), 3.38 (dd, $J_{gem}$ = −10, $J_{9',8'}$ = 3, C-9′ proton), 3.29 (s, OMe), 3.28 (s, OMe), 3.20 (quintet, $J_{7,6} = J_{7,8}$ = 6, C-7 H), 2.94 (br m, C-4′ H), 2.25 and 2.13 (2 H and 4 H multiplets, C-2, C-3, C-6 methylenes), 2.04 (s, OCOMe), 1.98 (s, OCOMe), 1.48 (m, C-9 H), 1.3–1.2 (br m, C-8, C-10, C-11, C-12, C-13, C-14, C-15 methylenes), 1.15 (s, Me on C-2′), 1.06 (d, $J$ = 7, Me on C-4′), 1.04 (s, Me on C-2′), 0.84 (br t, $J$ = 7, C-16 methyl), 0.83 (d, $J$ = 7, Me on C-9).

Acetylation of **3** (6.5 mg) using the procedure above gave 2.5 mg of malyngamide E, $[\alpha]^{25}_D$ +38.4° ($CHCl_3$, $c$ 0.13); $^1$H NMR spectrum identical to that of **6** obtained from acetylation of **2**.

Malyngamide D was recovered unchanged when a solution of 3 mg of **2** in 0.25 mL of acetic anhydride and 0.25 mL of pyridine was allowed to stand at room temperature for 3.5 h.

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**Registry No.**—**2**, 67488-04-4; **3**, 67488-05-5; **4**, 67488-06-6; **4** methyl ester, 67488-07-7; **5**, 67488-08-08; **6**, 67488-09-9; 3-methoxy-5-methyldodecanoic acid, 67488-10-2.

## References and Notes

(1) J. H. Cardellina, D. Dalietos, F-J. Marner, J. S. Mynderse, and R. E. Moore, *Phytochemistry*, in press.
(2) J. H. Cardellina, F-J. Marner, and R. E. Moore, submitted for publication.
(3) The alga, which was collected from Reefer 8 pinnacle and South Elmer pinnacle at Enewetak Atoll in the Marshall Islands, was previously identified as *Lyngbya gracilis* Gomont (ref 4). A reexamination of this cyanophyte shows that its morphology does not agree with the published description of *L. gracilis* from Enewetak [E. Y. Dawson, *Pac. Sci.*, **11**, 92 (1957)]; however, it is entirely consistent with descriptions of *L. majuscula* Gomont [E. Y. Dawson, *Pac. Sci.*, **8**, 373 (1954); T. V. Desikachary, "Cyanophyta", Indian Council of Agricultural Research, New Delhi, 1959, p 313].
(4) J. S. Mynderse, R. E. Moore, M. Kashiwagi, and T. R. Norton, *Science*, **196**, 538 (1977).
(5) Malyngamides D and E show mild antibiotic activity against *Mycobacterium smegmatis* and *B. subtilis*.
(6) Structural conclusions are based on the assumption that the angle dependence of vicinal hydroxyl proton coupling constants, $J_{HCOH}$, parallels the Karplus relationship for $J_{HCCH}$. See E. F. Kiefer, W. Gericke, and S. T. Amimoto, *J. Am. Chem. Soc.*, **90**, 6246 (1968), and references therein.
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# Notes

## Cationic π Cyclizations.[1] Alkenes vs. Alkynes as the π Participant

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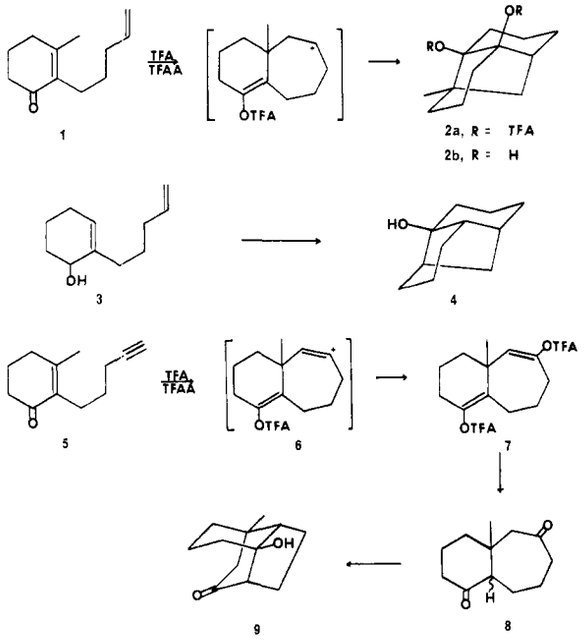
Terminal alkynes have been used as the π participant in a variety of cationic π cyclizations.[2] In those cases previously studied, the basic course of the cyclization has been the same as that observed with terminal alkenes. We now report a cyclization in which the change of π participant significantly affects the type of products observed. As part of our continuing studies on the synthetic utility of cationic π cyclizations of α,β-unsaturated enones[1,3] we investigated the cyclization of the enone **1**. Not surprisingly, treatment of enone **1**




with trifluoroacetic acid in trifluoroacetic anhydride[1,3b] led, in 71% yield, to a tricyclic diol assigned structure **2** in analogy with the known cyclization of alcohol **3** to tricyclic alcohol **4**.[4,5] Our interest in obtaining bicyclic products from this type of cyclization led us to examine the acetylenic enone **5**. Molecular models suggested that the geometry of the bicyclic vinyl cation **6** generated from cyclization of **5** would not favor further cyclization to a tricyclic product. In fact, the only product observed from TFA/TFAA cyclization of enone **5** was the bis(trifluoroacetate) **7**. Mild hydrolysis gave, in 85% yield, the diketone **8** as a mixture of cis and trans isomers. Based on the chemical shift of the angular methyl,[6] the major isomer is assumed to be the cis isomer. Mild base treatment of diketone **8** led to a tricyclic keto alcohol which is assigned the tricyclo[5.4.0.0$^{4,8}$]undecane structure **9**.[7]

These cyclization studies show that, in this system, use of the alkyne bond as the π participant allows isolation of bicyclic products rather than the tricyclic product obtained using an alkene bond as the π participant.[9] Application of this methodology to the synthesis of natural terpenoid systems is in progress.

## Experimental Section

The $^1$H NMR spectra were obtained on a Varian Associates HA-100 or T-60 spectrometer. The $^{13}$C NMR spectra were obtained in the Fourier transform mode on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby.

The vapor phase chromatographic (VPC) analyses were performed using a $\frac{1}{8}$ in. × 6 ft 10% Carbowax on Chromosorb W column or a $\frac{1}{8}$ in. × 6 ft 1.5% OV-101 on Chromosorb G column. All percent-composition values are reported as relative peak areas without correction for relative detector response. Preparative VPC separations for MS analyses were performed using a $\frac{1}{4}$ in. × 6 ft 10% SE-30 on Chromosorb A column.

All distillations were conducted as bulb-to-bulb (Kugelrohr) short-path distillations. The temperatures cited for these distillations are the maximum temperature of the oven during the distillation. "Brine" refers to a saturated aqueous solution of sodium chloride. Anhydrous ether was stored over sodium. *tert*-Butyl alcohol was distilled from calcium hydride.

**2-(4-Pentenyl)-3-methyl-2-cyclohexen-1-one (1).** Sodium hydride (176 mg, 7.4 mmol) was added to 80 mL of *tert*-butyl alcohol to generate sodium *tert*-butoxide. To this stirred solution was added 1.32 g (7.4 mmol) of 4-carbethoxy-3-methyl-2-cyclohexen-1-one (Hagemann's ester) in 10 mL of *tert*-butyl alcohol over a period of 20 min. Then 5-bromo-1-pentene (1 g, 6.7 mmol) in 10 mL of *tert*-butyl alcohol was added dropwise followed by 2 g of anhydrous powdered

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