Tetrahedron Vol. 36, pp. 1747 to 1751
Pergamon Press Ltd., 1980. Printed in Great Britain

THREE NEW VINYL ACETYLENES FROM THE MARINE RED ALGA *LAURENCIA*

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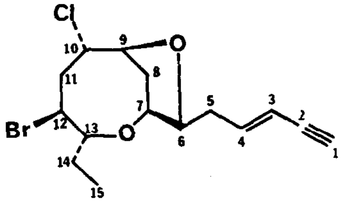
(*Received in the U.S.A. 9 August* 1979)

Abstract—The structures of three new halogenated vinyl acetylenes are described which are natural products from various species of the red seaweed *Laurencia*. The structure of chlorofucin (**1**) isolated from *Laurencia snyderae* was determined by X-ray diffraction analysis. Poiteol (**2**) was isolated from *Laurencia poitei* and its structure was also determined by single crystal X-ray diffraction experiments. The structure of obtusenyne (**3**) was based on a combination of chemical and spectral methods. The ^{13}C NMR spectra of these new compounds are presented and assignments made.

Halogenated secondary metabolites of the vinyl acetylene class are frequently encountered constituents of the marine red algal genus *Laurencia*. These substances, which are presumably derived from fatty acid biosynthesis, are all commonly related to their potential acyclic precursor laurediol.[1] The acetylenes represent a diverse and complicated structural class of *Laurencia* natural products, of which more than 30 representatives have been described.[2] In this paper we wish to present in detail the structures of three new vinyl acetylenes, chlorofucin (**1**), poiteol (**2**) and obtusenyne (**3**), which were isolated in the course of studies of various *Laurencia* species.



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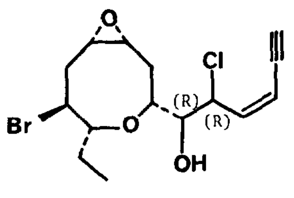

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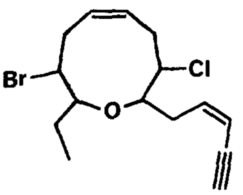

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Chlorofucin (**1**)

As part of our investigation of the natural chemical constituents of *Laurencia snyderae* Dawson from La Jolla, California, we described earlier the monobrominated sesquiterpene β-snyderol as the major lipid component.[3] From this source we now wish to describe a new vinyl acetylene, chlorofucin (**1**), which was isolated as the most abundant minor component (1% yield crude extract). Chlorofucin was isolated, as a crystalline solid, m.p. 86–88°, by silica gel chromatography of the chloroform-methanol extracts of the freshly collected alga.[4] Low resolution mass spectrometry of **1** suggested a molecular formula of $C_{15}H_{20}BrClO_2$ (M^+ *m/e* 346/348/350). The IR spectrum of **1** showed the presence of a terminal acetylene function (γ_{C-H} 3300 cm^{-1}), and the absence of the OH and CO groups. The high resolution ^1H NMR spectrum of **1** presented signals which could be assigned to a *trans* ene-yne function [5.50(1 H), d, 15 Hz; 6.09(1 H), ddd, 15, 7, 7 Hz; and 2.66(1 H), d, 2 Hz) and to an ethyl group [1.68(2 H), m and 1.07 (3 H), t, 7 Hz]. Six down-field one-proton multiplets (3.86–4.43) were also observed and assigned as α-ether and α-halogen protons. The ^{13}C NMR spectrum (Table 1) of **1** confirmed its molecular formula and revealed the presence of four carbons bearing oxygen in two ether linkages [84.0d, 83.0d, 79.3d and 69.9d]. Carbons bearing bromine and chlorine were observed at 51.4d and 61.2d, respectively. The *trans* ene-yne functionality was again recognized by carbon resonances at 76.4d, 82.2s, 111.3d and 141.8d. Four methylene carbons were observed (38.3t, 33.2t, 32.5t and 23.0t ppm), in addition to a single methyl group (11.7q ppm). Catalytic hydrogenation of **1** over Pd in diethyl ether gave in high yield the hexahydro derivative **4**, which provided a ^1H NMR spectrum similar to **1** except for the absence of the protons attributable to the ene-yne function. Based on mass spectral and ^{13}C NMR data chlorofucin was deduced to be bicyclic. Since only small quantities of **1** were available, the structure elucidation was completed by single crystal X-ray diffraction analysis. A computer generated perspective drawing of chlorofucin is presented in Fig. 1.

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Table 1. ^{13}C NMR assignments[a]

Carbon	**1**[b]	**2**[c]	**3**[d]	**6**[d]
1	76.4	84.4	83.0	82.8
2	82.2	79.4	80.3	80.0
3	111.3	111.3	110.0	110.9
4	141.8	142.2	140.9	141.1
5	38.3	61.0	35.6	35.8
6	84.0*	75.6	77.9†	72.3
7	69.9*	86.4	63.6	67.4
8	33.2	33.6	32.1	33.0
9	83.0*	52.7*	128.9*	131.7
10	61.2	53.3*	130.7*	126.0
11	32.5	NA	31.6	27.1
12	51.4	50.7	56.8	41.5
13	79.3*	80.6	75.4†	210.0
14	23.0	27.0	29.0	35.8
15	11.7	7.3	10.4	7.9

[a] Chemical shifts are reported in ppm relative to TMS(0); assignments were aided by off-resonance decoupling.

[b] Recorded in $CDCl_3$ solution.

[c] Recorded in d_6-acetone solution.

[d] Recorded in d_6-benzene solution.

*Assignments may be reversed.

†Assignments may be reversed.

NA Signal obscured by d_6-acetone.

Chlorofucin is closely related to another vinyl acetylene laurefucin, in that there is a chloro group at C-10 in chlorofucin rather than a hydroxyl as in laurefucin. In an attempt to relate these two natural products, **1** was treated with silver acetate in glacial acetic acid. This reaction yielded **5**, which contains an epimeric mixture of acetates at C-12. The C-10 chlorine appeared to be unreactive to these conditions and further attempts to interrelate these substances failed.

Poiteol

In chemical studies of Atlantic and Caribbean *Laurencia* species, we have investigated *L. poitei* from which the nonhalogenated rearranged sesquiterpene alcohol poitediol has been described.[5] Further studies of the extracts of this alga have now yielded a new halogenated vinyl acetylenic alcohol. Open column silica gel chromatography of the chloroform-methanol extract of

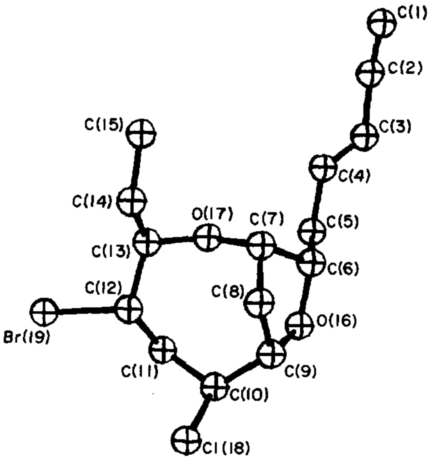
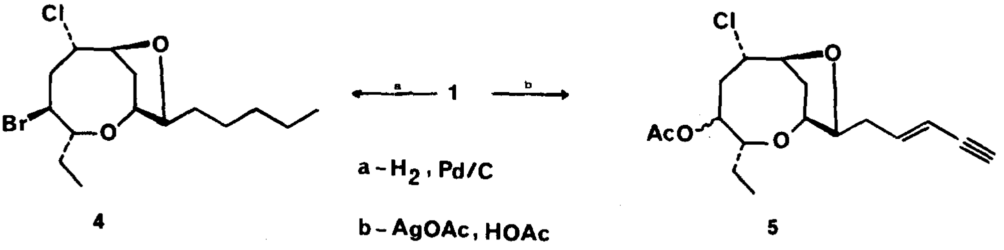


Fig. 1. The final X-ray model of chlorofucin. Both C(6) and C(7) have S absolute stereochemical designators.



Laurencia poitei, collected at Harry Harris State Park, Florida Keys, Florida (1974), yielded poiteol (2) as a crystalline solid, m.p. 151–154°. The IR spectrum of 2 showed both OH ($3450\,cm^{-1}$) and terminal acetylene functions ($3300\,cm^{-1}$). The ^1H NMR spectrum of poiteol showed resonances which were assigned to the *cis* ene-yne function [6.25(1 H), dd, 10, 10 Hz; 5.66(1 H), dd, 10, 2 Hz; and 3.27 (1 H), d, 2 Hz] and to an ethyl group [0.98(3 H), t, 7 Hz; 2.04(1 H) m]. The remainder of the NMR spectrum presented an extremely complex set of unassignable proton multiplets between 5.43 and 2.10 ppm. The ^{13}C NMR spectrum (Table 1) confirmed the presence of the pentene-yne system and showed resonances assigned to additional carbons bearing epoxide, hydroxyl, chlorine, bromine and the ether functions. To solve the structure of this interesting and more complex acetylene, poiteol was subjected to a single crystal X-ray diffraction experiment. Figure 2 illustrates a computer-tenerated perspective drawing of poiteol which defines absolute stereochemistry.

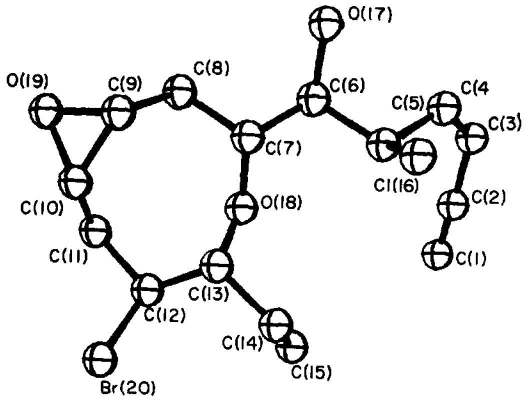
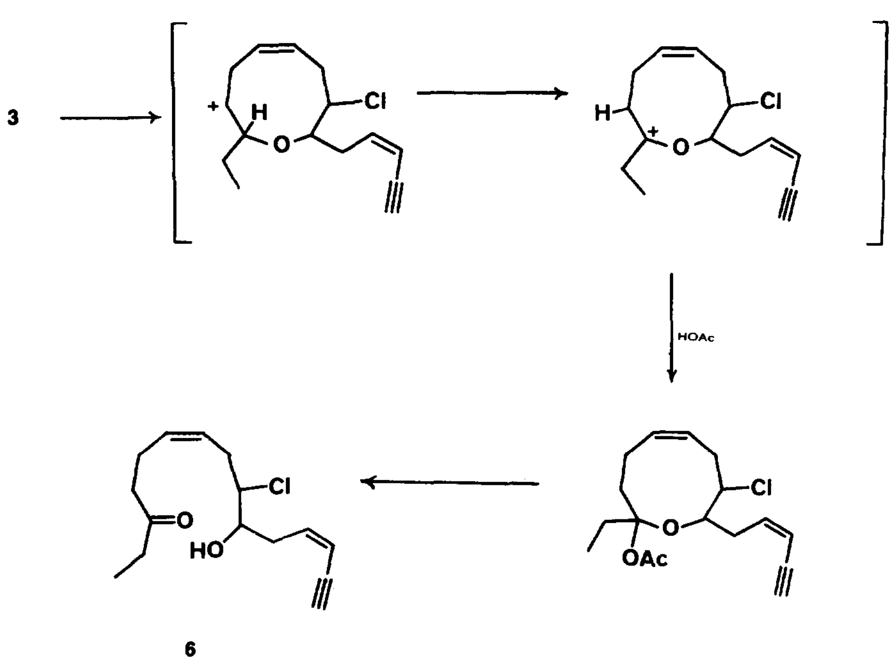


Fig. 2. Computer generated perspective drawing of the final X-ray model of poiteol less hydrogens. Bond distances and angles generally agree well with anticipated values, and C(6) and C(7) have R absolute stereochemical designators.

Obtusenyne

In our chemical studies of *Laurencia* species from the Mediterranean Sea several populations of *Laurencia obtusa* have been examined. While *Laurencia obtusa* from Spain and Greece mainly contain terpenoid products,[6] material from Positano, Italy wwas found to contain only halogenated acetylenes. From this alga a unique nine-membered ring acetylene obtusenyne (3) has been isolated. Obtusenyne was isolated in 1% yield from the crude extract of *L. obtusa* by silica gel chromatography of the chloroform-methanol extract. Compound 3 was analyzed by high resolution mass spectrometry and determined to have a molecular formula of $C_{15}H_{20}BrClO$ (observed 330.0388; calculated 330.0386). In addition, prominent fragments were observed at *m/e* 295 for $C_{15}H_{29}BrO$ (M^+–Cl) and *m/e* 265 for $C_{10}H_{15}BrClO$ (M^+–C_5H_5). The IR spectrum of obtusenyne showed the presence of the terminal acetylene function ($3300\,cm^{-1}$). The ^1H NMR spectrum of 3 exhibited bands which could be assigned to a *cis* ene-yne function [δ6.00 (1 H), ddd, 12, 8, 8 Hz; 5.49 (1 H), d, 12 Hz; and 3.07 (1 H), d, 2 Hz] and to an ethyl group [δ 0.91(3 H), t, 7 Hz; 1.84(1 H) m; and 1.50 (1 H) m] which are now common and readily recognized features of this structural class. A two proton multiplet at δ 5.64, however, indicated that 3 possessed further unsaturation. In addition, four signals between δ 3.84 and 4.20 were assignable to an α-bromine, an α-chlorine and two α-ether protons. The ^{13}C NMR spectrum (Table 1) confirmed the presence of the pentene-yne function and the additional disubstituted double bond in the molecule. Carbon resonances at 56.8d, 63.6d, 77.9d and 75.4d ppm were assigned to carbons bearing bromine, chlorine and oxygen (ether), respectively. From



Scheme 1.

mass spectral and NMR data obtusenyne was recognized as a cycle ether, however, the ring size was not suggested from these data.

Treatment of obtusenyne with silver acetate in glacial acetic acid at 25° for 8 hr gave a keto alcohol, in 80% yield, which was assigned structure **6**. The IR spectrum of **6** showed OH ($3450\,\mathrm{cm}^{-1}$), terminal acetylene ($3300\,\mathrm{cm}^{-1}$) and CO absorptions ($1715\,\mathrm{cm}^{-1}$). The CO group was assigned at C-13 based on an intense C_2H_5 fragmentation in the mass spectrum, and ^{13}C NMR (Table 1) signals at 35.8t (C-14) and 7.9q (C-15) which are indicative carbon resonances of ethyl ketones.[7] ^{13}C NMR data also confirmed the loss of bromine and the maintenance of chlorine in this compound. To locate the carbon which bears OH, a qualitative lanthanide induced shift-decoupling study was conducted. This study served to link the ene-yne function to the methylene at C-5 which was, in turn, coupled to an α-OH proton firmly established at C-6. The C-6 proton was further coupled to the α-chlorine proton at C-7 and the C-7-proton was subsequently shown to be adjacent to two methylene protons at C-8 and homoallylic to an olefinic bond at C-9–C-10.

The mechanism of the aforementioned selective and high yielding silver acetate reaction is proposed in Scheme 1. Removal of bromide by silver ion yields the intermediate carbonium ion at C-12 which undergoes a 1,2 hydride shift to form the more stable carbonium ion intermediate carbonium ion at C-11. Subsequent carbonium ion trapping with acetate yields an intermediate hemiketal acetate, which upon work-up with aqueous sodium bicarbonate gives the ring open keto alcohol **5**.

Since the CO group in **6** is at C-13 and the OH has been established to be at C-6, obtusenyne must possess a 9-membered ring. Obtusenyne is the first example of a 9-membered ring ether in this class.[8]

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian HR-220 spectrometer, ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer, and IR spectra were recorded on a Perkin–Elmer model 137 spectrophotometer. Low resolution mass spectra were obtained on a Hewlett–Packard 5930A mass spectrometer and high resolution mass spectra were obtained through the Department of Chemistry, UCLA.

Isolation of chlorofucin (**1**). Crude extract (20 g), obtained from the 1:1 $CHCl_3$–MeOH extraction of dried *Laurencia snyderae* (North Bird Rock, La Jolla, California, 1975), was applied to a column containing 200 g of silica gel (Grace Chemical). The column was eluted with a solvent gradient system from petroleum ether to benzene. Chlorofucin was isolated directly as a crystalline solid from fractions eluted with 10% benzene–petroleum ether, it was recrystallised from $CHCl_3$ (m.p. = 86–88°) and showed the following spectral features: $[\alpha]_D^{20} + 12.0°$ (c 1.4, $CHCl_3$) Mass spectrum: M^+ m/e 346/348/350 for $C_{15}H_{20}BrClO_2$. IR spectrum (CCl_4) 3300, 3010, 2950, 1450, 1420, 1380 1360, 1240, 1190, 1150, 1120, 1105, 1080, 1060, 1020, 970, 960, 925, 880 and $860\,\mathrm{cm}^{-1}$. ^1H NMR spectrum (220 MH_z), $CDCl_3$) δ 6.09 (1 H, ddd J = 15,7,7), 5.50 (1 H, d J = 15), 4.43 (1 H, m), 4.23 (1 H, m), 4.23 (1 H, m), 4.14 (1 H, bs), 3.98 (1 H, bs), 3.86 (1 H, m), 3.68 (1 H, m), 2.66 (1 H, d J = 2), 1.68 (2 H, m), 1.07 (1 H, t J = 7).

X-Ray crystallographic analysis of **1**. Crystals of chlorofucin were found to belong to the orthorhombic crystal class. Accurate lattice constants, determined from a least-squares fit of fifteen diffractometer measured 2θ values between 35° and 45°, were $\mathbf{a} = 9.203(1)$, $\mathbf{b} = 10.118(1)$ and $\mathbf{c} = 17.577(2)$. Systematic extinctions uniquely required the space group $P2_12_12_1$ and a density measurement indicated one molecule of composition $C_{15}H_{20}BrClO_2$ in the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer controlled four-circle diffractometer using graphite monochromated CuKα (1.54178 Å) radiation and a variable speed ω-scan. Periodically monitored standard reflections showed a slow decrease in intensity of ~5% during the time of data collection. After correction for Lorentz, polarization and background effects, 1193 (92%) of the reflections were judged observed ($F_0^2 \geq 3\sigma(F_0^2)$).

The position of the Br was deduced from the Patterson synthesis and the nonhydrogen atoms were located on subsequent electron density synthesis.[9] Hydrogens were located on a difference synthesis following partial refinement. Full matrix least squares refinements with anisotropic temperature factors for the nonhydrogen atoms, isotropic hydrogens and anomalous scattering corrections for Br and Cl have converged to a standard crystallographic residual of 0.049. The enantiomeric structure refined to a significantly higher 0.054.[10] Further crystallographic details can be found in the Supplementary Material described at the end of this paper.

Catalytic hydrogenation of **1**. Chlorofucin (50 mg) was dissolved in anhyd diethyl ether (30 ml) and added to a 50 ml filter flask containing a catalytic amount of 10% Pd–C (10 mg) and a magnetic stirring bar. The reaction vessel was fitted with a balloon and septum, purged with hydrogen and the balloon filled. After stirring at 25° for 8 hr, the hydrogen was removed, the solution filtered and the ether evaporated to yield the hexahydro derivative **4**, as an oil which did not require further purification. ^1H NMR spectrum: (220 MHz, $CDCl_3$) δ 4.55 (1 H, m), 4.27 (1 H, m), 4.00 (1 H, bs), 3.91 (1 H, m), 3.75 (1 H, m), 3.34 (1 H, m), 2.47 (1 H, dd J = 18,4), 1.07 (3 H, t J = 7), 0.91 (3 H, bt).

Silver acetate treatment of **1**. A soln of 100 mg of **1** in glacial AcOH was added slowly with stirring at room temp to a suspension of excess AgOAc in glacial AcOH. The mixture was stirred for 48 hr, filtered and the filtrate washed with ether. The ether–acetic acid soln was washed with water, followed by sat $NaHCO_3$aq, dried ($MgSO_4$), filtered and evaporated to yield a yellow oil. Thick layer chromatography on silica gel gave **5** (10 mg) as an inseparable epimeric mixture of acetates at C-12. ^1H NMR spectrum: (220 MHz, $CDCl_3$, incomplete) δ 2.05 (3 H, s) and 2.07 (3 H, s) OAc, 5.05 (1 H, m) and 4.93 (1 H, m) α-OAc, 6.27 (1 H, ddd J = 15,7,7) and 6.18 (1 H, ddd J = 15,7,7) C-3, 5.59 (1 H, d J = 18) and 5.82 (1 H, d J = 15).

Isolation of Poiteol (**2**). *Laurencia poitei* was collected in 1974 (Harry Harris State Park, Florida), air dried and Soxhlet extracted with chloroform methanol (1:1). 1 kg of dried alga yielded 30 g of dark green crude extract. The crude extract (30 g) was applied to a column containing 300 g of silica gel. The column was gradient eluted with pet. ether, benzene, diethyl ether mixtures. Poiteol crystallized from the polar fractions (diethyl ether, m.p. 151–154°) and provided the following spectral features: $[\alpha]_D^{20} + 116.7°$ (c 1.0, $CHCl_3$). ^1H NMR spectrum (220 MHz, $CDCl_3$) δ 6.25 (1 H, dd J = 10,10), 5.66 (1 H, dd J = 10,2), 5.43 (1 H, dd J = 10,2), 4.14 (1 H, m), 3.72 (1 H, m), 3.72 (1 H, m), 3.56 (2 H, m), 3.36 (1 H, m), 3.27 (1 H, d J = 2), 3.11 (1 H, m), 2.72 (1 H, m), 2.59 (1 H, m), 2.04 (1 H, m), 1.89 (1 H, m), 0.98 (3 H, t J = 7). IR spectrum: (KBr) 3450, 3300, 3010, 2950, 2900, 1460, 1440, 1090, 1060, 900 and $780\,\mathrm{cm}^{-1}$.

X-Ray crystallographic analysis of **2**. Crystals of poiteol were found to belong to the orthorhombic crystal class. Unit cell constants, determined by a least-squares fit of fifteen diffractometer measured 2θ-values between 35° and 45°, were $\mathbf{a} = 8.809(3)$, $\mathbf{b} = 9.752(4)$ and $\mathbf{c} = 18.936(7)$. Systematic extinctions were uniquely consistent with space group $P2_12_12_1$ and a density measurement indicated one molecule of composition $C_{15}H_{20}BrClO_3$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer controlled four-circle diffractometer using graphite monochromated CuKα radiation and a variable speed ω-scan. A smooth decay of ~10% was noted in periodically monitored standard reflections during the course of data collection. A total of 1308 reflections were surveyed and after correction for Lorentz, polarization and background effects, 1022 (78%) were judged observed ($F_0^2 \geq 3\sigma(F_0^2)$).

The Br atom position was determined via the Patterson synthesis and nonhydrogen atoms were located in subsequent electron density syntheses.[11] Hydrogens were located in a difference electron density synthesis after partial refinement. Full matrix least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms, isotropic hydrogens and anomalous scattering corrections for Br and Cl have converged to a standard crystallographic residual of 0.069. The enantiomeric structure gave a significantly higher 0.073 residual.[10] Further crystallographic details can be found in the Supplementary Material described at the end of this article.

Isolation of obtusenyne (**3**). Obtusenyne was isolated as an oil in 1% (crude extract) yield from air dried *Laurencia obtusa* (Positano, Italy, 1975) utilizing standard open column silica gel chromatography (15% benzene–petroleum ether elution). Obtusenyne provided the following spectral features: $[\alpha]_D^{20}+111.4°$ (c 2.8, $CHCl_3$). Mass spectrum M^+ m/e 330/332/334 for $C_{15}H_{20}BrClO$. IR spectrum (CCl_4) 3300, 2950, 1450 and 1200 cm^{-1}. ^{1}H NMR spectrum (220 MHz, CCl_4) δ 6.00 (1 H, ddd J = 12,8,8), 5.64 (2 H, m), 5.49 (1 H, d J = 12), 4.20 (2 H, m), 4.00 (1 H, m), 3.84 (1 H, m), 3.07 (1 H, d J = 2), 1.84 (1 H, m), 1.50 (1 H, m), 0.91 (1 H, t J = 7).

Silver acetate treatment of **3**. The same procedure was used here as in the treatment of **1**. The reaction was allowed to run for 8 hr. The product was isolated as an oil by thick layer chromatography (25% diethyl ether–petroleum ether) in 80% yield and provided the following spectral features: IR spectrum (film) 3450, 3300, 2950, 1750 and 1150 cm^{-1}. ^{1}H NMR spectrum (220 MHz, $CDCl_3$) δ 6.14 (1 H, ddd J = 12,8,8), 5.61 (1 H, d J = 12), 5.45 (2 H, m), 3.94 (1 H, m), 3.82 (1 H, m), 3.16 (1 H, bs), 1.02 (3 H, t J = 7).

Acknowledgements—This work is a result of research supported at the Scripps Institution by NOAA, Office of Sea Grant, Department of Commerce, under Grant No. 04-7-158-44121 project R/MP-18. The U.S. Government is authorized to produce and distribute reprints for governmental purposes, notwithstanding any copyright notation that may appear hereon. The authors are grateful for the close taxonomic guidance provided by Dr. Jim Norris, Smithsonian Institution, Washington, D.C.

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[8] While this work was in progress we became aware of the studies by R. H. Thomson *et al.* on obtusenyne. Comparison of samples between labs showed them to be identical. Their structure elucidation was aided by X-ray crystallography and confirms our structure proposal. The absolute stereochemistry is 6(S), 7(S), 12(S), 13(S). T. J. King, S. Imre, A. Oztunc and R. H. Thomson, *Tetrahedron Letters* 1453 (1979).

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