(*N,N*-dibutylcarbamoylmethyl)phosphonate (**3b**). However, the reaction temperature was increased to 25 °C and the stirring rate to 500 rpm. The first product observed (20 min) by monitoring the progress of the reaction was **3b**. However, as the reaction proceeded, a new product, eluting earlier than **3b**, steadily grew in concentration. A large amount of precipitate began to accumulate which eventually precluded syringe sampling. After a reaction time of 16 h, 100 mL of water was slowly added to aid dissolution of the accumulated precipitate. The phases were separated, and the aqueous layer was washed with 100 mL of methylene chloride. The organic layers were combined and worked up as previously described to yield only 12.7 g of an amber oil which was analyzed by GLC and found to be predominantly comprised of the new product (59%) and **3b** (4%). Distillation yielded a fraction [7.9 g; bp 105–106 °C (0.35 mmHg)] of a colorless oil which was the new product in 93% purity. NMR, IR, and GC/M identified the product as *N,N*-dibutyl-*n*-butoxyacetamide (**15b**). No products resulting from alkylation of possible intermediate **14b** could be detected.

Preparation of Tertiary (Carbamoylmethyl)phosphine Oxides 10. Into a 500-mL, three-necked, round-bottomed flask equipped with a thermowell, a mechanical stirrer, a condenser, and a septum was placed a solution of 0.11 mol of the chloroacetamide, 1.0 g of tetra-*n*-hexylammonium chloride, and 0.10 mol of the dialkylphosphine oxide in 150 mL of methylene chloride along with 100 mL of 50% sodium hydroxide. The solution was stirred at 300 rpm under a gentle reflux until GLC analysis of removed aliquots indicated the consumption of the starting materials. Workup as before (vide supra) produced the product, **10**, data for which are summarized in Tables I and II.

Preparation of Chloroacetamides 2. An adaptation of the Schotten–Baumann procedure was found most suitable. Thus, into a three-necked, round-bottomed flask equipped with a thermowell, a mechanical stirrer, a 250-mL pressure-equalizing addition funnel, and inert gas fittings was placed a solution of 0.10 mol of the amine in 100 mL of methylene chloride along with 100 mL of 20% by weight sodium hydroxide solution. With the temperature maintained at −25 °C under a gentle nitrogen purge and a stirring rate of 150 rpm, a solution of 12.4 g (0.11 mol) of chloroacetyl chloride in 50 mL of methylene chloride was added dropwise. When the addition was complete, the reaction mixture was allowed to stir an additional 15 min and then was transferred to a 500-mL separatory funnel. The phases were separated, and the aqueous layer was washed with three 50-mL portions of methylene chloride. The combined organic layer was washed with a solution comprised of 100 mL of saturated sodium chloride and 5 mL of concentrated hydrochloric acid, dried ($MgSO_4$), concentrated, and distilled under reduced pressure (Table III).

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Registry No. 2b, 2567-59-1; **2d**, 2675-89-0; **2g**, 20266-00-6; **2m**, 32461-85-1; **3a**, 7439-68-1; **3b**, 66258-30-8; **3c**, 7369-66-6; **3d**, 79373-07-2; **3e**, 79373-08-3; **3g**, 79391-52-9; **3h**, 66258-31-9; **3j**, 79373-09-4; **3k**, 79373-10-7; **3l**, 79373-11-8; **3m**, 79391-53-0; **6b**, 1809-19-4; **6c**, 6151-90-2; **6d**, 79373-12-9; **6e**, 3658-48-8; **6f**, 1809-14-9; **6j**, 79373-13-0; **6k**, 79373-14-1; **6l**, 13086-87-8; **8b**, 15754-54-8; **8f**, 3011-82-3; **10b**, 79373-15-2; **10f**, 79391-54-1; **10i**, 79391-55-2; chloroacetyl chloride, 79-04-9; *N*-butyl-1-butanamine, 111-92-2; *N*-methylmethanamine, 124-40-3; pyrrolidine, 123-75-1; 2-ethyl-1-hexanamine, 104-75-6.

Marine Natural Products: Halogenated Acetylenic Ethers from the Sea Hare *Aplysia Dactylomela*[1]

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From the extracts of a Caribbean sea hare, *Aplysia dactylomela*, one new halogenated sesquiterpene ether, **8**, isodeodactol ($C_{15}H_{25}O_2Br_2Cl$), and two isomeric pairs of new C_{15}-halogenated ethers having straight-chain carbon skeletons have been isolated: **3** and **4** ($C_{15}H_{20}OBrCl$); **5** and **6** ($C_{15}H_{20}O_2BrCl$). Compounds **3–6** belong to a class of fatty acid derived ethers characterized by ether rings of various sizes and a terminal enyne moiety. X-ray analysis confirmed that **3**, (3*E*)-12-*epi*-obtusenyne, contains a nine-membered ether ring with a trans terminal enyne group. Spectral analysis and chemical correlation established that **4** differs from **3** only in having a cis terminal enyne group. Ether **5** was found by X-ray analysis to have a cis-fused 1,5-dioxodecalin skeleton and a trans terminal enyne group. Detailed spectral analyses confirmed that ether **6** is the 3*Z* isomer of **5**. The structure of isodeodactol, **8**, was established by spectral analysis.

In previous work with extracts of the sea hare *Aplysia dactylomela*, we have isolated a variety of compounds[2] including the two halogenated ethers dactylyne (**1**)[3] and isodactylyne (**2**)[4] (Chart I). These ethers are representatives of a group of related ethers[5] of algal origin characterized by a straight-chain C_{15} carbon skeleton and a terminal enyne functionality. The extracts from *A. dactylomela* are rich in organics, and in this paper we describe the isolation of five new halogenated ethers, **3–6** and **8**, four of which belong to the group represented by **1** and **2**. All of the *Aplysia* isolates are considered to be of algal origin since such a dietary source has been established for

(1) This research was supported by Grants CA 17256 and 17562 awarded by the National Cancer Institute.

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Table I. Physical and Selected Spectral Properties of 3-6 and 8

compd	formula	mp, °C	$[\alpha]_D$ ($CHCl_3$), deg	UV (95% EtOH), nm (ϵ)
3	$C_{15}H_{20}OBrCl$	72-73	+73 (*c* 1.34)	225 (13 000)
4	$C_{15}H_{20}OBrCl$	oil	+73.5 (*c* 1.34)	224 (12 600)
5	$C_{15}H_{20}O_2BrCl$	74-75	−15.9 (*c* 0.63)	225 (15 800)
6	$C_{15}H_{20}O_2BrCl$	119-120	−21.3 (*c* 1.63)	221 (13 700)
8	$C_{15}H_{25}O_2Br_2Cl$	158-160	+18.9 (*c* 18.9)	

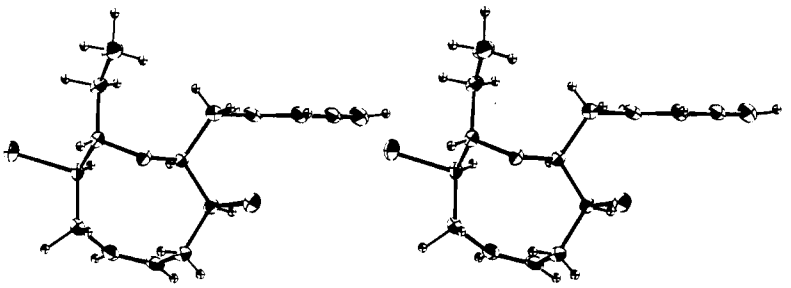

Figure 1. Stereoview of a single molecule in compound 3. The thermal elliposoids represent 50% probability.[18]

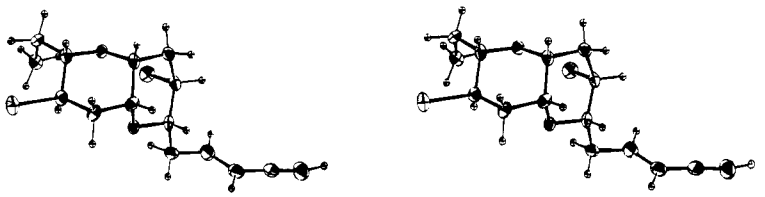

Figure 2. Stereoview of a single molecule in compound 5. The thermal elliposoids represent 50% probability.[18]

Aplysia californica metabolites.[6]

The new ethers were isolated from alcohol extracts of sea hare digestive glands through the following succession of steps: solvent partitioning, Sephadex LH-20 and silica gel chromatography, and, finally, high-pressure liquid chromatography (HPLC) over silica gel. The molecular formulas derived from X-ray diffraction data and/or high- or low-resolution mass spectral data, melting points, optical rotations, and UV data for 3–6 and 8 are summarized in Table I.

Compounds 3–6 were readily identified as ethers related to 1 and 2 by their C_{15} carbon skeletons, UV absorptions, and ^1H NMR resonances (see Table II), characteristic of *E* and *Z* terminal enyne groups (see H_1–H_4 signals). No hydroxyl or carbonyl absorptions were present in their IR spectra.

Comparison of the ^1H NMR data for 3 and 4, which have identical molecular formulas, indicated that these were an isomeric pair of compounds, each possessing two double bonds, see signals for H-3,4 and H-9,10. The similarity of the chemical shift and multiplicity data for all signals except those of H-1 and H-3 indicated that the compounds differed in structure only in configuration of the C-3,4 double bond, with 3 having the *E* configuration and 4 the *Z*. Detailed analysis of the ^1H NMR coupling data (Table II) allowed formulation of 3 and 4, without stereochemical detail, as possible structures. However, from this spectral data it was not possible to rigorously exclude alternate structures arising from interchange of heteroatom positions.

Ethers 5 and 6, designated (3*E*)- and (3*Z*)-dactomelyne, respectively, have identical molecular formulas with one more oxygen than 3 or 4. The ^1H NMR spectra of 5 and 6 each contain only two olefinic proton signals (see Table II, H-3,4) which could be assigned to a terminal enyne group on the basis of coupling between H-1 and H-3 and also from UV data. The magnitude of the coupling constants for H-3 and H-4 in 5 and 6 revealed that the configuration of the enyne double bond in 5 ($J_{3,4}$ = 16 Hz) is *E* while that in 6 ($J_{3,4}$ = 11 Hz) is *Z*. Since the ^1H NMR signals for protons on carbons 7 to 15 in 5 and 6 were virtually identical, these ethers were also considered to have identical structures except for the double bond ge-

Chart I

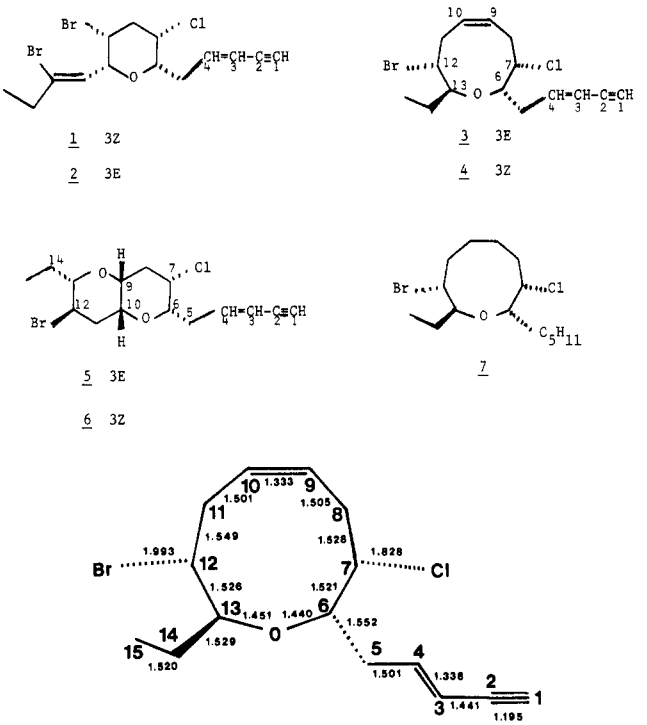

Figure 3. Chemical structure, numbering scheme, and bond distances (Å) for compound 3. Estimated standard deviations vary from 0.004 to 0.009 Å.

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Table II. ^{1}H NMR (360 MHz) Data for Ethers 3-6 in $CDCl_3$[a]

H on C	shift,[c] δ 3	4	5	6
1	2.85 (d, ~2)	3.18 (d, ~2)	2.83 (d, 2)	3.13 (d, 2)
3	5.62 (d, 16, ~2)	5.57 (d, 11, ~2)	5.62 (dd, 16, 2)	5.58 (d, 11, ~2)
4	6.05 (ddd, 16, 8, 8)	5.99 (m, 11, 8, 8)	6.22 (ddd, 16, 7.4, 7.4)	6.10 (ddd, 11, 7, 4.7, 4)
5	2.57 (m, 13, 8, 4), 2.82 (m, 13, 8)	2.82 (m, 14, 10, 8), 2.95 (m, 14, 8, 5)	2.45 (m, 2.56 (m)	2.70 (m), 2.75 (m)
6	3.68 (m)	3.77 (m)	3.47 (m)	3.56 (m)
7	3.83 (dd, 10, 10)	3.84 (m)	3.92 (m)	3.94 (m)
8	2.77 (m), 3.22 (br m)	2.75 (m, 14, 7), 3.25 (br m)	2.14 (m), 2.41 (br d, 15)	2.17 (m), 2.44 (br d, 15)
9	5.85 (m, 10, 10, 7)	5.85 (ddd, 10, 10, 7)	3.47 (m)	3.48 (m)[b]
10	5.46 (m, 10, 10, 4)	5.49 (ddd, 10, 10, 4)	3.59 (m)	3.60 (m)[b]
11	2.47 (m, 13, 4), 3.07 (m, 13, 11, 11)	2.46 (m, 12, 4), 3.10 (dd, 10, 12)	2.08 (m), 2.61 (m)	2.08 (m), 2.62 (m)
12	3.91 (m, 9, 11)	3.88 (m)	4.16 (ddd, 12, 10, 4)	4.18 (ddd, 12, 10, 4)
13	3.95 (m)	3.92 (m)	3.34 (m, 10, 5.5, 2.7)	3.34 (m, 10, 5.5, 2.7)
14	1.60 (m, 15, 7, 9), 2.19 (m, 15, 7)	1.80 (m, 15, 9.5, 7), 2.22 (m, 15, 7)	1.75 (m, 14.7), 1.90 (m, 14, 7, 2.7)	1.76 (m, 14, 7), 1.90 (m, 14, 7, 2.7)
15	1.04 (t, 7)	1.08 (t, 7)	0.98 (t, 7)	0.98 (t, 7)

[a] Assignments confirmed by homonuclear decoupling. [b] Assignments may be reversed. [c] Multiplicities and J values (in hertz) are given in parentheses.

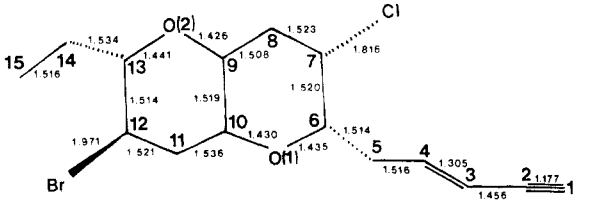

Figure 4. Chemical structure, numbering scheme and bond distances (Å) for compound **5**. Estimated standard deviations vary from 0.006 to 0.009 Å.

ometry. No structure, however, could be assigned unequivocally on the basis of ^{1}H NMR data.

Definitive structures for **3** and **5** were obtained by single-crystal X-ray diffraction analysis. Stereoscopic views of **3** and **5** are shown in Figures 1 and 2. Atom numbering, bond distances, and absolute configuration for both molecules are shown in Figures 3 and 4. Torsion angles and bond angles are available as supplementary material.

Both **3** and **5** contain a C_5 terminal enyne side chain, with a trans double bond [C(3)–C(4)], Cl substitution at C(7), and Br substitution at C(12). The absolute configuration at the chiral centers C(6), C(7), C(12), and C(13) is the same in both compounds: *S*, *S*, *R*, and *S*, respectively. Ether **5** also has 9(*R*),10(*S*) configuration. The nine-membered ether ring in **3** is uncommon but has been observed previously in obtusenyne,[7] isolated from *Laurencia obtusa*. Thus **3** is (3*E*)-12-*epi*-obtusenyne.

The bond distances in **3** and **5** are normal. Both rings in compound **5** are in the chair conformation and are cis-fused. The nine-membered ring in **3** shows strain which can be seen in the larger than normal endocyclic bond angles and several unusual endocyclic torsion angles. The conformation for C(5)–C(6) is the same in both compounds, but it is different for C(4)–C(5).

The complete structure for **4**, including the absolute configuration shown, was obtained by ^{1}H NMR analysis and chemical correlation with **3**. The conjugated enyne and the isolated double bond in **4** were assigned *Z* configurations on the basis of their 10–11 Hz coupling constants (see Table II). Catalytic hydrogenation of **4** with platinum in ethanol for 10 min yielded an oily octahydro derivative, **7** [$C_{15}H_{28}OBrCl$, $[\alpha]_D$ +2.63° (*c* 0.57, $CHCl_3$)], that retained all the chiral centers of the natural product and which was identical with the octahydro derivative obtained from **3** as judged by IR, mass, and ^{1}H NMR spectra and optical rotation. Thus **4** is 12-*epi*-obtusenyne.

The structure for compound **6**, (3*Z*)-dactomelyne, is based on a comparison of its spectral data with those of **5**, especially the high-resolution ^{1}H NMR data. The presence in **6** of a *Z* terminal enyne moiety is evident from UV data (Table I), the 11-Hz coupling of the olefinic protons (H-3,4) with each other, and the 2-Hz coupling of H-3 with the acetylenic proton, H-1. The acetylenic proton resonance in **6** occurs slightly farther downfield, δ 3.13, than the corresponding proton in **5**, just as is noted for similar *E*/*Z* pairs such as **1**/**2** and **3**/**4**. The olefinic proton H-4 is coupled to a pair of methylene protons (δ 2.70, 2.75), and these in turn are coupled to a single proton at δ 3.56 (H-6). This sequence provides evidence for postulating the same C(1) to C(6) skeleton in **6** as in **5**. The chemical shifts and multiplicities in the remainder of spectrum of **6** are identical with those in **5**, and thus an identical substitution and relative stereochemical pattern was assigned. The magnitude of the small downfield field shift (~0.1 ppm) of the H-6 proton in **6** relative to H-6 in **5** is the same as that noted for H-6 in **4** vs. **3**. Since this shift is attributable to the difference in double bond configuration at C(3,4), the relative position of oxygen and chlorine at C(6) and C(7), respectively, appears to be on solid ground. It appears highly likely that the absolute configurations of **5** and **6** are identical both on biogenetic grounds and from comparison of their optical rotations (see Table I). (3*Z*)-Dactomelyne with its cis double bond exhibits a larger rotation than **5**, a trend that is also evident in comparing the rotations of **1** with **2** and **3** with **4**.

The molecular formula for compound **8**, designated isodeodactol (Chart II), was established by a combination of low- and high-resolution mass spectral analysis. The highest mass peaks in the high-resolution spectrum occurred at *m*/*e* 351.0706 and 353.069 69, corresponding to $C_{15}H_{25}O_2ClBr$ (M^+ – Br) while a low-resolution spectrum (probe temperature 40 °C) yielded a series of ions at *m*/*e* 412.9, 415.1, 417.0, and 419.0, compatible with the formula $C_{15}H_{25}O_2ClBr_2$. The infrared spectrum contained hydroxyl absorption (3560 cm^{-1}) but lacked any carbonyl or triple bond absorption, and the ^{13}C spectrum revealed that there were no olefinic carbons. Thus, the two degrees of unsaturation required by the formula must be due to two rings. The 270-MHz ^{1}H NMR spectrum of **8** showed singlet ab-

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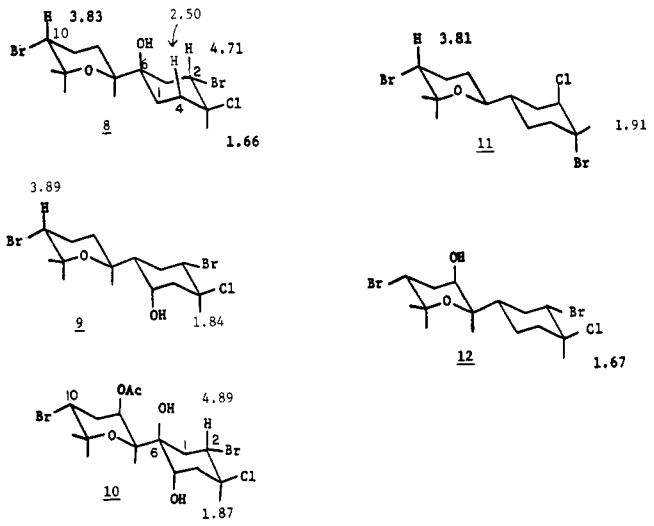
Chart II



sorptions for four quaternary methyl groups (δ 1.25, 1.32, 1.43, and 1.66), all of which must be deshielded by heteroatoms. Two one-proton signals occurred at δ 3.83 (dd, J = 11.5, 4.2 Hz) and 4.71 (dd, J = 13, 4.7 Hz), indicative of two molecular fragments of the type $CHXCH_2$ present in six-membered rings with an axial orientation for the deshielded protons. The chemical shift and multiplicity of these protons, as well as the position of the quaternary methyl signals, were very similar to absorptions found in the spectra of the sesquiterpene ethers deodactol[8] (**9**) and dihydroxydeodactol monoacetate[9] (**10**) isolated earlier by us from *A. dactylomela*, and also in those of 8-deoxyisocaespitol[10] (**11**) and caespitol[11] (**12**). Hence, the new ether was tentatively assigned structure **8**.

The elemental composition of the two rings proposed for isodeodactol (**8**) was supported by high-resolution mass spectral fragmentation data. Prominent ions were observed at m/e 205.025 63 ($C_8H_{14}O^{79}Br$), corresponding to the tetrahydropyran ring with its substituents, and also at 224.969 63/226.967 71 ($C_7H_{11}O^{35}Cl^{79}Br/C_7H_{11}O^{35}Cl^{81}Br$), corresponding to the substituted cyclohexane ring of **8**. Facile cleavage between the tetrahydropyran and cyclohexyl rings is also noted[8,9] for **9** and **10**.

In the ^{13}C NMR spectrum of **8** only three of the expected four singlet signals for quaternary carbons deshielded by oxygen or chlorine were observed, δ 71.29, 76.12, and 77.74. The fourth resonance was most likely coincident with one of the $CDCl_3$ peaks, as only a total of 14 resonances were observed. The central member of the $CDCl_3$ triplet, δ 79.68, was taller and broader than the other two, suggesting that this is the position of the fourth quaternary carbon signal. This is in agreement with what could be expected for **8**.

The chemical shifts of the methyl signals in the ^1H NMR spectrum of **8**, especially the δ 1.66 peak, match those of **12** (δ 1.17, 1.31, 1.37, and 1.67) more closely than those of **9–11**, thus providing support for the position and orientation of the chlorine atom in **8**. In both **9** and **10**, the resonance of the axial methyl group deshielded by chlorine is shifted downfield to 1.84–1.87 ppm by a 1,3-diaxial interaction with a hydroxyl group. One of the methine proton resonances in **8** (δ 4.71) occurs at nearly the same position as that of the C-2 proton in **10** (δ 4.89), which is farther downfield than the C-2 proton signal in **9** or **12** (δ 4.24, 4.39). This provides further evidence for the substituted cyclohexane ring as proposed for **8**, with the C-2 proton experiencing deshielding by the axial OH at C-6. The other methine resonance in **8** (δ 3.83) corresponds closely to the chemical shifts noted for the C-10 proton in **9** (δ 3.89) and **11** (δ 3.81), thus supporting the tetrahydropyran ring as formulated in **8**. The combined spectral evidence for isodeodactol is thus totally consistent with proposed structure **8**.

Further confirmation for proposed structure **8** is derived from the following ^1H NMR data. A one-proton doubled triplet signal (J = 13.5, 13.5, 4.1 Hz) is clearly visible at δ 2.50 as expected for the 4-axial proton in **8**, the downfield shift being due to deshielding by the 6-axial hydroxyl. A similar chemical shift is noted for the C-4 axial proton in **10**. Irradiation at δ 3.83 sharpened the singlet methyl signal occurring at δ 1.42. This is consistent with the location of one bromine at C-10 but does not rigorously exclude its possible location at C-8. The C-10 location for bromine is strongly inferred by analogy with **9–12**.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer 298, and UV spectra were taken on Perkin-Elmer Lamda 3, Varian Superscan 3, or Cary 118 spectrophotometers. NMR spectra were taken on Varian XL-100, Bruker 270, and Bruker HXS-360 instruments in the solvents specified; signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were taken on CEC 110 (Du Pont) and Hewlett-Packard 5985B spectrometers. A Perkin-Elmer 141 polarimeter was used for obtaining optical rotations. The chromatographic adsorbent used was Brinkmann silica gel 60 (230–400 mesh). An Altex 5-μm preparative (10 mm × 25 cm) silica gel column was used for HPLC separations.

Isolation of 3–6 and 8. The fractions obtained earlier[12] from extracts of digestive glands of a batch of sea hares, *A. dactylomela*, from Bimini, Bahamas, were utilized. A portion (51.28 g) of fraction E[12] (77.5 g) was chromatographed on Sephadex LH-20 (450 g, 2 in. × 3.25 ft column, in four runs) by using chloroform–methanol (1:1), and 16 fractions were collected. A portion (1.5 g) of the 15th fraction (4.29 g) was further chromatographed on silica gel (150 g) by using hexane with increasing amounts of chloroform to give five (I–V) major fractions. Ethers **3** (56 mg) and **4** (60 mg) were isolated from fraction II (150 mg) by HPLC over silica gel with hexane–dichloromethane (65:35) as eluant. HPLC fractionation of fraction IV (50 mg) on silica gel with hexane–dichloromethane (1:1) gave **5** (6.3 mg), **6** (16.3 mg), and **8** (3.7 mg).

(3*E*)-12-Epiobtusenyne (3): $[\alpha]_D$ +7.3° (c 1.34, $CHCl_3$); mp 72–73 °C (hexane); IR ($CHCl_3$) 3310, 2100, 1470, 1458, 1435, 1360, 1305, 1125, 1110, 998, 962 cm^{-1}; UV (ethanol) λ_{max} 225 nm (ε 13 000); 360-MHz ^1H NMR ($CDCl_3$) see Table II; high-resolution mass spectrum, $C_{15}H_{20}O^{79}Br^{35}Cl$ (M^+), obsd m/e 330.0385 (calcd 330.0386), other ions at low resolution (GC/MS) m/e (relative intensity) 297 (1), 295 (1), 269 (1), 267 (5), 265 (3), 231 (2), 229 (2), 189 (3), 187 (9), 185 (18), 149 (33), 147 (11), 133 (11), 132 (10), 131 (66), 129 (19), 121 (42), 117 (23), 115 (20), 107 (85), 105 (34), 95 (32), 93 (50), 91 (79), 79 (93), 77 (65), 67 (79), 65 (100).

12-*epi*-Obtusenyne (4): Colorless liquid; $[\alpha]_D$ +73.5° (c 1.34, $CHCl_3$); IR ($CHCl_3$) 3310, 2100 (vw), 1470, 1458, 1360, 1305, 1123, 1110, 990, 892, 820 cm^{-1}; UV (ethanol) λ_{max} 224 nm (ε 12 600); 360-MHz NMR ($CDCl_3$), see Table II; high-resolution mass spectrum, $C_{10}H_{15}O^{79}Br^{35}Cl$ ($M^+ - C_5H_5$), obsd m/e 264.9995 (calcd 264.9997), $C_{15}H_{20}O^{35}Cl$ (M^+ – Br) m/e (obsd) 251.1185 (calcd 251.1203); low-resolution (GC/MS), m/e (relative intensity) 297

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(1), 295 (2, M^+ - Cl), 269 (2), 267 (8), 265 (7), 231 (2), 229 (2), 189 (3), 187 (6), 185 (16), 149 (22), 147 (9), 133 (9), 132 (8), 131 (48), 129 (18), 121 (29), 117 (23), 115 (21), 107 (65), 105 (27), 95 (24), 93 (41), 91 (78), 79 (90), 77 (69), 67 (78), 65 (100).

(3*E*)-Dactomelyne (5): mp 74–75 °C (hexane); $[\alpha]_D$ -15.9° (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) 3310, 2110, 1460, 1440, 1425, 1325, 1115, 1060, 1005, 915, 830 cm^{-1}; UV (ethanol) λ_{max} 225 nm (ϵ 15800); 270-MHz ^1H NMR ($CDCl_3$), see Table II; mass spectrum, *m/e* (relative intensity) 350 (1, M^+), 348 (3), 346 (3), 313 (16), 311 (15), 285 (13), 283 (51), 281 (40), 247 (23), 245 (23), 213 (11), 208 (11), 207 (8), 206 (14), 205 (9), 203 (13), 201 (26), 165 (24), 149 (17), 147 (21), 137 (21), 135 (43), 133 (99), 129 (12), 127 (11), 125 (12), 123 (13), 121 (31), 119 (88), 117 (37), 115 (25), 109 (23), 107 (23), 105 (42), 103 (47), 91 (72), 83 (27), 81 (52), 79 (44), 65 (100).

(3*Z*)-Dactomelyne (6): mp 119–120 °C (hexane), $[\alpha]_D$ -21.3° (*c* 1.63, $CHCl_3$); IR ($CHCl_3$) 3310, 2100 (vw), 1460, 1440, 1425, 1320, 1112, 1092, 1060, 1000, 920, 830 cm^{-1}; UV (ethanol) λ_{max} 221 nm (ϵ 13700); 270-MHz ^1H NMR ($CDCl_3$), see Table II; high-resolution mass spectrum, $C_{15}H_{20}O_2{}^{79}Br^{35}Cl$, obsd *m/e* 346.03415 (calcd 346.03351), $C_{15}H_{20}O_2{}^{81}Br^{35}Cl$, obsd 348.03248, (calcd 348.03148), low resolution, *m/e* (relative intensity) 348 (1), 346 (1), 313 (7), 311 (6), 285 (4), 283 (20), 281 (15), 247 (18), 245 (20), 203 (11), 201 (23), 165 (22), 149 (7), 147 (20), 137 (18), 135 (39), 133 (100), 129 (10), 127 (10), 125 (6), 123 (11), 121 (29), 119 (66), 117 (22), 115 (15), 109 (21), 107 (21), 105 (40), 103 (30), 91 (55), 83 (50), 81 (48), 79 (43), 77 (52), 65 (77).

Isodeodactol (8): mp 158–160 °C (hexane); $[\alpha]_D$ +18.9° (*c* 0.37, $CHCl_3$); IR ($CHCl_3$) 3560, 1390, 1122, 1100, 1020 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.25 (3 H, s), 1.32 (3 H, s), 1.43 (3 H, s), 1.66 (3 H, s), 3.83 (1 H, dd, *J* = 11.5, 4.2 Hz), 4.71 (1 H, dd, *J* = 4.7, 13 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 20.97 (q), 23.13, 23.30, 27.79, 28.17, 31.04, 31.37, 38.03 (t), 40.04 (t), 57.05 (d), 60.73 (d), 71.29 (s), 76.12 (s), 77.74 (s); mass spectrum (70 eV, probe at 40 °C), *m/e* (relative intensity) [interpretation] 419.0 (0.7), 417.0 (3.1), 415.1 (3.2) [all M^+ - 15], 416.1 (1.2), 412.0 (0.7) [all M^+ - 18], 412.9 (2.6), 410.9 (1.3), 409.1 (0.6), 380.1 (3.7), 379.1 (4.4), 378.1 (2.2), 377.1 (4.3), 376.1 (2.3), 375.0 (3.7), 374.0 (9.9), 373.1 (2.6), 372.1 (16.4), 370.0 (7.6), 367.0 (4.8), 365.1 (9.1), 363.1 (7.6), 361.1 (5.1), 359.1 (2.5), 335.2 (2.2), 333.2 (4.4), 331.0 (3.1), 229.1 (5.4), 207.0 (94.7), 205.0 (100.0) [$(CH_3)_2CCHBrCH_2CH_2C(CH_3)$=$O^+$], 189.0 (14.0), 187.0 (17.7), 185.1 (35.7), 161.0 (11.8), 159.1 (13.5), 151.0 (14.8), 149.0 (24.7), 147.0 (13.8), 145.0 (14.4), 135.0 (19.1), 133.0 (22.2), 131.1 (12.6), 125.1 (51.1), 123.0 (10.6), 121.0 (24.4), 119.0 (30.3), 117.0 (26.7), 115.0 (16.7), 109.1 (46.3), 107.1 (85.9), 105.1 (34.2), 103.1 (17.3), 95.1 (24.4), 93.1 (38.6), 91.1 (64.8), 85.0 (27.8), 83.0 (44.8), 81.1 (39.8), 79.0 (45.8), 77.1 (48.9), 69.1 (33.5); high-resolution mass spectrum, obsd *m/e* (composition, interpretation, calcd millimass) 353.068 81 ($C_{15}H_{25}O_2{}^{37}Cl^{79}Br$ and $C_{15}H_{25}O_2{}^{35}Cl^{81}Br$, M^+ - Br, 353.069 69 and 353.070 60), 351.070 60 ($C_{12}H_{19}O^{35}Cl^{79}Br$, M^+ - Br, 351.072 64), 293.031 73 ($C_{12}H_{19}O^{35}Cl^{79}Br$, M^+ - Br - C_3H_6O, 293.030 77), 295.030 18 ($C_{12}H_{19}O^{37}Cl^{79}Br$ and $C_{12}H_{19}O^{35}Cl^{81}Br$, M^+ - Br - C_3H_6O, 295.027 82, 295.028 74), 224.969 63 ($C_7H_{11}O^{35}Cl^{79}Br$, cyclohexyl ring plus substituents, 224.968 17), 226.967 71 ($C_7H_{11}O^{35}Cl^{81}Br$, cyclohexyl ring plus substituents, 226.966 14), 205.025 63 ($C_8H_{14}O^{79}Br$, tetrahydropyran ring plus substituents, 205.022 79).

Hydrogenation of 3. To a stirred suspension of 20 mg of prereduced PtO_2 in 5 mL of ethanol under hydrogen (1 atm) was added 13.9 mg of **3** in 1.5 mL of ethanol. Hydrogenation was continued for 10 min, and the reaction mixture was filtered. After evaporation of the solvent the residue was passed through 5 g of silica gel with hexane as eluant to give 6.13 mg of **7** as a colorless oil: $[\alpha]_D$ -2.63° (*c* 0.57, $CHCl_3$); IR (film) 1450, 1115, 1080, 1010, 895 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) 0.80–1.10 (6 H, m), 1.20–2.40 (18 H, m), 3.50–3.90 (3 H, m), 4.18 (1 H, br d, *J* = 10 Hz); mass spectrum, *m/e* (relative intensity 342 (1, M^+), 340 (6), 338 (4), 284 (2), 282 (6), 280 (5), 247 (6), 246 (6), 245 (7), 244 (6), 240 (4), 238 (3), 219 (2), 217 (3), 205 (2), 204 (3), 203 (2), 202 (2), 201 (1), 165 (10), 161 (18), 159 (48), 158 (9), 123 (100), 117 (12), 109 (28), 97 (11), 96 (11), 95 (30), 93 (10), 83 (18), 82 (11), 81 (69), 79 (18), 69 (22), 67 (37), 55 (30).

Hydrogenation of 4. Hydrogenation of **4** (19.4 mg) in the same manner as described above for **3** gave 9.9 mg of the octahydro derivative **7** whose optical rotation and IR, NMR, and mass spectra were identical with those of **3**.

Table III. Crystallographic Data

parameter	compd 3		compd 5
	$C_{15}H_{20}OClBr$		$C_{15}H_{20}O_2ClBr$
fw	331.70		347.70
space group	*C*2		$P2_12_12_1$
Z	4		4
temp, °C	25	-135	-135
cell dimensions[a] *a*, Å	21.842 (7)	21.595 (7)	6.916 (7)
b, Å	5.353 (2)	5.196 (2)	8.908 (7)
c, Å	13.711 (6)	13.653 (6)	24.978 (13)
β, deg	92.59 (2)	92.69 (2)	
V, Å^3	1601.5	1530.3	1538.8
ρ_c, g/cm^3	1.376		
ρ_o,[b] g/cm^3	1.370		
λ (intensity data), Å	1.5418		0.7107
λ (2θ data), Å	1.540 56		0.709 26
unique rflctns	1765		1857
scan range, deg	$0 \leq 2\theta \leq 150$		$0 \leq 2\theta \leq 53$
unobsd rflctns	32 ($I \leq 2\sigma(I)$)		373 ($I \leq 2\sigma(I)$)
scan width, deg	1 + 0.14tan θ		0.95 + 0.2 tan θ
horizontal aperture width, mm	3.5 + 0.86 tan θ		2.5 + 0.86 tan θ
max time spent on a rflctns, s	60		90

[a] Determined by a least-squares fit of $+2\theta$ and -2θ values of 48 reflections taken from all octants in reciprocal space. [b] Determined by the method of floatation in an aqueous solution of potassium iodide.

X-ray Analysis. Colorless single crystals of **3** were obtained by evaporation from ethanol solution, and those of **5** were obtained by evaporation from hexane solution. The crystal system of **3** is monoclinic, space group *C*2, with four molecules in the unit cell. The crystal system of **5** is orthorhombic, space group $P2_12_12_1$, with four molecules in the unit cell. Suitable crystals of the two compounds, of sizes 0.51 × 0.34 × 0.25 mm^3 and 0.24 × 0.19 × 0.16 mm^3, respectively, were chosen for data collection. All data were taken at -135 °C on a CAD-4 automatic diffractometer equipped with Enraf-Nonius cold-stream cooling device. The crystals of **5** were unstable at room temperature. Crystallographic data and the parameters of intensity data collection are given in Table III. The intensity data were collected by using the θ–2θ scan technique. Of the total time spent on any reflection, two-thirds was spent for scanning the peak and one-sixth was spent for each of the left and right backgrounds. The standard reflections were used as monitors which showed a maximum intensity variation of ±3% during the period of data collection, for which appropriate scaling was applied. Lorentz and polarization corrections were applied to the intensity data, but no absorption corrections were made. Experimental weights, based on counting statistics,[13] were also assigned to each structure amplitude.

The structures were solved by Patterson and heavy-atom methods. The nonhydrogen atoms were refined anisotropically and the hydrogen atoms isotropically. Refinements were terminated when all shifts were less than 0.3σ. The final *R* values for all data are 0.049 for **3** and 0.067 for **5**.

All refinements were carried out by using a block-diagonal least-squares program,[14] and the anomalous dispersion effects due to the presence of Br and Cl atoms were taken into account in structure factor calculations. The scattering factors for Br, Cl, O, and C and the correction factors due to anomalous dispersion effects by Br and Cl were taken from the literature.[15] The scattering factors for H were taken from Stewart, Davidson, and

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Simpson.[16] Final parameters are available as supplementary material.

Determination of Absolute Configuration. The absolute configuration of the compounds were determined by the Bijvoet method using Br and Cl atoms as anomalous scatterers. Cu Kα and Mo Kα radiations were used for compounds **3** and **5**, respectively. Fifteen pairs of reflections for each compound were selected for this purpose. The selections were made on the basis of the largest values of $(F_+^2 - F_-^2/\sigma(F_o^2)$. Values of F_+^2 and F_-^2 were calculated according to the method of James.[17] Intensities I_{hkl} and $I_{\bar{h}\bar{k}\bar{l}}$ of the Friedel pairs were measured. The results are available as supplementary material. For both compounds all observations agreed, establishing the absolute configuration shown in all figures.

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Supplementary Material Available: Final positional parameters, anisotropic thermal parameters, hydrogen atom positional and thermal parameters, bond angles, observed and calculated Bijvoet differences, and torsion angles for **3** and **5** (11 pages). Ordering information is given on any current masthead page.

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Synthesis and Thermolysis of *A*-Norvinylallenes Related to Vitamin D[1]

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Coupling the lithium salt of allene hydrocarbon **9** with keto enol ether **10** produced a 12:1 diastereomeric mixture of *A*-norvinylallenones **6a** (6*R*) and **6d** (6*S*). The absolute configuration of *A*-norallenes **6a** (6*R*) and **6d** (6*S*) were assigned by comparison of their ^{13}C NMR and ^1H NMR spectra with those of the previously studied six-membered A-ring vinylallenes **4a** (6*R*) and **4d** (6*S*). Thermolysis of **6a** (140 °C, 24 h) afforded **11** (6%), **12** (5%), **13** (35%), and **14** (6%). A similar result was obtained for **6d**: **11** (~5%), **12** (~1%), **13** (39%), and **14** (~3%). Reduction ($NaBH_4$–$CeCl_3$/MeOH) of **6a** yielded vinylallenols **6b** (1*R*,6*R*) and **6c** (1*S*,6*R*). Similar reduction of **6d** gave **6e** (1*R*,6*S*) and **6f** (1*S*,6*S*). Thermolysis of the vinylallenols led to complex, undefinable products. The thermal behavior of *A*-norvinylallenes **6** is discussed in terms of previous results obtained for the six-membered-ring series.

Vinylallenes of the type **1** may undergo competitive thermal [1,5] sigmatropic shifts to afford the *E* (**2**) or *Z* (**3**) trienes[2] (Scheme I). A detailed investigation of the vitamin D type vinylallenes **4a–f** revealed that the *E* to *Z* pathway ratio is sensitive to the functional group at C_1.[2b,d] The desired *E* pathway, which corresponds to the vitamin D–triene system **5**, was observed to be maximal for the diastereomeric alcohols **4b** (1*R*,6*R*) and **4f** (1*S*,6*S*). In stark contrast, the corresponding epimeric alcohols **4c** (1*S*,6*R*) and **4e** (1*R*,6*S*), respectively, rearranged primarily by way of the *Z* pathway to afford the unnatural 7*Z* isomer of **5**. In order to develop a better understanding of this phenomenon, we have initiated studies of structurally modified vinylallenes. In this paper we report on the synthesis and thermal investigation of the corresponding *A*-nor analogues **6a–f**.

A further impetus for carrying out this investigation was the earlier finding that 3-deoxy-1α-hydroxyvitamin D_3 (**5a**), a biologically active analogue of 1α,25-dihydroxyvitamin D_3 (**8a**), exhibited selective biological activity.[3,4] Whereas the natural steroid hormone **8a** is the most active substance known[5] for eliciting both classical vitamin D mediated responses, intestinal calcium absorption (ICA) and bone calcium mobilization (BCM), the analogue **5a** exhibited only ICA, a characteristic of potential clinical

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