In preliminary experiments, we found that the addition of **1a** to CuCN·2LiCl furnished after allylation substantial amounts of the double insertion product **7**, besides the desired insertion product **6** (see Scheme II). However, the addition of 1 equiv of ZnI_2 to a THF solution of **1a** prior to the addition of CuCN·2LiCl considerably improves the selectivity of the reaction (the **6**:**7** ratio was now 95:5). These results proved to be quite general (see Table I). On the other hand, the addition of bis(iodomethyl)zinc **1c**[2d-g,3] to CuCN·2LiCl affords after allylation mainly the double methylene insertion product **7** (the **6**:**7** ratio was 9:91, 95% yield). Copper amides produce specifically the mono-insertion product and do not require the addition of ZnI_2 (see entries 5-8). By using iodomethylzinc phenolate (**1b**) instead of **1a**, even bulky copper nucleophiles such as 1-cyanoethylcopper undergo the 1,2-migration (see entry 4).

In conclusion, we have shown that iodomethylzinc derivatives are efficient a^1/d^1 multi-coupling reagents[11] which allow a selective linking of a nucleophile Nu and of an electrophile E with a methylene group. Further extensions of these studies are underway in our laboratories.

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Supplementary Material Available: Typical procedure and spectral data for new compounds (4 pages). Ordering information is given on any current masthead page.

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The Structure of Hemibrevetoxin-B: A New Type of Toxin in the Gulf of Mexico Red Tide Organism

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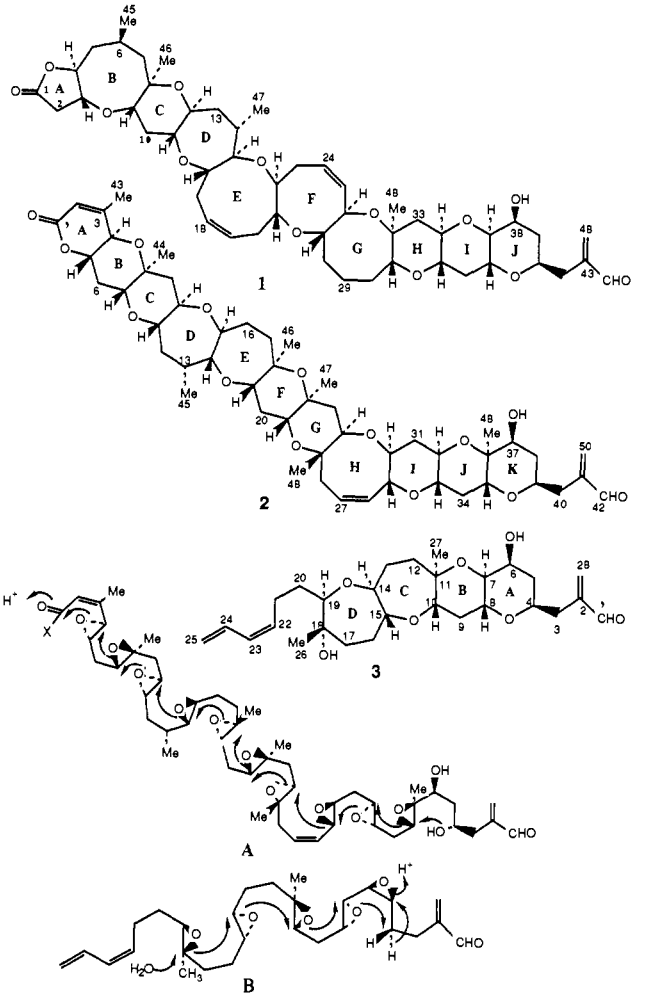
Brevetoxins, represented by brevetoxin-A (**1**)[1,2] and brevetoxin-B (**2**),[3] are polycyclic ethers isolated from the red tide organism, *Gymnodinium breve*, which forms blooms in the Gulf of Mexico. These potent neurotoxins are responsible for massive fish kills and human intoxication known as neurotoxic shellfish poisoning (NSP).[4,5] Because of their unprecedented structural feature, the unique mode of action on sodium channels,[6,7] and unusual biosynthetic pathway,[8,9] these compounds have been a subject of continuing studies in our laboratory and others. During the course of the studies, we have isolated a new series of compounds having molecular size about half that of brevetoxins. Earlier these compounds were referred to as GB-M, GB-N, and GB-4,[10] which we now name as hemibrevetoxin-A, -B, and -C, respectively. We believe that they have significant importance from the stand point of the biosynthesis of brevetoxins. In this communication, we wish to report the structure of hemibrevetoxin-B (**3**), the first in the series.



The methylene chloride extract of the cultured cells of *G. breve* was fractionated by flash chromatography and HPLC.[11] Hemibrevetoxin-B was obtained as a noncrystalline solid, $[\alpha]_D^{22}$ +115 ± 1 (*c* 0.1, $CHCl_3$), λ_{max} 222 nm (ϵ = 15 500). High resolution EIMS gave a molecular ion, *m/z* 490.2932, which corresponds to a molecular formula, $C_{28}H_{42}O_7$. The CIMS (isobutane) gave a M + 1 peak, *m/z* 491. The ^{13}C NMR spectrum revealed all 28 carbons, of which seven are sp^2 carbons.[12] Since these sp^2 carbons account for four of the eight unsaturations present in the molecule, it was assumed that **3** contains four rings. Analysis of the ^1H and DEPT spectra also provided evidence for the presence of nine aliphatic methylenes, eight oxygenated methines, and two

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(11) The cells were extracted with methylene chloride, and the extract was fractionated between petroleum ether and 90% methanol. The methanolic extract was purified by flash chromatography on SiO_2 first with methylene chloride-benzene-methanol (40:5:1) and then with methylene chloride-ethyl acetate-methanol (50:30:1). The compound **3** was obtained after purification by HPLC [normal phase, SiO_2, isooctane-isopropyl alcohol (4:1)] in a yield of about 1 mg from 4.5×10^9 cells.
(12) ^{13}C NMR (CD_2Cl_2) sp^2 carbons δ 194.00 (C-1, CHO), 148.41 (C-2), 136.34 (28 $=CH_2$), 133.07 (C-24), 132.62 (C-23), 129.91 (C-22), 117.27 (25 $=CH_2$); quaternary carbons δ 78.37, 74.66; oxygenated methines δ 87.20, 86.26, 85.45, 82.56, 72.47, 71.01, 66.66, 62.95; aliphatic methylenes δ 38.62, 37.92, 33.89, 33.20, 31.93, 30.69, 29.99, 29.26, 25.15; tertiary methyl groups δ 23.71 and 16.88.

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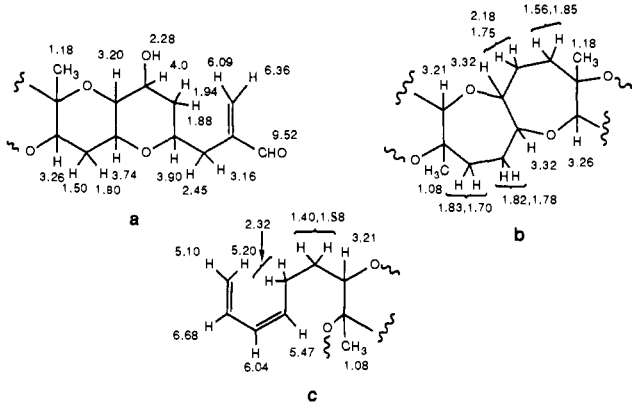
quaternary carbons bearing methyl groups and oxygen.

The information obtained from ^1H–^1H COSY plot, difference decoupling, *J*-resolved 2D NMR, and chemical shifts led to the connectivities shown in the partial structures, **a**, **b**, and **c**. The structure **a** contains an α-vinyl aldehyde moiety, which was found in all brevetoxins. The *J*-resolved spectrum was particularly useful in assigning the methylene proton signal in the partial structure **b**, which have close chemical shifts due to the near symmetricity



of the partial structure. The geometry of the diene in the partial structure **c** was determined as *Z* in comparison with proton–proton coupling constants and carbon chemical shifts in similar structures.[13-15]

The three partial structures, whose connectivities in NMR are disrupted by quaternary carbons, were combined together on the basis of the difference NOE and long-range coupling COSY spectral data. The methyl protons (H-27, δ 1.18) showed long-range couplings with protons, δ 3.20 (H-7), 3.26 (H-10), 1.85 (H-12a), and 1.56 (H-12b). The other methyl group (H-26, δ 1.08) showed couplings with protons, δ 3.21 (H-19) and 1.70 (H-17) (Figure 4 of Supplementary Material). NOE was observed between the methyl protons, H-27, and two methine protons, δ 3.32 (H-14) and 3.20 (H-7). Similarly, NOE was observed between the methyl protons, δ 1.08 (H-26), and two methylene protons, δ 1.83 and 1.70 (H-17). The oxygen function at C-6 is a hydroxyl group, because, in some spectra, the OH proton at C-6 was observable (δ 2.28) and showed two-bond and three-bond couplings with H-6 and H-5a,b, respectively. This structural arrangement, A/B ring and the side chain, is identical with the right terminus of all brevetoxin series. In fact the NMR data of the moiety are in good agreement with those of brevetoxin-A.[1] Therefore the all-trans–syn-trans structure was also assumed for **3**. The 18α configuration of the 18-hydroxyl group was also assumed from the biosynthetic consideration. We previously reported that hemibrevetoxin-A (GB-M) has also a terminal diene and a conjugated aldehyde.[10] Hemibrevetoxin-C (GB-4) has a conjugated aldehyde but no diene. Both compounds are considered to be closely related to hemibrevetoxin-B.

The structure **3** constitutes essentially the right half of brevetoxin molecules. It was speculated that brevetoxins are biosynthesized through a cascade of epoxide ring openings triggered by protonation on the carbonyl group at the left terminus of the carbon chain (**A**).[16] In view of the structures of the hemibrevetoxins, however, the cyclization may be better explained by an alternate mechanism (**B**),[16,17] in which the cascade is initiated from the right hand by the opening of *cis*-epoxide followed by a hydride ion transfer and consecutive *trans*-epoxide openings. Moreover, the structures of hemibrevetoxins with alkene tails affirm the polyene origin of brevetoxins.

Hemibrevetoxin-B causes the characteristic rounding of cultured mouse neuroblastoma cells as brevetoxin-A and -B and shows cytotoxicity at a concentration of 5 μmol.

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Supplementary Material Available: Figures of the ^1H–^1H COSY and ^1H and ^{13}C NMR spectra of **3** (6 pages). Ordering information is given on any current masthead page.

(13) A broad signal at δ 3.32 was assigned to the ring junction protons (H-14 and H-15) on the basis of comparison with protons in a similar environment in brevetoxin-B and synthetic model compounds (Prof. K. C. Nicolaou, private communication).

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Stepwise Reduction of Acetonitrile in [Tp′(CO)(PhC≡CMe)W(N≡CCH$_3$)][BF$_4$]

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Reduction of nitriles to amines with either hydrogen or hydride reagents is a common reaction,[1] but characterization of intermediates in nitrile reduction promoted with metal monomers has proved elusive.[2] Conversion of acetonitrile to ethylamine results when [(triars)Ru(NCMe)$_3$]$^{2+}$ is treated with NaBH$_4$ in methanol as [(triars)HRu(NH$_2$CH$_2$CH$_3$)$_2$]$^+$ forms.[3] Reduction of acetonitrile on metal clusters has yielded isolable intermediates.[4]

We report here stepwise reduction of coordinated acetonitrile by sequential hydride and proton addition reactions (Scheme I). Intermediate metal complexes have been isolated and characterized at each stage of the reduction (Table I).

Oxidation of K[Tp′W(CO)$_3$][5] with iodine followed by addition of MeC≡CPh yields Tp′W(CO)(I)(PhC≡CMe) [Tp′ = hydrotris(3,5-dimethylpyrazolyl)borate]. Abstraction of I$^-$ with [Ag][BF$_4$] in acetonitrile produces a royal blue cationic Tp′(CO)(PhC≡CMe)W(N≡CCH$_3$)$^+$ complex. The ^{13}C chemical shifts of the two alkyne carbons (215, 213 ppm) indicate that the alkyne $\pi_\perp$ orbital is donating into the vacant d_π orbital of this six-coordinate d^4 monomer.[6]

Low-temperature addition of Li[HBEt$_3$] to a THF solution of the cationic acetonitrile complex causes a color change, and orange crystals of Tp′(CO)(PhC≡CMe)W—N̈=CHMe were isolated in 70% yield. Salient ^1H data for the major isomer include a quartet at 6.26 ppm (1 H, J = 6 Hz) and a doublet at 1.78 ppm (3 H, J = 6 Hz), while ^{13}C NMR revealed alkyne carbons at 160 and 159 ppm, with the azavinylidene carbon[7] at 145 ppm exhibiting a $^1J_{CH}$ value of 167 Hz. The shift in ν_{CO} from 1940 cm^{-1} in the reagent to 1885 cm^{-1} is consistent with formation of a neutral product. A second isomer with similar spectroscopic

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