

Figure 3. (A) LEED photograph for ion-bombarded Cu(100), no anneal, 76 eV. (B) LEED photograph for ion-bombarded crystal immersed in 1 mM HCl for 5 min, 33 eV.

An initially clean and ordered Cu(100) single crystal electrode surface was exposed to 1 atm of high-purity oxygen gas for 5 min. No distinct LEED spots were visible, in the resulting pattern, at any energy. These results indicate complete destruction of the crystalline order on the initially prepared (100) surface. The Auger electron (AES) spectrum of this oxidized surface is shown in Figure 2B. Formation of multiple layers of copper oxide, about 2 nm thick, is indicated by the oxygen Auger transition, 510 eV. Bombardment of the Cu(100) surface with energetic Ar⁺ ions, without subsequent annealing, also results in disruption of the initially ordered single crystal surface, evidenced by the LEED pattern shown in Figure 3A; LEED spots are present, but they

are diffuse and considerably enlarged in comparison with the clean and annealed surface pattern.

Immersion of the oxidized surface into 1 mM HCl resulted in the same rest potential as that for the reduced surface, after 2 min. The LEED pattern following immersion in the dilute HCl solution, and emersion into vacuum is shown in Figure 1. Clearly, exposure of the oxide-coated Cu(100) surface to dilute HCl brought about the reappearance of sharp LEED spots. The LEED pattern shown in Figure 1 is characteristic of a Cu(100)($\sqrt{2} \times \sqrt{2}$)R45° structure; the AES spectrum is shown in Figure 2C. These LEED and AES results are identical with those observed when a clean, ordered Cu(100) surface is immersed directly in dilute HCl.⁴ These results are irrefutable evidence that the single crystallinity of the Cu(100) surface is restored when an amorphous or disordered oxidized surface is immersed in dilute HCl solution. The AES spectrum in Figure 2C shows chlorine but no oxygen.

Immersion of the oxidized surface in a 1 mM H₂SO₄ solution also resulted in reordering of the Cu(100) surface as evidenced by formation of a Cu(100)(2×2) LEED pattern;⁴ Figure 2D indicates that 1/4 coverage sulfate is responsible for the (2×2) pattern. Clearly, restoration of long-range order on an oxidized surface is not limited to HCl.

Figure 3B is a photograph of the LEED pattern observed when an ion-bombarded, unannealed, Cu(100) surface, Figure 3A, was immersed in 1 mM HCl and electrochemically oxidized. It can be seen that the diffuse intensity was substantially reduced, and a Cu(100)($\sqrt{2} \times \sqrt{2}$)R45° pattern was formed. 100 monolayers of Cu were oxidatively removed prior to formation of the ordered surface, Figure 3B. It is probable that electropolishing baths other than 1 mM HCl would lead to more facile restoration of crystalline order on the Cu electrode surface, and further studies are being pursued in this regard.

Data for the HCl-treated, ion-bombarded Cu surface, reported here, represent the first observations of electropolishing at the atomic level. It is clear that disordered single crystal surfaces may be restored in situ by electrolytic dissolution in mild acid solutions.

(4) Ehlers, C. B.; Villegas, I.; Stickney, J. L. *J. Electroanal. Chem.*, manuscript in preparation.

Zinc and Copper Carbenoids as Efficient and Selective α^1/δ^1 Multicoupling Reagents. 1

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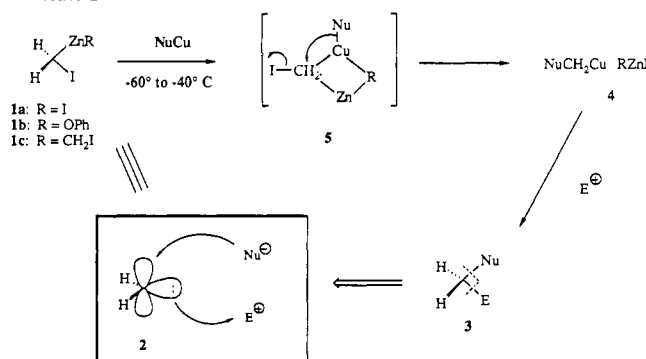
The high-covalent character and the consequent low reactivity of the carbon–zinc bond allow the synthesis of highly functionalized organozinc compounds RZnX. These organometallics can be converted to the corresponding copper derivatives RCu(CN)ZnX which react efficiently with various electrophiles.¹ Of special interest are functionalized organozinc halides in which the functional group can interact with the carbon–zinc bond leading to new reactivity patterns. Zinc carbenoids of type **1** belong to this category of reagents. They may be precursors of the carbene **2** and as such have found several synthetic applications.² Due

(1) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. J. *Org. Chem.* **1988**, 53, 2390. (b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, 29, 2395. (c) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* **1988**, 29, 3887. (d) Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berk, S. C. *Tetrahedron Lett.* **1988**, 29, 6693. (e) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, 53, 5789.

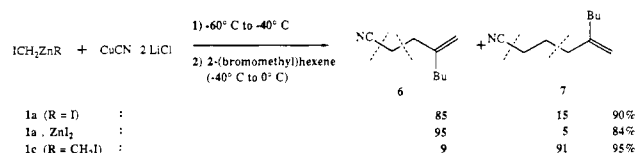
Table I. Products of Type 3 Obtained by the Reaction of an Organocopper NuCu and an Allylic Bromide or an Enone with the Iodomethylzinc Derivatives **1a** or **1b**

Entry	Zinc Carbenoid	Nucleophile (NuCu)	Electrophile	Products of Type 3	Yield (%) ^a
1	1a · ZnI ₂	CuCN · 2 LiCl	2-(bromomethyl)hexene		84 ^b
2	1a · ZnI ₂	NCCH ₂ Cu	2-(bromomethyl)hexene		91 ^b
3	1a · ZnI ₂	NC-CH ₂ Cu · 2 LiCl	(E)-4-phenyl-3-buten-2-one		76 ^c
4	1b	NC-CH(CH ₃)-Cu	2-(bromomethyl)hexene		69
5	1a		2-(bromomethyl)hexene		76
6	1a		2-(bromomethyl)hexene		68
7	1a	PhCH ₂ (CH ₃)N-Cu	2-(bromomethyl)hexene		64
8	1a	PhCH ₂ (CH ₃)N-Cu	3-bromo-2-methyl-1-propene		66 ^c
9	1a · ZnI ₂		2-(bromomethyl)hexene		96 ^b
10	1a · ZnI ₂		3-bromo-2-methylpropene		93 ^b
11	1a · ZnI ₂		2-(bromomethyl)hexene		74 ^b
12	1a	n-C ₁₀ H ₂₁ SCu	3-bromo-2-methyl-1-propene		75 ^{c,d}

^a Unless otherwise indicated, all yields refer to isolated yields of analytically pure products. ^b Less than 5% of the double insertion product is obtained. ^c GC yield. ^d A 10:1 mixture of THF:DMPU was used as solvent.

Scheme I

to its electronic nature, **2** may also sequentially react with a nucleophile^{3,4} Nu and an electrophile^{4,5} E to afford products of type **3** (see Scheme I).

Scheme II

We now report that iodomethylzinc iodide (**1a**), which is readily prepared from diiodomethane⁵ and zinc in THF, allows the realization of this synthetic operation in fair to good yields using a wide range of organocopper compounds as the nucleophiles Nu and allylic bromides or an enone as the electrophiles E; see Scheme I and Table I. Thus the addition of **1a** (1.6 equiv) to a THF solution of an organocopper NuCu (1.0 equiv) at -60 to -40° C leads to the insertion product **4** via an intermediate tentatively formulated as **5** in which the nucleophile Nu undergoes a 1,2-migration displacing the iodide of the CH₂I moiety. After the addition of an allylic bromide (0.6–0.7 equiv; -60 to 0° C) to the organocopper compounds **4**, the methylene insertion products **3** are obtained in good yields.⁶ Various classes of copper nucleophiles such as CuCN·2LiCl⁷ (see entry 1 of Table I), cyanomethylcopper derivatives⁸ (see entries 2–4), copper amides^{9a} (see entries 5–8), hetero-aryl copper compounds^{7,10} (see entries 9–11), and a copper thiolate⁹ (see entry 12) undergo the migration under our reaction conditions.

(2) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) Blanchard, E. P.; Simmons, H. E. *J. Am. Chem. Soc.* **1964**, *86*, 1337. (c) Simmons, H. E.; Blanchard, E. P.; Smith, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 1347. (d) Wittig, G.; Wingler, F. *Liebigs Ann. Chem.* **1962**, *656*, 18. (e) Wittig, G.; Wingler, F. *Chem. Ber.* **1964**, *97*, 2139, 2146. (f) Wittig, G.; Jautelat, M. *Liebigs Ann. Chem.* **1967**, *702*, 24. (g) Jautelat, M.; Schwarz, V. *Tetrahedron Lett.* **1966**, 5101. (h) Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 83.

(3) Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1961**, *650*, 1. (4) (a) Köbrich, G. *Angew. Chem.* **1967**, *79*, 15; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 41. (b) Köbrich, G. *Bull. Soc. Chim. Fr.* **1969**, 2712. (c) Villieras, J. *Bull. Soc. Chim. Fr.* **1967**, 1511, 1520. (d) Villieras, J.; Kirschleger, B.; Tarhouni, R.; Rambaud, M. *Bull. Soc. Chim. Fr.* **1986**, 471. (e) Villieras, J.; Tarhouni, R.; Kirschleger, B.; Rambaud, M. *Bull. Soc. Chim. Fr.* **1985**, 825. (f) Villieras, J.; Rambaud, M.; Kirschleger, B.; Tarhouni, R. *Bull. Soc. Chim. Fr.* **1985**, 837. (g) For the nucleophilic alkylation of functional carbenoids: (i) Villieras, J.; Reliquet, A.; Normant, J. F. *J. Organomet. Chem.* **1978**, *144*, 1, 263. (ii) Villieras, J.; Reliquet, A.; Normant, J. F. *Synthesis* **1978**, 27.

(5) (a) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151. (b) See also: Seyferth, D.; Bertouzos, H.; Todd, L. J. *J. Organomet. Chem.* **1965**, *4*, 18.

(6) Negishi, E.; Akiyoshi, K. *J. Am. Chem. Soc.* **1988**, *110*, 646. (b) Harada, T.; Hara, D.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3821. (c) Miller, J. A. *J. Org. Chem.* **1989**, *54*, 998. (d) Kocienski, P.; Wadman, S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363. (e) Negishi, E.; Akiyoshi, K.; O'Connor, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089. (7) Lipschutz, B. H. *Synthesis* **1987**, 325. (8) Corey, E. J.; Kuwajima, I. *Tetrahedron Lett.* **1972**, 487. (9) (a) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788. (b) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662. (10) Lipschutz, B. H.; Kozlowski, J. A.; Parker, P. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.

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 ZnI₂ 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-e,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 ZnI₂ (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 ¹/_d multi-coupling reagents¹¹ 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.

(11) (a) Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239. (b) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 3897. (c) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261.

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

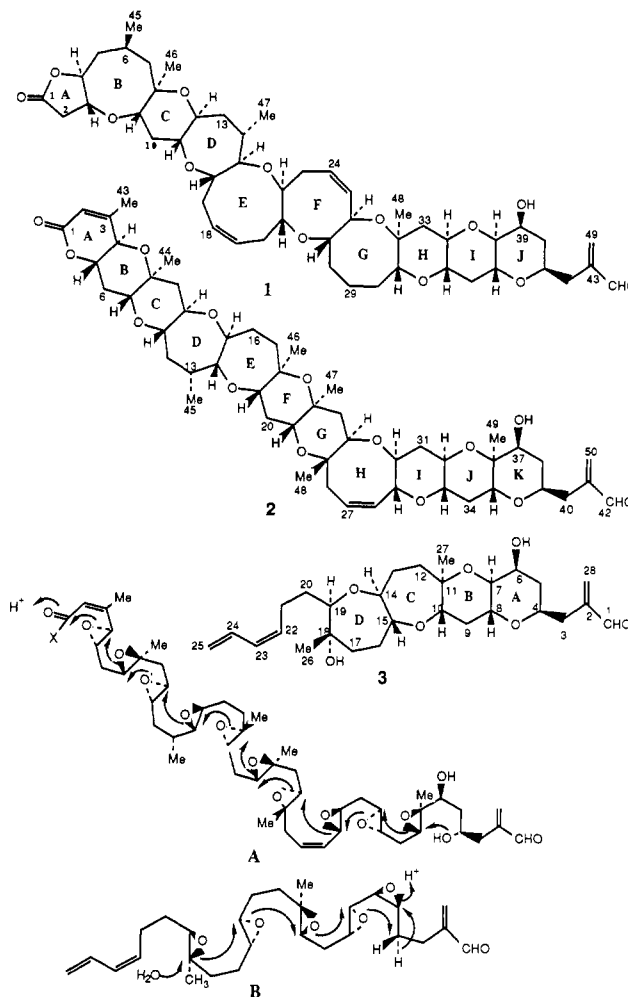
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Brevetoxins, represented by brevetoxin-A (**1**)^{1,2} and brevetoxin-B (**2**),³ are polycyclic ethers isolated from the red tide organism, *Gymnodinium breve*, which forms blooms in the Gulf of Mexico. These potent neurotoxins are responsible for 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, $[\alpha]_D^{22} +115 \pm 1$ (c 0.1, CHCl₃), λ_{max} 222 nm ($\epsilon = 15\,500$). High resolution EIMS gave a molecular ion, m/z 490.2932, which corresponds to a molecular formula, C₂₈H₄₂O₇. The CIMS (isobutane) gave a M + 1 peak, m/z 491. The ¹³C NMR spectrum revealed all 28 carbons, of which seven are sp² carbons.¹² Since these sp² 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

(1) Shimizu, Y.; Bando, H.; Chou, H. N.; Van Duyne, G.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 514-515.

(2) Pawlak, J.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144-1150.

(3) Lin, Y. Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775.

(4) Shimizu, Y. *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. I, pp 1-42.

(5) Mende, T. J.; Baden, D. G. *Trends Biochem. Sci.* **1978**, *3*, 209-211.

(6) Caterall, W. A. *Science* **1988**, *242*, 50-61, and the references cited therein.

(7) Huang, J. M. C.; Wu, H. C.; Baden, D. G. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 615-621.

(8) Chou, H. N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184-2185.

(9) Lee, M. S.; Repeta, D. S.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855-7856.

(10) Shimizu, Y. *Pure Appl. Chem.* **1982**, *54*, 1973-1980.

(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 SiO₂ 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, SiO₂, isooctane-isopropyl alcohol (4:1)] in a yield of about 1 mg from 4.5 × 10⁹ cells.

(12) ¹³C NMR (CD₂Cl₂) sp² carbons δ 194.00 (C-1, CHO), 148.41 (C-2), 136.34 (28 =CH₂), 133.07 (C-24), 132.62 (C-23), 129.91 (C-22), 117.27 (25 =CH₂); 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.