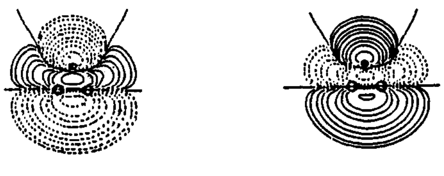
#59 **#60**

Figure 2. Countour plots of orbitals 59-60 for the plane of a three-membered ring in **4-Se3**.

bridgehead Si atoms.[15] It is probably not a conventional σ or π bond;[3,16] of course the line joining the bridgehead Si atoms does not always mean "a bond path".[19] An innovative explanation is "σ-bridged-π" bonding, which is a three-center bond as shown in Chart I.[3g]

The molecular structures and electronic states were calculated by the ab initio restricted Hartree-Fock method (RHF, DZP) for **3-Se3** and **4-Se3** (Table I).[20] The RHF geometry of **4-Se3** is in good agreement with the experimental results[21] and almost identical with the RHF geometry of **3-Se3**. The bond order of the Si$_1$···Si$_3$ bond is calculated to be 0.366 for both **3-Se3** and **4-Se3** (Chart II), and the orbital A for **3-Se3** (Chart III) shows little overlap between Si atoms.

The ^{77}Se and ^{29}Si NMR studies for **1-Se3** afforded surprising results.[22] ^{77}Se chemical shifts of normal silaselenanes are generally observed upfield (-199 to -614 ppm) from Me$_2$Se (0 ppm),[12,23] yet the ^{77}Se chemical shift of compound **1-Se3** is +830 ppm, which is downfield by more than 1000 ppm from the chemical shifts of normal silaselenanes. The ^{77}Se signals of **1-Se4** are observed in the middle region (+320.7, +273.2 ppm). On the other hand, the ^{29}Si NMR chemical shift of **1-Se3** is -59.0 ppm, which is similar to the chemical shift of three-membered-ring compound **2** (-64.8 ppm).[12] The values are far different from those of normal four-membered-ring compounds, e.g., tetramethyl-1,3-diselenadisiletane (^{77}Se NMR δ -199 ppm, ^{29}Si NMR δ -8.0 ppm).[23] The $J(^{29}\text{Si}-^{77}\text{Se})$ coupling constant for **1-Se3** (J = 48.5 Hz) is smaller than that for **2** (J = 78 Hz). It shows that the s character of the Si-Se bond in **1-Se3** is very low.

This result implies two possible explanations: (1) Both in **3-Se3** and in **4-Se3** there is no Si-Si bond which can be defined using the concept of the electron density analysis of Bader and coworkers.[3e,3k,24] The shorter bridgehead distance is a result of geometrical constraint.[3e] (2) The bond order is low, which does not reflect the magnitude of the three-center bonding. The bridgehead bond is considerably reinforced with the three-center bonding.[25] This type of bond exists both in **3-Se3** and in **4-Se3**.

We propose the latter explanation, since the structure and the NMR data of **1-Se3** are far different from those of normal disilaselenanes and rather resemble the selenadisilirane in several points. However, at this moment, we cannot show a clear bonding picture of the mysterious bridgehead bond.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on a Priority Area of Molecular Design with heteroatoms and for General Scientific Research from the Ministry of Education, Science and Culture, Japan. The numerical calculations were carried out on the HITAC M680H at the Production Engineering Research Laboratory, Hitachi Ltd.

Supplementary Material Available: Detailed information of the X-ray crystal analysis, including tables of crystal structure data, positional parameters, displacement parameters, torsional angles, and bond distances and angles (25 pages); tables of observed and calculated structure factors (25 pages). Ordering information is given on any current masthead page.

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[15] Allen predicted similar geometry in the 1,3-diborabicyclo[1.1.1]pentane system and showed the [1.1.1]propellane-type bonding picture.[3g]

[16] We reported that Streitwieser's ionic model[3i] can apply to the 2,4,5-trisilabicyclo[1.1.1]pentane system;[17] however, the Si-Se-Si angles of **1-Se3** go beyond the optimal value of the ionic model (80°). Clearly, the ionic model cannot be applied to this system. Lewis-Langmuir atomic charges were determined for **4-X3** according to the method reported by Allen[18] (Table II). These data show that the contribution of the ionic bonding in **4-Se3** (or **1-Se3**) is smaller than in others (see also ref 21).

[17] Ando, W.; Yoshida, H.; Kurishima, K.; Sugiyama, M. *J. Am. Chem. Soc.* **1991**, *113*, 7790.

[18] (a) Allen, L. C. *J. Am. Chem. Soc.* **1989**, *111*, 9115. (b) Allen, L. C. *J. Am. Chem. Soc.* **1989**, *111*, 9003. (c) Allen, L. C. Private communication.

[19] It is not unusual, because the same type of descriptions are often used for simplicity. For example, in metallocenes (Chart IV), the straight line joining metal and Cp does not mean a bond path. As for a bond path, see ref 3e,k.

[20] The calculation was carried out by the GAUSSIAN 82 program package. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab-initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986. The basis sets used here for the Se and Si atoms were double zeta plus polarization (DZP) types, which consisted of the Tatewaki-Huzinaga basis sets plus an extra d-function. Huzinaga, S. *Gaussian Basis Sets for Molecular Calculations*; Elsevier: Amsterdam, 1984. For the H atom, the 3-21G function was employed.

[21] The charge distribution is -0.18 for the Si atom and +0.01 for the Se atom. The results from ab initio calculations are reasonable, because the electronegativity difference between Si and Se is smaller than that between Si and carbon.[18b]

[22] ^{77}Se and ^{29}Si NMR spectra were recorded with a Brucker MSL 400 spectrometer with a 10-mm sample tube and multinuclear probehead. The spectral widths were 30000 and 125000 Hz operated at 76.4 and 79.4 MHz for ^{77}Se and ^{29}Si, respectively.

[23] (a) Boudjouk, P.; Bahr, S. R.; Thompson, D. P. *Organometallics* **1991**, *10*, 778. (b) Thompson, D. P.; Boudjouk, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1466.

[24] As yet we have never carried out the electron density analysis for **3-Se3** and **4-Se3**; however, according to Gordon's paper, no Si-Si bond critical point is found in **3-O3**, **4-O3**, **3-S3**, and **4-S3**.[3e]

[25] The RHF calculation for **4-Se3** afforded some orbitals, which mainly consisted of s orbitals (1s of H, 3s of Si, and 4s of Se, Scheme I, #53, #56-58, #61). They are essentially the same type orbital as the three-center orbitals, which consist of three hydrogen 1s orbitals.[26] The acute angle of **4-Se3** and the short Si$_1$···Si$_3$ length may be explained on the basis of the same concept as the geometrical distortion of the three-hydrogen system.[26] That is, the overlap of the 3s orbitals for the Si atoms lowers the energy of the three-center-bond-type orbitals, which also is consistent with the low s character of Si-Se bonds. The orbital #59-60 can be regarded as a σ-bridged-π bonding type orbital (Figure 2).

[26] Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; John Wiley & Sons: New York, 1985; Chapter 7.

Strong Organometallic "Anomeric" Effects. Long-Range Stereoelectronic Control of Cyclohexanone Conformation via a Transannular Metallacyclobutane Interaction

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Received August 29, 1991

The importance of stereoelectronic effects to the configuration and conformation of organic molecules has been generally recognized in a variety of contexts.[1] Here we present evidence for conformational control of the cyclohexanone ring system by a remote transition-metal center, communicated via a transannular electronic interaction across a metallacyclobutane framework. This unprecedented organometallic "anomeric" effect is demonstrated both in the solid state and in solution and is shown to be greater in magnitude than the anomeric effect in carbohydrate acetals.[1,2] A molecular orbital description for this interaction is proposed and supported by theoretical considerations.

The complexes under investigation, metallacyclobutane-substituted ketone derivatives **2-4**, were prepared as previously described[3] by the addition of enolates to cationic η^3-allyl complexes

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[1] See: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

[2] Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. Szarek, W. A.; Horton, D. *Anomeric Effects*; ACS Symposium Series 87; American Chemical Society: Washington, D.C., 1979.

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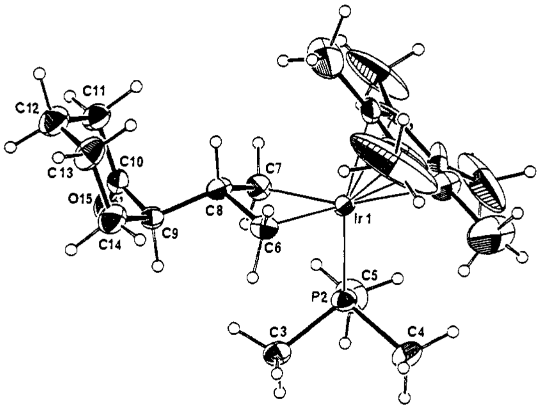
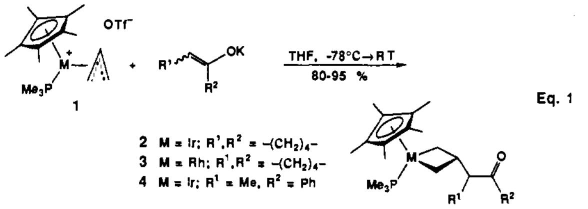


Figure 1. ORTEP diagram of **2**. Selected bond distances (Å): Ir1–C6, 2.126 (8); Ir1–C7, 2.114 (8); C6–C8, 1.539 (12); C7–C8, 1.531 (12); C8–C9, 1.553 (12); C9–C10, 1.497 (12); C10–O15, 1.237 (11), C10–C11, 1.491 (12); C11–C12, 1.527 (14); C12–C13, 1.523 (14); C13–C14, 1.536 (13); C14–C9, 1.546 (13). Selected bond angles (deg): C7–Ir1–C6, 66.3 (3); Ir1–C6–C8, 94.2 (5); Ir1–C7–C8, 94.9 (5); C7–C8–C6, 98.1 (6); C8–C9–C14, 112.7 (7); C8–C9–C10, 109.8 (7); C9–C10–C11, 116.9 (8); C(11)–C(10)–O(15), 121.8 (8); C(9)–C(10)–O(15), 121.3 (8). Final residuals: $R(F) = 0.0350$, $R_W(F) = 0.0365$.

1 (eq 1).[3] Anomalously low carbonyl absorption frequencies were recorded in the infrared spectra of complexes **2–4**,[4] suggesting an unanticipated weakening of the carbonyl bond, even for the acyclic addend. An X-ray structure determination[5] of complex **2** was undertaken to probe this anomaly; an ORTEP diagram of the molecular geometry and selected bond distances and angles are presented in Figure 1. While no unusual intermolecular electronic interactions or lattice effects are evident in the extended unit cell, *the sterically bulky metallacyclobutane substituent on the cyclohexanone ring unexpectedly occupies an axial position.*



Eq. 1

Solution spectroscopic analysis confirms that the diminished carbonyl bond strength and preferred axial orientation are not simply solid-state effects. The infrared spectrum of complex **2** in CH_2Cl_2 shows the carbonyl absorption at 1693 cm^{-1} (cf., ν_{CO} = 1709 cm^{-1} for 2-methylcyclohexanone and 2-cyclopropylcyclohexanone[3a] under identical conditions). No variation in the ^1H NMR coupling constants is observed between −50 and +80 °C, indicating a rigid cyclohexanone ring at ambient temperature. The cyclohexanone conformation was determined by fully assigning the complicated 500-MHz ^1H NMR spectrum. Even under optimum conditions (5% v/v CD_2Cl_2 in C_6D_6), however, the critical H2 signal coincides with the $H6_{ax}$ resonance (Figure 2a). The use of two-dimensional *J*-resolved spectroscopy[6] separates this signal into its two components (Figure 2b): H2 is a dtd, with the one large coupling (J = 10.5 Hz) to the β-metallacycle hydrogen (H_β), as shown by decoupling experiments.[7] Both the small *W* coupling to $H4_{eq}$ and the remaining two vicinal coupling constants of 4.5 Hz each are consistent only with H2 in the equatorial orientation. In the ^{13}C NMR spectrum, the diastereotopic metallacyclobutane α-carbons differ by just 0.6 ppm, consistent with the carbonyl oxygen directed away from the metallacyclobutane (Figure 1).

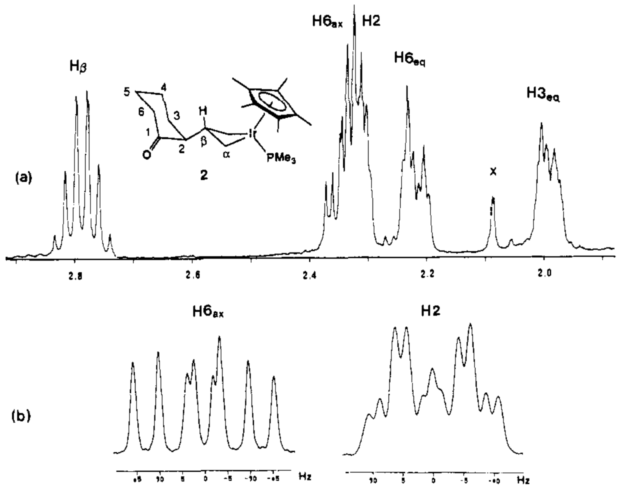


Figure 2. ^1H NMR spectra (500 MHz) of complex **2** (5% v/v CD_2Cl_2 in C_6D_6): (a) expansion of the 1.9–2.9 ppm region with assignments (x denotes impurity); (b) homonuclear *J*-resolved spectrum, cross-sectional ν_1 slices of the overlapping resonances at 2.3 ppm.

To determine whether this structural anomaly arises from a steric or an electronic effect, force field calculations were used to probe unanticipated steric effects in complex **2**. The minimized structure from these calculations virtually reproduces the crystal-structure geometry,[8,9] except that the cyclohexanone substituent is calculated to be 1.7 kcal/mol more stable in an equatorial position. This energy difference is close to the 1.3 kcal/mol stabilization calculated for equatorial over axial 2-isopropylcyclohexanone, although the experimentally determined energy difference in this case is only 0.4 kcal/mol.[10] We thus assume that the calculations also overstate the energy difference between conformers of complex **2** by about 1 kcal/mol.

On the basis of this analysis, the axial orientation preferred by complex **2** is attributed to a stereoelectronic effect. Because only the axial conformation is observed at room temperature ($K_{eq} \geq 30$), this species must be at least 2 kcal/mol more stable than the equatorial conformation. By superimposing this difference on the estimated 0.5 kcal/mol steric destabilization of the axial conformer, the magnitude of this effect in complex **2** is estimated to be ≥2.5 kcal/mol, substantially stronger than standard acetal anomeric effects.[1,2] To probe this effect further, the corresponding 4,4-dimethylcyclohexanone metallacyclobutane **5** was prepared;[3b] spectroscopic analysis indicates that 1,3-diaxial interactions now overwhelm the stereoelectronic preference for the axial organometallic substituent. The carbonyl absorption in the infrared spectrum (CH_2Cl_2) of **5** shifts to 1703 cm^{-1} (cf., ν_{CO} = 1708 cm^{-1} for 2-cyclopropyl-4,4-dimethylcyclohexanone[11]), and the ^1H NMR spectrum is unambiguous: H2 appears as a td, with large (11 Hz) couplings to both H_β and $H3_{ax}$. The ^{13}C NMR spectrum also reveals a 5 ppm separation of the diastereotopic metallacycle α-carbons, consistent with the expected proximity of the carbonyl

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(3) (a) Tjaden, E. B.; Stryker, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 6420. (b) Spectroscopic and analytical data are given as supplementary material.

(4) IR (KBr): complex **2**, ν_{CO} = 1691 cm^{-1}; **3**, 1695 cm^{-1}; **4**, 1675 cm^{-1}.

(5) Details of the crystallography are included as supplementary material.

(6) Aue, W. P.; Karhan, J.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 4226.

(7) The magnitude of this coupling constant indicates that rotation about the C_β–C2 bond is restricted.

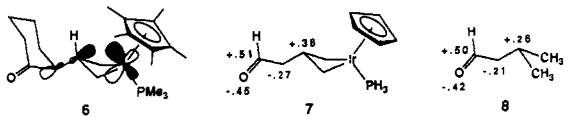
(8) Force field energy minimizations were performed by fixing the metal coordination geometry to the crystal-structure data and allowing the organic moieties to minimize without further restriction. Dihedral angles were driven full rotations to ensure a global energy minimum. The metallacyclobutane pucker angle minimizes essentially to the crystal-structure geometry, suggesting that the ring conformation itself results from steric rather than electronic considerations.

(9) Calculations were carried out on a Silicon Graphics workstation using the MMX version of Allinger's MM2 program (Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127). Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. *Advances in Molecular Modelling*, JAI Press: New York, 1990; pp 65–92. This program is available from Serena Software, P.O. Box 3076, Bloomington, IN 47402.

(10) Allinger, N. L.; Blatter, H. M. *J. Am. Chem. Soc.* **1961**, *83*, 994. See Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 239–243.

(11) Prepared by iodinolysis (Et_2O, −78 °C)[3a] of complex **5**. Details will be presented in a full account.

Chart I



6 7 8

oxygen to one metallacycle α-carbon in the equatorial conformation.

This new stereoelectronic effect can be attributed to a transannular interaction between an occupied metal spd hybrid orbital and the C_β–C2 σ^* orbital (cf., **6**, Chart I).[12] The polarization of the C_β–C2 bond is further delocalized into the carbonyl system by hyperconjugation with the CO π^* orbital.[13] Neither a statistically significant elongation of the Cβ–C2 bond nor a contraction of the C2–C1 bond, however, is observed in the crystal structure (Figure 1). Nonetheless, using the structurally determined bond distances, Fenske–Hall molecular orbital calculations[15] on model complex **7** show consistent metal-induced perturbations of the Mulliken atomic charges compared to the organic fragment **8**. Calculated orbital overlap populations are also consistent with the predicted polarization: the carbonyl and Cβ–C2 bonds are both weakened and the C2–C1 bond is strengthened compared to **8**. Finally, consistent with a transannular interaction, one occupied, substantially metal-centered frontier molecular orbital[16] (see structure **6**, Chart I) includes significant $\sigma^*_{C\beta-C2}$ character, confirming that this interaction is energetically reasonable and symmetry allowed.[17]

In summary, a novel transition-metal-mediated stereoelectronic effect has been identified for enolate-derived metallacyclobutane complexes, capable in favorable cases of controlling the conformation of the appended organic fragment. Further investigation of this interesting phenomenon is anticipated as complexes incorporating other metals, ancillary ligands, and substitution patterns are prepared.

Acknowledgment. We thank Dr. William E. Streib for the X-ray crystal structure determination, Dr. Feng Lin for assistance with NMR experiments, Dr. K. E. Gilbert and Prof. J. J. Gajewski for molecular modelling, Prof. E. R. Davidson and Dr. R. H. Cayton for instruction in MO calculations, and Profs. T. S. Widlanski and J. M. Takacs for helpful discussion. Financial support from the National Science Foundation and an American Cyanamid Faculty Award is gratefully acknowledged. We also thank Johnson Matthey, Inc. for a generous loan of precious metals.

Supplementary Material Available: Spectroscopic data, including selected decoupling, difference NOE, and *J*-resolved NMR spectra, for compounds **2–5**, descriptions of the calculational method and results, and details of the data collection and crystal structure solution for complex **2** (23 pages); tables of observed and calculated structure factors (7 pages). Ordering information is given on any current masthead page.

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(12) Direct transannular interactions between *d* and π^* orbitals of β-oxometallacyclobutane complexes have been discussed: Kemmitt, R. D. W.; McKenna, P.; Russell, D. R.; Prouse, L. J. S. *J. Chem. Soc., Dalton Trans.* **1989**, 345 and references therein.

(13) As described, this effect is a doubly homologous version of the well-documented "α-effect" in α-metalla-enolate complexes, $L_nMCH_2C(O)R$, which show substantial shifts of the carbonyl absorption frequencies to lower energy.[14]

(14) Coates, G. E.; Green, M. L. H.; Wade, K. *Organometallic Compounds*; Butler & Tanner, Ltd.: London, 1968; Vol. 2, p S215. Recent examples: Engelbrecht, J.; Greiser, T.; Weiss, E. *J. Organomet. Chem.* **1981**, *204*, 79. Vicente, J.; Chicote, M. T.; Cayuelas, J. A.; Fernandez-Baeza, J.; Jones, P. G.; Sheldrick, G. M.; Espinet, P. *J. Chem. Soc., Dalton Trans.* **1985**, 1163. Burkhardt, E. R.; Doney, J. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2022.

(15) Hall, M. B.; Fenske, R. F. *Inorg. Chem.* **1972**, *11*, 768. See the supplementary material for details.

(16) This metal orbital, qualitatively speaking, is the one previously involved in the central carbon to metal bond in the starting η^3-allyl cation **1**.

(17) Consistent with a metal-based electronic effect, replacement of the phosphine ligand with the π-acidic CO reduces the magnitude of the shift in ν_{CO} to about half that observed in complex **2**: Wakefield, J. B.; Stryker, J. M. Unpublished results.

Gambieric Acids: Unprecedented Potent Antifungal Substances Isolated from Cultures of a Marine Dinoflagellate *Gambierdiscus toxicus*

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Received September 26, 1991

Marine dinoflagellates produce many polyether compounds of chemical and biomedical importance, e.g., okadaic acid,[1] maitotoxin,[2] brevetoxins,[3] and ciguatoxins.[4] As many of them inhibit the growth of fungi,[5] we screened marine phytoplankton for new antifungal metabolites. Potent antifungal substances were found in one strain of *Gambierdiscus toxicus*,[6] an epiphytic species implicated in ciguatera as the source of maitotoxin and ciguatoxins.[7] While these toxins were retained in the algal cells during culture, the antifungals were released into the medium.[6] Activity-guided purification led to the discovery of four new polyethers, designated gambieric acid, A, B, C, and D (GA-A, GA-B, GA-C, and GA-D). Their property of inhibiting the growth of *Aspergillus niger* was of unprecedented potency, exceeding that of amphotericin B by a factor of 2×10^3.[8] In this communication we report the structures of GA-A (**1**) and GA-C (**2**), which are novel ladder-shaped polyethers.

G. toxicus (GII1 strain), isolated in the Gambier Islands, French Polynesia, was cultured in a seawater medium enriched with ES-1 nutrients[9] at 25 °C for 38 days. The medium (5000 L), free of algal cells, was passed through a column of Amberlite XAD-2. The crude antifungal compounds retained on the column were eluted with MeOH. Purification of the eluate was carried out by solvent partition and column chromatography.[10] Three active constituents were obtained: GA-A (0.6 mg), GA-B (0.15 mg), and a mixture of GA-C and GA-D (5.8 mg). The major activity resided in the mixture, but GA-C and GA-D were inseparable

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(1) Murakami, Y.; Oshima, Y.; Yasumoto, T. *Bull. Jpn. Soc. Sci. Fish.* **1982**, *48*, 69–72.

(2) Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem.* **1988**, *104*, 184–187.

(3) (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773–6775. (b) Shimizu, Y.; Chou, H.-N.; Bando, H.; Duyne, G. V.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 514–515.

(4) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929–8931.

(5) Nagai, H.; Satake, M.; Yasumoto, T. *J. Appl. Phycol.* **1990**, *2*, 305–308.

(6) Nagai, H.; Satake, M.; Murata, M.; Yasumoto, T. In *Toxic Marine Phytoplankton*; Graneli, E. et al., Eds.; Elsevier: New York, 1990; pp 385–390.

(7) Yasumoto, T.; Nakajima, I.; Bagnis, R.; Adachi, R. *Bull. Jpn. Soc. Sci. Fish.* **1977**, *43*, 1021–1026.

(8) GA-A, GA-B, and a mixture of GA-C and GA-D inhibited the growth of *A. niger* at 10, 20, and 10 ng/disk, respectively, by the paper disk method, while amphotericin B and okadaic acid were inhibitory at doses of 20 and 10 μg/disk, respectively. GA-A at a dose of 1 mg/kg showed no toxicity against mice upon an interaperitoneal injection. Cytotoxicity (IC50) of the mixture of GA-C and GA-D against mouse lymphoma L5178Y cells was 1.1 μg/mL when monitored by [^{3}H]thymidine incorporation.

(9) Provasoli, L. In *Proceedings of the U.S.–Japan Conference Held at Hakone*; September 12–15; Watanabe, A., Hattori, A., Eds.; Tokyo, 1966; pp 63–75.

(10) The crude antifungals eluted from the XAD-2 column were suspended in H_2O and extracted with Et_2O and then with 1-butanol. The 1-butanol extract was successively chromatographed on the following columns with solvents as indicated: Toyopearl HW-40 (Tosoh), CH_3OH/H_2O (1:1); Develosil ODS (Nomura Chem.), CH_3OH/H_2O (1:1, 7:3, 1:0); Develosil ODS-7, CH_3CN/H_2O (9:1); Develosil ODS-5, CH_3CN/H_2O (9:1); Develosil 60-5, $CHCl_3/CH_3OH/H_2O$ (200:10:1).

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