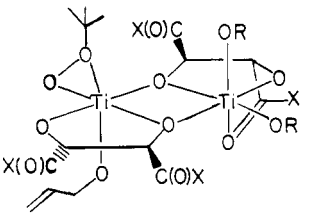
3 was prepared from 9.38 mmol each of $Ti(OEt)_4$, (*R,R*)-diethyl tartrate, and PhC(O)N(OH)Ph in CH_2Cl_2. Removal of solvent, dissolution in toluene, removal of toluene,[6] dissolution in 20 mL of ether, and filtration through dry Celite gave pale yellow plates after the filtrate was allowed to stand at room temperature overnight. The crystals were washed with ether (30 mL) and dried in vacuo (yield, 2.46 g, 51%).[9] Both compounds are very moisture sensitive and all manipulations were carried out in an atmosphere of dry nitrogen.

The structures of **2** and **3**, determined by X-ray diffraction,[10] are displayed in Figure 1. Although **2** is dimeric, its two halves being related by a crystallographically required twofold symmetry axis, one diolate oxygen atom of each tartramide ligand bridges two titanium atoms producing six-coordinate, pseudooctahedral coordination. Each titanium atom in **2** is facially coordinated by a tartramide ligand through the two diolate oxygen atoms, O(2) and O(3), and one of the carbonyl oxygen atoms, O(4). The two isopropoxide ligands are located trans to O(2) and O(4) and the coordination sphere of each metal is completed by the bridging oxygen atom. The Ti···Ti′ internuclear separation is 3.348 (3) Å. The planar Ti_2O_2 core is an asymmetric rhombus, with Ti–O(2) and Ti′–O(2) bond distances of 2.160 (9) and 1.973 (9) Å, respectively. The longer distance is the result of ring strain [O(2)–Ti–O(3) = 76.9 (4)°, O(2)–Ti–O(4) = 79.4 (4)°] and the influence of the good π-donor isopropoxide ligand [Ti–O(6) = 1.805 (9) Å] in the trans position [O(2)–Ti–O(6) = 159.1 (4)°].

Compound **3** also has a binuclear structure with the tartrate ester ligands bridging the two titanium atoms to form a Ti_2O_2 rhombus. A major difference between **2** and **3**, however, arises from the replacement of a terminal alkoxide by a chelating hydroxamate ligand, which has the additional effect of displacing the tartrate ester carbonyl functionality from the metal. This result is not surprising in view of the long Ti–O(4) bond, 2.204 (10) Å, found in **2**, which suggested that this link would be a weak one. In **3** the Ti_2O_2 core is nearly symmetric, probably because the trans influence and ring strain identified for **2** are not present. The two halves of **3** are related by a virtual, but not crystallographically required, *C*2 axis.

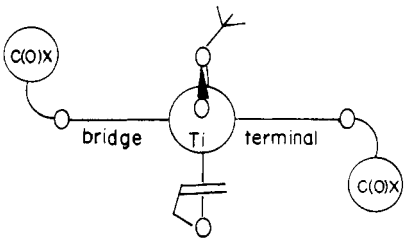
The weak coordination of the tartramide carbonyl oxygen atoms suggests that they will readily dissociate and recoordinate to the metal centers. This feature provides a means of exchanging the alkoxide ligands for the substrate molecules, *tert*-butyl hydroperoxide (TBHP) and allylic alcohol, via an intermediate in which one or both of the titanium atoms are pentacoordinate.

Although the structure found here is not the one employed in earlier discussions[3] of the mechanism for asymmetric epoxidation, it does have important features in common with the previous model. Exchange of two alkoxide ligands and dissociation of the carbonyl oxygen atom in **2**, or the equivalent loss of the hydroxamate and alkoxide ligands in **3**, exposes a meridional set of coordination positions on each titanium atom for binding the allylic alkoxide and potentially bidentate *tert*-butyl peroxide,[11] as shown in **4**. When this structure is viewed down the distal peroxide



4

oxygen–Ti bond axis (**5**), the symmetry of the tartrate "windmill



5

arms" is apparent. A major difference, however, is that there is no longer a local twofold symmetry axis on each titanium atom, so the number of structures like **5** that must be considered as transition states has now doubled (eight vs. four). Thus the present structures reveal important features of dimeric titanium tartrate complexes which should provide valuable insight into the mechanism of the asymmetric epoxidation of allylic alcohols.

Acknowledgment. This work was supported by grants to S.J.L. from the National Science Foundation (CHE 83-40679) and to K.B.S. from the National Institutes of Health (GM 28384). S.F.P. thanks the National Institutes of Health for a National Research Service Award (GM 09812). We are also grateful to M. G. Finn for helpful discussions.

Supplementary Material Available: Atomic positional and thermal parameters for compounds **2** and **3** (4 pages). Ordering information is given on any current masthead page.

(7) Analytical data for **2**. Anal. Calcd for $TiC_{24}H_{32}N_2O_6$: C, 58.54; H, 6.55; N, 5.69; Ti, 9.73; M_r, 492.4. Found: C, 58.77; H, 6.47; N, 5.90; Ti, 9.87; M_r (Signer method[8] in CH_2Cl_2), 997 (indicating a dimer).

(8) Clark, E. P. *Ind. Eng. Chem., Anal. Ed.* **1941**, *13*, 820.

(9) Analytical and spectroscopic data for **3**. Anal. Calcd for $TiC_{23}H_{27}NO_9$: C, 54.23; H, 5.34; N, 2.75; Ti, 9.40; M_r, 509.4. Found: C, 54.11; H, 5.44; N, 2.76; Ti, 9.35; M_r (Signer method[8] in CH_2Cl_2), 908 (indicating a dimer). IR (CH_2Cl_2, cm^{-1}): 1740 (ν_{CO}, tartrate); 1530 (ν_{CO}, hydroxamate). Proton and ^{13}C NMR are complex and will be reported at a later date.

(10) X-ray crystallography. Compound **2** crystallizes as a 1:1 toluene adduct in the orthorhombic system, space group $C222_1$ with a = 18.139 (3) Å, b = 16.240 (4) Å, c = 19.210 (3) Å, V = 5659.0 Å^3, and ρ_{calcd} = 1.264 g cm^{-3} for Z = 4. By use of 1823 unique, observed reflections collected at 225 K by diffractometry using Mo K$\bar{\alpha}$ (λ = 0.7107 Å) radiation out to 2θ = 50°, the structure was solved and refined by standard methods to a current value for the discrepancy index R_1 = 0.071. Compound **3** crystallizes in the monoclinic system, space group $P2_1$, with a = 12.488 (2) Å, b = 19.215 (4) Å, c = 11.838 (1) Å, β = 114.79 (1)°, V = 2578.8 Å^3, and ρ_{calcd} = 1.312 g cm^{-3} for Z = 2. The structure was refined by using 3179 reflections collected as above at 250 K to give R_1 = 0.067. Full details will be reported at a later date.

(11) Mimoun, H.; Chaumette, P.; Mignard, M.; Saussine, L.; Fischer, J.; Weiss, R. *Nouv. J. Chim.* **1983**, *7*, 467.

Total Syntheses of the Amaryllidaceae Alkaloids (±)-Haemanthidine and (±)-Pretazettine

Stephen F. Martin*[†] and Steven K. Davidsen

Department of Chemistry, The University of Texas Austin, Texas 78712

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Previous disclosures from these laboratories[2] have unveiled a general strategy for the synthesis of the alkaloids of the Amaryllidaceae family.[3] Interest in this class of alkaloids has been stimulated in part by reports of the potent anticancer and antiviral activity of the chemically labile base pretazettine (**2**).[4] Subsequent

(1) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980–1985.

(2) (a) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (b) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513.

(3) For reviews of the chemistry of the Amaryllidaceae alkaloids, see: (a) Fuganti, C. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, pp 83–164. (b) Grundon, M. F. In "Specialist Periodical Reports, The Alkaloids"; The Chemical Society: London, 1983; Vol. 13, pp 187–195, also Vol. 1–12. (c) Tsuda, Y. *Heterocycles* **1978**, *10*, 555.

(4) (a) Papas, T. S.; Sandhaus, L.; Chirigos, M. A.; Furusawa, E. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 88. (b) Furusawa, E.; Suzuki, N.; Furusawa, S.; Lee, J. Y. B. *Proc. Soc. Exp. Biol. Med.* **1975**, *149*, 771. (c) Furusawa, E.; Furusawa, S.; Lee, J. Y. B.; Patanavanich, S. *Ibid.* **1976**, *152*, 186; *Chemotherapy (Basel)* **1978**, *24*, 259. (d) Furusawa, E.; Lockwood, R. H.; Furusawa, S.; Lum, M. K. M.; Lee, J. Y. B. *Ibid.* **1979**, *25*, 308. (e) Furusawa, E.; Irie, H.; Combs, D.; Wildman, W. C. *Ibid.* **1980**, *26*, 36. (f) Furusawa, E.; Lum, M. K. M.; Furusawa, S. *Ibid.* **1981**, *27*, 277. (g) Furusawa, E.; Lockwood, R. H. *Proc. West. Pharmacol. Soc.* **1981**, *24*, 45.

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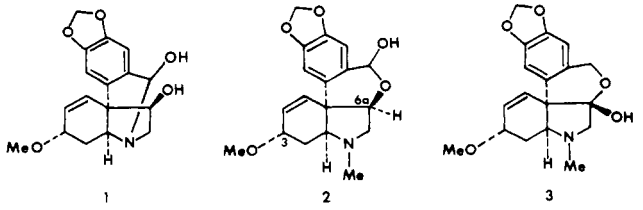
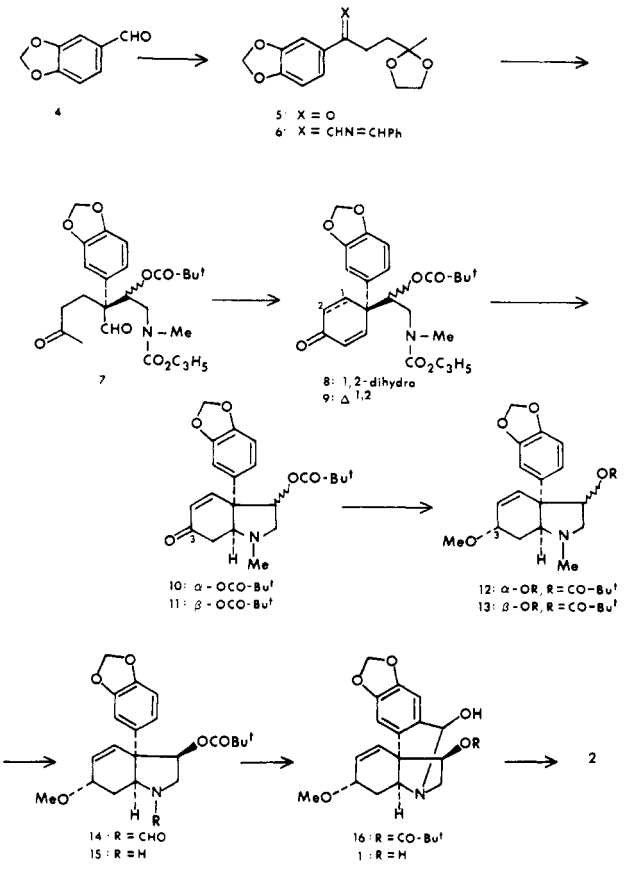


1 2 3

biological testing has revealed, however, that the activity of pretazettine in the Rauscher leukemia system does not appear to carry over into other experimental tumor models.[5] Despite this possible shortcoming in the biological area, pretazettine (**2**) together with the related compounds haemanthidine (**1**) and tazettine (**3**) continues to be an intriguing target for synthetic investigations. These efforts have culminated in reports of the total synthesis of haemanthidine by both Tsuda[6] and Hendrickson,[7] the synthesis of pretazettine by Tsuda,[6] and the synthesis of tazettine by Hendrickson[7] and Danishefsky.[8] A biomimetic approach to pretazettine, which was unexpectedly diverted to a synthesis of 6a-*epi*-pretazettine, has also been unveiled.[9] Inasmuch as Wildman[10] had previously discovered methods to effect the conversions of haemanthidine into pretazettine and of pretazettine into tazettine, any synthesis of haemanthidine constitutes in a formal sense a synthesis of pretazettine and tazettine. The synthetic transformation of tazettine into pretazettine via a multistep route has also been reported.[11] We now wish to describe a concise total synthesis of pretazettine (**2**) via haemanthidine (**1**) utilizing a strategy that features as a key step an efficient method for the construction of a quaternary carbon atom bearing highly functionalized appendages at a carbonyl center.[12]

In the event, reaction of piperonal (**4**) with the Grignard reagent derived from 2-methyl-2-(2-bromoethyl)-1,3-dioxolane[13] (3.3 equiv, 0 °C → room temperature, 16 h) followed by oxidation of the intermediate benzylic alcohol with pyridinium dichromate[14] (2.0 equiv, DMF, room temperature, 4 h) provided the monoprotected 1,4-dione **5** in 81% overall yield. The conversion of **5** to the key intermediate 4,4-disubstituted cyclohexenone **8** was readily effected in 63% overall yield by exploiting our general methodology for the geminal acylation–hydroxyalkylation at a carbonyl carbon via regiospecifically generated metallo enamines.[12] Thus, treatment of **5** with diethyl [(benzylideneamino)lithiomethyl]phosphonate (1.2 equiv, THF, −78 °C → reflux, 3 h) provided the 2-aza diene **6**, which underwent regioselective addition of *n*-butyllithium (1.1 equiv, −78 °C, 1 h) to afford an intermediate metallo enamine, which was treated sequentially with allyl (formylmethyl)-methylcarbamate[15] (1.2 equiv, −78 °C, 0.5 h), pivaloyl chloride (4.0 equiv, −78 °C → room temperature, 5 h), and 3 N aqueous HCl (room temperature, 18 h) to provide the δ-keto aldehyde **7**. Upon treatment with [pyrrolidine–33% aqueous AcOH–MeOH (1:3:30)], **7** cyclized smoothly to give the 4,4-disubstituted cyclohexenone **8** as a mixture (1.5:1) of diastereoisomers. The requisite double bond at C(1) of **9** was conveniently introduced

Scheme I



by bromination and subsequent dehydrobromination [(a) $PhNMe_3Br_3$, EtOAc, 25 °C, 24 h; (b) DBU, C_6H_6, 85 °C, 16 h; 73%] of **8**.

The palladium(0)-catalyzed[16] [$Pd(Ph_3P)_4$, Ph_3P, Bu(Et)-$CHCO_2H$, CH_2Cl_2, 25 °C, 12 h) removal of the allyloxycarbonyl function was accompanied by spontaneous cyclization to provide an inseparable mixture of the hydroindoles **10** and **11** (1.2:1, respectively) in 66% overall yield from **8**. Subsequent hydride reduction [DIBAL (5.0 equiv), THF, −78 °C, 20 min] of the mixture of **10** and **11** gave a mixture of four diastereomeric allylic alcohols. Although it was possible to separate these alcohols by HPLC, it proved to be more expeditious and efficient in practice to subject this mixture directly to sequential mesylation and methanolysis[8] to provide, after separation by conventional HPLC, the allylic methyl ethers **12** (35%) and **13** (24%). Interestingly, no products having the opposite configuration at the allylic position C(3) could be isolated.[17] Attempted oxidative N-demethylation[18] [Pt, O_2, aqueous dioxane (1:1), room temperature, 24 h] of **13** somewhat surprisingly afforded a 3:1 mixture containing the amide **14** as the major product together with the expected secondary amine **15**, which could be easily cycled to **14** by formylation (CH_3CO_2CHO, pyr, room temperature, 20 h). The Bischler-Napieralski cyclization ($POCl_3$, 80 °C, 6 h; H_2O) of **14** provided **16**, which was saponified (LiOH, MeOH, room temperature, 24 h) to afford haemanthidine (**1**) in 28% overall yield from **13**. The haemanthidine thus obtained, which was identical with an authentic sample, was converted by slight modification of the Wildman protocol[10] [MeI (xs), MeOH, room temperature, 6 h; aqueous $NaHCO_3$] into pretazettine (**2**), also identical in all respects with an authentic sample.[19]

(5) We thank Dr. Matthew Suffness in the National Products Branch of the Developmental Therapeutics Program at the National Cancer Institute for this information.

(6) (a) Tsuda, Y.; Ukai, A. Isobe, K. *Tetrahedron Lett.* **1972**, 3153. See also ref 3c.

(7) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781. Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E. *Ibid.* **1970**, *92*, 5538.

(8) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591; **1980**, *102*, 2838.

(9) White, J. D.; Chong, W. K. M.; Thirrung, K. *J. Org. Chem.* **1983**, *48*, 2300.

(10) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150.

(11) Kobayashi, S.; Kihara, M.; Shingu, T. *Heterocycles* **1979**, *12*, 1547.

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(13) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105. See also ref 2a.

(14) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(15) Prepared in 72% overall yield from commercially available (methylamino)acetaldehyde diethyl acetal by treatment with allyl chloroformate (1.2 equiv) [py, (3.0 equiv), CH_2Cl_2, 0 °C → room temperature, 1 h] followed by acid-catalyzed hydrolysis [THF–HCO_2H–HCl (50:10:1), room temperature, 4 h].

(16) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.

(17) In separate experiments it was demonstrated that each of the epimeric allylic alcohols obtained by reduction of either **10** or **11** with DIBAL afforded a single allylic methyl ether, **12** or **13**, respectively, upon sequential mesylation and methanolysis.

(18) Thomas, R. C. *J. Antibiot.* **1982**, *35*, 1202. We thank Dr. R. Gammill of The Upjohn Co. for bringing this procedure to our attention.

Thus, the Amaryllidaceae alkaloid haemanthidine (**1**) is available in 2.3% overall yield via a linear synthetic sequence that involves only 12 chemical operations from commercially available piperonal. Further extensions of this and related methodologies in the alkaloid field are in progress and will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (CA 21860) and the Robert A. Welch Foundation for generous support of this research.

(19) We thank Professor J. B. Hendrickson (Brandeis University), Dr. P. Jeffs (Smith-Kline-French), and Dr. H. Fales (National Institutes of Health) for providing authentic samples of haemanthidine, tazettine, and related alkaloids and Professor E. Furusawa (University of Hawaii) for an authentic sample of pretazettine hydrochloride.

Biosynthesis of Saxitoxin Analogues: The Unexpected Pathway

Yuzuru Shimizu,* Manuel Norte, Akira Hori, Almoursi Genenah, and Masaru Kobayashi

Department of Pharmacognosy and Environmental Health Sciences
College of Pharmacy, University of Rhode Island
Kingston, Rhode Island 02881

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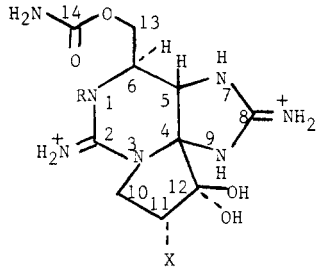
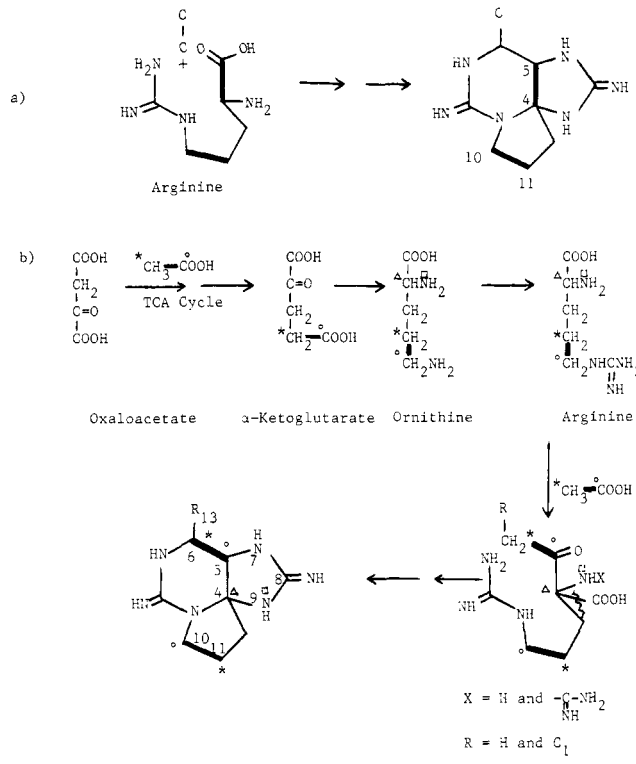
A group of dinoflagellate toxins represented by saxitoxin (**1**) have been extensively investigated because of their occurrences in edible shellfish and their importance as pharmacological tools.[1-3]



1: R = H, X = H
2: R = H, X = OSO_3^-
3: R = OH, X = H

However, only very limited knowledge is available regarding the biosynthetic origin of the unique tricyclic systems having perhydropurine rings.[4] In fact, such compounds as purine nucleotides,[5] C_7 sugars,[6] or arginine[3,7] were implicated as possible precursors, but actual feeding studies have been severely impeded by the nonheterotrophic nature of the photosynthetic toxin-producing dinoflagellates, which resist the utilization of exogeneous organic compounds.[6] After many unsuccessful feeding experiments with various amino acids and other plausible precursors, we decided to try feeding small simple molecules, which might penetrate more easily into the system. In an earlier experiment[3] feeding [2-^{13}C]glycine to a culture of *Gonyaulax tamarensis* resulted in the enrichment of all carbons in isolated gonyautoxin II (**2**)[8] but extra enrichment was observed with C-11 and C-12. This rather unusual enrichment of the two neighboring carbons from the single-labeled precursor was explained by assuming that glycine was incorporated into α-ketoglutarate via glyoxalate–TCA cycle pathway.[3] Since α-ketoglutarate is a precursor of arginine and related compounds, the result was considered to support the arginine precursor theory of the toxins (Scheme Ia).[3,7]

Scheme I



Feeding of [1,2-^{13}C]acetate to *G. tamarensis* also resulted in the modest enrichment of all carbons, but in this case extra enrichment was observed with C-5 and C-6 gonyautoxin II (**2**) and neosaxitoxin (**3**).[9,10] This enrichment of the two adjacent carbons, C-5 and C-6, by one acetate unit as indicated by the coupling pattern was in clear contradiction to the arginine precursor theory in which C-5 must come from C-1 of arginine (Scheme Ia). The experiment was further repeated using a toxic strain of *Aphanizomenon flos-aquae*, a blue-green alga, which had been reported to produce neosaxitoxin and other saxitoxin analogues.[11] We confirmed again the incorporation of [1,2-^{13}C]acetate into C-5

(1) Schantz, E. J. "Microbial Toxins"; Kadis, S., Ciegler, A., Agil, S. J., Eds.; Academic Press: New York, 1972; Vol. II.
(2) Shimizu, Y. "Marine Natural Products, Chemical and Biological Perspectives"; Scheuer, P. J., Ed.; Academic Press: New York, 1979; Vol. I, p 1.
(3) Shimizu, Y. *Pure Appl. Chem.* **1982**, *54*, 1973.
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(5) Mickelson, C. "Toxic Dinoflagellate Blooms"; Taylor, D. L., Seliger, H. H., Eds.; Elsevier North Holland: New York, 1979; p 494.
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(9) Shimizu, Y.; Hsu, C. P.; Fallon, W. E.; Oshima, Y.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1978**, *100*, 6791.
(10) *G. tamarensis* was cultured in the enriched seawater, Guillard F medium (80 L) under fluorescent illumination at 12 °C. Labeled sodium acetate (800 mg) was fed 20 days after inoculation, and the culture was left to grow for additional 8 days. The separation of the toxins was accomplished by a combination of Bio-Gel P-2 gel filtration chromatography and Bio-Rex 70 ion-exchange chromatography as previously reported (Oshima, Y.; Buckley, L. J.; Alam, M.; Shimizu, Y. *Comp. Biochem. Physiol. C* **1977**, *57C*, 31). Gonyautoxin II (**2**) (5.3 mg) and neosaxitoxin (**3**) (8 mg) were the major toxins in this culture, and the other toxins were insufficient for ^{13}C NMR measurement.
(11) Ikawa, M.; Wagner, K.; Faxall, T. L.; Sasner, J. J., Jr. *Toxicon* **1982**, *20*, 747.

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