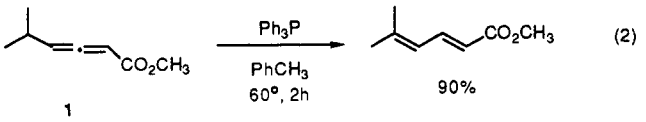
rather unlikely to be able to detect such a species in the acetylene isomerization even if it were an intermediate.



The isomerization of eq 2 was explored as a function of the phosphine to probe the mechanism of the reaction. Poorer donor trivalent phosphorus compounds like phosphites are almost unreactive as catalysts. On the other hand, more nucleophilic phosphines like hexamethylphosphorus triamide or, better, tri-*n*-butylphosphine lead to faster consumption of allene but considerable production of oligomeric products. To differentiate between nucleophilicity and basicity as the more important factor, tertiary amines were examined. *No reaction was observed!* While space limitations preclude further mechanistic speculation, the current observations support the concept of a series of prototropic shifts triggered by nucleophilic addition of the phosphine. The simplicity and extraordinary selectivity of the procedure make it a very practical approach for the synthesis of the very useful polyene carbonyl systems. Its extraordinary chemoselectivity enhances the utility of this new type of catalysis for internal redox compared to typical transition metal catalyzed processes.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. U.K. thanks the Alexander von Humboldt Foundation for a fellowship. Mass spectra were generously provided by the University of California—San Francisco Mass Spectrometry Center sponsored by the NIH Division of Research Resources.

Supplementary Material Available: Characterization data for the products of Table I and eq 1 as well as the substrate of entry 10 of Table I (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of Hemibrevetoxin B

K. C. Nicolaou,* K. Raja Reddy, Golfo Skokotas, Fuminori Sato,† and Xiao-Yi Xiao

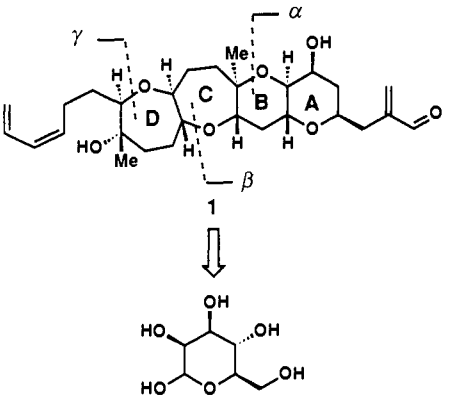
Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037
Department of Chemistry, 9500 Gilman Drive
University of California at San Diego
La Jolla, California 92093

Received June 3, 1992

Hemibrevetoxin B (**1**), isolated from *Gymnodinium breve*, is a member of the "red tide" associated class of marine neurotoxins.[1] Herein we report the first total synthesis of this structurally novel molecule in its naturally occurring form.

After several abortive attempts to construct the hemibrevetoxin B polycyclic skeleton by a convergent approach, we chose a linear route in which each ring was constructed sequentially starting from ring A and moving toward ring D (Scheme I). This, one ring at a time, sequential approach may also be Nature's way of forming the brevetoxins.[2]

Scheme I. Structure and Retrosynthetic Disconnections of Hemibrevetoxin B (**1**). Cyclization Sequence: α, β, γ



The total synthesis of hemibrevetoxin B (**1**) was executed as outlined in Scheme II. The mannose-derived[3] starting material **3** was converted to intermediate **4** by desilylation–benzylation, followed by removal of the acetonide and selective elaboration of the liberated diol using $^{n}Bu_2SnO$–BnBr and TBSOTf. Extension of the side chain of **4** to reach the allylic epoxide **5** was achieved by ozonolysis, followed by Wittig reaction, Dibal reduction, Sharpless epoxidation, SO_3Py oxidation, and a second Wittig olefination. Regio- and stereospecific ring closure of **5** under acidic conditions[4] led to the bicyclic intermediate **6** in 90% yield. Stitching the third ring required the intermediacy of compound **7**, which was derived from **6** by silylation, followed by hydroboration, aldehyde generation, conjugated ester formation, and hydrogenation. Sequential ester hydrolysis and desilylation of **7** followed by lactonization using the Yamaguchi protocol[5] furnished lactone **8**. Elaboration of lactone **8** using our previously developed technology[6,7] of thionolactone formation followed by organometallic reagent addition and a sulfur elimination sequence proceeded smoothly, furnishing the enol ether **9** in 70% overall yield. The alternative procedure via the enol triflate and side chain addition developed by Murai[8] gave **9** in 75% overall yield from **8**. Regio- and stereoselective hydroboration of **10** as previously developed[7] led to **10** (separated from a ca. 4:1 mixture of C-14 epimers), which was elaborated to tetracycle **11** by standard chemistry. Repeat of the side chain attachment as described above for **8** → **10** followed by Swern oxidation led to a mixture of epimeric ketones (C-19, hemibrevetoxin B numbering). Equilibration of this position with DBU in refluxing toluene followed by MeMgI addition led to a 3:2 epimeric mixture (at C-18, isomer **12** is the major product) of alcohols from which **12** was isolated by chromatography. Removal of both benzyl groups from **12** followed by differentiation of the generated hydroxyls and elaboration of the primary position led to methyl ester **13**. Introduction of the diene system was accomplished by selective desilylation followed by Swern oxidation, a Wittig reaction with the ylide derived from $PhSe(CH_2)_3Ph_3P^+I^-$–$^{n}BuLi$, and oxidation–syn-elimination of the resulting selenide. Finally, reduction of the ester group followed by Swern oxidation and in situ treatment[9]

* Author to whom correspondence should be addressed at The Scripps Research Institute.
† Visiting scientist from Dainippon Pharmaceutical Company, 1990–1992.

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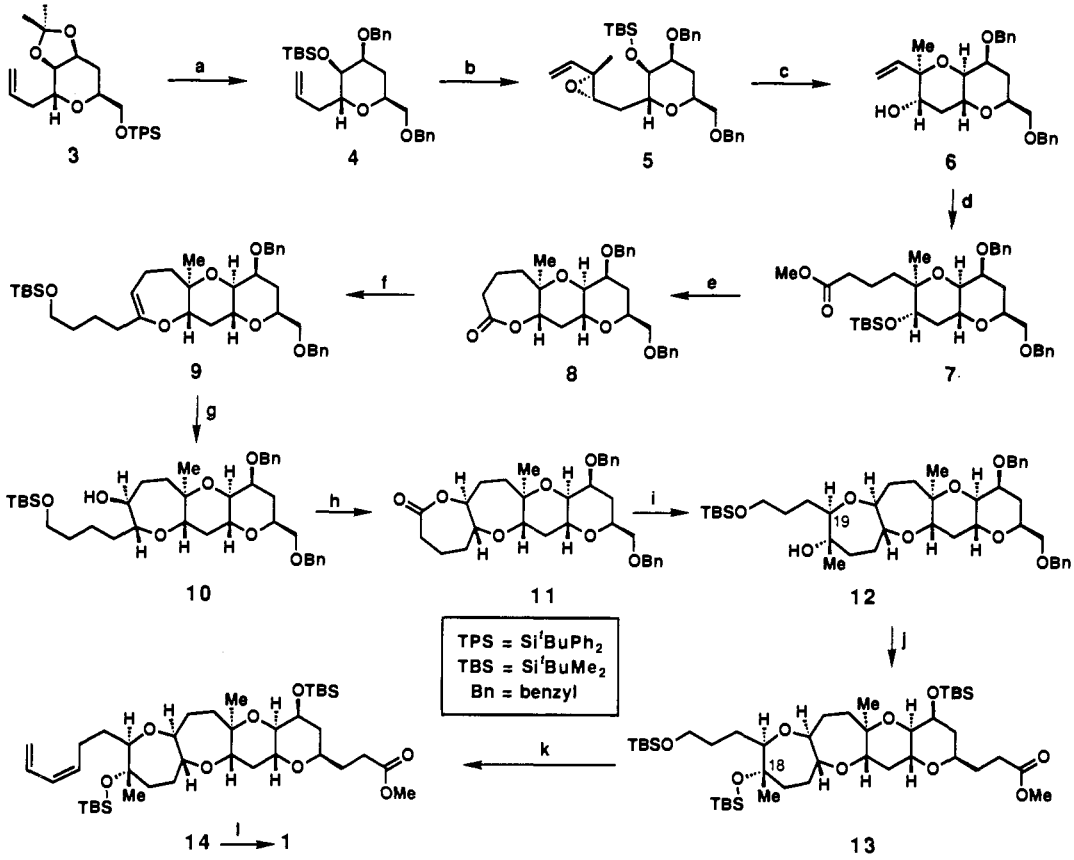
Scheme II. Total Synthesis of Hemibrevetoxin B[a]



[a] Reagents and conditions: (a) (i) 1.2 equiv of TBAF, THF, 25 °C, 1 h, 94%; (ii) 1.5 equiv of NaH, 0.2 equiv of ^{n}Bu$_4$NI, 1.2 equiv of BnBr, THF, 25 °C, 24 h, 90%; (iii) 5 equiv of 80% TFA, toluene, 0 °C, 15 min, 98%; (iv) 1.1 equiv of ^{n}Bu$_2$SnO MeOH, 60 °C, 1.5 h, then solvent replaced with DMF and treated with 1.5 equiv of BnBr, 1.2 equiv of CsF, 16 h, 25 °C, 81% (overall for this one-pot procedure); (v) 1.2 equiv of TBSOTf, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 96%; (b) (i) O_3, CH_2Cl_2, −78 °C, 10 min, then Ph_3P, 25 °C, 1 h; (ii) 1.2 equiv of $Ph_3P{=}C(Me)CO_2Me$, benzene, 80 °C, 2 h, 70%; (iii) 2.2 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 90%; (iv) 0.2 equiv of (+)-DET, 0.15 equiv of Ti(O^{i}Pr)$_4$, 1.5 equiv of ^{t}BuOOH, CH_2Cl_2, 4-Å molecular sieves, −40 → −20 °C, 16 h, 98%; (v) 2.5 equiv of SO_3·py, 4 equiv of Et_3N, CH_2Cl_2–DMSO (4:1), 0 °C, 2 h, 72%; (vi) 1.5 equiv of $Ph_3P^+CH_3Br^-$, 1.3 equiv of NaN(TMS)$_2$, THF, 0 °C, 1 h, 87%; (c) (i) 1.2 equiv of TBAF, THF, 25 °C, 2 h, 97%; (ii) 0.3 equiv of CSA, CH_2Cl_2, 0 °C, 5 h, 90%; (d) (i) 1.2 equiv of TBSOTf, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 85%; (ii) 1.2 equiv of BH_3·THF, THF, 0 °C, 1 h, NaOH–H_2O_2, 90%; (iii) Swern oxidation, 98%; (iv) 1.2 equiv of $Ph_3P{=}CHCO_2Me$, benzene, 25 °C, 3 h, 89%; (v) H_2, 5% Pd/C, EtOAc, 15 h, 96%; (e) (i) 1.5 equiv of LiOH·H_2O, THF–H_2O (1:1), 50 °C, 1 h, 92%; (ii) 1.2 equiv of TBAF, THF, 25 °C, 18 h, 95%; (iii) 1.1 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et_3N, THF, 0 °C, 1 h then 6 equiv of DMAP, benzene, 80 °C, 3 h, 97%; (f) (i) 2 equiv of Lawesson's reagent, toluene, 110 °C, 3 h, 82%; (ii) 3 equiv of TBSO(CH$_2$)$_4$(2-Th)(CN)CuLi$_2$, ether, −78 → 10 °C, 4 equiv of I(CH$_2$)$_4$I, 5 equiv of pempidine, 1 h, 85%; (g) 1.2 equiv of BH_3·THF, THF, 0 °C, 1 h, NaOH–H_2O_2, 89%; (h) (i) 1.1 equiv of Ac_2O, 1.2 equiv of DMAP, CH_2Cl_2, 1 h, 25 °C, 95%; (ii) 0.2 equiv of CSA, MeOH–CH_2Cl_2 (1:1), 0 °C, 1 h, 90%; (iii) 3 equiv of PDC, DMF, 16 h, 25 °C, 89%; (iv) 1.1 equiv of K_2CO_3, MeOH, 3 h, 25 °C, 82%; (v) 1.1 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et_3N, THF, 0 °C, 1 h, then 6 equiv of DMAP, benzene, 5 h, 80 °C; (i) (i) 1.2 equiv of Lawesson's reagent, toluene, 110 °C, 5 h, 75%; (ii) 3 equiv of TBSO(CH$_2$)$_3$(2-Th)(CN)CuLi$_2$, ether, −78 → 0 °C, 4 equiv of I(CH$_2$)$_4$I, 5 equiv of pempidine, 2 h, 85%; (iii) 1.2 equiv of BH_3·THF, THF, 0 °C, 1 h, NaOH–H_2O_2, 89%; (iv) Swern oxidation, 90%; (v) 0.3 equiv of DBU, toluene, 110 °C, 2 h, 92%; (vi) 1.1 equiv of MeMgI, ether, −78 → −10 °C, 4 h, 94%; (j) (i) H_2, Pd(OH)$_2$, EtOAc, 40 psi, 4 h, 89%; (ii) 1.2 equiv of ^{t}BuCOCl, 1.4 equiv of DMAP, CH_2Cl_2, 25 °C, 1 h, 90%; (iii) 2.2 equiv of TBSOTf, 2.5 equiv of 2,6-lutidine, CH_2Cl_2, 3 h, 25 °C, 82%; (iv) 2.2 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 15 min, 96%; (v) Swern oxidation; (vi) 1.1 equiv of $Ph_3P{=}CHCO_2Me$, benzene, 3 h, 80% for two steps; (vii) H_2, 5% Pd/C, EtOAc, 16 h, 95%; (k) (i) 0.2 equiv of CSA, MeOH–CH_2Cl_2 (1:1), 0 °C, 3 h, 86%; (ii) Swern oxidation, 90%; (iii) 1.5 equiv of $PhSe(CH_2)_3Ph_3P^+I^-$, 1.1 equiv of ^{n}BuLi, THF, −78 → 25 °C, 15 min, 72%; (iv) H_2O_2, $NaHCO_3$, THF, 16 h, 25 °C, 78%; (l) (i) 2.2 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 3 h, 95%; (ii) Swern oxidation, 1.5 equiv of $Me_2(CH_2)N^+I^-$, −78 → 25 °C, 24 h, 90%; (iii) SiF_4, CH_3CN–CH_2Cl_2 (1:1), 0 °C, 2 h, 82%.

of the resulting aldehyde with Eschenmoser's salt led, upon workup and desilylation,[10] to hemibrevetoxin B (**1**) in 70% overall yield from **14**. Synthetic **1** exhibited spectral data identical (IR, MS, UV, ^{1}H and ^{13}C NMR) to those of the naturally derived material.[11]

The described synthesis represents the first total synthesis of not only **1** but also any member of the brevetoxin class.[12]

Acknowledgment. We thank Drs. Dee H. Huang and Gary Suizdak, of The Scripps Research Institute, for their NMR and mass spectroscopic assistance, respectively. This work was financially supported by the National Institutes of Health and The Scripps Research Institute.

Supplementary Material Available: A listing of selected physical data (R_f, $[\alpha]_D$, IR, ^{1}H and ^{13}C NMR, and HRMS) for compounds **5–8**, **10**, **11**, **13**, **14**, and **1** (9 pages). Ordering information is given on any current masthead page.

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(11) We thank Professor Y. Shimizu for providing us with ^{1}H and ^{13}C NMR spectra of hemibrevetoxin B (**1**).

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