Novel Stereocontrolled Synthesis of the Nonacene Ring System of Brevetoxin A. Conformational-Reactivity Effects in Nine-Membered Rings

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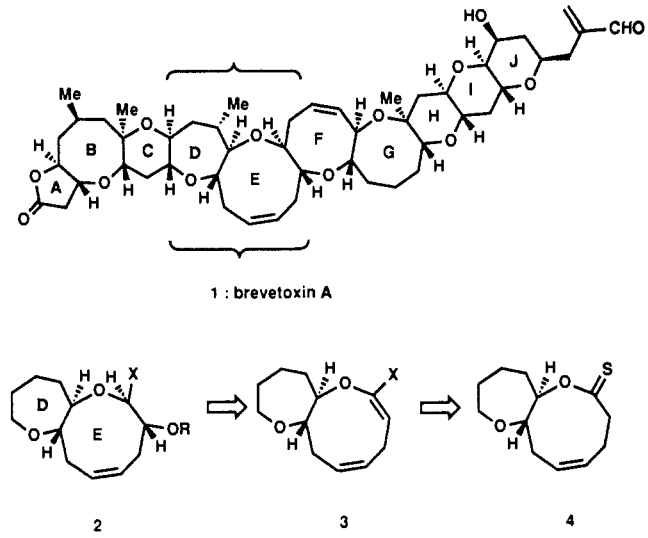
Brevetoxin A (**1**) is one of the most powerful ichthyotoxins isolated from the "red tide" dinoflagellate *Gymnodinium breve*. An X-ray crystallographic analysis established structure **1** for this neurotoxin.[1] It is a striking molecular web consisting of 10 oxygen-containing fused rings, ranging in size from five to nine membered and possessing 22 stereogenic centers. This molecular structure presents an opportunistic and formidable synthetic problem, particularly with regard to the construction of its medium-sized rings of which the nine-membered is perhaps the most challenging. In this communication we describe a novel and stereocontrolled construction of a model system representing the nonacene region of brevetoxin A (**1**).

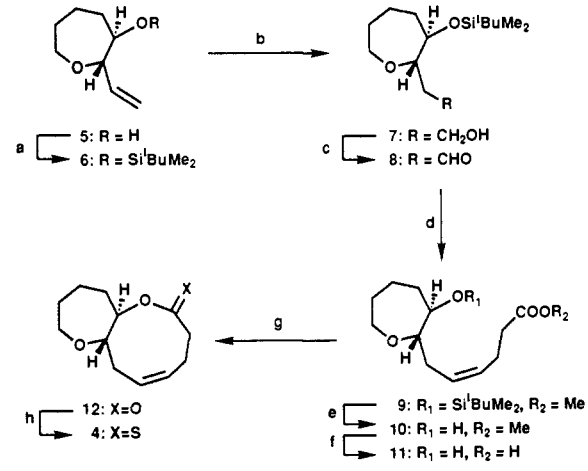
The strategy for the construction of **2** was based on the retrosynthetic analysis shown in Scheme I. Thus the thionolactone **4** was to serve as a precursor to diene **3**, which was expected to be converted to the desired intermediate **2** with regioselectivity, facial selectivity, and trans selectivity. The key intermediate thionolactone **4** was prepared in excellent overall yield from the previously reported[2] intermediate **5** as described in Scheme II. Thus silylation (95%) of the secondary hydroxyl group in **5** followed by hydroboration (97%) and oxidation led to aldehyde **8** via intermediates **6** and **7**. Wittig olefination of **8** led to compound **9** (80% from **7**), which was sequentially deprotected to give hydroxy acid **11** via **10** (80% overall). Lactonization of **11** via its 2-pyridylthiol ester[3] proceeded smoothly to produce lactone **12** in 79% yield, which was then converted to target thionolactone **4** by heating (180 °C) with Lawesson's reagent[4] in the presence of 1,1,3,3-tetramethylthiourea (94%).

The transformation of **4** to **3** was achieved by a series of novel reactions as depicted in Scheme III. A direct and efficient entry into the oxononadiene series was developed by the addition of Shiner's reagent (2-lithio-1,3-dioxolane)[5] to **4** followed by quenching with 1,4-diiodobutane and warming up in the presence of a nonnucleophilic base (*N*-methyl-2,2,6,6-pentamethylpiperidine). Compound **3** was thus produced in 68% yield, presumably via intermediates **13** and **14** and by the mechanism indicated in Scheme III. It is important to note that several other attempts to construct this nine-membered-ring system using more conventional methods were unsuccessful. The planned two-step conversion of **3** to **2** via epoxide formation and reductive opening was thwarted by the unexpected relative reactivity of the double

Scheme I



Scheme II. Synthesis of Thionolactone **4**[a]



[a] Reagents and conditions: (a) 1.5 equiv of TBDMSCl, 2.0 equiv of imidazole, DMF, 25 °C, 2 h, 95%; (b) 1.5 equiv of 9-BBN, THF, 0 °C, 3 h, then excess NaOH, excess H_2O_2, 0 °C, 97%; (c) 4.0 equiv of SO_3·py, 5.0 equiv of Et_3N, 1:1 DMSO–CH_2Cl_2, 0 °C, 2 h; (d) 2.5 equiv of $Ph_3P^+(CH_2)_3COOMe\ Br^-$, 2.0 equiv of $NaN(TMS)_2$, THF, −78 °C, 1 h, 80% from **7**; (e) 1.5 equiv of TBAF, THF, 0 °C, 2 h, 80%; (f) 3.0 equiv of LiOH, MeOH–THF–H_2O, 25 °C, 2 h, 100%; (g) 1.5 equiv of (py)SS(py), 1.5 equiv of PPh_3, CH_2Cl_2, 25 °C, 2 h, then 0.2 equiv of $AgClO_4$, toluene (0.02 M), 110 °C, 18 h, 79%; (h) 2.0 equiv of Lawesson's reagent, 2.0 equiv of 1,1,3,3-tetramethylthiourea, xylene, 180 °C, 2 h, 94%.

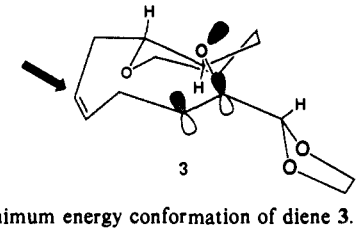


Figure 1. Minimum energy conformation of diene **3**.

bonds of **3**. Thus the epoxidation of **3** with dimethyldioxirane[6] occurred selectively at the disubstituted double bond, producing selectively the epoxide **15** (75% yield, ca. 4:1 ratio of β:α epoxides). MM2 calculations on **3** revealed a minimum conformation which may explain this regio- and stereochemical result (Figure 1). Thus, the lone pair of electrons of the nine-membered-ring oxygen

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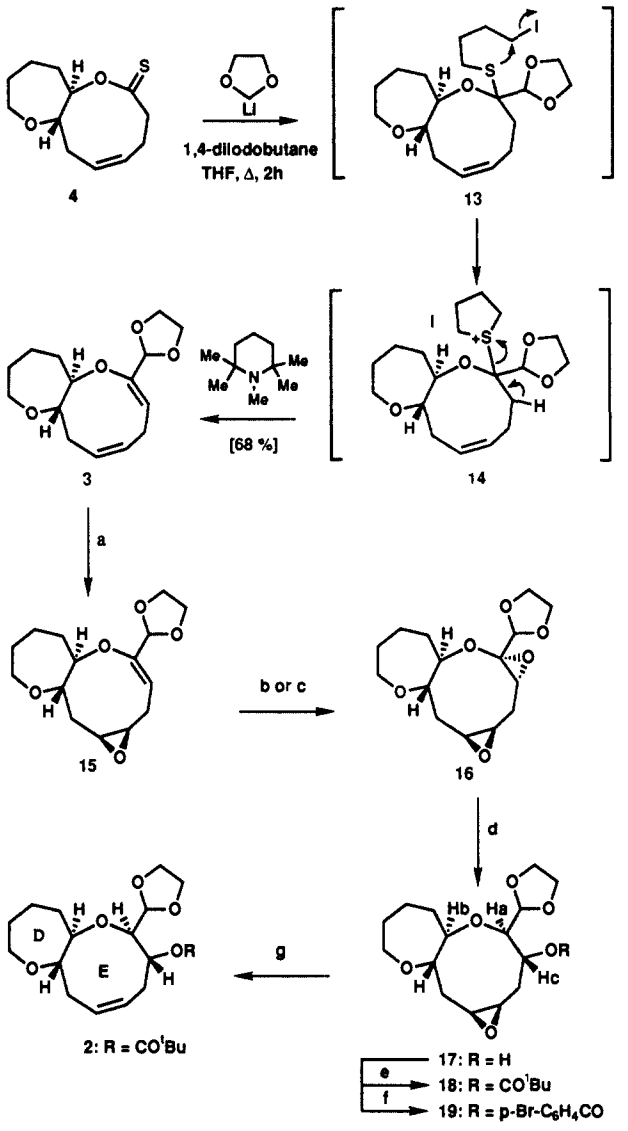
Scheme III. Construction of the DE Ring System (2) of Brevetoxin A (1)[a]



[a] Reagents and conditions: (a) excess dimethyldioxirane, acetone, 0 °C, 20 min, 89%; (b) 5.0 equiv of MMPP, DMF, 25 → 50 °C, 6 h, 75%; (c) 1.5 equiv of mCPBA, 2.0 equiv of $NaHCO_3$, CCl_4, 0 °C, 2 h; (d) excess Et_3SiH, 2.0 equiv of BH_3·THF, 0.1 equiv of TMSOTf, CH_2Cl_2 −20 → 25 °C, 2 h, 56% from **15**; (e) 2.0 equiv of $(CH_3)_3CCOCl$, py, 0 → 25 °C, 18 h, 94%; (f) 2.0 equiv of *p*-BrC_6H_4COCl, py, 0 → 25 °C, 18 h, 90%; (g) 10 equiv of WCl_6, 20 equiv of BuLi, −78 °C, 2 h, 80%.

are out of the plane of the p orbitals of the enol ether (accounting for its lower than expected reactivity toward electrophiles); furthermore, the β-face of the disubstituted double bond appears in this conformation to be more exposed to attack than the α-face, accounting for the predominance of the β-epoxide (Figure 1).[7] Further epoxidation with mCPBA transformed **15** to **16** again with considerable stereocontrol (ca. 4:1 α:β epoxide ratio). Reductive opening of the newly generated epoxide in **16** with Et_3SiH–BH_3·THF–TMSOTf occurred chemo- and regioselectively to furnish the desired skeleton **17** (ca. 56% overall yield from **15**). The stereochemical structure of **17** was tentatively assigned by NMR studies on its pivalate ester **18** (^1H NMR, 500 MHz, $CDCl_3$: NOE between H_a and H_b, ca. 14%; $J_{a,c}$ = 5.6 Hz) and was confirmed by X-ray crystallographic analysis of its *p*-bromobenzoate **19** (see ORTEP drawing, Figure 2). Finally, deoxygenation of **18** with WCl_6–nBuLi[8] led efficiently to the

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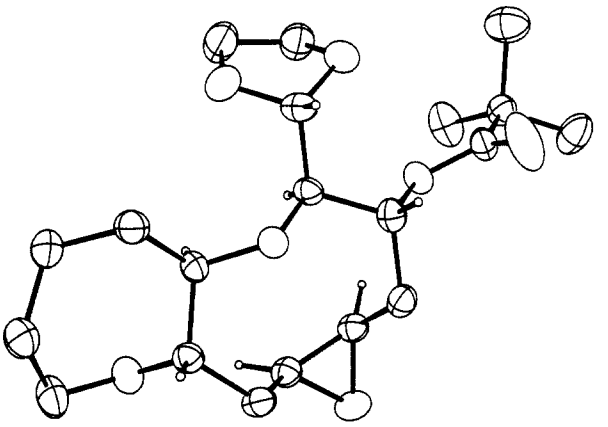

Figure 2. ORTEP drawing of **19**.

targeted intermediate **2** (R = CO'Bu) equipped with the proper functionality for further elaboration.

The described chemistry provides a possible solution to the construction of the challenging oxononacene region of brevetoxin A (**1**). A number of novel reactions and reagents were utilized, and some interesting and unusual conformational effects and reactivity patterns in this ring system were also uncovered. The potential of this technology in the synthesis of **1** and other marine natural products is currently being explored.

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Supplementary Material Available: Listing of R_f, $[\alpha]_D$, IR, ^1H NMR, and mass spectral data for compounds **12**, **4**, **3**, **15**, **17**, **18**, and **2** and X-ray crystallographic parameters for **19** (12 pages). Ordering information is given on any current masthead page.

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Deviations from the Simple Two-Parameter Model-Free Approach to the Interpretation of Nitrogen-15 Nuclear Magnetic Relaxation of Proteins

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^{13}C and ^{15}N nuclear magnetic relaxation data provide a wealth of information on the nature of internal motions of macromolecules in solution.[1] In general, the fast internal motions can be described by two model independent quantities:[2] a generalized order parameter S, which provides a measure of the amplitude of the motion, and an effective correlation time τ_e. This simple formalism has proved remarkably successful in accounting for relaxation data on small molecules and simple polymers, as well as for fragmentory data obtained from one-dimensional NMR measurements on

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