New Synthetic Strategies for the Construction of Medium-Size Cyclic Ethers. Stereocontrolled Synthesis of the BCD Ring Framework of Brevetoxin A†

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Brevetoxin A is the most potent (LC_{100} = 4 ng/mL) icthiotoxin isolated from the "red tide" dinoflagellate *Gymnodinium breve*. A recent X-ray crystallographic analysis[1] established structure **1** for this neurotoxin: a remarkable molecular framework 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 unusual and formidable synthetic challenge, particularly with regard to the construction of its medium-size ring systems. In this communication we describe novel synthetic technology and strategies for the synthesis of the BCD ring framework of brevetoxin A (**1**).

Focusing initially on the BCD ring system of brevetoxin A (**1**), and following the disconnections indicated in Scheme I with standard functional-group manipulations, intermediate **2** was generated. Recognizing the similarities in structure at the two ends of intermediate **2** as generated by this strategic analysis, we sought a "symmetrical" approach to its construction in which two identical groups were simultaneously functionalized. Scheme I depicts our adopted strategy, which relies on (a) the premise of final differentiation of the two hydroxyl groups in **2**; (b) the expectation of β attack on the double bonds of **3**; (c) the intermediacy of **4** as a precursor to **3** via new methodology; and (d) the simultaneous attachment of two two-carbon units on the carbonyl groups of key intermediate **5**. The successful execution of this strategy is described below.

A stereocontrolled and efficient synthesis of key intermediate **5** in its designated enantiomeric form is described in the supplementary material. Addition of excess reagent **6** (Scheme II) to the dicarbonyl compound **5** in the presence of $ZnBr_2$ resulted in the formation of a diastereomeric mixture of compound **7** (four isomers, 81% total yield).[2] Hydrogenolysis of all four benzyl groups in **7** followed by lactonization via the corresponding bis(pyridylthio) ester[3] gave the bis(lactone) **4** (mixture of four compounds, 76% overall). Introduction of the unsaturation in the eight-membered ring proceeded smoothly upon chemoselective desilylation (HF·pyridine, 85%) of **4** followed by exposure to Martin's reagent[4] (87%). Repetition of this sequence resulted in the formation of the doubly conjugated system **9** in excellent overall yield (82%).[5] Saturation of the double bonds in **9** followed by Lawesson[6] thionation furnished the dithionolactone **11** in 63% overall yield via dilactone **10**. The exchange of oxygen for sulfur at this stage as a prelude to the ensuing chemistry was crucial to its success and was based on previous observations in these laboratories.[7] Thus, addition of nBu_3SnLi to **11** followed by quenching with excess methyl iodide gave the bis(methylthio) ether **12** (86%). Double elimination of methyl mercaptan from **12** was induced by cuprous triflate leading to the bis(vinylstannane) **13** in 45% yield.[8] Transmetalation with nBuLi resulted in the conversion of **13** to the bis(lithio) derivative **14**, which was trapped with excess (benzyloxy)ethyl triflate to install the requisite two-carbon chain on both sides of the molecule, leading to compound **3**. The next operation required regio- and stereoselective attack of a hydroborating agent from the top side of **3**. Ample regiochemical precedent,[9] as well as MM2 calculations and modeling, was predictive of such a scenario. Indeed, hydroboration of **3** with thexylborane resulted in a single stereoisomer (73% yield) proven to possess the correct structure **2**. The stereochemical assignments in **2**, and its bis(acetate) **15** (prepared from **2** by standard conditions, 90% yield), were made on the basis of comparisons of the shifts and coupling constants of H_a and H_b of bis(acetate) **15** [H_a, δ 4.8, ddd, J = 10.2, 10.2, 2.6 Hz; H_b, δ 4.9, dd, J = 5.3, 5.3 Hz] with those of stereochemically defined models.[10] X-ray crys-

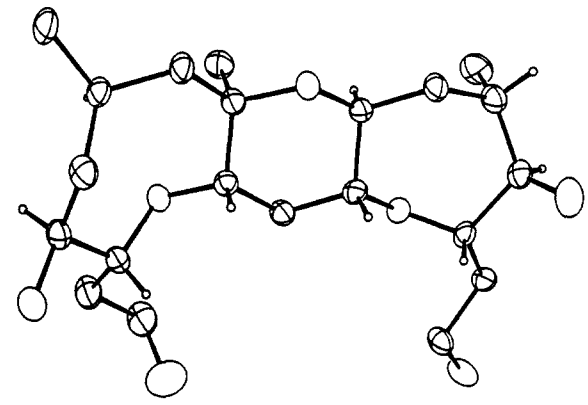
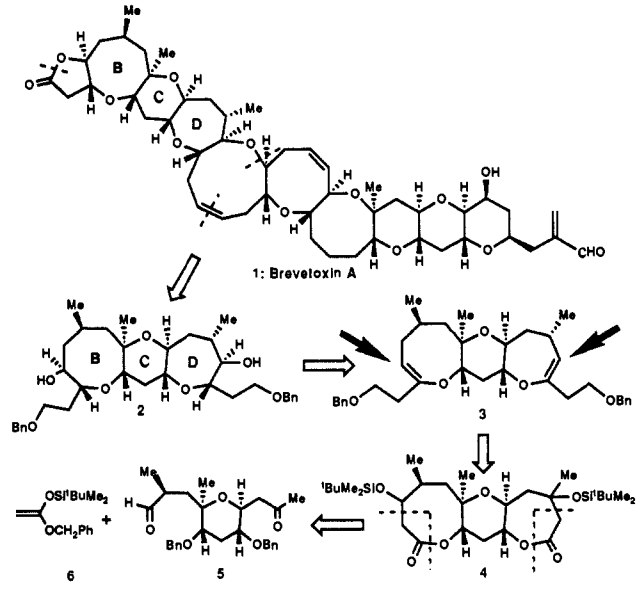


Figure 1. ORTEP drawing of compound **2**.

Scheme I. Retrosynthetic Analysis of Brevetoxin A[a]



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† This work was partially carried out at the University of Pennsylvania.

(1) Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 514. See also: Pawlak, M.; 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.

(2) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

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(5) The one-step approach to **9** from **4** gave a lower overall yield and thus was replaced with the more efficient sequence described.

(6) Sheibye, S.; Pederson, E. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229. For reviews, see: (a) Jones, B. A.; Bradshaw, J. S. *Chem. Rev.* **1984**, *84*, 17. (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1984**, *41*, 5061.

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(8) This sequence leading to vinylstannanes from thionolactones is a general process. Further examples demonstrating this methodology are available and will be included in a full account of this work.

(9) Brown, H. C.; Negishi, E. *Synthesis* **1974**, 77.

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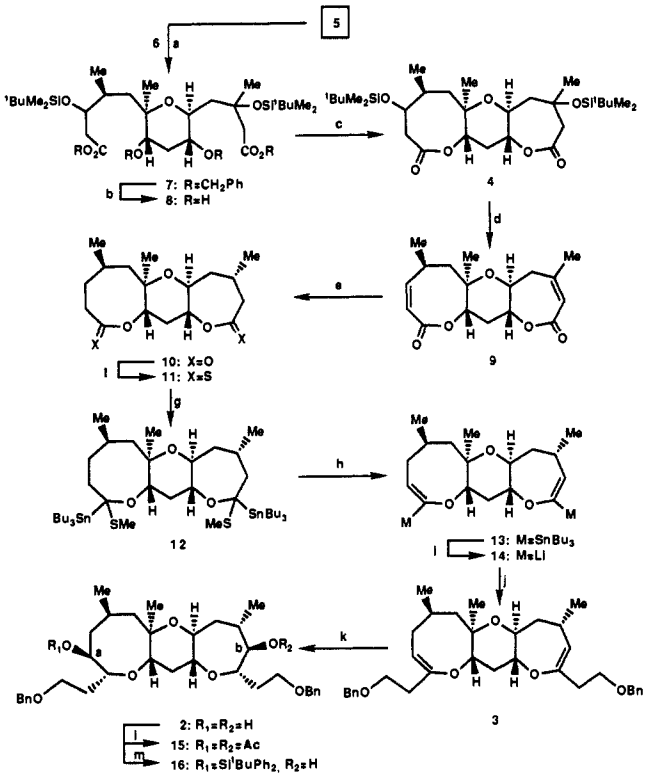
Scheme II. Synthesis of the BCD Ring Fragment of Brevetoxin A[a]



[a] Reagents and conditions: (a) 1.0 equiv of $ZnBr_2$, ether, −78 °C, then 3.0 equiv of **6**, 30 min, 81%; (b) H_2, $Pd(OH)_2$, THF, 25 °C, 3 h, 100%; (c) 2.5 equiv of $(pyrS)_2$, 2.5 equiv of PPh_3, CH_2Cl_2, 25 °C, 1 h, then 2.2 equiv of $AgClO_4$, toluene, 115 °C, 4 h, 76%; (d) (i) 1.0 equiv of HF·pyr, THF, 0 °C, 3 h, 85%, then 1.2 equiv of Martin's sulfurane, CH_2Cl_2, 0 °C, 30 min, 87%. (ii) 1.0 equiv of HF·pyr, THF, 0 °C, 4 h, 92%, then 1.2 equiv of Martin's sulfurane, CH_2Cl_2, 0 °C, 30 min, 92%; (e) H_2, 10% Pd on C, THF, 25 °C, 4 h, 100%; (f) 3.0 equiv of Lawesson's reagent, 3.0 equiv of 1,1,3,3-tetramethylthiourea, xylenes, 115 °C, 3 h, 63%; (g) 3.0 equiv of nBu_3SnLi, THF, −78 °C, 10 min, then 6.0 equiv of CH_3I, −78 °C, 15 min, 86%; (h) 4.0 equiv of $(CuOTf)_2$, benzene, 4.05 equiv of pentamethylpiperidine, 25 °C, 45%; (i) 3.0 equiv of nBuLi, THF, −78 °C, 5 min; (j) 5.0 equiv of (benzyloxy)ethyl triflate, 25 equiv of HMPA, 10 equiv of Et_3N, THF, −78 to 25 °C, 45 min, 65%; (k) 4.0 equiv of thexylborane, THF, 0 °C, 5 h, then 20 equiv of NaOH, 20 equiv of H_2O_2, 0 °C, 2 h, 73%; (l) 4.0 equiv of DMAP, 3.0 equiv of Ac_2O, CH_2Cl_2, 0 °C, 2 h, 90%; (m) 1.5 equiv of $^tBuPh_2SiCl$, 3.0 equiv of imidazole, DMF, 25 °C, 24 h, 82%.

tallographic analysis[11] of diol **2** confirmed the structures of these compounds (see ORTEP drawing, Figure 1). Capitalizing on the difference in the steric environment of the two hydroxyl groups in **3**, the mono(silyl ether) **16** was easily formed under standard conditions (82% yield).

The described chemistry offers a stereoselective route to the BCD ring system of brevetoxin A (**1**) which is appropriately functionalized for further elaboration. The synthesis demonstrates new synthetic technology for the construction of medium-size cyclic ethers from thionolactones via organostannanes and follows a highly economical strategy designed by recognizing the subtle symmetry present in the targeted intermediate **2**.

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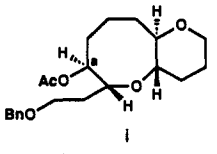
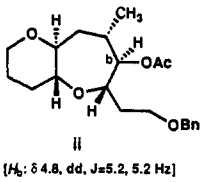
Supplementary Material Available: A scheme with reagents and conditions for the synthesis of intermediate **5** and listing of selected R_f, $[\alpha]$, ^1H NMR, and mass spectroscopic data for compounds **5**, **9**, **11**, **13**, **3**, **2**, and **16** as well as crystallographic data for compound **2** (18 pages). Ordering information is given on any current masthead page.

(10) These models include compounds i and ii, which were structurally defined by X-ray crystallographic analysis.[11]



i

[H_b: δ 4.9, ddd, J=10.0, 10.0, 2.5 Hz]



ii

[H_b: δ 4.8, dd, J=5.2, 5.2 Hz]

(11) We thank Dr. P. Carroll of the University of Pennsylvania for the X-ray crystallographic analyses described in this paper. Details will be published in a full account of this work.

Trifluoromethanesulfonic Acid Catalyzed Electrophilic Sulfuration of Alkanes (Cycloalkanes) with Elemental Sulfur to Dialkyl (Dicycloalkyl) Sulfides[1a,b]

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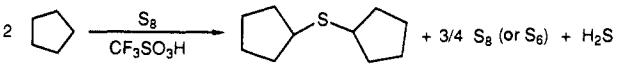
Selective functionalization of saturated hydrocarbons to the corresponding monosubstituted derivatives is a most desirable goal in hydrocarbon chemistry. We have found several superacid catalyzed electrophilic substitution reactions of alkanes such as alkylation,[2] oxyfunctionalization,[3] halogenation,[4] nitration[5] and formylation.[6] The key to these reactions lies in the σ-donor ability of C–H and C–C bonds under superacidic conditions.[7]

In continuation of these studies, we now report the facile electrophilic sulfuration of saturated hydrocarbons with elemental sulfur in trifluoromethanesulfonic acid medium. Heating of elemental sulfur with excess cyclopentane in trifluoromethanesulfonic acid (serving also as the reaction medium) in a stainless steel autoclave at 150 °C for 12 h gave, after cooling of the reaction mixture to room temperature followed by aqueous workup, dicyclopentyl sulfide in 46% isolated yield (based on the amount of sulfur consumed).



(1) (a) Dedicated to Professor Paul v. R. Schleyer for his 60th birthday. (b) Electrophilic Reactions at Single Bonds. 24. Part 23: Olah, G. A.; Heiliger, L.; Aniszfeld, R.; Prakash, G. K. S. *New. J. Chem.* In press.

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(8) 2-Propanethiol on treatment with trifluoromethanesulfonic acid exclusively gave diisopropyl sulfide.

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