and the C_3 trigonal plane is 68°). These data indicate that the possible Cu---Cu interaction is at best very weak but more probably that it is nonexistent.[17] For example, the Cu---Cu distance in **1** is about 0.3–0.6 Å longer than those in the tetramers $(CuX)_4$ (X = CH_2SiMe_3,[18] O-*t*-Bu,[19] or NEt_2[20]). A final point concerns the geometries at the sulfurs which are all pyramidal. This is, of course, in sharp contrast to the usual ether coordination in which the oxygen is normally planar.

In conclusion it is possible to summarize the results of this structural study as follows: (a) **1**, which corresponds to the higher order cuprate $Li_3Cu_2R_5$, is (at least in the phenyl case) an association of the $[CuR_3]^{2-}$ and $[CuR_2]^-$ moieties and Li^+ ions; (b) it bears little resemblance to the previously reported series of clusters $[Li_nCu_{5-n}Ph_6]^-$ which are based solely on the association of three $[CuPh_2]^-$ moieties with bridging Li^+ or Cu^+ ions; and (c) the moiety $[CuPh_3]^{2-}$ has, for the first time, been structurally characterized as part of a higher order cuprate salt. In addition, the ^{13}C NMR of Me_2S solutions of crystals of **1** shows similar peaks to those that were attributed by Bertz[7] to "Li_2CuPh_3" and "$LiCuPh_2$" prepared from CuBr and PhLi. Efforts are now underway to crystallize a pure species corresponding to the "Li_2CuPh_3" formula.

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Supplementary Material Available: Tables of crystallographic data, summary of data collection and refinement, bond distances and angles, anisotropic thermal parameters, and hydrogen coordinates and drawings of the two molecules in the asymmetric unit showing the atom-numbering scheme and anisotropic thermal ellipsoids for **1** (15 pages). Ordering information is given on any current masthead page.

(17) For calculations on d^{10}–d^{10} metal interactions, see: Mehrotra, P. K.; Hoffmann, R. *Inorg. Chem.* **1978**, *17*, 2187; Dedieu, A.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2074.
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Synthetic Studies on the Dioxepane Region of Brevetoxin B. New Synthetic Technology for the Construction of Oxepanes and Synthesis of a Model for the CDEF Ring Skeleton of Brevetoxin B

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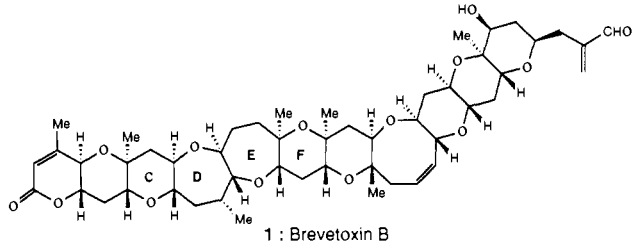
In exploring strategies toward the total synthesis of the marine toxin brevetoxin B (**1**),[1] it became apparent that the bis(oxepane)

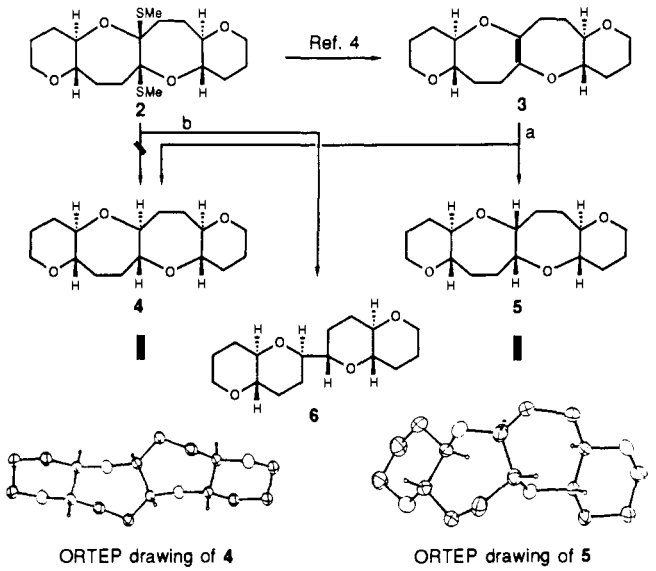


1 : Brevetoxin B

region of the molecule was posing a serious challenge. Our attempts to develop entries into this skeleton, applying conventional methods, or our recently developed technology for cyclic ether construction based on hydroxy epoxides,[2] hydroxy dithioketals,[3] or thionolactones[4,5] were thwarted by unexpected but often interesting reactions. In this communication we report the following: (a) some of these novel reactions; (b) new synthetic technology for the construction of complex oxepanes; and (c) application of this new technology to a successful synthesis of a series of models for the CDEF ring skeleton of brevetoxin B (e.g., **1**), representing the bis(oxepane) system and its adjacent rings. A second approach to this novel framework is also reported.

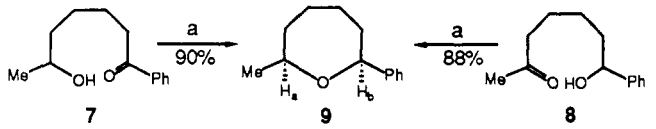
Scheme I outlines our early expectations and results in our quest to reach the CDEF skeleton of brevetoxin B (**1**) from intermediates **2** and **3**. Contrary to our previous assignments,[4] the $AgBF_4$–Et_3SiH reduction of **2** gave not the expected dioxepane framework **4** but instead the novel rearrangement product **6**.[6] Furthermore, reduction of the olefin **3** (easily derived from **2**)[4] under a variety of conditions led either exclusively to the cis isomer **5** or to an unfavorable mixture of the trans isomer **4** and **5** in which the requisite compound **4** was never formed in more than a 1:5 (**4**:**5**) ratio. The structures of compounds **4** and **5** have now been secured by X-ray crystallographic analysis (see ORTEP drawings, Scheme I)[7] and so has the structure of **6**.[6] In light of these results, it was

Scheme I[a]



[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$ catalyst, 12 h, **4**, 12%; **5**, 75%; (b) 10 equiv of Et_3SiH, 2.0 equiv of $AgBF_4$, 25 °C, 3 h, 95%.

Scheme II[a]



[a] Reagents and conditions: 10 equiv of Et_3SiH, 1.0 equiv of TMSOTf, CH_2Cl_2, 0 °C, 15 min.

† Merck Sharp & Dohme Postdoctoral Fellow, 1988–1989.
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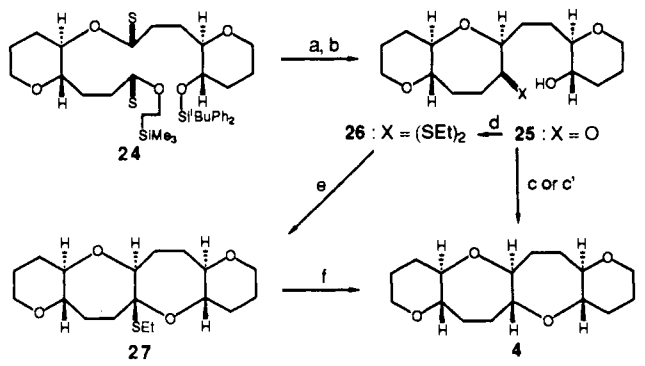
Scheme III[a]



[a] Reagents and conditions: (a) $h\nu$, toluene, 75 °C, 3 h, 66%; (b) 2.2 equiv of nBu$_4$NF, THF, 45 °C, 4 h, 95%; (c) 10 equiv of Et$_3$SiH, 1.0 equiv of TMSOTf, CH_2Cl_2, 0 °C, 10 min, 75% (trans:cis ca. 3:1); (c') 1.2 equiv of Ph_2MeSiH, 1.0 equiv of TMSOTf, CH_2Cl_2, 0 °C, 2 h, 88% (trans:cis ca. 4:1); (d) 20 equiv of EtSH, 0.5 equiv of $Zn(OTf)_2$, CH_2Cl_2, 25 °C, 8 h, 82%; (e) 2.5 equiv of $AgClO_4$, 4A molecular sieves, 3.0 equiv of $NaHCO_3$, $MeNO_2$, 25 °C, 1 h, 62%; (f) 2.0 equiv of mCPBA, CH_2Cl_2, 0 °C, 20 min, then 10 equiv of Et$_3$SiH, 1.0 equiv of $TiCl_4$, 0 °C, 20 min, 66%.

decided to initiate a search for a stepwise approach to this framework (**4**) based on new technology for securing the oxepane ring systems.

Inspired by the elegant work of Olah,[8] we designed the scenarios depicted in Scheme II as potential entries into the oxepane skeleton. Indeed, exposure of hydroxy ketones **7** or **8** to excess Et$_3$SiH and TMSOTf in CH_2Cl_2 at 0 °C resulted in the formation of oxepane **9** in excellent yield (90%) and with complete syn stereospecificity.[9] Table I demonstrates the applicability of this technology to complex systems relevant to the brevetoxin B (**1**) problem.

Application of the present technology, in combination with a second method for the construction of oxepanes based on photolytic closure of dithionoesters recently developed in these laboratories[10] led to the successful synthesis of the CDEF ring skeleton (**4**) of brevetoxin B (**1**). Scheme III outlines this construction starting with precursor **24**, the preparation of which is detailed in the Supplementary Material. Thus, photolysis[10] of **24** followed by fluoride-induced desilylation led to **25** in 60% overall yield. Ring closure of **25** under the influence of Et$_3$SiH–TMSOTf gave the trans system **4** as the major product accompanied by small amounts of its cis isomer **5** (75% total yield, trans:cis ca. 3:1).[11] A study of a variety of reagents and conditions[12] led to Ph_2MeSiH–TMSOTf as a superior reagent for the desired transformation (**25** → **4**, 88% total yield, trans:cis ca. 4:1, Scheme III). This reagent combination was crucial to the success of the more demanding situations of entries 9 and 10, Table I.

An alternative, multistep procedure was also developed for the conversion of **25** to **4** involving (a) dithioketalization to give **26** (82%); (b) hydroxydithioketal cyclization leading to **27** (62%); and (c) mCPBA oxidation of **27** followed by in situ reduction with Et$_3$SiH–$TiCl_4$ (66% overall).[13] Thus, the advantage of the newly developed direct method for the construction of oxepanes as described above became quite apparent.

Table I

Entry	Hydroxyketone	Oxepane	Yield (%)
1	**10** : X = H, OH; Y = O	**18**	90
2	**11** : X = O; Y = H, OH		79
3	**7** : X = H, OH; Y = O	**9**	83
4	**8** : X = O, Y = H, OH		85
5	**12** : X = Y = O		83
6	**13**	**19** (trans : cis ca 1 : 1)	50
7	**14**	**20** (trans : cis ca 3 : 1)[c]	75
8	**15**	**21** (trans : cis ca 3 : 1)[c]	81
9	**16**	**22** (trans : cis ca 3 : 1)[c]	55
10	**17**	**23** (trans : cis ca 6 : 1)[d]	62

[a] All compounds were enantiomerically pure except for those in entries 1–4 which were racemic. [b] Reagents and conditions: entries 1–8, same as described in Scheme II; entries 9 and 10, 2.0 equiv of Ph_2MeSiH, 1.0 equiv of TMSOTf, CH_2Cl_2, 0 °C, 2 h. [c] Isomers were separated chromatographically, and stereochemistry was tentatively assigned by comparisons with **4** and **5**. [d] Trans stereochemistry of the major isomer tentatively assigned on the basis of decoupling experiments ($J_{a,b}$ = 7.72 Hz) and comparisons with brevetoxin B (**1**) ($J_{a,b}$ = 7.73 Hz).

The described chemistry illustrates the difficulties associated with the dioxepane regional problem of brevetoxin B (**1**) and provides two possible solutions. The most direct approach relies on a new method for oxepane construction from hydroxyketones which proved to be applicable in highly complex situations relevant to the brevetoxin area. It is hoped that the reported results will facilitate the final stages of the projected brevetoxin B (**1**) synthesis and also find applications in other areas of organic synthesis.[14]

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Supplementary Material Available: Details for the synthesis of compound **24**, listing of R_f values and ^{1}H NMR data for compounds **4**, **5**, **9**, **14**–**27**, ^{13}C NMR data for compounds **4**, **5**, and **27**, and X-ray crystallographic analysis data for compounds **4** and **5** (19 pages). Ordering information is given on any current masthead page.

(7) These X-ray crystallographic analyses were carried out by Dr. Patrick Carroll of this department.

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(9) The syn stereochemistry of **9** was assigned by ^{1}H NMR spectroscopy on the basis of NOE experiments. Thus irradiation of Ha resulted in 12% enhancement of the Hb signal (500 MHz, $CDCl_3$).

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(11) Small amounts of a diol corresponding to reduction of **25** were also isolated in this reaction (ca. 10%). Similar byproducts were observed in varying yields in all entries of Table I.

(12) Other reagents effecting this transformation include the following: Ph_3SiH, Me_3SiH, $Me_2SiHSiH_2Me$, and Ph_3SnH (1–20 equiv, in combination with TMSOTf). Yields varied from 62–92% and the ratio trans:cis from ca. 3:1 to 1:1.

(13) Reduction of **27** under a variety of other conditions (e.g., nBu$_3$SnH–AIBN, Δ or $h\nu$; Raney Ni) led to the cis isomer **5**.

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