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Development of an Approach to the Synthesis of the ABC Ring System of Hemibrevetoxin B

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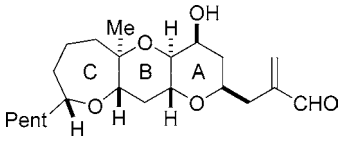
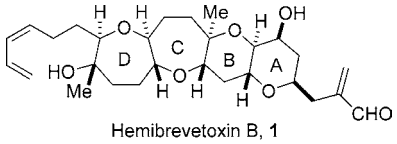
ABSTRACT



An efficient approach for the synthesis of a model of the ABC ring system of Hemibrevetoxin B is described. Key features include a ring expansion to yield the ring C oxepane, the reduction of a 2-furyl ketone with high levels of 1,3-stereocontrol, and an Achmatowicz oxidative ring expansion to yield the ring A tetrahydropyran. All seven stereogenic centers present in the model compound were controlled with high levels (>98:<2) of diastereoselectivity.

Hemibrevetoxin B (**1**, Figure 1) is the smallest member of the marine polycyclic ethers, a class of natural products which include the brevetoxins, the ciguatoxins, the maitotoxins, gambierol, and gymnocin.[1] Hemibrevetoxin B was isolated from cultured cells of the red tide organism *Gymnodinium breve* in 1989,[2] and its trans-fused polycyclic ring system raises many of the synthetic challenges posed by more complex polyether natural products. A number of total[3] and formal[4] syntheses of Hemibrevetoxin B have been reported.



Hemibrevetoxin B, **1**

Figure 1. Structure of Hemibrevetoxin B.

In this letter, we describe an approach to the synthesis of the ABC ring system of Hemibrevetoxin B;[5] in particular, we describe the synthesis of the model compound, **2**, which retains all of the structural features of the ABC ring system of the natural product. Our retrosynthetic analysis is shown in Figure 2.

Two alternative strategies for the preparation of the ABC ring system were envisaged, both of which would exploit a 2-furyl alcohol as a precursor of the A ring: a C→CA→ABC approach, featuring the cyclization of the pyran-2-one **4**, and a C→BC→ABC approach, exploiting the reductive rearrangement of the spirocyclic lactone **5**. We expected that the oxepane **6** could be prepared by THP→oxepane ring expansion of the aldol adduct **7**.

The acetal **9** was prepared by addition of MeMgBr to the δ-lactone **8** and acetalization (Scheme 1). Substitution of the acetal **9**, by treatment with propargyl trimethylsilane and

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(4) (a) Fujiwara, K.; Sato, D.; Watanabe, M.; Morishita, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 5243. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200. (c) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380. (d) For synthesis of an early intermediate, see: Holland, J. M.; Lewis, M.; Nelson, A. *J. Org. Chem.* **2003**, *68*, 747.

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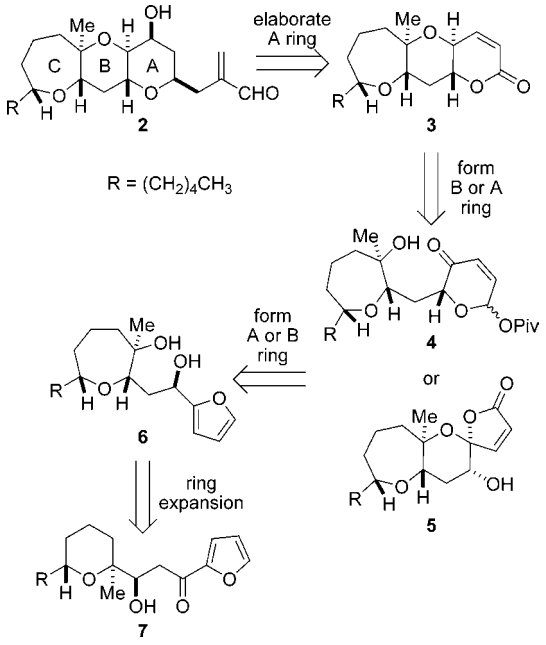
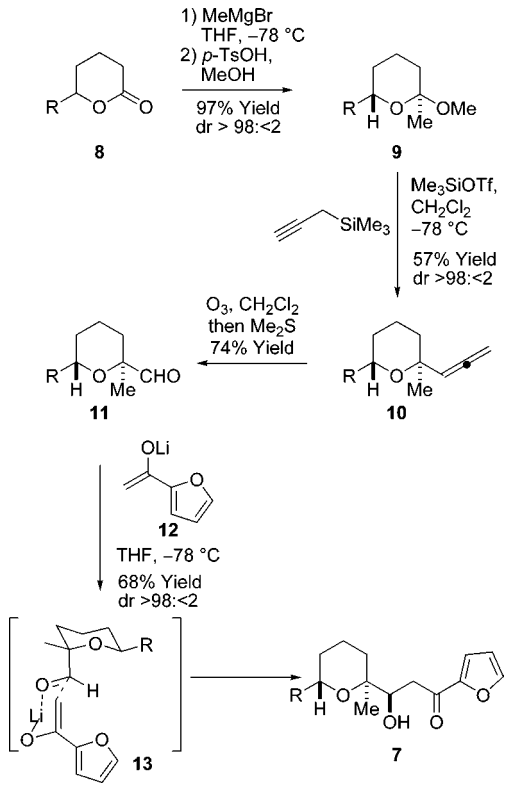


Figure 2. Retrosynthetic analysis.

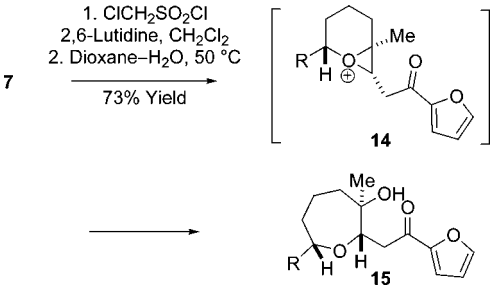
Me_3SiOTf, was highly diastereoselective (>98:<2) in favor of the allene **10** which stemmed from axial attack of the propargyl silane on the intermediate oxonium ion.[6]

Ozonolysis of the allene **10** yielded the 2-tetrahydropyranyl aldehyde **11**. The aldol reaction between the aldehyde **11** and the lithium enolate **12**, prepared by addition of methyl 2-furyl ketone to LDA, gave the corresponding aldol product **7** with >98:<2 diastereoselectivity. The sense of induction observed is the same as that observed by us[4d] in other additions to similar THPs with an axial 2-formyl group[7] and is consistent with the Felkin−Anh model[8] (see transition state model **13**).

Scheme 1. Synthesis of the Aldol Adduct



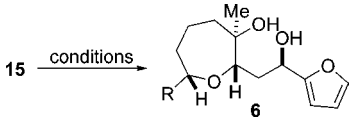
Scheme 2. THP → Oxepane Ring Expansion



Activation of the tetrahydropyranyl alcohol **7** as the corresponding chloromethanesulfonate, followed by heating to 50 °C in dioxane−water, resulted in ring expansion[9] to yield the oxepane **15** (Scheme 2). Remarkably, only a trace (<5%) of eliminated product was observed. The opening of the proposed epioxiranium ion intermediate **14** was highly regioselective, yielding the required oxepane **15** in 73% yield and <2% of its regioisomer, **7**.

A range of conditions were screened for high levels of 1,3-stereocontrol in the reduction of the ketone **15** (Table 1). Remarkably, subjecting the ketone **15** to Luche's conditions[10] (entry 5) gave the required alcohol **6** with >98:<2

Table 1. Diastereoselective Reduction of the Ketone **15**



entry	conditions[a]	diastereoselectivity[b]
1	$NaBH_4$, THF, 0 °C → rt	40:60
2	$^iBu_2AlH$, THF, −78 °C	50:50
3	Red-Al, THF, −78 °C	70:30
4	$NaBH_4$, Et_2BOMe, −78 → 0 °C	35:65
5	$NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C	>98:<2

[a] The concentration of the substrate was 0.05 M in all cases. [b] By analysis of the 500 MHz ^1H NMR spectrum of the crude product.

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diastereoselectivity and in 86% yield. Because chelation control is unlikely under these conditions,[11] the high level of 1,3-induction observed may be explained by the Evans polar model[12] as shown in Figure 3.

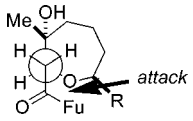
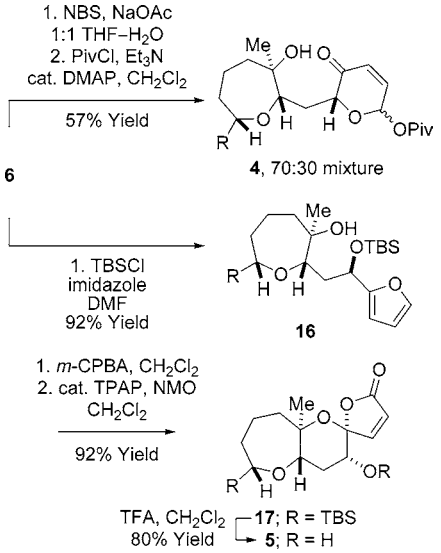


Figure 3. Model to explain the high levels of 1,3-induction in the reduction of ketone **15**.

Complementary approaches for the formation of the AC and BC ring systems from the oxepane **6** were identified (Scheme 3). Oxidation[13] of the 2-furyl alcohol **6**, and

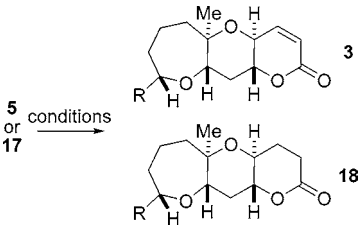
Scheme 3. Approaches for the Formation of the AC and BC Ring Systems



pivaloylation, resulted in the formation, and trapping, of the A ring as the 6-pivaloyloxy pyran-3-one **4**. Alternatively, silylation of the furyl alcohol **6** (→**16**) prevented its participation after the Achmatowicz oxidation:[13] hence, *m*-CPBA oxidation, followed by oxidation of the resulting spirocyclic hemiacetal, yielded the spirocyclic lactone **17** in which the B ring had been formed.[14] Desilylation of the spirocyclic lactone gave the corresponding alcohol **5**.

Conditions were screened for reductive rearrangement of the spirocyclic lactones **5** and **16** to yield the required fused tricyclic ring system (Table 2). For example, with 10 equiv

Table 2. Reductive Rearrangement of the Spirocyclic Lactones **5** and **17**



entry	starting material	conditions	yield[a] (%)
1	**17**	1.2 equiv of Me_3SiOTf, 1.2 equiv of Et_3SiH, 4 Å molecular sieves, CH_2Cl_2, 0 °C → rt, 2 h	**5**, 69
2	**17**	2 equiv of Me_3SiOTf, 10 equiv of Et_3SiH, $CDCl_3$, 0 °C → rt, 45 h	**3**, 20[b]
3	**5**	2 equiv of Me_3SiOTf, 10 equiv of Et_3SiH, $CHCl_3$, 0 °C → rt, 16 h	**3**, 20 **18**, 50
4	**5**	0.5 equiv of Me_3SiOTf, 5 equiv of Et_3SiH, $CHCl_3$, 0 °C → rt, 16 h	**3**, 32[c]

[a] Isolated yield of purified product. [b] Analysis of the crude reaction mixture by 500 MHz ^1H NMR spectroscopy revealed a 7:17:17:59 mixture of the compounds **17**:**3**:**18**:**5**. [c] Analysis of the crude reaction mixture by 500 MHz ^1H NMR spectroscopy revealed a 62:21:17 mixture of the compounds **3**:**18**:**5**.

of Et_3SiH and 2 equiv of Me_3SiOTf, the spirocyclic lactone **16** was transformed into the fused lactones **3** (20%) and **18** (50%) (entry 3). Alternatively, with 5 equiv of Et_3SiH and 0.5 equiv of Me_3SiOTf, the required unsaturated lactone **3** was obtained in 32% yield (entry 4). In both cases, Lewis acid-mediated ring opening yielded an oxonium ion which was reduced highly diastereoselectively, with axial attack of the reducing agent (Figure 4);[15] subsequent lactonization gave the fused tricyclic ring system.

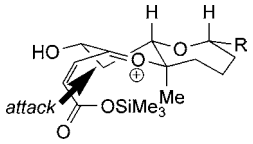


Figure 4. Diastereoselective reduction, with axial attack of the reagent, to yield the fused tricyclic lactones **3** and **18**.

Nucleophilic epoxidation of the α,*β*-unsaturated lactone **3**, with axial attack of the oxidant,[16] gave the α,*β*-epoxy lactone **19** with >98:<2 diastereoselectivity (Scheme 4); reductive ring opening,[17] α to the carbonyl group, gave the

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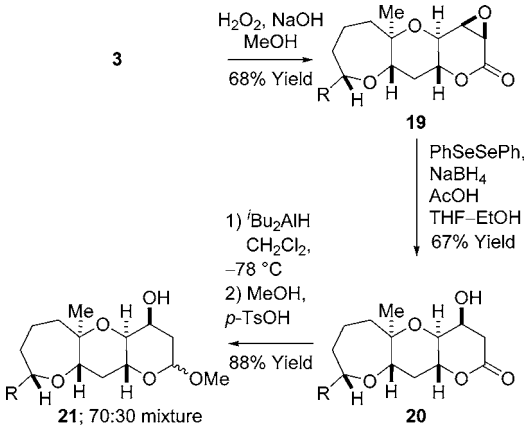
(17) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *37*, 12469.

Scheme 4. Installation of the C-8 Hydroxyl Group

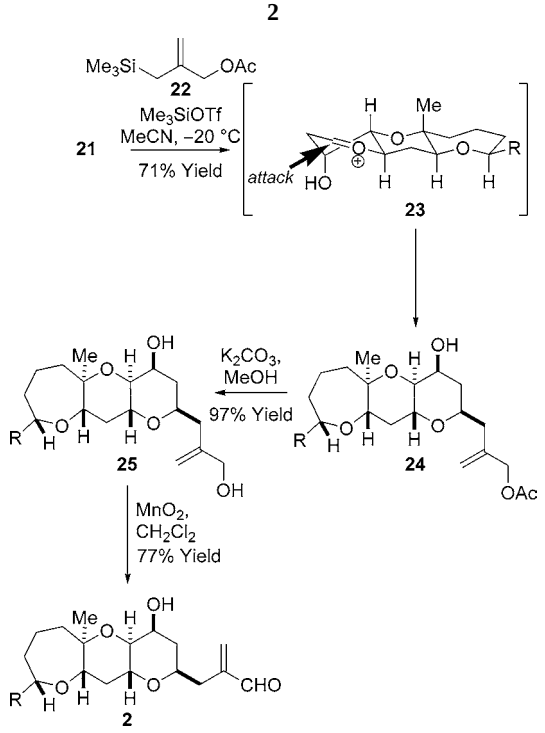


lactone **20** with an axial β-hydroxy group. Reduction of the lactone **20** with ^{i}Bu$_2$AlH, and acetalization, gave the acetal **21** as a 70:30 epimeric mixture.

Treatment of the epimeric acetals **21** with the allylic silane **22** and Me_3SiOTf yielded the substituted product **24** in which the side chain had been introduced with >98:<2 diastereoselectivity (Scheme 5); once more, the configuration of the new stereogenic center was controlled by axial attack of the reagent on the intermediate oxonium ion (see **23**).[3b,6] Deacetylation of **24** (→**25**), and allylic oxidation, yielded the model compound **2**.

Thus, methods have been developed to control all of the stereogenic centers of the model compound **2** with >98:<2 diastereoselectivity; in particular, the approach features the reduction of a ketone with high levels of 1,3-stereocontrol. We expect to be able to exploit these diastereoselective methods in a total synthesis of Hemibrevetoxin B featuring the desymmetrization of a centrosymmetric bicyclic intermediate.

Scheme 5. Completion of the Synthesis of Model Compound **2**



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Supporting Information Available: Experimental details, characterization data, ^{1}H NMR spectra for all new compounds, and ^{13}C NMR spectra for compounds **2**, **5**, **6a**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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