Oxiranyl Anions in Organic Synthesis: Application to the Synthesis of Hemibrevetoxin B

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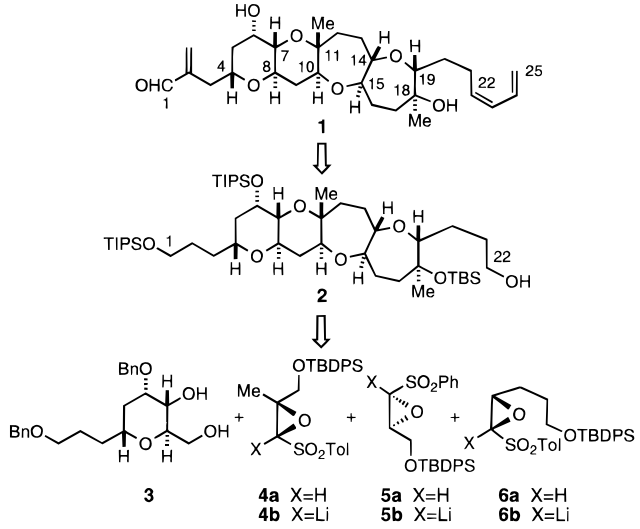
Hemibrevetoxin B (**1**),[1] isolated from cultured cells of the red tide organism *Gymnodinium breve*, is the smallest member of the polycyclic ether marine toxins and has about half of the skeleton of brevetoxins.[2] The unique 6,6,7,7-tetracyclic structure containing 10 stereocenters, an α-vinyl aldehyde moiety, and a *Z*-diene system has attracted the attention of synthetic chemists, and a variety of approaches have been explored.[3] Recently, the total syntheses of hemibrevetoxin B have been accomplished by using new synthetic methods: 6-*endo*-cyclization and dioxepane ring formation by the hydroboration of enol ether derived from thionolactone by Nicolaou,[4] the Lewis acid mediated intramolecular allylstannane−aldehyde condensation by Yamamoto,[5] and a double rearrangement−ring expansion of a 6,6-bicyclic ether to a dioxepane ring by the Nakata group.[6] In this paper, we report a new approach to the synthesis of hemibrevetoxin B based on recent oxiranyl anion methodology developed in our laboratory.[7] The strategy is illustrated by the stereocontrolled synthesis of **2**, which is elaborated by sequential coupling of three sulfonyl-stabilized oxiranyl anions **4b**, **5b**, and **6b** to the monocyclic diol **3**. Since Yamamoto has already described the conversion of **2** into hemibrevetoxin B,[5] our synthesis of **2** constitutes the formal total synthesis of the natural product.

The starting point for these investigations was the regioselective activation and protection of the two hydroxyl groups of **3**[8] by a one-pot procedure[7] to give triflate **7** in 98% yield. Treatment of a mixture of **4a**[9] and **7** with *n*-BuLi in THF/HMPA at −110 °C[7,10] provided the coupled product **8** in 90% yield. Stereospecific 6-*endo*-cyclization of **8** using *p*-toluenesulfonic acid (*p*-TsOH) led to the bicyclic ketone **9** in 90% yield. Reduction with $NaBH_4$ followed by desilylation gave **10** as the sole product.

Installation of the third ring involved the challenging preparation of the oxepane ring. Unfortunately, several attempts to couple a triflate derived from **10** with the oxiranyl anion **5b** were unsuccessful due to the considerable steric hindrance of the methyl group adjacent to the reaction site. This unexpected difficulty was circumvented by the reaction between an oxiranyl anion and an aldehyde. Thus, **10** was converted to aldehyde **11** by bis(silylation), followed by regioselective mono(desilylation) and SO_3·pyr oxidation. In order to prevent the decomposition of the unstable *cis*-oxiranyl anion,[10b] the addition of **5b**[7] to **11** was carried out by employing an *in situ* trapping method as described for **7** → **8**, furnishing a 3:1 mixture of products (88%), from which **12** was isolated in 63% yield. It is noteworthy that the lithiation of **5a** by *n*-BuLi is much faster than the butyl addition to the aldehyde. Exposure of **12** to BF_3·OEt_2 led to its clean cyclization to the tricyclic hydroxy ketone **13** (76%), whose hydroxyl group was removed by treatment with SmI_2[11] to give the ketone **14** in 64% yield.

Scheme 1. Retrosynthetic Analysis of Hemibrevetoxin B



The crucial oxepane formation was accomplished by one-carbon homologation of a 3-oxotetrahydropyran ring. The reaction of **14** with (trimethylsilyl)diazomethane ($TMSCHN_2$)[12] in the presence of BF_3·OEt_2 gave the seven-membered ketone **15** in 67% yield along with 17% of the isomeric ketone after acid hydrolysis of the intermediary trimethylsilyl enol ether. Formation of the sily enol ether in this ring expansion prevents the undesirable multiple homologation of the initially formed ketone and practically allows one-step access to an oxepane from a tetrahydropyran ring system. The stereoselective reduction of **15** proved to be more problematic, leading to the predominant formation of the undesired *cis*-alcohol under a variety of conditions.[13] In order to reverse the stereoselectivity, **15** was desilylated and subjected to the hydroxy-directed reduction with $Me_4NBH(OAc)_3$,[14] providing the *trans*-alcohol **16** as a single diastereoismer.

The third coupling of triflate **17** with epoxy sulfone **6a**[9] having a C_3 side chain proceeded uneventfully to afford **18** (96%), which, upon treatment with *p*-TsOH followed by BF_3·OEt_2, gave the tetracyclic ketone **19** in 67% yield. Repeat of the ring expansion with $TMSCHN_2$ provided ketone **20** in 62% yield. The addition of MeMgBr in toluene[3d] led to a 4:1

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(7) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158−8159.
(8) Prepared from tri-*O*-acetyl-D-glucal in nine steps. The details will be described in a full paper.
(9) Prepared according to the following: Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130−3136.
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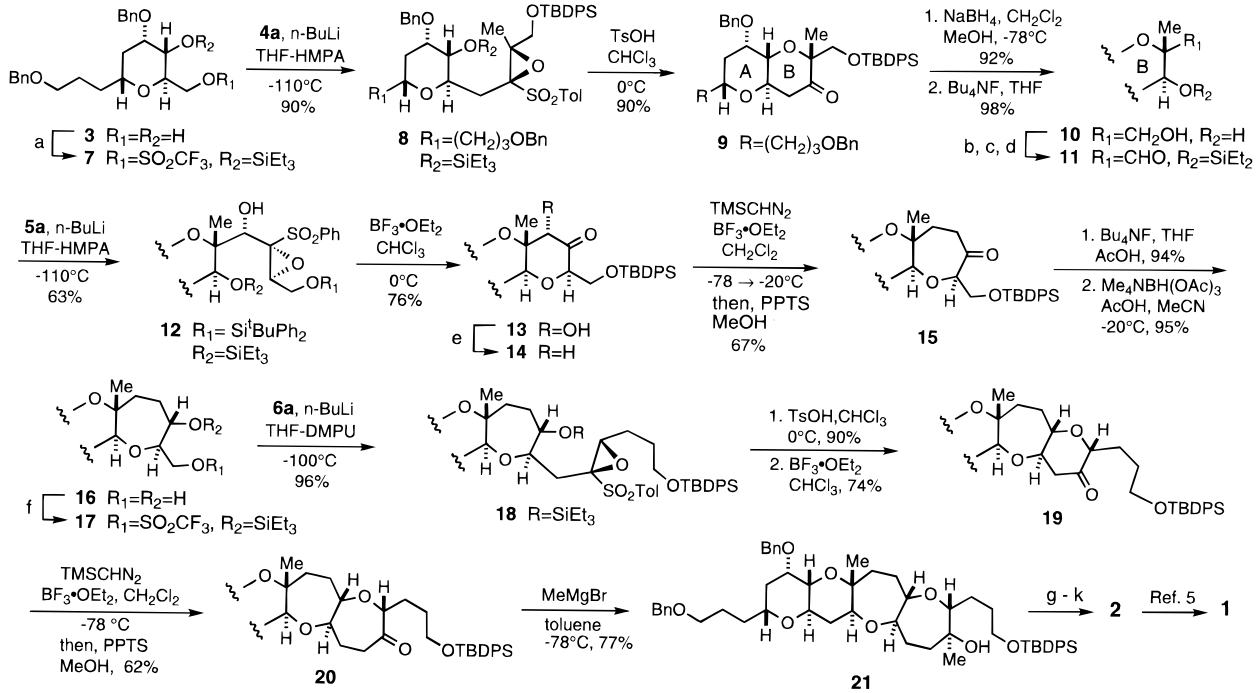
Scheme 2[a]



[a] (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, then TESOTf, 98%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 98%; (c) PPTS, CH_2Cl_2/MeOH, −20 °C, 92%; (d) SO_3·Py, DMSO/CH_2Cl_2, Et_3N, 96%; (e) SmI_2, HMPA, THF, MeOH, 0 °C,64%; (f) same as a, 83%; (g) Bu_4NF, THF, 97%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 80%; (i) $Pd(OH)_2$/C, H_2, MeOH, 92%; (j) TIPSOTf, 2,6-lutidine, 70 °C, 91%; (k) CSA, CH_2Cl_2/MeOH, 0 °C, 74%.

epimeric mixture of products from which **21** was isolated in 77% yield by chromatography. Finally, desilylation of **21** followed by bis(silylation) with *tert*-butyldimethylsilyl trifluoromethanesulfonate, debenzylation, bis(silylation) with triisopropylsilyl trifluoromethanesulfonate, and regioselective removal of the primary TBS group provided the alcohol **2** ($[\alpha]^{25}_D$ +24.8° (*c* 0.21, $CHCl_3$)) in 48% overall yield. The ^1H NMR spectrum of **2** was in complete agreement with that of an authentic sample kindly provided by Professor Y. Yamamoto, thereby completing the formal total synthesis of hemibrevetoxin B.

The present synthesis of hemibrevetoxin B using oxiranyl anions demonstrated a conceptually new approach to marine polycyclic ethers containing six- and seven-membered rings. Oxiranyl anions are unique reactive nucleophiles and the coupling with electrophiles represents an extraordinary means by which epoxides can be directly incorporated into organic molecules. Further applications of this methodology to the synthesis of other marine natural products are in progress.

Supporting Information Available: Characterization data for compounds **2** and **7**−**21** and ^1H NMR spectra of authentic and synthetic **2** (10 pages). See any current masthead page for ordering and Internet access instructions.

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