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A Convergent Strategy for the Synthesis of Polycyclic Ethers by Using Oxiranyl Anions

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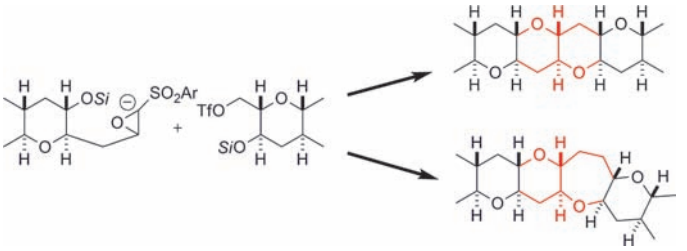
ABSTRACT



A new [X+2+Y]-type for the convergent synthesis of polycyclic ethers based on an oxiranyl anion strategy was developed. The sequence involves nucleophilic substitution of a triflate with an oxiranyl anion followed by 6-*endo* cyclization, ring expansion, and reductive etherification. The protocol features a flexible approach toward *trans*-fused polycyclic arrays consisting of six- and seven-membered ether rings from the same starting materials.

An ocean is a mine of natural products with potent physiological properties.[1] Among such products, ladder-shaped polyether marine toxins produced by the red tide and epiphytic dinoflagellates are known to have diverse biological activities such as neurotoxicity, cytotoxicity, and antifungal activity.[2] These biotoxins persist and accumulate in fish and shellfish throughout the food chain and ultimately can reach dangerous concentrations. Hence, humans are also at risk if they consume contaminated seafood. In addition to their interesting biological activities, massive and distinct structures of *trans*-fused cyclic ethers with sizes ranging from five- to nine-membered rings have attracted the attention of a number of synthetic chemists. The construction of their complex architectures necessitates a highly efficient synthetic methodology, and over the past two decades, a great deal of effort has been devoted to developing a new convergent methodology[3] to complete total synthesis for several of these marine toxins.[4]

We previously established a linear methodology for the synthesis of polycyclic ethers by using oxiranyl anions.[5,6]

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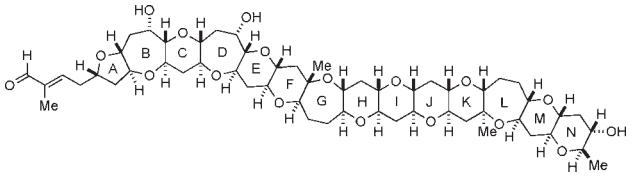
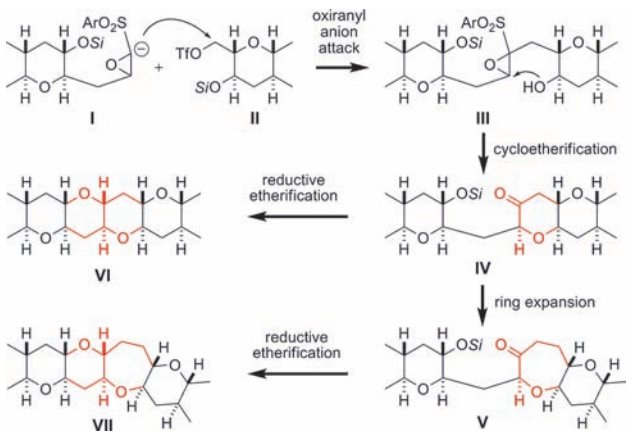


Figure 1. Structure of gymnocin-A.

This iterative procedure was applied to the synthesis of gambierol[7] and the ABCDEF ring fragment of yessotoxin and adriatoxin.[8] However, the stepwise synthesis of compounds with more than ten fused rings such as gymnocins[9] (Figure 1) is practically impossible owing to the large number of transformations required. It is therefore important to develop an efficient method for the construction of large toxins. We herein report a new convergent strategy for the synthesis of this class of molecules.

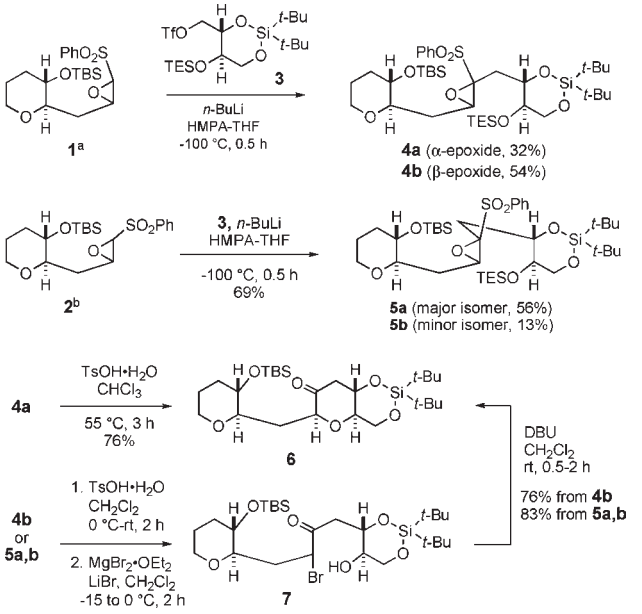
Scheme 1. Convergent Strategy for Polycyclic Ethers



Our synthetic strategy is outlined in Scheme 1. Alkylation of an oxiranyl anion generated from epoxy sulfone **I** with triflate **II** followed by cyclization of **III** provides a six-membered ketone **IV**, which serves as a precursor of the seven-membered ring **V** by a ring expansion reaction. After reductive etherification of ketones **IV** and **V**, a second six-membered ether ring is generated. Through the use of this strategy, two new six-six-membered and six-seven-membered ring systems **VI** and **VII** are constructed from the same starting materials.

The initial coupling reaction was performed with *cis*-epoxy sulfone **1** and *trans*-epoxy sulfone **2**, each consisting of a mixture of two diastereomers at the oxirane ring (Scheme 2). Lithiation of *cis*-**1** and *trans*-**2** with *n*-BuLi in the presence of triflate **3** in THF/HMPA at −100 °C afforded, respectively, the coupling products **4a**,**b** and **5a, b** in good yield. The diastereomeric ratios of the products were unchanged before and after the coupling reactions.

Scheme 2. Synthesis of the Tetrahydropyranyl Ketone **6**



[a] A 3:2 diastereomeric mixture. [b] A 3:1 diastereomeric mixture.

Acid-catalyzed stereoselective ring closure with *p*-TsOH in $CHCl_3$ at 55 °C proceeded only for the *cis*-(2*S*,3*R*)-diastereomer **4a** to afford ketone **6** in 76% yield. However, conversion of other diastereomers **4b** and **5** to ketone **6** could not be achieved under the same conditions. Instead, the reaction yielded detriethylsilylated products, and prolonged reaction times and elevated temperatures gave a complex mixture of products. Only the diastereomer **4a** could adopt a less hindered chair conformation suitable for 6-*endo* cyclization in the transition state.[10] The diastereomers **4b** and **5a,b** were then subjected to a three-step formal 6-*endo* cyclization according to previous studies.[11] Thus, acid-catalyzed removal of the triethylsilyl group followed by the epoxide-opening reaction with $MgBr_2 \cdot OEt_2$ afforded bromoketone **7**, which was then treated with DBU to furnish ketone **6** as a single diastereomer in 76−83% overall yields. This cyclization has the advantage that neither the stereochemistry of the bromoketone nor the stereochemistry of epoxy sulfones **4a,b** and **5a,b** are

(7) (a) Furuta, H.; Hasegawa, Y.; Mori, Y. *Org. Lett.* **2009**, *11*, 4382–4385. (b) Furuta, H.; Hasegawa, Y.; Hase, M.; Mori, Y. *Chem.—Eur. J.* **2010**, *16*, 7586–7595.

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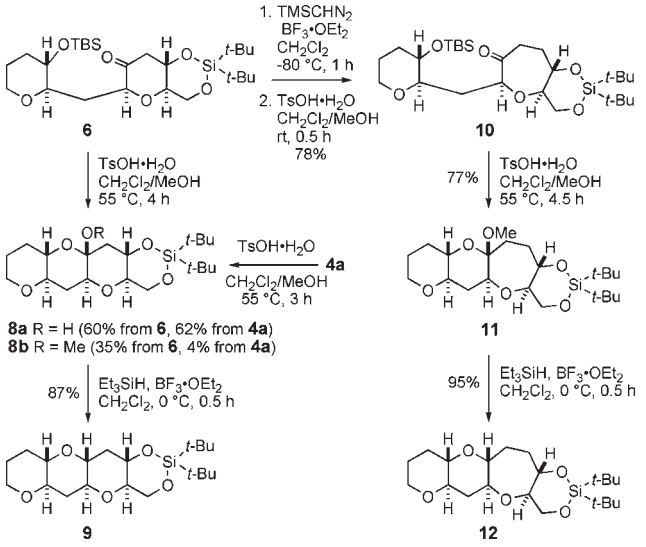
relevant, because all stereoisomers converge to the same requisite diastereomer with an equatorial substituent under base equilibration conditions.

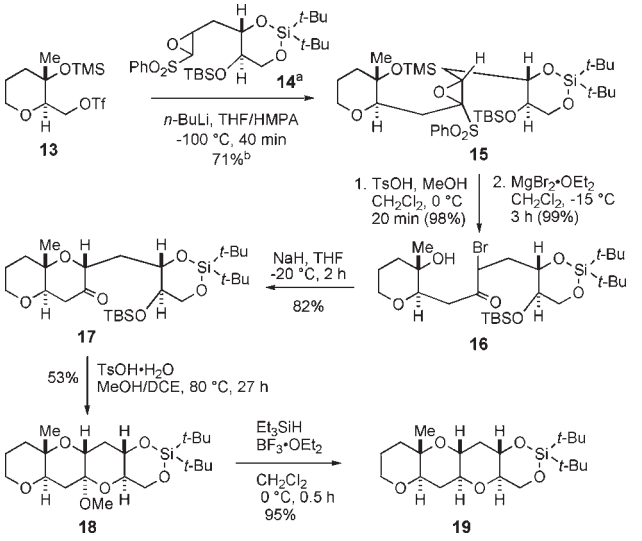
Scheme 3. Synthesis of Tricyclic Ethers **9** and **12**



The next step is a diverging point for our protocol where ketone **6** serves as a key precursor for polycyclic frameworks composed of six- and seven-membered ether rings (Scheme 3). The presence of seven-membered rings usually complicates the synthesis of marine polycyclic ethers. We solved this problem by ring enlargement. Thus, ketone **6** was subjected to a ring expansion reaction with trimethylsilyldiazomethane[11] in the presence of $BF_3 \cdot OEt_2$ followed by treatment of the resulting α-trimethylsilyl ketone with *p*-TsOH to afford the seven-membered ketone **10** in 66% yield. Heating the six-membered ketone **6** with *p*-TsOH in $CHCl_3$/MeOH at 55 °C caused sequential cleavage of the TBS group and acetalization, and a mixture of hemiacetal **8a** and acetal **8b** was obtained in 95% combined yield. Moreover, **8a** and **8b** were prepared directly from epoxy sulfone **4a** by treatment with the same acidic conditions. The acetal mixture was then reduced with triethylsilane in the presence of $BF_3 \cdot OEt_2$ to provide tricyclic ether **9** in 87% yield. In the case of the seven-membered ketone **10**, acetal **11** was obtained in 77% yield as the sole product under the same acidic conditions. Subsequent reductive etherification afforded tricyclic ether **12** with an oxepane ring in 95% yield.

We next investigated the synthesis of cyclic ether with an angular methyl group that is often encountered as a structural unit of marine toxins. The construction of such a ring system is also an important task.[12] The carbon–carbon bond formation between the methylated monocyclic triflate **13** and *trans*-epoxy sulfone **14** was performed under standard conditions (*n*-BuLi, THF/HMPA, −100 °C, in situ trapping method) to afford the product **15** in 71% yield (Scheme 4). Removal of the TES group followed by treatment with $MgBr_2 \cdot OEt_2$ provided bromoketone **16** in 91% overall yield. Intramolecular etherification of **16** with DBU proved to be less efficient than that of **7** owing to the low reactivity of the tertiary alcohol, giving the desired methyl-substituted bicyclic ketone **17** in only 22% yield.[13]

Scheme 4. Synthesis of the Methylated Polyether **19**



[a] A 9:1 *trans* and *cis* mixture. [b] Based on the consumed **14**.

After several attempts to forge the ether ring, treatment of **16** with NaH in THF at −20 °C proved the most expedient to afford the cyclic ketone **17** in 82% yield. Acetalization followed by reductive etherification of **17** provided polyether **19** with an angular methyl group in 44% yield for the two steps.

Finally, application of our convergent approach to the synthesis of larger molecules was demonstrated as shown in Scheme 5. A coupling reaction of the bicyclic epoxy sulfone **21**, prepared from diol **20**[14] as a mixture of four diastereomers at the epoxide site, with the monocyclic triflate **22** in the presence of *n*-BuLi at −100 °C afforded a diastereomeric mixture of epoxy sulfone **23** in 76% yield. Conversion of the products to the desired ketone was

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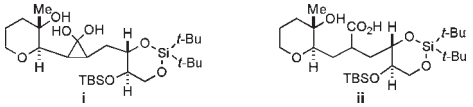
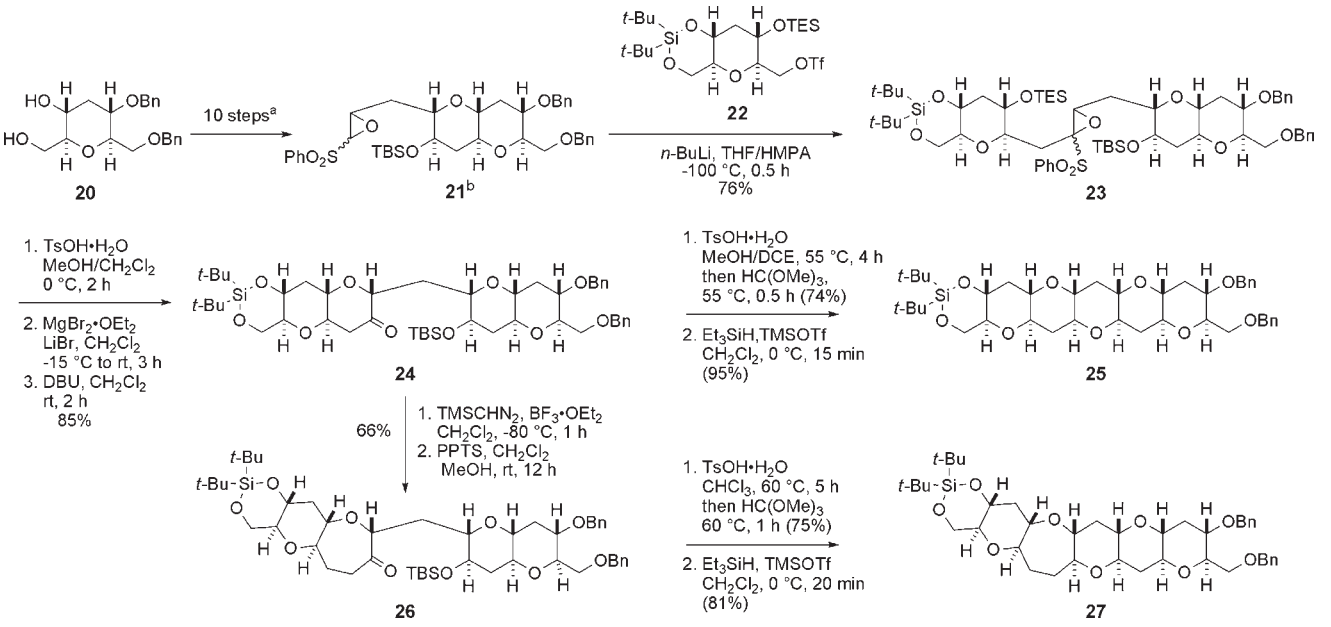
(13) A cyclopropane hydrate **i** was obtained in 23% yield under standard reaction conditions (1.1 equiv of DBU, CH_2Cl_2, rt). Treatment of **16** with 3.3 equiv of DBU afforded **17** in 32% yield and a carboxylic acid **ii**, a Favorskii rearrangement product, in 32% yield. See Supporing Information.



(14) Mori, Y.; Hayashi, H. *J. Org. Chem.* **2001**, *66*, 8666–8668.

Scheme 5. Synthesis of Pentacyclic Ring Systems **25** and **27**



[a] See Supporting Information. [b] A 1:1 *cis* and *trans* mixture.

accomplished through the standard three-step sequence involving removal of the TES group followed by bromoketone formation with $MgBr_2 \cdot OEt_2$ and cyclization with DBU, to afford the cyclic ketone **24** in 85% yield as a single isomer. A ring expansion reaction of **24** with trimethylsilyldiazomethane proceeded uneventfully to afford the seven-membered ketone **26** in 66% yield. The acid-catalyzed acetalization of ketones **24** and **26** followed by reductive etherification afforded pentacyclic polyethers **25** and **27**, respectively. The latter represents the FGHIJ ring system of gymnocin-A.

In conclusion, we have developed a new [X+2+Y]-type[15] convergent methodology for the synthesis of polycyclic ethers based on an oxiranyl anion strategy. The present method features a flexible approach toward polycyclic arrays consisting of six- and seven-membered ether rings from the same starting materials and allows for the construction of a methyl-substituted polyether ring system. Further development of the present technology and its application to the total synthesis of marine polycyclic ethers are in progress.

(15) The reader is referred to ref 3a for the terminology of the [X+2+Y] convergent synthesis.

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Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.