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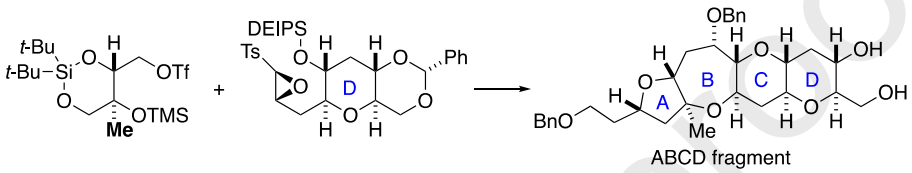

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Synthesis of the ABCD fragment of gymnocin-B

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ABSTRACT

A convergent synthesis of the ABCD fragment of gymnocin-B was accomplished. The tetracyclic ether ring system was synthesized by the construction of the BC ring system via the oxiranyl anion alkylation and ring expansion reaction, followed by the formation of the five-membered A-ring via a stereoselective radical cyclization reaction of a neopentyl-type iodide.

Ladder-shaped polyethers are marine natural products characterized by trans-fused cyclic ether skeletons and potent bioactivities.[1],[2] Gymnocin-B is a pentadecacyclic ether produced by the red-tide dinoflagellate *Karenia mikimotoi*,[3] and it shows potent cytotoxicity against mouse leukemia cells P388 (IC_{50} 1.7 μM). The first total synthesis of gymnocin-B was recently accomplished by Sittihan and Jamison,[4] and a synthetic study on the NO ring system was reported earlier by Tsukano and Sasaki.[5] We have also described a convergent synthesis of the GHIJKL fragment[6] based on the oxiranyl anion strategy.[7] As a continuation of our studies on the synthesis of gymnocin-B, we report herein a convergent synthesis of the ABCD fragment of gymnocin-B.

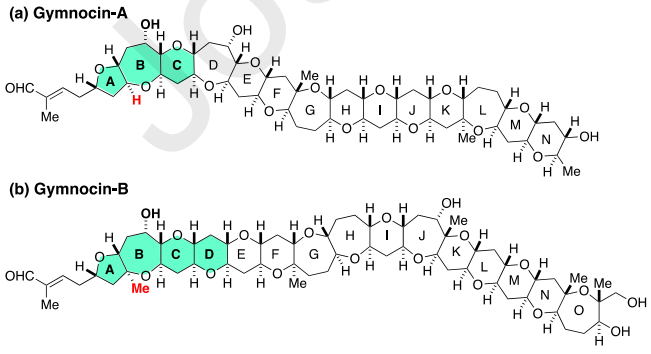
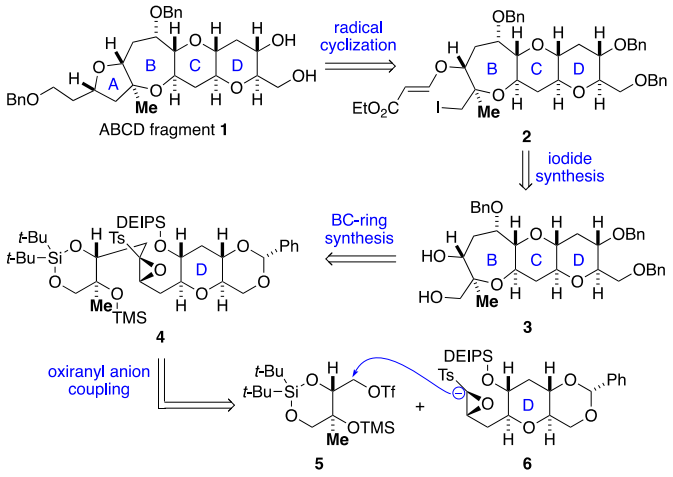


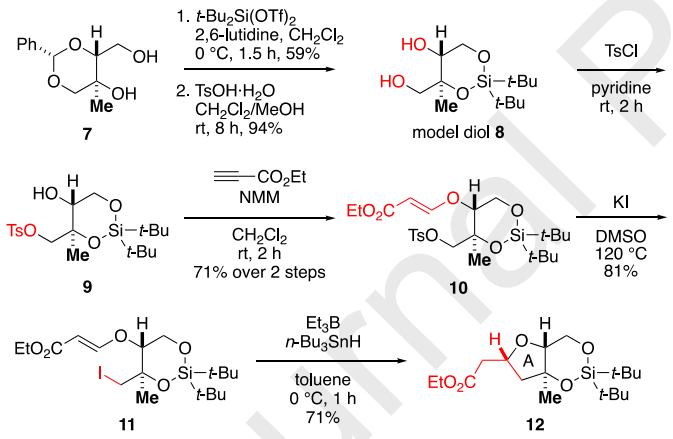
Figure 1. Structures of gymnocin-A and gymnocin-B.

The ABC system of gymnocin-B is largely similar to that of gymnocin-A, and it includes a five-seven-six membered ring with a 2-methyl-2-butenal side chain on ring A (Figure 1). The difference between the two gymnocins is the presence of an angular methyl group

at ABC system of gymnocin-B is more challenging, because of the difficulty in introducing a methyl group at the bridgehead position. Retrosynthesis of the ABCD fragment was performed based on the reported synthesis of the ABC system of gymnocin-A.[8] Synthesis of the A-ring moiety of the ABCD fragment **1** was planned by radical cyclization from alkyl iodide **2**, which would be prepared from BCD diol **3**.[9] This conversion is the key feature of our approach because it involves transformation from a neopentyl-type alcohol to an iodide. The BC ring system of **3** would be formed from coupling product **4**, which could be obtained by the nucleophilic substitution of oxiranyl anion **6** with alkyl triflate **5** bearing the methyl group.



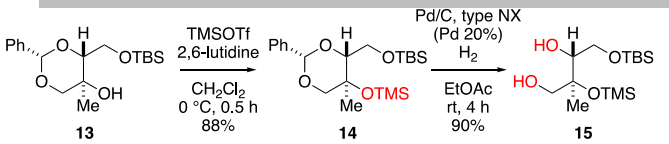
Scheme 1. Retrosynthetic analysis of the ABCD fragment of gymnocin-B.

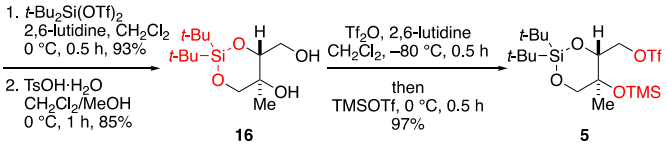


Scheme 2. Synthesis of neopentyl-type iodide **11** and radical cyclization.

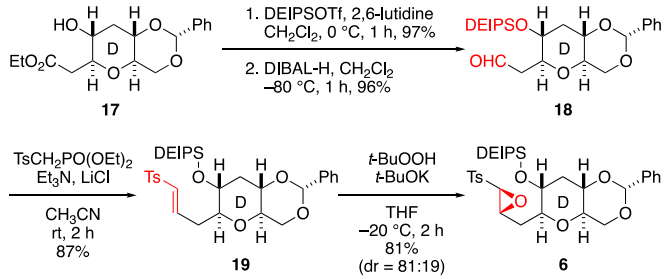
We began our study by using model diol **8** for the A-ring construction (Scheme 2). Diol **8** was prepared from known compound **7**[0] in two steps by silylene protection and removal of the benzylidene acetal group. The primary alcohol in **8** was selectively tosylated to afford **9**, and the remaining secondary alcohol in **9** was subjected to oxa-Michael reaction using ethyl propiolate to afford unsaturated ester **10**. Conversion of alkyl tosylate **10** to iodide **11** did not proceed at all upon heating with NaI and 18-crown-6 in acetone at reflux temperature. Fortunately, the reaction was promoted with KI at 120 °C in DMSO to give the desired iodide **11** in good yield, without the significant formation of any byproduct. Radical cyclization[0] of iodide **11** using triethylborane provided bicyclic product **12** in good yield as a single diastereomer.[10]

(a) S



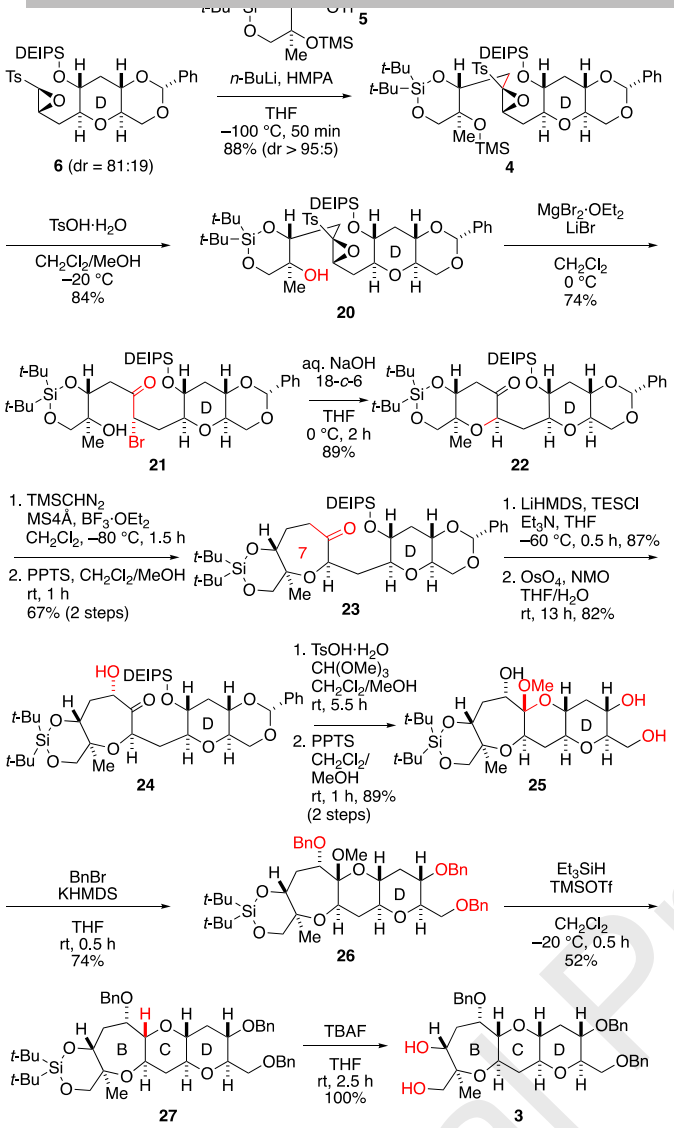


(b) Synthesis of D-ring epoxy sulfone **6.**



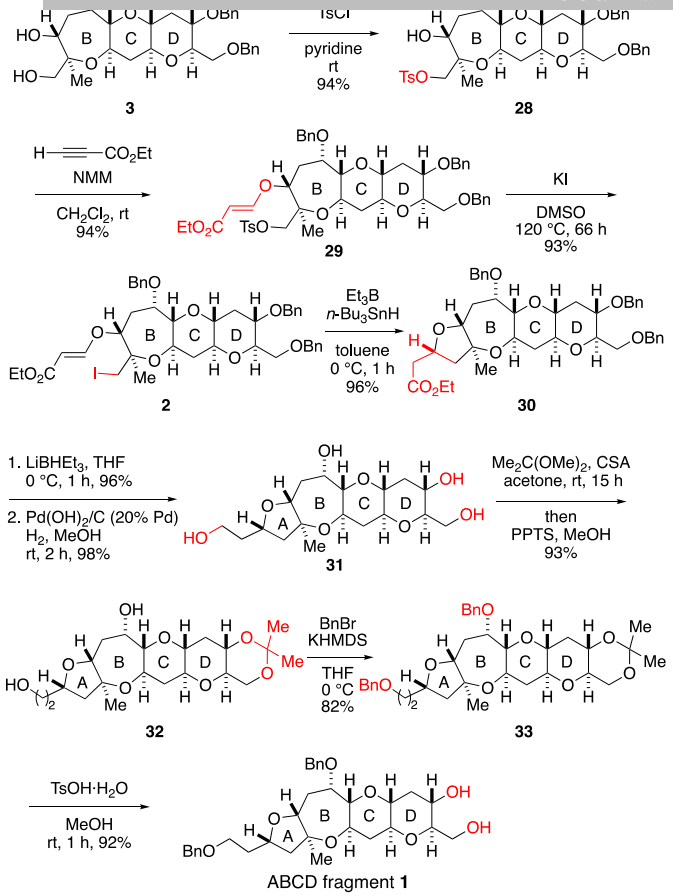
Scheme 3. Synthesis of alkyl triflate **5** and epoxy sulfone **6**.

We next focused on the preparation of the requisite alkyl triflate **5** (Scheme 3(a)). Tertiary alcohol **13**[11] was protected with TMS triflate to give **14**, which was subjected to hydrogenation using Pd/C (type NX catalyst) for removal of the benzylidene acetal group.[12] The obtained diol **15** was protected with a di-*tert*-butyl silylene group to form a 1,3,2-dioxasilinane ring, and demasking of the TMS and TBS groups afforded diol **16**. TMS protection of the tertiary alcohol in **15** was necessary because a five-membered 1,3,2-dioxasilolane ring was exclusively formed during the di-*tert*-butylsilylene protection of the corresponding 1,2,3-triol. Diol **16** was subjected to one-pot triflation and TMS protection to provide alkyl triflate **5**. Epoxy sulfone **6** was synthesized from known bicyclic ester **17**[13] (Scheme 3(b)), which upon diethylisopropylsilyl (DEIPS) protection[14] and DIBALH reduction provided aldehyde **18**. Horner–Wadsworth–Emmons reaction of **18** under Masamune–Roush conditions provided vinyl sulfone **19**, which was oxidized into epoxy sulfone **6** using *t*-BuOOH and *t*-BuOK.



Scheme 4. Synthesis of BCD diol **3**.

Having prepared alkyl triflate **5** and epoxy sulfone **6**, we next carried out oxiranyl anion coupling to give the corresponding product **4** in good yield (Scheme 4). Although **6** was an 81:19 mixture of β- and α-epoxides, the major β-epoxide reacted preferentially to provide the coupling product as a single diastereomer. The TMS group of **4** was selectively removed to give epoxy alcohol **20**, which was then treated with $MgBr_2 \cdot OEt_2$ and LiBr to afford bromoketone **21**. Williamson-type etherification from tertiary alcohol **21** proceeded smoothly when using aqueous NaOH in the presence of 18-crown-6,[15] and the obtained six-membered ketone **22** was subjected to ring expansion to furnish seven-membered ketone **23**.[16] Silyl enol ether formation, followed by oxidation with OsO_4, provided α-hydroxy ketone **24**.[0h, **Error! Bookmark not defined.**] Treatment of **24** with *p*-toluenesulfonic acid and trimethyl orthoformate facilitated simultaneous DEIPS group removal, methyl acetalization, and deprotection of the benzylidene acetal moiety to afford trihydroxy acetal **25**. Global protection of the hydroxy groups with benzyl bromide gave tribenzyl ether **26**. BCD diol **3** was obtained after reductive etherification of the methyl acetal,[17] followed by deprotection of the di-*tert*-butylsilylene group.



Scheme 6. Synthesis of ABCD fragment **1**.

The final step was the construction of the A ring in BCD diol **3** (Scheme 6). The primary alcohol of **3** was selectively tosylated to give hydroxy tosylate **28**, which was converted into unsaturated ester **29** by an oxa-Michael reaction. Transformation of **29** into iodide **2** was achieved under the reaction conditions outlined in Scheme 2. Thus, heating with potassium iodide in DMSO gave iodide **2**, and subsequent radical cyclization afforded tetracyclic ester **30** in high yield.[0, Error! Bookmark not defined.] The ester was reduced to an alcohol, and global deprotection of the benzyl groups afforded tetraol **31**. The 1,3-diol moiety was protected as an acetonide to give **32**, and the remaining dihydroxy groups in **32** were protected with benzyl groups to give **33**. Finally, deprotection of the acetonide provided ABCD fragment **1**, which could be readily subjected to the next oxiranyl anion coupling with a right-side fragment.

In conclusion, we have synthesized the ABCD fragment of gymnocin-B from alkyl triflate **5** and epoxy sulfone **6** using the oxiranyl anion strategy. The five-memberd A ring was constructed by a conversion from the neopentyl-type alcohol to the iodide followed by the stereoselective radical cyclization reaction. The synthesis has been accomplished in 28 steps from known diol **7**. Further synthetic study of gymnocin-B is ongoing in our laboratory.

Acknowledgments

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Supplementary data for this article can be found online at http://XXXXXX

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