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Total Synthesis of Gymnocin-A

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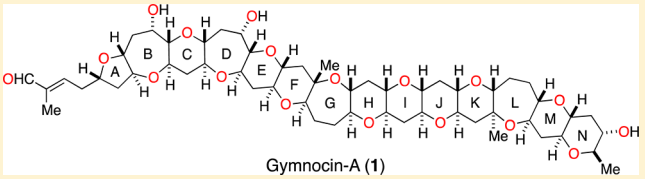
Supporting Information

ABSTRACT: A convergent total synthesis of cytotoxic marine natural polycyclic ether, gymnocin-A (**1**), is described. The synthesis features three iterations of an oxiranyl anion strategy, involving base-mediated cycloetherification, ring expansion, and reductive etherification, for the construction of the FGH fragment and for its coupling with the ABC and KLMN fragments.



INTRODUCTION

Gymnocin-A (**1**) is a polycyclic ether isolated from cultured cells of the red-tide dinoflagellate, *Karenia mikimotoi*, by Satake and co-workers.[1,2] This complex natural product exhibits potent cytotoxicity (IC_{50} = 1.3 μg/mL) against mouse leukemia P388 cells. The gross structure was determined by extensive 2D NMR and MS/MS experiments, and the absolute configuration was assigned via MTPA analysis.[2a]

A characteristic feature of **1** is its linear array of 14 contiguous fused rings; it is the third longest fused ring system among known polycyclic ethers, following brevisulcenal-F[3] and gymnocin-B[4] (Figure 1).

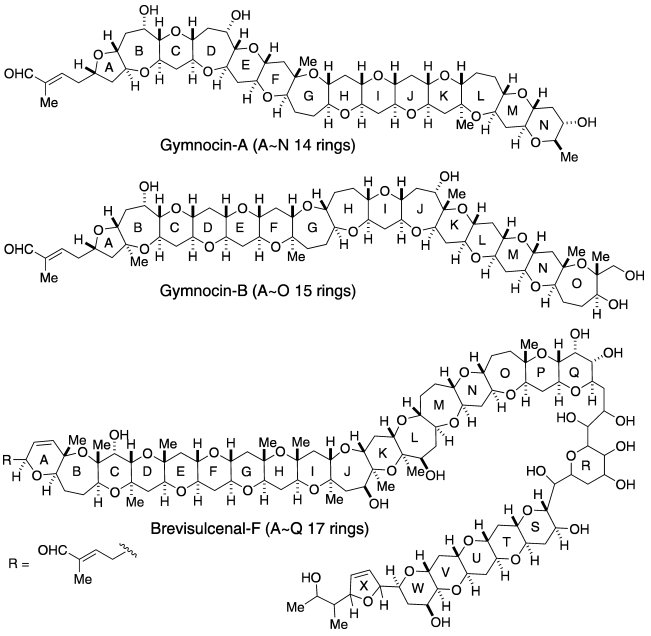


Figure 1. Three longest fused marine polycyclic ethers, gymnocin-A and -B, and brevisulcenal-F.

The synthesis of large and complex natural products such as gymnocins is a challenging task and requires a powerful and flexible methodology.[5] To date, the total synthesis of gymnocin-A has only been achieved by using an [X + 1 + X] approach[5a] based on the B-alkyl Suzuki–Miyaura cross-coupling of alkylboranes, generated from exocyclic enol ethers, with cyclic ketene acetal triflates or phosphates by Tsukano and Sasaki.[6,7] Our longstanding interest in the construction of polycyclic ethers using an oxiranyl anion led to the development of a new [X + 2 + X]-type convergent strategy, which facilitated the synthesis of large polycyclic ethers.[8] Herein, we report the total synthesis of gymnocin-A using this strategy. The successful implementation of the synthesis highlights the efficient assembly of polyether units by iterative coupling of oxiranyl anions and triflates.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. The retrosynthetic analysis of gymnocin-A (**1**) is outlined in Scheme 1. The intramolecular homology of the partial ring sequences of the BC and DE ring systems, as well as the FGH and KLM ring systems, allowed us to dissect **1** into ABC, FGH, and KLMN fragments **2**, **3**, and **4**, respectively. Considering the optimum convergency and flexibility, further disassembly of these fragments afforded building blocks **5**–**9**, where the F and K ring units (**7**) were identical. Thus, tetradecacyclic system **1** could be constructed through five iterations of oxiranyl anion coupling. In this context, we recently reported the convergent synthesis of ABC and KLMN fragments **2**[9] and **4**[10] of gymnocin-A.

Synthesis of FGH Triflate. The synthesis commenced with the preparation of FGH fragment **16**, a synthetic equivalent of **3**, which is a latent bridging unit between the ABC and KLNM domains. In situ alkylation of the oxiranyl anion generated from epoxy sulfone **8** with F ring triflate **7** afforded coupling product **10** in 71% yield (Scheme 2). Selective removal of the tertiary

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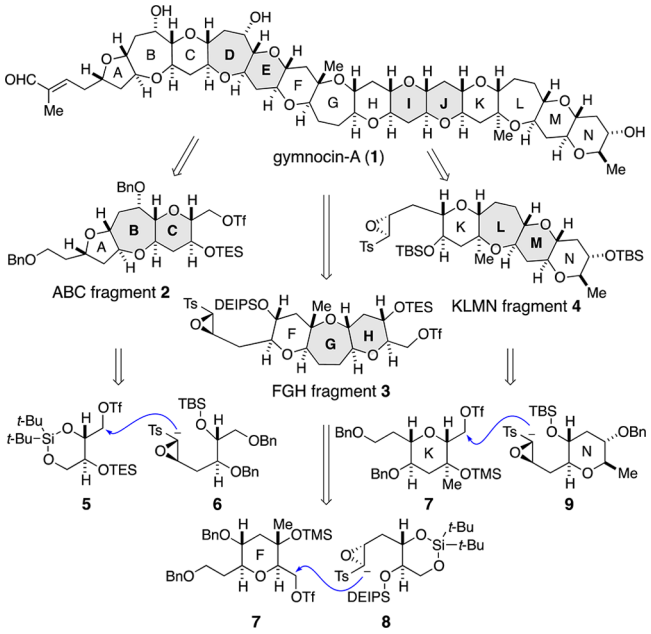
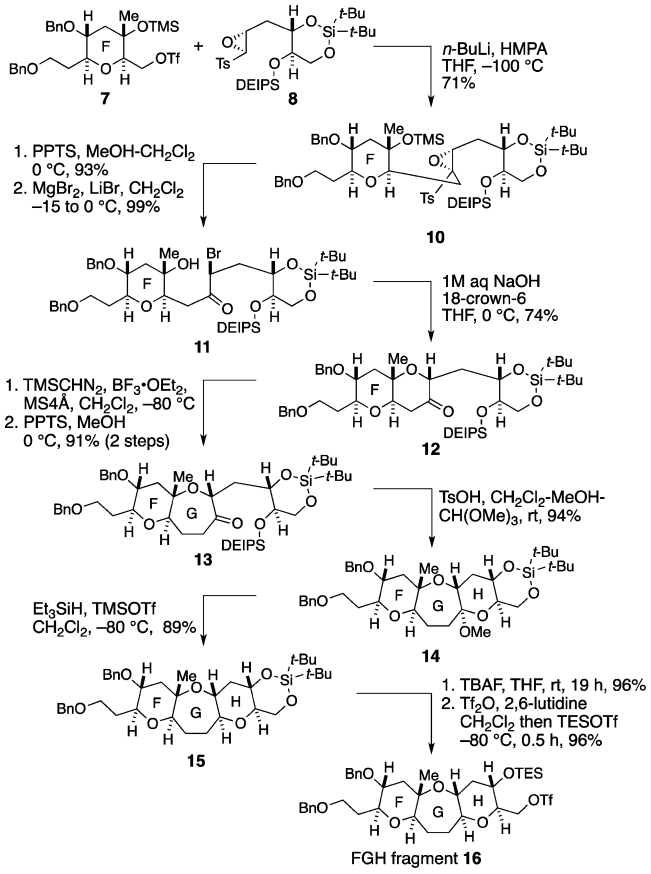
Scheme 1. Retrosynthetic Analysis of Gymnocin-A (1)

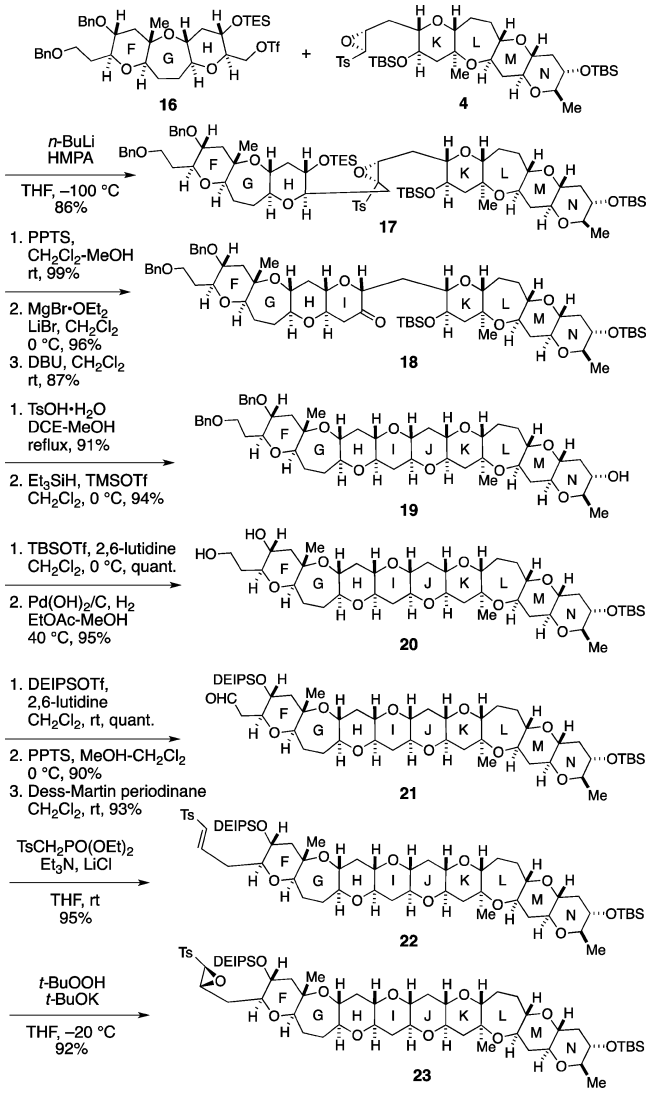


Scheme 2. Synthesis of FGH Triflate 16



TMS group in the presence of secondary DEIPS ether[11] with a catalytic amount of PPTS formed a tertiary alcohol that underwent epoxide ring opening with $MgBr_2 \cdot OEt_2$ to afford bromoketone **11**. The intramolecular S_N2 displacement of Br at the carbon α to ketone by sterically hindered tertially alcohol was successfully achieved by treatment with aqueous NaOH in

Scheme 3. Synthesis of FGHIJKLMN Epoxy Sulfone 23



the presence of 18-crown-6 to form ketone **12** in 74% yield. Ring expansion of the ketone using TMS-diazomethane[12] afforded seven-membered ketone **13** after treatment with acid. Exposure of **13** to TsOH in CH_2Cl_2–MeOH–$CH(OMe)_3$ resulted in the cleavage of the secondary DEIPS group and simultaneous acetalization to provide methyl acetal **14** in 94% yield. Notably, the use of DEIPS as the protecting group in **13** was important, because the use of TBS decreased the yield of **14** owing to difficulties in its selective removal in the presence of a cyclic silylene protecting group. Tricyclic FGH ring system **15** was furnished by the reduction of the acetal with Et_3SiH in the presence of TMSOTf. Removal of the di-*tert*-butylsilylene group with TBAF followed by one-pot triflation and TES protection of the resulting diol afforded FGH bridging fragment **16** in high yield.

Total Synthesis of Gymnocin-A. The stage was then set to couple ABC, FGH, and KLMN fragments **2**, **16**, and **4**, respectively. The order was decided so as to avoid the preparation of an unstable triflate of a long polycyclic ether, which would be derived from **2** and **3**. Thus, we first united FGH triflate **16** with KLMN fragment **4** by treating their mixture with *n*-BuLi to afford coupling product **17** in 86% yield (Scheme 3). TES-deprotection, bromoketone formation, and

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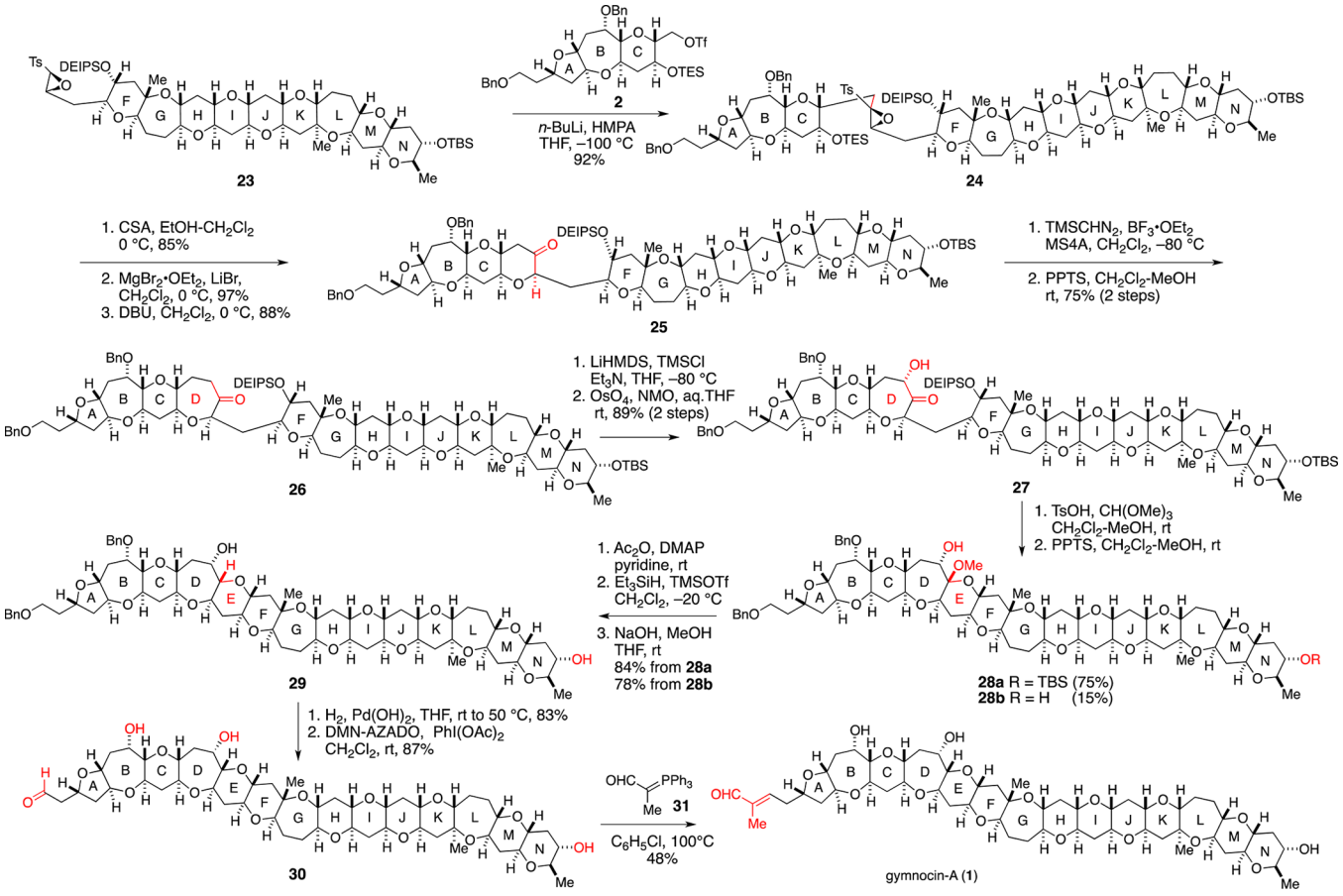
Scheme 4. Total Synthesis of Gymnocin-A (1)



DBU-mediated S_N2 cyclization provided six-membered ketone **18**. Treatment of **18** with TsOH led to the cleavage of the TBS groups and acetalization, which provided the methyl acetal, which was subsequently converted to nonacyclic alcohol **19** by reductive etherification. After reprotection of the N-ring hydroxy group as a TBS ether, both benzyl groups in **19** were removed by hydrogenation to obtain diol **20**. DEIPS protection of the diol followed by selective removal of the primary silyl ether and Dess-Martin oxidation afforded aldehyde **21**. The Horner–Wadsworth–Emmons reaction carried out under Masamune–Roush conditions[13] afforded vinyl sulfone **22**. FGHIJKLMN epoxy sulfone **23** was obtained by epoxidation with *tert*-butylhydroperoxide under basic conditions.

In the final coupling step, we were concerned that the large, rigid nonacyclic structure of **23** might suppress the solubility and reactivity of its oxiranyl anion at −100 °C which is necessary to prevent decomposition of unstable anions. However, to our delight, the coupling reaction between epoxy sulfone **23** and ABC triflate **2** proceeded smoothly to afford **24** in an excellent yield (Scheme 4). It should be emphasized that the oxiranyl anion generated from epoxy sulfone **23** still had very high reactivity at very low temperatures. The product was transformed into ketone **25** through a three-step sequence involving selective deprotection of the TES group in the presence of DEIPS and TBS groups, transformation of the epoxy sulfone moiety to a bromoketone, and cycloetherification with DBU. Ketone **25** was subjected to ring expansion with TMS-diazomethane to afford homologated ketone **26**. Stereoselective α-oxidation of the ketone was performed under Lee's conditions[14] using a TMS enol ether to obtain hydroxy ketone **27**. *p*-TsOH-catalyzed methanolysis of secondary DEIPS ether **27** in the presence of trimethyl orthoformate yielded methyl acetal **28a** and **28b**, after additional methanolysis of partially formed dimethyl orthoformate esters of the D and N ring alcohols. Reductive etherification was accomplished using the acetates of acetals **28a** and **28b**, accompanied by cleavage of the TBS group, to obtain diol **29** after deacetylation. In the final stage of the synthesis, we attempted to directly install an α,β-unsaturated aldehyde moiety onto trihydroxy aldehyde **30** without protection of the hydroxy groups, thus reducing the number of steps toward gymnocin-A as compared to the previous synthesis.[6] Debenzylation of **29** with H_2 and 20% $Pd(OH)_2$ in THF afforded the tetraol; the choice of solvent was critical for this reaction because of the low solubility of dibenzyl ether **29** and the resulting tetraol in conventional solvents (MeOH and AcOEt). Subsequent selective oxidation of the primary alcohol of the tetrol with DMN-AZADO and $PhI(OAc)_2$[15] furnished trihydroxy aldehyde **30** in 87% yield. The final Wittig olefination of aldehyde **30** with phosphorane **31**, which required forceful conditions (chlorobenzene, 100 °C, 7 h), completed the total synthesis of gymnocin-A (**1**) in 48% yield as an inseparable 91:9 trans and cis mixture.[16] The ^1H and ^{13}C NMR spectra of the synthetic material were identical to those of natural gymnocin-A.

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CONCLUSION

In conclusion, a convergent total synthesis of tetradecacyclic gymnocin-A (**1**) was achieved via five iterative oxiranyl anion couplings involving cycloetherification and reductive etherification. The use of highly reactive oxiranyl anions from small to large epoxy sulfones enabled the reproducible preparation and assembly of the ABC, FGH, and KLMN fragments. The synthetic method described here provides efficient access to this class of natural products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10082.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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