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Synthesis of the KLMN Fragment of Gymnocin-A Using Oxiranyl Anion Convergent Methodology

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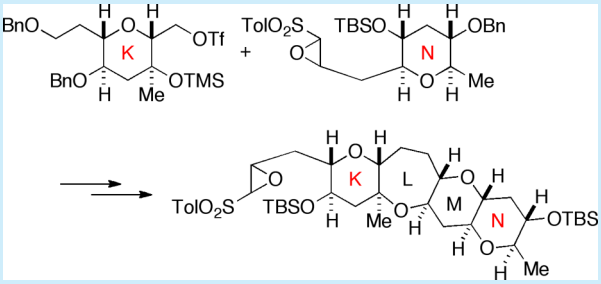
Supporting Information

ABSTRACT: Synthesis of the KLMN fragment of gymnocin-A has been achieved by a [*X* + 2 + *Y*]-type convergent strategy involving the coupling of a K-ring triflate and an N-ring epoxy sulfone. Fusions of the L ring and the M ring were carried out by intramolecular S_N2 substitution of a tertiary alcohol and reductive etherification to furnish the target molecule.



Marine dinoflagellates produce a number of complex bioactive molecules.[1] Gymnocin-A was isolated from a culture of red-tide dinoflagellate *Karenia mikimotoi*.[2] The structure of gymnocin-A (**1**) is characterized by a stunning array of 14 contiguous ether rings (Figure 1), the third longest marine polycyclic ether after brevisulcenal-F[3] and gymnocin-B[4] (17 and 15 contiguous rings, respectively). The potent cytotoxicity (IC_{50} = 1.3 μg/mL) against P388 mouse leukemia cells and the complex architecture make gymnocin-A an attractive target for synthetic chemists.[5] To date, only one total synthesis of gymnocin-A has been achieved by Tsukano and Sasaki using a Suzuki−Miyaura coupling strategy.[6] A structure−activity relationship study including truncated analogues was also reported by the same group.[7]

Construction of such a long ladder-like structure in a highly convergent manner is key in any total synthesis of marine polyether toxins.[8,9] We have recently reported a [*X* + 2 + *Y*]-type convergent strategy using an oxiranyl anion coupling, which integrates the construction of medium-ring ethers.[10−12] This unique methodology has prompted us to undertake a synthetic study of gymnocin-A, and here we report the synthesis of the KLMN fragment.

Retrosynthesis of the KLMN fragment **2** starts with disconnecting the C−O bond of the M ring. The unraveled seven-membered L ring could be constructed as a ring expansion reaction[13] of the six-membered ketone **3** (Scheme 1). This cyclic ketone would be accessible by intramolecular S_N2 substitution of bulky tertiary alcohol **4**, potentially a high-risk strategy to constructing the bicyclic ether containing an angular methyl group. Synthesis of **4** could be achieved by C−C bond formation between advanced building block K-ring triflate **5** and N-ring oxiranyl anion **6**, both of which would be prepared from 2-deoxy-D-ribose.

Synthesis of epoxy sulfone **16** began by tosylation and benzylation of methyl 2-deoxy-D-ribofuranoside (**7**) to give **8** (Scheme 2). Reduction of the tosylate with lithium triethylborohydride, followed by dithioacetalization, provided alcohol **10** in 91% yield over two steps. The resulting alcohol was converted to the unsaturated ester aldehyde **12** by reaction with ethyl propiolate followed by removal of the 1,3-dithiane. The SmI_2-mediated radical cyclization[14] of acyclic **12** afforded (3*S*,4*R*)- and (3*R*,4*S*)-hydroxy esters **13a** and **13b** in 71 and 22% yields, respectively. The secondary alcohol of the desired major isomer **13a** was protected with TBSOTf to afford ester **14**, which was also made by recycling the undesired (3*R*,4*S*)-isomer **13b** in a four-step process. The complete isomerization of the ester side chain of the undesired isomer was achieved by a retro-Michael/oxa-Michael reaction[15] after inversion of the C4 hydroxyl group.[16] Reduction of ester **14** with DIBALH and Horner−Wadsworth−Emmons (HWE) olefination of the resulting aldehyde with $TolSO_2CH_2P(O)(OEt)_2$ gave *trans*-vinylsulfone **15**. Subsequent epoxidation with *t*-BOOH/*t*-BuOK led to the desired *trans*-epoxy sulfone **16** as an 88:12 diastereomeric mixture.

Synthesis of the other coupling partner, K-ring triflate **5**, is shown in Scheme 3. Methyl 2-deoxy-D-ribofuranoside (**7**) was converted to unsaturated ester aldehyde **18** through a sequence including silylene protection of the 1,3-diol, dithioacetalization, oxa-Michael reaction with ethyl propiolate, and removal of the dithioacetal. SmI_2-mediated reductive cyclization of **18** on the rigid dioxasilinane ring proceeded stereoselectively to afford hydroxy ester **19** in 90% yield as a single diastereomer.

The ester was then reduced, and the resulting diol was protected as a dibenzyl ether (**20**). After removal of the silylene group and selective protection of the primary alcohol with a TBDPS group, the secondary alcohol was oxidized to give ketone **22**. Introduction of an axial methyl group with MeMgBr in Et_2O afforded the desired isomer **23** in 60% yield along with 39% of its epimer. Subsequent removal of the TBDPS group

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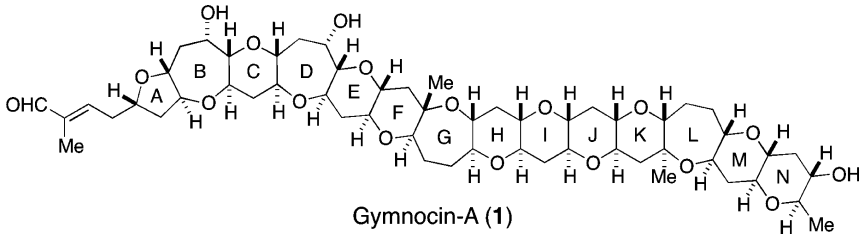
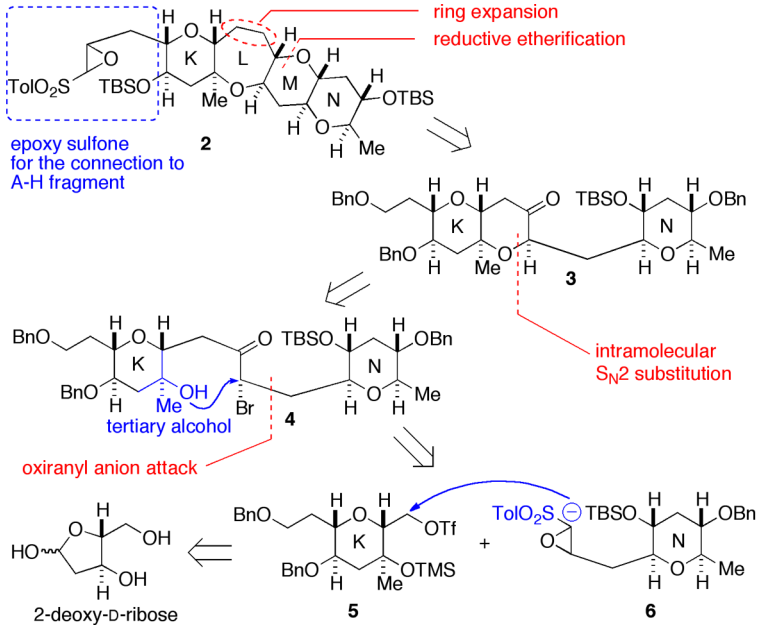
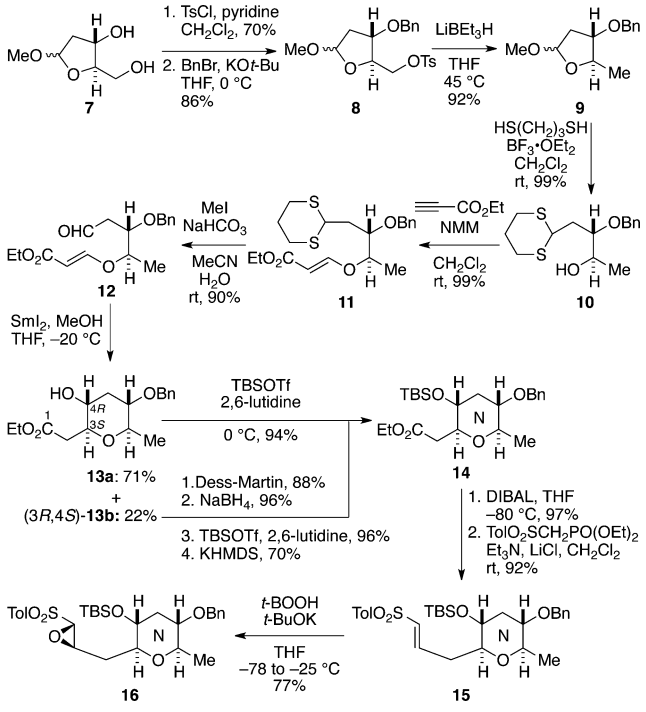


Figure 1. Structure of gymnocin-A (**1**).

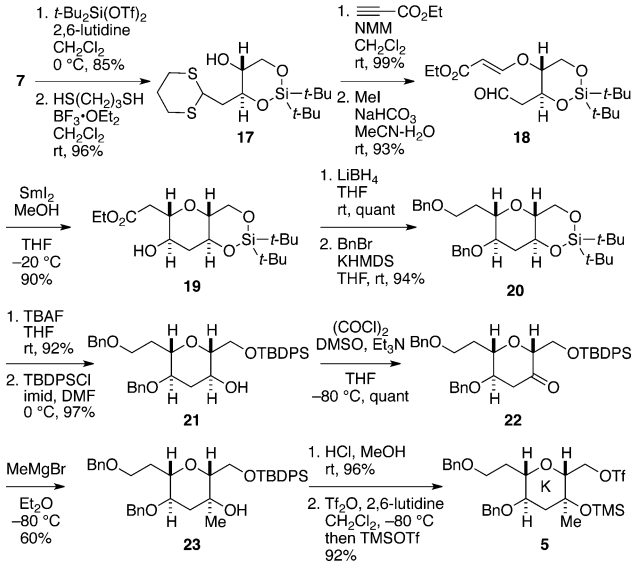
Scheme 1. Retrosynthetic Analysis of the KLMN Fragment 2



Scheme 2. Preparation of the N-Ring Epoxy Sulfone 16



Scheme 3. Preparation of the K-Ring Triflate 5



followed by a one-pot triflation–trimethylsilylation of the resulting diol afforded the desired K-ring triflate **5**.

Union of the K-ring triflate **5** and the N-ring epoxy sulfone **16** was achieved by oxiranyl anion alkylation (Scheme 4). A mixture of **5** and **16** was treated with *n*-BuLi in the presence of HMPA at −100 °C to provide the product **24** in 67% yield (76% conversion based on the recovered triflate). The reaction at −80 °C resulted in a significant drop in yield to 19% because

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Scheme 4. Reaction of the N-Ring Epoxy Sulfone 16 with the K-Ring Triflate 5

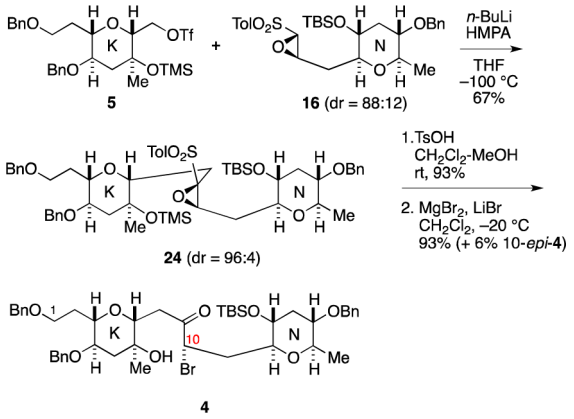
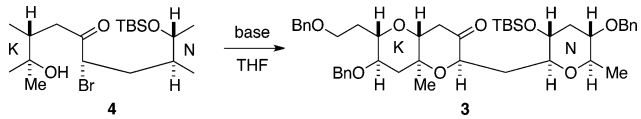


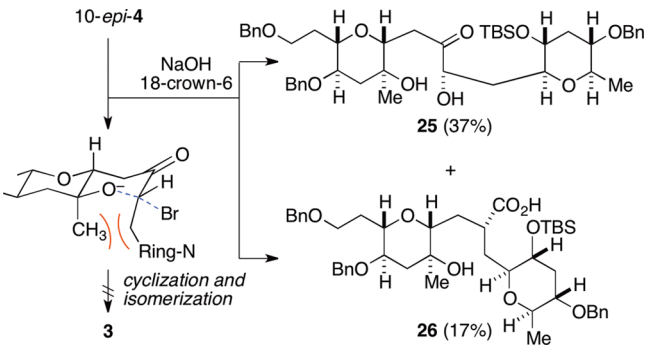
Table 1. Reaction Conditions for Base-Mediated Cyclization of 4 to 3



entry	base	additive	temp (°C)	time (h)	yield (%)
1	NaH		−10	3	37
2[a]	TMG		25	24	4
3	KHMDS		0	1	20
4	1 M aq NaOH		0	24	44
5	0.4 M n-Bu_4NOH in MeOH		−40	1	60
6	1 M aq NaOH	15-crown-5	0	24	81
7	1 M aq NaOH	18-crown-6	0	8	88

[a] CH_2Cl_2 was used as a solvent.

Scheme 5. Attempting the Cyclization Reaction Using 10-*epi*-4



of the instability of the oxiranyl anion at this temperature. Removal of the TMS group of **24** followed by bromination with $MgBr_2$ afforded bromoketone **4** (93%) along with a small amount of the minor isomer 10-*epi*-**4** (6%).

Ring fusion of **4** by intramolecular S_N2 reaction to bicyclic ether **3** containing an angular methyl group is a challenging task as the reaction sites are an unfavorable combination of a bulky tertiary alcohol and a secondary alkyl bromide, as dictated by the Williamson ether synthesis. We have previously reported that NaH is suitable for S_N2 cyclization in a similar system with a tertiary alcohol.[12a] The cyclization of **4** under the same conditions as before, however, resulted in the formation of **3** in only 37% yield (Table 1, entry 1). Several other conditions with NaH were tried but failed to give satisfactory yields. The low yield prompted us to re-examine other bases. When KHMDS and tetramethylguanidine (TMG) were used, the reactions were sluggish and gave even lower yields (entries 2 and 3). Cyclization using a weaker base such as hydroxide was then attempted to minimize decomposition of the substrate. Reaction with 1 M aqueous NaOH in THF afforded **3** as the sole product in 44% yield, along with 51% recovery of the bromoketone starting material (entry 4). The low reactivity may be due to the poor solubility of NaOH in THF. Addition of tetra-*n*-butylammonium hydroxide enhanced the reaction rate, but the yield was still moderate (entry 5). We found that addition of a crown ether greatly improved the yield (entry 6) and that 18-crown-6 is the best additive for the NaOH-mediated S_N2 cyclization to afford the desired product in 88% yield (entry 7).

Cyclization using NaOH and 18-crown-6 was also examined for the minor bromoketone isomer (10-*epi*-**4**). However, the desired product **3** was not obtained; instead, intermolecular substitution with hydroxide and a Favorskii rearrangement occurred to give **25** and **26**, respectively (Scheme 5). Ether ring formation is prevented by the steric repulsion between the axial methyl group and the N-ring moiety in the chairlike transition state. The marked difference of reactivity between the major isomer **4** and the minor isomer 10-*epi*-**4** can be attributed to their C10-configurations being *S* and *R*, respectively.

In preparation for the fusion of ring M, the six-membered ketone **3** was homologated with trimethylsilyldiazomethane to give the seven-membered ketone **27** in 91% yield (Scheme 6). Methyl acetalization and reductive etherification provided tetracyclic polyether **28**, with the construction of the full KLMN ring system. After debenzylation and protection of the resulting triol with TBSOTf, the primary silyl ether was selectively removed under acidic conditions. Dess-Martin oxidation of alcohol **29** to the aldehyde, followed by a HWE reaction, provided *trans*-vinyl sulfone **30**. The synthesis of the KLMN fragment **2** was completed by epoxidation of the vinyl sulfone with *t*-BuOOH/*t*-BuOK. This epoxy sulfone will be reacted with a triflate of the H-ring terminal fragment, the synthesis of which is in progress.

In conclusion, we have synthesized the KLMN fragment (**2**) of gymnocin-A from the N-ring epoxy sulfone **16** and the K-ring triflate **5**, which were prepared from 2-deoxy-D-ribose using a SmI_2-mediated reductive cyclization. Assembly of the two building blocks was achieved using our [*X* + 2 + *Y*]-type convergent strategy, where the fused cyclic ether bearing an angular methyl group was constructed by intramolecular S_N2 cyclization of a tertiary alcohol. Further studies toward the total synthesis of gymnocin-A are continuing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and ^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.

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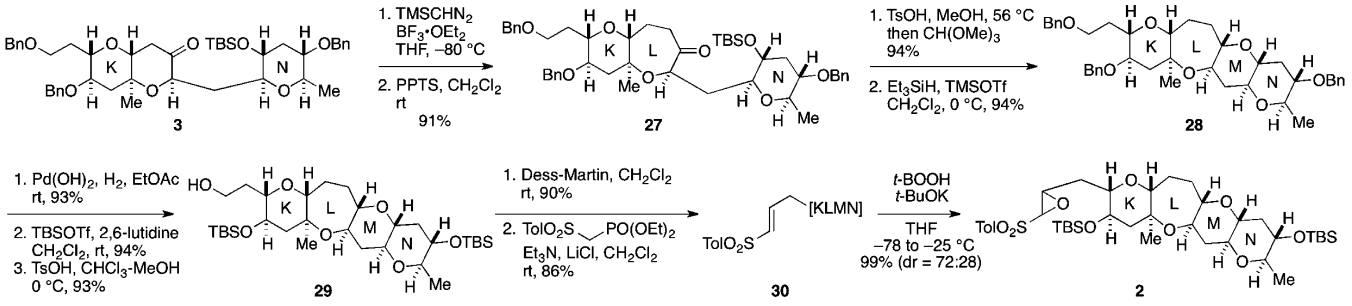
Scheme 6. Completion of the KLMN Fragment 2 Synthesis



Notes

The authors declare no competing financial interest.

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(16) DBU-mediated C3 isomerization of the ketone product of the Dess-Martin oxidation of **13b** resulted in a low yield due to *β*-elimination of benzyl alcohol.

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