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Synthetic study of gymnocin-A: synthesis of the ABC ring fragment

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ABSTRACT

The synthesis of the ABC ring fragment of gymnocin-A is described. The key feature of this approach was the convergent BC ring formation using an oxiranyl anion coupling, which was followed by intramolecular Williamson ether synthesis and the reductive etherification of an α-acetoxy acetal. The five-membered A ring was then constructed on the seven-membered B ring by radical cyclization of a β-alkoxy acrylate derivative.

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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 (Fig. 1), and it is the third longest known 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) of gymnocin-A against P388 mouse leukemia cells and its complex architecture make this compound an attractive target for synthetic chemists.[5] To date, only one total synthesis of gymnocin-A has been reported by Tsukano and Sasaki,[6] who later reported a structure–activity relationship (SAR) study on this compound and its truncated analogs.[7] Synthesis of the HIJK tetracyclic system through epoxide-opening cascade reactions was demonstrated by the Jamison group.[8]

We recently developed a divergent and convergent [X + 2 + Y] strategy using an oxiranyl anion coupling that is applicable to polycyclic ethers containing seven- and eight-membered ring ethers.[9] Based on this strategy, we have initiated a program for the synthesis of gymnocin-A by assembling three ring systems (ABC, FGH, and KLMN). Synthesis of the KLMN fragment has recently been accomplished in a convergent manner.[10] Herein, we report the synthesis of the ABC ring fragment **2**, which comprises a *trans*-fused 5-7-6 tricyclic ether ring system.

In our retrosynthetic analysis, the tetrahydrofuran ring A was to be constructed from β-alkoxy unsaturated ester **3** (Scheme 1). We envisaged that the BC ring system could be constructed through ring expansion and cycloetherification of **4**, which may be obtained from epoxy sulfone **5**. The epoxy sulfone could be disconnected to triflate **6** and epoxy sulfone **7**, and the latter could be related to 2-deoxy-D-ribose (**8**). The choice of a cyclic protecting group for triflate **6**[11] is crucial because the corresponding benzyl-protected acyclic triflate is unstable owing to a spontaneous decomposition by intramolecular attack of the benzyl ether oxygen on the triflate. The strategic decision to install the five-membered A ring onto the BC ring was guided by our preliminary studies, as shown in Scheme 2. We initially attempted to build a six-membered ether ketone onto the five-membered A ring (**9** → **10**) by intramolecular Williamson ether synthesis. However, the desired product could not be obtained, possibly because of the structural strain associated with the *trans*-fused 5-6 ring system. Another attempt to construct a five-membered ring on a tetrahydropyran ring by radical cyclization[12] of β-alkoxy unsaturated ester **11** led to the formation of a significant amount (35%) of the dehalogenation product **13**, along with the expected product **12**. This result indicated that the course of the cyclization reaction was influenced to some extent by conformational bias.

A possible solution to these problems could be the installation of a tetrahydrofuran ring on a conformationally more flexible seven-membered ring by radical cyclization of β-alkoxy acrylate **3**, which corresponds to **11**, at a later stage of the synthesis, as indicated in Scheme 1.

Benzyl-protected methyl 2-deoxy-D-ribofuranoside **14**[13] was subjected to dithioacetalization using 1,3-propanedithiol to give dithioacetal **15** (Scheme 3). Protection of the alcohol with TBSOTf followed by the removal of the dithioacetal group by MeI-assisted hydrolysis afforded aldehyde **17** in good yield. The Horner–Wads-

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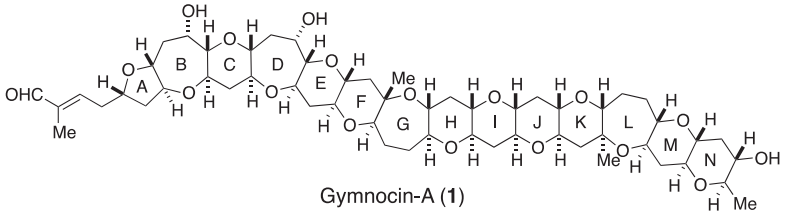
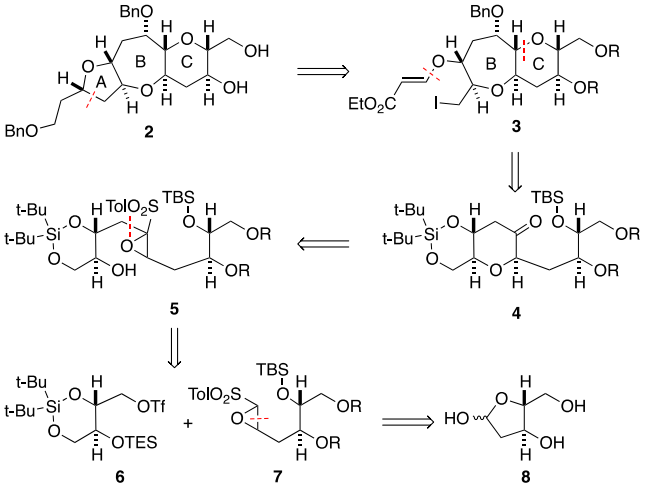
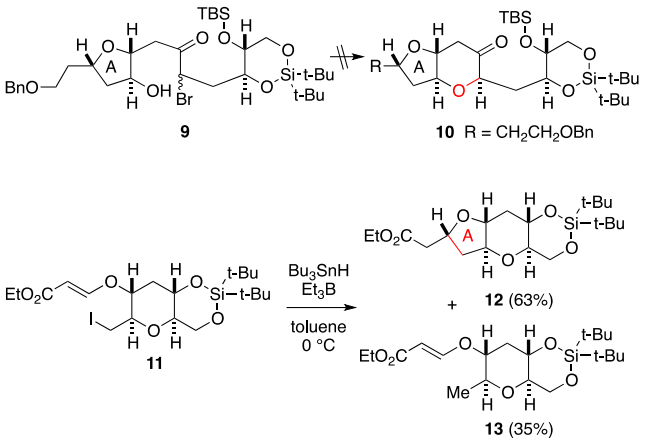


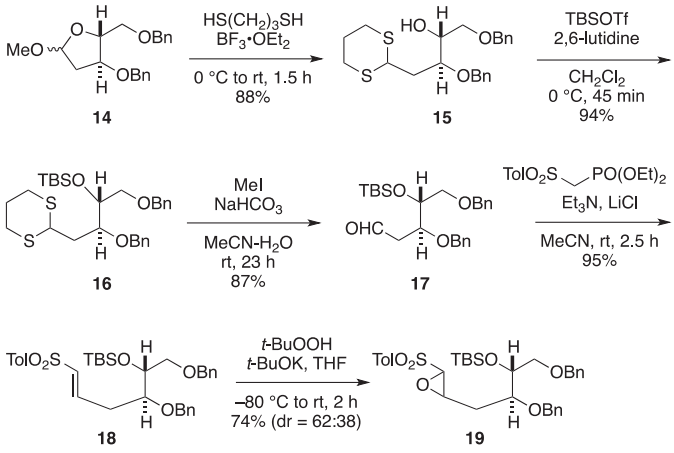
Figure 1. Structure of gymnocin-A (**1**).



Scheme 1. Retrosynthetic analysis of the ABC fragment **2**.



Scheme 2. Attempted cyclizations of **9** and **11**.



Scheme 3. Synthesis of epoxy sulfone **19**.

worth–Emmons reaction of this aldehyde with diethyl *p*-tolylsulfonylmethylphosphonate under Masamune–Roush conditions[14] provided vinyl sulfone **18**. Subsequent epoxidation with *t*-BuOOH/*t*-BuOK led to the desired building block **19** in 74% yield as a 62:38 diastereomeric mixture.

The BC ring system was constructed using our [X + 2 + Y]-type convergent method (Scheme 4). A mixture of triflate **6** and epoxy sulfone **19** was treated with *n*-BuLi to afford the coupling product **20** in high yield. Removal of the TES group followed by treatment with $MgBr_2{\cdot}OEt_2$ furnished bromo ketone **21** in 91% yield over the two steps. Exposure to DBU led to the smooth cyclization of **21** to give the thermodynamically stable ketone **22** as the sole product. This protocol was efficient because the diastereomers of **21** and, in turn, those of **20** converged to a single isomer of **22** by concomitant isomerization. A ring enlargement of the ketone with TMS-diazomethane[15] in the presence of $BF_3{\cdot}OEt_2$ afforded the seven-membered ketone **23** in 74% yield after acid treatment.

Introduction of a hydroxyl group into the B ring was achieved through a two-step process involving silyl enol ether formation, followed by osmium-mediated dihydroxylation. Dihydroxylation of the TMS enol ether of **23** proceeded in a single, well-defined stereochemical direction[6b] to afford α-hydroxyl ketone **24**, but only in moderate yield (66%), possibly owing to the susceptibility of the TMS ether to hydrolysis. In fact, a significantly improved yield (94%) was obtained by using the TES enol ether, which is more stable toward hydrolysis than the TMS ether. Subsequent selective cleavage of the TBS group and simultaneous acetal formation in the presence of an acid-sensitive silylene protecting group under acidic conditions required considerable experimentation and optimization. Success was finally realized by exposing **24** to 0.06 M $TsOH{\cdot}H_2O$ in CH_2Cl_2/MeOH/$HC(OMe)_3$ (5:1:5) at room temperature. Under these conditions, the desired α-hydroxy acetal **25a** was isolated in 72% yield along with 13% of the α-hydroxy-protected bis-acetal **26**, which on mild acid treatment gave an additional amount of **25a** (total yield 84%). It is worth noting that in this acetalization, the amount of added methanol is critical because increasing the ratio of methanol decreases the yield of the desired product owing to cleavage of the silylene group, whereas decreasing the methanol content retards the initial TBS cleavage reaction.

Reductive etherification of the methyl acetal group was required to complete the construction of the BC ring system. The expeditious route to **27a** would be the direct reductive etherification[16] of acetal **25a** without the protection of the free hydroxyl group at the α-position. However, the TMSOTf-mediated reduction gave the desired BC ring **27a** in 45% yield (Table 1, entry 1). As the use of other Lewis acids or reducing agents did not improve the yield,[17] we examined the reduction of the hydroxy-protected acetals. The TMS-protected derivative **25b** was directly converted to **27a** in a moderate yield under the same conditions (entry 2). Introduction of the TES protective group did not result in any

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