Total Synthesis of the Marine Ladder Polyether Gymnocin B

Satapanawat Sittihan1,†, Timothy F. Jamison1,*
1Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Abstract

Herein we report the first total synthesis of marine ladder polyether gymnocin B (1) based on a two-phase strategy. In Phase I, inspired by the proposed biosynthesis, epoxide-opening cascades assemble 10 out of 15 cyclic ether rings making up the molecular core. In the subsequent Phase II, coalescence elevates the molecular complexity further by coupling of these subunits. Our two-phase synthetic approach significantly improved the step efficiency of the synthesis of this class of natural products.

Graphical Abstract

Introduction

Isolated in 2005 from cultured cells of dinoflagellate Karenia mikimotoi, gymnocin B (1) is the second largest contiguous marine ladder polyether (MLP) with an array of 15 cyclic ethers (Scheme 1A).1 The backbone of 1 contains one tetrahydrofuran (THF), nine tetrahydropyrans (THPs), and five oxepanes, along with a 2-methyl-2-butenal side chain characteristic of the gymnocin family. In addition, 1 exhibits cytotoxicity against mouse lymphoid P388 cells at 1.7 μg/mL.1 Due to its relatively large size and molecular flexibility, absolute configuration determination of 1 demanded the development of a mild and efficient chromophore installation method, as well as extensive conformational and computational analysis.2 To date, only one synthetic attempt of 1 has been reported on a bicyclic model system.3

Since the isolation and structural elucidation of brevetoxin B in 1981,4 over 50 MLP natural products have been identified. The structural complexity and novelty of these molecules, as

*Corresponding Author: tfj@mit.edu.
†Present Addresses
Chulabhorn Graduate Institute, 906 Kamphaeng Phet 6, Talat Bang Khen, Lak Si, Bangkok, 10210, Thailand
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well as their impressive impacts on marine populations, stimulated the development of new methods of synthesis that target two key challenges: creative ring-forming tactics and convergent assembly of these rings by way of novel fragment-coupling strategies.\textsuperscript{5,6} With considerable effort from a number of laboratories, several MLPs have been made in this fashion by total synthesis, providing both the MLPs themselves and a few truncated variants for further biological evaluation.\textsuperscript{7,8} Convergent strategies have become a common practice in the synthesis of larger MLPs, prompting development of inventive yet practical fragment-coupling transformations.\textsuperscript{9}

In pursuit of a more efficient ring-forming strategy, chemists have drawn inspiration from proposed biosynthetic pathways, one of which involves a single, dramatic epoxide-opening cascade proposed by Nakanishi in 1985 (Scheme 1A).\textsuperscript{10} Despite strong precedence against the success of such proposed transformation,\textsuperscript{11} several laboratories have developed methods that emulate this hypothesis to synthesize MLP subunits. For instance, McDonald employed Lewis acids as initiators to effect epoxide-opening cascades of substrates bearing electronically unbiased “internal” disubstituted epoxides to generate polyoxepanes (Scheme 1B).\textsuperscript{12} Our group discovered that neutral water in combination with a pre-installed THP template could promote epoxide-opening cascades to result in the formation of polyTHP subunits (Scheme 1C).\textsuperscript{13}

We postulated that combining these cyclization methods with fragment-couplings would provide a two-phase approach for the rapid synthesis of MLPs such as 1. In Phase I (epoxide-opening cascades), several fragments that correspond to the core structure of gymnocin B (1) could be assembled efficiently (Scheme 2). Subsequently, the molecular complexity could be elevated in Phase II (coalescence), by convergent coupling of structural subsets. Herein, we document the first success of this two-phase approach, in the form of the first total synthesis of 1. Our strategy significantly improves the step efficiency of MLP synthesis as demonstrated by the average of three steps in the longest linear sequence (LLS) per the number of rings.

 Results and Discussion

 Retrosynthetic Analysis.

During the course of designing our synthesis, we strategically chose to disconnect 1 along the THP rings as shown in Scheme 2, Phase II. We reasoned that we could utilize Suzuki-Miyaura cross-coupling reactions along with subsequent transformations to generate these 6-membered rings in a stereocontrolled manner. We also recognized that the position of the Me substituents at the ring junctions of 1 were important considerations in deciding both the position and the resulting direction of the epoxide-opening cascade reactions to be performed in Phase I (Scheme 2). As the Shi ketone catalyst and other variants are synthetically accessible,\textsuperscript{14} we had the ability to generate epoxide substrates bearing the necessary stereochemistry based on the chosen cascade direction.

Based on this initial evaluation of our target molecule, the retrosynthetic analysis proceeded with the disconnection of 1 along the THP I ring, to provide two smaller fragments: ABCDEFGH (3) and JKLMNO (4). We envisioned that the latter could be assembled via the
union of KLM (7) and known ketene acetal phosphate (8). The formidable pseudoaxial Me61 would be installed diastereoselectively by taking advantage of axial Me62 in 8. Regarding the KLM fragment, we proposed that the polyTHP motif in 7 could be derived from a water-promoted epoxide-opening cascade of triepoxy alcohol 13 based on our previously reported results (Scheme 1C). However, whereas the polyTHP product shown in Scheme 1C features a non-functionalized THP template, 13 required a scaffold bearing functional group handles. Based on our experience with a 1,3-dioxane template,16 the dimethyl acetonide was chosen due to its similar conformational and electronic properties and ease of removal for further elaboration.

Similarly, 3 could be disconnected in a convergent manner through the E ring, giving rise to ABCD (5) and FGH (6). Containing two trans fused oxepanes, tricycle 6 maps onto the product of a Lewis acid-catalyzed epoxide-opening cascade of triepoxide 12 with Me59 serving as a directing group on one of the epoxides. Consisting of THF, THP, and oxepane rings in a single fragment, 5 presented a challenging target. Consequently, we chose two different cascades to construct the AB and CD subunits separately. For the unique fused THF-oxepane AB rings, we turned our attention to a bromonium-initiated epoxide-opening cascade due to its ability to tolerate formation of diverse ring sizes in a single transformation.17 Thus, epoxy alcohol 9 was chosen as the substrate precursor with Me58 capable of directing the cascade under electrophilic conditions. Finally, we arrived at our last retrosynthetic target, polyTHP 10. We posited that 10 would be derived from an epoxide-opening cascade of diepoxide 11, most likely operating under basic conditions due to the presence of an acid-sensitive vinyl epoxide moiety.

**Phase I – Epoxide-Opening Cascades**

**Synthesis of ABCD (20).—** As summarized in Scheme 3, we began the synthesis of ABCD (20) by assembling the CD subunit from diepoxide 11, accessible in nine steps LLS from 2-deoxy-D-ribose (14).18 Epoxide-opening cascades of 11 in water or under neutral aqueous conditions provided a low yield of 10 (Table 1, Entry 1 and 2). Inorganic bases and acidic additives delivered a moderate amount of the desired product (Entry 35). Subsequent pH screening studies revealed that 11 could not tolerate acidic aqueous conditions due to the presence of an acid-sensitive vinyl epoxide (Entry 6). Optimal yield of 10 was obtained at pH 11 (Entry 7). Reactions conducted at higher pH did not improve the yield (Entry 8). Thus, pH 11 phosphate buffer was chosen as the optimal condition for the formation of 10, which is the first reported example of a nucleophilic epoxide-opening cascade at basic pH.

Cascade product 10 then underwent Sharpless diastereoselective epoxidation19 to install the C10 stereochemistry, followed by alcohol protection as the PMB ether (Scheme 3). Subsequent addition of the cuprate generated from vinyl iodide 15 to the epoxide, provided a homoallylic alcohol, which was converted to benzyl ether 16. Asymmetric Shi epoxidation with Shi catalyst 17,14b followed by PMB removal, delivered 9 as the key substrate for the proposed bromonium-initiated cascade.

To forge the AB rings, we explored an unprecedented 7-endo-5-exo epoxide-opening cascade of 9.21 Similar to previous studies, the choice of bromonium initiator had no
significant effect on the reaction yields, while the choice of solvent proved critical. A combination of N-bromosuccinimide (NBS) as an initiator with hexafluoroisopropanol (HFIP) as solvent led to the AB ring construction in good yield. The success of this cascade relied on the electronic bias intrinsic to 9 and the site-selective bromonium formation which acted as an initiator. The cascade proceeded with complete regio- and diastereoselectivity although with incorrect C5 stereochemistry. However, a two-step elimination and hydroboration/oxidation procedure corrected the stereochemical discrepancy in 18. The C5 stereochemistry was confirmed by nOe experiments of an acetate derivative of 5. Further alcohol protection, followed by acid-catalyzed acetonide removal, provided diol 19. Selective iodination of the primary alcohol of 19, silylation of the secondary alcohol, and elimination of the alkyl iodide furnished ABCD (20).

Synthesis of FGH (25).—We next turned our attention to the construction of coupling partner FGH (25) (Scheme 4A). Accessible in eight steps LLS from geraniol (21), triepoxide 12 was subjected to conditions reported by McDonald for similar types of cascades. Among a variety of Lewis acids evaluated, boron trifluoride diethyl etherate (BF$_3$·OEt$_2$) delivered the highest yield of the trans fused oxepanes after subsequent silylation to furnish 22 (Table 2, Entry 1). The use of Yb(OTf)$_3$ also gave a comparable yield (Entry 2), but the reaction required a large excess of the Lewis acid promoter. More satisfactory and reproducible yields were obtained when the reactions were performed at low concentration (Entry 3), likely due to the avoidance of non-productive, intermolecular reaction pathways. The use of more coordinating ethereal solvents such as THF to attenuate the reactivity of BF$_3$ failed to give appreciable amount of 22 (Entry 4). Conversion of the 1,3-dioxan-2-one motif in 22 to a lactone was achieved via base-catalyzed carbonate removal, followed by oxidation/Wittig olefination of the liberated primary alcohol to provide enoate 23. Subsequent chemoselective conjugate reduction and a sequence of oxidation state manipulations revealed lactone 24. Finally, a three-step synthesis sequence of ozonolysis/reductive workup, silylation, and enol triflate formation furnished the requisite FGH (25).

Synthesis of KLM (28).—Our synthetic effort next focused on the construction of KLM (28). Shown in Scheme 4B, triepoxide 13, accessible in nine steps LLS from 14, was subjected to a variety of conditions (Table 3). Initial screening revealed that elevated temperatures were necessary for sufficient solubility of 13 in aqueous media (Entry 1 and 2), and the benzylidene and dimethyl acetal moieties could not tolerate aqueous acidic conditions (Entry 3). After some experimentation, it was determined that subjecting 13 to pH 8 aqueous buffer at 70 °C delivered tricycle 7 in optimal yield (Entry 4). Reactions performed at higher pH experienced erosion in yield (Entry 5). We believed that, compared to neutral pH, a slightly basic condition accelerated the formation of the first THP (i.e., ring M). The subsequent epoxide-opening events proceeded with higher rate due to the presence of a more rigid template generated after the first cyclization. Triepoxide 13 represented the most functionalized substrate to successfully undergo a water-promoted epoxide-opening cascade.24
In preparation for coalescence in Phase II, 7 underwent chemo- and regioselective reduction of the benzylidene acetal to reveal a 1,5-diol, which was converted to the corresponding bisPMB ether under Lewis acid catalysis in the presence of PMB donor 26. Subsequent acid-catalyzed acetonide removal liberated diol 27. A straightforward three-step reaction sequence then furnished KLM (28).

Phase II – Coalescence

Coalescence of ABCD (20) and FGH (25).—With both olefin 20 and enol triflate 25 in hand, we were ready to assemble the ABCDEFGH core of 1 via a Suzuki-Miyaura coupling reaction (Scheme 5A). To this end, hydroboration of 20 with 9-borabicyclo[3.3.1]nonane (9-BBN), followed by cross-coupling with 25, furnished desired adduct 29 in good yield. Attempts to use an enol phosphate analog of 25 were met with no success, which was similarly observed in Sasaki’s total synthesis of gymnocin A. Hydroboration/oxidation of 29 afforded alcohol 30 with incorrect stereochemistry at C20 due to the sterically encumbered Me59 shielding the bottom face of the molecule. After oxidation to the corresponding ketone, we were pleased to see that the C20 stereochemical discrepancy was corrected via base-promoted epimerization to the more thermodynamically favorable epimer 31. Attempts to perform glycal-epoxide rearrangement to convert 29 directly to 31 were unsuccessful. Reductive etherification of 31 with in situ exhaustive desilylation completed the synthesis of ABCDEFGH (3) in 29 steps LLS.

Coalescence of KLM (28) and O (8).—Union of KLM (28) and known ketene acetal phosphate O (8) to generate the JKLMO (4) proceeded by way of a B-alkyl Suzuki–Miyaura cross coupling of 28 to furnish adduct 32 (Scheme 5B). Our next challenge was the construction of the highly decorated O ring of 1. We were inspired by Rainier’s total synthesis of gambierol, in which two adjacent stereocenters situated on the oxepane E ring were set through an epoxidation/reduction sequence of a glycal whose molecular framework was similar to that of 32. The unusual facial selectivity of the DMDO epoxidation was explored via the use of computational studies. To implement this strategy, enol ether 32 was first treated with dimethyldioxirane (DMDO) and then methylmagnesium bromide instead of DIBAL. After acylation of the newly formed alcohol, the syn relationship of Me61 and Me62 was confirmed by nOe experiments of acetate 33. The choice of alkylating agent was critical as trimethylaluminum resulted in a lower yield. In a one-pot operation, we successfully installed two adjacent stereocenters on a flexible oxepane ring, including C51 and the formidable pseudoaxial methyl groups flanking the O ring.

Our next task was the elaboration of 33 in preparation for the final coupling step. To this end, desilylation, alcohol oxidation, and base-catalyzed deacetylation furnished hemiacetal 34. Direct reductive etherification attempt on 34 led to a mixture of benzyl ethers resulting from accompanying nonselective reduction of the benzylidene acetal. Therefore, we subjected 34 to acid-catalyzed acetal removal. Subsequent reductive etherification proceeded with concomitant exhaustive PMB removal to reveal a tetraol. The 1,3-diol moiety in the cyclized product was selectively protected as an acetonide to furnish diol 35. Partial oxidation of the 1,5-diol in 35 to a hemiacetal, followed by mild Takai–Utimoto olefination, afforded olefin 36. Attempts to use basic Wittig olefination resulted in facile elimination of...
benzyl alcohol at C37. At this point, the C51 stereochemistry was confirmed by nOe experiments. Finally, regioselective hydroboration/oxidation and oxidative lactonization of the resulting diol furnished JKLMNO (4), thus completing the synthesis in 29 steps LLS.

Completion of 1: Coalescence of ABCDEFGH (3) and JKLMNO (4).—The final stage of the synthesis is depicted in Scheme 5C. Similar to our previous strategies, 3 and 4 were converted to enol ether 37 and ketene acetal phosphate 38, respectively. Despite the complexity of the two fragments, Suzuki–Miyaura cross coupling proceeded smoothly to furnish desired adduct 39 in good yield. Hydroboration/oxidation led to an inseparable diastereomeric mixture of alcohols, which underwent a sequence of oxidation and epimerization to afford ketone 40 with the correct C34 stereochemistry. To forge the final I-ring, reductive etherification conditions were attempted on 40 but met with no success. Thus, we turned our attention to mixed thiketal formation. A combination of zinc trifluoromethanesulfonate (Zn(OTf)2) and ethanethiol with nitromethane as solvent32 effected the desired mixed thiketal formation with concomitant removal of the TES and dimethyl acetal groups. The resultant diol was subjected to silylation and reductive desulfurization under radical condition33 to furnish pentadecacyclic 41, thus completing the entire core of 1. Hydrogenolysis revealed a triol, whose primary alcohol was converted to an alkyl iodide, and remaining secondary alcohols were silylated to afford iodide 42. Finally, side-chain installation commenced with vinyl cuprate substitution on 42. After exhaustive desilylation with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), cross-metathesis with methacrolein and Hoveyda–Grubbs 2nd generation catalyst led to the successful isolation of 1. Characterization studies confirmed that synthetic gymnocin B was identical to the naturally occurring compound.18

Conclusion

In conclusion, our two-phase synthetic strategy culminated in the first total synthesis of gymnocin B (1), the second largest contiguous MLP natural product. During Phase I, four different epoxide-opening cascades were employed to rapidly assemble ten cyclic ethers, namely one THF, six THPs, and three oxepanes, of the fifteen rings comprising 1, or two-thirds of the molecular core. During coalescence (Phase II), a Suzuki–Miyaura reaction enabled convergent assembly of the ABCDEGDGH and JKLMNO fragments. This step-efficient two-phase approach may find further application in the synthesis of other MLP natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
(A) Proposed Biosynthesis of Gymnocin B (1) via the Epoxide-Opening Cascade of 2 (B) Lewis Acid-Initiated and (C) Water-Promoted Epoxide-Opening Cascades
Scheme 2.
Retrosynthetic Analysis of Gymnocin B (1)
Scheme 3.
Phase I – Synthesis of ABCD (20)
Scheme 4.
Phase I – (A) Synthesis of FGH (25) (B) Synthesis of KLM (28)
Scheme 5.
Phase II – (A) Synthesis of ABCDEFGH (3) (B) Synthesis of JKLMNO (4) (C) Completion of the Synthesis of Gymnocin B (1)
Table 1.

Optimization of epoxide-opening cascades of 11<sup>a</sup>

| Entry | Conditions | Yield of 10 (%) |
|-------|------------|----------------|
| 1     | dH<sub>2</sub>O, 70 °C, 4 d | trace          |
| 2     | pH 7 KP<sub>i</sub> buffer, 70 °C, 4 d | 10             |
| 3     | Cs<sub>2</sub>CO<sub>3</sub> (3000 mol %), MeOH, rt, 4 d | 38             |
| 4     | CSA (100 mol %), CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h | 45             |
| 5     | BF<sub>3</sub>·OEt<sub>2</sub> (25 mol %), CH<sub>2</sub>Cl<sub>2</sub>, −78 to 0 °C, 30 min | 35             |
| 6     | pH 4 KP<sub>i</sub> buffer, rt, 4 d | -              |
| 7     | pH 11 KP<sub>i</sub> buffer, rt, 4 d | 54             |
| 8     | pH 12 KP<sub>i</sub> buffer, rt, 4 d | 53             |

<sup>a</sup>Optimization was performed with 4:1 dr of 11.
Table 2.
Optimization of epoxide-opening cascades of 12<sup>a</sup>

| Entry | Conditions                      | Conc. (M) | Yield of 22 (2 steps, %) |
|-------|---------------------------------|-----------|--------------------------|
| 1     | BF<sub>3</sub>·OEt<sub>2</sub> (100 mol %), CH<sub>2</sub>Cl<sub>2</sub>, −40 °C, 15 min | 0.05      | 23                       |
| 2     | Yb(OITf)<sub>3</sub> (500 mol %), CH<sub>2</sub>Cl<sub>2</sub>, rt, 2h                | 0.05      | 21                       |
| 3     | BF<sub>3</sub>·OEt<sub>2</sub> (100 mol %), CH<sub>2</sub>Cl<sub>2</sub>, −40 °C, 15 min | 0.02      | 34                       |
| 4     | BF<sub>3</sub>·OEt<sub>2</sub> (100 mol %), THF, −40 or 0 °C                | 0.02      | -                        |

<sup>a</sup>Optimization studies were performed using >20:1 dr of 12.
Table 3.

Optimization of epoxide-opening cascades of 13$^a$

| Entry | Conditions                  | Yield of 7 (%) |
|-------|-----------------------------|----------------|
| 1     | pH 7 KP$_i$ buffer, rt, 4 d | $^b$           |
| 2     | pH 7 KP$_i$ buffer, 70 °C, 7 d | 18            |
| 3     | pH 4 KP$_i$ buffer, 70 °C, 7 d | -             |
| 4     | pH 8 KP$_i$ buffer, 70 °C, 7 d | 23            |
| 5     | pH 9 KP$_i$ buffer, 70 °C, 7 d | 19            |

$^a$Optimization studies were performed using 2:1 dr of 13.

$^b$Substrate was insoluble.