Natural products with unique and complex architectures present new challenges to organic synthesis. An example of such a molecule is longithorone A (1), a cytotoxic marine natural product with an unusual heptacyclic structure (Figure 1).\(^1\) Longithorone A was first disclosed in 1994, and to date its synthesis has not been reported. The challenge of a synthesis of 1 is heightened by the presence of two forms of chirality: stereogenic centers in rings A–E and atropisomerism arising from hindered rotation of quinone ring G through macrocycle F.\(^2\) Schmitz has presented a provocative hypothesis to explain the biosynthesis of 1 involving an intermolecular Diels–Alder cycloaddition between [12]-paracyclophanes 2 and 3 to form ring E and a transannular Diels–Alder reaction\(^3\) across 3 to simultaneously assemble rings A, C, and D.\(^4\) The isolation of longithorones B and C, [12]-paracyclophanes that exhibit atropisomerism and are closely related to 2 and 3 provide some support for this proposal.\(^1,4\)

Our plan for a synthesis of 1 is based on its proposed biosynthesis with an initial goal of constructing protected versions of 2 and 3 as single atropisomers followed by conversion to 1 using intermolecular and transannular Diels–Alder reactions. In this communication we report an enantioselective, biomimetic synthesis of longithorone A (1) that provides support for its proposed biosynthesis.

The synthetic strategy for protected versions of paracyclophanes 2 and 3 involved ene–yne metathesis macrocyclization reactions to generate the 1,3-disubstituted dienes of both paracyclophanes (Figure 2).\(^5\) An interesting dichotomy exists between intermolecular and intramolecular ene–yne metathesis reactions since intramolecular ene–yne metatheses afford 1,2-disubstituted dienes and intermolecular ene–yne metatheses afford 1,3-disubstituted dienes (Figure 3).\(^6,7\) To date, macrocyclization via ene–yne metathesis had not been reported, and it was unknown whether 1,2-disubstituted dienes or 1,3-disubstituted dienes would be generated. We hypothesized that macrocyclization of compounds 4 and 6 would resemble intermolecular ene–yne metathesis and generate 1,3-disubstituted dienes since the resulting [12]-paracyclophanes would be less strained than the [11]-paracyclophanes resulting from 1,2-disubstituted diene formation.

![Figure 1. Plan for a biomimetic synthesis of longithorone A. The stereogenic centers of 1 are controlled by the atropisomerism of 2 and 3.](image1)

![Figure 2. Paracyclophane syntheses using ene–yne metathesis macrocyclization and a removable atropisomer control element.](image2)

![Figure 3. Intramolecular and intermolecular ene–yne metathesis reactions lead to differentially substituted dienes.](image3)
yield.\textsuperscript{13–15} The acetylenic TMS group and phenolic TBS group were deprotected simultaneously with TBAF at 0°C, affording a phenol in 98% yield and 95% ee.\textsuperscript{16} A three-step procedure involving Lindlar hydrogenation of the terminal acetylene, TBAF-promoted removal of the TIPS group, and silylation of the phenol and benzylic alcohol with TBSCL produced 13 in 63% over three steps. Exposure of 13 to (Cy\textsubscript{3}P)\textsubscript{2}Cl\textsubscript{2}RuClPH and 1 atm of ethylene at high dilution and 40°C afforded paracyclophane 14 with >20:1 atropdiastereoselectivity.\textsuperscript{17} Compound 14 was isolated as an inseparable 2:2:1 mixture with an unusual paracyclophane that had lost a molecule of propane during the cyclization.\textsuperscript{18,19} Selective removal of the phenolic TBS group of 14 with TBAF at 0°C allowed for separation and delivered phenol 15 in 42% yield over two steps. Only the 1,3-disubstituted diene could be detected after the metathesis and desilylation steps. Ionic hydrogenation of the benzyl silyloxy group was accomplished in 69% yield using TFA and NaBH\textsubscript{4}CN followed by silylation of the phenol to afford 16 in 75% yield.

Synthesis of paracyclophane 21 also began from common intermediate 11 using a bromoaluminum reagent derived from 17 and the same enantioselective alkylation conditions that were successful in the synthesis of 13.\textsuperscript{14,15} Removal of all silicon-based protecting groups with TBAF afforded triol 18 in 97% yield and 90% ee over two steps.\textsuperscript{16} Compound 19 was produced in 86% yield by treatment of the triol with TBSCL and imidazole. Another ene–yne metathesis cyclization was performed by exposing 18 to the same conditions used for 13 → 14. However, this cyclization resulted in a 2.8:1 ratio of atropdiastereomers and a 3.9:1 (E-Z) ratio of double bond isomers favoring 20.\textsuperscript{19} In analogy to the conversion of 13 to 14, only the 1,3-disubstituted diene was detected. After chromatographic separation from the other cyclization products, compound 20 could be reproducibly isolated in 31% yield. The conversion of 20 to 21 was achieved in three steps comprising ionic hydrogenation with TFA and Et\textsubscript{3}SiH to remove the benzyl silyloxy group, selective removal of the primary alcohol TBS group with PPTS in EtOH, and oxidation of the allylic alcohol with Dess–Martin periodinane.\textsuperscript{20} Both paracyclophanes 16 and 21 exhibit atropisomerism with barriers to rotation that prevent racemization up to 100°C.\textsuperscript{21}

With enantioselective syntheses of paracyclophanes 16 and 21 achieved, we were in a position to test the proposed biosynthesis and, in the process, accomplish a biomimetic synthesis of lon-
githorone A (Scheme 2). An intermolecular Diels—Alder reaction between 16 and 21 was performed by treating 21 with 1.35 equivalents of 16 and Me₂AlCl at −20 °C affording 22 and a diastereomer in 70% yield as a 1:1.4 ratio disfavoring 22. Exposure of 16 and 21 to other Lewis acids such as TiCl₄, BF₃·OEt₂, SnCl₄, and Yb(OTf)₃ led to either no reaction, diminished selectivity for 22, or decomposition. ¹H NMR analysis indicated that the cycloaddition was completely endo selective with the diastereomers resulting from a lack of facial selectivity. Lewis acid catalysis of the intermolecular Diels—Alder reaction is required which indicates that if the biosynthesis of 1 involves a similar cycloaddition, a Diels—Alder may be involved at this step.¹⁸ The lack of substrate-based diastereoselectivity in the cycloaddition may also implicate a Diels—Alderase. Removal of both TBS groups from 22 with TBAF delivered 23 which was directly oxidized with iodosylbenzene to afford bisquinone 24. The bisquinone, which was observed by NMR and TLC underwent a transannular Diels—Alder reaction at room temperature over the course of 40 h to generate the A, C, and D rings of 1.⁴ The ee was determined at this stage since the enantiomers of this compound were separable by chiral HPLC. ¹⁹ ²⁰ Exposure of 24 for 15 h at 23 °C and a high ee of this reaction. ²¹ The assignments of absolute configuration in the asymmetric vinyl zinc reagents were made by analogy to other similar additions, the X-ray structure of compound 15a (see Supporting Information), and by comparison of the optical rotation of natural 1 to synthetic 1. ²² The ee was determined at this stage since the enantiomers of this compound were separable by chiral HPLC. ²³ ²⁴ The byproduct of this metathesis reaction is:

References


(10) For an example of the use of a benzylic substituent to control atropisomerism via A(1,3) strain, see: Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. J.; Trotter, B. W.; Katz, J. L. Angew. Chem., Int. Ed. 1998, 37, 2704–2708.

(11) Dibromide 8 was synthesized in three steps (*BuLi/DMF, NaBH₄, PBr₃) from 1,4-dibromo-2,5-dimethoxybenzene. Vinyl iodide 9 was synthesized in three steps (TIPSCl, Dess–Ed'; Martin periodinane, Ph₃P=CM(Me) from 4-pentyn-1-ol. See the Supporting Information for details.


(13) Alder reaction is required which was formed upon exposure of 16 to 21 for 15 h at 23 °C and a high ee of this reaction. ²¹ The assignments of absolute configuration in the asymmetric vinyl zinc reagents were made by analogy to other similar additions, the X-ray structure of compound 15a (see Supporting Information), and by comparison of the optical rotation of natural 1 to synthetic 1. ²² The ee was determined at this stage since the enantiomers of this compound were separable by chiral HPLC. ²³ ²⁴ The byproduct of this metathesis reaction is:

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Supporting Information Available: Details of experimental procedures and analytical data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.