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Biomimetic Synthesis of (−)-Longithorone A

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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.[1b] 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.[1a,4]

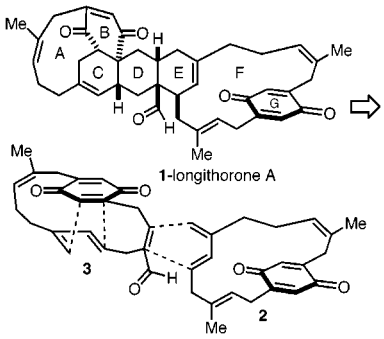


Figure 1. Plan for a biomimetic synthesis of longithorone A. The stereogenic centers of **1** are controlled by the atropisomerism of **2** and **3**.

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.

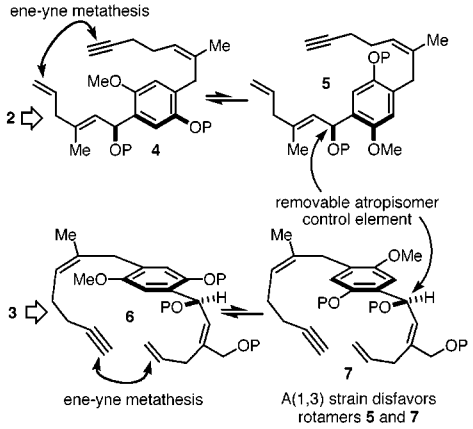


Figure 2. Paracyclophane syntheses using ene−yne metathesis macrocyclization and a removable atropisomer control element.

Strategically positioned benzylic hydroxyl groups would be used to gear the aromatic rings of **4** and **6** during the ene−yne metathesis macrocyclizations in order to control the atropisomerism of **2** and **3** (Figure 2). This should disfavor rotamers **5** and **7** due to A(1,3) strain and enforce an atropdiastereoselective cyclization.[8,9] Having served their purpose as control elements in the cyclizations, the benzylic hydroxyl groups would be removed reductively, yielding the cyclophanes as single atropisomers.

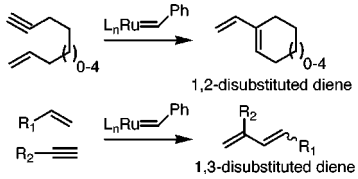
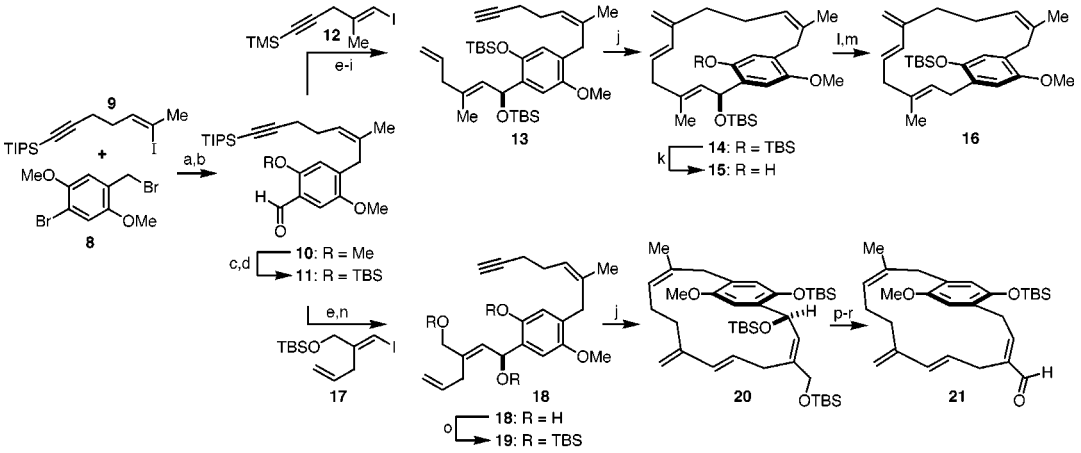


Figure 3. Intramolecular and intermolecular ene−yne metathesis reactions lead to differentially substituted dienes.

Scheme 1 depicts the synthesis of paracyclophanes **16** and **21** from aldehyde **11**. A two-step procedure for the conversion of **8**[10] and **9**[10] into **10** was accomplished using a Pd-mediated cross-coupling[11] between vinyl iodide **9** and a benzylic zinc reagent[12] derived from **8** in 98% yield. The coupling was followed by formylation of the aromatic bromide with ^{n}BuLi and DMF, delivering **10** in 94% yield. Selective demethylation was accomplished by treating **10** with BBr_3 followed by silylation with TBSOTf to generate **11** in 88% yield over two steps.

Conversion of benzaldehyde **11** to ene−yne **13** began with an enantioselective alkylation using a bromozinc reagent derived from **12** in combination with the lithium alkoxide of (1*S*,2*R*)-*N*-methylephedrine to provide the resulting benzylic alcohol in 91%

Scheme 1 [a]



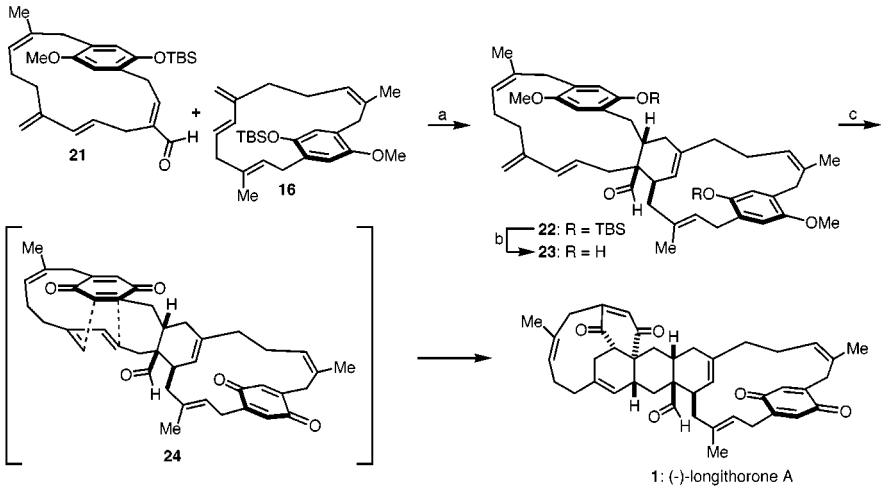
[a] Reagents: (a) Zn°, **8**, THF, 0 °C; $Pd(PPh_3)_4$, **9**, 23 °C, 98%. (b) ^nBuLi, Et_2O, −78 °C; DMF, −78→35 °C, 94%. (c) BBr_3, CH_2Cl_2, −78→23 °C. (d) TBSOTf, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 88% two steps. (e). ^{t}BuLi,. **12** or **17**, Et_2O, −78 °C; $ZnBr_2$, Et_2O, 0 °C; premixed ^{n}BuLi/(1*S*,2*R*)-*N*-methylephedrine, toluene, 0 °C; **11**, toluene, 0 °C, 95% ee, 91% for **11**+**12**. (f) TBAF, THF, 0 °C, 98%. (g) 5% $Pd/BaSO_4$, quinoline, 1 atm H_2, (1:1) 1-hexene:MeOH, 23 °C. (h) TBAF, THF, 0°→23 °C. (i) TBSCl, imidazole, DMF, 0°→23 °C, 63% three steps. (j) 0.5 eq. $(Cy_3P)_2Cl_2RuCHPh$, ethylene (1 atm), CH_2Cl_2, high dilution, 31% for **20**. (k) TBAF, THF, 0°→23 °C, 42% of **15** over two steps. (l) $NaCNBH_3$, TFA, CH_2Cl_2, 23 °C, 69%. (m) TBSOTf, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 75%. (n) TBAF, THF, 0°→23 °C, 90% ee, 97%. (o) TBSCl, imidazole, DMF, 23 °C, 86%. (p) TFA, Et_3SiH, CH_2Cl_2, 23 °C. (q) PPTS, EtOH, 45 °C, 46% two steps. (r) Dess−Martin periodinane, CH_2Cl_2, 23 °C, 99%.

yield.[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.[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 $(Cy_3P)_2Cl_2RuCHPh$ and 1 atm of ethylene at high dilution and 40 °C afforded paracyclophane **14** with >20:1 atropdiastereoselectivity.[17] Compound **14** was isolated as an inseparable 2.2:1 mixture with an unusual paracyclophane that had lost a molecule of propene during the cyclization.[18,19] Selective removal of the phenolic TBS 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 benzylic silyloxy group was accomplished in 69% yield using TFA and $NaBH_3CN$ followed by silylation of the phenol to afford **16** in 75% yield.

Synthesis of paracyclophane **21** also began from common intermediate **11** using a bromozinc reagent derived from **17** and the same enantioselective alkylation conditions that were successful in the synthesis of **13**.[14,15] Removal of all silicon-based protecting groups with TBAF afforded triol **18** in 97% yield and 90% ee over two steps.[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**.[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_3SiH to remove the benzylic silyloxy group, selective removal of the primary alcohol TBS group with PPTS in EtOH, and oxidation of the allylic alcohol with Dess−Martin periodinane.[20] Both paracyclophanes **16** and **21** exhibit atropisomerism with barriers to rotation that prevent racemization up to 100 °C.[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-

Scheme 2 [a]



[a] Reagents: (a) Me_2AlCl, CH_2Cl_2, −20 °C, 70%, 1:1.4 diastereomers. (b) TBAF, THF, 0 °C. (c) PhI(O), MeCN−H_2O, 0→25 °C, 90% two steps.

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 Me_2AlCl 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 $TiCl_4$, $BF_3{\cdot}OEt_2$, $SnCl_4$, 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[22] which indicates that if the biosynthesis of **1** involves a similar cycloaddition, a Diels−Alderase may be involved at this step.[23] 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 cycloaddition at room temperature over the course of 40 h to generate the A, C, and D rings of **1** and directly afford longithorone A in 90% yield from **22**. A synthetic sample of **1** was judged to be identical to a sample of the natural product by ^1H and ^{13}C NMR, IR, HRMS, and TLC analyses. The optical rotation of synthetic **1** was $[\alpha]_D$ −47.6° ($c = 0.00077$, CH_2Cl_2) while natural **1** was $[\alpha]_D$ −47.4° ($c = 0.00108$, CH_2Cl_2), thereby confirming that the absolute configuration of synthetic **1** matches natural **1**.

In summary, an enantioselective biomimetic synthesis of longithorone A has been accomplished that demonstrates the feasibility of the reactions proposed for the biosynthesis—albeit using nonenzymatic conditions. The syntheses of two [12]-paracyclophanes were realized by using the first examples of ene−yne metathesis macrocyclization. In both cases, 1,3-disubstituted dienes were generated, demonstrating a different mode of reactivity from all other reported examples of intramolecular ene−yne metathesis. A mechanistic basis for this result and the synthetic utility of ene−yne metathesis macrocyclization are under investigation. In addition, this synthesis presents a unique example of chirality transfer in complex molecule synthesis involving the use of stereogenic centers to control atropisomerism, removal of the stereogenic centers, and transfer of the atropisomerism back to stereogenic centers in the natural product.

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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.

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(10) Dibromide **8** was synthesized in three steps (^{n}BuLi/DMF, $NaBH_4$, PBr_3) from 1,4-dibromo-2,5-dimethoxybenzene. Vinyl iodide **9** was synthesized in three steps (TIPSCl, Dess−Martin periodinane, $Ph_3P{=}C(I)Me$) from 4-pentyn-1-ol. See the Supporting Information for details.
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(14) A 1:1 ratio of the vinyl bromozinc reagent to chiral ligand was crucial for the high ee of this reaction.
(15) The assignments of absolute configuration in the asymmetric vinyl zinc additions 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**.
(16) The ee was determined at this stage since the enantiomers of this compound were separable by chiral HPLC.
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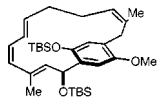
(18) The byproduct of this metathesis reaction is:



which was confirmed by X-ray analysis. For loss of propene during a metathesis macrocyclization, see: Joe, D. and Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635−8638.
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(20) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(21) Heating **16** and **21** to 100 °C for 1 h did not result in any loss of ee.
(22) None of the intermolecular Diels−Alder adduct **22** was formed upon exposure of **16** to **21** for 15 h at 23 °C or 1 h at 80 °C.
(23) For reports of apparent Diels−Alderases, see: (a) Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van den Heever, J. P.; Hutchinson, C. R.; Vederas, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11519−11520. (b) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748−8756.

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