Synthesis of (−)-longithorone A: Using organic synthesis to probe a proposed biosynthesis

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We present a full report of our enantioselective synthesis of (−)-longithorone A (1). The synthesis was designed to test the feasibility of the biosynthetic proposal for 1 put forward by Schmitz involving intermolecular and transannular Diels–Alder reactions of two [12]-paracyclophane quinones. We have found that if the biosynthesis does involve these two Diels–Alder reactions, the intermolecular Diels–Alder reaction likely occurs before the transannular cycloaddition. The intermolecular Diels–Alder precursors, [12]-paracyclophanes 38, 49, 59, and 60, were prepared atropselectively, providing examples of ene–yne metathesis macrocyclization. The 1,3-disubstituted dienes produced from the macrocyclizations represent a previously unreported substitution pattern for intramolecular ene–yne metathesis. Protected benzylic hydroxyl stereocenters were used as removable atropisomer control elements and were installed by using a highly enantioselective vinylzinc addition to electron-rich benzaldehydes 26 and 27.

An intriguing question in natural product biosynthesis is whether nature uses Diels–Alder reactions. The answer to this question appears to be yes, because there are many examples of spontaneous Diels–Alder reactions in biosyntheses (1) as well as recently documented examples (2–4) of enzymatically influenced Diels–Alder reactions. Longithorone A (**1**) is a marine natural product that attracted our attention because of its unusual structure, but even more so because of the biosynthetic proposal of Schmitz and co-workers (5, 6) that invoked two Diels–Alder reactions. Schmitz has proposed that **1** arises from the combination of [12]-paracyclophane quinones **2** and **3** by an intermolecular Diels–Alder reaction, affording ring E, and a transannular (7) Diels–Alder reaction, generating rings A, C, and D (Fig. 1).

We viewed this interesting proposal as an opportunity to use organic synthesis to make protected versions of **2** and **3** and test, in the laboratory, the feasibility of the proposed Diels–Alder reactions (8). In particular, we were hopeful that our experiments might suggest whether the intermolecular Diels–Alder reaction occurs preferentially between compound **4**, which has already undergone a transannular Diels–Alder, and paracyclophane **2** to generate **1** or between paracyclophanes **3** and **2** to generate **5**, followed by a transannular Diels–Alder to afford **1**.

The isolation (5) of longithorones B (9) and C, [12]-paracyclophane quinones that closely resemble the structures of **2** and **3**, provided some support for the proposed biosynthesis of longithorone A (Fig. 2).

We found it intriguing that longithorones B and C exhibit atropisomerism (10–12) and are single enantiomers. From these observations, we recognized that **2** and **3** must be constructed atropselectively to test whether the absolute and relative stereochemistry of **1** is derived solely from the planar chirality of **2** and **3**. Finally, the isolation of longithorone I suggested that the biosynthesis of **1** may first involve an intermolecular Diels–Alder reaction between **2** and **3** followed by a transannular cycloaddition. In this paper we present a full description of our synthesis (13), findings that elucidate the timing of the Diels–Alder reactions proposed for the biosynthesis of **1**, and additional examples of ene–yne metathesis macrocyclization demonstrating its usefulness in forming macrocyclic 1,3-disubstituted dienes.

The synthesis strategy for protected versions of **2** and **3** involved atropdiastereoselective ene–yne metathesis (14–16), macrocyclization of **6** and **7**, and simultaneous generation of the 1,3-disubstituted dienes of both paracyclophanes (Fig. 3).

The strategically positioned protected benzylic hydroxyl groups of **6** and **7** would be installed by enantioselective addition of vinylzinc reagents to the corresponding electron-rich benzaldehyde (17). These hydroxyl groups would then be used to gear the aromatic rings of **6** and **7** during the ene–yne metathesis macrocyclizations to set the atropisomerism of **2** and **3**. A(1,3) strain (18) should disfavor rotamers **8** and **9** and enforce an atropdiastereoselective (19, 20) macrocyclization. After having served their purpose as control elements in the macrocyclizations, the protected benzylic hydroxyl groups would be removed reductively, yielding the paracyclophanes as single atropisomers.

Our synthesis plan also relied upon ene–yne metathesis macrocyclization to generate 1,3-disubstituted dienes. It had been demonstrated that with terminal alkynes intramolecular (21–27) ene–yne metathesis generally affords 1,2-disubstituted dienes, whereas intermolecular (28–30) ene–yne metathesis yields 1,3-disubstituted dienes (Fig. 4).

Because ene–yne metathesis had not been applied to the synthesis of macrocycles, we hoped to use our system to test the preference for forming 1,2- vs. 1,3-disubstituted dienes in a macrocyclization.

Materials and Methods

Details describing chemical synthesis, general procedures, instrumentation, molecular modeling, optimization of ene–yne metathesis macrocyclization conditions, and substrate tables for macrocyclizations and enantioselective vinylzinc additions can be found in *Supporting Materials and Methods,* which is published as supporting information on the PNAS web site. The procedures for the synthesis of tetracycles **4** and **46**; macrocycles **14**–**20**; benzylic alcohols **25**, **28**, and **31**; enynes **33**, **37**, and **39**; paracyclophanes **35**, **38**, **41**, **44**, **45**, and **49**; truncated product **43**; model compounds **48**, and **50**–**53**; and advanced intermediates **54**–**56** and **58**; along with corresponding spectral data can also be found in *Supporting Materials and Methods*. For details descriptions of the synthesis of natural product **1**; vinyl iodides **23** and **30**; benzaldehydes **26** and **27**; benzylic alcohols **29** and **32**; enynes **34** and **40**; paracyclophanes **36**, **42**, **59**, and **60**; and advanced intermediates **61** and **52**, see ref 13.

Results and Discussion

Development of Ene–Yne Metathesis Macrocyclization. Before our initial disclosure (13) of the synthesis of **1**, macrocyclization using ene–yne metathesis had not been reported (31), and it was unknown whether 1,2-disubstituted dienes or 1,3-disubstituted dienes would be generated. We prepared a series of acyclic

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Abbreviations: TBS, *tert*-butyldimethylsilyl; ee, enantiomeric excess; TIPS, triisopropylsilyl; TBAF, tetrabutylammonium fluoride; OTf, trifluoromethansulfonate.

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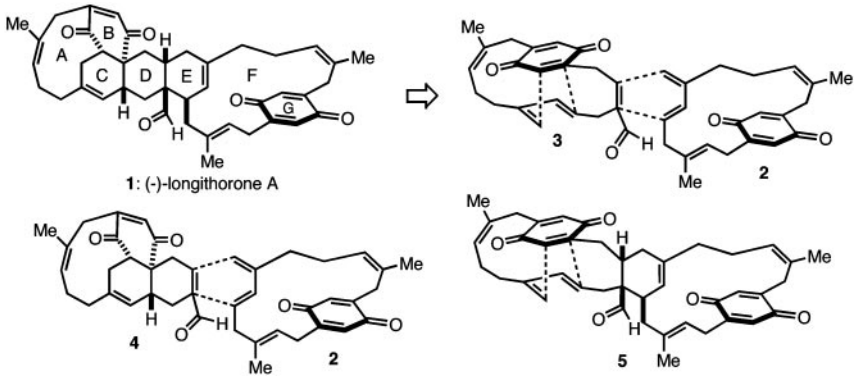


Fig. 1. Plan for a biomimetic synthesis of longithorone A (**1**). The order of the intermolecular and transannular Diels–Alder reactions is unknown.

enynes and subjected them to conditions optimized for macrocyclization by using catalyst **10** (Scheme 1). Pronounced selectivity for the formation of 1,3-disubstitued dienes over 1,2-disubstituted dienes was observed in the reaction, especially for ring sizes of 12 and greater. In a representative set of examples, enynes **11**–**15** were converted into 1,3-disubstituted diene macrocycles **16**–**20**.

An explanation for the preferred formation of 1,3-disubstituted products in these reactions is that the low effective molarity of the reacting terminal olefin and terminal alkyne simulates an intermolecular ene–yne cross metathesis, which is known to afford 1,3-disubstituted dienes. Furthermore, under an ethylene atmosphere (32, 33), intermolecular ene–yne metatheses have been shown to proceed by ethylene–yne cross metathesis followed by a terminal diene–olefin cross metathesis (28). We believe that our system behaves similarly: ethylene–yne cross metathesis occurs first, affording a terminal 1,3-diene, followed by terminal diene–olefin metathesis macrocyclization. The expected terminal 1,3-diene intermediates could be isolated from our ene–yne metathesis macrocyclizations when the reactions were stopped prematurely. Reexposure of the terminal dienes to the reaction conditions generated the 1,3-disubstituted diene macrocycles in high yields. On the basis of these initial results, we expected that macrocyclization of compounds **6** and **7** would also generate 1,3-disubstituted dienes, especially because the products of 1,3-disubstituted diene formation are larger macrocycles that may be less strained.

To probe the synthetic utility of the 1,3-disubstituted diene macrocycles generated from ene–yne metathesis, we performed intermolecular Diels–Alder reactions on diene macrocycle **16** (Scheme 2). Heating **16** with either maleic anhydride or *N*-phenylmaleimide afforded *endo* Diels–Alder adduct **21** or **22** in unoptimized yields of 30% and 79%, respectively. The structure of **22** was determined by x-ray analysis. Having demonstrated that we could synthesize 1,3-disubstituted dienes from an ene–yne metathesis macrocyclization and use them in Diels–Alder reactions, we focused our efforts toward the synthesis of **1**.

Installation of the Atropisomer Control Element. Before the macrocyclizations, it was necessary to enantioselectively install the benzylic stereocenters in **6** and **7** that would gear the ring closure and produce the required atropisomers of the paracyclophanes. It had been disclosed that addition of a *cis*- or *trans*-vinylzinc to benzaldehyde affords secondary benzylic alcohols in moderate enantioselectivities [86% and 73% enantiomeric excess (ee), respectively] when an ephedrine-based chiral ligand is used (34). However, addition of vinylzincs to other arylaldehydes was not reported. We investigated the enantioselective addition of the vinylzinc species derived from vinyl iodide **23** to several benzaldehydes with differing electronics and discovered that addition to electron-rich benzaldehydes proceeded with high enantioselectivity when a 1:1 ratio of ligand to vinylzinc was used (Scheme 3).

Under optimized conditions, addition of the vinylzinc species derived from **23** to 2,5-dimethoxybenzaldehyde (**24**) afforded benzylic alcohol **25** in 97% yield and 95% ee. High conversion was attained by employing an excess of the zinc reagent and chiral ligand. When applied to the functionalized systems, addition to benzaldehyde **26** generated **28** in 98% yield and 98% ee, and addition to benzaldehyde **27** produced **29** in 97% yield and 98% ee. Similarly, vinyl iodide **30** was converted to its corresponding vinylzinc species and added to **26** and **27**, affording **31**

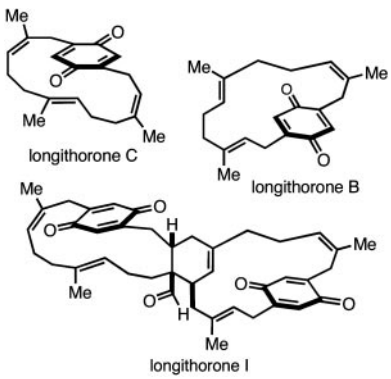


Fig. 2. Other members of the longithorone family may provide insight into the order of events in the biosynthesis of longithorone A.

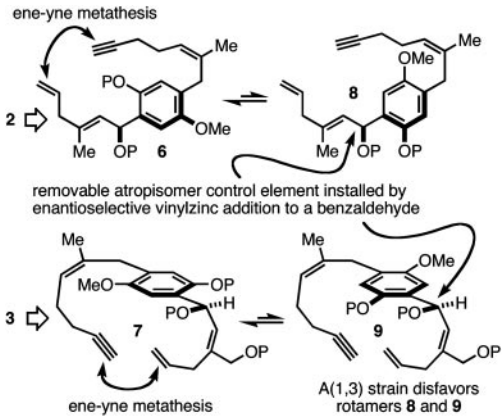


Fig. 3. Paracyclophane syntheses using ene–yne metathesis macrocyclization and a removable atropisomer control element.

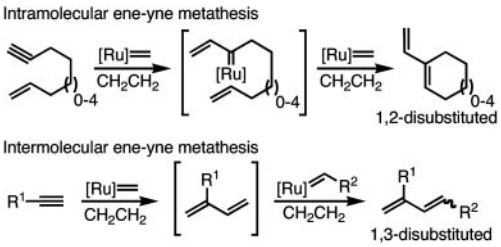
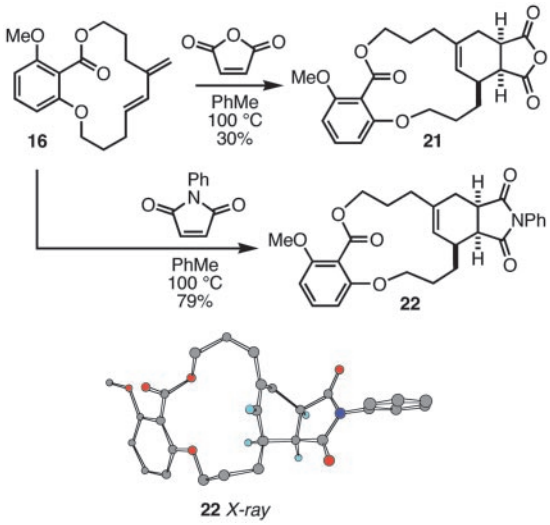


Fig. 4. Intramolecular and intermolecular ene–yne metathesis reactions lead to differentially substituted dienes.

in 97% yield and 94% ee and **32** in 91% yield and 95% ee, respectively. Compounds **28** and **29** were then converted to **39** and **40**, while **31** and **32** were converted to **33** and **34**, setting the stage for the critical ene–yne metathesis macrocyclizations.

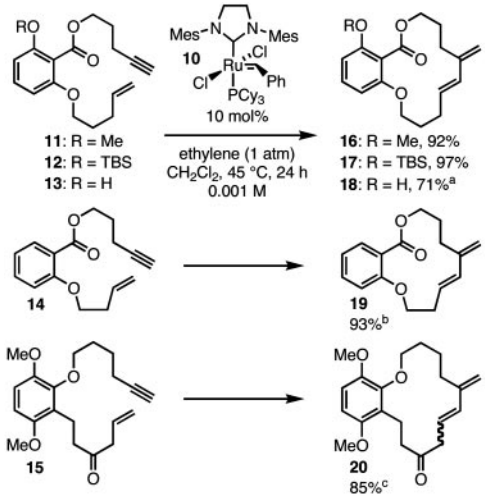
Application of Ene–Yne Metathesis Macrocyclization. Ene–yne metathesis macrocyclization of **33** and **34** proceeded with >25:1 atropdiastereoselectivity and >25:1 *E*:*Z* selectivity affording 1,3-disubstituted diene paracyclophanes **35** and **36** in 32% and 42% yield, respectively, after treatment with tetrabutylammonium fluoride (TBAF) (Scheme 4) (35–37). Interestingly, 1,2-disubstituted dienes were not formed. Both **35** and **36** were isolated along with unusual paracyclophane byproducts in which a methylene unit had been lost during the macrocyclization (38). Curiously, the benzylic TBS ether of **36** was not cleaved during TBAF treatment. An attempt to synthesize racemic paracyclophane **38** from enyne **37**, which lacked the benzylic stereocenter, resulted in a complex mixture of products, illustrating the importance of gearing during the macrocyclization.

Macrocyclization of **39** proceeded with 5.2:1 atropdiastereoselectivity and 3:1 *E*:*Z* selectivity to afford 1,3-disubstituted diene **41** in 47% yield (Scheme 5). Similarly, **40** underwent macrocyclization with 2.8:1 atropdiastereoselectivity and 3.9:1 *E*:*Z* selectivity, yielding 1,3-disubstitued diene **42** in 31% yield. Again, 1,2-disubstituted dienes were not observed. A variety of protecting groups were surveyed for the allylic and benzylic hydroxyl groups, with TBS affording the highest atropdiastereoselectivity and *E*:*Z* selectivity (39). Molecular modeling calculations offer some support for the observed disparity in atropdiastereoselectivity between **33**/**35** and **39**/**41** (see *Supporting Materials and Methods*). Interestingly, attempted ene–yne metathesis macrocyclization with the more reactive catalyst **10** afforded **43**, in which the side chain bearing the terminal alkyne had been truncated. The outcome seems to result from the increased activity of **10**, in particular its ability to react with trisubstituted olefins (35). This is an interesting example where use of the first-generation Grubbs catalyst is preferred over the imidazolidyl catalyst **10**, because the former avoids an undesired side reaction.

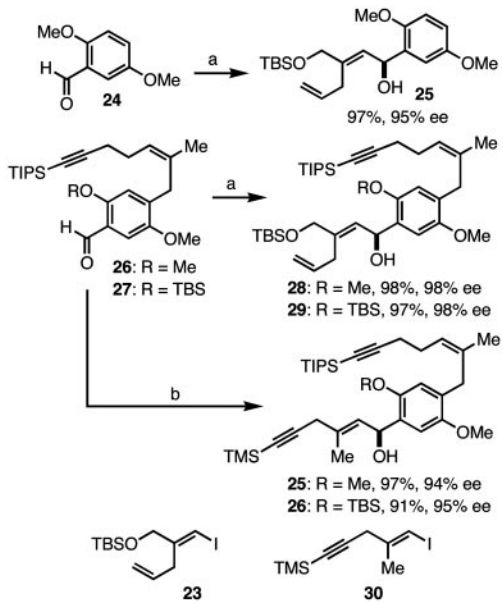


Scheme 2. Diels–Alder reactions with **16**.

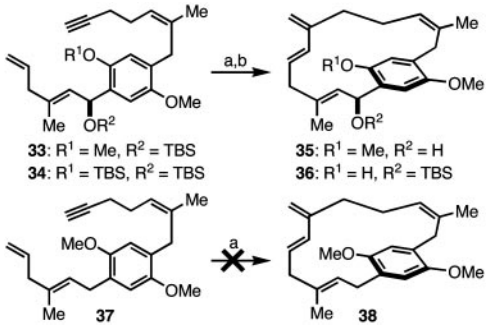
Investigating the Diels–Alder Sequence. Having served its purpose of controlling the atropdiastereoselectivity during the macrocyclization, the benzylic silyloxy group of **41** was removed under ionic hydrogenation conditions using trifluoroacetic acid and Et_3SiH, affording **44** in 58% yield as a single atropisomer



Scheme 1. Selected examples of ene–yne metathesis macrocyclization. Cy, cyclohexyl; TBS, *tert*-butyldimethylsilyl. a, 21% 1,2-Disubstituted diene. b, 7% acyclic terminal 1,3-diene. c, 4:1 Mixture of *E* and *Z* isomers, 9% acyclic terminal 1,3-diene, 4% dimers.



Scheme 3. Reagents and conditions: ^{t}BuLi, vinyl iodide, Et_2O, −78°C, 45 min; then $ZnBr_2$, Et_2O, 0°C, 1 h; then premixed ^{n}BuLi/(1*S*,2*R*)-*N*-methylephedrine, toluene, 0°C, 1 h; then aldehyde, toluene, 0°C, 1 h. Reaction a, with **23**; reaction b, with **30**. TIPS, triisopropylsilyl; TMS, trimethylsilyl.

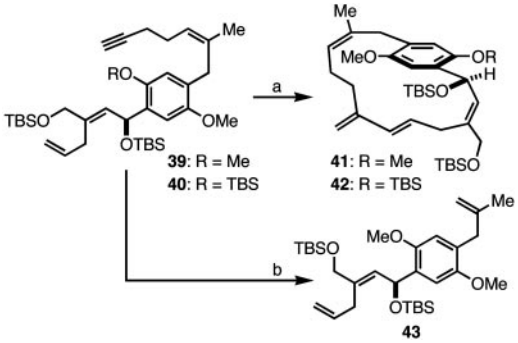


Scheme 4. Reagents and conditions: reaction a, 30–50 mol % $(Cy_3P)_2Cl_2RuCH{=}Ph$, ethylene [1 atm (101.3 kPa)], CH_2Cl_2, 45°C, 21 h, 0.003 M **33** and **34**; reaction b, TBAF, tetrahydrofuran, 0–23°C, 31% yield over two steps for **33** to **35**, 42% yield for **34** to **36**.

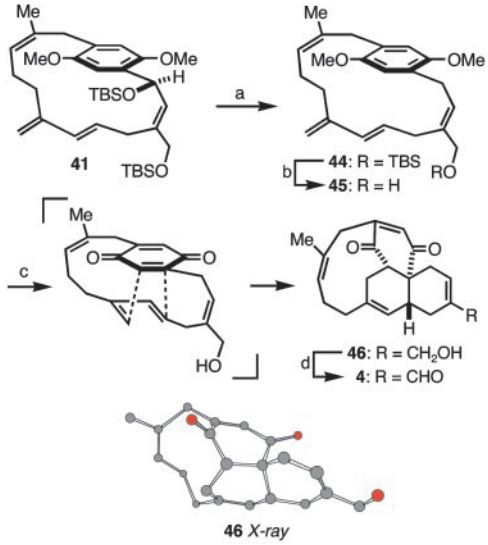
(Scheme 6). Removal of the TBS group generated **45** in 87% yield. Both **44** and **45** could be heated to 180°C without racemization, demonstrating the inability of the protected hydroquinone to rotate through the macrocycle. To mimic the proposed biosynthesis of the A–D ring system of **1**, paracyclophane **45** was oxidized with $(H_4N)_2Ce(NO_3)_6$ at room temperature, leading directly to tetracycle **46** in 32% yield. During this stereoselective reaction it is likely that the dimethylhydroquinone was oxidized to a quinone, and a facile transannular Diels–Alder reaction occurred, using the chiral plane of **45** to control the stereogenic centers of **46**. It is also possible that this transannular cyclization could have proceeded through a radical cation intermediate. The structure of **46** was determined by x-ray analysis. Finally, the enal **4** was generated in 80% yield after oxidation with Dess–Martin periodinane (40).

With the transannular Diels–Alder reaction of the proposed biosynthesis demonstrated, we investigated the subsequent intermolecular Diels–Alder reaction. Unfortunately, all attempts to generate pentacycle **48** from an intermolecular Diels–Alder cycloaddition of **4** with model diene 2-methyl-1,3-pentadiene (**47**) failed (Scheme 7). Use of heat, Me_2AlCl, $MeAlCl_2$, $BF_3{\cdot}OEt_2$, $TiCl_4$, $ZnCl_2$, or pyrrolidine hydrochloride salt to effect the cycloaddition returned unreacted starting material, decomposition products, or, in rare cases, products of hetero-Diels–Alder reactions between the diene and aldehyde.

Considering our inability to realize the intermolecular cyclization of **4** with the model diene system, we reevaluated the order of the two Diels–Alder reactions in the proposed biosynthesis. The structure of longithorone I (Fig. 2) suggested that an intermolecular Diels–Alder reaction might occur before the



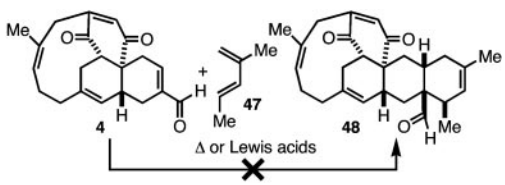
Scheme 5. Reagents and conditions: reaction a, 30–40 mol % $(Cy_3P)_2Cl_2RuCH{=}Ph$, ethylene (1 atm), CH_2Cl_2, 45°C, 40 h, 0.003 M **39** and **40**, 47% yield for **39** to **41**, 31% for **40** to **42**; reaction b, 30 mol % **10**, ethylene (1 atm), CH_2Cl_2, 45°C, 24 h.



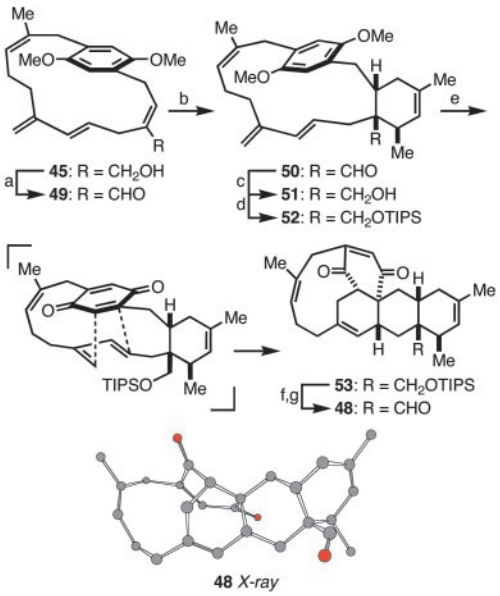
Scheme 6. Reagents and conditions: reaction a, trifluoroacetic acid, Et_3SiH, CH_2Cl_2, 23°C, 58% yield, 98% ee; reaction b, TBAF, tetrahydrofuran, 0–23°C, 87% yield, 98% ee; reaction c, $(H_4N)_2Ce(NO_3)_6$, $MeCN/H_2O$, 0–23°C, 32% yield, 98% ee; reaction d, Dess–Martin periodinane, CH_2Cl_2, 23°C, 80% yield.

transannular Diels–Alder reaction. We were pleased to discover that when paracyclophane alcohol **45** was oxidized, the corresponding enal (**49**) participated in a Me_2AlCl-promoted intermolecular Diels–Alder reaction with **47** to afford an inseparable 2.4:1 mixture of diastereomeric cycloadducts favoring the desired product **50** in 71% yield (Scheme 8). The products resulted from *endo* addition to the diastereotopic faces of enal **49**. Reduction of the aldehyde with $NaBH_4$ afforded alcohol **51**, which could be readily separated from its diastereomer. The free hydroxyl group was protected as the TIPS ether to produce **52** in 92% yield. Oxidation with Ag(II) dipicolinate afforded the pentacyclic transannular Diels–Alder product **53** in 14% yield. During this reaction the A–D ring system of **1** is generated stereoselectively from the transient quinone or via a radical cation intermediate. We suspected that the low yield of this reaction was a result of the incompatibility of the surprisingly reactive diene with the strong oxidants required for dimethylhydroquinone oxidation. Subsequent TIPS deprotection of **53** followed by oxidation with Dess–Martin periodinane delivered **48** in 63% yield over two steps. The structure of **48** was determined by x-ray analysis.

Having established the feasibility of an intermolecular-transannular Diels–Alder reaction sequence in a model system, we applied this strategy in a synthesis of longithorone A. Early efforts toward **1** used racemic dimethylhydroquinone paracyclophanes **38** and **49**, which underwent a Diels–Alder cycloaddition to generate **54**, its atropdiastereomer, and the corresponding minor diastereomers resulting from alternate facial selectivity in 52% yield (84% based on recovered **38**) and as an inseparable 2.2:2.2:1:1 ratio (Scheme 9). Although the reaction was *endo*



Scheme 7. Unsuccessful model intermolecular Diels–Alder reaction of **4** with **47**.



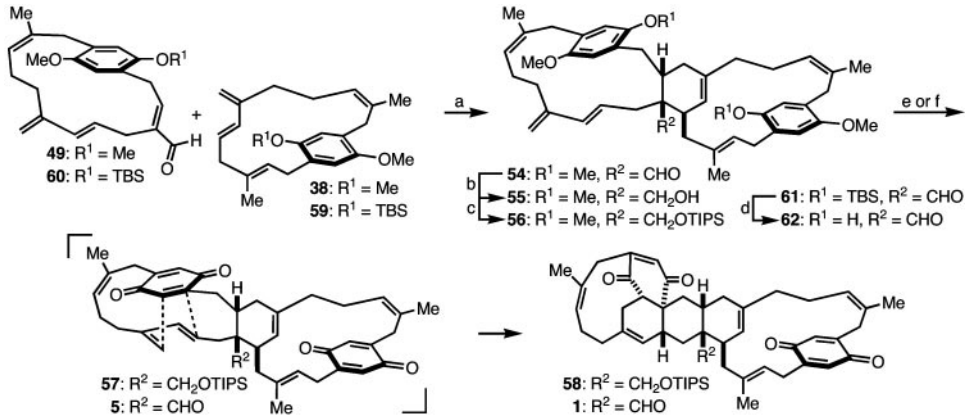
Scheme 8. Reagents and conditions: reaction a, Dess–Martin periodinane, CH_2Cl_2, 23°C, 99% yield; reaction b, **47**, Me_2AlCl, CH_2Cl_2, 0°C, 71% yield, 2.4:1 diastereomers; reaction c, $NaBH_4$, MeOH, 23°C, 99% yield; reaction d, TIPSOTf (OTf, trifluoromethanesulfonate), 2,6-lutidine, CH_2Cl_2, 0°C, 92% yield; reaction e, Ag(II) dipicolinate, PhH/H_2O, 23°C, 14% yield; reaction f, TBAF, tetrahydrofuran, 23°C; reaction g, Dess–Martin periodinane, pyridine, CH_2Cl_2, 23°C, 63% yield over two steps.

selective, both the major and minor products were produced in a 1:1 ratio with their corresponding atropdiastereomers, a consequence of using racemic paracyclophanes. Reduction of the mixture with $NaBH_4$ permitted separation of the major and minor facial diastereomers affording **55** and its atropdiastereomer as an inseparable 1:1 ratio in 56% yield. Protection of the primary alcohol as the TIPS ether produced **56** in 33% yield, which could be separated from its atropdiastereomer. Treatment of **56** with Ag(II) dipicolinate with sonication afforded TIPS-protected longithorone A (**58**) in low yield, presumably through bisquinone **57**. Unfortunately, attempted Ag(II)-promoted oxidation of the dimethylhydroquinones by using a pure sample of **55**, generated from deprotection of **56**, led to addition of the primary alcohol to the neighboring diene, affording the corresponding furan. Although we had proved the feasibility of the intermolecular-transannular Diels–Alder sequence as a means to construct the core structure of **1**, the final steps were unacceptable.

Completion of the Synthesis. At this juncture, we reconsidered our protection strategy for the hydroquinone portion of each paracyclophane. Our initial efforts to oxidize dimethylhydroquinone paracyclophanes **45**, **52**, and **56** with $(H_4N)_2Ce(NO_3)_6$ and Ag(II) dipicolinate suffered from low yields. Furthermore, the current route required unnecessary oxidation and protection modifications to aldehyde **54**. Therefore, we explored the use of mono-TBS-protected methylhydroquinones, which could be deprotected in high yield and oxidized under mild conditions with hypervalent iodine reagents (41). We synthesized paracyclophanes **59** and **60** as single atropisomers from **36** and **42**, respectively. The intermolecular Diels–Alder reaction was realized by treating **60** with 1.35 eq of **59** and Me_2AlCl at −20°C, affording **61** and its diastereomer in 70% yield as a 1:1.4 ratio resulting from a lack of facial selectivity (Scheme 9). Exposure of **59** and **60** to other Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, $SnCl_4$, and $Yb(OTf)_3$ led to no reaction, diminished selectivity for **61**, or decomposition. Lewis acid catalysis of the intermolecular Diels–Alder reaction is required, as formation of **61** could not be detected upon exposure of **59** to **60** for 15 h at 23°C or 1 h at 80°C. This finding suggests that a "Diels–Alderase" (42) may be involved at this step if the biosynthesis of **1** involves a similar intermolecular cycloaddition. Furthermore, the lack of substrate-based diastereoselectivity in the cycloaddition may also implicate a Diels–Alderase. Removal of both TBS groups from **61** with TBAF delivered **62,** which was directly oxidized with iodosylbenzene (43), affording bisquinone **5**. The bisquinone, which was detected by NMR and TLC, participated in a transannular Diels–Alder cycloaddition at room temperature over the course of 40 h to generate the A, C, and D rings of **1**, directly affording longithorone A in 90% yield from **61**. A synthetic sample of **1** was judged to be identical to a sample of the natural product by ^1H NMR, IR, high-resolution MS, and TLC analyses. The optical rotation of synthetic **1** was $[\alpha]_D = -47.6°$ ($c = 0.77$ mg/ml, CH_2Cl_2), whereas natural **1** was $[\alpha]_D = -47.4°$ ($c = 1.08$ mg/ml, CH_2Cl_2) thereby confirming that the absolute configuration of synthetic **1** matches that of natural **1**. Furthermore, the spontaneous formation of **1** from **5** suggests that if the biosynthesis of **1** involves a similar transannular Diels–Alder reaction, it can proceed in the absence of an enzyme.

Conclusion

An enantioselective synthesis of longithorone A has been accomplished, demonstrating that the reactions proposed by



Scheme 9. Reagents and conditions: reaction a, Me_2AlCl, CH_2Cl_2, −20°C, 52% yield and 2.2:2.2:1:1 diastereomers for **38** + **49**, 70% yield and 1:1.4 diastereomers for **59** + **60**; reaction b, $NaBH_4$, CH_2Cl_2/MeOH, 23°C, 56% yield; reaction c, TIPSOTf, 2,6-lutidine, CH_2Cl_2, 33% yield; reaction d, TBAF, tetrahydrofuran, 0°C; reaction e, Ag(II) dipicolinate, PhH/H_2O, sonication, 23°C, 7% yield for **56** to **58**; reaction f, iodosylbenzene, MeCN/H_2O, 0–23°C, 90% yield over two steps for **61** to **1**.

Schmitz for the biosynthesis are feasible. The synthesis suggests that in the biosynthesis of **1** the intermolecular Diels–Alder reaction occurs before the transannular Diels–Alder reaction because of the low reactivity of enal **4**. [12]-Paracyclophanes were synthesized in the ene–yne metathesis macrocyclization. In all cases, 1,3-disubstituted dienes were generated, demonstrating a mode of reactivity different from that observed in previously reported examples of intramolecular ene–yne metathesis. Secondary benzylic alcohols were synthesized in high yield by enantioselective vinylzinc additions to electron-rich benzaldehydes. Last, this synthesis is a unique example of chirality transfer in complex molecule synthesis: stereogenic centers are used to control planar chirality, and planar chirality is then used to control stereogenic centers in the natural product.

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