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Total Synthesis of Abyssomicin C, Atrop-abyssomicin C, and Abyssomicin D: Implications for Natural Origins of Atrop-abyssomicin C

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Abstract: In this article, the total syntheses of the antibiotic abyssomicin C (**1**) and its biologically inactive sibling abyssomicin D (**3**) are described. A number of unforseen roadblocks in our synthetic plan encouraged innovation, which culminated in the discovery of a new Lewis acid-templated Diels−Alder reaction. En route to abyssomicin C, we prepared and characterized its stable conformational isomer atrop-abyssomicin C (**57**), which in the presence of a strong acid underwent an unusual interconversion with the targeted natural product. Close inspection of the X-ray crystallographic structures of these compounds led to hypotheses on the mechanism of their interconversion. Attempted reduction of both atropisomers revealed that atrop-abyssomicin C afforded abyssomicin D much more readily, suggesting that this previously unknown atropisomer may be synthesized by the host organism and serves as a direct precursor of abyssomicin D. Finally, to gain insight into the mechanism of antiobiotic activity, several synthetic intermediates and designed analogues were evaluated for biological activity.

Introduction

In 2004, Süssmuth and Fielder reported the isolation and characterization of abyssomicin C (**1**, Figure 1) as part of their search for natural products possessing antibiotic activity via inhibition of the *p*-aminobenzoic acid (*p*ABA) biosynthetic pathway.[1] Of the 201 microbes screened, only the marine actinomycete strain *Verrocosispora* AB 18-032, collected from the depths of the Sea of Japan, met both requirements. Feeding experiments indicated that abyssomicin C (**1**) is an inhibitor of either aminodeoxychorismate synthase or aminodeoxychorismate lyase, enzymes responsible for the conversion of chorismate into *p*ABA, making **1** the first known natural inhibitor of these enzymes. Along with the active component **1**, which inhibited the growth of methicilin-resistant *Staphylococcus aureus* (MRSA, MIC = 4 μg mL^{-1}) and vancomycin-resistant *S. aureus* (VRSA, MIC = 13 μg mL^{-1}), two structurally related but inactive compounds, abyssomicin B (**2**) and D (**3**, Figure 1) were isolated. The presence of an α,β-unsaturated ketone in **1** and its absence in the inactive components (**2** and **3**) suggested that this potentially reactive functional group may serve as a Michael acceptor in both the mechanism of action and the biogenesis of **2** and **3**. Abyssomicin B (**2**) was proposed to derive from C (**1**) via a 1,4-addition of hydroxylamine followed by oxidation, while abyssomicin D (**3**) was believed to result from 1,4-hydride addition (presumably delivered from NADH), followed by an intramolecular Michael addition of the resulting enolate onto the neighboring tetronic ester.

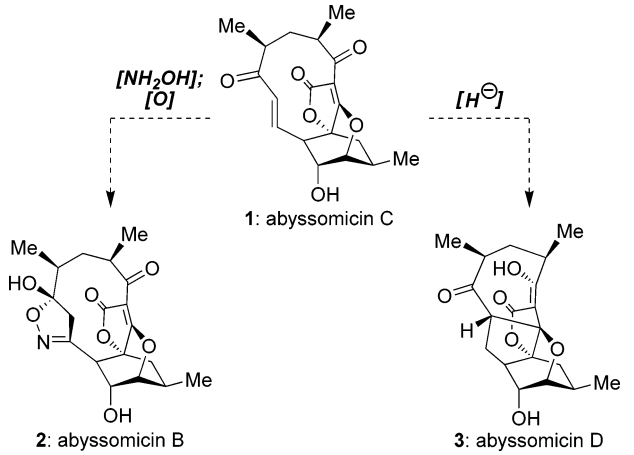

Figure 1. Molecular structures of the abyssomicins (**1**−**3**) and postulated biogeneses of **2** and **3**.

The structural novelty of abyssomicin C combined with its impressive biological activity spurred considerable interest among synthetic organic chemists. Its molecular architecture possesses a number of challenging structural elements that would need to be appropriately addressed in a total synthesis. These elements include a strained 11-membered macrocyclic ring, seven stereogenic centers, a potentially reactive α,β-unsaturated

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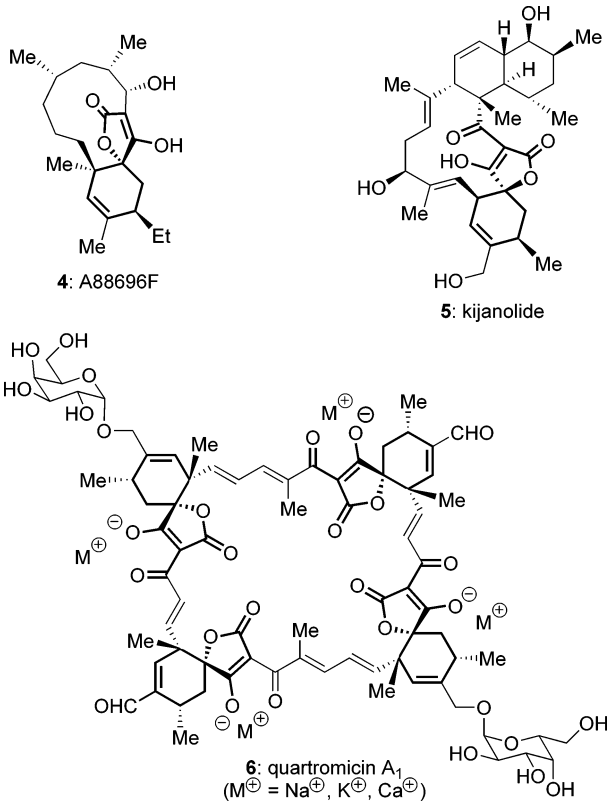

Figure 2. Selected examples of natural products containing the spiro tetronic acid cyclohexene structural motif.

ketone, and a novel fused tetronate oxabicyclo[2.2.2]octane core. The core of abyssomicin C (**1**) bears a close resemblance to other spiro tetronic acid[2] cyclohexene containing natural products, including A88696F[3] (**4**, Figure 2), kijanolide[4] (**5**), and quartromicin A_1[5] (**6**), suggesting that this novel motif may be derived from intramolecular trapping of a spiro tetronic acid cyclohexene oxide. To date, all synthetic approaches to this natural product have centered on this premise, including an elegant biomimetic total synthesis by Sorensen et al.,[6] formal total syntheses by Snider and Zou[7] and Couladouros et al.,[8] and model studies on the oxabicyclo[2.2.2]octane core by Maier et al.[9] and Georgiadis et al.[10] In the Sorensen et al. synthesis (Figure 3), this type of intramolecular epoxide opening was executed in the final step of the sequence affording the natural product (**1**) as a 1:1 mixture with a compound deemed iso-abyssomicin C, whose conclusive structural assignment was not published.[6]

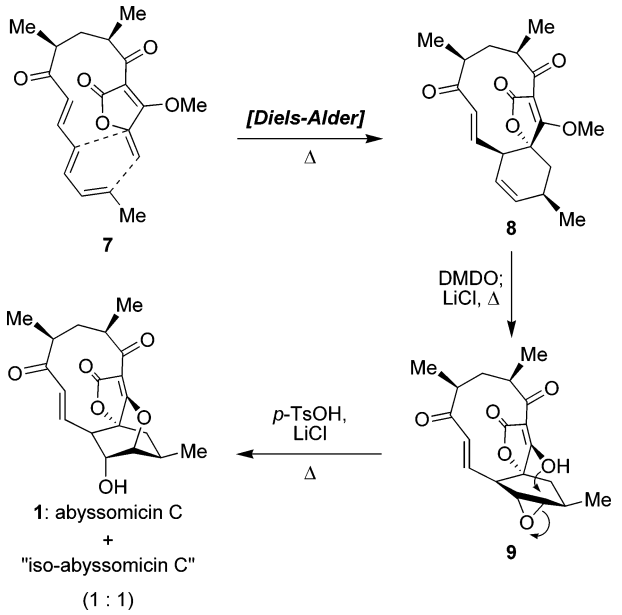

Figure 3. Key steps in Sorensen's biomimetic synthesis of abyssomicin C (**1**).

Intrigued by the structure and reactivity of abyssomicin C, we initiated a program directed toward the total synthesis of this compound. In this article, we describe in detail our efforts toward abyssomicin C (**1**) culminating in its total synthesis,[11] the identification of a more active atropisomer of **1**, the synthesis of abyssomicin D (**3**), the development of methods to achieve these goals, and the synthesis of a number of analogues designed to probe the mechanism of action of this novel antibiotic.

Retrosynthetic Design. Our approach to the synthesis of abyssomicin C (**1**) emphasized convergence with the ultimate goal of generating analogues from late stage intermediates with minimal effort (Figure 4). We elected to disassemble the C3−C8 macrocyclic ring of the natural product by ring-closing metathesis at C8−C9 and a lithiation/alkylation sequence at C2−C3, leading back to the oxabicyclo[2.2.2]octane core **11**, and the protected C3−C8 fragment **12** as potential precursors. The latter fragment was envisaged to arise from routine manipulation of the enzymatic desymmetrization product **13**,[12] while the oxabicyclic core **11** was dissected via the aforementioned epoxide trapping with the tetronic acid **14**. This Dieckmann condensation product[9a,10,13] was predicted to derive from **15**, which was itself anticipated to arise from the Diels−Alder adduct **16** via standard synthetic transformations.

Results and Discussion

Early Studies toward the Oxabicylic Core. Our work on the abyssomicins began with the preparation of (±)-**16** (Scheme 1), employing the Lewis acid-templated Diels−Alder reaction developed by Ward and Abaee.[14] Thus, the magnesium salt of 2,4-hexadienol (**17**) was reacted with *n*-butanol (to adjust the

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(13) For examples of similar Dieckmann cyclization reactions, see: (a) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708−8721. (b) Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673−4681.
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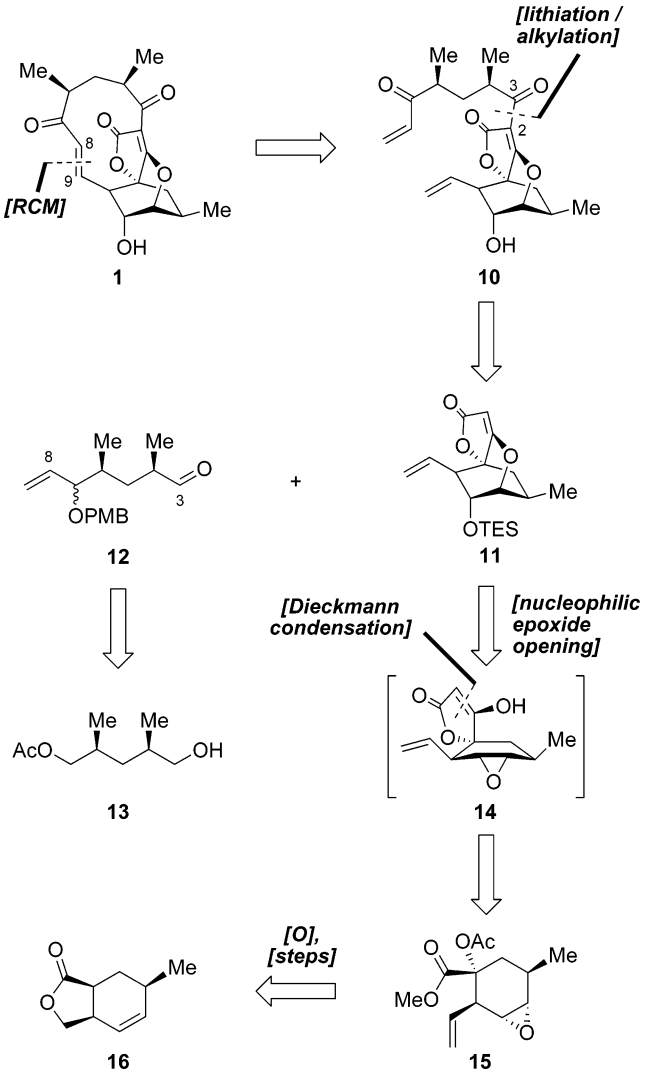
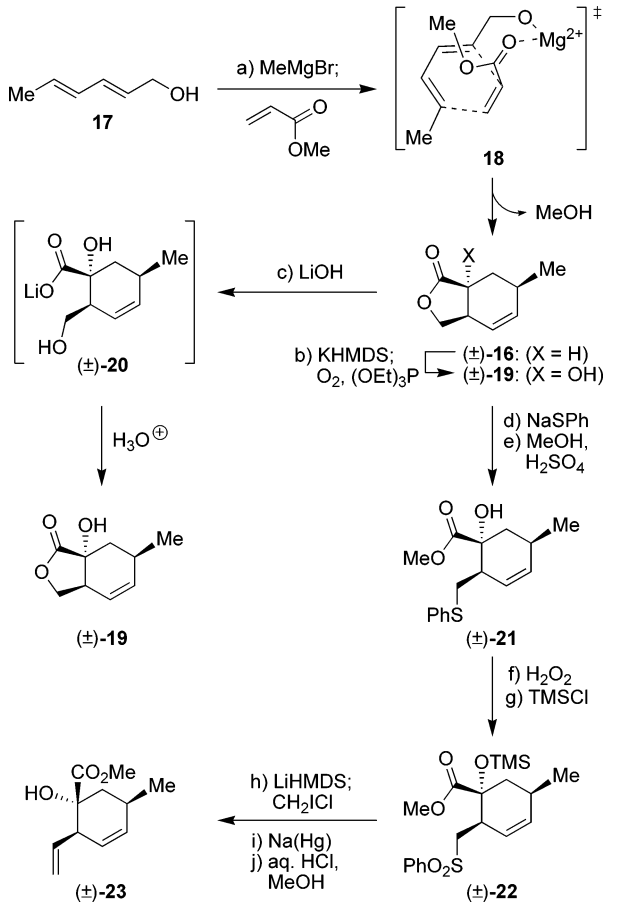


Figure 4. Retrosynthetic analysis of abyssomicin C (**1**). RCM: ring-closing metathesis.

Mg(II) salt aggregation state) and methyl acrylate, which after cycloaddition via the putative transition state **18** and extrusion of methanol, afforded the desired lactone (±)-**16** as a single diastereomer and in 90% yield. Quenching of the derived potassium enolate of (±)-**16** with oxygen and $(EtO)_3P$ then afforded the α-hydroxylation product (±)-**19** in 96% yield.[9a] While hydrolysis of this lactone was successful, attempts to manipulate the resulting salt (±)-**20** for the purpose of transforming the C9 alcohol into an olefin were not, instead leading to substantial amounts of the starting lactone (±)-**19**. To prevent re-lactonization, (±)-**19** was opened at the γ-position with the sodium salt of benzenethiol, and the resulting carboxylate was methylated. This afforded the thioether (±)-**21** in 82% yield for the two-step sequence. Thioether oxidation was achieved with catalytic ammonium molybdate and hydrogen peroxide, and the so-obtained crude sulfone was directly protected leading to the TMS ether (±)-**22** in a 72% overall yield. This enabled the execution of a Julia-type olefination[15] to install the C9 double bond as required for the proposed key olefin metathesis step. Thus, the sulfone was rapidly deprotonated in THF/DMPU (3:1) at −78 °C and quenched with chloroiodomethane, affording

Scheme 1. Synthesis of the Diene (±)-**23**[a]



[a] Reagents and conditions: (a) MeMgBr (1.0 equiv), *n*-BuOH (1.0 equiv), $PhCH_3$, 0 °C, 30 min; then methyl acrylate (10 equiv), 25 °C, 24 h, 90%. (b) KHMDS (1.5 equiv), THF, −78 °C, 30 min; then $(EtO)_3P$ (2.0 equiv), O_2 (excess), 1 h, 96%. (c) aq 1 M LiOH (2.0 equiv), THF, 25 °C, (not isolated). (d) NaH (2.0 equiv), PhSH (2.0 equiv), DMF, 0 °C; then **19** (1.0 equiv), 110 °C. (e) $(MeO)_3CH$ (15 equiv), H_2SO_4 (2.0 equiv), MeOH, 65 °C, 5 h, 82% (over two steps). (f) Ammonium molybdate (0.1 equiv), H_2O_2 (5.0 equiv), EtOH, 0 °C, 10 min. (g) TMSCl (1.2 equiv), Et_3N (3.6 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 72% (over two steps). (h) LiHMDS (1.0 equiv), THF/DMPU (3:1), −78 °C, 5 min; then ICH_2Cl (2.0 equiv), 15 min. (i) Na(Hg) (4.0 equiv), Na_2HPO_4 (7.3 equiv), THF/MeOH (1:1), −40 °C, 3 h. (j) aq 1 M HCl (0.01 equiv), MeOH, 25 °C, 15 min, 71% (over three steps). Abbreviations: KHMDS, potassium bis(trimethylsilyl)-amide; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; TMSCl, chlorotrimethylsilane; 4-DMAP, 4-(dimethylamino)pyridine; LiHMDS, lithium bis(trimethylsilyl)amide; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

a 5:1 mixture of chloromethylene sulfones, which was immediately subjected to a sodium amalgam reduction. This process generated the desired olefin along with partial to full cleavage of the TMS ether, whose complete deprotection was achieved by the action of catalytic aqueous HCl in MeOH, furnishing diene (±)-**23** in 71% overall yield.

Shortly after the execution of this work, Ward and Souweha published an enantioselective variant of the above Diels−Alder reaction (Figure 5) involving the use of a stoichiometrically generated diene−Zn(II)−BINOL−Mg(II) complex **24**.[16] Although structural characterization of this complex has not been achieved, control experiments suggested that Zn(II) serves as a bridge between BINOL and the diene, while Mg(II) serves as a Lewis acid to activate incoming dienophiles. Upon reaction

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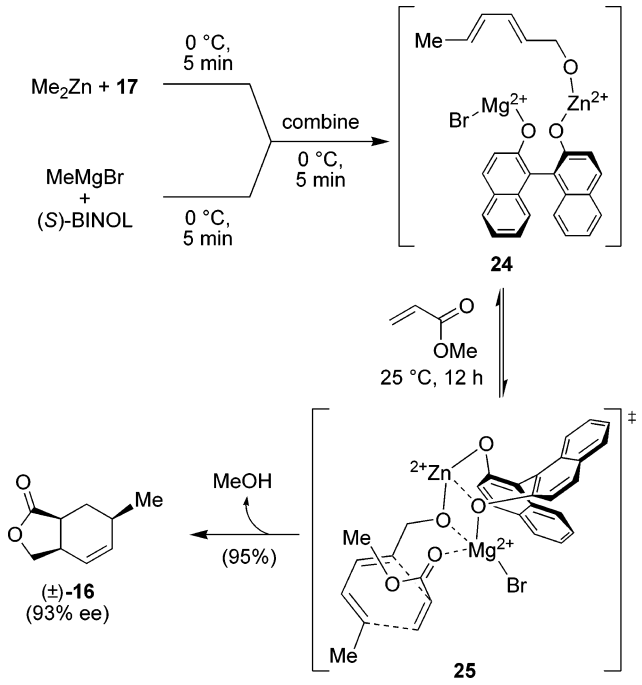


Figure 5. Ward's enantioselective Diels–Alder reaction via a bimetallic complex.[16]

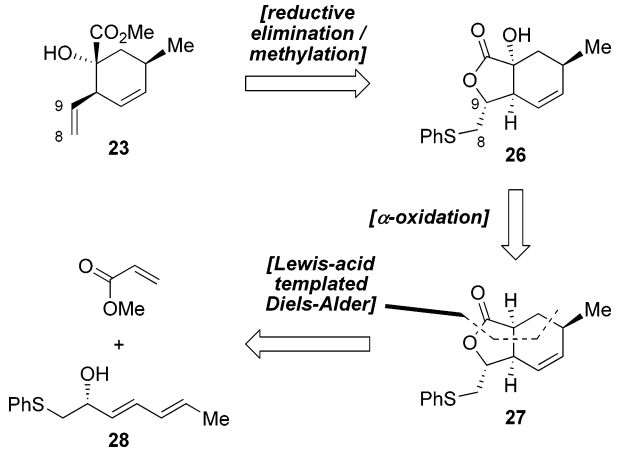
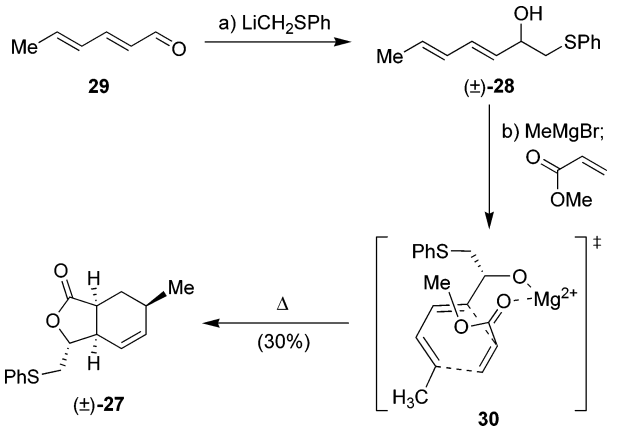


Figure 6. Second generation retrosynthetic analysis of **28**.

of this complex with methyl acrylate, an enantio- and diastereoselective Diels–Alder reaction ensues, presumably through transition state **25**, affording lactone (+)-**16** in 93% ee and 95% yield. Interestingly, this reaction proceeds much faster than the original racemic variant (Scheme 1) despite being carried out at higher dilution (0.02 vs 0.3 M). This reaction would have rendered our synthesis of **23** enantioselective; however, we were dissatisfied with inefficiencies in our existing route, and the use of stoichiometric BINOL and dimethyl zinc in the first step was less than desirable. Although we ultimately sought a more efficient process, the previous sequence (Scheme 1) provided sufficient quantities of (±)-**23** to explore subsequent steps in the synthesis of the natural product's core.

Improved Approach to 23. In re-evaluating our approach to **23**, we elected to keep several successful features from our previous work while eliminating unnecessary functional group manipulations, a theme that led to the more efficient approach depicted in Figure 6. It was thus envisioned that **23** could derive from **26**, a seemingly more complex molecule with an additional

Scheme 2. Synthesis of Racemic (±)-**28** and Attempted Diels–Alder Reaction To Give (±)-**27**[a]



[a] Reagents and conditions: (a) DABCO (1.5 equiv), thioanisole (1.5 equiv), *n*-BuLi (1.5 equiv), THF, 0 °C, 10 min; then 25 °C, 1 h; then **29** (1.0 equiv), −78 °C, 30 min, 65%. (b) MeMgBr (1.5 equiv), $PhCH_3$, 0 °C; then methyl acrylate (10 equiv), 55 °C, 24 h, 30%. Abbreviations: DABCO, 1,4-diazabicyclo[2.2.2]octane.

chiral center at C9. This functionality was intended to serve two functions: (a) it would act as a stereocontrol element enabling the enantioselective synthesis of **23** and (b) its extrusion via reductive elimination would provide access to the requisite olefin at C9. Compound **26** was expected to arise from α-hydroxylation of **27**, which was, in turn, expected to be derived from a diastereoselective Mg(II) templated Diels–Alder reaction between the chiral diene **28** and methyl acrylate. All that would then remain was the enantioselective synthesis of the secondary allylic alcohol **28**, a task that we felt modern synthetic methods could readily accomplish.

Diels–Alder Reaction Development. To test the Diels–Alder reaction in question, we prepared the racemic diene (±)-**28** via alkylation of 2,4-hexadienal (**29**) with lithiothioanisole[17] in 65% yield (Scheme 2). The magnesium salt of (±)-**28** was generated and treated with methyl acrylate at room temperature; however, unlike the smooth, albeit sluggish, reaction seen with the magnesium salt of 2,4-hexadienol (Scheme 1), the added bulk of the thiophenylmethylene unit was sufficient to suppress [4 + 2] cycloaddition. Elevation of the temperature to 55 °C allowed the desired Diels–Alder reaction to take place after 24 h with complete diastereoselectivity, although in only 30% yield, with the remainder of the starting material being consumed to a complex mixture of undesired products (Scheme 2). Also, unlike the reaction with 2,4-hexadienol, the addition of a sacrificial alcohol (*n*-BuOH or *i*-PrOH) did not enhance the yield or rate of reaction. Hoping to improve upon this situation, we screened a number of other Lewis acids (i.e., $TiCl_4$, $AlCl_3$, $Zn(OTf)_2$, $MgBr_2{\cdot}OEt_2$/*i*-Pr_2NEt,[18] and $MeAlCl_2$) hoping that modulating the strength of the Lewis acid might suppress decomposition or increase the rate of cycloaddition, although these pursuits proved to be fruitless, with the MeMgBr generated Mg(II)-diene salt being optimal. Temporarily thwarted, we turned to Ward's enantioselective variant of this reaction for inspiration (Figure 5). As the BINOL mediated reaction proceeds much faster (12 h) than the simple Mg(II) templated reaction (48 h), we had hoped that we could use a similar complex to

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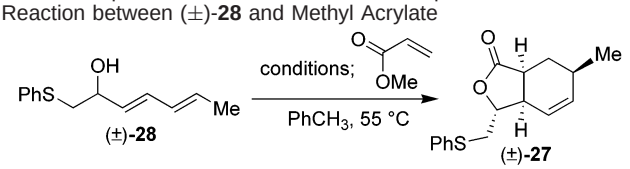
Table 1. Optimization of the Lewis-Acid Templated Diels−Alder Reaction between (±)-**28** and Methyl Acrylate



entry	auxiliary	base[a]	time[b]	yield[c]
1	none	MeMgBr (1.0 equiv)	24 h	30%
2	(±)-BINOL	Me_2Zn (1.0 equiv), MeMgBr (1.0 equiv)[d]	24 h[e]	< 5%[f]
3	 **31**	Me_2Zn (1.0 equiv), MeMgBr (1.0 equiv)[d]	36 h	35%
4	 **32**	MeMgBr (2.0 equiv)	24 h	49%
5	 **33**	MeMgBr (2.0 equiv)	48 h	55%
6	**33** (2.0 equiv)	MeMgBr (3.0 equiv)	48 h	70%
7	**33** (3.0 equiv)	MeMgBr (4.0 equiv)	12 h	80%

[a] Addition of base was performed at 0 °C before addition of methyl acrylate (10 equiv) and warming to 55 °C. [b] Reaction times reflect the time at which consumption of the diene was complete as measured by ^{1}H NMR spectroscopy on the crude reaction mixture unless stated otherwise. [c] Isolated yield unless stated otherwise. [d] Reaction performed according to the conditions summarized in Figure 5. [e] Reaction stopped before completion affording 80% of recovered diene. [f] Trace product detected in the ^{1}H NMR spectrum of recovered diene.

enhance the rate of cycloaddition. We thus attempted to generate the diastereomeric mixture of (±)-**28**−Zn(II)−(±)−BINOL−MgBr complexes following the established protocol[16] (Table 1), and to our surprise, only trace amounts of (±)-**27** were detected; however, decomposition of the diene was slowed, leading to 80% starting material recovery after 24 h (entry 2). In a parallel experiment, BINOL was replaced with catechol (**31**, entry 3), which led to a substantial improvement (35% yield), along with complete diene decomposition after 36 h. Optimistic that the catechol system was catalyzing the intended cycloaddition, albeit slowly, we investigated the structurally similar 2-aminophenols. It was reasoned that in this reaction manifold, the Lewis basic amine would interact with the Mg(II) salt of the diene while the Mg(II) bound to the phenol would serve to activate and orient the incoming dienophile. Using commercial 2-aminophenol (**32**, entry 4) with 2 equiv of MeMgBr led to an immediate increase in reaction turnover, affording a 49% yield of (±)-**27** with complete consumption of (±)-**28** after 24 h. Auxiliaries possessing alkylated nitrogen including the commercially available 2-(pyrrolidin-1-yl)phenol **33**[19] exhibited a slower rate of cycloaddition, along with an extended lifetime of the diene. Encouraged by these results, the number of equivalents of **33** and MeMgBr was incremented (entries 6 and 7) causing the yield of (±)-**27** to climb up to 80% with 3 equiv of **33** and 4 equiv of MeMgBr. Although the use of 3 equiv of **33** is less than ideal, the auxiliary could be removed by washing with aqueous 2 M HCl and recovered (80% recovery) by careful neutralization with concentrated NH_4OH. We suspect that the requirement for excess auxiliary is a consequence of the relatively poor affinity between Mg(II) and amine.

Enantioselective Synthesis of the Oxabicyclic[2.2.2]octane Core. With a productive and selective Diels−Alder cycloaddtion in hand, we returned to the enantioselective synthesis of the tetronate core as shown in Scheme 3. Alkylation of the known Weinreb amide **34**[20] with lithiothioanisole[17] afforded the ketone **35** in 81% yield. Corey's Me-(*R*)-CBS catalyst[21] and catecholborane served to reduce this ketone enantioselectively, affording hydroxy compound **28** in 90% ee and 95% yield. As expected from a literature precedent,[22] and confirmed by the eventual conversion of **28** to abyssomicin C (**1**), this reaction occurs with the diene behaving as the larger of the two ketone substituents in the putative transition state **36** (Scheme 3). Subjecting our now enantio-enriched diene to the previously described Diels−Alder conditions afforded the adduct **27** as a single diastereomer (80% yield), presumably through the transition state **37**. The desired hydroxy lactone **26** was prepared from this adduct via α-hydroxylation in 74% yield, setting the stage for the key Julia-type reductive elimination. Our early approaches toward this goal employing less direct methods, specifically oxidation to the corresponding sulfone followed by reduction with Na(Hg) amalgam[15] or Mg(0)/$HgCl_2$,[23] were met with little success. It was then discovered that the direct reduction of the thioether at C8 proceeds smoothly with a catalytically generated lithium 4,4′-di-*tert*-butylbiphenyl radical anion.[24] The resulting carbanion causes an elimination reaction that fractures the lactone, leading simultaneously to the requisite olefin at C9 and a carboxlate anion. Methylation of the latter functionality with MeI in the same reaction vessel proceeded better than an isolation/methylation sequence leading to the skipped diene **23** in 99% yield. A vanadium directed epoxidation of the C11−C12 olefin was then attempted with $VO(acac)_2$ and *t*-BuOOH.[25] While this delivered the intended epoxide with complete stereo- and regiocontrol, the reaction was inefficient, requiring repeated addition of the catalyst to push the reaction to completion (up to 0.4 equiv). We found that we could improve the efficiency of this process using rarely employed $VO(OEt)_3$[26] (0.2 equiv) with the same stoichiometric oxidant, a protocol that afforded the desired epoxide in 93% yield as a single stereoisomer. Routine acetylation of the free alcohol then afforded the acetoxy methyl ester **15** (95% yield), setting the stage for the key Dieckmann condensation reaction. Deprotonation of **15** with 2.5 equiv of LiHMDS at −78 °C, followed by warming to room temperature[9a,10,13] and quenching with saturated aqueous NH_4Cl,[10] generated the tetronic acid **14**, which was not isolated. Instead, the aqueous/organic mixture was heated to reflux for 2 h, effecting the intramolecular trapping

(19) (a) 2-(Dimethylamino)phenol was also used with near identical results. (b) Commercially available from a number of sources; however, we prepared this compound by reaction of 2-aminophenol (1.0 equiv) with 1,4-dibromobutane (1.05 equiv) and *i*-Pr_2NEt (3.0 equiv) in toluene (1.3 M) at 65 °C for 12 h (see Supporting Information).

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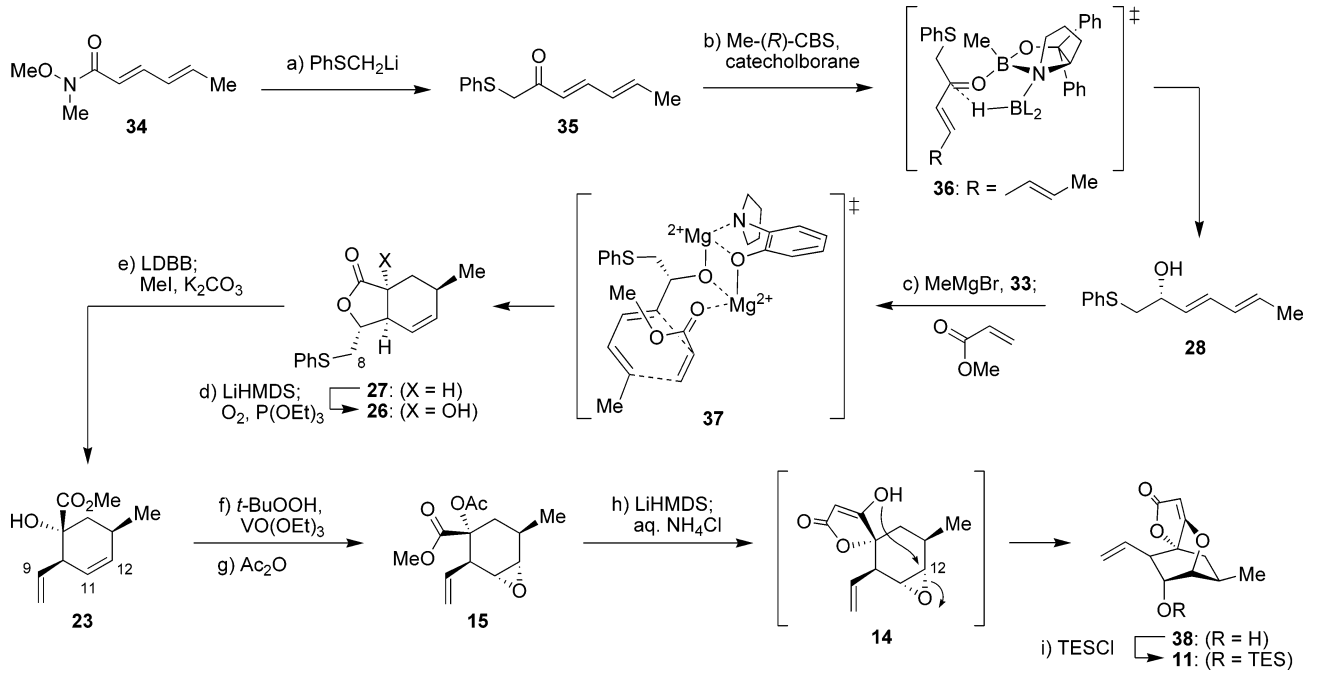
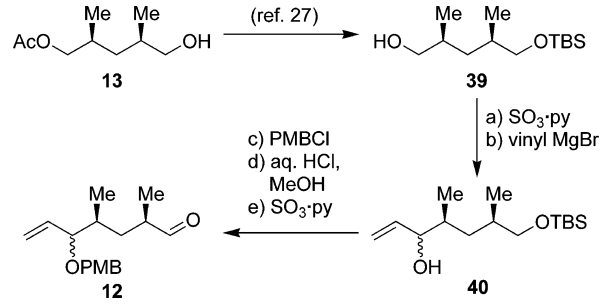
Scheme 3. Improved Synthesis of Enantioenriched **23** and Its Conversion to the Tes-Protected Core **11**[a]



[a] Reagents and conditions: (a) DABCO (1.5 equiv), thioanisole (1.5 equiv), *n*-BuLi (1.5 equiv), THF, −78 °C, 10 min; then 25 °C, 1 h; then **34** (1.0 equiv), −78 °C, 45 min, 81%. (b) (*R*)-CBS (0.1 equiv), catecholborane (1.1 equiv), CH_2Cl_2, −78 °C, 12 h, (95%, 90% ee). (c) **33** (3.0 equiv), MeMgBr (4.0 equiv), $PhCH_3$, 0 °C, 10 min; then methyl acrylate (10 equiv), 55 °C, 12 h, 80%. (d) LiHMDS (1.5 equiv), THF, −78 °C, 30 min; then $(EtO)_3P$ (2.0 equiv), O_2 (excess), 1 h, 74%. (e) Li (9.6 equiv), 4,4′-di-*tert*-butylbiphenyl (0.5 equiv), THF, 0 °C, 1 h; then **26** (1.0 equiv), −48 °C, 3 h; quench with MeOH, remove excess Li, concentrate; then K_2CO_3 (1.0 equiv), MeI (10 equiv), DMF, 60 °C, 10 min, 99%. (f) *t*-BuOOH (3.0 equiv), $VO(OEt)_3$ (0.2 equiv), CH_2Cl_2, 25 °C, 4 h, 93%. (g) Ac_2O (3.0 equiv), 4-DMAP (0.05 equiv), Et_3N, 25 °C, 12 h, 95%. (h) LiHMDS (2.5 equiv), THF, −78 °C, 10 min; then 25 °C, 1 h; then saturated aq NH_4Cl, 66 °C, 2 h. (i) TESCl (1.4 equiv), imidazole (2.8 equiv), 4-DMAP (0.05 equiv), DMF, 25 °C, 2 h, 97% (over two steps). Abbreviations: (*R*)-CBS, (*R*)-(+)-2-methyl-CBS-oxazaborolidine.

Scheme 4. Synthesis of C3−C8 Precursor **12**[a]



[a] Reagents and conditions: (a) *i*-Pr_2NEt (3.0 equiv), SO_3·pyridine (3.0 equiv), CH_2Cl_2/DMSO (2:1), 0 °C, 20 min. (b) Vinyl MgBr (2.0 equiv), THF, −78 °C, 74% (over two steps). (c) NaH (2.0 equiv), PMBCl (2.0 equiv), tetra-*n*-butylammonium iodide (0.1 equiv), DMF, 25 °C, 2 h, 82%. (d) aq 1 M HCl (0.01 equiv), MeOH, 25 °C, 1 h. (e) *i*-Pr_2NEt (3.0 equiv), SO_3·pyridine (3.0 equiv), CH_2Cl_2/DMSO (2:1), 0 °C, 20 min, 84% (over two steps). Abbreviations: DMSO, dimethylsulfoxide; PMBCl, 4-methoxybenzoyl chloride.

of the epoxide exclusively at C12,[8,9a,10] leading to **38**, containing the desired tetronate fused oxabicyclo[2.2.2]octane framework. Chromatographic purification of **38** was met with some decomposition, so the crude product was immediately protected as its TES ether **11**, providing a near quantitative yield (97%) for the two-step sequence.

Synthesis of C3−C8 Fragment. To maximize convergence, we had hoped to attach the macrocyclic portion of the molecule in a fashion that would require minimal post-coupling manipulations. To this end, we prepared the aldehyde **12** using routine chemical transformations as shown in Scheme 4. Starting from the enzymatic desymmetrization product **13**,[12] the known TBS ether **39**[27] was prepared using established procedures. Parikh−Doering oxidation of **39**, followed by alkylation with vinyl magnesium bromide, afforded **40** as a 3:2 mixture of allylic alcohols that were not separated (74%, over two steps). Three standard steps, namely, PMB protection (82% yield), TBS ether cleavage, and another Parikh−Doering oxidation (84%, over two steps), afforded the mixture of aldehydes **12** that were carried into the next step without separating each diastereomer.

Fragment Coupling and Attempted Completion of the Synthesis. With the C3−C8 fragment **12** and the core **11** in hand, we began investigating the final stages of the synthesis of abyssomicin C (**1**, Scheme 5). Treating the protected core fragment **11** with *t*-BuLi at −78 °C effected clean lithiation at C2.[28] Quenching of this anion with the mixture of aldehydes **12** afforded a mixture of inseparable diastereomers (61% yield) that was subjected to deprotection with DDQ, affording another inseparable mixture **41** in 96% yield (LC/MS characterization). Treatment of **41** with Grubbs' second-generation catalyst **42**[29] in refluxing CH_2Cl_2 (0.001 M) did not achieve ring-closing metathesis as desired but instead led to dimeric products (identified in the crude LC/MS trace). Assuming that the steric bulk of the TES group prevented macrocyclization, this group was removed with catalytic aqueous HCl/methanol in 94% yield affording the mixture of triols **44**. Selective oxidation of the two allylic alcohols was achieved with excess IBX, leading to **10** in 64% yield. Attempted ring-closing metathesis of **10** with

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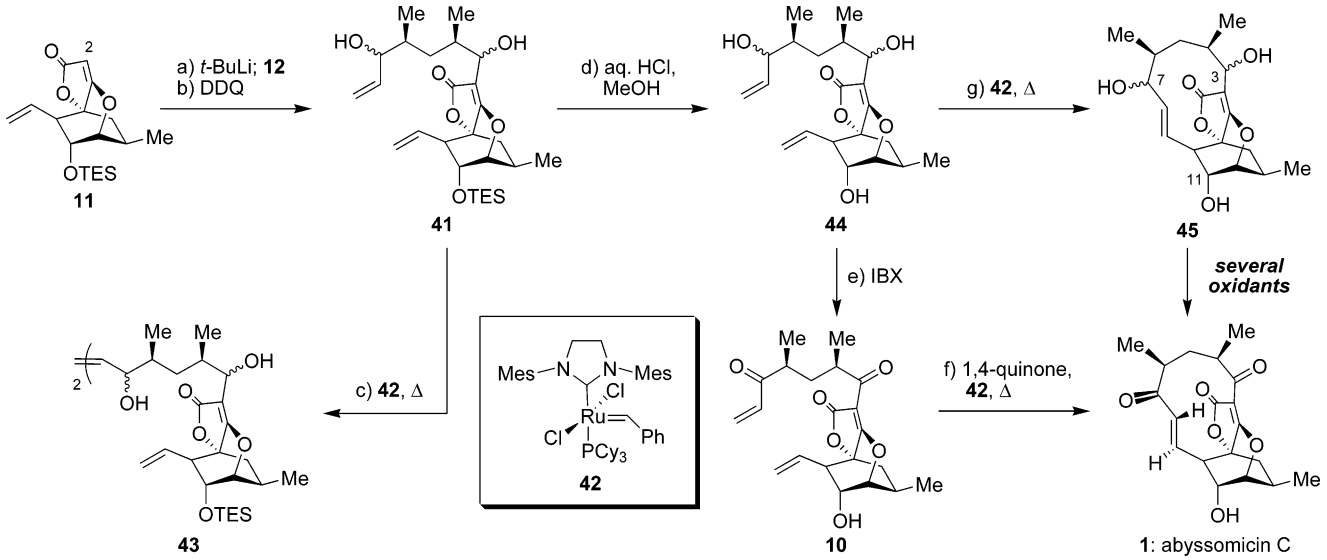
Scheme 5. Attempted Synthesis of Abyssomicin C (**1**) via Ring-Closing Metathesis[a]



[a] Reagents and conditions: (a) *t*-BuLi (1.2 equiv), THF, −78 °C, 30 min; then **12** (1.1 equiv), 15 min, 61%. (b) DDQ (3.0 equiv), CH_2Cl_2: saturated aq $NaHCO_3$ (10:1), 25 °C, 30 min, 96%. (c) **42** (0.05 equiv), CH_2Cl_2 (0.001 M), 40 °C, 1 h. (d) aq 1 M HCl (0.01 equiv), MeOH, 25 °C, 1 h, 94%. (e) IBX (5.0 equiv), DMSO, 25 °C, 64%. (f) **42** (0.1 equiv), 1,4-benzoquinone (0.2 equiv), CH_2Cl_2 (0.002 M), 40 °C, 1 h, 14%. (g) **42** (0.05 equiv), CH_2Cl_2 (0.002 M), 40 °C, 1 h, 78%. Abbreviations: DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; IBX, *o*-iodoxyiodobenzene.

catalytic **42** in CH_2Cl_2 generated a complex mixture of unidentified byproducts. Conducting the same reaction with 1,4-benzoquinone, hoping to suppress Ru(III) mediated isomerization reactions,[30] did allow the isolation of small quantities (14% yield) of abyssomicin C (**1**) as an inseparable 2:1 mixture with **10**, with the rest of the material being consumed to a mixture of unidentified byproducts. Whereas **10** proved to be a poor ring-closing metathesis substrate, the diastereomeric mixture of triols **44** closed quite effectively under standard conditions, leading to the ring-closed mixture of triols **45** in 78% yield (LC/MS characterization). Unfortunately, all attempts to oxidize **45** to **1** with selective oxidants (i.e., IBX and MnO_2) afforded only singly oxidized products, presumably the result of intramolecular hemiketalization following the first oxidation. Attempts to use stronger oxidants (i.e., Dess−Martin, PDC, and Swern) were not successful, leading to oxidation of the unactivated alcohol at C11. Suspecting that the two additional sp^2 centers in **10** (relative to **45**) were responsible for its reluctance to cyclize, we elected to design an improved substrate with the same hybridization pattern as **45**, which was devoid of the intramolecular hemiketalization problem.

Completion of the Synthesis of Abyssomicin C. We speculated that blocking one carbonyl group of the cyclization precursor as a dithioacetal at either C3 or C7 would prevent this undesired hemiketalization from occurring. The carbonyl at C3 was selected to undergo this modification, as we anticipated that this change would be less likely to interfere with the ring-closing metathesis step. The execution of this strategy began (Scheme 6) by quenching the lithiated species of **11** with the known aldehyde **46**,[31] leading to a mixture of secondary alcohols (75% yield) that was oxidized with IBX to afford the ketone **47** (90% yield). The corresponding dithiolane was prepared by thioketalization with 1,2-ethanedithiol and $BF_3 \cdot OEt_2$ in 90% yield. Standard deacetylation with K_2CO_3 in MeOH then afforded diol **48** in 97% yield. A shorter approach to **48** was also developed via alkylation of the lithio derivative of **11** with lactone **49**[32] affording a crude lactol, which was thioketalized directly to furnish the desired adduct in 76% yield over the two-step sequence. Oxidation of **48** with IBX occurred chemoselectively, affording an aldehyde that was immediately reacted with vinyl magnesium bromide leading to a 2:3 mixture of allylic alcohols (**50**) in 65% combined yield. As anticipated, **50** served as an excellent ring-closing metathesis substrate furnishing a 2:3 mixture of C8−C9 *trans*-allylic alcohol products **51a** and **51b** in 85% yield upon exposure to catalyst **42**.

As we initiated the ring-closing metathesis strategy, concern existed that this step could afford atropsiomers at the C8−C9 double bond resulting from hindered rotation of this olefin through the center of the macrocycle. This form of atropisomerism has been observed in *trans*-olefin containing medium-sized rings.[33] Interestingly, **51a** and **51b** are each formed as only the desired atropisomer as evidenced by key NOE resonances of the purified allylic alcohols (see Figure 7). Our proposed rationale for this atropselectivity is based on facial selection in the ring-closing metathesis step. After initiation of the reaction by the catalyst at the less hindered olefin at C8, approach of the activated ruthenium carbene species to the C9 olefin could theoretically occur from either the *si* or the *re* face (Figure 7). Approach from the *re* face leads to the metallocyclobutane intermediate **53**, which after cycloreversion would afford the observed products **51a** and **51b**. The alternate approach from the *si* face would lead to metallocyclobutane **54**, whose decomposition would afford **55**. The failure to

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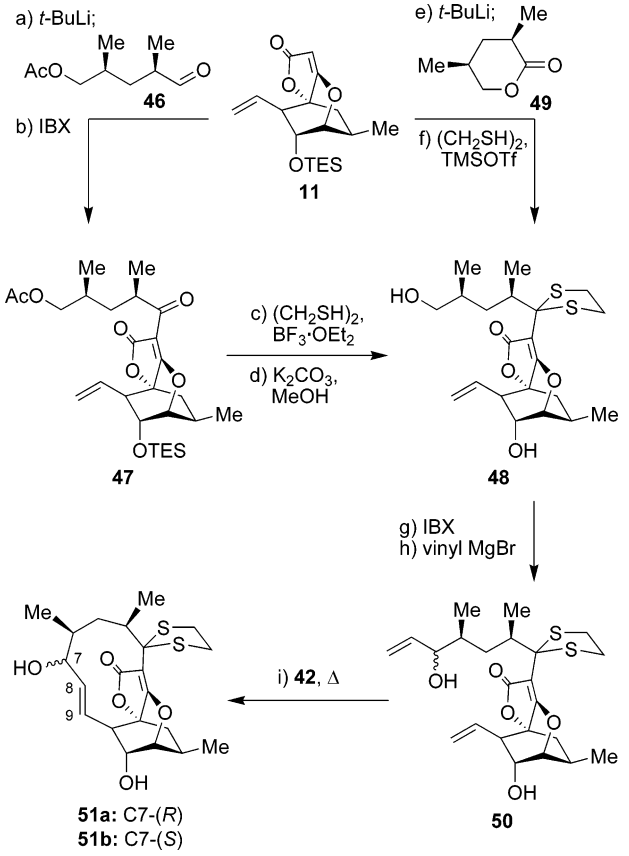
(32) Prepared according to the sequence reported for *ent*-**49** using (*R*)-(+)-α-methylbenzylamine; see: Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 888−894.
(33) (a) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546−5556. (b) Sudau, A.; Munch, W.; Nubbemeyer, U.; Bats, J. W. *J. Org. Chem.* **2000**, *65*, 1710−1720. (c) Anderson, E. A.; Davidson, J. E. P.; Harrison, J. R.; O'Sullivan, P. T.; Burton, J. W.; Collins, I.; Holmes, A. B. *Tetrahedron* **2002**, *58*, 1943−1971.

Scheme 6. Synthesis of Abyssomicin C Carbocyclic Framework **51a**,**b** via Ring-Closing Metathesis[a]



[a] Reagents and conditions: (a) *t*-BuLi (1.2 equiv), THF, −78 °C, 30 min; then **46** (1.1 equiv), 15 min, 75%. (b) IBX (2.5 equiv), DMSO, 25 °C, 45 min, 90%. (c) $BF_3{\cdot}OEt_2$ (5.0 equiv), 1,2-ethanedithiol (5.0 equiv), CH_2Cl_2, 25 °C, 12 h, 90%. (d) K_2CO_3 (3.4 equiv), MeOH, 25 °C, 4 h, 97%. (e) *t*-BuLi (1.2 equiv), THF, −78 °C, 30 min; then **49** (1.1 equiv), 15 min. (f) 1,2-Ethanedithiol (4.0 equiv), TMSOTf (1.0 equiv), −78 °C, 1 h, 76% (over two steps). (g) IBX (2.5 equiv), DMSO, 25 °C, 45 min. (h) Vinyl MgBr (3.0 equiv), THF, −78 °C, 15 min, 65% (over two steps). (i) **42** (0.05 equiv), CH_2Cl_2 (0.002 M), 40 °C, 1 h, 85%. Abbreviations: TMSOTf, trimethylsilyl trifluoromethanesulfonate.

observe **55** suggests that the neighboring tetronic ester provides sufficient steric bulk as to prevent the latter pathway from occurring.

Pressing forward in the total synthesis (Scheme 7), the treatment of **51a** and **51b** with a DMSO solution of IBX chemoselectively oxidized the allylic alcohol, leading to **56** (50% yield). Anticipating that a single deprotection separated **56** from abyssomicin C (**1**), this dithioketal intermediate was reacted with $PhI(OTFA)_2$ in 10:1 CH_3CN/H_2O to remove the protecting group moiety. To our surprise, a stable compound (**57**) was isolated in 71% yield whose spectroscopic data did not match that of the previously reported natural product, despite being very similar to it. While attempting to obtain extensive NMR data on **57** in unstabilized $CDCl_3$, we fortuitously observed its slow isomerization into abyssomicin C (**1**), eventually leading to a 2:1 equilibrium mixture of the two after 24 h favoring the targeted natural product (**1**). Purification of **1** by preparative TLC afforded a compound whose spectroscopic and physical properties matched those of abyssomicin C as previously reported.[1,6] Although this meant that our total synthesis of abyssomicin C (**1**) was complete, the structure of the synthetic intermediate **57** remained a mystery. X-ray crystallographic

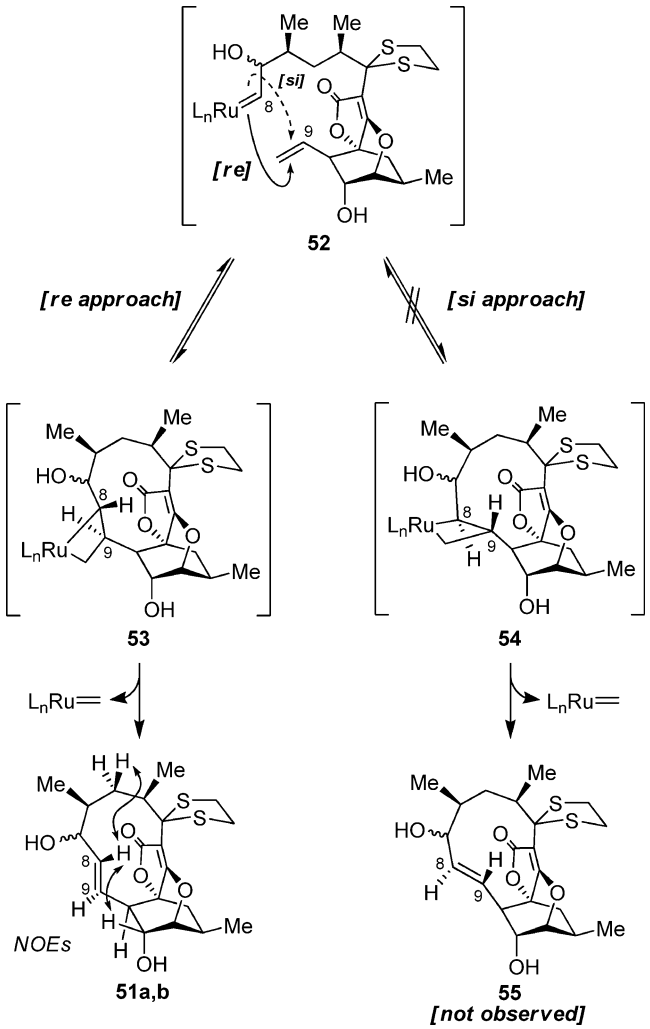


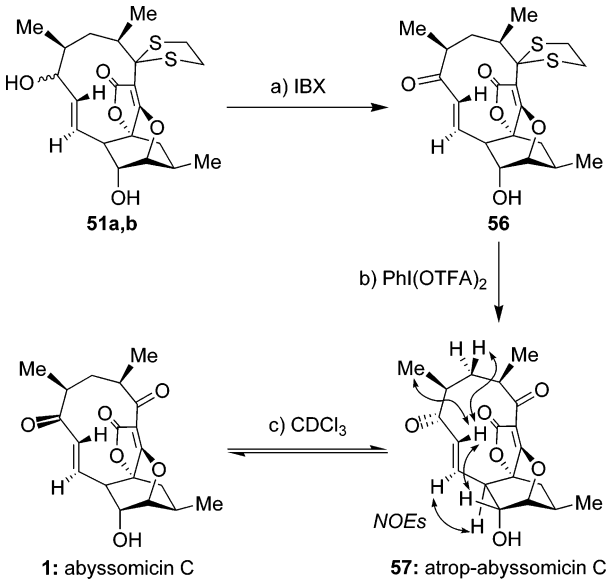
Figure 7. Proposed rationale for the formation of **51a**,**b** and not **55** by the ring-closing metathesis reaction.

analysis was required to determine that **57** is a diastereomeric atropisomer of abyssomicin C (**1**) that we aptly named atrop-abyssomicin C (see ORTEP drawing, Figure 8).

Structural Differences. Comparison of the X-ray structures of abyssomicin C (**1**)[1] and atrop-abyssomicin C (**57**) reveals subtle but important differences (Figure 9). The most striking deviation between the two lies in the α,β-unsaturated ketone region of the molecule (Figure 9a). In abyssomicin C (**1**), the carbonyl adopts a transoid conformation with respect to the C8−C9 olefin (O═C7−C8═C9, ϕ = 144.8°), whereas in atrop-abyssomicin C (**57**), the carbonyl adopts a cisoid conformation (O═C7−C8═C9, ϕ = 26.9°). Not surprisingly, the dithiolane precursor **56** adopts a very similar conformation (Figure 8, O═C7−C8═C9, ϕ = 37.1°). As the enone moiety in **57** exhibits a higher degree of conjugation between the C7 carbonyl and the C8−C9 olefinic bond than **1**, it was expected that **57** would be a more reactive Michael acceptor, and further studies appear to indicate that this hypothesis is correct. Other regions of the macrocyclic ring exhibit observable structural deviations, especially around the C19 methyl (C19−C6−C7═O, **1**: ϕ = −39.0° vs **57**: ϕ = 91.9°; Figure 9c) and the C3 carbonyl (O═C3−C2═C16, **1**: ϕ = 33.8° vs **57**: ϕ = 56.8°) residues.

Closer inspection of the X-ray structures of **1** and **57** suggests substantial strain within each macrocyclic ring. In both struc-

Scheme 7. Synthesis of Abyssomicin C (**1**) via Atrop-abyssomicin (**57**)[a]



[a] Reagents and conditions: (a) IBX (2.5 equiv), DMSO, 25 °C, 45 min, 50%. (b) $PhI(OTFA)_2$ (3.0 equiv), CH_3CN/H_2O (10:1), 25 °C, 10 min, 71%. (c) Unstabilized $CDCl_3$, 25 °C, 24 h, 67% (100% based on recovered starting material). Abbreviations: $PhI(OTFA)_2$, bis(trifluoroacetoxy)iodobenzene.

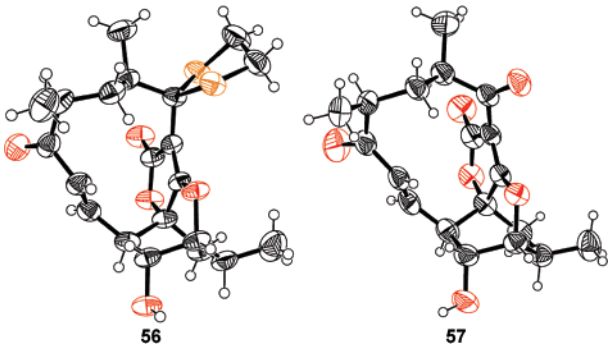


Figure 8. X-ray based ORTEP drawings of the dithiolane **56** and atrop-abyssomicin **57**. Spheres are drawn at the 50 and 40% probability level, respectively.

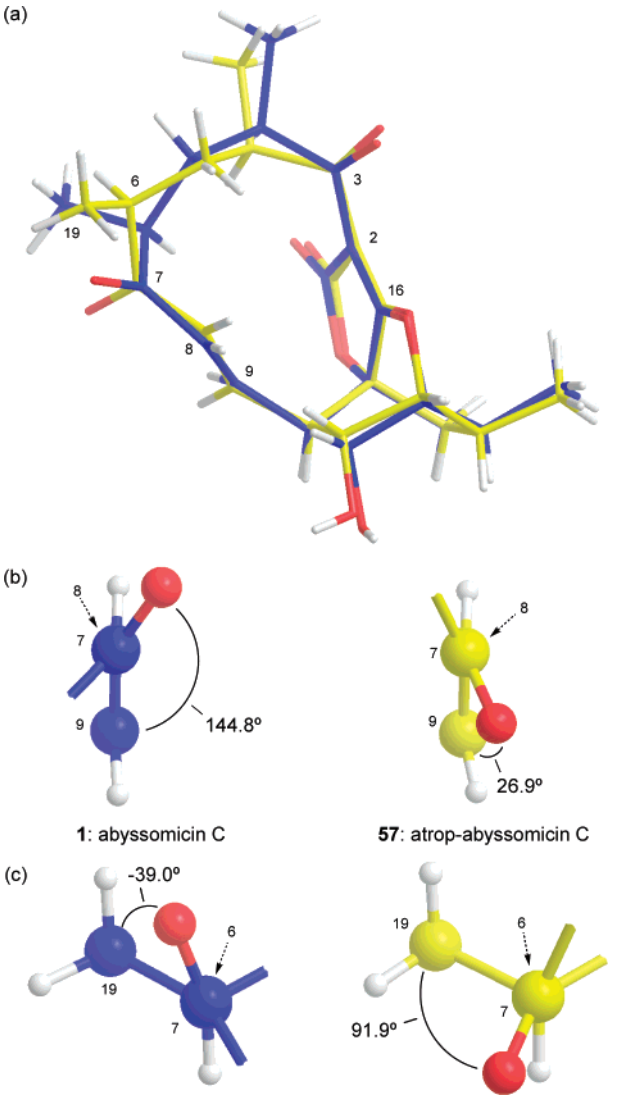


Figure 9. (a) Overlay of the X-ray derived structures of abyssomicin C (**1**, blue) and atrop-abyssomicin C (**57**, yellow). (b) View down the C7−C8 bond for **1** and **57**. (c) View down the C7−C6 bond for **1** and **57**.

tures, the C8−C9 olefin exhibits a deviation from planarity as the result of twisting, as evidenced by the C10−C9═C8−C7 dihedral angles of 166.9° in **1** and 165.9° in **57**.[34] Furthermore, the sp^2 center at C2 is substantially pyramidalized in both compounds, deviating from planarity by roughly 7° in **1** and 11° in **57**.

Mechanism of Atropisomer Interconversion. Most literature examples of room temperature atropisomerism result from a sterically hindered or blocked rotation, such as that found in substituted biaryls[35] or *trans*-olefin containing medium-sized rings,[33] although examples of stable conformers in strained medium-sized rings that lack an obvious steric repulsion have been observed.[36] As no obvious steric obstructions appear to prevent the rotation of the C6−C7 and C7−C8 σ-bonds in compounds **1** and **57**, short of some minor eclipsing interactions, it was surprising that early attempts to convert atrop-abyssomicin C (**57**) to abyssomicin C (**1**) under thermal conditions (i.e., refluxing MeOH or toluene at 180 °C, xylenes, and microwave irradiation)[11] were unsuccessful. Thermal equilibration was eventually achieved by refluxing in 1,2-dichlorobenzene at 180 °C (Table 2, entry 2) for 12 h, affording a 1:1 mixture of isomers at equilibrium, albeit with substantial decomposition.

Hoping to learn more about the acid-catalyzed interconversion of **1** and **57**, a number of other conditions was screened that failed to effect isomerization (entries 3−6, Table 2) including TFA, $BF_3{\cdot}OEt_2$, CSA, and aqueous 1 M HCl. As expected, the addition of catalytic ethereal HCl to **57** in a variety of deuterated organic solvents (entries 7−10) rapidly gave rise to equilibrium mixtures of **1** and **57** with $CDCl_3$ affording the best ratio (2.5:1) favoring abyssomicin C (**1**). Interestingly, subjecting **57** to the conditions employed in the final step of Sorensen's synthesis (*p*-TsOH, LiCl, CH_3CN, 50 °C, 2 h)[6] also causes this isomerization to take place, presumably from the in situ generation of HCl.

The high thermal barrier to interconversion, the absence of steric interactions to prevent interconversion, and the substantial

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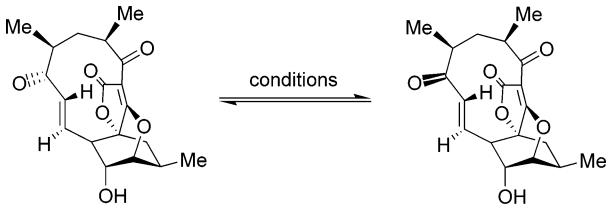
(36) (a) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953−4956. (a) Anastasiou, D.; Campi, E. M.; Chaouk, H.; Jackson, W. R. *Tetrahedron* **1992**, *48*, 7467−7478.

Table 2. Acid-Catalyzed Isomerization of Atrop-abyssomicin C (**57**) and Abyssomicin C (**1**)



entry	conditions[a]	time (h)	ratio (**57**:**1**)[b]
1	unstabilized $CDCl_3$	24	1.0:2.0
2	d_4-1,2-dichlorobenzene, 180 °C	12	1.0:1.0
3	TFA/CH_2Cl_2 (1:1)	24	n.r.[c]
4	BF_3·OEt_2 (1.0 equiv)/CH_2Cl_2	24	n.r.
5	CSA (1.0 equiv)/CH_2Cl_2	24	n.r.
6	1 M aq HCl/THF (1:3)	24	n.r.
7	1 M HCl in Et_2O (0.2 equiv)/d_6-THF	1	1.6:1.0
8	1 M HCl in Et_2O (0.2 equiv)/CD_3CN	1	1.4:1.0
9	1 M HCl in Et_2O (0.2 equiv)/CD_2Cl_2	1	1.0:2.2
10	1 M HCl in Et_2O (0.2 equiv)/$CDCl_3$	1	1.0:2.5
11	*p*-TsOH (1.0 equiv), LiCl (5.0 equiv)/CD_3CN, 50 °C	2	2.0:1.0[d]

[a] All reactions were performed at 25 °C on **57** (1 mg) unless indicated otherwise. [b] Ratio is at equilibrium and was determined by integration of the H-7 and H-8 ^{1}H NMR (500 MHz) signals. [c] n.r. = no reaction as determined by NMR spectroscopy in MeOD after aqueous workup. [d] Equilibrium ratio not determined.

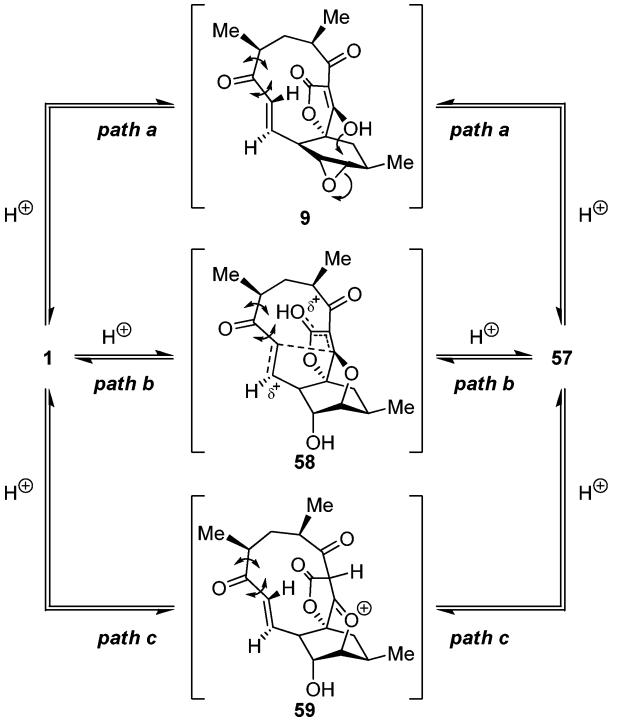


Figure 10. Proposed mechanisms for the acid-catalyzed interconversion of abyssomicin C (**1**) and atrop-abyssomicin C (**57**).

strain in the ground state of each atropisomer of abyssomicin C begs two hypotheses. The first is that the high thermal barrier to interconversion is mostly the result of an even more strained transition state. The second is that the mechanism of the acid-catalyzed isomerization must operate in a manifold that relieves this strain.

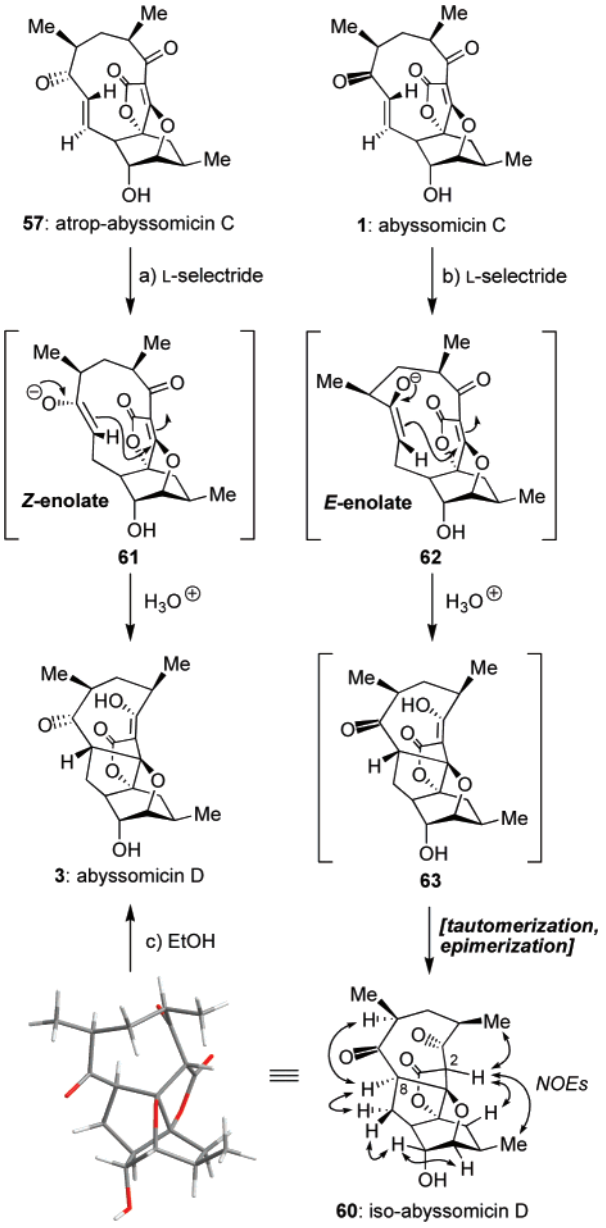
Figure 10 depicts three possible avenues through which this isomerization could occur. The first possibility (path a) involves protonation of either atropisomer on the tetronate core by HCl. This could render the tetronate a sufficiently good leaving group such that the C11 hydroxy group could re-close onto C12, generating the postulated biosynthetic precursor **9**, which could be flexible enough so as to allow C6−C7 and C7−C8 bond rotation before retrapping of the protonated epoxide. One problem with this hypothesis is the fact that we have not detected any epoxy compound during our isomerization studies to date, suggesting that this pathway is not likely operational. Alternatively (path b), protonation of an oxygen atom on the tetronate core could render C16 electron deficient, allowing it to draw π-electron density through space from the suitably poised olefin at C8−C9. This bridging interaction would draw C8 closer to the tetronate core (see **58**, Figure 10), relieving strain. Our last and preferred hypothesis (path c) is that the core of the molecule is protonated by the strong acid at C2 affording the oxocarbenium ion **59** (Figure 10). This would convert the already deformed sp^2 center into one that is completely pyramidalized, relieving strain in the macrocyclic system and allowing the requisite σ-bond rotation to occur.

Synthesis of Abyssomicin D. To test the proposed biomimetic synthesis of abyssomicin D[1] (**3**, Figure 1), both abyssomicin C (**1**) and atrop-abyssomicin C (**57**) were subjected to reduction with L-Selectride (Scheme 8). Reduction of atrop-abyssomicin (**57**) occurs cleanly at −78 °C leading to abyssomicin D (**3**, 60% yield). Interestingly, reduction of abyssomicin (**1**) at the same temperature does not furnish any abyssomicin D (**3**) at all, leading instead to a mixture of compounds whose major component, compound **60**, was isolated in 44% yield and characterized through a combination of NMR and computational modeling studies (see Supporting Information for details). These distinct outcomes likely result from the ground-state conformation of the α,β-unsaturated ketone moiety within these substrates prior to hydride delivery. Thus, 1,4-reduction of the cisoid enone in **57** most likely leads to the transient formation of the *Z*-enolate **61**, which after intramolecular Michael addition onto the tetronate moiety and aqueous workup leads directly to abyssomicin D (**3**). On the other hand, the transoid enone of **1** should result in the formation of the *E*-enolate **62**, whose reaction with the tetronate core should afford **63**, an apparent conformational isomer of abyssomicin D (**3**). As this is not the product isolated from the reaction, tautomerization and epimerization must take place at C2 and C8, respectively, affording **60**. Interestingly, while attempting to obtain crystals of **60** (for X-ray analysis) in ethanol, it was discovered that complete isomerization to abyssomicin D (**3**) took place. Repeating the experiment with monitoring by TLC indicated that **60** converted completely to **3** in under 3 h at room temperature, presumably via a series of proton transfers and bond rotations.

The differing reactivity between abyssomicin C (**1**) and its atropisomer **57** under 1,4-reduction conditions suggests that abyssomicin D (**3**) may arise from reduction of the more reactive atrop-abyssomicin C (**57**) and not the originally isolated natural product (**1**) as previously hypothesized.[1] This pathway is supported by a kinetics experiment whereby incubation of both **1** and **57** with the NADH analogue **64**[37] in $CDCl_3$ at 55 °C led to near complete consumption of **57** and only 30% consumption of **1** after 48 h (Figure 11). Analysis of the crude ^{1}H NMR

(37) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156.

Scheme 8. 1,4-Reduction of Abyssomicin C (**1**) and Atrop-abyssomicin C (**57**) Leading to Iso-abyssomicin D (**60**) and Abyssomicin D (**3**), Respectively[a]



[a] Reagents and conditions: (a) L-Selectride (1.2 equiv), THF, −78 °C, 30 min, 60%. (b) L-Selectride (1.2 equiv), THF, −78 °C, 30 min, 44%. (c) EtOH, 25 °C, 3 h, 100%. Abbreviations: L-selectride, lithium tri-*sec*-butylborohydride.

spectra following this experiment indicated that **57** had been converted predominately to abyssomicin D (**3**), while abyssomicin C (**1**) afforded neither previously isolated form of abyssomicin D (**3** or **60**). Although these experiments support the notion that atrop-abyssomicin C (**57**) may be a product of biosynthesis, further experimentation with the host organism would be required for unequivical confirmation of this hypothesis.

Synthesis of Analogues and Biological Evaluation. One of our initial goals in this program was the synthesis of analogues for biological and mechanistic evaluations, with a particular interest in the preparation of analogues involving substitution along the C3−C8 portion of the macrocyclic ring. It was thus dissappointing to find that the ring-closing metathesis step

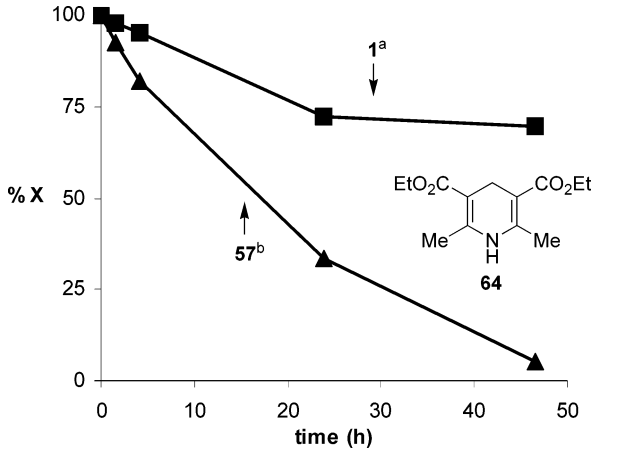
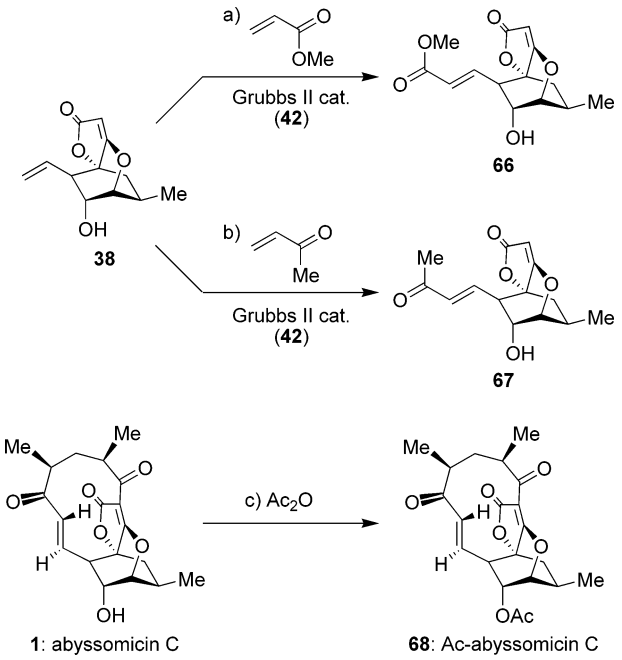


Figure 11. Graph showing the rate of disappearance of abyssomicin C (**1**) and atrop-abyssomicin C (**57**) in their reactions with the NADH analog **64** (5.0 equiv) in $CDCl_3$ (determined by ^1H NMR spectrum integration against 2,6-di-*tert*-butyl-4-methylphenol as an internal standard). (a) Neither abyssomicin D (**3**) nor iso-abyssomicin D (**60**) were detected in the crude ^1H NMR spectrum of the product. (b) Abyssomicin D (**3**) was the only product detected in the crude ^1H NMR spectrum.

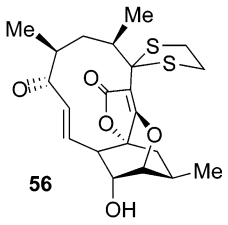
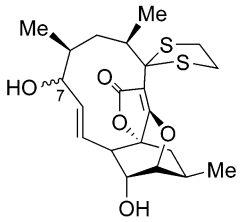
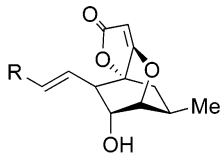
Scheme 9. Synthesis of Simplified Analogues **66** and **67** via Cross-Metathesis and Ac-abyssomicin C (**68**)[a]



[a] Reagents and conditions: (a) **42** (0.05 equiv), methyl acrylate (10 equiv), CH_2Cl_2 (0.1 M), 40 °C, 1 h, 84%. (b) **42** (0.05 equiv), methyl vinyl ketone (10 equiv), CH_2Cl_2 (0.1 M), 40 °C, 1 h, 89%. (c) Ac_2O (15 equiv), Et_3N, 25 °C, 63%.

(Scheme 6) is not a general process within this structural series and that adjusting the length or methyl substitution pattern of the hydrocarbon chain (C3−C8) prevents efficient macrocyclization (data not shown). We instead prepared a number of simpler analogues based on the core of the natural product as shown in Scheme 9. Cross metathesis reactions of the core compound **38** with methyl acrylate or methyl vinyl ketone afforded two potential Michael acceptor compounds **66** and **67** (in 84 and 89% yield, respectively). Furthermore, the free hydroxy group of abyssomicin C (**1**) was acylated under standard conditions affording **68** in 63% yield to determine whether or not this functionality is important for activity. These compounds

Table 3. Minimal Inhibitory Concentrations (MICs) of Abyssomicin C Analogues against Methicillin-Resistant *S. aureus* (MRSA)[a]

entry	compound	MIC (μM)
1	**1**: abyssomicin C	20
2	**57**: atrop-abyssomicin C	15
3	**68**: Ac-abyssomicin C	20
4	 **56**	70
5	 **51a**: C7-(*R*)	>500
6	**51b**: C7-(*S*)	>500
7	 **38**: (R = H)	>500
8	**66**: (R = CO_2Me)	>500
9	**67**: (R = $C(O)CH_3$)	>500

[a] MIC values were determined with serial dilutions in 96-well plates against a 1:10 000 dilution in nutrient broth (DIFCO) of a 24 h culture of methicillin-resistant *S. aureus* (ATCC 33591) at 35 °C. Reported MIC values reflect the concentration at which no growth could be visually detected after 24 h.

as well as other synthetic intermediates were screened for activity in a minimal inhibitory concentration (MIC) assay against methicillin-resistant *S. aureus* (MRSA), and the results obtained are provided in Table 3. As anticipated, atrop-abyssomicin C (**57**), with its more reactive Michael acceptor, is a slightly more potent agent than abyssomicin C (**1**). Acylated abyssomicin C (**68**) showed essentially the same activity as the parent natural product, suggesting that the C11 hydroxy group is not involved in hydrogen bonding in the active site of the targeted enzyme, unless the compound serves as a prodrug to **1** through enzymatic acetate hydrolysis. The dithiolane protected compound **56**, with its α,β-unsaturated ketone intact and in the more reactive cisoid conformation (see Figure 8), shows activity, although less so than the two abyssomicin C atropisomers. As expected, based on the proposed mechanism of action, the allylic alcohols **51a** and **51b** are not active (entries 5 and 6). The simplified core compounds **38**, **66**, and **67** (entries 7−9) also lack activity, suggesting that a properly oriented Michael acceptor is required for activity. The use of a simple nutrient broth was required in this assay (yeast extract), as conducting the MIC assays in more complex media (Mueller Hinton II) resulted in the entire loss of activity, suggesting that the use of these compounds as bacterialcidal agents in vivo may be problematic.

Conclusion

Described in this full account is a successful total synthesis of the recently discovered antibiotic abyssomicin C (**1**) and its inactive cousin abyssomicin D (**3**). En route to these natural products, a number of roadblocks encouraged innovation leading to the development of a new Lewis acid-templated Diels−Alder reaction. During this program, atrop-abyssomicin C (**57**) was discovered, which demonstrated an unusual form of atropisomerism and a novel acid-catalyzed conformational equilibration. The identification of **57** enabled the hypothesis that this previously unknown atropisomer is synthesized by the host organism and that it may serve as a biosynthetic precursor to abyssomicin D (**3**). Its eventual isolation from natural sources will, therefore, not be surprising. Finally, a number of analogues based on synthetic intermediates were screened for activity against MRSA, further expanding our understanding of the structure−activity relationships within the abyssomicin scaffold.

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Supporting Information Available: Experimental procedures and compound characterization, complete ref 1b, and copies of select ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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