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Total Synthesis of (±)-Phomactin A. Lessons Learned from Respecting a Challenging Structural Topology[||]

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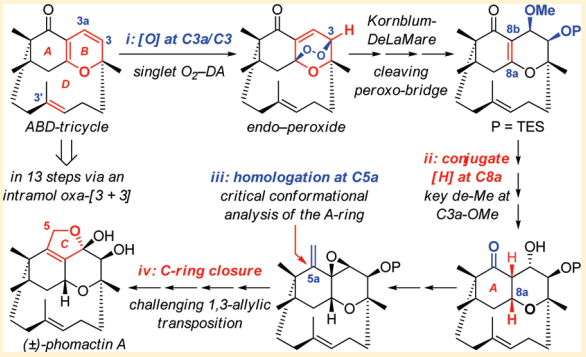
Supporting Information

ABSTRACT: Our struggles and ultimate success in achieving a total synthesis of phomactin A are described. Our strategy features an intramolecular oxa-[3 + 3] annulation to construct its unique ABD-tricyclic manifold. Although the synthesis would constitute a distinctly new approach with the 12-membered D-ring of phomactin A being assembled simultaneously with the 1-oxadecalin at an early stage, the ABD-tricycle represents a unique structural topology that would pose a number of unprecedented challenges. One challenge concerned elaborating this tricycle to have oxygenation at the proper carbon atoms. To overcome this, we would utilize a Kornblum−DeLaMare ring-opening of a peroxide bridge as well as a challenging late-stage 1,3-allylic alcohol transposition. Further, the structural intricacies of the ABD-tricycle were uncovered by a conformational analysis that would be critical for the C5a-homologation.



INTRODUCTION

(+)-Phomactin A was isolated by Sugano and Sato et al. from the culture filtrate of a marine fungus, *Phoma* sp. (SANK 11486), a parasite collected from the shell of *Chionoecetes opilio* off the coast of the Fukui Prefecture in Japan (Figure 1).[1−5] It was determined to possess moderate PAF aggregation inhibitory ability (IC_{50} = 10 mM), and its structure and absolute configuration were unambiguously determined using a crystal structure of the C3-*p*-bromobenzoate derivative (see **1**). In the last 15 years, the phomactins, and particularly, the unusual ABCD-tetracyclic topology of (+)-phomactin A, have attracted an immense amount of efforts and interests from the synthetic community.[6−8] There have been five total syntheses[9] of the phomactins with Pattenden[10] and Halcomb[11] each completing the syntheses of phomactin A.

Our strategy toward (±)-phomactin A[12] features an intramolecular oxa-[3 + 3] annulation[13−17] of **7** developed in our lab (Figure 2).[18] It is noteworthy that while the oxa-[3 + 3] annulation[19,20] dates back more than 60 years,[21] an intramolecular variant of this reaction was not known, especially in the context of natural product total synthesis.[13−17,22] It took great effort to overcome a number of struggles including an unexpected competing annulation pathway that formed a mixture of atropisomers as a result of the other ketone of diketo-enal **7** undergoing the annulation (Figure 2).[12a−d]

Our approach to phomactin A differs from all others by the 12-membered D-ring being constructed simultaneously with the 1-oxadecalin at an early stage, and it could prove to be a facile total synthesis route to the challenging structure of phomactin A. Yet, whatever difficulties we overcame in the construction of **6**, much greater challenges lay ahead, for this ABD-tricycle represents a unique structural topology[12b] that would pose a number of unprecedented challenges. More specifically, the Spartan model of **8** (Figure 2) reveals a highly strained and caged motif with the plane of the AB-ring being in close proximity with the D-ring olefin at C3′.

Certain challenges arose during our synthesis, and our success in overcoming them are illustrated in Figure 2. Retrosynthetically, lactol formation (C-ring construction) from vinyl epoxide **2** was needed to complete the total synthesis of (±)-phomactin A. We utilized a 1,3-allylic alcohol transposition of **2** and subsequent ring-closure to overcome this obstacle. Vinyl epoxide **2** was made via homologation of a C5a carbonyl, similar to **3**, finding that careful conformational analysis would lead us to pursue an epoxy ketone, which allowed approach of an incoming nucleophile by minimizing the steric hindrance along the A-ring. At this stage, the challenge of reducing the AB-ring junction was overcome by utilizing a conjugate reduction at C8a of an intermediate diketone from **4** that would exclusively form the alcohol at C3a of **3**, while not touching the carbonyl at C5a. The task of transforming ABD-tricycle **6** to vinylogous ester **4** was accomplished by utilizing an oxidation sequence of a singlet-oxygen

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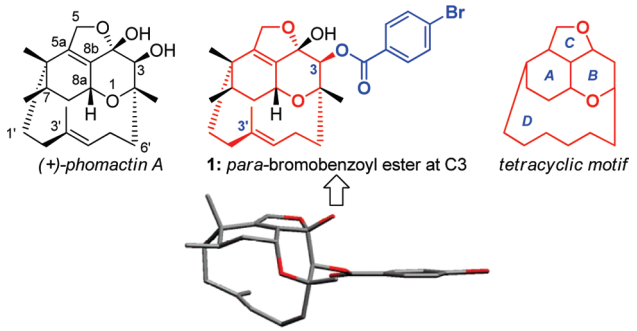


Figure 1. (+)-Phomactin A and its C3-*p*-bromobenzoyl ester derivative.

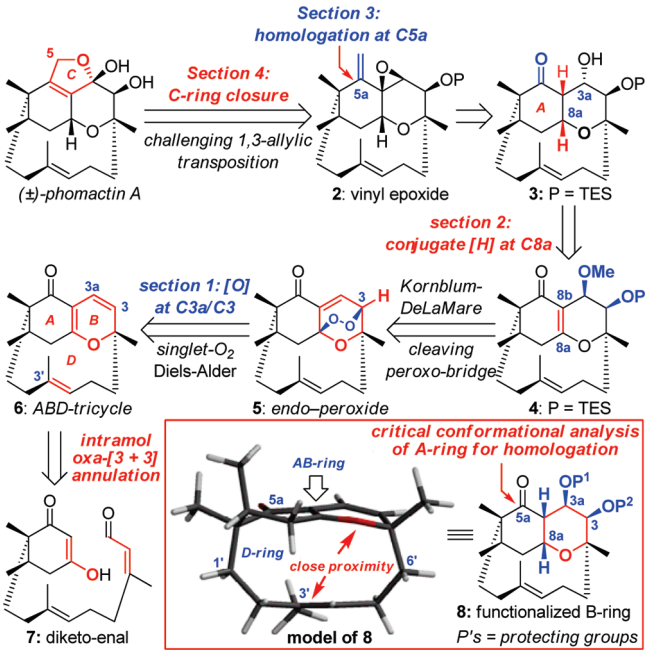


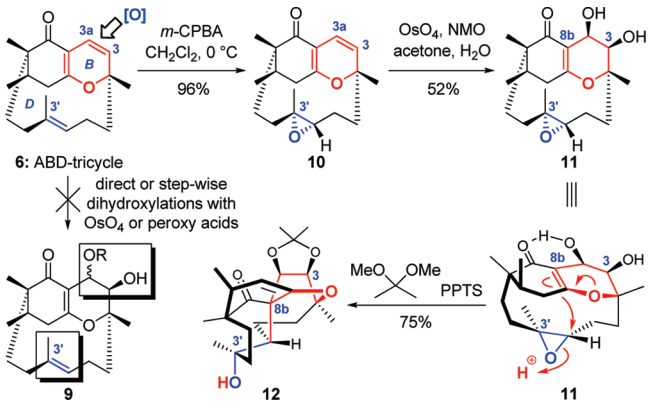
Figure 2. Challenges in the synthesis of phomactin A.

hetero-Diels–Alder (HDA) and a Kornblum–DeLaMare ring-opening. The ABD-tricycle **6** was accessed by an intramolecular oxa-[3 + 3] annulation of diketo-enal **7** developed in our lab.[12] Herein, we report details of our efforts to meet these challenges en route to a total synthesis of (±)-phomactin A.

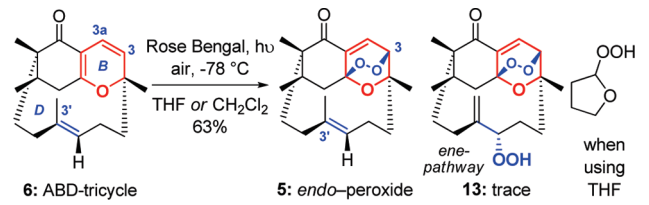
RESULTS AND DISCUSSION

1. Oxidations of C3 and C3a in ABD-Tricycle 6. Despite our desire to homologate at an early stage,[23a] we were forced to examine oxidation[23b] of the C3-3a olefin of ABD-tricycle **6** for we observed that C5a-homologation of a simple oxadecalin would only provide complex mixtures.[23b] This oxidation would require selectivity of the B-ring over the C3′-olefin. Unfortunately, exposure of **6** to either *m*-CPBA or peracetic acid resulted not in the desired diol **9** but in the rapid epoxidation of the belt olefin at C3′ to afford epoxide **10** (Scheme 1). We had underestimated the reactivity of the C3′-olefin relative to the B-ring pyran system. It is likely that the strain in the 12-membered D-ring renders the C3′-olefin twisted toward pyramidalization, thereby enhancing its reactivity toward electrophiles. In addition, an attempt to

Scheme 1. C3-3a Oxidation: B-Ring Reactivity versus C3′-Olefin



Scheme 2. Synthesis of *endo*-Peroxide 5



dihydroxylate the B-ring system of **6** only led to the slow consumption of starting material with no observable product formation.

At this point, we pondered the possibility of the belt olefin being "protected" as its epoxide. There are a number of ways to convert an epoxide into an olefin; whether these methods could work on such a hindered system is doubtful, but valuable information could be gleaned. Thus, we attempted an exhaustive oxidation of **6** using buffered peracetic acid or *m*-CPBA; however, these efforts led to initial epoxidation of the C3′-olefin followed by decomposition. Osmium-catalyzed dihydroxylation of the pyran in **10** was then attempted and gave diol **11** in moderate yield. Subsequently, we attempted to protect the diol as an acetonide, yet the conditions provided the unexpected teteracycle **12** resulting from an acid-promoted transannular addition of the vinylogous ester to the epoxide. While this transformation exemplifies the ambiphilic nature of the vinylogous ester double bond, it underscores the ability of the AB-ring to interact with functionalities on the belt because of their close proximity (see model in Figure 2). Protection of the diol functionality in **11** with TMSCl was also attempted, but a mixture of products was obtained even when excess of base was present to ensure that HCl was not promoting any transannular reactions. Further, attempts to hydrogenate of the enone in **11** (Pd/C, or Crabtree) met with formation of an unidentified product, thereby further quelling our hope of using the epoxide system.

It then occurred to us[22p] that the use of singlet oxygen to react in a Diels–Alder fashion could be a viable option for the required oxygenation, whereby the B-ring 2*H*-pyran would serve as the diene. As shown in Scheme 2, upon irradiation with a 300-W lamp of a −78 °C solution of ABD-tricycle **6** containing Rose Bengal as sensitizer and an air bubbler, we were excited to observe the

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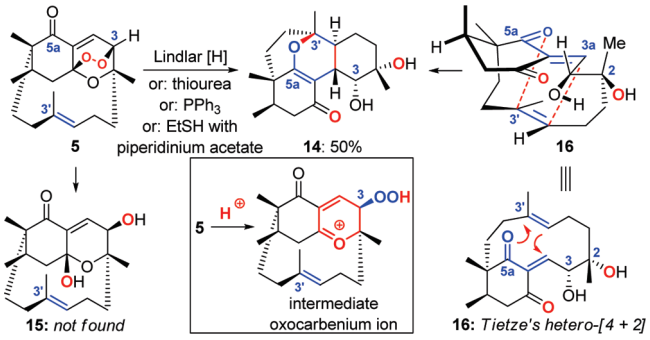
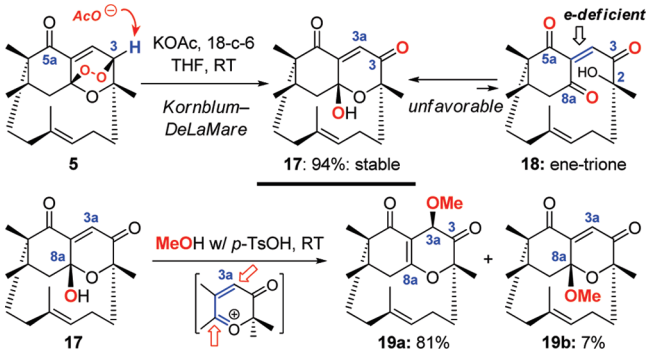
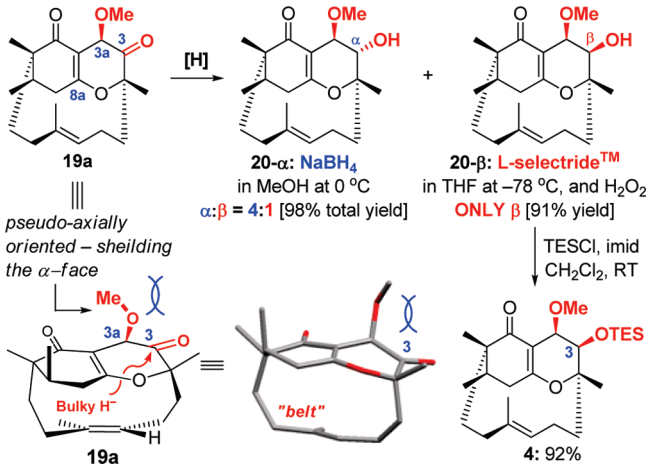
Scheme 3. Unexpected Tetracycle 14 from the *endo*-Peroxide Reduction



Scheme 4. *endo*-Peroxide Ring-Opening and C3a-Oxygenation



Scheme 5. The Critical C3-Ketone Reduction



desired *endo*-peroxide **5**. The ene-product **13** was also detected existing at only a low level, and there was no observation of [2 + 2] cycloadduct. Not only is the reactivity of $^1O_2$ toward this system remarkable, as the [4 + 2] reaction occurs at −78 °C, this result represented a major breakthrough, as we had discovered how to selectively oxidize the chromenone system in the presence of the belt olefin at C3′. An additional benefit of the oxidation is the stereochemically correct installment of the C-3 β-oxygenation. The peroxide was noted to be *remarkably* crystalline, and we obtained an X-ray structure of **5** (vide infra), which dramatically illustrates the unique structural topology of this novel tetracycle. It is noteworthy that on a number of occasions, a contaminant assigned as the THF−hydroperoxide was found; to prevent any possible explosion-related problems, the reaction solvent was changed to CH_2Cl_2, which performed comparably.

With the identity of *endo*-peroxide **5** confirmed, we began investigating conditions to open the peroxide bridge.[24] While reaction of *endo*-peroxide **5** with milder acids such as AcOH would normally provide starting material, cationic reductions ($BF_3 \cdot OEt_2$ with TES-H) led to complex mixtures, possibly due to formation and reactivity of an oxocarbenium ion intermediate (see box in Scheme 3). To avoid acidic conditions, we then pursued a reduction of the peroxide functionality, noting that a great variety of methods exist which reliably cleave the unstable O−O bond. A very mild and chemoselective method for the reduction of *endo*-peroxides is the use of thiourea in MeOH. This reaction cleanly afforded an unknown compound that was later assigned as **14**, while the desired hemiketal **15** or even diol **16** was not seen (Scheme 3). Intriguingly, the action of Lindlar's catalyst and H_2 rapidly afforded the same compound **14**. Furthermore, exposure of the peroxide to PPh_3 afforded a mixture of compounds in the crude ^{1}H NMR, but after silica gel chromatography, **14** was again isolated.

It is also noteworthy that exposure of **5** to EtSH in the presence of a trace amount of piperidinium acetate led to the clean formation of an intermediate within 5 min, which began to rearrange to the HDA adduct within 30 min in an NMR tube, and after sitting overnight, the solution consisted solely of **14**. Mechanistically, this HDA cycloaddition reaction likely arises from a hemiketal **15** after reduction that would be in equilibrium with the open diketone **16**, and cyclization then affords tetracycle **14**. Related HDA reactions have been extensively investigated notably by Tietze, among others.[25]

In an interesting turn of events, while we were attempting to add acetate anion in a 1,4-fashion into the enone system of **5**, we isolated ene-dione **17** when using KOAc in the presence of 18-Crown-6 (Scheme 4). While this was not anticipated, it turned out to be a known protocol developed by Kornblum and DeLaMare to ring-open *endo*-peroxides through a deprotonation pathway.[26] It is noteworthy that ene-dione **17** did not give ene-trione **18** which could suffer from the aforementioned HDA pathway; it is likely that **18** is disfavored because of its highly electron-deficient olefin C3a relative to that of **15**. Although this process destroyed the C3 stereochemistry, the reaction was very clean with no other products observed. Further, it represented the first successful attempt to open the peroxide in a productive manner and presented us with a number of possible routes to advance our chemistry toward phomactin A.

After failed attempts with cationic reduction of hemiketal **17** (TFA/$NaCNBH_3$, TFA, or $BF_3 \cdot OEt_2$ with TES-H), we considered the formation of vinylogous esters via a 1,3-shift, finding that solvolysis by MeOH[27a,b] in the presence of acid reliably generated vinylogous ester **19a** (Scheme 4). We screened a number of acids and discovered that *p*-TsOH afforded the best results, although the reaction was never driven to completion and did afford a small amount of methoxyketal **19b**. It is reasonable to suggest that vinylogous ester **19a** and methoxyketal **19b** were both derived from an oxocarbenium ion intermediate.

Faced with the critical C3-reduction, we found that upon exposure of vinylogous ester **19a** to $NaBH_4$ in MeOH, a mixture

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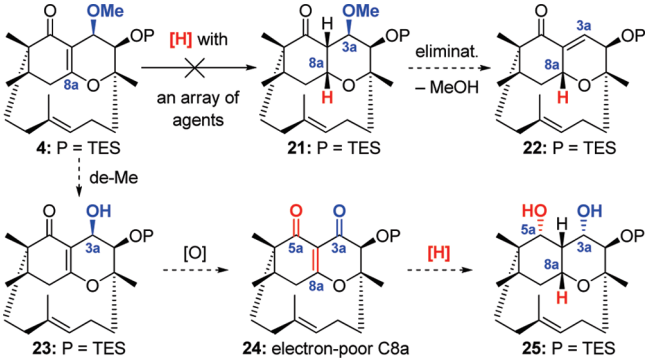
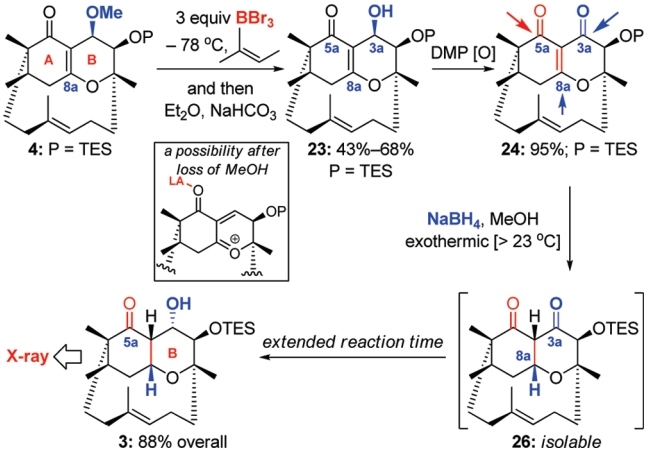
Scheme 6. Attempting to Directly Reduce C8a



Scheme 7. Successful Demethylation and Oxidation



of α- and β-alcohols were isolated in a 4:1 ratio (Scheme 5). The ratio did not appear to be temperature dependent, and thus we decided to investigate other reducing agents to see if the desired isomer could be formed exclusively. Fortunately, L-Selectride gave the desired β-alcohol **20**-β exclusively in 91% yield! An ensuing protection of the C3-OH with TESCl then provided TES-ether **4**.

This stereochemical outcome appeared to be counterintuitive because we had initially reasoned that the OMe group could sterically out-compete the "belt," thereby shielding the top face from nucleophiles more effectively and leading to hydride delivery, especially a small hydride, from the bottom face. However, in hindsight, by examining the Spartan model (see Scheme 5), it would appear that the C3a-OMe group is pseudoaxially oriented. Small hydrides could get by with relative ease from the top face, but in the case of a more bulky hydride, the C3a-OMe group was able to completely prevent the reagent approaching from the top face. This success completes the task of oxidizing C3 and C3a, and more importantly the stereochemistry of C3 was set despite temporarily losing it in the Kornblum–DeLaMare process.[26]

2. Reduction of C8a and C8b at the AB-Ring Junction. The reduction story is more straightforward than the C3-C3a oxidation described above. Early attempts to directly reduce C8a through conjugate hydride addition failed; no condition that we screened (L-Selectride, CuI/LAH, Na/IPA) was capable of this transformation to the desired ketone **21** or enone **22** after elimination of MeOH (Scheme 6). While unfortunate in the sense that the methyl ether could have served as a good protecting group strategy, we decided to attempt to activate the system toward conjugate reduction through introduction of a second carbonyl group. Thus, removal of the methyl ether and oxidation of the corresponding allylic alcohol **23** to diketone **24** became our focal point. To note, we recognized that an exhaustive reduction of **24** could potentially occur to give diol **25** in a highly stereoselective manner because our plan had all along relied upon the belt blocking the bottom face of the chromanone to assist in setting the C-8a stereocenter, unlike what had been done previously by both Halcomb[11] and Pattenden.[10] Further, we were cognizant that using strong Lewis acids to demethylate could provide a preponderance of undesired products via an intermediate oxocarbenium ion (see the box in Scheme 7) after loss of MeOH.

To demethylate, we exposed **4** to BBr_3 and obtained the desired alcohol **23** (Scheme 7). Although initially in low yield, this success is highly fortuitous because of the many potential problems.[28] First, the highly sensitive TES ether could just as easily have been cleaved with use of BBr_3 or any HBr present. Second, it is remarkable that the C3a-OMe group simply does not act as a leaving group to form an oxocarbenium ion. In contrast, when we screened a few other systems known for their ability to remove methyl ethers such as TMS-I,[29] removal of both methyl and TES ethers was observed along with the formation of many unidentified products, likely through one such oxocarbenium ion. With the free alcohol **23** in hand, we were set to investigate its oxidation to diketone **24** (Scheme 7). We were again apprehensive regarding this transformation because of the foreseen possibility of forming an oxocarbenium species upon initial activation of the allylic alcohol by an oxidizing species. While both TPAP and PCC oxidations were slow, and produced traces of the desired diketone **24**, we were excited when Dess–Martin periodinane rapidly and quantitatively provided access to diketone **24**.

At this point, we needed to reduce C8a and C8b at the AB-ring junction. A literature search showed that the dihydrochromandione motif in **24**, or other related systems, was relatively unknown and/or underinvestigated, and although the proposed conjugate reduction to this system was unprecedented, we were hopeful that the additional electron-withdrawing group should provide sufficient reactivity toward a hydride source. Our first attempt using $NaBH(OAc)_3$, an extremely mild hydride source, returned only starting material. The second attempt employed excess $NaBH_4$ to give a mixture of diketone **26** and desired β-hydroxyketone **3**. In subsequent trials, **24** could be reduced cleanly to **3** especially at elevated temperatures. With β-hydroxyketone **3** in hand at last, the stereochemistry at C8a was finally set, and a single-crystal X-ray structure of **3** (vide infra) was attained to further confirm our success. This allowed us to pursue the next objective.

3. Homologation at C5a in the A-Ring. *a. Initial Failures in a Brief Exploration.* The third task is to install the 20th and final carbon via homologation at C5a. Given the resistance of the C5a-carbonyl to attack by hydride, the smallest conceivable nucleophile, during the formation of **3**, we recognized that there might be severe difficulties in the need of adding a larger carbon nucleophile. Toward the goal of homologation, since Tebbe's olefination as well as a Pd-catalyzed cross-coupling of enol

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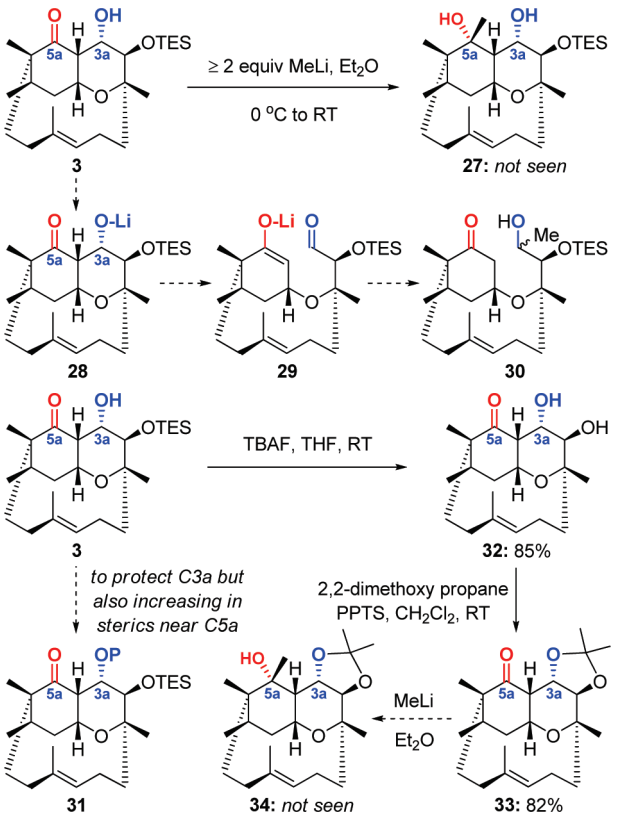
Scheme 8. Unsuccessful Attempts at MeLi Addition



phosphates[30] to give carbonylated products both failed, we elected to investigate the use of small one-carbon nucleophiles, adopting MeLi as the "gold standard" to judge if a compound was reactive toward a nucleophile.

Unfortunately, upon treating β-hydroxyketone **3** with MeLi for extended reaction times, some sort of fragmentation reaction appeared to occur (Scheme 8). While the desired addition product **27** was not seen, the fragmentation that took place may be attributed to a retro-aldol reaction through intermediates such as **28** and **29**. The tentatively assigned structure of the final product is shown as **30**, although it was not fully characterized.

We then considered protecting C3a, but silylation of C3a-OH would lead to additional steric congestion near C5a; instead, we decided to pursue acetonide **33**. Thus, removal of the TES ether with TBAF readily afforded diol **32**, which was then exposed to 2,2-dimethoxypropane and PPTS at room temperature, leading to the crystalline acetonide **33** in good yield. Unfortunately again, exposure of acetonide **33** to MeLi did not afford the desired addition product. These failures led us to think deeply about how we could retool our plans. We began to realize that the unique structural topology of the ABD-tricycle may exist in a number of different conformations depending upon the substitution patterns, and perhaps a more reactive conformation would allow addition to the C5a-carbonyl.

b. A Meticulous and Critical NMR Observation. We then conducted a critical conformational analysis based on NMR observations made along the way. Many of the compounds containing the vinylogous ester functionality had possessed broadened ^{1}H and ^{13}C NMR spectra, to such an extent that the ^{13}C NMR had to be recorded at elevated temperature. We rationalized that this was due to a conformational exchange that occurred in solution. Subsequently, we observed that compounds which have been reduced such as β-hydroxyketone **3** no longer exhibited this troublesome characteristic. Additionally, when diketone **24** was reduced to β-hydroxyketone **3**, an interesting change occurred in the ^{1}H NMR that gave us significant insight into our proposed conformations of these systems.

A selected region of the ^{1}H NMR for compounds **6** and **3** is shown in Figure 3. The resonance at δ 2.9 ppm in the NMR spectrum of ABD-tricycle **6** was assigned as the H8α proton (α denoting proton being down), noting the rather highly deshielded nature of its chemical shift. At the time, we believed that this proton was pseudoaxial because in addition to deshielding from the α,β-unsaturated carbonyl motif, it could experience anisotropic deshielding from the belt olefin at C3′. This proposal could be wrong, as the effect was not suppressed after epoxidation of the C3′-olefin (see epoxide **10**, vide supra). Nevertheless, we observed that when the C8a carbon is no longer sp^2-hybridized but is instead sp^3-hybridized, the H8α proton no longer experiences this dramatic deshielding effect. This observation was first made in the NMR spectrum of *endo*-peroxide **5** (not shown here) in which the H7α methyne proton is now likely pseudoaxial, thereby possibly experiencing anisotropic deshielding from the C3′-olefin and shifting its NMR signal significantly downfield. This is distinctly observed in β-hydroxyketone **3** with H7α (δ = 2.8 ppm), the natural product, and indeed all compounds where C8a is sp^3-hybridized. These unique and meticulous observations led us to examine the A-ring conformation more carefully because we felt that its conformation likely plays a crucial role in the reactivity of the C5a-carbonyl toward nucleophiles.

c. A Strategic Conformational Analysis. We chose to first examine ketone **19a** and β-hydroxyketone **3** because (1) no reduction of the C5a-carbonyl in **19a** occurred when using L-Selectride to reduce the C3-ketone, and (2) $NaBH_4$ did not reduce the C5a-carbonyl group in β-hydroxyketone **3**. Upon examination of the minimized Spartan model of vinylogous ester **19a** and the X-ray structure of β-hydroxyketone **3**, we found other unique conformational elements (Figure 4) in addition to fully validating the aforementioned possible positions of the H8α proton in systems where C8a is sp^2-hybridzied, and of the H7 proton where C8a is sp^3-hybridized. In vinylogous ester **19a**, the α-Me group in the A-ring (red) is pseudoequatorial with the β-Me group (blue) being pseudoaxial, thereby blocking any incoming nucleophiles toward the C5a-carbonyl group.

More importantly, we were mesmerized by the X-ray structure of β-hydroxyketone **3**, which revealed a very different conformation with its AB-ring junction carbon atoms being both sp^3-hybridized instead of sp^2 as in **19a**. The structure showed near-perfect chairs that comprise the cis-fused 1-oxadecalinic AB-ring. With this conformational preference, the β-Me group (blue) is now pseudoequatorial with the α-Me group (red) turning to occupy the pseudoaxial position. We believe that the orientation of the α-Me group (red) is responsible for the fact that the C5a carbonyl is not reduced by $NaBH_4$: it is sterically inaccessible, even by a nucleophile as small as a hydride.

In contrast, the AB-ring junction of *endo*-peroxide **5** consists of sp^3-hybridized C8a and sp^2-hybridized C8b (Figure 5). This set of hybridizations forces the A-ring into a twisted-boat, thereby bending both methyl groups back toward pseudoequatorial positions. It is noteworthy that this A-ring conformation is very similar to that of phomactin A itself (Figure 1). More importantly,

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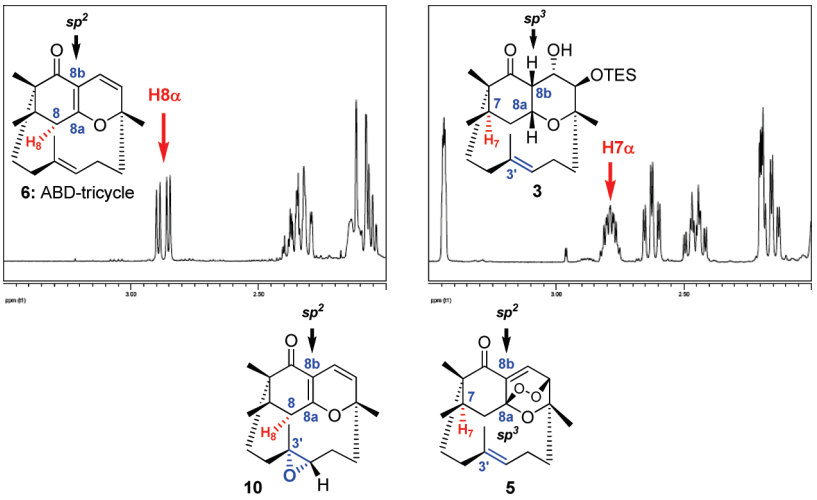


Figure 3. ^{1}H NMR of ABD-tricycle **6** and β-hydroxyketone **3**.

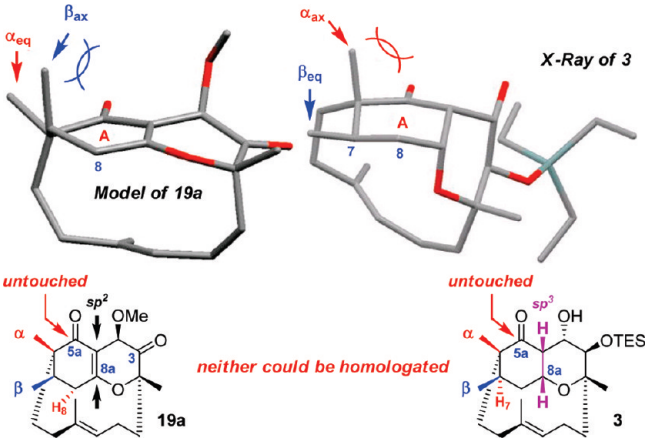


Figure 4. Conformational analysis for **19a** and **3**.

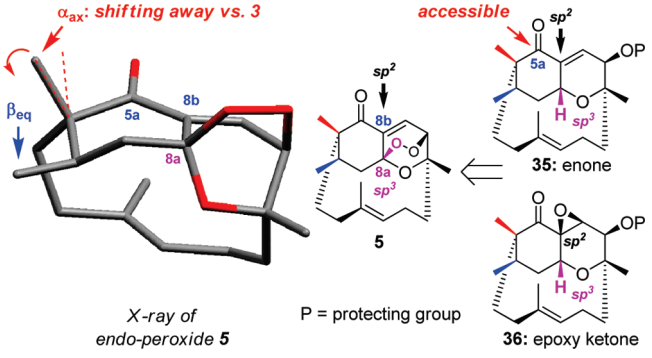
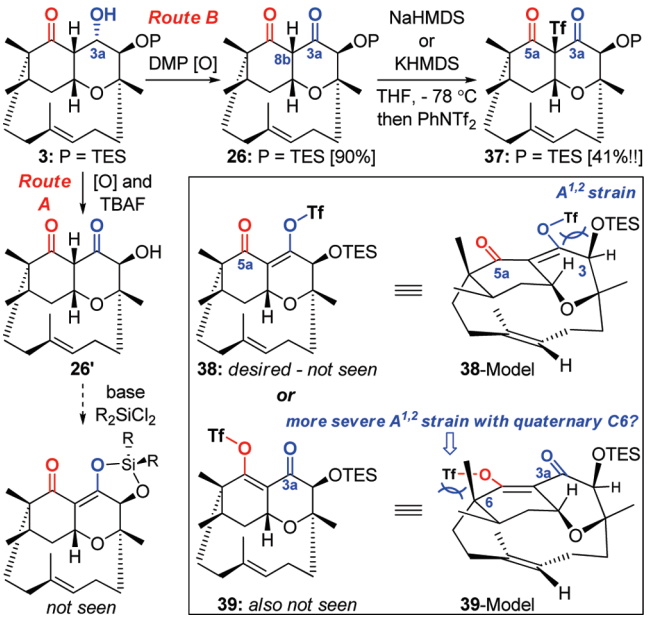


Figure 5. Rationale for choosing **35** and **36**.

the β-Me group (blue) remains pseudoequatorial as in **3**, but the α-Me group (red) shifts away versus its respective position in **3**. We hoped that this minor shift would be present in compounds such as enone **35** and epoxy ketone **36**, in which C8a is sp^3-hybridized and C8b is sp^2-hybridized (pseudo-sp^2 for **36**). With the A-ring in the twisted-boat conformation and both Me groups bending away, there would be enough exposure of the π^*-orbital of the C5a-carbonyl for the nucleophilic attack to occur.

Scheme 9. Problems in the Vinylogous Ester Synthesis



d. The Experimental Realization. With the above conformational analysis, syntheses of enone **35** and epoxy ketone **36** became our focal points, but this would once again represent another challenging experimental endeavor. Here, we had two possible routes in mind (Scheme 9). The first route would involve oxidation of the C3a alcohol in **3** and desilylation to give **26′**, which would then be tied up with the C3a-carbonyl as a silicon-protected vinylogous ester (Route A). This silicon-tethered species would then be used to investigate the addition of an appropriate alkyllithium or oxygenated alkyllithium species. Unfortunately, after oxidation and desilylation to **26′**, exposure of the resultant alcohol to Ph_2SiCl_2 and Me_2SiCl_2 never provided the desired product, thereby thwarting the alkyllithium strategy.

The other route (Route B) would involve generation of an enol triflate such as **38**, which in turn would be utilized for Pd(0)-catalyzed carbonylation chemistry. If successful, this approach could land us very near to the natural product. Toward that goal,

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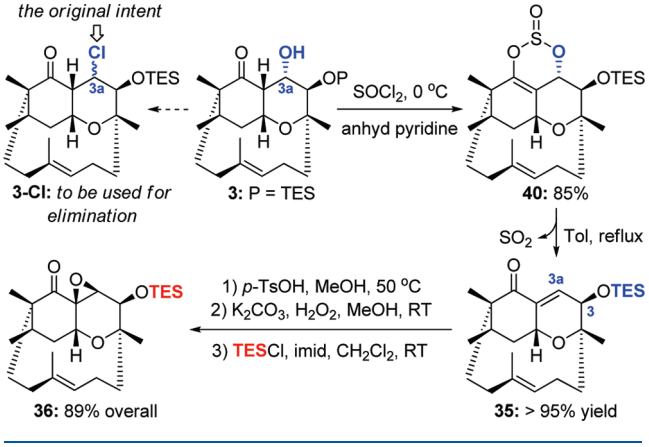
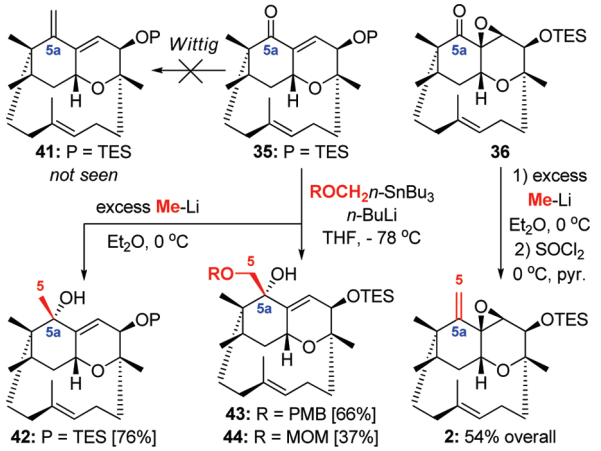
Scheme 10. Serendipitous Success in the Enone Synthesis



Scheme 11. Successful C5a-Homologations



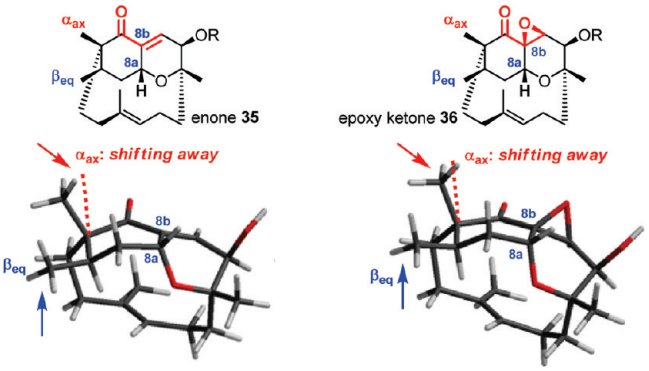


Figure 6. Reaffirming the conformations in **35** and **36**.

we readily oxidized β-hydroxyketone **3** to diketone **26** in 90% yield with Dess–Martin reagent. Unfortunately, enolate generation with Na- or KHMDS and reaction with Commin's reagent ($PhNTf_2$) provided the C-triflated product **37** rather than the enol triflates **38** or **39** (in the box), which may owe to the latter enol triflates suffering from severe allylic strain.

In another serendipitous event, when we decided to eliminate the secondary alcohol to construct the enone through chlorination with $SOCl_2$ and pyridine (see **3-Cl** in Scheme 10), we were surprised to isolate the crystalline cyclic enol–sulfite **40** as the major product in good yield. We were intrigued by the ESI mass spectrum of the compound, as the observed base peak consisted of $(M - SO_2 + Na)^+$. This led us to explore whether a thermal retro-Diels–Alder reaction could afford the desired enone. Indeed, upon treatment of the sulfite in refluxing toluene for 2 h, complete conversion to enone **35** was observed. This truly was a quantitative reaction and required no purification, just heating and solvent removal. It is noteworthy that the chemistry of cyclic enol–sulfites would appear to be an underexplored area with only a few references reporting their isolation being found.[31]

At last, we were able to prepare epoxy ketone **36** from **35** in three steps, as epoxidation of the enone motif in **35** did not take place unless the TES group was removed (Scheme 10). Spartan models reaffirmed our initial conformational assessment of enone **35** and epoxy ketone **36**, which contain sp^3-hybridized C8a and sp^2-hybridized C8b (pseudo-sp^2-hybridized C8b for **36**) at the AB-ring junction (Figure 6) and displayed the desired twisted-boat conformation in the A-ring. We would now investigate the requisite homologation.

Our first attempt at addition to enone **35** in an effort to generate **41** employed a methyl Wittig reagent generated from Ph_3PCH_3Br and *n*-BuLi; however, no reaction was observed (Scheme 11). Surprisingly, enone **35** was unreactive toward Wittig olefination even at 100 °C, and even exposure to MeMgBr provided no reaction! Exposure to MeLi finally afforded the desired tertiary alcohol **42** in good yield as a single diastereomer with the new methyl group having come from the sterically less hindered β-face of **35**.

Encouraged by this outcome, we employed an oxygenated methyllithium source using the PMB-stannane[32] (Scheme 11). Thus, after transmetalation in THF and addition of enone **35**, PMB ether **43** was retrieved. Aside from PMB, the other most common stannane used is the MOM ether,[33] yet the addition to enone **35** was more complicated by the apparent difficult transmetalation, as a significant amount of *n*-butyl addition was observed. Nonetheless, MOM ether **44** was isolated as a white solid. Lastly, we were also able to homologate epoxy ketone **36** via addition of MeLi followed by elimination using $SOCl_2$ to give vinyl epoxide **2**. These experiments illustrate our success in homologating a difficult C5a-carbonyl through a thoughtful conformational analysis that was made possible from meticulous and critical NMR observations.

4. Completion of the Total Synthesis. At this point, we had exerted an immense amount of effort to overcome a number of difficult transformations: (a) oxidation at C3 and C3a; (2) reduction at C8a; (3) homologation at C5a. We had learned to truly respect the unique structural topology that ABD-tricycle **6** possesses, and that it had posed a number of unprecedented challenges. What remained for the total synthesis was the lactol formation (C-ring construction), and this became the most challenging endeavor of the entire total synthesis, not just because of material supplies but once again due to the unique structural topology.

a. The Diene Route. We were not all that interested in the simple methylated compound **42** but decided to see how the tertiary alcohol could be functionalized. We had two possible routes in which alcohol **42** could be used (Scheme 12). The first route (Route A) would involve rearrangement of tertiary alcohol **42** to enone **43**, which could potentially be used to make an allylic

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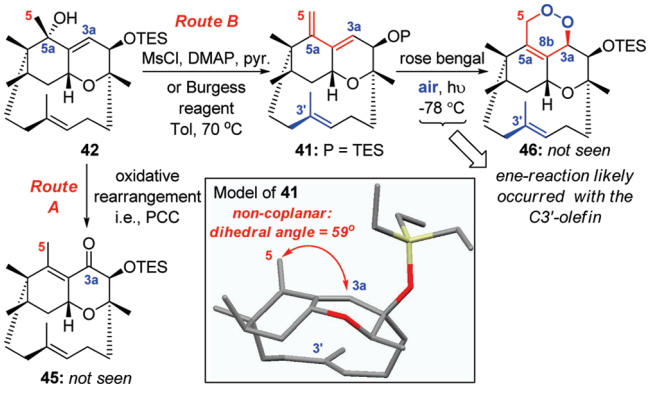
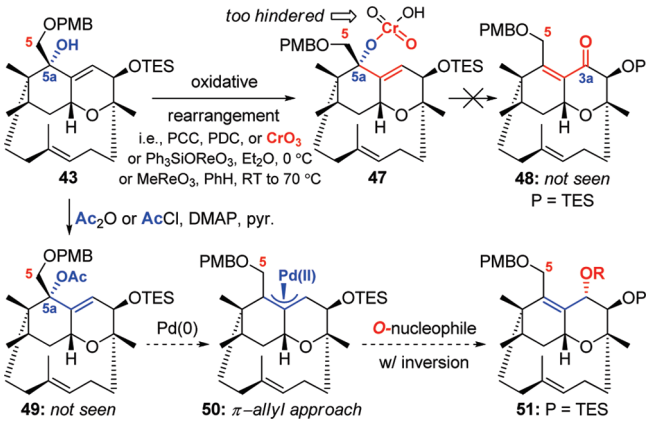
Scheme 12. A Design Flaw in the Diene Route



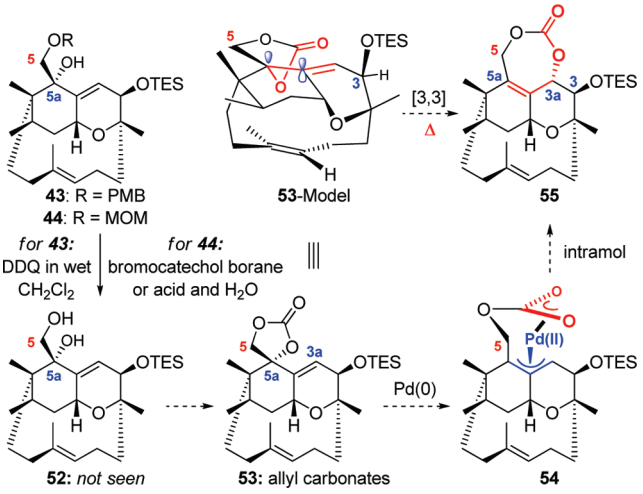
Scheme 13. Initial Thoughts on the Allyl Alcohol Route



alcohol via deprotonation at C5 with subsequent exposure to oxygen electrophiles. Unfortunately, exposure of **42** to PCC produced only unidentified baseline material, instead of enone **45**, thereby quickly eliminating this route.

The other route (Route B) would involve generation of diene **41** and then another $^1O_2$-Diels–Alder reaction to give **46**. We envisioned that reduction of **46** could afford a 1,4-diol en route to C-ring formation. Toward this goal, we investigated the elimination of tertiary alcohol **42** to diene **41**. $POCl_3$ in pyridine was unreactive, while MsCl in DMAP/pyridine provided the diene as an inseparable mixture with some unidentified side products. Alternatively, the Burgess reagent is well-known for its ability to eliminate a wide range of alcohols in a mild manner.[34] Consequently, treatment of alcohol **42** with a small excess of Burgess reagent at 70 °C rapidly induced elimination to diene **41**. Unfortunately, diene **41** again coeluted with byproducts, and we were not able to attain high purity for full characterizations. Nevertheless, we exposed this impure diene to singlet oxygen and found no desired *endo*-peroxide **46**; only decomposition along with possible ene-reaction products were observed. The model of **41** reveals that the diene motif is not coplanar, thereby exposing a potential design flaw in this diene route (Scheme 12). Since the terminal carbons of the diene (C5 and C3a) are at a dihedral angle of 59°, it would be prohibited from participating in any form of cycloaddition as a 4π-component. Hence, we abandoned the diene route altogether.

Scheme 14. The Best Allyl Alcohol Approach Failed



b. The Allyl Alcohol Route. An allylic alcohol route employing PMB-ether **43** or MOM-ether **44** appeared to be even more enticing than the diene route. As shown in Scheme 13, we again attempted oxidative rearrangement using PMB-ether **43** but more aggressively this time in an attempt to construct PMB-protected hydroxy enone **48**, which should be steps away from phomactin A. However, with Cr[35,36]- and Re[37]-based reagents, we observed only slow decomposition of the starting material.

We then wondered if acylation of the tertiary alcohol in PMB-ether **43** would enable the use of Pd π-allyl chemistry through complex **50** to formally migrate the double bond and place the oxygenation as shown in **51** (Scheme 13). Exposure of tertiary alcohol **43** to acylation as well as formylation conditions[38] may have provided the desired acetate or addition product, but the high impurity resulting from the reaction forced us to abandon this approach. At this point we became very interested in obtaining carbonate **53** in the hope of transposing the allylic alcohol stepwise through revisiting palladium π-allyl chemistry via complex **54**,[39−41] or thermally via a seemingly well positioned [3,3]-sigmatropic rearrangement (see model of **53** in Scheme 14).[42] However, an attempted removal of the PMB group using DDQ in CH_2Cl_2/H_2O met with failure[43] while exposure of MOM-ether **44** to bromocatechol borane resulted in extensive decomposition. Further, an attempted acidic hydrolysis resulted in removal of the TES ether, yet not in the desired cleavage product **52**. Given the uncertainty of π-allyl chemistry, we were forced to abandon what we believed at the time was the best route for completing the total synthesis.

c. The Vinyl Epoxide Route. The key to the success of the vinyl epoxide route would reside in a nucleophilic ring-opening of vinyl epoxide **2**. If this ring-opening proceeds regioselectively at C5 via a S_N2' pathway, it would have been most welcome at this stage of our efforts (Scheme 15). An array of conditions, including Pd(0)-mediated and Lewis acidic conditions were screened over a period of almost two years, but we never observed the desired 1,4-diol **57**.[44] Yet, when using $Mg(OTf)_2$, we found a product that appeared to be derived from an S_N1-like process with MeOH adding at C8b. Consequently, we seized the opportunity and synthesized 1,2-diol **58** using $Mg(OTf)_2$ in wet CH_3CN.[45] Resilylating the C3-OH was necessary, as it did not survive the conditions.

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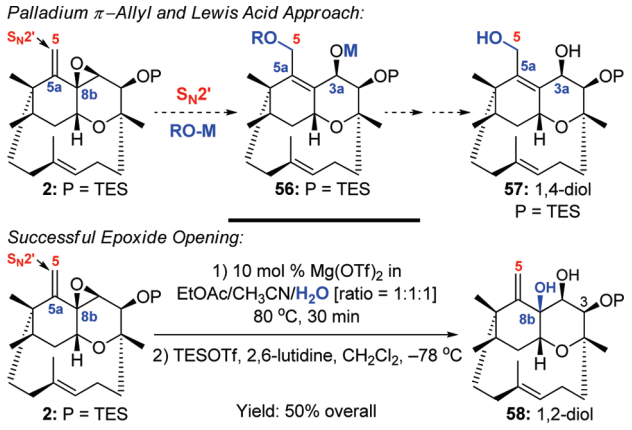
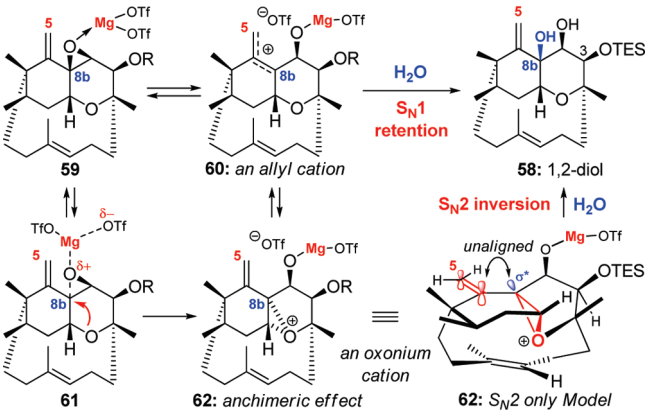
Scheme 15. An Enticing S_N2' Addition Approach



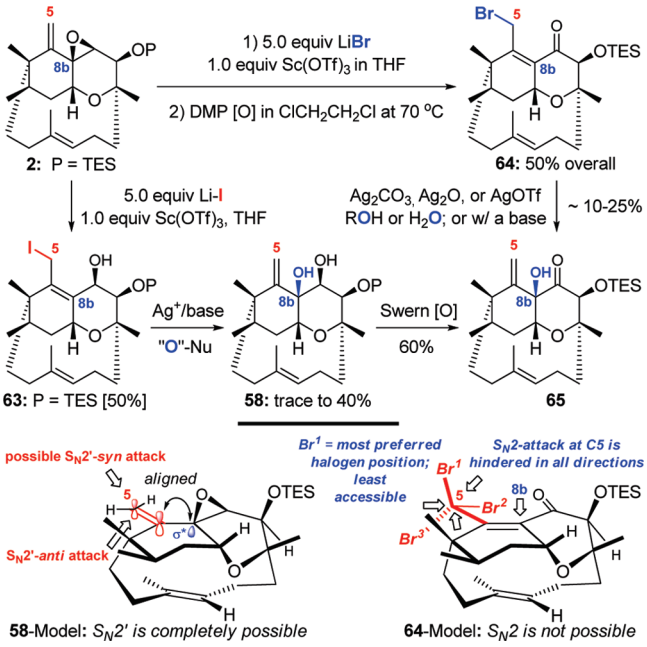
Scheme 16. Possible Pathways to 1,2-Diol 58



The formation of 1,2-diol **58** and a stereochemically retentive S_N1-like process intrigued us. As shown in Scheme 16, the formation of an allyl cation species, such as **60** via activation of **59** that allows for a straightforward retentive S_N1 addition to give **58** represented one possibility, although true cationic species are not often considered as part of intermediates even in Lewis acid-promoted nucleophilic ring-openings. Even if the ring-opening occurs, it would be highly reversible in this context. Perhaps a more plausible pathway would involve an intermediate in which an anchimeric assistance takes place through the pyranyl oxygen atom (**61**→**62**), thereby rendering an overall process of S_N2 addition in an inverted fashion. In addition, from the model, it appeared that if such an anchimeric assistance indeed existed, S_N2 addition could proceed faster, whereas the S_N2' addition pathway could be slowed or even suppressed because the σ^*_{C-O} (of the oxonium bond) is not aligned with the π-system of the C5a-C5 *exo*-cyclic olefin in the conformation assumed by **62**. The following experiment would actually support this assertion.

As shown in Scheme 17, the S_N2' addition pathway was indeed possible when we used LiI, and in the presence of $Sc(OTf)_3$, the desired allyl iodide **63** could be attained. Likewise, when using LiBr followed by DMP oxidation, bromo-enone **64** could be isolated in 50% overall yield. Thus, both **63** and **64** represented possible solutions to our problem. However, attempts to displace

Scheme 17. A Successful S_N2' Addition with Halides



the bromide using Ag salts and an oxygen nucleophile only led to α-hydroxyketone **65** in low yields, while allyl iodide **63** led to 1,2-diol **58**! Despite our high level of confidence for a straightforward S_N2/S_N1-addition, the S_N2' addition pathway was unexpectedly dominant here. Models again revealed the delicate balance between various competing pathways dictated by sterics and/or stereoelectronics. In **58**, the σ^*_{C-O} of the epoxide is now perfectly aligned with the π-system of the C5a-5 *exo*-cyclic olefin, thereby allowing the S_N2' addition to proceed either in an anti and/or syn manner. On the other hand, in bromo-enone **64**, the S_N2 addition pathway (attack at C5) is impeded by surrounding sterics regardless of the position of the bromide leaving group (though it would likely prefer position *Br*^{1}, which provides the least allylic strain). Consequently, the less hindered S_N2' addition pathway through C8b would come to dominate. At this stage, we would pursue a 1,3-allylic alcohol transposition of α-hydroxyketone **65**

We first attempted to transpose alcohol **65** by employing Cr- or Re-based reagents. Unfortunately, these conditions failed to provide any transposed alcohol and instead afforded products attributed to diol cleavage. We then turned back to 1,2-diol **58** (Scheme 18) and were very pleased to find that 1,3-allylic alcohol transposition was successful using PCC on alumina to give **66**, although epoxidation had taken place on the initially transposed olefin at C8b and C5a. Such an epoxidation had been reported by Dauben,[35] Herz,[36] and more recently by McIntosh.[46] Subsequent treatment of **66** with Ph_3P-I_2[47] afforded hydroxy enal **67**. Although it might appear to be counterintuitive, intermediates **A**–**D** would provide a very reasonable description of events that took place in both of these transformations. An ensuing Luche reduction of hydroxy enal **67** gave 1,4-diol **57**. We had finally transposed 1,2-diol **58** to 1,4-diol **57**, which represents the equivalent of the original intent of adding an oxygen nucleophile via S_N2' from vinyl epoxide **2**.

As illustrated in Scheme 19, we then envisioned a Meerwein–Ponndorf–Verley process of self-redox to access hydroxy enone **69** because the proposed transition state **68** looked almost too perfect to

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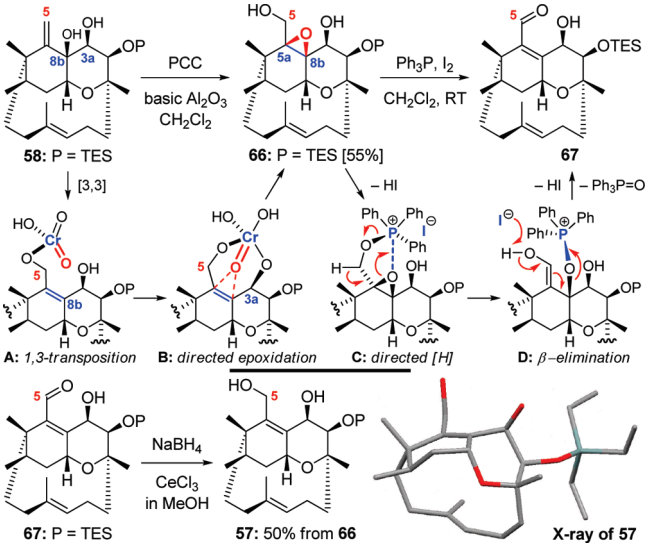
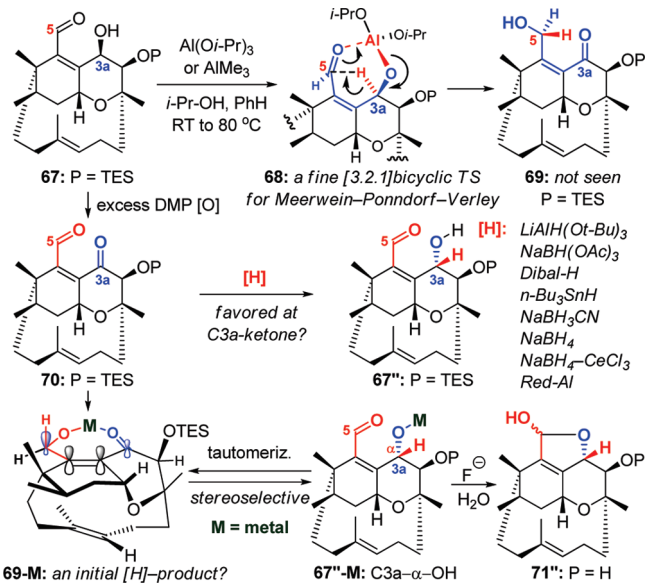
Scheme 18. A Mystery in the Epoxidation



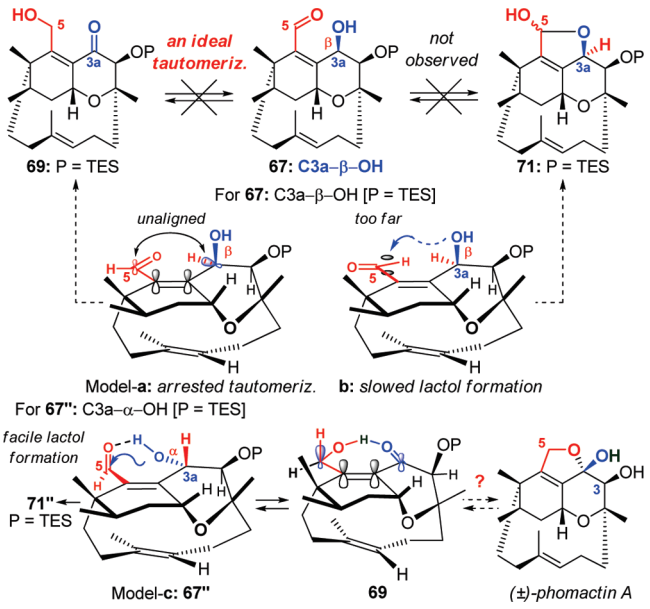
Scheme 19. Attempts to Correct the Oxidation States



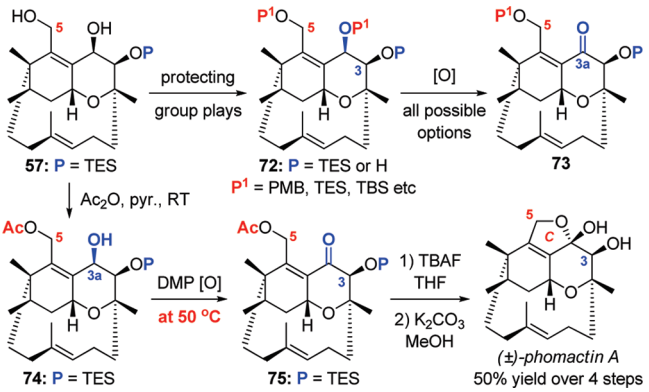
ignore. When that process failed with $Al(Oi\text{-}Pr)_3$ or $AlMe_3$, we turned to keto aldehyde **70** in the hope of being able to reduce the presumably more reactive aldehyde in a chemoselective manner. A number of hydride sources were tried, yet we never found a reduced aldehyde product; instead, it appeared that the C3a ketone had been reduced. We were bewildered by this result for it suggested that a C3a-ketone was more favored than the C5-aldehyde reduction.

A steric argument would not seem sufficient to explain this result; instead, there could be an initial C5-aldehyde reduction to give metal complex **69-M**, and a subsequent stereoselective tautomerization that would lead to **67″-M** in which only the stereoelectronically aligned proton (red) tautomerized exclusively from the top face (Scheme 19). We then subjected **67″** to desilylation to give a product that appeared to be **71″**.

Scheme 20. A Contrast to the C3a-*β*-OH in 67



Scheme 21. The Final Obstacle: Protecting Groups



From these assertions, we would expect **69-M** to lactolize and form the C-ring, yet more intriguingly, hydroxy enal **67** with C3a-*β*-OH did not appear to readily tautomerize to **69**, or lactolize to **71** (Scheme 20), with the former being welcome for an eventual total synthesis. A possible rationale is shown by models of **67** and **67″**, which revealed that the only difference is the C3a stereochemistry. For **67**, H3a is not stereoelectronically aligned for a tautomerization process (see model-a), and C3a-*β*-OH is not well suited for the lactolization because it is pseudoaxial and too far away from C5 (model-b).

On the other hand, for **67″**, we observed a product after TBAF deprotection of the C3 silyl ether that appeared to have undergone lactolization toward **71″** yet not toward phomactin A. Here, the C3a-α-OH is pseudoequatorial and well situated for a facile lactolization (model-c). While H3a in **67″** is stereoelectronically aligned and could lead to an equilibrating tautomerization process with **69**, the facile lactolization likely drives this equilibrium toward the aforementioned lactolized product **71″** (in this case: P = TES). While these speculations are intriguing, it is not known if the actual natural

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product itself would suffer from such a tautomerization process. We decided to forego any further experiments with hydroxy-enal **67** and return our attention to 1,4-diol **57** to complete the total synthesis.

As shown in Scheme 21, after a number of protection strategies failed, we managed to first acylate C5-OH and subsequently found that oxidation of the C3a-OH group employing Dess–Martin periodinane reagent at 50 °C would give enone **75**. Highly concerned with the previous equilibrium discussions, we pursued the ensuing deprotection sequence via first desilylation prior to deacetylation in the hope that lactolization would simply occur to form the lactol C-ring. This sequence was a success, and we were able to complete our total synthesis of (±)-phomactin A in 24 steps from ABD-tricycle **6** and 35 steps from Rawal's amino diene.

CONCLUSION

We have described here our struggles and ultimate success in achieving a total synthesis of phomactin A. Our initial fascination with phomactin A was born out of our interest in applying an intramolecular oxa-[3 + 3] annulation strategy to construct its unique ABD-tricyclic manifold. This exercise would establish a distinctly new approach for a possible total synthesis, with the 12-membered D-ring of phomactin A being assembled simultaneously with the 1-oxadecalin at an early stage. Elaborating the ABD-tricycle to phomactin A would entail four major operations: (1) oxidation at C3/C3a; (2) reduction at C8a; (3) homologation at C5a; (4) lactol formation for the C-ring construction. We believe that in addition to learning new chromenone chemistry, completing a total synthesis of the structurally challenging phomactin A would serve to greatly elevate the visibility of our oxa-[3 + 3] annulation strategy.

The ABD-tricycle represents a unique structural topology that would pose a number of unprecedented challenges. Comprised of a highly strained caged motif, the plane of the AB-ring is in close proximity with the D-ring olefin at C3′; this feature led to an immense struggle in the oxidations at C3/C3a. We identified a solution using $^1O_2$-Diels–Alder followed by a Kornblum–DeLaMare process to cleave the resulting *endo*-peroxo-bridge. While reduction at C8a was fortunately less exciting, requiring only proper electronic deficiency, a critical A-ring conformational analysis was needed to successfully homologate at the sterically congested C5a. This would then set us up to close the C-ring, which would prove to be the most challenging endeavor of all.

Each operation represented a major lesson in organic synthesis, and with each passing lesson we learned to respect the unique structural intricacies of this de novo tricyclic system. While certainly not the most elegant way in completing the synthesis, we have no regrets in pursuing this exercise. In hindsight, it proved to be a fertile training ground for learning to find solutions to any given problem, to think and deduce logically, to observe and characterize meticulously, to be persistent when needed, and to be daring when there is no other way.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data for all new compounds, ^{1}H NMR and ^{13}C NMR spectra, and X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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DEDICATION

‖With the deepest respect and most heartfelt appreciation, this paper is dedicated to Professor Gilbert Stork on the very special occasion of his 90th birthday.

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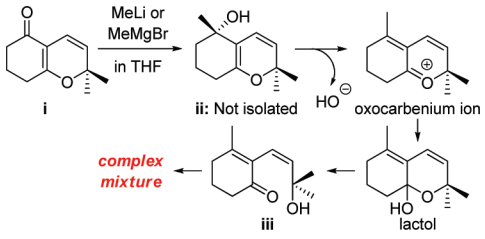
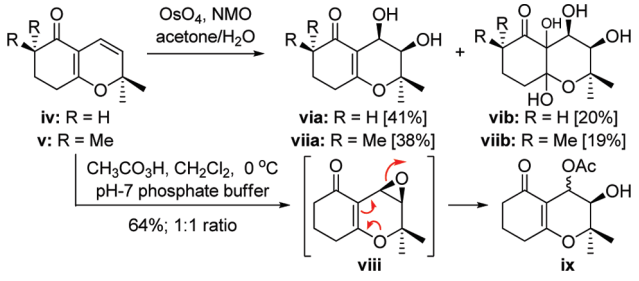
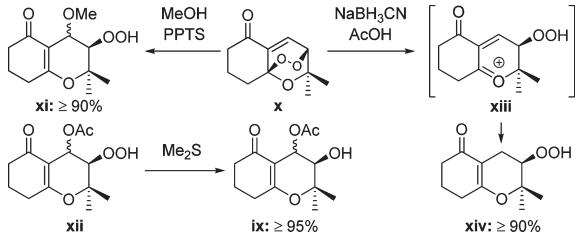


(b) Osmium tetraoxide oxidation of model system **iv** or **v** provided mixtures of diols **via**/**b** and **viia**/**b**, respectively, in modest to good combined yield. We were somewhat surprised that the tetrasubstituted olefin was dihydroxylated at all, even with the more hindered model **i**. In addition, peracetic acid oxidation of **iv** afforded mixtures of the *cis*/*trans*-hydroxy acetates **ix** via indiscriminate ring-opening of the epoxide intermediate **viii** by the acetate anion.



(24) Using model **x**, our first investigations centered on the hope of adding an oxygen nucleophile in a 1,4-fashion into the enone, which could then eliminate the peroxide to restore the strong conjugation of

the vinylogous ester moiety. This possibility was rapidly realized when simply stirring peroxide **x** in MeOH with cat. PPTS, which resulted in the formation of hydroperoxides **xi**. $NaCNBH_3$ reduction of **x** surprisingly did not reduce the O−O bond but did reduce oxocarbenium ion **xiii**, presumably formed by protonation of the peroxide, to afford hydroperoxide **xiv**. Dimethyl sulfide also reduces peroxide **xii** very effectively to **ix**.



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