Total Synthesis of (+/−)-Phomactin A. Lessons Learned from Respecting a Challenging Structural Topology

4 AUTHORS, INCLUDING:

Grant S Buchanan

10 PUBLICATIONS **158** CITATIONS

SEE PROFILE

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

Grant S. Buchanan[a], **Kevin P. Cole**[b], **Yu Tang**[c,*], and **Richard P. Hsung**[a,*]

[a]Division of Pharmaceutical Sciences and Department of Chemistry University of Wisconsin, Madison, WI 53705

[b]Chemical Product R&D, Eli Lilly and Company, Indianapolis, IN 46284

[c]School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072 P. R. China

Abstract
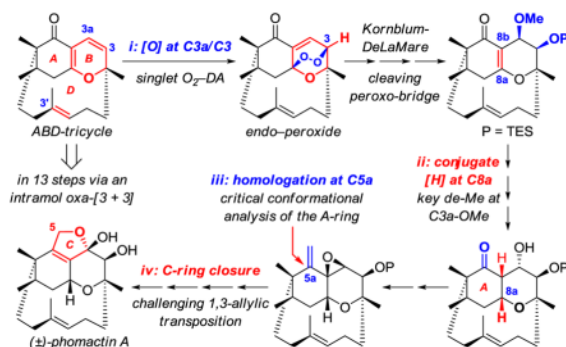
Our struggles and ultimate success in achieving a total synthesis of phomactin A are described. Our strategy features an intramolecular *oxa*-[3 + 3] annulation to construct its unique ABD-tricyclic manifold. Although the synthesis would constitute a distinctly new approach with the 12-membered D-ring 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-*para*-bromobenzoate derivative [see **1**]. In the last fifteen years, the phomactins, and particularly,

rhsung@wisc.edu, tangyu@qibebt.ac.cn.

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 A.

Our strategy towards (±)-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 sixty 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 ABring 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 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 towards electrophiles. In addition, an attempt to 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 due to 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 *2H*-pyran would serve as the diene. As shown in Scheme 2, upon irradiation with a 300-Watt 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 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$_3$·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 minutes, which began to rearrange to the HDA adduct within 30 minutes 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 due to 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 towards phomactin A.

After failed attempts with cationic reduction of hemiketal **17** [TFA/NaCNBH₃, TFA, or BF₃·OEt₂ 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 NaBH₄ in MeOH, a mixture 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 pseudo-axially 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 leading 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 towards 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 due to 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 messy, 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. Literature searching showed that the dihydro-chromandione motif in **24**, or other related systems, was relatively unknown and/or under-investigated, 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 twentieth 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. Towards the goal of homologation, since Tebbe's olefination as well as a Pd-catalyzed cross-coupling of enol 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 towards 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 provoked us to think deeply about how we could re-tool 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, 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 4. 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 pseudo-axial because in addition to deshielding from the α,βu-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 pseudo-axial, 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 towards 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 touch 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 5] 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 pseudo-equatorial with the β-Me group [blue] being pseudo-axial, 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-*oxa*-decalinic AB-ring. With this conformational preference, the β–Me group [blue] is now pseudo-equatorial with the α-Me group [red] turning to occupy the pseudo-axial 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 6]. This set of hybridizations forces the A-ring into a twisted-boat, thereby bending both methyl groups back toward pseudo-equatorial positions. It is noteworthy that this A-ring conformation is very similar to that of phomactin A itself [Figure 1]. More importantly, the β-Me group [blue] remains pseudo-equatorial 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.

(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 alkyl lithium or oxygenated alkyl lithium 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 alkyl lithium 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. Towards that goal, 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 hours, 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 under-explored 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 7], 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 towards 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 methyl lithium source using the PMB-stannane[32] [Scheme 11]. Thus, after transmetallation 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 transmetallation, 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; and (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.

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 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 co-eluted 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. 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 degrees, it would be prohibited from participating in any form of cycloaddition as a 4π-component. Hence, we abandoned the diene route altogether.

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 the 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] Re-silylating the C3-OH was necessary as it did not survive the conditions.

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 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 $Ph_3P\text{-}I_2$[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 pass on. When that 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 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 submitted **67″** to desilylation to give a product that appeared to be **71′**.

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 pseudo-axial 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 towards **71″** yet not towards phomactin A. Here, the C3a–α–OH is pseudo-equatorial 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 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; and (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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. For isolations of phomactins A-G, see (a) Sugano M, Sato A, Iijima Y, Oshima T, Furuya K, Kuwano H, Hata T, Hanzawa H. J Am Chem Soc. 1991; 113:5463.(b) Sugano M, Sato A, Iijima Y, Oshima T, Furuya K, Haruyama H, Yoda K, Hata T. J Org Chem. 1994; 59:564.(c) Sugano M, Sato A, Iijima Y, Oshima T, Furuya K, Kuwano H, Hata T. J Antibiot. 1995; 48:1188. [PubMed: 7490234]

2. For isolation of phomactin H, see: Koyama K, Ishino M, Takatori K, Sugita T, Kinoshita K, Takahashi K. Tetrahedron Lett. 2004; 45:6947.

3. For isolation of related Sch 47918, see: (a) Chu M, Truumees I, Gunnarsson I, Bishop WR, Kreutner W, Horan AC, Patel MG, Gullo VP, Puar MS. J Antibiot. 1993; 46:554. [PubMed: 8500998] For isolations of related (+)-Sch 49026, (+)-Sch 49027, and (+)-Sch 49028, see: (b) Chu M, Patel MG, Gullo VP, Truumees I, Puar MS, McPhail AT. J Org Chem. 1992; 57:5817.For correcting the assignment of Sch 49028, see: (c) Cheing JWC, Goldring WPD, Pattenden G. Chem Commun. 2003:2788.

4. For biosynthesis, see: Tokiwano T, Fukushi E, Endo T, Oikawa H. Chem Commun. 2004:1324.

5. For medicinal chemistry and biological studies, see: (a) Stafforinif DM, McIntyre TM, Zimmerman GA, Prescott SM. Crit Rev in Clin Lab Sciences. 2003; 40:643.(b) Sugano M, Sato A, Saito K, Takaishi S, Matsushita Y, Iijima Y. J Med Chem. 1996; 39:5281. [PubMed: 8978857] (c) Braquet P, Touqui L, Shen TY, Varaftig BB. Pharm Rev. 1987; 39:97. [PubMed: 3303066] (d) Nagase T, Ishii S, Kume K, Uozumi N, Izumi T, Ouchi Y, Shimizu T. J Clin Investigations. 1999; 104:1071. (e) Zhu X, Lambertino AT, Houghton TJ, McGilvra JD, Xu C, Rawal VH, Leff AR. Life Sciences. 2003; 73:3005. [PubMed: 14519449]

6. For an excellent review on synthetic efforts toward phomactins, see: Goldring WPD, Pattenden G. Acc Chem Res. 2006; 39:354. [PubMed: 16700534]

7. Also see: Cole KP, Hsung RP. ChemTracts. 2003; 16:811.

8. For synthetic approaches, see: (a) Foote KM, Hayes CJ, Pattenden G. Tetrahedron Lett. 1996; 37:275.(b) Chen D, Wang J, Totah NI. J Org Chem. 1999; 64:1776. [PubMed: 11674261] (c) Seth PP, Totah NI. J Org Chem. 1999; 64:8750.(d) Seth PP, Totah NI. Org Lett. 2000; 2:2507. [PubMed: 10956533] (e) Kallan NC, Halcomb RL. Org Lett. 2000; 2:2687. [PubMed: 10990428] (f) Chemler SR, Danishefsky SJ. Org Lett. 2000; 2:2695. [PubMed: 10990430] (g) Seth PP, Chen D, Wang J, Gao X, Totah NI. Org Lett. 2000; 56:10185.(h) Foote K, John M, Pattenden G. Synlett. 2001:365.(i) Mi B, Maleczka R. Org Lett. 2001; 3:1491. [PubMed: 11388849] (j) Chemler SR, Iserloh U, Danishefsky SJ. Org Lett. 2001; 3:2949. [PubMed: 11554815] (k) Houghton T, Choi S, Rawal VH. Org Lett. 2001; 3:3615. [PubMed: 11700095] (l) Mohr PJ, Halcomb RL. Org Lett. 2002; 4:2413. [PubMed: 12098260] (m)DiBlasi CM, Hamblett CL, Leighton JL. Abstracts of Papers, 224th National Meeting of the American Chemical SocietyBoston, MAFall;2002 :ORGN-364.(n)DiBlasi CM. PhD Dissertation. Columbia University2003Thesis Advisor: Professor James L. Leighton(o) Balnaves AS, McGowan G, Shapland PDP, Thomas EJ. Tetrahedron Lett. 2003; 44:2713.(p) Cheing JWC, Goldring WPD, Pattenden G. Chem Commun. 2003:2788.(q) Ryu K, Cho YS, Jung SI, Cho CG. Org Lett. 2006; 8:3343. [PubMed: 16836401] (r) Huang J, Wang H, Wu C, Wulff WD. Org Lett. 2007; 9:2799. [PubMed: 17580880] (s) Seth PP, Chen D, Wang J, Gao X, Totah NI. Tetrahedron Lett. 2007; 48:4605. [PubMed: 18575571] (t) Peng W, Lee CS. Synlett. 2008:142.Furuya YK, Hata T, Kuwano H. J Antibiot. 1995; 48:1188. [PubMed: 7490234] (u) Ciesielski J, Canterbury DP, Frontier AJ. Org Lett. 2009; 11:4374. [PubMed: 19736911] (v) Shapland PDP, Thomas EJ. Tetrahedron. 2009; 65:4201.(w) Schwartz KD, White JD. Org Lett. 2011; 13:248. [PubMed: 21162546]

9. For total synthesis of (+)-phomactin D, see: (a) Miyaoka H, Saka Y, Miura S, Yamada Y. Tetrahedron Lett. 1996; 37:7107.For total synthesis of (±)-phomactin B2, see: (b) Huang J, Wu C, Wulff WD. J Am Chem Soc. 2007; 129:13366. [PubMed: 17929921] For total synthesis of (±)-phomactin G, see: (c) Goldring WPD, Pattenden G. Org Biomol Chem. 2004; 2:466. [PubMed: 14770224]

10. For total synthesis of (±)-phomactin A, see: (a) Goldring WPD, Pattenden G. Chem Commun. 2002:1736.For detailed full papers, see: (B) Diaper CM, Goldring WPD, Pattenden G. Org Biomol Chem. 2003; 1:3949. [PubMed: 14664384] (c) Foote KM, Hayes CJ, John MP, Pattenden G. Org Biomol Chem. 2003; 1:3917. [PubMed: 14664383]

11. For total synthesis of (+)-phomactin A, see: Mohr PJ, Halcomb RL. J Am Chem Soc. 2003; 125:1712. [PubMed: 12580592]

12. For an initial communication on the regiochemical issues in the intramolecular oxa-[3 + 3] annulation, see: (a) Cole KP, Hsung RP. Org Lett. 2003; 5:4843. [PubMed: 14653688] For an initial communication on recognition of the unique structural topology of ABD-tricycle **6**, see: (b) Cole KP, Hsung RP. Chem Commun. 2005:5784.For an initial communication on revised and enantioselective approach to ABD-tricycle **6** see: (c) You L, Hsung RP, Bedermann AA, Kurdyumov AK, Tang Y, Buchanan GS, Cole KP. Adv Syn Catal. 2008; 350:2885.For an initial communication on completion of our total synthesis of (±)-phomactin A, see: (d) Tang Y, Cole KP, Buchanan GS, Li G, Hsung RP. Org Lett. 2009; 11:1591. [PubMed: 19260663]

13. Harrity JPA, Provoost O. Org Biomol Chem. 2005; 3:1349. [PubMed: 15827625]

14. Hsung RP, Kurdyumov AV, Sydorenko N. Eur J Org Chem. 2005; 1:23.

15. Hsung RP, Wei L-L, Sklenicka HM, Shen HC, McLaughlin MJ, Zehnder LR. Trends in Heterocyclic Chem. 2001; 7:1–24.

16. Hsung, RP.; Cole, KP. Strategies and Tactics in Organic Synthesis. In: Harmata, M., editor. Elsevier Science. Vol. 4. Pergamon Press; Oxford, UK: 2004. p. 41

17. Buchanan GS, Feltenberger JB, Hsung RP. Curr Org Syn. 2010; 7:363.

18. (a) Hsung RP, Shen HC, Douglas CJ, Morgan CD, Degen SJ, Yao LJ. J Org Chem. 1999; 64:690. [PubMed: 11674130] (b) Hsung RP, Wei LL, Sklenicka HM, Douglas CJ, McLaughlin MJ, Mulder JA, Yao L. Org Lett. 1999; 1:509.(c) Shen HC, Wang J, Cole KP, McLaughlin MJ, Morgan CD, Douglas CJ, Hsung RP, Coverdale HA, Gerasyuto AI, Hahn JM, Liu J, Wei LL, Sklenicka HM, Zehnder LR, Zificsak CA. J Org Chem. 2003; 68:1729. [PubMed: 12608785] (d) Kurdyumov AV, Lin N, Hsung RP, Gullickson GC, Cole KP, Sydorenko N, Swidorski JJ. Org Lett. 2006; 8:191. [PubMed: 16408872]

19. For recent related recent studies, see: (a) Sagar R, Park J, Koh M, Park SB. J Org Chem. 2009; 74:2171. [PubMed: 19193119] (b) Yamamoto Y, Itonaga K. Org Lett. 2009; 11:717. [PubMed: 19117489] (c) Zhong W, Lin F, Chen R, Su W. Synthesis. 2008:2561.(d) Hubert C, Moreau J, Batany J, Duboc A, Hurvois JP, Renaud JL. Adv Synth Catal. 2008; 350:40.(e) Zhu M-K, Wei Q, Gong L-Z. Adv Synth Catal. 2008; 350:1281.(f) Brioche JCR, Goodenough KM, Whatrup DJ, Harrity JPA. J Org Chem. 2008; 73:1946. [PubMed: 18254645] (g) Yavari I, Sabbaghan M, Hossaini Z. Synlett. 2008:1153.(h) Zhong W, Lin F, Chen R, Su W. Synthesis. 2008:2561.(i) Brioche JCR, Goodenough KM, Whatrup DJ, Harrity JPA. Org Lett. 2007; 9:3491. [PubMed: 17685530] (j) Lee YR, Xia L. Synthesis. 2007:3240.(k) Epstein OL, Rovis T. J Am Chem Soc. 2006; 128:16480. [PubMed: 17177379] (l) Sheibani H, Mosslemin MH, Behzadi S, Islami MR, Saidi K. Synthesis. 2006:435.

20. For earlier work, see: (a) Appendino G, Cravotto G, Tagliapietra S, Nano GM, Palmisano G. Helv Chim Acta. 1990; 73:1865.(b) Schuda PF, Price WA. J Org Chem. 1987; 52:1972.(c) de March P, Moreno-Mañas M, Casado J, Pleixats R, Roca JL. J Heterocycl Chem. 1984; 21:85.(d) Tietze, LFv; Kiedrowski, G.; Berger, B. Synthesis. 1982:683.(e) de Groot A, Jansen BJM. Tetrahedron Lett. 1975; 16:3407.

21. For some of the earliest work in oxa-[3+ 3] annulations, see: (a) Ikawa M, Stahmann MA, Link KP. J Am Chem Soc. 1944; 66:902.(b) Seidmna M, Link KP. J Am Chem Soc. 1952; 74:1885.

22. For some applications of oxa-[3 + 3] annulations in natural product syntheses, see: (a) Seijiro Hosokawa S, Matsushita K, Tokimatsu S, Toriumi T, Suzuki Y, Tatsuta K. Tetrahedron Lett. 2010; 51:5532.(b) Jeso V, Nicolaou KC. Tetrahedron Lett. 2009; 50:1161. [PubMed: 20161287] (c) Yamashita S, Iso K, Hirama M. Org Lett. 2008; 10:3413. [PubMed: 18630922] (d) Brioche JCR, Goodenough KM, Whatrup DJ, Harrity JPA. Org Lett. 2007; 9:3941. [PubMed: 17760451] (e) Kurdyumov AV, Hsung RP. J Am Chem Soc. 2006; 128:6272. [PubMed: 16683764] (f) Liu H, Siegel DR, Danishefsky SJ. Org Lett. 2006; 8:423. [PubMed: 16435850] (g) Monda M, Puranik VG, Argade NP. J Org Chem. 2006; 71:4992. [PubMed: 16776532] (h) Olson BS, Trauner D. Synlett. 2005:700.(i) Malerich JP, Maimone TJ, Elliott GI, Trauner D. J Am Chem Soc. 2005; 127:6276. [PubMed: 15853334] (j) Lee YR, Wang X. Bull Korean Chem Soc. 2005; 26:1933.(k) Sunazuka T, Handa M, Nagai K, Shirahata T, Harigaya Y, Otoguro K, Kuwajima I, Õmura S. Tetrahedron. 2004; 60:7845.(l) Hu H, Harrison TJ, Wilson PD. J Org Chem. 2004; 69:3782. [PubMed: 15153009] (m) Kurdyumov AV, Hsung RP, Ihlen K, Wang J. Org Lett. 2003; 5:3935.

[PubMed: 14535747] (n) Hsung RP, Cole KP, Zehnder LR, Wang J, Wei LL, Yang XF, Coverdale HA. Tetrahedron. 2003; 59:311.(o) Malerich JP, Trauner D. J Am Chem Soc. 2003; 125:9554. [PubMed: 12903998] (p) Cole KP, Hsung RP. Tetrahedron Lett. 2002; 43:8791.(q) Sunazuka T, Handa M, Nagai K, Shirahata T, Harigaya Y, Otoguro K, Kuwajima I, Ōmura S. Org Lett. 2002; 4:367. [PubMed: 11820881] (r) McLaughlin MJ, Hsung RP. J Org Chem. 2001; 66:1049. [PubMed: 11430073] (s) Zehnder LR, Hsung RP, Wang J, Golding GM. Angew Chem Int Ed. 2000; 39:3876.

23. (a) We treated a model system **i** with MeLi or MeMgBr in the hope of producing alcohol **ii**. However, we only observed a complex mixture, implying instability of the initial Me-Li addition and that it may lead to the reactive oxocarbenium ion, which could then undergo a number of possible reactions.
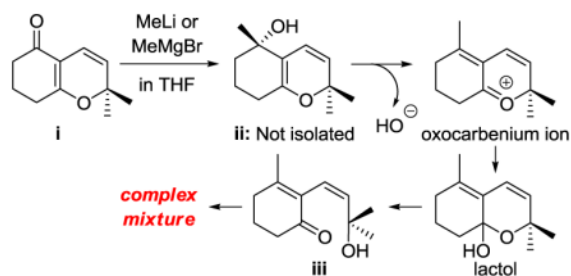
(b) Osmium tetraoxide oxidation of model system **iv** or **v** provided mixtures of diols **via/b** and **viia/b**, respectively in modest to good combined yield. We were somewhat surprised that the tetrasubstituted olefin was dihydroxylated at all even with the more hindered model **i**. In addition, 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.
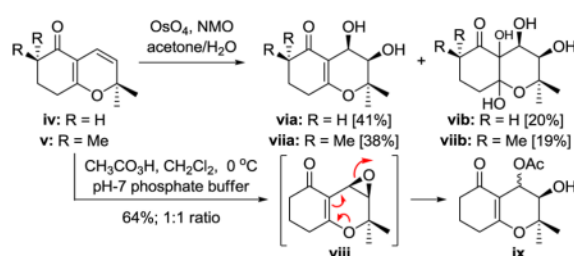
24. Using model **x**, our first investigations centered on the hope of adding an oxygen nucleophile in a 1,4-fashion into the enone, which could then eliminate the peroxide to restore the strong conjugation of the vinylogous ester moiety. This possibility was rapidly realized when simply stirring peroxide **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**.
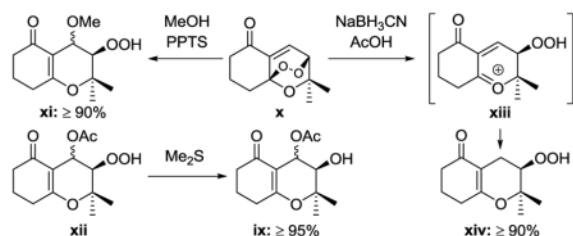
25. Tietze LF, Rackelmann N. Pure and Appl Chem. 2004; 76:1967.For beautiful reviews on tandem reactions, see: (a) Tietze LF. Chem Rev. 1996; 96:115. [PubMed: 11848746] (b) Tietze LF, Beifuss U. Angew Chem, Int Ed. 1993; 32:131.(c) Tietze LF. J Heterocycl Chem. 1990; 27:47.

26. Kornblum N, DeLaMare HE. J Am Chem Soc. 1951; 73:880.

27. See the supporting information for (a) solvolysis of **17** with *i*-PrOH; and (b) acylation of **17**.

28. See the supporting information for details about the demethylation of **4**.

29. Jung ME, Lyster MA. J Org Chem. 1977; 42:3761–3764.

30. (a) See the supporting information for the unsuccessful attempts at a direct C5a-homologation with Tebbe's reagent and a Pd(0)-coupling with a cyclic enol phosphate; and see Nicolaou KC, Shi GQ, Gunzer JL, Gartner GP, Yang Z. J Am Chem Soc. 1997; 119:5467.

31. Sheppard WA. J Org Chem. 1968; 33:3297.

32. Ferezou J-P, Julia M, Li Y, Liu L-W, Pancrazi A, Porteu F. Bull Soc Chim Fr. 1994; 131:865.

33. Shiozaki M. J Org Chem. 1991; 56:528–532.

34. Burgess EM, Penton HR, Taylor EA. J Am Chem Soc. 1970; 92:5244.

35. Dauben WG, Michno DM. J Org Chem. 1977; 42:682.

36. Sundararaman P, Werner Herz W. J Org Chem. 1977; 42:813.

37. For some examples, see: (a) Gordon MS, Jacob J, Espenson JH, Jensen JH. Organometallics. 1998; 17:1835.(b) Wang G, Jimtaisong A, Luck RL. Organometallics. 2004; 23:4522.(c) Osborn JA, Bellemin-Laponnaz S, Gisie H, Le Ny JP. Angew Chem Int Ed. 1997; 36:976.(d) Grubbs RH, Morrill C. J Am Chem Soc. 2005; 127:2842. [PubMed: 15740106] (e) Osborn JA, Le Ny JP, Bellemin-Laponnaz S. Tetrahedron Lett. 2000; 41:1549.

38. Attempts at direct transposition of allylic alcohol **43** using AcOH were attempted. See the supporting information for details.

39. (a) Overman LE, Zipp GG. J Org Chem. 1997; 62:2288. [PubMed: 11671546] (b) Overman LE, Campbell CB, Knoll FM. J Am Chem Soc. 1978; 100:4822.(c) Overman LE, Knoll FM. Tetrahedron Lett. 1979; 20:321.

40. Grieco PA, Takigawa T, Bongers SL, Tanaka H. J Am Chem Soc. 1980; 102:7587.

41. Batey RA, Lee EE. J Am Chem Soc. 2005; 127:14887. [PubMed: 16231944]

42. For a related precedent, see: Hünig S, Reichelt H. Chem Ber. 1986; 119:1772.

43. During the reaction, the starting material was consumed as monitored by TLC with a more-polar, highly fluorescent product was formed, which did not elute from the chromatography column, even after flushing with EtOAc. We believe that the oxonium intermediate from the PMB removal process is too hindered for the attack of water to form the hemiacetal intermediate, and is instead intercepted by the tertiary alcohol, and oxidized to give a quinone.

44. See the supporting information for conditions used to open the epoxide.

45. For related protocols, see: (a) Boyer FD, Hanna I. J Org Chem. 2005; 70:1077. [PubMed: 15675876] (b) Iranpoor N, Shekarriz M, Shiriny F. Syn Commun. 1998; 28:347.

46. For a recent example, see: (a) Chai Y, McIntosh MC. Tetrahedron Lett. 2004; 45:3269. [PubMed: 20376298] Also see: (b) Sundararaman P, Herz W. J Org Chem. 1977; 42:813.(c) Chu A, Mander LN. Tetrahedron Lett. 1988; 29:2727.

47. Wydra H, Paryzek Z. Tetrahedron Lett. 1984; 25:2601.
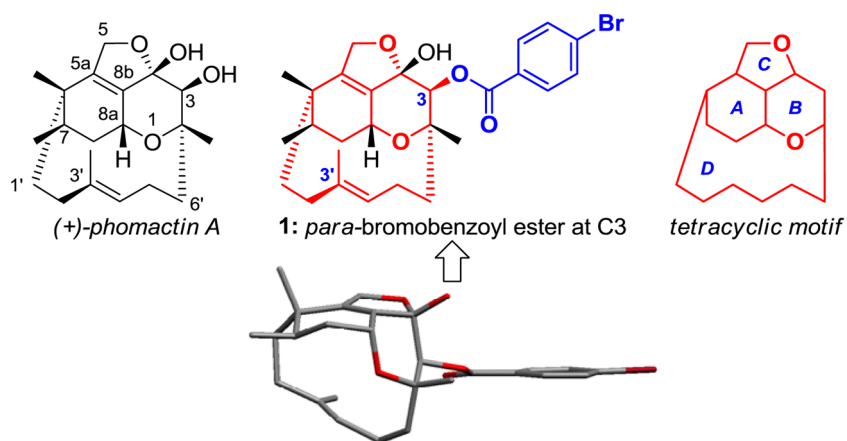
Figure 1.
(+)-Phomactin A and Its C3-*Para*-Bromobenzoyl Ester Derivative.
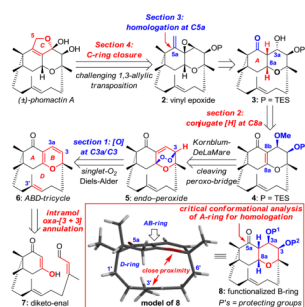
Figure 2.
Challenges in the Synthesis.
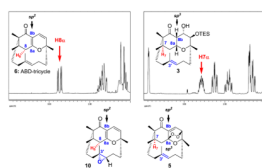
Figure 4.
^{1}H NMR of ABD-Tricycle **6** and β–Hydroxyketone **3**.
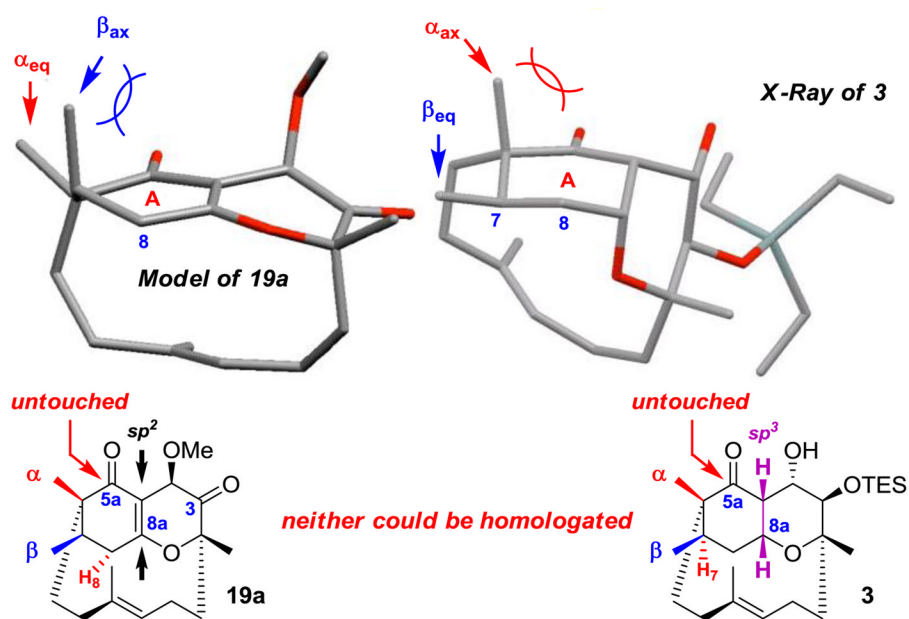
Figure 5.
Conformation Analysis for **19a** and **3**.
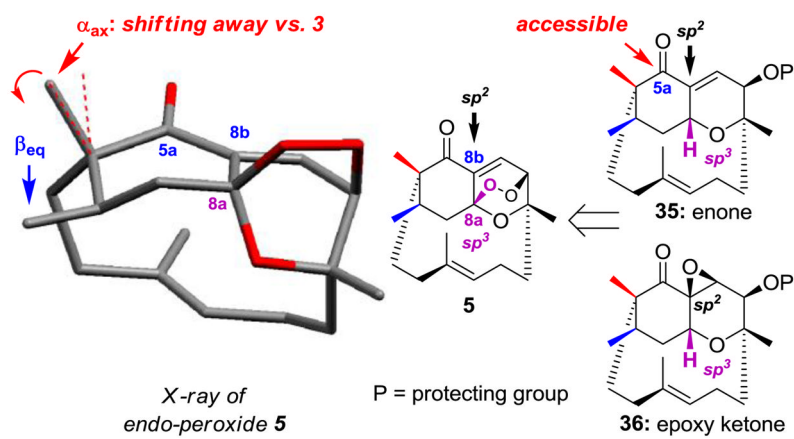
Figure 6.
Rationale for Choosing **35** and **36**.
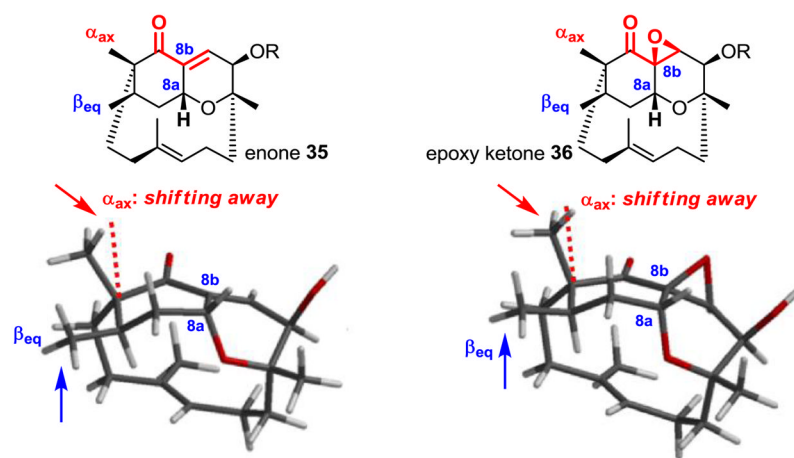
Figure 7.
Reaffirming the Conformations in **35** and **36**.
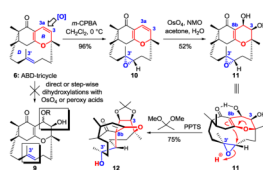
Scheme 1.
C3–3a Oxidation: B-Ring Reactivity Versus C3′-Olefin.

Scheme 2.
The *Endo*-Peroxide Solution.
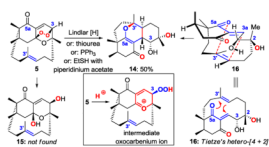
Scheme 3.
Surprise in the *Endo*-Peroxide Reduction.
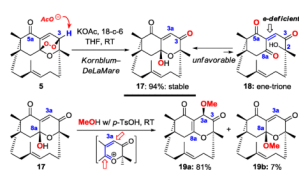
Scheme 4.
Endo-Peroxide Ring-Opening and C3a-Oxygenation.
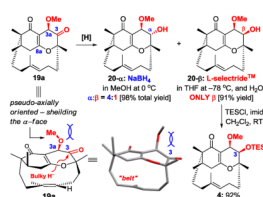
Scheme 5.
The Critical C3-Ketone Reduction.
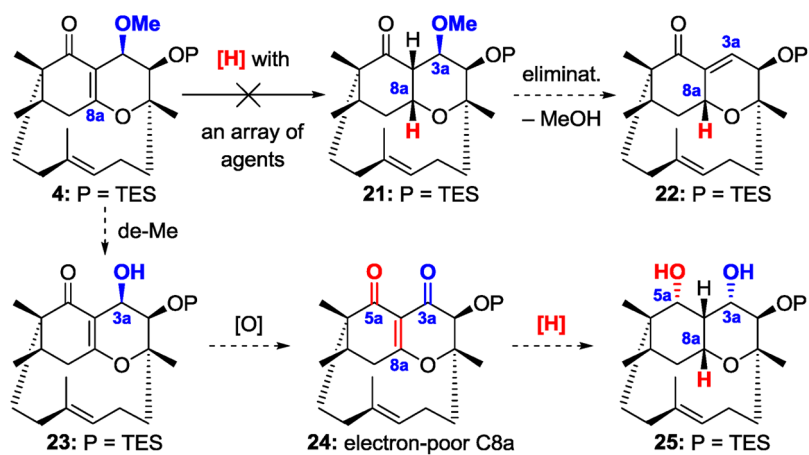
Scheme 6.
Attempting to Directly Reduce C8a.
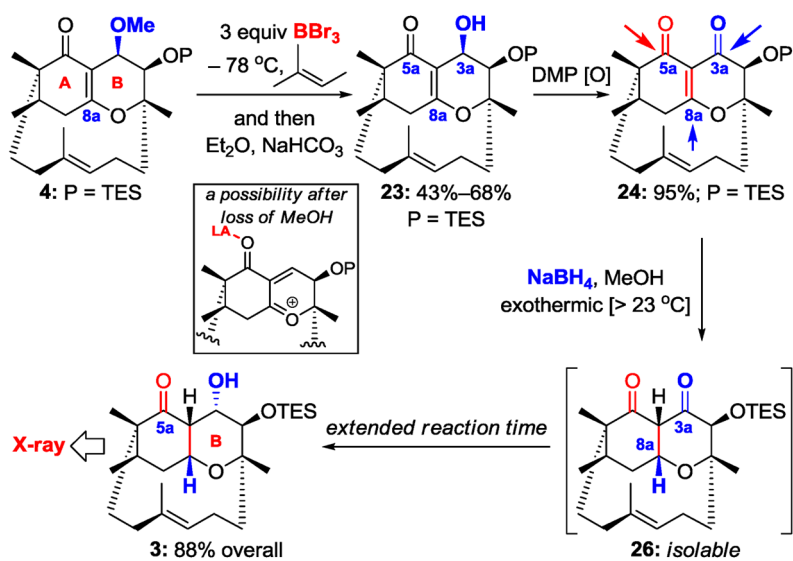
Scheme 7.
Successful Demethylation and Oxidation.
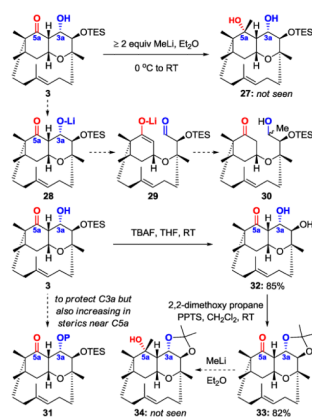
Scheme 8.
Unsuccessful Attempts at MeLi Addition.
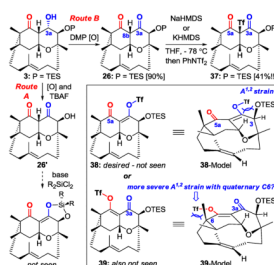
Scheme 9.
Problems in the Vinylogous Ester Synthesis.
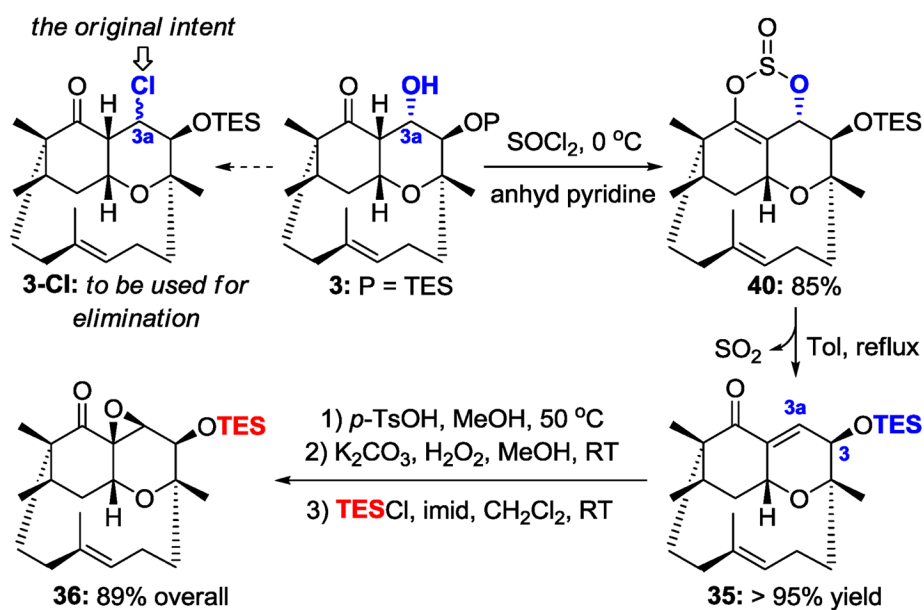
Scheme 10.
Serendipitous Success in the Enone Synthesis.
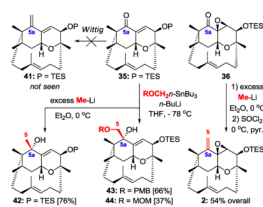
Scheme 11.
Successful C5a-Homologations.
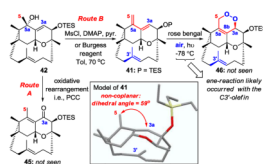
Scheme 12.
A Design Flaw in the Diene Route.
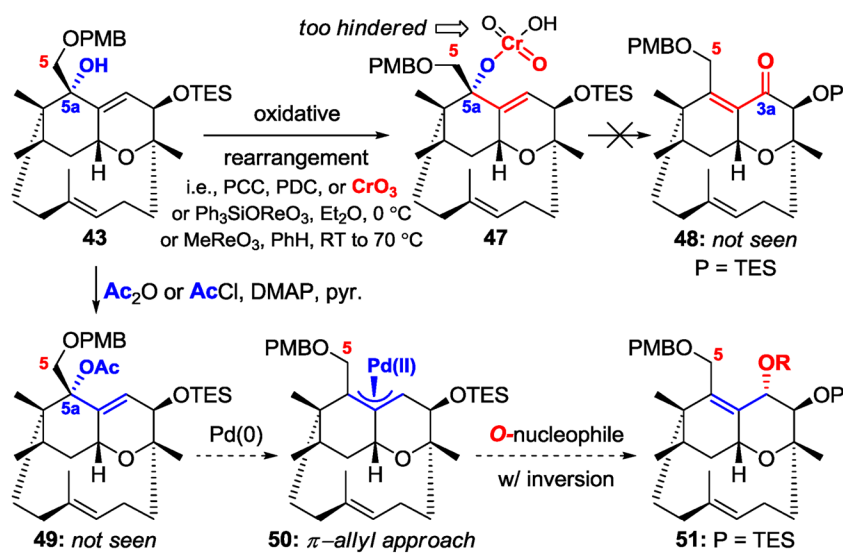
Scheme 13.
Initial Thoughts on the Allyl Alcohol Route.
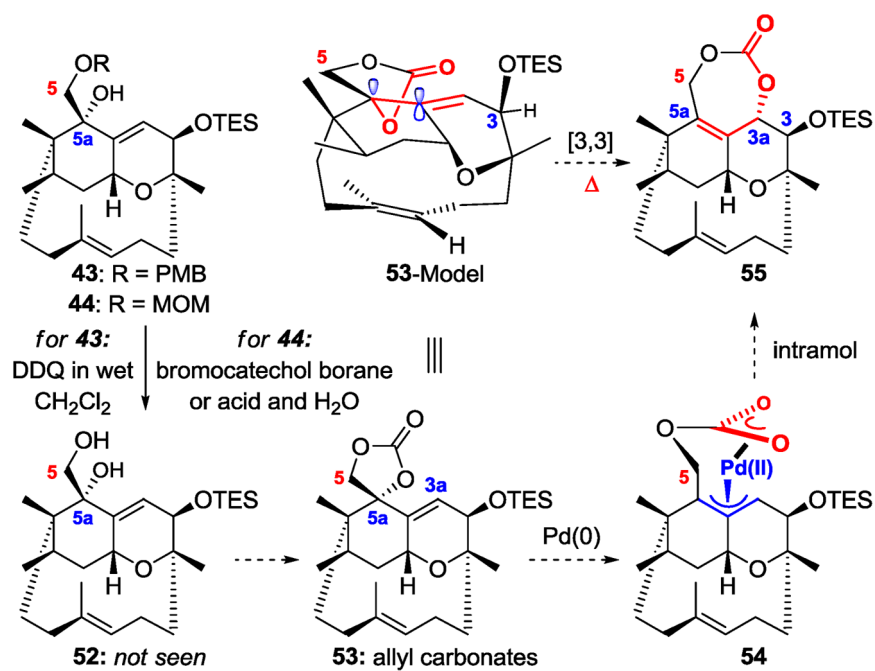
Scheme 14.
The Best Allyl Alcohol Approach Failed.
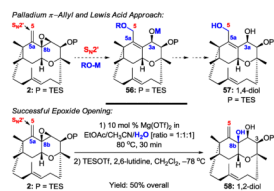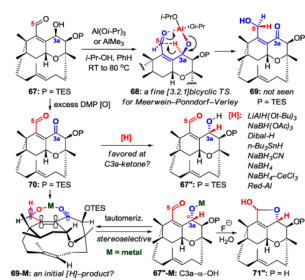
Scheme 15.
An Enticing S_N2'–Addition Approach.
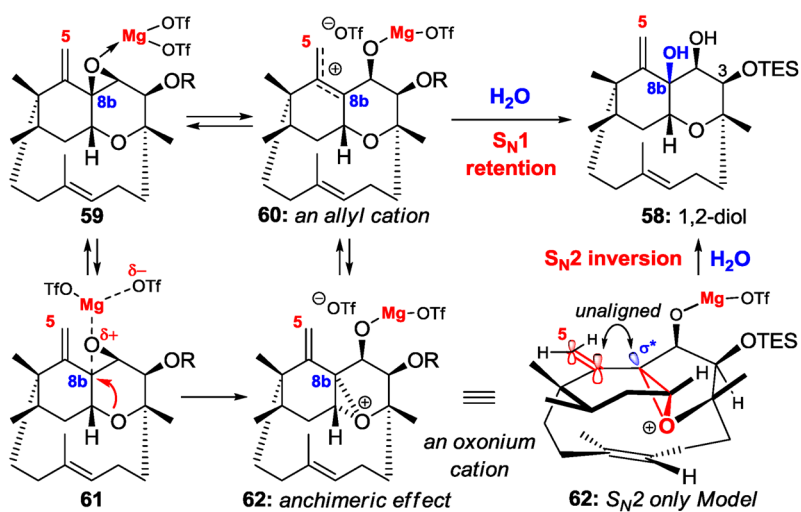
Scheme 16.
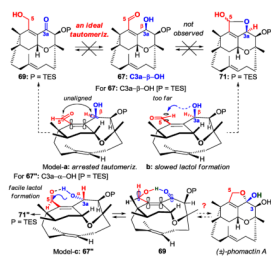Possible Pathways to 1,2-Diol **58**.
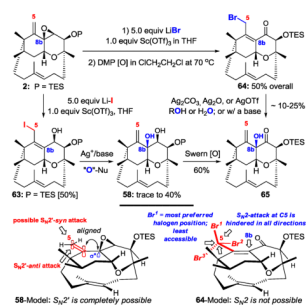
Scheme 17.
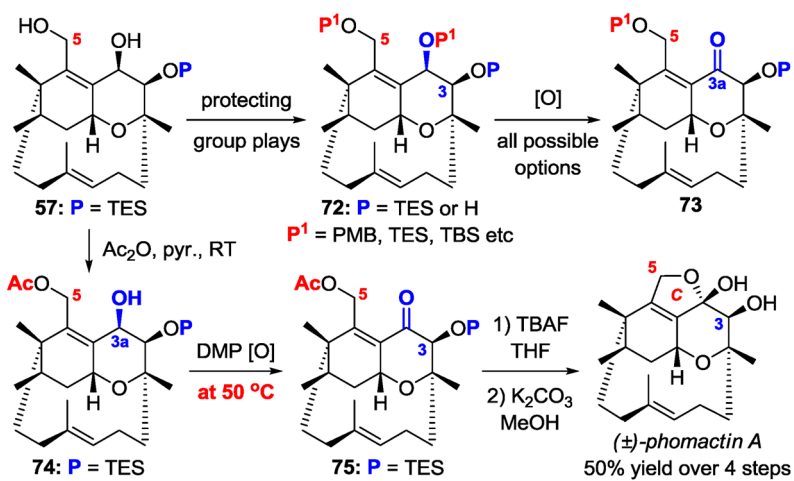A Successful S_N2' Addition with Halides.
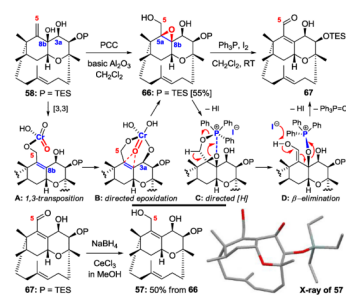
Scheme 18.
A Mystery in the Epoxidation.

Scheme 19.
Attempts to Correct the Oxidation States.

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

Scheme 21.
The Final Obstacle: Protecting Groups.