Studies towards Selective Synthesis of Resveratrol-based Oligomeric Natural Products

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Abstract

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Chapter 1. Recent synthetic approaches towards the resveratrol family of oligomeric natural products

This chapter outlines some of the past and present efforts in the field of resveratrol-based oligomeric natural product synthesis. Both biosynthetic approaches and stepwise synthetic approaches are discussed to present the current level of understanding regarding the controlled synthesis of these molecules in order to place the studies described in chapter 2 and 3 in better context.

Chapter 2. Development of a general synthetic method towards different dimeric structures of the resveratrol family

We have developed a general approach to achieve selective synthesis of the major dimeric architectures within the resveratrol family with the use of a unique key common intermediate possessing three aryl rings. Syntheses of three subclasses of resveratrol dimeric structures are reported.

Chapter 3. Synthetic efforts towards dihydrobenzofuran-containing higher order resveratrol oligomers

Finally, this chapter describes our current studies towards more complex members of the resveratrol family. A concise approach for dihydrobenzofuran ring installation on the seven-membered carbon framework of resveratrol-based oligomers is reported. The formation of 7,5-
fused ring natural product cores via Friedel-Crafts cyclizations provides controlled access to some of the highly complex architectures within the resveratrol family.
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To my family and friends
Chapter 1

Recent Synthetic Approaches towards the Resveratrol Family of Oligomeric Natural Products
1.1 Introduction

In 1940, resveratrol (1) was identified in the roots of a Japanese plant called white hellebore (Veratrum grandiflorum O. Loes) by Takaoka.\(^1\) Since then, this relatively small natural product has been isolated from more than 72 different plants around the world, including various Dipterocarpaceae species in Southeast Asia and China, and grapevines from North America, Africa, and Europe.\(^2\) In nature, plants produce resveratrol (1) to enable their survival, with this molecule being a phytoalexin to fight infections caused by bacteria or fungi.\(^3\) Over the past several decades, this small molecule has drawn great attention from the scientific community for its impressive anti-inflammatory, cardiovascular protective, anti-aging, and tumor suppressant activity shown in both in vivo and in vitro analyses.\(^4\) For instance, research has shown that the non-stabilized radicals generated from 1 could selectively inhibit both catalytic activities of COX-1 (Scheme 1) involved in prostaglandin synthesis, which is unique in comparison to other non-steroidal anti-inflammatory drugs (NSAID) currently in clinical use since most of them are COX-2 selective.\(^5\)

Alongside with 1, a large family of stereochemically diverse resveratrol-based oligomers (such as 4 to 15) are also produced by plants to fight environmental stress.\(^6\) To date,
several hundred distinct natural products derived from resveratrol as a synthetic building block have been isolated and reported.\textsuperscript{7} These structures include a wide range of complex carbocyclic and heterocyclic systems, and they also possess powerful anti-oxidant capability and interesting biological activities that includes antifungal, anticancer, and HIV-inhibitory properties. For example, one resveratrol tetramer, vaticanol C (12), has marked tumor activities against colon carcinoma cell lines with potency levels much higher than resveratrol (1) (IC\textsubscript{50} = 3.0 \mu M and 3.2 \mu M in HL60 and SW480 cell lines, respectively).\textsuperscript{8} Furthermore, preliminary screens have shown that 10 acts through an apoptosis-inducing interaction with mitochondrial proteins directly, which is unique from many other apoptosis-inducing chemotherapeutics in clinical use such as etoposide and camptothecin. Unfortunately, despite all the promising early findings on these compounds (such as 4 to 15), no extensive biological studies have been performed on this large group of natural products and their analogues. One of the main reasons that limit such scientific explorations is the inability of synthetic chemistry to prepare resveratrol’s more complex oligomers in large quantities. Therefore, to develop a concise and general synthetic route towards these compounds has remained a keen interest in the synthetic community over the past decades, and a considerable amount of prior work has been done in this field \textit{via} both biosynthetic approaches and stepwise synthetic approaches. This introductory chapter will outline some previous efforts through selected examples in the two areas mentioned above in order to place the solutions developed during the course of the research described in Chapter 2 and 3 in better context.
1.2 Biosynthetic hypothesis

In nature, the synthesis of resveratrol (1) in plants involves four enzymes that act at different stages of the biosynthetic pathway: phenylalanine ammonia lyase (PAL), cinnamic acid 4-hydroxylase (C4H), 4-coumarate:CoA ligase (4CL) and stilbene synthase (STS). The biosynthesis of resveratrol starts with the amino acid phenylalanine. The first two enzymes in this reaction series, PAL and C4H, convert phenylalanine into p-coumaric acid (4-coumaric acid), which then is attached to the pantetheine group of Coenzyme-A by 4CL to produce 4-coumaroyl-CoA. Finally, STS catalyzes the terminating condensation of resveratrol (1) from one molecule of 4-coumaroyl-CoA and three molecules of malonyl-CoA, which originate from fatty acid biosynthesis.
Although resveratrol (1) is known to be the product of an enzyme-based synthesis, how the dimeric and higher-order structures are constructed is still uncertain. Often, radical reactions are expected to be involved in the synthesis of resveratrol oligomers. Scheme 2 shows a proposed biosynthesis for ε-viniferin (18). Although many radicals can be formed from resveratrol, this proposal only shows reactivity of two possibilities. These two radicals unite to give 17, a material that undergoes rearomatization and phenol attack onto the remaining quinone methide to afford the desired compound.  

![Scheme 2: Biosynthesis of ε-viniferin (18) from resveratrol.](image)

Sotheeswaran et al. proposed that resveratrol oligomers can be classified biogenetically into two groups, I and II, depending on whether they have dihydrobenzofuran rings (group I) or not (group II). In group-I compounds, the dihydrobenzofuran ring of the final target is attributed to that of ε-viniferin (18). Scheme 3 shows one selected example of a plausible biogenetic pathway of group I resveratrol-based tetramers based on this notion, one that involves coupling of two ε-viniferin (18) molecules.
The group II polyphenols, by contrast, are proposed to be formed directly from resveratrol monomers without ε-viniferin (18) being an intermediary. One proposed mechanism involves a step-by-step coupling of three resveratrol units via hypothetical radicals. Examples for this group are seen in the biogeneses of the trimers stemonoporol (28) and copalliferol A (29) and from trans-resveratrol (Scheme 4).12
1.3 Biosynthetic approaches

One major challenge to synthesize resveratrol-based oligomers through biosynthetic approaches is to achieve high control in radical positioning since varied resonance alternatives of the resveratrol radical can lead to many different products. Most past endeavors towards the synthesis of resveratrol oligomers have followed biomimetic design strategies and have encountered this challenge in their endeavors. In 1977, Langcake and Pryce first reported their efforts to dimerize resveratrol molecules through exposure of 1 to horseradish peroxidase in the presence of H$_2$O$_2$ (Scheme 5).$^{13}$ Along with recent similar experiments conducted by Sako and co-workers who used single-electron transfer reagents (K$_3$[Fe(CN)$_6$], Ag$^+$, Cu$^+$, Cu$^{2+}$, and Mn$^{II}$ derivatives) as radical initiators,$^{14}$ no desired ε-viniferin (18) was ever characterized from all these attempts. In all cases, non-natural analog 33, which can be formed by uniting the O- and C-centered radicals of the most readily oxidized phenol within 1, was obtained as the predominant product and characterized. Of course, experiments of this type did not result in quantitative yields, and many other products, besides 33, can be found within the reaction mixtures, though the identity of these molecules has not been determined.
Niwa’s group reported the biotransformation (with help of horseradish, soybean, and fungus peroxidase) and chemical conversion of oligostilbenes and resveratrol. In this study, resveratrol was treated with several kinds of peroxidases and inorganic reagents so as to prepare ε-viniferin (18). Among several inorganic reagents, thallium(III) nitrate in methanol at –50 °C gave the desired ε-viniferin (18) in 68% yield based on recovered starting material; however, only 30% of the starting material was consumed during the course of reaction. On the other hand, no peroxidases tested in their experiments provided ε–viniferin (18), but a mixture of some other stilbene dimers, such as 33, pallidol (9), and leachianol F (34), was obtained.
Moreover, the only other known example of oxidative coupling of resveratrol (1) to generate ε-viniferin (18), with a moderate yield of 30%, was reported by Lin’s group, which described the chemical-induced dimerization by means of methanol and a one-electron oxidant (FeCl₃·6H₂O, Scheme 7).¹⁷

All the studies mentioned above have shown that biosynthetic approaches to resveratrol oligomerization starting with 1 are extremely difficult to achieve in a controlled and selective manner and the dominant product of such type of investigations often result in an analog/structural isomer of a natural product. Thus, more recent efforts have shifted towards using resveratrol derivatives to address the challenge of controlled radical generation of the resveratrol framework. For example, Hou and his co-workers utilized bulky t-butyl groups on the
resveratrol framework to favor a regioselective coupling reaction between the C-centered radicals of the \textit{para}-disposed phenol. In this case, the treatment of modified resveratrol 35 with horseradish peroxidase (HRP) and H₂O₂ in aqueous acetone gave the desired coupling product (37) in 35% yield. Subsequently, the \textit{t}-butyl substituents were efficiently removed from the substrate through exposure to strong acid to complete first total synthesis of quadrangularin A (38) in 11 steps.¹⁸ This strategy demonstrates the protective power of \textit{t}-butyl groups on the resveratrol skeleton for the alternative reactive positions upon radical generation to ensure regioselectivity of the coupling.

More recently, this approach has been applied to the synthesis of other naturally occurring oligostilbenes, such as gneafrcicanin F (40) and gnemonol M (41).¹⁹ Here, the regioselective, oxidative coupling of 5-\textit{tert}-butylisorhapontigenin (39) catalyzed by FeCl₃·6H₂O was used as the key synthetic step. However, whether this method can be applied to other stilbene core structures still requires further investigations.
Another example along the same lines was performed by Velu’s group who examined the reactivity of partially protected form of resveratrol upon oxidation using an efficient one electron oxidant.\(^{20}\) In their study, methyl ethers were used to mask two of the three hydroxyl groups in resveratrol (42), leaving only the para-disposed phenol free for radical formation. By looking at dimerization of 42 with the aid of different metal oxidants in different solvent systems, stilbenoid oligomers with totally different carbon skeletons were obtained, revealing very interesting reactivity (Scheme 10). For instance, when 42 was treated with AgOAc, the δ-viniferin skeleton (43) was obtained, and a solvent effect was observed: when the reaction was carried out in CH\(_2\)Cl\(_2\), the yield was roughly twice the one obtained from CH\(_2\)Cl\(_2\)/MeOH (2:1 v/v). On the other hand, when the same starting compound was treated with FeCl\(_3\)·6H\(_2\)O, the reaction outcome was different for each solvent: protected amelopsin F (46) and pallidol (45) were formed only in CH\(_2\)Cl\(_2\). The addition of methanol to the FeCl\(_3\)·6H\(_2\)O/CH\(_2\)Cl\(_2\) mixture gave rise to a new tricuspidatol A analogue (44). One explanation for the differences in reactivities with different oxidants is that AgOAc is a soft Lewis acid that tends to form complexes with the olefinic bridges of stilbenes, while Fe\(^{3+}\) species are hard Lewis acids that prefer to interact with the oxygen atoms of the phenolic groups. In addition, the solvent effect can be attributed to MeOH’s ability to solvate silver ion and displace H\(_2\)O molecules from FeCl\(_3\)·6H\(_2\)O complexes. In general, the biomimetic dimerization of stilbenes by means of one-electron oxidants usually
leads to low yields of dimeric products with low selectivity, and most compounds formed from such reactions are not natural products.

Another piece of pioneer work in the field of biomimetic approach towards oligomerization of resverarol was conducted by the Niwa group, who adopted the concept of looking at a higher-order structure in this family, especially ε-viniferin (18), as an alternative starting group for the preparation of many dimeric cores. In this case, they used a a non-selective, acid-catalyzed rearrangement reaction to obtain ampelopsin B (8), ampelopsin D (6), isoampelopsin D (50), and ampelopsin F (7) along with several other side products in differing amounts (Scheme 11). In the case of path a, the reaction starts with the protonation of the double bond, followed by cyclization to form a seven-membered ring to give ampelopsin B (8). In the case of path b, an acid initially protonates the oxygen atom on the dihydrobenzofuran ring, an event which is followed by nucleophilic attack of the double bond. Then, a five-membered ring intermediate is formed. To prepare both 6 and 50, the subsequent deprotonation of the intermediate gives the natural product. To obtain 7, the second nucleophilic attack of the double
bond against the intermediate and the subsequent deprotonation gives the dibenzobicyclo[3,2,1]-octadiene skeleton.

Another example of using ε-viniferin (18) as a starting compound for oligomerization to synthesize higher-order structures was also presented by the Niwa group. Here, 18 was oxidatively coupled with resveratrol (1) under the action of horseradish peroxidase (HRP) in acetone to form davidiol A (54), which is a resveratrol trimer with a fused 7,5-bicyclic system. Although the reaction gave a slightly better yield of 2.7% when the coupling resveratrol partner was protected, complicated mixtures containing many other natural products and natural product analogs were formed. In contrast, when treating only resveratrol with HRP, neither ε-viniferin (18) nor dividiol A (54) was found. As one can see from the examples above, selectivity and control still remain a major challenge in building resveratrol-based oligomers from ε-viniferin...
(18), but their study highlights an intriguing idea that 18 might be the real building block for many of the higher-order structures of the family in nature since other family members that cannot be synthesized from resveratrol directly could be derived from this dimeric structures.

As a final count, besides radical chemistry, cation-based dimerizations of stilbene derivatives have also been explored. Scheme 13 shows one example in this field carried out by the Aguirre group.23 The stilbene derivatives with a general structure (55) underwent retro-Ritter reactions to regioselectively generate cations to promote cyclodimerization to afford various indane (59) and tetralin (60) ring systems similar to the resveratrol family. Unfortunately, application of this method to appropriately functionalized resveratrol phenols has not yet proven effective to give the same carbon skeleton, leading usually to tetralin products.
1.4 Stepwise synthetic approaches

In recent years, stepwise synthetic approaches have gained popularity among the synthetic community for resveratrol oligomerization since most biogenetic methods have provided inefficient results. However, those methods usually are specifically tailored towards one or two structure subsets of these natural products in order to achieve controlled synthesis. The syntheses selected in this section are categorized based on different molecular architectures possessed by the targeted natural products.

One example to prepare the indane-containing resveratrol dimers was presented by the Sarpong group in 2009, who used a Pd-catalyzed Larock annulation to provide expedient access to a subset of resveratrol-derived natural products (Scheme 14). Starting from a brominated permethylated resveratrol (62), a Heck-type cyclization cascade between 61 and 62 afforded indene 64 in 53% yield, which is an oxidized form of quadrangularin A (38). Then, oxidative cyclization of 64 using iron(III) chloride provided pentalene 65, which possesses the core for pallidol (9). In addition, a Larock pentannulation between o-bromobenzaldehyde (63) and 61 provided a 1:1 mixture of 66 and 67, which could be transformed to paucifloral F (4) via hydrogenation and global deprotection. This synthetic sequence is highly convergent and proceeds in three steps from tolane 61 and bromobenzaldehyde 63. This simple and efficient method could potentially be applied to synthesize more complex, functionally diverse resveratrol-based analogues.
A more recent example in the field of indane-containing resveratrol oligomers synthesis was reported by the Sun group,²⁵ wherein a concise synthetic strategy involving an intermediary 2-arylchalone (68) was used to prepare quadrangularin A (38) and pallidol (9) starting from commercially available 3,5-dimethoxybenzoic acid. As indicated in Scheme 15, a Lewis acid-catalyzed Nazarov cyclization of 68 afforded the trans-2,3-aryl indanone 69 in 85% yield. Next, in order to install the olefin functionality in the molecule, a Ramberg–Bäcklund olefination sequence was performed to provide the permethylated quadrangularin A (70), which could then undergo hydroboration/oxidation, intramolecular Friedel–Crafts alkylation and deprotection to complete the total synthesis of pallidol (9). One important note regarding this synthesis is that this sequence followed the studies presented later in Chapter 2, and is predicated on our group’s discoveries.
Another different synthesis was conducted by Kim and Choi to access the seven-membered carbocyclic ring systems within the resveratrol family, such as shoreaphenol and malibatol A (Scheme 16).\textsuperscript{26} Aryloxyketone 72 was chosen as the starting compound, and a regioselective Bi(OTf)\textsubscript{3}-catalyzed cyclodehydration provided ready access to 3-arylbenzofuran (73). To introduce an aryl group at the C2 position of the benzofuran, a Pd-catalyzed direct C–H activation of benzofuran and subsequent cross-coupling with aryl halide was successfully carried out to provide 74. Next, a Corey–Chaykovsky protocol for the synthesis of epoxide was adopted to furnish the trans-epoxide 75, setting the stage for the following seven-membered ring formation. Finally, a stereoselective epoxide ring opening \textit{via} nucleophilic attack by the neighboring aromatic group catalyzed by Bi(OTf)\textsubscript{3} was implemented to construct the seven-membered ring within the targeted natural products (76 and 77). This final C–C bond formation
represents a possible mechanism for Nature’s formation of seven-membered rings within the family.

Scheme 16. Synthesis of a permethylated form of shoreaphehol and malibatol A based on two key Bi(OtF)₃-catalyzed reactions.

In addition to the example described above for the polyphenolic benzofuran formation, Chen and his co-workers recently reported a general strategy for the synthesis of hexacyclic dimeric resveratrol polyphenolic benzofurans and its application to the total synthesis of malibatol A (81) and shoreaphehol (82). As shown in Scheme 17, with benzyl ether 78 in hand, the formation of the benzofuran ring proceeded very smoothly through its initial benzylic deprotonation (LiTMP), followed by an intramolecular cyclization and subsequent dehydration, to deliver pentacyclic benzofuran (79). Next, epoxidation of stilbene 79 under the bromohydrin protocol (NBS, NaOH), followed by treatment of the resulting epoxide (80) with BBr₃ resulted in the concomitant cyclization and global demethylation as a one-pot process to afford racemic malibatol A (81) as a single diastereoisomer in 20% yield. Finally, oxidation of malibatol A (81) in the presence of PDC afforded shoreaphehol (82) with a modest yield of 46%. One note worth mentioning here is that the epoxide opening step with BBr₃ to form 81 still requires further
investigation to confirm and fully understand the rationale behind the stereoselectivity as opposite stereochemistry was observed when similar reactions were performed in our laboratory.

The final synthesis listed in this chapter targeted a completely different set of resveratrol-based natural products: hopeanol (90) and hopeahainol A (89), which are two unique members within the resveratrol family with modest antitumor activity profiles. A biosynthetic hypothesis proposed by the isolation chemists postulated the hopeanol (83) as the precursor of the hopeahainol A (82) as these two compounds differ in terms of their aryl oxidation patterning. The first total synthesis of these two natural products was first reported by Nicolaou, Chen and coworkers in 2009 (Scheme 18). Starting from the benzylic alcohol (83), a number of reactions, including esterification, Grignard reaction and deprotection of the TBS group, transformed the
starting compound into hydroxy ester (84). Treatment of 84 with p-TsOH in CH₂Cl₂ initiated an intramolecular Friedel–Crafts reaction to afford the rearranged polycycle 86. Then, exposure of δ-lactone 86 to KOtBu in THF led, upon quenching with aqueous NH₄Cl solution, to olefinic γ-lactone 88. The mechanism for this process was a Grob-type fragmentation/lactonization cascade. The final stages of the synthesis involved an epoxidation of the resulting olefin with mCPBA and an intramolecular Friedel–Crafts reaction, followed by oxidation to afford, upon global deprotection, hopeahainol A (89). Despite a hypothesis that defined hopeanol (83) as the biosynthetic precursor to hopeahainol A (89), the latter was converted under basic conditions (NaOMe in MeOH) to hopeanol (90) in 80% yield.

1.5 Conclusion

This chapter has outlined two main approaches towards total synthesis of resveratrol-based oligomers. Resveratrol and its higher-order structures are particularly interesting due to their unique structures and impressive biological properties as evidenced by recent research results on their chemistry and biology. Although biomimetic studies have offered very
interesting insights into how resveratrol oligmerization happens in nature, achieving selectivity using these methods is still a major challenge that requires further exploration. Developed around different appropriate building blocks that are remote from resveratrol itself, stepwise synthetic approaches have started to gain more attention, and have provided controlled and selective synthesis towards certain members of the family. Despite all these successes, a universal approach to access diverse carbogenic complexity within the resveratrol class is still needed as dozens of different strategies are required to cover the entire family if only targeting individual subclass one by one. Over the past five years, a tremendous amount of research effort has been devoted by our group to develop a general method to selectively synthesize various resveratrol oligomers with different molecular architectures. The next two chapters will outline part of the studies carried out within our polyphenol research program.

References:


Chapter 2

Development of a General Synthetic Method towards Different Dimeric Structures of the Resveratrol Family
2.1 Introduction

As discussed in Chapter 1, most attempts to date to prepare resveratrol-based oligomers have derived from strategies based on their proposed biosynthesis (Scheme 1). Radical generation from single-electron transfer via various chemicals or enzymes in nature is expected to promote formation of one or many higher-order structures in the family. Unfortunately, biosynthetic approaches often result in low yields of oligomerization with low selectivity. Moreover, in cases where some selectivity has been observed, the dominant product is typically the non-natural product analog (3), which can be obtained by uniting the oxygen- and carbon-centered radicals of the most readily oxidized phenol within resveratrol (1). Although a total synthesis of quadrangularin A (8) was achieved in 35% yield through a highly engineered resveratrol analog by the Hou group, it still could not offer a general solution to access the diverse carbogenic frameworks of this group of natural products. In addition, cation-based polymerization of functionalized resveratrol-based phenols has not been reported to successfully provide the correct natural product structures in a controlled manner. On the other hand, although stepwise synthetic methods have gained more and more attention towards this family of natural products in recent years, they usually are designed to target only one or two structure subsets of these molecules in order to conquer the selectivity problem presented in biomimetic synthesis. Thus, dozens of different syntheses would be required to prepare the entire family. Prior to our work, no solution had been reported to selectively afford most dimeric or any higher-order structures in the resveratrol family. The development of such a solution was our main objective.
2.2 Strategic considerations – identification of common building blocks

Much like all the previous work in this field described in Chapter 1, we started our quest towards resveratrol oligomerization using protected forms of resveratrol (1) as starting materials. Although our proposed ideas to dimerize two resveratrol analog units appeared reasonable at first glance, all attempts in our laboratory failed to form the first carbon-carbon bond between the two molecules. Scheme 2 shows some selected key approaches we carried out. Unfortunately, these efforts only led to loss of the bromine handle without productive C–C bond formation.
Given the results presented in the literature and these failures of our own, we concluded that dimerization of resveratrol-like structures to achieve selective oligomer synthesis would be quite challenging without any of the chemicals or enzymes that may be involved in catalyzing such transformations in nature (assuming that nature even has controlled synthesis as a goal). As such, we hypothesized that a different building block, one more structurally removed from resveratrol (1), was required in this case to address the problems faced in attempting to control multiple reactive sites through biomimetic pathways. Thus, we examined every structure isolated and characterized within this class to look for any general patterns that might serve as a potential clue for the proper alternate starting material and synthetic approach. After intensive study, we noted that one interesting feature that resides in a few natural products (18 – 23) is the number of aromatic rings (Scheme 3).
For instance, in contrast to most structures that would appear to be generated from direct resveratrol oligomerization, diptoindonesin D (20) and paucifloral F (18) possess only three aromatic rings instead of four. In fact, a number of natural products in the entire class have three, five, seven, and even nine aryl rings. Although these odd numbers of aromatic rings in nature are likely formed from degradation of normal resveratrol-based oligomers [paucifloral F (18) could result from cleavage of the lone alkene within ampelopsin D (21), for example], they inspired the idea that perhaps an alternate strategy to synthesize these compounds would be to build them up in a more stepwise fashion through the addition of single aryl rings onto resveratrol (1). Based on the above observation, we proposed a key building block with three aryl rings arrayed around the same core structure (24) which we hoped could be used to gain controlled access to the structural complexity of the entire family through judicious choice of reagents (Scheme 4). In this structure, the resveratrol-like B ring and the C ring can be modified and coupled with additional functional groups to provide a wide range of precursors to different family members. The next several
sections describe our exploitation of this synthetic design to uncover numerous diverse dimeric architectures.

Scheme 4. Proposed universal three aryl ring precursors capable of accessing a diverse range of structures in the resveratrol family.

2.3 Preparation of building blocks and total synthesis of indane-based members of the resveratrol class

2.3.1 Preparation of the building blocks

Scheme 5 shows a general approach for preparation of the key intermediates anticipated to access the carbogenic diversity of the resveratrol family at the dimeric level. Starting from 3,5-dimethoxybenzaldehyde or 3,5-dimethoxybenzoic acid (25), hydride reduction with NaBH$_4$ or LiAlH$_4$ provided the corresponding benzyl alcohol, which was followed by Br replacement (SN$_2$), aromatic bromination (by electrophilic aromatic substitution), and phosphonate formation (26). Then, the first C–C bond-forming event in the synthesis was achieved through a Horner-Wadsworth-Emmons olefination between the phosphonate (26) and a selected aldehyde to give a stilbene derivative (27). Finally, nucleophilic addition of the lithiated form of 27 to an appropriate benzaldehyde derivative led to the desired bi-benzylic alcohol (28). Within this whole sequence, the following points are notable: 1) all the intermediates listed in Scheme 5 (compounds 29-31) were prepared in high yield even when conducted on scales of up to 50 g; 2) no chromatographic separations were required for any of the steps, with a final crystallization being all that was needed to access the desired intermediates in pure form.
With this triaryl intermediate in hand, our hope was that exposure of 28 and its derivatives to various electrophiles (bromine, oxygen, and proton) could enable the controlled generation of the diverse carbogenic cores possessed by the natural products within the resveratrol family.

2.3.2 Total synthesis of indane-based members of the resveratrol class

To test this hypothesis with common intermediates 28, we targeted several indane-containing resveratrol oligomers. Our initial efforts involved exposure of these bis-benzylic alcohols to various Brønsted and Lewis acids. As shown in Scheme 6 using intermediate 29 for illustrative purposes, we believed that treatment with acid would initially activate the alcohol to generate cation 32 followed by a regioselective cyclization by the double bond to afford 33; the aryl rings on the newly formed five-membered ring were expected to be arrayed in a trans fashion to minimize strain built up in the transition state. The resultant cation could be attacked by the acid’s nucleophilic conjugate base directly. As indicated in Scheme 6, a number of different nucleophiles could be installed onto the indane ring system; for instance, exposure of 29 to stoichiometric BiCl₃ or BiBr₃ enabled the direct introduction of halogen atoms on the five-
membered ring in good yield (~80%). On the other hand, if an acid with a non-nucleophilic counterion was used, the addition of a different nucleophile can intercept the sequence at cation 33 prior to its β-elimination to access different cyclic products. Interestingly, this cyclization required a stoichiometric amount of a proton source or a Lewis acid, as no reaction was detected when catalytic amounts of the reagents were used.

With this newly developed chemistry in hand, we were ready to tackle some of the simple indane-based natural products of the resveratrol family (Scheme 7). Controlled exposure of 29 to TFA in CH₂Cl₂ at −30 °C to −20 °C for 5 h followed by a basic workup to hydrolyze the resultant trifluoroacetate ester afforded alcohol 39 in 75% yield. One important note regarding this cyclization is that reaction temperature and time required careful control. At −78 °C, the carbocation formed immediately upon addition of the acid as the solution turned a deep purple color instantaneously. The nucleophilic attack of the alkene was observed once the reaction was warmed to −60 °C, but it proceeded slowly at this temperature. The cyclization proceeded more rapidly with increasing temperature, but other products were also formed as the temperature
increased. After much experimentation, we found that reaction temperatures between –30 ºC and –20 ºC were optimal to allow this reaction to proceed quickly and efficiently while minimizing formation of by-products. Next, the resulting alcohol (40) was smoothly converted into one of the simplest resveratrol-based natural products, paucifloral F (18), in 84% overall yield through Dess–Martin periodinane mediated oxidation followed by BBr₃-induced global demethylation. In contrast, if 29 was exposed to p-TsOH and p-methoxy-α-toluenethiol at –30 ºC following concentration of the reaction medium to near dryness facilitated nucleophilic attack, compound 37 was obtained in 57% yield. The fourth aromatic ring having been added, this new tetraaryl intermediate (37) could then be converted smoothly into the natural product ampelopsin D (21) via a stereoselective Ramberg-Bäcklund reaction under Meyers’s modified conditions (one which afforded a 5:1 ratio of separable E- and Z-isomers) followed by BBr₃-mediated phenol deprotection. To prepare isoampelopsin D (38), ampelopsin D (21) was treated with HCl in MeOH at 80 ºC for 2 h to facilitate the smooth isomerization of its central olefin to the seemingly more thermodynamically stable tetra-substituted olefin of 38 in near quantitative yield (96%).
Following similar reaction conditions, all of the other key starting intermediates (30 and 31) behaved in the same manner chemically despite major electronic differences based on resonance. Scheme 8 shows the total syntheses of isopaucifloral F (41) and quadrangularin A (8), which have interchanged pendant phenol ring systems compared to paucifloral F (18) and ampelopsin D (21). Indeed, these two natural products could be obtained when building block 30 was subjected to the same reaction sequence discussed above; the only difference between Scheme 7 and Scheme 8 is the deprotection conditions needed to access isopaucifloral F (41). Deprotection of permethylated isopaucifloral F using BBr$_3$ resulted a mixture of unknown compounds. Thus, 9-I-BBN was chosen here instead to perform this transformation. Based on
the results presented thus far, it appeared to us that any resveratrol-derived structure possessing a single cyclopentane ring system could be obtained from appropriate triaryl precursors. This hypothesis has been reinforced by the total syntheses of other natural product-like analogues with different substitution patterns on the aryl rings using this general approach.\textsuperscript{13}

![Scheme 8. Total synthesis of two resveratrol-based natural products (14 and 8) from key building block 30.]

Reagents and conditions: a) n-BuLi (1.0 equiv), THF, 78 °C, 20 min; then 4-methoxybenzaldehyde (1.0 equiv), 25 °C, 4 h, 71%; b) TFA (1.0 equiv), CH₂Cl₂, -30 °C to 20 °C, 5 h; then K₂CO₃ (10 equiv), MeOH, 25 °C, 5 min, 93%; c) Dess-Martin periodinane (1.2 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25 °C, 3 h, 96%; d) 9-BBN (1.0 M in hexanes, 10 equiv), CH₂Cl₂, 40 °C, 30 min, 72%; e) TsOH (1.0 equiv), CH₂Cl₂, -30 °C to 20 °C, 5 h; p-methoxy-ω-diol-ene-9(3.0 equiv), then concentration to near dryness, 25 °C, 12 h, 65%; f) mCPBA (3.0 equiv), NaHCO₃ (10 equiv), CH₂Cl₂, 0 °C, 3 h, 70%; g) t-BuCH₂OH/HCCl₄ (5/1), K₂CO₃ (20 equiv), 80 °C, 12 h, 55%; h) BBN (1.0 M in CH₂Cl₂, 12 equiv), CH₂Cl₂, 25 °C, 6 h, 75% of 8, 14% of internal alkene isomer, 9-HBBN=9-hydroxy-9-borabicyclo(3.3.1)nonane.

There are a few additional points worth noting at this juncture. First, in order to introduce the fourth aromatic ring in an ampelopsin D-like system, one could imagine that permethylated paucifloral F(42) or its congener derivatives (43) could serve as appropriate intermediates. However, the carbonyl group within paucifloral F (42) proved entirely resistant to any olefination procedure other than Tebbe methylation. Among nearly a dozen reactions attempted (Scheme 9), including the use of Petasis-type reagents\textsuperscript{14} and Wittig olefination under salt-free conditions, most cases resulted in α-deprotonation or showed no reactivity.
On the other hand, it also proved challenging to install the fourth ring through the alcohol/halide (43) intermediate as various reactions we attempted (including Grignard reaction and a SmI₂-promoted coupling reaction) only gave back starting material. The only successful method was to incorporate a sulfur nucleophile via a stepwise version of the acid-catalyzed cyclization/nucleophilic addition cascade shown above; it was crucial to perform this reaction under solvent-free conditions with a large excess of nucleophile present to prevent the formation of the β-elimination product. In addition, we found that a lanthanide-promoted reaction, one which employed a full equivalent of a reagent such as In(OTf)₃ in a neat solution of p-methoxy-α-toluenethiol, could quickly generate the same desired product (37) from the precursor alcohol (39) as well. Incorporation of a sulfide nucleophile through standard S₂N₂ displacement of a mesylate did not succeed, likely due to the steric hindrance created by the aromatic ring which resides on the same side of the cyclopentane ring as the incoming nucleophile.
It is also worth noting that the deprotection of protected ampelopsin D (45) and quadrangularin A (54) always afforded a mixture of both exocyclic and internal olefins. Using 45 for illustrative purposes, this final deprotection step we found produced a 5:1 mixture of both ampelopsin D (21) and isoampelopsin D (38) under the best conditions; these structures were obtained in pure form in near quantitative yield by treating the product mixture with Ac₂O, chromatographically separating the resultant acetates, and using KCN in MeOH to effect ester hydrolysis. We attempted all three types of cleavage methods for phenolic methyl ethers (Table 3), but none of the conditions could prevent the formation of at least small quantities of isoampelopsin D (38), which was inseparable from ampelopsin D (21) using chromatography. As indicated in Table 3, the external double bond of the indane ring could be readily isomerized to the more stable internal one with either proton sources or Lewis acids.

Table 3. Attempts to deprotect permethylated ampelopsin D (45).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂SO₄, MeOH, 80 °C</td>
<td>permethylated 38</td>
</tr>
<tr>
<td>2</td>
<td>TFA, CH₂Cl₂, -78 °C to 90 °C, 48 h</td>
<td>only permethylated 38 is observed</td>
</tr>
<tr>
<td>3</td>
<td>Py·HCl, 200 °C, 4 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>benzenemethol, K₂CO₃, DMF, 23 °C</td>
<td>unidentified complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>Li₂EuH, THF, 0 °C to 23 °C, 2 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>Ph₃P·H₂, THF, 23 °C, 12 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>AlCl₃, toluene, 23 °C to 80 °C, 12 h</td>
<td>partial deprotection of 38</td>
</tr>
<tr>
<td>8</td>
<td>BB₃, ESH, CH₂Cl₂, 23 °C, 6 h</td>
<td>partial deprotection of 38</td>
</tr>
<tr>
<td>9</td>
<td>BB₃, EtCO₂H, CH₂Cl₂, 0 °C to 23 °C, 6 h</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>BB₃, Et₃N, CH₂Cl₂, 0 °C to 23 °C, 6 h</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>SbF₅·Me₂S, DCE, 0 °C to 80 °C, 12 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>12</td>
<td>fresh BB₃ (in dry box), CH₂Cl₂, 0 °C to 23 °C, 6 h</td>
<td>21:38 (1:1)</td>
</tr>
<tr>
<td>13</td>
<td>B₄H₁₀·BN, CH₂Cl₂, 23 °C to 50 °C, 2 h</td>
<td>unidentified complex mixture</td>
</tr>
<tr>
<td>14</td>
<td>MeSiCl₃, NaI, CH₃CN, 23 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

2.4 Total synthesis of bicyclic natural products in the resveratrol class
After we successfully completed the total syntheses of several simple indane-based members of the resveratrol family, our next goal was to access a higher level of molecular complexity within the resveratrol class. With quadrangularin A (8) and ampelopsin D (21) in hand, we wondered whether we could utilize them as starting materials for those natural products that possess an additional ring appended onto their indane core. Pallidol (23), with its symmetric [3.3.0]-bicyclic architecture, and ampelopsin F (22), with its more congested [3.2.1]-bicyclic frame, are one C–C bond away from our proposed precursors (8 and 21). The Niwa group proposed a plausible biogenesis of these higher-order structures through a nonselective, acid-catalyzed rearrangement of the dimer ε-viniferin (4), and they demonstrated this concept by exposure of ε-viniferin to HCl (Scheme 10), which afforded a number of products including ampelopsin F (22).16 Mechanistically speaking, the reactive quinone methide (47), which was formed through dihydrofuran ring opening followed by nucleophilic attack of the olefin, served as an intermediate towards multiple different structures. To prepare ampelopsin D (21) and ampelopsin D (38), rearomatization of 47 via deprotonation of the indane ring system led to 21, which could partially or fully isomerize to 38. On the other hand, the second nucleophilic attack of the quinone methide directly via a Friedel-Crafts alkylation by the electron-rich B-ring followed by deprotonation enabled the formation of the dibenzobicyclo[3,2,1]octadiene skeleton (22). Along similar lines, pallidol could also potentially be synthesized from an ε-viniferin-like structure with the opposite arrangement of B- and C-rings upon treatment of acids (specific reactions are not shown here).
This mechanism was also supported by Li’s recent work towards the first total synthesis of gnemonol M as shown in Scheme 11. In this example, a strong Lewis acid (AlCl$_3$) catalyzed a one-pot debutylation/Friedel–Crafts alkylation sequence with 48, a bisisorhapontigenin A analog, which gave rise to gnemonol M (51), a structural analogue of ampelopsin F (22), in 76% yield.

Given this knowledge, we wondered if we could also use electrophilic activation of the olefin within both permethylated ampelopsin D (45) and quadrangularin A (54) to form the correct quinone methide structure proposed by the Niwa group (Scheme 10), which could then undergo a Friedel–Crafts alkylation to access the desired bicyclic architectures in a controlled fashion. Such a sequence would establish a relationship between the systems of 21 and 8 and the
bicyclic structures of other indane-containing family members (i.e., 22 and 23) that has yet to be proposed in the literature.

To perform the experimental evaluation of our hypothesis, however, we had to address at least two major issues with its laboratory execution. First, we had to identify an appropriate electrophile to activate the olefin; second, we needed to ensure correct facial selectivity with respect to electrophile addition since the intramolecular Friedel–Crafts alkylation necessarily occurs with the proper stereochemistry (Scheme 12). In this case, both required quinone methides 52 and 55 can be accessed only if the electrophile approaches from the β-face; however, the adjacent C-ring would seem to only make it possible for 55 to achieve this stereochemical requirement readily.
Scheme 12 outlines our efforts towards electrophilic activation of the olefins within both permethylated ameloposin D (45) and quadrangularin A (54). Although it could, in principle, be accomplished by straightforward protonation of the olefin under appropriate Lewis or Brønsted acidic conditions, we failed to complete this concise transformation after several attempts. In our initial experiments, a proton caused only olefin isomerization under a variety of conditions (including H2SO4, TFA, HCl, HBr, CSA, and p-TsOH in a variety of polar and nonpolar solvents at different temperatures). Moreover, the starting materials were usually recovered untouched when subjected to Lewis acids. In addition to direct acid activation, we also tried an indirect transformation via an epoxide intermediate. However, all efforts to form epoxides with these olefins led to intractable mixtures of compounds or recovered starting material. Consequently, an
alternative electrophile was needed, one that could be easily replaced by hydrogen at the indicated positions within both 53 and 56 following cyclization.

Because bromine addition to a double bond is reversible prior to terminating nucleophilic attack,\textsuperscript{18} we turned our attention to halogen electrophiles because such a reversible addition might increase the likelihood of obtaining the appropriate quinone methide intermediates with the requisite stereochemistry. Moreover, the replacement of halogen atoms with hydrogen is a standard transformation, and there are many different types of methods to choose from for this purpose. As indicated in Scheme 13, our hypothesis was realized when we used molecular bromine as the activating electrophile. Exposure of permethylated quadrangularin A (54) to 2 equivalents of Br\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} at –78 °C, followed by slow warming to 25 °C, afforded the desired bicyclic core (60) with three extra halogen atoms attached in 81% yield. To elucidate the order of bromination, we performed a series of experiments using fewer equivalents of bromine under the same reaction conditions. The studies showed that the course of events for this cascade cyclization started with initial bromination of the indicated position within the A-ring to afford 57, followed by a site-selective bromination of the second 3,5-dimethoxybenzene ring system to generate 58. Both of these halogenations occur rather smoothly and quickly at –78 °C. However, the final alkene halogenation only occurs once the reaction temperature has reached at least 0 °C (based on TLC analysis). This finding revealed the order of nucleophilicities of these three electron rich positions within the molecule. Additionally, it was observed that the two 4-methoxybenzene rings in this system were less reactive towards electrophilic addition than the three positions mentioned above, as one might expecte. From this intermediate, pallidol (23) was synthesized in 63% overall yield through hydrogenative replacement of all three bromines within 60 followed by global deprotection of the phenolic ethers mediated by BBr\textsubscript{3}.
Application of the same reaction conditions to permethylated ampelopsin D (45) provided access to the [3.2.1]-bicyclic core of ampelopsin F (22). For this specific structure (62), catalytic hydrogenation only replaced the two bromine atoms on the aromatic rings, leaving the sterically hindered tertiary alkyl bromide untouched. Thus, a radical-based dehalogenation was used to complete the target molecule (22) in this case.
Several aspects of this key cascade deserve further comment. First of all, although the mechanism of this bromination/Friedel–Crafts alkylation sequence requires 3 equivalents of electrophilic halogen, only 2 equivalents of reagent were used in our reactions (with the isolated yield of pallidol being higher than could be achieved with 2 equivalents of reagent alone). In fact, the reaction proceeded more cleanly and with higher yield when 2 equivalents of reagent were used instead of 3 equivalents. Based on a series of mechanistic investigations, we postulate that the third equivalent of bromine actually comes from aerial oxidation of bromide in solution. In our initial experiments, significant variations in reaction times were observed as the reactions were conducted under an argon atmosphere without care for deoxygenating the solvent. This finding might suggest that adventitious oxygen is needed in the solution to drive the final cyclization to completion. We tried to verify this hypothesis by conducting this reaction in argon-sparging solution with exactly 2 equivalents of bromine added. As we predicted, the absence of oxygen in the solution completely prevented the Friedel–Crafts element of the sequence (stopping at 58, cf. Scheme 13), while exposure to an oxygen atmosphere (O₂ balloon...
enabled the cyclization to proceed to completion in just a few minutes. While we have been unable to find other examples of in situ bromine generation through oxygen exposure, the concept has been documented for the synthesis of molecular iodine,\textsuperscript{20} our current belief is that the highly electron rich nature of the substrate and/or other reactive intermediates involving this substrate might play an important role in this aerial oxidation process. Moreover, since the addition of radical scavengers such as TEMPO did not hinder the reaction, we believe that an electrophilic mechanism, not a radical one, is operational. Secondly, it is still unclear whether the aryl bromine atoms influence the cyclization step or if the initial double bond geometry is critical to the stereochemistry of the product. Although the alkene precursors used in this reaction exist in both $E$- and $Z$-forms in nature, no natural products are known to possess different configuration in either the pallidol or ampelopsin F cores.

To address this question, we conducted a series of experiments using alkene 63, which is the permethylated form of the natural product parthenocissin A.\textsuperscript{21} Upon exposure of 63 to NBS (2 equiv) in THF at −78 °C, the isolated aromatic bromination product was characterized with the original alkene geometry intact. However, upon standing neat or in solution at 25 °C for just a few hours, this material spontaneously isomerized to 58. Exposure of 63 to 2 equivalents of Br$_2$ or 3 equivalents of NBS under standard reaction conditions afforded only cyclization product 60.
indicating that either alkene isomerization precedes cyclization, perhaps promoted by the acidic protons in solution (driven by the steric interaction between the bromine atom on A ring and the D ring), and only the correct double bond geometry would give rise to the final cyclization product, or both olefin isomers would ultimately provide the same product. Finally, it is worth noting that the extra aryl bromides within both 60 and 62 are situated perfectly to attach the extra carbon fragments needed to complete the dihydrofuran ring systems of both ampelopsin H (64) and vaticanol C (65), indicating that they could have additional use beyond cyclization itself. Recently, these two molecules (64 and 65) were completed by two of my colleagues.

2.5 Total synthesis of natural products and analogues bearing a seven-membered carbocycle

The above sections have illustrated our success with the key building block (28) we proposed as a general platform to access core structural motifs within the resveratrol family. In fact, additional complexity and structural diversity can be achieved from this structure. Seven-membered carbocycles, motifs possessed by both hopeaphenol E (19) and diptoindonesin D (20) as well as numerous other natural products, are another major structural element in this class we decided to tackle. Using ampelopsin B (67) as an example (Scheme 17), the Niwa group also
proposed a biogenesis for these types of seven-membered ring structures. Starting with ε-viniferin (4), protonation of the double bond followed by nucleophilic attack by the neighboring electron rich 3,5-dimethoxybenzene ring affords the desired seven-membered ring to give ampelopsin B (67). Furthermore, they demonstrated the concept of this Friedel–Crafts cyclization by epoxidation of the ε-viniferin pentaacetate (68) followed by epoxide opening under basic conditions to generate ampelopsin A (69) (Scheme 18).

We wondered if these seven-membered rings would become accessible through an electrophilic activation/Friedel–Crafts cyclization sequence by oxidizing the bis-benzylic alcohol to its ketone counterpart (70). Table 4 lists various conditions we tried on the ketone (70) to achieve this cyclization reaction.
As can be observed following inspection of Table 4, various proton sources and molecular bromine activate the alkene and effect the transformation smoothly; any attempts to epoxidize this bis-benzylic ketone (70) gave poor results probably due to the electronic nature of the system. Interestingly, when 70 was exposed to bromine in CH$_2$Cl$_2$ (Scheme 19), no aromatic bromination on the two 3,5-dimethoxybenzene ring was observed. Rather, the electron-withdrawing nature of the carbonyl group renders the olefin as the most electron-rich domain of the molecule. Thus, the seven-membered ring (73) was produced cleanly without any aryl halogenations when 70 was reacted with only 1 equivalent of Br$_2$. One challenge presented by this reaction, however, was product isolation since the resulting bromide proved sensitive to light and silica gel. The extremely reactive nature of this substrate also made it difficult to use this bromine atom as a handle to install other functional groups. For instance, upon exposure to AcOH in the presence of a silver salt (AgOAc), intermediate 73 quickly underwent a thermodynamically favored phenonium shift to give 76 in 62% yield (confirmed by X-ray crystallographic analysis). This migration presumably started with the conversion of the benzylic bromide of 73 into a carbocation (74), followed by nucleophilic attack by the neighboring phenol.
ring to afford intermediate 75. Then, a regioselective cyclopropane opening as induced by the strategically positioned ortho- and para-disposed alkoxy groups within 75 and a terminating attack by acetate onto the resultant quinone methide could afford 76, which could be converted into a regioisomeric and fully protected analogue of diptoindonesin D (77, compare to 2) via simple acetate cleavage and alcohol oxidation.

Scheme 10. Synthesis of a protected nonnatural resveratrol oligomer (77) via a bromonium-induced cascade sequence followed by an acid-induced phenonium shift.

Unfortunately, no condition screened (Table 5) enabled the direct replacement of the bromine atom within 73 with the requisite oxygen atom needed for the natural product. Furthermore, we also tried various conditions to carry out benzylic oxidation of the acid-mediated cyclization product to install the oxygen at the correct position (Table 6). However, no sign of oxidation was ever observed at that specific carbon.
The only successful introduction of the requisite oxygen into the seven-membered ring system thus far involved treatment of 70 with 1,1,1-trifluorodimethyldioxirane (generated in situ using OXONE, 1,1,1-trifluoroacetone, and Na$_2$EDTA buffer$^{25}$) in MeCN at 25 °C. In this Friedel-Crafts cyclization, a protected form of hemsleyanol E (80) was generated in moderate yield (34%). Subsequent oxidation then completed the synthesis of protected diptoindonesin D (81).$^{26}$
2.6 Conclusion

In summary, we have developed a general approach to achieve the controlled synthesis of the major dimeric architectures within the resveratrol family. Distinct from all past endeavors in this field was the identification and use of a unique precursor possessing three aryl rings. With this key building block in hand, a series of orchestrated cascade sequences initiated by simple reagents (such as bromine and Brønsted acids) led to a diverse array of oligomeric natural products that encompass nearly all the carbogenic diversity of the resveratrol dimers. At the dimeric level, as detailed in previous sections, we have completed total syntheses of ampleopsin D, ampelopsin F, pallidol, paucifloral F, quadrangularin A, isoampleopsin D, isopaucifloral F, structural analogs of diptoindonesin A and hemsleyanol E during our initial investigation using our methods. Since most of our synthetic routes are fewer than 10 steps from the common intermediates, the majority of the natural products accessed to date could potentially be prepared on gram scale as they can be obtained in 7% to 54% overall yield from commercial materials. Another important note is that all syntheses reported in this chapter are racemic. One thought to tackle this issue is to develop an enantioselective version of the cation-based cyclization to form the indane system, and some preliminary results recently obtained by one of my colleagues have shown that we could indeed achieve asymmetric syntheses of some other dimeric structures in...
the resveratrol family. Based on the foundation laid by the work outlined in this chapter, our group has synthesized over 20 different natural products within this class; our ongoing work is to develop such highly selective and robust pathways for every isolate within the resveratrol class through our key building block.

This work is a collective effort between me and several other colleagues in the group. I was very fortunate to work very closely with Dr. Alexandros Zografos, who has been an amazing mentor to me on this project, during my first year on total syntheses of ampelopsin D, ampelopsin F, pallidol, paucifloral F, quadrangularin A, isoampelopsin D, isopaucifloral F, structural analogs of diptoindonesin A, hemsleyanol E. Audrey Ross developed the In(OTf)$_3$-catalyzed alcohol replacement by sulfur nucleophile and investigated the bromine-induced cyclization, and performed some studies on the role of oxygen in the bromine-promoted cyclization. Steven Breazzano completed the syntheses of protected hemsleyanol E (80) and diptoindonesin D (81).

References:


In the absence of the sulfur nucleophile, only an alkene product resulting from β-elimination was observed.


Isopaucifloral F (41) represents a likely, but not yet isolated, natural product structure.


This general transformation was inspired, in part, by the reported ability to replace activated alcohols with silicon nucleophiles in the presence of InCl3: (a) M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chem., Int. Ed.* **2004**, *43*, 1414–1416; for other references concerning related


19 Stock bromine solutions in CH₂Cl₂ were employed in all these experiments to ensure that exactly 2 equiv of the halogen were employed.


26 Of all synthetic materials, 80 and 81 has not yet succumbed to complete deprotection despite dozens of attempts.
Experimental Data for Compounds Listed in Chapter 2

**General Procedures.** All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et₂O) and methylene chloride (CH₂Cl₂) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

**Abbreviations.** NBS = N-bromosuccinimide, TFA = trifluoroacetic acid, KHMDS =
potassium bis(trimethylsilyl)amide, \( p \)-TsOH = para-toluenesulfonic acid, \( m \)CPBA = \( m \)-chloroperoxybenzoic acid, 9-I-BBN = 9-iodo-9-borabicyclo[3.3.1]nonane, AIBN = 2,2’-azobisisobutyronitrile, TMS = trimethylsilyl.

1-(bromomethyl)-3,5-dimethoxybenzene (S1). \( \text{NaBH}_4 \) (1.11 g, 30.0 mmol, 2.0 equiv) was added slowly to a solution of 3,5-dimethoxybenzaldehyde (2.44 g, 15.0 mmol, 1.0 equiv) in MeOH (30 mL) at 0 °C. After 30 min of stirring at 0 °C, the reaction contents were quenched by the slow addition of water (20 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (\( \text{MgSO}_4 \)), and concentrated to afford the desired alcohol intermediate (2.43 g, 99% yield) as a white solid which was carried forward without further purification. Next, pyridine (0.017mL, 0.212 mmol, 0.05 equiv) and PBr\(_3\) (0.400 mL, 4.25 mmol, 1.0 equiv) were added sequentially and slowly to a portion of this newly-formed alcohol (0.715 g, 4.25 mmol, 1.0 equiv) in \( \text{Et}_2\text{O} \) (20 mL) at 25 °C, and the resultant mixture was heated at 40 °C for 3 h. Upon completion, the reaction contents were quenched carefully with ice water (15 mL), poured into water (10 mL), and extracted with \( \text{Et}_2\text{O} \) (3 × 20 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried (\( \text{MgSO}_4 \)), and concentrated to afford alkyl halide S1 (1.50 g, 93% yield) as an amorphous white solid which was carried forward without additional purification. S1: \( R_f = 0.66 \) (silica gel, EtOAc/hexanes, 1:1); IR (film) \( \nu_{\text{max}} \) 3002, 2960, 2838, 1597, 1465, 1429, 1348, 1325, 1300, 1264, 1206, 1158, 1064, 992, 931, 836, 693, 650 cm\(^{-1}\); \(^1\text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.54 (d, \( J = 2.1 \) Hz, 2 H), 6.39 (t, \( J = 2.1 \) Hz, 1 H), 4.42 (s, 2 H), 3.80
(s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.9, 139.7, 107.0 (2 C), 100.6, 55.4 (2 C), 33.6; HRMS (MALDI-FTMS) calcd for C$_9$H$_{11}$BrO$_2$$^+$$[M^+]$ 229.9942, found 229.9937.

**Diethyl 2-bromo-3,5-dimethoxybenzylphosphonate (26).** To a solution of alkyl bromide S1 (1.34 g, 5.80 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (60 mL) at 0 °C was added solid NBS (0.516 g, 2.89 mmol, 0.5 equiv) in a single portion. After stirring the resultant solution for 30 min at 0 °C, a second aliquot of NBS was added (0.516 g, 2.89 mmol, 0.5 equiv) and the reaction was stirred for an additional 30 min at 0 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ (10 mL), poured into H$_2$O (20 mL), and extracted with EtOAc (3 × 70 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO$_4$), and concentrated to give the desired halogenated intermediate (1.70 g, 95% yield) as a white solid which was carried forward without additional purification. Next, a portion of this newly formed aryl bromide (1.00 g, 3.22 mmol, 1.0 equiv) was dissolved in THF (5 mL) and added dropwise at 0 °C to a THF solution of the anion of diethylphosphite, which had been prepared by adding KHMDS (11.6 mL, 0.5 M in toluene, 5.80 mmol, 1.8 equiv) to a solution of diethylphosphite (0.830 mL, 6.44 mmol, 2.0 equiv) in THF (20 mL) at 0 °C and stirring for 15 min. After 5 min of stirring at 0 °C, the reaction contents were warmed to 25 °C and stirred for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH$_4$Cl (10 mL), poured into water (15 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried (MgSO$_4$), and concentrated. The resultant light yellow product was left under high vacuum for 24 h to remove any residual diethylphosphite, ultimately affording phosphonate 26 (1.07 g, 91% yield) as a white solid. 26: $R_f$ = 0.15 (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{max}$ 2981, 2938, 2907, 2837, 1592, 1456,
Horner–Wadsworth–Emmons Olefination Products (27). KOT-Bu (57.1 mL, 1.0 M in THF, 57.1 mmol, 1.05 equiv) was added dropwise over the course of 5 min to a solution of phosphonate 24 (20.0 g, 54.4 mmol, 1.0 equiv) in THF (250 mL) at −78 °C. After 20 min of stirring at −78 °C, a solution of the desired aldehyde (7.04 g, 51.7 mmol, 0.95 equiv) in THF (50 mL) was added at −78 °C. The resultant solution was stirred at −78 °C for 1 h, and then at 25 °C for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (150 mL), poured into water (100 mL), and extracted with EtOAc (3 × 500 mL). The combined organic layers were then washed with water (100 mL) and brine (100 mL), dried (MgSO₄), and concentrated to give resveratrol derivatives 27 (all in 98% yield) as white powders which were carried forward without additional purification.

S2: Rf = 0.61 (silica gel, EtOAc/hexanes, 1:1); IR (film) νmax 3002, 2937, 2836, 1719, 1589, 1511, 1454, 1415, 1341, 1286, 1252, 1203, 1163, 1082, 1023, 962, 827 cm⁻¹; ¹H NMR (300
MHz, CDCl$_3$ $\delta$ 7.50 (d, $J = 8.7$ Hz, 2 H), 7.41 (d, $J = 16.2$ Hz, 1 H), 6.98 (d, $J = 16.2$ Hz, 1 H), 6.91 (d, $J = 9.0$ Hz, 2 H), 6.80 (d, $J = 2.7$ Hz, 1 H), 6.42 (d, $J = 2.7$ Hz, 1 H), 3.88 (s, 3 H), 3.86 (s 3 H), 3.83 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.6, 159.5, 156.8, 138.9, 131.1, 129.7, 128.1, 125.8, 114.1, 104.9, 102.4, 98.7, 56.3, 55.5, 55.3; HRMS (MALDI-FTMS) calcd for C$_{17}$H$_{17}$BrO$_3^+$ [M$^+$] 348.0361, found 348.0362.

S3: $R_f = 0.55$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\text{max}}$ 3001, 2957, 2938, 2837, 1592, 1457, 1418, 1353, 1288, 1230, 1204, 1155, 1083, 1022, 959, 829, 650 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.50 (d, $J = 15.9$ Hz, 1 H), 6.94 (d, $J = 15.9$ Hz, 1 H), 6.80 (d, $J = 2.7$ Hz, 1 H), 6.71 (d, $J$= 2.4 Hz, 2 H), 6.43 (d, $J = 2.7$ Hz, 1 H), 6.42 (t, $J = 2.1$ Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.9, 159.5, 156.8, 138.9, 138.5, 131.5, 128.4, 104.9,102.7, 100.3, 99.1, 56.3, 55.5, 55.3; HRMS (FAB) calcd for C$_{18}$H$_{19}$BrO$_4^+$ [M$^+$] 378.0467, found 378.0484.

S4: $R_f = 0.53$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{\text{max}}$ 2951, 2923, 1578, 1511, 1454, 1226, 1157, 1021 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38 (d, $J = 16.1$ Hz, 1 H), 7.08 (m, 2 H), 6.96 (d, $J = 16.1$ Hz, 1 H), 6.86 (d, $J = 8.7$ Hz, 1 H), 6.79 (d, $J = 2.3$ Hz, 1 H), 6.41 (d, $J = 1.9$ Hz, 1H), 3.95 (s, 3 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.5, 156.8, 149.3, 149.1, 138.8, 131.4, 130.0, 126.0, 120.3, 111.2, 109.1, 104.8, 102.4, 98.7, 56.3, 55.9, 55.8, 55.5; HRMS (FAB) calcd for C$_{18}$H$_{19}$O$_4^+$ [M$^+$] 378.0467, found 378.0473. (This compound was characterized by Steven Breazzano.)
General procedure to access key triaryl intermediates (28). \( n \)-BuLi (37.7 mL, 1.6 M in THF, 60.3 mmol, 1.05 equiv) was added slowly over the course of 5 min to a solution of resveratrol derivative 27 (20.0 g, 57.4 mmol, 1.0 equiv) in THF (400 mL) at \(-78 \, ^\circ C\), ultimately yielding a light yellow solution. After 20 min of stirring at \(-78 \, ^\circ C\), a solution of the appropriate aldehyde (9.52 g, 57.4 mmol, 1.0 equiv) in THF (200 mL) was added slowly at \(-78 \, ^\circ C\), and the resultant mixture was stirred for 1 h at \(-78 \, ^\circ C\), warmed slowly to 25 \, ^\circ C\, and stirred for an additional 4 h at 25 \, ^\circ C\. Upon completion, the reaction contents were quenched with saturated aqueous NH\(_4\)Cl (250 mL), poured into water (100 mL), and extracted with EtOAc (3 \times 1 L). The combined organic layers were then washed with water (300 mL) and brine (300 mL), dried (MgSO\(_4\)), and concentrated. The resultant light yellow oils crystallized upon standing and were then triturated with EtOAc (3 \times 10 mL) to give the desired triaryl intermediates as white solids.

\((E)-(2,4\text{-dimethoxy}-6-(4\text{-methoxystyryl})\text{phenyl}-(3,5\text{-dimethoxyphenyl})\text{methanol} \, (29)\): \( R_f = 0.40 \) (silica gel, EtOAc/hexanes, 1:1); IR (film) \( \nu_{\text{max}} \) 3509, 3001, 2938, 2837, 1604, 1511, 1458, 1307, 1244, 1204, 1175, 1153, 1059, 1032, 966, 930, 833, 736 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.36 (d, \( J = 8.7 \, \text{Hz, 2 H} \)), 7.28 (d, \( J = 16.2 \, \text{Hz, 1 H} \)), 6.88 (d, \( J = 16.2 \, \text{Hz, 1 H} \)), 6.86 (d, \( J = 8.7 \, \text{Hz, 2 H} \)), 6.74 (d, \( J = 2.1 \, \text{Hz, 1 H} \)), 6.54 (d, \( J = 2.0 \, \text{Hz, 2 H} \)), 6.45 (d, \( J = 2.1 \, \text{Hz, 1 H} \)), 6.33 (t, \( J = 2.4 \, \text{Hz, 1 H} \)), 6.22 (d, \( J = 9 \, \text{Hz, 1 H} \)), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 1 H), 3.74 (s, 6 H), 3.72 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 160.5, 159.8, 159.4, 158.6, 147.5, 138.7, 131.5, 129.9, 127.8, 124.4, 121.7, 114.0, 103.8, 103.1, 98.6, 98.3, 70.0, 55.7, 55.3, 55.1; HRMS (MALDI-FTMS) calcd for C\(_{26}\)H\(_{28}\)O\(_6\) \([\text{M}^+\]) 436.1886, found 436.1870.

\((E)-(2,4\text{-dimethoxy}-6-(3,5\text{-dimethoxystyryl})\text{phenyl})-(3,5\text{-dimethoxyphenyl})\text{methanol} \)
(30): 88% yield, Rf = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) νmax 3508, 3001, 2938, 2837, 1599, 1510, 1459, 1425, 1323, 1283, 1246, 1203, 1152, 1064, 1035, 964, 835, 799, 736 cm−1; 1H NMR (300 MHz, CDCl3) δ 7.36 (d, J = 15.9 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 15.9 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.74 (d, J = 2.4 Hz, 1 H), 6.56 (d, J = 2.1 Hz, 2 H), 6.48 (d, J = 2.4 Hz, 1 H), 6.38 (t, J = 2.1 Hz, 1 H), 6.23 (d, J = 9.9 Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 6 H), 3.77 (s, 3 H), 3.73 (s, 3 H); 13C NMR (75 MHz, CDCl3) δ 160.9, 159.8, 158.8, 158.3, 139.1, 138.2, 136.8, 132.0, 127.1, 126.9, 122.3, 113.4, 104.6, 103.3, 100.3, 99.1, 69.8, 55.7, 55.4, 55.3, 55.2; HRMS (FAB) calcd for C26H28O6: [M+H]+ 436.1886, found 436.1870.

(E)-[2,4-dimethoxy-6-(3,4-dimethoxystyryl)phenyl]-(3,5-dimethoxyphenyl)methanol

(31): 68% yield, Rf = 0.26 (silica gel, EtOAc/hexanes, 1:2); IR (film) νmax 3003, 2955, 2917, 1590, 1508, 1454, 1258, 1204, 1150 cm−1; 1H NMR (300 MHz, CDCl3) δ 7.31 (s, 1 H), 7.01 (m, 2 H), 6.90 (d, J = 16.1 Hz, 1 H), 6.88 (app s, 1 H), 6.78 (d, J = 2.3 Hz, 1 H), 6.57 (m, 2 H), 6.50 (d, J = 2.4 Hz, 1 H), 6.37 (app t, J = 2.3 Hz, 1 H), 6.27 (d, J = 9.5 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 6 H); 13C NMR (75 MHz, CDCl3) δ 161.0, 160.4, 159.2, 149.5, 148.1, 139.1, 132.2, 130.7, 125.1, 122.3, 120.6, 111.5, 109.1, 104.4, 103.6, 99.2, 98.6, 70.3, 56.4, 56.3, 56.2, 55.8, 55.6; HRMS (MALDI-FTMS) calcd for C27H30O7: [M+H]+ 466.1992, found 466.1995. (This compound was characterized by Steven Breazzano.)

3-(3,5-dimethoxyphenyl)-4,6-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-ol

(39). To a solution of aldol adduct 29 (0.150 g, 0.344 mmol, 1.0 equiv) in CH2Cl2 (10 mL) at −78 °C was added in a single portion a solution of TFA (0.027 mL, 0.344 mmol, 1.0 equiv) in CH2Cl2 (0.2 mL). The resultant dark purple reaction mixture was then warmed slowly to −20 °C over the
course of 30 min and stirred for 5 h at \(-20^\circ C\). Upon completion, the reaction mixture was quenched sequentially with solid K$_2$CO$_3$ (0.475 g, 3.44 mmol, 10 equiv) and MeOH (10 mL), warmed to 25 \(^\circ C\), and stirred for 15 min at 25 \(^\circ C\). The reaction contents were then poured into water (15 mL) and extracted with EtOAc (3 \times 40 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried (MgSO$_4$), and concentrated. The resultant brown oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to give alcohol 39 (0.113 g, 75\% yield) as an amorphous white solid. 39: \(R_f = 0.41\) (silica gel, EtOAc/hexanes, 1:1); IR (film) \(\nu_{max} 2935, 1597, 1512, 1463, 1405, 1248, 1151, 1060, 829\) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl$_3$) \(\delta 7.09 (d, J = 8.7 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 6.65 (d, J = 2.1 Hz, 1 H), 6.42 (d, J = 2.1 Hz, 1 H), 6.27 (t, J = 2.3 Hz, 1 H), 6.17 (d, J = 2.4 Hz, 2 H), 5.13 (app t, J = 5.7 Hz, 1 H), 4.19 (d, J = 6.9 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.59 (s, 3 H), 3.18 (d, J = 6.6 Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl$_3$) \(\delta 161.7, 160.4, 158.5, 157.1, 146.9, 146.3, 134.0, 128.7, 122.9, 113.9, 105.5, 99.7, 99.4, 99.3, 98.0, 82.5, 66.1, 55.6, 55.3, 55.2, 54.7\); HRMS (MALDI-FTMS) calcd for C$_{26}$H$_{28}$O$_6$ \([M^+]\) 436.1886, found 436.1870. Because this compound is very difficult to purify, only the rude NMR spectra are included in the spectra section.

**Paucifloral F (18).** Dess–Martin periodinane (0.152 g, 0.358 mmol, 1.2 equiv) was added in a single portion to a solution of alcohol 39 (0.130 g, 0.298 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (8 mL) at 25 \(^\circ C\), and the resultant slurry was stirred for 1 h at 25 \(^\circ C\). Upon completion, the reaction contents were quenched with saturated aqueous Na$_2$SO$_3$ (1.5 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 \(^\circ C\). The reaction contents were then poured into saturated aqueous NaHCO$_3$ (5 mL) and extracted with EtOAc (3 \times 10 mL). The combined
organic layers were washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated to afford permethylated paucifloral F 42 (0.122 g, 97% yield) as a light yellow oil which was carried forward without additional purification. 42: Rf = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) νmax 1696, 1614, 1474, 1347, 1155, 1082, 1005, 842 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.02 (d, J = 8.7 Hz, 2 H), 6.90 (d, J = 2.1 Hz, 1 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.70 (d, J = 2.1 Hz, 1 H), 6.32 (app t, J = 2.4 Hz, 1 H), 6.16 (d, J = 2.4 Hz, 2 H), 4.44 (d, J = 2.7 Hz, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 3.65 (d, J = 3.0 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 205.9, 162.0 (2 C), 160.8, 158.6, 157.8, 145.9, 138.7, 137.6, 131.5, 128.8, 114.2 (2 C), 106.4, 105.1 (2 C), 98.1, 96.4, 64.1, 55.8, 55.6, 55.2, 51.9.

Finally, a solution of this newly synthesized ketone (0.035 g, 0.081 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) was added dropwise to a commercially-prepared solution of BBr₃ (0.770 mL, 1.0 M in CH₂Cl₂, 0.810 mmol, 10 equiv) at 0 °C, and the resultant solution was stirred for 6 h at 0 °C. Upon completion, the reaction mixture was quenched with water (5 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant light pink product was purified by flash column chromatography (silica gel, CH₂Cl₂/Methanol, 9:1) to give paucifloral F (0.025 g, 86% yield) as an amorphous white solid. 18: Rf = 0.06 (silica gel, CH₂Cl₂/Methanol, 9:1); IR (film) νmax 3334, 1696, 1614, 1514, 1474, 1347, 1155, 1082, 1005, 842 cm⁻¹; ¹H NMR (300 MHz, Acetone-d₆) δ 8.75 (s, 1 H), 8.49 (s, 1 H), 8.27 (s, 1 H), 8.07 (s, 2 H), 6.96 (d, J = 8.7 Hz, 2 H), 6.78 (d, J = 8.7 Hz, 2 H), 6.72 (s, 2 H), 6.19 (app t, J = 2.1 Hz, 1 H), 6.02 (d, J = 2.1 Hz, 2 H), 4.38 (d, J = 2.7 Hz, 1 H), 3.50 (d, J = 2.7, 1 H); ¹³C NMR (75 MHz, Acetone-d₆) δ 205.5, 160.2, 159.5, 157.5, 156.7, 147.3, 140.0, 134.8, 131.8, 129.6, 116.3, 110.2, 106.3, 101.6, 100.5, 65.3, 52.1; HRMS (MALDI-FTMS) calcd for C₂₁H₁₇O₆⁺[M + H⁺] 365.1025,
found 365.1055. All spectroscopic data for this synthetic material match those reported by Ito and co-workers for natural paucifloral F (18).

**Sulfide 37.** Solid p-TsOH (0.039 g, 0.229 mmol, 1.0 equiv) was added in a single portion to a solution of aldol adduct 29 (0.100 g, 0.229 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL) at −50 °C. The resultant mixture was then warmed slowly to −30 °C over the course of 20 min and stirred for an additional 5 h at −30 °C. Once this operation was complete, the reaction contents were warmed to 0 °C, p-methoxy-α-toluenethiol (0.096 mL, 0.687 mmol, 3.0 equiv) was added in a single portion, and the resultant mixture was concentrated to a minimum volume (approximately 0.2 mL). The resultant solution was then stirred for 12 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resulted yellow product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give a sulfide 37 (0.075 g, 57%) as a light yellow oil. Alternatively, p-methoxy-α-toluenethiol (0.240 mL, 1.72 mmol, 3.0 equiv) and p-TsOH (0.099 g, 0.573 mmol, 1.0 equiv) were added to a highly concentrated solution of alcohol 39 (0.250 g, 0.573 mmol, 1.0 equiv) in CH₂Cl₂ (0.5 mL) at 25 °C. The resulting yellow-green solution was stirred for 24 h at 25 °C under the strict exclusion of light. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant light green product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to give a sulfide 37 (0.269 g, 82%) as a light
yellow oil. 37: \( R_f = 0.71 \) (silica gel, EtOAc/hexanes, 1:1); IR (film) \( \nu_{\text{max}} \) 2995, 2934, 2831, 1607, 1512, 1463, 1421, 1326, 1303, 1249, 1203, 1175, 1154, 1061, 1035, 934, 830 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\), 1:1 mixture of diastereomers) \( \delta \) 7.13 (d, \( J = 8.4 \) Hz, 2 H), 7.07 (d, \( J = 8.7 \) Hz, 2 H), 7.04 (d, \( J = 9.0 \) Hz, 2 H), 7.03 (d, \( J = 8.4 \) Hz, 2 H), 6.84 (d, \( J = 2.4 \) Hz, 2 H), 6.80 (d, \( J = 2.7 \) Hz, 2 H), 6.79 (s, 1 H), 6.77 (s, 1 H), 6.74 (d, \( J = 8.7 \) Hz, 2 H), 6.53 (d, \( J = 1.5 \) Hz, 1 H), 6.45 (d, \( J = 1.5 \) Hz, 1 H), 6.36 (br m, 3 H), 6.28 (br m, 2 H), 6.18 (br m, 4 H), 4.55 (s, 1 H), 4.53 (d, \( J = 2.7 \) Hz, 1 H), 4.22 (app t, \( J = 7.2 \) Hz, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.69 (s, 3 H), 3.68 (s, 6 H), 3.61 (s, 3 H), 3.57 (s, 6 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 1:1 mixture of diastereomers) \( \delta \) 161.5, 161.3, 160.5, 160.3, 158.5, 157.0, 156.8, 147.1, 146.5, 146.2, 145.3, 135.7, 133.5, 133.5, 130.3, 130.0, 129.8, 128.6, 124.1, 123.7, 113.9, 113.8, 113.7, 113.3, 105.5, 100.8, 100.4, 98.9, 98.5, 98.1, 97.9, 97.9, 64.6, 60.3, 57.2, 56.7, 55.5, 55.2, 54.0, 53.7, 36.0, 34.9; HRMS (MALDI-FTMS) calcd for C\(_{34}\)H\(_{35}\)O\(_6\)S\(_2\) [M – H\(^+\)] 571.2154, found 571.2168.

**Ampelopsin D (21).** Solid NaHCO\(_3\) (0.257 g, 3.06 mmol, 5.0 equiv) and \( m\)CPBA (70%, 0.317 g, 1.84 mmol, 3.0 equiv) were added sequentially to a solution of sulfide 37 (0.350 g, 0.612 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (20 mL) at 0 °C to give a milk-colored slurry. After warming this mixture to 25 °C and stirring for 3 h, the reaction contents were quenched with saturated aqueous NaHCO\(_3\) (15 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO\(_4\)), and concentrated. The resultant off-white solid was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give the desired sulfone intermediate (0.289 g, 78%) as a yellow-pink oil. Next, finely powdered KOH (0.186 g, 3.31 mmol, 20 equiv) was
added in a single portion to a solution of a portion of this newly synthesized adduct (0.100 g, 0.166 mmol, 1.0 equiv) in a mixture of CCl₄/t-BuOH/H₂O (5/5/1, 3.8 mL/3.8 mL/0.79 mL) at 25 °C. The resultant slurry was then stirred for 12 h at 80 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (2 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant light yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give both the desired alkene (45, 0.042 g, 52%) as a yellow oil along with a small portion of its exocyclic olefinic regioisomer (0.013 g, 15%) as a light yellow oil. 45: Rᶠ = 0.53 (silica gel, EtOAc/hexanes, 1:1); IR (film)ν_max 2995, 2934, 2836, 1606, 1509, 1463, 1288, 1248, 1203, 1175, 1152, 1065, 1036, 827 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.20 (d, J = 8.7 Hz, 2 H), 7.18 (d, J = 8.4 Hz, 2 H), 7.09 (s, 1 H), 6.85 (d, J = 1.8 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.72 (d, J = 8.7 Hz, 2 H), 6.33 (d, J = 1.8 Hz, 1 H), 6.29 (d, J = 2.1 Hz, 1 H), 6.27 (d, J = 2.1 Hz, 1 H), 4.36 (s, 1 H), 4.25 (s, 1 H), 3.93 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.71 (s, 6 H), 3.62 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 161.5, 160.6, 158.4, 158.0, 157.6, 148.1, 145.6, 142.7, 137.3, 130.0, 129.6, 127.9, 126.0, 122.1, 114.1, 113.7, 105.3, 99.1, 97.5, 94.9, 58.0, 57.9, 55.6, 55.2 (2 C); HRMS (MALDI-FTMS) calcd for C₃₄H₃₄O₆⁺ [M⁺] 538.2355, found 538.2357. Finally, permethylated ampelopsin D (45, 0.050 g, 0.090 mmol, 1.0 equiv) was added as a solution in CH₂Cl₂ (5 mL) at 25 °C to a freshly-prepared solution of BBr₃ [made by dissolving solid BBr₃ (0.271 g, 1.08 mmol, 12 equiv) in CH₂Cl₂ (5 mL) at 25 °C in dry box], and the resulting solution was stirred for 6 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (15 mL), poured into water (15 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO₄), and concentrated. The resultant light
yellow solid was purified by flash column chromatography (silica gel, CH$_2$Cl$_2$/MeOH, 9:1) to afford a 5/1 mixture of ampelopsin D and isoampelopsin D (0.041 g combined, 89% overall) as colorless oils. These regioisomers were obtained individually in near quantitative yield (95%) following acetylation [Ac$_2$O, pyridine], chromatographic separation via flash column chromatography, and acetate hydrolysis [cat. KCN, MeOH]. 21: $R_f = 0.03$ (silica gel, CH$_2$Cl$_2$/MeOH, 9:1); IR (film) $\nu_{\text{max}}$ 3339, 1604, 1465, 1374, 1335, 1238, 1147, 1010, 834, 650 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 8.30 (br s, 1 H), 8.20 (br s, 1 H), 8.11 (br s, 1 H), 7.97 (br s, 2 H), 7.85 (br s, 1 H), 7.18 (d, $J = 8.7$ Hz, 2 H), 7.12 (d, $J = 8.7$ Hz, 2 H), 7.04 (app t, $J = 0.6$ Hz, 1 H), 6.81 (d, $J = 1.8$ Hz, 1 H), 6.75 (d, $J = 8.4$ Hz, 2 H), 6.66 (d, $J = 8.7$ Hz, 2 H), 6.30 (d, $J = 2.1$ Hz, 1 H), 6.11 (m, 3 H), 4.29 (s, 1 H), 4.15 (s, 1 H); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 159.7, 159.3, 157.3, 156.7, 156.1, 149.3, 147.6, 143.1, 137.4, 131.0, 129.7, 128.9, 123.8, 122.7, 116.3, 116.0, 106.5, 103.8, 101.3, 98.4, 59.5, 58.7; HRMS(MALDI-FTMS) calcd for C$_{28}$H$_{22}$O$_6^+$ [M$^+$] 454.1416, found 454.1448. All spectroscopic data for this synthetic material match those reported by Niwa and co-workers for natural ampelopsin D (21).$^2$

**Isoampelopsin D (38).** Concentrated HCl (50 μL, 0.600 mmol, 5.5 equiv.) was added to a solution of ampelopsin D (21, 5.0 mg, 0.110 mmol, 1.0 equiv) in MeOH (0.5 mL) at 25 °C, and the resultant mixture was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was quenched with water (3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO$_4$), and concentrated. The resulted light yellow product was purified by flash column chromatography (silica gel, CH$_2$Cl$_2$/MeOH, 9:1) to give isoampelopsin D 38 (4.8 mg, 96%) as a colorless oil. 38: $R_f = 0.13$ (silica gel, CH$_2$Cl$_2$/MeOH, 9:1); IR (film) $\nu_{\text{max}}$ 3411, 2810, 1680, 1628, 1511, 1443, 1371, 1333,
1206, 1149, 1055, 1006, 833 cm$^{-1}$; $^1$H NMR (300 MHz, methanol-$d_4$) $\delta$ 7.11 (d, $J = 8.4$ Hz, 2 H), 7.07 (d, $J = 8.7$ Hz, 2 H), 6.73 (d, $J = 8.7$ Hz, 2 H), 6.66 (d, $J = 8.7$ Hz, 2 H), 6.17 (d, $J = 2.1$ Hz, 1 H), 6.06 (d, $J = 1.5$ Hz, 1 H), 6.06 (d, $J = 2.1$ Hz, 2 H), 5.99 (t, $J = 2.1$ Hz, 1 H), 4.80 (s, 1 H), 3.84 (s, 2 H); $^{13}$C NMR (75 MHz, methanol-$d_4$) $\delta$ 158.9, 158.7, 157.5, 156.5, 154.0, 150.4, 149.9, 144.0, 136.6, 132.1, 131.1, 130.2, 128.9, 125.4, 116.3, 115.8, 108.1, 101.4, 100.7, 56.7, 32.2; HRMS (MALDI-FTMS) calcd for C$_{28}$H$_{22}$O$_6$ $^+$ [M$^+$] 454.1416, found 454.1428. All spectroscopic data for this synthetic material match those reported by Niwa and co-workers for natural isoampelopsin (38).$^2$

**Total Synthesis of Quadrangularin A (8) and Isopaucifloral F (41).** These two natural products were synthesized from intermediate 30 exactly as described above for ampelopsin D (21) and paucifloral F (18) by substituting 3,5-dimethoxybenzaldehyde in the Horner-Wadsworth-Emmons reaction leading to intermediate S3. Only the final deprotection leading to isopaucifloral F (41) in Scheme 8 is fundamentally different from the steps outlined above, so only this procedure is defined specifically on the ensuing pages.
S5: R_f = 0.48 (silica gel, EtOAc/hexanes, 1:1); IR (film) \( \nu_{\text{max}} \) 3475, 2934, 2837, 1596, 1512, 1463, 1429, 1304, 1245, 1203, 1149, 1046, 935, 831, 735 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.95 (d, \( J = 8.7 \) Hz, 2 H), 6.75 (d, \( J = 8.7 \) Hz, 2 H), 6.65 (d, \( J = 1.8 \) Hz, 1 H), 6.41 (d, \( J = 2.1 \) Hz, 1 H), 6.34 (app t, \( J = 2.7 \) Hz, 1 H), 6.32 (d, \( J = 2.1 \) Hz, 2 H), 5.18 (t, \( J = 6.0 \) Hz, 1 H), 4.26 (d, \( J = 7.2 \) Hz, 1 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.54 (s, 3 H), 3.13 (t, \( J = 6.9 \) Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 161.6, 160.8, 157.7, 157.1, 146.1, 144.2, 136.5, 128.2, 123.3, 113.3, 105.8, 99.7, 99.2, 98.5, 82.2, 67.5, 55.6, 55.2, 55.1, 53.3; HRMS (MALDI-FTMS) calcd for C\(_{26}\)H\(_{28}\)O\(_6\)\(^+\) [M\(^+\)] 436.1886, found 436.1870.

Permethylated Isopaucifloral F. R_f = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) \( \nu_{\text{max}} \) 3001, 2935, 2837, 1713, 1596, 1511, 1462, 1431, 1305, 1247, 1204, 1151, 1065, 1036, 835 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.94 (d, \( J = 8.7 \) Hz, 2 H), 6.89 (d, \( J = 2.1 \) Hz, 1 H), 6.79 (d, \( J = 8.7 \) Hz, 2 H), 6.69 (d, \( J = 2.1 \) Hz, 1 H), 6.36 (app t, \( J = 2.1 \) Hz, 1 H), 6.24 (d, \( J = 2.1 \) Hz, 2 H), 4.51 (d, \( J = 2.4 \) Hz, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.66 (s, 3 H), 3.61 (d, \( J = 2.7 \) Hz, 2 H), 3.52 (d, \( J = 2.4 \) Hz, 1 H), 3.23 (s, 3 H), 3.15 (s, 3 H), 2.52 (s, 6 H), 2.47 (s, 6 H), 2.42 (s, 6 H), 2.37 (s, 6 H), 2.32 (s, 6 H), 2.27 (s, 6 H), 2.22 (s, 6 H), 2.17 (s, 6 H), 2.12 (s, 6 H), 2.07 (s, 6 H), 2.02 (s, 6 H), 1.97 (s, 6 H), 1.92 (s, 6 H), 1.87 (s, 6 H), 1.82 (s, 6 H), 1.77 (s, 6 H), 1.72 (s, 6 H), 1.67 (s, 6 H), 1.62 (s, 6 H), 1.57 (s, 6 H), 1.52 (s, 6 H), 1.47 (s, 6 H), 1.42 (s, 6 H), 1.37 (s, 6 H), 1.32 (s, 6 H), 1.27 (s, 6 H), 1.22 (s, 6 H), 1.17 (s, 6 H), 1.12 (s, 6 H), 1.07 (s, 6 H), 1.02 (s, 6 H), 0.97 (s, 6 H), 0.92 (s, 6 H), 0.87 (s, 6 H), 0.82 (s, 6 H), 0.77 (s, 6 H), 0.72 (s, 6 H), 0.67 (s, 6 H), 0.62 (s, 6 H), 0.57 (s, 6 H), 0.52 (s, 6 H), 0.47 (s, 6 H), 0.42 (s, 6 H), 0.37 (s, 6 H), 0.32 (s, 6 H), 0.27 (s, 6 H), 0.22 (s, 6 H), 0.17 (s, 6 H), 0.12 (s, 6 H), 0.07 (s, 6 H), 0.02 (s, 6 H), -0.01 (s, 6 H).
Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 205.4, 161.9, 161.0, 158.1, 157.7, 141.5, 138.5, 138.4, 135.4, 127.9, 113.8, 106.6, 106.0, 98.9, 96.4, 77.2, 65.3, 55.8, 55.6, 55.3, 55.2, 50.9; HRMS (MALDI-FTMS) calcd for C$_{26}$H$_{26}$O$_6^+$ [M$^+$] 434.1742, found 434.1746.

**Isopaucifloral F (41).** 9-I-BBN (1.61 mL, 1.0 M in hexanes, 1.61 mmol, 7.0 equiv) was added dropwise to a solution of permethylated isopaucifloral F (0.100 g, 0.240 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (10 mL) at 25 $^\circ$C. The reaction solution turned a red color immediately, and was immediately heated at 40 $^\circ$C for 30 min with continued stirring. Upon completion, the reaction mixture was cooled to 25 $^\circ$C, quenched with water (15 mL) and extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried (MgSO$_4$), and concentrated. The resultant red oil was purified by flash column chromatography (silica gel, CH$_2$Cl$_2$/MeOH, 9:1) to afford isopaucifloral F (0.063 g, 72%) as colorless oil. **41:** $R_f = 0.06$ (silica gel, CH$_2$Cl$_2$/MeOH, 9:1); IR (film) $\nu_{max}$ 3349, 1691, 1602, 1512, 1418, 1342, 1251, 1149 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.13 (s, 3 H), 7.35 (s, 2 H), 6.89 (d, $J = 8.7$ Hz, 2 H), 6.74 (d, $J = 8.7$ Hz, 2 H), 6.71 (d, $J = 2.1$ Hz, 1 H), 6.24 (t, $J = 2.1$ Hz, 1 H), 6.11 (d, $J = 2.1$ Hz, 2 H), 4.48 (d, $J = 2.4$ Hz, 1 H), 3.42 (d, $J = 2.7$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 205.1, 160.2, 159.6, 156.8, 156.6, 143.3, 140.1, 135.7, 135.3, 128.9, 116.1, 110.3, 107.0, 102.1, 100.7, 66.3, 51.4; HRMS (MALDI-FTMS) calcd for C$_{21}$H$_{16}$O$_6^+$ [M$^+$] 364.0947, found 364.0961.

**S6:** $R_f = 0.55$ (silica gel, EtOAc/hexanes, 1:1); IR (film) $\nu_{max}$ 2999, 2936, 2836, 1595, 1511, 1446, 1428, 1329, 1302, 1247, 1206, 1175, 1153, 1090, 1067, 1035, 830, 736 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.03 (d, $J = 8.7$ Hz, 2 H), 6.92 (d, $J = 8.7$ Hz, 2 H), 6.74 (d, $J = 8.4$ Hz, 2 H).
Hz, 4H), 6.55 (d, J = 1.2 Hz, 1 H), 6.35 (d, J = 1.8 Hz, 2 H), 6.26 (d, J = 1.8 Hz, 2 H), 4.29 (d, J = 6.9 Hz, 1 H), 4.24 (d, J = 7.5 Hz, 1 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 6 H), 3.53 (s, 3 H); 13C NMR (75 MHz, CDCl3) δ 161.1, 160.7, 158.5, 157.8, 157.0, 145.9, 145.1, 136.8, 130.3, 130.1, 129.1, 128.3, 124.1, 113.7, 113.3, 105.8, 100.4, 99.0, 98.6, 66.4, 56.2, 56.0, 55.6, 55.3, 34.9, 29.7; HRMS (MALDI-FTMS) calcd for C34H36O6S+ [M+H+] 572.2233, found 572.2233.

54: Rf = 0.50 (silica gel, EtOAc/hexanes, 1:1); IR (film) νmax 2995, 2925, 2831, 1593, 1509, 1462, 1246, 1202, 1151, 1061, 1035 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.24 (d, J = 9.0 Hz, 2H), 7.12 (s, 1 H), 7.05 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 2.1 Hz, 1 H), 6.77 (d, J = 8.7 Hz, 2 H), 6.75 (d, J = 8.7 Hz, 2 H), 6.45 (d, J = 2.1 Hz, 2 H), 6.33 (d, J = 2.1 Hz, 1 H), 6.31 (app t, J = 2.1 Hz, 1 H), 4.32 (d, J = 4.2 Hz, 2 H), 3.93 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.74 (s, 6 H), 3.61 (s, 3 H); 13C NMR (75 MHz, CDCl3) δ 161.4, 160.9, 158.4, 157.8, 157.4, 147.7, 145.2, 142.2, 137.9, 130.0, 129.7, 127.8, 126.8, 122.4, 113.7, 105.3, 99.1, 97.6, 94.8, 59.2, 56.8, 55.5, 55.2 (3C); HRMS (MALDI-FTMS) calcd for C34H34O6S+ [M – 2H+] 538.2374, found 538.2355.

Quadrangularin A (8). 8: Rf = 0.03 (silica gel, CH2Cl2/MeOH, 9:1); IR (film) νmax
3306, 1603, 1511, 1459, 1339, 1242, 1149, 1004, 833, 650 cm⁻¹; 1H NMR (300 MHz, MeOH-d3) δ7.13 (d, J = 8.7 Hz, 2 H), 6.98 (s, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.70 (d, J = 1.8 Hz, 1 H), 6.62 (d, J = 8.7 Hz, 2 H), 6.60 (d, J = 8.7 Hz, 2 H), 6.22 (d, J = 2.1 Hz, 2 H), 6.17 (d, J = 1.8 Hz, 1 H), 6.09 (t, J = 2.1 Hz, 1 H), 4.17 (br s, 1 H), 4.03 (br s, 1 H); 13C NMR (75 MHz, MeOH-d3) δ 159.7 (2 C), 157.4, 156.5, 156.2, 149.7, 147.7, 143.4, 138.5, 131.2 (2 C), 130.3, 128.9 (2 C), 125.4, 123.1, 116.0 (4 C), 106.6 (2 C), 103.8, 101.5, 98.4, 61.2, 58.1; HRMS (MALDI-FTMS)
calcd for C_{28}H_{22}O_{6}^+ [M^+] 454.1416, found 454.1440. All spectroscopic data for this synthetic material match those reported by Païs and co-workers for natural quadrangularin A (8).³

Chloride S7. Solid BiCl₃ (0.076 g, 0.240 mmol, 1.05 equiv) was added in a single portion to a solution of alcohol 29 (0.100 g, 0.229 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL) at −78 °C. The resultant reaction mixture was then warmed slowly to −30 °C over the course of 1 h and stirred for 3 h at −30 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO₄), and concentrated. The resultant yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give chloride S7 (0.090 g, 86% yield) as a light yellow oil. S7: Rf = 0.58 (silica gel, EtOAc/hexanes, 1:1); IR (film) v_max 2924, 2853, 1727, 1608, 1596, 1514, 1490, 1463, 1428, 1332, 1305, 1251, 1203, 1179, 1146, 1095, 1066, 1035, 927, 827, 788, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.08 (d, J = 8.7 Hz, 2 H), 6.84 (d, J = 9.0 Hz, 2 H), 6.64 (d, J = 1.8 Hz, 1 H), 6.42 (d, J = 2.1 Hz, 1 H), 6.30 (t, J = 2.4 Hz, 1 H), 6.22 (d, J = 2.4 Hz, 2 H), 5.27 (d, J = 6.0 Hz, 1 H), 4.28 (d, J = 6.3 Hz, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.69 (s, 6 H), 3.59 (s, 3 H), 3.56 (t, J = 6.6 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 161.8, 160.4, 158.7, 156.9, 146.3, 144.5, 133.6, 128.4, 123.7, 114.1, 105.6, 100.1, 98.3, 77.2, 68.4, 65.7, 56.1, 55.6, 55.4, 55.2; HRMS (FAB) calcd for C_{26}H_{20}O_{5}Cl^+ [M^+] 454.1547, found 454.1554.
Monobrominated intermediate 57. Solid NBS (3.2 mg, 0.018 mmol, 1.0 equiv) was added in a single portion to a solution of permethylated quadrangularin A (54, 10 mg, 0.018 mmol, 1.0 equiv) in THF (5 mL) at –78 °C. The resultant solution was stirred for 5 min at –78 °C and then was slowly warmed to 25 °C over the course of 3 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford bromide 57 (8.0 mg, 72%) as a light yellow oil. 57: \( R_f = 0.50 \) (silica gel, EtOAc/hexanes, 1:1); IR (film) \( \nu_{\text{max}} \): 2934, 1592, 1511, 1460, 1330, 1252, 1204, 1177, 1157, 1034, 829, 732 cm⁻¹; \(^1\)H NMR (300 MHZ, CDCl₃): 8.07 (s, 1 H), 7.16 (d, \( J = 8.7 \) Hz, 2 H), 7.05 (d, \( J = 8.7 \) Hz, 2 H), 6.75 (d, \( J = 3.9 \) Hz, 2H), 6.72 (d, \( J = 3.9 \) Hz, 2 H), 6.44 (d, \( J = 2.1 \) Hz, 2 H), 6.34 (s, 2 H), 6.31 (m, 1 H), 4.26 (s, 2 H), 3.93 (s, 3 H), 3.74 (s, 3 H), 3.74 (s, 6 H), 3.72 (s, 3 H), 3.64 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \): 161.0, 158.7, 157.9, 157.0, 156.0, 147.9, 142.0, 141.2, 137.0, 136.8, 130.3, 130.1, 129.8, 129.0, 128.4, 127.8, 113.7, 105.2, 98.0, 97.3, 96.3, 59.0, 56.9, 56.3, 55.9, 55.5, 55.2; HRMS (MALDI-FTMS) calcd for C₃₄H₃₃BrO₆⁺ \([M^+]\) 616.1461, found 616.1439.

Dibrominated intermediate 58. A solution of Br₂ (2.90 μL, 0.056 mmol, 1.0 equiv) in CH₂Cl₂ (0.5 mL) was added dropwise to a solution of permethylated quadrangularin A (54, 0.030g, 0.056 mmol, 1.0 equiv) in CH₂Cl₂ (3.0 mL) at –78 °C. The resultant solution was stirred at –78 °C for 2 h, warmed slowly to 25 °C over the course of 1 h, and stirred for an additional 1 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic
layers were then washed with water (15 mL) and brine (15 mL), dried (MgSO₄), and concentrated. The resultant product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give bromide 58 (0.033 g, 83%) as a light yellow oil. 58: Rf = 0.50 (silica gel, EtOAc/hexanes, 1:1); IR (film) υmax 2954, 1586, 1511, 1460, 1330, 1252, 1177, 1034 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.08 (s, 1 H), 7.27 (d, J = 2.4 Hz, 1 H), 7.16 (d, J = 8.7 Hz, 2 H), 7.10 (d, J = 8.7 Hz, 2 H), 6.76 (d, J = 8.7 Hz, 2 H), 6.70 (d, J = 8.7 Hz, 2 H), 6.38 (d, J = 2.7 Hz, 1 H), 6.33 (d, J = 1.8 Hz, 2 H), 4.71 (s, 1 H), 4.15 (s, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.74 (s, 3H), 3.72 (s, 3 H), 3.62 (s, 3 H), 3.60 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.6, 158.9, 157.8, 157.0, 156.9, 156.0, 146.1, 142.2, 141.4, 136.8, 130.2, 129.6, 129.2, 128.4, 113.9, 113.3, 105.3, 104.4, 98.0, 97.1, 96.5, 58.3, 56.9, 56.3, 55.5, 55.2, 55.1, 54.3; HRMS (MALDI-FTMS) calcd for C₃₄H₃₂Br₂O₆⁺ [M⁺] 694.0566, found 694.0540.

Cascade Product 60. A solution of Br₂ (8.60 μL, 0.167 mmol, 2.0 equiv) in CH₂Cl₂ (0.1 mL) was added dropwise to a solution of permethylated quadrangularin A (54, 0.045 g, 0.083 mmol, 1.0 equiv) in CH₂Cl₂ (4.5 mL) at −78 °C. The resultant solution was stirred at −78 °C for 2 h, warmed slowly to 25 °C over the course of 1 h, and stirred for an additional 1 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (3 mL), poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant yellow-orange oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give trihalogenated adduct 60 (0.052 g, 81%) as a pale yellow oil. 60: Rf = 0.40 (silica gel, EtOAc/hexanes, 1:1); IR (film) υmax 3434, 2956, 2919, 2862, 2091, 1643, 1511, 1462, 1330, 1247, 1211, 1175, 1149, 1111, 1083, 1036, 998 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.49 (d, J =
8.7 Hz, 2 H), 6.80 (br d, J = 8.7 Hz, 6 H), 6.39 (s, 1 H), 6.27 (s, 1 H), 5.59 (s, 1 H), 5.10 (s, 1 H), 4.53 (s, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.77 (s, 6 H), 3.62 (s, 3 H), 3.55 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 158.2, 157.9, 157.5, 156.9, 155.8, 155.3, 145.9, 144.3, 136.3, 135.4, 129.7, 126.5, 126.2, 113.0, 99.5, 98.4, 97.1, 96.2, 78.1, 70.9, 56.8, 56.6, 55.6, 55.1, 51.5; HRMS (MALDI-FTMS) calcd for C\(_{34}\)H\(_{32}\)Br\(_3\)O\(_6\)^+ [M + H\(^+\)] 772.9746, found 772.9756.

**Pallidol (23).** Activated Pd/C (10%, 13.7 mg, 0.013 mmol, 0.5 equiv) was added in a single portion to a solution of tribromide 60 (20.0 mg, 0.026 mmol, 1.0 equiv) in MeOH (2.5 mL) at 25 °C, and then H\(_2\) gas was bubbled slowly and continuously through the solution for 24 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (5 mL), and extracted with EtOAc (3 \(\times\) 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO\(_4\)), and concentrated. The resultant colorless oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give permethylated pallidol (10.6 mg, 76%) as an amorphous white solid. Next, a portion of this newly synthesized adduct (5.0 mg, 0.009 mmol, 1.0 equiv) was dissolved in CH\(_2\)Cl\(_2\) (0.5 mL) and treated with BBr\(_3\) (0.108 mL, 1.0 M solution in CH\(_2\)Cl\(_2\), 0.108 mmol, 12 equiv) at 0 °C. The resultant red mixture was stirred for 4 h at 0 °C, and then stirred for an additional 20 h at 25 °C. Upon completion, the reaction mixture was quenched with water (5 mL), poured into water (5 mL), and extracted with EtOAc (3 \(\times\) 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO\(_4\)), and concentrated. The resultant product was purified by preparative TLC (silica gel, CH\(_2\)Cl\(_2\)/MeOH, 9:1) to give pallidol (3.4 mg, 83%) as an off-white solid. **23:** \(R_f = 0.01\) (silica gel, CH\(_2\)Cl\(_2\)/MeOH, 9:1); IR (film) \(\nu_{max}\) 3368, 2957, 2919,
2850, 1601, 1512, 1459, 1333, 1244, 1168, 1124, 1036, 985, 833 cm\(^{-1}\); \(^1\)H NMR (300 MHz, acetone-\(d_6\)) \(\delta\) 8.03 (app d, \(J = 5.7\) Hz, 4 H), 7.79 (s, 2 H), 6.98 (d, \(J = 8.4\) Hz, 4 H), 6.70 (d, \(J = 8.4\) Hz, 4 H), 6.62 (s, 2 H), 6.19 (d, \(J = 1.5\) Hz, 2 H), 4.56 (br s, 2 H), 3.79 (br s, 2 H); \(^{13}\)C NMR (75 MHz, acetone-\(d_6\)) \(\delta\) 159.3, 156.3, 155.3, 150.3, 137.7, 129.0, 123.2, 115.8, 103.3, 102.5, 60.5, 53.9; HRMS (MALDI-FTMS) calcd for C\(_{28}\)H\(_{22}\)O\(_6\)\(^+\) [M\(^+\)] 454.1414, found 454.1416. All spectroscopic data for the permethylated form of this synthetic material in DMSO-\(d_6\) match those reported by Zaman and co-workers for the same naturally-derived compound.\(^4\)

**Ampelopsin F (22).** A solution of Br\(_2\) (2.87 \(\mu\)L, 0.056 mmol, 2.0 equiv) in CH\(_2\)Cl\(_2\) (0.1 mL) was added dropwise to a solution of permethylated ampelosin D (45, 15.0 mg, 0.028 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (1.5 mL) at –78 \(^\circ\)C. The resultant solution was stirred at –78 \(^\circ\)C for 2 h, warmed slowly to 25 \(^\circ\)C over the course of 1 h, and stirred for an additional 1 h at 25 \(^\circ\)C. Upon completion, the reaction was quenched with saturated aqueous NaHCO\(_3\) (3 mL), poured into water (3 mL), and extracted with EtOAc (3 \(\times\) 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO\(_4\)), and concentrated. The resultant light yellow residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford tribromide 62 (11.5 mg, 53%) as a light yellow oil. Next, solid AIBN (0.8 mg, 0.005 mmol, 1.0 equiv) was added in a single portion at 25 \(^\circ\)C to a solution of tribromide 62 (4.0 mg, 0.005 mmol, 1.0 equiv) and (TMS)\(_3\)SiH (0.0143 mL, 0.046 mmol, 9.0 equiv) in toluene (0.7 mL) that had been carefully degassed by bubbling argon for 20 min directly into the solvent. The resultant solution was then heated at 100 \(^\circ\)C for 8 h. Upon completion, the reaction contents were cooled to 25 \(^\circ\)C, concentrated, and purified directly by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford permethylated ampelopsin F (2.4 mg, 89%) as a light yellow oil.
Finally, after repeating the previous reaction, this newly synthesized adduct (3.0 mg, 0.006 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (0.5 mL) and treated with BBr₃ (0.083 mL, 1.0 M solution in CH₂Cl₂, 0.083 mmol, 12 equiv) at 0 °C. The resultant red mixture was stirred for 4 h at 0 °C, and then stirred for an additional 15 h at 25 °C. Upon completion, the reaction mixture was quenched with water (3 mL), poured into water (3 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant orange-red residue was purified by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 9:1) to afford ampelopsin F (2.5 mg, 90%) as an offwhite solid. 22: Rᵣ = 0.13 (silica gel, CH₂Cl₂/MeOH, 9:1); IR (film) νₘₐₓ 3361, 2953, 2920, 2847, 1598, 1496, 1471, 1330, 1240, 1165, 1121, 1035, 985, 833 cm⁻¹; ¹H NMR (300 MHz, acetone-d₆) δ 8.04 (s, 1 H), 7.98 (s, 1 H), 7.97 (s, 1 H), 7.91 (s, 1 H), 7.83 (s, 1 H), 7.40 (s, 1 H), 7.09 (d, J = 8.4 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 2 H), 6.76 (d, J = 8.4 Hz, 2 H), 6.57 (d, J = 8.7 Hz, 2 H), 6.52 (d, J = 1.8 Hz, 1 H), 6.44 (d, J = 1.8 Hz, 1 H), 6.15 (d, J = 2.1 Hz, 1 H), 6.07 (d, J = 1.8 Hz, 1 H), 4.19 (d, J = 0.6 Hz, 1 H), 4.13 (d, J = 0.6 Hz, 1 H), 3.65 (br s, 1 H), 3.36 (br s, 1 H); ¹³C NMR (75 MHz, acetone-d₆) δ 158.6, 157.8, 157.2, 156.2, 156.0, 153.1, 147.6, 147.4, 134.8, 135.5, 129.9, 129.3, 127.8, 115.6, 115.5, 113.4, 105.7, 104.2, 101.9, 101.6, 58.2, 50.5, 49.7, 47.2; HRMS (MALDI-FTMS) calcd for C₂₈H₂₂O₆⁺ [M⁺] 454.1416, found 454.1402. All spectroscopic data for this synthetic material match those reported by Niwa and co-workers for natural ampelopsin F (22).²
Alkene 63: \( R_f = 0.49 \) (silica gel, EtOAc/hexanes, 1:1); IR (film) \( \nu_{\text{max}} \) 2995, 2924, 2831, 1593, 1508, 1465, 1247, 1201, 1151, 1059, 1037 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.35 (d, \( J = 8.7 \) Hz, 2 H), 7.06 (d, \( J = 8.7 \) Hz, 2 H), 6.88 (d, \( J = 8.7 \) Hz, 2 H), 6.80 (d, \( J = 8.7 \) Hz, 2 H), 6.51 (d, \( J = 1.8 \) Hz, 1 H), 6.39 (s, 1 H), 6.34 (d, \( J = 1.8 \) Hz, 2 H), 6.33 (app t, \( J = 2.1 \) Hz, 1 H), 6.29 (d, \( J = 2.1 \) Hz, 1 H), 4.32 (d, \( J = 2.7 \) Hz, 1 H), 3.92 (d, \( J = 2.7 \) Hz, 1 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 6H), 3.58 (s, 3 H), 3.55 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 160.7, 160.2, 158.6, 157.8, 157.1, 148.4, 144.9, 141.5, 137.7, 130.2, 130.0, 129.7, 128.0, 124.9, 113.6, 113.5, 105.8, 99.7, 99.5, 97.8, 63.2, 55.2, 54.9, 54.5; HRMS (FAB) calcd for C\(_{34}\)H\(_{34}\)O\(_6\)^+ [M – 2H\(^+\)] 538.2374, found 538.2355.

Transient dibrominated intermediate S8. Solid NBS (1.6 mg, 0.009 mmol, 2.0 equiv) was added in a single portion to a solution of permethylated quadrangularin A derivative 63 (5.0 mg, 0.009 mmol, 1.0 equiv) in THF (2 mL) at –78 °C. The resultant solution was stirred for 30 min at –78 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO\(_3\) (2 mL) at –78 °C, poured into water (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (3 mL) and brine (3 mL), dried (MgSO\(_4\)), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford bromide S8 (6.4 mg, 99%) as a light yellow oil. S8: \( R_f \) = 0.35 (silica gel, EtOAc/hexanes, 1:2); IR (film) \( \nu_{\text{max}} \) 2926, 2849, 1776, 1710, 1591, 1510, 1461, 1432, 1327, 1294, 1248, 1201, 1176, 1035 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.42 (d, \( J = 8.7 \) Hz, 2 H), 7.23 (d, \( J = 8.7 \) Hz, 2 H), 6.85 (d, \( J = 9.0 \) Hz, 2 H), 6.81 (d, \( J = 8.7 \) Hz, 2 H), 6.68 (s, 1H), 6.35 (s, 1H) 6.34 (d, \( J = 2.7 \) Hz, 1 H), 6.28 (d, \( J = 2.7 \) Hz, 1 H), 4.44 (s, 1 H), 4.27 (s, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 3.66 (s, 3 H), 3.60 (s, 3 H); \(^{13}\)C NMR (75
MHz, CDCl₃) δ 159.3, 158.8, 158.1, 156.6, 156.0, 145.8, 143.5, 139.9, 135.7, 131.2, 130.8, 129.5, 128.7, 128.4, 128.2, 113.9, 113.6, 113.5, 113.3, 105.3, 98.5, 96.7, 64.6, 56.9, 56.3, 55.6, 55.2, 55.1, 53.7. Upon standing at 25 °C neat or in solution, S7 converted quantitatively into alkene isomer 58.

**Ketone 70.** Solid NaHCO₃ (3.30 g, 39.4 mmol, 10 equiv) and Dess–Martin periodinane (1.67 g, 3.94 mmol, 1.0 equiv) were added sequentially in single portions to a solution of alcohol 29 (1.72 g, 3.94 mmol, 1.0 equiv) in CH₂Cl₂ (30 mL) at 25 °C, and the resultant slurry was stirred for 2 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na₂SO₃ (10 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous NaHCO₃ (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried (MgSO₄), and concentrated to afford ketone 70 (1.66 g, 97% yield) as a white solid. 70: Rᵣ = 0.45 (silica gel, EtOAc/hexanes, 1:1); IR (film) νₓₘₐₓ 3003, 2938, 2838, 1668, 1595, 1512, 1456, 1426, 1351, 1316, 1301, 1273, 1252, 1204, 1175, 1157, 1118, 1080, 1065, 1032, 989, 971, 928, 831, 782, 765, 736, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, J = 8.7 Hz, 2 H), 6.99 (d, J = 2.4 Hz, 2 H), 6.98 (d, J = 16.2 Hz, 1 H), 6.84 (d, J = 2.1 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 2 H), 6.74 (d, J = 15.9 Hz, 1 H), 6.63 (app t, J = 2.4 Hz, 1 H), 6.42 (d, J = 2.4 Hz, 1 H), 3.91 (s, 3 H), 3.79 (s, 6 H), 3.78 (s, 3 H), 3.68 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 197.3, 161.3, 160.8, 159.5, 158.4, 140.4, 137.7, 131.0, 129.6, 128.0, 123.1, 121.4, 114.0, 107.3, 105.7, 101.1, 97.7, 55.8, 55.5 (2 C), 55.3; HRMS (MALDI-FTMS) calcd for C₂₆H₂₆O₆⁺ [M⁺] 434.1729, found 434.1725.
**7-Membered Ring Bromide 73.** A solution of Br₂ (0.024 mL, 0.460 mmol, 1.0 equiv) in CH₂Cl₂ (0.4 mL) was added dropwise to a solution of ketone 70 (0.200 g, 0.460 mmol, 1.0 equiv) in CH₂Cl₂ (0.2 mL) at –78 °C. The reaction mixture was then stirred for 1 h at –78 °C, warmed slowly to 0 °C over the course of 1 h, and then stirred for 3 h at 0 °C and an additional 12 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (2 mL), poured into water (1 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated to afford bromide 73 (0.118 g, 50%) as a white solid that was utilized immediately in subsequent chemistry. [Note: this product is especially light sensitive, so it must be kept away from sunlight at all times].

**7-Membered Ring Acetate 76.** Solid AgOAc (0.073 g, 0.438 mmol, 3.0 equiv) was added in a single portion to a solution of bromide 73 (0.075 g, 0.146 mmol, 1.0 equiv) in neat AcOH (5 mL) at 25 °C. The reaction flask was then wrapped with aluminum foil to protect its contents from light, and stirring was continued at 25 °C for 3 h. Upon completion, the reaction mixture was neutralized with saturated aqueous NaHCO₃ (3 mL), poured into water (3 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant yellow oily residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give acetate 76 (0.045 g, 62%) as a crystalline white solid. 76: Rᶠ = 0.25 (silica gel, EtOAc/hexanes, 1:1); IR (film) νmax 3001, 2939, 2837, 1732, 1669, 1600, 1512, 1460, 1315, 1235, 1152, 1100, 1059, 1034, 963, 834, 792, 735 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.87 (d, J = 5.4 Hz, 1 H), 6.83 (d, J = 7.5 Hz, 2 H), 6.82 (d, J = 2.7 Hz, 1 H), 6.63 (d, J = 8.7 Hz, 2 H), 6.47 (d, J = 2.4 Hz, 1 H),
6.45 (d, J = 2.1 Hz, 1 H), 6.30 (d, J = 2.1 Hz, 1 H), 4.81 (d, J = 5.4 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 3H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 1.95 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 194.2, 170.3, 162.2, 160.6, 159.5, 158.9, 158.0, 143.1, 141.3, 131.2, 129.3, 122.6, 115.0, 113.4, 107.8, 103.2, 101.8, 97.9, 69.7, 56.0, 55.6, 55.4, 55.1, 51.6, 21.2; HRMS (MALDI-FTMS) calcd for C\(_{28}\)H\(_{29}\)O\(_8\)\(^{\text{+}}\) [M + H\(^{+}\)] 493.1862, found 493.1847.

Permethylated Diptoindonesin D Analog 77. Finely powdered K\(_2\)CO\(_3\) (0.121 g, 0.873 mmol, 10 equiv) was added in a single portion to a solution of acetate 76 (0.043 g, 0.087 mmol, 1.0 equiv) in MeOH (8 mL) at 25 \(^\circ\)C, and the resultant slurry was stirred for 12 h at 25 \(^\circ\)C. Upon completion, the reaction contents were neutralized with saturated aqueous NH\(_4\)Cl (5 mL), poured into water (5 mL), and extracted with EtOAc (3 \(\times\) 10 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO\(_4\)), and concentrated. The resultant colorless residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give an inseparable mixture of alcohol and lactol (2.5:1, 0.039 g, 78%
combined). Alcohol and lactol: Rf = 0.16 (silica gel, EtOAc/hexanes, 1:1); IR (film) ʋmax 3469, 2933, 2839, 1664, 1600, 1511, 1460, 1312, 1249, 1211, 1149, 1096, 1057, 1036, 987, 935, 833, 735 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 6.89 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 2.4 Hz, 1 H), 6.67 (d, J = 8.7 Hz, 2.8 H), 6.60 (d, J = 2.4 Hz, 1 H), 6.52 (d, J = 2.1 Hz, 1.8 H), 6.44 (d, J = 2.1 Hz, 1 H), 6.32 (d, J = 2.1 Hz, 0.4 H), 6.04 (d, J = 1.8 Hz, 0.8 H), 5.88 (d, J = 5.4 Hz, 1 H), 5.54 (d, J = 5.7 Hz, 0.4 H), 4.76 (d, J = 6.0 Hz, 0.4 H), 4.66 (d, J = 6.0 Hz, 1 H), 3.96 (s, 1.2 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 4.2 H), 3.71 (s, 1.2 H), 3.69 (s, 4.2 H), 3.58 (s, 1.2 H); 13C NMR (75 MHz, CDCl3) δ 194.3, 162.0, 161.6, 160.1, 159.8, 159.2, 158.7, 158.4, 157.8, 155.4, 154.3, 151.8, 141.1, 140.8, 140.4, 131.9, 131.5, 128.9, 123.3, 120.9, 119.8, 117.8, 113.5, 108.2, 107.8, 104.8, 103.5, 102.5, 97.8, 97.2, 97.0, 94.8, 79.3, 67.5, 56.1, 55.9, 55.4, 55.3, 55.2, 55.0, 54.7, 53.6, 47.8; HRMS (MALDI-FTMS) calcd for C26H27O7 [M + H]+ 451.1757, found 451.1756. Dess–Martin periodinane (0.049 g, 0.115 mmol, 1.0 equiv) and solid NaHCO3 (0.097 g, 1.15 mmol, 10 equiv) were added sequentially in single portions to a solution of alcohol and lactol (0.052 g, 0.115 mmol, 1.0 equiv) in CH2Cl2 (10 mL) at 25 ºC, and the resultant slurry was stirred for 1.5 h at 25 ºC. Upon completion, the reaction contents were quenched with saturated aqueous Na2SO3 (3 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 ºC, poured into water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with saturated aqueous NaHCO3 (3 × 10 mL), dried (MgSO4), and concentrated to give the desired permethylated diptoindonesin A analog (0.051 g, 99%) as a light yellow oil. 77: Rf = 0.33 (silica gel, EtOAc/hexanes, 1:1); IR (film) ʋmax 3008, 2939, 2837, 1668, 1592, 1512, 1462, 1327, 1295, 1250, 1211, 1157, 1070, 1023, 974, 928, 832, 732; 1H NMR (300 MHz, CDCl3) δ 6.98 (d, J = 2.4 Hz, 1 H), 6.91 (d, J = 8.1 Hz, 2 H), 6.69 (d, J = 9.2 Hz, 2 H), 6.64 (d, J = 2.4 Hz, 1 H), 6.52 (d, J = 2.1 Hz, 1 H), 6.47 (d, J = 2.1 Hz, 1 H), 5.18 (s, 1
H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.70 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 195.3, 192.5, 163.0, 162.6, 161.1, 159.9, 158.4, 141.9, 136.7, 129.9, 129.4, 122.5, 116.8, 113.8, 105.8, 105.4, 104.0, 98.8, 66.7, 56.8, 56.1, 55.7, 55.5, 55.1; HRMS (MALDI-FTMS) calcd for C$_{26}$H$_{25}$O$_7$ $^+[M + H]^+$ 449.1556, found 449.1619.

References


38: isospekopsin D
MeOD, 300 MHz
38; isompekopsin D
MeOD. 75 MHz
$\text{CDCl}_3$, 300 MHz
Chapter 3

Synthetic Efforts Towards Dihydrobenzofuran-containing Higher Order Resveratrol Oligomers
3.1 Introduction

After our initial success preparing many of the dimeric structures within the resveratrol family, we directed our efforts towards developing key carbon-carbon bond forging reaction sequences to access far higher levels of architectural complexity within this class of natural products. Vaticanol A (1) was selected as our next target to demonstrate our synthetic approach. This natural product was first isolated from the stem bark of the Southeast Asian plant Vatica rassak (Dipterocarpaceae) in 2000 by the Tanaka group. Structurally, it is a polycyclic resveratrol trimer that possesses not only cyclopentane and cycloheptane systems, but also a dihydrobenzofuran ring along with six attendant stereocenters. To date, five diastereomers of vaticanol A (2-6, Figure 1) have been isolated from various plants in Asia, and preliminary research in recent years has shown that these molecules exhibit interesting and unique biological activities. For instance, vaticanols A (1) and E (6) exhibited antidiabetogenic activities in animal studies, while amurenin G (5) has proven to be a potent natural SIRT1 inhibitor that can rescue doxorubicin responsiveness via down-regulation of multidrug resistance 1 and could potentially be a useful agent for chemoresistance reversal by suppressing FoxO1 activity and MDR1 expression in MCF-7/ADR cells. Prior to our work, no total syntheses or synthetic studies towards any of these natural products had been reported in the literature. Our goal globally is to apply the knowledge gained from our past studies in this class of natural products to access these structures individually in a controlled fashion. We anticipated two key challenges in this work: 1) selective functionalization of a dimeric precursor towards the natural product, and 2) an efficient method for dihydrobenzofuran ring formation on a highly electron-rich system.
3.2 Development of a general method for dihydrobenzofuran ring formation and initial model studies

As discussed in the previous chapter, we have already obtained synthetic tools for two common carbon frameworks, the indane and seven-membered carbon ring systems that are found in many of the resveratrol-based natural products. Therefore, we focused our research on solving the last challenge needed to access vaticanol A-like structures (1-6, Figure 1), which entailed forming five-membered dihydrobenzofuran rings. Here, the natural product ampelopsin B (7, Scheme 1) was chosen as an initial target to serve as a model system for more complex structures such as vaticanol A (1). Ampelopsin B (7) was first isolated from the roots of *Ampelopsis brevipedunculata var. hancei*, a plant that has been used as an anti-inflammatory agent in the treatment of hepatitis and nephritis in Asia. As indicated in Scheme 1, this resveratrol dimer contains a seven-membered all-carbon ring adjoined by a dihydrobenzofuran. Retrosynthetically, 7 could be derived from dihydrobenzofuran ring formation from the seven-membered ring ketone (8), which in turn could arise from acid-catalyzed cyclization of the oxidized form of our key building block previously described in chapter 2. In the next subsection, we outline three main synthetic strategies we have pursued to reduce this general plan to practice.
3.2.1 Electrophilic activation/cyclization approach

Our first strategy (Scheme 2) was to install the fourth aryl ring to establish the correct carbon-carbon connection through a Grignard reaction with an appropriate benzyl Grignard reagent. Next, the product would undergo dehydration followed by electrophilic activation of the resultant olefin to cyclize to the desired 5-membered oxygen ring system (11), which then could hopefully be converted to ampelopsin B (7). From the outset, the stereoselectivity of the ring closing step was not certain. Indeed, the one stereogenic center in this relatively flat molecule (10) is quite remote from the reactive center; thus, we anticipated that the proposed electrophile could add from either side of the molecule. If such absence of selectivity were observed, however, we felt it would be acceptable as this approach would enable access to other structural diversity in this natural product family. For example, balanocarpol (13) with its two dihydrofuran ring stereocenters reversed [relative to ampelopsin B (7)] could potentially be synthesized from a reaction sequence similar to this method with a few modifications.

Starting from the seven-membered ring ketone (8), the addition of 4-methoxy- benzyl magnesium chloride was carried out successfully at −78 °C to give an ~1.3:1 mixture of the expected tertiary alcohol, indicating that there indeed is minimal selectivity between the α- and the β-face of the ketone within this structure. Next, this mixture of alcohols was dehydrated stereoselectively via the Burgess reagent at reflux to yield alkene (10) as the major isomer (~2:1 ratio), which we surmise to be the thermodynamically favored alkene isomer based on the steric
bulk possessed by the adjoining phenolic methyl ether. However, the resultant olefin proved to be unreactive towards various electrophiles (including Brønsted acids, Lewis acids, and molecular bromine). Attempted epoxidation or hydroboration of the double bond similarly failed to provide positive results.

![Scheme 2. Attempts to synthesize the dihydrobenzofuran ring through an electrophilic activation of the olefin intermediate (10).](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-TsOH, toluene, 80 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>TFA, CH₂Cl₂, 0 °C to 23 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>pK(TFA)₂, CH₂Cl₂, 0 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>Hg(OCCF₃)₂, THF, 0 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>Br₂, CH₂Cl₂, 78 °C to 23 °C</td>
<td>bromination on the aryl rings</td>
</tr>
<tr>
<td>6</td>
<td>mCPBA, NaN₂CO₂, CH₂Cl₂, 23 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>7</td>
<td>BH₃·THF, THF, 23 °C</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) (4-methoxybenzyl)magnesium chloride (4.0 equiv), THF, -78 °C to 25 °C, 3h, 76%; (b) Burgess reagent (5.0 equiv), THF, reflux, 12 h, 68%.

We suspected that one possible reason for the lack of this substrate’s reactivity (i.e., 10) during the cyclization step might be the protected nature of the proposed nucleophile. Consequently, through controlled exposure of 8 to 1.0 equivalent of BBr₃ in CH₂Cl₂ at −78 °C, we could achieve selective deprotection of the phenolic methyl ether closest to the biaryl ketone followed by standard addition of a p-methoxybenzyl group to that newly unveiled phenol to give compound 14 (Scheme 3), a molecule which then could be deprotected again after Grignard addition and dehydration to reveal the free phenol of 16 with expected enhanced nucleophilicity relative to the protected phenolic methyl ether (i.e., 10) previously mentioned. Thus, with 16 in hand, a variety of Lewis and Brønsted acids (such as p-TsOH, TFA and PhSeBr) were tested in...
an effort to promote the proposed cyclization. We found success in ring formation with the treatment of 16 with AgOAc in CH$_2$Cl$_2$ under reflux for 12 h to afford 17 in 20% yield. However, no dihydrofuran was formed. Instead, we obtained the fully aromatic benzofuran system of (17), a motif which could presumably have formed by the intermediacy of the desired dihydrobenzofuran ring that was likely oxidized under the reaction conditions. Further attempts to functionalize the resultant benzofuran compound (17) are discussed in the next subsection, although we note here that this approach, and several other explorations, never gave a dihydrobenzofuran ring directly.

3.2.2 Photocyclization Approach

In addition to the electrophilic-activation/cyclization approach discussed above, another strategy we carried out to install the dihydrobenzofuran ring on the seven-membered ring structure was inspired by the work from the Meador group.$^8$

As shown in Scheme 4, their studies showed that a series of substituted 2,3,5,6 tetraarylbenzo[1,2-\(b\):5,4-\(b\')]difurans (20) could be synthesized following photocyclization of o-
alkoxyphenyl ketones (18), materials whose systems bear some similarity to our substrate (14) prepared via selective phenol deprotection and PMB re-protection. Indeed, as shown in Scheme 5, irradiation of ketone 14 using light from a mercury lamp presumably leads to the formation of a biradical intermediate, 21, via a triplet state intramolecular abstraction of a benzyloxy hydrogen by the carbonyl oxygen. This biradical intermediate can then undergo a 1,5-cyclization to afford the cyclized product 22. Further irradiation of 22 was then presumed to generate the core of amurenens I (23) via a dehydration/photocyclization/rearomatization sequence.

Scheme 5. Photocyclization of 14 leads to a method to form the core of amurenens I (23).

Reagents and conditions: a) BBr₃ (1.0 equiv), CH₂Cl₂, -78 °C, 1 h, 92%; b) p-methoxybenzyl chloride (2.0 equiv), K₂CO₃ (5.0 equiv), TBAI (0.2 equiv), acetone, reflux, 12 h, 97%; c) 0.01 M solution in benzene, 23 °C, 4 h, 75%.

Table 1. Optimization of photocyclization of 14.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hν, 0.02 M in benzene, 23 °C, 2 h</td>
<td>75% conversion</td>
</tr>
<tr>
<td>2</td>
<td>hν, 0.01 M in benzene, 23 °C, 0.5 h</td>
<td>85% conversion</td>
</tr>
<tr>
<td>3</td>
<td>hν, 0.001 M in benzene, 23 °C, 0.5 h</td>
<td>95% conversion</td>
</tr>
<tr>
<td>4</td>
<td>hν, 0.01 M in benzene, 23 °C, 4 h</td>
<td>23 (amurenens I core)</td>
</tr>
<tr>
<td>5</td>
<td>Sunlight, CDCl₃, 23 °C, 48 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>
As listed in Table 1, this photocyclization to 22 required a specific wavelength (350 nM) and proceeded more efficiently with a more dilute solution. Unfortunately, the tertiary alcohol 22 was very prone to dehydration and yielded the corresponding benzofuran (i.e., 17) under even mildly acidic conditions (e.g., dehydration is readily catalyzed by exposure to silica gel upon standing) or at elevated temperatures. However, if treated carefully, adduct 22 could be isolated and used in attempts for alcohol deoxygenation under radical/ionic/noble metal-based conditions. As shown in Table 2, however, these attempts have thus far proven fruitless as 17 was the dominant product consistently isolated from our experiments.

Moreover, while catalytic reduction of simpler benzofuran systems has provided cis-dihydrobenzofurans, to our knowledge, no methods for reducing 2,3-disubstituted benzo[b]furans to the trans-dihydrobenzofuran have been reported. Common reduction conditions (e.g., H2/Pd/C, TFA/Et3SiH) applied to other complex benzofurans were not
suitable for our systems (Table 3); either recovered starting material or complex mixtures of products were obtained. It is also worth noting that experiments seeking to use high-pressure hydrogenation as well as substrates bearing substituents with different electronic effects (based on phenol modulation) also failed to yield positive results. As such, although we have developed two approaches to prepare the desired natural product core (17), an alternative strategy was needed in order to access the correct oxidation state for ampelopsin B (7).

Of course, this highly efficient sequence involving photocyclization and dehydration could be applied in the synthesis of other highly functionalized, polycyclic polyphenols in the resveratrol family, such as malibatol A (27)\(^\text{12}\) and shoreaphenol (28)\(^\text{13}\) as listed in Figure 2, as long as the goal is benzofuran formation.
3.2.3 Oxidative Cyclization and total synthesis of ampelopsin B

In light of the studies above and our continued quest to develop a general method for the dihydrofuran ring formation, we decided next that instead of creating the two quaternary stereocenters in the 5-membered oxygen ring in one cyclization, we would adopt a stepwise approach to ensure the correct oxidation state of the final product. In the 1970s, Schofield and co-workers reported the formation of benzofuran and 2,3-dihydrobenzofuran derivatives via phenol oxidation using DDQ (Scheme 6).14

Their studies have shown that DDQ could exclusively oxidize the 4-hydroxyphenyl ring in presence of a 2-hydroxyphenyl ring to generate the corresponding p-quinone methides, which then could undergo an intramolecular nucleophilic addition by the neighboring ortho-hydroxy group to afford the desired 2,3-dihydrobenzofuran (31). Their success gave us confidence in the application of this synthetic strategy (Scheme 7) in our own system.
We anticipated that there would be two challenges that needed to be addressed eventually in this sequence: 1) installing the correct stereochemistry at the carbonyl carbon, and 2) cyclizing the dihydrofuran ring in a stereoselective manner. As a model study, with Grignard addition product 35 in hand, we decided to test whether the catalytic hydrogenation of its dehydration product would allow addition of hydrogen from the $\beta$-face of the molecule to provide the reversed stereochemistry required for the two pendant aromatic rings on the seven-membered ring. Interestingly, as indicated in Scheme 8, treatment of tertiary alcohol (35) with Et$_3$N and SOCl$_2$ at $-78$ °C afforded a mixture of olefin isomers ($36:37 = 1:3$) with reversed stereoselectivity compared to those generated from the Burgess dehydration ($36:37 = 2:1$). To our surprise, the following hydrogenation reaction was stereospecific: the olefin mixture with 36 as the dominant isomer yielded 38 as the major product; the one with 37 as the major alkene gave rise to a mixture of diastereomers with 39 predominating. This outcome suggests that there is a significant difference in the structural conformations of 36 and 37. One hypothesis based on evidence of simple molecular models is that the seven-membered ring of 36 is in a pseudo-chair conformation, in which the alkene’s $\beta$-face is blocked by only the para-substituted phenyl ring, while a pseudo-boat conformation of 37 encourages the addition of hydrogen from the $\beta$-face as the $\alpha$-face approach is shielded by the adjacent methoxyl group. Unfortunately, when we applied this approach to the real system with the correct protecting groups needed for the DDQ-initiated cyclization (Scheme 9), the olefin’s stereochemistry was very difficult to manipulate through switching the reaction conditions because the significantly increased steric bulk possessed by the adjoining phenolic benzyl ether strongly favors the alkene geometry with the aryl ring pointing away (41). Indeed, the dehydration occurred readily during the Grignard reaction with only one alkene isomer isolated. Furthermore, the subsequent hydrogenation could
be readily stopped after the cleavage of benzyl ethers, and further reduction of 42 only resulted in decomposition. These results, while discouraging, reflect a common occurrence with materials in the resveratrol class: small changes often result in large differences in reactivity, even for seemingly simple steps.

Nevertheless, another approach to construct the desired carbon–carbon bond at the carbonyl carbon was necessary, for which we pondered attempting a nucleophilic addition at this position via an o-quinone methide intermediate (Scheme 10); this approach has been frequently used in organic synthesis.\(^\text{16}\) For example, the formation of o-quinone methides from o-(α-hydroxyalkyl)-phenols through thermal/photochemical/acid-catalyzed elimination has been well
documented in the literature, although the challenge here is overall stability/lifetime of the species (such as 44) in terms of their ease of use.

![Scheme 10: Proposed route to introduce the fourth aryl ring via an o-quinone methide intermediate.](image)

Starting with 46, LiAlH₄ reduction at ambient temperature converted the ketone to its corresponding bis-benzylic alcohol (43), which readily underwent elimination during acidic workup to provide the o-quinone methide (44) in 83% yield in one step. In contrast to some simple short-lived quinone methides that are difficult to isolate under normal circumstances, this substrate (44) proved stable enough to be characterized, perhaps due to the electron-donating substituents on its aryl rings and the extended conjugation to the neighboring aromatic ring. With this reactive intermediate in hand, successful nucleophilic addition to the electron deficient site of the o-quinone methide afforded a mixture of the alkylation products in a 5:1 ratio of diastereomers, with the one attacking from the α-face of the molecule as the dominant product. The subsequent benzyl ether deprotection and DDQ-induced cyclization proceeded smoothly as expected to give the tretramethylated ampelopsin B (34) in 54% yield. In this case, the final oxidative cyclization step gave the more thermodynamically stable trans-disposed dihydrofuran ring exclusively, probably due to strain minimization during the transition state. However, it is also possible that any cis-disposed products formed during the cyclization could be isomerized into the trans-materials under the slightly acidic conditions used.
At this stage, a total synthesis of ampelopsin B (7) was carried out to demonstrate the synthetic utility of the newly developed chemistry. The tert-butyldimethylsilyl (TBS) group was selected to replace the methyl ether as the phenol protecting group due to its ease of installation and removal. As shown in Scheme 12, a reaction sequence very similar to the one discussed above was applied, but several elements are notable. First, after global deprotection of 8 by BBr₃, selective re-protection of the four free phenol groups (except the one located ortho to the carbonyl) could be achieved by utilizing the stabilizing hydrogen-bonding interaction between the ketone and the neighboring phenol.¹⁸ Second, LiAlH₄ reduction step gave a 5:1 mixture of alcohols (52) and the quinone methide (51) upon workup. Slow conversion of 52 to 51 can occur by heating the mixture in CDCl₃ for 8 hours. Third, the selectivity of the Grignard addition was improved in this substrate, (8:1 with our desired diastereomer as the dominant one) probably due to the increased steric bulk around the reaction site as contributed by the TBS groups. Finally, while it is known that dihydrobenzofuran ring opening could be easily catalyzed by proton or
Lewis acids, the dihydrobenzofuran was intact after TBS deprotection under basic conditions (TBAF).

**Scheme 12. Total synthesis of ampelopsin B (7) via oxidative cyclization.**

Reagents and conditions: a) TBSCl (6.5 equiv), imidazole (6.0 equiv), CH\(_2\)Cl\(_2\), 23 ^\circ\mathrm{C}, 6 h, 73% b) LiAlH\(_4\) (5.0 equiv), THF, 45 ^\circ\mathrm{C}, 2.5 h, 5:1 mixture of 52 and 51, 88%; c) CICl\(_2\), 40 ^\circ\mathrm{C}, 8 h, 85% d) (4-benzyloxybenzyl)magnesium chloride (6.0 equiv), THF, -78 ^\circ\mathrm{C} to 25 ^\circ\mathrm{C}, 4 h, 6:1 mixture of 53 and the other isomer, 85%; e) Pd/C (19%, 1.0 equiv), H\(_2\), EIOAc/MeOH (1:1), 25 ^\circ\mathrm{C}, 1.5 h, 92%; f) DDQ (1.25 equiv), benzene, 25 ^\circ\mathrm{C}, 1 h, 96%; g) TBAF (6.0 equiv), THF, 0 ^\circ\mathrm{C}, 2 h, 95%.

### 3.3 Initial attempts at electrophile-induced cyclization led to unique scaffolds of both natural and non-natural origin

With the synthetic tools to prepare the dihydrobenzofuran ring in hand, we next turned our attention towards the construction of the 7,5-fused ring system possessed by vaticanol A and related structures (1-6). Retrosynthetically, the precursor needed for the final dihydrofuran ring formation could be derived from an electrophilic activation/Friedel–Crafts cyclization sequence of a biaryl ketone such as 57, which, in turn, could arise from a lithium-halogen exchange reaction of 58 followed by a nucelophilic addition to 3,5-dimethoxybenzaldehyde (Scheme 13).

The requisite aryl bromide was known to be synthesizable from a selective aromatic bromination at the most nucleophilic site of ampelopsin D (59) in protected form.
In fact, the sequence to prepare 57, the precursor for Friedel–Crafts cyclization, was carried out smoothly as we expected. Starting with 60, we were able to selectively and cleanly monobrominate in 90% yield (based on recovered starting material) upon its exposure to a substoichiometric amount of N-bromosuccinimide (NBS) in CH₂Cl₂ with slow warming from –78 °C to ambient temperature over the course of 3 hours. Next, the brominated product was treated with n-BuLi to induce the newly installed bromine atom to undergo lithium-halogen exchange, enabling subsequent introduction of the commercially available 3,5-dimethoxybenzaldehyde to install the fifth aryl ring in 65% yield. Oxidation of the resultant bis-benzylic alcohol with Dess–Martin periodinane then completed the synthesis of compound 61 (Scheme 14) in 52% overall yield starting from 60.
With this preparative work in hand, our goal now was to expose this key adduct (61) to an appropriate electrophile to effect the synthesis of the seven-membered ring of the target as expressed by intermediate 56. Based on our previous work on the synthesis of seven-membered rings, both Brønsted acid and electrophilic bromine sources were the ideal candidates for our utilization. Since we expected that in the electrophilic activation step the electron-rich B-ring would be attacked prior to the olefin due to its high nucleophilicity and in analogy to our work on the pallidol and ampelopsin F systems (cf. Chapter 2), a second site-selective bromination of 61 with 1 equivalent of NBS was carried out to block the reactive site on the B-ring (Scheme 14). In addition, this newly installed bromine atom could also deactivate the B-ring towards further electrophilic attack in hope of shutting down the competing Friedel–Crafts cyclization pathway to the ampelopsin F core (vide infra).

Unfortunately, during our initial attempts to effect electrophile-induced Friedel-Crafts cyclization of 62 to form 63 (Scheme 15), all efforts to use proton (including $p$-TsOH, HCl, HBr, HNO$_3$ among other acids) as an activator failed due to olefin isomerization (i.e., 67) followed by retro-Friedel–Crafts acylation upon heating to give 68. On the other hand, activation of the olefin within 62 by molecular bromine or NBS successfully led to the formation of a 7,5-fused ring structure (66) along with a unique tricyclic core (65) resulting from double Friedel–Crafts cyclization. During this reaction, we postulate that electrophilic activation of the alkene occured.
from the β-face to generate intermediate 64. The steric bulk of the ketone and E-ring system should prevent rotation of the newly-formed quinone methide away from its initial positioning. As such, we expected that subsequent Friedel–Crafts cyclization by the E-ring onto the quinone methide should occur in a stereoselective fashion to complete a synthesis of 69 with all its relative stereochemistry established as in vaticanol A (1). However, although the cyclization occurred as we planned, the isolation of 69 proved to be rather difficult in our hands as the elimination to alkenes proceeded too fast during the reaction. Furthermore, all our attempts to reduce this olefin (66) resulted in the selective removal of the ketone functionality, leaving the alkene untouched. Interestingly, if Et₂SBr·SbBrCl₅ (bromodiethylsulfide bromopentachloroantimonate, BDSB),¹⁹ a bromonium source our group had recently developed, was used to activate the cyclization, the dominant product became tricyclic structure 65, which was a minor side-product under the previously described conditions. The basis for this unique selectivity and the mechanism for this Friedel-Crafts cyclization are currently being investigated in our group.
Overall, although this electrophile-induced cyclization approach could not lead us to vaticanol A (1), it demonstrated the concept of formation of a 7,5-fused ring system via a quinone methide intermediate and laid the foundation for our next strategy to construct the desired carbon skeleton. Moreover, this reaction sequence could be potentially applied to the total synthesis of upunaphenol G (70), which is another resveratrol-based natural product bearing the same structural motif as 66.

3.4 Oxidative Cyclization to form the 7,5-fused ring system

3.4.1 Initial model studies
In light of the results from our initial attempts to synthesize the vaticanol A core, we decided to adopt an alternative strategy to generate the quinone methide precursor for the Friedel–Crafts cyclization. With the success of DDQ-initiated oxidative cyclization to form the dihydrobenzofuran ring, we wondered whether a similar phenol oxidation could promote the desired Friedel–Crafts alkylation without generation of an internal alkene. To test our hypothesis, we first conducted a model study for this oxidative seven-membered ring formation from the bis-benzylic ketone (71), which could be easily prepared by our standard method for the synthesis of the biaryl alcohol followed by oxidation and hydrogenation. Treatment of 71 with DDQ in two solvent systems (benzene and CH₂Cl₂) afforded two different results. The desired Friedel–Crafts cyclization occurred smoothly to form the seven-membered ring ketone (77) in 73% yield in CH₂Cl₂ at ambient temperature; the reaction in the less polar solvent benzene only gave an alternate compound which was characterized to be the six-membered hemiketal ring (74) based on ¹H NMR spectroscopy analysis, material we surmise to result from a nucleophilic attack of the carbonyl group onto the quinone methide followed by H₂O attack during work-up.

Scheme 17. Model studies of DDQ-promoted Friedel-Crafts cyclization.

Reagents and conditions: (a) DDQ (1.5 equiv), benzene, 25 °C, 12 h, 54%; (b) DDQ (1.5 equiv), CH₂Cl₂, 25 °C, 8 h, 73%.
3.4.2 Formation of the 7,5-fused ring system via DDQ-promoted oxidative cyclization

The stage was now set to apply this oxidative cyclization to the synthesis of vaticanol A core. Starting from the five-membered ring alcohol 78, nucleophilic addition of $p$-benzyloxy-$\alpha$-toluenethiol to the carbocation generated upon exposure to $p$-TsOH afforded the tetraaryl intermediate (79) with a different phenol protecting group on the aryl ring to later be subjected to oxidation. Next, a Ramberg-Bäcklund reaction using Meyers’s modified conditions yielded a ~3:1 ratio of separable $E$- (80) and $Z$-alkenes. Monobromination of 80 followed by the previously described lithium-halogen exchange/nucleophilic addition sequence installed the fifth aryl ring on the molecule. Upon oxidation, catalytic hydrogenation of the ketone (81) with Pd/C deprotected the benzyl ether and stereoselectively reduced the olefin in one pot to give 82. During this step, the last stereocenter on the indane ring was set via addition of H$_2$ from the opposite face of the adjacent C-ring. This stereocontrolled reduction would also hopefully prevent nucleophilic attack of the B-ring onto the $p$-quinone methide of the D-ring due to their trans relationship.
As in the previous model study, treatment of this phenol (82) with DDQ in CH₂Cl₂ smoothly afforded a ~7:1 mixture of cyclization products 84 and 85 after 8 h. Based on molecular modeling, the stereocontrol in the final ring closure could be explained by a highly possible π-π stacking interaction of the quinone methide and its C-ring neighbor. As indicated in Scheme 19, initial results showed a change in product ratio with prolonged reaction time; an increased amount of 85 (close to 1:1 after 48 h) was observed, indicating that epimerization of 84 to 85 occurred in the slightly acidic reaction solution. One possible mechanism to account for this reaction is through an acid-catalyzed tautomerization involving intermediate 86. Although this reaction still requires further investigation and optimization, this observation has potential in developing reaction conditions to selectively access 84 and 85 in a stereoselective fashion. While 84 can serve as the precursor for pauciflorol A (3) and suffruticosol A (4), 85 possesses the bicyclic core with all of its relative stereochemistry established for vaticanol A (1) and suffruticosol B (2).
3.5 Progress towards the total synthesis of resveratrol-based natural products with the 7,5-fused ring systems
With the natural product cores 84 and 85 in hand, studies towards the final dihydrofuran ring installations in these highly complex molecules could begin. As shown in Scheme 20 using 84 for illustrative purposes, a sequence of methylation, selective deprotection, and reduction led to the bis-benzylic alcohol (87) in 75% yield over three steps. Despite the ease of o-quinone methide formation in the ampelopsin B (7) system, this o-(α-hydroxalkyl)-phenol adduct (87) did not undergo elimination spontaneously during acidic work-up. Various acid-catalyzed elimination conditions (including HCl, p-TsOH and AcOH at different temperatures) were screened to induce an efficient o-quinone methide formation of 87. In fact, the o-quinone methide (88) in this 7,5-fused ring system is rather challenging to work with. Accessing 88
requires heating in neat acetic acid at 80 °C for 2 h to initiate the elimination, and the resultant quinone methide is very unstable; it cannot be isolated and has to be used immediately. Addition of freshly prepared Grignard reagent into the in situ-generated o-quinone methide (88) afforded an ~3:1 mixture of diastereomers 89 and 90 in 69% yield. Based on what we learned from our previous work and molecular modeling, we believe that the stereoselectivity of this Grignard addition should be controlled by the positioning of the para-substituted aryl ring on the seven-membered ring; the major isomer (90) of this reaction should be the one with nucleophiles attacking the quinone methide from the more accessible β-face. Catalytic hydrogenation cleaved the benzyl ether smoothly in nearly quantitative yield to provide the precursor for the last dihydrofuran ring closure. The two preliminary experiments with this DDQ cyclization precursor, both conducted on a single milligram scale, afforded one single diastereomer, whose 1H NMR and mass spectra suggest the formation of the desired dihydrobenzofuran ring; a definitive answer on the product structure and its relative stereochemistry should be obtained in the near future. According to our prediction, the more thermodynamically stable trans-disposed dihydrofuran ring should be prepared via this oxidative cyclization pathway. Final deprotection of this DDQ cyclization adduct with BBr₃ should give us the natural product pauciflorol A (3), which could then undergo isomerization under acidic conditions to give suffruticosol A (4) possessing a cis-disposed dihydrofuran ring.
As a final demonstration of the robustness of the developed sequences, two more members of this natural product family, vaticanol A (1) and suffruticosol B (2), are also currently being prepared from 85 following the reaction reaction sequence discussed above. As indicated in Scheme 21, Grignard addition to the o-quinone methide in this system also afforded a mixture of diastereomers (91 and 92) with the dominant isomer expected to be the one with nucleophiles approaching from the more accessible α-face. In contrast to the systems described in Scheme 20, both 91 and 92 could potentially lead to the natural product targets, suffruticosol B (2) and vaticanol A (1), respectively, using the same critical steps discussed above.

One major challenge we foresee with the end game of these syntheses lies within the final deprotection step. Since Lewis acids can promote dihydrobenzofuran ring-opening, there is a possibility that those rings in all our natural product targets can not survive BBr₃-mediated cleavage of methyl ethers. In that case, an alternative strategy with different phenol protecting groups is needed. Using pauciflorol A (3) as an example, Scheme 22 shows one of our proposed solutions to overcome this potential deprotection issue.
Starting with the adduct 84, a global deprotection via BBr₃ followed by a selective benzyl ether reprotection and NaBH₄ reduction should generate the desired bis-benzylic alcohol 93 for the o-quinone methide formation. Then, with 93 in hand, a similar elimination/Grignard addition sequence is expected to afford adduct 94. Here, a different Grignard reagent with TBS protecting group is used to set the stage for the following TBAF-mediated TBS deprotection of the phenol involved in DDQ oxidation. Furthermore, we expect the steric bulk of the benzyl ethers to improve the stereoselectivity of this Grignard reaction to strongly favor the β-face addition. Finally, benzyl ether cleavage via catalytic hydrogenation of the DDQ cyclization adduct should provide desired pauciflorol A(3) with the dihydrobenzofuran ring intact.

3.6 Conclusion

In conclusion, we have developed a concise approach for dihydrobenzofuran ring installation on the seven-membered carbon framework of the resveratrol family of oligomeric natural products. The formation of 7,5-fused ring natural product cores via Friedel-Crafts cyclizations provides controlled access to some of the highly complex architectures within the resveratrol
family. Although further studies are required to complete the total synthesis of four resveratrol trimers (1-4), this work proves our original concept of using of a common intermediate distinct from the biosynthetic starting material to achieve a diverse carbogenic complexity within the resveratrol class in a selective fashion and seems poised to deliver the final targets soon.

This work is a collective effort between me and several other very talented colleagues in the group. I want to thank Dr. Alexandros Zografos for preliminary attempts to form dihydrobenzofuran units on the ampelopsin B core. Dr. Christos Stathakis worked alongside with me for over a year trying to solve the challenges with the dihydrobenzofuran formation, and he first developed the oxidative dihydrobenzofuran synthesis approach and completed the total synthesis of ampelopsin B (7).

References:


Experimental Data for Compounds Listed in Chapter 3

**General Procedures.** All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et2O) and methylene chloride (CH2Cl2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (\(^1\)H and \(^{13}\)C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorptionionization) technique. All experiments described in this chapter were in initial discovery stage, and conducted using milligram-scale materials. Thus, the yields and structure assignments listed here
are speculative, and the reaction conditions are currently being modified and improved in our laboratory for eventual publication in a peer-reviewed journal.

**Abbreviations.** NBS = N-bromosuccinimide, TFA = trifluoroacetic acid, KHMDS = potassium bis(trimethylsilyl)amide, \( p\)-TsOH = *para*-toluenesulfonic acid, \( m\)CPBA = *meta*-chloroperoxybenzoic acid, TBAI = tetrabutylammonium iodide

**Seven-membered ketone (8).** To a solution of biaryl ketone (characterized as Ketone 70 in supporting information in chapter 2) (0.508 g, 1.17 mmol, 1.0 equiv) in toluene (10 mL) at 25 °C was added solid \( p\)-TsOH (0.556 g, 2.93 mmol, 2.5 equiv) in a single portion. The resultant solution was heated at 80 °C for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO\(_3\) (20 mL), poured into H\(_2\)O (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO\(_4\)), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to afford seven-membered ketone 8 (0.315 g, 62%) as a light pink powder. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta 7.14 \) (d, \( J = 2.7 \) Hz, 1 H), 6.70 (d, \( J = 8.7 \) Hz, 2 H), 6.60 (d, \( J = 8.7 \) Hz, 2 H), 6.53 (d, \( J = 2.7 \) Hz, 1 H), 6.27 (d, \( J = 2.1 \) Hz, 1 H), 5.70 (d, \( J = 2.1 \) Hz, 1 H), 4.65 (dd, \( J = 2.7 \), 8.1 Hz, 1 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.58 (s, 3 H), 3.52 (s, 3 H), 3.52 (dd, \( J = 2.7 \), 13.8 Hz, 1 H), 2.93 (dd, \( J = 6.9 \), 13.8 Hz, 1 H).
General procedure for Grignard addition to ketone 8. The appropriate Grignard reagent (1.84 mL, 0.5 M in THF, 4.0 equiv) was added dropwise over the course of 5 min to a solution of 8 (0.1 g, 0.23 mmol, 1.0 equiv) in dry THF (10 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min, warmed slowly to 25 °C, and stirred for an additional 2 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL), poured into water (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (30 mL) and brine (30 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford the addition products S1.

10: To a solution of the Grignard addition product 9 (0.05 g, 0.090 mmol, 1.0 equiv) in dry THF (10 mL) at 25 °C was added solid Burgess reagent (0.107 g, 0.449 mmol, 5.0 equiv) in a single portion. The resultant reaction mixture was then heated to reflux and stirred at 75 °C for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (15 mL), poured into H₂O (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to afford a 2:1 mixture of alkene isomers (45% of 10, 23% of the other isomer) as a light yellow powder. 10: ^1^H NMR (400 MHz, CDCl₃) δ 7.11 (d, J = 8.7 Hz, 2 H), 6.84 (s, 1 H), 6.75 (d, J = 8.7 Hz, 2 H), 6.71 (d, J = 8.8 Hz, 2 H), 6.64 (d, J = 2.4 Hz, 1 H), 6.52 (d, J = 2.4 Hz, 1 H), 6.29 (d, J = 2.2 Hz, 1 H), 6.24 (d, J = 2.4 Hz, 1 H), 4.31 (dd, J = 6.0, 13.6 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 3.51 (s, 3 H), 3.41 (s, 3 H), 2.81 (dd, J = 6.0, 13.6 Hz, 1 H).
**Scheme S2.**

Reagents and conditions: a) BBr₃ (1.0 equiv), CH₂Cl₂, -78 °C, 1 h, 92%; b) p-methoxybenzyl chloride (2.0 equiv), K₂CO₃ (5.0 equiv), TBAI (0.2 equiv), acetone, reflux, 12 h, 97%; c) 0.01 M solution in benzene, 23 °C, 4 h, 75%.

**46:** To a solution of seven-membered ketone 8 (0.1 g, 0.230 mmol, 1.0 equiv) in CH₂Cl₂ (5 mL) at −78 °C was added in a single portion a solution of BBr₃ (0.23 mL, 1.0 M in CH₂Cl₂, 0.230 mmol, 1.0 equiv) in CH₂Cl₂. The resultant yellow-brown reaction mixture was then stirred for 1 h at −78 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL), poured into H₂O (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant yellow-brown oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to give 46 (0.089 g, 92% yield) as light yellow oil. **46:** ¹H NMR (300 MHz, CDCl₃) δ 14.13 (s, 1 H), 7.33 (d, J = 2.4 Hz, 1 H), 6.82 (d, J = 8.4 Hz, 2 H), 6.93(d, J = 2.4 Hz, 1 H), 6.62 (d, J = 8.7 Hz, 2 H), 6.22 (d, J = 2.4 Hz, 1 H), 6.14 (d, J = 2.4 Hz, 1 H), 5.10 (m, 1 H), 3.90(s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.529 (m, 2 H).

**14:** Solid K₂CO₃ (0.594 g, 4.305 mmol, 5.0 equiv), p-methoxybenzyl chloride (0.23 mL, 1.722 mmol, 2.0 equiv) and tetrabutylammonium iodide (0.062 g, 0.172 mmol, 0.2 equiv) were added sequentially to a solution of 46 (0.362 g, 0.861 mmol, 1.0 equiv) in dry actone (20 mL) at 25 °C. The resultant reaction mixture was then sealed and heated at reflux (80 °C) for 12 h. Upon completion, the reaction mixture was diluted with EtOAc (30 mL), quenched with saturated
aqueous K$_2$CO$_3$ (80 mL), and extracted with EtOAc (3 × 120 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO$_4$), and concentrated. The resultant residue was purified by flash column chromatography (Et$_3$N-deactivated silica gel, EtOAc/hexanes, 1:7) to afford the desired ketone 14 (0.033 g, 97%) as a light yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.32 (d, $J = 8.8$ Hz, 2 H), 7.11 (d, $J = 2.8$ Hz, 1 H), 6.85 (d, $J = 8.8$ Hz, 2 H), 6.63 (d, $J = 8.4$ Hz, 2 H), 6.56 (d, $J = 8.8$ Hz, 2 H), 6.53 (d, $J = 2.8$ Hz, 1 H), 6.30 (d, $J = 2.0$ Hz, 1 H), 5.70 (d, $J = 2.4$ Hz, 1 H), 5.02 (dd, $J = 12.0$, 23.2 Hz, 2 H), 4.65 (dd, $J = 4.0$, 6.8 Hz, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.54 (s, 3 H), 3.53 (s, 3 H), 3.52 (dd, $J = 4.0$, 13.8 Hz, 1 H), 2.92 (dd, $J = 7.2$, 14.0 Hz, 1 H).

16: Activated Pd/C (10%, 0.0042 g, 0.004 mmol, 0.5 equiv) was added in a single portion to a solution of 15 (0.005 g, 0.008 mmol, 1.0 equiv) in MeOH (2 mL) at 25 °C, and then H$_2$ gas was bubbled slowly and continuously through the solution for 2 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (2 mL), and extracted with EtOAc (3 ×5 mL). The combined organic layers were then washed with water (2 mL) and brine (2 mL), dried (MgSO$_4$), and concentrated to give 16 (0.0035 g, 86% yield) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.18 (app d, $J = 8.8$ Hz, 3 H), 7.08 (d, $J = 8.8$ Hz, 2 H), 6.76 (app dd, $J = 8.8$ Hz, 4 H), 6.55 (d, $J = 2.4$ Hz, 1 H), 6.53 (d, $J = 2.4$ Hz, 1 H), 6.29 (d, $J = 2.8$ Hz, 1 H), 6.26 (d, $J = 2.8$ Hz, 1 H), 5.08 (s, 1 H), 4.54 (dd, $J = 6.0$, 13.2 Hz, 1 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.43 (s, 3 H), 2.88 (dd, $J = 6.0$, 13.6 Hz, 1 H), 2.92 (dd, $J = 7.2$, 14.0 Hz, 1 H).
**22:** A 0.001 M benzene (19 mL) solution containing 14 (0.01 g, 0.019 mmol) was vigorously degassed under argon for 1 h and irradiated under argon using light from a 450 W Hanovia mercury lamp fitted with a Pyrex glass filter for 30 min. The reaction solution turned fluorescent after radiation. Upon completion, the solvent was removed under reduced pressure to afford the cyclized product 22 (0.0095 g, 95% yield), which required no further purification. $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 7.67 (d, $J = 8.4$ Hz, 2 H), 6.99 (d, $J = 8.7$ Hz, 2 H), 6.73 (d, $J = 2.4$ Hz, 2 H), 6.67 (d, $J = 8.4$ Hz, 2 H), 6.41 (d, $J = 2.7$ Hz, 1 H), 6.36 (d, $J = 2.1$ Hz, 1 H), 6.11 (d, $J = 2.1$ Hz, 1 H), 5.85 (s, 1 H), 5.18 (brd, $J = 5.4$ Hz, 1 H), 3.89 (d, $J = 13.5$ Hz, 1 H), 3.32 (s, 3 H), 3.14 (s, 3 H), 3.09 (s, 3 H), 3.08 (s, 3 H), 2.89 (dd, $J = 6.0, 13.8$ Hz, 1 H).

**17:** To a solution of 22 (0.01 g, 0.018 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.5 mL) at 25 °C was added solid p-TsOH (0.003 g, 0.018 mmol, 1.0 equiv) in a single portion. The resultant solution was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ (2 mL), poured into H$_2$O (2 mL), and extracted with EtOAc (3 × 6 mL). The combined organic layers were then washed with water (3 mL) and brine (3 mL), dried (MgSO$_4$), and concentrated to give the desired benzofuran 17 (0.008 g, 88% yield) which was carried forward without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J = 6.8$ Hz, 2 H), 6.95 (app dd, $J = 10.8$ Hz, 3 H), 6.69 (m, 3 H), 6.54 (d, $J = 9.0$ Hz, 2 H), 6.43 (d, $J = 2.4$ Hz, 1 H), 5.48 (brd, $J = 4.8$ Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.61 (s, 3 H), 3.51 (brs, 1 H), 3.48 (s, 3 H).

**23:** A 0.01 M benzene (1.9 mL) solution containing 14 (0.01 g, 0.019 mmol) was vigorously degassed under argon for 1 h and irradiated under argon using light from a 450 W Hanovia
mercury lamp fitted with a Pyrex glass filter for 4 h. The reaction solution turned fluorescent after radiation. Upon completion, the solvent was removed under reduced pressure to afford a mixture of products. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to afford 23 (0.007 g, 75% yield) as a pale yellow powder. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.39 (s, 1 H), 7.89 (d, \(J = 16.4\) Hz, 1 H), 7.48 (d, \(J = 16.4\) Hz, 1 H), 7.01 (d, \(J = 2.0\) Hz, 1 H), 6.71 (app dd, \(J = 8.0, 12.4\) Hz, 4 H), 6.47 (d, \(J = 8.8\) Hz, 2 H), 5.73 (m, 1 H), 4.10 (s, 3 H), 3.96 (s, 3 H), 3.87 (s, 3 H), 3.72 (m, 2 H), 3.58 (s, 3 H).

23 [ X-ray structure ]

36/37: Procedure A: To a solution of 35 (0.05 g, 0.079 mmol, 1.0 equiv) in dry THF (10 mL) at 25 \(^\circ\)C was added solid Burgess reagent (0.094 g, 0.395 mmol, 5.0 equiv) in a single portion. The resultant reaction mixture was then heated to reflux and stirred at 75 \(^\circ\)C for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO\(_3\) (30 mL), poured into H\(_2\)O (20 mL), and extracted with EtOAc (3 \(\times\) 50 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO\(_4\)), and concentrated. The
resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford a 2:1 mixture of alkene isomers (48% of 36, 24% of 37) as a yellow oil. Procedure B: A solution of 35 (0.105 g, 0.166 mmol, 1.0 equiv) and Et$_3$N (0.139 mL, 0.996 mmol, 6.0 equiv) in CH$_2$Cl$_2$ (6 mL) was cooled to -78 °C. A solution of SOCl$_2$ (0.024 mL, 0.332 mmol, 2.0 equiv) in CH$_2$Cl$_2$ (0.5 mL) was added dropwise over approximately 3 min. The reaction was then stirred at -78 °C for 45 min. Upon completion, the reaction was quenched by the addition of MeOH. The solvent was then evaporated to dryness and the crude reaction mixture was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford a mixture of 37 and 36 in 3:1 ratio in 95% yield as a light yellow oil. 36: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.10 (d, $J$ = 8.7 Hz, 4 H), 6.80–6.70 (m, 5 H), 6.63 (d, $J$ = 2.7 Hz, 1 H), 6.52 (d, $J$ = 2.4 Hz, 2 H), 6.29 (d, $J$ = 2.2 Hz, 1 H), 6.23 (d, $J$ = 2.6 Hz, 1 H), 5.01 (s, 1 H), 4.32 (dd, $J$ = 13.0, 5.6 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 3.51 (s, 3 H), 3.41 (s, 3 H), 2.81 (dd, $J$ = 13.4, 5.8 Hz, 1 H). 37: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39–7.29 (m, 5 H), 6.99–6.96 (m, 4 H), 6.84–6.74 (m, 5 H), 6.34 (d, $J$ = 2.5 Hz, 1 H), 6.20 (d, $J$ = 2.3 Hz, 1 H), 5.59 (d, $J$ = 2.3 Hz, 1 H), 5.00 (s, 1 H), 4.60 (dd, $J$ = 4.8, 3.0 Hz, 1 H), 3.89 (s, 1 H), 3.70 (s, 1 H), 3.49 (s, 1 H), 3.44 (s, 1 H), 2.66 (dd, $J$ = 13.0, 4.9 Hz, 1 H).

38: Activated Pd/C (10%, 0.035 g, 0.033 mmol, 1.0 equiv) was added in a single portion to a 2:1 mixture of 36 and 37 (0.020 g, 0.033 mmol, 1.0 equiv) in EtOAc (4 mL) at 25 °C, and then H$_2$ gas was bubbled slowly and continuously through the solution for 6 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (2 mL), and extracted with EtOAc (3 ×5 mL). The combined organic layers were then washed with water (2 mL) and brine.
(2 mL), dried (MgSO₄), and concentrated to give 38 and 39 in 2:1 ratio (0.016 g, 82%) as a colorless oil. 38: ¹H NMR (400 MHz, CDCl₃) δ 6.83 (d, J = 8.8 Hz, 2 H), 6.62 (d, J = 8.4 Hz, 2 H), 6.56 (d, J = 8.5 Hz, 2 H), 6.50 (d, J = 8.8 Hz, 2 H), 6.26 (s, 1 H), 6.08 (d, J = 2.5 Hz, 1 H), 5.63 (d, J = 2.5 Hz, 1 H), 4.94 (app t, J = 7.7 Hz, 1 H), 4.06 (dd, J = 13.8, 2.9 Hz, 1 H), 3.70 (s, 3 H), 3.66 (s, 3 H), 3.52 (s, 3 H), 3.50 (s, 3 H), 3.48 (s, 3 H), 3.20 (d, J = 6.7 Hz, 1 H), 2.81 (dd, J = 13.9, 5.4 Hz, 1 H).

39: Activated Pd/C (10%, 0.055 g, 0.052 mmol, 1.0 equiv) was added in a single portion to a 3:1 mixture of 37 and 36 (0.032 g, 0.052 mmol, 1.0 equiv) in EtOAc (5 mL) at 25 °C, and then H₂ gas was bubbled slowly and continuously through the solution for 6 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (2 mL), and extracted with EtOAc (3 ×5 mL). The combined organic layers were then washed with water (2 mL) and brine (2 mL), dried (MgSO₄), and concentrated to give 39 and 38 in 3:1 ratio (0.027 g, 85%) as a colorless oil. 39: ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, J = 8.7 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 6.68 (d, J = 8.4 Hz, 2 H), 6.62 (d, J = 8.4 Hz, 2 H), 6.39 (d, J = 2.5 Hz, 1 H), 6.24 (d, J = 2.5 Hz, 1 H), 6.21 (d, J = 2.5 Hz, 1 H), 6.15 (d, J = 2.6 Hz, 1 H), 4.83 (t, J = 7.7 Hz, 1 H), 4.47 (dd, J = 12.8, 6.0 Hz, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 3.35 (s, 3 H), 2.93 (dd, J = 14.6, 6.1 Hz, 1 H).

40: Solid K₂CO₃ (0.164 g, 1.189 mmol, 5.0 equiv), benzyl chloride (0.109 mL, 0.952 mmol, 4.0 equiv) and tetrabutylammonium iodide (0.018 g, 0.048 mmol, 0.2 equiv) were added sequentially to a solution of 46 (0.1 g, 0.238 mmol, 1.0 equiv) in dry acetone (10 mL) at 25 °C.
The resultant reaction mixture was then sealed and heated at reflux (80 °C) for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (30mL), and extracted with EtOAc (3 × 60 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to afford the desired ketone 40 (0.115 g, 95% yield) as a light yellow solid. 40: ¹H NMR (400 MHz, CDCl₃) δ 7.42 - 7.31 (m, 5 H), 7.13 (d, J = 2.8 Hz, 1 H), 6.65 (d, J = 8.8 Hz, 2 H), 6.56 (d, J = 8.4 Hz, 2 H), 6.54 (d, J = 2.8 Hz, 1 H), 6.30 (d, J = 2.0 Hz, 1 H), 5.71 (d, J = 2.0 Hz, 1 H), 5.11 (q, J = 12.0 Hz, 1 H), 4.66 (dd, J = 7.2, 2.8 Hz, 1 H), 3.88 (s, 3 H), 3.70 (s, 3 H), 3.54 (s, 3 H), 3.53 (s, 3 H), 3.53 (dd, J = 2.8, 13.6 Hz, 1 H), 2.93 (dd, J = 7.2, 14.0 Hz, 1 H).

41: The freshly prepared Grignard reagent (1.48 mL, 0.5 M in THF, 4.0 equiv) was added dropwise over the course of 5 min to a solution of 8 (0.1 g, 0.185 mmol, 1.0 equiv) in dry THF (10 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min, warmed slowly to 25 °C, and stirred for an additional 2 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL), poured into water (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (30 mL) and brine (30 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to afford 41 (0.135 g, 85% yield) as a yellow oil. 41: ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 2.4 Hz, 1 H), 7.38-7.22 (m, 10 H), 6.75-6.67 (m, 7 H), 6.51 (d, J = 8.8 Hz, 2 H), 6.37 (d, J = 2.4 Hz, 1 H), 6.13 (d, J = 2.4 Hz, 1 H), 5.73 (d, J = 2.8 Hz, 1 H), 4.98 (s, 2 H), 4.80 (brs, 1 H), 4.74 (d, J = 9.6 Hz, 1 H), 4.40 (d, J = 8.4
Hz, 1 H), 3.87 (s, 3 H), 3.65 (s, 3 H), 3.57 (s, 3 H), 3.48 (s, 3 H), 3.06 (dd, $J = 2.8, 10.0$ Hz, 1 H), 2.83 (dd, $J = 6.0, 14.0$ Hz, 1 H).

**42**: Activated Pd/C (10%, 0.030 g, 0.029 mmol, 2 equiv) was added in a single portion to a solution of **41** (0.01 g, 0.014 mmol, 1.0 equiv) in EtOAc (2 mL) at 25 ºC, and then H$_2$ gas was bubbled slowly and continuously through the solution for 4 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (2 mL) and brine (2 mL), dried (MgSO$_4$), and concentrated to give **42** (0.007 g, 92%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.06 (d, $J = 2.4$ Hz, 1 H), 6.68 – 6.52 (m, 9 H), 6.41 (d, $J = 2.4$ Hz, 1 H), 6.07 (d, $J = 2.7$ Hz, 1 H), 5.61 (d, $J = 3.0$ Hz, 1 H), 4.71 (app d, $J = 5.7$ Hz, 1 H), 4.58 (1, 2 H), 3.83 (s, 3 H), 3.66 (s, 3 H), 3.60 (s, 3 H), 3.56 (s, 3 H), 3.09 (app d, $J = 13.8$ Hz, 1 H), 2.67 (dd, $J = 6.3$, 14.4 Hz, 1 H).

**44**: To a stirred solution of ketone **46** (0.042 g, 0.010 mmol, 1.0 equiv) in dry THF (5 mL) at 25 ºC, solid LiAlH$_4$ (0.006 g, 0.150 mmol, 1.5 equiv) was added at once. The resultant reaction mixture was stirred at 25 ºC for 1.5 h. Upon completion, the reaction mixture was quenched with saturated aqueous Rochelle's salt (5mL), poured into water (5 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated to give the desired o-quinone methide (0.0356 g, 88% yield) as a red-orange solid. **44**: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.04 (s, 1 H), 6.87 (d, $J = 2.4$ Hz, 1 H), 6.82 (d, $J = 8.8$ Hz, 2 H), 6.67 (d, $J = 2.4$ Hz, 2 H), 6.59 (d, $J = 2.4$ Hz, 1 H), 5.68 (brs, 1 H),
5.57 (d, $J = 2.4$ Hz, 1 H), 5.05 (app t, $J = 4.4$ Hz, 1 H), 3.86 (s, 3 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.08 (app d, $J = 5.6$, 2 H).

47: The freshly prepared Grignard reagent (4-benzyloxybenzyl)magnesium chloride (0.1 mL, 0.5 M in THF, 4.0 equiv) was added dropwise over the course of 5 min to a solution of 44 (0. 005 g, 0.012 mmol, 1.0 equiv) in dry THF (3 mL) at –78 °C. The resultant solution was stirred at –78 °C for 30 min, warmed slowly to 25 °C, and stirred for an additional 2 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH$_4$Cl (5 mL), poured into water (3 mL), and extracted with EtOAc (3 × 12 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO$_4$), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to afford the addition product as a colorless oil (0.006 g, 85% yield). Next, activated Pd/C (10%, 0.009 g, 0.008 mmol, 1.0 equiv) was added in a single portion to a solution of the newly synthesized adduct ( 0.005 g, 0.008 mmol, 1.0 equiv) in a 1:1 mixture of EtOAc and MeOH (2 mL) at 25 °C, and then H$_2$ gas was bubbled slowly and continuously through the solution for 1 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (2 mL), and extracted with EtOAc (3 ×5 mL). The combined organic layers were then washed with water (2 mL) and brine (2 mL), dried (MgSO$_4$), and concentrated to give 47 (0.004 g, 92% yield) as a colorless oil. 47: $^1$H NMR (400 MHz, CDCl$_3$) δ 6.86 (d, $J = 8.4$ Hz, 2 H), 6.65 (d, $J = 8.4$ Hz, 2 H), 6.56 (d, $J = 8.4$ Hz, 2 H), 6.50 (d, $J = 8.4$ Hz, 2 H), 6.30 (d, $J = 2.4$ Hz, 1 H), 6.27 (d, $J = 2.4$ Hz, 1 H), 5.96 (d, $J = 2.8$ Hz, 1 H), 5.65 (d, $J = 2.8$ Hz, 1 H), 4.76 (m, 2 H), 4.63 (s, 1 H), 4.20 (s, 1 H), 3.72 (s, 3 H), 3.66 (s, 3 H), 3.52 (s, 3 H), 3.48 (s, 3 H), 3.24 (app t, $J = 6.8$ Hz, 2 H), 2.82 (dd, $J = 5.6$, 13.6 Hz, 1 H).
34: The freshly prepared 0.1 M DDQ solution in benzene (0.249 mL, 0.0249 mmol, 1.5 equiv) was added slowly to a solution of 47 (0.009 g, 0.0166 mmol, 1.0 equiv) in benzene (1.5 mL) at 25 °C. The resultant solution was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was filtered and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to afford 34 (0.004 g, 53% yield) as a pale yellow oil. 34: 1H NMR (300 MHz, CDCl₃) δ 7.11 (d, J = 8.4 Hz, 2 H), 6.97 (d, J = 8.1 Hz, 2 H), 6.74 (d, J = 8.4 Hz, 2 H), 6.69 (d, J = 8.1 Hz, 2 H), 6.46 (d, J = 2.4 Hz, 1 H), 6.36 (d, J = 2.1 Hz, 1 H), 6.25 (d, J = 2.4 Hz, 1 H), 6.22 (d, J = 2.1 Hz, 1 H), 5.81 (d, J = 11.4 Hz, 1 H), 5.29 (app d, J = 4.5 Hz, 1 H), 4.72 (s, 1 H), 4.18 (d, J = 11.1 Hz, 1 H), 3.87 (s, 3 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.24 (dd, J = 4.5, 16.8 Hz, 2 H), 3.28 (app d, J = 17.7 Hz, 1 H).

49: To a stirred solution of 8 (0.050 g, 0.115 mmol, 1.0 equiv) in dry CH₂Cl₂ (5 mL) at 25 °C, BBr₃ (1.73 mL, 1.73 mmol, 15.0 equiv) was added at once. The resultant reaction mixture was stirred at 65 °C for 72 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (10 mL), poured into water (5 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, MeOH/CH₂Cl₂, 1:9) to afford 49 (0.020 g, 48% yield) as a pale yellow powder. 49: 1H NMR (300 MHz, acetone-d₆) δ 14.17(s, 1 H), 7.26 (d, J = 2.4 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.73(d, J = 2.4 Hz, 1 H), 6.56 (d, J = 8.7 Hz, 2 H), 6.20 (d, J = 2.7 Hz, 1 H), 6.11 (d, J = 2.4 Hz, 1 H), 5.08 (app d, J = 5.7 Hz, 1 H), 3.62 (dd, J = 6.6, 16.5 Hz, 1 H), 3.50 (app d, J = 16.2 Hz, 1 H).
50: To a stirred suspension of 49 (0.040 g, 0.110 mmol, 1.0 equiv) in dry CH$_2$Cl$_2$ (12 mL) at 25 °C, imidazole (0.060 g, 0.880 mmol, 8.0 equiv) and TBSCl (0.091 g, 0.605 mmol, 5.5 equiv) were added sequentially. The resultant reaction mixture was stirred at 25 °C for 6 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH$_4$Cl (10 mL), poured into water (5 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:20) to afford 50 (0.066 g, 73% yield) as a yellow oil. 

50: $^1$H NMR (400 MHz, CDCl$_3$) δ 13.81 (s, 1 H), 7.40 (d, $J = 2.4$ Hz, 1 H), 6.72 (d, $J = 8.0$ Hz, 2 H), 6.57 (d, $J = 2.8$ Hz, 1 H), 6.53 (d, $J = 8.8$ Hz, 2 H), 6.14 (d, $J = 2.4$ Hz, 1 H), 5.98 (d, $J = 2.4$ Hz, 1 H), 5.00 (d, $J = 6.4$ Hz, 1 H), 3.54 (d, $J = 15.2$ Hz, 1 H), 3.39 (dd, $J = 6.4$, 15.6 Hz), 1.01 (s, 9 H), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.85 (s, 9 H), 0.26 s (6 H), 0.20 (s, 3 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), -0.074 (s 3 H).

51/52: To a stirred solution of 50 (0.010 g, 0.012 mmol, 1.0 equiv) in dry THF (2 mL) at 25 °C, was added a 1.0 M solution of LiAlH$_4$ (0.002 g, 0.06 mmol, 5.0 equiv) in Et$_2$O. The resultant reaction mixture was stirred at 45 °C for 2.5 h. Upon completion, the reaction mixture was quenched with saturated aqueous Rochelle’s salt (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated to give a 5:1 mixture of 52 and 51 (0.008 g, 88% yield) as a orange solid.
The freshly prepared Grignard reagent (4-benzyloxybenzyl)magnesium chloride (0.05 mL, 0.5 M in THF, 4.0 equiv) was added dropwise over the course of 5 min to a solution of 51 (0.020 g, 0.025 mmol, 1.0 equiv) in dry THF (3 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min, warmed slowly to 25 °C, and stirred for an additional 2 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (5 mL), poured into water (3 mL), and extracted with EtOAc (3 × 12 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:20) to afford the addition product as a yellow oil (0.021 g, 85% yield). Next, Activated Pd/C (10%, 0.011 g, 0.010 mmol, 1.0 equiv) was added in a single portion to a solution of this newly synthesized adduct (0.010 g, 0.010 mmol, 1.0 equiv) in a 1:1 mixture of EtOAc and MeOH (2 mL) at 25 °C, and then H₂ gas was bubbled slowly and continuously through the solution for 1 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer), poured into water (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with water (2 mL) and brine (2 mL), dried (MgSO₄), and concentrated to give 53 (0.008 g, 92%) as a yellow oil. 53: ¹H NMR (300 MHz, CDCl₃) δ 6.80 (d, J = 8.4 Hz, 2 H), 6.60 (d, J = 8.4 Hz, 2 H), 6.50-6.47 (m, 3 H), 6.39 (d, J = 8.4 Hz, 2 H), 6.21 (d, J = 2.4 Hz, 1 H), 5.81 (d, J = 2.4 Hz, 1 H), 5.64 (d, J = 2.4 Hz, 1 H), 4.74 (dd, J = 2.4, 2.4 Hz, 1 H), 4.63 (dd, J = 5.4, 10.5 Hz, 1 H), 3.95 (dd, J = 2.7, 14.1 Hz, 1 H), 3.81 (s, 1 H), 3.29-3.11 (m, 2 H), 2.86 (dd, J = 5.7, 13.8 Hz), 1.00 (s, 9 H), 0.90 (s, 9 H), 0.84 (s, 9 H), 0.77 (s, 9 H), 0.22 s (6 H), 0.14 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H), -0.06 (s, 3 H), -0.07 (s, 3 H), -0.16 (s 3 H).
54: The freshly prepared 0.05 M DDQ solution in benzene (0.12 mL, 0.006 mmol, 1.25 equiv) was added slowly to a solution of 53 (0.005 g, 0.005 mmol, 1.0 equiv) in benzene (1 mL) at 25 °C. The resultant solution was stirred at 25 °C for one hour. Upon completion, the reaction mixture was filtered and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:20) to afford 54 (0.004 g, 86% yield) as a yellow oil. 

54: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.09 (d, $J = 8.7$ Hz, 2 H), 6.88 (d, $J = 8.7$ Hz, 2 H), 6.73 (d, $J = 8.4$ Hz, 2 H), 6.61 (d, $J = 8.7$ Hz, 2 H), 6.34 (d, $J = 2.1$ Hz, 1 H), 6.29 (d, $J = 2.4$ Hz, 1 H), 6.13 (d, $J = 2.1$ Hz, 2 H), 5.70 (d, $J = 11.4$ Hz, 1 H), 5.19 (app t, $J = 4.2$, 1 H), 4.12 (d, $J = 11.4$ Hz, 1 H), 3.55 (dd, $J = 4.5$, 17.7 Hz, 1 H), 3.25 (app d, $J = 16.8$ Hz, 1 H), 0.99 (s, 9 H), 0.98 (s, 9 H), 0.95 (s, 9 H), 0.92 (s, 9 H), 0.26 s (3 H), 0.25 (s, 3 H), 0.20 (s, 3 H), 0.19 (s, 3 H), 0.14 (s, 3 H), 0.13 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H).

7: To a stirred solution of 54 (0.005 g, 0.005 mmol, 1.0 equiv) in dry THF (1 mL) at 0 °C, was added a 0.1 M solution of TBAF (0.3 mL, 0.03 mmol, 6.0 equiv) in THF. The resultant reaction mixture was stirred at 0 °C for 1 h. Upon completion, the reaction mixture was quenched with water (3 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed and concentrated. The resultant residue was purified by flash column chromatography (silica gel, MeOH/CH$_2$Cl$_2$, 1:9) to afford 7 (0.002 g, 95% yield) as a light yellow powder. 

7: $^1$H NMR (400 MHz, acetone-$d_6$) δ 8.38 (s, 1 H), 8.08 (s, 1 H), 8.00 (s, 1 H), 7.09 (d, $J = 8.4$ Hz, 2 H), 6.94 (d, $J = 8.8$ Hz, 2 H), 6.76 (d, $J = 8.8$ Hz, 2 H), 6.64 (d, $J = 8.8$ Hz, 2 H), 6.42 (d, $J = 2.4$ Hz, 1 H), 6.33 (d, $J = 2.0$ Hz, 1 H), 6.22 (d, $J = 2.0$ Hz, 1 H), 6.05 (d, $J = 2.0$ Hz, 1 H), 5.72 (d, $J = 11.4$ Hz, 1 H), 5.22 (app t, $J = 4.0$, 1 H), 4.18 (d, $J = 11.6$ Hz, 1 H), 3.59 (dd, $J = 4.4$, 17.2 Hz, 1 H), 3.18 (app d, $J = 16.8$ Hz, 1 H).
S2: Solid NBS (0.069, 0.390 mmol, 0.5 equiv) was added in a single portion to a solution of 60 (0.420 g, 0.780 mmol, 1.0 equiv) in CH₂Cl₂ (25 mL) at –78 °C. The resultant solution was stirred for 1 h at –78 °C, slowly warmed to 25 °C over 2 h. Upon completion, the reaction mixture was quenched with saturated aqueous Na₂SO₃ (5 mL), poured into saturated aqueous NaHCO₃ (20 mL), and extracted with EtOAc (3 × 60 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), dried (MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to afford bromide S2 (0.217 g, 90% yield based on recovered starting material) as a yellow oil. S2: ¹H NMR (300 MHz, CDCl₃) δ 8.07 (s, 1 H), 7.19 (d, J = 8.7 Hz, 2 H), 7.14 (d, J = 9.0 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.72 (d, J = 8.7 Hz, 2 H), 6.35 (s, 1 H), 6.33 (d, J = 2.1 Hz, 2 H), 6.24 (t, J = 2.4 Hz, 1 H), 4.34 (s, 1 H), 4.19 (s, 1 H), 3.93 (s, 3 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.68 (s, 6 H), 3.65 (s, 3 H).

61: n-BuLi (0.304 mL, 1.6 M in THF, 0.486 mmol, 1.5 equiv) was added slowly over the course of 5 min to a solution of the newly synthesized bromide (0.200 g, 0.323 mmol, 1.0 equiv) in THF (25 mL) at –78 °C, ultimately yielding a light yellow solution. After 20 min of stirring at –78 °C, a solution of 3,5-dimethoxybenzaldehyde (0.108 g, 0.648 mmol, 2.0 equiv) in THF (5 mL) was added slowly at –78 °C, and the resultant mixture was stirred for 1 h at –78 °C, warmed slowly to
25 °C, and stirred for an additional 6 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH₄Cl (30 mL), poured into water (10 mL), and extracted with EtOAc (3 × 80 mL). The combined organic layers were then washed with water (30 mL) and brine (30 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to afford the addition product as a yellow oil (0.148 g, 65% yield). Next, Dess–Martin periodinane (0.108 g, 0.255 mmol, 1.5 equiv) and solid NaHCO₃ (0.143 g, 1.7 mmol, 10.0 equiv) was added in a single portion to a solution of alcohol (0.120 g, 0.170 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL) at 0 °C, and the resultant slurry was stirred for 1 h at 0 °C, warmed slowly to 25 °C, and stirred for an additional 1 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na₂SO₃ (10 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous NaHCO₃ (15 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to afford ketone 61 (0.112 g, 93% yield) as a yellow oil. 61: ¹H NMR (300 MHz, CDCl₃) δ 7.15 (d, J = 8.7 Hz, 2 H), 7.12 (d, J = 2.1 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 6.77 (app d, J = 8.7 Hz, 3 H), 6.67 (t, J = 2.4 Hz, 1 H), 6.60 (d, J = 9 Hz, 2 H), 6.37 (s, 1 H), 6.33 (d, J = 2.1 Hz, 2 H), 6.25 (t, J = 2.4 Hz, 1 H), 4.27 (s, 2 H), 3.81 (s, 3 H), 3.76 (s, 6 H), 3.70 (s, 3 H), 3.69 (s, 6 H), 3.67 (s, 3 H).

62: Solid NBS (0.025 g, 0.142 mmol, 1.0 equiv) was added in a single portion to a solution of 61 (0.100 g, 0.142 mmol, 1.0 equiv) in CH₂Cl₂ (15 mL) at −78 °C. The resultant solution was stirred for 2 h at −78 °C, slowly warmed up to 25 °C, and stirred for an additional 1 h at 25 °C. Upon
completion, the reaction contents were quenched with saturated aqueous Na$_2$SO$_3$ (10 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous NaHCO$_3$ (20 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried (MgSO$_4$), and concentrated to give 62 (0.010 g, 93% yield), which was used without further purification. 62: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, $J = 8.8$ Hz, 2 H), 7.12 (d, $J = 2.4$ Hz, 2 H), 6.89 (d, $J = 8.8$ Hz, 2 H), 6.78 (app d, $J = 8.4$ Hz, 3 H), 6.68 (t, $J = 2.4$ Hz, 1 H), 6.61 (d, $J = 8.8$ Hz, 2 H), 6.38 (s, 1 H), 6.29 (d, $J = 2.8$ Hz, 1 H), 5.98 (d, $J = 2.4$ Hz, 1 H), 4.98 (s, 1 H), 4.16 (s, 1 H), 3.86 (s, 3 H), 3.80 (s, 6 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 3.55 (s, 3 H).

65: Solid BDSB$^1$ (0.007 g, 0.013 mmol, 1.0 equiv) was added in a single portion to a solution of 61 (0.01 g, 0.013 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (3 mL) at −78 °C. The resultant solution was stirred for 2 h at −78 °C, warmed slowly to 25 °C, and stirred for an additional 8 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na$_2$SO$_3$ (5 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous NaHCO$_3$ (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to afford 65 (0.008 g, 85% yield) as a light pink solid. 65: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.17 (d, $J = 2.4$ Hz, 1 H), 6.60 (d, $J = 8.8$ Hz, 2 H), 6.48 (d, $J = 2.4$ Hz, 1 H), 6.44 (d, $J = 8.8$ Hz, 2 H), 6.33 (m, 3 H) 6.22 (dd, $J = 2.8$, 8.8 Hz, 1 H), 5.95
(dd, J = 2.4, 8.8 Hz, 1 H), 5.44 (dd, J = 2.8, 8.8 Hz, 1 H), 4.84 (s, 1 H), 4.73 (s, 1 H), 4.54 (s, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.62 (s, 3 H).

66 [ X-ray structure ]

66: A solution of Br₂ (3.34 μL, 0.013 mmol, 1.0 equiv) in CH₂Cl₂ (0.1 mL) was added dropwise to a solution of 62 (0.01 g, 0.013 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) at –78 ºC. The resultant solution was stirred at –78 ºC for 2 h, warmed slowly to 25 ºC over the course of 1 h, and stirred for an additional 10 h at 25 ºC. Upon completion, the reaction contents were quenched with saturated aqueous NaHCO₃ (5 mL), poured into water (10 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to afford 66 (0.005 g, 50% yield) as a pale yellow powder. 66: ¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, J = 8.4 Hz, 2 H), 7.09 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 6.60 (d, J = 2.4 Hz, 1 H) 6.53 (d, J = 2.8 Hz, 1 H), 6.27
(s, 1 H), 6.23 (app s, 2 H), 5.86 (d, J = 2.8 Hz, 1 H), 5.79 (s, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H),
3.80 (s, 3 H), 3.76 (s, 3 H), 3.71 (s, 6 H), 3.69 (s, 3 H), 3.54 (s, 3 H).

66 [ X-ray structure ]

**71**: Compound 71 was prepared through a similar reaction sequence as compound 29 in Chapter 2 followed by catalytic hydrogenation using Pd/C. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.96 (d, J = 2.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2 H), 6.66(d, J = 8.4 Hz, 2 H), 6.64 (t, J = 2.4 Hz, 1 H), 6.34 (d, J = 2.4 Hz, 1 H), 6.32 (d, J = 2.4 Hz, 1 H), 4.71 (s, 1 H), 3.80 (s, 3 H ), 3.79 (s, 6 H), 3.66 (s, 3 H), 2.69 (m, 4 H).

**74**: Solid DDQ (0.008 g, 0.035 mmol, 1.5 equiv) was added in a single portion to a solution of 71 (0.010 g, 0.024 mmol, 1.0 equiv) in benzene (2 mL) at 25 °C. The resultant solution was stirred for 12 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated
aqueous NaHCO₃ (3 mL) at 25 °C, poured into water (3 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (3 mL) and brine (3 mL), dried (MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford 74 (0.006 g, 54% yield) as a colorless oil. 74: ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 2.0 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 6.64 (t, J = 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 4.82 (dt, J = 4.4 Hz, 1H), 4.66 (s, 1H), 3.80 (s, 9H), 3.63 (s, 3H), 2.87 (dd, J = 4.0, 14.0 Hz, 1H), 2.72 (dd, J = 9.2, 14.0 Hz, 1H).

77: Solid DDQ (0.008 g, 0.035 mmol, 1.5 equiv) was added in a single portion to a solution of 71 (0.010 g, 0.024 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) at 25 °C. The resultant solution was stirred for 8 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (3 mL) at 25 °C, poured into water (3 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (3 mL) and brine (3 mL), dried (MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford 77 (0.007 g, 73% yield) as a pale yellow oil. 77: ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, J = 2.8 Hz, 1H), 6.93 (d, J = 2.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 6.26 (d, J = 2.0 Hz, 1H), 5.70 (d, J = 2.0 Hz, 1H), 4.65 (dd, J = 5.6, 6.8 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.58 (s, 3H), 3.53 (s, 4H), 2.92 (dd, J = 13.6, 6.8 Hz, 1H).

79: p-benzyloxy-α-toluenethiol (0.265 g, 1.15 mmol, 10.0 equiv) and p-TsOH (0.022 g, 0.115 mmol, 1.0 equiv) were added to a highly concentrated solution of alcohol 78 (0.05 g, 0.115
mmol, 1.0 equiv) in CH₂Cl₂ (5 mL) at 25 °C. The resulting yellow-green solution was stirred for 72 h at 25 °C under the strict exclusion of light. Upon completion, the reaction mixture was diluted with EtOAc (10 mL), quenched with saturated aqueous NaHCO₃ (15 mL), poured into water (15 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant light green product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) to give a sulfide 79 (0.022 g, 30% yield) as a light yellow oil.

80: Solid NaHCO₃ (0.0323 g, 0.385 mmol, 5.0 equiv) and mCPBA (70%, 0.057 g, 0.231 mmol, 3.0 equiv) were added sequentially to a solution of sulfide 79 (0.050 g, 0.077 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL) at 0 °C to give a milk-colored slurry. After warming this mixture to 25 °C and stirring for 3 h, the reaction contents were quenched with saturated aqueous NaHCO₃ (15 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant yellow-brown oil was used in the following reaction without further purification. Next, finely powdered KOH (0.165 g, 2.93 mmol, 20.0 equiv) was added in a single portion to a solution of a portion of this newly synthesized adduct (0.100 g, 0.147 mmol, 1.0 equiv) in a mixture of CCl₄/t-BuOH/H₂O (5/5/1, 5 mL/5 mL/1 mL) at 25 °C. The resultant slurry was then stirred for 6 h at 80 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (15 mL) and brine (15 mL), dried (MgSO₄), and concentrated. The resultant dark brown oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to give both the desired alkene (80, 0.026 g, 29%
yield) as a yellow-brown oil along with a small portion of its exocyclic olefinic regioisomer (0.009 g, 10% yield) as a yellow-brown oil. **80:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 (m, 5H), 7.26 (app d, $J = 8.8$ Hz, 4 H), 7.18 (s, 1 H), 6.93 (d, $J = 1.6$ Hz, 2 H), 6.84 (app d, $J = 8.8$ Hz, 4 H), 6.40 (d, $J = 2.0$ Hz, 2 H), 6.33 (t, $J = 2.4$ Hz, 1 H), 5.02 (s, 2 H), 4.46 (s, 1 H ), 4.34 (s, 1 H), 3.96 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 6 H), 3.65 (s, 3 H).

**Scheme S4.**

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81: Solid NBS (0.017, 0.098 mmol, 0.5 equiv) was added in a single portion to a solution of **79** (0.12 g, 0.195 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (10 mL) at −78 °C. The resultant solution was stirred for 4 h at −78 °C. Upon completion, the reaction mixture was quenched with saturated aqueous Na$_2$SO$_3$ (5 mL) at −78 °C, poured into saturated aqueous NaHCO$_3$ (15 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) to afford bromide **S3** (0.051 g, 75% yield based on recovered starting material) as a brown-yellow oil. Next, $n$-BuLi (0.09 mL, 1.6 M in THF, 0.144 mmol, 2.0 equiv) was added slowly over the course of 5 min to a solution of the **S3** (0.05 g, 0.072 mmol, 1.0 equiv) in THF (15 mL) at −78 °C, ultimately yielding a dark-brown solution. After 20 min of stirring at −78 °C, a solution of 3,5-dimethoxybenzaldehyde (0.072 g, 0.432 mmol, 6.0 equiv) in THF (5 mL) was added slowly at −78 °C, and the resultant mixture was stirred for 1 h at −78 °C, warmed slowly to 25 °C, and stirred for an additional 7 h at 25 °C.
Upon completion, the reaction contents were quenched with saturated aqueous NH$_4$Cl (20 mL), poured into water (10 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:2) to afford the addition product as yellow oil (0.031 g, 55% yield). Finally, Dess–Martin periodinane (0.024 g, 0.058 mmol, 1.5 equiv) was added in a single portion to a solution of alcohol (0.03 g, 0.038 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (5 mL) at 0 °C, and the resultant slurry was stirred for 1 h at 0 °C, warmed slowly to 25 °C, and stirred for an additional 1 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na$_2$SO$_3$ (5 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous NaHCO$_3$ (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to afford ketone 81 (0.027 g, 90% yield) as a pale yellow oil.

81: 1H NMR (400 MHz, CDCl$_3$) δ 7.33 (br d, $J = 4.8$ Hz, 5H), 7.15 (d, $J = 8.4$ Hz, 2 H), 7.12 (d, $J = 2.4$ Hz, 2 H), 6.90 (d, $J = 8.8$ Hz, 2 H), 6.77 (app d, $J = 8.8$ Hz, 3 H), 6.54(app dd, $J = 8.8$ Hz 4 H), 6.38 (s, 1 H), 6.34 (d, $J = 2.4$ Hz, 2 H), 6.25 (d, $J = 2.4$ Hz, 2 H), 4.93 (s, 2 H), 4.28 (s, 2 H), 3.81 (s, 6 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.69 (s, 6 H).

82: Activated Pd/C (10%, 0.054 g, 0.051 mmol, 2.0 equiv) was added in a single portion to a solution of 81 (0.020 g, 0.026 mmol, 1.0 equiv) in EtOAc (3 mL) at 25 °C, and then H$_2$ gas was bubbled slowly and continuously through the solution for 4 h. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of
EtOAc to ensure quantitative transfer), poured into water (2 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed with water (4 mL) and brine (4 mL), dried (MgSO₄), and concentrated to give **82** (0.016 g, 90% yield) as a colorless oil. **82**: ¹H NMR (400 MHz, CDCl₃) δ 6.99 (d, J = 2.4 Hz, 1 H), 6.61 (d, J = 8.4 Hz, 2 H), 6.65 (d, J = 8.8 Hz, 2 H), 6.61 (t, J = 2.4 Hz, 1 H), 6.54 (s, 4 H), 6.47 (s, 1 H), 6.33 (t, J = 2.4 Hz, 1 H), 6.22 (d, J = 2.4 Hz, 2 H), 4.42 (s, 1 H), 4.39 (d, J = 2.0 Hz, 1 H), 3.79 (s, 3 H), 3.79 (s, 9 H), 3.75 (s, 6 H), 3.72 (s, 3 H), 3.34 (dd, J = 11.2, 4.0 Hz, 1 H), 3.17 (t, J = 2.0 Hz, 1 H), 2.82 (dd, J = 14.0, 4.0 Hz, 1 H), 2.34 (dd, J = 12.0, 14.0 Hz, 1 H).

**84/85**: Solid DDQ (0.013 g, 0.056 mmol, 2.0 equiv) was added in a single portion to a solution of **82** (0.02 g, 0.028 mmol, 1.0 equiv) in CH₂Cl₂ (4 mL) at 25 ºC. The resultant solution was stirred for 10 h at 25 ºC. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL) at 25 ºC, poured into water (3 mL), and extracted with EtOAc (3 x 15 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant brown residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 2:1) to afford a mixture of **84** and **85** (0.013 g, 65%) as a light yellow solid. **84**: ¹H NMR (400 MHz, CDCl₃) δ 6.99 (d, J = 2.4 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 2 H), 6.58 (d, J = 8.8 Hz, 2 H), 6.55 (d, J = 8.8 Hz, 2 H), 6.44 (d, J = 8.8 Hz, 2 H), 6.41 (d, J = 2.8 Hz, 1 H) 6.39 (s, 1 H) 6.37 (t, J = 2.4 Hz, 1 H), 6.26 (d, J = 2.4 Hz, 2 H), 4.43 (s, 1 H ), 4.37 (d, J = 2.0 Hz, 1 H), 4.29 (d, J = 11.2 Hz, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 3.73 (s, 6 H), 3.69 (s, 3 H), 3.59 (dd, J = 11.6, 2.4 Hz, 1 H), 3.33 (t, J = 2.4 Hz, 1 H), 3.31 (s, 3 H). **85**: ¹H NMR (400 MHz, CDCl₃) δ 6.98 (d, J = 8.4 Hz, 1 H), 6.85 (d, J = 8.0 Hz, 2 H), 6.58 (app dd, J = 8.8 Hz, 4 H), 6.44 (d, J = 2.8 Hz, 1 H), 6.42 (s, 1 H), 6.30 (t, J = 2.4 Hz, 1 H), 6.19
S4: Solid K$_2$CO$_3$(0.010 g, 0.075 mmol, 5.0 equiv) and methyl iodide (0.005 mL, 0.075 mmol, 5.0 equiv) were added sequentially to a solution of 84 (0.01 g, 0.015 mmol, 1.0 equiv) in dry
actone (5 mL) at 25 °C. The resultant reaction mixture was then sealed and heated at reflux (80 °C) for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried (MgSO₄), and concentrated. The resultant residue was used in the next reaction without purification. Next, to a solution of ketone (0.01 g, 0.014 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) at –78 °C was added in a single portion a solution of BBr₃ (0.014 mL, 1.0 M in CH₂Cl₂, 0.014 mmol, 1.0 equiv) in CH₂Cl₂. The resultant yellow-brown reaction mixture was then warmed up to 25 °C immediately, and was stirred at this temperature for 30 min. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL), poured into H₂O (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant bright-yellow oil was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1) to give S₄ (0.009 g, 92% yield) as a yellow oil. S₄: ¹H NMR (400 MHz, CDCl₃) δ 11.14 (s, 1 H), 7.09 (d, J = 2.4 Hz, 1 H), 6.85 (d, J = 8.8 Hz, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.74 (d, J = 8.8 Hz, 2 H), 6.64 (d, J = 8.8 Hz, 2 H), 6.53 (d, J = 2.8 Hz, 1 H) 6.34 (s, 1 H) 6.29 (t, J = 2.4 Hz, 1 H), 6.12 (d, J = 2.4 Hz, 2 H), 4.74 (d, J = 5.2 Hz, 1 H), 4.24 (d, J = 6.8 Hz, 1 H) 3.83 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.66 (s, 9 H), 3.56 (s, 3 H), 3.48 (m, 1 H), 3.17 (t, J = 8.0 Hz, 1 H).

87: To a stirred solution of S₅ (0.005 g, 0.007 mmol, 1.0 equiv) in a 1:1 mixture of MeOH/THF (2 mL) at 0 °C, solid NaBH₄ (0.001 g, 0.028 mmol, 4.0 equiv) was added at once. The resultant reaction mixture was stirred at 0 °C for 30 min, warmed slowly to 25 °C over the course of 1 h, and stirred for an additional 1 h at 25 °C. Upon completion, the reaction mixture was quenched
with water (3 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (4 mL) and brine (4 mL), dried (MgSO₄), and concentrated to give 87 (0.004 g, 86% yield) as a colorless oil. 87: ¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1 H), 7.01 (d, J = 2.4 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 6.65 (d, J = 8.8 Hz, 2 H), 6.43 (br s, 1 H), 6.32 (d, J = 2.8 Hz, 1 H), 6.25 (t, J = 2.4 Hz, 1 H), 6.21 (s, 1 H), 6.05 (d, J = 2.0 Hz, 2 H), 4.59 (d, J = 6.4 Hz, 1 H), 4.35 (d, J = 5.6 Hz, 1 H) 3.84 (s, 3 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.60 (s, 6 H), 3.57 (s, 3 H), 3.54 (s, 3 H), 3.42 (br s, 1 H), 3.17 (t, J = 5.6 Hz, 1 H).

89/90: At 25 °C, 87 (0.004 g, 0.006 mmol, 1.0 equiv) was dissolved in neat acetic acid. The reaction mixture was heated at 80 °C for 2 h. Upon completion, the reaction solution was diluted with toluene, and the solvent was removed under reduced pressure. Immediately after co-evaporating with toluene five times to remove traces of acids and water, the orange-red reaction residual was redissolved in dry THF for the following Grignard reaction. The freshly prepared Grignard reagent (0.044 mL, 0.5 M in THF, 5.0 equiv) was added dropwise over the course of 5 min to a solution of 88 (0.003 g, 0.004 mmol, 1.0 equiv) in dry THF (1 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min, warmed slowly to 25 °C, and stirred for an additional 8 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH₄Cl (2 mL), poured into water (2 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 3:7) to afford the desired Grignard addition products (0.0025 g for 90, 51% yield; 0.001 g for 89, 17% yield). 90: ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.37 (m, 5 H), 6.92
(app t, $J = 8.8$ Hz, 4 H), 6.82 (d, $J = 8.8$ Hz, 2 H), 6.69 (d, $J = 8.8$ Hz, 2 H), 6.64 (d, $J = 9.2$ Hz, 2 H), 6.58 (d, $J = 8.8$ Hz, 2 H), 6.41 (d, $J = 2.4$ Hz, 1 H), 6.32 (t, $J = 2.4$ Hz, 1 H), 6.22 (d, $J = 2.4$ Hz, 2 H), 6.18 (d, $J = 2.8$ Hz, 2 H), 6.09 (s, 1 H), 5.03 (s, 2 H), 4.51 (dd, $J = 10.4$ Hz, 1 H), 4.39 (d, $J = 2$ Hz, 1 H), 4.30 (d, $J = 11.6$ Hz, 2 H), 3.97 (s, 3 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.67 (s, 6 H), 3.58 (s, 3 H), 3.40 (s, 1 H), 3.31 (s, 3 H).

**89:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44-7.37 (m, 5 H), 7.07 (app dd, $J = 8.8$ Hz, 4 H), 6.85 (d, $J = 2.4$ Hz, 2 H), 6.78 (app dd, $J = 8.8$ Hz, 4 H), 6.67 (d, $J = 8.8$ Hz, 2 H), 6.53 (d, $J = 8.8$ Hz, 2 H), 6.25 (app t, $J = 2.4$ Hz, 2 H), 6.02 (d, $J = 2.4$ Hz, 2 H), 6.00 (s, 1 H), 4.99 (s, 2 H), 4.67 (dd, $J = 10.0$ Hz, 2 H), 4.32 (d, $J = 5.6$ Hz, 1 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.61 (s, 6 H), 3.55 (s, 3 H), 3.48 (s, 3 H), 3.21 (t, $J = 10.0$ Hz, 1 H).

**S5:** Activated Pd/C (10%, 0.0005 g, 0.005 mmol, 2.0 equiv) was added in a single portion to a solution of **90** (0.002 g, 0.002 mmol, 1.0 equiv) in EtOAc (3 mL) at 25 °C, and then H$_2$ gas was bubbled slowly and continuously through the solution for 30 min. Upon completion, the reaction mixture was filtered through Celite to remove insoluble particulates (using several washes of EtOAc to ensure quantitative transfer). The combined organic layers were then concentrated to give **S5** (0.002 g, 99% yield) as a colorless oil. **S5:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.91 (d, $J = 8.4$ Hz, 2 H), 6.88 (d, $J = 8.4$ Hz, 2 H), 6.69 (d, $J = 8.8$ Hz, 2 H), 6.67 (d, $J = 8.8$ Hz, 2 H), 6.64 (d, $J = 8.8$ Hz, 2 H), 6.57 (d, $J = 8.8$ Hz, 2 H), 6.42 (d, $J = 2.8$ Hz, 1 H), 6.32 (t, $J = 2.4$ Hz, 1 H), 6.21 (d, $J = 2.0$ Hz, 1 H), 6.19 (d, $J = 2.4$ Hz, 1 H), 6.09 (s, 1 H), 4.59 (s, 1 H), 4.51 (dd, $J = 10.5$, 6.1 Hz, 1 H), 4.40 (d, $J = 2.0$ Hz, 1 H), 4.29 (d, $J = 11.5$ Hz, 1 H), 4.19 (s, 1 H), 3.96 (dd, $J = 2.8$ Hz, 2 H).
= 2.4, 9.6 Hz, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.66 (s, 6 H), 3.58 (s, 3 H), 3.31 (s, 
3 H).

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