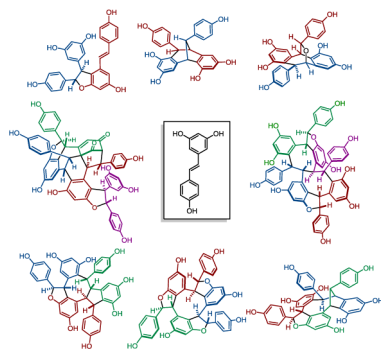# CHEMICAL REVIEWS

Chemistry and Biology of Resveratrol-Derived Natural Products

Mitchell H. Keylor,[†] Bryan S. Matsuura,[†] and Corey R. J. Stephenson*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

CONTENTS

1. INTRODUCTION

Since the dawn of the 20th century, the average life expectancy at birth has nearly doubled due to advances in science and medicine. As medical records grew more reliable, it became apparent that, while overall life span was increasing, there were significant epidemiological differences between geographical regions, with people from countries such as Japan, France, and Switzerland enjoying longer life expectancy as compared to other regions of the world. The causative factors for these disparities in both mortality and morbidity have been attributed not only to genetics but also to the contributions of highly variable lifestyle and environmental influences.[1] Barring differences in modernization and public health policy, diet is the most significant epidemiological factor cross-culturally and is thought to be a profoundly important contributor to health and overall well-being.

Prior to the early 1990s, there was a general consensus in support of the belief that moderate alcohol consumption significantly lowered the risk of coronary heart disease (CHD).[2] However, it was not clear whether this was true of all alcoholic beverages or which constituents in the drinks were responsible for these beneficial properties.[3] In 1992, Siemann and Creasy[4] reported that resveratrol (1) was present in significant

concentrations in red wine, drawing attention to the fact that it was also an active principle found in Japanese and Chinese folk medicines used to treat ailments related to the liver, skin, heart, and lipid metabolism.[5] The discovery of resveratrol in wine was particularly timely; although the correlation between high fat and cholesterol consumption and coronary heart disease was widely accepted,[6] certain populations, namely the French, had a low incidence of CHD mortality despite a diet and lifestyle that exposed these individuals to elevated risk factors.[7] The cardioprotective ability of resveratrol, its oligomers, along with other phytochemicals present in wine, appeared to resolve this "French Paradox" and advanced the notion that a chemical constituent of one's diet could be beneficial to health.[8] Although the reality of the French Paradox remains contentious,[9,10] research into the health benefits of resveratrol has exploded as a result. The reported biological activities of resveratrol are numerous, including antioxidant,[11] anticancer,[12] antidiabetic,[13,14] cardioprotective,[15] and even antiaging properties,[16] to name a few. The body of literature regarding the biological activity of resveratrol is expansive and beyond of the scope of this review. We invite the readers to the following resources for background on this exciting and ongoing field of research.[17−21]

Despite its enormous popularity, resveratrol is but a single compound in a large, structurally diverse class of oligomeric stilbenoids that are present in the wines and foods that we consume.[22,23] Until recently, access to these oligomeric natural products was limited to isolation from natural sources, which severely hampered their biological evaluation. The scientific interest in resveratrol has undoubtedly instigated the renewed attention in these compounds by the chemical community. Advances in the characterization, isolation techniques, and synthesis of these natural products have significantly enriched our understanding of their chemistry and biology. Our review seeks to document the history and recent progress in the isolation, chemical synthesis, and biology of this fascinating class of phytochemicals, while providing new insight on the biosynthesis and future prospects for the field as a whole.

2. RESVERATROL BIOSYNTHESIS AND BIOLOGICAL ROLE IN THE PLANT

Resveratrol, among many natural stilbenoids, shares a common biosynthetic pathway responsible for the production of cinnamic acids and flavonoids (e.g. naringenin, Scheme 1) through the phenylpropanoid pathway.[24] Phenylalanine, a product of the shikimate pathway, undergoes a series of enzymatic reactions to produce the linear tetraketide 2. This intermediate is critical for the synthesis of flavonoids through constitutively expressed chalcone synthase.[25] The gene encoding stilbene synthase, on the other hand, is transcribed only when induced by stimuli such as pathogenic invasion, physical trauma, or UV irradiation.[26] It is important to consider any externalities imposed on the plant by this diversion of biosynthetic resources. Though resveratrol and its derivatives are found in lignified stem tissue, they are deliberately not produced in photosynthetic tissues where they have been shown to interfere with ion transport and associated redox processes.[27] These cellular effects are partially responsible for the cytotoxicity of resveratrol and its derivatives against invasive pathogens, and have implications for the treatment of human disease (see section 8).[28]

Resveratrol can undergo several structural modifications after its biosynthesis. These derivatizations can increase its antifungal

Scheme 1. Resveratrol (A) Biosynthesis and (B) Post-Synthetic Modification and Derivatization
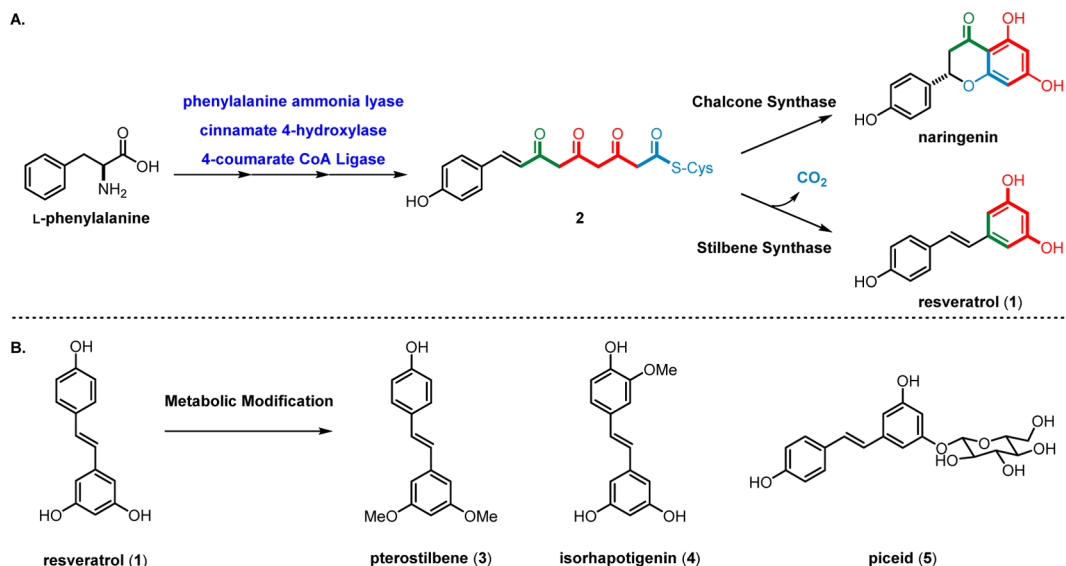
activity and alter the antioxidant properties of the stilbene, rendering its oxidation by laccase enzymes more facile.[29] The glycosylation of **1**, as seen in the resveratrol adduct piceid (**5**), is thought to aid in the storage and translocation of resveratrol within the cell tissues as well as protect resveratrol from oxidation.[30] Alternatively, the resveratrol monomer can be oligomerized to form complex polyphenolic secondary metabolites composed of 2−8 resveratrol units. Collectively, these natural products are referred to as the "resveratrol oligomers" and are the subject of this review.

Resveratrol oligomers, like many secondary metabolites, are chiefly expressed as biological defense compounds and occur as dimers, trimers, tetramers, and higher-order oligomers in plants. The biological role of resveratrol and its oligomers within plants was first described in the 1970s by Langcake and Pryce.[31] They identified resveratrol as the compound responsible for the formation of fluorescent lesions on the leaves of *Vitis vinifera* upon infection with the plant pathogens *Botrytis cinerea* (gray mold) and *Plasmopara viticola* (powdery mildew). Although resveratrol itself did not possess particularly potent antifungal properties, its expression during pathogenic invasion was the first indication of such a role in *V. vinifera*. This was further supported by the observation that resveratrol expression was inducible by fungal inoculation and ultraviolet light irradiation, and that the local concentration of **1** increased nearer to the site of the lesion.[32]

A more comprehensive comparison between susceptible and resistant species of grape vines revealed that the fungal lesions on the leaves of resistant species contained relatively low quantities of resveratrol but rather high concentrations of the oligomeric resveratrol natural products α-viniferin (**6**) and ε-viniferin (**7**) (see section 3.2).[33] Unlike resveratrol, these compounds exhibited potent antifungal activity and were present in high concentrations in fungal-resistant cultivars of the grape vine. Even at this early stage, Langcake, Pryce, and others[34] had speculated that these molecules were the products of the oxidative oligomerization of resveratrol. Drawing on the known chemistry of related lignan phytoalexins such as licarin A,[35] they demonstrated that **1** could be dimerized to produce more potent antifungal compounds, indicating that resveratrol was a precursor to the actual phytoalexins in the plant.[36,37] It is

now believed that while most oligomers are produced endogenously, some may in fact be formed by the action of oxidase enzymes that are part of the invasive fungus.[38] Whether this is part of a "detoxifying" process of fungal origin that enables pathogenesis or a plant-designed defense mechanism that exploits the invading species' metabolic machinery for its own demise is currently unknown.

3. ISOLATION AND CHARACTERIZATION OF RESVERATROL OLIGOMERS

The first reported resveratrol oligomer was characterized 50 years ago by single-crystal X-ray diffraction (XRD) analysis.[34,39,40] Over the next quarter-century, approximately 25 structurally related compounds were identified. As the number of natural product reports increased, structural patterns emerged, including the presence of dihydrobenzofuran and indane moieties, as well as bicyclic [3.2.1] and [3.3.0] ring systems. Today, >300 resveratrol oligomers have been characterized, largely due to the advent of advanced NMR and chromatographic technologies.[41] Additionally, the search for these natural products has recently been incentivized by a series of reports lauding the broad spectrum biological activities of resveratrol.[12,14−17] In the plant kingdom, resveratrol oligomers have now been isolated from the following nine families: Dipterocarpaceae, Vitaceae, Cyperaceae, Gnetaceae, Fabaceae (Leguminosae), Paeoniaceae, Apiaceae (Umbelliferae), Haemodoraceae, and Musaceae. In this section, five representative case studies are presented which we feel speak to the beauty of these molecules and highlight dedicated efforts required to elucidate their complex architectures.

The structural elucidation of these natural products has been accomplished using a combination of mass spectrometry (MS) with UV−vis, infrared (IR), and NMR spectroscopy. Although the connectivity of these compounds can typically be deciphered through detailed analysis of the 2D NMR spectra (COSY, HSQC, HMBC), the relative and absolute configurations have often been difficult to resolve. Notably, vicinal coupling constants are notoriously poor predictors of relative configuration within the five- and seven-membered ring systems which are prevalent in this class of natural products,[42] leading to a number of structural misassignments[43] and

revisions.[44,45] Modern NOE(SY) and ROESY experiments have enabled assignment of relative configuration to a reasonable level of accuracy, although the determination of absolute configuration remains a difficult task. Typically only derivatives of the natural products are capable of forming crystals suitable for XRD analysis, which introduces concerns about compound stability and propensity for skeletal rearrangement. The development of circular dichroism (CD) has helped to address this challenge, but suffers from a dependence on analogy to previous reports. In this approach, the absolute configurations are assigned on the basis of observed Cotton effects[46−48] in the CD spectra and can be inferred by comparison to the spectral signatures of analogous structures whose absolute configurations were previously determined. The risk in this approach is apparent: an error in assignment can propagate through the literature as spectroscopists rely on the original report as their reference spectrum. Nonetheless, the assignments for the resveratrol oligomers are reasonably well-supported.

The most relevant example of this is the assignment of the absolute configuration of (−)-ε-viniferin (7) by Kurihara and co-workers.[49] This assignment has been highly influential as a large number of resveratrol oligomers are believed to derive from 7. Indeed, the absolute configurations of several higher-order oligomers have been deduced on the basis of biomimetic transformations of optically pure (−)-ε-viniferin.[50−52] Kurihara et al. prepared permethylated derivatives of the *syn* and *anti* diastereomers of 7 in order to determine the relative configuration of the natural sample. As expected, the *anti* diastereomer was found to be consistent with the NMR data for the enantiopure authentic sample. The final assignment of (−)-ε-viniferin as 7a(R), 8a(R) was made by comparison of the CD spectrum of a hydrogenated sample of 7 to the CD spectrum that had been used for the assignment of gnetin F (8) 5 years prior (Figure 1).[53] The stereochemical assignment of 8,
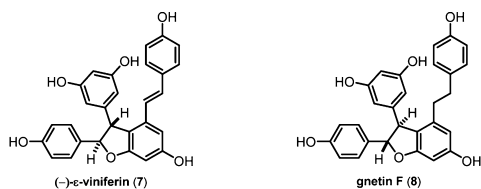
Figure 1. Establishing the absolute configuration of (−)-ε-viniferin.

in turn, had been established by comparison to the CD spectra of benzofuranoid neolignans whose absolute configurations were determined by X-ray crystallography.[54]

3.1. Hopeaphenol

The first resveratrol oligomer ever characterized was hope-aphenol (9, Figure 2), a resveratrol tetramer isolated by Coggon et al.[34,39,40] Originally isolated in 1951 from the
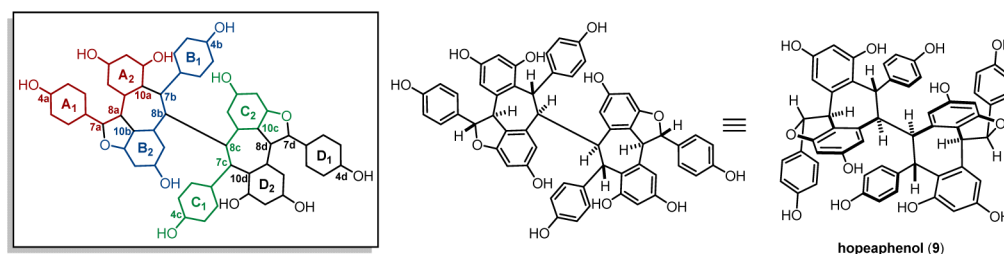
heartwood of *Hopea odorata* and *Balanocarpus heimii*, two members of the Dipterocarpaceae family, another 15 years passed before the structure was solved. Ultimately, the isolation and characterization of this natural product were made possible by its poor solubility, enabling its isolation by crystallization and eventually its structural determination by single-crystal XRD of a dibromo-decamethyl ether derivative. It was known that exposure of the permethyl ether compound to electrophilic halide sources did not induce skeletal rearrangement, and therefore analysis of this derivative enabled the assignment of the absolute structure of hopeaphenol itself. Interestingly, stilbenes had not yet been reported as occurring in any Dipterocarpaceous plants at this time, but the researchers correctly assumed that the biosynthesis occurs through the oligomerization of resveratrol (1), which had been identified some 20 years earlier.[55] However, it was not until a decade later that ε-viniferin (7), the building block for hopeaphenol (and nearly all higher-order oligomers), was identified. Indeed, the absolute configuration of (−)-ε-viniferin (7), as determined by Kurihara and co-workers in 1990, was consistent with the absolute configuration of the dihydrobenzofurans in (−)-9, the structure reported by Coggon and co-workers.

In 1992, Kawabata et al. were able to confirm the structure of hopeaphenol using advanced NMR spectroscopic methods that were unavailable at the time of its initial isolation.[56] Despite the complex polycyclic scaffold of hopeaphenol (9), its C_2-axis of symmetry halves the number of resonances observed in the NMR spectra. Determining such structures by NMR spectroscopic methods is confounded by difficulty in distinguishing between equivalent nuclei. For equivalent, hydrogen-bearing carbons that are covalently bonded, it is possible to ascertain the connectivity using isotopomeric asymmetry. In hopeaphenol there are three possible isotopic combinations for 8b and 8c: $^{12}C-^{12}C$ (97.8%), $^{12}C-^{13}C$ (2.18%), and $^{13}C-^{13}C$ (0.01%). Although the latter is below detection limits, the broken symmetry of the $^{12}C-^{13}C$ species can be exploited. Using INEPT (insensitive nuclei enhancement through polarization transfer), LSPD (long-range selective proton decoupling), COLOC (correlation through long range coupling), and HMBC, these researchers were able to unequivocally establish the 8b−8c connectivity through detection of the $^1J(C-H)$ and $^2J(C-H)$ coupling constants across the H−$^{12}C-^{13}C$−H spin system.

3.2. Viniferins

In 1976, Ingham and co-workers discovered that groundnut hypocotyls accumulate a mixture of *cis*- and *trans*-resveratrol in response to infection by the nonpathogenic fungus, *Helminthosporium carbonum*, representing the first time that resveratrol had been implicated as a phytoalexin.[57] Shortly thereafter, Langcake and Pryce discovered that resveratrol also accumu-

Figure 2. Numbering scheme for hopeaphenol.
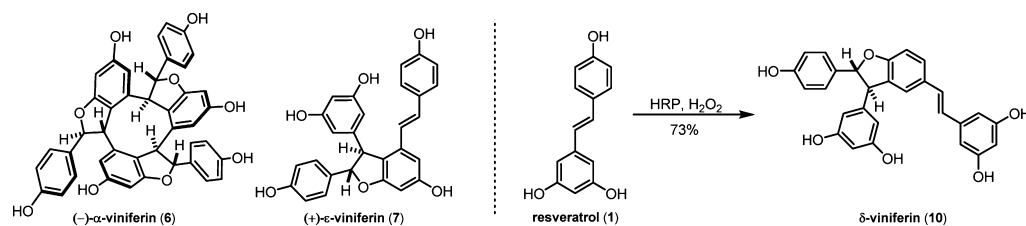
Figure 3. Identification of α- and ε-viniferin, phytoalexin constituents of *Vitis vinifera*.
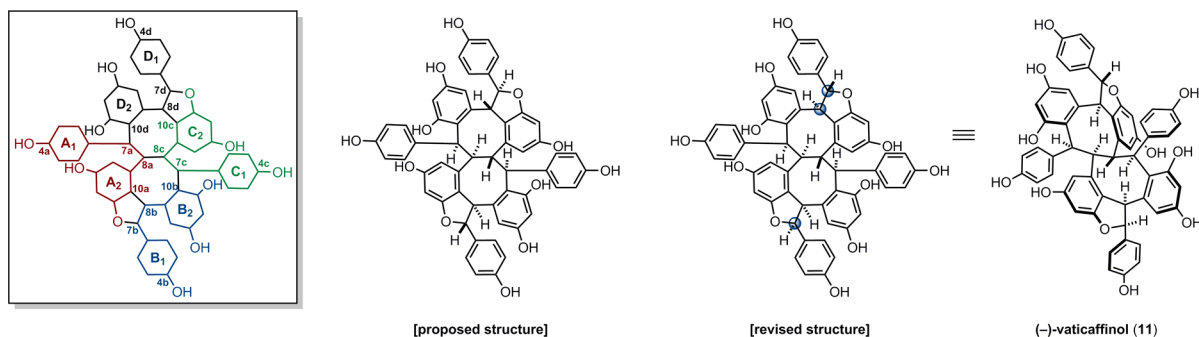
Figure 4. Reassignment of the structure of vaticaffinol.

lates in the leaves and lignified stem tissue of grapevines that have been infected with fungus or exposed to UV irradiation.[37] Resveratrol, although not constitutively expressed in the leaves, was present at a significant concentration (50−400 μg/g fresh weight in leaves and 700 μg/g in stem tissue). In search of other resveratrol-derived materials, they extracted vine leaves from the grapevine *Vitis vinifera* (Vitaceae family) that had been infected with the necrotrophic fungus, *Botrytis cinerea*. Structural elucidation using a combination of derivatization, MS, UV−vis, and NMR studies, enabled the identification of ε-viniferin (**7**), a *trans*-dehydrodimer of resveratrol, as well as α-viniferin (**6**), a resveratrol cyclotrimer (Figure 3). Due to the relatively low antifungal activity of resveratrol as compared to the viniferin oligomers, these researchers proposed that resveratrol should *not* be considered a phytoalexin. Rather, they proposed that resveratrol serves as a biosynthetic precursor to the more active viniferins, drawing analogy to the oxidative oligomerization of cinnamyl alcohols (monolignols) during the biosynthesis of phenylpropanoid lignans. This insightful hypothesis was experimentally supported by the oxidative dimerization of resveratrol upon treatment with horseradish peroxidase (HRP) and H_2O_2, although the regioisomeric *trans*-dehydrodimer, δ-viniferin (**10**), was isolated (Figure 3).[36]

While the structure of α-viniferin (**6**) was proposed in their prior communication, limited structural evidence was presented.[37] In a follow-up paper, these authors shared their efforts toward elucidating the structure of this resveratrol cyclotrimer.[58] Impressively, the structural assignment was made using only ^{1}H NMR spectroscopy, as there was not enough material to obtain a ^{13}C NMR spectrum. It was assumed that each of the 2,3-dihydrobenzofurans were *trans* because this was the only relative configuration that had been found thus far in natural isolates. Next, the relative disposition of the three dihydrobenzofurans about the 9-membered ring was assigned using circular dichroism and ^{1}H NMR spectroscopy. Because the compound was optically active, the cyclotrimer could not have a C_3-axis of symmetry, and the ^{1}H NMR data were consistent with this observation. Using a Dreiding model to

rationalize observed coupling constants based on the Karplus curve, α-viniferin (**6**) was proposed to have a *trans, cisoid, trans, transoid, trans* stereostructure, as depicted in Figure 3.

In 1990, the proposed structure of α-viniferin was confirmed by Kitanaka and co-workers using a combination of single- (HETCOR) and multiple- (COLOC) bond heteronuclear correlation NMR experiments, which today have been supplanted by HSQC and HMBC, respectively.[59] NOESY experiments supported the relative configuration proposed by Langcake and Pryce. Kitanaka et al. found that the Cotton effects of the CD spectrum obtained on their sample from *Caragana chamlagu* (Fabaceae) showed opposite curves to those previously reported, and (+)-α-viniferin was therefore deemed antipodal. This supports the hypothesis that these oligomers are synthesized from ε-viniferin (**7**), as Vitaceous plants are known to produce the (+)-isomer of this resveratrol dimer while nearly all other resveratrol-producing plant families synthesize the enantiomer. Notably, α-viniferin has since demonstrated a wide range of interesting biological activities (see section 8.2).

3.3. Vaticaffinol

Fifteen years after the milestone discovery of the structure of hopeaphenol (**9**), Sultanbawa and Bladon reported the isolation (from *Vatica affinis*) and structural elucidation of a second resveratrol tetramer, vaticaffinol (**11**) (Figure 4).[60] Unlike hopeaphenol, in which the vicinal 7/8b, 7/8c and magnetically equivalent 8b/8c protons do not couple (Figure 2), decoupling experiments on vaticaffinol revealed vicinal coupling through 7a−8a−8c−7c at the core of the molecule (Figure 4). Hopeaphenol has a C_2-axis of symmetry, resulting in just four observable aliphatic proton signals, whereas the ^{1}H NMR spectrum of vaticaffinol has eight distinct proton resonances. Additionally, the physical properties of **11** (mp =280 °C, [α]$_D$ = −22.5°) were found to be distinct from those of **9** (mp = 350 °C, [α]$_D$ = −407°). It is worth noting that ε-viniferin (**7**) was isolated from the same extract, representing the first report of the dimer from the Dipterocarpaceae, and lending credence to
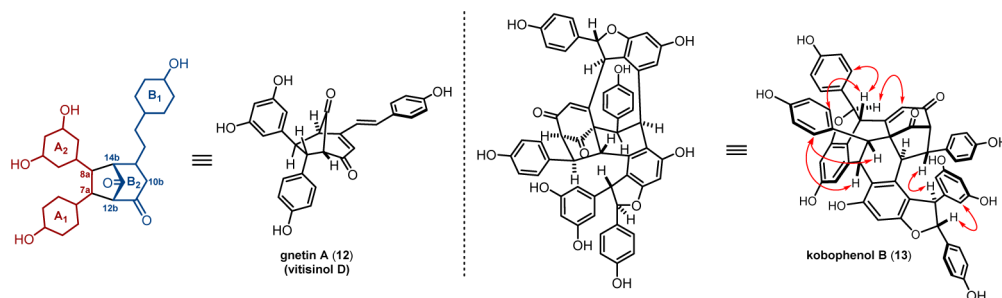
Figure 5. Resveratrol oligomers with a dearomatized A_2 resorcinol ring.

Scheme 2. Atropisomerism of Shoreaketone and Its Acid-Mediated Interconversion to Isohopeaphenol Monomethyl Ether
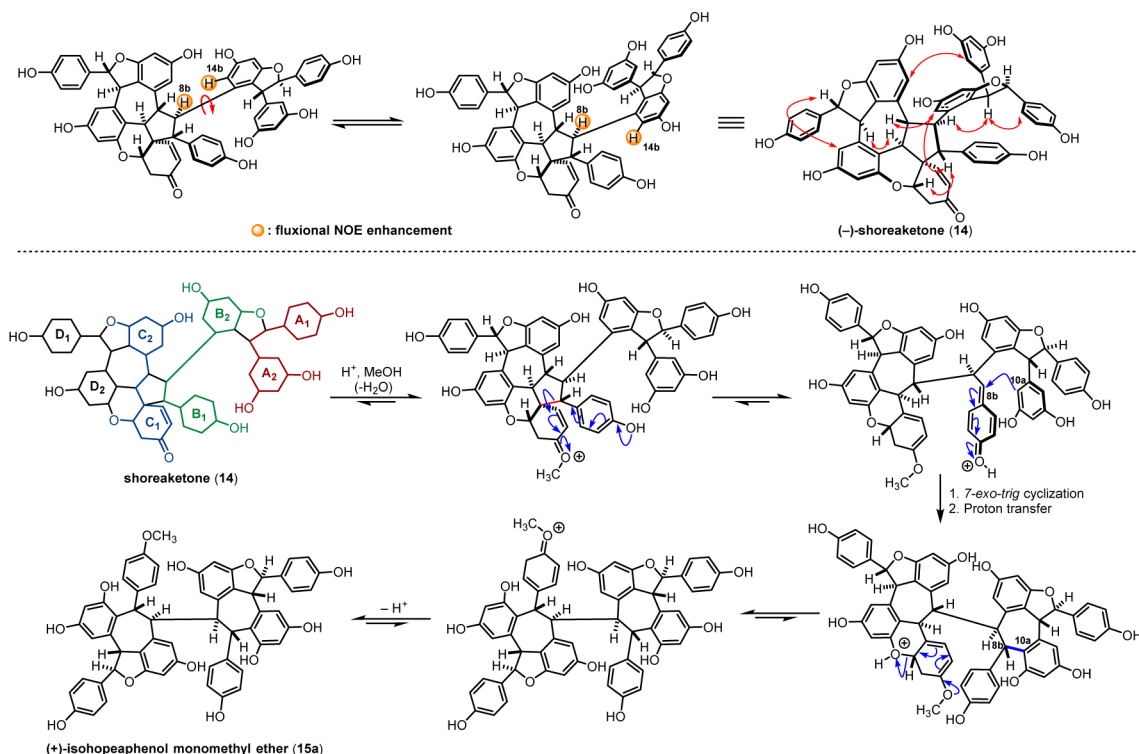
the hypothesis that tetramers such as **9** and **11** are formed via the oxidative coupling of **7** (see section 5.4.2).

Several years after these initial reports, Sotheeswaran and Kraus revised the stereochemical assignment of **11** using a sample isolated from *Stemonoporus canaliculatus*.[44] Using NOE and [1]H-homodecoupling experiments, the relative configuration at 7b/8b was revised from *trans* to *cis*, and an NOE correlation between 7a, 8a, and 8d led them to invert the stereogenic centers at 7d and 8d so as to place 8d *cisoid* to 7a and 8a (Figure 4). This stereochemical revision has important implications with respect to the biogenesis of these compounds. The previously proposed diastereomer of vaticaffinol would have required the crossed coupling of (+)- and (−)-ε-viniferin for this to be true, whereas in the revised structure, the nonepimerizable C-3 stereogenic centers of each of the dihydrobenzofurans are of the same absolute configuration.

3.4. Gnetin A and Kobophenol B

In 1982, a team of researchers discovered and reported the structure of gnetin A (**12**) (Figure 5), a bicyclo-[3.2.1]-octen-dione based resveratrol dimer isolated from *Gnetum leyboldii* (Gnetaceae).[61] The connectivity about the bicyclic core could

be deduced through a combination of ^{13}C NMR chemical shift and ^{1}H NMR coupling analyses, and the substitution pattern and relative configuration of the vicinal arenes were deduced through evaluation of 3-bond coupling constants and homodecoupling experiments. An identical structure was later isolated from the roots of *Vitis thunbergii* (Vitaceae) by Chen and co-workers and given a second name, vitisinol D.[62]

In 1991, Kawabata et al. elucidated the structure of kobophenol B (**13**) (Figure 5), a highly complex resveratrol tetramer isolated from the subterranean parts of *Carex pumila*.[63] Mass spectra of the natural product and its peralkyl and peracetyl derivatives demonstrated that it was a resveratrol tetramer. IR spectroscopy indicated that the molecule contained both conjugated (1640 cm^{-1}) and isolated (1740 cm^{-1}) carbonyl groups, and the presence of ^{13}C resonances at δ 194.0 and 203.4 was consistent with this observation. The previous report of the structure of gnetin A validated the proposal of a bicyclo-[3.2.1]-octen-dione. The remaining connectivity was determined through extensive HETCOR and COLOC correlation NMR experiments. Relative stereochemical assignments were made using NOESY, and selected examples of these enhancements are highlighted in Figure 5. As

Scheme 3. Regioisomeric Modes of Resveratrol Dimerization
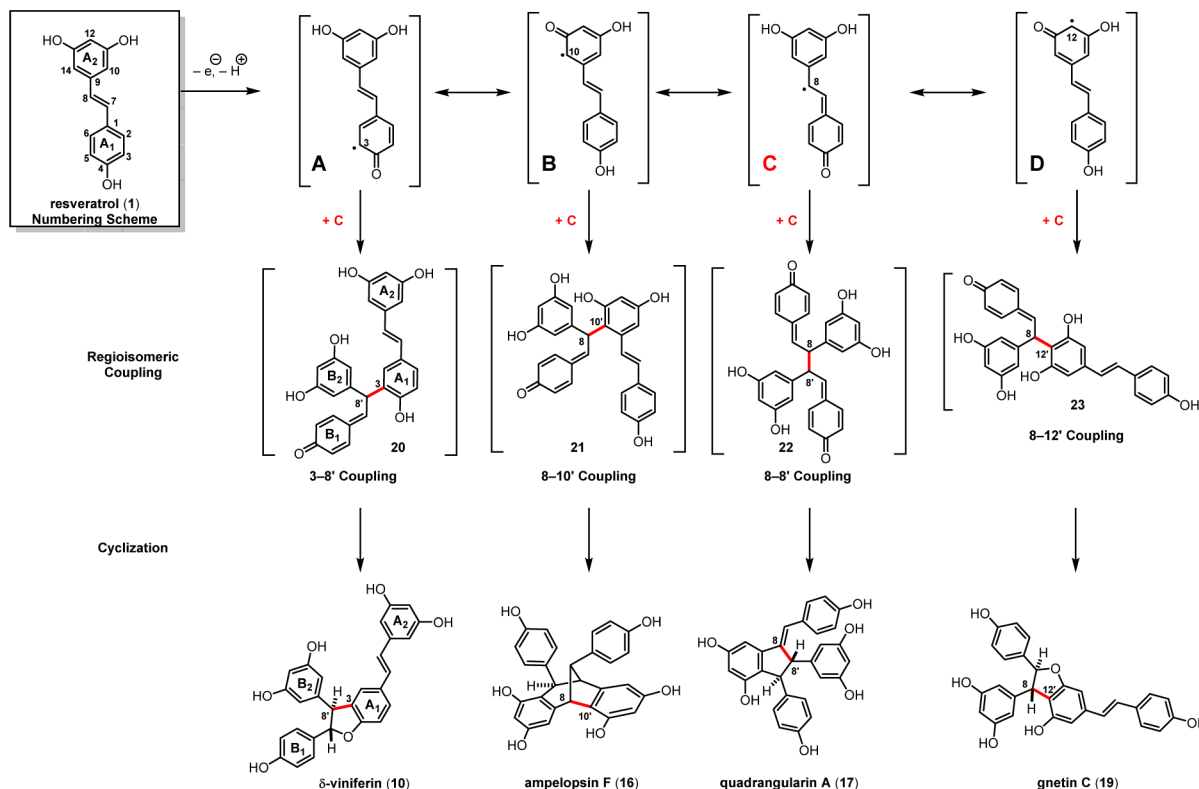
with the foregoing tetramers, kobophenol B (**13**) is proposed to arise from the oxidative coupling of two molecules of ε-viniferin (**7**), which has been isolated from the same plant source.

3.5. Shoreaketone

In 2005, Ito and co-workers reported the structure of shoreaketone (**14**) (Scheme 2), a resveratrol tetramer that was isolated from three species of Dipterocarpaceous plants: *Shorea uliginosa, Shorea hemsleyana, and Vateria indica*.[64,65] While gnetin A (**12**) and kobophenol B (**13**) each contained dearomatized resorcinol rings, shoreaketone is characterized by a dearomatized phenol. This molecule represents the first example of an atropisomeric resveratrol oligomer, although hindered rotation had been observed previously at reduced temperatures for other oligomers.[66,67] At ambient temperature, each of the rotational isomers of **14** were configurationally stable. Using variable-temperature (VT) NMR, these researchers were able to observe interconversion of the isomers by the variance in signal enhancement of the NOE between H-8b and H-14b (Scheme 2) and via anisotropic effects on the chemical shift of several protons.

Once the connectivity had been established through extensive COSY, HSQC, and HMBC experiments, the relative configuration and ring conformations of **14** were determined using ROESY. Selected dipolar couplings are highlighted in Scheme 2. The relative proportions of the two conformers were dependent on solvent polarity, viscosity, and temperature. This equilibrium could be shifted to populate predominantly one rotamer when the spectra were recorded with increasing concentrations of deuterium oxide (D_2O) in acetone-d_6. Interestingly, subjection of **14** to either trifluoromethanesulfonic acid or sulfuric acid in methanol resulted in its skeletal rearrangement to the monomethyl ether derivative **15a** of

(+)-isohopeaphenol (Scheme 2). As the stereochemical information at each of the dihydrobenzofurans should be unchanged by this rearrangement, the authors proposed the absolute configuration for shoreaketone based on a previously reported assignment for (−)-isohopeaphenol (**15**, see Scheme 17, B).[44,65]

4. THE BIOSYNTHESIS OF RESVERATROL DIMERS

The resveratrol oligomers are a highly diverse class of natural products that are produced by a small set of phylogenetically distant plant families.[68] Although the number of individual resveratrol-based natural products is >300, there are many characteristic structural motifs that are conserved across the oligostilbene producing plants. There have been several attempts to phenotypically classify the resveratrol oligomers based on the presence of these conserved structural motifs, a position which has waned in popularity as the field matured. Instead, as Cichewicz and Kouzi posited, a genotypic approach to oligomer classification that presents the oligomers based on their biological source is more useful, since it provides a link between taxonomy and chemical structure.[42] However, this approach is still imperfect and does not account for the possibility of biosynthetic pathways that are conserved between plant families. In this review we will classify the natural products on the basis of the regioisomeric mode of their dimerization, and will employ the numbering scheme favored by Kawabata and co-workers (Scheme 3),[49] which conveniently standardizes the arenes of each resveratrol subunit as A_1/A_2 for the phenol and resorcinol rings, respectively. In the literature, the resveratrol unit designated "A" is usually arbitrarily assigned and each successive resveratrol subunit is then assigned the next letter in the alphabet (e.g., "B", "C", ...).

Scheme 4. Proposed Biosynthesis of the 8−10′ Dimers
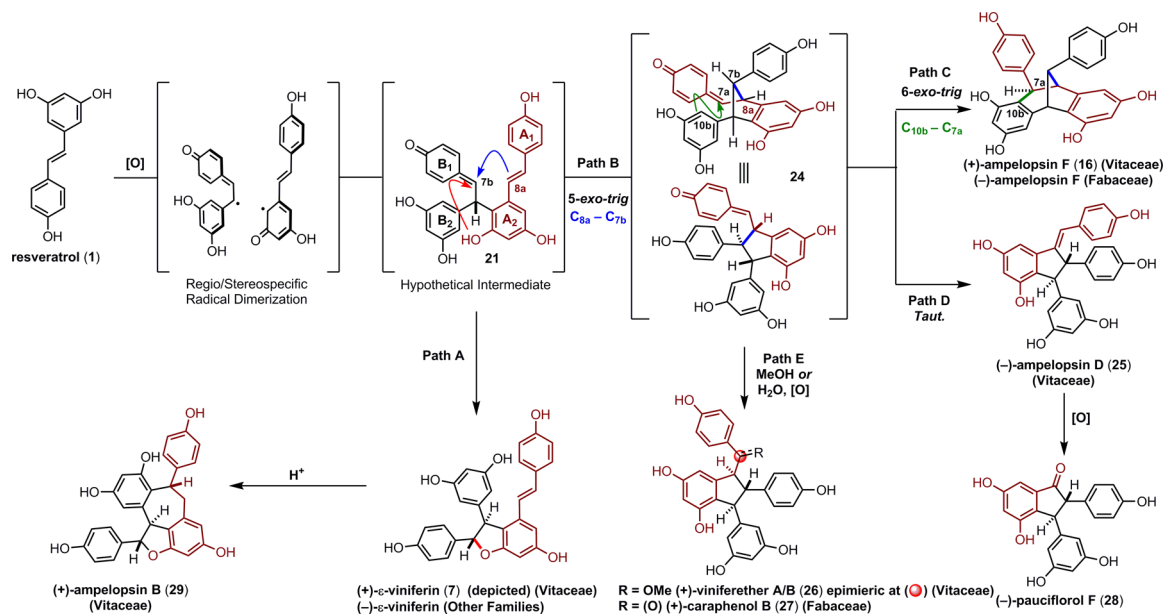
Scheme 5. Niwa's Brønsted-Acid-Mediated Conversion of ε-Viniferin to Various 8−10′ Dimers

	(+)-ampelopsin B (29)	(+)-ampelopsin F (16)	(−)-ampelopsin D (25)	(−)-isoampelopsin D
aq. HCl, rt 50h	38%	8%	---	---
TfOH/CH₃NO₂, rt 10h	---	38%	---	---
TfOH/MeOH, reflux, 7d	---	21%	14%	8%
H₂SO₄/MeOH, reflux, 5d	13%	19%	6%	10%
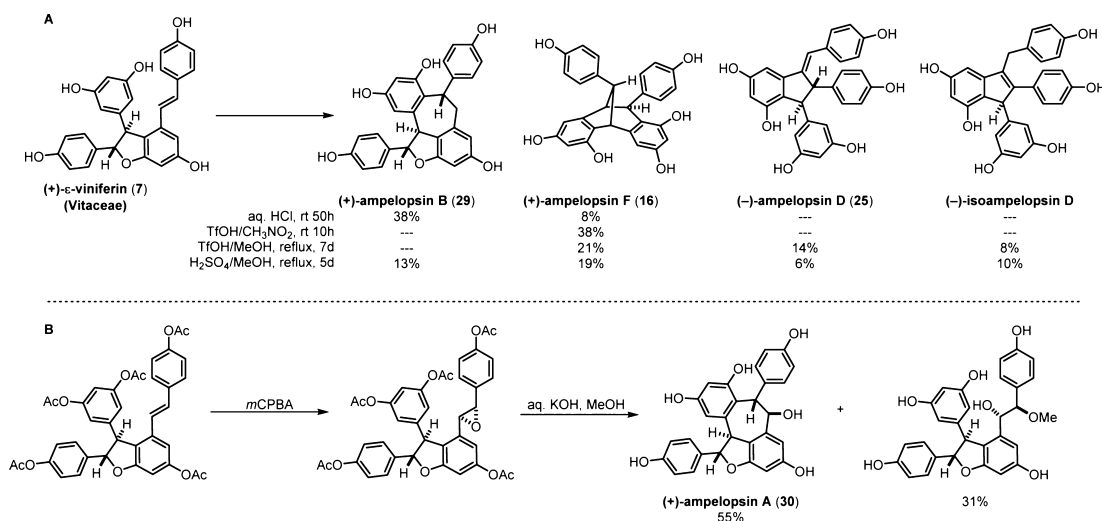
Resveratrol oligomerization appears to proceed via the coupling of oxidatively generated phenoxyl radicals (Scheme 3, **A−D**) as originally proposed by Langcake and Pryce.[37] The dimerization typically occurs through three regioisomeric modes: the 8−10′ coupling (as found in ε-viniferin (**7**) and ampelopsin F (**16**)[69]), 8−8′ coupling (quadrangularin A (**17**)[70,71] and pallidol (**18**)[72]), and 3−8′ coupling (e.g., δ-viniferin (**10**), Scheme 3). Several exotic regioisomers, like the 8−12′ (gnetin C (**19**))[61] or the 12−12′ coupling (amurensin M),[73] have also been identified, but they are relatively uncommon. Following dimerization, highly reactive *para*-quinone methides such as **20−23** can undergo numerous regiodivergent Friedel−Crafts reactions, nucleophilic trappings, or tautomerizations. Although the divergent reactivity of these intermediates quickly generates an impressive number of complex architectures, nearly all of the resveratrol natural products can be reduced to these initial bond disconnections.

In the section below, we will outline the biosynthesis of the resveratrol natural products and present as much of the skeletal diversity as possible. Our objective is not to provide a comprehensive list of natural products (for this the reader is directed to refs 41, 42), but rather to methodically delineate a plausible biogenic relationship between compounds possessing very different topologies. These "proposed" biosyntheses are strongly supported by empirical studies on the biogenesis of these natural products, with several of the ensuing schemes representing a compilation of many years of work and, at times, dozens of papers. Where appropriate, experimental data will be included to supplement the biosynthetic relationships as presented. In the following reaction schemes, each of the natural products is depicted as a single stereoisomer. However, due to the existence of antipodal resveratrol oligomers that derive from enantiomeric starting materials, there will sometimes be apparent changes in the molecule's configuration with respect to these starting materials.[74] In these instances, we do not mean to imply a biosynthetic epimerization, but rather only to depict the structure in the reported configuration.

Scheme 6. Proposed Biogenic Relationship Between ε-Viniferin and the 8−10′ Dibenzocycloheptane Dimers
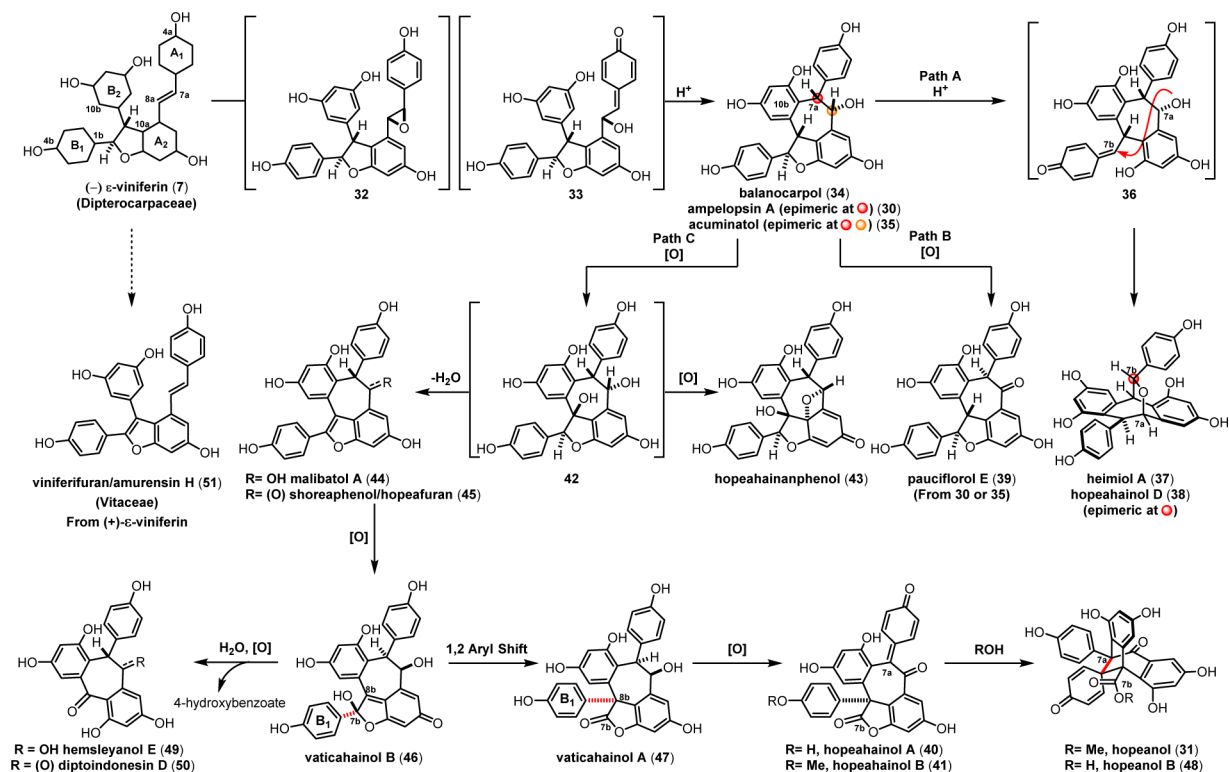
4.1. Biosynthesis of 8−10′ Dimers

The 8−10′ connectivity is by far the most prevalent found among resveratrol-derived oligomeric natural products.[42] The parent molecule of 8−10′ oligomers, ε-viniferin (7), has the relatively uncommon distinction of being a natural product that is found naturally in both enantiomeric forms.[75] (−)-ε-Viniferin is found in several plant families such as Dipterocarpaceae, Gnetaceae, Cyperaceae, and Fabaceae (Leguminosae), while its enantiomer, (+)-ε-viniferin, is exclusively found in plants from the family Vitaceae (Scheme 4).[41] Upon oxidation of 1 and 8−10′ dimerization, hypothetical *para*-quinone methide intermediate 21 can follow divergent cyclization pathways to generate either ε-viniferin via an oxa-conjugate addition (Scheme 4, path A), or *para*-quinone methide 24 through a vinylogous Friedel−Crafts reaction (path B). From here, a second intramolecular cyclization yields the bridged [3.2.1] bicyclic dimer ampelopsin F (16)[69] (path C), while tautomerization yields the indane isomer ampelopsin D (25) (path D).[76] The existence of the intermediate *para*-quinone methide 24 is strongly supported by the isolation of viniferethers A/B (26),[77] the products of the nucleophilic trapping of 24 by methanol (path E). Caraphenol B (27) likely follows a similar biosynthesis: hydration of 24 with water, followed by oxidation forms the benzylic ketone.[43] Oxidative cleavage of the olefin of ampelopsin D (25) results in the formation of the natural product pauciflorol F (28),[78] which was inadvertently synthesized by Oshima and co-workers 11 years before its eventual isolation.[76]

Given the ubiquity of the 8−10′ dihydrobenzofuran motif in the resveratrol oligomers, it appears that ε-viniferin plays a central role in the biosynthesis of the entire class of 8−10′ dimers and oligomers. The biogenic relationship of 7 to ampelopsins F (16), D (25), and B (29) was delineated by Niwa and co-workers[50] through a series of biomimetic

Brønsted-acid-mediated rearrangements of natural (+)-ε-viniferin (Scheme 5, A). Additionally, they were able to convert peracetyl 7 to ampelopsin A (30) through an epoxidation/fragmentation/cyclization sequence in 55% overall yield (Scheme 5, B). The optical rotations of each of these synthetically derived compounds were compared to reported values for the isolated natural products, verifying that (+)-ε-viniferin was their biogenic precursor and by analogy, confirming their absolute configuration.

4.2. Biosynthesis of Oxidized 8−10′ Dimers

Plants found in the Dipterocarpaceae family synthesize an array of highly oxidized and structurally rearranged 8−10′ dibenzocycloheptane dimers that are unique to this plant family. Although no unified biosynthesis of these rearranged 8−10′ dimers has been proposed, the biogenic relationship between 7 and hopeanol (31),[79] for example, can be inferred from the isolation of several natural products of intermediate levels of oxidation and rearrangement that ultimately lead to 31. The efforts of the Tan and Ito groups in the isolation and detailed characterization of these fascinating (and surprisingly stable) natural products provide key insight into the biogenic relationships of these compounds.

Following epoxidation of the *para*-hydroxy styrene of 7, *trans*-stilbene oxide 32 can undergo a dearomative epoxide fragmentation to generate intermediate 33, which is prone to an intramolecular 7-*exo trig* Friedel−Crafts cyclization to afford (+)-balanocarpol (34)[80] or its epimers (−)-ampelopsin A (30)[81,82] and acuminatol (35)[83] (Scheme 6). The epimeric [3.2.2] oxabicyclic natural products heimiol A (37)[84] and hopeahainol D (38)[85] possibly derive from an intramolecular etherification of the C_{7b}−O_{7a} bond upon an acid-mediated formation of *para*-quinone methide 36 (path A). A direct benzylic alcohol oxidation of 30 or 35 to the ketone affords pauciflorol E 39 (path B).[78]

Scheme 7. Proposed Biosynthesis of the 8−8′ Dimers

R = H leachianol F/G (53)
R = Me parthenostilbenin A/B (54)
R = Et quadrangularin B/C (55)
(Vitaceae, Fabaceae, others)

Path C
ROH

(±)-pallidol (18)
(Vitaceae, Fabaceae, others)

Path A
C₂-symmetric
2 × 5-exo-trig
C₁₀ₐ − C₇ᵦ
C₁₀ᵦ − C₇ₐ

C₂−symmetric 22

meso 22

Path B
meso
1 × 5-exo-trig
C₁₀ᵦ − C₇ₐ

52

Taut.

(−)-quadrangularin A (17)
(Vitaceae)

Path D
H₂O

tricuspidatol A (57)
(Vitaceae)

restrytisol A (56)
(B. cinerea)

Taut.

58

Path E
H₂O

amurensin A (59)
(Vitaceae)

The biogenic relationship between the (+)-balanocarpol (**34**), hopeanol (**31**), and the hopeahainols A/B (**40/41**)[86] can be deduced from the isolation of several oxidized intermediary natural products. The oxidation of **34** may occur through the hypothetical intermediate **42**, since the natural product hopeahainanphenol (**43**)[87] would represent a product of its oxidative dearomatization. Dehydration of intermediate **42** may lead to the formation of (−)-malibatol A (**44**),[88] a plausible biosynthetic precursor to the several other oxidized 8−10′ dimers. The oxidation of benzylic alcohol **44** yields the natural product shoreaphenol (**45**)[89] (also known as hopeafuran),[90] although biosynthesis via a formal dehydrogenation of pauciflorol E (**39**) cannot be ruled out. The biogenic relationship between (−)-malibatol A (**44**) and the hope-anols/hopeahainols is supported by the isolation of the oxidized 8−10′ dimers vaticahainols B (**46**) and A (**47**).[91] Vaticahainol B (**46**) is presumably derived from a diastereoselective oxidative dearomatization of **44**, perhaps through an epox-idation. A stereoselective 1,2 aryl migration from **46** yields vaticahainol A (**47**). Subsequent C_{8a} oxidation and oxidative dearomatization of phenol A_1 would yield the natural product hopeahainol A (**40**). The biogenic relationships between hopeanol (**31**),[79] hopeanol B (**48**),[86] and hopeahainols A (**40**) and B (**41**) are supported by total synthesis (see sections 7.1.4−7.1.5).[92] Upon trapping with water, vaticahainol B (**46**)[91] can undergo an oxidative cleavage of its C_{7b}−C_{8b} bond followed by hydrolysis of 4-hydroxybenzoate to hemsleyanol E (**49**)[93] (or its epimer) and diptoindonesin D (**50**),[94] which differ only in the oxidation state at the C_{8a} benzylic position.

The isolation of the rearranged dibenzocycloheptane natural products demonstrates another level of chemical diversity that is available to Dipterocarpaceous plants. These transformations also provide insight to how other plant families may perform oxidative modifications to other dimers, as in the case of the

conversion of **7** to viniferifuran (**51**) (also known as amurensin H)[95] (Scheme 6) or ampelopsin D (**25**) to pauciflorol F (**28**) (Scheme 4).

4.3. Biosynthesis of 8−8′ Dimers

The natural products pallidol (**18**)[71] and quadrangularin A (**17**) (formerly known as cyphostemmin B)[70,71] were the first 8−8′ dimers isolated from Vitaceae. The 8−8′ dimers are relatively uncommon regioisomers and have been isolated from a limited number of plant families, primarily from Vitaceae. The proposed 8−8′ dimeric intermediate **22** has two para-quinone methides and two vicinal stereogenic centers, which promote unusual diversification reactions when compared to the regioisomeric 8−10′ and 3−8′ dimers. The relative config-uration of these vicinal stereocenters has important con-sequences from a product determination standpoint. The C_2-symmetric diastereomer of **22** has the correct relative configuration to undergo the sequential Friedel−Crafts cyclizations necessary to form the [3.3.0] bicyclic core of pallidol (**18**) (Scheme 7, path A). After the first cyclization reaction of meso **22**, however, the anti,anti-configuration of the resultant quinone methide **52** would prevent a second cyclization reaction due to the thermodynamically unfavorable formation of a trans-fused bicyclo[3.3.0]octane (Scheme 7, path B).[96] Tautomerization of para-quinone methide intermediate **52** to the E-alkene provides (−)-quadrangularin A (**17**). There are several natural products that presumably derive from the nucleophilic trapping of quinone methide indane **52** (path C) including leachinols F/G (**53**),[97] parthenostilbenins A/B (**54**),[98] and quadrangularins B/C (**55**).[71] It is probable that these natural products are actually isolation artefacts, since methanol and ethanol were used as extraction solvents for **54** and **55**, respectively. The isomeric furan dimers restrytisol A (**56**)[38] and tricuspidatol A (**57**),[99] which derive from the double addition of water across the para-quinone methide

Scheme 8. Oxidized Derivatives of 8−8′ Dimeric Natural Products
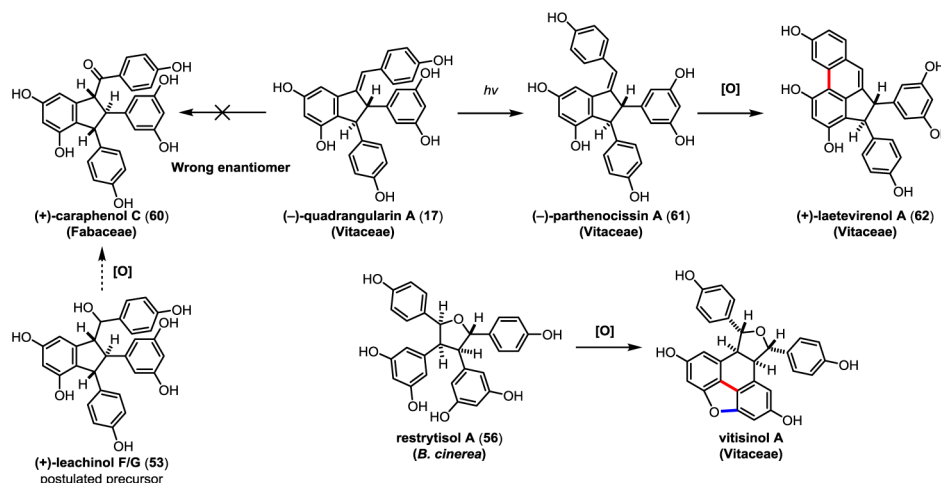
Scheme 9. Whole Cell *B. Cinerea*-Mediated Dimerization of 1 to 8−8′ Dimers
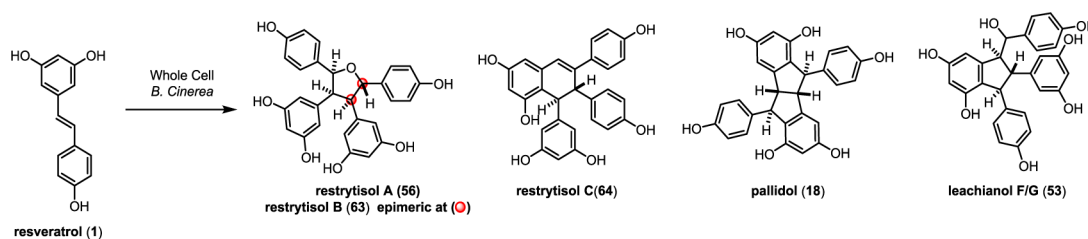
Scheme 10. 3−8′ Dimers are Commonly the Major Isomers Formed on Exposure of Resveratrol to Oxidants
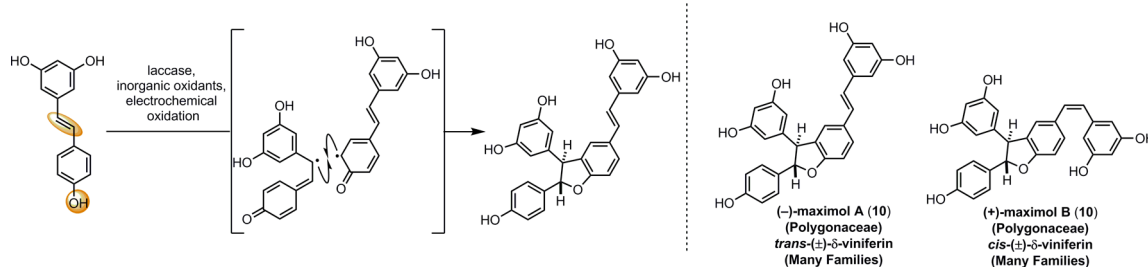
stereoisomers of **22** (path D), provide indirect evidence for the existence of both the *meso-* and C_2-symmetric diastereomers. Amurensin A (**59**)[100] is the product of trapping of water onto the linear mono-*para*-quinone methide **58**, a tautomer of **22** (Scheme 7, path E).

So far, quadrangularin A (**17**) has only been isolated from Vitaceae as the (−) optical isomer, but the oxidized derivative caraphenol C (**60**),[43] isolated from Fabaceae, appears to derive from (+)-quadrangularin A, or intermediate **52**, suggesting that other plant families are capable of biosynthesizing the opposite enantiomer of **17**. However, this has yet to be substantiated (Scheme 8). Quadrangularin A (**17**) can undergo an alkene isomerization, generating its *Z*-isomer parthenocissin A (**61**).[101] An oxidative cyclization reaction, perhaps through a 6π electrocyclic ring closure followed by dehydrogenation, yields laetevirenol A (**62**).[102] It is unknown whether the interconversion of **17** to **61** and **62** is mediated by enzymes or if they are simply the result of background isomerization/oxidation. For a related discussion on the proposed biosynthesis of these oxidized 8−8′ dimers, see section 5.5.1.

In 2000, Cichewicz and Kouzi demonstrated that the grape pathogen *B. cinerea* could exogenously produce resveratrol dimers when supplemented with resveratrol in its fermentation broth.[38] They isolated three natural products: two 8−8′ dimers, restrytisols A/B (**56/63**) and the dihydronaphthylene restrytisol C (**64**), which were isolated as optically active compounds. In addition, they isolated two other 8−8′ resveratrol dimers (Scheme 9), pallidol (**18**) and leachinols F/G (**53**), indicating that *B. cinerea* is capable of producing an array of 8−8′ dimers and that some fraction of these dimers can be formed through uncontrolled oxidation. The authors suggest that fungi not only induce the expression of resveratrol in plants, but may also produce oligomers by fungal laccase catalysis. They further speculate that fungi utilize this as a mechanism for detoxifying resveratrol and other chemical defenses of the plant and that the presence of certain resveratrol oligomers in plant extracts can be attributed in part to nonplant based pathogens.

4.4. Biosynthesis of 3−8′ Dimers

The 3−8′ dimers (Scheme 10) are one of the least structurally diverse group of resveratrol natural products. The most

Scheme 11. Biosynthesis of Higher-Order Oligomers Is Convergent in Nature and Employs Both Radical and Polar Mechanisms
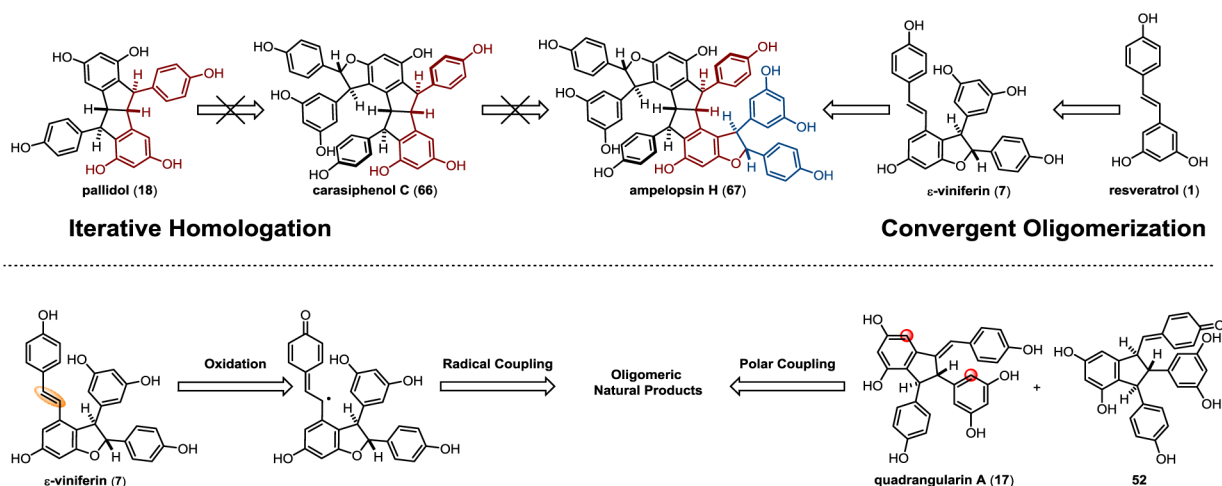
abundant compound in this class, δ-viniferin (**10**),[103] also commonly called the "resveratrol-*trans*-dehydrodimer", is found in many families of resveratrol producing plants. δ-Viniferin was inadvertently synthesized by Langcake and Pryce during their seminal isolation studies on grape phytoalexin compounds when they attempted to produce ε-viniferin (**7**) from resveratrol using horseradish peroxidase (HRP) and H_2O_2.[36] A subsequent report by Jeandet[103] was the first to identify δ-viniferin as a major constituent of resveratrol oxidation by fungal laccases. These findings, along with a report by Cichewicz and co-workers,[38] advanced the notion that the resveratrol dimers are not exclusively synthesized endogenously by the plant, but can be generated extracellularly by other organisms. The 3–8′ dimers formed in this manner are typically isolated as racemates, since laccases/peroxidases, which differ by the metal oxidant in their active sites (Cu[104] vs Fe[105]), are fairly promiscuous enzymes capable of oxidizing a wide range of substrates. When resveratrol is oxidized by inorganic oxidants, δ-viniferin is typically the major product, indicating an inherent regioisomeric preference during an uncontrolled dimerization reaction. The biomimetic oxidation of resveratrol has since been studied by numerous groups following these seminal contributions.[106–111] Because this compound predominately forms during the uncontrolled oxidation of resveratrol, δ-viniferin is often referred to as a "non-natural" resveratrol dimer. Despite this classification, **10** has been isolated as an optically active constituent of *Rheum maximowiczii* (Polygonaceae) called maximol A along with its alkene isomer **65** (Scheme 10).[112] Interestingly, the optical rotation of maximol A nearly matches the $[\alpha]_D$ of 99.5% enantiopure δ-viniferin obtained by chiral separation of a racemic sample.[113]

5. BIOSYNTHESIS OF HIGHER-ORDER RESVERATROL OLIGOMERS

The chemical defense against pathogenic invasion is a continuous evolutionary arms race between the invasive species and the host plant. In this scenario, the survival of the plant relies partly on its ability to rapidly generate novel defense compounds in response to pathogenesis. The regioisomeric dimerization modes described in the preceding sections constitute the foundation for the biosynthesis of a diverse collection of higher-order resveratrol oligomers. Indeed,

biosynthesis of the higher-order natural products proceeds in a similar fashion to the resveratrol dimers, and several structural motifs found in the resveratrol dimers are conserved in the more complex oligomeric compounds. The resveratrol dimers are almost universally generated by an oxidative radical coupling. In contrast, the higher-order oligomers can be the product of *either* an oxidative coupling to resveratrol/ε-viniferin *or* an intermolecular Friedel–Crafts reaction (Scheme 11). One stringent structural requirement for the oxidative oligomerization is the presence of the 4-hydroxy stilbene moiety found in both resveratrol and **7**. At a glance, the biosynthesis of the resveratrol oligomers would appear to be the product of an iterative oligomerization sequence, wherein a resveratrol dimer such as pallidol (**18**) would undergo successive homologation reactions, in a fashion similar to polyketide natural products (Scheme 11).[114] Instead, it would appear that the majority of oligomerization reactions are convergent processes, wherein tetramers are the product of a dimerization of dimers, pentamers a crossed dimerization of a trimer and a dimer, and so forth.

As is the case with other resveratrol based natural products, several stereoisomers of the same carbon skeleton have been isolated. This has led to speculation on whether the oligomerization occurs in a random or controlled fashion. However, there is little known about the biogenic pathways responsible for the formation of these natural products. In the following sections, we will depict the dimerization and cyclization reactions that are likely involved in the biosynthesis of these oligomers. The molecules chosen are representative of as many of the carbon skeletons found within this class of natural products.

5.1. Biosynthesis of 8–10′ Trimers

The 8–10′ trimers have been isolated from most plant families that biosynthesize resveratrol oligomers such as Vitaceae, Dipterocarpaceae, Cyperaceae, etc. In 2012, Pan et al. established the biosynthetic relationship between ε-viniferin (**7**), gnetin H (**68**),[53] and miyabenol C (**69**)[115] via a HRP-mediated cross trimerization of **7** and resveratrol (**1**) to afford **68** and **69** in 3.3% and 3.4% yields, respectively (Scheme 12).[52] The gnetin H isolated from that reaction was subjected to a Brønsted-acid-mediated isomerization, yielding ampelopsin G (**70**) (4.5%), amurensin G (**71**) (8.4%), wilsonol B (**72**)

Scheme 12. Pan's Biosynthetic Reactions on the Formation of the 10−8′ Trimers
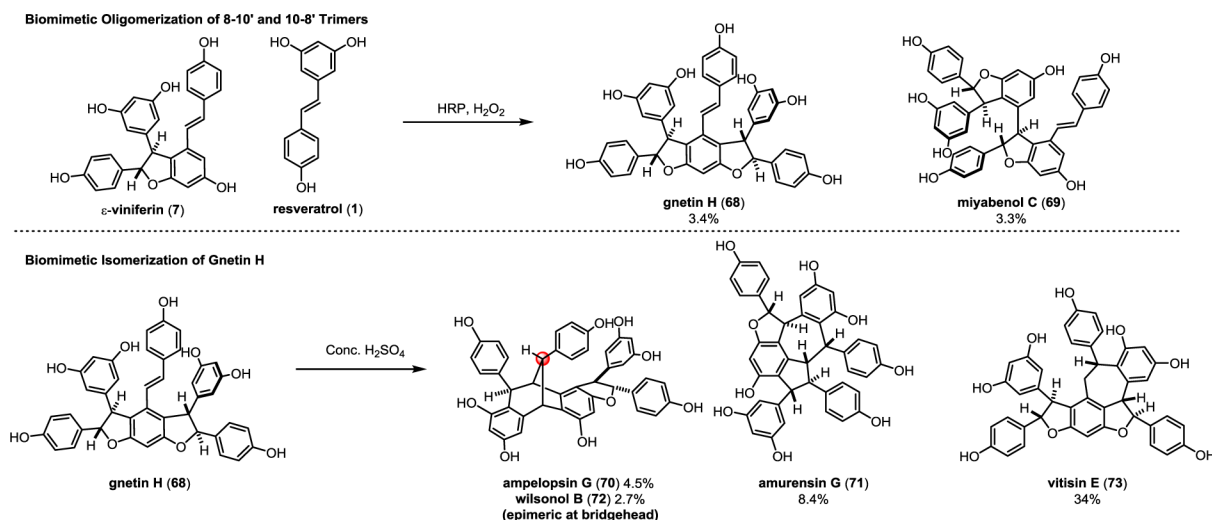
(2.7%), and vitisin E (**73**) (34%), suggesting a common biosynthetic origin. These studies were also able to confirm the absolute configuration for compounds **68**−**73**.

The 8−10′ trimers have two distinct modes of oligomerization: (1) the 10 position of ε-viniferin (**7**) can cross couple with the 8′ position of resveratrol, to afford the gnetin H (**68**) regioisomer (Scheme 12, path A) or (2) the 8 position ε-viniferin can cross couple with the 10′ position of resveratrol to give the miyabenol C (**69**) scaffold (path G).

As the apparent biosynthetic precursor for many of the resveratrol oligomers, gnetin H (**68**) can conceivably be interconverted into other oligomers through a series of acid-mediated Friedel−Crafts reactions. Protonation/fragmentation of the 11b dihydrobenzofuran (Scheme 13 for numbering scheme) reconstitutes the highly reactive quinone methide **74** (Scheme 13, path B). In a fashion analogous to the biosynthesis of ampelopsins D/F (**25**/**16**), a vinylogous Friedel−Crafts (5-exo-trig) cyclization of **74** would generate para-quinone methide **75** through the formation of the C_{8b}−C_{7a} bond (path D). This intermediate is presumably the precursor for two isomeric natural product scaffolds. A 7-exo-trig cyclization (C_{10c}−C_{7b}) yields 5,7-fused indane skeleton found in the natural products vaticanol A (**76**) (Scheme 13, path E),[116] amurensin G (**71**),[95] and suffruticosol B (**77**),[117] among others (see Scheme 14). This ring system is prevalent among resveratrol trimers found in several families of oligostilbene producing plants.

Alternatively, intermediate **75** can be nucleophilically trapped by a transannular (6-exo-trig) Friedel−Crafts cyclization (C_{10a}−C_{7b}, path F), generating the [3.2.1]bicyclooctane cores of ampelopsin G (**70**),[69] and wilsonol B (**72**).[52] Finally, the direct protonation of the gnetin H (**68**) stilbene could promote cyclization to the natural product vitisin E (**73**),[118] via intermediate **78**.

Although the corresponding oxidation/cyclization reactions have not been reported for miyabenol C (**69**), its relationship between other natural products can be deduced in a similar manner as described above. Acidification of **69** and fragmentation of its dihydrobenzofuran would regenerate para-quinone methide **79** (Scheme 12, path H), which can undergo an intramolecular vinylogous Friedel−Crafts (5-exo-trig) cyclization to form the C_{8a}−C_{7b} bond (path K). The resultant quinone methide **80** can undergo two transannular

cyclization reactions: an intramolecular 6-exo-trig cyclization (C_{14b}−C_{7a}, path L) yields the carbon skeleton of carasiphenol B (**81**)[119] while an alternative 9-exo-trig cyclization (C_{10c}−C_{7a}, path M) yields the natural product suffruticosol C (**82**).[117] Finally, the direct oxidation of miyabenol C (**69**) can initiate an intramolecular formal [3 + 2] cycloaddition to form a 9-membered ring, yielding the cyclic trimer α-viniferin (**6**) (path I).

5.2. Biosynthesis of Oxidized 8−10′/10−8′ Trimers

Several oxidized resveratrol trimers have been isolated from plants in the Dipterocarpaceae family. In 2005, Ito and co-workers isolated a series of resveratrol trimers including the cotylelophenols A (**83**), B (**84**), and C (**85**),[120] which are oxidized derivatives of pauciflorol A (**86**)[75] (Scheme 14). This series of natural products provides an exquisite snapshot of the biogenic relationship between these compounds that is likely relevant to the previously discussed oxidized dibenzocycloheptane dimers in section 4.2. Cotylelophenol C (**85**) is formed from pauciflorol A (**86**) in a net 4 electron oxidation, and is in the same oxidation level as cotylelophenol B (**84**). These natural products are likely interconverted via a Brønsted-acid-mediated rearrangement. Cotylelophenol B is the logical biosynthetic precursor to cotylelophenol A (**83**) via a stereoselective 1,2 aryl shift, mirroring the relationship between vaticahainol B (**46**) and A (**47**) (Scheme 6). In 2014, Ge and Tan reported the isolation and structural elucidation of dipterocarpol C (**87**),[121] a remarkable oxidized derivative of vaticanol E[122] that is presumably formed from **84** upon hydration of the quinone methide and subsequent oxidative cleavage of the vicinal diol. The presence of the hydrolytically labile phenol ester is the first direct evidence for the oxidative cleavage of the dihydrobenzofuran moiety in the resveratrol oligomers. The analogous structure for the related natural products hemsleyanol E (**49**)/diptoindonesin D (**50**) has not yet been reported (Scheme 6).

A similar set of oxidations have been observed for the cyclic 8−10′ trimers, wherein dearomatization of (+)-α-viniferin (**6**)[123] yields grandiphenol C (**88**)[124] which can interconvert to caraphenol A (**89**)[43] by a dehydration reaction. An oxidation/rearrangement of benzofuran **89** affords grandiphenol D (**90**),[124] while oxidative cleavage converts **89** into hopeachinol B (**91**).[125]

Scheme 13. Divergent Biosynthesis of Regioisomeric 10–8′ and 8–10′ Trimers
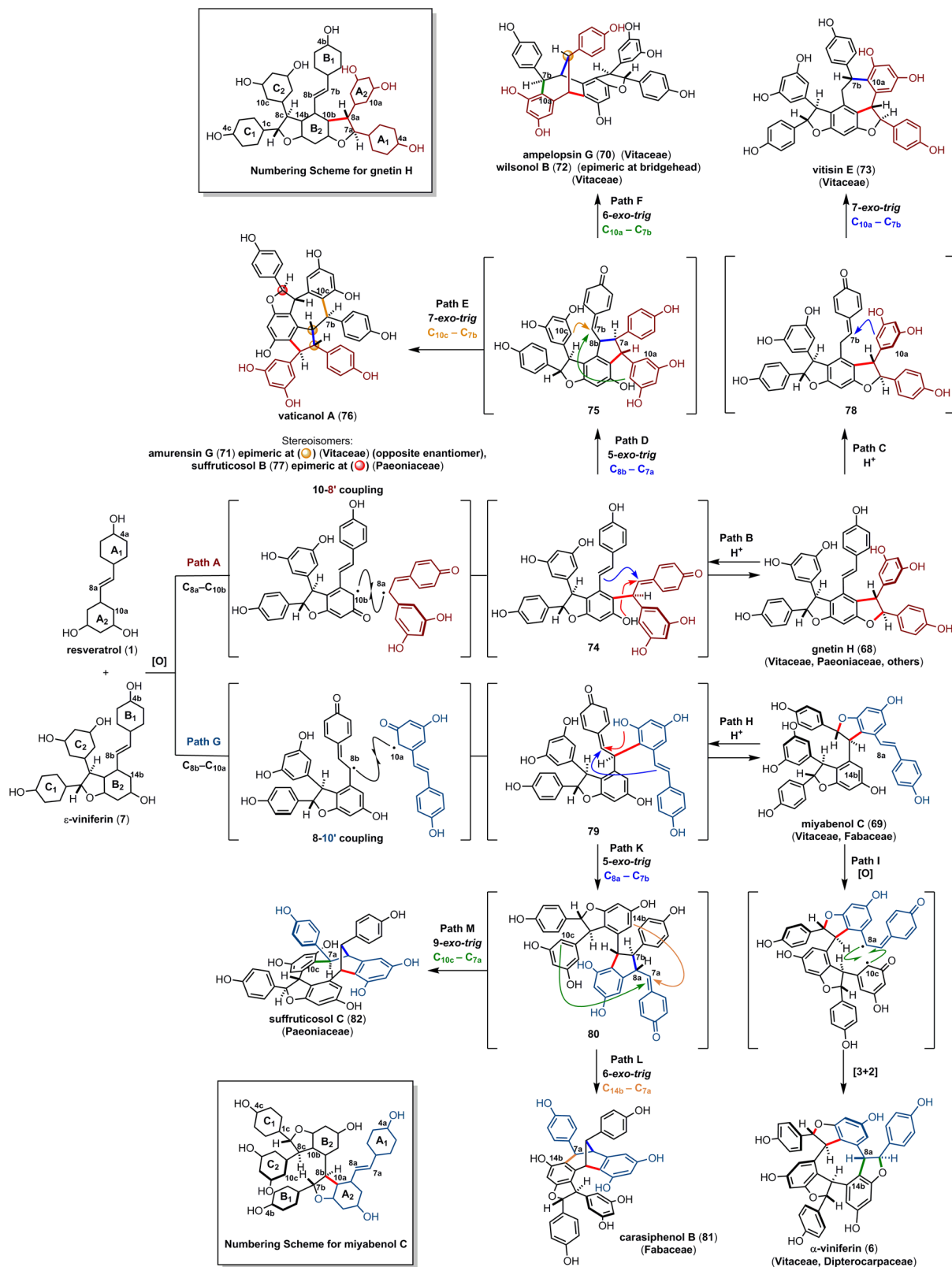
Taken together, these natural products provide a compelling unified mechanism for the biogenesis of the oxidized Dipterocarpaceous resveratrol oligomers. The biosynthetic machinery responsible for the oxidation of **86**, **6**, and the dimers **34** and **35** (section 4.2, Scheme 6) appears to be highly conserved, given the structural homology of several of the isolated natural products. The isolation of **87** provides a clear mechanistic rationale for the biogenesis of the resveratrol dimers hemsleyanol E (**49**) and diptoindonesin D (**50**). Very little is known about the enzymes that are responsible for this

Scheme 14. Oxidized 8−10′ Trimers from Dipterocarpaceae

pauciflorol A (86)
vaticanol E (epimeric at ○)
(Dipterocarpaceae)

cotylelophenol C (85)
(Dipterocarpaceae)

cotylelophenol B (84)
(Dipterocarpaceae)

cotylelophenol A (83)
(Dipterocarpaceae)

dipterocarpol C (87)
(Dipterocarpaceae)
Derived from vaticanol E stereoisomer
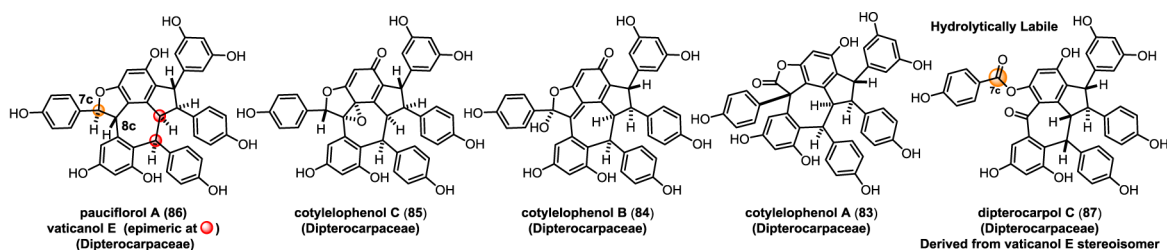
Oxidized Pauciflorol A Derived Natural Products

(+)-α-viniferin (6)
(Dipterocarpaceae, Fabaceae)

grandiphenol C (88)
(Dipterocarpaceae)

caraphenol A (89)
(Dipterocarpaceae and Fabaceae)

grandiphenol D (90)
(Dipterocarpaceae)

hopeachinol B (91)
(Dipterocarpaceae)
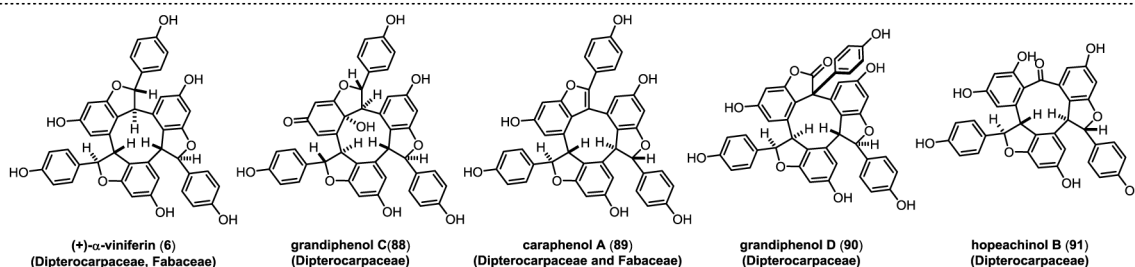
Oxidized α-Viniferin Derived Natural Products

Scheme 15. Proposed Biosynthesis of the 8−10′ Tetramers
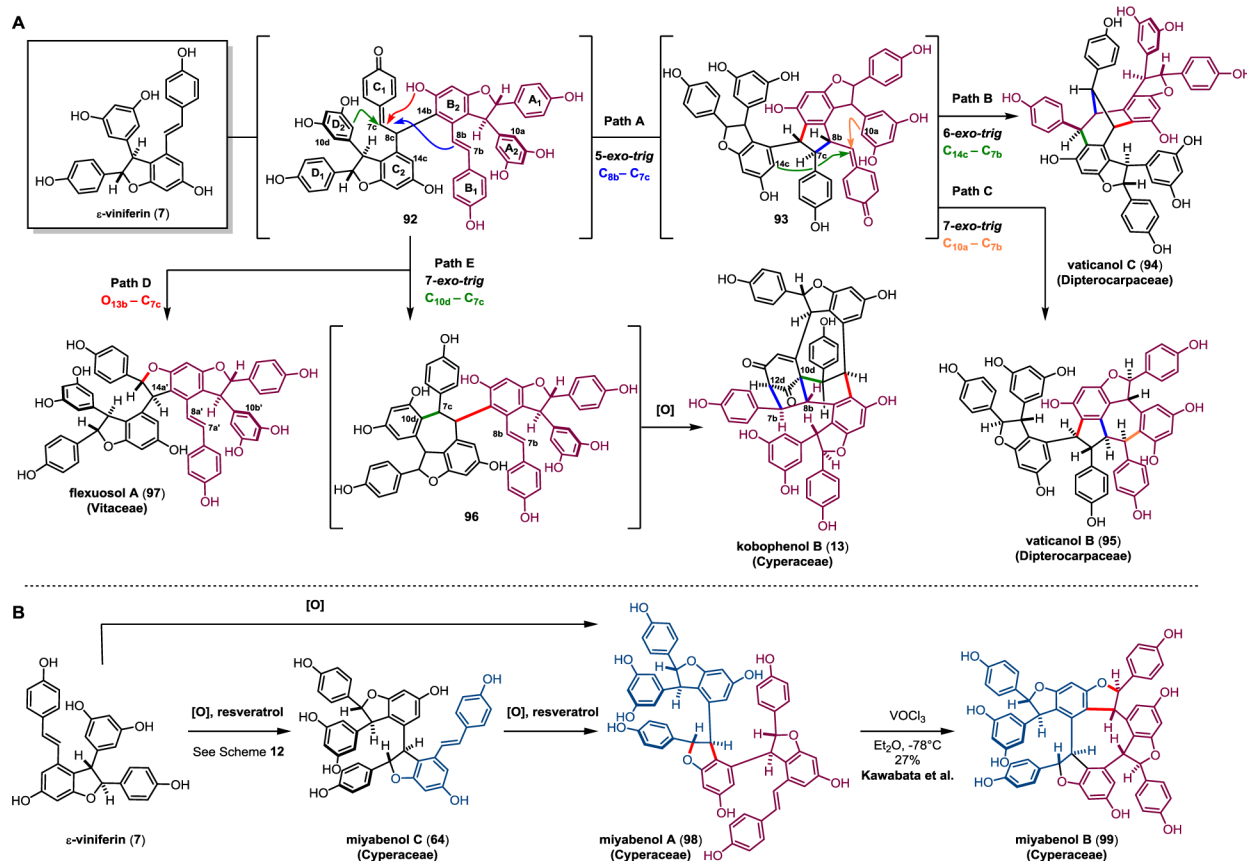
oxidation chemistry which so far has only been identified in Dipterocarpaceae. The resveratrol dimer viniferifuran (amurensin H) (**51**) (Section 4.2, Scheme 6) and caraphenol A (**89**) (Scheme 14) have been isolated from Vitaceae and Fabaceae, but it is not known at this time if these are synthesized in a similar fashion.

5.3. Biosynthesis of 8−10′ Tetramers

In contrast to the regioisomeric crossed 8−10′/10−8′ trimerization modes of **7** with resveratrol (Scheme 12), the 8−10′/10−8′ *homocoupling* modes of **7** are degenerate and therefore form *para*-quinone methide **92** as a single regioisomer (Scheme 15, path A). As a result, there is a narrower product distribution available from the divergent reactivity of hypothetical intermediate **92**. A vinylogous Friedel−Crafts (5-*exo*-

Scheme 16. Proposed Biosynthesis of the 8−8′ Trimers (A) and Tetramers (B)
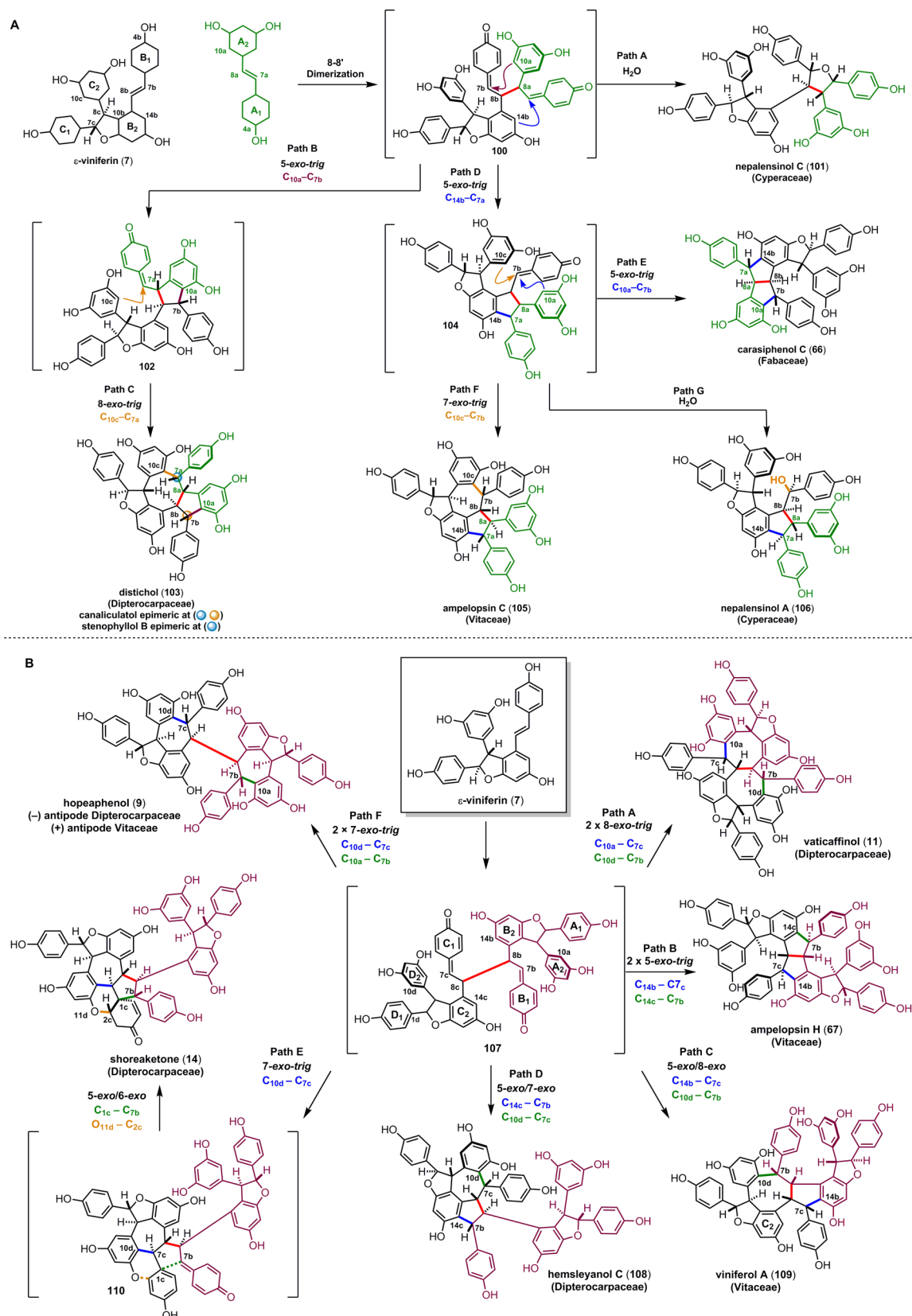
trig) cyclization forms the C_{8b}−C_{7c} bond of quinone methide **93** (path A). This intermediate, by analogy to ampelopsins F/G (**16/70**) (Schemes 4 and 12, respectively), can undergo a transannular *6-exo-trig* cyclization resulting in the tetramer

vaticanol C (**94**) (C_{14c}−C_{7b}, path B) or a *7-exo-trig* affording the vaticanol B (**95**)[116] skeleton (C_{10a}−C_{7b}, path C). An intramolecular oxa-conjugate addition of **92** yields the natural product flexuosol A (**97**) (path D);[126] however, this natural

Scheme 17. Studies of the Biosynthesis of 8−8′ Trimers (A) and Tetramers (B)
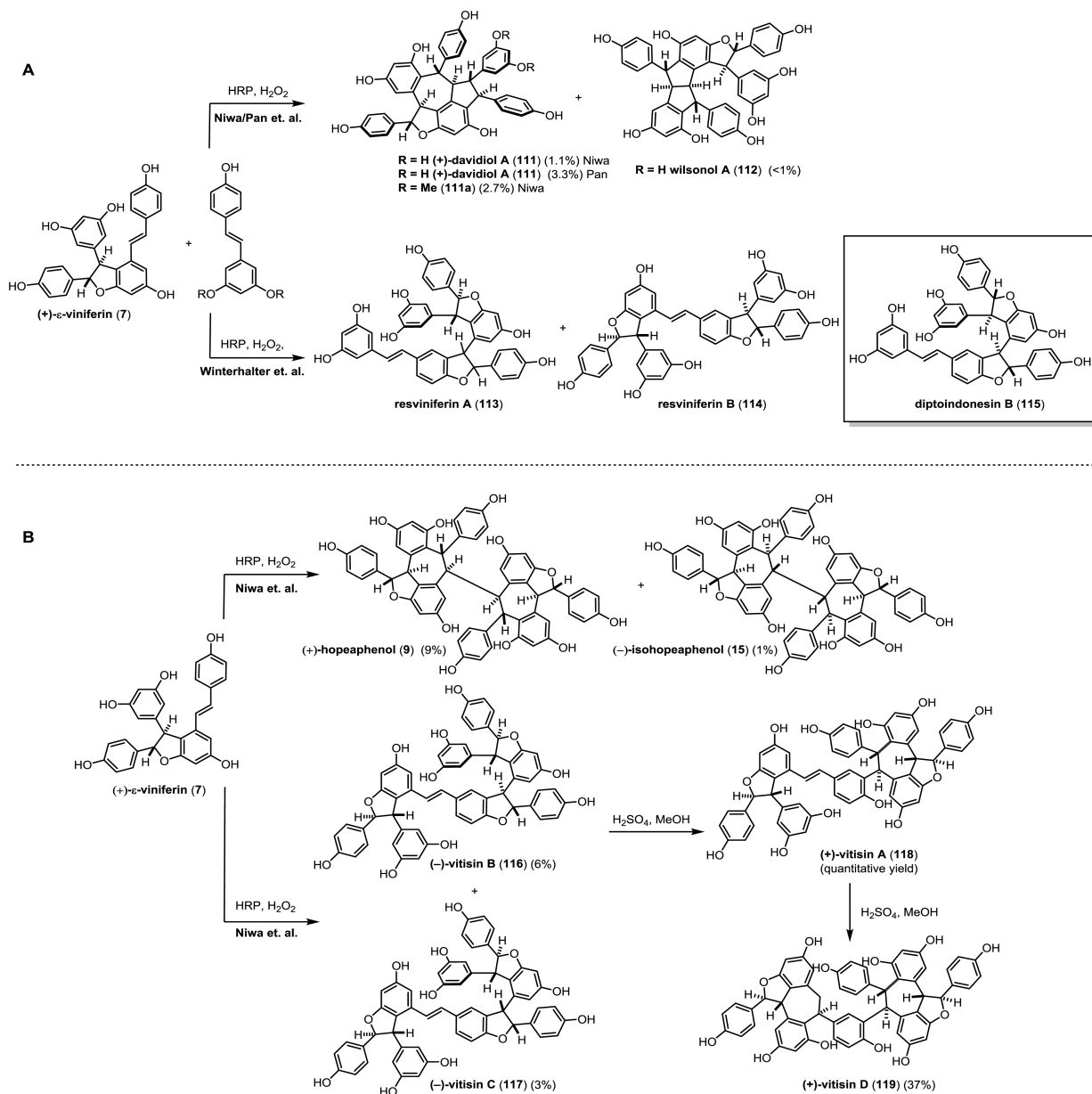
product maps onto the *meso* stereoisomer of gnetin H (**68**), ampelopsin E.[76] Finally, a 7-*exo* cyclization of quinone methide **92** (C$_{10d}$−C$_{7c}$, path E) yields the hypothetical intermediate **96**, which upon oxidation can undergo a formal dearomative [3 + 2] annulation, forming the bicyclo-[3.2.1]-octen-dione core of kobophenol B (**13**) (see section 3.4 for isolation).

The miyabenol oligomers are an unusual set of regioisomeric 8−10′ oligomers that possess dihydrobenzofuran motifs that alternate in absolute configuration (Scheme 15, path B). The biosynthesis of miyabenol A (**98**)[115,127] is somewhat ambiguous and can possibly operate through iterative homologations of resveratrol, analogous to its trimeric counterpart miyabenol C (**69**) (section 5.1). The direct dimerization of two homochiral molecules (−)-ε-viniferin can also account for the alternating configurations found in the dihydrobenzofurans of **98**. Miyabenol A (**98**) can undergo an additional oxidative formal [3 + 2], yielding the cyclic tetramer miyabenol B (**99**), which shares structural homology to the trimer α-viniferin (**6**).

Impressively, Kawabata and co-workers were able to successfully interconvert miyabenol A (**98**) to miyabenol B (**99**) using vanadium oxytrichloride in 27% yield, representing one of the earliest applications of this strategy to validate the biogenic relationship between related resveratrol oligomers.[127]

5.4. Biosynthesis of 8−8′ Trimers and Tetramers

5.4.1. Biosynthesis of 8−8′ Trimers.
Although the 8−8′ trimers are biosynthesized through a crossed coupling of **7** and **1**, there are fewer possible cyclization and dimerization reaction pathways as compared to their 8−10′ counterparts, since there is only one intermediate generated during the radical coupling. Linear bis-*para*-quinone methide **100** has two electrophilic sites, allowing it to undergo dissymmetric cyclization reactions (Scheme 16). The existence of this intermediate is strongly supported by the isolation of the tetraarylfuran dimer, nepalensinol C (**101**), which is the product of the double addition of water to **100** (path A).[128] Intermediate **100** can undergo two regioisomeric 5-*exo-trig* cyclization reactions, that

are product determining. Upon cyclization to form the C_{10a}–C_{7b} bond of **102** (path B), a subsequent Friedel–Crafts (8-*exo-trig*) cyclization produces dibenzocyclooctane natural products distichol (**103**),[129] or its stereoisomers canaliculatol,[130] and stenophyllol B (path C).[131] Alternatively, formation of the C_{14b}–C_{7a} bond (path D) produces the highly versatile intermediate **104**. A second 5-*exo-trig* arylation of **104** (C_{10a}–C_{7b}, path E) affords the pallidol (**18**) derivative carasiphenol C (**66**),[132] whereas the intramolecular 7-*exo-trig* cyclization of **104** forms ampelopsin C (**105**)[82] (path F), a member of a larger group of stereoisomeric 5,7-fused indane trimers. Finally, the nucleophilic trapping of **104** with water (path G) yields nepalensinol A (**106**)[128] and is indirect evidence for the existence of **104** itself.

5.4.2. Biosynthesis of 8–8′ Tetramers. Like the 8–8′ trimers, the 8–8′ tetramers are widely distributed between the various families of oligomer producing plants. They are the products of the oxidative dimerization of two molecules of ε-viniferin (**7**), with **107** as the presumed biosynthetic intermediate for a diverse series of resveratrol tetramers (Scheme 16, path B). This bis-*para*-quinone methide can undergo either symmetric cyclization modes, delivering products such as hopeaphenol (**9**, path F),[34] vaticaffinol (**11**, path A),[60] and ampelopsin H (**67**, path B),[76] or dissymmetric cyclizations to form viniferol A (**109**, path C)[133] and hemsleyanol C (**108**, path D).[93] It is reasonable to infer that these cyclizations occur through the same mechanisms as the trimers and dimers. The tetramer shoreaketone (**14**) (see section 3.5) features a highly functionalized spirocyclic cyclopentane that derives from quinone methide **110** through a dearomative Friedel–Crafts cyclization between carbons C_{1c} and C_{7b}. An oxa-conjugate addition onto the presumed spirocyclohexadienone (not pictured) forms the O_{11d}–C_{2c} bond to generate the spirocyclohexene found in shoreaketone. Ito and co-workers were able to demonstrate a Brønsted-acid-mediated rearrangement of shoreaketone (**14**) to (+)-iso-hopeaphenol methyl ether (**15a**) in quantitative yield (see section 3.5), establishing its absolute configuration and its identity as an 8–8′ tetramer.[65]

5.4.3. Empirical Support for Proposed Biosyntheses of 8–8′ Trimers and Tetramers. In order to investigate the biosynthesis of the resveratrol oligomers, Niwa[51] and Pan[52] have studied the oxidative cross-coupling of (+)-ε-viniferin (**7**) and resveratrol using horseradish peroxidase (HRP) and H_2O_2 (Scheme 17, path A). Although these reactions were non-selective, they were successful in procuring isolable quantities of davidiol A (**111**)[134] from the reaction in 1–3% overall yield. Niwa and co-workers were also able to cross-dimerize **7** with pterostilbene (**3**) to get **111a**, a methylated analogue of davidiol A in 2.7% yield. The Pan group was also able to isolate a very small quantity (<1%) of the natural product wilsonol A (**112**),[52] a diastereomer of carasiphenol C (**66**) that they had isolated from *V. wilsonae*, which was not observed previously. Since the absolute configuration of (+)-ε-viniferin (**7**) was known, both groups were able to deduce the relative and absolute configurations of davidiol A (**111**) and wilsonol A (**112**) using these biomimetic reactions.

Winterhalter and co-workers corroborated these findings during their investigations on the large scale HRP/H_2O_2 oxidation reaction of resveratrol and ε-viniferin.[109] In this complex mixture of products, they isolated and characterized two non-natural 3–8′ trimers named resviniferins A (**113**) and B (**114**) (Scheme 17, path A). Although they were unable to

assign the relative configurations of these compounds, **113** has the same gross structure as the natural product diptoindonesin B (**115**) and is likely (bio)synthesized in similar fashion.[135]

The groups of Niwa[136] and Pan[52] have also performed biomimetic peroxidase mediated homocoupling of (+)-ε-viniferin (**7**) to study the biogenesis of the resveratrol tetramers. This oxidation unselectively produces an array of resveratrol oligomers. From this mixture, they were able to isolate the 8–8′ tetramers (+)-hopeaphenol (**9**, 9%) and (−)-isohopeaphenol (**15**, 1%), both of which matched the spectral data of the authentic samples (Scheme 17, path B). However, in a fashion analogous to the conversion of resveratrol to δ-viniferin (**10**), ε-viniferin (**7**) can also dimerize in a 3–8′ mode to generate tetramers such as vitisin B (**116**, 6%) and C (**117**, 3%). They also found that vitisin B (**116**)[137] could be quantitatively converted to vitisin A (**118**)[138] by acidic cyclization in MeOH. Vitisin A (**118**) was further reacted in the same conditions to produce vitisin D (**119**) in 37% yield. Since the absolute configuration of **7** was known (isolated from *Vitis coignetiae*), Niwa and co-workers were able to infer the absolute configurations of (+)-vitisin A (**118**), (+)-vitisin B (**116**), (−)-vitisin C (**117**),[139] (+)-vitisin D (**119**),[118] (+)-hope-aphenol (**9**), (−)-isohopeaphenol (**15**), and (−)-viniferal[139] by analogy.[52,136]

5.5. Biosynthesis of 3–8′ Trimers and Tetramers

The 3–8′ oligomers are a smaller class of resveratrol natural products possessing the same *trans*-dihydrobenzofuran found in δ-viniferin (**10**) that were initially isolated from Vitaceous plants. It is unknown whether or not these natural products are biosynthesized endogenously, like δ-viniferin (**10**), or if they are the result of uncontrolled oxidation. Unlike **10**, the 3–8′ oligomers are typically isolated as optically active compounds since they derive from chiral starting materials. The trimer parthenocissin B (**120**), for instance, appears to be the product of oxidative cross coupling of parthenocissin A (**61**)[101] and resveratrol (**1**), while the tetramer vitisin B (**116**) is the 3–8′ dimer of two molecules of ε-viniferin (**7**) (Scheme 18). Further complicating the biogenic origins of these natural products is the fact that, for several 3–8′ oligomers, both dihydrobenzofuran diastereoisomers can be found in the plant extract, suggesting that these radical couplings are the result of nonspecific oxidation. Unlike the 8–8′ or the 8–10′ trimers and tetramers, which are primarily the result of ε-viniferin or resveratrol oligomerization, a surprising variety of substrates appear to be competent coupling partners for the 3–8′ oligomerization (Scheme 18). These include indane stilbenes quadrangularin A (**17**)/parthenocissin A (**61**) as plausible precursors for laetevirenols A–F,[102] linear dimeric stilbene amurensin A (**59**) for wenchowenol (**121**),[140] or ε-viniferin (**7**) for vitisins A (**118**), B (**116**), and C (**117**) (vide infra).[137–139]

5.5.1. Unified Biosynthesis of the Laetevirenols. In 2008, the Pan group isolated an unusual series of dihydrobenzofuran-containing indane natural products called the laetevirenols[102] which are parthenocissin A/quadrangularin A (**61**/**17**) derivatives that contain an unusual 3–8′ dihydrobenzofuran motif. Through a series of biomimetic oxidation reactions, Pan and co-workers were able to establish the biogenic relationship between quadrangularin A (**17**), the parthenocissins, and the laetevirenols (Scheme 19). Irradiation of parthenocissin A (**61**) with UV light effected its conversion into (−)-quadrangularin A (**17**) in 30% yield. A smaller fraction of the starting material was converted into the unusual

Scheme 18. Proposed Biogenesis of the 3–8′ Trimers and Tetramers

parthenocissin A (61)
(Vitaceae)

parthenocissin B (120)
(Vitaceae)

vitisin B (113)
(Vitaceae)

ε-viniferin (7)

[O]

amurensin A (59)
(Vitaceae)

wenchowenol (121)
(Vitaceae)

vitisin A (115)
(Vitaceae)
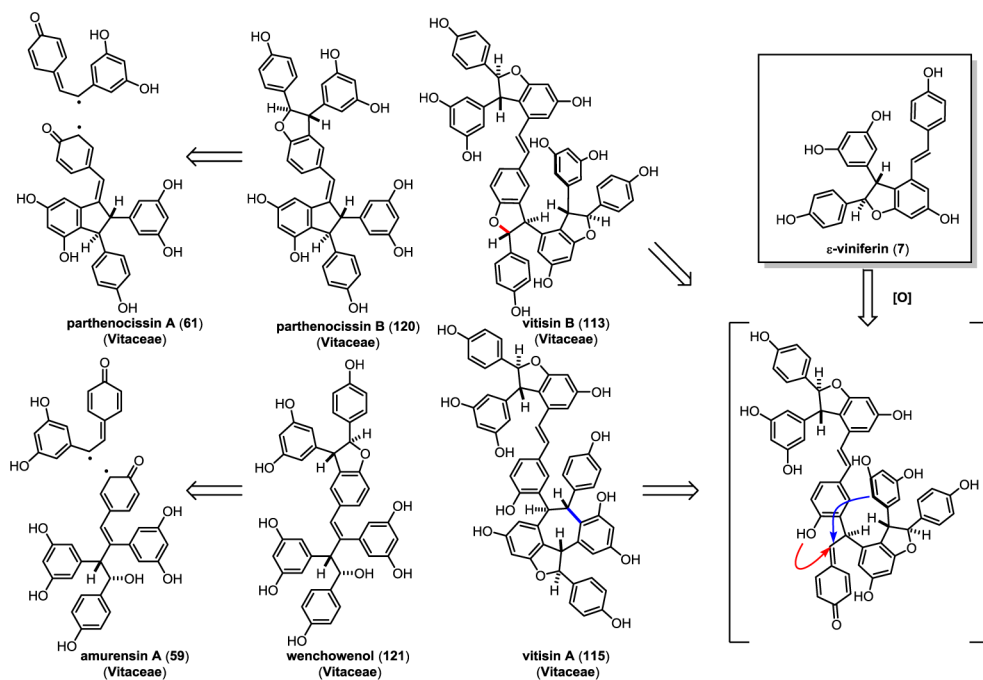
Scheme 19. Pan's Biogenic Studies of the Parthenocissins and Laetevirenols

(+)-laetevirenol C (123)

Resveratrol, HRP/H₂O₂
14%

(−)-quadrangularin A (17)

Resveratrol, HRP/H₂O₂
14% yield

(−)-laetevirenol D (122)

(+)-laetevirenol B (125)

hv
Yield not reported

hv
30% yield

(+)-laetevirenol A (62)

hv
24% yield

(+)-laetevirenol E (124)

Resveratrol, HRP/H₂O₂
15% yield

(−)-parthenocissin A (61)

hv, O₂
6π-electrocyclization
9% yield

hv, O₂
6π-electrocyclization
21% yield

Resveratrol, HRP/H₂O₂
15% yield

(−)-parthenocissin B (120)

Resveratrol, [O]

(−)-laetevirenol F (126)

(−)-laetevirenol G (127)

Scheme 20. Oligomerization by Intermolecular Trapping of Quinone Methide Intermediates
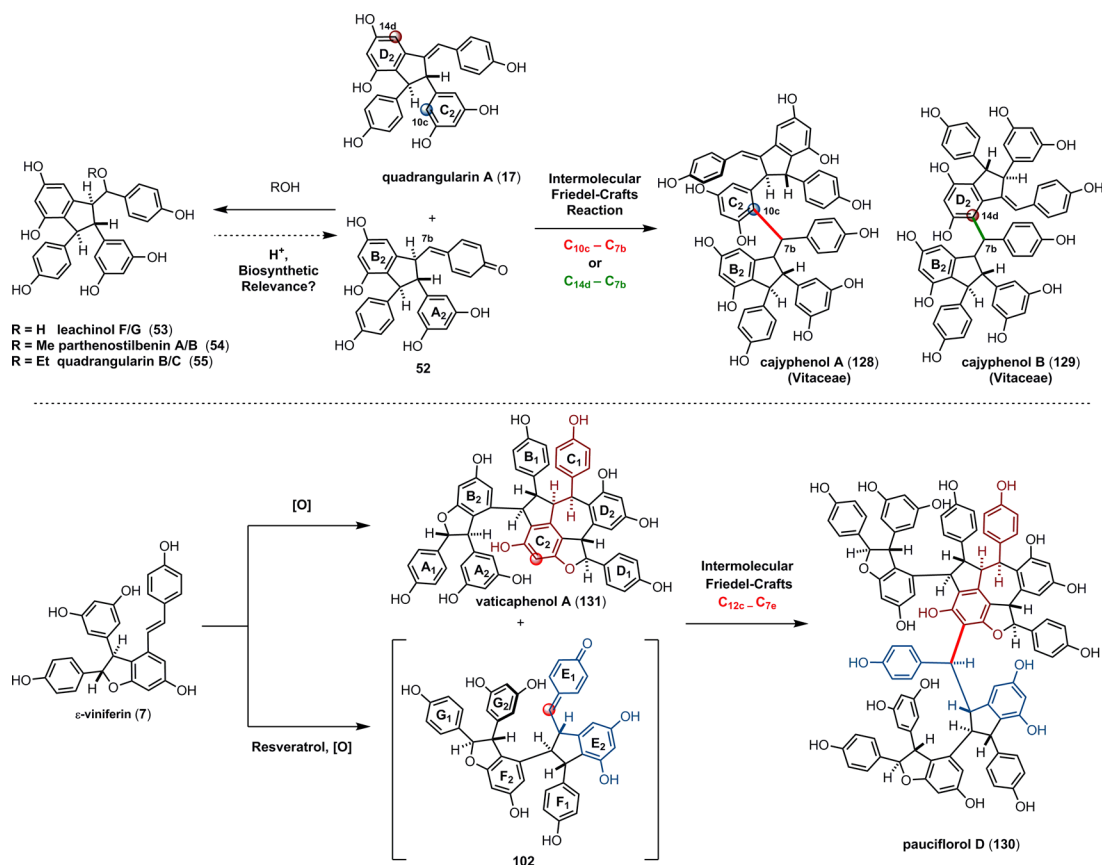
dihydroacephenanthrylene natural product laetevirenol A (**62**) through a UV-light mediated oxidative 6π-electrocyclization in 10% yield. An HRP-mediated, intermolecular oxidative coupling of (−)-quadrangularin A (**17**) and resveratrol provided a 1:1 mixture of laetevirenol D (**122**) and laetevirenol C (**123**), supporting the hypothesis that quadrangularin A (**17**) is a precursor for these natural products. A similar set of experiments demonstrated an analogous biogenic relationship between (−)-parthenocissin A (**61**), (−)-parthenocissin B (**120**), and laetevirenol E (**124**), which were also isolated as a 1:1 mixture of diastereomers.

Although these oxidative coupling reactions do not occur with any diastereoselectivity, it is important to mention that parthenocissin B (**120**) was isolated in 5-fold greater abundance than **122** and **124** and 500-fold greater abundance than **123** from the plant material. Irradiation of parthenocissin B (**120**) with UVA afforded laetevirenol D (**122**) in 24% yield (confirming their structural relationship as alkene isomers), and phenanthrene derivative laetevirenol B (**125**) in 21% yield. Analogous isomerization of laetevirenol E (**124**) to laetevirenol C (**123**) was evident by HPLC. The absolute configurations of these compounds was established by comparison of its CD spectra with the spectra of (−)-ampelopsin D (**25**), whose absolute configuration is known.[50]

The intermolecular oxidative cross coupling of quadrangularin A (**17**), a trisubstituted stilbene, and ε-viniferin (**7**) was unprecedented; previous biomimetic dimerization reactions were homo/heterocouplings of resveratrol (**1**) or ε-viniferin (**7**), which are disubstituted stilbenes. The next year, the same group disclosed the isolation of two related resveratrol tetramers, laetevirenols F/G (**126**/**127**). Due to the large

distance between the 7c/8c protons and the indane 7a/8a protons, the relative configuration of each of these natural products is currently unknown. They proposed a tentative structure for **126** and **127**, which they inferred by comparison of their HPLC behavior to that of the structurally related trimers **120** and **124**, though they stress that this is speculative and the true configuration of the 7c/8c stereogenic centers may be reversed. The authors postulate that the biogenesis of these tetramers is the result of an iterative oxidative homologation of resveratrol onto **120**, since it is the most abundant trimer extracted from the plant, though it is also possible that **126/127** are the result of a more convergent heterocoupling of parthenocissin A (**61**) and δ-viniferin (**10**).

5.6. Oligomerization via Polar Mechanisms

The impressive chemical diversity of the resveratrol natural products is the result of the multiple regioisomeric radical coupling and Friedel−Crafts cyclization pathways available upon the oxidation of resveratrol. For a majority of the resveratrol dimers, trimers, and tetramers, oligomerization occurs through an *intermolecular* radical coupling, followed by an *intramolecular* Friedel−Crafts cyclization. Typically, an intramolecular cyclization or tautomerization of an intermediate *para*-quinone methide can outcompete most intermolecular processes. However, intermolecular functionalization can in fact occur. Several resveratrol dimers such as parthenostilbenin A/B (**54**) and quadrangularin B/C (**55**) (Scheme 7) are the products of solvolysis of electrophilic intermediates. It is perhaps unsurprising to find that the electron rich arenes of the resveratrol natural products themselves can also react with the quinone methides generated during the dimerization of

Scheme 21. Biogenic Hypothesis for the Formation of Stemonoporol and Copalliferols A and B
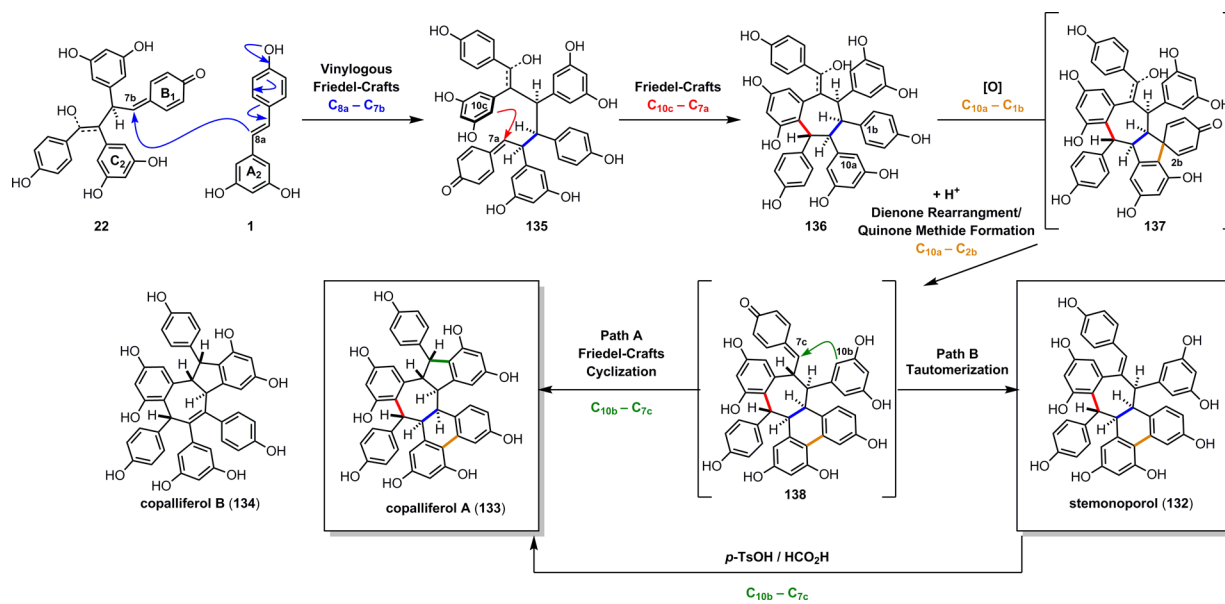
resveratrol. For instance natural products cajyphenol A (**128**) and B (**129**), isolated from *Cayratia japonica* (Vitaceae) are regioisomeric tetramers of the cross coupling of quadrangularin A (**17**) and its penultimate biosynthetic intermediate **52** (Scheme 20). A more complex natural product pauciflorol D (**130**) (Dipterocarpaceae),[78] is a resveratrol heptamer that arises from the trapping of the 8−8′ trimeric quinone methide **102** (precursor for canaliculatol and distichol (**103**), Scheme 16, part A)[129,130] by the 8−10′ tetramer vaticaphenol A (**131**)[141] (Scheme 20). This intermolecular oligomerization mode is common to many resveratrol oligomers including pentamers,[142] hexamers,[143] heptamers,[144] and octamers.[145] Thus, the biogenesis of the higher-order oligomers can be reduced to the same intermediates invoked for the biosynthesis of the dimers, trimers, and tetramers. Nonetheless, it remains unclear whether the plant exerts any form of stereo- or regiospecificity, or if the observed products of the oligomerization process are just reflective of the inherent reactivity of the random coupling of bulky reaction partners. Additionally, it is unknown whether the active electrophiles (e.g., **52** and **104**) are intercepted immediately upon formation or if they are generated from the corresponding solvent adducts (e.g., **53** or **106**). This reversible ionization may also be operative in the previously described biosynthetic routes to the resveratrol dimers, trimers, and tetramers, and has been implemented in de novo synthetic approaches to these natural products (see section 7).[146−148]

5.6.1. Biosynthesis of Stemonoporol, Copalliferol A and B. Stemonoporol (**132**)[149] and copalliferols A (**133**)[150] and B (**134**)[151] are among the first trimeric resveratrol natural products identified, isolated from several Dipterocarpaceous plants by Sotheeswaran and co-workers in the early 1980s. These highly unusual resveratrol trimers feature a benzocyclo-heptane core (as opposed to the dibenzocycloheptane core found in the 8−10′ dimers, section 4.2) and were the first resveratrol oligomers discovered that were not derived from ε-viniferin (**7**). The core cycloheptane structure of stemonoporol (**132**) and the copalliferols A and B (**133/134**) is suggestive of a unique trimerization mechanism. The 8−8′ dimerization of resveratrol forms the reactive bis-*para*-quinone methide **22**

(possibly formed reversibly from amurensin A (**59**)). Interception of **22** by resveratrol (**1**) through an intermolecular, vinylogous Friedel−Crafts reaction forging C_{8a}−C_{7b} bond (Scheme 21), followed by tautomerization or hydrolysis, would afford **135**. A subsequent intramolecular 7-*exo-trig* cyclization of trimeric intermediate **135** (bond C_{10c}−C_{7a}) yields benzocycloheptane **136**. The oxidation of the B_1 phenol, followed by intramolecular Friedel−Crafts cyclization of the A_2 resorcinol, provides the intermediate spirocyclohexadienone **137**, which, upon a phenol−dienone rearrangement[152] and ionization of the carbon 7c, yields the divergent *para*-quinone methide **138**. An intramolecular 5-*exo-trig* cyclization (path A) forges the final ring of copalliferol A (**133**). Tautomerization of **138**, on the other hand, yields stemonoporol (**132**). The biogenic relationship between these two natural products was established by Sotheeswaran and co-workers, who converted **132** to **133** via a cyclization reaction using formic acid.[153] Copalliferol B **134** is presumably generated from a series of related reactions.

5.7. Potential Role of Dirigent Proteins in Resveratrol Oligomer Biosynthesis

Most of what is currently known about the biosynthesis of the resveratrol natural products has been inferred through isolation studies and biomimetic reactions. Due to its structure, the oxidation of (**1**) is facile, and can be mediated by a number of constituents found in plants including endogenous peroxidases, exogenous fungal laccases, and even reactive oxygen species generated by UV irradiation.[38,103,154] A long-standing question, which has yet to be answered, is what are the factors that dictate product determination? In the absence of any stereocontrolling element, resveratrol displays little regioisomeric or stereo-chemical preference during its dimerization or oligomerization. However, a majority of the resveratrol natural products are isolated as optically active compounds, implying that the radical coupling is mediated by some chiral entity. In 1997, Davin and Lewis isolated an unusual protein, *Fi*DIR1, which could mediate the regiospecific and enantioselective dimerization of coniferyl alcohol (**139**) into the dimeric lignan (+)-pinoresinol (**140**) (Scheme 22).[155] These "dirigent" proteins (Latin:

Scheme 22. Potential Role of Dirigent Proteins in the Stereoselective Coupling of Resveratrol
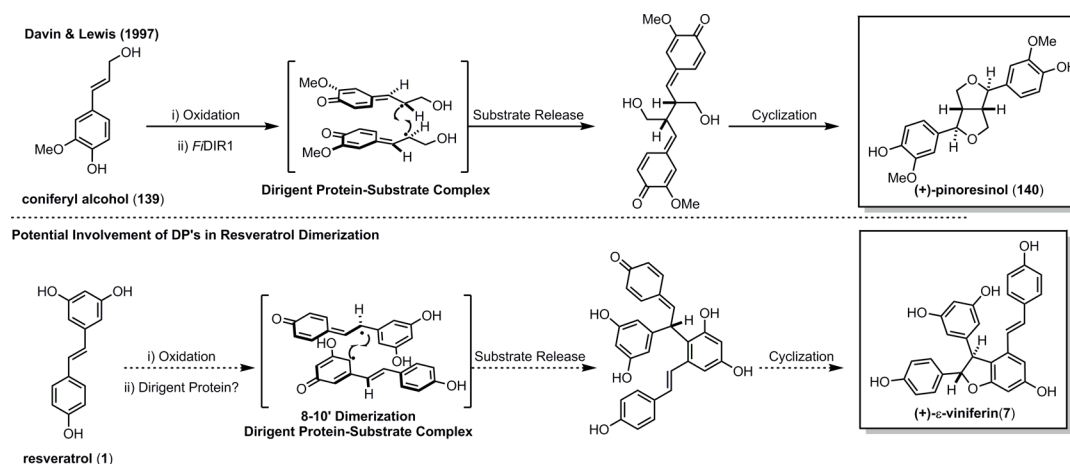
dirigere, to align or guide) did not possess any oxidase activity in their own right, but rather, they had the remarkable ability to capture and dimerize the phenoxyl radical of conferyl alcohol (**139**) faster than the background rate of self-dimerization/oligomerization.[156] They also found that *Fi*DIR1 could enantioselectively dimerize the phenoxyl radicals of **139** generated from different peroxidases, laccases, and even inorganic oxidants such as ceric ammonium nitrate (CAN). In the absence of the dirigent protein, **139** dimerizes as a complex mixture of racemic regioisomers in a fashion similar to resveratrol. Like the resveratrol oligomers, several regioisomeric and antipodal lignans have been isolated.[157] The structural similarity of the resveratrol oligomers and lignans, their homologous biosynthesis, and identities as phytoalexins, has led to speculation that the resveratrol dimerization is controlled by dirigent proteins;[42,154,157,158] however, there have not been any studies that have successfully identified the cellular components responsible for the stereoselective biosynthesis of the resveratrol oligomers. Thus, this tantalizing hypothesis remains unsubstantiated. The only certainty is that there is much work to be done to fully elucidate the biosynthesis of this fascinating class of molecules.

6. BIOMIMETIC SYNTHESES
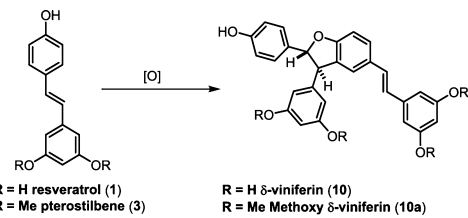
The challenge of biomimetic synthesis has captivated the synthetic community for over a century. Conceptually developed by Robinson following his historic synthesis of tropinone in 1917,[159,160] the strategy of imitating a biogenic reaction sequence has been used to validate biosynthetic hypotheses, and in many instances is recognized as the most efficient means to construct complex natural products. The resveratrol natural products are particularly well-suited for biomimetic synthesis because of the convergent nature of their oligomerization, which can be used to quickly introduce molecular complexity. The challenge in the synthesis of resveratrol based natural products is principally an issue of chemoselectivity, since the products of dimerization have similar electrochemical potentials as resveratrol itself and are prone to overoxidation. As described in the preceding sections, the arene rings of resveratrol can undergo a number of cyclization reactions upon oligomerization, which have proven difficult to control. These inherent properties of resveratrol as well as a lack of appropriate chemoselective reaction methodologies have hindered progress in this area.

In the following sections we will describe several biomimetic approaches to the resveratrol natural products. This task is somewhat complicated by the biogenic studies of natural product isolation groups who sought to establish their absolute configuration through semisynthesis. These studies are often cited to highlight the disadvantages of biomimetic approaches to the resveratrol oligomers. However, it is important to acknowledge that the primary motivations for these investigations were elucidating the structure and providing empirical support for the biogenesis of these compounds, rather than their total synthesis. In this review, we will attempt to differentiate these investigations to properly contextualize their findings and to accurately present the successes and unsolved problems in the biomimetic synthesis of these natural products.

6.1. Biomimetic Synthesis of δ-Viniferin

The first synthesis of a resveratrol dimer, δ-viniferin (**10**), was described by Langcake and Pryce in 1977, during their isolation and structure elucidation of α-(**6**) and ε-(**7**) viniferin.[36] Drawing on the biosynthesis of a structurally related lignan natural product licarin A,[35] they proposed that an oxidative oligomerization of resveratrol could conceivably generate ε-viniferin (**7**). By subjecting resveratrol to the horseradish peroxidase (HRP)/H_2O_2 oxidation conditions developed by Wallis and co-workers,[161] Langcake and Pryce isolated δ-viniferin (**10**) in 40% yield. These reaction conditions have since become a popular tool for structure elucidation of the resveratrol natural products and have been highly influential in subsequent biomimetic syntheses.

Since this seminal contribution, several groups have successfully dimerized resveratrol into δ-viniferin (**10**) using a variety of oxidation strategies, including enzymatic,[107,148,162] organic,[106,163] inorganic,[108,164,165] and photochemical oxidations.[111] The selectivity and yield for direct dimerization of resveratrol to δ-viniferin (**10**) have improved dramatically since the initial experiment by Langcake and Pryce. Table 1 summarizes the dimerization reactions that have been developed for the selective synthesis of **10**. The chemical oxidation by Sako (Table 1, entry 8), using AgOAc, was the first high-yielding biomimetic nonezymatic oxidation reaction and could be performed on a preparative scale.[165] The high regioselectivity of this dimerization reaction was also observed with ε-viniferin (**7**), where they obtained 40% yield of vitisin B (**116**) and 32% of an unidentified tetrameric didehydrodimer

Table 1. Biomimetic Syntheses of δ-Viniferin

R = H resveratrol (**1**)
R = Me pterostilbene (**3**)

R = H δ-viniferin (**10**)
R = Me Methoxy δ-viniferin (**10a**)

entry	reaction conditions	yield	ref
1[a]	Cu[II]SO$_4$, MeCN, rt	16%	164
2[a]	DPPH, MeOH	18%	106
3[a]	various peroxidases, acetone/EtOH	13−21%	108
4[a]	laccase, n-BuOH	31%	107
5[b]	AgOAc, DCM	36%	168
6[a]	galvinoxyl radical, ethanol, rt	41%	163
7[a]	graphitic carbon nitride (hv, 410 nm), lutidine, air, MeCN, rt	85%	111
8[a]	AgOAc, MeOH, 50 °C	86%	165
9[a]	MnO$_2$, DCM, rt	91%	108
10[a]	HRP/H$_2$O$_2$, H$_2$O/acetone, pH 8	93%	148
11[a]	FeCl$_3$, acetone, rt	97%	108

[a]R = H resveratrol (**1**). [b]R = Me pterostilbene (**3**).

for an impressive 72% combined yield (Scheme 23). Two years later, Niwa (Table 1, entries 9 and 11) disclosed two separate

Scheme 23. Sako's Biomimetic Synthesis of Vitisin B

(+)-ε-viniferin (**7**)
(isolated from natural sources)

vitisin B (**116**)
+ 32% unidentified
tetrameric didehydrodimer
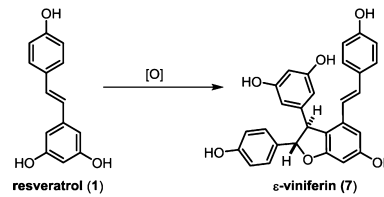
conditions that were chemoselective and were slightly higher yielding using MnO$_2$ or FeCl$_3$ as stoichiometric oxidants. Recently, a catalytic method us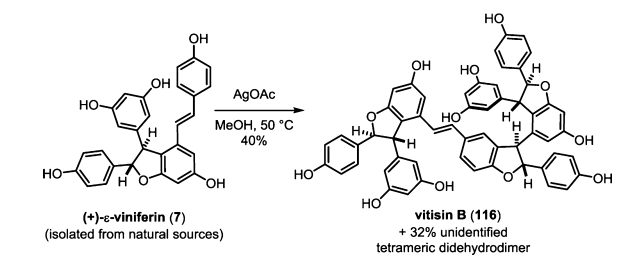ing graphitic nitride to dimerize resveratrol via an aerobic photochemical oxidation was reported by Wang and co-workers, which provided δ-viniferin (**10**) in high yield and with good regioselectivity (Table 1, entry 7).

6.2. Biomimetic Synthesis of ε-Viniferin

Although the 3−8′ dimerization of resveratrol can be obtained in high yield by a variety of methods, that regioisomer is rare among the resveratrol oligomers, thus limiting the utility for a general synthesis of other members of the natural product family. The selective synthesis of the 8−10′ dimer ε-viniferin (**7**), on the other hand, would be much more impactful from a synthetic standpoint, since it is the biogenic precursor for a majority of the resveratrol natural products. The principal challenge in the biomimetic synthesis of **7** is that its oxidation potential is nearly the same as resveratrol (E^{ox} = +1.15 V vs +1.14 V vs SCE, respectively[165]). This limitation does not exist for the synthesis of δ-viniferin (**10**), where dimerization alkylates the phenol of resveratrol which dramatically attenuates its reactivity. As a consequence there are very few reaction conditions that can successfully mediate the conversion of resveratrol (**1**) to **7**.

In 1998, Pezet isolated a laccase-like stilbene oxidase from the plant pathogen *B. cinerea* that had the remarkable ability to dimerize resveratrol to ε-viniferin (**7**) in 97% yield (Table 2,

Table 2. Biomimetic Syntheses of ε-Viniferin

resveratrol (**1**)

ε-viniferin (**7**)

entry	reaction conditions	yield	ref
1	*B. cinerea* laccase-like stilbene oxidase	97%	154
2	FeCl$_3$, MeOH/H$_2$O, rt	30%	166
3	K$_3$Fe(CN)$_6$, K$_2$CO$_3$, MeOH/H$_2$O, rt	22%[a]	108
4	Tl(NO$_3$)$_3$, MeOH, −50 °C	30%	108

[a]Obtained as a 1:1:0.7 mixture of **7**:**10**:**18**.

entry 1).[154] Resveratrol analogues, such as 4,4′-dihydroxystilbene or pterostilbene (**3**) (11,13-dimethoxyresveratrol), were also competent substrates that could be rapidly oxidized by the enzyme. In corroboration with other studies, the isolated stilbene oxidase was only active on substrates containing a free phenol; alkylated substrates such as 4-methoxystilbene were unreactive. Although the optical rotation of **7** generated in the reaction was not measured, these results suggest that some fraction of ε-viniferin (**7**) could in principle be an exogenously synthesized natural product. It is unclear how the stilbene oxidase controls the regioselectivity of this dimerization, since other peroxidases and laccases tend to produce δ-viniferin (**10**) preferentially. This oxidative dimerization was conducted on a microgram scale, and it has yet to be implemented in preparative synthesis.

A scalable and selective biomimetic syntheses of ε-viniferin (**7**) did not appear until 2004, when Yao and co-workers described the dimerization of resveratrol to **7** with FeCl$_3$ in MeOH in 30% yield and with 40% recovery of resveratrol (Table 2, entry 2).[166] This reaction was performed on 0.5 g scale and has since been implemented for the synthesis of other resveratrol dimers.[167] They were able to derivatize **7** to phenanthroline **141** upon photooxidation of **7** in 20% yield (Scheme 24).

Scheme 24. Oxidative Photocyclization of 7

ε-viniferin (**7**)

141
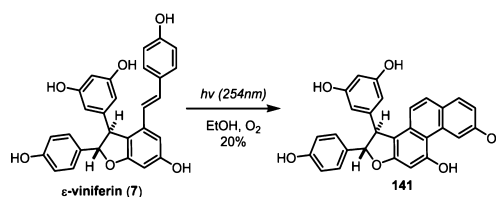
One year later, Niwa and co-workers also reported a series of reaction conditions that could selectively generate ε-viniferin (**7**).[108] If potassium hexacyanoferrate (K$_3$Fe(CN)$_6$) was used as the stoichiometric oxidant, 22% of **7** could be isolated as a mixture of resveratrol dimers with 40% recovered resveratrol (Table 2, entry 3). Much higher product selectivity could be achieved using Tl(NO$_3$)$_3$ as the oxidant. This reaction was found to be highly temperature sensitive, yielding 30% **7** as the sole reaction product (56% recovered starting material) at −50

Table 3. Biomimetic Dimerization of Resveratrol

R = H δ-viniferin (10)
R = Me methylated δ-viniferin (10a)

R = H quadrangularin A (17)
parthenocissin A (61)
R = OH leachinol F/G (53)
R= OEt quadrangularin B/C (55)

R = H ampelopsin F (16)
R = Me methylated ampelopsin F (16a)

R = H pallidol (18)
R = Me methylated pallidol (18a)

R = H tricuspidatol A (57)
R = Me methylated tricuspidatol (57a)

R = H resveratrol (1)
R = Me pterostilbene (3)
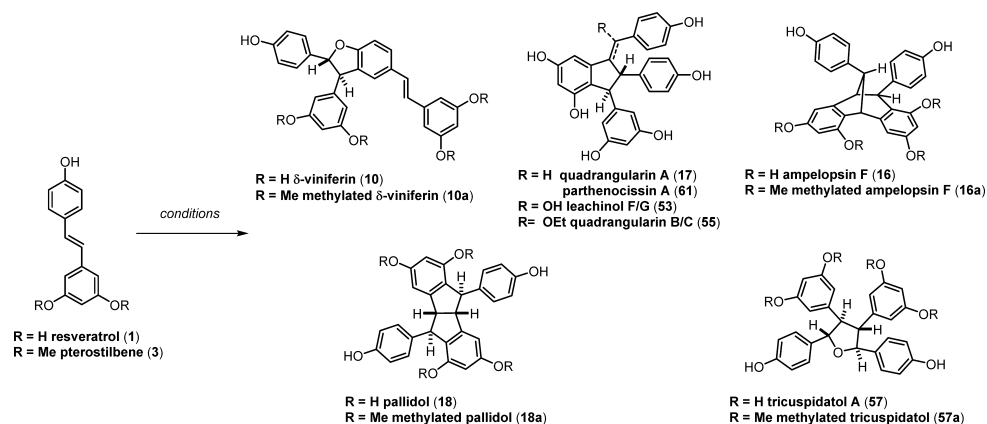
entry	reaction conditions	10	16	53/55	18	57	ref
1	K$_3$Fe(CN)$_6$, K$_2$CO$_3$, MeOH/H$_2$O, rt	23%	—	—	16%	—	108
2	horseradish peroxidase, aq acetone	13%	—	—	10%	—	108
3	soybean peroxidase, aq EtOH	12%	—	14%[b]	10%	—	108
4[a]	FeCl$_3$·6H$_2$O, CH$_2$Cl$_2$	—	7%	—	10%	—	168
5[a]	FeCl$_3$·6H$_2$O, CH$_2$Cl$_2$/MeOH (7:3 v/v)	—	—	—	—	29%	168
6[a]	Pt anode/cathode in MeCN/0.2 M LiClO$_4$ (+1.00 V vs Ag/AgNO$_3$)	—	8%	—	14%	—	170
7	horseradish peroxidase, acetone/pH 8.0 buffer	93%[c] (89%)[d]	—	—	—	—	148
8	horseradish peroxidase, acetone/pH 6.0 buffer	—	—	55%[c,e] (24%)[d,e]	—	—	148
9	horseradish peroxidase, acetone/pH 5.0 buffer	—	—	—	20%[c] (19%)[d]	—	148
10	horseradish peroxidase, acetone/pH 4.0 buffer	28%[c] (26%)[d,f]	—	—	—	—	148
11	NaNO$_2$/pH 3.0 buffer, MeOH	2%	—	—	—	1%	171

[a]R = Me (pterostilbene, **3**). [b]2:1 mixture of **55/53**. [c]HPLC yield. [d]Isolated yield. [e]Product was **53**. [f]*cis*-δ-viniferin is major pdt.

°C, but gave complete decomposition at −30 °C (Table 2, entry 4). Collectively, these methodologies highlight the importance of oxidant identity in the regioselective synthesis of resveratrol dimers. It is unclear how these oxidants avoid overoxidation while maintaining high levels of product selectivity. These remarkable findings are promising leads toward a reagent-controlled, chemoselective synthesis of the resveratrol oligomers.

6.3. Biomimetic Synthesis of Other Resveratrol Dimers

Despite the previous successes in the synthesis of the dihydrobenzofuran dimers, strategies to selectively synthesize more complex dimeric architectures, such as quadrangularin A (**17**), pallidol (**18**), or ampelopsin D/F (**25/16**), remained a significant synthetic challenge. In their studies on the biogenic origins of the resveratrol dimers, Niwa and co-workers disclosed several oxidation conditions which could yield various nonbenzofuran containing natural products.[108] Using the same conditions described in section 6.2, they found that K$_3$Fe(CN)$_6$ could oxidize resveratrol, yielding a mixture of **7**, **10**, and up to 16% of pallidol (**18**) (Table 3, entry 1). Oxidizing resveratrol with HRP in acetone afforded a mixture of **10** (13% yield) and **18** (10% yield) (Table 3, entry 2), while soybean peroxidase in ethanol produced a mixture of δ-viniferin (**10**) (12% yield), pallidol (**18**) (10% yield), quadrangularin B/C (**55**) (9% yield), and leachinol F/G (**53**) (5% yield) (Table 3, entry 3), with a 24% combined yield of 8−8′ dimers. Although the chemoselectivity of these biomimetic oxidations was modest at best, this study was the first to demonstrate the feasibility of

performing a reagent controlled dimerization of resveratrol, developing distinct conditions to synthesize 3−8′, 8−10′, and 8−8′ dimers.

A subsequent study by Velu and co-workers sought to understand the effects of solvent polarity and oxidant choice on chemoselectivity during dimerization of resveratrol analogues.[168] Using FeCl$_3$ as their single electron oxidant, they found that they could influence product distribution by switching between "hard" and "soft" solvents or oxidants.[169] When **3** was oxidized with FeCl$_3$ in CH$_2$Cl$_2$, they observed 10% and 7% yield of methylated pallidol (**18a**) and ampelopsin F (**16a**), respectively (Table 3, entry 4). In a mixture of CH$_2$Cl$_2$ and methanol, **3** dimerized primarily to give the tricuspidatol derivative **57a** in 29% yield (Table 3, entry 5). These results compare favorably to the enzymatic oxidation of resveratrol by *B. cinerea* laccase enzymes which yielded the isomeric tetraaryl furan restrytisols A/B (**56/63**) (section 4.3).[38] The authors also observed that solvent could influence the product distribution of several non-natural resveratrol analogues, independent of the oxidant identity, albeit in relatively low isolated yields. Kam and co-workers isolated a similar yield of permethylated **16** and **18** in the electrochemical oxidation of permethylated **1** (Table 3, entry 6), corroborating those findings.[170] In both of these approaches, the modest yields were the result of stilbene overoxidation into an intractable mixture of polymeric material.

In 2012, Pan and co-workers examined the effects of reaction pH on the product distribution of a peroxidase mediated

Scheme 25. Interconversion of Leachinol F/G to Parthenocissin A and Quadrangularin A
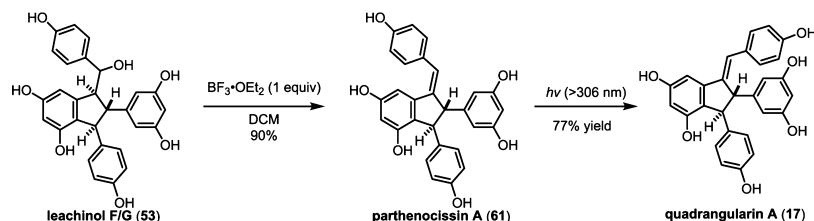
Scheme 26. Hou Synthesis of Quadrangularin A
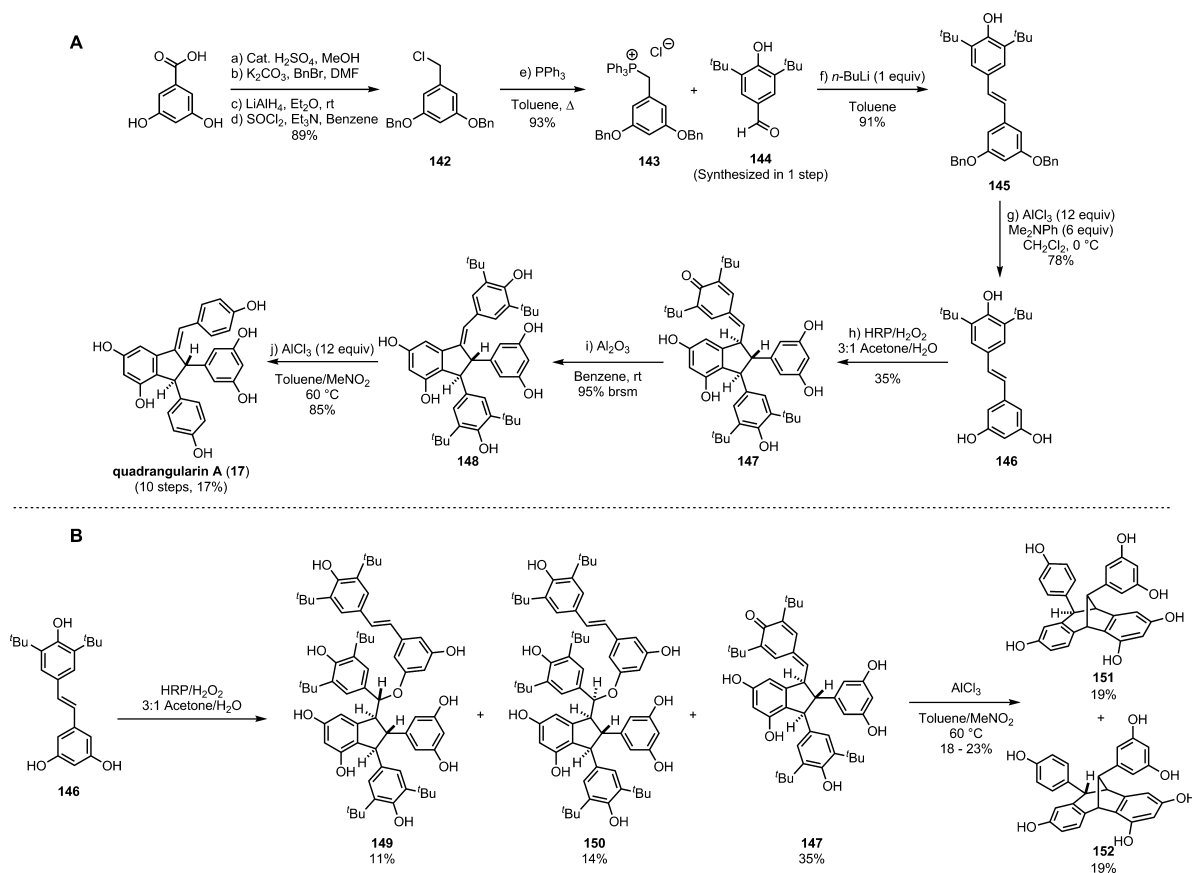
dimerization of resveratrol.[148] They performed peroxidase-mediated dimerizations of **1** at pH 4.0, 5.0, 6.0, and 8.0 (Table 3, entries 7−10). By adjusting the reaction basicity to pH 8.0, they isolated 89% yield of **10** as the major regioisomer. In mildly acidic conditions at pH 6.0, they observed a dramatic change in product distribution, with a 55% HPLC yield of a 1:1 mixture of leachinol F/G (**53**), isolating 24% yield on preparative scale. At pH 5.0 they detected an enrichment in pallidol (**18**) formation (19% isolated), while at pH 4.0, they isolated primarily *cis*-**10** in 26% yield (28% HPLC yield). At more acidic conditions (pH of 3.0), they observed no conversion, due to the increased oxidation potential of resveratrol under those conditions. A prior report by d'Ischia and co-workers utilizing NaNO₂ as an oxidant at the same pH identified **10** and **57** in minute quantities (<2%), corroborating the poor reactivity at low pH (Table 3, entry 11).[171] These results indicate the pH sensitivity of the dimerization reaction, enabling the selective enrichment of one regioisomer over the other. This simplified purification, which was performed by HPLC due to the polarity of the compound mixtures. Furthermore, they performed the dimerization on a preparative

scale for the purposes of synthesis and biological evaluation (see section 8.4). They could interconvert leachianols F/G (**53**) (as a 1:1 mixture), into parthenocissin A (**61**) using BF₃·OEt₂ in 90% yield (Scheme 25). Subsequent irradiation of **61** with >306 nm light cleanly isomerized it to the corresponding (*E*)-isomer, quadrangularin A (**17**) in 77% yield. This report clearly demonstrated the pH-sensitive nature of the dimerization of resveratrol and its impact on product distribution. The scalability of the procedure is also notable; this method was capable of producing **61** and **17** in 50 and 30 mg quantities, respectively.

6.3.1. Hou and Li Synthesis of Quadrangularin A via an Arene Protecting Group Strategy. Despite the fact that the resveratrol oligomers have been known since the 1960s, very little effort was initially invested toward their total synthesis. Studies such as those discussed above on the biomimetic dimerization of resveratrol (**1**) or pterostilbene (**3**), highlighted significant challenges in achieving high chemoselectivity, regioselectivity, and useful yields. The important innovations during this time period were the identification of the impact of oxidant, solvent choice, and pH on product

Table 4. Regioselective Dimerizations of 146
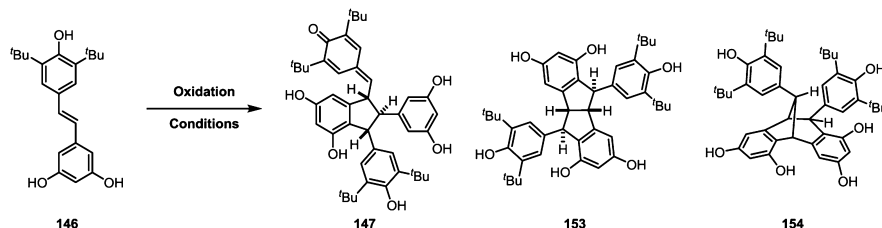
entry	reaction conditions	147	153	154
1	Ag$_2$CO$_3$, CH$_2$Cl$_2$	59%[a]	—	—
2	MnO$_2$, CH$_2$Cl$_2$	54%[a]	—	—
3	FeCl$_3$·6H$_2$O, benzene/acetone 2:1	—	55%[a]	—
4	FeCl$_3$·6H$_2$O, CH$_2$Cl$_2$	—	—	45%[a]

[a]Reported as % conversion.

Scheme 27. Li's Synthesis of Protected Restrytisol Dimers and Interconversion to Pallidol
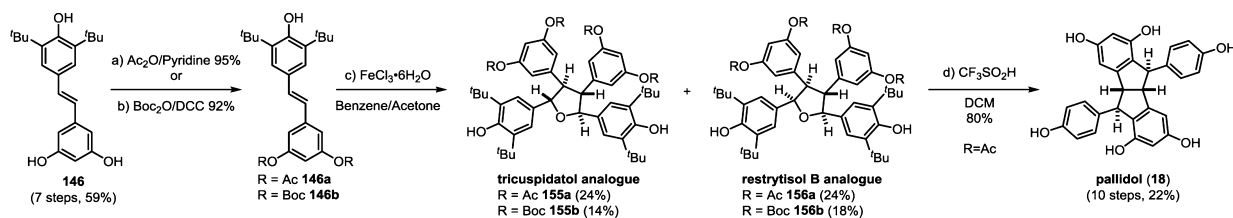
selectivity. However, given the complexity of these reactions, it was impossible to predict which natural products would be generated under chosen conditions, and research in this area was largely driven by empirical observation.

In 2006, Hou and co-workers disclosed a target-oriented biomimetic synthesis of quadrangularin A (17), which was the first synthesis of a fully elaborated indane containing resveratrol dimer.[172] The key innovation of this approach was the identification of the 2,6-di-*t*-butyl motif as a blocking group to prevent unwanted 3−8′ coupling that is typical for the uncontrolled oxidation of resveratrol, a method pioneered by Müller[173] and Wallis[174] in their investigations on lignan biosynthesis.

Stilbene 145 was synthesized from 3,5-dihydroxybenzoic acid in six steps. Although 143 and 144 were synthesized *de novo*, the benzyl bromide of 142 and benzaldehyde 144 are now commercially available. Treatment of *tert*-butyl stilbene 145 with AlCl$_3$ and dimethylaniline enabled the selective dealkylation of its benzyl ethers generating 2,6-di-*tert*-butyl resveratrol 146 in 78% yield. This compound was then oxidized with HRP and H$_2$O$_2$ in an acetone/water mixture over 2 days, affording the cyclized *para*-quinone methide 147 in 35% yield on 0.5 g scale. Curiously, this reaction also produces trimeric intermediates 149 and 150 in 11% and 14% yield, which are the products of trapping of the monomer-based resorcinol onto product 147 (Scheme 26, section B). Compound 147 is a direct analogue of the 8−8′ dimerization intermediate 52 outlined in section 4.3 and provides support for the presence of quinone-methide intermediates in the biosynthesis of quadrangularin A (17). Tautomerization of 147 with basic alumina in benzene provides protected quadrangularin A (148) in 64% yield, along with 31% recovered starting material. Finally, a Lewis-acid-mediated retro-Friedel−Crafts reaction dealkylates 148 with concomitant extrusion of isobutylene,[175,176] affording quadrangularin A (17) in 85% yield. Overall, this reaction sequence provides quadrangularin A

(17) in 10 total steps in 17% overall yield and is an excellent demonstration of the step-efficiency that biomimetic synthesis can offer. In a later communication, Li and co-workers attempted a direct deprotection of mixture of 147, 148, and 150, which lead to an interesting skeletal rearrangement to compounds 151 and 152, non-natural analogues of ampelopsin F (16).[177]

6.3.2. Li's Approach to Quadrangularin A, Pallidol, and Ampelopsin F by a Regioselective Oxidative Coupling. Expanding upon the work of the Hou group, Li and co-workers reported a series of oxidations of stilbene 146 using inorganic oxidants in several solvent systems.[178] In this communication, the Li group reports reaction conversions and percent recovered starting material, but in several cases, these values add up to more than 100%, making yield estimation difficult. They found that when 146 was oxidized by 1 equiv of either Ag$_2$CO$_3$ or MnO$_2$ in CH$_2$Cl$_2$, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl$_3$·H$_2$O as an oxidant in 2:1 benzene/acetone, they observed 55% reaction conversion to protected pallidol (153) with 45% recovery of starting material. Finally, opposite regioselectivity could be achieved if FeCl$_3$·6H$_2$O was used as the oxidant in CH$_2$Cl$_2$, delivering protected ampelopsin F (154) in 45% reaction conversion with 25% recovered starting material. These results corroborate the findings described by Niwa[108] and Velu[168] demonstrating that it is possible to influence product distribution by changing solvent and/or stoichiometric oxidant. Deprotection of 153 and 154 with AlCl$_3$ in toluene/MeNO$_2$ proceeded uneventfully for pallidol (18) and ampelopsin F (16) in 85% and 76% isolated yields, respectively. The synthesis of ampelopsin F (16) is the first example of a selective, biomimetic synthesis of an 8−10′ dimer.

6.3.3. Li's Synthesis of Protected Tetraaryl Furan Dimers. In 2014, Li and co-workers reported the synthesis protected analogues of tricuspidatol A (155a/b) and restrytisol

Table 5. Optimization of Aerobic Resveratrol Dimerization
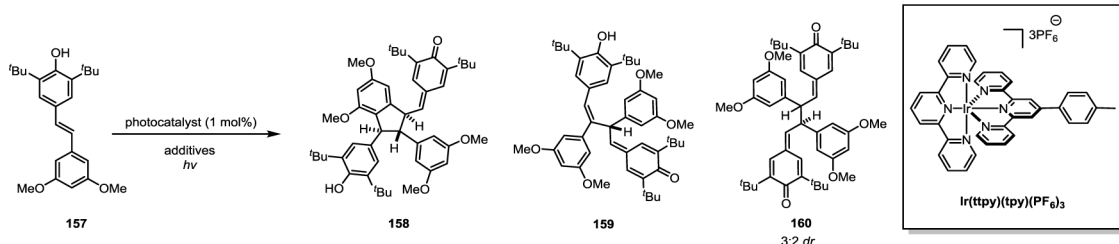
entry	photocatalyst	solvent	oxidant	additive	time	yield	product
1	Ir(ttpy)(tpy)(PF$_6$)$_3$	acetone	O$_2$	—	2 d	38%	158
2	Ir(ttpy)(tpy)(PF$_6$)$_3$	acetone/MeOH	O$_2$	NaOMe	5 h	47%	159
3[a]	—	acetone/MeOH	O$_2$	NaOMe	2 h	55%	159
4[a]	—	CCl$_4$	O$_2$	KO^{t}Bu	1 h	60−80%	160
5[b]	—	THF	FeCp$_2$PF$_6$	KHMDS	30 min	99%	160

[a]Reaction was shielded from light. [b]Reaction performed on decagram scale.

Scheme 28. Total Synthesis of Quadrangularin A and Pallidol by Stephenson and Coworkers
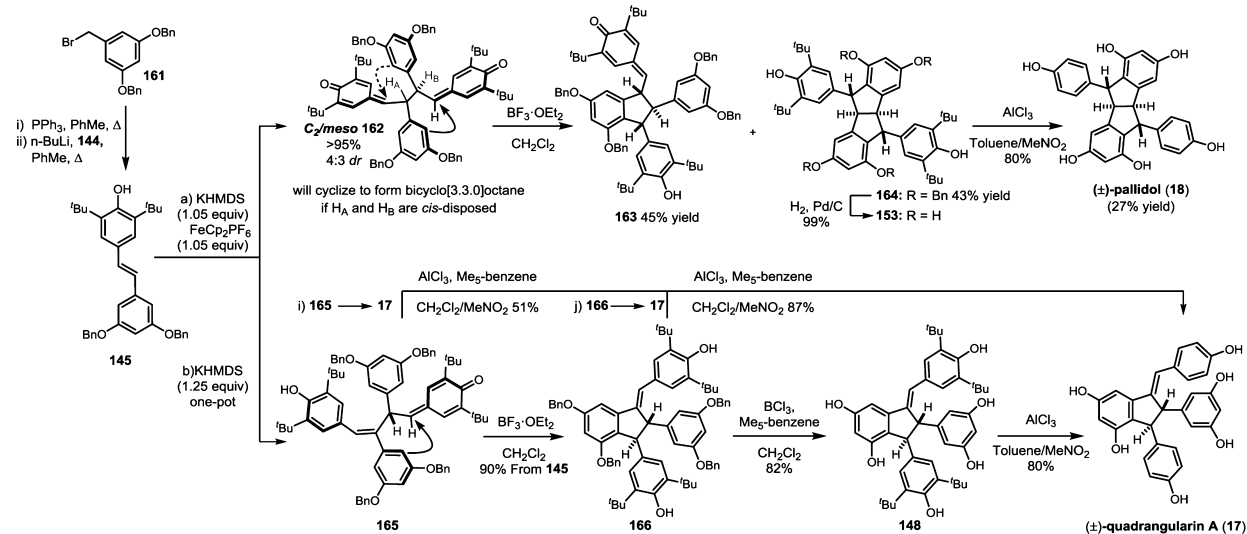
B (**156a/b**) (Scheme 27).[179] Upon acylation of the resorcinol of **146** with Ac$_2$O or Boc$_2$O and oxidation with FeCl$_3$·6H$_2$O they observed the formation of **155a/b** and its nonsymmetrical isomer **156a/b**. The acylated stilbene **146a** gave higher combined yield of the tetraaryl furan dimers **155a** and **156a** (48% yield as a 1:1 mixture), whereas the Boc-protected derivative **146b** afforded a slightly lower yield (32% combined as a 1:1.3 mixture) of **155a/155b**. Interestingly, deprotection of the mixture of **155a** and **156a** in neat CF$_3$SO$_2$H did not provide tricuspidatol (**57**) or restrytisol B (**63**) but rather pallidol (**18**) in 80% yield.

6.3.4. Stephenson's Synthesis of Quadrangularin A and Pallidol from Bioinspired Quinone-Methides. Recently, Stephenson and co-workers disclosed a scalable biomimetic synthesis of quadrangularin A (**17**) and pallidol (**18**).[180] Drawing on design principles delineated by the Hou and Li groups, they developed a highly efficient dimerization of the *tert*-butylated resveratrol derivative **146**. Their initial approach, using the strongly oxidizing photocatalyst, Ir(tpy)-(ttpy)(PF$_6$)$_3$,[181] was competent for the selective aerobic oxidation of **157** to the cyclized *para*-quinone methide **158** over a period of 2 days in 38% yield (Table 5, entry 1).

Owing to the pH-dependence of the oxidation potential of resveratrol and phenols,[182] they sought to improve the efficiency of the reaction by performing it under alkaline conditions. In the presence of excess NaOMe and 1% photocatalyst under aerobic conditions, full consumption of **157** was observed in 5 h to give a slightly improved 47% yield (Table 5, entry 2). However, instead of quinone methide **158**, they isolated the linear dimer **159**. Control experiments revealed that the photocatalyst was not needed and that the reaction was proceeding via aerobic oxidation (Table 5, entry 3). Further optimization revealed that when the aerobic oxidation of **157** was performed in CCl$_4$ and KO^{t}Bu, quinone methide **160** was the major product (Table 5 entry 4), indicating that product selectivity was both pH- and solvent-dependent. Importantly, dimers **159** and **160** are analogues of the two other biosynthetic intermediates of the 8−8′ dimers and are precursors to pallidol (**18**) and amurensin A (**59**) (see section 4.3). A modification of the reaction conditions using 1.05 equiv of FeCp$_2$PF$_6$ as a stoichiometric oxidant and KHMDS as the base improved scalability and increased the yield to 95−99% on a decagram scale.

Starting from commercially available benzyl bromide **161**, stilbene **145** was prepared in two steps in 81% overall yield.

Scheme 29. Synthesis of Indane-Based Resveratrol Dimers from a Common Building Block
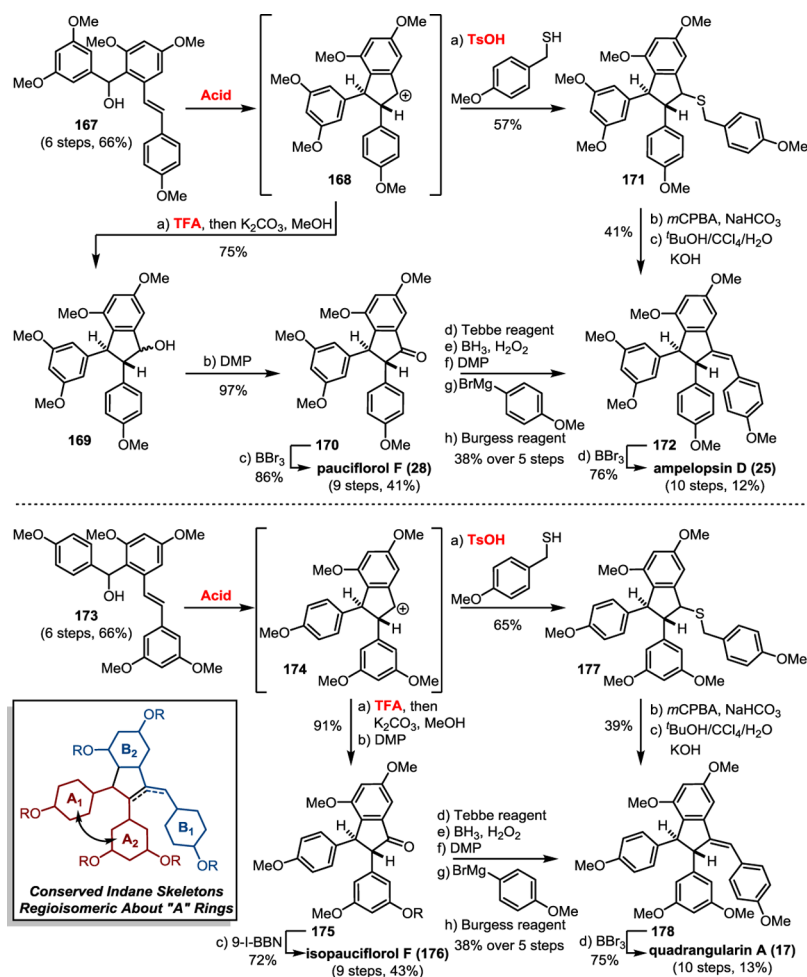
The ferrocenium-mediated dimerization of **145** in THF yielded a 4:3 mixture of *meso/dl* diastereomers of **162** in quantitative yield. The relative configuration of the vicinal stereocenters in **162** had important consequences on product formation (see section 4.3). Namely, upon exposure to BF₃·OEt₂, **162** was transformed to a mixture of protected pallidol (**164**, 43%) and quinone methide **163** (45%). Hydrogenation followed by an AlCl₃ mediated de-*tert*-butylation reaction afforded pallidol (**18**) in 27% overall yield from **161**.

The synthesis of quadrangularin A (**17**) proceeded in a similar fashion, starting from the oxidative dimerization of **145**. It was discovered that bis-*para*-quinone methide **145** could be interconverted to the mono-*para*-quinone methide quantitatively by tautomerization under strongly basic conditions. By adding another equivalent of KHMDS to the original dimerization reaction, they could synthesize **165** in one step with no loss of yield. Quadrangularin A (**17**) could be accessed from **165** by one-, two-, or three-step sequences, through the intermediacy of **166** and **148**, in 51%, 88%, and 65% yield, respectively (Scheme 28). Here, Lewis acids served to promote cyclization, global debenzylation, and removal of the *tert*-butyl groups, while Me₅-benzene sequestered the benzyl cations generated during the dealkylation step.[183,184] Quadrangularin A (**17**), therefore, could be accessed in 4 steps/41%, 5 steps/64%, or 6 steps/47% overall yield from commercially available **161**. The scalability of this route enabled the rigorous evaluation of

the antioxidant properties of these natural products and their congeners (see section 8.4).

7. *DE NOVO* SYNTHETIC APPROACHES

The strategies outlined in the previous section were incredibly important to advance the understanding of resveratrol reactivity under conditions designed to emulate the chemical environment in which its oligomerization is achieved within plant cells. However, until recently,[180] these strategies have failed to meet material requirements for systematic physical and biochemical evaluation. Given their impressive biological activities, elusive mechanisms of action, and fascinating molecular architectures, the resveratrol oligomers have been the target of synthetic chemists for years. In 2007,[185] Snyder and co-workers published a powerful de novo strategy to resveratrol dimers that has evolved and flourished in the interim, resulting in a series of pioneering and inspirational syntheses of complex molecules within this class. This work and the contributions of other research groups to this area are presented below.

7.1. Synthesis of Resveratrol Dimers Using Cationic Cyclizations and Skeletal Rearrangements

7.1.1. Snyder's Synthesis of Indane-Containing Resveratrol Dimers From a Common Building Block. While there is tremendous chemical diversity within the resveratrol class of oligomeric natural products, they are characterized by highly conserved carbogenic cores (see section 4−5). Of the various structural subtypes, Snyder and co-workers elected to

Scheme 30. Electrophile-Promoted Interconversion of Indane Dimers to [3.2.1] and [3.3.0] Bicyclooctanes
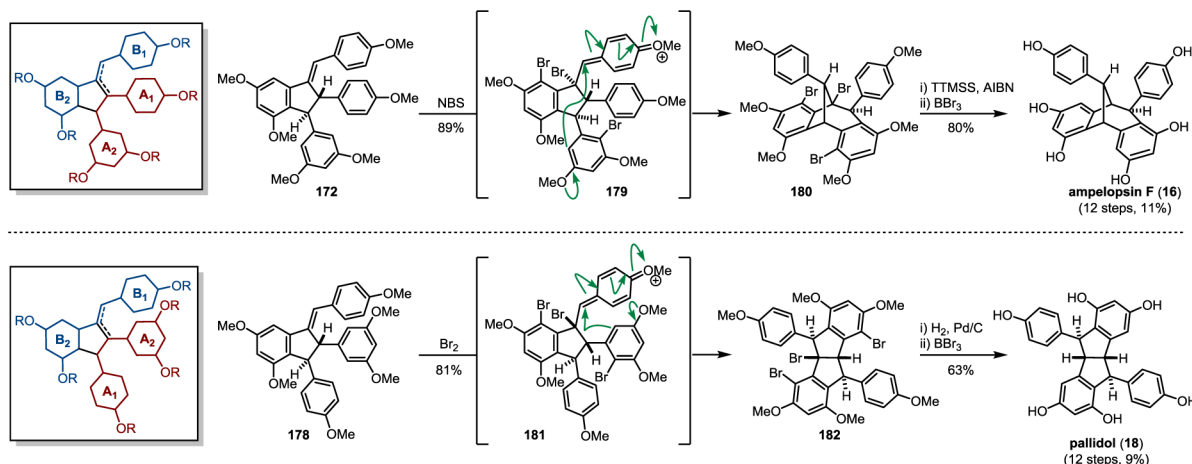
target indane-derived resveratrol natural products ampelopsin D (**25**) and quadrangularin A (**17**), realizing that a modular approach to these compounds would potentially lay the foundation for the synthesis of higher-order oligomers possessing these core structures. Specifically, the indane-containing resveratrol oligomers can be divided into two regioisomeric classes depending on the relative positioning of the phenol (A_1) and resorcinol (A_2) components of the resveratrol monomer whose ethylene bridge comprises two of the three carbons in the indane ring (Scheme 29, inset). This observation enabled the retrosynthetic design of triaryl starting materials **167** and **173** (Scheme 29) which, by careful temperature control, could be channeled through chemoselective acid-promoted cyclizations to generate regioisomeric *trans*-configured 2,3-diaryl indanyl cations **168** and **174**.[185]

When the cyclization was promoted by TFA, the intermediate cation was trapped by the conjugate base (trifluoroacetate) in solution. Quenching of the trifluoroacetate adduct with adventitious water in the presence of base resulted in formation of the corresponding benzyl alcohol **169**, which was subsequently oxidized to the protected indanone **170**. Pauciflorol F (**28**) was revealed by a global demethylation using BBr$_3$.

Alternatively, by employing a Brønsted acid whose conjugate base is less nucleophilic (TsOH), the intermediate indanyl cation could be captured by a benzyl mercaptan, yielding **171**, which served as a nucleophilic proxy to append a *para*-methoxy styryl group at this position through an ensuing Meyer's modified Ramberg−Bäcklund reaction.[186,187] This gave a 5:1 mixture of *E/Z* olefin isomers that were separated chromatographically. The (*E*)-isomer (**172**), a protected derivative of the natural product ampelopsin D (**25**), was demethylated using BBr$_3$ to give a 5:1 mixture of the desired natural product (**25**) and its internal alkene isomer, isoampelopsin D (see Scheme 5, A). Isolation of these materials required peracetylation prior to chromatographic separation and subsequent KCN promoted hydrolysis. A logical redesign of their starting alcohol (**173**) enabled access to the regioisomeric materials isopauciflorol F (**176**) and quadrangularin A (**17**) through an identical reaction sequence. Notably, a 5-step method for the interconversion of pauciflorol F (**28**) to ampelopsin D (**25**) (and isopauciflorol F (**176**) to quadrangularin A (**17**)) has since been developed (see section 7.1.3).[188]

7.1.2. Snyder's Interconversion of Indane Dimers to [3.3.0] and [3.2.1] Bicyclooctanes.

In an extension of these seminal studies, Snyder sought to exploit the inherent polarization of the methoxy styrene moiety present in the natural products ampelopsin D (**25**) and quadrangularin A (**17**) to effect their interconversion to the remaining two dimeric structural subtypes: the bicyclo[3.2.1]octanes and the bicyclo[3.3.0]octanes.[189] Each of these transformations was to be accomplished via electrophilic activation of these olefins to generate cationic quinone methide intermediates. Intramolecular trapping by a proximal resorcinol would provide the desired carbogenic cores. While this would ideally be accomplished using a Brønsted acid, the authors had already observed that both **172** and **178** are susceptible to olefin isomerization under acidic conditions. Therefore, electrophilic bromination reagents were chosen as alternative promoters, which smoothly transformed **172** and **178** to the trihalo natural product precursors **180** and **182** through the intermediacy of quinone methide cations **179** and **181**, respectively (Scheme 30). Sequential hydrodehalogenation and demethylation provided the natural products ampelopsin F (**16**) and pallidol (**18**).

By quenching the electrophilic cyclization at various time intervals, the researchers were able to elucidate the order of halogenation events leading to each of the bicyclooctane cores. Namely, bromination of the electron-rich resorcinol rings takes place prior to olefin activation, with halogenation of the B_2-ring occurring first for both regioisomers. This can be rationalized by the additional stabilization of the Wheland intermediate by two alkyl substituents for the B_2-ring as compared to one for the A_2-ring. The high yields obtained for the electrophilic cyclizations warrant further discussion. Theoretically, halonium formation could take place from either face of the olefin, yet only one of the resultant configurations enables the subsequent bicyclooctane formation. To account for this, the authors propose that bromination of the A_2-rings provides enough steric encumbrance to bias olefin activation to occur from the opposite face. Rehybridization (sp^2−sp^3) of the bromine-bearing aliphatic carbon induces molecular reorganization, orienting the dearomatized B_1-ring *para*-quinone methide such that it can be captured by the vicinal A_2-ring (in pallidol synthesis) or the transannular A_2-ring (in ampelopsin F synthesis).

Scheme 31. Synthesis and Structural Reassignment of Caraphenols B and C
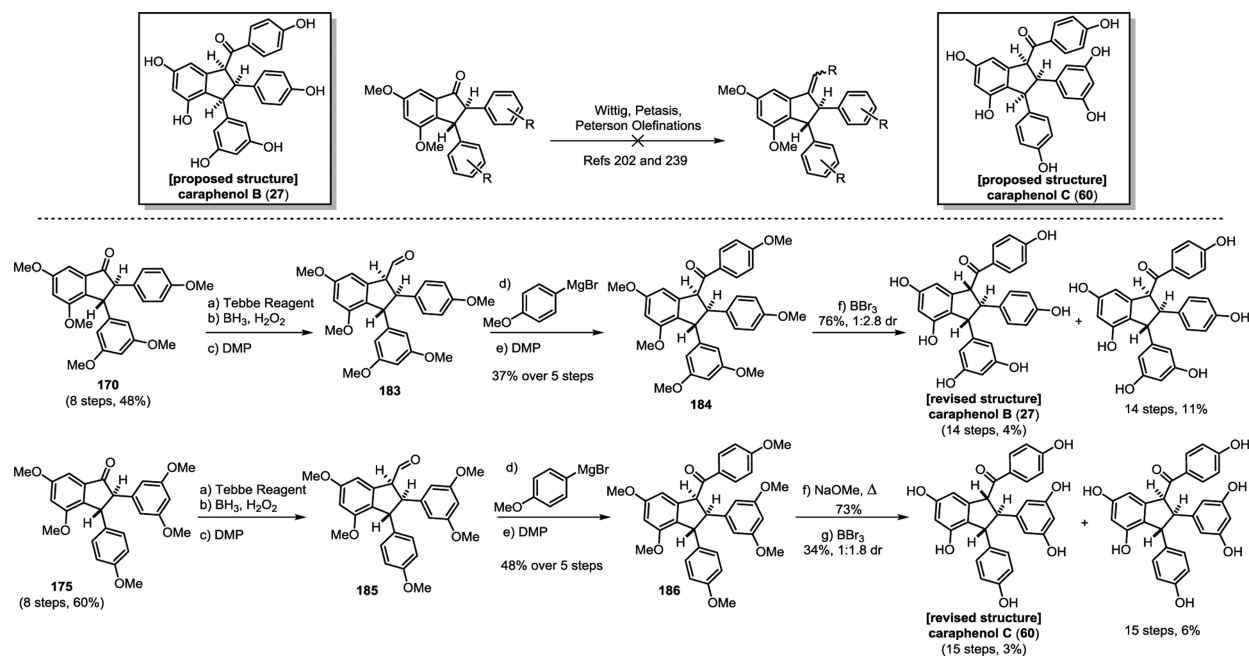
To explore whether olefin geometry had any influence over these events, they subjected the (Z) olefin isomer of **178** to the bromination conditions and obtained either **178** or **182**, depending on whether the reaction was quenched at −78 °C or warmed to room temperature, respectively. This result suggests that another mechanism may be operative, whereby bromonium formation is not facially selective but occurring reversibly via exchange with free olefin in solution.[190,191] This mechanism is likely active when bromination takes place so as to position the quinone methide anti to the nucleophilic resorcinol, whereas the mechanism proceeding through the syn configuration is rendered irreversible by the Friedel−Crafts cyclization event.

7.1.3. Synthesis and Structural Revision of Caraphenols B and C by Snyder and Brill.
As described in section 4−5, nearly all of the indane-based resveratrol dimers possess either a *trans,trans* or *cis,trans* relative configuration about the vicinal indane stereocenters. Two exceptions to this were caraphenols B (**27**) and C (**60**) (Scheme 31), which were originally proposed to have an all-*cis* arrangement of the indane substituents.[43] Synthesis of each of the proposed structures revealed that these natural products had been misassigned. As most of the indane dimers possess a *trans,trans* relative configuration, Snyder and Brill completed the synthesis of these frameworks with this arrangement and confirmed their structures by comparison to the spectroscopic data for the natural compounds.[188] Relying on their previous syntheses of pauciflorol F (**28**) and isopauciflorol F (**176**), a reaction sequence was developed for functionalization of the indanone. These aryl ketones have been historically challenging to functionalize, and several attempts to use these indanones as intermediates in the synthesis of resveratrol oligomers have failed (Scheme 31).

Treatment of permethylated indanones **170** and **175** with Tebbe's reagent[192] provided the corresponding exocyclic methylene, which was subjected to anti-Markovnikov hydration and oxidation. Notably, the hydroboration proceeds from the opposite face of the neighboring D ring, thus yielding the

cis,trans diastereomer of **183** and **185**. Grignard addition to the aldehydes and oxidation of the resultant benzyl alcohols afforded **184** and **186**. The α-stereocenter was not configurationally stable under the acidic conditions required for demethylation, and some of **184** epimerized to the corresponding *trans,trans* diastereomer in the course of this reaction. The epimers were isolated by HPLC, and the *trans,trans* compound was identified as caraphenol B (**27**). For **186**, epimerization of the α-center was performed prior to demethylation under alkaline conditions to yield the thermodynamically favored *trans,trans* isomer. However, over the course of the demethylation with BBr₃, some of the material epimerized back to the *cis,trans* isomer. Again, the *trans,trans* configured product was identified as caraphenol C (**60**) by comparison with spectra for the natural sample.

7.1.4. Nicolaou and Chen's Synthesis of Hopeahainol A and Hopeanol.
Just three years after their initial isolation, Nicolaou and Chen disclosed an impressive synthesis of the biosynthetically related resveratrol dimers, hopeahainol A (**40**) and hopeanol (**31**).[92] These unusual structures are each thought to derive from skeletal rearrangement of resveratrol dimers, presumably via an oxidative rearrangement of malibatol A (**44**) (see section 4.2). As these structures can conceivably be interconverted under thermodynamic control, Nicolaou, Chen, and co-workers targeted the synthesis of hopeahainol A (**40**), whose cycloheptane core would be assembled through a 7-*exo* cyclization onto a cationic *para*-quinone methide intermediate (Scheme 32).

In the forward sense, benzylic alcohol **187** was esterified with phenylglyoxalic acid **188** to give keto ester **189**. Exposure of **189** to 4-methoxyphenyl magnesium bromide resulted in selective addition to the aryl ketone, followed by desilylation gave **190** as a 1:1 mixture of diastereomers. While **190** was formed as a diastereomeric mixture, this was inconsequential for subsequent synthetic operations, as the stereochemical information at these centers was ultimately destroyed.

As previously demonstrated by the Snyder group in the context of resveratrol oligomer synthesis, treatment of benzylic

Scheme 32. Total Synthesis of Hopeanol and Hopeahainol A by Nicolaou and Chen
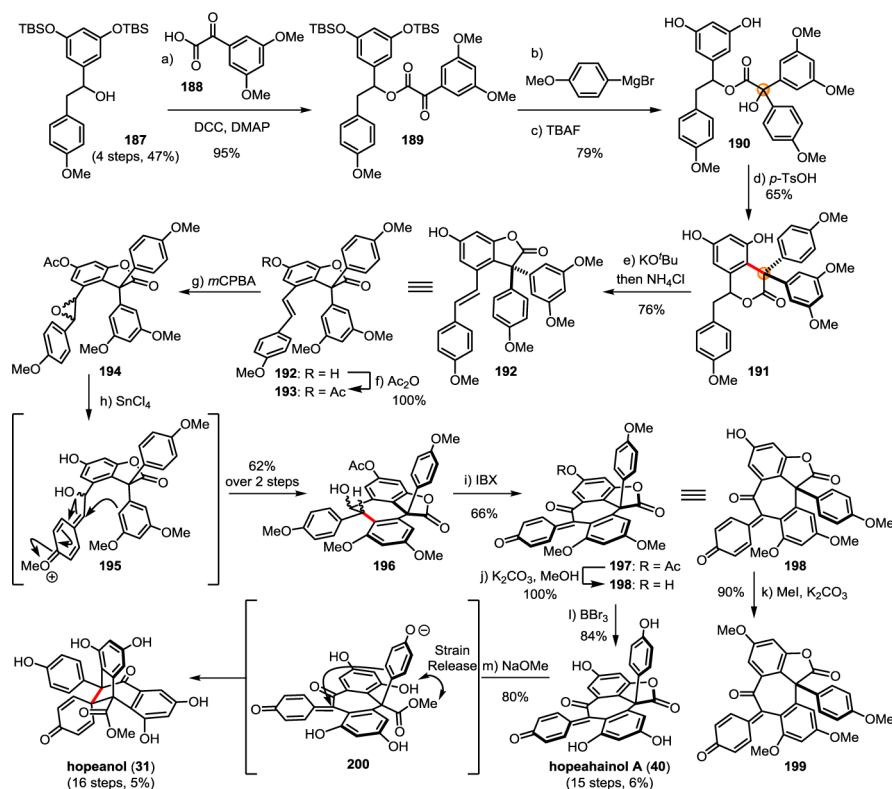
alcohols such as **190** with Brønsted acids promotes rapid ionization to generate reactive carbocations. Indeed, exposure of **190** to TsOH facilitates *para*-OMe-assisted ionization to generate a highly electrophilic *para*-quinone methide cation which engages the pendant resorcinol ring in Friedel−Crafts alkylation, yielding lactone **191**. Treatment of the lactone with KO*t*Bu followed by acidification with saturated aq NH$_4$Cl resulted in rearrangement to *γ*-lactone **192**. Geometric considerations suggest that this mechanism proceeds via an E2-elimination of the lactone, followed by condensation of the free phenol onto the acid. Acetylation of the remaining phenol (**193**), followed by epoxidation of the stilbene gave **194** as a 1:1 mixture of epoxide stereoisomers. Exposure of this material to Lewis acid (SnCl$_4$) promoted regioselective epoxide opening to generate the cationic quinone methide **195**, which was trapped by the adjacent resorcinol ring through a 7-*exo* Friedel−Crafts alkylation to give **196** as a 2:1 mixture of diastereomers. Comparison of **196** (a protected adduct of vaticahainol A **47**) with the natural products reveals that it is only two oxidation states away from the protected form of hopeahainol A (**40**). This redox adjustment was made in a single operation using an excess of IBX,[193,194] giving the *α*-keto quinone methide compound **197**. Exchange of the acetyl group for a methyl group afforded permethyl hopeahainol A (**199**), whose ^{1}H NMR matched those reported for this derivative.[86] Treatment with BBr$_3$ effected global demethylation to give the desired hopeahainol A (**40**, 4.6 mg). Methanolysis of the strained *γ*-lactone under alkaline conditions produced the ring-opened intermediate **200**, which adopts a conformation that permits spontaneous rearrangement to hopeanol (**31**, 0.8 mg). This impressive transformation occurs in the reverse direction of that which had been proposed; in fact, attempted conversions of hopeanol (**31**) to hopeahainol A (**40**) were unsuccessful

under a variety of conditions, demonstrating the utility of synthesis in elucidating plausible biosynthetic pathways. In their follow up report,[195] these researchers were able to synthesize the natural products in enantiomerically pure form by employing an Itsuno−Corey[196,197] reduction to establish the absolute configuration of starting bibenzyl **187**. Through their studies, Nicolaou and Chen were able to confirm the reported acetylcholinesterase inhibitory activity of hopeahainol A (**40**) but not the reported cytotoxic activity of hopeanol (**31**).

7.1.5. Snyder's Syntheses of Heimiol A, Hopeahainol D, Hopeahainol A, and Hopeanol. Encouraged by their success with electrophilic cascade cyclizations of triaryl building blocks, Snyder and co-workers targeted the synthesis of dibenzocycloheptanes, which are present in a number of resveratrol based oligomers.[185] Here, the preferred cyclization mode of the stilbene precursor was modified by utilizing benzophenone **201**, an oxidized variant of the previously employed doubly benzylic alcohols **167/173**. Upon electrophilic activation of the stilbene with Br$_2$, the desired cycloheptanone was formed via the intermediacy of a cationic *para*-quinone methide (Scheme 33). However, upon exposure to AgOAc in the presence of AcOH, this material underwent an unexpected aryl migration (presumably via dearomatized phenonium **204**), ultimately providing the non-natural compounds **206** and **207**, which are methylated congeners of the natural products hemsleyanol E (**49**) and diptoindonesin D (**50**), respectively (section 4.2, Scheme 6).

On the basis of these preliminary studies, Snyder and co-workers sought to exploit the instability of the benzylic halide substrates of type **202** for the synthesis of strained bicyclic natural products heimiol A (**37**) and hopeahainol D (**38**).[198] Through redesign of the parent triaryl building block **201**, these researchers were able to access the core structure of these

Scheme 33. Preliminary Efforts Towards Dibenzocycloheptanones by Snyder and Coworkers

lactol **210**, which the authors rationalized on the basis of steric encumbrance from the phenol ring of perbenzylated **209**. A subsequent Kishi reduction[205] served to rectify the oxidation state of **211** to that of the natural products and resulted in epimerization of the stereogenic center formed in the previous step, presumably via an intermediate *para*-quinone methide cation. Hydrogenolysis of **212** gave the natural product hopeahainol D (**38**, 3.3 mg) whereas epimerization could again be achieved under Lewis acidic conditions, thus yielding the natural product heimiol A (**37**, 0.5 mg).

On the basis of their ability to form cycloheptanones using electrophilic cyclization chemistry, Snyder and co-workers were able to design a route to the natural products hopeanol (**31**) and hopeahainol A (**40**) (Scheme 35).[206] It was found that the cyclization of triaryl precursor **201** could be accomplished using Brønsted acid rather than electrophilic halides. This was an important development as it enabled the key cyclization without introducing atoms to the molecular framework that are not part of the natural products. Notably, a shorter route (4 steps, 56%) to **201** was now available through direct, regioselective bromination of permethyl resveratrol. Vinylogous protonation of **201** using *para*-TsOH generated an intermediate cationic *para*-quinone methide that was captured through a 7-*exo* cyclization by the pendant resorcinol ring to give **213**. Leveraging the homologation chemistry employed in their synthesis of heimiol A (**37**) and hopeahainol D (**38**) (*vide supra*), the researchers were able to convert the cycloheptanone **213** into the diol **214**. Here, the use of a Brønsted acid (AcOH) to promote the epoxide opening resulted in trapping by the conjugate base (acetate) rather than Meinwald rearrangement. Oxidation of the primary alcohol to aldehyde **215** followed by addition of 4-methoxyphenyl magnesium bromide gave diol **216a/b** as a 1.3:1 mixture of epimers in favor of **216b**. Next, a number of Brønsted acids were screened in an effort to promote a Pinacol rearrangement[207,208] of the diol. They found that the 1 equiv of VAPOL phosphoric acid **217**[209] could efficiently promote the Pinacol rearrangement of **216b** with high diastereoselectivity (>18:1 dr). Varying yields and epimeric ratios at the newly formed quaternary center of **218** were obtained depending on the acid used, with enantiopure phosphoric acids giving the best results. While the carbon framework of **218** was consistent with that of the natural products, the oxidation state needed to be increased by four. Three of these oxidations could be accomplished in a single

molecules using a halolactonization/Friedel−Crafts cascade (Scheme 34). Namely, homologation of triaryl ketone **201** through a three-step sequence entailing Johnson−Corey−Chaykovsky epoxidation,[199,200] Meinwald rearrangement,[201] and Pinnick−Lindgren oxidation[202,203] yielded the corresponding acid **208**. Here, the pendant carboxylic acid serves as a nucleophilic trap for the labile benzylic halide formed upon electrophilic activation of the stilbene. Whether δ-lactone or cycloheptanone formation takes place first is unclear, but rapid construction of the bicyclo[3.2.2]nonane core structure **209** present in epimeric natural products heimiol A (**37**) and hopeahainol D (**38**) was achieved. A number of electrophilic halide sources were screened, with the I⁺ source IDSI [(Et₂SI)₂Cl·SbCl₆][204] being the only one to provide the desired product **209** in useful yields. Unfortunately the yield of this transformation is not reported, but it can be inferred that it proceeds in 40−50% conversion based on previously reported yields for the global demethylation of other resveratrol dimers.[185,189]

At this point, the methyl groups were exchanged for benzyl ethers for fear that the harsh conditions required for demethylation may result in destruction of a late-stage intermediate. Benzyl protection at the outset was not feasible because it interfered with the homologation sequence (**201** → **208**). Nucleophilic addition of 4-benzyloxyphenyl lithium to the perbenzylated lactone **209** gave a single diastereomer of

Scheme 34. Synthesis of Heimiol A and Hopeahainol D by Snyder et al.

Scheme 35. Synthesis of Hopeahainol A and Hopeanol by Snyder et al.

Scheme 36. Chen's Synthesis of Malibatol A and Shoreaphenol

step by treatment of **218** with Jones reagent, giving 27% of spirocyclohexadienone **220** through the intermediacy of phenonium **219**. Surprisingly, the aldehyde was not oxidized under these conditions. Compound **220** could be converted to the protected hopeanol (**221**) through Pinnick–Lindgren oxidation and esterification, but its deprotection was not possible. A number of synthetic precursors also failed to deprotect using standard BBr₃ conditions, resulting in decomposition and/or rearrangement of the material. Ultimately, the researchers found that acid **222**, obtained by Pinnick–Lindgren oxidation of **218**, could be dealkylated with BBr₃, with co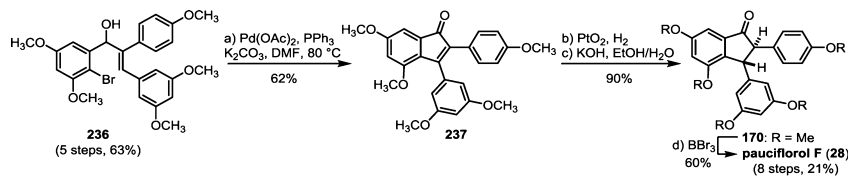ncomitant formation of the γ-lactone yielding dibenzocycloheptane **223**. This compound was then immediately protected with benzyl bromide. The three remaining oxidations were accomplished in one pot using ceric ammonium nitrate (CAN). This gave a perbenzyl derivative which could be dealkylated using BCl₃ to reveal the natural product hopeahainol A (**40**, 60 mg) in good yield. Methanolysis using the conditions reported by Nicolaou and Chen gave hopeanol (**31**, 11 mg).

7.1.6. Chen's Synthesis of Malibatol A and Shorea-phenol (Hopeafuran). In 2010, Chen and co-workers disclosed a synthesis of malibatol A (**44**) and shoreaphenol (**45**), two benzofuran-containing resveratrol dimers (Scheme 36).[210] Chen's strategy to these natural products was conceptually similar to that of Kim and Choi (see section 7.2.3),[219] consisting of benzofuran construction followed by electrophile-promoted 7-membered ring formation. From benzophenone **224**, reminiscent of those used by Snyder and co-workers in their synthesis of resveratrol dimers,[185] benzofuran synthesis was achieved by deprotonation of the

benzyloxy ether using lithium tetramethylpiperidide (LiTMP), attack of the resultant alkyl lithium onto the ketone, and acid-promoted dehydration. Epoxidation followed by a one-pot cyclization/demethylation sequence gave malibatol A (**44**). Further oxidation afforded shoreaphenol (hopeafuran) (**45**).

7.1.7. Synthesis of Laetevirenol A by Heo et al. In 2012, Heo and co-workers disclosed a synthesis of laetevirenol A (**62**) (Scheme 37),[211] a member of a dimeric subclass of resveratrol oligomers containing phenanthrene ring systems

Scheme 37. Synthesis of Laetevirenol A by Heo et al.

Scheme 38. Synthesis of Pauciflorol F by She and Pan

Scheme 39. Mizoroki−Heck/Friedel−Crafts Sequence To Access Oxidized Forms of Resveratrol Dimers

that are likely generated biosynthetically through an oxidative 6π-electrocyclization from parthenocissin A (**61**), as demonstrated by Pan et al. (see section 5.5.1).[102] Retrosynthetically, the strategy was to construct the phenanthrene first through a one-pot Suzuki−Miyaura coupling/aldol condensation cascade, with late-stage formation of the indane through an intramolecular Friedel−Crafts cyclization onto triaryl-substituted olefin **232**. Phenylacetonitrile **226**, prepared in two steps from dimethoxy benzyl bromide, was subjected to cross coupling with aldehyde **227** under microwave irradiation in the presence of base, providing the desired phenanthrene **228** in good yield. Hydrolysis of the nitrile and peptide coupling afforded the corresponding Weinreb amide, which was efficiently converted to triaryl ketone **230** upon treatment with the phenyl Grignard reagent **229**. The final arene was introduced through another Grignard addition, and dehydration to the required olefin **232** was achieved using Brønsted acid. Toluene sulfonic acid proved to be best-suited for this transformation, affording a 5:1 ratio of E/Z alkene isomers. In fact, prolonged exposure to TsOH with heating also promoted the desired intramolecular Friedel−Crafts reaction to **235**, albeit in modest yield. Alternatively, exposure of **232** to FeCl₃ promoted oxidative cyclization to acephenanthrylene **233**, as was found by Sarpong (section 7.2.2). This was converted into cis-permethyl laetevirenol A (**234**) via catalytic hydrogenation.[216] Demethylation of **235** proceeded quantitatively to give laetevirenol A (**62**).

7.2. Synthesis of Resveratrol Dimers Using Transition-Metal Catalysis

7.2.1. She and Pan's Synthesis of Pauciflorol F by a Pd-Mediated Intramolecular Heck Cyclization.
In 2006, She, Pan, and co-workers disclosed the first de novo approach to resveratrol dimers, featuring a Pd-catalyzed intramolecular 5-endo Mizoroki−Heck cyclization[212,213] onto an allylic alcohol (Scheme 38).[214] While the key substrate **236** could be synthesized in just 5 steps using well-established methods, two of these steps were redox manipulations of the benzylic carbon. Nonetheless, reacting **236** with Pd(OAc)₂/PPh₃ resulted in its conversion to indenone **237**, presumably via a tandem Mizoroki−Heck cyclization/Saegusa−Ito oxidation[215]

sequence. The researchers were able to reduce the α,β-unsaturated enone to the corresponding cis-2,3-dihydroindanone (not shown) and epimerize the α-stereogenic center under alkaline conditions to give **170**. Finally, global demethylation using BBr₃ revealed the natural product pauciflorol F (**28**).

7.2.2. Sarpong's Synthesis of Pauciflorol F and related Carbogenic Cores by a Pd-Mediated Intermolecular Heck Cyclization Cascade.
Two years after the seminal publication by Snyder,[185] Sarpong and co-workers disclosed an alternative approach to the carbogenic cores of resveratrol dimers.[216] Snyder had demonstrated that bromoresveratrol derivative **238** could be efficiently lithiated and reacted with benzaldehydes to form the corresponding alcohols. Sarpong and co-workers envisioned that metalation of this substrate with a redox active catalyst such as palladium would, with appropriately designed substrates, lead to the construction of the indane and indanone cores of several resveratrol dimers. In particular, coupling of **238** with resveratrol-derived tolane **239** enabled rapid assembly of benzofulvene dimers representing the carbon skeletons of pallidol and related congeners (Scheme 39). Here, oxidative insertion of Pd⁰ into the C−Br bond produces a π-acidic Pdᴵᴵ−aryl species that coordinates the electron-rich tolane. Polarization of the alkyne by the para-disposed methoxy group facilitates regioselective migratory insertion to the Pdᴵᴵ−aryl bond, in turn generating a nucleophilic vinyl palladium species **240**. Upon coordination of the neighboring olefin, this vinyl−Pd undergoes sequential insertion and β-hydride elimination to yield **241**, an unsaturated form of the natural product parthenocissin A (**61**). Treatment of **241** with FeCl₃·6H₂O resulted in the production of **246**, likely through a series of single electron oxidation/deprotonation events (**242** → **245**). As previously described, She and co-workers demonstrated that indenone dimer **237** could be converted to the natural product pauciflorol F (**28**) (Scheme 38).[214] On the basis of the high level of regiocontrol observed in their synthesis of benzofulvene dimers,[216] Sarpong and co-workers envisioned that a similar Heck coupling strategy using a different aryl-

Scheme 40. Sarpong's Synthesis of Pauciflorol F Using a Larock Annulation
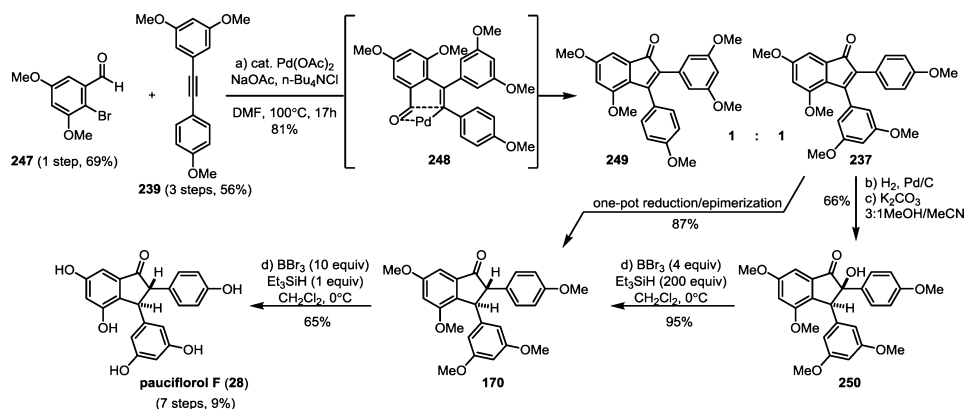
Scheme 41. Synthesis of Benzofuran-based Resveratrol Dimers Using C–H Activation
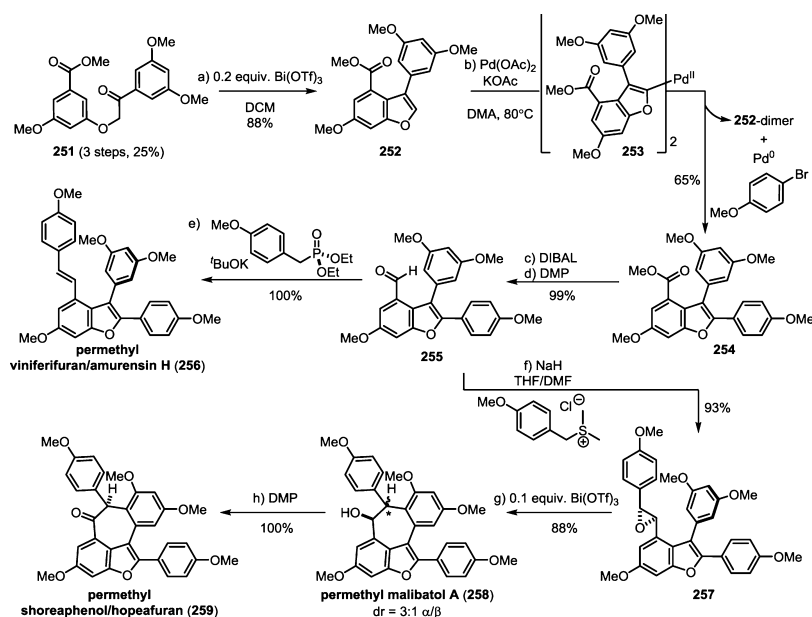
halide electrophile could provide a highly convergent route to **237**, and therefore an efficient synthesis of pauciflorol F (**28**).[217] Namely, the use of a brominated benzaldehyde precursor **247**, rather than the previously employed stilbene derivative, would provide the corresponding indenone **237**, through a Larock-type annulation (Scheme 40).[218] In practice, the cascade cyclization proceeded in good yield (81%), although a 1:1 mixture of regioisomers **237/249** with respect to the tolane-derived arenes was obtained.

Reduction of **237** to the corresponding *cis*-2,3-diaryl indane was accomplished by hydrogenation over Pd/C, as was performed by She et al.[214] An interesting observation was made by Sarpong and co-workers during their subsequent attempts to epimerize *cis*-**170** to its *trans* isomer, leading them to bring into question the structural assignments made by Snyder and She in their respective publications.[189,214] Instead of the reported *trans*-indenone **170**, the authors isolated the α-ketol product **250**. By comparison of the spectral data for **250** to those reported for **170**, it appeared as though each of these groups had also obtained **250** in similar transformations. Undesired formation of **250** could be avoided by performing the reduction and epimerization in one pot, suggesting that O$_2$ was promoting the enol oxidation. However, Sarpong and co-

workers again ran into difficulty when they attempted to deprotect **170** using the conditions employed by She and Snyder, isolating just 35% (conditions not shown) of pauciflorol F (**28**) as compared to the reported 86% and 60% yields.[185,214] The use of α-ketol **250** in these experiments would require both reduction (via disproportionation of **13**) and global dealkylation to complete the synthesis of **28**. To gain insight into the feasibility of this transformation, Sarpong and co-workers subjected **250** to the reported conditions for the deprotection and obtained just 10% of pauciflorol F (**28**), suggesting that disproportionation may be possible but is inefficient under these conditions. On the other hand, performing the deprotection of **170** in the presence of added reductant (Et$_3$SiH) improved the yield of the natural product pauciflorol F (**28**) substantially.

7.2.3. Kim's Syntheses of Benzofuran-Containing Resveratrol Dimers Using C–H Activation. In 2009, Kim and Choi reported a general strategy to access the privileged 7,5-ring system ubiquitous in resveratrol-derived oligostilbe-noids,[219] relying on the well-established acid-promoted cyclo-dehydration of α-aryloxyketones to form benzofuran **252** from **251** (Scheme 41).[220] Bi(OTf)$_3$ was found to be optimal from the Lewis and Brønsted acids that were screened. Arylation at

Scheme 42. Synthesis of Diptoindonesin G using C−H Activation
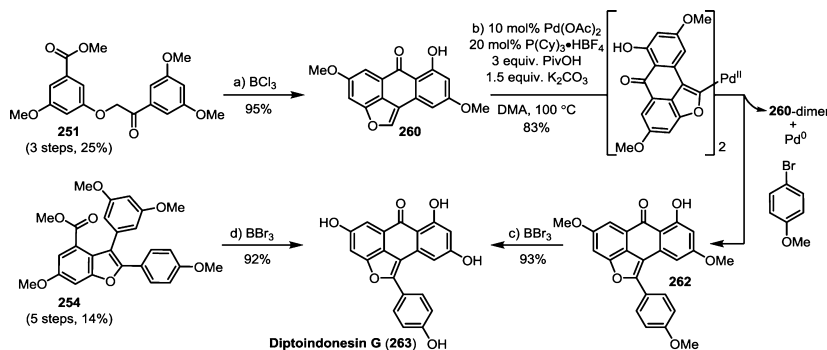
Scheme 43. Synthesis of Pauciflorol F Using a Nazarov/C−H Arylation Sequence
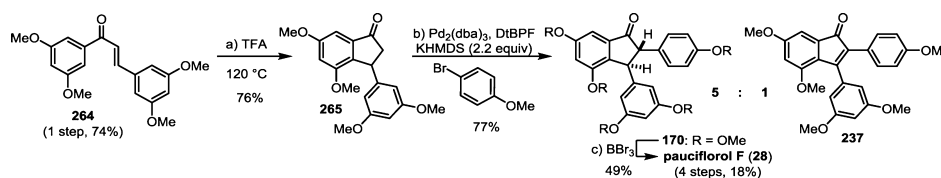
C-2 of the benzofuran was accomplished through a Pd-mediated Heck cross coupling that is initiated via direct C−H activation.[221] Here, C-2 palladation likely takes place through either an electrophilic aromatic substitution (S$_E$Ar) or concerted metalation-deprotonation (CMD)[222] process to form bisaryl-Pd^{II} complex **253**. Reductive elimination gives a dimer of benzofuran **252** and generates the required Pd^0-complex for oxidative addition to 4-bromoanisole. The authors consistently isolated a mixture of desired **254** and the dimer of **252**, suggesting that the metalation/reductive elimination pathway is competitive with oxidative addition to the Ar−X bond. This is perhaps unsurprising given that an electron-rich aryl halide was used, 20 mol % of the Pd^{II} precatalyst was employed, and the reaction was run open to air.

Reduction of ester **254** provided the aldehyde **255**, which was the branching point for the synthesis of each of the three natural product analogues. Olefination by a standard Horner−Wadsworth−Emmons protocol yielded viniferifuran analogue **256**. Epoxidation of **255** by a Johnson−Corey−Chaykovsky protocol afforded racemic **257**. Exposure of **257** to acidic conditions at cryogenic temperatures gave malibatol A analogue **258** and its epimer in a product distribution that was influenced by the identity of the acid catalyst. Subsequent oxidation yielded shoreaphenol analogue **259**.

In a subsequent report, Kim and co-workers achieved the synthesis of diptoindonesin G (**263**) using intermediates **251** and **254** (Scheme 42).[223] From **254**, a tandem Friedel−Crafts acylation/global demethylation was possible using the highly acidic BBr$_3$. Alternatively, treatment of **251** with the less acidic BCl$_3$ promoted both cyclodehydration and Friedel−Crafts acylation, but only led to dealkylation of the phenol *ortho* to the so-formed diaryl ketone. Arylation of the benzofuran was again accomplished by direct C−H activation, this time using modified Fagnou conditions.[224] In combination with the use of bulky phosphine ligands, these conditions dramatically improved the yield of the cross-coupling as compared to the previously and eliminated formation of significant amounts of homodimeric products.

7.2.4. Yang and Heo's Syntheses of Pauciflorol F by a Pd-Mediated α-Arylation. In 2011, Yang and co-workers

reported an approach to pauciflorol F (**28**) employing an α-arylation reaction of 3-aryl-indanone **265** (Scheme 43).[225] Here, **265** was prepared through a Nazarov cyclization[226] of the chalcone precursor **264**, a strategy that has since been utilized by other groups for the synthesis of this natural product.[211,227,228] While the synthesis was racemic, the arylation was diastereoselective, providing exclusively the *trans*-2,3-diaryl indanone derivative (**170**). Under the optimized cross-coupling conditions, an excess of KHMDS was used, resulting in the formation indenone **237** as a byproduct through product enolization and Saegusa−Ito oxidation. Notably, the product distribution was influenced by the precatalyst, ligand, and base employed. Heo and co-workers were able to largely eliminate this problem by the use of fewer equivalents of a weaker base (NaO^{t}Bu).[211] Additionally, these researchers were able to achieve the first asymmetric synthesis of (+)-pauciflorol F (**28**) by subjecting She's indenone intermediate **237** (*vide supra*)[214] to an enantioselective baker's yeast-promoted conjugate reduction. Flynn and co-workers subsequently achieved the asymmetric synthesis of both enantiomers of pauciflorol F using a chiral auxiliary-directed Nazarov cyclization,[228] and found that Heo and co-workers had misassigned the configuration of the natural product generated through their synthesis.

7.2.5. Studer's Synthesis of Indane Dimers by a Pd-Catalyzed Decarboxylative Arylation and Oxidative Heck Coupling. As discussed previously, the two types of indane dimers formed in nature fundamentally differ only in the substitution pattern of the phenol and resorcinol rings about the C−2 and C−3 positions of the indane ring. Studer and co-workers therefore envisaged that a synthetic route that introduced these aryl groups from a common intermediate would be an attractive and flexible strategy for oligomer synthesis.[146] Retrosynthetically, these researchers arrived at intermediate **266** as a suitable candidate for this purpose (Scheme 44). Previously, Studer et al. had demonstrated that doubly allylic quaternary carboxylates such as **266** can be decarboxylated and regio- and stereospecifically coupled with a variety of aryl iodides.[229,230] Application of this method to **266** gave the desired arylated indene products **267** and **268** with

Scheme 44. Synthesis of Resveratrol Dimers using a Decarboxylative Arylation/Oxidative Mizoroki−Heck Sequence

Scheme 45. Asymmetric Synthesis of δ-Viniferin Using a Rh-Catalyzed C−H Insertion

complete regioselectivity in moderate yields (65% and 57%, respectively, Scheme 44).

To complete the syntheses of the gross structures of regioisomers quadrangularin A (**17**) and ampelopsin D (**25**), these researchers again employed their own cross-coupling methodology: a nitroxide-mediated oxidative Heck arylation.[231] As with the previous step in the synthesis, this reaction was more effective for the quadrangularin A core **178** than for **172**, the core of ampelopsin D. Of note, TEMPO derivative **269** had to be used for the ampelopsin D substrate in order to suppress formation of an unidentified byproduct. The coupling reactions were completely regioselective for each of the boronic acids used, adding exclusively to the less substituted carbon of the indene. Additionally, the subsequent β-hydride eliminations were completely regio- and stereoselective, providing exclusively the exocyclic alkenes as the (E)-isomers. The authors rationalize the (E)-selectivity on the basis of allylic strain minimization. Finally, C−C bond formation took place from the opposite face of the indene than the C−3 aryl group, thereby giving products **172** and **178** with the requisite *trans*

relative configuration. Each of these compounds were deprotected using BBr$_3$ to reveal the natural products quadrangularin A (**17**) and ampelopsin D (**25**). Quadrangularin A precursor **178** was converted to the natural product pallidol (**18**) by a known two-step procedure.[227]

7.2.6. Shaw's Asymmetric Synthesis of δ-Viniferin by C−H Insertion. Recently, Shaw and co-workers disclosed a general strategy to dihydrobenzofuran synthesis via the intramolecular C−H insertion of diaryl rhodium-carbenoids to methylenes of *para*-methoxybenzyl protected phenols.[232] This is a highly impactful development as 2,3-diaryl-dihydrobenzofurans have traditionally been difficult to synthesize in an efficient manner. The reported method utilizes easy to prepare starting materials, and occurs with high levels of diastereo- and enantiocontrol. Interestingly, the insertion preferentially yields the *cis*-diastereomer. However, it has been shown that *cis*-dihydrofurans bearing an anisole or phenol at the 2-position can be epimerized under acidic[233] or basic[234] conditions. Shaw and co-workers exploited this for the asymmetric synthesis of δ-viniferin (**10**) (Scheme 45).

Scheme 46. Paradigm for the Synthesis of Higher-Order Oligomers through Iterative (A) Homologation and (B) Dihydrobenzofuran Synthesis

Scheme 47. Synthesis of Higher-Order Oligomers Containing Bicyclo[3.3.0]octane Cores

The requisite diaryl hydrazone **271** was easily synthesized by the condensation of hydrazine on to benzophenone **270**. Oxidation of the hydrazone to the corresponding diazo compound by MnO$_2$ followed by exposure of the crude material to Rh$_2$(S-PTAD)$_4$ effected the smooth conversion to *cis*-dihydrobenzofuran **272** with high diastereo- and enantioselectivity. A one-pot demethylation/epimerization was accomplished by treatment with BCl$_3$/TBAI, and the phenols were reprotected to give peracetyl compound **273**. A Mizoroki–Heck olefination with styrene **274** followed by global deprotection provided (+)-(*E*)-δ-viniferin (**10**),[112] representing the first asymmetric synthesis of a dihydrobenzofuran-containing resveratrol dimer.

7.3. Synthesis of Higher-Order Resveratrol Oligomers: Reagent-Controlled Bromination of Resveratrol Dimers as a General Strategy for Trimer and Tetramer Synthesis

The stereo- and regiochemical outcome of the bromonium-promoted cascade cyclizations developed by Snyder et al. (section 7.1.1) for the synthesis of bicyclic dimers has significant consequences for the synthesis of higher-order resveratrol oligomers. Although the oxidations involved in the biosynthesis of resveratrol oligomers proceed via single electron transfers, these polar oxidations nonetheless provide insight into the substrate contribution to the regiochemistry observed during oligomer biogenesis.[235,236] While the requirement for hydrodehalogenation negatively impacts the step- and atom-economy for the synthesis of dimeric natural products, the complete regioselectivity observed for these transformations has enabled the synthesis of a number of higher-order oligomers. Recall that the carbocyclic scaffolds present at the cores of these dimeric natural products are conserved across the

entire series of natural products belonging to this class. Therefore, these seemingly extraneous aryl bromides actually provide functional handles with which to target the construction of 2,3-diaryldihydrobenzofurans for the synthesis of trimeric and tetramer resveratrol-derived oligomeric natural products (Scheme 46, path A). Through an impressive series of syntheses, Snyder and co-workers have successfully capitalized on this opportunity.[237] These endeavors are described in the sections below.

7.3.1. Synthesis of Higher-Order Oligomers Containing Bicyclooctane Cores. Treatment of the tribromo-pallidol derivative **182** with 2 equiv of *n*-butyllithium resulted in selective metal–halogen exchange of the aryl bromides (Scheme 47). The product monobromide (not shown) was then exposed to 1 equiv of NBS resulting in selective bromination of the less hindered resorcinol ring to give **276**. Another lithium halogen exchange, this time using *tert*-butyllithium (3 equiv), resulted in formation of the corresponding dianion, which was selectively reacted with 3,5 dimethoxy benzaldehyde at the aryl lithium (not shown). This is somewhat surprising given the greater reactivity expected of a tertiary aliphatic anion (pK$_a$ ~53) versus that of an aryl-lithium species (pK$_a$ ~43), and suggests that perhaps sterics are responsible for the observed selectivity. The product was then homologated to aldehyde **277** using conditions employed in the synthesis of dimeric products heimiol (**37**) and hopeahainol D (**38**) (see Scheme 46, path A).[198] The intermediate aldehyde **277** was obtained as a 5.5:1 mixture of chromatographically separable diastereomers. During the course of the homologation sequence, the methoxy protecting groups were exchanged for benzyl ethers. In spite of the harsh conditions required for

Scheme 48. Synthesis of Higher-Order Oligomers Containing Bicyclo[3.2.1]octane Cores
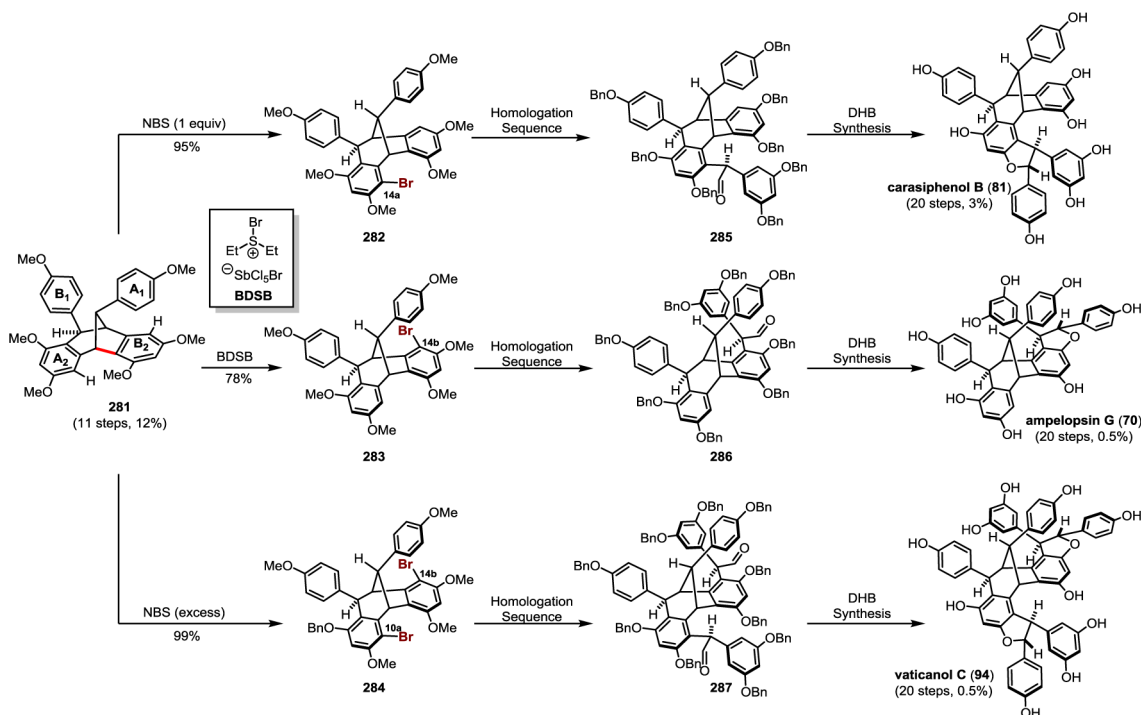
demethylation (35−45 equiv BBr$_3$, sealed tube, 70 °C, 3−4 days), the deprotected compound was obtained in 85−95% yield.

Construction of the critical dihydrobenzofuran moiety was achieved through a three-step sequence (Scheme 46, path B) consisting of Grignard addition of 4-benzyloxyphenyl magnesium bromide to the aldehyde 277, global hydrogenolysis, and acidic resin-promoted C−O bond formation, presumably via the intermediacy of benzyl alcohol derived cationic para-quinone methide intermediates such as 275. The benzylic alcohols survive global hydrogenolysis and were carried on as a mixture of diastereomers (dr ∼10:1) through the dihydrobenzofuran synthesis to give carasiphenol C (66, 25 mg). The trans-product of 66 is thermodynamically favored, and is likely enriched under the acidic conditions employed for the cyclization. Isolation of the natural product was accomplished by reverse-phase HPLC.

For the synthesis of resveratrol tetramer ampelopsin H (67) (Scheme 47), debrominated pallidol derivative 278 was brominated regioselectively on each of the resorcinol rings to give C$_2$-symmetrical 279, which was subjected to two-directional[238,239] homologation to yield dialdehyde 280 in good yield (Scheme 46, A). Aldehyde 280 was obtained as a diastereomeric mixture (dr ∼1.8:1), from which recrystallization of the major (C$_2$-symmetric, shown) diastereomer was possible. Epimerization of the minor isomer could also be achieved, but required strong base (KHMDS), which the authors propose is due to the resistance of the aldehyde to enolization caused by its proximity to the electron rich aromatic rings. From here, the identical dihydrobenzofuran synthesis (Scheme 46, path B) afforded the desired natural product ampelopsin H (67, 6.7 mg), again as an approximately 10:1 mixture of the desired natural product and what is presumably a dihydrobenzofuran stereoisomer.

With a [3.3.0] trimer and tetramer completed, these researchers turned their attention to the [3.2.1] ampelopsin F

derivative 281 as a starting point for extension of this chemistry to higher-order oligomers containing this core.[237] Unlike permethyl pallidol (278), regioselective monobromination of permethyl ampelopsin F (281) was only possible through a combination of reagent and stoichiometry control. Specifically, treatment of 281 with 1 equiv of NBS resulted in selective bromination of the C$_{14a}$ on the resorcinol A$_2$ yielding 282. The use of an in-house developed reagent, bromodiethylsulfonium bromopentachloroantimonate(V) (BDSB),[240] selectively yielded 283 (Scheme 48). Other brominating reagents exclusively yielded 282 or 284. Finally, addition of 2 equiv of NBS smoothly transformed 281 to the dibromide 284. Application of the same alkylation/homologation/protecting group exchange/dihydrobenzofuran formation sequence to these intermediates provided the natural products, carasiphenol B (81, 2.4 mg), ampelopsin G (70, 2.0 mg), and vaticanol C (94, 1.2 mg). Impressively, the team demonstrated that this strategy was scalable and could isolate 55 mg of >90% pure carasiphenol C (66) from one deprotection/cyclization sequence.

7.3.2. Synthesis of Vaticanol A, an Indane-Derived Resveratrol Trimer.
In 2014, Snyder and co-workers completed the first total synthesis of a resveratrol oligomer containing a 7,5-fused indane ring system, vaticanol A (76) (Scheme 49).[147] Starting from permethyl pauciflorol F (170) the dibromoampelopsin D derivative 289 was prepared through a 6-step sequence previously developed for the synthesis of caraphenols B (27) and C (60).[188] Note that the styrenyl phenol is orthogonally protected with respect to the remaining arenes in the molecule; this was performed in an attempt to achieve selective quinone methide formation later in the synthetic sequence. Formation of the dianion of 289 through lithium-halogen exchange with subsequent addition of 3,5-dimethoxybenzaldehyde gave the monoalkylated product 290 without formation of its regioisomer or the doubly alkylated product. Oxidation gave biaryl ketone 291, which contains 5 of

Scheme 49. Total Synthesis of Vaticanol A Through *in Situ* Generation and Reactions of *para*-Quinone Methides
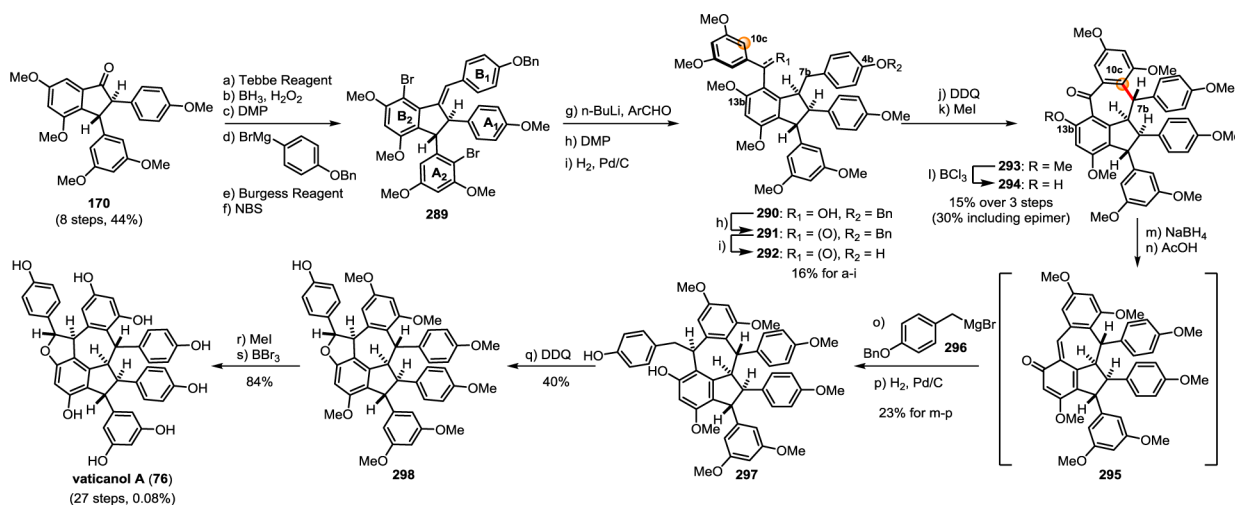

the 6 aromatic rings found in the natural product. Hydrogenolysis of **291** cleaves the benzyl ether and stereoselectively reduces the olefin, yielding **292** in 16% yield from **170**. A variety of oxidants were screened in an effort to selectively dehydrogenate the exposed phenol to its corresponding quinone methide. Ultimately, it was found that prolonged exposure to DDQ at room temperature oxidized the B_1 phenol of **292**, initiating 7-*exo-trig* cyclization (C_{10c}–C_{7b}). The subsequent global methylation gave **293** as 1:1 mixture of diastereomers at C_{7b}. A selective demethylation of the C_{13} methoxy group afforded dibenzocycloheptanone **294** in 15% yield over the 3 steps.

At this stage, 5 of the 6 aryl rings of the natural product were built into the framework. To complete the synthesis, a redox manipulation, addition of the final arene, construction of the dihydrobenzofuran, and global deprotection were required. The team planned to introduce the aryl ring through nucleophilic addition to an *in-situ*-generated *ortho*-quinone methide, which required adjustment of the oxidation state of **294**. Reduction with NaBH$_4$ provided the corresponding alcohol in 91% as a mixture of epimers, which, upon treatment with acetic acid, ionized to the *ortho*-quinone methide **295**. *In situ* exposure of this material to an excess of Grignard reagent **296** and hydrogenolysis of the benzyl ether afforded **297** in 25% over the three steps, along with 25% of the undesired product epimer. Oxidative dihydrobenzofuran closure was achieved by treatment of **297** with DDQ, providing the thermodynamically favored *trans* diastereomer of **298**. Attempts to directly deprotect **298** with BBr$_3$ were unsuccessful, necessitating methylation of the free phenol prior to exposure to BBr$_3$. This yielded a sample containing vaticanol A (**76**, 0.9 mg), whose spectral data matched those reported by Tanaka and co-workers. This remarkable achievement was possible through careful design of protecting group strategy which enabled selective *in situ* generation and cyclizations of *para*-quinone methides and is the state of the art in the synthesis of the resveratrol natural products.

7.3.3. Synthesis of 9-Membered Ring Containing Resveratrol Trimer, Caraphenol A. Recently, Snyder and Wright disclosed a synthesis of caraphenol A (**89**), a resveratrol trimer belonging to a subclass of resveratrol oligomers containing strained 9-membered rings (Scheme 50).[241] On the basis of a series of model studies, these researchers

demonstrated the viability of Friedel–Crafts chemistry for 9-membered ring formation under conformationally controlled conditions. As such, the synthesis of caraphenol A (**89**) commenced with **299**, which was prepared in 3 steps from 3,5-dibenzyloxy benzyl alcohol. Here, the researchers used the previously developed homologation/dihydrobenzofuran synthesis sequence (Scheme 46, paths A + B). The phenols were reprotected as benzyl ethers, and the silyl protecting group cleaved yielding benzofuran **301** in 54% yield from **299**. The resulting primary benzyl alcohol **301** was oxidized to the corresponding carboxylic acid through sequential Dess–Martin/Pinnick–Lindgren oxidations, and the product acid was esterified with **302** to give tetraaryl dihydrobenzofuran **303** in 81% overall yield. In a clever synthetic operation, this compound was subjected to an anionic Fries rearrangement[242,243] and *in situ* silyl ether formation to provide **304** in 80% yield, which possesses the correct connectivity of the aryl rings that will ultimately comprise the 9-membered ring. Another three-step homologation of the benzophenone, identical to that performed at the beginning of the synthesis, afforded benzyl alcohol **305**. Oxidation with DMP provided the corresponding ketone **306** in 82% overall yield from **304**, which, upon exposure to HCl, underwent cyclodehydration. Cleavage of the silyl ether afforded **308**/**307** as a 2.8:1 mixture of atropisomers. **307** could be readily interconverted to the required atropisomer **308** by thermal equilibration. Functional group interconversion of benzyl alcohol **308** to allyl alcohol **309** was achieved in two steps by a Dess–Martin oxidation followed by the addition of vinyl lithium to the corresponding ketone as 1:1 mixture of isomers. The doubly activated allylic/benzylic alcohol was ionized with MsOH, triggering a 9-*exo-trig* Friedel–Crafts reaction to provide the carbocycle **310**. Oxidative cleavage of the alkene **310** provided aldehyde **311** in 46% yield from **306**. Addition of the aryl Grignard reagent to **311** yielded the penultimate intermediate **312**, which was subjected to the usual conditions for debenzylation/dihydrobenzofuran formation (Scheme 46). The natural product, caraphenol A (**89**), was thus obtained in 23 steps from commercially available materials in an impressive 7.8% overall yield. Astonishingly, Wright and Snyder report isolating 317 mg in the final reaction, preparing as much as 600 mg of **89** thus far!

Scheme 50. Total Synthesis of Caraphenol A by Snyder and Wright
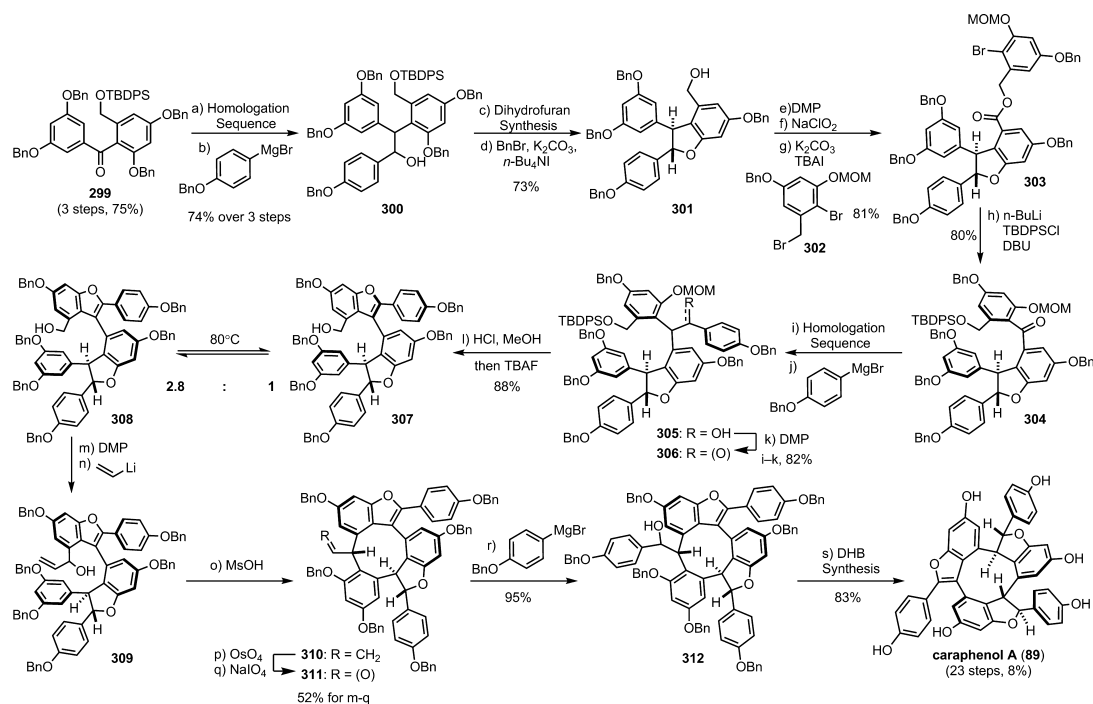
8. BEYOND THE PLANT: THERAPEUTIC POTENTIAL OF RESVERATROL OLIGOMERS

Since the popularization of resveratrol at the end of the 20th century, an enormous number of studies have been undertaken in an effort to define its pharmacological profile. In spite of these efforts, resveratrol's mode of action appears to be fairly indiscriminate when one considers the number of intracellular processes it has been claimed to influence. This "broad spectrum" biological activity is likely a reflection of the intrinsic reactivity of the trihydroxylated stilbene as a redox-active molecule. Mounting evidence suggests that resveratrol and its oligomers exert their effects via interference with signal transduction cascades and epigenetic pathways rather than direct inhibition of enzymes designated for specific purposes. Nonetheless, implementation of resveratrol in human therapeutic applications is forestalled by its poor bioavailability and an incomplete understanding of its pharmacodynamics. In light of this, interest in the pharmacological potential of resveratrol oligomers has recently increased, and preliminary explorations into their bioactivity are promising. Indeed, the probability of selective modification of targets within a chiral cellular environment is rapidly enhanced as a relatively small 2-dimensional molecule (resveratrol) is transformed into a complex 3-dimensional structure. Here, we present frontiers in this area of science with an emphasis on the mechanisms underlying observed biological activities.

8.1. Resveratrol Oligomers as Anticancer Agents

The biochemical processes accompanying carcinogenesis are loosely categorized into three major phases: tumor initiation, promotion, and progression.[244] In 1997, Pezzuto and co-workers reported that resveratrol was a potential cancer chemopreventive agent, exhibiting anti-initiation, antipromotion, and antiprogression activities.[12] In this study, these effects manifested themselves as antioxidant and antimutagenic behavior, inhibition of cyclooxygenase (COX-1, ED_{50} = 15 μM) and hydroperoxidase (ED_{50} = 3.7 μM), and induction of

promyelocytic leukemia cell differentiation (the phenomenon by which cancerous cells appear and behave like normal cells of the tissue in which they exist), respectively. Readers interested in the potential of resveratrol as an anticancer agent are directed to a recent review.[20] Here, we will focus on the resveratrol oligomers, which unsurprisingly have also attracted significant attention in this regard. However, most of these biological studies have required the laborious extraction and purification of the oligomers from plant matter.[245] Because the resveratrol-producing stilbene synthase is not constitutively expressed, these compounds are typically isolated as a minute fraction of the plant's weight. Obviously, this approach is limiting with respect to the diversity of assays that can be performed and the purity with which the subject compounds can be obtained. Nonetheless, the oligomers have demonstrated a broad range of interesting biological activities, and hold promise as a source of natural products-inspired drug development.

As is typical of most explorations into the biological activities of natural product classes, the resveratrol oligomers have primarily been examined for their anticancer properties (Table 6). This topic has recently been reviewed,[246] and therefore we will attempt to provide a concise overview of these studies with context as to the significance of the selected examples. The anticarcinogenic effects of resveratrol oligomers have principally been ascribed to cytotoxicity and induction of apoptosis, although antimutagenic and antiproliferative activities have also been observed. Unfortunately, many investigations in this area did not extend beyond initial toxicity studies of the oligomers against one or multiple cancer cell lines, which provide no information about the mechanisms of action. Several groups have since taken a more rigorous approach to these studies, and as a result we are beginning to understand the specific actions of these compounds within cells to which their observed biological activities can be attributed.

Table 6. Cytotoxicities of Resveratrol Oligomers Against Various Cancer Cell Lines

cell lines; refs	most active compd	(EC$_{50}$, μM)^a	cell lines; refs	most active compd	(EC$_{50}$, μM)^a
Cervical (Adeno)carcinoma			Colon (Adeno)carcinoma		
HeLa; 87, 247−251	pauciflorol B	2.8	DLD-1; 265, 285	vaticanol C	N/A
HSG; 252	sophorastilbene A	108.0	COLO-201; 265, 285	vaticanol C	N/A
KB; 66, 87, 141, 251, 253, 145	peracetyl ampelopsin A	0.8	Lung (Adeno)carcinoma		
Ovarian (Adeno)carcinoma			A-549; 250, 253, 254, 258, 272, 273	cis-vitisin A	0.93
1A9; 253	peracetyl ampelopsin A	1.0	NCI-H446; 269, 272, 273	α-viniferin	16.1
SK-OV-3; 254	cis-vitisin A	0.17	NCI-H460; 272	kobophenol A	200
Breast (Adeno)carcinoma			NCI-H1299; 250	vaticanol A	19.7
MCF-7; 247−250, 253, 255−258	peracetyl ampelopsin A	2.8	SPC-A-1; 272		
MDA-MB-231; 250, 257, 259	hopeachinol E	14.3	Liver Carcinoma		
BJMC-3879; 286	vaticanol C	8.0	Hep-G2; 248, 249, 258, 259, 274	hopeachinol J	12.4
BC-1; 141	(−)-vatdiospyroidol	4.2	SMMC-7721; 259	hopeachinol F	10.4
Leukemia			Clear Cell Renal Carcinoma		
P-388; 260, 289	(−)-hopeaphenol	5.2	Caki-1; 253	peracetyl ampelopsin A	5.5
EHEB; 261	N/A	N/A	Prostate (Adeno)carcinoma		
WSU-CLL and ESKOL; 261	ε-viniferin	6.7	LNCaP; 265	vaticanol C	N/A
Jurkat; 262	miyabenol C	29.4	PC-3; 265	α-viniferin	N/A
HL-60; 247, 252, 258, 289, 263−267	vaticanol C	3.0	Neuroblastoma		
K-562; 262, 265	miyabenol C	18.7	SH-SY5Y; 265, 275	vaticanol C	N/A
Myeloma			C6; 249	gnetin H	18.7
U-266; 262	miyabenol C	12.1	Sarcoma		
RPMI-8226; 262	miyabenol C	20.8	S-180; 276	extract-Vat. indica	29.5
Lymphoma			SaOS-2; 253	peracetyl ε-viniferin	11.3
U-937; 262, 265, 268	heyneanol A	6.6	Oral Squamous Carcinoma		
Colon (Adeno)carcinoma			HSC-2; 252	sophorastilbene A	27.0
HCT-116; 257, 259, 269, 270	α-viniferin	6.6	HSC-3; 252	(+)-α-viniferin	60.0
HT-29; 248, 249, 257, 269	α-viniferin	32.6	Malignant Melanoma		
Caco-2; 269	α-viniferin	16.1	SK-MEL-2; 253, 254	vitisin B	4.9
Col-2; 141	(−)-vatdiospyroidol	2.1			
HCT-8; 253	peracetyl ampelopsin	5.7			
SW-480; 265, 270, 285, 271	A vaticanol C	3.2			

^{a}All values reported as (μg/mL) have been converted to EC$_{50}$ (μM) for the sake of comparison.

8.2. Potential Modes of Action: Case Studies on the Cellular Effects of Two Resveratrol Oligomers

8.2.1. α-Viniferin: A Resveratrol Cyclotrimer with Diverse Biological Activity. The structure of α-viniferin (**6**) was first proposed by Langcake and Pryce in 1977.[37,58] This oligomer has now been identified from a number of plants in the Fabaceae and Cyperaceae families that have traditionally been employed in East Asian folk medicine. It has consistently outperformed other compounds within this class in assays of cytotoxicity, anti-inflammatory activity, and enzyme inhibition. As such, it represents one of the most well-studied resveratrol oligomers in the context of biological activity. Here, we will present the molecular mechanisms by which this compound exerts its biological effects, which could very well be representative of the mode of action for the larger class of natural products. Much of the knowledge that we have on this subject has come from the dedicated efforts of Kim and co-workers, who have thoroughly investigated the cellular effects of α-viniferin (**6**) from both a phenotypic and genotypic perspective.[277−279]

Initial work revealed that **6** could inhibit the cyclooxygenase activity of prostaglandin H$_2$ synthase (IC$_{50}$ = 7.0 μM), a pharmacological target for the treatment of fever, inflammation, and heart disease. To better understand this behavior, these researchers explored the effects of **6** on the activity and expression of cyclooxygenase (COX) isozymes and inducible nitric oxide synthase (iNOS). α-Viniferin showed a dose-dependent inhibitory effect on COX-2 activity but only weakly inhibited COX-1. COX-1 is expressed constitutively in most tissues and is essential to functions other than inflammatory response, while COX-2 is up-regulated in response to inflammatory mediators such as lipopolysaccharides (LPS) or cytokines. Additionally, **6** inhibited the transcription of COX-2 genes in LPS-activated murine (mouse) macrophages. Likewise, **6** inhibited the synthesis of the iNOS transcript. Transcription of the iNOS gene, like that of COX-2, is performed as a response mechanism. The nitrite content in the culture medium of these macrophages could also be used as an indicator of nitric oxide (NO) production when measured against a control. Nitric oxide (NO) plays an important role in cellular signaling, and iNOS has been implicated in auto-immune and inflammatory processes. A significant reduction in NO production was found when **6** was administered with LPS simultaneously (IC$_{50}$ = 2.7 μM), but this effect was not observed when the macrophages were treated 12 h after stimulation, indicating a preventive (down-regulation) but not a therapeutic (inhibitory) role for **6**. The mRNA initiation site of the murine iNOS gene is preceded by a TATA box, and the promoter region is composed of several conserved binding sequences for recruitment of transcription factors such as NF-κB, STAT, C/EBP, CREB, and OCT.[280] In their initial study, Kim and co-workers found that **6** did not inhibit NF-κB transactivation in LPS-stimulated murine macrophages, in contrast to activity that had previously been reported for monomeric resveratrol (**1**).[281]

In a follow-up study, Kim and co-workers were able to elucidate several ways by which α-viniferin influences signal transduction pathways and ultimately autoimmune and inflammatory response in murine macrophages.[279] Interferon (IFN)-γ is a pleiotropic cytokine involved in both innate immune surveillance and adaptive immunity against pathogenic infection. By participation in an array of cell signaling pathways, this homodimeric protein, produced chiefly in helper T (Th)-1 cells and natural killer (NK) cells, influences cell growth and differentiation, potentiates responses to mitogens, and modulates gene expression and redox homeostasis. Its two transmembrane receptor subunits, termed α and β, do not associate under normal cellular conditions but are assembled upon binding of INF-γ.[282] The intracellular domains of these subunits bear tyrosine kinases known as "Janus"-kinases (JAK)-1 and -2, which upon assembly can phosphorylate the intracellular domain of the complete $(\alpha_2\beta_2)$ INF-γ receptor complex. Phosphorylation of each of the α-subunits activates the complex for recognition by two molecules of a transcription factor known as "the signal transducer and activator of transcription-1" (STAT-1), which upon binding are phosphorylated at tyrosine (Tyr^{701}) residues by the associated JAK kinases. The two phosphorylated STAT-1 molecules form a homodimer upon dissociation from the complex, and are each further phosphorylated at serine (Ser^{727}) residues by a p38 mitogen-activated protein (MAP)-kinase.[282] The resultant activated STAT-1 translocates to the nucleus, where it specifically binds to the IFN-γ activated consensus sequence (GAS)-motif on the promoter regions of various genes including those of inducible nitric oxide synthase (iNOS), CXC chemokines (chemoattractants), and IFN regulatory factor (IRF)-1.[279] The latter is a transcription factor that serves as a feedback loop to enforce transcriptional control of IFN-γ-regulated secondary genes. Dysregulation of this complex signal transduction pathway has been implicated in immunosuppression, evasion of immune detection by malignant neoplasms, and tumor angiogenesis. Kim and co-workers were able to establish that α-viniferin (6) suppresses IFN-γ-induced STAT-1 activation in murine macrophages by inhibiting Ser^{727} phosphorylation by the p38 MAP kinase. Specifically, 6 was found to inhibit STAT-1 phosphorylation by the MAP kinase 3 (MAPK-3), also known as extracellular signal-regulated kinase (ERK)-1. As a consequence of this inhibition, differential attenuation of the mRNA levels of INF-γ/STAT-1-inducible inflammatory mediators iNOS (and [NO] levels), CXC chemokines, and IRF-1 was achieved in a dose-dependent manner.

Recently, the anti-inflammatory mechanism of α-viniferin (6) in BV2 murine microglial cells was explored.[283] In this study, previously reported activities such as decreased production of NO and prostaglandins were confirmed, and new mechanisms by which 6 influences lipopolysaccharide (LPS)-induced expression of proinflammatory mediators were elucidated. Namely, it was found that 6 downregulates iNOS and COX-2 expression via inhibition of the activity of the transcription factors NF-$\kappa\beta$. These proteins are involved in an enormous number of cellular processes, including immune/inflammatory responses, growth and development, and apoptosis.[284] Analogously to STAT-1, phosphorylation is a prerequisite for NF-$\kappa\beta$ activation, homo/heterodimerization, and translocation. However, unlike STAT-1, NF-$\kappa\beta$ itself is not phosphorylated. Rather, cytoplasmic NF-$\kappa\beta$ is typically sequestered by the one of the aptly named "inhibitor of kappa B" (IκB) proteins, of which there are three (α, β, and γ). Independently, these proteins each mask the conserved N-terminal nuclear localization sequence (NLS) of NF-$\kappa\beta$. In response to various inflammatory nuclei, the α-, β-, and γ-subunits aggregate to form the IκB kinase (IKK) complex, resulting in phosphorylation of the α-subunit and release of NF-$\kappa\beta$ for translocation to the nucleus.[284] The equilibrium controlling this phosphorylation event is influenced by a number of kinases, including phosphoinositide 3-kinase (PI3K); MAP-kinases; and protein kinases A (PKA), B (known as Akt), and C (PKC).[283] Dysregulation of NF-$\kappa\beta$-mediated events has been implicated in the pathogenesis of cancer, arthritis, inflammation, neurodegenerative diseases, and heart disease. Kim and co-workers demonstrated that 6 was able to downregulate iNOS and COX-2 expression by interfering with PI3K/Akt-mediated release of NF-$\kappa\beta$ from the IKK complex. Furthermore, these researchers showed that heme oxygenase-1 (HO-1) expression was upregulated by 6, which in turn inhibits NO and prostaglandin production. HO-1 catalyzes the degradation of heme to biliverdin, carbon monoxide, and iron, and is involved in cellular redox homeostasis. As HO-1 is not constitutively expressed, its expression is induced by a variety of oxidative stimuli and is regulated by nuclear transcription factor erythroid 2-related factor 2 (Nrf2). In this study, α-Viniferin significantly increased the DNA-binding activity of Nrf2 in a dose-dependent manner and increased the expression of Nrf2 in the nuclear compartment.

8.2.2. Vaticanol C: A Cytotoxic Resveratrol Tetramer.

In 2002, Ito and co-workers isolated a resveratrol tetramer that they named vaticanol C (94) from the Dipterocarpaceous plant, *Vatica rassak*.[271,285] In this initial report, it was found that 94 induced apoptosis in three colon cancer cell lines, with observable morphological changes such as nuclear condensation and fragmentation, as well as DNA ladder formation. In a series of follow-up publications, these groups were able to elucidate several of the mechanisms contributing to the induction of apoptosis in a variety of cancer cell lines by 94. A family of cysteine-dependent aspartate-directed proteases (Caspases) are known to play essential roles in the initiation (initiator caspases) and execution (effector caspases) of programmed cell death. Western blot analyses revealed that 94 activated the effector caspases-3, but not initiator caspase-8, although it was later found that 94 does activate caspase-8 in mammary carcinoma cells BJMC 3879.[286] It is known that the effector phase of apoptosis is largely dictated by upstream events at the mitochondria, where mitochondrial membrane permeabilization, loss of potential, and release of cytochrome *c* are triggered via the action of the permeability transition pore complex (PTPC). As such, these researchers examined the influence of vaticanol C (94) on these mitochondrial processes. It was shown that the amount of released cytochrome *c* following treatment with 94 increased time-dependently, and that the mitochondrial membrane potential was markedly decreased after 12 h. This is interesting as ε-viniferin (7) and hopeaphenol (9) have each demonstrated the ability to prevent loss of mitochondrial membrane potential, while vitisin A (118) showed similar activity to vaticanol C (94).[287,288] Additionally, the initiator caspase-9, which is activated through binding with the apoptotic protease activating factor-(APAF)-1/cytochrome *c* complex, was indeed found to be activated concurrently with the release of cytochrome *c* in the cells treated with 94. These events can be prevented by the antiapoptotic regulatory protein Bcl-2, and it was found that growth suppression by 94 was

Table 7. Selected Studies of Enzyme Inhibition by Resveratrol Oligomers

target enzymes and pathological implications	active compds; refs	IC$_{50}$ (μM)
Cytochrome P 450 (CYP)		
heme-containing superfamily of oxidase enzymes responsible for the metabolism of both endogenous and exogenous substrates; these are the main enzymes involved in drug metabolism	α-viniferin; 294	0.9
	suffruticosol B; 263	N/A
	ε-viniferin; 295	N/A
Cyclooxygenase (COX)-1 and -2		
key enzymes responsible for the conversion of arachidonic acid to prostaglandins; implicated in pain, fever, inflammation and tumorigenesis.	δ-viniferin-glucopyranoside; 296	3.7
	α-viniferin; 277, 278, 283	4.9
Inducible Nitric Oxide Synthase (iNOS)		
transcription of iNOS gene is controlled by a variety of inflammatory mediators such as lipopolyssacharides (LPS) or cytokines; nitric oxide (NO) plays an important role in cellular signaling and iNOS has been implicated in autoimmune and inflammatory processes	vitisin A; 297, 298	3.9
	vitisin B; 297	4.7
	ε-viniferin; 261, 299	N/A
	α-viniferin; 283, 279	N/A
Protein Kinase C (PKC)		
phosphorylating enzymes with key roles in signal transduction such as regulating transcription, membrane structure, immune response, and cell growth; overexpression implicated in cancer, diabetes, cardiovascular disease, and Alzheimer's disease, among others	α-viniferin; 300, 301	62.5
	kobophenol A; 300	52.0
	miyabenol C; 273, 300	27.5
Sphingosine Kinase 1 (SK1)		
lipid kinase that catalyzes the formation of sphingosine-1-phosphate, an important signaling molecule involved in vascular and immune regulation; SK1 has been implicated in cancer progression.	ampelopsin A; 256	N/A
	balanocarpol; 256	N/A
Acetylcholine Esterase (AChE)		
catalyzes the hydrolysis of the neurotransmitter acetylcholine to acetate and choline at near-diffusion rates, a critical reaction for synaptic transmission; inhibition has been targeted for treatment of neurodegenerative diseases such as Alzheimer's	α-viniferin; 302, 303	2.0
	vitisin A; 304	1.0
	heyneanol A; 304	1.7
	others; 86, 91, 121, 195, 277, 304	
HIV-1 Integrase/MOS-1 Transposase		
polynucleotidyl transferases catalyze the excision, transfer, and reintegration of DNA fragments, an essential process for genome evolution; retroviruses such as HIV rely on integrases for the incorporation of viral DNA into the host genome	hopeaphenol; 305	7.0
	pallidol; 305	9.0
Xanthine Oxidase (XO)		
oxidase enzyme containing a molybdopterin-ligated molybdenum oxo- that catalyzes the oxidation of hypoxanthine to xanthine and further to uric acid; XO also produces ROS and has been targeted for chemotherapeutic applications in cardiovascular diseases	vaticanol A; 91	23.3
Topoisomerase II (Topo II)		
modifies DNA by breaking and religating each of the strands of the phosphodiester backbone, resulting in strain-releasing relaxation of supercoiled DNA and catenation/decatenation of circular DNA, both important processes for cell reproduction (cancer)[306]	hemsleyanol C; 316	1.0
	α-viniferin-glucopyranoside; 316	4.0
	nepalensinol B; 128	0.022
	nepalensinol F; 307	5.5
Multidrug Resistance-Associated Protein 1 (MRP1)		
functions as a transporter of various endogenous substrates such as folates, glutathione disulfide (GSSH), glutathionated-, glucoronidated- or sulfated-steroids, leukotrienes, prostaglandins and bile salts, as well as exogenous xenobiotics including a wide range of therapeutic agents[308]	(+)-α-viniferin; 309	0.8
	sophorastilbene A; 309	3.1

significantly reduced in Bcl-2 overexpressant clones. Notably, this preventive effect was not observed for the anticancer agent taxol. Collectively, these results seem to suggest that **94** may be affecting the mitochondrial membrane proteins that constitute the PTPC, although no direct evidence for this was presented.

In a subsequent study on the apoptotic effects of vaticanol C (**94**) in the HL-60 human leukemia cell line, Ohguchi and co-workers discovered an additional signal transduction pathway controlling cell survival that is affected by this molecule.[289] The Ras-Raf-MEK-ERK pathway[290] and the PI3K/Akt pathway[291] are additional kinase-mediated cascades that couple signals cell surface receptors to transcription factors and that play important roles in regulating apoptotic cellular events. In this study, it was found that levels of phosphorylated MEK, ERK, and Akt were significantly reduced in cells treated with **94**, but only at fairly high concentrations (10 μM). These effects were coupled with a significant loss of Bcl-2-associated death promoter (Bad) phosphorylation. Bad is a pro-apoptotic member of the Bcl-2 protein family, which upon phosphorylation by Akt releases the pro-survival proteins Bcl-xL and Bcl-2 that it normally sequesters through complexation. The phosphorylated Bad then binds to the 14-3-3 protein, while Bcl-xL and Bcl-2 prevent cytochrome *c* release from the mitochondrial membrane by inhibiting pore formation. Thus, it was suggested that vaticanol C (**94**) may induce apoptosis via a mechanism involving prevention of Bad-phosphorylation and therefore inhibition of pro-survival signaling pathways.

Recently, Inoue and co-workers discovered that vaticanol C (**94**) activates peroxisome proliferator-activated receptor (PPAR)-α and β/δ in vitro and in vivo.[292] PPARs are a family of nuclear receptor proteins that function as ligand-dependent transcription factors and that play various roles in lipid and carbohydrate metabolism as well as cell differentiation and development. Each of the PPARs forms heterodimers with the 9-*cis*-retinoic acid receptor (RXR) prior to binding consensus response elements in the promoter regions of the genes whose expression they regulate.[293] In this study, it was found that **94** activates PPARα and β/δ in cell-based reporter assays, which was confirmed by induced expression of PPAR-responsive genes in wild-type, but not PPARα-knockout mice. Thus, **94** has potential in prevention of lifestyle-related diseases, as PPARα is currently targeted by marketed drugs for hyperlipidemia.

8.3. Modulation of Enzyme Activity by Resveratrol Natural Products

In addition to the cytotoxicity, anti-inflammatory, and other properties described above, a large number of studies have been performed to determine the ability of various resveratrol oligomers to inhibit specific enzymes. Selected examples of these biological activities are outlined in Table 7.

8.4. Resveratrol and its Oligomers as Antioxidants

Oxidative damage not only to membrane lipids but also to nucleic acids and enzymes can have deleterious effects on various processes that are fundamental to cell function and survival. Due to the polyphenolic structure of resveratrol and its oligomers, the biological activities of these compounds are often ascribed to their radical-trapping antioxidant activity.[8] However, these conclusions are lacking adequate experimental support, as investigators often assay only the position of their *thermodynamic* equilibrium with oxidants in solution, and not whether the chemistry is *kinetically* competitive under biologically relevant conditions.[11,310] As a result, it has been

inaccurately asserted by many that certain resveratrol oligomers are or are not "antioxidants" on the basis of their ability to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH) or other radicals in solution phase assays. These experiments often ignore not only the *rates* at which the analytes are acting as "radical-trapping antioxidants", but also the fact that *antioxidant behavior is not limited to radical scavenging ability*.[321] Many compounds can influence the redox environment within the cell through other mechanisms, such as induction of the expression of endogenous detoxifying and antioxidant defense enzymes and proteins, including glutathione, glutathione peroxidase, and heme oxygenase.

Despite the hype surrounding the antioxidant properties of resveratrol, it was not until 2003 that someone performed a kinetic study on its radical-trapping ability. Valgimigli and co-workers determined the rate of peroxyl radical-trapping by resveratrol in homogeneous chlorobenzene solution to be 2.0×10^5 M^{-1} s^{-1},[311] which is approximately 16 times lower than that of α-tocopherol, (α-TOH, $k_{inh} = 3.2 \times 10^6$ M^{-1} s^{-1}), nature's ubiquitous radical-trapping antioxidant.[312] Recently, Pratt and co-workers systematically evaluated the radical trapping efficacies of resveratrol dimers quadrangularin A (**17**) and pallidol (**18**) along with their 2,6-di-*tert*-butylated analogues in homogeneous organic solution, lipid bilayers, and cell culture.[180] Similar to resveratrol, the dimeric natural products and their analogues did not react with peroxyl radicals in homogeneous solution at a rate that was competitive with α-TOH. However, in lipid bilayers ^{t}Bu$_2$-resveratrol **146** and ^{t}Bu$_2$-quadrangularin A **148** were each found to be highly effective; in fact, these compounds were superior to α-TOH itself (10- to 16-fold for (**146**) and 4-fold for (**148**), depending on whether the oxidation was mediated by lipophilic or aqueous peroxyl radicals). Finally, the effective concentrations for inhibition of lipid peroxidation in cultured human erythroblasts were determined. Again, the natural products were far less effective than their *tert*-butylated analogues, and **146** was shown to have an EC$_{50}$ one-third that of α-TOH. Not only are the natural products expected to be less soluble than the *tert*-butylated analogues in the lipid milieu, but the reactivity of the phenolic O−H can also be reduced due to its H-bonding interaction with phosphatidylcholine moieties and/or water at the lipid/aqueous interface, an interaction that is diminished by the bulky *tert*-butyl moieties. Now that systematic studies of these types of compounds have extended past homogeneous solution into lipid bilayers and cell culture, they challenge the popular belief that the biological activities of the natural products derive from their ability to trap radicals. Curiously, although ^{t}Bu$_2$-pallidol **153** was inefficient at preventing lipid peroxidation in bilayers, it was surprisingly potent (EC$_{50}$ = 0.39 μM) in cell culture, suggesting that it likely operates through a mechanism other than direct radical trapping. To account for this, Pratt and co-workers postulated that **153** may act as a modulator of the Kelch-like ECH-associated protein 1 (Keap1)-nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element (ARE) pathway.[313,314]

The Keap1-Nrf2-ARE pathway represents one of the central mechanisms by which cells combat oxidative stress and xenobiotic-induced damage. Under normal conditions, Keap1 binds to and represses the transcription factor Nrf2 in the cytoplasm by promoting its ubiquitination by the appended Cullin (CuI)-3-based ubiquitin E3 ligase and subsequent proteasomal degradation.[313,314] Oxidants and electrophiles present during oxidative stress cause modification of cysteine

residues in the Keap1 backbone, inducing conformational changes that lead to the release of Nrf2. This basic leucine zipper (bZIP) transcription factor then translocates to the nucleus where it heterodimerizes with small Maf proteins (also bZIP transcription factors) and activates genes containing antioxidant response elements (ARE) in their promoter regions, including those for glutathione and other antioxidant proteins, drug metabolizing enzymes and transporters, and other transcription factors. It is known that cancer cells hijack this signal transduction pathway to support their malignant growth, and dysregulation has also been associated with the pathogenesis of multiple sclerosis (MS) and diabetic nephropathy.[313,314]

Recently, Pan and co-workers evaluated the ability of three resveratrol dimers, quadrangularin A (**17**), pallidol (**18**), and parthenocissin A (**61**), to activate Nrf2 *in vitro*.[315] The breast cancer cell line, MCF-7, was transfected with an ARE-luciferase reporter plasmid containing 10 copies of the ARE (5′-GTGACAAAGCA-3′), and the cells were exposed to resveratrol and the three dimers (7.5−30 μM in 0.1% v/v DMSO as vehicle). Resveratrol induced ARE-luciferase activity dose-dependently, with a 2.5-fold increase at 7.5 μM. Parthenocissin A (**61**) and quadrangularin A (**17**) were each found to have no effect at all doses, while pallidol (**18**) showed a 3-fold induction at the highest dose (30 μM). This finding lends credence to the supposition by Pratt and co-workers that the *tert*-butylated pallidol analogue **153** may be acting on this signal transduction pathway in human erythroblasts, especially when considering the improved cell permeability that the bulky substituents are expected to impart. Further studies are needed to determine whether other oligomers and their analogues exhibit more potent Nrf2 activation, and if certain structural features such as a C_2 axis of symmetry correlate with activity.[316]

9. CONCLUDING REMARKS

The broad spectrum biological activities of resveratrol and its oligomers, as evidenced by the range of cell lines against which they were found to be cytotoxic and the multitude of enzymes which they were demonstrated to either inhibit or down-regulate, speaks to the pharmacological potential of this class of natural products. At the same time, such diverse biological activity is a bit disconcerting, as it implies that these molecules are perhaps nonspecific with respect to their pharmacodynamics. In spite of this, the moderate potency (low micromolar) observed in the majority of the *in vitro* assays delineated above and the historically low bioavailability of chemopreventive and chemotherapeutic polyphenols render them relatively nontoxic.[317,318] Taken together, this data raises concerns about whether the concentrations required for efficacy are attainable *in vivo*. While the aglycones of polyphenols can be absorbed fairly efficiently in the small intestine, many of the naturally occurring glycoconjugates are not, although the aglycones typically undergo rapid metabolic glucuronidation and sulfation in the small intestine, liver, and kidneys. However, in order for the hydrophilic metabolites to be excreted, cellular efflux transporters must operate in concert with these phase II bioconjugation pathways, a process which could have profound effects on the bioavailability and apparent half-life of the polyphenols.[319]

While the resveratrol oligomers possess only micromolar potencies in the *in vitro* assays in which they have been examined, this should not justify their uncritical dismissal as candidate scaffolds for drug development. Indeed, the "nano-molar rule" (the selective development of compounds with nanomolar *in vitro* potency) has recently been challenged,[320] and it is imperative that we not allow advances in predictive technologies to engender a myopic approach to drug discovery. To better understand the behavior of these molecules in biological systems and enable the development of more potent analogs, systematic structure−activity relationship (SAR) studies must be performed. Limited commentary on the structural features correlated to bioactivity exists in the literature, and typically consists of retrospective conjecture based on observed IC$_{50}$ values for a given set of isolated natural products. It would be beneficial for researchers to perform these studies on analogues that have been rationally designed, as this would enable a more generalized understanding of which physical properties can be exploited in the development of more potent congeners. To date, progress in this area has been hampered by existing synthetic technologies, which have largely been incapable of providing materials in sufficient quantities for their systematic evaluation, although several strategies have recently been reported that hold promise in this regard (see sections 6 and 7). While resveratrol oligomers are a relatively new target in the area of complex molecule synthesis, they offer unique challenges and therefore opportunities for valuable contributions to synthetic chemistry and an improved biological understanding of one of the most widely distributed groups of natural products in the plant kingdom.

AUTHOR INFORMATION

Corresponding Author

*E-mail: crjsteph@umich.edu.

Author Contributions

[†]M.H.K. and B.S.M. contributed equally.

Notes

The authors declare no competing financial interest.

Biographies

Mitchell H. Keylor received a B.S. in Biochemistry from Stonehill College in 2011 and an M.A. in Chemistry from Boston University in 2013. He is currently a Ph.D. candidate at the University of Michigan under the direction of Professor Corey Stephenson, where he is pursuing the biomimetic total synthesis of resveratrol-derived oligomeric natural products.
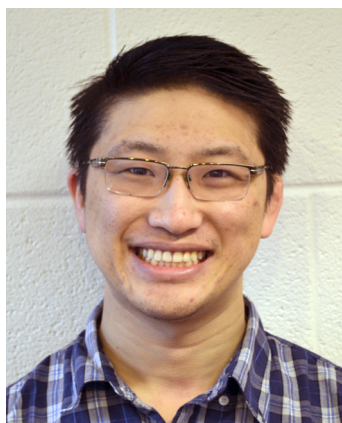
Bryan S. Matsuura received his B.A. from Boston University in 2009 and started his Ph.D. studies in the same year. He is currently a Ph.D. candidate under the supervision of Professor Corey R. J. Stephenson, studying the biomimetic synthesis of the resveratrol oligomers and the degradation of biomass derived polymers using visible-light photoredox catalysis.

Corey R. J. Stephenson completed his Ph.D. at the University of Pittsburgh under Professor Peter Wipf followed by postdoctoral research with Professor Erick M. Carreira at ETH Zürich. In 2007, he joined the Department of Chemistry at Boston University as an Assistant Professor, and in 2013, he was promoted to Associate Professor and moved to the University of Michigan. His research interests are broadly focused on complex molecule synthesis, biomass degradation, and catalysis.

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