Chemistry and Biology of Resveratrol-Derived Natural Products
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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.6 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).5 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. In 1992, Siemann and Creasy6 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,9 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 contentious9,10 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 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
activity and alter the antioxidant properties of the stilbene, rendering its oxidation by laccase enzymes more facile.\textsuperscript{29} The glycosylation of \textbf{1}, as seen in the resveratrol adduct piceid (\textbf{5}), is thought to aid in the storage and translocation of resveratrol within the cell tissues as well as protect resveratrol from oxidation.\textsuperscript{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.\textsuperscript{31} They identified resveratrol as the compound responsible for the formation of fluorescent lesions on the leaves of \textit{Vitis vinifera} upon infection with the plant pathogens \textit{Botrytis cinerea} (gray mold) and \textit{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 \textit{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 \textbf{1} increased nearer to the site of the lesion.\textsuperscript{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 \textit{α}-viniferin (\textbf{6}) and \textit{ε}-viniferin (\textbf{7}) (see section 3.2).\textsuperscript{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\textsuperscript{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,\textsuperscript{35} they demonstrated that \textbf{1} could be dimerized to produce more potent antifungal compounds, indicating that resveratrol was a precursor to the actual phytoalexins in the plant.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{42} leading to a number of structural misassignments\textsuperscript{43} and
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 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. 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. 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 7α(R), 8α(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). The stereochemical assignment of 8, in turn, had been established by comparison to the CD spectra of benzofuranoid neolignans whose absolute configurations were determined by X-ray crystallography.

3.1. Hopeaphenol

The first resveratrol oligomer ever characterized was hopeaphenol (9, Figure 2), a resveratrol tetramer isolated by Coggon et al. 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-decachloro 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. 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. Despite the complex polycyclic scaffold of hopeaphenol (9), its C2-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: 12C−12C (97.8%), 12C−13C (2.18%), and 13C−13C (0.01%). Although the latter is below detection limits, the broken symmetry of the 12C−13C 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−12C−13C−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. Shortly thereafter, Langcake and Pryce discovered that resveratrol also accumu-
lates in the leaves and lignified stem tissue of grapevines that have been infected with fungus or exposed to UV irradiation. 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 H2O2, although the physical properties of α-viniferin were different from those previously reported, and (+)-α-viniferin was therefore deemed antipodal. This supports the hypothesis that these oligomers are synthesized from ε-viniferin (7), as Vitaceae 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. Vaticaaffinis

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, vaticaaffinin (11) (Figure 4). Unlike hopeaphenol, in which the vicinal 7/8b, 7/8c and magnetically equivalent 8b/8c protons do not couple (Figure 2), decoupling experiments on vaticaaffinin revealed vicinal coupling through 7a−8a−8c−7c at the core of the molecule (Figure 4). Hopeaphenol has a C1-axis of symmetry, resulting in just four observable aliphatic proton signals, whereas the 1H NMR spectrum of vaticaaffinin 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
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 1H-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 vatica **f**i**l** 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 13C NMR chemical shift and 1H 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 13C 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.
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\(_2\)O) 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”, ...).
Resveratrol oligomerization appears to proceed via the coupling of oxidatively generated phenoxyl radicals (Scheme 3, A–D) as originally proposed by Langcake and Pryce. The dimerization typically occurs through three regioisomeric modes: the 8–10′ coupling (as found in ε-viniferin (7) and amelopsin F (16)), 8–8′ coupling (quadrangularin A (17)) and pallidol (18), and 3–8′ coupling (e.g., δ-viniferin (10), Scheme 3). Several exotic regioisomers, like the 8–12′ (gnetin C (19)) or the 12–12′ coupling (amurensin M), have also been identified, but they are relatively uncommon. Following dimerization, highly reactive paraquinone 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. In these instances, we do not mean to imply a biosynthetic epimerization, but rather only to depict the structure in the reported configuration.
4.1. Biosynthesis of 8–10′ Dimers

The 8–10′ connectivity is by far the most prevalent found among resveratrol-derived oligomeric natural products. The parent molecule of 8–10′ oligomers, e-viniferin (7), has the relatively uncommon distinction of being a natural product that is found naturally in both enantiomeric forms. (−)-e-Viniferin is found in several plant families such as Dipterocarpaceae, Gnetaceae, Cyperaceae, and Fabaceae (Leguminosae), while its enantiomer, (+)-e-viniferin, is exclusively found in plants from the family Vitaceae (Scheme 4). Upon oxidation of 1 and 8–10′ dimerization, hypothetical para-quinone methide intermediate 21 can follow divergent cyclization pathways to generate either e-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) (path C), while tautomerization yields the indane isomer ampelopsin D (25) (path D). 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 benzyl ketone.74 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 e-viniferin plays a central role in the biosynthesis of the entire class of 8–10′ dimers and oligomers. The biogenetic relationship of 7 to ampelopsins F (16), D (25), and B (29) was delineated by Niwa and co-workers through a series of biomimetic Bronsted-acid-mediated rearrangements of natural (+)-e-viniferin (Scheme 5, A). Additionally, they were able to convert paracetacetyl 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 (+)-e-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 dearamative 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 hopehainanol D (38)85 possibly derive from an intramolecular etherification of the C7α-O7α bond upon an acid-mediated formation of para-quinone methide 36 (path A). A direct benzyl alcohol oxidation of 30 or 35 to the ketone affords pauciflorol E 39 (path B). 

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

The biogenic relationship between the (+)-balanocarpol (34), hopeanol (31), and the hopeahainols A/B (40/41) 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) would represent a product of its oxidative dearomatization. Dehydration of intermediate 42 may lead to the formation of (-)-malibatol A (44), a plausible biosynthetic precursor to the several other oxidized 8′-alkenes (45) (also known as hopeafuran), although biosynthesis via a formal dehydrogenation of paraflorol E (46) cannot be ruled out. The biogenic relationship between (-)-malibatol A (44) and the hopeahainols/hopeahainanphenols is supported by the isolation of the oxidized 8–10′ dimers vaticahainols B (46) and A (47). Vaticahainol B (46) is presumably derived from a diastereoselective oxidative dearomatization of 44, perhaps through an epoxidation. A stereoselective 1,2 aryl migration from 46 yields vaticahainol A (47). Subsequent C8a oxidation and oxidative dearomatization of phenol A1 would yield the natural product hopeahainol A (40). The biogenic relationships between hopeanol (31), hopeanol B (48), and hopeahainols A (40) and B (41) are supported by total synthesis (see sections 7.1.4–7.1.5). Upon trapping with water, vaticahainol B (46) can undergo an oxidative cleavage of its C7a–C8b bond followed by hydrolysis of 4-hydroxybenzoate to hemsleyanol E (39), since the natural product (+)-balanocarpol (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). 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), parthenostilbenins A/B (54), and quadrangularins B/C (55). 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) and tricuspidatol A (57), which derive from the double addition of water across the para-quinone methide...
stereoisomers of 22 (path D), provide indirect evidence for the existence of both the meso- and C₂-symmetric diastereomers. Amurensin A (59) 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), 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). An oxidative cyclization reaction, perhaps through a 6π electrocyclic ring closure followed by dehydrogenation, yields laetevirenol A (62). 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. 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 stable
Scheme 11. Biosynthesis of Higher-Order Oligomers Is Convergent in Nature and Employs Both Radical and Polar Mechanisms

Iterative Homologation

**Convergent Oligomerization**

Oxidation  Radical Coupling  Oligomeric Natural Products  Polar Coupling

\[ \text{o-viniferin (7)} \Rightarrow \text{\textit{ε}-viniferin (10)} \Rightarrow \text{o-viniferin (7)} \]

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 pathogens. The regiosomeric 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/\textit{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). Instead, it would appear that the majority of oligomerization reactions are convergent processes, wherein tetrramers 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′ Trimmers

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 \textit{ε}-viniferin (7), gnetin H (68), and miyabenol C (69) via a HRP-mediated cross trimerization of 7 and resveratrol (1) to afford 68 and 69 in 33% and 34% yields, respectively (Scheme 12). The gnetin H isolated from that reaction was subjected to a Bronsted-acid-mediated isomerization, yielding amelopsin G (70) (4.5%), amurenin G (71) (8.4%), wilsonol B (72)
(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) regiosomer (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 ampeopins 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_{4b}–C_{7b} bond (path D). This intermediate is presumably the precursor for two isomeric natural product scaffolds. A 7-exo-trig cyclization (C_{10k}–C_{7b}) yields 5,7-fused indane skeleton found in the natural products vaticanol A (76) (Scheme 13, path E),116 amurenisin G (71),119 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_{10k}–C_{7b} path F), generating the [3.2.1]bicyclooctane cores of ampeopins 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_{4b}–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_{7b} path L) yields the carbon skeleton of caraphenol B (81)119 while an alternative 9-exo-trig cyclization (C_{10b}–C_{7b} 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 trimmer α-viniferin (6) (path I).

5.2. Biosynthesis of Oxidized 8–10′/10′–8′ Trimmers

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)121 (Scheme 14). This series of natural products provides an exquisite snapshot of the biogenenic 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 vaticainhol 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 vaticainol E122 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 hopeachinol B (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)45 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
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
oxidation chemistry which so far has only been identified in Dipterocarpaceae. The resveratrol dimer viniferifuran (amurenensis 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-
trig) cyclization forms the C$_{8a}$−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
product maps onto the meso stereoisomer of gnetin H (68), ampelopsin E. Finally, a 7-exo cyclization of quinone methide 92 (C10d−C7c, 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 8−8′ oligomers that possess dihydrobenzofuran motifs that alternate in absolute conﬁguration (Scheme 15, path B). The biosynthesis of miyabenol A (98) 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′ Trimmers and Tetramers

5.4.1. Biosynthesis of 8−8′ Trimmers. 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 canulicol,130 and stenophyllol B (path C).131 Alternatively, formation of the C_{14a}−C_{7a} bond (path D) produces the highly versatile intermediate 104. A second 8-exo-trig arylation of 104 (C_{10a}−C_{7b} path E) affords the pallidil (18) derivative carasphenol C (66),132 whereas the intramolecular 7-exo-trig cyclization of 104 forms ampelopsin C (105)133 (path F), a member of a larger group of stereoismeric 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 tautomers (Scheme 16, path B). This bis-para-quinone methide can undergo either symmetric cyclization modes, delivering products such as hopeaphenol (9, path F),34 vaticaflavin (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 dearomatizing Friedel–Crafts cyclization between carbons C_{14a} and C_{7b}. An oxa-conjugate addition onto the presumed spirocyclohexadienone (not pictured) forms the O_{14a}−C_{7b} bond to generate the spirocyclohexene found in shoreaketone. Ito and co-workers were able to determine a Bronsted-acid-mediated rearrangement of shoreaketone (14) to (+)-iso-hopelaphenol methyl ether (15a) in quantitative yield (see section 3.5), establishing its absolute configuration and its identity as an 8′−8′′ tetramer.63

5.4.3. Empirical Support for Proposed Biosyntheses of 8′−8′′ Trimmers and Tetramers. In order to investigate the biosynthesis of the resveratrol oligomers, Niwa51 and Pan52 have studied the oxidative cross-coupling of (+)-ε-viniferin (7) and resveratrol using horseradish peroxidase (HRP) and H_{2}O_{2} (Scheme 17, path A). Although these reactions were non-selective, they were successful in producing isolable quantities of didaviol 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 didaviol 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),53 a diastereomer of carasphenol 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 didaviol 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_{2}O_{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 diphtoindonesin B (115) and is likely (bio)synthesized in similar fashion.135

The groups of Niwa136 and Pan52 have also performed biomimetic peroxidase mediated homocoupling of (+)-ε-viniferin (7) to study the biogenesis of the resveratrol tetraters. 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),138 (−)-hopeaphenol (9), (−)-isohopeaphenol (15), and (−)-viniferol139 by analogy.

5.5. Biosynthesis of 3′−8′ Trimmers 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 an 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 quaquadrularin A (17)/parthenocissin A (61) as plausible precursors for laevenerol A−F,102 linear dimeric stilbene amurenis B (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 Laeveneroles. In 2008, the Pan group isolated an unusual series of dihydrobenzofuran-containing indane natural products called the laeveneroles102 which are parthenocissin A/quadrularin 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 quadrularin A (17), the parthenocissins, and the laeveneroles (Scheme 19). Irradiation of parthenocissin A (61) with UV light effected its conversion into (−)-quadrularin 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

Scheme 19. Pan’s Biogenic Studies of the Parthenocissins and Laetevirenols
dihydroacephenanthrylene natural product laetevirenol A (62) through a UV-light mediated oxidative π-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.

The intermolecular oxidative cross coupling of quadrangularin A (17), a trisubstituted stilbene, and ε-viniferin (7) was unprecendented; previous biomimetic dimerization reactions were homo/heterocouplings of resveratrol (1) or ε-viniferin (7), which are dissubstituted 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 intramolecular radical coupling, followed by an intramolecular Friedel–Crafts cyclization. Typically, an intramolecular cyclization or tautomerization of an intermediate para-quione 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 quione methides generated during the dimerization of...
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resveratrol. For instance natural products cajayphenol A (128) and B (129), isolated from Cayratia japonica (Vitaceae) are regioisomeric tetraters of the cross coupling of quadrangularin A (17) and its penultimate biosynthetic intermediate 52 (Scheme 20). A more complex natural product paucilinol 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) (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 involved 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 unclear whether the act or 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 copalliferol 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 benzocycloheptane 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 e-viniferin (7). The core cycloheptane structure of stemonoporol 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, FiDIR1, 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:
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**6. BIOMIMETIC SYNTHESSES**

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, 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 (6) and ε-7 (7) viniferin. Drawing on the biosynthesis of a structurally related lignan natural product licarin A, they proposed that an oxidative oligomerization of resveratrol could conceivably generate ε-viniferin (7). By subjecting resveratrol to the horseradish peroxidase (HRP)/H$_2$O$_2$ oxidation conditions developed by Wallis and co-workers, 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, organic, inorganic, and photochemical oxidations. 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. 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 dihydrodimer.
In 1998, Pezet isolated a laccase-like stilbene oxidase from the plant pathogen B. cinerea (7) that had the remarkable ability to dimerize resveratrol to ε-viniferin (7) in 97% yield (Table 2).

Table 2. Biomimetic Syntheses of ε-Viniferin

| entry | reaction conditions | yield | ref |
|-------|---------------------|-------|-----|
| 1     | B. cinerea laccase-like stilbene oxidase | 97% | 154 |
| 2     | FeCl₃, MeOH/H₂O, rt | 30% | 166 |
| 3     | K₃Fe(CN)₆, K₂CO₃, MeOH/H₂O, rt | 22% | 108 |
| 4     | Ti(NO₃)₄, MeOH, −50 °C | 30% | 108 |

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

conditions that were chemoselective and were slightly higher yielding using MnO₂ or FeCl₃ as stoichiometric oxidants. Recently, a catalytic method using graphitic nitride to dimerize resveratrol via an aerobic photochemical oxidation was reported by Wang and co-workers, which provided ε-viniferin (7) in high yield and with good regioselectivity (Table 1, entry 7).

Table 1. Biomimetic Syntheses of δ-Viniferin

| entry | reaction conditions | yield | ref |
|-------|---------------------|-------|-----|
| 1     | Cu²⁺, SO₄⁻, MeCN, rt | 16% | 164 |
| 2     | DPPH, MeOH | 18% | 106 |
| 3     | various peroxidases, acetone/EtOH | 13–21% | 108 |
| 4     | laccase, n-BuOH | 31% | 107 |
| 5     | AgOAc, DCM | 36% | 168 |
| 6     | galvinoxyl radical, ethanol, rt | 41% | 163 |
| 7     | graphitic carbon nitride (hv, 410 nm), lutidine, air, MeCN, rt | 85% | 111 |
| 8     | AgOAc, MeOH, 50 °C | 86% | 165 |
| 9     | MnO₂, DCM, rt | 91% | 108 |
| 10    | HRP/H₂O₂, H₂O/acetone, pH 8 | 93% | 148 |
| 11    | FeCl₃, acetone, rt | 97% | 108 |

*R = H resveratrol (1), §R = Me pterostilbene (3).

Although the ε-viniferin (7) did not appear until 2004, when Yao and co-workers described the dimerization of resveratrol to 7 with FeCl₃ in MeOH in 30% yield and with 40% recovery of resveratrol (Table 2, entry 2). This reaction was performed on 0.5 g scale and has since been implemented for the synthesis of other resveratrol dimers. They were able to derivatize 7 to phenanthrolone 141 upon photooxidation of 7 in 20% yield (Scheme 24).

Scheme 24. Oxidative Photocyclization of 7

One year later, Niwa and co-workers also reported a series of reaction conditions that could selectively generate ε-viniferin (7). If potassium hexacyanoferrate (K₃Fe(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 Ti(NO₃)₄ 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
toward a reagent-controlled, chemoselective synthesis of the conditions described in section 6.2, they found that K₃Fe(CN)₆, 16% of pallidol ([18]) could oxidize resveratrol, yielding a mixture of more complex dimeric architectures, such as quadrangularin A (17), dihydrobenzofuran dimers, strategies to selectively synthesize. Despite the previous successes in the synthesis of the

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 amelpopin 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. Using the same conditions described in section 6.2, they found that K₃Fe(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. Using FeCl₃ as their single electron oxidant, they found that they could influence product distribution by switching between “hard” and “soft” solvents or oxidants. When 3 was oxidized with FeCl₃ in CH₂Cl₂, they observed 10% and 7% yield of methylated pallidol (18a) and amelpopin F (16a), respectively (Table 3, entry 4). In a mixture of CH₂Cl₂ and methanol, 3 dimerized primarily to give the tricuspidatol derivative S7a 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 (section 4.3). 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. 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

| entry | reaction conditions | 10 | 16 | 53/55 | 18 | 57 | ref |
|-------|---------------------|----|----|-------|----|----|-----|
| 1     | K₃Fe(CN)₆, K₂CO₃, MeOH/H₂O, rt | 23% | — | — | 16% | — | 108 |
| 2     | horseradish peroxidase, aq acetone | 13% | — | — | 10% | — | 108 |
| 3     | soybean peroxidase, aq EtOH | 12% | — | — | 14% | — | 108 |
| 4     | FeCl₃·6H₂O, CH₂Cl₂ | — | 7% | — | 10% | — | 168 |
| 5     | FeCl₃·6H₂O, CH₂Cl₂/MeOH (7:3 v/v) | — | — | — | 29% | — | 168 |
| 6     | Pt anode/cathode in MeCN/0.2 M LiClO₄ (+1.00 V vs Ag/AgNO₃) | — | 8% | — | 14% | — | 170 |
| 7     | horseradish peroxidase, acetone/pH 8.0 buffer | 93% | (89%) | — | — | — | 148 |
| 8     | horseradish peroxidase, acetone/pH 6.0 buffer | — | — | 55% | (24%) | — | 148 |
| 9     | horseradish peroxidase, acetone/pH 5.0 buffer | — | — | 20% | (19%) | — | 148 |
| 10    | horseradish peroxidase, acetone/pH 4.0 buffer | 28% | (26%) | — | — | — | 148 |
| 11    | NaNO₂/pH 3.0 buffer, MeOH | 2% | — | — | — | 1% | 171 |

*R = Me (pterostilbene, 3).

168:2:1 mixture of S5/S3. *HPLC yield. *Isolated yield. *Product was S3. Cis-δ-viniferin is major pdt.
dimerization of resveratrol. 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, 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). 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...
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. The key innovation of this approach was the identification of the 2,6-di-tert-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 and Wallis 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 AlCl3 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 H2O2 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 significant amounts of resorcinol onto product 153, which are the products of trapping of the monomer-based trimeric intermediates 149 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O as an oxidant in 2:1 benzene/acetone, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4).

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. 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 Ag2CO3 or MnO2 in CH2Cl2, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O 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 FeCl3·H2O was used as the oxidant in CH2Cl2 delivering protected ampelopsin F (154) in 45% reaction conversion with 25% recovered starting material. These results corroborate the findings described by Niwa and Velu demonstrating that it is possible to influence product distribution by changing solvent and/or stoichiometric oxidant. Deprotection of 153 and 154 with AlCl3 in toluene/MeNO2 proceeded uneventfully for 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. 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 Ag2CO3 or MnO2 in CH2Cl2, they observed 59% and 54% reaction conversion to quinone methide 147 with 64% and 76% recovered starting material, respectively (Table 4). Using FeCl3·H2O 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 FeCl3·H2O was used as the oxidant in CH2Cl2 delivering protected ampelopsin F (154) in 45% reaction conversion with 25% recovered starting material. These results corroborate the findings described by Niwa and Velu demonstrating that it is possible to influence product distribution by changing solvent and/or stoichiometric oxidant. Deprotection of 153 and 154 with AlCl3 in toluene/MeNO2 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 of protected analogues of tricuspidatol A (155a/b) and restrytisol...
Upon acylation of the resorcinol of 146 with Ac₂O or Boc₂O and oxidation with FeCl₃·6H₂O 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 CF₃SO₂H did not provide tricuspidatol (57) or рестрйтисол Б (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). 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(ppy)(tpy)(PF₆)₃, 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, 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 CCl₄ and KOtBu, 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 FeCp₂PF₆ 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.
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, 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
target indane-derived resveratrol natural products ampelopisin 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 (A₁) and resorcinol (A₂) 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 enabled access to the regioisomeric materials isopauci B-ring (28) and pallidol F (16) revealed by a global demethylation using Br$_2$. 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 a ensuing Meyer’s modified Ramberg–Bäcklund reaction. 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 ampelopisin D (25), was demethylated using Br$_2$ to give a 5:1 mixture of the desired natural product (25) and its internal alkene isomer, isomelpopisin D (see Scheme 5, A). Isolation of these materials required peracylation 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 pauciiflorol F (28) to ampelopisin D (25) (and isopauciflorol F (176) to quadrangularin A (17)) has since been developed (see section 7.1.3).  

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 ampelopisin D (25) and quadrangularin A (17) to effect their interconversion to the remaining two dimeric structural subtypes: the bicyclo[3.2.1]octanes 179 and 180 which smoothly transformed 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 ampelopisin 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$^3$–sp$^3$) of the bromine-bearing aliphatic carbon induces molecular reorganization, orienting the deaminated B$_2$-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 ampelopisin F synthesis).
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.\textsuperscript{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.\textsuperscript{93} 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.\textsuperscript{186} Relying on their previous syntheses of paucilfiorol F (28) and isopaucilfiorol F (176), a reaction sequence was developed for functionalization of the indane. 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\textsuperscript{92} 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 BBr\textsubscript{3}, 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).\textsuperscript{92} These unusual structures are each thought to derive from skeletal 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 phenyglyoxal 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

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**Scheme 31. Synthesis and Structural Reassignment of Caraphenols B and C**

![Scheme 31](image-url)
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 KOtBu followed by acidification with saturated aq NH4Cl 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 (SnCl4) 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 (40). Further 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. 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 Br2, 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). Through redesign of the parent triaryl building block 201, these researchers were able to access the core structure of these
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, Meinwald rearrangement, and Pinnick–Lindgren oxidation 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 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] 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.

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 lactol 210, which the authors rationalized on the basis of steric encumbrance from the phenol ring of perbenzylated 209. A subsequent Kishi reduction 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). 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. Vinlylogous 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 Bronsted 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 Bronsted acids were screened in an effort to promote a Pinacol rearrangement of the diol. They found that the 1 equiv of VAPOL phosphoric acid 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

Scheme 34. Synthesis of Heimiol A and Hopeahainol D by Snyder et al.
step by treatment of \( \text{218} \) with Jones reagent, giving 27% of spirocyclohexadienone \( \text{220} \) through the intermediacy of phenonium \( \text{219} \). Surprisingly, the aldehyde was not oxidized under these conditions. Compound \( \text{220} \) could be converted to the protected hopeanol (\( \text{221} \)) through Pinnick−Lindgren oxidation and esterification, but its deprotection was not possible. A number of synthetic precursors also failed to deprotect using standard \( \text{BBr}_3 \) conditions, resulting in decomposition and/or rearrangement of the material. Ultimately, the researchers found that acid \( \text{222} \), obtained by Pinnick−Lindgren oxidation of \( \text{218} \), could be dealkylated with \( \text{BBr}_3 \), with concomitant formation of the \( \gamma \)-lactone yielding dibenzocycloheptane \( \text{223} \). 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 \( \text{BCl}_3 \) to reveal the natural product hopeahainol A (\( \text{40} \), 60 mg) in good yield. Methanolysis using the conditions reported by Nicolaou and Chen gave hopeanol (\( \text{31} \), 11 mg).

7.1.6. Chen’s Synthesis of Malibatol A and Shoreaphenol (Hopeafuran). In 2010, Chen and co-workers disclosed a synthesis of malibatol A (\( \text{44} \)) and shoreaphenol (\( \text{45} \)), 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 \( \text{224} \), reminiscent of those used by Snyder and co-workers in their synthesis of resveratrol dimers,\(^{185}\) benzofuran synthesis was achieved by deprotonation of the benzoyloxy 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 (\( \text{44} \)). Further oxidation afforded shoreaphenol (hopeafuran) (\( \text{45} \)).

7.1.7. Synthesis of Laetevirenol A by Heo et al. In 2012, Heo and co-workers disclosed a synthesis of laetevirenol A (\( \text{62} \)) (Scheme 37),\(^{211}\) a member of a dimeric subclass of resveratrol oligomers containing phenanthrene ring systems.
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 arena was introduced through another Grignard addition, and dehydrogenation to the required olefin \(232\) was achieved using Brensted 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 FeCl\(_3\) promoted oxidative cyclization to acohenanthrylene \(233\), as was found by Sarpong (section 7.2.2). This was converted into \(\text{cis}\)-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 S-endo Mizoroki–Heck cyclization\(^{12,213}\) onto an allylic alcohol (Scheme 38).\(^{214}\) 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)\(_2\)/PPh\(_3\) resulted in its conversion to indenone \(237\), presumably via a tandem Mizoroki–Heck cyclization/Saegusa–Ito oxidation.\(^{215}\) The researchers were able to reduce the \(\alpha,\beta\)-unsaturated enone to the corresponding \(\text{cis}\)-2,3-dihydroindanone (not shown) and epimerize the \(\alpha\)-stereogenic center under alkaline conditions to give \(238\). Finally, global demethylation using BBr\(_3\) revealed the natural product pauciflorol F \((28)\).

#### 7.2.2. Sarpong's Synthesis of Pauciflorol F and related Carbogenic Cores by a Pd-Mediated Intramolecular 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 metatation 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 Pd\(_0\) into the C–Br bond produces a π-acidic Pd\(_{\beta}\)–aryl species that coordinates the electron-rich tolane. Polarization of the alkyn by the para-disposed methoxy group facilitates regioselective migratory insertion to the Pd\(_{\beta}\)–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 FeCl\(_3\)-6H\(_2\)O resulted in the production of \(246\), likely through a series of single electron oxidation/deprotonation events (\(242 \rightarrow 245\)).

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-
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 O2 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 (Et3SiH) 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 oligostilbenoids,219 relying on the well-established acid-promoted cyclodehydration 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 42](image)

Scheme 43. Synthesis of Pauciflorol F Using a Nazarov/C–H Arylation Sequence

![Scheme 43](image)

C-2 of the benzofuran was accomplished through a Pd-mediated Heck cross coupling that is initiated via direct C–H activation.\textsuperscript{221} Here, C-2 palladation likely takes place through either an electrophilic aromatic substitution (S\textsubscript{E}Ar) or concerted metalation-deprotonation (CMD)\textsuperscript{222} process to form bisaryl-Pd\textsuperscript{2+} complex 253. Reductive elimination gives a dimer of benzofuran 252 and generates the required Pd\textsuperscript{2+} 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\textsuperscript{2+} 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 malabatol 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 diptoindoenesin G (263) using intermediates 251 and 254 (Scheme 42).\textsuperscript{223} From 254, a tandem Friedel–Crafts acylation/global demethylation was possible using the highly acidic BBr\textsubscript{3}. Alternatively, treatment of 251 with the less acidic BCl\textsubscript{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.\textsuperscript{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).\textsuperscript{225} Here, 265 was prepared through a Nazarov cyclization\textsuperscript{226} of the chalcone precursor 264, a strategy that has since been utilized by other groups for the synthesis of this natural product.\textsuperscript{211,227,228} While the synthesis was racemic, the arylation was diasteroselective, 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\textsubscript{Bu}).\textsuperscript{221} Additionally, these researchers were able to achieve the first asymmetric synthesis of (+)-pauciflorol F (28) by subjecting She’s indenone intermediate 237 (vide supra)\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{229,230} Application of this method to 266 gave the desired arylated indene products 267 and 268 with...
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. 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 BB₃ 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 acidic²³³ or basic²³⁴ conditions. Shaw and co-workers exploited this for the asymmetric synthesis of δ-viniferin (10) (Scheme 45).
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 MnO₂ followed by exposure of the crude material to Rh₂(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 BCl₃/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), 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. 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. These endeavors are described in the sections below.

7.3.1. 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 MnO₂ followed by exposure of the crude material to Rh₂(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 BCl₃/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), representing the first asymmetric synthesis of a dihydrobenzofuran-containing resveratrol dimer.

**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 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. 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. 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 (pKₓ ∼53) versus that of an aryl-lithium species (pKₓ ∼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). 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...
demethylation (35–45 equiv BBr₃, 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 C₂-symmetrical 279, which was subjected to two-directional238,239 homologation to yield dialdehyde 280 in good yield (Scheme 46, A). Aldehyde 280 was obtained as a diastereomeric mixture (dr ∼10:1), from which recrystallization of the major (C₂-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. 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 C₁₄α on the resorcinol A₂ 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 alklylation/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 dibromoaapplepsin 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 S of
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 B1 phenol of 292, initiating 7-exo-trig cyclization (C_{10c}−C_{1b}). The subsequent global methylation gave 293 as 1:1 mixture of diastereomers at C_{1b}. 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 NaBH4 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 BBr3 were unsuccessful, necessitating methylation of the free phenol prior to exposure to BBr3. 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). 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 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/benzyl 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!
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. In 1997, Pezzuto and co-workers reported that resveratrol was a potential cancer chemopreventive agent, exhibiting anti-initiation, antipromotion, and antiproliferation activities. 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. 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. 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, 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.

Scheme 50. Total Synthesis of Caraphenol A by Snyder and Wright

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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) isoforms 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 many 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 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. 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).
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 autoimmunity and inflammatory response in murine macrophages. 

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 by 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 IFN-γ. 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 (αβ) 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) residues by the associated JAK subunits. The two phosphorylated STAT-1 molecules form a homodimer upon dissociation from the complex, and are each further phosphorylated at serine (Ser) residues by a p38 mitogen-activated protein (MAP)-kinase.

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. The latter is a transcription factor that 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. The latter is a transcription factor that

Analogously to STAT-1, phosphorylation is a prerequisite for NF-κB activation, homo/heterodimerization, and translocation. However, unlike STAT-1, NF-κB itself is not phosphorylated. Rather, cytoplasmic NF-κB 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-κB. In response to various inflammatory stimuli, 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-κB for translocation to the nucleus. 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). Dysregulation of NF-κB-mediated activities 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-κB 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 Dpterocarpaceae plant, Vatica rassak. 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. 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). 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 | IC50 (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        |
|                                                                                                                                                                                                                                           | sulfatrucol 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 lipopolysacharides (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.                                      | ampepolios 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 | N/A        |
| **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 integrase 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       |
|                                                                                                                                                                                                                                           | hemseleyanol C; 316 | 1.0        |
|                                                                                                                                                                                                                                           | α-viniferin-glucopyranoside; 316 | 4.0        |
|                                                                                                                                                                                                                                           | nepalesinol B; 128  | 0.022      |
|                                                                                                                                                                                                                                           | nepalesinol F; 307  | 5.5        |
|                                                                                                                                                                                                                                           | (+)-α-viniferin; 309 | 0.8        |
|                                                                                                                                                                                                                                           | sophorastilbene A; 309 | 3.1        |

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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 pathway290 and the PI3K/Akt pathway291 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.294 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.295,310 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 reox 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 activity. Valgimigli and co-workers determined the rate of peroxyl radical-trapping by resveratrol in homogeneous chlorobenzene solution to be 2.0 × 10⁶ M⁻¹ s⁻¹,311 which is approximately 16 times lower than that of α-tocopherol, (α-TOH, k_αα = 3.2 × 10⁶ M⁻¹ s⁻¹), nature’s ubiquitous radical-trapping antioxidant.322 Recently, Pratt and co-workers systematically evaluated the radical trapping efficiencies 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.320 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 146 and 146-β₂-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 lipopholic 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 EC₅₀ 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-buty methyl esters. 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 146-pallidol 153 was inefficient at preventing lipid peroxidation in bilayers, it was surprisingly potent (EC₅₀ = 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 (Cul)-3-based ubiquitin E3 ligase and subsequent proteasomal degradation.315,314 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-butyalted 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 C3 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 IC50 values for a given set of isolated natural products. It would be beneficial for researchers to perform these studies on analogues that have beenrationally 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.

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Notes

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