A Scalable Biomimetic Synthesis of Resveratrol Dimers and Systematic Evaluation of their Antioxidant Activities**

Bryan S. Matsuura, Mitchell H. Keylor, Bo Li, YuXuan Lin, Shelby Allison, Derek A. Pratt, and Corey R. J. Stephenson*

Abstract: *An efficient synthetic route to the resveratrol oligomers quadrangularin A and pallidol is reported. It features a scalable biomimetic oxidative dimerization that proceeds in excellent yield and with complete regioselectivity. A systematic evaluation of the natural products and their synthetic precursors as radical-trapping antioxidants has revealed that, contrary to popular belief, this mode of action is unlikely to account for their observed biological activity.*

The resveratrol (**1**) oligomers are a diverse set of polyphenolic natural products, the stress-factor-induced biosynthesis of which constitutes an important chemical defense mechanism in many plants.[1] Numerous reports of their health-promoting potential have generated widespread interest in these compounds,[2] much of which has been focused on their capacity as radical-trapping antioxidants (RTAs). However, systematic studies of this activity are lacking, since investigators often assay only the position of their thermodynamic equilibrium with oxidants in solution, and not whether the relevant radical-trapping reactions are kinetically competitive under physiological conditions.[3]

With their intriguing biological activities and fascinating molecular architectures, the resveratrol oligomers have inspired a number of synthetic endeavors.[4] Early work aimed to replicate nature's approach, which is believed to involve single-electron oxidative coupling processes. While construction of these molecules in such a fashion would support their proposed biogenesis, efforts to date have resulted in low yields and/or complex mixtures of products. Recognizing this shortcoming, Snyder and co-workers developed powerful de novo strategies towards resveratrol dimers[5b,c,6c,d] and higher-order oligomers.[7] These impressive studies prompted a number of subsequent syntheses, including innovative approaches from the Nicolaou/Chen,[6a] Sarpong,[6b] and Studer[5f] groups. Following this precedent, we sought to rapidly access chemical diversity from common intermediates in a controlled fashion, and to address lingering questions regarding the role of resveratrol-derived natural products as bioactive small molecules. The total synthesis of pallidol (**2**)[8] and quadrangularin A (**3**),[9] and the systematic evaluation of their RTA activities, are reported herein.

Owing to the electron-rich nature of resveratrol ($E_{(ox)} <$ 0.7 V vs Ag/AgCl),[10] we reasoned that its oxidation by a visible-light photoredox catalyst would be feasible,[11] thus enabling catalytic generation of the requisite phenoxyl radical for dimerization. In considering our reaction design, we drew inspiration from the seminal report of Hou and Li,[5a] in which they demonstrated that *tert*-butyl resveratrol derivative **4a** (Scheme 1) could be dimerized regioselectively. However, as a result of apparent issues with oxidation and oligomerization of product dimers in the reaction mixtures, we instead elected to use the benzyl-protected resveratrol derivative **4b**. Preliminary efforts using photoredox catalysis resulted in mixtures of the dimeric isomers **5**, **6**, and **8** (Scheme 1) in yields highly dependent on the solvent and the presence/absence of base.[12] Extensive reaction optimization[13] revealed that the phenoxide of **4b**[14] undergoes a remarkably efficient and selective dimerization to bis-quinone methide **5** (60–80%) under aerobic conditions, but a significant decrease in selectivity and reproducibility was observed on scale-up. To overcome this limitation, we exchanged O_2 for ferrocenium hexafluorophosphate ($[FeCp_2]PF_6$)[15] as the oxidant, which reliably provided **5** in more than 95% yield on decagram scale. To the best of our knowledge, this represents the highest yield and largest scale yet reported for oxidative dimerization of a resveratrol derivative.[4]

The dimerization produces an inseparable mixture of *meso* and *dl* diastereomers **5/5′**, and the relative configuration of the vicinal stereogenic centers has important (and likely biogenically relevant) consequences for the synthesis of pallidol (**2**) and quadrangularin A (**3**; Scheme 1). The *dl* diastereomer of **5** has the correct relative configuration to undergo two sequential cyclizations to provide the [3.3.0] ring system present in pallidol (**2**). By contrast, after the initial Friedel–Crafts reaction of *meso-***5**, the *anti/anti* configuration of product indane **6** precludes a second cyclization event owing to the thermodynamically unfavorable formation of a *trans*-fused bicyclo[3.3.0]octane.[16] Addition of BF$_3$·OEt$_2$ to a dilute solution of **5/5′** at −78°C gave the desired pallidol derivative **7a** in 43% yield of isolated product. The remaining mass balance was **6** (45%) and a complex mixture of oligomerized material. Hydrogenolysis of **7a** followed by
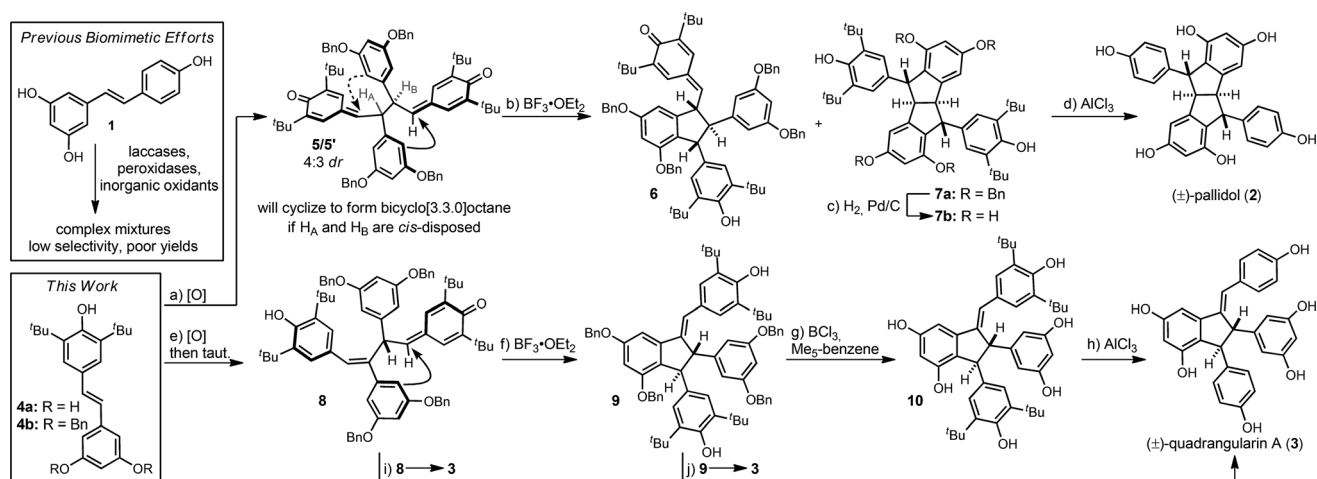
[*] B. S. Matsuura,[+] M. H. Keylor,[+] Prof. Dr. C. R. J. Stephenson
Department of Chemistry, University of Michigan
Ann Arbor, MI 48109 (USA)
E-mail: crjsteph@umich.edu

B. Li, Y. Lin, S. Allison, Prof. Dr. D. A. Pratt
Department of Chemistry, University of Ottawa
Ottawa, ON K1N 6N5 (Canada)
E-mail: dpratt@uottawa.ca

[+] These authors contributed equally to this work.

Scheme 1. The total synthesis of pallidol (**2**) and quadrangularin A (**3**): a) KHMDS (1.05 equiv), [FeCp$_2$]PF$_6$ (1.05 equiv), THF, 0°C, 30 min, 95%; b) BF$_3$·OEt$_2$ (2 equiv), CH$_2$Cl$_2$, −78°C, 40 min, 88%, **6/7a** ca. 1:1; c) Pd/C (30 wt%), H$_2$ (1 atm), 3:2 EtOAc/MeOH, RT, 12 h, 95%; d) AlCl$_3$ (12 equiv, 2.25 M in CH$_3$NO$_2$), toluene, 60°C, 30 min, 80%; e) KHMDS (1.05 equiv), [FeCp$_2$]PF$_6$ (1.05 equiv), THF, 0°C, 30 min, then KHMDS (1.25 equiv), 15 min; f) BF$_3$·OEt$_2$ (2 equiv), CH$_2$Cl$_2$, −78°C, 5 min, 90% over 3 steps; g) BCl$_3$ (12 equiv), Me$_5$-benzene (20 equiv), CH$_2$Cl$_2$, −78°C, 2 h, 82%; h) AlCl$_3$ (12 equiv, 2.25 M in CH$_3$NO$_2$), toluene, 60°C, 30 min, 80%; i) Me$_5$-benzene (40 equiv), AlCl$_3$ (25 equiv, 0.6 M in CH$_3$NO$_2$) slow addition, CH$_2$Cl$_2$, 0°C, then 60°C, 15 min, 51%; j) Me$_5$-benzene (40 equiv), AlCl$_3$ (24 equiv, 0.5 M in CH$_3$NO$_2$) slow add'n, CH$_2$Cl$_2$, 0°C, then 60°C, 1 h, 88%, 5:1 mixture of quadrangularin A (**3**) to its internal alkene isomer. Bn = benzyl, *t*Bu = *tert*-butyl, taut. = tautomerization, KHMDS = potassium hexamethyldisilazide, [FeCp$_2$]PF$_6$ = ferrocenium hexafluorophosphate, THF = tetrahydrofuran, Me$_5$-benzene = pentamethylbenzene.

removal of the *tert*-butyl groups through a retro-Friedel–Crafts reaction[17] provided pallidol (**2**; 76%, 2 steps).

Note that in quadrangularin A (**3**), the stereochemical information at one of these centers is ultimately destroyed, which enabled the development of a one-pot dimerization/base-mediated isomerization that provides **8** in nearly quantitative yield from **4b** (Scheme 1). The tautomerization is diastereoconvergent, giving exclusively the (*E*)-stilbene isomer of **8** as a racemic mixture. Quadrangularin A (**3**) could be accessed from **8** in one, two, or three steps in 51%, 73%, and 55% yields, respectively. Here, Lewis acids serve to promote cyclization, global debenzylation, and removal of the *tert*-butyl groups, while Me$_5$-benzene was essential in preventing oxygen-to-carbon transfer of the transiently formed benzyl cations.[18]

Bis-quinone methides such as **5** have long been invoked as intermediates in the biosynthesis of resveratrol oligomers, but their existence remains unsubstantiated. Although seemingly trivial, the use of alkylated resveratrol derivative **4b** proved to be crucial to the success of this strategy since it tempers the redox potential of the stilbene, prevents the formation of regioisomeric dimers or undesired oligomers, and improves substrate solubility in nonpolar solvents, an effect critical for product chemoselectivity. Furthermore, despite the lability generally associated with quinone methides,[19] which are typically generated and reacted in situ,[7c] dimers **5**, **6**, and **8** were found to be bench stable and could be purified by flash chromatography. This stability proved instrumental in the tautomerization of **5/5′** to **8** under strongly basic conditions while maintaining "switchable" Friedel–Crafts reactivity under Lewis acidic conditions.

With these compounds in hand, we compared their peroxyl radical trapping activities in homogenous organic solution, lipid bilayers, and cell culture. Peroxyl radicals

mediate lipid peroxidation, a process that has been linked to myriad degenerative diseases that resveratrol has been suggested to prevent.[20] Our studies in solution (chlorobenzene) were carried out with the peroxyl radical clock methodology,[21] a kinetic competition method by which the rate constant for the reaction of a given antioxidant with a peroxyl radical (k_{inh}) can be obtained from the dependence of lipid autoxidation products on antioxidant concentration.[12] While the poor solubility of the natural products precluded direct determinations of their k_{inh} values, the benzylated synthetic precursors were soluble and values of k_{inh} were readily determined (Table 1, see footnote [i]). These results reveal that *t*Bu$_4$-quadrangularin A **9** ($6.8 \times 10^4 M^{-1} s^{-1}$) is slightly more reactive than *t*Bu$_2$-resveratrol **4b** ($5.9 \times 10^4 M^{-1} s^{-1}$), while *t*Bu$_4$-pallidol **7a** ($2.5 \times 10^4 M^{-1} s^{-1}$) is less reactive. The k_{inh} value for **7a**, which lacks an activating alkene, is indistinguishable from that of the common synthetic antioxidant BHT (once the two-fold statistical advantage of pallidol is considered). The reactivities of the authentic natural products could be estimated from the relative rate constants given above and the known rate constant for resveratrol, which was determined by Valgimigli and co-workers to be $2.0 \times 10^5 M^{-1} s^{-1}$.[22] These rate constants are all much smaller than that for α-tocopherol (α-TOH, $k_{inh} = 3.2 \times 10^6 M^{-1} s^{-1}$), a ubiquitous radical-trapping antioxidant in nature,[23] thus suggesting that **1**, **2**, and **3** are unlikely to owe their biological activities to RTA activity.

The RTA activities of the corresponding dealkylated compounds were then determined in the lipid bilayers of unilammelar vesicles of egg phosphatidylcholine, again by using a competitive kinetics approach,[12] but this time with a fluorogenic α-TOH derivative.[24] The relative rate constants determined this way (Table 1) clearly indicate an inversion in the relative reactivity between the natural products and their

Table 1: Radical-trapping antioxidant activity of resveratrol, pallidol, and quadrangularin A and their synthetic precursors in solution (chlorobenzene), lipid bilayers (of egg phosphatidylcholine), and cell culture (human erythroblasts). Data are also given for the benchmark phenolic antioxidants α-tocopherol and BHT (2,6-di-*tert*-butyl-4-methylphenol).

	Solution	Lipid Bilayers		Cells	Cytotoxicity
	k_{inh}[a] (PhCl) [M^{-1} s^{-1}]	k_{rel},[b] n[c] (ROO·$_{lipid}$)[d]	k_{rel},[b] n[c] (ROO·$_{aq}$)[d]	EC$_{50}$ [μM]	EC$_{50}$ [μM]
resveratrol (**1**)	2.0×10^{5}[e]	<0.01	<0.01	12.6±0.9	118±14
pallidol (**2**)[f]	8.5×10^{4}[g]	<0.01	<0.01	8.1±0.9	205±11
quadrangularin A (**3**)	2.3×10^{5}[g]	<0.01	<0.1	3.4±0.4	63.5±3.0
α-tocopherol (α-TOH)	3.2×10^{6}[e]	1.8±0.2, 2.0[h]	1.3±0.1, 2.0[h]	0.15±0.01	>100
*t*Bu$_2$-resveratrol (**4a**)	$(5.9 \pm 0.8) \times 10^{4}$[i]	17.9±3.3, 1.8±0.1	21.0±6.8, 1.8±0.1	0.051±0.004	10.2±0.3
*t*Bu$_4$-pallidol (**7b**)[f]	$(2.1 \pm 0.3) \times 10^{4}$[i]	<0.01	<0.01	0.39±0.07	10.2±0.4
*t*Bu$_4$-quadrangularin A (**10**)	$(6.2 \pm 0.9) \times 10^{4}$[i]	7.5±0.6, 1.9±0.1	<0.1	0.21±0.03	8.7±0.5
BHT	$(2.2 \pm 0.1) \times 10^{4}$[i]	<0.01	<0.01	12.7±1.5	49.5±2.0

[a] Second-order rate constant for the reaction with (linoleyl) peroxyl radicals. [b] Second-order rate constant for the reaction with peroxyl radicals relative to the fluorescent probe H$_2$B-PMHC. [c] Number of peroxyl radicals trapped per molecule of test compound. [d] Initiated with MeOAMVN (lipid soluble) and AAPH (water soluble), respectively. [e] Determined at 30°C from the inhibited autoxidation of styrene, see Ref. [22]. [f] Since two equivalent units exist on the same molecule, the observed rate constant has been divided by 2. [g] Estimated from the value for resveratrol and the relative reactivities of the corresponding synthetic precursors (*tert*-butylated analogues). [h] From Ref. [24b]. [i] Determined at 37°C by using the peroxyl radical clock methodology on resorcinol ring protected (benzyl) compounds.

synthetic precursors when compared to the measurements in homogenous solution; **1**, **2** and **3** were largely ineffective in competing for peroxyl radicals with the fluorogenic α-TOH derivative, whereas their *tert*-butylated analogues were very effective. In fact, these compounds were superior to α-TOH (10- to 16-fold for **4a** and 4-fold for **10**, depending on whether the oxidations were mediated by lipophilic or hydrophilic peroxyl radicals).

Barclay,[25] Niki,[26] and others have shown that the inherent reactivity of RTAs with peroxyl radicals (i.e., the solution k_{inh} values) is far less important than their physical properties when in a lipid bilayer, and the present results underscore this. Not only are the natural products expected to be less soluble than the *tert*-butylated analogues in the lipid milieu, but the reactivity of their key phenolic O—H groups will be lowered to a greater extent owing to H bonding with phosphatidylcholine moieties and/or water at the interface.[27,28] These results further support the notion that resveratrol and its related natural products are not sufficiently reactive as RTAs for this to be their mode of action in a biological context.[29,30]

The above results provide important insight into the trends we observed in cultured human erythroblasts. Lipid peroxidation was induced by diethylmaleate treatment, assayed by competitive oxidation of the antioxidant and a lipophilic fluorogenic probe (C11-BODIPY$^{581/591}$),[31] and measured by flow cytometry. Again, the natural products were far less effective at inhibiting lipid peroxidation than their *tert*-butylated analogues. In the case of pallidol and quadrangularin A, the difference in their half maximal effective concentration (EC$_{50}$) values is roughly 20-fold (8.1 and 3.4 vs. 0.39 and 0.21 μM, respectively), whereas for resveratrol, the difference is almost 250-fold (12.6 μM vs. 51 nM). In fact, *tert*-butylated resveratrol is even more effective in cell culture than α-TOH (EC$_{50}$ = 0.15 μM), a result that is consistent with its significantly higher reactivity in lipid bilayers and reinforces the fact that dynamics must trump inherent reactivity in heterogeneous systems.[25,26]

Interestingly, **4a** is the most reactive radical-trapping antioxidant we have yet to study in cell culture (even more so than the naphthyridinols),[24b] and its EC$_{50}$ value under the experimental conditions was 200-fold lower than the corresponding EC$_{50}$ values for inducing cell death—a much larger margin than for the natural products. Curiously, although the *tert*-butylated pallidol **7b** was inefficient at trapping radicals in lipid bilayers, it was surprisingly potent against lipid peroxidation in cell culture, thus suggesting that it may operate through a different mechanism, possibly one involving the induction of the expression of genes controlled by the antioxidant response element (ARE).[32] Further investigation is required to understand the mechanism of the comparatively poor antioxidant activity of the natural products, which is almost certainly not due to their RTA activity.

In summary, we have developed a highly efficient and scalable oxidative dimerization of *tert*-butylated resveratrol derivative **4b** to generate uniquely stable and synthetically versatile quinone methides. The "built-in" reactivity of these bioinspired intermediates was leveraged in the synthesis of dimeric natural products pallidol (**2**; 6 steps, 26% yield) and quadrangularin A (**3**; 5 steps, 54% yield), which represents the most efficient syntheses of these dimers to date. Through systematic evaluation of the antioxidant activities of the natural products and their synthetic precursors, we ascertained that the natural products examined in this study are not kinetically competitive as radical-trapping antioxidants under biologically relevant conditions. Preliminary data suggest that this biomimetic synthetic strategy will be applicable to the synthesis of higher-order resveratrol oligomers. Efforts to delineate these syntheses and to better understand the dichotomous behavior of the natural products and their *tert*-butylated precursors in homogenous solution versus lipid bilayers and cultured human cells are underway.

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