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Synthesis of Resveratrol Tetramers via a Stereoconvergent Radical Equilibrium

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Abstract

Persistent free radicals have become indispensable in the synthesis of organic materials by living radical polymerization. However, examples of their use in the synthesis of small molecules are rare. Herein, we report the application of persistent radical and quinone methide intermediates to the synthesis of the resveratrol tetramers nepalensinol B and vateriaphenol C. The spontaneous cleavage and reconstitution of exceptionally weak carbon-carbon bonds has enabled a stereoconvergent oxidative dimerization of racemic materials in a transformation that likely coincides with the biogenesis of these natural products. The efficient synthesis of higher-order oligomers of resveratrol will facilitate the biological studies necessary to elucidate their mechanism(s) of action.

Resveratrol (**1**), a naturally occurring and biologically important polyphenol (**1**), is widespread within the plant kingdom, where it serves as the progenitor to an arsenal of phytoalexins – antimicrobial defense compounds which accumulate rapidly at sites of pathogenesis to neutralize invading microorganisms and promote plant survival (**2**). Several resveratrol oligomers (dimers, trimers, tetramers) have been shown, primarily via in vitro studies, to exert biological effects which transcend this natural role, including, but not

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Supplementary Materials:

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limited to, anti-inflammatory, immunomodulatory, and cytotoxic activities (3). Unfortunately, the requirement for laborious extraction and purification of resveratrol oligomers from plant matter has imposed severe limitations on the extent to which their mechanism(s) of action can be elucidated. It is therefore imperative that synthetic advances be made to confirm or refute the biological activities ascribed to the isolated natural products, to identify chemical frameworks which hold potential as small molecule chemopreventives and/or chemotherapeutics, and to enable structural modification for both structure-activity relationship (SAR) studies and the development of congeners with improved potency, efficacy, and bioavailability. Although the synthetic community has presented several innovative approaches to the resveratrol dimers (4–10), access to higher-order oligomers remains a serious challenge. In 2011, Snyder and coworkers reported a *de novo* synthetic approach to this problem, accessing several higher-order oligomers through homologation of dimeric core structures (11), a strategy which has since been employed in two additional trimer syntheses (12, 13), and which represents the only successful strategy to date for the preparation of these compounds.

Organisms which produce resveratrol (**1**) are able to harness the reactivity of delocalized phenoxyl radicals (e.g. **1**•, Fig. 1) generated upon its oxidation; the resultant oligomers are typically isolated as optically active materials (3). Although biomimetic approaches have been reported (14–17), such remarkable levels of regio-, chemo-, and stereoselectivity have proven challenging to replicate in the laboratory due to the transient nature of the putative radical and quinone methide intermediates (Fig. 1, inset). We reasoned that if these intermediates could be rendered more persistent (18), then it would be possible to gain the advantages of efficiency offered by biomimicry without sacrificing the modularity offered by *de novo* synthetic approaches. Recently, we were able to recapitulate one mode of resveratrol oligomerization for the synthesis and antioxidant evaluation of two dimeric natural products, quadrangularin A (**2**) and pallidol (**3**) (Fig. 1) (19). The synthesis featured a remarkably persistent bis(*p*-quinone methide) intermediate **4a**, similar to those (e.g. **5**) invoked by Niwa, Pan and coworkers in their studies on the structural elucidation and biogenesis of resveratrol trimers and tetramers from ϵ -viniferin (**6**) (14–17). This biosynthetic logic can similarly be applied to higher-order oligomers, in principle providing access to the gamut of 8–8'; linked resveratrol tetramers (e.g. **7**, **8**) through a convergent oxidative coupling of ϵ -viniferin (**6**) followed by regio- and/or stereodivergent cyclizations of the resultant bis(*p*-quinone methide) **5** (Fig. 1) (3).

The proposed oxidative coupling presented several challenges. First, dimerization of a racemic form of **6** could, in principle, provide products derived from both homo- and hetero-dimerization between the (+)- and (–)-enantiomers; the (+)/(–) product is not represented in any known resveratrol oligomer. Furthermore, the dimerization reaction would generate two additional stereocenters, suggesting that the formation of six stereoisomers of product **5** is possible (Fig. S9) (20). Finally, it was unclear whether the intended double intramolecular cyclization of **5** would exhibit inherent preferences for specific regio- and stereochemical outcomes. Each hemisphere of tetramer **5** possesses two resorcinol moieties which are both capable of engaging each prochiral *p*-quinone methide in Friedel–Crafts cyclizations. The possibility for both symmetrical (2×5-*exo-trig*, 2×7-*exo-*

trig, 2×8-*exo-trig*) and unsymmetrical (5-*exo-trig*/7-*exo-trig*, 5-*exo-trig*/8-*exo-trig*) cyclization modes, each capable of producing several diastereoisomers (Fig. S10) (20), posed a daunting challenge.

Herein, we describe the execution of this strategy for the efficient biomimetic total synthesis of the resveratrol tetramers nepalensinol B (**7**) (21, 22) and vateriaphenol C (**8**) (23). Critical to the success of these efforts was the identification and rigorous characterization of an unconventional equilibrium between isolable dimeric (**4a/b**) and tetrameric (**5a/b**) bis(*p*-quinone methide) intermediates and their monomeric phenoxyl radicals (Fig. 1) (24), a physical property initially explored as a mechanistic curiosity, but which we have found to have remarkable – and potentially biogenically relevant – implications for dynamic stereocontrol in the context of resveratrol oligomer (bio)synthesis. Synthetic access to these natural products and their derivatives will enable further explorations of their already promising biological activities. For instance, nepalensinol B (**7**) is a potent inhibitor of topoisomerase II (IC₅₀ = 0.02 µg/mL) (22); this is 3000 times more potent than etoposide (VP-16, IC₅₀ = 70 µg/mL) (25), a clinically approved chemotherapeutic on the WHO model list of essential cytotoxic and adjuvant medicines (26).

During our studies toward resveratrol dimers (19), we discovered that intermediate **4a**, which was isolated as a 4:3 mixture of *meso:DL* diastereomers, could be quantitatively isomerized to *trans,trans*-indane **9** (Fig. 2), a product which can only derive from *meso-4a*. Although it was tempting to conclude that epimerization of *DL-4a* was proceeding via tautomerization followed by stereorandom vinylogous protonation, independent preparation of the presumptive intermediates and their subjection to these reaction conditions did not lead to any detectable formation of **9** (Fig. S7) (27). Thus, an alternate mechanism had to be responsible. In 1969, Becker reported that bis(*p*-quinone methides) similar to **4a** equilibrate in chloroform solution at room temperature with the corresponding monomeric phenoxyl radicals through a homolytic C–C bond scission process analogous to that of Gomberg's historic triphenylmethyl radical (24, 28). To probe whether such a mechanism could be operative for this transformation, a thermal crossover experiment was performed using differentially protected derivatives of **4**, and indeed our observations were consistent with the formation of a statistical mixture of homo- and cross-coupled products (Fig. S8) (27). Intrigued by this unusual reactivity, we undertook an extensive analysis of the homolytic dissociation equilibrium of **4a** and related derivatives.

Solutions of the bis(*p*-quinone methide **4a** in 1,2-dichlorobenzene yielded prominent EPR spectra at room temperature (Fig. 3a). The spectrum is fully consistent with what is expected for the phenoxyl radical derived from **1a** (hereafter **1a•**, Fig. 3b); the hyperfine coupling constants derived from the simulated spectrum are in good agreement with values from related compounds in the literature (29), as well as those predicted from the spin density distribution in **1a•** calculated using density functional theory (DFT) at the B3LYP/TZVP level of theory (Fig. 3c) (30, 31). Integration of the signals afforded $K_{eq}(\mathbf{1a}\bullet/\mathbf{4a}) = 1.8 \times 10^{-10}$ M (32). Spectra were recorded at several temperatures between 10 and 50 °C and the corresponding equilibrium constants used to provide an estimate of the thermodynamics of the homolysis–recombination process (Fig. 3d). Corresponding experiments were carried out by UV/Vis spectroscopy – with an expanded temperature range up to 85 °C (33) – by

following the increase in intensity of the low energy absorption maximum at 414 nm (which was attributed to **1a**• with $\epsilon = 79,000 \text{ M}^{-1}\text{cm}^{-1}$, *vide infra*) as a function of temperature (Fig. 3e) (34). The measurements agree that the central C–C bond dissociation enthalpy (BDE) in **4a** is $17.0 \pm 0.7 \text{ kcal/mol}$. Although this is not the weakest C–C bond reported to date (the C–C BDE in the 4,4'-dimer of 2,6-di-*t*-Bu-4-methoxyphenoxy is reported to be a mere $6.1 \pm 0.5 \text{ kcal/mol}$) (35), it does afford a meaningful equilibrium at room temperature.

To provide insight into the kinetics associated with this process, **4a** was subjected to laser flash photolysis (LFP) with the 308 nm emission of a nanosecond-pulsed XeCl excimer laser and the rates of recombination of the radicals were recorded. The transient species generated by photolysis exhibited the same low energy absorption centered at 414 nm as in the spectrum of **4a** (27). The decay of this absorbance could be fit to a second-order function using the extinction coefficients determined from the UV-Vis/EPR equilibrium experiments to afford the radical recombination rate constants, k_r (Fig. 3f). Although **1a**• features substantial spin density at C₈ (resveratrol numbering, Fig. 1) – enabling its dimerization at that position to give **4a** – the recombination rates were insensitive to the presence of O₂. Rate constants in the absence and presence of oxygen were found to be within error ($6.7 \pm 1.5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ and $7.4 \pm 1.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ respectively), with the combined data set affording $k_r = 6.9 \pm 1.4 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$. The homolysis rate constant could be estimated from the equilibrium constant and recombination rate constant to be $k_f = 1.2 \times 10^{-2} \text{ s}^{-1}$.

The homolytic dissociation equilibrium held tremendous potential for the biomimetic preparation of higher-order resveratrol oligomers. Drawing on the similarity between the putative biogenesis of 8–8' resveratrol dimers and tetramers (Fig. 1), we sought to realize a selective dimerization of *e*-viniferin (**6**) (or a suitably substituted derivative). In their total synthesis of the resveratrol trimer caraphenol A (**12**), Snyder and Wright reported a highly effective eight-step preparation of aldehyde **10**, which we have leveraged for the present synthesis. This intermediate was converted into *t*-Bu-*e*-viniferin derivative **6a** almost exclusively as the (*E*)-isomer via Wittig olefination with phosphonium salt **11a** in 85% yield (Fig. 4a). With **6a** in hand, we were poised to explore the key oxidative coupling reaction.

Despite concerns about stereo- and regioselectivity in the proposed transformations, our observations in the diastereoconvergent cyclization of **4a** (*vide supra*, Fig. 2) suggested that thermodynamic differentiation of the various diastereoisomers of **5** – interconvertible via C–C homolysis-recombination – may afford some level of selectivity upon oxidative coupling, whereas the conformational requirements for productive orbital overlap may favor selected cyclization modes in the ensuing Friedel–Crafts reactions. Remarkably, subjection of **6a** to our ferrocenium-mediated oxidative dimerization conditions afforded the desired tetrameric bis(*p*-quinone methide) **5a** as nearly a single diastereoisomer (ca. 19:1 major isomer : all other isomers) – derived from the coupling of two monomers of the same absolute configuration (Fig. 4b). Although stereoselectivity has been observed previously in biomimetic dimerizations of racemic precursors (36–38), examples are rare and typically proceed via polar, irreversible mechanisms. Although it is possible that the stereochemical outcome of oxidative coupling of **5a** is kinetically determined during the dimerization event itself, it is far more likely that initial coupling produces a mixture of diastereomers which rapidly equilibrate in solution via bond homolysis–recombination.

To support this hypothesis, we subsequently carried out analogous characterization of the **5a/6a•** equilibrium as described above for **4a/1a•**. Once again, EPR spectra consistent with **6a•** were obtained from room temperature samples of **5a** (Fig. S1a–c) (27) and the temperature dependence of the equilibrium constants (Fig. S1d, also determined by UV-Vis spectroscopy – Fig. S1e) (27) once again enabled the determination of the key C–C BDE in **5a** to be 17.1 ± 0.4 kcal/mol – within error of **4a**, as were the kinetics: $k_t = 2.0 \pm 1.1 \times 10^7$ M⁻¹s⁻¹ (Fig. S1f) and $k_f = 3.6 \times 10^{-3}$ s⁻¹. Given the overall similarity of the kinetics and thermodynamics of homolysis-recombination of tetramer **5a** when compared to dimer **4a**, the equilibration of **5a** to nearly a single diastereomer was likely. Gratifyingly, exposure of **5a** to BF₃·OEt₂ at –60 °C followed by warming to –30 °C furnished a mixture of just two regioisomeric (3.5:1 ratio) cyclization products: **12a** (44%, single diastereomer) and **13/14a** (9%, 9:1 *dr*) (Fig. 4b). Each of these compounds derive from the *trans,cisoid* (*S*)/(*S*) (or (*R*)/(*R*)) diastereomer of **5a**. However, this does not unequivocally demonstrate that this is the lowest energy diastereomer of **5a**, only that the cyclization of this diastereomer is favored over that from the (*R*)/(*S*) configuration. Structures **12a**, **13a**, and **14a** represent the carbon skeletons of nepalensinol B (**7**) (21, 22), vateriaphenol C (**8**) (23), and hopeaphenol (**15**) (39). The stereochemical outcome of the Friedel–Crafts cyclization leading to major product **12a** is complementary to that achieved by Snyder and coworkers through iterative homologation of the pallidol (**3**) core, which is capable of producing the stereoisomer ampelopsin H (**11**).

Global debenzoylation of **12a** and **13/14a** via Pd/C-mediated hydrogenolysis proceeded in 45% and 60% yields, respectively (27). However, attempts at removal of the four remaining *tert*-butyl groups were unsuccessful under a variety of reaction conditions, resulting in decomposition to an intractable mixture. Although extensive investigation of this transformation may have eventually revealed less destructive conditions for dealkylation of the penultimate intermediates, the use of an isosteric functional group with increased lability which could nevertheless enforce regio- and diastereoselectivity upon oxidative coupling of **6** seemed to be a more attractive solution. Our initial thoughts focused on the use of trimethylsilyl (TMS) groups in place of the ^tBu moieties. To our surprise, given the vast literature on the chemistry of hindered phenols and phenoxyl radicals, the persistence of 2,6-di-TMS-phenoxyl radicals had yet to be investigated. High accuracy CBS–QB3 quantum chemical calculations (40) predicted that the O–H BDEs in 2,6-di-TMS-4-methylphenol (**S2**) and 2,6-di-^tBu-4-methylphenol (BHT) were 80.7 and 78.6 kcal/mol, respectively (41, 42), suggesting that the electronic effects of TMS and ^tBu groups on the thermodynamic stability of phenoxyl radicals are similar. Moreover, the reactivity of **S2** toward peroxy radicals in inhibited autoxidations of styrene was essentially indistinguishable from that of BHT ($k = 1.4 \times 10^4$ vs. 2.1×10^4 M⁻¹s⁻¹, respectively) (Fig. S6) (27) – suggesting that the kinetics of the reactions of the silylated phenol and phenoxyl radicals would be similar to that of their *t*-butylated counterparts.

Accordingly, **1b** (Fig. 1) could be readily oxidatively dimerized to the corresponding bis(*p*-quinone methide) dimer **4b**. Crystals of the *meso* isomer of **4b** suitable for X-Ray analysis were obtained (Fig. 2) (27), confirming its identity as a bis(*p*-quinone methide) and seemingly revealing a conformational preference for antiparallel alignment of the carbonyl

moieties, likely resulting from the combined influence of sterics and dipole minimization. Like its *tert*-butylated predecessor, **4b** yielded a prominent EPR spectrum at room temperature that was consistent with the phenoxyl radical derived from **1b** (Fig. S2a–c) (27). Efforts to determine the temperature dependence of the **4b/1b**• equilibrium were limited by the fact that **4b** was not sufficiently persistent to obtain reproducible spectra above 50 °C, instead undergoing an unusual rearrangement to a derivative of the natural product δ -viniferin (27). Nevertheless, a Van't Hoff plot of the available data between 10 and 50 °C afforded an estimate of the C–C BDE of 16.4 ± 0.5 kcal/mol (Fig. S2d–e) (27) – only slightly lower (and within error) of that in **4a**. The recombination rate constant was determined by laser flash photolysis of **4b** to be $k_r = 5.3 \pm 3.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ (Fig. S2f) – almost one order of magnitude faster than that obtained for **4a** and explaining the slightly (5-fold) less favorable equilibrium, given the similar values of k_f (2.1×10^{-2} and $1.2 \times 10^{-2} \text{ s}^{-1}$ for **4b** and **4a**, respectively).

Likewise, the TMS derivative of ϵ -viniferin, **6b**, proved to be a competent substrate for FeCp₂PF₆-mediated oxidative dimerization (Fig. 4b), and the resultant bis(*p*-quinone methide) **5b** was found to undergo the same homolysis–decomposition (Fig. S3) (27) as **4b**. Cyclization with BF₃·OEt₂ at –78 °C cleanly afforded **12b** (59%, single diastereomer) and **13/14b** (15%, 9:1 *dr*), respectively. The increased reactivity of the silylated derivative **5b** was evident as it was less stable to silica gel chromatography and could be cyclized at a lower temperature than the ^tBu analogue. Cyclization at slightly elevated temperatures (–60 °C) afforded **12b** and **13/14b** in a 1.3:1 regioisomeric ratio, suggesting that the current level of product selectivity is sensitive to conformational effects. Furthermore, allylic strain minimization prior to 7-*exo-trig* cyclization would predict the hopeaphenol isomer **14b** to predominate, and therefore the observed preference for formation of the vateriaphenol C core **13b** suggests a likely contribution of transannular strain and/or conformational restriction in controlling facial selectivity during attack of the prochiral *p*-quinone methides. Hydrogenolysis of **13/14b** followed by protodesilylation afforded vateriaphenol C (**8**) and hopeaphenol (**15**) in 60% yield over 2 steps as a 9:1 mixture of diastereoisomers. Subjecting **12b** to the same reaction sequence provided nepalensinol B (**7**) in 75% yield over two steps.

The total syntheses of resveratrol tetramers nepalensinol B (**7**, 5.1% overall yield) and vateriaphenol C (**8**, 1.1% overall yield) described herein required only 13 linear synthetic steps. Critical to our strategy was the application of thermodynamic stereocontrol in the dimerization of persistent free radicals, a process which we have extensively characterized. The efficiency of the route has enabled the preparation of sufficient quantities of material that the biological activities of these natural products can now be more thoroughly evaluated.

Supplementary Material

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Fig. 1. Synthetic design

Merging *de novo* and biomimetic strategies allows for selective, scalable, and efficient preparation of resveratrol oligomers by the use of persistent radical and bis(*p*-quinone methide) intermediates (Bn, benzyl).

Fig. 2. Diastereoconvergent cyclization of 4a
(TFA, trifluoroacetic acid).

Fig. 3. Characterization of homolytic dissociation equilibrium of representative bis(*p*-quinone methide) **4a**

(a) Experimental (black) and fitted (red) EPR spectrum of **1a•** recorded at 295 K. (b) Experimental (black) and calculated (red) hyperfine coupling constants for **1a•**. (c) Spin density distribution in **1a•** predicted by DFT (B3LYP/TZVP). (d) Temperature dependence of equilibrium constants determined by EPR (black) and UV-Vis (red) spectroscopy and corresponding calculated thermochemical parameters. The error bars represent standard deviations for three or more combined measurements. (e) Temperature dependence of absorbance corresponding to **1a•** (inset: full spectrum of **4a** at 323 K). (f) Second-order decay of absorbance at 414 nm following nanosecond-pulsed irradiation of **4a** at 308 nm under an atmosphere of either nitrogen (black) or oxygen (red).

Fig. 4. 13-step total synthesis of resveratrol tetramers

(A) Preparation of ϵ -viniferin derivatives, reagents and conditions are as follows: $i\text{-Pr}_2\text{NH}$, $n\text{-BuLi}$, THF, then **11a/b**, then **10**, -78°C to RT, then 0°C , TBAF, 0.5 h, 85% for **6a**, 80% for **6b**. (B) Synthesis of nepalensinol B and vateriaphenol C, reagents and conditions are as follows: (a) THF, 0°C , then KHMDS, then FeCp_2PF_6 , 97% for **5a**, 63% (14% recovered SM) for **5b**; (b) For **5a**, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , -60°C to -30°C , (44% **12a** + 9% **13/14a**). For **5b**, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , -78°C , (59% **12b** + 15% **13/14b**); (c) 1. Pd/C (30 wt%), MeOH/EtOAc (1:1 v/v), H_2 (1 atm), filter, concentrate, then 2. TFA (0.05 M) in $\text{CH}_2\text{Cl}_2/\text{MeNO}_2$ (1:1 v/v), 75% for **7**, 60% for **8/15**. THF = tetrahydrofuran, TBAF = tetra-*n*-butylammonium fluoride, KHMDS = potassium hexamethyldisilazide, dr = diastereomeric ratio, SM = starting material, RSM = recovered starting material.