Synthesis of vitisin A & D: Thermal isomerization enabled by a persistent radical equilibrium

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Abstract: The first total synthesis of the resveratrol tetramers vitisin A and vitisin D is reported. Electrochemical generation and selec-tive dimerization of persistent radicals is followed by thermal isomerization of the symmetric C8b–C8c dimer to the C3c–C8b isomer, providing rapid entry into the vitisin core. Sequential acid-mediated rearrangements consistent with the proposed biogenesis of these compounds afford vitisin A and vitisin D. The rapid synthesis of these complex molecules will allow for further study of their pharmacological potential.

Main Text

Resveratrol and its oligomers comprise a natural product class of hundreds of structurally distinct compounds; however, challenges associated with isolating individual molecules in adequate supply and purity have precluded rigorous evaluation of their pharmacological potential.[1] Numerous research groups have devised innovative synthetic approaches to access these complex molecules, including cationic cyclizations,[2–10] transition metal catalysis,[11–17] and reagent-controlled bromination.[18–20] It is proposed that oligomerization events in nature occur through phenoxyl radical intermediates.[1] Indeed, this biosynthetic hypothesis has inspired our own efforts in this area. We recently reported the use of persistent phenoxyl radicals (e.g. **1**) for the synthesis of resveratrol dimers pallidol and quadrangularin A,[21] and tetramers vateriaphenol C and nepalensinol B (**2**, Figure 1A).[22,23] Herein, we leverage the facile equilibrium between persistent phenoxyl radicals and their corresponding quinone methide dimers (i.e. **5R** and **5A/5B**, respectively, Figure 1B) to access the C3c–C8b connectivity en route to the first total synthesis of vitisin A and vitisin D (**3** and **4**, Figure 1A).

A new opportunity for C3–C8′ resveratrol oligomer synthesis was discovered while investigating the **5A**–**5R** equilibrium. Discontinuity in the Van't Hoff analysis above 50 °C suggested an alternative and irreversible reaction path was accessible to **5R** (see Figure S3 of the Supporting Information).[22] Importantly, no such discontinuity was observed in corresponding experiments with dimers featuring *tert*-butyl groups in lieu of the TMS groups in **5A/5R**. Subsequent NMR analysis revealed that upon heating the C8–C8′ dimer **5A** had rearranged to the δ-viniferin core **6**. We speculated that this rearrangement proceeded via the intermediacy of the C3–C8′ dimer **5B**, which was assumed to be less energetically favorable than the C8–C8′ dimer **5A** but primed to lose the trimethylsilyl group and aromatize the phenolic moiety. Indeed, computations suggest that the C3–C8′ dimer **5B** is 5.4 kcal/mol higher in free energy than the C8–C8′ dimer **5A**. However, the simple fact that **5R** is in equilibrium with **5A** (for which the C–C bond dissociation enthalpy was previously determined to be 16.4 kcal/mol[22]), implies

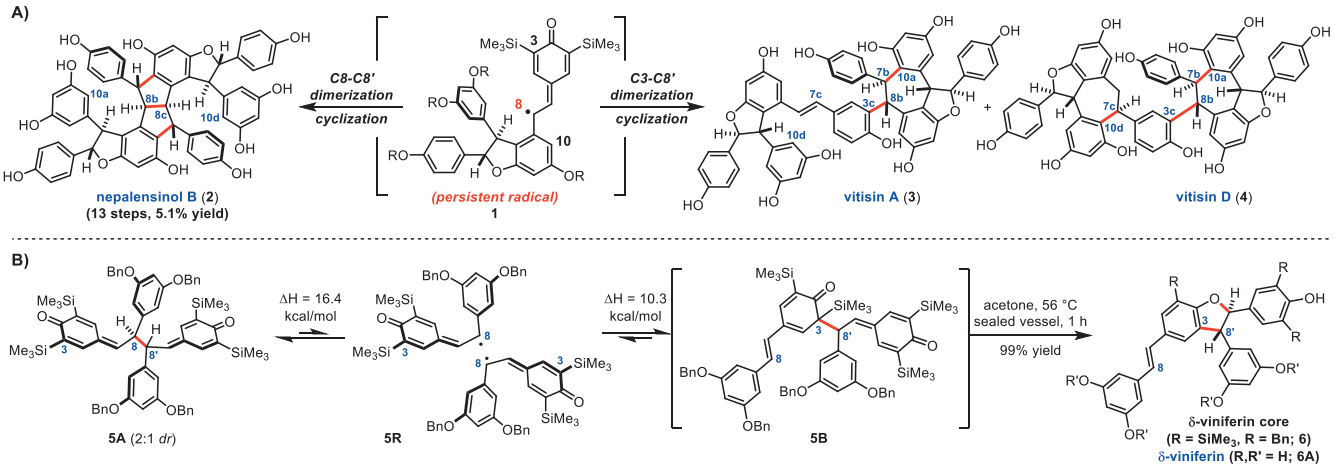

Figure 1. A) Divergent reactivity of regioisomeric quinone methide dimers in the synthesis of resveratrol tetramers. B) Discovery of C8b–C8c to C3c–C8b isomerization from thermodynamic study of persistent radical equilibria.

that it is also in equilbrium with the C3–C8′ dimer **5B (**$\Delta\Delta H$ = 6.1 kcal/mol). Presumably, **5B** is not observed due to its rapid decomposition to the δ-viniferin core (**6**). Computations predict that unimolecular expulsion of the TMS cation proceeds with a significant barrier,[24] suggesting that adventitious water in the acetone promotes desilylation and concomitant aromatization. Remarkably, the C8–C8′ to C3–C8′ isomerization and subsequent cyclization to **6** occurs in nearly quantitative yield (Figure 1B).

The difference in free energy of the corresponding *tert*-butylated dimers is 13.8 kcal/mol, which is consistent with the fully reversible equilibrium observed between the C8–C8′ dimers and the phenoxyl radicals derived therefrom. In contrast, the C3–C8′ and C8–C8′ dimers which lack ortho substitution are computed to be essentially equivalent in energy and therefore are funneled toward the δ-viniferin core. These computations are consistent with the hypothesis that resveratrol oligomerization proceeds through common intermediates that are subsequently isomerized in enzymatic processes,[1] yet, in the absence of enzymatic machinery, the inherent preference for the C3–C8′ product is clear. In fact, numerous research groups have realized the direct conversion of resveratrol (**S1**) to δ-viniferin (**6A**, Figure 1B) through single electron oxidation strategies (see Table S1 of the Supporting Information for a summary of these efforts).[25–32] While excellent yields for conversion to **6A** have been realized, extension of this strategy to higher-order oligomers has not achieved the same degree of success. The most noteworthy example was reported by Sako and co-workers in their semi-synthesis of vitisin B (**5**).[31] By treating isolated (+)-ε-viniferin (**S4**) with silver acetate in methanol at elevated temperatures (50 °C), they observed conversion to vitisin B (**7A**) in 40% yield on 20 milligram scale (see Figure S2 of the Supporting Information). The C3c–C8b-fused resveratrol tetramers exhibit some of the more potent reported biological activities among members of the resveratrol oligomer class; therefore, an approach to their synthesis reliant on readily available materials is desirable. For example, vitisin B (**7A**) was found by Lee and co-workers to be a potent

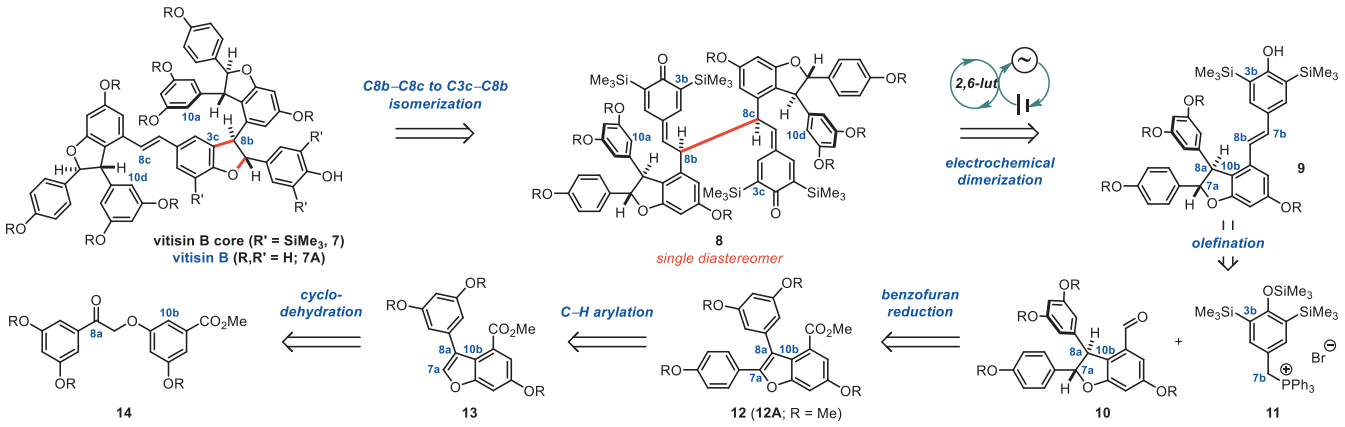

Figure 2. Retrosynthetic analysis for the synthesis of vitisin tetramers based on this late stage homolytic isomerization.

inhibitor of the NS3 helicase of hepatitis C (IC_{50} = 3 nM), while vitisin A (**3**) was also active against the same target (IC_{50} = 35 nM).[33] To the best of our knowledge, similarly rigorous biological analysis of vitisin D (**4**) has not yet been reported, so we envision that total synthesis will facilitate further biological study of this subset of resveratrol oligomers.

Quinone methide dimer **8** serves as the linchpin for the proposed isomerization approach to the C3c–C8b resveratrol tetramers (Figure 2). Importantly, this scaffold forms exclusively as a single diastereomer upon oxidation of racemic starting material **9**, meaning dimerization occurs selectively between the same enantiomeric precursors in the same fashion required to access vitisin B (**7A**). Preservation of this stereochemical integrity during C8b–C8c to C3c–C8b isomerization would directly convert **8** to the core of vitisin B (**7**). As **7A** is proposed to be the biogenic precursor to both **3** and **4**,[34] this novel formal [1,5]-shift could in principle provide access to multiple biologically active members of the C3c–C8b tetramers. Hypothesizing that the late-stage C8b–C8c to C3c–C8b isomerization would be preceded by our recently reported method for the electrochemical dimerization of phenylpropenoid scaffolds,[35] attention turned to the synthesis of the dimerization starting material – protected ε-viniferin analog **9**. This scaffold was previously prepared using an approach developed by the Snyder group in one of their seminal contributions to this field;[20] however, it was envisioned that a benzofuran precursor (i.e. **12**) might offer a more direct route to the desired dihydrobenzofuran fragment. Kim and Choi recently reported the modular synthesis of **12A** in their approach to permethylated analogs of viniferifuran, shoreaphenol, and malibatol A,[12] providing excellent precedent for such a strategy. Our overall synthetic proposal was not without significant questions: 1) Could we build upon Kim and Choi's route with an appropriate phenol protection strategy to ultimately reveal the natural products? 2) Would the stereochemical integrity of **8** be preserved during isomerization to **7**, or would escape from the solvent cage lead to complex mixtures of products? With these key considerations in mind, the synthesis of C3c–C8b resveratrol tetramers commenced.

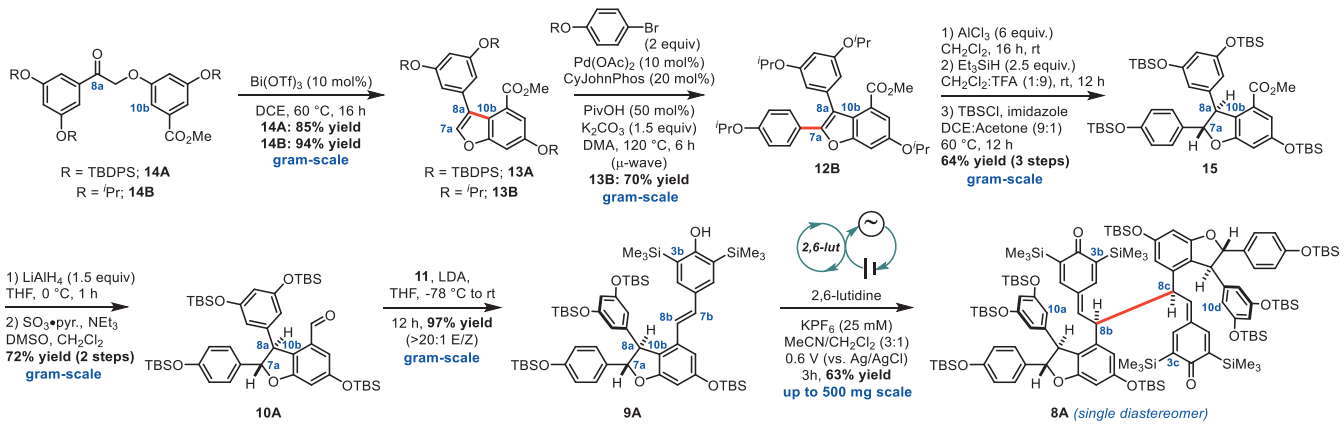

Figure 3. Synthesis of silyl-protected *bis*-quinone methide **8A**.

Silyl protection of the phenols appeared to be the logical choice, as they could, in principle, be removed along with the ArTMS groups in a single step. Gratifyingly, cyclodehydration of **14A** afforded benzofuran **13A** in 85% yield; however, C–H arylation of **13A** did not occur – instead these efforts were plagued by silyl deprotection. Benzyl ethers could be replaced for silyl ethers at this stage to allow for elaboration to **15** (see Figure S5 of the Supporting Information for details). Alternatively, isopropyl ethers have been demonstrated to be similarly robust to methyl, yet more readily cleaved, so this protection strategy was employed to access **15** in a shorter sequence (Figure 3). After C–H arylation,[36] **12B** was converted to **15** by Lewis acid-mediated deprotection,[37] Kishi reduction,[38] and silyl protection in a three-step sequence that did not require intermediate purification. Reduction of the C8b-ester and a Parikh-Doering oxidation[39] delivered aldehyde **10A**, and a Wittig olefination[40] smoothly afforded the silyl protected ε-viniferin analog **9A**. At this point, our dimerization method utilizing anodic oxidation was employed to access bis-quinone methide tetramer **8A**.[35] Deviation from the published conditions was required to ensure full solubility, and, after adding dichloromethane as a co-solvent and decreasing the electrolyte concentration by half, **9A** was converted to the desired quinone methide tetramer **8A** in 63% yield (Figure 3).

With the silyl-protected tetrameric material in hand, the key C8b–C8c to C3c–C8b isomerization step was next investigated. In order to determine if the persistent radicals would escape the solvent cage prior to the formal [1,5]-shift, possibly leading to mismatched C3c–C8b oligomers, a crossover experiment was performed with **5A** and a differentially protected analog (see Figure S4 of Suppporting Information). Indeed, the crossover products were observed, suggesting C–C fragmentation and diffusion is competitive with isomerization. However, the dimer model system was not sufficient to determine if the stereochemical integrity of **8A** would be completely eroded. Subjecting **8A** to the thermal isomerization conditions readily accessed the vitisin B core (**7B**), but as a mixture of four C3c–C8b dihydrobenzofuran (DHB) isomers (Figure 4, Sequence 1). Increasing the temperature improved the *trans/cis* ratio of the DHB rings, presumably due to thermal epimerization; however, the facial

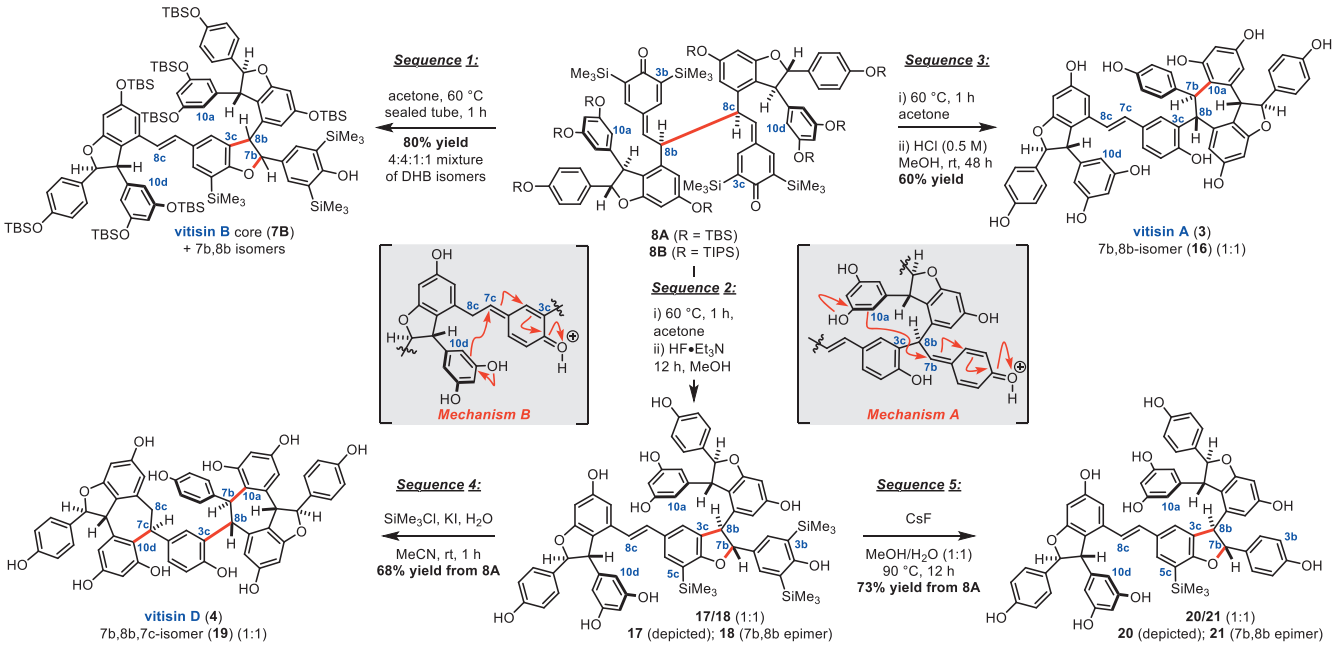

Figure 4. C8b–C8c to C3c–C8b isomerization, Friedel-Crafts cyclizations, and deprotections deliver vitisin A (**3**) and vitisin D (**4**).

selectivity of addition to C3c remained unchanged. To support the hypothesis that the formal [1,5]-shift only occurs through the relative configuration depicted by **8A**, a second crossover experiment between **8A** and the corresponding TIPS-protected analog **8B** was performed (Figure 4, Sequence 2). After thermal isomerization, an aliquot was removed and analyzed by HRMS. The mass for the crossover product was observed, further supporting that C–C fragmentation and diffusion is competitive with the formal [1,5]-shift. To evaluate the stereochemical outcome of the crossover experiment, HF-triethylamine was added to the reaction mixture to cleave the silyl ethers. This isomerization-deprotection sequence afforded two compounds – **17** and **18**. These *trans*-DHB isomers arise from each possible facial addition to C3c during the formal [1,5]-shift of the **8A** scaffold, suggesting that the stereochemical integrity is preserved during the thermal isomerization. The *O*-silyl deprotection conditions also resulted in epimerization of *cis*-DHB isomers to the corresponding *trans*-DHBs, which is well precedented in the literature,[16,17] thereby delivering only the two observed products.

Inspired by these results, we set out to develop conditions for *O*-silyl deprotection and protodesilylation to complete the synthesis. Global desilylation was achieved by addition of a methanolic solution of hydrochloric acid upon completion of the isomerization of **8A** (Figure 4, Sequence 3) yielding vitisin A (**3**) and its C7b, C8b-isomer. Vitisin A (**3**) is proposed to arise from vitisin B (**7A**) in the biosynthesis of these compounds.[34] Acid-mediated cleavage of the C7b–O bond affords a quinone methide to which C10a of the adjacent resorcinol ring adds in a 7-*exo*-*trig* cyclization (Mechanism A, Figure 4). Of note, the C10a–C7b bond formation exclusively

delivers the relative configuration depicted in Figure 4, with the C8b configuration dictating the facial selectivity of the cyclization.

In an attempt to prevent Friedel-Crafts rearrangement and directly reveal vitisin B (**7A**), intermediates **17**/**18** were next exposed to milder protodesilylation conditions.[41] Remarkably, vitisin D (**4**) and the isomer **19** were isolated after treating **17**/**18** with $SiMe_3Cl$, KI, and H_2O in MeCN for one hour (Figure 4, Sequence 4). These compounds are the result of two acid-promoted cyclizations; after cyclization to vitisin A (**3**) *in situ*, protonation of the stilbene at C8c results in formation of the quinone methide tautomer, which is trapped by 7-*exo*-*trig* cyclization by C10d of the adjacent resorcinol ring (Mechanism B, Figure 4). Acid-mediated conversion of vitisin A (**3**) to vitisin D (**4**) has been proposed in the biosynthesis of these compounds,[34] thus it is perhaps unsurprising that the *in-situ* generation of hydroiodic acid would give rise to **4** and **19**.

Alkaline conditions were next attempted in an effort to target vitisin B (**7A**).[42–44] It was quickly determined that the C3/5b aryl silyl groups are cleaved via fluoride-mediated-desilylation; however, the C5c-TMS group remains intact (Figure 4, Sequence 5). Our investigations have demonstrated that the C3c–C8b DHB is quite labile, and in fact, conversion to vitisin A (**3**) has been observed under a range of conditions (see Table S6 of the Supporting Information). Despite an extensive evaluation of desilylation conditions, access to vitisin B (**7A**) from this approach remains an outstanding challenge, the solution to which will be reported in due course.

Herein we have reported the first total synthesis of the resveratrol tetramers vitisin A (**3**, 3.3% overall yield) and vitisin D (**4**, 3.7% overall yield) in 10 and 11 steps from **14A**, respectively. Our approach utilizes persistent radicals to enable a unique, late-stage, formal [1,5]-shift. These persistent radicals are generated under mild anodic oxidative conditions, and the two successive steps afford rapid conversion of dimeric material to resveratrol tetramers in a manner that mimics their proposed biosynthesis.

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