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Communication

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

Kevin J. Romero,[1] Mitchell H. Keylor,[1] Markus Griesser,[2] Xu Zhu,[1] Ethan J. Strobel,[1] Derek A. Pratt[2,*] and Corey R. J. Stephenson[1,*]

[1]Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, USA

[2]Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5

Supporting Information Placeholder

ABSTRACT: The first total synthesis of the resveratrol tetramers vitisin A and vitisin D is reported. Electrochemical generation and selective 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. Computational results suggest that this synthetic approach mimics Nature's strategy for constructing these complex molecules. 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.

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] transition metal catalysis,[3] and reagent-controlled bromination.[4] It has been proposed that in nature, oligomerization proceeds via 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 C8–C8′ resveratrol dimers pallidol and quadrangularin A,[5] and tetramers nepalensinol B (**3**) and vateriaphenol C (**4**, Figure 1).[6,7] It has further been proposed that interconversion of the C8–C8′ and C3–C8′ constitutional isomers is the key step in the divergent biogenesis of related natural products possessing C3–C8′ connectivity.[1] Herein, we leverage the facile equilibrium between persistent phenoxyl radicals and their corresponding quinone methide dimers (i.e. **1** and **2**, respectively, Figure 1) to achieve the first total synthesis of vitisin A and vitisin D (**6** and **7**, Figure 1).

A new opportunity for C3–C8′ resveratrol oligomer synthesis was discovered while investigating the **8A**–**9A** equilibrium (Figure 2A). Discontinuity in the Van't Hoff analysis above 50 °C suggested an alternative and irreversible reaction path was accessible to **9A** (see Figure S3 of the Supporting Information).[6] Importantly, no such discontinuity was observed in corresponding experiments with dimers featuring *tert*-butyl groups (**8B**/**9B**) in lieu of the TMS groups in **8A**/**9A**. Subsequent NMR analysis revealed that upon heating the C8–C8′ dimer **8A** had rearranged to the δ-viniferin core **11**. We speculated that this rearrangement proceeded via the intermediacy of the C3–C8′ dimer **10A**, which was assumed to be less energetically favorable than the C8–C8′ dimer **8A** but primed to lose the trimethylsilyl group and aromatize the phenolic moiety. Indeed, computations suggest that the C3–C8′ bond in **10A** is 7.4 kcal/mol weaker than the C8–C8′ bond in **8A**.[8] However, the simple fact that **9A** is in equilibrium with **8A** (for which the C8–C8′ bond dissociation enthalpy was previously determined to be 16.4 kcal/mol[6]), implies that it is also in equilibrium with the C3–C8′ dimer **10A**. Presumably,

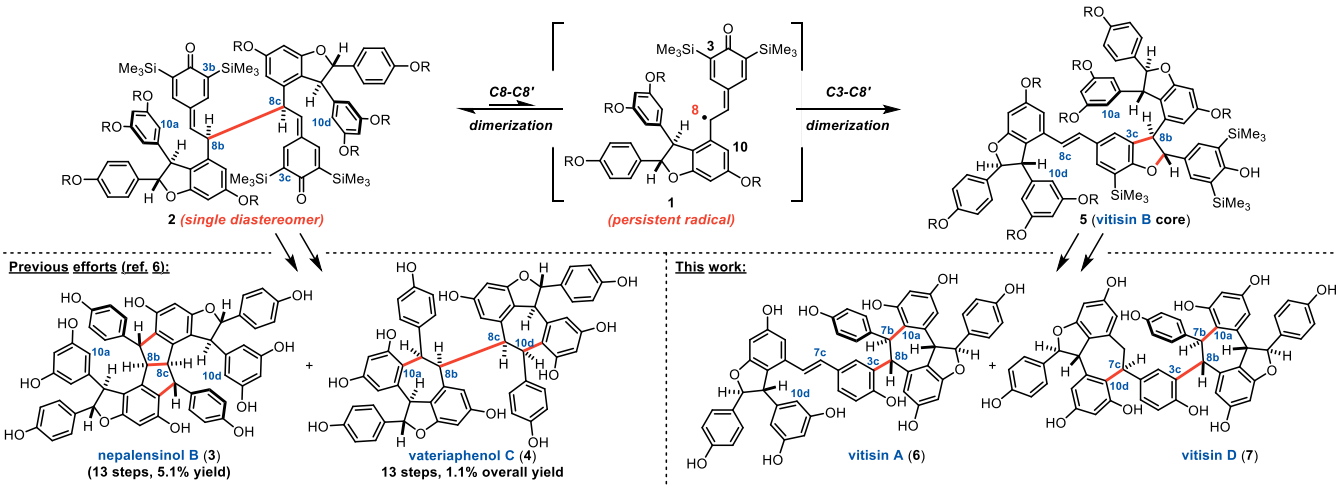

Figure 1. Divergent reactivity of persistent radicals in the synthesis of resveratrol tetramers.

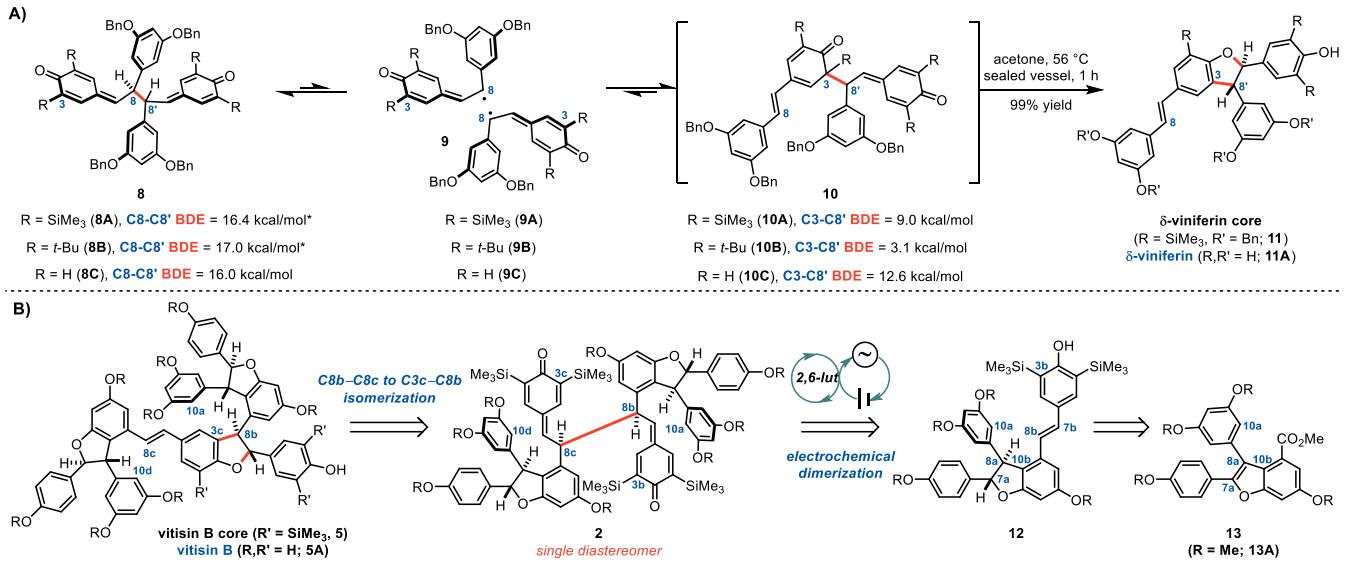

Figure 2. A) Discovery of C8b–C8c to C3c–C8b isomerization from thermodynamic study of persistent radical equilibria. B) Retrosynthetic analysis for the synthesis of vitisin tetramers based on this late stage homolytic isomerization. *C8-C8′ BDEs determined experimentally;[6] BDEs for the corresponding C3-C8′ dimers are given relative to these experimental values.[8]

10A is not observed due to its rapid decomposition to the δ-viniferin core (**11**). Computations predict that unimolecular expulsion of the TMS cation proceeds with a significant barrier,[9] suggesting that adventitious water in the acetone promotes desilylation and concomitant aromatization. Remarkably, the C8–C8′ to C3–C8′ isomerization and subsequent cyclization to **11** occurs in nearly quantitative yield (Figure 2A).

The difference in the C-C BDEs of the corresponding *tert*-butylated dimers (**8B**/**10B**) is nearly twice as large (13.9 kcal/mol), reflecting the greater steric repulsion in the C3–C8′ dimer resulting from the shorter C–C bonds relative to C–Si bonds. Indeed, the C3–C8′ and C8–C8′ BDEs in the dimers which lack any ortho substitution (**8C**/**10C**) are computed to be only 3.6 kcal/mol apart, funneling both of these intermediates toward the δ-viniferin core. These computations are consistent with the hypothesis that resveratrol oligomerization relies upon equilibration of the C8–C8′ and C3–C8′ constitutional isomers.[1] In fact, numerous research groups have realized the direct conversion of resveratrol (**S1**) to δ-viniferin (**11A**, Figure 2A) through single electron oxidation strategies (see Table S1 of the Supporting Information for a summary of these efforts).[10] While excellent yields for conversion to **11A** 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 (**5A**).[10g] By treating isolated (+)-ε-viniferin (**S4**) with silver acetate in methanol at elevated temperatures (50 °C), they observed conversion to vitisin B (**5A**) in 40% yield on 20 milligram scale (see Figure S2 of the Supporting Information). The C3c–C8b-fused resveratrol tetramers exhibit some of the most compelling biological activities among members of the resveratrol oligomer class reported to date; therefore, an approach to their synthesis reliant on readily available materials is desirable. For example, vitisin B (**5A**) was found by Lee and co-workers to be a potent inhibitor of the NS3 helicase of hepatitis C (IC_{50} = 3 nM), while vitisin A (**6**) was also active against the same target (IC_{50} = 35 nM).[11] To the best of our knowledge, similarly rigorous biological analysis of vitisin D (**7**) has not yet been reported.

Quinone methide dimer **2** serves as the linchpin for the proposed isomerization approach to the C3c–C8b resveratrol tetramers (Figure 2B). Importantly, this scaffold forms exclusively as a single diastereomer upon oxidation of racemic starting material **12**, meaning dimerization occurs selectively between the same enantiomeric precursors in the same fashion required to access vitisin B (**5A**). Preservation of this stereochemical integrity during C8b–C8c to C3c–C8b isomerization would directly convert **2** to the core of vitisin B (**5**). As **5A** is proposed to be the biogenic precursor to both **6** and **7**,[12] 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,[13] attention turned to the synthesis of the dimerization starting material – protected ε-viniferin analog **12**. This scaffold was previously prepared using an approach developed by the Snyder group in one of their seminal contributions to this field;[4c] however, it was envisioned that a benzofuran precursor (i.e. **13**) might offer a more direct route to **9**. Kim and Choi recently reported an approach to **13A** to access permethylated resveratrol dimers,[3b] providing an excellent starting point for our synthesis.

Execution of this plan commenced with the preparation of the requisite benzofuran precursor while adopting a new protecting group strategy, and gratifyingly, cyclodehydration of **14A** afforded benzofuran **15A** in 85% yield (Figure 3). Unfortunately, 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 **16** (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 **16** in a shorter sequence with fewer protecting group manipulations (Figure 3). After C–H arylation,[14] **13B** was converted to **16** by Lewis acid-mediated deprotection,[15] Kishi reduction,[16] and silyl protection in a three-step sequence that did not require intermediate purification. Reduction of the C8b-ester and a Parikh-Doering oxidation[17] delivered aldehyde

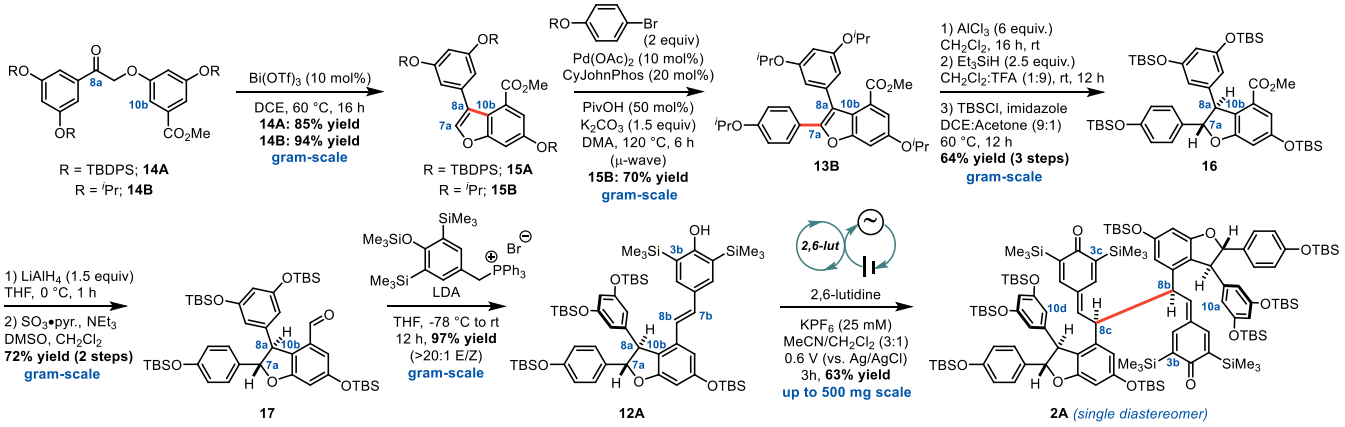

Figure 3. Synthesis of silyl-protected *bis*-quinone methide **2A** from the electrochemical dimerization of **12A**.

17, and a Wittig olefination[18] smoothly afforded the silyl protected ε-viniferin analog **12A**. At this point, our dimerization method utilizing anodic oxidation was employed to access **2A**.[13] 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, **12A** was converted to the desired quinone methide tetramer **2A** 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 **8A** 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 **2A** would be completely eroded. Subjecting **2A** to the thermal isomerization conditions readily accessed the vitisin B core (**5B**), but as a mixture of four C3c–C8b dihydrobenzofuran (DHB) isomers (Sequence 1, Figure 4). Increasing the temperature improved the *trans/cis* ratio of the DHB rings, presumably due to thermal epimerization; however, the facial selectivity of C3c–C8b recombination remained unchanged. Gratifyingly, the TBS ethers were readily cleaved with HF-triethylamine to afford two compounds – **19** and **20**. These *trans*-DHB isomers arise from each possible facial addition of C8b to C3c during the formation of **18** (Sequence 1, Figure 4) 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,[3f,g] thereby delivering only the two observed products. To support the hypothesis that the formal [1,5]-shift only occurs through the relative configuration depicted by **2A**, a second crossover experiment between **2A** and the corresponding TIPS-protected analog **2B** was performed (Figure 4). After thermal isomerization, the crossover product was observed, further supporting that C–C fragmentation and diffusion is competitive with in-cage recombination to yield the isomer. However, upon TBS deprotection with HF-triethylamine, **19** and **20** were the only observed products, suggesting that thermal isomerization proceeds without loss of stereochemical integrity afforded by C8b–C8c dimerization.

Inspired by these results, we set out to develop conditions for *O*-silyl deprotection and protodesilylation to complete the

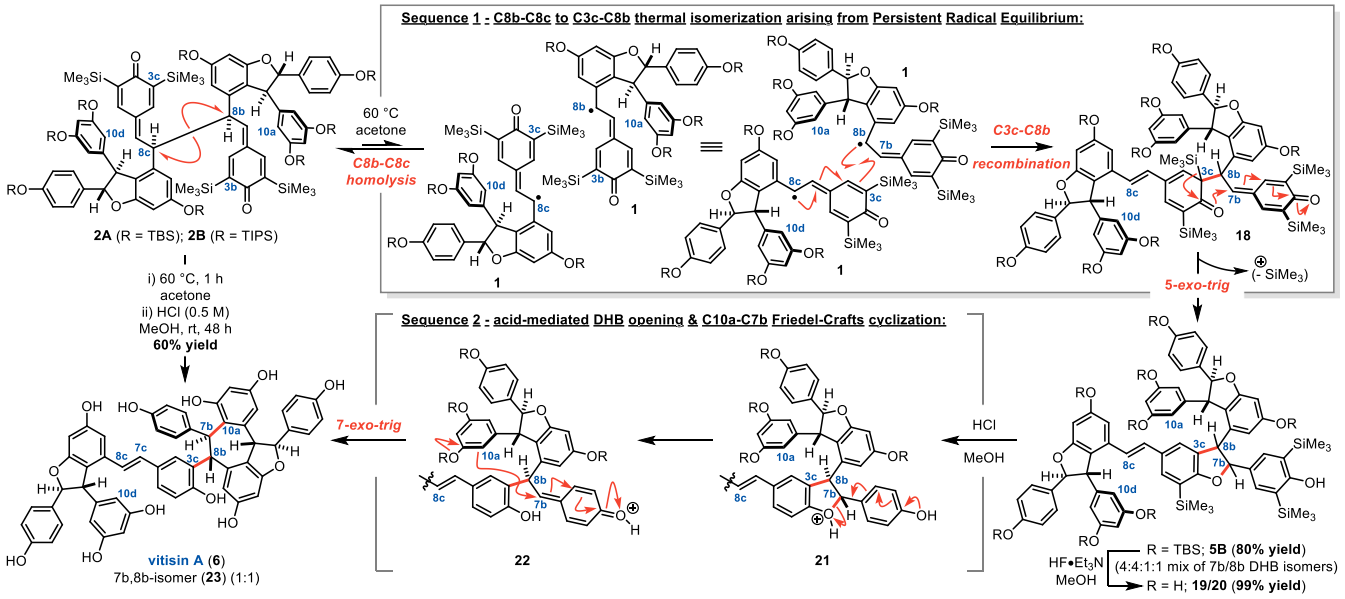

Figure 4. C8b–C8c to C3c–C8b isomerization, Friedel-Crafts cyclization, and deprotections deliver vitisin A (**3**).

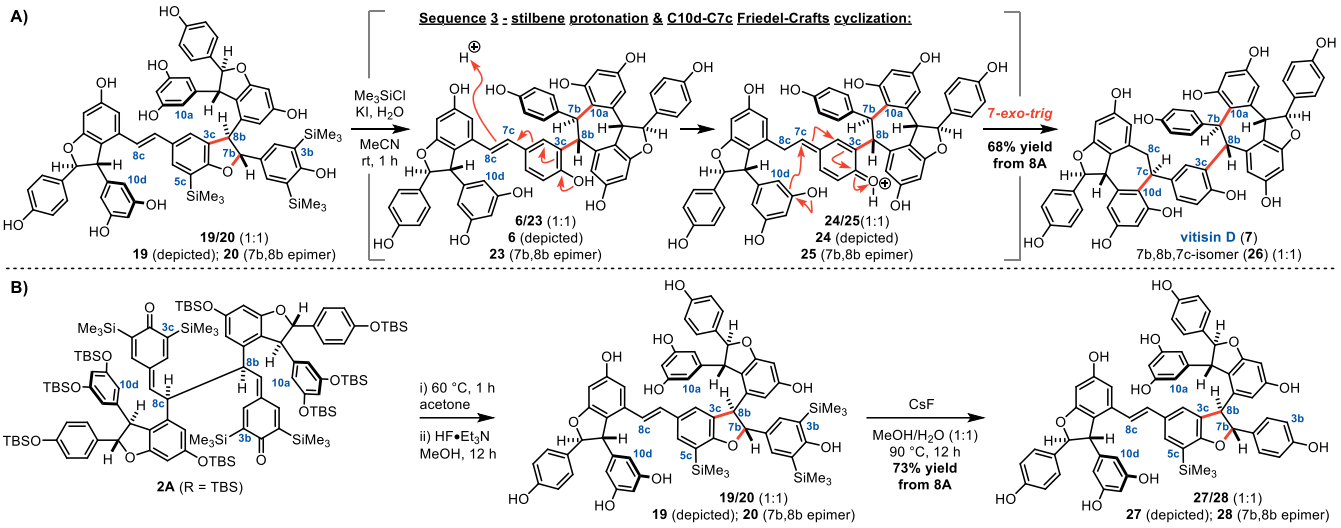

Figure 5. A) C8b–C8c to C3c–C8b isomerization, Friedel-Crafts cyclizations, and deprotections deliver vitisin D (**4**). B) C5c-TMS group survives fluoride-mediated desilylation attempts.

synthesis. Global desilylation was achieved by addition of a methanolic solution of hydrochloric acid upon completion of the isomerization of **2A** yielding vitisin A (**6**) and its C7b, C8b-isomer (**23**). Vitisin A (**6**) is proposed to arise from vitisin B (**5A**) in the biosynthesis of these compounds.[12] Acid-mediated cleavage of the C7b–O bond upon protonation of the DHB (**21**) affords a quinone methide (**22**) to which C10a of the adjacent resorcinol ring adds in a 7-*exo-trig* cyclization (Sequence 2, 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 (**5A**), intermediates **19/20** were exposed to milder protodesilylation conditions.[19] Remarkably, vitisin D (**7**) and the isomer **26** were isolated after treating **19/20** with Me_3SiCl, KI, and H_2O in MeCN for one hour (Figure 5A). These compounds are the result of two acid-promoted cyclizations; after cyclization to vitisin A (**6**) *in situ* (Sequence 2, Figure 4), protonation of the stilbene at C8c results in formation of the quinone methide tautomer **24/25**, which is trapped by 7-*exo-trig* cyclization by C10d of the adjacent resorcinol ring (Sequence 3, Figure 5A). Acid-mediated conversion of vitisin A (**6**) to vitisin D (**7**) has been proposed in the biosynthesis of these compounds,[12] thus it is perhaps unsurprising that the *in-situ* generation of hydroiodic acid would give rise to **7** and **26**.

Alkaline conditions were next attempted in an effort to target vitisin B (**5A**).[20] It was quickly determined that the C3/5b aryl silyl groups are cleaved via fluoride-mediated-desilylation; however, the C5c-TMS group remains intact (**27/28**, Figure 5B). Our investigations have demonstrated that the C3c–C8b DHB is quite labile, and in fact, conversion to vitisin A (**6**) occurs under a range of conditions (see Table S6 of the Supporting Information). Despite an extensive evaluation of desilylation conditions, access to vitisin B (**5A**) 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 that is consistent with the biosynthetic hypothesis of these complex molecules. The persistent radicals arise from mild anodic oxidative conditions, and the subsequent biomimetic transformations rapidly convert dimeric intermediates to tetrameric structures, which will enable the investigation of the pharmacological potential of these complex molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: (insert DOI link here).

Experimental procedures and characterization data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

crjsteph@umich.edu; dpratt@uottawa.ca

ORCID

Kevin J. Romero: 0000-0001-7604-3996
Mitchell H. Keylor: 0000-0002-9842-7234
Markus Griesser: 0000-0002-7810-1560
Xu Zhu: 0000-0002-8856-2045
Ethan J. Strobel: 0000-0001-9047-0839
Derek A. Pratt: 0000-0002-7305-745X
Corey R. J. Stephenson: 0000-0002-2443-5514

Notes

The authors declare no competing financial interests.

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(8) Computations were carried out with B3LYP-D3/6-311G(d,p). This approach significantly overestimates the C-C BDEs for which comparison to experiment is possible (**8A** and **8B**) due to an overestimation of the dispersion interactions between the trimethylsilyl and *t*-butyl groups with neighboring aryl rings. Omission of these substituents brings the C8-C8' BDE into good agreement with experiment. Omission of dispersion corrections to any of these calculations leads to massive underestimations in the C-C BDEs (see Supporting Information for additional information). These observations will be expanded upon in a future report.

(9) Incorporation of a SMD solvent model parameterized for acetone suggests a barrier of 21.7 kcal/mol, implying that this reaction cannot compete with C3−C8′ bond homolysis and return to the C8−C8′ dimer.

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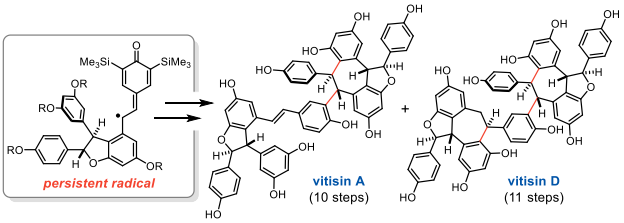

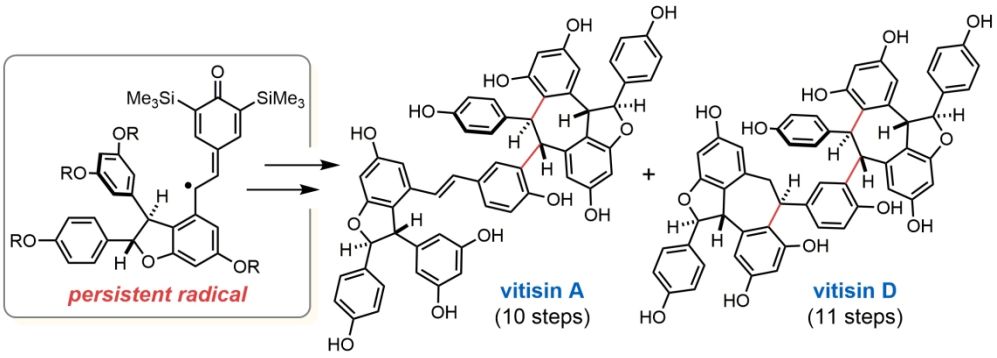

TOC Graphic

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