

Total Synthesis of Resveratrol-Based Natural Products: A Chemoselective Solution**

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The past decade has witnessed tremendous interest in the relatively small natural product resveratrol (**1**, Figure 1) primarily because of its promising and selective array of in vitro and in vivo activity against a collection of disease states, including inflammation, heart disease, aging, and cancer.^[1] In fact, its truly unique biochemical profile, coupled with its relatively high concentration in red wine (ca. 100 μM) and near absence in white varieties and grape juice, has led to the popularly held notion that resveratrol is the main protagonist for the so-called “French paradox”.^[2] Amazingly, however, virtually no effort has been devoted to the large family of resveratrol-based oligomers (such as **2–8**)^[3] produced combinatorially by plants throughout the world in response to environmental stress; initial screening suggests these compounds should have similar, if not superior, activity profiles to resveratrol itself.^[4] Herein, we provide a means to begin this exploration by outlining the first general synthetic approach capable of accessing all the carbogenic diversity posed by this family, a solution fueled by a new idea for the selective generation of natural product structures in instances in which nature abandons discrimination to achieve evolutionary advantage.^[5]

To date, all attempts to prepare resveratrol-based natural products have derived from strategies that parallel their presumed biogenesis, that is, the generation of radicals or carbocations from **1** through its exposure to different chemicals or enzymes.^[6–11] Typically, mixtures of compounds were observed^[6–8] and, in those rare instances when selectivity was achieved, solely nonnatural products resulted.^[9,10] Thus far, only a highly engineered resveratrol fragment has proven capable of leading to an actual dimeric natural product within this class.^[11] Given this state of affairs, we wondered if a structural solution might exist for this general chemoselec-

tivity problem, one empowered by the identification of hidden relationships between their seemingly divergent architectures. Such an answer arose when we considered natural products such as paucifloral F (**7**) and diptoindonesin A (**8**), isolates whose structures are incongruent with the notion of direct resveratrol oligomerization since they possess

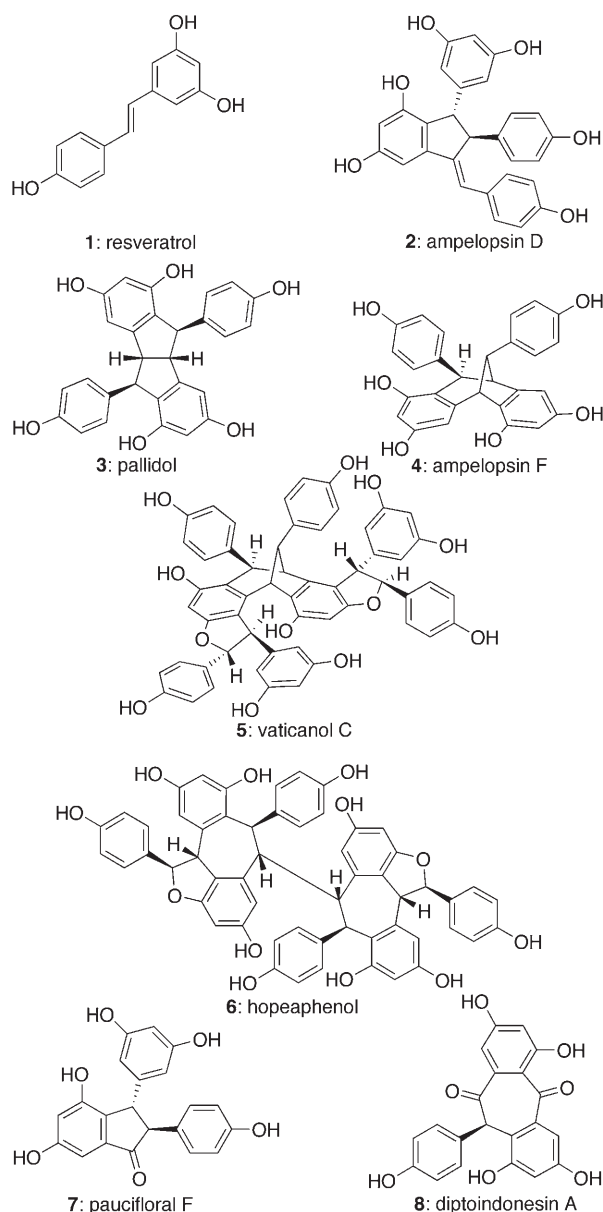


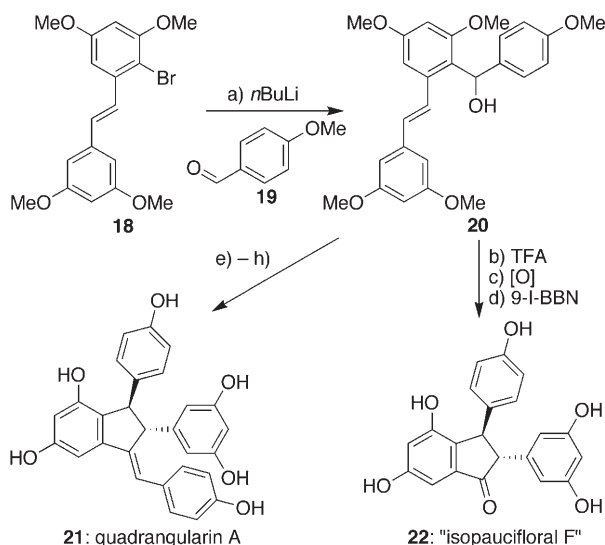
Figure 1. Selected examples of polyphenolic natural products presumed to arise from the union of resveratrol monomers.

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[**] We thank Drs. J. Decatur and Y. Itagaki for assistance with NMR spectroscopy and mass spectrometry, respectively. We also thank the National Science Foundation (CHE-0619638) for the acquisition of an X-ray diffractometer. Financial support for this work was provided by Columbia University, Amgen, and Eli Lilly. S.A.S. is a Camille and Henry Dreyfus New Faculty Awardee.

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The other building block is **20** (Scheme 2), which differs from biaryl alcohol **11** architecturally (in terms of the positioning of two of its three aromatic rings), but behaves

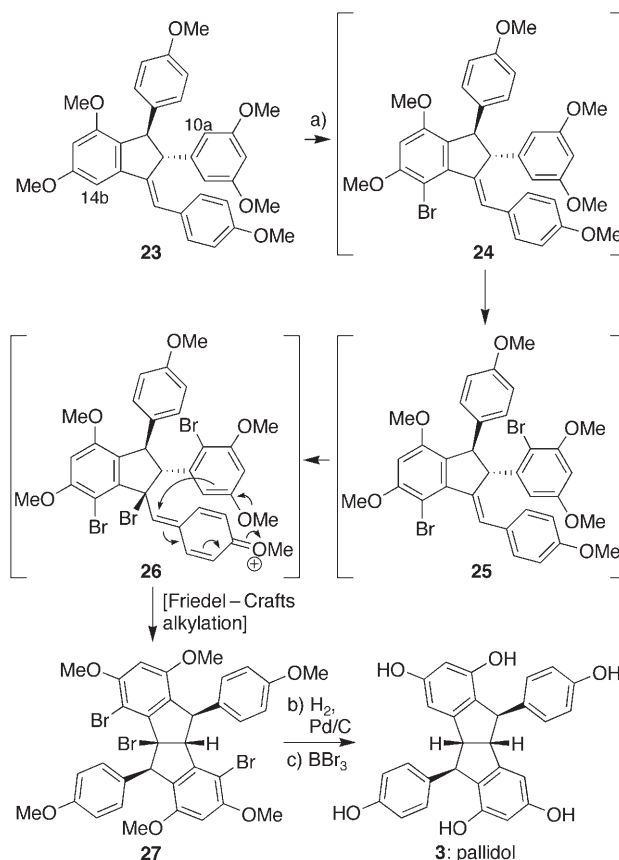


Scheme 2. Total synthesis of two resveratrol-based natural products (**21** and **22**) from key building block **20**. a) *n*BuLi (1.0 equiv), THF, -78°C , 20 min; then **19** (1.0 equiv), $-78 \rightarrow 25^{\circ}\text{C}$, 4 h, 71%; b) TFA (1.0 equiv), CH_2Cl_2 , $-30 \rightarrow -20^{\circ}\text{C}$, 5 h; then K_2CO_3 (10 equiv), MeOH, 25°C , 5 min, 93%; c) Dess–Martin periodinane (1.2 equiv), NaHCO_3 (5.0 equiv), CH_2Cl_2 , 25°C , 3 h, 98%; d) 9-*I*-BBN (1.0 M in hexanes, 10 equiv), CH_2Cl_2 , 40°C , 30 min, 72%; e) TsOH (1.0 equiv), then concentration to near dryness, 25°C , 12 h, 65%; f) *m*CPBA (3.0 equiv), NaHCO_3 (10 equiv), CH_2Cl_2 , $0 \rightarrow 25^{\circ}\text{C}$, 3 h, 70%; g) *t*BuOH/ $\text{H}_2\text{O}/\text{CCl}_4$ (5/1/5), KOH (20 equiv), 80°C , 12 h, 55%; h) BBr_3 (1.0 M in CH_2Cl_2 , 12 equiv), CH_2Cl_2 , 25°C , 6 h, 75% of **21**, 14% of internal alkene isomer. 9-*I*-BBN = 9-iodo-9-borabicyclo[3.3.1]nonane.

in the same manner chemically. Indeed, as indicated in Scheme 2, when this intermediate was subjected to the reaction sequences outlined above, what resulted were total syntheses of quadrangularin A (**21**) and isopaucifloral F (**22**),^[20] the structures of which, as expected, display the opposite array of pendant phenol ring systems as those accessed from **11**.^[21] Consequently, it would appear, on the basis of these collated results, that any resveratrol-derived structure possessing a single cyclopentane ring system can be obtained cleanly from appropriate triaryl precursors.

What, though, about more complex intermediates such as pallidol (**3**) and ampelopsin F (**4**, Figure 1), which possess an additional ring appended onto a cyclopentane core? Prior explorations with naturally derived materials had established that their complexity could arise alongside several other architectures by treating dihydrofuran-bearing substrates, such as vaticanol C (**5**, Figure 1) and hopeaphenol (**6**, Figure 1), with strong acid.^[19] We wondered whether electrophilic activation of the olefins within both ampelopsin D (**2**) and quadrangularin A (**21**), followed by a Friedel–Crafts alkylation onto the resultant quinone methide, could accomplish the same objective in a controlled manner.

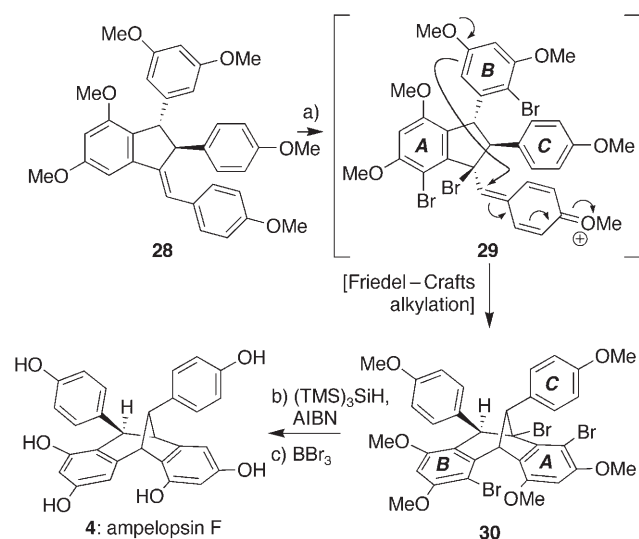
As shown in Scheme 3, that conjecture proved to be correct if bromine was utilized as the activating species.^[22] In the event, exposure of permethylated quadrangularin A (**23**)



Scheme 3. Sequential, cascade-based halogenation to access pallidol (**3**): a) Br_2 (2.0 equiv), CH_2Cl_2 , -78°C , 2 h, then slow warming to 25°C , 1 h, 81%; b) H_2 , Pd/C (20%, 0.2 equiv), MeOH, 25°C , 24 h, 76%; c) BBr_3 (1.0 M in CH_2Cl_2 , 12 equiv), CH_2Cl_2 , 0°C , 4 h, then 25°C , 20 h, 83%.

to two equivalents of molecular bromine in CH_2Cl_2 at -78°C and subsequent slow warming to ambient temperature over several hours accomplished a highly selective cascade sequence that provided bicycle **27** in 81% yield. On the basis of a series of control experiments leading to the isolation of both **24** and **25**, the course of events is known to involve the initial halogenation of the C-14b position, followed by bromination of the second 3,5-dimethoxybenzene ring system. Although both of these halogens are extraneous in terms of the goal structure,^[23] each served a critical role in ensuring that the terminating ring closure leading to **27** was stereoselective. Indeed, as revealed by molecular models, the C-10a bromine atom provided a significant amount of steric bulk to its ring system, forcing the third bromine atom to be added solely from the opposite side of the molecule; the C-14b bromide then prevented rotation of the newly formed quinone methide (**26**) away from its initial, perfect positioning for the final closure, thereby assuring that only **27** was formed. From this key intermediate (**27**), pallidol (**3**) was then accessed in 63% overall yield by hydrogenative replacement

of all three bromides by using a catalytic amount of activated Pd/C, followed by BBr₃-induced cleavage of all six methyl ethers. As documented in Scheme 4, the same sequence of

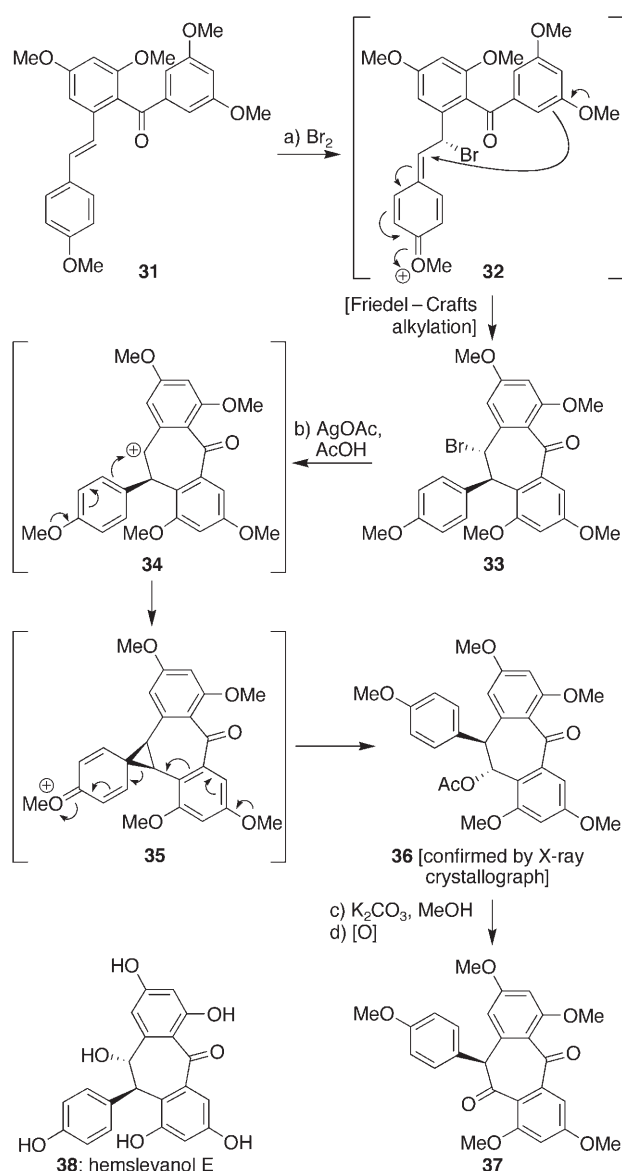


Scheme 4. Sequential, cascade-based halogenation to access ampelopsin F (**4**): a) Br₂ (2.0 equiv), CH₂Cl₂, –78°C, 2 h, then slow warming to 25°C, 1 h, 53%; b) (TMS)₃SiH (9.0 equiv), AIBN (1.0 equiv), toluene, 100°C, 8 h, 89%; c) BBr₃ (1.0 M in CH₂Cl₂, 12 equiv), CH₂Cl₂, 0°C, 4 h, then 25°C, 15 h, 90%. TMS = trimethylsilyl, AIBN = 2,2'-azobisisobutyronitrile.

events with permethylated ampelopsin D (**28**) selectively afforded ampelopsin F (**4**). In this case, radical conditions [(TMS)₃SiH, AIBN] were used to replace the three bromine atoms left by the cascade sequence.^[24] Of course, although an ideal synthesis of any molecule would avoid the addition of extra atoms, in these two cases the absence of atom economy would appear to have the benefit of such potential access to even greater molecular complexity in the resveratrol class. Indeed, the aryl halides within intermediate **30** are positioned perfectly to attempt construction of the dihydrofuran rings that would lead to vaticanol C (**5**, Figure 1).

Finally, the remaining element of carbogenic complexity possessed by the resveratrol family, the seven-membered rings of compounds such as diptoinonesin A (**8**, Figure 1), could be obtained through an electrophilic activation/cyclization sequence similar to that just described. In this case, the key starting material is ketone **31** (Scheme 5), the oxidized form of building block **11**, which afforded **33** in 50% yield of isolated product following its exposure to bromine. Although work with this highly sensitive intermediate is only in its initial stages, the halogen handle within **33** is likely to be a key tool for efforts to synthesize the carbon–carbon bond uniting the two halves of hopeaphenol (**6**, Figure 1) and generate the additional oxygen function of both diptoinonesin A (**8**, Figure 1) and the related natural product hemsleyanol E (**38**).^[25]

Equally important, this halogen atom has already enabled access to a collection of nonnatural analogues through a molecular rearrangement that, despite its facility, does not



Scheme 5. Alternate use of key intermediate **11** to access the unique architectures of related, nonnatural natural products (such as **37**) through a bromonium-induced cascade sequence followed by an acid-induced phenonium shift: a) Br₂ (1 equiv), CH₂Cl₂, –78°C, 1 h, then 25°C, 12 h, 50%; b) AgOAc (3.0 equiv), AcOH, 25°C, 4 h, 62%; c) K₂CO₃ (10 equiv), MeOH, 25°C, 12 h, 78%; d) Dess–Martin periodinane (1.2 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25°C, 1 h, 99%.

appear to be employed by nature in its construction of this molecule class.^[26] Indeed, exposure of bromide **33** to an excess of AgOAc (3.0 equiv) in AcOH at 25°C^[27] led to the smooth synthesis of acetate **36** in 62% yield. This unique structure (confirmed by X-ray crystallographic analysis), in which the pendant aryl ring has migrated, likely resulted from a thermodynamically favored phenonium shift following the generation of cation **34**; the strategically positioned *ortho*- and *para*-disposed alkoxy groups within the resultant intermediate (**35**) then effected ring opening to provide a single, and new, electrophilic site for a terminating acetate attack.^[28] Subsequent cleavage of the acetate within **36** (K₂CO₃,

MeOH) then provided a protected regioisomeric analogue of hemsleyanol E in 78% yield, and oxidation of the resultant alcohol led to the corresponding diptoindonesin A congener as expressed by structure **37**.

In conclusion, we have established that the entire array of carbogenic complexity posed by the resveratrol family of natural products, along with several additional isosteres, can be accessed smoothly and selectively from building blocks quite distinct from the compound postulated for their biosynthesis.^[29] Apart from revealing previously hidden structural relationships within the architectural diversity possessed by this compound class, the efficiency of the developed routes (four to seven steps from **9** and **18**, each natural product accessed in 7 to 46% overall yield from commercial materials) ensures that the biochemical studies needed to elucidate their full medicinal potential can finally begin in earnest. Future efforts are focused not only on achieving this critical objective, but also on synthesizing the most complex members of this fascinating family of secondary metabolites. We expect that the general principle illustrated by this work, namely the use of common, but nonobvious, precursors to access molecular diversity selectively through reagent-induced cascades, will prove applicable to many classes of polymeric molecules.

Received: July 24, 2007

Published online: September 21, 2007

Keywords: chemoselectivity · natural products · resveratrol · total synthesis

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a pure enough form to verify its connectivity through NOE experiments (owing to its sensitivity), we have substituted the acetate within structure **36** for chloride with retention of configuration. This compound, along with **36** and **37**, possess the four aryl protons of the 3,5-dimethoxybenzene rings tightly and consistently grouped between $\delta = 6.40$ and 6.90 ppm; by contrast, bromide **33** possesses one of these signals as an outlier at $\delta = 5.76$ ppm, presumably the one that is in close proximity to the halogen atom.

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