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Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block

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Abstract: Although biomimetic approaches have proven capable of converting resveratrol (**1**) concurrently into many of the more complex oligomers produced by plants throughout the world (such as **2**−**10**), methods to access single members of the family have proven far more difficult to identify. Herein is described a strategy-level solution based on the use of a common building block, one distinct from Nature's starting material, that can participate in a variety of highly selective, reagent-controlled reaction cascades. These endeavors have led to the controlled synthesis of 25 natural products and analogues, molecules whose architectures encompass nearly all the carbogenic diversity of the resveratrol family.

1. Introduction

Among polyphenol-based natural products, resveratrol (**1**, Figure 1) is one of the most widely distributed, having been isolated thus far from no fewer than 72 different plants, including grapevines from North America, Africa, and Europe, and various *Dipterocarpaceae* species in Southeast Asia and China.[1] The ubiquity of this phytoalexin and its more complex and stereochemically diverse cousins (**2**−**10**),[2] molecules produced in varying ratios and amounts in hopes of facilitating organismal survival,[3] is likely a reflection of their potent antifungal activity. Research over the past three decades, however, has revealed that these natural products also possess a wide array of additional activity, many with potential utility for human health.

For instance, resveratrol (**1**) has demonstrated potent anti-inflammatory, cardiovascular protective, antiaging, neuroprotective, and tumor suppressant properties in both *in vitro* and *in vivo* screens.[4] In fact, given this unique activity profile in combination with its relatively high concentration in red wine (∼100 μM or 3 to 5 mg per 750 mL bottle) and near absence in white varietals and grape juice, it has even been advocated by some as the agent responsible for the "French paradox", the notion that red wine consumption can counterbalance the negative health effects of a diet rich in fat and cholesterol.[5,6] Most of the more complex structures also have biological activity, with some of the more interesting being hopeaphenol (**4**), whose monomeric subunits exhibit HIV inhibitory properties,[7] and vaticanol C (**3**), which has marked activity against colon carcinoma cell lines (IC_{50} = 3.0 and 3.2 μM in HL60 and SW480 cell lines, respectively).[8,9] Preliminary screens of the latter agent have, in fact, revealed that it acts through an apoptosis-inducing interaction with mitochondrial proteins distinct from many other agents currently in clinical use.

(1) Resveratrol was originally isolated from the roots of white hellebore, and later, from the roots of the Japanese knotweed. (a) Takaoka, M. *Proc. Imp. Acad. Tokyo* **1940**, *16*, 405–407. (b) Hillis, W. E.; Inoue, T. *Phytochemistry* **1967**, *6*, 59–67.

(2) For the isolation and characterization of these natural products, see: (a) Li, W. W.; Ding, L. S.; Li, B. G.; Chien, Y. Z. *Phytochemistry* **1996**, *42*, 1163–1165. (b) Tanaka, T.; Ito, T.; Nakaya, K.; Iinuma, M.; Riswan, S. *Phytochemistry* **2000**, *54*, 63–69. (c) Coggon, P.; Janes, N. F.; King, T. J.; Wallwork, S. C. *J. Chem. Soc.* **1965**, 406–408. (d) Ito, T.; Tanaka, T.; Iinuma, M.; Iliya, I.; Nakaya, K.; Ali, Z.; Takahashi, Y.; Sawa, R.; Shirataki, Y.; Murata, J.; Darnaedi, D. *Tetrahedron* **2003**, *59*, 5347–5363. (e) Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849–4854. (f) Supudompol, B.; Likhitwitayawuid, K.; Houghton, P. J. *Phytochemistry* **2004**, *65*, 2589–2594. (g) Sahadin; Hakim, E. H.; Juliawaty, L. D.; Syah, Y. M.; bin Din, L.; Ghisalberti, E. L.; Latip, J.; Said, I. M.; Achmad, S. A. *Z. Naturforsch., C: Biosci.* **2005**, *60*, 723–727. (h) Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932–937.

(3) Seeram, N. P.; Kulkarni, V. V.; Padhye, S. *Oxid. Stress Dis.* **2006**, *20*, 17–32.

(4) For seminal and representative work, see the following and references cited therein: (a) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnsworth, N. R.; Kinghorn, A. D.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218–220. (b) Howitz, K. T.; Bitterman, K. J.; Cohen, H. Y.; Lamming, D. W.; Lavu, S.; Wood, J. G.; Zipkin, R. E.; Chung, P.; Kisielewski, A.; Zhang, L.-L.; Scherer, B.; Sinclair, D. A. *Nature* **2003**, *425*, 191–196. (c) Walle, T.; Hsieh, F.; DeLegge, M. H.; Oatis, J. E.; Walle, U. K. *Drug Metab. Dispos.* **2004**, *32*, 1377–1382. (d) Wood, J. G.; Rogina, B.; Lavu, S.; Howitz, K.; Helfand, S. L.; Tatar, M.; Sinclair, D. *Nature* **2004**, *430*, 686–689. (e) Chen, G.; Shan, W.; Wu, Y.; Ren, L.; Dong, J.; Ji, Z. *Chem. Pharm. Bull.* **2005**, *53*, 1587–1590. (f) Baur, J. A.; et al. *Nature* **2006**, *444*, 337–342. (g) Milne, J. C.; et al. *Nature* **2007**, *450*, 712–717. (h) Boocock, D. J.; Faust, G. E. S.; Patel, K. R.; Schinas, A. M.; Brown, V. A.; Ducharme, M. P.; Booth, T. D.; Crowell, J. A.; Perloff, M.; Gescher, A. J.; Steward, W. P.; Brenner, D. E. *Cancer Epidemiol. Biomarkers Prev.* **2007**, *16*, 1246–1252. (i) Kim, D.; Nguyen, M. D.; Dobbin, M. M.; Fischer, A.; Sananbenesi, F.; Rodgers, J. T.; Delalle, I.; Baur, J. A.; Sui, G.; Armour, S. M.; Puigserver, P.; Sinclair, D. A.; Tsai, L.-H. *EMBO J.* **2007**, *26*, 3169–3179. (j) Heiss, E. H.; Schilder, Y. D. C.; Dirsch, V. M. *J. Biol. Chem.* **2007**, *282*, 26759–26766.

(5) For reviews, see: (a) Saiko, P.; Szakmary, A.; Jaeger, W.; Szekeres, T. *Rev. Mutation Res.* **2007**, *658*, 68–94. (b) Walle, T.; Hsieh, F.; DeLegge, M. H.; Oatis, J. E.; Walle, U. K. *Drug Metab. Dispos.* **2004**, *32*, 1377–1382. (c) Athar, M.; Back, J. H.; Tang, X.; Kim, K. H.; Kopelovich, L.; Bickers, D. R.; Kim, A. L. *Toxicol. Appl. Pharmacol.* **2007**, *224*, 274–278. (d) Soleas, G. J.; Diamandis, E. P.; Goldberg, D. M. *Clin. Biochem.* **1997**, *30*, 91–113. (e) Kopp, P. *Eur. J. Endocrinol.* **1998**, *138*, 619–620.

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Despite this promising array of biochemical behavior, the clinical potential of these compounds and their analogues has barely been tapped; such work, in fact, has only been performed thus far with resveratrol (**1**).[4c,d] In our opinion, this state of affairs is primarily a reflection on the respective ease of their syntheses, as **1** has been accessed through several routes in gram quantities[10] while its more complex oligomers have generally proven incapable of being synthesized in quantities greater than the minute amounts obtainable from natural sources.[11−14] Most of the endeavors toward the higher-order structures have been biomimetic in design,[11] meaning the exposure of **1** to either single chemicals or enzymes in attempts to probe what architectures can result. Under radical conditions, arrays of products similar to those found in Nature are often generated, and in those rare instances where selectivity in product formation is observed, non-natural products (such as **12**, Scheme 1) are typically obtained.[11a,b] Cation-based dimerizations of stilbene derivatives, though unreported with resveratrol (**1**) itself, afford similar results as compounds of general structure **13** provide regioisomeric mixtures of both indane (**16**) and tetralin (**17**) ring systems alongside a number of additional architectures pertinent to the resveratrol class.[12,13] Only through structural modification has it proven possible to temper the reactivity of resveratrol (**1**), with a recent report from the Hou group revealing that analogue **18** could be dimerized regioselectively to **20** in 35% yield en route to quadrangularin A (**21**).[14] As of yet, however, there are no solutions to selectively synthesize most dimeric targets or any higher-order structure in the resveratrol family.

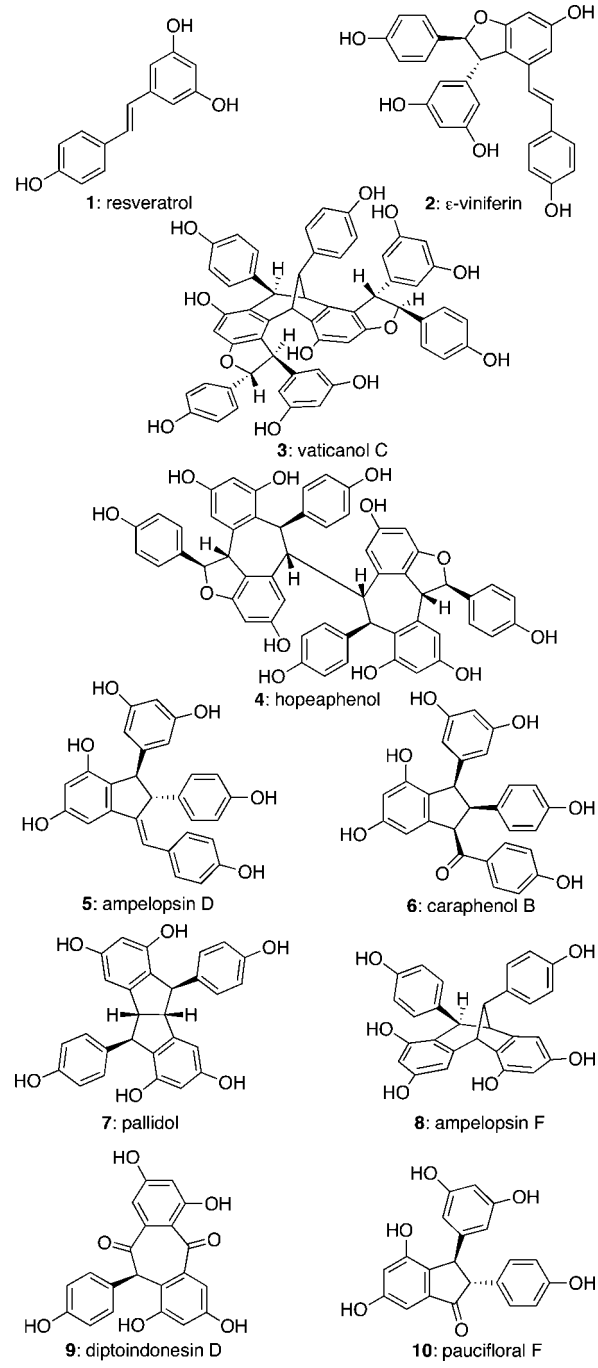


Figure 1. Selected natural products believed to arise from the union of resveratrol monomers.

(6) Though the jury is still out on this conjecture, particularly given that *in vivo* human studies have yet to parallel those conducted *in vitro* and glycosylated forms of **1** possess greater bioavailability, the thought remains provocative, especially since reactive radical intermediates can be generated quite easily at either terminus of the molecule. One manifestation of this chemistry is the ability of the nonstabilized radicals generated from resveratrol (**1**) to selectively inhibit the cyclooxygenase and peroxidase activity of the COX-1 enzyme involved in prostaglandin synthesis, behavior that is unique in comparison to every other nonsteroidal anti-inflammatory drug (NSAID) in clinical use as they inhibit only the cyclooxygenase reactions of the COX enzymes: (a) Szewczuk, L. M.; Forti, L.; Stivala, L. A.; Penning, T. M. *J. Biol. Chem.* **2004**, *279*, 22727–22737. (b) Szewczuk, L. M.; Lee, S. H.; Blair, I. A.; Penning, T. M. *J. Nat. Prod.* **2005**, *68*, 36–42. (c) Romero-Perez, A. I.; Ibern-Gomez, M. *J. Agric. Food Chem.* **1999**, *47*, 1533–1536.

(7) Dai, J.-R.; Hallock, Y. F.; Cardellina, J. H.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 351–353.

(8) (a) Ohguchi, K.; Akao, Y.; Matsumoto, K.; Tanaka, T.; Ito, T.; Iinuma, M.; Nozawa, Y. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 353–356. (b) Ito, T.; Akao, Y.; Yi, H.; Ohguchi, K.; Matsumoto, K.; Tanaka, T.; Iinuma, M.; Nozawa, Y. *Carcinogenesis* **2003**, *24*, 1489–1497.

(9) These activities are mentioned specifically for their uniqueness. For more thorough information on the activity of each oligomeric natural product, see the original isolation paper and references therein as cited in ref 2.

(10) For selected examples of resveratrol total synthesis, see: (a) Botella, L.; Nájera, C. *Tetrahedron* **2004**, *60*, 5563–5570. (b) Takaya, Y.; Terashima, K.; Ito, J.; He, Y.-H.; Tateoka, M.; Yamaguchi, N.; Niwa, M. *Tetrahedron* **2005**, *61*, 10285–10290. (c) Chen, G.; Shan, W.; Ren, L.; Dong, J.; Ji, Z. *Chem. Pharm. Bull.* **2005**, *53*, 1587–1590.

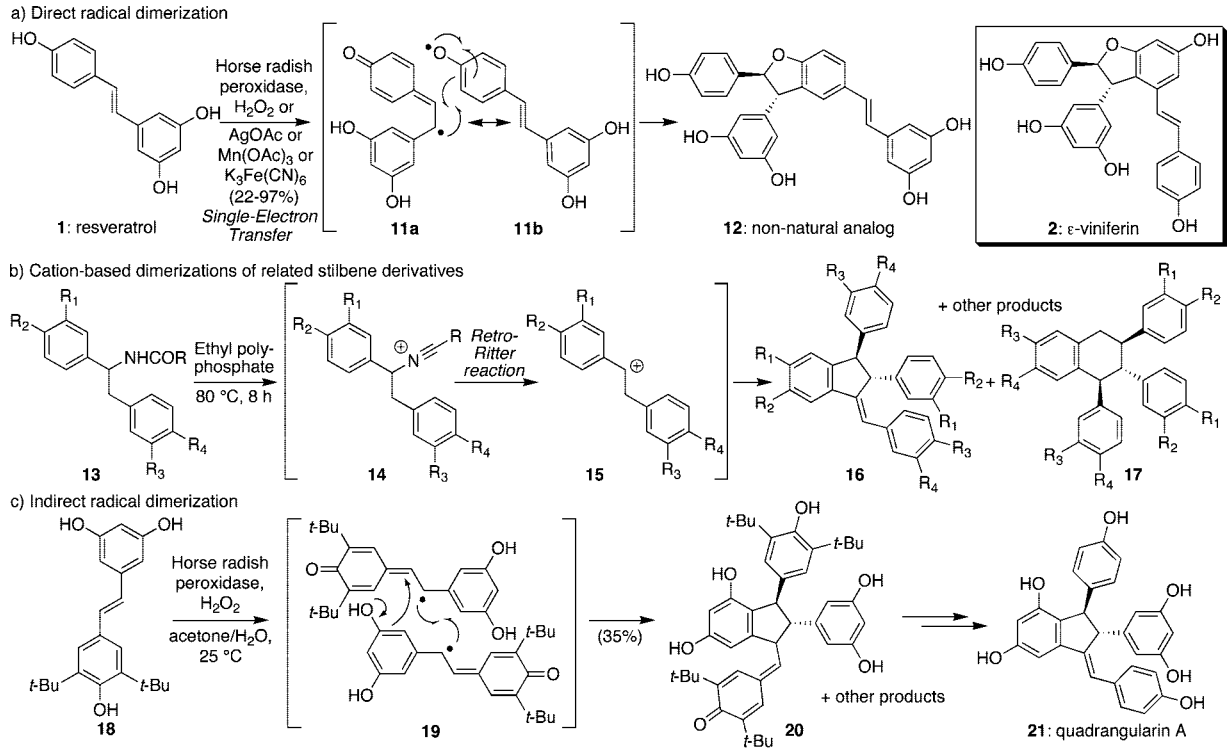
(11) (a) Langcake, P.; Pryce, R. J. *J. Chem. Soc., Chem. Commun.* **1977**, 208–210. (b) Sako, M.; Hosokawa, H.; Ito, T.; Iinuma, M. *J. Org. Chem.* **2004**, *69*, 2598–2600. (c) Adesanya, S. A.; Nia, R.; Martin, M.-T.; Boukamcha, N.; Montagnac, A.; Païs, M. *J. Nat. Prod.* **1999**, *62*, 1694–1695. (d) Niwa, M.; Ito, J.; Terashima, K.; Koizumi, T.; Takaya, Y.; Yan, K.-X. *Heterocycles* **2000**, *53*, 1475–1478. (e) Thomas, N. F.; Velu, S. S.; Weber, J.-F. F.; Lee, K. C.; Hadi, H. A.; Richomme, P.; Rondeau, D.; Noorbatcha, I.; Awang, K. *Tetrahedron* **2004**, *60*, 11733–11742.

(12) (a) Aguirre, J. M.; Alesso, E. N.; Iglesias, G. Y. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1353–1358. (b) Aguirre, J. M.; Alesso, E. N.; Ibanez, A. F.; Tombari, D. G.; Iglesias, G. Y. M. *J. Heterocycl. Chem.* **1989**, *26*, 25–27. (c) Li, X.-C.; Ferreira, D. *Tetrahedron* **2003**, *59*, 1502–1507.

(13) For other synthetic approaches to indane ring systems, some of which use carbocations to initiate C−C bond construction, see: (a) Alesso, E. N.; Bianchi, D. E.; Iglesias, G. Y. M.; Sierra, M. G.; Aguirre, J. M. *Aust. J. Chem.* **1994**, *47*, 1237–1247. (b) Lattke, E.; Knorr, R. *Chem. Ber.* **1981**, *114*, 1600–1609. (c) Appelbe, Z.; Casey, M.; Keaveney, C. M.; Kelly, C. J. *Synlett* **2002**, 1404–1408. (d) Malik, M. S.; Rastogi, S. N.; Singh, M. M.; Sreenivasulu, S.; Agnihotri, A.; Kalra, V.; Kaboj, V. P. *Eur. J. Med. Chem.* **1989**, *24*, 193–197. (e) For reactions involving the chemistry of indane and indene systems, see: Lantana, B.; Aguirre, J. M.; Finkelstein, L.; Alesso, E. N.; Brunet, E.; Moltrasio, G. Y. *Synth. Commun.* **2004**, *34*, 625–641. It is important to note that most of these examples do not possess phenols on their aromatic rings; in our experience, the addition of such domains imparts different reactivity in even the simplest of reactions.

(14) Li, W.; Li, H.; Li, Y.; Hou, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 7609–7611.

Scheme 1. Previous Attempts To Synthesize Resveratrol-Based Oligomers through Selective Dimerization Reactions



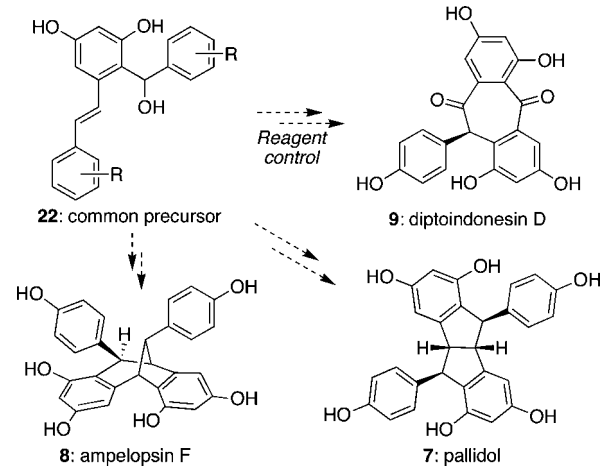
Herein we delineate our efforts to address this problem. Rather than attempt to control the reactivity of resveratrol (**1**) along the biosynthetic pathways described above, we have instead focused on developing an alternate strategy that utilizes a unique starting point for synthetic explorations. As described in the ensuing sections, we have identified a common building block that is capable of being controllably converted into 5-, 6-, and 7-membered rings as well as [3.3.0]-, [3.2.1]-, and [3.2.2]-bicycles through carefully orchestrated cascade reactions initiated by relatively simple reagents. These structural subtypes encompass much of the carbogenic complexity of the resveratrol class, including 11 natural products (9 of which have been synthesized for the first time) and 14 natural product-like analogues.[15]

2. Results and Discussion

2.1. Common Building Block Identification. Given the difficulty highlighted above in controlling the reactivity of resveratrol (**1**) as well as our own failures in dimerizing resveratrol selectively by attaching different phenolic protecting groups (acetate, methyl ether, or glycosyl) at varying positions, we came to the conclusion that efforts with resveratrol (**1**) itself were unlikely to deliver the solutions needed for selective oligomer synthesis. Thus, we carefully examined every structure within the class, looking for any clues or general patterns that might identify an alternate synthetic approach. After much study, one key feature appeared to reside in a few isolates that are slightly different from their cousins. These molecules include diptoindonesin D (**9**, cf. Figure 1) and paucifloral F (**10**, cf. Figure 1), natural products whose structures appear incongruent with direct resveratrol oligomerization since they possess an odd number

(15) For a preliminary account of our work in this area, see: Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186–8191.

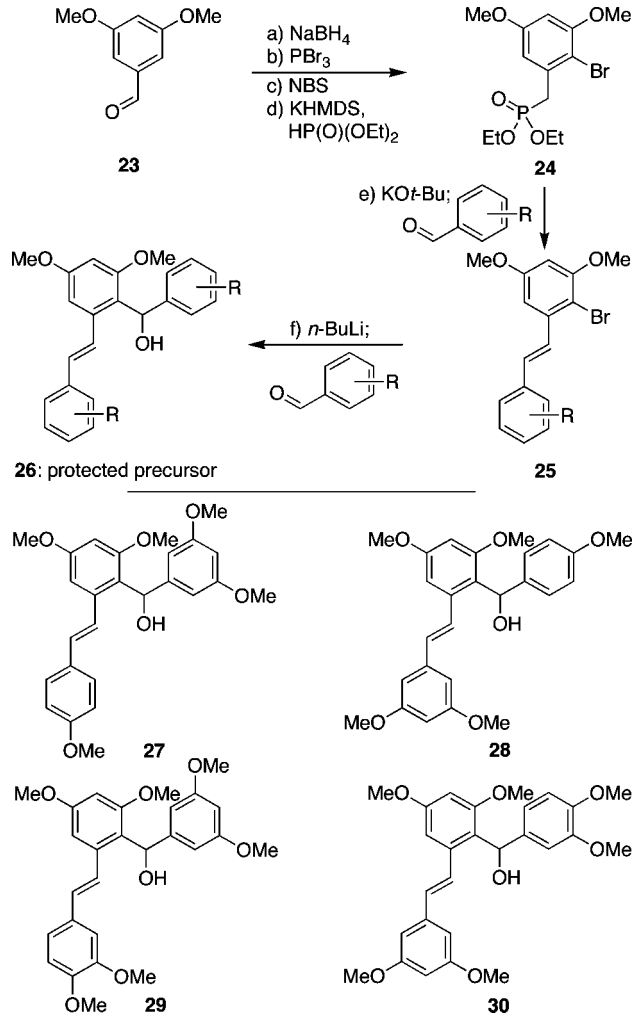
Scheme 2. Idea for the Controlled Synthesis of the Resveratrol Class from a Common Precursor (**22**) through Reagent Control



of aromatic rings; in fact, there are several in the entire class that have three, five, seven, and even nine aryl rings. Though these compounds are likely formed from normal resveratrol-based oligomers [paucifloral F (**10**) resulting from the biochemical equivalent of ozonolysis of the lone alkene within ampelopsin D (**5**, cf. Figure 1)], their mere existence suggested to us that perhaps a generalized building block, one with three aryl rings arrayed in the same core structure (**22**, Scheme 2), could enable controlled access to the extraordinary structural complexity and diversity of the entire family through reagent control. The next several subsections of this manuscript verify this hypothesis, illustrating that molecules of structure **22** can be converted into a diversity of architectures in high yield.

2.2. Preparation of Building Blocks and Total Synthesis of Indane-Based Members of the Resveratrol Class. Of the many conceivable variants of our postulated general building block, we anticipated that only four would be required to access the

Scheme 3. Generalized Synthesis of Key Precursors (**27**−**30**)[a]



[a] Reagents and conditions: (a) $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 30 min; (b) PBr_3 (1.0 equiv), pyridine (0.05 equiv), Et_2O, 40 °C, 3 h, 93% over two steps; (c) NBS (1.0 equiv), CH_2Cl_2, 0 °C, 1 h, 95%; (d) $HP(O)(OEt)_2$ (2.0 equiv), KHMDS (0.5 M in toluene, 1.8 equiv), THF, 0 °C, 15 min, then add substrate, 25 °C, 12 h, 91%; (e) KO*t*-Bu (1.0 M in THF, 1.0 equiv), THF, −78 °C, 20 min, then *p*-methoxybenzaldehyde (0.95 equiv), −78 °C, 1 h, then 25 °C, 12 h, 94%; (f) *n*-BuLi (1.0 equiv), THF, −78 °C, 20 min; then *p*-methoxybenzaldehyde (1.0 equiv), −78 −25 °C, 4 h, 83%. NBS = *N*-bromosuccinimide, KHMDS = potassium bis(trimethylsilyl)amide.

complete diversity of the resveratrol family. These intermediates, compounds **27**−**30**, were prepared in high yield as shown in Scheme 3 (the scheme legend provides yields for intermediate **27**; see the Supporting Information for the other intermediates) via the indicated route that featured simple functional group manipulations in combination with Horner−Wadsworth−Emmons olefination and nucleophilic addition reactions as critical C−C bond-forming events. Of note, no chromatographic separations were required for any of the steps, with a final crystallization being all that was needed to access the desired intermediates in pure form. Moreover, all the steps proceeded smoothly even when conducted on scales up to 50 g. The sequence is also only four steps in length if commercial 3,5-dimethoxybenzyl bromide is used as the starting point.

Our initial synthetic efforts with these pieces (**27**−**30**) sought to explore their behavior upon exposure to acid. As shown in Scheme 4 using intermediate **27** for illustrative purposes, we believed that treatment with a stoichiometric amount of a proton source would initially generate cation **31** followed by a regioselective cyclization to **32**, a compound whose aryl rings on the newly formed carbocyclic skeleton would be arrayed in a *trans* fashion to minimize strain. The fate of this intermediate would then likely be determined by the identity of the acid's counterion, with a nucleophilic species attacking **32** directly while a non-nucleophilic counterion might enable the introduction of any number of other nucleophiles in a separate event.

In the initial test, controlled exposure of **27** to TFA in CH_2Cl_2 at −30 °C → −20 °C for 5 h, followed by a basic workup to hydrolyze the resultant trifluoroacetate ester, afforded alcohol **33** in 75% yield. This intermediate was smoothly converted into one of the simplest resveratrol-based natural products, paucifloral F (**10**), in 84% overall yield via Dess-Martin periodinane-mediated oxidation followed by BBr_3-induced global demethylation. However, if **27** was exposed to an acid possessing a much less nucleophilic counterion, such as *p*-TsOH, then it proved possible to arrest the sequence at cation **32** and ultimately generate compound **35** in 57% yield by introducing *p*-methoxy-α-toluenethiol (**34**) at −30 °C and concentrating the reaction medium to near dryness.[16] This new tetraaryl intermediate could then be converted smoothly into the natural product ampelopsin D (**5**) via a highly stereoselective Ramberg−Bäcklund reaction[17] using Meyers' modified conditions[18] (one which afforded a 5:1 ratio of separable *E*- and *Z*-isomers) followed by BBr_3-mediated phenol deprotection. If this natural product was then exposed to HCl in MeOH at 80 °C for 2 h, its central olefin could be isomerized smoothly in near quantitative yield (96%) to the more thermodynamically stable tetra-substituted olefin of isoampelopsin D (**36**).[19]

With these successes in hand, we then sought to explore the generality of the developed sequences with each of the other three forms of our common building block (i.e., **28**−**30**, cf. Scheme 3). Despite major electronic differences from **27**, these intermediates all reacted in an analogous manner. When building block **28** was subjected to the reaction sequences outlined above, what resulted were total syntheses of isopaucifloral F (**37**, Scheme 5)[20] and quadrangularin A (**21**), natural products whose pendant phenol ring systems are interchanged, as expected, from those accessed from **27**. Similarly, natural product-like analogues **38** and **39** were accessed from building block **29**, while compounds **40**, **41**, and **42** were smoothly generated from **30** in the indicated overall yields. Of these adducts, compound **42** is a fully deprotected analogue of

(16) In the absence of the sulfur nucleophile, only an alkene product resulting from β-elimination was observed. Sulfide **35** could also be accessed in 82% yield from alcohol **33** upon its treatment with *p*-TsOH and *p*-methoxy-α-toluenethiol (**34**) in CH_2Cl_2 at 25 °C; see Supporting Information for full details.

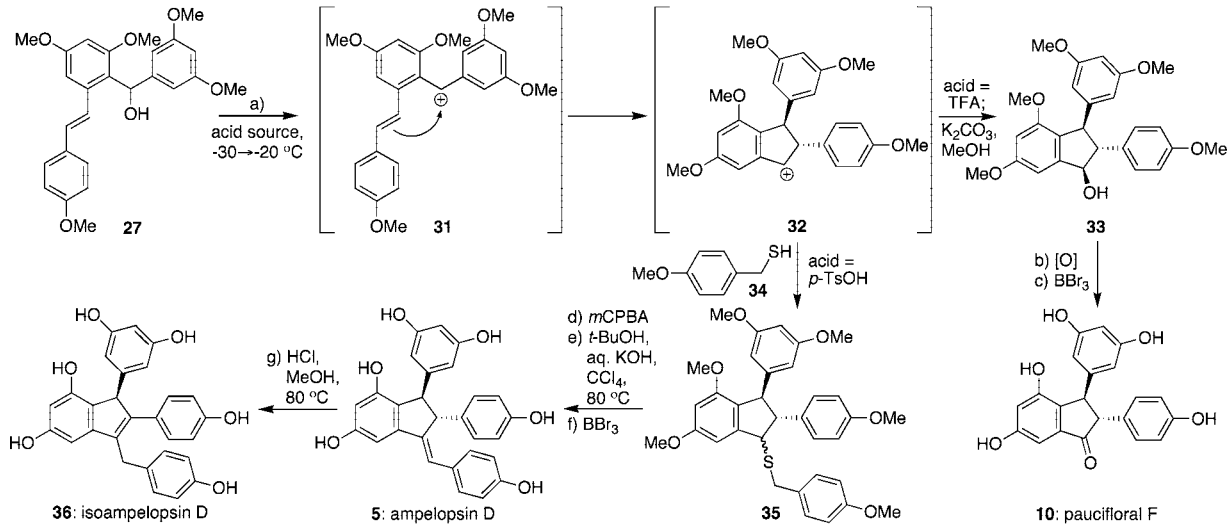
(17) For a recent review of this reaction, see: Taylor, R. J. K. *Chem. Commun.* **1999**, 217–227.

(18) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510–7512. No other procedure affords as favorable and/or controlled ratio of alkene products.

(19) This step produced a 5:1 mixture of both ampelopsin D (**5**) and isoampelopsin D (**36**) which were obtained in pure form in near quantitative yield by treating the product mixture with Ac_2O, chromatographically separating the resultant acetates, and using NaCN to then effect ester hydrolysis. In addition, the separable alkene isomer produced in the earlier Ramberg−Bäcklund step reflects a fully protected form of the natural product parthenocissin A: Tanaka, T.; Iinuma, M.; Murata, H *Phytochemistry* **1998**, *48*, 1045–1049. Isoampelopsin D was first reported in ref 30a.

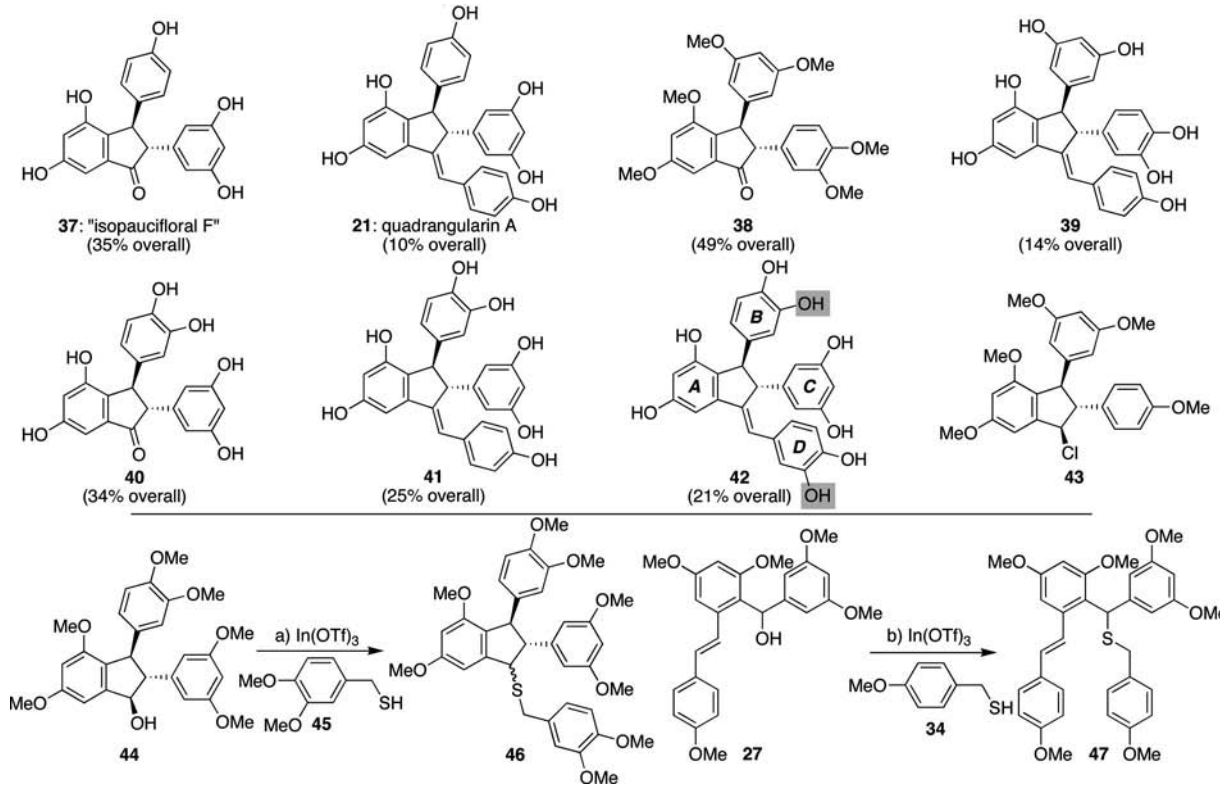
(20) Although we have indicated that compound **37** is isopaucifloral F, it is important to note that this is our own designation, as this structure, like **39**−**42**, has not yet been isolated from Nature though it certainly bears a natural product-like architecture.

Scheme 4. Total Synthesis of Three Resveratrol-Based Natural Products (**5**, **10**, and **36**) from Key Building Block **27**[a]



[a] Reagents and conditions: (a) for **33**: TFA (1.0 equiv), CH_2Cl_2, −30 → −20 °C, 5 h; then K_2CO_3 (10 equiv), MeOH, 25 °C, 5 min, 75%; for **35**: *p*-TsOH (1.0 equiv), CH_2Cl_2, −30 → −20 °C, 5 h; then concentration to near dryness; then **34** (3.0 equiv), 25 °C, 12 h, 57%; (b) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 97%; (c) BBr_3 (1.0 M in CH_2Cl_2, 10 equiv), CH_2Cl_2, 0 °C, 6 h, 86%; (d) *m*CPBA (3.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 0 → 25 °C, 3 h, 78%; (e) *t*-BuOH/H_2O/CCl_4 (4/1/4), KOH (20 equiv), 80 °C, 12 h, 52%; (f) BBr_3 (1.0 M in CH_2Cl_2, 12 equiv), CH_2Cl_2, 25 °C, 6 h, 76% of **5**, 13% of **36**; (g) conc. HCl (10 equiv), MeOH, 80 °C, 2 h, 95%. TFA = trifluoroacetic acid, *p*-TsOH = *p*-toluenesulfonic acid, *m*CBPA = *m*-chloroperoxybenzoic acid.

Scheme 5. Additional Natural Products and Natural Product-Like Analogues Created through the General Pathways Defined in Scheme 4 and the Development of Conditions To Generate Thioethers from Benzylic Alcohols[a]



[a] Reagents and conditions: (a) $In(OTf)_3$ (1.0 equiv), **45** (2.6 equiv), 25 °C, 90 min, 85%, 100% based on recovered **44**; (b) $In(OTf)_3$ (1.0 equiv), **34** (3.0 equiv), CH_2Cl_2, −10 °C, 5 min, 96%.

the natural product gnetulin,[21] an isolate that possesses methyl groups on the highlighted phenols.

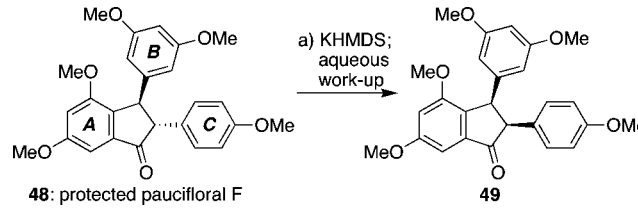
The following points are notable. First, while these adducts are small relative to many natural products, they issued several unexpected synthetic challenges. For example, any alteration of protecting groups within **27** (in either aromatic ring, cf.

(21) Siddiqui, Z. S.; Rahman, M.; Khan, M. A.; Lavaud, C.; Massiot, G.; Nuzillard, J. M.; Connolly, J. D.; Rycroft, D. S. *Tetrahedron* **1993**, *49*, 10393–10396.

(22) Petasis, N. A.; Bzowej, E. I. *J. Org. Chem.* **1992**, *57*, 1327–1330.

Scheme 3) prevented successful nucleophilic addition of the final carbon fragment, one of several instances where major changes in chemical reactivity resulted from only minor protecting group alterations. Also, the ketone within paucifloral F (**10**) and isopaucifloral F (**37**) proved entirely resistant to any olefination procedure other than Tebbe methylenation. As such, the ability to incorporate a sulfide nucleophile directly in the cyclization step provided the only means, out of nearly a dozen attempted, including the use of Petasis-type reagents[22] and Wittig olefination under salt-free conditions, to install the fourth aromatic ring of the larger targets. Second, several of the deprotected polyphenols possessing 3,4-dihydroxy systems (cf. Scheme 5) proved quite unstable, decomposing completely within hours, and sometimes minutes, in their isolation following phenol deprotection.[23] For example, the demethylated version of **38** could never be characterized. Third, a number of different nucleophiles could be installed onto the indane ring system during the course of the acid-catalyzed cyclization; for instance, exposure of **28** to stoichiometric $BiCl_3$ enabled a direct synthesis of compound **43** in 86% yield. Finally, to incorporate the 3,4-dihydroxyphenyl D-ring system of analogue **42**, a slightly different approach was needed from that described above in that thiol **45** (prepared *in situ* due to its lability)[24] decomposed in our standard acid-catalyzed cyclization. A solution to this problem was found in a lanthanide-promoted reaction, one which employed a full equivalent of a reagent such as $In(OTf)_3$[25] in a neat solution of the sulfide, to quickly generate the desired product from a precursor alcohol (i.e., **44** → **46**). Based on initial screening, this transformation proceeds for benzylic sulfides in combination with benzylic alcohols (as demonstrated by the conversion of **27** into **47** where no indane synthesis was observed), and it would seem that simple triflic acid, while likely present when these lanthanide salts are added to organic solvents,[26] cannot account for the process. This conclusion is based on the knowledge that triflic acid alone leads to starting material decomposition and the ratio of diastereomers produced in compounds such as **46** does not mirror the outcome when a precursor carbocation is generated using *p*-TsOH.[27]

Scheme 6. Synthesis of *cis*-Disposed Indane Systems[a]



48: protected paucifloral F **49**

[a] Reagents and conditions: (a) KHMDS (1.1 equiv), THF, −78 °C, 5 min, then slow warming to 25 °C, 15 h, 82%.

Finally, Indane-based structures with the more rare *cis*-disposed aryl rings of caraphenol B and C (**6**, cf. Figure 1)[28] are also accessible through these chemistries, as shown in Scheme 6 through epimerization of permethylated paucifloral F (**48**). This event leading to **49** requires enolization with KHMDS for 15 h in THF at 25 °C followed by a water quench that presumably gives the product of selective, kinetic proton capture.[29] It is important to note, however, that while any attempt to cleave the methyl ethers on compounds like **49** does effect phenol deprotection, it also returns the material to the original *trans*-stereochemistry.

2.3. Total Synthesis of Bicyclic Natural Products in the Resveratrol Class. We turned our attention next to a higher level of molecular complexity, namely to those natural products within the resveratrol class that possess an additional ring appended onto their indane core. Examples include pallidol (**7**, cf. Figure 1), with its symmetric [3.3.0] architecture, and ampelopsin F (**8**, cf. Figure 1), with its more congested [3.2.1] bicyclic frame.

As established by Niwa and co-workers,[11d,30] the likely biogenesis of these architectures is a nonselective, acid-catalyzed rearrangement of the resveratrol dimer ϵ-viniferin (**2**, Scheme 7). Indeed, these researchers showed that exposure of this isolate to HCl led to a number of structures, presumably through the intermediacy of reactive quinone methide **50**. For instance, rearomatization of **50** via loss of the proton flanking its quinone methide domain leads to ampelopsin D (**5**), a structure that can partially or fully isomerize to isoampelopsin D (**36**) under the reaction conditions. Alternatively, if the electron-rich B-ring within **50** attacks the quinone methide directly via a Friedel−Crafts alkylation, then the bicyclic architecture of ampelopsin F (**8**) results. By analogy, a dihydrofuran starting material possessing the opposite arrangement of B- and C-rings (i.e., **51**) would provide a means to generate pallidol (**7**), though this operation has not yet been demonstrated experimentally.

Given this knowledge, we wondered if elements of this uncontrolled biogenesis could be adapted to create both pallidol (**7**) and ampelopsin F (**8**) selectively from natural products already in our possession. This idea is expressed in Scheme 8, wherein electrophilic activation of the olefin within both ampelopsin D (**5**) and quadrangularin A (**21**), followed by a Friedel−Crafts alkylation onto the resultant quinone methide, could presumably lead to a single product.

(23) Such facile oxidation, even under care to exclude oxygen and light, may explain why no natural products of these general structures have yet been isolated except for those like gnetulin that likely temper such oxidation potential through partial phenol protection.

(24) The synthesis of this fragment was adapted from Vetter, S. *Synth. Commun.* **1998**, *28*, 3219–3223.

(25) Other metal triflates which were successfully employed in this reaction include $Bi(OTf)_3$ and $Yb(OTf)_3$. If any solvent is present, significant amounts of carbocation elimination products are observed. This general transformation was inspired, in part, by the reported ability to replace activated alcohols with silicon nucleophiles in the presence of $InCl_3$: (a) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414–1416. For other references concerning related reactivity, see: (b) Weïwer, M.; Coulombel, L.; Duñach, E. *Chem. Commun.* **2006**, 332–334. (c) Ghosh, R.; Maiti, S. *J. Mol. Catal. A* **2007**, *264*, 1–8. Standard incorporation of a sulfide component through S_N2 displacement of a tosylate or other activated alcohol (such as that obtained by Mitsunobu conditions) did not succeed, likely due to the bulk of the aromatic neighbor which resides on the same side as the incoming nucleophile. (d) For a representative reference for this alternate procedure, see: Kolanos, R.; Siripurapu, U.; Pullagurla, M.; Riaz, M.; Setola, V.; Roth, B. L.; Dukat, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1987–1991.

(26) For a leading reference on this element of reactivity, see: Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179–4182.

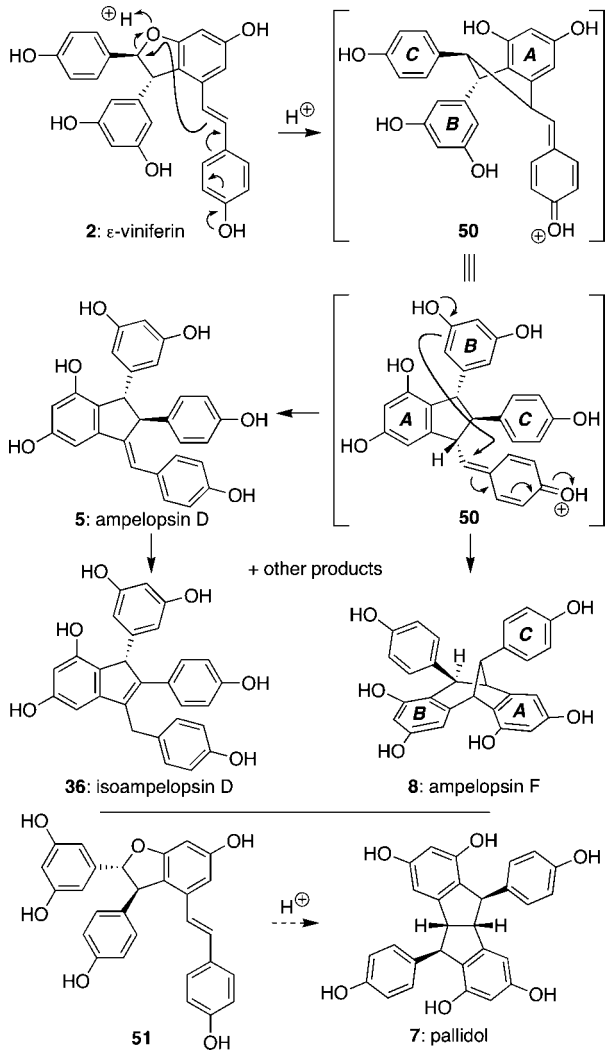
(27) The product ratio for the TfOH conditions was 1:1 while $In(OTf)_3$ gave 3:2 favoring the relative stereochemistry of **44**.

(28) For the isolation, see: (a) Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849–4854. (b) For another approach to this type of architecture, see: Zhu, J.; Zhong, C.; Lu, H.-F.; Li, G.-Y.; Sun, X. *Synlett* **2008**, 458–462.

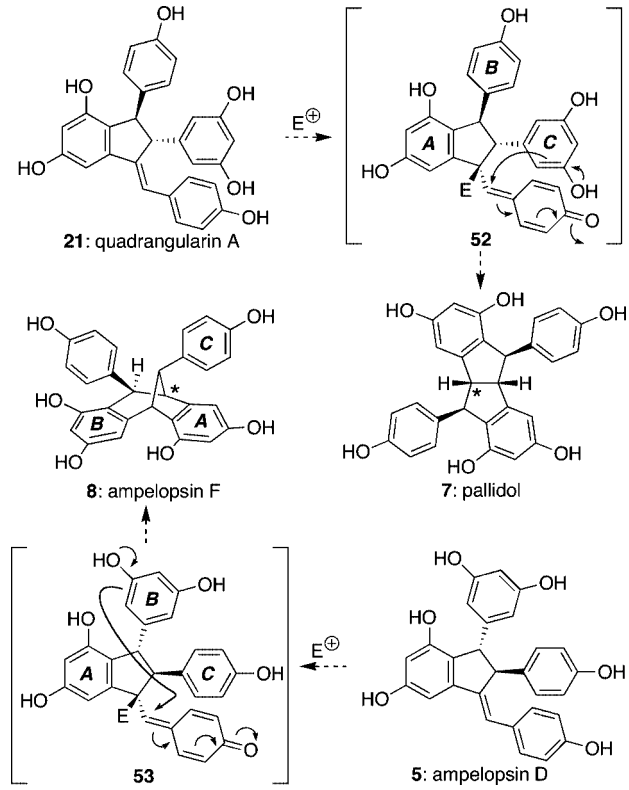
(29) Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168–1173. We found that 15 h of exposure were needed to get complete deprotonation of the starting material; sterics could be playing a role in this time requirement.

(30) (a) Takaya, Y.; Yan, K.-X.; Terashima, K.; Ito, J.; Niwa, M. *Tetrahedron* **2002**, *58*, 7259–7265. (b) Takaya, Y.; Yan, K.-X.; Terashima, K.; He, Y.-H.; Niwa, M. *Tetrahedron* **2002**, *58*, 9265–9271.

Scheme 7. Known Means To Access Ampelopsin F (**8**) and Other Structures from ε-Viniferin (**2**)



Scheme 8. Attempt To Create Both Pallidol (**7**) and Ampelopsin F (**8**) via a Unique Biogenetic Connection



However, while this plan is easily drawn, there are at least two issues with its laboratory execution. The first is the identity of an appropriate electrophile since the ideal candidate, a proton, effects only olefin isomerization (i.e., **5** → **36**, cf. Scheme 7) under a variety of conditions (including H_2SO_4, TFA, HCl, HBr, CSA, and *p*-TsOH in a variety of polar and nonpolar solvents at different temperatures). Consequently, an alternative electrophile is needed, one that can be replaced by hydrogen at the starred positions within both **7** and **8** following cyclization (see Scheme 8). The second is the facial selectivity with which the electrophile adds, since both quinone methides **52** and **53** can be accessed only if the activating species approaches from the β-face; indeed, while this stereochemical requirement would appear reasonable with **52**, the adjacent C-ring would seem to make it impossible for **53**.

We hypothesized that it might be possible to overcome both of these issues in a single, cascade-based operation by using a halogen electrophile. This choice was predicated on the knowledge that their addition to alkenes is reversible,[31] thereby enabling a greater likelihood of obtaining reactive intermediates with the requisite stereochemistry, and their replacement with hydrogen is a standard transformation. As indicated in Scheme 9, the cyclization event was realized when molecular bromine was used as the activating species. Exposure of permethylated quadrangularin A (**54**) to 2 equiv of this halogen source in CH_2Cl_2 at −78 °C, followed by slow warming to 25 °C, afforded the desired bicycle (**58**) with three extra halogen atoms attached in 81% yield. Based on a series of experiments using less bromine under the same reaction conditions, the course of events for this transformation is known to begin with initial halogenation of the indicated position within the A-ring to afford **55**, followed by a site-selective bromination of the C-ring to generate **56**.[32] Both of these halogenations occur smoothly and relatively quickly at −78 °C; the final alkene halogenation, however, only occurs once the reaction temperature has reached at least 0 °C as based on TLC analysis. From this intermediate, pallidol (**7**) was synthesized in 63% overall yield via hydrogenative replacement of all three bromides within **58** followed by global deprotection of the phenolic ethers (as achieved by exposure to BBr_3 in CH_2Cl_2 for 12 h at 25 °C). Application of the same reactions to permethylated forms of **41** and **42** (cf. Scheme 5) led to total syntheses of cararosinol C and D (**59** and **60**, cf. Scheme 9)[33] in the indicated overall yields (the starred positions are the sites of bromine incorporation), while their application to permethylated ampelopsin D (**61**, Scheme 10) provided access to the [3.2.1]-bicyclic core of ampelopsin F (**63**), with a radical-based dehalogenation assisting in the completion of the target molecule (**8**) in this case.

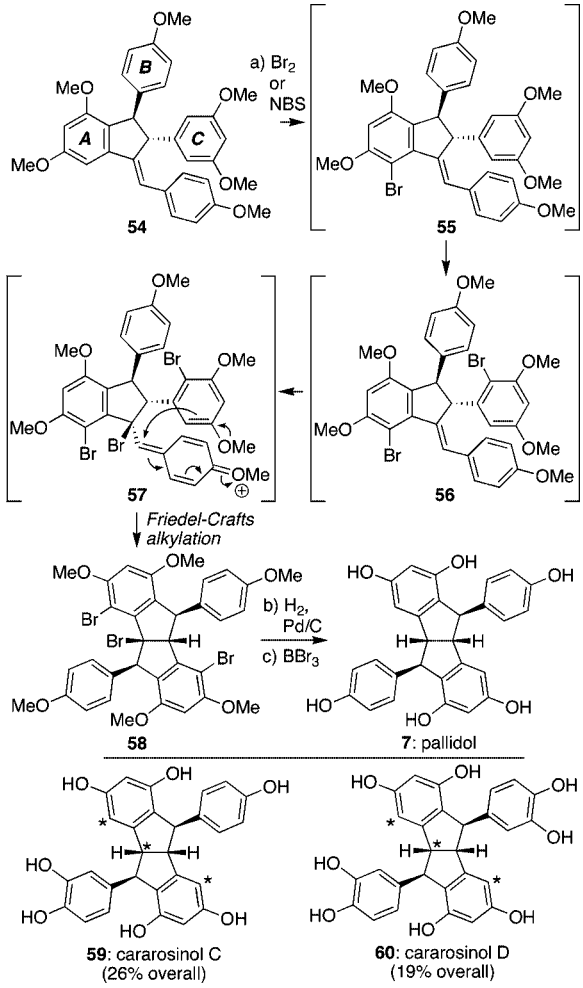
Several elements of the core cyclization in these sequences are notable. Particularly interesting is the mechanism of bromine

(31) For a leading introduction to this concept of halonium transfer between alkenes, see: Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131–137.

(32) Both **55** and **56** were isolated and fully characterized (see Supporting Information for more details).

(33) Yang, G.; Zhou, J.; Li, Y.; Hu, C. *Planta Med.* **2005**, *71*, 569–571.

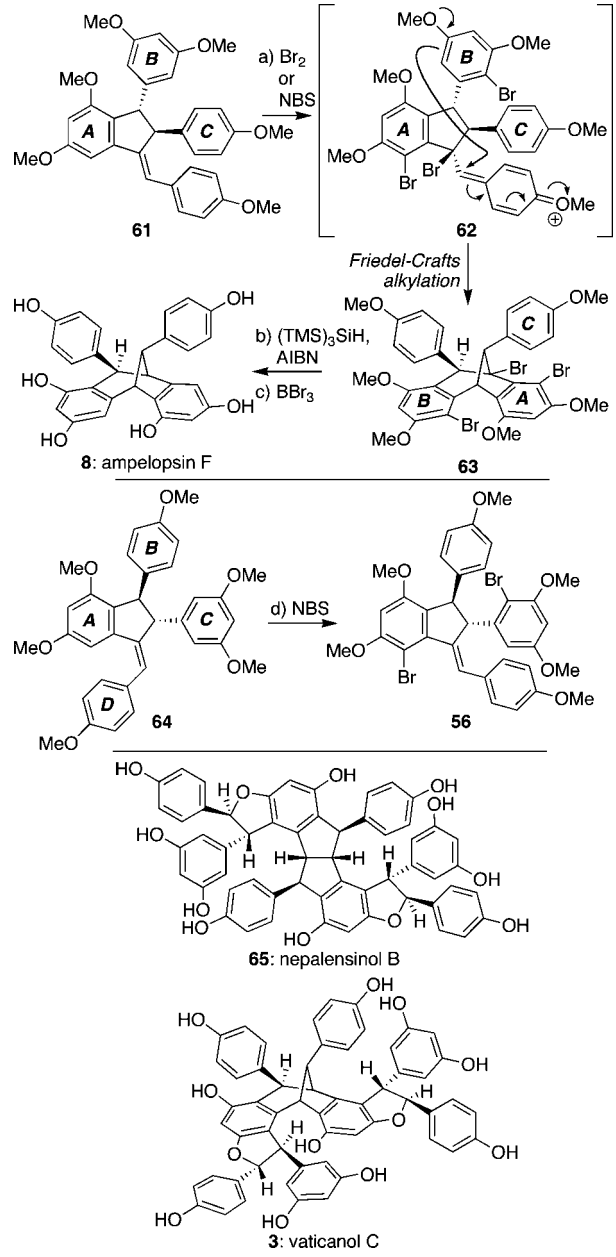
Scheme 9. Sequential, Cascade-Based Halogenation To Access Pallidol (**7**), Cararosinol C (**59**), and Cararosinol D (**60**)[a]



[a] Reagents and conditions: (a) Br_2 (2.0 equiv), CH_2Cl_2, −78 °C, 4 h, then slow warming 25 °C 1 h, 81% or NBS (3.0 equiv), CH_2Cl_2, 25 °C 2 h, 80%; (b) H_2, Pd/C (20%, 0.2 equiv), MeOH, 25 °C, 12 h, 76%; (c) BBr_3 (1.0 M in CH_2Cl_2, 12 equiv), CH_2Cl_2, 0 °C, 4 h, then 25 °C, 12 h, 83%.

incorporation as 3 equiv of electrophilic halogen are added while only 2 equiv of reagent were used (with the isolated yield of pallidol being higher than could be achieved with 2 equiv of reagent alone).[34] Based on a series of mechanistic investigations, we have established that the third equivalent of bromine derives from aerial oxidation of bromide in solution. In our initial experiments, we observed significant variations in reaction times when the reaction was conducted under an argon atmosphere without care for deoxygenating the solvent, suggesting that adventitious oxygen was needed to promote the final cyclization. This suspicion was verified when sparging the solution with argon when 2 equiv of bromine were present completely prevented the Friedel−Crafts element of the sequence (stopping at **56**, cf. Scheme 9), while the addition of an oxygen atmosphere to the solution enabled the reaction to proceed to completion in just a few minutes. While we have been unable to find other examples of *in situ* bromine generation through oxygen exposure, the concept has been documented for the synthesis of

Scheme 10. Sequential, Cascade-Based Halogenations To Access Ampelopsin F (**8**)[a]



[a] Reagents and conditions: (a) Br_2 (2.0 equiv), CH_2Cl_2, −78 °C, 1 h, then slow warming to 25 °C 5 h, 53% or NBS (3.0 equiv), CH_2Cl_2, 25 °C, 5 h, 89%; (b) $(TMS)_2SiH$ (9.0 equiv), AIBN (1.0 equiv), toluene, 100 °C, 5 h, 89%; (c) BBr_3 (1.0 M in CH_2Cl_2, 12 equiv), CH_2Cl_2, 0 °C, 4 h, then 25 °C, 12 h, 90%; (d) NBS (2.0 equiv), THF, −78 °C, 30 min, aqueous quench, then standing, 25 °C, 5 h, 99%; TMS = trimethylsilyl, AIBN = 2,2′- azobisisobutyronitrile.

molecular iodine;[35] our current belief is that the highly electron-rich nature of the substrate assists in the process, suggesting that the overall reaction is not general. We also believe that an electrophilic mechanism is reasonable since the addition of radical scavengers such as TEMPO does not hinder the reaction, and the transformation proceeds with superior facility if NBS (3 equiv) is used instead; for example, a yield of 89% was obtained for the conversion of **61** into **63**.

(34) Stock bromine solutions in CH_2Cl_2 were employed in all these experiments, and reaction scales were sufficiently large (∼50 to 75 mg) so as to ensure that exactly 2 equiv of the halogen were employed.

(35) For selected examples, see: (a) Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769–3775. (b) Srinivasan, R.; Merritt, V. Y.; Hsu, J. N. C.; op het Veld, P. H. G.; Laarhoven, W. H. *J. Org. Chem.* **1978**, *43*, 980–985.

What remains unclear is whether the aryl bromine atoms play a role in the cyclization step or if the initial double bond geometry is critical to the stereochemistry of the product.[36] The latter is the more interesting question, since no natural products are known to possess different stereochemistry in either the pallidol or ampelopsin F cores, while the alkene precursors used are known to exist in both *E*- and *Z*-forms in Nature. We have tried to address this question by experimenting with alkene **64**, the permethylated form of the natural product parthenocissin A[19] obtained as a minor side-product from our efforts described above (cf. Scheme 4). We have found that after initial halogenation of its A and B rings at −78 °C upon exposure to NBS (2 equiv) in THF, we obtain material with the original alkene geometry intact. Upon standing neat or in solution at 25 °C for just a few hours, however, this material isomerizes to **56**. Exposure of **64** to 2 equiv of Br_2 or 3 equiv of NBS under standard reaction conditions affords only cyclization product **58**, indicating that either alkene isomerization precedes cyclization, perhaps promoted by some species in solution, and double bond geometry may be critical to the final adduct's stereochemistry, or both olefin isomers ultimately provide the same product.

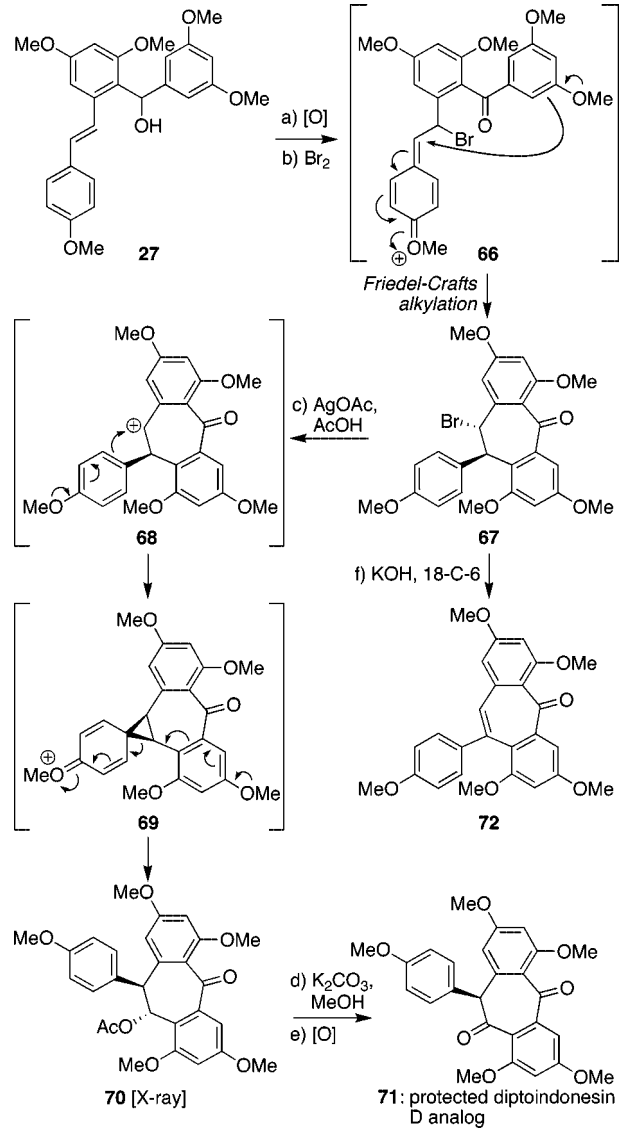
Finally, while an ideal synthesis would avoid the incorporation of extra atoms, the lack of atom economy in these sequences may have one benefit: the ability to access even greater molecular complexity.[37] Indeed, the aryl bromides within both **58** and **63** are situated perfectly to attach the extra carbon fragments needed to complete the dihydrofuran ring systems of both nepalensinol B (**65**)[38] and vaticanol C (**3**). This hypothesis is the subject of current investigations.

2.4. Total Synthesis of Natural Products and Analogues Bearing a Seven-Membered Carbocycle. The major remaining element of carbogenic complexity possessed by the resveratrol class is seven-membered carbocycles, motifs displayed by both hopeaphenol (**4**) and diptoindonesin D (**9**) as well as numerous other natural products. These systems have also proven accessible from our common intermediates, but only after the alcohol function has been oxidized to the corresponding ketone.

As shown in Scheme 11, when the oxidized form of intermediate **27** was exposed to molecular bromine in CH_2Cl_2, it participated in an electrophilic activation/Friedel−Crafts cyclization sequence very similar to that described above in section 2.3. In this case, however, with a ketone flanking both dimethoxyphenyl rings, the alkene proved to be the most electron-rich domain of the molecule, and **67** was produced smoothly without any aryl halogenation. Though the isolated yield for this compound is moderate (51%), this outcome primarily reflects the difficulty in achieving its isolation, as **67** is sensitive to light and silica gel. For instance, upon exposure to AcOH in the presence of a silver salt,[39] intermediate **67** quickly rearranges into **70** in 62% yield. This unique structure, confirmed by X-ray crystallographic analysis, is the likely product of a thermodynamically favored phenonium shift initiated by the conversion of the benzylic bromide of **67** into a carbocation (i.e., **68**), followed by regioselective cyclopropane opening as induced by the strategically positioned *ortho*- and *para*-disposed alkoxy groups within **69** and a terminating attack by acetate onto the resultant quinone methide. Though this intermediate does not possess the connectivities of any known natural product, it could be converted into a regioisomeric and fully protected analogue of diptoindonesin D (**71**, compare to **9** in Figure 1) via simple acetate cleavage and alcohol oxidation.

Unfortunately, no condition screened has yet enabled the bromine atom within **67** to be replaced directly with the oxygen atom needed to access the correct connectivity of diptoindonesin D. We have only been able to induce its elimination under

Scheme 11. Synthesis of Seven-Membered Rings via a Bromonium-Induced Cascade Sequence Followed by an Acid-Induced Phenonium Shift To Afford Non-Natural Resveratrol-Based Oligomers (i.e., **70** and **71**)[a]



[a] Reagents and conditions: (a) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 2 h, 97%; (b) Br_2 (1 equiv), CH_2Cl_2, −78 °C, 1 h, then 25 °C, 12 h, 50%; (c) AgOAc (3.0 equiv), AcOH, 25 °C, 3 h, 62%; (d) K_2CO_3 (10 equiv), MeOH, 25 °C, 12 h, 78%; (e) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1.5 h, 99%; (f) KOH (10 equiv), 18-Crown-6 (0.1 equiv), THF, 40 °C, 12 h, 92%.

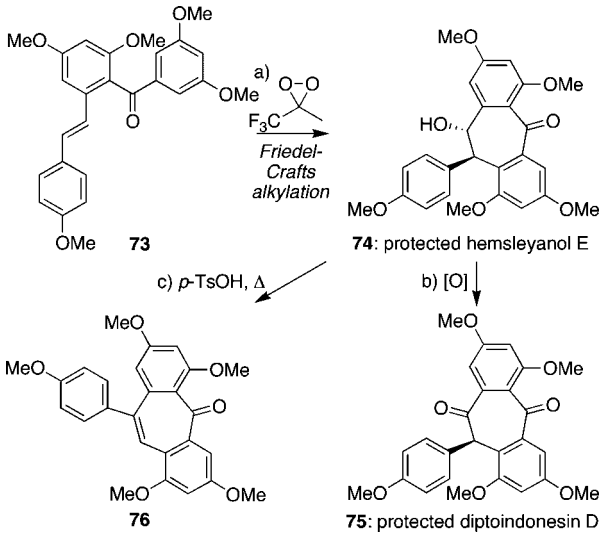
(36) For instance, we originally postulated (ref 15) that the B-ring halide could assist in determining the ease by which bromine could add to the correct face of the alkene, while the A-ring halide might prevent rotation of the quinone methide prior to cyclization, thereby assuring that only the correct relative stereochemistry was obtained.

(37) For an interesting commentary on utilizing bromine as a protective device, see: Effenberger, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 1699–1700.

(38) Yamada, M.; Hayashi, K.; Hayashi, H.; Ikeda, S.; Hoshino, T.; Tsutsui, K.; Tsutsui, K.; Iinuma, M.; Nozaki, H. *Phytochemistry* **2006**, *67*, 307–313.

(39) (a) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563–2565. (b) Miesch, M.; Cotté, A.; Frank-Neumann, M. *Tetrahedron Lett.* **1993**, *34*, 8085–8086.

Scheme 12. Total Synthesis of Protected Diptoindonesin D (**75**)[a]



[a] Reagents and conditions: (a) 1,1,1-trifluoroacetone (excess), $NaHCO_3$ (8.0 equiv), Oxone (5.0 equiv), MeCN/0.4 mM EDTA in H_2O (3:1), 25 °C, 3 h, 34%; (b) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 96%; (c) *p*-TsOH (10 equiv), toluene, 65 °C, 12 h, 96%.

strongly basic conditions to afford alkene **72**, a molecule whose double bond is unreactive in our hands.[40] What does lead to the diptoindonesin D (**9**) architecture is the use of a different electrophile with the same starting ketone (i.e., **73**, Scheme 12). Indeed, if this material is reacted with 1,1,1-trifluorodimethydioxirane (generated *in situ* using OXONE, 1,1,1-trifluoroacetone, and Na_2EDTA buffer)[41] in MeCN at 25 °C, a protected form of the natural product hemsleyanol E (**74**)[42] is generated in 34% yield. Oxidation then completed the synthesis of protected diptoindonesin D (**75**).[43]

It is worth noting that the absence of any natural products bearing the general architectures possessed by our synthetic diptoindonesin D analogues (**70** and **71**, cf. Scheme 11) may reflect the fact that natural product-like structures, such as **74** (cf. Scheme 12), are not easily ionized. For instance, rearrangement of **74** into **76** was observed only upon exposure to an excess of relatively strong acid at 65 °C in a nonpolar solvent such as toluene; in polar solvents at any temperature, and in toluene at 25 °C, **74** was recovered unchanged even when several equivalents of strong proton sources were present.

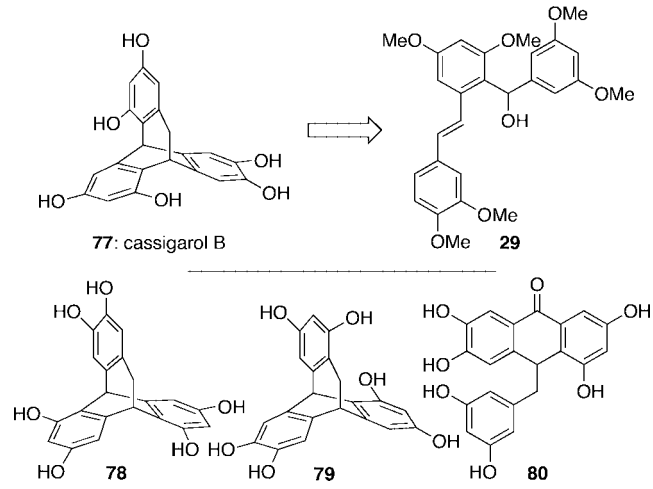


Figure 2. Additional architectures (**77**−**80**) accessible from our common synthetic precursors.

2.5. Explorations To Access Other Molecular Frameworks. Given the successful synthesis of much of the major carbogenic complexity possessed by the resveratrol family of natural products, we wondered if our starting materials could produce additional architectures, such as that possessed by cassigarol B (**77**, Figure 2).[44] This molecule was isolated in 1988 by Kozawa and co-workers, and though it possesses ring systems reminiscent of resveratrol-based structures, such a connection was not suggested by these isolation chemists. Our hypothesis was that this structure and resveratrol could be related and that the former could be accessed from building block **29**. This thought would prove true. Interestingly, in the process of synthesizing **77**, we also uncovered the means to convert intermediate **29** selectively into a six-membered carbocycle (**80**) as well as two additional [3.2.2]-bicycles (**78** and **79**), molecules that possess the same carbogenic core as cassigarol B (**77**) but have their aryl rings rotated 120° and 240° counterclockwise, respectively. As with all of the chemistry described thus far, the key to these sequences is the control of reaction conditions with simple reagents combined with alteration of the group uniting the upper two aromatic rings.

Scheme 13 presents several different routes capable of preparing cassigarol B (**77**) in two to four steps from key intermediate **29**. The longer of these sequences begins similarly to that described above, namely alcohol oxidation followed by treatment with *p*-TsOH at 60 °C, conditions by which we can access both **82** and **84** (each of whose structures were confirmed by X-ray crystallographic analysis). The outcome of this step, and its level of selectivity, depends on the amount of acid employed and the total reaction time, with the use of 3 equiv of *p*-TsOH and 24 h of stirring at 60 °C providing **82** with 9:1 selectivity over **84**, and more acid (5 equiv) and a greater reaction time (36 h) leading solely to **84** in near quantitative yield. Based on the ease of converting isolated **82** into **84** (and not the reverse) as well as DFT calculations revealing that **84** is 16 kcal/mol more stable, we are confident that this opening sequence involves the initial formation of **82**. However, since the C-ring in this system is more electron-rich than that explored above for the synthesis of diptoindonisin D (cf. Scheme 12), subsequent acid activation of the ketone under more forcing reaction conditions enabled a second Friedel−Crafts reaction

(40) Other attempts included the use of potassium superoxide and LiOH in THF/H_2O.

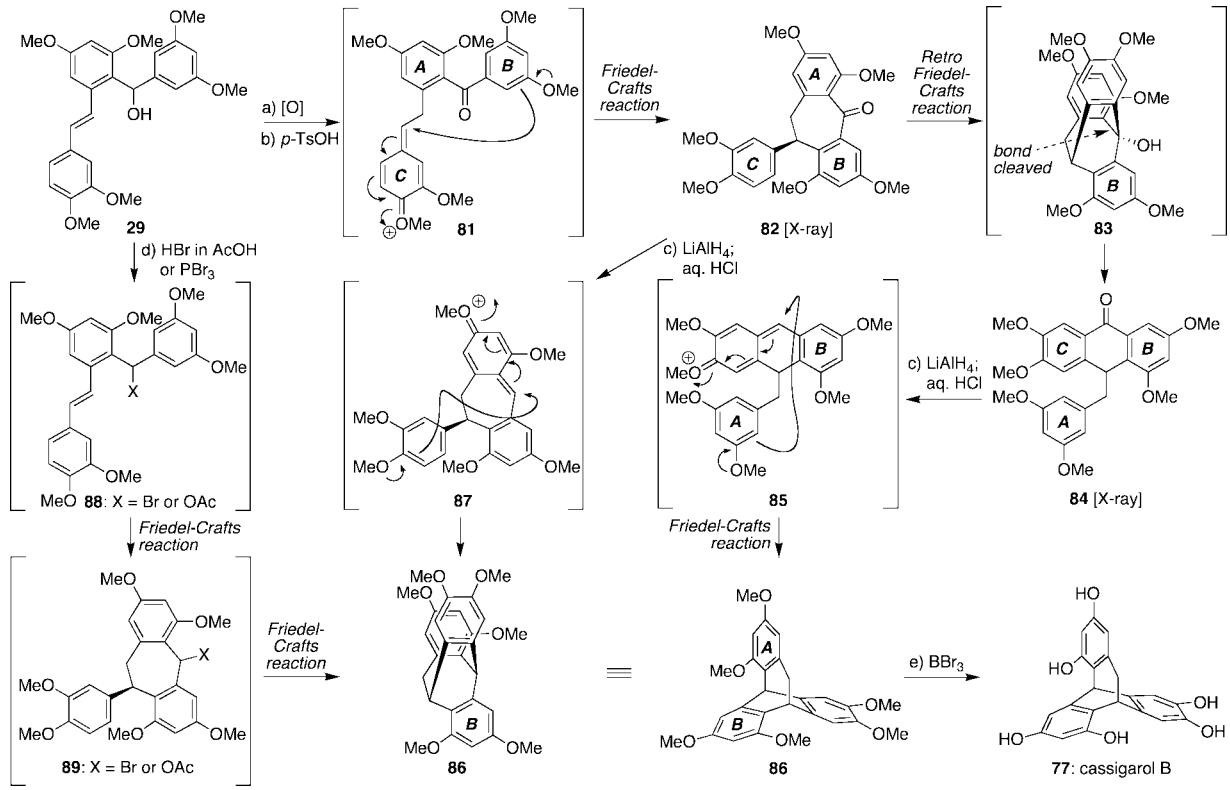
(41) These conditions were taken from past efforts to synthesize the epothilones: Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschanger, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973. Although this reaction appears simple, it proved exceedingly difficult to achieve. No other epoxidation reagent afforded the desired product, and only through the use of *in situ* generated 1,1,1-trifluorodimethyldioxirane was the reaction successful. The presence of methyl ether protection may be responsible, as other efforts with biologically derived materials bearing acetate protection have proven more easily epoxidizable: see ref 30b.

(42) Tanaka, T.; Ito, T.; Nakaya, K; Iinuma, M.; Takahashi, Y.; Naganawa, H.; Riswan, S. *Heterocycles* **2001**, *55*, 729–740.

(43) Of all synthetic materials, **71**, **74**, or **75** has not yet succumbed to complete deprotection despite dozens of attempts. The use of BBr_3 in CH_2Cl_2 affords a monomethylated adduct in all three cases with low solubility in any solvent compatible with such a powerful Lewis acid; most other protocols only excise the methyl ether adjacent to the central ketone.

(44) Baba, K.; Maeda, K.; Tabata, Y.; Doi, M.; Kozawa, M. *Chem. Pharm. Bull.* **1988**, *36*, 2977–2983.

Scheme 13. Total Synthesis of Cassigarol B (**77**)[a]



[a] Reagents and conditions: (a) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 96%; (b) for **82**: *p*-TsOH (2.0 equiv), toluene, 60 °C, 48 h, 85% of **82**, 8% **84**; for **84**: *p*-TsOH (8.0 equiv), toluene, 60 °C, 72 h, 83%; (c) $LiAlH_4$ (5.0 equiv), THF, 25 °C, 2 h; aq. HCl (20 equiv), 25 °C, 2 h, 91%; (d) HBr (33% in AcOH, 1.0 equiv), CH_2Cl_2, −78 °C, 1 h, then 25 °C, 12 h, 74% or PBr_3 (1.0 equiv), pyridine (0.05 equiv), 40 °C, 3 h, 58%; (e) BBr_3 (1.0 M in CH_2Cl_2, 10 equiv), CH_2Cl_2, −78 → 25 °C, 12 h, 87%.

to occur, one that constructed the new six-membered ring within intermediate **83**. This adduct, however, has not been isolated. We believe it is rapidly converted into **84** via a retro Friedel−Crafts reaction initiated by the addition of a proton onto ring A, with breaking of the indicated bond.

Despite the structural uniqueness of these two products (**82** and **84**), each could be funneled into a protected form of cassigarol B (**86**) following exposure to $LiAlH_4$ in THF at 0 °C and an acidic reaction quench, presumably via the indicated mechanistic pathways. BBr_3-induced methyl ether cleavage then completed the synthesis of the natural product (**77**) in 87% yield. The permethylated form of cassigarol B (**86**) could also be accessed directly from **29** upon its exposure to either PBr_3 in pyridine at 25 °C or a mixture of 33% HBr in AcOH at 25 °C. In both of these cases, we believe that the benzylic alcohol was initially exchanged for either a bromine or an acetate; pure cation generation would be unlikely as this should lead to indane formation. This group exchange "protects" the benzylic position until Friedel−Crafts cyclization to **89** occurs and then serves as a leaving group to allow the same end-game (via **87**) to occur as described above.

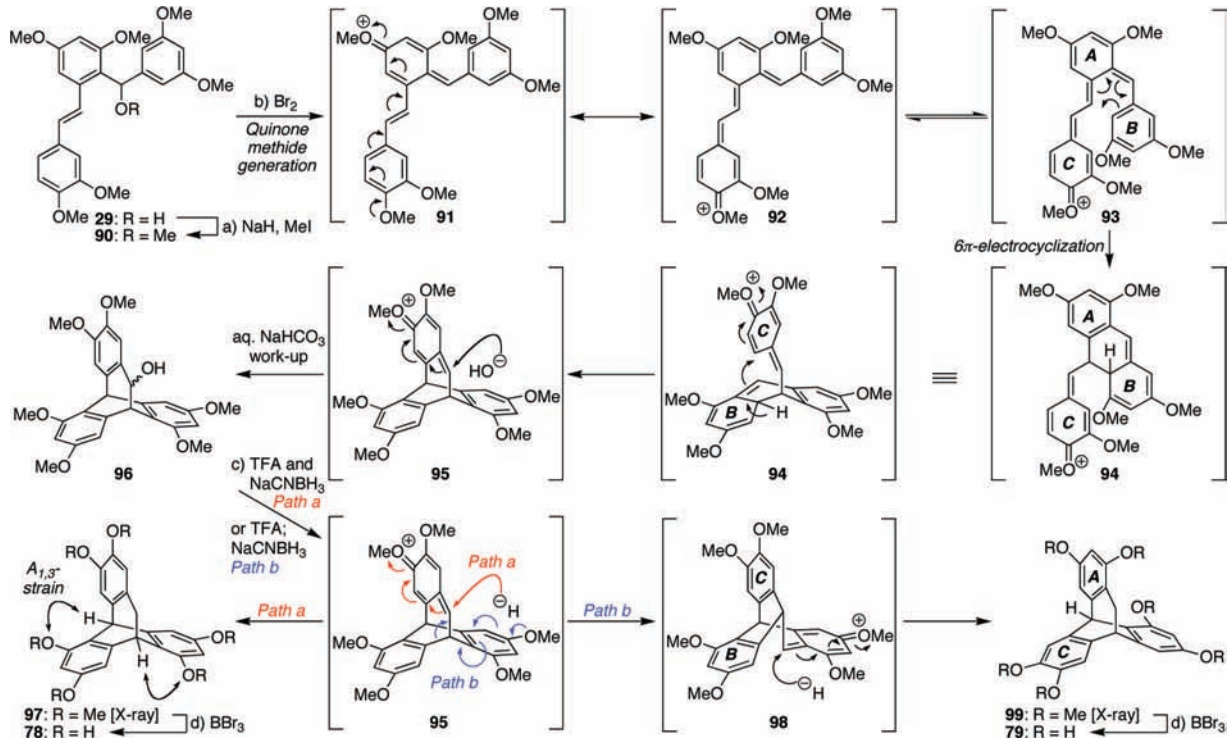
The key intermediate to access cassigarol B analogues **78** and **79** is methyl ether **90** (Scheme 14, prepared from **29** via treatment with NaH and MeI), a compound that upon its careful exposure to 2 equiv of molecular bromine in CH_2Cl_2 at −78 °C, followed by slow warming to 25 °C over several hours and subsequent stirring with mild aqueous base, could be converted into bicycle **96** in 52% yield. This structurally unique product is the putative result of an orchestrated sequence of four C−O and C−C bond forming and cleaving events. As indicated, we believe the process begins with halogen activation of the benzylic methyl ether, converting it into a leaving group. Upon expulsion by one of the strategically positioned *ortho*- or *para*-methoxy groups, a series of quinone methides (**91**, **92**, and **93**) is then obtained. Of these reactive species, one (**93**) can funnel to putative intermediate **94** via a 6π-electrocyclization.[45] Rearomatization of ring B within **94** through loss of a proton, attended by attack of the benzylic carbon onto the aromatic system of the pendant quinone methide, would afford bicyclic intermediate **95**. Finally, attack by water (or hydroxide) upon workup could then account for the formation of bicycle **96**, a compound which was obtained as a 1:1 mixture of stereoisomers (an expected result since both faces of the quinone methide within **95** are equally accessible).[46]

From here, protected forms of both analogues (**97** and **99**) could be accessed selectively from **96**. For instance, concurrent treatment with both TFA and $NaCNBH_3$ in CH_2Cl_2 resulted in the smooth synthesis of **97** in 87% yield, likely via mechanistic pathway A. However, if **96** was exposed to the same acid for 3 h at 25 °C without any added $NaCNBH_3$, quinone methide **95** participated in an intramolecular rearrangement via mecha-

(45) Though this step is drawn as a pericyclic process, it could also reflect a formal 6π-like ring formation, using the phenols within the labeled B-ring to achieve C−C bond construction in a stepwise manner.

(46) The reaction does not appear to be caused by trace acid as might be generated upon the addition of molecular bromine to solvent possessing adventitious water; any attempt to utilize catalytic acid with **90** leads either to cassigarol B in protected form (**86**) or indane architectures. For a related precedent for the terminating acid-induced cyclization leading to a [3.2.2]-bicycle, see: Gao, C.; Cao, D.; Xu, S.; Meier, H. *J. Org. Chem.* **2006**, *71*, 3071–3076.

Scheme 14. Selective Synthesis of a Cassigarol B Analogues (**78** and **79**) via a Proposed Cascade-Sequence Involving Two C−C Bond Formations[a]



[a] Reagents and conditions: (a) NaH (10 equiv), THF, 0 °C, 30 min, then MeI (5 equiv), THF, 25 °C, 4 h, 96%; (b) Br_2 (1.0 equiv), CH_2Cl_2, −78 °C, 2 h, then slow warming to 25 °C, 1 h; aq. $NaHCO_3$, 25 °C, 10 min, 52%; (c) for **97**: TFA (6.0 equiv, added in batches), $NaCNBH_3$ (50 equiv), CH_2Cl_2, 0 °C, 1 h; 25 °C, 2 h, 87%; for **99**: TFA (12 equiv), CH_2Cl_2, 0 °C, 30 min; 25 °C, 3 h, then $NaCNBH_3$ (10 equiv), 25 °C, 3 h, 83%; (d) BBr_3 (1.0 M in CH_2Cl_2, 10 equiv), CH_2Cl_2, −78 → 25 °C, 3 h, 78% for **78**, 81% for **79**.

nistic pathway B which led to **98**, a new quinone methide that upon introduction of $NaCNBH_3$ was reduced to **99** in 83% yield. Based on these results, **99** appears to be the thermodynamic product following acidic activation of intermediate **96**, given that the resultant rearranged architecture has only one $A_{1,3}$-like interaction between a bridgehead proton and an aromatic methyl ether, while **97** has two such interactions.[47] In both cases, exposure to BBr_3 afforded the phenol forms of these analogues (**78** and **79**).

2.6. Metal-Initiated Reaction Cascades. While the sequences above define ways to prepare the majority of carbogenic skeletons within the resveratrol family, the ability to selectively access additional architectures, particularly non-natural ones, should facilitate biochemical discoveries. One way to meet this objective lies in the realm of exposing our generalized intermediates to transition metals. For instance, preliminary screens have established that treatment of **27** (Scheme 15) with a catalytic amount of $PdCl_2$(benzonitrile)$_2$ enabled access to heterocycle **100** in 75% yield (alongside a 22% yield of **102**; olefin stereochemistry unverified). This Wacker oxidation product (**100**) is the likely product of initial metal coordination to the alkene, followed by a regioselective *anti*-insertion of oxygen as dictated by the polarity of the double bond and the presence of chloride in the reaction mixture.[48] However, when **27** was exposed to a chloride-free palladium source [$Pd(OAc)_2$] in the presence of $Cu(OAc)_2$ and an oxygen atmosphere,[49] only **102** was synthesized. This compound presumably reflects initial coordination of the hydroxyl group within **27** to the metal center, followed by *syn*-addition to produce intermediate **101** and β-hydride elimination. Of these two compounds, **102** proved unstable and, if exposed to concentrated HCl in *i*-PrOH at 25 °C for 16 h, could be converted into α,β-unsaturated ketone **106** in 90% yield. This product is believed to result from the sequence shown involving acid-induced isomerization to form an isobenzofuran (**103**), followed by trapping with oxygen (with regiochemistry of addition determined by the phenol positioning and the drive for rearomatization of the benzene ring) that ultimately affords **105** following disproportionation.[50] A terminating aldol condensation could then account for the formation of **106**.[51] Of course, while such an α,β-unsaturated product could be obtained easily from available precursors like paucifloral F (**10**, cf. Figure 1) through an oxidation, this reaction serves to showcase another unique cascade sequence that is possible with our general precursors.[52]

(47) Some preliminary DFT calculations reveal that compound **99** is 1.13 kcal/mol more stable than compound **97**.

(48) For studies illustrating how ligand change can adjust the mechanism for Wacker-type processes, see: (a) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037. (b) Takacs, J. M.; Jiang, X. *Curr. Org. Chem.* **2003**, *7*, 369–396.

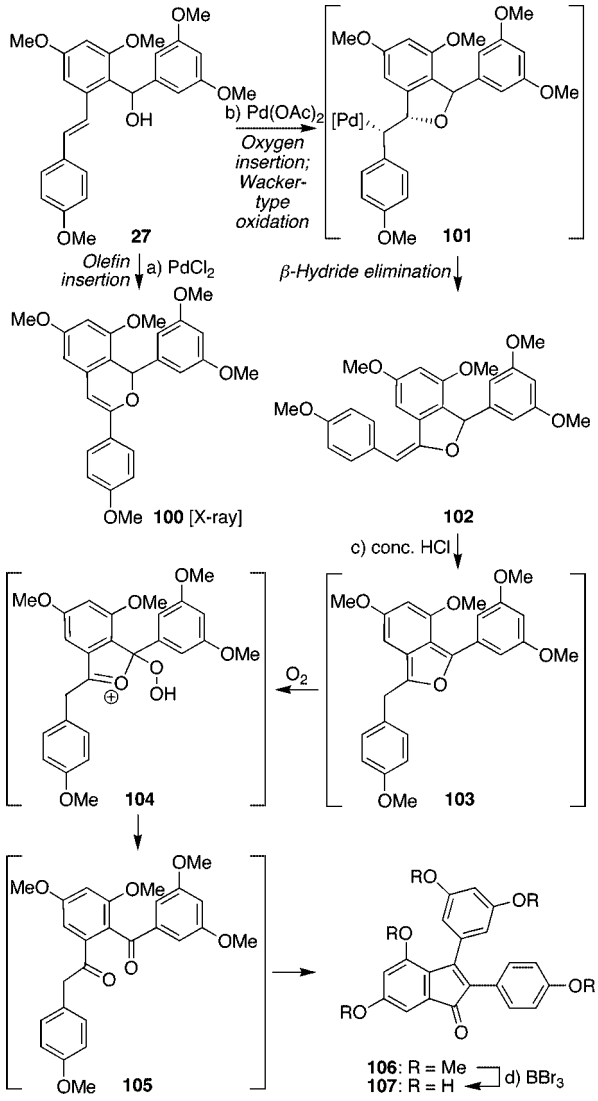
(49) For the genesis of the latter set of palladium-based cyclization conditions, see: Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318–2323.

(50) For a precedent for such trapping in a related system, see: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H.-S. *J. Am. Chem. Soc.* **2002**, *124*, 2190–2201, and references therein.

(51) Compound **105** has been prepared separately and converted to **106** under the same reaction conditions as circumstantial support for the final ring closure leading to the observed product. See the Supporting Information for full details.

(52) This reaction sequence works with other members of our key intermediate family as well. See the Supporting Information for full details.

Scheme 15. Creation of a Natural Product-Like Structure (**107**) through Metal and Acid-Initiated Cascade Sequences[a]

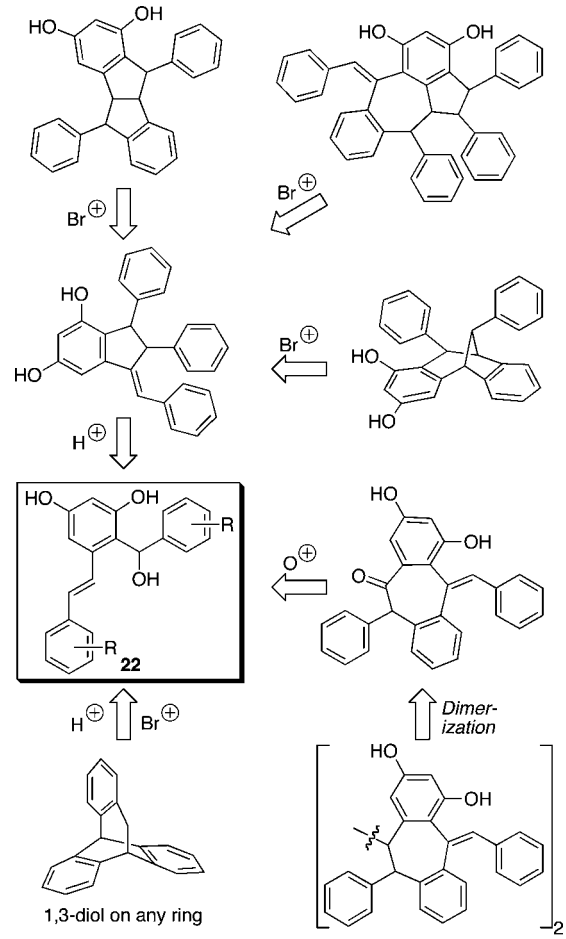


[a] Reagents and conditions: (a) $PdCl_2$(benzonitrile)$_2$ (0.2 equiv), $CuCl_2$ (0.2 equiv), O_2 atm, DMF, 50 °C, 3 h, 75% of **100**, 22% of **102**; (b) $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (0.2 equiv), O_2 atm, *i*-PrOH, 60 °C, 5 h, 87% of **102**; (c) conc. HCl (10 equiv), *i*-PrOH, 25 °C, 16 h, 90%; (d) BBr_3 (1.0 M in CH_2Cl_2, 12 equiv), CH_2Cl_2, −78 → 25 °C, 12 h, 88%.

3. Conclusion

Although past biomimetic studies with resveratrol have revealed the ability to harness reaction pathways that can concurrently generate arrays of oligomeric natural products, this work illustrates that it is possible to selectively synthesize those same adducts. The key for achieving that control proved to be the identification of a unique precursor, one distinct from the building block postulated in standard biosynthetic schemes, in combination with orchestrated cascade sequences initiated by relatively simple reagents (such as bromine, proton, and dioxirane). Based on the wealth of architectures and natural products that have been obtained, most in fewer than 10 steps from commercial materials and on relatively large scales, generalized structure **22** may constitute a privileged intermediate for the preparation of the resveratrol class. As shown in Scheme 16, our long-term goal is to develop pathways of such robustness that every isolate within the resveratrol class can be traced

Scheme 16. Toward a Unified Retrosynthetic Analysis for the Resveratrol Class of Natural Products



retrosynthetically to **22**. The progress denoted here lays some of those foundations, and work is continuing to establish the additional connections outlined. We are also attempting to determine if other diverse, oligomeric natural product families can be controllably accessed by way of structurally unique, common intermediates.

Acknowledgment. This paper is dedicated to Prof. E. J. Corey on the occasion of his 80th birthday. We thank Drs. J. Decatur and Y. Itagaki for NMR spectroscopic and mass spectrometric assistance, respectively, and Dr. Christos Stathakis, Mr. Trevor Sherwood, Mr. Michael Kissner, and Ms. Violeta Rodríguez Ruiz for the preparation of some of our synthetic intermediates. We also thank the National Science Foundation (CHE-0619638) for the acquisition of an X-ray diffractometer and Prof. Gerard Parkin and members of his group for obtaining our crystal structures. Financial support for this work was provided by Columbia University, the National Science Foundation (predoctoral fellowship to S.P.B.), Amgen, and Eli Lilly. S.A.S. is a Camille and Henry Dreyfus New Faculty Awardee.

Supporting Information Available: Experimental procedures, compound characterization, copies of spectral data, X-ray crystallographic structures, and complete refs 4f and 4g. This material is available free of charge via the Internet at http://pubs.acs.org.

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