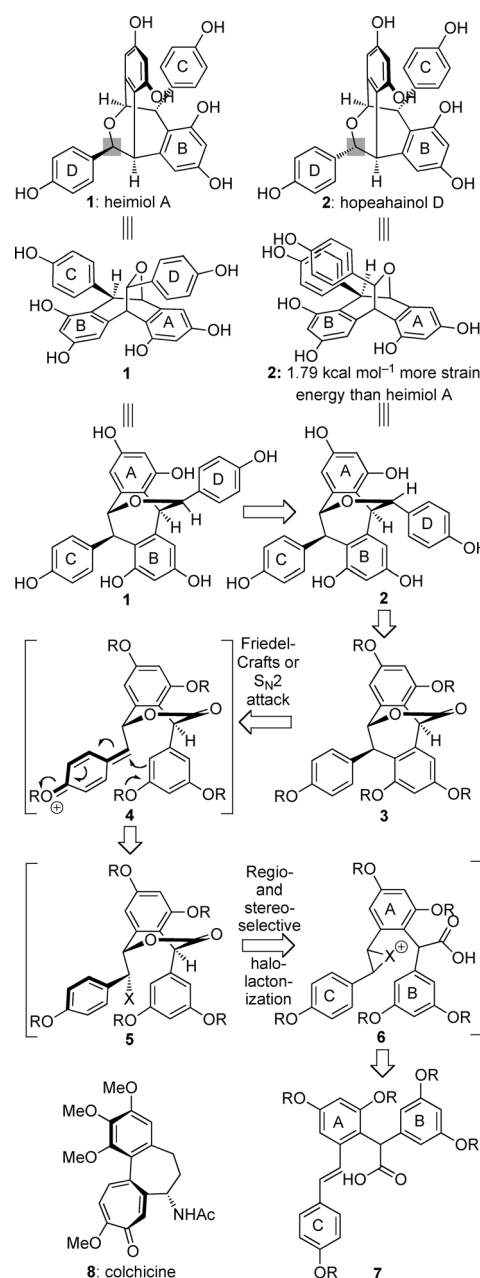


Total Syntheses of Heimiol A, Hopeahainol D, and Constrained Analogues**

Scott A. Snyder,* Nathan E. Wright, Jason J. Pflueger, and Steven P. Breazzano

Although synthetic chemists have become quite adept at preparing individual ring systems of diverse size and complexity, there remains a pressing need for more powerful tools and strategies to address their concurrent formation, particularly in contexts where they are fused together into compact and constrained frameworks. In 2001, Weber and co-workers reported their isolation and characterization of an architectural challenge in need of such solutions in the form of the oxidized resveratrol dimer **1** (Scheme 1).^[1] This compound, which they named heimiol A, after its plant source (*Neobalanacarpus heimii*), merges one six-membered and two seven-membered ring systems into a [3.2.2] bicycle that displays four chiral centers, and it has since been shown to possess some antioxidant activity.^[2] Eight years later, a team led by Tan reisolated the same material (**1**) from a different plant along with a much smaller amount of a compound they assigned as hopeahainol D (**2**);^[3] its structure differs from **1** only in its stereochemistry about the highlighted position (Scheme 1). Upon initial inspection, and as drawn in the first orientation shown in Scheme 1 that is typical of the isolation papers, the synthetic challenge of these molecules is hidden, much in the way that the two fused seven-membered rings and lone chiral center of colchicine (**8**)^[4] look deceptively simple. However, if one considers the two additional drawings that are provided for these targets, then a better appreciation for their true three-dimensional shape and overall synthetic challenge can be gleaned. Indeed, the third set of these renderings indicates that both materials provide the difficult task of arraying two aromatic rings and a bridging oxygen atom on the same side of a conserved seven-membered carbocyclic core, while the second set shows that the lone stereochemical change impacting the orientation of ring D in **1** and **2** imparts a significant thermodynamic strain penalty to



Scheme 1. Drawing from the lessons of colchicine (**8**) and the challenges of seven-membered ring synthesis: a retrosynthetic analysis of heimiol A (**1**) and hopeahainol D (**2**) empowered by thermodynamic strain energies and a novel halonium-induced cascade.

hopeahainol D (calculated as $1.79 \text{ kcal mol}^{-1}$).^[5] Herein, we describe a synthetic approach empowered by a novel electrophilic iodine source which forged the entire bicyclic core in a

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single, stereocontrolled operation from an acyclic precursor. We then highlight how both ($\pm$)-**1** and ($\pm$)-**2** can be synthesized from the same advanced intermediate by taking into account that final strain energy difference, and show how the developed strategy can also afford unique [3.2.1] dimeric resveratrol cores possessing even higher strain energy differences than **1** and **2**.

Our retrosynthetic analysis of heimiol A (**1**) and hopeahainol D (**2**) is shown in the bottom half of Scheme 1. Given the indicated strain difference between these natural products,^[6] we anticipated that **2** might be a biosynthetic precursor to **1**, an idea that had not been advanced by the original isolation team, but one that is hinted at circumstantially based on the relative amounts of **1** and **2** obtained. We then excised ring D from **2**, projecting that it could be added with stereocontrol through an appropriate, substrate-controlled strategy onto protected lactone **3**. Though specific phenol protecting groups have not been defined for this new compound, particularly mild excision conditions were anticipated to be necessary given the fragile positioning of the ether linkage within the final targets (**1** and **2**) relative to one of their phenols (see below). Overall, while these initial operations appear simple, they have set the stage for the key retrosynthetic disconnection of these targets, one which we hoped could readily address the challenge of forming their *cis*-disposed cores.

Indeed, as shown, we anticipated that the entire [3.2.2] bicycle of **3** could arise from the acyclic precursor **7** in a single, stereocontrolled step through a halolactonization/Friedel–Crafts cascade that would sequentially forge two new bonds and three rings without leaving any trace of the electrophilic halogen activator. The initial stereochemical requirements of the opening operations of this process (**7**→**5**), coupled with a likely kinetic preference for the quinone methide of **4** to exist on the β face as shown to minimize strain, was expected to produce **3** with the desired, and necessary relative stereochemistry following the final cyclization. Of course, this plan was fully dependent on the ability of some electrophilic halogen to chemoselectively engage the lone double bond of **7** in advance of and/or in lieu of potentially deleterious electrophilic aromatic substitution reactions with its electron-rich systems, substitutions which could prevent the Friedel–Crafts reaction. However, if the requisite chemoselectivity could be achieved, then the approach would afford an expeditious solution for a challenging ring synthesis. Moreover, it would solve a stereochemical problem that our past work towards resveratrol oligomers had not achieved.^[7] Indeed, as shown in Scheme 2A, we could readily fashion seven-membered rings with a *trans* disposition of groups (such as **10** and **11**) through electrophile-induced cascades from alcohol **9**, materials pertinent to vast majority of the family such as vaticanol A (**12**).^[8] However, we have been unable to convert these materials into anything resembling the much more unique, all-*cis* disposed frameworks of heimiol A (**1**) and hopeahainol D (**2**).

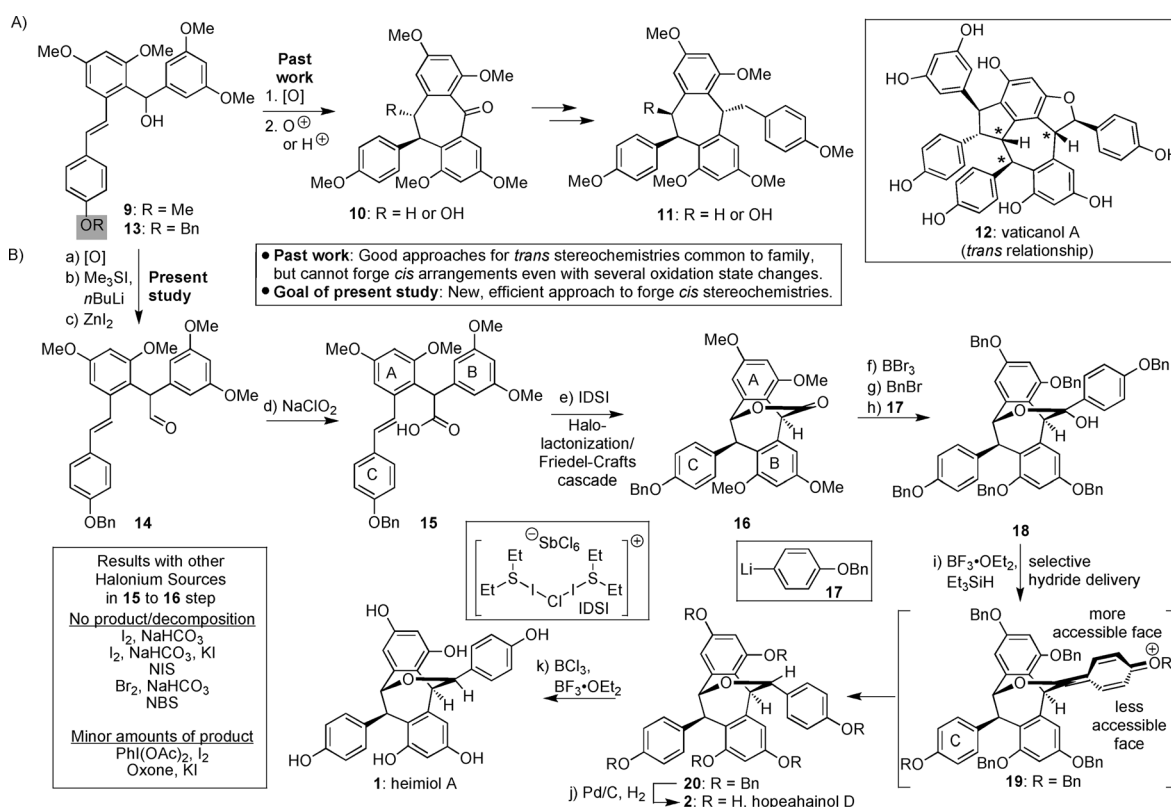
Fortunately, we were able to reduce the general plan outlined in Scheme 1 to practice, though there were several subtle, and unexpected, elements of chemical reactivity en route. Initial operations (Scheme 2B) converted triaryl alco-

hol **13** into carboxylic acid **15** through a sequence employing an oxidation, a Corey–Chaykovski reaction^{[9]/ZnI₂ rearrangement^[10] to generate aldehyde **14**, and a terminating Pinnick oxidation.^[11] Critical to the yield of this sequence (68% overall) was benzyl protection of the highlighted phenol as its methyl ether analogue (i.e. **9**), which led to only 30–40% yield overall. Given the observed instability of the intermediate epoxide, we attribute this yield difference to its more rapid decomposition when a methyl ether was present as a result of its slightly greater electron-donating capability through the conjugated π system.}

With these operations setting the stage for the key transformation of the sequence, **15** was then exposed to a number of standard, stoichiometric halogen sources in a variety of solvents in hopes of forging **16** in a single operation (see inset box for selected reagents). Unfortunately, none afforded any evidence of the cyclized material irrespective of the rate and/or order of addition. However, we found that if electrophilic iodine in the form of iodine/hypoiodide was generated in situ either by reacting PhI(OAc)₂ with I₂ or under heterogeneous conditions with Oxone and KI,^[12] the desired [3.2.2] bicyclic system of **16** could be formed in modest amounts (ca. 20% in the latter case) alongside several uncharacterized side products that were suggestive of over- and/or nonselective halogenation. While this finding was encouraging, a superior material throughput was needed for effective prosecution of the sequence.

Pleasingly, we discovered that when we used our recently developed unique iodonium source, IDSI,^[13] in MeCN at 25°C, **16** could be produced much more smoothly and in higher yield with just a total of 2 minutes for the reaction time. This reagent was the only stoichiometric, direct halogen source that gave product in any yield, suggesting its potential for other unique iodonium-induced cyclizations. Intriguingly, its brominated counterpart (BDSB) also afforded cyclized material, but effected bromination of the aromatic rings also (presumably following cyclization), thus indicating that IDSI has unique chemoselectivity for this event. With this key step accomplished, the methyl ethers were removed by exposure to BBr₃, thus affording an overall yield of 36% for these two critical operations.

Reprotection with benzyl ethers (to provide a protecting group that could later be cleaved under mild conditions) then provided a lactone to test the stereocontrolled incorporation of the final aryl ring in the form of reagent **17**. We hoped that the bulk of the C ring would afford diastereocontrol in that addition and, in line with our expectations, intermediate **18** was formed smoothly as a single stereoisomer. Much more importantly, the same selectivity was subsequently observed with a much smaller nucleophile (Et₃SiH) after the tertiary alcohol was ionized with BF₃·OEt₂, thereby forming protected hopeahainol D (**20**) cleanly in 57% overall yield. Hydrogenation over catalytic Pd/C then excised the benzyl ethers to afford a concise, and fully stereocontrolled, total synthesis of hopeahainol D (**2**) in just 10 operations from key the starting material **13**. Finally, as a test of our proposed biogenetic theory, exposure of hopeahainol D (**2**) to a mixture of BF₃·OEt₂ and BCl₃ in MeOH at 25°C resulted in complete and quantitative epimerization of the desired chiral center to



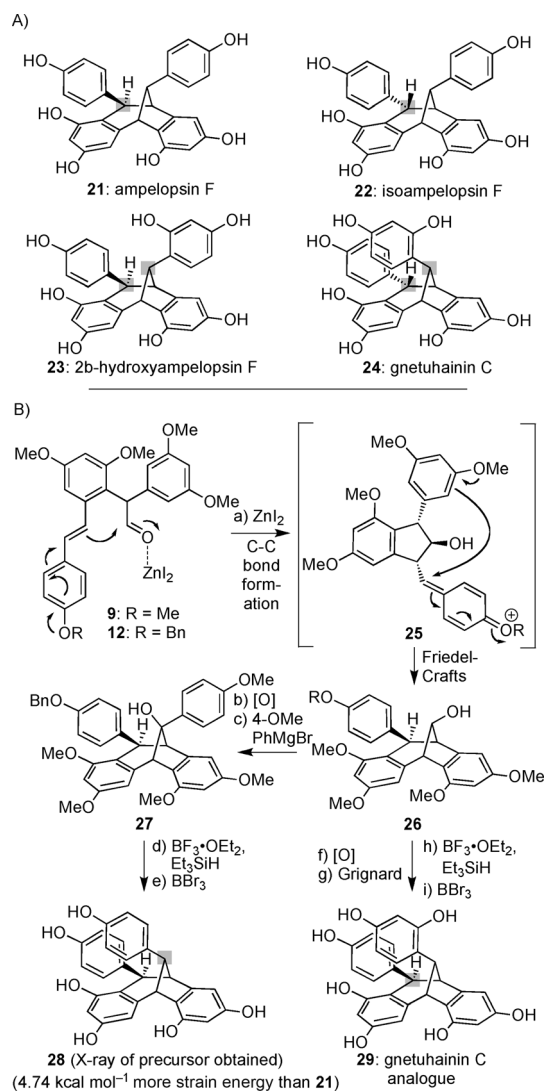
Scheme 2. A) The challenges of heimiol A (**1**) and hopeahainol D (**2**) in context: forming *cis*-disposed systems where past efforts have given *trans*-materials. B) Total synthesis of **1** and **2** through an IDSI-empowered cascade: a) Dess–Martin periodinane (1.2 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2 , 25 °C, 2 h, 99%; b) Me_3SiI (10 equiv), $nBuLi$ (9.0 equiv), THF, 0 °C, 1 h; c) ZnI_2 (1.0 equiv), benzene, 25 °C, 5 min, 80% over 2 steps; d) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (8.0 equiv), resorcinol (10 equiv), THF/*t*BuOH (1:1), 25 °C, 12 h, 85%; e) IDSI (2.0 equiv), MeCN, 25 °C, 2 min; f) BBr_3 (1.0 M in CH_2Cl_2 , 25 equiv), CH_2Cl_2 , 25 °C, 24 h, 36% over 2 steps; g) $BnBr$ (30 equiv), K_2CO_3 (30 equiv), nBu_4NI (2.0 equiv), acetone, reflux, 89%; h) 4-benzyloxybromobenzene (50 equiv), $nBuLi$ (50 equiv), THF, –78 °C, 20 min; i) $BF_3 \cdot OEt_2$ (10 equiv), Et_3SiH (50 equiv), CH_2Cl_2 , –78 → 25 °C, 10 min, 57% over 2 steps; j) H_2 (1 atm), Pd/C (10%, 5.0 equiv), EtOAc/MeOH (1:1), 25 °C, 12 h, 79%; k) $BF_3 \cdot OEt_2$ (8.0 equiv), BCl_3 (1.0 M in CH_2Cl_2 , 2.0 equiv), MeOH, 25 °C, 2.5 h, 99%. Bn = benzyl, IDSI = $(Et_2Si)_2Cl-SbCl_6$, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide, THF = tetrahydrofuran.

that of heimiol A (**1**).^[14] Such a conversion supports the hypothesis that **2** may, in fact, be a biogenetic precursor to **1**.^[15] And, as confirmation of the necessity of the earlier protecting group exchange (part of the **16** into **18** conversion), we discovered that permethylated heimiol A could not be successfully deprotected under standard BBr_3 conditions; thus, it was fortunate that the lactone scaffold (i.e. **16**) was robust enough to undergo such a methyl ether cleavage.^[16]

Finally, outside of these two natural products, there is one other set of resveratrol-based dimers that are diastereomeric about a single position and that have groups arrayed *cis* on a similar seven-membered ring; several of these compounds are shown in Scheme 3 (**21–24**),^[17] but only ampelopsin F (**21**) has been synthesized to date.^[7,18] Pleasingly, application of the lessons learned from the syntheses of **1** and **2** has afforded the means to access such skeletons as well, thus leading to the preparation of two highly strained dimeric resveratrol analogues. Two operations proved key to this sequence. The first was a C–C bond construction cascade which forged the parent [3.2.1] framework from aldehyde **15** using similar reaction conditions (ZnI_2) as the case previously discussed (i.e. **13** → **14**, Scheme 2), differing only in reaction time. We believe that longer exposure enables an attack of the nucleophilic alkene

onto the Lewis acid activated carbonyl to give **25**; this intermediate then undergoes a second cyclization to generate the observed [3.2.1] bicycle, a structure reminiscent of ampelopsin F (**31**), which is missing only the apical aromatic ring. In the second key operation, the developed sequence used to incorporate the final ring of the hopeahainol D architecture (**16** → **2**) was applied with two different Grignard reagents and the ketone derived from **26**. This process afforded smooth syntheses of both **28** and **29**, structures containing the uniquely positioned apical ring of gnetuhainin C (**24**) in a highly strained format. To give a sense of that strain, **28** is calculated to have 4.74 kcal mol^{–1} more strain energy than ampelopsin F (**21**).^[5] We believe that both **28** and **29** are structures that could reasonably be observed in nature given: 1) the general absence of diastereocontrol with the known resveratrol-derived [3.2.1] cores and 2) their overall stability despite such strain. For example, under no conditions could we epimerize the other ring-based stereocenter of **29** through a retro Friedel–Crafts/Friedel–Crafts center to generate gnetuhainin C (**24**).^[19]

In conclusion, we have successfully accomplished the first total syntheses of the unique resveratrol-derived dimers heimiol A (**1**) and hopeahainol D (**2**) in a racemic, but



Scheme 3. A) Resveratrol dimers also diastereomeric about one or two centers. B) Application of the developed cascade-based approach to forge other strained, *cis*-disposed resveratrol dimers with a different bicyclic framework: a) ZnI_2 (1.0 equiv), benzene, 25 °C, 3 h, 63 % from **16**; b) $(\text{COCl})_2$ (5.0 equiv), DMSO (10 equiv), CH_2Cl_2 , $-30 \rightarrow 25$ °C, 1 h, then Et_3N (15 equiv), 80%; c) 4-MeOC₆H₄MgBr (1.0 M in THF, 10 equiv), THF, 25 °C, 20 min, 83%; d) $\text{BF}_3 \cdot \text{OEt}_2$ (10 equiv), Et_3SiH (30 equiv), CH_2Cl_2 , $-78 \rightarrow 25$ °C, 10 min, 99%; e) BBr_3 (1.0 M in CH_2Cl_2 , 30 equiv), CH_2Cl_2 , 25 °C, 24 h, 74%; f) $(\text{COCl})_2$ (5.0 equiv), DMSO (10 equiv), CH_2Cl_2 , $-30 \rightarrow 25$ °C, 1 h, then Et_3N (15 equiv), 86%; g) 2,4-(MeO)₂C₆H₃MgBr (0.5 M in THF, 5.0 equiv), THF, 25 °C, 20 min, 99%; h) $\text{BF}_3 \cdot \text{OEt}_2$ (10 equiv), Et_3SiH (30 equiv), CH_2Cl_2 , $-78 \rightarrow 25$ °C, 10 min, 84%; i) BBr_3 (1.0 M in CH_2Cl_2 , 30 equiv), CH_2Cl_2 , 40 °C, 24 h, 82%.

concise, stereoselective, and efficient manner. In the process, we established a potential biogenetic relationship between these materials. Critical elements of the developed sequence include an iodolactonization/intramolecular Friedel–Crafts cascade reaction empowered by the unique iodonium source IDSI which constructed the entire [3.2.2] bicycle with the requisite all-*syn* stereochemistry from an acyclic precursor. Also required were orchestrated and stereocontrolled elaborations to create the strained framework of hopeahainol D (**2**). In addition, the controlled diversion of intermediates en-

route coupled with elements of the overarching strategy has afforded access to other complex architectures possessing high strain analogous to the [3.2.1] cores of ampelopsin F and gnetuhainin C. More globally, this work highlights the symbiotic relationship between efficiency-minded synthetic designs and the need for reagents of appropriate power and selectivity to reduce those plans to practice,^[20] with IDSI and its sister halogen reagents being tools which we believe have much potential.

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