Natural Product Synthesis

DOI: 10.1002/ange.201311299

9-Membered Carbocycle Formation: Development of Distinct Friedel–Crafts Cyclizations and Application to a Scalable Total Synthesis of (±)-Caraphenol A**

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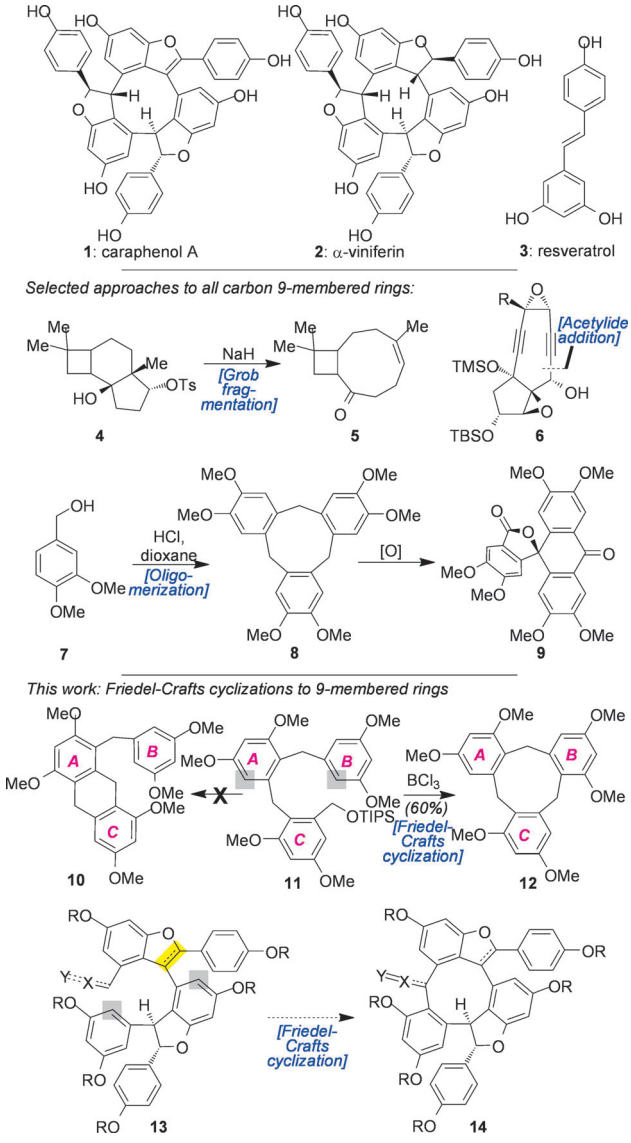
Abstract: *Explorations into a series of different approaches for 9-membered carbocycle formation have afforded the first reported example of a 9-exo-dig ring closure via a Au^{III}-promoted reaction between an alkyne and an aryl ring as well as several additional, unique Friedel–Crafts-type cyclizations. Analyses of the factors leading to the success of these transformations are provided, with the application of one of the developed 9-membered ring closures affording an efficient and scalable synthesis of the bioactive resveratrol trimer caraphenol A. That synthesis proceeded with an average yield of 89% per step (7.8% overall yield) and has provided access to more than 600 mg of the target molecule.*

While forming any medium-sized ring requires an approach capable of overcoming significant entropic and enthalpic penalties,[1] the challenge in meeting that requirement is often more pronounced in systems composed only of carbon atoms, such as the 9-membered rings of caraphenol A (**1**)[2] and α-viniferin (**2**),[3] two oligomeric forms of the natural product resveratrol (**3**)[4,5] which are bioactive (including acetylcholinesterase inhibition, anti-inflammatory properties, and potential value as probes for elucidating key pathways in Alzheimer's disease and drug resistance in tumors) (Scheme 1).[6] Indeed, without the more obvious and established array of productive cyclization strategies afforded by heteroatoms, only a handful of approaches have proven capable of accessing fully carbocyclic variants. For 9-membered rings, that includes Grob fragmentations (such as **4**→**5**),[7] highly context specific C–C bond constructions such as the acetylide addition leading to enediyne **6**,[8] and ring-closing olefin metathesis (not shown).[9] Given this landscape, as well as the unique and sp^2-rich patterning of **1** and **2** (and 11 other related molecules)[10] that effectively precludes the application of these three established strategies, we sought to identify additional approaches capable of forging strained, 9-membered carbocycles. Herein, we show that a variety of Friedel–



Scheme 1. Strategies and tactics for the synthesis of 9-membered rings pertinent to natural products such as caraphenol A (**1**) and α-viniferin (**2**).

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[**] We thank Dr. John Decatur and Dr. Yasuhiro Itagaki for NMR spectroscopic and mass spectrometric assistance, Alison Xiang Gao for the synthesis of some intermediates, and Marian Deuker for early studies. We also thank NSF (CHE-0619638) for an X-ray diffractometer and Prof. Gerard Parkin, Dr. Aaron Sattler, and Dr. Wesley Sattler for performing crystallographic analyses that aided our design. Financial support was provided by the National Institutes of Health (R01-GM84994), Bristol-Myers Squibb, Eli Lilly, Amgen, the NSF (Predoctoral Fellowship to N.E.W.), and the Research Corporation for Science Advancement (Cottrell Scholar Award to S.A.S.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201311299.

Crafts-type reactions promoted by either Au^{III} or Brønsted acids are competent in this regard with functionally rich substrates. In addition to providing what we believe is the first example of a 9-*exo*-dig ring closure, late-stage application of one of the developed approaches has enabled the completion of an efficient and highly scalable total synthesis of caraphenol A (**1**).

Our interest in exploring Friedel–Crafts chemistry to forge 9-membered rings derived, in part, from the published conversion of **7** into **8**.[11] This transformation constitutes one of only three examples (both involving benzylic alcohols)[12] we have identified where this ring size has resulted from such a reaction without the possible intervention of a heteroatom within the substrate; those two additional cases afforded a 9-membered ring in 2.5% yield[13a] and bicyclic alkaloids in a more efficient process.[13b–d] That rarity within constrained systems may not be surprising in light of the potential reversibility and rearrangement potential of such processes.

Although the specific application of this transformation to the synthesis of caraphenol A (**1**) or α-viniferin (**2**) is precluded by the inability to directly convert 3,5-dimethoxybenzyl alcohol into the same type of framework as well as the facile rearrangement of frameworks such as **8** into smaller carbocycles like **9** upon oxidation,[14] it did lead us to synthesize model compound **11** over 6 steps (see Supporting Information) as an initial model for cyclization. Gratifyingly, we were able to obtain 9-membered ring **12** in 60% yield following exposure of **11** to BCl_3 in CH_2Cl_2; an additional 19% was recovered as the benzyl chloride. Worth noting is that despite the possibility for both 6- and 9-membered ring formation via the respective attack of the highlighted carbons in rings A and B onto the benzylic cation derived from ionization of the benzylic alcohol attached to ring C, no 6-membered ring formation was observed (i.e. **11**→**10**).[15,16]

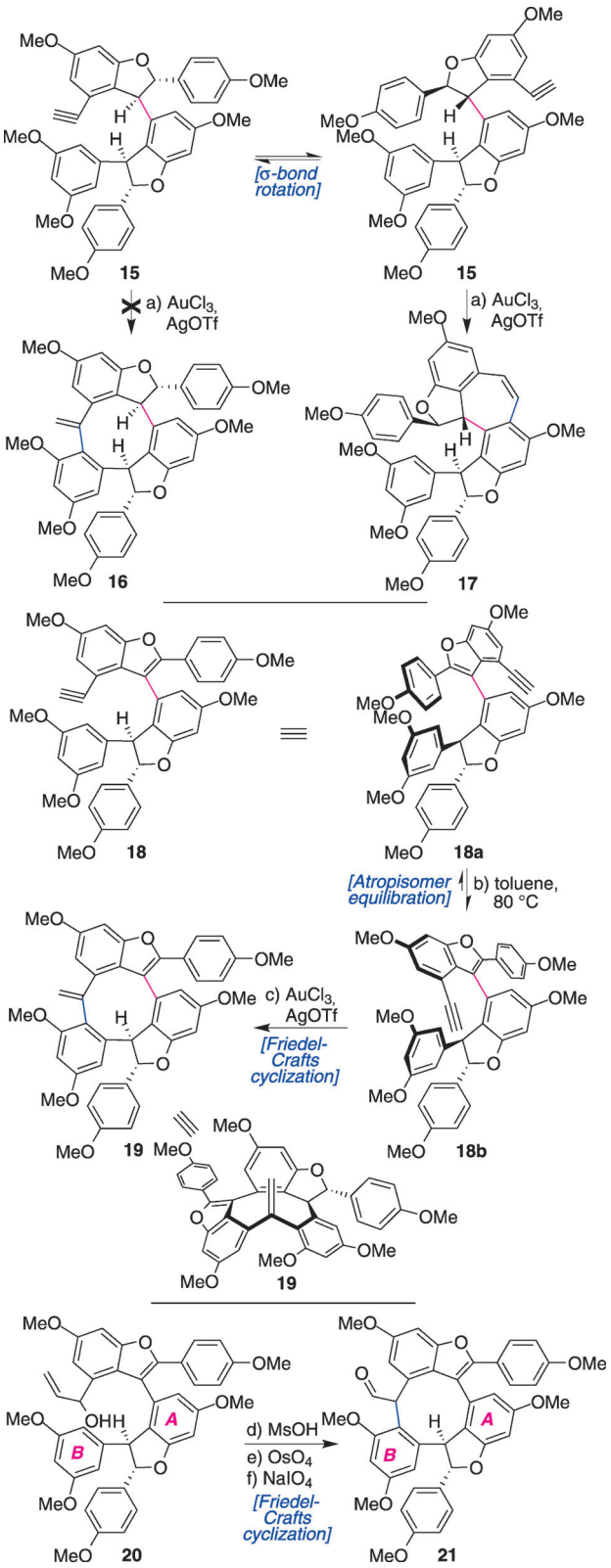
With this result in hand, we elected to probe variants of such Friedel–Crafts transformations via different electrophilic activation (i.e. non-primary benzylic cations) with more highly functionalized materials. That approach is shown here in generalized format as precursor **13**, where the goal was to effect cyclizations that could incorporate additional functionality on the 9-membered ring to access **1** and/or **2** based on the oxidation state of the bond highlighted in yellow. Unclear was whether the presence of dihydrofuran or furan-ring systems on the core test framework would aid or detract from the ease of cyclization given the restrictions on rotational freedom that their presence would impart.

Our first substrate for evaluation was alkyne **15** (see Supporting Information for preparation), a material that we hoped to convert into **16** through a 9-*exo*-dig closure (Scheme 2). When it was exposed to a variety of cationic Au complexes, only the combination of $AuCl_3$ and AgOTf[17] activated the alkyne for nucleophilic attack. In this case, however, it exclusively afforded 7-*endo*-dig cyclization product **17** (typically in >90% yield). Fortunately, conformational analysis using simple molecular models suggested a possible solution to this issue of positional control. Namely, if one of the dihydrobenzofuran rings systems within **15** was replaced with its fully oxidized benzofuran variant, the reaction trajectory leading to the 7-membered ring would incur significantly more strain, while the strain accompanying 9-membered ring formation appeared to be relatively unchanged. As a result, perhaps the balance would be shifted to larger ring synthesis.

Pleasingly, that inference from models proved true as the exposure of substrate **18** to the same conditions ($AuCl_3$/AgOTf in 1,2-chloroethane at 25°C for 2 h) afforded 9-*exo*-dig cyclization product **19** in >90% yield.[18] We believe this reaction constitutes the first example of such a cyclization mode and that its success is indeed the result of high conformational control. In support of that assertion, **18** exists as a mixture of atropisomers about the bond highlighted at 25°C and only atropisomer **18b** underwent productive cyclization; **18a** was recovered unchanged (noting that it can be equilibrated to a mixture favoring **18b** in a ca. 2.5:1 ratio through separate heating in toluene at 80°C).[19] Thus, it would appear that the productive atropisomer forces the alkyne into close proximity with its nucleophilic partner while the other (**18a**) prevents this pair from effectively interacting at all in either a 7-*endo*-dig or 9-*exo*-dig cyclization.

Despite this success, compound **19** proved to be a dead-end in terms of a potential total synthesis of either **1** or **2** in that its newly generated exocyclic olefin could not be manipulated further using a variety of standard approaches. Specifically, exposure to stoichiometric OsO_4 in the presence of several activators afforded only recovered starting material, while ozonolysis and hydroboration led to decomposition. The additional, more three-dimensional, representation of **19** within Scheme 2 may explain these outcomes, as it highlights that the exocyclic alkene is blocked from the α-face by the benzene ring of the seemingly remote dihydrobenzofuran ring system, while the neighboring methoxy substituent blocks the β-approach. As such, a final cyclization attempt was made with substrate **20**, hoping that its allylic alcohol could afford a 9-membered ring through acid-catalyzed generation of an allylic cation and subsequent Friedel–Crafts reaction. This transformation would concurrently generate a pendant vinyl group removed from the above described steric crowding to hopefully allow for further manipulation. The price for that new handle, however, was the addition of several competitive cyclization pathways, in that the reactive cation could lead to both 6- and 8-membered carbocycles if ring A attacked, while both 9- and 11-membered carbocycles could result from ring B attack. In the event, exposure of **20** to an excess of MsOH (50 equiv) in THF at 25°C[20] afforded only the 9-membered carbocycle as a single diastereomer about the new stereocenter and in 80% yield. Equally pleasing, the vinyl group within that material could be converted to the exocyclic aldehyde of **21** through oxidative cleavage.

With model studies complete, we then set out to utilize appropriately protected intermediates[21] to attempt a total synthesis of caraphenol A (**1**). Starting from ketone **22** (Scheme 3, prepared in 3 steps from commercially-available 3,5-dibenzyloxybenzyl alcohol, see Supporting Information), the dihydrofuran ring system of the target was first obtained via a four-pot, 7-operation process involving Corey–Chaykovsky epoxidation,[22] ZnI_2-mediated Meinwald rearrangement,[23] and Grignard addition to afford triaryl **24**, followed

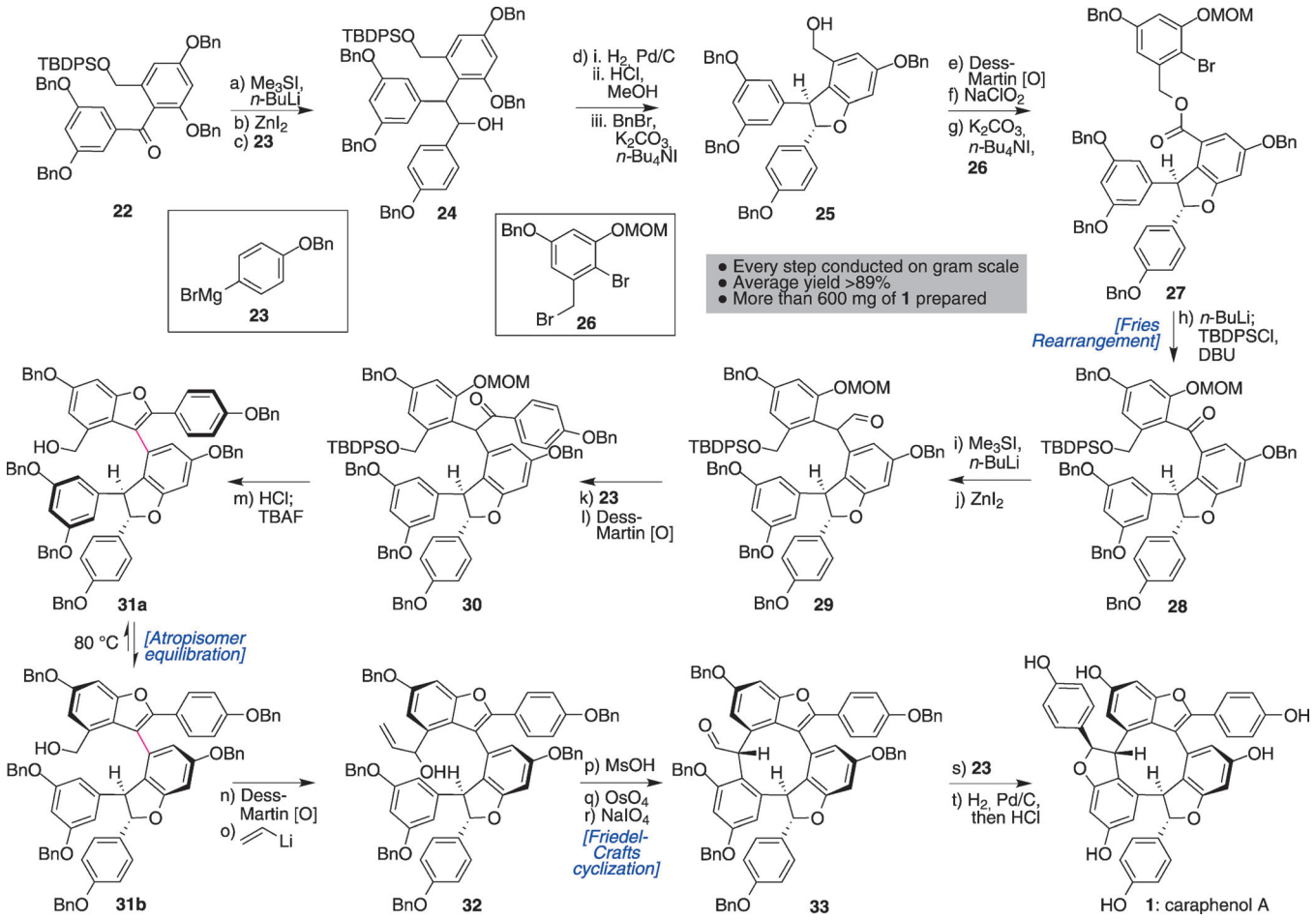


Scheme 2. Explorations into key 9-membered ring formation and further elaboration: a) $AuCl_3$ (0.1 equiv), AgOTf (0.3 equiv), $ClCH_2CH_2Cl$, 25 °C, 2 h, >90%; b) toluene, 80 °C, 24 h, 99%; c) $AuCl_3$ (0.1 equiv), AgOTf (0.3 equiv), $ClCH_2CH_2Cl$, 25 °C, 2 h, >90%; a) MsOH (50 equiv), THF, 25 °C, 3 h, 80%; b) OsO_4 (0.4 equiv), NMO (10 equiv), acetone/H_2O (5/1), 25 °C, 12 h; c) $NaIO_4/SiO_2$ (3 equiv), CH_2Cl_2, 25 °C, 20 min, 75% over 2 steps. Tf = triflate, Ms = methanesulfonate, THF = tetrahydrofuran, NMO = *N*-morpholine *N*-oxide.

by benzyl ether cleavage, acid-catalyzed dihydrofuran formation and silyl deprotection, and phenol reprotection. These operations collectively provided **25** in 80% yield from **24** as a 10:1 mixure of separable, *trans*- and *cis*-disposed dihydrofuran diastereomers. With an eye now towards appending the needed benzofuran ring onto this material, the free alcohol within **25** was oxidized to a carboxylic acid and esterified to generate **27**. Subsequent treatment with *n*BuLi in THF at −94 °C with warming to 25 °C over the course of 30 min, followed by treatment with TBDPSCl, effected an anionic Fries rearrangement[24] and in situ protection of the resulting alcohol to afford ketone **28** in 80% yield. Then, use of the same three-step homologation/Grignard sequence that opened the synthesis, followed by oxidation, provided ketone **30** as a 1:1 mixture of diastereomers about the undefined center.

With all the atoms of the core now in place, the stage was set to attempt benzofuran formation. Pleasingly, treatment with HCl in a 1:1 mixture of THF and MeOH at 40 °C for 12 h effected MOM ether cleavage and subsequent cyclodehydration to afford the desired aromatic system; solvent removal, and in situ exposure to TBAF then completed the one-pot synthesis of alcohol **31**. This material was obtained as a mixture of atropisomers that could be equilibrated to a separable 2.8:1 mixture in favor of **31b**, the isomer which in model systems was capable of productive 9-membered ring formation under Friedel–Crafts conditions; recycling of **31a** through additional equilibrations and separation enriched material supplies of **31b**. With this key material (**31b**) in hand, it was converted into the allylic alcohol cyclization precursor **32** through Dess–Martin oxidation and vinyllithium addition.[25] Pleasingly, conditions developed in the model substrate worked effectively here in cyclizing **32** to the desired 9-membered ring in 73% yield, needing only some additional heat (50 °C) to initiate and complete the desired event. Subsequent oxidative cleavage to **33**, addition of the final aromatic ring, benzyl ether cleavage, and acid-catalyzed closure of the final dihydrofuran afforded (±)-caraphenol A (**1**). This material was identical in all respects (^{1}H NMR, ^{13}C NMR, HRMS) to that obtained from natural sources.[2] Overall, the route to **1** required 23 steps from commercial materials and, while highly linear, it was extremely efficient. Indeed, the average yield per step was 89.5% (accounting for an overall yield of 7.8%), each transformation was performed on gram scale, and more than 600 mg of the final target was synthesized overall. To put that amount of material in perspective, it not only reflects the largest amount of any resveratrol trimer yet synthesized,[5c] but also affords a favorable alternative to natural isolation where 60 kg of dried plant material afforded 60 mg of **1** following extensive purification.[2]

In conclusion, a number of substrates and cyclization conditions were identified that could overcome an array of entropic and enthalpic penalties to form strained, 9-membered carbocycles successfully from acyclic precursors. These processes are arguably the most complex examples of medium-sized ring formations utilizing Friedel–Crafts-type processes and are remarkable given that a number of additional reaction pathways could also have occurred to



Scheme 3. Total synthesis of caraphenol A (**1**): a) Me_3SI (6 equiv), *n*BuLi (1.6 M in hexanes, 5 equiv), THF, 0 °C, 1 h; b) ZnI_2 (1 equiv), benzene, 25 °C, 15 min; c) **23** (1.0 M in THF, 1.1 equiv), THF, 25 °C, 10 min, 74% over 3 steps; d) H_2 (1 atm), 10% Pd/C (0.5 equiv Pd), $NaHCO_3$ (0.2 equiv), EtOAc/MeOH (1/1), 25 °C, 6 h, filter, concentrate; then HCl (1.25 M in MeOH, 4 equiv), MeOH, 25 °C, 6 h, concentrate; then BnBr (8 equiv), K_2CO_3 (12 equiv), nBu_4NI (0.5 equiv), acetone, 25 °C, 12 h, 80% (10:1 d.r.); e) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 25 °C, 30 min; f) $NaClO_2$ (3 equiv), NaH_2PO_4 (8 equiv), 2-methyl-2-butene (20 equiv), THF/*t*BuOH (1/1), 25 °C, 12 h; g) 26 (1.1 equiv), K_2CO_3 (5 equiv), nBu_4NI (0.1 equiv), acetone, reflux, 2 h, 81% over 3 steps; h) *n*BuLi (1.6 M in hexanes, 1.5 equiv), THF, −94 to 25 °C, 30 min, then TBDPSCl (4 equiv), DBU (1 equiv), 50 °C, 12 h, 80%; i) Me_3SI (10 equiv), *n*BuLi (1.6 M in hexanes, 8 equiv), THF, 0 °C, 1 h; j) ZnI_2 (3 equiv), benzene, 25 °C, 30 min; k) 23 (1.0 M in THF, 1.1 equiv), THF, 25 °C, 10 min, 74%; l) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 25 °C, 30 min, 82% over 4 steps; m) HCl (1.25 M in MeOH, 20 equiv), THF/MeOH (1/1), 40 °C, 12 h, concentrate; then TBAF (1.0 M in THF, 1.2 equiv), THF, 50 °C, 12 h, 88%; n) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 25 °C, 30 min, 93%; o) vinyllithium (~1.0 M in THF, 2 equiv), THF, −78 °C, 10 min; p) MsOH (72 equiv), THF, 50 °C, 45 min, 73% over 2 steps; q) OsO_4 (2.5% in *t*BuOH, 0.2 equiv), NMO (3 equiv), acetone/H_2O (10/1), 25 °C, 8 h; r) $NaIO_4$ (0.7 mmol g^{-1} on SiO_2, 5 equiv), CH_2Cl_2, 25 °C, 1 h, 76% over 2 steps; s) 23 (1.0 M in THF, 1.2 equiv), THF, 0 °C, 10 min, 95%; t) H_2 (1 atm), 10% Pd/C (2 equiv Pd), EtOAc/MeOH (1/1), 25 °C, 2.5 h, filter then HCl (1.25 M in MeOH), MeOH, 25 °C, 5 min, 83%.

afford alternate ring sizes. By exploring a number of different modes of electrophilic activation, they also include the first reported example of a 9-*exo*-dig ring closure, with key conformational analyses providing a sense of the parameters that rendered such processes possible. Finally, application of one of the developed approaches affected the critical cyclization that enabled a highly efficient and scalable total synthesis of the natural product caraphenol A (**1**). Further explorations of these processes are underway and will be reported in due course. Moreover, with ample supplies of **1** now available, biochemical evaluations of its properties can commence in earnest; given that other molecules in this class have been identified as potential probes and treatments for many disease areas,[6b–f] these future studies could be of high value.

Received: December 30, 2013
Published online: February 23, 2014

Keywords: Friedel–Crafts reaction · gold · natural products · resveratrol · total synthesis

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