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Harnessing Quinone Methides: Total Synthesis of (±)-Vaticanol A**

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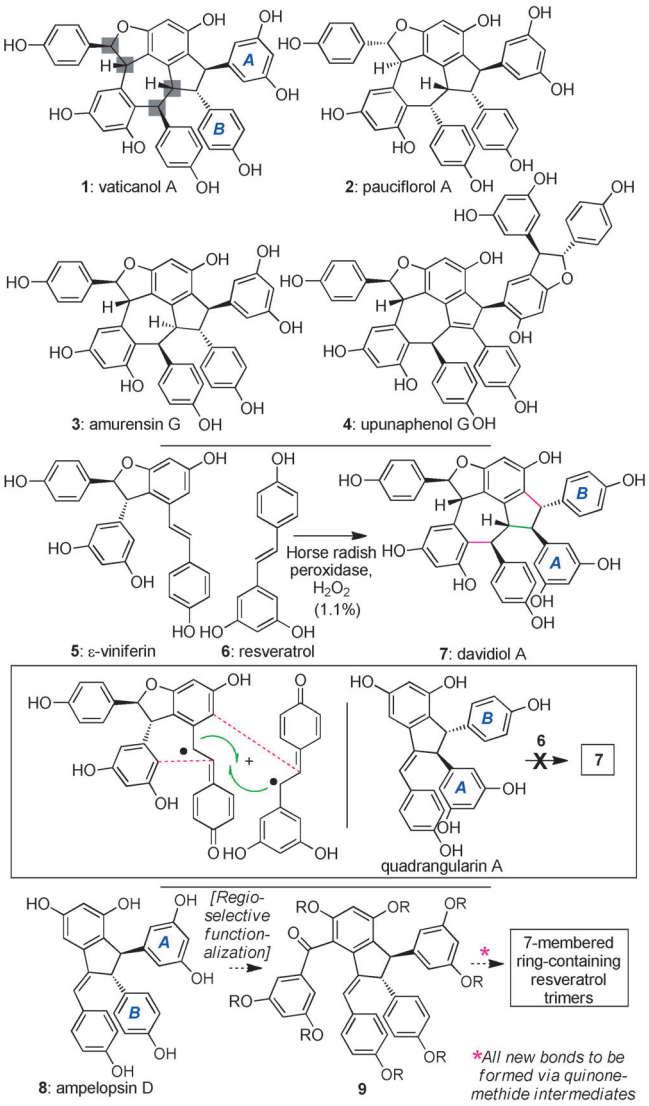
Abstract: *Although quinone methides are often postulated as intermediates in the biosynthesis of many polyphenolic natural products, deploying their power in a laboratory setting to achieve similar bond constructions has sometimes proven challenging. Herein, a total synthesis of the resveratrol trimer vaticanol A has been achieved through three instances of quinone methide chemistry. These operations, one of which succeeded only under very specific conditions, expediently generated its [7,5]-carbocyclic core, afforded a unique sequence for dihydrobenzofuran formation, and concurrently generated, in addition to the target molecule, a series of diastereomers reflective of many other isolates.*

Over the course of the past decade, the resveratrol class of oligomeric polyphenols has elicited significant attention due to their unique structural complexity and striking array of biochemical activities. Indeed, their diverse architectures have inspired the development of several novel synthetic strategies, tactics, and reactions,[1–3] while their antifungal, anti-HIV, cytotoxic, anti-inflammatory, and antibacterial properties have afforded a valuable platform for probing physiological function.[4] One of the most intriguing sub-collections within the family are trimeric materials containing a fused [7,5]-carbocyclic core, an appended dihydrofuran system, and up to six stereogenic centers.[5] To date, six members have been isolated with a common architectural framework exemplified by vaticanol A (**1**, Scheme 1),[5e] differing only in stereochemical configuration about one or more of the highlighted positions (as in **2** and **3**); another 3 diastereomeric materials, such as davidiol A (**7**),[5b] possess an



Scheme 1. Structures of several unique resveratrol trimers (**1**–**3**), past approaches for their synthesis, and a generalized approach to fashion the entire collection.

exchanged positioning and orientation of the labeled A- and B-rings. These variances, while seemingly subtle in a flat drawing, confer a range of three-dimensional architectural presentations and biological properties. The latter includes the ability of vaticanol A (**1**) to combat parasites and impact diabetes by inhibiting the elevation of glucose levels[6] and of amurensin G (**3**) to inhibit SIRT1 and rescue doxorubicin-responsiveness by down regulation of MDRII.[7,8] Moreover, these cores also serve as progenitors to complex, higher-order

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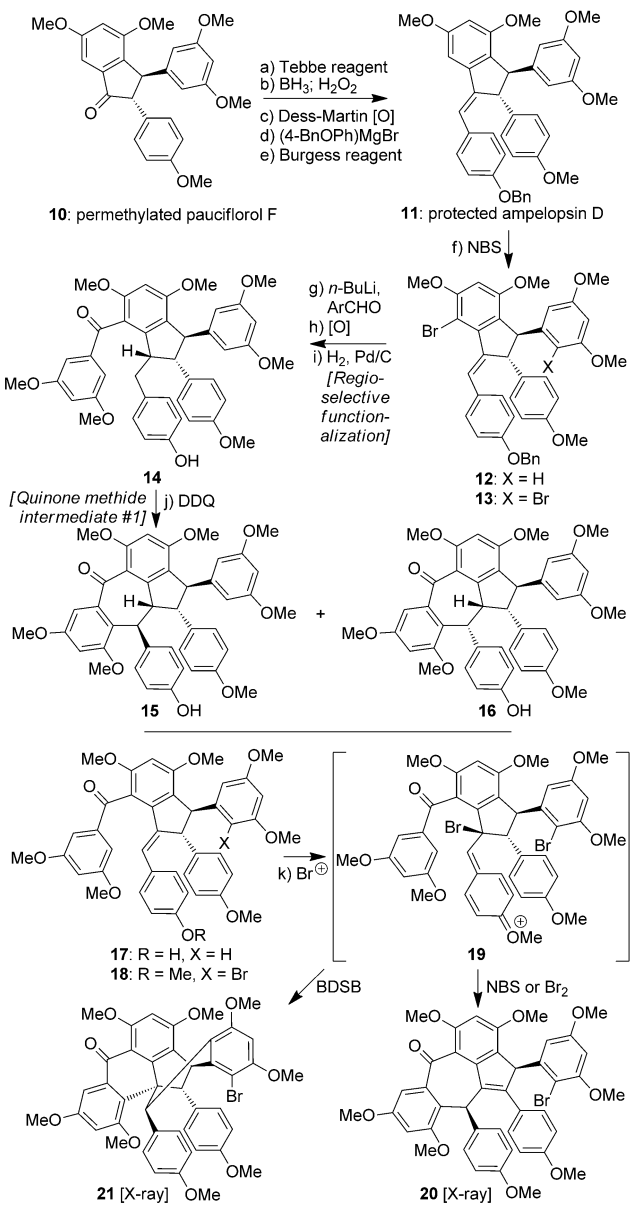
materials such as upunaphenol G (**4**),[9] compounds whose activity profiles remain largely unexplored and which have proven difficult to isolate in significant quantity from natural sources. Herein, we describe the first synthetic approach capable of delivering these materials, work achieving a total synthesis of vaticanol A (**1**) and a number of diastereomeric analogs through a flexible design featuring several carefully orchestrated and executed C–C and C–O bond-forming operations, the majority of which depended upon careful deployment of quinone methide chemistry.[10]

To date, the only successful synthetic explorations toward materials of this type have issued from the Niwa group.[11] Their approach, shown in Scheme 1, was a biomimetic study wherein ε-viniferin (**5**) was exposed to resveratrol (**6**) under radical-generating conditions. The outcome was the concurrent formation of an array of products out of which davidiol A (**7**) was obtained in 1.1% yield following extensive purification. No compound with the general architectural arrangement of **1**–**3** was reported. As indicated within the inset box, the desired trimer (**7**) was the product of three bond-forming reactions, two of which (colored in pink) likely involved quinone methide intermediates. However, the non-selectivity observed in this event is unsurprising given the high reactivity of these species and the number of other radical intermediates not explicitly shown that also can arise from each piece.[1]

Our approach, shown in the lower panel of Scheme 1, sought a distinctly different set of bond constructions starting from ampelopsin D (**8**)[5a] or a simplified variant, materials whose syntheses we had already accomplished[2ab] and that contain the conserved portion of **1**–**3** and their three additional known diastereomers. Our hope was that if this core could be regioselectively functionalized to reach **9**, then potentially all diastereomeric variants of the group could be accessed through the C–C bond constructions used to forge the 7-membered ring and dihydrofuran ring systems, either through differential reagent or substrate-controlled reactions. These plans, in general terms, mirror those that we have outlined previously for the controlled synthesis of other trimeric and tetrameric members of the resveratrol class.[2c] However, as will be shown, the new framework upon which they are tested here afforded a number of critical challenges, unexpected findings, and a need for a distinct dihydrofuran ring-synthesis approach unlike that developed previously. As an additional unique element, all new bonds from proposed intermediate **9** would arise through quinone methide chemistry where, unlike Nature's seemingly uncontrolled biosynthesis employing such species, we hoped to harness their capacity for highly selective events; given that previous biomimetic efforts have already shown that the combination of the ampelopsin D regioisomer quadrangularin A and resveratrol (**6**) does not lead directly to any member of the [7,5]-bicyclic family (see inset box),[12] this alternative, step-wise approach could be uniquely valuable for the class as a whole.

As shown in Scheme 2, our efforts began from permethylated pauciflorol F (**10**), prepared in 8 steps in 44% overall yield through previously delineated chemistry.[2ab] From here, use of 4 transformations also developed by our group,[2e] followed by a regioselective dehydration as mediated by the Burgess reagent[13] in toluene at 80 °C, afforded a fully protected variant of ampelopsin D (**11**) in which the newly installed aromatic ring possessed differential phenolic protection from its 5 counterparts.[14] These operations collec-

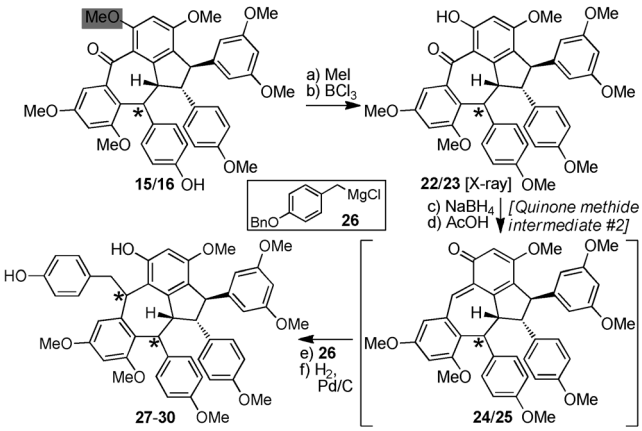


Scheme 2. Explorations into generating the [7,5]-carbocyclic core: a) Tebbe reagent (0.5 M in toluene, 1.0 equiv), THF, 0 °C, 2 h, 82%; b) BH_3·THF (2.6 equiv), THF, 25 °C, 12 h, then $NaOH/H_2O_2$, 0 °C, 5 h; c) Dess–Martin periodinane (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 0→25 °C, 1 h; d) (4-BnOPh)MgBr (3.0 equiv), THF, 0→25 °C, 2 h; e) Burgess reagent (3.0 equiv), toluene, 80 °C, 2 h, 46% overall (4 steps); f) NBS (0.95 equiv), CH_2Cl_2, −35→25 °C, 7 h; g) *n*BuLi (2.0 equiv), THF, −78 °C, 20 min, then 3,5-dimethoxybenzaldehyde (3.0 equiv), −78→25 °C, 2 h, 44% overall (2 steps), 76% b.r.s.m. (2 steps); h) Dess–Martin periodinane (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 0→25 °C, 2 h, 94%; i) 10% Pd/C (0.20 equiv), H_2, EtOAc, 8 h, 93%; j) DDQ (1.5 equiv), CH_2Cl_2, 25 °C, 12 h, 30%, 46% b.r.s.m. for **15**, 28%, 44% b.r.s.m. for **16**; k) Br_2 (1.0 equiv), CH_2Cl_2, −78→25 °C, 13 h, 50% **20** and trace of **21**; BDSB (1.0 equiv), CH_2Cl_2, −78→25 °C, 10 h, 85% **21**. NBS = *N*-bromosuccinimide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

tively proceeded in 38% yield (82% average yield per step). With nearly 6 g of this material in hand, the stage was now set to attempt regioselective functionalization of this highly electron-rich material. In line with prior experience,[2c] our reaction of choice was electrophilic aromatic substitution with bromine and, following meticulous optimization, reliable reaction conditions were identified to achieve the desired site-selective functionalization. That process involved exposure of **11** to sub-stoichiometric amounts of NBS (0.95 equiv) for 4 h in CH_2Cl_2 at −35 °C (internal reaction temperature). On 200 mg scale, it afforded the desired mono-brominated product (**12**) in a 12:1 preference over its dibrominated congener (**13**); on larger scale, the reaction was less selective (**12**:**13**:**11** = 3:1:1), likely due to challenges in maintaining equally precise temperature control.[15] Pressing forward, lithium-halogen exchange followed by the addition of 3,5-dimethoxybenzaldehyde smoothly afforded the desired adduct in 44% yield over two steps (76% b.r.s.m.).[16] Subsequent oxidation and one-pot benzyl ether deprotection/double bond hydrogenation under standard conditions (H_2, Pd/C) afforded **14** as a single stereoisomer (87% yield, 2 steps). This material was now poised to attempt construction of the 7-membered ring of the targets through an oxidative Friedel–Crafts-like reaction via the intermediacy of a quinone methide.

To our surprise, this transformation proved extremely difficult to achieve. Indeed, exposure of **14** to a variety of standard oxidants [CAN, Ag_2O, $PhI(OAc)_2$, $PhI(OTFA)_2$, MnO_2, *p*-chloranil][17] failed to deliver any indication of appropriately cyclized materials, even when the carbonyl group of the substrate was removed (structure not shown) to enhance the nucleophilicity of the attacking ring. Only when substrate **14** was exposed to DDQ in CH_2Cl_2 at 25 °C for 12 h was **15** and **16** obtained as an 1:1 mixture of separable diastereomers in 58% yield (90% b.r.s.m.). Different reaction conditions, as well as separate re-exposure of these products to the optimized protocol (and several variants thereof) afforded no interconversion, suggesting that this ratio could not be altered. From our perspective, however, access to both materials was of high value in that **15** reflected the core of targets like vaticanol A (**1**), while **16** possessed the stereochemistry of pauciflorol A (**2**).

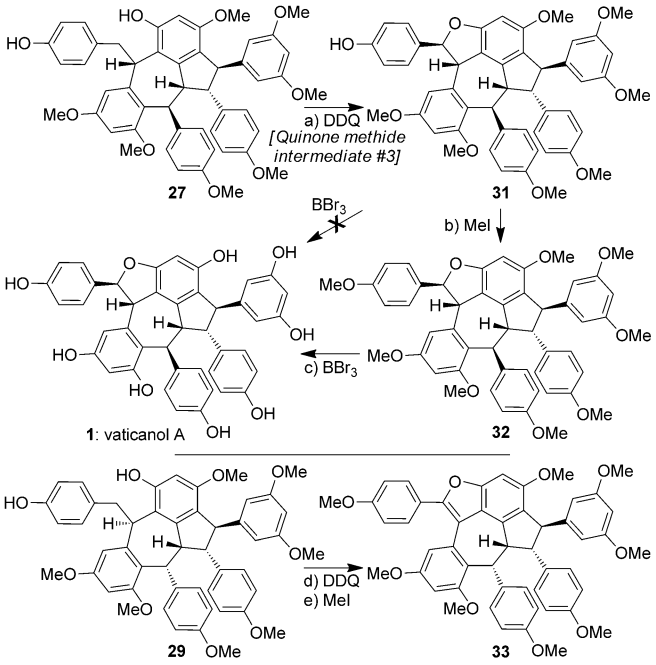
Unclear is why this single set of reaction conditions is uniquely effective, noting that several other strategies and approaches based on non-oxidative Friedel–Crafts chemistry also failed. For instance, efforts to access a quinone methide from alkene **17**[18] through acidic tautomerization (TFA, BF_3, HFIP) were uniformly unsuccessful. The only other instance in which a 7-membered ring was obtained occurred when bromonium electrophiles (NBS or Br_2) were used with the related substrate **18** (its most electron-rich ring was previously halogenated), but that product (**20**) contained an unmodifiable olefin in the form of the core of upunaphenol G (**4**, cf. Scheme 1); intriguingly, use of our recently-developed, highly-reactive bromonium source $Et_2SBr{\cdot}SbCl_5Br$ (BDSB),[19] afforded a different polycycle (**21**, verified by X-ray), presumably via the same postulated intermediate (**19**).[20]



Scheme 3. Use of an *o*-quinone methide to generate the complete carbocyclic cores of vaticanol A (**1**) and its congeners: a) MeI (5 equiv), K_2CO_3 (3 equiv), acetone, 75 °C, 12 h; b) BCl_3 (1.0 M in CH_2Cl_2, 1.0 equiv), CH_2Cl_2, −78 °C, 20 min, 51% overall for **22**, 80% overall for **23**; c) $NaBH_4$ (3.0 equiv), MeOH/THF (1:1), 0→25 °C, 1 h, 91%; d) AcOH, 80 °C, 2 h; e) **26** (5.0 equiv), THF, −78→25 °C, 5.5 h; f) 10% Pd/C (1 equiv), EtOAc/MeOH (1:1), 25 °C, 2 h, 25% over 3 steps (41% b.r.s.m.) for **27** and **28**, 20% over 3 steps (25% b.r.s.m.) for **29**, 41% over 3 steps (51% b.r.s.m.) for **30**.

Nevertheless, with the 7-membered ring accessed in the form of both **15** and **16**, attention now focused on dihydrofuran generation. Our plan, as shown in Scheme 3, was to attempt the incorporation of the final aromatic ring through nucleophilic addition onto an in situ-generated quinone methide in advance of a final, oxidatively-induced ring-closure via a third quinone methide.[21] Critical to the opening elements of this effort was the selective unmasking of the highlighted methylated phenol within **15**/**16**. Thus, pressing forward, **15** and **16** were separately exposed to MeI and K_2CO_3 to engage the sole free phenol previously critical to the formation of their 7-membered rings, and then, upon controlled exposure to BCl_3 in CH_2Cl_2 at −78 °C for 20 min, the methyl ether adjacent to the carbonyl was selectively cleaved. At this stage, one of the diastereomers (**23**) was crystalline, with X-ray analysis verifying that its stereochemistry about the starred carbon corresponded to pauciflorol A (**2**); phenol **22** thus reflected the framework of vaticanol A (**1**). From here, quinone methides **24** and **25** were obtained following separate exposure to $NaBH_4$ and subsequent treatment with AcOH at 80 °C to facilitate elimination of the intermediate alcohol. Although **24** and **25** were moderately stable and could be purified, for practical purposes they were reacted immediately following work-up with Grignard reagent **26**. That event, followed by reductive cleavage of its benzyl ether protecting group, afforded the complete set of all diastereomers about the two starred carbons to fully probe our ability to access multiple variants of the final targets.[22] For **27** and **28**, derived from compound **15**, the diastereomeric ratio about the new center was 1:1, while for **29** and **30**, formed from **16**, the ratio was 1:2.[23,24]

With these materials in hand, our final efforts sought to determine if four different natural products and natural product-like cores could be accessed through a final oxidative



Scheme 4. Completion of the total synthesis of vaticanol A (**1**) and a congener (**33**): a) DDQ (1.5 equiv), CH_2Cl_2, 25 °C, 1 h, 40%; b) MeI (500 equiv), K_2CO_3 (10 equiv), acetone, 75 °C, 3 h, 88%; c) BBr_3 (1.0 M in CH_2Cl_2, 16 equiv), CH_2Cl_2, −78→25 °C, 12 h, 95%, d) DDQ (1.5 equiv), CH_2Cl_2, 25 °C, 1 h, 15%, b) MeI (500 equiv), K_2CO_3 (10 equiv), acetone, 75 °C, 3 h, 92%.

cyclization leading to a *trans*-configured dihydrofuran ring system. As matters transpired, such cores could only be formed from those materials (**27** and **29**) in which the two sp^3-hydridized acyclic side-chains off the 7-membered core (at the starred positions within Scheme 3) were *trans* to one another. As shown in Scheme 4, **27** afforded the final carbon framework of vaticanol A (**31**) in 40% yield following exposure to DDQ while **29** provided, after methylation of the free phenol, the more highly oxidized benzofuran **33**.[25] By contrast, those materials where the side-chains were in a relative *cis* orientation (i.e. **28** and **30**, see Supporting Information for exact structures) afforded only decomposition. Given that all frameworks within the class of [7,5]-bicyclic congeners, with only one exception, possess these substituents in a *trans* orientation, this outcome might suggest biogenetic relevance to these constructions. And, while we could not reduce the double bond within **33** to afford materials like pauciflorol A (**2**), we were able, following methylation of the free phenol within **31**, to fully deprotect compound **32** with BBr_3 in CH_2Cl_2 in near quantitative yield to generate vaticanol A (**1**), spectroscopically matching naturally-derived material.[5e] Critically, the same deprotection did not succeed with **31**, with the observation instead of several precipitated materials that were partially demethylated. These results reveal that the order of deprotection is critical with such highly polar compounds in order to maintain solubility; we have made this observation elsewhere and believe it could explain some of the challenges in achieving such deprotections with other polyphenolic materials more generally.[26]

In conclusion, we have developed an approach leading to the first total synthesis of (±)-vaticanol A (**1**) that utilized reactive quinone methides as enabling intermediates for key bond constructions. While the route was relatively linear, it proceeded with a high level of efficiency in an average yield of 76% per step and 14 steps overall from a previously obtained natural product. In addition, most of the route has proven scalable, with many of its operations performed on gram quantities. Critical elements include an expedient formation of the [7,5]-core through a highly challenging oxidative ring closure that has worked to date only under one set of conditions, several chemo- and positionally selective functionalizations on a highly electron-rich core, and a unique approach for dihydrobenzofuran formation using two quinone methide intermediates, one of which was isolable. Additionally, some highly unique non-natural analogs and frameworks, such as **20**, **21**, and **33** were synthesized. Finally, we anticipate that the use of this sequence commencing with quandrangularin A [drawn in the inset box of Scheme 1, the structural congener of ampelopsin D (**8**, cf. Scheme 1) with positionally switched A- and B-rings], should afford materials reflective of davidiol A (**7**) and its diastereomers. Work to explore that potential is currently underway.

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[14] Use of acidic conditions to effect the same dehydration afforded alkene isomerization to tetrasubstituted endocyclic variants. Also, efforts to shorten this sequence to **11** by using metathesis or Heck-based reactions to add the fourth aromatic ring were unsuccessful.

[15] We reported[2a,b] that it was possible to achieve a monobromination of the structurally related permethylated quadrangularin A on 10 mg scale in 72% yield for intermediate characterization; the ampelopsin D framework was more difficult to control and required significant optimization to proceed effectively on scale.

[16] The presence of the dibrominated material in this sequence posed no problems in that though it fully lithiated, it did not dialkylate, allowing for it to converge into the desired product.

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[20] Alkyl bromides within another resveratrol framework have also proven unstable, leading to alkenes and rearranged products.[2a]

[21] The ketone of **15**/**16**, just like in protected pauciflorol F (**10**), cannot, in our hands, be engaged directly by a Grignard nucleophile; thus, the use of this quinone-methide based alternative was essential.

[22] To the best of our knowledge, the first example of a 1,4-conjugate addition of a Grignard reagent into an *ortho*-quinone methide resulting in a C–C bond was reported by R. W. Van de Water, D. J. Magdziak, J. N. Chau, T. R. R. Pettus, *J. Am. Chem. Soc.* **2000**, *122*, 6502.

[23] Interestingly, while the variances in these ratios indicate that there is differential substrate bias due to relatively remote chiral centers, that effect was sometimes more pronounced. For instance, in the $NaBH_4$ step, ketone **22** was reduced without any diastereocontrol, while compound **23** afforded only a single diastereomer of alcohol.

[24] The starting benzylic alcohol needed for quinone methide generation was also recovered, presumably as a product of water addition onto the *ortho*-quinone methide during the reaction or upon work-up.

[25] Such differential reactivity involving DDQ has been shown once before, with dihydrofuran formation being more rare: K. Schofield, R. S. Ward, A. M. Choudhury, *J. Chem. Soc. C* **1971**, 2834.

[26] M. I. Chiriac, S. A. Snyder, unpublished results. For a recent example of a sensitive dihydrofuran, see S. J. O'Malley, K. Tan, A. Watzke, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 13496.

