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Structural Revision and Total Synthesis of Caraphenol B and C

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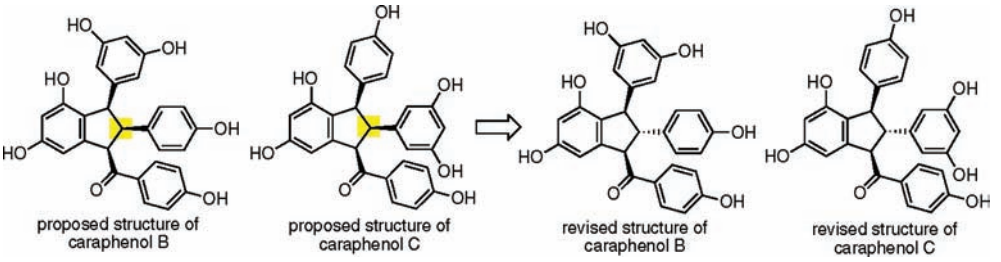
ABSTRACT



Chemical syntheses of two stereochemically unique resveratrol dimers, caraphenols B and C, have shown that their structures are misassigned. Thoughts on their potential chemical etiology led to an alternate structural proposal that has been confirmed through synthesis, one indicating that the substituents on their respective indane systems exist in a relative *trans,trans* orientation rather than the originally postulated all-*cis* arrangement.

Throughout the world, plants utilize resveratrol and the hundreds of molecules derived from its self-merger as a front line chemical defense against fungal infection.[1] Such ubiquity may be a consequence of the family's tremendous architectural diversity, with the structures of the natural products drawn within Figure 1 (**1**–**8**) reflecting a small subset of the dimeric materials within the collection, cores whose further decoration with additional resveratrol units at multiple positions affords even greater complexity.[2] Interest in these materials during the past decade has been high,[3] be it from efforts to understand their biogenesis,[4] test the power of specific synthetic strategies and methods against specific frameworks,[5] or study their chemical biology more fully (particularly for properties outside fungal infection).[6]

Our endeavors have been focused largely on the synthetic front, with our key goal being the identification of a unified and global synthetic approach capable of delivering any member within the family in a controlled fashion.[7]

(1) For a review, see: Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 586–621.

(2) For a review on oligomeric natural products, see: Snyder, S. A.; ElSohly, A. M.; Kontes, F. *Nat. Prod. Rep.* **2011**, *28*, 897–924.

(3) For a review on resveratrol synthetic work, see: Snyder, S. A. In *Biomimetic Organic Synthesis*; Poupon, E., Nay, B., Eds.; Wiley-VCH: Weinheim, 2011; pp 695 – 721.

(4) (a) Langcake, P.; Pryce, R. J. *J. Chem. Soc., Chem. Commun.* **1977**, 208–210. (b) Takaya, Y.; Yan, K.-X.; Terashima, K.; He, Y.-H.; Niwa, M. *Tetrahedron* **2002**, *58*, 9265–9271. (c) Sako, M.; Hosokawa, H.; Ito, T.; Iinuma, M. *J. Org. Chem.* **2004**, *69*, 2598–2600. (d) Yao, C.-S.; Lin, M.; Wang, Y.-H. *Chin. J. Chem.* **2004**, *22*, 1350–1355. (e) Takaya, Y.; Terashima, K.; Ito, J.; He, Y.-H.; Tateoka, M.; Yamaguchi, N.; Niwa, M. *Tetrahedron* **2005**, *61*, 10285–10290. (f) He, Y.-H.; Takaya, Y.; Terashima, K.; Niwa, M. *Heterocycles* **2006**, *68*, 93–100. (g) Li, W.; Li, H.; Li, Y.; Hou, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 7609–7611. (h) Velu, S. S.; Buniyamin, I.; Ching, L. K.; Feroz, F.; Noorbatcha, I.; Gee, L. C.; Awang, K.; Abd. Wahab, I.; Weber, J.-F. F. *Chem.—Eur. J.* **2008**, *14*, 11376–11384. (i) Li, W.; Luo, Y.; Li, H.; Zang, P.; Han, X. *Synthesis* **2010**, 3822–3826. (j) Li, W.; Li, H.; Wang, A. X.; Luo, Y.; Zang, P. *J. Chem. Res.* **2010**, *14*, 118–120.

(5) For recent, selected papers, see: (a) Jeffrey, J. L.; Sarpong, R. *Tetrahedron Lett.* **2009**, *50*, 1969–1972. (b) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450–5453. (c) Kim, I.; Choi, J. *Org. Biomol. Chem.* **2009**, *7*, 2788–2795. (d) Nicolaou, K. C.; Wu, R. T.; Kang, Q.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3440–3443. (e) Nicolaou, K. C.; Kang, Q.; Wu, T. R.; Lim, C. S.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 7540–7548. (f) Chen, Y.-K.; Kang, Q.; Wu, T. R. *Molecules* **2010**, *15*, 5909–5927. (g) Sun, X.; Zhong, C.; Zhu, J.; Chang, J. *Tetrahedron Lett.* **2011**, *52*, 2815–2817. (h) Yang, Y.; Philips, D.; Pan, S. *J. Org. Chem.* **2011**, *76*, 1902–1905.

(6) Biological explorations are extensive. For recent work, see: Wood, J. G.; Rogina, B.; Lavu, S.; Howitz, K.; Helfand, S. L.; Tatar, M.; Sinclair, D. *Nature* **2004**, *430*, 686–689 and references therein.

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To date, we have synthesized over 20 different natural products at the dimeric, trimeric, and tetrameric levels encompassing a range of different types of ring systems, including indanes, seven-membered rings, dihydrofurans, and bicyclic frameworks. It was in this vein that the structures of caraphenols B and C (**1** and **2**),[8] two isolates from the dried roots of *Caragana sinica* (which has been used as a folk medicine in China to treat hypertension and contusions), caught our attention.[9,10]

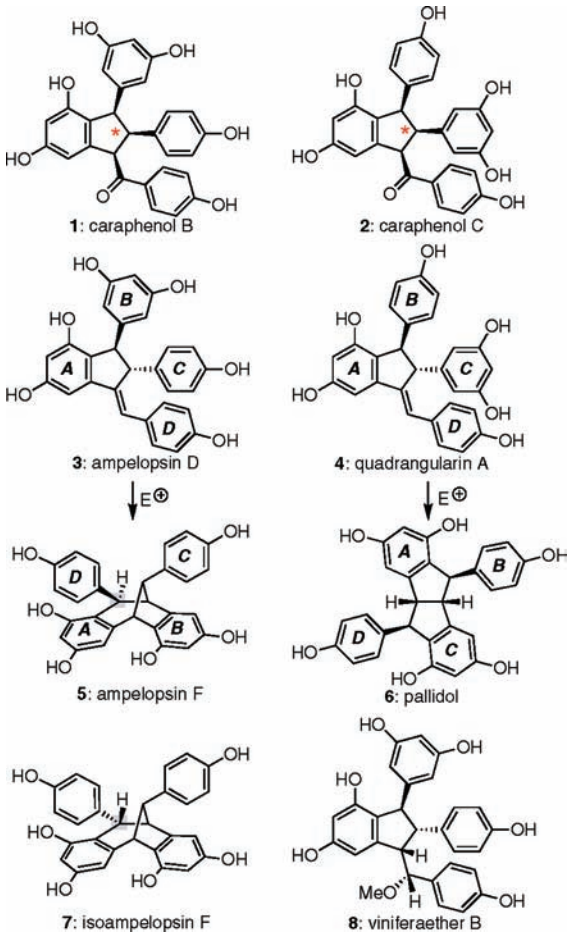


Figure 1. Structures of selected dimeric resveratrol-based natural products (not drawn with absolute stereochemistry).

Although many indane-based natural products are known within the family, these would appear to be the only two materials that orient their pendant substituents in an all-*cis* orientation, with specific novelty at the two starred positions.[11] Indeed, other members, such as ampelopsin D (**3**)[12] and quadrangularin A (**4**)[13] place their labeled B- and C-aryl rings *trans*. As we have recently shown,[7a,b] indane-based materials such as **3** and **4** can subsequently be converted into other dimeric cores like ampelopsin F (**5**)[12] and pallidol (**6**)[14] through electrophilic activation in a potentially biomimetic process. To the best of our knowledge, however, no material yet isolated can similarly be traced to the unique stereochemistry of caraphenol B and C; other diastereomers of **5** and **6** exist, such as **7**,[7d,8] but they reflect alteration in double bond geometry in what would be similar electrophile-induced cyclizations of indane starting materials, not variations in core ring stereochemistry. Intriguingly, reduced variants of **1** and **2** obtained from alternate plant sources (such as **8**)[15] also match the *trans*-stereochemical arrangement typical of the family. In this communication, we show through chemical synthesis that the structures of caraphenol B and C (**1** and **2**) are misassigned and, in line with the rest of the family, possess an all-*trans* configuration of substituents on its indane core.

Our efforts to forge the all-*cis* stereochemical arrangement of the proposed structure of caraphenol B (**1**) began from permethylated ampelopsin D (**9**)[7a,b] as shown in Scheme 1. Following a standard reaction sequence involving dihydroxylation of its lone olefin, oxidation of the resultant secondary alcohol under Swern conditions, and elimination using *p*-TsOH in benzene at 80 °C, we accessed α,β-unsaturated ketone **10** in 45% overall yield. Our hope was that hydrogenation of its lone double bond, as controlled by the single chiral center within the molecule, would generate the needed all *cis*-stereochemical arrangement of the target. Pleasingly, this expectation was met as compound **11** was produced as a single diastereoisomer in 73% yield using catalytic Pd/C and H_2 in a 3:1 mixture of MeOH and EtOAc containing Et_3N.[16] Subsequent removal of the methyl ethers with BBr_3 then afforded **1**. However, as noted in the inset table within Scheme 1, our synthetic material possessed signals for its three aliphatic protons in its ^1H NMR spectrum with multiplicities and coupling constants similar to those reported for the natural isolate, but with very different chemical shifts.

Although we were unable to obtain a crystalline variant of synthetic **1** to verify its connectivity unambiguously, we note the following in support of our structural assignment: (1) a crystal structure was obtained of the hydrogenation

(8) Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849–4854.

(9) Caraphenol B has been reisolated: Choi, C. W.; Choi, Y. H.; Cha, M.-R.; Yoo, D. S.; Kim, Y. S.; Yon, G. h.; Choi, S. U.; Kim, Y. H.; Ryu, S. Y. *Bull. Korean Chem. Soc.* **2010**, *31*, 3448–3450.

(10) For an approach to the caraphenols, see: Zhu, J.; Zhong, C.; Lu, H.-F.; Li, G.-Y.; Sun, X. *Synlett* **2008**, 458–462.

(11) There is one other *cis*-disposed indane ring that we have identified, but it is directly attached to an eight-membered ring and thus is unique in that it is not an isolated system: Yan, K.-X.; Terashima, K.; Takaya, Y.; Niwa, M. *Tetrahedron* **2001**, *57*, 2711–2715.

(12) Takaya, Y.; Yan, K.-X.; Terashima, K.; Ito, J.; Niwa, M. *Tetrahedron* **2002**, *58*, 7259–7265.

(13) Adesanya, S. A.; Nia, R.; Martin, M.-T.; Boukamcha, N.; Montagnac, A.; Païs, M. *J. Nat. Prod.* **1999**, *62*, 1694–1695.

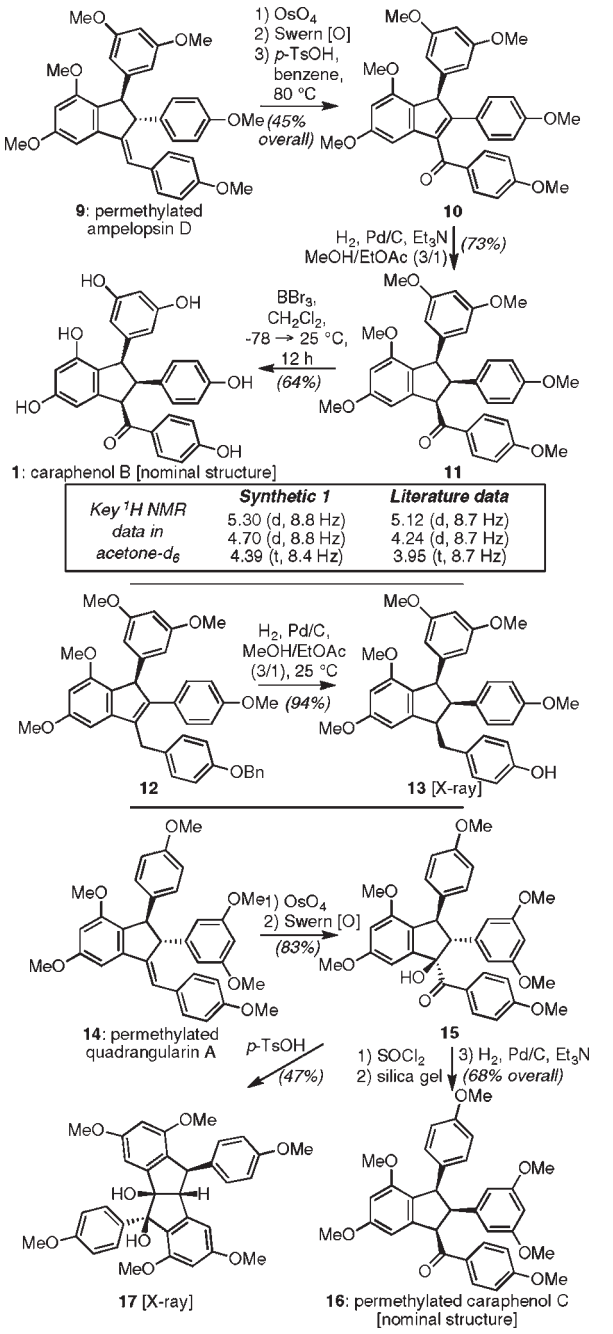
(14) Khan, M. A.; Nabi, S. G.; Prakash, S.; Zaman, A. *Phytochemistry* **1986**, *25*, 1945–1948.

(15) (a) Fujii, F.; He, Y.-H.; Terashima, K.; Takaya, Y.; Niwa, M. *Heterocycles* **2005**, *65*, 2461–2469. For other examples, see:(b) Ohyama, M.; Tanaka, T.; Iinuma, M. *Phytochemistry* **1995**, *38*, 733–740. (c) Kim, H. J.; Saleem, M.; Seo, S. H.; Jin, C.; Lee, Y. S. *Planta Med.* **2005**, *71*, 973–976.

(16) In the absence of base, the ketone was also competitively reduced. For a recent case where Et_3N was also valuable in a hydrogenation, see: Coquerel, Y.; Rodriguez, J. *Arkivoc* **2008**, 227–237.

(17) Compound **12** was synthesized as part of an early approach attempting to form the ketone of **1** through oxidation chemistry; such reactions did not succeed.

Scheme 1. Synthetic Efforts to Prepare the Proposed Structures of Caraphenols B and C Indicating the Need for a Revision



product of **12** (i.e., **13**),[17] and following methylation of its phenol, its NMR spectra were identical to those of an over-reduced variant of **11** generated through hydrogenation in the absence of Et_3N; (2) the positioning and coupling constants of the indane protons in **11** are nearly the same as those in synthetic **1**, suggesting that no rearrangement or stereochemical change[18] occurred during the BBr_3 deprotection; and (3) extensive HSQC, HMBC, and NOESY experiments confirm the proposed linear structure of **1**, including the observation of expected NOE enhancements between the indane protons.[19] Finally, the synthesis of the permethylated variant of caraphenol C (**16**) through a similar route from permethylated quadrangularin A (**14**) afforded material with a ^{1}H NMR spectrum that was similarly distinct from natural caraphenol C in terms of peak placements; deprotection of this material did not prove possible as side reactions predominated, likely due to Friedel–Crafts chemistry as noted by the conversion of intermediate **15** into **17** (structure confirmed by X-ray analysis). As such, assuming accuracy in our syntheses, alternate structures for caraphenols B and C were needed.

Our hypothesis, as hinted during the opening discussion, was a *trans,trans* arrangement of substituents which would alter the stereochemistry in **1** and **2** at the starred carbons indicated in Figure 1. Despite this seemingly profound change in terms of how aryl rings would be situated, we believed that these materials would have spectral properties consistent with the data sets of the natural isolates. For example, the original isolation team based their stereochemical assignment on three separate NOE enhancements between the indane ring protons,[8] the same three we also observed with our synthetic **1**; our own molecular mechanics optimizations, however, indicated that these NOE enhancements could also occur in *trans*-oriented materials. Moreover, our global experience with rings of this type in the resveratrol class has revealed that coupling constants of indane protons cannot be correlated directly to *cis*- or *trans*-arrangements as is possible in many cyclohexane systems.

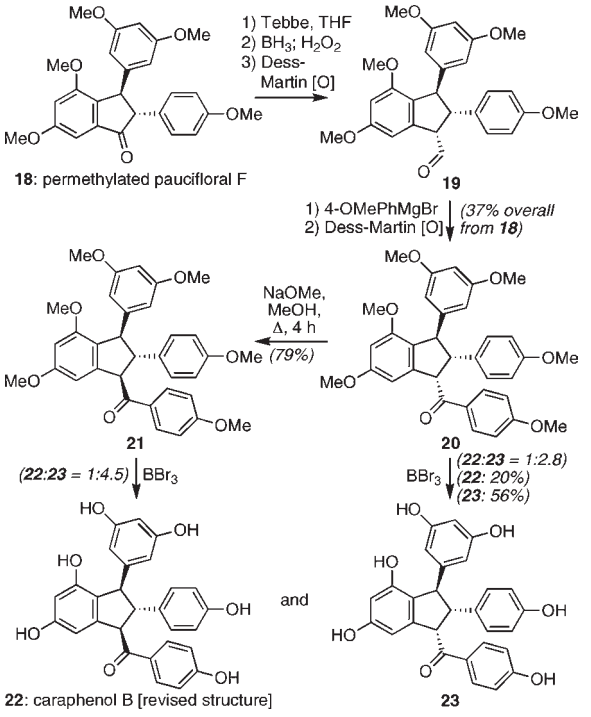
As such, we set out to prepare these materials as well as other diastereomeric variants to provide full confirmation for this alternate structural hypothesis. Our route to our revised structure for caraphenol B (i.e., **22**) is shown in Scheme 2, wherein initial operations afforded compound **20** in five standard chemical steps[20] from protected paucifloral F (**18**)[7a,b] by way of aldehyde **19**. The stereochemistry of this material (**20**) could be isomerized to the all-*trans* arrangement of **21** through the action of NaOMe in MeOH at 65 °C, providing a compound with coupling constants and proton positionings similar to those reported for natural caraphenol B. Upon deprotection of **21** with BBr_3, however, we obtained a 1:4.5 ratio of **22** and **23**; a similar outcome occurred following deprotection of **21**, with a 1:2.8 ratio of **22** and **23** obtained in higher yield (76% combined, separable by HPLC or careful preparative thin-layer chromatography). These outcomes may result from reprotonation of an intermediate boron-based enolate. Thus far, we have been unable to convert **23** into **22** under any basic conditions, but all spectroscopic data for **22** match those of the natural isolate. As such, though the final yield of **22** is nonoptimal,[21] we identified the structure of caraphenol B.

(18) A trace amount of a side product was obtained from the final deprotection leading to **1**; we believe this material to be epimeric at the carbon adjacent to the ketone. It was formed in low quantities and was difficult to purify, preventing full characterization.

(19) See Supporting Information for full details.

(20) Some of these opening steps were also performed in the following account: Sun, X.; Lin, G.; Hu, C.; Dong, J. Chinese Patent Application CN 1634826 A 20050706.

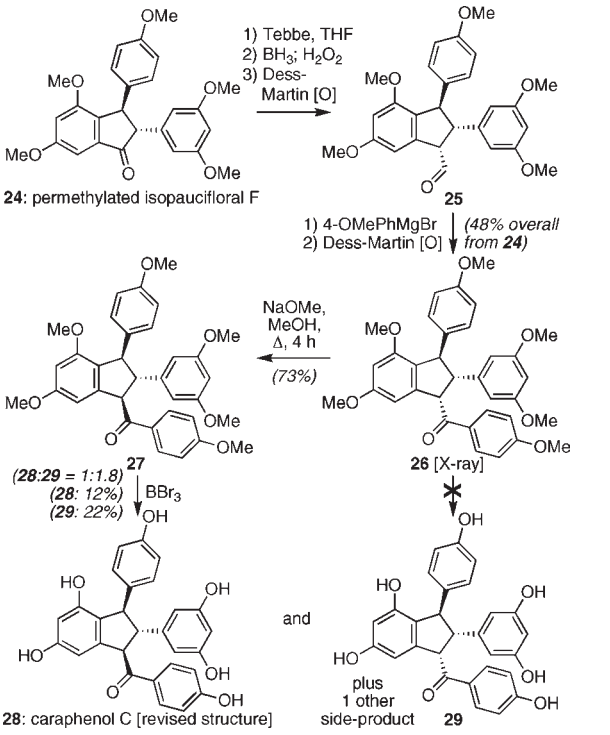
Scheme 2. Total Synthesis and Structural Confirmation of Caraphenol B as **22**



Finally, application of an analogous route with permethylated isopaucifloral F (**24**, Scheme 3) provided both **28** and **29** in an ~1:1.8 ratio and more modest final yield,[22] with the only difference here being that compound **26** (structure confirmed by X-ray) could not be deprotected successfully[23] and at least one additional uncharacterized side product was formed. As expected, however, **28** matched all data for natural caraphenol C.

In conclusion, this work has demonstrated that the structures originally reported for two unique natural products within the resveratrol class are in error and should be revised to the *trans*-based arrangement[24] typical of the entire family (i.e., that of **22** and **28**). As such, it remains an open question whether or not Nature really samples any stereochemical diversity within its resveratrol-derived indane cores. Future work is directed toward improving the stereocontrol needed to access the revised structures of caraphenols B and C exclusively and evaluating the biochemical potential of all materials.

Scheme 3. Total Synthesis and Structural Confirmation of Caraphenol C as **28**



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Supporting Information Available. Full characterization, experimental procedures, spectra, and ORTEPs. This information is available free of charge via the Internet at http://pubs.acs.org.

(21) Several attempts were made to deprotect earlier intermediates and utilize a different protecting group in this final step, but this approach has not yet proven viable.

(22) These materials were not separable by standard chromatography, and the yield for **28** and **29** refers to the NMR ratios of the combined mixture; a portion was purified by HPLC for characterization.

(23) Friedel–Crafts reactions of the type observed earlier within **15** appear to be responsible; the arrangement of the aryl rings were again key with this overall synthetic challenge and are likely the reason for the lower final yields of **28** and **29** relative to those of **22** and **23**.

(24) In fact, the cores of the revised caraphenols can be found in higher-order structures where additional resveratrol units are attached: Yang, G. X.; Hu, C. Q. *Chin. Chem. Lett.* **2003**, *14*, 1048–1050.