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Concise Synthesis of Pauciflorol F Using a Larock Annulation

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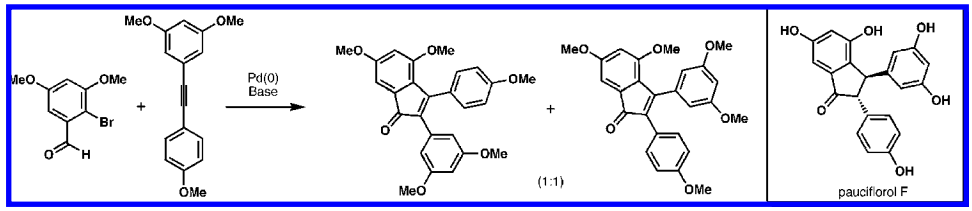
ABSTRACT



A Pd-catalyzed Larock annulation provides expedient access to a subset of resveratrol-derived natural products. The reported approach resulted in the structural revision of an intermediate en route to the natural product pauciflorol F, the total synthesis of which proceeded in two steps from the requisite pentannulation product.

Polyphenolic natural products such as resveratrol and its derivatives (Figure 1)[1] have emerged as important synthetic targets due to their diverse architectures and their potential medicinal utility. Many of these compounds are produced by various plants in response to infection or stress.[2] Recent reports have demonstrated that resveratrol inhibits cancer growth in vitro[3] and extends the lifespan of living organisms, including fruit flies and the turquoise killifish.[4] To date, the specific mechanism of action of resveratrol in humans remains elusive due to its rapid metabolism and relatively low bioavailability.[5] Several dimeric resveratrol metabolites (e.g., **2**−**5**, Figure 1), which presumably arise from radical dimerizations of **1**, have shown biological activities comparable to or greater than their parent monomer.[6] For example, a mixture of resveratrol dimers and oligostilbenes isolated from *Caragana sinica* exhibited in vitro stimulation of osteoblast proliferation at concentrations as low as 100 pg/mL.[6d]

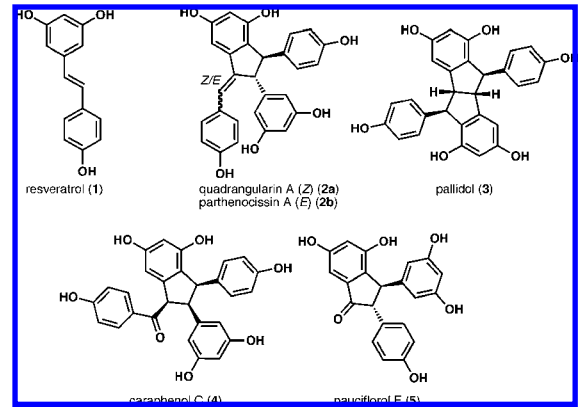


Figure 1. Selected resveratrol-derived natural products.

However, most biological studies of resveratrol and its congeners have concentrated on plant models. Consequently, relatively little is known about the potential benefits of these molecules to human health. A more thorough exploration of the properties, mechanism of action and biochemical significance of resveratrol and its derivatives requires efficient and versatile syntheses of these molecules and their unnatural analogues.

(1) Takaoka, M. *Proc. Imp. Acad. Tokyo* **1940**, *16*, 405–407.
(2) Langcake, P.; Pryce, R. *J. Physiol. Plant Pathol.* **1976**, *9*, 77–86.
(3) 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.
(4) Valenzano, D. R.; Terzibasi, E.; Genade, T.; Cattaneo, A.; Domenici, L.; Cellerino, A. *Curr. Biol.* **2006**, *16*, 296–300.
(5) Bertelli, A. A. E.; Giovannini, L.; Stradi, R.; Bertelli, A.; Tillement, J. P. *Int. J. Tiss. Reac.* **1996**, *18*, 67–71.

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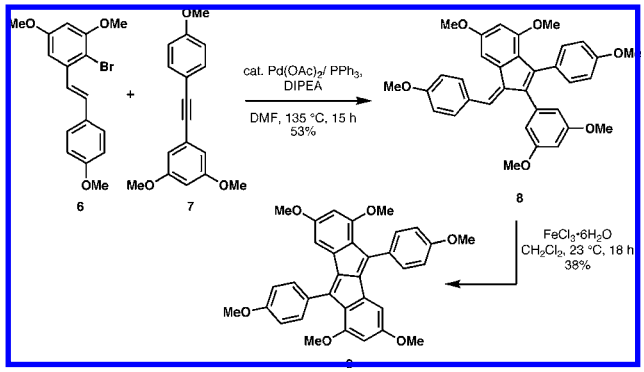
Several research groups have recently reported syntheses of resveratrol-derived compounds. In 2006, Li et al. employed the biomimetic dimerization of a resveratrol derivative for the total synthesis of quadrangularin A (**2a**, Figure 1).[7a] In the same year, She, Pan, and co-workers reported the total synthesis of pauciflorol F by employing a Pd-catalyzed 5-*endo* Heck cyclization strategy.[7b] Snyder et al. subsequently reported the syntheses of several polyphenolic natural products, including **2a**, **3**, and **5**.[7c,d]

As a part of a program to develop concise synthetic routes to resveratrol-derived compounds, we recently reported a domino Heck cyclization/pentannulation process, which provided the scaffold of a subset of dimeric resveratrol-derived compounds (Scheme 1).[8] The single-pot preparation

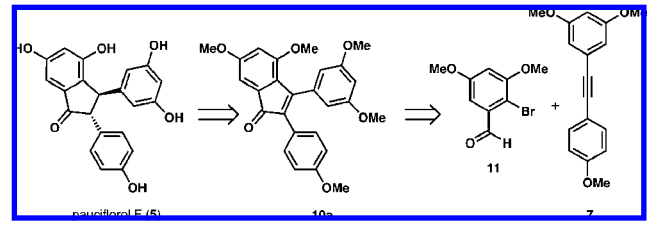
Scheme 1. Heck Pentannulation Cascade



of the dimeric resveratrol framework (see **8**) employed the Pd-catalyzed reaction of bromostilbene derivative **6** and tolane **7**. Oxidative cyclization of **8** using iron(III) chloride provided pentalene **9**, which is the core for pallidol (**3**) and related fused [3.3.0] bicyclic molecules.

We envisioned that compounds such as pauciflorol F (**5**, Scheme 2) could arise from a 2,3-disubstituted indenone

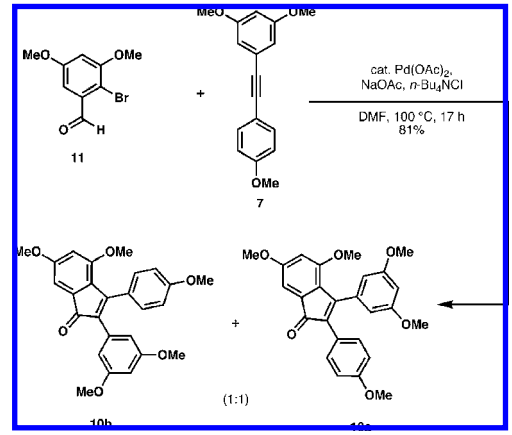
Scheme 2. Retrosynthetic Analysis of **5**



precursor (e.g., **10a**) using a related carbocyclization strategy. Encouraged by the wide substrate scope of Larock's Pd-catalyzed annulation of alkynes to form 2,3-disubstituted 1-indenones,[9] we imagined obtaining **10a** from *o*-bromobenzaldehyde **11**[10] and tolane **7**.[8]

When a mixture of **11** and **7** was subjected to Larock's original annulation conditions,[9] a 1:1 mixture of indenone regioisomers **10a** and **10b** was obtained, which could be separated by column chromatography (Scheme 3).

Scheme 3. Synthesis of Indenones **10a** and **10b**



Regiocontrol in the Larock pentannulation to form indenones remains a challenge,[11] as confirmed by our observations in the reaction of **7** and **11**. However, either regioisomer (i.e., **10a** or **10b**) provides access to a resveratrol-derived compound (i.e., pauciflorol F, **5**, or its regioisomer isopauciflorol F[7d]).

Our initial studies examined the conversion of **10a** (Scheme 4) to the resveratrol-derived natural product pauciflorol F. Reduction of the indenone double bond was accomplished using heterogeneous catalytic hydrogenation conditions (Pd/C, H_2), which yielded *cis* indanone **12**. Epimerization of the C(2) stereocenter of **12** was attempted

(6) (a) Ohyama, M.; Tanaka, T.; Iinuma, M. *Phytochemistry* **1995**, *38*, 733–740. (b) Ohyama, M.; Tanaka, T.; Iinuma, M. *Chem. Pharm. Bull.* **1994**, *42*, 2117–2120. (c) Adesanya, S. A.; Nia, R.; Martin, T. M.; Boukamcha, N.; Montagnac, A.; Pais, M. *J. Nat. Prod.* **1999**, *62*, 1694–1695. (d) Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849–4854. (e) Li, W. W.; Ding, L. S.; Li, B. G.; Chien, Y. Z. *Phytochemistry* **1996**, *42*, 1163–1165. (f) Tanaka, T.; Ito, T.; Nakaya, K.; Iinuma, M.; Riswan, S. *Phytochemistry* **2000**, *54*, 63–69. (g) Coggon, P.; Janes, N. F.; King, T. J.; Wallwork, S. C. *J. Chem. Soc.* **1965**, 406–408. (h) 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. (i) Supudompol, B.; Likhitwitayawuid, K.; Houghton, P. *J. Phytochemistry* **2004**, *65*, 2589–2594. (j) Sahadin, E. H.; Hakim, L. D.; Juliawaty, Y. M.; Syah, L. B. D.; Ghisalberti, E. L.; Latip, J.; Said, I. M.; Achmad, S. A. Z. *Naturforsch., C: Biosci.* **2005**, *60*, 723–727. (k) Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932–937.

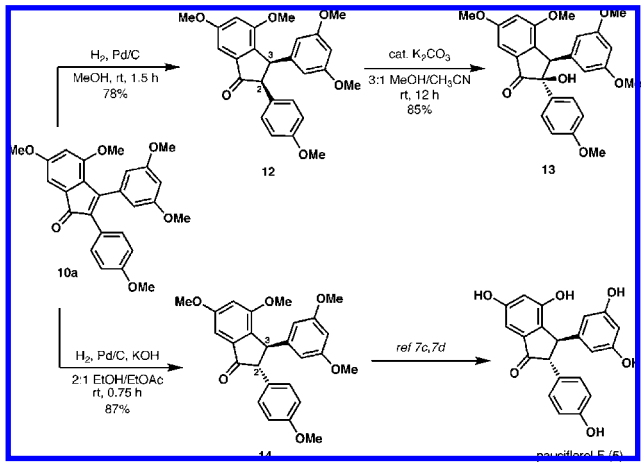
(7) For selected synthetic investigations of resveratrol-derived natural products, see: (a) Li, W.; Li, H.; Li, Y.; Hou, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 7609–7611. (b) Bo, C.; Lu, J.-P.; Xie, X.-G.; She, X.-G.; Pan, X.-F. *Chin. J. Org. Chem.* **2006**, *26*, 1300–1302. (c) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186–8191. (d) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753–1765.

(8) Jeffrey, J. L.; Sarpong, R. *Tetrahedron Lett.* **2009**, *50*, 1969–1972.

(9) (a) Larock, R. C.; Doty, M. J. *J. Org. Chem.* **1993**, *58*, 4579–4583. For previous examples of palladium-catalyzed syntheses of indenones, see also: (b) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550–2559. (c) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *J. Organomet. Chem.* **1992**, *436*, C9−C12. (d) Liebeskind, L. S.; South, M. S. *J. Org. Chem.* **1980**, *45*, 5426–5429.

(10) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508–4509.

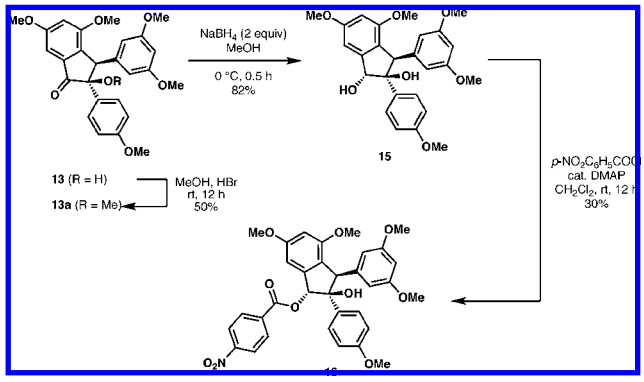
Scheme 4. Hydrogenation Studies of Indenone **10a**



using substoichiometric amounts of K_2CO_3 in a 3:1 mixture of MeOH and CH_3CN. However, instead of the expected *trans*-indanone isomer (i.e., **14**), the α-hydroxy indanone **13** was isolated. The structure of **13** was corroborated by IR, which showed an absorption band at 3434 cm^{-1} (consistent with an O−H stretch). Additionally, the ^{13}C NMR spectrum of **13** showed a signal at 85.7 ppm, suggestive of a quaternary carbon bound to oxygen.

Further support for α-hydroxy indanone **13** was obtained by a series of chemical conversions, as illustrated in Scheme 5. Reduction of the carbonyl group of **13** with $NaBH_4$

Scheme 5. Chemical Transformations of **13**



furnished diol **15**, whose relative stereochemistry was assigned by analogy to a previous report.[12a] Esterification of the secondary hydroxyl group of **15** with *p*-nitrobenzoyl-chloride gave **16** in 30% yield, along with unreacted **15**. Alternatively, methanolysis of **13** in the presence of HBr gave a 1:1 mixture of **13a** and **13**.

The ease with which α-ketol **13** forms from **12** under the indicated conditions is somewhat surprising, given that simple indanones seldom undergo rapid α-hydroxylation in air. However, perarylated indanones are known to readily undergo oxygenation upon formation of the corresponding enolate.[12]

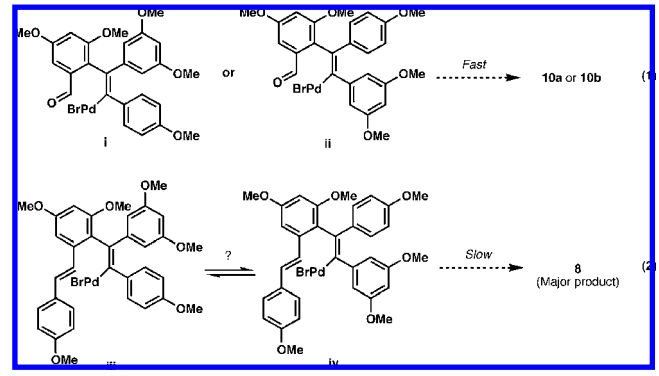
We were successful in circumventing the formation of α-ketol **13** by performing the hydrogenation of **10a** and subsequent epimerization at C(2) to yield **14** in one pot (Scheme 4), following the precedent of Zimmerman.[13] This one-pot protocol avoided the exposure of the incipient indenolate to oxidants such as molecular oxygen, which may promote α-hydroxylation.

During the course of our studies, careful inspection of the literature describing the two existing total syntheses of pauciflorol F[7b−d] exposed some discrepancies regarding the previously established structural assignments of three compounds related to the natural product.

The first manifestation of an inconsistency arose from comparison of the previously reported ^1H NMR data for permethylated pauciflorol F (**14**) and its *cis*-disposed analogue (i.e., **12**).[7d] It was reported that enolization of **14** with KHMDS and subsequent quenching with water afforded the product of kinetic proton capture (i.e., **12**), drawing from an analysis of a related system by Zimmerman.[13] However, the two doublets characteristic of the aliphatic hydrogens at C(2) and C(3) (see **14**) are absent from the data reported for **12**.[7d] Instead, two singlets are reported, one at 2.99 ppm (OH), which is shifted significantly upfield from what would be expected, and one at 4.62 ppm (CH). The spectral data associated with the compound reported as **12** were thus in good agreement with α-ketol **13**.[14]

Interestingly, it was also indicated that treatment of the compound previously assigned as **12** (which we now believe to be **13**) with BBr_3 did effect global phenol deprotection[7d] and yielded pauciflorol F (i.e., both **13** and **14** furnished pauciflorol F when treated with BBr_3, Scheme 6), albeit in low yield.[15] This surprising observation is also consistent

(11) On the basis of our previous observations during the synthesis of **8** (ref 8), we expected the reaction of **7** and **11** to proceed with good regiocontrol. The observed 1:1 regioselectivity in the formation of **10a** and **10b** may be the result of a fast cyclization of organopalladium intermediates **i** and **ii** (eq 1). If the analogous cyclization of organopalladium intermediates **iii** or **iv** is slow, a fast equilibration via de-carbopalladation may be favorable, which could have led to improved regioselectivity in the formation of **8**.

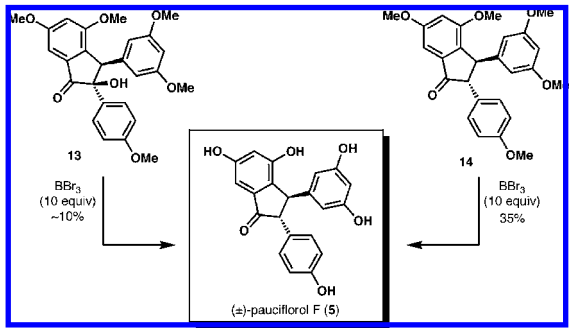


(12) (a) Alesso, E. N.; Finkielsztein, L. M.; Lantaño, B.; Bianchi, D. E.; Moltrasio Iglesias, G. Y.; Aguirre, J. M. *Aust. J. Chem.* **1997**, *50*, 149–152. (b) Marco, J. L. *Synth. Commun.* **1996**, *26*, 4225–4231.

(13) Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168–1173.

(14) For a detailed analysis and comparison of the ^1H NMR spectral data for **12**−**14**, see the Supporting Information.

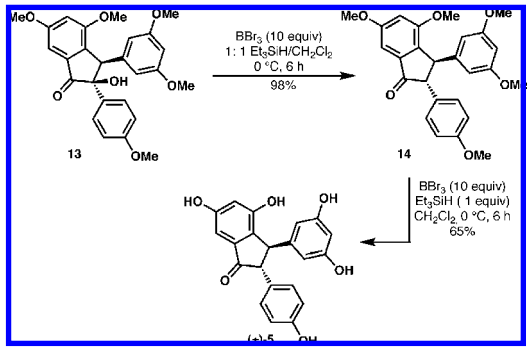
Scheme 6. BBr_3-Mediated Formation of Pauciflorol F



with data presented by She, Pan, and co-workers in their communication of the first total synthesis of pauciflorol F.[7b] Both reports suggested the feasibility of converting a compound consistent with **13** to pauciflorol F upon treatment with BBr_3. This transformation would require both global methyl ether cleavage and reductive removal of the C(2) hydroxyl group. Although we have also been successful in accomplishing the conversion of **13** and **14** to **5** using the reported conditions,[7b] the reported yield for the conversion of **13** to **5** by She and Pan (60% yield) was far greater than what we obtained (trace amounts).

To gain insight into the surprising conversion of **13** to **5** using BBr_3 in the absence of an added reductant,[16] we have conducted a series of studies to better understand this transformation, as illustrated in Scheme 7. The addition of

Scheme 7. Ionic Reductions of **13**



Et_3SiH significantly increases the efficiency of the transformation, suggesting an ionic reduction mechanism may be operative. Importantly, the use of 1 equiv of Et_3SiH and excess BBr_3 proved to be beneficial and converted **14** to pauciflorol F (**5**) in 65% yield.

Additionally, studies of several α-ketol compounds (see **17**−**20**, Figure 2) have revealed that the C(2) aryl substituent

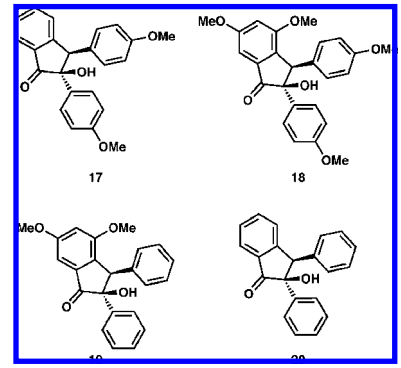


Figure 2. α-Ketol model compounds.

must possess a para-methoxy group (as in **17** and **18**) in order for the ionic reduction to proceed. α-Ketols **17** and **18** yielded 87% and 95% of the corresponding indanones upon exposure to BBr_3 and Et_3SiH,[17] whereas **19** and **20** were both unreactive under these conditions.

In conclusion, we have applied a palladium-catalyzed cascade reaction to the synthesis of the resveratrol-derived natural product pauciflorol F. The synthetic sequence is highly convergent and proceeds in three steps from tolane **7** and bromobenzaldehyde **11**. This simple resveratrol-derived compound should serve as a building block for more complex, functionally diverse analogues. Additionally, we have revised the structural assignments for the precursors of permethylated pauciflorol F, which demonstrate that hydroxylation of perarylated indanones is a facile process. Current efforts are focused on the optimization of the regiocontrol in the Larock annulation and its application to the preparation of more complex resveratrol-derived natural products.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Following our own studies in this area, it came to our attention that Snyder obtained low yields in the BBr_3-mediated phenol deprotection of the compound we now believe to be **13**. Snyder, S. A. Personal communication (Email correspondence on Sep 16, 2009).

(16) One possible mechanism for the reductive removal of the C(2) hydroxyl group of **13** involves a BBr_3-mediated disproportionation.

(17) For details, see the Supporting Information.