Tetrahedron Letters 50 (2009) 1969–1972

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An approach to the synthesis of dimeric resveratrol natural products via a palladium-catalyzed domino reaction

Jenna L. Jeffrey, Richmond Sarpong *

Department of Chemistry, University of California, Berkeley, CA 94720, USA

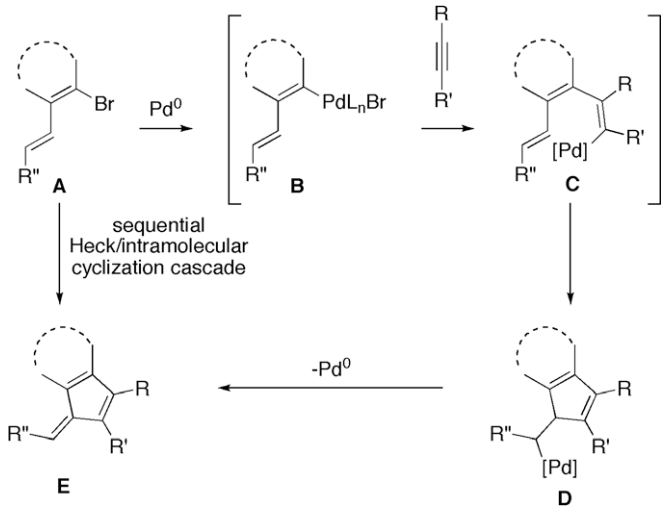
ARTICLE INFO

Article history:
Received 29 January 2009
Revised 6 February 2009
Accepted 10 February 2009
Available online 14 February 2009

ABSTRACT

A route for the rapid assembly of the carbon framework of several resveratrol natural products is presented. A palladium-catalyzed domino reaction of bromostilbene derivative **6** and tolane **7**, involving two sequential Heck coupling reactions, provides access to the benzofulvene-based core of various resveratrol-derived natural products. The carbon skeleton of pallidol and its congeners is achieved by a Lewis acid-induced Nazarov-type oxidative cyclization of **9**.

Palladium-catalyzed domino reactions, coupled with carefully designed substrates, allow for rapid establishment of molecular complexity in the total synthesis of complex natural products.[1] The addition of an aryl- or alkenylpalladium species to a triple or double bond provides an intermediate poised to participate in subsequent reactions. The reactive organopalladium intermediate may be trapped in various ways, for example, by reaction with an additional equivalent of a triple or double bond. Scheme 1 depicts one such scenario, involving a sequential Heck/intramolecular cyclization cascade.



Scheme 1. A Palladium-catalyzed cascade.

Exploiting the potential for domino sequences, multiple carbon-carbon bonds can be formed in a single synthetic operation through a palladium-catalyzed cascade. Furthermore, the sub-

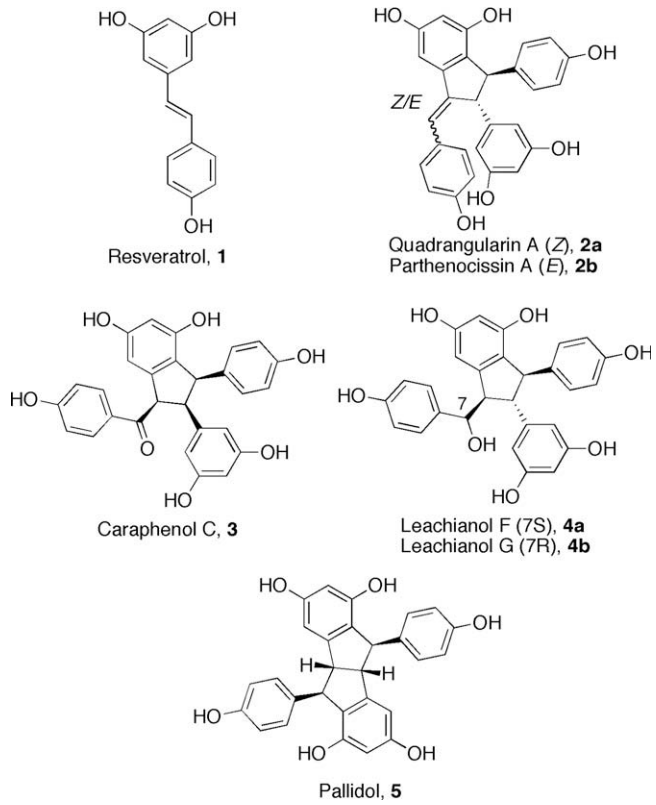


Figure 1. Selected resveratrol-derived natural products.

* Corresponding author. Tel.: +1 510 643 6312; fax: +1 510 642 9675.
E-mail address: rsarpong@berkeley.edu (R. Sarpong).

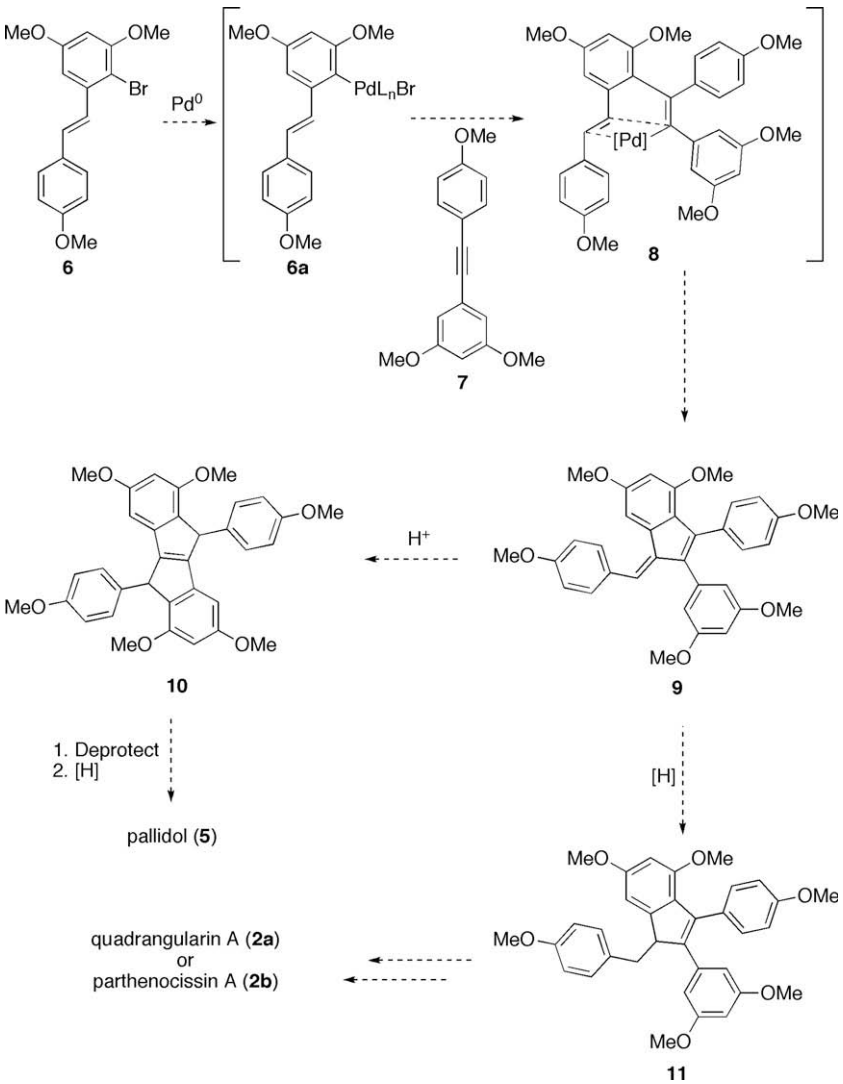
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.067

strates and reaction conditions may be tailored to produce a desired functional group or structural motif. For example, depending on the nature of the diene (**A**, Scheme 1)—cyclic, acyclic or aryl—a palladium-catalyzed cascade could give rise to either differentially substituted fulvene-based compounds or the analogous benzofulvene-containing structures (see **E**).

We recognized the potential utility of these palladium-catalyzed domino reactions in accessing the benzofulvene-based core of several biologically important resveratrol derivatives. Resveratrol (**1**, Fig. 1) was first isolated from the roots of *Veratrum grandiflorum* in 1940.[2] It was later classified as a phytoalexin (i.e., a toxin produced by plants in response to infection or stress).[3] In further biological studies, resveratrol displayed both anti-inflammatory and anti-carcinogenic properties in vivo,[4] and significantly extended the lifespan of vertebrates.[5] To date, the specific mechanism of action of resveratrol remains elusive due to its rapid metabolism. Several resveratrol-derived natural products have shown biological activities comparable to their parent monomer, for example, in vitro stimulation of osteoblast proliferation at concentrations as low as 10^{-10} g/mL.[6d] However, a thorough exploration of the properties and uses of resveratrol congeners requires efficient, facile, and versatile syntheses of these molecules.

In 2007, Snyder et al. reported a chemoselective approach to the synthesis of several polyphenolic natural products believed to result from resveratrol dimerizations.[7a,b] Snyder employed an easily accessible building block containing three aromatic rings, which was subjected to a series of electrophile-promoted cascades to complete the total syntheses of five resveratrol-based natural products, including quadrangularin A (**2a**) and pallidol (**5**).[7a] This strategy was recently extended to the synthesis of other members of the resveratrol class.[7b] A previous synthesis of quadrangularin based on a biomimetic dimerization of a resveratrol derivative has also been reported.[7c] In this Letter, we report our progress to date on a strategy for the synthesis of a subset of dimeric resveratrol-based natural products.

We sought to probe the synthetic versatility of a palladium-catalyzed cascade that would provide rapid access to several resveratrol-based natural products. Specifically, we envisioned a tandem Heck/intramolecular cyclization cascade between bromostilbene derivative **6** and tolane **7** (Scheme 2). In accordance with our proposed mechanism, we expected initial regioselective addition of the arylpalladium species **6a** to **7**, which we anticipated would be governed by the electronics of the aromatic ring substituents of **7**. Proximity-driven insertion of the resultant alkenylpalladium intermediate into the pendant double bond (see **8**) should afford



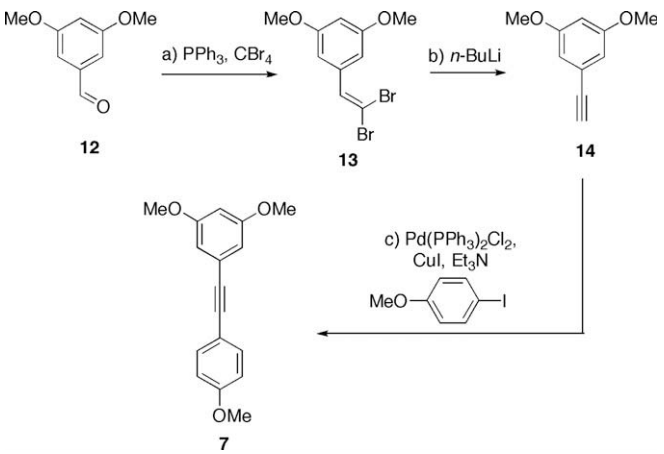
Scheme 2. Proposed cascade.

9 following β-hydride elimination. Such a cascade would form two carbon–carbon bonds in a single step to provide an intermediate containing all of the carbon atoms present in several important resveratrol derivatives.

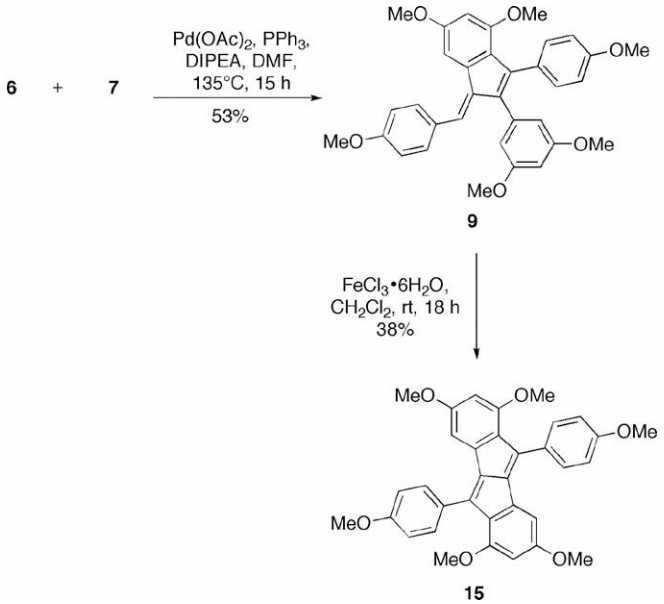
From common intermediate **9**, we anticipated that selective reduction of the exocyclic double bond could likely be achieved using the method employed by Katzenellenbogen and co-workers to reduce tri-substituted arylindenes.[8] Indene **11** could then serve as a precursor to either quadrangularin A (**2a**) or parthenocissin A (**2b**).

To access the carbon skeleton present in pallidol (**5**), we expected a Nazarov-type cyclization of **9** would provide **10**.[9] The methyl ethers could presumably be cleaved with BBr_3. Reduction of the tetrasubstituted double bond could then be achieved following the precedent of Brand and Krey (Scheme 2).[10]

Our synthetic investigations commenced with the preparation of bromide **6**. Following the procedure employed by Snyder et al., **6** was synthesized from commercially available 3,5-dimethoxybenzaldehyde (**12**) in five steps (75% overall yield).[7a] Tolane **7**[11] was also assembled from **12**. Under standard Ramirez olefination conditions, **12** was converted to dibromide **13** in 60% yield (Scheme 3).[12] Subsequent treatment with *n*-BuLi for 10 h, followed by quenching with water, afforded terminal alkyne **14** in 94% yield, completing a Corey–Fuchs sequence.[13,14] Finally, alkyne **14** was cross-coupled to *p*-iodoanisole under standard Sonogashira conditions to afford tolane **7** in 99% yield (56% overall yield from **12**).[15]



Scheme 3. Synthesis of tolane **7**. Reagents and conditions: (a) CBr_4 (2.0 equiv), PPh_3 (4.0 equiv), CH_2Cl_2, 0 °C, 1 h, 60%; (b) *n*-BuLi (2.8 equiv), THF, −78 °C→25 °C, 10 h, 94%; (c) CuI (0.1 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), Et_3N (0.1 M), 25 °C, 18 h, 99%.



Scheme 4. Synthesis of **9** and **15**.

Preliminary investigations confirmed the viability of our proposed cascade—when **6** and **7** were subjected to standard Heck conditions ($Pd(OAc)_2$, PPh_3, DIPEA, DMF, 135 °C, 15 h), **9**[16] was isolated as a bright red solid in 53% yield (Scheme 4). Slow diffusion of pentane into a solution of **9** in CH_2Cl_2 resulted in the formation of crystals suitable for X-ray diffraction. The ORTEP representation of **9** (Fig. 2) revealed an *E* orientation of the exocyclic double bond, as in parthenocissin A (**2b**).

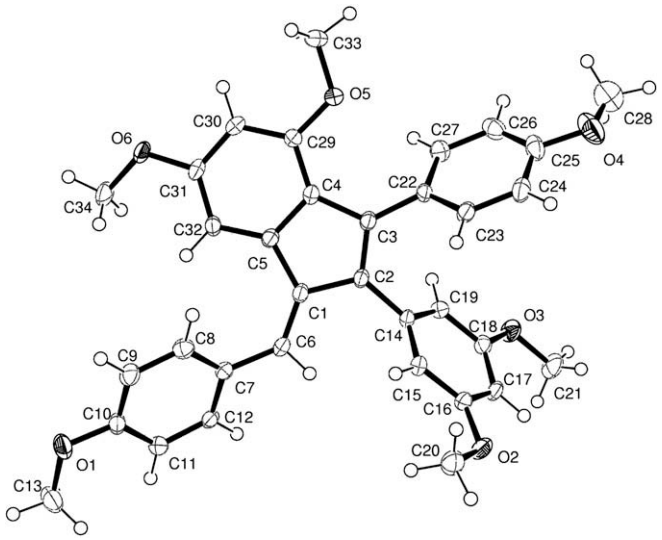


Figure 2. Molecular structure of **9**; ellipsoids drawn at the 50% probability level.

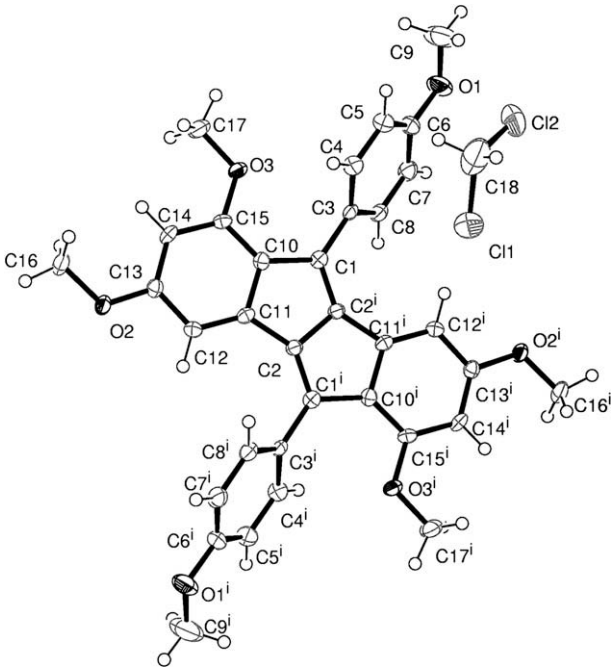


Figure 3. ORTEP representation of **15**; ellipsoids drawn at the 50% probability level.

With **9** in hand, a variety of Lewis and Bronsted acids were tested in an effort to form **10** via our proposed Nazarov-type cyclization (Scheme 2). We found success with the treatment of **9** with $FeCl_3{\cdot}6H_2O$ (1 equiv) in CH_2Cl_2 to yield diene **15**[17] in 38% yield as a maroon solid (Scheme 4). Although **10** was not observed, pentalene **15** could presumably have formed via the intermediacy of **10**, which was likely oxidized under the reaction conditions. Alternatively, **15** may have resulted directly from **9** via a cyclodehydrogenation in keeping with the precedent of Kovacic.[18] Slow evaporation of a CH_2Cl_2 solution of **15** yielded X-ray quality crystals, which confirmed the connectivity of **15** (Fig. 3). Attempts to reduce **15**, as well as the exo- and endocyclic double bonds of **9**, are ongoing.

In conclusion, we have demonstrated a novel palladium-catalyzed cascade reaction, which assembles the carbon framework of several resveratrol-derived natural products. Starting from two readily accessible building blocks, we have synthesized potential precursors to a large family of natural products, including quadrangularin A, parthenocissin A, and pallidol. Studies on the functionalization of these compounds and completion of the total syntheses of a series of resveratrol-based natural products are underway and will be reported in due course.

Acknowledgments

The authors are grateful to UC Berkeley and the NIH (NIGMS GM84906-01) for generous financial support. We would also like to thank Dr. Antonio DiPasquale for obtaining the X-ray structures of **9** and **15**.

Supplementary data

Experimental details and characterization data for all new compounds; X-ray structures of **9** and **15**, structure refinement details, tables of atomic coordinates, thermal parameters, bond lengths, and bond angles. This material is available upon request from the authors. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 718629 and 718630. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.067.

References and notes

1. For a review of domino reactions in organic synthesis, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; For a review of the Heck reaction in modern synthesis and a list of several examples of palladium-catalyzed cascade reactions, see: (b) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411.
2. Takaoka, M. *Proc. Imp. Acad. Tokyo* **1940**, *16*, 405–407.
3. Langcake, P.; Pryce, R. J. *Physiol. Plant Pathol.* **1976**, *9*, 77–86.
4. 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.
5. Valenzano, D. R.; Terzibasi, E.; Genade, T.; Cattaneo, A.; Domenici, L.; Cellerino, A. *Curr. Biol.* **2006**, *16*, 296–300.
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, ; Hakim, E. H.; Juliawaty, L. D.; Syah, Y. M.; bin Din, L.; 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. (a) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186–8191; b Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**. doi: 10.1021/ja806183r.; (c) Li, W.; Li, H.; Li, Y.; Hou, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 7609–7611.
8. Anstead, G. M.; Ensign, J. L.; Peterson, C. S.; Katzenellenbogen, J. A. *J. Org. Chem.* **1989**, *54*, 1485–1491.
9. (a) Nazarov, I. N.; Zaretskaya, I. I. *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.* **1942**, 200–209; For a review of the Nazarov cyclization, see: (b) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1–158.
10. Brand, K.; Krey, W. *J. Prakt. Chem.* **1925**, *110*, 10–25.
11. **7**: To a solution of *p*-iodoanisole (0.100 g, 0.427 mmol), $Pd(PPh_3)_2Cl_2$ (0.015 g, 0.0214 mmol), and CuI (0.0081 g, 0.0427 mmol) in Et_3N (5 mL) under N_2 was added ethynylbenzene **14** (0.0970 g, 0.598 mmol). The solution was stirred at rt for 18 h. The solvent was removed in vacuo and the crude brown residue was purified by flash chromatography (6:1 hexanes/EtOAc) to give 0.113 g (99% yield) of 7 as a colorless oil. R_f 0.52 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.67 (s, 2H), 6.43 (s, 1H), 3.80 (s, 3H), 3.77 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.72, 159.88, 133.32, 125.07, 115.36, 114.20, 110.37, 109.37, 103.12, 101.74, 89.18, 88.28, 81.78, 55.62; IR (film) ν_{max} 3002, 2957, 2935, 2837, 2216, 1650, 1588, 1511, 1452, 1419, 1357, 1347, 1290, 1248, 1205, 1156, 1121, 1064, 1031 cm^{-1}; HRMS (ESI) m/z 269.1178 [$(M+H)^+$; calcd for $[C_{17}H_{17}O_3]^+$: 269.1172].
12. Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747.
13. (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772; For a review of alkyne synthesis using phosphorous compounds, see: (b) Eymery, F.; Iorga, B.; Savignac, P. *Synthesis* **2000**, 185–213.
14. Nakamura, H.; Kuroda, H.; Saito, H.; Suzuki, R.; Yamori, T.; Maruyama, K.; Haga, T. *Chem. Med. Chem.* **2006**, *1*, 729–740.
15. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470; For a review of organopalladium chemistry in organic synthesis, see: (b) Sonogashira, K. *Synthesis* **2002**, *1*, 493–529.
16. Compound **9**: To a flame-dried Schlenk tube containing $Pd(OAc)_2$ (0.007 g, 0.031 mmol) and triphenylphosphine (0.016 g, 0.062 mmol) was added a solution of bromide **6** (0.050 g, 0.154 mmol), tolane **7** (0.081 g, 0.301 mmol), and *N*,*N*-diisopropylethylamine (DIPEA) (0.08 mL, 0.461 mmol) in DMF (1 mL) via syringe. The combined reaction mixture was evacuated, backfilled with N_2 ($\times$3), sealed, and heated in an oil bath at 135 °C for 15 h. The reaction mixture was allowed to cool to rt, diluted with Et_2O (10 mL), and washed with 1% aqueous HCl (3 $\times$ 5 mL). The combined aqueous washings were reextracted with Et_2O (2 $\times$ 5 mL). The combined organic extracts were washed with 1% aqueous HCl (5 mL), brine (2 $\times$ 5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a dark red residue. The crude product was purified by flash chromatography (12:1 hexanes/EtOAc) to afford 0.0437 g (53% yield) of **9** as a bright red solid. R_f 0.70 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 3H), 7.03 (s, 1H), 6.99 (s, 1H), 6.92 (d, J = 5.0 Hz, 2H), 6.79 (m, 2H), 6.41 (m, 2H), 6.37 (m, 1H), 6.29 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.70 (m, 3H), 3.62 (s, 6H), 3.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.15, 159.44, 159.27, 158.44, 158.33, 141.19, 140.64, 139.63, 138.90, 137.95, 137.40, 132.47, 131.38, 131.10, 129.46, 127.90, 124.58, 124.43, 113.98, 113.96, 113.44, 112.44, 109.82, 108.49, 102.04, 99.70, 99.58, 99.03, 55.83, 55.66, 55.64, 55.55, 55.42, 55.32; IR (film) ν_{max} 2998, 2936, 2836, 1591, 1559, 1540, 1509, 1462, 1421, 1282, 1247, 1203, 1174, 1153, 1105, 1065 cm^{-1}; HRMS (ESI) m/z 536.2198 [(M^+); calcd for $[C_{34}H_{32}O_6]^+$: 536.2199]; mp 158–159 °C.
17. Compound **15**: To a solution of **9** (0.0171 g, 0.0319 mmol) in CH_2Cl_2 (1 mL) was added $FeCl_3{\cdot}6H_2O$ (0.009 g, 0.0319 mmol). The reaction mixture was stirred at rt for 18 h, diluted with CH_2Cl_2 (5 mL), washed with water (3 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc) to give 0.0065 g (38% yield) of **15** as a maroon solid. R_f 0.50 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.8 Hz, 4H), 6.91 (d, J = 8.8 Hz, 4H), 6.37 (d, J = 2.0 Hz, 2H), 5.95 (d, J = 2.0 Hz, 2H), 3.85 (s, 6H), 3.64 (s, 6H), 3.52 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.71, 159.61, 156.22, 146.79, 142.30, 140.10, 139.14, 130.78, 128.11, 118.08, 112.79, 101.68, 98.47, 97.19, 69.72, 55.57, 55.47, 55.45, 53.98; IR (film) ν_{max} 2927, 1596, 1508, 1462, 1390, 1360, 1246, 1200, 1151, 1085 cm^{-1}; HRMS (ESI) m/z 534.2035 [(M^+); calcd for $[C_{34}H_{30}O_6]^+$: 534.2042]; mp 242–243 °C.
18. Kovacic, P.; Jones, M. B. *Chem. Rev.* **1987**, *87*, 357–379.