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

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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, e.g., 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.

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 substrates 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**, Figure 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

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Supplementary Material

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).

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metabolism. Several resveratrol-derived natural products have shown biological activities comparable to their parent monomer, e.g., *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 Communication, 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 accord 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 **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 selective reduction of the exocyclic double bond could likely be achieved using the method employed by Katzenellenbogen *et al.* 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 *et al.* (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

Preliminary investigations confirmed the viability of our proposed cascade—when **6** and **7** were subjected to standard Heck conditions ($\text{Pd}(\text{OAc})_2$, 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** (Figure 2) revealed an *E* orientation of the exocyclic double bond, as in parthenocissin A (**2b**).

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 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (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** (Figure 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

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11. 7: To a solution of *p*-iodoanisole (0.100 g, 0.427 mmol), Pd(PPh₃)₂Cl₂ (0.015 g, 0.0214 mmol), and CuI (0.0081 g, 0.0427 mmol) in Et₃N (5 mL) under N₂ 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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)⁺; calculated for [C₁₇H₁₇O₃]⁺: 269.1172].
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16. 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), toluene 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 N₂ (x 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 Et₂O (10 mL) and washed with 1% aqueous HCl (3 × 5 mL). The combined aqueous washings were reextracted with Et₂O (2 × 5 mL). The combined organic extracts were washed with 1% aqueous HCl (5 mL), brine (2 × 5 mL), dried over MgSO₄, 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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⁺); calculated for [C₃₄H₃₂O₆]⁺: 536.2199]; MP 158–159 °C.
17. 15: To a solution of 9 (0.0171 g, 0.0319 mmol) in CH₂Cl₂ (1 mL) was added FeCl₃•6H₂O (0.009 g, 0.0319 mmol). The reaction mixture was stirred at rt for 18 h, diluted with CH₂Cl₂ (5 mL), washed with water (3 mL), brine (5 mL), dried over MgSO₄, 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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⁺); calculated for [C₃₄H₃₀O₆]⁺: 534.2042]; MP 242–243 °C.
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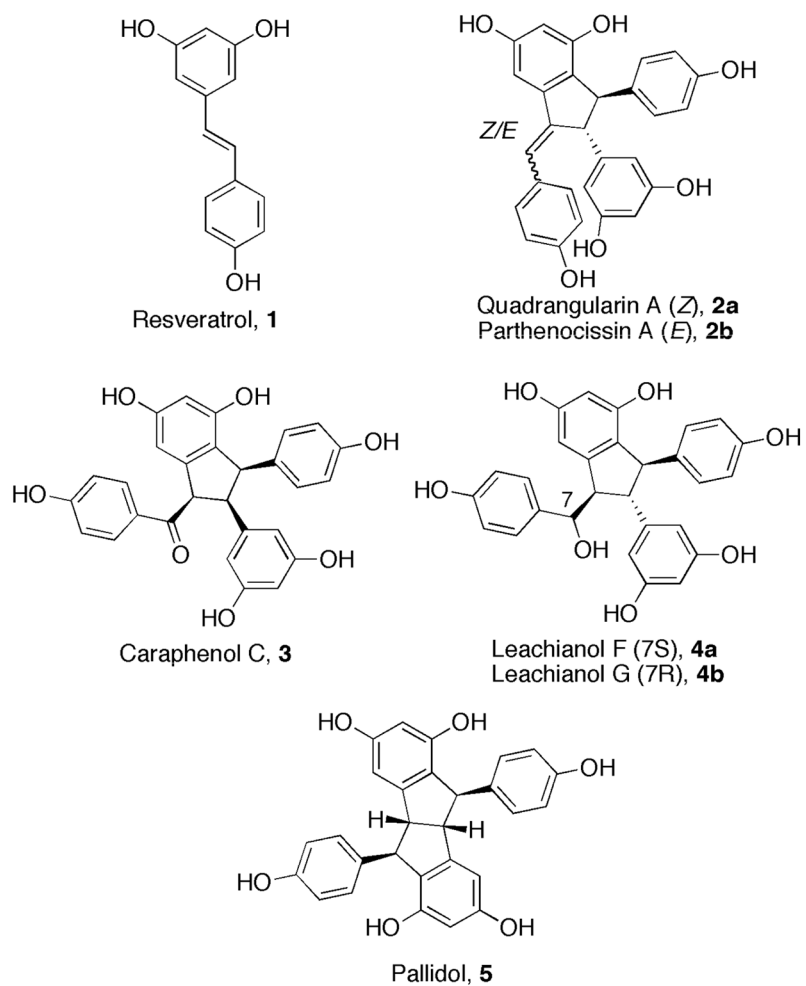


FIGURE 1.
Selected resveratrol-derived natural products.

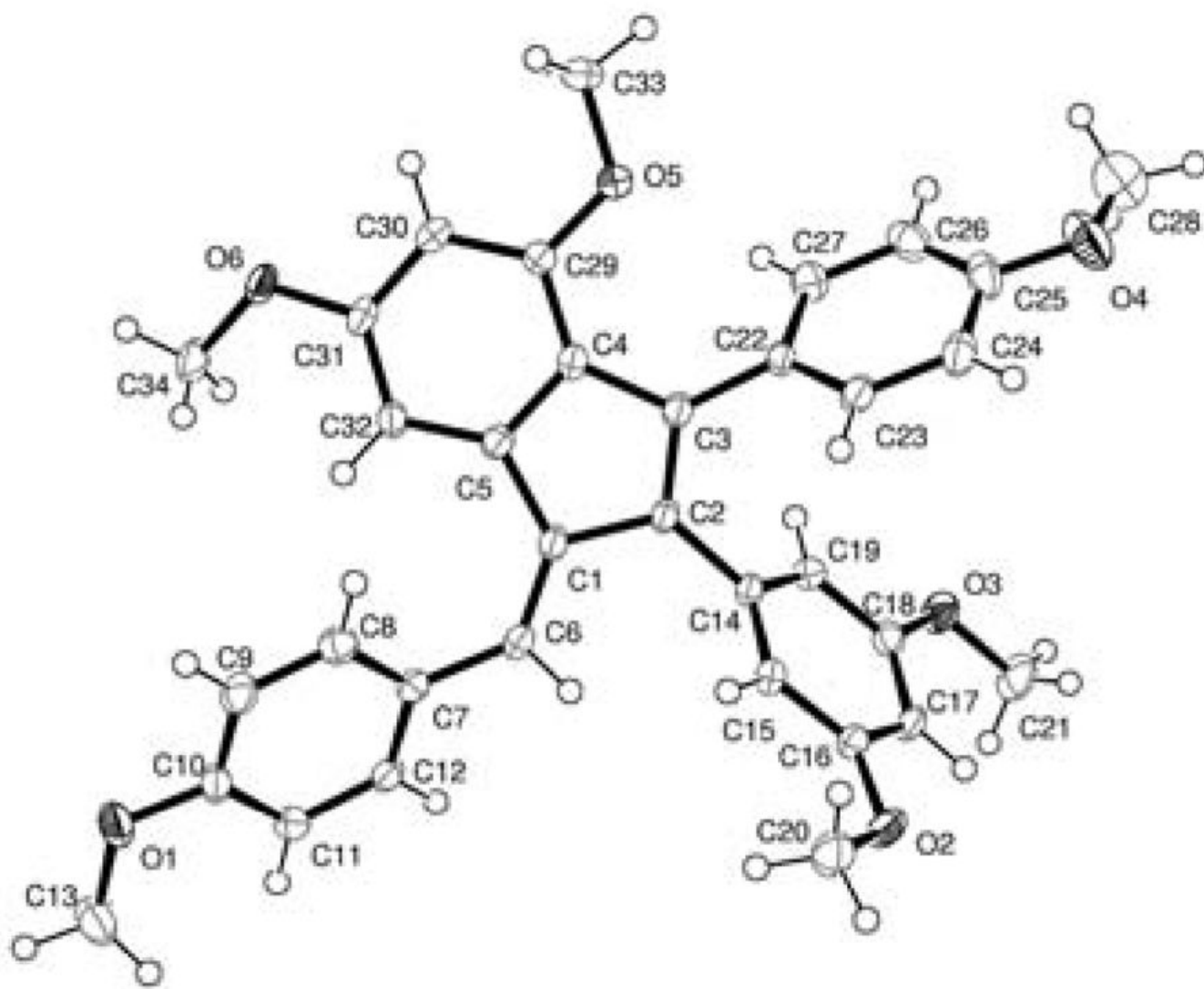


FIGURE 2.
Molecular structure of **9**; ellipsoids drawn at the 50% probability level.

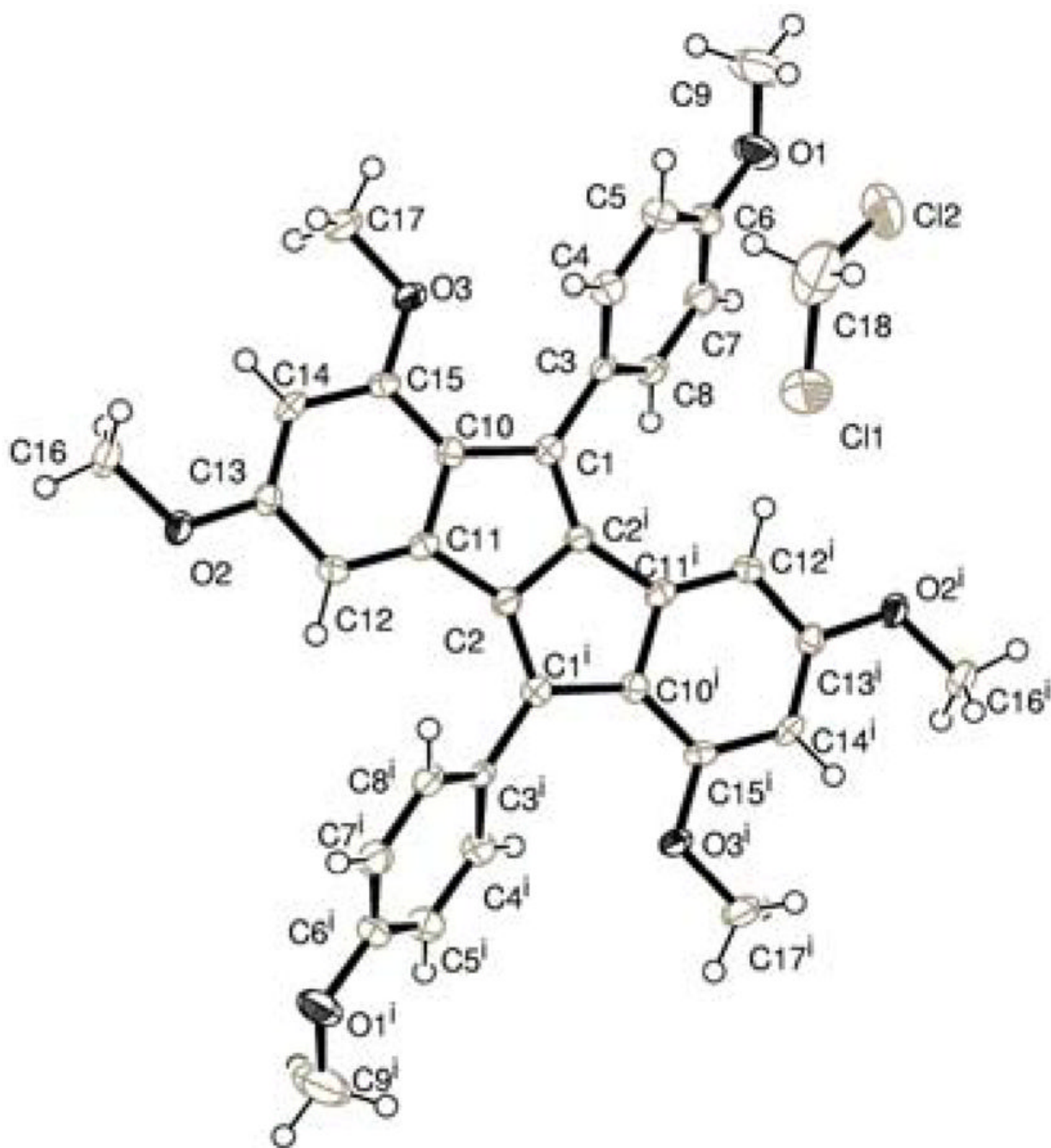
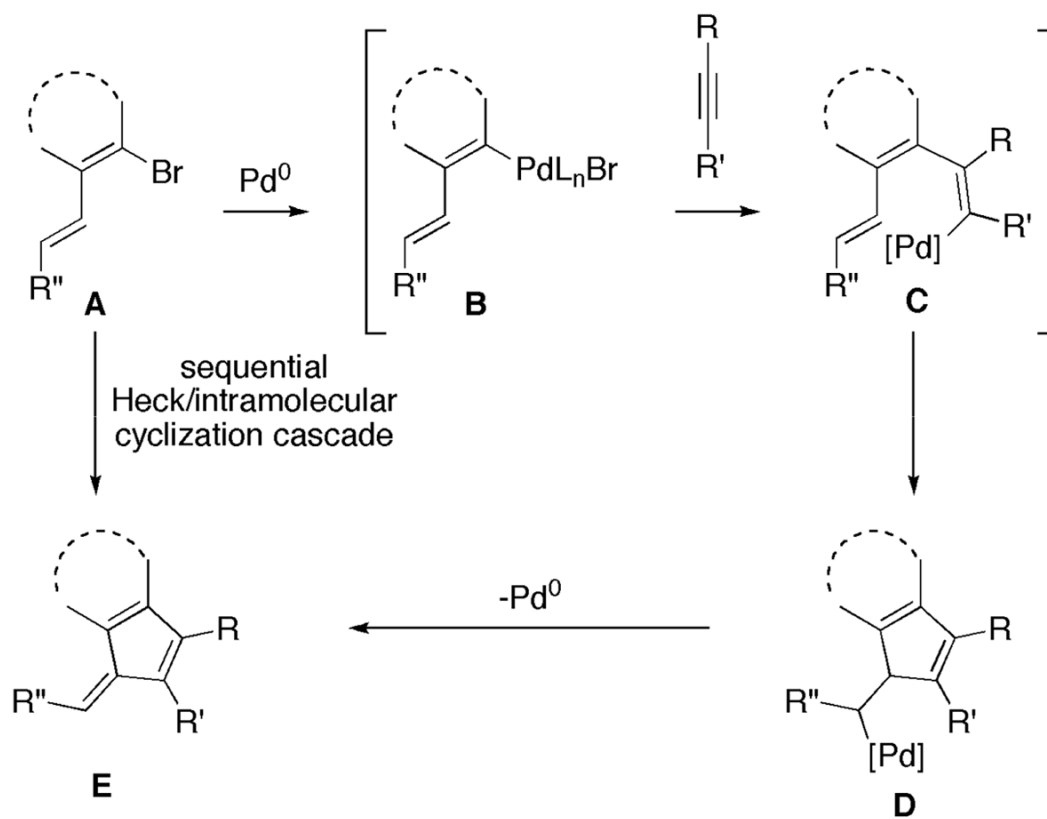
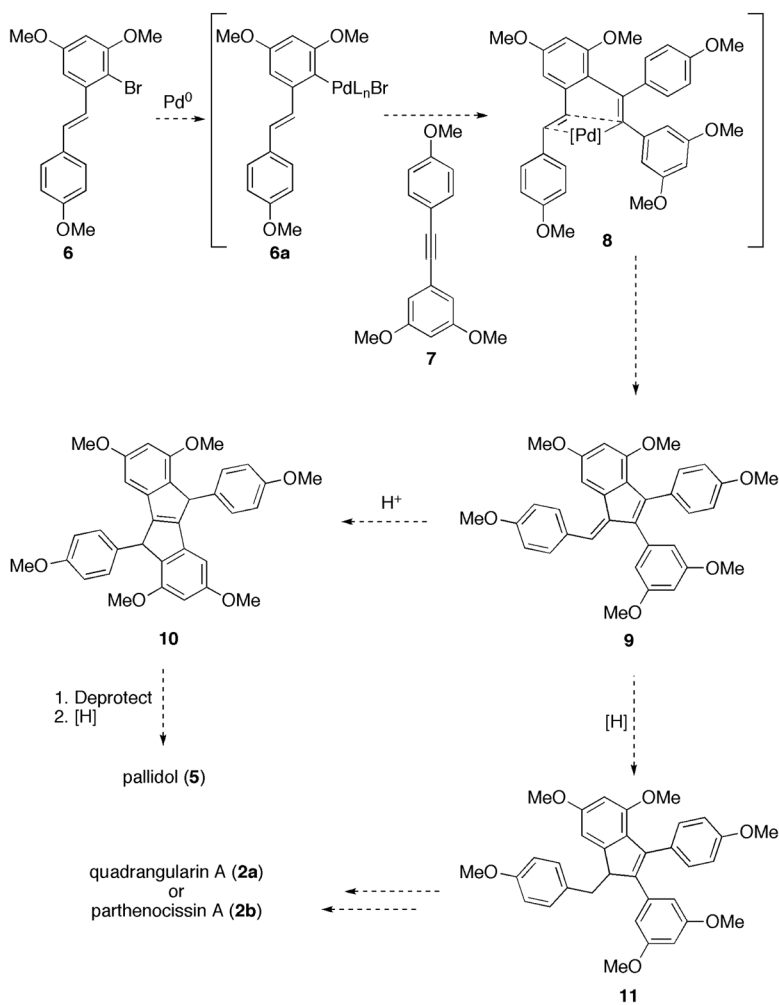


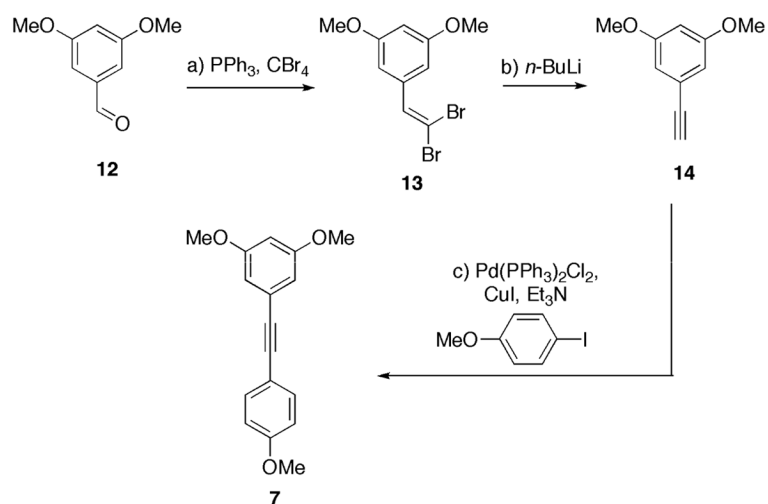
FIGURE 3.
ORTEP representation of **15**; ellipsoids drawn at the 50% probability level.



SCHEME 1.
A Palladium-Catalyzed Cascade

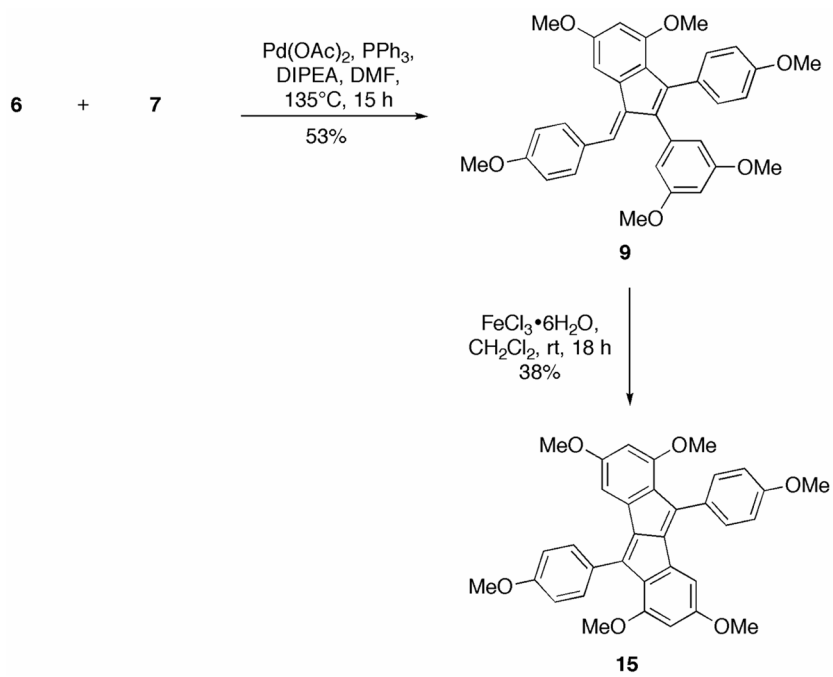


SCHEME 2.
Proposed Cascade

**SCHEME 3.**

Synthesis of Tolane 7

a) CBr_4 (2.0 equiv), PPh_3 (4.0 equiv), CH_2Cl_2 , 0°C , 1 h, 60%; b) $n\text{-BuLi}$ (2.8 equiv), THF, $-78^\circ\text{C} \rightarrow 25^\circ\text{C}$, 10 h, 94%; c) CuI (0.1 equiv), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.05 equiv), Et_3N (0.1 M), 25°C , 18 h, 99%.



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