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Studies Directed toward the Synthesis of Hamigeran B: A Catalytic Oxidative Cyclization

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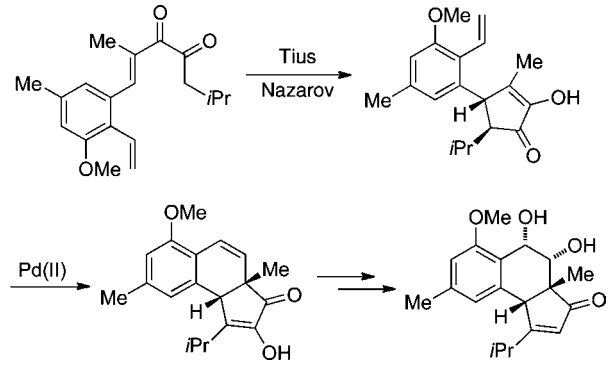
ABSTRACT

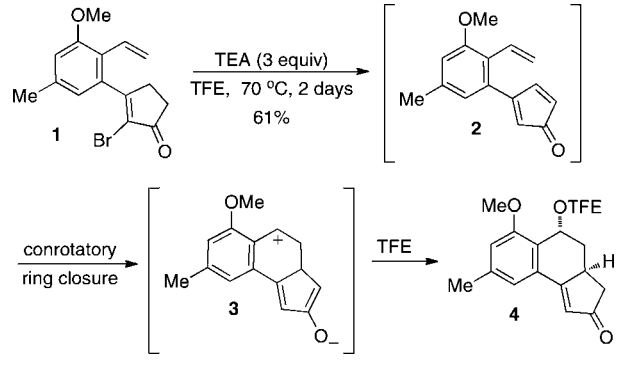


An approach to the synthesis of hamigeran B is described. Key steps include a Tius−Nazarov cyclization and a palladium-catalyzed oxidative cyclization of an α-hydroxyenone.

We recently reported the electrocyclization of a series of cyclopentadienones under relatively mild conditions.[1] For example, treatment of **1** with triethylamine (TEA) in trifluoroethanol (TFE) afforded **4** through the intermediacy of **2** and **3** (Scheme 1). Compound **4** possesses the carbocyclic skeleton of the antiviral agent hamigeran B (**5**),[2] whose activity against the polio and herpes viruses, coupled with low cytotoxicity, has made it an attractive target for synthesis.[3]

A precursor for **5** that would use the methodology exemplified in Scheme 1 would contain a methyl group as shown in compound **6**. Unfortunately, treatment of **6** with base under our standard conditions resulted only in the isolation of **7** in low yield (Scheme 2).[4] Rather than abandon the target, we realized that precursors similar to those we would use for the cyclopentadienone electrocyclization could also be used for other carbon−carbon bond forming pro-

Scheme 1. Electrocyclization of a Cyclopentadienone



(1) Harmata, M.; Zheng, P.; Schreiner, P. R.; Navarro-Vazquez, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1966. (b) Harmata, M.; Zheng, P.; Schreiner, P. R.; Navarro-Vazquez, A. *Tetrahedron Lett.* **2007**, *48*, 5919.
(2) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79.

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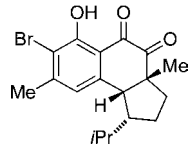
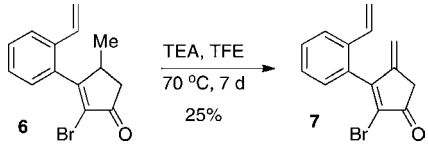


5, hamigeran B

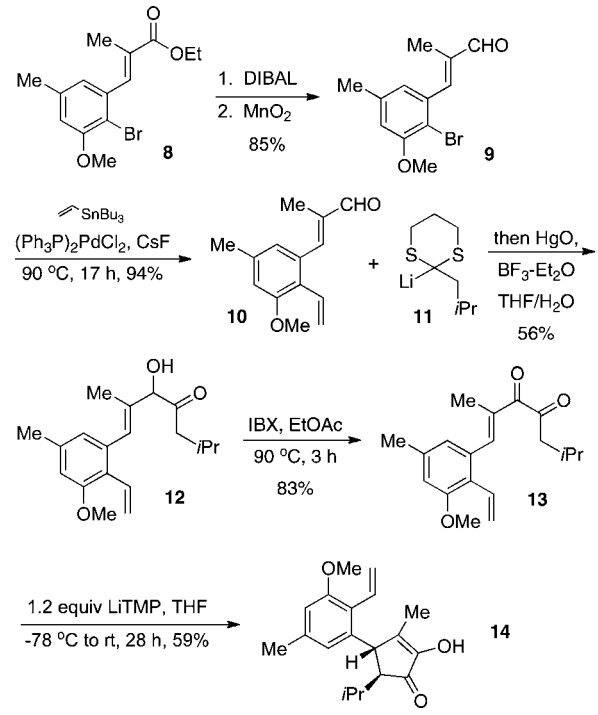
cesses that could lead to the synthesis of hamigeran B and various congeners. We describe herein our progress toward that goal.

Scheme 2



Our original plan called for the synthesis of **14**, whose enolic hydroxy group would be activated in some way to allow elimination, but we realized that enol could also function as a nucleophile, as will be seen. The synthesis of **14** is shown in Scheme 3. The readily available ester **8**[5] was reduced with DIBAL and oxidized to the corresponding aldehyde with excess MnO_2 in excellent overall yield. A Stille coupling with tributylvinyl stannane gave **10**, which could also be prepared by a Suzuki coupling with the pinacol boronate ester of vinyl boronic acid in high yield.[6] The reaction of **10** with the dithiane organolithium **11**[7] led to the ketol **12** after hydrolysis in 56% yield. Oxidation of this compound with IBX[8] afforded the dione **13**, which was cyclized according to the Tius protocol[9] by treatment with LiTMP from −78 °C to room temperature affording **14** in 59% yield.[10] The relative stereochemistry of **14** was assigned on the basis of the anticipated stereochemistry of the intermediate enolate and the selection rules for electrocyclization, which call for a conrotatory ring closure in Nazarov and related cyclizations.[11] However, since the stereogenic

Scheme 3. Synthesis of Compound **14**



center bearing the isopropyl group will be destroyed, for this particular purpose the relative stereorelationships in **14** are not of importance.[12]

We did, in fact, prepare the triflate of **14** and treat it with various bases to attempt cyclopentadienone formation, but none of these experiments were productive. However, we were inspired by a paper by Widenhoefer[13] concerning the intramolecular oxidative cyclization of simple alkenes with β-diketones. We thus treated **14** under the Wacker reaction conditions associated with this process and were pleased to find that cyclization occurred smoothly to afford **17** in high yield. The process presumably took place via nucleophilic attack of the enol of **14** on the styryl double bond, which had been activated by Pd(II) as in the case of **15**. Palladium hydride elimination from **16** then afforded **17**. Regeneration of Pd(II) took place by the typical Cu(I) to Cu(II) cycle illustrated in Scheme 4. It is noteworthy that the use of α-hydroxyenones as nucleophiles is rather rare, and we venture to anticipate that many other opportunities to discover their synthetic utility exist.[14]

Compound **17** was actually obtained as a mixture of the dione containing varying amounts of the enol **18**, and isomerization with triethylamine in the presence of some silica gel to give **18** proved relatively facile (Scheme 5).

(3) For a review of the area, see: (a) Clive, D. L. J.; Wang, J. *Org. Prep. Proced. Int.* **2005**, *37*, 1. For relevant work appearing after the review, see: (b) Miesch, L.; Welsch, T.; Rietsch, V.; Miesch, M. *Chem.—Eur. J.* **2009**, *15*, 4394. (c) Taber, D. F.; Tian, W. *J. Org. Chem.* **2008**, *73*, 7560. (d) Arnaiz, E.; Blanco-Urgoiti, J.; Abdi, D.; Dominguez, G.; Castells, J. P. *J. Organomet. Chem.* **2008**, *693*, 2431. (e) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem.—Eur. J.* **2005**, *11*, 951. (f) Sperry, J. B.; Wright, D. L. *Tetrahedron Lett.* **2005**, *46*, 411.

(4) Zheng, P.; Harmata, M. Unpublished results from these laboratories.

(5) Harmata, M.; Hong, X. *Org. Lett.* **2004**, *6*, 2201.

(6) See Supporting Information.

(7) Kayser, M. M.; Zhao, H.; Chen, G.; Feicht, A. *ARKIVOC (Gainesville, FL, U.S.)* **2002**, *12*, 47.

(8) Moore, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

(9) (a) Batson, W. A.; Sethumadhavan, D.; Tius, M. A. *Org. Lett.* **2005**, *7*, 2771. (b) Uhrich, E. A.; Batson, W. A.; Tius, M. A. *Synthesis* **2006**, *13*, 2139.

(10) When the reaction was conducted with LiHMDS, the yield was only 44%.

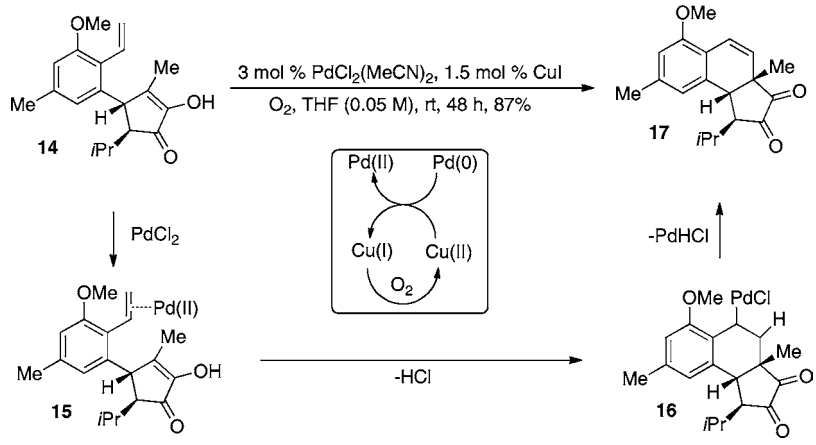
(11) (a) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732. (b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (d) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.

(12) It is worth noting that a slight light broadening in the proton NMR of **14** suggested hindered rotation, presumably about the bond between the cyclopentyl and arene rings. This phenomenon has yet to be studied.

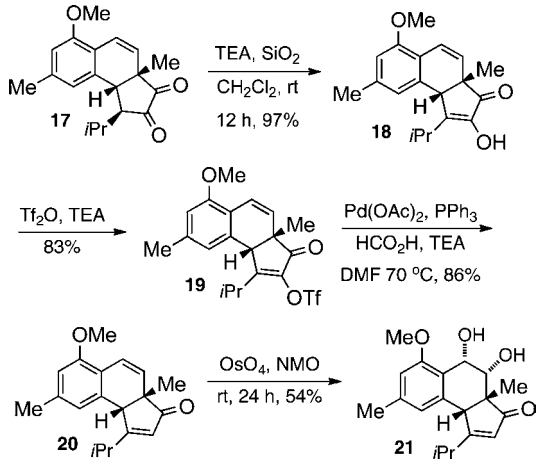
(13) (a) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (b) Liu, C.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem.—Eur. J.* **2004**, *10*, 6343.

(14) Trost, B. M.; Dong, G.; Wance, J. A. *Chem.—Eur. J.* **2010**, *16*, 6265.

Scheme 4. Oxidative Cyclization of **14**



Scheme 5. Preparation of an Advanced Intermediate



Functionalization of **18** as a triflate and palladium-catalyzed reduction gave **20** in very good overall yield. The dihydroxylation of **20** was conducted under standard conditions and afforded **21** in moderate yield. Although NMR data convinced us of the structures of our intermediates, it was gratifying to find that **21** was a crystalline solid and its structure was confirmed by X-ray analysis.

In summary, we have prepared a highly functionalized intermediate toward the synthesis of hamigeran B using a Tius−Nazarov cyclization and an oxidative cyclization in which the enol form of an α-diketone served as the nucleophilic agent. Efforts to convert this intermediate (**21**) to hamigeran B are in progress and further study of the chemistry of α-hydroxyenones is in progress, and results will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for new compounds and X-ray crystallographic data of compound **21** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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