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A Catalytic, Asymmetric Formal Synthesis of (+)-Hamigeran B

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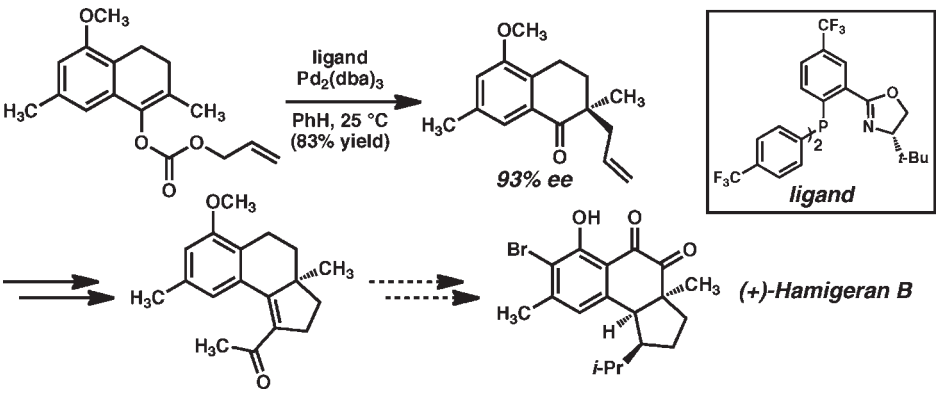

A concise asymmetric, formal synthesis of (+)-hamigeran B is reported. A Pd-catalyzed, decarboxylative allylic alkylation, employing a trifluoromethylated derivative of *t*-BuPHOX, is utilized as the enantioselective step to form the critical quaternary carbon center in excellent yield and enantioselectivity. The product is converted in three steps to a late-stage intermediate previously used in the synthesis of hamigeran B.

The hamigerans are a family of molecules isolated from the poecilosclerid sponge *Hamigera tarangaensis* by Bergquist and Fremont (family Anchinoidae, syn. Phorbasidae) in 2000 from the Hen and Chicken Islands off the eastern coast of New Zealand.[1] Hamigeran B (**1**), which has been of particular interest due to its potent in vitro activity against the P-388 leukemia cell line and against both herpes and polio viruses with little cytotoxicity against the host cells,[1] has a unique tricarbocyclic skeleton possessing a substituted aromatic system fused to a [4.3.0] bicycle containing three contiguous stereocenters and, as such, has received continued attention from synthetic chemists.[2,3]

Previous syntheses of hamigeran B have utilized a photoinitiated intramolecular [4 + 2] cycloaddition of a hydroxy-*o*-quinodimethane by Nicolaou,[4] Meyers' amino-alcohol auxiliary by Clive and Wang,[5] a Pd-catalyzed

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(5) (a) Clive, D. L. J.; Wang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3406–3409. (b) Clive, D. L. J.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 7731–7733. (c) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773–2784.

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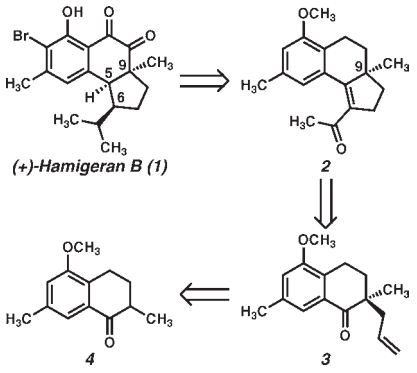
Scheme 1. Retrosynthetic Analysis of (+)-Hamigeran B



asymmetric allylic alkylation followed by an intramolecular Heck reaction by Trost,[6] and an intramolecular Rh-mediated C−H insertion of a α-aryl−α-diazoketone followed by a Friedel−Crafts cyclization by Taber and Tian[7] in the construction of the carbocyclic core. Most recently, Miesch and co-workers performed a racemic total synthesis in which an intramolecular, alkynylogous Mukiyama aldol reaction was utilized to form the tricyclic core.[8,9] Importantly, they also showed that the stereochemistry at C(9) of **2** can been used to set the proper relative stereochemistry at C(5) and C(6). Herein, we report a catalytic, asymmetric formal synthesis of (+)-hamigeran B via interception at Miesch and co-workers' enone **2**.

Our retrosynthetic analysis of hamigeran B (Scheme 1) thus focused on efficiently generating the absolute stereochemistry of the all-carbon quaternary stereocenter at C(9) of enone **2**. With the goal of setting this stereocenter via an enantioselective, decarboxylative alkylation,[10] we envisioned first disconnecting the cyclopentene ring of **2** via an aldol condensation to α-allyl tetralone **3**, which could be accessed via the asymmetric allylation chemistry developed within our group,[11] from tetralone **4** as the key racemic starting material.

Studies for the enantioselective synthesis of tetralone **3** focused on the asymmetric, decarboxylative allylic alkylation of allyl enol carbonate **5**, available in 91% yield from known tetralone **4**[12,5a,5c] (Scheme 2). Preliminary investigation of the alkylation reaction of **5** used 4 mol % of the complex derived from $Pd_2(dba)_3$ and (*S*)-*t*-BuPHOX (**6**) as ligand in THF at 35 °C to afford the desired tetralone **3** with moderate yield and good enantioselectivity (Table 1, entry 1). Screening of various solvents with the use of **6** as ligand[13] revealed that benzene provides the highest levels of enantioselectivity and yield (entry 3). It was also found that the trifluoromethylated derivative of (*S*)-*t*-BuPHOX (i.e., **7**)[14] resulted in higher enantiomeric excesses and shorter reaction times, even with the use of only 1 or 2 mol % of catalyst (entries 4−6). Lowering the reaction temperature to 25 °C resulted in the formation of **3** in 94% ee, with the use of only 2 mol % of $Pd_2(dba)_3$ and 5 mol % of ligand **7**, albeit with a reduction in rate and yield (entry 7).

Having effectively set the absolute stereochemistry of the all-carbon quaternary center, C(9), we turned our efforts toward achieving the formal total synthesis of (+)-hamigeran B through the formation of the cyclopentene ring of **2** (Scheme 2). Ru-catalyzed cross metathesis[15] of olefin **3** with methyl vinyl ketone using catalyst **8**[16] affords diketone **9** in 66% yield. Our initial attempts to form the cyclopentyl ring of the target structure (i.e., either enone **2** or alcohol **11**) via traditional aldol condensation reactions resulted in complex mixtures of products, presumably due to nonselective enolization of diketone **10**.[17] Hoping to utilize the α,β-unsaturation of enone **9** to ensure regioselective enolate formation,[18] we attempted to directly form the cyclopentene ring from compound **9**. CuH-mediated,[19] domino conjugate reduction−cyclization of **9** using Stryker's reagent[20] at 0 °C afforded desired ketoalcohol **11** as a single diastereomer, albeit in low yields (10−20%) with the remainder of the starting material converting to conjugate reduction product **10**. It was found, however, that decreasing the temperature of the reaction to −40 °C resulted in an improved 52% yield of desired product **11** and only a 26% yield of conjugate reduction product **10**. Alcohol **11** was then dehydrated with $SOCl_2$ and catalytic DMAP in pyridine[21] to afford

(6) (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480–4481. (b) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem.—Eur. J.* **2005**, *11*, 951–959.

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(9) While preparing this manuscript, a synthesis of (±)-**1** appeared; see: Lau, S. Y. W. *Org. Lett.* **2011**, *13*, 347–349.

(10) For a review, see: Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476–1491.

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(12) von Ruzicka, L.; Hösli, H.; Hofmann, K. *Helv. Chim. Acta* **1936**, *19*, 370–377.

(13) For list of solvents screened, see Supporting Information.

(14) (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

(15) For a review, see: Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

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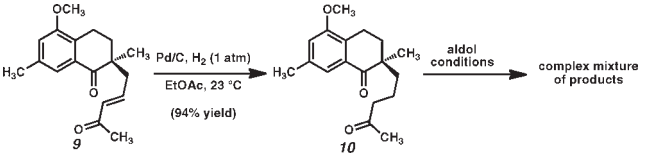
(17) Diketone **10** was accessed by hydrogenation of enone **9**. Subjecting **10** to a variety of aldol conditions led to complex product mixtures. For this reason, this strategy was not pursued further.



(18) For a review, see: Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12–21.

(19) For a review, see: Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927.

(20) Chiu, P.; Szeto, C.; Geng, Z.; Cheng, K. *Org. Lett.* **2001**, *3*, 1901–1903.

(21) (a) Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213–5225. (b) Hagiwara, H.; Takeuchi, F.; Nozawa, M.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2004**, *60*, 1983–1989.

Scheme 2. Enantioselective Formal Synthesis of (+)-Hamigeran B

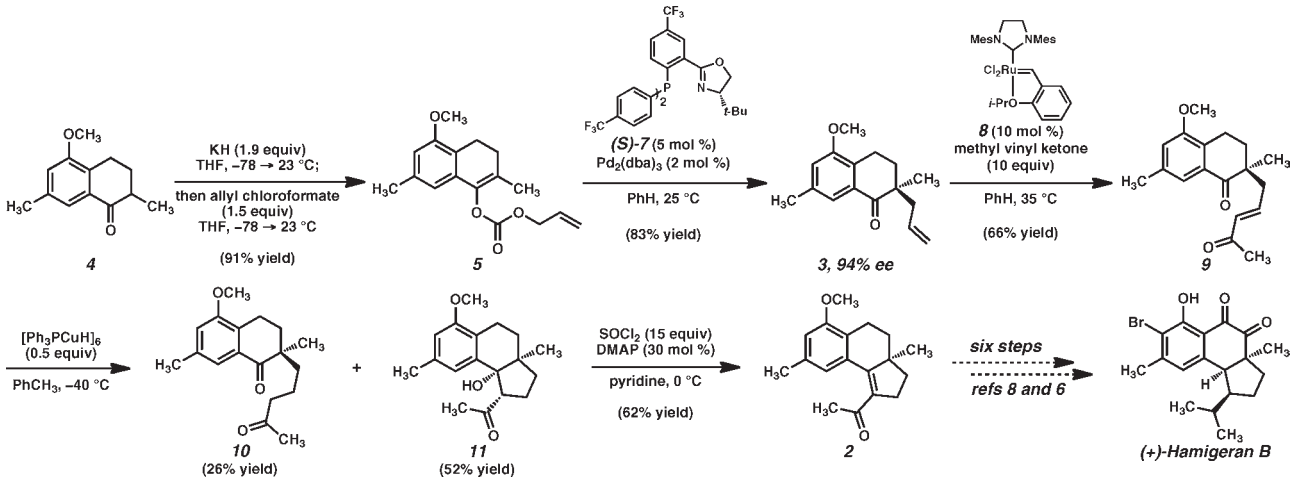
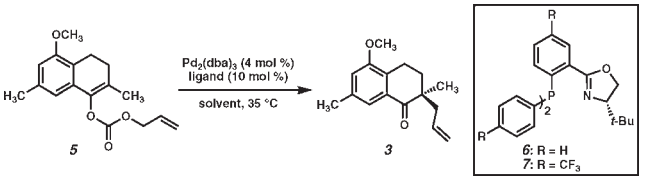


Table 1. Asymmetric Allylation of Allyl Enol Carbonate **5**



entry	solvent	ligand	time (h)	yield[a] (%)	ee[b] (%)
1	THF	**6**	24	71	88
2	Et_2O	**6**	24	74	84
3	PhH	**6**	24	99	92
4	PhH	**7**	1	97	93
5[c]	PhH	**7**	2	91	91
6[d]	PhH	**7**	2	94	91
7[d,e]	PhH	**7**	11	83	94

[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC. [c] 1 mol % $Pd_2(dba)_3$ and 2.5 mol % **7**. [d] 2 mol % $Pd_2(dba)_3$ and 5 mol % **7**. [e] 25 °C.

enone **2**, which has previously been converted to hamigeran B in six steps.[6,8] Thus our asymmetric, formal synthesis of (+)-hamigeran B was complete.

In summary, we have developed an expedient and concise formal synthesis of (+)-hamigeran B. A key tricyclic intermediate, **2**, en route to the synthesis of hamigeran B has been prepared in only five steps from known tetralone **4**. The route features a key asymmetric, Pd-catalyzed decarboxylative allylic alkylation reaction that proceeds with excellent yield and enantioselectivity, allowing us to produce α-quaternary tetralone **3** in 94% ee. Ru-mediated cross metathesis of tetralone **3** with methyl vinyl ketone, followed by a CuH-mediated domino conjugate reduction−cyclization, established the core tricyclic skeleton of intermediate **2**. This general strategy (asymmetric alkylation, cross metathesis, reductive cyclization) is being applied to other bioactive natural products and will be reported in due course.

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Supporting Information Available. Experimental details and NMR spectra of all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.