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Org Lett. Author manuscript; available in PMC 2012 March 4.

Published in final edited form as:

Org Lett. 2011 March 4; 13(5): 825–827. doi:10.1021/ol102669z.

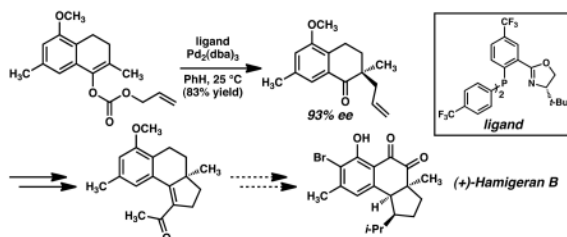
A Catalytic, Asymmetric Formal Synthesis of (+)-Hamigeran B

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Abstract



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 Anchinoidea, syn. Phorbasiadae) 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 P-388 leukemia cell line and against both herpes and polio viruses with little cytotoxicity against the host cells,¹ has a unique tricyclic 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 photo-initiated intramolecular [4 + 2] cyclo-addition of a hydroxy-*o*-quinodimethane by Nicolaou,⁴ Meyers' amino-alcohol auxiliary by Clive and Wang,⁵ a Pd-catalyzed 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 Tian⁷ 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 be used to set the proper relative stereochemistry at C(5)

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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,c} (Scheme 2). Preliminary investigation of the alkylation reaction of **5** used 4 mol % of the complex derived from Pd₂(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 ligand¹³ 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 formation of **3** in 94% ee, with the use of only 2 mol % of Pd₂(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 metathesis¹⁵ 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 non-selective 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 reagent²⁰ 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 26% yield of conjugate reduction product **10**. Alcohol **11** was then dehydrated with SOCl₂ and catalytic DMAP in pyridine²¹ to afford 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.

Supplementary Material

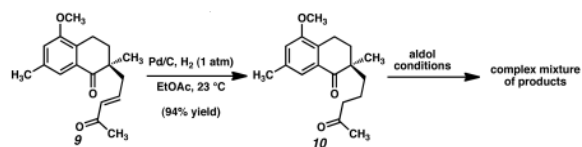
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Acknowledgments

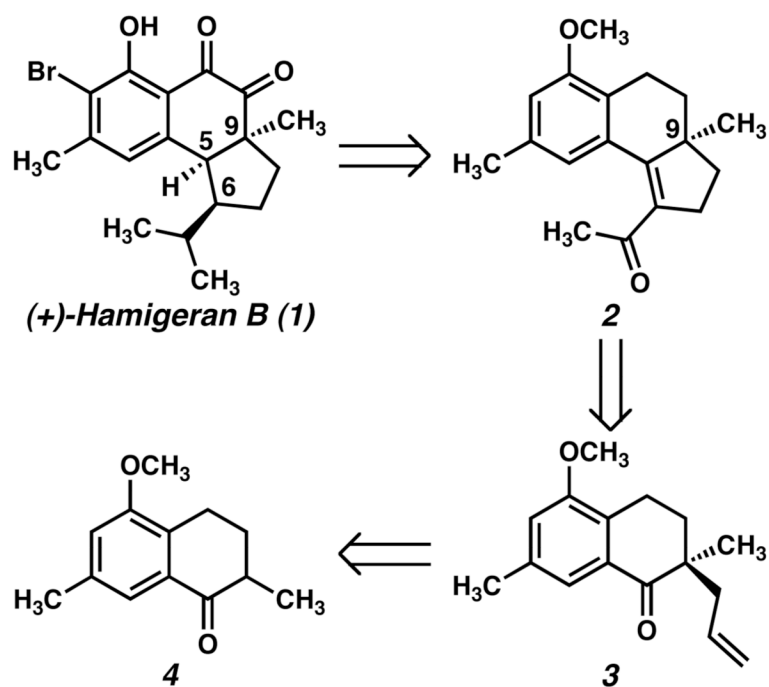
This publication is based on work supported by Award No. KUS-11-006-02, made by King Abdullah University of Science and Technology (KAUST). Additionally, the authors wish to thank NIH-NIGMS (R01 GM 080269-01), Abbott Laboratories, Amgen, the Gordon and Betty Moore Foundation, and Caltech for financial support and Materia, Inc for the kind donation of catalyst **8**. Dr. Douglas C. Behenna is gratefully acknowledged for assistance in the preparation of the manuscript.

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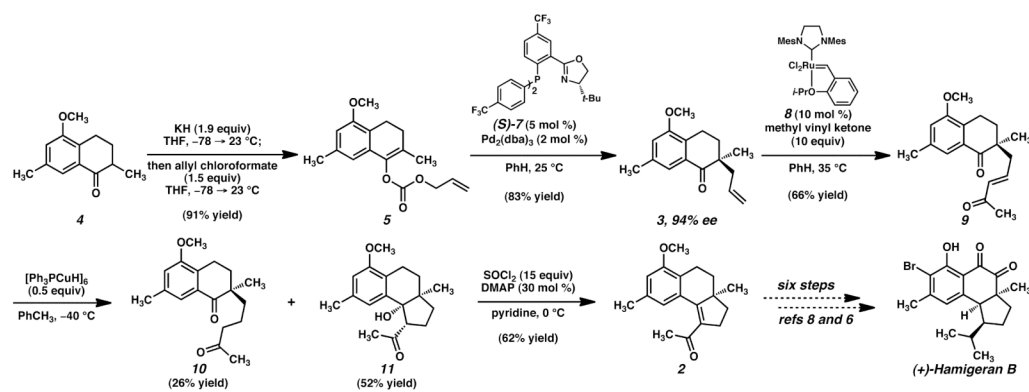
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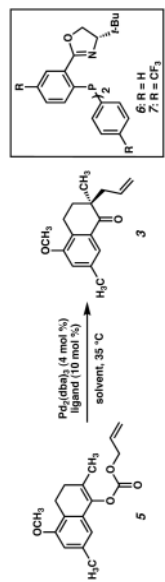


Scheme 1.
Retrosynthetic Analysis of (+)-Hamigeran B.



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 ₂ O	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

^aIsolated yield.^bEnantiomeric excess determined by chiral HPLC.^c1 mol % Pd₂(dba)₃ and 2.5 mol % **7**.^d2 mol % Pd₂(dba)₃ and 5 mol % **7**.^e25 °C.