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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 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 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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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>.

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

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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.