## A Concise Formal Synthesis of (–)-Hamigeran B

## Biao Jiang,\*<sup>,†,‡,§</sup> Ming-ming Li,<sup>†</sup> Ping Xing,<sup>†</sup> and Zuo-gang Huang<sup>‡</sup>

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, Shanghai Advanced Research Institute, Chinese Academy of Sciences, 99 Haike Road, Shanghai 201210, China, and Shanghai Institute for Advanced Immunochemical Studies, ShanghaiTech University, 99 Haike Road, Shanghai 201210, China

jiangb@sioc.ac.cn

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A concise and efficient formal synthesis of (–)-hamigeran B is reported. The critical intermediate was synthesized from 3-methoxy-5-methylphenyl trifluoromethanesulfonate with an 11-steps 7.2% total yield route. The chiral quaternary carbon was efficiently and steroselectively constructed through an intermolecular Pauson–Khand reaction and a Claisen rearrangement reaction with >99% *ee*; the cyclohexane B was then closed through an aldehyde Friedel–Crafts cyclization. Lastly, the isopropenyl group of ring C was introduced through a Suzuki coupling reaction.

Hamigeran B (1) is a member of the hamigerans which were first isolated from the poecilosclerid sponge *Hami*gera tarangaensis by Bergquist and Fromont.<sup>1</sup> Hamigeran B shows 100% *in vitro* inhibition against herpes and polio viruses at a concentration of 132  $\mu$ g per disk and exhibits little cytotoxity. It also has strong *in vitro* antitumor activity against P-388 (IC<sub>50</sub> = 13.5  $\mu$ M). Because of its unique tricarbocyclic skeleton and high bioactivity, hamigeran B has been an attractive target for synthesis.

Since the first total synthesis of hamigeran B by the Nicolaou group,<sup>2</sup> several asymmetric and racemic total syntheses<sup>3</sup> or its core tricarbocyclic skeleton<sup>4</sup> have been reported. The generation of the three continuous chiral centers in (–)-hamigeran B could be achieved by asymmetric hydrogenation controlled by the stereocenter at C(9).<sup>3a,d,4b</sup>

Our retrosynthetic analysis of hamigeran B (Scheme 1) focused on constructing the Miesch's diene intermediate **2** which contains a chiral quaternary carbon center at C(9). The cyclohexane ring of **2** could be constructed through a Friedel–Crafts cyclization, and the isopropenyl group at C(5) could be introduced through a Suzuki cross-coupling from aldehyde **3**. The aldehyde **3** could be constructed by

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<sup>&</sup>lt;sup>†</sup> Shanghai Institute of Organic Chemistry.

<sup>&</sup>lt;sup>‡</sup> Shanghai Advanced Research Institute.

<sup>§</sup> ShanghaiTech University.

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the [3,3]-sigmatropic rearrangement from a chiral cyclopentenol 4. Cyclopentenol 4 was synthesized by an intermolecular Pauson–Khand reaction of aryl propyne with ethylene<sup>5</sup> and subsequent 1,2-reduction.

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



We prepared the aryl propyne **6** via Sonogashira coupling of the readily available triflate **5** and propyne.<sup>6</sup> Alkyne **6** was then subjected to different Pauson–Khand conditions with ethylene to afford the cyclopentenone **7** (Table 1). Only moderate yields were achieved when NMO, TMANO, or "BuSMe was used as a promoter because of the relative bulky 3-methoxy-5-methylphenyl moiety (entries 1-3).<sup>7</sup> However, an excellent result was achieved when excessive Me<sub>2</sub>S (30 equiv) was applied with the reaction temperature raised to 130 °C (entry 5). The reaction was very clean; the cyclopentenone **7** was separated by simple filtration through a Celite pad, and no further purification was needed.

 Table 1. Optimization of the Intermolecular Pauson-Khand
 Reaction of 6 with Ethylene



<sup>*a*</sup> The pressure of ethylene used is  $\sim$ 30 bar. <sup>*b*</sup> Yield of isolated product.

We anticipated a direct enantioselective carbonyl reduction of 7 to produce the key chiral intermediate cyclopentenol 4. Unfortunately, we were able to obtain only low to moderate *ee* values under the conditions of CBS or Midland reduction.<sup>8</sup> The reactions normally proceeded slowly, and the byproducts increased gradually. This indicated that the steric hindrance of the cyclopentenone 7 might have prevented the approach of chiral reagents. Therefore, we seek other accesses to chiral cyclopentenol 4. Among which, kinetic resolution is a good choice. Cyclopentone 7 was first converted into the corresponding racemic cyclopentenol in almost quantitative yield via a Luche reduction (Scheme 2), and then the gross product was subjected directly to the Pd-catalyzed oxidative resolution conditions developed by the Stoltz group.<sup>9</sup> Nearly optically pure cyclopentenol 4 (>99% ee) was obtained in 43% yield, and cyclopentenone 7 could be recovered in 52% yield by this procedure. This reaction could be applied well to a 15-g scale, and the recovered cyclopentenone 7 could be recycled.





Next, chiral allylic alcohol **4** was subjected to Claisen rearrangement conditions. However, neither Ireland– Claisen<sup>10</sup> nor Johnson–Claisen<sup>11</sup> conditions could work. A reductive Claisen rearrangement, reported also by the Stoltz group, proved to be effective (Scheme 3).<sup>12</sup> Cyclopentenol **4** was converted into the corresponding vinyl ester **8** via a Hgcatalyzed vinylation,<sup>13</sup> and **8** was prone to [3,3]-sigmatropic rearrangement in the presence of DIBAL-H to yield alcohol **9**. The configuration of the chiral quaternary carbon center contained in **9** was controlled by the substrate **4**.

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Scheme 3. Construct of the A/B/C Tricarbocyclic Skeleton



Table 2. Construct of the A/B/C Tricarbocyclic Skeleton



<sup>*a*</sup> In a 0.1 M solution, *ortho/para* = 1:1. <sup>*b*</sup> In a 0.008 M solution, *ortho/para* = 3:2. <sup>*c*</sup> Isolated yield of ortho isomer.

Subsequently, we tried to close the cyclohexane B through a Friedel–Crafts reaction (Table 2). Friedel–Crafts cyclization of 9 or its oxidation product carboxylic acid (R = COX) failed (entries 1, 3). Cyclization of its sulfonates ( $R = CH_2OT_s$ ) with the *ortho*-MeO-directed lithiation of the benzene ring was also problematic (entry 2). A direct Friedel–Crafts cyclization with aldehyde (R = CHO) was also tried (entries 4–6). Oxidation of 9 with DMP afforded the aldehyde 3, and cyclization according to the Taber

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Scheme 4. Synthesis of Key Intermediate 2



protocol by treatment with  $BF_3 \bullet Et_2O$  in diluted ether at 0 °C afforded diene **10** in 44% yield (*ortho/para* = 3:2).<sup>14</sup>

Hydrogenation of the less substituted double bond using Adam's catalyst in EtOH gave a nearly quantitative yield, and the crude product was treated directly with  $Py \cdot HBr_3$  in dry DCM at 0 °C and afforded the allyl bromide 11 in 85% yield (Scheme 4).<sup>15</sup> A Suzuki coupling of 11 with an isopropenyl borate gave diene 2 with the desired isopropenyl group,<sup>16</sup> which had previously been converted to hamigeran B in five steps.<sup>3b,e,4b</sup> Therefore, we completed the formal synthesis of (–)-hamigeran B.

In summary, we have developed an efficient and concise formal synthesis of (–)-hamigeran B in an 11-step, 7.2% total yield. The key steps involve an intermolecular Pauson– Khand reaction and a reductive Claisen rearrangement. The route is highly enantioselective and essentially free of protecting groups. Besides, minimum or no column chromatography separations and purifications in most of the steps were needed because of the generally high conversions as well as excellent regioslectivity and yields. In fact, we have presented a general and efficient method to construct a chiral quaternary carbon center containing a five-membered ring, via a Pauson– Khand/asymmetric reduction/[3,3]-sigmatropic process.

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Supporting Information Available. Full experimental details, spectroscopic data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR for compounds 2-11. This material is available free of charge via the Internet at http://pubs.acs.org.

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