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Enantioselective Approach to (−)-Hamigeran B and (−)-4-Bromohamigeran B via Catalytic Asymmetric Hydrogenation of Racemic Ketone To Assemble the Chiral Core Framework

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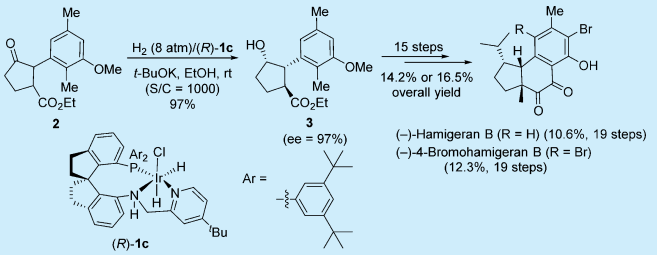
Supporting Information

ABSTRACT: A new strategy featuring an iridium-catalyzed asymmetric hydrogenation of a racemic ketone via dynamic kinetic resolution to generate a cyclopentanol with three contiguous stereocenters and a SmI_2-promoted pinacol coupling to install the six-membered ring with correct stereochemistry has been described for the enantioselective total synthesis of (−)-hamigeran B (19 steps, 10.6% overall yield) and (−)-4-bromohamigeran B (19 steps, 12.3% overall yield).



Natural products continue to inspire the development of asymmetric catalysts for enantioselective synthesis.[1] The hamigerans, a family of biologically active molecules isolated from the sponge *Hamigera tarangaensis*, have drawn much attention from synthetic chemists owing to their unique [6,6,5]- and [6,7,5]-tricyclic carbon skeletons bearing three or four contiguous stereogenic centers (Figure 1).[2] In 2001,

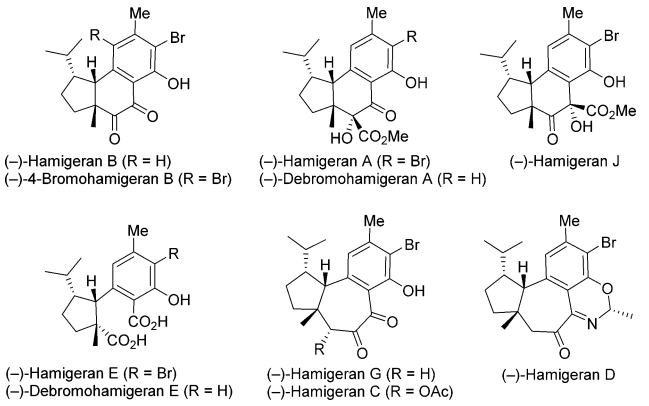


Figure 1. Molecular structures of selected hamigerans.

Nicolaou et al.[3] reported the first synthesis of hamigerans, by means of photoenolization of racemic or optically active substituted benzaldehydes and subsequent Diels−Alder trapping of the generated hydroxyl-*o*-quinodimethanes to construct the chiral core framework in racemic or enantiomerically pure form, respectively. Since then, several other syntheses have been developed, and most of them have focused on the synthesis of hamigeran B,[4] which has strong in vitro activity against herpes and polio viruses but little cytotoxicity.[2] Clive and Wang[5] synthesized (−)-hamigeran B by using Meyer's auxiliary to construct the chiral quaternary stereocenter. Taber and Tian[6] described an enantioselective strategy involving the use of optically pure citronellol and an intramolecular C−H insertion of an *α*-aryl-*α*-diazoketone followed by a Friedel−Crafts cyclization to install the chiral core structure. Trost et al.[7] used a Pd-catalyzed asymmetric allylic alkylation followed by an intramolecular Heck reaction to install the quaternary carbon center. Jiang et al.[8] reported a formal synthesis involving the construction of the chiral quaternary stereocenter by means of Pd-catalyzed oxidative resolution of a racemic aryl-substituted cyclopentenol combined with a reductive Claisen rearrangement. Recently, Stoltz et al.[9] reported a Pd-catalyzed asymmetric decarboxylative allylic alkylation to access the quaternary carbon center as part of an asymmetric formal synthesis of (+)-hamigeran B. In addition, there have been other reports on the synthesis of racemic hamigeran B[10] and on the nonenantioselective construction of the core tricyclic carbon skeleton of various hamigerans.[11]

We recently developed several methods for highly efficient asymmetric hydrogenation with the goal of improving the efficiency of enantioselective syntheses of the core frameworks of naturally occurring bioactive molecules.[12] These successes encouraged us to devote more effort to the development of new efficient asymmetric hydrogenations for facile enantioselective synthesis of other challenging targets. We noted that the hamigerans have a chiral core consisting of an aryl-substituted cyclopentane framework and that almost all of the chiral centers are located on the cyclopentane ring. Inspired by this unique structural characteristic, we set out to investigate the use of asymmetric hydrogenation of racemic 2-(3-methoxy-2,5-dimethylphenyl)-3-(ethoxycarbonyl)cyclopentanone (**2**) via

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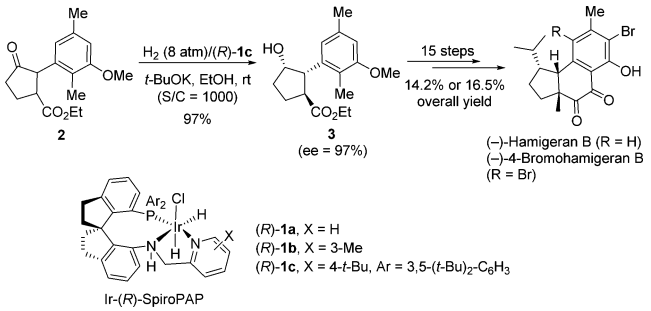
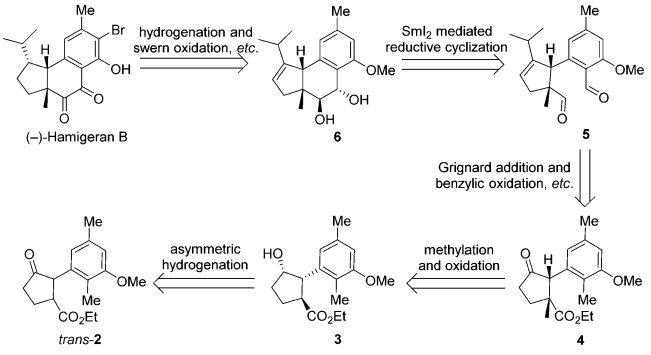
dynamic kinetic resolution (DKR) to access the chiral core framework. We herein report that chiral iridium complexes Ir–(*R*)-SpiroPAP **1**, which have a spiro pyridine–aminophosphine ligand,[13] efficiently catalyzed the transformation of **2** to chiral cyclopentanol **3**, allowing us to achieve enantioselective total syntheses of (−)-hamigeran B and its 4-bromo analogue (Scheme 1).

Scheme 1. Enantioselective Synthesis of (−)-Hamigeran B and (−)-4-Bromohamigeran B via a Catalytic Asymmetric Hydrogenation of Racemic Ketone



Our retrosynthetic analysis of (−)-hamigeran B is outlined in Scheme 2. Our strategy was to focus on the construction of the

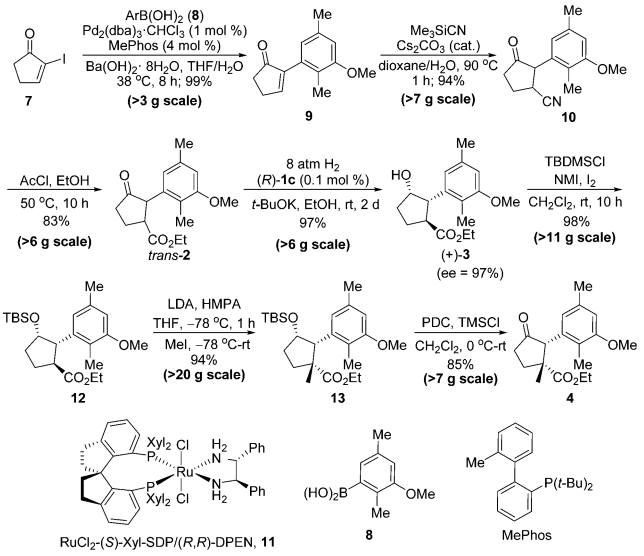
Scheme 2. Retrosynthetic Analysis of (−)-Hamigeran B



chiral aryl-substituted cyclopentane framework. We expected that catalytic asymmetric hydrogenation would provide chiral cyclopentanol **3**, which has three contiguous stereocenters, and that subsequent methylation with methyl iodide would generate the quaternary carbon center. The resulting methylated product would be oxidized to cyclopentanone **4**, which would serve as a precursor for installation of the isopropyl group. Several subsequent functional transformations, including benzylic oxidation,[14] would provide dialdehyde **5**. An intramolecular SmI_2-mediated reductive cyclization of the dialdehyde[15] would provide tricyclic intermediate **6**. Finally, by using the Ir-catalyzed hydrogenation method developed by Trost et al.[7] followed by Swern oxidation and several other transformations, we would convert **6** to the target molecule.

The Suzuki coupling of 2-iodocyclopent-2-enone (**7**)[16] and arylboronic acid **8**,[17] both known compounds, in the presence of 1 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 4 mol % of MePhos yielded α-aryl-substituted cyclopentenone **9** in 99% yield (Scheme 3).[18] 1,4-Addition of Me_3SiCN to cyclopentenone **9** according to Chen's procedure,[19] followed by conversion of the nitrile group of the addition product **10** to an ester group,

Scheme 3. Enantioselective Synthesis of Ketone 4



afforded cyclopentanone **2** in 78% as a *trans* isomer yield for the two steps.

The asymmetric hydrogenation of racemic ketone **2** via DKR to afford optically active cyclopentanol **3**, with its three contiguous stereocenters, was the key step of our strategy. First, we investigated the ruthenium complex $RuCl_2$–(*S*)-Xyl-SDP/(*R*,*R*)-DPEN (**11**), which efficiently catalyzes the hydrogenation of racemic α-arylcycloketones,[20] and we found that it gave **3** in only moderate yield and enantioselectivity (ethyl ester, 46% yield, 76% ee; isopropyl ester, 30% yield, 82% ee), but with high diastereoselectivity (*trans*/*cis* > 99:1). Next, we studied chiral iridium complexes **1**, which bear a spiro pyridine–aminophosphine ligand,[13] and found that (*R*)-**1c** catalyzed the production of (+)-**3** in 97% yield with 97% ee and >99:1 *trans*/*cis* selectivity (for details, see the Supporting Information). The hydrogenation is through the direct reduction of one of the enantiomers of *cis*-**2**, which are generated by base-promoted epimerization of *trans*-**2**. The observation of a minor amount of *cis*,*cis*-**3** in the hydrogenation system provides evidence to support this conclusion. The longer reaction time favored the epimerization of *cis*,*cis*-**3** to *trans*,*cis*-**3**, resulting high diastereoselectivity. The absolute configuration of (+)-**3** was assigned as (1*S*,2*S*,3*S*) by inference from the X-ray crystal structure of lactone **16** (Scheme 4). The hydrogenation of racemic ketone **2** could be performed on a gram scale without reduction in either the yield or the selectivity. The hydroxyl group was then protected with *tert*-butylchlorodimethylsilane (TBSCl) at room temperature;[21] subsequent treatment of the protected compound with lithium diisopropylamide in THF at −78 °C and trapping with methyl iodide yielded methylated product **13** in 94% yield. Compound **13** was oxidized with pyridinium dichromate/trimethylsilyl chloride according to Palomo's procedure[22] to afford ketone **4** in 85% yield; no epimerization of the α-arylated stereogenic center was observed. Note, however, that **4** was unstable and had to be stored at 0 °C for no more than a week. Thus, we accomplished the enantioselective synthesis of key chiral intermediate **4**, which has the necessary adjacent chiral quaternary and aryl-substituted stereocenters.

The introduction of the bulky isopropyl group adjacent to the aryl group on the cyclopentane ring with the correct

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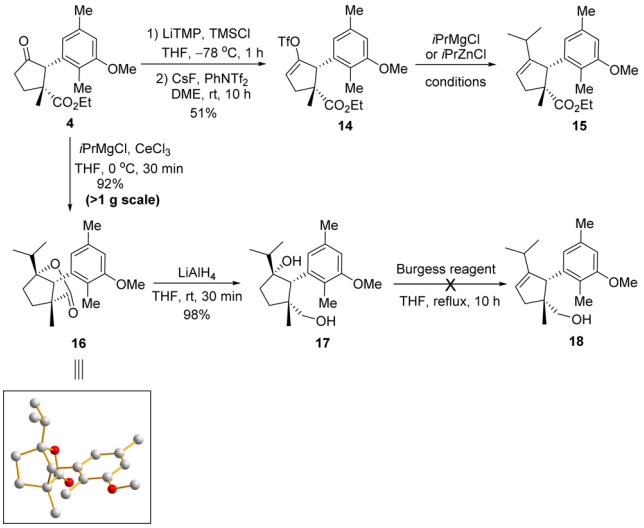
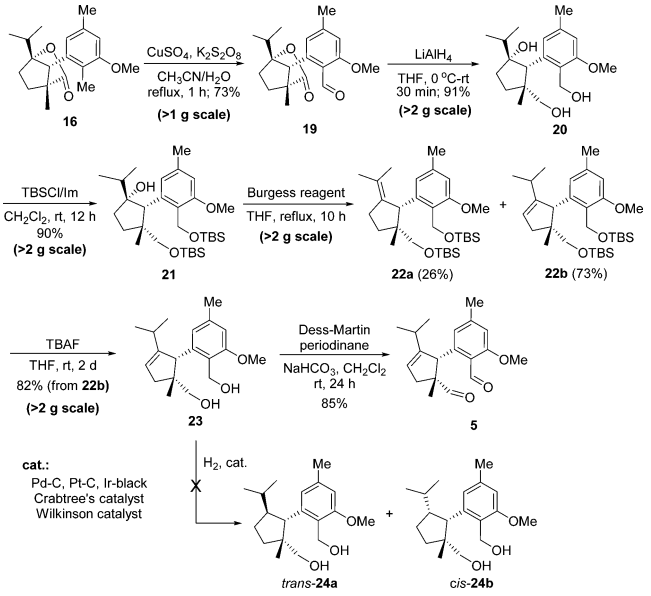
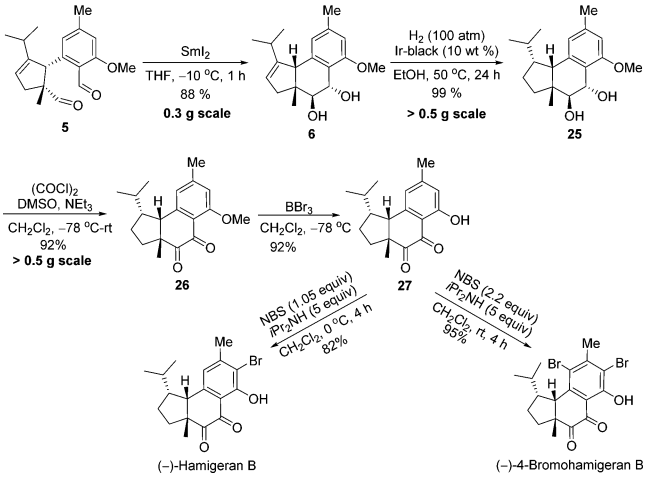
Scheme 4. Attempts To Introduce Isopropyl Group



Scheme 5. Enantioselective Synthesis of Dialdehyde 5



Scheme 6. Enantioselective Syntheses of (−)-Hamigeran B and (−)-4-Bromohamigeran B



stereochemistry had previously been demonstrated to be a challenge in the synthesis of hamigeran B.[4] Initially, we attempted to install the isopropyl group by using transition-metal-catalyzed cross-coupling reactions (Scheme 4). Reaction of ketone **4** with lithium 2,2,6,6-tetramethylpiperidide and trimethylsilyl chloride yielded a silyl enol ether, which was converted to enol triflate **14** in 51% yield (two steps) by reaction with *N*-phenylbis(trifluoromethanesulphonimide) by means of Corey's method.[23] However, coupling of enol triflate **14** with isopropylmagnesium chloride or isopropylzinc chloride catalyzed by either a palladium or a nickel catalyst did not afford desired product **15**. Thus, we tried to introduce the isopropyl group by addition of a Grignard reagent and elimination of the resulting hydroxyl group. In the presence of cerium chloride, ketone **4** reacted with isopropylmagnesium chloride to provide lactone **16** in 92% yield, and X-ray diffraction analysis of a crystal of **16** showed its absolute configuration to be (1*R*,4*R*,7*R*). However, elimination of the ester group of **16** to form a trisubstituted olefin was unsuccessful. Lactone **16** could be reduced to diol **17** with $LiAlH_4$, but subsequent elimination of the tertiary hydroxyl group with Burgess reagent to **18** failed.

Instead, lactone **16** was oxidized with potassium persulfate in the presence of copper sulfate to give aldehyde **19** in 73% yield according to a literature method[14] (Scheme 5). Aldehyde **19** was reduced to alcohol **20** with $LiAlH_4$, and the hydroxyl group was protected with TBSCl to yield **21** in 82% yield over two steps. Note that **21** was synthesized from ketone **4** in four steps without purification of the intermediates and a higher overall yield (57%). We were delighted to find that reaction of **21** with Burgess reagent afforded tetrasubstituted olefin **22a** and trisubstituted olefin **22b** in 26% and 73% yields, respectively. After removal of the TBS group of **22b** with tetrabutylammonium fluoride, olefins **23** were isolated in 82% yield. Olefin **23** was oxidized with Dess−Martin periodinane to dialdehyde **5** in 85% yield. In summary, dialdehyde **5** was synthesized in seven steps from ketone **4** in 21.9% overall yield. We also attempted the direct hydrogenation of olefin **23** to diol **24** using various catalysts, but without success.

Dialdehyde **5** was subjected to pinacol coupling mediated by SmI_2 to generate tricyclic product **6** as a single diastereomer in 88% yield (Scheme 6). By means of Ir-black-catalyzed hydrogenation,[7] **6** was converted to diol **25** in 99% yield with the correct stereochemistry of the isopropyl group. The *cis*-oriented isopropyl group and aryl group on the five-membered ring and the *trans*-orientated hydroxyl groups on the six-membered ring were confirmed by nuclear Overhauser enhancement spectroscopy. Diol **25** was subjected to Swern oxidation[5] and subsequent demethylation with BBr_3 to produce diketone **27** in 85% yield for two steps.[3] Finally, selective bromination of diketone **27** with a slight excess of *N*-bromosuccinimide in the presence of diisopropylamine afforded (−)-hamigeran B in 82% yield.[7] With 2.2 equiv of *N*-bromosuccinimide, (−)-4-bromohamigeran B was obtained in 95% yield.[10a] The NMR spectroscopic data and the optical rotations of our synthetic (−)-hamigeran B ($[\alpha]_D^{26}$ −167.3 (*c* 0.15, CH_2Cl_2)) and (−)-4-bromohamigeran B ($[\alpha]_D^{26}$ −80.0 (*c* 0.10, CH_2Cl_2)) were identical to those of the corresponding natural products ($[\alpha]_D^{25}$ −151.1 (*c* 0.15, CH_2Cl_2) and $[\alpha]_D^{25}$ −81.2 (*c* 0.37, CH_2Cl_2),[2] respectively). Thus, we accomplished the enantioselective total syntheses of (−)-hamigeran B (19

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steps and 10.6% overall yield)[24] and (−)-4-bromohamigeran B (19 steps, 12.3% overall yield).

In conclusion, we developed a new strategy for the enantioselective construction of the chiral core framework of the hamigeran family of natural products. The strategy features an iridium-catalyzed asymmetric hydrogenation of a racemic ketone via DKR to afford a cyclopentanol moiety with three contiguous stereocenters as well as a SmI_2-promoted pinacol coupling to install the six-membered ring with the correct stereochemistry. With this efficient strategy, the enantioselective total syntheses of (−)-hamigeran B and (−)-4-bromohamigeran B were achieved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00369.

Experimental procedures, characterization of the products, and X-ray data for compound **16** (PDF)

X-ray crystallographic data for **16** (CIF)

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Notes

The authors declare no competing financial interest.

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(24) This synthesis is comparable to the best result achieved by Trost et al. (for (−)-hamigeran B, 10% overall yield, 15 steps); see ref 7.

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