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Formal total synthesis of (−)-hamigeran B from a chemo-enzymatically prepared building block with quaternary chiral center

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ABSTRACT

A formal total synthesis of (−)-hamigeran B was achieved in 17 steps from commercially available ethyl 2-oxocyclopentanecarboxylate. Carbonyl reductase-catalyzed asymmetric reduction and the subsequent chemical transformations furnished an enantiomerically pure synthetic intermediate, (*R*)-5-formyl-2-isopropyl-5-methylcyclopent-1-en-1-yl trifluoromethylsulfonate. Suzuki-Miyaura coupling with Gao's arylboronate [2-(2-formyl-3-methoxy-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane], under $PdCl_2(dppf)\bullet CH_2Cl_2$ catalysis, and the subsequent cyclization by way of intramolecular reductive SmI_2-mediated 1,2-diol formation provided a tricyclic skeleton with a tetrasubstituted double bond between C-1 and C-9b. Upon hydrogenation of this double bond, the proper stereochemistry of the remaining chiral centers was established. Exclusive addition of the hydrogen atom from the β-face occurred, owing to the shielding of the α-face with a bulky TBS protective group on the C-4 alcohol. The hydrogenation products were transformed into Clive's synthetic precursor for (−)-hamigeran B.

1. Introduction

In 2000, (−)-hamigeran B (**1**) was isolated from marine sponge, *Hamigera tarangaensis*, and found to show antiviral activity.[1] Since then, many efforts have been devoted to its chemistry and many total and formal total syntheses have been achieved.[2–16] We envisaged that Clive's diketone (1*R*,3a*R*,9b*R*)-**2**,[5] a synthetic precursor for **1**, could be synthesized by stepwise transformation involving: 1) Suzuki-Miyaura coupling between Gao's arylboronate **3**[17] and (*R*)-**4** with the proper branched side chain and quaternary chiral center; and 2) SmI_2-mediated ring closure[16] as the key steps (Scheme 1). The cyclopentenoid (*R*)-**4** would be available from (*S*)-**5**, and its alkenyl triflate moiety was expected to aid in the palladium-catalyzed C–C bond formation.

2. Results and discussion

To this end, in the same manner as the synthesis of its antipode (*R*)-**5**,[18] (*S*)-**5** was synthesized from **6** by enzyme-catalyzed asymmetric reduction and 8 additional chemical transformations of the resulting stereochemically pure (1*R*,2*S*)-**7**. 1-Methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO)-catalyzed oxidation[19] of the primary alcohol furnished (*R*)-**4** in 84% yield (Scheme 2). Its counterpart, arylboronate **3**, was prepared from 3,5-dihydroxytoluene[20] in 4 steps.[17,21,22]

Suzuki-Miyaura coupling between **3** and (*R*)-**4** was accomplished under Gao's conditions with $PdCl_2(dppf)\bullet CH_2Cl_2$ as the catalyst to furnish (*R*)-**8** in 68% yield (Scheme 2). Switching the palladium catalyst to PEPPSI-IPr or PEPPSI-SIPr, which had been reported to be effective for the coupling of sterically hindered substrates,[23] the yield of **8** decreased (*ca.* 40%). When the coupling between **3** and another triflate (*S*)-**5** was attempted, only an undesired borate ester on the primary alcohol in **5** and a homo-coupling byproduct originating from **3** were observed. Moreover, all attempts at Stille coupling, which was successful with a very similar cyclopentenyl triflate and alkenylstannane[24] failed with the corresponding aryltrimethylstananne instead of **3**.

The coupling product (*R*)-**8** was revealed to be a 56:44 mixture of two rotamers judging by its ^1H NMR spectrum as shown in section 4.3. The next step, the ring closure of **8**, proceeded almost quantitatively by treatment with SmI_2 in tetrahydrofuran (THF) at −20 °C. In contrast to the normal facial selectivity which prefers *cis*-1,2-diol formation, the preference for the *trans*-isomer in an intramolecular fashion had been reported in a similar substrate with a rigid structure and bulky neighboring substituents.[16] In our case, two diastereomers (3a*R*,4*R*,5*R*)-**9a** (51%) and (3a*R*,4*S*,5*S*)-**9a** (49%) formed, which presumably originated from each rotamer in (*R*)-**8**, and were separated by silica gel column chromatography.

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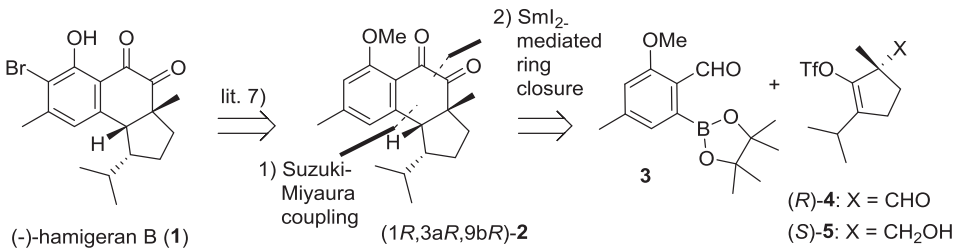
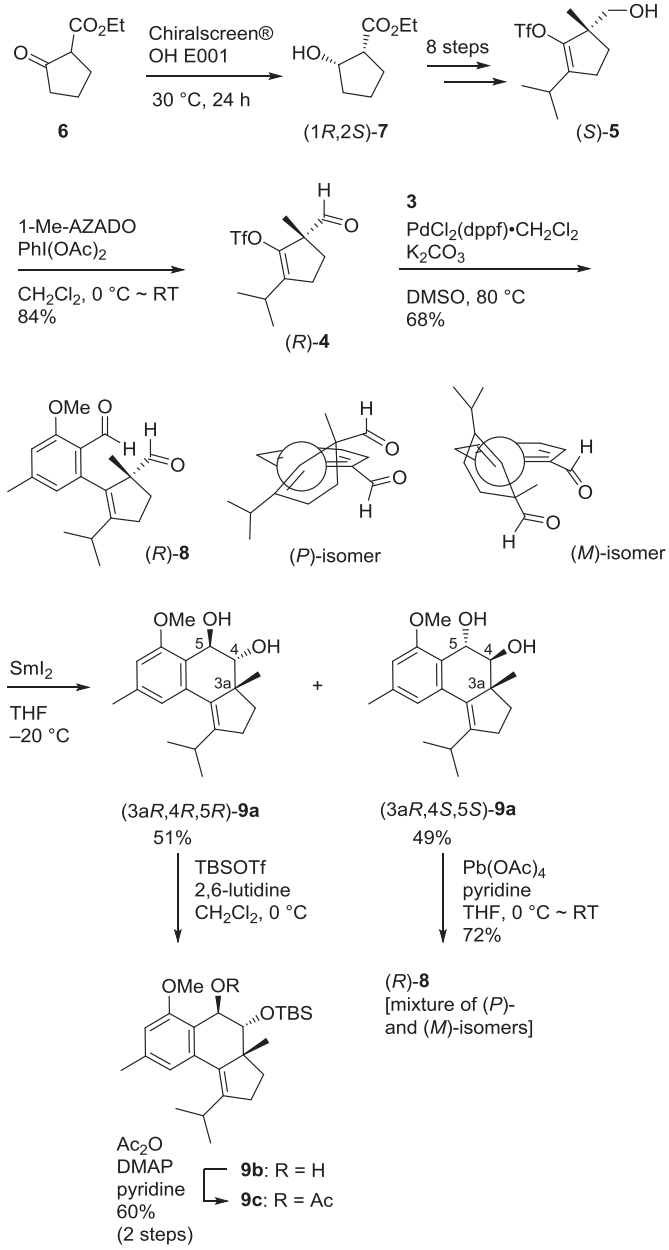


Scheme 1. Synthetic plan for (−)-hamigeran B (**1**) and the precursor (1*R*,3a*R*,9b*R*)-**2**, by the coupling between aromatic segment **3** and cyclopentenoid segment (*R*)-**4** and subsequent ring closure.



Scheme 2. Suzuki-Miyaura coupling between **3** and (*R*)-**4** and the SmI_2-mediated ring closure.

The *trans*-stereochemistries of both diastereomers were assigned by the comparison of nuclear Overhauser effect (nOe) and coupling constants in ^{1}H NMR spectra as depicted in Fig. 1. Upon irradiation at methyl group at C-3a, nOe was observed at H-4 (4.0%) for (3a*R*,4*R*,5*R*)-**9a**, but at H-3 (2.0%) for (3a*R*,4*S*,5*S*)-**9a**. Coupling constants between H-4 and H-5 were agreeable for *trans*-isomers; 0 Hz for (3a*R*,4*R*,5*R*)-**9a** and 7.4 Hz for (3a*R*,4*S*,5*S*)-**9a** as shown in Fig. 1. It is also noted that both of ^{1}H NMR spectra of (3a*R*,4*R*,5*R*)-**9a** and (3a*R*,4*S*,5*S*)-**9a** were different from that of previously reported corresponding *cis*-**9a**.[17]

The final task was the installation of the correct stereochemistry at C-1 and C-9b by hydrogenation. Clive's pioneering work[7] revealed that a large substituent oriented over the α-face at C-4 is necessary to control the stereochemistry at C-1 and C-9b to yield the desired (1*R*,9b*R*)- stereochemistry upon hydrogenation of the double bond between C-1 and C-9b.

Thus, (3a*R*,4*R*,5*R*)-**9a** was submitted to the following sequence to form **2**. As expected from the 1,3-diaxial repulsion of bulky protective group on the C-5 hydroxy group and C-3a methyl group, less sterically hindered alcohol at C-4 was protected with a *tert*-butyldimethylsilyl (TBS) group (Scheme 2). The remaining *pseudo*-axially oriented secondary alcohol at C-5 was then protected with a small acetyl group to minimize the blocking of the β-face upon hydrogenation.

In contrast, such desired approach of hydrogen atoms from the β-face cannot be expected for (3a*R*,4*S*,5*S*)-**9a** which has both substituents at C-4 and C-5 in the *pseudo*-equatorial orientation, as shown in Fig. 1. Therefore, this diastereomer was recycled into the cyclization precursor (*R*)-**8**, by C—C bond cleavage of the *trans*-1,2-diol moiety by oxidation with lead tetraacetate in 72% yield (Scheme 2). The resulting (*R*)-**8** became a mixture of rotamers again, as in almost same ratio as the above-mentioned Suzuki-Miyaura coupling product, as indicated by the ^{1}H NMR spectrum.

The hydrogenation of **9c** catalyzed by Pd (5%) on charcoal was sluggish even under high pressure of hydrogen gas. Desired (1*R*,3a*R*,4*R*,5*R*,9b*R*)-**10a** was obtained only in as low as 28% yield with recovery of starting material (48%) (Scheme 3). To overcome the low efficiency, the catalyst loading was increased from 5% to 10% under a higher concentration of the substrate in ethanol. Under these conditions, deoxygenation at the benzylic C-5 position also occurred, and (1*R*,3a*R*,4*S*,9b*R*)-**11a** was the major product with complete consumption of the starting material. Hydrogenolysis at the benzylic position alleviated the steric hindrance, possibly promoting hydrogenation of the tetrasubstituted double bond, although an intermediate for this pathway was not detected in the crude products of the reaction. $Pd(OH)_2$ brought about the same deoxygenation at the benzylic C-5 position. Subsequent deprotection of the TBS ether in **11a** furnished **11b** in 82% yield from **9c**.

In contrast to the hydrogenation of conjugated tetrasubstituted bond (type A[6–8] and type B[12]), nobody has achieved the hydrogenation of an isolated double bond between C-1 and C-9b such as in **9c**. A possible intermediate, in which the double bond was isomerized to the disubstituted, sterically less hindered C-1 and C-2 positions (type C)[3–5,9,10] was not detected in our experiments.

Alcohol **11b** had been synthesized as an intermediate for