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# Enantioselective Total Synthesis of Aperidine

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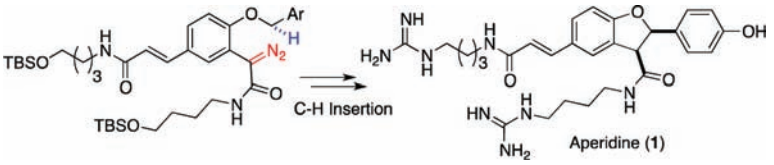
## ABSTRACT




**An efficient total synthesis of aperidine was accomplished using a Rh-catalyzed C−H insertion of a *cis*-dihydrobenzofuran ring. To circumvent the facile epimerization of the *cis*-dihydrobenzofuran ring, we designed and prepared the C−H insertion precursor diazoamide by Raines' protocol. Finally, the efficient incorporation of a guanidine group and mild deprotection conditions yielded this labile natural product.**

Aperidine (**1**)[1] and hordatine A (**2**)[2] were isolated from beer as muscarinic $M_3$ receptor antagonists (Figure 1). Recently, we reported their absolute structures and described their antagonist activity toward the $\alpha_1$ adrenoceptor as well.[3] To evaluate their potential as lead compounds for drug development,[4] an ample supply and flexible preparation methods for **1** and **2** are strongly required. In previous studies of the enantioselective total synthesis of the *trans*-isomer **2**,[3] selective formation of the *cis*-isomer **1** was unfortunately prevented by the facile isomerization between these two diastereomers. In general, the higher thermodynamic stability of the *trans* configuration during isomerization renders the *trans*-isomer predominant in neolignans, and the *cis*-isomer is rarely observed in Nature. Therefore, few reports have described the synthesis of *cis*-dihydrobenzofuran rings, reflecting the scarcity and instability of natural products containing *cis*-dihydrobenzofuran.[5]

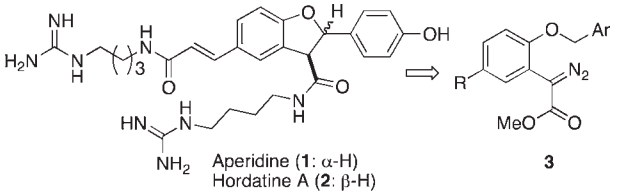



**Figure 1.** Structure and synthetic strategy for **1**.

Recently, we developed a novel methodology to construct optically active *trans*-dihydrobenzofuran rings via rhodium carbenoid-mediated intramolecular C−H insertion of aryl diazoesters in the presence of a chiral auxiliary.[6] Utilizing this methodology, we accomplished

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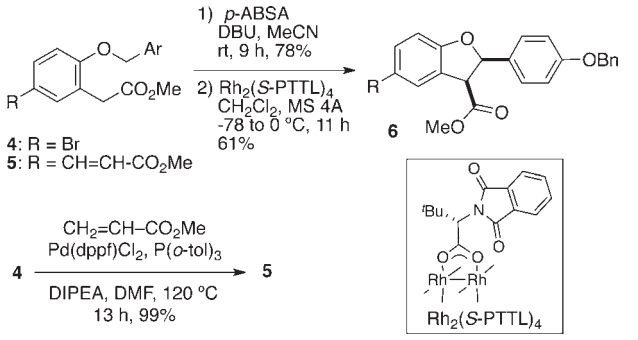
the total synthesis of several natural products.[7] The highly *cis*-selective construction from the diazoester itself using $Rh_2(S\text{-PTAD})_4$ and $Rh_2(S\text{-PTTL})_4$ was reported, respectively, by the Davies[8] and Hashimoto[5] groups. On the basis of these findings, we envisioned that optimization and refinement of the reaction conditions to **3** would provide an optically active *cis*-dihydrobenzofuran ring of **1**, as shown in Scheme 1. Herein, we describe an enantioselective synthesis of (−)-aperidine (**1**) with improvements to the synthetic route employed for **2**.[3]

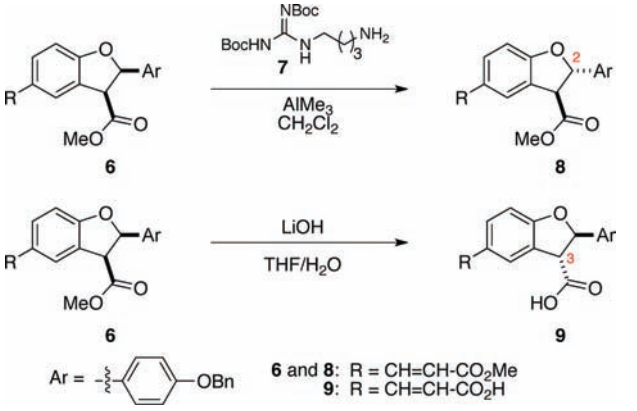
**Scheme 1.** Construction of *cis*-Dihydrobenzofuran Ring of **6**




To construct the *cis*-dihydrobenzofuran ring, a precursor of the C−H insertion reaction was prepared from **4** by a previously described method.[7a] The side chain was incorporated using the Heck reaction of **4** with methyl acrylate to provide the *trans*-cinnamic ester derivative **5**. After installing a diazo group by treating with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU, a C−H insertion reaction was investigated using several rhodium catalysts and conditions. The rhodium carbenoid-mediated intramolecular C−H insertion reaction proceeded with an increasing *cis* selectivity upon decreasing the temperature. Furthermore, the Hashimoto catalyst $Rh_2(S\text{-PTTL})_4$[9] gave the best results among several catalysts tested to furnish predominantly a *cis*-dihydrobenzofuran ring **6** (Scheme 1).

With the desired dihydrobenzofuran **6** in hand, we turned our attention to incorporation of the agmatine unit **7**. Treatment of **6** with the di-Boc-agmatine **7**[10] and $AlMe_3$, however, resulted in epimerization at the C-2 position prior to the desired amide bond formation to give **8**. This reaction presumably proceeded through the *p*-quinone-methide intermediate, which was promoted by the Lewis acid $AlMe_3$. Next, hydrolysis of **6** by treatment with LiOH proceeded, accompanied by the concomitant epimerization at the α-position of the ester group, to give **9** (Scheme 2). Consequently, we were confronted with the formidable task of avoiding competitive epimerization, which generated the *trans* configuration in preference to the conversions required for introduction of the agmatine units. Therefore, construction of the *cis*-dihydrobenzofuran ring in a later stage of the total synthesis, at least after introduction of the side chains, was required.

**Scheme 2.** Epimerization of **6** under Acidic and Basic Conditions




A diazoamide with embedded side chains could potentially ameliorate the disadvantages of the above-described approach through a sequence of conversions after the C−H insertion reaction. However, attempts to promote C−H insertion of the diazoamide possessing protected guanidine groups were unsuccessful. These results suggested that a side chain could be incorporated as a protected butanol amine, i.e., **9** (Scheme 3). After hydrolysis of the diester **5**, condensation of the resultant carboxylic acid with **9** gave the amide **10**. Although the diazo transfer reaction proceeded smoothly in **5**, the same reaction with the amide **10** did not give the desired diazo compound due to the lower $pK_a$ of the α amide group. Recently, Raines and co-workers reported an efficient conversion to a diazo group from an azide functionality using a novel phosphine reagent **13**.[11] Considering its high reactivity and the mild required reaction conditions, this procedure would be suitable for incorporating the diazo group into **10**. After bromination of the ester **10** through the silylketene acetal intermediate, displacement of the bromide with $NaN_3$ gave the desired α-azide amide **12**. Upon treatment of **12** with **13**, phosphine-mediated activation of the azide group and amide bond formation proceeded smoothly to form an acyl triazene intermediate **14**. Without purification of **14**, subsequent transformation by treatment with aqueous $NaHCO_3$ successfully furnished the diazoamide **15**.

The desired diazoamide **15** in hand, we then focused on constructing the *cis*-dihydrobenzofuran ring. Upon

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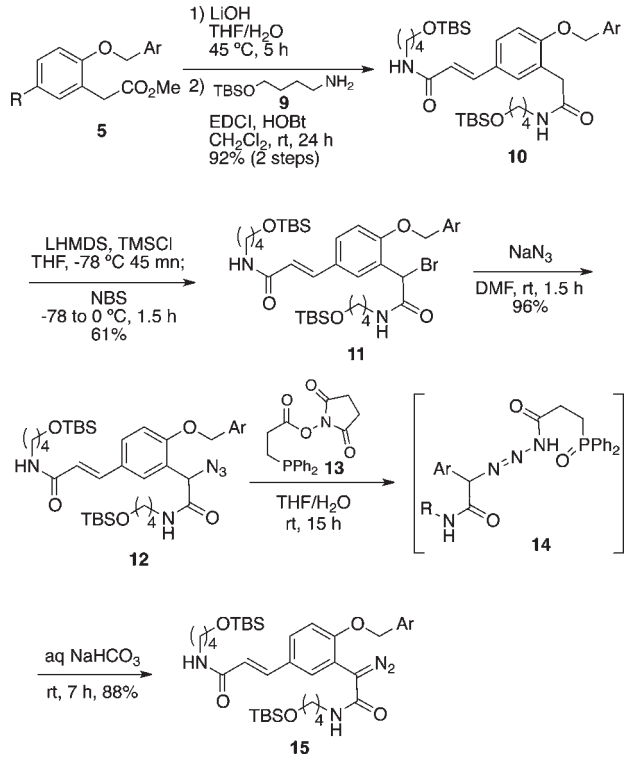
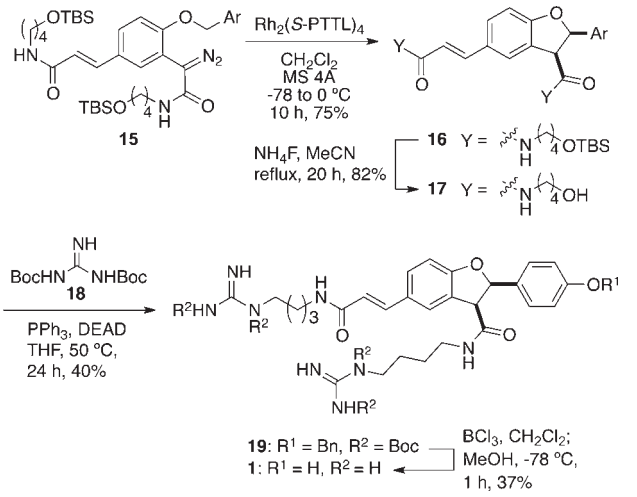
**Scheme 3.** Preparation of C−H Insertion Precursor **15**




**Scheme 4.** Completion of the Total Synthesis of **1**




treatment of **15** with 4 mol % Hashimoto catalyst $Rh_2$(*S*-PTTL)$_4$ at −78 °C, the C−H insertion reaction proceeded smoothly to exclusively afford the *cis*-dihydrobenzofuran **16** in 75% yield in a completely stereoselective manner (Scheme 4). The reaction proceeded even in the presence of the amide group, which could have decreased the activity of the catalyst. Because the labile *cis*-dihydrobenzofuran **16** can readily undergo epimerization under acidic as well as basic conditions, extra mild conditions were required for further conversion. After cleavage of both TBS ethers of **16** by $NH_4F$, a guanidine moiety was incorporated into **17** by the Mitsunobu reaction.[12] Upon treatment of the di-Boc guanidine **18** in the presence of the corresponding alcohol **17** with DEAD and $PPh_3$, smooth amination proceeded to provide the protected aperidine **19**.

After numerous attempts to circumvent the facile epimerization during the final deprotection step, we found that simultaneous cleavage of the Bn ether and Boc groups of **19** could be performed by treatment with $BCl_3$[13] at −78 °C, and careful workup provided **1**. Presumably, Lewis acid- mediated cleavage of the Bn ether proceeded by $BCl_3$, and HCl-mediated hydrolysis of the Boc group proceeded after addition of MeOH to the reaction mixture. After removal of the solvent and resultant $B(OMe)_3$, purification was performed by the sequential combination of gel filtration and HPLC separation.[14] All spectral data of **1** ($^1$H, $^{13}$C NMR, IR, and HRMS) were identical to those of the natural product, and the optical rotation, $[\alpha]^{25}_D = -54$ (*c* 0.14, MeOH), agreed well with reported value of previously the (2*R*,3*S*)-**1**, $[\alpha]^{25}_D = -57$ (*c* 0.2, MeOH).

In conclusion, an enantioselective total synthesis of aperidine (**1**) was accomplished in 10 steps from the readily available arylacetic acid derivative **4**. Our stereoselective synthesis featured the *cis*-selective construction of a dihydrobenzofuran ring utilizing a Rh-catalyzed C−H insertion of the diazoamide **15**, which was efficiently synthesized by Raines' protocol. After incorporation of a guanidine group by the Mitsunobu reaction, all protecting groups were efficiently removed by treatment with $BCl_3$ at low temperatures, even in the presence of an unstable *cis*-dihydrobenzofuran ring. The final deprotection step did not proceed with noticeable epimerization, suggesting that electrostatic interactions between the embedded guanidine and phenol of **1** may play a critical role in maintaining the *cis*-configuration despite an inherent preference for the epimer and generation of the *trans*-isomer **2**.[3] Thus, we achieved the first asymmetric synthesis of **1** using careful manipulations.

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**Supporting Information Available.** Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Detailed experimental procedures and spectral data are described in the Supporting Information.