ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Total Synthesis of (−)-Hippodamine by Stereocontrolled Construction of Azaphenalene Skeleton Based on Extended One-Pot Asymmetric Azaelectrocyclization

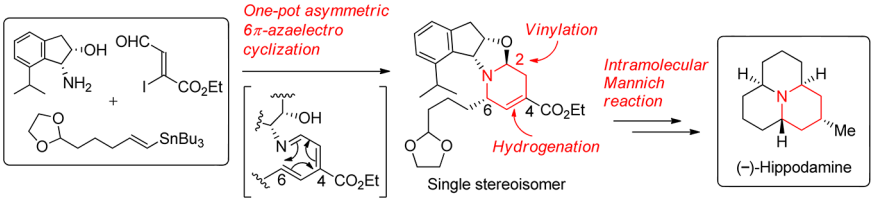
Shintaro Fujita, Taku Sakaguchi, Toyoharu Kobayashi,[†] Hiroshi Tsuchikawa,[‡] and Shigeo Katsumura*

School of Science and Technology, Kwansei Gakuin University, Gakuen 2-1, Sanda, Hyogo 669-1337, Japan

katsumura@kwansei.ac.jp

Received April 20, 2013

ABSTRACT



The first asymmetric total synthesis of (−)-hippodamine has been accomplished via the concise construction of its azaphenalene core, which is featured by the 2,4,6-chiral piperidine synthesis based on one-pot asymmetric azaelectrocyclization in the partially activated substituent system and the subsequent intramolecular Mannich reaction.

Ladybird beetles (Coccinellidae) are known to be beneficial insects controlling the ecosystem of harmful agricultural pests such as aphids and scale insects; however they also have some natural enemies such as ants and quails. To protect themselves, they utilize an interesting defense mechanism. When threatened, they release droplets of an oily and bitter tasting fluid from the joints to repulse their predators. The process is known as "reflex bleeding".[1] From these secretions in some species, several defensive alkaloids have been isolated and characterized,[2] and most of them have a methylated-perhydro-9b-azaphenalene ring system represented by myrrhine (**1**),[2a] precoccinelline (**2**),[2b] and hippodamine (**3**)[2c,d] (Figure 1). This intriguing structural feature stimulated a number of synthetic chemists to develop a novel synthetic strategy for this type of compound.[3−5] Since the first total synthesis of myrrhine (**1**) was reported by Ayer in 1976,[3a] various synthetic methods have been reported for precoccinelline (**2**),[3b,4] hippodamine (**3**),[3a,b,4f,5] and their *N*-oxides. Although elegant and efficient constructions of the azaphenalene framework have been developed, the syntheses of hippodamine (**3**) were not fully refined; for example it was obtained as an

[†] Present address: School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan.

[‡] Present address: Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama, Toyonaka, Osaka 560-0043, Japan.

(1) Happ, G. M.; Eisner, T. *Science* **1961**, *134*, 329.

(2) (a) Tursch, B.; Daloze, D.; Braekman, J. C.; Hootele, C.; Pasteels, J. M. *Tetrahedron* **1975**, *31*, 1541. (b) Tursch, B.; Daloze, D.; Dupont, M.; Pasteels, J. M.; Tricot, M. C. *Experientia* **1971**, *27*, 1380. (c) Tursch, B.; Daloze, D.; Pasteels, J. M.; Cravador, A.; Braekman, J. C.; Hootele, C.; Zimmermann, D. *Bull. Soc. Chim. Belg.* **1972**, *81*, 649. (d) Tursch, B.; Daloze, D.; Braekman, J. C.; Hootele, C.; Cravador, A.; Losman, D.; Karlsson, R. *Tetrahedron Lett.* **1974**, 409.

(3) For syntheses of myrrhine, see: (a) Ayer, W. A.; Dawe, R.; Eisner, R. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473. (b) Mueller, R. H.; Thompson, M. E.; DiPardo, R. M. *J. Org. Chem.* **1984**, *49*, 2271. (c) Gerasyuto, A. I.; Hsung, R. P. *J. Org. Chem.* **2007**, *72*, 2476. (d) Díaz-Gavilán, M.; Galloway, W. R. J. D.; O'Connell, K. M. G.; Hodkingson, J. T.; Spring, D. R. *Chem. Commun.* **2010**, *46*, 776.

(4) (a) Ayer, W. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 1494. (b) Mueller, R. H.; Thompson, M. E. *Tetrahedron Lett.* **1979**, 1991. (c) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032. (d) Yue, C.; Nicolay, J. F.; Royer, J.; Husson, H. P. *Tetrahedron* **1994**, *50*, 3139. (e) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. *Org. Lett.* **2002**, *4*, 3459. (f) Gerasyuto, A. I.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 4899.

(5) (a) Mueller, R. H.; Thompson, M. E. *Tetrahedron Lett.* **1980**, 1093. (b) Rejzek, M.; Stockman, R. A.; Hughes, D. L. *Org. Biomol. Chem.* **2005**, *3*, 73.

10.1021/ol4010917

unexpected isomerization product or via an intermediate accompanied by the undesired isomer. Moreover, its asymmetric total synthesis has not yet been achieved. Herein, we present the first total synthesis of (−)-hippodamine (**3**) by a target-oriented approach based on our one-pot asymmetric azaelectrocyclization protocol, in which all stereogenic centers of the objective azaphenalene ring have been created in a highly stereocontrolled manner.

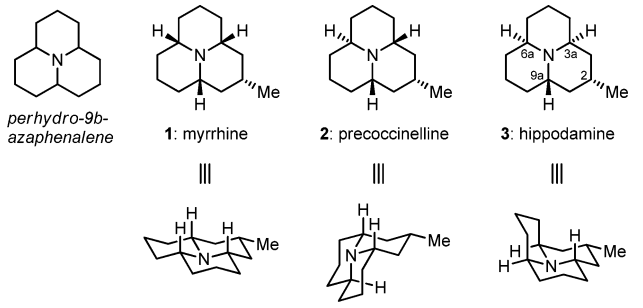


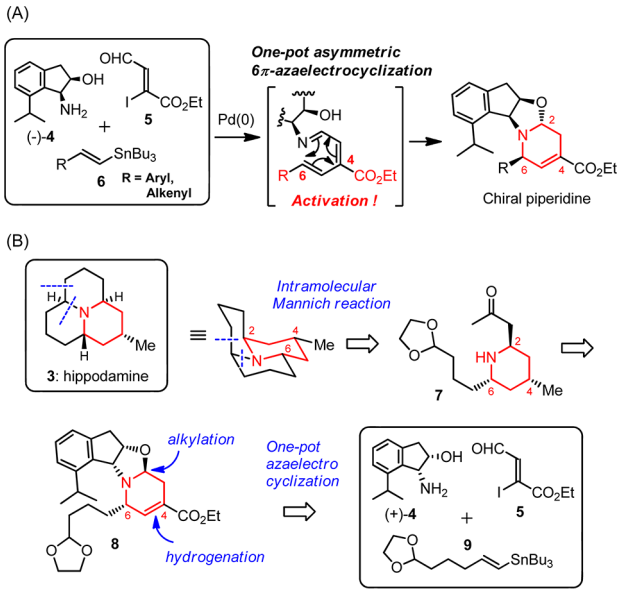
Figure 1. Structure of azaphenalene alkaloids.

Over the past five years, we have developed synthetic methods for multisubstituted chiral piperidine compounds based on a one-pot asymmetric azaelectrocyclization protocol from (−)-7-isopropyl-*cis*-1-amino-2-indanol (**4**), ethyl (*Z*)-2-iodo-4-oxobutenoate **5**, and vinylstannane **6** (Scheme 1A).[6] This reaction integration of three components[7] is a practical variant of a stepwise one under the kinetic conditions[8] and has played an important role in our recent accomplishments of natural alkaroid syntheses.[6b,d−f] We expected that this strategy could be applied to the facile asymmetric synthesis of hippodamine (**3**). As shown in our retrosynthesis (Scheme 1B), we envisioned the azaphenalene ring of **3** could be stereoselectively constructed by the intramolecular Mannich reaction of 2β,4α,6α-trisubstituted chiral piperidine compound **7**, whose substitution pattern would be favorable for the desired cyclization. The 2β and 4α substituents of **7** would be derived from the tetracyclic compound **8** by stereoselective alkylation of the aminal moiety and diastereoselective hydrogenation of the olefin moiety based on its characteristic structure.

The enantiomerically pure compound **8** including the C-6 stereogenic center was planned to be synthesized in one step via one-pot asymmetric 6π-azaelectrocyclization from three components: (+)-**4**, **5**, and 6,6-ethylenedioxy-1-hexenylstannane **9**.

Our synthesis commenced with the examination of a one-pot azacyclization (Scheme 2). Based on our accumulated

Scheme 1. (A) Chiral Piperidine Synthesis via One-Pot Asymmetric 6π-Azaelectrocyclization; (B) Retrosynthesis of Hippodamine



knowledge, not only the C-4 ester but also the C-6 arylic or alkenyl group in the azatriene was essential for the smooth electrocyclization as described in Scheme 1A.[6,9] Therefore optimization of the reaction conditions would be required in the case of vinylstannane **9** which has a saturated alkyl moiety. To obtain a criterion, we first attempted the reaction utilizing our previously established conditions.[6a] Thus, the mixture of conventionally prepared (+)-**4**[10] and ethyl (*Z*)-2-iodo-4-oxobutenoate **5**[9] in DMF was added to stannane **9**[11] and stirred in the presence of a Pd catalyst at 80 °C. Surprisingly, the reaction proceeded smoothly in only 20 min to afford the desired tetracyclic aminal **8** in 81% yield as a single stereoisomer. This unexpected but favorable result clearly showed that the accelerative effect of the C-6 olefinic substituent was not significant under these one-pot thermal conditions in contrast with that of C-4 ester, which led to the extension of the applicable scope of C-6 substituents.[12]

With the optically pure compound **8** in hand, we next examined its conversion to 2β,4α,6α-trisubstituted piperidine intermediate **7** (Scheme 3). According to our previous reports,[6b,f] the conjugated double bond of compound **8** was reduced by Raney nickel to afford the desired 4α ester **10** in 84% yield with excellent chemo- and stereoselectivity confirmed by an NOE experiment. To avoid the steric repulsion with the C-6α substituent which was completely restricted in pseudoaxial conformation, the reduction was considered to occur predominantly from the less hindered β-face. Then, the chemoselective reduction of ethyl ester to

(6) (a) Kobayashi, T.; Nakashima, M.; Hakogi, T.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3809. (b) Kobayashi, T.; Hasegawa, F.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3813. (c) Kobayashi, T.; Takeuchi, K.; Miwa, J.; Tsuchikawa, H.; Katsumura, S. *Chem. Commun.* **2009**, 3363. (d) Li, Y.; Kobayashi, T.; Katsumura, S. *Tetrahedron Lett.* **2009**, *50*, 4482. (e) Sakaguchi, T.; Kobayashi, S.; Katsumura, S. *Org. Biomol. Chem.* **2011**, *9*, 257. (f) Kobayashi, T.; Hasegawa, F.; Hirose, Y.; Tanaka, K.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2012**, *77*, 1812.

(7) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404.

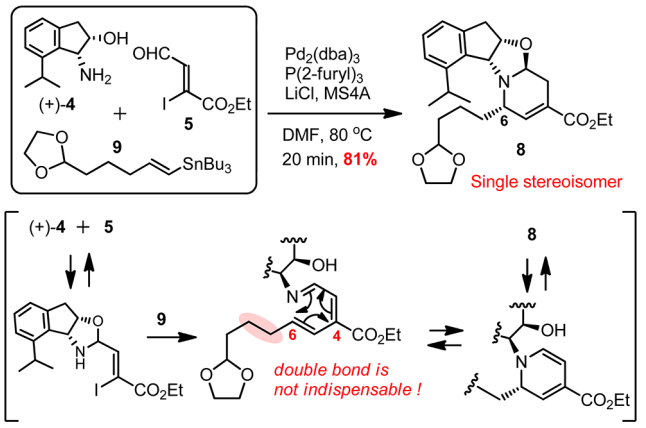
(8) Tanaka, K.; Katsumura, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660.

(9) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099.

(10) Kobayashi, T.; Tanaka, K.; Miwa, J.; Katsumura, S. *Tetrahedron: Asymmetry* **2004**, *15*, 185.

(11) The stannane **9** was readily synthesized from 5-hexyn-1-ol in three steps; see the Supporting Information.

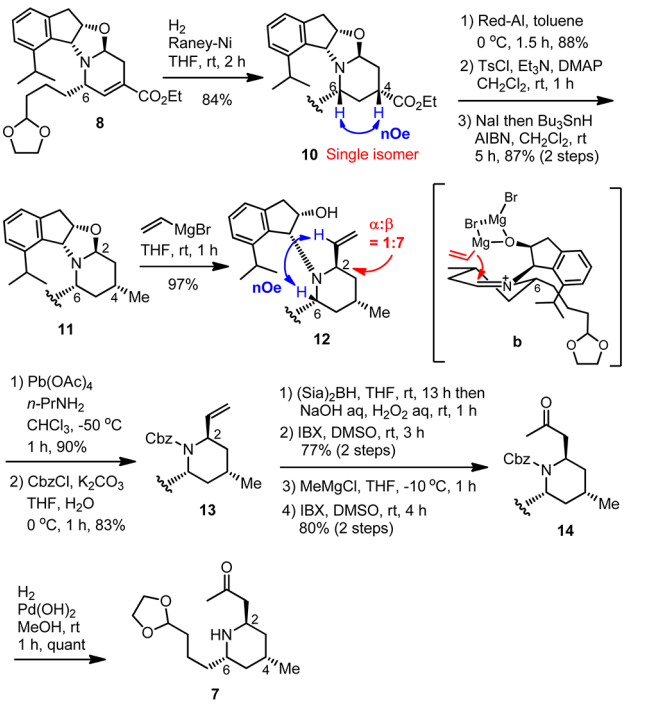
Scheme 2. One-Pot Asymmetric 6π-Azaelectrocyclization Using (+)-**4**, **5**, and Vinylstannane **9**



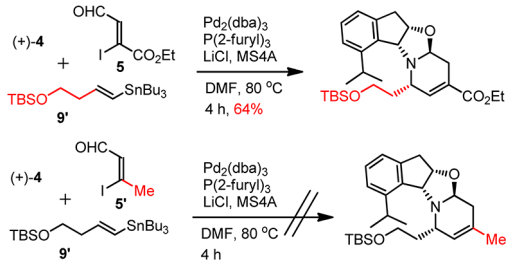
alcohol by Red-Al and the subsequent two-step deoxygenation[13] gave the 4α methyl derivative **11** in good yield. Next, in order to construct the third stereogenic center at C-2, the stereoselective vinylation was examined on the basis of our previous result.[14] When the aminal **11** was treated with excess vinylmagnesium bromide at room temperature, to our delight the reaction proceeded successfully to give the vinylated piperidine **12** in 97% yield with good selectivity (α:β = 1:7). The C-2 configuration was determined by the NOE correlation between the vinyl and H-6 proton, and the stereoselectivity could be explained as follows. As shown in the intermediary iminium structure **b** (Scheme 3), the indanol moiety on the nitrogen atom was confined to the opposite side of the C-6α alkyl substituent, and then the directing effect of the alkoxide on the Grignard reagent resulted in the β-preferred vinylation. After the removal of the indanol moiety in **12** with lead tetraacetate[15] under the established conditions,[6b] the resulting secondary amine was protected with Cbz. The minor C-2α isomer was easily separated in this step to give pure compound **13** in 83% yield. Next, the double bond of **13** was transformed into methyl ketone through a four-step sequence: disiamylborane-mediated hydroboration–oxidation and IBX oxidation gave the corresponding aldehyde, followed by methylation with MeLi and then IBX oxidation to produce the ketone **14**, which was finally converted to the desired chiral piperidine **7** by the hydrogenolysis of the Cbz group in quantitative yield.

With the key cyclization precursor obtained, we next turned our attention to the stereoselective intramolecular Mannich reaction (Scheme 4). To the compound **7** in benzene was added *p*-toluenesulfonic acid monohydrate, and the mixture was stirred under reflux with a Dean–Stark trap for 5 h. Gratifyingly, the reaction progressed cleanly to give the desired azaphenalene **15** in 91% yield as a single isomer. As we expected, the fourth stereogenic center was completely controlled by the appropriate substituents on piperidine **7**. More specifically, in two possible conformations of the intermediary bicyclic iminium as shown in structures **c** and **d**, which were formed by the first cyclization of the aldehyde to the amine, the conformer **c** leading to the ***epi*-15** was thought to be unfavorable due to the severe 1,3-diaxial interaction; therefore the second cyclization proceeded predominantly through conformer **d**. Finally, by reference to Ayer's literature,[3a] the ketal **15** was deoxgenated via a dithioketalization–desulfuration method to complete the total synthesis of hippodamine. The spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS) were in good agreement with those of the natural product,[5b,16] and the $[\alpha]_D$ value was measured for the first time.

Scheme 3. Synthesis of 2,4,6-Trisubstituted Piperidine Compound **7**



(12) In supplemental experiments, the 4-siloxy-1-butenylstannane **9′** also gave the cyclization product, but compound **5′**, possessing a C-4 methyl group instead of the ester group, did not afford the desired product under the same conditions.



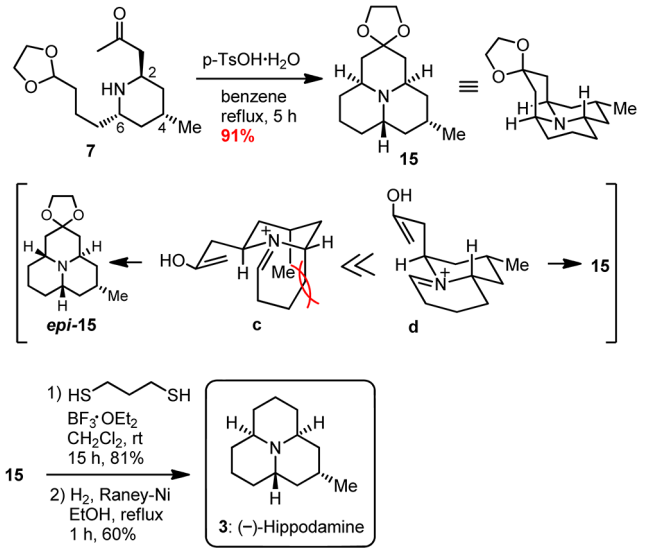
(13) Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* **1983**, 795.

(14) The methylation at the C-2 position of the aminal derivative possessing C-4-methyl and C-6-siloxypropyl substituents with the same relative configuration as compound **11** afforded the desired product with high diastereoselectivity. See ref 6f.

(15) Suginome, H.; Umeda, H.; Masamune, T. *Tetrahedron Lett.* **1970**, *11*, 4571.

(16) Lebrun, B.; Braekman, J. C.; Daloze, D. *Magn. Reson. Chem.* **1999**, *37*, 60.

Scheme 4. Intramolecular Mannich Reaction of **7** and Completion of Total Synthesis of (−)-Hippodamine



In summary, we accomplished the first asymmetric total synthesis of (−)-hippodamine by achieving the concise construction of its azaphenalene core, which was featured by two points. (1) The piperidine nucleus with the C-6 chiral center was created by a one-pot asymmetric azaelectrocyclization in the partially activated substituent system, which extended the potential of this protocol. (2) The remaining three stereogenic centers of the desired azaphenalene framework were fluently built in a highly stereocontrolled manner by utilizing the characteristic structural features of each substrate in each step. We demonstrated here that the synthetic method developed from the chiral piperidine scaffold became a powerful strategy for the synthesis of azaphenalene-type alkaloids.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research on Innovative Areas 22106541 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. The experimantal details of reactions and ^{1}H and ^{13}C NMR spectra of the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.