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Stereoselective Synthesis of 7-*epi*-Incarvilline

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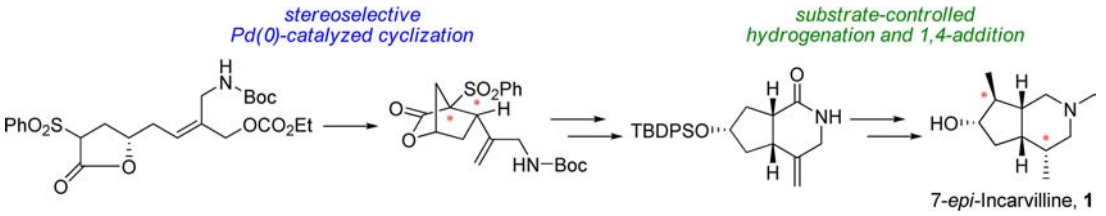
ABSTRACT



The enantioselective synthesis of 7-*epi*-incarvilline for formal syntheses of (−)-incarvilline, (+)-incarvine C, and (−)-incarvillateine is described. The key features of our synthesis involve (1) stereoselective construction of the optically active bicyclic lactone utilizing Pd(0)-catalyzed allylic alkylation, (2) efficient transformation of the bridged bicyclic lactone to the key bicyclic lactam skeleton, and (3) stereoselective elaborations of two stereocenters via a substrate-controlled catalytic hydrogenation and a 1,4-addition.

A new class of monoterpene alkaloids including (−)-incarvilline (**2**), (+)-incarvine C (**3**), and (−)-incarvillateine (**4**) was first isolated from the plant *Incarvillea sinensis* (Figure 1).[1] These incarvillea alkaloids have been used traditionally as the Chinese folk medicine "jiaohao" because of their potent analgesic properties.[1a,2] (−)-Incarvilline (**2**) and (−)-incarvillateine (**4**), which is biosynthetically subjected to originate by dimerization of (+)-incarvine C (**3**),[3c] were considered as the major components responsible for any pharmacological effects. Structurally, the five contiguous stereocenters are compactly arranged on the common bicyclic piperidine backbone, and the unique molecular architecture provided an intriguing synthetic challenge. Accordingly, these monoterpenes have attracted considerable attention from the synthetic and medicinal communities.[3]

Recently, we have extensively studied the syntheses and applications of bridged bicyclic lactones as equivalents of the optically active disubstituted hydroxycyclopentanes,[4a] employing substrate-controlled Pd(0)-catalyzed cyclizations and subsequent isomerization.[4] Taking advantage of a highly diastereoselective construction of bicyclic lactones, the lactone intermediates were used for the efficient syntheses of various natural products including brefeldin A,[4b,c] bacillariolide III,[4d] and a natural iridoid.[4f] These successful applications prompted us to attempt the total synthesis of bioactive incarvillea alkaloids. Herein, we describe an enantioselective synthesis of 7-*epi*-incarvilline (**1**) as an advanced key intermediate for formal syntheses of (−)-incarvilline (**2**), (+)-incarvine C (**3**), and (−)-incarvillateine (**4**).

[†] These authors contributed equally to this work.

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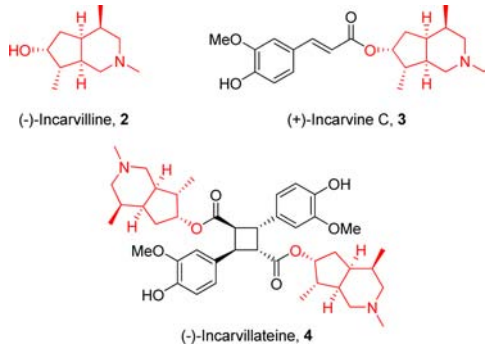
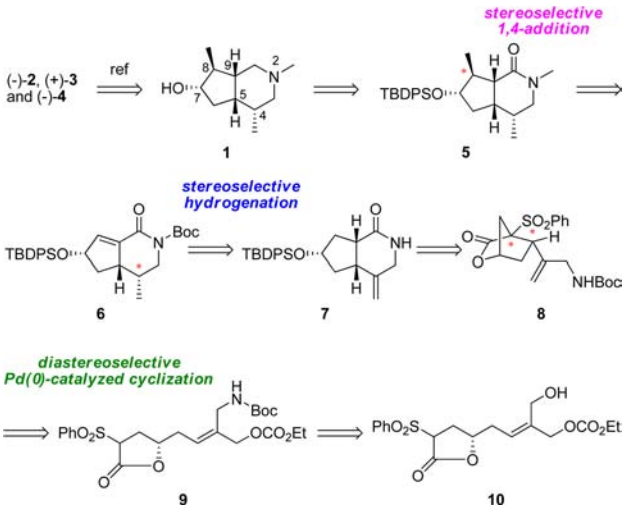


Figure 1. Structures of (−)-incarvilline and the related alkaloids.

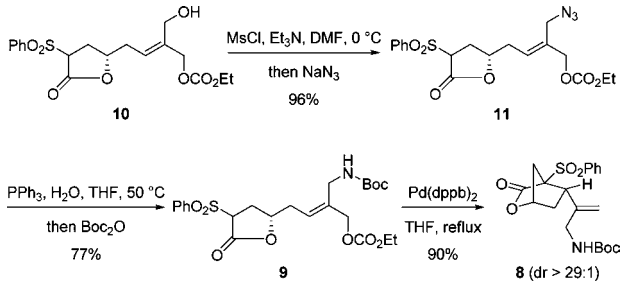
Our retrosynthetic plan toward alkaloid **1** is outlined in Scheme 1. The overall strategy was based on the substrate-controlled stereocontrol of the five contiguous stereocenters within the final intermediate **1**. Thus, our synthesis initially focused on the stereoselective construction of the highly functionalized bicyclic lactam **7**, which consists of a *cis*-fused bicyclic skeleton, three stereocenters, and an *exo*-methylene. The two stereocenters with the methyl substituent of **1** could be diastereoselectively elaborated by a stereoselective catalytic hydrogenation and a 1,4-addition, respectively. The bicyclic lactam **7** was readily accessible via an isomerization of the bicyclic lactone **8**, which would be constructed through the substrate-controlled Pd(0)-catalyzed cyclization of γ-lactone **9** employing the procedure that we developed.[4] The cyclization precursor **9** was expected to be conveniently prepared from intermediate **10** via an amine substitution.

Scheme 1. Retrosynthetic Analysis



Synthesis of **1** commenced from the advanced γ-lactone **10** which was previously reported by our group (Scheme 2).[4f] Mesylation of **10** and NaN_3 treatment of the resulting mesylate yielded azide **11**. Azide **11** was carefully reduced under Staudinger conditions, and the resulting primary amine was protected with Boc_2O to give carbamate **9**.[5] With the desired precursor **9** available, we investigated a diastereoselective palladium(0)-catalyzed cyclization. The intramolecular allylic alkylation in the presence of $Pd(dppb)_2$ in THF proceeded smoothly to furnish the desired bicyclic lactone **8** in 90% yield and with excellent diastereoselectivity (> 29:1).[4] The high diastereoselectivity is likely due to the preference of the Pd−π-allyl complex with a less steric repulsion between the benzenesulfonyl group and the R substituent.[6] As expected, cyclization of the azide precursor **11** under the same conditions provided low diastereoselectivity (2:1), which implied a size effect of the R-substituent on the diastereoselectvity.

Scheme 2. Synthesis of [2.1.2] Bicyclic Lactone **8** by Pd(0)-Catalyzed Cyclization



With the optically active bicyclic lactone **8** available, we executed construction of the *cis*-fused bicyclic backbone of **1** (Scheme 3). Desulfonylation of **8** with Na/Hg 6% in the presence of $B(OH)_3$ effectively afforded the bicyclic lactone **12** in 91% yield.[7] Boc-deprotection of **12** with a combination of TMSOTf and 2,6-lutidine and a spontaneous intramolecular amidation produced the *cis*-fused bicyclic lactam **13**. After protection of alcohol **13** with TBDPSCl, exposure of lactam **7** to catalytic hydrogenation conditions (Pd/C, H_2) resulted in a stereoselective reduction of *exo*-methylene to afford lactam **14** in 98% yield with a good diastereoselectivity (> 7:1, assigned by ^{1}H NMR).[3a] The diastereomeric mixture of **14**, which was inseparable by chromatograpy, was purified after Boc-protection to give an optically pure lactam **15** in 98% yield.[8]

At the conversion stage from bicyclic lactam **15** to 7-*epi*-incarvilline **1**, we encountered a challenging task for the stereoselective incorporation of the methyl substituent on the C8 stereocenter (Scheme 4). After intensive investigation

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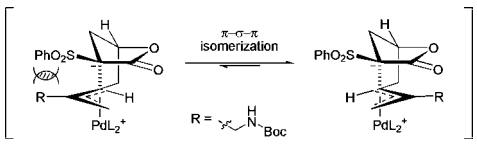
(6) A plausible mechanism of Pd(0)-catalyzed cyclization.



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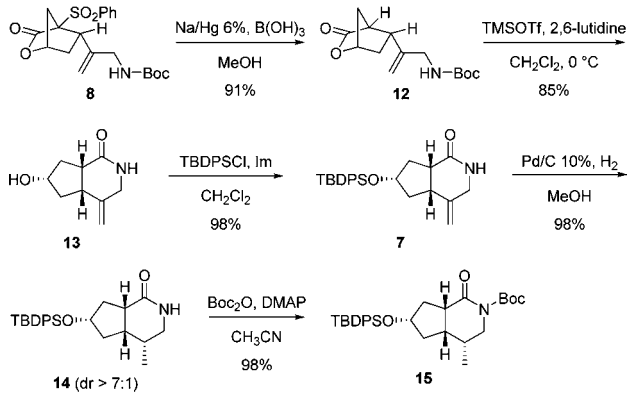
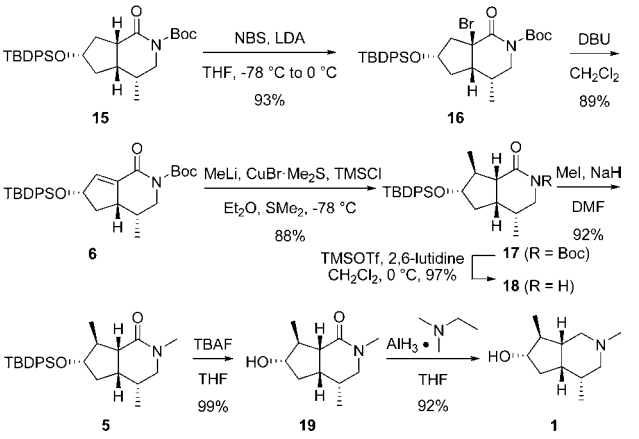
Scheme 3. Synthesis of the Fused Bicyclic Lactam **15**



for an efficient construction of the C8 stereocenter, we focused on the substrate-controlled stereoselective 1,4-addition. To generate a requisite Michael acceptor, our initial attempt utilizing a sequence of α-phenylselenylation of amide **15** and subsequent selenoxide elimination resulted in a *syn*-elimination involving a *β*-hydrogen at the ring junction. Thus, we turned our attention to an alternative procedure for a selective *anti*-elimination involving the C8 hydrogen. Diastereoselective α-bromination of amide **15** with LDA and *N*-bromosuccinimide in THF afforded **16**.[9] Exposure of α-bromolactam **16** to DBU in CH_2Cl_2 successfully afforded the desired Michael acceptor **6** in high yield.[10] The TMS-promoted Michael addition reaction of **6** with Me_2CuLi exclusively produced the desired lactam **17** in 88% yield without the observation of other diastereomer.[11] The excellent stereoselectivity is likely mainly due to an attack of Me_2CuLi on the convex face of the cyclopentene moiety. Careful Boc-deprotection of **17** with TMSOTf and 2,6-lutidine followed by *N*-methylation of the resultant lactam **18** furnished lactam **5**. Sequential TBDPS deprotection of **5** and amide reduction[12] finally provided 7-*epi*-incarvilline **1**, a core and advanced intermediate for syntheses of (−)-incarvilline (**2**), (+)-incarvine C (**3**), and (−)-incarvillateine (**4**). All spectral data of the synthetic

Scheme 4. Synthesis of 7-*epi*-Incarvilline (**1**) via Stereoselective 1,4-Addition of Me_2CuLi



7-*epi*-incarvilline (**1**) were identical to those of the authentic **1**. The correct C7 stereochemistries for **2**−**4** are provided by Mitsunobu reaction of **1** with the corresponding carboxylic acid.[3]

In summary, we have accomplished the substrate-controlled asymmetric synthesis of 7-*epi*-incarvilline (**1**) via a high-yielding sequence from the known intermediate **10**. The key features of our synthesis include diastereoselective construction of the [2.1.2] bicyclic lactone **8** using a stereoselective Pd(0)-catalyzed cyclization, isomerization of the bridged bicyclic lactone **12** to the *cis*-fused bicyclic lactam **13** and elaboration of two stereocenters via stereoselective catalytic hydrogenation and Michael addition. Considering the efficiency and synthetic feasibility of the synthetic route, our synthetic strategy seems widely applicable to structurally related alkaloids.

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Supporting Information Available. Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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