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Synthetic studies on isoschizogamine: construction of [3.3.1] bicyclic aminal core by using oxidative skeletal rearrangement

Hirofumi Ueda, Akihiro Takada, Hidetoshi Tokuyama *

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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This article is dedicated to memory of the late Professor Emeritus Keiichiro Fukumoto

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ABSTRACT

The tetracyclic core structure of isoschizogamine containing aminal functionality was constructed by oxidative skeletal rearrangement of a 1,2-diaminoethene derivative. The 1,2-diaminoethane was prepared by palladium-catalyzed allylation at the 4*a* position of a 1,2,3,4-tetrahydro-β-carboline derivative and subsequent lactam formation. After the oxidative skeletal rearrangement using dimethyldioxirane, the allyl group was removed by a three-step sequence to provide the tetracyclic core skeleton of isoschizogamine with aminal functionality.

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Biologically active polycyclic alkaloids containing aminal functionality have often been found in nature. Among them, isoschizogamine (**1**), isolated from the shrub of *Schizozygia caffaeoides*,[1] is a member of the schizozygane indole alkaloid (Fig. 1). Since schizozygane family compounds typically possess a hexacyclic ring system including an indoline skeleton, the structure of isoschizogamine was initially assigned as compound **1′**, an epimer of schizogamine (**5**) at the C-7 position (Fig. 2).[2] Later, Hajicek et al. revised the structure **1′** to **1** with a densely fused tetrahydroisoquinoline core containing four consecutive stereogenic centers and aminal functionality.[3]

The densely fused aminal structures in **1** have posed a formidable synthetic challenge and inspired significant interest from the synthetic community. The first racemic total synthesis of **1** was achieved by Heathcock and co-workers in 1999,[4] which was followed by the recently completed Fukuyama's first asymmetric total synthesis.[5] In addition, three synthetic studies have been reported to date.[6]

During the course of our research program on synthetic studies on dimeric indole alkaloid, (+)-haplophytine (**11**), we developed a strategy for the construction of [3.3.1] bicyclic aminal framework from indole derivative **7** by a sequential oxidative skeletal rearrangement (Scheme 1).[7] The plausible reaction mechanism of the

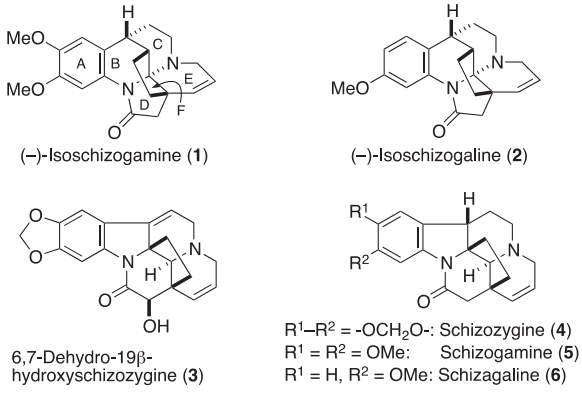

Figure 1. Schizogamine alkaloids.

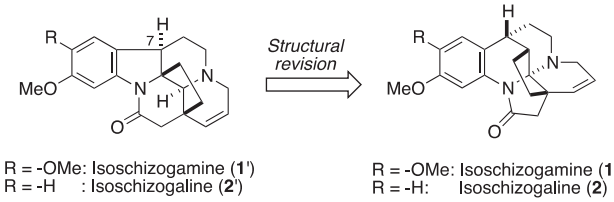

Figure 2. Structural revision of isoschizogamine (**1**).

* Corresponding author.
E-mail addresses: tokuyama@mail.pharm.tohoku.ac.jp, tokuyama@m.tohoku.ac.jp (H. Tokuyama).

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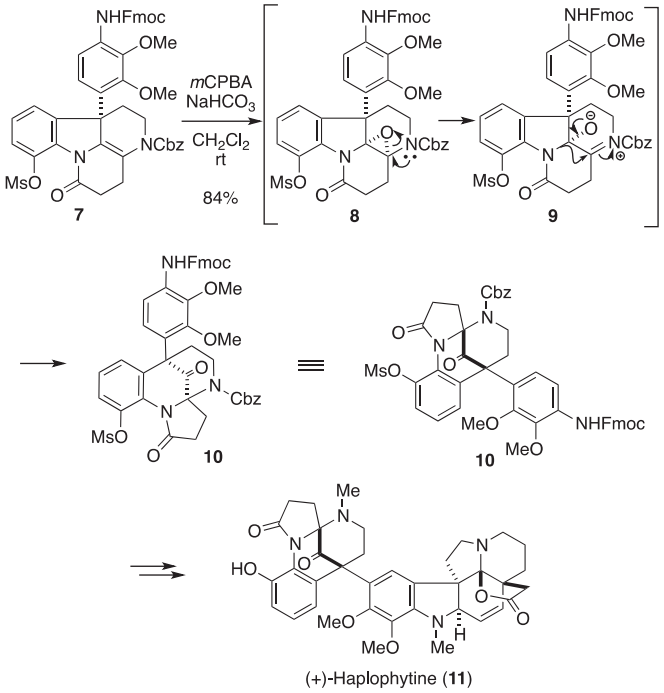
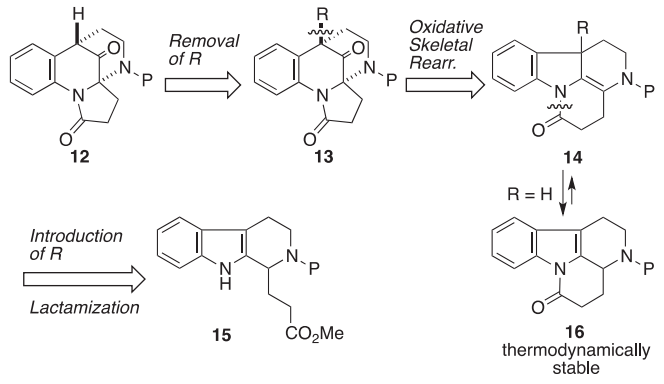


Scheme 1. Development of oxidative skeletal rearrangement in total synthesis of (+)-haplophytine (**11**).

sequence is epoxidation of the 1,2-diaminoethene moiety and spontaneous ring opening of epoxide by nitrogen of the Cbz carbamate to afford a zwitterionic species **9**. Then, 1,2-shift of the C–N bond by a way of semi-pinacol type rearrangement[8] gives the [3.3.1] bicyclic aminal system. We considered that this strategy should serve as a powerful means for construction of a broad range of polycyclic alkaloids containing densely fused aminal from easily accessible substrates. Herein, we describe stereoselective construction of the [3.3.1] bicyclic aminal core of **1** by utilizing the oxidative skeletal rearrangement developed in our group.



Scheme 2. Synthetic strategy for tetracyclic core of isoschizogamine (**1**).

Our synthetic strategy for **12**, a possible intermediate for isoschizogamine (**1**), is shown in Scheme 2. For construction of the [3.3.1] bicyclic aminal skeleton, we planned to conduct the oxidative skeletal rearrangement of **14**. Compound **14** would be readily prepared from tetrahydro-β-carboline **15** by introduction of the substituent at the C-7 position and lactamization of the resultant indolenine derivative with migration of the double bond. Introduction of a substituent at the C-7 position is necessary to prevent tautomerization from the 1,2-diaminoethene form **14** to the thermodynamically more stable indole form **16**. After construction of the aminal structure, the substituent should be removed to obtain **12**. Tetrahydro-β-carboline **15** would be prepared from tryptamine via Bischler–Napieralski reaction.[7c,9]

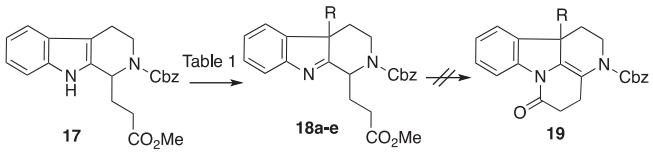
We initiated research by exploration of a suitable substituent at the C-7 position. First, tetrahydro-β-carboline derivative **17**, which was prepared from tryptamine derivative by a three-step sequence,[10] was subjected to halogenation conditions (Table 1). Disappointingly, fluorination[11] and chlorination[12] conditions resulted in formation of complex mixtures containing trace amounts of haloindolenines (entries 1 and 2). On the other hand, iodination[7a,b] by using *N*-iodosuccinimide (NIS) proceeded smoothly to give the corresponding iodoindolenine **18c** in a high yield (entry 3). In addition, installation of the acetoxy group took place nicely by treatment of **17** with $Pb(OAc)_4$[13] to give **18d** in <64% yield (entry 4).

On the other hand, treatment with *N*-(phenylseleno)phthalimide (*N*-PSP)[14] in the presence of 10-camphorsulfonic acid (CSA) did not provide the desired product **18e**. Although we have succeeded in the introduction of iodo and acetoxy groups at the C-7 position, these compounds could not be converted to the desired lactam **19** under a variety of conditions due to elimination of substituent.

With these unsuccessful results, we then examined the introduction of a more robust substituent, an allyl group, and the subsequent lactamization (Scheme 3). The desired allylation at the C-7 position proceeded smoothly when tetrahydro-β-carboline derivative **17** was subjected to palladium catalyzed allylation conditions reported by Rawal and co-workers[15] to furnish allyl indolenine **20** as a 1.7:1 mixture of diastereomers.

Unexpectedly, the next lactamization reaction was strongly dependent on the relative stereochemistry between the allyl group and the ester side chain. After chromatographic separation, two

Table 1
Introduction of substituents at C-7 position



Entry	Reagents (equiv)	Solvent	Temp	Time (min)	R	Yield
1	Selectfluor (1.5)	CH_3CN	rt	10	F	Complex mixture
2	*t*-BuOCl (1.1)	CH_2Cl_2	0 °C	10	Cl	Complex mixture
3	NIS (1.5)	CH_2Cl_2	rt	5	I	**18c**, 89%
4	$Pb(OAc)_4$ (1.5)	CH_2Cl_2	rt	5	OAc	**18d**, <64%
5	CSA (2.0), *N*-PSP (3.0)	CH_2Cl_2	rt	5	SePh	Complex mixture

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