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DEVELOPMENT OF SAMARIUM DIODIDE-PROMOTED REDUCTIVE CARBON-NITROGEN BOND CLEAVAGE REACTION OF α -AMINO CARBONYL COMPOUNDS: APPLICATION TO THE SYNTHESIS OF BIOLOGICALLY ACTIVE ALKALOIDS

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Abstract – Samarium diiodide (SmI_2) is a mild and selective one electron transfer reagent, and has become an important tool for developing a variety of useful and unique transformations. SmI_2 has been utilized in a wide range of synthetic transformations ranging from interconversion of functional groups to carbon-carbon bond forming reactions. Among the various reactions developed for SmI_2 , we focused our attention on its use for fragmentation reactions. We have already established a regioselective carbon-carbon bond cleavage reaction of γ -halo carbonyl compounds, and its utilization in the synthesis of various types of biologically active natural products. However, a SmI_2 -promoted reductive carbon-nitrogen bond cleavage reaction has received relatively little attention. In this review article, we would like to describe a general carbon-nitrogen bond cleavage reaction of α -amino carbonyl compounds and the utilization of this methodology in the synthesis of a number of bioactive alkaloids, since this reaction proceeds in relatively high yield under mild reaction conditions.

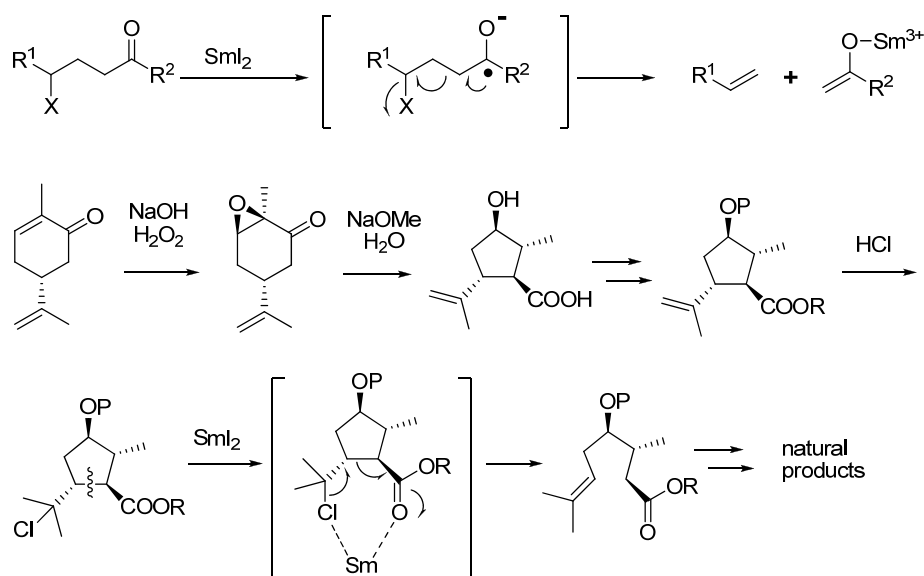
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1. INTRODUCTION

Samarium diiodide (SmI_2), probably the most versatile lanthanide compound, was firstly introduced as a useful synthetic tool in organic synthesis by Kagan and co-workers,¹ thereafter, this reagent rapidly became an established reagent for developing a variety of useful and unique transformations.² Due to the characteristic feature of samarium(II) to revert to the more stable samarium(III) oxidation state, SmI_2 is recognized to be a mild and selective one-electron transfer reagent and has been utilized in a wide range of synthetic transformations ranging from interconversion of functional groups to carbon-carbon bond forming reactions.

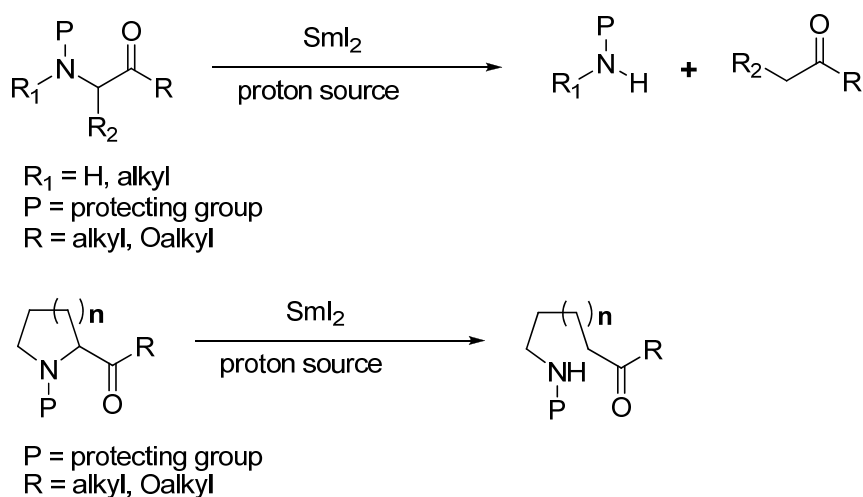


Scheme 1. SmI_2 -promoted regioselective carbon-carbon bond cleavage reaction of γ -halo carbonyl compounds

Among the various reactions developed for SmI_2 , we focused our attention on its use for fragmentation

reactions. Regarding the fragmentation reactions employing SmI_2 as a powerful one-electron reducing reagent, much effort has been devoted to studying the reductive deoxygenation of α -hydroxy or α -alkoxy carbonyl compounds, however, its application to a regioselective carbon-carbon or carbon-nitrogen bond cleavage reaction has received relatively little attention. We have already established a regioselective carbon-carbon bond cleavage reaction of γ -halo carbonyl compounds, and this strategy was utilized in the synthesis of various types of natural products³ (Scheme 1).

In continuation of our work on the synthesis of biologically active natural products using SmI_2 , we were interested in researching a general carbon-nitrogen bond cleavage reaction of α -amino carbonyl compounds (Scheme 2), and are able to obtain successful results concerning systematic investigation of SmI_2 -promoted reductive carbon-nitrogen bond cleavage reaction.⁴



Scheme 2. SmI_2 -promoted regioselective carbon-nitrogen bond cleavage reaction of α -amino carbonyl compounds

2. GENERAL CARBON-NITROGEN BOND CLEAVAGE REACTION⁴

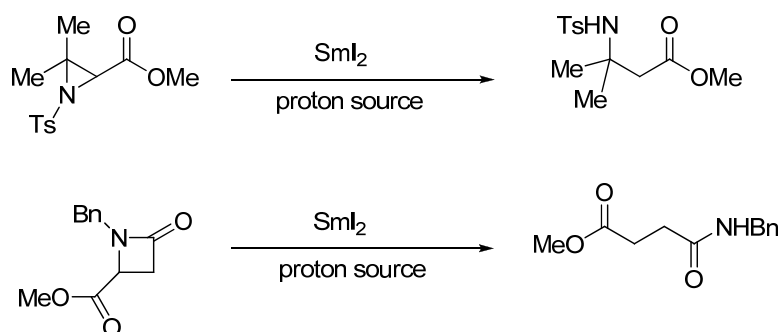
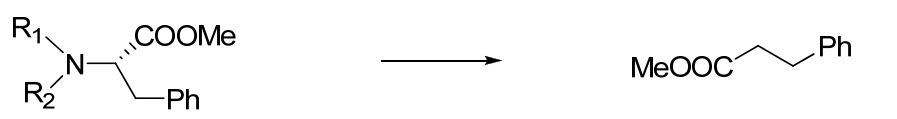


Figure 1. Reductive carbon-nitrogen bond cleavage of α -amino carbonyl compounds with SmI_2 reported by Molander

Attractive examples of SmI₂-promoted carbon-nitrogen bond cleavage reaction were reported by Molander and Stengel using 2-acylaziridines and 4-acylazetid-2-one as starting materials (Figure 1),⁵ in which the leaving amino groups (nitrogen-containing groups) were involved in highly strained three- or four-membered rings. Similar fragmentation reactions were also employed in the reductive removal of an *N*-substituted benzotriazolyl group,⁶ and in the isonitrile–nitrile rearrangement.⁷

Initially, we applied the SmI₂-promoted carbon-nitrogen bond cleavage reaction to phenylalanine derivatives,⁸ and the results obtained are summarized in Table 1.

Table 1. Reductive C-N bond cleavage reaction of phenylalanine derivatives



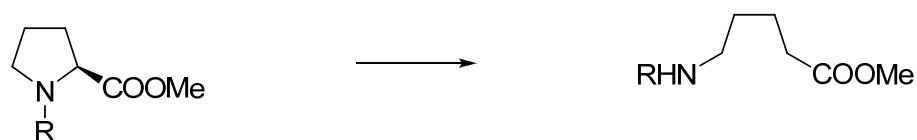
R ₁	R ₂	Proton source	Reaction time	Yield (%)
H	H	MeOH	30 min	73
H	H	pivalic acid	15 min	80
H	Me	MeOH	30 min	71
H	Bn	MeOH	2.5 h	85
Me	Me	MeOH	< 5 min	90
Bn	Bn	MeOH	4 h	93
H	Ac	MeOH	15 min	99
H	Boc	MeOH	N.R.	-
H	Boc	pivalic acid	N.R.	-
H	Boc	DMAE	N.R.	-
Me	Cbz	MeOH	N.R.	-

Reaction conditions: starting material (0.5 mmol); SmI₂ (5 equiv.); HMPA (5 equiv.); proton source (2.5 equiv.); solvent (THF); 0 °C to rt
N.R. = no reaction

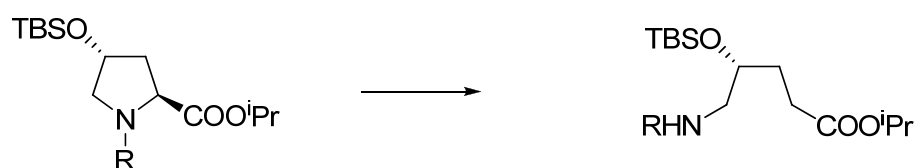
Based on the above results, it was concluded that reductive carbon-nitrogen bond cleavage reaction with SmI₂ has a generality and is applicable to the wide variety of amino functions including primary, secondary and tertiary amines, and also amide groups as leaving groups. The fragmentation usually took place within 30 min in the presence of a proton source, such as MeOH or pivalic acid, to provide methyl dihydrocinnamate in high yields, although a relatively prolonged reaction time was required in the case of benzyl-substituted amines as leaving groups. The reactions of proline derivatives⁹ (Table 2) and ethyl pipercolinate derivatives¹⁰ (Table 3), in which the leaving amino groups were involved in the cyclic systems, under the same reaction conditions as above gave the corresponding fragmentation products in good yields. The fragmentation could be applied not only to α -amino esters but also to α -amino ketones. Thus, treatment of α -acetylpiperidine derivatives¹¹ with SmI₂ also furnished the desired compounds, in

high yields, in which both alkyl and acyl derivatives of amines could be used as leaving groups (Table 3). Interestingly, the reaction of *N*-(2-oxopropyl)phthalimide with SmI_2 in THF–HMPA in the presence of MeOH yielded phthalimide in 72% yield (Table 3). This result suggested that 2-oxopropyl group might be used as a protecting group for a nitrogen atom of amino-, amide, or imide-functions.

Table 2. Reductive C–N bond cleavage reaction of proline derivatives



R	Proton source	Reaction time	Yield (%)
H	MeOH	30 min	62
H	pivalic acid	10 min	73
Bn	MeOH	9 h	82
Boc	MeOH	N.R.	-
Boc	pivalic acid	N.R.	-
Boc	DMAE	N.R.	-



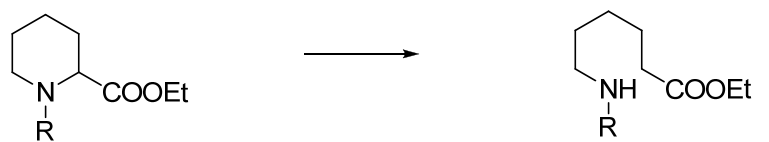
R	Proton source	Reaction time	Yield (%)
H	MeOH	1.5 h	88
Bn	MeOH	7.5 h	99
Cbz	MeOH	N.R.	-

Reaction conditions: starting material (0.5 mmol); SmI_2 (5 equiv.); HMPA (5 equiv.); proton source (2.5 equiv.); solvent (THF); 0 °C to rt
N.R. = no reaction

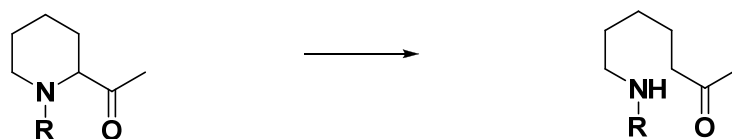
We next investigated the effect of proton sources, and found that *N,N*-dimethylaminoethanol (DMAE) was also effective for this reaction as well as MeOH and pivalic acid (Table 4). It should be noted that this reaction can be carried out under neutral reaction conditions in the presence of other functional groups, such as alkyl ester, alkyl ether, imide and amide groups. Moreover, this reaction proceeded in the presence or absence of HMPA, however, the presence of HMPA proved desirable in terms of yields and reaction times (Tables 2, 3 and 4). These results were in agreement with those observed in the reductive deoxygenation reactions, since HMPA was recognized to increase the rate of the reaction of SmI_2 .¹² As can be seen in Table 2, the fragmentation product bearing a primary amino function sometimes afforded the cyclization compound. This type of conversion will provide a useful route for the synthesis of

naturally occurring or biologically interesting piperidine derivatives in optically active forms. Indeed, heating of isopropyl δ -amino- γ -*tert*-butyldimethylsiloxyvalerate in THF for 2 days gave 5-*tert*-butyldimethylsiloxy-2-piperidone in 75% yield.

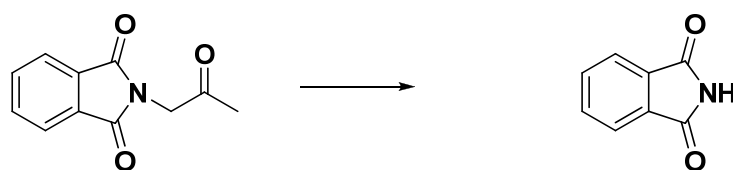
Table 3. Reductive C-N bond cleavage reaction of pipercolinate, 2-acetylpiperidine, and a phthalimide derivatives



R	Proton source	Reaction time	Yield (%)
Me	MeOH	<5 min	86
Bn	MeOH	<5 min	89
Ac	MeOH	45 min	78
Boc	MeOH	N.R.	-
Boc	pivalic acid	N.R.	-
Boc	DMAE	N.R.	-



R	Proton source	Reaction time	Yield (%)
Me	MeOH	1 min	87
Bn	MeOH	1 min	96
Ac	MeOH	<5 min	94
Boc	MeOH	<5 min	96

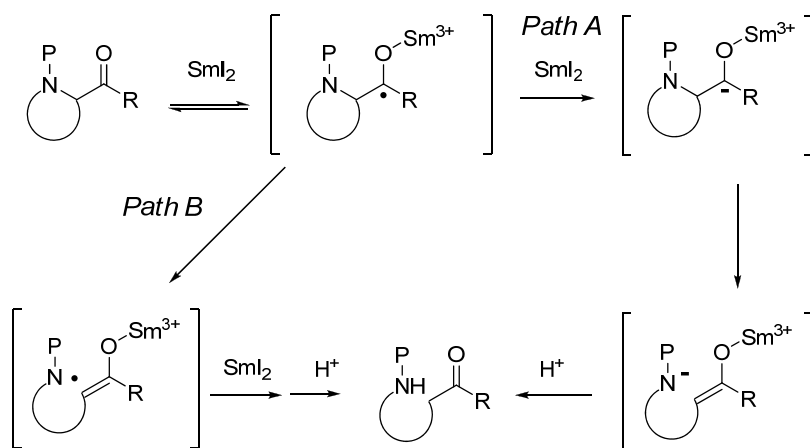


Proton source	Reaction time	Yield (%)
MeOH	1 min	72

Reaction conditions: starting material (0.5 mmol); SmI_2 (5 equiv.); HMPA (5 equiv.); proton source (2.5 equiv.); solvent (THF); 0 °C to rt

N.R. = no reaction

Thus, we were able to develop a general reductive carbon-nitrogen bond cleavage reaction employing SmI_2 in THF-HMPA. The proposed reaction mechanism was shown in Scheme 3.



Scheme 3. Proposed reaction mechanism for the fragmentation

Table 4. Investigation of the proton source and the effect of HMPA in reductive fragmentation

entry	substrate	product	reaction time	proton source	additive	yield (%)
1			5 h	MeOH	none	65
			1.5 h	MeOH	HMPA	88
			40 min	pivalic acid	HMPA	82
			45 min	DMAE	HMPA	90
2			18 h	MeOH	none	85
			9 h	MeOH	HMPA	82
			1 h	pivalic acid	HMPA	92
			2 h	DMAE	HMPA	78
3			36 h	MeOH	none	76
			7.5 h	MeOH	HMPA	99
			45 min	pivalic acid	HMPA	88
			1.5h	DMAE	HMPA	93
4			12 h	MeOH	none	50
			45 min	MeOH	HMPA	78
			<5 min	pivalic acid	HMPA	86
			10 min	DMAE	HMPA	71

Reaction condition: substrate (0.5 mmol); SmI_2 (5 equiv.); HMPA (5 equiv.); proton source (2.5 equiv.); solvent (THF), 0 °C to rt

Since this reaction proceeds in relatively high yield under mild reaction conditions and seems to be applicable to the wide variety of α -amino carbonyl compounds, we planned its utilization for the synthesis of (-)-adalinine.¹³

3. FIRST GENERATION SYNTHESIS OF (-)-ADALININE¹⁴

(-)-Adalinine **1**, isolated from the secretion of the European two-spotted ladybird beetle, *Adalia bipunctata*, as a minor component, together with major alkaloid (-)- adaline **2**, is a simple piperidine alkaloid with a chiral quaternary carbon center, and the structure of **1** was determined by spectroscopic methods.¹⁵ This alkaloid was shown to be present in all of the life cycle stages of *Adalia bipunctata*, as well as in the adults of a related species, *A. decempunctata*.¹⁵ Adalinine **1** has also been proposed to be biosynthetically derived from the major alkaloid adaline (**2**) via a retro-Mannich reaction¹⁵ (Figure 2).

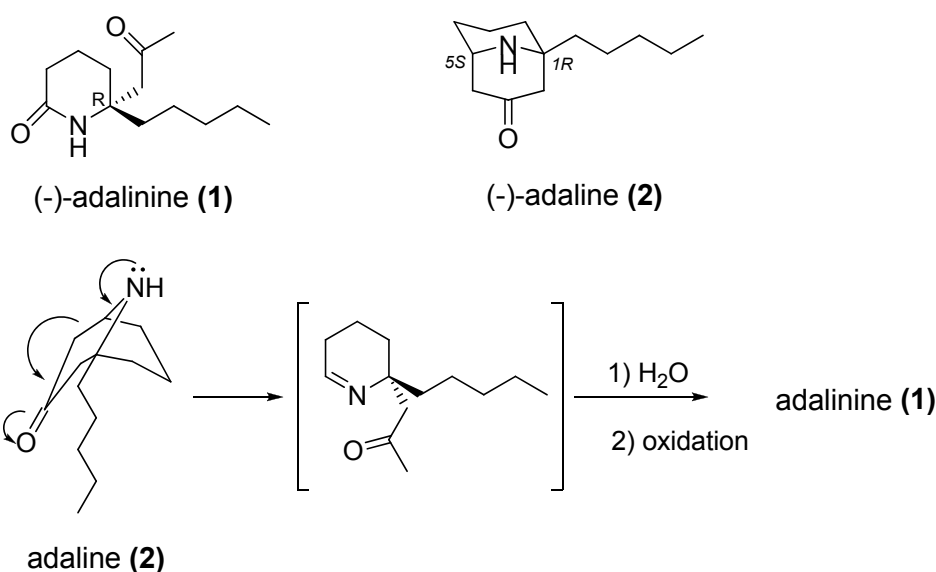


Figure 2. Structures of (-)-adalinine and (-)-adaline

The relatively simple alkaloid **1** seems to be the target molecule for the application of newly developed synthetic methods and strategies. Consequently, one chiral synthesis¹⁶ of **1** leading to the determination of its absolute configuration and three syntheses of its racemate¹⁷ have been reported.

Our devised retrosynthetic route to (-)-adalinine (**1**) is depicted in Figure 3, in which we envisaged that a chiral quaternary carbon center could be constructed with the desired stereochemistry via Michael addition of a pentyl group to enaminone **A**, readily accessible from (*S*)-(-)-pyroglutamic acid, by the control of the stereochemistry of the ester function on the pyrrolidine ring. Moreover, a ring enlargement of pyrrolidine derivative **B** to δ -lactam would easily be achieved by application of a samarium-promoted fragmentation reaction, followed by recyclization of the resulting amino ester **C**.

Thus, the requisite optically active pyrrolidine derivative bearing a chiral quaternary carbon center was prepared starting from thiolactam (**3**).¹⁸ Treatment of **3** with bromoacetone and subsequent desulfurization of thioether (**4**) with triphenylphosphine¹⁹ gave (*Z*)-enaminone (**5**). After protection of the amino group of **5**, the resulting (*E*)-Boc-enaminone (**6**) was subjected to Michael addition with pentylmagnesium bromide in the presence of a copper sulfide-dimethyl sulfide complex²⁰ to provide the desired pyrrolidine (**7**).

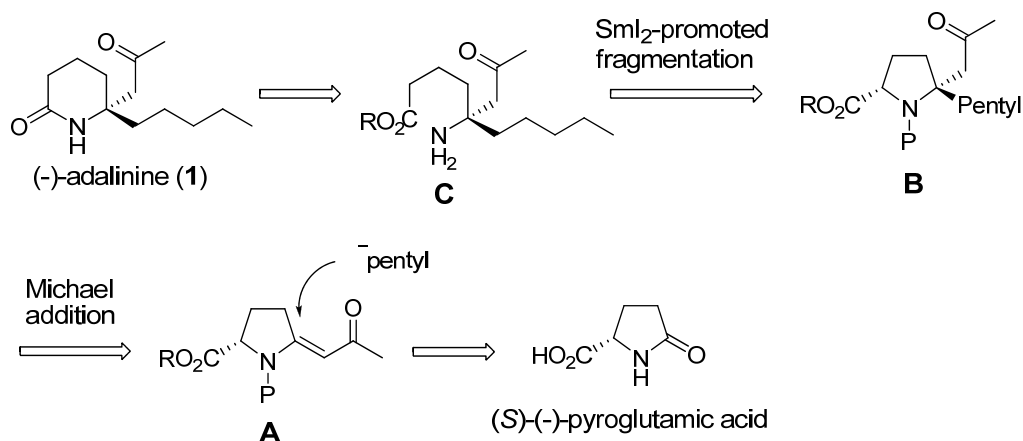
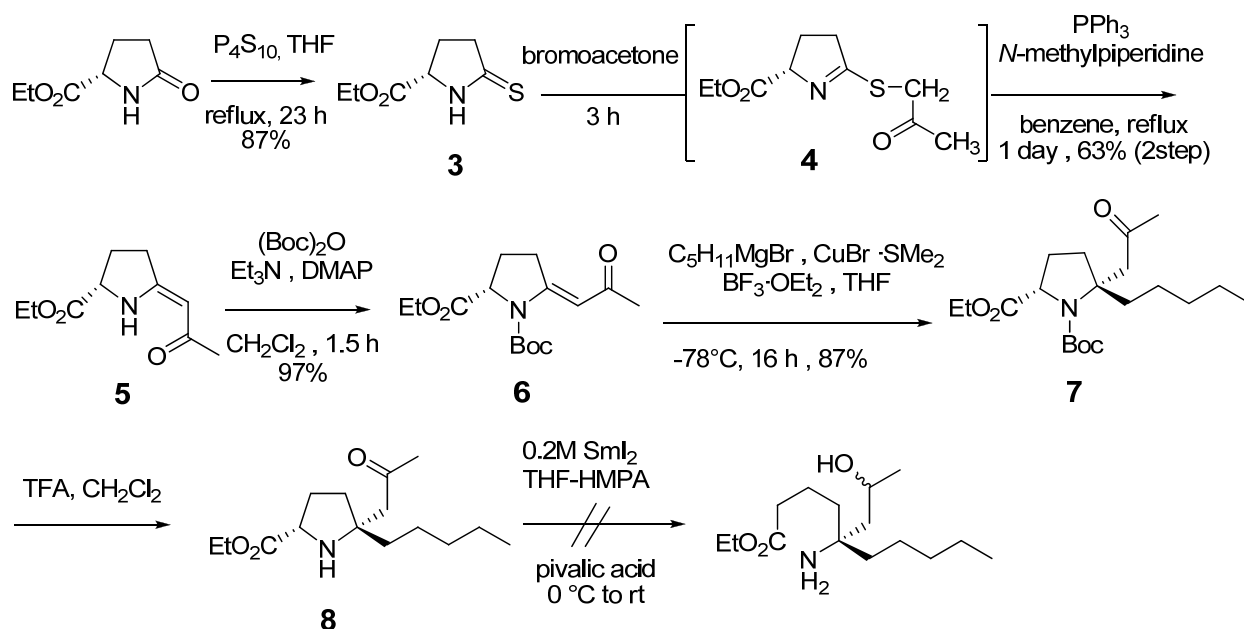


Figure 3. Retrosynthetic route for (-)-adalinine

Although the stereochemistry of the newly generated chiral center could not be determined at this stage, it was assumed that the major product (**7**) should have the correct stereochemistry for natural product synthesis, since Michael addition of a pentyl group would be expected to take place from the less hindered side of enaminone (**6**). With the desired pyrrolidine derivative available, we first investigated a samarium-promoted carbon-nitrogen bond cleavage reaction for keto ester (**7**) or its de-Boc derivative (**8**); however, none of the desired fragmentation product could be obtained. We thought that this result might be caused by the presence of another reactive site, such as a ketone carbonyl function (Scheme 4).

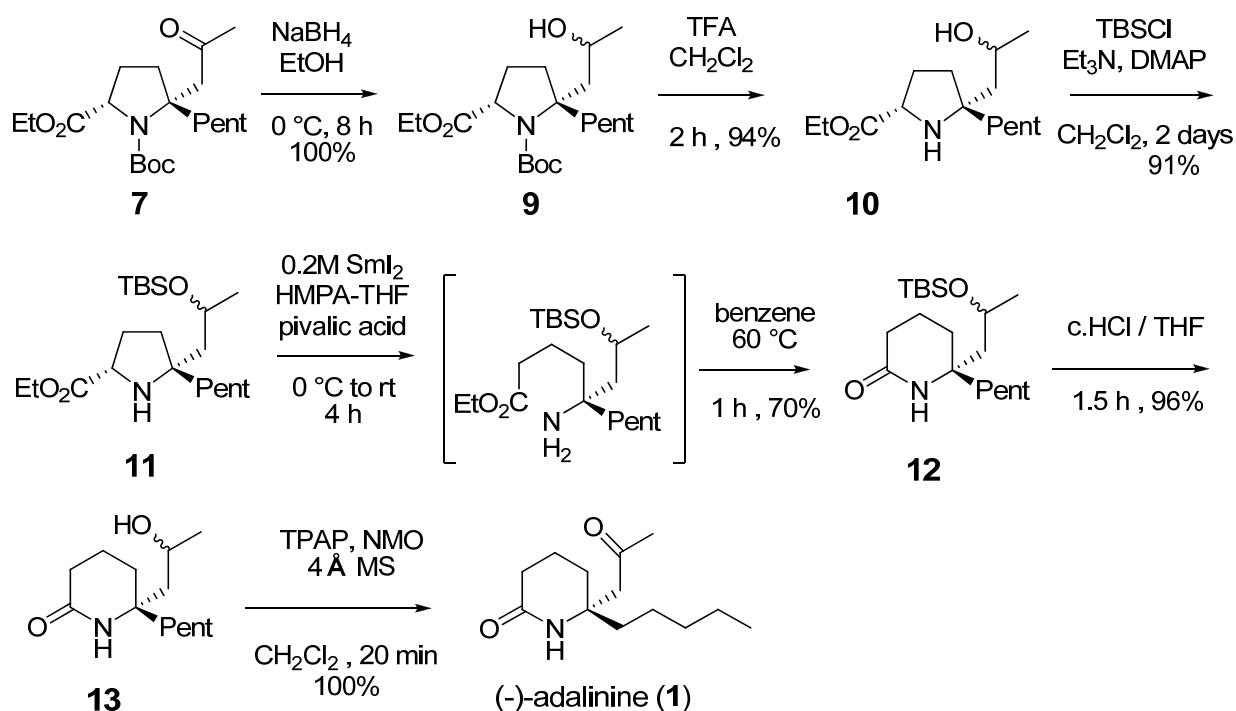


Scheme 4. Construction of the carbon quaternary center of (-)-adalinine

Ketone (**7**) was, therefore, reduced with NaBH_4 to give alcohol (**9**) as an inseparable diastereoisomeric mixture (*ca.* 1:1). After deprotection of the Boc group on treatment with TFA, the resulting alcohol (**10**)

was further converted to silyl ether (**11**) in the usual manner (Scheme 5). Attempted fragmentation reaction of **11** with 5 equiv of samarium iodide in THF-HMPA (7:1) in the presence of pivalic acid as a proton source took place the carbon-nitrogen bond cleavage smoothly, and simultaneous cyclization of the resulting δ -amino ester to give the desired δ -lactam (**12**) in 70% yield.²¹ In our previous study on this fragmentation reaction,⁴ a co-solvent HMPA usually required only 5 equiv; however, it was found that the use of a smaller amount of HMPA or its absence in the conversion of **11** to **12** decreased the yield, remarkably. Finally, desilylation of **12** on acid hydrolysis with hydrochloric acid, followed by oxidation of the resulting alcohol (**13**) with TPAP and NMO according to the reported procedure¹⁶ gave (-)-adalinine **1** (Scheme 5). Spectroscopic data (¹H and ¹³C NMR, MS, IR) of **1** including specific optical rotation $\{[\alpha]_D -30.4 (c 0.8, \text{CH}_2\text{Cl}_2); \text{lit.},^{16} [\alpha]_D -28.3 (c 1.6, \text{CH}_2\text{Cl}_2)\}$ were identical with those reported.¹⁶

Thus, we were able to apply a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction to the chiral synthesis of **1** successfully.



Scheme 5. Synthesis of (-)-adalinine

4. SYNTHESIS OF (+)-FRBRIFUGINE AND (-)-ISOFRBRIFUGINE²²

Febrifugine (**14**) and isofebrifugine (**15**) were isolated from the roots of *Dichroa febrifuga* Lour. (Chinese Name: Cháng Shan) in 1947,²³ and are recognized as active principles against malaria.²⁴ Structures including the absolute stereochemistries of those alkaloids were unambiguously established by their syntheses in 1999 (Figure 4).²⁵

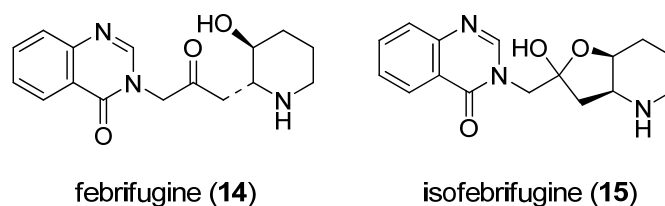
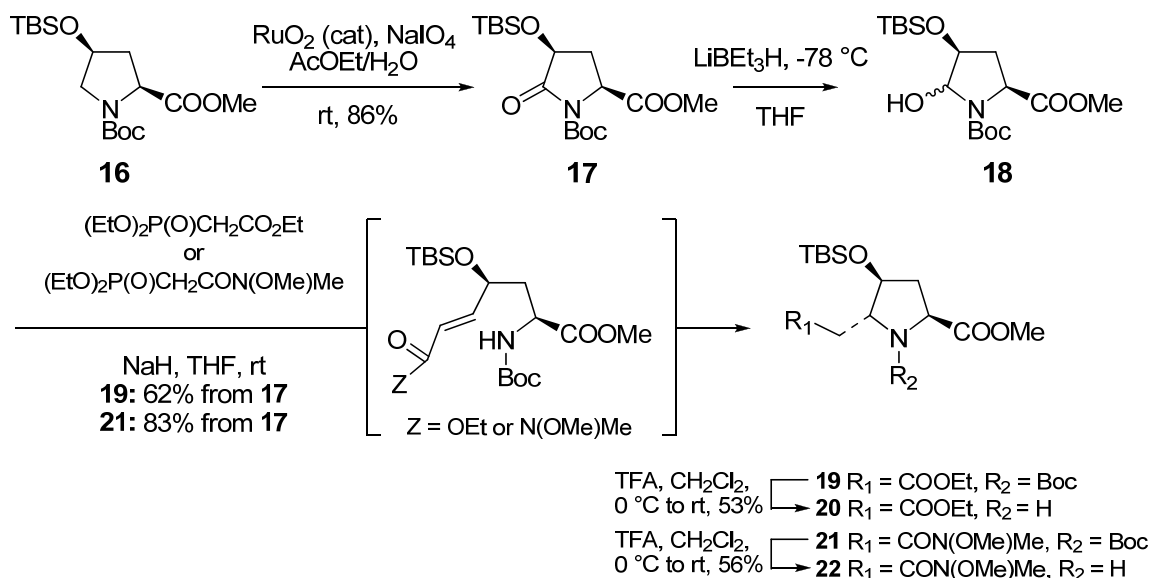


Figure 4. The structures of (+)-febrifugine (**14**) and (+)-isofebrifugine (**15**)

Since these alkaloids exhibit the attractive biological activity, a number of their racemic and chiral syntheses have been established.²⁶ Applying SmI₂-promoted carbon-nitrogen bond cleavage reaction of α -amino carbonyl compounds, we attempted the synthesis of potential anti-malarial piperidine alkaloids, febrifugine (**14**) and isofebrifugine (**15**).

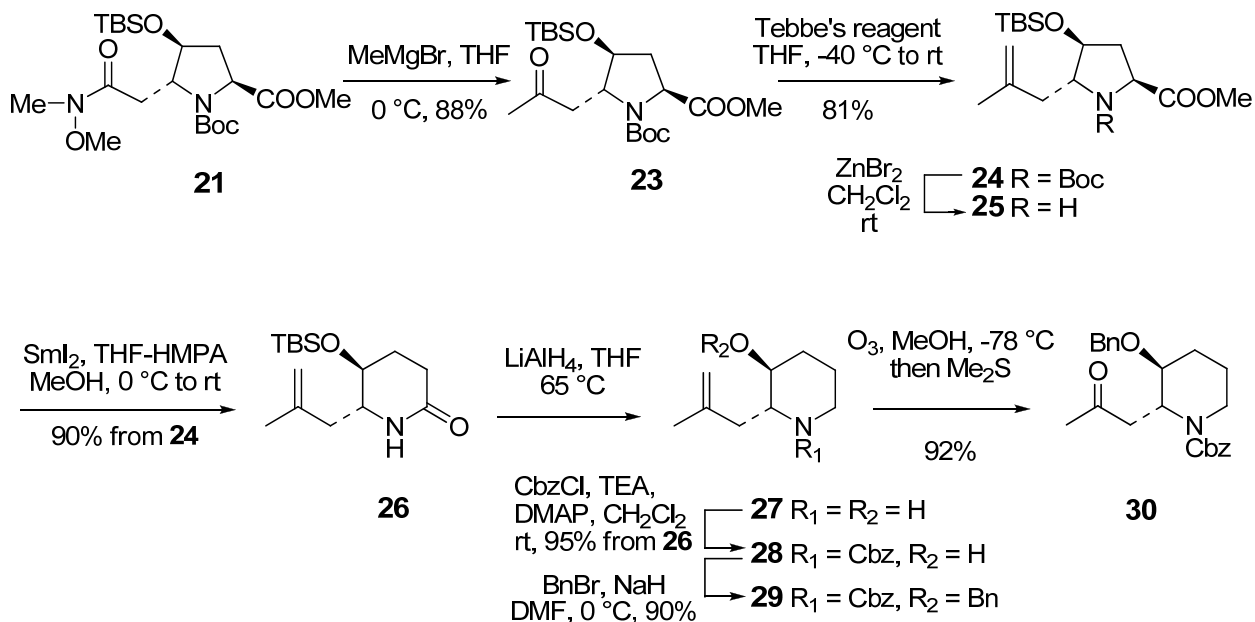
Our synthesis of (+)-febrifugine starts from the stereoselective preparation of 4-hydroxy-5-alkyl-L-prolinate, as follows.

Oxidation of methyl *N*-Boc-(4*S*)-*tert*-butyldimethylsilyloxy-L-prolinate (**16**) with ruthenium tetroxide according to the literature gave lactam (**17**).²⁷ In order to synthesize (+)-febrifugine, a stereoselective introduction of an alkyl side chain at the 5-position of **17** with the 2,5-*trans*-stereochemistry would be required. Although a number of strategies have been developed for stereoselective introduction of an alkyl side chain at the 5-position of pyroglutamic acid ester,²⁸ some of them were found to have a limitation, in terms of nucleophilic species, conversion yield, reaction conditions, and stereoselectivity. Among the various reaction conditions attempted, we could find that a tandem Horner-Emmons-Michael reaction²⁹ gave the best results for introducing the desired alkyl side chain, in terms of yield and stereoselectivity. Thus, lactam (**17**) was reduced with lithium triethylborohydride to give aminal (**18**), which without purification, was treated with triethylphosphonoacetate in the presence of sodium hydride to afford diester (**19**) in 62% from **17**. Although diester (**19**) was obtained as a mixture of the amide rotamers, the stereochemistry at the 5-position was assumed to be *R*-configuration based on the analysis of the NMR spectral data. To determine the stereoselectivity of this reaction, the *N*-Boc group of **19** was removed by treatment with trifluoroacetic acid to give amine (**20**) as the sole product. The spectroscopic data of **20** clearly indicated that a tandem Horner-Emmons-Michael reaction proceeded, stereoselectively, and the stereochemistry at the 5-position of **19** would be controlled during the intramolecular Michael addition of the nitrogen to the α,β -unsaturated ester, generated by the Horner-Emmons reaction, where the addition of the nitrogen might occur from the sterically less hindered side of the substrate.^{29b} As the difficulties were mentioned for the selective reduction of the ethyl ester to manipulate the side chain prior to the reduction of the methyl ester, we attempted to prepare a more versatile precursor for further modification of the side chain.



Scheme 6. Synthesis of *trans*-2,5-disubstituted pyrrolidine derivatives

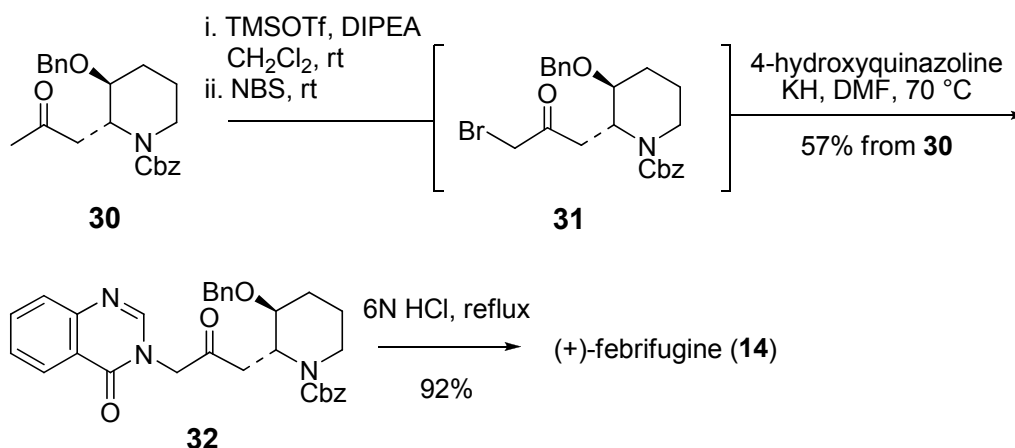
Treatment of **18** with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate in the presence of sodium hydride provided amide-ester (**21**) in 83% from **17**. The configuration at the 5-position of **21** was assumed to be *R* based on the analyses of NOE experiments, and was unambiguously determined by the X-Ray crystallographic analysis of the corresponding NH compound (**22**) (Scheme 6).



Scheme 7. Sml_2 -promoted transformation of pyrrolidine to piperidine derivative

Since we could achieve the introduction of the side chain at the 5-position with the desired stereochemistry, we focused our attention on further utilization of amide-ester (**21**) in the synthesis of (+)-febrifugine. Treatment of **21** with methylmagnesium bromide gave ketone (**23**), as the sole product, which was further converted into olefin (**24**) by methylenation with the Wittig reagent in 43% yield.

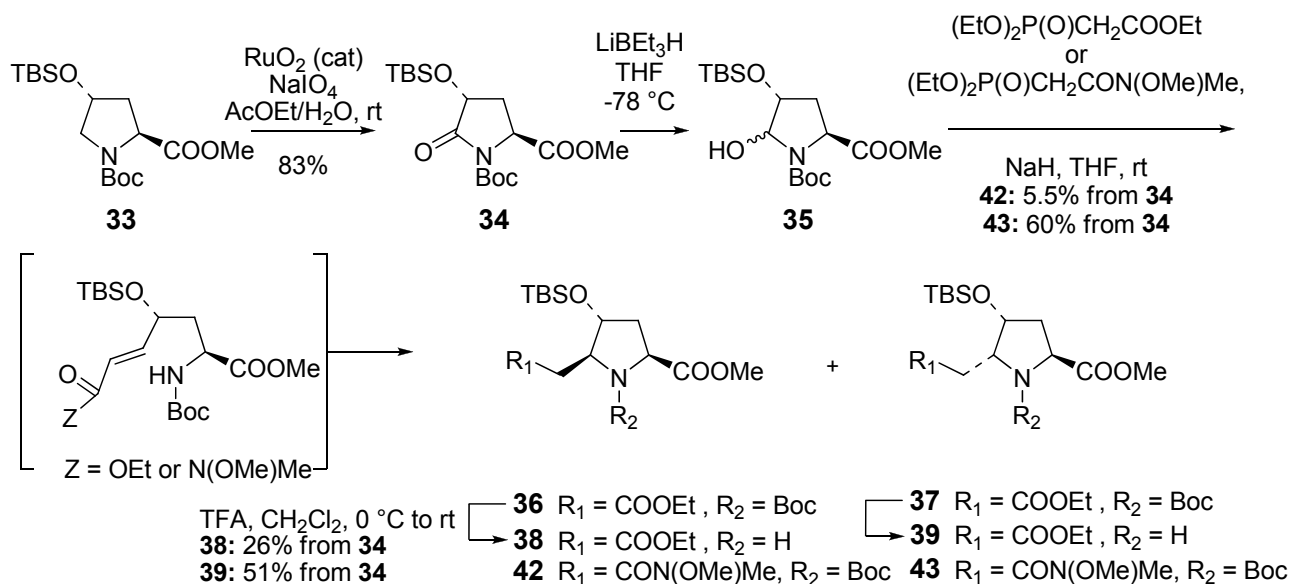
Olefin (**24**) was also synthesized by treatment of **23** with Tebbe's reagent³⁰ in an improved yield. After selective removal of the Boc group of **24** with zinc bromide, the resulting amine (**25**) was subjected to the key reductive fragmentation reaction by using SmI_2 in the presence of MeOH as the proton source to give δ -lactam (**26**) arising from a recyclization of the carbon-nitrogen bond cleavage product, in 90% yield. Lithium aluminum hydride reduction of **26**, followed by treatment of the resulting hydroxy-amine (**27**) with CbzCl afforded carbamate (**28**), where deprotection of the silyl group was observed during the reduction of the amide function. Protection of the secondary hydroxy group of **28** with benzyl bromide in the presence of sodium hydride gave benzyl ether (**29**), which, on ozonolysis, followed by the usual reductive work-up with methyl sulfide, furnished methyl ketone (**30**) in 83% yield from **28** (Scheme 7). Bromination of **30** was achieved by treatment with trimethylsilyl triflate and subsequently with *N*-bromosuccinimide to give bromo-ketone (**31**), which, without purification, was further coupled with 4-hydroxyquinazoline in the presence of potassium hydride in DMF to provide the protected febrifugine (**32**) (Scheme 8).



Scheme 8. Synthesis of (+)-febrifugine

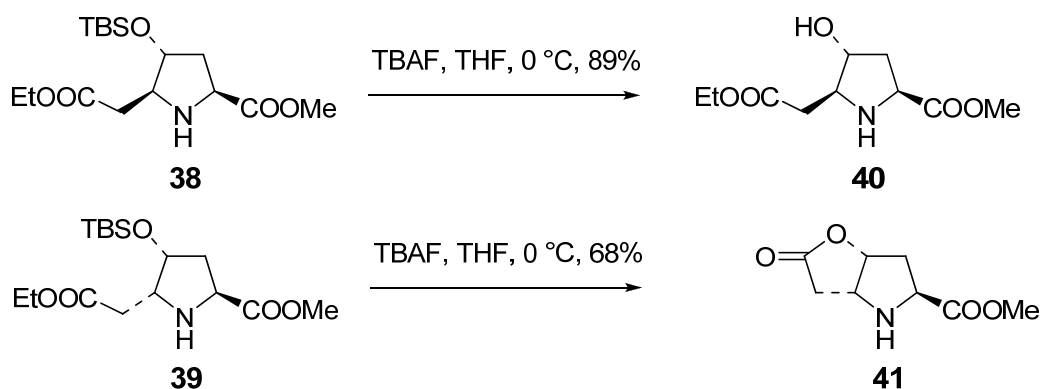
Finally, deprotection of **32** with 6N hydrochloric acid furnished (+)-febrifugine (**14**) in 92% yield. The spectroscopic data of the synthesized compound including the specific optical rotation were comparable to those reported in the literatures, mp 139-140 °C; $[\alpha]_{\text{D}} +16.0$ (c 0.4, MeOH) {lit.,^{23b} mp 139-140 °C; lit.,^{26b} mp 138-139 °C; lit.,^{23c} $[\alpha]_{\text{D}} +13.0$ (c 0.65, MeOH)}. Thus, we could develop a novel synthetic pathway to (+)-febrifugine by employing SmI_2 -promoted reductive carbon-nitrogen bond cleavage, as a key reaction. Since this strategy is applicable to the construction of functionalized piperidine rings in optically active forms, we next attempt the stereoselective synthesis of (-)-isofebrifugine, an antipodal form of the natural product, due to the accessibility of a starting material.

For the synthesis of (-)-isofebrifugine, an introduction of an alkyl side chain at the 5-position of 4-hydroxypyroglutamate would be required with the relative stereochemistry of 2,5-*trans*- and 4,5-*cis*-relationships (Scheme 9).



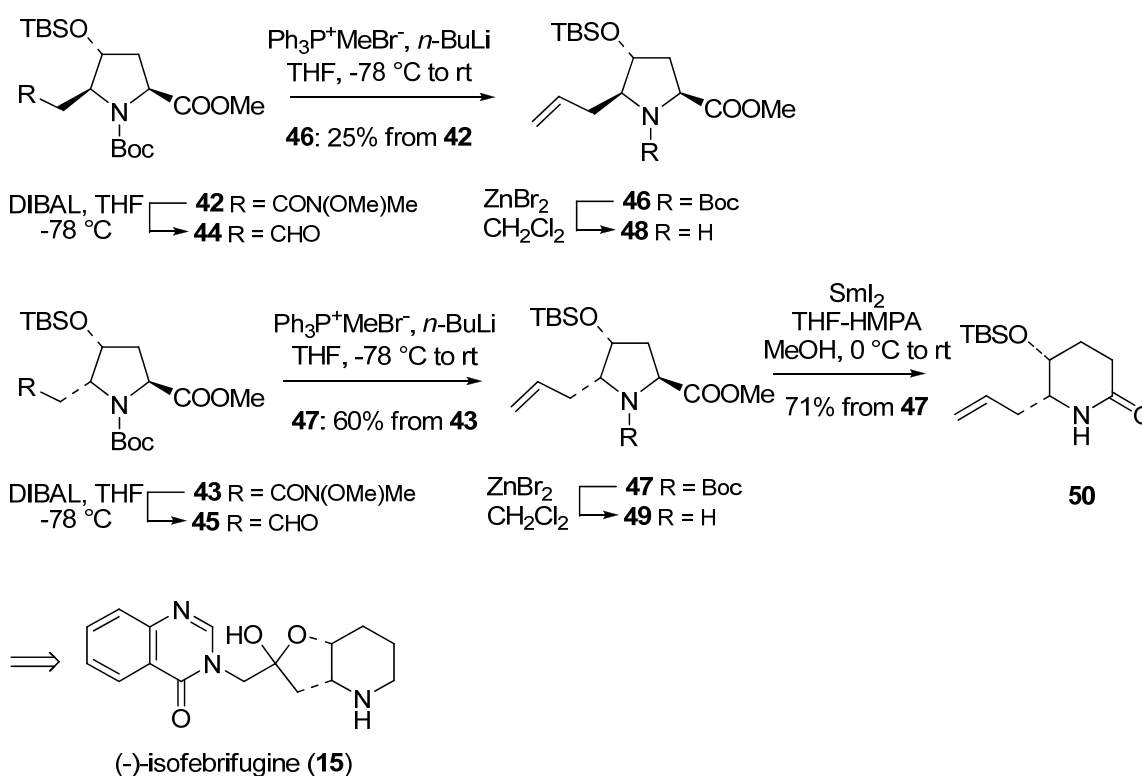
Scheme 9. Stereoselective synthesis of pyrrolidine derivative

Thus, a commercially available (4*R*)-hydroxy-L-proline was converted into the known *N*-Boc methyl ester (**33**),²⁷ which on oxidation with ruthenium tetroxide, gave lactam (**34**) in 83% yield. Reduction of the lactam (**34**) with lithium triethylborohydride as described above, afforded aminated (**35**). A tandem Horner-Emmons-Michael reaction of **35** with triethyl phosphonoacetate and sodium hydride in THF gave an inseparable mixture of diastereomers (**36** and **37**), which, on deprotection of the *N*-Boc group with trifluoroacetic acid gave separable two compounds (**38** and **39**) in 77% yield, in a ratio of *ca.* 1 : 2. The structures of these compounds (**38** and **39**) were determined by treatment with tetrabutylammonium fluoride to furnish alcohol (**40**) and lactone (**41**), respectively (Scheme 10).



Scheme 10. Structure determination of **38** and **39**

When a tandem Horner-Emmons-Michael reaction of **35** was carried out by using diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate as the Wittig reagent, the ratio of the products (**42** and **43**) was improved to *ca.* 1 : 11, where the desired compound (**43**) was found to be the major product. After separation by silica gel column chromatography, those amides (**42** and **43**) were converted into the secondary amines, respectively, as follows. Diisobutylaluminum hydride reduction of amides (**42** and **43**), followed by methylenation of the resulting aldehydes (**44** and **45**) with methyltriphenylphosphonium bromide and *n*-butyllithium, provided olefins (**46** and **47**).



Scheme 11. Synthesis of (-)-isofebrifugine

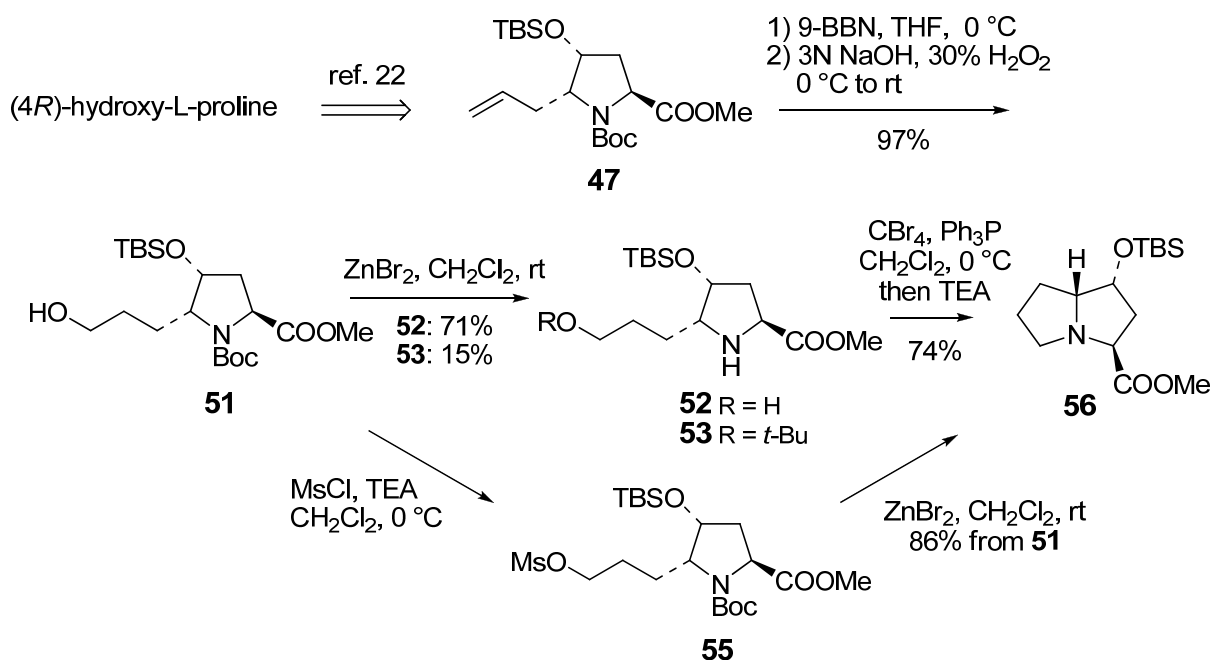
Selective removal of the *N*-Boc groups of **46** and **47** was achieved by treatment with zinc bromide as described above to give amines (**48** and **49**), respectively. With the desired compound (**49**) in hands, we attempted its conversion into the corresponding δ -lactam by means of samarium diiodide-promoted reductive fragmentation reaction. Treatment of **49** with samarium diiodide in the presence of methanol as the proton source in THF-HMPA afforded the desired δ -lactam (**50**) in 71% yield. Again, spectroscopic data of **50** were identical with those reported in the literature^{26m} except for the sign of optical rotation, $\{[\alpha]_{\text{D}} +4.6 (c 0.2, \text{CHCl}_3); \text{lit.},^{26\text{m}} [\alpha]_{\text{D}} -4.5 (c 1.05, \text{CHCl}_3)\}$. Since *ent*-**50** was already transformed into (+)-isofebrifugine (**15**),^{26h} this synthesis constitutes the formal synthesis of (-)-isofebrifugine (Scheme 11).

Again, we were able to establish novel chiral syntheses of (+)-febrifugine and (-)-isofebrifugine. Although the synthesis of isofebrifugine gave the antipodal form of the natural product, we believe that the strategy developed here should provide a useful tool for finding new anti-malarial drugs.

5. NOVEL CHIRAL SYNTHESIS OF INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS:

SYNTHESIS OF (+)-(8*R*, 8*aR*)-PERHYDRO-8-INDOLIZIDINOL AND (-)-DEOXYNUPHARIDINE³¹

Indolizidine and quinolizidine alkaloids, with their wide range of structural and stereochemical features, are large class of natural products that have, over the year, provoked an extraordinary amount of activity by synthetic organic chemists.³² As mentioned above, we have developed a SmI₂-promoted reductive carbon-nitrogen bond cleavage reaction of α -amino esters, where proline derivatives were successfully transformed to the corresponding δ -lactams in good yields. The effectiveness of this reaction for the construction of ring-enlarged lactams leads us to consider its further application toward the indolizidine and quinolizidine alkaloids in optically active forms.

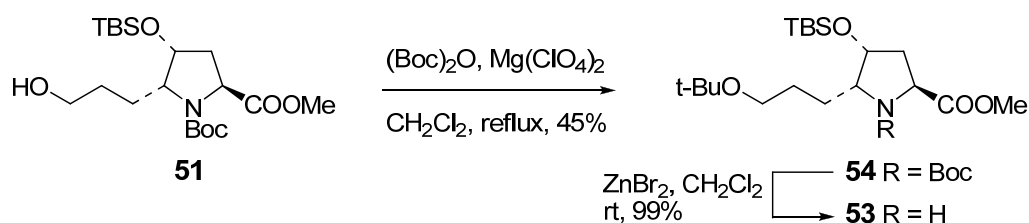


Scheme 12. Preparation of a key precursor for SmI₂-promoted fragmentation

Our synthesis of indolizidine alkaloid commenced with the synthesis of the known proline derivative (**47**), which was readily accessible via known procedures from (4*R*)-hydroxy-L-proline. Hydroboration of **47** with 9-BBN in THF, followed by oxidative treatment with alkaline hydrogen peroxide gave the primary alcohol (**51**). Removal of the Boc group of **51** on treatment with zinc bromide³³ in CH₂Cl₂ afforded the desired amino-alcohol (**52**) together with *tert*-butyl ether (**53**), in 71 and 15% yields, respectively (Scheme

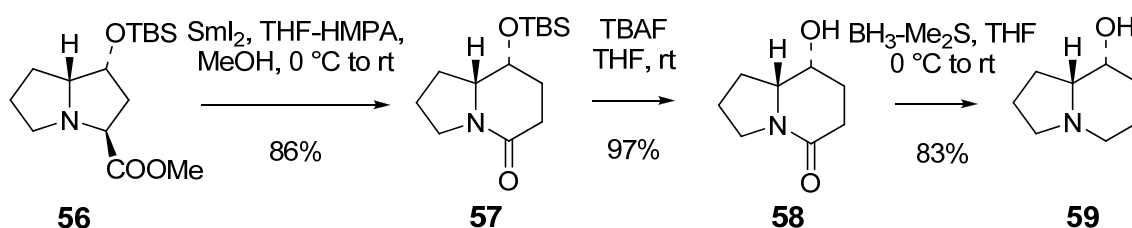
12).

The structure of **53** was confirmed by its alternative preparation from **51** involving an etherification³⁴ with (Boc)₂O and Mg(ClO₄)₂, followed by deprotection of the *N*-Boc group of the resulting ether (**54**) with zinc bromide in CH₂Cl₂ (Scheme 13). In order to synthesize the bicyclic compound, the precursor for a reductive carbon-nitrogen bond cleavage reaction, the primary alcohol (**52**) was reacted with carbon tetrabromide in the presence of triphenylphosphine in CH₂Cl₂ to give the alkoxyphosphonium salt, which on treatment with triethylamine (TEA) furnished the bicyclic compound (**56**) in 74% yield from **52**.³⁵ Compound (**56**) was alternatively prepared from **51** by mesylation with methanesulfonyl chloride in CH₂Cl₂, followed by deprotection of the *N*-Boc group of mesylate (**55**) with zinc bromide in CH₂Cl₂, in 86% overall yield.



Scheme 13. Structure determination of ether (**53**)

Since the desired bicyclic ester (**56**) in hands, we focused our attention on its conversion to the corresponding δ -lactam by means of a SmI₂-promoted reductive carbon-nitrogen bond cleavage reaction. Treatment of **56** with SmI₂ in THF-HMPA in the presence of MeOH as the proton source at 0 °C to room temperature for 2 h provided indolizidinone (**57**) in 86% yield, where a reductive carbon-nitrogen bond cleavage, followed by recyclization of the resulting amino-ester occurred, simultaneously. Deprotection of the silyl group of **57** with tetrabutylammonium fluoride (TBAF) in THF afforded hydroxy-lactam (**58**),³⁶ which was further converted to (+)-(8*R*, 6*R*)-perhydro-8-indolizidinol (**59**) by reduction with borane-methylsulfide complex according to the known procedure³⁶ The spectroscopic data of **10** were identical with those reported in the literature³⁶ except for the sign of optical rotation {[α]_D +19.9 (c=1.2, CHCl₃); lit.,³⁶ [α]_D -17.4 (c=1.15, CHCl₃)} (Scheme 14).

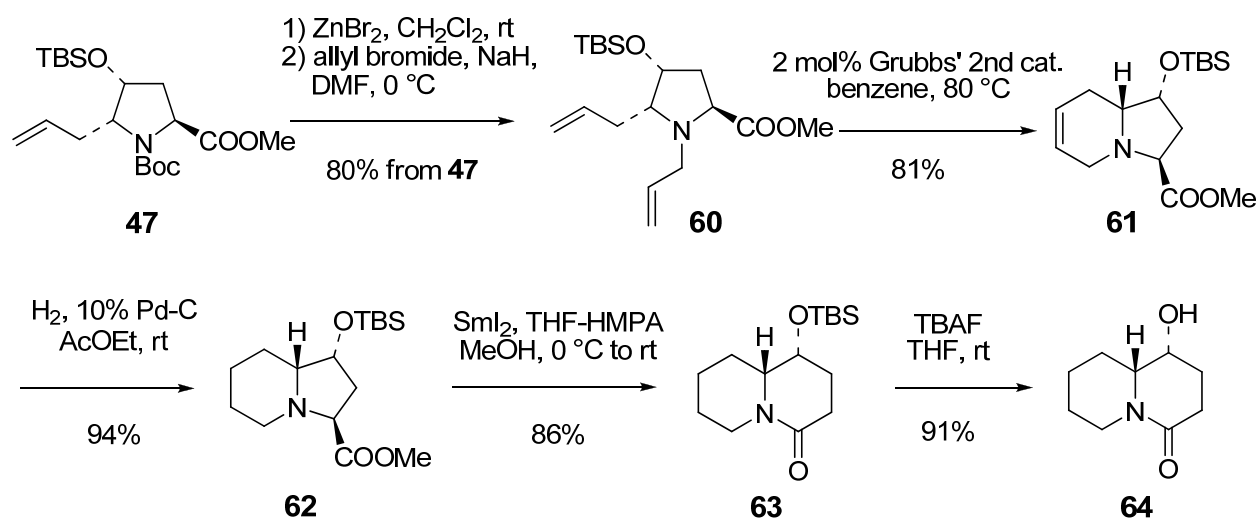


Scheme 14. Synthesis of (+)-(8*R*, 6*R*)-perhydro-8-indolizidinol

Since we were able to establish a new synthetic procedure for indolizidine alkaloids by employing a SmI_2 -promoted reductive carbon-nitrogen bond cleavage reaction as a key step, we planned to extend the utilization of this strategy to the synthesis of quinolizidine alkaloids.

As a model study, a synthesis of 1-hydroxy-4-quinolizidinone was investigated as follows.

Removal of the *N*-Boc group of **47** with zinc bromide in CH_2Cl_2 , followed by allylation of the resulting amine with allyl bromide in the presence of sodium hydride in DMF gave the *N*-allyl compound (**60**) in 80% from **47**. Ring closing metathesis (RCM)³⁷ of **60** with 2 mol% of Grubbs' 2nd generation catalyst in refluxing benzene provided the olefinic bicyclic compound (**61**), which on catalytic reduction over palladium on carbon in AcOEt gave the saturated bicyclic compound (**62**). Application of a SmI_2 -promoted reductive carbon-nitrogen bond cleavage reaction to **62** under the same reaction conditions as described for the synthesis of **59** furnished the desired quinolizidinone (**63**) in 86% yield. Deprotection of the silyl group of **63** with tetrabutylammonium fluoride in THF gave hydroxy-lactam (**64**). Although the synthesis of lactam (**64**) has already been achieved, none of its spectroscopic data were reported in the literature,³⁸ unfortunately (Scheme 15).



Scheme 15. Construction of a chiral quinolizidine compound

Applying this strategy, we started the synthesis of biologically active quinolizidine alkaloids.

(-)-Deoxynupharidine (**65**) and (-)-7-epi-deoxynupharidine (**66**), isolated from plants of the genus *Nuphar*,³⁹ are sesquiterpene alkaloids based on a quinolizidine core with a furan ring. The dried rhizomes of *Nuphar japonicum* DC. and *Nuphar pumilum* (TIMM.) DC., are used in folk medicine for tonic, haemostatic and diuretic purposes in China and Japan. It has also been recognized that (-)-deoxynupharidine exhibited an immunosuppressive effect,⁴⁰ a central paralysis effect⁴¹ and weak anti-metastatic activity,⁴² and (-)-7-epi-deoxynupharidine showed insecticidal activity³⁹ (Figure 5).

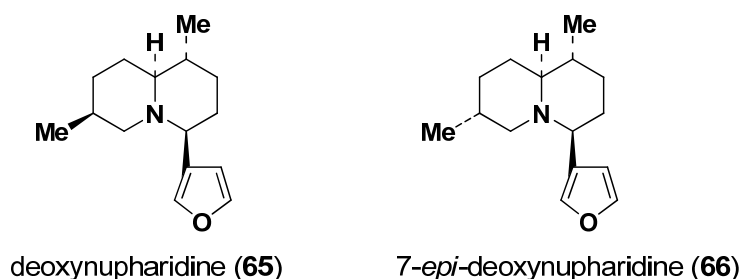
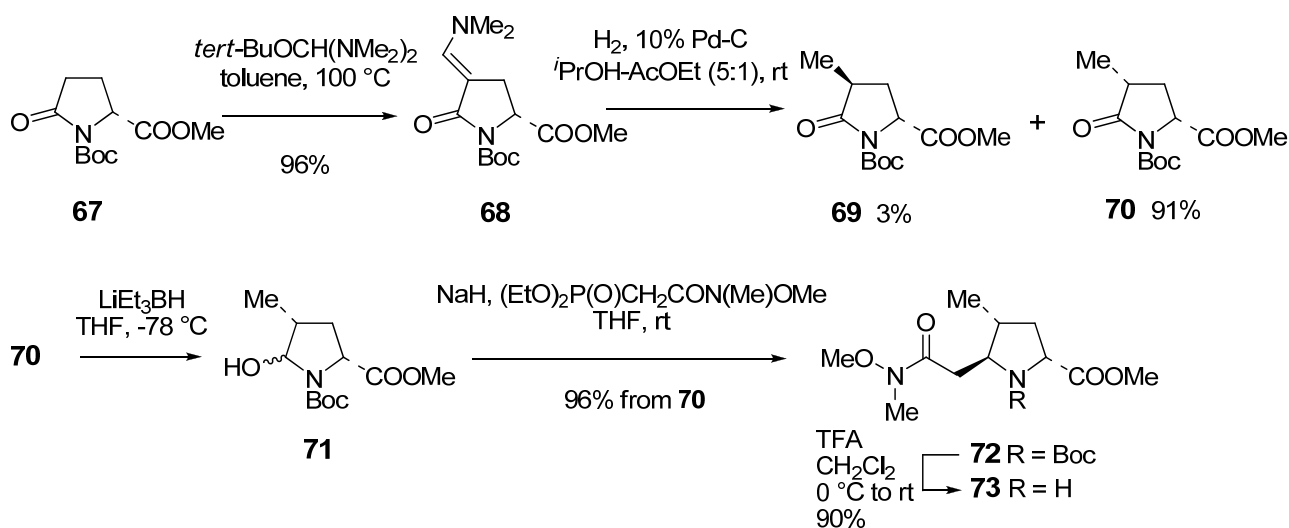


Figure 5. Structures of (-)-deoxynupharidine and (-)-7-*epi*-deoxynupharidine

Although several syntheses of deoxynupharidine (**65**) have been achieved, most of them led to the synthesis of the target compound in racemic form.⁴³ Very recently, Harrity and co-workers published a stereocontrolled chiral synthesis of **65** by employing a formal [3+3] cycloaddition reaction to obtain a piperidine nucleus.⁴⁴

Our synthesis starts from a stereoselective construction of the 1-methyl-4-quinolizidinone ring system in an optically active form.

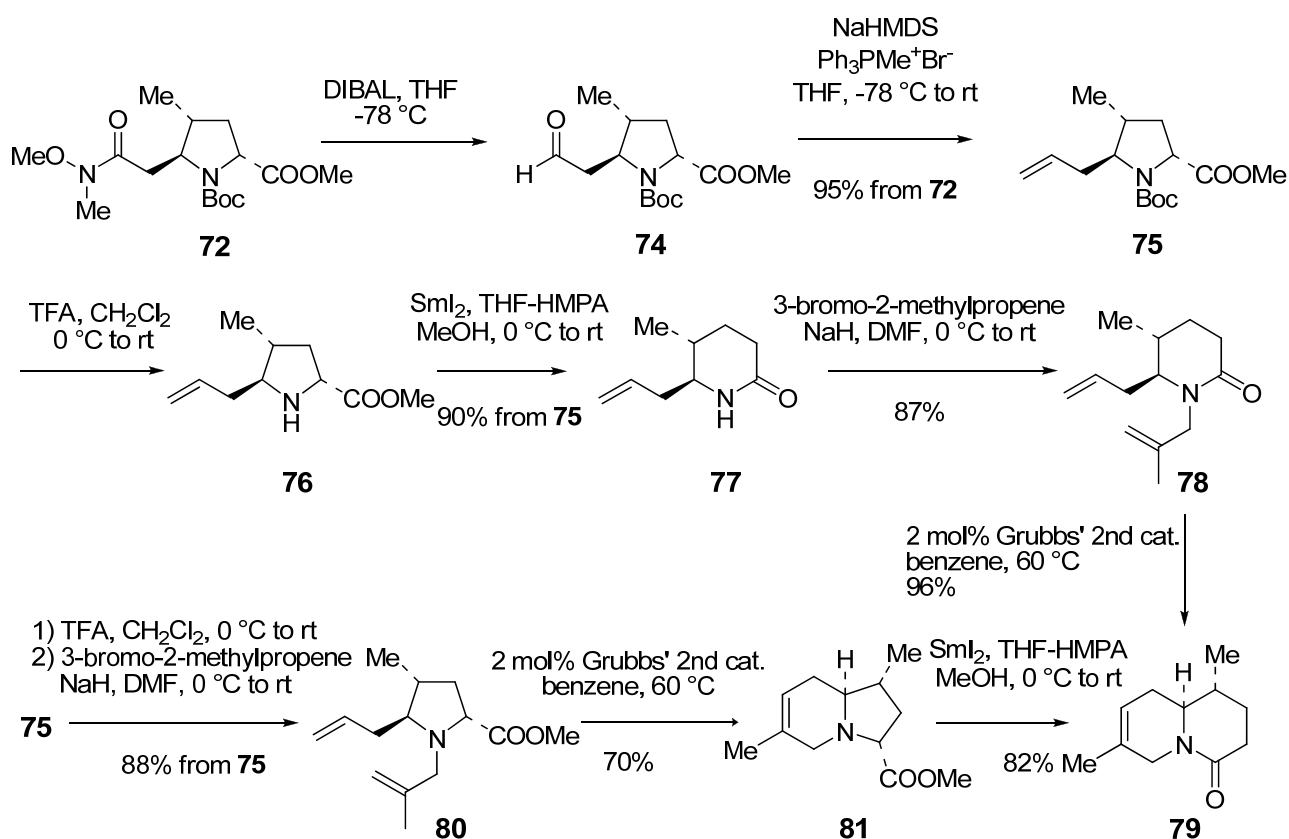


Scheme 16. preparation of a starting pyrrolidine

Thus, methyl *N*-*tert*-butoxycarbonylpyroglutamate (**67**), readily accessible from commercially available (*R*)-pyroglutamic acid, was reacted with Bredreck's reagent⁴⁵ in toluene at 100 °C to give enaminone (**68**). Catalytic reduction of **68** over 10% palladium on carbon in *i*PrOH-AcOEt afforded the methylated pyroglutamates (**69** and **70**), in 3 and 91% yields, respectively. Reduction of the major product (**70**) with lithium triethylborohydride in THF at -78 °C gave aminal (**71**), which, on treatment with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate⁴⁶ in THF in the presence of sodium hydride

furnished amide (**72**) in 96% yield from **70**. The stereochemistry at the 5-position of **72** was assumed to be *S*, by comparison of the NMR data of **73** with those of the related compounds prepared by us previously,³¹ and finally determined by its conversion to the natural product (Scheme 16).

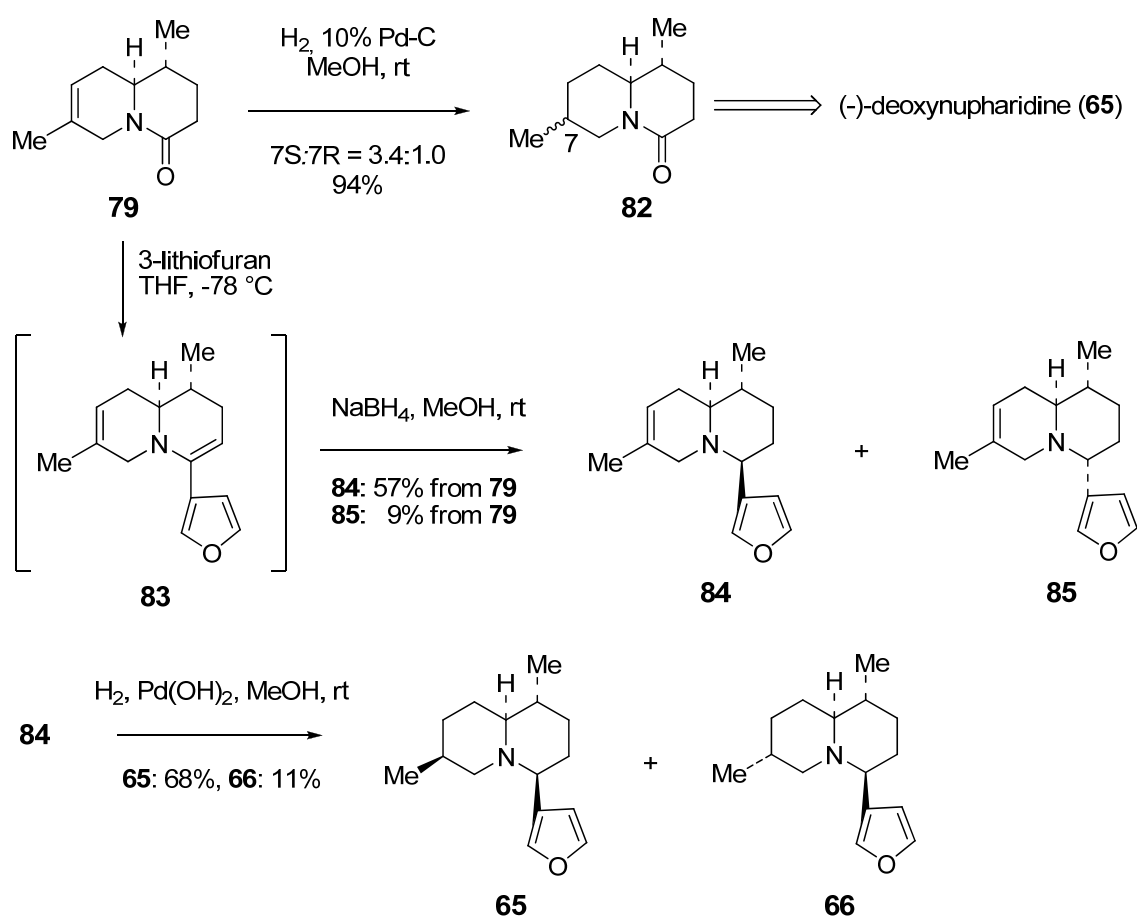
Chemoselective reduction of **72** with DIBAL provided the corresponding aldehyde (**74**), which was treated with methyltriphenylphosphonium bromide in the presence of sodium hexamethyldisilazide to afford alkene (**75**). After removal of the *N*-Boc group of **75** with trifluoroacetic acid in CH₂Cl₂, the resulting amine (**76**) was subjected to a SmI₂-promoted reductive carbon-nitrogen bond cleavage reaction as described before to provide the ring enlarged lactam (**77**) in 90% yield from **75**. Alkylation of **77** with 3-bromo-2-methylpropene in the presence of sodium hydride in DMF, followed by RCM of the resulting olefin (**78**) with 2 mol% of Grubbs' 2nd generation catalyst in refluxing benzene for 2 h afforded the bicyclic lactam (**79**). Lactam (**79**) was alternatively synthesized from **75**, in which the construction of bicyclo-system was carried out prior to a samarium diiodide-promoted fragmentation, as follows (Scheme 17).



Scheme 17. Synthesis of the quinilizidine derivative

Removal of the *N*-Boc group of **75** with trifluoroacetic acid in CH₂Cl₂, followed by alkylation with 3-bromo-2-methylpropene as described before gave the alkene (**80**). RCM of **80** with 2 mol% of Grubbs'

2nd generation catalyst in refluxing benzene afforded the bicyclic ester (**81**). Again, application of a SmI₂-promoted carbon-nitrogen bond cleavage reaction to **81** furnished the desired lactam (**79**) in 82% yield. Thus, this reaction was found to be able to apply to both secondary amine and tertiary amine, successfully. Catalytic reduction of **79** over 10% palladium on carbon in MeOH gave lactam (**82**) as a mixture of the diastereomers at the 7-position, in a ratio of 7*S*:7*R*=3.4:1.0. Although lactam (**82**) has already been converted to (-)-deoxynupharidine by Harrity and his co-workers,⁴⁴ we decided to adopt an alternative route to (-)-deoxynupharidine, in which we planned to introduce a furyl moiety to the lactam function prior to a reduction of the carbon-carbon double bond.



Scheme 18. Synthesis of (-)-deoxynupharidine and (-)-7-epi-deoxynupharidine

Treatment of **79** with 3-lithiofuran in THF at -78 °C, followed by treatment with sodium borohydride in methanol afforded a mixture of the furyl compounds (**84** and **85**). In this conversion, we first attempted DIBAL reduction for the intermediate (**83**) after installation of a furan ring according to the literature reported by Harrity,⁴⁴ in which, they proposed a carbinolamine as the intermediate in their synthesis. However, we mentioned that DIBAL was not effective for this reduction, unfortunately, and we could confirm the presence of an enamine as an intermediate by the analysis of its NMR spectra. Our

experimental results using sodium borohydride as the reducing agent for the intermediate might support the presence of an enamine (**83**) as the intermediate in our synthesis (Scheme 18).

Finally, a catalytic reduction of **84** over palladium hydroxide in methanol gave (-)-deoxynupharidine (**65**) and its 7-epimer (**66**) in 79% yield, in a ratio of 68:11.

Thus, we were able to synthesize both indolizidine and quinolizidine alkaloids by using a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage, as a key step.

6. SYNTHESIS OF DIPIPERIDINE TYPE ALKALOIDS, (+)-CYTISINE, (-)-KURARAMINE, (-)-ISO KURARAMINE, AND (-)-JUSSIAEIINE A⁴⁷

Naturally occurring lupine alkaloids having a wide range of structural and stereochemical features, continue to provide challenging synthetic targets.⁴⁸ Among them, (-)-cytisine (**86**)⁴⁹ has received special attention⁵⁰ and several synthetic methods have been developed,⁵¹ since it has been shown to be an important probe in nicotinic acetylcholine receptor research⁵² and shows high affinity at neuronal nicotinic receptors.⁵³

(+)-Kuraramine (**87**) and (+)-jussiaeiine A (**88**), isolated from *Sophora flavescens*⁵⁴ and *Ulex jussiaei*,⁵⁵ respectively, are dipiperidine-type alkaloids with two chiral centers at the 3 and 5 positions of the piperidine ring. Those alkaloids are known to be oxidative metabolites of *N*-methylcytisine. Another dipiperidine-type alkaloid, (+)-isokuraramine (**89**)⁵⁶ was also isolated from the fresh flowers of *Sophora flavescens* as a minor constituent, and its structure was determined to be the diastereoisomer of (+)-kuraramine by spectroscopic methods.⁵⁶ However, little attention has been focused on the chiral synthesis of these alkaloids (Figure 6).

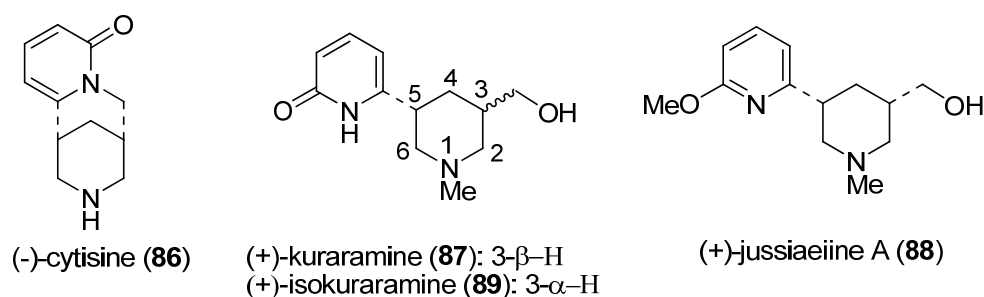
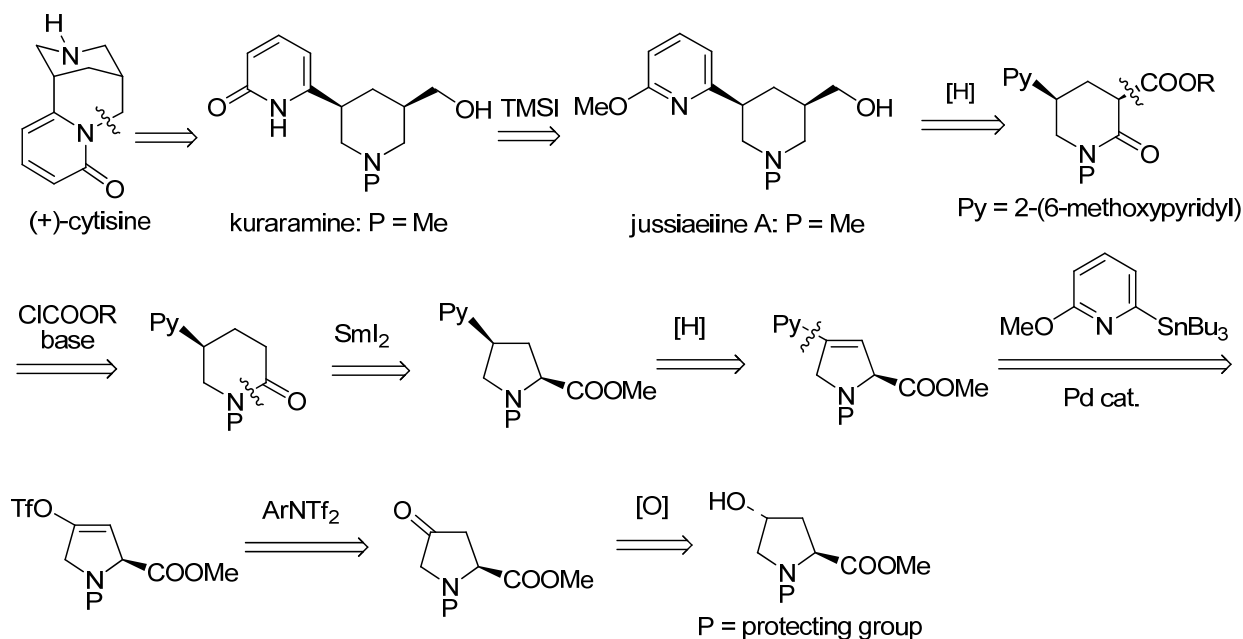


Figure 6. Structures of dipiperidine alkaloids

Thus, we planned to establish a novel synthetic route to these alkaloids, including cytisine, via a common synthetic intermediate. The key feature of our synthesis is based on a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction of an α -amino ester, as described above.

Based on a retrosynthetic analysis of these alkaloids as depicted in Scheme 19, we decided to exploit a readily available 4*R*-hydroxy-*L*-proline derivative as a starting material to synthesize the enantiomers of the aforementioned natural products, since the use of the antipodal starting material, *D*-hydroxyproline, should lead to the synthesis of natural products if this synthetic strategy can be established.



Scheme 19. Retrosynthetic path to dipiperidine alkaloids

Thus, methyl 4-oxo-*L*-prolinate (**90**) was converted to the corresponding triflate (**91**) in three steps. Treatment of **91** with 2-tributylstannyl-6-methoxypyridine (**92**) in the presence of a palladium catalyst⁵⁷ afforded the coupling product (**93**). Hydrogenation of **93** over 10% palladium-charcoal in MeOH gave **94**, stereoselectively. After removal of the Boc group, samarium diiodide-promoted reductive fragmentation of the resulting amine (**95**), followed by simultaneous cyclization of the resulting δ -amino ester was carried out in THF-HMPA in the presence of methanol as a proton source to give the desired common intermediate, the δ -lactam (**96**) (Scheme 20).

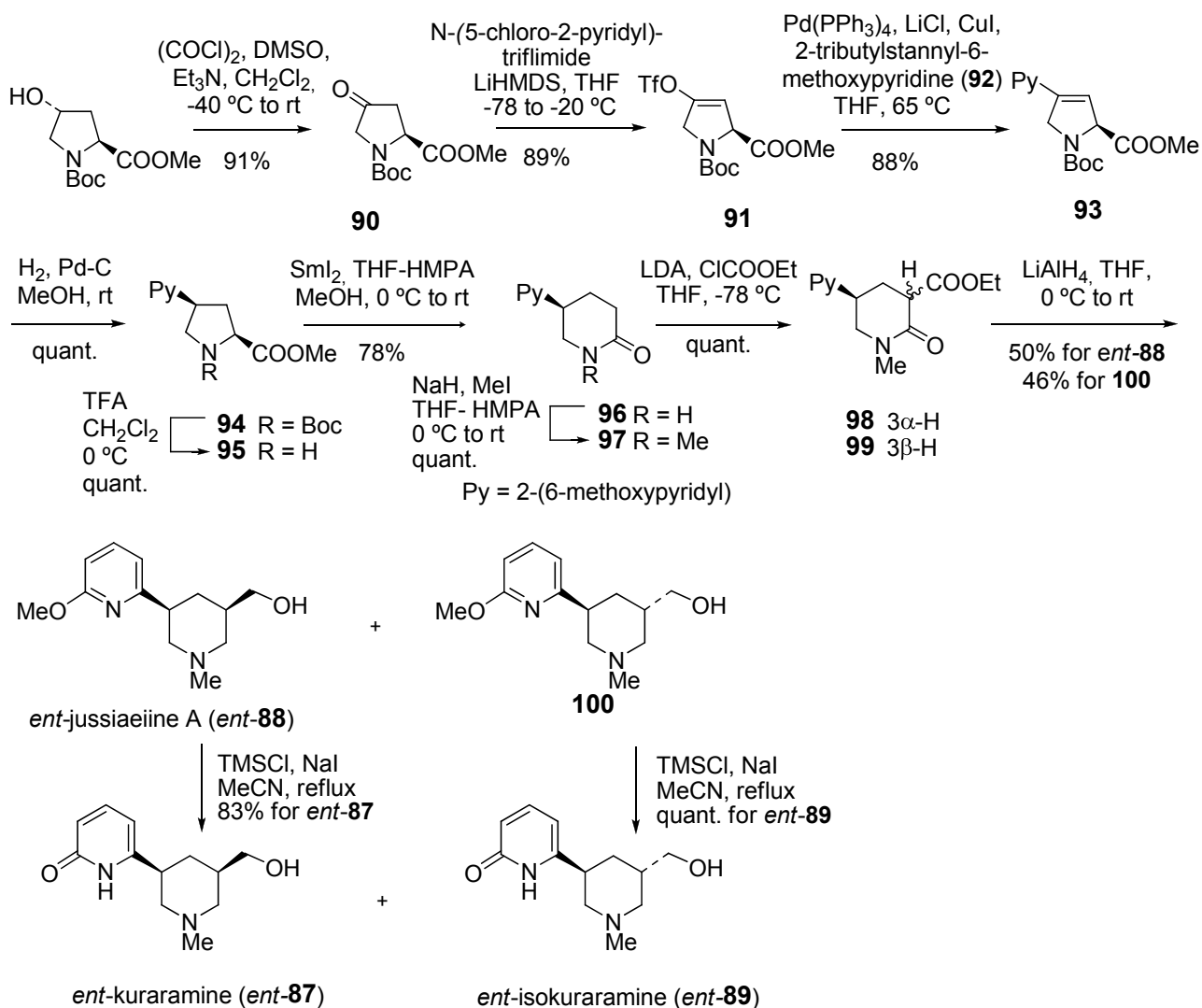
N-Methylation of **96** with iodomethane and sodium hydride in THF-HMPA furnished the corresponding *N*-methylpiperidone (**97**), which was further converted into hydroxymethyl derivative as follows.

Treatment of amide (**97**) with ethyl chlorocarbonate in the presence of LDA in THF gave an inseparable mixture of diastereomers (**98** and **99**), in a ratio of *ca.* 1:1. Reduction of the amide and ester functions of the mixture with LiAlH₄ in THF afforded amino-alcohols (*ent*-**88** and **100**) in respective yields of 50% and 46%. The spectroscopic data of *ent*-**88** obtained here were identical to those reported for (+)-jussiaeïne A. Moreover, the sign of the optical rotation of the synthetic compound corresponded to that of the antipode, {*ent*-**88**, [α]_D -5.2 (c=0.5, CHCl₃); lit.,⁵⁵ [α]_D +3.3 (c=0.26, CHCl₃)}. Therefore, we

were able to establish the first enantioselective synthesis of (-)-jussiaeiine A. Jussiaeiine A *ent*-**3** was converted into (-)-kuraramine *ent*-**2** by treatment with iodotrimethylsilane in refluxing acetonitrile.⁵⁸

Again, the physicochemical properties of *ent*-**87** were identical to those reported in the literature, except for the sign of optical rotation⁵⁹ {*ent*-**87**: mp 78-80 °C, $[\alpha]_D -3.6$ (c=2.1, EtOH); lit.,⁵⁴ $[\alpha]_D +8.4$ (c=0.52, EtOH)}.

The same treatment of the diastereoisomeric compound (**100**) gave isokuraramine *ent*-**89** as an amorphous solid, $[\alpha]_D -93.0$ (c=2.1, EtOH).⁵⁶

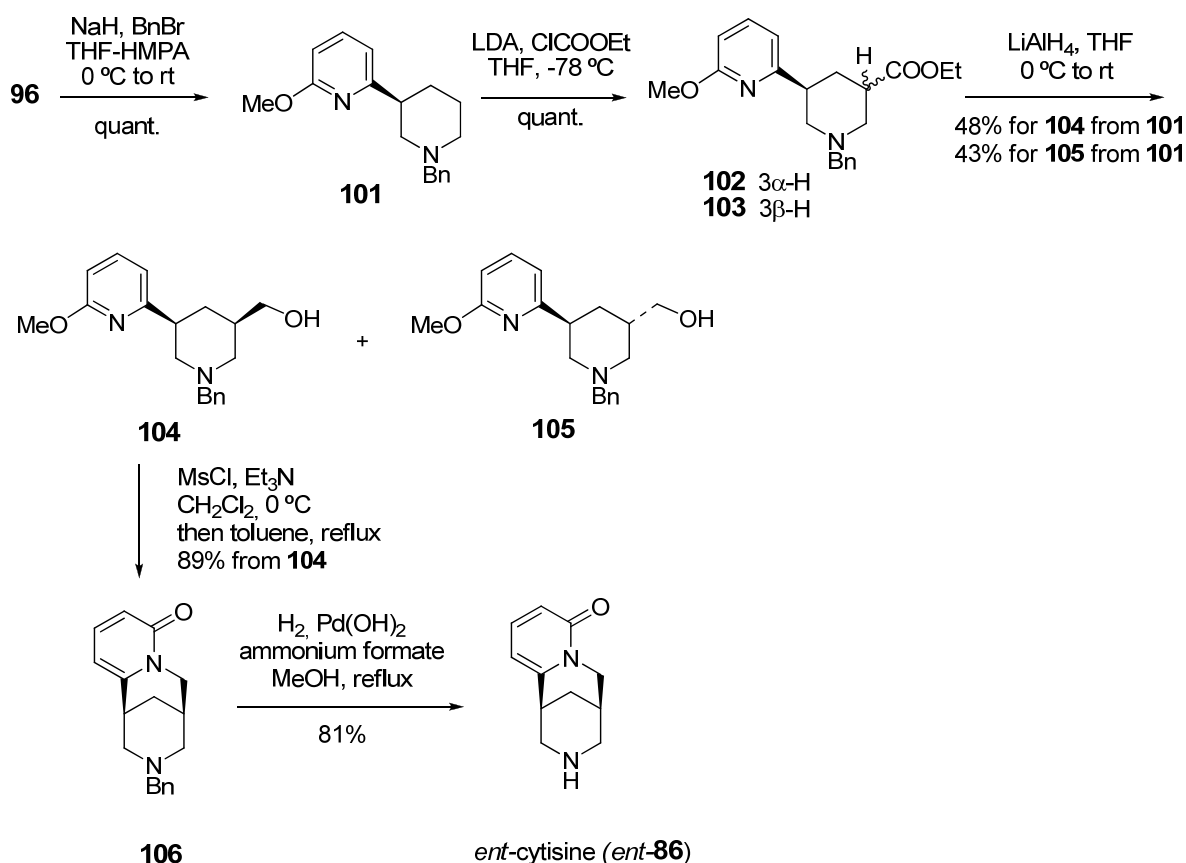


Scheme 20. Synthesis of *ent*-Jussiaeiine A, *ent*-Kuraramine and *ent*-Isokuraramine

To achieve the total synthesis of (+)-cytisine from the common intermediate (**96**) through the formation of a carbon-nitrogen bond, as shown in Scheme 21, *N*-benzylation of **96** and subsequent ethoxycarbonylation of **101** with ethyl chlorocarbonate in the presence of LDA were carried out to provide a mixture of diastereoisomeric β -ketoesters (**102** and **103**) in a ratio of *ca.* 1:1.

Although the attempted isomerization of the mixture to the thermodynamically more stable 3,5-*cis*-compound under various reaction conditions, such as basic treatment of a mixture of **102** and **103** with lithium diisopropylamide in THF, sodium hydride in appropriate solvents, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene, did not improve the ratio, reduction of the mixture with LiAlH₄ gave the primary alcohols (**104** and **105**), in respective yields of 48% and 43%. Finally, mesylation of **104** followed by thermal cyclization of the mesylate yielded tricyclic compound (**106**). Debenzylation of **106** under the hydrogenolysis conditions furnished *ent*-**86**, whose spectroscopic data were identical to those reported in the literature⁶⁰ except for the sign of optical rotation {*ent*-**1**: mp 152-153 °C, [α]_D+113.5 (c=0.3, EtOH); lit.,⁶¹ mp 152-153 °C, lit.,⁶⁰ [α]_D-110 (c=0.5, EtOH)} (Scheme 21).

In summary, we have established novel and facile syntheses of dipiperidine-type lupine alkaloids, including cytisine. Although these syntheses give the antipodal forms of the natural products, we believe that the strategy developed here should be a useful tool for finding new drugs that are biologically related to cytisine.



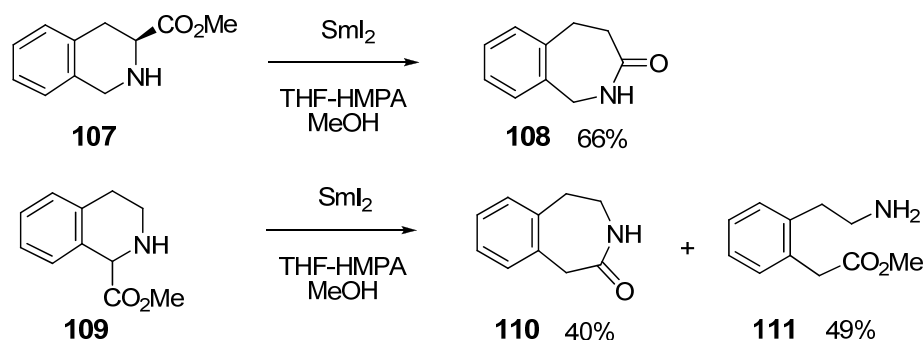
Scheme 21. Synthesis of *ent*-cytisine

7. SYNTHESIS OF (+)-APHANORPHINE⁶²

In the above-mentioned syntheses of bioactive alkaloids, we have applied a SmI₂-promoted reductive

fragmentation reaction of α -amino esters to proline derivatives yielding the corresponding δ -lactams in good yields, where a regioselective carbon-nitrogen bond cleavage reaction, followed by a recyclization of the resulting amino-esters took place, simultaneously. This reaction is obviously a useful synthetic tool for a construction of ring-enlarged lactams. To extend the usefulness of this strategy, we are interested in a conversion of 1,2,3,4-tetrahydroisoquinoline derivatives having an ester group at the 1- or 3-position to the corresponding benzazepinones.

Thus, (3*S*)-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**107**)⁶³ was treated with SmI_2 in THF-HMPA in the presence of MeOH as the proton source to give the corresponding lactam (**108**) in 66% yield. Similar reaction of 1-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**109**)⁶³ also provided the desired lactam (**110**) together with the ring-opened primary amine (**111**), in 40 and 49% yields, respectively. The later (**111**) could be converted to the former (**110**) by heating in benzene or by treatment with sodium methoxide (Scheme 22).



Scheme 22. SmI_2 -promoted reductive fragmentation of isoquinoline derivatives

Since transformation of the isoquinoline derivatives having an ester group at the 1- or 3-position to the corresponding seven-membered lactams was found to be successful by application of a SmI_2 -promoted reductive carbon-nitrogen bond cleavage reaction, we planned to utilize this strategy to the synthesis of aphanorphine and related compound aiming at searching new analgesic candidates. (-)-Aphanorphine (**112**), isolated from the freshwater bluegreen alga *Aphanizomenon flosaquae* in 1988,⁶⁴ is a natural compound with potent analgesic activity. In 1992, we established a novel synthetic route to (\pm)-aphanorphine via the amylinium intermediate.⁶⁵ Thereafter, a formal synthesis of (-)-aphanorphine was also achieved by using an enzymatic process.⁶⁶

Owing to its interesting biological activity, a number of syntheses of **112** have been reported to date.⁶⁷ Our synthetic plan for aphanorphine was based on an intramolecular cyclization⁶⁸ of a seven-membered lactam, as depicted in Figure 7.

In this synthesis, we decided to exploit a readily accessible (*S*)-tyrosine derivative as a starting material to

synthesize the enantiomer of natural aphanorphine,⁶⁶ since the use of the antipodal starting material, (*R*)-tyrosine, should lead to the synthesis of the natural product, if this synthetic strategy can be established.

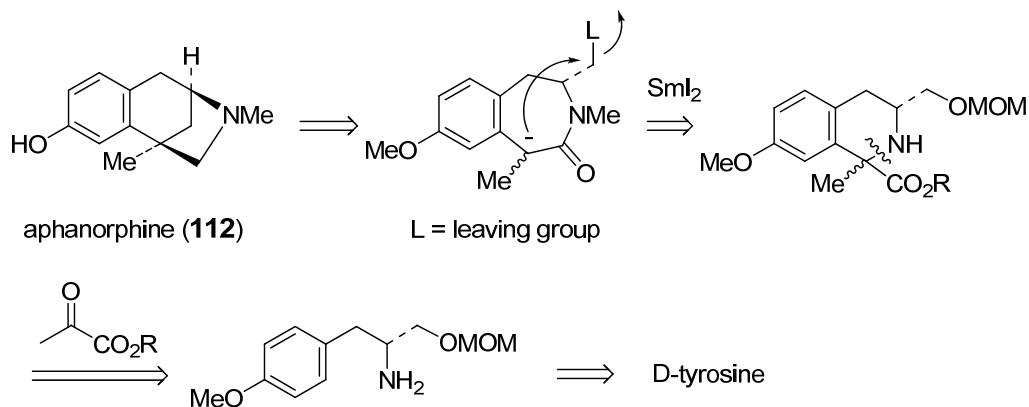
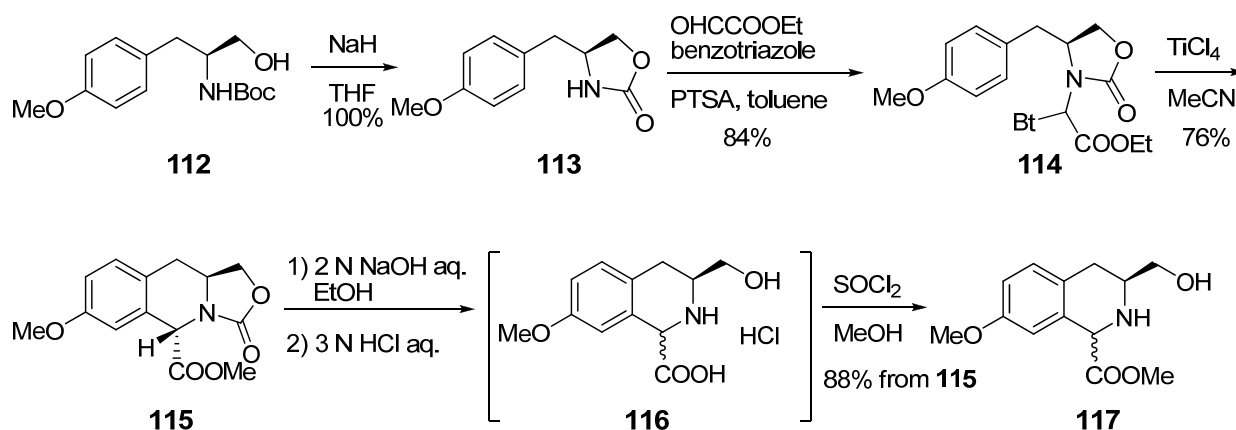


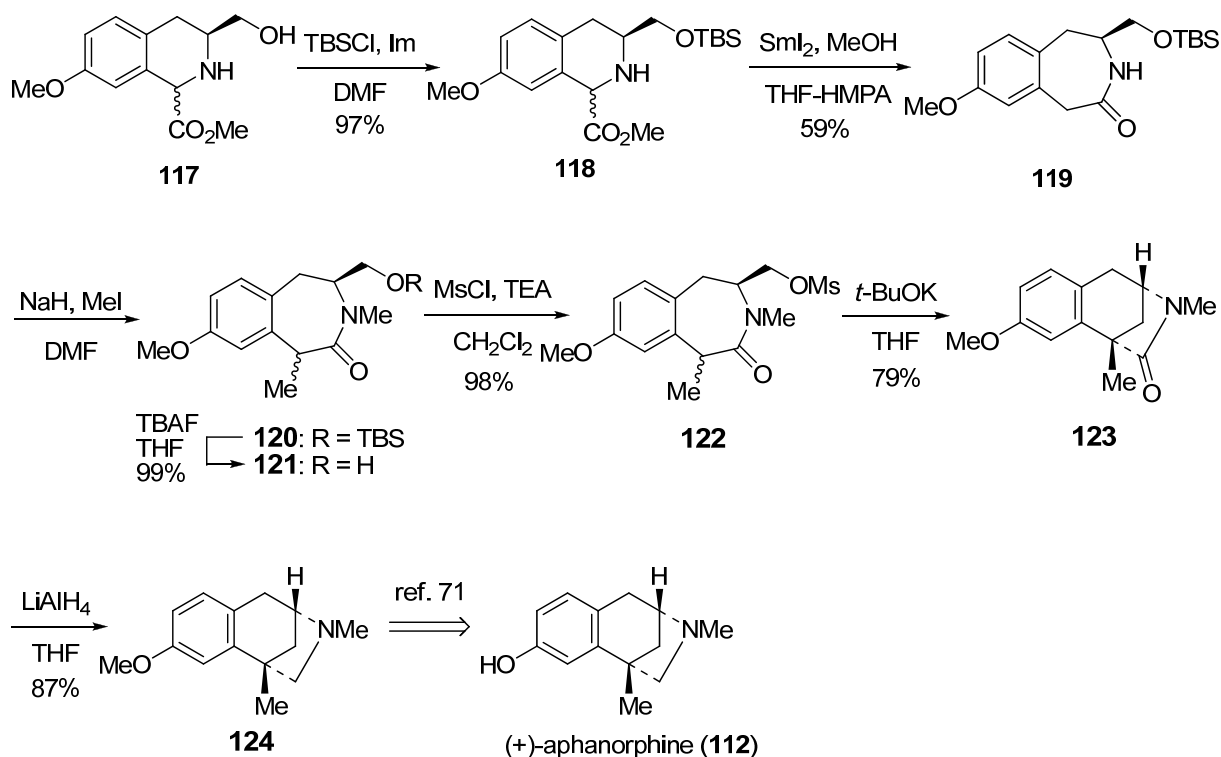
Figure 7. Synthetic plan for aphanorphine

The known compound (**112**)⁶⁹ was converted to oxazolidinone (**113**), which on treatment with ethyl glyoxylate and benzotriazole in the presence of *p*-toluenesulfonic acid in refluxing toluene afforded ester (**114**). Reaction of **114** with TiCl_4 in acetonitrile⁷⁰ gave the corresponding isoquinoline derivative (**115**), as a single stereoisomer, in 76% yield. Hydrolysis of **115** with 2 N NaOH, followed by acidification with 3 N HCl gave acid (**116**), which, without purification was esterified with thionyl chloride in methanol to provide ester (**117**) as an inseparable diastereoisomeric mixture, in a ratio of *ca.* 3:1, in 88% yield from **115**. In this conversion, partial epimerization at the 1-position obviously occurred, however, this stereogenic center will be removed at the later stage of this synthesis. Therefore, ester (**117**) was used without separation in the next step (Scheme 23). In this synthesis, it was recognized that the benzotriazole method developed by Katritzky⁷⁰ was obviously superior to the other procedures for the preparation of the desired 1,2,3,4-tetrahydroisoquinoline.



Scheme 23. Synthesis of the key isoquinoline derivative

After silylation of **117** with *tert*-butyldimethylsilyl chloride and imidazole in the usual manner, the resulting silyl derivative (**118**) was subjected to the SmI_2 -promoted ring expansion reaction in THF-HMPA in the presence of MeOH as the proton source to furnish the desired benzazepinone (**119**), as the sole product, in 59% yield. Methylation of **119** with iodomethane in the presence of sodium hydride in DMF afforded the *N*- and *C*-methylated lactam (**120**) in 98% yield. Deprotection of the silyl group of **120** with tetrabutylammonium fluoride gave alcohol (**121**) as a mixture of the diastereomers in a ratio of 3.3:1. The stereochemistry of the *C*-methyl group of the major product would be assumed to *R* configuration by comparison of its ^1H NMR data with that of the racemic compound.⁶⁸ The primary alcohol (**121**) was further converted to mesylate (**122**) by treatment with methanesulfonyl chloride and triethylamine in 79% yield.



Scheme 24. Synthesis of (+)-aphanorphine

Finally, treatment of **122** with potassium *tert*-butoxide in refluxing THF gave amide (**123**), which on reduction with lithium aluminum hydride provided (-)-8-*O*-methylaphanorphine (**124**). The spectroscopic data for the synthesized compound (**124**) including specific optical rotation $\{[\alpha]_{\text{D}} -9.72$ ($c=0.67$, CHCl_3); lit.,⁷¹ $[\alpha]_{\text{D}} -7.40$ ($c=0.35$, CHCl_3) $\}$ were identical with those reported.⁷¹ Since (-)-**124** was already converted to (+)-aphanorphine (*ent*-**112**) by a demethylation,⁷⁰ this synthesis constitutes its total synthesis (Scheme 24).

We were able to apply this ring expansion reaction to 6,7-dioxygenated 1,2,3,4-tetrahydroisoquinoline

derivatives derived from L-dopa, successfully, to provide the corresponding seven-membered lactams. This strategy will provide a useful tool to synthesize aphanorphine-related compounds aiming at searching new analgesic candidates.

8. SYNTHESIS OF BULGARANINE⁷²

Plants of the genus *Fumaria* have been used in some parts of Asian and eastern European countries as folk medicines for their antipyretic, analgesic, and diuretic properties.⁷³ Because benzindenoazepines are expected to exhibit potential biological activities of medicinal interest, interest in the development of new synthetic methodology for this class of alkaloids continues unabated.⁷⁴

Bulgaramine (**126**) was isolated from Herba *Fumaria officinalis*⁷⁵ as a member of benzindenoazepines that are a distinct group of alkaloids, probably derived biogenetically from the rearrangement of spirobenzylisoquinolines.⁷⁶ On the basis of this consideration, a spirobenzylisoquinoline alkaloid, fumaricine (**125**), has been successfully transformed to bulgaramine, supporting the biogenetic hypothesis⁷⁷ (Figure 8). Furthermore, benzindenoazepine derivatives have been employed as key intermediates for transformation to rheadine and protopine alkaloids.⁷⁸

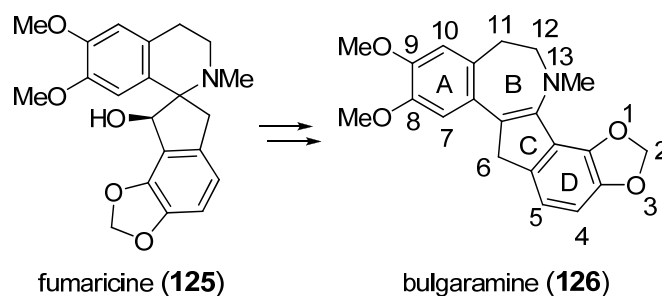
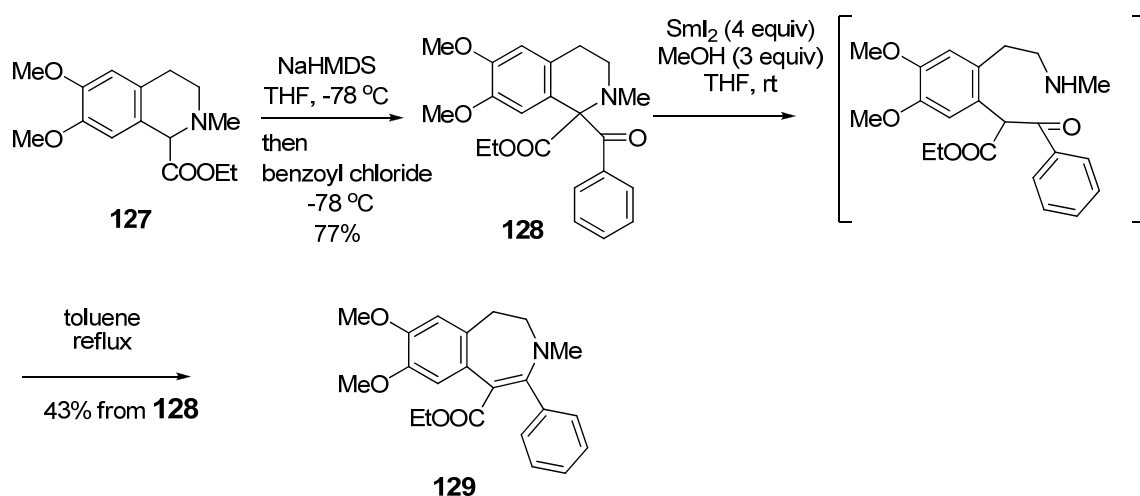


Figure 8. Conversion of fumaricine to bulgaramine.

Total synthesis of bulgaramine (**126**) has recently been achieved by Giese and co-workers by using an intramolecular cyclopentannulation of the Fischer aminocarbene complex as a key reaction to give the desired ring system,⁷⁹ and this is the only report of total synthesis for this alkaloid. The crucial step for synthesis of this class of alkaloids obviously lies in the facile construction of a benzindenoazepine ring system.⁸⁰ As mentioned above, we developed a SmI₂-promoted regioselective carbon-nitrogen bond cleavage reaction of α -amino carbonyl compounds. In relation to a project directed at the synthesis of bioactive alkaloids by application of this methodology, we are interested in establishing an entirely new, perhaps practical and general route for the total synthesis of a unique benzindenoazepine alkaloid, bulgaramine.

Prior to synthesis of the natural product, we investigated efficient and mild reaction conditions for the

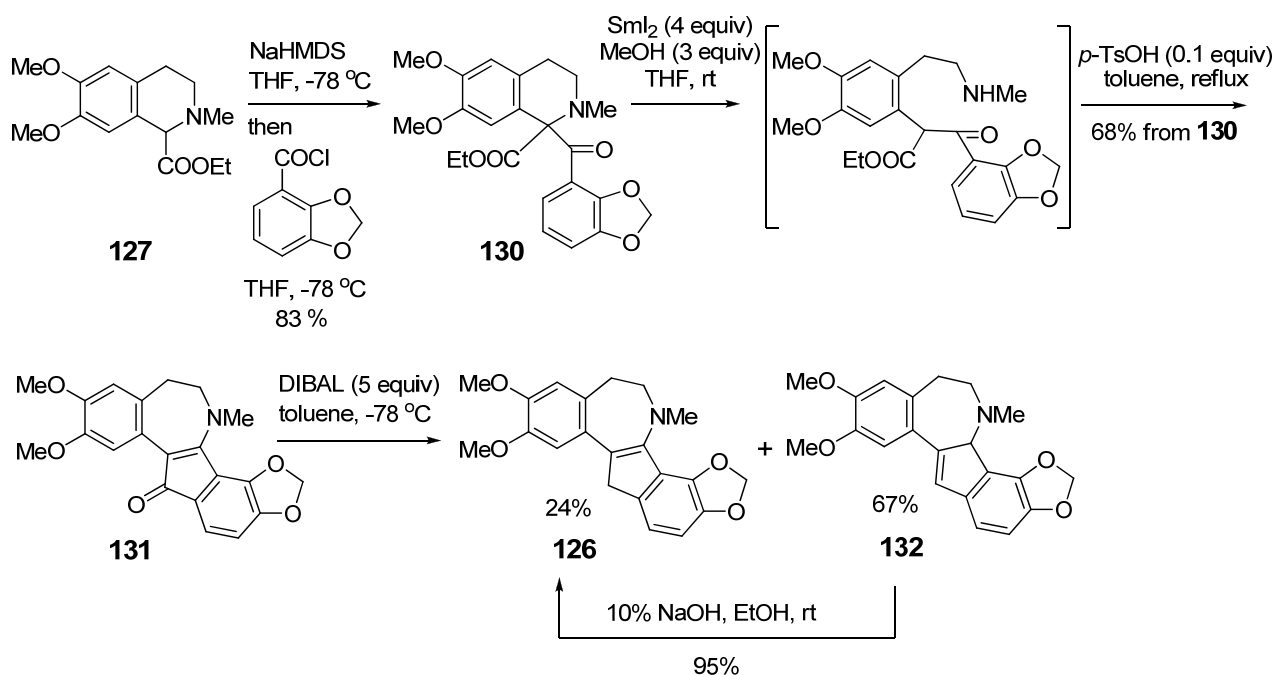
SmI₂-promoted bond cleavage reaction of an ester (**128**) derived from the known 1-ethoxycarbonyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**127**)⁸¹ by installation of a benzoyl group at the 1-position. Attempted SmI₂-promoted reductive carbon-nitrogen cleavage reaction of **128** in THF at ambient temperature for 1 h in the presence of MeOH as a proton source afforded a bond-cleaved compound, which without further purification was subjected to a recyclization in refluxing toluene to give the desired product (**129**) in 43% yield from **128**.⁸² Thus, we were able to develop a new route for transformation of an isoquinoline skeleton to a functionalized benzazepine ring system by simple reaction sequence (Scheme 25).



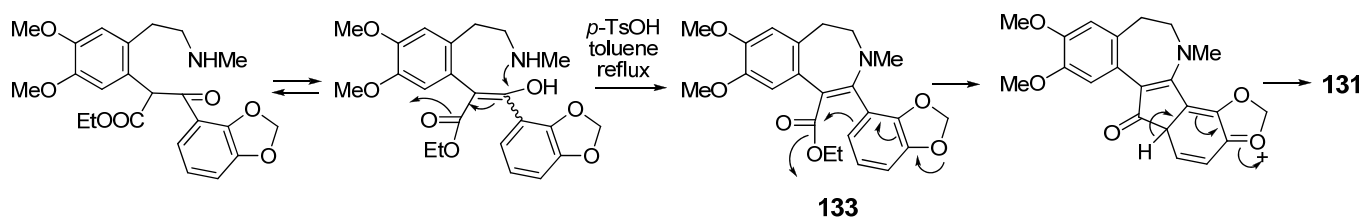
Scheme 25. SmI₂-promoted carbon-nitrogen bond cleavage reaction

By establishing a synthetic route to the basic skeleton of the natural product, we started the synthesis of bulgaramine as follows. Treatment of tetrahydroisoquinoline derivative (**127**) with 2,3-methylenedioxybenzoyl chloride⁸³ in THF in the presence of NaHMDS in THF afforded the 1-benzoyl derivative (**130**) in 83% yield. Reductive carbon-nitrogen bond cleavage reaction of **130** with SmI₂ (4 equiv) in THF in the presence of MeOH (3 equiv) as the proton source at room temperature for 30 min gave a secondary amine, which on treatment with *p*-TsOH monohydrate (0.1 equiv) in refluxing toluene furnished the desired benzindenoazepine-type compound (**131**) directly in 68% yield from **130**. It is noteworthy that the bond-cleaved compound was converted to benzindenoazepin-6-one (**131**) by treatment with *p*-TsOH in reasonable yield, probably due to the presence of an electron-donating methylenedioxy group on the D-ring, which might facilitate the cyclization of a relatively unstable enamino-ester to the more stable tetracyclic compound (**131**) (Scheme 26). Actually, when this cyclization was attempted in toluene in the absence of *p*-TsOH, enamino-ester (**133**) was isolated in 40% yield as the major product, which could be transformed to **131** in refluxing toluene containing *p*-TsOH in 81% yield. The plausible reaction mechanism is depicted in Scheme 27.

Finally, reduction of the carbonyl group of **131** at the 6-position was investigated under various reaction conditions. Usually, reduction of enaminones with various hydride donors, such as lithium borohydride, sodium borohydride, zinc borohydride, sodium acetoxyborohydride, or lithium aluminum hydride, provides the corresponding carbon-carbon double bond reduced ketones or corresponding alcohols, but the attempted reduction of **131** under similar reaction conditions did not give any reduced products. Fortunately, we are able to find a practical route for the conversion of **131** to the target compound (**126**) in which DIBAL was employed as the reducing agent.



Thus, the reduction of ketone (**131**) with DIBAL (5 equiv) in toluene at $-78\text{ }^{\circ}\text{C}$ for 24 h afforded bulgaramine (**126**), in 24% yield, together with the isomer **132**^{77,79} in 67% yield. Further transformation of **132** to **126** was achieved by treatment with 10% NaOH in EtOH at room temperature for 19 h in 95% yield (Scheme 26).



This synthesis provides a facile and entirely new route for construction of a benzindenoazepine ring skeleton in a small number of steps with reasonably high yield, in which a SmI_2 -promoted regioselective carbon-nitrogen bond cleavage reaction, followed by acid-catalyzed formation of a benzindenoazepin-6-one ring system, was involved as the key step. By exploiting this strategy, we succeeded in a concise synthesis of a benzindenoazepine alkaloid, bulgaramine, starting from the known tetrahydroisoquinoline derivative (**127**) in 4 or 5 steps in 50% overall yield.

9. SECOND GENERATION SYNTHESIS OF (-)-ADALININE⁸⁴

In 1999, we have developed a novel carbon-nitrogen bond cleavage reaction of α -amino carbonyl compounds by using SmI_2 as a one-electron transfer reagent.⁴ Thereafter, this strategy was recognized to be a general and widely applicable synthetic tool for the synthesis of various types of naturally occurring alkaloids, in which proline derivatives have mainly been employed as the chiral starting materials as shown above. The plausible mechanism for the fragmentation was depicted in Figure 9 as exemplified by the reaction of α -amino esters with SmI_2 , where samarium-containing 5-membered intermediates might be involved as the active species.

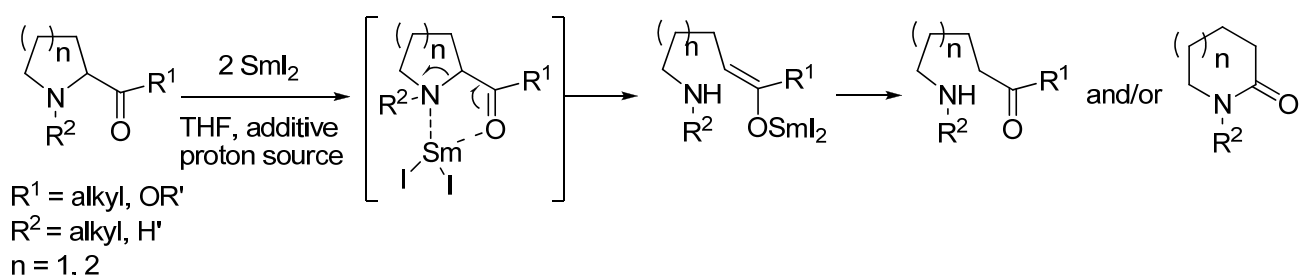


Figure 9. Proposed mechanism for a reductive C-N bond cleavage of α -amino carbonyl compounds

To extend the usefulness of this strategy, we decided to apply a SmI_2 -promoted fragmentation reaction to a 3-oxopyrrolidine derivative with expectation of a bond cleavage between the 1(N) and 2(C) positions, site-selectively, since an obtained product would be a suitable precursor for the synthesis of coccinellid alkaloids adalidine (**1**) and adaline (**2**) as shown in Figure 10.

Thus, the precursors having a quaternary carbon center at the 5-position for a SmI_2 -promoted fragmentation reaction were prepared starting from (4*R*)-hydroxyproline.

First, we synthesized a 3-oxopyrrolidine derivative (**133**) possessing (1,3-dioxolan-2-yl)propyl group at the 5-position, as the precursor for the synthesis of (-)-adalidine (**1**). However, the attempted SmI_2 -promoted carbon-nitrogen bond cleavage reactions of **133** in appropriate solvent in the presence of several kinds of additives produced an inseparable mixture of the reduction products (**134**) instead of the desired fragmentation product (**135**) (Scheme 28).

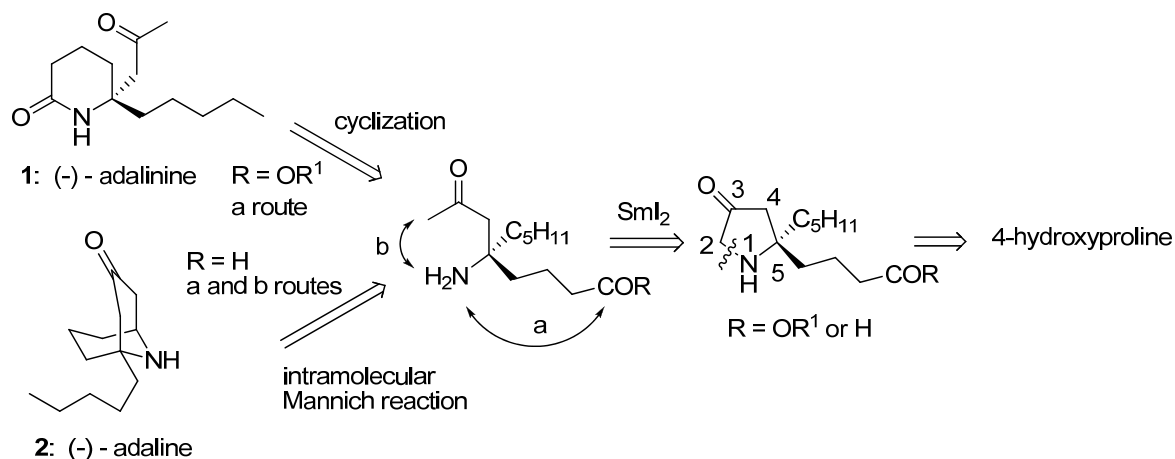
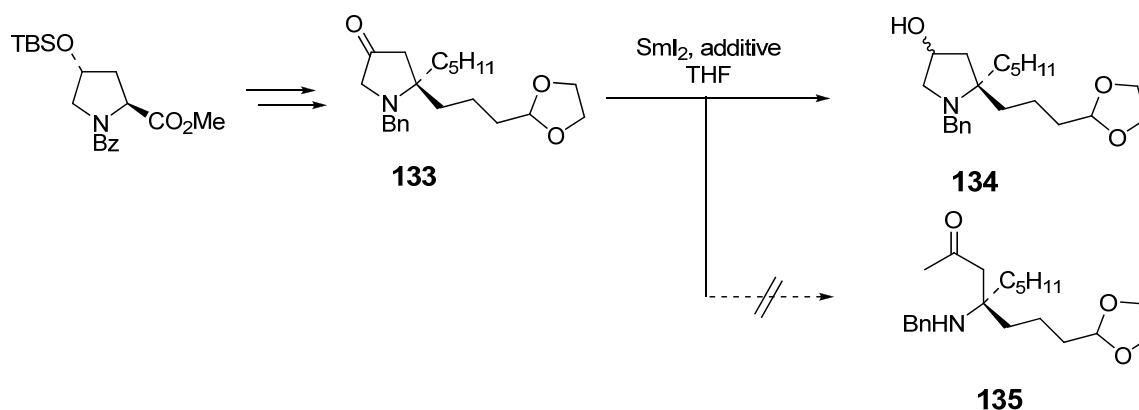


Figure 10. Synthetic plan for coccinellid alkaloids



Scheme 28. SmI_2 -promoted fragmentation of **133**

It would be conceivable, based upon examination of proposed reaction mechanism for a regioselective carbon-nitrogen bond fragmentation of α -amino carbonyl compounds with SmI_2 , that a participation of samarium metal in forming a cyclic intermediate between carbonyl and amino functions might play an important role to accelerate the fragmentation as shown in Figure 10. However, a formation of such samarium-involved 5-membered intermediate seems to be sterically disfavor for **133** (Figure 11).

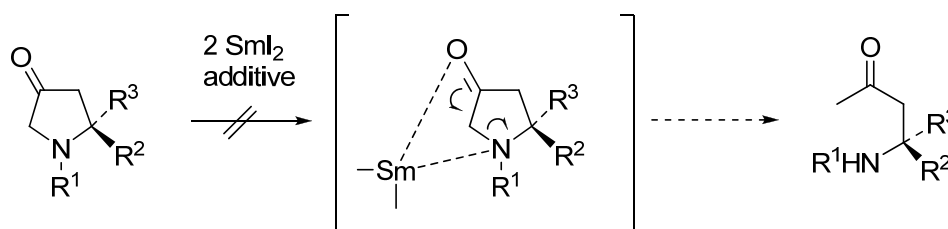


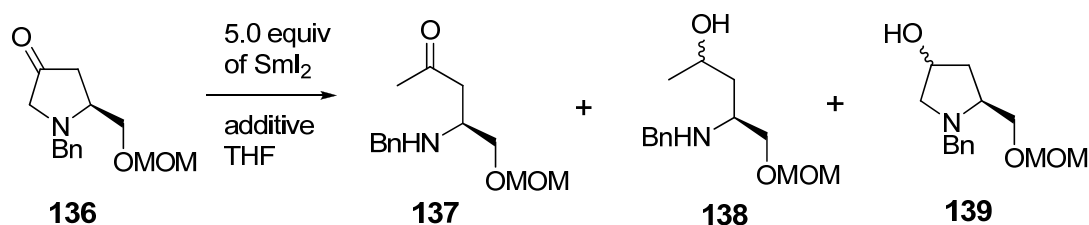
Figure 11. Reaction of 3-oxopyrrolidines with SmI_2

Given these considerations, we sought to prepare the known 3-oxopyrrolidine derivative (**136**) having a functional group at the 5-position that can generate a reasonably tight coordination with samarium metal.

SmI₂-promoted carbon-nitrogen bond cleavage reaction of **136** was investigated under several reaction conditions, and the results obtained were summarized in Table 5.

Treatment of **136** with 5 equivalents of SmI₂ in THF in the presence of HMPA and MeOH as an additive and a proton source, respectively, at 0 °C for 5 min afforded the secondary alcohols (**139**) in 88% yield (Entry 1). By changing the proton source to *N,N*-dimethylaminoethanol (DMEA), the similar reaction gave the fragmentation product with further reduction of the carbonyl group to furnish the secondary amine (**138**), as an inseparable mixture of the diastereoisomers, in 42% yield (Entry 2).

Table 5. SmI₂-promoted C-N fragmentation of **136**



Entry	Additive (equiv)	Time	Temp. (°C)	Product	Yield (%)
1	HMPA (5.0) + MeOH (2.5)	5 min	0	139	88
2	DMEA (10.0)	10 min	0	138	42
3	MeOH (2.5)	1 h	0	137	44
4	MeOH (2.5)	3 h	-78	139	63

By using MeOH as a proton source in the absence of HMPA, the desired ketone (**137**) could be isolated from the reaction mixture in 44% yield. When this reaction was carried out at -78 °C for 3 h, the reduction product (**139**) was again isolated in 63% yield. Similar reaction at room temperature afforded the reduction product (**139**) as the sole isolable product. It is reasonably assumed that the reaction of **136** with SmI₂ would probably proceed through the chelation intermediate to facilitate the desired fragmentation as depicted in Figure 12.

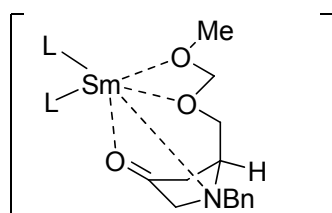
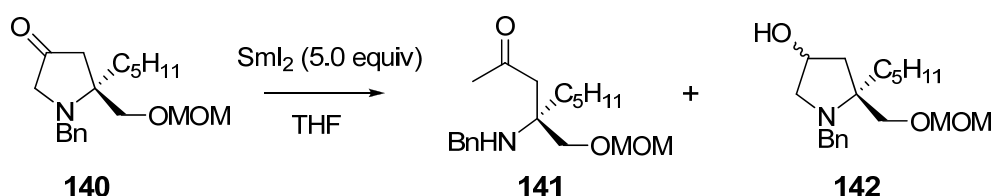


Figure 12. Assumed chelation intermediate for the fragmentation of **136**

Next, we attempted to find the best proton source for 5,5-disubstituted 3-oxopyrrolidine derivative having a similar substitution pattern to the target natural product.

First, the fragmentation of **140**, prepared from (4*R*)-hydroxyproline, was carried out by using SmI₂ (5.0 equivalents) in THF-HMPA at 0 °C for 15 h, however, only decomposition of the starting material was observed (Entry 1). We note in advance that proton sources play an important role in this fragmentation reaction. We, therefore, decided to find the best proton source in THF solution by screening, and the results obtained were summarized in Table 6.

Table 6. Screening of proton sources for SmI₂-promoted fragmentation



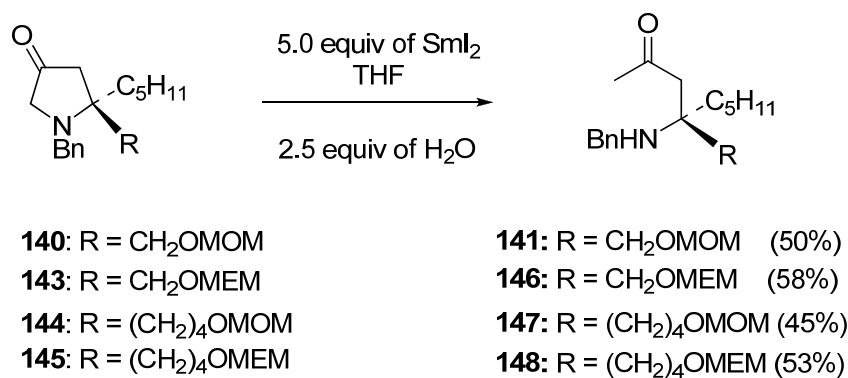
Entry	Additive (equiv)	Time	Temperature	Products (yield)
1	HMPA (5.0) + MeOH (2.5)	15 h	0 °C	decompose
2	DMEA (10)	10 min	0 °C	142 (75%)
3	MeOH (2.5)	2 h	0 °C	141 (trace), 142 (50%)
4	Nil ₂ (0.05)	6 h	0 °C to rt	142 (25%), 140 (58%)
5	Nil ₂ (0.05) + MeOH (2.5)	4 h	0 °C	142 (43%)
6	HMPA (5.0)+ MeOH (2.5)	5 min	0 °C	142 (85%)
7	HMPA (5.0) + <i>tert</i> -BuOH (2.5)	6 h	0 °C	142 (68%)
8	<i>tert</i> -BuOH (2.5)	15 h	0 °C	142 (10%)
9	<i>tert</i> -BuOH (2.5)	2 h	reflux	142 (60%)
10	H ₂ O (2.5)	2 h	0 °C	141 (50%)

With the presence of MeOH as the proton donor in THF-HMPA, the reaction of **140** with SmI₂ (5.0 equivalents) at 0 °C for 5 min gave the secondary alcohols (**142**) as an inseparable diastereoisomeric mixture in 85% yield in a ratio of ca. 1:1 (Entry 6). As can be seen in Table 6, almost all of proton sources; such as *N,N*-dimethylethanolamine (DMEA), *tert*-BuOH and the combination of those proton sources were also found to be ineffective for this fragmentation (Entries 2, 4, 5, 7-9). When MeOH (2.5 equiv) was employed as the proton source in THF solution, formation of the desired product (**141**) was observed in a trace amount (< 3%) (Entry 3). However, the yield of **141** could not be improved under the variety of reaction conditions attempted by the use of MeOH, unfortunately. We are very pleased to find that the choice of water as a proton source afforded the desired carbon-nitrogen bond cleavage product (**26**) in moderate yield (Entry 10). Although the pivotal role was still unclear at present, it has been

recognized that the use of water as the proton donor sometimes induced profound impact on variety of factors; such as the reaction rate, mechanism, and stereoselectivity for SmI₂-mediated one-electron transfer reactions.⁸⁵

Since a methoxymethyl protecting group of the primary alcohol in **136** and **140** was found to be effective for the expected fragmentation, we further investigated a possibility of other types of protecting groups expecting a formation of chelation intermediate by employing water as the proton donor. Again, the attempted fragmentation of the compounds (**140**, **143**, **144** and **145**) with SmI₂ provided the corresponding carbon-nitrogen cleavage products in moderate yields, and the results were summarized in Table 7. Although the exact reason was not clear at present, the use of water as a proton source furnished the desired product in reasonable yields.

Table 7. Fragmentation reactions for 3-oxopyrrolidine derivatives

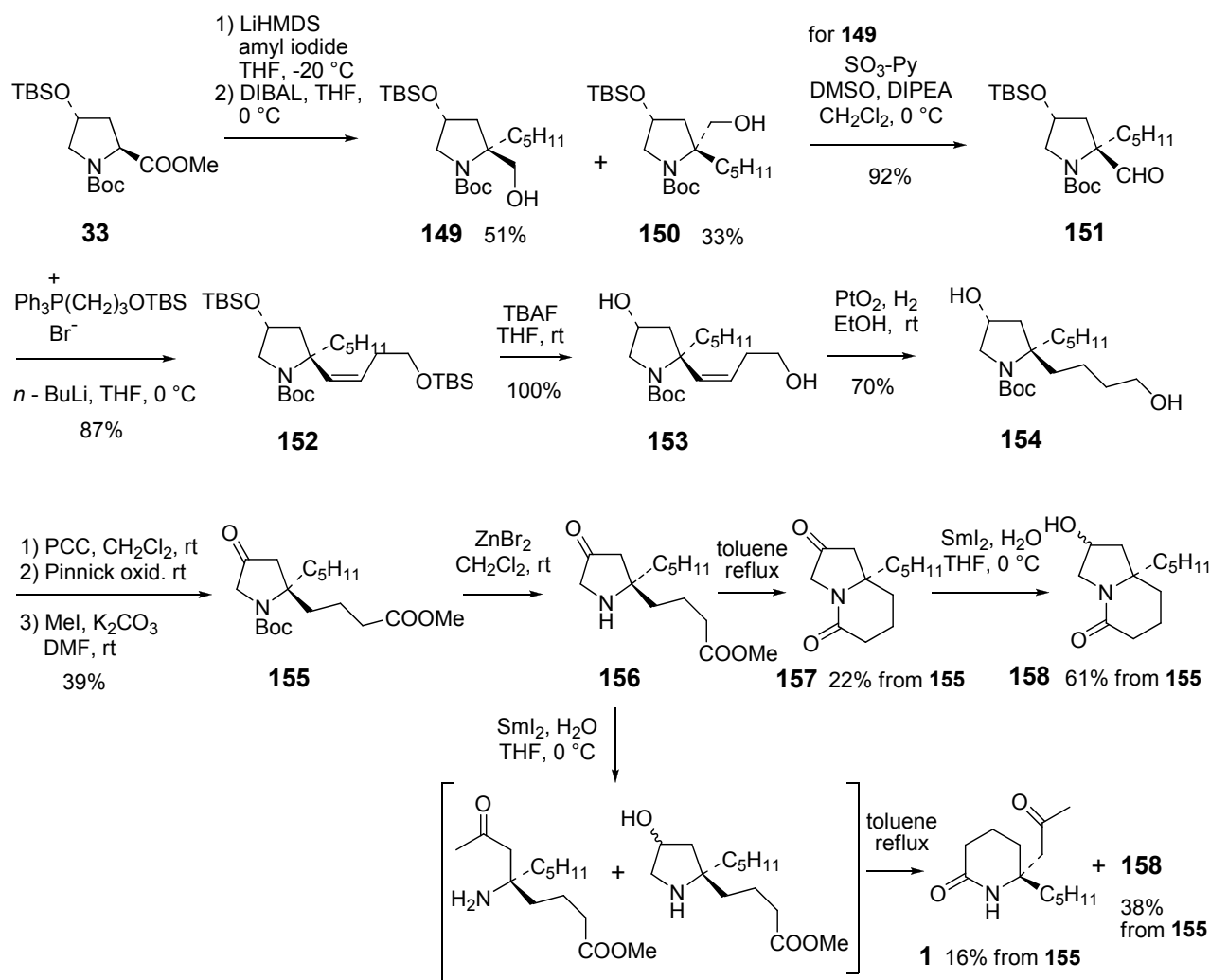


These results obviously indicated that formation of a chelation intermediate between samarium metal and heteroatoms on the protecting groups seems to play an important role to take place a SmI₂-promoted bond cleavage reaction.

Given these considerations, we assumed that an ester might also serve as a suitable functional group to generate a chelation intermediate with samarium metal. Therefore, we decided to synthesize a precursor having an ester function on the side chain for SmI₂-promoted carbon-nitrogen bond cleavage reaction in the synthesis of adalinine. Alkylation of the known ester (**33**) with amyl iodide in the presence of LiHMDS in THF, followed by reduction of a mixture of diastereoisomeric esters with DIBAL gave the primary alcohols (**149** and **150**) in 51% and 33% yield, respectively. Oxidation of the major alcohol (**149**) with SO₃-Py and subsequent Wittig reaction of the resulting aldehyde (**151**) with the phosphonium salt afforded (*Z*)-olefin (**152**) in 87% yield. After deprotection of the silyl group of **152** on treatment with TBAF, olefinic diol (**153**) was hydrogenated over platinum oxide to provide the saturated diol (**154**). Oxidation of both hydroxyl groups of **154**, followed by Pinnick oxidation⁸⁶ of the resulting aldehyde with

NaClO₂ gave the corresponding acid. Finally, esterification of the acid with methyl iodide in the presence of potassium carbonate furnished the desired ester (**155**).

With the requisite carbonyl compound (**155**) in hand, a SmI₂-promoted carbon-nitrogen bond cleavage reaction was attempted. The desired precursor thus obtained was subjected to SmI₂-mediated reductive carbon-nitrogen bond cleavage reaction exploiting water as the proton donor by two routes (Scheme 29).



Scheme 29. Synthesis of (-)-adalinine (**1**)

Removal of *N*-Boc group of ester (**155**) by treatment with ZnBr₂ gave amine (**156**), which was heated in toluene to furnish the bicyclic lactam (**157**). Treatment of **157** with 5.0 equivalents of SmI₂ in THF in the presence of 2.5 equivalents of water at 0 °C for 3 h, however, afforded the reduction product (**158**) as the major product in 61% yield as a mixture of diastereoisomers, together with 22% of the recovered starting material (**157**). On the other hand, a similar treatment of amine (**156**) with 5.0 equivalents of SmI₂ in THF in the presence of 2.5 equivalents of water at 0 °C for 30 min generated two products, which, without

separation, were heated at reflux in toluene to give (-)-adalinine (**1**), in 16% yield from **156**, together with the bicyclic alcohol (**158**) in 38% yield.

In summary, we were able to establish an alternative stereoselective chiral synthesis of (-)-adalinine (**1**) by employing a SmI₂-promoted reductive carbon-nitrogen bond cleavage reaction of a 3-oxopyrrolidine derivative as a key reaction. In this synthesis, we assumed that the formation of samarium-involved chelation intermediate would play an important role for the desired fragmentation. It is noteworthy that water was the best proton source for this reaction, although the reasons remained unclear. This methodology seems to be applicable to various types of 3-oxo-pyrrolidine and -piperidine derivatives.

10. CONCLUSION

The use of samarium diiodide as a mild and selective one-electron transfer agent has become an important tool in organic synthesis. This reagent proved to be an outstanding versatile reagent in stereoselective reactions to synthesize highly functionalized, structurally complex organic compounds inaccessible by established conventional methods. We have already established a regioselective carbon-carbon bond cleavage reaction of γ -halo carbonyl compounds, and its utilization in the synthesis of various types of biologically active natural products. However, a SmI₂-promoted reductive carbon-nitrogen bond cleavage reaction has received relatively little attention. In this review article, we would like to discuss a general carbon-nitrogen bond cleavage reaction of α -amino carbonyl compounds newly developed in our laboratory, and utilization of this methodology in the synthesis of a number of bioactive alkaloids, since this reaction proceeds in relatively high yield under mild reaction conditions. Although we did not mention in this manuscript, enantioselective synthesis of (*R*)-deoxydysibetaine and (-)-4-*epi*-dysibetaine was also achieved by employing this methodology as a key reaction.⁸⁷

We hope that this methodology is recognized as one of the versatile synthetic tools, and many organic chemists employ this reaction in the synthesis of useful bioactive compounds including natural products.

ACKNOWLEDGEMENTS

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 10. *N*-Substituted pipercolinates were prepared from ethyl pipercolinate by alkylation with the suitable alkyl halide and ^tPr₂NEt or by acetylation with Ac₂O.
 11. 2-Acetyl-*N*-alkylpiperidine derivatives were prepared from ethyl pipercolinate *via* four steps involving *N*-alkylation with alkyl halide, hydrolysis of the ester, conversion of the acid to the Weinreb's amide (S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815), and treatment of the amide with MeMgBr; the *N*-acetyl compound was derived from the *N*-benzyl derivative by reductive debenylation over Pd/C in the presence of Ac₂O; the *N*-Boc derivative was prepared according to the known procedure: S. Aoyagi, T.-C. Wang, and C. Kibayashi, *J. Am. Chem. Soc.*, 1993, **115**, 11393.
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