Efficient syntheses of bioactive alkaloids by means of samarium diiodide and cobalt carbonyl complex

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Abbreviations

The following abbreviations were used in this dissertation.

Solvents and reagents

AIBN	2,2'-azobisisobutyronitrile
CMMP	cyanomethylenetrimethylphosphorane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAPh	4-(dimethylamino)phenyl
DMEA	*N,N*-dimethylethanolamine
DMF	*N,N*-dimethylformamide
DMPU	*N,N*-dimethyl propylene urea
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoramide
MS	molecular sieves
NaHMDS	sodium hexamethyldisilazide
NMO	*N*-methylmorpholine *N*-oxide
Py	pyridine
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMANO	trimethylamine *N*-oxide

Functional and protecting groups

Ac	acetyl
Bn	benzyl
Boc	*t*-butoxycarbonyl

n-Bu	*normal*-butyl
t-Bu	*tertiary*-butyl
Cy	cyclohexyl
Et	ethyl
Me	methyl
MOM	methoxymethyl
Ns	2-nitrobenzenesulfonyl
Phth	phthaloyl
i-Pr	isopropyl
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

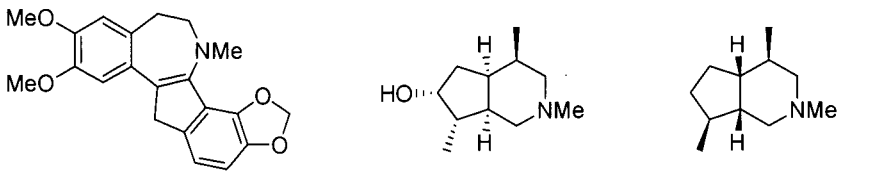
Others

aq.	aqueous
atm.	atmosphere
cat.	catalyst
d.r.	diastereomeric ratio
Eq.	equivalent
NOE	nuclear Overhauser effect
PG	protecting group
S.M.	starting material
temp.	temperature

General Introduction

In the field of natural product synthesis, recent developments within organic chemistry provides us with a significant challenge that the target is synthesized by means of completely concise and practical methodologies. Moreover, the results obtained from these challenges would contribute to tremendous progress not only in organic chemistry but also in the area of life science. It goes without saying that the constructions of efficient and selective synthetic methods have made progress for producing potential medicines in the pharmaceutical industry. We would recognize that up to 80% of approved medicines in Japan consist of natural products or its derivatives. Surprisingly, although the human genome has been radically elucidated today, most chemists say that the natural product synthesis may take the initiative in developing promising medicines and this tendency will last into the future.

In this dissertation, I described three natural products below (**Figure 1**).



Bulgaramine (1) **(-)-Incarvilline (2)** **(+)-α-Skytanthine (3)**

Figure 1. Structures of Target Alkaloids

It is a well-known fact that alkaloids such as morphine have potent biological activities dating back from ancient times. Without exception, bulgaramine (**1**) may have antipyretic and analgesic activities[1], (-)-incarvilline (**2**) has antinociceptive activity[2], and (+)-α-skytnathine (**3**) has an activity on the central nervous system[3], respectively. With consideration of bioactive aspects and intriguing structural features, the purpose of these research projects is to establish efficient synthetic routes toward the three alkaloids by exploiting samarium diiodide and cobalt carbonyl complex.

Chapter 1.
Concept of Samarium Diiodide-promoted Reductive Carbon-Nitrogen Bond Cleavage Reaction

1. Background

Samarium(II)diiodide (SmI_2) is a green solid composed of samarium and iodide, with a melting point of 520 °C where the samarium atom has a coordination number of seven (**Figure 2**). It can be formed by high temperature decomposition of SmI_3 (the more stable iodide), but a convenient laboratory preparation is to react Sm powder with 1,2-diiodoethane in anhydrous THF[4]. It is commercially available as a dark blue 0.1 M solution in THF.

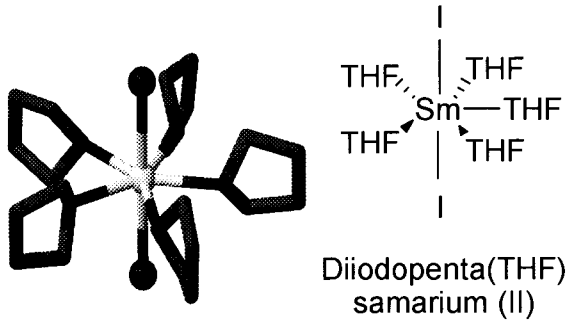
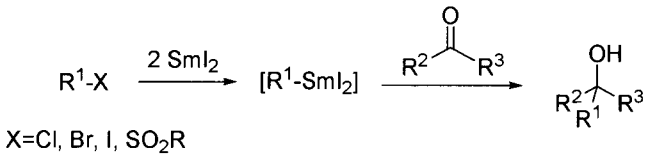


Figure 2. Structure of Samarium (II) Diiodide in THF Solution

Several remarkable features of SmI_2 in the organic synthesis can be summarized as follows:

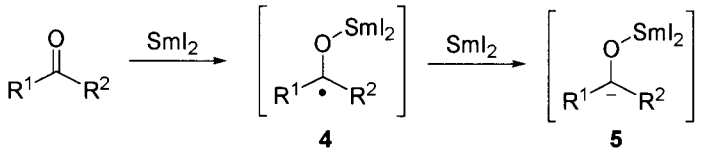
1) Working as a powerful electron transfer agent
2) Coordination to oxygen and sulfur atoms
3) Inducing regio- and stereo-selectivities by its affinity for the reaction center of an carbonyl group
4) Distinctive transition state because of its large ionic radius

First used in organic chemistry by Kagan in 1977[5], SmI_2 has gained increasing popularity as a reagent for carbon-carbon bond formation such as a Barbier reaction (similar to the Grignard reaction) (**Scheme 1**)[6].



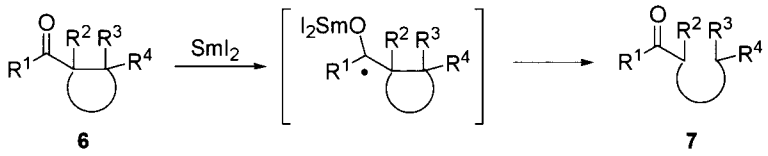
Scheme 1. Barbier Reaction

The large reducing potential of SmI_2 (up to -2.05 V in the presence of HMPA) allows access to a rich array of reactive intermediates. As shown in **Scheme 2**, a carbonyl moiety can be reductively activated to form a reactive ketyl radical **4**, which, under appropriate conditions, can be further reduced to provide access to carbanion **5**.



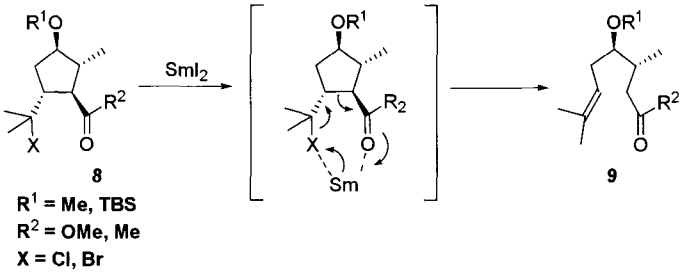
Scheme 2. SmI_2-mediated Activation of Carbonyl Compound

A cleavage of carbon-carbon σ-bond is often promoted by SmI_2. An intramolecular bond cleavage reaction at the α-position of carbonyl compound **6** generates the ring-opened carbonyl compound **7** (**Scheme 3**).



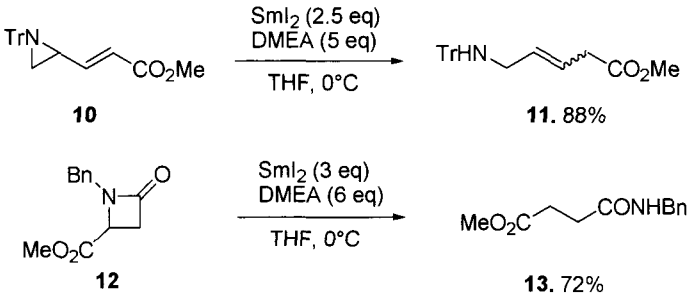
Scheme 3. SmI_2-mediated C-C Bond Cleavage Reaction at the α-Position of Carbonyl Compound

In the few examples of SmI_2-mediated fragmentations, Honda reported regioselective carbon-carbon bond cleavage reaction of γ-haloketone compounds **8**, which were readily accessible from (-)-carvone, by treatment of SmI_2 (**Scheme 4**)[7]. These optically pure bond cleaved compounds **9** are useful materials for some chiral syntheses.



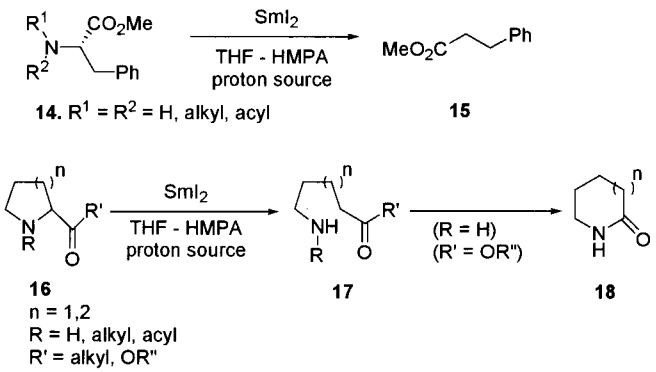
Scheme 4. SmI_2-mediated C-C Bond Cleavage Reaction by Honda

Reductive cleavage of α-amino functionality is also less common to the best my knowledge. Molander and Stengel showed that acyl aziridines **10** and azetidinones **12** underwent facile ring fragmentation in the presence of *N*,*N*-dimethylethanolamine (DMEA) (**Scheme 5**)[8].



Scheme 5. SmI_2-mediated Fragmentation of Aziridine and Azetidinone

In 1999, Honda and Ishikawa reported further development of SmI_2-promoted reductive deamination of α-aminocarbonyl compounds **14**[9]. In their report, the successful results concerning systematic investigation of a SmI_2-promoted regioselective carbon-nitrogen bond cleavage reaction of α-aminocarbonyl compounds **16** were revealed and then the corresponding fragmentation products **17** bearing a primary amino and ester functional groups sometimes afforded the recyclized compounds **18**, namely ring enlarged lactames (**Scheme 6**).



Scheme 6. SmI_2-mediated Reductive C-N Bond Cleavage Reaction

Because of its useful and efficient methodology for organic synthesis, its application to the various syntheses of alkaloids has been successfully performed (**Figure 3**)[10].

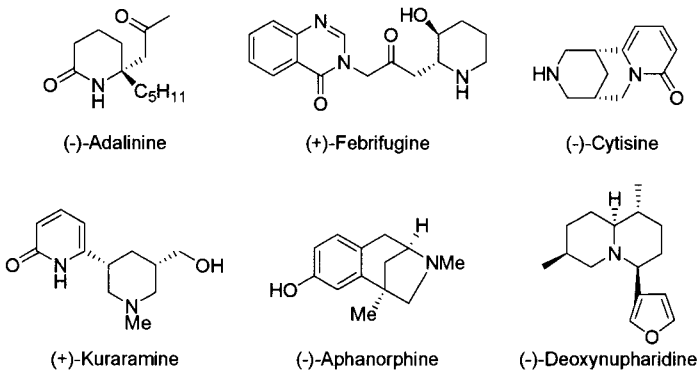
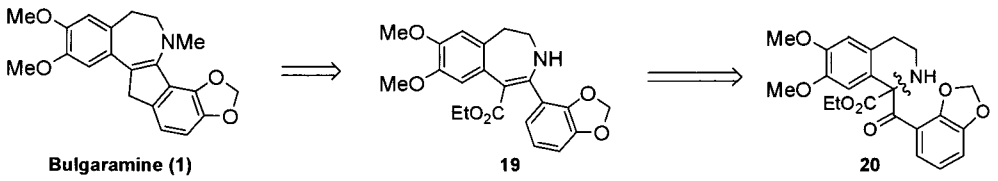


Figure 3. Various Alkaloids Synthesized by Using SmI_2-promoted C-N Bond Cleavage Reaction

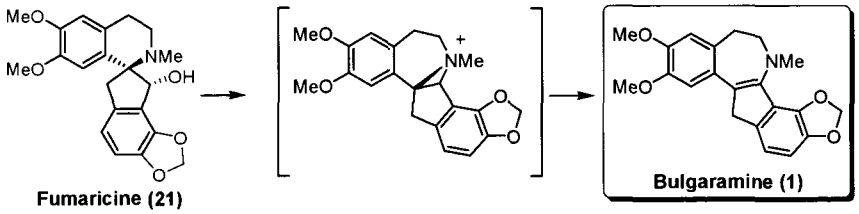
During course of related projects, we envisioned to synthesize bulgaramine (**1**) by employing SmI_2-promoted reductive carbon-nitrogen bond cleavage reaction and corresponding cyclization reaction. We anticipated that the binding bond of the carbon at 1-position to the nitrogen at 2-position of tetrahydroisoquinoline derivative **20** would be cleaved by appropriate treatment of SmI_2 and the corresponding amine and ketone moieties would be reacted to construct the benzazepine **19** (**Scheme 7**).



Scheme 7. Further Application to Bulgaramine Synthesis

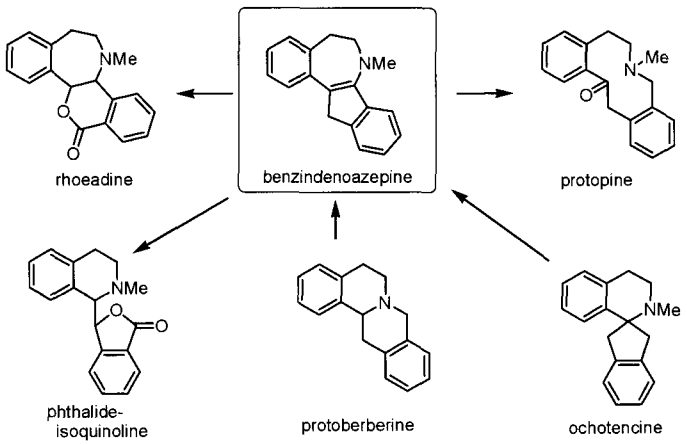
2. Facile Synthesis of a Benzindenoazepine Alkaloid, Bulgaramine

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[1]. Various chemical constituents have been extracted from these plants, including a series of compounds based on the benzindenoazepine ring system[11]. In 1984, bulgaramine (**1**) was isolated from *Fumaria officinalis* as a member of benzindenoazepines that were a distinct group of alkaloids, probably derived biogenetically from the rearrangement of spirobenzylisoquinolines[12]. On the basis of this consideration, a spirobenzyl isoquinoline alkaloid, fumaricine (**21**), has been successfully transformed to bulgaramine via aziridium cation, supporting the biogenetic hypothesis (**Scheme 8**)[13].



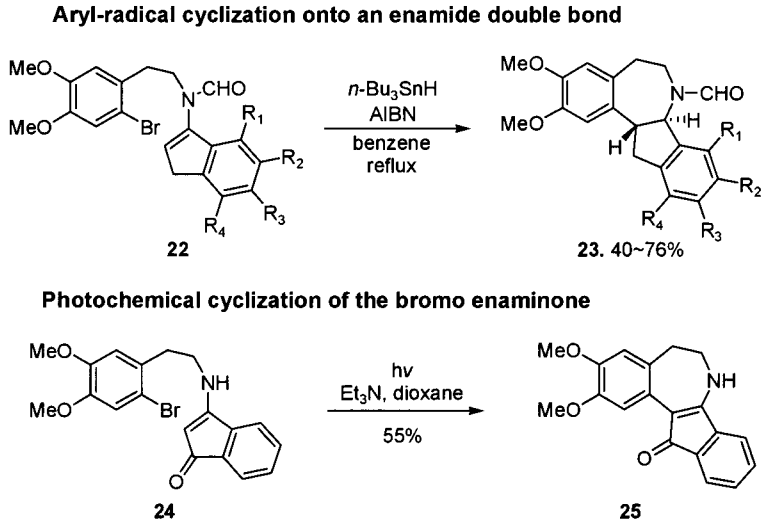
Scheme 8. Conversion of Fumaricine to Bulgaramine

The benzindenoazepine skeleton has occupied a central position in the biogenetic scheme linking with protoberberine, rhoeadine, protopine, phthalideisoquinoline, and ochotencine typed alkaloids[14]. Therefore, development of novel synthetic methodology of benzindenoazepine framework deserves careful attention (**Scheme 9**).



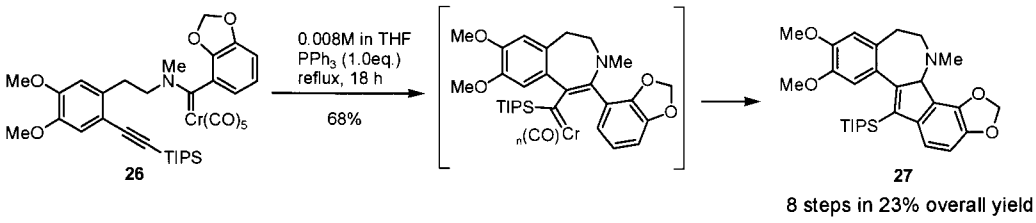
Scheme 9. Biogenetic Linking with Benzindenoazepine Skeleton

Concerning the formation of benzindenoazepine skeleton, Dominguez has addressed two synthetic reports. First, a synthesis of benz[*d*]indeno[1,2-*b*]azepine from bromoaryl enamide **22** could be achieved by way of a regioselective *7-endo-trig* radical cyclization with tri-*n*-butyltin hydride[15]. Second, the similar type of synthesis has been achieved by photochemical cyclization of the corresponding bromo enaminone **24** (**Scheme 10**)[16].



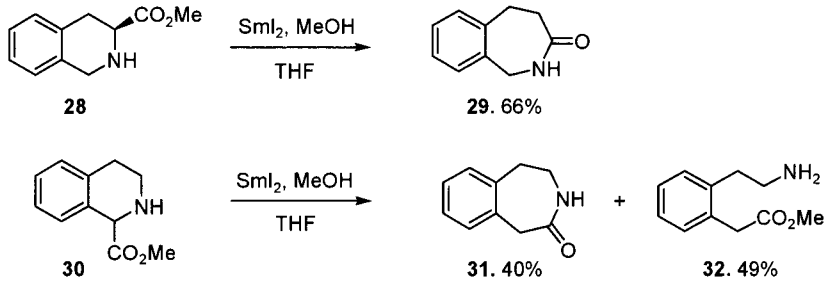
Scheme 10. Previous Syntheses of Benzindenoazepine Framework

In 2005, Giese has achieved the first total synthesis of bulgaramine (**1**) with a longest linear sequence of eight steps and overall yield of 23% from commercially available 3,4-dimethoxyphenethyl alcohol. An intramolecular cyclopentannulation of the Fischer aminocarbene complex **26** gives the desired cycloadduct **27** in one step, and this is the only report of total synthesis for bulgaramine (**1**) (**Scheme 11**)[17].



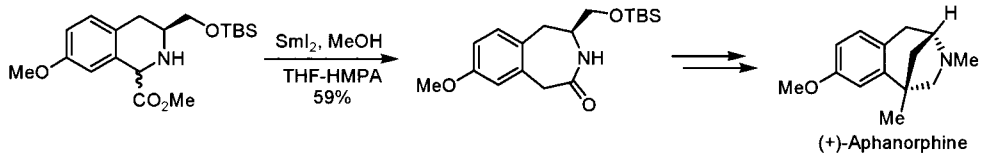
Scheme 11. Cyclopentannulation of Fischer Aminocarbene Complexes: Total Synthesis of Bulgaramine by Giese

In 1999, Honda developed a SmI_2-promoted regioselective carbon-nitrogen bond cleavage reaction of α-aminocarbonyl compounds. Moreover, this method was successfully applied to the 1,2,3,4-tetrahydrosioquinoline derivatives **28** and **30** providing the corresponding ring expanded the seven-membered lactams **29** and **31**, respectively (**Scheme 12**)[18].



Scheme 12. SmI_2-promoted Reductive Deamination of the Isoquinoline Derivatives

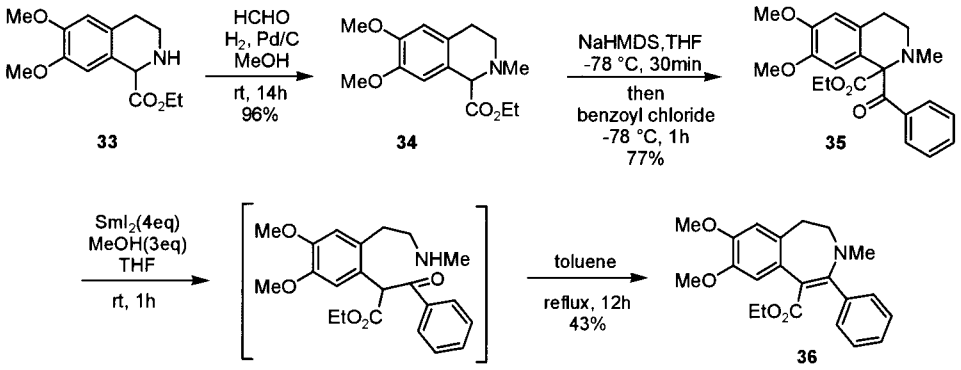
This strategy was also adapted to an enantioselective total synthesis of (+)-aphanorphine in 2005 (**Scheme 13**)[10e]. On the basis of previous results, we decided to examine how to establish general synthetic routs for benzindenoazepine alkaloid, bulgaramine (**1**).



Scheme 13. Synthesis of (+)-Aphanorphine

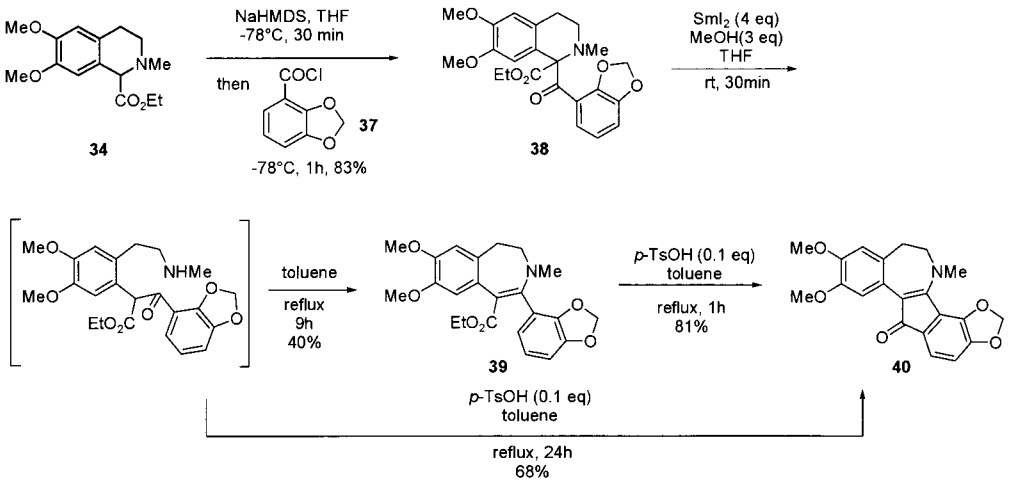
In the beginning, we decided to investigate efficient and mild reaction conditions for the SmI_2-promoted bond cleavage reaction of an ester **35**. The known tetrahydroisoquinoline **34**[19] was prepared by treatment of **33**[20] with modified condition, 37% formalin in MeOH in the presence of a catalytic amount of 10% palladium on carbon under an atmospheric pressure of hydrogen, in excellent yield. Installation of a benzoyl group was achieved by treatment of **34** with benzoyl chloride in the presence of NaHMDS in THF to give **35** in 77% yield. Attempted SmI_2-promoted deamination of **35** in the presence of MeOH as a proton source afforded a bond-cleaved compound, and then which, without further purification, was subjected under the refluxing toluene condition to give the desired product **36** in 43% yield from **35**. (The deethoxycarbonyl analogue of **36**[21] was

generated as a byproduct under these reaction conditions.) Thus, we were able to develop a model route for transformation of a functionalized isoquinoline skeleton to a benzazepine ring by simple reaction sequence (**Scheme 14**).



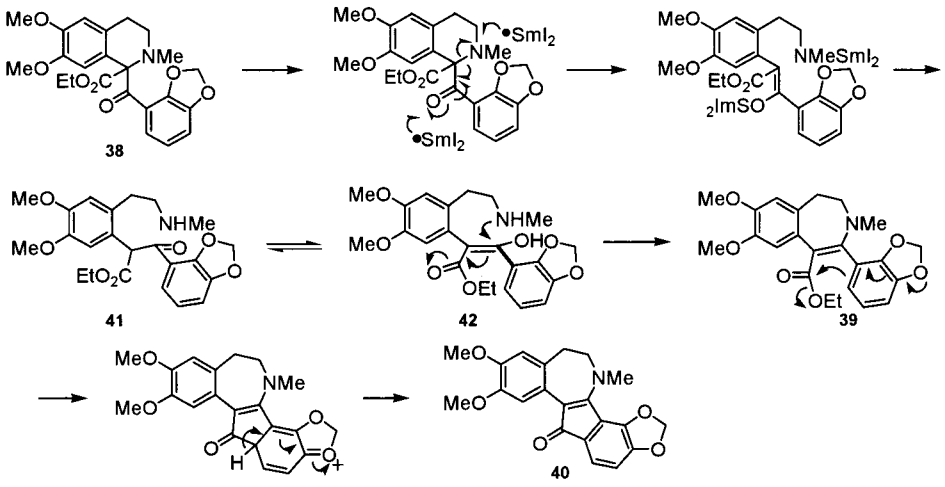
Scheme 14. SmI_2-promoted C-N Bond Cleavage Reaction of **35**

Focused on the synthesis of bulgaramine (**1**), we launched on the preparation of the known 2,3-methylenedioxybenzoyl chloride **37** following in previous literature[22]. Treatment of tetrahydroisoquinoline derivative **34** with the prepared acid chloride **37** in the presence of NaHMDS in THF afforded the 1-benzoyl derivative **38** in 83% yield. Reductive carbon-nitrogen bond cleavage reaction of **38** with SmI_2 (4 equiv) in the presence of MeOH (3 equiv) at room temperature for 30 min gave a secondary amine, which in the refluxing toluene for 9 h furnished the corresponding benzazepine **39**. Further refluxing of enaminoester **39** in the presence of catalytic amount of *p*-TsOH for 1h gave a benzindenoazepinone **40** in 81% yield. Thus, after cleavage reaction, the fragments were treated with *p*-TsOH (0.1 equiv) in refluxing toluene for 24 h to furnish the desired benzindenoazepinone **40** directly in 68% yield from **38** (**Scheme 15**).



Scheme 15. SmI_2-promoted Ring Transformation of **38**

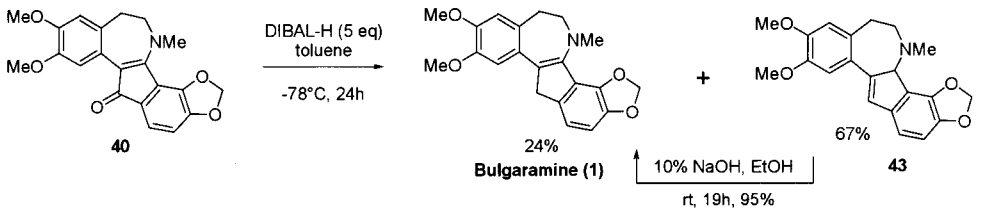
The plausible reaction mechanism of the key steps is depicted in **Scheme 16**. It is noteworthy that the bond cleaved compound (**41** or **42**) was converted to benzindenoazepin-6-one **40** by treatment with *p*-TsOH in reasonable yield, probably due to the presence of an electron-donating methylenedioxy group on the aromatic ring, which might facilitate the conversion of a relatively unstable enamino-ester **42** to the more stable tetracyclic compound **40.**



Scheme 16. Plausible Reaction Mechanism for the Formation of Benzindenoazepinone **40**

Finally, reduction of the carbonyl group at the 6-position of **40** was investigated under various reaction conditions. Fortunately, the reduction of ketone **40** with DIBAL-H (5 equiv) in toluene at -78 °C for 24 h afforded bulgaramine (**1**) in 24% yield, together with the isomer **43**[13] in 67% yield. Further transformation of **43** to **1** was achieved by treatment with 10% NaOH in EtOH

at room temperature for 19 h in 95% yield. The spectroscopic data of the synthesized compound including its melting point, 205-206 °C (lit.[12] m.p. 209 °C), were identical to those reported in the literature. We succeed in a concise synthesis of bulgaramine (**1**) in 5 steps in 50% overall yield (**Scheme 17**).



Scheme 17. Total synthesis of Bulgaramine (**1**)

Chapter 2.
Concept of Diastereoselective Intramolecular Pauson-Khand Reaction

1. Background

Generally, organocobalt compounds in organic synthesis have three notable features[23].

1) A high affinity to carbon-carbon π-bonds
2) A high affinity to carbonyl groups
3) Formation of square-planar bipyramidal six-coordination structures

The first type of characteristic reaction is caused by a mutually bridged bond between the two π-bonds of acetylene and the cobalt-cobalt bond of dicobalt hexacarbonyl to generate a dicobalt-alkyne complex (**Figure 4**).

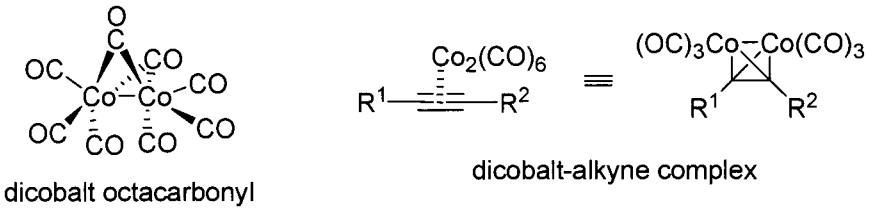
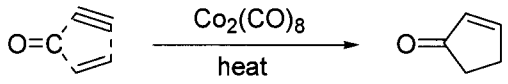


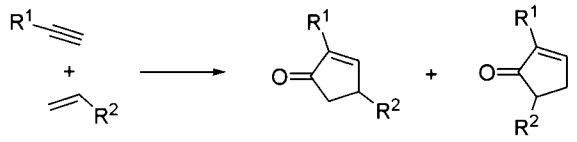
Figure 4. Structures of Dicobalt Carbonyl Complex

Pauson-Khand reaction is formally a [2+2+1] cycloadditon in which a triple bond, a double bond and carbon monoxide form a cyclopentenone (**Scheme 18**). The reaction was first discovered and reported in detail by Ihsan U. Khand and Peter L. Pauson in the seventies in the course of study on various alkene and alkyne complexes derived from $Co_2(CO)_8$[24]. Concerning the scope and limitations, this dramatic transformation is quite tolerant of substrate structure. The most satisfactory alkynes are acetylene and simple terminal alkynes. Strained cyclic alkenes are generally good substrates; however, steric hindrance around the double bond reduces cycloaddition reactivity considerably[25].



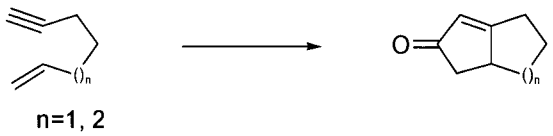
Scheme 18. Connectivity of Pauson-Khand Reaction

With respect to regioselectivity in an intermolecular Pauson-Khand reaction, the bulkier substituent of the alkyne is placed adjacent to the carbonyl in the cyclopentenone product. Unsymmetrical olefins usually give mixtures of regioisomers (**Scheme 19**).



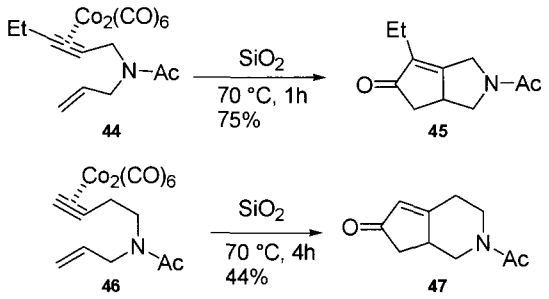
Scheme 19. Regiochemistry of the Intermolecular Pauson-Khand Reaction

In 1981, Schore introduced the intramolecular version of this reaction (**Scheme 20**)[26]. Until recently, this version allowed the formation of 5.5- and 5.6-fused bicyclic enones with generally greater levels of efficiency and good conversion yield. Despite of limitation by steric hindrance, the intramolecularity permits satisfactory results with terminal, internal, and even trisubstituted alkenes.



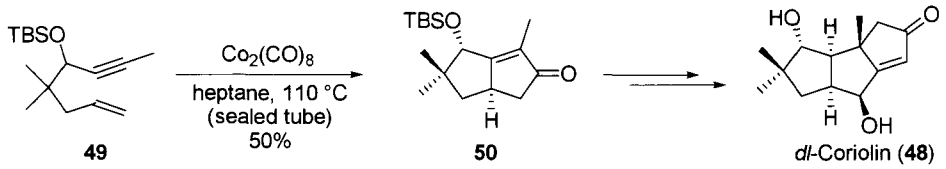
Scheme 20. Intramolecular Pauson-Khand Reaction

In 1990, Brown and Pauson reported that Pauson-Khand cyclization of *N*-acetyl enyne derivatives (**44** and **46**) gave the azabicyclo[3.3.0]octenones **45** and azabicyclo[4.3.0]nonenones **47** with the best conditions being heated to 70 °C of the silica-adsorbed substrate (**Scheme 21**)[27]. This reaction tolerates a wide range of remote functionality including ethers, alcohols, ketones, ketals, esters, tertialy amines, tertialy amides, thioethers, and aromatic and heteroaromatic rings.



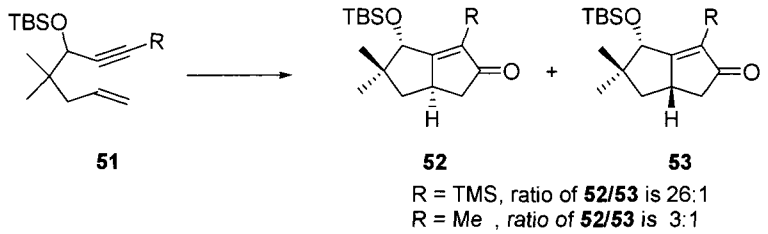
Scheme 21. Syntheses of Nitrogen Heterocycles via Pauson-Khand Cyclization

I would like to exemplify the representative synthesis of natural product, *dl*-coriolin (**48**), by exploiting an intramolecular Pauson-Khand reaction as a key step, which was presented by Magnus in 1983[28]. He proved that the cyclization of **49** diastereoselctively took place and readily provided the bicyclic enone **50** bearing desired stereochemistries (**Scheme 22**).



Scheme 22. Total Synthesis of *dl*-Coriolin

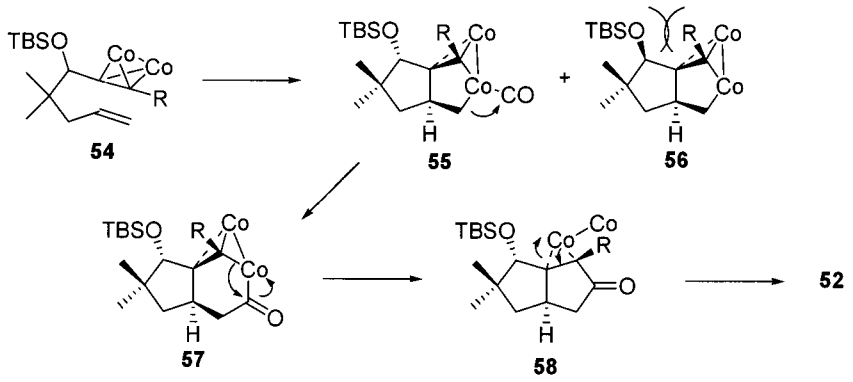
Concerning with mechanism of the Pauson-Khand reaction, the only evidence is the unambiguous observation that the alkyne complex is involved in the first stage of the process. No intermediates have been detected beyond this alkyne complex; however, in 1985, Magnus and Principe proposed a working hypothesis, which was rationalized on the stereochemical outcome of the synthesis of substituted bicyclo[3.3.0]octenones (**Scheme 23**)[29].



Scheme 23. Syntheses of the Bicyclo[3.3.0]octenone **52** and **53**

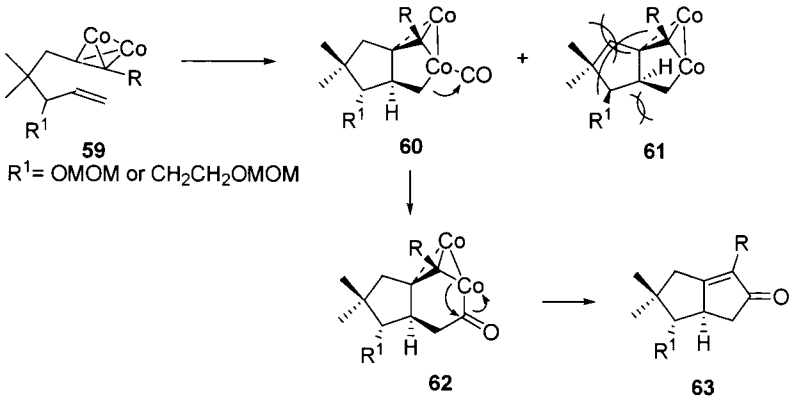
The size of the group on the terminal acetylene (R-) has clearly influenced on the outcome

of the 1,3-stereoselectivity. It could be rationalized on controlling the repulsion of transition state **55** and **56** (**Scheme 24**).



Scheme 24. Working Mechanistic Hypothesis to Explain the 1,3-Stereoselectivity

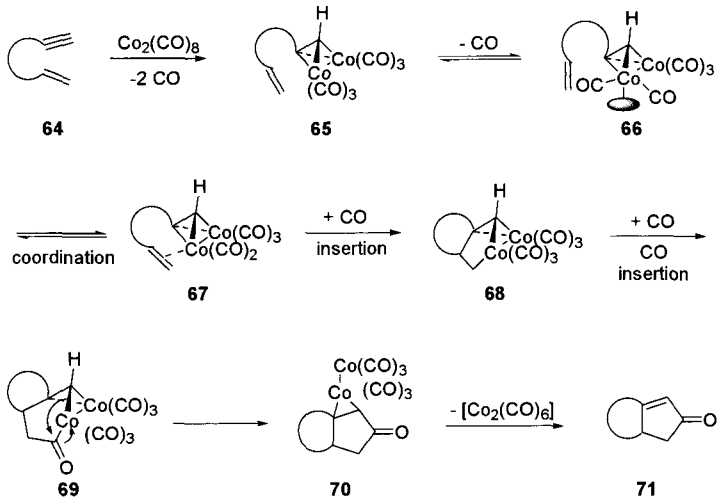
On the other hand, the 1,2 stereoselectivity of **63** probably depends on the repulsion between allylic functionality (R^1) and 5-membered metal cycle (**60** or **61**). Considering with this interaction, **60** may be a favorable intermediate in the reaction course (**Scheme 25**).



Scheme 25. Working Mechanistic Hypothesis to Explain the 1,2-Stereoselectiviy

A generally accepted mechanism is outlined in **Scheme 26**. The cobalt-alkyne complex **65** is usually pre-formed by reaction of an alkyne with dicobalt octacarbonyl, normally in high yield. The step of loosing carbon monoxide ligand from cobalt atom is reversible, and is thought to be rate determining (**65** to **66**). An alkene can then complex to the coordinatively unsaturated metal (**66** to **67**). The first carbon-carbon bond forming reaction takes place between the less hindered end of the alkyne and the alkene, and it is the step that explains the regioselectivity with respect to

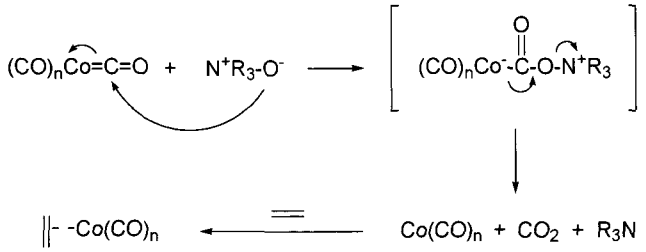
the alkyne (**67** to **68**). Carbon monoxide insertion into the cobaltacycle takes place (**68** to **69**), followed by reductive elimination (**69** to **70**) and decomplexation of the metal from the cyclopentenone (**70** to **71**).



Scheme 26. Proposed Mechanism for an Intramolecular Pauson-Khand Reaction

The early examples of the Pauson-Khand reaction were generally performed under an atmosphere of carbon monoxide in inert solvents at relatively high temperatures for prolonged periods of time. Due to these harsh conditions, in many cases, the main drawback was its relatively low scope and poor conversions.

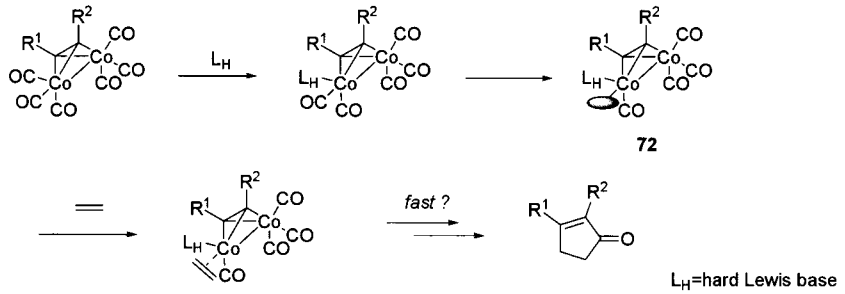
In early nineties, Schreiber[30] and Jeong[31] independently introduced that the use of amine *N*-oxides promoted the Pauson-Khand reaction and it has become the most popular way. The *N*-oxides act by oxidizing one CO ligand, which is transformed into CO_2, thus forming a vacant site in the cobalt cluster.



Scheme 27. Accelerating the Pauson-Khand Reaction by *N*-Oxides

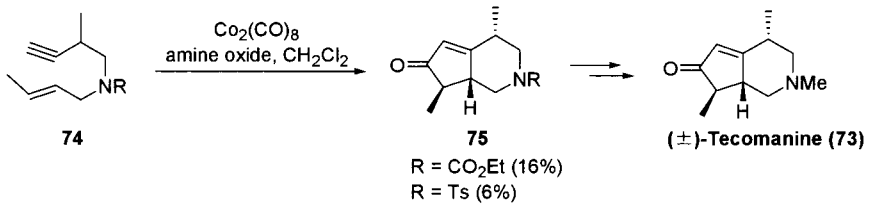
Another way to accelerate this reaction is by the addition of different chemical compounds.

Several sulfides and sulfoxides have shown excellent results, especially in the intermolecular version of the reaction[32]. Hard Lewis bases on low-valent organotranstion metal carbonyl **72** are known to make the coordinated CO ligands labile and promote the ligand liberation (**Scheme 28**).



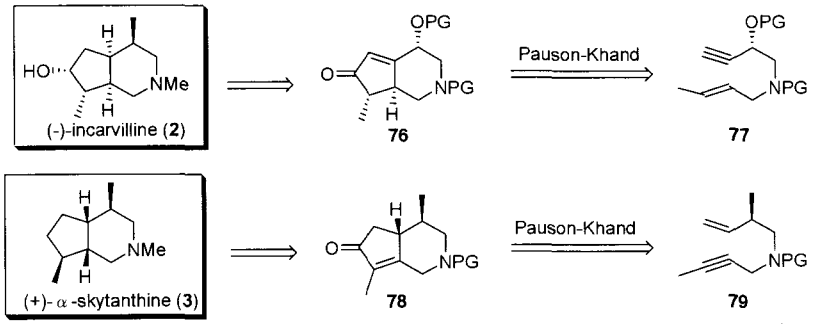
Scheme 28. Ligand Liberation by Coordinated Hard Lewis Base

The Pauson-Khand reaction has been used as the key step in a number of alkaloid syntheses[25]. In 2003, Schore reported a straightforward methodology to the synthesis of (±)-tecomanine (**73**) using an intramolecular Pauson-Khand cyclization, but in his cases, the desired cycloaddition isomers **75** (R=CO_2Et or Ts) could be isolated in only low yield, probably due to poor diastereoselectivity (**Scheme 29**)[33].



Scheme 29. Synthesis of (±)-Tecomanine.

All previous results have encouraged us to investigate the new system relying on this reaction when planning the synthesis of monoterpene alkaloids. The purpose of our research projects is to demonstrate that an intramolecular Pauson-Khand reaction is applicable to the chiral synthesis of two alkaloids, (-)-incarvilline (**2**) and (+)-α-skytanthine (**3**), bearing azabicyclo[4.3.0]nonane framework (Scheme **30**).



Scheme 30. Synthetic Plan for the both alkaloids Possessing Azabicyclo[4.3.0]nonane Framework

2. Diastereoselective Formal Synthesis of a Monoterpene Alkaloid, (-)-Incarvilline

Recent investigations of the plant *Incarvilla sinensis*, which has been used to treat rheumatism and relieve pain as a traditional Chinese medicine, led to the isolation of a various types of monoterpene alkaloids with a wide range of structural and stereochemical features (**Figure 5**)[34]. Among them, (-)-incarvillateine (**80**) carrying a characteristic cyclobutane ring has been recognized to exhibit significant antinociceptive activity on the pain model mouse induced by formalin[2]. Compared with antinociceptive effects of incarvillateine and morphine, the ED_{50} values of (-)-incarvillateine (**80**) were about 1.06 (early phase) and 1.33 (later phase) times lower than those of morphine. It has been also suggested that the antinociceptive effect arose from the activation of μ- and κ-opioid receptors and adenosine receptor[35].

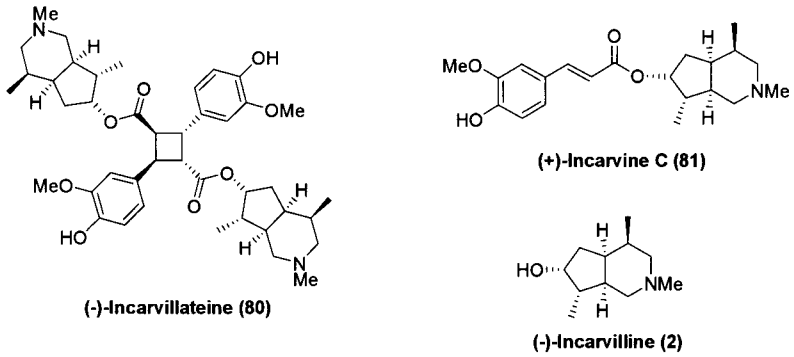
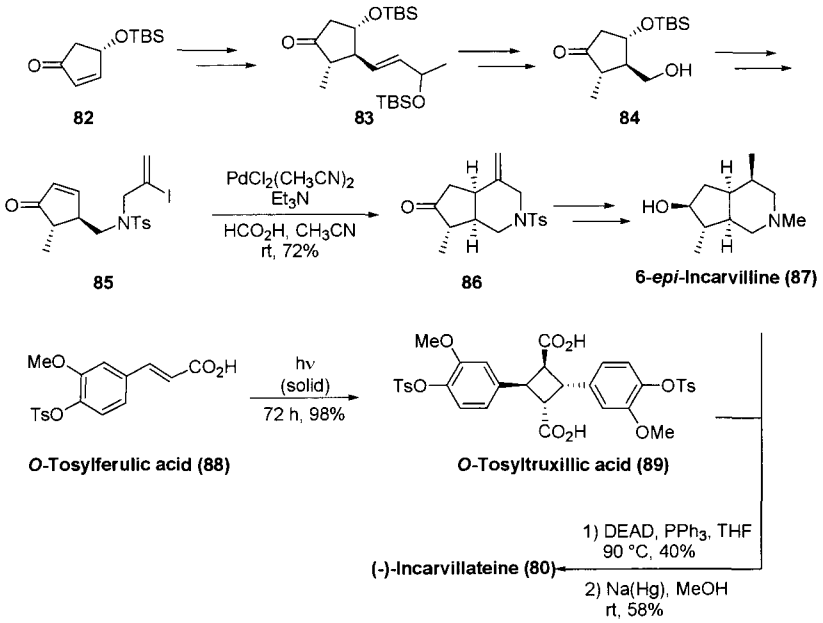


Figure 5. Structures of Typical Alkaloids in *Incarvillia sinensis*

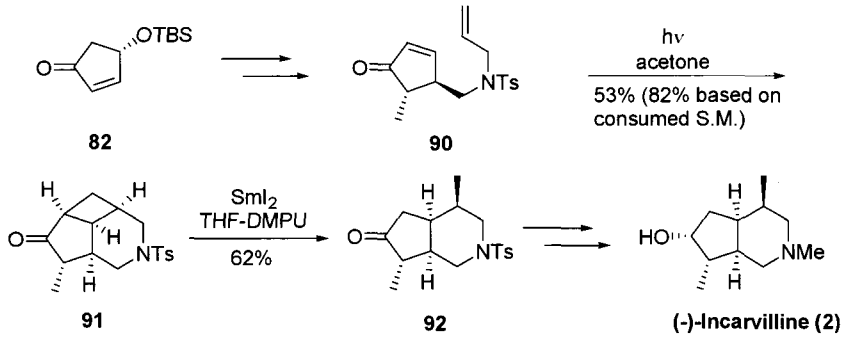
(-)-Incarvillateine (**80**) was supposed to generate biosynthetically via dimerization of (+)-incarvine C (**81**), a hydroxycinnamate derivative of (-)-incarvilline (**2**). In fact, the first total synthesis of (-)-incarvillateine (**80**) utilizing photochemical dimerization of a hydroxycinnamic acid derivative **88** and subsequent esterification with (+)-6-*epi*-incarvilline (**87**) was achieved by Kibayashi and his colleagues in 2004[36]. Their synthetic strategy of these natural products utilized *6-epi*-incarvilline (**87**) as a common precursor, which was assembled by a three-component coupling reaction using (4*S*)-4-siloxy-2-cyclopenten-1-one **82** to construct an appropriately trisubstituted cyclopentanone **83**, followed by ring closure to the *cis*-perhydro-2-pyridine skeleton by means of a reductive Heck-type reaction (**85** to **86**). Furthermore, topochemically controlled [2+2]photodimerization of cinnamic acid derivatives **88** in the solid state for the stereospecific construction of a cyclobutane ring was also investigated as a means to access (-)-incarvillateine

(**80**) (**Scheme 31**).



Scheme 31. First total Synthesis of (-)-Incarvillateine by Kibayashi

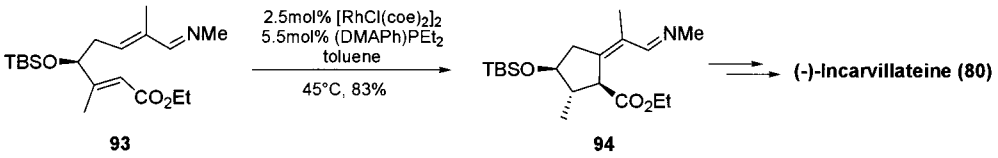
Kibayashi also addressed the alternative synthesis of (-)-incarvilline (**2**), employing an intramolecular enone-olefin [2+2] photocycoaddition (**90** to **91**) followed by a SmI_2-induced cyclobutane ring-opening reaction (**91** to **92**) as key sequence (**Scheme 32**)[37].



Scheme 32. Alternative Route to (-)-Incavilline by Kibayashi

Because of the unique structural features and intriguing biological profile of (-)-incarvillateine (**80**), after our report in 2007, two groups have been achieved its total syntheses in publication until now. In 2008, Ellman reported an asymmetric synthesis of (-)-incarvillateine (**80**) employing an intramolecular alkylation of an olefinic C-H bond to set two of the stereocenters with simultaneous stereospecific introduction of an exocyclic, tetrasubstituted

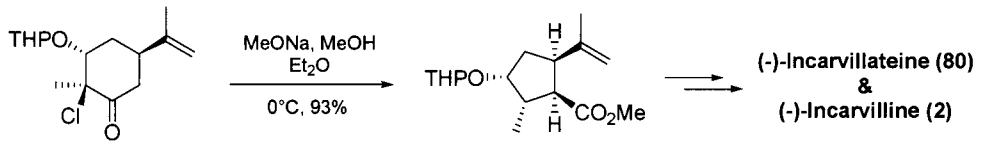
alkene framework upon which the bicyclic piperidine could rapidly be assembled (**Scheme 33**)[38].



93 94

Scheme 33. Total Synthesis of (-)-Incarvillateine by Ellman

In 2009, Jia achieved an enantioselective total synthesis of (-)-incarvilline (**2**) and (-)-incarvillateine (**80**) from (-)-carvone as a starting chiral material[39]. His present synthesis features a notable Favorskii rearrangement of the *O*-protected chlorohydrin derivative of (-)-carvone to construct four of the five contiguous stereocenters on the bicyclic piperidine moiety (**Scheme 34**).

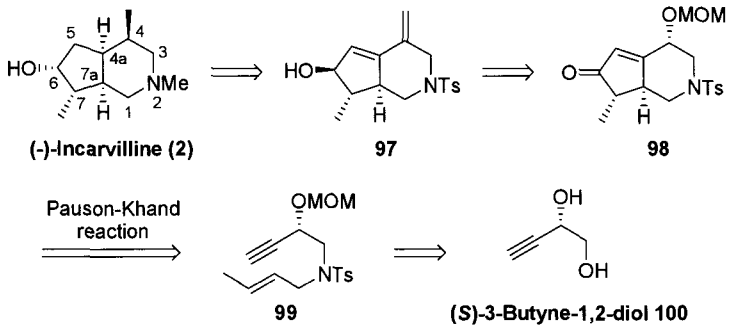


95 96

Scheme 34. Total Synthesis of (-)-Incarvillateine and (-)-Incarvilline by Jia

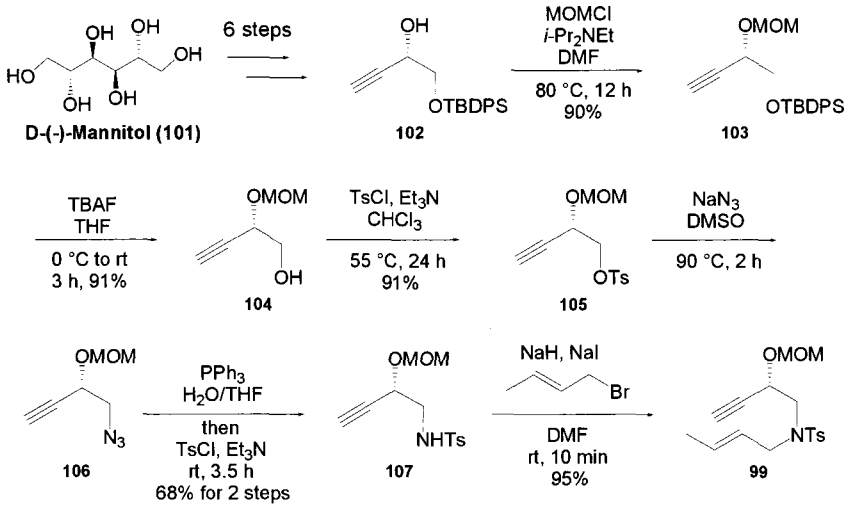
Thus, development of a new synthetic strategy for (-)-incarvilline (**2**), which is core unit of (-)-incarvillateine (**80**), would be an important research subject for finding potential antinociceptiv compounds.

Our retrosynthetic analysis of (-)-incarvilline (**2**) was depicted in **Scheme 35**. We decided to exploit an intramolecular Pauson-Khand reaction of (*S*)-*N*-[(*E*)-2-butenyl]-*N*-[2-(methoxy methoxy)-3-butynyl]-*p*-toluenesulfonamide **99** as a key step because the relative stereochemistry between the 7- and 7a-positions should be controlled by employing *E*-olefin as the starting material. The desired absolute configuration at the 7a-position should also be affected to the stereochemistry at the 4-position by assuming steric repulsion between the propargylic functional group and dicobalt-alkyne complex generated in the intermediate of intramolecular Pauson-Khand reaction.



Scheme 35. Retrosynthetic Analysis for (-)-Incarvilline

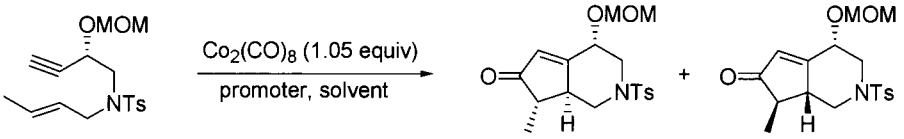
Our first aim was the synthesis of the optically pure enyne-amide **99** from the known (*S*)-1-*tert*-butyldimethylsiloxy-3-butyn-2-ol **102**[40], which was readily accessible from commercially available D-(-)-mannitol (**101**). Methoxymethylation of the secondary alcohol **102** afforded **103** in good yield and then desilylation of **103** with tetrabutylammonium fluoride gave primary alcohol **104** in 91% yield. The obtained alcohol **104** was converted to tosylate **105** in 91% yield. Treatment of **105** with sodium azide in DMSO gave azide **106**, which without further purification was subjected to Staudinger reaction[41] with triphenylphosphine in aqueous THF, and subsequent tosylation of the resulting amine with tosyl chlroride to provide tosylamide **107** in 68% yield from **105**. *N*-alkylation of **107** with *trans*-crotyl bromide in the presence of NaH provided the desired enyne-amide **99** in 95% yield (**Scheme 36**).



Scheme 36. Preparation of the Precursor **99** for Pauson-Khand Reaction

Investigation of intramolecular Pauson-Khand cyclization of enyne-amide **99** was

summarized in **Table 1**. First, **99** was treated with 1.05 equiv. of dicobalt octacarbonyl [$Co_2(CO)_8$] in toluene at 110 °C for 2 h under argon to furnish bicyclic compounds **98** and **108** in 54 and 7% yields, respectively (*Entry 1*).

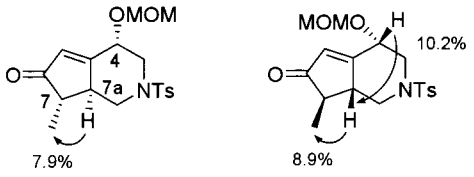


99 **98** **108**

entry	promoter (equiv)	solvent	atm.	temp. (°C)	time (h)	yield (%) **98**	**108**
1	none	toluene	Ar	110	2	54	7
2	NMO (10)	CH_2Cl_2	Ar	rt	9	45	5
3	*n*-BuSMe (3.5)	DCE	Ar	83	24	58	7
4	*n*-BuSMe (3.5)	DCE	CO	83	2.5	66	7
5	*t*-BuSMe (3.5)	DCE	Ar	83	2.5	62	6
6	*t*-BuSMe (3.5)	DCE	CO	83	2.5	73	8

Table 1. Investigation for Pauson-Khand Reaction of **99**

As expected, the stereochemistry of the minor product **108** was assumed to have 7*R*-methyl and 7a*R*-hydrogen based on the analysis of its 2D-NMR spectral data, in which NOEs were observed between 4-H and 7a-H, and also 7-methyl and 7a-H as shown in **Figure 6.** Thus, the major product **98** was confirmed to have the desired stereochemistry for the synthesis of the target compound.



98 **108**

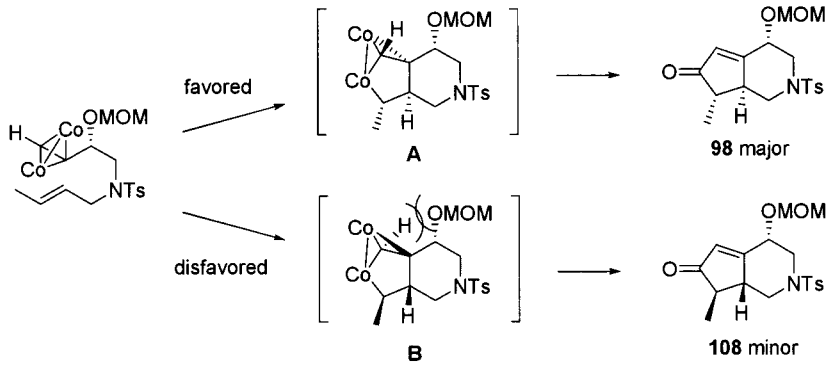
Figure 6. Structure Determination of **98** and **108**

(Ovserved NOEs are indicated by arrows)

To improve the isolation yield of Pauson-Khand product, we attempted to add the promoter in the reaction system according to previous literatures. When **99** was treated with 1.05 equiv. of $Co_2(CO)_8$ in CH_2Cl_2 in the presence of 10 equiv. of *N*-methylmorpholine oxide (NMO), which was found by Schrieber[30], the reaction was smoothly proceed at ambient temperature; however, the

yield was decreased to 50% with a formation of diastereoisomers (*Entry 2*). By changing a promoter to butyl methyl sulfides, which was found by Sugihara[32] as a possible promoter for Pauson-Khand reaction, the similar reaction was carried out in refluxing dichloroethane (DCE) under argon to give **98** in slightly better yield (*Entry 3*). We found that conversion yield could be slightly improved by changing atmosphere from argon to carbon monoxide and by changing sulfides from normal-butyl methyl sulfide to tertiary-butyl methyl sulfide (*Entries 4* and *5*). Finally, the best result was obtained to give **98** in 73% yield together with **108** in 8% yield when the reaction was carried out by employing 1.05 equiv. of $Co_2(CO)_8$ with the presence of 3.5 equiv. of *tert*-butyl methyl sulfide in refluxing DCE under carbon monoxide atmosphere for 2.5 h (*Entry 6*).

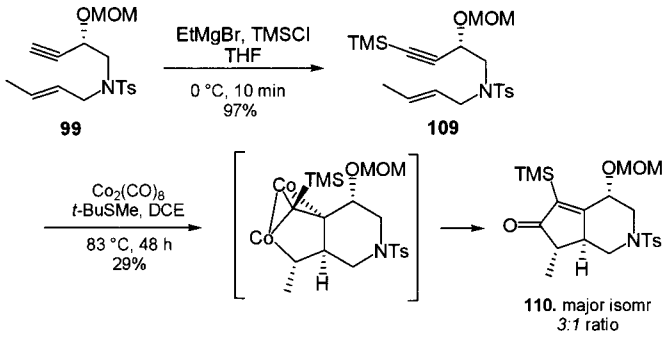
The stereoselectivity can be rationalized by assuming that the cyclization would proceed through the sterically favored intermediate **A** leading to **98**, rather than the intermediate **B**, in which the steric repulsion between MOM group and dicobalt complex moieties was observed, as shown in **Scheme 37**.



Scheme 37. Intermediates for Pauson-Khand Reaction

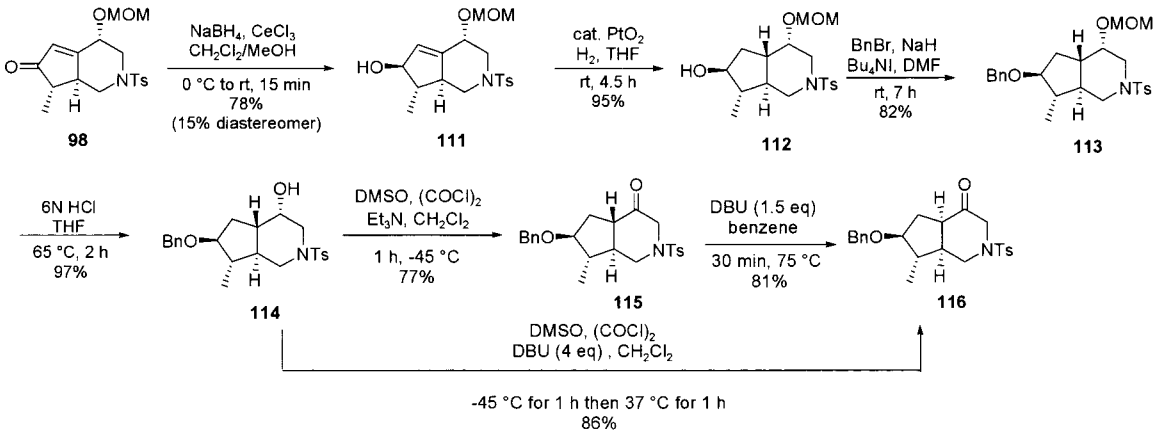
We next studied the improvement of diastereoselectivity by installation of trimethylsilyl group to terminal alkyne of **99**, because we anticipated the increase of repulsion effect in the transition state by following Mukai's results[42]. Preparation of trimethylsilyl derivative **109** was carried out in the reaction of **99** with trimethylsilyl chloride in the presence of ethylmagnesium bromide as the base in 97% yield. Further attemptaion of intramolecular Pauson-Khand cyclization of **109** under the same reaction conditions as *Entry 6* in **Table 1** gave a mixture of diastereoisomers **110** in 29% yield in a ratio of 3:1. Therefore, we concluded the poor yield of

cycloaddition was indicated that the steric repulsion between trimethylsilyl and methoxymethyoxy groups would be excessive and cyclization process did not work well (Scheme **38**).



Scheme 38. Pauson-Khand Reaction of the Internal Alkyne **109**

Our attention moves on conversion of azabicyclo[4.3.0]nonenone **98** to (-)-incarvilline (**2**). Luche reduction[43] of enone **98** afforded β-alcohol **111** in 78% yield as a major compound and together with its epimer **6-*epi*-111** in 15% yield, respectively. Further reduction of **111** under hydrogen atmosphere with catalytic platinum oxide gave *trans*-fused compound **112** as a sole product in 95% yield. The changing protecting groups from **112** into **114** were performed via benzyl ether **113** in good yield. Swern oxidation of **114** gave ketone **115** in 77% yield, and then isomerization of **115** on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene furnished thermodynamically stable *cis*-fused bicycle **116** in 81% yield. It is noteworthy that conversion of **114** to **116** could be achieved in one step where the replacement of triethylamine by DBU in Swern oxidation successfully gave **116** in 86% yield.



Scheme 39. Synthesis of **116**

Both *trans*- and *cis*-fused bicycles (**115** and **116**) were unambiguously determined by observation of NOEs as depicted in **Figure 7**.

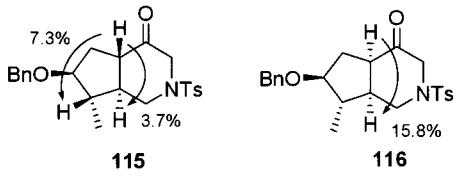
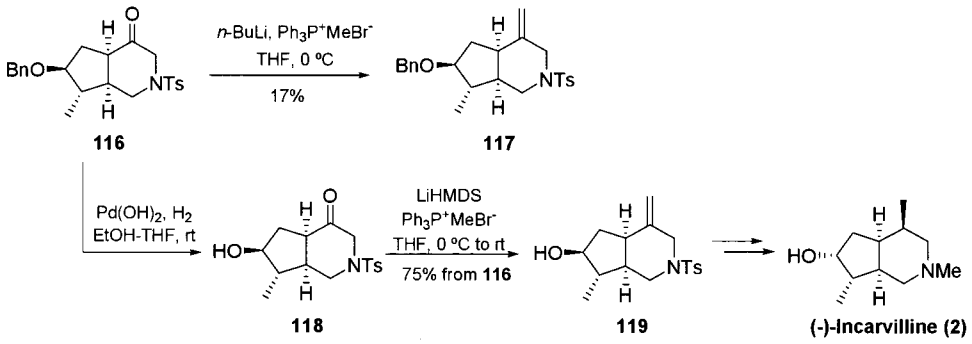


Figure 7. Structure Determination of **115** and **116**

(Observed NOEs are indicated by arrows.)

Ketone **116** was subjected to the Wittig reaction on treatment with methyltriphenyl phosphonium bromide in the presence of base under various reaction conditions; however, the desired olefin **117** was isolated in poor yield (up to 17%). Attempted Peterson olefination[44], Takai-Nozaki methylenation[45], and olefination with Tebbe reagent[46] were also found to be unsuccessful. Fortunately, we could get a result that Wittig reaction of debenzyl product **118** with 6 equiv. of methyltriphenylphosphonium bromide in the presence of lithium hexamethyldisilazide (LiHMDS) afforded the *exo*-olefin **119** in 75% yield. Since this compound **119** has been already transformed into (-)-incarvilline (**2**) via a few steps by Kibayashi[36], our synthesis constitutes its formal synthesis (**Scheme 40**).



Scheme 40. Formal Synthesis of (-)-Incarvilline

3. Stereocontrolled Synthesis of a Monoterpene Alkaloid, (+)-α-Skytanthine

(+)-α-Skytanthine (**3**) has been isolated from *Skytanthus acutus* (Apocynaceae) as a minor monoterpene piperidine alkaloid together with its diastereoisomers, β-, γ-, and δ-skytnathines (**Figure 8**)[47]. Their structures including absolute stereochemistry have been determined on the basis of partial and total syntheses[48]. It was addressed by Gatti and Marotta in 1966 that (+)-α -skytanthine (**3**) exhibited an activity on the central nervous system similar to nicotine in the experiment of intraperitoneal administration to model mice[3].

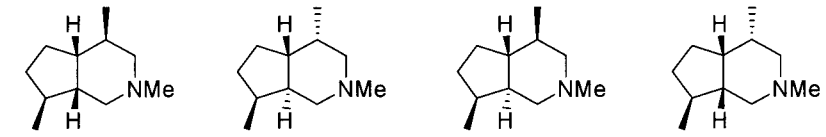
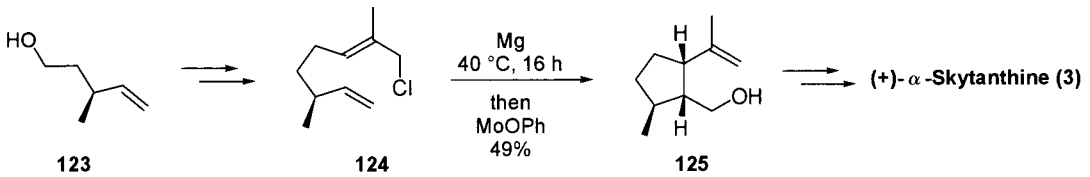


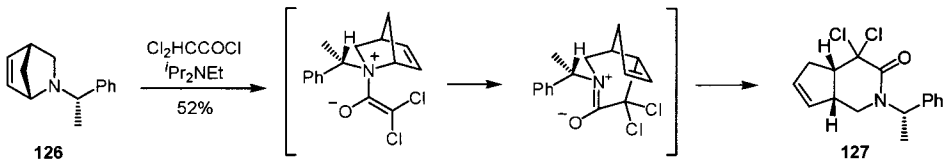
Figure 8. Bicyclic Monoterpene Alkaloids Isolated from *Skytanthus acutus*

Regarding the total synthesis of skytanthine, four groups have so far completed chiral syntheses of (+)-α-skytanthine (**3**) as listed below. The first total sythesis of (+)-α-skytanthine (**3**) was achieved by Oppolzer in 1986[49]. In his synthesis, enantiomerically pure (+)-α-skytanthine (**3**) was synthesized via the magnesium-ene reaction starting from (*S*)-3-methyl-1-penten-5-ol **123** (**Scheme 41**).



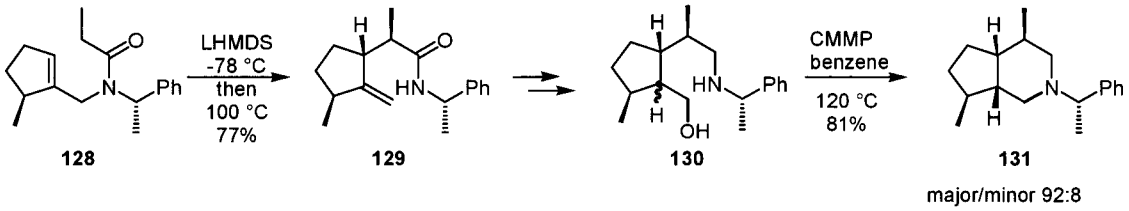
Scheme 41. First Synthesis of (+)-α-Skytanthine by Oppolzer

Next, the induction of all stereogenic centers in the target alkaloids, (+)-α-skytanthine (**3**) starting from a chiral phenylethylamine **126** was achieved via a hetero-Diels-Alder reaction followed by the stereospecific ketene aza-Claisen rearrangement by Pombo-Villar in 1993[50].



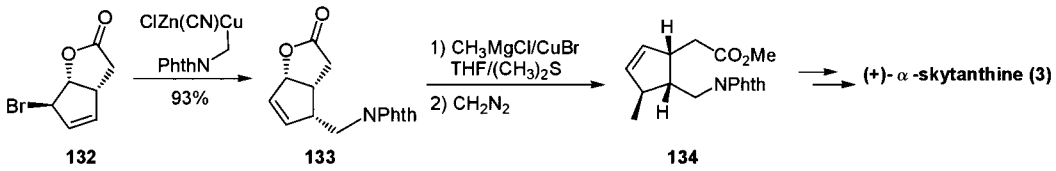
Scheme 42. Key Steps in the Total Synthesis of (+)-α-Skytanthine (**3**) by Pombo-Villar

Furthermore, utilizing asymmetric aza-Claisen rearrangement and a cyanomethylenetrimethyl phosphorane (CMMP), which was developed by Tsunoda as a new reagent showing to mediate the dehydrocyclization of the amino alcohol **130** to give the corresponding *N*-heterocycle **131**, as a key step, (+)-α-skytanthine (**3**) was synthesized stereoselectively in 1996 (**Scheme 43**)[51].



Scheme 43. Synthesis of (+)-α-Skytanthine by Tsunoda

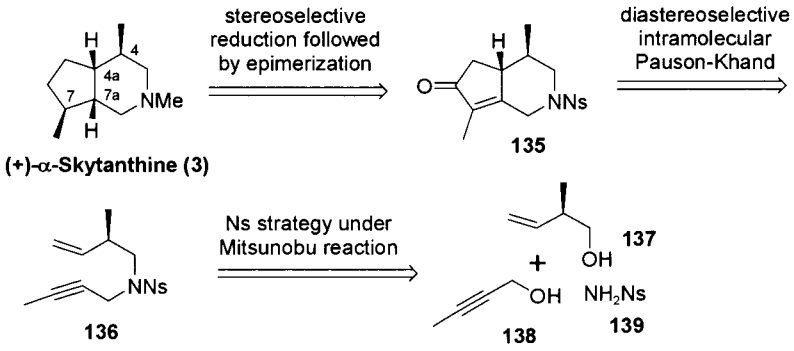
In 2002, Helmchen reported the alternative enantioselective synthesis of (+)-α-skytanthine (**3**) whose key step was conjugated nucleophilic substitutions (S_N2' *anti*-reactions) with C_1 zinc cyanocuprate (**Scheme 44**)[52].



Scheme 44. Enantioselective Synthesis of (+)-α-Skytanthine by Helmchen

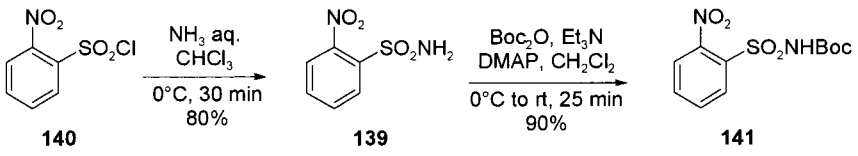
As mentioned in the previous section, we have already proved that the intramolecular Pauson-Khand cyclization was a useful tool for construction of azabicyclo[4.3.0]nonane ring system. Due to the structural similarity between (-)-incarvilline (**2**) and (+)-α-skytanthine (**3**), we thought that an intramolecular Pauson-Khand reaction would be also applicable to synthesis of skytanthines.

Our retrosynthetic route to a (+)-α-skytanthine (**3**) involving an intramolecular Pauson-Khand reaction is depicted in **Scheme 45**. The desired stereochemistry at the 7a-position of (+)-α -skytanthine (**3**) could be constructed stereoselectively by catalytic reduction of an enone, and a methyl group at the 7-position would be epimerized from the β-side to the sterically less hindered α-side of the product by base treatment. The enone **135** could be derived from an optically active enyne **136** by application of an intramolecular Pauson-Khand reaction, in which a newly generated stereogenic center at the 4a-position would be constructed with the desired stereochemistry by reflection of the stereochemistry of the methyl group at the 4-position in the starting enyne **136**. Finally, enyne **136** could be obtained by condensation of three components, alkenyl alcohol **137**, alkynyl alcohol **138**, and 2-nitrobenzenesulfonamide **139**.



Scheme 45. Retrosynthetic Analysis of (+)-α-Skytanthine

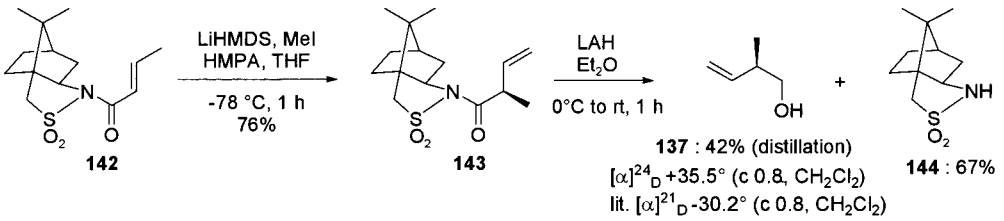
We commenced to prepare the *N*-Boc-2-nitrobenezenesulfonamide (NsNHBoc) **141**, which was developed by Fukuyama as useful nitrogen source (**Scheme 46**)[53]. Using it as both a protecting and activating group, a highly efficient synthetic method for a secondary amine could be established[54].



Scheme 46. Preparation of *N*-Boc-2-Nitrobenzenesulfonamide **141**

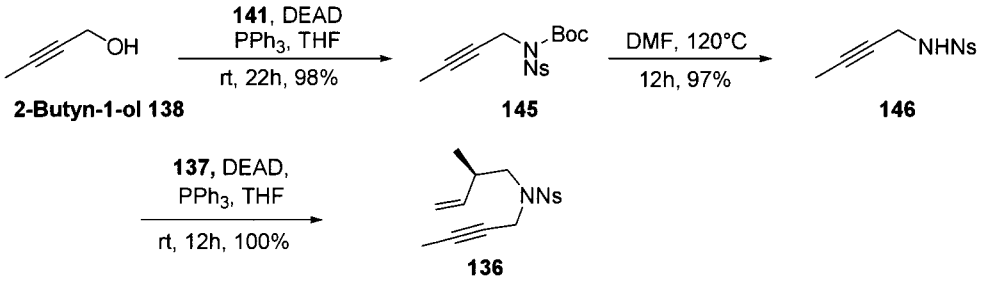
We also prepared the chiral alkenyl alcochol, (*R*)-2-methyl-3-buten-1-ol **137**, by following Golec's

protocols (**Scheme 47**)[55].



Scheme 47. Synthesis of (*R*)-2-Methyl-3-buten-1-ol **137**

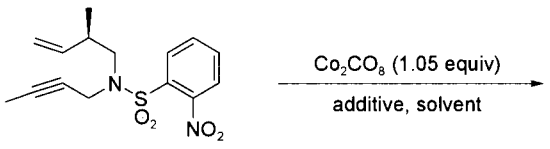
Treatment of 2-butyn-1-ol **138** with prepared **141** under Mitsunobu reaction condition[56] gave alkynylamide **145** in 98% yield. After removal of the Boc group from **145** by heating in DMF at 120 °C, the resulting secondary amide **146** was further reacted with prepared (*R*)-2-methyl-3-buten-1-ol **137** under similar Mitsunobu reaction condition to afford the desired enyne-amide **136** with sufficient yield (**Scheme 48**).



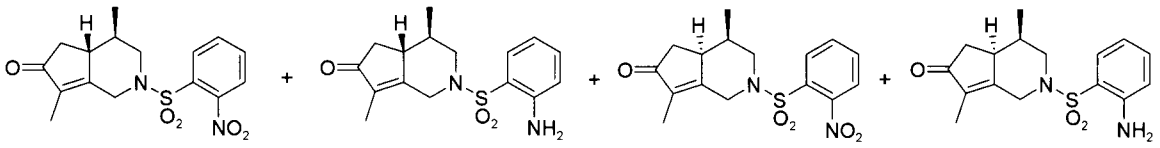
Scheme 48. Preparation of Enyne **136**

We next explored optimal reaction conditions for an intramolecular Pauson-Khand reaction, and the results obtained are summarized in **Table 2**. First, we attempted Pauson-Khand reaction of **136** with dicobalt octacarbonyl (1.05 equiv) in dichloromethane in the presence of NMO[30] (10 equiv) and molecular sieves 4Å under an atmospheric pressure of argon at 0°C to room temperature for 24 h to give a mixture of diastereoisomeric cyclization products (**135** and **148**) in 20 and 3% yields, respectively (*entry 1*). In addition, formation of the reductive products (**147** and **149**) was also observed during this reaction. Therefore, to find optimal reaction condition, Pauson-Khand reactions of **136** with dicobalt octacarbonyl in various solvent systems in the presence or absence of an additive were also investigated. The use of *tert*-butyl methyl sulfide[32] in refluxing DCE under carbon monoxide atmosphere, the best reaction conditions for the

synthesis of (-)-incarvilline (**2**) (see **Table 1**), afforded the desired product **147** in 49% yield together with the undesired reduction product **149** in 7% yield (*entry 3*). The reaction in toluene at 60 °C without an additive gave four isomers (**135**, **147**, **148**, and **149**) in 27, 32, 7, and 6% yields, respectively (*entry 4*). It should be noted that the reaction in carbon tetrachloride in the presence of MS 4Å gave bicyclic enone (**135** and **148**) in 33 and 10% yields, respectively, without formation of reduction products (*entry 5*). Surprisingly, by the use of hexafluorobenzene not containing hydrogen as the solvent, the nitro group was completely reduced to furnish amino derivatives (**147** and **149**), in 42 and 6% yields, as isolable products (*entry 6*). Although the mechanism for the reduction of a nitro group in Pauson-Khand reaction is still not clear at present, the best result was obtained when enyne **136** was treated with dicobalt octacarbonyl (1.05 equiv) in aqueous THF in the presence of trimethylamine *N*-oxide[31] (5 equiv) as the additive at ambient temperature for 7 h to give the desired product **147** in 71% yield (*entry 2*).



136



135 **147** **148** **149**

						yield (%)			
entry	additive (equiv)	solvent	atm	temp.(°C)	time (h)	**135**	**147**	**148**	**149**
1	NMO (10), MS4Å	CH_2Cl_2	Ar	0 to rt	24	20	19	3	3
2	TMANO·H_2O(5)	THF/H_2O (3:1)	-	rt	7	6	71	-	8
3	*t*-BuSMe (3.5), MS4Å	DCE	CO	83	3	-	49	-	7
4	none	toluene	CO	60	24	27	32	7	6
5	MS4Å	CCl_4	CO	77	24	33	-	10	-
6	MS4Å	C_6F_6	CO	80	24	-	42	-	6

Table 2. Investigation for Pauson-Khand Reaction of **136**

We could explain the two reasons why diastereoselectivity appeared throughout the

intermediate in Pauson-Khand reaction. One is the repulsion between allylic proton and olefinic proton when the olefine coordinated to vacant site of alkyne-cobalt complex. The other is the 1,2 pseudo diaxial repulsion when carbon monoxide inserted to the alkyl chain.

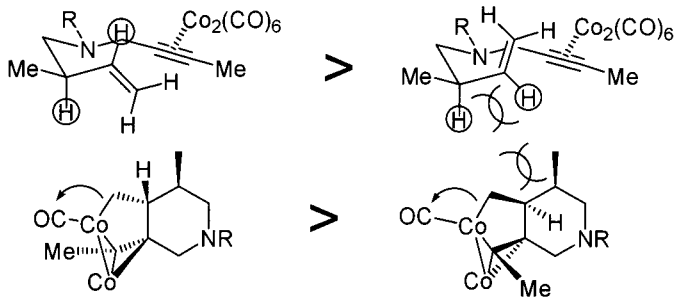
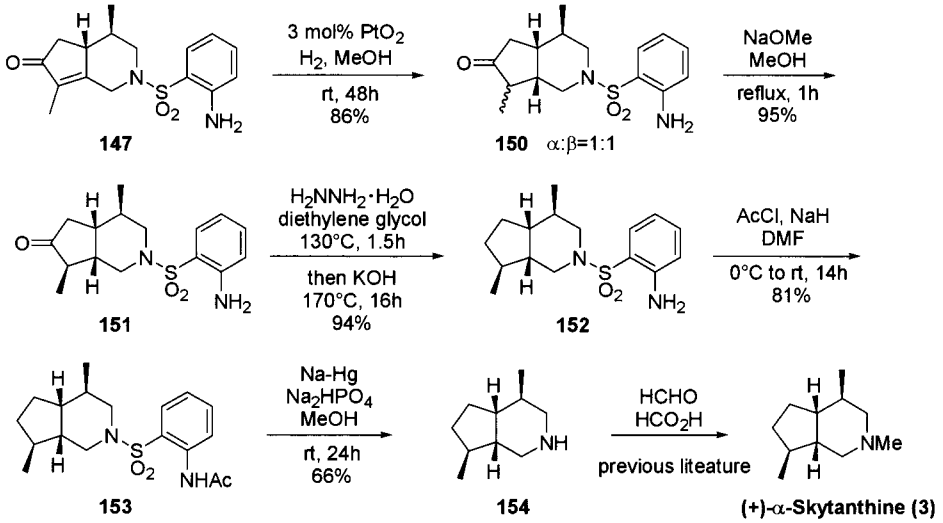


Figure 9. Plausible Intermediate for Pauson-Khand Reaction of **136**

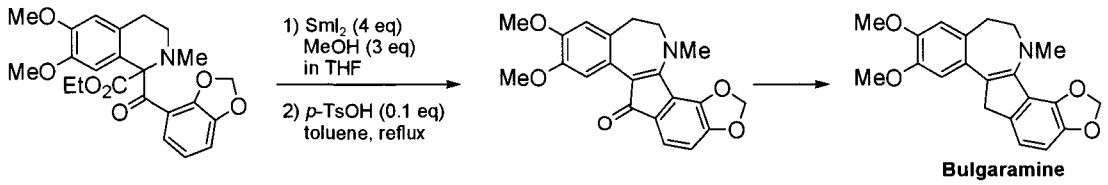
Catalytic hydrogenation of enone **147** over platinum oxide in MeOH gave ketone **150** in a ratio of approximately 1:1 as an inseparable mixture of diastereoisomers in 86% yield, which upon treatment with sodium methoxide in refluxing MeOH afforded the thermodynamically stable ketone **151** as a single isomer in 95% yield. Conversion of ketone **151** to the corresponding methylene derivative **152** was successfully achieved by Wolff-Kishner reduction in 94% yield. Difficulties were initially encountered in removal of the 2-aminobenzenesulfonyl group of **152**. Several attempted condition were unfortunately failed and only one procedure, treatment of **152** with sodium-amalgam according to Huang's[57], was successful to give the desired secondary amine **154** in low yield. To improve the conversion yield to **154**, amine **152** was converted to its acetyl derivative **153** prior to its reduction by treatment with acetyl chloride. Again, treatment of **153** with the same condition provided **154** in 66% yield. In addition, amine **154** was also obtained in 39% yield from **153** by treatment with sodium naphthalenide. Finally, *N*-methylation of amine **154** with formaldehyde and formic acid afforded (+)-α-skytanthine (**3**), whose spectroscopic data were identical to those previously reported (**Scheme 49**)[50].



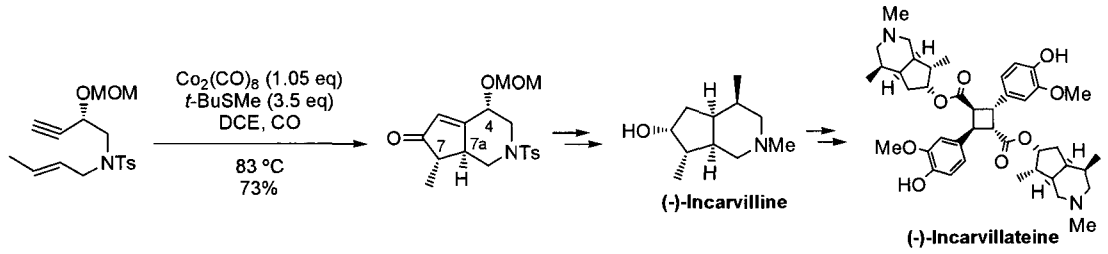
Scheme 49. Total Synthesis of (+)-α-Skytanthine

Summary

Author has reached the final conclusion that three alkaloids described in the introduction could be synthesized by means of two significant metal reagents, samarium diiodide and dicobalt octacarbonyl. Summaries of each synthesis are follows:

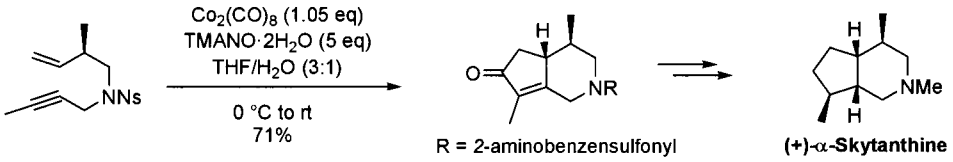


Bulgaramine, which belongs to the group of *Fumaria* showing antipyretic and diuretic activities, possesses the benzindenoazepine as core framework. It is also notable because bulgaramine would occupy biosynthetically central position of alkaloids extracted from plants *Fumaria officinalis*. We were able to establish a facile and new route for construction of a benzindenoazepine ring skeleton in a few steps. Our results obtained herein could be highlighted that SmI_2-promoted reductive carbon-nitrogen bond cleavage reaction and sequentially catalytic acid-promoted re-ring formation reaction were efficient methods for conversion of the tetrahydro-isoquinoline derivative to the corresponding benzindenoazepinone. Compared with the previous synthesis of bulgaramine, the 5 operations and 50% total yield were an outstanding success. It is no exaggeration to say that the monumental synthesis of bulgaramine could be achieved at this time.



Incarvillateine, one of the novel monoterpene alkaloids, has been found to exhibit more potent antinociceptive activity comparable to that of morphine in a foramalin-induced pain model in mice. We were able to establish diastereoselective formal synthesis of (-)-incarvilline, the key intermediate for the synthesis of (-)-incarvillateine, using an intramolecular Pauson-Khand

reaction of the corresponding enyne-amide as a key step. In this synthesis, we could reveal as follows; the best condition of Pauson-Khand reaction gained from experimental investigation was when *tert*-butyl methyl sulfide was used as promoter under carbon monoxide atmosphere. The configuration of the 7-methyl group and 7a-bicyclic junction of the (-)-incarvilline was diastereoselectively controlled with influence of the stereochemistry of 4-methoxymethoxyl group. After our publication in 2007, two groups have already addressed the total synthesis of (-)-incarvilline and (-)-incarvillatein. Thus it is clearly indicated that our studies have had an extent impact to the related subjects in synthesis of (-)-incarvilline.



(+)-α-Skytanthine, which was extracted from *Skytanthus acutus*, shows the nicotine-like activity on the central nervous synstem in model mice. We were able to complete an alterative stereocontrolled synthesis of (+)-α-skytanthine by employing the intramolecular Pauson-Khand reaction as key step. In this synthesis, we found that the configuration of the cyclized product was stereoselectively constructed by reflection of the stereochemistry of the allylic methyl group on the starting enyne. Interestingly, it was found that a nitro group was reduced to an amino group by Pauson-Khand reaction even with use of a solvent not containing hydrogen.

Finally, I expect that these methodologies developed here provide an efficient and practical tool for synthesis of bioactive natural products and I would be glad if these results contribute to accelerate the progress in the organic chemistry.

Acknowledgements

I would like to express my sincerest gratitude and upmost appreciation to Professor Toshio Honda (Hoshi University) for his stellar and kind tutelage, not to mention encouragement throughout my research.

I am also greatly indebted to Professor Masayoshi Tsubuki (Hoshi University) for his precise instructions and helpful suggestions in my research.

The advice and cooperation that Assistant Professor Kazunori Takahashi (Hoshi University) gave me in these studies is very much appreciated too.

Many thanks go to Dr. Hirotake Mizutani, Dr. Miho Katoh, Dr. Hidenori Namiki, Dr. Masayuki Watanabe, Dr. Hiroki Shigehisa, Dr. Sohichiro Matsuo and Dr. Toyohiko Kikuchi for their kind advice and cooperation.

I am thankful all the members of Synthetic Medicinal Chemistry at Hoshi University for working hard together.

I also thank all the members of Apparatus Center at Hoshi University for measuring spectroscopic data.

Finally, I appreciate my family for supporting my academic life.

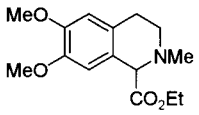
Kyosuke Kaneda

Dec. 2nd, 2009

Experimental Section

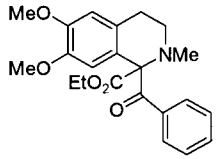
General Experimental Procedures. Melting points were measured with a Yanagimoto MP apparatus and were uncorrected. Optimal rotations were measured with JASCO DIP-360. IR spectra were recorded as thin films using a JASCO FT/IR-200 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL GSX-270, JEOL LA-500, and Bruker AV-400 for a solution in $CDCl_3$, and chemical shifts were reported on the δ-scale from TMS as an internal standard. MS spectra were measured with a JEOL JMS-600 and JMS-SX 120 spectrometers. Elemental analyses were performed on a Yanaco-MT5.

<Chapter 1-2>



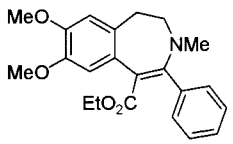
Ethyl 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 34

A solution of **33** (7.60 g, 28.7 mmol) and 37 % formalin (2.35 mL, 31.6 mmol) in MeOH (140 mL) in the presence of 10% palladium on carbon (916 mg, 0.86 mmol) was stirred at ambient temperature for 14 h under hydrogen balloon pressure. After removal of the insoluble material by filtration through a Celite pad, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (1:2, v/v) gave **34** (7.70 g, 96%) as a colorless oil. IR νmax: 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.72 (s, 1H), 6.61 (s, 1H), 4.30-4.17 (m, 2H), 4.21 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.31 (ddd, J = 11.6, 6.1, 5.4 Hz, 1H), 2.91 (ddd, J = 16.0, 6.1, 5.4 Hz, 1H), 2.79 (ddd, J = 16.0, 6.1, 5.4 Hz, 1H), 2.63 (ddd, J = 11.6, 6.1, 5.4 Hz, 1H), 2.51 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 148.1, 147.1, 126.5, 123.3, 111.3, 108.9, 67.2, 60.7, 55.7, 55.6, 48.6, 43.5, 28.0, 14.2; HRMS *m/z* (EI) Calcd for $C_{15}H_{21}NO_4$ (M^+) 279.1470, Found 279.1487.



Ethyl 1-benzoyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 35

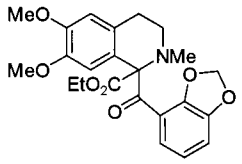
To a stirred solution of **34** (2.90 g, 10.4 mmol) in THF (42 mL) was slowly added NaHMDS (1.9 M in THF solution, 6.58 mL, 12.5 mmol) at –78 °C under Ar atmosphere. After being stirred for 30 min at same temperature, benzoyl chloride (1.23 mL, 10.4 mmol) was added dropwise to the mixture, and the whole was stirred for further 1 h at same temperature. The reaction mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The organic layer washed with brine and dried over Na_2SO_4. Evaporation of solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (5:1, v/v) gave **35** (3.05 g, 77%) as a pale yellow oil. IR νmax: 1731, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, J = 8.4 Hz, 2H), 7.39-7.37 (m, 1H), 7.23-7.20 (m, 2H), 6.65 (s, 1H), 6.64 (s, 1H), 4.31-4.18 (m, 2H), 3.85 (s, 3H), 3.65 (s, 3H), 3.30-3.14 (m, 2H), 3.00 (dd, J = 11.6, 6.3 Hz, 1H), 2.74 (d, J = 15.0 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.0, 169.8, 148.6, 146.7, 135.2, 132.5, 130.0 (2), 127.8 (2), 126.3, 124.6, 112.2, 111.2, 79.2, 60.9, 55.8, 55.7, 47.7, 41.2, 28.9, 14.3; HRMS *m/z* (EI) Calcd for $C_{22}H_{25}NO_5$ (M^+) 383.1732, Found 383.1708.



Ethyl 7,8-dimethoxy-3-methyl-4-phenyl-2,3-dihydro-1*H*-benzazepine-5-carboxylate 36

To a stirred solution of **35** (61 mg, 0.16 mmol) in the presence of MeOH (19 μL, 0.48 mmol) in THF (1 mL) was added SmI_2 (0.2 M in THF solution, 3.20 mL, 0.64 mmol) at ambient temperature under Ar atmosphere. After being stirred for 1 h, the resulting mixture was treated with saturated $NaHCO_3$ solution, and then filtrated through Celite pad to remove the insoluble material. The filtrate was extracted with $CHCl_3$ and the organic layer was dried over Na_2SO_4. Evaporation of solvent gave a residue, which was subjected to short column chromatography on silica gel. Elution with $CHCl_3$/MeOH (5:1, v/v) gave the cleaved product. Without further purification, the product was dissolved in toluene (4 mL) and the whole was heated to 110 °C. After being stirred for 12 h

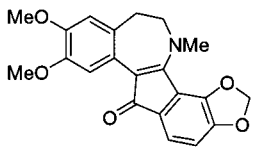
at the same temperature, the resulting mixture was concentrated under reduced pressure. Then the residue was purified by column chromatography on silica gel. Elution with hexane-EtOAc (4:1 v/v) gave **36** (25.1 mg, 43%) as a white powder. m.p.109-110 °C; IR νmax: 1699, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.34 (m, 5H), 7.21 (s, 1H), 6.64 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.68 (q, *J* = 7.1 Hz, 2H), 3.63-3.60 (m, 2H), 3.05-3.02 (m, 2H), 2.45 (s, 3H), 0.76 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1, 152.1, 146.9, 146.6, 140.3, 133.0, 129.5 (2), 128.4, 128.3, 128.1 (2), 112.1, 111.1, 108.9, 60.5, 60.0, 56.0, 55.9, 42.6, 34.3, 13.6; MS *m/z* (EI) 367(M^+); HRMS Calcd for $C_{22}H_{25}NO_4$ (M^+) 367.1783, Found 367.1779. *Anal.* Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.02; H, 6.96; N, 3.82.



Ethyl 1-[(2,3-methylenedioxy)benzoyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 38

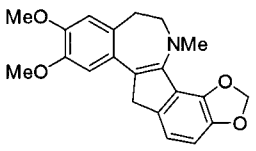
To a stirred solution of **34** (3.70 g, 13.3 mmol) in THF (50 mL) was slowly added NaHMDS (1.9 M in THF solution, 8.58 mL, 16.3 mmol) at –78 °C under Ar atmosphere. After being stirred for 30 min at the same temperature, a solution of 2,3-(methylenedioxy)benzoyl chloride (2.72 g, 14.8 mmol) in THF (24 mL) was added dropwise to the mixture, and the whole was stirred for further 1 h at the same temperature. The reaction mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The organic layer washed with brine and dried over Na_2SO_4. Evaporation of solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (2:1, v/v) gave **38** (4.69 g, 83%) as a pale yellow powder. m.p.114-115 °C; IR νmax: 1731, 1681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.80 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 6.53 (dd, *J* = 8.3, 7.8 Hz, 1H), 6.06 (s, 1H), 6.03 (s, 1H), 4.32-4.16 (m, 2H), 3.86 (s, 3H), 3.70 (s, 3H), 3.23-3.11 (m, 2H), 3.02-2.94 (m, 1H), 2.74-2.67 (m, 1H), 2.63 (s, 3H), 1.28 (t, *J* =7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.0, 169.4, 148.5, 148.20, 148.16, 146.6, 126.4, 124.1, 122.7, 120.0, 118.9, 111.9, 111.5, 111.0, 101.5, 79.4, 60.9, 55.7, 55.5, 47.5, 41.1, 28.7, 14.1; MS *m/z* (EI) 427 (M^+); HRMS Calcd for $C_{23}H_{25}NO_7$ (M^+) 427.1631, Found 427.1627. *Anal.* Calcd for $C_{23}H_{25}NO_7$: C, 64.68; H, 5.90; N, 3.28. Found: C,

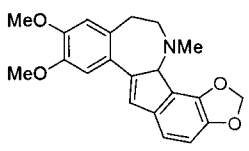
64.63; H, 5.90; N, 3.23.



8,9-Dimethoxy-13-methyl-12,13-dihydro[1,3]dioxolo[6,7]indeno[2,1-*a*][3]benzazepin-6(11*H*)-one 40

To a stirred solution of **38** (2.08 g, 4.87 mmol) in the presence of MeOH (0.60 mL, 14.6 mmol) in THF (24 mL) was added SmI_2 (0.2 M in THF solution, 98 mL, 19.5 mmol) at ambient temperature under Ar atmosphere. After being stirred for 30 min, the resulting mixture was treated with saturated $NaHCO_3$ solution, and then filtrated through Celite pad to remove the insoluble material. The filtrate was extracted with $CHCl_3$ and the organic layer was dried over Na_2SO_4. Evaporation of solvent gave a residue, which was subjected to short column chromatography on silica gel. Elution with $CHCl_3$/MeOH (10:1, v/v) gave the cleaved product. Without further purification, the product was dissolved in toluene (49 mL) in the presence of *p*-TsOH·H_2O (93 mg, 0.49 mmol), and the whole was heated to 110 °C. After being stirred for 24 h at same temperature, the resulting mixture was treated with saturated $NaHCO_3$ soution, and extracted with EtOAc. The red organic layer was washed with brine and dried over Na_2SO_4. Evaporation of solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (1:1, v/v) gave **40** (1.21 g, 68%) as a dark red solid. m.p. 196-197 °C; IR vmax: 1567, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.13 (d, J = 7.5 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 6.58 (s, 1H), 6.04 (s, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.72-3.70 (m, 2H), 3.25 (s, 3H), 3.03-3.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 161.0, 152.2, 147.3, 146.4, 139.5, 131.8, 130.1, 125.3, 118.3, 116.0, 112.0, 111.3, 110.2, 107.6, 101.1, 59.0, 55.93, 55.85, 43.6, 34.4; MS *m/z* (EI) 365(M^+); HRMS Calcd for $C_{21}H_{19}NO_5$ (M^+) 365.1263, Found 365.1253. *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.73; H, 5.29; N, 3.80.



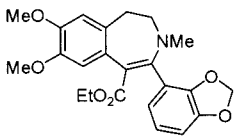


Bulgaramine (1) and **8,9-Dimethoxy-13-methyl-11,12,13,13a-tetrahydro[1,3]dioxolo-[6,7]indeno[2,1-*a*][3]benzazepine 43**

To a stirred solution of **40** (50 mg, 0.14 mmol) in toluene (3 mL) was slowly added DIBAL (1.02 M in hexane solution, 0.68 mL, 0.69 mmol) at -78 °C under Ar. After being stirred for 24 h at the same temperature, triethylamine (0.38 mL, 2.74 mmol) was added to the mixture and then the whole was gradually warmed up to ambient temperature. The resulting mixture was treated with H_2O and extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (2:1, v/v) gave bulgaramine (**1**) (12.1 mg, 24%); m.p. 205-206 °C (lit. [12], 209 °C); IR νmax: 1518, 1457, 1246 cm^{-1}; ^1H NMR δ: 7.03 (s, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.71 (s, 1H), 6.03 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.84 (s, 2H), 3.25-3.22 (m, 2H), 3.01-2.99 (m, 2H), 2.93 (s, 3H); ^{13}C NMR δ: 147.0, 146.8, 146.4, 144.2, 138.6, 136.2, 133.4, 127.8, 127.0, 121.1, 116.2, 112.9, 110.8, 105.4, 100.6, 56.1, 56.0, 53.6, 43.2, 39.8, 33.7; MS (EI) *m/z* 351 (M^+). HRMS Calcd for $C_{21}H_{21}NO_4$ (M^+) 351.1470, found 351.1475. The spectroscopic data of the synthesized bulgaramine (**1**) were identical with those reported in the literature[12].

Further elution with EtOAc gave the olefinic isomer **43** (32.1 mg, 67%) as a pale orange crystal; m.p. 155-156 °C; IR νmax: 1508, 1459 cm^{-1}; ^1H NMR δ: 6.96 (s, 1H), 6.83 (s, 1H), 6.76 (s, 2H), 6.62 (s, 1H), 6.04 (s, 1H), 5.98 (s, 1H), 4.87 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.74-3.68 (m, 1H), 3.50-3.43 (m, 1H), 3.37 (ddd, *J* = 14.1, 6.2, 2.2 Hz, 1H), 2.60-2.52 (m, 1H), 2.22 (s, 3H); ^{13}C NMR δ: 148.4, 148.2, 147.2, 146.6, 143.0, 138.8, 133.0, 128.9, 127.9, 124.1, 113.7 (2), 111.8, 107.5, 101.4, 69.8, 56.8, 56.0, 55.9, 34.6, 32.5; MS (EI) *m/z* 351 (M^+). HRMS Calcd for $C_{21}H_{21}NO_4$ (M^+) 351.1470, found 351.1469. *Anal.* Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.59; H, 6.28; N, 3.94.

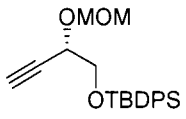
Isomerization of 43 to bulgaramine (1): To a solution of **43** (19 mg, 54 μmol) in EtOH (1 mL) was added 10 % NaOH solution (1 mL) at ambient temperature. After being stirred for 19 h at the same temperature, the mixture was diluted with H_2O and extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was crystallized from hexane to furnish bulgaramine (**1**)(18 mg, 95%).



Ethyl 4-[(2,3-methylenedioxy)phenyl]-7,8-dimethoxy-3-methyl-2,3-dihydro-1*H*-benzazepine-5-carboxylate 39

Ester **39** was obtained from **38** (314 mg, 0.74 mmol) and SmI_2 (0.2 M in THF solution, 14.7 mL, 2.96 mmol) by using the same procedure as described for the synthesis of **40**. In this conversion, however, the recyclization of the cleaved product was carried out in the absence of *p*-TsOH. Crude product was purified by column chromatography on silica gel using hexane-EtOAc (2:1, v/v) as eluant to give **39** (121 mg, 40%) as a white powder. m.p. 165-166 °C; IR νmax: 1693 cm^{-1}; ^1H NMR δ: 7.26 (s, 1H), 6.85-6.77 (m, 3H), 6.65 (s, 1H), 6.01 (s, 2H), 3.88 (s, 6H), 3.78 (q, J = 7.1 Hz, 2H), 3.66 (t, J = 5.2 Hz, 2H), 3.00 (brs, 2H), 2.51 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ: 170.2, 147.32, 147.31, 146.94, 146.87; 145.0, 133.0, 128.6, 123.4, 122.0, 121.5, 112.2, 110.8, 109.4, 108.9, 101.1, 62.1, 60.0, 56.0, 55.8, 41.4, 33.8, 13.7; MS (EI) *m/z* 411 (M^+). HRMS Calcd for $C_{23}H_{25}NO_6$ (M^+) 411.1682, Found 411.1656. *Anal.* Calcd for $C_{23}H_{25}NO_6$: C, 67.14;H, 6.12; N, 3.40. Found: C, 66.84 H, 6.20, N, 3.37.

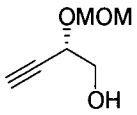
<Chapter 2-2>



(*S*)-(2-methoxymethoxy-3-butynyloxy)*tert*-butyldiphenylsilane 103

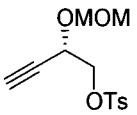
To a stirred solution of (*S*)-1-[(*tert*-butyldiphenylsilyl)oxy]-3-butyn-2-ol **102** (6.49 g, 21.4 mmol) in DMF (86 mL) was added chloromethyl methyl ether (3.42 mL, 44.9 mmol) over the period of 15 min under argon. The mixture was heated at 80 °C for 12 h. After being cooled to room temperature, the mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The ethereal solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to silica gel column chromatography. Elution with hexane-EtOAc (10:1, v/v) afforded the silyl product **103** (7.11 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ +55.6 (*c* 1.0,

$CHCl_3$); IR νmax: 3290, 2930, 2360, 1478, 1430 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.72-7.68 (m, 4H), 7.46-7.35 (m, 6H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.48 (ddd, *J* = 6.9, 4.9, 2.1 Hz, 1H), 3.86 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.81 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.39 (s, 3H), 2.38 (d, *J* = 2.1 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 135.5, 133.1, 129.7, 127.6, 94.4, 74.3, 66.8, 66.4, 55.5, 26.6, 19.1; HRMS *m/z* (CI) Calcd for $C_{22}H_{29}O_3Si$ (M^++H) 369.1886, Found 369.1881.



(*S*)-2-Methoxymethoxy-3-butyn-1-ol 104

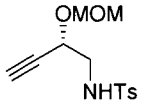
To a stirred solution of **103** (6.50 g, 17.7 mmol) in THF (89 mL) was added tetrabutylammonium fluoride (1M TBAF in THF solution, 21.2 mL, 21.2 mmol) at 0 °C. The solution was warmed up to ambient temperature over the period of 3 h. The mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (2:1, v/v) gave alcohol **104** (2.10 g, 91%) as a colorless oil. $[\alpha]_D^{26}$ +205 (*c* 0.90, $CHCl_3$); IR νmax: 3200, 2359, 2338, 2255, 2118 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 4.93 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.46-4.41 (m, 1H), 3.77 (t, *J* = 5.6 Hz, 2H), 3.42 (s, 3H), 2.92-2.88 (brs, 1H), 2.51 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 94.4, 79.3, 75.0, 67.3, 65.0 (2), 55.7; HRMS *m/z* (CI) Calcd for $C_6H_{11}O_3$ (M^++H) 131.0708, Found 131.0684.



(*S*)-(2-Methoxymethoxy)-3-butynyl *p*-toluenesulfonate 105

A solution of **104** (431 mg, 3.32 mmol) and *p*-toluenesulfornyl chloride (1.26 g, 6.63 mmol) in $CHCl_3$ (13 mL) in the presence of Et_3N (1.38 mL, 9.95 mmol) was stirred at ambient temperature for 10 h. To this solution was added *N,N*-dimethylaminopyridine (40 mg, 0.33 mmol), and the resulting solution was stirred at 55 °C for 6 h. The mixture was treated with saturated NH_4Cl solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over

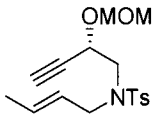
Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (3:1, v/v) gave tosylate **105** (853 mg, 91%) as a colorless oil. $[\alpha]_D^{28}$ +91.8 (*c* 1.00, $CHCl_3$); IR νmax: 3280, 2960, 2895, 2119, 1599, 1360, 1178 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.83-7.78 (m, 2H), 7.37-7.34 (m, 2H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.9 Hz, 1H), 4.56 (ddd, *J* = 7.3, 4.4, 2.1 Hz, 1H), 4.19 (dd, *J* = 10.5, 4.4 Hz, 1H), 4.13 (dd, *J* = 10.5, 7.3 Hz, 1H), 3.35 (s, 3H), 2.46 (s, 3H), 2.44 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 145.0, 132.7, 129.8, 127.9, 94.2, 77.6, 75.7, 70.4, 63.5, 55.7, 21.6; HRMS *m/z* (EI) Calcd for $C_{13}H_{16}O_5S$ (M^+) 284.0718, Found 284.0728.



(*S*)-*N*-[2-(Methoxymethoxy)-3-butynyl]-*p*-toluenesulfonamide 107

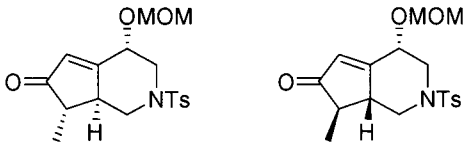
To a stirred solution of **105** (3.80 g, 13.4 mmol) in DMSO (45 mL) was added sodium azide (2.61 g, 40.1 mmol) at 90 °C, and the mixture was stirred for 2 h at the same temperature. After being cooled to room temperature, the mixture was treated with water and extracted with Et_2O. The ethereal solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave azide **106**, which without further purification, was dissolved into THF-H_2O (1:1)(54 mL). After addition of triphenylphosphine (3.51 g, 13.4 mmol) to this solution, the mixture was stirred at ambient temperature for 1.5 h. To this mixture were successively added THF (27 mL), triethylamine (5.60 mL, 40.1 mmol), and *p*-toluenesulfonyl chloride (5.08 g, 26.8 mmol), and the whole was stirred at the same temperature for further 2 h. The mixture was treated with saturated NH_4Cl solution, and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (4:1, v/v) gave tosylamide **107** (2.53 g, 68% from **105**) as a colorless oil. $[\alpha]_D^{28}$ +115 (*c* 1.01 $CHCl_3$); IR νmax: 3275, 2945, 2895, 2120, 1599, 1330, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.78-7.74 (m, 2H), 7.33-7.30 (m, 2H), 5.05-5.01 (m, 1H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 4.35 (ddd, *J* = 5.1, 4.3, 2.0 Hz, 1H), 3.35 (s, 3H), 3.32 (ddd, *J* = 13.2, 7.9, 4.3 Hz, 1H), 3.16 (ddd, *J* = 13.2, 7.9, 5.1 Hz, 1H), 2.44 (d, *J* = 2.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.6, 136.9, 129.7, 127.0, 94.4, 79.2, 75.4, 64.7, 56.0, 47.0, 21.5; HRMS *m/z* (EI) Calcd for $C_{13}H_{17}NO_4S$ (M^+) 283.0878,

Found 283.0900.



(*S*)-*N*-[(*E*)-2-Butenyl]-*N*-[2-(methoxymethoxy)-3-butynyl]-*p*-toluenesulfonamide 99

A suspension of **107** (2.19 g, 7.74 mmol) and sodium hydride (325 mg, 8.13 mmol) in DMF (26 mL) was stirred at room temperature for 10 min under argon. To this mixture was added *trans*-crotyl bromide (1.03 mL, 8.51 mmol), and the whole was stirred for further 10 min at the same temperature. The mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (3:1, v/v) gave enyne **99** (2.46 g, 95%) as a pale yellowish oil. $[\alpha]_D^{28}$ +108 (*c* 1.00, $CHCl_3$); IR νmax: 3270, 2940, 2895, 2116, 1599, 1495, 1340, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.73-7.70 (m, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.68-5.53 (m, 1H), 5.25-5.12 (m, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.64-4.55 (m, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.05-3.81(m, 2H), 3.44-3.36 (m, 2H), 3.33 (s, 3H), 2.45 (d, *J* = 2.1 Hz, 1H), 2.43 (s, 3H), 1.63 (dd, *J* = 6.3, 1.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.2, 137.3, 131.2, 130.0, 127.3, 125.0, 94.3, 75.0, 65.4, 55.8, 51.1, 50.0, 45.5, 21.5, 17.6; HRMS *m/z* (EI) Calcd for $C_{17}H_{24}NO_4S$ (M^++H) 338.1426, Found 338.1414.



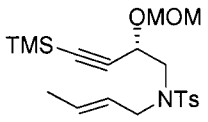
(4*S*,7*S*,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one 98 and **(4*S*,7*R*,7a*R*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one 108**

A solution of **99** (100 mg, 0.30 mmol) in dichloroethane (3 mL) in the presence of dicobalt octacarbonyl (107 mg, 0.31 mmol) was heated at 83 °C under an atmospheric pressure of CO. To this mixtue was added *t*-BuSMe (0.13 mL, 1.04 mmol), and the whole was stirred at the same temperature for further 2.5 h. After being cooled to room temperature, the mixture was filtered

through Celite pad to remove the insoluble materials. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (1:1, v/v) gave **98** (79.1 mg, 73%) and **108** (8.7 mg, 8%) as pale colorless needles, respectively.

98: m.p. 149-151 °C; $[\alpha]_D^{32}$ -146 (*c* 1.00, $CHCl_3$); IR νmax: 2920, 1704, 1634, 1599, 1499, 1460, 1340, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 0.9 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.61 (d, *J* = 7.2 Hz, 1H), 4.60 (m, 1H), 4.26-4.23 (m, 2H), 3.40 (s, 3H), 2.95-2.92 (m, 1H), 2.52 (dd, *J* = 13.1, 1.8 Hz, 1H), 2.43 (s, 3H), 2.06 (t, *J* = 11.5 Hz, 1H), 1.91 (dq, *J* = 7.5, 2.7 Hz, 1H), 1.21 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 209.1, 172.0, 143.9, 133.8, 129.8, 129.2, 127.4, 94.5, 67.6, 55.9, 51.8, 50.7, 45.2, 44.6, 21.5, 14.7; HRMS *m/z* (CI) Calcd for $C_{18}H_{24}NO_5S$ (M^++H) 366.1376, Found 366.1375. *Anal.* Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.82. Found: C, 59.02; H, 6.49; N, 3.76.

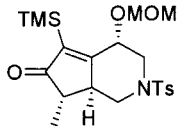
108: m.p. 122-124 °C; $[\alpha]_D^{27}$ +158 (*c* 1.01, $CHCl_3$); IR νmax: 2935, 1714, 1634, 1599, 1499, 1460, 1348, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.10 (t, *J* = 1.3 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.58-4.54 (m, 1H), 4.26 (ddd, *J* = 11.0, 6.4, 1.7 Hz, 1H), 4.20 (ddd, *J* = 11.3, 6.1, 1.7 Hz, 1H), 3.41 (s, 3H), 2.72-2.68 (m, 1H), 2.44 (s, 3H), 2.23 (t, *J* = 11.0 Hz, 1H), 2.00 (t, *J* = 11.3 Hz, 1H), 1.98 (dq, *J* = 7.3, 2.4 Hz, 1H), 1.22 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.2, 176.3, 144.2, 133.4, 130.0, 127.4, 125.8, 95.9, 72.3, 56.0, 51.4, 50.6, 48.0, 44.4, 21.6, 14.8; HRMS *m/z* (EI) Calcd for $C_{18}H_{23}NO_5S$ (M^+) 365.1290, Found 365.1297. *Anal.* Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.82. Found: C, 59.12; H, 6.30; N, 3.83.



(*S*)-*N*-[(*E*)-2-Butenyl]-*N*-[2-(methoxymethoxy)-4-trimethylsilyl-3-butynyl]-*p*-toluenesulfonamide 109

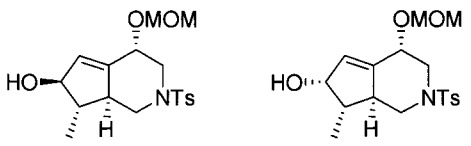
To a stirred solution of **99** (250 mg, 0.742 mmol) in THF (74 mL) was added ethylmagnesium bromide (0.91 M in THF solution, 4.08 mL, 3.71 mmol) at 0 °C under argon. After being stirred for 45 min, trimethylsiliyl chloride (0.94 mL, 7.42 mmol) was added to the mixture, and the resulting mixture was stirred for further 10 min at the same temperature. The mixture was treated with saturated NH_4Cl solution and extracted with Et_2O. The ethereal layer was washed with brine

and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (8:1, v/v) gave trimethylsilyl compound **109** (295 mg, 97%) as a pale yellowish oil. $[\alpha]_D^{28}$ +116 (*c* 1.00, $CHCl_3$); IR νmax: 2960, 2895, 2175, 1595, 1340, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.75-7.70 (m, 2H), 7.31-7.27 (m, 2H), 5.65-5.52 (m, 1H), 5.25-5.13 (m, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.61-4.53 (m, 2H), 4.05-3.83 (m, 2H), 3.43-3.32 (m, 2H), 3.32 (s, 3H), 2.43 (s, 3H), 1.64-1.61 (m, 3H), 0.16 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.1, 137.6, 131.0, 129.5, 127.3, 125.1, 101.9, 94.2, 92.0, 66.0, 55.7, 51.0, 49.9, 21.5, 17.6, 0.0; HRMS *m/z* (CI) Calcd for $C_{20}H_{32}NO_4SiS$ (M^++H) 410.1821, Found 410.1798.



(4*S*,7*R*/*S*,7a*R*/*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-5-trimethylsilyl-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one 110

The intramolecular Pauson-Khand reaction for **109** (150 mg, 0.367 mmol) was carried out for 48 h by using the same conditions as for the preparation of **98** to give **110** (46 mg, 29%) as an inseparable mixture of diastereoisomers. Careful separation by column chromatography on silica afforded the major isomer as pure compound. Data for the major isomer of **110**: IR νmax: 2960, 1760, 1695, 1600, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69-7.66 (m, 2H), 7.35-7.32 (m, 2H), 4.79-4.78 (m, 1H), 4.72 (d, *J* = 7.1 Hz, 1H), 4.59 (d, *J* = 7.1 Hz, 1H), 4.26-4.20 (m, 2H), 3.40 (s, 3H), 2.98-2.92 (m, 1H), 2.48-2.47 (m, 1H), 2.43 (s, 3H), 2.04 (t, *J* = 11.4 Hz, 1H), 1.84-1.78 (m, 1H), 1.17 (d, *J* = 7.4 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.1, 177.5, 143.8, 140.9, 133.6, 129.7, 127.5, 94.0, 67.2, 55.7, 52.1, 50.6, 46.4, 44.5, 21.5, 14.5, -0.7; HRMS *m/z* (EI) Calcd for $C_{21}H_{31}NO_5SiS$ (M^+) 437.1692, Found 437.1691.



(4*S*,6*R*,7S,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-6-ol 111 and

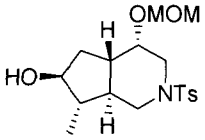
(4*S*,6*S*,7S,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)-

2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-6-ol 6-*epi*-111

To a stirred solution of **98** (620 mg, 1.70 mmol) in CH_2Cl_2-MeOH (1:1)(17 mL) containing cerium chloride (210 mg, 0.85 mmol) was added sodium tetrahydroborate (107 mg, 2.55 mmol) portionwise at ambient temperature, and the resulting mixture was stirred for further 15 min. The mixture was treated with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with acetone-CH_2Cl_2 (1:8, v/v) gave alcohol **111** (487 mg, 78%) as colorless oil, together with its diastereomer **6-*epi*-111** (92 mg, 15%) as colorless powder.

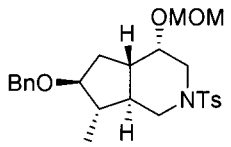
111: $[\alpha]_D^{26}$ +2.60 (*c* 1.01, $CHCl_3$); IR νmax: 3450, 2890, 1599, 1338, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.66 (s, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.45 (d, *J* = 4.9 Hz, 1H), 4.29 (dd, *J* = 2.1, 1.8 Hz, 1H), 4.09 (ddd, *J* = 12.5, 2.1, 1.8 Hz, 1H), 4.03 (ddd, *J* = 11.1, 6.4, 1.8 Hz, 1H), 3.38 (s, 3H), 2.60-2.55 (m, 1H), 2.43 (dd, *J* = 12.5, 1.8 Hz, 1H), 2.43 (s, 3H), 1.99 (t, *J* = 11.1 Hz, 1H), 1.79 (br s, 1H), 1.58-1.52 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.5, 141.2, 133.6, 131.3, 129.6, 127.5, 93.3, 83.7, 67.0, 55.5, 52.5, 50.9, 47.4, 47.0, 21.5, 17.1; HRMS *m/z* (EI) Calcd for $C_{18}H_{25}NO_5S$ (M^+) 367.1453. Found 367.1479.

6-*epi*-111: m.p. 113-114 °C; $[\alpha]_D^{29}$ -91.1 (*c* 1.01, $CHCl_3$); IR νmax: 3420, 2890, 1599, 1340, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.84 (dd, *J* = 2.1, 1.8 Hz, 1H), 4.65 (d, *J* = 7.1 Hz, 1H), 4.62 (d, *J* = 7.1 Hz, 1H), 4.43 (t, *J* = 6.1 Hz, 1H), 4.30 (dd, *J* = 2.1, 1.8 Hz, 1H), 4.18-4.14 (m, 1H), 4.09 (dt, *J* = 12.5, 1.8 Hz, 1H), 3.39 (s, 3H), 2.71-2.66 (m, 1H), 2.42 (s, 3H), 2.35 (dd, *J* = 12.5, 2.1 Hz, 1H), 1.86 (t, *J* = 11.2 Hz, 1H), 1.77-1.70 (m, 1H), 1.43 (br s, 1H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 144.4, 143.4, 133.9, 130.7, 129.6, 127.5, 93.7, 76.8, 67.6, 55.6, 52.3, 50.6, 45.7, 41.9, 21.5, 12.5; HRMS *m/z* (EI) Calcd for $C_{18}H_{25}NO_5S$ (M^+) 367.1453. Found 367.1483. *Anal.* Calcd for $C_{18}H_{25}NO_5S$: C, 58.83; H, 6.86; N, 3.81. Found: C, 58.93; H, 6.78; N, 3.75.



(4*S*,4a*S*,6*S*,7*S*,7a*S*)-4-Methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]pyridin-6-ol 112

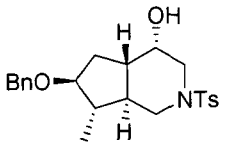
A solution of **111** (102 mg, 0.28 mmol) in THF (5 mL) in the presence of PtO_2 (0.63 mg, 2.78 μmol) was stirred at room temperature for 4.5 h under hydrogen. After removal of the insoluble material by filtration through Celite pad, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (1:1, v/v) gave alcohol **112** (97 mg, 95%) as the sole product, as a colorless oil. $[\alpha]_D^{26}$ -57.5 (*c* 1.00, $CHCl_3$); IR νmax: 3500, 2955, 2930, 2895, 1599, 1460, 1342, 1162 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 4.76 (d, *J* = 7.1 Hz, 1H), 4.62 (d, *J* = 7.1 Hz, 1H), 4.08-3.95 (m, 2H), 3.91-3.87 (m, 1H), 3.80 (m, 1H), 3.42 (s, 3H), 2.43 (s, 3H), 2.25 (dd, *J* = 12.6, 1.6 Hz, 1H), 2.05 (t, *J* = 10.6 Hz, 1H), 2.02-1.89 (m, 1H), 1.68-1.47 (m, 4H), 1.37-1.23 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.4, 133.6, 129.5, 127.4, 95.5, 79.3, 70.0, 55.7, 50.3, 49.2, 46.6, 45.2, 42.5, 34.9, 21.4, 16.2; HRMS *m/z* (CI) Calcd for $C_{18}H_{28}NO_5S$ (M^++H) 370.1688, Found 370.1713.



(4*S*,4a*S*,6*S*,7*S*,7a*S*)-6-Benzyloxy-4-methoxymethoxy-7-methyl-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[c]pyridine 113

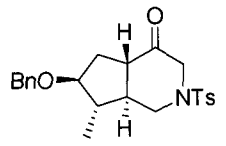
A solution of **112** (910 mg, 2.47 mmol), tetrabutylammonium iodide (182 mg, 0.49 mmol), and benzyl bromide (0.61 mL, 5.43 mmol) in DMF (12 mL) in the presence of sodium hydride (296 mg, 7.40 mmol) was stirred at ambient temperature for 7 h. The mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (3:1, v/v) gave benzyl ether **113** (934 mg, 82%) as a colorless oil. $[\alpha]_D^{26}$ -30.0 (*c* 1.00, $CHCl_3$); IR νmax: 2952, 2928, 2892, 1599, 1494, 1456, 1345, 1165 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 8.2 Hz, 2H), 7.31-7.21 (m, 7H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.06 (d, *J* = 12.5 Hz, 1H), 3.99 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.81 (br s, 1H), 3.59 (t, *J* = 5.0 Hz,

1H), 3.41 (s, 3H), 2.40 (s, 3H), 2.23 (d, J = 12.5 Hz, 1H), 2.04 (t, J = 10.6 Hz, 1H), 1.97-1.44 (m, 5H), 1.09 (d, J = 6.4 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.2, 138.3, 133.5, 129.4, 128.2, 128.2, 127.4, 127.3, 95.4, 86.1, 71.2, 69.9, 55.6, 50.3, 49.1, 45.2, 44.2, 42.3, 31.5, 21.3; HRMS *m/z* (EI) Calcd for $C_{25}H_{33}NO_5S$ (M^+) 459.2079, Found 459.2079.



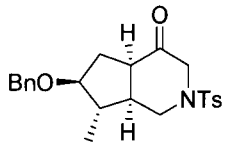
(4*S*,4a*S*,6*S*,7*S*,7a*S*)-6-Benzyloxy-7-methyl-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]pyridin-4-ol 114

A solution of **113** (454 mg, 0.99 mmol) in THF (10 mL) and 6*N* HCl (2 mL) was heated at 65 °C for 2 h. After being cooled to 0 °C, the solution was treated with saturated sodium hydrogen carbonate solution, and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (2:1, v/v) gave alcohol **114** (397 mg, 97%) as colorless needles. m.p. 135-136 °C; $[\alpha]_D^{25}$ -43.5 (*c* 1.00, $CHCl_3$); IR νmax: 3450, 2951, 2940, 2898, 2870, 1599, 1494, 1460, 1345, 1163 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.65 (d, J = 8.2 Hz, 2H), 7.34-7.25 (m, 7H), 4.49 (d, J = 11.7 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 4.01-3.87 (m, 3H), 3.57-3.61 (m, 1H), 2.43 (s, 3H), 2.38 (dd, J = 12.3, 1.4 Hz, 1H), 2.16 (t, J = 7.9 Hz, 1H), 2.06 (t, J = 10.4 Hz, 1H), 1.87-1.68 (m, 2H), 1.55-1.50 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.7, 138.4, 133.4, 129.7, 128.3, 127.58, 127.51, 127.48, 86.1, 71.4, 64.9, 52.6, 50.7, 46.1, 44.3, 42.1, 31.7, 21.5, 17.0; HRMS *m/z* (CI) Calcd for $C_{23}H_{30}NO_4S$ (M^++H) 416.1895, Found 416.1872. *Anal.* Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.39. Found: C, 66.19; H, 7.11; N, 3.42.



(4a*S*,6*S*,7*S*,7a*S*)-6-Benzyloxy-7-methyl-2-(*p*-toluenesulfonyl)octahydro-4*H*-cyclopenta[*c*]pyridin-4-one 115

To a stirred solution of oxalyl chloride (80 μL, 0.90 mmol) in CH_2Cl_2 (3 mL) was added a solution of DMSO (98 μL, 1.38 mmol) in CH_2Cl_2 (1 mL) at -78 °C under argon, and the resulting solution was stirred at the same temperature for 10 min. A solution of **114** (287 mg, 0.69 mmol) in CH_2Cl_2 (3 mL) was added to the solution, and the whole was stirred at -45 °C for further 1 h. The mixture was treated with triethylamine (0.39 mL, 2.77 mmol), and warmed to room temperature over the period of 20 min. The solution was treated with saturated NH_4Cl solution, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-acetone (3:1, v/v) gave ketone **115** (221 mg, 77%) as colorless needles. m.p. 113-115 °C; $[\alpha]_D^{25}$ +36.5 (*c* 1.00, $CHCl_3$); IR νmax: 2960, 2878, 1732, 1599, 1458, 1494, 1345, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.2 Hz, 2H), 7.36-7.27 (m, 7H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 3.86 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.84 (d, *J* = 15.5 Hz, 1H), 3.56 (ddd, *J* = 8.1, 5.8, 2.7 Hz, 1H), 3.44 (d, *J* = 15.5 Hz, 1H), 2.85 (t, *J* = 10.8 Hz, 1H), 2.56 (ddd, *J* = 13.1, 10.4, 7.9 Hz, 1H), 2.44 (s, 3H), 1.97 (ddd, *J* = 14.2, 10.4, 8.1 Hz, 1H), 1.85 (ddd, *J* = 14.2, 7.9, 2.7 Hz, 1H), 1.82-1.75 (m, 1H), 1.50-1.42 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 202.6, 144.1, 134.0, 133.0, 129.9, 128.4, 127.7, 127.6, 127.5, 85.2, 71.6, 54.3, 52.9, 48.7, 47.3, 45.6, 28.7, 21.5, 16.6; HRMS *m/z* (EI) Calcd for $C_{23}H_{27}NO_4S$ (M^+) 413.1661, Found 413.1677. *Anal.* Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.77; H, 6.48; N, 3.44.

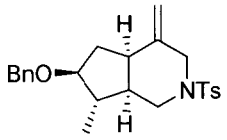


(4a*R*,6*S*,7*S*,7a*S*)-6-Benzyloxy-7-methyl-2-(*p*-toluenesulfonyl)-octahydro-4*H*-cyclopenta[*c*]pyridin-4-one 116

Method A: A solution of **115** (220 mg, 0.53 mmol) and DBU (119 μL, 0.80 mmol) in benzene (5.3 mL) was heated at 80 °C for 30 min. After being cooled to room temperature, the mixture was treated with saturated NH_4Cl solution, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a solid, which was recrystallized from EtOAc-Et_2O to give *cis*-compound **116** (178 mg, 81%) as colorless needles.

Method B (One-pot procedure): To a stirred solution of oxalyl chloride (76 μL, 0.89 mmol) in

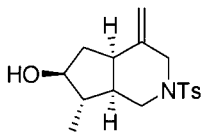
CH_2Cl_2 (3 mL) was added a solution of DMSO (97 μL, 1.37 mmol) in CH_2Cl_2 (2 mL) at -78 °C under argon, and the resulting solution was stirred at the same temperature for 10 min. A solution of **114** (284 mg, 0.68 mmol) in CH_2Cl_2 (2 mL) was added to the solution, and the whole was stirred at -45 °C for further 1 h. The mixture was treated with DBU (0.42 mL, 2.74 mmol), and stirred at room temperature for 2 h, and also at 40 °C for 1 h. The solution was treated with saturated NH_4Cl solution, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-acetone (3:1, v/v) gave ketone **116** (242 mg, 86%) as colorless needles, which was identical with the authentic sample obtained by **Method A**. m.p. 150-151 °C; $[\alpha]_D^{21}$ -14.8 (*c* 1.00, $CHCl_3$); IR νmax: 2952, 2870, 1718, 1599, 1494, 1458, 1348, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 8.2 Hz, 2H), 7.34-7.24 (m, 7H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 3.73 (dd, *J* = 17.1, 1.2 Hz, 1H), 3.53-3.46 (m, 3H), 2.83-2.75 (m, 2H), 2.44 (s, 3H), 2.36-2.29 (m, 1H), 2.22 (dt, *J* = 13.4, 5.9 Hz, 1H), 2.11-2.05 (m, 1H), 1.86-1.80 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 205.8, 144.1, 138.3, 132.7, 129.9, 128.3, 127.68, 127.54, 127.50, 84.8, 70.9, 55.7, 47.8, 46.9, 44.2, 43.3, 31.4, 21.6, 17.2; HRMS *m/z* (EI) Calcd for $C_{23}H_{27}NO_4S$ (M^+) 413.1661, Found 413.1652. *Anal.* Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.94; H, 6.65; N, 3.32.



(4a*R*,6*S*,7*S*,7a*R*)-6-Benzyloxy-7-methyl-4-methylene-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]pyridine 117

To a stirred solution of methyltriphenylphosphonium bromide (553 mg, 1.55 mmol) in THF (5 mL) was added *n*-BuLi (1.59 M in THF solution, 0.65 mL, 1.03 mmol) at 0 °C under argon, and the resulting solution was stirred at the same temperature for 1 h. A solution of **116** (213 mg, 0.52 mmol) in THF (5 mL) was added to the mixture, and the whole was stirred at the same temperature for further 30 min. The mixture was treated with water, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (7:1,

v/v) gave the recovered starting material **116** (151 mg, 71%) and the desired olefin **117** (35 mg, 17%), respectively. $[\alpha]_D^{26}$ -2.28 (*c* 1.00, $CHCl_3$); IR νmax: 2926, 2955, 2869, 1650, 1596, 1494, 1454,1348, 1162 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.68-7.65 (m, 2H), 7.35-7.24 (m, 7H), 4.93 (s, 1H), 4.89 (s, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 3.75 (d, *J* = 12.9 Hz, 1H), 3.55-3.48 (m, 1H), 3.48 (d, *J* = 12.9 Hz, 1H), 3.34 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.77 (dd, *J* = 12.1, 8.4 Hz, 1H), 2.69-2.63 (m, 1H), 2.43 (s, 3H), 2.11-2.01 (m, 1H), 1.85-1.62 (m, 3H), 1.05 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 141.7, 138.5, 133.7, 129.7, 128.3, 127.61, 127.51, 127.47, 112.8, 100.5, 86.2, 71.6, 49.8, 46.3, 45.0, 42.3, 40.4, 35.1, 21.5, 18.3; HRMS *m/z* (EI) Calcd for $C_{24}H_{29}NO_3S$ (M^+) 411.1868, Found 411.1840.

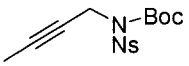


(4a*R*,6*S*,7*S*,7a*R*)-7-Methyl-4-methylene-2-(*p*-toluenesulfonyl)octahydro-1*H*-cyclopenta[*c*]-pyridin-6-ol 119

A solution of **116** (77 mg, 0.19 mmol) in THF (5 mL) and EtOH (10 mL) in the presence of palladium hyroxide on carbon (6.50 mg, 9.35 μmol) was hydrogenated under an atmospheric pressure of hydrogen at ambient temperature for 24 h. After removal of the insoluble material, the filtrate was concentrated to give alcohol **118**, which without further purification, was used in the next reaction. To a stirred solution of methyltriphenylphosphonium bromide (401 mg, 1.12 mmol) in THF (6 mL) was added LiHMDS (1.0 M in THF solution, 0.94 mL, 0.94 mmol) at 0 °C under argon, and the resulting solution was stirred at the same temperature for 30 min. A solution of **118** obtained above in THF (4 mL) was added to the mixture, and the whole was warmed to room temperature over the period of 6 h. The mixture was treated with saturated NH_4Cl solution, and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (1:1, v/v) gave the desired olefin **119** (45 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ -30.0 (*c* 0.61, $CHCl_3$); IR νmax: 3500, 2955, 2927, 2870, 2257, 1650, 1595, 1495, 1456, 1345, 1162 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.92 (s, 1H), 4.90 (s, 1H), 3.79 (d, *J* = 12.8 Hz, 1H), 3.71 (q, *J* = 7.4 Hz, 1H), 3.54 (d, *J* = 12.8 Hz,

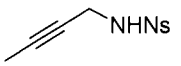
1H), 3.11 (dd, J = 12.2, 4.8 Hz, 1H), 3.00 (dd, J = 12.2, 6.4 Hz, 1H), 2.63 (q, J = 8.3 Hz, 1H), 2.43 (3H, s), 2.10-2.00 (m, 1H), 1.83-1.57 (m, 3H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 143.4, 142.0, 133.6, 129.6, 127.4, 112.6, 79.0, 50.3, 46.0, 44.7, 44.3, 37.6, 29.6, 21.4, 16.8; HRMS m/z (EI) Calcd for $C_{17}H_{24}NO_3S$ (M^+) 321.1398, Found 321.1388. The spectroscopic data were identical with those reported in the literature[36].

<Chapter 2-3>



_N_-(_tert_-Butoxycarbonyl)-_N_-(2-butynyl)-2-nitrobenzenesulfonamide 145

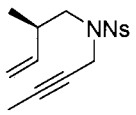
To a stirred solution of 2-butyn-1-ol **138** (0.29 mL, 3.48 mmol), _N_-Boc-2-nitrobenzene-sulfonamide **141** (1.00 g, 3.31 mmol) and triphenylphosphine (1.79 g, 6.62 mmol) in THF (7 mL) was added diethylazodicarboxylate (2.2 M DEAD in toluene solution, 3.01 mL, 6.22 mmol) at ambient temperature. After being stirred for 22 h at the same temperature, the mixture was concentrated to remove the solvent. The residue was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (3:1, v/v) gave **145** (1.15g, 98%) as colorless needles. m.p. 108-109 °C; IR νmax: 2982, 1738, 1545, 1441, 1369 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (dd, J = 6.7, 2.0 Hz, 1H), 7.79-7.74 (m, 3H), 4.49 (d, J = 2.3 Hz, 2H), 1.85 (t, J = 2.3 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.8, 147.8, 134.3, 133.3, 132.8, 131.9, 124.5, 85.5, 80.1, 73.9, 37.2, 27.8, 3.6; HRMS _m/z_ (CI) Calcd for $C_{15}H_{19}N_2O_6S$ (M^++H) 355.0963, Found 355.0984. _Anal._ Calcd for $C_{15}H_{18}N_2O_6S$: C, 50.84; H, 5.12; N, 7.90. Found: C, 50.85; H, 5.09; N, 7.97.



_N_-(2-Butynyl)-2-nitrobenzenesulfonamide 146

A stirred solution of **145** (354 mg, 1.00 mmol) in DMF (4 mL) was heated to 120 °C for 12 h. After being cooled to room temperature, the mixture was treated with H_2O and extracted with Et_2O. The organic layer was washed with brine and then dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (5:2, v/v) furnished **146** (247 mg, 97%) as colorless needles. m.p. 112-113 °C; IR νmax: 3307, 1538, 1420, 1337, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J = 1.6 Hz,

1H), 7.94-7.91 (m, 1H), 7.80-7.73 (m, 2H), 5.61 (t, J = 5.4 Hz, 1H), 3.96-3.93 (m, 2H), 1.46 (t, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.9, 134.2, 133.7, 132.8, 131.6, 125.4, 81.6, 72.7, 34.0, 3.2; HRMS *m/z* (CI) Calcd for $C_{10}H_{11}N_2O_4S$ (M^++H) 255.0439, Found 255.0430. *Anal.* Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02. Found: C, 47.25; H, 4.02; N, 10.91.



(*R*)-*N*-(2-Butynyl)-*N*-(2-methyl-3-butenyl)-2-nitrobenzenesulfonamide 136

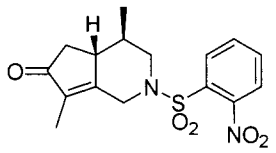
To a stirred solution of **146** (6.12 g, 24.1 mmol), (*R*)-2-methyl-3-buten-1-ol **137** (2.73 mL, 26.5 mmol) and triphenylphosphine (7.82 g, 28.9 mmol) in THF (48 mL) was slowly added diethylazodicarboxylate (2.2 M DEAD in toluene solution, 13.1 mL, 28.9 mmol) at ambient temperature. After being stirred for 12 h at same temperature, the mixture was concentrated under reduced pressure to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (3:1, v/v) gave **136** (7.79 g, 100%) as colorless needles. m.p. 61-62 °C; $[\alpha]_D^{24}$ +2.57 (*c* 1.00, $CHCl_3$); IR νmax: 3080, 2974, 2923, 1546, 1373, 1358, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03-8.02 (m, 1H), 7.71-7.61 (m, 3H), 5.68 (ddd, J = 17.4, 10.3, 7.7 Hz, 1H), 5.07 (dd, J = 17.6, 0.9 Hz, 1H), 5.00 (dd, J = 10.3, 0.9 Hz, 1H), 4.14 (d, J = 2.4 Hz, 2H), 3.31(d, J = 7.6 Hz, 2H), 2.55-2.48 (m, 1H), 1.64 (t, J = 2.4 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 140.6, 133.5, 132.9, 131.3, 130.9, 124.0, 115.3, 82.0, 71.7, 51.9, 37.2, 36.2, 17.4, 3.3; HRMS *m/z* (EI) Calcd for $C_{15}H_{18}N_2O_4S$ (M^+) 322.0987, Found 322.0974. *Anal.* Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69. Found: C, 55.85; H, 5.65; N, 8.61.

Typical procedure for Pauson-Khand reaction of 136

Entry 2. To a solution of **136** (3.20 g, 9.94 mmol) in THF (75 mL) was added dicobalt octacarbonyl (3.93 g, 10.9 mmol) at ambient temperature under an argon atmosphere. After being stirred for 2 h, the reaction mixture was cooled to 0 °C in ice bath and then a solution of trimethylamine *N*-oxide dihydrate (TMANO•$2H_2O$, 5.52g, 49.7 mmol) in H_2O (25 mL) was added dropwise to the mixture at the same atmosphere. After being stirred for further 7 h at room temperature, the mixture was quenched with 5% HCl solution (50 mL) at 0 °C and stirred for

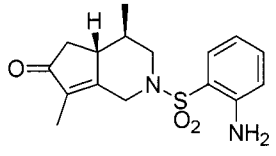
further 12 h. The resulting solution was extracted with Et_2O, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (1:1, v/v) furnished **135**, **147**, and **149** as amorphous products.

Entry 4. To a solution of **136** (3.08 g, 9.52 mmol) in toluene (100 mL) was added dicobalt octacarbonyl (3.78 g, 10.5 mmol) at ambient temperature under an argon atmosphere. After being stirred for 2 h, the stirred mixture was heated at 60 °C under an atmospheric pressure of CO for 24 h. After being cooled to room temperature, the mixture was filtrated through Celite pad to remove the insoluble materials. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (1:1, v/v) gave **135**, **147**, **148**, and **149** as amorphous products, respectively.



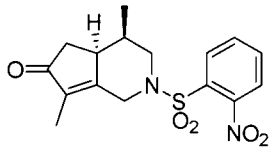
(4*R*,4a*R*)-4,7-Dimethyl-2-[(2-nitrophenyl)sulfonyl]-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one 135

$[\alpha]_D^{25}$ –119 (*c* 1.00, $CHCl_3$); IR νmax: 1704, 1544, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.06-8.04 (m, 1H), 7.75-7.64 (m, 3H), 4.82 (dd, *J* = 14.4, 1.6 Hz, 1H), 3.87 (ddd, *J* = 13.2, 4.0, 1.8 Hz, 1H), 3.60 (d, *J* = 14.4 Hz, 1H), 2.70 (dd, *J* = 13.2, 11.3 Hz, 1H), 2.60 (dd, *J* = 18.7, 6.4 Hz, 1H), 2.30-2.27 (m, 1H), 2.03 (dd, *J* = 18.7, 2.6 Hz, 1H), 1.77-1.76 (m, 3H), 1.58-1.50 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.5, 162.9, 148.1, 135.7, 133.9, 132.0, 131.8, 130.9, 124.3, 51.9, 45.1, 45.0, 39.0, 38.6, 17.3, 8.0; HRMS *m/z* (EI) Calcd for $C_{16}H_{18}N_2O_5S$ (M^+) 350.0936, Found 350.0909.



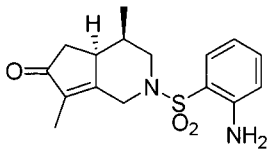
(4*R*,4a*R*)-2-[(2-Aminophenyl)sulfonyl]-4,7-dimethyl-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta[*c*]pyrindin-6-one 147

$[\alpha]_D^{23}$ –80.5 (*c* 1.00, $CHCl_3$); IR νmax: 3475, 3372, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34-7.30 (m, 1H), 6.79-6.74 (m, 2H), 5.12 (br s, 2H), 4.73 (dd, *J* = 13.6, 1.2 Hz, 1H), 3.86 (ddd, *J* = 12.3, 3.8, 1.6 Hz, 1H), 3.31 (d, *J* = 13.6 Hz, 1H), 2.55 (dd, *J* = 18.7, 6.4 Hz, 1H), 2.42 (dd, *J* = 12.3, 11.5 Hz, 1H), 2.17 (m, 1H), 1.98 (dd, *J* = 18.7, 2.6 Hz, 1H), 1.72 (dd, *J* = 1.6, 1.2 Hz, 3H), 1.57-1.45 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.7, 163.6, 146.3, 135.4, 134.4, 130.1, 117.83, 117.75, 117.27, 52.0, 45.2, 45.0, 39.0, 37.9, 17.3, 7.9; HRMS *m/z* (EI) Calcd for $C_{16}H_{20}N_2O_3S$ (M^+) 320.1194, Found 320.1201.



(4*R*,4a*S*)-4,7-Dimethyl-2-[(2-nitrophenyl)sulfonyl]-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta[*c*]pyrindin-6-one 148

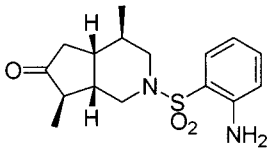
$[\alpha]_D^{26}$ +47.5 (*c* 1.00, $CHCl_3$); IR νmax: 1704, 1546, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.06-8.04 (m, 1H), 7.77-7.70 (m, 2H), 7.68-7.65 (m, 1H), 4.85 (dd, *J* = 14.3, 1.5 Hz, 1H), 3.81 (ddd, *J* = 12.8, 2.5, 2.0 Hz, 1H), 3.62 (d, *J* = 14.3 Hz, 1H), 3.22 (dd, *J* = 12.8, 2.3 Hz, 1H), 2.93-2.89 (m, 1H), 2.43 (dd, *J* = 19.1, 6.4 Hz, 1H), 2.27-2.19 (m, 1H), 2.18 (dd, *J* = 19.1, 2.4 Hz, 1H), 1.81-1.80 (m, 3H), 0.73 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.1, 161.0, 148.1, 137.0, 133.9, 131.78, 131.73, 131.03, 124.3, 52.1, 45.5, 41.5, 36.8, 31.6, 10.3, 7.9; HRMS *m/z* (EI) Calcd for $C_{16}H_{18}N_2O_5S$ (M^+) 350.0936, Found 350.0913.



(4*R*,4a*S*)-2-[(2-Aminophenyl)sulfonyl]-4,7-dimethyl-1,2,3,4,4a,5-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one 149

Compound **149** could not be isolated as a single product and was obtained as a mixture with **147**. Selected data for **149**: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.35-7.30 (m, 1H), 6.80-6.74 (m, 2H), 5.13 (br s, 2H), 4.71 (dd, *J* = 13.4, 1.4 Hz, 1H), 3.72 (ddd, *J* = 12.0, 2.6, 2.0 Hz, 1H), 3.33 (d, *J* = 13.4, Hz, 1H), 2.87 (dd, *J* = 12.0, 2.4 Hz, 1H), 2.84-2.79 (m, 1H),

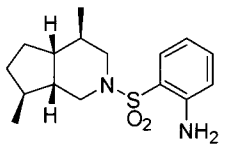
2.40-2.35 (m, 1H), 2.22-2.17 (m, 2H), 1.74 (dd, J = 2.0, 1.3 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.4, 162.1, 146.4, 136.7, 136.7, 134.5, 130.2, 117.8, 117.7, 117.3, 52.0, 45.7, 41.6, 36.8, 31.3, 10.6.



(4*R*,4a*R*,7*R*,7a*S*)-2-[(2-Aminophenyl)sulfonyl]-4,7-dimethyloctahydro-6*H*-cyclopenta[*c*]pyridin-6-one 151

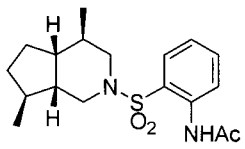
A solution of **147** (3.90 g, 12.2 mmol) in MeOH (120 mL) in the presence of PtO_2 (84 mg, 0.37 mmol) was stirred at room temperature for 24 h under an atmosphere of hydrogen. The mixture was filtrated through Celite pad to remove the insoluble materials, and the filtrate was again subjected to catalytic hydrogenation over PtO_2 (84 mg, 0.37 mmol) as described above. After removal of the insoluble materials by filtration, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (3:2, v/v) furnished inseparable mixture of diastereomers **150** in a ration of ca. 1:1 (3.37 g, 86 %) as a colorless oil.

A stirred solution of mixture **150** (430 mg, 1.34 mmol) and NaOMe (233 mg, 4.01 mmol) in MeOH (13 mL) was heated at 65 °C for 1h. After being cooled to room temperature, the mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (3:2, v/v) furnished a single diastereomer **151** (410 mg, 95%) as a colorless oil. $[\alpha]_D^{24}$ –24.5 (*c* 1.00, $CHCl_3$); IR νmax: 3479, 3377, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (dd, J = 8.0, 1.5 Hz, 1H), 7.31 (ddd, J = 8.3, 7.2, 1.5 Hz, 1H), 6.79-6.73 (m, 2H), 5.04 (brs, 2H), 3.79-3.73 (m, 2H), 2.79 (dd, J = 12.7, 3.5 Hz, 1H), 2.41-2.33 (m, 1H), 2.31 (dd, J = 18.9, 6.5 Hz, 1H), 2.32-2.22 (m, 1H), 2.19 (t, J = 11.8, 1H), 1.91-1.85 (m, 1H), 1.75 (ddd, J = 12.6, 6.1, 1.8 Hz, 1H), 1.59-1.48 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 219.4, 146.2, 134.3, 130.2, 118.1, 117.7, 117.2, 51.5, 45.6, 43.6, 42.9, 42.7, 39.2, 32.1, 17.0, 12.2; HRMS *m/z* (EI) Calcd for $C_{16}H_{22}N_2O_3S$ (M^+) 322.1351, Found 322.1331.



(2-{[(4*R*,4a*R*,7*R*,7a*R*)-4,7-Dimethyloctahydro-2*H*-cyclopenta[*c*]pyridine-2-yl]sulfonyl}phenyl)amine 152

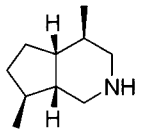
A stirred solution of **151** (460 mg, 1.43 mmol) and hydrazine monohydrate (0.69 mL, 14.3 mmol) in diethylene glycol (14 mL) was heated at 130 °C for 1.5 h. After removal of an excess hydrazine under reduced pressure, KOH (942 mg, 14.3 mmol) was added to the mixture and whole was heated at 170 °C. After being stirred for 16 h at same temperature, the resulting solution was treated with saturated NH_4Cl solution and extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (3:1, v/v) furnished **152** (416 mg, 94%) as a colorless oil. $[\alpha]_D^{24}$ +37.1 (*c* 1.00, $CHCl_3$); IR νmax: 3479, 3377, 2952, 2870, 1620cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.30-7.26 (m, 1H), 6.75-6.71 (m, 2H), 5.07 (brs, 2H), 3.63-3.55 (m, 2H), 2.73 (dd, *J* = 12.1, 3.7 Hz, 1H), 2.10 (t, *J* = 11.3 Hz, 1H), 2.03-1.86 (m, 2H), 1.75-1.66 (m, 1H), 1.56-1.39 (m, 4H), 1.22-1.12 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 133.9, 130.3, 118.3, 117.5, 117.0, 51.9, 47.0, 45.3, 45.0, 33.0, 32.3, 31.8, 27.7, 19.2, 17.4; HRMS *m/z* (EI) Calcd for $C_{16}H_{24}N_2O_2S$ (M^+) 308.1558, Found 308.1580.



(2-{[(4*R*,4a*R*,7*R*,7a*R*)-4,7-Dimethyloctahydro-2*H*-cyclopenta[*c*]pyridine-2-yl]sulfonyl}phenyl)acetamide 153

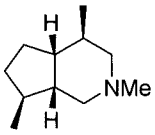
A soution of **152** (450 mg, 1.46 mmol) and AcCl (0.22 mL, 2.92 mmol) in the presence of sodium hydride (60% in oil, 88 mg, 2.19 mmol) in DMF (14 mL) was stirred for 14 h at 0 °C to room temperature. The reaction mixture was treated with water and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave residue,

which was subjected to column chromatography on silica gel. Elution with hexane-EtOAc (4:1, v/v) afforded **153** (412 mg, 81%) as a colorless oil. $[\alpha]_D^{25}$ +26.8 (*c* 1.00, $CHCl_3$); IR νmax: 3355, 2952, 2871, 1708, 1334, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.53 (brs, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58-7.54 (m, 1H), 7.23-7.18 (m, 1H), 3.57-3.51 (m, 2H), 2.68 (dd, *J* = 12.0, 3.7 Hz, 1H), 2.21 (s, 3H), 2.07 (t, *J* = 11.2 Hz, 1H), 1.97-1.87 (m, 2H), 1.79-1.67 (m, 1H), 1.56-1.40 (m, 4H), 1.21-1.16 (m, 1H), 0.94 (d, *J* = 6.2 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 136.5, 134.0, 129.6, 124.3, 123.6, 122.8, 51.8, 46.8, 45.2, 44.7, 33.1, 32.2, 31.7, 27.6, 25.1, 19.1, 17.3; HRMS *m/z* (CI) Calcd for $C_{18}H_{26}N_2O_3S$ (M^+) 350.1664, Found 350.1639.



(4*R*,4a*R*,7*S*,7a*R*)-4,7-Dimethyloctahydro-1*H*-cyclopenta[*c*]pyridine 154

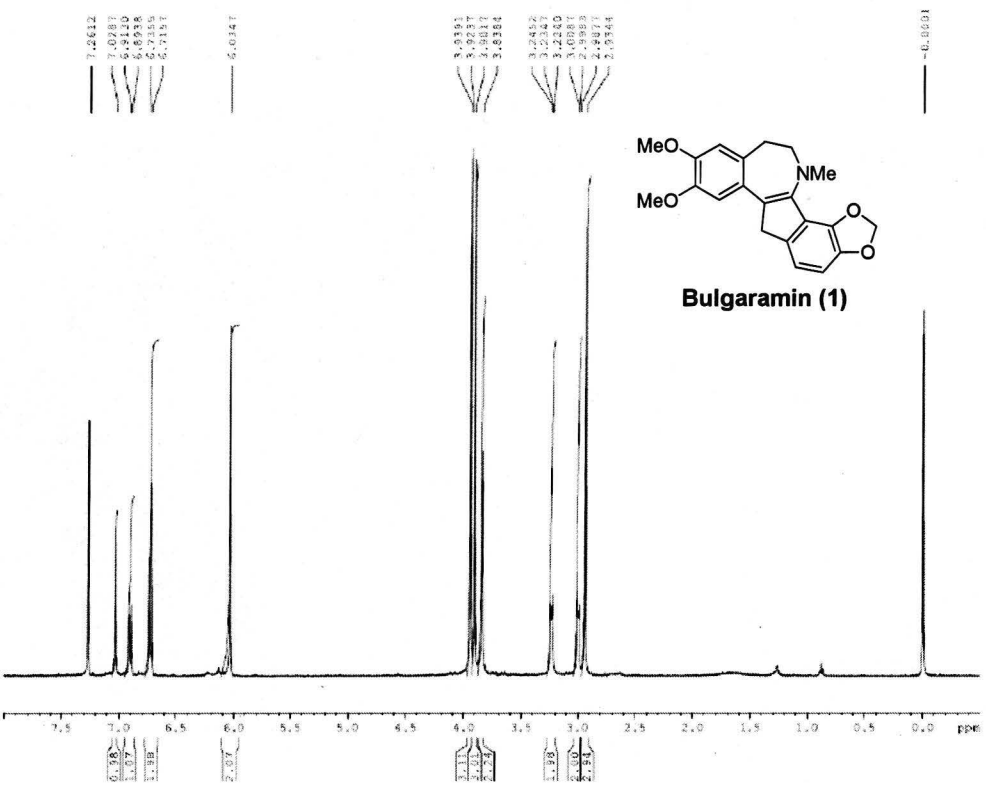
To a stirred suspension of **153** (230 mg, 0.66 mmol) in MeOH (7 mL) in the presence of anhydrous disodiumhydrogenphosphate, (933 mg, 6.57 mmol) was added sodium mercury-amalgam (1.15 g) at ambient temperature. After being stirred for 24 h, the mixture was filtrated through Celite pad to remove the insoluble materials. Concentration of the filtrate gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$-MeOH-25%NH_4OH (100:100:1, v/v) gave **154** (67 mg, 66%) as a colorless oil. $[\alpha]_D^{26}$ +34.1 (*c* 1.00, $CHCl_3$); IR νmax: 3308, 2950, 2869 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.99 (d, *J* = 12.7 Hz, 1H), 2.92 (dd, *J* = 12.7, 3.9 Hz, 1H), 2.84 (dd, *J* = 13.0, 4.2 Hz, 1H), 2.16 (dd, *J* = 12.3, 11.2 Hz, 1H), 2.11 (brs, 1H), 2.01-1.90 (m, 2H), 1.75-1.65 (m, 1H), 1.56-1.45 (m, 2H), 1.34-1.26 (m, 2H), 1.24-1.17 (m, 1H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.4, 47.1, 45.9, 45.6, 33.2, 32.7, 32.2, 28.0, 19.5, 17.7; HRMS *m/z* (CI) Calcd for $C_{10}H_{20}N$ (M^++H) 154.1596, Found 154.1587. The spectroscopic data were identical with those reported in previous literature[50].

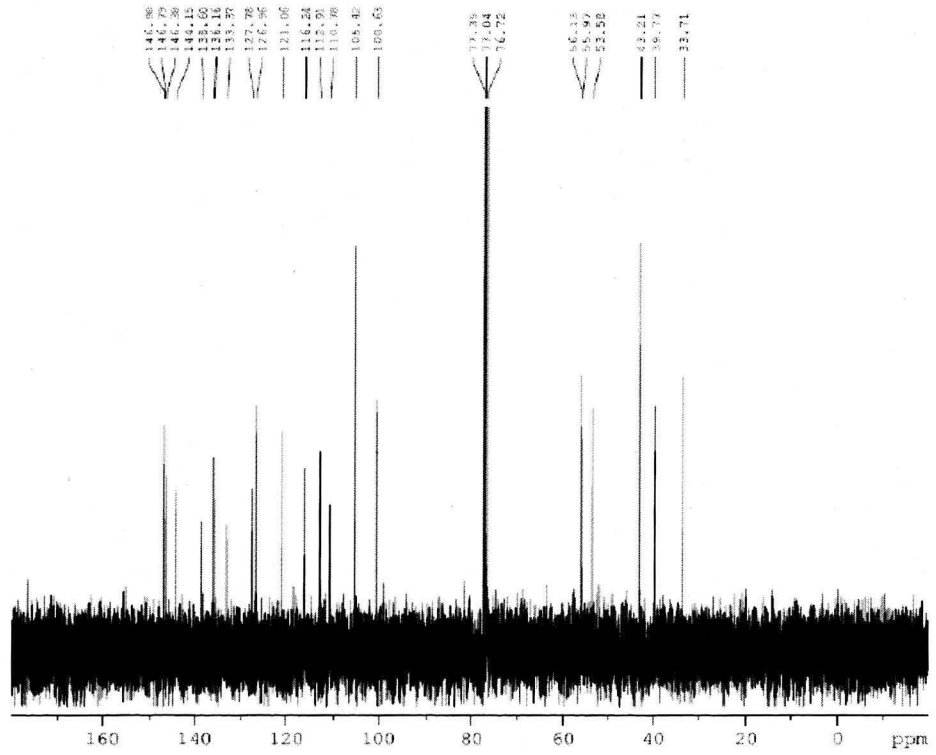


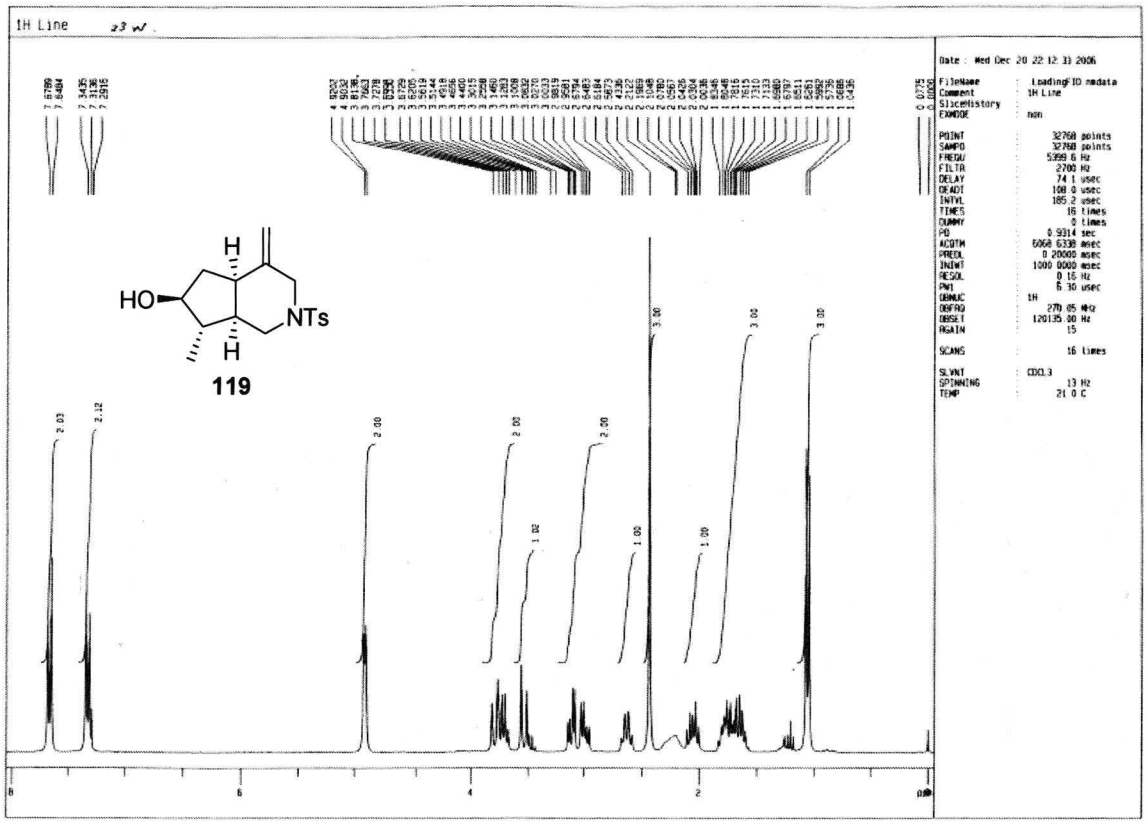
(+)-α-Skytanthine (3)

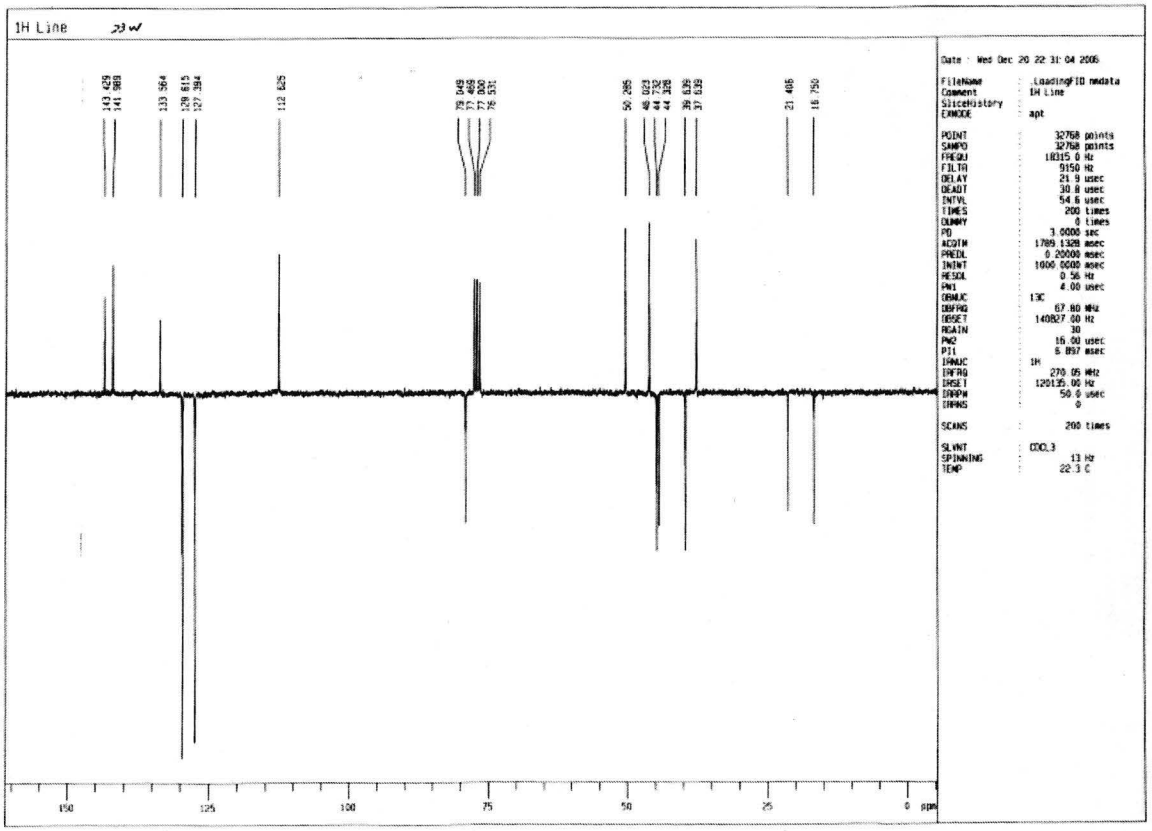
N-Methylation of **154** was carried out by using the previously reported procedure to provide (+)-α-skytanthine (**3**). $[\alpha]_D^{28}$ +66.5 (*c* 1.40, CH_2Cl_2) (lit[50]: $[\alpha]_D^{20}$ +79); IR νmax: 3370, 2925, 2854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.83 (d, *J* = 11.8 Hz, 1H), 2.69 (dd, *J* = 7.6, 1.7 Hz, 1H), 2.24 (s, 3H), 2.11-2.00 (m, 1H), 2.07 (dd, *J* = 11.7, 3.9 Hz, 1H), 1.97-1.88 (m, 1H), 1.76-1.66 (m, 1H), 1.53 (t, *J* = 10.6 Hz, 1H), 1.52-1.37 (m, 4H), 1.21-1.12 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.3, 55.6, 48.1, 46.8, 44.9, 33.7, 32.8, 32.3, 27.5, 19.5, 17.9; HRMS *m/z* (EI) Calcd for $C_{11}H_{21}N$ (M^+) 167.1674, Found 167.1667. The spectroscopic data obtained were superimposable with those previously reported.[50].

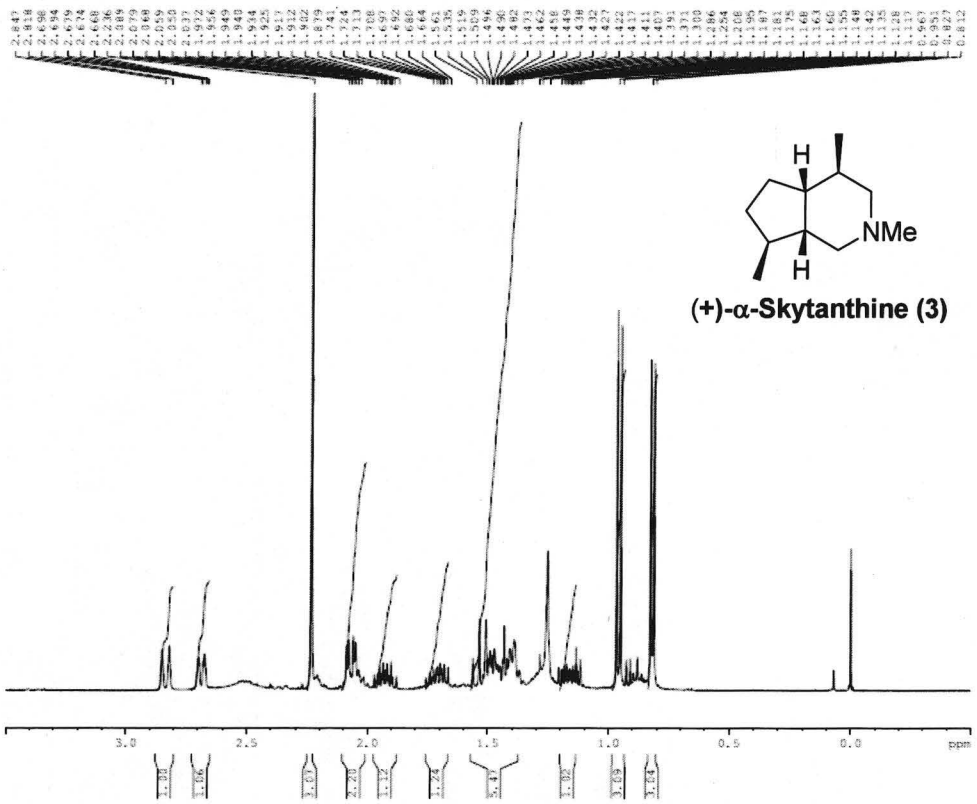
Selective ^{1}H and ^{13}C NMR data

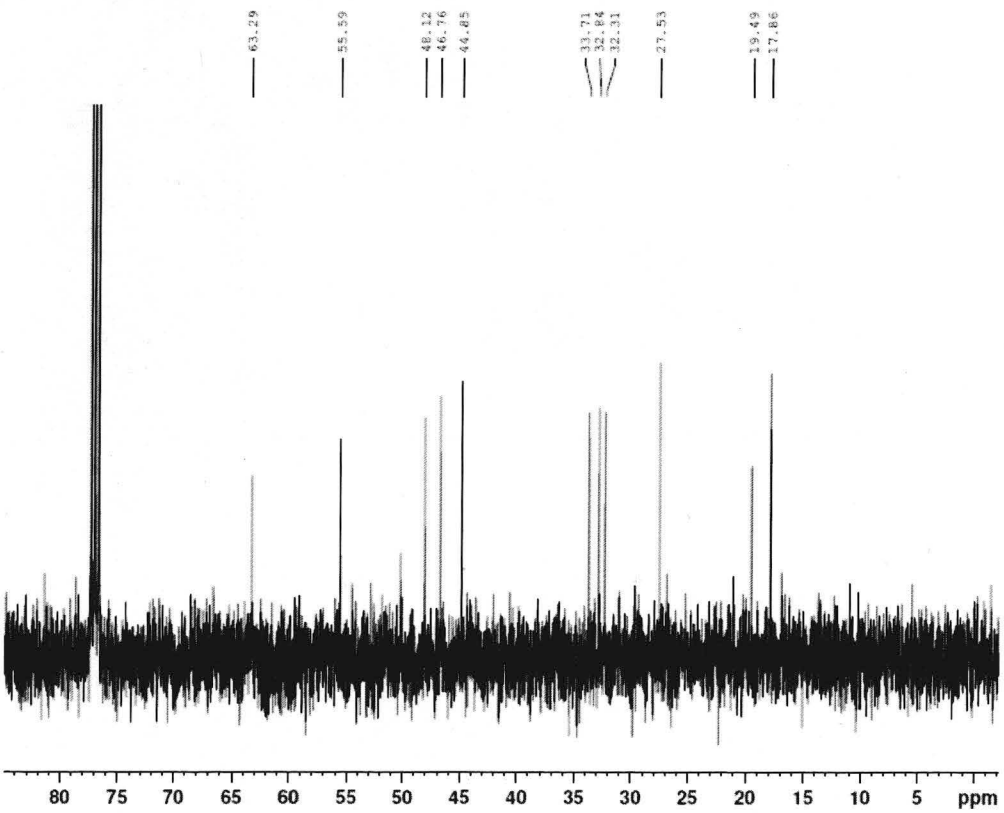





1H Line
HO
NTs
H
H
119


1H Line


NMe
H
H
(+)-α-Skytanthine (3)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


63.29
55.59
48.12
46.76
44.85
33.71
32.84
32.31
27.53
19.49
17.86
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
ppm

References

1) Blasko, G., Spirobenzylisoquinoline and related alkaloids, *Alkaloids* **1990**, *38*, 157-224.

2) Nakamura, M.; Chi, Y. -M.; Yan, W. -M.; Nakasugi, Y.; Yoshizawa,T.; Irino, N.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S., Strong antinociceptive effect of incarvillateine, a novel monoterpene alkaloid from *Incarvillea sinensis, J. Nat.Prod.* **1999**, *62*, 1293-1294.

3) Gatti, G. L.; Marotta, M., The pharmacological and psychopharmacological activity of skytanthine, the alkaloid of *Skytanthus actus*, *Annali dell'Istituto Superiore di Sanita* **1966**, *2*, 29-40.

4) Girard, P.; Namy, J. L.; Kagan, H. B., Divalent lanthanide derivatives in organic synthesis. 1. Mild preparation of samarium iodide and ytterbium iodide and their use as reducing or coupling agents, *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698.

5) Namy, J. L.; Girard, P.; Kagan, H. B., A new preparation of some divalent lanthanide iodides and their usefulness in organic synthesis, *Nou. J. Chim.* **1977**, *1*, 5-7.

6) Review of SmI_2; (a) Steel, P. G., Recent developments in lanthanide mediated organic synthesis, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727-2751. (b) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S., Samarium diiodide mediated reactions in total synthesis, *Angew. Chem., Int. Ed.* **2009**, *48*, 7140-7165.

7) Honda, T.; Naito, K.; Yamane, S.; Suzuki, Y., Samarium(II) iodide promoted reductive fragmentation of γ-halo carbonyl compounds: Application to the enantiospecific synthesis of (-)-oudemansin A, *J. Chem. Soc., Chem. Commun.* **1992**, 1218-1220.

8) Molander, G. A.; Stengel, P. J., Reduction of 2-acylaziridines by samarium(II) iodide. An efficient and regioselective route to β-amino carbonyl compounds, *Tetrahedron* **1997**, *53*, 8887-8912.

9) Honda, T.; Ishikawa, F., Reductive deamination of α-amino carbonyl compounds by means of samarium iodide, *Chem. Commun.* **1999**, 1065-1066.

10) (a) Honda, T.; Kimura, M., Concise enantiospecific synthesis of a coccinellied alkaloid, (-)-adalinine, *Org. Lett.* **2000**, *2*, 3925-3927. (b) Katoh, M.; Matsune, R.; Nagase, H.; Honda, T., Stereocontrolled synthesis of a potent antimalarial alkaloid, (+)-febrifugine, *Tetrahedron Lett.* **2004**, *45*, 6221-6223. (c) Honda, T.; Takahashi, R.; Namiki, H., Syntheses of (+)-cytisine,

(-)-kuraramine, (-)-isokuraramine, and (-)-jussiaeiine A, *J. Org. Chem.* **2005**, *70*, 499-504. (d) Katoh, M.; Mizutani, H.; Honda, T., Stereoselective synthesis of Nuphar quinolizidine alkaloid, (-)-deoxynupharidine, *Tetrahedron Lett.* **2005**, *46*, 5161-5163. (e) Katoh, M.; Inoue, H.; Suzuki, A.; Honda, T. Enantioselective synthesis of (+)-aphanorphine by means of samarium diiodide promoted reductive carbon-nitrogen bond-cleavage reaction, *Synlett* **2005**, 2820-2822.

11) (a) Blasko, G.; Hussain, S. F.; Freyer, A. J.; Shamma, M., A new class of isoquinoline alkaloids: the indenobenzazepines, *Tetrahedron Lett.* **1981**, *22*, 3127-3130. (b) Murugesan, N.; Blasko, G.; Minard, R. D.; Shamma, M., An efficient conversion of berberine into a rhoeadine via an indenobenzazepine, *Tetrahedron Lett.* **1981**, *22*, 3131-3134. (c) Blasko, G.; Murugesan, N.; Hussain, S. F.; Minard, R. D.; Shamma, M.; Sener, B.; Tanker, M., Revised structure for fumarofine, an indenobenzazepine type alkaloid, *Tetrahedron Lett.* **1981**, *22*, 3135-3138. (d) Blasko, G.; Murugesan, N.; Freyer, A. J.; Gula, D. J.; Sener, B.; Shamma, M., The indenobenzazepine-spirobenzylisoquinoline rearrangement; stereocontrolled syntheses of (±)-raddeanine and (±)-yenhusomine, *Tetrahedron Lett.* **1981**, *22*, 3139-3142. (e) Blasko, G.; Murugesan, N.; Freyer, A. J.; Minard, R. D.; Shamma, M., Revised structures for fumaritridine and fumaritrine: two indenobenzazepine type alkaloids, *Tetrahedron Lett.* **1981**, *22*, 3143-3146.

12) Yakimov, G. I.; Mollov, N. M.; Leet, J. E.; Guinaudeau, H.; Freyer, J.; Shamma, M., Bulgaramine, a new indenobenzazepine alkaloid, *J. Nat. Prod.* **1984**, *47*, 1048-1049.

13) Blasko, G., Synthesis of bulgaramine, a new indenobenzazepine alkaloid, *Acta Chim. Hung.* **1991**, *128*, 819-822.

14) Hanaoka, M.; Kim, S. K.; Inoue, M.; Nagami, K.; Shimada, Y.; Yasuda, S., Chemical Transformation of Protoberberines.VII. Efficient conversion of protoberberines into benzindenoazepines via 8,14-cyclobines, *Chem. Pharm. Bull.* **1985**, *33*, 1434-1443.

15) Fidalgo, J.; Castedo, L.; Dominguez, D., Aryl-radical cyclization onto an enamide double bond. A route to benz[*d*]indeno[1,2-*b*]azepines, *Tetrahedron Lett.* **1993**, *34*, 7317-7318.

16) Fidalgo, J.; Castedo, L.; Dominguez, D. A photochemical synthesis of benz[*d*]indeno[1,2-*b*] azepines, *Heterocycles* **1994**, *39*, 581-589.

17) Giese, M. W.; Moser, W. H., Construction of the benzindenoazepine skeleton via cyclopent-

annulation of Fischer aminocarbene complexes: total synthesis of bulgaramine, *J. Org. Chem.* **2005**, *70*, 6222-6229.

18) Katoh, M.; Inoue, H.; Honda, T., Further studies on a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction: synthesis of (+)-aphanorphine, *Heterocycles* **2007**, *72*, 497-516.

19) Matsuo, I.; Takahashi, T.; Oki, S., Synthesis of isoquinoline derivatives.II. Synthesis of acyl derivatives of (±)-*N*-methylcalycotomine and 6,7-dimethoxy-3,4-dihydro-1-isoquinoline carboxamide derivatives. *Yakugaku Zasshi* **1964**, *84*, 711-715.

20) Zalan, Z.; Martinek, T. A.; Lazar, L.; Sillanpaa, R.; Fulop, F., Synthesis and conformational analysis of tetrahydroisoquinoline- and piperidine-fused 1,3,4,2-oxadiazaphosphines, new ring systems, *Tetrahedron* **2006**, *62*, 2883-2891.

21) Kessar, S. V.; Singh, P.; Kaur, N. P.; Chawla, U.; Shukla, K.; Aggarwal, P.; Venugopal, D., Fluoride ion promoted reaction of α-halo silanes: synthesis of stilbenes, epoxides, cyclopropanes, benzazepines, and phthalidylisoquionolines, *J. Org. Chem.* **1991**, *56*, 3908-3912.

22) Mitscher, L. A.; Flynn, D. L.; Gracey, H. E.; Drake, S. D., Quinolone antimicrobial agents.2. Methylenedioxy positional isomers of oxolinic acid, *J. Med. Chem.* **1979**, *22*, 1354-1357.

23) Omae, I., Characteristic reactions of group 9 transition metal compounds in organic synthesis, *Appl. Organometal. Chem.* **2009**, *23*, 91-107.

24) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. Organocobalt complexes. Part II. Reaction of acetylenehexacarbonyldicobalt complexes, $(R^1C_2R^2)Co_2(CO)_6$, with norbornene and its derivatives, *J. Chem. Soc. Perkin Trans. 1* **1973**, 977-981.

25) (a) Schore, N. E., The Pauson-Khand cycloaddition reaction for synthesisi of cyclopentenones, *Org. React.* **1991**, *40*, 1-90. (b) Geis, O.; Schmalz, H. -G., New developments in the Pauson-Khand reaction, *Angew. Chem., Int. Ed.* **1998**, *37*, 911-914. (c) Brummond, K. M.; Kent, J. L., Recent advances in the Pauson-Khand reaction and related [2+2+1] cycloadditions, *Tetrahedron* **2000**, *56*, 3263-3283. (d) Fletcher, A. J.; Christie, S. D. R., Cobalt mediated cyclisations, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657-1668. (e) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J., The Pauson-Khand reaction, a powerful synthetic tool for the synthesis of complex molecules, *Chem. Soc. Rev.* **2004**, *33*,

32-42. (f) Bonaga, L. V. R.; Krafft, M. E., When the Pauson-Khand and Pauson-Khand type reactions go away: A plethora of unexpected results, *Tetrahedron* **2004**, *60*, 9795-9833.

26) Schore, N. E.; Croudace, M. C., Prepartation of bicyclo[3.3.0]oct-1-en-3-one and bicyclo [4.3.0]non-1(9)-en-8-one via intramolecular cyclization of α,ω-enynes, *J. Org. Chem.* **1981**, *46*, 5436-5438.

27) Brown, S. W.; Pauson, P. L., The synthesis of nitrogen heterocycles via the intramolecular Khand reaction: formation of tetra- and hexa-hydrocyclopenta[*c*]pyrrol-5(1*H*)-ones and hexahydro-6*H*-2-pyrindin-6-ones, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1205-1209.

28) Exon, C.; Magnus, P., Stereoselectivity of intramolecular dicobalt octacarbonyl alkene-alkyne cycliztions: Short synthesis of *dl*-coriolin, *J. Am. Chem. Soc.* **1983**, *105*, 2477-2478.

29) Magnus, P.; Principe, L. M., Origins of 1,2- and 1,3-stereoselectivity in dicobaltoctacarbonyl alkene-alkyne cyclizations for the synthesis of substituted bicyclo[3.3.0]octenones, *Tetrahedron Lett.* **1985**, *26*, 4851-4854.

30) Shambayati, S.; Crowe, W. E.; Schrieber, S. L., *N*-oxide promoted Pauson-Khand cyclization at room temperature, *Tetrahedron Lett.* **1990**, *31*, 5289-5292.

31) Jeong, N., Chung, Y. K.; Lee, S. H.; Yoo, S. -E., A dramatic acceleration of the Pauson-Khand reaction by trimethylamine *N*-oxide, *Synlett* **1991**, 204-206.

32) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M., The intra- and intermolecular Pauson-Khand reaction promoted by alkyl methyl sulfides, *Synlett* **1999**, 771-773.

33) Ockey, D. A.; Lewis, M. A.; Schore, N. E., A short synthesis of (±)-tecomanine via a Pauson-Khand-based route, *Tetrahedron* **2003**, *59*, 5377-5381.

34) (a) Chi, Y.; Yan, W. -M.; Li, J. -S., An alkaloid from *Incarvillea sinensis*, *Phytochemistry* **1990**, *29*, 2376-2378. (b) Chi, Y. -M.; Yan, W. -M.; Chen, D. -C.; Noguchi, H.; Iitaka, Y.; Sankawa, U., A monoterpene alkaloid from *Incarvillea sinensis*, *Phytochemistry* **1992**, *31*, 2930-2932. (c) Chi, Y. -M.; Hashimoto, F.; Yan, W. -M.; Nohara, T.; Yamashita, M.; Marubayashi, N., Monoterpene alkaloids from *Incarvillea sinensis*. VI. Absolute stereochemistry of incarvilline and structure of a new alkaloid, hydroxyincarvilline, *Chem. Pharm. Bull.* **1997**, *45*, 495-498.

35) Chi, Y.; Nakamura, M.; Yoshizawa, T.; Zhao, X. -Y.; Yan, W. -M.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S., Pharmacological study on the novel antinociceptive agent, a novel

monoterpene alkaloid from *Incarvillea sinensis*, *Biol. Pharm. Bull.* **2005**, *28*, 1989-1991.

36) Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C., Total synthesis of (-)-incarvilline, (+)-incarvine C, and (-)-incarvillateine, *J. Am. Chem. Soc.* **2004**, *126*, 16553-16558.

37) Ichikawa, M.; Aoyagi, S.; Kibayashi, C., Total synthesis of (-)-incarvilline, *Tetrahedron Lett.* **2005**, *46*, 2327-2329.

38) Tsai, A. S.; Bergman, R. G.; Ellman, J. A., Asymmetric synthesis of (-)-incarvillateine employing an intramolecular alkylation via Rh-catalyzed olefinic C-H bond activation, *J. Am. Chem. Soc.* **2008**, *130*, 6316-6317.

39) Zhang, F.; Jia, Y., Total synthesis of (-)-incarvilline and (-)-incarvillateine, *Tetrahedron* **2009**, *65*, 6840-6843.

40) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F., Enantioselective formation of functionalized 1,3-disubstituted allenes: Synthesis of α-allenic ω-carbomethoxy alcohols of high optical purity, *J. Org. Chem.* **1991**, *56*, 1083-1088.

41) Staudinger, H.; Meyer, J., New organic compounds of phosphorus III. Phosphine methylene derivatives and phosphinimines, *Helv. Chim. Acta* **1919**, *2*, 635-646.

42) Mukai, C.; Kim, J. S.; Uchiyama, M.; Hanaoka, M., Diastereocomplementary construction of optically active bicyclo[4.3.0]nonenone skeleton based on Pauson-Khand reaction, *Tetrahedron Lett.* **1998**, *39*, 7909-7912.

43) Luche, J. -L., Lanthanides in organic chemistry. 1. Selective 1,2 reductions of conjugated ketone [2], *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

44) Peterson, D. J., A carbonyl olefination reaction using silylsubstituted organometallic compounds, *J. Org. Chem.* **1968**, *33*, 780-784.

45) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H., Wittig-type reaction of dimetalated carbodianion species as produced by zinc reduction of *gem*-polyhalogen compounds in the presence of Lewis acids, *Bull. Chem. Soc., Jpn.* **1980**, *53*, 1698-1702.

46) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S., Olefin homologation with titanium methylene compounds [12], *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613.

47) (a) Casinovi, G. C.; Garbarino, J. A.; Marini-Bettolo, G. B., Structure of alkaloid of *Skytanthus actus*, *Chem. Ind.* **1961**, 243-254. (b) Djerassi, C.; Kutney, J. P.; Shamma, M., Alkaloid

studies-XXXII. Studies on *skytanthus acutus Meyen.* The structure of the monoterpenoid alkaloid skytanthine, *Tetrahedron* **1962**, *18*, 183-188.

48) Eisenbraun, E. J.; Bright, A.; Appel, H. H., The absolute configuration and partial synthesis of α-, β-, γ- and δ-skytanthine, *Chem. Ind.* **1962**, 1242-1243.

49) Oppolzer, W.; Jacobsen, E. J., Enantioselective syntheses of (+)-α-skytnathine, (+)-δ-skytanthine and (+)-iridomyrmecin by an intramolecular magnesium-ene reaction, *Tetrahedron Lett.* **1986**, *27*, 1141-1144.

50) Cid, M. M.; Pombo-Villar, E., Enantioselective synthesis of 3-azabicyclo[4.3.0]nonane alkaloids, *Helv. Chim. Acta* **1993**, *76*, 1591-1607.

51) Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Ito, S., Formation of heterocycles by the Mitsunobu reaction. Stereoselective synthesis of (+)-α-skytanthine, *Tetrahedron Lett.* **1996**, *37*, 2463-2466.

52) Helmchen, G.; Ernst, M., A novel route to iridoids: Enantionselective syntheses of iridomyrmecin and α-skytanthine, *Synthesis* **2002**, 1953-1955.

53) Fukuyama, T.; Cheung, M.; Kan, T., *N*-carboalkoxy-2-nitorobenzenesulfonamides: A practical preparation of *N*-Boc, *N*-Alloc-, and *N*-Cbz-protected primary amines, *Synlett* **1999**, 1301-1303.

54) Kan, T.; Fukuyama, T., Ns strategies: A highly versatile synthetic method for amines, *Chem. Commun.* **2004**, 353-359.

55) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R.; Jones, S. D.; Murdoch, R., Total syntheses of close analogues of the immunosuppressant FK506, *Tetrahedron* **1994**, *50*, 809-826.

56) Mitsunobu, O., The use of diethyl azocarboxylate and triphenylphosphine in synthesis and transformation of natural products, *Synthesis* **1981**, 1-28.

57) Liu, L. -X.; Huang, P. -Q., S_N2 reaction of 2-substituted 3-piperidinol mesylate with retention of configuration: application to the asymmetric synthesis of (2*R*,3*S*)-CP-99,994, *Tetrahedron: Asymmetry* **2006**, *17*, 3265-3272.

List of Publications

This dissertation is written on the basis of the following original publications:

1. Facile Synthesis of a Benzindenoazepine Alkaloid, Bulgaramine, Via Samarium Diiodide Promoted Ring Expansion of an α-Aminocarbonyl Compound, Toshio Honda, Eriko Aranishi, Kyosuke Kaneda, *Org. Lett.* **2009**, *11*, 1857-1859. (Chapter 1-2)

2. Diastereoselective Foraml Synthesis of a Monoterpene Alkaloid, (-)-Incarvilline, Toshio Honda, Kyosuke Kaneda, *J. Org. Chem.* **2007**, *72*, 6541-6547. (Chapter 2-2)

3. Stereocontrolled synthesis of (+)-α-skytanthine by means of an intramolecular Pauson-Khand reaction, Kyosuke Kaneda, Toshio Honda, *Tetrahedron* **2008**, *64*, 11589-11593. (Chapter 2-3)