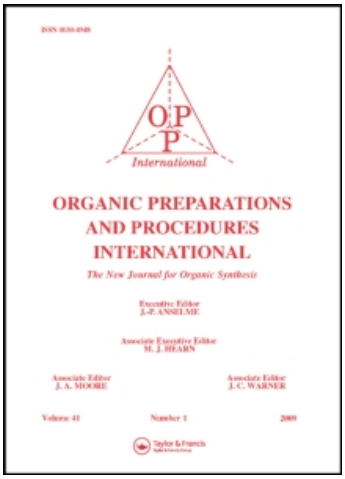

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RECENT PROGRESS IN THE SYNTHESIS AND REACTIONS OF SUBSTITUTED PIPERIDINES. A REVIEW

Chia-Lin J. Wang[a]; Mark A. Wuonola[a]
[a] The Du Pont Merck Pharmaceutical Co., Experimental Station, Wilmington, DE

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RECENT PROGRESS IN THE SYNTHESIS AND REACTIONS OF SUBSTITUTED PIPERIDINES. A REVIEW

Chia-Lin J. Wang* and Mark A. Wuonola

The Du Pont Merck Pharmaceutical Co.
Experimental Station, P. O. Box 80353
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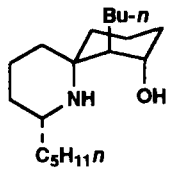
INTRODUCTION

A large number of piperidine-containing compounds are biologically and medicinally interesting.[1] For example, perhydrohistrionicotoxin (**1**) inhibits the ion transport mechanism of the cholinergic receptor;[2] nojirimycin (**2a**) and 1-deoxynojirimycin (**2b**) inhibit glucosidases;[3] antibiotic DKP 593A (**3**) possesses anti-tumor activity;[4] solenopsin A (**4a**) and B (**4b**) exhibit hemolytic, insecticidal, and antibiotic activity;[5] and *cis*-4-(phosphonomethyl)-2-piperidinecarboxylic acid (CGS 19755) (**5**) is a potent and selective *N*-methyl-D-aspartate (NMDA) antagonist.[6]



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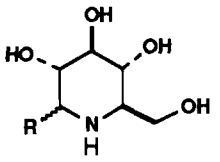
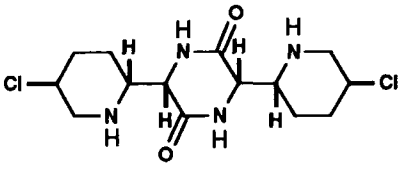


2

a. R = OH
b. R = H



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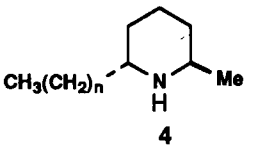
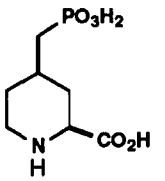


4

a. n = 10
b. n = 12



5

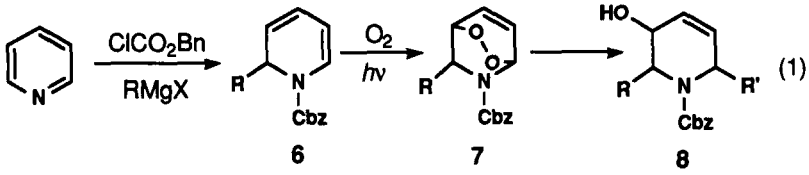
Therefore, it is not surprising that many new methods have been developed for the synthesis of piperidine derivatives. Recently, an excellent monograph[7] and three informative articles[1,8] on piperidine compounds have appeared. Our own review covers the literature from 1980 to 1991; however, those materials that were extensively described in the previous reviews will not be covered again here.

I. SYNTHESIS

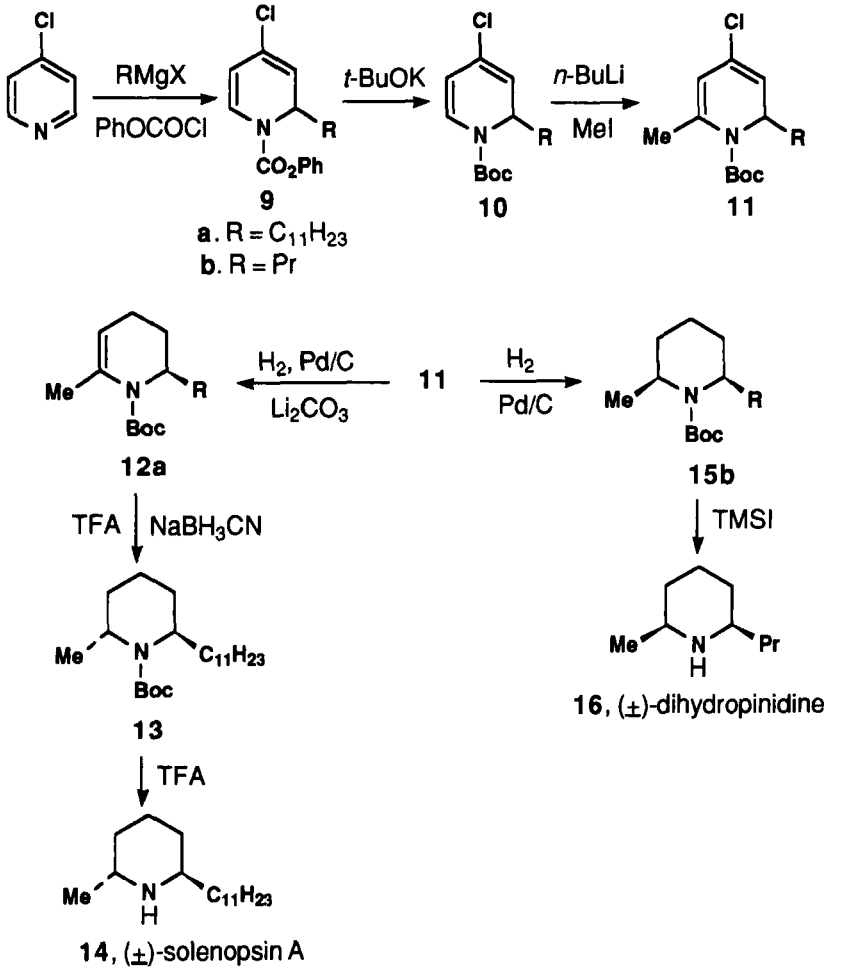
1. From Pyridine Derivatives

Reduction of pyridine derivatives by dissolving metal in alcohol or by catalytic hydrogenation is a useful route for the synthesis of piperidine derivatives.[8a] Another valuable method involves

the reaction of Grignard reagents or other nucleophiles with 1-acylpyridinium salts. Natsume and Ogawa synthesized 2,6-disubstituted piperidin-3-ols **8** from endoperoxides **7** and enol ethers such as ethyl vinyl ether in the presence of $SnCl_2$. Compounds **7** were derived by photooxidation of 1,2-dihydropyridines **6**, which in turn were prepared by the addition of Grignard reagents to 1-acylpyridinum salts (Eq. 1).[9]



Comins stereoselectively prepared *cis*- and *trans*-2,6-disubstituted piperidines, e. g., (±)-solenopsin A and (±)-dihydropinidine from the readily prepared 1-acyl-1,2-dihydropyridine intermediates **9a** and **9b** (Scheme 1).[10] A mixture of 4-chloropyridine and undecylmagnesium bromide

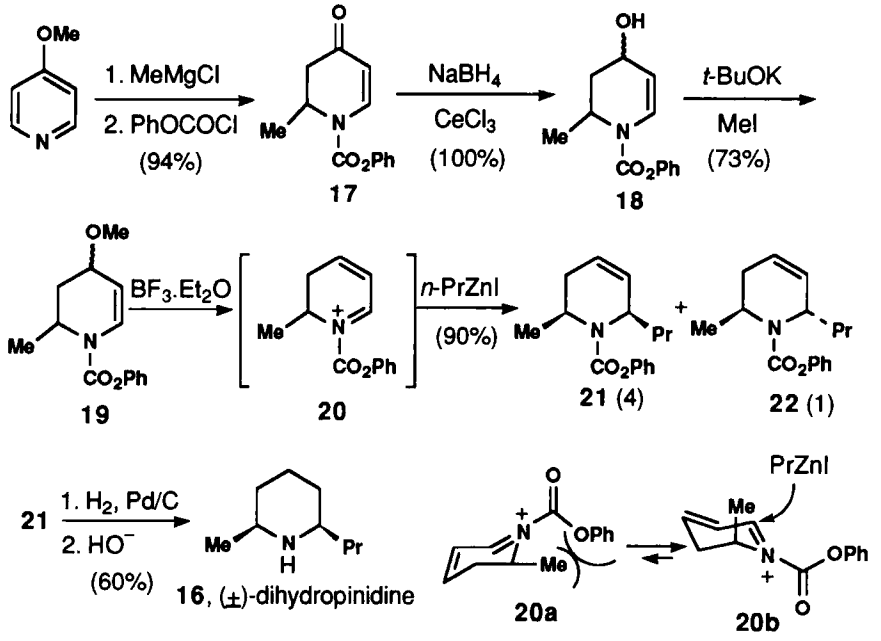


Scheme 1

in THF at -78° was treated with phenyl chloroformate to give the 1,2-dihydropyridine **9a**. Crude **9a** was converted into the *N*-Boc derivative **10a** and then a methyl group was introduced at C6 by directed-lithiation methodology to afford **11a**. Compound **11a** was partially reduced to the tetrahydropyridine **12a**, which was subjected to $NaBH_3CN$/trifluoroacetic acid (TFA) reduction to yield *trans* **13** as the major product (*trans*:*cis* = 90:10). The Boc group in **13** was cleaved by TFA to afford (±)-solenopsin A (**14**).

To synthesize the *cis*-2,6-dialkylpiperidine, (±)-dihydropinidine, compound **11b** was prepared in a similar manner from 4-chloropyridine and *n*-propylmagnesium chloride. Catalytic hydrogenation of **11b** provided *cis*-piperidine derivative **15b** stereoselectively. Upon treatment of **15b** with trimethylsilyl iodide (±)-dihydropinidine (**16**) was obtained.

Alternatively, (±)-dihydropinidine was synthesized from 4-methoxypyridine (Scheme 2).[11]

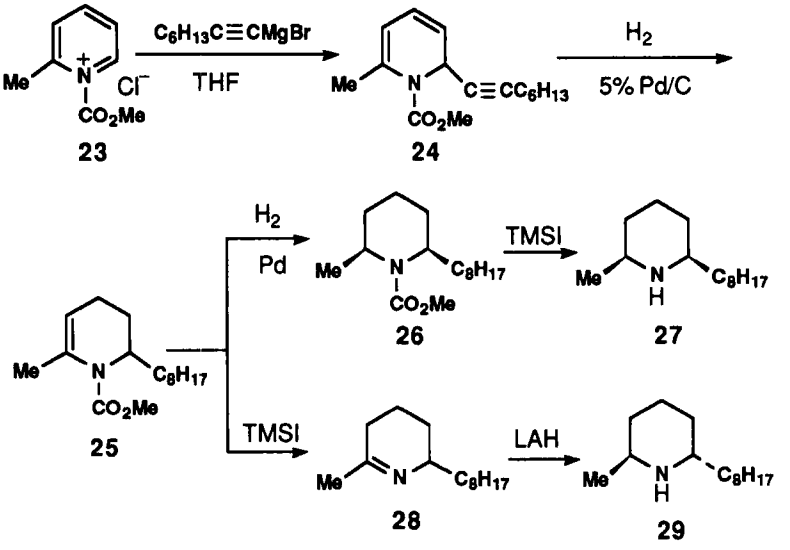


Scheme 2

The key step involves the addition of *n*-propylzinc iodide to **19** in the presence of boron trifluoride etherate. The organozinc iodide added mainly to the α-position of the conjugated iminium ion **20**. The stereochemical outcome of this reaction is proposed to arise from a stereoelectronically preferred axial attack of the alkylzinc iodide on **20b**.

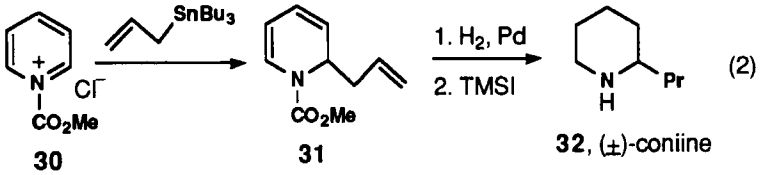
Yamaguchi reported that reaction of *N*-methoxycarbonyl-2-alkylpyridinium salt **23** with the alkynyl Grignard reagent 1-octynylmagnesium bromide gave exclusively the 2,6-disubstituted 1,2-dihydropyridine **24**, from which either the *cis*- or the *trans*-2,6-dialkylpiperidine was synthesized selectively (Scheme 3).[12] Careful hydrogenation of **24** over 5% Pd/C afforded the 1,2,3,4-tetrahydropyridine **25**, which was further hydrogenated over Pd black to give the *cis*-dialkylpiperidine **26**.

Demethoxycarbonylation of **26** with trimethylsilyl iodide yielded *cis*-2-methyl-6-octylpiperidine (**27**). On the other hand, when **25** was treated with trimethylsilyl iodide, a cyclic imine **28** was obtained. Reduction of **28** with $LiAlH_4$ gave *trans*-2-methyl-6-octylpiperidine (**29**) as the major product.



Scheme 3

Allyltributyltin regioselectively alkylated the *N*-(alkoxycarbonyl)pyridinium salt **30** at the α-position to give the 2-allyl-1,2-dihydropyridine **31**, which was converted into (±)-coniine (**32**) (Eq. 2).[13]

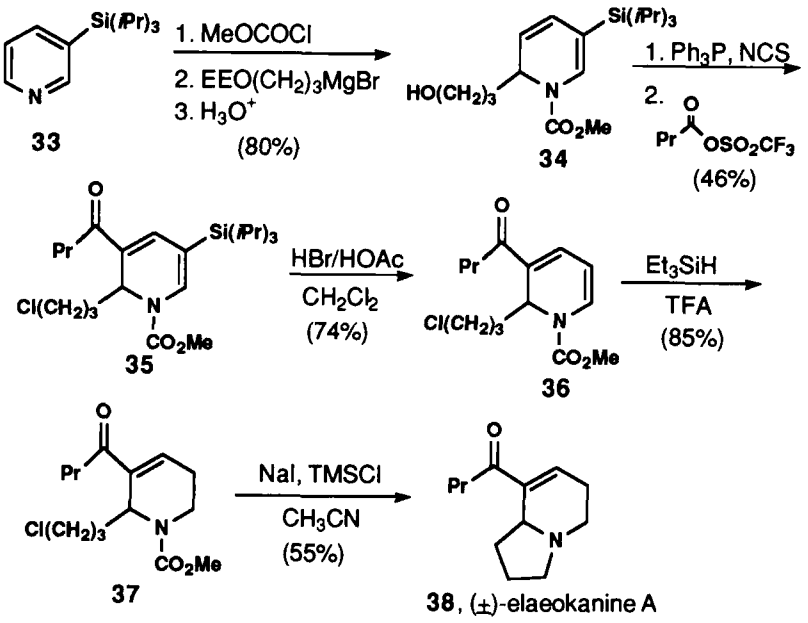


The regioselective addition of Grignard reagents to the phenoxycarbonyl salts of 3-(trialkylsilyl)pyridines was studied.[14] Most of the 3-(trialkylsilyl)pyridine salts gave a mixture of dihydropyridines on reaction with aliphatic Grignard reagents.

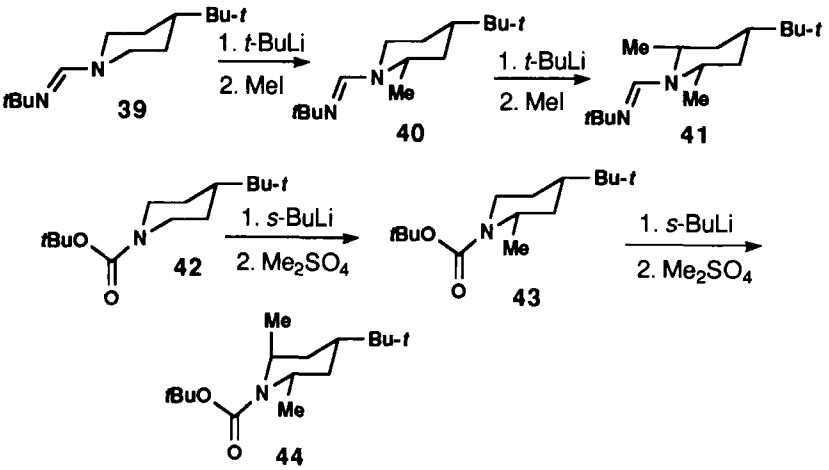
However, all reactions using alkyl or aryl Grignard reagents and the 1-phenoxycarbonyl salt of 3-(triisopropylsilyl)pyridine, or 4-chloro-3-(triisopropylsilyl)pyridine, gave exclusively 1,2-dihydropyridines resulting from attack of the Grignard reagents at the C6 position of the pyridinium salt. This methodology was used to prepare (±)-elaeokanine A (**38**) (Scheme 4).

2. From Piperidine Derivatives

The 2-substituted and 2,6-disubstituted piperidines can be obtained from alkylation of α-lithiopiperidines. Monoalkylation of α-lithio-*N*-(*N'*-*t*-butylformimidoyl)-4-*t*-butylpiperidines gave equatorial 2-substituted piperidines, which in turn proceeded to give diequatorial 2,6-disubstituted piperidines when subjected to a second lithiation-alkylation procedure (Scheme 5).[15] The



Scheme 4

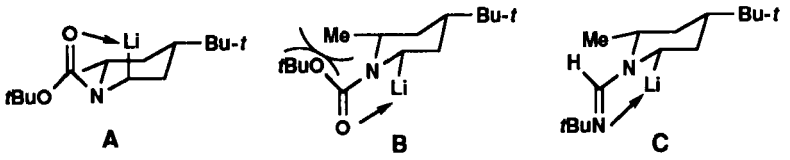


Scheme 5

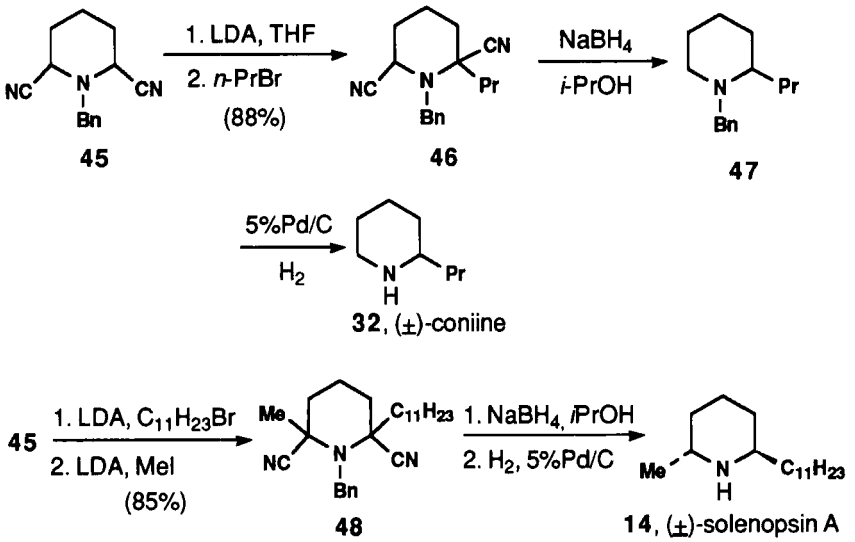
stereochemical result of the second alkylation is different than in alkylation of α-lithio-2-substituted piperidines that are stablized by the *N*-(*t*-butoxycarbonyl) group; these gave the axial 6-substituted piperidines upon treatment with electrophiles.

To account for the diequatorial products of formamidines and the equatorial-axial products of the BOC derivatives, Meyers offered an explanation in terms of the differing steric requirements of the stabilizing groups. In the BOC system, orientation **A** is more favorable than **B** because of the steric interaction between the *t*-butoxy group of BOC and the methyl group in **B**. Alkylation proceeded with retention producing the axial product. In the case of the *t*-butylformamidine **C**, the hydrogen on the

imine is in proximity to the 6-methyl substituent, which is of minor steric concern. Equatorial alkylation led to the observed diequatorial products.



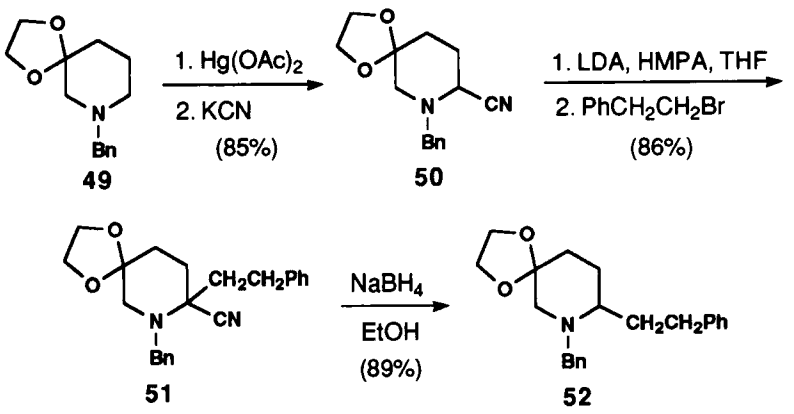
Takahashi described the synthesis of 2-substituted and 2,6-disubstituted piperidines from 1-benzyl-2,6-dicyanopiperidine (**45**) (Scheme 6).[16] Reaction of **45** with *n*-propyl bromide in THF containing LDA gave **46**. Decyanation of **46** with $NaBH_4$ in *i*-PrOH at 70° yielded **47**, which was hydrogenated to afford (±)-coniine. Alkylation of **45** with undecyl bromide, followed by a second alkylation with methyl iodide, provided **48**. Subsequent decyanation and hydrogenation gave (±)-solenopsin A and its *cis* isomer in a 3:1 ratio.



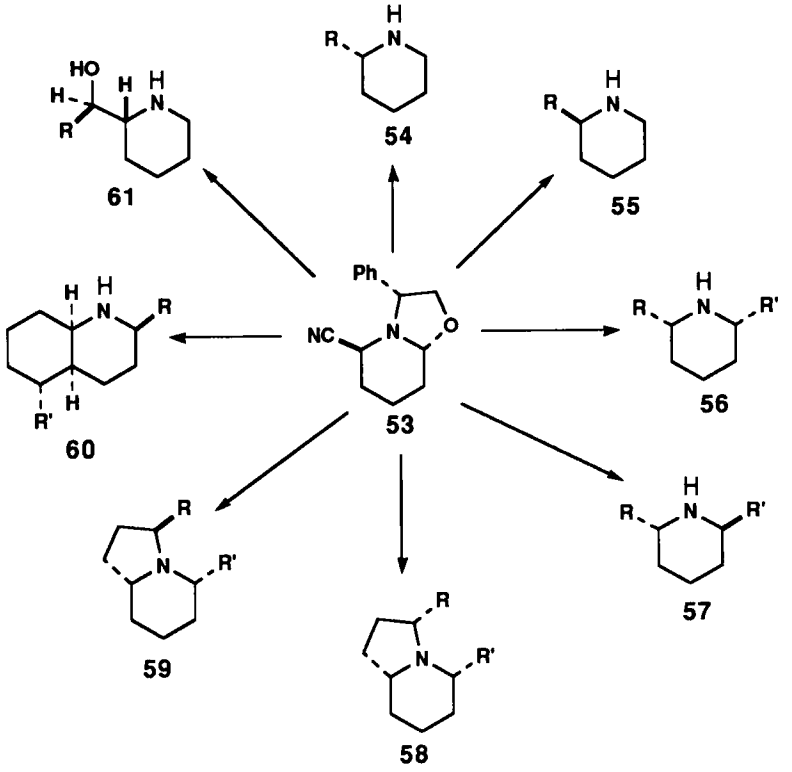
Scheme 6

A synthetic route to the 2,5-disubstituted piperidines from 1-benzyl-3,3-(ethylenedioxy)piperidine (**49**) was reported by Hoornaert (Scheme 7).[17] Mercuric acetate oxidation of **49** in aqueous acetic acid, followed by the addition of cyanide, regioselectively gave 1-benzyl-2-cyano-5,5-(ethylenedioxy)piperidine (**50**). The α-aminonitrile **50** was alkylated with phenethyl bromide in the presence of LDA and HMPA in THF to afford **51**. Reductive decyanation with $NaBH_4$ in ethanol yielded **52**.

Husson used 2-cyano-6-phenyloxazolopiperidine **53**, which was prepared from (-)-phenylglycinol and glutaraldehyde in the presence of potassium cyanide, as a stable chiral 1,4-dihydropyridine equivalent for the asymmetric synthesis of substituted piperidines. This approach has been covered by one of the previous reviews.[7] A schematic summary is shown here (Scheme 8).[18]



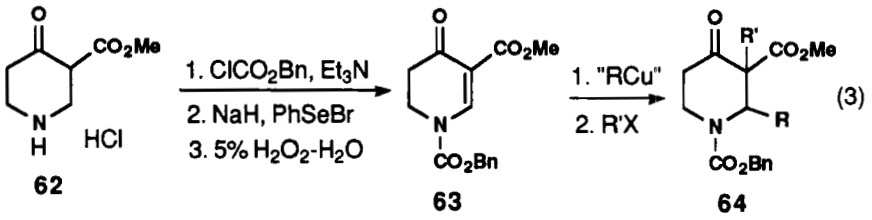
Scheme 7



Scheme 8

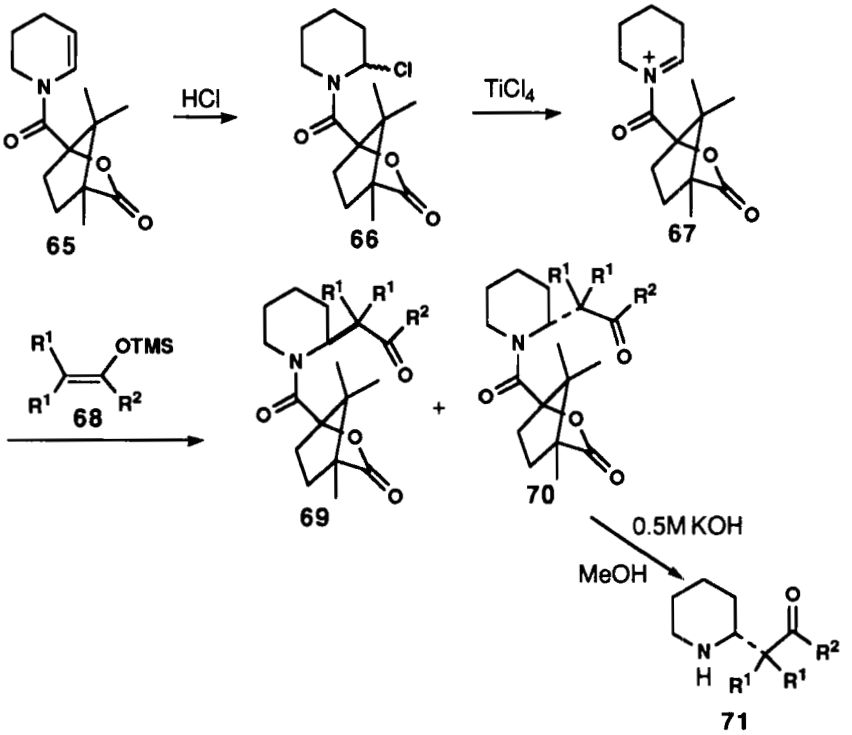
The 2,3-substituted-4-piperidones **64**, which are valuable synthons for the preparation of the alkaloids and pharmaceuticals, were prepared from enone **63**, which in turn, was obtained from 3-carbomethoxy-4-piperidone hydrochloride (**62**).[19] Reaction of **62** with benzyl chloroformate, followed by alkylation with phenyl selenium bromide and elimination of phenyl selenic acid, gave enone **63**. Organocuprates underwent conjugate addition to **63** and the resulting 2-substituted piperidones could

be further alkylated with electrophiles to yield the 2,3-substituted-4-piperidones **64** (Eq. 3).



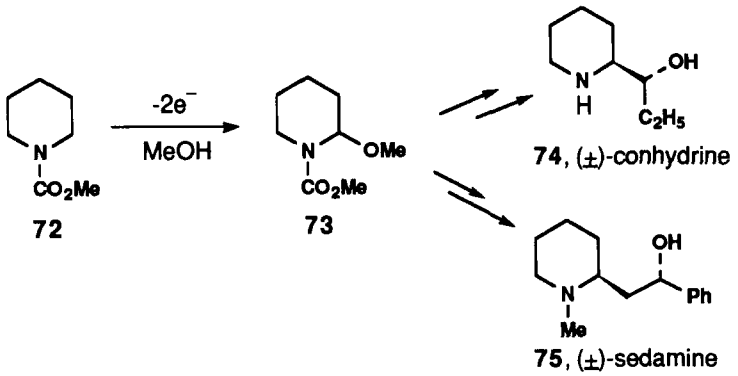
(3)

Wanner developed a method for the asymmetric amidoalkylation mediated by a chiral enamide **67** and demonstrated its utility in the synthesis of 2-substituted piperidines with high enantiomeric purity.[20] Treatment of the readily available **65** with a solution of HCl in CH_2Cl_2 at -78°, followed by addition of $TiCl_4$ or $SnCl_4$ and enol ether **68**, gave the amidoalkylation products **69** and **70** in a 35:65 or 6:94 ratio. The chiral auxiliary group was cleaved by base hydrolysis to afford the 2-substituted piperidines **71** (Scheme 9).



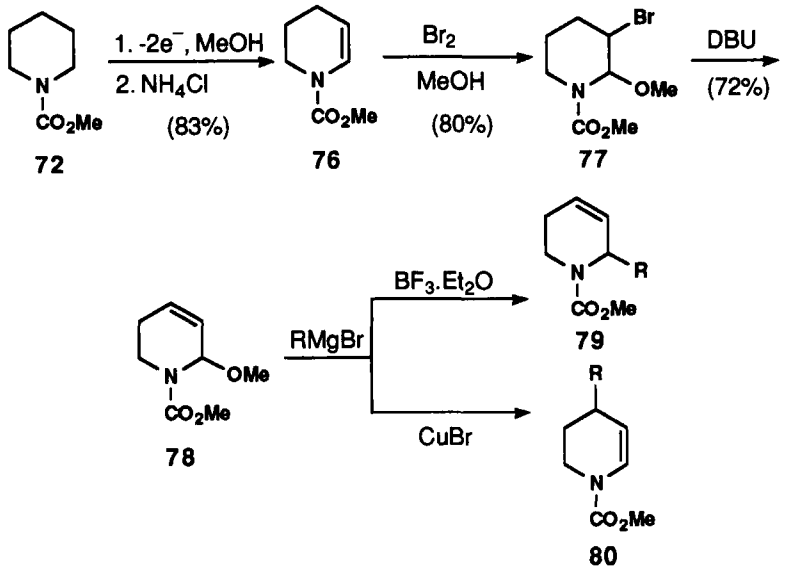
Scheme 9

Shono reported that anodic oxidation of *N*-carbomethoxypiperidine (**72**) in MeOH gave 2-methoxy carbamate **73**, which was used as an intermediate to synthesize 2-substituted piperidines such as (±)-conhydrine (**74**) and (±)-sedamine (**75**) (Scheme 10).[21]



Scheme 10

Regioselective introduction of alkyl groups to the 2- or 4-position of a piperidine ring using anodic oxidation as a key step was also described by Shono (Scheme 11).[22] Anodic oxidation of **72** in



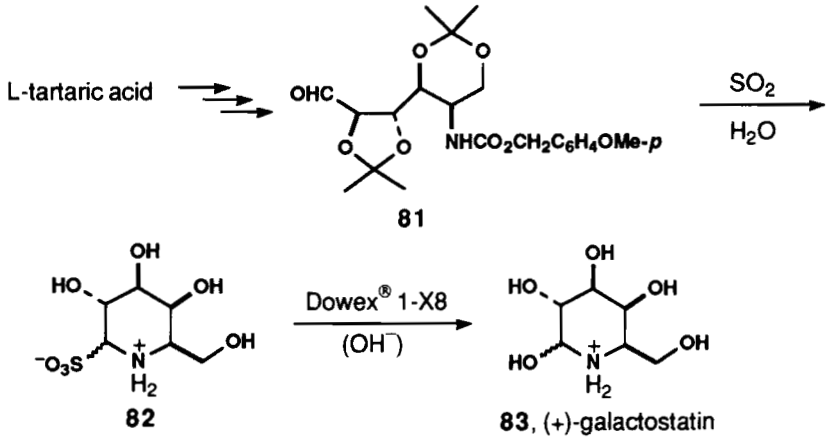
Scheme 11

MeOH, followed by three successive reactions, namely, the elimination of MeOH, the bromomethoxylation of Δ^2-*N*-carbomethoxypiperidine (**76**), and the dehydrobromination of compound **77**, afforded 2-methoxy-Δ^3-N-carbomethoxypiperidine (**78**). Reaction of Grignard reagents such as ethyl or phenyl magnesium bromide with **78** in the presence of $BF_3.Et_2O$ yielded the 2-substituted piperidines **79**. Using CuBr instead of $BF_3.Et_2O$ for the above reaction gave the 4-substituted piperidines **80**.

3. Cyclization Methods

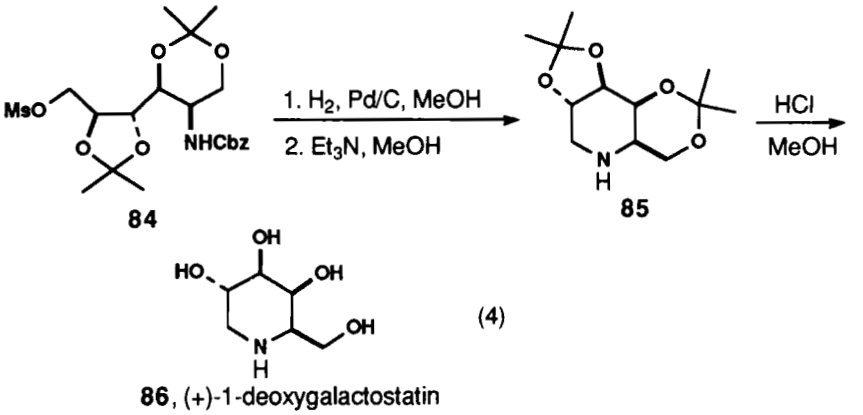
Cyclization of amines with carbonyls, halides, epoxides, and sulfonates have been commonly used to prepare piperidine derivatives.[23] Kibayashi reported the synthesis of galactosidase inhibitor (+)-galactostatin (**83**) by intramolecular cyclization of the aldehyde **81**, which was derived from L-

tartaric acid (Scheme 12).[24] Exposure of **81** to aqueous sulfurous acid at room temperature resulted in deprotection and formation of the bisulfite adduct to yield **82**. Subsequently, **82** was applied to a column of ion-exchange resin and eluted with water to furnish (+)-galactostatin (**83**).



Scheme 12

Another galactosidase inhibitor, (+)-1-deoxygalactostatin (**86**), was prepared by cyclization of the mesylate **84** (Eq. 4). Hydrogenolysis of **84** in the presence of Pd/C followed by treatment with triethylamine afforded **85**. Deprotection with hydrochloric acid in methanol led to (+)-1-deoxygalactostatin (**86**).

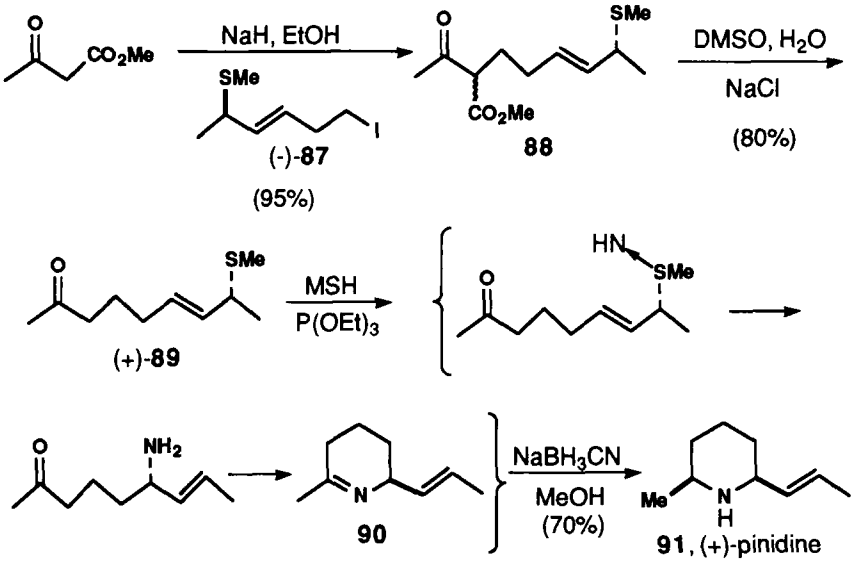


(4)

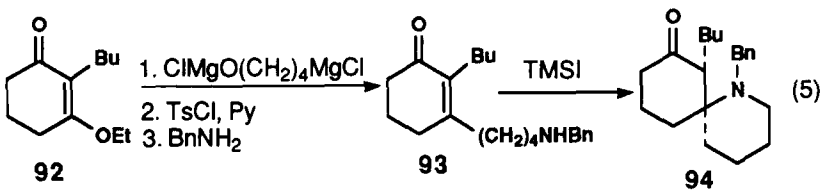
An enantioselective synthesis of (+)-pinidine (**91**) was recently described (Scheme 13).[25] Alkylation of the sodium enolate of methyl acetoacetate with (-)-**87** [from (*S*)-(-)-ethyl lactate] afforded keto-ester **88**, which was decarboxylated to furnish (+)-**89**. Upon exposure to *O*-mesitylene-sulfonyl hydroxylamine (MSH) and triethylphosphite, (+)-**89** underwent oxidative amination and concomitant [2,3]-sigmatropic rearrangement and intramolecular imine formation to yield **90**. Reduction of **90** *in situ* by the addition of $NaBH_3CN$ afforded (+)-pinidine (**91**).

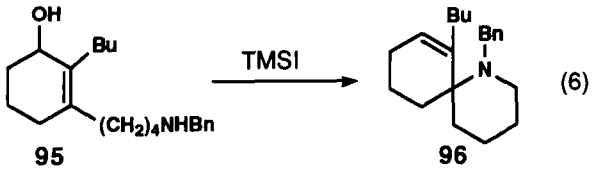
Godleski reported the development of two trimethylsilyl iodide catalyzed amine spirocycliza-

tion reactions.[26] The first readily affected the Michael reaction of the enone **93** to provide **94** predominantly (Eq. 5). Enone **93** was derived from **92** by treatment with: 1. $ClMgO(CH_2)_4MgCl$; 2. *p*-toluenesulfonyl chloride (*p*-TsCl), pyridine (Py); and 3. benzyl amine ($BnNH_2$), DMSO. The second catalyzed an intramolecular S_N2' reaction of the allylic alcohol **95**, providing the spiro olefin **96** (Eq. 6).

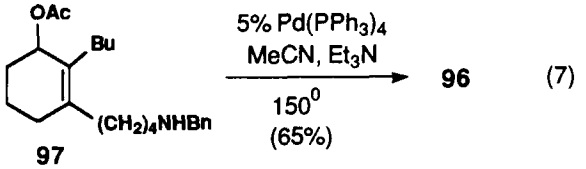


Scheme 13

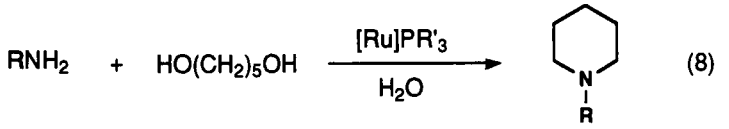




Godleski also found that amino allylic acetate **97** could be cyclized in the presence of $Pd(PPh_3)_4$ catalyst to the spirocyclic olefin **96** (Eq. 7).[27] This methodology has been applied to a formal total synthesis of perhydrohistrionicotoxin (**1**).

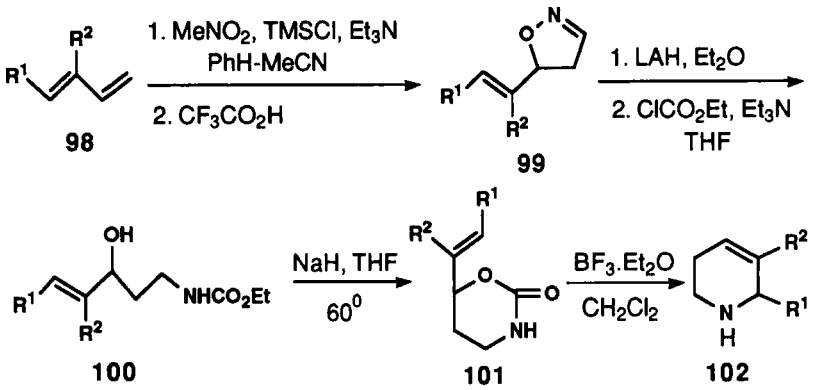


Aliphatic and aromatic primary amines can directly react with 1,5-pentanediol in the presence of a ruthenium catalyst modified with phosphine ligands to give the *N*-substituted piperidines in fair to good yields (Eq. 8).[28]



(8)

Decarboxylative cyclization of allylic cyclic carbamates **101** leading to the 2-substituted Δ^3-piperidines **102** was described by Wang (Scheme 14).[29] Addition of trimethylsilyl ester of



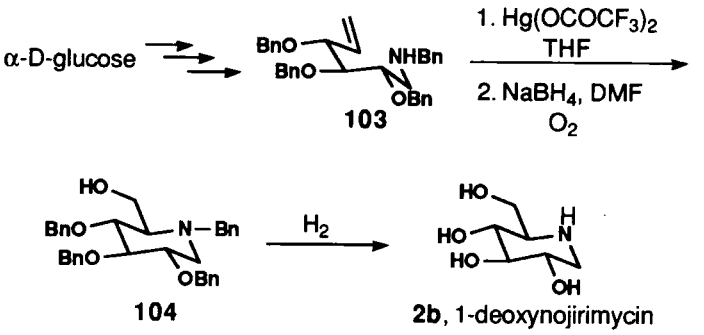
Scheme 14

aci-nitromethane to diene **98** gave 2-isoxazoline **99**. Treatment of **99** with $LiAlH_4$, followed by ethyl chloroformate in the presence of triethylamine, yielded **100**, which was converted into **101** smoothly using sodium hydride at 60°. Finally, upon reacting **101** with boron trifluoride etherate a decarboxylative cyclization occurred to give **102**. Moderately high yields of the cyclization were obtained when R^1 is electron-donating or R^2 is a trimethylsilyl group, which can stabilize a β-carbonium ion. This observation supports the premise that a carbonium ion or ion pair is an intermediate in the decarboxylative cyclization.

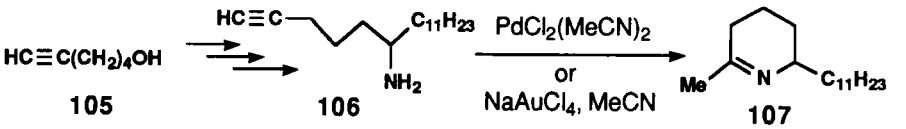
Electrophiles such as $Hg(OAc)_2$, PhSeCl, $HgCl_2$, and $AgNO_3$-initiated cyclization of alkenyl amine derivatives has been commonly employed to build up the piperidine skeleton.[30] An example of applying the intramolecular aminomercuration was reported by Ganem in the synthesis of 1-deoxynojirimycin (**2b**) (Scheme 15).[31] Treatment of **103**, prepared from α-D-glucose, with mercuric trifluoroacetate, followed by reductive oxygenation with $NaBH_4/DMF/O_2$ gave the cyclization product **104**, which was hydrogenated to afford 1-deoxynojirimycin (**2b**).

Intramolecular addition of an amine to a carbon-carbon triple bond in the 5-alkynylamine **106** producing the 1,3,4,5-tetrahydropyridine **107** could be catalyzed either by $PdCl_2(MeCN)_2$ or by $NaAuCl_4$ (Scheme 16).[32] The starting 1-undecyl-5-hexynylamine (**106**) was prepared from 5-hexyn-1-ol (**105**) by the following reactions: 1. EtMgBr, Me_3SiCl; 2. pyridinium chlorochromate (PCC); 3. *n*-$C_{11}H_{23}MgBr$; 4. *p*-TsCl, Py; 5. NaN_3; 6. $LiAlH_4$; and 7. KF, DMSO. Since the product cyclic imine

107 had been stereoselectively reduced to solenopsin A (**14**)[33], the above method opened another effective route to the *trans*-2,6-disubstituted piperidines.

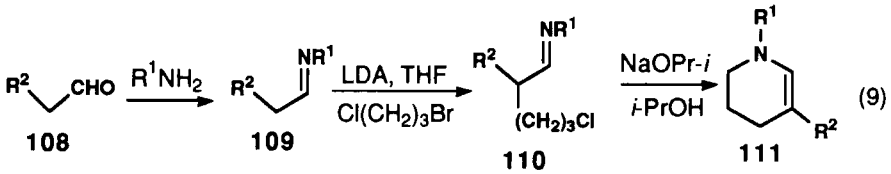


Scheme 15

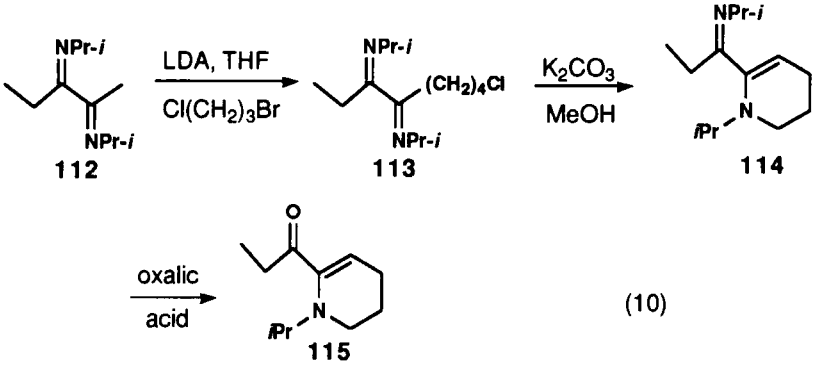


Scheme 16

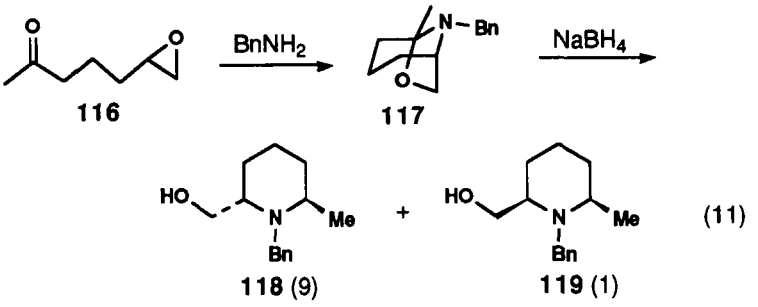
The 1,5-dialkyl-1,2,3,4-tetrahydropyridines **111**, easily accesible from δ-chloroaldimines **110**, are useful building blocks for alkaloid synthesis.[34] The synthetic strategy involves a straightforward construction of **111** from simple aldehydes **108** *via* imination to aldimines **109**, α-alkylation with 1-bromo-3-chloropropane to afford δ-chloroaldimines **110**, and ring closure with sodium isopropoxide to the final products (Eq. 9).



Similarily, the 1,6-dialkyl-1,2,3,4-tetrahydropyridine **115** was prepared from the α-diimine **112** (Eq. 10).[35]

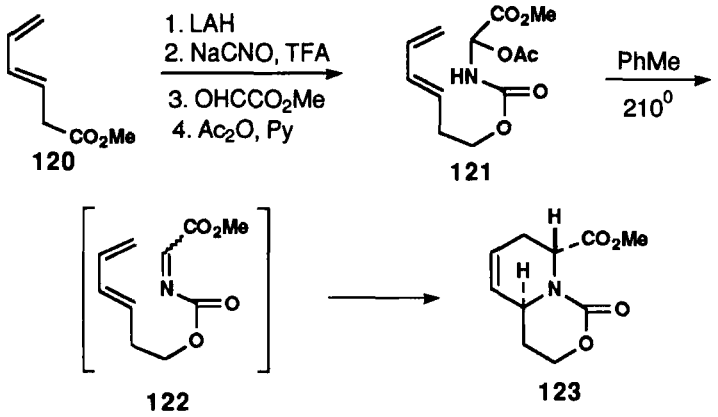


The imine-epoxide rearrangement, followed by hydride reduction has been used to prepare the substituted piperidine derivatives with control of stereochemistry.[36] Treatment of keto-epoxide **116** with benzylamine in the presence of 3Å molecular sieves gave the bicyclic product **117**. Reduction of **117** with $NaBH_4$ yielded the piperidine derivative as a mixture of *trans* -**118** and *cis* -**119** with the *trans* product predominating (Eq. 11). This methodology has been used to synthesize (+)-solenopsin A (**14**).



4. Diels-Alder Reactions

The Diels-Alder reaction of an imine with a diene offers a short and potentially stereospecific route to a wide range of the piperidine derivatives.[37] Weinreb reported that upon heating at 210° in toluene for 2h, compound **121** cyclized (80% yield) through the imine intermediate **122** to give the bicyclic adduct **123** (Scheme 17).[38] Compound **121** was prepared from diene ester **120** by a four-step procedure: 1. $LiAlH_4$; 2. NaCNO, TFA; 3. $OHCCO_2Me$; and 4. Ac_2O, Py.

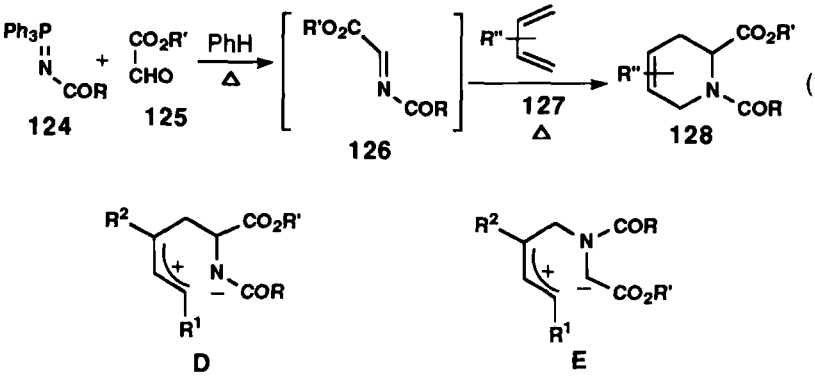


Scheme 17

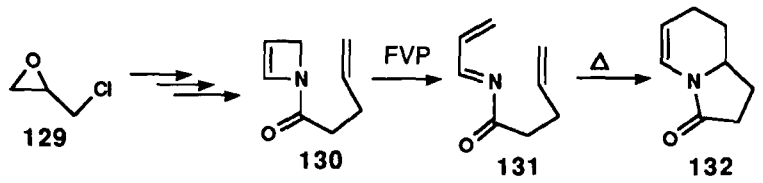
An intermolecular Diels-Alder reaction of imines **126**, prepared from *N*-acetylphosphineimine **124** and glyoxylates **125**, with dienes **127** to furnish the piperidine derivatives **128** was described by Jung (Eq. 12).[39]

Reaction of imines **126** with unsymmetrical dienes having a substituent in the 1-position proceeds regiospecifically with the substituent ending up α to the nitrogen atom in the product. As

expected the product was produced *via* the more stable polar transition state (or intermediate) **D**, in which the negative charge rests on the activated nitrogen atom, rather than **E**.



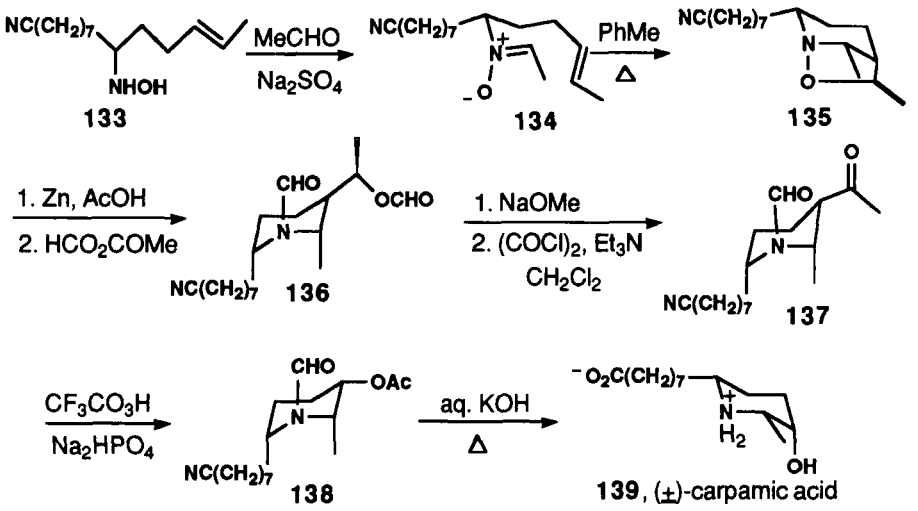
Several groups,[40-43] especially those of Fowler,[40] Ghosez,[41] and Boger,[42] have studied the use of azadienes to prepare piperidine compounds. Recently, Jung reported a novel approach for the preparation of 1-acyl-1-azabutadiene **131**, namely, the thermal electrocyclic ring opening of 1-acyl-2-azetine **130**, and subsequent Diels-Alder reaction of diene **131**.[44] Flash vacuum pyrolysis of **130** at 540-550° at 5 torr cleanly generated **131**, which upon refluxing in benzene for 28h produced the enamide **132** in 46% yield (Scheme 18). Compound **130** was prepared efficiently from epichlorohydrin (**129**) in five steps: 1. Ph_2CHNH_2; 2. (a) methanesulfonyl chloride (MsCl), Et_3N (b) HCl, Et_2O; 3. H_2, $Pd(OH)_2$; 4. $HC{=}(CH_2)_2COCl$; and 5. KOBu-*t*.



Scheme 18

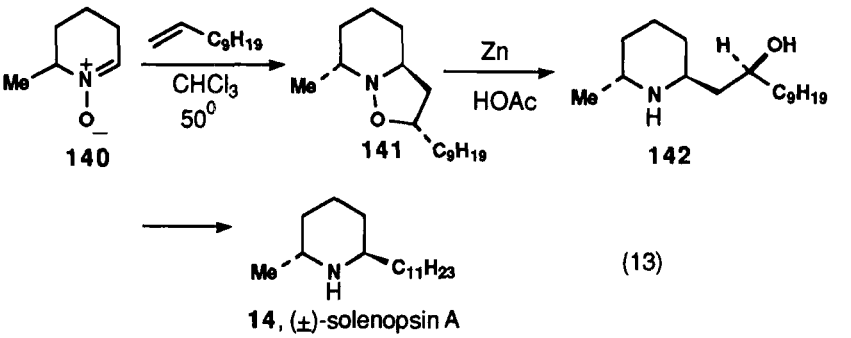
5. 1,3-Dipolar Cycloadditions

Nitrone cycloaddition is an efficient method to synthesize substituted piperidines.[45] Holmes reported that nitrone **134**, prepared from hydroxyamine **133**, underwent cycloaddition to give **135**.[46] Reductive cleavage of the N–O bond in **135**, followed by formylation of the resulting 1,3-amino alcohol, afforded **136**. Selective cleavage of the formate ester with methoxide yielded the corresponding secondary alcohol which was oxidized under Swern condition to give the methyl ketone **137**. Baeyer-Villiger oxidation of **137** gave acetate **138**, which upon vigorous base hydrolysis provided (±)-carpamic acid (**139**) (Scheme 19).

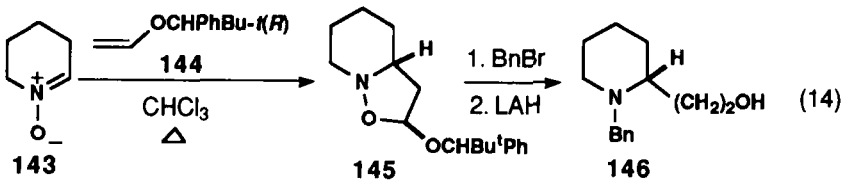


Scheme 19

Cycloaddition of an alkene to a 2-alkyl-2,3,4,5-tetrahydropyridine 1-oxide takes place preferentially by orthogonal approach of the alkene to the nitrone in a conformation in which the 2-alkyl substituent is equatorial, to give an isoxazolidine which furnishes a *trans*-2,6-dialkylpiperidine by reductive cleavage of the N–O bond.[47] Carruthers has used this methodology to prepare (±)-solenopsin A (**14**). 2-Alkyl-2,3,4,5-tetrahydropyridine 1-oxide (**140**) was reacted with undec-1-ene to give the isoxazolidine **141**, which was reductively cleaved by zinc in acetic acid to afford **142** as a single *trans* isomer. Conversion of **142** into (±)-solenopsin A (**14**) was effected by reduction of the corresponding phenoxythioxocarbonate with tri-*n*-butylstannane (Eq. 13).

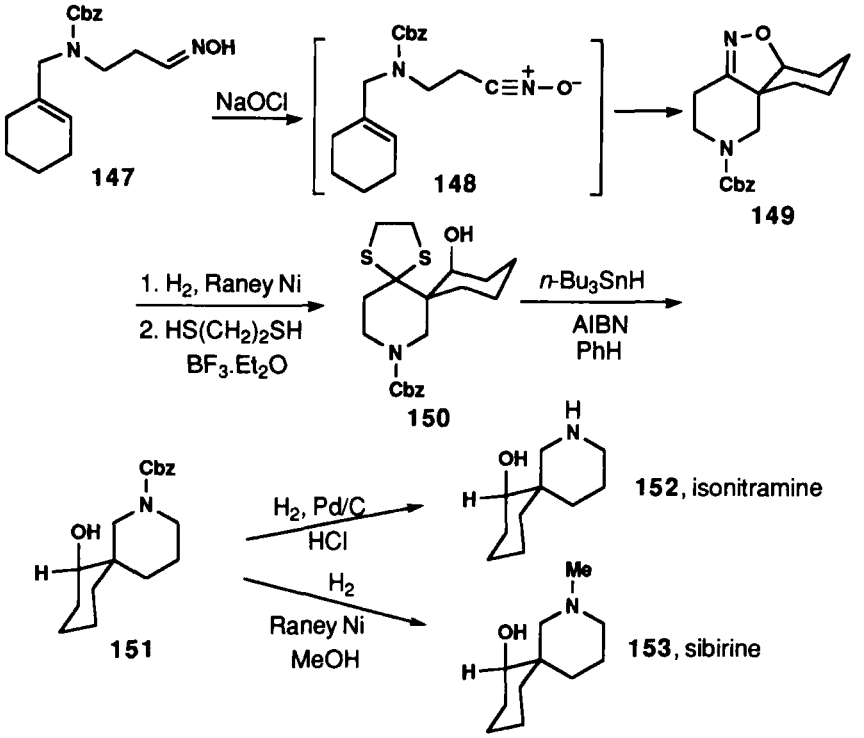


Chiral dipolarophiles have been employed in the asymmetric nitrone cycloaddition.[48] The cycloaddition of 2,3,4,5-tetrahydropyridine-*N*-oxide (**143**) with (*R*)-2,2-dimethyl-1-phenylpropyl vinyl ether (**144**) gave isoxazolidine **145** (Eq. 14). In order to determine the degree of chiral induction in this cycloaddition, compound **145** was converted into **146** by reduction of the derived *N*-benzyl bromide salt with $LiAlH_4$, and the optical purity was determined by ^1H NMR spectrum in the presence of a chiral shift reagent to have an e.e. >95%.



(14)

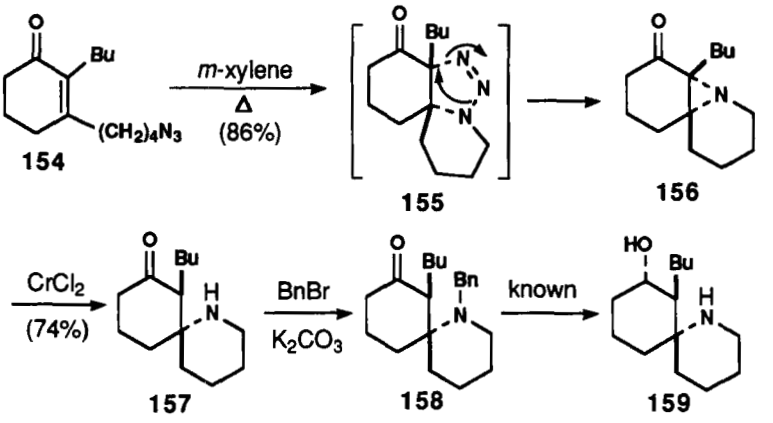
The nitrile oxide cycloaddition was also found to accommodate the construction of piperidine derivatives.[49] Kozikowski reported a synthesis of isonitramine (**152**) and sibirine (**153**) based on an intramolecular nitrile oxide cycloaddition.[49a] Treatment of oxime **147** with aqueous sodium hypochlorite gave the nitrile oxide **148** which was cyclized to **149**. Hydrogenation of **149** followed by conversion of the resulting carbonyl group into its dithiolane derivative afforded **150**. A standard tri-*n*-butyltin hydride reduction of **150** produced **151**. Lastly, removal of the Cbz group by hydrogenolysis gave isonitramine (**152**). By carrying out the hydrogenolysis of the Cbz group with Raney nickel in methanol, the *N*-methyl derivative of **152** was produced, which is the natural product sibirine (**153**) (Scheme 20).



Scheme 20

Sha applied an intramolecular 1,3-dipolar cycloaddition of an alkyl azide and an enone to a formal total synthesis of (±)-desamylperhydrohistrionicotoxin (**159**) (Scheme 21).[50] Upon refluxing of azide **154** in *m*-xylene an aziridine **156** was obtained through the intermediate triazoline **155**. Chromous chloride reduction of **156** gave amino ketone **157**, which was benzylated to **158**. Since

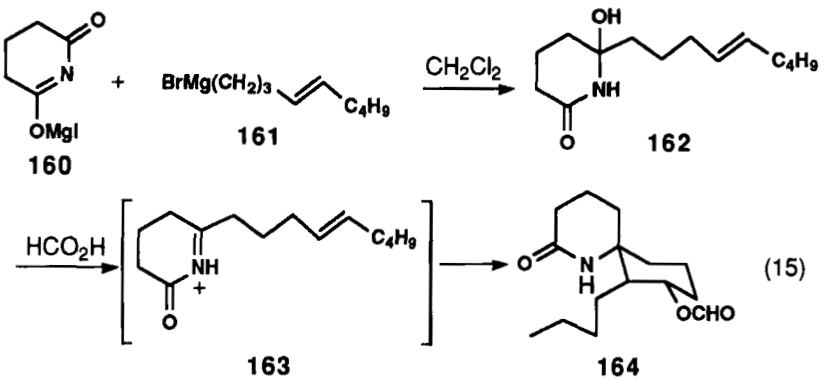
compound **158** had been converted into **159**,[27a] this work constituted its formal total synthesis.



Scheme 21

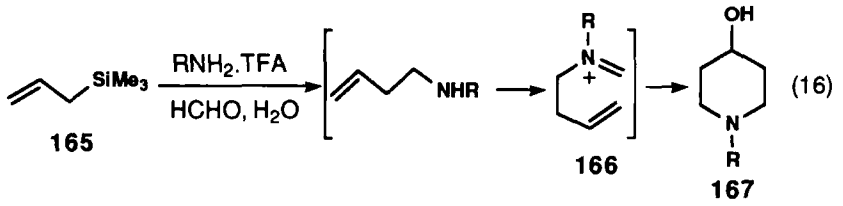
6. Alkene- and Alkyne-Iminium Ion Cyclizations

Intramolecular alkene-iminium cyclizations have been useful for the preparation of substituted piperidines.[51] Evans reported that treatment of carbinolamide **162**, prepared from the glutarimide salt **160** and the Grignard reagent **161**, with formic acid gave the iminium ion intermediate **163**, which was cyclized to afford lactam **164** (Eq. 15).[52] Compound **164** was a key intermediate in the synthesis of (±)-perhydrohistrionicotoxin.

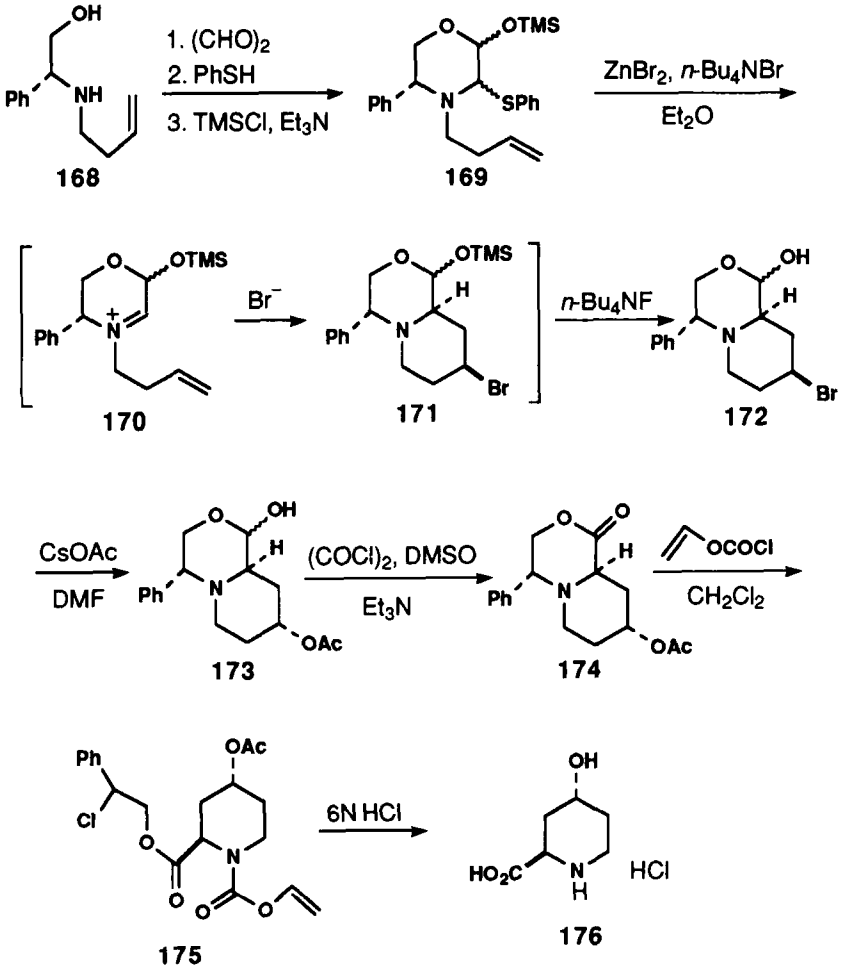


Grieco demonstrated that a variety of 4-hydroxypiperidines **167** may be formed under aqueous conditions by treating **165** with alkyl amines and formaldehyde. The homoallylic amine intermediate **166** underwent an iminium ion cyclization to give **167** (Eq. 16).[53]

Considerable attention has been drawn to the stereoselective synthesis of pipecolic acid derivatives because of their biological activity[6] and many of them are naturally occurring.[54] A preparation of optically pure 4-substituted pipecolic acid derivatives *via* iminium ion cyclizations was reported.[55]

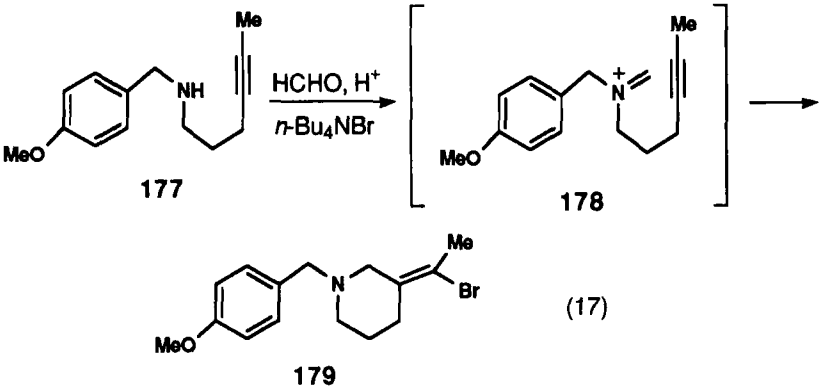


Treatment of **169**, prepared from (*R*)-*N*-(3-butenyl)-2-phenylglycinol (**168**), with zinc bromide and *n*-Bu_4NBr gave the intermediate **170**, which was cyclized to **171** and subsequently desilylated to **172**. Substitution of bromine by an acetoxy group was effected by cesium acetate and the resulting **173** was oxidized by the Swern method. Cleavage of **174** by vinyl chloroformate followed by acidic hydrolysis of the resulting carbamate **175** ultimately yielded (2*R*, 4*R*)-(+)-hydroxypipecolic acid (**176**) (Scheme 22).



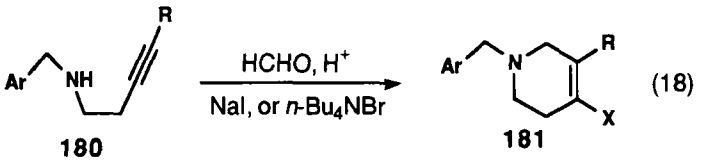
Scheme 22

Nucleophile-promoted alkyne-iminium ion cyclizations were described by Overman.[56] Treatment of **177** with formaldehyde in the presence of camphorsulfonic acid and *n*-Bu_4NBr afforded the exocyclic vinyl bromide **179** in 90% yield through the iminium ion intermediate **178** (Eq. 17).[56a] The



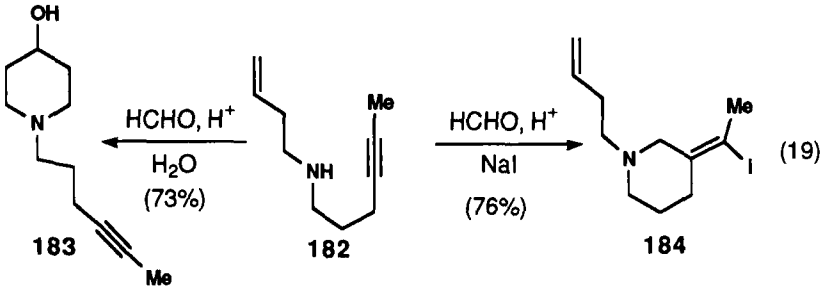
(17)

reaction failed without the addition of the nucleophile *n*-Bu_4NBr. Other nucleophiles such as NaI, NaN_3, or NaSCN could also be used under aqueous conditions to give vinyl iodide, vinyl azide, or vinyl thiocyanate, respectively. Weaker nucleophiles such as thiophenol were less effective, yielding <15% of the cyclization product. Cyclization of terminal alkyne **180a** or the silylalkyne **180b** occurred predominantly in the endocyclic sense to afford the 1,2,5,6-tetrahydropyridines **181** (Eq. 18).



(18)

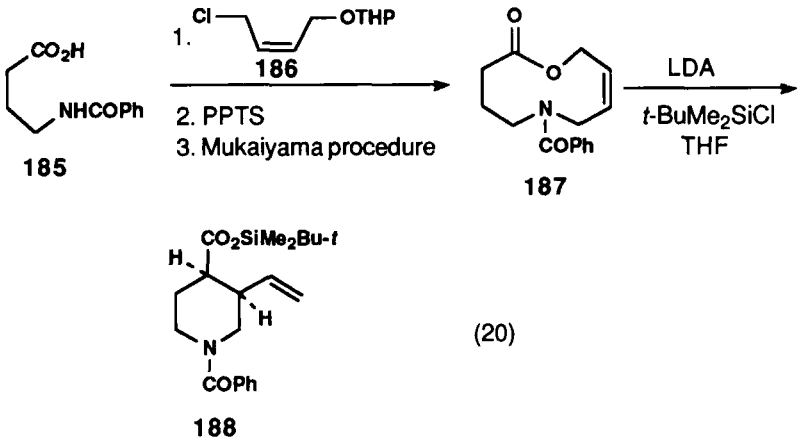
The pronounced sensitivity of alkynes to cyclizations in the presence of nucleophiles was illustrated by conversions of the formaldiminium ion derived from **182** in which an alkyne and alkene compete as intramolecular nucleophiles. Thus, while cyclization of **182** in H_2O (HCHO, camphorsulfonic acid, 100°) afforded the 4-hydroxypiperidine **183** in 73% yield, treatment of **182** under the same conditions in the presence of 10 equiv. of NaI afforded vinyl iodide **184** in 76% yield as a result of exclusive participation of the intramolecular alkyne nucleophile (Eq. 19).



(19)

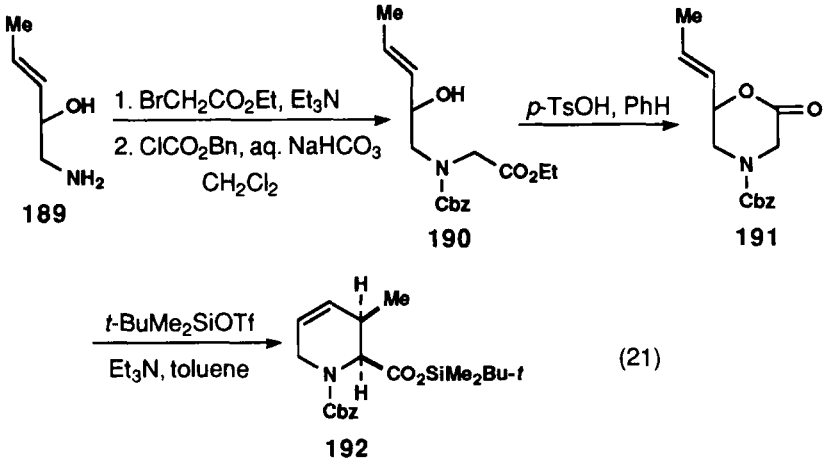
7. Claisen and Cope Rearrangements

Funk used a stereospecific Claisen rearrangement of the (*E*)-silyl ketene acetal derived from azalactone **187** as the key step in the construction of the 3,4-disubstituted piperidine ring.[57] Subjection of **187**, prepared from *N*-benzoyl-4-aminobutyric acid (**185**) by a three-step procedure (1. NaH, **186**; 2. pyridinium *p*-toluenesulfonate (PPTS), MeOH; 3. 2-chloro-1-methylpyridinium iodide, Et_3N, 0.005 M in MeCN), to the silylation conditions (1.2 equiv. of LDA, 1.2 equiv. of *t*-$BuMe_2SiCl$, THF, -70°) produced the expected rearrangement product **188** in 93% yield (Eq. 20).



(20)

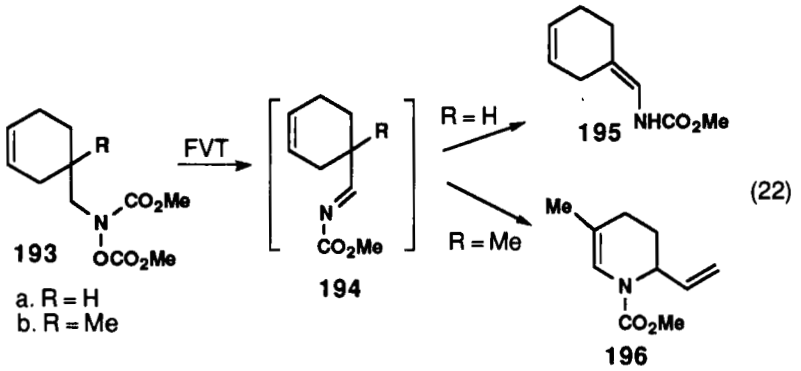
Angle reported a stereoselective synthesis of $\Delta^{4,5}$-pipecolic acid derivatives by the conformationally restricted ketene-acetal Claisen rearrangement.[58] The known amino alcohol **189** was alkylated with ethyl bromoacetate and the resulting secondary amine was protected as the carbobenzyloxy carbamate to give hydroxy ester **190**. Treatment of **190** with *p*-TsOH afforded lactone **191**, which was subjected to the silylation and rearrangement (*t*-$BuMe_2SiOTf/Et_3N$/toluene/reflux) to yield **192** in 75% yield (Eq. 21).



(21)

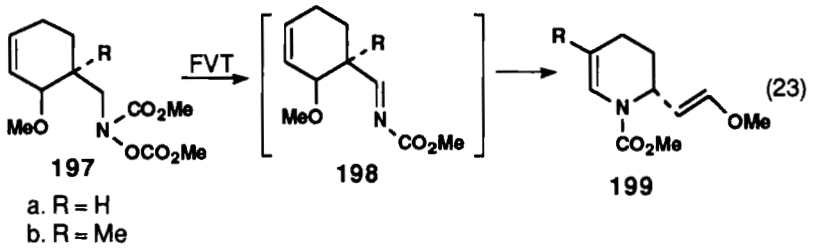
The 1-aza-Cope rearrangement of *N*-acylimines was studied by Fowler.[59] Flash vacuum pyrol-

ysis of **193b** gave the Cope rearranged product **196** in 10% yield. When R is H (**193a**), a *N*-acylimine-enamide isomerization occurred rather than the desired aza-Cope rearrangement and **195** was isolated in 30% yield (Eq. 22). However, compound **197b**, a methoxy substituted derivative of **193b**,



(22)

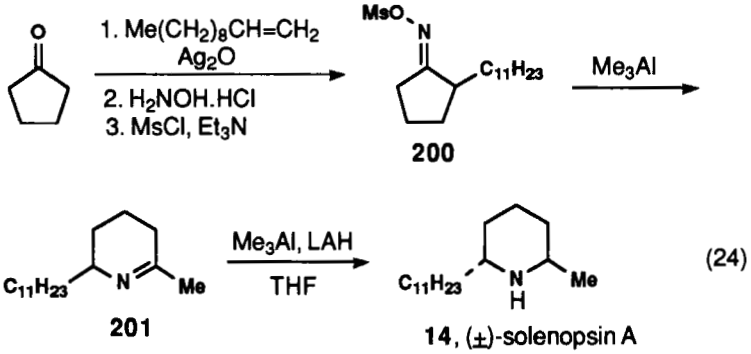
underwent the aza-Cope rearrangement at 50° to afford **199b** in 55% yield. In contrast to the unsubstituted derivative **193a**, **197a** also gave the rearranged product **199a** in 25% yield (Eq. 23).



(23)

8. Beckmann Rearrangement

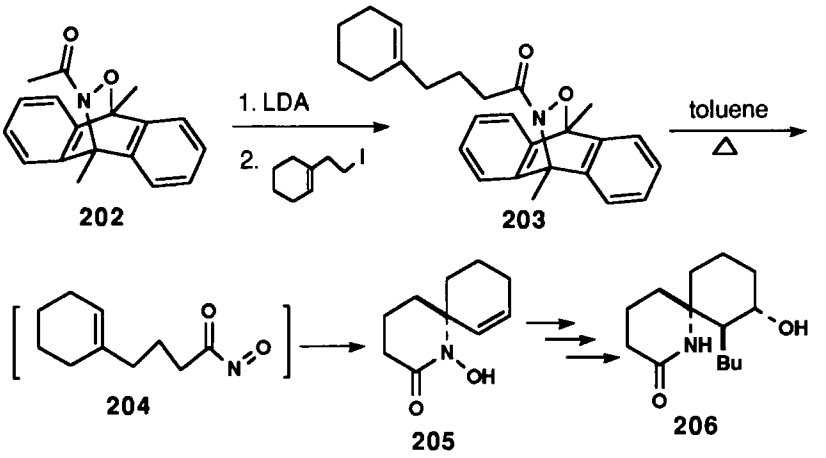
Yamamoto has developed an effective and convenient synthesis of (±)-solenopsin A (**14**) which involves the Beckmann rearrangement-alkylation reaction promoted by organoaluminum reagents and a stereoselective reduction of the imino functional group.[60] The starting oxime sulfonate **200** was prepared from cyclopentanone in three steps: 1. 1-undecene, Ag_2O; 1. $H_2NOH.HCl$; and 3. MsCl, Et_3N. Treatment of oxime mesylate **200** with trimethylaluminum gave the rearranged product imine **201**. Finally, a stereoselective reduction of the imine was realized by using $Me_3Al/LiAlH_4$ to afford almost exclusively (> 95%) the *trans* product, (±)-solenopsin A (**14**) (Eq. 24).



(24)

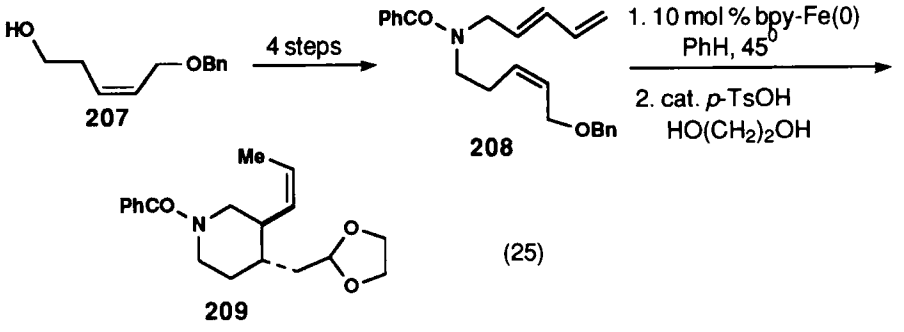
9. Ene Reactions

Keck described a formal total synthesis of (±)-perhydrohistrionicotoxin by utilizing an intramolecular ene reaction for construction of the spirocyclic skeleton.[61] Alkylation of the known **202**, a Diels-Alder adduct of (nitrosocarbonyl)methane and 9,10-dimethylanthracene, with (2-iodoethyl)-1-cyclohexene (LDA, THF-HMPA, -78°,1h, then -20°, 12h) proceeded smoothly to give **203** in 72% yield (Scheme 23). Thermolysis of **203** in refluxing toluene afforded the key spirocyclic hydroxamic acid **205** in quantitative yield *via* intramolecular ene reaction of an intermediate acylnitroso **204**. Compound **205** was subsequently converted into **206**, a known intermediate for the synthesis of (±)-perhydrohistrionicotoxin, by a series of steps.



Scheme 23

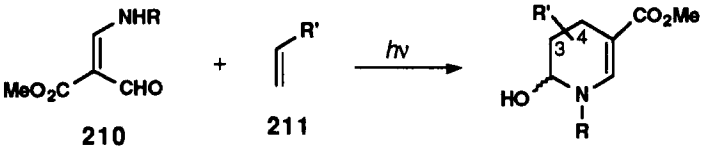
A stereoselective preparation of *N*-acylpiperidines using catalytic iron-mediated ene carbocyclization of trienes was reported by Takacs.[62] Treatment of azatriene **208**, prepared from (*Z*)-1-(benzyloxy)-2-penten-5-ol (**207**) *via* the sequence: 1. phthalimide, $EtO_2CN{=}NCO_2Et$, Ph_3P; 2. $H_2NNH_2.H_2O$, EtOH; 3. PhCOCl, pyridine; and 4. LDA, THF, (*E*)-1-chloro-2,4-pentadiene, with 10 mol percent iron catalyst effected carbocyclization to give a crude mixture of enol ethers, which were converted into acetal **209** in an overall 71% yield (Eq. 25).



(25)

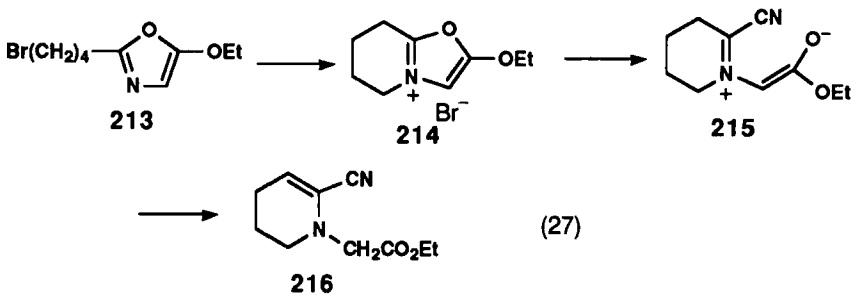
10. Miscellaneous Methods

Synthesis of 2-hydroxy-1,2,3,4-tetrahydropyridines **212** by regioselective photochemical cycloaddition of enamine-carbaldehydes **210** and alkenes **211** was described by Tietze (Eq. 26).[61] Compounds **210** were prepared by condensation of methyl diformylacetate with amines such as ammonia, methylamine, or *t*-butylamine. Irradiation of a solution of **210** and **211** (molar ratio 1:50) in Et_2O or CH_3CN with a high-pressure mercury lamp yielded **212**. When R' is an electron-withdrawing group (e.g., CN or CO_2Me), 4-substituted **212** was obtained. An electron-donating R' (e.g., OEt or $OSiMe_3$) gave 3-substituted **212**.



210 (R = H, Me, *t*-Bu) **211** **212** (26)

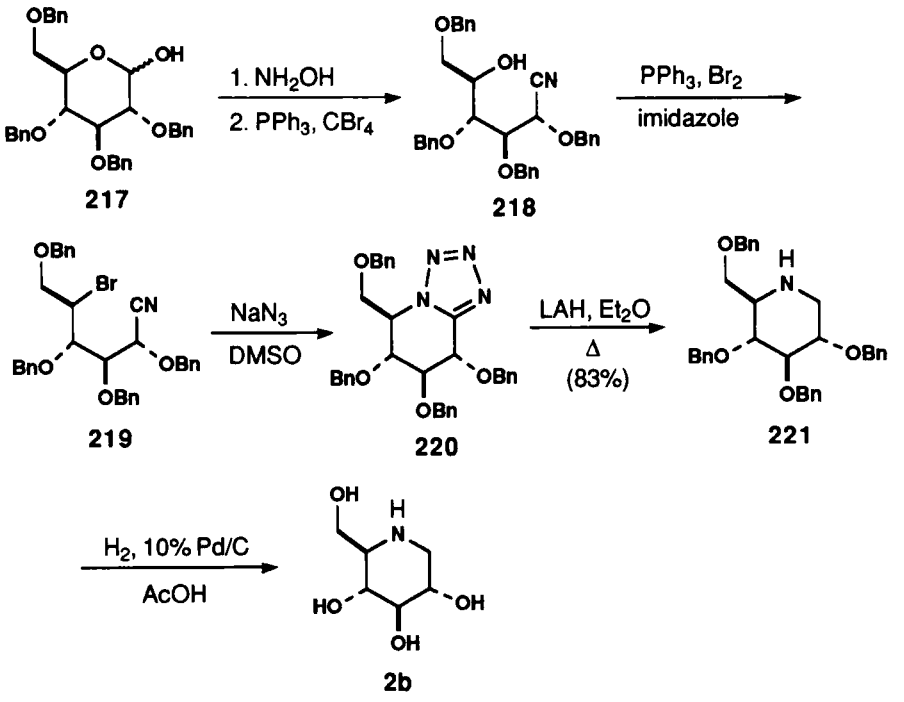
Hassner reported that upon heating of the oxazole **213**, prepared from 5-bromovaleronitrile and ethyl diazoacetate, with KCN in acetone in the presence of catalytic amount of NaI, the tetrahydropyridine **216** was produced in quantitative yield (Eq. 27).[62] Apparently, addition of cyanide ion to the oxazolium salt **214** was followed by ring opening to the azomethine ylide **215**, which underwent a proton shift to furnish **216**.



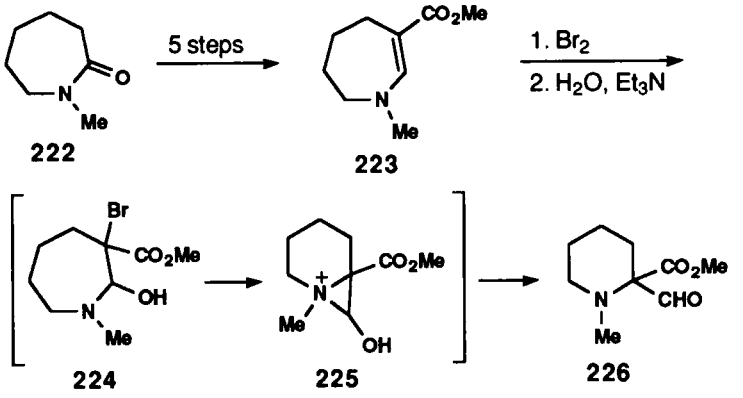
213 **214** **215** **216** (27)

A novel synthesis of 1-deoxynojirimycin (**2b**) from the tetrazole **220** appeared recently (Scheme 24).[63] The tetra-*O*-benzylglucose (**217**) was converted into the bromonitrile **219** by three steps: 1. NH_2OH; 2. CBr_4, PPh_3; and 3. Br_2, PPh_3, imidazole. Treatment of **219** with NaN_3 in DMSO at 110-125° gave **220**, which was reduced with an excess of $LiAlH_4$ to yield 83% of **221**. Hydrogenolysis of **221** (10% Pd/C, AcOH, 8 bar) afforded 1-deoxynojirimycin (**2b**).

Synthesis of 2,2-disubstituted piperidines *via* ring contraction of 7-membered heterocyclic enamino esters was reported.[64] *N*-methylcaprolactam (**222**) was converted into the enamino ester **223** by: 1. LDA, $(MeO)_2CO$; 2. P_2S_5; 3. MeI; 4. Et_3N; and 5. Raney Ni. After treatment of **223** with bromine followed by water-triethylamine a ring contraction occurred through intermediates **224** and **225** and the resulting piperidine **226** was isolated in 90% yield (Scheme 25). This methodology has been used to synthesize (±)-perhydrohistrionicotoxin.[64b]



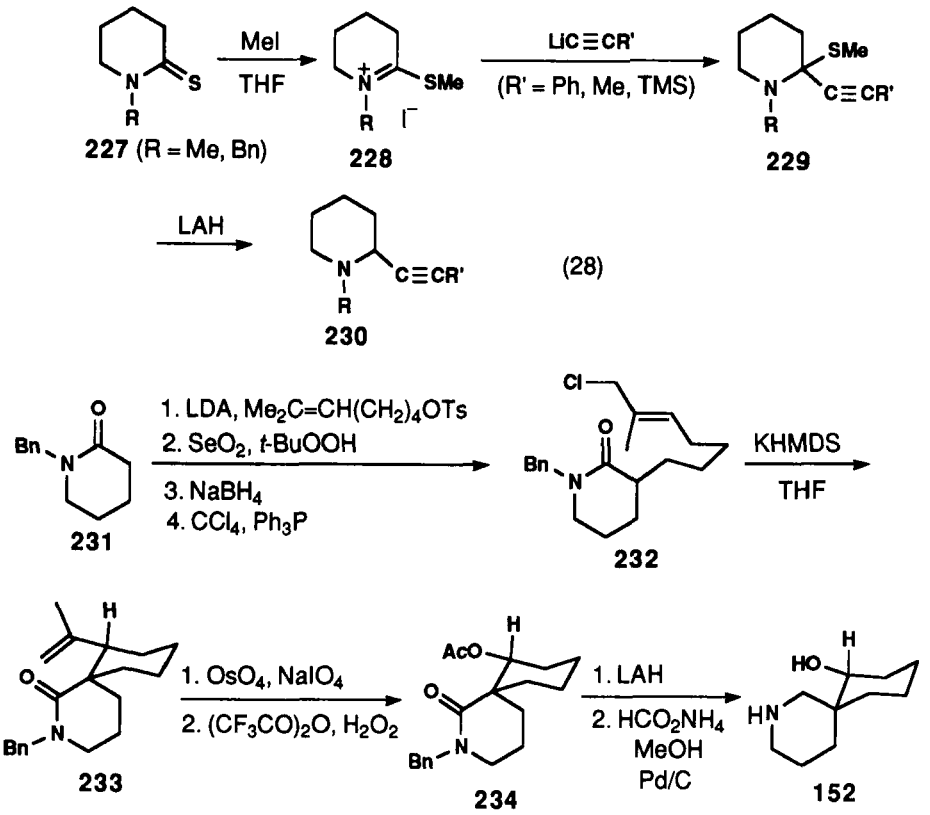
Scheme 24



Scheme 25

Takahata reported the preparation of 2-substituted piperidines **230** by first alkylation of the *S*-alkylthioamidium salts **228**, derived from thiolactams **227**, with lithium acetylides and then reduction with $LiAlH_4$ (Eq. 28).[65]

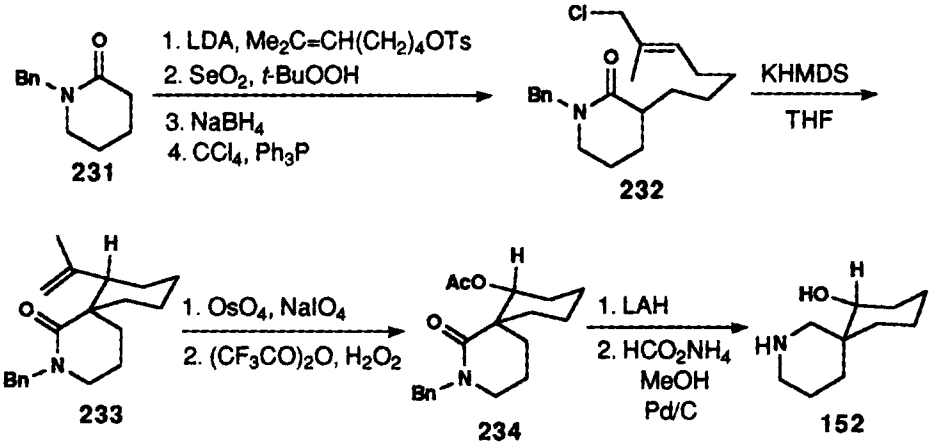
The spirocyclic alkaloid, isonitramine (**152**) has been synthesized in a highly stereoselective manner by intramolecular S_N2' lactam enolate alkylation route (Scheme 26).[66] Treatment of **232**, prepared from the known *N*-benzyl δ-valerolactam (**231**), with potassium hexamethyldisilazane



Scheme 26

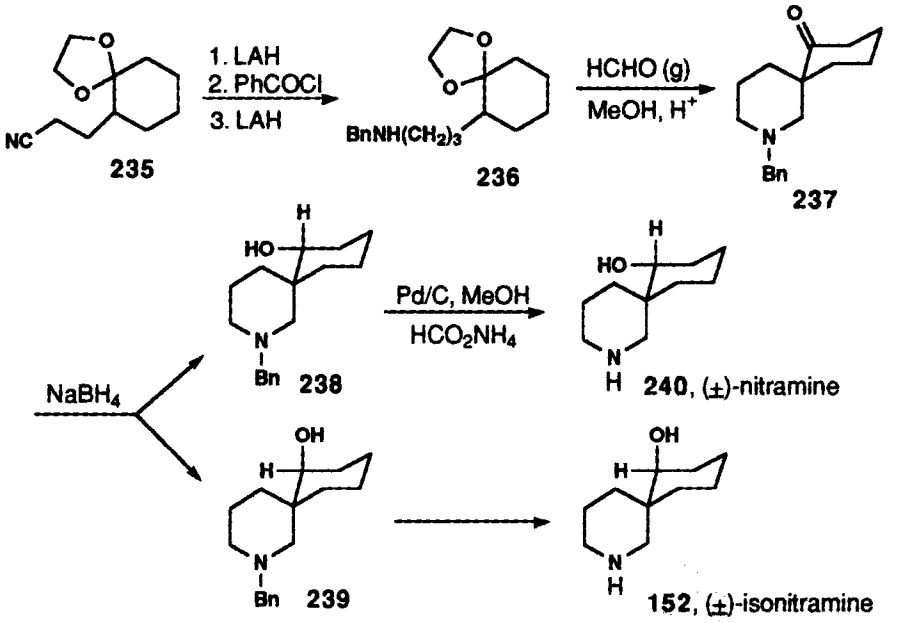
(KHMDS) in THF gave the cyclized product **233** in 62% yield with a 43 to 1 stereoselectivity. The observed high stereoselectivity can best be rationalized by considering that reaction proceeds via chair-like transition state geometry with the electrophilic allylic chloride in an equatorial position. The isopropenyl group of lactam **233** was transformed into an acetyl function by Lemieux-Johnson oxidation followed by Baeyer-Villiger oxidation to afford **234**. Reduction of **234** with $LiAlH_4$ produced *N*-benzyl isonitramine, which was hydrogenated to afford isonitramine (**152**).

Carruthers has synthesized the alkaloids (±)-nitramine (**240**) and (±)-isonitramine (**152**) by employing an intramolecular Mannich reaction (Scheme 27).[67] The readily available nitrile **235** was converted into **236** by sequential $LiAlH_4$ reduction, benzoylation, and again $LiAlH_4$ reduction. Cyclization was effected by bubbling gaseous formaldehyde into a solution of **236** in methanol containing hydrochloric acid. The resulting spirocyclic ketone **237** (60% yield) was reduced with $NaBH_4$ to afford a mixture of the alcohols **238** and **239** (ca. 1:1) which were separated by silica gel chromatography. Debenzylation of **238** and **239** gave **240** and **152**, respectively.



231 232 233 234 152

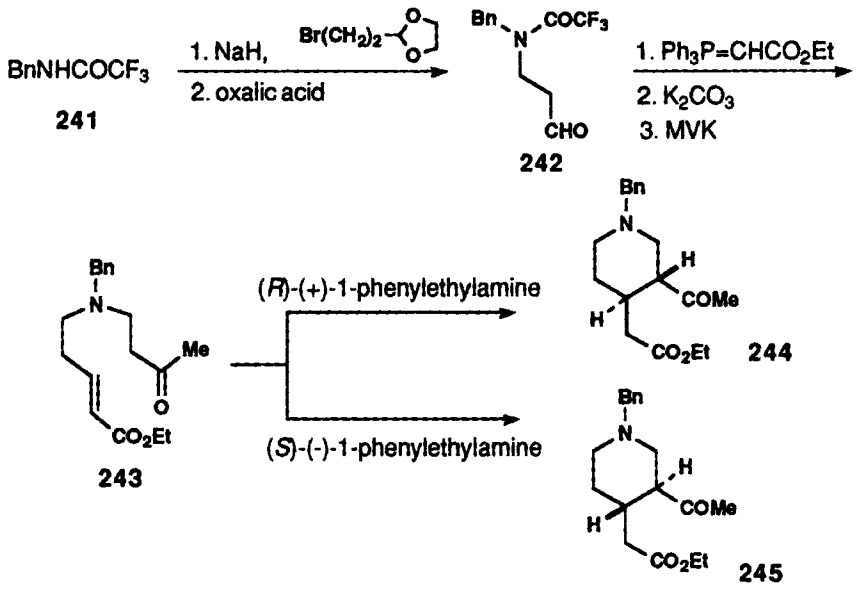
Scheme 26



235 236 237 238 240, (±)-nitramine 239 152, (±)-isonitramine

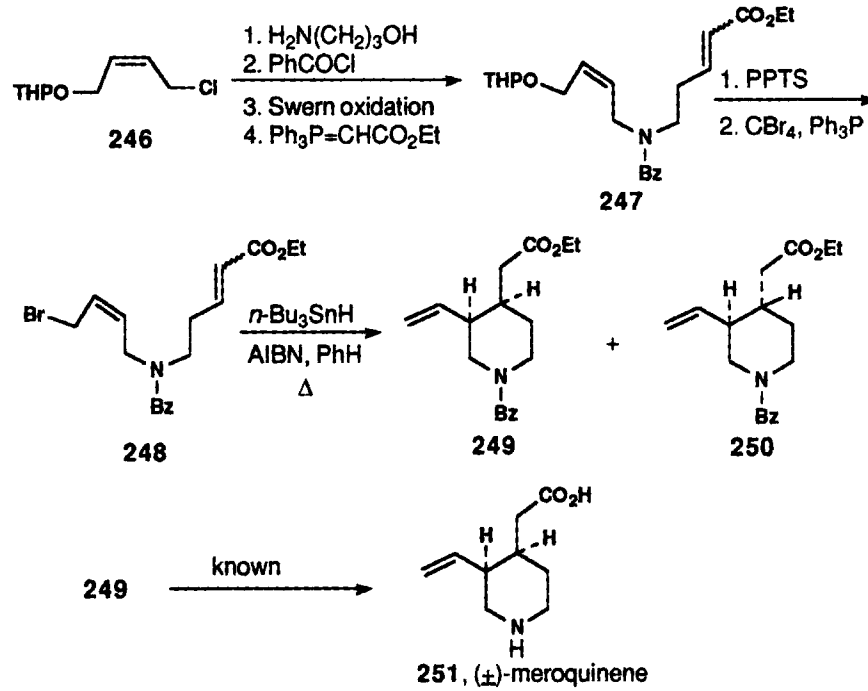
Scheme 27

An asymmetric intramolecular Michael reaction was used to construct the chiral piperidines **244** and **245** which were the intermediates for the synthesis of several alkaloids (Scheme 28).[68] Treatment of **241** with 2-(2-bromoethyl)-1,3-dioxolane using sodium hydride as a base followed by hydrolysis of the resulting acetal afforded the aldehyde **242**. The Wittig-type reaction of **242**, followed by base hydrolysis and reaction of methyl vinyl ketone (MVK), gave the key intermediate **243**. Compound **243** was then treated with 1 equiv. of (*R*)-(+)-1-phenylethylamine as a chiral base in THF at 5-10° in the presence of 5Å molecular sieves to furnish the optically active cycloadduct **244** in 90% e.e.(78% yield). On the other hand, **245** was obtained in 91% e.e.(83% yield) when (*S*)-(-)-1-phenylethylamine was used.



Scheme 28

Synthesis of (±)-meroquinene (**251**) *via* allylic radical cyclization was reported by Yoo (Scheme 29).[69] The key intermediate **248** was prepared from **246** in a straightforward manner as



Scheme 29

shown in Scheme 29. The separated *cis* and *trans* isomers of **248** were then subjected to the radical

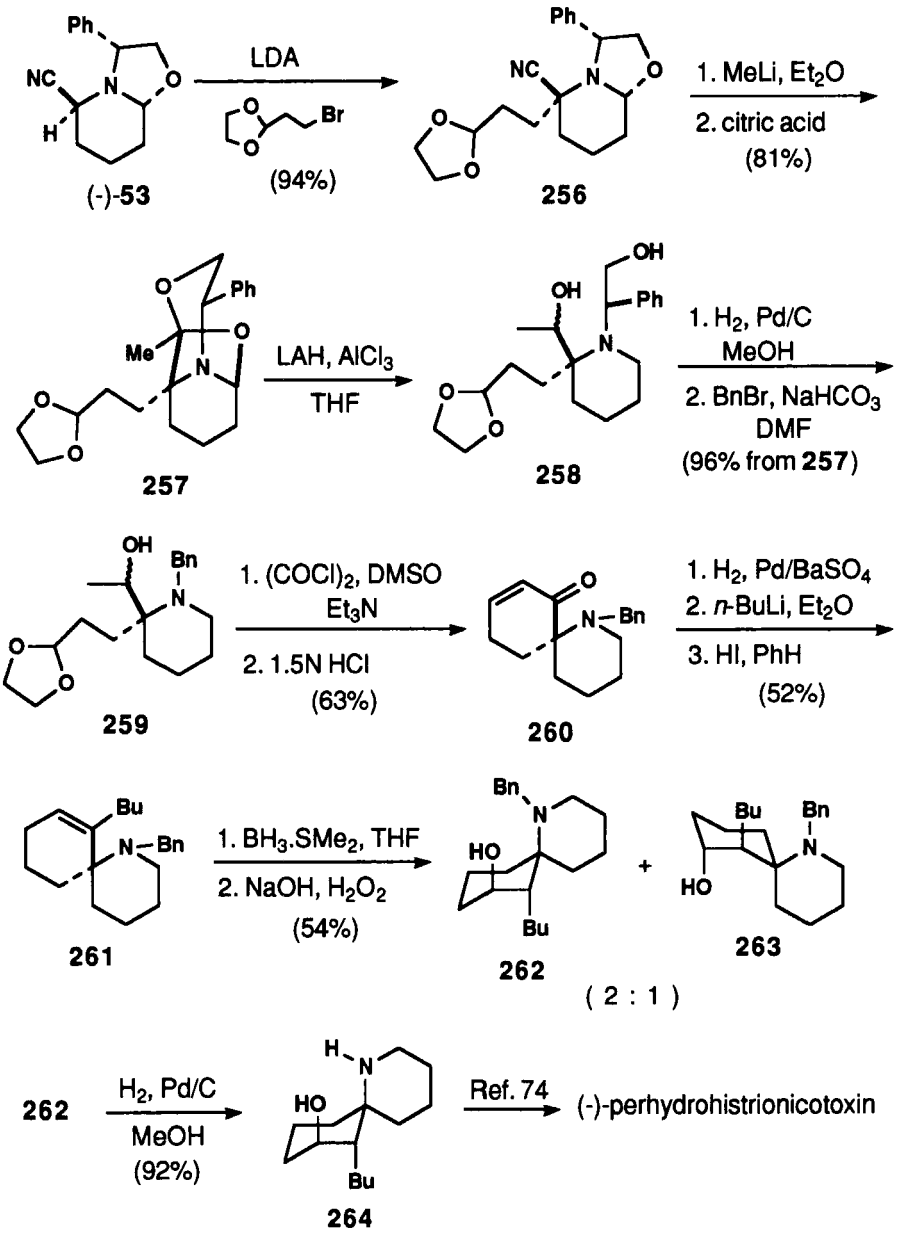
cyclization conditions (n-Bu_3SnH, azobisisobutyronitrile, benzene, reflux). In both cases a mixture of **249** and **250** was obtained (ca. 1:1). After separation by chromatography **249** was converted into **251** according to the known method.[70]

Pearson described the synthesis of azaspirocyclic **255** *via* the organoiron complex **252** (Scheme 30).[71] Diisobutylaluminium hydride (DIBAL-H) reduction of **252**, followed by conversion of the resulting alcohol into the tosylate, gave **253** which was then treated with Ph_3CBF_4 and worked up with aqueous NH_4PF_6 to furnish the hexafluorophosphate **254**. Treatment of **254** with benzylamine in refluxing nitromethane followed by oxidative removal of the iron afforded **255**. This methodology was applied to a formal total synthesis of (±)-perhydrohistrionicotoxin.[72]

II. REACTIONS

Husson has achieved an asymmetric formal synthesis of (-)-perhydrohistrionicotoxin (**1**) from the 2-cyano-6-phenyloxazolopiperidine (-)-**53** (Scheme 31).[73] The condesation of the anion derived from (-)-**53** with 2-(2-bromoethyl)-1,3-dioxolane proceeded with retention of configuration to give **256**. Treatment of **256** with methyllithium in ether followed by hydrolysis with citric acid afforded the tricyclic ketal **257**. Reduction of **257** with $LiAlH_4/AlCl_3$ yielded **258** which was treated sequentially with H_2/Pd–C to remove the chiral appendage, then with benzyl bromide to furnish **259** in an overall 96% yield. Swern oxidation of **259** followed by refluxing in 1.5N HCl gave the enone **260**. The next step was 1,4-reduction of the conjugated ketone with H_2/Pd–$BaSO_4$. It is interesting to note that the N-benzyl group was not affected under this condition. Treatment of the resulting ketone with n-BuLi and then with HI in refluxing benzene afforded the olefin **261**. A hydroboration-oxidation reaction of **261** gave the epimeric alcohols **262** and **263** in a 2:1 ratio. Finally, hydrogenolysis of **262** yielded (-)-**264**. Since the transformation of (±)-**264** into (±)-perhydrohistrionicotoxin is known,[74] the synthesis of (-)-**264** represents a formal synthesis of (-)-perhydrohistrionicotoxin (**1**).

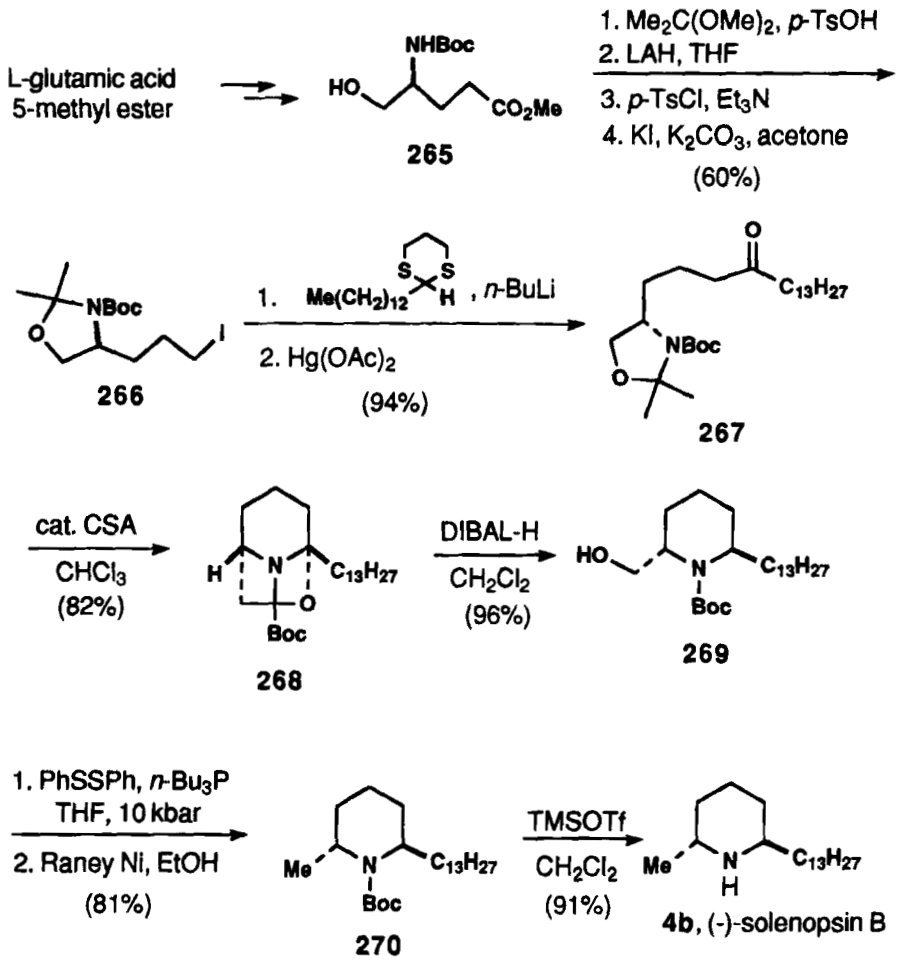
An enantioselective synthesis of (-)-solenopsin B (**4b**) was described by Kotsuki starting from L-glutamic acid 5-methyl ester, in which stereoselective reduction of the bicyclic N,O-ketal **268** with DIBAL-H was the key step (Scheme 32).[75] A similar strategy was disclosed by Wasserman for the synthesis of racemic compounds.[36] L-Glutamic acid 5-methyl ester was first converted into **265** according to the known method.[76] Then compound **265** was transformed into **267** in a straightforward manner as shown in Scheme 32. Upon treatment **267** with a catalytic amount of (+)-(S)-camphor-10-sulfonic acid (CSA) in refluxing chloroform, a transketalization occurred to yield the bicyclic N,O-ketal **268**. Reduction of **268** with DIBAL-H in CH_2Cl_2 at 0° provided the *trans* alcohol **269**. The stereoselectivity of this reduction was excellent (>99%) judging by the TLC and ^1H NMR of the crude products. Reaction of **269** with the Hata's reagent, n-Bu_3P-PhSSPh,[77] at 10 kbar pressure and 62° for 40h followed by desulfurization with Raney Ni gave the deoxygenated product **270**. Without using the high pressure, the sulfurization reaction was slow and the yield of the resulting phenylsulfide was only 28% along with 55% of the recovery starting material. Finally, deprotection of the Boc group with 3 equiv. of trimethylsilyl triflate in CH_2Cl_2 afforded (-)-solenopsin B (**4b**).



Scheme 31

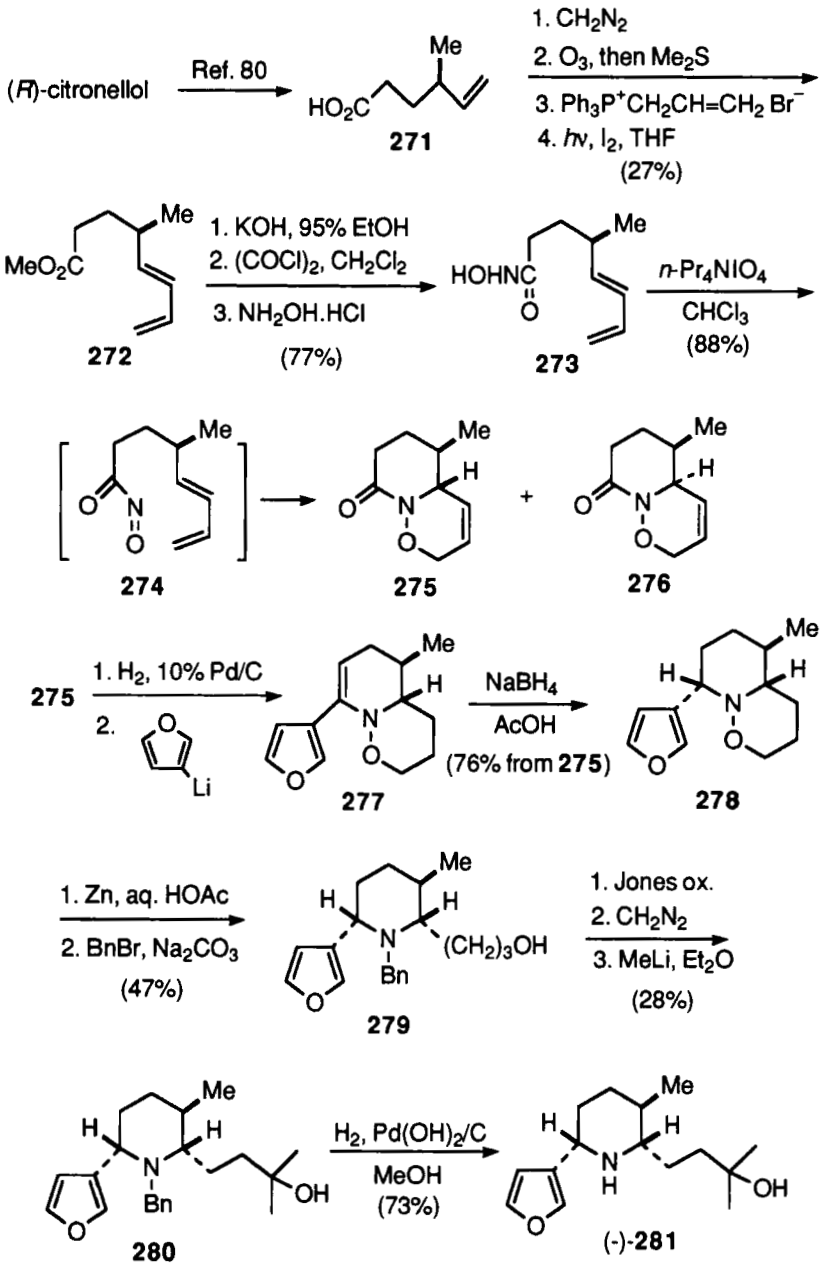
Kibayashi has reported the total synthesis of alkaloids such as (±)-dihydropinidine (**16**) by intramolecular nitroso Diels-Alder reaction.[78] Recently, he described the total synthesis of (-)-nupharamine (**281**) *via* an asymmetric nitroso Diels-Alder reaction (Scheme 33).[79]

The starting compound **271** was prepared from (*R*)-citronellol according to the known procedures.[80] Then **271** was converted into the key intermediate **273** uneventfully as shown in Scheme 33.



Scheme 32

Oxidation of **273** with tetrapropylammonium periodate at 0° resulted in *in situ* generation of the *N*-acylnitroso compound **274**, which smoothly underwent intramolecular [4+2] cycloaddition to afford a 1.8:1 mixture (88% yield) of the oxazino lactams **275** and **276**. Hydrogenation of the chromatographically separated **275** followed by treatment with 3-lithiofuran in ether gave the enamine **277**, which was without isolation subjected to $NaBH_4$ reduction to provide **278** in an overall 76% yield. Reductive N–O bond cleavage with zinc in aqueous acetic acid followed by reaction with benzyl bromide afforded **279**. Compound **279** was then converted into the tertiary alcohol **280** by 1. Jones oxidation; 2. CH_2N_2; and 3. excess MeLi, Et_2O, -78°. Finally, the benzyl group was removed by hydrogenolysis to yield (-)-**281** in 73% yield.



Scheme 33

III. CONCLUSION

In this review we have attempted to include various synthetic methodologies to prepare substituted piperidines. We have also examplified several recent asymmetric syntheses of piperidine alka-

loids in the *Reactions Section* because we believe that asymmetric synthesis of substituted piperidines will become more and more important. We attempted to cover all pertinent references although a few valuable contributions might have been missed.

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