A Convenient Access to the Piperidine Ring by Cyclization of Allylsilyl Substituted *N*-Acyliminium and Iminium Ions: Application to the Synthesis of Piperidine Alkaloids

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Abstract: This review relates a new access to the piperidine ring by intramolecular cyclization of acyl iminium and iminium ions substituted by an allylsilyl side chain as an internal Π-nucleophile. This methodology was applied to the synthesis of piperidine alkaloids.

Keywords: Piperidine, iminium ions, *N*-acyliminium ions, indolizidine, quinolizidine.

1. INTRODUCTION

The piperidine ring is a structural subunit found in a large number naturally occurring alkaloids. The stereoselective synthesis of functionalized piperidines has received considerable attention due to the broad range of their biological activity and their versatility as key synthetic intermediates [1].

As part of our program to expand the synthetic utility of allylsilyl functionalized substrates for the synthesis of piperidine-containing natural products [2,3], we have imagined a scheme where the piperidine ring would be formed by a Mannich type intramolecular cyclization reaction starting from substituted amino and amido ethylallylsilyl derivatives.

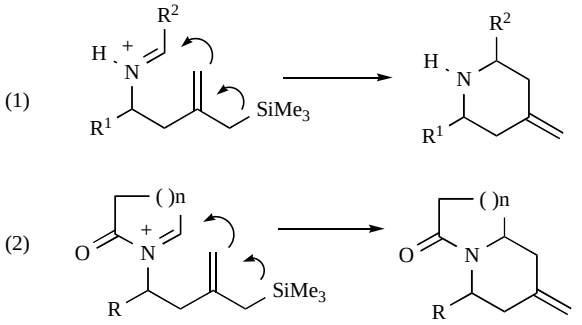

Fig. (1). Allylsilane- iminium and *N*-acyliminium cyclizations.

These reactions have proved to be a very powerful method for elaboration of substituted piperidine rings (eq. 1) and indolizidine and quinolizidine ring systems (eq. 2) with an efficient control of stereoselectivity.

2. SUBSTITUTED PIPERIDINES

2.1. 2-Indolyl-4-methylenepiperidines

The synthesis of protected 2-aryl-4-piperidines by an intramolecular Mannich type cyclization of imino acetals has been studied extensively in the last decades [4-6] as their application as intermediates to the synthesis of polycyclic compounds with potential therapeutic activity [7-9].

2-Aryl-4-methylenepiperidines can be prepared from the corresponding 2-aryl-4-piperidones [10]; however, the direct synthesis of methylenepiperidines has been described using allylsilanes [11] and vinylsilanes [12].

We have found that intramolecular cyclization of an allylsilane on an indoloimino group constituted an excellent route to 3-indolyl-4-methylenepiperidines [13]. Condensation between 1-(phenylsulfonyl)indole-3-carbaldehyde **(1)** and aminoallylsilane **(2)** in dry benzene afforded imine **(3)** which was cyclized with dry p-TsOH. The cyclization process (*via* the iminium salt **(4))** led to the expected 4-methylenepiperidine **(5)** as the major product (51% yield) accompanied by tetrahydropyridines **(6)** (10%) resulting from the double bond isomerisation in the acidic reaction conditions.

Then, this methodology was applied to the synthesis of 2-methyleneindolo [2,3-a]quinolizidines **(9)** which can be considered as valuable intermediates of the pentacyclic normavacurine derivative **(7)** (R=H) *via* the epoxyindolo [2,3-a]quinolizidine **(8)** (R = H) [14].

The synthesis of the *N*-hydoxyethylpiperidine **(10)** (Scheme **3**) has recently been described by us from the iminoallylsilane **(3)** through an intramolecular Mannich type reaction (Scheme **1**) [13]. Treatment of the alcohol **(10)** with t-BuOK for 3h at 0°C followed by reduction of the spiroindolenine **(11)** afforded 4-methyleneindolo [2,3-a]quinolizidine **(12)** as major product in 82% yield. Products **(13)** (<5%) and tetrahydropyridine **(14)** (8%) were isolated as by products.

The efficient preparation of the 4-methyleneindolo [2,3-a]quinolizidine **(12)** in three steps from allylsilane **(3)** constitutes a new formal synthesis of indole alkaloid normavacurine basic framework.

In the context of our studies on the synthesis of indolo [2,3-a]quinolizidine systems by means of intramolecular cyclization of *N*-(2-hydroxyethyl)-2-(1-phenylsulfonyl-3-

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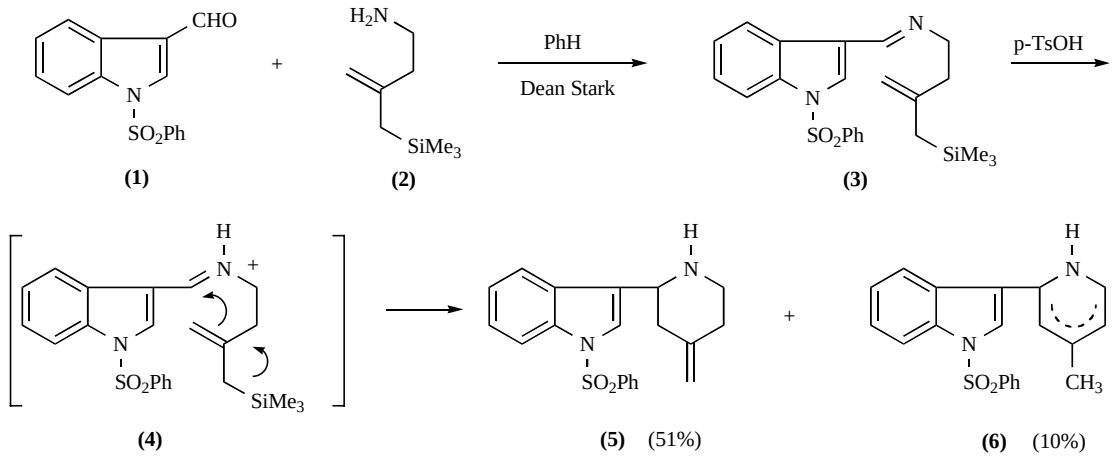
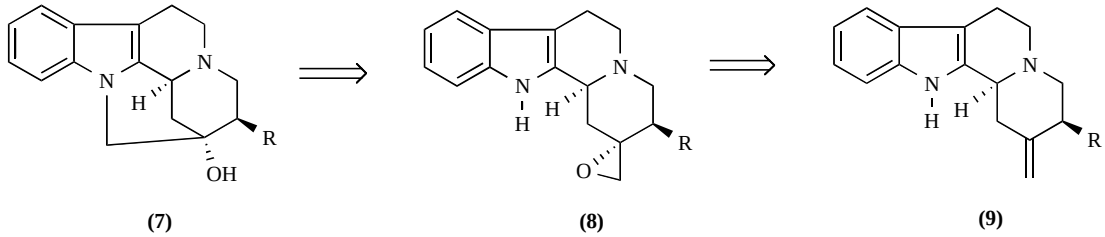
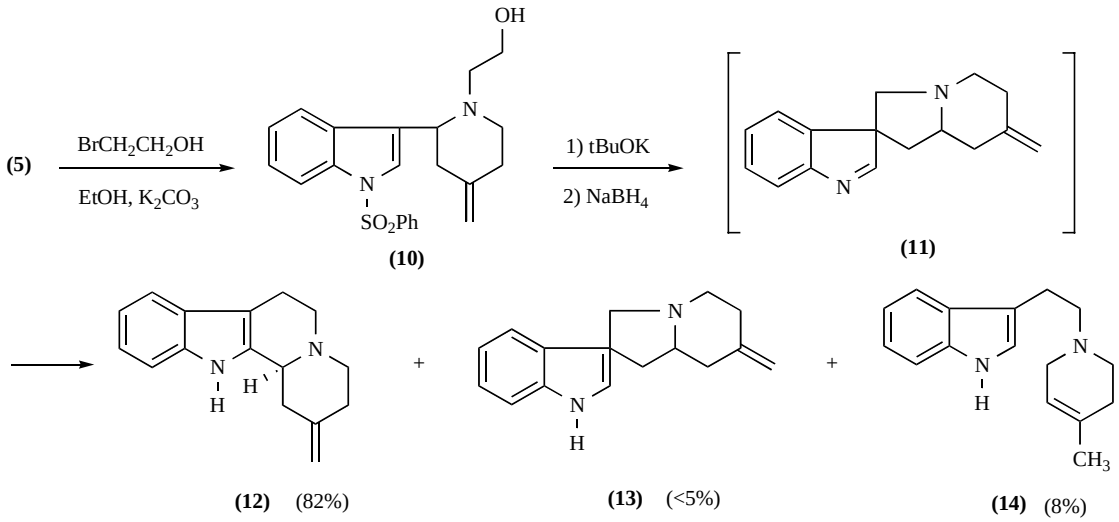


Scheme 1. Synthesis of 2-indolyl-4-methylenepiperidines.



Scheme 2. Retrosynthetic analysis of 2-methylenindolo- [2,3-a]quinolizidines.



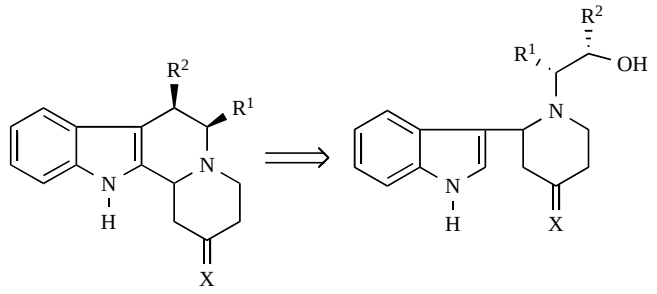
Scheme 3. Synthesis of 2-methylene-4-indolo[2,3-a]quinolizidines.

indolyl)piperidine (**16**), we described recently the preparation of racemic 2-methyleneindolo[2,3-a]quinolizidine **(15)** [15].

We have chosen to use (*R*)-phenylglycinol as asymmetric starting primary amine ; because of its suitable functionalization for our final purposes and its well known chiral induction on C-2 pyridines derivatives [16].

The preparation of piperidines **(16)** was carried out by condensation of aminoallylsilanes **(17)** and **(17a)** with 1-phenylsulfonylindole-2-carbaldehyde **(18)**. Condensation of indolecarbaldehyde **(18)** with aminoallylsilanes **(17,17a)** in refluxing CH_2Cl_2 in the presence of 4Å molecular sieves led in to the formation of oxazolidines **(19a)** and **(19b)**, but after longer reaction times (14 h) a 1.5 : 1 mixture of C-2 epimeric piperidines **(16a)** and **(16b)** was obtained with a 41% yield (Scheme **6**).

Then, piperidine **(16a)** was submitted to K^tBuO treatment followed by addition of $BF_3.Et_2O$ to promote the rearrangement to the desired quinolizidines, unfortunately only degradation products were obtained (Scheme **7**).

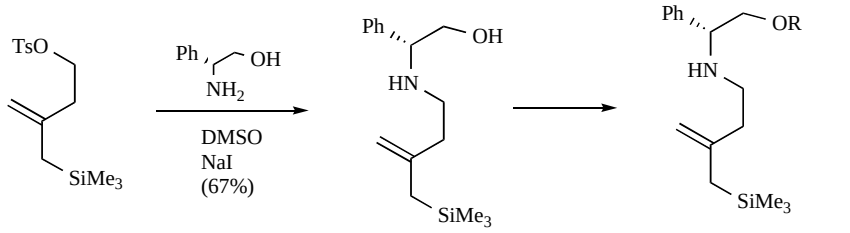


(15) X = CH_2, R^1 = R^2 = H **(16)** X = O

Scheme 4. Retrosynthetic analysis of 2-indolyl-4-methylenepiperidines.

products and, as contrained α-aminoacids, they have been used as building blocks in the synthesis of peptidomimetics. We have developed a new access to 5-substituted pipecolic acids based on an intramolecular allylsilane-iminium ion addition. Our approach relies on chiral *N*-cyanomethyl-4-phenyloxazolidine **(21)** which is efficiently prepared from (*R*)-(-)-phenylglycinol. According to the literature procedure [18], **(21)** was alkylated with iodide **(23)** derived from alcohol **(22)** [19] to afford a 3 : 1 mixture of the allylsilyl diastereomers **(24)** and **(25)** in 75% yield (Scheme **8**).

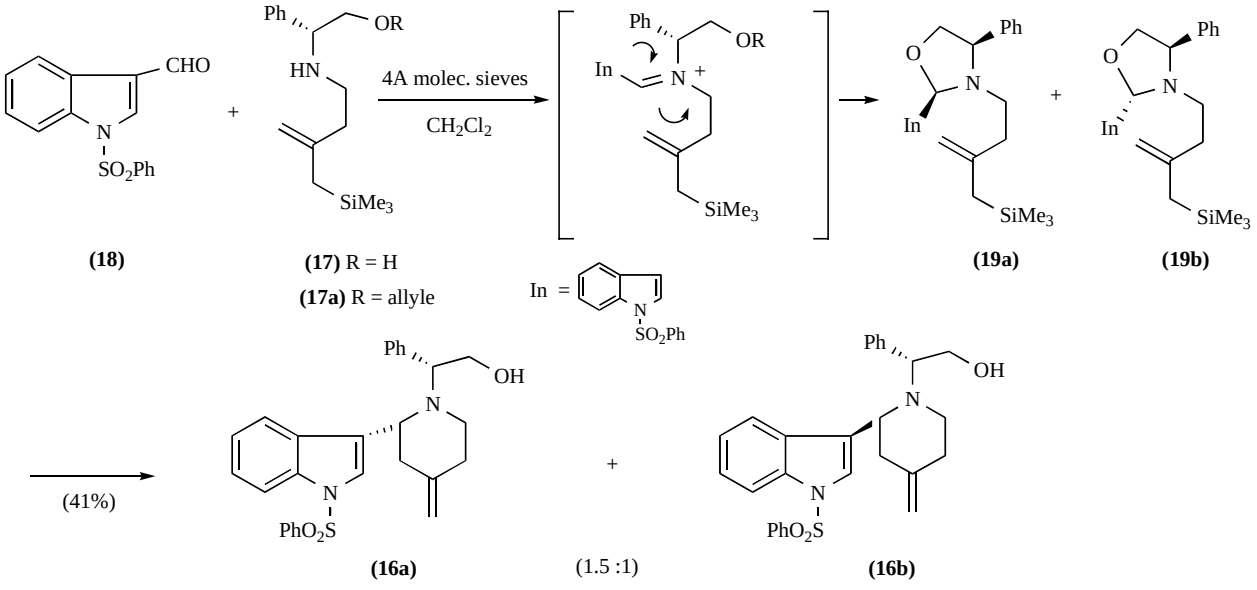
The intramolecular cyclization reaction was performed by treating the oxazolidines **(24)** and **(25)** with trimethylsilyltrifluoromethanesulfonate (TMSOTf). In these condi-



(17)

(17a) R = allyl
(17b) R = TBDPS
(17c) R = TMS

Scheme 5. Synthesis of chiral aminoallylsilanes.



(18) **(17)** R = H **(17a)** R = allyle **(19a)** **(19b)**

(41%) **(16a)** (1.5 :1) **(16b)**

Scheme 6. Synthesis of chiral 2-indolyl-4-methylenepiperidines.

In conclusion, a serie of diastereomeric piperidines **(16)** has been obtained and characterized. The cyclization of these compounds was studied, we only observed a degradation of the starting material and not the formation of the desired attended quinolizidine **(20)**.

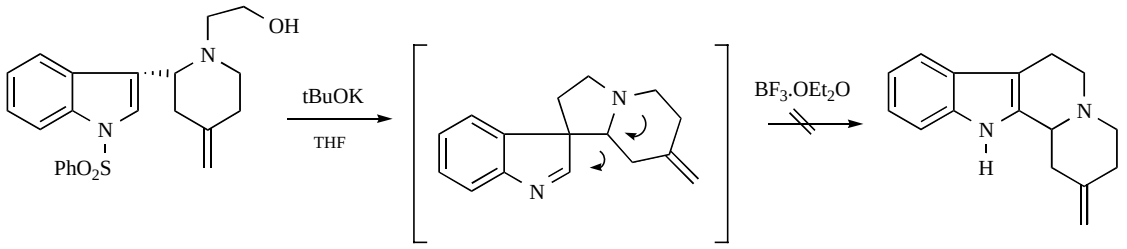
2.2. 5-Substituted Pipecolic Acids

Substituted pipecolic acids are the subject of many investigations [17]. They have been used as key intermediates in the synthesis of different types of piperidine-like natural

tions, piperidines **(27)** were obtained in 96% yield *via* the iminium ion intermediate **(26)** (Scheme **9**).

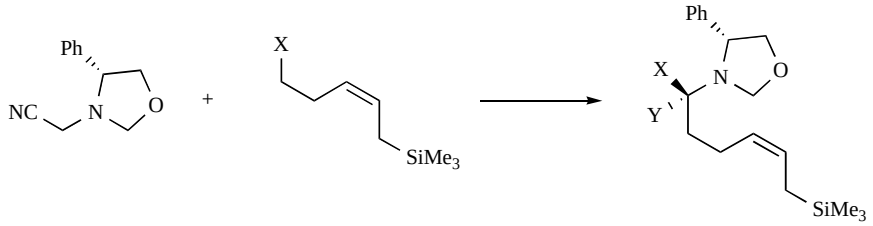
Stirring a solution of 2-cyanopiperidines **(27a)** and **(27b)** in a 1M solution of HCl gas in ethylacetate afforded a 4 : 1 mixture of lactones **(28)** and **(29)** in 77% yield. Similar reaction of **(27c)** gave lactone **(30)** in 60% yield (Scheme **10**).

Lactones **(28), (29)** and **(30)** were quantitatively converted to the corresponding pipecolic acid derivatives **(31), (32)** and **(33)** (Scheme **11**) respectively, upon cleavage of the lactone ring and hydrogenolysis of the benzylic O-N bond in the presence of Pearlman's catalyst [20].



(16a) **(20)**

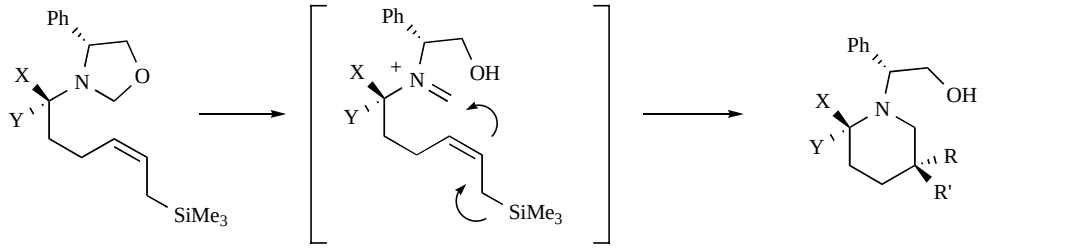
Scheme 7. Cyclization of piperidine **(16a)**.



(21) **(22)** X = OH
(23) X = I

(24) X = CN, Y = H
(25) X = H, Y = CN

Scheme 8. Synthesis of allylsilyloxazolidines.

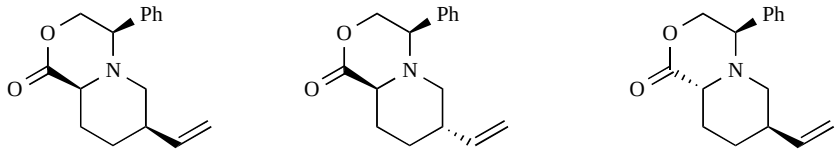


(24) X = CN, Y = H
(25) X = H, Y = CN

(26)

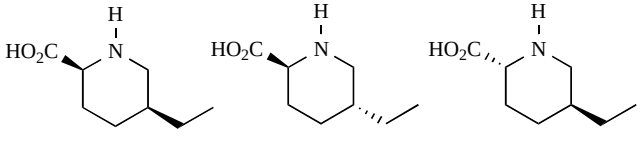
(27a) X = CN, R = H, R' = CH=CH$_2$
(27b) X = CN, R' = H, R = CH=CH$_2$
(27c) X = R = H, Y = CN, R' = CH=CH$_2$

Scheme 9. Synthesis of piperidines **(27)**.



(28) **(29)** **(30)**

Scheme 10. Piperidinolactones.



(31) **(32)** **(33)**

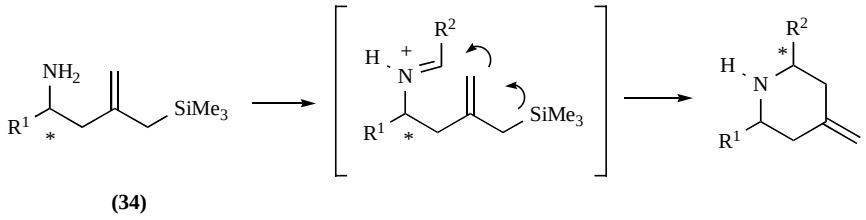
Scheme 11. 5-Ethyl pipecolic acids.

2.3. 2,6-cis-Disubstituted 4-methylenepiperidines

Many natural biologically active compounds contain the piperidine ring system as a common structural element. Among the numerous piperidines, cis and trans-2,6-dialkyl-piperidines represent an important class of alkaloids isolated from insects, amphibians or plants [21]. The stereoselective synthesis of piperidines, and notably 2,6-cis-disubstituted piperidines, has received considerable attention [22,23].

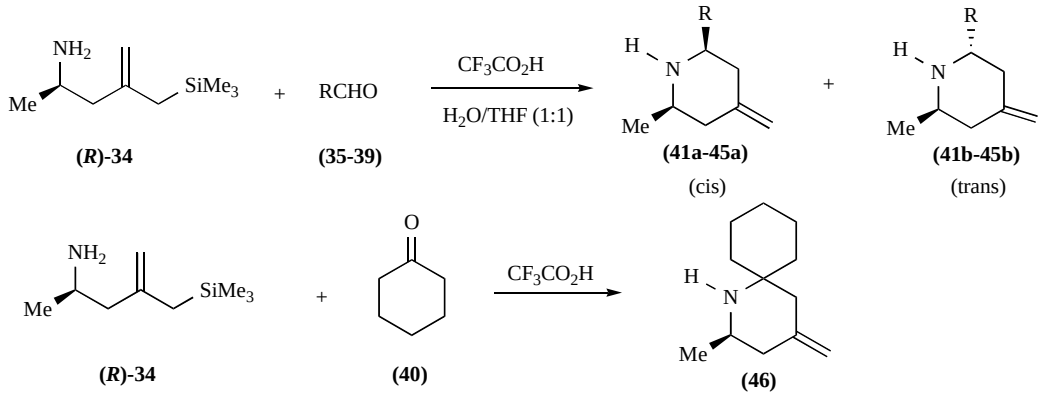
In our case, the piperidine ring would be formed by a Mannich type intramolecular cyclization starting from aminoallylsilanes **(34)** (Scheme **12**) [24].

Since numerous natural piperidines are substituted by a methyl group at the 2 position, we have chosen to prepare piperidines **(41-46)** by condensation of the methyl substi-



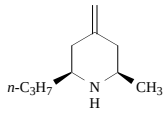
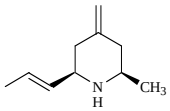
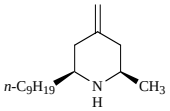
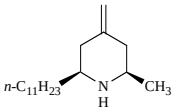
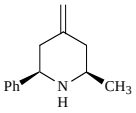
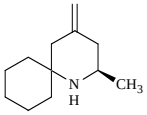
(34)

Scheme 12. Strategy of synthesis of 2,6-disubstituted piperidines.



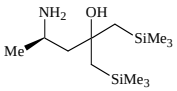
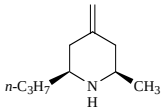
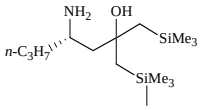
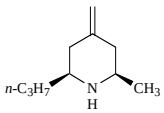
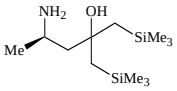
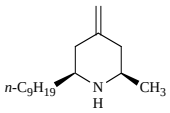
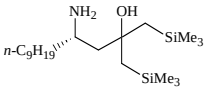
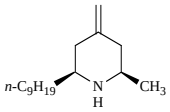
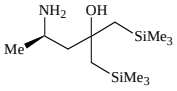
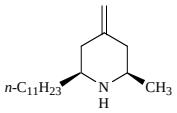
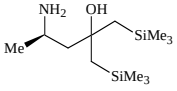
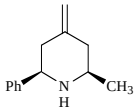
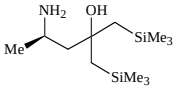
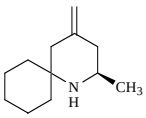
Scheme 13. Addition of aminoallylsilanes **(*R*)-(34)** on carbonyl compounds.

Table 1. Synthesis of 2-methyl-6-alkyl-4-methylenepiperidines from the Aminoallylsilane *R*-(34)

Carbonyl Compound	Major Product	de[a]	Yield[b]	ee[b]
n-C_3H_7CHO (**35**)	 (**41a**)	84 %	49 %	n.d. ($[\alpha]_D^{21}$ = -4)
CH_3CH=CHCHO (**36**)	 (**42a**)	n.d.	32 %	78 %[c]
n-$C_9H_{19}CHO$ (**37**)	 (**43a**)	84 %	49 %	28 %[d]
n-$C_{11}H_{23}CHO$ (**38**)	 (**44a**)	82 %	58 %	38 %[d]
PhCHO (**39**)	 (**45a**)	86 %	70 %	76 %[d]
 (**40**)	 (**46**)	/	46 %	24 %[c]

[a] determined by ^{1}H NMR on the crude product; [b] determined on the major isolated piperidine; [c] determined by ^{1}H NMR of the (*R*)- mandelic acid ammonium salt; [d] determined by GC-MS of the Mosher's acid derivative.

Table 2. Synthesis of 2-methyl-6-alkyl-4-methylenepiperidines from the Aminohydroxysilanes (47)

	Aminoalcohol	Carbonyl Compound	Major Product	de[a]	Yield[b]	ee[b]
1	 **(*R*)-47a**	*n*-C_3H_7CHO (**35**)	 (**41a**)	82%	53%	n.d. ($[\alpha]_D^{21}$ = -5.5)
2	 **(*S*)-47b**	CH_3CHO (**41**)	 (**41a**)	82%	32%	n.d. ($[\alpha]_D^{21}$ = -5.5)
3	 **(*R*)-47a**	*n*-$C_9H_{19}CHO$ (**37**)	 (**43a**)	84%	73%	74%[d]
4	 **(*S*)-47c**	CH_3CHO (**41**)	 (**43a**)	78%	53%	76%[d]
5	 **(*R*)-47a**	*n*-$C_{11}H_{23}CHO$ (**38**)	 (**44a**)	84%	70%	64%[d]
6	 **(*R*)-47a**	PhCHO (**39**)	 (**45a**)	90%	70%	84%[d]
7	 **(*R*)-47a**	 (**40**)	 (**46**)	/	25%	14%[c]

[a] determined by ^1H NMR on the crude product; [b] determined on the major isolated piperidine; [c] determined by ^1H NMR of the (R)- mandelic acid ammonium salt; [d] determined by GC-MS of the Mosher's acid derivative.

tuted aminoallylsilane **(*R*)-(34)** on carbonyl compounds **(35-40)** (Scheme **13**).

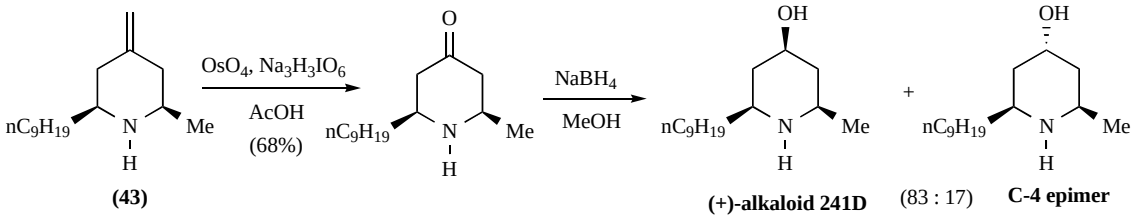
Reaction of the aminoallylsilane **(*R*)-(34)** with aldehydes **(35-39)** and cyclohexanone **(40)** in the presence of trifluoroacetic acid in a mixture water-THF (1:1) at room temperature for 24 h led to a mixture of cis and trans 4-methylenepiperidines. The results are summarized in Table **1**.

In order to improve yields and minimize racemisation during the oxidation step, we studied the preparation of piperidines **(41-46)** from the β-aminohydroxysilanes **(47),** precursors of the β-aminoallylsilane **(*R*)-(34)**. Reaction of the β-aminohydoxysilanes **(47)** with carbonyl derivatives **(35, 37-41)** in the presence of trifluoroacetic acid led to a mixture of cis and trans-4-methylenepiperidines. The results are summarized in Table **2**.

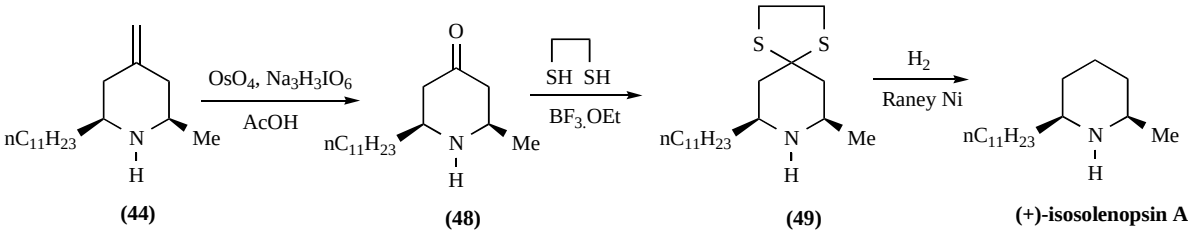
As in the preceeding results, in all cases, the cis-diastereomers were predominant. Comparison of these results with those mentioned in Table **1** shows that diastereoselectivity is about the same but enantioselectivity is significantly increased.

We have used this last strategy for the total synthesis of the two piperidine alkaloids : (+)-alkaloid 241D which possess an interesting biological activity as noncompetitive blocker of the nicotinic receptor channel complex [25] and (+)-isosolenopsin A known as possess antibacterian, antifongic, insecticide and phytocid activities.

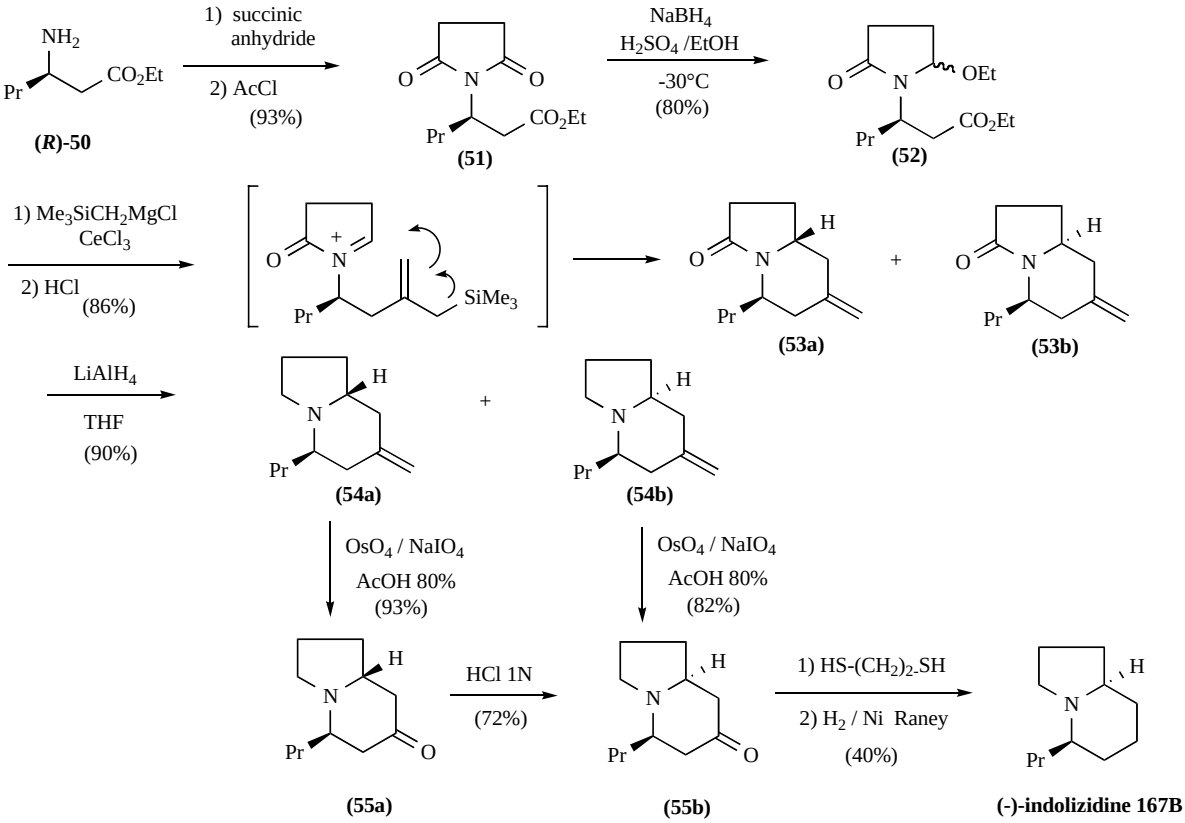
Various asymmetric synthesis of (+)-alkaloid 241D has been described [26]. We have used methylenepiperidine **(43)** as starting material to prepare this alkaloid according to the sequence outlined in Scheme **14**. (+)-Alkaloid 241D and its C-4 epimer were obtained in a ratio 83 : 17, the natural pro-



Scheme 14. Synthesis of (+)-alkaloid 241D.



Scheme 15. Synthesis of (+)-isosolenopsin A.



Scheme 16. Enantioselective synthesis of (-)-indolizidine 167B by intramolecular allylsilane-*N*-acyliminium cyclization.

duct was isolated in a 66% yield. Consequently, (+)-alkaloid 241D was obtained in six steps from methyl crotonate in an overall yield of 23%.

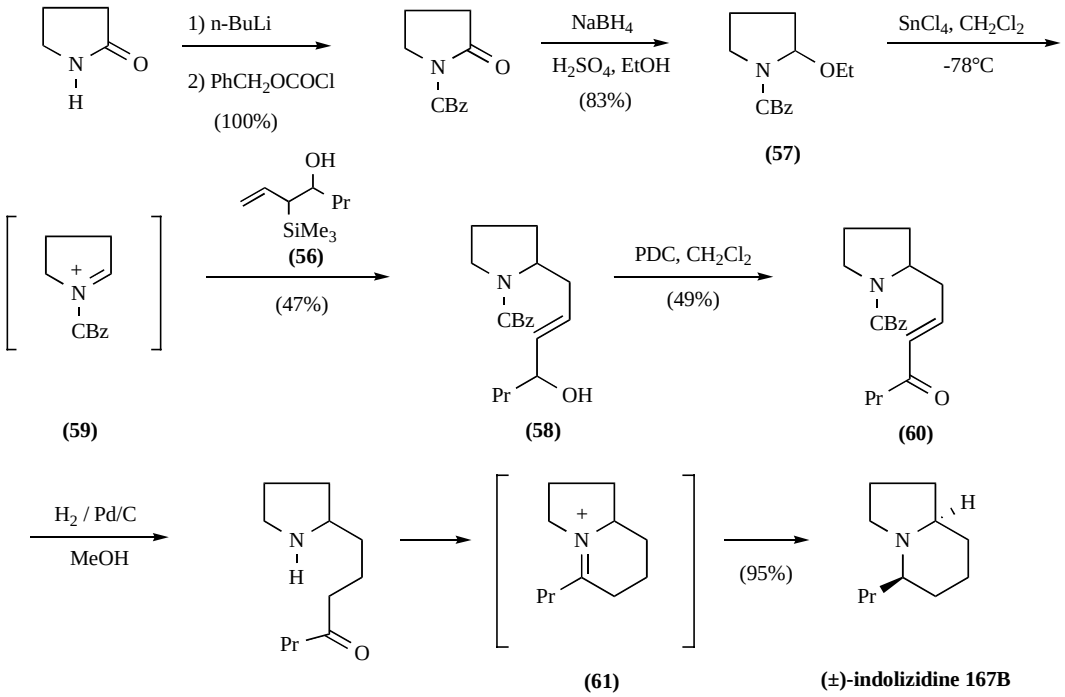
(+)-Isosolenopsin A [27] was prepared from 4-methylenepiperidine **(44)** (Scheme **15**). Oxidation of **(44)** with osmium tetroxide led to the piperidin-4-one **(48),** treatment of **(48)** with an excess of ethanethiol gave the dithiolane derivative **(49)** in 82% yield. Finally, **(49)** was converted into (+)-isosolenopsin A in 43% yield using Raney nickel in reflux methanol.

We have described a new approach for the enantioselective synthesis of 2,6-disubstituted-4-methylenepiperidines. Piperidines were obtained with good yields and excellent diastereoselectivities. This methodology was applied to the synthesis of (+)-alkaloid 241D and (+)-isosolenopsin A [28].

3. INDOLIZIDINES

3.1. Indolizidine 167B

Indolizidine 167B, one of the simplest amphibian indolizidine alkaloids, was originally found as a trace component in the skin secretions of a frog belonging to the genus Dendrobates captured on the Isla Colon Panama [29]. The structure and relative stereochemistry shown in scheme **16** are



Scheme 17. Synthesis of (±)-indolizidine 167B by intermolecular cyclization of allylsilane on *N*-acyliminium derived from pyrrolidin-2-one.

now accepted as correct although the absolute configuration of the natural product remains uncertain [30]. The lack of availability of the natural material and the important biological activities of the compound make this alkaloid an ideal target for total synthesis [31-38].

3.1.1. Intramolecular Cyclization

We have found that intramolecular cyclization of an allylsilane on an acyliminium ion constituted an excellent route to nitrogen bicyclic ring systems [39]. This method represents an efficient and stereoselective strategy for the preparation of 5-substituted indolizidines.

The source of chirality was the aminoester **(*R*)-50** which was prepared according to Davies' methodology [40]. Synthesis of the indolizidine skeleton was carried out as shown in scheme **16**. Reaction of **(*R*)-50** with succinic anhydride and then with acetyl chloride in refluxing toluene gave imide **(51)**, then **(51)** was reduced into ethoxylactam **(52)**. In the next step, **(52)** was treated with two equivalents of the cerium reagent derived from trimethylsilymethylmagnesium chloride and $CeCl_3$. The mixture was then hydrolysed with 1N HCl to give methyleneindolizidinones **(53a)** and **(53b)** in a 4:1 ratio. Reduction of the mixture of lactams **(53a)** and **(53b)** with lithium aluminium hydride gave methyleneindolizidines **(54a)** and **(54b)** which were separated by flash chromatography.

Osmium tetroxide catalysed periodate oxidation of olefinic bond of **(54a)** and **(54b)** led respectively to indolizidin-3-ones **(55a)** and **(55b)**. Upon treating an aqueous solution of **(55a)** with HCl 1N the thermodynamically more stable indolizidinone **(55b)** was obtained through a retro-Mannich fragmentation-cyclization process. The last two steps were the conversion of **(55b)** into its dithiolane and subsequent desulfurisation using Raney nickel. The synthesis of (-)-indolizidine 167B has been achieved in 7 steps with a 17% overall yield from ethyl (3*R*)-3-aminohexanoate **(50)** with an enantiomeric excess of 93% [41].

3.1.2. Intermolecular Cyclization

The intermolecular reaction between hydroxyalkyl-substituted allylsilanes and the acyliminium ion coming from pyrrolidin-2-one constitutes a new route to 5-substituted indolizidines (Scheme **17**).

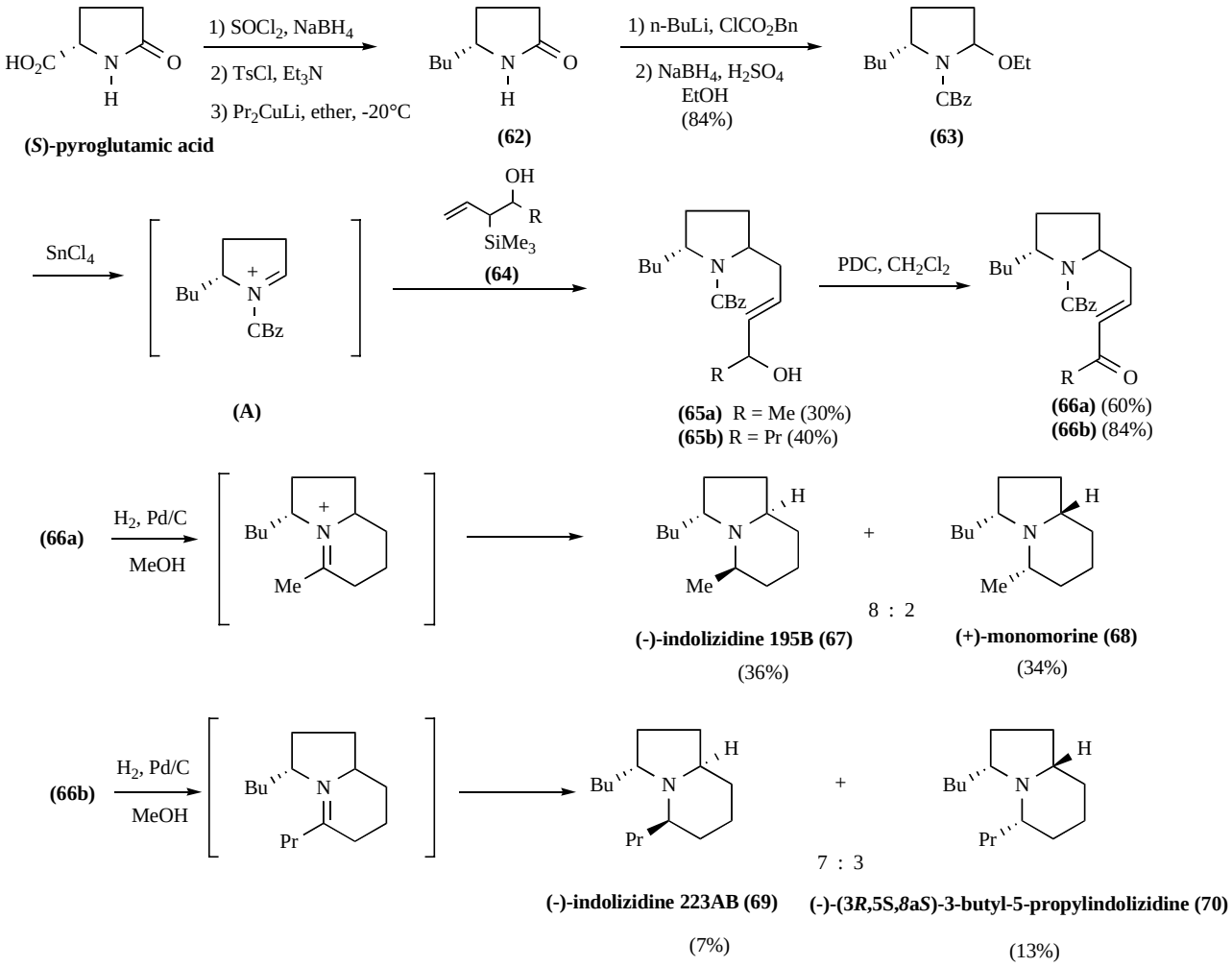
Hydroxyallylsilane **(56)** was synthesised as described [42] by reaction of the reagent prepared from allyltrimethylsilane, sec-butyllithium and titanium tetraisopropoxide with aldehydes. The key step of the synthesis is the intermolecular addition of the allylsilyl functional group of alcohol **(56)** on the acyliminium ion derived from ethoxycarbamate **(57)**.

Treatment of a mixture of ethoxycarbamate **(57)** and hydroxyallylsilane **(56)** with one equivalent of stannic chloride resulted in the formation of **(58)** *via* the acyliminium ion intermediate **(59)**. Subsequent oxidation of alcohol **(58)** with pyridinium dichromate then catalytic hydrogenation (H_2 over Pd/C) of ketone **(60)** induced hydrogenolysis of the CBz group, reduction of the double bond of the side chain and reduction of the iminium ion intermediate **(61)** to give indolizidine 167B.

The synthesis of (±)-indolizidine 167B has been achieved in five steps in 18% overall yield from pyrrolidin-2-one [43].

3.2. 3,5-Disubstituted Indolizidines

Most of the indolizidine alkaloids are disubstituted by alkyl chains at the 3,5 positions. These compounds have been attractive targets for synthesis because of their potential biological activities [29]. Accordingly, novel strategies for the



Scheme 18. Synthesis of 3,5-disubstituted indolizidines from L-pyroglutamic acid.

preparation of substituted indolizidines have received considerable attention [44-50].

The allylsilyl functional group is a weak carbon nucleophile for trapping *N*-acyliminium ions, thus provides a useful method for intramolecular carbon-carbon bond formation [51,52]. We have applied this methodology towards the synthesis of indolizidine alkaloids (*vide supra*). We described here a new approach of 3,5-disubstituted indolizidines based on an intermolecular addition of allylsilanes on an *N*-acyliminium ion starting from L-pyroglutamic acid used as chiral precursor.

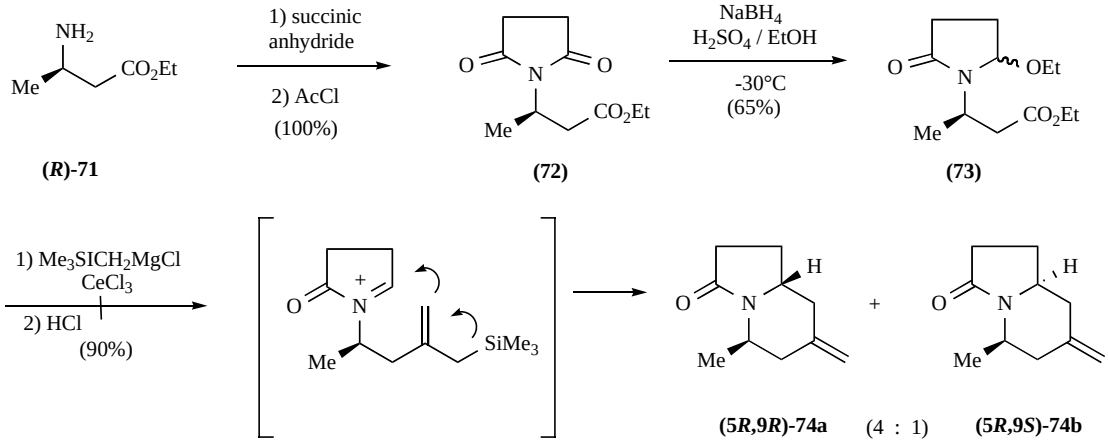
Preparation of lactam **(62)** was accomplished starting from the commercially available *S*-(-)-pyroglutamic acid according to a previously described procedure [53,54]. Next, lactam **(62)** was protected (n-BuLi, benzyl chloroformate) then converted to ethoxycarbamate **(63)**, isolated as a mixture of two diastereomers according to Hiemstra's procedure [55,56]. Condensation of allylsilanes **(64)** onto iminium ion **A** generated *in situ* by treatment of **(63)** with stannous chloride led to compounds **(65a)** and **(65b)**. The next two steps were straightforward : oxidation (pyridinium dichromate) of **(65a)** and **(65b)** afforded α,β-ethylenic ketones **(66a)** and **(66b)**.

On hydrogenation over palladium on carbon **(66a)** gave a mixture of indolizidines **(67)** and **(68)** which were separated by flash chromatography. They were identified as (-)-indolizidine 195B and (+)-monomorine respectively. In the same manner, the hydrogenation of **(66b)** provided a mixture of isomers **(69)** and **(70)** and respectively identified as (-)-indolizidine 223AB and (-)-(3*R*,5*S*,8a*S*)-3-butyl-5-propylindolizidine.

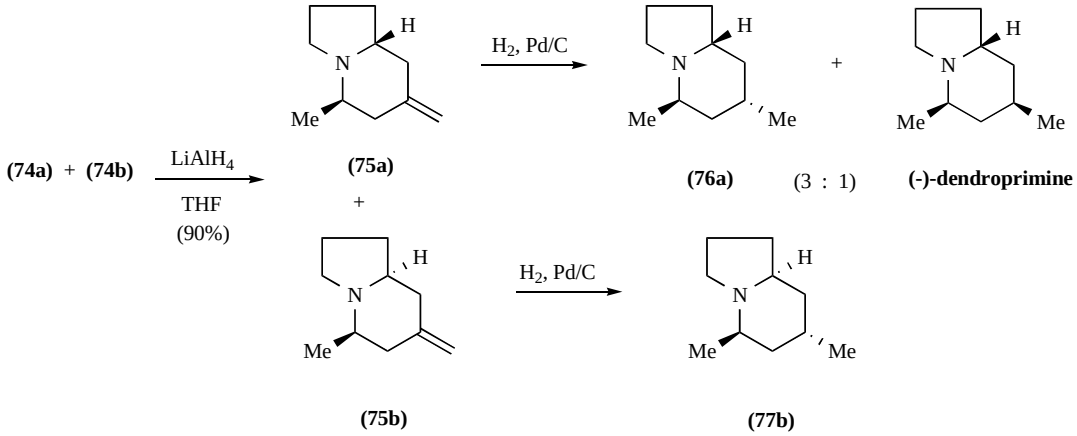
These four indolizidines were obtained in five steps with overall yields of about 8% [57].

3. 3. (-)-Dendroprimine

(-)-Dendroprimine is an alkaloid isolated from *Dendrobium primulinum* Lindl (*Orchidaceae*) and shown to be a 5,7-dimethylindolizidine [58]. Its relative configuration was determined after the synthesis of the four racemic diastereomers of this indolizidine and a conformational analysis of these diastereomers has been discussed [59,60]. Its identification as (5*R*,7*S*,9*R*)-5,7dimethylindolizidine has been firmly established [61]. We describe here the first asymmetric synthesis of this alkaloid [62]; two others synthesis were recently published [63,64].



Scheme 19. Access to indolizidine precursors of dendroprimine starting from chiral 2-aminopropanoate **(71)**.



Scheme 20. Access to (-)-dendroprimine by treatment with $LiAlH_4$ then H_2/Pd of indolizidinones **(74)**.

The first steps of our synthesis were carried out as shown in scheme **19**. The starting material was ethyl 2-aminopropanoate **(*R*)-(71)**. Chirality was introduced with isomer **(*R*)-71** and **(*S*)-71**, which were prepared by a Michael reaction according to Davies'procedure from ethyl crotonate and respectively (*R*)- and (*S*)-*N*-benzyl-α-methylbenzyl-amine [40]. Reaction of **(71)** with succinic anhydride and then with acetyl chloride gave imide **(72)**, it was then reduced into ethoxylactam **(73)**. Compound **(73)** was treated with the cerium reagent derived from trimethylsilylmagnesium chloride and cerium chloride. The mixture was then hydrolysed with 1N HCl to give methyleneindolizidinones **(74a)** and **(74b)** in a 4:1 ratio.

These diastereomers could not be separated. According to Scheme **20**, in a first step the reduction of the lactam functional group of cyclization products **(74a)** and **(74b)** with lithium aluminium hydride afforded a 4:1 mixture of methyleneindolizidines **(75a)** and **(75b)** in a quantitative yield. These isomers were separated to give **(75a)** and **(75b)** in 50 and 18% yields. Palladium-catalysed hydrogenation of **(75a)** was found to be stereoselective, giving a mixture of **(76a)** and (-)-(dendroprimine) in a 3:1 ratio. In similar conditions, **(75b)** led to compound **(77b)**.

Another way (Scheme **21**) was studied to access to (-)-dendroprimine : hydrogenation of the crude mixture of cyclization products **(74a)** and **(74b)** over palladium on carbon provided a mixture of lactams **(77a)**, **(78a)** and **(79a)** in which isomer **(77a)** was preponderant (**(77a**/**78a**/**79a)** = 15:65:20). Flash column chromatography gave pure **(79a)** in 18% yield, but **(77a)** and **(78a)** could not be separated (50% yield). A mixture of the three isomers was used without purification for the next step. This mixture was then reduced with lithium aluminium hydride to give the indolizidines **(76a)**, dendroprimine and **(77b)**. In conclusion, (-)-dendroprimine was obtained in five steps with overall yields of 17 and 20% [62].

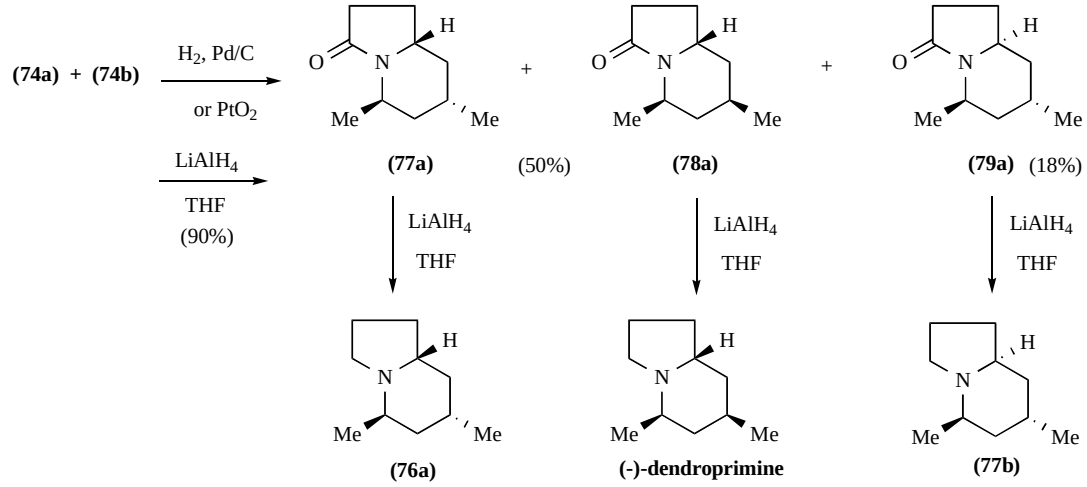
4. QUINOLIZIDINES

4.1. Myrtine and Epimyrtine

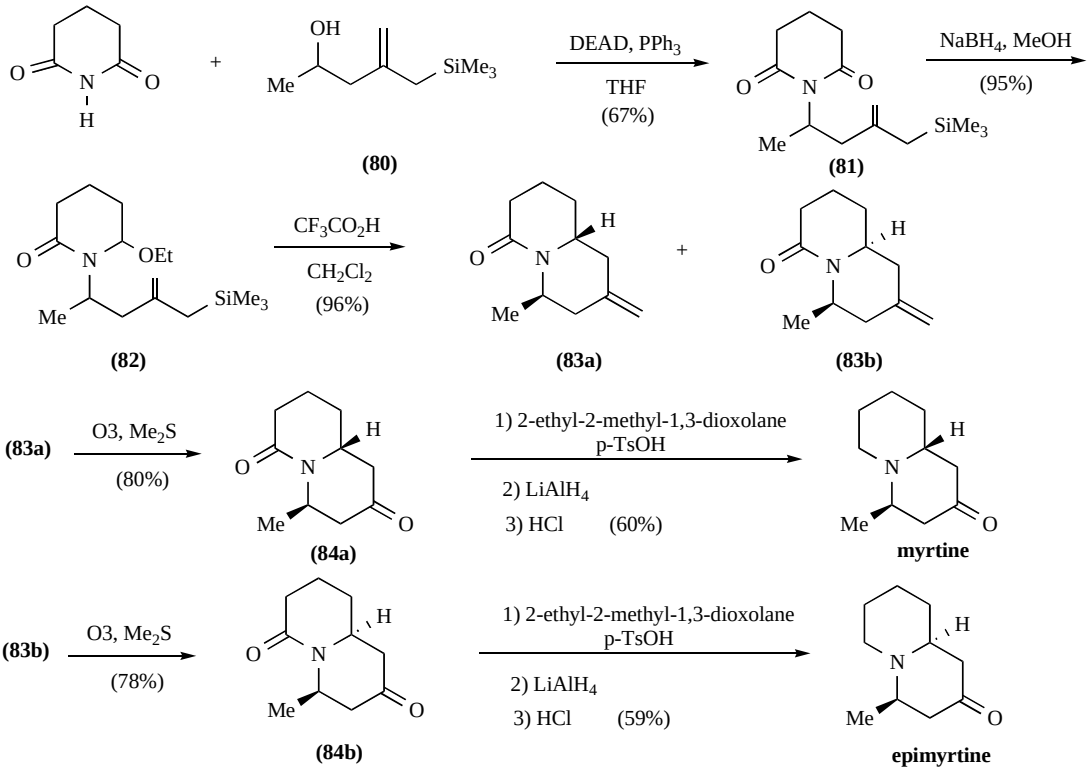
(+)-Myrtine and (-)-epimyrtine are quinolizidine alkaloids isolated from *Vaccinium myrtillus* (Ericaceae) [65,66]. Several syntheses of these compounds as racemic mixture have been described, [65-68] only two enantioselective synthesis of (+)-myrtine [66,68], (-)-myrtine [70] and three synthesis of (-)-epimyrtine have been published [71,72,73].

4.1.1. Synthesis of (±)-myrtine and (±)-epimyrtine

These compounds have been prepared according to scheme **22**, the synthesis of hydroxyalkylallylsilane **(80)** is



Scheme 21. Access to (-)-dendroprimine by treatment with H_2/C then $LiAlH_4$ of indolizidinones **(74)**.

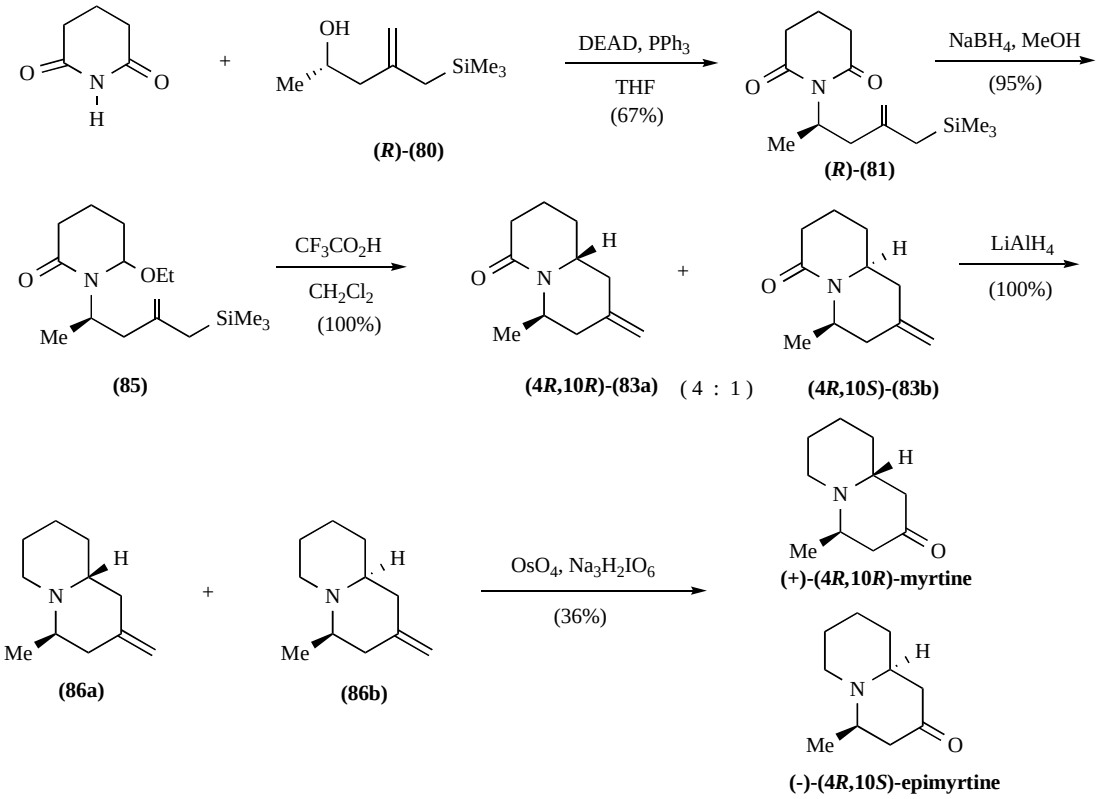


Scheme 22. Synthesis of (±)-myrtine and (±)-epimyrtine.

accomplished in 40% yield following the Trost's procedure [74]. Reaction of glutarimide with alcohol **(80)** under Mitsunobu reaction conditions afforded imide **(81)** in 67% yield. Reduction of **(81)** was carried out with an excess of sodium borohydride in methanol at 0°C to give **(82)** as a mixture of two diastereomers which were not separated. The hydroxylactam **(82)** was then cyclized to the quinolizidine isomers **(83a)** and **(83b)** on treatment with 4 equiv. of trifluoroacetic acid in a 7:3 ratio. Then, ozonolysis of **(83a)** and **(83b)** followed by reduction with dimethylsulfide furnished respectively **(84a)** and **(84b)**. Protection of the carbonyl group by ketalisation with 2-ethyl-2-methyl-1,3-dioxolane and *p*-toluenesulfonic acid, reduction of the amide function with lithium aluminium hydride then quantitative removal of the protecting group (HCl treatment) afforded (±)-myrtine and (±)-epimyrtine. These syntheses were achieved in seven steps and 20% overall yield [75].

4.1.2. Synthesis of (+)-myrtine and (-)-epimyrtine

We used a similar strategy to prepare the enantiopure compounds starting from (*S*)-2-(hydroxypropyl)allyltri-methylsilane **(80)** (Scheme **23**). Compound **(*S*)-(80)** was obtained in quantitative yield by cerium mediated trimethylsilylmethylmagnesium chloride addition to ethyl (*S*)-3-hydroxybutanoate as we described [76]. The first three steps of the enantioselective synthesis were those previously de-



Scheme 23. Enantioselective synthesis of (+)-myrtine and (-)-epimyrtine.

scribed for the synthesis of racemic compounds (*vide supra*). Condensation of alcohol **(*S*)-(80)** with glutarimide under Mitsunobu conditions led to (+)-imide **(*R*)-81** in 67% yield. Reduction of **(*R*)-81** with sodium borohydride afforded hydroxylactam **(85)** as a 1:1 mixture of isomers in 95% yield. Treatment of hydroxylactam **(85)** with trifluoroacetic acid in methylene chloride gave a 7:3 mixture of the two isomeric bicyclic compounds **(4*R*,10*R*)-83a** and **(4*R*,10*S*)-83b** in quantitative yield. Reduction of this mixture of lactams with lithium aluminium hydride gave a 7:3 mixture of methylenequinolizidines **(86a)** and **(86b)** in quantitative yield. Osmium tetroxide-catalysed periodate oxidation of the olefinic bond of quinolizidines **(86a)** and **(86b)** under carefully controlled conditions led to a 7:3 mixture of the two diastereomeric alkaloids (+)-myrtine and (-)-epimyrtine. These alkaloids were obtained in five steps from (*S*)-2-(2-hydroxypropyl) allylsilane **(80)** with an overall yield of 23% and a high enantiomeric purity. This synthesis constitutes the first total synthesis of naturally occurring (-)-epimyrtine and confirms the configuration 4*R*,10*S* which was assigned previously to this compound [77].

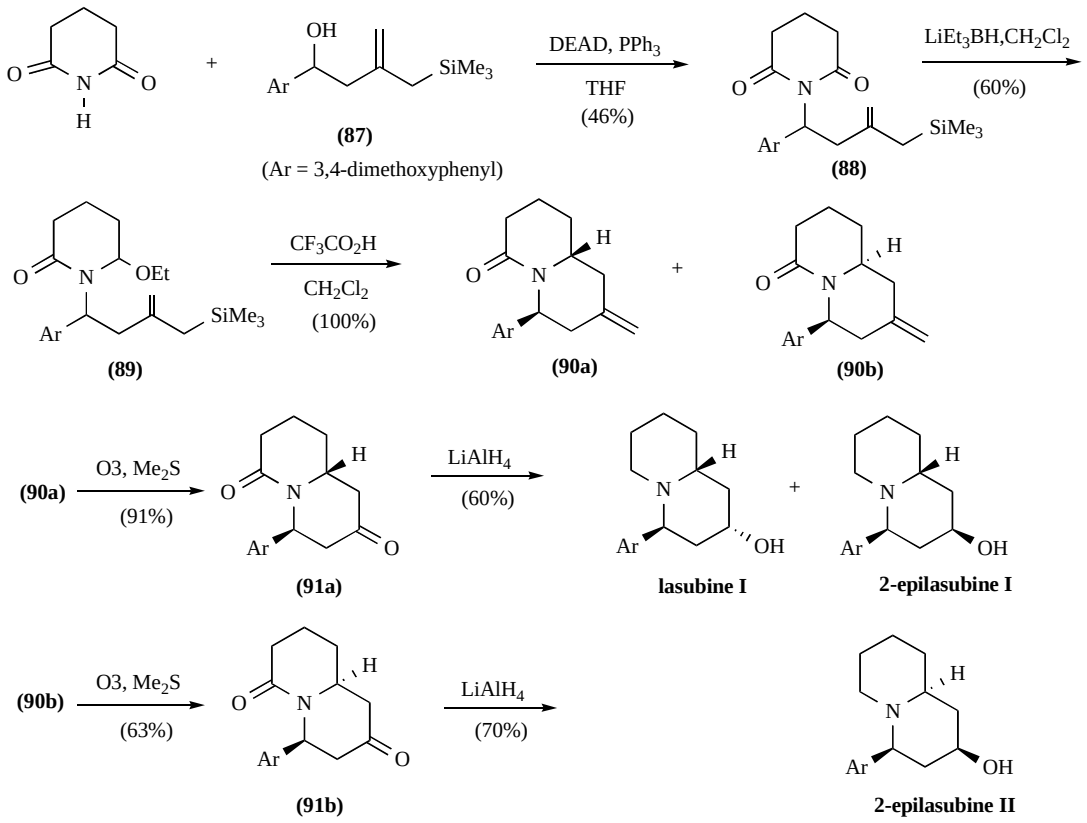
4.2. Lasubines

The Lythraceae alkaloids constitute a large family of natural products, most of which contain 4-arylquinolizidine substructures. Among them are the quinolizidine alkaloids lasubine I and lasubine II which have been isolated from *Lagerstroemia subscotata* Koehne [78]. Numerous racemic [69, 79-81] and asymmetric total syntheses of these alkaloids have been described [82-91].

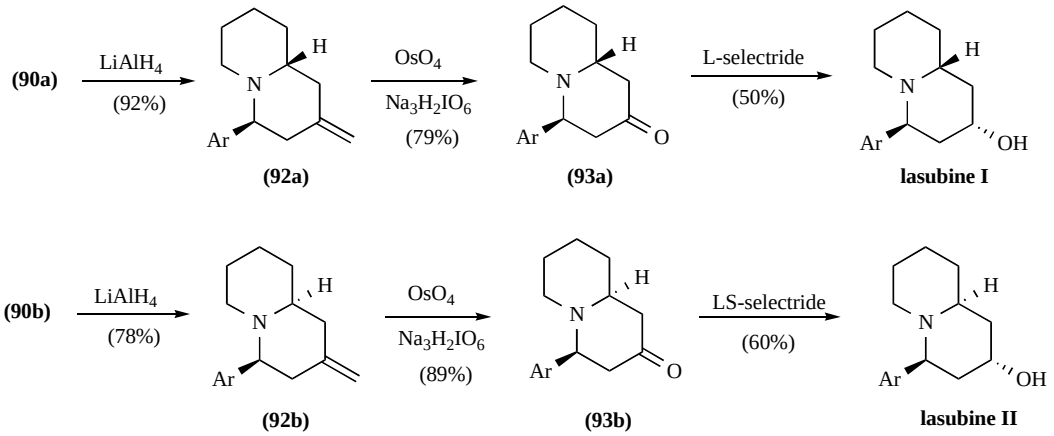
4.2.1. Synthesis of (±)-lasubine I and (±)-lasubine II

The first steps of our synthesis were carried out as shown in scheme **24**. The starting material was the 2-(2-hydroxyethyl)allylsilane **(87)** which was prepared in 86% yield by indium mediated allylsilylation of 3,4-dimethoxybenzaldehyde, as already described [92]. Condensation of alcohol **(87)** with glutarimide under Mitsunobu conditions led to imide **(88)** in 46% yield. Reduction of **(88)** with diisobutylaluminium hydride afforded hydroxylactam **(89)** isolated as a mixture of isomers, a higher yield of a single isomer were obtained when using lithium triethylborohydride as reducing reagent. The reduction had to be performed at -78°C to prevent formation of ring opening products [93]. Treatment of hydroxylactam **(89)** with trifluoroacetic acid in methylene chloride gave a mixture of isomeric bicyclic compounds **(90a)** and **(90b)** in a quantitative yield and a 4:1 ratio when the reaction was performed at -78°C.

Then, we examined two routes to the quinolizidine alkaloids lasubine I and lasubine II from methylenequinolizidinones **(90a)** and **(90b)**. They involved oxidation of the methylene group into carbonyle which was then stereoselectively reduced to the hydroxyle group. The shortest route consisted in the ozonolysis of the methylene group followed by the simultaneous reduction of the two carbonyl groups of keto lactams **(91a)** and **(91b)**. Thus, treatment of **(90a)** with ozone then with dimethyl sulphide afforded the expected keto lactam **(91a)** in 91% yield. Ozonolysis of **(90b)** led to keto lactam **(91b)** in 63% yield. Reduction of **(91a)** with lithium aluminium hydride afforded in 60% yield a 1:1.2 mixture of lasubine I and 2-epilasubine I which were separated as their



Scheme 24. Synthesis of (±)-lasubines I and II and (±)-2-epilasubine II.

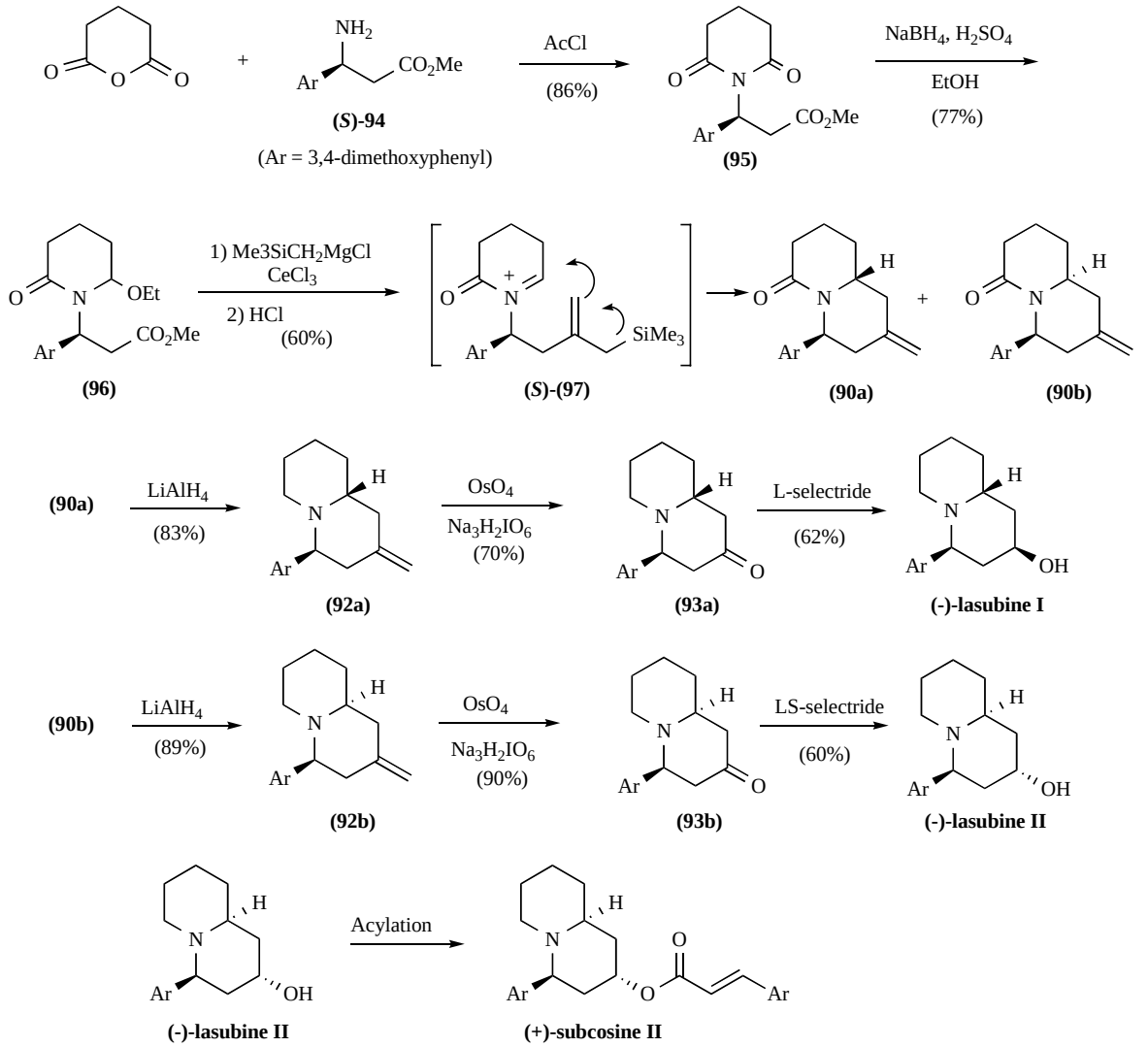


Scheme 25. Synthesis of (±)-lasubine I and II.

acetates. In the same way, reduction of **(91b)** gave 2-epilasubine II in 70% yield.

In order to circumvent the stereochemical difficulty we decided to reduce first the lactam group (Scheme **25**) to obtain quinolizidines whose conformation should not be distorted by the junction with the piperidone ring. Lactams **(90a)** and **(90b)** were reduced with lithium aluminium hydride to give methylenequinolizidines **(92a)** and **(92b)** in respectively 92% and 78% yields. Osmium tetroxide catalysed periodate oxidation of the olefinic bond of methylenequinolizidines **(92a)** and **(92b)** under carefully controlled conditions led to the already described 2-oxoquinolizidines **(93a)** and **(93b)** in respectively 79% and 89% yields. The final step is a reduction of the carbonyl group. The use of borohydride in the reduction of **(93a)** has been described to give lasubine in an excellent yield [94,95]. In our hands, this reaction afforded a 1:1 mixture of (±)-lasubine I and (±)-epilasubine I. Stereoselective reduction of quinolizidin-2-one **(93a)** to (±)-lasubine I was achieved in 50% yield with lithium tri-sec-butylborohydride (L-selectride). Quinolizidinone **(93b)** was selectively converted to (±)-lasubine II with lithium trisamylborohydride (LS-selectride) in 60% yield.

In conclusion, (±) lasubine I and (±)-lasubine II were obtained in six steps from 2-(2-hydroxyethyl)allylsilane **(87)** in 8% and 7.4% yields respectively [96].



Scheme 26. Enantioselective synthesis of (-)-lasubines I and II and (+)-subcosine II.

4.2.2. Synthesis of (-)-lasubine I, (-)-lasubine II and (+)-subcosine II

A similar strategy was attempted from (+)-(3*R*)-ethyl-3-hydroxy-3-(3,4-dimethoxyphenyl)propionate but racemisation was observed during the Mitsunobu reaction [97]. So we developed another strategy (Scheme **26**) to prepare these natural optically active compounds based on the intramolecular acyliminium ion allylsilane cyclisation of intermediate **(97)** generated from ethoxylactam **(96)**. Chirality is introduced with the β-aminoester **(*S*)-(94)**.

(*S*)-β-Aminoester **(94)** was prepared according to Davies'procedure [40]. Reaction of **(*S*)- (94)** with glutaric anhydride then with acetyl chloride in refluxing toluene gave imide **(95)** in 86% yield. Imide **(95)** was reduced into ethoxylactam **(96)** which was isolated as a mixture of two diastereomers. In the next step, ethoxylactam **(96)** was treated with the cerium reagent derived from $CeCl_3$ and trimethylsilylmethylmagnesium chloride. The mixture was then hydrolysed with 1N HCl to give methylenequinolizidinones **(90a)** and **(90b)** in a 1:5 ratio and 60% yield. Reduction of lactams **(90a)** and **(90b)** with lithium aluminium hydride in refluxing THF for 12 h gave methylenequinolizidines **(92a)** and **(92b)** in 83% and 92% yields respectively. Osmium tetroxide catalysed periodate oxidation of the olefinic bond of **(92a)** and **(92b)** under carefully controlled conditions led to quinolizidin-2-ones **(93a)** and **(93b)** in 70 and 90% yields. The final step is the reduction of the carbonyl group. Stereoselective reduction of **(93a)** with L-selectride provided (-)-lasubine I in 62% yield. Quinolizidin-2-one **(93b)** was selectively converted to (-)-lasubine II with LS-selectride in 65% yield. Acylation of (-)-lasubine II with 3,4-dimethoxycinnamic anhydride gave (+)-subcosine II in 60% yield (Scheme **26**).

In conclusion, we describe the total synthesis of (-)-lasubine I, (-)-lasubine II and (+)-subcosine II using intramolecular cyclization of *N*-acyliminium ion **(*S*)-97**. (-)-Lasubine I and (-)-lasubine II were obtained in six steps with overall yields of 7 and 14%, respectively. (+)-Subcosine was prepared in seven steps with an overall yield of 9%. These three compounds were obtained with a high enantiomeric purity. These results constitute the first total synthesis of naturally occurring (-)-lasubine II and (+)-subcosine II and unambiguously establish their absolute configuration as 2*S*,4*S*,10*S* [98].

CONCLUSION

We described in this paper a new access to the piperidine ring which is a fundamental structure found in a large number of natural or non natural compounds possessing a broad range of biological activities. Our approach, based on an inter or intra- molecular addition of an allylsilane on iminium or *N*-acyliminium ions has been revealed as an efficient stereo and enantioselective way to mono or bicyclic compounds possessing the piperidine ring in their structure.

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