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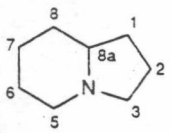
Hydroxylated Indolizidines and their Synthesis

Janine Cossy and Pierre Vogel

1. Introduction

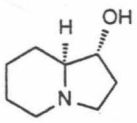
The indolizidine (octahydroindolizine) ring system is found in bewildering profusion in nature. A large proportion of alkaloids incorporate this moiety, ranging from bicyclic alkaloids to some highly complex structures like those of Aspidosperma alkaloids.[1] In this review surveying the literature until June 1991, we shall be concerned exclusively with simple indolizidine alkaloids and analogues possessing at least one hydroxyl or acetoxy group and, except for



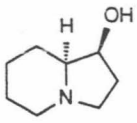
indolizomycin ((-)-**31**) and cyclizidine ((-)-**32**) whose skeletons are annulated to three-membered rings, with those structures which are not annulated to other carbocycles.

The alkaloids under survey can be classified into two main sub-groups: (A) the hydroxy- and polyhydroxyindolizidines not substituted by carbon substituents (Table 1) and (B) those that are alkylated or arylated on the ring (Table 2). The former sub-group includes (-)-swainsonine ((-)-**5**) and (+)-castanospermine ((+)-**7**), two potent inhibitors of mannosidases and glucosidases, respectively, enzymes that are essential in the biosynthetic processing of polysaccharides and glycoproteins.[2] Because the removal of specific mannosyl and glucosyl residues from the glycoprotein surface of viral envelopes plays a crucial role in host cell recognition and replication, glycosidase inhibitors show promise for chemotherapeutic treatment of viral diseases, including AIDS.[3] The transformation of normal cells to cancer cells is known to be accompanied by changes in the composition of the sugar side-chains of glycoproteins. Levels of glycosidase enzymes are raised in the serum of some cancer patients, and are thought to be involved in the process of metathesis. Polyhydroxylated indolizidines that are carbohydrate analogues in which

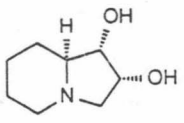
Table 1. Naturally occurring hydroxy- and polyhydroxyindolizidines that are not substituted by alkyl or aryl groups.[5]



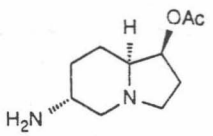
(-)-**1**



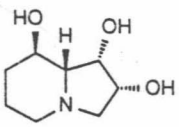
(+)-**2**



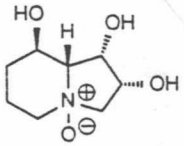
(-)-**3**



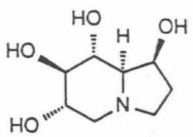
(-)-**4**: slaframine



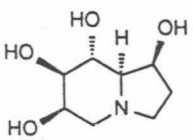
(-)-**5**: swainsonine



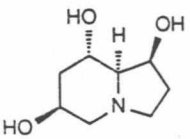
(-)-**6**: swainsonine N-oxide



(+)-**7**: castanospermine



(+)-**8**: 6-*epi*-castanospermine

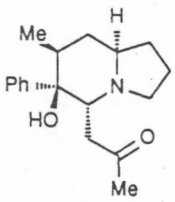


(+)-**9**: 7-deoxy-6-*epi*-castanospermine

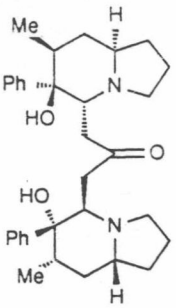
the oxygen atom of the pyranose or furanose ring has been replaced by a nitrogen function (sugar-shape alkaloids[4]) are being used to investigate the role of glycosidases in these processes. A notable consequence of these properties has been an upsurge of interest in the synthesis of natural polyhydroxylated indolizidine alkaloids and of unnatural analogues for structure-activity studies.

This account will be concerned with the syntheses of natural and unnatural hydroxy and polyhydroxyindolizidine derivatives. We have chosen to classify them according to the number of hydroxy (or acetoxy) groups they bear.

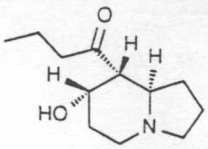
Table 2. Naturally occurring C-substituted hydroxy- and polyhydroxyindolizidines



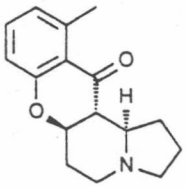
10: crepidamine



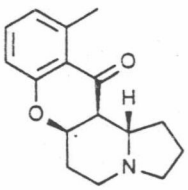
11: dendrocrepine



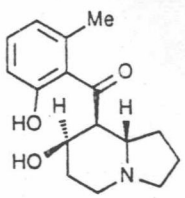
(-)-**12**: elaeokanine C



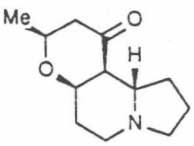
13: elaeocarpine



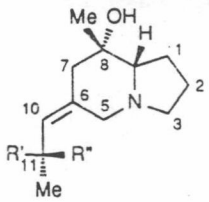
(+)-**14**: isoelaeocarpine

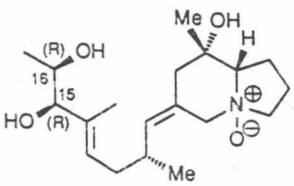


(+)-**15**: isoelaeocarpicine

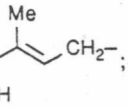


16: elaeokanine E

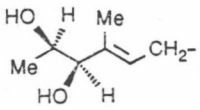




23: N-oxide of pumiliotoxin 323 A



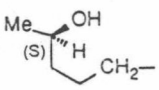
17: R'= ; R"=H : pumiliotoxin A (307A'; 307A")



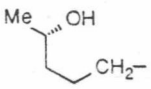
18: R'= ; R"=H : pumiliotoxin B (323 A)

19: R'= n-C_4H_9; R"=H : pumiliotoxin 251 D

20: R'= n-C_3H_7; R"=H : pumiliotoxin 237 A

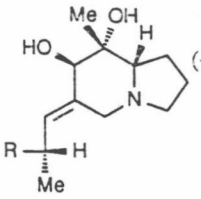


21: R'= ; R"=H : pumiliotoxin 267 C



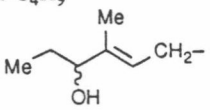
22: R'= ; R"=OH : pumiliotoxin 267 D

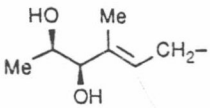
Table 2 (continued)

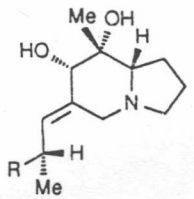


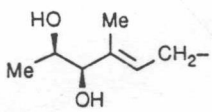
24: R= n-C_3H_7 : allopumiliotoxin 253 A

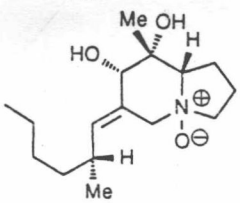
(+)-**25**: R= n-C_4H_9 : allopumiliotoxin 267 A

26: R=  : allopumiliotoxin B (323B'; 323 B")

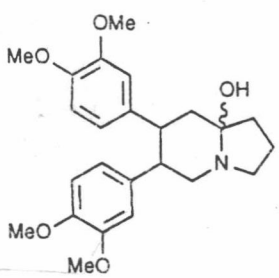
(+)-**27**: R=  : allopumiliotoxin 339 A



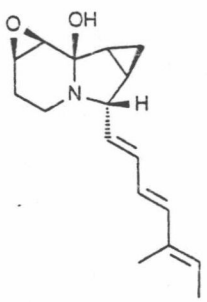
28: R=  : allopumiliotoxin 339 B



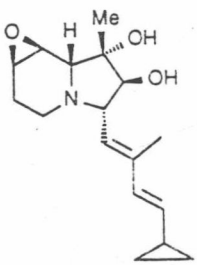
29: N-oxide of allopumiliotoxin 267 A



(+)-**30**: 13a-hydroxysepticine



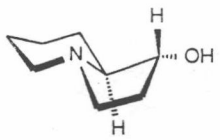
(-)-**31**: indolizomycin



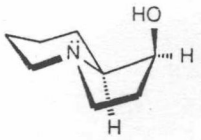
(-)-**32**: cyclizidine

2. The 1-hydroxyindolizidines (octahydroindolizin-1-ols)

Detailed studies on the biosynthesis (see sections 13, 14) of (-)-slaframine ((-)-**4**) and (-)-swainsonine ((-)-**5**) in the fungus *Rhizoctonia leguminicola* has shown that (-)-(1R,8aS)-1-hydroxyindolizidine ((-)-**1**) is present in the fungus together with traces of (+)-(1S,8aS)-1-hydroxyindolizidine ((+)-**2**).[6a] (-)-**1** was also found in the diablo locoweed (*Astragalus oxyphysus*) which produces (-)-swainsonine.[6b]



(-)-**1** (*trans*)

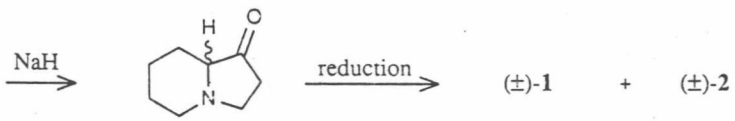


(+)-**2** (*cis*)

A first synthesis of racemic *cis*-1-hydroxyindolizidine ((±)-**1**) was proposed by Sternbach and Kaiser in 1952.[7] Hydrogenation (50 atm.) of (±)-1-oxoindolidizine ((±)-**33**) in AcOH in the presence of platinum catalyst afforded a mixture of amino-alcohols whose picrates were recrystallized to give pure picrate of (±)-**2**. Ketone (±)-**33** was obtained according to the method of Clemo and Ramage[8] (Scheme 1) by alkylation of (±)-ethyl picolate with ethyl 3-bromo-propanoate followed by Dieckmann cyclization and decarboxylation.

Scheme 1

(±)-ethyl picolate



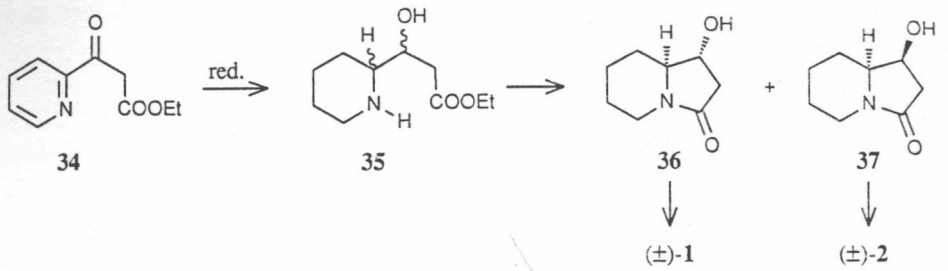
(±)-**33**

Aaron and co-workers[9] studied the hydrogenation of (±)-**33** in the presence of various catalysts such as PtO_2, Rh/C or Pd/C and obtained mixture in which the racemic *cis* isomer (±)-**2** was the major product that could be isolated pure by fractional distillation. Because of intramolecular hydrogen bonding of the hydroxy group with the amine function, as evidenced by IR spectroscopy,[9] the *cis* isomer (±)-**2** is more volatile than the *trans* isomer (±)-**1**. Reduction of (±)-**33** with K/EtOH in benzene afforded a 91:9 mixture of (±)-**1** and (±)-**2**.[9]

Another approach to the synthesis of 1-hydroxyindolizidines is based on the thermal, intramolecular aminolysis of a 9:1 mixture of the *erythro* and *threo* ethyl β-hydroxy-β-(2-piperidyl)propanoate (**35**) which gives a 1:9 mixture of the *trans* and *cis*-3-oxo-1-hydroxy-indolizidines (**36** + **37**).[10] These lactams were separated by column chromatography and reduced (by Clemmensen or with $LiAlH_4$)[10] into (±)-**2** and (±)-**1**, respectively.[9] Compound **35** was obtained by reduction of ethyl β-oxo-β-(2-pyridyl)propanoate (**34**) (Scheme 2).[10]

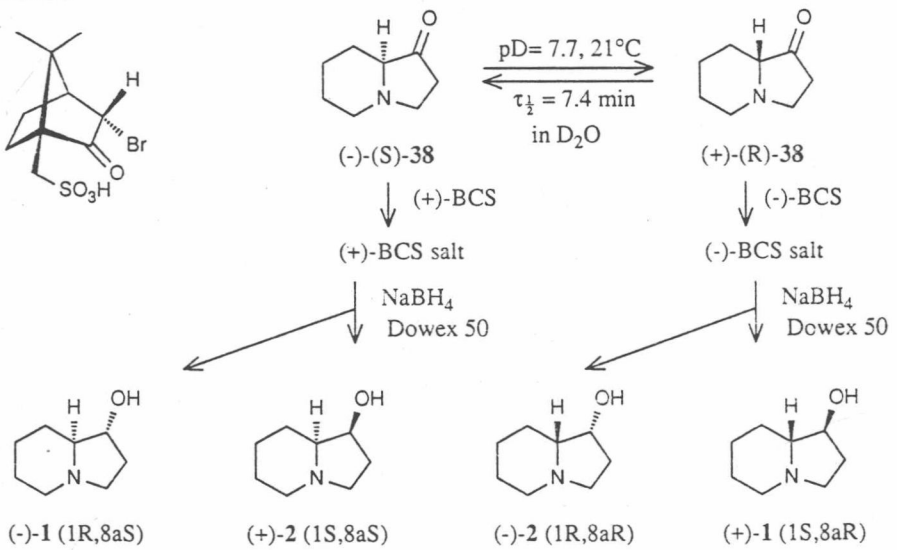
In 1987, Harris and Harris[11] presented a first approach to the preparation of the four diastereomers of 1-hydroxyindolizidines ((-)-**1**, (+)-**2**, (+)-**1**, (-)-**2**) in high optical purity. Racemic 1-oxoindolizidine ((±)-**38**) can be resolved by fractional crystallization of the (+)-3-bromo-camphor-8-sulfonic acid ((+)-BCS) salt from acetone.[12] The configuration of (-)-(S)-**38** was

Scheme 2



established by conversion into (+)-(S)-indolizidine.[13] The enantiomeric (-)-(R)-indolizidine had been obtained by ambiguous transformations into (+)-coniine which was correlated with D-pipecolic acid.[14] Because of the extremely facile racemization of optically active

Scheme 3

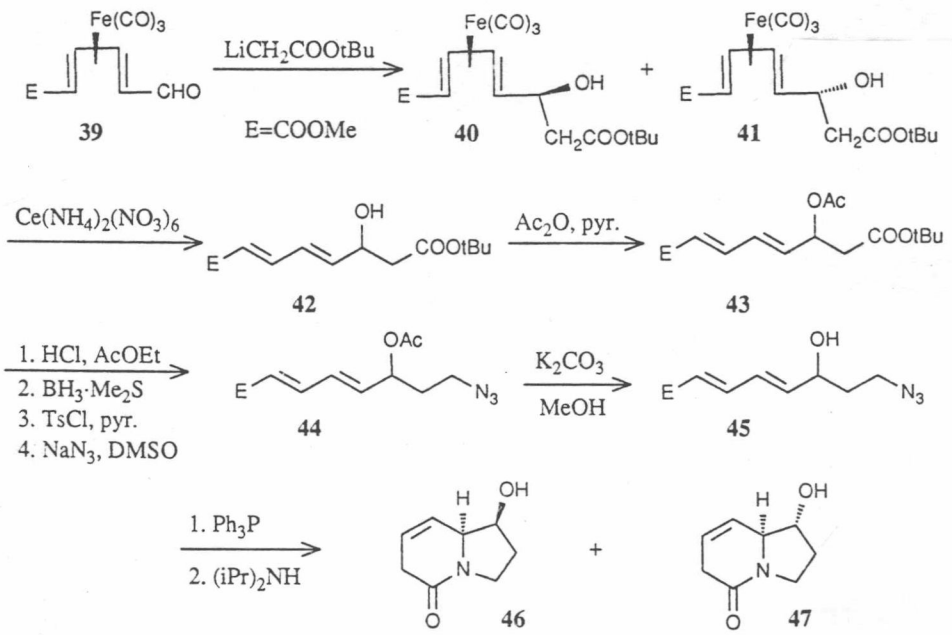


1-oxoindolizidine, its reduction with $NaBH_4$ into mixture of *cis* and *trans*-1-hydroxyindolizidines does not allow one to isolate these compounds with high optical purity. However, the salt formed with either enantiomer of BCS can be obtained pure and remains stable. Thus, treatment of (±)-**38** with (+)-BCS in acetone gave a (+)-BCS salt which was reduced with $NaBH_4$ in EtOH to give a mixture of (-)-**1** and (+)-**2** that were separated by ion-exchange resin chromatography. Similarly, treatment of (±)-**38** with (-)-BCS gave the corresponding diastereomeric (-)-BCS salt whose reduction with $NaBH_4$ afforded (-)-**2** and (+)-**1** (Scheme 3).[11]

Carrié and co-workers[15a] have developed a new approach (Scheme 4) to the indolizines based on transformation of the optically pure tricarbonyl(diene)iron complex **39**. The reaction of the lithium enolate of tert-butyl acetate with **39** led to a 2:1 mixture of alcohols **40** and **41** separated by flash chromatography. Decomplexation of each isomer with cerium (IV) salt in

MeOH gave dienol **42** whose hydroxyl group was protected as an acetate. Hydrolysis of the *tert*-butyl ester under acidic conditions, followed by reduction with $BH_3{\cdot}Me_2S$ complex gave the corresponding primary alcohol that was esterified as a tosylate. Reaction of the latter with NaN_3 in DMSO afforded azide **44**. Reduction of the azide **45** with Ph_3P in aqueous THF liberated the corresponding primary amine which cyclized spontaneously. The crude reaction mixture was then heated in the presence of $(iPr)_2NH$ giving a 4:1 mixture of indolizidines **46** and **47** which were separated by chromatography.

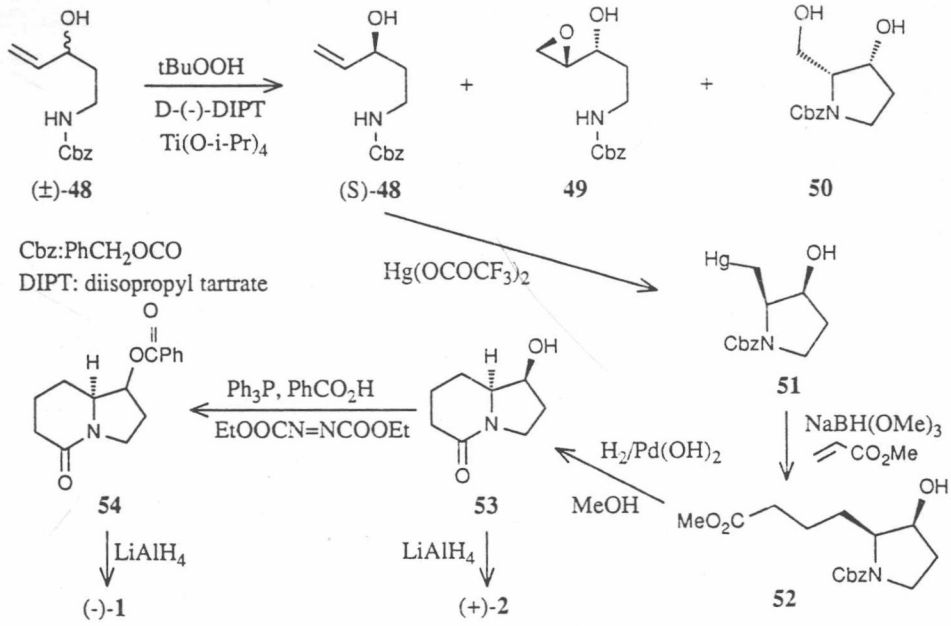
Scheme 4



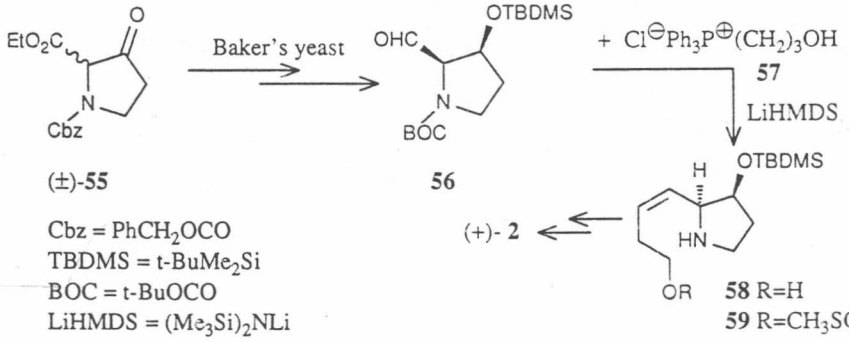
An enantioselective synthesis of (-)-**1** and (+)-**2** have been reported recently by Takahato and co-workers[15b] based on the Sharpless kinetic resolution of N-benzyloxycarbonyl-3-hydroxy-4-pentenylamine ((±)-**48**). Asymmetric epoxidation of (±)-**48** gave a mixture of (S)-**48** (44%), the epoxy alcohol **49** (33%) and the pyrrolidine (2R,3R)-**50** (14%) (Scheme 5). Stereoselective intramolecular amidomercuration of (S)-**48** with $Hg(OCOCF_3)_2$ in tetrahydrofuran followed by the radical Michael addition with methyl acrylate in the presence of $NaBH(OMe)_3$ provided **52**. Catalytical hydrogenolysis in MeOH led to indolizidinone **53** whose reduction with $LiAlH_4$ gave (+)-**2**. Mitsunobu displacement reaction on **53** gave **54** which was reduced with $LiAlH_4$ into (-)-**1**.

Sibi and Christensen[16] have proposed recently a synthesis of (+)-(1S,8aS)-1-hydroxyindolizidine ((+)-**2**) which implies a Wittig condensation of the L-prolinal derivative **56** with the three-carbon synthon **57** giving alcohol **58**. An intramolecular cyclization via mesylate (methanesulfonate) **59** afforded (+)-**2**. The L-prolinal derivative **56** was obtained from the protected 3-ketoproline ethyl ester **55** through enantioselective reduction with baker's yeast (immobilized with calcium alginate) followed by interchange of the Cbz (benzoyl) to the BOC

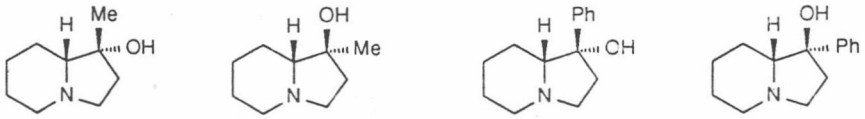
Scheme 5



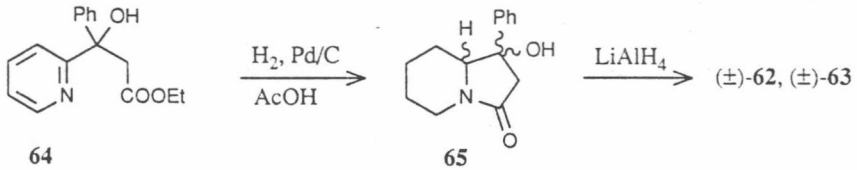
(*tert*-butyloxycarbonyl) protecting group and protection of the hydroxy group as *tert*-butyldimethylsilyl ether (TBDMS).



Mixtures of isomeric 1-hydroxy-1-methylindolizidines ((±)-**60**, (±)-**61**) and 1-hydroxy-1-phenylindolizidines((±)-**62**, (±)-**63**) were obtained from the reaction of 1-oxoindolizidine ((±)-**38**, (Scheme 3) with the appropriate Grignard reagent. The resulting alcohols were separated by chromatographic and distillation techniques.[17] Lactams **65** which are reduced into (±)-**62** and



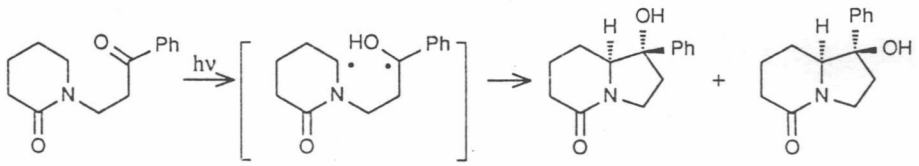
(±)-**63** with $LiAlH_4$, were obtained by a cyclization reaction consecutive to the catalytic hydrogenation of the 2-pyridylcarbinol **64** in acetic acid.[18] Other potential precursors of (±)-**62** and (±)-**63** were prepared by Gramain and co-workers[19] using an intramolecular photoreduction



64 **65**

of a carbonyl group by a lactam. The methodology (Scheme 6) implies a regioselective abstraction of an hydrogen atom α to the nitrogen atom of the amide group in **66** by the triplet excited state (n, π*) of the benzoyl moiety, leading to the diradical intermediate **67** which cyclizes into (±)-**68** (18%) and (±)-**69** (27%).

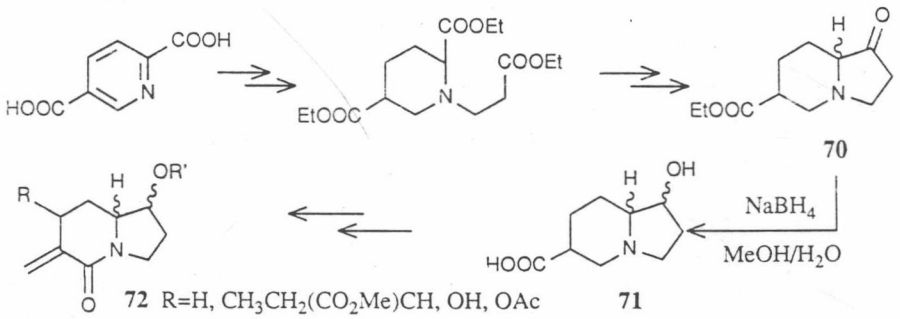
Scheme 6



66 **67** (±)-**68** (±)-**69**

For their synthesis of dl-camptothecin, Rapoport and co-workers[20] have developed a synthesis of racemic 1-hydroxyindolizidine-6-carboxylic acid (**71**) (the relative configuration was not established). The bicyclic keto-acid **70**, obtained in 85% yield from pyridine-2,5-dicarboxylic acid (Scheme 7) was reduced with $NaBH_4$ in aqueous methanol into **71**. This compound was then converted into other 1-hydroxyindolizine derivatives **72**.

Scheme 7



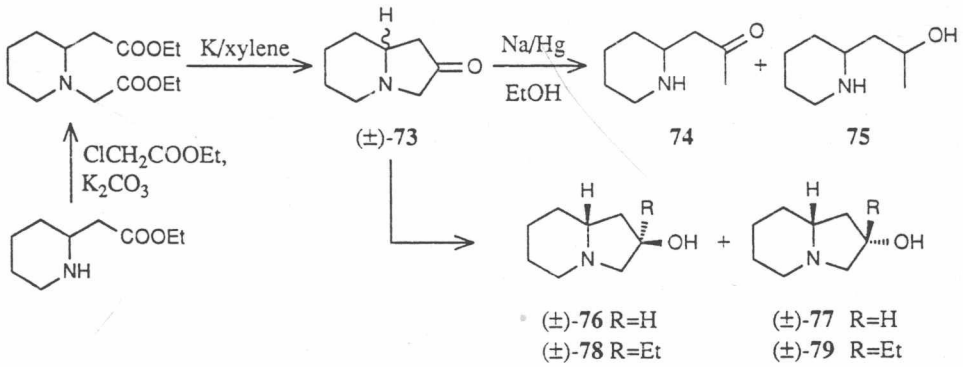
72 R=H, $CH_3CH_2(CO_2Me)CH$, OH, OAc R'= H, Ac **71**

3. The 2-hydroxyindolizidines (octahydroindolizin-2-ols)

The 2-hydroxyindolizidines have not been found yet in nature. In 1937, Clemo and Metcalfe[21a] reported on the synthesis of (±)-2-oxoindolizine (±)-**73** (Scheme 8). The latter was

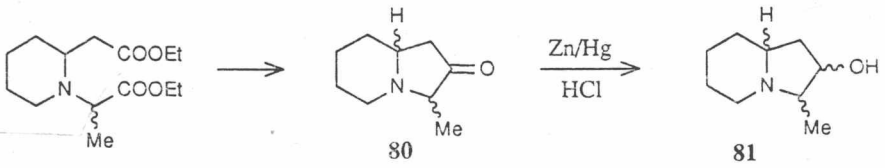
reduced with sodium amalgam in EtOH into a mixture of *trans*-2-hydroxyindolizidine ((±)-**76**) and isopelletierine (**74**). Two minor components of the reduction mixture were 1-(2-piperidyl)-propan-2-ol (**75**) and *cis*-2-hydroxyindolizidine ((±)-**77**).[9] Catalytic hydrogenation (Rh/C) or $LiAlH_4$ reduction of (±)-**73** gave (±)-**76** and (±)-**77** which were separated and purified by column chromatography.[9] Addition of EtMgBr to (±)-**73** gave a mixture of the 2-ethyl-2-hydroxyindolizi-

Scheme 8



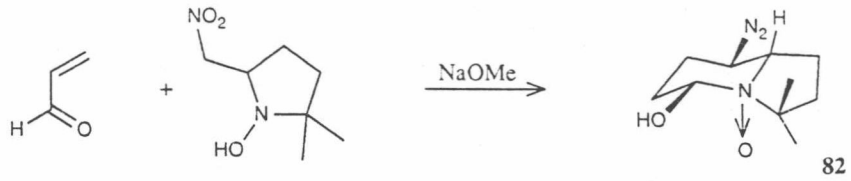
dine (±)-**78** and (±)-**79**.[21] The relative configuration (*trans* vs *cis*) of the 2-hydroxyindolizidines was established by Aaron and co-workers.[9] The *trans*-isomer (±)-**76** was more volatile than the *cis*-isomer (±)-**77** and because of weak intramolecular hydrogen bonding between the hydroxy and amine functions in (±)-**76**, as evidenced by IR spectroscopy.

The Dieckmann condensation of ethyl 2-[1-(2-ethoxycarbonylmethyl)piperidinyl]-propanoate gave 3-methyl-2-oxo-indolizidine (**80**) whose reduction with Zn/Hg and concentrated aqueous HCl led to a mixture of diastereomeric 3-methyl-2-hydroxyindolizidines (**81**).[21b]



4. The 5-hydroxy-4-oxyindolizidines

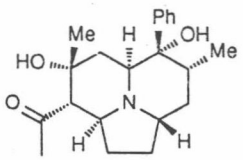
The 3-hydroxy- and 5-hydroxyindolizidines being aminals are not expected to be stable compounds, and this may explain why these systems have not been described yet. Nevertheless, the corresponding N-oxides are expected to be stable compounds. This is illustrated by the work of Green and Lamchen[22] who have obtained the 3,3-dimethyl-8-nitro-4-oxy-octahydroindolizidin-5-ol derivative **82** (probably the stereoisomer where the hydroxy and nitro groups occupy equatorial positions) through condensation of 2,2-dimethyl-5-nitromethylpyrrolidin-1-ol and propenal in the presence of NaOMe.



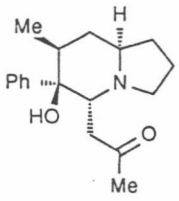
82

5. The 6-hydroxyindolizidines (octahydroindolizin-6-ols)

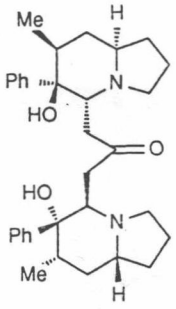
No synthesis of 6-hydroxyindolizidines have been reported yet. There are very rare compounds in nature also. The three alkaloids, crepidine (**83**),[23] crepidamine (**10**), and dendrocrepine (**11**), isolated from *Dendrobium crepidatum*,[24] are the unique representatives of this class of natural hydroxyindolizidines.



83

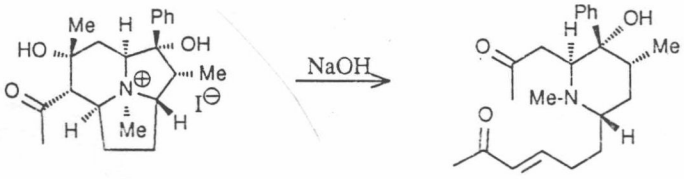


10



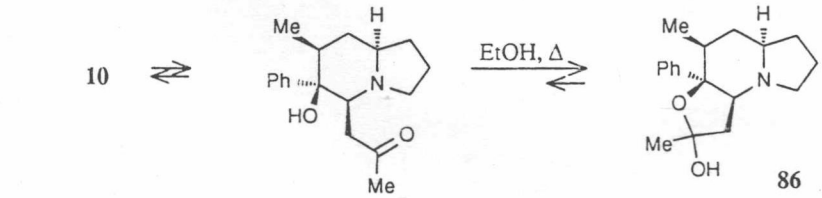
11

Crepidine (**83**) whose structure was established by X-ray diffraction studies[23b] forms methiodide (**84**) with MeI which undergoes alkaline degradation with 2 N NaOH at 20°C into the optically inactive amorphous base **85**.[24]



84 **85**

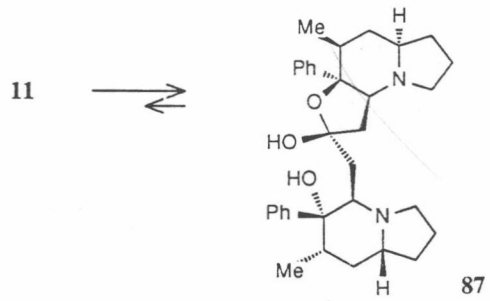
Crepidamine (**10**), which is optically inactive, has an IR spectrum in CCl_4 typical (ν_{OH} = 3470 cm^{-1}) for a *trans*-fusion of the rings in the indolizidine system allowing for OH···N bonding.



86

Crepidamine is easily isomerized into isocrepidamine (**86**) by boiling in EtOH, as indicated here-above. The IR spectrum of **86** also shows (ν_{OH} = 3290 cm^{-1}) strong intramolecular OH···N bonding.

Dendrocrepine (**11**), which is optically inactive, is easily isomerized to isodendrocrepine (**87**) by boiling in EtOH or by chromatography on neutral alumina.

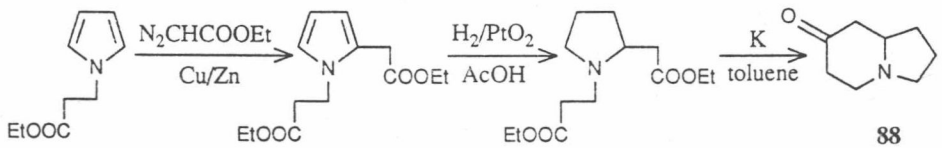


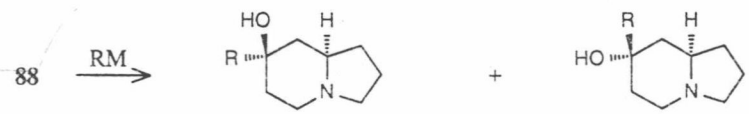
87

6. The 7-hydroxyindolizidines (octahydroindolizin-7-ols)

The first 7-hydroxyindolizidine derivatives were reported by Holden and Rapen[25] in 1963. Treatment of 7-oxoindolizidine (**88**), prepared according to Scheme 9, by EtMgI and led to a 7-ethyl-7-hydroxyindolizidine whose relative configuration was not determined (**89a** or **90a**).

Scheme 9





89 90

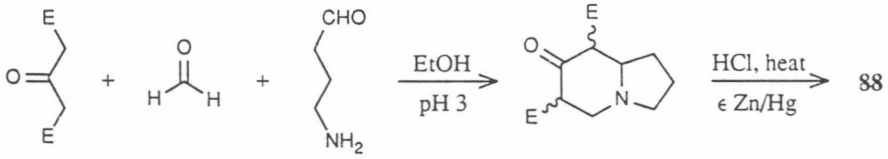
RM: EtMgI
RM: PhLi
RM: 2,6-$Me_2C_6H_3Li$

	R
a	Et
b	Ph
c	2,6-$(Me)_2C_6H_3$
d	H

Beckett and co-workers[26a] reacted phenyllithium with **88** and obtained the racemic 7-hydroxy-7-phenylindolizidines **89a** and **90a** which were separated by fractional crystallization. The derivative **90c** was obtained in a similar way by reacting **88** with 2,6-dimethylphenyllithium.[26b] The aryl substituted 7-hydroxyindolizidines and their acetates showed a weak antitremorine action in the mouse.[26] Parent compounds (±)-**89d** was obtained by reduction of **88**

with potassium in EtOH. The *trans* isomer (±)-**90d** was the major product of catalytic hydrogenation (Ru/C) of **88**. Compound (±)-**90d** is slightly more volatile than (±)-**89d** and shows typical OH···N bonding in its IR spectrum.[27]

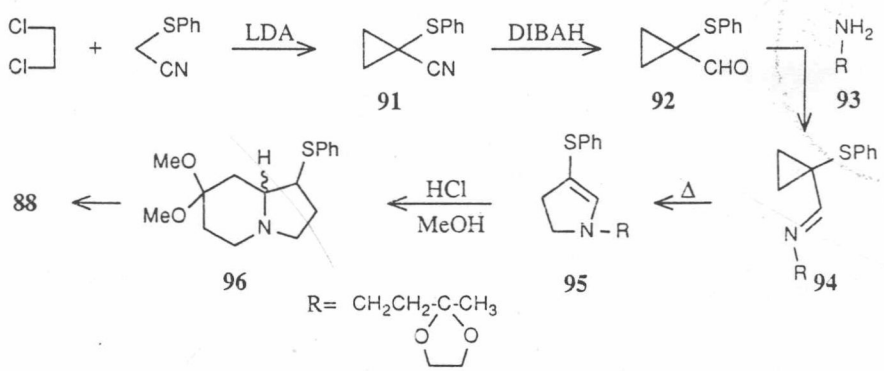
Scheme 10



E=COOEt

An earlier method for the preparation of **88** was proposed by Lions and Willison,[26] it involves the condensation of γ-aminobutyraldehyde with diethyl acetone dicarboxylate and formaldehyde in EtOH at pH 3, followed by decarboxylation of the ketodiester in boiling dilute HCl with a trace of zinc amalgam (Scheme 10). A third approach to the preparation of (±)-7-oxoindolizidine (**88**) has been proposed by Stevens and co-workers[29] (Scheme 11). Condensation of 1,2-dichloroethane with benzenesulfenylacetonitrile in the presence of a strong base (lithium diisopropylamide: LDA) gave the cyclopropanecarbonitrile derivative **91** whose reduction with diisobutylaluminium hydride (DIBAH) gave the corresponding aldehyde **92**. The latter condensed with primary amine **93** to give the cyclopropane aldimine **94** that rearranged on heating to **95**. Acidic treatment led to **96** whose desulfurization with Raney nickel and acidic hydrolysis afforded **88**.

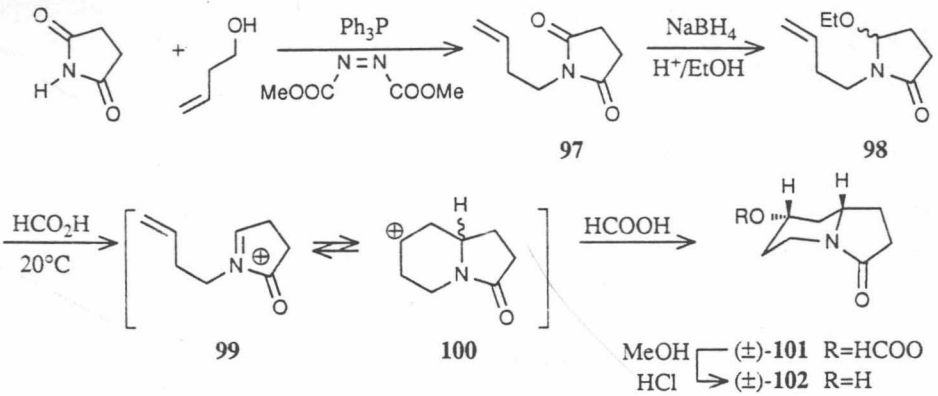
Scheme 11



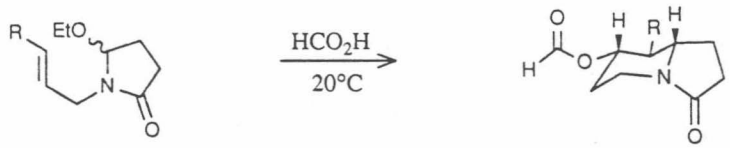
During the last 15 years cationic π-cyclization of N-acyliminium ion intermediates has been applied in the synthesis of various heterocyclic systems.[30-36] The method is illustrated in Scheme 12 for the synthesis of 7-hydroxy-3-oxoindolizidine derivatives.

Mitsunobu coupling of succinimide with allylic alcohol gave imide **97** which was reduced selectively into **98** with $NaBH_4$ in slightly acidic EtOH. Treatment of **98** with formic acid engendered the formation of the N-acyliminium ion intermediate **99** which underwent electrophilic cyclization into the secondary alkyl cation intermediate **100**. The latter was

Scheme 12



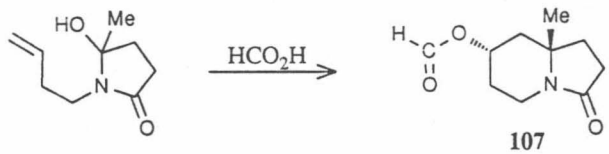
quenched by formic acid and gave (±)-**101** nearly quantitatively as a crystalline product. The reaction was highly stereoselective, giving the *cis*-isomer in which the formate moiety occupies an equatorial position (by ^{1}H-NMR).[31] Hydrolysis of (±)-**101** with aqueous MeOH/HCl gave the crystalline alcohol (±)-**102**. Cyclization of the (E)-pentenyl and (E)-hexenyl derivatives **103** and **104** under similar conditions afforded the corresponding methyl and ethyl derivative (±)-**105** and (±)-**106** with high stereoselectivity. The equatorial positions for both formate and alkyl groups, and the axial H-C(8a) configuration follow from the values of the H-H vicinal coupling constant in their ^{1}H-NMR spectra.



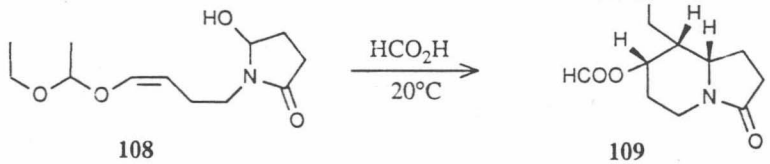
103 R=Me
104 R=Et

(±)-**105** R=Me
(±)-**106** R=Et

This method, developed by Speckamp and co-workers,[30-32] is quite general and has been applied to the preparation of *trans*-7-formyloxy-8a-methylindolizidine (**107**) by HCOOH



107

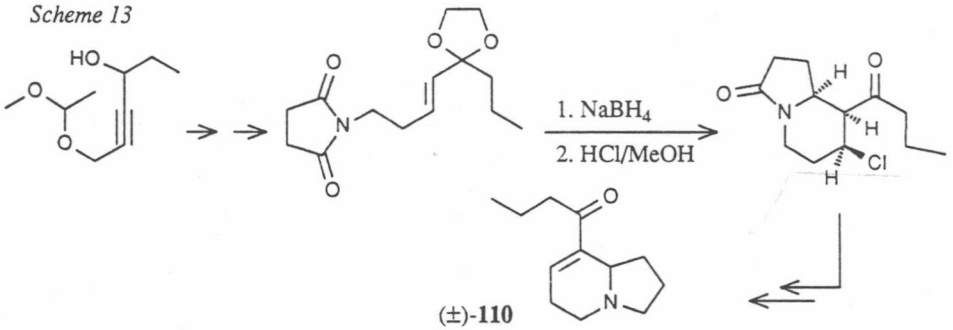


108

109

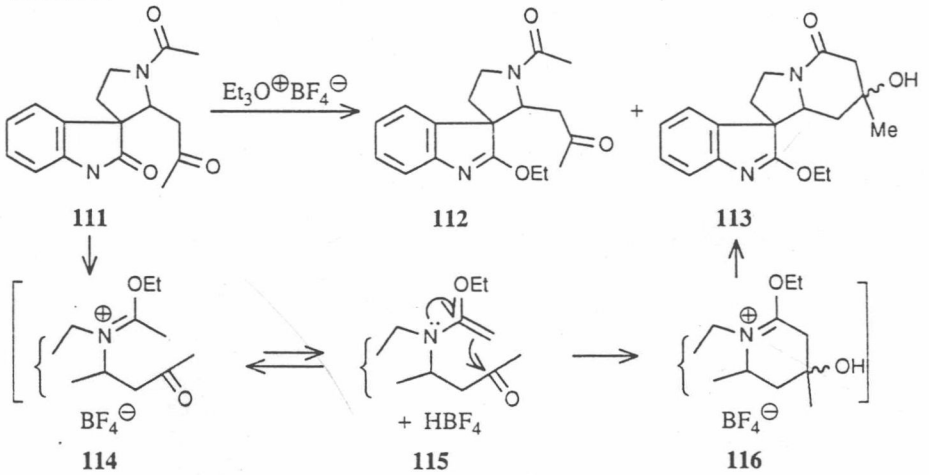
treatment of 1-but-3-enyl-5-hydroxy-5-methyl-pyrrolidin-2-one[30b] and to the synthesis of the *Elaeocarpus* alkaloid elaeokanine A (**110**).[32] In a model study, the protected allyloxy derivative **108** was cyclized into **109** in only 20% yield. (±)-Elaeokanine A ((±)-**110**) was finally obtained following the sequence of reactions shown in Scheme 13.

Scheme 13



Treatment of the oxoindole derivative **111** with the Meerwein's reagent Et_3OBF_4, followed by neutralization with aqueous K_2CO_3 gave a mixture of the expected iminoether **112** and about 5-10% yield of the 7-hydroxy-7-methyl-5-oxoindolizidine derivative **113** (configuration at C(7) unknown).[37] The formation of product **113** can be interpreted in terms of formation of the

Scheme 14



111 **112** **113**

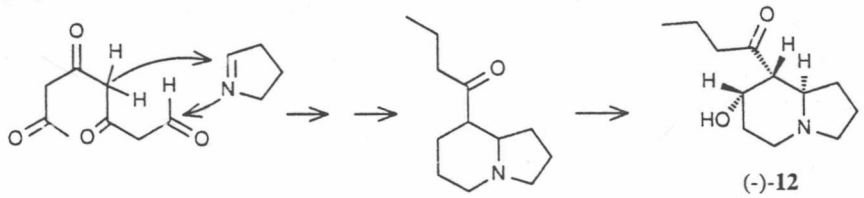
114 **115** **116**

iminium salt intermediate **114** which can equilibrate with the α-ethoxyenamine **115** (Scheme 14). The latter undergoes an intramolecular cross-aldolisation giving the iminium ion intermediate **116** whose neutralization with aqueous K_2CO_3 affords finally **113**.[37]

7. Elaeokanine C

Elaeokanine C ((-)-**12**) is an *Elaeocarpus* alkaloid[38] which was isolated from the leaves of *Elaeocarpus kaniensis* by Johns and co-workers.[39] This compound is a *trans*-7-hydroxyindolizi-

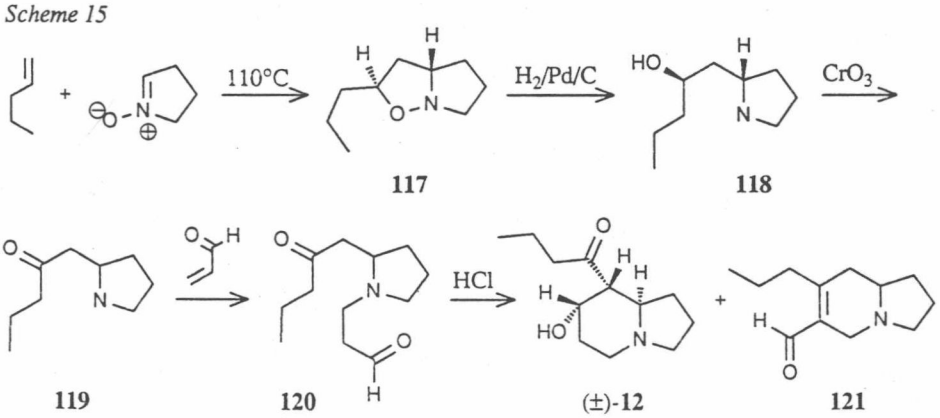
dine derivative which could be derived biosynthetically from the condensation of ornithine and a C_8-polyketide.



(-)-**12**

In 1979, Tufariello and Ali[40] described the first general approach to the total syntheses of (±)-elaeokanine A ((±)-**10**) and (±)-elaeokanine C ((±)-**12**) based on nitrone cycloaddition (Scheme 15). The cycloaddition of 1-pyrroline-1-oxide with pentene is highly regio- and stereoselective and furnishes isoxazolidine **117** in 72% yield. Catalytic hydrogenation (Pd/C) of

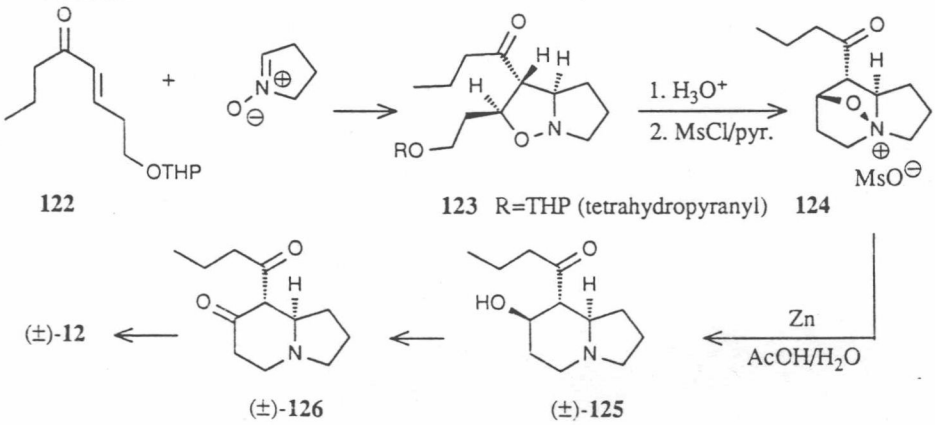
Scheme 15



117 **118** **119** **120** (±)-**12** **121**

117 gave the β-aminoalcohol **118** whose oxidation (Jones) afforded ketone **119**. Addition of acrolein to **119** gave the unstable adduct **120** which on treatment with concentrated HCl led to a separable 3:1 mixture of (±)-**12** and enal **121**. Treatment of **120** with *t*-BuOK gave (±)-**110** and **121** in a 4:1 ratio.

Scheme 16



122 **123** R=THP (tetrahydropyranyl) **124**

(±)-**12** (±)-**126** (±)-**125**