# ASYMMETRIC SYNTHESIS XXV.[1] DIASTEREOSELECTIVE SYNTHESIS OF INDOLIZIDINEDIOL ALKALOID ANALOGS

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**Abstract** — The asymmetric synthesis of 3-methylindolizidine-1,2-diol, analog of indolizidine-1,2-diol alkaloids, has been achieved from the chiral 2-cyano-6-oxazolopiperidine synthon (1). The synthesis commenced with 1,2 addition of the anion of 1 on crotonaldehyde leading to 8 with enantioselective formation of the first hydroxyl group. Epoxidation of the double bond followed by hydrogenolysis of the benzyl appendage led to the amino epoxides (13). Finally the five membered ring construction was accomplished by employing cyclization of 13.

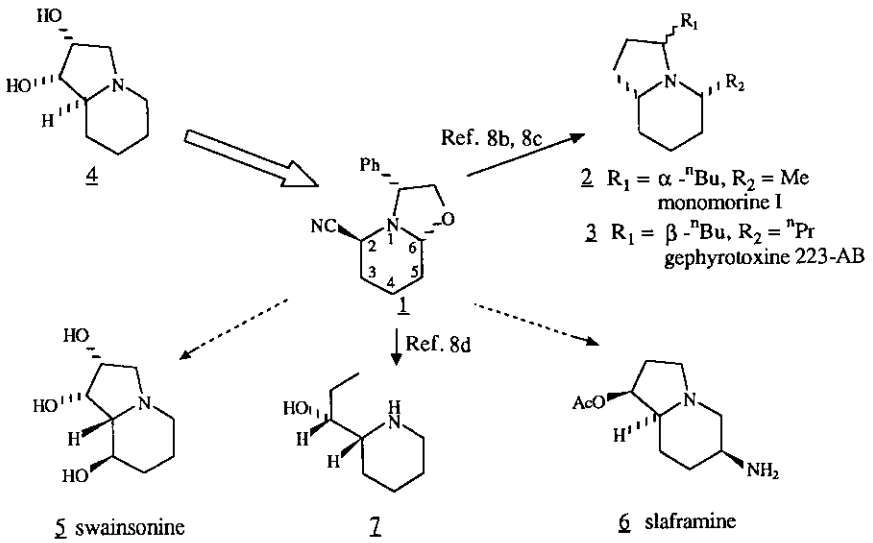
Indolizidine alkaloids can be classified in two main families : i) alkyl-substituted derivatives (found in the animal and vegetal kingdoms)[2] such as monomorine-I (2) (Figure) and gephyrotoxine 223-AB (3) (in ants and frogs respectively) and ii) hydroxylated compounds extracted from fungi (eg. 4 - 6).[3]

This last series exhibits different biological properties ; of special interest is the inhibition of glycoprotein synthesis recently demonstrated for swainsonine (5) and its congeners.[3] As a consequence *in vitro* activity against viruses,[3,4] particularly HIV,[4c] has been claimed for some compounds. Tetra- or trihydroxylated indolizidines are frequently encountered as natural products, however a dihydroxylated indolizidine has also been isolated recently by Harris who found that minor amounts of indolizidine diol (4) are produced by *Rhizoctonia leguminicola*, the fungus which produces the two toxic alkaloids : swainsonine (5) and slaframine (6).[5]

Most of the syntheses of natural polyhydroxylated indolizidines[6] are based upon the use of sugars as starting materials and involve a large number of steps.[7]

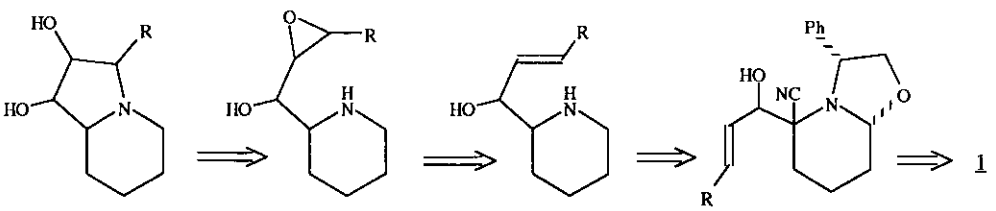
We are developing a new and general approach to the asymmetric synthesis of alkaloids, called the CN(R,S) method[8e] starting from the chiral synthon (1).[8a] Enantiospecific preparations of alkylindolizidines (2) and (3) represent some of the numerous applications of this strategy.[8b,c]

Our interest in the functionalized indolizidines (4 - 6) led us to propose an extension of our previous work to the syntheses of this type of structure and in particular of analogs bearing an alkyl side chain as in compounds of type 2 or 3. Indeed modifications of the hydrophilicity of hydroxylated compounds by the introduction of a lipophilic chain is of interest from a biological point of view. Furthermore, as synthon (1) is a 1,4-dihydropyridine equivalent it is possible to envisage functionalizations at C-3 or C-5 positions of the piperidine ring opening a route to the total synthesis of polysubstituted alkaloids (eg. 5 or 6). In this paper, we report the asymmetric synthesis of a 3-methyl analog of the natural indolizidinediol (4).[5,9]



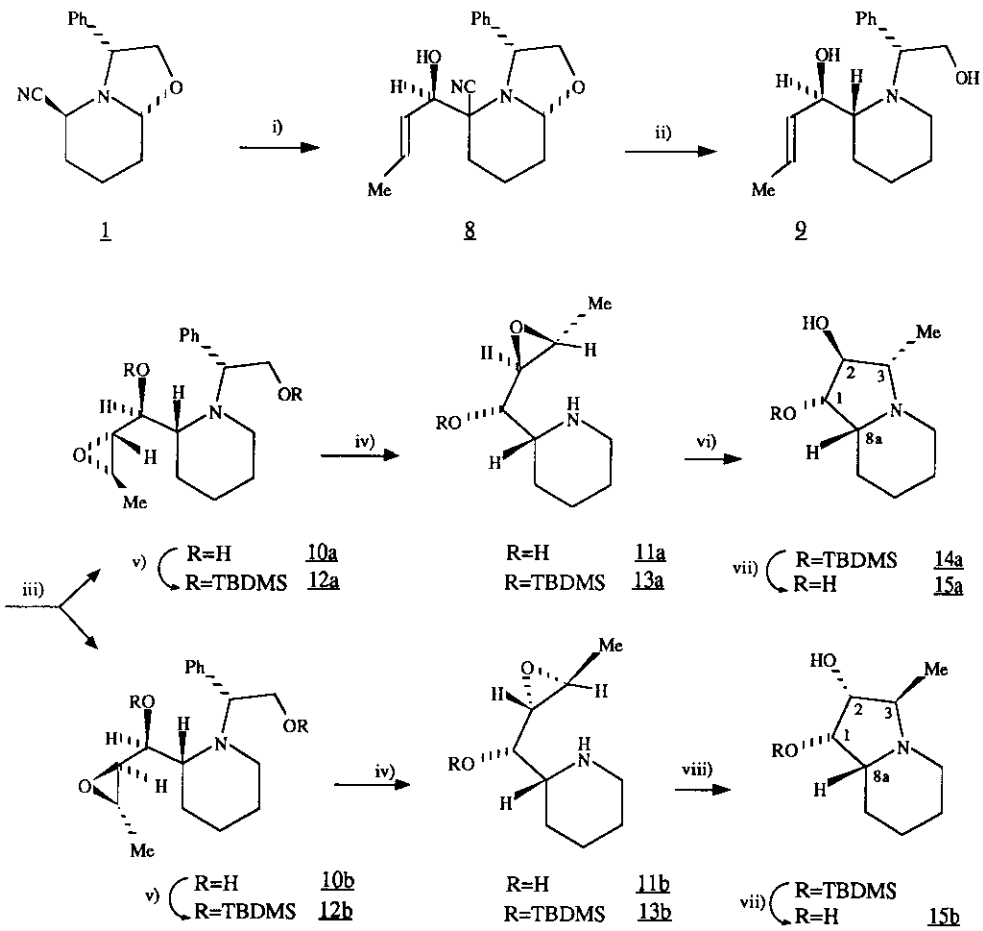

Figure

We have shown previously[8d] that alkylation of synthon (1) with propionaldehyde led to (-)-β-conhydrine (7) (Figure) which has the same absolute configuration as swainsonine (5) at C-1 and C-8a. On the basis of this result the generation of a second hydroxyl group with concomitant formation of a five membered ring could result from the nucleophilic attack of the piperidine nitrogen on an epoxide (Scheme 1).




Scheme 1

The reaction of a carbanion with a $\alpha,\beta$-unsaturated aldehyde is known to give 1,2-addition under kinetic conditions.[10] In the present case, treatment of synthon (1) sequentially with LDA (- 78°C, THF) and crotonaldehyde led to the formation of a mixture of two isomers, from which the major compound (8) (Scheme 2) was easily isolated in a 60% yield. The minor isomer was always found in very small quantities (< 2%) and although not fully characterized, was tentatively assigned as an epimer of 8 at the carbon bearing the hydroxyl group. Compound (8) was reduced to the diol (9) in 98% yield by treatment with sodium borohydride in boiling ethanol. A stereoselective epoxidation of the double bond of the diol (9) was obtained by reaction with trifluoroperacetic acid[11] (which involved the presence of a strong acid avoiding the formation of the N-oxide) at low temperature to give a mixture of two diastereoisomeric epoxides (10)




Reagents : i) LDA, THF, -78°C, $CH_3$-CH=CH-CHO ; ii) $NaBH_4$, EtOH, $\Delta$ ; iii) $CF_3CO_3H$, $CH_2Cl_2$, -50°C ; iv) $H_2$, Pd/C, MeOH, room temperature; v) TBDMSCl, imidazole, $CH_2Cl_2$ ;vi) $\Delta$, 72 h, PhMe; vii) $BF_3.OEt_2$, MeCN, -5° to 25°C, 2 h; viii) MeOH, room temperature, 24 h.

Scheme 2

(ratio 8:2) in a 60% yield. Although the separation of isomers was possible at this stage it appeared tedious and it was decided to leave this separation until a subsequent step. Hydrogenolysis of the chiral appendage of the mixture (10) gave almost quantitatively the secondary amine (11) (as diastereoisomers) which gave only a complex mixture in attempts to form the indolizidine ring system by intramolecular reaction of the epoxide and amine functions. It was clear that Payne rearrangement[12] of $\alpha$-hydroxy epoxide function might occur, thus we decided to protect the hydroxyl function. Using a large excess (8 equiv.) of tert-butyldimethylsilyl chloride in classical conditions ($CH_2Cl_2$, imidazole),[13] diols (10) were silylated to 12. At this stage the diastereoisomeric mixture was then readily separated by flash chromatography on silica gel to furnish the two components (12a) and (12b), respectively in 57% and 26% yield from 10.[14] Each isomer was then treated separately by the same sequence of reactions. Deprotection of the nitrogen was obtained by hydrogenolysis ($H_2$, Pd/C) to give the secondary amines (13a) (91% yield) and (13b) (74% yield). Final cyclization to the indolizidine (14a) was achieved in 86% yield by single heating in toluene for 72 h whereas 13b cyclised smoothly in methanol at room temperature to yield 14b (78%) after 24 h. It has been shown by Stork[15] that - in the absence of other structural restraints - intramolecular attack of a carbanion on an equally substituted epoxide yields preferentially the smaller ring regardless of its size (3, 4, 5 or 6 membered). In the present case, owing to the known difficulty of formation of azetidine[16] and to the significant cyclic strain of the fused 4 + 6 membered ring system the cyclisation to a four membered ring can be ruled out. Careful examination of spectra data of 14a confirmed this assertion. $^{13}C$ - $^{1}H$ two dimensional correlation nmr permitted the precise attribution of diagnostic protons. The stereochemistry of the indolizidines (14a) and (14b) was then deduced from its 400 MHz $^{1}H$ nmr spectrum : the *trans* relationship between the two oxygen atoms in 14a was established from the value of the coupling constant between H-1 and H-2 : $J_{1,2}$ = 1.7 Hz in sharp contrast with the 7 Hz value for the indolizidinediol (4) described by Harris[5] and 6.1 Hz in the case of swainsonine (5). These last values agreed also with the *cis* relationship of the OH groups in *cis* isomer (14b) which exhibits $J_{1,2}$ = 6.5 Hz. Protons H-1 and H-8a are *cis* in compound (14a) since the coupling constant $J_{1\text{-}8a}$ is 5.5 Hz compared with 3.7 Hz in 5 (*cis*) and 9 Hz in 4 (*trans*) and in agreement with our previous synthesis of $\beta$-conhydrine (7).[8d]

Deprotection of 14a and 14b was achieved with $BF_3.Et_2O$. The resulting diols were obtained in 71% (15a) and 67% (15b) yield after purification.

Access to other compounds - natural or analogs - are being envisaged by this new strategy eg *cis*-diols as major components or trihydroxylated compound of the swainsonine series.

## *EXPERIMENTAL*

Infrared spectre (ir) were recorded in chloroform solution on a Perkin-Elmer 297 Spectrophotometer. Peaks yielding structural informations are reported. $^1H$ and $^{13}C$ nmr spectra were recorded in $CDCl_3$ (tetramethylsilane as an internal standard, $\delta$ : 0) on a Brucker AC-200 and/or AC-400 and/or AC-250 instruments. Mass spectrometry was performed on a AEI ms 50 by the ms service of the ICSN at Gif.

**Aminonitrile (8)** — To a solution of LDA [prepared from 3.5 ml (24.8 mmol) of diisopropylamine and 15.6 ml (24.8 mmol) of 1.6 M BuLi in hexane] in 30 ml of THF, cooled to -70°C under nitrogen, was added a solution of 2.565 g (11.25 mmol) of 1[8b] in 5 ml of THF over 15 min. The yellow solution was stirred for 15 min and 2.6 ml of crotonaldehyde were then added. The solution was stirred at -70°C for 3 h and then quenched by addition of saturated ammonium chloride solution. The mixture was extracted with methylene chloride (3 x 20 ml) and the combined organic layers were dried and concentrated to dryness. The resulting yellow oil was flash chromatographied (hexane/ether : 70:30) to give 2 g (60%) of white crystals. mp 96°C (hexane) ; $[\alpha]_D^{20}$ -113° (c 0.82, $CHCl_3$) ; ms, m/z (relative intensity) : 298 ($M^{+\cdot}$, 10), 254(80), 227(100) ; $^1H$ nmr (400 MHz, $CDCl_3$,) $\delta$ : 7.03-7.38 (m, 5H, Ar), 5.31 (dq, J = 16, 6.5 Hz, 1H, $CH_3CH$=C), 5.21 (dd, J = 16, 6 Hz, 1H, =CH-CHOH), 4.21 (dd, J = 9, 3 Hz, 1H, PhCHN or $CH_2O$), 4.10 (dd, J = 9, 3 Hz, and t, J = 9 Hz, 2H, N-CH-O and PhCHN or $CH_2O$), 3.70 (brd, J = 6 Hz, 1H, CH-OH), 3.73 (dd, J = 9, 3 Hz, 1H, PhCHN or $CH_2O$), 1.53 (d, J = 6.5 Hz, 3H, Me), 1.38-2.20 (m, 6H, ring $CH_2$) ; $^{13}C$ nmr (50 MHz, $CDCl_3$) $\delta$ : 17.5, 19.6, 29.1, 31.0, 61.4, 66.5, 73.3, 76.5, 92.6, 117.7, 127.2, 127.7, 128.3, 129.2, 144.4. Anal. Calcd for $C_{18}H_{22}N_2O_2$ : C, 72.45 ; H, 7.43 ; N, 9.38. Found : C, 72.31 ; H, 7.49 ; N, 9.55.

**Diol (9)** — Sodium borohydride (1.8 g, 47 mmol) was added in small portions to a solution of aminonitrile (8) (1.8 g, 6.04 mmol) in 40 ml of absolute ethanol. The mixture was refluxed for 1 h, cooled to room temperature and then poured into water. Extraction by methylene chloride (5 x 20 ml) followed by drying ($Na_2SO_4$) and removal of solvent led to diol (9) as a colorless oil (1.6 g ; 98% yield) which is pure enough for next step. $[\alpha]_D^{20}$ -39° (c 0.8, $CHCl_3$) ; ms, m/z (relative intensity) : 275 ($M^{+\cdot}$, 5), 244(75), 204(100), 84(87) ; $^1H$ nmr (200 MHz, $CDCl_3$) $\delta$ : 7.20-7.50 (m, 5H, Ar), 5.76 (dq, J = 15, 6.5 Hz, 1H, $H_3C$-CH=), 5.16 (ddd, J = 15, 8, 0.8 Hz, 1H, =CH-CHOH), 4.26 (t, J = 8 Hz, 1H, CHOH), 4.13 (t, J = 6 Hz, 1H, NCHPh), 3.90 (dd, J = 10, 6 Hz, 1H, $CH_2OH$), 3.78 (dd, J = 10, 6 Hz, 1H, $CH_2OH$), 3.00 (m, 1H, NCH2 eq), 2.50 (m, 1H, NCHCHOH), 1.63 (d, J = 6.5 Hz, 3H, $CH_3$), 1.10-3.20 (m, 6H, piperidine ring) ; $^{13}C$ nmr (50 MHz, $CDCl_3$) $\delta$: 17.5, 19.9, 20.1, 20.8 (x 2), 44.0, 57.6, 64.0, 66.3, 68.8, 127.4, 128.3, 128.4, 128.9, 132.1, 141.0. Anal. Calcd for $C_{17}H_{25}NO_2$ : C, 74.14 ; H, 9.15 ; N, 5.08. Found : C, 73.87 ; H, 9.20 ; N, 5.14.

**Epoxy-diols (10)** — A solution of diol (9) (1.51 g, 5.5 mmol) in 25 ml of methylene chloride was treated at

-50°C with 4.1 ml (15.4 mmol) of a $CH_2Cl_2$ solution of trifluoroperacetic acid (prepared as described by Emmons[17]). Stirring was maintained at -50°C for 2.5 h and at -30°C for 1 h. The mixture was allowed to warm to room temperature and was extracted with methylene chloride after treatment with a 10% sodium carbonate solution up to pH 9. The extracts were dried ($Na_2SO_4$) and the solvent was removed. The crude product was purified by flash chromatography on silica gel ($CH_2Cl_2$-MeOH 95:5) giving 0.96 g of 10 (60%). A careful separation on silica gel gave an analytical sample of the major epoxide (10a) as colorless crystals : mp 88°C (hexane) ; $[\alpha]_D^{20}$ -7° (c 1, $CHCl_3$) ; ms, m/z (relative intensity) : 291 ($M^{+\cdot}$, 5), 260(100), 291(3), 204(94), 84(75) ; $^1$H nmr (400 MHz, $CDCl_3$) $\delta$ : 7.15-7.45 (m, 5H, Ar), 4.15 (t, J = 6 Hz, 1H, NC<u>H</u>Ph), 3.98 (dd, J = 12, 6 Hz, 1H, C<u>H</u>$_2$OH), 3.80 (dd, J = 12, 6 Hz, 1H, C<u>H</u>$_2$OH), 3.71 (dd, J = 10, 6 Hz, 1H, C<u>H</u>OH), 2.98 (m, 3H), 2.80 (m, 1H), 2.50 (brd, J = 4 Hz, 1H, OC<u>H</u>-CHOH), 1.25-1.70 (m, 6H), 1.25 (d, J = 6 Hz, 3H, $CH_3$) ; $^{13}$C nmr (50 MHz, $CDCl_3$) $\delta$ : 17.0, 20.3, 21.5, 22.0, 44.7, 52.3, 55.0, 61.0, 63.6, 66.6, 67.5, 127.5, 128.1, 128.4, 140.9 ; Anal. Calcd for $C_{17}H_{25}NO_3$ : C, 70.07 ; H, 8.64 ; N, 4.80. Found : C, 70.10 ; H, 8.64 ; N, 4.69.

<u>Disilylated compounds (12)</u> — Epoxy-diol (10) (670 mg, 2.3 mmol) in 5 ml of methylene chloride was treated under nitrogen atmosphere with 1.725 g of t-butyldimethylsilyl chloride (11.5 mmol) and 625 mg of imidazole (9.2 mmol). A white precipitate rapidly appeared and the reaction mixture was stirred at room temperature for 15 h. Water (10 ml) was added and the organic layer was decanted, the mixture was extracted with methylene chloride (3 x 5 ml) and the extracts were dried ($Na_2SO_4$) and the solvent removed. Purification on silica gel (hexane-ether 92:8) permitted isolation of 681 mg of major isomer (12a) as an oil (57%) and 310 mg of minor isomer (12b) (26%). <u>Major isomer</u> (12a) : $[\alpha]_D^{20}$ + 5° (c 1, $CHCl_3$) ; ms, m/z (relative intensity) : 521 ($M^{+\cdot}$, 5), 318(90), 375(100) ; $^1$H nmr (400 MHz, $CDCl_3$) $\delta$ : 7.10-7.40 (m, 5H, Ar), 4.08 (t, J = 4 Hz, 1H, PhC<u>H</u>N), 3.97 (dd, J = 8, 4 Hz, 1H, C<u>H</u>$_2$O), 3.88 (dd, J = 8, 4 Hz, 1H, C<u>H</u>$_2$O), 3.77 (t, J = 4 Hz, 1H, C<u>H</u>-OSi), 2.92 (m, 1H, C<u>H</u>N), 2.77 (m, 1H, CH$_2$C<u>H</u>-O), 2.73 (m, 1H, C<u>H</u>O-CHOSi), 2.55 (m, 1H, C<u>H</u>N), 1.16 (d, J = 6 Hz, 3H, $CH_3$), 0.92 (s, 9H, Bu), 0.83 (s, 9H, Bu), 0.10 (s, 6H, Si$(CH_3)_2$), -0.80 (s, 6H, Si$(CH_3)_2$); $^{13}$C nmr (50 MHz, $CDCl_3$) $\delta$ : -5.2, -5.3, -4.6, -4.5, 17.4, 18.3, 26.0, 45.9, 53.2, 60.7, 61.3, 63.9, 64.3, 73.3, 128.2, 128.3, 128.35. Anal. Calcd for $C_{29}H_{53}NO_3Si_2$ : C, 66.99 ; H, 10.27 ; N, 2.69. Found : C, 67.67; H, 10.25 ; N, 2.56. <u>Minor compound</u> (12b) $[\alpha]_D^{20}$ + 50° (c 2.27, $CHCl_3$) ; ms, m/z (relative intensity) : 519($M^{+\cdot}$, 10), 504(65), 462(82), 318(100), 84(64) ; $^1$H nmr (250 MHz, $CDCl_3$) $\delta$ : 7.20-7.50 (m, 5H, Ar), 4.35 (m, 1H, PhC<u>H</u>N), 4.20 (dd, J = 4, 8 Hz, 1H, C<u>H</u>$_2$O), 4.05 (m, 1H, C<u>H</u>$_2$O), 3.00 (ddd, J = 2.0, 5.2, 11.0 Hz, 1H, C<u>H</u>N), 2.90 (m, 1H, C<u>H</u>OSi), 2.85 (m, 1H, CH$_3$C<u>H</u>-O), 2.75 (dt, J = 11.5, 3.5 Hz, 1H, C<u>H</u>N), 2.33 (td, J = 11.5, 2.5 Hz, 1H, C<u>H</u>N), 1.30 (d, J = 6.0 Hz, 3H, $CH_3$), 0.88 (s, 18H, Bu), 0.05 (s, 12H, Si$(CH_3)_2$) ; $^{13}$C nmr (62.5 MHz, $CDCl_3$) $\delta$ : -5.4, -5.3, -4.7, -4.6, 17.3, 18.2, 24.4, 25.9, 47.0, 50.8, 59.3, 60.9, 61.7, 62.3, 68.7,

126.5, 127.9, 128.2, 141.9. Anal. Calcd for $C_{29}H_{53}NO_3Si$ : C, 66,99 ; H, 10.27 ; N, 2.69. Found : C, 67.21 ; H, 10.25 ; N, 2.71.

**Secondary amine (13a)** — Compound (12a) (380 mg, 0.73 mmol) was dissolved in 10 ml of methanol. 20 mg of Pd on charcoal (5%) were added. The mixture was stirred for 7 h under a hydrogen atmosphere. Catalyst was removed by filtration on a celite bed and the solution was evaporated to dryness. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$-MeOH 95:5) to give 190 mg of 13 (91%) as a colorless oil. $[\alpha]_D^{20}$ + 1° (c 1.6, $CHCl_3$), ms, m/z (relative intensity) : 285 ($M^{+\cdot}$, 15), 270(30), 227(85), 84(100) ; $^1$H nmr (200 MHz, $CDCl_3$) $\delta$ : 3.12 (m, 1H, N-C<u>H</u>$_2$), 3.04 (t, J = 7 Hz, 1H, C<u>H</u>-OSi), 2.85 (dq, J = 5.5, 2 Hz, 1H, $H_3$C-C<u>H</u>-O), 2.66 (dd, J = 8, 2 Hz, 1H, O-C<u>H</u>-CHOSi), 2.58 (m, 1H, N-C<u>H</u>), 2.28 (brs, 1H, NH), 1.30 (d, J = 5.5 Hz, 3H, $CH_3$), 0.93 (s, 9H, Bu), 0.16 (s, 6H, $Me_2$Si) ; $^{13}$C nmr (50 MHz, $CDCl_3$) $\delta$ : -6.8, -5.8, 17.3, 24.7, 26.5, 26.7, 28.9, 46.9, 53.3, 60.3, 61.6, 78.9. Anal. Calcd for $C_{15}H_{31}NO_2Si$ : C, 63.10 ; H, 10.94 ; N, 4.90. Found : C, 62.70 ; H, 10.73 ; N, 4.75.

**Secondary amine (13b)**— Compound (12b) (168 mg, 0.32 mmol) was dissolved in 10 ml of methanol. 20 mg of Pd on charcoal (5%) were added. This mixture was stirred for 1 h under a hydrogen atmosphere. Filtration on a celite bed and evaporation to dryness gave after flash chromatography on silica gel ($CH_2Cl_2$-MeOH 95:5) pure compound (13b) (68 mg, 74% yield) as a colorless oil. $[\alpha]_D^{20}$ -7° (c 1.90, $CHCl_3$) ; ms, m/z (relative intensity) : 285 ($M^{+\cdot}$, 5), 270(13), 111(43), 84(100) ; $^1$H nmr (250 MHz, $CDCl_3$) $\delta$ : 3.25 (dd, J = 6.2, 4.8 Hz, 1H, C<u>H</u>-OSi), 3.15 (m, 1H, N-C<u>H</u>$_2$), 2.88 (qd, J = 5.5, 2.5 Hz, 1H, $CH_3$-C<u>H</u>-O), 2.80 (dd, J = 6.5, 2.5 Hz, 1H, O-C<u>H</u>-CHOSi), 2.65 (m, 1H, N-C<u>H</u>), 2.05 (brs, 1H, N<u>H</u>), 1.32 (d, J = 5.5 Hz, 3H, $CH_3$), 0.90 (s, 9H, Bu), 0.05 (s, 6H, Si$(CH_3)_2$) ; $^{13}$C nmr (62.5 MHz, $CDCl_3$) $\delta$ : -4.7, -4.0, 17.3, 18.3, 24.7, 25.9, 26.9, 28.7, 46.9, 53.3, 59.7, 60.6, 75.8. Anal. Calcd for $C_{15}H_{31}NO_2Si$ : C, 63.16 ; H, 10.88 ; N, 4.91. Found : C, 63.18 ; H, 10.61 ; N, 4.92.

**Indolizidine (14a)**— A toluene solution (20 ml) of 13a (180 mg, 0.6 mmol) was refluxed under an argon atmosphere for 96 h. The solvent was evaporated to give a dark residue. Flash chromatography on silica gel with $CH_2Cl_2$/MeOH 95:5 gave 150 mg (86%) of 14a as a colorless oil. $[\alpha]_D^{20}$ + 1.6° (c 2.3, $CHCl_3$) ; ms, m/z (relative intensity) : 285 ($M^{+\cdot}$, 50), 270(27), 170(40) ; $^1$H nmr (400 MHz, $CDCl_3$) $\delta$ : 3.90 (dd, J = 5.5, 1.75 Hz, 1H, H-1), 3.62 (dd, J = 7, 1.75 Hz, 1H, H-2), 3.14 (brd, J = 10.5 Hz, 1H, H-5 eq), 2.05 (ddd, J = 10.5, 5.5, 3 Hz, 1H, H-8a), 1.93 (dq, J = 7, 7 Hz, 1H, H-3), 1.85 (brd, J = 12 Hz, 1H), 1.76 (dt, J = 10.5, 3 Hz, 1H, H-5 ax), 1.20-1.60 (m with d = 7 Hz at 1.25 ppm, 8H), 0.92 (s, 9H, Bu), 0.10 (s, 6H, $SiMe_2$) ; $^{13}$C nmr (50 MHz, $CDCl_3$) $\delta$ : -4.8, -4.5, 15.6 ($CH_3$), 18.3, 24.1, 24.8, 25.3, 51.5 (C-5), 67.9 (C-8a), 68.2 (C-3), 80.0 (C-1), 87.0 (C-2). Anal. Calcd for $C_{15}H_{31}NO_2Si$ : C, 63.16 ; H, 10.88 ; N, 4.91. Found : C, 63.36 ; H, 10.77 ; N, 4.87.

**Indolizidine (14b)**— A methanol solution (10 ml) of 13b (68 mg, 0.24 mmol) was stirred for 24 h under argon atmosphere to give after flash chromatography on silica gel ($CH_2Cl_2$-MeOH 95:5) pure 14b (53 mg, 78% yield) as a colorless oil. $[\alpha]_D^{20}$ + 30° (c 1.8, $CHCl_3$) ; ms, m/z (relative intensity) : 285 ($M^{+\cdot}$, 17), 270(33), 228(48), 111(100), 96(86), 84(72) ; $^1H$ nmr (250 MHz, $CDCl_3$) δ : 4.15 (dd, J = 6.5, 5.5 Hz, 1H, CH-OSi), 3.90 (m, 1H, CH-OH), 3.15 (m, 1H, $CH_2N$), 2.95 (m, 1H, O-H), 1.97 (dq, J = 6.5, 6.5 Hz, 1H, $CH_3$-CH), 1.75 (m, 1H, CHN), 1.15 (d, J = 6.5 Hz, 3H, $CH_3$), 0.90 (s, 9H, Bu), 0.10 (s, 6H, $Si(CH_3)_2$) ; $^{13}C$ nmr (62.5 MHz, $CDCl_3$) δ : -5.0, -4.8, 11.5, 18.6, 24.4, 24.8, 25.0, 25.9, 51.7, 65.6, 69.3, 71.5, 72.4. Anal. Calcd for $C_{15}H_{31}NO_2Si$ : C, 63.16 ; H, 10.88. Found : C, 63.07 ; H, 10.76.

**Indolizidine diol (15a)**— To 40 mg (0.16 mmol) of compound (14b) in 5 ml of dry acetonitrile were slowly added 80 μl (0.64 mmol) of $BF_3.Et_2O$ at - 5°C and were allowed to warm to room temperature for 1.5 h. Then 4 equivalents of water were added slowly and the resulting solution was evaporated to dryness. The residue was washed with ether and dichloromethane and the resulting crude diol was purified by flash chromatography on silica gel (Acetone, $CHCl_3$, $H_2O$, $NH_4OH$, 75 : 12.5 : 10 : 2.5) to yield 17 mg of pure product (71% yield). $[\alpha]_D^{20}$ - 7° (c 1.9, MeOH) ; ms, m/z (relative intensity) : 171 ($M^{+\cdot}$, 13), 156(36), 111(100), 96(45), 84(64) ; $^1H$ nmr (250 MHz, $CD_3OD$) δ : 3.75 (brd, J = 2.9 Hz, 1H, NCHCH-OH), 3.58 (dd, J = 0.7, 3.6 Hz, 1H, $CH_3CHCH$-OH), 3.40 (m, 1H, $NCH_2$), 2.90 (dt, J = 11.5, 3.0 Hz, 1H, N-CH), 2.80 (dq, J = 3.6, 7.1 Hz, 1H, $CH_3$-CH), 2.62 (td, J = 3.0, 12.3 Hz, 1H, N-$CH_2$), 1.30-1.85 (m, 6H, $CH_2$-$CH_2$-$CH_2$), 1.25 (d, J = 7.0 Hz, 3H, $CH_3$). $^{13}C$ nmr (62.5 MHz, $CD_3OD$) δ : 14.6, 22.7, 23.7, 24.0, 52.5, 70.5, 72.0, 77.1, 82.1, Hrms Calcd for $C_9H_{17}NO_2$ : 171.1259. Found : 171.1267.

**Indolizidine diol (15b)**— The same procedure as for 15a was followed to obtain 16 mg of pure product (67% yield). $[\alpha]_D^{20}$ + 14° (c 0.49, MeOH) ; ms, m/z (relative intensity) : 171 ($M^{+\cdot}$, 15), 156(30), 111(100), 96(50), 84(28) ; $^1H$ nmr (250 MHz, $CD_3OD$) δ : 4.40 (dd, J = 5.3, 8.2 Hz, 1H, $CH_3CHCH$-OH), 4.25 (dd, J = 3.1, 5.4 Hz, 1H, NCH-CH-OH), 3.60 (m, 1H, $NCH_2$), 3.50 (dq, J = 7.4 Hz, 1H, $CH_3$-CH), 3.15 (m, 1H, N-CH), 2.85 (td, J = 3.8, 12.2 Hz, 1H, $NCH_2$), 1.50-2.10 (m, 6H, $CH_2$-$CH_2$-$CH_2$), 1.35 (d, J = 6.9 Hz, 3H, $CH_3$); $^{13}C$ nmr (62.5 MHz, $CD_3OD$) δ : 10.5, 23.2, 23.7, 24.0, 52.2, 67.0, 69.8, 70.2, 71.2 . Hrms Calcd for $C_9H_{17}NO_2$: 171.1259. Found : 171.1257.

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Received, 26th February, 1990