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Radical Cyclizations of 1,4-Dihydropyridines. Synthesis of Chiral fused Nitrogen Heterocycles. Synthesis of Lupinine and Epilupinine.

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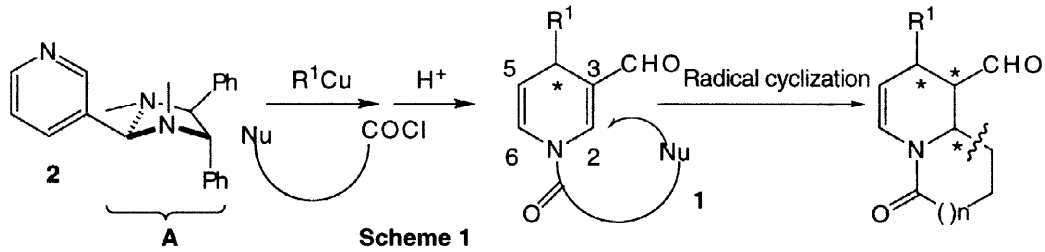
Abstract: Radical cyclizations of 1-(4-iodoalkanoyl)-3-formyl-4-methyl-1,4-dihydropyridines are described and discussed. A regio and diasteroselective reaction is obtained under ultrasonic conditions. An application to the synthesis of lupinine and epilupinine is shown. © 1998 Elsevier Science Ltd. All rights reserved.

Due to their great importance, particularly in the field of quinolizidine and indolizidine alkaloids, the construction of chiral fused nitrogen heterocycles has attracted large attention and a number of interesting approaches have been proposed.[1] Chiral 1,4 dihydropyridines **1** with an exocyclic substituent are excellent precursors of such compounds by the way of cyclization reactions involving one of the two double bonds (scheme 1).[2] These double bonds are well differenciated as the C2-C3 one is trisubstituted and activated by an electron withdrawing group, whereas the C5-C6 one is disubstituted and non activated. It should thus be possible to take advantage of this difference to control the regioselectivity of the cyclization step. Moreover, due to the presence of a stereogenic center at C4, it should be possible to influence both the diastereo and enantioselectivity of the reaction. It is well known that the presence of an electron-withdrawing group dramatically accelerates the addition of a nucleophilic alkyl radical onto an alkene.[3] Therefore, we decided to investigate radical cyclizations onto the C2-C3 double bond. In this paper we want to report the full results of a study on this topic.[4]



Several radical cyclizations onto enamide double bonds have been reported.[5] These include a radical annelation of a 4-unsubstituted-1,4-dihydropyridine, bearing a suitable exocyclic nitrogen sustituent and an electron withdrawing group (ester) on the C3 position, published by Beckwith.[6] However, despite the presence

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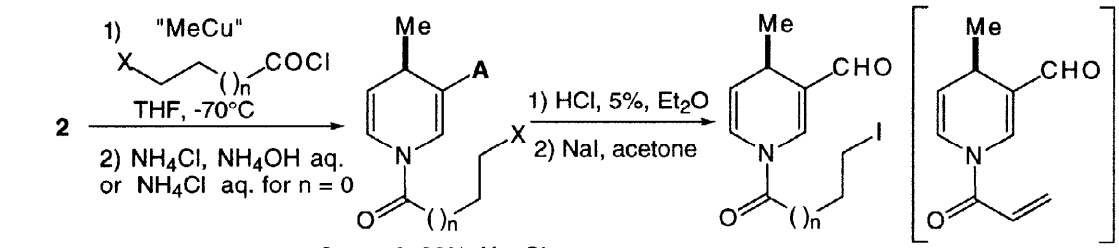
of the ester functionality, a non regioselective cyclization was observed. Furthermore, as the bicyclic product contained an enamine, difficulties were encountered during isolation. In our case this problem should be avoided due to the presence of an acyl group on the nitrogen. The same author has also described a cyclization of *N*- acyl -2-substituted 2,3,4-pyridones by an intramolecular addition which was found to occur on the opposite face to the C2 substituent.[7] However, to our knowledge, nothing was known about the stereochemical influence of a C4 substituent on such cyclizations.

Preparation of 1,4-dihydropyridines

The requisite starting chiral 1,4-dihydropyridines **3a-c** (de = 95 %, determined by ^{1}H NMR) were prepared by addition of an acid chloride (3-chloropropanoyl, 4-chlorobutanoyl or 5-bromopentanoyl) to aminal **2** in the presence of MeCu. When the reaction was performed using chloropropanoyl chloride (n = 0), variable amounts (10-20%) of the aldehyde **4** were obtained. The formation of **4** was essentially avoided (<10%) by quick hydrolysis of the reaction mixture with an aqueous solution of NH_4Cl rather than NH_3/NH_4Cl. The chloro-aldehydes, obtained by acidic hydrolysis of the dihydropyridine aminals, were then transformed into the corresponding iodo derivatives **5a-c** by standard procedure. These somewhat unstable compounds were directly used for radical cyclizations. By analogy with our previous work, the absolute stereochemistry of the new stereogenic center was postulated to be R starting from an aminal of S,S configuration.

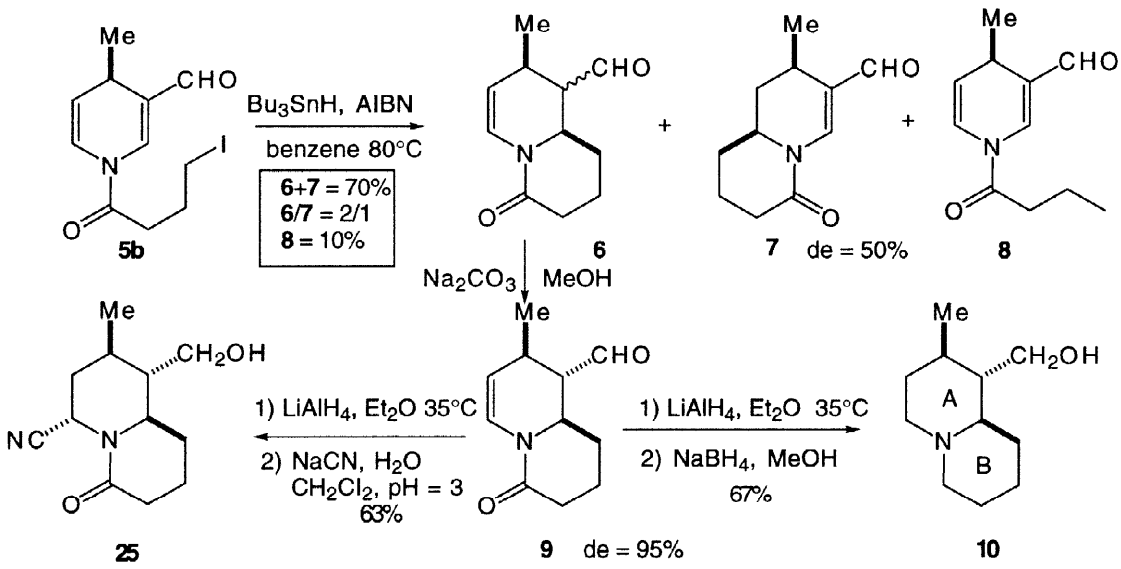


Scheme 2

Cyclization with Bu_3SnH

Slow addition of a 0.2 M solution of a mixture of Bu_3SnH (1 equivalent) and AIBN (10%) to a 0.1 M solution of the dihydropyridine aldehyde **5b** (n = 1) in boiling benzene afforded the cyclized products **6** and **7** in a 2/1 ratio (80% yield, Scheme 3) and the reduced dihydopyridine **8** (10%). The bicycle **6**, a mixture of two diastereomers (de = 80%) resulting from cyclization on the C2-C3 double bond, was converted to diastereomerically pure **9** by treatment with a suspension of Na_2CO_3 in methanol. This compound was then reduced in two steps (scheme 3) to the crystalline quinolizine **10** (92% ee as shown by ^{31}P NMR[8]). X-Ray analysis of **10** (fig 1) showed that the quinolizine presented a double chair conformation in which all the substituents of ring A were equatorial. Therefore, the 6-exo-trig cyclization onto C2 had occured cis to the C4 substituent to give a radical which was trapped on the less hindered face to give **6**. This bicycle is configurationally unstable at the C3 position and was therefore totally isomerized under basic conditions to give **9**. Starting from an aminal of a S,S configuration a bicycle of C2R, C3S, C4R was obtained. Compound **7**, resulting from cyclization onto the C5-C6 double bond was a mixture of cis and trans diastereomers (de = 50%). These diastereomers were separated by thin layer chromatography and the relative configuration of each one was established by ^{1}H NMR analysis (nOe) and shown to be *cis* for the major diastereomer (fig 2) and

trans for the minor one. Therefore, the cyclization onto the C5-C6 double bond occured, again, mainly *cis* to the C4 substituent.



Scheme 3

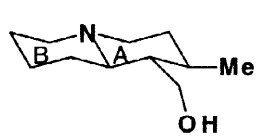


fig. 1

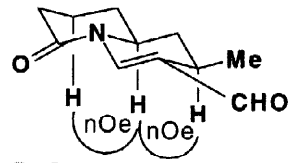
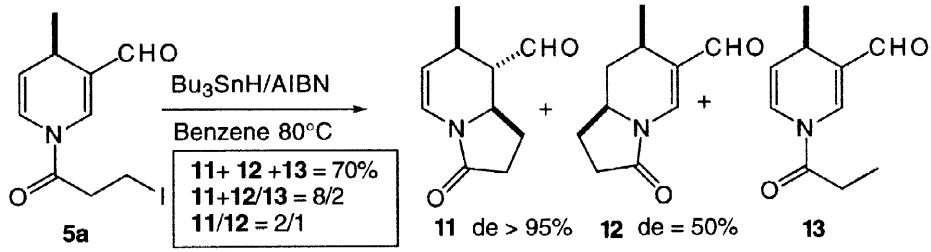


fig. 2

The dihydropyridine aldehyde **5a** (n = 0), when treated under the same conditions as for **5b**, gave almost the same results (scheme 4): two bicycles **11** and **12** (2/1) and the dihydropyridine **13**. Compound **11** (cyclization onto C2), obtained as a single diastereomer, was configurationaly stable under basic conditions. A ^{1}H NMR analysis (nOe, fig.3) showed a *cis* relationship between the C2 and the C4 substituents.



Scheme 4

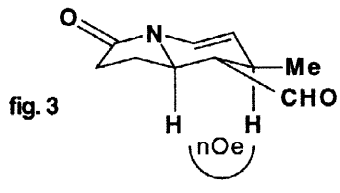
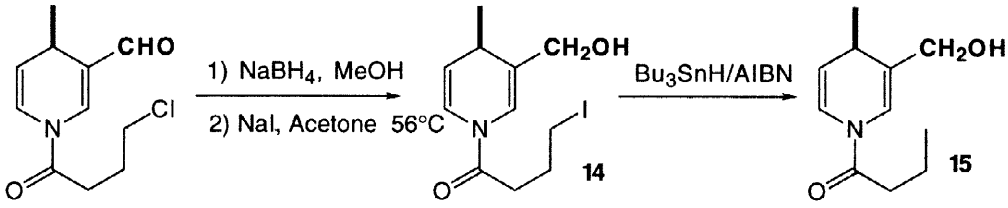


fig. 3

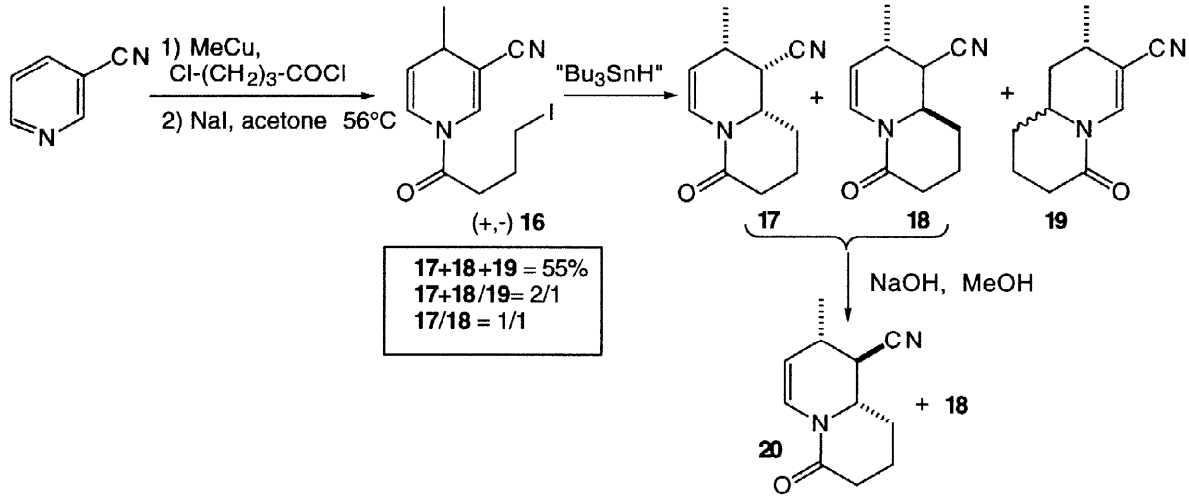
As with the 6-exo-trig cyclization, the 5-exo-trig occurs *cis* to the C4 substituent. Compound **12** (cyclization onto C6) was obtained as a mixture of two diastereomers (de = 50%). Noteworthy was the increase of the proportion of the reduced product as compared with the formation of the 6 membered ring.

The influence of the aldehyde on the cyclization was then studied. The alcohol **14**, prepared as shown in Scheme 5, when submitted to the cyclization conditions, afforded in quantitative yield, the reduction product **15**. Therefore, the presence of the aldehyde function seems to be crucial for the two possible (C2 or C6) cyclizations. If the influence of an electron withdrawing group on C3 is obvious for the C2 cyclization, its influence on the C5-C6 double bond is more obscure.



Scheme 5

Then, we decided to replace the aldehyde by a nitrile and to study the influence of this transformation on the cyclization. The racemic 3-cyano-1,4-dihydropyridine **16** was easily prepared from 3-cyanopyridine [9] according to the following scheme.



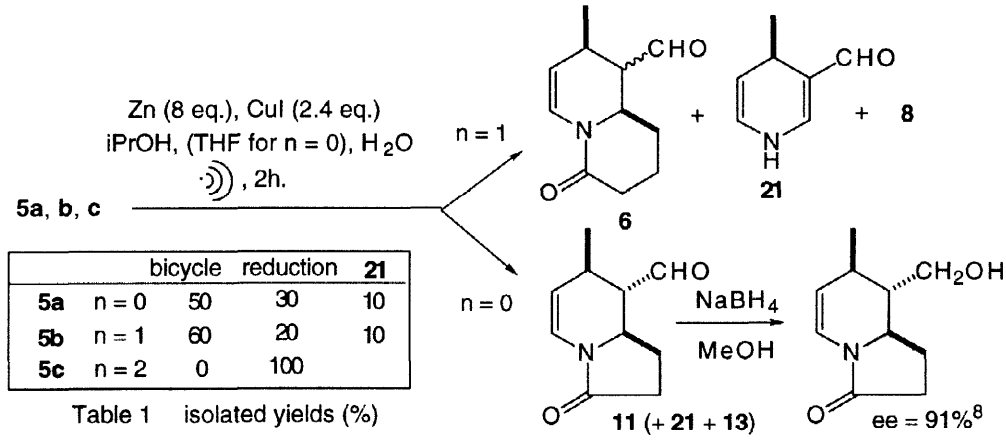
Scheme 6

Treatment of **16** under standard conditions (Bu_3SnH/AIBN) afforded four bicyclic compounds: two diasteromers (de = 0) **17** and **18** arising from cyclization onto C2, and two diasteromers **19** (de = 0) arising from cyclization onto the C6. The regioselectivity of the reaction, again, favours the C2 cyclization (**17+18/19** = 2/1). The mixture of **17** and **18**, after separation of **19**, was treated with a solution of NaOH in MeOH (15%). ^1H NMR analysis showed that **17** was quantitatively isomerised to **20** whereas **18** remained unchanged. We can therefore postulate that **17** arised from a *cis* cyclization to give the all *cis* derivative which can be isomerised into **20** whereas **18** arised from a *trans* cyclization. Whatever the relative stereochemistry of the C2 cyclized products, this cyclization was not selective (de = 0) whereas the corresponding one observed

with the aldehydes was entirely selective! Therefore, the presence of the aldehyde is crucial for the diastereoselectivity of the annelation.

Cyclization under sonication

Attempts to increase the regioselectivity of the cyclization by using $(Me_3Si)_3SiH$ [10] or Lewis acids ($LiClO_4$) [11] offered no improvement. Finally, we used the sonication conditions as described by Luche [12] (scheme 7). Under these conditions, **5b** (n = 1) three products were formed, the diastereomeric bicycles **6** arising from C2 cyclization, the reduced dihydropyridine **8** and the deacetylated compound **21** resulting from the hydrolysis of the amide functionality (table 1). The reaction was remarkably regioselective, indeed no trace of a C6 cyclization product was detected. After treatment of **6** under alkaline conditions the corresponding diastereomer **9** was obtained.

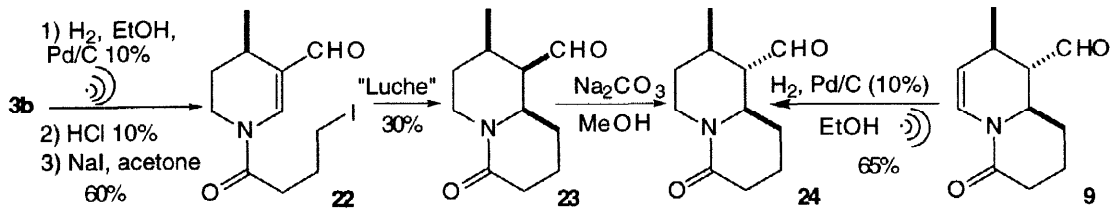


		bicycle	reduction	21
5a	n = 0	50	30	10
5b	n = 1	60	20	10
5c	n = 2	0	100	

Table 1 isolated yields (%)

Scheme 7

Due to the insolubility of **5a** in iPrOH, the reaction with this aldehyde was carried out in a mixture of iPrOH and THF (1/1). Similar selectivities were observed (50% yield). The bicycle **11** was obtained as a unique diastereomer with an ee of 91% (determined on the corresponding alcohol, scheme 7).[8] Therefore, under sonication, the *cis* stereochemistry of the cyclization was preserved. We have also tested the possibility of construction of seven membered rings[13] from the dihydropyridine **5c**. Unfortunately, only the reduction product was obtained. The tetrahydropyridine **22**, which was found to be unreactive with Bu_3SnH, gave under the Luche conditions, the *cis* cyclized product **23** in modest yield. The postulated relative configuration was confirmed by isomerization of **23** to give **24** which was also obtained by hydrogenation of **9** (scheme 8).



Scheme 8

Discussion

The stereoselectivity of the cyclization might arise from the conformation of the dihydropyridine ring. This conformation essentially depends upon the substituents on the ring[14] : e.g. dihydronicotamide is planar,[15]

but a 4-pyridyl-3,5-diacetyldihydropyridine has a boat conformation, the C4-pyridine ring lying in a pseudoaxial position.[16] Empirical, semi-empirical or *ab-initio* method calculations on the related 1,4-cyclohexadiene lead to the unique conclusion that the ring is plane, but the energy profile upon distorsion from planarity is quite flat.[17] Moreover, an X ray analysis of a C4-substituted -1,4 - dihydropyridine prepared for another purpose showed a flat conformation.[18] The fate of our cyclization was studied by performing AM1 calculations.[19] The geometries of the initial radicals and those of the four transition states (cyclization onto C2 or onto C6 respectively, *cis* or *trans* to C4 Me) were optimized, and the corresponding energies calculated (Table 2). It appears that: 1) the initial dihydropyridine ring is nearly planar, in agreement with the previous calculations on 1,4-cyclohexadiene;[17] 2) the conjugate cyclization (onto C2) is, in both cases (whether the EWG is -CHO or -CN), favoured; 3) the energy difference between *cis* and *trans* cyclization onto C2 is much more important for -CHO than for -CN, in both cases the *cis* approach being preferred. Nevertheless, the energy difference cannot account for the *cis* specific cyclization for the aldehydes. However, an energy partition analysis does not reveal a straightforward interaction term anymore. The failure to correctly predict the energy differences for the transition states in this case is due to the nature of the MO calculations, because the second order energy terms (Van der Waals type interactions) are minimized due to the use of centered orbitals preventing consequent polarization (even more sophisticated *ab-initio* calculations would not lead to improved results for the same reasons). However, the geometry of the transition states, and particularly the variation in dihedral angles between the incoming carbon radical, the EWG (-CHO or -CN) on C3 and the methyl group on C4 may give good insight as to the nature of these interactions (Table 3). Thus the radical approach onto C2 pushes the EWG on C3 to the opposite side of the ring in order to minimize steric interactions. It should be also noted that the dihedral angle between the EWG and the methyl group on C_4 either decreases (when the radical reacts on the side opposite to Me), leading to an important gauche repulsion, or increases (when the radical reacts cis to Me) decreasing the strain between EWG and Me (fig. 4). The difference in steric hindrance, as measured by the A value,[20] between CHO (A = 0,56-0,73 ; 0,8 kcal.mol^{-1}) and CN (A = 0,2 kcal. mol^{-1}) accounts for the different stereoselectivities for these two substituents.

Table 2 : Energy differences (kcal.mol^{-1}) between transition and initial states

Cyclization	Substituant	CHO	CN
on C2	cis to Me	8.88	8.24
on C2	trans to Me	9.57	8.48
on C6	cis to Me	9.18	8.56
on C6	trans to Me	9.60	8.49

Table 3 : Dihedral angles ω between C -C2-C3-EWG (ω1) and EWG-C3-C4-Me (ω2)

Substituant	CHO	CN	CHO	CN
ω	ω1	ω1	ω2	ω2
initial	-	-	-62.16	-63.29
C cis to Me	73.98	74.85	-70.15	-71.09
C trans to Me	-70.39	-70.93	-47.91	-47.00

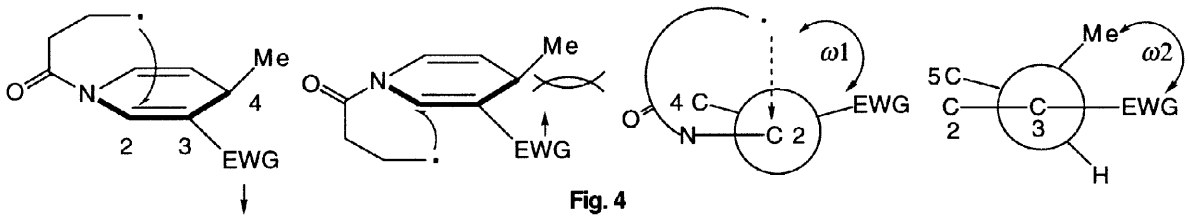


Fig. 4

Applications

As shown in scheme 3 reduction of **9** using $LiAlH_4$ afforded an enamine which was reduced with $NaBH_4$ to give the quinolizine **10**. In fact, better yields (82%) are obtained by performing first a catalytic hydrogenation of the double bond and then, reduction ($LiAlH_4$) of the aldehyde and the amide functions. But, for synthetic purposes, it might be preferable to functionalize the enamine. Indeed, we have prepared cyanoquinolizine **25**, as a single diastereomer, by using NaCN under the conditions described by Polniasziek and Belmont (scheme 3).[21]

The easy access to quinolizines has prompted us to investigate the synthesis of two lupin alkaloids, (-)-lupinine **26** and (+)-epilupinine **27**.[1] In these natural quinolizines there is no substituent at the C4 position. Therefore, we decided to prepare the dihydropyridine **28** bearing a labile silyl substituent as a temporary stereochemical marker (scheme 9).[22] Addition of a silyl copper reagent[23] to **2**, in the presence of chlorobutanoyl chloride, afforded the corresponding dihydropyridines **28** in good yield (table 4, scheme 10). As shown in the table, the best result (de = 85%) was obtained by using Ph_3SiCu prepared with CuI. The iodo dihydropyridine **29** was then obtained with a yield of 78 %. The cyclization, performed under Bu_3SnH, AIBN conditions yielded a complex mixture. With the same reagents, but under sonication,[24] a mixture of the two regioisomers (C2 and C6 cyclization, 2/1) was obtained in low yield (25%). The use of diiodosamarium[25] also gave a mixture of the two regioisomeres in a 2/1 ratio (50% yield). Finally, the best result was achieved using Luche conditions. The bicycle **30** was selectively obtained with a yield of 50% as a unique and stable *cis* diastereomer which can be isomerised into **31** with DBU in THF. The bicycles **30** and **31** are ideal precursors of lupinine and epilupinine. Indeed, after reduction ($NaBH_4$), desilylation (Bu_4NF), catalytic hydrogenation (Pd/C) and reduction ($LiAlH_4$), lupinine or epilupinine were obtained with a global yield of 16 % and 20% respectively with a ee's of 85%.[8]

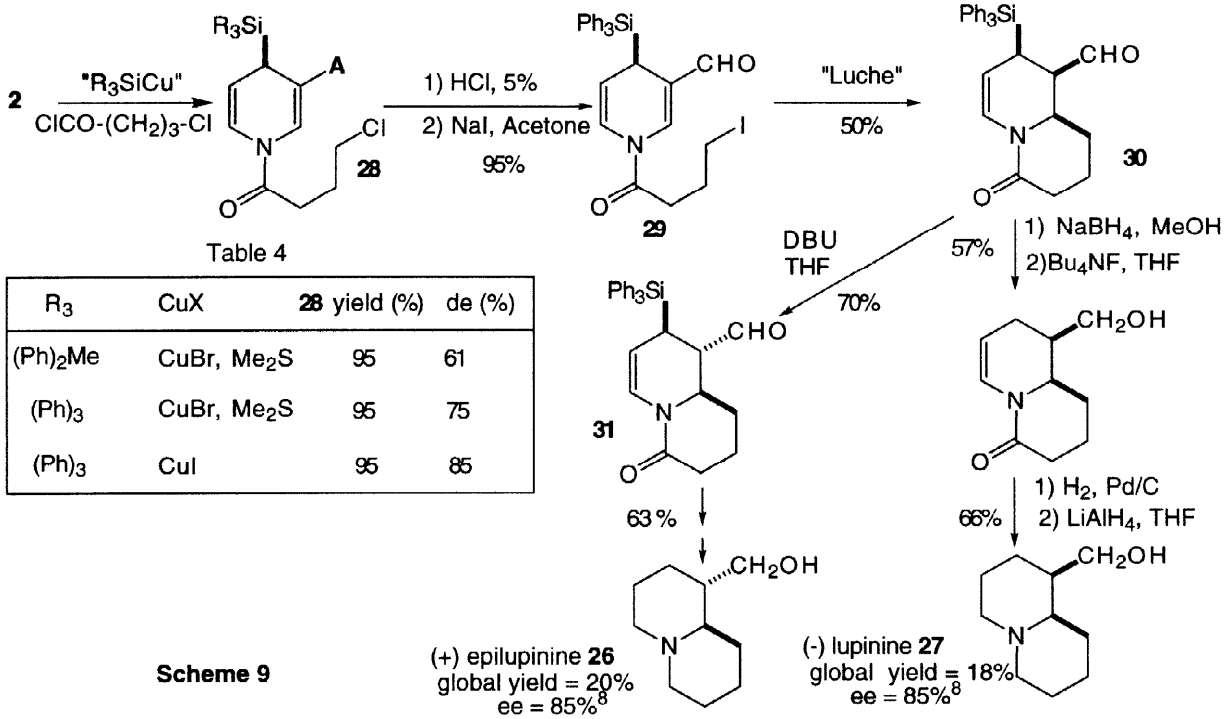


Table 4

R_3	CuX	**28** yield (%)	de (%)
$(Ph)_2Me$	CuBr, Me_2S	95	61
$(Ph)_3$	CuBr, Me_2S	95	75
$(Ph)_3$	CuI	95	85

Scheme 9

Conclusion

Chiral 1,4-dihydropyridines bearing an exocyclic functionalized nitrogen substituent are easily obtained from pyridine aminals. They are excellent precursors of chiral fused nitrogen heterocycles by the way of a regio and diastereoselective radical cyclization which occurs, according to the Luche procedure, onto the C2-C3 double bond and cis to the C4 substituant. Such a strategy opens an easy access to quinolizidine and indolizidine alkaloids.

Experimental Section

General. ^1H NMR spectra were recorded in $CDCl_3$ solutions at 200 or 400 MHz on a Bruker AC 200 or ARX 400 spectrometer with tetramethylsilane (0.00 ppm) as an internal reference. ^{13}C NMR were recorded at 100 or 50 MHz in $CDCl_3$ with tetramethylsilane (0.00 ppm) as the internal reference. Chemical shifts are given in ppm (δ); coupling constants J, are reported in Hz. Infrared spectra (IR) were obtained on a Perkin Elmer 1420 infrared spectrometer. Peaks are reported in cm^{-1}. Optical rotations were measured with a Perkin Elmer 141 polarimeter. All solvents used in reactions were distilled from appropriate drying agents before use. All reactions were carried out under a positive atmosphere of dry nitrogen or argon unless otherwise indicated. Organocopper reagents were prepared from the corresponding organolithium derivative by using a CuBr, Me_2S complex or CuI. Reactions under sonication conditions were performed in a ultrasound cleaning bath Sonoclean (50KHz).

General procedure for the addition of organocopper reagents onto 2: To a solution of the appropriate organometallic reagent (RCu or R_2CuLi, 1.5 equiv.) in THF (30 mL for 1 mmol) is added a solution of pyridine aminal **2** (1 equiv.) in THF (10 mL). The resulting mixture is cooled to -70°C and then the acyl chloride (1.5 equiv.) is slowly added. The mixture is stirred 6h at -60°C (TLC) and warmed to room temperature. The reaction is then quenched by addition of an aqueous solution of NH_4OH/NH_4Cl (1/1) or an aqueous solution of NH_4Cl (see text). The mixture is diluted with Et_2O and washed with an aqueous solution of NH_4Cl. The organic layer is dried (Na_2CO_3) and concentrated in vacuo to afford a yellow oil which is checked by ^1H NMR and then purified by column chromatography (SiO_2, cyclohexane/ether = 70/30).

(3a) 1-(3-chloropropanoyl)-3-(1,3-dimethyl-4(S),5(S)-diphenylimidazolidin-2-yl)-4(R)-methyl-1,4- dihydropyridine.(yield = 80 %): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 0.5H), 7.36 - 7.10 (m, 10.5H), 7.03 (s, 0.5H), 6.53 (d, J = 8.2 Hz, 0.5H), 5.2 (m, 1H), 5.12 (m, 1H), 4.22 (s, 0.5H), 4.20 (s, 0.5H), 3.89 (m, 3H), 3.81 (d, J = 7.7 Hz, 0.5H), 3.58 (dd, $J_1 = J_2 = 7.7$ Hz, 1H), 3.30 (m, 0.5H), 3.25 (m, 0.5H), 3.06 (m, 1H), 2.98 (m, 1H), 2.22 (s, 1.5H), 2.18 (s, 1.5H), 2.15 (s, 1.5H), 2.1 (s, 1.5H), 1.28 (2d, J = 7.15 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 140.17, 139.89, 139.84, 128.52, 128.41, 128.08, 127.99, 127.38, 127.20, 123.73, 123.32, 122.48, 121.93, 121.07, 120.43, 115.05, 87.24, 86.25, 77.44, 77.11, 76.69, 75.52, 38.92, 38.77, 37.41, 37.30, 36.42, 36.25, 34.66, 29.49, 28.98, 22.54, 22.50; IR (film): 2940, 2860, 2695, 1665, 1630 cm^{-1}; Anal. calcd for $C_{26}H_{30}N_3Cl$ O (435.99) : C, 71.63; H, 6.94; N, 9.64. Found : C, 71.65; H, 6.92; N, 9.61.

(4) 1-Acryloyl-3-formyl-4(R)-methyl-1,4-dihydropyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.42 (s, 1H), 7.68 (s, 1H), 6.89 (s, 1H), 6.68 (dd, $J_1 = 16.7$ Hz, $J_2 = 9.7$ Hz, 1H), 6.58 (dd, $J_1 = 16.7$ Hz, $J_2 = 2.2$ Hz, 1H), 6.0 (dd, $J_1 = 9.73$ Hz, $J_2 = 2.25$ Hz, 1H), 5.26 (m, 1H), 3.41 (m, 1H), 1.20 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 119.22, 162.81, 141.04, 133.04, 125.64, 124.47, 122.0, 114.58, 32.38, 22.2.

(3b) 1-(4-chlorobutanoyl)-3-(1,3-dimethyl-4(S),5(S)-diphenylimidazolidin-2-yl)-4(R)-methyl-1,4-dihydropyridine (92 %): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (s, 0.5H), 7.27 - 7.1 (m, 11H), 6.61 (d, J = 8.2 Hz, 0.5H), 5.18 (m, 0.5H), 5.10 (m, 0.5H), 4.24 (s, 0.5H), 4.18 (s, 0.5H), 3.86 (d, J = 7.7 Hz, 0.5H), 3.80 (d, J = 7.7 Hz, 0.5H), 3.74 (m, 2H), 3.56 (d, J = 7.7 Hz, 0.5H), 3.55 (d, J = 7.7 Hz, 0.5H), 3.26 (m, 1H), 2.71 (m, 2H), 2.21 (s, 1.5H), 2.18 (m, 2H), 2.17 (s, 1.5H), 2.16 (s, 1.5H), 2.12 (s, 1.5H), 1.27 (2d, J = 7.15 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.44, 140.48, 140.20, 139.92, 128.72, 128.64, 128.30, 128.14, 127.70, 127.41, 123.31, 123.14, 122.81, 122.43, 121.66, 120.91, 114.73, 87.72, 86.58, 77.74, 77.4, 75.85, 75.72, 44.58, 37.52, 34.86, 30.32, 30.15, 29.70, 29.13, 27.56, 22.85; IR

(film): 2940, 2860, 2695, 1665, 1630 cm^{-1}; Anal. calcd for $C_{27}H_{32}N_3ClO$ (450.02) : C, 72.12 ; H, 7.18 ; N, 9.35. Found : C, 72.18 ; H, 7.15 ; N, 9.31.

(3c) 1-(4-bromopentanoyl)-3-(1,3-dimethyl-4(S),5(S)-diphenylimidazolidin-2-yl)-4(R)-methyl-1,4-dihydropyridine (89 %): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 0.5H), 7.34 – 7.1 (m, 11H), 6.60 (d, J = 8.2 Hz, 0.5H), 5.18 (m, 0.5H), 5.11 (m, 0.5H), 4.25 (s, 0.5H), 4.20 (s, 0.5H), 3.9 - 3.4 (m, 4H), 3.49 (m, 0.5H), 3.47 (m, 0.5H), 2. 62 (m, 1H), 2.54 (m, 1H), 2.23 (s, 1.5H), 2.20 (s, 1.5H), 2.19 (s, 1.5H), 2.17(s, 1.5H), 1.9 (m, 4H), 1.29 (2d, J = 7.15 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.09, 140.53, 140.26, 139.34, 128.38, 128.25, 128.19, 127.68, 123.23, 121.84, 120.97, 114.70, 87.72, 86.58, 75.81, 75.79, 68.05, 37.56, 35.03, 34.95, 33.40, 32.27, 25.74, 23.46, 23.27, 22.94, 22.78; IR (film): 2940, 2860, 2695, 1665, 1630 cm^{-1}.

(28) 1-(4-chlorobutanoyl)-3-(1,3-dimethyl-4(S),5(S)-diphenylimidazolidin-2-yl)-4(R)-triphenylsilyl-1,4-dihydropyridine (92 %); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88-7.06 (m, 26H), 6.91 (m, 1H), 6.28 (d, *J* =7.5 Hz, 0.5H), 5.38 (m, 1H), 4.22 (s, 0.5H), 4.12 (s, 0.5H), 3.71-3.48 (m, 4H), 3.26 (d, *J* =8.4 Hz, 0.5H), 3.16 (d, *J* =8.4 Hz, 0.5H), 2.38 (s, 1.5H), 2.31 (s, 1.5H), 2.2-1.78 (m, 4H), 1.76 (s, 1.5H), 1.72 (s, 1.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.86, 140.61, 139.85, 136.58, 136.48, 135.99, 135.21, 134.17, 133.46, 129.98, 128.35, 127.95, 127.49, 123.95, 123.20, 122.85, 120.37, 111.53, 111.09, 85.37, 78.19, 78.05, 77.25, 77.05, 44.72, 37.90, 37.53, 30.33, 30.15, 29.49, 29.0, 27.55, 27.40.

General procedure for the hydrolysis of the dihydropyridine-aminals: To a solution of dihydropyridines **3a-c** (0.5 mmol) in Et_2O (20 mL) is added, at room temperature, HCl 5% (10 mL). The yellow solution is stirred 1h, poured into Et_2O (50 mL) and washed with NH_4Cl aqueous solution. The organic layer is dried (Na_2CO_3) and concentrated in vacuo to afford a yellow oil. Purification by column chromatography (SiO_2, cyclohexane/ether = 1/1) afforded the pure chloro-aldehydes.

1-(3-Chloropropanoyl)-3-formyl-4(R)-methyl-1,4-dihydropyridine (88%): $[\alpha]_D^{25}$ = -214 (*c* = 0.045, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.24 (s, 1H), 7.95 (s, 0.5H), 7.34 (s, 0.5H), 7.12 (m, 0.5H), 6.56 (m, 0.5H), 5.28 (m, 1H), 3.91 (m, 2H), 3.40 (m, 1H), 3.08 (m, 2H), 1.2 (d, J = 6.7 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.3, 190.5, 166.1, 139.5, 138.4, 120.1, 119.4, 116.3, 38.2, 36.3, 25.9, 22.1; IR (film) 1740, 1670 cm^{-1}; Anal. calcd for $C_{10}H_{12}NClO_2$ (213.66): C, 56.21; H, 5.66; N, 6.56. Found: C, 56.24; H, 5.69; N, 6.53.

1-(4-Chlorobutanoyl)-3-formyl-4(R)-methyl-1,4-dihydropyridine (87%): $[\alpha]_D^{25}$ = -189 (c = 0.047, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.43 (s, 1H), 7.92 (s, 0.5H), 7.44 (m, 0.5H), 6.64 (m, 0.5H), 5.26 (m, 1H), 3.71 (t, J = 6.4 Hz, 2H), 3.41 (m, 1H), 2.79 (m, 2H), 2.22 (m, 2H), 1.2 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.96, 168.50, 139.50, 125.58, 120.22, 116.06, 44.05, 30.12, 27.0, 26.11, 22.39; IR (film) 1740, 1670 cm^{-1}; Anal. calcd for $C_{11}H_{14}NClO_2$ (227.69): C, 58.03; H, 6.20; N, 6.15. Found: C, 58. 04; H, 6.23; N, 6.12.

1-(4-bromopentanoyl)-3-formyl-4(R)-methyl-1,4-dihydropyridine (95%): $[\alpha]_D^{25}$ = -140 (c = 0.022, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.4 (s, 1H), 7.9 (s, 0.5H), 7.3 (s, 0.5H), 7.0 (s, 0.5H), 6.5 (s, 0.5H), 5.2 (m, 1H), 3.35 (m, 3H), 2.60 (m, 2H), 1.9 (m, 4H), 1.12 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ191.14, 168.65, 139.51, 125.04, 120.27, 115.65, 33.22, 32.17, 31.71, 26.78, 25.96, 22.74, 22.36; IR (film) 1740, 1670 cm^{-1}; Anal. calcd for $C_{12}H_{16}NBrO_2$ (286.17): C, 50.37; H, 5.64; N, 4.89. Found: C, 50.40; H, 5.67; N, 4.86.

(28) 1-(4-Chlorobutanoyl)-3-formyl-4(R)- triphenylsilyl -1,4-dihydropyridine (88 %): $[\alpha]^{20}_D$ =-244 (*c* = 0.012, CHCl3); ^1H NMR ($CDCl_3$, 400 MHz) δ) δ 9.27 (s, 1H), 7.72-7.23 (m, 16H), 6.98 (s, 0.5H), 6.78 (m, 0.5H), 6.15 (m, 0.5H), 5.39 (m, 1H), 3.98 (d, *J* = 5.9 Hz, 1H), 3.59 (t, *J* = 5.6 Hz, 2H), 2.31 (m, 2H), 2.0 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.09, 167.35, 140.20, 136.43, 135.93, 132.33, 130.15, 129.88, 128.29, 127.71, 124.04, 121.87, 112.27, 44.18, 30.10, 26.95, 22.75; Anal. calcd $C_{28}H_{26}ClNO_2$ (471.5): C, 71.24; H, 5.55; N, 2.97; Found: C, 71.30; H, 5.56; N, 2.93.

(5a-c , 16 and 29) General procedure for the transformation of chloro-derivatives into iodo-derivatives. A solution of dihydropyridines aldehydes (0.3 mmoL) in a saturated solution of NaI in acetone (10 mL) is heated under reflux for 12 h. After cooling to room temperature, water (10 mL) is added and

the reaction mixture is diluted with CH_2Cl_2 (50 mL) and washed with water. The organic layer is dried (Na_2CO_3) and concentrated in vacuo to afford a crude yellow solid which is used for further applications without any purification.

(5a) 1-(3-Iodopropanoyl)-3-formyl-4(R)-methyl-1,4-dihydropyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.42 (s, 1H), 7.94 (s, 1H), 6.49 (m, 1H), 5.24 (m, 1H), 3.40 (m, 3H), 3.20 (m, 2H), 1.19 (d, J = 6.7 Hz, 3H).

(5b) 1-(4-Iodobutanoyl)-3-formyl-4(R)-methyl-1,4-dihydropyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.36 (s, 1H), 7.7 (s, 1H), 6.72 (s, 1H), 5.18 (dd, J_1 = 8.2 Hz, J_2 = 4.4 Hz, 1H), 3.37 (m, 1H), 3.28 (t, J = 6.4 Hz, 2H), 2.67 (t, J = 6.9 Hz, 2H), 2.17 (m, 2H), 1.12 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.02, 167.84, 139.29, 125.56, 120.23, 116.06, 33.78, 27.71, 26.11, 22.39.

(5c) 1-(4-Iodopentanoyl)-3-formyl-4 (R)-methyl-1,4-dihydropyridine. ^1H NMR ($CDCl_3$, 200 MHz) δ 9.4 (s, 1H), 7.9 (s, 0.5H), 7.3 (s, 0.5H), 7.0 (s, 0.5H), 6.5 (s, 0.5H), 5.2 (m, 1H), 3.35 (m, 1H), 3.19 (m, 2H), 2.60 (m, 2H), 1.9 (m, 4H), 1.12 (d, J = 6.7 Hz, 3H).

(16) 1-(4-idobutanoyl)-3-cyano-4-methyl-1,4-dihydropyridine. First, the chloro-dihydropyridine is prepared starting from 3-cyanopyridine according the general procedure for the addition of organocopper reagents on **2** (88%).^1H NMR ($CDCl_3$, 400 MHz) δ 7.8 (s, 0.5H), 7.26 (s, 0.5H), 7.08 (s, 0.5H), 6.57 (s, 0.5H), 5.08 (m, 1H), 3.64 (t, J = 6.2Hz, 2H), 3.21 (m, 1H), 2.67 (t, J = 6.9hz, 2H), 2.18 (m, 2H), 1.30 (d, J = 6.9Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.40, 133.54, 120.23, 118.14, 112.40, 96.04, 43.91, 29.66, 26.89, 26.81, 22.49. Then, the iodo-derivative **16** is prepared. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.8 (s, 0.5H), 7.29 (s, 0.5H), 7.18 (s, 0.5H), 6.57 (s, 0.5H), 5.06 (m, 1H), 3.32 (t, J = 6.6Hz, 2H), 3.21 (m, 1H), 2.62 (t, J = 7Hz, 2H), 2.20 (m, 2H), 1.33 (d, J = 6.6Hz, 3H).

(29) 1-(4-iodobutanoyl)-3-formyl-4(R)- triphenylsilyl -1,4-dihydropyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.29 (s, 1H), 7.72-7.2 (m, 16H), 6.96 (s, 0.5H), 6.75 (m, 0.5H), 6.18 (m, 0.5H), 5.4 (m, 1H), 3.87 (d, *J* = 5.9 Hz, 1H), 3.22 (m, 2H), 2.26 (m, 2H), 2.0 (m, 2H).

General procedure for the cyclization wih Bu_3SnH/AIBN: To a boiling solution of iodo aldehydes (1 mmol) in benzene (100 mL) is slowly added (4h), under argon, a solution of Bu_3SnH (1 mmol) and AIBN (0.01 mmol) in benzene (50 mL). After disappearence of the starting material, as shown by TLC (SiO_2, ether), the reaction mixture is concentrated in vacuo and purified by column chromatography (SiO_2, ether) affording the reaction products. Yields are given in tables and in the text.

General procedure for the cyclization under ultrasonic conditions: A suspension of Zn (Aldrich 325 mesh, 500mg, 8mmol) and CuI (356 mg, 2.4 mmol) in water (2 mL) is stirred in an ultrasound cleaning bath, under argon atmosphere, for 3 min. To the resulting black mixture is slowly added (1h) a solution of the iodo-aldehydes (1 mmol) in isopropanol (1 mL) or isopropanol/THF (1/1 , 5mL, see text). The yellow-black suspension is stirred under sonication for 2 h and then diluted with water (5 mL) and CH_2Cl_2 (10 mL). The solid is removed by filtration over celite and washed several times with CH_2Cl_2. The combined organic layers are washed with water, dried (Na_2CO_3) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, ether). Yields are given in tables and in the text.

(6) (1R,2R,9aR)-2-methyl-6-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizine-1-carbaldehyde. (major diastereomer). ^1H NMR ($CDCl_3$, 400 MHz) δ 9.58 (d, J = 5 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 5.08 (m, 1H), 3.82 (dm, J = 12.5 Hz, 1H), 2.82 (m, 1H), 2.7 - 0.5 (m, 7H), 1.10 d, J = 7.7 Hz, 3H).

(7) (2R,9aS)-2-methyl-6-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizine-3-carbaldehyde. (major diastereomer) $[\alpha]_D^{25}$ = + 76 (*c* = 0.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.33 (s, 1H), 8.06 (s, 1H), 3.49 (m, 1H), 2.67 (m, 2H), 2.49 (m, 1H), 2.12 (m, 1H), 2.08 (m, 1H), 1.79 (m, 1H), 1.56 (m, 1H), 1.36 (m, 1H), 1.24 (d, J = 6.7 Hz, 3H).

(7) (2R,9aR)-2-methyl-6-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizine-3-carbaldehyde. (minor diastereomer) ^1H NMR ($CDCl_3$, 400 MHz) δ 9.35 (s, 1H), 8.12 (s, 1H), 3.66 (m, 1H), 2.81 (m,

1H), 2.71 (m, 1H), 2.51 (m, 1H), 2.04 (m, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1.61 (m, 2H), 1.25 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H).

(9) (1S,2R,9aR)-2-methyl-6-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizine-1-carbaldehyde. Isomerization of 6: Na_2CO_3 (500 mg) is added to a solution of **6** (193 mg, 1 mmol) in of methanol (50mL). The resulting mixture is stirred at room temperature for 12 h. The salt is removed by filtration. The solution is diluted with water (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts are dried over Na_2CO_3 and concentrated in vacuo. The residue is purified by flash chromatography (SiO_2, ether) to give 172 mg (89%) of **9** as a white crystalline compound. mp 65°C; $[\alpha]_D^{25}$ = +154 (*c* = 0.012, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.73 (d, J = 4.1 Hz, 1H), 7.24 (dd, J_1 = 8.45 Hz, J_2 = 2.4 Hz, 1H), 4.99 (dd, J_1 = 8.45 Hz, J_2 = 2.13 Hz, 1H), 3.72 (ddd, J_1 = J_2 = 10.5 Hz, J_3 = 3.80 Hz, 1H), 2.65 (m, 1H), 2.52 (m, 1H), 2.41 (m, 1H), 2.20 (ddd, J_1 = J_2 = 10.5 Hz, J_3 = 4.1Hz, 1H), 2.0 (m, 2H), 1.72 (m, 1H), 1.59 (m, 1H), 1.02 (d, J = 6.94 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.06, 167.26, 122.55, 113.72, 59.29, 54.36, 32.23, 29.09, 28.02, 19.42, 19.22; IR (film) 2920, 2860, 2800, 2700, 1720, 1645 cm^{-1}; Anal. calcd for $C_{11}H_{13}NO_2$ (193.24): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.39; H, 7.79; N, 7.24.

(11) (7R,8R,8aR)-7-methyl-3-oxo-1,2,3,7,8,8a-hexahydro-indolizine-8-carbaldehyde.mp 82°C, $[\alpha]_D^{25}$ = +10 (*c* = 0.022, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.85 (d, J = 2.5 Hz, 1H), 6.80 (dd, J_1 = 8 Hz, J_2 = 2.4 Hz, 1H), 4.93 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 3.84 (ddd, J_1 = J_2 = 10.4 Hz, J_3 = 5.9 Hz, 1H), 2.69 (m, 1H), 2.42 (m, 3H), 2.19 (ddd, J_1 = J_2 = 2.5 Hz, J_3 = 10.4 Hz, 1H), 1.76 (m, 1H), 1.15 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.85, 171.08, 120.37, 114.23, 58.94, 55.0, 31.10, 30.42, 25.33, 19.50; Anal. calcd for $C_{10}H_{13}NO_2$ (179.22): C, 67.02; H, 7.31; N, 7.82. Found: C, 67.03; H, 7.30; N, 7.80 .

(12) 7-methyl-3-oxo-1,2,3,7,8,8a-hexahydro-indolizine-6-carbaldehyde. (major diastereomer) mp 98°C, ^1H NMR ($CDCl_3$, 400 MHz) δ 9.35, *9.33* (2s, 1H), 7.62, *7.58* (2s, 1H), 3.91, *3.73* (2m, 1H), 2.72 (m, 1H), 2.55 (m, 2H), 2.32 (m, 3H) 1.74 (m, 1H), 1.30 (d, J = 6.6 Hz, 3H), 1.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.07, 172.84, 139.50, 126.89, 55.30, 39.02, 31.32, 27.93, 26.53, 18.68.

(13) 1-Propanoyl-3-formyl-4(R)-methyl-1,4-dihydropyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.41 (s, 1H), 7.94 (s, 0.5H), 7.37 (s, 0.5H), 7.10 (m, 0.5H), 6.58 (m, 0.5H), 5.20 (m, 1H), 3.39 (m, 1H), 2.59 (m, 2H), 1.25 (t, J = 7.5 Hz, 3H), 1.18 (d, J = 7.1 Hz, 1.5H), 1.18 (d, J = 7.1 Hz, 1.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.05, 166.0, 139, 120.3, 119.6, 115.73, 26.82, 26.03, 22.43, 8.51.

(*17* + 18) 2-methyl-6-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizine-1-carbonitriles. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, J = 8.3Hz, 2H), 5.12 (dd, J_1 = 8.3Hz, J_2 = 5.3Hz, 1H), *4.95 (dd, J_1 = 8.6Hz, J_2 = 1.8Hz, 1H)*, 3.69 (dd, J_1 = 11Hz, J_2 = 3.9Hz, 1H), 3.55 (dd, J_1 = 11Hz, J_2 = 3.9Hz, 1H), *2.83 (m, 1H)*, 2.7 - 1.5 (m, 15H), 1.22 (m, 6H); IR (film) 2920, 2860, 2800, 2700, 2200; 1700, 1645 cm^{-1}.

(19) 2-methyl-6-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizine-3-carbonitriles. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, J = 1.7Hz, 1H), 3.55 (m, 1H), 2.75 - 1.38 (m, 9H), 1.24 (m, 3H).

(20+18) Isomerization of 17 + 18

To a solution of the mixture **18 + 19** (47.5mg, 0.25 mmol) in methanol (15 mL) is added an aqueous solution of NaOH (15%, 10mL). The resulting solution is stirred at room temperature for 12 h, diluted with water (15 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer is dried (Na_2CO_3) and concentrated in vacuo. The residue is purified by flash chromatography (SiO_2, ether) to give 43 mg (85%) of the mixture **20+18.** (Only **20** is described). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 4.84 (d, J = 8.5 Hz, 1H), 3.71 (m, 1H), 3.02 (m, 1H), 2.75 (m, 1H), 2.0 (m, 1H), 2.05 (m, 4H), 1.25 (d J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 126.0, 124.1, 110.0, 55.2, 39.13, 32.18, 30.67, 29.52, 20.0, 18.65.

(23) (1R,2R,9aR)-2-methyl-6-oxo-octahydro-quinolizine-1-carbaldehyde. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.90 (d, J = 4.9Hz, 1H), 5.1 (d, J = 14Hz, 1H), 3.47 (m, 2H), 2.64 - 1.04 (m, 10H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.19, 169.38, 62.91, 55.0, 35.92, 33.12, 32.96, 32.45, 28.82, 19.95.

(24) (1S,2R,9aR)-2-methyl-6-oxo-octahydro-quinolizine-1-carbaldehyde.

The quinolizine **24** is prepared by isomerization of **23** (80%, according the procedure used for the isomerization of **6**) or by hydrogenation of **9** (65%, according the procedure used for the hydrogenation of **3b**). $[\alpha]^{25}D$ = +37 (c = 0.020, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.66 (d, J = 4.6Hz, 1H), 4.85 (dm, J = 13.4Hz, 1H), 3.55 (m, 1H), 2.90 (m, 3H), 2.12 (ddd, $J_1 = J_2$ = 10.5Hz, J_3 = 4.6Hz, 1H), 2.0 - 1.35 (m, 5H), 1.08 (m, 2H), 0.95 (d, J = 6.6Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.47, 169.37, 61.16, 55.11, 41.66, 38.28, 32.78, 28.32, 26.37, 18.79, 10.52; IR (film) 2920, 2860, 2800, 2700, 1720, 1645 cm^{-1}; Anal. calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78 ; N, 7.17 . Found: C, 67.70; H, 8.79; N, 7.12.

(10) Preparation of (1S,2R,9aR)-(2-methyl-octahydro-quinolizine-1-yl)methanol
To a solution of **9** (193 mg, 1mmol) in ether (90 mL) at room temperature is added a solution of $LiAlH_4$ (3mL of a 1 M solution in ether). The resultant mixture is stirred under reflux for 2h and then cooled to room temperature. EtOAc (15 mL) is carefully added. The reaction mixture is diluted with NH_4Cl aqueous solution (60 mL), washed with water, dried (Na_2CO_3) and concentrated in vacuo to give a crude compound which is diluted in methanol (30 mL) and cooled to 0°C. $NaBH_4$ (76mg, 2mmol) is then added, the reaction mixture is stirred for 30 min and then diluted with water (30 mL) and CH_2Cl_2 (10 mL). The organic layer is dried (Na_2CO_3) and concentrated in vacuo. The residue is purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 93/7) to give 123 mg (67%) of a white crystalline compound. mp 72°C, $[\alpha]_D^{25}$ = +124 (*c* = 0.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.83 (dd, J_1 = 11.5 Hz, J_2 = 2.2 Hz), 3.77 (dd, J_1 = 11.5 Hz, J_2 = 2.2 Hz), 2.83 (m, 2H), 2.20 - 1.10 (m, 14H), 0.99 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 62.96, 59.76, 57.26, 56.55, 50.50, 34.26, 30.95, 29.90, 25.63, 24.78, 20.11; Anal. calcd for $C_{11}H_{21}NO$ (183.29): C, 72.08 ; H, 11.55 ; N, 7.64. Found : C, 78.07 ; H, 11.55 ; N, 7.62.

(14) Preparation of 1-(4-Iodobutanoyl)-3-hydroxymethyl-4(R)-methyl-1,4-dihydropyridine.
$NaBH_4$ (380 mg, 10 mmol) is added to a solution of **5b** (216.5 mg, 1mmol) in MeOH (10 mL) at 0°C. The resulting mixture is stirred for 30 min and then diluted with water (10 mL) and CH_2Cl_2 (50 mL). The organic layer is dried (Na_2CO_3) and concentrated in vacuo. The residue is purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 93/7) to give 177 mg (77%) of the chloro-alcool. $[\alpha]^{25}D$ = -54 (c = 0.023, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.1 (s, 0.5H), 7.03 (d, J = 8.5Hz, 0.5H), 6.61 (s, 0.5H), 6.51 (d, J = 8.3Hz, 0.5H), 4.95 (m, 1H), 4.08 (m, 2H), 3.58 (t, J = 6Hz, 2H), 3.57 (m, 1H), 3.05 (m, 1H), 2.59 (m, 2H), 2.08 (m, 2H), 1.12 (d, J = 6.9Hz, 1.5H), 1.10 (d, J = 6.9Hz, 1.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.05, 147.99, 125.52, 124.63, 121.48, 120.50, 118.76, 118.18, 114.08, 63.16, 62.93, 44.58, 30.05, 29.15, 28.91, 27.38, 21.84, 21.69. The chloro-alcool is transformed into the iodo derivative **14** according the general procedure for iodo derivatives **5a-c.** ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20 (s, 0.5H), 7.12 (d, J = 7.9Hz, 0.5H), 6.68 (s, 0.5H), 6.57 (d, J = 8Hz, 0.5H), 5.0 (m, 1H), 4.27 (m, 1H), 3.30 (m, 2H), 3.14 (m, 1H), 2.58 (m, 2H), 2.18 (m, 2H), 1.16 (m, 3H).

(22) Preparation by hydrogenation of 3b: An erlenmeyer flask containing a mixture of **3b** (1.5g, 3.45 mmol) and Pd/C 10% (36 mg) in ethanol (10mL) under H_2 atmosphere is placed in an ultrasound cleaning bath for 5h. After filtration the reaction mixture is concentrated in vacuo and the residue purified by flash chromatography (SiO_2, cyclohexane/ether 70/30) to give 294 mg (65%) of the chloro-tetrahydropyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (s, 0.5H), 7.28 - 7.1 (m, 10.5H), 4.18 (m, 0.5H), 4.16 (s, 0.5H), 4.09 (s, 0.5H), 3.8 (m, 1.5H), 3.72 (m, 2H), 3.54 (m, 1.5H), 3.3 (m, 0.5H), 2.75 - 2.56 (m, 3H), 2.22 (m, 2H), 2.17 (s, 1.5H), 2.14 (s, 1.5H), 2.09 (s, 1.5H), 2.05 (s, 1.5H), 1.25 (d, J = 7.5Hz, 1.5H), 1.16 (d, J = 7.5Hz, 1.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.63, 170.43, 141.43, 141.26, 129.76, 129.45, 129.38, 129.27, 129.21, 128.83, 128.61, 125.85, 124.93, 123.76, 120.60, 119.76, 89.54, 88.48, 78.79, 78.52, 77.29, 77.0, 46.04, 41.05, 38.70, 38.41, 36.36, 32.16, 31.52, 31.19, 29.85, 28.94, 28.72, 21.02, 20.58, 20.07. The aminal of the obtained tetrahydropyridine is removed according the general procedure of hydrolysis of dihydropyridines to give the corresponding chloro-aldehyde (736 mg, 93%). $[\alpha]^{20}D$ = - 88 (c = 0.110, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.3 (s, 1H), 8.07 (s, 0.5H), 7.5 (s, 0.5H), 4.28 (m, 0.5H), 3.9 (m, 0.5H), 3.7 (t, J = 5.9Hz, 2H), 3.65 (m, 0.5H), 3.29 (m, 0.5H), 2.87 (m, 1H), 2.8 (m, 2H), 2.22 (m, 2H), 1.78 (m, 2H), 1.11 (d, J = 6.9Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.15, 190.09, 170.49, 143.29, 141.96, 126.6, 126.38, 61.78, 60.30, 44.17, 40.17, 37.59, 30.90, 30.02, 27.59, 27.00, 26.74, 23.3; IR (film) 2940, 1666, 1610, 1400, 1295, 1135; MS (FAB, GLY) 232, 230, 194, 133, 126, 96, 77, 69, 55, 41. The obtained chloro-aldehyde is transformed into the corresponding iodo-aldehyde **22** according the general procedure for iodo-derivatives **5a-c.** ^1H NMR ($CDCl_3$, 400 MHz) δ 9.3 (s, 1H), 8.02 (m, 0.5H), 4.25 (m, 0.5H), 3.89 (m,

0.5H), 3.58 (m, 0.5H), 3.34 (t, J = 6.2Hz, 2H), 3.29 (m, 0.5H), 2.87 (m, 1H), 2.75 (m, 2H), 2.23 (m, 2H), 1.11 (d, J = 7.15Hz, 3H).

(25) Preparation of (1S,2R,4S,9aR)-1-hydroxymethyl-2-methyl-octahydro-quinolizine-4-carbonitrile. KCN (390 mg, 5.4 mmol) is added to a solution of the alcool (82 mg, 0,45 mmol) obtained by reduction of **9** (see preparation of **10**) in a mixture of water and CH_2Cl_2 (1/1 , 8 mL) at room temperature. The pH is adjusted to 3-4 with HCl (10%) and the solution is stirred for 12h, diluted with NaOH 2N (4 mL) and extracted with CH_2Cl_2 (3 x 20 mL). After concentration in vacuo the residue is purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 95/5) to give **25** (24 mg, 63%). $[\alpha]^{25}D$ = +265 (c = 0.013, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.76 (m, 3H), 2.72 (m, 1H), 2.48 (ddd, $J_1 = J_2$ = 11Hz, J_3 = 2.6Hz, 1H), 2.34 (ddd, J1 = J2 = 10.3Hz, J3 = 2.6Hz, 1H), 2.12 (m, 1H), 1.92 (m, 2H), 1.80 (m, 1H), 1.70 (m, 2H), 1.53 (m, 1H), 1.30 (m, 1H), 1.09 (m, 1H), 1.02 (d, J = 6.2Hz, 3H), 0.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.71, 57.58, 55.73, 54.95, 50.60, 36.39, 30.41, 27.41, 25.64, 24.24, 19.57; IR (film) 3400, 2920, 2220, 1450 cm^{-1}. MS (IC) 208, 180, 166, 150, 110; Anal. calcd for $C_{12}H_{20}N_2O$ (208:30): C, 69.19 ; H, 9.68 ; N, 13.45. Found : C, 69.17 ; H, 9.72 ; N, 13.43.

(30) (1R,2R,9aR)-2-triphenylsilyl-6-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizine-1-carbaldehyde. $[\alpha]^{25}$ = + 58 (c = 0.023, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (d, J = 4.9Hz, 1H), 7.58 - 7.26 (m, 16H), 5.45 (d, J = 8.8Hz, 1H), 3.77 (m, 1H), 2.96 (m, 1H), 2.52 (m, 1H), 2.31 (m, 1H), 1.92 (m, 2H), 1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.95, 167.40, 136.05, 132.32, 130.42, 128.13, 124.35, 107.89, 58.33, 50.04, 32.40, 27.16, 25.81, 19.58.

(27) Preparation of (-) lupinine . **30** is reduced according the preparation of **14** (95%). $[\alpha]^{20}D$ = + 38 (c = 0.025, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 - 7.25 (m, 15H), 7.22 (m, 1H), 5.29 (d, J = 7.7Hz, 1H), 3.63 (m, 3H), 2.88 (m, 1H), 2.39 (m, 3H), 1.9 (m, 2H), 1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.01, 136.20, 136.04, 129.82, 128.12, 127.87, 123.78, 109.0, 60.91, 60.60, 41.07, 35.15, 32.72, 29.19, 27.13. Bu_4NF (1.8 mL, 1.5 mmol) is added to a solution of the obtained alcool (200 mg, 0.46 mmol) in THF (50 mL). The resulting mixture is stirred at room temperature for 15 min, diluted with a saturated aqueous solution of Na_2CO_3, extracted with CH_2Cl_2 (100mL). After concentration in vacuo, the residue is purified by column chromatography (SiO_2, AcOEt) (63%). $[\alpha]^{20}D$ = - 15 (c = 0.025, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.19 (d, J = 8.4Hz, 1H), 5.02 (m, 1H), 3.78 (dd, J_1 = 10.5Hz, J_2 = 4.9Hz, 1H), 3.68 (m, 1H), 3.46 (dd, J_1 = 10.5Hz, J_2 = 8.04Hz, 1H), 2.52 (m, 1H), 2.37 (m, 1H), 2.22 (m, 1H), 2.08 (m, 1H), 1.87 (m, 2H), 1.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.56, 123.94, 107.45, 60.63, 57.34, 38.42, 32.36, 27.02, 25.67, 20.04; MS (I E) 181 (100%), 150 (95%), 80 (75%); Anal. calcd $C_{10}H_{15}NO_2$ (181.23) : C, 66.27 ; H, 8.34 ; N, 7.73. Found : C, 66.24 ; H, 8.38 ; N, 7.72. Pd/C 10% (10 mg) is added to a solution of the obtained product (52 mg, 0.28 mmol). The resulting mixture is stirred for 12h under H_2 atmosphere. Pd/C is removed by filtration. After concentration in vacuo, the residue is directly reduced with $LiAlH_4$ according the preparation of **10** to give a crude compound wich is purified by column chromatograpy (SiO_2, Et_2O/MeOH 9/1) to give (-) lupinine **27** (31 mg, 66%). $[\alpha]^{20}D$ = - 18 (c = 0.025, EtOH); ee = 85%.[8] Spectral data are identical with those reported. [26]

(26) Preparation of (+) epilupinine. DBU (0.5 mL, 3.2 mmol) is added to a solution of **30** (275 mg, 0.63 mmol) in THF (30 mL). The solution is heated under reflux for 4 h, diluted with water (10 mL) and extracted with Et_2O (50mL). After concentration in vacuo, the residue is purified by column chromatography (SiO_2, Et_2O) to give **31** (141 mg, 63%). $[\alpha]^{20}D$ = + 30 (c = 0.054, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.21 (d, J = 1.9Hz, 1H), 7.58 - 7.30 (m, 15H), 7.24 (d, J = 7.6Hz, 1H), 5.39 (d, J = 7.7 Hz, 1H), 3.46 (m, 1H), 2.98 (m, 1H), 2.57 (m, 1H), 2.33 (m, 1H), 1.90 (m, 2H), 1.69 (m, 1H), 1.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.94 136.30, 132.67, 131.32, 128.43, 127.89, 123.42, 110.65, 56.07, 54.0, 32.65, 28.11, 24.99, 19.74. The epilupinine **26** is then obtained according the procedure for the preparation of lupinine.(67 mg, 63%). $[\alpha]^{20}D$ = + 27 (c = 0.032, EtOH); ee = 85%.[8] Spectral data are identical with those reported. [26]

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