Tetrahedron Vol 49, No 46, pp 10629-10642, 1993
Printed in Great Britain

0040-4020/93 $6 00+ 00

Enantioselective Synthesis of Indolizine Derivatives by Rearrangement-Cyclization of Isoxazoline-5-spirocyclopropanes

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(*Received in UK* 4 *August* 1993, *accepted* 10 *September* 1993)

Abstract (3*S*,7*S*,8a*S*)-3-Methyl-7-hydroxyoctahydroindolizine (**13**) was prepared with an enantiomeric excess of 74%, in five steps starting from enantiomerically pure (*S*)-(+)-5-nitro-2-pentanol (**5**) (3*S*,5*S*,7*S*,8a*S*)-(-)-3-Methyl-5-phenyl-7-hydroxyoctahydroindolizine (**15**) and (3*S*,5*R*,7*R*,8a*R*)-(+)-3-methyl-5-phenyl-7-hydroxyoctahydroindolizine (**16**) were also obtained starting from (**5**) with an ee of 96 % The synthetic strategy required the enantioselective enzymatic reduction of 5-nitro-2-pentanone (**4**) to **5** (> 99% ee) and its conversion to (*R*)-(-)-2-chloro-5-nitropentane (**7**) (> 90% ee) Cycloadditions of the corresponding nitrile oxide prepared in situ from **7** with methylenecyclopropane (**8**) or 1-methylene-2-phenylcyclopropane (**9**) produced chiral isoxazolines **1** and **2**, which were converted by thermolysis to 2,3,5,6-tetrahydro-3-methylindolizin-7(1*H*)-one (**10**), and 2,3,5,6-tetrahydro-3-methyl-5-phenylindolizin-7(1*H*)-ones (**11**) and (**12**) respectively The enantioselectivity of the thermal rearrangement is dependent on the experimental conditions and on the structures of the chiral isoxazolines Catalytic hydrogenation of the indolizinones **10**, **11** and **12**, afforded the substituted hydroxyoctahydroindolizines **13**, **15** and **16** with high stereoselective control of all stereogenic centers

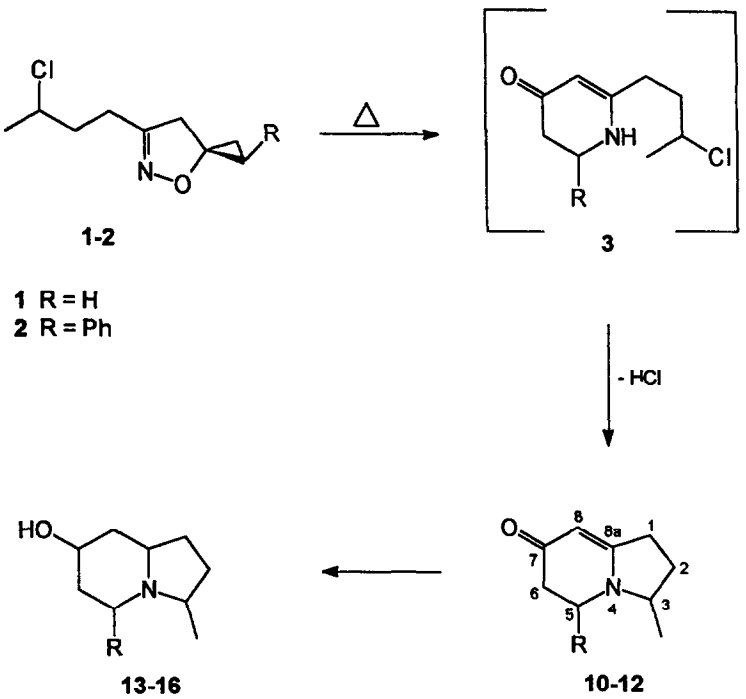
In recent years the synthesis of indolizines has been the object of much research, owing to the great interest primarily derived from the presence of these heterocyclic structures in several alkaloids isolated from the skin extracts of neotropical frogs.[1] Although several methods of synthesis of racemic indolizine derivatives have been published, a limited number of enantioselective syntheses have been reported.[2] We have recently developed a general strategy for the synthesis of substituted 2,3,5,6-tetrahydroindolizin-7(1*H*)-ones by sequential rearrangement-cyclization of isoxazoline-5-spirocyclopropanes [3] which can be utilized to afford chiral indolizinones This strategy applied to the suitable enantiomerically pure isoxazolines **1,2** would produce chiral indolizinones **10-12**, provided that the rearrangement and the subsequent cyclization of the intermediate pyridone **3**[4] could occur with control of the stereochemistry of the stereogenic centers (Scheme 1). Finally, the reduction of the enaminonic moiety in **10-12** should

afford chiral 7-hydroxyoctahydroindolizines **13**, **15** and **16** containing three or four stereogenic centers

Results and Discussion

The common precursor for the synthesis of chiral isoxazoline-5-spirocyclopropanes **1,2** is the enantiomerically pure (*R*)-(-)-2-chloro-5-nitropentane (**7**), which was prepared as summarized in Scheme 2.

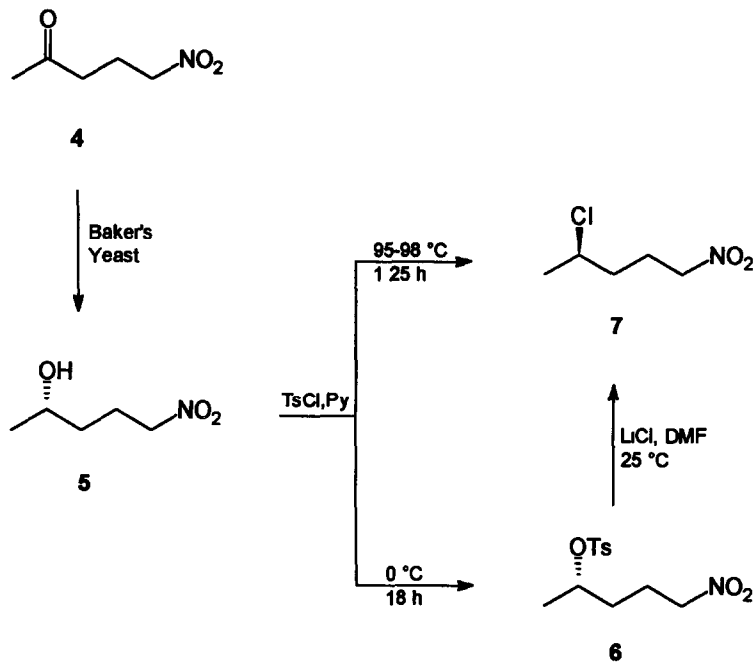
Scheme 1



The enantioselective reduction of 5-nitro-2-pentanone (**4**) with baker's yeast afforded (*S*)-(+)-5-nitropentan-2-ol (**5**) in 74% yield and >99% ee determined by ^{1}H-NMR of the corresponding Mosher's ester[5] The reduction procedure was a modified version of those reported,[6a,b] improving the yield and the enantiomeric excess of the compound **5**.[7] Then, **5** was converted to (*R*)-(-)-2-chloro-5-nitropentane (**7**) in two different ways· by conversion of the corresponding tosylate (*S*)-(+)-**6** with LiCl in DMF (43% overall yield of **7**) or by heating at 95-98 °C the mixture of **5**, TsCl, and pyridine for 1.25 h (77% yield) Both methods afforded compound **7** with the same optical purity (>90% ee) The enantiomeric excess was determined by comparison of the chiral column G C analyses of compound **7** and of racemic mixture (±)-**7**.[8] The tosylate **6** is an intermediate of the latter reaction in fact (±)-**6** was converted to (±)-**7** (77% yield) when heated in pyridine and pyridinium chloride (1 equiv) at 95-100 °C for 1 h

This is the first example of direct conversion of a 1,4-nitroalcohol to a nitrochloride by TsCl in hot pyridine, although this reaction was observed as a side reaction in the tosylation of phenols, simple alcohols and sugars [9] The same reaction applied to 1,2-nitroalcohols afforded only the corresponding tosylates [10]

Scheme 2



The nitrile oxide, generated in situ from **7** by the Mukaiyama method,[11] reacted with methylenecyclopropane (**8**) (Scheme 3) or with 1-methylene-2-phenylcyclopropane (**9**) (Scheme 4) affording the adducts **1** (73% yield) or **2** (75%, 1 1 diastereoisomeric ratio), respectively.

The thermal rearrangement of **1** was carried out in refluxing DMF containing 1 equiv of K_2CO_3 for 2 5 h and afforded **10** in 65% yield (Method A).

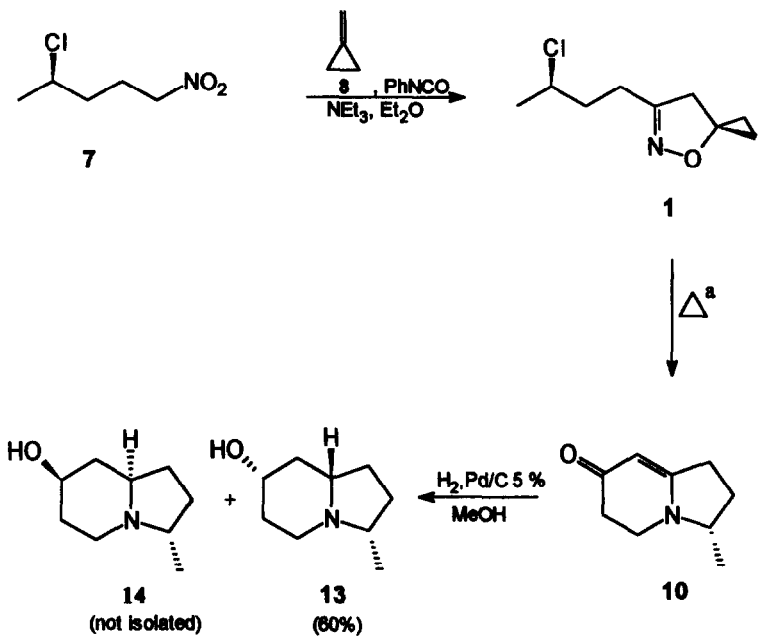
We were not able to determine directly the enantiomeric excess of **10** by either different analytical (GC or HPLC with chiral phases) or spectroscopic techniques (^{1}H-NMR in presence of chiral shift reagents or chiral solvating agents, or after reaction of **10** with Mosher's acid chloride) The absolute configuration of the predominant enantiomer was assumed to be (3*S*), assuming that a S_N2 displacement of the C-Cl bond of the intermediate **3** would invert the configuration of the stereogenic center.

Reduction of **10** with hydrogen on Pd/C in methanol afforded (3*S*,7*S*,8a*S*)-3-methyl-7-hydroxyoctahydroindolizine (**13**) in 60 % yield The hydrogenation occurred mainly on the less hindered face of the enaminonic moiety, leading to **13**, although a

minor compound detected by MS and ^{1}H-NMR (less than 10% in the crude reaction mixture) was identified as diastereoisomer (3*S*,7*R*,8a*R*)-**14**, deriving from the opposite attack.

The enantiomeric purity of **13** was determined by chiral column GC analysis[8] and a value of 17% ee was found This was reasonably assumed as the ee of indolizinone **10** too. As will be discussed later, the enantiomeric purity of **13** was dependent on the rearrangement conditions. compound **13** was obtained in higher enantiomeric excess (49 %)carrying out the thermolysis of **1** for 2 5 h in refluxing mesitylene (Method B) and then reducing **10** (obtained in 60 % yield). A further improvement in the optical purity of **13** was obtained carrying out the thermal rearrangement by FVT (Flash Vacuum Thermolysis) at 400 °C and 10^{-3}mbar (Method C). This process afforded **10** in 41% yield (32% of the starting material was recovered) and after catalytic hydrogenation a more enantiomerically enriched **13** was obtained (74% ee)

Scheme 3



[a] Rearrangement was carried out in three different ways **Method A** 1eq K_2CO_3, DMF, 2 5 h reflux **Method B** Mesitylene, 2 5 h reflux **Method C** FVT (Flash Vacuum Thermolysis), 400 °C, 10^{-3} mbar

A trans-fused structure was assigned to compound **13** on the basis of the strong Bohlmann band at 2803 cm^{-1} in the IR spectrum[12-15] (see Table 1). This assignment was confirmed by the ^{1}H-NMR spectrum of **13**. The proton H-8a is upfield shifted to a value lower than 2.05 ppm because of a trans orientation with respect to the nitrogen lone pair.[12-15] The stereochemistry of the methyl and hydroxy groups was assigned on the basis of the chemical shift of the protons H-3 and H-7, and of the ^{13}C-NMR chemical shift of the methyl group The observed value (3.62 ppm)

of the proton on C-7 is close to the value reported for the axial carbinolic proton in the trans-fused 7-hydroxy octahydroindolizine (3.47 and 4 02 ppm for the axial and equatorial protons, respectively)[12] indicating an equatorial configuration for the hydroxy group. The chemical shift value of the proton H-3 (2.15 ppm), indicates a pseudoaxial configuration for this hydrogen,[13] the upfield shift being a consequence of the trans orientation of this hydrogen with respect to the nitrogen lone pair. Accordingly, the other diastereoisomer **14** showed a downfield chemical shift of the hydrogen H-3 at 3 22 ppm, in agreement with the reported data for the 3-methyl octahydroindolizine[13] (3.30 ppm) in which the methyl group is in pseudoaxial position Furthermore, the ^{13}C-NMR chemical shift of the methyl group (18 3 ppm), very close to the reported value for the pseudoequatorial methyl in the 3-methyl octahydroindolizine (18 8 ppm),[15] is consistent with the pseudoequatorial configuration of the methyl in position 3 in compound **13**

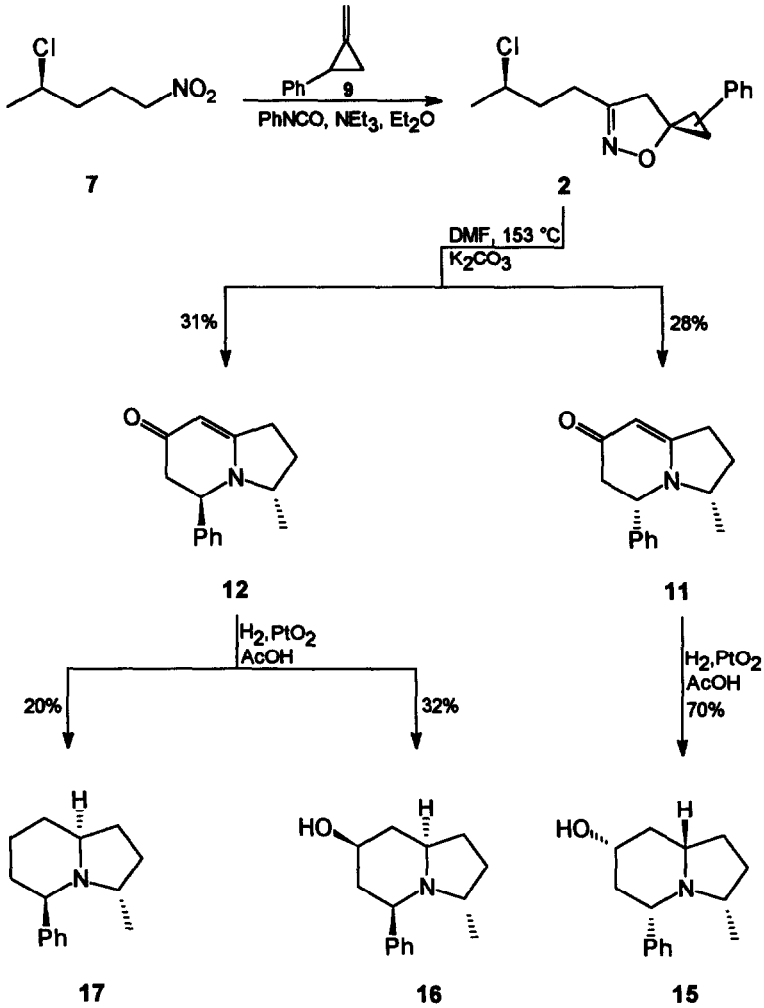
The rearrangement of isoxazoline **2** was carried out in refluxing DMF with 1 equiv of K_2CO_3 for 0 5 h, affording a mixture of two diastereoisomers **11** and **12** (75 % yield, 1 . 1.2 ratio, by ^{1}H-NMR) formerly characterized as a racemic mixture in a previous work[3] (Scheme 4) The two isomers were separated by flash column chromatography producing (3*S*,5*R*)-(-)-**12** in 31% yield and (3*S*,5*S*)-(+)-**11** in 28% yield Also in this case we were not able to determine directly the enantiomeric excess, which was assumed to be at least equal to that determined for the corresponding reduced products

The reductions of **11** and **12** were carried out in 7-8 h with hydrogen on PtO_2 in acetic acid [16,17] We changed the hydrogenation condition with respect to the previous reduction of **10** because in MeOH, using Pd/C as catalyst, up to three different diastereoisomers were obtained, in different ratios depending on reaction time [17] Furthermore, in the hydrogenation of **11**, reductive cleavage of the N-CHPh- bond was observed.[18]

Reduction of **11** (see Scheme 4) gave (3*S*,5*S*,7*S*,8a*S*)-(-)-3-methyl-5-phenyl-7-hydroxyoctahydroindolizine (**15**) in 70% yield and 96% ee, determined as described later The hydrogenation was highly stereoselective occurring only on the less hindered face of the indolizinone **11**, that is, on the face opposite to the phenyl and methyl groups

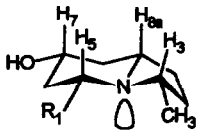
The strong Bohlmann bands in the IR spectrum (see Table 1) at 2809 and 2741 cm^{-1} indicate a trans-fusion of the two rings[12-15] This assignment is confirmed by the chemical shift of proton H-8a that resonates at 2 17 ppm (very close to the chemical shift of the same proton in **13**) All substituents are in equatorial positions. the proton on C-5, even undergoing the phenyl deshielding effect, resonates at 3 06 ppm, because of its trans orientation with respect to the lone pair of the nitrogen atom, and its great coupling constant of 11.0 Hz with the axial proton on C-6 confirms its axial position The resonance of proton of H-3 at 2.35 ppm, is consistent with its axial position. Moreover, the methyl group, which faces the phenyl group, experiences a very strong shielding effect, resulting in a chemical shift of 0.31 ppm. The fact that the phenyl group is constrained to a faced conformation with respect to the methyl is confirmed by a molecular model study by using a molecular mechanics program.[19]

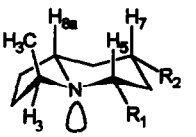
Scheme 4.



Concerning the hydroxy group, the resonance of the proton H-7 at 3 77 ppm is in accordance with its axial position, the value being very close to that of the corresponding proton in **13**, apart from a small deshielding effect (observed also for the proton on C-3) due to the phenyl group The reduction of **12** with hydrogen on PtO_2 in AcOH gave stereoselectively (3*S*,5*R*,7*R*,8a*R*)-(+)-3-methyl-5-phenyl-7-hydroxyoctahydroindolizine (**16**) (32% yield), in addition to the dehydroxylated compound **17** (20 % yield) The gas chromatographic ratio of the two products did not change during the reaction, which was complete after 8 h This means that dehydroxylation could not have occurred after **16** had left the catalyst surface. It had been observed that in the hydrogenation of simple cyclohexanones,[17] dehydroxylation occurred on PtO_2 in AcOH to a small extent

Table 1. IR Bohlmann bands and most significant chemical shifts of compounds **13-17.**





13 $R_1 = H_5$ (eq)
15 $R_1 = Ph$

14 $R_1 = H_5$ (eq), $R_2 = OH$
16 $R_1 = Ph$, $R_2 = OH$
17 $R_1 = Ph$, $R_2 = H$

	IR (cm^{-1})	^{1}H-NMR (δ, ppm)				
		H-3	H-5 (ax)	H-7	H-8a	CH_3
13	2803	2 15 (m)	—	3 62 (m)	<2 05	1 09 (d)
14	n d	3 22 (m)	—	3 60 (m)	2 74 (m)	0 94 (d)
15	2809, 2741	2 35 (m)	3 06 (dd) J = 11 2, 2 9 Hz	3 77 (m)	2 17 (m)	0 31 (d)
16	2794, 2717	3 18 (m)	3 48 (dd) J = 11 0, 2 7 Hz	3 73 (m)	2 68 (m)	0 71 (d)
17	2796, 2723	3 23 (m)	3 40 (dd) J = 10 0, 2 9 Hz		2 55 (m)	0 72 (d)

An increase in this process is observed by adding one microdrop of concentrated HCl In our case the same result was achieved by carrying out the hydrogenation of racemic **12** on PtO_2 in EtOH with a drop of conc HCl, obtaining after 5 h **17** in 72% yield On the other hand, attempts to reduce **12** in neutral conditions in EtOH on PtO_2 or on Pt black[17] yielded no appreciable results, the reactions being very slow (no reduction after 5 h was observed)

Both **16** and **17** show strong Bohlmann bands in the 2800-2700 range (Table 1), owing to the trans fusion of the rings The proton H-8a still resonates at low chemical shift (2.68 ppm in **16**, and 2 55 ppm in **17**), the proton H-5 has a chemical shift of 3 48 ppm in **16** and 3 40 ppm in **17**, and it is a doublet of doublets, with a large coupling constant of 11 0 Hz in **16** and 10 0 Hz in **17**, in accordance with the axial position of this proton. This means that the phenyl group is equatorial and the methyl group is consequently in pseudoaxial position: indeed, the proton on C-3 now resonates at 3 18 ppm (3.23 ppm in **17**), very close to the value of the chemical shift of the same proton in **14**, and the methyl group resonates at 0.71 ppm (0 72 ppm in **17**), not undergoing the strong phenyl shielding effect Therefore, the stereochemistry of the catalytic

hydrogenation of **12** is determined mainly by the attack on the less hindered face of the enaminonic moiety (i.e to the opposite side of the phenyl group).

The enantiomeric purity of **16** was determined by chiral phase HPLC[20] and an enantiomeric excess of 96 % was found. The same value of ee was measured for **15**, by treating racemic and enantiomerically enriched aminoalcohols **15** with 1 equivalent of (+)-MPTA acid (Mosher' s acid), and analysing the corresponding $CDCl_3$ solutions of the obtained salts by ^{1}H-NMR.[21] The splitting of the methyl signal allowed us to calculate a value of 96 % ee. The same technique, applied to the racemic **16**, failed, even adding more than one equivalent of Mosher's acid, and no splitting of the methyl signal was observed.

In order to justify the results concerning the enantioselectivity in the formation of indolizinones **10**, **11** and **12**, and for extension of the reduction products, the rearrangement conditions and the structure of the isoxazolines **1,2** have to be considered The process that leads to a loss of enantioselectivity would reasonably be ionic cleavage of the C-Cl bond, that could equally well occur both in **1-2** and **3** (see Scheme 1). On the other hand, an S_N2 displacement of the chlorine in **3** by the secondary nitrogen atom would afford indolizinone **10-12** with inversion of configuration. Therefore, using a non-polar solvent such as mesitylene instead of the DMF/K_2CO_3 system to carry out the reaction, the rate of ionic cleavage of the C-Cl bond decreases and a higher ee is obtained Ionic cleavage is further limited if the rearrangement is carried out in vapour phase, where an optical yield of 74 % was obtained for **10** (a racemization process, involving the homolytic cleavage of the C-Cl bond at high temperature cannot be excluded) In the same way, if a substituent is present, such as the phenyl group, on the cyclopropane ring of the isoxazoline, thereby accelerating the rearrangement process[3], a great increase in the ee of the final product is achieved (96 %), even when carrying out the reaction in DMF/potassium carbonate.

Conclusions

Enantiomerically enriched substituted octahydroindolizines were easily prepared in five steps, starting from 5-nitro-2-pentanone (**4**) in overall yields ranging from 7% to 17% Enzymatic reduction of the nitroketone allowed us to obtain a chiral starting material with a very high (>99%) enantiomeric purity. On the other hand, the γ-nitroketone **4** was prepared on large scale from the inexpensive starting materials methyl vinyl ketone and nitromethane. The hydrogenation of the indolizinones **10**, **11** and **12** occurred stereoselectively (substituents in positions 5 guided the attack of the hydrogen to the less hindered face of the enaminonic moiety) affording 7-hydroxyoctahydroindolizines **13-16** with three or four stereogenic centers The enantiomeric purity of indolizinoles **15** and **16** was satisfactory, while this synthetic strategy did not allow us to obtain the indolizinole **13** with an ee higher than 74%

Finally, a large variety of substituents in position 3 of indolizinones could be introduced by using differently substituted γ-nitroketones as starting material The synthesis and consequent enzymatic reduction of some γ-nitroketones is under investigation. In the same way, the use of differently substituted methylenecyclopropanes, permits the introduction of various groups in position 5.

Experimental section

Racemic 5-nitro-2-pentanol (**5**) was prepared as reported.[22] Melting points were determined with a Buchi 510 apparatus. IR spectra were recorded with a Perkin Elmer 881 spectrophotometer. ^{1}H- and ^{13}C-NMR were recorded with a Varian Gemini 200 MHz MS spectra were obtained with a Hewlett Packard A 5790-5970 GC-MS instrument Elemental analysis were performed with a Perkin Elmer 240 C instrument. Optical rotations were measured using a Perkin-Elmer 245 polarimeter. The R_f values refer to TLC on 0.25 mm silica gel plates (Merck F254) HPLC analyses were performed with a Gilson apparatus (mod. 302, pumps mod. 305, UV Det. mod. 116).

(*S*)-(+)-5-Nitro-2-pentanol (5). Baker's yeast (40 g) was slowly added to a solution of glucose (1 g) in water (180 mL) at 30-35 °C under mechanical stirring. Then, **4** (950 mg, 7.25 mmoles) was added to the suspension The reaction was monitored by G.C and after 4 d was stopped (conversion 89 %) Celite (3 g) and saturated NaCl (150 ml) were added, and the mixture extracted with 150 mL of diethyl ether by using a continuous liquid-liquid extraction apparatus for 18 h The solvent was then evaporated, obtaining a crude reaction mixture chromatographed by FCC (Flash Column Chromatography) (eluant ethyl acetate + hexane, 1 · 2) affording **5** (762 mg, 79%). Pure **5** (716 mg, 74%) was obtained by Kugelrohr distillation (130 °C/4 6 mbar)

5 Colourless oil, R_f 0 18 $[\alpha]^{20}_D$ = +18.5° (c=0 92, chloroform), ee > 99% (by ^{1}H-NMR of the Mosher ester)[5] Reported data: $[\alpha]^{20}_D$ = +16.9° (c = 1.70, chloroform), ee = 97%;[6a] $[\alpha]^{20}_D$ = +17 0° (c = 2 00, chloroform), ee = 100% (determined by GC method on chiral phase).[6b]

(*R*)-(-)-2-Chloro-5-nitropentane (7) Method A A stirred mixture of **5** (399 mg, 3 mmol), tosyl chloride (570 mg, 3 mmol), and anhydrous pyridine (250 mg, 3 1 mmol) was heated for 75 min in an oil bath at 95-98 °C The mixture was then cooled at rt, 5 mL of water were added and extracted with ether The organic layer was washed with 5% HCl, with saturated Na_2CO_3, and with water The organic layer was left overnight over Na_2SO_4 and then concentrated The residual oil was chromatographed (ethyl acetate + hexane, 1 . 3) affording 422 mg of **7** Pure **7** (351mg, 77%) was obtained after Kugelrohr distillation (130 °C/2 mbar)

7. Colourless oil, R_f 0 69 $[\alpha]^{20}_D$ = - 28 7 ° (c = 0.79, chloroform), ee > 90% (by GC on chiral phase) [8] Anal calcd for $C_5H_{10}ClNO_2$. C, 39 62; H, 6 65, N, 9.24 Found C, 39 41, H, 6 83, N, 8 97 MS *m/z* (rel intensity) 88 (M^+-CH_3CCl, 20), 69 (100), 68 (32), 67 (23), 65 (22), 63 (63), 62 (22), 55 (19), 53 (21), 45 (25), 43 (54), 41 (100) ^{13}C-NMR δ 74 9 (t), 57 2 (d), 36 6 (t), 25 3 (q), 24 5 (t), ^{1}H-NMR δ 4 41 (t, J = 6 8 Hz, 2 H), 4 03 (m, 1 H), 2.35-2.00 (m, 2 H), 1.90-1 65 (m, 2 H), 1 52 (d, J = 6 4 Hz, 3H) IR (neat) 2980, 2950, 1555, 1440, 1380, 1260 cm^{-1}.

Method B. A solution of tosylate **6** (150 mg, 0 5 mmol) in 2.5 mL of anhydrous DMF was added to LiCl (44 mg, 1 05 mmol) in 2 5 mL of DMF. The solution was left at rt under stirring and nitrogen atmosphere for 24 h Water (10 mL) was added and extracted with Et_2O (4 x 10 mL) The organic layer was then washed with water and dried over sodium sulfate Chromatography gave **7** (51 mg, 68%) $[\alpha]^{20}_D$ = -29 2 ° (c = 0.53, chloroform)

(*S*)-(+)-5-Nitro-2-tosyloxypentane (6). 5 (74 mg, 0.56 mmol), tosyl chloride (125 mg, 0.66 mmol) and 0 5 mL of anhydrous pyridine were mixed cooling to -5 °C in an ice/salt bath and left under stirring at 0 °C for 5 h. Water (1 mL) was added, and the solution extracted with chloroform (4 x 5 mL), washed with diluted sulfuric acid, saturated sodium carbonate and then with water The organic layer was dried over sodium sulfate and evaporated. Chromatography (chloroform) gave **6** (100 mg, 63%)

6 Colourless oil, R*f* 0.55 $[\alpha]^{20}_D$ = +1,4° (c=0.71, chloroform). Anal. calcd for $C_{12}H_{17}O_5NS$. C, 50.16, H, 5.96, N, 4.87. Found · C, 50 47; H, 6 09; N, 4.48. MS *m/z* (rel intensity) 199 (13), 173 (18), 172 (50), 155 (100), 116 (60), 108 (16), 107 (16), 92 (11), 91 (83), 69 (36), 68 (20), 65 (29) ^{13}C-NMR ($CDCl_3$) δ 143 3 (s), 134.0 (s), 129.9 (d, 2 C), 127.6 (d, 2 C), 78.6 (d), 75 6 (t), 32.9 (t), 24 5 (t), 23.8 (q), 20.7 (q); ^{1}H-NMR δ 7.77 (d, J = 8 3 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 4 65 (m, 1H), 4 32 (td, J = 6.8, 2.4 Hz, 2 H), 2.44 (s, 3 H), 2.05-1.87 (m, 2 H), 1.65 (m, 2 H), 1 23 (d, J = 6.3 Hz, 3 H) IR (neat) 2980, 2950, 1600, 1440, 1360, 1180, 1100, 900, 810, 610 cm^{-1}.

(3'*R*)-(-)-6-(3'-Chlorobutyl)-4-oxa-5-azaspiro[2.4]hept-5-ene (1). A solution of **7** (450 mg, 2.98 mmol) in 10 mL of anhydrous diethyl ether was cooled to -60 °C in an acetone/dry ice bath Under stirring and nitrogen atmosphere, methylenecyclopropane (850 mg, 1[illegible].7 mmol) was added by cannula, followed by phenyl isocyanate (709 mg, 5.96 mmol) and NEt_3 (60 mg, 0.596 mmol). The solution was left at 0 °C for 0.5 h and at rt for 60 h, then filtered on Celite layer and evaporated. Chromatography (dichloromethane + hexane, 5 . 2) afforded **1** (405 mg, 73 %).

1 Colourless oil, R*f* 0 43 $[\alpha]^{20}_D$ = -32 6 ° (c = 0.72, chloroform). Anal. calcd for $C_9H_{14}ClNO$ · C, 57.60; H, 7 52; N, 7 46. Found C, 58.00, H, 7.37; N, 7 74. Spectroscopic data are identical to those reported for the racemic mixture [3]

(3*S*)-(+)-3-Methyl-2,3,5,6-tetrahydroindolizin-7(1*H*)-one (10). Method A. A solution of **1** (358 mg, 1 91 mmol) and potassium carbonate (265 mg, 1 91 mmol) in 40 mL of anhydrous DMF was refluxed under nitrogen for 2 5 h After concentration under vacuum, chromatography (CH_2Cl_2 + MeOH, 10 . 1) gave **10** (187 mg, 65 %). A further purification was achieved by Kugelrohr distillation (110-130 °C/ 10^{-3} mbar).

10 Colourless oil, R*f* 0.43 $[\alpha]^{20}_D$ = +13.8 ° (c = 0 54, chloroform) Anal. calcd for $C_9H_{13}NO$ · C, 71 46, H, 8.66; N, 9 29 Found : C, 71 09; H, 8 84, N, 9 20 Spectroscopic data are identical to those reported for the racemic mixture.[3]

Method B A solution of **1** (190 mg, 1.02 mmol) in 20 mL of anhydrous mesitylene was refluxed under nitrogen atmosphere for 2 5 h After cooling at rt 1.02 eq of MeONa in MeOH were added, the solution concentrated under vacuum and the residue chromatographed affording **10** (92 mg, 60 %) $[\alpha]^{25}_D$ = +35 ° (c = 0 60, chloroform)

Method C 1 (150 mg, 0 8 mmoles) was subjected to FVT (400 °C, 10^{-3} mbar) by vaporization at 90-100 °C. The pyrolysis gave, after treatment with 1 eq of NaOH in methanol, evaporation of the solvent and chromatography, **10** (50 mg, 41%), besides the unreacted **1** (48 mg, 32 %)

(3*S*,7*S*,8a*S*)-3-Methyl-7-hydroxyoctahydroindolizine (13) A solution of **10** (50 mg, 0.33 mmol) in 10 mL of MeOH was added to a stirred suspension of Pd/C 5% (100 mg) in 3 mL of MeOH. The mixture was left under H_2 (1 atm) at rt for 4 d The catalyst was then filtered on a

Celite layer, washing with methanol, the solvent evaporated and the residue chromatographed (CH_2Cl_2 + MeOH +NEt_3, 10 · 1 : 0.001) affording **13** (0.20 mmol, 60 %). Further purification was obtained by Kugelröhr distillation (75 °C/0.05 mbar).

13. Colourless oil, R_f 0.15. Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found· C, 69.02; H, 10.77; N, 9.20 MS *m/z* (rel intensity) 155 (M^+, 9), 154 (14), 141 (12), 140 (100), 110(20), 96 (13), 83 (15), 82 (18), 80 (29), 69 (20), 68 (25), 67 (11); ^{13}C-NMR δ 69.7 (d), 63.9 (d), 59 8 (d), 48.0 (t), 40.2 (t), 34 6 (t), 31 0 (t), 28.1(t), 18.3 (q), ^{1}H-NMR δ 3 62 (m, 1H), 3.10 (ddd, *J* = 10 8, 3.8, 2 6 Hz, 1H), 2.50 (s br, 1H), 2 15 (m, 1H), 2.05-1.20 (m, 10 H), 1.09 (d, *J* = 6.11 Hz, 3H), IR ($CDCl_3$) 3609, 3400 (br), 2803, 2967, 2948, 2875, 1447, 1364 cm^{-1}

In the crude reaction mixture **14** (10%) was identified by MS and ^{1}H-NMR

14 MS *m/z* (rel intensity) 155 (M^+, 8), 154 (7), 141 (9), 140 (100), 138 (10), 110 (22), 96 (11), 82 (11), 80 (18), 69 (17), 68 (19), 67 (9); ^{1}H-NMR ($CDCl_3$) δ 3.60 (m, 1 H), 3.22 (m, 1 H), 2 96 (ddd, *J* = 12.6, 4 5, 2 5 Hz, 1 H), 2 74 (m, 1 H), 2.57 (dt, *J* = 12.6, 2.9 Hz, 1 H), 2 00-1 05 (m, 9 H), 0 94 (d, *J* = 6.3 Hz, 3 H)

(1*RS*,3'*R*)-1-Phenyl-6-(3'-chlorobutyl)-4-oxa-5-azaspiro[2.4]hept-5-ene (2) 7 (318 mg, 2 1 mmol) and 1-methylene-2-phenylcyclopropane (332 mg, 2.52 mmol) were dissolved in 18 mL of anhydrous diethyl ether Phenyl isocyanate (499 mg, 4 2 mmol) and NEt_3 (42 2 mg, 0.42 mmol) were added under nitrogen atmosphere. The solution was left under stirring at rt for 4 d. After filtration, the solvent was evaporated and the residue oil chromatographed (ethyl acetate + petroleum ether, 1 5) obtaining **2** as a 1 1 mixture of two diastereoisomers (414 mg, 75%)

2. Oil, R_f 0 41. Spectroscopic data are identical to those reported for the racemic mixture [3]

Rearrangement of 2 A solution of **2** (700 mg, 2 67 mmol) and potassium carbonate (367 mg, 2 67 mmol) in 60 mL of DMF, was refluxed for 0 5 h under nitrogen The solvent was removed under vacuum and the residue chromatographed (CH_2Cl_2 + MeOH, 20 1) obtaining an approximately 1 2 1 mixture (by ^{1}H-NMR)of **12** and **11** (R_f 0 35, 454 mg, 75%) Further chromatography (acetone) gave pure **12** (189 mg, 31%) and **11** (170 mg, 28%)

12. Colourless solid, mp 114-115 °C R_f 0 75 $[\alpha]^{20}_D$ =-76 6 ° (c = 0.67, chloroform). Anal Calcd for $C_{15}H_{17}NO$ C, 79 26, H, 7 54, N, 6 16 Found · C, 79.34, H, 7.59, N, 6 12. Spectroscopic data are identical to those reported for the racemic mixture [3]

11 Colourless solid, mp 85-86 °C R_f 0 63 $[\alpha]^{20}_D$ =+146 6 ° (c = 0 56, chloroform). Anal Calcd for $C_{15}H_{17}NO$ C, 79 26, H, 7.54, N, 6 16 Found · C, 79.16, H, 7 54, N,6 12 Spectroscopic data are identical to those reported for the racemic mixture [3]

(3*S*,5*S*,7*S*,8a*S*)-(-)-3-Methyl-5-phenyl-7-hydroxyoctahydroindolizine (15). A solution of **11** (220 mg, 0 97 mmol) in 6 mL of acetic acid was added to a stirred prehydrogenated suspension of PtO_2 (17 mg) in 6 mL of acetic acid The solution was left under hydrogen at 1 Atm for 7 h. The solution was filtered on a Celite layer, washing with acetic acid, and then concentrated under vacuum Water (12 ml) and 6 ml of NaOH 3 M were added to the residue. The obtained suspension was then extracted with dichloromethane (10 x 10 mL) and dried overnight over sodium sulfate After filtration and evaporation of the solvent, the residue was chromatographed (CH_2Cl_2 + MeOH + NEt_3, 20 1 0 001) affording **15** (157 mg, 70%)

15. Colourless solid, mp 91-92 °C, R*f* 0.25. $[\alpha]^{20}_D$ =-28.8° (c = 1.09, chloroform), 96% ee (by HPLC).[20] Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.90; H, 9.40; N, 5.87 MS *m/z* (rel intensity) 231 (M^+, 4), 216 (100), 186 (11), 154 (16), 132 (13), 131 (15), 130 (11), 112 (26), 105 (21), 104 (55), 103 (20), 91 (22), 84 (23), 82 (20), 77 (22); ^{13}C-NMR ($CDCl_3$) δ 143.7 (s), 128 3 (d, 2 C), 128.1 (d, 2 C), 127 4 (d), 69.6 (d), 67.4 (d), 65.6 (d), 59.9 (d), 44.9 (t), 40 2 (t), 32.4 (t), 28.4 (t), 22.5 (q); ^{1}H-NMR ($CDCl_3$) δ 7.40-7.20 (m, 5 H), 3.77 (m, 1 H), 3.06 (dd, *J* = 11.2, 2.9 Hz, 1 H), 2.35 (m, 1 H), 2.25-2.10 (m, 2 H), 2.05-1.60 (m. 4 H), 1.60-1.20 (m, 3 H), 0.31 (d, *J* = 6.0 Hz, 3 H); IR ($CDCl_3$) 3610, 3416 (br), 3066, 3031, 2995, 2946, 2875, 2809, 2741, 1373, 1106 cm^{-1}.

(3*S*,5*R*,7*R*,8a*R*)-(+)-3-Methyl-5-phenyl-7-hydroxyoctahydroindolizine (16). A solution of **12** (215 mg, 0.95 mmol) in 6 mL of acetic acid was added to a stirred prehydrogenated suspension of PtO_2 (18 mg) in 6 mL of acetic acid. The mixture was left under hydrogen at 1Atm for 8 h. The solution was filtered on a Celite layer, washing with acetic acid, and then evaporated under vacuum. Water (12 mL) and a solution of NaOH 3 M (6 mL) were added, and the suspension extracted with dichloromethane (10 x 10 mL), drying overnight over sodium sulfate. After filtration and concentration, the residual oil was chromatographed (CH_2Cl_2 + MeOH + NEt_3, 20 . 1 : 0 001) affording **16** (70 mg, 32 %) and **17** (41 mg, 20%).

16. Oil, R*f* 0.22. $[\alpha]^{20}_D$ = + 88.0° (c = 0.48, chloroform), 96% ee (by ^{1}H-NMR of the salts with Mosher' s acid) [21] Anal. Calcd for $C_{15}H_{21}NO$· C, 77.88, H, 9.15; N, 6.05. Found· C, 77.57, H, 9 57; N, 6.21 MS *m/z* (rel intensity) 231 (M^+, 6), 230 (4), 217 (17), 216 (100), 154 (15), 112 (15), 104 (17), 91 (8), 77 (7), ^{13}C-NMR ($CDCl_3$) δ 143.3 (s), 128 2 (d, 2 C), 127 4 (d, 2 C), 126 8 (d), 69.8 (d), 60.0 (d), 56.1 (d), 52.8 (d), 45.6 (t), 41.1 (t), 30 0 (t), 29.7 (t), 13.9 (q); ^{1}H-NMR ($CDCl_3$) δ 7.40-7.20 (m, 5 H), 3.73 (m, 1 H), 3.48 (dd, *J* = 11.0, 2 7 Hz, 1 H), 3 18 (m, 1 H), 2.68 (m, 1 H), 2 25-2.15 (m, 1 H), 2.10-1.85 (m, 3 H), 1.60-1.15 (m, 4 H), 0.71 (d, *J* = 6 6 Hz, 3 H); IR (neat) 3550-3200 (br), 3087, 3061, 3027, 2959, 2869, 2794, 2717, 1453, 1380, 1370, 1171, 1136, 1114, 1067, 1028, 1011 cm^{-1}

17. Colourless oil, R*f* 0.31, $[\alpha]^{20}_D$ =+56 8 ° (c = 0 40, chloroform). MS *m/z* (rel intensity) 215 (M^+, 6), 200 (100), 138 (15), 104 (12), 91 (11), 77 (4), 70 (6); ^{13}C-NMR ($CDCl_3$) δ 143 5 (s), 128.1 (d, 2), 127.5 (d, 2 C), 126.6 (d), 63 3 (d), 58.0 (d), 53.6 (d), 36 8 (t), 31 9 (t), 30 1 (t), 29 2 (t), 25.1 (t), 13 8 (q), ^{1}H-NMR ($CDCl_3$) δ 7.40-7.15 (m, 5 H), 3.40 (dd, *J* = 10.0, 2 9 Hz, 1 H), 3 23 (m, 1 H), 2 55 (m, 1 H), 2.05-1 60 (m, 5 H), 1.55-1.05 (m, 5 H), 0 72 (d, *J* = 6.6 Hz, 3 H), IR (neat) 3065, 3028, 2936, 2873, 2796, 2723, 562, 1452, 1369, 1325, 1304, 1289, 1168, 1128, 1107, 1056 cm^{-1}

Acknowledgment

The authors thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST 60%, 40%), and Mrs B. Innocenti for HPLC analysis and Dr. C. Faggi for technical assistance

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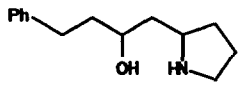
18) The following open chain product 

was recovered in 14% yield and characterized. MS m/z (rel intensity) 216 (1), 202 (1), 98 (10), 91 (13), 84 (100); ^{13}C-NMR ($CDCl_3$) δ 142.6 (s), 128.4 (d), 128.2 (d), 125 6 (d), 68.4 (d), 56.5 (d), 54 1 (d), 39 8 (t), 39.3 (t), 33.1 (t), 32 0 (t), 28.9 (t), 21.5 (q); ^{1}H-NMR ($CDCl_3$) δ 7 35-7 10 (m, 5 H), 3.98 (m, 1 H), 3 57 (m, 1 H), 3 25-3.15 (m, 2 H), 2.90-2.55 (m, 2 H), 2.00-1.35 (m, 7 H), 1.17 (d, J = 6.2 Hz, 3 H)

19) PC-Model®, Serena Software

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