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A Short Enantioselective Access to 2,3,6-Trialkylpiperidines and 5,8-Dialkylindolizidines.

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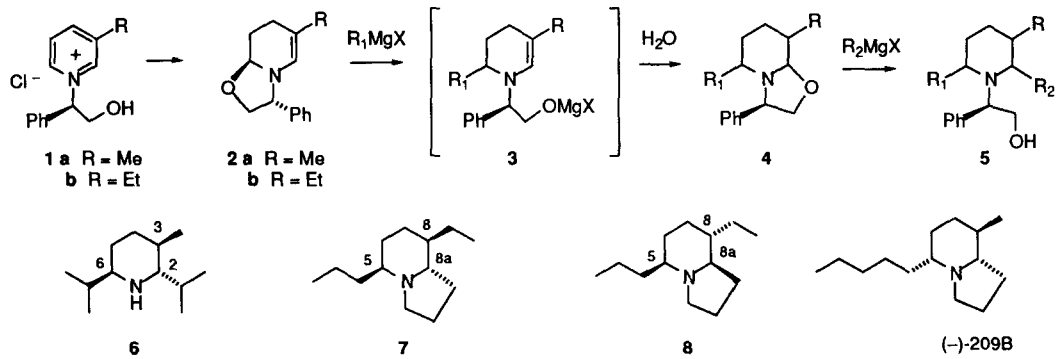
Abstract: An enantioselective access to 2,3,6-trialkylpiperidines **5** is described. This sequence is illustrated by the four-step syntheses, from salts **1**, of piperidine **6** and indolizidines **7** and **8**. The overall yields are in the range 10–15 %. The stereochemistry of intermediates is discussed, supported by two X-ray studies, and comparison with analogs. Stereochemical properties of intermediate oxazolidine derivatives **4** were used to orient the syntheses towards different diastereoisomers such as **7** or **8**.

We recently reported[1] that the sodium dithionite reduction of new chiral pyridinium salts such as **1** (Scheme 1) gave, after filtration of the intermediate 1,4-dihydropyridines over alumina, oxazolidines **2** in good yield. In a preliminary communication,[1c] we also demonstrated that treatment of these oxazolidines with Grignard reagents led to intermediates of type **3**. These intermediates spontaneously cyclized upon hydrolysis, affording new derivatives **4**, ready for further Grignard alkylation to give 2,3,6-trisubstituted piperidines **5**. This sequence was illustrated by a short synthesis (four steps from readily available salt **1a**) of the enantiomer of natural indolizidine (–)-209B.[1c] In this paper we now describe experimental and stereochemical details of this reaction sequence (**2**-->**5**) exemplified in particular by the four-step syntheses from salts **1** of piperidine **6** and analogs **7**,**8** of indolizidine (–)-209B.

Scheme 1



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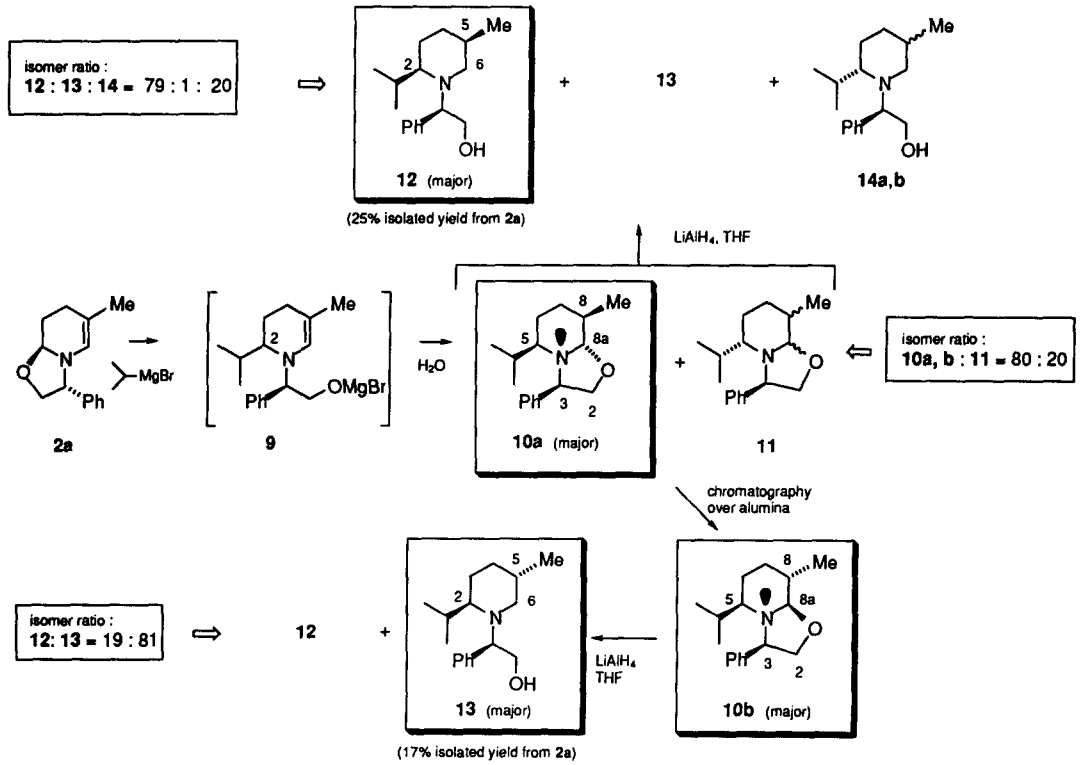
Treatment of oxazolidine **2a** (Scheme 2) with an excess of isopropylmagnesium bromide in ether at –78°C gave, after hydrolysis of the crude reaction product (**9**), a mixture of new oxazolidines in 92 % yield. In principle, eight diastereoisomers could be formed, but careful analysis (*vide infra*) showed that the mixture consisted essentially of oxazolidines **10a,b** and **11** (undefined mixture of isomers) in a ratio of 80 : 20 (in favour of **10a,b**). ^{1}H NMR analysis was especially valuable for the structural analysis of these oxazolidine intermediates. In the crude mixture, obtained immediately after the reaction, the isomer **10a**, characterized by a H-8a proton appearing as a doublet ($J_{H\text{-}8a,\ H\text{-}8}$ = 6.4 Hz) at 4.37 ppm, largely predominates. On the other hand, chromatography of this crude product over alumina resulted in the practically complete disappearance of this isomer with formation of a new major oxazolidine derivative **10b** with a H-8a proton now shielded at 3.35 ppm ($J_{H\text{-}8a,\ H\text{-}8}$ = 8.4 Hz).[2] This chromatographic process thus gave access to a new intermediate **10b** and, in addition, allowed separation of oxazolidines **10a,b** from isomers **11**.

Scheme 2



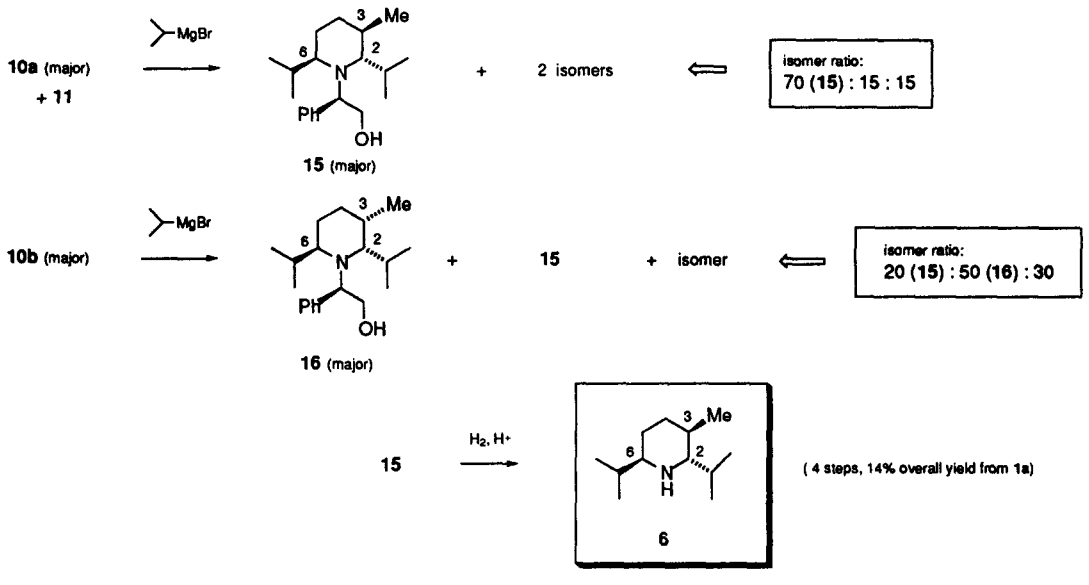
We attributed structures **10a** and **10b** to the primary (kinetic) product and the final (thermodynamic) product, respectively, on the basis of the following observations. The deshielding of the H-8a proton in derivative **10a** suggests an oxazolidine ring in which the H-8 proton is *trans* to phenyl group and *syn* to the nitrogen doublet (for related stereochemical assigments see discussion in reference 1a). The thermodynamic product **10b** presents H-8a characteristics which are in favour of an oxazolidine ring arranged as depicted in the

scheme (see also reference 1a for related structures). A particular feature of the structure **10b** is the strong shielding at 0.24 ppm of one of the two methyl groups of the isopropyl substituent, an effect very likely to be due to interactions with the phenyl ring. The absolute configuration of the methyl groups at position 8 was difficult to assign only on the basis of NMR spectroscopy, but could be unambiguously deduced from comparison with the compounds of a related series[1a] and from the results of X-ray analysis of further derivatives (*vide infra*).

$LiAlH_4$ reduction of oxazolidine **10b** ("thermodynamic product" containing a small amount of **10a**) gave, as expected, a mixture of two alcohols **12** and **13** whose proportions (19 : 81 respectively) were determined by GC analysis.[3] $LiAlH_4$ reduction of the "kinetic" mixture containing major oxazolidine **10a** gave again the two alcohols **12** and **13** and two new products **14a,b** (resulting from the reduction of isomers **11**) in a ratio **12** : **13** : **14** (2 isomers) = 79 : 1 : 20 (16 + 4), respectively. Thus, reduction of the "kinetic product" gave preferentially isomer **12** with an excellent selectivity at C-3 (> 96 % d.e.) while the "thermodynamic product" gave preferentially isomer **13** with modest selectivity at C-3 (61 % d.e.).

We next turned our attention to the syntheses of trisubstituted hindered piperidines depicted in Scheme 3. Thus, treatment of the above "kinetic" mixture (**10a** major) with isopropylmagnesium bromide in ether gave a mixture of three isomers in a 70 : 15 : 15 ratio. The structures of the two minor isomers were not established but the structure of the major piperidine **15**, isolated in 32 % yield after chromatography on silica gel, was established with certainty. Indeed, hydrogenolysis of the phenylethanol auxiliary gave piperidine **6** whose corresponding HCl salt furnished crystals suitable for X-ray analysis.

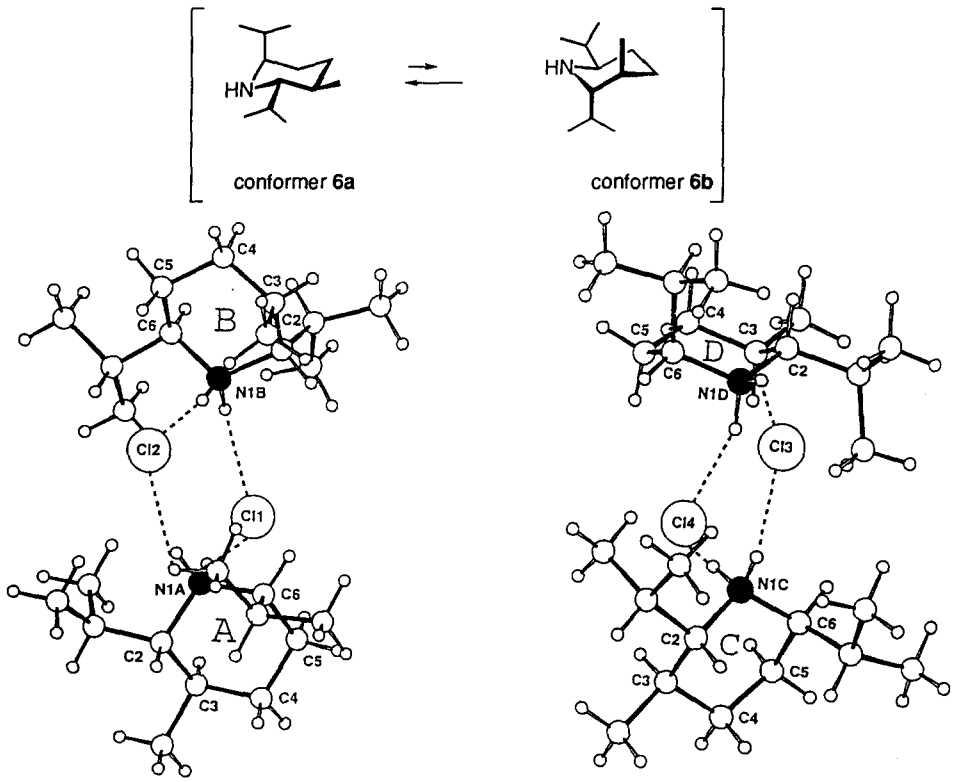
Scheme 3



The X-ray structure of piperidine **6**.HCl is depicted in Figure 1. The salt crystallized with four independent molecules (named A, B, C, D) in the asymmetric unit. The salient feature is the ability of the piperidine ring to adopt two different chair conformations with opposite torsion angles, resulting in two

conformers **6a** and **6b**. In conformer **6a**, exhibited by three molecules (A, C and D), the substituents at C2, C3 and C6 are respectively in equatorial, equatorial and axial positions while in conformer **6b**, adopted by the molecule B, these substituents are axial, axial and equatorial. Of course, these two conformations correspond to the same absolute configuration C2(*S*), C3(*R*), C6(*R*) . The energy difference between the two conformers, estimated by the molecular mechanics calculations (Macromodel, MM2, force field)[4,5] is 0.5 Kcal /mole. This value corresponds to a relative population of 70 % for **6a** and 30 % for **6b** at 293K, which correlates nicely with the observed crystal distribution of 75 : 25. In the crystal, these four molecules form two dimers. As seen in the Figure, each dimer results from the association of two molecules bridged by two chlorine ions by means of hydrogen bonds of type N^+-H···Cl^-, involving the nitrogen atoms and the chloride ions.

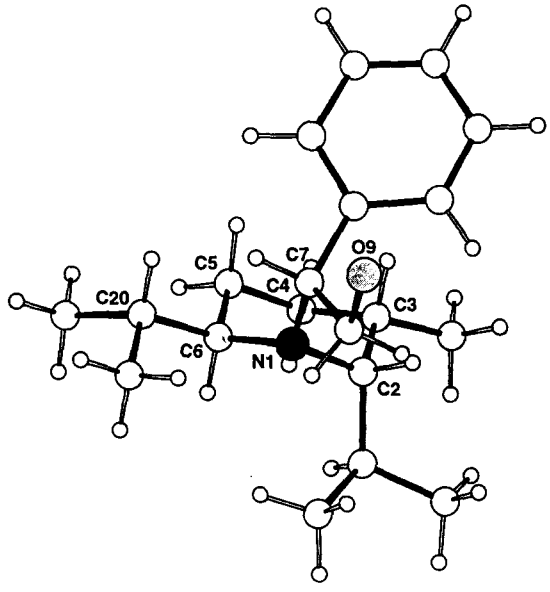
Figure 1



X-ray analysis of piperidine **6**.HCl. The two dimers are represented : molecules A and B (conformers **6a** and **6b**), Cl1 and Cl2 ions for one dimer ; molecules C and D (conformer **6a** only), Cl3 and Cl4 ions for the other. Geometric characteristics : $N1_A$···Cl1 = 3.108(6), Cl1···$N1_B$ = 3.206(6) Å, angle $N1_A$-Cl1-$N1_B$ = 95.2°, $N1_A$···Cl2 = 3.143(7), Cl2···$N1_B$ = 3.131(6) Å, angle $N1_A$-Cl2-$N1_B$ = 96.0° ; $N1_C$···Cl3 = 3.120(6), Cl3···$N1_D$ = 3.165(5) Å, angle $N1_C$-Cl3-$N1_D$ = 94.1°, $N1_C$···Cl4 = 3.134 (5), Cl4···$N1_D$ = 3.143(6) Å, angle $N1_C$-Cl4-$N1_D$ = 94.3°, distances Cl1···Cl2 = 4.205 (3), $N1_A$···$N1_B$ = 4.607(7), Cl3···Cl4 = 4.261(3), $N1_C$···$N1_D$ =4.663 (8) Å.

Treatment of **10b** ("thermodynamic" mixture) with isopropylmagnesium bromide in ether (Scheme 3) gave again a mixture of three isomers in a 50 : 30 : 20 ratio. The structure of the isomer representing 30 % of the mixture was not determined while the minor isomer was assigned the structure **15** by comparison with an authentic sample obtained from **10a**. The major isomer **16** could not be separated from **15** but crystallization gave a pure sample of this product whose structure was thus established by X-Ray analysis. The molecule is shown in Figure 2, with the absolute configuration deduced from the known C7(*R*) sterochemistry.The X-ray analysis showed that in both molecules of the asymmetric unit, the piperidine ring exhibits the same chair conformation with isopropyl substituents at C2 and C6, respectively, in axial and equatorial positions, and methyl group at C3, equatorial.

Figure 2



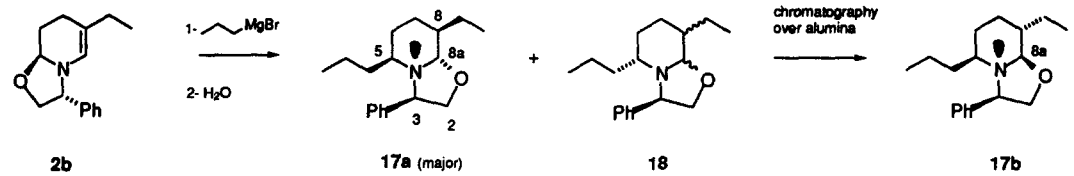
X-ray analysis of piperidine **16**.

These results in the isopropyl series not only illustrate the usefulness of our short enantioselective approach to chiral trisubstituted piperidines but, in addition, they complete our knowledge of the essential stereochemical features of the synthetic sequence depicted in Scheme 1 which is now secured by X-ray analyses.

With these informations in hands, we next fixed our attention to the syntheses of 5,8-disubstituted indolizidines in order to complete our previous work on the synthesis of indolizidine (–)-209B.[1c, 6] For this purpose, we targeted the enantioselective synthesis of indolizidine **7** as a model. Treatment of oxazolidine **2b** (Scheme 4) with *n*-propylmagnesium bromide gave oxazolidine derivatives **17,18** under the conditions very similar to those reported in the isopropyl series (cf Scheme 2), as shown in particular by ^{1}H NMR spectroscopy. The crude product of the reaction ("kinetic" mixture) contained oxazolidine **17a** as the major

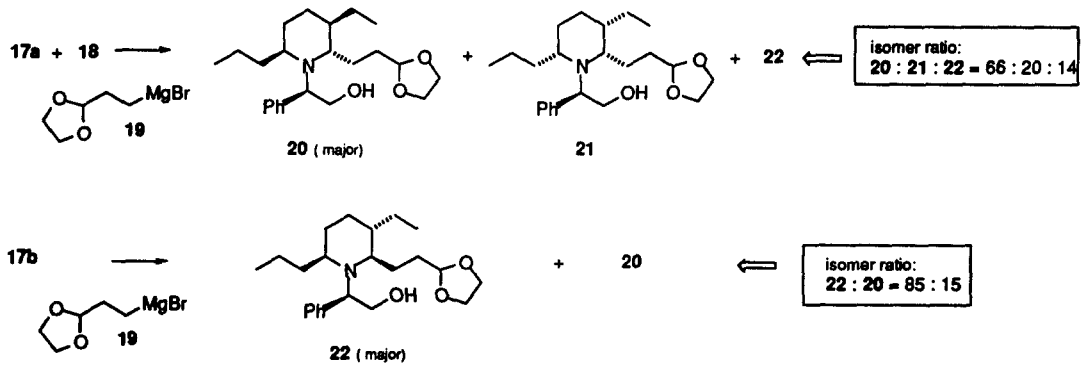
component (characteristic H-8a at 4.39 ppm, $J_{H\text{-}8a,\ H\text{-}8}$ = 5.5 Hz), and chromatography over alumina provided pure oxazolidine **17b** ("thermodynamic" product, characteristic H-8a at 3.44 ppm, $J_{H\text{-}8a,\ H\text{-}8}$ = 8.7 Hz). GC analysis of the alcohols obtained after $LiAlH_4$ reduction gave results very similar to those depicted in Scheme 2 for the isopropyl species, allowing an evaluation of the d. e. of the Grignard attack on **2b** which was 50 %. This d.e. has been raised to 70 % using the manganese complex *n*-propyl-Mn/ LiCl (prepared from the corresponding Grignard and $MnCl_4Li_2$) in THF without affecting the reaction yield.

Scheme 4



Treatment of the "kinetic" mixture (**17a** major, Scheme 5) with Grignard reagent **19**[7] gave predominantly the expected isomer **20**. This product was accompanied by isomers **21** and **22** in a ratio 66 : 20 : 14, respectively. In the same conditions, pure "thermodynamic" oxazolidine **17b** gave piperidine **22** as the major adduct along with isomer **20** in a 85 : 15 ratio. Noteworthy is the fact that the stereochemical outcome of the second Grignard addition is similar for oxazolidines **10a** and **17a**, giving piperidines **15** and **20** with the same arrangement of alkyl groups, and different in the case of oxazolidines **10b** and **17b**, giving the piperidine 2,6-*trans* **16** from **10b** and the piperidine 2,6-*cis* **22** from **17b**. It is very likely that the presence of a bulky isopropyl group at C-6 in oxazolidine **10a-b** hindered the otherwise favoured *cis* attack, but this difference can also be attributed to different reactivity of the Grignard reagents, a factor which can modify stereochemical interactions at the transition state.[8]

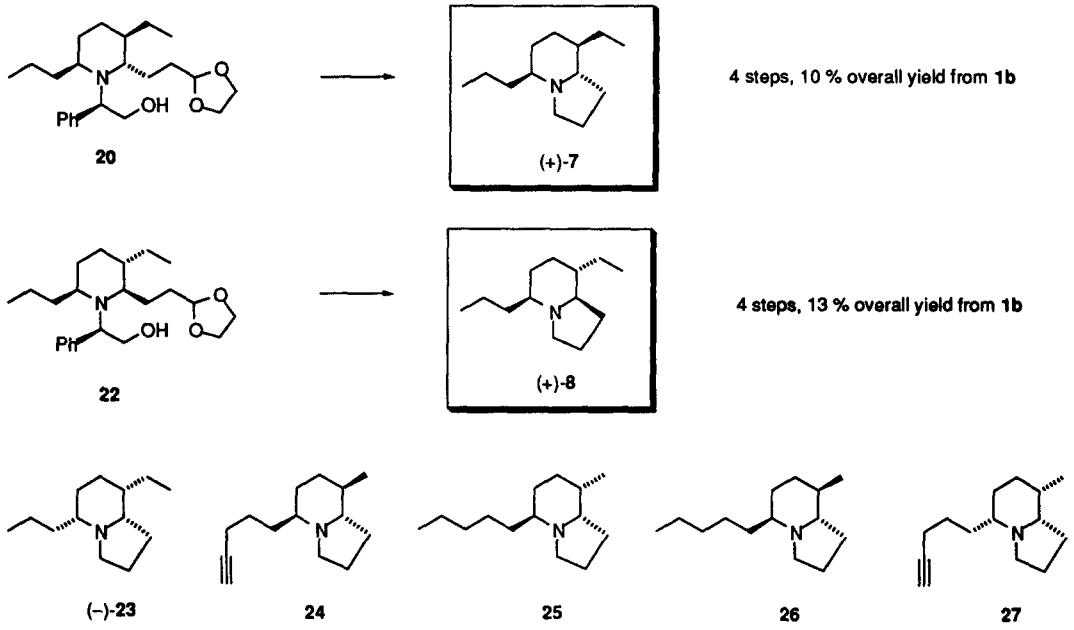
Scheme 5



The structures of products **20**, **21**, **22** were further confirmed after hydrogenolysis in acidic medium which gave in one step indolizidines (+)-**7**, (−)-**23** and (+)-**8** respectively.[9] The stereochemistry of indolizidine

(+)-**8** was easily elucidated by comparison of its NMR data and rotatory power with those of natural and synthetic indolizidine 209B.[1b, 6] The 5,8a-*trans* relationship of indolizidine (+)-**7** was evident from characteristic NMR data which are very different from those of *cis* derivatives. The configuration of the ethyl group at position 8 was further confirmed after comparison of ^{13}C NMR data with those of an analog **24**.[10] It is also in agreement with the predicted stereochemistry arising from the arrangement of the starting oxazolidine **17a**. These last assignments allowed us to revise the structure of an indolizidine 209B isomer which was originally formulated as **25** in our preliminary communication[1c] and must now be reassigned to **26** accordingly. Structure of indolizidine **23** was finally deduced from NMR data comparison with the analog **27**[10] and the sign of its rotatory power. This last compound possesses a clear *cis* relationship between the substituents at C-5 and C-8a and is a diastereoisomer (not an enantiomer) of indolizidine (+)-**8** as shown by GC analysis.

Scheme 6



In conclusion, we have shown that the present approach offers a practical access to 2,3,6-trialkylpiperidines and 5,8-dialkylindolizidines. The overall process in each case requires four steps and one chromatographic separation of diastereoisomers. In particular, this synthetic approach takes advantages of the selective manipulation of oxazolidine stereochemistry ("kinetic" or "thermodynamic") to orient the synthesis towards different diastereoisomers.

EXPERIMENTAL

Syntheses of substituted piperidines 6 and 12–15:

(3*R*, 5*R*, 8*R*, 8a*S*)-5-Isopropyl-8-methyl-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine (10a). To a stirred suspension of magnesium (820 g, 35 mmol, 5.3 equiv.) in dry Et_2O (5 ml) was added dropwise 2-bromopropane (1.98 g, 15.8 mmol, 2.5 equiv.) in dry Et_2O (15 ml) over a period of 0.5 h. After further stirring for 30 min at room temperature, oxazolidine **2a** (1.39 g, 6.46 mmol), in dry Et_2O (15 mL), was added dropwise at – 78°C over a period of 1 h. The reaction was stirred at 0°C for 1 h followed by another 3 h at room temperature. The excess reagent was eliminated with saturated aqueous NH_4Cl. The residue was extracted with Et_2O (3x50 ml) and the combined organic phases were dried ($MgSO_4$), filtered through celite, and concentrated. Oxazolidine **10a**, accompanied by a small amount of **10b** (less than 10 %) and **11** [undeterminated mixture of diastereoisomers, estimated ratio **10/11** : 80/20 (*vide infra*)], was obtained as a pale yellow oil (1.54 g, 5.94 mmol, 90 % yield). The crude mixture can be stored at - 20 °C without change in the isomer ratio, but in $CDCl_3$, a slow equilibration of **10a** in favour of **10b** was observed. Crude mixture: MS (EI) *m/z* [relative intensity (r.i.)] 259 ($M^{+\cdot}$, 3), 258 (6), 216 (100), 104 (45); MS (CI) (isobutane) *m/z* (r.i.)260 ($[M+H]^+$, 100), 216 (6); HRMS (EI): Calcd. for $C_{17}H_{25}NO$ ($M^{+\cdot}$) 259.1936, found 259.1932.; oxazolidine **10a:** ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.82 (d, *J*=6.7Hz, 3H, CH_3CHCH_3), 0.93 (d, *J*=6.7Hz, 3H, CH_3CHCH_3), 1.04 (d, *J*=6.7Hz, 3H, CH_3), 1.33 (m, 1H, H-7), 1.48-1.71 (m, 3H, 2xH-6, H-7), 1.86 (m, 1H, H-8), 1.88 (septuplet-doublet, *J*=7.2, 6.8Hz, 1H, CH_3CHCH_3), 2.34 (ddd, *J*=7.2, 7.0, 5.2Hz, 1H, H-5), 3.67 (dd, *J*=5.0, 4.8Hz, 1H, H-2), 4.28 (dd, *J*=5.2, 5.0Hz, 1H, H-2), 4.32 (dd, *J*=5.2, 4.8Hz, 1H, H-3), 4.37 (d, *J*=6.4Hz, 1H, H-8a), 7.24-7.42 (m, 5H, $5xH_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 17.8 (CH_3), 18.4 (CH_3CHCH_3), 18.8 (C-6), 20.5 (CH_3CHCH_3), 25.7 (C-7), 28.5 (CH_3CHCH_3), 31.0 (C-8), 60.0 (C-5), 63.6 (C-3), 72.1 (C-2), 94.4 (C-8a), 127.2 (C_{arom}), 127.6 ($2xC_{arom}$), 128.3 ($2xC_{arom}$), 141.8 (Cq).

(3*R*, 5*R*, 8*S*, 8a*R*)-(–)-5-Isopropyl-8-methyl-3-phenyl-hexahydro-oxazolo[3,2-a]pyridine (10b). The above mixture of crude oxazolidine **10a** (570 mg, 2.2 mmol) was chromatographied over neutral alumina (30g), using CH_2Cl_2–pentane as eluent, to give pure oxazolidine **10b** (273 mg, 1.05 mmol, 44 % yield) as colourless oil: $[\alpha]_D$ – 69 (*c* 2.2, $CHCl_3$); MS (EI) *m/z* (r.i.) 259 ($M^{+\cdot}$, 1), 216 (100), 104 (25); MS (CI) (isobutane) *m/z* (r.i.) 260 ($[M+H]^+$, 100), 216 (8); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.24 (d, *J*=6.7Hz, 3H, CH_3CHCH_3), 0.73 (d, *J*=6.7Hz, 3H, CH_3CHCH_3), 1.00 (m, 1H, H-7), 1.03 (d, *J*=6.1Hz, 3H, CH_3), 1.20-1.55 (m, 2H, 2xH-6), 1.65-1.92 (m, 3H, H-8, H-3, H-7), 2.23 (dt, *J*=10.5, 2.4Hz, 1H, H-5), 3.35 (d, *J*=8.4Hz, 1H, H-8a), 3.63 (m, 1H, H-3), 3.67 (m, 1H, H-2), 4.10 (t, *J*=8.0Hz, 1H, H-2), 7.13-7.42 (m, 5H, $5xH_{arom}$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 15.2 (CH_3CHCH_3), 17.2 (CH_3CHCH_3), 20.6 (CH_3), 24.1 (C-6), 28.9 (CH_3CHCH_3), 31.6 (C-7), 35.6 (C-8), 66.0 (C-3), 68.1 (C-5), 75.0 (C-2), 102.0 (C-8a), 126.8 (C_{arom}), 127.6 ($2xC_{arom}$), 128.1 ($2xC_{arom}$), 144.8 (Cq); HRMS (EI): Calcd. for $C_{17}H_{25}NO$ ($M^{+\cdot}$) 259.1936, found 259.1916.

(2*R*, 5*R*)-(–)-2-Isopropyl-5-methyl-1-[(1*R*)-1-phenyl-2-hydroxyethyl]piperidine (12). The crude mixture (1.54 g, 5.95 mmol), resulting from treatment of oxazolidine **2a** with isopropylmagnesium bromide and containing oxazolidine **10a** as the major component, was reduced with $LiAlH_4$ (340 mg, 8.9 mmol, 1.5 equiv.) in dry THF (100 mL) at reflux during 1 h. Usual work-up gave a mixture (1.48 g) of four diastereoisomers **12** : **13** : **14** (2 isomers) in a ratio of 77 : 1.3 : 21.7 (17.5 + 4.2) respectively, as determined by GC analysis (*t*-butyldimethylsilyl derivatives). Chromatography over alumina [120 g, gradient heptane–AcOEt from 100/0 to 90/10] allowed isolation of piperidine **12** (431 mg, 28 % yield) as a colourless oil: $[\alpha]_D$ –53 (*c* 1.3, $CHCl_3$); MS (EI) *m/z* (r.i.) 261 ($M^{+\cdot}$, 1.5), 260 (3), 230 (97), 218 (100), 98 (98); MS (CI) (isobutane) *m/z* (r.i.) 318 ($[M+C_4H_9]^+$, 24), 262 ($[M+H]^+$, 100), 244 (36); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.72 (d, *J*=6.0Hz, 3H, CH_3CHCH_3), 0.78 (d, *J*=6.0Hz, 3H, CH_3), 0.93 (d, *J*=6.0Hz, 3H, CH_3CHCH_3), 1.17 (m, *J*=11.5Hz, 1H, H-4), 1.38 (m, 2H, 2xH-3), 1.46 (m, 1H, H-4), 1.78 (m, 1H, H-5), 2.05 (m, 1H, CH_3CHCH_3), 2.08 (m, 1H, H-2), 2.54 (dd, *J*=14.4, 11.5Hz, 1H, H-6), 2.83 (m, *J*=14.4Hz, 1H, H-6), 3.72 (dd, *J*=10.7, 4.2Hz, 1H, CH_AH_BOH), 3.87 (dd, *J*=10.7, 5.4Hz, 1H, CH_AH_BOH), 4.03 (dd, *J*=5.4, 4.2Hz, 1H, $NCHCH_2OH$), 7.24-7.43 (m, 5H, $5xH_{arom}$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 19.8 (CH_3), 20.6 (CH_3CHCH_3), 20.8 (CH_3CHCH_3), 20.9 (C-3), 25.6 (C-5), 26.4 (CH_3CHCH_3), 29.0 (C-4), 51.3 (C-6), 59.3 (C-2), 63.7 (CH_2OH), 65.8 ($NCHCH_2OH$), 127.5 (C_{arom}), 128.4 ($2xC_{arom}$), 128.9 ($2xC_{arom}$), 141.9 (Cq); HRMS (CI): Calcd. for $C_{17}H_{28}NO$ (MH^+) 262.2171, found 262.2196. A small amount of isomers **14a** and **14b** were isolated for characterization. Piperidine **14a**: MS (EI) *m/z* (r.i.) 261 ($M^{+\cdot}$, 8), 260 (43), 230 (37), 218 (100), 98 (37); MS (CI) (isobutane) *m/z* (r.i.) 318 ($[M+C_4H_9]^+$, 18), 262 ($[M+H]^+$, 100), 244 (32); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.87 (d, *J*=6.8Hz, 3H, CH_3), 0.97 (d, *J*=6.7Hz, 3H, CH_3CHCH_3), 1.02 (d, *J*=6.7Hz, 3H, CH_3CHCH_3), 1.06-1.12 (m, 4H, 2xH-4, 2xH-3), 1.13 (m, 1H, H-5), 2.16 (dd, *J*=12.7, 3.4Hz, 1H, H-6), 2.32 (m, 1H, H-2), 2.40-2.60 (m, 2H, CH_3CHCH_3, H-6), 3.65 (dd, *J*=10.4, 5.2Hz, 1H, CH_AH_BOH), 3.93 (dd, *J*=10.4, 8.3Hz, 1H, CH_AH_BOH), 4.23 (dd, *J*=8.3, 5.2Hz, 1H, $NCHCH_2OH$), 7.15-7.40 (m, 5H, $5xH_{arom}$); ^{13}C (75 MHz, $CDCl_3$) δ (ppm) 17.8 (CH_3CHCH_3), 18.5 (CH_3CHCH_3), 20.4 (CH_3), 20.6 (C-3), 26.8 (2C, CH_3CHCH_3, C-5), 29.3 (C-4), 50.3 (C-6), 61.6 (CH_2OH), 62.7 ($NCHCH_2OH$), 62.9 (C-2), 127.7 (C_{arom}), 128.4 ($2xC_{arom}$), 128.9 ($2xC_{arom}$), 138,8 (Cq). Piperidine **14b**: MS (EI) *m/z* (r.i.) 261 ($M^{+\cdot}$, 1), 260 (6), 230 (24), 218 (100), 98 (34); MS (CI) (isobutane) *m/z* (r.i.) 318 ($[M+C_4H_9]^+$, 35), 262 ($[M+H]^+$, 100), 244 (30); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.79 (d, *J*=6.5Hz, 3H, CH_3), 0.96 (d, *J*=6.5Hz, 3H, CH_3CHCH_3), 0.98 (d, *J*=6.5Hz, 3H, CH_3CHCH_3), 1.21-1.26 (m, 2H, 2xH-3), 1.38 (t, *J*=10.9Hz, 1H, H-6), 1.56 (m, 1H, H-4), 1.65 (m, 1H, H-5), 2.13 (m, 1H, H-2), 2.63 (m, 1H, CH_3CHCH_3), 2.90 (m, *J*=10.9Hz, 1H, H-6), 3.57 (dd, *J*=10.4, 5.4Hz, 1H, CH_AH_BOH), 4.07 (t, *J*=5.4Hz, 1H, $NCHCH_2OH$), 4.43 (dd, *J*=10.4, 5.4Hz, 1H, CH_AH_BOH), 7.17 (dd, *J*=8.0, 2.0Hz, 2H, $2xH_{arom}$), 7.20-7.42 (m, 3H, $3xH_{arom}$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 14.7 (CH_3), 19.8 (CH_3CHCH_3), 20.4 (CH_3CHCH_3), 24.5 (C-3), 26.7 (C-5), 32.1 (CH_3CHCH_3), 33.4 (C-4), 53.6 (C-6), 58.8 (C-2), 59.5 (CH_2OH), 62.5 ($NCHCH_2OH$), 127.7 (C_{arom}), 128.3 ($2xC_{arom}$), 129.1 ($2xC_{arom}$), 135.1 (Cq).

(2*R*, 5*S*)-(+)-2-Isopropyl-5-methyl-1-[(1*R*)-1-phenyl-2-hydroxyethyl]piperidine (13). Pure oxazolidine **10b** (546 mg, 2.1 mmol) was treated with an excess of $LiAlH_4$ under the conditions used for the preparation of piperidine **12**. Work-up gave a mixture (528 mg) of two diastereoisomers **12** : **13** in a ratio 32 : 68 as determined by GC analysis (trimethylsilyl derivatives). Chromatography over alumina (see purification of

12 for conditions) gave pure piperidine **13** as an oil (235 mg, 0.9 mmol, 43 % yield): $[\alpha]_D$ + 45 (*c* 1.6, $CHCl_3$); MS (EI) *m/z* (r.i.) 261 ($M^{+\cdot}$, 3.5), 260 (3), 230 (65), 218 (100), 98 (10); MS (CI) (isobutane) *m/z* (r.i.) (318 ($[M+C_4H_9]^+$, 22), 262 ($[M+H]^+$, 100), 244 (30); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.72 (d, *J*=6.6Hz, 3H, CH_3), 0.84 (m, 1H, H-4), 0,89 (d, *J*=6.8Hz, 3H, CH_3CHCH_3), 0.91 (d, *J*=6.8Hz, 3H, CH_3CHCH_3), 1.27 (m, 1H, H-3), 1.34 (m, 1H, H-5), 1.59 (m, 1H, H-3), 1.73 (dt, *J*=12.5, 2.6Hz, 1H, H-4), 1.92 (t, *J*=11.0Hz, 1H, H-6), 2.32 (m, 1H, CH_3CHCH_3), 2.45 (dt, *J*=10.8, 2.6Hz, 1H, H-2), 2.72 (ddd, *J*=11.0, 3.6, 2.0Hz, 1H, H-6), 4.06-4.17 (m, 2H, CH_AH_BOH), 4.25 (t, *J*=6.5Hz, 1H, $NCHCH_2OH$), 7.23-7.28 (m, 1H, H_{arom}), 7.37 (t, *J*=7.5Hz, 2H, $2xH_{arom}$), 7.50 (d, *J*=7.5Hz, 2H, $2xH_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.4 (CH_3CHCH_3), 19.7 (CH_3), 20.6 (CH_3CHCH_3), 24.8 (C-3), 27.3 (CH_3CHCH_3), 31.8 (C-5), 33.9 (C-4), 56.4 (C-6), 59.5 (CH_2OH), 60.5 ($NCHCH_2OH$), 63.8 (C-2), 126.8 (C_{arom}), 128.4 ($4xC_{arom}$), 141.1 (Cq); HRMS (CI): Calcd. for $C_{17}H_{28}NO$ ($[M+H]^+$) 262.2171, found 262.2147.

(2*S*, 3*R*, 6*R*)-(+)-2,6-Diisopropyl-3-methyl-1-[(1*R*)-1-phenyl-2-hydroxyethyl]piperidine (15). The crude mixture resulting from the treatment of oxazolidine **2a** with an excess of isopropylmagnesium bromide (798 mg, 3.1 mmol,"kinetic" mixture containing major oxazolidine **10a**) was further treated with an excess of isopropylmagnesium bromide in Et_2O at 0°C, using the same procedure and workup, to give a mixture of three isomers (900 mg, ratio by GC analysis: 70 : 15 : 15). Chromatography over silica gel using a gradient of heptane-AcOEt afforded the major diastereoisomer **15** (372 mg, 32 % yield) which crystallized as colourless crystals in a mixture of CH_2Cl_2–pentane: mp 47°C; $[\alpha]_D$ + 12 (*c* 1.7, $CHCl_3$); MS (EI) *m/z* (r.i.) 272 (9), 260 (100), 140 (25); MS (CI) (isobutane) *m/z* (r.i.) 304 ($[M+H]^+$, 100), 286 (99); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.35 (m, 1H, H-4), 0.74 (d, *J*=6.3Hz, 3H, CH_3); 0.90 (d, *J*=6.5Hz, 3H, CH_3CHCH_3); 1.04 (m, 1H, H-4); 1.06 (d, *J*=6.5Hz, 3H, CH_3CHCH_3), 1.09 (m, 2H, 2xH-5), 1.13 (d, *J*=7.1Hz, 3H, CH_3CHCH_3), 1.17 (d, *J*=7.1Hz, 3H, CH_3CHCH_3), 1.46 (m, 1H, CH_3CHCH_3), 1.95 (m, 1H, H-3), 2.03 (m, *J*=9.5, 6.5Hz, 1H, CH_3CHCH_3), 2.49 (m, *J*=9.8, 6.5Hz, 1H, H-6), 2.56 (dd, *J*=9.8, 3.6Hz, 1H, H-2), 3.55 (dd, *J*=10.0, 6.0Hz, 1H, CH_AH_BOH), 3.86 (t, *J*=10.0Hz, 1H, CH_AH_BOH), 4.15 (dd, *J*=10.0, 6.0Hz, 1H, $NCHCH_2OH$), 7.22-7.41 (m, 5H, $5xH_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 20.5 (CH_3CHCH_3), 21.1 (2C, CH_3CHCH_3, CH_3CHCH_3), 21.4 (CH_3CHCH_3), 21.7 (CH_3), 24.4 (C-5), 28.9 (C-4), 29.3 (CH_3CHCH_3), 29.9 (C-3), 32.2 (CH_3CHCH_3), 59.5 (C-6), 60.8 ($NCHCH_2OH$), 62.9 (CH_2OH), 64.8 (C-2), 127.7 (C_{arom}), 128.4 ($2xC_{arom}$), 129,64 ($2xC_{arom}$), 142.1 (Cq); HRMS (CI): Calcd. for $C_{20}H_{34}NO$ ($[M+H]^+$) 304.2640, found 304.2630.

(2*S*, 3*R*, 6*R*)-(–)-2,6-Diisopropyl-3-methylpiperidine (6). Piperidine **15** (974 mg, 3.2 mmol) was dissolved in a mixture of EtOAc (30 mL), ethanol (30 mL) and aqueous 20 % HCl solution (15 mL). A catalytic amount of 10 % Pd/C was added and the mixture was stirred under an hydrogen atmosphere overnight. After filtration over celite, water (50 mL) was added and the resulting solution was washed twice with CH_2Cl_2 (2x50 ml). The aqueous phase was alkalinized with 30 % NH_4OH in water and then extracted with AcOEt (3x50 mL). The combined AcOEt phases were dried ($MgSO_4$), acidified with a HCl–MeOH solution, and evaporated. Flash chromatography of the residue on silica gel using CH_2Cl_2-10 % MeOH as eluent gave piperidine **6**.HCl (489 mg, 70 %). Colourless crystals, suitable for X-ray analysis were obtained from CH_2Cl_2- pentane: mp 205-210°C. Analytical data for the free base: $[\alpha]_D$ – 17 (*c* 1.7, $CHCl_3$); ; MS (EI) *m/z* (r.i.) 140 (100); MS (CI)

(isobutane) 184 ([M+H]$^+$, 100), 140 (11); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.86 (d, *J*=6.7Hz, 3H, C*H*$_3$CHCH$_3$, C*H*$_3$CHCH$_3$), 0.89 (d, *J*=6.7Hz, 3H, CH$_3$CHC*H*$_3$), 0.92 (d, *J*=6.7Hz, 3H, CH$_3$CHC*H*$_3$), 0.94 (d, *J*=6.8Hz, 3H, CH$_3$), 1.27 (m, 1H, H-4), 1.55 (m, 2H, 2xH-5), 1.58 (m, 1H, H-4), 1.60 (m, 1H, H-3), 1.82 (m, *J*=6.6, 2.0Hz, 1H, CH$_3$C*H*CH$_3$), 1.98 (m, *J*=6.7Hz, 1H, CH$_3$C*H*CH$_3$), 2.15 (t, *J*=6.0Hz, 1H, H-6), 2.37 (dd, *J*=8.7, 4.9Hz, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 16.6 (*C*H$_3$CHCH$_3$), 18.9 (CH$_3$), 19.4 (CH$_3$CH*C*H$_3$), 20.0 (C*H*$_3$CHCH$_3$), 20.7 (CH$_3$CHC*H*$_3$), 25.8 (C-5), 27.5 (CH$_3$C*H*CH$_3$), 28.3 (C-4), 28.7 (CH$_3$C*H*CH$_3$), 31.3 (C-3), 57.8 (C-2), 62.37 (C-6).

Crystal data of 6.HCl. A small colourless crystal (0.30 x 0.40 x 0.40 mm) grown of CH_2Cl_2- pentane was used.$C_{12}H_{26}N^+Cl^-$, M_W = 219.80, monoclinic, space group P 2_1, Z = 8 (four molecules in the asymmetric unit), a = 9.409 (3), b = 13.457 (2), c = 22.375 (7) Å, β = 96.65 (2)°, V = 2814 Å^3, d_c = 1.04 g cm^{-3}, F(000) = 976, λ (Cu Kα) = 1.5418 Å, μ = 2.16 mm^{-1} ; 4346 data measured (Nonius CAD-4 diffractometer), 4224 unique (R int = 0.073) of which 2883 were considered as observed with I ≥ 3.0 σ(I) ; absorption ignored.
The structure was solved by direct methods using *SHELXS86* [11a] and refined by full-matrix least-squares with *SHELX76* [11b] minimizing the function Σw (Fo-|Fcl)^{12}. The hydrogen atoms located in difference Fourier maps were fitted at theoretical positions (d C-H or N-H = 1.00 Å), and assigned an isotropic displacement parameter equivalent to that of the bonded atom, plus 10 %. Convergence was reached at R = 0.054 and R_w = 0.070 with $R_w = [\Sigma w(Fo-|Fcl)^2 / \Sigma wFo^2]^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.0028\ Fo^2]$. The absolute configuration has been confirmed by calculations with the inverse configuration giving R = 0.056 and Rw = 0.073.The residual electronic density was comprise between -0.23 and 0.38 e Å^{-3} in the final difference map. Lists of the fractional atomic coordinates, thermal parameters, distances, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material (CIF file).

(2*S*, 3*S*, 6*R*)-2,6-Diisopropyl-3-methyl-1-[(1*R*)-1-phenyl-2-hydroxyethyl]piperidine (16). Treatment of oxazolidine **10b** (650 mg, 2.5 mmol, "thermodynamic product" containing a small amount of **10a**) with an excess of isopropylmagnesium bromide under the above conditions, gave a mixture of three piperidines in a 20 (**15**) : 50 (**16**) : 30 ratio. Chromatography on silica gel gave an inseparable mixture of diastereoisomers **16** and **15** (285 mg, GC analysis **16** : **15** = 70 : 30). Crystallization from CH_2Cl_2-pentane gave a small amount of pure major piperidine **16** as colourless crystals suitable for X-ray analysis: [α]$_D$ + 11 (*c* 1.3, $CHCl_3$); MS (EI) *m/z* (r.i.) 272 (19), 260 (100), 140 (62); MS (CI) (isobutane) *m/z* (r.i.) 304 ([M+H]$^+$, 100), 286 (99); ^{1}H NMR (400 MHz, $CDCl_3$, at 53°C) δ (ppm) 0.38 (m, 1H, H-4), 0.55 (d, *J*=6.3Hz, 3H, C*H*$_3$CHCH$_3$), 0.97 (d, *J*=6.3Hz, 6H, CH$_3$CHC*H*$_3$, CH$_3$), 1,05 (m, 1H, H-4), 1,06 (d, *J*=6.5Hz, 3H, C*H*$_3$CHCH$_3$), 1,08 (d, *J*=6.5Hz, 3H, CH$_3$CHC*H*$_3$), 1.09 (m, 2H, 2xH-5), 1.39 (m, 1H, H-3), 1.99 (m, *J*=6.3, 3.0Hz, 1H, CH$_3$C*H*CH$_3$), 2.14 (m, *J*=6.5, 2.3Hz, 1H, CH$_3$C*H*CH$_3$), 2.58 (m, 1H, H-6), 2.65 (dd, *J*=8.9, 4.1Hz, 1H, H-2), 3.63 (dd, *J*=10.8, 6.9Hz, 1H, C*H*$_A$H$_B$OH), 3.94 (dd, *J*=10.8, 8.6Hz, 1H, CH$_A$*H*$_B$OH), 4.14 (dd, *J*=8.6, 6.9Hz, 1H, NC*H*CH$_2$OH), 7.20-7.38 (m, 5H, 5xH$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 20.4 (*C*H$_3$CHCH$_3$), 21.1(2C, CH$_3$CHC*H*$_3$, C*H*$_3$CHCH$_3$), 21.4 (CH$_3$CHC*H*$_3$), 21.7 (CH$_3$), 24.4 (C-5), 28.9 (C-4), 29.2 (CH$_3$C*H*CH$_3$), 29.9 (C-3), 32.1 (CH$_3$C*H*CH$_3$), 59.3 (C-6), 60.6 (N*C*HCH$_2$OH), 62.8 (*C*H$_2$OH), 64.7 (C-2), 127.6 (C$_{arom}$), 128.3 (2xC$_{arom}$), 129.6 (2xC$_{arom}$),142.1 (Cq).

Crystal data. A small colourless crystal (0.33 x 0.66 x 0.66 mm) grown of CH_2Cl_2-pentane was used.$C_{20}H_{33}NO$, M_W = 303.49, monoclinic, space group P 2_1, Z = 4 (two molecules in the asymmetric unit,

named A and B), a = 14.323 (8), b = 9.859 (6), c = 15.037 (8) Å, β = 113.86 (2) °, V = 1942 $Å^3$, d_c = 1.04 g cm^{-3}, F(000) = 672, λ (Mo Kα) = 0.7107 Å, μ = 0.05 mm^{-1} ; 3760 data measured (Philips PW1100 diffractometer), 3629 unique (R int = 0.140) of which 1723 were considered as observed with I ≥ 3.0 σ(I) ; absorption ignored.

The structure was solved by direct methods using *SHELXS86* [11a] and refined by full-matrix least-squares with *SHELX76* [11b] minimizing the function $\Sigma w (Fo-|Fc|)^2$. In both molecules of the asymmetric unit, most of atoms showed large anisotropic displacement parameters, particularly those of the methyl and isopropyl groups. In molecule B, the isopropyl group at C6 was found disordered with two positions of equal occupancy, deduced by rotation about the C6-C20 bond. So this group was refined isotropically only. Except that one of the hydroxyl group O9-H, not located, all the hydrogen atoms were calculated at theoretical positions (d C-H= 1.00 Å), and assigned an isotropic displacement parameter equivalent to that of the bonded atom, plus 10 %. Convergence was reached at R = 0.078 and R_w = 0.104 with $R_w = [\Sigma w(Fo-|Fc|)^2 / \Sigma wFo^2]^{1/2}$ and w = $1/[\sigma^2(Fo)+ 0.00557\ Fo^2]$. The residual electronic density was comprise between -0.23 and 0.25 e $Å^{-3}$ in the final difference map. Given the short O···O intermolecular distances, in the crystal the molecules are linked in infinite chains according to the scheme: $O9_B$-H (x,y,z-1) ···$O9_A$-H (x,y,z)···$O9_B$ (1-x,0.5+y,1-z) with the respective distances $O9_B$-H···$O9_A$ = 2.882 and $O9_A$-H···$O9_B$ = 2.850 Å. Lists of fractional atomic coordinates, displacement parameters, distances, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material (CIF file).

Syntheses of substituted indolizidines 7 and 8:

(3*R*, 5*S*, 8*R*, 8a*S*)-8-Ethyl-3-phenyl-5-propyl-hexahydrooxazolo[3,2a]pyridine (17a). To a stirred suspension of magnesium (1.5 g, 63 mmol, 5.3 equiv.) in dry Et_2O (10 ml) was added dropwise bromopropane (3.63 g, 29 mmol, 2.5 equiv.) in dry Et_2O (30 ml) over a period of 0.5 h. After further stirring for 30 min at room temperature, oxazolidine **2b** (2.71 g, 11.83 mmol), in dry Et_2O (30 mL), was added dropwise at - 78°C over a period of 1 h. The reaction was warmed to 0°C for 1 h and to room temperature for 3 h. The excess reagent was eliminated with saturated aqueous NH_4Cl. The residue was extracted with Et_2O (3x50 ml) and the combined organic phases were dried ($MgSO_4$), filtered through celite and concentrated. The crude clear yellow oil (2.94 g) so obtained consisted mainly of "kinetic" title adduct **17a**: MS (EI) *m/z* (r.i.) 273 ($M^{+\cdot}$, 5), 230 (100), 148 (25), 104 (34); MS (CI) (isobutane) *m/z* (r.i.) 330 ($[M+C_4H_9]^+$, 2), 318 (11), 274 ($[M+H]^+$, 100); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.79 (t, *J*=7.2Hz, 3H, $CH_2CH_2CH_3$), 0.94 (t, *J*=7.3Hz, 3H, CH_2CH_3), 1.28 (m, 2H, $CH_2CH_2CH_3$), 1.30 (m, 1H, H-7), 1.31-1.45 (m, 2H, $CH_AH_BCH_3$, H-6), 1.62 (m, 2H, $CH_2CH_2CH_3$), 1.65-1.70 (m, 4H, H-3, H-7, $CH_AH_BCH_3$, H-6), 2.64 (m, 1H, H-5), 3.64 (t, *J*=4.7Hz, 1H, H-2), 4.30-4.33 (m, 2H, H-2, H-3), 4.39 (d, *J*=5.5Hz, 1H, H-8a), 7.20-7.42 (m, 5H, $5xH_{arom}$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 11.7 (CH_2CH_3), 14.3 ($CH_2CH_2CH_3$), 19.4 ($CH_2CH_2CH_3$), 22.6 (CH_2CH_3), 24.1 (C-6), 24.8 ($CH_2CH_2CH_3$), 36.5 (C-7), 37.7 (C-8), 54.2 (C-5), 63.8 (C-3), 71.8 (C-2), 93.3 (C-8a), 127.2 (C_{arom}), 127.4 ($2xC_{arom}$), 128.4 ($2xC_{arom}$), 142.1 (Cq).

(3*R*, 5*S*, 8*S*, 8a*R*)-8-Ethyl-3-phenyl-5-propyl-hexahydrooxazolo[3,2a]pyridine (17b). The above crude "kinetic" mixture (1.55 g) was chromatographied over neutral alumina using CH_2Cl_2-pentane (5 : 95) as eluent. Oxazolidine **17b** (705 mg, 41 % from **2b**) was isolated as pale yellow oil; $[\alpha]_D$ – 6 (*c* 1.6, $CHCl_3$); MS (EI) *m/z* (r.i.) 273 ($M^{+\cdot}$, 5), 230 (100), 148 (25), 104 (34); MS (CI) (isobutane) *m/z* (r.i.) 330 ($[M+C_4H_9]^+$, 2), 318 (11), 274 ($[M+H]^+$, 100); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.50 (t, *J*=7.1Hz, 3H, $CH_2CH_2CH_3$), 0.88 (m, 1H, H-7), 0.90 (m, 1H, $CH_AH_BCH_2CH_3$), 0.97 (t, *J*=7.5Hz, 3H, CH_2CH_3), 1.10 (m, 2H, $CH_2CH_2CH_3$), 1.18 (m, 1H, $CH_AH_BCH_3$), 1.19 (m, 1H, H-7), 1.45 (m, 1H, H-6), 1.66 (m, 1H, H-8), 1.75 (m, 1H, $CH_AH_BCH_3$), 1.82 (m, 1H, H-6), 1.93 (m, 1H, $CH_AH_BCH_2CH_3$), 2.30 (m, 1H, H-5), 3.44 (d, *J*=8.7Hz, 1H, H-8a), 3.62 (t, *J*=7.6Hz, 1H, H-2), 3.70 (t, *J*=7.6Hz, 1H, H-3), 4.13 (t, *J*=7.6Hz, 1H, H-2), 7.15-7.45 (m, 5H, $5xH_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.1 (CH_2CH_3), 13.9 ($CH_2CH_2CH_3$), 18.7 ($CH_2CH_2CH_3$), 24.7 (CH_2CH_3), 28.4 ($CH_2CH_2CH_3$), 31.4 (C-6), 37.0 (C-7), 42.4 (C-8), 62.0 (C-5), 65.9 (C-3), 74.8 (C-2), 100.4 (C-8a), 126.9 (C_{arom}), 127.2 ($2xC_{arom}$), 128.3 ($2xC_{arom}$), 145.1 (Cq); HRMS (EI): Calcd. for $C_{18}H_{27}NO$ ($M^{+\cdot}$) 273.2084, found 273.2088.

(2*S*, 3*R*, 6*S*)-(–)-2-[2-(1,3)-Dioxolan-2-yl-ethyl]-3-ethyl-1-[(1*R*)-1-phenyl-2-hydroxyethyl] -6-propylpiperidine (20). To a stirred suspension of magnesium turnings (200 mg, 8.24 mmol, 1.5 equiv.) in dry THF (1 ml) was added dropwise 2-(2-bromoethyl)-1,3-dioxolane (995 mg, 5.49 mmol) in THF (15 ml). The reaction was initiated by adding a few drops of 1,2-dibromoethane. The mixture was maintained below 40°C by periodic cooling with ice. After complete addition and further stirring for 15 min at room temperature, the resulting solution of Grignard reagent **19** was ready for use. To this solution was then added dropwise at ambient temperature, during 0.5 h, the crude mixture resulting from the treatment of oxazolidine **2b** with an excess of *n*-propylmagnesium bromide (591 mg, 2.16 mmol,"kinetic" mixture containing major oxazolidine **17a**) in THF (10 mL). The resulting mixture was further stirred for 3 h. The excess reagent was eliminated with saturated aqueous NH_4Cl. The residue was extracted with Et_2O (3x50 ml) and the combined organic phases were dried ($MgSO_4$), filtered through celite and concentrated to give an oil consisting of a mixture of piperidines **20**, **21**, **22** in a 66 : 20 : 14 ratio (GC analysis). Chromatography over silica gel (40 g),using a gradient of AcOEt-heptane, gave pure isomer **20** as an oil (195 mg, 0.52 mmol, 24 % yield): $[\alpha]_D$ – 21 (*c* 1.7, $CHCl_3$); MS (EI) *m/z* (r.i.) 344 (98), 332 (100), 274 (55); MS (CI) (isobutane) *m/z* (r.i.) 422 ($[M+C_4H_9]^+$, 25), 376 ($[M+H]^+$, 100), 358 (31), 256 (48), 254 (16); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.67 (t, *J*=7.3Hz, 3H, CH_2CH_3), 0.93 (t, *J*=7.1Hz, 3H, $CH_2CH_2CH_3$), 0.94 (m, 1H, H-5), 0.95 (m, 1H, $CH_AH_BCH_3$), 1.07 (m, 1H, H-3), 1.09 (m, 2H, 2xH-4), 1.24 (m, 1H, H-5), 1.28 (m, 1H, $CH_AH_BCH_3$), 1.31 (m, 2H, $CH_2CH_2CH_3$), 1.38 (m, 1H, $CH_AH_BCH_2CH_3$), 1.65 (m, 1H, $CH_2CHHCHO_2$), 1.68 (m, 1H, $CH_AH_BCH_2CH_3$), 1.70 (m, 1H, $CH_AH_BCH_2CHO_2$), 1.85 (m, 1H, $CH_AH_BCH_2CHO_2$), 1.90 (m, 1H, $CH_2CHHCHO_2$), 2.72 (m, 1H, H-2), 3.10 (m, 1H, H-6), 3.62 (dd, *J*=10.0, 6.2Hz, 1H, CH_AH_BOH), 3.85 (m, 1H, OCH_2CH_2O), 3.89 (m, 1H, CH_AH_BOH), 3.97 (m, 1H, OCH_2CH_2O), 4.17 (dd, *J*=10.0, 6.2Hz, 1H, $NCHCH_2OH$), 4.92 (t, *J*=4.2Hz, 1H, $CH_2CH_2CHO_2$), 7.18-7.36 (m, 5H, $5xH_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 10.8 (CH_2CH_3), 14.3 ($CH_2CH_2CH_3$), 20.0 ($CH_2CH_2CH_3$), 24.1 ($CH_2CH_2CHO_2$), 24.8 (C-5), 25.5 (CH_2CH_3), 26.2 (C-4), 31.0 ($CH_2CH_2CHO_2$), 35.6 ($CH_2CH_2CH_3$), 38.2 (C-3), 51.0 (C-6), 57.9 (C-2), 59.5 ($NCHCH_2OH$), 61.1 (CH_2OH), 64.7 (2C, OCH_2CH_2O), 104.5 ($CH_2CH_2CHO_2$), 127.2 (C_{arom}), 128.1 ($2xC_{arom}$), 129.2 ($2xC_{arom}$), 141.3 (C_q); HRMS (CI): Calcd. for $C_{28}H_{38}NO_3$ ($[M+H]^+$) 276.2851, found 279.2822. Pure piperidine **21** (45 mg) was also isolated as an oil: $[\alpha]_D$ – 22 (*c*

1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.63 (m, 1H, H-4), 0.68 (t, *J*=6.0Hz, 3H, $CH_3CH_2CH_2$), 0.81 (t, *J*=7.3Hz, 3H, CH_2CH_3), 1.10 (m, 1H, H-4), 1.20 (m, 1H, $CH_AH_BCH_3$), 1.24 (m, 1H, H-5), 1.29 (m, 2H, $CH_2CH_2CH_3$), 1.40 (m, 1H, H-3), 1.48 (m, 1H, $CH_AH_BCH_2CHO_2$), 1.54 (m, 1H, H-2), 1.58 (m, 2H, $CH_2CH_2CH_3$), 1.61 (m, 1H, $CH_AH_BCH_2CHO_2$), 1.63 (m, 1H, $CH_AH_BCH_3$), 1.70 (m, 1H, H-5), 1.74 (m, 1H, $CH_2CHHCHO_2$), 2.56 (m, 1H, H-6), 2.80 (m, *J*=10.0Hz, 1H, H-2), 3.77 (m, 2H, CH_2OH), 3.88 (m, 2H, OCH_2CH_2O), 3.96 (m, 1H, NCHCH2OH), 4.88 (t, *J*=4.5Hz, 1H, $CH_2CH_2CHO_2$), 7.18-7.40 (m, 5H, $5xH_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 12.7 (CH_3CH_2), 14.3 ($CH_3CH_2CH_2$), 19.4 (C-5), 21.2 (C-4), 23.1 (CH_2CH_3), 25.9 ($CH_2CH_2CH_3$), 26.1 ($CH_2CH_2CHO_2$), 32.2 ($CH_2CH_2CH_3$), 32.8 (CH_2CH_2CHO), 37.8 (C-3), 53.8 (C-6), 57.7 (C-2), 63.9 (CH_2OH), 65.0 (3C, OCH_2CH_2O, NCHCH2OH), 104.7 ($CH_2CH_2CHO_2$), 127.5 (C_{arom}), 128.5 ($2xC_{arom}$), 128.6 ($2xC_{arom}$), 141.9 (C_q).

(1*R*, 2*R*, 3*S*, 6*S*)-(–)-2-[2-[1,3]Dioxolan-2-yl-ethyl]-3-ethyl-1-(1-phenyl-2-hydroxyethyl)-6-propylpiperidine (22). Treatment of oxazolidine **17b** (500 mg, 1.83 mmol) with an excess of Grignard reagent **19**, using the conditions used for the preparation of piperidine **20**, gave a mixture of two products **20** and **22** in a ratio of 15 : 85 (GC analysis). The major product **22** was isolated as an oil (422 mg, 1.13 mmol, 62 % yield) after chromatography over silica gel using a gradient of AcOEt-heptane: $[\alpha]_D$ – 56 (*c* 1.6, $CHCl_3$); MS (EI) *m/z* (r.i.) 344 (90), 332 (100), 274 (64); MS (CI) (isobutane) *m/z* (r.i.) 376 ($[M+H]^+$, 100), 358 (18), 256 (54), 254 (8); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.72 (t, *J*=7.4Hz, 3H, CH_2CH_3), 0.95 (t, *J*=7.1Hz, 3H, $CH_2CH_2CH_3$), 0.98 (m, 1H, $CH_AH_BCH_2CHO_2$), 1.02 (m, 1H, H-4), 1.17 (m, 1H, H-5), 1.20 (m, 1H, $CH_AH_BCH_2CHO_2$), 1.30 (m, 3H, $CH_2CH_2CHO_2$, H-3), 1.35 (m, 1H, H-4), 1.40 (m, 2H, $CH_AH_BCH_2CH_3$, $CH_AH_BCH_3$), 1.70 (m, 2H, $CH_AH_BCH_2CH_3$, $CH_AH_BCH_3$), 1.71 (m, 2H, $CH_2CH_2CH_3$), 1.73 (m, 1H, H-5), 2.27 (m, *J*=9.7Hz, 1H, H-2), 2.97 (m, *J*=8.9Hz, 1H, H-6), 3.70-3.97 (m, 7H, CH_2OH, OCH_2CH_20, NCHCH2OH), 4.61 (t, *J*=4.8Hz, 1H, $CH_2CH_2CHO_2$), 7.22-7.40 (m, 5H, $5xH_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 12.2 (CH_2CH_3), 14.4 ($CH_2CH_2CH_3$), 19.5 (C-5), 21.4 (C-4), 22.9 (CH_2CH_3), 24.9 (2C, $CH_2CH_2CH_3$, $CH_2CH_2CHO_2$), 32.2 (2C, $CH_2CH_2CH_3$, $CH_2CH_2CHO_2$), 37.5 (C-3), 53.5 (C-6), 56.7 (C-2), 63.6 (CH_2OH), 64.6 (2C, OCH_2CH_2O), 64.6 (NCHCH2OH), 104.4 ($CH_2CH_2CHO_2$), 127.3 (C_{arom}), 128.2 ($2xC_{arom}$), 128.7 ($2xC_{arom}$), 141.4 (Cq); HRMS (CI): Calcd. for $C_{23}H_{38}NO_3$ ($[M+H]^+$) 276.2852, found 279.2868.

(5*S*, 8*R*, 8a*S*)-(–)-8-Ethyl-5-propyl-octahydroindolizidine (7). Piperidine **20** (280 mg, 0.75 mmol) was dissolved in a mixture of EtOAc (20 ml), ethanol (20 ml) and a aqueous 20 % HCl solution (10 ml). A catalytic amount of 10 % Pd/C was added and the mixture was stirred under hydrogen atmosphere for 3 days. The aqueous phase was alkalinized with 30 % NH_4OH in water and then extracted with AcOEt (3x50 mL). The combined AcOEt phases were dried ($MgSO_4$), acidified with a HCl-MeOH solution, and evaporated. Flash chromatography of the residue on silica gel using CH_2Cl_2-8 % MeOH as eluent gave indolizidine **7**.HCl (117 mg, 0.5 mmol, 67 % yield). Analytical data for the free base: $[\alpha]_D$ – 18 (*c* 0.8, $CHCl_3$); MS (EI) *m/z* (r.i.) 195 ($M^{+\cdot}$, 10), 152 (100); MS (CI) (isobutane) *m/z* (r.i.) 196 ($[M+H]^+$, 100); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.88 (t, *J*=7.0Hz, 3H, CH_2CH_3), 0.93 (t, *J*=7.0Hz, 3H, $CH_2CH_2CH_3$), 1.05 (m, 1H, $CH_AH_BCH_3$), 1.08 (m, 1H, H-6), 1.10 (m, 1H, H-8), 1.30 (m, 1H, $CH_AH_BCH_2CH_3$), 1.36 (m, 2H, $CH_2CH_2CH_3$), 1.40 (m, 1H, H-1), 1.45 (m, 1H, $CH_AH_BCH_2CH_3$), 1.50 (m, 1H, $CH_AH_BCH_3$), 1.60 (m, 1H, H-2), 1.65 (m,

1H, H-6), 1.73 (m, 2H, 2xH-7), 1.80 (m, H, H-2), 1.92 (m, 1H, H-1), 2.18 (m, 1H, H-8a), 2.68 (q, *J*=8.8Hz, 1H, H-3), 2.87 (dt, *J*=8.8, 3.2Hz, 1H, H-3), 3.03 (m, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.2 ($CH_2\mathit{C}H_3$), 14.5 ($CH_2CH_2\mathit{C}H_3$), 20.7 (C-2), 20.9 ($CH_2\mathit{C}H_2CH_3$), 24.2 (C-6), 24.8 ($\mathit{C}H_2CH_2CH_3$), 26.1 ($\mathit{C}H_2CH_3$), 27.6 (C-7), 29.5 (C-1), 43.6 (C-8), 49.0 (C-3), 55.3 (C-5), 60.6 (C-8a); HRMS (EI): Calcd. for $C_{13}H_{25}N$ ($M^{+\cdot}$) 195.1987, found 195.2001.

(5*S*, 8*S*, 8a*R*)-(+)-8-Ethyl-5-propyl-octahydroindolizidine (8). Piperidine **22** (371 mg, 1.9 mmol) was hydrogenated under the conditions used for the preparation of indolizidine **7** to give pure indolizidine **8**, HCl (312 mg, 73 % yield) as colourless needles. Analytical data for the free base: $[\alpha]_D$ + 99 (*c* 1.7, $CHCl_3$); MS (EI) *m/z* (r.i.) 195 ($M^{+\cdot}$, 5), 152 (100); MS (CI) *m/z* (r.i.) 196 ($[M+H]^+$, 100); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.90 (t, *J*=7.3Hz, 3H, $CH_2C\mathit{H}_3$), 0.93 (t, *J*=7.0Hz, 3H, $CH_2CH_2C\mathit{H}_3$), 0.96 (m, 1H, H-1), 1.10 (m, 1H, H-7), 1.26 (m, 1H, $CH_3C\mathit{H}HCH_2$), 1.30 (m, 1H, $C\mathit{H}_AH_BCH_2CH_3$), 1.32 (m, 1H, H-8), 1.40 (m, 1H, H-6), 1.45 (m, 1H, $CH_2CH\mathit{H}CH_3$), 1.49 (m, 1H, H-7), 1.58 (m, 1H, $C\mathit{H}_AH_BCH_3$), 1.70 (m, 1H, H-6), 1.80 (m, 2H, 2xH-2), 1.88 (m, 1H, $CH_A\mathit{H}_BCH_2CH_3$), 1.90 (m, 1H, H-1), 1.91 (m, 1H, H-8a), 2.02 (m, 1H, $CH_A\mathit{H}_BCH_3$), 2.17 (m, 1H, H-5), 2.23 (q, *J*=9.3Hz, 1H, H-3), 3.40 (dt, *J*=9.3, 3.5Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 10.8 ($CH_2\mathit{C}H_3$), 14.2 ($CH_2CH_2\mathit{C}H_3$), 18.8 ($CH_2\mathit{C}H_2CH_3$), 20.1 (C-2), 25.7 (C-7), 28.6 ($\mathit{C}H_2CH_2CH_3$), 29.3 (C-1), 30.4 ($\mathit{C}H_2CH_3$), 36.1 (C-6), 42.3 (C-8), 51.7 (C-3), 63.6 (C-5), 70,4 (C-8a); Anal. Calcd. for $C_{13}H_{26}ClN$: C, 67.29; H, 11.30; N, 6.04; Cl, 15.37; found: C, 67.33; H, 11.01; N, 5.87; Cl, 15.01.

(5*R*, 8*S*, 8a*S*)-(−)-8-Ethyl-5-propyl-octahydroindolizidine (23). Piperidine **21** (40 mg, 0.1 mmol) was hydrogenated under the conditions used for the preparation of indolizidine **7** to give pure indolizidine **23**.HCl (13.5 mg, 54 %, colourless oil) as colourless needles. Analytical data for the free base: $[\alpha]_D$ − 86 (*c* 1.2, $CHCl_3$); MS (EI) *m/z* (r.i.) 195 ($M^{+\cdot}$, 7), 152 (100); MS (CI) (isobutane) *m/z* (r.i.) 196 ($[M+H]^+$, 100); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.87 (m, 1H, H-1), 0.88 (t, *J*=7.3Hz, 3H, $CH_2C\mathit{H}_3$), 0.92 (t, *J*=7.0Hz, 3H, $CH_2CH_2C\mathit{H}_3$), 1.05 (m, 1H, H-7), 1.17 (m, 1H, H-8), 1.21 (m, 1H, $CH_2C\mathit{H}HCH_3$), 1.22 (m, 1H, $C\mathit{H}_AH_BCH_2CH_3$), 1.33 (m, 1H, H-6), 1.43 (m, 1H, $CH_2CH\mathit{H}CH_3$), 1.47 (m, 1H, $C\mathit{H}_AH_BCH_3$), 1.48 (m, 1H, H-7), 1.61 (m, 1H, H-8a), 1.62 (m, 1H, H-2), 1.64 (m, 1H, H-6), 1.78 (m, 1H, H-2), 1.80 (m, 1H, $CH_A\mathit{H}_BCH_2CH_3$), 1.88 (m, 2H, H-1, H-5), 1.93 (m, 1H, $CH_A\mathit{H}_BCH_3$), 1.98 (m, 1H, H-3), 3.27 (dt, *J*=8.7, 2.2Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.2 ($CH_2\mathit{C}H_3$), 14.6 ($CH_2CH_2\mathit{C}H_3$), 19.2 ($CH_2\mathit{C}H_2CH_3$), 20.6 (C-2), 26.1 (C-7), 29.3 ($\mathit{C}H_2CH_3$), 20.0 (C-1), 31.3 ($\mathit{C}H_2CH_2CH_3$), 37.1 (C-6), 43.2 (C-8), 52.0 (C-3), 63.6 (C-5), 70.1 (C-8a); HRMS (EI): Calcd. for $C_{13}H_{25}N$ ($M^{+\cdot}$) 195.1987, found 195.1993.

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References and Notes

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2. Monitoring the reaction by ^{1}H-NMR in $CDCl_3$ also allowed us to observe the formation of a transient third intermediate characterized by a H-8a proton appearing as a doublet ($J_{H\text{-}8a,\ H\text{-}8}$ = 2.6 Hz) at 3.82 ppm. Accordingly, a *5R, 8S, 8aS* configuration can be proposed for this unstable intermediate.

3. GC analyses were performed on a capillary column after derivatization of the alcoholic functions as *t*-butyldimethylsilyl groups.

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9. In our hands these indolizidine derivatives were found to be sensitive to aerial degradation. We believe this instability to be due to formation of carbonate salts by atmospheric CO_2, and thus preferred to purify these compounds as HCl salts (see experimental).

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