Pergamon

Tetrahedron Vol. 51, No. 27, pp. 7527-7546, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00376-2

Synthetic Studies on Indole Alkaloids VIII.[1] Synthesis and Reactivity of Asymmetric 2-Indolyl-4-methylenepiperidines

David Miguel,[a] Anna Diez,[a] Yves Blache,[a] Javier Luque,[b] Modesto Orozco,[c] Roland Remuson,[d] Yvonne Gelas-Mialhe,[d] Mario Rubiralta[a]*

a. Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona. 08028 Barcelona, Spain

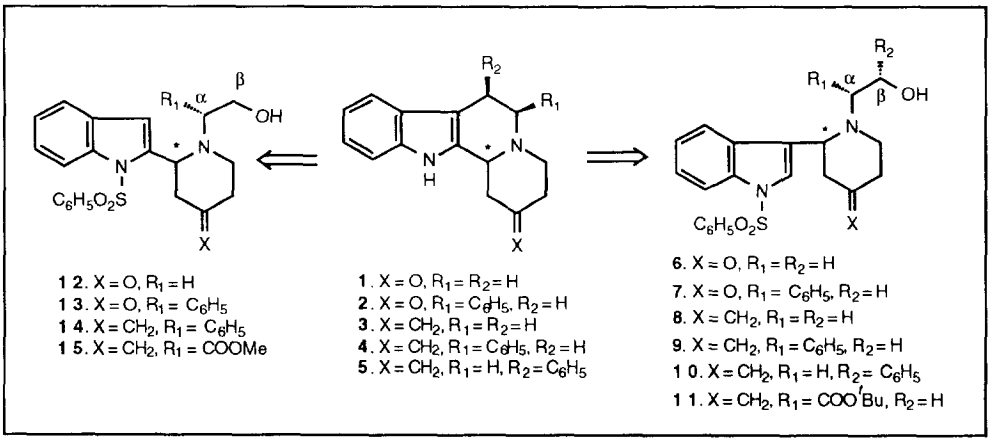
b. Laboratory of Physical Chemistry, Faculty of Pharmacy, University of Barcelona. 08028-Barcelona, Spain

c. Department of Biochemistry and Physiology, Faculty of Chemistry, University of Barcelona. 08028-Barcelona, Spain

d. Laboratoire de Chimie des Substances Naturelles, (URA 485), Université Blaise Pascal. 63177 Aubière Cedex, France

Abstract: The synthesis of asymmetric 2-indolyl-4-methylenepiperidines **8-11** and **14-15** by condensation of an aminoallylsilane with an indole carbaldehyde, followed by intramolecular cyclization of the intermediate, is described. The reactivity of *N*-(2-hydroxyethyl)indolylpiperidines **9** and **14** with K^{t}BuO to give indolo[2,3-*a*]quinolizidines is studied. Some unexpected results are obtained due to the influence of the α-phenyl ring.

In the context of our studies on the synthesis of indolo[2,3-*a*]quinolizidine systems, such as **1**, by means of intramolecular cyclization of *N*-(2-hydroxyethyl)-2-(1-phenylsulfonyl-3-indolyl)piperidine **6** with "K^{t}BuO/BF_3.Et_2O",[2] we described recently the preparation of racemic 2-methyleneindolo[2,3-*a*]quinolizidine **3**.[3] The starting 2-indolyl-4-methylenepiperidine **8** had been prepared by condensation of 1-



12. X = O, R_1 = H
13. X = O, R_1 = C_6H_5
14. X = CH_2, R_1 = C_6H_5
15. X = CH_2, R_1 = COOMe

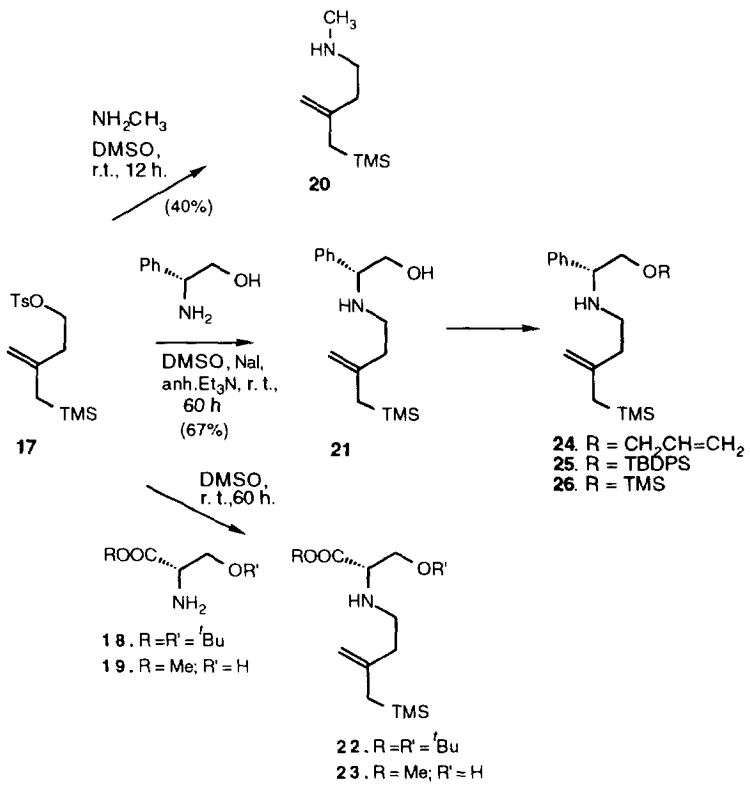
1. X = O, R_1 = R_2 = H
2. X = O, R_1 = C_6H_5, R_2 = H
3. X = CH_2, R_1 = R_2 = H
4. X = CH_2, R_1 = C_6H_5, R_2 = H
5. X = CH_2, R_1 = H, R_2 = C_6H_5

6. X = O, R_1 = R_2 = H
7. X = O, R_1 = C_6H_5, R_2 = H
8. X = CH_2, R_1 = R_2 = H
9. X = CH_2, R_1 = C_6H_5, R_2 = H
10. X = CH_2, R_1 = H, R_2 = C_6H_5
11. X = CH_2, R_1 = COO^{t}Bu, R_2 = H

Scheme 1

(phenylsulfonyl)indole-3-carbaldehyde with 3-trimethylsilylmethyl-3-butenylamine, followed by acid-catalyzed intramolecular cyclization of the intermediate iminoallylsilane.[4] In addition, we have reported the synthesis of chiral 2-aryl-4-piperidones, potential key intermediates in the synthesis of chiral indolo[2,3-*a*]quinolizidin-2-ones **2**, by reaction of an appropriate 2-aryl-1,1-dimethyl-4-oxopiperidinium iodide and (*R*)-(-)-phenylglycinol.[5]

On the basis of these precedents we planned to prepare asymmetric 2-methyleneindolo[2,3-*a*]quinolizidine **4** by applying the K^{t}BuO reaction on chiral 2-indolyl-4-methylenepiperidine **9**. This piperidine should be directly obtainable by condensation of chiral aminoallylsilane **21** with an indole-3-carbaldehyde, with spontaneous intramolecular cyclization of the intermediate iminium salt. We first checked the value of the aminoallylsilane reaction with amine **20**. We then chose to use (*R*)-(-)-phenylglycinol as the asymmetric starting primary amine, because of its suitable functionalization for our final purposes and its well known chiral induction on C-2 of piperidine derivatives.[6] The use of protected (*S*)-(-)-serines as other chiral hydroxyethyl derivatives was also anticipated.

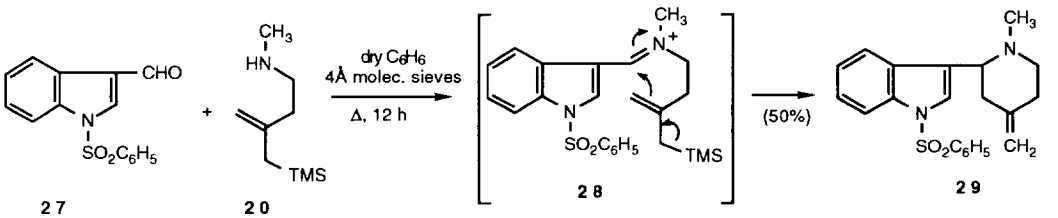


Scheme 2

Thus, aminoallylsilanes **20-23** were prepared by reaction of tosylate **17**[4] with methylamine, (*R*)-(-)-phenylglycinol, and protected (*S*)-(-)-serines **18** and **19** (see Scheme 2).[7] Aminoalcohol **21** was then protected as an allyl ether (**24**), and as silyl ethers (**25** and **26**). As expected, all compounds **20-26** showed

the same general spectroscopic features with regard to the aminoallylsilane moiety (see experimental part).

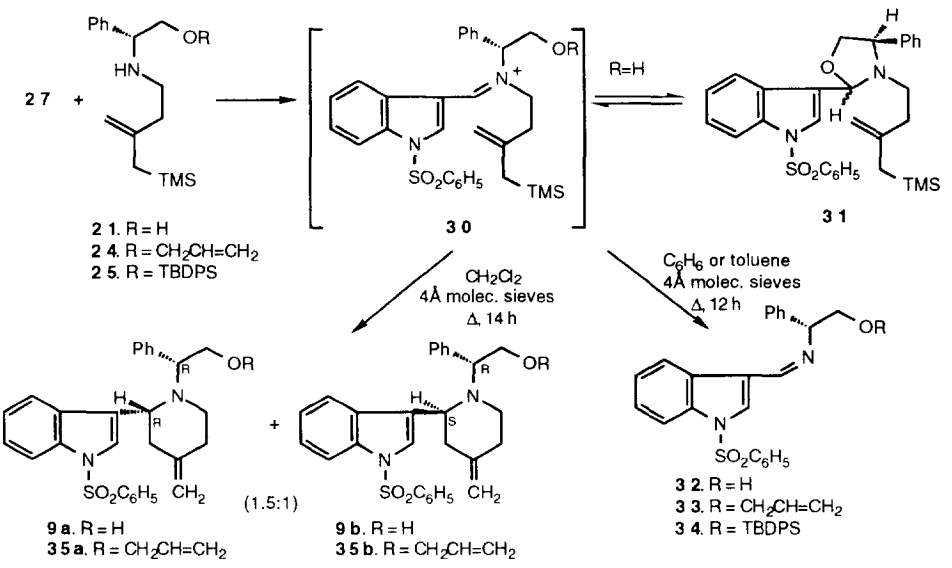
Condensation of 1-(phenylsulfonyl)indole-3-carbaldehyde **27** with aminoallylsilane **20** in dry refluxing C_6H_6 in the presence of 4Å molecular sieves yielded the corresponding 2-indolyl-4-methylenepiperidine **29** in 50% yield (Scheme 3). This transformation occurs by an intramolecular Mannich-type cyclization on the intermediate allylsilane-iminium salt **28**. The ^1H NMR spectrum of piperidine **29** shows a characteristic C-2 axial proton at δ 3.20 as a double doublet, and two broad singlets at δ 4.70 and 4.75 corresponding to the olefinic protons.



Scheme 3

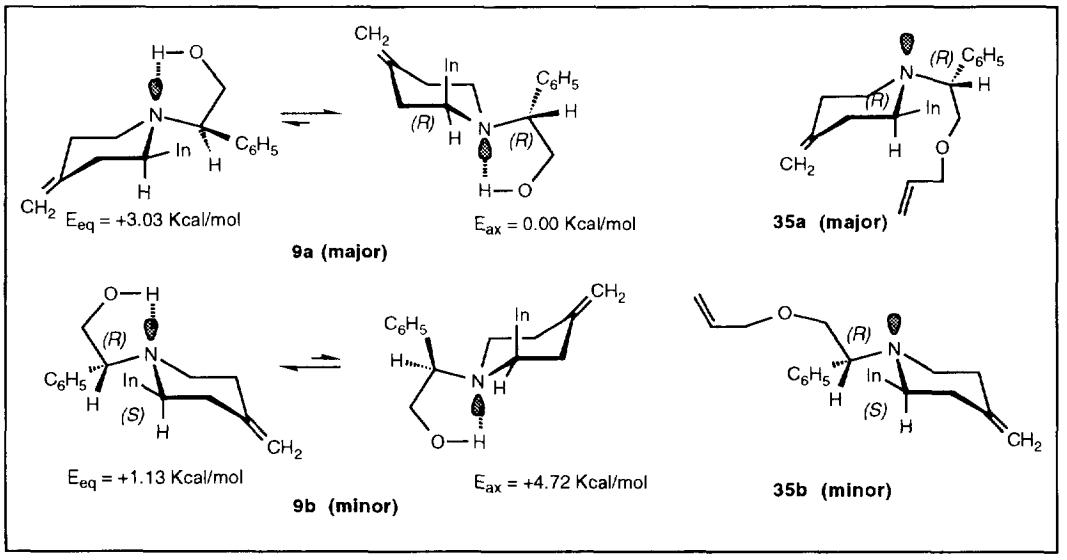
However, when the chiral aminoallylsilane **21** was condensed with aldehyde **27** in the same experimental conditions, imine **32** was the major product, isolated along with small amounts of piperidines **9a,b** (Scheme 4). The formation of oxazolidines **31** was also detected on the NMR spectra of the crude reaction mixture (δ_H 5.50, 2-H; δ_C 92.1, C-2). However, it was impossible to isolate them as they were quickly degraded.[8-10] The fragmentation product **32** was identified by the signals at δ 8.50 (^1H NMR) and δ 154.4 (^{13}C NMR) corresponding to the imine function, and by the loss of the ethylallylsilane moiety. A similar cleavage[11] was observed when aldehyde **27** was condensed with the protected aminoallylsilanes **24** and **25** in C_6H_6. In the case of **24** the formation of indolylpiperidines **35a** and **35b** was also detected.

We subsequently attempted to stabilize the intermediate allylsilane-iminium salts in order to circumvent the cleavage, and to increase the piperidine formation with respect to the competing oxazolidine ring closure when using aminoallylsilane **21**.[12] The best results were obtained when aldehyde **27** and aminoallylsilane **21** were condensed in refluxing CH_2Cl_2 in the presence of 4Å molecular sieves. Initially, formation of oxazolidine **31** was observed,[8] but after longer reaction times (14 h) a 1.5:1 mixture of C-2 epimeric piperidines **9a** and **9b** was obtained, with a yield of 41% (Scheme 4). The most striking ^1H NMR difference between **9a** and **9b** was the chemical shift of the piperidine C-2 methine proton. Thus, while in isomer **9b** 2-H appears at δ 3.55 as a double doublet with a *trans* diaxial coupling constant (J = 12 Hz), in **9a** it appears as a triplet (J = 5 Hz) at δ 4.29 (Δδ = 0.74). This implies that the major product **9a** presents the indolyl substituent in an axial orientation.[13] Once the piperidine ring is formed by attack of the double bond on either side of the intermediate iminium salt, the phenyl group on C-α becomes oriented as a result of the establishment of a hydrogen bond between the hydroxy group and the piperidine nitrogen atom. The absolute configuration on C-2 could be inferred by considering that when C-2 is *(S)*, the indolyl substituent does not interact with the phenyl ring situated on the other side of the piperidine ring. However, when C-2 has an *(R)* configuration, a piperidine conformational change avoids the steric hindrance between the phenyl ring and the indolyl substituent (Scheme 5). Furthermore, this conformational change is also consistent with the wide chemical shift difference (Δδ 0.5 ppm) observed for the diastereotopic methylene protons on the β-position, due to the



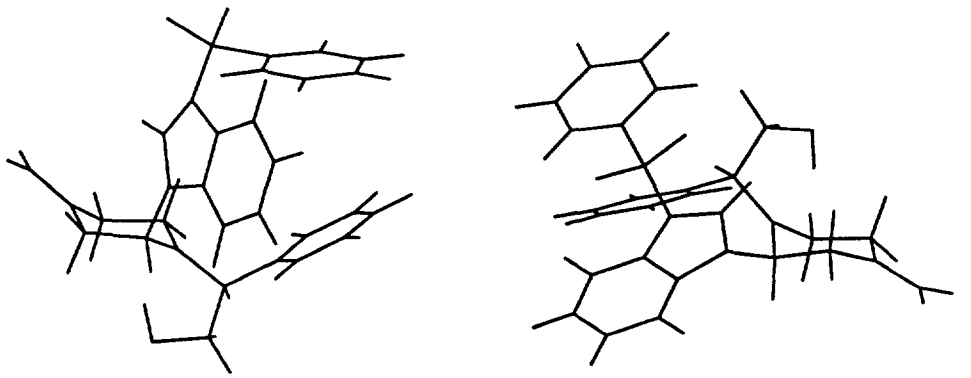
Scheme 4

influence of the indolyl substituent. Thus, piperidines **9** showed the characteristic ^{1}H NMR signals of the chiral exocyclic chain as a doublet of doublets at δ~3.90 for the methine α-proton and two double doublets for the non-equivalent β-protons at δ 3.38 and 4.05 in **9b**, and δ 3.85 and 3.95 in **9a**.



Scheme 5

These conclusions, inferred from the NMR data, were further supported by theoretical calculations. A systematic conformational analysis of the equatorial-axial equilibrium of piperidines **9a-b** showed that the axial conformation of structure **9a** is about 3 Kcal/mol more stable than the equatorial form. In contrast, when the configuration on C-2 is changed from *(R)*-**9a** to *(S)*-**9b**, the equatorial conformation becomes more stable by 3.6 Kcal/mol. Moreover, comparison of the most stable conformation of **9a** and **9b** shows a small preference for the *(αR,2R)*-diastereomer (about 1 Kcal/mol), which is in agreement with the experimental data.

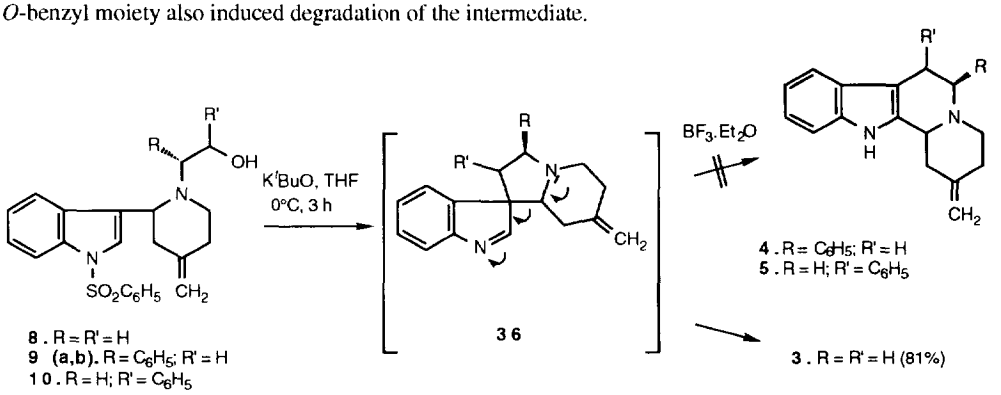


9a (major isomer) **9b (minor isomer)**

Figure 1. Computer-simulated representation of the conformations showing the global minimum energy of compounds **9a** and **9b**.

When the same reaction conditions were used to condense aminoallylsilane **24** and aldehyde **27**, a 1.5:1 mixture of indolylpiperidines **35a** and **35b** was obtained in 66% yield. In this case, the *O*-protected hydroxyethyl substituent has free rotation, and both piperidines **35a** (major) and **35b** (minor) showed an equatorial disposition for the C-2 indolyl substituent. In the ^{1}H NMR spectra, the C-2 axial protons appeared as a double doublets, at δ 3.60 for **35b** and δ 4.20 for **35a**.[14] However, this chemical shift difference can only be due to the electronic effect of the protected oxygen atom. So we can speculate that when C-2 has an *(R)* configuration, the phenyl ring is as far away as possible from the indolyl substituent when the chain is folded so that the oxygen atom is close to 2-H. Conversely, when C-2 is *(S)* the interaction of the aromatic groups is avoided by a rotation of the chain which leaves the oxygen atom far away from 2-H (Scheme 5). In this case, no big differences should be observed in the ^{13}C NMR spectra with regard to the chemical shift of C-2, which is consistent with the values found (δ 58.1 for **35a** and 58.2 for **35b**).[15]

Once we had piperidines **9** in hand, we assayed their reactivity with K^{t}BuO, using our usual methodology for preparation of indolo[2,3-*a*]quinolizidine systems.[2a, 3] In particular, 2-methyleneindolo[2,3-*a*]quinolizidine (**3**) had been obtained in 81% yield from piperidine **8**, and the rearrangement of the intermediate spiroindolenine had been shown to occur spontaneously (Scheme 6).[3] Piperidines **9a** and **9b** were independently submitted to K^{t}BuO treatment followed by addition of $BF_3.Et_2O$ to promote the rearrangement to the desired quinolizidines, since no spontaneous evolution of the intermediate was observed. Unfortunately, only degradation products were obtained. Assays to verify the correct formation of the intermediate by $NaBH_4$ reduction also failed, indicating that the *N*-benzylic spiroindolenine **36** was degraded in the basic reaction conditions.[16] The reaction was then tested on piperidine **10**,[17] with the same negative results, indicating that the *O*-benzyl moiety also induced degradation of the intermediate.



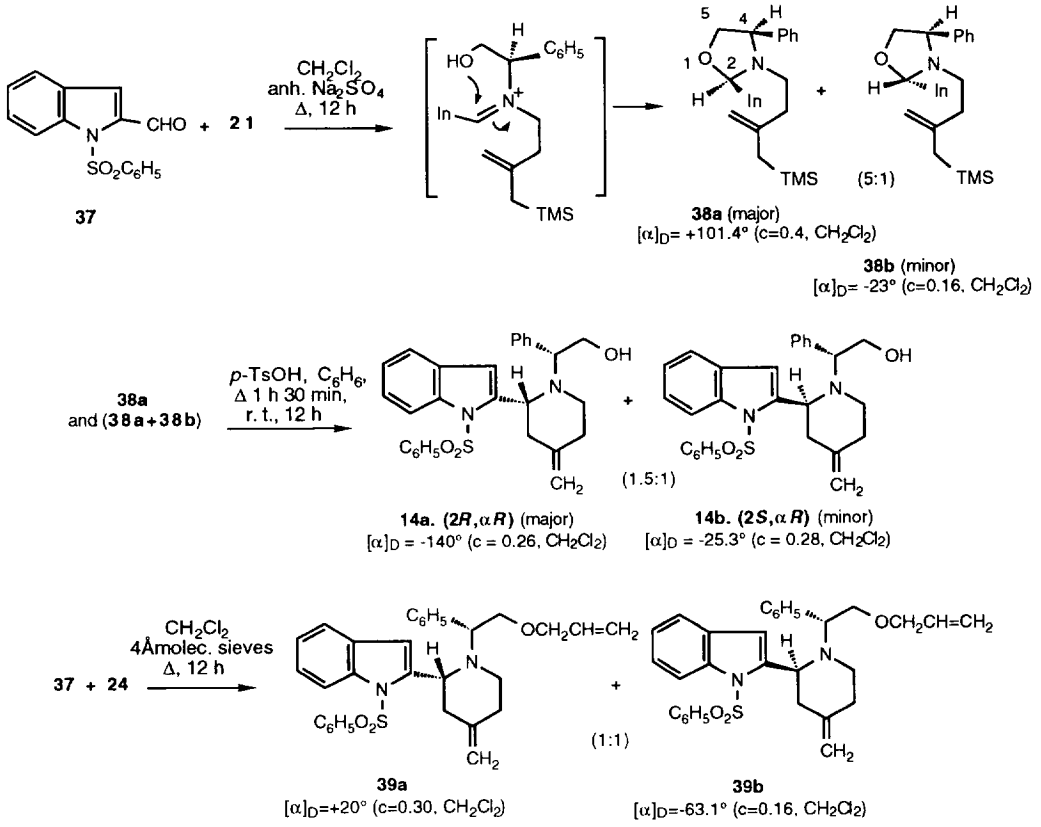
Scheme 6

In view of these results, we studied the behaviour of the 2-indolyl analogues **14** of piperidines **9**, since their treatment with K^{t}BuO should lead to a mixture of the desired indolo[2,3-*a*]quinolizidine **4** and the pyrido[1',2':1,2]pirazino[4,3-*a*]indole **42**, derived from the cyclization upon the indole nitrogen atom (Scheme 10).[2b]

The preparation of piperidines **14** was carried out by condensation of aminoallylsilanes **21** and **24** with 1-phenylsulfonylindole-2-carbaldehyde (**37**) using CH_2Cl_2 as the solvent. Condensation of indolecarbaldehyde **37** with aminoallylsilane **21** yielded exclusively oxazolidines **38a,b** (99%) as a 5:1 diastereomeric mixture (Scheme 7). The main characteristic features of the major oxazolidine **38a** were the methine proton at δ 6.18 in the ^1H NMR spectrum, and the C-2 methine carbon at δ 90.3 in the ^{13}C NMR. The configuration of the chiral centers was determined by 2D NOE experiments. Thus, a NOE correlation of the singlet at δ 6.18 (2-H) with the double doublet at δ 4.13 (4-H) and with the multiplet at δ 2.90 (NCH_2) was observed, which demonstrated a *syn* relationship between 2-H and 4-H. Since the absolute configuration at C-4 is *(R)*, the absolute configuration at C-2 could be determined as being *(R)*. An intense NOE correlation was also observed between the aromatic In-3H proton and one of the C-5 methylene protons (δ 4.26). The minor oxazolidine **38b** was assigned as the *(2S, 4R)* isomer.

When oxazolidine **38a** was refluxed in dry C_6H_6 in the presence of anhydrous *p*-TsOH, a 1.5:1 mixture of indolylpiperidines **14a** and **14b** was obtained in 59% yield (Scheme 7). When the mixture of **38a** and **38b** was submitted to cyclization the same diastereomeric proportion of **14** was obtained, which makes it clear that the cyclization occurs *via* the ring opening to the intermediate iminium salt (addition reaction). In this case, both

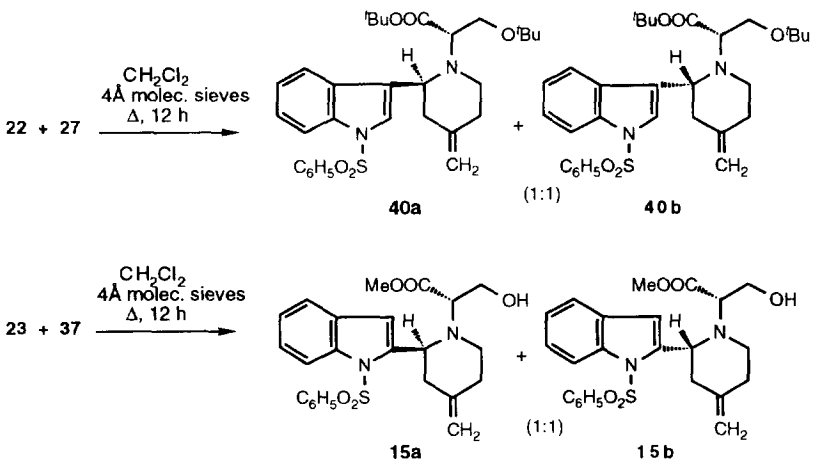
2-(2-indolyl)-piperidines **14** presented an axial disposition of the 2-indolyl substituent, as shown by the ^1H NMR signals of the C-2 proton: a triplet at δ 5.10 (J = 5 Hz) for **14a** (major), and at δ 4.44 (J = 6.8 Hz) for **14b** (minor isomer).



Scheme 7

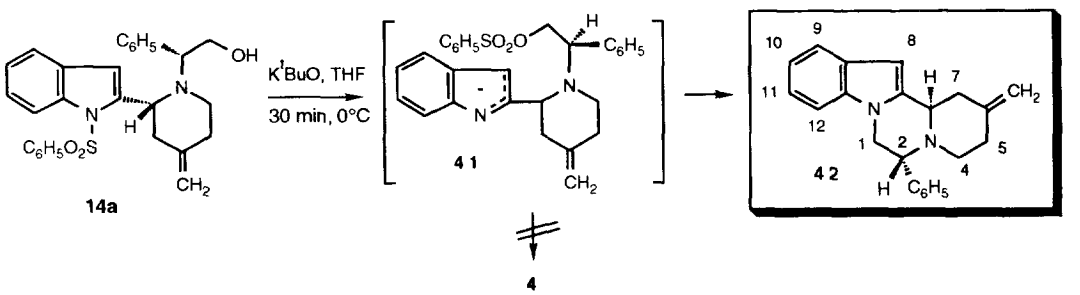
Alternatively, condensation of indolecarbaldehyde **37** and aminoallylsilane **24** gave in 50% yield an equimolecular mixture of indolylpiperidines **39a** and **39b**, which were identified on the basis of their spectral data.

In view of the poor diastereoselectivity observed so far we also tried the use of (*S*)-(-)-serine protected derivatives **18** and **19** as chiral auxiliaries, hoping for an electronic aid in the chiral induction. Thus, reaction of aminoallylsilane **22** with indole-3-carbaldehyde **27** yielded piperidines **40a,b** (63% yield) as an equimolecular diastereomeric mixture (Scheme 8). It is worth mentioning that in contrast to the α-phenyl series, in this case no oxazolidine formation was observed, not even when the reaction was monitored by tlc. Another relevant difference between the α-methoxycarbonyl series and the previous one was that both piperidines **40** showed an equatorial disposition for the indolyl substituent. Similarly, the reaction of aminoallylsilane **23** with indole-2-carbaldehyde **37** led to an equimolecular mixture of piperidines **15a,b** (26% yield). Thus, neither the methoxycarbonyl nor the bulkier *t*-butyl ester group improved the diastereoselectivity of the cyclization process.



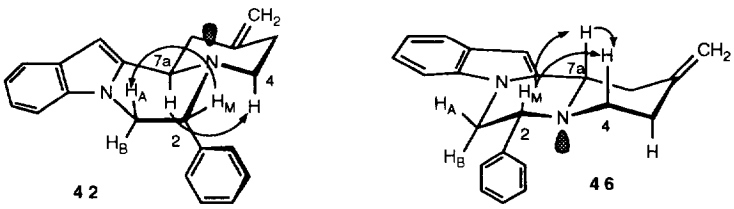
Scheme 8

We then proceeded to the cyclization assays of piperidine **14a**. Thus, when piperidine **14a** was submitted to the K^{t}BuO treatment, compound **42** was obtained in 61% yield as the only product, as a result of the attack of the indole nitrogen atom upon the β-carbon (Scheme 9). Other reaction conditions using Et_2O as the solvent also failed to yield the indolo[2,3-*a*]quinolizidine **4**, and **42** was always found as the only cyclized compound. When Li^{t}BuO was used as the base no cyclization was observed, and the starting product was fully recovered. The absence of a signal corresponding to an indole-NH proton, a singlet at δ 6.31 corresponding to 8-H, and a double doublet at δ 3.57 corresponding to the axial angular 7a-H proton were the most characteristic ^{1}H NMR spectral data of compound **42**, together with a downfield shift of the *N*-alkyl chain protons (1-H and 2-H). All assignments were confirmed by COSY (H,H) experiments.



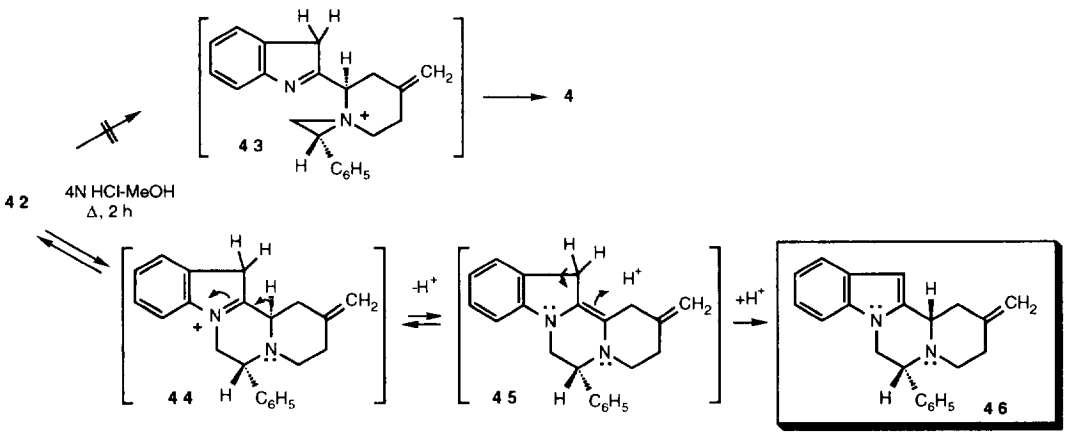
Scheme 9

The absolute configuration of C-7a was determined on the basis of the 2D NOESY experiments. Thus, 2-H (δ 4.30) showed an intense NOE correlation with 4-H_e (δ 3.06) and with only one of the vicinal protons (1-H_A, δ 4.50); the angular methine proton (7a-H) was correlated with 4-H_a (δ 2.30), 7-H_e (δ 2.74), and the phenyl *ortho* proton (δ 7.00). These correlations are consistent only with a spatial arrangement corresponding to the (2*R*, 7a*R*) compound **42** (Scheme 10). This finding proved that the major piperidine **14a** had a (2*R*, α*R*) configuration, which is consistent with the observations made on the 3-indolyl series (see Scheme 5).



Scheme 10. The arrows indicate the most relevant NOE correlations.

Since it is known that in some cases pyridopyrazinoindoles rearrange into the corresponding indolo[2,3-*a*]quinolizidines on acid treatment through an aziridinium salt intermediate type **43**,[2a] we submitted compound **42** to reflux in 4N HCl (Scheme 11). Monitoring of the reaction by tlc showed the total transformation of **42** after 2 h. Compound **46**, obtained in 65% yield, was characterized as being the epimer on C-7a of **42**, and not the expected indoloquinolizidine **4**. Thus, **46** showed very similar spectral data to those of **42**, and the 2D NOESY experiments showed intense correlations between the methine 7a-H proton and both 2-H and 4-H_a, confirming the new stereochemistry. Such epimerization can be accounted for by the strength of the C1-C12b bond allowing a process similar to the epimerization of indolo[2,3-*a*]- and benzo[*a*]quinolizidine alkaloids.[18]



Scheme 11

CONCLUSION

In this work we have shown that our allylsilane methodology can be used as a general method for the preparation of chiral non-racemic 2-indolyl-4-methylenepiperidines. A series of 6 pairs of diastereomeric piperidines (**9**, **14**, **15**, **35**, **39**, **40**) and racemic **10** have been obtained and characterized. The steric hindrance between the indolyl substituent and the phenyl ring used as the chiral auxiliary is shown to be higher when the indolyl substituent is attached to the piperidine ring by its 3-position (**9**) than when it is attached by its 2-position (**14**). However, the induction observed in the cyclization step is the same in both cases, and the (2*R*, α*R*) diastereomer is obtained as the major product in a ratio of 1.5:1. The use of an ester group on the α-position as the chiral auxiliary did not show any induction in the cyclization step.

We have also studied the K^{t}BuO cyclization process of *N*-(2-hydroxyethyl)-2-indolylpiperidines **9** and **14**, and have found that the α-phenyl group plays an important role. Thus, in the case of **9**, the intermediate spiroindolenine **36** is highly unstable, and total degradation is observed. In the case of **14**, the anionic intermediate **41** is formed, but the cyclization only occurs on the indole nitrogen atom. Furthermore, the stability of the pyridopyrazinoindole structure **42** accounts for the epimerization at the angular carbon atom (C-7a) observed in hot aqueous acidic medium yielding **46**.

EXPERIMENTAL

Methods for theoretical calculations. The conformational analysis of 2-indolyl-4-methylenepiperidines **9a-b** was performed with the force-field CVFF,[19,20] as implemented in the program DISCOVER.[21] A Morse potential for bond stretching and a scaling factor of 0.25 for 1-4 interactions were used in calculations. Cross-term energy contributions were also considered. A dielectric constant of 1.0 was used. Energy minimizations were carried out with a conjugate gradient method until the value of the maximum derivative was less than 0.001 Kcal/mol. Computations were performed on an IRIS (Silicon graphics) workstation.

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 mm, SDS). TLC was performed on SiO_2 (silica gel 60 F254, Macherey-Nagel) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Dragendorff or hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CID, Barcelona.

***N*-Methyl-3-(trimethylsilylmethyl)-3-butenamine (20).** To a solution of tosylate **17** (12 g, 38.5 mmol) in dry DMSO (30 ml), NaI (catalytic amount) and Et_3N (3.9 g, 38.5 mmol) were added under N_2 atmosphere, and the mixture was cooled to -10°C. Methylamine (385 mmol) was added, and the mixture was stirred at room temperature overnight. The solution was diluted with AcOEt (200 ml), washed with a mixture of brine and 10% aqueous NaOH. The organic extracts were washed again with brine, dried and the solvent removed to give a liquid which was distilled (68-70°C, 1 mmHg) yielding amine **20** (2.6 g, 40%): ^{1}H NMR 1.49 (br s, 1H, NH), 1.51 (s, 2H, CH_2SiMe_3), 2.12 (t, J = 6.4 Hz, 2H, CH_2CH_2N), 2.40 (s, 3H, NCH_3), 2.65 (t, J = 6.4 Hz, 2H, CH_2N), 4.54 and 4.58 (2s, 1H each, $=CH_2$); ^{13}C NMR -1.0 ($SiMe_3$), 26.6 (CH_2SiMe_3), 36.5 (NCH_3), 38.5 ($=CCH_2$), 50.0 (CH_2N), 108.5 ($=CH_2$), 145.4 ($C=CH_2$). Anal. Calcd for $C_9H_{21}NSi$: C, 63.08; H, 12.35. Found: C, 63.09; H, 12.30.

***(R)-N*-(2-Hydroxy-1-phenylethyl)-3-(trimethylsilylmethyl)-3-butenamine (21).** To a solution of tosylate **17** (11.8 g, 38 mmol) in dry DMSO (26 ml), anhydrous Et_3N (5.3 ml), NaI (130 mg) and (*R*)-(-)-phenylglycinol (7.8 g, 57 mmol) were added at room temperature. The mixture was stirred for 60 h at room temperature under N_2 atmosphere, and the reaction was quenched by addition of AcOEt (50 ml). The resuting solution was washed with brine (15 ml), basified with aqueous 10% NaOH (pH = 10), and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried and evaporated to give a brown oil, which was flash chromatographed (AcOEt) yielding amine **21** (7.05 g, 67%): $[\alpha]_D$ = -43° (c = 1.2, $CHCl_3$); mp 72-73°C (acetone); ^1H NMR 0.03 (s, 9H, $SiCH_3$), 1.50 (s, 2H, $=CCH_2Si$), 2.15 (t, *J* =7 Hz, 2H, $=CCH_2$), 2.60 (m, 3H, OH and NCH_2), 3.55 (dd, *J* =7 and 8.5 Hz, 1H, NCH), 3.72 (dd, *J* =8.5 and 3 Hz, 1H, CH_AOH), 3.80 (dd, *J* =7 and 3 Hz, 1H, CH_BOH), 4.60 and 4.65 (2s, 1H each, $=CH_2$), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR -0.2 ($SiCH_3$), 26.5 ($SiCH_2$), 38.5 ($=CCH_2$), 45.0 (NCH_2), 64.8 (NCHPh), 66.6 (CH_2OH), 108.6 ($=CH_2$), 127.8, 128.0, 128.8, 140.7 (Ar-*ipso*), 145.1 (=C). Anal. Calcd for $C_{16}H_{27}NOSi$: C, 69.27; H, 9.82; N, 5.05. Found: C, 69.50; H, 9.57; N, 5.05.

***N*-[2-*t*-Butoxy)-1-(*t*-butoxycarbonyl)ethyl]-3-(trimethylsilylmethyl)-3-butenamine (22).** To a solution of the tosylate **17** (1.02 g, 3.3 mmol) in dry DMSO (24 ml) anhydrous Et_3N (0.61 ml), NaI (61 mg) and commercial *(S)*-(-)-serine *t*-butyl ester *t*-butyl ether **18** (610 mg, 2.8 mmol) were added at room temperature. The mixture was stirred for 72 h at room temperature under N_2 atmosphere, and the reaction was quenched by addition of AcOEt (60 ml). The resulting solution was washed with brine, basified with aqueous 10% NaOH (pH=10), and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried and evaporated. The residue was flash chromatographed (CH_2Cl_2:CH_3OH, 99:1) yielding amine **22** (394 mg, 35%): ^1H NMR 0.01 (s, 9H, $SiMe_3$), 1.13 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.50 (s, 2H, CH_2TMS), 2.14 (m, 2H, $=CCH_2$), 2.60 (m, 1H, CH_AN), 2.76 (m, 1H, CH_BN), 3.26 (t, *J* = 5.5 Hz, 1H, CHN), 3.46 (dd, *J* = 5.5 and 8.5 Hz, 1H, CH_AO), 3.52 (dd, *J* = 5.5 and 8.5 Hz, 1H, CH_BO), 4.55 and 4.62 (2s, 1H each, $=CH_2$); ^{13}C NMR -1.4 (TMS), 26.6 (CH_2TMS), 27.3 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$), 38.5 ($=CCH_2$), 45.9 (CH_2N), 62.3 (CHN), 63.0 (CH_2O), 72.8 ($(CH_3)_3CO$), 80.8 ($(CH_3)_3COCO$), 108.3 ($=CH_2$), 145.0 ($C=CH_2$), 172.7 (COO); MS *m/z* (%) 256 (M^+ -$CO_2{}^tBu$, 11), 230 (11), 200 (4), 174 (30), 118 (100). Anal. Calcd. for $C_{19}H_{39}NSiO_3$: C, 63.86; H, 10.92; N, 3.92. Found: C, 63.92; H, 10.91; N, 4.12.

***N*-[2-Hydroxy-1-(methoxycarbonyl)ethyl]-3-(trimethylsilylmethyl)-3-butenamine (23).** Operating as above, from tosylate **17** (700 mg, 2.24 mmol), and serine methyl ester hydrochloride (**19**, 700 mg, 4.5 mmol), aminoallylsilane **23** was obtained (200 g, 35%): $[\alpha]_D$ = -11° (c = 0.5, $CHCl_3$); IR (NaCl) 3100-3600 (OH), 1739 (CO), 1651 ($=CH_2$) cm^{-1}; ^1H NMR 0.00 (s, 9H, $SiMe_3$), 1.50 (s, 2H, CH_2Si), 2.12 (t, *J* = 7.5 Hz, 2H, $=CCH_2$), 2.54-2.65 (m, 3H, OH and NCH_2), 2.72-2.81 (m, 1H, CHCOOMe), 3.35 (dd, *J* = 6 and 5 Hz, 1H, CH_AOH), 3.58 (dd, *J* = 11.5 and 6 Hz, 1H, CH_BOH), 4.58 and 4.61 (2s, 1H each, $CH_2=$); ^{13}C NMR -1.9 ($Si(CH_3)_3$), 26.1 (CH_2TMS), 37.6 ($=CCH_2$), 45.4 (CH_2N), 51.3 (CHN), 61.8 (CH_2OH), 62.4 (OCH_3), 107.9 ($=CH_2$), 144.2 ($C=CH_2$), 172.7 (CO). Anal. Calcd for $C_{12}H_{25}NSiO_3$: C, 55.56; H, 9.72; N, 5.40. Found: C, 55.86; H, 9.47;N, 5.14.

***N*-[2-(Allyloxy)-1-phenylethyl]-3-(trimethylsilylmethyl)-3-butenamine (24).** To a suspension of NaH (79 mg, 1.98 mmol) in dry THF (2 ml) a solution of aminoalcohol **21** (500 mg, 1.8 mmol) in dry THF

(3 ml) was slowly added. After stirring for 50 min at room temperature under N_2 atmosphere, allyl bromide (0.31 ml, 3.61 mmol) was added, and the solution was stirred for 15 h at room temperature. The reaction mixture was diluted with Et_2O and washed with aqueous 10% K_2CO_3 and with brine. The organic extracts were dried and evaporated to furnish an oil which was flash chromatographed (hexane:AcOEt, 6:4) yielding the silylether **24** (350 mg, 61%): $[\alpha]_D$= -35° (c = 0.9, $CHCl_3$); IR (CCl_4) 3300-3400 (NH), 1635 (=CH_2) cm^{-1}; ^1H NMR 0.00 (s, 9H, $SiCH_3$), 1.50 (s, 2H, CH_2Si), 2.28 (t, J = 7 Hz, 1H, =CCH_2), 2.60 (m, 2H, CH_2N), 3.44 (t, J = 8 Hz, 1H, CH_AO), 3.52 (dd, J =8 and 3.5 Hz, 1H, CH_BO), 3.92 (dd, J = 8 and 3.5 Hz, 1H, NCH), 4.00 (d, J = 6 Hz, 2H, OCH_2CH=), 4.60 and 4.65 (2s, 1H each, C=CH_2), 5.20 (m, 2H, CH=CH_2), 5.90 (m, 1H, CH=), 7.25-7.45 (m, 5H, ArH); ^{13}C NMR -1.4 ($SiCH_3$), 26.6 (CH_2Si), 38.5 (=CCH_2), 45.5 (CH_2N), 63.0 (NCHPh), 71.8 (OCH_2CH), 75.4 (OCH_2CH=), 108.3 (C=CH_2), 116.6 (CH=CH_2), 127.2, 127.5, and 128.2 (Ar), 134.6 (=CH), 141.0 (Ar-*ipso*), 145.2 (=C); MS *m/z* (%) 286 (2), 258 (1), 246 (33), 190 (34). Anal. Calcd for $C_{19}H_{31}NOSi$: C, 71.92; H, 9.77; N, 4.41. Found: C, 71.90; H, 9.74; N, 4.40.

***N*-[2-(*t*-Butyldiphenylsilyloxy)-1-phenylethyl]-3-(trimethylsilylmethyl)-3-butenamine (25).** A mixture of alcohol **21** (482 mg, 1.74 mmol), imidazole (296 mg, 4.35 mmol) and TBDPSCl (0.55 ml, 2.09 mmol) in dry DMF was stirred at room temperature for 20 h under N_2 atmosphere. The reaction mixture was poured onto ice-H_2O and was extracted with CH_2Cl_2. The organic phase was dried and evaporated to give an oil which was flash chromatographed (hexane:AcOEt, 8:2) to yield the silylated compound **25** (810 mg, 90%): $[\alpha]_D$= -30° (c = 0.4, $CHCl_3$); IR (CCl_4) 3120-3160 (NH), 1635 (=CH_2) cm^{-1}; ^1H NMR 0.10 (s, 9H, $SiCH_3$), 1.10 (s, 9H, $C(CH_3)_3$), 1.60 (s, 2H, =CCH_2Si), 2.25 (t, J = 7 Hz, 2H, =CCH_2), 2.70 (m, 2H, NCH_2), 3.70 (d, J = 7 Hz, 2H, CH_2OSi), 3.90 (t, J = 7 Hz, 1H, NCH), 4.70 and 4.80 (2s, 1H each, =CH_2), 7.25-7.35 (m, 5H, ArH), 7.35-7.50 (m, 6H, ArH), 7.65-7.70 (t, J = 7 Hz, 4H, ArH); ^{13}C NMR -1.3 ($SiCH_3$), 19.2 ($C(CH_3)_3$), 26.6 (=CCH_2), 26.9 ($C(CH_3)_3$), 38.6 (=CCH_2), 45.4 (CH_2N), 65.3 (NCHPh), 69.0 (CH_2OSi), 108.7 (=CH_2), 127.2, 127.7, 127.7, 128.2, and 129.7 (Ar), 133.4, 133.6, and 135.6, 141.0 (Ar-*ipso*), 145.3 (*C*=CH_2); MS *m/z* (%) 516 (M^++1, 0.1), 501 (1), 389 (9), 330 (25), 318 (10), 310 (21), 247 (77). Anal. Calcd for $C_{32}H_{45}NOSi_2$: C, 74.57; H, 8.74; N, 2.72. Found: C, 74.58; H, 8.70; N, 2.73.

***N*-[1-Phenyl-2-(trimethylsilyloxy)ethyl]-3-(trimethylsilylmethyl)-3-butenamine (26).** A solution of alcohol **21** (300 mg, 1.08 mmol), Et_3N (0.18 ml, 1.3 mmol) and TMSCl (0.16 ml, 1.3 mmol) in dry THF (5 ml) was stirred for 17 h at room temperature under N_2 atmosphere. The reaction mixture was poured on ice-H_2O, and extracted with Et_2O and CH_2Cl_2, at neutral pH. The combined organic extracts were dried and evaporated to obtain amine **26** (270 mg, 71%), which was used without further purification: mp 64-65°C. $[\alpha]_D$= -45° (c = 0.9, CH_2Cl_2); IR (CCl_4) 3300-3390 (NH), 1635 (=CH_2) cm^{-1}; ^1H NMR 0.00 and 0.10 (2s, 9H each, $SiCH_3$), 1.50 (s, 2H, CH_2Si), 2.20 (t, J = 7 Hz, 2H, =CCH_2), 2.60 (m, 2H, CH_2N), 3.60 (t, J = 8.3 Hz, 1H, CH_AOSi), 3.70 (dd, J = 8.3 and 3.5 Hz, 1H, CH_BOSi), 3.82 (dd, J = 8.3 and 3.5 Hz, 1H, NCHPh), 4.60 and 4.65 (2s, 1H each, =CH_2), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR -1.3 ($SiCH_3$), 0.58 ($SiCH_3$), 26.6 ($SiCH_2$), 37.9 (=CCH_2), 45.2 (CH_2N), 65.0 (NCHPh), 67.4 (CH_2OSi), 108.6 (=CH_2), 127.5, 127.8, and 128.3 (Ar), 140.1 (Ar-*ipso*), 145.0 (=C); MS *m/z* (%) 246 (28), 172 (8), 150 (91).

1-Methyl-4-methylene-2-[1-(phenylsulfonyl)-3-indolyl]piperidine (29). To a solution of aldehyde **27** (916 mg, 3.2 mmol) in dry C_6H_6 (100 ml), amine **20** (0.5 g, 2.9 mmol) and 4Å molecular sieves were added. The mixture was stirred at 0°C for 45 min under N_2 atmosphere, at room temperature for 1h and refluxed with a Dean-Stark trap for 12 h. The mixture was cooled, filtered and evaporated to give an oil which was flash chromatographed (CH_2Cl_2-CH_3OH, 98:2) yielding piperidine **29** (633 mg, 59%). **29.HCl**: mp 128°C-130°C (acetone); IR ($CHCl_3$) 1715 (=CH_2) cm^{-1}; ^1H NMR 2.10 (s, 3H, CH_3), 1.90- 2.65 (m, 5H, 3-H, 5-H and 6-H_a), 3.10 (ddd, J = 12, 5 and 3 Hz, 1H, 6-H_e), 3.20 (dd, J = 12 and 3.5 Hz, 1H, 2-H_a), 4.70 and 4.75 (2s, 1H each, =CH_2), 7.20-7.55 (m, 7H, ArH), 7.85 (t, J = 7.7 Hz, 2H, ArH), 8.05 (d, J = 7.7 Hz, 1H, In-7H); ^{13}C NMR 34.3 (C-5), 41.7 (C-3), 43.4 (NCH_3), 57.2 (C-6), 62.5 (C-2), 108.4 (=CH_2), 113.7 (In-C7), 120.9 (In-C4), 123.2 and 123.5 (In-C5 and In-C2), 124.9 (In-C6), 126.7 (Ar-*o*), 129.2 (Ar-*m*), 133.8 (Ar-*p*), 136.0 (In-C7a), 138.0 (Ar-ipso), 145.6 (C-4); MS *m/z* (%) 366 (M^+, 40), 343 (7), 270 (8), 225 (118). Anal. Calcd for $C_{21}H_{22}O_2N_2S.HCl.3/5H_2O$: C, 61.03; H, 5.86; N, 6.78; S, 7.75. Found: C, 61.24; H, 6.03; N, 6.85; S, 7.34.

(2S,αR)* and *(2R,αR)* 1-(1-Phenyl-2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-methylenepiperidines (9a,b).** To a solution of aldehyde **27** (103 mg, 0.36 mmol) in dry CH_2Cl_2 (10 ml), amine **21** (100 mg, 0.36 mmol) and 4Å molecular sieves were added. The mixture was stirred for 13 h at room temperature under N_2 atmosphere, then refluxed for 14 h. The crude mixture was cooled, filtered, evaporated, and the residue was flash chromatographed (CH_2Cl_2). **Piperidine 9a *(αR,2R) (45 mg, 24%): $[\alpha]_D$= -43° (c = 1, CH_2Cl_2); IR ($CHCl_3$) 3350 (OH) cm^{-1}; ^1H NMR 2.20-2.40 (m, 2H, 5-H), 2.50-2.57 (m, 2H, 3-H), 2.65 (m, 1H, 6-H_a), 2.90 (dt, J = 12 and 5 Hz, 1H, 6-H_e), 3.85 (dd, J = 11 and 5 Hz, 1H, CH_AOH), 3.95 (m, 2H, CH_BOH and NCHPh), 4.29 (t, J = 5 Hz, 1H, 2-H_e), 4.60 and 4.75 (2s, 1H each, =CH_2), 7.10-7.45 (m, 11H, ArH), 7.55 (s, 1H, In-2H), 7.80 (d, J = 7 Hz, 2H, ArH), 8.00 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 34.3 (C-5), 41.2 (C-3), 46.6 (C-6), 56.9 (C-2), 60.6 (CH_2OH), 64.0 (NCHPh), 108.9 (=CH_2), 113.8 (In-C7), 120.6 (In-C5), 123.2 (In-C4), 124.2 (In-C6), 124.9, 126.6, 127.2, 128.2, 129.1, 133.7 (In-C2), 135.2, 137.8, 139.2, 144.9 (=C); MS *m/z* (%) 472 (M^+, 3), 454 (2), 441 (100), 365 (26), 300 (14), 270 (11), 218 (13), 194 (16), 182 (44), 167 (19), 118 (73). Anal. Calcd for $C_{28}H_{28}N_2O_3S.H_2O$: C, 68.63; H, 6.17; N, 5.72. Found: C, 68.65; H, 6.22; N, 5.69. **Piperidine 9b *(αR,2S)*** (30 mg, 17%): $[\alpha]_D$= -32.8° (c = 0.5, CH_2Cl_2); ^1H NMR (500 MHz) 2.00 (td, J = 11 and 4 Hz, 1H, 5-H_a), 2.20-2.45 (m, 3H, 5-H_e, 3-H_e and 6-H_a), 2.63 (t, J = 12 Hz, 1H, 3-H_a), 3.25 (dt, J =11 and 4 Hz, 1H, 6-H_e), 3.38 (dd, J =11 and 4 Hz, 1H, CH_AOH), 3.55 (dd, J =12 and 3 Hz, 1H, 2-H_a), 3.9 (dd, J = 11 and 4 Hz, 1H, CHPh), 4.05 (t, J = 11 Hz, 1H, CH_BOH), 4.55 and 4.60 (2s, 1H each, =CH_2), 6.85 (d, J = 3.6 Hz, 1H, ArH), 6.9 (d, J = 2 Hz, 1H, ArH), 7.20-7.55 (m, 9H, ArH), 7.75 (d, J = 7 Hz, 1H, In-4H), 7.95 (dd, J = 8 and 2 Hz, 2H, ArH), 8.10 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 34.8 (C-5), 43.1 (C-3), 46.6 (C-6), 58.4 (C-2), 60.1 (CH_2OH), 62.8 (NCHPh), 108.3 (=CH_2), 114.2, 120.7, 123.4, 124.5, 125.2, 126.7, 128.2, 129.3, 133.9, and 135.5 (Ar), 144.9 (=C); MS *m/z* (%) 472 (M^+, 3), 441 (100), 332 (23), 301 (96), 270 (5), 218 (10), 207 (22), 182 (13), 118 (95).

1-(2-Allyloxy-1-phenylethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-methylenepiperidines (35a,b). To a solution of aldehyde **27** (90 mg, 0.31 mmol) in dry CH_2Cl_2 (5 ml) a solution of amine **20** (100 mg, 0.31 mmol) in dry CH_2Cl_2 (2 ml), 4Å molecular sieves and anhydrous Na_2SO_4 were added. The

mixture was stirred for 18 h at room temperature under N_2 atmosphere, then refluxed for 18 h. The reaction mixture was cooled, filtered, evaporated, and the residue was flash chromatographed (CH_2Cl_2:hexane 7:3). **Isomer 35a** (64 mg, 40%): $[\alpha]_D$= -5.3° (c = 0.56, CH_2Cl_2); IR ($CHCl_3$) 1600, 1650 (=CH_2) cm^{-1}; ^1H NMR (500 MHz) 2.30 (m, 2H, 5-H), 2.40 (td, *J* =11.6 and 3 Hz, 1H, 3-H_e), 2.50 (t, *J* = 7.5 Hz, 1H, 6-H_a), 2.70 (t, *J* =10 Hz, 1H, 3-H_a), 3.00 (dt, *J* =11.6 and 3 Hz, 1H, 6-H_e), 3.75 (dd, *J* =15 and 10 Hz, 1H, CHPhCH_AO), 3.90 (m, 4H, C*H*PhC*H*$_B$O and CH_2CH=), 4.20 (dd, *J* =10 and 3 Hz, 1H, 2-H_a), 4.70 (2s, 1H each, C=CH_2), 5.20-5.30 (m, 2H, CH=CH_2), 5.90 (m, 1H, C*H*=CH_2), 7.10-7.40 (m, 9H, ArH), 7.45 (t, *J* = 7.5 Hz, 1H, ArH), 7.60 (s, 1H, In-2H), 7.80 (d, *J* = 7.5 Hz, 2H, ArH), 7.90 (d, *J* = 7.5 Hz, 1H, ArH), 8.00 (d, *J* = 7.5 Hz, 1H, In-7H); ^{13}C NMR 34.5 (C-5), 42.5 (C-3), 47.9 (C-6), 58.1 (C-2), 61.6 (CHPh), 70.8, 72.1 (CHPhCH_2O and OCH_2CH=), 107.8 (C=CH_2), 113.8 (In-C7), 117.1 (CH=CH_2), 121.6 (In-C5), 123.1 (In-C4), 124.2 (In-C6), 124.9 (In-C2), 126.7, 127.7, 128.5, 129.1, 129.2, 133.7, 134.7, 145.5; MS *m/z* (%) 512 (M^+·1), 441 (57), 372 (1), 300 (21), 270 (10). Anal. Calcd for $C_{31}H_{32}N_2O_3S.3/2H_2O$: C, 69.01; H, 6.49; N, 5.19; S, 5.93. Found: C, 68.73; H, 6.30; N, 5.15; S, 5.53. **Isomer 35b** (43 mg, 26%): $[\alpha]_D$= -39° (c = 0.3, CH_2Cl_2); ^1H NMR 1.96 (td, *J* =10, 5 Hz, 1H, 6-H_a), 2.28 (m, 3H, 5-H and 3-H_e), 2.52 (t, *J* =10 Hz, 1H, 3-H_a), 3.10 (dt, *J* =10 and 5 Hz, 1H, 6-H_e), 3.60 (dd, *J* =10 and 3 Hz, 1H, 2-H_a), 3.77 (m, 4H, CH_2OCH_2), 4.02 (t, *J* =5 Hz, 1H, CHPh), 4.54 and 4.61 (2s, 1H each, =CH_2), 5.00 (m, 2H, CH=CH_2), 5.70 (m, 1H, C*H*=CH_2), 6.96 (m, 2H, ArH), 7.24 (m, 4H, ArH), 7.34 (t, *J* = 8 Hz, 1H, ArH), 7.40 (t, *J* = 8 Hz, 2H, ArH), 7.48 (m, 1H, In-2H), 7.91 (m, 3H, ArH), 8.04 (d, *J* = 8 Hz, 1H, In-7H); ^{13}C NMR 34.5 (C-5), 42.5 (C-3), 48.0 (C-6), 58.2 (C-2), 61.8 (CHPh), 70.7, 71.9 (CHPhCH_2O and OCH_2CH=), 107.9 (C=CH_2), 113.9 (In-C7), 116.7 (CH=CH_2), 121.5, 123.2 (In-C4), 125.0, 126.7, 127.1, 127.8, 129.2, 129.7, 133.8, 134.7 (C*H*=CH_2), 136.0, 138.0, 145.5 (*C*=CH_2).

1-(2-Hydroxy-2-phenylethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-methylenepiperidines (10a,b). To a solution of 2-[1-(phenylsulfonyl)-3-indolyl]-4-methylenepiperidine[4] (249 mg, 0.7 mmol) in absolute EtOH (4 ml) styrene oxyde (0.08 ml, 0.7 mmol) was added. The reaction mixture was stirred for 15 min at room temperature under N_2 atmosphere, and refluxed for 4 h. The mixture was cooled, concentrated, and the residue was flash chromatographed (CH_2Cl_2) to isolate the two isomers **10a** and **10b**. **Isomer 10a** (higher Rf, 76 mg, 23%): ^1H NMR 2.18 (dd, *J* = 13 and 3 Hz, 1H, CH_AN), 2.25 (td, *J* = 12 and 3 Hz, 1H, 5-H_e), 2.38 (m, 1H, 5-H_e), 2.42 (d, *J* = 12 Hz, 1H, 3-H_e), 2.50 (td, *J* = 13 and 12 Hz, 1H, NCH_B), 2.60 (br t, *J* = 12 Hz, 1H, 3-H_a), 3.40 (dt, *J* = 10.8 and 4.3 Hz, 1H, 6-H_e), 3.62 (dd, *J* = 10.8 and 3.2 Hz, 1H, 2-H_a), 4.73 (dd, *J* = 10.8 and 3.2 Hz, 1H, CHOH), 4.72 and 4.76 (2s, 1H each, =CH_2), 6.97 (dd, *J* = 7.6 and 2.5 Hz, 2H, ArH), 7.14-7.49 (m, 9H, ArH), 7.50 (s, 1H, In-2H), 7.68 (d, *J* = 7 Hz, 1H, ArH), 7.81 (d, *J* = 7 Hz, 2H, ArH), 7.97 (d, *J* = 8 Hz, 1H, In-7H); ^{13}C NMR 34.1 (C-5), 41.8 (C-3), 52.9 (C-6), 60.5 (C-2), 61.6 (CH_2N), 68.7 (CHOH), 108.8 (=CH_2), 113.8 (In-C7), 120.0 (In-C5), 123.3 (In-C4), 124.0 (In-C6), 125.0, 125.6, 126.5, 127.2, 128.1, 129.2, 133.7, 135.2, 137.9, and 141.9 (Ar), 144.6 (*C*=CH_2); MS *m/z* (%) 472 (M^+· 5), 441 (59), 365 (80), 300 (11), 270 (11), 224 912), 182 (300, 118 (39), 77 (100). **Isomer 10b** (lower Rf, 49 mg, 15%): ^1H NMR 2.27-2.75 (m, 8H, 3-H, 5-H , 6-H and CH_2N), 3.05 (m, 1H, 6-H), 3.97 (dd, *J* = 5 and 3.5 Hz, 1H, CHOH), 4.19 (dd, *J* = 9.7 and 3.6 Hz, 1H, 2-H_a), 4.76 and 4.84 (2s, 1H each, =CH_2), 6.91 (dd, *J* = 7.6 and 5 Hz, 2H, ArH), 7.10-7.45 (m, 8H, ArH), 7.57 (s, 1H, ArH), 7.60 (d, *J* = 5 Hz, 1H, ArH), 7.82 (d, *J* = 5 Hz, 2H, ArH), 8.00 (d, *J* = 5 Hz, 1H, In-7H); MS *m/z* (%) 441 (M^+, 4), 365 (25), 310 (12), 270 (13), 224 (29), 194 (40), 141 (14), 107 (28), 77 (100).

***(R)*-1-Phenyl-*N*-[1-(phenylsulfonyl)-3-indolylmethylene]-2-hydroxyethylamine (32).** To a solution of indole-3-carbaldehyde **27** (536 mg, 1.9 mmol) in dry C_6H_6 (80 ml), amine **21** (400 mg, 1.5 mmol) and 4Å molecular sieves were added. The mixture was stirred for 30 min at room temperature under N_2 atmosphere, and refluxed for 12 h with a Dean-Stark trap. The reaction mixture was cooled, filtered and the solvent was evaporated to give an oil which was chromatographed (Al_2O_3, CH_2Cl_2:hexane, 95:5, then CH_2Cl_2) yielding piperidine **9a** (lower Rf, 108 mg, 16%), piperidine **9b** (29 mg, 4%) and imine **32** (higher Rf, 149 mg, 19%). **Imine 32**: $[\alpha]_D$= +77° (c = 1.1, CH_2Cl_2); IR ($CHCl_3$) 3400 -3600 (OH), 1644 (CH=N) cm^{-1}; ^1H NMR 2.60 (br s, 1H, OH), 3.90 (m, 2H, C*H*$_2$OH), 4.50 (m, 1H, CHPh), 7.20-7.60 (m, 10H, ArH), 7.80-8.10 (m, 4H, ArH), 8.50 (d, *J* = 6.5 Hz, 1H, In-7H), 8.60 (s, 1H, CH=N); ^{13}C NMR 67.8 (CH_2OH), 77.3 (CHPh), 113.1 (In-C7), 120.2, 122.9, 124.2, 125.6, 126.7, 127.2, 127.8, 128.5, 129.3, 130.0, 134.1, 135.2, 137.4, and 140.7 (Ar), 155.5 (CH=N); MS *m/z* (%) 404 (M^+, 2), 374 (27), 373 (100). Anal. Calcd for $C_{23}H_{20}O_3N_2S.1/2H_2O$: C, 66.81; H, 5.08; N, 6.77; S, 7.74. Found: C, 66.76; H, 5.53; N, 6.32; S, 7.78.

2-Allyloxy-1-phenyl-*N*-[1-(phenylsulfonyl)-3-indolylmethylene]ethylamine (33). To a solution of indole-3-carbaldehyde **27** (342 mg, 1.2 mmol) in dry toluene (20 ml) a solution of amine **24** (254 mg, 0.8 mmol) in dry toluene (20 ml) and 4Å molecular sieves were added. The mixture was stirred for 3 h at room temperature under N_2 atmosphere, and refluxed for 22 h. The mixture was cooled, filtered and the solvent evaporated to give an oil which was flash chromatographed (hexane-AcOEt, 85:15) yielding pure imine **33** (225 mg, 63%): IR (NaCl) 1650 (CH=N) cm^{-1}; ^1H NMR 4.30 (t, *J* = 10 Hz, 1H, CHPhC*H*$_A$O), 4.40 (dd, *J* = 10 and 4 Hz, 1H, CHPhC*H*$_B$O), 4.60 (dd, *J* = 10 and 4 Hz, 1H, CHPh), 4.70 (d, *J* = 5 Hz, 2H, C*H*$_2$CH=), 5.20 (m, 2H, CH=C*H*$_2$), 6.00 (m, 1H, C*H*=CH$_2$), 7.10-7.80 (m, 14H, ArH), 8.40 (m, 1H, In-7H), 8.50 (s, 1H, CH=N); ^{13}C NMR 71.9 (CHPh*C*H2), 75.3 (*C*H$_2$CH=), 75.4 (CHPh), 113.1 (In-C7), 116.6 (CH=*C*H$_2$), 120.9, 122.5, 123.4, 124.2, 125.0, 125.6, 126.3, 126.7, 127.0, 127.2, 127.3, 128.1, 128.4, 129.3, 129.6, 129.9, 134.0, 134.6, 134.7, and 135.5 (Ar), 141.2 (*C*=CH$_2$), 154.5 (CH=N); MS *m/z* (%) 444 (M^+,1), 428 (1), 387 (32), 386 (100), 385 (39), 374 (2), 373 (9). Anal. Calcd for $C_{26}H_{24}N_2O_3S$: C, 70.27; H, 5.40; N, 6.30. Found: C, 70.19; H, 5.52; N, 6.23.

2-(*t*-Butyldiphenylsilyloxy)-1-phenyl-*N*-[1-(phenylsulfonyl)-3-indolylmethylene]ethylamine (34). To a solution of indole-3-carbaldehyde **27** (672 mg, 2.36 mmol) in dry toluene (100 ml) amine **25** (810 mg, 1.57 mmol) and 4Å molecular sieves were added. The mixture was stirred for 30 min at room temperature under N_2 atmosphere, and refluxed for 16 h. The mixture was cooled, filtered and the solvent evaporated to give an oil which was flash chromatographed (hexane-AcOEt, 8:2) yielding pure imine **34** (460 mg, 45%): $[\alpha]_D$= +14° (c = 0.5, CH_2Cl_2); IR (CCl_4) 1650 (CH=N) cm^{-1}; ^1H NMR 1.00 (s, 9H, SiMe3), 3.90 (m, 2H, CH_2O), 4.45 (m, 1H, CHPh), 7.15 (t, *J* = 7 Hz, 1H, ArH), 7.25-7.65 (m, 21H, ArH), 7.85 (d, *J* = 7 Hz, 2H, ArH), 8.00 (d, *J* = 7 Hz, 1H, In-7H), 8.60 (s, 1H, CH=N); ^{13}C NMR 19.2 (*C*(CH$_3$)$_3$), 26.9 (C(*C*H$_3$)$_3$), 66.9 (CH_2O), 77.8 (CHPh), 113.3 (In-C7), 123.8, 124.3, 125.7, 126.8, 127.3, 127.5, 127.7, 128.4, 129.4, 129.5, 129.6, 130.0, 134.1, 135.6, and 141.1 (Ar), 154.5 (CH=N); MS *m/z* (%) 643 (M^+, 0.5), 586 (60), 502 (3), 438 (8), 374 (24), 373 (87). Anal. Calcd for $C_{39}H_{38}O_3N_2SSi$: C, 70.9; H, 6.06; N, 4.24. Found: C, 71.10; H, 6.38; N, 3.93.

(2R,4R)* and *(2S,4R)* 4-Phenyl-2-[1-(phenylsulfonyl)-2-indolyl]-3-[3-(trimethylsilyl-methyl)-3-butenyl]-1,3-oxazolidines (38a,b).** To a solution of 1-(phenylsulfonyl)indole-2-carbaldehyde **37** (514 mg, 1.8 mmol) in dry CH_2Cl_2 (10 ml) amine **21** (500 mg, 1.8 mmol) and anhydrous Na_2SO_4 were added. The mixture was stirred for 1 h at room temperature under N_2 atmosphere, and refluxed for 48 h. The reaction mixture was cooled, filtered and the solvent evaporated to yield a mixture of oxazolidines **38** (979 mg), which was flash chromatographed (hexane-CH_2Cl_2, 1;1) to isolate the diastereomers in a 5:1 proportion. **Oxazolidine 38a *(2R,4R) (lower Rf, 810 mg, 82%): $[\alpha]_D$ = +101.4° (c = 0.14, CH_2Cl_2); IR (NaCl) 1620 (=CH_2) cm^{-1}; ^1H NMR (500 MHz) 0.11 (s, 9H, SiC*H*3), 1.61 (s, 2H, C*H*2SiMe3), 1.97 (m, 2H, =CCH_2), 2.90 (m, 2H, CH_2N), 3.73 (t, *J* =9 Hz, 1H, CH_AO), 4.13 (dd, *J* =9 and 6 Hz, 1H, CHPh), 4.26 (dd, *J* =9 and 6 Hz, 1H, CH_BO), 4.41 and 4.48 (2s, 1H each, =CH_2), 6.18 (s, 1H, OCHN), 7.29 (t, *J* = 7.5 Hz, 1H, In-5H), 7.33 (s, 1H, In-3H), 7.36 (t, *J* = 7.5 Hz, 2H, In-6H), 7.42-7.62 (m, 7H, ArH), 8.07 (d, *J* = 8 Hz, 2H, Ar-*o*), 8.16 (d, *J* = 8 Hz, 1H, In-7H); ^{13}C NMR -1.5 (SiMe3), 27.2 (*C*H2SiMe3), 36.9 (=*C*CH_2), 51.8 (CH_2N), 68.6 (CHPh), 72.5 (CH_2O), 90.3 (OCHN), 107.7 (=CH_2), 111.8 (In-C3), 114.6 (In-C7), 121.4 (In-C4), 123.5 (In-C5), 124.9 (In-C6), 127.1, 127.6, 127.8, 128.6, 128.8, 133.5, 138.0, 140.0, 142.0, and 145.0 (Ar); MS *m/z* (%) 417 (14), 277 (10), 246 (1), 132 (100). Anal. Calcd for $C_{31}H_{36}N_2O_3SSi$: C, 68.37; H, 6.61; N, 5.14. Found: C, 68.91; H, 6.85; N, 5.07. **Oxazolidine 38b *(2S,4R)*** (higher Rf, 162 mg, 16%): $[\alpha]_D$ = -23.1 (c = 0.16, CH_2Cl_2); ^1H NMR 0.10 (s, 9H, SiC*H*3), 1.20 (s, 2H, C*H*2SiMe3), 2.10-2.30 (m, 2H, =CCH_2), 2.70-2.80 (m, 1H, NCH_A), 2.90-3.00 (m, 1H, NCH_B), 3.80-4.00 (m, 2H, OCH_A and OCH_B), 4.40 and 4.65 (2s, 1H each, =CH_2), 4.95 (t, *J* = 7 Hz, 1H, CHPh), 5.30 (s, OCHN), 6.65 (s, 1H, In-3H), 7.10-7.70 (m, 12 H, Ar-H), 7.73 (d, *J* = 7 Hz, 1H, In-4H), 8.25 (d, *J* = 7 Hz, In-7H).

***(2S,αR)* and *(2R,αR)*-1-(1-Phenyl-2-hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-methylene-piperidines (14a,b).** To a solution of anhydrous *p*-TsOH (1.8 mmol) in dry C_6H_6 (20 ml), a solution of oxazolidines **38a,b** (5:1, 979 mg) in dry C_6H_6 (20 ml) and anhydrous Na_2SO_4 were added. The mixture was refluxed for 1.5 h under N_2 atmosphere. The crude reaction mixture was filtered and the solvent evaporated furnishing an oil which was dissolved in CH_2Cl_2 and washed several times with 10% aqueous Na_2CO_3. The organic layer was dried and evaporated to give a residue which was flash chromatographed (Et_2O-hexane, 1:1) yielding pure isomers **14a** and **14b**. **Piperidine 14a** (higher Rf, 216 mg, 25%): $[\alpha]_D$= -25.3° (c = 0.28, CH_2Cl_2); IR (KBr) 3600-3200 (OH), 1673 (=CH_2) cm^{-1}; ^1H NMR (500 MHz) 2.37 (m, 4H, 3-H and 5-H), 2.96 (m, 1H, 6-H), 3.12 (m, 1H, 6-H), 3.99 (dd, *J* =13.4 and 8.8 Hz, 1H, C*H*$_A$OH), 4.16 (m, 2H, C*H*$_B$OH and CHPh), 4.60 and 4.83 (2s, 1H each, =CH_2), 5.10 (t, *J* =5 Hz,1H, 2-H_e), 6.83 (s,1H, In-3H), 7.31-7.71 (m, 11H, ArH), 7.91 (d, *J* = 7.5 Hz, 2H, Ar-*o*), 8.45 (d, *J* = 8 Hz, 1H, In-7H); ^{13}C NMR 34.4 (C-5), 42.6 (C-3), 45.2 (C-6), 57.1 (CHPh), 61.5 (CH_2OH), 64.7 (C-2), 109.1 (=CH_2), 111.2 (In-C3), 115.3 (In-C7), 120.7 (In-C4), 123.8 (In-C5), 124.5 (In-C6), 126.4, 126.9, 127.9, 128.1, 129.3, 133.9, 137.2, 139.5, and 142.5 (Ar), 144.1 (*C*=CH_2); MS *m/z* (%) 441 (10), 301 (6). **Piperidine 14b** (lower Rf, 289 mg, 34%): $[\alpha]_D$= -140.4° (c = 0.26, CH_2Cl_2); IR (KBr) 3800 -3400 (OH), 1641 (=CH_2) cm^{-1}; ^1H NMR (500 MHz) 1.14-2.14 (m, 3H, 3-H and 5-H), 2.14-2.26 (m, 2H, 5-H and 6-H_a), 3.06 (dt, *J* =10.6 and 4 Hz, 1H, 6-H_e), 3.41 (dd, *J* = 10 and 5 Hz, 1H, C*H*$_A$OH), 3.92 (t, *J* = 10 Hz, 1H, CHPh), 4.07 (dd, *J* = 10 and 5 Hz, 1H, C*H*$_B$OH), 4.37 and 4.51 (2s, 1H each, =CH_2), 4.44 (t, *J* = 6.8 Hz, 1H, 2-H_e), 6.84 (s, 1H, In-3H), 6.99-7.07 (m, 2H, ArH), 7.13-7.30 (m, 7H, ArH), 7.42 (m, 2H, ArH),

7.56 (d, J = 7.5 Hz, 2H, Ar-*o*), 8.18 (d, J = 7.7 Hz, 1H, In-7H); ^{13}C NMR 34.1 (C-5), 44.0 (C-3), 46.3 (C-6), 57.2 (CHPh), 60.1 (CH_2OH), 62.6 (C-2), 108.5 (=CH_2), 111.5 (In-C3), 115.3 (In-C7), 121.0 (In-C4), 123.9 (In-C5), 124.6 (In-C6), 126.1, 127.9, 128.0, 129.2, 129.5, 133.8, and 134.7 (Ar), 143.9 (*C*=CH_2); MS *m/z* (%) 442 (23), 441 (76), 331 (11), 300 (14). Anal. Calcd for $C_{28}H_{28}N_2O_3S.2H_2O$: C, 66.12; H, 6.29; N, 5.51. Found: C, 66.12; H, 6.23; N, 5.21.

1-[(2-Allyloxy-1-phenyl)ethyl]-2-[1-(phenylsulfonyl)-2-indolyl]-4-methylenepiperidines (39a,b). To a solution of indole-2-carbaldehyde **37** (77 mg, 0.27 mmol) in dry CH_2Cl_2 (5 ml), a solution of amine **24** (86 mg, 0.27 mmol) in dry CH_2Cl_2 (2 ml), 4Å molecular sieves and anhydrous Na_2SO_4, were added. The mixture was stirred for 18 h at room temperature under N_2 atmosphere, and refluxed for 20 h. The mixture was cooled, filtered and the solvent evaporated to give an oil which was flash chromatographed (CH_2Cl_2-hexane, 7:3) yielding pure isomers **39a** and **39b**. **Piperidine 39a** (higher Rf, 25 mg, 18%): $[\alpha]_D$= +20° (c = 0.3, CH_2Cl_2); IR ($CHCl_3$) 1668 (=CH_2) cm^{-1}; ^{1}H NMR 2.20 (m, 3H, 3-H and 5-H), 2.25 (m, 1H, 3-H), 2.55 (m, 1H, 6-H_a) 3.00 (dt, J = 12.6 and 5 Hz, 1H, 6-H_e), 3.80 (dd, J =9.5 and 6.3 Hz, 1H, CH_AO), 3.95 (dd, J = 9.5 and 5 Hz, 1H, CH_BO), 4.00 (dd, J = 6.3 and 1.5 Hz, 2H, CH_2CH=), 4.10 (t, J = 5 Hz, 1H, CHPh), 4.50 and 4.65 (2s, 1H each, C=CH_2), 4.85 (dd, J = 7.5 and 5 Hz, 1H, 2-H_e), 5.20 (m, 2H, CH=CH_2), 5.90 (m, 1H, C*H*=CH_2), 6.80 (s, 1H, In-3H), 7.10-7.60 (m, 11H, ArH), 7.80 (d, J = 7.6 Hz, 2H, Ar-*o*), 8.20 (d, J = 7.6 Hz, 1H, In-7H); ^{13}C NMR 34.3 (C-5), 44.0 (C-3), 47.0 (C-6), 58.0 (C-2), 60.8 (CHPh), 68.5 (CHPhCH_2O), 72.2 (CH_2CH=), 108.4 (C=CH2), 110.0 (In-C3), 115.2 (In-C7), 117.1 (CH=CH2), 120.8 (In-C4), 123.7 (In-C5), 124.3 (In-C6), 126.5, 126.7, 127.8, 128.0, 129.2, 133.7, 134.7, 138.0, 144.5; MS *m/z* (%) 512 (M^+), 441. Anal. Calcd for $C_{31}H_{32}N_2O_3S$: C, 72.65; H, 6.25; N, 5.47; S, 6.25. Found: C, 72.30; H, 6.37; N, 5.28; S, 5.93. **Piperidine 39b** (lower Rf, 22 mg, 16%): $[\alpha]_D$= -63.1° (c = 0.16, CH_2Cl_2); IR (NaCl) 1671 (=CH_2) cm^{-1}; ^{1}H NMR 2.29 (m, 4H, 3-H, 5-H, 6-H_a), 2.42 (dd, J = 15.2 and 5 Hz, 1H, 3-H), 3.00 (m, 1H, 6-H_e), 3.60 (dd, J = 10 and 5 Hz, 1H, CH_AO), 3.90 (m, 3H, CH_BO and CH_2CH=), 4.25 (t, J = 5 Hz, 1H, CHPh), 4.51 and 4.63 (2s, 1H each, C=CH_2), 4.75 (t, J = 5 Hz, 1H, 2-H_e), 5.10 (m, 2H, CH=CH_2), 5.80 (m, 1H, C*H*=CH_2), 7.00 (s, 1H, In-3H), 7.21-7.32 (m, 7H, ArH), 7.36 (t, J = 7.5 Hz, 2H, Ar-*m*), 7.50 (m, 2H, ArH), 7.62 (d, J = 7.5 Hz, 2H, Ar-*o*), 8.18 (d, J = 8 Hz, 1H, In-7H).

1-[(2-*t*-Butoxy-1-*t*-butoxycarbonyl)ethyl]-2-[1-(phenylsulfonyl)-3-indolyl]-4-methylenepiperidines (40a,b). To a solution of aldehyde **27** (643 mg, 2.25 mmol) in dry CH_2Cl_2 (15 ml), amine **22** (765 mg, 2.14 mmol), anhydrous Na_2SO_4 and 4Å molecular sieves were added. The mixture was refluxed for 12 h. The mixture was cooled, filtered, evaporated and the residue was flash chromatographed (Hexane:AcOEt, 75:25), yielding a mixture of diastereomeric piperidines **40a,b** (750 mg, 63%): ^{1}H NMR (500 MHz) 1.12 and 1.33 (2s, 9H each, $C(CH_3)_3$), 2.23 (t, 1H, 3-H_e), 2.29 (1H, 5-H_a), 2.35 (m, 1H, 5-H_e), 2.51 (td, J = 2.5 and 11.25 Hz, 1H, 6-H_a), 2.57 (1H, 3-H_a), 3.21 (dt, J = 3 and 11.25 Hz, 1H, 6-H_e), 3.41 (dd, J = 5 and 7.75 Hz, 1H, CHN), 3.44 (dd, J = 5 and 8.75 Hz, 1H, CH_AO), 3.59 (1H, CH_BO), 4.07 (dd, J = 3.5 and 10.5 Hz, 1H, 2-H_a), 4.61 and 4.69 (2s, 1H each, =CH_2), 7.15 (td, J = 1 and 7.75, 1H, ArH), 7.25 (1H, ArH), 7.39 (2H, ArH), 7.47 (2H, ArH), 7.84 (2H, ArH), 7.91 (2H, ArH);^{13}C NMR (500 MHz) 27.4 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 35.0 (C-5), 42.7 (C-3), 48.2 (C-6), 58.6 (CH_2O), 59.7 (C-2), 62.1 (CHN), 72.9 ($CO_2C(CH_3)_3$), 80.3 ($OC(CH_3)_3$), 107.9 (=CH_2), 146.2 (C-4), 171.3 (CO).

1-[(2-Hydroxy-1-methoxycarbonyl)ethyl]-2-[1-(phenylsulfonyl)-2-indolyl]-4-methylenepiperidines (15a,b). To a solution of indole-2-carbaldehyde **37** (104 mg, 0.36 mmol) in dry CH_2Cl_2 (4 ml), a solution of amine **23** (95 mg, 0.36 mmol) in dry CH_2Cl_2 (4 ml) and 4Å molecular sieves were added. The reaction mixture was stirred for 16 h at room temperature under N_2 atmosphere and refluxed for 48 h. The mixture was cooled, filtered and evaporated furnishing an oil which was flash chromatographed (CH_2Cl_2-hexane, 7:3) yielding pure isomers **15. Piperidine 15a** (higher Rf, 24 mg, 14%): $[\alpha]_D$= -87.8° (c = 0.32, CH_2Cl_2); IR (NaCl) 3800 -3300 (OH), 1731 (C=O) cm^{-1}; ^1H NMR (500 MHz) 2.15 (t, *J* = 11 Hz, 1H, 3-H_a), 2.29 (m, 2H, 5-H), 2.36 (d, *J* = 11.5 Hz, 1H, 3-H_e), 2.60 (td, *J* = 10.7 and 5 Hz, 1H, 6-H_a), 3.07 (dt, *J* = 10 and 2.5 Hz, 1H, 6-H_e), 3.68 (s, 3H, CH_3), 3.70 (m, 2H, CH_2OH), 3.75 (m, 1H, $CHCOOCH_3$), 4.61 and 4.72 (2s, 1H each, $=CH_2$), 4.90 (dd, *J* = 10 and 2.5 Hz, 1H, 2-H_a), 6.75 (s, 1H, In-3H), 7.23 (t, *J* = 7.5 Hz, 1H, In-5H), 7.29 (t, *J* = 8.5 Hz, 1H, In-6H), 7.39 (t, *J* = 7.5 Hz, 2H, Ar-*m*), 7.47 (d, *J* = 8 Hz, 1H, In-4H), 7.52 (t, *J* = 8 Hz, 1H, Ar-*p*), 7.75 (d, *J* = 7.5 Hz, 2H, Ar-*o*), 8.17 (d, *J* = 8.5 Hz, 1H, In-7H); ^{13}C NMR 34.5 (C-5), 44.5 (C-3), 47.1 (C-6), 51.3 (CH_3), 58.5 (C-2), 58.8 (CH_2OH), 61.4 ($CHCOOCH_3$), 109.1 ($=CH_2$), 110.3 (In-C3), 115.1 (In-C7), 120.9 (In-C4), 123.8 (In-C5), 124.6 (In-C6), 126.4 (Ar-*o*), 129.2 (Ar-*m*), 133.7 (Ar-*p*), 142.9, 143.9, 171.2 ($COOCH_3$); MS *m/z* (%) 455 (M^++1, 1), 425 (5), 424 (16), 423 (59), 396 (9), 395 (34), 313 (47). Anal. Calcd for $C_{24}H_{26}O_5N_2S.H_2O$: C, 61.01; H, 5.93; N, 5.93; S, 6.77. Found: C, 61.45; H, 5.82; N, 5.70; S, 6.61. **Piperidine 15b** (lower Rf, 20 mg, 12%): $[\alpha]_D$= +3.63 (c = 0.22, CH_2Cl_2); ^1H NMR (500 MHz) 2.22 (d, *J* = 6 Hz, 1H, 3-H), 2.25 (d, *J* = 6 Hz, 1H, 5-H), 2.32 (m, 1H, 5-H), 2.47 (dd, *J* = 13 and 5 Hz, 1H, 3-H), 2.78 (m, 1H, 6-H),3.02 (m, 1H, 6-H), 3.38 (s, 3H, CH_3), 3.61 (m, 1H, CH_AOH), 3.73 (m, 1H, CH_BOH), 3.82 (m, 1H, $CHCOOCH_3$), 4.59 and 4.75 (2d, 1H each, $=CH_2$), 4.89 (t, *J* = 5 Hz, 1H, 2-H_e), 6.86 (s, 1H, In-3H), 7.22 (t, *J* = 7.5 Hz, 1H, In-5H), 7.29 (t, *J* = 8 Hz, 1H, In-6H), 7.39 (t, *J* = 8 Hz, 2H, Ar-*m*), 7.44 (d, *J* = 7.5 Hz, 1H, In-4H), 7.52 (t, *J* = 7.5 Hz, 1H, Ar-*p*), 7.66 (d, *J* = 7 Hz, 2H, Ar-*o*), 8.23 (d, *J* = 8.5 Hz, 1H, In-7H); ^{13}C NMR 34.4 (C-5), 41.4 (C-3), 44.4 (C-6), 51.6 (CH_3), 56.4 (C-2), 58.9 (CH_2OH), 64.5 ($CHCOOCH_3$), 109.9 ($=CH_2$), 111.9 (In-C3), 115.5 (In-C7), 120.9 (In-C4), 123.9 (In-C5), 124.7 (In-C6), 126.2 (Ar-*o*), 129.2 (Ar-*m*), 133,8 (Ar-*p*), 143.3 ($C=CH_2$), 172.7 ($COOCH_3$).

***(2R,7aS)*-6-Methylene-2-phenyl-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1´,2´:1,2]-pyrazino-[4,3-*a*]indole (42).** To a solution of alcohol **14a** (200 mg, 0.42 mmol) in dry THF (3 ml) recently sublimed K^{t}BuO (104 mg, 0.93 mmol) was added portionwise, at 0°C under N_2 atmosphere. The mixture was stirred at 0°C for 30 min, poured on aqueous NH_4Cl, and extracted with Et_2O. The organic layers were dried and evaporated to give an oil which was flash chromatographed (CH_2Cl_2-hexane, 7:3) yielding **42** (76 mg, 57%): $[\alpha]_D$= +61° (c = 0.42, CH_2Cl_2); IR (NaCl) 1656 ($=CH_2$) cm^{-1}; ^1H NMR 2.19 (ddd, *J* = 13, 4.5 and 2.5 Hz, 1H, 5-H_e), 2.32 (dd, *J* = 10.75 and 2.5 Hz, 1H, 4-H_e), 2.37 (*J* = 13, 3.25 and 1 Hz, 1H, 5-H_a), 2.46 (t, *J* = 13 Hz, 1H, 7-H_a), 2.74 (ddd, *J* = 13.25, 3.5 and 1.5 Hz, 1H, 7-H_e), 3.06 (ddd, *J* = 10.75, 4.25 and 2.5 Hz, 1H, 4-H_a), 3,56 (dd, *J* = 10.75 and 2.5 Hz, 1H, 7a-H_a), 4.32 (dd, *J* =5 and 2.5 Hz, 1H, 2-H_e), 4.37 (dd, *J* =11.75 and 2.5 Hz, 1H, 1-H_e), 4.51 (dd, *J* = 11.75 and 5 Hz, 1H, 1-H_a), 4.67 and 4.74 (2d, 1H each, $=CH_2$), 6.31 (s, 1H,8-H), 7.00 (t, *J* = 2 Hz, 1H, ArH), 7.01 (t, *J* = 1.5 Hz, 1H, ArH), 7.13 (td, *J* =7.5 and 1.5 Hz, 1H, 10-H), 7.17 (td, *J* = 7.25 and 1.5 Hz, 1H, 11-H), 7.20-7.25 (m, 3H, ArH), 7.28 (d, *J* =7.5 Hz, 1H, 12-H), 7.62 (d, *J* = 7.5 Hz, 1H, 9-H); ^{13}C NMR 33.8 (C-5), 39.9 (C-7), 46.6 (C-1), 52.9 (C-4), 54.6 (C-7a), 60.7 (C-2), 96.0 (C-8), 108.8 ($=CH_2$), 108.8 (C-12), 119.9 (C-10), 120.1 (C-9), 120.6 (C-

11), 127.9, 128.3, 128.7, 136.4 (C-7b), 138.2 (C-12a), 144.7 (*C*=CH_2); MS *m/z* (%) 314 (M^+, 100), 299 (7), 257 (14), 245 (43). Anal. Calcd for $C_{22}H_{22}N_2.H_2O$: C, 79.52; H, 7.23; N, 8.43. Found: C, 79.03, H, 6.81; N, 8.17.

***(2S,7aS)*-6-Methylene-2-phenyl-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1′,2′:1,2]-pyrazino-[4,3-*a*]indole (46).** A solution of pyrazinoindole **42** (48 mg, 0.15 mmol) in MeOH (11 ml) and 4N HCl (11 ml) was refluxed for 3 h. Once cooled, the solution was neutralized by careful addition of solid Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and evaporated to give an oil which was flash chromatographed (CH_2Cl_2-hexane, 7:3) yielding compound **46** (31 mg, 65%): $[\alpha]_D$= -32° (c = 0.1, CH_2Cl_2); ^{1}H NMR 1.86 (dddd, *J* = 13, 10, 3 and 1.5 Hz, 1H, 4-H_a), 2.18 (dq, *J* = 13 and 3 Hz, 1H, 5-H_e), 2.30 (td, *J* = 13 Hz, 1H, 5-H_a), 2.55 (td, *J* = 13 and 1.5 Hz, 1H, 7-H_a), 2.91 (ddd, *J* = 13, 5 and 3 Hz, 1H, 4-H_e), 2.94 (dt, *J* = 13 and 3 Hz, 1H, 7-H_e), 3.50 (dd, *J* = 11.5 and 2 Hz, 1H, 7a-H_a), 3.74 (dd, *J* = 11.5 and 4 Hz, 1H, 2-H_a), 4.00 (t, *J* = 11.5 Hz, 1H, 1-H_a), 4.23 (dd, *J* = 11.5 and 4 Hz, 1H, 1-H_e), 4.76 and 4.85 (2d, *J* = 2 and 1.5 Hz, 2H, =CH_2), 6.31 (s, 1H, 8-H), 7.08 (dd, *J* = 7 and 1 Hz, 1H, 10-H), 7.11 (t, *J* =2 Hz, 1H, ArH), 7.13 (dd, *J* = 7 and 1.5 Hz, 1H, ArH), 7.18 (dd, *J* = 7.8 and 1.5 Hz, 1H, ArH), 7.35-7.48 (m, 4H, ArH), 7.58 (dt, *J* = 8 and 1 Hz, 1H, 9-H);^{13}C NMR 34.3 (C-5), 39.3 (C-7), 49.3 (C-1), 53.0 (C-4), 61.4 (C-7a), 66.0 (C-2), 95.6 (C-8), 108.6 (C-12), 108.8 (=CH_2); 119.9 (C-10), 120.2 (C-9), 120.8 (C-11), 128.3 (Ar), 128.9 (Ar), 135.7 (C-7b), 137.0 (C-12a), 139.9 (Ar-ipso), 145.0 (*C*=CH_2); MS *m/z* (%): 314 (M^+, 100), 299 (3), 245 (36). Anal. Calcd for $C_{22}H_{22}N_2.H_2O$: C, 79.52; H, 7.23; N, 8.43. Found: C, 79.70; H, 6.89; N, 8.75.

ACKNOWLEDGEMENTS

Support for this research has been provided by the CIRIT (Generalitat de Catalunya) through grant QFN92-4303.

REFERENCES AND NOTES

1. For part VII, see: Diez, A.; Vila, C.; Rubiralta, M. *Tetrahedron*, **1993**, *49*, 4063-4072.
2. a) Rubiralta, M.; Diez, A.; Vila, C.; Troin, Y.; Feliz, M. *J. Org. Chem.* **1991**, *56*, 6292-6298; b) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.*, **1989**, *54*, 5591-5597.
3. Diez, A.; Miguel, D.; Vila, C.; Rubiralta, M.; Remuson, R.; Gelas-Miahle, Y. *Heterocycles*, **1992**, *34*, 13-16.
4. Rubiralta, M.; Diez, A.; Miguel, D.; Remuson, R.; Gelas-Miahle, Y. *Synth. Commun.*, **1992**, *22*, 359-367.
5. Rubiralta, M.; Diez, A.; Vila, C.; Castells, J.; López, I. *Heterocycles*, **1992**, *34*, 643-650.
6. a) Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P. *J. Am. Chem. Soc.*, **1983**, *105*, 7754-7755; b) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991, pp. 272-281.
7. The same reaction sequence was carried out starting from 2-ethyl-3-trimethylsilylmethyl-3-butenol. Tosylation and treatment with *(R)*-(-)-phenylglycinol furnished the expected aminoallylsilane in only 13% yield.
8. The fact that oxazolidines **38** were stable and presented no manipulation problem indicates that the electron

withdrawing effect of the protected 3-indolyl substituent when attached on the oxazolidine 2-position must be responsible for the instability of **31**.

9. Since the stereoselective formation of oxazolidines from iminium salts had been described as solvent-dependent,[10] other reaction conditions using EtOH as the solvent were assayed, which led to the same results.
10. a) Agami, C.; Rizk, T. *Tetrahedron*, **1985**, *41*, 537-540; b) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211-4214.
11. The structure of imines **32** and **33** was confirmed by synthesis. Condensation between aldehyde **27** and *(R)*-(-)-phenylglycinol afforded *trans* -imine **32** in 90% yield. Its protection by treatment with NaH and allylbromide furnished imine **33**.
12. For ring-chain tautomerism of 1,3-oxazolidines, see: a) Fülöp, F.; Bernáth, G.; Mattinen, J.; Pihlaja, K. *Tetrahedron*, **1989**, *45*, 4317-4324; b) Parkkinen, A.; Fülöp, F.; Pihlaja, K. *Acta Chemica Scandinava*, **1990**, *44*, 364-367; c) Fülöp, F.; Lázár, L.; Bernáth, G.; Sillanpää, R.; Pihlaja, K. *Tetrahedron*, **1993**, *49*, 2115-2122.
13. Rubiralta, M.; Luque, J.; Orozco, M.; Diez, A.; López, I. *Heterocycles*, **1992**, *34*, 449-456.
14. All assignments were confirmed by 2D COSY (H,H) and (H,C) experiments, and decoupling experiments. Thus, irradiation at δ 4.20 in the ^{1}H NMR spectrum of **35a**, showed a simplification of the triplet (δ 2.70) corresponding to 3-H_a. The benzylic α-H was located in the multiplet at δ 3.90, where the allylic protons mask part of the ABM system characteristic of the phenylglycinol derivatives.
15. Even if we indicate the probable stereochemistry of compounds **35a** and **35b**, it has not been confirmed yet.
16. Piperidine **9** was stable under treatment with *n*-BuLi in THF at 0°C. Since *n*-BuLi does not cleave the indole *N*-phenylsulfonyl protecting group, only the reaction intermediates had to be affected by the base. Furthermore, since the formation of the spiroindolenine was not detected, the phenylsulfonylated intermediate is probably the sensitive species.
17. Piperidine **10** was prepared by alkylation of 2-(1-phenylsulfonyl-3-indolyl)-4-methylenepiperidine[4] with phenyloxirane (see experimental part).
18. a) Zhang, L.-H.; Gupta, A.K.; Cook, J.M. *J. Org. Chem.*, **1989**, *54*, 4708-4712; b) Gaskell, A.J.; Joule, J.A. *Tetrahedron*, **1967**, *23*, 4053-4063.
19. Dauber-Osguthorpe, P.; Roberts, V.A.; Osguthorpe, D.J.; Wolff, J.; Genest, M.; Hangler, A. T. *Proteins: Structure, Function and Genetics*, **1988**, *4*, 31.
20. Hagler, A. T.; Stern, P.S.; Sharon, R.; Becker, J. M.; Najder, F. *J. Am. Chem. Soc.*, **1979**, *101*, 6842.
21. Discover. BIOSYM Technologies, Co., 1991.

(*Received in UK* 29 *March* 1995; *revised* 10 *May* 1995; *accepted* 12 *May* 1995)