Pergamon

Tetrahedron Vol. 50, No. 44, pp. 12713-12726, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00805-1

Syntheses of 3-Phenyl Substituted Indolizidin-2-ones and a Pyrrolizidin-2-one on the Route to Constrained Potential NK_1 Receptor Antagonists

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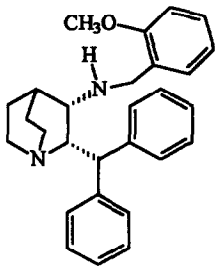
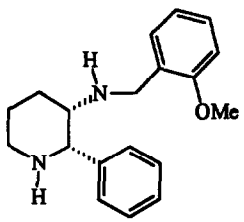
Abstract: 5-Benzoyl substituted isoxazolidines **3a,b** and **4a,b**, obtained by 1,3-dipolar cycloadditions of pyrroline N-oxide and tetrahydropyridine N-oxide to phenyl vinyl ketone, undergo a rearrangement to 3-phenyl-2,5,6,7-tetrahydro-3H-pyrrolizin-2-one and 3-phenyl-2,3,5,6,7,8-hexahydroindolizin-2-one, catalysed by Al_2O_3, followed by a Michael addition to a second molecule of phenyl vinyl ketone. Isoxazolidines **3a,b**, in presence of an excess of phenyl vinyl ketone, undergoes another rearrangement to a 6,7-dibenzoylindolizidin-7-ol (**21**) by a non-reductive isoxazolidine ring cleavage. Isoxazolidines **4a,b** do not undergo this second rearrangement, but give the expected 3-phenyl-indolizidin-2-one (**2**), as a single diastereoisomer, by reductive N-O bond cleavage with $Mo(CO)_6$. The reaction mechanism for the new rearrangements are discussed.

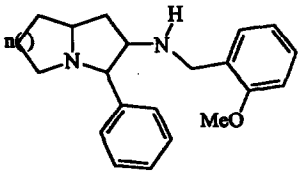
In the last years several non-peptidic NK_1 receptor antagonists[1] have been extensively studied for their potential usefulness in many pathological conditions. CP-96345[2] and CP-99994[3] are among the most potent NK_1 receptor antagonists known up to day, and may represent the prototypes of a class of structures containing aza-heterocyclic rings as the main skeleton.



CP-96345



CP-99994



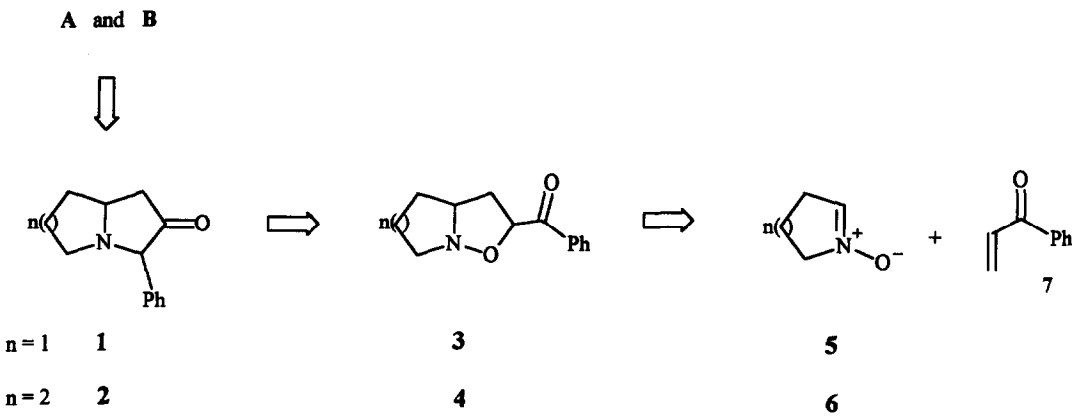
n = 1 **A**

n = 2 **B**

Due to the widespread occurrence of pyrrolizidine and indolizidine skeletons throughout many families of biologically active compounds and our ongoing interest in the synthesis and application of N-bridgehead azaheterocycles,[4] we envisioned structures of type **A** or **B** (n = 1, 2) as constrained analogues of both CP-96345 and CP-99994, which could represent, whether or not potent NK_1 receptor antagonists, powerful tools for the development of a pharmacophoric model.

We, therefore, planned the synthesis of compounds **A** and **B** in a racemic form starting from the 3-phenyl substituted pyrrolizidin-2-one (n=1) **1** and indolizidin-2-one (n=2) **2** which could be synthesized through the methodology, novel for this class of N-bridgehead compounds, described in the following retrosynthetic scheme (Scheme 1).[5] It consists of a 1,3-dipolar cycloaddition of a cyclic (five or six membered) nitrone to phenyl vinyl ketone followed by a reductive cleavage of the N-O bond in the isoxazolidines **3** (or **4**) and an *in situ* intramolecular condensation of the resulting ketoamine. The only one close precedent of this methodology, to the best of our knowledge, was found in a synthesis of 3-hydroxy proline by a japanese group.[6]

SCHEME 1

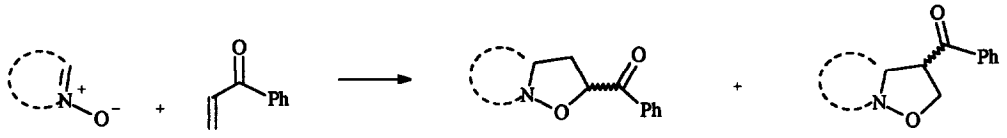


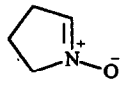
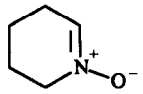
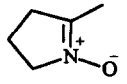
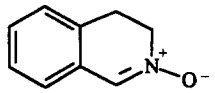
In contrast to the vast collection of the literature dealing with the 1,3-dipolar cycloadditions of nitrones with alkenes,[7] no reports were available, to the best of our knowledge, on the cycloadditions to phenyl vinyl ketone, whereas methyl vinyl ketone has received broader interest.[7,8] We have, then, studied briefly the cycloaddition of phenyl vinyl ketone (**7**) to cyclic nitrones **5**, **6**, **8** and **9**.

Phenyl vinyl ketone (**7**), easily available from the corresponding Mannich base,[9] reacted with the nitrones readily at room temperature affording rather complex mixtures of regioisomeric compounds (Table 1). The formation of 4-regioisomers (isoxazolidine numberings) is expected by FMO consideration, because of the strong electron-withdrawing character of the benzoyl group.[10] However, Tufariello in the cycloaddition of the nitrone **9** with methyl vinyl ketone obtained regioselectively a 5-acetyl isoxazolidine.[8] Each regioisomer was also present as a pair of diastereoisomers, deriving from an *exo* or *endo* approach of the reactants, but the *exo/endo* ratio was detectable from the ^1H NMR of the crude reaction mixture only for the 5-regioisomeric compounds and only tentatively assigned on the basis of the observation of the coupling pattern of the H5

(isoxazolidine numberings) resonance in the ^1H NMR spectrum (Table 1) in agreement with similar assignments made in the literature.[11] For example, in adduct **3a,b**, the *exo* product **3a** shows a triplet at δ 5.23 ppm (J=7.8 Hz) for the H5 (isoxazolidine numberings), whereas the *endo* product **3b** shows a doublet of doublet at δ 5.20 ppm (J=8.0, 5.6 Hz). The same applies for adducts **10a,b** and **11a,b**, whereas both 5-regioisomeric (isoxazolidine numberings) adducts **4a,b** show doublet of doublets. In this case the assignment of the *exo* stereochemistry to the major compound has been made by analogy. A better structure elucidation needed a careful separation of the isomers. But the separation and purification of the complex cycloaddition mixtures proved to be impracticable, by column chromatography, due to the very low stability shown by the adducts on silica gel, particularly of those from the five-membered nitrones. In all cases, enriched mixtures of the stereoisomers in lower amount and besides other rearrangement products were obtained.

TABLE 1



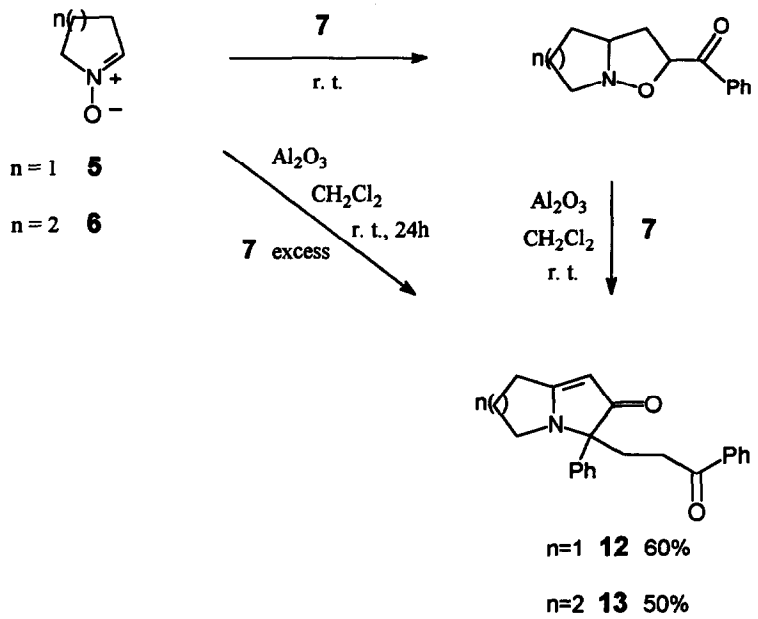
	Reaction condition	Regioisomeric 5:4 ratio	exo/endo ratio (5 regioisomer)	Yield %
 **5**	CH_2Cl_2, r.t, 12 h	6 : 1	**3a,b** 1.4 : 1	68
 **6**	CH_2Cl_2, r.t, 24 h	5 : 1	**4a,b** 2.5 : 1	33
 **8**	C_6H_6, r.t, 48 h	3 : 1	**10a,b** 5.6 : 1	71
 **9**	CH_2Cl_2, r.t, 24 h	1 : 1.5	**11a,b** 2.7 : 1	63

The observation of the low stability of the benzoyl isoxazolidines, particularly on treatment on silica gel, attracted our interest and prompted us to study various conditions to steer efficaciously the reactivity of the compounds. It was found that treatment of the isoxazolidines with an excess of phenyl vinyl ketone in the presence of neutral Alumina (Type I) gave the dehydro-pyrrolizidinone **12**

and indolizidinone **13** (Scheme 2). For synthetic purpose, it was found practical to run the cycloaddition of the nitrone with an excess of the phenyl vinyl ketone (4 ÷ 5 eq.) to obtain overall yields of 60% and 50% for **12** and **13**, respectively. Isoxazolidines **10** and **11** gave only decomposition products in the same conditions.

The structural assignment was based on the analysis of ^{1}H and ^{13}C NMR spectra. The enaminone mojety is evidenced by the presence of a singlet for the proton (at δ 5.10 ppm for **12** and δ 5.02 ppm for **13**) and appropriate resonances for C1 and C2 carbon atoms (δ 90.8 and 198.8 ppm for **12** and δ 95.7 and 199.1 ppm for **13**, respectively). The phenyl group resonances are also highly diagnostic for the assignment of the structure, showing two different phenyl groups, only one vicinal to a carbonyl. The data confirm the structures shown as products of the rearrangement of the 5-benzoyl isoxazolidine ring followed by a Michael addition to a second molecule of phenyl vinyl ketone, rearrangement unprecedented to the best of our knowledge. The only close precedent is the thermal rearrangement of *exo*-methylene isoxazolidines to pyrrolidinones discovered by Uccella and co-workers[12] and later reinvestigated by Tufariello and Padwa.[13] In the present case, however, the dehydropyrrolidinones are formed at room temperature by simple catalysis of alumina.

SCHEME 2

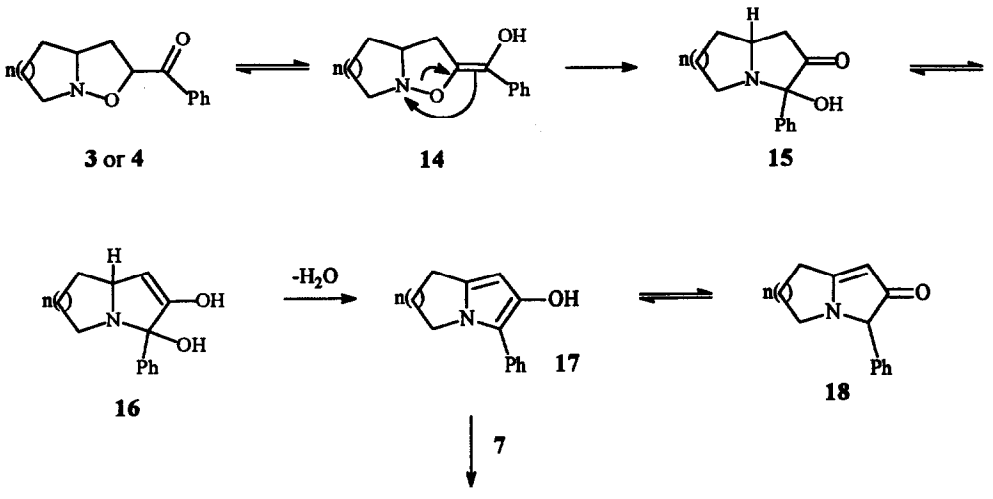


On this ground the mechanism shown in Scheme 3 can be proposed. The role of the alumina (or silica gel) could be to favour the enolisation of the ketone. The *exo*-methylene form **14** undergoes an isoxazolidine-pyrrolidine rearrangement to give the ketone **15** in equilibrium with the enol **16** (Scheme 3). Elimination of H_2O from this intermediate gives the hydroxy-pyrrole derivative **17** which is in equilibrium with the enaminone **18**. Finally **17** undergoes a Michael addition to a second molecule of phenyl vinyl ketone to give **12** or **13**. A similar reactivity of 3-hydroxy-pyrroles, like **17**,

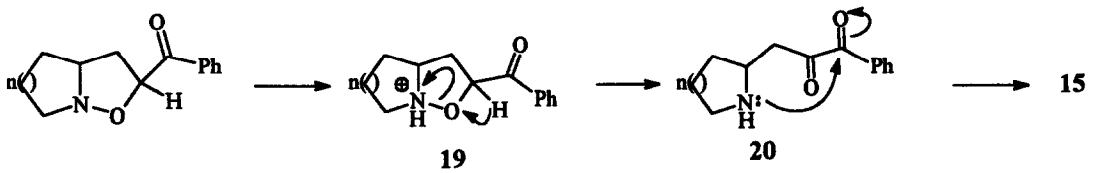
has been recently documented by Wasserman.[14]

The role of alumina (or silica gel) on the rearrangement suggests, however, a second mechanism for the formation of the ketol **15**. The coordination of a Lewis acid or a proton to the nitrogen is able to open the isoxazolidine ring *via* the transfer of the acidic proton α to the benzoyl group as shown in Scheme 4. The resulting diketone **20**, condenses to give the same ketol **15** of Scheme 3.

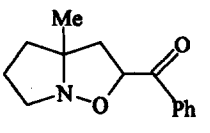
SCHEME 3



SCHEME 4



As a confirmation of the mechanisms proposed, the intermediate **18** (n = 1) derived from the isoxazolidines **3**, could be also observed *via* ^{1}H-NMR (characteristic synglets at δ 4.99 and 4.51 ppm for the H1 and H3 protons, respectively), although attempt of isolation failed for its very low stability. Moreover, the methyl substituted isoxazolidines **10** in the same conditions (alumina, excess phenyl vinyl ketone, methylene-chloride) underwent complete decomposition. These compounds, having a bridgehead methyl, cannot give the intermediate **17** (or **18**). However, from these data, a conclusion cannot be drawn on which of the two mechanism proposed is more likely.



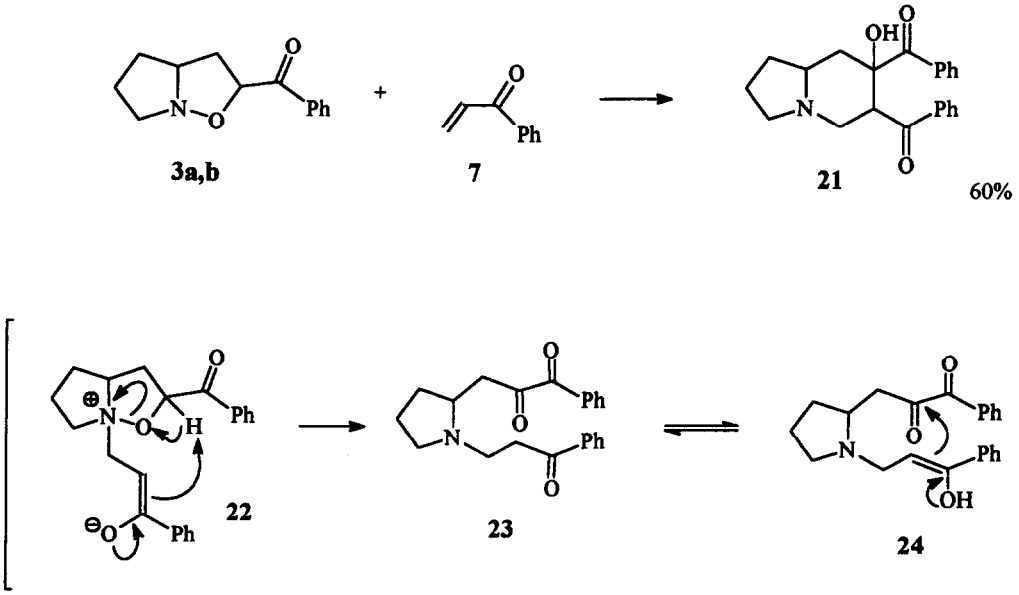
10

The pyrroleisoxazolidines **3**, as already pointed out, resulted rather unstable and reactive. In fact, in the presence of an excess of phenyl vinyl ketone, they undergo another unexpected transformation.

Upon treatment of the pyrroleisoxazolidines **3** with phenyl vinyl ketone **7** (one equivalent in benzene at room temperature, without alumina!) the indolizidine **21** was isolated in good yield (60%). It was also found that, on running the cycloaddition with an excess of **7** for a prolonged time, **21** was the only compound isolated. Structure assignment has been made on the basis of NMR experiment (^{1}H and ^{13}C) including COSY and HETCOR. The signal of H6 (dd at δ 4.49 ppm, J=11.8; 3.8 Hz) bonded with C6 (δ 48.0 ppm), the presence of two carbonyl resonances (δ 205.7 and 202.7 ppm) and the quaternary C7 resonance (δ 81.9 ppm) are highly diagnostic for the structure assignment. Moreover, the IR spectrum shows an absorption at 3414 cm^{-1}, typical of O-H stretching.

The formation of **21** seems to originate from a mechanism analogous to that shown in Scheme 4. An initial Michael addition of the isoxazolidine nitrogen to **7** should afford the isoxazolidinium enolate intermediate **22** which is able to abstract (intramolecularly or intermolecularly) the acidic proton α to benzoyl group to afford the triketone **23** with ring opening. Triketone **23** undergoes ring closure by an intramolecular aldol condensation (Scheme 5).

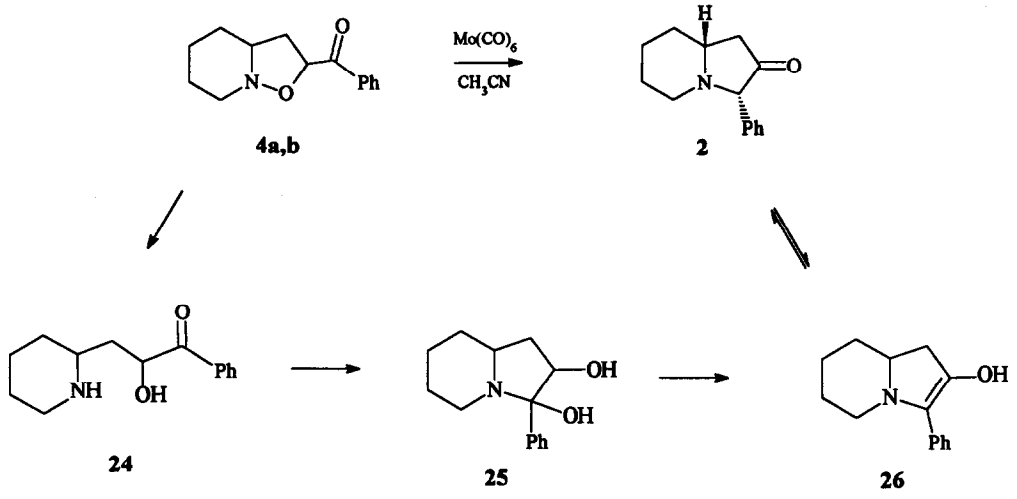
SCHEME 5



An analogy to this mechanism can be found in the non-reductive opening of isoxazolidinium salt caused by bases.[15] In our case the added base is not necessary because of the *in situ* formation of a strong enolate base, and the reaction does not require high temperature because of the intramolecular activation. However, the reaction is not of general applicability. Isoxazolidines **4a,b** don't give the analogous reaction, that is probably connected with the strain of a pyrroleisoxazoline structure, and methyl vinyl ketone, with isoxazolidines **3a,b**, leads to a complex reaction mixture.

Since the purification of cycloadducts by chromatography was inconvenient for a good chemical yield, the product of cycloadditions was used without purification for the synthesis of the target ketones **1** and **2**. Our hypothesis envisioned the reduction of N-O bond followed by *in situ* condensation of the amino-ketone **24** formed (Scheme 6). To achieve the selective N-O bond reduction it was used $Mo(CO)_6$ in refluxing acetonitrile containing 10% water, a methodology recently reported for the reductive cleavage of isoxazolidines.[16] In these conditions, the isoxazolidines **3a,b** failed to give the expected pyrrolizinone, affording only poor yield of unidentified products, whereas the isoxazolidines **4a,b** afforded a 45% yield (isolated, overall on two steps) of one single diastereoisomeric indolizidinone **2**.

SCHEME 6



Also isoxazolidines **10** and **11**, in the same conditions, failed to give the relative ketones, and afforded only complex mixtures of products. Ni-Raney, tested as a reducing agent, did not provide any reduction product in these cases.

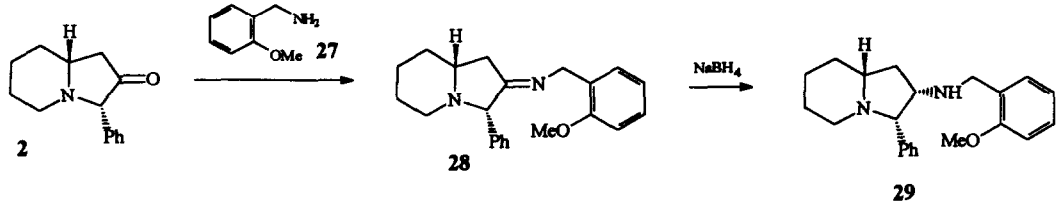
Ketone **2** shows a singlet at δ 3.46 ppm for H3 in the ^{1}H-NMR spectrum and a carbonyl (δ 212.2 ppm) and C3 (δ 76.3 ppm) resonances in the ^{13}C-NMR, diagnostic for the assignment. The *trans*-{H8a-Ph} relationship has been assigned on the basis of the observation of characteristic strong absorptions, at 2791 and 2756 cm^{-1} in the IR spectrum, known as Bohlmann's bands,[17] and associated with the number of axial protons antiperiplanar with the nitrogen lone pair in these N-bridgehead compounds.[18] The observation of these bands is diagnostic for a *trans*-fusion of the two rings in **2** and for the *trans*-{H8a-Ph}. The formation of a single diastereoisomer is explained by the formation of **2** as the most thermodinamically stable isomer in the equilibrium with the enol form **26** (Scheme 6).

The isolation of the ketone **2** realizes the achievement of our goal, consisting in the discovery of a new methodology for the synthesis of N-bridgehead bicyclic ketones. Unfortunately this process is limited, as yet, to the obtainment of indolizidinones. For the synthesis of our target NK_1 receptor antagonists, a direct consequence resulted in the possibility of producing, at this stage, only

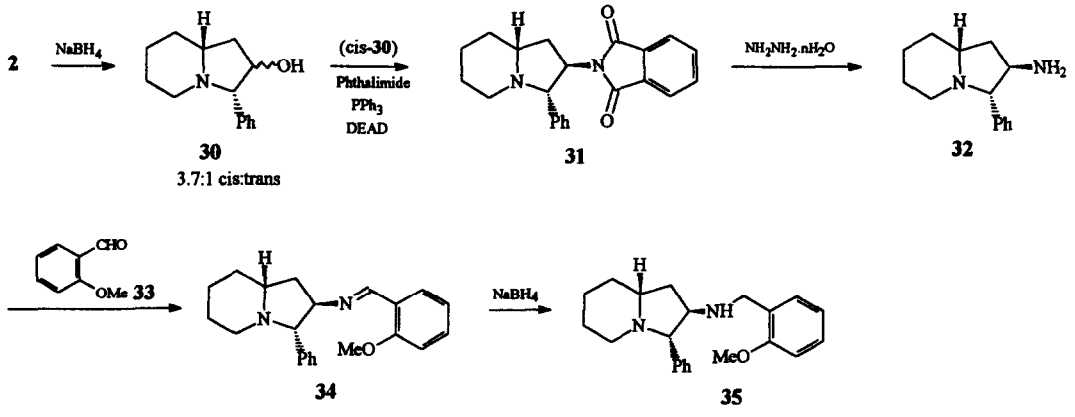
molecules of type **B**.

The *cis*-substituted indolizidinamine **29** has been synthesized in two steps (46% yield) by condensation of the ketone **2** with *o*-methoxybenzylamine (**27**) followed by reduction with $NaBH_4$. The reduction is highly stereoselective, affording only the product deriving from the attack of the hydride *anti* to the phenyl group (Scheme 7). To obtain the *trans* isomer **35** an inversion of the stereochemistry at C2 was required. This was achieved by a Mitsunobu reaction.[19] The ketone **2** was reduced to a mixture of isomeric *cis* and *trans* (3.7:1) alcohols **30** by $NaBH_4$. The major *cis*-alcohol **30** treated with DEAD, PPh_3 and phthalimide gave the phthalimidoylindolizidine **31** in 65% yield. The *trans*-substituted indolizidine **31** afforded the amine **32** by treatment with hydrazine hydrate. The amine **32** gave, by condensation with *o*-methoxybenzaldehyde (**33**), the imine **34** which was reduced *in situ* with $NaBH_4$ to give the *trans*-substituted indolizidinamine **35** with a 57% yield on three steps (Scheme 8).

SCHEME 7



SCHEME 8



Compounds **29** and **35** were active as NK_1 receptor antagonists only at micromolar level in functional tests, but further studies are in progress to make use of these results for the design of more potent analogues.

EXPERIMENTAL SECTION

All the reaction were run under nitrogen atmosphere using anhydrous solvents. Melting points (m.p.) were measured with an RCH Kofler apparatus. ^{1}H and ^{13}C-NMR ($CDCl_3$) spectra were recorded on a Varian Gemini (^{1}H 200 MHz); notation s, d, t, q, m e br indicate singlet, doublet, triplet, quartet, multiplet and broad, respectively. IR spectra were recorded in $CDCl_3$ with a Perkin-Elmer 881 spectrofotometer. Mass spectra (MS) were recordeds on 5792A Hewlett-Packard and QMD 1000 Carlo Erba instruments. Microanalyses were measured with a Perkin-Elmer 240 C instrument. Phenyl vinyl ketone (**7**) was synthesized according to ref. 9. Nitrones **5**, **6** and **9** were synthesised according to general procedure from the corresponding amines (see ref. 7). Nitrone **8** was synthesised according to ref. 20.

Cycloaddition of nitrones to phenyl vinyl ketone (7)

A 1 M solution of 1 equivalent of the nitrone and 1 equivalent of phenyl vinyl ketone (7) is stirred at room temperature for the appropriate time (see Table 1). The reaction mixture is concentrated and quickly chromatographed on a short pad of silica gel to give compounds as mixtures of cycloadducts on ^{1}H-NMR monitoring. Further separation by flash column chromatography gives enriched fractions of the isomers.

exo-**3a:** ^{1}H-NMR: δ 8.12-7.90 (m, 2H), 7.65-7.40 (m, 3H), 5.23 (t, J=7.8 Hz, 1H), 4.13-3.98 (m, 1H), 3.87-3.70 (m, 1H), 3.51-2.70 (m, 2H), 2.46 (ddd, J=12.0; 7.5; 4.5 Hz, 1H), 2.15-1.60 (m, 4H); ^{13}C-NMR: δ 195.7 s, 135.3 s, 133.5 s, 129.1 d (2C), 128.5 d (2C), 79.8 d, 66.0 d, 56.5 t, 38.7 t, 30.7 t, 23.6 t; MS: m/z (relative intensity) 217 ($M^{\bullet+}$, 25), 200 (24), 161 (50), 124 (34), 105 (100), 84 (63), 77 (100). *endo*-**3b:** ^{1}H-NMR: δ 8.12-7.98 (m, 2H), 7.61-7.31 (m, 3H), 5.20 (dd, J=8.0; 5.6 Hz, 1H), 3.82-3.65 (m, 1H), 3.45-3.29 (m, 1H), 3.09-2.95 (m, 1H), 2.94 (ddd, J=12.4; 7.8; 5.6 Hz, 1H), 2.28 (ddd, J=12.4; 8.0; 3.5 Hz, 1H), 2.15-1.86 (m, 2H), 1.84-1.54 (m, 2H). ^{13}C-NMR: δ 197.5 s, 134.8 s, 133.1 d, 129.1 d (2C), 128.3 d (2C), 78.8 d, 65.3 d, 57.0 t, 38.7 t, 31.2 t, 24.0 t.

exo-**4a:** ^{1}H-NMR: δ 8.12-7.99 (m, 2H), 7.66-7.40 (m, 3H), 5.28 (dd, J=9.3;3.8 Hz, 1H), 3.59-3.43 (m, 1H), 2.70-2.49 (m, 2H), 2.32-2.18 (m, 1H), 2.08-1.12 (m, 7H); ^{13}C-NMR: δ 195.4 s, 135.0 s, 133.4 d, 128.9 d (2C), 128.5 d (2C), 76.8 d, 65.9 d, 55.1 t, 32.7 t, 29.1 t, 24.7 t, 23.5 t; IR: 3069, 2948, 1690, 1598, 1448, 1223 cm^{-1}. MS: m/z (relative intensity) 231 ($M^{\bullet+}$, 29), 214 (45), 200 (13), 126 (100), 105 (100), 98 (65), 84 (81), 77 (100). *endo*-**4b:** ^{1}H-NMR: δ (the only discerned signal) 5.44 (dd, J=9.7; 4.5 Hz, 1H); ^{13}C-NMR: δ (the only discerned signals) 78.1 d, 59.5 d, 50.4 t, 33.5 t.

exo-**10a:** ^{1}H-NMR: δ 8.12-7.99 (m, 2H), 7.68-7.39 (m, 3H), 5.27 (t, A part of an AXY system, J=8.0 Hz, 1H), 3.41-3.21 (m, 1H), 3.18-2.99 (m, 1H), 2.63 (X part of an AXY system, J=12.4; 8.0 Hz, 1H), 2.41 (Y part of an AXY system, J=12.4; 8.0 Hz, 1H), 2.25-1.65 (m, 4H), 1.32 (s, 3H); ^{13}C-NMR: δ 195.9 s, 135.3 s, 133.4 d, 129.1 d (2C), 128.5 d (2C), 79.3 d, 72.5 s, 55.4 t, 44.6 t, 36.6 t, 26.0 q, 23.4 t. MS: m/z (relative intensity) 231 ($M^{\bullet+}$, 18), 216 (10), 202 (2), 188 (4), 126 (19), 105 (100), 98 (65), 77(100). *endo*-**10b:** ^{1}H-NMR: δ 8.12-8.04 (m, 2H), 7.62-7.39 (m, 3H), 5.23 (dd, A part of an AXY system, J=8.2; 6.6 Hz, 1H), 3.50-3.32 (m, 1H), 3.25-3.05 (m, 1H), 2.71 (X part of an AXY system, J=12.4; 6.6 Hz, 1H), 2.55 (Y part of an AXY system, J=12.4; 8.2 Hz, 1H), 2.20-1.70 (m, 4H), 1.25 (s, 3H); ^{13}C-NMR: δ 197.7 s, 134.9 s, 133.1 d, 129.2 d (2C), 128.4 d (2C), 78.8 d, 72.5 s, 55.6 t, 45.3 t, 37.4 t, 25.3 q, 24.2 t; MS: m/z (relative intensity) 231 ($M^{\bullet+}$, 87), 216 (20), 202 (17), 188 (78), 126 (8), 105 (100), 98 (14), 77 (38).

exo-**11a**: ^{1}H-NMR: δ 8.09-7.99 (m, 2H), 7.73-7.42 (m, 4H), 7.19-7.05 (m, 3H), 5.43 (t, J=8.5 Hz, 1H), 3.29-2.75 (m, 4H), 2.31-2.17 (m, 2H); ^{13}C-NMR: d 197.8 s, 135.9 s, 135.0 s, 133.2 s (aromatic carbons not assigned), 81.4 d, 64.2 d, 49.8 t, 39.3 t, 30.2 t; IR: 3069, 3027, 2958, 2928, 2856, 1687, 1597, 1448, 1276, 1250, 1227 cm-1; MS: m/z (relative intensity) 279 ($M^{\cdot+}$, 14), 248 (4), 147 (64), 130 (27), 129 (40), 115 (19), 105 (100), 91 (15), 77 (100). *endo*-**11a**: ^{1}H-NMR: δ 8.12-8.06 (m, 2H), 7.59-7.39 (m,4H), 7.28-7.11 (m, 3H), 5.47 (dd, J=9.4;4.0 Hz, 1H), 4.63 (t, J=8.7 Hz, 1H), 3.35.2.12 (m, 6H); ^{13}C-NMR: δ 196.2 s, 136.4 s, 135.1 s, 132.9 s (aromatic carbons not assigned), 78.8 d, 62.2 d, 48.5 t, 38.4 t, 29.6 t; IR: 3069, 3027, 2929, 2854, 1677, 1597, 1447, 1277, 1222 cm^{-1}; MS: m/z (relative intensity) 279 ($M^{\cdot+}$, 8), 248 (26), 174 (63), 159 (51), 148 (41), 147(100), 130 (90), 115 (82), 105 (100), 91 (46), 77 (100). **4-Benzoyl regioisomer** (isoxazolidine numbering): ^{1}H-NMR: δ 7.92-7.87 (m, 2H), 7.63-7.39 (m, 4H), 7.26-6.98 (m, 3H), 5.23 (d, J=7.7 Hz, 1H), 4.65 (dd, J=10.1; 7.9 Hz, 1H), 4.41 (ddd, J=10.1; 6.5; 7.7 Hz, 1H), 4.02 (dd, J=7.9; 6.5 Hz, 1H), 3.40-2.85 (m, 4H); ^{13}C-NMR: δ 198.7 s, 137.3 s, 135.1 s, 133.4 s (aromatic carbons not assigned), 70.7 t, 65.9 d, 58.0 d, 48.7 t, 28.7 t; IR: 3067, 3029, 2928, 2856, 1680, 1596, 1447, 1360, 1278, 1234 cm^{-1}; MS: m/z (relative intensity) 279 ($M^{\cdot+}$, 7), 248 (100), 174 (9), 148 (38), 147 (100), 130 (61), 105 (100), 91 (57), 77 (100).

Synthesis of 3(3'-phenyl-3'-oxo)propyl-3-phenyl-2,5,6,7-tetrahydro-3H-pyrrolizin-2-one (12).
To a solution of pyrroline-N-oxide (**5**) (340 mg, 4 mmol) in methylene chloride (3 mL) was added slowly a solution of 1.247 g (9.4 mmol) of 7 in 6 mL of methylene chloride, and 5 g of neutral alumina (Type I). After 12 h at room temperature, the mixture was filtered, concentrated, and the oily residue was flash chromatographed (eluent ethyl acetate-petroleum ether 1:1) to give 789 mg of **12** (60% yield).

12: Rf=0.17 (eluent ethyl acetate-petroleum ether 1:1); ^{1}H-NMR: δ 7.96-7.91 (m, 2H), 7.60-7.22 (m. 8H), 5.10 (s, 1H), 3.36 (ddd, J=9.5; 8.4; 4.8 Hz, 1H), 3.17 (ddd, J=9.5; 8.1; 6.6 Hz, 1H), 2.92-2.83 (m, 2H), 2.79-2.51 (m,4H), 2.32-1.97 (m, 2H); ^{13}C-NMR: δ 203.4 s, 198.8 s, 183.4 s, 136.2 s (2C), 133.0 d, 128.6 d (2C), 128.4 d (2C), 127.8 d (2C), 127.7 d, 125.8 d (2C), 90.8 d, 72.8 s, 44.2 t, 31.9 t, 27.7 t, 27.1 t, 22.8 t; IR: 3065, 2934, 2877, 1708, 1679, 1648, 1598, 1529, 1448, 1304 cm^{-1}; MS: m/z (relative intensity) 331 ($M^{\cdot+}$, 50), 302 (10), 226 (20), 222 (46), 212 (100), 198 (100), 184 (13), 182 (14), 170 (18), 115 (23), 110 (17), 105 (46), 91 (22), 77 (100); Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.45; H, 6.70; N, 4.05.

Synthesis of 3(3'-phenyl-3'-oxo)propyl-3-phenyl-2,3,5,6,7,8-hexahydroindolizin-2-one (13)
To a solution of 3,4,5,6-tetrahydropyridine-*N*-oxide (**6**) (547 mg, 5.5 mmol) in methylene chloride (10 mL) was added slowly a solution of 2.181 g (16.5 mmol) of 7 in 6 mL of methylene chloride, and 8 g of neutral alumina (Type I). After 14 h at room temperature, the mixture was filtered, concentrated, and the oily residue was flash chromatographed (eluent ethyl acetate-petroleum ether 3:1, then methanol). Concentration of the most polar fraction gave 955 mg of **13** (50% yield).

13: m.p. 95-96°C (diethyl ether). ^{1}H-NMR: d 7.97-7.94 (m, 2H), 7.59-7.53 (m, 1H), 7.48-7.42 (m, 2H), 7.37-7.24 (m, 5H), 5.02 (s, 1H), 3.18-3.07 (m, 1H), 3.05-3.58 (m, 6H), 2.55-2.40 (m,1H), 1.88-1.61 (m, 4H); ^{13}C-NMR: d 200.3 s, 199.1 s, 177.4 s, 136.5 s (2C), 133.2 d, 128.9 d (2C), 128.6 d (2C), 128.2 d (2C), 128.0 d, 126.0 d (2C), 95.8 d, 75.1 s, 40.5 t, 31.9 t, 26.5 t, 25.4 t, 22.5 t, 19.2 t; IR: 3064, 2957, 2869, 1679, 1642, 1509, 1447, 1360, 1243 cm^{-1}; MS: m/z (relative intensity) 345

(M^{+},40), 317 (3), 240 (3), 238 (3), 226 (19), 213 (100), 212 (91), 198 (16), 184 (28), 156 (12), 115 (19), 105 (53), 77 (81); Anal. Calcd for $C_{23}H_{23}NO_2$: C,79.97; H, 6.71; N, 4.05. Found: C, 79.98; H, 6.66; N, 4.17.

Synthesis of 6,7-dibenzoyl-7-hydroxy-1, 2, 3, 5, 6, 7, 8, 8a-octahydroindolizine (21).

A solution of pyrroline-*N*-oxide (**5**) (1.2 g, 14 mmol) and phenyl vinyl ketone (**7**) (1.188 g, 9 mmol) in benzene (30 mL) was stirred at room temperature for 24 h. After concentration of the solution and flash chromatography (eluent petroleum ether-ethyl acetate 3:2) 961 mg of **21** (R_f = 0.28) (61%) was obtained as a solid.

21: m.p. = 110-111°C (ethanol); ^{1}H-NMR: δ 8.29-8.24 (m, 2H), 8.09-8.04 (m, 2H), 7.66-7.37 (m, 6H), 5.72 (d, J=2.6 Hz, 1H, OH), 4.51 (dd, J=11.9; 3.8 Hz, 1H), 3.24 (dd, J=10.8; 3.8 Hz, 1H), 3.07 (td, J=8.3; 2.7 Hz, 1H), 2.82-2.66 (m, 1H), 2.61 (t, J=11.4 Hz, 1H), 2.45 (dd, J=13.4; 2.7 Hz, 1H), 2.28 (q, J=8.7 Hz, 1H), 2.00-1.71 (m, 3H), 1.58-1.32 (m, 2H); ^{13}C-NMR: δ 205.7 s, 202.7 s, 135.6 s, 134.5 s, 133.7 d, 132.6 d, 130.2 d (2C), 128.6 d (2C), 128.5 d (2C), 127.9 d (2C), 81.9 s, 57.8 d, 52.6 t, 50.4 t, 48.0 d, 40.5 t, 29.5 t, 21.3 t; IR: 3424 (br), 3030, 2972, 1660, 1597, 1218 cm^{-1}; MS: m/z (relative intensity) 349 (M^{+}, 13), 331 (2), 244 (81), 226 (9), 217 (52), 201 (68), 124 (11), 112 (11), 105 (100), 96 (26), 83 (18), 77 (74); Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.71; H, 6.80; N, 4.31.

Synthesis of 3-phenyl-1, 2, 3, 5, 6, 7, 8, 8a-octahydroindolizin-2-one (2).

A solution of nitrone **6** [obtained by oxydation of N-hydroxypiperidine (505 mg, 5 mmol) at 0°C with yellow HgO (4.4 g, 20.4 mmol)] and phenyl vinyl ketone (**7**) (1.188 g, 7 mmol) in methylene chloride (10 mL), was stirred 48 h at room temperature. The solution was concentrated and the residue dissolved in acetonitrile (50 mL) and H_2O (1 mL). After addition of $Mo(CO)_6$ (924 mg, 3.5 mmol) the mixture was refluxed 4 h and concentrated. Flash chromatography (eluent petroleum ether-ethyl acetate 10:1) gave 490 mg of **2** (45% yield of two steps). Using for the reaction the isolated isoxazolidines **3a,b** (0.5 eq. di $Mo(CO)_6$; 15 eq. di H_2O) ketone **2**, only slightly more pure, was obtained in 47% yield.

2: R_f=0.34 (eluent petroleum ether-ethyl acetate 10:1), oil; ^{1}H-NMR: δ 7.39-7.29 (m, 5H), 3.46 (s, 1H), 2.93 (dm, J=11.4 Hz, 1H), 2.66-2.48 (m, 1H), 2.50 (dd, J=17.0; 5.3 Hz, 1H), 2.30-1.82 (m, 4H), 1.75-1.13 (m, 4H); ^{13}C-NMR: δ 212.2 s, 136.4 s, 128.4 d (2C), 128.3 d (2C), 127.8 d, 76.3 d, 60.3 d, 51.1 t, 43.5 t, 31.2 t, 25.5 t, 24.6 t; IR: 3067, 3033, 2940, 2855, 2791 and 2756 (Bohlmann's bands), 1755, 1493, 1499, 1441, 1247, 1135 cm^{-1}; MS: m/z (relative intensity) 215 (M^{+}, 2), 214 (1), 186 (100), 172 (13), 158 (9), 145 (15), 132 (21), 118 (16), 104 (43), 91 (18); Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.07; H,8.09; N, 6.28.

Synthesis of cis-(2S*,3S*)-2-o-methoxybenzylamino-3-phenyl-1, 2, 3, 5, 6, 7, 8, 8a-octahydroindolizine (29).

A solution of ketone **2** (215 mg, 1 mmol), *o*-methoxybenzylamine (**27**, 274 mg, 2 mmol) and *p*-TsOH (catalytic) in benzene (4 mL) was heated at reflux for 3 h. After concentration, and elimination of the excess amine by kugel rohr distillation, the residue was dissolved in anhydrous EtOH (2.5 mL) and cooled at 0°C. Sodium borohydride (67 mg, 1.7 mmol) was added in small portions and, after 2 h at 0°C, the reaction mixture was left at room temperature for 12 h. After the usual work up, flash

chromatography (eluent petroleum ether-ethyl acetate 1:1) gave 155 mg of **29** (46% yield).

29: (R_f = 0.30, eluent petroleum ether-ethyl acetate 1:1) ^{1}H-NMR: δ 7.36-7.20 (m, 5H), 7.16 (td, J=7.7; 1.9 Hz, 1H), 6.92 (dd, J=7.3; 1.9 Hz, 1H), 6.80 (tm, J=7.3 Hz, 1H), 6.74 (br d, J=8.1 Hz, 1H), 3.59 (s, 3H), 3.58 (d, J=13.9 Hz, 1H), 3.31 (d, J=7.3 Hz, 1H), 3.27 (d, J=13.9 Hz, 1H), 3.15 (td, J=7.3; 5.7 Hz, 1H), 2.94-2.81 (m, 1H), 2.22 (ddd, J=11.8; 7.6; 6.1 Hz, 1H), 2.29-2.12 (m, 1H), 1.90-1.19 (m, 8H), 1.39 (td, J=11.1; 5.5 Hz, 1H); ^{13}C-NMR: δ 157.5 s, 138.5 s, 129.6 d, 129.0 d (2C), 128.0 s, 127.9 d (2C), 127.8 d, 126.8 d, 120.0 d, 109.8 d, 74.0 d, 63.7 d, 57.2 d, 54.8 d, 51.7 t, 47.1 t, 39.2 t, 31.2 t, 25.4 t, 24.7 t; IR: 3026, 2935, 2859, 2790 and 2755 (Bohlmann's bands), 1605, 1495, 1465, 1240, 1120 cm^{-1}; MS: m/z (relative intensity) 336 ($M^{\cdot+}$, 3), 239 (5), 216 (4), 199(9), 172 (100), 144 (12), 121 (27), 104 (29), 91 (70); Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H,8.39; N, 8.33. Found: C, 78.26; H, 8.79; N, 8.00.

Synthesis of cis-(2S*,3S*)- and trans-(2R*,3S*)-2-hydroxy-3-phenyl-1, 2, 3, 5, 6, 7, 8, 8a-octahydroindolizine (30).

To a solution of ketone **2** (237 mg, 1.1 mmol) in anhydrous EtOH (2.5 mL), cooled at 0°C, sodium borohydride (67 mg, 1.7 mmol) was added in small portions and, after 2 h at 0°C, the reaction mixture was left at room temperature for 12 h. After the usual work up, concentration of the organic solution gave 230 mg (96%) of a pure mixture of the *cis* and *trans* alcohols **30** in 3.7:1 ratio. Major *cis* isomer can be separated in part by flash chromatography (eluent methylene chloride-methanol (added of 1% NH_4OH) 20:1).

cis-**30:** R_f = 0.38; m. p.= 77-78 °C; ^{1}H-NMR: δ 7.41-7.20 (m, 5H), 4.26-4.15 (m, 1H), 3.25 (d, J=5.8 Hz, 1H), 2.92-2.84 (m, 1H), 2.44 (ddd, J=13.2; 7.6; 7.0 Hz, 1H), 2.10-1.95 (m, 1H), 1.91-1.19 (m, 9H); ^{13}C-NMR: δ 137.0 s, 129.0 d (2C), 128.4 d (2C), 127.4 d, 75.5 d, 72.0 d, 63.4 d, 51.5 t, 40.6 t, 31.3 t, 25.4 t, 24.7 t; IR: 3582, 3083, 3029, 2938, 2854, 2793, 1605, 1449, 1442, 1225, 1058 cm^{-1}; MS: m/z (relative intensity) 217 ($M^{\cdot+}$, 8), 173 (36), 172 (100), 140 (6), 96 (3), 91 (25), 84 (27), 77 (100); Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.35; H, 9.04; N, 6.05.

trans-**30:** Rf = 0.32; ^{1}H-NMR: δ (the only discerned signals) 4.03 (ddd, J=7.9; 5.3; 2.9 Hz, 1H), 3.05 (d, J=5.3 Hz, 1H), 2.71 (dm, J=10.7 Hz, 1H).

Synthesis of trans-(2R*,3S*)-2-phtalimidoyl-3-phenyl-1, 2, 3, 5, 6, 7, 8, 8a-octahydroindolizine (31).

To a solution of alcohol *cis*-**30** (180 mg, 0.83 mmol), phthalimide (162 mg, 1.1 mmol) and PPh_3 (298 mg, 1.1 mmol) in anhydrous THF (5 mL), DEAD (191 mg, 1.1 mmol) was added slowly and the reaction left at room temperature for 12 h. The solid obtained after concentration was washed with diethyl ether and the solid residue recrystallized from ethanol gave 188 mg of **31** (yield 65%).

31: m. p. = 179-180°C (ethanol); ^{1}H-NMR: δ 7.82-7.65 (m, 4H), 7.32-7.20 (m, 5H), 4.60 (ddd, J=11.6; 8.3; 4.4 Hz, 1H), 3.70 (d, J=8.3 Hz, 1H), 2.93-2.68 (m, 2H), 2.29-2.14 (m, 1H), 2.08-1.24 (m, 8H); ^{13}C-NMR: δ 168.0 s (2C), 139.9 s, 133.8 d (2C), 131.8 s (2C), 128.4 d (2C), 127.6 d (3C), 123.1 d (2C), 71.7 d, 63.5 d, 55.6 d, 50.6 t, 34.5 t, 31.3 t, 25.4 t, 24.3 t; IR: 3005, 2938, 1708 (very strong), 1601, 1360, 1221cm^{-1}; MS: m/z (relative intensity) 346 ($M^{\cdot+}$, 5), 269 (3), 199 (100), 198 (77), 172 (74), 156 (18), 104 (35), 97 (31), 76 (18).

Synthesis of trans-(2R*,3S*)-2-o-methoxybenzylamino-3-phenyl-1, 2, 3, 5, 6, 7, 8, 8a-octahydro-indolizine (35).

A solution of **31** (139 mg, 0.4 mmol) and hydrazine hydrate (100 μL, 10.3 mg, 1 mmol) in ethanol (8 mL) was heated at reflux for 15 h. After filtration on celite and concentration were obtained 102 mg of amine **32** pure enough to be utilized for the next reaction without purification. [**32:** ^{1}H-NMR: δ 7.40-7.18 (m, 5H), 3.22 (ddd, J=9.7; 6.6; 3.4 Hz, 1H), 2.90 (d, J=6.6 Hz, 1H), 2.90-2.60 (m, 2H), 2.69 (dm, J=11.0 Hz, 1H), 2.45-2.28 (m, 1H), 1.96 (dd, J=13.0; 10.0 Hz, 1H), 1.92-1.20 (m, 8H); ^{13}C-NMR: δ 140.8 s, 128.3 d (2C), 127.7 d (2C), 127.3 d, 79.2 d, 62.8 d, 58.3 d, 50.6 t, 39.1 t, 31.1 t, 25.2 t, 24.2 t]. The amine **32** was dissolved in ethanol (1 mL) and to the solution added *o*-anisaldehyde (**33**, 68 mg, 0.5 mmol) and anhydrous sodium carbonate. After 3 h at room temperature, the reaction mixture was cooled at 0°C and sodium borohydride (24 mg, 0.6 mmol) added in small portions. After 24 h at room temperature the mixture was subjected to normal work up. Flash chromatography (eluent petroleum ether-ethyl acetate 3:2) gave 77 mg of **35** (overall yield 57%).

35: ^{1}H-NMR: δ 7.40-7.23 (m 5H), 7.17 (td, J=7.7; 1.8 Hz, 1H), 6.98 (dd, J=7.4; 1.8 Hz, 1H), 6.80 (tm, J=7.4 Hz, 1H), 6.76 (br d, J=7.7 Hz, 1H), 3.65 (s, 4H), 3.06-2.96 (m, 2H), 2.66 (m, 1H), 2.32 (m, 1H), 1.90-1.18 (m, 11H); ^{13}C-NMR: δ 157.5 s, 142.1 s, 129.8 d, 128.2 d (2C), 128.1 d, 128.0 d (2C), 127.9 s, 127.1 d, 120.2 d, 110.0 d, 77.7 d, 64.1 d, 63.3 d, 54.9 q, 50.9 t, 48.1 t, 37.7 t, 31.3 t, 25.4 t, 24.4 t; IR: 3029, 2940, 2793 and 2757 (Bohlmann's bands), 1600, 1492, 1454, 1242 cm^{-1}; MS: m/z (relative intensity) 336 ($M^{\cdot+}$, 23), 239 (31), 199 (20), 198 (49), 172 (100), 121 (64), 90 (100), 77 (76); Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.64; H, 8.46; N, 8.18.

Acknowledgment. Authors thank M.U.R.S.T. (Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome-Italy) (IMI Grant n. 56665) for partial financial support and a fellowship for M. F. Cordero.

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(*Received in UK* 4 *August* 1994; *revised* 9 *September* 1994; *accepted* 16 *September* 1994)