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Synthesis of 8-Amino-3-oxoindolizidine-1-carboxylic Acid Derivatives as Conformationally Restricted Templates for Use in Design of Peptide Mimetics

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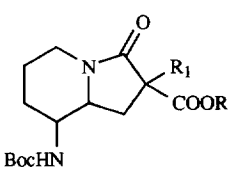
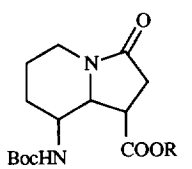
Abstract.- The synthesis of new 8-*tert*-butyloxycarbonylamino-3-oxoindolizidine-1-carboxylic acid esters with different stereochemistry at position 1, 8, and 8a is described. Three different paths from ornithine derivatives have been utilized. These compounds can be employed as new templates in synthetic analogues of bioactive peptides.

An approach to peptide mimetics research is centered on the introduction of conformationally restricted residues into biologically active peptides.[1,2] The resulting analogues bridge the gap between simple peptide analogues and the completely nonpeptide structures, constituting an important database to study the active conformations of peptides. On these bases, efforts have been devoted to the development of a wide range of



I



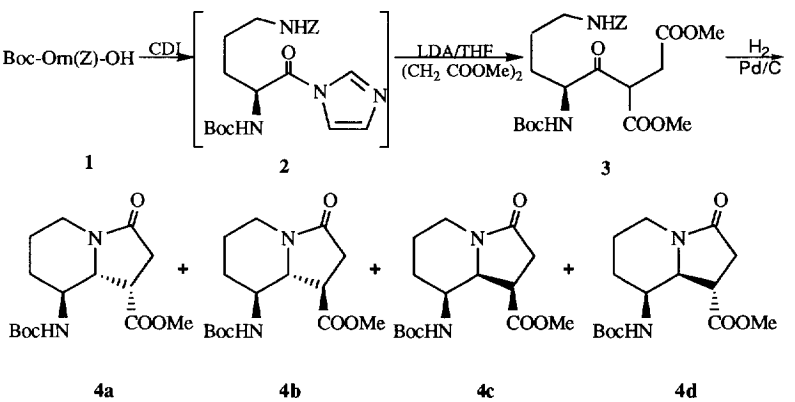
II

small molecules carrying the pharmacophoric groups in the appropriate spatial orientation consistent with the bioactive conformations.[3-5] In this sense, we have recently studied the effects of the replacement of one or two contiguous amino acids by a 3-oxoindolizidine-2-carboxylic acid moiety (**I**) in some active fragments of neuropeptides such as neurotensin or cholecystokinin.[6,7] Following our work in this field, we have directed our interest to the preparation of compounds **II** which, carrying the carboxylate group at C-1 position of oxoindolizidine ring, allow us to enlarge the conformational range enforced by this type of skeleton.

RESULTS AND DISCUSSION

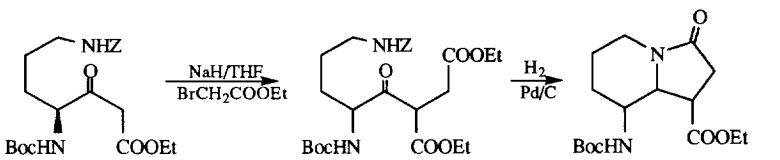
Our first approach to the synthesis of 3-oxoindolizidine derivatives **II** involves, as summarized in Scheme 1, two consecutive intramolecular cyclizations starting from the open-chain precursor **3.** This compound was obtained in 23% yield by acylation of the lithium salt of dimethyl succinate with the ornithine

derived imidazolide **2**, following a procedure similar to that described for the preparation of some amino acid derived β-ketoesters.[8] Compound **3** was shown to be by ^{1}H-NMR a 1:1 mixture of the two expected diastereoisomers at the C-3 center. This mixture was hydrogenated at room temperature over Pd/C at 40 psi; under these conditions, the removal of the Z protecting group of **3**, the reductive amination and the subsequent lactamization take place in a one-pot reaction,[6,9] providing access to oxoindolizidine derivatives **4a-4c** (5:2.5:2 ratio, 78% overall yield) which were separated chromatographically. Traces of the expected additional diastereoisomer **4d** were also detected. The chiral purity of these indolizidine derivatives was verified through the formation of the Mosher amide derivatives.[10] According to the obtained results (^{1}H-NMR and HPLC), the indolizidines derived from **3** were optically pure compounds.



Scheme 1

Since the preparation of compound **3** following the mentioned path gave poor yield, we used a second option, shown in Scheme 2, for the synthesis of the alternative precursor target **6**. This method involved the alkylation of the previously described[11] ornithine-derived β-ketoester **5** with ethyl bromoacetate using NaH as base. Although the reaction did not take place under the conditions (0 °C, 2 h) described by Hoffman and Kim[12] for closely related compounds, an increase in the temperature (25 °C) and time of reaction (12 h) allowed us to obtain compound **6** (88% yield) as 1:1 mixture of two diastereoisomers as determined by ^{1}H-NMR spectroscopy. Catalytic hydrogenation of this mixture as before provided access to oxoindolizidines **7a-7c** (7:4:4 ratio) in 68% overall yield. As above, traces of a fourth isomer could also be detected. Unfortunately, ^{1}H-NMR and HPLC analysis of the corresponding Mosher amide derivatives revealed that these oxoindolizidines were 3:2 mixtures of the corresponding enantiomeric pairs **7a/7a'**, **7b/7b'** and **7c/7c'**, indicating that partial racemization occurs following this second synthetic pathway. Bearing in mind that the analogous cyclization of the open intermediate **3** yields enantiomerically pure compounds, we assume that the mentioned mixture of enantiomers found in compounds **7** arises from the racemic character of C-5 of the precursor **6**. Since the procedure of Hoffman and Kim for the preparation of related products has been reported[12] to yield enantiomerically pure compounds, the epimerization must occur during the alkylation of **5**, and is probably due to the modifications we have introduced in the original method of these authors .



5 6 7a(a'): 8S(R), 8aR(S),1S(R)
7b(b'): 8S(R), 8aR(S),1R(S)
7c(c'): 8S(R), 8aS(R),1R(S)

Scheme 2

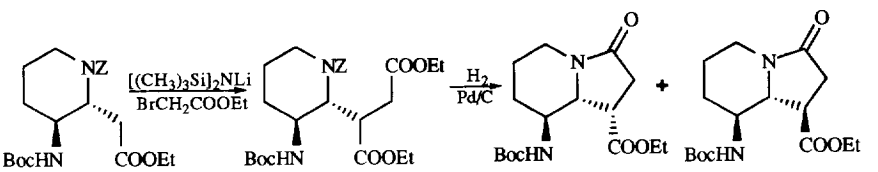
The configuration at C-8a of these 3-oxoindolizidine derivatives was established on the basis of $J_{8,8a}$ coupling constants values (Table 1). These data allowed us to propose the *trans* relative disposition between H-8 and H-8a protons of the oxoindolizidines **4a**, **4b**, **7a(a')** and **7b(b')** ($J_{8,8a}$ = 10 Hz) and the *cis* disposition between the same protons for the compounds **4c** and **7c(c')** ($J_{8,8a}$= 2.5 Hz). In both series, certain stereoselectivity in the intramolecular reductive amination step generating C-8a asymmetric carbon (*ca.* 3:1 total ratio in favour of *trans* disposition between H-8 and H-8a protons) has been observed. This degree of stereocontrol is, however, lower than that observed during the synthesis of compounds **I** and other related derivatives[7] following a similar process.

Table 1.—Significant ^{1}H-NMR data of 3-oxoindolizidine derivatives **4** and **7** (300 MHz, $CDCl_3$)

	δ ppm								Hz	
Comp.	NH	H-5	H-8	H-8a	H-1	H-2	H-7	H-6	$J_{8,8a}$	$J_{1,8a}$
4a	4.41	4.09 2.55	3.38	3.62	3.31	2.75 2.48	2.14 1.52	1.70	10.2	8.6
4b	4.58	4.05 2.51	3.32	3.40	3.24	2.65	2.10 1.70-1.51		10.1	5.8
4c	4.72	4.15 2.68	4.09	3.81	3.08	2.71 2.65	1.96 1.70-1.50		2.6	5.3
7a	4.40	4.12 2.57	3.42	3.64	3.32	2.79 2.59	2.20 1.52	1.70	10.3	8.2
7b	4.65	4.15 2.58	3.38	3.49	3.22	2.75 2.65	2.18 1.52	1.75	10.1	5.7
7c(c')	4.68	4.08 2.65	4.02	3.77	3.05	2.56	1.92 1.65-1.48		2.5	5.7

Finally, since the racemization ocurring during the mentioned second method arises from the enolization of carbonyl group of β-keto esters **5** or **6** towards positions 4 or 5 respectively, we decided to prevent this problem by using the (2*R*,3*S*)-3-amino-2-piperidineacetic acid derivative **8**, stereoselectively prepared[11] from **5**,

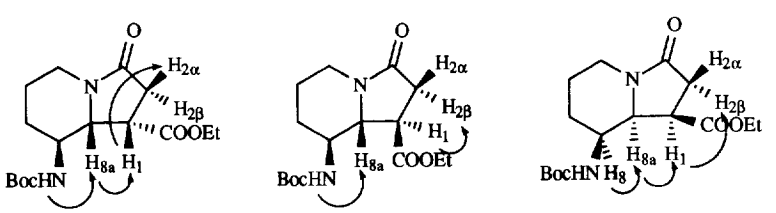
as starting material. Although the alkylation[13] of ester **8** (Scheme 3) required stronger basic conditions, we found that its reaction with ethyl bromoacetate in THF at -78 °C in the presence of lithium bis(trimethylsilyl) amide provided a 1:4 diasteroisomeric mixture (measured by HPLC) of **9a,b** in 61% overall yield. The chromatographic separation of these products was shown to be difficult; although pure samples of them for characterization purposes could be obtained, we used directly the diastereoisomeric mixture in the next step. Thus, after catalytic hydrogenation as before, **9a,b** was converted into a 1:6 mixture of the optically pure oxoindolizidines **7a** and **7b** (64% overall yield), which could by easily separated by chromatography. This third path offers a good way for the preparation of enantiomerically pure H_8,H_{8a}-*trans* 8-amino-3-oxoindolizidine-1-carboxylic acid derivatives. A high degree of stereocontrol at the final C-1 chiral center, favouring the formation of **7b**, has been found during this process and thus, the resulting isomers ratio is reversed respect to that obtained following the first of the synthetic methods (1:6 **7a-7b** ratio *vs.* 2:1 **4a-4b** ratio) reported in this work.



8 **9a(b): 3S(R)** **7a** **7b**

Scheme 3

The assignment of the configuration at C-1 was made by ^{1}H-NMR and NOE experiments on the derivatives **7a**, **7b** and **7c(c')** (Figure 1). Thus, compound **7a** showed strong dipolar exchange of magnetization (NOE) between protons NH-H_{8a}, H_{8a}-H_1 and H_1-$H_{2\alpha}$, and weak NOE between protons H_{8a}-$H_{2\alpha}$, confirming the *trans* disposition of H_8 and H_{8a} and suggesting a *cis* disposition between H_{8a} and H_1. In the case of compound **7b**, the strong NOE's observed between protons NH-H_{8a}, H_1-$H_{2\beta}$ and the weak NOE found for H_{8a}-$H_{2\alpha}$ allowed us to propose a *trans* disposition between H_{8a} and H_1. The compound **7c(c')** shows strong NOE's between H_8-H_{8a}, H_{8a}-H_1 and H_1-$H_{2\beta}$ and weak NOE between H_{8a} and $H_{2\beta}$, confirming a *cis* disposition between H_8-H_{8a} and H_{8a}-H_1.



7a **7b** **7c**

Figure 1.- NOE's observed for compounds **7a**, **7b** and **7c**.

The assignment of the configuration of the corresponding methyl esters **4a**, **4b** and **4c** was made by correlation of their ^{1}H-NMR spectra and, especially, of their $J_{1,8a}$ coupling constant values (Table 1) with those of compounds **7a**, **7b** and **7c(c')**. Thus, the compounds **4a** and **7a** have the absolute stereochemistry 1S,8S,8aR, **4b** and **7b** are 1R,8S,8aR, **4c** and, in the case of **7c(c')**, the major enantiomer **7c** are 1R,8S,8aS and the fourth diastereoisomer **4d**, presumably, is 1S,8S,8aS.

The protected oxoindolizidine derivatives **II** synthesized according to these pathways are suitable for incorporation into higher peptides following standard procedures.

EXPERIMENTAL

Monodimensional ^{1}H-NMR and NOE spectra were recorded at 300 MHz with a Varian XL-300, using TMS as internal standard (Table 1). NOESY spectra were recorded in $CDCl_3$ at 600 ms. A 1.5-second relaxation delay was used in these experiments. ^{13}C-NMR spectra were registered on a Varian Gemini 200 (50 MHz). The purity of the synthesized compounds was checked by thin-layer chromatography (TLC) on silica gel DC-Alufolien (Merck 60F$_{254}$). Silica gel (230-400 mesh, Merck) was used for flash column chromatography. Analytical HPLC was carried out on a Waters apparatus (Bondapak C_{18}, 3.9 × 300 mm) with 40:60 (A) and 55:45 (B) CH_3CN/H_2O (0.05% TFA) as eluents (flow rate 1 mL/min) and with UV (210 nm) detection. Elemental analyses were obtained on a CHN-O-rapid instrument. Melting points were determined in a Reichert-Jung Kofler apparatus and are uncorrected. Boc-Orn(Z)-OH was purchased from Bachem.

*Methyl 8-Benzyloxycarbonylamino-5(*S)-tert-*butyloxycarbonylamino-3(*R,S)-*methoxycarbonyl-4-oxooctanoate* (**3**).

To a cooled (-78 °C) solution of lithium diisopropilamide [prepared from 1.6 M n-BuLi in hexane (4.10 ml, 6.55 mmol) and diisopropylamine (0.92 ml, 6.55 mmol)] in dry THF, a solution of dimethyl succinate (0.86 ml, 6.55 mmol) in dry THF was added at such a rate as to maintain the temperature below -75 °C. When the addition was complete, a solution of **2**, prepared *in situ* from Boc-Orn(Z)-OH (2.00 g, 5.46 mmol) and carbonyldiimidazole (0.97 g, 6.00 mmol) in dry THF was added. Stirring was continued for 15 min at -78 °C, and then, the reaction was quenched by rapid addition of 1N HCl. The reaction mixture was diluted with EtOAc, and the organic layer was decanted, washed successively with water, 5% $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. Purification on a silica gel column (1:4 to 1:2 EtOAc-hexane) gave 0.62 g (23%) of the diastereoisomeric mixture as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.38 (s, 9H, Boc CH_3), 1.52 (m, 3H, H-6 and H-7), 1.95 (m, 1H, H-6), 2.87-2.92 (m, 2H, H-2), 3.18 (m, 2H, H-8), 3.63, 3.66, 3.67 and 3.69 (4 s, 6H, $CO_2C\underline{H}_3$), 4.21 (m, 1H, H-3), 4.47 and 4.61 (2m, 1H, H-5), 4.80 and 4.90 (2d, 2H, NH), 5.00 (s, 2H, Z CH_2), 7.15 (m, 5H, Z C_6H_5). Anal. Calc. for $C_{24}H_{34}N_2O_9$: C 58.29, H 6.93, N 5.66. Found: C 58.10, H 7.08, N 5.35.

*Ethyl 8-Benzyloxycarbonylamino-5(*S,R)-tert-*butyloxycarbonylamino-3(*R,S)-*methoxycarbonyl-4-oxooctanoate* (**6**).

To a solution of the β-ketoester **5** (1.00 g, 2.30 mmol) in dry THF cooled at 0 °C, NaH (80% suspen-

sion in oil, 2.50 mmol) was added, and the mixture was stirred at the same temperature for 15 min. After addition of ethyl bromoacetate (0.31 ml, 2.80 mmol), the stirring was continued at room temperature for 12 h. Solvent was removed and the residue was diluted with EtOAc, washed with H_2O and brine and dried over Na_2SO_4. Evaporation and purification on a silica gel column (1:3 EtOAc-hexane) yielded 1.10 g (88%) of the title product as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (m, 6H, $CO_2CH_2C\underline{H}_3$), 1.42 (s, 9H, Boc CH_3), 1.52-1.60 (m, 3H, H-7, H-6), 1.98 (m, 1H, H-6), 2.85-3.00 (m, 2H, H-2), 3.21 (m, 2H, H-8) 4.10-4.20 (m, 5H, $CO_2C\underline{H}_2CH_3$, H-3), 4.53 and 4.70 (2m, 1H, H-5), 5.07 (s, 2H, Z CH_2), 5.12 and 5.20 (2d, 2H, NH), 7.33 (m, 5H, Z C_6H_5). Anal. Calc. for $C_{26}H_{38}N_2O_9$: C 59.76, H 7.33, N 5.36. Found: C 59.58, H 7.01, N 5.12.

*1-Alkoxycarbonyl-8-*tert*-butyloxycarbonylamino-3-oxoindolizidines* (**4**) *and* (**7**).

Compound **3** (0.70 mmol) in MeOH, or **6** (1.00 mmol) in EtOH, were hydrogenated at room temperature and 40 psi of pressure for 48 h in the presence of 10% Pd/C as catalyst. After filtration of the catalyst and evaporation of the solvent, the resulting mixture was purified on a silica gel column (1:3 EtOAc-hexane to EtOAc) to yield the following compounds:

(1*S*, 8*S*, 8a*R*) **4a** as a colorless oil (42% yield). HPLC t_R= 5.81 min. (eluent A). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 172.2, 171.5, 155.5 (CO), 79.6 (Boc C), 61 1 (C-8a), 52.3 (CH_3 ester) 48.9 (C-8), 38.8 (C-1), 39.9, 33.8, 31.7, 23.2 (CH_2), 28.3 (Boc CH_3) Anal. Calc. for $C_{15}H_{24}N_2O_5$: C 57.67, H 7.74, N 8.97. Found: C 57.41, H 7.96, N 8.53.

(1*R*, 8*S*, 8a*R*) **4b** as a colorless oil (21% yield). HPLC t_R= 6.43 min. ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 173.0, 170.6,155.6 (CO), 79.9 (Boc C), 63.8 (C-8a), 52.9 (C-8), 52.4 (CH_3 ester), 39.4 (C-1), 40.5, 33.9, 31.4, 23.5 (CH_2), 28.2 (Boc CH_3). Anal. Calc. for $C_{15}H_{24}N_2O_5$: C 57.67, H 7.74, N 8.97. Found: C 57.49, H 7.91, N 9.13.

(1*R*, 8*S*, 8a*S*) **4c** as a pale yelow oil (14% yield). HPLC t_R= 6.96 min. ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 173.8, 171.6, 155.6 (CO), 79.8 (Boc C), 62.2 (C-8a), 52.3 (CH_3 ester), 46.8 (C-8), 37.6 (C-1), 39.9, 33.3, 29.5, 18.3 (CH_2), 28.7 (Boc CH_3). Anal. Calc. for $C_{15}H_{24}N_2O_5$: C 57.67, H 7.74, N 8.97. Found: C 57.83, H 7.91, N 8.61.

[1*S(R)*, 8*S(R)*, 8a*R(S)*] **7a(a')** as a white solid (32% yield), mp.: 103 °C. HPLC t_R= 6.57 min. (eluant A). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 171.8, 171.6 and 154.6 (CO), 79.6 (Boc C). 61.3 (ester CH_2), 61.2 (C-8a), 48.8 (C-8), 38.9 (C-1), 39.9, 33.8, 31.8 , 23.2 (CH_2), 28.2 (Boc CH_3), 13.9 (ester CH_3). Anal. Calc. for $C_{16}H_{26}N_2O_5$: C 58.88, H 8.03, N 8.58. Found: C 58.93, H 7.91, N 8.35.

[1*R(S)*, 8*S(R)*, 8a*R(S)*] **7b(b')** as a pale yelow oil (18% yield). HPLC t_R= 7.70 min. ^{13}C-NMR (50 MHZ, $CDCl_3$) δ: 171.7, 170.6, 155.6 (CO), 79.9 (Boc C), 63.5 (C-8a), 61.4 (CH_2 ester), 53.1 (C-8), 39.4 (C-1), 40.6, 33.9, 31.5, 23.5 (CH_2), 28.2 (Boc CH_3), 14.1 (CH_3 ester). Anal. Calc. for $C_{16}H_{26}N_2O_5$: C 58.88, H 8.03, N 8.38. Found: C 58.61, H 7.94, N 8.27.

[1*R(S)*, 8*S(R)*, 8a*S(R)*] **7c(c')** as a pale yelow oil (18% yield). HPLC t_R= 7.94 min. ^{13}C-NMR (50MHz, $CDCl_3$) δ: 172.6, 171.8, 155.6 (CO), 80.1 (Boc C), 62.3 (C-8a), 61.5 (CH_2 ester), 46.8 (C-8), 37.9 (C-1), 38.9, 33.5, 28.9, 18.4 (CH_2), 28.3 (Boc CH_3), 14.2 (CH_3 ester). Anal. Calc. for $C_{16}H_{26}N_2O_5$: C 58.88, H 8.03, N 8.38. Found: C58.77, H 8.02, N 8.79.

1H-NMR data of all these compound are included in Table 1.

*Ethyl 3(*S*)- and 3(*R*)-Ethoxycarbonyl-3-[(1-benzyloxycarbonyl-3-*tert*-butyloxycarbonylamino)-piperidine]propionate* (**9a** *and* **9b**).

A solution of compound **8** (0.30 g, 0.69 mmol) in dry THF was added to a solution 1M of lithium bis(trimethylsilyl)amide (2.20 mmol) in THF. After 20 min, a solution of ethyl bromoacetate (0.16 ml, 1.42 mmol) in THF and HMPA (0.42 mmol) was added at -75 °C. Stirring was continued for 4 h at room temperature, and then the mixture was treated with 10% NH_4Cl and extracted with ether. The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated to yield 0.27g of crude title compounds in 1:4 ratio. Purification on a silica gel column (1:4 EtOAc-hexane) gave 9 mg of the minor isomer (**9a**), 189 mg of mixture of isomers and 13 mg of the major isomer (**9b**) (combined yield 61%). (**9a**). HPLC t_R= 14.53 min. (eluent B). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.10-1.21 (m, 6H, $CO_2CH_2C\underline{H}_3$), 1.36 (s, 9H, Boc CH_3), 1.55-1.95 (m, 4H, H-4', H-5'), 2.59 (dd, *J*= 3.5, 17 Hz, H-2), 2.95 (dd, *J*= 10.7, 17 Hz, H-2), 3.15 (m, 1H, H-6'), 3.25 (m, *J*= 3.5, 10.7 Hz, H-3) 3.75 (m, 1H, H-3'), 3.94-4.10 (m, 5H, H-6', $CO_2C\underline{H}_2CH_3$), 4.36 (m, *J*= 11 Hz, H-2'), 4.83 (d, 1H, NH), 5.06 (s, 2H, Z CH_2), 7.30 (m, 5H, Z C_6H_5). (**9b**). HPLC t_R=15.91 min. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.12-1.26 (m, 6H, $CO_2CH_2C\underline{H}_3$), 1.32 (s, 9H, Boc CH_3), 1.52-1.85 (m, 4H, H-4', H-5'), 2.21 (m, 1H, H-2), 2.55-2.72 (m, 2H, H-6' H-2), 3.20 (m, *J*= 4.3, 10.7 Hz, H-3) 3.65 (m, 1H, H-3'), 4.05-4.30 (m, 6H, H-2', H-6', $CO_2C\underline{H}_2CH_3$), 4.71 (d, 1H, NH), 5.10 (s, 2H, Z CH_2), 7.30 (m, 5H, Z C_6H_5). Anal. Calc. for $C_{26}H_{38}O_8N_2$: C 61.66, H 7.51, N 5.53. Found: C 61.83, H 7.7.42, N 5.23.

*8(*S*)-tert-Butyloxycarbonylamino-1(*S*)- and (*R*)-ethoxycarbonyl-3-oxoindolizidines* (**7a** and **7b**).

The above mentioned mixture of **9 a** and **b** (0.21 g, 0.40 mmol) was dissolved in EtOH and hydrogenated at room temperature and 40 psi of pressure for 12 h, using 10% Pd/C as catalyst. After filtration of the catalyst and evaporation of the solvent, the residue was purified chromatographically (1:3 EtOAc-hexane to EtOAc) to give **7a** (11.7 mg, 9% yield) and **7b** (71.7 mg, 55% yield) whose ^{1}H and ^{13}C-NMR data are identical to those of compounds **7a(a')** and **7b(b')**.

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