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One-Pot Stereospecific Synthesis of 8a-Hydroxy- and 8a-Alkoxy-2,2,8-trisubstituted-3-oxoindolizidines. Mechanistic Studies on the Elaboration of the 8a-Substituted Indolizidine Ring

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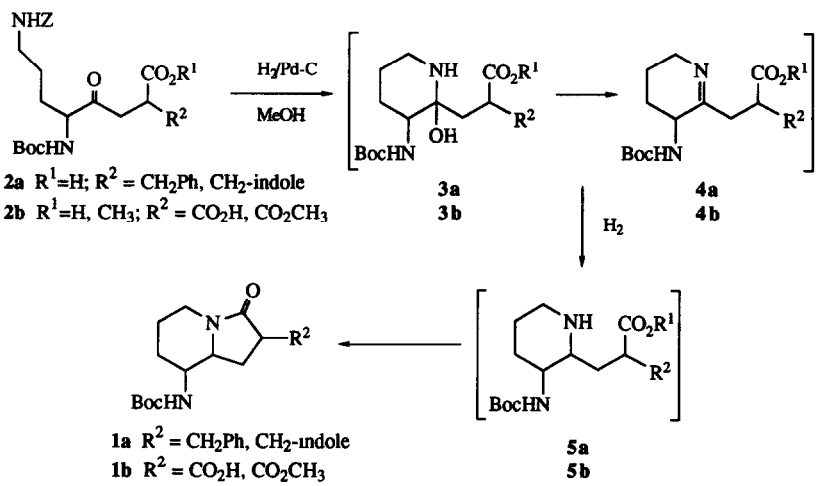
Abstract.—Stereospecific solvent-dependent synthesis of 8a(*R*)-alkoxy-8(*S*)-*tert*-butyloxycarbonyl-amino-2(*S*)-benzyl-3-oxoindolizidine-2-carboxylic acid or the corresponding methyl 8a(*S*)-hydroxy-2-carboxylate derivative, by hydrogenation of a conveniently protected α-benzyl-γ-ketodiester derived from ornithine, is described. The formation of an hemiaminal is proposed to rationalize the stereospecificity in the generation of the asymmetric centers, C-2 and C-8a, while the alcoholysis of a lactone intermediate, probably through a $B_{AL}2$ mechanism, can explain the formation of indolizidines bearing a free carboxylic acid when the reactions are carried out in alcoholic solvents.

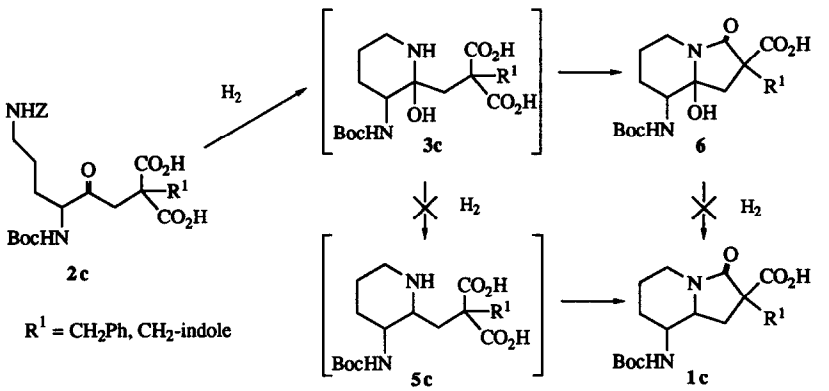
As part of our program directed to synthesize conveniently substituted bicyclic lactams for use as peptide conformation mimetics,[1] we planned an approach to the synthesis of 3-oxoindolizidines **1** from the γ-ketoacids or γ-ketodiesters **2**, according to scheme 1. We expected that, under reductive conditions, the corresponding



Scheme 1

deprotected ketoacids or ketoesters cyclized to the piperidines **5**, via hemiaminals **3** and/or imines **4**, suitable for an easy conversion to **1**. When this approach was followed using compounds **2a** and **2b**, the target 2-monosubstituted 3-oxoindolizidines **1a** and **1b** were directly formed in the hydrogenation medium with high stereocontrol at C-8a.[2,3] Before completion of the reaction, intermediate hemiaminals and piperidines **3a** and **5a** could be detected and characterized.[2] However, attempts to extend this approach to the preparation of the 2-

aralkyl-3-oxoindolizidine-2-carboxylic acid analogues **1c**, from the disubstituted malonic acids **2c**, did not lead to these indolizidines but to the 8a-hydroxy derivatives **6** [3] (Scheme 2). This fact seems to indicate that, in this case, the reaction proceeds through the formation of the monocyclic hemiaminal **3c** and that the γ-lactamization to **6** is faster than the hydrogenolysis to the piperidines **5c**. By other hand, the intramolecular N-acylation of **3c** seems to prevent the subsequent reduction to **1c** under the hydrogenation conditions used. These unexpected results and the current interest in indolizidine chemistry, particularly in hydroxylated indolizidines, due to the large number of indolizidine alkaloids with biological properties,[4-9] led us to study in detail the catalytic hydrogenation of disubstituted malonates derived from suitable protected ornithine derivatives.



Scheme 2

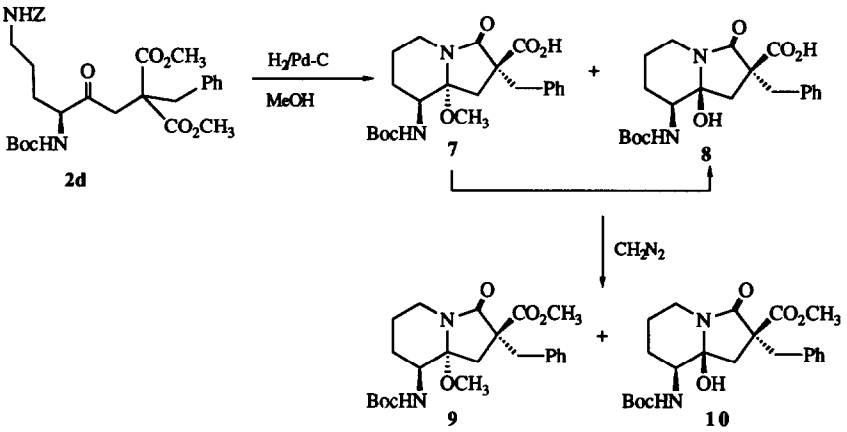
RESULTS AND DISCUSSION

As shown in scheme 3, the starting material for this study was the 2-benzyl-4-ketodiester **2d**, which was prepared from Boc-Orn(Z)-OH as previously described.[3] Catalytic hydrogenation of compound **2d** in methanol, for 4 h at room temperature and 30 psi of pressure, using Pd-C as catalyst, gave, after purification, a mixture of the 8a-methoxy- and 8a-hydroxy-2-carboxylic acid derivatives **7** and **8** as single isomers. Compound **8** was formed by hydrolysis of the methoxy derivative **7** during manipulation of the reaction since, when the course of the reaction was followed by HPLC the exclusive transformation of compound **2d** to the 8a-methoxy derivative **7** was observed. Taking into account that a slow conversion of this hygroscopic derivative into **8** was also observed during storage, the reaction mixture **7** + **8** was inmediately transformed into the more stable methyl ester derivatives **9** and **10**.[10]

The ^{1}H NMR spectra of **7-10** (Table 1) did not show signals for the H-8a proton and, therefore, the H-1 protons appeared as two doublets with large geminal coupling constants. Singlets at 3.01 and 3.08 ppm for **7** and **9**, respectively, indicated the presence of the *O*-methylated hemiaminal, while the interchangeable signal at 4.50 ppm in compound **10** was attributed to the OH resonance. The ^{13}C NMR spectra of compounds **7-10** showed quaternary signals at 90.17, 85.49, 90.03 and 85.94 ppm, respectively, characteristic of the hemiaminal carbon C-8a (Table 2).[11,12]

The assignment of the absolute configuration at the two new generated asymmetric centers, C-2 and C-8a, was made by 2D ^{1}H NMR NOESY experiments on the methyl ester derivatives **9** and **10** (Figure 1). Thus, compound **10** showed strong dipolar exchange of magnetization (NOE) between protons $H_{1\beta}$-H_8 and $H_{1\beta}$-2-CH_2 indicating that both H-8 and 2-benzyl group are of the same side of the molecule. Furthermore, strong NOE was observed between $H_{1\alpha}$-OH protons. These results suggest a *trans* disposition between the H-8 proton and the OH group. In contrast, in the case of the 8a-methoxy derivative **9** strong NOE's were observed between

protons H_8-OCH_3, $H_{1\beta}$-OCH_3 and $H_{1\beta}$-2-CH_2, that locate the OCH_3 and the 2-CH_2Ph groups and the H-8 proton in a *cis* disposition. Considering that the configuration at C-8 is fixed as *S* by the starting L-Orn, compounds **9** and **10** have the absolute stereochemistry 2*S*,8*S*,8a*R* and 2*S*,8*S*,8a*S*, respectively.



Scheme 3

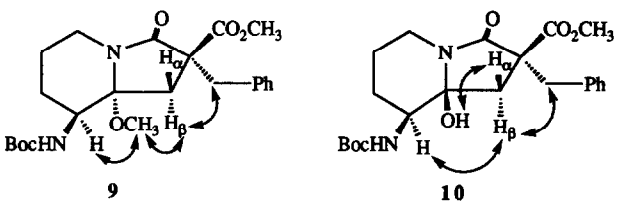
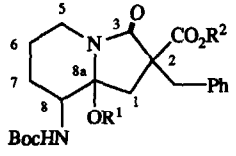


Figure 1.- Important observed NOE's for compounds **9** and **10**

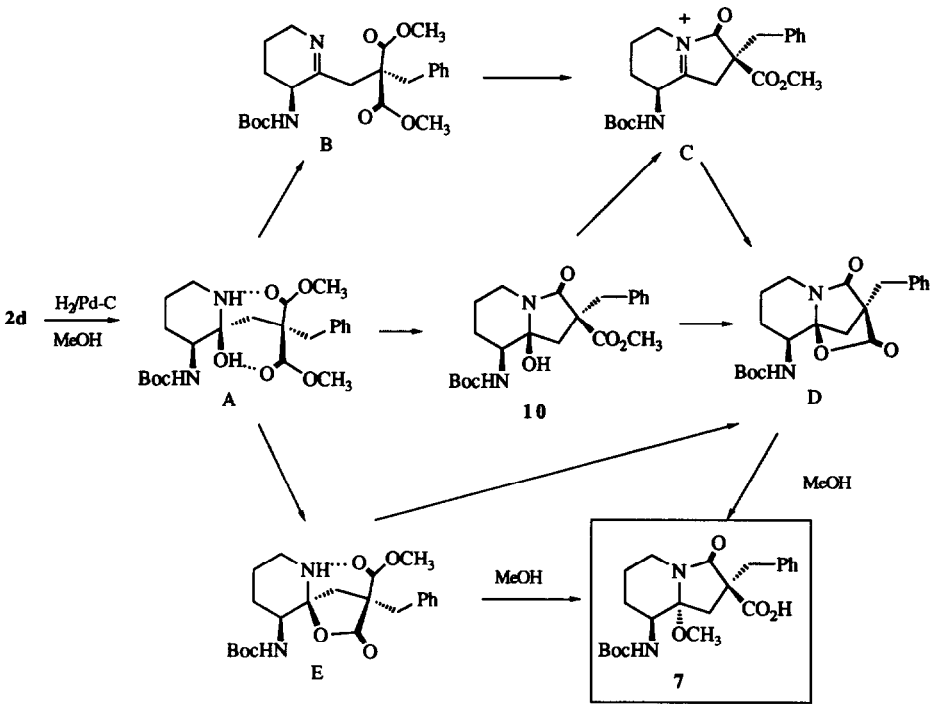
Two possible mechanisms starting from the intermediate hemiaminal A and involving the formation of intermediate lactones as key step can be proposed for explaining the formation of the carboxylic acid **7** and the stereochemical results of the cyclization (Scheme 4). Thus, assuming that the 2-alkyl and 3-amino groups are in equatorial disposition in the chair-shaped piperidine ring, the hydrolysis of the methyl ester to the corresponding carboxylic acid may take place through the lactone D, in which displacement of carboxylate by attack of the solvent (MeOH) on the alcohol carbon atom would lead directly to the 8a-methoxyindolizidine **7**. This alkyl-oxygen fission probably occurs by a $B_{AL}2$ mechanism,[13-15] since only the isomer in which the C-8a becomes wholly inverted during the fission was obtained.Tricyclic lactone D might be formed by intramolecular ester alkylation of the iminium ion C, which can arise from the 8a-hydroxy derivative **10** or by the more improbable intramolecular *N*-acylation of the imine intermediate B by the methyl ester. [16] The second pathway involves the formation of the spirolactone intermediate E, that can either evolve to lactone D or be directly hydrolyzed by the alcoholic solvent, following again a $B_{AL}2$ mechanism. In the latter case, a rapid γ-lactamization of the methoxypiperidine formed, exclusively through the methyl ester residue, would explain the formation of the 2-carboxylic acid derivative. At this point, it should be noted that no stereospecificity at C-2 was found in a similar catalytic hydrogenation using the ketodiacids **2c** (Scheme 2).[3] This fact seems to indicate that stereocontrol al C-2 is not only ruled by the possibility of hydrogen bond formation [17] in piperidine A but also by concerted-like

Table 1.—^{1}H NMR Data of 8a-alkoxy and 8a-hydroxy-3-oxoindolizidine derivatives **7-12** (300 MHz)



Compd.	R^1	R^2	Solvent	δ ppm (J, Hz)									
				H-1	H-5	H-6	H-7	H-8	NH	2-CH_2	R^1	R^2	Boc
7	Me	H	DMSO-d_6	2.38 (15.7) 2.26	3.68 2.43	1.57 1.07	1.57 1.35	2.73	6.18	3.21 (13.4) 2.92	3.01 (CH_3)	—	1.40
8	H	H	DMSO-d_6	1.99 (14.5) 1.79	3.55 2.69	1.66 1.22	1.55 1.22	2.99	5.78	2.80	—	—	1.35
9	Me	Me	$CDCl_3$	2.56 (15.8) 2.33	3.92 2.51	1.57 1.14	1.57	2.51	4.72	3.25	3.08 (CH_3)	3.81	1.45
10	H	Me	$CDCl_3$	2.43 (14.4) 2.28	3.84 2.90	1.76 1.44	1.76 1.66	3.25	4.93	3.52 (14.2) 3.04	4.50 (OH)	3.83	1.44
11	Et	H	DMSO-d_6	2.45 (15.4) 2.20	3.70 2.50	1.60 1.13	1.60 1.29	2.65	6.05	3.20 (13.7) 2.90	3.07 (CH_2) 1.10 (CH_3)	—	1.43
12	Et	Me	$CDCl_3$	2.57 (15.6) 2.32	3.90 2.51	1.57 1.14	1.57	2.51	4.75	3.25	3.40 (CH_2) 3.12 (CH_2) 1.14 (CH_3)	3.81	1.46

processes involving the formation of the tricyclic lactone D and its hydrolysis by the methanol or the methanolysis of the spirolactone B and the γ-lactamization through the methyl ester.



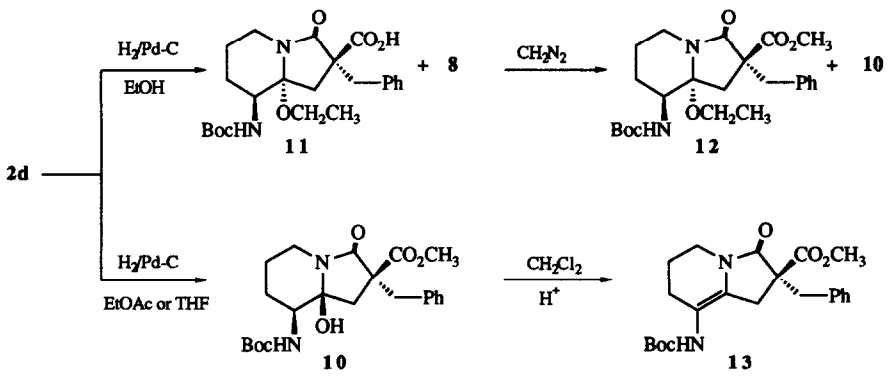
Scheme 4

The implication of the alcoholic solvent in the proposed cyclization mechanisms was demonstrated when compound **2d** was hydrogenated in EtOH instead MeOH, to give the 8a-ethoxy analogue **11** together with variable amounts of the hydroxy derivative **8**, coming again from the alkoxy derivative (Scheme 5). Treatment of this mixture with diazomethane afforded the corresponding methyl ester derivatives **12** and **10**, respectively. Both ethoxy substituted compounds **11** and **12** showed the spectroscopic characteristics of the 1,1-amino ethers similarly to those indicated for the OCH_3 analogues (Tables 1 and 2).

Finally, the hydrogenation reaction was achieved in non-alcoholic solvents, such as EtOAc or THF. In both cases the 8a-hydroxyindolizidine **10** was obtained as the only reaction product. An hemiaminal intermediate A, with two intramolecular hydrogen bonding, must be again claimed to explain the stereospecificity of the reaction. The stability of compound **10** in MeOH or EtOH solutions seems to support the spirolactone mechanism over the iminium ion pathway.

The 1,1-amino alcohols and the amino ethers here described easily lose one molecule of water or alcohol when treated with acids, as evidenced from the transformation of compound **10** into the 8,8a-enamino derivative **13** in CH_2Cl_2 and in the presence of TFA as catalyst.

It must be noted that 8a-unsubstituted indolizidine analogues **1c** were obtained by introduction of the 2-aralkyl substituent into the 3-oxoindolizidine-2-carboxylate skeleton **1b** (R^2=CO_2CH_3).[3] However, in contrast to that happens in the direct formation of the 2-aralkyl-2-carboxylate-8a-substituted indolizidines here reported, only a moderate stereocontrol at C-2 was found in this alkylation reaction to give, in this case, the 2*R* diastereomer as the major compound (2*R*/2*S* ~ 5).



Scheme 5

In summary, a solvent-dependent stereospecific preparation of (2*S*, 8*S*, 8a*R*)-8a-alkoxy- or (2*S*, 8*S*, 8a*S*)-8a-hydroxy-2,2,8-trisubstituted-3-oxoindolizidines was achieved by catalytic hydrogenation of α-benzyl-γ-ketodiesters derived from ornithine. Considering the high degree of functionalization of the compound here described, they might serve as convenient synthetic intermediates for the preparation of different indolizidine analogues.

Table 2.—Significant ^{13}C NMR data of compounds **7-12** (50 MHz)

Compd.	Solvent	C-2	C-8	C-8a	2-CH_2	R^1	R^2
7	DMSO-d_6	57.09	55.10	90.17	36.00	47.92	172.10 (CO)
8	DMSO-d_6	57.18	56.25	85.49	36.40	—	173.75 (CO)
9	$CDCl_3$	57.03	55.38	90.03	36.72	48.28	169.78(CO) 52.82 (CH_3)
10	$CDCl_3$	57.22	56.24	85.94	36.58	—	169.26 (CO) 53.44 (CH_3)
11	$CDCl_3$	57.24	55.41	90.39	37.16	56.31 (CH_2) 15.04 (CH_3)	172.17 (CO)
12	$CDCl_3$	57.08	55.50	89.74	36.77	56.02 (CH_2) 14.96 (CH_3)	169.67 (CO) 52.83 (CH_3)

EXPERIMENTAL

^1H NMR monodimensional and NOESY spectra were recorded with a Varian XL-300 spectrometer operating at 300 MHz, using TMS as internal standard (Table 1). NOESY spectra were recorded in $CDCl_3$ and benzene-d_6 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, Table 2). Mass spectra were obtained with a Vacuum Generators VG 12-250 spectrophotometer. Elemental analyses were obtained on a CHN-O-RAPID instrument. Analytical

TLC was performed on aluminium sheets coated with 0.2 mm layer of silica gel 60 F_{254} (Merck). Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Compounds were detected with UV light (250 nm) and ninhydrin spray. Analytical HPLC was carried out on a Waters apparatus (4 x 250 mm, LiChrosorb C_{18}, 5 μm) with 70:30 CH_3CN/H_2O (0.05% TFA) as eluent (Flow rate 1 mL/min) with UV (214 nm) detection.

Hydrogenation Reactions of Compound 2d

Method A: Reaction in MeOH

Compound **2d** (2.3 g, 4 mmol) in MeOH (140 mL) was hydrogenated at room temperature and 30 psi of pressure for 4h, using 10% Pd-C (230 mg) as catalyst. After filtration of the catalyst and evaporation of the solvent, the resulting residue was purified on a silica gel column, using CH_2Cl_2-MeOH 50:1, to give the following compounds:

8(S)-tert-*Butyloxycarbonylamino-2(S)-benzyl-8a(R)-methoxy-3-oxoindolizidine-2-carboxylic acid* **(7).** Yield: 1.04 g (63%), foam. HPLC t_R=9.73 min. Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C 63.14, H 7.23, N 6.69. Found: C 62.89, H 7.35, N 6.70.

8(S)-tert-*Butyloxycarbonylamino-2(S)-benzyl-8a(S)-hydroxy-3-oxoindolizidine-2-carboxylic acid* **(8).** Yield: 0.26 g (16%), foam. HPLC t_R=7.48 min. Anal. Calcd. for $C_{21}H_{28}N_2O_6$: C 62.36, H 6.98, N 6.93. Found: C 62.04, H 7.31, N 6.85.

Method B: Reaction in EtOH

Compound **2d** (0.8 g, 1.4 mmol) in EtOH (50 mL) was hydrogenated for 4 h in the conditions described for method A. After a similar work up the following compound was obtained:

8(S)-tert-*Butyloxycarbonylamino-2(S)-benzyl-8a(R)-ethoxy-3-oxoindolizidine-2-carboxylic acid* **(11).** Yield: 0.37 g (61%). HPLC t_R=12.93 min. Anal. Calcd. for $C_{23}H_{32}N_2O_6$: C 63.87, H 7.46, N 6.48. Found: C 63.49, H 7.61, N. 6.36.

A lower Rf compound, identified as **8** (116 mg, 21%), was also obtained.

Method C: Reaction in aprotic solvents

Compound **2d** (1 g, 1.7 mmol) in EtOAc or THF (60 mL) was hydrogenated for 20 h as described for methods A and B. After filtration of the catalyst and evaporation of the solvent, the residue was purified on a silica gel column using EtOAc-hexane 1:1 as eluent to give the following compound:

8(S)-tert-*Butyloxycarbonylamino-2(S)-benzyl-8a(S)-hydroxy-2(S)-methoxycarbonyl-3-oxoindolizidine* **(10).** Yield: 0.6 g (83%, EtOAc); 0.57 g (79%, THF). HPLC t_R=11.56 min. Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C 63.14, H 7.23, N 6.69. Found: C 63.28, H 7.42, N 6.54.

8(S)-tert-*Butyloxycarbonylamino-2(S)-benzyl-8a(R)-methoxy-2(S)-methoxycarbonyl-3-oxoindolizidine* **(9).**

An ethereal solution of diazomethane (from N-nitrosomethylurea, 0.5 g) was added, at 0°C, to a 4:1 mixture of compounds **7** and **8** (0.9 g, 2.1 mmol) in THF (20 mL). After 1 h of reaction the solvents were evaporated and the resulting residue was purified on a silica gel column using EtOAc-hexane 1:2 as eluent, to yield 0.53 g (56%) of the product as a foam. HPLC t_R=19.25 min. Anal. Calcd. for $C_{23}H_{32}N_2O_6$: C 63.87, H 7.46, N 6.48. Found: C 63.70, H 7.57, N 6.60. MS: 432 (M^+), 400 (M^+-CH_3OH), 376 (M^+-^{t}Bu), 317, 91.

Compound **10** (0.13 g, 15%) was also obtained.

8(S)-tert-*Butyloxycarbonylamino-2(S)-benzyl-8a(R)-ethoxy-2(S)-methoxycarbonyl-3-oxoindolizidine* **(12).**

An etheral solution of diazomethane was added, at 0°C, to a mixture of compounds **11** and **8** (0.18 g, 0.4 mmol, **11/8** ~ 3:1), in THF (5 mL). After stirring for 1 h at this temperature, the solvents were evaporated and the residue was purified on a silica gel column using EtOAc-hexane 1:3 as eluent, to give 0.12 g (64%) of

12. HPLC t_R=27.23 min. Anal. Calcd. for $C_{24}H_{34}N_2O_6$: C 64.55, H 7.67, N 6.27. Found: C 64.51, H 7.43, N 6.12.

Compound **10** (34 mg, 19%) was also obtained.

8-tert-Butyloxycarbonylamino-2(S)-benzyl-2(S)-methoxycarbonyl-3-oxo-$\Delta^{8,8a}$-hexahydroindolizine **(13).**

A solution of compound **10** (0.1 g, 0.24 mmol) and TFA (5.7 μL, 0.05 mmol) in CH_2Cl_2 (10 mL) was stirred for 3 h at room temperature. After evaporation of the solvent, the resulting residue was purified by preparative TLC using Et_2O/EtOAc 40:1 as eluent, to yield 53 mg (55%) of the title compound. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30-7.13 (m, 5H, Ph), 5.25 (s, 1H, NH), 3.80 (s, 3H, CO_2CH_3), 3.40 (m, 1H, H-5), 3.27 (d, 1H, 2-CH_2, J=14.2), 3.11 (d, 1H, H-1, J=17.1), 3.10 (d, 1H, 2-CH_2), 2.71 (d, 1H, H-1), 2.04 (m, 2H, H-5, H-7), 1.75 (m, 2H, H-6, H-7), 1.45 (s, 9H, Boc CH_3), 1.45 (m, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.48, 170.76 and 155.80 (CO), 135.57, 129.97, 128.22, 127.07 (Ar), 109.03 (C-8 and C-8a), 80.05 (Boc, C), 56.13 (C-2), 52.93 (OCH_3), 39.59, 38.77, 30.59 and 25.96 (C-1, C-5, C-7 and 2-CH_2), 28.22 (Boc, CH_3), 20.42 (C-6). Anal. Calcd. for $C_{22}H_{28}N_2O_5$: C 65.98, H 7.04, N 7.00. Found: C 66.11, H 7.29, N 6.67.

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