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Synthesis of 2-Substituted 8-Amino-3-oxoindolizidine-2-carboxylic Acid Derivatives as Peptide Conformation Mimetics

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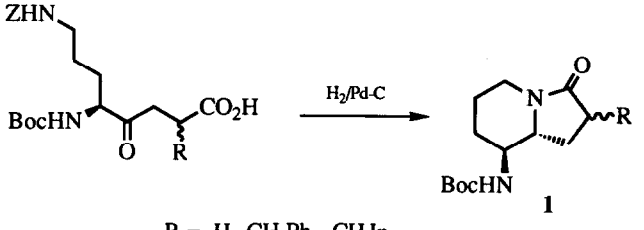
Abstract.— The synthesis of methyl 8-*tert*-butyloxycarbonylamino-3-oxoindolizidine-2-carboxylate and its alkyl derivatives bearing Phe, Trp and Asp side chains at C_2 position are described. These bridged bicyclic lactams, obtained with high and moderate stereocontrol at C_{8a} and C_2, respectively, have appropriate N- and C-protecting groups making them suitable for incorporation as spacers into higher peptides.

The study of constrained analogues of bioactive peptides have acquired great popularity in an attempt to establish three-dimensional structure-bioactivity relationships and to develop new pharmaceutical agents with prolonged action or more selective properties.[1]

In recent years, efforts have been made to synthesize compounds designed to mimic particular secondary structures, specially β- and γ-turns.[2,3] In this sense, heterocyclic and aromatic compounds, lactams and bicyclic systems have been inserted into different peptides of biological interest as non peptidic substitutes of β-turns.[3-7] Among bicyclic systems, nitrogen bridged bicyclic lactams, such as indolizidine derivatives[8] and thio analogues[9] have been described to mimic the central part of a β-turn.[10]

In a previous communication we reported a readily accesible route to 8-amino-3-oxoindolizidine derivatives **1** as conformationally restricted ornithyl pseudodipeptides.[11] As shown in scheme 1, the most important aspect of this synthesis is the rapid construction of the 3-oxoindolizidine skeleton in one step, involving two consecutive intramolecular cyclizations, with high degree of stereocontrol at C_{8a}.



1

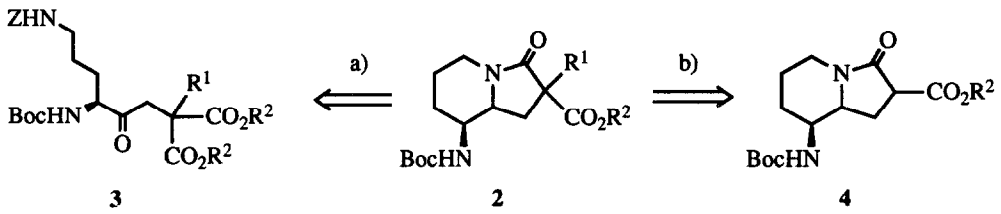
R = H, CH_2Ph, CH_2In

Scheme 1

Taking into account that amino acid side chains play an important role in receptor recognition,[3] we have now focused our interest on the preparation of 2-substituted 8-amino-3-oxoindolizidine-2-carboxylic acid derivatives **2** having side chains at C_2 position. These building blocks have also amino and carboxylic functions to extend the peptide chain C- and N-terminally.

Based upon our prior studies on the preparation of **1**,[11] two retrosynthetic strategies were envisaged for the synthesis of the target compounds **2** (scheme 2). Strategy a) would imply the use of the 4-ketodiesters **3**, in which the amino acid side chain R^1 has been previously introduced. Strategy b) would imply the elaboration of

the common 3-oxoindolizidine-2-carboxylate skeleton **4** and the subsequent introduction of the corresponding amino acid side chain.



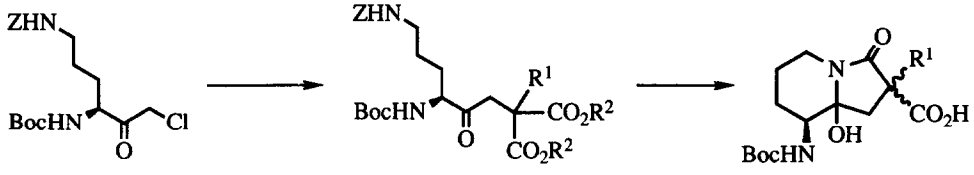
3 **2** **4**

Scheme 2

The present paper describes the synthesis of the 3-oxoindolizidines **2** in which the R^1 substituent is the Phe, Trp and Asp side chain, respectively.

RESULTS AND DISCUSSION

Since it could be expected that alkylation of linear malonic esters proceeded in higher yield than that of 3-oxoindolizidine-2-carboxylates, we first examined strategy a). With this end, compound **6**, obtained from dimethyl malonate and conveniently protected ornithine chloromethyl ketone,[12,13] was alkylated with benzyl bromide and methiodide of gramine to provide the disubstituted malonates **7** and **8** in 88% and 76% yield, respectively (scheme 3). Surprisingly, when the dicarboxylic acids **9** and **10**, obtained by saponification of **7** and **8**, were hydrogenated under the same conditions as those used for the synthesis of **1**,[11] the target oxoindolizidines were not formed but the corresponding 8a-hydroxy derivatives **11** and **12**, as deduced from NMR and mass spectra. Thus, compounds **11** and **12**, obtained as mixtures of two diastereoisomers, did not show signals for the H_{8a} proton in their ^1H NMR spectra, while quaternary carbon signals appeared at 93.1 and 90.8 ppm for compound **11**, and at 90.3 and 85.5 ppm for **12**, attributed to the hemiaminal carbon C_{8a}.[14,15] 8a-Substituted indolizidines were also obtained by hydrogenation of the disubstituted dimethyl malonates **7** and **8**.[16]



5

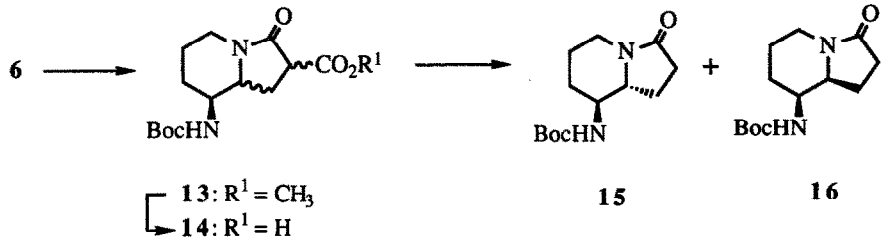
6: $R^1 = H$; $R^2 = CH_3$
7: $R^1 = CH_2Ph$; $R^2 = CH_3$
8: $R^1 = CH_2In$; $R^2 = CH_3$
9: $R^1 = CH_2Ph$; $R^2 = H$
10: $R^1 = CH_2In$; $R^2 = H$

11: $R^1 = CH_2Ph$
12: $R^1 = CH_2In$

Scheme 3

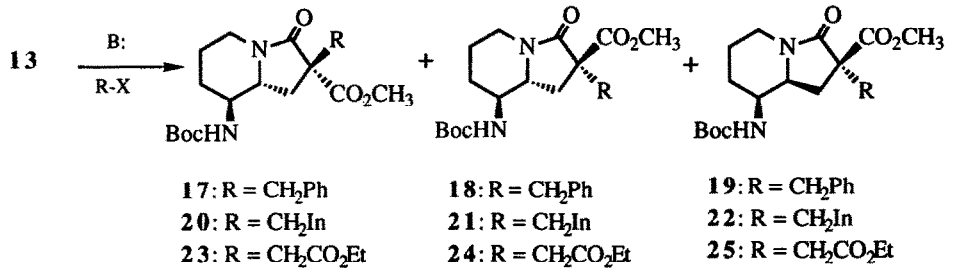
The desired methyl 8-*tert*-butyloxycarbonylamino-3-oxoindolizidine-2-carboxylate (**13**) was formed in high yield, when the monosubstituted malonate derivative **6** was hydrogenated for 15 h at room temperature and

15 psi of pressure, using Pd-C as catalyst (Scheme 4). Indolizidine **13** showed a complex ^{1}H NMR spectrum in which the expected presence of diastereomers at the C_2 centre was observed. The diastereomeric mixture **13** was not separated, since it is well known that half-esters of monosubstituted malonic acids are subject to a rapid racemization which prevents their resolution.[17,18] In order to determine the stereoselectivity of the intramolecular reductive amination and to assign the configuration at the C_{8a} position, the carboxylic acid **14**, obtained by saponification of **13** with NaOH, was decarboxylated to provide the 2-unsubstituted 3-oxoindolizidines **15** and **16** in a 12:1 ratio, as measured by HPLC. The $J_{8,8a}$ coupling constant values in the ^{1}H NMR spectra of these compounds allowed us to assign the *R* configuration for C_{8a} of the major diastereomer **15** ($J_{8,8a}$=9.8 Hz) and the *S* configuration for the minor one **16** ($J_{8,8a}$=2.8 Hz).



Scheme 4

According to strategy b), the 3-oxoindolizidine-2-carboxylate **13** was used as common intermediate in the synthesis of the analogues containing Phe, Trp and Asp side chains at C_2 position. Alkylation of compound **13** with benzyl bromide and methiodide of gramine using sodium methoxide as base gave the corresponding 2-arylmethyl substituted diastereoisomers **17-19** (65% total yield) and **20-22** (58% total yield), respectively, in an approximately 10:2:1 ratio, in both cases (Scheme 5). These diastereomeric mixtures were separated chromatographycally.



Scheme 5

The stereochemistry at C_2 and C_{8a} of compounds **17-22** was assigned by ^{1}H NMR spectroscopy (Table 1). Thus, the configuration at C_{8a} in compounds **17**, **18**, **20** and **21** with $J_{8,8a}$ of ~ 9.5 Hz, indicating a *trans* disposition between H_8 and H_{8a} protons, was assigned as *R*, while $J_{8,8a}$values of ~ 3 Hz indicated that the configuration of C_{8a} is *S* in diastereomers **19** and **22**. The shielding observed for the H_{8a} proton in compounds **17**, **19**, **20** and **22** when compared with the same proton in compounds **18** and **21** and in the non arylmethyl substituted analogues indicated that the arylmethyl chain and the H_{8a} are in *cis* disposition. Moreover, a shielding for the H_8 proton was observed in compounds **18** and **21**, in agreement with the presence of the arylmethyl moiety in *cis* disposition.

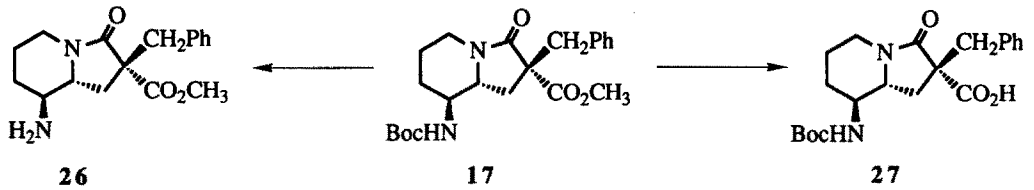
Table 1. Significant ^1H NMR data of 3-oxoindolizidine derivatives **13-22**, **26** and **27** (300 MHz, $CDCl_3$)

	δ (ppm)											
Compd.	H-1	H-1'	H-2	H-5	H-5'	H-6	H-6'	H-7	H-7'	H-8	H-8a	$J_{8,8a}$ (Hz)
13	2.15-2.65		3.15	4.07	2.50	1.76	1.35	2.08	1.35	3.15	3.44	—
14[a]	2.50	2.12	3.28	4.07	2.60	1.78	1.43	2.08	1.25	3.45	3.28	—
15[a]	2.17	1.93	2.38	4.07	2.52	1.74	1.48	2.08	1.26	3.28	3.08	9.8
16	2.05	1.85	2.35	4.13	2.66	1.63	1.49	1.96	1.69	3.93	3.62	2.8
17	2.39	2.27	—	4.04	2.18	1.67	1.48	1.97	0.94	3.23	1.74	9.1
18	2.53	2.53	—	3.99	2.48	1.65	1.18	1.90	1.18	2.63	3.09	9.7
19	2.26	2.15	—	4.04	2.32	1.47		1.93	1.32	3.64	2.32	2.9
20	2.32	2.24	—	3.93	2.02	1.53	1.35	1.87	0.84	3.16	2.02	8.9
21	2.60	2.02	—	3.94	2.43	1.53	1.37	1.81	1.10	2.43	3.06	9.9
22	2.43	2.15	—	3.94	2.42	1.53	1.36	1.81	1.10	3.50	2.43	2.8
26[b]	2.28		—	3.78	2.28	1.64	1.23	1.91	1.23	2.73	2.49	9.9
27	2.15		—	3.76	2.15	1.69	1.18	1.79	1.04	3.00	2.06	8.5

[a] From reference 11. [b] Registered in DMSO-d_6

The alkylation of the 3-oxoindolizidine-2-carboxylate **13** with ethyl bromoacetate proceeded in poor yield when sodium methoxide was used as base; therefore, the reaction was carried out, under similar conditions, but using NaH. In this way, a mixture of 2-substituted diastereomers was obtained in 59% yield. Although this mixture could not be separated, its ^1H NMR spectrum showed the presence of two major diastereomers in an approximately 5:1 ratio which were temptatively assigned as **23** and **24**, respectively. Traces of a third diastereoisomer, presumably compound **25**, were also detected. Due to the complexity of the ^1H NMR spectrum and to the lack of significant shielding effects caused by the arylmethyl chain, this temptative assignment was based on the results of the precedent alkylations of indolizidine **13** and on the ratio of isomers at C_{8a} in this starting compound.

Finally, the possibility of introducing all these N- and C-protected building blocks into higher peptides was demonstrated by the partial deprotections of compound **17** using either TFA or NaOH to provide the N- or C-deprotected analogues **26** or **27** (scheme 6).



26 **17** **27**

Scheme 6

The synthetic route described in this paper represents an efficient methodology for the synthesis of 8-amino-3-oxoindolizidine-2-carboxylate derivatives bearing different amino acid side chains at C_2 position. These compounds could be employed as new building blocks able to provide an interesting variation in conformational restraint for use in synthetic analogues of bioactive peptides.

EXPERIMENTAL PROCEDURES

^1H NMR spectra were recorded with a Varian EM 390 or a Varian XL-300 spectrometers operating at 90 or 300 MHz, respectively, using TMS as internal standard. ^{13}C NMR spectra were registered on a Varian XL-300 (75 MHz). 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 (254 nm) and ninhydrin spray. Analytical HPLC was carried out on a Beckman apparatus (4.6 x 250 mm, Ultrasphere C-18, 5 mm) with Et_3N/H_3PO_4 buffer (TEAP, PH=3)/CH_3N system as eluent (Flow rate 1 mL/min) with UV (210 nm) detection. Boc-Orn(Z)-OH was purchased from Bachem and was of the L-configuration.

Boc-Orn(Z)-CH_2Cl (**5**)

To a solution of Boc-Orn(Z)-OH (9.9 g, 27 mmol) in dry THF (60 mL) were successively added, at 0°C, N-methylmorpholin (3.2 mL, 29 mmol) and isobutylchloroformate (3.8 mL, 29 mmol). After stirring for 1 h at 0°C, the reaction mixture was filtered, the filtrate cooled at -10°C and then, an ethereal solution of diazomethane (from N-nitroso-N-methylurea, 5.5 g) was added. After 15 min of reaction, a solution of 2N HCl/MeOH (15 mL, 30 mmol) was added and the stirring continued until N_2 evolution ceased. The solution was neutralized with Et_3N and the solvents were evaporated. The resulting residue was dissolved in EtOAc (200 mL), washed with H_2O and the organic layer was dried over Na_2SO_4. Evaporation and purification on a silica gel column (EtOAc-hexane, 1:2) yielded 8.83 g (82%) of the product as a white solid. m.p. 80-82°C (EtOAc-hexane). ^1H NMR (90 MHz, $CDCl_3$): δ 1.40 (s, 9H, Boc CH_3), 1.20-1.90 (m, 4H, β- and γ-Orn CH_2), 3.20 (m, 2H, δ-Orn CH_2), 4.20 (s, 2H, CH_2Cl), 4.43 (m, 1H, α-Orn CH), 5.03 (s, 2H, Z CH_2), 7.30 (s, 5H, Z C_6H_5). Anal. Calcd. for $C_{19}H_{27}ClN_2O_5$: C 57.21, H 6.82, Cl 8.89, N 7.02. Found: C 57.45, H 7.00, Cl 8.99, N 7.28.

*Methyl 8-benzyloxycarbonylamino-5(*S*)-*tert*-butyloxycarbonylamino-2-methoxycarbonyl-4-oxooctanoate* (**6**)

A mixture of compound **5** (7.9 g, 19.8 mmol) and sodium iodide (2.97 g, 19.8 mmol) in 1,2-dimethoxyethane (60 mL) was stirred at room temperature for 15 min and then added to a solution of freshly prepared sodium salt of dimethylmalonate (3.43 g, 22 mmol) in 1,2-dimethoxyethane (10 mL). Stirring was continued for 1 h, the solvent removed and the residue was extracted with chloroform (100 mL) and washed with H_2O (100 mL). The organic layer was dried (Na_2SO_4) and evaporated leaving a residue which was purified on a silica gel column with EtOAc-hexane (1:4) as eluent to provide 9.3 g (95%) of the product. m.p. 98-99°C. ^1H NMR (90 MHz, $CDCl_3$): d 1.40 (s, 9H, Boc CH_3), 1.40-1.96 (m, 4H, 6-H and 7-H), 3.20 (m, 4H, 3-H and 8-H), 3.70 (s, 6H, CO_2CH_3), 3.86 (t, 1H, 2-H, J=6 Hz), 4.20 (m, 1H, 5-H), 5.10 (s, 2H, Z CH_2), 7.30 (s, 5H, Z C_6H_5). Anal. Calcd. for $C_{24}H_{34}N_2O_9$: C 58.29, H 6.93, N 5.66. Found: C 58.10, H 6.98, N 5.35.

*Methyl 2-benzyl-8-benzyloxycarbonylamino-5(*S*)-*tert*-butyloxycarbonylamino-2-methoxycarbonyl-4-oxooctanoate* (**7**)

To a solution of compound **6** (0.99 g, 2 mmol) in 1,2-dimethoxyethane (25 mL) were added sodium methoxide (0.16 g, 3 mmol) and benzyl bromide (0.72 mL, 6 mmol). After stirring overnight at room temperature, the solvent was evaporated and the residue was extracted with EtOAc (100 mL). The organic extract was washed with H_2O (50 mL), dried (Na_2SO_4) and evaporated to yield, after purification on a silica gel column (EtOAc-hexane, 1:2), 1.03 g (88%) of the product as a syrup. ^1H NMR (90 MHz, $CDCl_3$): d 1.38 (s, 9H, Boc CH_3), 1.10-1.93 (m, 4H, 6-H and 7-H), 3.06 (m, 2H, 3-H), 3.16 (m, 2H, H-8), 3.40 (m, 2H, Bzl CH_2), 4.20 (m, 1H, 5-H), 5.03 (s, 2H, Z CH_2), 7.30 (s, 5H, Z C_6H_5). Anal. Calcd. for $C_{31}H_{40}N_2O_9$: C 63.68, H 6.89, N 4.79. Found: C 63.47, H 6.99, N, 4.50.

Methyl 8-benzyloxycarbonylamino-5(S)-tert-butyloxycarbonylamino-2-(indole-3-yl) methyl-2-methoxycarbonyl-4-oxooctanoate (**8**)

A solution of **6** (1.98 g, 4 mmol) in MeOH (50 mL) was treated, at 0°C, with sodium methoxide (0.22 g, 4 mmol), gramine (0.7 g, 4 mmol) and methyl iodide (0.5 mL, 8 mmol). Stirring was continued for 1 h at 0°C. After filtration and evaporation of the solvent, the residue was extracted with EtOAc (150 mL) and washed with H_2O (50 mL). The organic layer was dried (Na_2SO_4) and evaporated to yield a residue which was chromatographed on a silica gel column using EtOAc-hexane (1:2) as eluent: 1.9 g (76%), syrup. ^1H NMR (90 MHz, $CDCl_3$): d 1.40 (s, 9H, Boc CH_3), 1.20-2.00 (m, 4H, 6-H and 7-H), 3.03 (m, 2H, H-8), 3.13 (m, 2H, H-3), 3.50 (m, 2H, Ind. CH_2), 4.10 (m, 1H, H-5), 5.00 (s, 2H, Z CH_2), 6.83-7.50 (m, 10H, Ind. and Z C_6H_5), 8.46 (s, 1H, NH^i). Anal. Calcd. for $C_{33}H_{41}N_3O_9$: C 63.55, H 6.62, N 6.74. Found: C 63.90, H 6.58, N 6.64.

2-Substituted 8(S)-tert-butyloxycarbonylamino-8a-hydroxy-3-oxoindolizidine-2-carboxylic acids **11** *and* **12**. *General procedure.*

Compounds **7** and **8** (1.5 mmol) were dissolved in MeOH (30 mL) and stirred for 3 h at room temperature in the presence of 2N NaOH (3 mmol). After evaporation of the MeOH, the obtained residue was dissolved in H_2O (20 mL), acidifed with 1N HCl to pH=3 and extracted with EtOAc (2 x 100 mL). The organic extracts were dried (Na_2SO_4) and evaporated to dryness to give crude dicarboxylic acid derivatives **9** and **10**, which were dissolved in MeOH (100 mL) and hydrogenated at room temperature and 30 psi of pressure for 18 h, using 10% Pd-C as catalyst. After filtration of the catalyst and evaporation, the resulting residue was purified on a silica gel column using $CHCl_3$-MeOH 95:5 containing 1% AcOH as eluent. The following compounds were obtained by this general procedure:

2-Benzyl derivative **11**. Yield: 53% (from **7**), white foam. ^1H NMR (300 MHz, DMSO-d_6) d 1.35 and 1.36 (s, 9H, Boc CH_3), 1.20-1.75 (m, 4H, H-6 and H-7), 2.05-2.36 (m, 2H, H-1), 2.47 and 2.65 (m, 1H, H-5), 2.90-3.26 (m, 3H, H-8 and Bzl CH_2), 3.75 (m, 1H, H-5), 6.80 and 6.88 (d, 1H, 8-NH), 7.13-7.30 (m, 5H, Bzl C_6H_5). ^{13}C NMR (75 MHz, DMSO-d_6): d 176.4, 174.2, 173.4 and 172.3 (CO), 155.1 and 155.0 (Boc CO), 93.1 and 90.8 (C_{8a}), 77.8 and 77.7 (Boc C), 58.1 and 57.8 (C_2), 53.7 and 52.2 (C_8), 41.7, 40.8, 31.7, 30.7, 27.6, 23.5 and 23.1 (CH_2), 28.2 and 28.1 (Boc CH_3). MS: 360 (M^+-44), 342 (M^+-61), 286, 227, 91.

2-(Indole-3-yl)methyl derivative **12**. Yield: 57% (from **8**), foam. ^1H NMR (300 MHz, DMSO-d_6) d 1.29 and 1.38 (s, 9H, Boc CH_3), 1.20-1.70 (m, 4H, H-6 and H-7), 1.97 and 2.11 (m, 2H, H-1), 2.34 and 2.68 (m, 1H, H-5), 2.96 (m, 2H, CH_2-Ind, H-8), 3.25 (m, 1H, CH_2-Ind), 3.56 (m, 1H, H-5), 5.50 and 5.83 (d, 1H, 8-NH), 6.87-7.51 (m, 5H, indole), 10.74 and 10.91 (s, 1H, NH^i). ^{13}C NMR (75 MHz, DMSO-d_6): d 174.0, 173.3, and 172.1 (CO), 154.9 (Boc CO), 90.3 and 85.5 (C_{8a}), 77.9 and 77.8 (Boc C), 57.4 and 56.8 (C_2), 55.8 and 54.9 (C_8), 41.2, 40.9, 36.1, 35.4, 26.7, 26.5, 23.5 and 22.9 (CH_2), 28.2 and 28.1 (Boc CH_3). MS: 443 (M^+), 381 (M^+-61), 130.

8(S)-tert-Butyloxycarbonylamino-2-methoxycarbonyl-3-oxoindolizidine (**13**)

Compound **6** (2.5 g, 5 mmol) in MeOH (150 mL) was hydrogenated at room temperature and 30 psi of pressure in the presence of 10% Pd-C as catalyst. After filtration of the catalyst and evaporation, the resulting residue was purified on a silica gel column, using EtOAc-hexane (1:1) as eluent, to give 1.5 g (95%) of the title compound as a white foam. ^{13}C NMR (75 MHz, $CDCl_3$): d 171.0, 170.6, 168.4 and 167.9 (CO), 159.9 and 155.6 (Boc CO), 80.0 (Boc C), 60.9 and 60.0 (C_{8a}), 53.4 and 53.1 (C_8), 52.6 (CO_2CH_3), 48.0 and 47.7 (C_2), 39.8 (C_5), 31.4, 27.5, 26.9, 23.7, 23.4, (CH_2), 28.3 (Boc CH_3). Anal. Calcd. for $C_{15}H_{24}N_2O_5$: C 57.68, H 7.74, N 8.97. Found: C 57.50, H 7.38, N 8.75. ^1H NMR data recorded in Table 1.

8(S)-tert-Butyloxycarbonylamino-3-oxoindolizidine-2-carboxylic acid(**14**)[11]

A solution of compound **4** (0.72 g, 2.8 mmol) and 2N NaOH (2 mL, 4 mmol) in MeOH (10 mL) was stirred at room temperature for 1 h. After evaporation of the MeOH, water (10 mL) was added, the solution acidified with 1N HCl to pH=3, and the product extracted with EtOAc (2 x 50 mL). The organic layer was dried

(Na_2SO_4) and evaporated to dryness to give a white foam (0.61 g, 90%). Anal. Calcd. for $C_{14}H_{22}N_2O_5$: C 56.36, H 7.43, N 9.39. Found: C 56.21, H 7.79, N 9.07.

Decarboxylation of compound **14**

A solution of compound **14** (0.43 g, 1.4 mmol) in dioxane (25 mL) was refluxed for 15 h. The solvent was evaporated to give a mixture of compounds **15** and **16** in a 12:1 ratio (measured by HPLC, eluent CH_3CN-TEAP (25:75). These compounds were separated on a silica gel column using CH_2Cl_2-MeOH (40:1) as eluent:
8(S)-tert-Butyloxycarbonylamino-3-oxo-8a(R)-indolizidine **(15).** Yield: 260.5 mg (71%), foam. HPLC t_R=12.39 min, eluent CH_3CN-TEAP (25:75). Anal. Calcd. for $C_{13}H_{22}N_2O_3$: C 61.39, H 8.72, N 11.01. Found: C 61.43, H 8.59, N 10.75. ^1H NMR data recorded in Table 1.
8(S)-tert-Butyloxycarbonylamino-3-oxo-8a(S)-indolizidine **(16).** Yield: 19.7 mg (5.5%), foam. HPLC t_R=10.94 min, eluent CH_3CN-TEAP (25:75). Anal. Calcd. for $C_{13}H_{22}N_2O_3$: C 61.39, H 8.72, N 11.01. Found: C 61.28, H 8.80, N 10.69. ^1H NMR data recorded in Table 1.

Synthesis of 2-benzyl-8(S)-tert-butyloxycarbonylamino-2-methoxycarbonyl-3-oxoindolizidine derivatives **17-19**

To a solution of compound **13** (1 g, 3.2 mmol) in dry 1,2-dimethoxyethane (30 mL) were added freshly prepared sodium methoxide (0.26 g, 4.8 mmol) and benzyl bromide (0.56 mL, 6.4 mmol). After stirring overnight at room temperature, the solvent was evaporated and the residue was dissolved in EtOAc (100 mL) and washed with H_2O (50 mL). The organic extract was dried (Na_2SO_4), concentrated in vacuo and purified on a silica gel column (EtOAc-hexane, 1:2) to yield the following compounds:
(8*S*, 8a*R*, 2*R*) Isomer **17**: Yield: 640 mg (50%). Anal Calcd. for $C_{22}H_{30}N_2O_5$: C 65.65, H 7.51, N 6.96. Found: C 65.52, H 7.70, N 7.02.
(8*S*, 8a*R*, 2*S*) Isomer **18**: Yield: 132 mg (10.3%). Anal Calcd. for $C_{22}H_{30}N_2O_5$: C 65.65, H 7.51, N 6.96. Found: C 65.73, H 7.38, N 6.98.
(8*S*, 8a*S* 2*S*) Isomer **19**: Yield: 58 mg (4.5%). Anal Calcd. for $C_{22}H_{30}N_2O_5$: C 65.65, H 7.51, N 6.96. Found: C 65.48, H 7.71, N 6.76.
^1H NMR data of all these compound are recorded in Table 1.

Synthesis of 8(S)-tert-butyloxycarbonylamino-2-methoxycarbonyl-2-(indole-3-yl)methyl-3-oxoindolizidine derivatives **20-22**

To a solution of **13** (1 g, 3.2 mmol) in dry 1,2-dimethoxyethane (30 mL) were added, at 0°C, sodium methoxide (0.26 g, 4.8 mmol), gramine (0.56 g, 3.2 mmol) and methyl iodide (0.4 mL, 6.4 mmol). After stirring at 0°C for 15 min and overnight at room temperature, the solvent was evaporated. The resulting residue was extracted with EtOAc (100 mL), washed with H_2O (50 mL), dried over Na_2SO_4 and evaporated. The residue was purified first on a silica gel column using EtOAc-hexane (1:1) followed by preparative TLC (EtOAc/Hex, 1:2) to give the following compounds:
(8*S*, 8a*R*, 2*R*) Isomer **20**: Yield: 639 mg (45.2%). Anal Calcd. for $C_{24}H_{31}N_3O_5$: C 65.29, H 7.08, N 9.52. Found: C 65.13, H 7.21, N 9.47.
(8*S*, 8a*R*, 2*S*) Isomer **21**: Yield: 120 mg (8.5%). Anal Calcd. for $C_{24}H_{31}N_3O_5$: C 65.29, H 7.08, N 9.52. Found: C 65.34, H 7.19, N 9.62.
(8*S*, 8a*S*, 2*S*) Isomer **22**: Yield: 61 mg (4.3%). Anal Calcd. for $C_{24}H_{31}N_3O_5$: C 65.29, H 7.08, N 9.52. Found: C 65.44, H 6.95, N 9.26.
^1H NMR data of these compound are listed in Table 1.

Synthesis of 8(S)-tert-butyloxycarbonylamino-2-methoxycarbonyl-2-ethoxycarbonylmethyl-3-oxoindolizidine derivatives **23-25**

To a solution of compound **13** (0.77 g, 2.5 mmol) in dry 1,2-dimethoxyethane (20 mL) was added NaH (0.72 g, 3 mmol). After evolution of hydrogen ceased, ethyl bromoacetate (0.7 mL, 6 mmol) was added and stirring continued at room temperature for 2 days. The solvent was evaporated, the resulting residue was extracted with EtOAc (100 mL) washed with H_2O (50 mL), dried over Na_2SO_4 and evaporated to dryness. The

residue was chromatographed on a silica gel column using EtOAc-hexane (1:2) as eluent to yield 0.58 g (59%) of a mixture of the diastereoisomeric compound **23-25**. ^{1}H NMR of de mixture (300 MHz, $CDCl_3$): d 1.24 and 1.25 (t, 3H, OCH_2CH_3), 1.35 (m, 1H, H-7), 1.44 (s, 9H, Boc CH_3), 1.53 (m, 1H, H-6), 1.78 (m, 1H, H-6), 2.13 (m, 1H, H-7), 2.34 (dd, 1H, H-1), 2.63 (m, 2H, H-1 and H-5), 2.82 (d, 1H, 2-CH_2), 3.08 (d, 1H, 2-CH_2), 3.30 and 3.22 (m, 1H, H-8a), 3.51 (m, 1H, H-8), 3.58, 3.75 and 3.78 (s, 3H, CO_2CH_3), 4.09 (m, 1H, H-5), 4.12 (q, 2H, OCH_2CH_3), 4.40 (br d, 1H, 8-NH). Anal. Calcd. for $C_{19}H_{30}N_2O_7$: C 57.27, H 7.59, N 7.03. Found: C 57.21, H 7.41, N 6.95.

8(S)-Amino-2(R)-benzyl-2-methoxycarbonyl-3-oxo-8a(R)-indolizidine **(26)**

A solution of compound **17** (0.4 g, 1 mmol) in 1:2 TFA-CH_2Cl_2 mixture (10 mL) was stirred at 0°C for 30 min and for 2 h at room temperature. Evaporation of the solvents gave 0.42 g (98%) of the product as trifluoroacetate salt. Anal. Calcd. for $C_{19}H_{23}F_3N_2O_5$: C 54.81, H 5.57, N 6.73. Found: C 54.59, H 5.83, N 6.66. ^{1}H NMR data of this compound are recorded in Table 1.

2(R)-Benzyl-8(S)-tert-butyloxycarbonylamino-3-oxo-8a(R)-indolizidine-2-carboxylate **(27)**

To a solution of compound **17** (0.5 g, 1.24 mmol) in MeOH (40 mL) was added 2N NaOH (0.93 mL, 1.86 mmol). After stirring at room temperature for 3 h the solvents were evaporated. The resulting residue was dissolved in H_2O (20 mL), acidified with 1N HCl to pH 3 an extracted with EtOAc (2 x 100 mL). The organic layer was dried over Na_2SO_4, evaporated to dryness and the residue purified on a silica gel column (CH_2Cl_2-MeOH, 10:1) to give 0.45 g (93%) of the product. Anal. Calcd.for $C_{21}H_{28}N_2O_5$: C 64.93, H 7.26, N 7.21. Found: C 64.81, H 7.29, N 6.94. ^{1}H NMR data are recorded in Table 1.

REFERENCES AND NOTES

1. Olson, G.L.; Voss, M.E.; Kahn, M.; Madison, U.S.; Cook, C.M. *J. Am. Chem. Soc.* **1990**, *112*, 323-333, and references therein.
2. Morgan, B.A.; Gainor, J.A. *Ann. Rep. Med. Chem.*. **1989**, *24*, 243-252.
3. Hölzemann, G. *Kontakte* (Darmstadt) **1991**, *1*, 3-12.
4. Brandemeier, V.; Feigel, M. *Tetrahedron* **1989**, *45*, 1365-1376.
5. Feigel, M. *J. Am. Chem. Soc.* **1986**, *108*, 181-182.
6. Freidinger, R.M. *J. Org. Chem.* **1985**, *50*, 3631-3633.
7. Toniolo, C. *Int. J. Pep. Protein Res.* **1990**, *35*, 287-300.
8. Kanh, M.; Devens, B. *Tetrahedron Lett.* **1986**, *27*, 4841-4844.
9. Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647-650.
10. Sato, K.; Nagai, U. *J. Chem. Soc. Perkin Trans I* **1986**, 1231-1234.
11. Gómez-Monterrey, I.; Domínguez, M.J.; González-Muñiz, R.; Harto, J.R.; García-López, M.T. *Tetrahedron Lett.* **1991**, *32*, 1089-1092.
12. García-López, M.T.; González-Muñiz, R.; Harto, J.R. *Tetrahedron Lett.* **1988**, *29*, 1577-1580.
13. García-López, M.T.; González-Muñiz, R.; Harto, J.R. *Tetrahedron* **1988**, *44*, 5131-5138.
14. Takechi, H.; Tatenchi, S.; Nachida, M.; Nishibata, Y.; Aoe, K.; Sato, Y.; Kanaoka, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3142-3152.
15. Bajusz, S.; Szell, E.; Badgy, D.; Barazas, E.; Horwath, G.; Dioszegi, M.; Fittler, Z.; Szabo, G.; Juhasz, A.; Tomori, E.; Szilagyi, G. *J. Med. Chem.* **1990**, *33*, 1729-1735.
16. Studies on these cyclizations of disubstituted malonic acid derivatives are now in progress.
17. Hargreaves, M.K.; Khan, M.A. *J. Chem. Soc. Perkin Trans. 2* **1973**, 1204-1207.
18. Fournié-Zaluski. M.C.; Lucas-Soroca, E.; Devin, J.; Roques, B.P. *J. Med. Chem.* **1986**, *29*, 751-757.