Stereochemical and mechanistic studies on the formation of the 3-oxoindolizidine skeleton from ornithine derivatives

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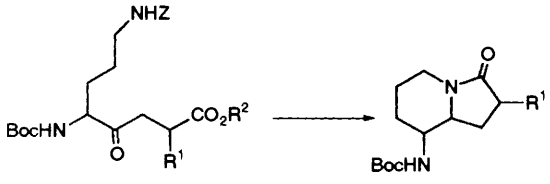
The reaction sequence that converts Boc-L- or Boc-D-Orn(Z)-OH into 8-amino-3-oxoindolizidine-2-carboxylate derivatives has been examined, in order to determine the step during which partial racemization occurs. By using chiral derivatizating agents, it has been demonstrated that the temperature-dependent racemization takes place during the intramolecular reductive amination process, involved in the elaboration of the indolizidine ring by hydrogenation of the corresponding 4-keto diester derived from ornithine. It was shown from deuterium labelling experiments that this process proceeds through an equilibrium between imine–enamine intermediates which also accounts for the high stereoselectivity in the generation of the C-8a centre of the indolizidine skeleton.

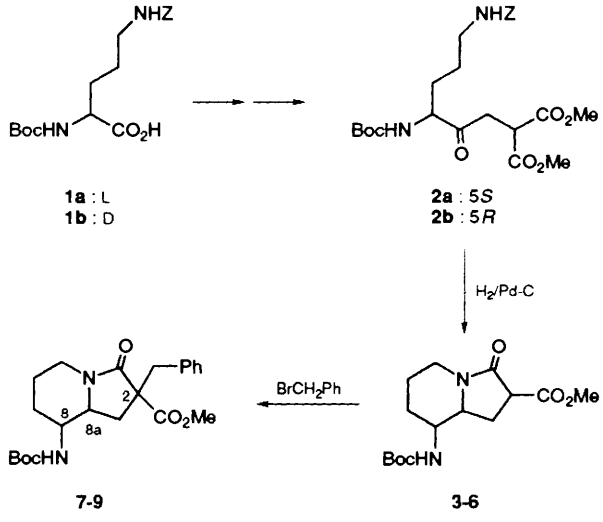
As a part of our studies on the synthesis of appropriately substituted bicyclic lactams to be used in conformationally restricted peptides,[1] we have previously reported a one-pot procedure for the synthesis of 2-substituted 3-oxoindolizidines† from 2-substituted 4-oxooctanoates derived from suitably protected ornithine derivatives (Scheme 1).[2]



Scheme 1

This procedure, involving hydrogenolysis of the Z group, intramolecular reductive amination and γ-lactamization, gave 8,8a-*trans*-oxoindolizidines (*trans*/*cis* ≈12) which could be alkylated at position 2, as is shown in Scheme 2.[3] When the 8-amino-2-benzyl-3-oxoindolizidine-2-carboxylates **7–9**, obtained from Boc-Orn(Z)-OH (**1a**), were individually introduced into the *C*-terminal hexapeptide fragment of Neurotensin (NT_{8-13}, H-Arg-Arg-Pro-Tyr-Ile-Leu-OH) replacing the dipeptide Pro^{10}-Tyr^{11}, a mixture of two diastereoisomeric hexapeptide analogues resulted in each case.[4] As the BOP and HOBt–DCC coupling methods, used in the solid-phase synthesis of these NT_{8-13} constrained analogues, usually proceed without racemization,[5,6] this result indicated that each of the incorporated 3-oxoindolizidines **7–9** should be a mixture of the corresponding pair of enantiomers **7ab–9ab**. Assuming this fact, it was clear that the chiral centre of the starting Orn derivative **1a** was racemized during the synthetic sequence, to give enantiomeric indolizidines with 8*S* and 8*R* configurations. On examination of this sequence, the 4-keto diester formation, from alkylation of the ornithine halogenomethyl ketone derivative with dimethyl malonate, and the reductive amination, to give the piperidine moiety in the oxoindolizidines, appeared to be the most probable racemizing steps. Because of our interest in the construction of a variety of nitrogen bridged bicyclic rings, by intramolecular reductive amination of keto esters derived from ornithine as a key step, we decided to carry out a study on the stereochemical course of the reaction to the 3-oxoindolizidines **3–6** from the enantiomerically pure L- and D-ornithine derivatives **1a** and **1b**. This paper deals with this study and with the mechanism that accounts for the aforementioned racemization.

† 'Indolizidine' is an alternative name for octahydroindolizine.

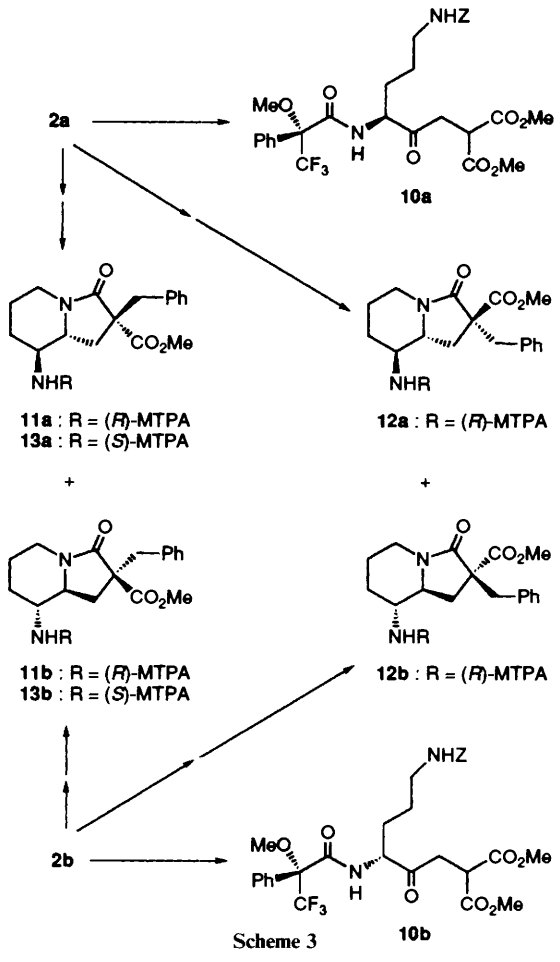


Compd.	C-2, C-8, C-8a	Compd.	C-2, C-8, C-8a
3a,7a	*R,S,R*	**3b,7b**	*S,R,S*
4a,8a	*S,S,R*	**4b,8b**	*R,R,S*
5a,9a	*S,S,S*	**5b,9b**	*R,R,R*
6a	*R,S,S*	**6b**	*S,R,R*

Scheme 2

Results and discussion

By the described procedure,[3] L- and D-ornithine derivatives **1a** and **1b** were converted into the corresponding 4-keto diesters **2a** and **2b** which, after removal of the Boc protecting group, were treated with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-(+)-MTPA-OH][7,8] in the presence of BOP as coupling agent.[5] Initial attempts to evaluate the diastereoisomeric purity of the resulting crude MTPA derivatives **10a** and **10b** (Scheme 3) by HPLC analysis were unsuccessful because both compounds showed identical retention times in various



Scheme 3

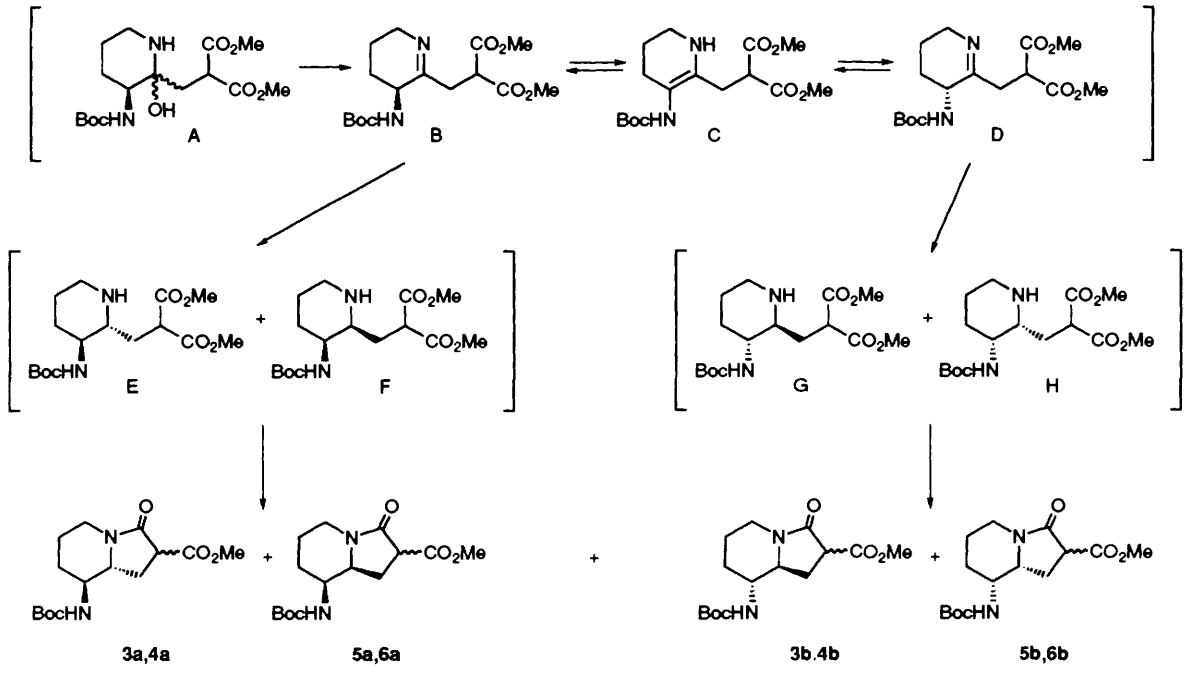
solvent systems. Therefore, ^{1}H NMR analysis, with a 300 MHz instrument, was performed after purification by column chromatography. Although the ^{1}H NMR spectra of derivatives **10a** and **10b** showed a unique pattern of signals in each case, very small chemical-shift differences between the spectra were observed. The diastereoisomeric purity was then assessed by comparing the ^{1}H NMR spectra of the compounds to those obtained from an artificial 3:1 mixture of derivatives **10a** and **10b**, in which the non-equivalence of the 7-H protons and the OMe group of the MTPA moiety in these diastereoisomers was clearly observed. From this result, it can be concluded that, within the limits of the NMR analysis, the synthesis of the 4-keto diesters is a non-racemizing process.

In order to verify that the ornithine chiral centre is racemized during the construction of the indolizidine skeleton, separable diastereoisomeric 2,2-disubstituted 3-oxoindolizidines **7–9** were prepared from 4-keto diesters **2a** and **2b**.[3] The 2-monosubstituted-3-oxoindolizidine analogues **3–6** could not be used for the enantiomeric purity determination because the acidity of the 2-H proton prevented the resolution of epimers at this position.[9,10] On the other hand, it was important that the alkylation at the 2-position of the previously formed indolizidine ring did not affect the stereochemistry of the other two asymmetric centres, C-8 and C-8a. The 2,2-disubstituted derivatives **9** could not be used for this purpose either, since these minor 8,8a-*cis* indolizidines were obtained in < 5% yield. Similarly to the keto diesters **2**, compounds **7** and **8** were derivatized with (*R*)-(+)-MTPA-OH, after removal of the Boc protection. When the resulting (*R*)-MTPA-containing 3-oxoindolizidines **11** and **12** were analysed by HPLC, it was shown that, independent of the starting keto diester **2a** or **2b**, all of them were mixtures of two diastereoisomers (Scheme 3). Thus, mixtures of diastereoisomers **11a** and **11b** were obtained in 6.3:1 and 1:5.8 ratio, starting from pure enantiomers **2a** and **2b**, respectively, by formation of the indolizidine ring at 14 °C, alkylation and final derivatization (Table 1). In the same reactions, mixtures of the diastereoisomers **12a** and **12b** were also formed in 5.4:1 ratio (from **2a**) and 1:3.9 ratio (from **2b**), respectively. These results demonstrate that racemization occurs during the reductive amination of the indolizidine ring-forming step and, thereby, compounds **3–6** and the 2-benzyl derivatives **7–9** are always obtained as enantiomeric mixtures.

Since the indolizidine ring of compounds **11** and **12** was synthesized either from the same keto diester or under strictly identical conditions from enantiomeric keto diesters, the degree of racemization should be the same. Therefore, the differences in the values of the diastereoisomeric excess (de) found for compounds **11a**, **12a**, **11b** and **12b** indicate a problem of kinetic resolution in the derivatization with (*R*)-(+)-MTPA-OH. In order to minimize this problem, derivatization of the mixtures of enantiomers **7a** and **7b**, obtained from the keto diesters **2a** and **2b**, was consecutively repeated using a large excess of the more reactive (*S*)-(+)- and (*R*)-(−)-MTPA chlorides (Table 1).[8] Under these conditions, the use of (*S*)-(+)-MTPA-Cl, led to the diastereoisomers **11a** and **11b** with the same de value in both cases. However, (*R*)-(−)-MTPA-Cl afforded the diastereoisomeric derivatives **13a** and **13b**, enantiomers of **11b** and **11a**, respectively, with de's of 77 and 66% (Table 1). These results indicated that in our case, the use of the MTPA chlorides did not avoid the kinetic resolution problem and, therefore, the enantiomeric excess obtained using chiral MTPA derivatives must be considered as approximate.

The mixtures of diastereoisomeric MTPA-containing 3-oxoindolizidine derivatives, **11a,b** and **12a,b**, were carefully purified by column chromatography and analysed by ^{1}H NMR. Accurate integration of the 1-H, 7-H, 8a-H and 2-CH_2 proton signals allowed the determination of the diastereoisomeric composition, which was very similar to that found by the HPLC analysis. In the ^{1}H NMR spectra of each MTPA-diastereoisomeric pair, the $\Delta\delta(\delta_a - \delta_b)$ value is in agreement with the theoretical predictions of the MTPA model.[7,8] According to this model, the MTPA derivatives exist in a conformation in which the 8-H proton, the C=O carbonyl bond and the trifluoromethyl group are located in the same plane. Thus, protons 1-H and 8a-H are more shielded in derivatives **11a** and **12a** than in their corresponding diastereoisomers **11b** and **12b** (negative $\Delta\delta$ values), due to the anisotropic effects of the phenyl group of the (*R*)-MTPA on these protons. However, the positive $\Delta\delta$ values for the 7-H protons indicated that, in the diastereoisomers **11b** and **12b**, these protons are located on the same side as the aromatic ring of the MTPA residue (Table 2).

Owing to the kinetic resolution problem found in the synthesis of the MTPA-containing 3-oxoindolizidine derivatives **11**, **12** and **13**, we attempted to determine directly the enantiomeric composition of **7** and **8** by forming diastereoisomeric complexes *in situ* with chiral solvating agents or chiral lanthanide shift reagents.[11–14] Unfortunately, both attempts were unsuccessful. Thus, the ^{1}H NMR spectra of compounds **7** and **8**, in $CDCl_3$ or C_6D_6 and in the presence of increasing amounts of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (ATFE) (1–4 equiv.), showed no non-equivalent signals. By using tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato)praseodymium [Pr(fod)$_3$] (0.1–0.3 equiv.), the peak-broadening in the proton resonances of compound **7** prevented the analysis of the spectra. Moreover, the singlets corresponding to the CO_2Me and Boc groups, which could be clearly distinguished from the other resonances, appeared as single signals. Since the reductive amination intermediates must play a crucial role in the racemization process of the ornithine chiral centre during the cyclization, we decided to study the mechanism of this process.



Scheme 4

Table 1 HPLC evaluation of the MTPA-derivatized 3-oxoindolizidines

Starting 4-Keto diester	Hydrogenation temperature (°C)	MTPA derivative	Diastereoisomeric **a**:**b** ratio (de, %)		
			(*R*)-(+)-MTPA-OH	(*S*)-(+)-MTPA-Cl	(*R*)-(−)-MTPA-Cl
2a	14	**11a** + **11b**	6.3:1 (73)	5.3:1 (68)	—
2b	14	**11a** + **11b**	1:5.8 (71)	1:5.3 (68)	—
2a	14	**12a** + **12b**	5.4:1 (69)	—	—
2b	14	**12a** + **12b**	1:3.9 (59)	—	—
2a	14	**13a** + **13b**	—	—	7.6:1 (77)
2b	14	**13a** + **13b**	—	—	1:4.9 (66)
2a	40	**11a** + **11b**	2.3:1 (39)	2.1:1 (35)	—
2a	40	**13a** + **13b**	—	—	2.8:1 (47)

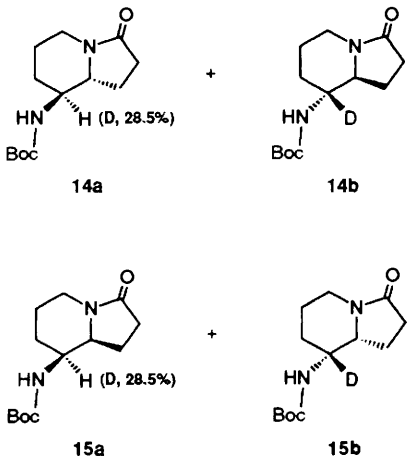
Table 2 Significant differences in the ^{1}H NMR [$(CD_3)_2CO$] chemical shifts of the diastereoisomeric mixtures **11a**/**11b** and **12a**/**12b**

Mixture	Δδ(**a**–**b**), ppm		
	1-H	7-H	8a-H
11a + **11b**	−0.26	+0.11, +0.12	−0.16
12a + **12b**	−0.29, −0.17	+0.11, +0.16	−0.14

Based on our previous findings, this kind of reductive amination can proceed through either the corresponding hemiaminal (A) or imine intermediates (B),[2,15,16] as indicated in Scheme 4. However, racemization of the starting Orn derivative is only possible from the second route. Thus, starting from the *S*-keto diester **1a**, direct hydrogenation of imine B should afford the (3*S*)-piperidines E and F that, after γ-lactamization should give the corresponding (8*S*)-3-oxoindolizidine derivatives **3a** and **4a**, and **5a** and **6a**, respectively. Additionally, the (3*R*)-imine intermediate D, generated from B through the imine-enamine equilibrium, should afford the (8*R*)-3-oxoindolizidines **3b**–**6b**, enantiomers of **3a**–**6a**. Nevertheless, a certain participation of the diastereoisomeric mixture of hemiaminals A, as intermediates in the synthesis of compounds **3a**–**6a**, could not be discarded.

As the imine–enamine rearrangements are favoured by heating, to support the above suggested mechanism the 4-keto diester **2a** was hydrogenated at 40 °C and the route for the synthesis of 2-benzyl-3-oxoindolizidine-2-carboxylates was followed (Scheme 2). Derivatization with (*R*)-(+)-MTPA-OH of the resulting compound **7** afforded the mixture of diastereoisomers **11a** and **11b** with a 39% de (Table 1). This excess was considerably lower than that obtained when the hydrogenation was performed at 14 °C (de 73%), and this result is consistent with the imine–enamine mechanism. Therefore, the racemization takes place in competition with the hydrogenation and is a temperature-dependent process.

Although all attempts to isolate or detect the imine intermediate were unsuccessful, its involvement in the proposed mechanism was indirectly established by an assay of isotopic labelling with deuterium. For this purpose, compound **2a** was hydrogenated, at 40 °C, using deuteriated methanol (MeOD) as solvent, to give the corresponding mixture of 3-oxoindolizidines **3**–**6** which, to facilitate the ^{1}H NMR analysis, was saponified and decarboxylated to the corresponding 2-unsubstituted derivatives **14** and **15** (Scheme 5). The ^{1}H NMR spectra of **14** and **15** indicated that the incorporation of deuterium had taken place exclusively at position 8 and at the 8-NH group. In both cases, the integration of the signals revealed that 57% of 8-H was labelled with deuterium, while the 8-NH group only incorporated 14% of this isotope. The isotopic labelling found at the 8-NH group was attributed to the expected hydrogen–deuterium exchange between the NH of the urethane moiety and the deuteriated solvent. However, the incorporation of deuterium at position 8 can only be explained through the existence of the proposed imine-enamine rearrangement. The



Scheme 5

fact that diastereoisomers **14** and **15** showed identical incorporation of deuterium indicated that both compounds were exclusively obtained by reduction of the imine intermediate. If compound **15** came from the hydrogenation of the enamine C, at least in part, the isotopic labelling of this compound should be lower than that of **14**, which can be formed only through the imine intermediate. Considering that the change from MeOH to MeOD does not induce any solvent isotope effect,[17,18] the measured amount of deuterium incorporated at C-8 (57%) can serve to quantify the extent of the racemization, which at 40 °C was 28.5% (de, 43%). Racemization of other amino acid derivatives in the course of an intermolecular reductive amination process has been described.[19]

The high stereoselectivity at C-8a for the 3-oxoindolizidines (8a*R**/8a*S**, 12:1) can also be easily explained by this mechanism involving reduction of the imine intermediates. Thus, it should be expected that hydrogenation occurs preferentially at the upper face of imine B or at the lower face of imine D to give the more stable piperidines E or G, having a *trans*-diequatorial relative disposition of the substituents.

In conclusion, it has been demonstrated that the construction of the indolizidine skeleton by hydrogenation of ornithine derivatives takes place with racemization. This racemization proceeds *via* a temperature-dependent equilibrium between the corresponding imine-enamine intermediates, involved in the reductive amination reaction. The isotopic labelling with deuterium of the synthesized 3-oxoindolizidine derivatives has been found to be a good method for determining the enantiomeric purity of these compounds.

Experimental

^{1}H NMR spectra were recorded with a Varian XL-300 spectrometer operating at 300 MHz, using TMS as internal standard. Elemental analyses were obtained on a CNH-O-RAPID instrument. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck). Silica gel 60 (320–400 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 Waters apparatus using a Nova-Pack C_{18} (3.9 × 150 mm, 4 μm) column with (*a*) CH_3CN (*b*) H_2O [0.05% trifluoroacetic acid (TFA)] as eluent (flow rate, 1 cm^3 min^{-1}) and UV detection (214 nm).

Derivatization with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid

General procedure. A solution of the appropriate γ-keto diester or 3-oxoindolizidine derivative (0.25 mmol) in CH_2Cl_2 (4 cm^3) was treated with TFA (2 cm^3). After being stirred at room temperature for 1 h, the mixture was evaporated to dryness. The resulting residue was dissolved in CH_2Cl_2 (5 cm^3) and treated with BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate; 0.28 mmol), (*R*)-(+)-MTPA-OH (0.28 mmol) and triethylamine (0.53 mmol). The mixture was stirred at room temperature for 5 h and then evaporated. The residue was extracted with EtOAc (50 cm^3) and the extract was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness. Compounds were purified on a silica gel column using the solvent system specified in each case. ^{1}H NMR data are given in Table 3.

Dimethyl (3*S*,2′*R*)-6-benzyloxycarbonylamino-3-[2′-methoxy-2′-(trifluoromethyl)phenylacetamido]-2-oxohexylmalonate 10a. Chromatography (eluent EtOAc–hexane; 1:2) gave **10a** as a syrup (61%) from **2a** (Found: C, 57.2; H, 5.6; N, 4.3. $C_{29}H_{33}F_3N_2O_5$ requires C, 57.05; H, 5.45; N, 4.6%); HPLC: t_R = 11.69 min (*a*–*b*, 50:50).

Dimethyl(3*R*,2′*R*)-6-benzyloxycarbonylamino-3-[2′-methoxy-2′-(trifluoromethyl)phenylacetamido]-2-oxohexylmalonate 10b. Chromatography (eluent EtOAc–hexane; 1:2) gave **10b** as a syrup (41%) from **2b** (Found: C, 56.9; H, 5.55; N, 4.5. $C_{29}H_{33}F_3N_2O_9$ requires C, 57.05; H, 5.45; N, 4.6%); HPLC: t_R = 11.69 min (*a*–*b*, 50:50).

Methyl (2*R*,8*S*,8a*R*,2′*R*)- and (2*S*,8*R*,8a*S*,2′*R*)-2-benzyl-8-[2′-methoxy-2′-(trifluoromethyl)phenylacetamido]-3-oxoindolizidine-2-carboxylate 11a and 11b. Chromatography (eluent EtOAc–hexane; 1:1) gave **11a** (62%) and **11b** (61%) as a white foam from **7** (**2a**) and **7** (**2b**), respectively (Found: C, 62.5; H, 5.7; N, 5.4. $C_{27}H_{29}F_3N_2O_5$ requires C, 62.5; H, 5.6; N, 5.4%); HPLC: t_R = 51.75 min (**11a**) and 56.61 (**11b**) (*a*–*b*, 35:65).

Methyl(2*S*,8*S*,8a*R*,2′*R*)- and (2*R*,8*R*,8a*S*,2′*R*)-2-benzyl-8-[2′-methoxy-2′-(trifluoromethyl)phenylacetamido]-3-oxoindolizidine-2-carboxylate 12a and 12b. Chromatography (eluent EtOAc–hexane; 1:1) gave **12a** (61%) and **12b** (59%) as foam from **8** (**2a**) and **8** (**2b**), respectively (Found: C, 62.6; H, 5.9; N, 5.5. $C_{27}H_{29}F_3N_2O_5$ requires C, 62.5; H, 5.6; N, 5.4%); HPLC: t_R = 22.53 min (**12a**) a 24.88 (**12b**) (*a*–*b* 40:60).

Derivatization with α-methoxy-α-(trifluoromethyl) phenylacetyl chlorides

General procedure. A solution of the 3-oxoindolizidine derivative **7** (3.2 mg, 8 μmol) in TFA (200 μm^3) was stirred at room temperature for 2 h. After evaporation of the mixture, the resulting residue was dissolved in pyridine (0.5 μm^3). The solution was treated with (*S*)-(+)-MTPA-Cl or (*R*)-(−)-MTPA-Cl (30 μm^3, 160 μmol) and stirred at room temperature for 5 h. After addition of water (25 cm^3), the mixture was evaporated to dryness and the crude reaction mixtures were evaluated by HPLC (Table 1).

Synthesis of deuteriated 3-oxoindolizidines 14 and 15

A solution of compound **2a** (2 g, 4 mmol) in MeOD(25 cm^3) was hydrogenated at 40 °C and 30 psi of pressure in the presence of Pd–C (10%; 200 mg) as catalyst. After the catalyst had been filtered off, evaporation of the filtrate compounds gave **3–6** (1.24 g, 98%). This diastereoisomeric mixture (1.15 g, 3.7 mmol) in MeOH (25 cm^3) was treated with NaOH (2 mol dm^{-3}; 1.9 cm^3, 3.8 mmol) and stirred at room temperature for 1 h. After evaporation of the mixture, the residue was dissolved in water and washed with EtOAc. The aqueous layer was acidified to pH 3 with HCl (1 mol dm^{-3}), and extracted with EtOAc (100 cm^3). The organic extract was dried (Na_2SO_4) and evaporated to give the corresponding carboxylic acid as a white foam (1.0 g, 91%). This compound was dissolved in dioxane (50 cm^3) and refluxed overnight. Evaporation of the mixture gave a mixture of compounds **14** and **15** (12:1). These compounds

Table 3 Significant ^{1}H NMR chemical shifts of MTPA-derivatized analogues (300 MHz)

Compd.	1-H	2-H	5-H	6-H	7-H	8-H	8a-H	2-CH_2	CO_2Me	OMe
10a[a]	—	3.89	4.68	2.04 1.65	1.55	3.22	—	—	3.71	3.33
10b[a]	—	3.93	4.68	1.95 1.56	1.33	3.22	—	—	3.70	3.46
11a[b]	2.35 2.10	—	3.91 2.23	1.72 1.42	1.88 1.42	3.67	2.20	3.19 3.00	3.74	3.45
11b[b]	2.36	—	3.91 2.23	1.72 1.42	1.77 1.30	3.67	2.36	3.26 3.04	3.74	3.45
12a[b]	2.26 1.79	—	3.94 2.53	1.27 0.86	1.90 1.54	3.05	3.37	3.21 3.13	3.62	3.46
12b[b]	2.55 1.96	—	3.94 2.53	1.67 1.16	1.79 1.38	2.95	3.51	3.23 3.16	3.67	3.44

[a] In $CDCl_3$. [b] From the corresponding diastereoisomeric mixture [in $(CD_3)_2CO$].

were separated on a silica gel column using CH_2Cl_2–MeOH (40:1) as eluent.

Compound **14** (63%) δ_H(300 MHz, $CDCl_3$) 4.43 (0.86 H, br s, 8-NH), 4.07 (1 H, m, 5-H), 3.28 (0.43 H, m, 8-H), 3.08 (1 H, m, 8a-H), 2.52 (1 H, m, 5-H), 2.38 (2 H, m, 2-H), 2.17 (1 H, m, 1-H), 2.08 (1 H, m, 7-H), 1.93 (1 H, m, 1-H), 1.74 (1 H, m, 6-H), 1.48 (1 H, m, 6-H), 1.41 (9 H, s, CH_3 Boc) and 1.26 (1 H, m, 7-H).

Compound **15** (5%) δ_H(300 MHz, $CDCl_3$) 5.27 (0.86 H, br s, 8-NH), 4.13 (1 H, m, 5-H), 3.93 (0.43 H, m, 8-H), 3.62 (1 H, m, 8a-H), 2.66 (1 H, m, 5-H), 2.35 (2 H, m, 2-H), 2.05 (1 H, m, 1-H), 1.96 (1 H, m, 7-H), 1.85 (1 H, m, 1-H), 1.69 (1 H, m, 7-H), 1.63 (1 H, m, 6-H), 1.49 (1 H, m, 6-H) and 1.41 (9 H, s, CH_3 Boc).

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Paper 5/03971A
Received 20th *June* 1995
Accepted 4th *July* 1995