Synthesis and Ring Opening of Methyl 2-Alkyl-3-(alkyl/aryl)-1-benzoylaziridine-2-carboxylates: Synthesis of Polysubstituted Amino Acids

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Keywords: Aziridines / Oxazolines / Ring expansion reactions / α-Hydroxy β-amino acids / β-Hydroxy α-amino acids

A new method for the preparation of 2,2,3-trisubstituted methyl 1-benzoylaziridine-2-carboxylates is reported. These compounds have been obtained starting from α-alkyl β-amino acids by formation of the lithium dianion and reaction with iodine. The aziridines undergo ring expansion or ring opening, depending on the substituents of the aziridine ring and on the reaction conditions. Following these methods, both α-substituted α-hydroxy β-amino acids and α-substituted β-hydroxy α-amino acids have been synthesised.

Introduction

Non-proteogenic amino acids are constituents of biologically active compounds.[1] Among them, α-alkyl β-hydroxy α-amino acids are part of molecules such as neurotropic lactacystin[2] and the immunosuppressive agent myriocin.[3] Furthermore, if these molecules are inserted in a polypeptide structure, they have a marked effect both on the peptide conformation and on its biological activity.[4]

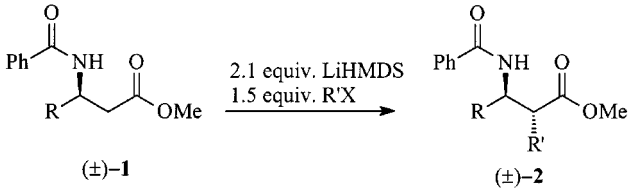
The synthetic methods for the preparation of α-alkyl β-hydroxy α-amino acids are still few,[5] usually utilising proteogenic amino acids, such as alanine[6] or threonine[7] as starting material. We describe here a new and stereoselective synthesis of α-alkyl β-hydroxy α-amino acids starting from α-alkyl β-amino acids, by the intermediate formation and ring opening of 2,2,3-trisubstituted *N*-benzoyl-2-(methoxycarbonyl)aziridines (methyl 1-benzoylaziridine-2-carboxylates), which have never been prepared in the past.[8] These compounds have been obtained starting from α-alkyl β-amino acids, by formation of the lithium dianion and reaction with iodine. They underwent ring expansion or ring opening, depending on the substituents of the aziridine ring and on the reaction conditions.

Results and Discussion

i. Synthesis of Methyl 2-Alkyl-3-(alkyl/aryl)-1-benzoylaziridine-2-carboxylates

The *anti* α-alkyl β-amino acids *rac*-**2a–g** have been synthesised starting from fully protected β-amino acids *rac*-**1a** and *rac*-**1b**. These compounds have been easily obtained from commercially available 3-aminobutanoic acid and from 3-amino-3-phenylpropanoic acid,[9] by protection of the amino group by Schotten–Baumann reaction and esterification of the carboxy group by reaction with thionyl chloride and methanol.[10] Although these compounds have been used in the racemic form, it is well known that β-amino acids can be obtained in the enantiomerically pure form by kinetic resolution of the corresponding phenylacetylamides by reaction with enzyme PGA, which selectively hydrolyse amides of α- and β-amino acids of the L series.[11]

The alkylation was performed in dry THF, by formation of the lithium dianion of *rac*-**1a** and *rac*-**1b** with 2 equivalents of LiHMDS and subsequent addition of the alkylating agent (Scheme 1, Table 1). The reaction temperature was critical in order to obtain a good chemical yield (–30 °C for *rac*-**1a** and –15 °C for *rac*-**1b**) and a complete *anti* selectivity:[12] when the reaction was carried out at lower or higher temperatures (i.e. –78 °C or room temperature), low yields were obtained.



Scheme 1

Table 1. Alkylation reaction of β-benzamido methyl esters **1a–b**

Entry	Substrate	Product	R	R′	*anti*/*syn* ratio	Yield (%)
1	**1a**	**2a**	Me	Me	> 99:1	71
2	**1a**	**2b**	Me	Et	> 99:1	86
3	**1a**	**2c**	Me	Allyl	> 99:1	63
4	**1a**	**2d**	Me	Benzyl	> 99:1	61
5	**1b**	**2e**	Ph	Me	> 99:1	61
6	**1b**	**2f**	Ph	Allyl	> 99:1	70
7	**1b**	**2g**	Ph	Benzyl	> 99:1	80

The next step was the formation of three membered rings starting from α-alkyl β-benzamido methyl esters *rac*-**2a–g** by the intermediate formation of the lithium enolate of the α-alkyl α-iodo β-benzamido derivative which spontaneously afforded the aziridine (Equation 1).

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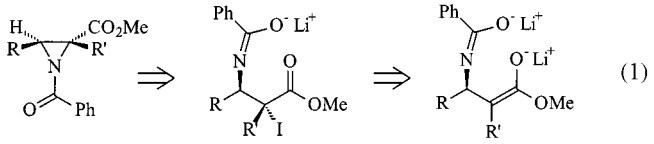
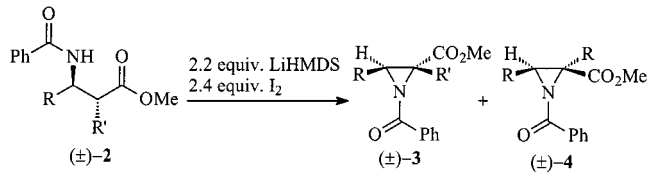


(1)

The lithium dianion was obtained by reaction of *rac*-**2a–g** with 2.2 equivalents of LiHMDS in dry THF at room temperature. When the metalation was performed at lower temperature (such as 0 °C or less) the reaction did not occur, probably owing to the steric hindrance at C2. The reaction proceeded by the intermediate formation of the *N*-lithium anion of the 2-iodo derivative, which spontaneously afforded the ring closure product: after reaction workup only starting material and aziridines were obtained, without any traces of the intermediate 2-iodo derivative. The lithium dianion was originally treated with iodine (2.5 equiv.) at low temperature (–15 °C to –30 °C), with the idea of synthesising 2,4,4,5-tetrasubstituted oxazolines, as we previously obtained in the cyclisation of methyl 3-benzoylaminobutanoate[10a] or methyl 3-benzoylamino-3-phenylpropanoate.[10b] No oxazolines were obtained in any of the reactions. On the contrary, the corresponding *N*-benzoylaziridines *rac*-**3a–g** and *rac*-**4a–g** were synthesised in good yields and high diastereomeric ratios (Scheme 2 and Table 2).

Moreover, when NaHMDS was utilised instead of LiHMDS, completely different results were obtained: in this case the direct formation of *syn*-α-alkyl-α-hydroxy-β-benzoylamino acids was observed,[13] probably by means of the intermediate formation of 2,4,4,5-tetrasubstituted oxazolines, which hydrolysed during the workup.

The stereochemical outcome of the aziridine formation was quite satisfactory: indeed the *trans*/*cis* diastereomeric ratios ranged from 78:22 to 99:1 and the yields were always high: a low yield was obtained only in the formation of *rac*-**3g** (Entry 7), probably owing to the steric hindrance of both



Scheme 2

substituents at C2 and C3 (a phenyl group and a benzyl group, respectively) of the starting *rac*-**2g**.

The stereochemistry of *cis*- and *trans*-aziridines was established by NOEDIFF experiments on *rac*-**3d**, *rac*-**4a**, and *rac*-**3f** (Figure 1). Methyl *trans*-1-benzoyl-2-benzyl-3-methylaziridine-2-carboxylate *rac*-**3d** showed a strong enhancement of the C2 benzylic hydrogens, by irradiating the C3 methyl group, thus showing a *cis* relationship between the methyl and the benzyl groups. On the other hand, *rac*-**4a** shows an enhancement of the 2-methyl group, by irradiating the C3 hydrogen, thus showing a *cis* relationship between the C3 hydrogen and the C2 methyl group. On the contrary, the irradiation of signals of *rac*-**3f** showed no NOEDIFF effects, owing to the *trans* relationship between the C3 hydrogen and the C2 allylic group. The other substituents (phenyl and methoxycarbonyl groups) showed no NOEDIFF effect, owing to their structure. On the basis of these results, the stereochemistry of the other compounds has been attributed by comparison of their ^{1}H-NMR chemical shifts.

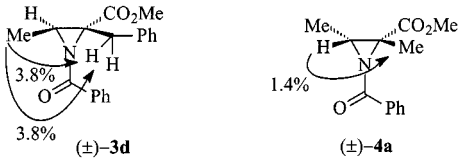


Figure 1. Determination of the stereochemistry of aziridines **3** and **4** by means of NOEDIFF experiments performed on **3d** and **4a**

ii. Ring Opening of Methyl *trans*-2-Alkyl-1-benzoyl-3-methylaziridine-2-carboxylates *rac*-3a–d

Aziridine-2-carboxylic acids are common intermediates for the synthesis of α- and β-amino acids,[14] thus their ring opening can afford both β-functionalised α-amino acids and α-functionalised β-amino acids, which are all important classes of compounds. From the opening of methyl 2-alkyl-3-(alkyl/aryl)-1-benzoylaziridine-2-carboxylates we can obtain polysubstituted α- or β-amino acids. These molecules are part of biologically active compounds and can be introduced in a polypeptide, in order to enhance their rigidity and their resistance towards peptide hydrolysis.

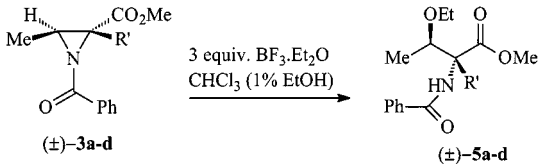
N-Benzoylaziridines *rac*-**3** and *rac*-**4** may furnish, upon ring opening, both α- or β-amino acids, simply by changing the reaction conditions. Furthermore the substituents of the aziridine ring play an importance role in the steric and regi-

Table 2. Cyclisation reaction of α-alkyl β-benzamido methyl esters **2a–g**, by reaction with iodine

R	Entry	R′	LiHMDS: *t* (h), *T* (°C)	I_2: *t* (h), *T* (°C)	**3/4** ratio	Yield (%)
Me	1	Me	5, 20	16, –30	80:20	90
Me	2	Et	5, 20	16, –30	78:22	59
Me	3	Allyl	5, 20	16, –30	82:18	80
Me	4	Benzyl	5, 20	16, –30	99:1	82
Ph	5	Me	5, 20	16, –15	85:15	60
Ph	6	Allyl	5, 20	16, –15	94:6	70
Ph	7	Benzyl	5, 20	16, –15	99:1	40

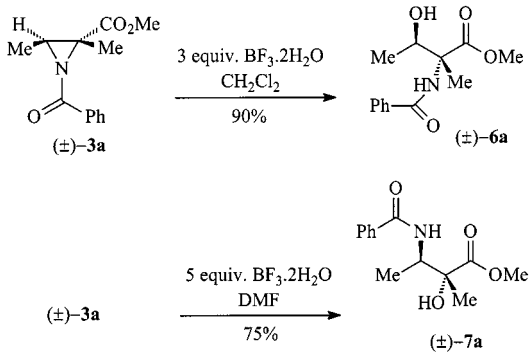
ochemical outcome. Zwanenburg and co-workers have extensively studied the ring opening of 3-substituted aziridine-2-carboxylic acid esters both when the substituent is an aliphatic chain[15] or an aromatic ring.[16] They have demonstrated that aliphatically substituted aziridinecarboxylates are much more reluctant to undergo ring opening reactions than the corresponding 3-aryl compounds. Thus for aliphatically substituted aziridine-2-carboxylates, *N*-activation by acylation or tosylation is a prerequisite for successful ring opening reactions, while 3-aryl-substituted aziridine-2-carboxylates can easily be opened as free aziridines, owing to the presence of the phenyl group which can stabilise an incipient carbocation. Following this behaviour, our methyl 2,3-(dialkyl/aryl)-1-benzoylaziridine-2-carboxylates afford two different results, whether the 3-substituent was a methyl group (**a–d**) or a phenyl group (**e–g**).

When *N*-benzoylaziridines *rac*-**3a–d** were treated with $BF_3 \cdot Et_2O$ in chloroform, ring opening was observed (Scheme 3): owing to BF_3 catalysis, the small amount of ethanol, which is present in commercially available chloroform as a stabilising agent (about 1%), reacted as a nucleophile with the aziridine ring, affording an *anti*-α-alkyl-α-amino-β-ethoxy methyl ester in quantitative yield.



Scheme 3

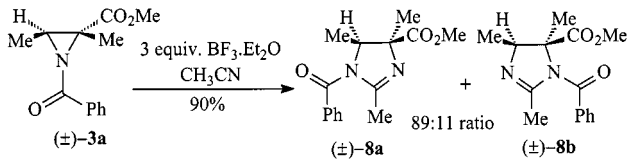
This reaction has already been observed by Okawa and co-workers[17] in the ring opening of benzyl (2*S*)-1-benzyloxycarbonylaziridine-2-carboxylate and methyl (2*S*,3*S*)-1-benzyloxycarbonyl-3-methylaziridine-2-carboxylate, obtained from serine and threonine, respectively. In the presence of a catalytic amount of $BF_3 \cdot Et_2O$ and several alcohols, β-alkoxy α-amino acids were obtained in generally good yields and with complete control of regioselectivity. In our hands, by treating *N*-benzoylaziridines *rac*-**3a–g** with $BF_3 \cdot Et_2O$ in ethanol-containing chloroform, the exclusive formation of the β-alkoxy α-benzamido methyl esters *rac*-**5a–d** was observed. The regiochemistry was confirmed by ^{1}H-NMR analysis: the signal for the hydrogen of the amide group was a singlet, thus the amido group was in the α position. When the ring opening of *rac*-**3a–g** with $BF_3 \cdot Et_2O$ was performed in dichloromethane (thus in the absence of ethanol), a regioisomeric mixture of oxazolines was obtained. It is well known that *N*-activated aziridines can undergo ring expansion[18] with the formation of oxazolines, which, upon mild hydrolysis, can furnish α-hydroxy β-amino acids or β-hydroxy α-amino acids. In our case, mixtures of 5-(methoxycarbonyl)oxazolines and 4-(methoxycarbonyl)oxazolines were obtained so that other solvents were tested, in order to achieve stereochemical control. We utilised the commercially available $BF_3 \cdot 2\,H_2O$ as Lewis acid, so that water could act as an external nucleophile.[19] The reaction was performed in THF, dichloromethane, DMF, and acetonitrile. While the reaction in THF afforded only the starting material, opposite results were obtained in dichloromethane and DMF (Scheme 4).



Scheme 4

In both reactions, water acted efficiently as an external nucleophile, affording a single product, but the opposite regiochemistry was obtained. Thus in dichloromethane the β-hydroxy α-amino acid derivative *rac*-**6a** was obtained in good yield, while in DMF the reaction afforded the α-hydroxy β-amino acid derivative *rac*-**7a** in lower yield (5 equiv. of $BF_3 \cdot 2\,H_2O$ was needed).[20] The stereo- and regiochemical outcome were confirmed by comparison of the data with those reported in the literature.[10b,21]

On the other hand, when the ring opening of *rac*-**3a** was performed with $BF_3 \cdot H_2O$ in acetonitrile, a complex mixture was obtained, as both the acetonitrile and the water behaved as nucleophiles. Hence, when the reaction was performed in the absence of water, i.e. with $BF_3 \cdot Et_2O$ in acetonitrile, a 89:11 regioisomeric mixture of the *cis*-4,5-dihydro-1*H*-imidazoles *rac*-**8a** and *rac*-**8b** was achieved (Scheme 5). The *cis* relationship among the substituents of *rac*-**8a** and *rac*-**8b** was demonstrated by NOEDIFF experiments (Figure 2). Both compounds showed a strong enhancement of the C3 hydrogen, by irradiating the C2 methyl group, thus showing a *cis* relationship. The regiochemistry was assigned by comparison of the chemical shifts of the dihydroimidazole substituents: both substituents at C5 were more shielded in *rac*-**8a** [δ = 1.29 (d, 3 H), 4.50 (q, 1 H)] than the substituents at C4 of *rac*-**8b** [δ = 1.18 (d, 3 H), 4.28 (q, 1 H)], owing to the deshielding effect of the carbonyl of the benzamido group. The methyl α to the methoxycarbonyl group showed the opposite behaviour [*rac*-**8a**: δ = 1.51; *rac*-**8b**: δ = 1.58].



Scheme 5

The formation of these heterocycles was previously observed by Hiyama[22] and more recently by Zwanenburg[15] in the reaction of methyl 3-alkylaziridine-2-carboxylates, for the synthesis of α,β-diamino acids. In both cases, the reaction afforded a single product: Zwanenburg assumed that

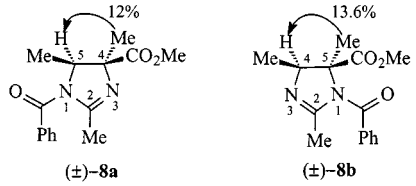
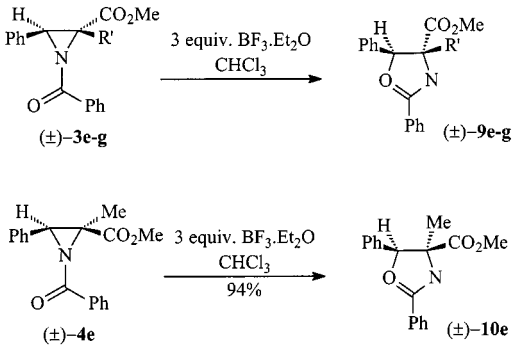


Figure 2. Determination of the stereochemistry of 4,5-dihydro-1*H*-imidazoles **8a** and **8b** by means of NOEDIFF experiments

this reaction proceeded by means of an initial attack of acetonitrile at C3 of the aziridine with inversion of configuration, followed by ring closure involving a reaction of the nitrogen atom, which was originally in the three membered ring, with the nitrilium group.

iii. Ring Opening of Methyl 2-Alkyl-1-benzoyl-3-phenylaziridine-2-carboxylates 3e–g

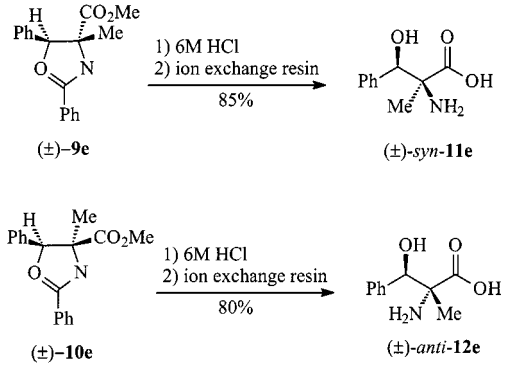
The behaviour of methyl 2-alkyl-1-benzoyl-3-phenylaziridine-2-carboxylates *rac*-**3e–g** and *rac*-**4e** was quite different from what we have just shown. Indeed they easily underwent ring expansion, regardless of the solvent and the ligand of the BF_3 utilised. Hence, by utilising ethanol-containing chloroform or acetonitrile as solvent or $BF_3 \cdot H_2O$ as Lewis acid, no evidence of the addition products was obtained; on the contrary the exclusive formation of methyl *trans*-4-alkyl-2,5-diphenyloxazoline-4-carboxylates *rac*-**9e–g** from *trans*-*N*-benzoylaziridines *rac*-**3e–g** and of methyl *cis*-4-methyl-2,5-diphenyloxazoline-4-carboxylates *rac*-**10e** from *cis*-*N*-benzoylaziridine *rac*-**4e** was observed (Scheme 6).



Scheme 6

The aziridine exclusively underwent ring expansion, which was totally stereo- and regioselective. Starting from *trans*-*N*-benzoylaziridines, only *trans*-oxazolines are obtained. The regiochemistry was confirmed by comparison of the ^{1}H-NMR spectra with similar compounds[22] and with methyl 4-alkyl-2,5-diphenyloxazoline-4-carboxylates[10b], and the stereochemistry was confirmed by NOEDIFF experiments performed on *rac*-**9f**. Indeed, the irradiation of signals of *rac*-**9f** showed no NOEDIFF effects, owing to the *trans* relationship between the C3 hydrogen and the C2 allyl group, as we previously observed for *rac*-**3f**.

The hydrolysis of oxazolines *rac*-**9e** and *rac*-**10e** with 6 M HCl in refluxing methanol followed by purification on ion-exchange resin, afforded the *syn*-2-amino-3-hydroxy-2-methyl-3-phenylpropanoic acid *rac*-**11e** and the *anti*-2-amino-3-hydroxy-2-methyl-3-phenylpropanoic acid *rac*-**12e**, respectively. The structures were confirmed by comparison with data reported in the literature[5c,6,23] (Scheme 7).



Scheme 7

Conclusions

In this paper we have shown a new method for the synthesis of 2,2,3-trisubstituted *N*-benzoylaziridines. As these molecules contain a methoxycarbonyl group, they can be easily transformed into polysubstituted α- or β-amino acids. The *N*-benzoylaziridine ring can undergo both ring opening at C2 or C3 and ring expansion: methyl 2-alkyl-1-benzoyl-3-methylaziridine-2-carboxylates preferentially undergo regioselective ring opening at C2 or C3, depending on the reaction conditions, while methyl 2-alkyl-1-benzoyl-3-phenylaziridine-2-carboxylates preferentially undergo ring expansion, with total regio- and stereocontrol and the exclusive formation of methyl 4-alkyl-2,5-diphenyloxazoline-4-carboxylates.

Following these methods, both α-substituted α-hydroxy β-amino acids and α-substituted β-hydroxy α-amino acids have been obtained. Furthermore, the synthesis of 4,5-dihydro-1*H*-imidazoles has been obtained by ring opening of methyl 2-alkyl-1-benzoyl-3-methylaziridine-2-carboxylates in acetonitrile, which behaves both as solvent and as nucleophile. These compounds are precursors of α-substituted α,β-diamino acids.

Experimental Section

General: NMR spectra were recorded with a Gemini Varian spectrometer at 300 or 200 MHz (^{1}H NMR) and at 75 or 50 MHz (^{13}C NMR). – Chemical shifts are reported in δ values relative to the solvent peak of $CHCl_3$, set at δ = 7.27. – Infrared spectra were recorded with an FT-IR NICOLET 205 spectrometer. – Melting points were determined in open capillaries and are uncorrected. – Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). – THF was distilled from sodium benzophenone ketyl.

General Method for the Alkylation of Methyl 3-Benzamidobutanoate (*rac*-1a) and Methyl 3-(Benzamido)-3-phenylpropanoate (*rac*-1b): LiHMDS (4.2 mmol, 1 M sol. in THF, 4.2 mL) was added to a

stirred solution of ester **1** (2 mmol) in dry THF (10 mL) under nitrogen at 0 °C. The mixture was stirred for 1 h, then cooled to –60 °C for **1a** and to –30 °C for **1b**. The alkylating agent (see Table 1) (3 mmol) in dry THF (10 mL) was added and the mixture was stirred overnight, while the temperature was increased to room temperature. An aqueous saturated solution of ammonium chloride (20 mL) was added, THF was removed under reduced pressure and replaced with dichloromethane. The organic layer was separated, washed twice with water, dried with sodium sulfate, and concentrated. The compounds were obtained pure as oils or solids (if solid, m.p. is reported) after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluent).

***rac*-2a:** M. p. 71–73 °C. – IR (film): $\tilde{\nu}$ = 3353, 1733, 1638 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.25 (d, 6 H, *J* = 7.0 Hz, C*H*$_3$CHN + C*H*$_3$CHCO), 2.74 (dq, 1 H, *J* = 3.8, 7.0 Hz, CH$_3$*CH*CO), 3.72 (s, 3 H, OCH$_3$), 4.33–4.45 (m, 1 H, CHN), 7.21 (d, 1 H, *J* = 8.3 Hz, NH), 7.35–7.52 (m, 3 H, Ph), 7.79–7.83 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.6, 19.0, 43.5, 47.2, 51.5, 126.6, 128.1, 131.0, 134.3, 166.5, 175.9. – $C_{13}H_{17}NO_3$ (235.3): calcd. C 66.36, H 7.28, N 5.95; found C 66.31, H 7.22, N 5.99.

***rac*-2b:** IR (film): $\tilde{\nu}$ = 3319, 1736, 1643 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.85 (t, 3 H, *J* = 6.9 Hz, CH$_2$*CH*$_3$), 1.14 (d, 3 H, *J* = 7.0 Hz, C*H*$_3$CHN), 1.43–1.62 (m, 2 H, *CH*$_2$CH$_3$), 2.42 (ddd, 1 H, *J* = 4.0, 6.5, 8.8 Hz, *CH*CH$_2$CH$_3$), 3.62 (s, 3 H, OCH$_3$), 4.31–4.42 (m, 1 H, CHN), 7.18–7.41 (m, 3 H, Ph), 7.58–7.77 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 11.7, 19.6, 23.3, 45.3, 51.2, 51.3, 126.6, 128.2, 131.0, 134.2, 166.3, 176.0. – $C_{14}H_{19}NO_3$ (249.3): calcd. C 67.45, H 7.68, N 5.62; found C 67.47, H 7.70, N 5.59.

***rac*-2c:** IR (film): $\tilde{\nu}$ = 3264, 1733, 1636 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.16 (d, 3 H, *J* = 6.9 Hz, CHNC*H*$_3$), 2.13–2.41 (m, 2 H, C*H*$_2$CH=CH$_2$), 2.53–2.66 (m, 1 H, C*H*CHN), 3.62 (s, 3 H, OCH$_3$), 4.28–4.48 (m, 1 H, CHN), 4.85–5.05 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.53–5.78 (m, 1 H, CH$_2$C*H*=CH$_2$), 7.05–7.37 (m, 4 H, NH + Ph), 7.58–7.70 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 19.5, 34.2, 45.4, 49.4, 51.4, 117.2, 126.6, 128.2, 131.1, 134.2, 166.2, 175.2. – $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.33, N 5.62; found C 68.89, H 7.37, N 5.68.

***rac*-2d:** M.p. 111–113 °C. – IR (film): $\tilde{\nu}$ = 3351, 1733, 1635 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.23 (d, 3 H, *J* = 6.9 Hz, CHNC*H*$_3$), 2.84–3.06 (m, 3 H, CHC*H*$_2$Ph), 3.61 (s, 3 H, OCH$_3$), 4.43–4.55 (m, 1 H, CHN), 7.13–7.58 (m, 9 H, NH + Ph), 7.81–7.88 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 19.7, 36.1, 45.5, 51.1, 51.8, 126.4, 126.7, 128.1, 128.6, 131.2, 134.3, 138.1, 166.4, 175.3. – $C_{19}H_{21}NO_3$ (311.4): calcd. C 73.29, H 6.80, N 4.50; found C 73.34, H 6.89, N 4.52.

***rac*-2e:** IR (film): $\tilde{\nu}$ = 3419, 1735, 1638 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.37 (d, 3 H, *J* = 7.1 Hz, CHC*H*$_3$), 3.11 (dq, 1 H, *J* = 4.7, 7.1 Hz, C*H*CH$_3$), 3.61 (s, 1 H, OCH$_3$), 5.39 (dd, 1 H, *J* = 4.8, 9.0 Hz, CHN), 7.18–7.56 (m, 9 H, NH + Ph), 7.82–7.92 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 29.6, 44.6, 51.9, 55.4, 126.1, 127.0, 127.5, 128.6, 131.6, 134.2, 140.5, 166.8, 176.3. – $C_{18}H_{19}NO_3$ (297.4): calcd. C 72.71, H 6.44, N 4.71; found C 72.66, H 6.49, N 4.74.

***rac*-2f:** IR (film): $\tilde{\nu}$ = 3320, 1733, 1635 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.28–2.56 (m, 2 H, C*H*$_2$CH=CH$_2$), 3.02–3.12 (m, 1 H, C*H*CHN), 3.53 (s, 3 H, OCH$_3$), 5.02–5.14 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.48 (dd, 2 H, J = 4.9, 8.8 Hz, CHN), 5.69–5.86 (m, 1 H, CH$_2$C*H*=CH$_2$). – ^{13}C NMR ($CDCl_3$): δ = 35.1, 50.6, 51.8, 53.5, 118.1, 126.0, 127.0, 127.5, 128.1, 131.7, 133.9, 134.0, 140.5, 166.6, 175.4. – $C_{20}H_{21}NO_3$ (323.4): calcd. C 74.28, H 6.55, N 4.33; found C 74.20, H 6.52, N 4.36.

***rac*-2g:** IR (film): $\tilde{\nu}$ = 3317, 1736, 1642 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.96–3.16 (m, 2 H, C*H*$_2$Ph), 3.16–3.28 (m, 2 H, C*H*CH$_2$Ph), 3.46 (s, 3 H, OCH$_3$), 5.44 (dd, 1 H, *J* = 3.6, 8.7 Hz, CHN), 7.06–7.30 (m, 13 H, Ph), 7.92–7.98 (m, 2 H, Ph), 8.08 (d, 1 H, *J* = 8.7 Hz, NH). – ^{13}C NMR ($CDCl_3$): δ = 37.1, 51.8, 53.0, 126.0, 126.8, 127.0, 127.5, 128.6, 128.8, 131.6, 137.9, 140.4, 166.5, 175.4. – $C_{24}H_{23}NO_3$ (373.5): calcd. C 77.19, H 6.21, N 3.75; found C 77.23, H 6.24, N 3.81.

General Method for the Synthesis of Methyl 2-Alkyl-3-(alkyl/aryl)-1-benzoylaziridine-2-carboxylates *trans-rac*-3 and *cis-rac*-4: LiHMDS (5.5 mmol, 1 M sol. in THF, 5.5 mL) was added to a stirred solution of α-alkyl β-benzamido methyl esters *rac*-**2a–g** (2.5 mmol) in dry THF (10 mL) under nitrogen at room temperature. The mixture was stirred for 5 h at room temperature, then cooled to the temperature reported in Table 2, and iodine was added (6 mmol, 1.52 g) in dry THF (10 mL). The mixture was stirred overnight while the temperature reached room temperature, then an aqueous saturated solution of ammonium chloride was added, THF was removed under reduced pressure and replaced with ethyl acetate. The organic layer was separated, washed twice with an aqueous saturated solution of sodium thiosulfate, twice with water, dried with sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluent).

***rac*-3a:** IR (film): $\tilde{\nu}$ = 1738, 1685 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.34 (d, 3 H, *J* = 5.7 Hz, C*H*$_3$CHN), 1.56 (s, 3 H, C*H*$_3$CCO$_2$CH$_3$), 3.09 (q, 1 H, *J* = 5.7 Hz, CHN), 3.37 (s, 3 H, OCH$_3$), 7.31–7.43 (m, 3 H, Ph), 7.69–7.78 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 13.4, 14.0, 42.2, 45.7, 52.1, 127.9, 128.1, 128.5, 132.1, 133.6, 169.7, 176.4. – $C_{13}H_{15}NO_3$ (233.3): calcd. C 66.94, H 6.48, N 6.00; found C 66.98, H 6.44, N 5.95.

***rac*-4a:** IR (film): $\tilde{\nu}$ = 1747, 1678 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.29 (s, 3 H, C*H*$_3$CCO$_2$CH$_3$), 1.36 (d, 3 H, *J* = 5.8 Hz, C*H*$_3$CHN), 2.78 (q, 1 H, *J* = 5.8 Hz, CHN), 3.83 (s, 3 H, OCH$_3$), 7.32–7.58 (m, 3 H, Ph), 8.01–8.10 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 13.6, 17.8, 42.5, 48.4, 52.6, 128.4, 132.8, 133.7, 169.4, 176.9. – $C_{13}H_{15}NO_3$ (233.3): calcd. C 66.94, H 6.48, N 6.00; found C 66.91, H 6.50, N 5.99.

***rac*-3b:** IR (film): $\tilde{\nu}$ = 1734, 1684 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.10 (t, 3 H, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.45 (d, 3 H, *J* = 5.8 Hz, C*H*$_3$CHN), 1.75 (dq, 1 H, *J* = 7.4, 14.3 Hz, C*H*HCH$_3$), 2.25 (dq, 1 H, *J* = 7.0, 14.3 Hz, CH*H*CH$_3$), 3.21 (q, 1 H, *J* = 5.8 Hz, CHN), 3.48 (s, 3 H, OCH$_3$), 7.31–7.58 (m, 3 H, Ph), 7.75–7.86 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ 10.1, 13.7, 22.2, 43.0, 49.8, 52.0, 128.2, 132.2, 133.7, 169.4, 176.5. – $C_{14}H_{17}NO_3$ (247.3): calcd. C 68.00, H 6.93, N 5.66; found C 68.06, H 6.95, N 5.71.

***rac*-4b:** IR (film): $\tilde{\nu}$ = 1734, 1684 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.78 (t, 3 H, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.35 (d, 3 H, *J* = 5.7 Hz, C*H*$_3$CHN), 1.62 (q, 2 H, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.80 (q, 1 H, *J* = 5.7 Hz, CHN), 3.82 (s, 3 H, OCH$_3$), 7.31–7.58 (m, 3 H, Ph), 8.02–8.15 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ 10.4, 13.9, 25.7, 40.1, 52.0, 52.2, 128.3, 132.7, 133.9, 169.4, 176.4. – $C_{14}H_{17}NO_3$ (247.3): calcd. C 68.00, H 6.93, N 5.66; found C 67.95, H 6.99, N 5.68.

***rac*-3c:** IR (film): $\tilde{\nu}$ = 1735, 1683 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.48 (d, 3 H, *J* = 5.8 Hz, CHNC*H*$_3$), 2.50 (dd, 1 H, *J* = 6.6, 15.2 Hz, C*H*HCH=CH$_2$), 3.06 (dd, 1 H, *J* = 6.4, 15.2 Hz, CH*H*CH=CH$_2$), 3.28 (q, 1 H, *J* = 5.8 Hz, CHN), 3.50 (s, 3 H,

OCH_3), 5.11–5.29 (m, 2 H, $CH_2CH{=}CH_2$), 5.62–6.06 (m, 1 H, $CH_2CH{=}CH_2$), 7.31–7.55 (m, 3 H, Ph), 7.85–7.98 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.5, 33.9, 43.4, 48.6, 52.8, 118.5, 128.8, 129.5, 132.9, 133.5, 169.8, 176.7. – $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.52, H 6.66, N 5.37.

***rac*-4c:** IR (film): $\tilde{\nu}$ = 1735, 1683 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.38 (d, 3 H, *J* = 5.7 Hz, $CHNCH_3$), 2.39–2.44 (m, 2 H, $CH_2CH{=}CH_2$), 2.86 (q, 1 H, *J* = 5.7 Hz, CHN), 3.82 (s, 3 H, OCH_3), 4.78–4.92 (m, 2 H, $CH_2CH{=}CH_2$), 5.29–5.55 (m, 1 H, $CH_2CH{=}CH_2$), 7.31–7.55 (m, 3 H, Ph), 8.00–8.08 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.3, 36.8, 40.7, 48.6, 52.8, 119.7, 128.9, 129.5, 133.3, 133.5, 169.8, 176.7. – $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.54, H 6.57, N 5.37.

***rac*-3d:** IR (film): $\tilde{\nu}$ = 1734, 1676 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.53 (d, 3 H, *J* = 5.9 Hz, CH_3CHN), 3.20 (d, 1 H, *J* = 15.6 Hz, CHHPh), 3.39 (q, 1 H, *J* = 5.9 Hz, CHN), 3.46 (s, 3 H, OCH_3), 3.58 (d, 1 H, *J* = 15.6 Hz, CHHPh), 7.15–7.58 (m, 8 H, Ph), 7.65–7.80 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.6, 34.1, 43.4, 49.2, 52.3, 126.4, 126.8, 128.2, 128.8, 129.3, 132.3, 132.7, 136.8, 169.3, 176.6. – $C_{19}H_{19}NO_3$ (309.4): calcd. C 73.77, H 6.19, N 4.53; found C 73.82, H 6.12, N 4.55.

***rac*-3e:** IR (film): $\tilde{\nu}$ = 1736, 1684 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.42 (s, 3 H, CH_3CN), 3.57 (s, 3 H, OCH_3), 4.32 (s, 1 H, CHN), 7.25–7.56 (m, 8 H, Ph), 7.82–7.95 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.2, 21.0, 29.7, 49.3, 52.6, 60.4, 127.8, 128.3, 128.5, 132.6, 133.2, 133.6, 143.7, 169.2, 176.4. – $C_{18}H_{17}NO_3$ (295.3): calcd. C 73.20, H 5.80, N 4.74; found C 73.27, H 5.79, N 4.77.

***rac*-4e:** IR (film): $\tilde{\nu}$ = 1736, 1684 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.49 (s, 3 H, CH_3CN), 3.51 (s, 3 H, OCH_3), 3.78 (s, 1 H, CHN), 7.25–7.56 (m, 8 H, Ph), 7.82–7.95 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.0, 21.0, 48.5, 52.6, 60.4, 127.8, 128.3, 128.5, 132.6, 133.2, 133.6, 143.7, 169.2, 176.4. – $C_{18}H_{17}NO_3$ (295.3): calcd. C 73.20, H 5.80, N 4.74; found C 73.27, H 5.79, N 4.77.

***rac*-3f:** IR (film): $\tilde{\nu}$ = 1737, 1680 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.38 (dd, 1 H, *J* = 7.12 Hz, $CHHCH{=}CH_2$), 2.65 (dd, 1 H, *J* = 9.1 Hz, $CHHCH{=}CH_2$), 3.65 (s, 3 H, OCH_3), 4.41 (s, 1 H, CHN), 4.72–5.02 (m, 2 H, $CH_2CH{=}CH_2$), 5.55–5.79 (m, 1 H, $CH_2CH{=}CH_2$), 7.22–7.63 (m, 10 H, Ph), 7.85–7.98 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 32.1, 49.9, 50.7, 52.5, 118.1, 127.9, 128.4, 128.5, 128.6, 132.3, 132.6, 132.9, 133.3, 168.7, 176.0. – $C_{20}H_{19}NO_3$ (321.4): calcd. C 74.75, H 5.96, N 4.36; found C 74.81, H 6.00, N 4.40.

***rac*-3g**: IR (film): $\tilde{\nu}$ = 1744, 1671 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.10 (AB, 2 H, *J* = 15.0 Hz, CH_2Ph), 3.61 (s, 3 H, OCH_3), 4.46 (s, 1 H, CHN), 7.01–7.52 (m, 8 H, Ph), 7.62–7.77 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 32.9, 50.5, 51.8, 52.5, 126.4, 128.1, 128.3, 128.5, 128.7, 129.4, 132.5, 133.5, 136.6, 168.8, 176.1. – $C_{15}H_{17}NO_3$ (371.4): calcd. C 77.61, H 5.70, N 3.77; found C 77.65, H 5.73, N 3.79.

Ring Opening of Methyl *trans*-2-Alkyl-1-benzoyl-3-methylaziridine-2-carboxylates *rac*-3a–d with BF_3/Et_2O in $CHCl_3$. – Synthesis of Methyl 2-Alkyl 2-benzamido-3-ethoxybutanoates *rac*-5a–d: A solution of aziridine *rac*-**3a–d** (0.2 mmol) and $BF_3{\cdot}Et_2O$ (0.6 mmol, 0.076 mL) in chloroform (5 mL) was stirred at room temperature for 1.5 h. Then the reaction mixture was diluted with dichloromethane, washed twice with water, dried with sodium sulfate, and concentrated. The product *rac*-**5** was obtained pure as an oil after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluent).

***rac*-5a:** 88% yield. – IR (film): $\tilde{\nu}$ = 3417, 1739, 1652 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.18 (t, 3 H, *J* = 6.5 Hz, CH_3CH_2O), 1.26 (d, 3 H, *J* = 5.8 Hz, CH_3CHO), 1.74 (s, 3 H, CH_3CN), 3.48 (dq, 1 H, *J* = 6.5, 12 Hz, CH_3CHHO), 3.67 (dq, 1 H, *J* = 6.5, 12.0 Hz, CH_3CHHO), 3.78 (s, 3 H, OCH_3), 3.92 (q, 1 H, *J* = 5.8 Hz, CHN), 7.08 (s, 1 H, NH), 7.30–7.60 (m, 3 H, Ph), 7.70–7.85 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 15.1, 15.5, 20.2, 52.5, 63.8, 65.5, 78.1, 126.9, 128.5, 131.4, 134.8, 166.9, 172.4. – $C_{15}H_{21}NO_4$ (279.3): calcd. C 64.50, H 7.58, N 5.01; found C 64.55, H 7.63, N 5.08.

***rac*-5b:** 92% yield. – IR (film): $\tilde{\nu}$ = 3413, 1734, 1669 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.80 (t, 3 H, *J* = 7.5 Hz, CCH_2CH_3), 1.06 (t, 3 H, *J* = 6.6 Hz, OCH_2CH_3), 1.31 (d, 3 H, *J* = 6.8 Hz, CH_3CHO), 1.90–2.15 (m, 1 H, $CCHHCH_3$), 2.42–2.63 (m, 1 H, C–CHH–CH_3), 3.31–3.45 (m, 1 H, $OCHHCH_3$), 3.52–3.64 (m, 1 H, $OCHHCH_3$), 3.82 (s, 3 H, OCH_3), 4.32 (q, 1 H, *J* = 6.8 Hz, CH_3CHO), 7.21 (s, 1 H, NH), 7.40- 7.63 (m, 3 H, Ph), 7.80–7.98 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 8.5, 15.5, 24.4, 29.7, 52.7, 64.0, 65.7, 78.4, 126.9, 128.6, 131.4, 135.0, 167.2, 172.2. – $C_{16}H_{23}NO_4$ (293.4): calcd. C 65.51, H 7.90, N 4.77; found C 65.58, H 7.84, N 4.79.

***rac*-5c:** 90% yield. – IR (film): $\tilde{\nu}$ = 3417, 1734, 1669 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.09 (t, 3 H, *J* = 6.6 Hz, OCH_2CH_3), 1.31 (d, 3 H, *J* = 6.6 Hz, CH_3CHO), 2.82 (dd, 1 H, *J* = 6.9, 13.8 Hz, $CHHCH{=}CH_2$), 3.28 (dd, 1 H, *J* = 8.1, 13.8 Hz, $CHHCH{=}CH_2$), 3.35–3.48 (m, 1 H, $OCHHCH_3$), 3.55–3.65 (m, 1 H, $OCHHCH_3$), 3.81 (s, 3 H, OCH_3), 4.28 (q, 1 H, *J* = 6.6 Hz, CH_3CHO), 4.95–5.13 (m, 2 H, $CHHCH{=}CH_2$), 5.60–5.68 (m, 1 H, $CHHCH{=}CH_2$), 7.35 (s, 1 H, NH), 7.40–7.58 (m, 3 H, Ph), 7.68–7.85 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 15.4, 35.8, 52.6, 65.6, 68.3, 76.4, 118.8, 126.8, 128.5, 131.4, 132.4, 135.2, 166.6, 172.2. – $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.90, H 7.60, N 4.63.

***rac*-5d:** 90% yield. – IR (film): $\tilde{\nu}$ = 3412, 1727, 1651 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.06 (t, 3 H, *J* = 6.9 Hz, OCH_2CH_3), 1.46 (d, 3 H, *J* = 6.6 Hz, CH_3CHO), 3.27–3.48 (m, 2 H, $OCHHCH_3$ + CHHPh), 3.52–3.64 (m, 1 H, $OCHHCH_3$), 3.74–3.85 (m, 1 H, CHHPh), 3.87 (s, 3 H, OCH_3), 4.55 (q, 1 H, *J* = 6.6 Hz, CH_3CHO), 6.98–7.24 (m, 6 H, NH + Ph), 7.30–7.55 (m, 3 H, Ph), 7.60–7.78 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 15.5, 15.8, 36.7, 52.5, 65.7, 69.9, 76.0, 126.7, 128.1, 128.3, 128.5, 128.7, 129.7, 131.3, 136.1, 167.2, 171.7. – $C_{21}H_{25}NO_4$ (355.4): calcd. C 70.96, H 7.09, N 3.94; found C 70.99, H 7.04, N 3.89.

Ring Opening of Methyl *trans*-1-Benzoyl-2,3-dimethylaziridine-2-carboxylate *rac*-3a with $BF_3{\cdot}2H_2O$ in CH_2Cl_2. – Synthesis of Methyl *anti*-2-Benzamido-3-hydroxy-2-methyl-3-phenylpropanoate *rac*-6a: A solution of aziridine **3a** (0.22 mmol, 50 mg) and $BF_3 \cdot 2\,H_2O$ (0.66 mmol, 0.016 mL) in dichloromethane (5 mL) was stirred at room temperature for 16 h. The reaction mixture was then diluted with dichloromethane, washed twice with a 1 M aqueous solution of Na_2CO_3, dried with sodium sulfate, and concentrated. The product **6a** was obtained pure as an oil after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluent) in 90% yield. – IR (film) $\tilde{\nu}$ = 3395, 1734, 1653, 1522 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.12 (d, 3 H, *J* = 6.4 Hz, CH_3CHO), 1.74 (s, 3 H, CH_3CN), 3.86 (s, 3 H, OCH_3), 4.21 (dq, 1 H, *J* = 6.4, 10.1 Hz, CHO), 5.28 (d, 1 H, *J* = 10.1 Hz, OH), 7.35–7.65 (m, 4 H, NH+Ph), 7.75–7.85 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 18.9, 20.2, 53.3, 59.6, 65.7, 71.2, 127.1, 128.7, 132.1, 167.8, 178.9. – $C_{13}H_{17}NO_4$ (251.3): calcd. C 62.14, H 6.82, N 5.57; found C 62.11, H 6.84, N 5.53.

Ring Opening of Methyl *trans*-1-Benzoyl-2,3-dimethylaziridine-2-carboxylate *rac*-3a with $BF_3 \cdot 2\,H_2O$ in DMF. – Synthesis of Methyl *anti*-3-Benzamido-2-hydroxy-2-methyl-3-phenylpropanoate *rac*-7a:

A solution of aziridine *rac*-**3a** (0.22 mmol, 50 mg) and $BF_3{\cdot}2H_2O$ (1.1 mmol, 0.027 mL) in *N*,*N*-dimethylformamide (5 mL) was stirred at room temperature for 16 h. Then the reaction mixture was diluted with dichloromethane, washed twice with water, dried with sodium sulfate and concentrated. The product *rac*-**7a** was obtained pure as an oil after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluent) in 75% yield. – IR (film) $\tilde{\nu}$ = 3360, 1743, 1638 cm^{-1}. – ^1H NMR (C_6D_6): δ = 1.01 (d, *J* = 7.0 Hz, 3 H, CH_3CHN), 1.38 (s, 3 H, CH_3CN), 3.18 (s, 3 H, OCH_3), 4.83 (dq, 1 H, *J* = 7.0, 10.0 Hz, CHN), 6.33 (d, *J* = 10.0 Hz, NH), 6.91–7.50 (m, 3 H, Ph), 7.65–7.88 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 16.1, 23.7, 30.3, 50.3, 53.2, 77.2, 126.8, 127.0, 128.0, 128.6, 131.5, 131.6, 134.5, 167.1, 176.2. – $C_{13}H_{17}NO_4$ (251.3): calcd. C 62.14, H 6.82, N 5.57; found C 62.18, H 6.79, N 5.58.

Ring Opening of Methyl *trans*-1-Benzoyl-2,3-dimethylaziridine-2-carboxylate *rac*-3a with $BF_3 \cdot Et_2O$ in CH_3CN. – Synthesis of Methyl *cis*-2,4,5-Trimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate *rac*-8a and of Methyl *cis*-2,4,5-Trimethyl-4,5-dihydro-1*H*-imidazole-5-carboxylate *rac*-8b: A solution of aziridine **3a** (0.22 mmol, 50 mg) and $BF_3{\cdot}Et_2O$ (0.66 mmol, 0.016 mL) in acetonitrile (5 mL) was stirred at room temperature for 16 h. Then the solvent was removed and replaced with dichloromethane, the mixture was washed twice with a 1 M aqueous solution of Na_2CO_3, dried with sodium sulfate, and concentrated. The products *rac*-**8a** and *rac*-**8b** were obtained pure as an oil after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluent) in 80% and 10% yield.

***rac*-8a:** IR (film) $\tilde{\nu}$ = 1734, 1684, 1624 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.29 (d, 3 H, *J* = 6.6 Hz, CH_3CHN), 1.51 (s, 3 H, CH_3CN), 1.80 (s, 3 H, $CH_3C{=}N$), 3.78 (s, 3 H, OCH_3), 4.50 (q, 3 H, *J* = 6.6.Hz, CH_3CHN), 7.32–7.58 (m, 5 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 15.8, 24.4, 25.0, 52.3, 64.5, 75.3, 128.4, 128.5, 131.0, 131.5, 158.2, 168.1, 172.2 – $C_{15}H_{18}N_2O_2$ (274.3): calcd. C 65.68, H 6.61, N 10.21; found C 65.73, H 6.64, N 10.25.

***rac*-8b:** IR (film) $\tilde{\nu}$ = 1734, 1669, 1634 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.18 (d, 3 H, *J* = 6.6 Hz, CH_3CHN), 1.58 (s, 3 H, CH_3CN), 1.99 (s, 3 H, $CH_3C{=}N$), 3.79 (s, 3 H, OCH_3), 4.28 (q, 3 H, *J* = 6.6.Hz, CH_3CHN), 7.32–7.58 (m, 5 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 15.3, 19.2, 24.7, 29.7, 52.3, 64.7, 74.7, 127.0, 127.6, 128.6, 131.5, 136.0, 157.9, 168.5, 172.0 – $C_{15}H_{18}N_2O_2$ (274.3): calcd. C 65.68, H 6.61, N 10.21; found C 65.73, H 6.64, N 10.25.

Ring Opening of Methyl *trans*-2-Alkyl-1-benzoyl-3-phenylaziridine-2-carboxylates *rac*-3e–g and Methyl *cis*-1-Benzoyl-2-methyl-3-phenylaziridine-2-carboxylate *rac*-4e with $BF_3{\cdot}Et_2O$ in $CHCl_3$. – Synthesis of Methyl *trans*-4-Alkyl-2,5-diphenyloxazoline-2-carboxylates *rac*-9e–g and Methyl *cis*-4-Methyl-2,5-diphenyloxazoline-2-carboxylate *rac*-10e: A solution of aziridine (0.2 mmol) and $BF_3 \cdot Et_2O$ (0.6 mmol, 0.076 mL) in chloroform (5 mL) was stirred at room temperature for 1.5 h. The reaction mixture was then diluted with dichloromethane, washed twice with water, dried with sodium sulfate, and concentrated. The product was obtained pure as an oil after silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluent).

***rac*-9e:** 95% yield. – IR (film) $\tilde{\nu}$ = 1734, 1652 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.10 (s, 3 H, CH_3CN), 3.87 (s, 3 H, OCH_3), 6.12 (s, 1 H, CHO), 7.20–7.60 (m, 8 H, Ph), 8.05–8.15 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 22.2, 52.9, 77.7, 85.7, 126.1, 127.1, 128.2, 128.3, 128.6, 131.8, 136.1, 163.8, 174.4. – $C_{13}H_{15}NO_3$ (233.3): calcd. C 66.94, H 6.48, N 6.00; found C 66.99, H 6.53, N 5.95.

***rac*-10e:** 94% yield. – IR (film) $\tilde{\nu}$ = 1736, 1653 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.81 (s, 3 H, CH_3CN), 3.17 (s, 3 H, OCH_3), 5.42 (s, 1 H, CHO), 7.20–7.60 (m, 8 H, Ph), 8.05–8.15 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 26.0, 51.8, 79.9, 90.1, 125.8, 128.1, 128.4, 128.7, 131.9, 136.1, 164.8, 174.4. – $C_{13}H_{15}NO_3$ (233.3): calcd. C 66.94, H 6.48, N 6.00; found C 66.99, H 6.53, N 5.95.

***rac*-9f:** 98% yield. – IR (film) $\tilde{\nu}$ = 1732, 1652 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.17 (ABX, 2 H, *J* = 6.9, 7.5, 13.9 Hz, $CH_2CH{=}CH_2$), 3.85 (s, 3 H, OCH_3), 4.81–4.96 (m, 2 H, $CH_2CH{=}CH_2$), 5.51–5.66 (m, 1 H, $CH_2CH{=}CH_2$), 6.01 (s, 1 H, CHO), 7.31–7.60 (m, 8 H, Ph), 8.08–8.15 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 40.8, 52.7, 81.1, 85.7, 118.5, 126.6, 128.1, 128.4, 128.7, 131.9, 132.4, 135.6, 164.0, 173.8. – $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.54, H 6.66, N 5.38.

***rac*-9g:** 98% yield. – IR (film) $\tilde{\nu}$ = 1727, 1654 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.52 (d, 1 H, *J* = 13.6 Hz, $CHHPh$), 2.68 (d, 1 H, *J* = 13.6 Hz, $CHHPh$), 3.69 (s, 3 H, OCH_3), 5.97 (s, 1 H, CHO), 7.30–7.60 (m, 13 H, Ph), 8.07–8.12 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 42.9, 52.5, 81.9, 86.6, 126.6, 126.7, 127.2, 127.9, 128.2, 128.4, 128.7, 128.8, 130.2, 131.9, 135.5, 136.1, 163.8, 174.0. – $C_{19}H_{19}NO_3$ (309.4): calcd. C 73.77, H 6.19, N 4.53; found C 73.74, H 6.20, N 4.50.

Hydrolysis of Methyl *trans*-4-Methyl-2,5-diphenyloxazoline-4-carboxylate *rac*-9e. – Synthesis of *syn*-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic Acid *rac*-11e: A solution of oxazoline *rac*-**9e** (0.21 mmol, 50 mg) in methanol (1 mL) and 6 M HCl (5 mL) was heated at reflux for 15 h, then cooled and concentrated under reduced pressure, before water (5 mL) was added. The mixture was adsorbed on cation exchange resin. The resin was then washed with water until the washing came out neutral, then with 2 M aqueous NH_4OH to recover the amino acid *rac*-**11e** in 85% yield. – M.p. 195–198 °C (dec.). – ^1H NMR (D_2O): δ = 1.29 (s, 3 H, CH_3CN), 5.10 (s, 1 H, CHO), 7.30–7.45 (m, 5 H, Ph). – ^{13}C NMR (D_2O): δ = 18.4, 65.3, 74.7, 127.4, 129.2, 129.7, 137.9, 161.2.

Hydrolysis of Methyl *cis*-4-Methyl-2,5-diphenyloxazoline-4-carboxylate *rac*-10e. – Synthesis of *anti*-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic Acid *rac*-12e: For the procedure see hydrolysis of *rac*-**9e**: 80% yield. M.p. 202–205 °C (dec.); ref.[6] m.p. 204–206 °C (dec.). – ^1H NMR (D_2O): δ = 1.55 (s, 3 H, CH_3CN), 5.00 (s, 1 H, CHO), 7.28–7.45 (m, 5 H, Ph). – ^{13}C NMR (D_2O): δ = 20.4, 65.8, 75.6, 127.7, 129.4, 129.9, 139.7, 160.4.

Acknowledgments

This work was supported in part by M.U.R.S.T. Cofin '98 (Roma) and by University of Bologna (funds for Selected Research Topics).

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[20] As both C2 and C3 positions are not activated for the substitution, the solvent plays a crucial role. In DMF the reaction proceeds with lower yield and requires more Lewis acid than in dichloromethane. In these conditions the C2 attack is favoured, probably owing to the coordinating effect of DMF. Acetonitrile shows an intermediate behaviour, affording a regioisomeric mixture. With 3-phenyl-substituted aziridines (see further) different results are obtained because the phenyl group stabilises the incipient carbocation at C3 and the solvent effect is overwhelmed, so that the C2 attack is never observed.
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Received July 27, 1999
[O99465]