Synthesis and Ring Opening of 2-Alkyl 2-Carboxymethyl 3-Alkyl/Aryl *N*-Benzoyl Aziridines: Synthesis of Polysubstituted Amino Acids

Carmela Papa, and Claudia Tomasini*

Dipartimento di Chimica "G.Ciamician" - Università di Bologna
Via Selmi 2, 40126 Bologna, Italy
Email: tomasini@ciam.unibo.it

Keywords: 2,2,3-Trisubstituted *N*-Benzoyl Aziridines, 2,4,4,5-Tetrasubstituted Oxazolines, Ring Expansion, α-Hydroxy β-Amino Acids, β-Hydroxy α-Amino Acids.

Summary: A new method for the preparation of 2,2,3-trisubstituted 2-carboxymethyl *N*-benzoyl aziridines is reported. These compounds have been obtained starting from α-alkyl β-amino acids by formation of the lithium dianion and reaction with iodine. They undergo ring expansion or ring opening, according to the substituents of the aziridine ring and to 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 as starting material proteogenic amino acids, such as alanine [6] or treonine.[7] 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 2-carboxymethyl *N*-benzoyl aziridines, 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 undergo ring expansion or ring opening, according to the substituents of the aziridine ring and to the reaction conditions.

Results and Discussion

i. Synthesis of 2-Alkyl 2-Carboxymethyl 3-Alkyl/Aryl *N*-Benzoyl Aziridines.

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 3-amino butanoic acid, which is purchasable, and from 3-amino 3-phenyl propanoic acid [9] by protection of the amino group by Schotten-Baumann reaction and esterification of the carboxyl 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] if the reaction is carried out at lower or higher temperatures (i. e. –78 °C or room temperature), low yields are obtained.

Scheme 1.

Table 1.

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 (Figure 1).

Figure 1.

The lithium dianion was obtained by reaction of *rac*-**2a-g** with 2.2 equivalents of LiHMDS in dry THF at room temperature. If the metalation is performed at lower temperature (such as 0 °C or less) the reaction does not occur, probably owing to the steric hindrance at C2. The reaction proceeds by the intermediate formation of the *N*-lithium anion of the 2-iododerivative, which spontaneously affords the ring closure: after reaction work-up only starting material and aziridines are obtained, without any traces of the intermediate 2-iododerivative. 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-benzoylamino butanoate [10a] or methyl 3-benzoylamino 3-phenyl propanoate.[10b] No oxazolines were obtained in any reactions, on the contrary the corresponding *N*-benzoyl aziridines *rac*-**3a-g** and *rac*-**4a-g** were synthesised in good yields and high diastereomeric ratios (Scheme 2 and Table 2).

Scheme 2.

Table 2.

Moreover, if the NaHMDS is utilised instead of LiHMDS, completely different results are obtained: in that case the direct formation of *syn* α-alkyl α-hydroxy β-benzoylamino acids is observed,[13] probably by means of the intermediate formation of 2,4,4,5-tetrasubstituted oxazolines, which hydrolyse during the work-up.

The stereochemical outcome of the aziridine formation is quite satisfactory: indeed the *trans*/*cis* diastereomeric ratios range from 78:22 to 99:1 and the yields are always high: a low yield was obtained only in the formation of *rac*-**3g** (entry 7), probably owing to the steric hindrance of both 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 2). *Trans* 2-benzyl 2-carboxymethyl 3-methyl *N*-benzoyl aziridine *rac*-**3d** shows 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** shows no NOEDIFF effects, owing to the *trans* relationship between the C3 hydrogen and the C2 allylic group. The other substituents (phenyl and carboxymethyl groups) show 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 2.

ii. Ring Opening of *trans* 2-Alkyl 2-Carboxymethyl 3-Methyl *N*-Benzoyl Aziridines *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 2,3-dialkyl/aryl 2-carboxymethyl *N*-benzoyl aziridine we can obtain polysubstituted α- or β-amino acids. Those 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-benzoyl aziridines *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 have great importance in the steric and regiochemical outcome. Zwanenburg and co-workers have extensively studied the ring opening of 3-substituted aziridine 2-carboxylic esters both when the substituent is an aliphatic chain [15] and when is an aromatic ring. [16] They have demonstrated that aliphatically substituted aziridine carboxylates 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, due to the presence of the phenyl which can stabilise an incipient carbocation. Following this behaviour, our 2,3-dialkyl/aryl 2-carboxymethyl *N*-benzoyl aziridines afford two different results, weather the 3-substituent is a methyl group (**a-d**) or a phenyl group (**e-g**).

When *N*-benzoyl aziridines *rac*-**3a-d** where treated with $BF_3.Et_2O$ in chloroform, the ring opening was observed (Scheme 3): owing to the BF_3 catalysis, the little amount of ethanol, which is present in commercially available chloroform as stabilising agent (about 1%), reacted as 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 coworkers [17] in the ring opening of benzyl (2*S*)-1-benzyloxycarbonyl-2-aziridine-carboxylate and methyl (2*S*,3*S*)-1-benzyloxycarbonyl-3-methyl-2-aziridine carboxylate, obtained from serine and treonine respectively. In the presence of a catalytic amount of $BF_3.Et_2O$ and several alcohols, β-alkoxy α-amino acids were obtained in generally good yields and complete control of regioselectivity. In our hands, by treating *N*-benzoyl aziridines *rac*-**3a-g** with $BF_3.Et_2O$ 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 ^1H NMR analysis: indeed the hydrogen of the amide group is a singlet, thus the amido group is in the α position. When the ring opening of *rac*-**3a-g** with $BF_3.Et_2O$ was performed in methylene chloride (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-carboxymethyl oxazolines and 4-carboxymethyl oxazolines were obtained so that other solvents were tested, in order to have stereochemical control. We utilised as Lewis acid the commercially available $BF_3.2H_2O$, so that water can act as external nucleophile.[19] The reaction was performed in THF, methylene chloride, DMF and acetonitrile. While the reaction in THF afforded only the starting material, in methylene chloride and DMF we obtained opposite results (Scheme 4).

Scheme 4.

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

On the other hand, if the ring opening of *rac*-**3a** is performed with $BF_3.H_2O$ in acetonitrile, a complex mixture is obtained, as both the acetonitrile and the water behave as nucleophile. So, when the reaction is performed in the absence of water, i. e. with $BF_3.Et_2O$ in acetonitrile, a 89:11 regioisomeric mixture of the *cis*-4,5-dihydro-1*H*-imidazoles *rac*-**8a** and *rac*-**8b** is achieved (Scheme 5). The *cis*-relationship among the substituents of *rac*-**8a** and *rac*-**8b** was demonstrated by NOEDIF experiments (Figure 3), indeed both compounds show a strong enhancement of the C3 hydrogen, by irradiating the C2 methyl group, thus showing a *cis* relationship between them. The regiochemistry was attributed by comparison of the chemical shifts of the

dihydroimidazole substituents: indeed both substituents at C5 are more shielded in *rac*-**8a** [δ: 1.29 (d, 3H), 4.50 (q, 1H)] then the substituents at C4 of *rac*-**8b** [δ: 1.18 (d, 3H), 4.28 (q, 1H)], owing to the deshielding effect of the carbonyl of the benzamido group. The methyl α to the carboxymethyl group shows the opposite behaviour [*rac*-**8a**: δ = 1.51 ppm; *rac*-**8b**: δ = 1.58 ppm].

Scheme 5.

Figure 3.

The formation of these heterocycles was previously observed by Hiyama [22] and more recently by Zwanenburg [15] in the reaction of 3-alkyl 2-carboxymethyl aziridines, for the synthesis of α,β-diamino acids. In both cases the reaction affords a single product: Zwanenburg assumes that this reaction proceeds *via* 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 2-Alkyl 2-Carboxymethyl 3-Phenyl *N*-Benzoyl Aziridines 3e-g.

The behaviour of 2-alkyl 2-carboxymethyl 3-phenyl *N*-benzoyl aziridines *rac*-**3e-g** and *rac*-**4e** is quite different from what we have just shown: indeed they easily undergo ring expansion, regardless the solvent and the ligand of the BF_3 utilised. So, by utilising ethanol containing chloroform or acetonitrile as solvent or $BF_3.H_2O$ as Lewis acid, no evidences of the addition products were obtained; on the contrary the exclusive formation of *trans* 2,5-diphenyl 4-alkyl 4-carboxymethyl oxazolines *rac*-**9e-g** from *trans N*-benzoyl aziridines *rac*-**3e-g** and of *cis* 2,5-diphenyl 4-methyl 4-carboxymethyl oxazoline *rac*-**10e** from *cis N*-benzoyl aziridine *rac*-**4e** was observed (Scheme 6).

Scheme 6.

The aziridine undergo exclusively ring expansion, which is totally stereo- and regioselective, so starting from *trans N*-benzoyl aziridines, only *trans* oxazolines are obtained. The regiochemistry is confirmed by comparison of the ^{1}H NMR spectra with similar compounds [22] and with 2,5-diphenyl 4-alkyl 4-carboxymethyl oxazolines [10b], and the stereochemistry is confirmed by NOEDIF experiments performed on *rac*-**9f**. Indeed, the irradiation of signals of *rac*-**9f** shows 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 6M HCl in refluxing methanol followed by purification on ion exchange resin, afforded respectively 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**, whose 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*-benzoyl aziridines. As these molecules contain a carboxymethyl group, they can be easily transformed in polysubstituted α- or β-amino acids. The *N*-benzoyl aziridine ring can undergo both ring opening at C2 or C3 and ring expansion: 2-alkyl 2-carboxymethyl 3-methyl *N*-benzoyl aziridines preferentially undergo regioselective ring opening at C2 or C3, depending on the reaction conditions, while 2-alkyl 2-carboxymethyl 3-phenyl *N*-benzoyl aziridines preferentially undergo ring expansion,

with total regio- and stereocontrol and the exclusive formation of 2,5-diphenyl 4-alkyl 4-carboxymethyl oxazolines.

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 2-alkyl 2-carboxymethyl 3-methyl *N*-benzoyl aziridines in acetonitrile, which behaves both as solvent and as nucleophile. These compounds are precursors of α-substituted α,β-diamino acids.

EXPERIMENTAL

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 7.27 ppm. - 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-Phenyl 3-Benzamidopropanoate *rac*-1b: LiHMDS (4.2 mmol, 1M sol. in THF, 4.2 mL) was added to a stirred solution of ester **1** (2 mmol) in dry THF (10 mL) under nitrogen atmosphere at 0 °C. The mixture was stirred 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 increasing till room temperature. An aqueous saturated solution of ammonium chloride (20 mL) was added, then THF was removed under reduced pressure and replaced with methylene chloride. The organic layer was separated, washed twice with water, dried over sodium sulphate 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 eluant).

rac-**2a:** M. p. 71-73 °C. - IR (film) ν = 3353, 1733, 1638 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.25 (d, 6H, *J* = 7.0 Hz, C*H*$_3$CHN + C*H*$_3$CHCO), 2.74 (dq, 1H, *J* = 3.8, 7.0 Hz, CH$_3$*CH*CO), 3.72 (s, 3H, OCH_3), 4.33-4.45 (m, 1H, CHN), 7.21 (d, 1H, *J* = 8.3 Hz,

NH), 7.35-7.52 (m, 3H, Ph), 7.79-7.83 (m, 2H, 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): ν = 3319, 1736, 1643 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, 3H, *J* = 6.9 Hz, CH_2CH_3), 1.14 (d, 3H, *J* = 7.0 Hz, CH_3CHN), 1.43-1.62 (m, 2H, CH_2CH_3), 2.42 (ddd, 1H, *J* = 4.0, 6.5, 8.8 Hz, $CHCH_2CH_3$), 3.62 (s, 3H, OCH_3), 4.31-4.42 (m, 1H, CHN), 7.18-7.41 (m, 3H, Ph), 7.58-7.77 (m, 2H, 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): ν = 3264, 1733, 1636 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.16 (d, 3H, *J* = 6.9 Hz, $CHNCH_3$), 2.13-2.41 (m, 2H, $CH_2CH{=}CH_2$), 2.53-2.66 (m, 1H, CHCHN), 3.62 (s, 3H, OCH_3), 4.28-4.48 (m, 1H, CHN), 4.85-5.05 (m, 2H, $CH_2CH{=}CH_2$), 5.53-5.78 (m, 1H, $CH_2CH{=}CH_2$), 7.05-7.37 (m, 4H, NH + Ph), 7.58-7.70 (m, 2H, 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): ν = 3351, 1733, 1635 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.23 (d, 3H, *J* = 6.9 Hz, $CHNCH_3$), 2.84-3.06 (m, 3H, $CHCH_2Ph$), 3.61 (s, 3H, OCH_3), 4.43-4.55 (m, 1H, CHN), 7.13-7.58 (m, 9H, NH + Ph), 7.81-7.88 (m, 2H, 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): ν = 3419, 1735, 1638 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.37 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 3.11 (dq, 1H, *J* = 4.7, 7.1 Hz, $CHCH_3$), 3.61 (s, 1H, OCH_3), 5.39 (dd,

1H, *J* = 4.8, 9.0 Hz, CHN), 7.18-7.56 (m, 9H, NH + Ph), 7.82-7.92 (m, 2H, 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): ν = 3320, 1733, 1635 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 2.28-2.56 (m, 2H, C*H*$_2$CH=CH$_2$), 3.02-3.12 (m, 1H, C*H*CHN), 3.53 (s, 3H, OCH_3), 5.02-5.14 (m, 2H, CH_2CH=C*H*$_2$), 5.48 (dd, 2H, J = 4.9, 8.8 Hz, CHN), 5.69-5.86 (m, 1H, CH_2C*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): ν = 3317, 1736, 1642 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 2.96-3.16 (m, 2H, C*H*$_2$Ph), 3.16-3.28 (m, 2H, C*H*CH_2Ph), 3.46 (s, 3H, OCH_3), 5.44 (dd, 1H, *J* = 3.6, 8.7 Hz, CHN), 7.06-7.30 (m, 13H, Ph), 7.92-7.98 (m, 2H, Ph), 8.08 (d, 1H, *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 2-Alkyl 2-Carboxymethyl 3-Alkyl/Aryl *N*-Benzoyl Aziridines *trans*-*rac*-3 and *cis*-*rac*-4: LiHMDS (5.5 mmol, 1M 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 atmosphere at room temperature. The mixture was stirred 5 h at room temperature, then was 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 thiosulphate, twice with water, dried over sodium sulphate and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 9:1 as eluant).

rac-**3a:** IR (film): ν = 1738, 1685 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.34 (d, 3H, *J* = 5.7 Hz, C*H*$_3$CHN), 1.56 (s, 3H, C*H*$_3$CCO_2CH_3), 3.09 (q, 1H, *J* = 5.7 Hz, CHN), 3.37 (s, 3H, OCH_3), 7.31-7.43 (m, 3H, Ph), 7.69-7.78 (m, 2H, 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): ν = 1747, 1678 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 3H, C*H*$_3$CCO_2CH_3), 1.36 (d, 3H, *J* = 5.8 Hz, C*H*$_3$CHN), 2.78 (q, 1H, *J* = 5.8 Hz, CHN), 3.83 (s, 3H, OCH_3), 7.32-7.58 (m, 3H, Ph), 8.01-8.01 (m, 2H, 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): ν = 1734, 1684 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.10 (t, 3H, *J* = 7.4 Hz, CH_2C*H*$_3$), 1.45 (d, 3H, *J* = 5.8 Hz, C*H*$_3$CHN), 1.75 (dq, 1H, *J* = 7.4, 14.3 Hz, C*H*HCH_3), 2.25 (dq, 1H, *J* = 7.0, 14.3 Hz, CH*H*CH_3), 3.21 (q, 1H, *J* = 5.8 Hz, CHN), 3.48 (s, 3H, OCH_3), 7.31-7.58 (m, 3H, Ph), 7.75-7.86 (m, 2H, 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): ν = 1734, 1684 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 0.78 (t, 3H, *J* = 7.4 Hz, CH_2C*H*$_3$), 1.35 (d, 3H, *J* = 5.7 Hz, C*H*$_3$CHN), 1.62 (q, 2H, *J* = 7.4 Hz, C*H*$_2$$CH_3$), 2.80

(q, 1H, *J* = 5.7 Hz, CHN), 3.82 (s, 3H, OCH_3), 7.31-7.58 (m, 3H, Ph), 8.02-8.15 (m, 2H, 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): ν = 1735, 1683 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.48 (d, 3H, *J* = 5.8 Hz, CHNC*H*$_3$), 2.50 (dd, 1H, *J* = 6.6, 15.2 Hz, C*H*HCH=CH_2), 3.06 (dd, 1H, *J* = 6.4, 15.2 Hz, CH*H*CH=CH_2), 3.28 (q, 1H, *J* = 5.8 Hz, CHN), 3.50 (s, 3H, OCH_3), 5.11-5.29 (m, 2H, $CH_2CH=CH_2$), 5.62-6.06 (m, 1H, $CH_2CH=CH_2$), 7.31-7.55 (m, 3H, Ph), 7.85-7.98 (m, 2H, 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): ν = 1735, 1683 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.38 (d, 3H, *J* = 5.7 Hz, CHNC*H*$_3$), 2.39-2.44 (m, 2H, C*H*$_2$CH=CH_2), 2.86 (q, 1H, *J* = 5.7 Hz, CHN), 3.82 (s, 3H, OCH_3), 4.78-4.92 (m, 2H, $CH_2CH=CH_2$), 5.29-5.55 (m, 1H, $CH_2CH=CH_2$), 7.31-7.55 (m, 3H, Ph), 8.00-8.08 (m, 2H, 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): ν = 1734, 1676 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.53 (d, 3H, *J* = 5.9 Hz, C*H*$_3$CHN), 3.20 (d, 1H, *J* = 15.6 Hz, C*H*HPh), 3.39 (q, 1H, *J* = 5.9 Hz, CHN), 3.46 (s, 3H, OCH_3), 3.58 (d, 1H, *J* = 15.6 Hz, CH*H*Ph), 7.15-7.58 (m, 8H, Ph), 7.65-7.80 (m, 2H, 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): ν = 1736, 1684 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 3H, C*H*$_3$CN), 3.57 (s, 3H, OCH_3), 4.32 (s, 1H, CHN), 7.25-7.56 (m, 8H, Ph), 7.82-7.95 (m, 2H, 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): ν = 1736, 1684 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 3H, C*H*$_3$CN), 3.51 (s, 3H, OCH_3), 3.78 (s, 1H, CHN), 7.25-7.56 (m, 8H, Ph), 7.82-7.95 (m, 2H, 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): ν = 1737, 1680 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 2.38 (dd, 1H, *J* = 7.12 Hz, C*H*HCH=CH_2), 2.65 (dd, 1H, *J* = 9.12 Hz, CH*H*CH=CH_2), 3.65 (s, 3H, OCH_3), 4.41 (s, 1H, CHN), 4.72-5.02 (m, 2H, CH_2CH=C*H*$_2$), 5.55-5.79 (m, 1H, CH_2C*H*=CH_2), 7.22-7.63 (m, 10H, Ph), 7.85-7.98 (m, 2H, 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): ν = 1744, 1671 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 3.10 (AB, 2H, *J* = 15.0 Hz, C*H*$_2$Ph), 3.61 (s, 3H, OCH_3), 4.46 (s, 1H, CHN), 7.01-7.52 (m, 8H, Ph), 7.62-7.77 (m, 2H, 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 *trans* 2-Alkyl 2-Carboxymethyl 3-Methyl *N*-Benzoyl Aziridines *rac*-3a-d with BF_3/Et_2O in $CHCl_3$: Synthesis of Methyl 2-Alkyl 2-Benzamido 3-Ethoxy Butanoates *rac*-5a-d.

A solution of aziridine *rac*-**3a-d** (0.2 mmol) and $BF_3.Et_2O$ (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 methylene chloride, washed twice with water, dried over sodium sulphate and concentrated. The product *rac*-**5** was obtained pure as an oil after silica gel chromatography (cyclohexane:ethyl acetate 9:1 as eluant).

rac-**5a:** 88% yield. - IR (film): ν = 3417, 1739, 1652 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.18 (t, 3H, *J* = 6.5 Hz, C*H*$_3$CH$_2$O), 1.26 (d, 3H, *J* = 5.8 Hz, C*H*$_3$CHO), 1.74 (s, 3H, C*H*$_3$CN), 3.48 (dq, 1H, *J* = 6.5, 12 Hz, CH$_3$C*H*HO), 3.67 (dq, 1H, *J* = 6.5, 12 Hz, CH$_3$CH*H*O), 3.78 (s, 3H, OCH$_3$), 3.92 (q, 1H, *J* = 5.8 Hz, CHN), 7.08 (s, 1H, NH), 7.30-7.60 (m, 3H, Ph), 7.70-7.85 (m, 2H, 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): ν = 3413, 1734, 1669 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 0.80 (t, 3H, *J* = 7.5 Hz, CCH$_2$C*H*$_3$), 1.06 (t, 3H, *J* = 6.6 Hz, OCH$_2$C*H*$_3$), 1.31 (d, 3H, *J* = 6.8 Hz, C*H*$_3$CHO), 1.90-2.15 (m, 1H, CC*H*HCH$_3$), 2.42-2.63 (m, 1H, C-CH*H*-CH$_3$), 3.31-3.45 (m, 1H, OC*H*HCH$_3$), 3.52-3.64 (m, 1H, OCH*H*CH$_3$), 3.82 (s, 3H, OCH$_3$), 4.32 (q, 1H, *J* = 6.8 Hz, CH$_3$C*H*O), 7.21 (s, 1H, NH), 7.40- 7.63 (m, 3H, Ph), 7.80-7.98 (m, 2H, 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): ν = 3417, 1734, 1669 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 1.09 (t, 3H, *J* = 6.6 Hz, OCH_2CH_3), 1.31 (d, 3H, *J* = 6.6 Hz, CH_3CHO), 2.82 (dd, 1H, *J* = 6.9, 13.8 Hz, $CHHCH=CH_2$), 3.28 (dd, 1H, *J* = 8.1, 13.8 Hz, $CHHCH=CH_2$), 3.35-3.48 (m, 1H, $OCHHCH_3$), 3.55-3.65 (m, 1H, $OCHHCH_3$), 3.81 (s, 3H, OCH_3), 4.28 (q, 1H, *J* = 6.6 Hz, CH_3CHO), 4.95-5.13 (m, 2H, $CHHCH=CH_2$), 5.60-5.68 (m, 1H, $CHHCH=CH_2$), 7.35 (s, 1H, NH), 7.40-7.58 (m, 3H, Ph), 7.68-7.85 (m, 2H, 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): ν = 3412, 1727, 1651 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = ^{1}H NMR ($CDCl_3$): δ = 1.06 (t, 3H, *J* = 6.9 Hz, OCH_2CH_3), 1.46 (d, 3H, *J* = 6.6 Hz, CH_3CHO), 3.27-3.48 (m, 2H, $OCHHCH_3$ + $CHHPh$), 3.52-3.64 (m, 1H, $OCHHCH_3$), 3.74-3.85 (m, 1H, $CHHPh$), 3.87 (s, 3H, OCH_3), 4.55 (q, 1H, *J* = 6.6 Hz, CH_3CHO), 6.98-7.24 (m, 6H, NH + Ph), 7.30-7.55 (m, 3H, Ph), 7.60-7.78 (m, 2H, 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 *trans* 2,3-Dimethyl 2-Carboxymethyl *N*-Benzoyl Aziridine *rac*-3a with $BF_3.2H_2O$ in CH_2Cl_2: Synthesis of Methyl *anti* 2-Benzamido 2-Methyl 3-Hydroxy 3-Phenylpropanoate *rac*-6a.

A solution of aziridine **3a** (0.22 mmol, 50 mg) and $BF_3.2H_2O$ (0.66 mmol, 0.016 mL) in methylene chloride (5 mL) was stirred at room temperature for 16 h. Then the reaction mixture was diluted with methylene chloride, washed twice with a 1M aquous solution

of Na_2CO_3, dried over sodium sulphate and concentrated. The product **6a** was obtained pure as an oil after silica gel chromatography (cyclohexane:ethyl acetate 9:1 as eluant) in 90% yield.

IR (film) ν = 3395, 1734, 1653, 1522 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.12 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CHO), 1.74 (s, 3H, C*H*$_3$CN), 3.86 (s, 3H, OCH_3), 4.21 (dq, 1H, *J* = 6.4, 10.1 Hz, CHO), 5.28 (d, 1H, *J* = 10.1 Hz, OH), 7.35-7.65 (m, 4H, NH+Ph), 7.75-7.85 (m, 2H, 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 *trans* 2,3-Dimethyl 2-Carboxymethyl *N*-Benzoyl Aziridine *rac*-3a with $BF_3.2H_2O$ in DMF: Synthesis of Methyl *anti* 2-Hydroxy 2-Methyl 3-Benzamido 3-Phenyl propanoate *rac*-7a.

A solution of aziridine *rac*-**3a** (0.22 mmol, 50 mg) and $BF_3.2H_2O$ (1.1 mmol, 0.027 mL) in dimethylformamide (5 mL) was stirred at room temperature for 16 h. Then the reaction mixture was diluted with methylene chloride, washed twice with water, dried over sodium sulphate and concentrated. The product *rac*-**7a** was obtained pure as an oil after silica gel chromatography (cyclohexane:ethyl acetate 9:1 as eluant) in 75% yield.

IR (film) ν = 3360, 1743, 1638 cm^{-1}. - ^1H NMR (C_6D_6): δ = 1.01 (d, *J* = 7.0 Hz, 3H, CH_3C*H*N), 1.38 (s, 3H, CH_3CN), 3.18 (s, 3H, OCH_3), 4.83 (dq, 1H, *J* = 7.0, 10.0 Hz, CHN), 6.33 (d, *J* = 10.0 Hz, NH), 6.91-7.50 (m, 3H, Ph), 7.65-7.88 (m, 2H, 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 *trans* 2,3-Dimethyl 2-Carboxymethyl *N*-Benzoyl Aziridine *rac*-3a with $BF_3.Et_2O$ in CH_3CN: Synthesis of *cis* 2,4,5-Trimethyl 4-Carboxymethyl 4,5-dihydro-1*H*-imidazole *rac*-8a and of *cis* 2,4,5-Trimethyl 5-Carboxymethyl 4,5-dihydro-1*H*-imidazole *rac*-8b

A solution of aziridine **3a** (0.22 mmol, 50 mg) and $BF_3.Et_2O$ (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 methylene chloride, the mixture was washed twice with a 1M aqueous solution of Na_2CO_3, dried over sodium sulphate 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 eluant) in 80 % and 10 % yield.

rac-**8a:** IR (film) ν = 1734, 1684, 1624 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.29 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CHN), 1.51 (s, 3H, CH_3CN), 1.80 (s, 3H, $CH_3C{=}N$), 3.78 (s, 3H, OCH_3), 4.50 (q, 3H, *J* = 6.6.Hz, CH_3CHN), 7.32-7.58 (m, 5H, 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) ν = 1734, 1669, 1634 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.18 (d, 3H, *J* = 6.6 Hz, C*H*$_3$CHN), 1.58 (s, 3H, CH_3CN), 1.99 (s, 3H, $CH_3C{=}N$), 3.79 (s, 3H, OCH_3), 4.28 (q, 3H, *J* = 6.6.Hz, CH_3CHN), 7.32-7.58 (m, 5H, 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 *trans* 3-Phenyl 2-Alkyl 2-Carboxymethyl *N*-Benzoyl Aziridines *rac*-3e-g and *cis* 3-Phenyl 2-Methyl 2-Carboxymethyl *N*-Benzoyl Aziridine *rac*-4e

with BF_3/Et_2O in $CHCl_3$: Synthesis of *trans* 2,5-Diphenyl 4-Alkyl 4-Carboxymethyl Oxazolines *rac*-9e-g and *cis* 2,5-Diphenyl 4-Methyl 4-Carboxymethyl Oxazoline *rac*-10e.

A solution of aziridine (0.2 mmol) and $BF_3.Et_2O$ (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 methylene chloride, washed twice with water, dried over sodium sulphate and concentrated. The product was obtained pure as an oil after silica gel chromatography (cyclohexane:ethyl acetate 9:1 as eluant).

rac-**9e:** 95% yield. - IR (film) ν = 1734, 1652 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.10 (s, 3H, C*H*$_3$CN), 3.87 (s, 3H, OCH_3), 6.12 (s, 1H, CHO), 7.20-7.60 (m, 8H, Ph), 8.05-8.15 (m, 2H, 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) ν = 1736, 1653 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 1.81 (s, 3H, C*H*$_3$CN), 3.17 (s, 3H, OCH_3), 5.42 (s, 1H, CHO), 7.20-7.60 (m, 8H, Ph), 8.05-8.15 (m, 2H, 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) ν = 1732, 1652 cm^{-1}. - ^1H NMR ($CDCl_3$): δ = 2.17 (ABX, 2H, *J* = 6.9, 7.5, 13.9 Hz, C*H*$_2$CH=CH$_2$), 3.85 (s, 3H, OCH_3), 4.81-4.96 (m, 2H, $CH_2CH=CH_2$), 5.51-5.66 (m, 1H, $CH_2CH=CH_2$), 6.01 (s, 1H, CHO), 7.31-7.60 (m, 8H, Ph), 8.08-8.15 (m, 2H, 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) ν = 1727, 1654 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ = 2.52 (d, 1H, *J* = 13.6 Hz, C*H*HPh), 2.68 (d, 1H, *J* = 13.6 Hz, CH*H*Ph), 3.69 (s, 3H, OCH_3), 5.97 (s, 1H, CHO), 7.3-7.60 (m, 13H, Ph), 8.07-8.12 (m, 2H, 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 *trans* 2,5-Diphenyl 4-Methyl 4-Carboxymethyl Oxazoline *rac*-9e: Synthesis of *syn* 2-Amino 2-Methyl 3-Hydroxy 3-Phenylpropanoic Acid *rac*-11e

A solution of oxazoline *rac*-**9e** (0.21 mmol, 50 mg) in methanol (1 mL) and 6M HCl (5 mL) was refluxed for 15 h, then was cooled and concentrated under reduced pressure and water (5 mL) was added. The mixture was adsorbed on cation exchange resin, then the resin was washed with water until the washing came out neutral, then with 2M aquoeus NH_4OH to recover the amino acid *rac*-**11e** in 85% yield.

M.p. = 195-198 °C (dec.). - ^{1}H NMR (D_2O): δ = 1.29 (s, 3H, CH_3CN), 5.10 (s, 1H, CHO), 7.30-7.45 (m, 5H, 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 *cis* 2,5-Diphenyl 4-Methyl 4-Carboxymethyl Oxazoline *rac*-10e: Synthesis of *anti* 2-Amino 2-Methyl 3-Hydroxy 3-Phenylpropanoic Acid *rac*-12e

For the procedure see hydrolysis of *rac*-**9e**: 80% yield.

M.p. = 202-205 °C (dec.); litt.:[6] m.p. = 204-206 °C (dec.). - ^{1}H NMR (D_2O): δ = 1.55 (s, 3H, CH_3CN), 5.00 (s, 1H, CHO), 7.28-7.45 (m, 5H, Ph). - ^{13}C NMR (D_2O): δ = 20.4, 65.8, 75.6, 127.7, 129.4, 129.9, 139.7, 160.4.

Aknowledgments: 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).

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

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

entry	R	R’	LiHMDS t (h), T (°C)	I_2 t (h), T (°C)	**3** : **4** ratio	Yield (%)
1	Me	Me	5, 20	16, -30	80 : 20	90
2	Me	Et	5, 20	16, -30	78 : 22	59
3	Me	Allyl	5, 20	16, -30	82 : 18	80
4	Me	Benzyl	5, 20	16, -30	99 : 1	82
5	Ph	Me	5, 20	16, -15	85:15	60
6	Ph	Allyl	5, 20	16, -15	94 : 6	70
7	Ph	Benzyl	5, 20	16, -15	99 : 1	40

References

[1] For general reviews see: (a) R. M. Williams, *Synthesis of Optically Active Amino Acids*; Pergamon Press, Oxford, **1989**; (b) R. O. Duthaler, *Tetrahedron*, **1994**, *50*, 1539-1650; (c) M. Goodman, S. Ro, In *Burger's Medicinal Chemistry and Drug Discovery, 5th Edition*; Wolff, M., Ed.; Wiley and Sons: New York, **1995**, pp. 803-861; (d) S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, W. D. Lubell, *Tetrahedron*, **1997**, *53*, 12789-12854.

[2] See for example: (a) J. S. Panek, C. E. Masse, *Angew. Chem. Int. Ed.* **1999**, *38*, 1093-1095; (b) E. J. Corey, W. Li, G. A. Reichard, *J. Am. Chem. Soc.* **1998**, *120*, 2330-2336; (c) E. J. Corey, W. Li, T. Nagamitsu, *Angew. Chem. Int. Ed.* **1998**, *110*, 1784-1787; (d) H. Uno, J. E. Baldwin, A. T. Russell, *J. Am. Chem. Soc.* **1994**, *116*, 2139-2140; (e) T. Nagamitsu, T. Sunazuka, S. Omura, P. A. Sprengler, A. B. Smith III, *J. Am. Chem. Soc.* **1996**, *118*, 3584-3590; (f) N. Chida, J. Takeoka, N. Tsutsumi, S. Ogawa, *Chem. Commun.* **1995**, 793-794.

[3] A. V. R. Rao, M. K. Gurjar, T. R. Devi, K. R. Kumar, *Tetrahedron Lett.* **1993**, *34*, 1653-1656.

[4] (a) E. Altmann, K. H. Altmann, M. Mutter, *Angew. Chem. Int. Ed.* **1988**, *27*, 858-859; (b) H. Mickos, K. Sundberg, B. Lüning, *Acta Chem. Scand.* **1992**, *46*, 989-993.

[5] (a) C: Cativiela, M. D. Diaz-de-Villegas, J. A. Gàlvez, *Tetrahedron* **1996**, *52*, 687-694; (b) R. Pires, K. Burger, *Synthesis* **1996**, 1277-1279; (c) S. H. Pines, S. Karady, M. A. Kozlowski, M. Sletzinger, *J. Org. Chem.* **1968**, *33*, 1762-1767; (d) Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron*

1988, *44*, 5253-5262; (e) H. Shao, J. K. Rueter, M. Goodman, *J. Org. Chem.* **1998**, *63*, 5240-5244.

[6] R. Grandler, U. Kazmaier, *Eur. J. Org. Chem.* **1998**, 409-417.

[7] (a) D. Seebach, J. D. Aebi, *Tetrahedron Lett.* **1983**, *24*, 3311-3314; (b) D. Seebach, J. D. Aebi, M. Gander-Coquoz, R. Naef, *Helv. Chim. Acta* **1987**, *70*, 1194-1216.

[8] A synthesis of benzyl (2*S*,3*R*)-*N*-(benzyloxycarbonyl)-2,3-dimethyl-aziridine-2-carboxylate is reported in ref. [5e].

[9] W. M. Rodionow, E. A. Postovkaja, *J. Am. Chem. Soc.* **1929**, *51*, 841-852.

[10] (a) G. Cardillo, L. Gentilucci, A. Tolomelli, C. Tomasini, *J. Org. Chem.* **1998**, *63*, 2351-2353; (b) G. Cardillo, A. Tolomelli, C. Tomasini, *Eur. J. Org. Chem.* **1999**, 155-161.

[11] (a) D. Rossi, G. Lucente, A. Romeo, *Experientia* **1977**, *33*, 1557-1559; (b) V. A. Soloshonok, V. K. Svedas, V. P. Kukhlar, A. G. Kirilenko, A. V. Rybakova, V. A. Solodenko, N. A. Fokina, O. V. Kogut, I. Y. Galaev, E. V. Kozlova, I. P. Shishkina, S. V. Galushko, *Synlett* **1993**, 339-341; (c) V. A. Soloshonok, N. A. Fokina, A. V. Rybakova, I. P. Shishkina, S. V. Galushko, A. E. Sorochinsky, V. P. Kukhlar, M. V. Savchenko, K. V. Svedas, *Tetrahedron: Asymmetry* **1995**, *7*, 1601-1610; (d) G. Cardillo, A. Tolomelli, C. Tomasini, *J. Org. Chem.* **1996**, *61*, 8651-8654.

[12] (a) D. Seebach, H. Estermann, *Tetrahedron Lett.* **1987**, *28*, 3103-3106; (b) D. Seebach, H. Estermann, *Helv. Chim. Acta* **1988**, *71*, 1824-1839.

[13] A. M. Nocioni, C. Papa, C. Tomasini, *Tetrahedron Lett.* **1999**, *40*, 8453-8456.

[14] (a) H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry*, **1997**, *8*, 1693-1715; (b) B. Zwanenburg, L. Thjis, *Pure Appl. Chem.*, **1196**, *68*, 735-738; (c) D. Tanner, *Angew. Chem. Int. Ed.* **1994**, *33*, 599-619; (d) P. E. Fanta in *Heterocyclic Compounds with Three- and Four-membered Rings*, Part 1 (Ed.: A. Weissberg), Wiley Interscience, New York, **1964**, p. 524.

[15] J. Legters, J. G. H. Willems, L. Thijs, B. Zwanenburg, *Trav. Chim. Pays-Bas* **1992**, *111*, 59-68.

[16] J. Legters, L. Thijs, B. Zwanenburg, *Trav. Chim. Pays-Bas* **1992**, *111*, 16-21.

[17] K. Nakajima, M. Neya, S. Yamada, K. Okawa, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3049-3050.

[18] (a) D. Ferraris, W. J. Drury III, C. Cox, T. Lectka, *J. Org. Chem.* **1998**, *63*, 4568-4569 and references therein; (b) G. Cardillo, L. Gentilucci, A. Tolomelli, *Chem. Commun.* **1999**, 167-168.

[19] When the reaction was carried out in methylene chloride and water (50:1 ratio) with $BF_3.Et_2O$, only the starting aziridine was recovered.

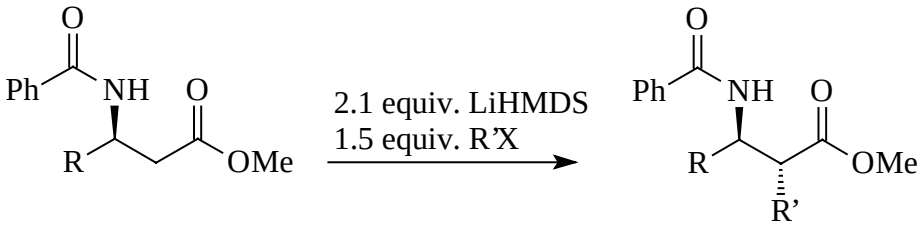
[20] As both C2 and C3 positions are not activated for the substitution, the solvent plays a crucial role. In DMF the reaction proceeds with lower yield and requires more Lewis acid than in methylene chloride. In these conditions the C2 attack is favoured, probably owing to the coordinating effect of 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.

[21] Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron* **1988**, *44*, 5253-5262.

[22] T. Hiyama, H. Koide, S. Fujita, H. Nozaki, *Tetrahedron* **1973**, *29*, 3137-3139.

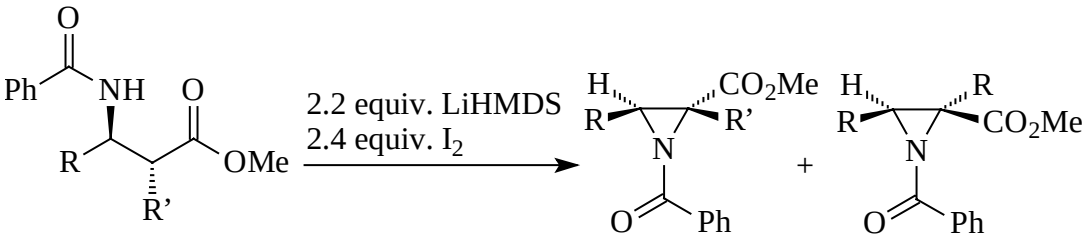
[23] D. Seebach, T. Weber *Helv. Chim. Acta* **1984**, *67*, 1650-1661.

Scheme 1.



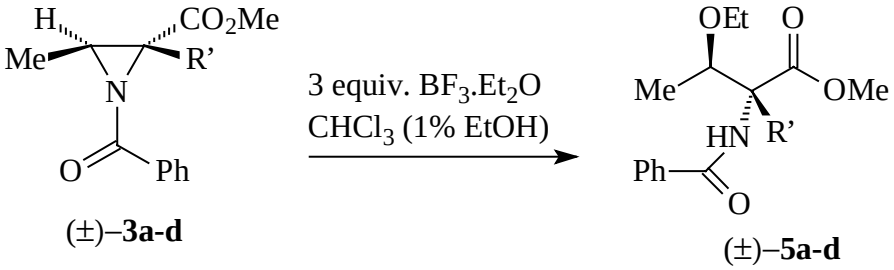
(±)–**1** (±)–**2**

Scheme 2.



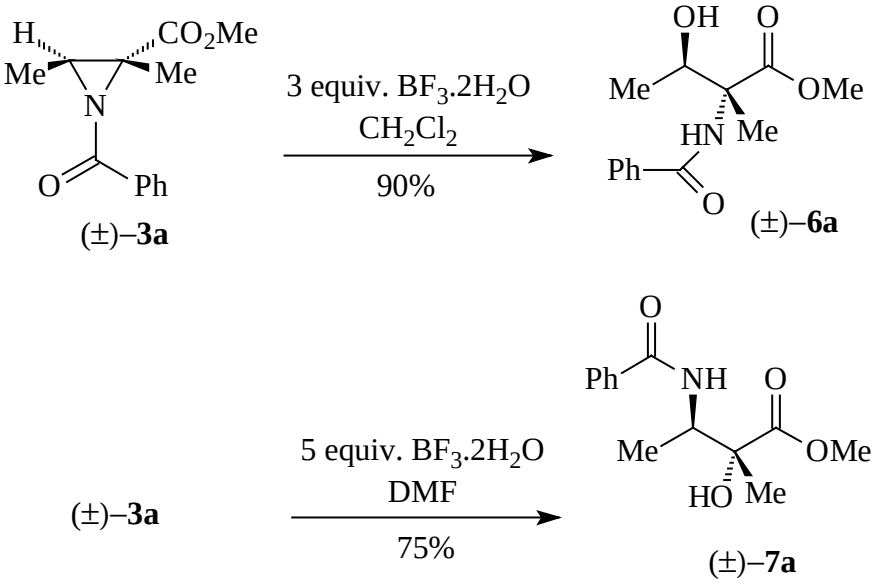
(±)–**2** (±)–**3** (±)–**4**

Scheme 3.

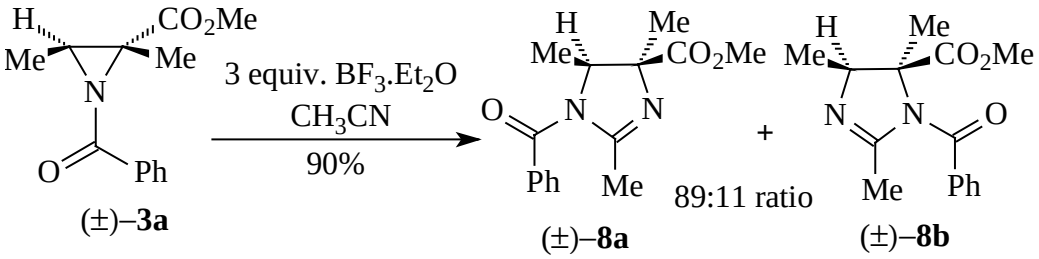


(±)–**3a-d** (±)–**5a-d**

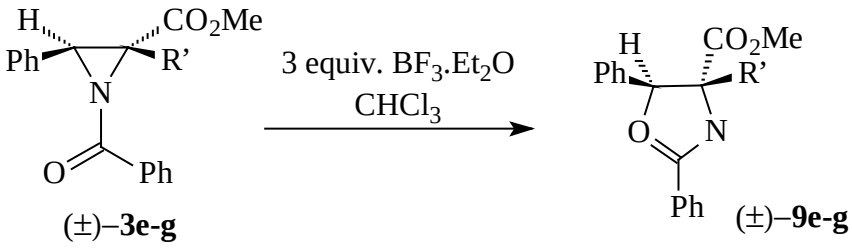
Scheme 4.



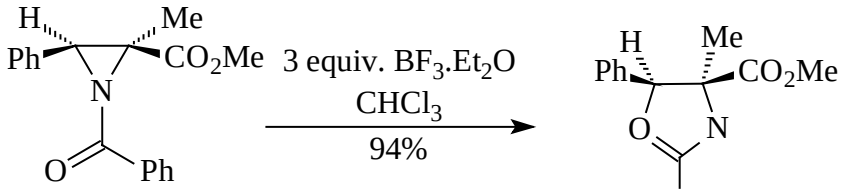
Scheme 5.



Scheme 6.

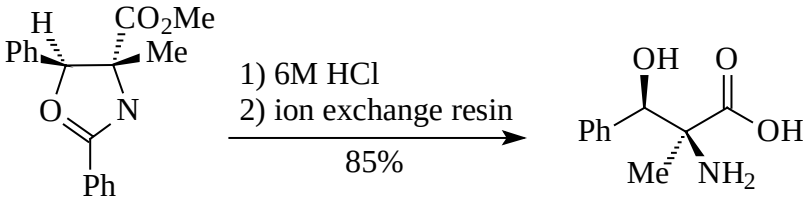


(±)–**3e-g** (±)–**9e-g**

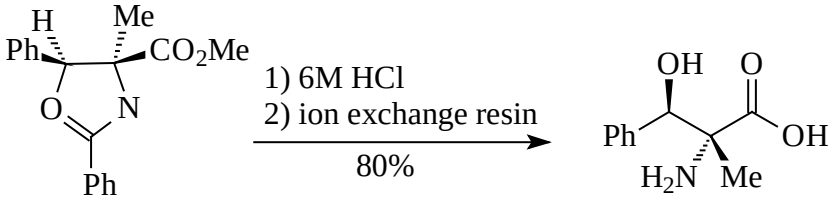


(±)–**4e** (±)–**10e**

Scheme 7.



(±)–**9e** (±)-*syn*-**11e**



(±)–**10e** (±)-*anti*-**12e**

Figure 1.

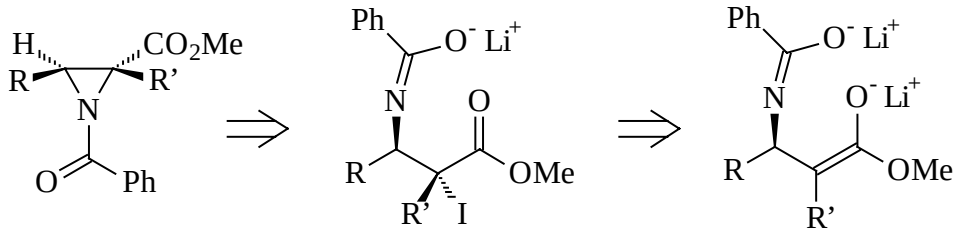
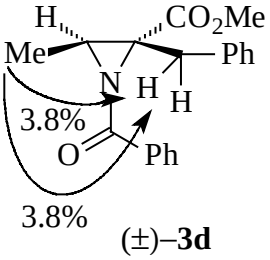
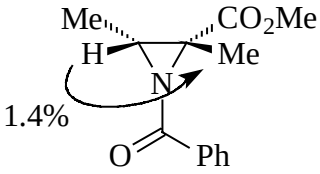


Figure 2.

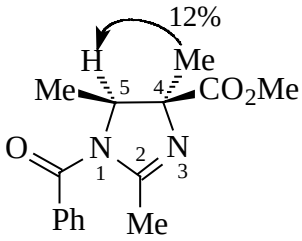


(±)–**3d**

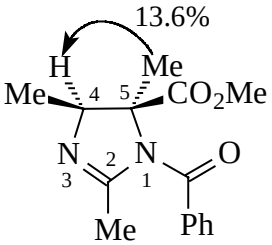


(±)–**4a**

Figure 3.



(±)–**8a**



(±)–**8b**

Graphical Abstract