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TETRAHEDRON

Diastereoselective Synthesis of *Syn,syn*- and *Syn,anti*-2,4-Diamino-3-hydroxyglutaric Acid Derivatives from Ethyl α-Acyl Alaninates

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Abstract. *Syn,syn*- and *syn,anti*-isomers of the four possible diastereomers of *O,N,N'*-protected 2,4-diamino-3-hydroxyglutaric acid derivatives **3-7** were diastereoselectively obtained. *Syn,syn* isomers of oxazolines **3** were selectively achieved by an aldol-like reaction in protic conditions between α-metallated ethyl isocyanoacetate **1** and α-acyl alaninates **2**. Derivatives **4** with a *syn,anti*-configuration were obtained under epimerization reaction conditions, whereas derivatives **5-7** with a *syn,syn*-configuration were selectively obtained under kinetic reaction conditions.

Non proteinogenic β-hydroxy α-amino acids (serine analogues) appear in several biologically important naturally occurring peptides such as lysobactin,[1] lactacystin,[2] telomycin[3] and aureobasidin.[4] It has been suggested that a hydroxyl group placed on the backbone of an amino acid plays an active role in binding to a receptor protein or a bio-membrane. When such amino acids are incorporated into peptides, the hydroxyl group plays an essential role in constraining the peptide structure into a specific conformation required for receptor interaction, through inter or intramolecular hydrogen bonding.[5,6]

Other structural characteristics introducing conformational constraint into peptides are the presence of side chains, mainly a methyl group in the α- or β-positions,[4a] and the *N*-methyl substitution in some of the amine groups of the amino acid component.[4b] These features improve the resistance of peptides to proteases and increase their ability to form trans-membrane helical ion channels[5c].

In light of these considerations, the development of new methods for the preparation of β-hydroxy-α-methyl-α-amino acid derivatives is a challenge in organic synthesis. A good strategy could be based on the nucleophilic addition of organometallic reagents to *N*-protected α-acyl alaninates. In analogous substrates, as *N*-protected α-amino aldehydes, the facial selectivity of such reactions has been shown to be dependent on the metal and the nature of the protecting group. Thus, for C-nucleophilic reagents, *syn*-selectivity[7] became dominant via chelation control tuned by the bulk of the protecting groups, whereas *anti*-selectivity was improved by the use of large *N*-protecting groups, such as *N,N*-dibenzyl, due to a steric inhibition to the chelation.[7]

Even though alkylidene or bis(methylthio)methylene[8] *N*-protecting groups have been shown to be powerful tools in α-amino acid synthesis,[9] their use has not been frequent because of their ability to enhance epimerization

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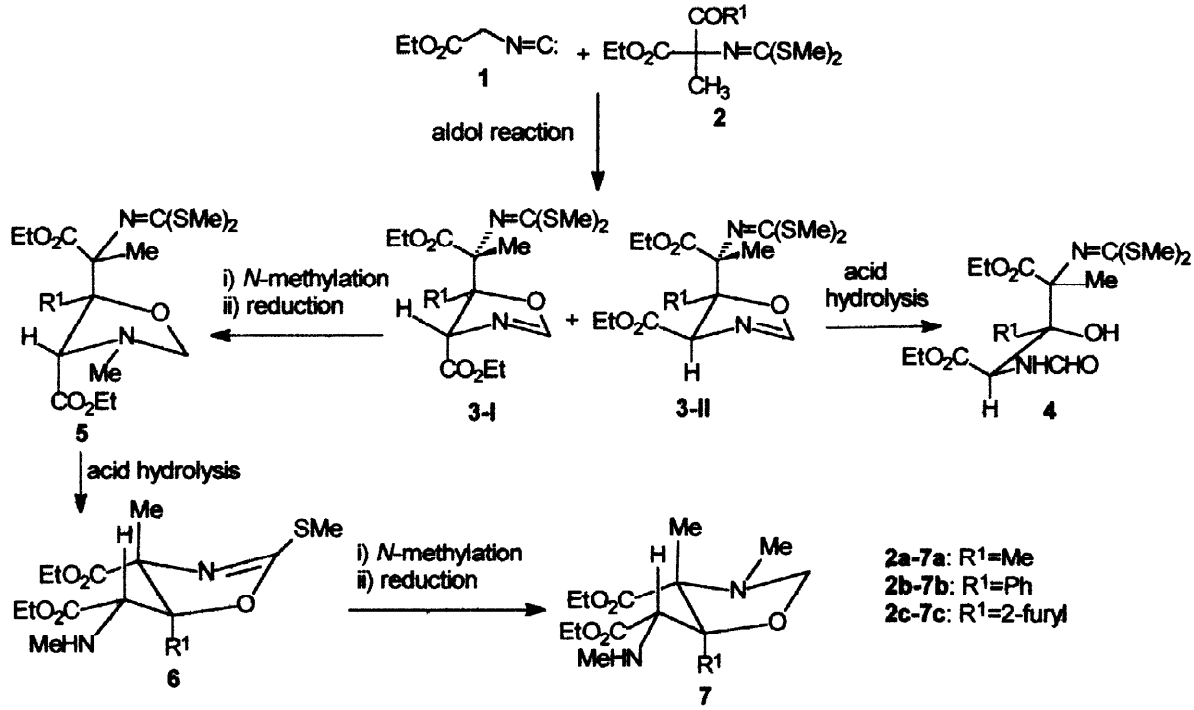
of the α-methylenic hydrogen in the amino acid backbone. However, this problem is intrinsically precluded in α-quaternized[10] amino acid derivatives and so, the imino derivative protecting groups can be selected to achieve *facial selectivity* based on metal chelation by the trigonal nitrogen atom (*syn-facial selectivity*)[11] in the *syn*-diastereoselective synthesis of glutaric acid derivatives.

We have recently reported that the aldol-like reaction of α-metallated ethyl isocyanoacetate **1** with α-acyl alaninates **2** under protic conditions (MOR/ROH; M: Li, Na, K, Tl; R: Me, Et, ^{t}Bu) led to a mixture of two diastereomeric oxazolines **3-I/3-II** with good diastereomeric excesses (Scheme 1).[12] In this paper, a tentative mechanism to justify the observed full *facial diastereoselectivity* and the high *simple diastereoselectivity*[13] in favour of isomers **3-I** (*syn,syn*) is proposed. Furthermore, two different sets of glutaric acid derivatives have been diastereoselectively obtained from oxazolines **3**. Derivatives **4a-c** with a *syn,anti* configuration have been obtained under epimerization conditions, whereas derivatives **5**, **6** and **7** have been selectively obtained under kinetic control conditions (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

1. Diasteroselective Synthesis of Oxazolines 3

Compound **2a** (Scheme 1, R^1=Me) was selected as the electrophilic partner of the aldol-like reaction using a wide variation in the nature of the base/solvent system.[14] In all the cases studied, only two of the four possible diastereomers of oxazolines **3** were obtained[15] which were epimeric at the oxazoline carbon C-4. Besides, when a mixture of **3a-I/3a-II** (66/34) was treated with NaOMe in CD_3OD at 25°C for 0.5 h at the same concentration as

that of the reaction conditions, no deuterium incorporation was observed by ^{1}H NMR analysis of the crude reaction mixture. Therefore, a kinetic control in the formation of both oxazolines **3-I** and **3-II** can be proposed to explain the observed diastereoselectivity.[12]

In order to explain the general predominance of the isomer **3-I** over its epimer **3-II**, two transition states,[16] TS* A and TS* B (Figure 1), starting from a *Z*-chelated[17] enolate can be considered.

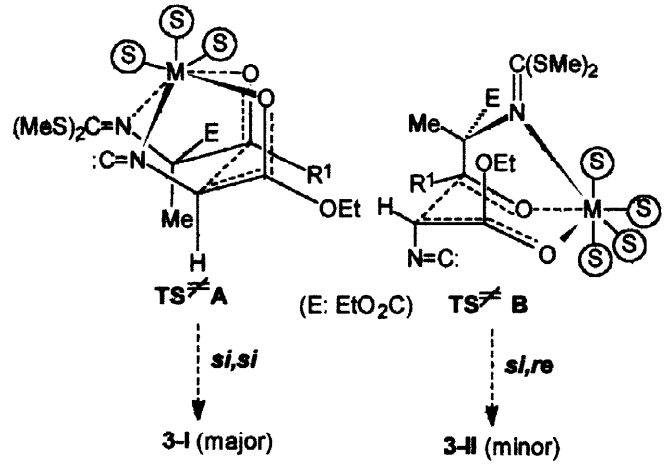


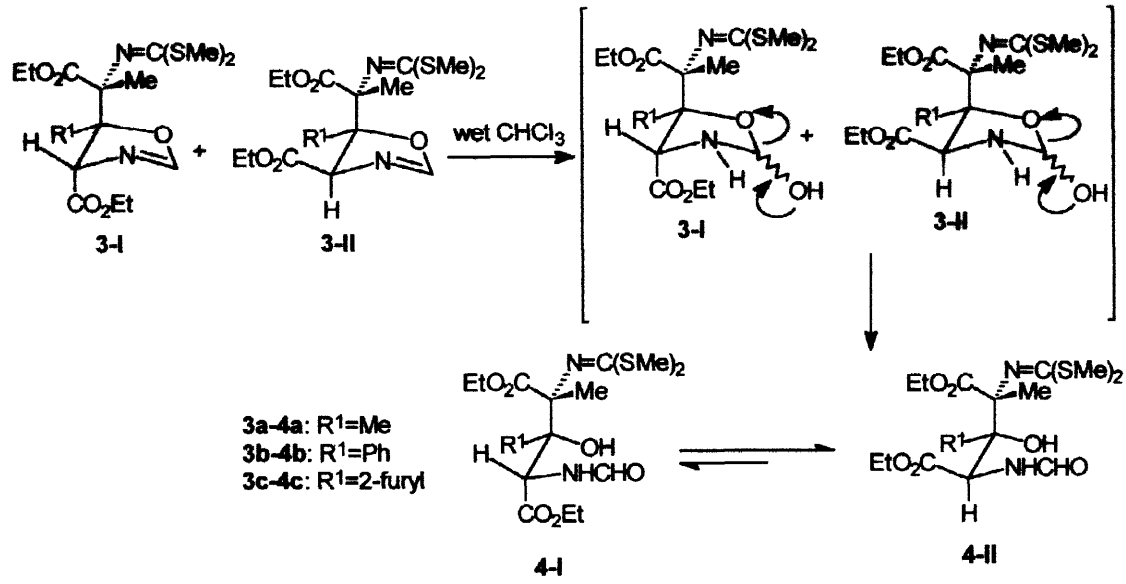
Figure 1. *Si,si* and *si,re* approaches for the aldol-like reaction of enolates **1** and α-acyl alaninates **2**.

TS* A is reasonably more stable than TS* B because the counter-ion in the former is able to promote a better template effect, and thus, a *si,si*-approach is favoured over a *si,re*-approach. In support of this hypothesis, the best diastereoselectivity was found for the softest cation (K^+>Na^+>>Li^+; **3a-I/3a-II**: 84/16, 80/20, 66/34) which is the most coordinative one. On the other hand, and as a consequence of the steric crowding present in TS* A, the solvent bulk could have a large influence on its stability, and so, for a given cation, the diastereoselectivity will decrease with the solvent molecular size (MeOH<EtOH<^{t}BuOH). This is in agreement with previously reported data (MeOH<EtOH<^{t}BuOH; **3a-I/3a-II**: 84/16, 84/16, 59/41 for K^+).[12]

On the other hand, the observed increase of the retro-Claisen reaction by the heteronucleophilic attack of the alkoxide on the carbonyl group of the acyl alaninate **2** when ^{t}BuOH or Li^+ were used in the reaction can also be justified. Thus, when the bulkiest solvent (^{t}BuOH) and/or the less coordinative counter-ion (Li^+) were used, the energies of both transition states are increased, and therefore, the competitive retro-Claisen reaction becomes significant.

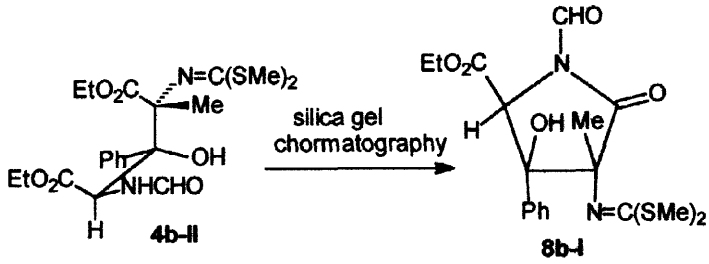
2. Hydrolysis and Ring-Opening Isomerization of Oxazolines **3a-c**

Oxazolines **3-I** and **3-II** were stable compounds when isolated. However, when these compounds were left standing in wet $CHCl_3$, they suffered an hydrolysis and a concomitant ring-opening isomerization to glutaric acid derivatives **4**, which showed a progressive epimerization to the most stable isomer **4-II**[18] (Scheme 2).

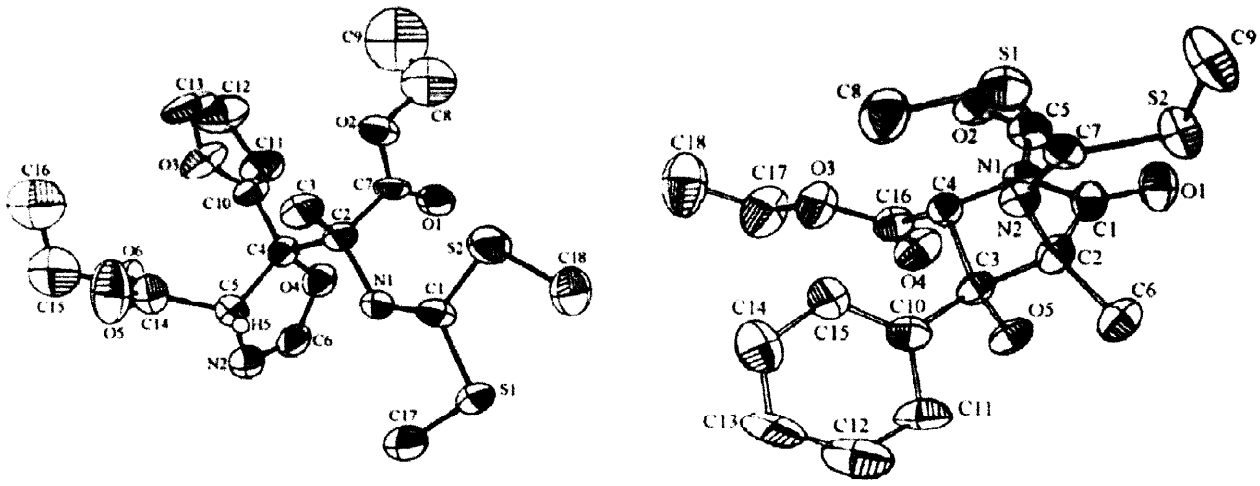


Scheme 2

In addition, when a mixture of oxazolines **3a-I/3a-II** (84/16) was treated with AcOH (1.8 M) in EtOH (20°C, 1.5 h) using Schöllkopf's procedure,[19] glutaric derivative **4a** (Scheme 2, R^1=Me) was isolated as a mixture of **4a-I/4a-II** (70/30). The epimer **4a-I** was purified by crystallization and shown to be stable in the solid state or in freshly prepared solutions (EtOAc/hexane). The filtrate, which was enriched in the isomer **4a-II** (**4a-I/4a-II**: 20/80), epimerized completely to isomer **4a-II** (20°C, 3 days).[18] Under the same reaction conditions, the oxazoline mixtures **3b-I/3b-II** (90/10) and **3c-I/3c-II** (88/12) gave the glutaric derivatives **4b-II** (Scheme 2, R^1=Ph; 30%) and **4c-II** (Scheme 2, R^1=2-furyl, 63%), respectively, as single isomers. The observed low yield for **4b-II** was due to an extensive fragmentation of **3b-I/3b-II** to ethyl *N*-[bis(methylthio)methylene]alaninate (55%) and ethyl α-benzoylglycinate (55%). Attempted chromatographic purification of **4b-II** (silica gel: EtOAc/hexane: 50/50) promoted a complete epimerization and concomitant cyclization to pyroglutamate **8b-I** which was unequivocally characterized by its spectroscopic and X-Ray data (Figure 2) (Scheme 3).



Scheme 3



3c-I **8b-I**

Figure 2. ORTEP projections of X-Ray structures of compounds **3c-I** and **8b-I**.

3. N-Methylation and Reduction of Oxazolines **3** *and* **6**

Mixtures of epimeric oxazolines **3-I/3-II** (Scheme 1) were submitted to Meyers *N*-methylation-reduction procedure[20] (MeOTf-$NaBH_4$). Oxazolidines **5** were isolated as diastereomeric mixtures **5-I/5-II** in identical ratio to that of the starting oxazolines **3**.

Acid hydrolysis (oxalic acid, 5 equiv., THF/H_2O: 4/1, 20°C, 48 h) of oxazolidines **5** gave rise to 2-methylthiooxazolines **6** (with the same epimeric ratio) via a ring-opening of oxazolidine **5** followed by an intramolecular nucleophilic attack of the hydroxyl group of the open-chain intermediate on the iminodithiocarbonate moiety.

N-methylation-reduction of mixtures of epimeric 2-methylthiooxazolines **6-I/6-II** (Scheme 1) gave rise to oxazolidines **7** which were isolated as epimeric mixtures of **7-I/7-II** in identical ratios to those of the starting oxazolines **6**.

From these experimental results, it can be stated that *N*-methylation-reduction of **3** to **5** and the oxazolines **6** to oxazolidines **7**, as well as the acid hydrolysis of oxazolidines **5** to oxazolines **6**, occurs with retention of configuration.

4. Configurational Assignment

Oxazolines ***3a-c***. The relative configurations of the stereogenic centres of oxazolines **3** were established on the basis of ^{1}H NMR 1D NOE experiments and the X ray structure of compound **3c-I**. Oxazolines **3-I** and **3-II** were epimers at the CH carbon (*vide supra*). The *syn*[11] relative configuration of the quaternary carbon of the all epimeric compounds was unequivocally established as 1'R*,4S* and the configurational assignment was deduced as 1'R*,4S*,5S* from the X-Ray data for compound **3c-I** (Figure 2).

The NOE effects observed for oxazolines **3c-I** and **3c-II** are gathered in Figure 3. Upon irradiation of the hydrogen H-4 (s, 5.40 ppm) of isomer **3c-I**, a 5.9% of NOE enhancement was observed on the CH_3-C1' (s, 1.64 ppm) signal. However, no NOE effect was observed between the hydrogen H-4 (s, 5.57 ppm) of isomer **3c-II** and the CH_3-C1' (s, 1.48 ppm) signal. These results are in agreement with the X Ray structure for **3c-I** and a configurational assignment of oxazolines **3-I** as (1'R*,4R*,5S*) and derivatives **3-II** as (1'R*,4S*,5S*) isomers can be unequivocally proposed. The assignment of the other oxazolines **3a** and **3b** was based on a comparison of the 1D NOE data of both epimers **3-I** and **3-II**[21] with those of **3c-I** and **3c-II**.

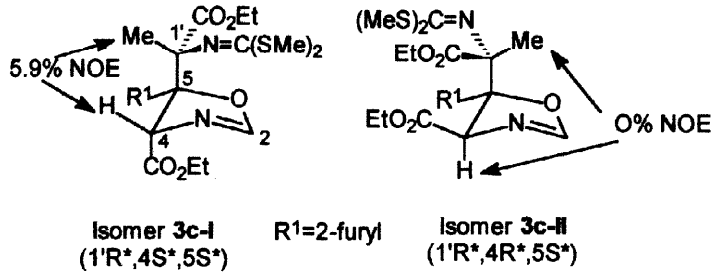


Figure 3. Observed NOE effects for oxazolines **3c-I** and **3c-II**

Glutaric acid derivatives ***4***. The configurational assignment of the quaternary carbon of glutaric acid derivatives **4** was derived as *syn*[11] for both isomers **4-I** and **4-II** from the relative configurations previously established for oxazolines **3**. The relative configuration of the carbon CH was tentatively established on the basis of the stabilities observed for derivatives **4**, the observed NOE effects for derivatives **4a-I** and **4a-II** and the calculated distances from conformational analysis of the two possible *syn,syn*[11] and *syn,anti*[11] epimers of derivatives **4-I** and **4-II**.

The conformational analysis of *syn,syn* and *syn,anti* epimers of derivatives **4** was carried out with the MMX molecular mechanic force field[22] integrated in the PC MODEL package software.[23] Structures with torsion angles close to those of minimum energy were used as initial trial conformers and they were minimized by the Newton-Raphson block-diagonal method[28] up to a gradient root mean square less than 0.1 kcal/Å. The search of the significant populated conformers was carried out from the previous structures by a molecular dynamic simulation during 50 ps at 600 K after a heating period time of 5 ps from 0 K. The constant temperature of 600 K was kept during all the simulation by coupling to an external bath with a relaxation constant of 0.5 ps. Structures were saved each 1 ps and independent minimised with the MMX force field.[22] All conformers were selected from the conformational global minimum and 3 kcal/mol above it.

The conformational analysis of the two epimers of **4a** put forward an average distance between H-4 and Me-C-2 of 2.90 Å in the *syn,syn* isomer and 2.98 Å in the *syn,anti* epimer. These results are in qualitative agreement with the observed NOE effects on the Me-C-2 group which was higher for the *syn,syn* isomer.

Upon irradiation of the hydrogen H-4 of isomer **4a-I** (s, 4.92 ppm) and isomer **4a-II** (s, 4.78 ppm), a 8.0% and 7.0% of NOE enhancements were respectively observed on the CH_3-C2' signals (isomer **4a-I**: s, 1.59 ppm; isomer **4a-II**: s, 1.56 ppm).

On the other hand, the formation of a single epimer for derivatives **4b** and **4c** precludes the application of the above criteria to these compounds. However, the calculation of the equilibrium constants for the inter conversion between each pair of epimers from the conformational analysis results could tentatively support the configurational assignment. Equilibria constants were calculated[29] taking into account the results of the previous conformational analysis. The results are given in the Table 1.

Table 1. Free Energies, G^0_{isomer} (kcal/mol), for the *syn,syn* and *syn,anti* isomers of compounds **4a-c**.

Compound	Isomer	G^0_{isomer}	K[a]
4a	*syn,syn*	24.4	25.0
	syn,anti	22.5	
4b	*syn,syn*	32.7	6.4
	syn,anti	31.6	
4c	*syn,syn*	31.6	2.8
	syn,anti	31.0	

[a]Calculated epimerization constants at 298°K for *syn,syn* and *syn,anti* isomerization.

The data shown in the Table 1 indicate that *syn,anti* epimers are more stable than *syn,syn* isomers for all the glutaric acid derivatives **4a-c**. These results, together with the isomerization experimentally observed, allow the tentative assignments of epimers **4-I** as *syn,syn* isomers and **4-II** as *syn,anti* stereoisomers.

Derivatives **5**, **6** *and* **7**. The configurational assignment of compounds **5-7** can be established from the observed stereochemical results in their chemical transformation reactions. As the initial epimeric ratios are unchanged in all subsequent chemical transformations of these compounds, their relative configurations correlate directly with the previously established assignments of oxazolines **3-I** and **3-II**. Thus, a *syn,syn* configuration can be assigned to all isomers **I** and the *syn,anti* configuration to all isomers **II**

CONCLUSIONS

The aldol like reaction between ethyl isocyanoacetate **1** and the α-acyl alaninates **2** in protic medium enables the preparation of oxazolines **3** with full *facial diastereoselectivity* and a high *simple diastereoselectivity* in favor of isomers **3-I** (*syn,syn*). Two different sets of glutaric acid derivatives can be obtained from oxazolines

3: compounds **4a-c** with a *syn,anti* configuration were selectively obtained under thermodynamical control, whereas derivatives **5**, **6** and **7** were prepared as *syn,syn* isomers under kinetic control.

EXPERIMENTAL SECTION

Solvents were reagent grade and used without purification and distilled before use: CH_2Cl_2 from CaH_2, Et_2O and THF from sodium benzophenone ketyl. TLC was performed on plates of silica gel precoated with 0.20 mm Kieselgel 60 F_{254}. Flash columns were packed with 230-240 mesh silica gel. Melting points were measured in open capillary tubes and are uncorrected. NMR spectra were obtained at 300 MHz (^1H) and 75.5 MHz (^{13}C) and the chemical shifts are reported as δ values relative to TMS. X-Ray data was collected at 213 K.

Syntheses of 2-acyl-*N*-[bis(methylthio)methylene]alanine (ethyl ester) (**4a-c**) from ethyl *N*-[bis(methylthio)-methylene]alaninate[30] were carried out as previously reported.[31]

Diastereoselective Syntheses of Oxazolines **3**. *General Procedure.*

To a suspension of metallic alkoxide (1 mmol) in the anhydrous alcohol (1 mL) was added under an atmosphere of dry argon, a prepared solution of ethyl isocyanoacetate **1** (0.113 g, 1 mmol) and alaninate **2a-c** (1 mmol) in anhydrous alcohol (1 mL). The reaction mixture was stirred for 15 min and then was diluted with water (1.5 mL). Stirring was continued for 10 min and then the mixture was extracted with $CHCl_3$ (3x5 mL). The combined organic extracts were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure.

(1'R*,4S*,5S*)-5-{1'-[Bis(methylthio)metylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-5-methyl-4,5-dihydrooxazole, 3a-I and (1'R*,4R*,5S*)-5-{1'-[Bis(methylthio)methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-5-methyl-4,5-dihydrooxazole, 3a-II. According to the general procedure, starting from **2a** (1g, 3.8 mmol), KOEt/EtOH at 0°C. After a flash chromatography (EtOAc/hexanes: 1/1) a colorless oil (1.22 g) was obtained and identified as a mixture of diastereomers **I/II** (84/16) of **3a** (yield: 85%) and ethyl *N*-[bis(methylthio)methylene]alaninate (0.080 g) which was identified by comparison of its spectral data with those of an authentic sample.[30] Analytical sample of diastereomeric racemate **3a-I** as a colorless oil was obtained by a flash chromatography (EtOAc/hexanes: 25/75) from the isomer mixture. IR (film): 3080, 1730, 1640, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J=7.2 Hz), 1.30 (t, 3H, J=7.2 Hz), 1.41 (s, 3H), 1.59 (s, 3H), 2.35 (s, 3H), 2.55 (s, 3H), 4.16 (qd, 1H, J=7.2, 3.9 Hz), 4.23 (qd, 1H, J=7.2, 3.9 Hz), 4.25 (q, 2H, J=7.2 Hz), 5.12 (d, 1H, J=2.1 Hz), 6.93 (d, 1H, J=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 15.2, 16.3, 17.5, 17.6, 61.1, 61.6, 71.4, 72.5, 90.7, 155.8, 161.6, 170.1, 170.7. Analysis Calcd. for $C_{15}H_{24}N_2O_5S_2$: C, 47.86; H, 6.43; N, 7.45. Found: C, 47.92; H, 6.37; N, 7.65. The minor isomer **3a-II** could be identified by its spectral data in the reaction mixture. ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J=7.2 Hz), 1.31 (t, 3H, J=7.2 Hz), 1.36 (s, 3H), 1.59 (s, 3H), 2.30 (s, 3H), 2.55 (s, 3H), 4-10-4.29 (m, 4H), 5.19 (d, 1H, J=2.1 Hz), 6.95 (d, 1H, J=2.1

Hz). ^{13}C NMR ($CDCl_3$) δ 13.7, 14.1, 15.3, 16.5, 17.5, 28.9, 61.0, 61.7, 71.4, 71.9, 90.7, 155.5, 161.6, 170.2, 170.7.

(1'R*,4S*,5S*)-5-{1'-[Bis(methylthio)methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-5-phenyl-4,5-dihydrooxazole, 3b-I, and (1'R*,4R*,5S*)--5-{1'-[Bis(methylthio)methylene]-amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-5-phenyl-4,5-dihydrooxazole, 3b-II. According to the general procedure, starting from **2b** (1.000 g, 3.07 mmol), KOEt/EtOH at 25°C. After flash chromatography (EtOAc/hexanes: 40/60) two fractions were obtained. The first one (0.071 g) was a mixture of the compound **8** (80%) and ethyl benzoate (20%), and the second fraction (1.156 g) was identified as a mixture of isomers **3b-I and 3b-II** (90/10).

Pure **3b-I** was obtained as a crystalline white solid by recrystallization (n-hexane). MP 68-69°C. IR (KBr) 3090, 1745, 1725, 1640, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, J=7.2 Hz), 1.27 (t, 3H, J=7.2 Hz), 1.28 (s, 3H), 2.56 (s, 3H), 2.70 (s, 3H), 3.64 (qd, 1H, J=7.2, 10.8 Hz), 3.88 (qd, 1H, J=7.2, 10.8 Hz), 4.11 (qd, 1H, J=7.2, 10.8 Hz), 4.16 (qd, 1H, J=7.2, 10.8 Hz), 5.67 (d, 1H, J=2.1 Hz), 7.04 (d, 1H, J=2.1 Hz), 7.27 (m, 3H), 7.26-7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.4, 13.8, 15.5, 16.5, 20.0, 60.7, 61.7, 72.4, 74.9, 93.7, 126.6, 127.2, 127.8, 137.3, 154.7, 162.6, 169.2, 170.7. Anal. Calcd. for $C_{20}H_{26}N_2O_5S_2$: C, 54.78; H, 5.948 N, 6.39. Found: C, 54.61; H, 5.87; N, 6.43.

The minor isomer **3b-II** could be identified by its spectral data in the reaction mixture. ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, J=7.2 Hz), 1.06 (t, 3H, J=7.2 Hz), 1.41 (s, 3H), 2.46 (s, 3H), 2.54 (s, 3H), 3.72 (q, 2H, J=7.2 Hz), 4.05 (q, 2H, J=7.2 Hz), 5.66 (d, 1H; J=2.1 Hz), 7.18 (d, 1H, J=2.1 Hz), 7.25-7.28 (m, 3H), 7.66-7.68 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.6, 13.8, 15.5, 16.4, 19.6, 60.7, 61.7, 72.4, 74.8, 93.6, 126.2, 127.3, 127.8, 137.3, 154.8, 162.6, 169.2, 170.6.

(1'R*,4S*,5S*)-5-{1'-[Bis(methylthio)methylene]amino-1'methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-5-(2'-furyl)-4,5-dihydrooxazole, 3c-I, and (1'R*,4R*,5S*)-5-{1'[Bis(methylthio)methylene]-amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-5-(2'-furyl)-4,5-dihydrooxazole, 3c-II. According to the general procedure, starting from **2c** (0.968 g, 3.07 mmol), KOEt/EtOH at 20°C. After flash chromatography (EtOAc/hexanes: 40/60) two fractions were obtained. The first one (0.200 g) was identified by its analytical data as a mixture of the compound **8** (82%) and ethyl furoate (18%). The second fraction (0.959 g, 2.24 mmol, yield: 73%) was a mixture of the isomers **3c-I** and **3c-II** (88/12). The derivative **3c-I** was isolated as a white solid by recrystallization (ethyl acetate/hexane), M.P.: 70-72°C, and characterized by X-Ray[32], IR and NMR. The ORTEP drawing is outlined in the Figure 2. IR (KBr) 3140, 1740, 1645, 1585 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, J=7.2 Hz), 1.17 (7, 3H, J=7.2 Hz), 1.64 (s, 3H), 2.45 (s, 3H), 2.55 (s, 3H), 3.95 (qd, 1H, J=7.2, 8.7 Hz), 4.00 (qd, 1H, J=7.2, 8.7 Hz), 4.03 (qd, 1H, J=7.2, 11.0 Hz), 4.09 (qd, 1H, J=7.2, 11.0 Hz), 5.40

(d, 1H, J=1.8 Hz), 6.33 (dd, 1H, J=3.3, 2.0 Hz), 6.41 (dd, 1H, J=3.3, 0.9 Hz), 7.05 (d, 1H, J=1.8 Hz), 7.36 (dd, 1H, J=2, 0.9 Hz). ^{13}C NMR ($CDCl_3$) δ 13.7, 13.7, 15.3, 16.3, 17.8, 61.3, 61.5, 72.0, 73.9, 91.1, 109.6, 110.3, 142.3, 149.5, 155.1, 161.9, 169.1, 169.8. Analysis Calcd. for $C_{18}H_{24}N_2O_6S_2$: C, 50.45; H, 5.65; N, 6.54. Found: C, 50.21; H, 5,70; N, 6.48.

The minor isomer **3c-II** was identified from the reaction mixture by its spectral data. ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J=7.2 Hz), 1.31 (t, 3H, J=7.2 Hz), 1.48 (s, 3H), 2.32 (s, 3H), 2.55 (s, 3H), 3.90-4.30 (m, 4H), 5.57 (d, 1H, J=1.8 Hz), 6.33 (dd, 1H, J=3.3, 2.0 Hz), 6.43 (dd, 1H, J=3.3, 0.9 Hz), 7.07 (d, 1H, J=1.8 Hz), 7.28 (dd, 1H, J=2.0, 0.9 Hz).

Hydrolysis of Oxazolines **3a**, **3b** *and* **3c**. *General Procedure*

Oxazolines **3a-c** were hydrolyzed with AcOH/EtOH at different temperatures and reaction times to yield the glutaric acid derivatives **4**. Glutaric derivatives **4a-I/4a-II** and **4c-II** (as a single isomer) were obtained from **3a-I/3a-II** and **3c-I/3c-II** mixtures, respectively, by reaction at 20°C for 1.5 h. Glutaric acid derivative **4b-II** (as a single isomer) was obtained from **3b-I/3b-II** mixture at 20°C for 3.5.h.

To a solution of oxazoline **3a-c** (2.66 mmol, 2.28 mmol, 2.33 mmol, respectively) (as an epimeric mixture) in EtOH (8.3 mL) was added AcOH (2 mL, 1.8 M) and the reaction mixture was stirred at rt or 50°C for 1.5 h or 3h. Then, it was concentrated under vacuum and the crude product was dissolved in $CHCl_3$ (5 mL) and H_2O (3 mL). The solution was extracted with $CHCl_3$ (3x10 mL), washed with H_2O to pH 7 and dried over $MgSO_4$. The solvent was removed under vacuum and the residue analyzed by TLC and ^{1}H NMR spectroscopy.

Diethyl (2R*,3S*,4S*)-2-[bis(methylthio)methylene]amino-4-formylamino-3-hydroxy-2,3-dimethylglutarate, 4a-I, and diethyl (2R*,3S*,4R*)-2-[bis(methylthio)methylene]amino-4-formylamino-3-hydroxy-2,3-dimethylglutarate, 4a-II.. According to the general procedure, from a mixture of **3a-I/3a-II** (84/16) (1 g, 2.66 mmol) were obtained 0.566 g (1.49 mmol, yield 56%) of the title diasteromeric racemates **4a-I/4a-II** (70/30). The major isomer was isolated (0.150 g) by recrystallization (EtAcO/n-hexane) and the minor isomer 4a-II (0.200 g) was obtained by precipitation of the filtrate at rt for 3 days. Both compounds showed spectral data in agreement with the title structures.

4a-I. Crystalline white solid. MP (EtOAc/n-hexane) 111-112°C. IR (KBr) 3400, 1730, 1680, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J=7.2 Hz), 1.29 (t, 3H, J=7.2 Hz), 1.33 (s, 3H), 1.59 (s, 3H), 2.42 (s, 3H), 2.57 (s, 3H), 4.06 (s, 1H), 4-00-4.20 (m, 4H), 4.92 (d, 1H, J=7.8 Hz), 7.12 (d, 1H, J=7.8 Hz), 8.18 (s, 1H), ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 15.6, 16.7, 17.8, 21.8, 55.8, 61.4, 61.8, 72.6, 76.5, 160.4, 163.8, 170.8, 171.9. Anal. Calcd. for $C_{15}H_{26}N_2O_6S_2$: C, 45.67; H, 6.65; N, 7.11. Found: C, 45.73; H, 6.81; N, 7.18.

4a-II. Crystalline white solid. MP (EtOAc/hexane) 109-110°C. IR (KBr) 3400, 1730, 1680, 1580 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.29 (t, 6H, J=7.2 Hz), 1.37 (s, 3H), 1.56 (s, 3H), 2.41 (s, 3H), 2.57 (s, 3H), 3.97-4.23 (m, 4H), 4.78 (d, 1H, J=7.8 Hz), 6.91 (d, 1H, J=7.8 Hz), 8.15 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.8, 14.0, 15.5, 16.6, 17.8, 21.7, 55.8, 61.3, 61.7, 72.6, 76.6, 160.3, 163.8, 170.7, 171.9. Anal. Calcd. for $C_{15}H_{26}N_2O_6S_2$: C, 45.67; H, 6.65; N, 7.11. Found: C, 45.82; H, 6.71; N, 7.02.

Diethyl (2R*,3S*,4R*)-2-[bis(methylthio)methylene]amino-4-formylamino-3-hydroxy-2-methyl-3-phenylglutarate, 4b-II. According to the general procedure, from **3b-I/3b-II** (90/10) (1 g, 2.28 mmol) at rt for 3.5 h was obtained a crude product (0.840 g) which shown three spots by TLC. The three components of the mixture were identified by ^1H NMR as a single racemic diastereomer of the glutarate derivative **4b-II** (26%), *tert*-butyl acetate (74%) and ethyl *N*-[bis(methylthio)methylene]alaninate **10** (74%). Flash chromatography of the reaction mixture (EtOAc/hexanes: 50/50) allowed for the separation of four fractions which were identified as the derivative **10** (0.267 g), as a new compound originated into the column which was identified as (2R*,3R*,4S*) ethyl *N*-formyl-4-[bis(methylthio)methylene]amino-3-hydroxy-3-phenyl-pyroglutamate **8b-I** by its spectral data and X-Ray diffraction analysis[35], as *tert*-butyl acetate (0.294 g) and one single racemate **4b-II** (0.226 g) of the title compound. All attempts to recrystallize the racemate **4b-II** occurred with disproportionation to compounds **10** and **11**.

4b-II. White solid. MP 96-97°C. IR (KBr) 3300, 1725, 1670, 1585 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.70 (t, 3H, J=7.2 Hz), 1.08 (t, 3H, J=7.2 Hz), 1.51 (s, 3H), 2.56 (s, 3H), 2.565 (s, 3H), 3.73 (qd, 1H, J=7.2, 10.8 Hz), 3.78 (qd, 1H, J=7.2, 10.8 Hz), 3.91 (qd, 1H, J=7.2, 10.8 Hz), 4.83 (s, 1H), 5.45 (d, 1H, J=6.6 Hz), 7.27-7.29 (m, 3H), 7.60-7.66 (m, 2H), 7.96 (d, 1H, J=6.6 Hz), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.1, 13.4, 15.7, 16.7, 19.3, 57.1, 60.9, 61.6, 73.7, 80.2, 127.2, 127.3, 127.9, 139.0, 160.6, 163.7, 170.4, 172.0. Anal. Calcd. for $C_{20}H_{28}N_2O_6S_2$: C, 52.61; H, 6.18; N, 6.14. Found: C, 52.77; H, 6.09; N, 6.21.

8b-I. White solid, MP 137-138°C. ORTEP drawing was obtained by X Ray diffraction analysis (Figure 3). IR (KBr) 3450, 1770, 1745, 1700, 1570 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H, J=7.2 Hz), 1.63 (s, 3H), 2.18 (s, 3H), 2.50 (s, 3H), 4.17 (qd, 1H, J=7.2, 10.8 Hz), 4.23 (qd, 1H, J=7.2, 10.8 Hz), 4.29 (s, 1H), 5.525 (s, 1H), 7.35-7.39 (m, 3H), 7.63-7.66 (m, 2H), 9.15 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.7, 13.6, 15.9, 16.2, 58.7, 62.4, 74.3, 81.1, 127.4, 127.7, 128.5, 135.8, 160.1, 164.8, 168.7, 172.5. Analysis Calcd. for $C_{20}H_{28}N_2O_6S_2$: C, 52.62; H, 6.18; N, 6.14. Found: C, 52.81; H, 6.19; N, 6.11.

Diethyl (2R*,3S*,4R*)-2-[bis(methylthio)methylene]amino-4-formylamino-3-(2'-furyl)-3-hydroxy-2-methylglutarate, 4c-II. According to the general procedure from **3c-I/3c-II** (88/12) (1g, 2.33 mmol) the title

compound was obtained as a single isomer (0.655 g) and purified by recrystallization giving a crystalline white solid. MP 113-114 °C (EtOAc/n-hexane). Yield: 63%. IR (KBr) 3380, 1750, 1730, 1675, 1555 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.96 (t, 3H, J=7.2 Hz), 1.08 (t, 3H, J=7.2 Hz), 1.78 (s, 3H), 2.51 (s, 3H), 2.56 (s, 3H), 3.75-3.96 (m, 4H), 4.48 (s, 1H), 5.24 (d, 1H, J=6.6 Hz), 6.30 (dd, 1H, J=3.3, 1.8 Hz), 6.33 (dd, 1H, J=3.3, 0.9 Hz), 7.45 (dd, 1H, J=1.8, 0.9 Hz), 7.83 (d, 1H, J=6.6 Hz), 8.22 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.4, 15.5, 16.5, 17.2, 56.2, 61.0, 61.5, 74.0, 79.5, 108.8, 110.0, 142.4, 152.8, 160.2, 164.8, 168.7, 170.8. Analysis Calcd. for $C_{18}H_{26}N_2O_7S_2$: C, 48.42; H, 5.87; N, 6.28. Found: C, 48.53; H, 5.86; N, 6.13.

*Synthesis of Oxazolidines **5a-c**. General Procedure*

Oxazolidines **5a-c** were obtained from oxazolines **3a-c** by *N*-methylation and reduction following the procedure described by Meyers.[20] To a solution of oxazoline **3a-c** (5.32 mmol) as epimeric mixture in 66 mL of CH_2Cl_2 under atmosphere of dry argon, were added MeOTf (1.74 g, 10.64 mmol) and the reaction mixture was stirred at rt over 2 h. Then, the reaction was cooled to 0°C and a solution of $NaBH_4$ (0.402 g, 10.64 mmol) in dry THF (29 mL) and MeOH (6 mL) was added. The temperature was maintained at 0°C for 30 min and then was allowed to warm to 25°C and H_2O (10 mL) added. The reaction mixture was extracted with $CHCl_3$ (3x25 mL) and the combined organic extracts were dried on $MgSO_4$, the solvent was eliminated under reduced pressure and the crude product was analyzed by TLC and fractionated by flash chromatography.

(1'R*,4S*,5S*)-5-{1'-[Bis(methylthio)methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-3,5-dimethyloxazolidine, 5a-I and (1'R*4R*,5S*)--5-{1'-[bis(methylthio)methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-3,5-dimethyloxazolidine, 5a-II. According to the general procedure, from **3a-I/3a-II** (84/16) (2 g, 5.31 mmol) were obtained a reaction mixture containing oxazolidines **5a-I** and **5a-II** in a ratio 84/16. These compounds were isolated by a flash chromatography (EtOAc/hexanes: 25/75): **5a-I** (0.963 g, yield 46%) and **5a-II** (0.183 g, yield 9%).

5a-I. White solid. MP (EtOAc/n-hexane): 46-47°C. IR (KBr) 2820, 2740, 1725, 1740, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J=7.2 Hz), 1.29 (t, 3H, J=7.2 Hz), 1.36 (s, 3H), 1.58 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 2.54 (s, 3H), 4.10 (s, 1H), 4.11 (qd, 1H, J=7.2, 10.8 Hz), 4.16 (qd, 1H, J=7.2, 10.8 Hz), 4.20 (qd, 1H, J=7.2, 10.8 Hz), 4.25 (qd, 1H, J=7.2, 10.8 Hz), 4.33 (d, 1H, J=0.9 Hz), 4.68 (d, 1H, J=0.9 Hz). ^{13}C NMR ($CDCl_3$) δ 13.8, 13.8, 14.1, 15.4, 16.5, 18.0, 19.0, 34.2, 60.4, 61.0, 68.9, 86.8, 90.0, 159.7, 171.0, 171.6. Analysis Calcd. for $C_{16}H_{28}N_2O_5S_2$: C, 48.96; H, 7.19; N, 7.14. Found: C, 49.06; H, 7.16; N, 7.12.

5a-II. Colorless oil IR (film) 2820, 2740, 1725, 1740, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, J=7.2 Hz), 1.29 (t, 3H, J=7.2 Hz), 1.35 (s, 3H), 1.64 (s, 3H), 2.40 8s, 3H), 2.43 (s, 3H), 2.55 (s, 3H), 3.97 (s, 1H),

4.11 (qd, 1H, J=7.2, 10.8 Hz), 4.16 (qd, 1H, J=7.2, 10.8 Hz), 4.21 (qd, 1H, J=7.2, 10.8 Hz), 4.71 (qd, 1H, J=7.2, 10.8 Hz), 4.41 (d, 1H, J=1.3 Hz), 4.71 (d, 1H, J=1.3 Hz). ^{13}C NMR ($CDCl_3$) δ 13.7, 14.1, 15.9, 16.8, 18.3, 19.6, 36.2, 60.7, 61.2, 69.8, 73.6, 87.4, 89.2, 160.4, 170.8 171.6. Anal. Calcd. for $C_{16}H_{28}N_2O_5S_2$: C, 48.96; H, 7.19; N, 7.14. Found: C, 49.12; H, 7.14; N, 7.21.

(1'R*,4S*,5S*)-{1'-[Bis(methylthio)methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-3-methyl-5-phenyloxazolidine, 5b-I, and (1'R*,4R*,5S*)-{1'-[bis(methylthio)methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbonyl-3-methyl-5-phenyloxazolidine, 5b-II. According to the general procedure, from **3b-I/3b-II** (90/10) (2.33 g, 5.46 mmol) was obtained a reaction crude (2.02 g) that by TLC (EtOAc/hexanes: 50/50) showed one spot. By ^{1}H NMR it was identified as a epimeric mixture (90/10) of the titled compounds. The mixture was purified by flash chromatography to give the **5b-I** and **5b-II** as a colorless oils. Yield: 84%. IR (film) 2820, 2740, 1725, 1580 cm^{-1}. Analysis Calcd. for $C_{21}H_{30}N_2O_5S_2$: C, 55.48; H, 6.65; N, 6.16. Found: C, 55.39; H, 6.68; N, 6.05.

5b-I. ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J=7.2 Hz), 1.28 (s, 3H), 1.31 (t, 3H, J=7.2 Hz), 2.35 (s, 3H), 2.51 (s, 3H), 2.60 (s, 3H), 3.72 (q, 2H, J=7.2 Hz), 4.10 (qd, 1H, J=7.2, 10.8 Hz), 4.19 (qd, 1H, J=7.2, 10.8 Hz), 4.54 (s, 1H), 4.70 (s, 2H), 7.20-7.22 (m, 3H), 7.52-7.72 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.5, 13.9, 15.6, 16.8, 19.4, 33.6, 59.9, 61.1, 70.3, 72.4, 86.6, 93.2, 126.5, 127.0, 127.8, 139.2, 160.5, 170.5, 171.8.

5b-II. ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J=7.2 Hz), 1.26 (t, 3H, J=7.2 Hz), 1.28 (s, 3H), 2.43 (s, 3H), 2.49 8s, 3H), 2.55 (s, 3H), 3.70-3.76 (m, 2H), 4.04-4.24 (m, 2H), 4.65 (s, 1H), 4.77 (s, 2H), 7.15-7.22 (m, 3H), 7.51-7.54 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.2, 14.0, 15.3, 16.8, 18.8, 34.6, 60.0, 60.6, 66.7, 71.8, 87.7, 92.9, 126.5, 126.6, 126.9, 139.9, 160.4, 170.5, 171.4.

(1'R*,4S*,5S*)-5-{1'-[Bis(methylthio)methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbony-5-(2'-furyl)-3-methyloxazolidine, 5c-I, and (1'R*,4R*,5S*)-5-{1'-[bis(methylthio)-methylene]amino-1'-methyl}ethoxycarbonylmethyl-4-ethoxycarbony-5-(2'-furyl)-3-methyloxazolidine, 5c-II. According to the general procedure, from **3c-I/3c-II** (88/12) (2.276 g, 5.27 mmol) were obtained 1.910 g of a crude product as colorless oil which was analyzed by TLC (EtOAc/hexanes: 50/50) showing two spots. By ^{1}H NMR the crude product was identified as an epimeric mixture (88/12) of the title compounds. By flash chromatography were obtained 1.496 g of the pure **5c-I** and 0.204 g of the **5c-II**. Yield: 72%.

5c-I. Colorless oil. IR (film) 2800, 2730, 1725, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J=7.2 Hz), 1.18 (t, 3H, J=7.2 Hz), 1.49 (s, 3H), 2.33 (s, 3H), 2.48 (s, 3H), 2.49 (s, 3H), 3.91 (qd, 1H, J=7.2, 10.5 Hz),

3.96 (qd, 1H, J=7.2, 10.5 Hz), 4.04 (q, 2H, J=7.2 Hz), 4.40 (s, 1H), 4.42 (d, 1H, J=2.1 Hz), 4.79 (d, 1H, J=2.1 Hz), 6.31 (dd, 1H, J=1.5, 3.3 Hz), 6.43 (dd, 1H, J=3.3, 0.9 Hz), 7.31 (dd, 1H, J=1.5, 0.9 Hz). ^{13}C NMR ($CDCl_3$) δ 13.7, 13.8, 15.4, 16.5, 18.6, 35.5, 60.5, 61.0, 70.3, 72.6, 87.9, 90.7, 109.4, 110.0, 141.3, 152.3, 159.8, 170.2, 170.8. Anal. Calcd. for $C_{19}H_{30}N_2O_6S_2$: C, 51.10; H, 6.77; N, 6.27. Found: C, 51.38; H, 6.62; N, 6.32.

5c-II. Colorless oil. IR (film) 2800, 2730, 1725, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz), 1.20 (t, 3H, J=7.2 Hz), 1.64 (s, 3H), 2.37 (s, 3H), 2.44 (s, 3H), 2.53 (s, 3H), 3.97 (qd, 1H, J=7.2, 10.8 Hz), 4.02 (qd, 1H, J=7.2, 10.8 Hz), 4.06 (qd, 1H, J=7.2, 10.8 Hz), 4.17 (qd, 1H, J=7.2, 10.8 Hz), 4.32 (s, 1H), 4.50 (d, 1H, J=2.7 Hz), 4.86 (d, 1H, J=2.7 Hz),6.31 (dd, 1H, J=3.3, 1.8 Hz), 6.44 (dd, 1H, J=3.3, 0.6 Hz), 7.25 (dd, 1H, J=1.8, 0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 13.5, 13.7, 15.4, 16.5, 18.0, 35.6, 60.7, 61.1, 71.1, 73.1, 88.2, 90.7, 109.0, 110.1, 141.1, 152.7, 159.9, 170.0, 171.0. Anal. Calcd. for $C_{19}H_{30}N_2O_6S_2$: C, 51.10; H, 6.77; N, 6.27. Found: C, 50.98; H, 6.82; N, 6.18.

Hydrolysis of Oxazolidines **5a-c**. *General Procedure*

To a mixture of oxazolidine **5a-c** (12.75 mmol) and oxalic acid dihydrate (1.61 g, 12.75 mmol) were added THF (16 mL) and H_2O (4 mL). The reaction mixture was stirred for 48 h at rt. Then, it was extracted with $CHCl_3$ at acid pH and the extract was discarded. The pH of the aqueous phase was adjusted to 12 with ammonia and it was extracted with $CHCl_3$ (3x20 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated by elimination of the solvent under reduced pressure. The reaction crude was analyzed by TLC and the products were characterized by IR, ^{1}H and ^{13}C NMR.

(1'S*,4R*,5S*)-4-Ethoxycarbonyl-5-[1'-methylamino-1'-ethoxycarbonyl]methyl-4,5-dimethyl-2-methylthio-4,5-dihydrooxazole, 6a-I.. According to the general procedure described above, from **5a-I** (1 g, 2.55 mmol) were obtained 0.627 g of a reaction crude which was characterized as a single racemate of the title compound. The pure compound was obtained by recrystallization (EtOAc/n-hexane) of the crude product. Yield: 74%. White solid. MP 51-52°C. IR (KBr) 3430, 1730, 1680, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J=7.2 Hz), 1.31 (t, 3H, J=7.2 Hz), 1.37 (s, 3H), 1.38 (s, 3H), 2.38 (s, 3H), 2.93 (s, 3H), 3.74 (s, 1H), 4.15 (qd, 1H, J=7.2, 10.8 Hz), 4.18 (qd, 1H, J=7.2, 10.8 Hz), 4.19 (qd, 1H, J=7.2, 10.8 Hz), 4.27 (qd, 1H, J=7.2, 10.8 Hz), 4.42 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.8, 14.0, 14.05, 21.7, 23.5, 37.2, 61.2, 61.5, 64.6, 69.2, 71.7, 155.0, 169.1, 175.5. Analysis Calcd. for $C_{14}H_{24}N_2O_5S$: C, 50.59; H, 7.28; N, 8.43. Found: C, 50.72; H, 7.31; N, 8.28.

(1'R*,4S*,5S*)-4-Ethoxycarbonyl-5-[1'methylamino-1'-ethoxycarbonyl]methyl-4-methyl-2-methylthio-5-phenyl-4,5-dihydrooxazole, 6b-I, and (1'S*,4R*,5SS*)-4-Ethoxycarbonyl-5-[1'-methylamino-

1'-ethoxycarbonyl]methyl-4-methyl-2-methylthio-5-phenyl-4,5-dihydrooxazole, 6b-II.. According to the general procedure described above, from **5b-I/5b-II** (90/10) (1.158 g, 2.55 mmol) a colorless oil (0.864 g, yield 86%) was obtained. The analysis of the crude product showed a single spot by TLC (EtOAc/hexanes: 50/50). The mixture was purified by flash chromatography to give a mixture (90/10) of the epimeric racemates **6b-I/6b-II**. IR (film) 3450, 1750, 1600 cm^{-1}. Anal. Calcd. for $C_{19}H_{26}N_2O_5S$: C, 57.85; H, 6.64; N, 7.10. Found: C, 57.72; H, 6.71; N, 7.24.

6b-I. ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=7.2 Hz), 1.05 (t, 3H, J=7.2 Hz), 1.32 (s, 3H), 2.42 (s, 3H), 3.03 (s, 3H), 3.92 (qd, 1H, J=7.2, 10.8 Hz), 4.01 (q, 2H, J=7.2 Hz), 4.07 (qd, 1H, J=7.2, 10.8 Hz), 4.44 (s, 1H), 4.91 (s, 1H), 7.24-7.33 (m, 3H), 7.48-7.50 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.47, 13.52, 14.1, 21.2, 36.8, 61.0, 61.0, 66.4, 67.3, 75.2, 126.7, 127.2, 127.2, 140.2, 156.5, 168.4, 174.0.

6b-II. ^1H NMR ($CDCl_3$) δ 0.79 (t, 3H, J=7.2 Hz), 1.10 (t, 3H, J=7.2 Hz), 1.30 (s, 3H), 2.37 (s, 3H), 3.02 (s, 3H), 3.86-4.12 (m, 4H), 4.43 (s, 1H), 4.96 (s, 1H), 7.29-7.38 (m, 3H), 7.48-7.50 (m, 2H). The assignment of ^{13}C NMR signals for this minor isomer from the mixture was not unequivocal.

(1'S*,4R*,5S*)-4-Ethoxycarbonyl-5-[1'methylamino-1'-ethoxycarbonyl]methyl-5-(2'-furyl)-4-methyl-2-methylthio-4,5-dihydrooxazole, 6c-I. According to the general procedure described above, from **5c-I** (1.132 g, 2.55 mmol) a crude white solid (0.891 g, yield 90%) was obtained. The analysis of this crude product by TLC shown one spot which was characterized as the title compound by IR, ^1H and ^{13}C NMR and purified by recrystallization. MP (CH_2Cl_2/*n*-hexane) 42-43°C. IR (KBr) 3500-3400, 1750, 1585 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.04 (t, 3H, J=7.2 Hz), 1.14 (t, 3H, J=7.2 Hz), 1.40 (s, 3H), 2.40 (s, 3H), 3.03 (s, 3H), 3.98 (qd, 1H, J=7.2, 10.8 Hz), 4.08 (q, 2H, J=7.2 Hz), 4.10 (qd, 1H, J=7.2, 10.8 Hz), 4.53 (s, 1H), 4.65 (s, 1H), 6.32 (dd, 1H, J=3.3, 1.2 Hz), 6.34 (dd, 1H, J=1.5, 3.3 Hz), 7.25 (dd, 1H, J=1.5, 1.2 Hz). ^{13}C NMR ($CDCl_3$) δ 13.6, 13.7, 14.1, 20.2, 36.8, 61.2, 65.3, 66.7, 73.8, 75.3, 108.3, 110.3, 142.0, 153.3, 157.0, 167.7, 173.7. Analysis Calcd. for $C_{17}H_{24}N_2O_6S$: C, 53.11; H, 6.29; N, 7.29. Found: C, 53.07; H, 6.29; N, 7.32.

Synthesis of Oxazolidines **7a-c**. *General Procedure*

The synthesis of oxazolines **7a-c** were carried out from the oxazolidines **6a-c** following the general procedure of *N*-methylation and reduction described above for the synthesis of oxazolidines **5a-c**.

(1'S*,4R*,5S*)-4-Ethoxycarbonyl-3,4,5-trimethyl-5-[1'-methylamino-1'-ethoxycarbonyl]methyl]oxazolidine, 7a-I. According to the procedure described for the synthesis of **5a-c**, from **6a-I** (0.880 g, 2.66 mmol) a colorless oil was obtained (0.402 g, yield 50%). The analysis of the crude product by TLC (EtOAc/hexanes:

50/50) revealed one spot which was identified as a single racemic diastereomer of the title compound ***rac*-24a**. IR (film) 3500, 2800, 2700, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.25 (s, 3H), 1.30 (t, 3H, J=7.2 Hz), 1.31 (t, 3H, J=7.2 Hz), 2.21 (s, 3H), 2.24 (s, 3H), 2.94 (s, 1H), 2.95 (d, 1H, J=9.3 Hz), 3.53 (d, 1H, J=9.3 Hz), 4.18 (s, 1H), 4.24 (q, 2H, J=7.2 Hz), 4.19 (qd, 1H, J=7.2, 10.8 Hz), 4.27 (qd, 1H, J=7.2, 10.8 Hz). ^{13}C NMR ($CDCl_3$) δ 8.0, 13.9, 14.0, 20.2, 37.2, 40.3, 60.8, 61.2, 70.4, 71.2, 71.5, 71.8, 169.4, 171.8. Analysis Calcd. for $C_{14}H_{26}N_2O_5$: C, 55.61; H, 8.67; N, 9.26. Found: C, 55.81; H, 8.69; N, 9.24.

(1'S*,4R*,5S*)-4-Ethoxycarbonyl-3,4-dimethyl-5-[1'-methylamino-1'-ethoxycarbonyl]methyl]-5-phenyloxazolidine, 7b-I, and (1'R*,4R*,5S*)-4-Ethoxycarbonyl-3,4-dimethyl-5-[1'-methylamino-1'-ethoxycarbonyl]methyl]-5-phenyloxazolidine, 7b-II .The synthesis was achieved from the epimeric mixture of **6b-I/6b-II** (90:10) (1g, 2.65 mmol) following the procedure described above for the synthesis of **5a-c**. The obtained crude product (0.740 g) showed a single spot by TLC (EtOAc/hexanes: 10/90) which was identified as a mixture of two epimeric racemates **7b-I/7b-II** (90/10) by ^1H NMR analysis. The crude mixture of the title compounds was dissolved in dry CH_2Cl_2 and a stream of dry hydrogen chloride was bubbled trough the solution. The solid product (0.668 g) was identified as **7b-I. HCl** and purified by recrystallization. MP (EtOAc/n-hexane) 60-61°C. Yield: 70%. Analysis Calcd. for $C_{19}H_{29}ClN_2O_5$: C, 56.92; H, 7.29; N, 6.99. Found: C, 57.13; H, 7.18; N, 6.73.

7b-I (hydrochloride). IR (KBr) 3500, 1750, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.77 (t, 3H, J=7.2 Hz), 0.93 (t, 3H, J=7.2 Hz), 1.34 (s, 3H), 2.23 (s, 3H), 2.30 (s, 3H), 3.23 (d, 1H, J=9.45 Hz), 3.60 (d, 1H, J=9.45 Hz), 3.80 (qd, 1H, J=7.2, 11.1 Hz), 3.86 (qd, 1H, J=7.2, 11.1 Hz), 3.88 (s, 1H), 3.85 (qd, 1H, J=7.2, 10.8 Hz), 4.00 (qd, 1H, J=7.2, 10.8 Hz), 4.89 (bs, 2H), 7.27-7.31 (m, 3H), 7.48-7.52 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 8.3, 13.8, 13.9, 37.8, 40.7, 62.0, 62.4, 69.7, 72.1, 72.5, 77.5, 128.1, 128.8, 129.1, 139.3, 171.6, 172.7.

The compound **7b-I** was obtained by treatment of its hydrochloride with an aqueous saturated solution of $NaHCO_3$ and isolated by extraction with $CHCl_3$ and drying over $MgSO_4$ to give a colorless oil which was identified as **7b-I** from its IR and ^1H and ^{13}C NMR spectra. Isomer **7b-II** was identified in the mother liquor together the major isomer **7b-I**.

7b-I. IR (film) 3480, 2700, 1745 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.79 (t, 3H, J=7.2 Hz), 1.02 (t, 3H, J=7.2 Hz), 1.31 (s, 3H), 2.27 (s, 3H), 2.31 (s, 3H), 3.16 (d, 1H, J=9.15 Hz), 3.62 (d, 1H, J=9.15 Hz), 3.64 (s, 1H), 3.82 (qd, 1H, J=7.2, 11.1 Hz), 3.89 (qd, 1H, J=7.2, 11.1 Hz), 3.90 (qd, 1H, J=7.2, 10.8 Hz), 4.06 (qd, 1H, J=7.2, 10.8 Hz), 4.94 (s, 1H), 7.24-7.29 (m, 3H), 7.44-7.51 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 8.1, 13.3, 13.6, 37.3, 40.4, 60.3, 60.7, 69.5, 71.1, 71.5, 75.6, 127.4, 128.4, 128.7, 137.8, 168.8, 170.4.

7b-II. ^{1}H NMR ($CDCl_3$) δ (key signals) 1.32 (s, 3H), 2.29 (s, 3H), 2.32 (s, 3H), 3.13 (d, 1H, J=9.1).

(1'S*,4R*,5S*)-4-Ethoxycarbonyl-5-(2'-furyl)-3,4-dimethyl-5-[1'-methylamino-1'-ethoxycarbonyl] methyloxazolidine, 7c-I.. The synthesis was achieved from the oxazoline **6c-I** (0.550 g, 1.43 mmol) following the procedure described above for the synthesis of **5a-c**. The obtained crude product (0.250 g) showed two spots by TLC (EtOAc/hexanes: 40/60). The separation by a flash chromatography allowed for the isolation of the two fractions of 0.070 g and 0.130 g, respectively. The first one was identified as a mixture of the initial oxazoline **6c-I** (53%) and the single racemate **7c-I** (7%). The second fraction was identified as the ethyl 2-(2-furoyl)-*N,N*-dimethylglycinate by its spectral data (yield: 40%).

Ethyl 2-(2-furoyl)-*N,N*-dimethylglycinate. IR (film) 3130, 3110, 1730, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, J=7.2 Hz), 2.52 (s, 6H), 4.23 (q, 2H, J=7.2 Hz), 4.65 (s, 1H), 6.58 (dd, 1H, J=1.5, 3.3 Hz), 7.41 (dd, 1H, J=3.3, 0.6 Hz), 7.64 (dd, 1H, J=1.5, 0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 42.3, 42.3, 60.9, 72.5, 112.3, 118.8, 146.8, 167.4, 182.1.

7c-I. ^{1}H NMR ($CDCl_3$) (in the mixture together **6c-I**) δ 1.07 (t, 3H, J=7.2 Hz), 1.13 (t, 3H, J=7.2 Hz), 1.64 (s, 3H), 2.38 (s, 3H), 2.45 (s, 6H), 3.77 (q, 2H, J=7.2 Hz), 3.91 (s, 1H), 3.93 (qd, 1H, J=7.2, 10.8 Hz), 4.04 (qd, 1H, J=7.2, 10.8 Hz), 4.72 (d, 1H, J=1.2 Hz), 4.93 (d, 1H, J=1.2 Hz), 6.25 (dd, 1H, J=3.3, 1.2 Hz), 6.26 (dd, 1H, J=3.3, 1.2 Hz), 7.43 (dd, 1H, J=1.8, 1.2 Hz).

NMR Analysis of Metallic Enolates from Ethyl Isocyanoacetate 1. In a reaction flask provided with a magnetic stirrer bar under argon, freshly cut metal (Li or Na) (0.442 mmol) was introduced. The tube was then sealed with a septum and degassed CD_3OD (0.5 mL) was added through a metal cannula. When the metal was completely dissolved, ethyl isocyanoacetate **1** (0.050 g, 0.442 mmol) was added to the solution, which developed a strong color. Then, the mixture was cannulated into a NMR tube under Ar provided with a septum. ^{1}H and ^{13}C NMR spectra were registered at rt using TMS as internal reference. A single isomer was observed for all enolates.

Lithium Enolate 1. ^{1}H NMR (CD_3OD) δ 1.17 (t, 3H, J=7.0), 3.60 (q, 2H, J=7.0), 5.33 (s, 1H). ^{13}C NMR (CD_3OD) δ 18.1, 58.3, 160.5, 160.5, 166.7

Sodium Enolate 1. ^{1}H NMR (CD_3OD) δ 1.25 (t, 3H, J=7.0), 3.68 (q, 2H, J=7.0), 5.30 (s, 1H). ^{13}C NMR (CD_3OD) δ 19.3, 59.1, 164.6, 166.7, 167.7.

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