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Diastereoselective Reduction of α-Acyl-N-[Bis(methylthio)methylene]alaninates and Phenylalaninates: Synthesis of α,α-Disubstituted β-Hydroxy α-Amino Esters

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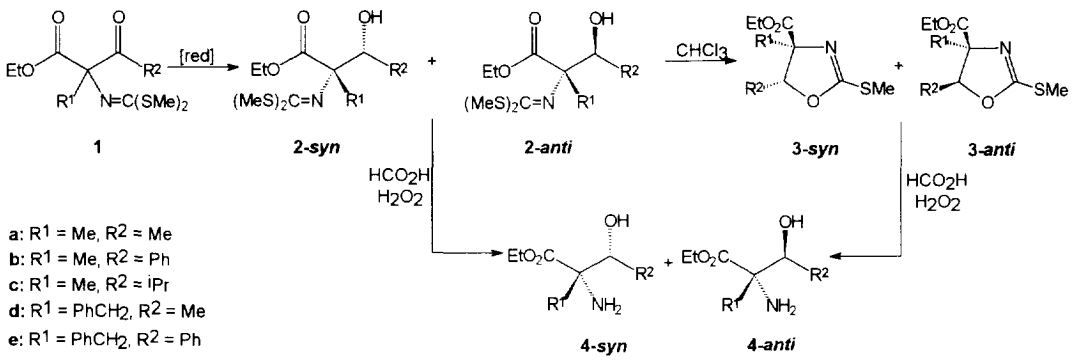
Abstract: Chemoselective reduction of the carbonyl group in α-acyl-N-[Bis(methylthio)methylene]-alaninates **1a-c** and phenylalaninates **1d,e** allowed for the diastereoselective synthesis of both the syn and the anti isomers of the corresponding N-protected α,α-disubstituted β-hydroxy-α-amino esters **2**. The stereochemistry of the process was tuned by switching between chelation-controlled and non-chelation-controlled conditions for the reduction. Compounds **2** can be transformed into the corresponding N-unprotected α-quaternized β-hydroxy-α-amino esters **4.**

β-hydroxy α-amino acids are known to play relevant physiological roles as enzymatic inhibitors[1] and components of peptidases.[2] This has prompted the development of a wide variety of asymmetric syntheses of such α-amino acids in recent times.[3] Especially challenging is the presence of a substituent different from hydrogen on the nitrogen-bearing carbon. The importance of this unusual substitution pattern in new drug design is underlined by the conformational constraints imposed by α,α-disubstituted α-amino acids to peptides, which render them more resistant to proteases and modifies their active receptor recognition.[4] Among the synthetic possibilities, the diastereoselective reduction of carbonyl compounds is one of the most versatile methods of asymmetric formation of a C-OH bond. The diastereoselective reduction of acyclic α-aminosubstituted ketones[5] has been justified with the classical Cram-chelate model.[6] A reactive conformation with an almost coplanar arrangement of the carbonyl and the chelating substituent at the α-carbon is selected, and hydride attack takes place on the less hindered diastereotopic face of the C=O bond. However, the concurrence of other factors, such as substitution on nitrogen, simultaneous presence in the molecule of other chelating groups, or conformational constraints, can modify the discussion of the observed diastereoselectivities. We report herein our results on the chelation-controlled and non-chelation-controlled diastereoselective reduction of the α-amino acid derived acyclic ketones[7] **1** with a wide variety of reducing agents, in order to obtain stereocontrol in the preparation of either the *syn* or the *anti* diastereomers[8] of α,α-disubstituted[9] N-protected β-hydroxy α-amino esters **2**

(Scheme). The corresponding N-unprotected β-hydroxy α-amino esters **4** can be obtained by oxidative hydrolysis of either the β-hydroxy α-amino esters **2** or the cyclized derivatives **3**.



Scheme

The results of the reduction of the carbonyl group of compounds **1a-e** are given in table 1. These data showed that the reduction of compound **1a** with borohydrides in alcoholic solvents favored the formation of the **2a-*syn*** diastereomer (entries 1 - 6). It was striking to notice that an increase of the bulkiness of the alcohol did not improve the diastereoselectivity, regardless the fact of the role played by the alcoholic solvent in borohydride mediated hydrogen transfers.[10] Using $LiBH_4$ and $Zn(BH_4)_2$ in Et_2O (entries 7 and 8), the percentage of **2a-*anti*** increased as compared with the result obtained in MeOH (entries 5 and 6).

The application of the conditions given in entry 1 ($NaBH_4$, MeOH, 0°C) to a variety of substituted ketones (**1b-e**) is given in entries 9 - 12. The increase of the steric bulkiness of R^2 in compounds **1b,c** (entries 9 and 10) as compared with **1a** (entry 1) had a deleterious effect in the diastereoselectivity of the reduction. However, a high selectivity in the reduction of compounds **1d,e** was obtained (entries 11 and 12) in favor of the **2d,e-*syn*** isomers, which were isolated as their cyclized derivatives **3d,e-*syn***.

The results of the reduction of the carbonyl group in compounds **1a-e** with $LiAlH_4$ in THF are given in entries 13 - 17. It was noticed that these reductions with $LiAlH_4$ did not affect the ester group and followed the same stereochemical trends as previously outlined for the reactions with alkaline borohydrides (entries 1 - 12).

The diastereoselectivity of the reduction of ketone **1a** with DIBAH showed a high dependence with the solvent (entries 18 - 20). A progressive increase of the **2a-*syn*** isomer was observed on passing from THF to Et_2O and CH_2Cl_2 solution. The turnover in diastereoselectivity was achieved by addition of $TiCl_4$ (entry 21). This last conditions (DIBAH, CH_2Cl_2, -78°) was applied to the reduction of the carbonyl group of compounds **1b-e** (entries 22 - 25). The ***anti*** isomers were also favored in the reduction of compounds **1c** and **1d** (entries 23 and

24). However, the phenyl derivatives **1b** and **1e** (entries 22 and 25) were recovered unreacted, probably due to stereoelectronic requirements.

Table 1: Reduction of compounds **1a-e**

Entry	Compound	Reducing Agent	Solvent	Additive	T (°C)	t (h)	Product	*syn* : *anti* ratio[a]	Yield (%)[b]
1	**1a**	$NaBH_4$	MeOH	---	0	0.50	**2a**	80 : 20	98
2	**1a**	$NaBH_4$	EtOH	---	0	0.50	**2a**	70 : 30	98
3	**1a**	$NaBH_4$	^iPrOH	---	0	0.75	**2a**	65 : 35	98
4	**1a**	KBH_4	MeOH	---	0	1.0	**2a**	70 : 30	98
5	**1a**	$LiBH_4$	MeOH	---	-20	1.0	**2a**	85 : 15	90
6	**1a**	$Zn(BH_4)_2$	MeOH	---	-20	3.0	**2a**	75 : 25	45
7	**1a**	$LiBH_4$	Et_2O	---	0	2.5	**2a**	55 : 45	98
8	**1a**	$Zn(BH_4)_2$	Et_2O	---	0	1.0	**2a**	65 : 35	98
9	**1b**	$NaBH_4$	MeOH	---	0	3.0	**2b**	70 : 30	70
10	**1c**	$NaBH_4$	MeOH	---	0	4.0	**2c**	75 : 25	80
11	**1d**	$NaBH_4$	MeOH	---	0	4.0	**3d**[c]	85 : 15	70
12	**1e**	$NaBH_4$	MeOH	---	0	4.0	**3e**[c]	98 : --	65
13	**1a**	$LiAlH_4$	THF	---	-78	1.0	**2a**	90 : 10	95
14	**1b**	$LiAlH_4$	THF	---	-78	1.0	**2b**	70 : 30	90
15	**1c**	$LiAlH_4$	THF	---	-78	1.0	**2c**	75 : 25	90
16	**1d**	$LiAlH_4$	THF	---	-78	1.0	**3d**[c]	85 : 15	98
17	**1e**	$LiAlH_4$	THF	---	-78	1.0	**3e**[c]	98 : --	60
18	**1a**	DIBAH	CH_2Cl_2	---	-78	3.0	**2a**	70 : 30	95
19	**1a**	DIBAH	Et_2O	---	-78	3.0	**2a**	55 : 45	95
20	**1a**	DIBAH	THF	---	-78	1.5	**2a**	45 : 55	95
21	**1a**	DIBAH	CH_2Cl_2	$TiCl_4$	-78	72	**2a**	20 : 80	90
22	**1b**	DIBAH	CH_2Cl_2	$TiCl_4$	-78	72	---	-- : --	---
23	**1c**	DIBAH	CH_2Cl_2	$TiCl_4$	-78	72	**2c**	35 : 65	70
24	**1d**	DIBAH	CH_2Cl_2	$TiCl_4$	-78	72	**3d**[c]	20 : 80	90
25	**1e**	DIBAH	CH_2Cl_2	$TiCl_4$	-78	72	---	-- : --	---

a) Determined by integration of the ^{1}H-NMR (300 MHz) spectra of the crude reaction products. b) Isolated. c) *In situ* cyclization to the corresponding oxazolines was observed.

These stereochemical results can be interpreted on the basis of Hammond's postulate,[11] admitting early transition states on the reaction coordinate for the exothermic reactions (reactant like transition states). According to the generalized Curtin-Hammett principle,[12] the energy differences at transition-state levels can then be evaluated from the interactions present in the initial states. The stereochemical outcome of the reductions with alkaline borohydrides in alcohols as well as $LiAlH_4$ in THF, namely the highly preferential

formation of the *syn* isomers, is in agreement with a non-chelation-controlled *Re* attack on the Felkin-Ahn transition state **A#** (Figure 1).

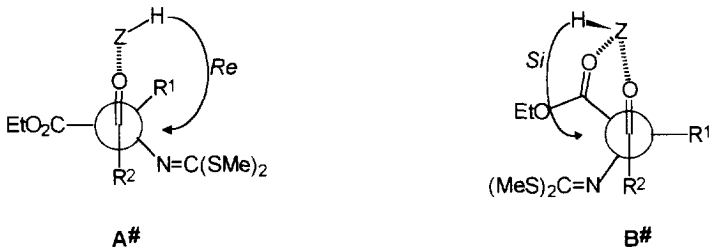


Figure 1

From frontier orbital theory standpoint, on the basis of a higher electronegativity of the ester than of the iminodithiocarbonate group, and in the absence of overriding steric considerations as shown by the molecular mechanics calculations, this approach would also be consistent with an antiperiplanar attack to the bond with the lowest lying σ^*-orbital.[13]

Competition between non-chelation-control (**A#**, *Re* attack) and chelation-control (**B#**, *Si* attack) plays a role in the reactions with $LiBH_4$ and $Zn(BH_4)_2$ in Et_2O, as well as DIBAH reductions. It is surprising to note that chelation between both carbonyl groups is favored over chelation between the carbonyl oxygen of the ketone and the sp^2-nitrogen of the iminodithiocarbonate group.[14] It is also worth mentioning that the reduction with DIBAH can also be justified by a *Re* attack on a dimeric transition state **C#** (Figure 2), which relies on DIBAH propensity to self-aggregation in non-coordinative solvents (CH_2Cl_2 > Et_2O > THF), the diastereomeric excesses being modified in this sense (table 1, entries 18 - 20). Therefore, hydride delivery giving rise to the minor diastereomer **2a-*anti*** through a *Si* attack on transition state **B#** (Z = Al^{i}Bu$_2$) is comparatively less disfavored than the internal *Re* attack on **C#** when THF is used as solvent. Chelation-control is definitively the predominant reaction path in the presence of the highly coordinative $TiCl_4$.

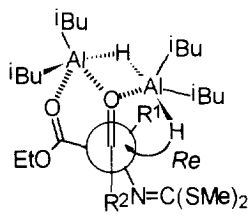


Figure 2

Finally, compounds **2** spontaneously cyclized to the corresponding oxazolines **3** ($CHCl_3$, 48 h, 25°C, 98%). As model examples, the N-unprotected β-hydroxy α-amino esters **4a,d-*syn*** and **4a,d-*anti*** were obtained without racemization *via* an oxidative hydrolysis[7] of the iminodithiocarbonate protecting group of the acyclic compounds **2a** (HCO_2H/H_2O_2, 24h, 25°C). Oxidative ring opening of the oxazolines **3a-*syn*** and **3a-*anti*** also resulted in β-hydroxy α-amino esters **4a-*syn*** and **4a-*anti*** (Scheme).

In summary, the tuning between chelation and non-chelation-control by the appropriate choice of reaction conditions provided access to highly substituted *syn* and *anti* α,α-disubstituted β-hydroxy α-amino esters from α-amino acid derived ketones as starting materials. Extending these observations is the subject of ongoing studies.

EXPERIMENTAL SECTION

All starting materials were commercially available research-grade chemicals and used without further purification. Compounds **1** were synthesized from the N-[bis(methylthio)methylene-protected alanine or phenylalanine ethyl esters and the corresponding acyl halides[15]. All starting materials were commercially available research-grade chemicals and were used without further purification. THF and Et_2O were distilled after refluxing over Na/benzophenone. CH_2Cl_2 was dried over CaH_2 and freshly distilled under argon prior to use. All reactions were carried out under argon. Silica gel F_{254} has been used for TLC, and the spots were detected with UV. Flash column chromatographies were carried out with Merck silica gel 60. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with TMS as internal reference, and full assigment of ^{13}C NMR spectra have been carried out with the aid of the DEPT-135 pulse sequence.

Reductions with Borohydrides in Alcoholic Solvents. General Procedure. To a solution of borohydride (0.60 mmol) in the corresponding anhydrous alcohol ROH (1.5 mL), at 0°C in the case of $NaBH_4$ or KBH_4 and at -20°C in the case of $LiBH_4$ or $Zn(BH_4)_2$, was added dropwise a solution of **1** (0.50 mmol) in anhydrous ROH (0.6 mL). After 0.5 - 4 h the reaction mixture was hydrolyzed with H_2O (1.0 ml) and was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (3 x 50 mL) and were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a pale yellow liquid which was purified by column chromatography (hexane : ethyl acetate, 80 : 20).

Reduction of 1a with $LiBH_4$ and $Zn(BH_4)_2$ in Et_2O. General Procedure. To a solution of $LiBH_4$ or $Zn(BH_4)_2$ (0.60 mmol) in Et_2O (2.0 mL) at 0°C was added dropwise a solution of **1a** (115 mg, 0.50 mmol) in Et_2O (0.6 mL). After 1 h ($Zn(BH_4)_2$) or 2.5 h ($LiBH_4$) the reaction mixture was hydrolyzed with H_2O (2.0 ml).

The organic phase was decanted and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (3 x 50 mL) and were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a pale yellow liquid which was purified by column chromatography (hexane : ethyl acetate, 80 : 20).

Reductions with $LiAlH_4$. General Procedure. To a solution of $LiAlH_4$ (80 mg, 2.0 mmol) in THF (2.0 mL) at -78°C was added dropwise a solution of **1** (0.50 mmol) in THF (0.6 mL). After 1 h the reaction mixture was hydrolyzed with H_2O (2.5 ml). The organic phase was decanted and the aqueous was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (3 x 50 mL) and were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a pale yellow liquid which was purified by column chromatography (hexane : ethyl acetate, 80 : 20).

Reductions with DIBAH. General Procedure. To a solution of **1** (0.50 mmol) in the apropriate solvent (Table 1, entries 18 - 20) (0.65 mL) at -78°C was added dropwise a 1M solution of DIBAH in toluene (1.2 mL, 1.2 mmol). At the end of the reaction the reaction mixture was hydrolyzed with H_2O (2.5 ml). The organic phase was decanted and the aqueous was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (3 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a the pale yellow liquid which was purified by column chromatography (hexane : ethyl acetate, 80 : 20).

In the case of the runs in the presence of $TiCl_4$ (Table 1, entries 21 - 25), to a solution of **1** (0.50 mmol) in CH_2Cl_2 (0.65 mL) at -78°C was added dropwise a 1M solution of $TiCl_4$ in CH_2Cl_2 (0.60 mL, 0.60 mmol). The solution was stirred for 10 min at -78°C. A 1M solution of DIBAH in CH_2Cl_2 (1.2 mL, 1.2 mmol) was added dropwise, and all operations were continued as above.

***anti*-Ethyl N-[Bis(methylthio)methylene]-2-(1-hydroxyethyl)-alaninate (2a-*anti*)**. Colorless oil (70%). IR (film) ν 3500, 1740, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (2H, m), 4.01 (1H, m), 2.56 (3H, s), 2.38 (3H, s), 1.50 (3H, s), 1.27 (3H, t, ^3J = 7 Hz), 1.19 (3H, d, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.3, 162.1, 73.9, 70.5, 61.5, 19.3, 18.4, 17.2, 16.1, 15.0. Anal. Calcd. for $C_{10}H_{19}NO_3S_2$: C, 45.26; H, 7.22; N, 5.28. Found: C, 45.12; H, 7.32; N, 5.36.

***syn*-Ethyl N-[Bis(methylthio)methylene]-2-(1-hydroxyethyl)-alaninate (2a-*syn*)**. Colorless oil (80%). IR (film) ν 3500, 1740, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (2H, m), 4.01 (1H, m), 2.56 (3H, s), 2.38 (3H, s), 1.38 (3H, s), 1.27 (3H, t, ^3J = 7 Hz), 1.14 (3H, d, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9, 172.3 161.6, 71.3, 61.1, 16.2, 16.1, 15.2, 14.4, 13.9. Anal. Calcd. for $C_{10}H_{19}NO_3S_2$: C, 45.26; H, 7.22; N, 5.28. Found: C, 45.14; H, 7.16; N, 5.24.

***anti*-Ethyl N-[Bis(methylthio)methylene]-2-(1-phenyl-1-hydroxymethyl)-alaninate (2b-*anti*)**. Colorless oil (30%). IR (film) ν 3500, 1735, 1585; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (5H, m), 4.92 (1H, s), 4.18

(2H, m), 2.56 (3H, s), 2.43 (3H, s), 1.52 (3H, s), 1.10 (3H, t, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6, 162.6, 137.7, 128.6, 127.5, 126.0, 91.6, 76.4, 61.0, 19.6, 15.6, 14.9, 14.1.

***syn*-Ethyl N-[Bis(methylthio)methylene]-2-(1-phenyl-1-hydroxymethyl)-alaninate (2b-*syn*)** Colorless oil (65%). IR (film) ν 3500, 1735, 1585; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (5H, m), 5.00 (1H, s), 4.18 (2H, m), 2.57 (3H, s), 2.46 (3H, s), 1.28 (3H, s), 1.24 (3H, t, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.6, 162.5, 135.6, 128.3, 127.4, 126.1, 87.4, 72.2, 61.9, 22.0, 15.5, 14.5, 14.4. Anal. Calcd. for $C_{15}H_{21}NO_3S_2$: C, 55.02; H, 6.46; N, 4.28. Found: C, 55.25; H, 6.34; N, 4.26.

***anti*-Ethyl N-[Bis(methylthio)methylene]2-(1-hydroxy-2-methylpropyl)-alaninate (2c-*anti*).** Colorless oil (45%). IR (film) ν 3500, 1740, 1580; ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (2H, m), 3.57 (1H, m), 2.54 (3H, s), 2.37 (3H, s), 1.75 (1H, m), 1.60 (3H, s), 1.26 (3H, t, ^3J = 7 Hz), 1.02 (3H, d, ^3J = 7 Hz), 0.88 (3H, d, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.4, 166.5, 94.5, 75.6, 61.6, 29.6, 26.0, 19.7, 19.0, 14.5, 14.4. Anal. Calcd. for $C_{12}H_{23}NO_3S_2$: C, 49.12; H, 7.90; N, 4.77. Found: C, 49.24; H, 7.65; N, 4.97.

***syn*-Ethyl N-[Bis(methylthio)methylene]2-(1-hydroxy-2-methylpropyl)-alaninate (2c-*syn*)**. Colorless oil (65%). IR (film) ν 3500, 1740, 1580; ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (2H, m), 3.63 (1H, m), 2.55 (3H, s), 2.36 (3H, s), 1.83 (1H, m), 1.45 (3H, s), 1.26 (3H, t, ^3J = 7 Hz), 1.00 (3H, d, ^3J = 7 Hz), 0.92 (3H, d, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.5, 166.5, 92.6, 74.7, 61.8, 29.6, 20.2, 19.3, 18.3, 14.4, 14.2. Anal. Calcd. for $C_{12}H_{23}NO_3S_2$: C, 49.12; H, 7.90; N, 4.77. Found: C, 49.20; H, 8.01; N, 4.86.

***anti*-4-Benzyl-4-ethoxycarbonyl-5-methyl-2-methylthio-Δ^2-oxazoline (3d-*anti*)**. Colorless oil (85%). IR (film) ν 1740, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (5H, m), 4.82 (1H, q, ^3J = 7 Hz), 4.15 (2H,m), 4.10 (2H, m), 3.07 (1H, A part of an AB, J_{AB} = 15 Hz), 2.90 (1H, B part of an AB, J_{AB} = 15.0 Hz), 2.55 (3H, s), 1.65 (3H, d, ^3J = 7 Hz), 1.12 (3H, t, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.3, 167.8, 136.1, 30.3, 128.2, 126.8, 83.8, 79.3, 61.5, 39.7, 15.1, 14.4, 14.1. Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.58; H, 6.57; N, 4.72

***syn*-4-Benzyl-4-ethoxycarbonyl-5-methyl-2-methylthio-Δ^2-oxazoline (3d-*syn*)** Colorless oil (75%). IR (film) ν 1740, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (5H, m), 4.65 (1H, q, ^3J = 7 Hz), 4.15 (2H, m), 4.15 (2H, m), 3.27 (1H, A part of an AB, J_{AB} = 15 Hz), 3.06 (1H, B part of an AB, J_{AB} = 15 Hz), 2.47 (3H, s), 1.55 (3H, d, ^3J = 7 Hz), 1.25 (3H, t, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.3, 167.6, 135.6, 130.1, 128.1, 126.9, 88.7, 77.3, 61.6, 43.7, 16.6, 14.5, 14.3. Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.60; H, 6.55; N, 4.70.

***syn*-4-Benzyl-4-ethoxycarbonyl-5-phenyl-2-methylthio-Δ^2-oxazoline (3e-*syn*)**: Colorless oil (65%). IR (film) ν 1740, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (10H, m), 5.80 (1H, s), 4.18 (2H, m), 2.60 (3H, s), 2.56 (1H, A part of an AB, J_{AB} = 15.0 Hz), 2.45 (1H, B part of an AB, J_{AB} = 15.0 Hz), 1.19 (3H, t, ^3J = 7 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.98, 166.78, 135.93, 135.17, 130.16, 128.53, 128.34, 127.77, 126.60, 126.51, 81.23, 77.27, 61.63, 42.31, 14.42, 14.03. Anal. Calcd. for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.67; H, 5.78; N, 3.90.

Synthesis of 4-Ethoxycarbonyl-4,5-dimethyl-2-methylthio-Δ^2-oxazolines 3a. A solution of **2a** (**2a-*anti*** : **2a-*syn*** = 20 : 80) (132 mg, 0.5 mmol) in $CHCl_3$ (1.0 mL) was stirred at 25°C for 48 h. The solvent was eliminated under reduced pressure and the residue was purified by column chromatography (hexane : ethyl acetate, 80 : 20).

***anti*-Ethoxycarbonyl-4,5-dimethyl-2-methylthio-Δ^2-oxazoline (3a-*anti*).** Colorless oil (20%). IR (film) ν 1745, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (1H, q, ^{3}J = 7 Hz), 4.23 (2H, m), 2.47 (3H, s), 1.39 (3H, d, ^{3}J = 7 Hz), 1.37 (3H, s), 1.30 (3H, t, ^{3}J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.1, 167.5, 86.5, 76.4 , 61.3, 24.8, 16.1, 14.2, 13.8.

***syn*-Ethoxycarbonyl-4,5-dimethyl-2-methylthio-Δ^2-oxazoline (3a-*syn*).** Colorless oil (80%). IR (film) ν 1745, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (1H, q, ^{3}J = 7 Hz), 4.23 (2H, m), 2.50 (3H, s), 1.53 (3H, s), 1.39 (3H, d, ^{3}J = 7 Hz), 1.30 (3H, t, ^{3}J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.4, 167.0, 82.8, 75.2, 61.6, 19.4, 15.1, 14.1, 13.9. Anal. Calcd. for $C_9H_{15}NO_3S$: C, 49.75; H, 6.96; N, 6.45. Found: C, 49.84; H, 6.87; N, 6.58.

Synthesis of β-Hydroxy-α-amino esters 4. General Procedure. To a well stirred solution of alcohols **2a** or oxazolines **3d** (0.75 mmol) in HCO_2H (1.14 mL) at 0°C, 30% H_2O_2 (4.85 mmol, 0.49 mL) and p-toluenesulphonic acid (5 mg) was successively added . The reaction mixture was slowly warmed up to 10°C over 4 h and was stirred at room temperature for 20 h. The solvent was eliminated under reduced pressure. H_2O (3.5 mL) was added and the solution evaporated to dryness. The residue was suspended in H_2O (7.0 mL) at 0°C and neutralized with 30% aqueous NH_3 solution. The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (3 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a crude reaction product which was purified by column chromatography (hexane : ethyl acetate, 50 : 50).

***anti*-Ethyl 2-(1-Hydroxyethyl)alaninate (4a-*anti*).** Colorless oil (15%). IR (film) ν 3300, 1745; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (1H, q, ^{3}J = 7 Hz), 4.20 (2H, m), 1.55 (3H, s, 1.40 (3H, d, ^{3}J = 7 Hz), 1.30 (3H, t, ^{3}J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 81.4, 64.9, 62.3, 23.5, 16.0, 14.2.

***syn*-Ethyl 2-(1-Hydroxyethyl)alaninate (4a-*syn*).** Colorless oil (75%). IR (film) ν 3300, 1745; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (1H, q, ^{3}J = 7 Hz), 4.20 (2H, m), 1.55 (3H, s), 1.42 (3H, d, ^{3}J = 7 Hz), 1.28 (3H, t, ^{3}J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.4, 77.8, 63.4, 62.4, 19.7, 15.3, 14.1. Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.07; H, 9.29; N, 8.73.

***anti*-2-(1-Hydroxyethyl)phenylalaninate (4d-*anti*).** Colorless oil (10%). IR (film) ν 3300, 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (5H, m), 5.56 (1H, q, ^{3}J = 7 Hz), 4.20 (2H, m), 3.14 (1H, A part of an AB, J_{AB} = 14 Hz), 2.78 (1H, B part of an AB, J_{AB} = 14 Hz), 1.46 (3H, d, ^{3}J = 7 Hz), 1.20 (3H, t, ^{3}J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 134.3, 128.5, 127.8, 127.3, 78.2, 67.4, 61.5, 41.4, 29.9, 13.9, 13.5.

***syn*-2-(1-Hydroxyethyl)phenylalaninate (4d-*syn*)**. Colorless oil (75%). IR (film) ν 3300, 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (5H, m), 4.87 (1H, q, ^{3}J = 7 Hz), 4.20 (2H, m), 3.27 (1H, A part of an AB, J_{AB} = 14 Hz), 2.98 (1H, B part of an AB, J_{AB} = 14 Hz), 1.66 (3H, d, ^{3}J = 7 Hz), 1.31 (3H, t, ^{3}J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2, 133.8, 129.8, 129.5, 128.9, 78.4, 65.5, 62.3, 38.8, 29.7, 15.1, 13.9. Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.69; H, 8.12; N, 5.83

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