Tetrahedron Vol. 49, No. 2, pp. 497-506, 1993
Printed in Great Britain

0040-4020/93 $5.00+.00

Stereospecific Synthesis of N-[Bis(methylthio)methylene]-α,β- Didehydroamino Acid Methyl Esters, New Synthons in the Synthesis of α-Amino Acids

Carlos Cativiela*, Maria D. Diaz de Villegas

Instituto de Ciencia de Materiales de Aragón. Departamento de Química Orgánica, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain.

(*Received in UK* 20 *October* 1992)

key words: Stereospecific dehydration, stereoisomers, didehydroamino acids, amino acids, E-Z isomerization

***ABSTRACT**: N-[Bis(methylthio)methylene]-α,β-didehydroamino acid methyl esters **4a-c** have been prepared with total geometric selectivity from easily accesible β-hydroxyamino acids through N-[bis(methylthio)methylene]-β-hydroxyamino acid methyl esters **3a-c** as intermediates. The (E)-isomers can be easily converted into the corresponding (Z)-isomers in the presence of a catalytic amount of titanium (IV) chloride.*

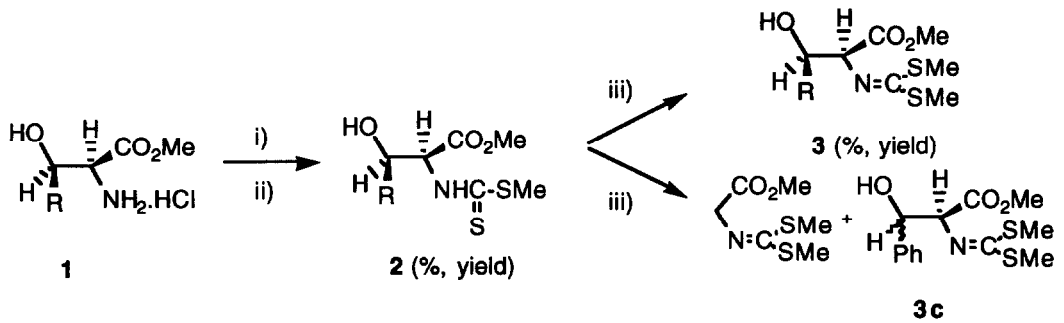
Didehydroamino acid derivatives are an important class of compounds which include natural products, biosynthetic intermediates, substructural units in didehydropeptides and starting materials for the synthesis of uncommon or natural optically-active amino acids.[1]

Stable derivatives of 2-aminoacrylic acid are known to undergo a variety of reactions to give α-amino acids, but the final deprotection of the amino group is sometimes troublesome. Hydrolysis of the acyl group in N-acyl derivatives, for example, requires prolonged heating in concentrated acids[2] or alkali[3], which is not always compatible with selective deprotection or sensitive compounds. Methyl 2-(benzylideneamino)acrylate, which has proved to be a useful intermediate for the preparation of α-amino acids[4,5] and can be deprotected selectively under mild conditions, is rather unstable and undergoes extensive dimerization in solution at room temperature.[5] Alkyl 2-(diphenylmethyleneamino)acrylates can be deprotected selectively under mild conditions and are described[6] as stable compounds both in their pure form and in solution. Nevertheless, in some experimental conditions dimerization of the diphenylmethyleneamino group competes with the desired reaction.[7]

In the course of our research into the asymmetric synthesis of α-amino acids we have developed a stereospecific synthesis of N-[bis(methylthio)methylene]-α,β-didehydroamino acid methyl esters **4a-e,** which are stable derivatives of α,β-didehydroamino acids, can be easily hydrolyzed and are stable under a variety of experimental conditions. These compounds are also new synthons in the synthesis of α-amino acid derivatives and can act as dipolarophiles in 1,3-dipolar cycloadditions in the synthesis of 1-aminocyclopropanecarboxylic acid (ACC).[8]

Construction of the α,β carbon-carbon double bond in N-diphenylmethylene α,β-didehydroamino acid derivatives has been achieved by a variety of routes including the Wittig olefination[9] , the Mannich reaction[6], and β-elimination processes.[10] In our case the β-elimination process proved to be an effective route to N-[bis(methylthio)methylene]-α,β-didehydroamino acid methyl esters **4a-c**, as the preparation of the α-ketoamino acid derivative necesary for the Wittig olefination could not be achieved, and methyl N-[bis(methylthio)methylene]glycinate did not react with trimethyl(methylene)ammonium iodide in the conditions we tested.

3-Hydroxy-2-methylthiocarbamoyl esters **2a,c** were readily prepared from the methyl ester hydrochloride of the corresponding amino acid, carbon disulphide and methyl iodide, and the subsequent reaction with methyl iodide in the presence of potassium carbonate afforded N-[bis(methylthio) methylene]amino methyl esters **3a,b**. However the reaction was unsatisfactory in the case of N-[bis(methylthio)methylene]phenylserine methyl ester **3c**, as potassium carbonate in acetone is a sufficiently strong base to promote a retro-aldol reaction, and in the reaction conditions a mixture of benzaldehyde, methyl N-[bis(methylthio)methylene]glycinate and *erythro* and *threo* N-[bis(methylthio)methylene]phenylserine methyl ester **3c** was obtained (Scheme 1).



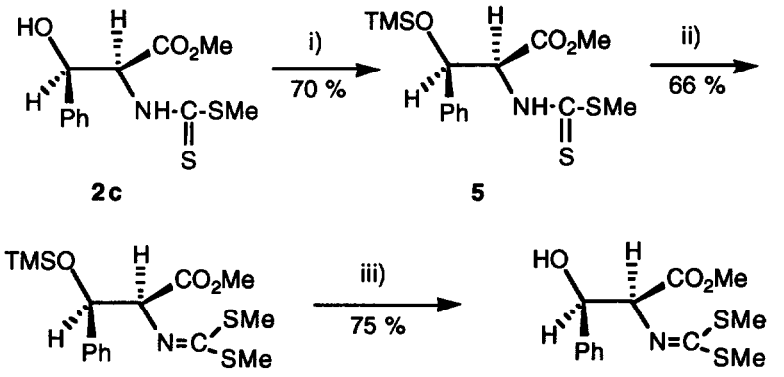
1 **2** (%, yield) **3c**

i) CS_2, Et_3N, $CHCl_3$; i) MeI; iii) MeI, K_2CO_3, acetone

R = H	**1a**	**2a** (70)	**3a** (65)
R = Me	**1b**	**2b** (84)	**3b** (60)
R = Ph	**1c**	**2c** (88)	

Scheme 1

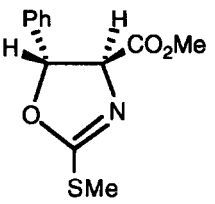
In order to obtain **3c** as the *threo* stereoisomer it was necessary to protect the alcohol in the form of trimethylsilyl ether to afford compound **5**, which readily reacted with methyl iodide in the presence of potassium carbonate to afford O-trimethylsilyl-N-[bis(methylthio)methylene] phenylserine methyl ester **6**. Compound **6** was converted into **3c** by using Dowex-50W8X in methanol as a desilylating agent (Scheme 2).



i) TMSCl/imidazole, DMF; ii) MeI, K_2CO_3, acetone; iii) DOWEX50W8X, MeOH

Scheme 2

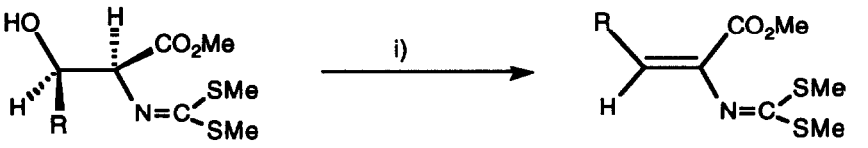
It is important to note that an attempted desilylation of compound **6** to form **3c** using tetra n-butylammonium fluoride under the usual conditions was unsuccessful due to the fact that fluoride ion in THF is a sufficiently strong base to promote the retro-aldol reaction, and desilylation in some usual acidic media (such as citric acid) led to cyclization of **3c** to the heterocyclic compound **7** (Figure 1).



7

Figure 1

N-[Bis(methylthio)methylene]amino esters **3a-c** can be stereoselectively dehydrated by using the DiPCD/copper(I) chloride system[10] to afford (E)-N-[bis(methylthio)methylene]-α,β-didehydroamino esters **4a,c** in satisfactory yields (Scheme 3).



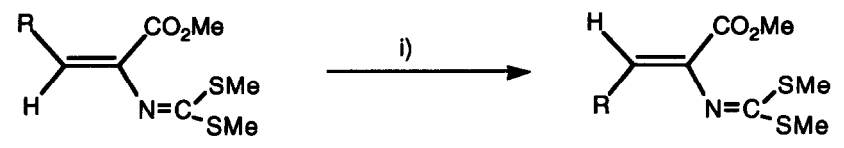
3 **4** (% yield)

i) DiPDC/CuCl, dry CH_2Cl_2

R = H	**3a**	**4a** (75)
R = Me	**3b**	**4b** (65)
R = Ph	**3c**	**4c** (60)

Scheme 3

Preparation of (Z)-isomers **4d,e** by this route would involve the use of expensive or unavailable *erythro* amino acids but this drawback can be easily overcome as (E)-isomers were isomerized under very mild conditions to the thermodynamically more stable (Z)-isomers. In this way, compounds **4b** and **4c**, after standing overnight in a dichloromethane solution in the presence of a catalytic amount of titanium (IV) chloride, afforded **4d** and **4e** in nearly quantitative yields (Scheme 4). To the best of our knowledge, it is the first time that this system has been used to promote olefin isomerization.



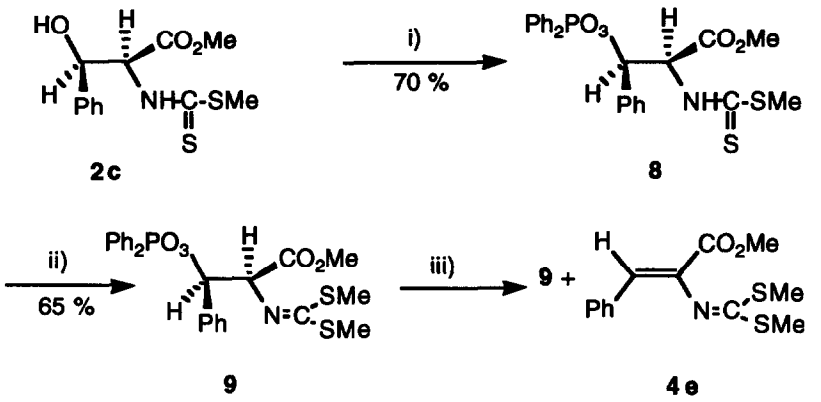
4 **4** (% yield)

i) $TiCl_4$, dry CH_2Cl_2

R = Me	**4b**	**4d** (90)
R = Ph	**4c**	**4e** (95)

Scheme 4

An attempt to obtain (E)-methyl N-[bis(methylthio)methylene]-2-aminocinnamate **4c** from **2c** through the triphenylphosphorus-protected phosphonophenylserine derivative **8** using Paquet procedure[11] was unsuccessful. Although the phosphorilated compound **8** was easily methylated to afford **9** in high yields, conversion into the corresponding didehydroamino acid derivative by treatment with an organic base occurred very slowly even in refluxing toluene, and after 15 days only a 50% conversion was achieved to afford the olefin of (Z)-configuration (Scheme 5).



i) Diphenylphosphochloridate, ether; ii) MeI, K_2CO_3, acetone; iii) Et_3N, toluene

Scheme 5

The geometry of the products was determined by considering their NMR spectral data. The isomer in which the olefinic proton resonates at the lower field in the ^{1}H-NMR spectrum should be the (Z)-isomer based upon the application of substituent shielding constants.[12] Confirmation was obtained from NOE experiments involving irradiation of the carbomethoxyl protons. In each pair of isomers of **4** the isomer in which the olefinic proton resonated downfield exhibited greater NOE enhancement (indicating that the protons are spatially closer together) which permitted firm identification of the (Z)-isomers. Measurement of the long range ^{13}C-^{1}H coupling constants between the olefinic proton and the carboxylic carbon in the fully-coupled ^{13}C-NMR spectra was not possible due to the coupling of the carboxylic carbon with the methylthio groups, which complicated the spectra.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer. ^{1}H-NMR spectra at 300 MHz and ^{13}C-NMR spectra at 75 MHz were recorded on a Varian Unity-300 in $CDCl_3$ solution. Mass spectra (MS) were determined on a high-resolution VG-AutoSpec spectrometer.

All reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Diisopropylcarbodiimide (DiPCD), copper (I) chloride, titanium (IV) chloride 1.0 M solution in dichloromethane and diphenylphosphochloridate were purchased from Aldrich Chemical Co. TLC was performed on Merk precoated silica-gel plates. Gravity column chromatography was performed using 70-230 mesh (Merk) silica-gel and flash chromatography was performed using 230-400 mesh (Merk) silica-gel.

α-Amino acid methyl ester hydrochlorides 1b,c:
The compounds were prepared from the commercial d,l-amino acids which were esterified by conventional procedures

Methyl 3-hydroxy-2-methylthiocarbamoylpropanoate (2a):
To a solution of serine methyl ester hydrochloride **1a** (9.33 g, 60 mmol) and carbon disulphide (4.8 g, 63 mmol) in chloroform (60 mL) was added dropwise Et_3N (12.72 g, 126 mmol) with stirring at room temperature. The solution was stirred for 1 h at room temperature and MeI (9.94 g, 70 mmol) was added, then the resulting solution was refluxed for 1h protected from light. After cooling the solution was washed with water (2 x 40 mL) and evaporated to dryness in vacuo. The residue was dissolved in Et_2O (40 mL) and the resulting solution was washed with water (2 x 25 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to give **2a** as a pale yellow oil; yield: 8.78 g (70%). IR (neat): ν = 3310, 1740, 1508 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.55 (s, 3H), 3.74 (s, 3H), 4.02 (d, 2H, J = 3.3 Hz), 5.22-5.25 (m, 1H), 8.20 (brs, 1H). ^{13}C NMR ($CDCl_3$): δ = 18.1, 52.8, 60.7, 61.7, 170.1, 200.3. HRMS (EI): m/z = 209.0180 (M^+, calc for $C_6H_{11}NO_3S_2$ 209.0180).

Methyl *threo*-3-hydroxy-2-methylthiocarbamoylbutanoate (2b):
To a solution of threonine methyl ester hydrochloride **1b** (10.17 g, 60 mmol) and carbon disulphide (4.8 g, 63 mmol) in chloroform (60 mL) was added dropwise Et_3N (12.72 g, 126 mmol) with stirring at room temperature. The solution was stirred for 1 h at room temperature and MeI (9.94 g, 70 mmol) was added, then the resulting solution was refluxed for 1h protected from light. After cooling the solution was washed with water (2 x 40 mL) and evaporated to dryness in vacuo. The residue was dissolved in Et_2O (40 mL) and the resulting solution was washed with water (2 x 25 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to give **2b** as a pale yellow oil; yield: 11.2 g (84%). IR (neat): ν = 3302, 1741, 1498 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.29 (d, 3H, J = 6.6 Hz), 2.66 (s, 3H), 3.80 (s, 3H), 4.45 (dq, 1H, J = 2.1, 6.6 Hz), 5.39 (dd, 1H, J = 2.1, 8.4 Hz), 7.74 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$): δ = 18.4, 20.1, 52.8, 63.5, 68.1, 170.6, 201.7. HRMS (EI): m/z = 223.0340 (M^+, calc for $C_7H_{13}NO_3S_2$ 223.0332).

Methyl *threo*-3-hydroxy-2-methylthiocarbamoyl-3-phenylpropanoate (2c):
To a solution of *threo*-phenylserine methyl ester hydrochloride **1c** (13.89 g, 60 mmol) and carbon disulphide (4.8 g, 63 mmol) in chloroform (60 mL) was added dropwise Et_3N (12.72 g, 126 mmol) with stirring at room temperature. The solution was stirred for 1 h at room temperature and MeI (9.94 g, 70 mmol) was added, then the resulting solution was refluxed for 1h protected from light. After cooling the solution was washed with water (2 x 40 mL) and evaporated to dryness in vacuo. The residue was dissolved in Et_2O (40 mL) and the resulting solution was washed with water (2 x 25 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to give **2c** as a pale yellow oil; yield: 15 g (88%). IR (neat): ν = 3310, 1740, 1493 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.52 (s, 3H), 3.72 (s, 3H), 5.35 (d, 1H, J = 3.0 Hz), 5.55 (dd, 1H, J = 3.0, 7.8 Hz), 7.25-7.35 (m, 5H), 7.83 (d, 1H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ = 18.1, 52.7, 64.1, 73.0, 125.7, 128.2, 128.4, 139.1, 169.9, 200.9. HRMS (EI): m/z = 237.0457 (M^+- CH_3SH, calc for $C_{11}H_{11}NO_3S$ 237.0459).

Methyl N-[bis(methylthio)methylene]serinate (3a):
To a solution methyl 3-hydroxy-2-methylthiocarbamoylpropanoate **(2a)** (10.45 g, 50 mmol) in acetone (30 mL) was added MeI (8.52 g, 60 mmol) and anhydrous potassium carbonate (9.66 g, 70 mmol). The resulting mixture was refluxed for 1h protected from light. After cooling the mixture was filtered and evaporated to dryness in vacuo. The residue was dissolved in Et_2O (30 mL) and the resulting solution was washed with water (2 x 20 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to give **3a** as a pale yellow oil; yield: 7.25 g (65%). IR (neat): ν = 3486, 1732, 1574 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.41 (s, 3H), 2.56 (s, 3H), 3.73 (s, 3H), 3.91 (d, 2H, J = 4.8 Hz), 4.48 (t, 1H, J = 4.8 Hz). ^{13}C NMR ($CDCl_3$): δ = 14.8, 15.0, 52.2, 64.1, 65.7, 166.5, 170.6. HRMS (EI): m/z = 223.0343 (M^+, calc for $C_7H_{13}NO_3S_2$ 223.0332).

Methyl N-[bis(methylthio)methylene]threoninate (3b):
To a solution methyl *threo*-3-hydroxy-2-methylthiocarbamoylbutanoate **(2b)** (11.85 g, 50 mmol) in acetone (30 mL) was added MeI (8.52 g, 60 mmol) and anhydrous potassium carbonate (9.66 g, 70 mmol) The resulting mixture was refluxed for 1h protected from light. After cooling the mixture was filtered and evaporated to dryness in vacuo. The residue was dissolved in Et_2O (30 mL) and the resulting solution was washed with water (2 x 20 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to give **3b** as a pale yellow oil; yield: 7.11 g (60%). IR (neat): ν = 3506, 1737, 1681 cm^{-1}. ^1H NMR ($CDCl_3$)· δ = 1.15 (d, 3H, J = 6.6 Hz), 2.40 (s, 3H), 2.52 (s, 3H), 2.84 (d, 1H, J = 7.8 Hz), 3.69 (s, 3H), 4.13 (d, 1H, J = 3.9 Hz), 4.16-4.26 (m, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.8, 14.9, 20.3, 52.1, 69.0, 69.5, 166.2, 170.4. HRMS (EI): m/z = 190.0550 (M^+- SCH_3, calc for $C_7H_{12}NO_3S$ 190.0537).

Methyl *threo*-3-trimethylsilyloxy-2-methylthiocarbamoyl-3-phenylpropanoate (5)
To a solution of methyl *threo*-3-hydroxy-2-methylthiocarbamoyl-3-phenylpropanoate **(2c)** (14.25 g, 50 mmol) in DMF (30 mL) was added imidazole (9.04 g, 135 mmol) and trimethylsilyl chloride (7.23 g, 67 mmol) with stirring at room temperature. The solution was stirred for 20 h at room temperature and water was added (60 mL), then the resulting solution was extracted with hexane (3 x 60 mL). The organic extract was dried ($MgSO_4$) and evaporated to dryness in vacuo. Flash chromatography (hexane/EtOAc 8:2) gave the product **5** as a yellow oil; yield: 12.5 g (70%). IR (neat): ν = 3378, 1736, 1486 cm^{-1}. ^1H NMR ($CDCl_3$): δ = -0.02 (s, 9H), 2.46 (s, 3H), 3.73 (s, 3H), 5.33 (d, 1H, J = 2.1 Hz), 5.43 (dd, 1H, J = 2.1, 8.1 Hz), 7.15-7.30 (m, 5H), 7.47 (d, 1H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$): δ = -0.3, 18.1, 52.5, 65.2, 73.9, 125.6, 127.9, 128.3, 139.8, 169.4, 200.6. HRMS (FAB): m/z = 358.0976 (MH^+, calc for $C_{15}H_{24}NO_3SiS_2$ 358.0966).

Methyl *threo*-3-trimethylsilyloxy-2-N-[bis(methylthio)methylene]amino-3-phenylpropanoate (6):
To a solution methyl *threo*-3-trimethylsilyloxy-2-methylthiocarbamoyl-3-phenylpropanoate **(5)** (17.85 g, 50 mmol) in acetone (30 mL) was added MeI (8.52 g, 60 mmol) and anhydrous potassium carbonate (9.66 g, 70 mmol) The resulting mixture was refluxed for 1h protected from light. After cooling the mixture was filtered and evaporated to dryness in vacuo. The residue was dissolved in Et_2O (30 mL) and the resulting solution was washed with water (2 x 20 mL), dried

($MgSO_4$), and evaporated to dryness in vacuo to give **6** as a pale yellow oil; yield: 12.24 g (66%). IR (neat): ν = 1742, 1563 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.00 (s, 9H), 2.40 (s, 3H), 2.46 (s, 3H), 3.49 (s, 3H), 4.59 (d, 1H, J = 6.6 Hz), 5.10 (d, 1H, J = 6.6 Hz), 7.20-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ = 0.0, 14.8, 15.5, 51.7, 73.1, 76.7, 127.0, 127.6, 127.8, 141.3, 163.6, 170.2. HRMS (FAB): m/z = 372.1112 (MH^+, calc for $C_{16}H_{26}NO_3SiS_2$ 372.1123).

Methyl N-[bis(methylthio)methylene]phenylserinate (3c):
To a solution methyl *threo*-3-trimethylsilyloxy-2-N-[bis(methylthio)methylene]amino-3-phenylpropanoate **(6)** (18.55 g, 50 mmol) in methanol (150 mL) was added Dowex-50 (5 g) in moist form.[13] The resulting suspension was stirred for 2h at room temperature. After completion the mixture was filtered, diluted with methylene chloride (300 mL), washed with sat. aq $NaHCO_3$ solution (2 x 100 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to give **3c** as a pale yellow oil; yield: 11.21 g (75%). IR (neat): ν = 3346, 1740, 1598 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3H), 2.45 (s, 3H), 3.55 (d, 1H, J = 7.2 Hz), 3.62 (s, 3H), 4.50 (d, 1H, J = 3.9 Hz), 5.22 (dd, 1H, J = 3.9, 7.2 Hz), 7.20-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ = 15.0, 15.2, 52.2, 70.4, 74.8, 126.1, 127.6, 128.1, 141.0, 165.4, 170.0. HRMS (EI): m/z = 299.0131 (M^+, calc for $C_{13}H_{17}NO_3S_2$ 298.9657).

Methyl N-[bis(methylthio)methylene]-2-aminoacrylate (4a).
To a solution of methyl N-[bis(methylthio)methylene]serinate **(3a)** (11.15 g, 50 mmol) in dry CH_2Cl_2 (150 mL) was added 1,2-diisopropylcarbodiimide (12.62 g, 100 mmol) and CuCl (1.48 g, 15 mmol) The resulting mixture was stirred for 20h protected from light. After completion the mixture was filtered, washed with water (3 x 100 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo. Flash column chromatography (silica-gel; hexane/EtOAc, 90:10) gave **4a** as a pale yellow oil; yield: 7.68 g (75%). IR (neat): ν = 1735, 1569 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.50 (s, 6H), 3.78 (s, 3H), 5.06 (s, 1H), 5.78 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.8, 52.2, 110.6, 144,4, 163.9, 165.9. HRMS (EI): m/z = 205.0230 (M^+, calc for $C_7H_{11}NO_2S_2$ 205.1231).

(E)-Methyl N-[bis(methylthio)methylene]-2-aminocrotonate (4b).
To a solution of methyl N-[bis(methylthio)methylene]threoninate **(3b)** (11.85 g, 50 mmol) in dry CH_2Cl_2 (150 mL) was added 1,2-diisopropylcarbodiimide (12.62 g, 100 mmol) and CuCl (1.48 g, 15 mmol) The resulting mixture was stirred for 20h protected from light. After completion the mixture was filtered, washed with water (3 x 100 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo. Flash column chromatography (silica-gel; hexane/EtOAc, 90:10) gave **4b** as a pale yellow oil; yield: 7.11 g (65%). IR (neat): ν =1719, 1566 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.03 (d, 3H, J = 7.5 Hz), 2.47 (s, 6H), 3.72 (s, 3H), 5.57 (c, 1H, J = 7.5 Hz) ^{13}C NMR ($CDCl_3$): δ = 13.8, 14.8, 51.5, 125.6, 138,0, 164.3, 164.8. HRMS (EI): m/z = 219.0382 (M^+, calc for $C_8H_{13}NO_2S_2$ 219.0387).

(E)-Methyl N-[bis(methylthio)methylene]-2-aminocinnamate (4c).
To a solution of methyl *threo*-N-[bis(methylthio)methylene]phenylserinate **(3c)** (14.95 g, 50 mmol) in dry CH_2Cl_2 (150 mL) was added 1,2-diisopropylcarbodiimide (12.62 g, 100 mmol) and CuCl (1.48 g, 15 mmol) The resulting mixture was stirred for 20h protected from light. After completion the mixture was filtered, washed with water (3 x 100 mL), dried ($MgSO_4$), and evaporated to

dryness in vacuo. Flash column chromatography (silica-gel; hexane/EtOAc, 90:10) gave **4c** as a pale yellow oil; yield: 8.43 g (60%). IR (neat): ν = 1724, 1560 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.52 (s, 6H), 3.70 (s, 3H), 6.36 (s, 1H), 7.20-7.40(m, 5H). ^{13}C NMR ($CDCl_3$): δ = 15.0, 51.8, 123.6, 127.4, 128.0, 128.4, 134.7, 138.6, 165.1, 166.3. HRMS (EI): m/z = 281.0556 (M^+, calc for $C_{13}H_{15}NO_2S_2$ 281.0544).

(Z)-Methyl N-[bis(methylthio)methylene]-2-aminocrotonate (4d).
To a solution of (E) methyl N-[bis(methylthio)methylene]-2-aminocrotonate **(4b)** (2.19 g, 10 mmol) in dry CH_2Cl_2 (20 mL) was added 1.0 M solution of titanium (IV) chloride in CH_2Cl_2 (2 mL, 2 mmol). The resulting mixture was stirred for 24h at room temperature. After completion the solution was quenched with 10 mL of 1N HCl. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to afford **4d** as a pale yellow oil; yield: 1.97 g (90%). IR (neat): ν = 1721, 1570 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.58 (d, 3H, J = 7.2 Hz), 2.45 (s, 6H), 3.69 (s, 3H), 6.25 (c, 1H, J = 7.2 Hz) ^{13}C NMR ($CDCl_3$): δ = 12.5, 14.7, 51.8, 129.9, 138,4, 163.9, 165.1. HRMS (EI): m/z = 219.0382 (M^+, calc for $C_8H_{13}NO_2S_2$ 219.0387).

(Z)-Methyl N-[bis(methylthio)methylene]-2-aminocinnamate (4e).
To a solution of (E) methyl N-[bis(methylthio)methylene]-2-aminocinnamate **(4c)** (2.81 g, 10 mmol) in dry CH_2Cl_2 (20 mL) was added 1.0 M solution of titanium (IV) chloride in CH_2Cl_2 (2 mL, 2 mmol). The resulting mixture was stirred for 24h at room temperature. After completion the solution was quenched with 10 mL of 1N HCl. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to afford **4e** as a white solid, m. p. 85 °C; yield: 2.67 g (95%). IR (nujol): ν = 1708, 1561 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.53 (s, 6H), 3.81 (s, 3H), 7.06 (s, 1H), 7.20-7.35 (m, 3H), 7.45-7.50 (M, 2H). ^{13}C NMR ($CDCl_3$): δ = 14.9, 52.3, 123.5, 128.3, 129.6, 134.4, 136.0, 164.5, 166.6. HRMS (EI): m/z = 281.0537 (M^+, calc for $C_{13}H_{15}NO_2S_2$ 281.0554).

Methyl *threo*-O-diphenylphosphoryl-3-hydroxy-2-methylthiocarbamoyl-3-phenylpropanoate (8):
To a stirred solution of methyl *threo*-3-hydroxy-2-methylthiocarbamoyl-3-phenylpropanoate **(2c)** (2.40 g, 8.4 mmol) in anhydrous ether (7.5 mL) was added diphenylphosphochloridate (5.68 g, 21.1 mmol) and pyridine (1.67 g, 21.1 mmol) The resulting mixture was stirred for 24h at room temperature and a white solid appeared. The solution was filtered, washed thoroughly with hexane, washed with water and dried to afford **8** as a white solid, m. p. 112 °C; yield: 3 g (70%). IR (nujol): ν = 3193, 1761, 1753 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.54 (s, 3H), 3.58 (s, 3H), 5.78 (dd, 1H, J = 4.5, J = 7.8 Hz), 6.06 (dd, 1H, J = 4.5, J = 8.4 Hz), 6.98-7.34 (m, 15H), 7.84 (d, 1H, J = 7.8 Hz).^{13}C NMR ($CDCl_3$): δ = 18.2, 52.8, 63.4(d), 79.9(d), 119.8(d), 119.9(d), 125.4(d), 125.5(d), 126.6, 128.5, 129.2, 129.6, 129.8, 134.6(d), 150.1(d), 150.2(d), 168.1, 201.4. ^{31}P NMR ($CDCl_3$): δ = -11.9. HRMS (FAB): m/z = 518.0848 (MH^+, calc for $C_{21}H_{25}NO_6PS_2$ 518.0860).

Methyl *threo*-O-diphenylphosphoryl-3-hydroxy-2-N-[bis(methylthio)methylene]-2-amino-3-phenylpropanoate (9):

To a solution of methyl *threo*-O-diphenylphosphoryl-3-hydroxy-2-methylthiocarbamoyl-3-phenylpropanoate **(8)** (2.58 g, 5 mmol) in acetone (10 mL) was added MeI (852 mg, 6 mmol) and anhydrous potassium carbonate (966 mg, 7 mmol). The resulting mixture was refluxed for 1h protected from light. After cooling the mixture was filtered and evaporated to dryness in vacuo. The residue was dissolved in Et_2O (10 mL) and the resulting solution was washed with water (2 x 10 mL), dried ($MgSO_4$), and evaporated to dryness in vacuo to give **6** as a white oil; yield: 1.72 g (65%). IR (neat): ν = 1744, 1588 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.38 (s, 3H), 2.45 (s, 3H), 3.46 (s, 3H), 4.84 (d, 1H, J = 6.6 Hz), 6.10 (dd, 1H, J = 6.6 , J = 8.1 Hz), 6.90-7.40 (m, 15H). ^{13}C NMR ($CDCl_3$): δ = 14.7, 14.9, 51.9, 70.1(d), 82.3(d), 119.7(d), 119.8(d), 124.8(d), 124.9(d), 127.4, 128.0, 128.7, 129.3, 129.4, 135.8, 150.1(d), 150.4(d),165.8, 167.9. ^{31}P NMR ($CDCl_3$): δ = -12.4. HRMS (FAB): m/z = 532.1009 (MH^+, calc for $C_{25}H_{27}NO_6PS_2$ 532.1017).

Acknowledgement: This work was made possible by the generous financial support of the Dirección General de Investigación Científica y Técnica (Project PB91-0696).

REFERENCES

1. (a) Noda, K.; Shimohigashi, Y.; Izumya, N.; in *The Peptides*, Vol. 5, Academic Press, New York, 1983, p. 285. (b) Stammer, C.H.; in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins* Vol. 6, Marcel Dekker Inc., New York, 1983, p. 285. (c) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159. (d) Martell, A.E. *Acc. Chem. Res.* **1989**, *22*, 115.
2. (a) Asquith, R.S.; Yeung, K.W., Otterburn, M.S. *Tetrahedron Lett.* **1977**, *33*, 1633. (b) Bergman, E.D.; Chun-Hsu, L. *Synthesis* **1973**, 44. (c) Behringer, H., Fakler, E. *Liebigs Ann. Chem.* **1949**, *564*, 73.
3. Bregovec, I.; Jakorcic, T. *Monatsh. Chem.* **1972**, *103*, 288.
4. Ohler, E.; Schmidt, U. *Chem. Ber.* **1979**, *112*, 107
5. Wulf, G.; Bohnke, H. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*. 90.
6. Tarzia, G.; Balsamini, C.; Spadoni, G.; Duranti, E. *Synthesis* **1988**, 514.
7. Balsamini, C.; Tarzia, G.; Spadoni, G.; Salvatori, A.; Staccioli, L. *Org.Prep.Proced.Int.* **1991**, *23*, 122.
8. Buñuel E.; Cativiela, C.; Diaz de Villegas, M.D., Jimenez, A.I. *Synlett* **1992**, 579.
9. O'Donnell, M.J.; Arasappan, A.; Hornback, W.J.; Huffman, J.C. *Tetrahedron Lett*, **1990**, *31*, 157.
10. Balsamini, C.; Duranti, E.; Mariani, L.; Salvatori, A.; Spadoni, G. *Synthesis* **1990**, 779.
11. Paquet, A. *Tetrahedron Lett*, **1990**, *31*, 5269.
12. Matter, U.E.; Pascual, C.; Prest, E.; Pross, A.; Simon, W. ; Sternhell, S. *Tetrahedron* **1969**, *25*, 691.
13. Dowex-50 (fluka) was soaked in 4N HCl overnight and then washed with distilled water until acid-free (tested with $AgNO_3$ solution) and used in moist form.