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Resolution of 2-methoxy-2-(2'-thiazinyl)glycinates

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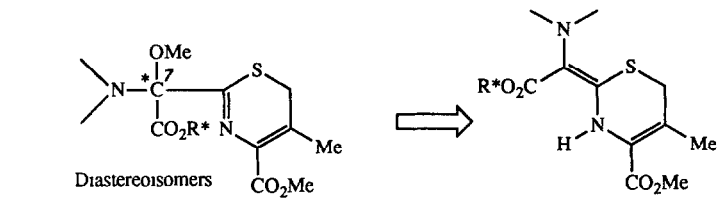
Abstract : The synthesis and the resolution of α-methoxy α-(2'-thiazinyl)glycinate diastereoisomers, using (S)-(-)-ethyl lactate as a resolving reagent, is described The X-ray crystal structure of a pure diastereoisomer is reported These chirally substituted thiazines are key intermediates for multistep syntheses of 7-methoxy cephems

We recently reported[1] different ways for multistep syntheses of cephems, analogues of cephalosporins and cephamycins (7-methoxycephalosporins) The strategies developed were tested on racemic mixtures We wanted to make our syntheses enantioselective in order to approach biologically active compounds sought after as antibiotics or enzyme inhibitors from the β-lactam series

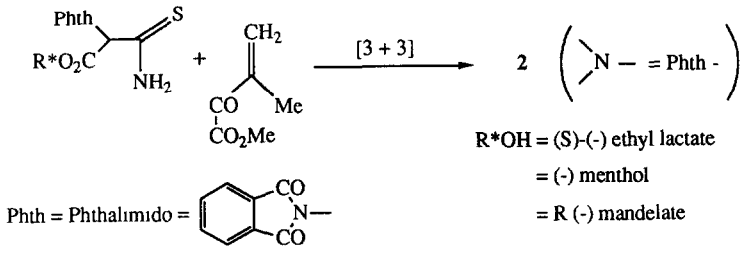
More recently, we published a method giving access to multifunctional carbon chiral precursors derived from α-methoxy-α-cyanoglycinates[2] The synthesis, the resolution and the configuration of the α-methoxy-α-(2'-thiazinyl)glycinates **1** are now described With this new synthesis, the asymmetric centre appears during the regioselective introduction of the required methoxy group (position 7 of the eventual cephem backbone) into the 2'-thiazinylideneglycinate **2**, a reactional intermediate with a high developed structure, containing a chiral auxiliary



Scheme 1

Results and discussion

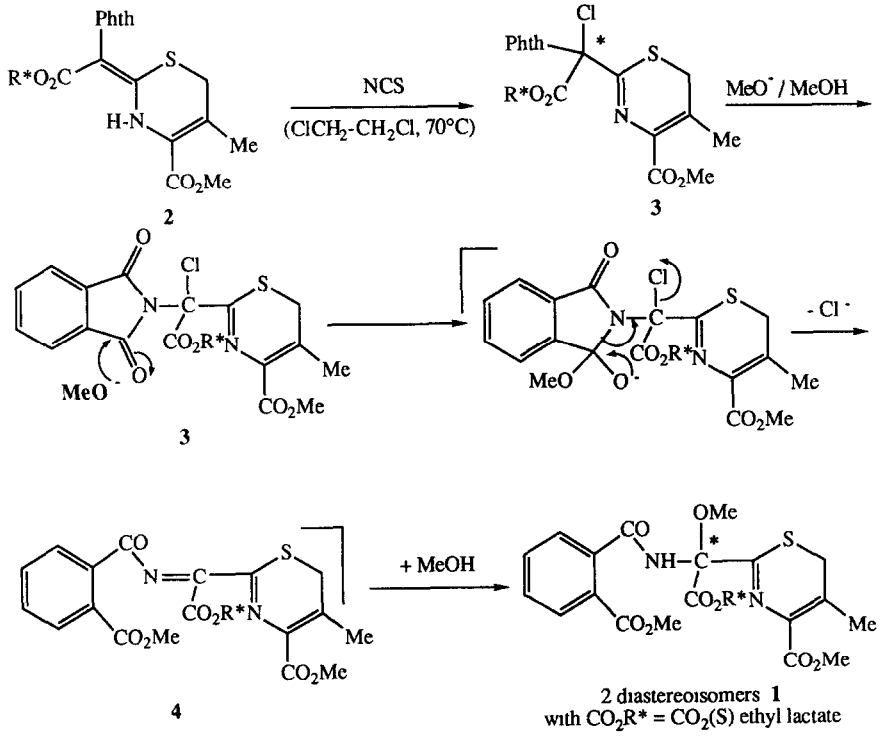
Following our recently described methodology[2], we introduced a chiral auxiliary (R*OH = ethyl lactate, menthol or mandelic alcohol) from the beginning of the synthesis using a N-protected α-cyanoglycinate Addition of hydrogen sulphide to the nitrile group led to the corresponding chiral thioamides The 1,3-thiazinic derivative **2** resulted from a previously tested [3+3] cycloaddition[3] between the optically active thioamide and a vinylic keto-ester (scheme 2)



Scheme 2

Comparison of the results led to the preference for the (S)-(-)-ethyl lactate as the chiral auxiliary Its modest cost allowed us to work on preparative scales In addition the easy interpretation of the ^1H NMR peaks arising from the compounds obtained in the following steps gave the best results for the evaluation of the diastereoisomers ratios

The subsequent reaction of N-chlorosuccinimide on the extracyclic double bond of the thiazine **2** led to the electrophilic addition of a chlorine atom to the enamine system This sought after regioselective reaction introduced a second asymmetric centre However, induction was not observed in the chlorinated compound **3**, but a mixture of diastereoisomers in a ratio of 50/50 The following methoxylation, conforming to the mechanism we already described[3a], reacting by the acylimine intermediate **4**, in any case implies a racemisation of the asymmetric centre

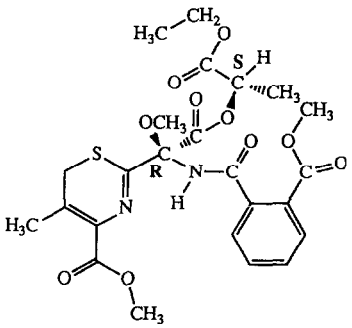


Scheme 3

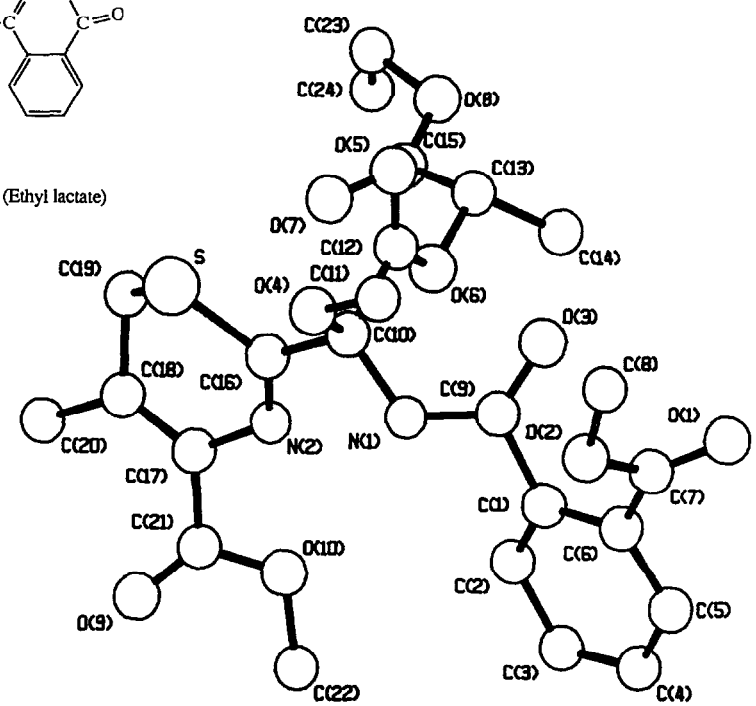
The chlorination of the carbone position 2' was followed by the action of a methanolic solution of lithium methoxide at -70°C Opening of the phthaloyl protection in *ortho*-methoxycarbonylbenzoyl (OMCB) eliminated the chloride anion Finally, the acylimine **4** added methanol giving **1** (scheme 3) To avoid a part of transesterification of the ethyl lactate moiety by methanol, the methoxylation reaction can be carried out using methoxytributyltin (Bu_3SnOMe) instead of lithium methoxide

The ^1H NMR spectrum of the product derived from this reaction clearly showed a splitting of most of the peaks, due to the presence of two diastereoisomers in the approximate ratio 50/50 Although the Rf of the two diastereoisomers **1a** and **1b** were close in TLC, a pure diastereoisomer was isolated by careful chromatography on silica gel They can be resolved by means of HPLC

Absolute configuration was determined from the X-ray structure of the pure diastereoisomer crystallized in diethyl ether The PLUTO diagram is illustrated below



Diastereoisomer Ia . R - S (Ethyl lactate)



PLUTO diagram

Table 1 Fractional Atomic Coordinates($\times 10^4$) and Equivalent Isotropic Thermal Parameters($Å^2 \times 10^3$)

	x	y	z	Ueq
S	1851 6(27)	8664 9(18)	-61 2(7)	54(1)
O(1)	6633(10)	11987(6)	2441(2)	100(5)
O(2)	6850(8)	11888(6)	1623(2)	81(4)
O(3)	4292(7)	10283(4)	1725(2)	60(3)
O(4)	4435(6)	9395(5)	480(2)	51(3)
O(5)	3436(7)	7827(4)	1151(2)	61(3)
O(6)	1598(6)	9023(4)	1423(2)	48(3)
O(7)	-893(11)	7845(9)	1137(3)	161(6)
O(8)	-943(11)	6864(10)	1836(3)	213(7)
O(9)	-1773(9)	12222(5)	-255(2)	87(4)
O(10)	-1018(9)	12295(5)	519(2)	82(4)
N(1)	3251(8)	10834(5)	988(2)	44(3)
N(2)	746(7)	10484(5)	448(2)	41(3)
C(1)	3503(9)	12232(6)	1630(3)	47(4)
C(2)	2152(11)	12805(7)	1519(3)	61(5)
C(3)	1875(13)	13949(8)	1718(3)	77(6)
C(4)	2880(14)	14412(8)	2037(3)	82(6)
C(5)	4289(14)	13838(8)	2153(3)	81(6)
C(6)	4621(12)	12737(7)	1938(3)	63(5)
C(7)	6095(12)	12166(8)	2037(3)	70(5)
C(8)	8266(12)	11151(11)	1679(4)	104(8)
C(9)	3740(9)	11021(6)	1453(3)	46(4)
C(10)	3142(9)	9697(6)	763(2)	39(4)
C(11)	5932(10)	9452(9)	725(3)	71(6)
C(12)	2779(8)	8730(6)	1145(2)	43(4)
C(13)	1058(10)	8177(7)	1770(3)	55(5)
C(14)	634(15)	8827(11)	2244(3)	96(7)
C(15)	-331(14)	7626(10)	1539(4)	115(7)
C(16)	1814(9)	9722(6)	405(2)	39(4)
C(17)	-436(8)	10600(6)	95(2)	42(4)
C(18)	-936(10)	9743(7)	-197(3)	50(4)
C(19)	-231(10)	8563(7)	-136(3)	59(5)
C(20)	-2279(12)	9812(9)	-546(3)	86(6)
C(21)	-1125(10)	11771(7)	86(3)	55(5)
C(22)	-1681(17)	13446(8)	547(4)	116(8)
C(23)	-2048(27)	6074(22)	1617(13)	116(18)
C(24)	-3688(18)	6478(38)	1722(17)	149(23)
C(23a)	-2630(16)	6734(29)	1810(14)	113(21)
C(24a)	-2993(35)	5712(29)	1477(14)	140(22)

Ueq is defined as one third of the trace of the orthogonalised Uij tensor

Table 2 Intramolecular Distances(Å) and Angles(°) with Estimated Standard Deviations in Parentheses

a) Bonds

S-C(16)	1 761(7)	S-C(19)	1 816(9)
O(1)-C(7)	1 209(10)	O(2)-C(7)	1 339(10)
O(2)-C(8)	1 500(13)	O(3)-C(9)	1 225(9)
O(4)-C(10)	1 401(9)	O(4)-C(11)	1 456(10)
O(5)-C(12)	1 189(9)	O(6)-C(12)	1 315(9)
O(6)-C(13)	1 437(9)	O(7)-C(15)	1 223(14)
O(8)-C(15)	1 31(2)	O(8)-C(23)	1 450(10)
O(8)-C(23a)	1 468(10)	O(9)-C(21)	1 202(10)
O(10)-C(21)	1 327(9)	O(10)-C(22)	1 452(12)
N(1)-C(9)	1 351(9)	N(1)-C(10)	1 454(9)
N(2)-C(16)	1 282(10)	N(2)-C(17)	1 407(9)
C(1)-C(2)	1 376(12)	C(1)-C(6)	1 406(12)
C(1)-C(9)	1 495(10)	C(2)-C(3)	1 449(12)
C(3)-C(4)	1 338(14)	C(4)-C(5)	1 42(2)
C(5)-C(6)	1 431(12)	C(6)-C(7)	1 461(14)
C(10)-C(12)	1 558(10)	C(10)-C(16)	1 504(10)
C(13)-C(14)	1 536(13)	C(13)-C(15)	1 497(14)
C(17)-C(18)	1 342(10)	C(17)-C(21)	1 480(11)
C(18)-C(19)	1 503(11)	C(18)-C(20)	1 502(12)
C(23)-C(24)	1 520(1)	C(23a)-C(24a)	1 522(1)

b) Angles

C(16)-S-C(19)	96 1(4)	C(7)-O(2)-C(8)	116 7(7)
C(10)-O(4)-C(11)	116 6(6)	C(12)-O(6)-C(13)	117 0(6)
C(15)-O(8)-C(23)	116 0(8)	C(15)-O(8)-C(23a)	116 2(9)
C(23)-O(8)-C(23a)	42 3(3)	C(21)-O(10)-C(22)	116 0(7)
C(9)-N(1)-C(10)	124 0(6)	C(16)-N(2)-C(17)	121 8(6)
C(2)-C(1)-C(6)	120 9(7)	C(2)-C(1)-C(9)	119 8(7)
C(6)-C(1)-C(9)	119 1(7)	C(1)-C(2)-C(3)	119 8(8)
C(2)-C(3)-C(4)	120 0(9)	C(3)-C(4)-C(5)	120 8(9)
C(4)-C(5)-C(6)	119 8(9)	C(1)-C(6)-C(5)	118 3(9)
C(1)-C(6)-C(7)	121 5(7)	C(5)-C(6)-C(7)	120 2(8)
O(1)-C(7)-O(2)	122 3(9)	O(1)-C(7)-C(6)	125 4(8)
O(2)-C(7)-C(6)	112 2(7)	O(3)-C(9)-N(1)	125 1(7)
O(3)-C(9)-C(1)	120 9(6)	N(1)-C(9)-C(1)	114 0(6)
O(4)-C(10)-N(1)	113 9(6)	O(4)-C(10)-C(12)	110 3(6)
O(4)-C(10)-C(16)	105 1(5)	N(1)-C(10)-C(12)	112 4(5)
N(1)-C(10)-C(16)	107 7(6)	C(12)-C(10)-C(16)	106 9(6)
O(5)-C(12)-O(6)	126 1(7)	O(5)-C(12)-C(10)	123 0(6)
O(6)-C(12)-C(10)	110 7(6)	O(6)-C(13)-C(14)	107 1(7)
O(6)-C(13)-C(15)	106 0(7)	C(14)-C(13)-C(15)	111 6(8)
O(7)-C(15)-O(8)	122(1)	O(7)-C(15)-C(13)	127(1)
O(8)-C(15)-C(13)	110 7(9)	S-C(16)-N(2)	123 7(6)
S-C(16)-C(10)	115 9(5)	N(2)-C(16)-C(10)	120 3(6)
N(2)-C(17)-C(18)	124 5(7)	N(2)-C(17)-C(21)	113 0(6)
C(18)-C(17)-C(21)	122 5(7)	C(17)-C(18)-C(19)	118 4(7)
C(17)-C(18)-C(20)	125 7(7)	C(19)-C(18)-C(20)	115 6(7)
S-C(19)-C(18)	110 8(6)	O(9)-C(21)-O(10)	121 2(7)
O(9)-C(21)-C(17)	126 7(7)	O(10)-C(21)-C(17)	112 0(6)
O(8)-C(23)-C(24)	110 1(4)	O(8)-C(23a)-C(24a	108 2(4)

Conclusion

The determination of the stereochemistry at the asymmetric centre bearing the methoxy functionality, which is the future position 7 at the cephem skeleton, makes the compounds **1a** and **1b** potential chiral precursors for our present syntheses of structural analogues of cephamycins (antibiotics of broader antibacterial activity, β-lactamase stability and improved pharmacokinetic properties) Moreover these results allow the comparison and the confirmation of structures for chiral reaction intermediates accessible by other pathways[5]

Experimental.

^1H and ^{13}C NMR spectra were recorded on a JEOL instrument J N M FX 90-MHz Chemical shifts are reported as δ values in ppm down field from internal standard (Me_4Si) with notations specifying the number of protons, the multiplicity of the signal s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and the coupling constants IR spectra were measured in KBr with a PERKIN-ELMER 1420 spectrophotometer Mass spectra were recorded on a Varian MAT 311 spectrometer at 70 eV Optical rotatory powers were measured at 20°C using a AA 10 OPTICAL ACTIVITY polarimeter

The purity of the compounds was monitored by thin layer chromatography (tlc) on silica gel plates Column chromatography was carried out on silica gel (Merck, Kieselgel 60) The resolution of diastereoisomers was tested by means of HPLC Milton Roy CM 4000 pump - LDC 3100 detector (254 nm) - equipped with a Spherisorb 5 column - eluent CH_2Cl_2, flow 1 mL/mn Elemental microanalyses were performed by the Central Service of Microanalysis of the CNRS (Vernaison, France) Melting points were determined using a microscope with a Kofler hot stage and were uncorrected

Ethyl 2'-cyano-2'-phthalimido-2-acetoxy propanoate: This preparation was recently described[2]

Ethyl 2'-phthalimido-2'-thiocarbamoyl-2-acetoxy propanoate: A stream of H_2S gas was passed through a solution of the nitrile 3 3 g (10 mmol) (ratio of diastereoisomers 50/50) in a 2/1 mixture of pyridine/triethylamine (150 mL) for 1 h 30 The solution was stirred for 6 h at room temperature, then degassed and concentrated under reduced pressure The residue was dissolved in AcOEt (100 mL), and the resulting solution was washed with dilute HCl (100 mL) and then with water (3 x 50 mL), dried ($MgSO_4$), and then concentrated The crude product was purified by chromatography on silica gel (eluent petroleum ether /AcOEt 50/50) to give a white foam 2 95 g Yield = 81% The ratio of diastereoisomers A/B can be measured by NMR ^1H (before and after chromatography) A/B = 65/35 to 70/30 depending of the runs

Diastereoisomer A NMR ^1H ($CDCl_3$) δ 1 29 (t, J = 7 2 Hz, 3H, $\underline{CH_3}CH_2$), 1 53 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$), 4 25 (q, J = 7 2 Hz, 2H, $CH_3\underline{CH_2}$), 5 29 (q, J = 7 Hz, 1H, $CH_3\underline{CH}$), 5 91 (s, 1H, CH), 7 84 (s, 4H, Phth), 8 06 and 9 58 (2 br s, 2H, NH_2) ^{13}C (C_6D_6) δ 14 46 ($\underline{C}H_3CH_2$), 17 00 ($\underline{C}H_3CH$), 61 17 (N-$\underline{C}$H-C=S), 62 73 ($CH_3\underline{C}H_2$), 71 58 ($CH_3\underline{C}H$), 124 41, 132 93 et 134 75 (C_6H_4), 166 37 and 171 25 (C=O esters), 167 74 (C=O Phth), 196 69 (C=S)

Diastereoisomer B NMR ^1H ($CDCl_3$) δ 1 25 (t, J = 7 2 Hz, 3H, $\underline{CH_3}CH_2$), 1 50 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$), 4 25 (q, J = 7 2 Hz, 2H, $CH_3\underline{CH_2}$), 5 29 (q, J = 7 Hz, 1H, $CH_3\underline{CH}$), 5 89 (s, 1H, CH), 7 84 (s, 4H, Phth), 8 06 and 9 29 (2 br s, 2H, NH_2) ^{13}C (C_6D_6) δ 14 46 ($\underline{C}H_3CH_2$), 17 00 ($\underline{C}H_3CH$), 60 91 (N-

CH-C=S), 62 28 (CH_3CH_2), 71 91 (CH_3CH), 124 41, 132 93 and 134 75 (C_6H_4), 166 37 and 171 25 (C=O esters), 167 74 (C=O Phth), 197 01 (C=S) IR (CCl_4) cm^{-1} 3460, 3320 (NH_2), 1780, 1725 (C=O Phth), 1760, 1735 (C=O esters) MS m/e $M^{+\cdot}$ = 364, 246, 204, 192, 188, 148, 130, 104 Anal Calcd for $C_{16}H_{16}N_2O_6S$ (364 37) C 52 74 H 4 43 N 7 69 Found C 52 67 H 4 78 N 7.39

2-(2'-Thiazinylidene)glycinate 2 A solution of 3 6 g (10 mmol) thioamide (mixture of diastereoisomers), 1 6 g (12 mmol) of vinyl ketoester[4] and a trace of hydroquinone in dry chloroform (80 mL) was cooled in a ice water bath and saturated with dry HCl for 10 mn The resulting mixture was then stirred for 15 h at room temperature The residue obtained by removal of the solvent under reduced pressure was dissolved in AcOEt, washed with water, dried (Na_2SO_4) and then chromatographed on silica gel (eluent petroleum ether /AcOEt 50/50) to give a yellow foam 2 86 g Yield = 60% NMR ^1H ($CDCl_3$) δ 1 19 (t, J = 7 Hz, 3H, CH_3CH_2), 1 35 (d, J = 7 Hz, 3H, CH_3CH), 2 30 (s, 3H, CH_3C=C), 3 30 (s, 2H, SCH_2), 3 90 (s, 3H, CO_2CH_3), 4 12 (q, J = 7 Hz, 2H, CH_3CH_2), 5 18 (q, J = 7 Hz, 1H, CH_3CH), 7 84 (br s, 4H, Phth), 11 52 (s, 1H, NH) ^{13}C ($CDCl_3$) δ 13 92 (CH_3CH_2), 17 01 (CH_3CH-), 19 81 (CH_3C=C), 30 54 (SCH_2), 52 60 (CH_3O), 61 09 (CH_3CH_2O), 68 28 (CH_3CH-O), 89 19 (N-C=C-CH_3), 123 70, 131 34 and 134 18 (C_6H_4), 125 33 (N-C=C-CH_3), 159 62 and 162 55 (N-C=C-N), 164 20, 167 39, 167 91 and 170 61 (C=O) IR (KBr) cm^{-1} 3400 (NH), 1780, 1720 (C=O Phth), 1660 (C=O esters) MS m/e 474 ($M^{+\cdot}$), 402, 356, 324, 296, 284, 132, 104 Anal Calcd for $C_{22}H_{22}N_2O_8S$ (474 49) C 55 69 H 4 67 N 5 90 Found C 55 96 H 4 86 N 5 76

2-Chloro-2-(2'-thiazinyl)glycinate 3 To a stirred solution of 2 38 g (5 mmol) 2-(2'-thiazinylidene) glycinate **2** in 60 mL of 1,2-dichloroethane, were added 0 7 g (5 2 mmol) of N-chlorosuccinimide After heating for 4 h at 70°C, the reaction mixture was concentrated under reduced pressure and extracted with AcOEt The organic solution was washed with brine, dried (Na_2SO_4) and then concentrated Chromatography on silica gel (eluent CH_2Cl_2) gave 1 g (white foam) Yield = 40% Ratio of diastereoisomers 50/50 (as shown by NMR on the crude compound) Crystallization in diethyl ether gave a pure diastereoisomer of unknown configuration, mp = 172-173°C $[\alpha]_D^{20}$ = -25 4 (c = 0 83 , $CHCl_3$) NMR ^1H ($CDCl_3$) δ 1 26 (t, J = 7 Hz, 3H, CH_3CH_2), 1 48 (d, J = 7 Hz, 3H, CH_3CH-), 2 35 (s, 3H, CH_3C=C), 3 50 (s, 2H, SCH_2), 3 56 (s, 3H, CO_2CH_3), 4 19 (q, J = 7 Hz, 2H, CH_3CH_2), 5 22 (q, J = 7 Hz, 1H, CH_3CH), 7 79 (br s, 4H, Phth) ^{13}C ($CDCl_3$) δ 14 18 (CH_3CH_2), 16 80 (CH_3CH-), 20 55 (CH_3C=C), 32 36 (SCH_2), 51 52 (CH_3O), 61 54 (CH_3CH_2O), 72 01 (CH_3CH-O), 80 04 (N-C-C=N), 96 24 (N-C=C-CH_3), 123 89, 131 73, 134 66 (C_6H_4), 129 91 (N-C=C-CH_3), 155 64 (S-C=N), 162 73, 164 55, 165 04, 169 57 (C=O) IR (KBr) cm^{-1} 1758, 1720 (C=O Phth), 1735 (C=O esters), 1258 (C-O-) MS m/e 508/510 ($M^{+\cdot}$) Anal Calcd for $C_{22}H_{21}N_2O_8SCl$ (508 93) C 51 92 H 4 16 N 5 50 Found C 51 61 H 4 09 N 5 46

2-Methoxy-2-(2'-thiazinyl)glycinate 1 A stirred solution of 0 5 g (1 mmol) 2-chloro-2-(2'-thiazinyl) glycinate **3** in 60 mL of anhydrous MeOH and 0 7 g (2 1 mmol) Bu_3SnOCH_3 under nitrogen, was heated under reflux for 24 h At the end of the reaction monitored by TLC, the mixture was concentrated under reduced pressure and extracted with acetonitrile The resulting solution was washed with 3 x 50 mL of hexane (elimination of tin compounds) then with 50 mL of water, dried (Na_2SO_4), concentrated and then chromatogaphed on silica gel (eluent petroleum ether /AcOEt 50/50) to give a yellow foam 0 38 g Yield = 70% A further chromatogaphy on silica gel (Ref Silica gel 60 - 230-400 mesh ASTM-Merck 9385) was necessary to separate the two diastereoisomers (ratio 50/50 as shown by NMR ^1H)

Pure diastereoisomer (**R-S** ethyl lactate)**1a** White crystals (Diethyl ether), mp = 142-143°C $[\alpha]_D^{20}$ = -5 1 (c = 1 37 , $CHCl_3$) NMR ^1H ($CDCl_3$) δ 1 25 (t, J = 7 Hz, 3H, $\underline{CH_3}CH_2$), 1 45 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$), 2 34 (s, 3H, $\underline{CH_3}C{=}C$), 3 16 and 3 76 (2d, J = 15 4 Hz, 2H, SCH_2), 3 49 (s, 3H, CH_3O), 3 76 and 3 87 (2s, 6H, 2 CO_2CH_3), 4 17 (q, J = 7 Hz, 2H, $CH_3\underline{CH_2}$), 5 23 (q, J = 7 Hz, 1H, $CH_3\underline{CH}$-), 7 59-7 81 (m, 4H, C_6H_4), 8 33 (s, 1H, NH) ^{13}C ($CDCl_3$) δ 14 11 ($\underline{C}H_3CH_2$), 16 85 ($\underline{C}H_3CH$-), 20 49 ($\underline{C}H_3C{=}C$), 30 38 ($S\underline{C}H_2$), 51 91 and 52 63 (3 $\underline{C}H_3O$), 61 41 ($CH_3\underline{C}H_2O$), 69 87 ($CH_3\underline{C}H$-O), 86 59 (N-$\underline{C}$-C=N), 127 38, 129 66, 130 18, 130 50, 130 77, 131 67, 133 63 and 136 62 (N-$\underline{C}{=}\underline{C}$-$CH_3$ and $\underline{C}_6H_4$), 159 06 (S-$\underline{C}$=N), 164 92, 165 44, 167 26, 167 98 and 170 32 ($\underline{C}$=O) IR (KBr) cm^{-1} 3330 (NH), 1790 (C=O Phth), 1730, 1700-1690 (C=O esters) MS m/e (I%) **EI** $M^{+\cdot}$ = 536 (very small), 163 (base peak *o*-CH_3O_2C-C_6H_4-CO^+) - **CI** (Methane reagent) $(M+1)^+$ = 537 (100), 504 (52), 475 (11), 163 (23), 148 (11), 119 (22) Anal Calcd for $C_{24}H_{28}N_2O_{10}S$ (536 55) C 53 72 H 5 26 N 5 22 Found C 53 66 H 5 51 N 4 78.

Enriched diastereoisomer (**S-S** ethyl lactate) **1b** (d e = 40 %) Foam NMR ^1H ($CDCl_3$) δ 1 20 (t, J = 7 Hz, 3H, $\underline{CH_3}CH_2$), 1 59 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$), 2 32 (s, 3H, $\underline{CH_3}C{=}C$), 3 23 and 3 88 (2d, J = 15 5 Hz, 2H, SCH_2), 3 48 (s, 3H, CH_3O), 3 74 and 3 87 (2s, 6H, 2 CO_2CH_3), 4 14 (q, J = 7 Hz, 2H, $CH_3\underline{CH_2}$), 5 25 (q, J = 7 Hz, 1H, $CH_3\underline{CH}$-), 7 59-7 81 (m, 4H, C_6H_4), 8 21 (s, 1H, NH) ^{13}C ($CDCl_3$) δ 14 05 ($\underline{C}H_3CH_2$), 16 85 ($\underline{C}H_3CH$-), 20 49 ($\underline{C}H_3C{=}C$), 30 44 ($S\underline{C}H_2$), 51 91 and 52 63 (3 $\underline{C}H_3O$), 61 35 ($CH_3\underline{C}H_2O$), 70 71 ($CH_3\underline{C}H$-O), 87 44 (N-$\underline{C}$-C=N), 127 38, 127 77, 128 66, 130 12, 130 31, 131 74, 133 69 and 136 88 (N-$\underline{C}{=}\underline{C}$-$CH_3$ and $\underline{C}_6H_4$), 159 26 (S-$\underline{C}$=N), 164 86, 165 96, 167 20, 168 17 and 169 80 ($\underline{C}$=O)

X-Ray Structure Détermination of 1a

Crystal data : - $C_{24}H_{28}N_2O_{10}S$, M = 536 6, orthorhombic, space group $P2_12_12_1$ (No 19), a = 8 645(2), b = 11 567(3), c = 27 181(4) Å, U = 2718 0 $Å^3$, Z = 4, D_{calc} = 1 31 gcm^{-3}, F(000) = 1128 Monochromatic Mo - Kα radiation, λ = 0 71069 Å, μ = 1 7 cm^{-1}

Data were collected using a crystal ca 0 2 x 0 2 x 0 15 mm on an **Enraf-Nonius** CAD4 diffractometer in the θ-2θ mode with Δθ = (0 6 + 0 35 tan θ)° and a maximum scan time of one minute A total of 2757 unique reflections were measured for 2°<θ<25° and +h+k+l, and 1613 reflections with $|F^2|>3\sigma(F^2)$ were used in the refinement, where $\sigma(F^2) = \{\sigma^2(I) + (0\ 04\ I)^2\}^{1/2}/Lp$ There was no crystal decay and no correction was applied for absorption

The structure was solved by direct methods using **SHELXS - 86**[6] and non-hydrogen atoms refined by full matrix least squares with anisotropic thermal parameters, except for **C**(23) and **C**(24) which are disordered between two orientations of the ethyl group and were refined isotropically with constraints on the **O-C**, **C-C** and **O ·C** distances Hydrogen atoms could not be located on a difference map and were omitted With a weighting scheme of $W = 1/\sigma^2(F)$ the refinement converged at R = 0 065, R' = 0 032, for 316 variables, S = 2 9, (Δ/σ) max = 0 2, $(\Delta\rho)$ max, min = + 0 46, - 0 43 e $Å^{-3}$

Programs from the **Enraf-Nonius** SDP-Plus package were run on a micro **VAX** computer Atomic coordinates for non hydrogen atoms are listed in Table 1, with bond lengths and angles in Table 2

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