Synthesis and Stereochemical Studies of 2-Substituted Thiazolidine-4-carboxamide Derivatives

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A series of new 2-substituted thiazolidine-4-carboxamide derivatives which have potentially useful immunological properties, have been synthesized in a stereoselective manner by coupling 2-subsituted thiazolidine-4-carboxylic acids with amines or amino esters. The structure of these compounds was established by combination of NMR methods and by X-ray analysis.

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Introduction.

In the course of our work on the chemistry of amidic derivatives of (*R*)-thiazolidine-4-carboxylic with potential immunomodulating properties [1-4], we have recently investigated the synthesis and characterization of new dipeptides containing (*R*)-thiazolidine-4-carboxylic acid [1] and structural analogues of known immunological activity [5-7]. Furthermore, structural elucidation of these compounds is a challenging task, which demands a combination of the data from NMR technique and X-ray analysis.

In the present paper, we report the syntheses of a variety of 2-substituted thiazolidine-4-carboxamide derivatives from (*R*)-cysteine in three steps and their stereochemical structures have been determined by NMR technique and X-ray data.

Results and Discussion.

2-Substituted thiazolidine-4-carboxylic acids **1-3** were prepared from (*R*)-cysteine hydrochloride and the corresponding carbonyl compounds as described in Scheme 1.

Thiazolidine-4-carboxylic acid **1** was isolated in only one isomeric form (4*R*), while 2-phenylthiazolidine-4-carboxylic acid **2** was obtained in a mixture of two diastereoisomers.

The stereochemistry of C-2 of compound **2** with respect to C-4 can be resolved using NMR spectroscopy which permit distinction between the two diastereoisomers: two sets of resonance with different intensities were observed for H-2, H-4, H5a and H5b protons. Previously, Szilágyi and Györgydeák [8,9] as well observed that the sum of coupling constants between geminal protons H-5a and H-5b with H-4 of 2-phenylthiazolidine-4-carboxylic acid for the (2*R*, 4*R*) isomer (J = 16.0 Hz) is greater than the (2*S*, 4*R*) isomer's one (J = 13.5 Hz). These assignments are confirmed without ambiguity by the 2D NOESY spectrum of **2**. For the (2*R*, 4*R*) isomer, an NOE correlation was observed between the H-2 proton signal at 5.55 ppm and H-4 at 3.90 ppm, showing that these protons are in a *cis* relationship. For (2*S*, 4*R*) isomer, no correlation was observed between H-2 and H-4.

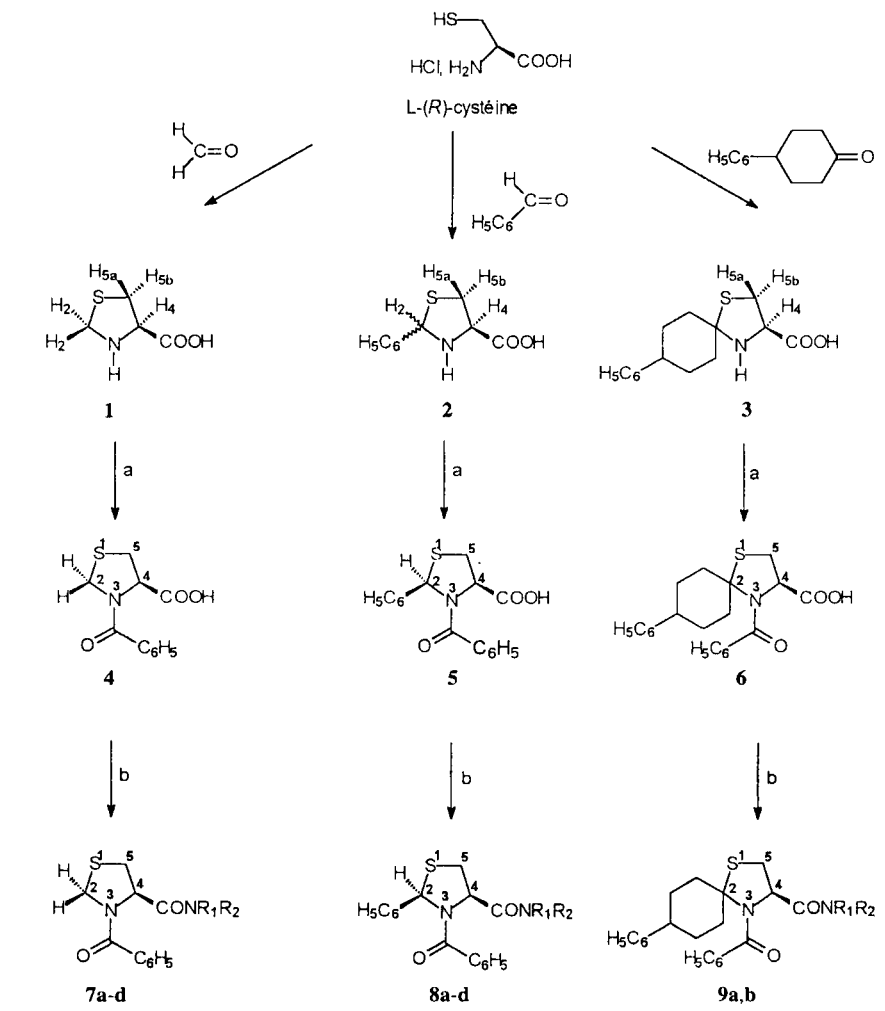
1-Thia-4-azaspiro[4,5]decane-3-carboxylic acid **3** was obtained in a mixture 3:2 of two diastereoisomers, arising from a *cis/trans* ring forming isomerism.

Good yields of compounds **4-6** were obtained by *N*-acylation of acids **1-3** by benzoyl chloride as shown in Scheme 1. Next, by using isobutyl chloroformate and *N*-methylmorpholine, compounds **4-6** were coupled with amines or amino esters to afford carboxamides **7-9**.

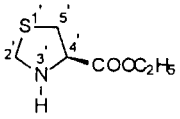
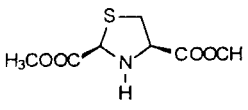
The structures of compounds **4-9** were confirmed by analyses of their ^{1}H NMR, as described in the Experimental. The NMR techniques are particularly useful for the structure configuration and conformation of molecules [10,11]. In this paper, one- and two-dimensional NMR spectroscopies were used to characterize our products.

The ^{1}H NMR spectra of compounds **4-6** show at room temperature only one conformation around the amidic bond: *s-cis* conformation for compounds **4,5** and *s-trans* conformation for compound **6**, according to the nomenclature established by Goodman [12] for *N*-acylthiaproline. The ^{1}H NMR spectra of several compounds **7-9** recorded at differents temperatures show the presence of conformers resulting from rotation around the peptide bond.

Scheme I



Reagents: a) NaOH - H_2O - C_6H_5COCl; b) IBCF, NMM, HNR_1R_2

Compound 7-9	a	b	c	d
HNR_1R_2	$NH_2CH_2C_6H_5$	$NH_2CH_2COOCH_3$		

From NMR data, it appears therefore that compounds **5**,**6** and **8**,**9** were obtained in only one diastereoisomer from a diastereomeric mixture **2** and **3**. Thus, we can assume that only the major diastereoisomer reacts, but more probably, this result can be explained by interconversion of the two diastereoisomers [1]. In fact, it is well known that diastereoisomers at the C-2 position of thiazolidines equilibrate by a ring opening mechanism [8,13-20].

Next, our attention was focused on the determination of the absolute configuration at stereocenter C-2 of thiazolidines **5** and **8**. A nuclear Overhauser enhancement spectroscopy (NOESY) experiment was performed with compounds **5** and **8**. However, no significant correlations for the H-2 and H-4 protons were observed to establish a (2*R*, 4*R*) configuration. In regards of optical rotation values published by Szilágyi and Györgydeák on *N*-acetyl-2-phenylthiazolidine-4-carboxylic acid [8,9], we can suggest a *cis* (2*R*, 4*R*) stereochemistry for compounds **5** and **8**, confirmed by an X-ray structure of compound **8b**, obtained by coupling **5** with methyl glycinate (Figure 1).

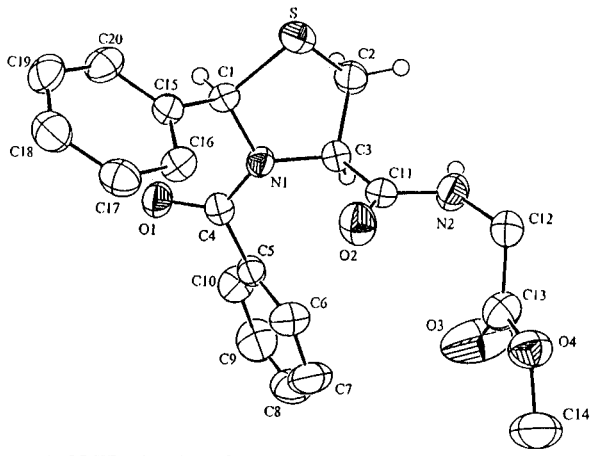


Figure 1. ORTEP drawing of **8b**.

The *N*-acylation of 1-thia-4-azaspiro [4,5]decane-3-carboxylic acid **3** gave only a *cis* isomer. This result has been determined previously by X-ray analysis [2]. By analogy, carboxamides **9** should present the same configuration *cis* (Scheme 1).

Based on the absolute value of the specific rotations of carboxamides **7-9** (see Experimental), the condensation which involved the carboxy group at C-4 of thiazolidines **4-6** may have proceeded without partial racemization.

The crystal structure of **8b**, recrystallized from ether/-methanol (2:1), shows an absolute (2*R*, 4*R*) configuration. This study also proves that the conformation of the molecule in the solid state is *S-cis*. The molecular structure of **8b** is shown in Figure 1. The thiazolidine ring (S/C1/N1/-C3/C2) exhibits a formal envelope conformation. The conformational flexibility of the ring is confirmed by the different conformations found in various thiazolidine derivatives [21-23]. This conformation is characterized by the rough planarity of the C(1)-N(1)-C(3)-C(2) fragment (the torsion angle is equal to 19.2 °C) and by the high deviation of the S atom (0.82 Å) from the best plane defined by the atoms mentioned above.

EXPERIMENTAL

All compounds were characterized by using the methods of elemental analyses, IR, NMR spectroscopy and X-ray analysis. Microanalyses were carried out by the Service Central d'Analyses, Centre National de la Recherche Scientifique, Vernaison (France). Infrared spectra were taken on a Shimadzu FTIR-8201PC spectrometer in potassium bromide pellets for solids and as liquid films for oils. Proton and carbon NMR spectra were recorded on a Bruker AC 200 spectrometer. The samples were dissolved in DMSO-d_6 or in $CDCl_3$. All measurements were performed at 293 K. The chemical shift values were referenced to internal tetramethylsilane (TMS from CEA Saclay, France). The signals were assigned after examination of distortionless enhancement by polarization transfer (DEPT) and 2D homonuclear ^1H-^1H correlation (COSY) spectra. Several 2D NOESY experiments were performed at different mixing times. The acquired matrices were made up of 256 FIDs of 1024 points and were zero-filled to 512 points in F1 before Fourier transformation, as described in previous work [14,15]. Chemical shift values and IR data for all compounds are summarized in this Experimental section and these data are in agreement with the proposed structures. Melting points were determined on a Buchi N°510 apparatus and were uncorrected. X-Ray analysis was

Table 1

Physical and Analytical Data of Compounds **7-9**

Compound N°	Yield (%)	$[\alpha]_D^{20}$ (C, Solvent)	Mp (°C)	Formula	Calcd (%) C	H	N	S	Found (%) C	H	N	S
7a	54	-159 (18, DMSO)	118	$C_{18}H_{18}N_2O_2S$	66.26	5.52	8.59	9.82	66.09	5.70	8.72	9.76
7b	39	-155 (14, DMSO)	—	$C_{14}H_{16}N_2O_4S$	54.55	5.19	9.09	10.39	54.68	5.29	8.91	10.31
7c	41	-320 (21, DMSO)	—	$C_{17}H_{20}N_2O_4S$	53.68	5.26	7.37	16.84	53.51	5.32	7.30	16.91
7d	37	-87 (17, DMSO)	—	$C_{18}H_{20}N_2O_6S_2$	50.94	4.72	6.60	15.09	51.02	4.60	6.69	15.20
8a	49	+41 (14, DMSO)	212	$C_{24}H_{22}N_2O_2S$	71.64	5.47	6.97	7.96	71.50	5.59	6.78	7.88
8b	46	-115 (13, DMSO)	192	$C_{20}H_{20}N_2O_4S$	62.50	5.21	7.29	8.33	62.72	5.33	7.14	8.27
8c	37	+54 (16, DMSO)	—	$C_{23}H_{21}N_2O_4S_2$	60.93	4.64	6.18	14.13	60.80	4.60	6.29	14.28
8d	37	+51 (17, DMSO)	—	$C_{18}H_{20}N_2O_6S_2$	36.09	5.26	10.43	24.06	35.85	5.50	10.88	24.23
9a	41	-139 (11, DMSO)	182	$C_{29}H_{30}N_2O_2S$	74.04	6.38	5.96	6.81	74.22	6.55	6.02	6.66
9b	43	-106 (15, DMSO)	166	$C_{25}H_{28}N_2O_4S$	66.37	6.19	6.19	7.08	66.19	6.07	6.38	7.31

Table 2

Spectral Data of Compounds **7-9**

Compound N°	IR (KBr) (cm^{-1})	^{1}H NMR DMSO-d_6 δ (ppm) R2	H4	H5a, H5b	C_6H_5	NR_1R_2
7a	3191, 1675, 1620	4.40 (d, 1H) 4.70 (d, 1H)	4.80 (dd)	3.2-3.5 (m)	7.0-7.5 (m)	4.10 (d, 2H), 7.10 (s, NH), 7.0-7.5 (m, 5H)
7b	3300, 1747, 1676, 1633	4.70 (d, 2H)	5.20 (dd)	3.20 (m)	7.0-7.5 (m)	3.80 (s, 3H), 4.10 (d, 2H), 8.20 (s, 1H)
7c	1743, 1664, 1618	4.70 (m, 2H)	5.20 (dd)	3.1-3.5 (m)	7.4-7.6 (m)	1.30 (t, 3H), 3.1-3.5 (m, 2H), 4.20 (q, 2H), 4.70 (m, 2H), 5.10 (dd, 1H)
7d	1740, 1738, 1658, 1622	4.60 (d, 1H) 4.80 (d, 1H)	5.15 (dd)	3.3-3.6 (m)	7.4-7.6 (m)	3.3-3.6 (m, 2H), 3.80 (s, H), 3.85 (s, 3H), 5.05 (dd, 1H), 6.40 (s, 1H) [a], 6.00 (dd, 1H), 5.80 (s, 1H) [b]
8a	3319, 1681, 1618	7.4-7.8 (m, 5H) 6.20 (s, 1H)	5.50 (dd)	3.4-3.6 (m)	7.4-7.8 (m)	4.20 (d, 2H), 7.4-7.8 (m), 8.20 (s, 1H)
8b	3310, 1755, 1681, 1620	7.4-7.8 (m, 5H) 6.20 (s, 1H)	5.00 (m)	3.1-3.5 (m)	7.4-7.8 (m)	3.80 (s, 3H), 4.00 (d, 2H), 7.80 (s, 1H)
8c	1747, 1708, 1666	7.1-7.4 (m, 5H) 6.20 (s, 1H)	4.90 (dd)	3.1-3.5 (m)	7.1-7.4 (m)	1.30 (t, 3H), 3.1-3.5 (m, 2H), 4.20 (q, 2H), 4.70 (m, 2H), 5.10 (dd, 1H)
8d	1740, 1738, 1662, 1630	7.4-7.6 (m, 5H) 6.20 (s, 1H)	5.15 (dd)	3.3-3.6 (m)	7.4-7.6 (m)	3.3-3.6 (m, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 5.05 (dd, 1H), 6.40 (s, 1H) [a], 6.00 (dd, 1H), 5.80 (s, 1H) [b]
9a	3307, 1687, 1614	1.4-2.5 (m, 8H) 2.70 (m, 1H), 7.1-7.4 (m, 5H)	4.90 (m)	3.1-3.4 (m)	7.1-7.4 (m)	4.40 (d, 2H), 6.40 (s, 1H), 7.1-7.4 (m, 5H)
9b	3300, 1753, 1679	1.4-2.5 (m, 8H) 2.70 (m, 1H) 7.1-7.5 (m, 5H)	4.80 (m)	3.1-3.4 (m)	7.1-7.5 (m)	3.80 (s, 3H), 4.00 (d, 2H), 6.70 (s, 1H)

[a] Major conformer (70%); [b] Minor conformer (30%).

Table 3

Selected Bond Lengths [Å] and Angles [deg] for Compound **8b**

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Atom 3	Angle
S	C2	1.799(5)	C2	S	C1	89.4(2)
S	C1	1.815(4)	C4	N1	C3	123.9(3)
N1	C4	1.363(5)	C4	N1	C1	116.9(3)
N1	C1	1.475(5)	C3	N1	C1	115.4(3)
N2	C11	1.353(5)	C1	N1	C15	114.8(3)
N2	C12	1.433(6)	N1	C1	S	105.2(3)
N1	C3	1.467(5)	S	C15	C1	110.9(3)
O1	C4	1.223(5)	S	C3	C2	104.1(3)
O2	C11	1.212(5)	N1	C3	C11	112.5(3)
C1	C15	1.507(6)	N1	C3	C2	104.9(3)
C2	C3	1.535(6)	C11	C3	C2	111.1(3)
C3	C11	1.530(6)	O1	C4	N1	120.2(4)
C4	C5	1.490(6)	N1	C4	C5	119.6(4)

recorded on a CAD4 Enraf-Nonius diffractometer. Optical rotation was measured on a polarimeter ATAGO Polax L. When required, the separation of crude reaction products was performed by chromatography on silica gel column (70-230 mesh). L-(−)-*R*-Cysteine hydrochloride hydrate was purchased from Aldrich Company, $[\alpha]_D^{20}$ +5.2 °C (*c* = 2.5, 1*N* HCl), M_r = 157.61.

General Procedure for the Preparation of Acids (**1-3**).

To a stirred solution of L-(−)-*R*-cysteine hydrochloride hydrate (15.8 g, 0.1 mole) and potassium acetate (9.8 g, 0.1 mole) in a mixture of water and ethanol (150 ml, 2:1, v/v) 0.1 mole of the appropriately aldehyde or phenylcyclohexanone were added. The reaction mixture was stirred for 1 hour at room temperature and for 1 hour at 90 °C. After cooling, the precipitate obtained was collected by filtration; the crude product was recrystallized from hot water.

(4*R*)-Thiazolidine-4-carboxylic Acid (**1**).

This compound was obtained as a white powder, yield 91%, mp 203 °C; ir (potassium bromide): ν 1627 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.80 (dd, 1H, H5a), 3.10 (dd, 1H, H5b), 3.75 (t, 1H, H4), 4.05 (d, 1H, H2), 4.30 (d, 1H, H2): $[\alpha]_D^{20}$ -141 °C (*c* = 1.3, DMSO).

Anal. Calcd. for $C_4H_7NO_2S$: C, 36.09; H, 5.26; N, 10.43; S, 24.06. Found: C, 35.85; H, 5.05; N, 10.88; S, 24.23.

(2*R*, 4*R*) and (2*S*, 4*R*)-2-Phenylthiazolidine-4-carboxylic Acid (**2**).

This compound was obtained as a mixture of inseparable diastereoisomers, white powder, yield 82%, mp 190 °C; ir (potassium bromide): ν 1625 cm^{-1}; ^1H nmr (DMSO-d_6) isomer *cis* (2*R*, 4*R*) (45%): δ 3.15 (dd, 1H, H5a), 3.40 (dd, 1H, H5b), 3.90 (dd, 1H, H4), 5.55 (s, 1H, H2), 7.20-7.50 (m, 5H). isomer *trans* (2*S*, 4*R*) (55%): δ 3.20 (dd, 1H, H5a), 3.35 (dd, 1H, H5b), 4.30 (dd, 1H, H4), 5.75 (s, 1H, H2), 7.20-7.50 (m, 5H): $[\alpha]_D^{20}$ -127 °C (*c* = 8, DMSO).

Anal. Calcd. for $C_{10}H_{11}NSO_2$: C, 57.42; H, 5.26; N, 6.70; S, 15.31. Found: C, 57.69; H, 5.06; N, 6.55; S, 15.29.

(3*R*)-8-Phenyl-1-thia-4-azaspiro[4,5]decane-3-carboxylic Acid (**3**).

This compound was obtained as a mixture of inseparable diastereoisomers, white powder, yield 88%, mp 252 °C; ir (potassium bromide): ν 1620 cm^{-1}; ^1H nmr (DMSO-d_6) major isomer (60%): δ 1.40-2.30 (m, 9H, cyclohexyl), 2.90 (dd, 1H, H5a), 3.30 (dd, 1H, H5b), 4.20 (dd, 1H, H4), 7.20-7.50 (m, 5H). minor isomer (40%): δ 1.40-2.30 (m, 9H, cyclohexyl), 2.90 (dd, 1H, H5a), 3.30 (dd, 1H, H5b), 4.05 (t, 1H, H4), 7.20-7.50 (m, 5H): $[\alpha]_D^{20}$ -98 °C (*c* = 8, DMSO).

Anal. Calcd. for $C_{15}H_{19}NSO_2$: C, 64.98; H, 6.86; N, 5.05; S, 11.55. Found: C, 64.76; H, 6.97; N, 4.92; S, 11.69.

General Procedure for *N*-Acylation of Acids.

Benzoyl chloride was purchased from various suppliers. Acylation has been realized by the well-known Schotten-Baumann procedure.

To a chilled solution of acid **1-3** (0.03 mole) in a mixture of NaOH 1*N* (30 ml) and *tert*-butyl alcohol (23 ml) was added slowly, at 0 °C, benzoyl chloride (0.035 mole). The mixture was kept for 10 hours at room temperature, acidified at *p*H 1, then extracted 3 times with ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and evaporated.

(4*R*)-*N*-Benzoylthiazolidine-4-carboxylic Acid (**4**).

This compound was obtained as a colorless syrup, yield 52%; ir (potassium bromide): ν 1624, 1712 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.50 (m, 2H, H5a, H5b), 4.30 (m, 2H, H2), 3.75 (dd, 1H, H4), 7.30-7.80 (m, 5H): $[\alpha]_D^{20}$ -153 °C (*c* = 10.9, DMSO).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.69; H, 4.64; N, 5.91; S, 13.50. Found: C, 55.81; H, 4.51; N, 6.02; S, 13.67.

(2*R*, 4*R*)-*N*-Benzoyl-2-Phenylthiazolidine-4-carboxylic Acid (**5**).

This compound was obtained as a white powder, yield 63%, mp 182 °C; ir (potassium bromide): ν 1597, 1716 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.10-3.70 (m, 2H, H5a, H5b), 4.90 (t, 1H, H4), 6.20 (s, 1H, H2), 7.10-7.60 (m, 10H): $[\alpha]_D^{20}$ +97 °C (*c* = 19, DMSO).

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.17; H, 4.79; N, 4.47; S, 10.22. Found: C, 65.04; H, 4.89; N, 4.51; S, 10.09.

cis-(3*R*)-*N*-Benzoyl-8-phenyl-1-thia-4-azaspiro[4,5]decane-3-carboxylic Acid (**6**).

This compound was obtained as a white powder, yield 66%, mp 226 °C; ir (potassium bromide): ν 1602, 1737 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.30-2.80 (m, 9H, cyclohexyl), 3.30 (m, 2H, H5a, H5b), 4.90 (dd, 1H, H4), 7.20-7.60 (m, 10H): $[\alpha]_D^{20}$ -115 °C (*c* = 20, DMSO).

Anal. Calcd. for $C_{22}H_{23}NO_3S$: C, 69.29; H, 6.04; N, 3.67; S, 8.40. Found: C, 69.12; H, 6.15; N, 3.51; S, 8.51.

General Procedure for the Preparation of Carboxamides (**7-9**).

Benzylamine and methyl glycine ester hydrochloride were purchased from various suppliers. (4*R*)-Ethyl thiazolidine-4-carboxylate and (2*R*, 4*R*)-dimethyl thiazolidine-2,4-dicarboxylate were prepared by esterification of the correspondant corresponding acid [3].

To a chilled solution of *N*-benzoyl amino acids **4-6** (0.01 mole) in a mixture of dry tetrahydrofuran and *N,N*-dimethylformamide (10 ml, 1:1, v/v), *N*-methyl morpholine (0.011 mole) and isobutyl chloroformate (0.011 mole) were added at -10 °C. The mixture was kept at -10 °C during for 5 minutes and amine or aminoacid (0.01 mole) in dry tetrahydrofuran (5 ml) were added. The mixture was stirred at 0 °C for 1 hour, at 25 °C for 8 hours, then filtered and evaporated to dryness. The remaining residue was taken up with ethyl acetate (10 ml) and washed twice with 5% $NaHCO_3$, 2*N* HCl and water. The organic layer was dried over sodium sulfate. The oily residue was purified by chromatography on silica gel with ethyl acetate/hexane to give compounds **7-9**; see Tables 1 and 2 for physical constants and spectral data.

X-Ray Structure Analyses of Methyl *N*-[(2*R*, 4*R*)-*N*-Benzoyl-2-phenylthiazolidin-4-ylcarbonyl] Glycinate (**8b**).

A colorless crystal having the approximate dimensions 0.3/0.2/0.1 mm was mounted on a CAD4 Enraf–Nonius diffractometer. The data were collected at room temperature with MoK_α radiation (λ = 0.71073 Å). The unit cell was determined from 25 reflections selected by the CAD4 routines [24].

Crystallographic data: $C_{20}H_{20}N_2O_4S$, M_w = 384.44, monoclinic $P2_1$ (N° 4), a = 6.1072(8), b = 20.257(3), c = 7.540(1) Å, β = 94.182(7) °C, V = 930.3(2) $Å^3$, Z = 2, $\rho_{calc.}$ = 1.372 $g.cm^{-3}$, F (000) = 404, μ = 0.203 mm^{-1}, 1940 reflections measured, 1273 unique data with $I > 2\sigma(I)$ (see Table 3).

A total of 1940 intensities were reduced with the XCAD4PC data reduction program [25]. The structure was solved in the noncentrosymmetric monoclinic space group $P2_1$ with direct methods and refined by full-matrix least-squares methods (based on F^2) [2]. All non-hydrogen atoms were refined with anisotropic thermal parameters and the hydrogen atoms bonded to carbons were included in calculated positions and refined with a riding model. The choice of enantiomer was checked between the R–R and S–S configurations by inversion of all positional parameters. The absolute structure Flack parameter of 0.09(13) clearly argue for the expected choice of *cis* (2*R*, 4*R*) configuration. The final residuals with 245 parameters are: R_1 (F^2) = 0.039 and wR_2 (F^2) = 0.079 for $I > 2\sigma(I)$ and GOF = 1.027.

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REFERENCES AND NOTES

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