Tetrahedron Vol. 48, No. 43, pp. 9567-9576, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Asymmetric Synthesis of Pyrrolo[2,1-*b*][1,3,4]thiadiazepine Derivatives

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(*Received in UK* 13 *July* 1992)

Abstract: The asymmetric synthesis of compound **2**, with potential ACE inhibitory activity, is reported. The key intermediate **3** contains the novel heterocyclic nucleus pyrrolo[2,1-*b*][1,3,4]thiadiazepine. This compound has been prepared through a sequence involving pyrrole thiocyanation, followed by reductive cleavage of the thiocyanate group, and cyclization of the resulting halo-thiol in the key synthetic steps.

The renin-angiotensin system constitutes an important mechanism involved in the regulation of blood pressure. Modulation of this system, especially, through inhibition of angiotensin-converting enzyme (ACE; EC 3.4.15.1) has assumed increasing importance in the therapy of hypertension.[1]

In the context of our studies on potential antihypertensive drugs, we have reported in a previous paper[2] the synthesis of the pyrrolo[1,2-*b*][1,2]diazepine derivative **1** (see Figure 1). The interesting properties of **1** as ACE inhibitor prompted us to extend the study to the preparation of its analogue **2** as an isosteric modification of **1**. This compound contains as a characteristic feature the pyrrolo[2,1-*b*][1,3,4]thiadiazepine nucleus. This class of heterocycle has not been previously described in the literature. Moreover, the 3*R*,1'*S* configuration was considered necessary for an optimal binding to the active site of the enzyme.[3] Thus, a stereospecific synthesis from easily available chiral starting materials was envisaged.

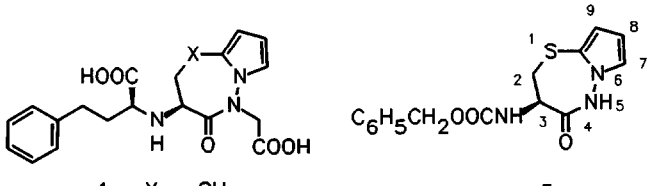
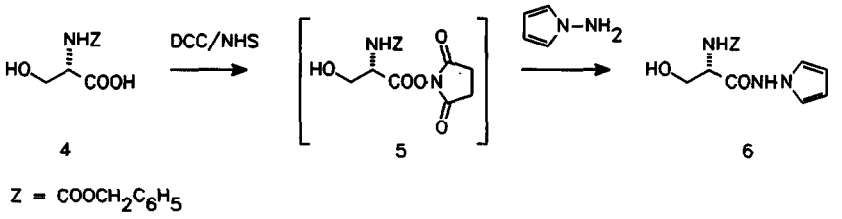


Figure 1

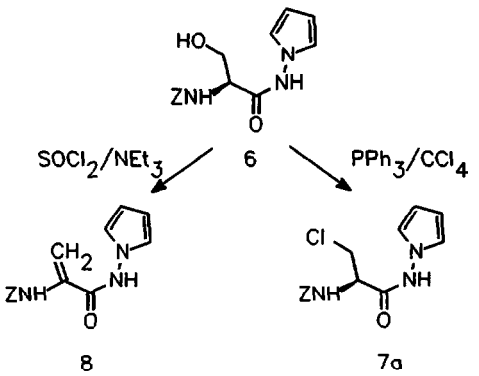


Scheme 1

The key intermediate **3** possesses the characteristic framework pyrrolo[2,1-*b*][1,3,4]thiadiazepine, and the 3*R* configuration. Our synthetic procedure was devised on the basis of final formation of the thiadiazepine S1-C2 bond through an intramolecular displacement of a halogen atom by a thiol group.

An N-protected derivative of L-serine was selected as the chiral precursor. Thus, *N*-carbobenzoxy-L-serine (**4**) was converted to succinimidyl ester **5** on treatment with *N*-hydroxysuccinimide and *N,N'*-dicyclohexylcarbodiimide. The active ester **5** was treated without previous purification with *N*-aminopyrrole,[4] to afford amide **6** under smooth conditions in 54% overall yield. This sequence allowed to avoid any intermediate protection of the serine alcoholic function (see Scheme 1).

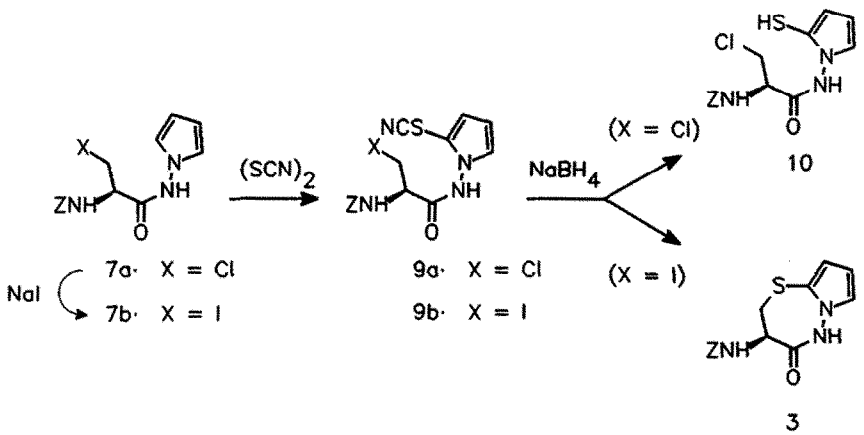
The subsequent transformation of compound **6** into the chloro derivative **7** was attempted under a variety of reaction conditions. Treatment with thionyl chloride caused extensive degradation of the product, which was attributed to the sensitivity of the pyrrole nucleus to the acidic byproducts of the reaction. On the other hand, when this reaction was carried out in the presence of triethylamine, the only isolated product was the elimination compound **8** in 45% yield. Appearance of two vinylic protons at δ 5.45 and 5.80 in the NMR spectrum, and IR absorption bands at 1670 and 1640 cm^{-1} due to the conjugated carbonyl group were characteristic for this stucture. Interestingly, elimination occurred even in the presence of the equimolecular amount of amine, which should be required to neutralize the hydrochloric acid produced in the formation of the chloride. These results suggested that essentially neutral reaction conditions would be necessary to effect this transformation. Among the variety of reagents available to convert alcohols into the corresponding chlor-



Scheme 2

ides, the combination triphenylphosphine-carbon tetrachloride is known to react with primary and secondary alcohols without neither producing acidic byproducts nor requiring basic conditions.[5] According to this, reaction of alcohol **6** with triphenylphosphine in a carbon tetrachloride-dimethylformamide solution afforded chloride **7a** at room temperature in excellent yield, no elimination product being formed under these conditions (see Scheme 2).

Our next goal was the introduction of a sulfur atom on the pyrrole ring. Aromatic substitutions by sulfur electrophiles provide a general method of formation of mercapto derivatives.[6] Thus, thiocyanogen and thiocyanogen halides react with activated aromatic compounds to yield aryl thiocyanates,[7] which can be regarded as protected forms of the thiol group. Pyrrole itself has been thiocyanated in methanolic solution with *in situ* generated thiocyanogen at very low temperature[8a] or with copper(II) thiocyanate at 0 °C.[8b] Although thiocyanation of pyrrole was initially believed to take place at position 3, further evidences[9] revealed that the actual product of this reaction was 2-thiocyanatopyrrole. In our case, reaction of **7a** with thiocyanogen, generated from potassium thiocyanate and bromine at -70 °C, gave thiocyanate **9a** in 72% yield. In the IR spectrum, an absorption band at 2160 cm^{-1} was characteristic for the thiocyanato group. As expected, in the NMR spectrum, the three nonequivalent pyrrole protons at δ 6.20, 6.63, and 6.85 showed a coupling pattern consistent with substitution at position 2.[9a] Cleavage of thiocyanates to give the corresponding thiols has been effected either under hydrolytic[6] or under reductive conditions.[6] Sodium borohydride was selected as the suitable reagent to effect this cleavage because of the smooth reaction conditions required and the compatibility with the other functional groups present in the molecule. In similar cases, the *in situ* generated arylthiol either from a thiocyanate[10] or from a disulfide function[11] displaced a side-chain chlorine atom with formation of an eight- or a seven-membered cyclic thioether. However, in our case, although treatment of thiocyanate **9a** with sodium borohydride at room temperature gave rise to the disappearance of the thiocyanate function, the desired bicyclic compound was not obtained from the reaction mixture. Instead, in one run, a small amount of the unstable thiol **10** was isolated. Support for this structure rather than the disulfide analogue was obtained on potentiometric titration. Thus, two acidic groups were found for compound **10**, which were assigned to thiol and amide-NH functions. However, this compound failed to cyclize to **3** on heating even in the presence of bases and potassium iodide, and led only to untrac-

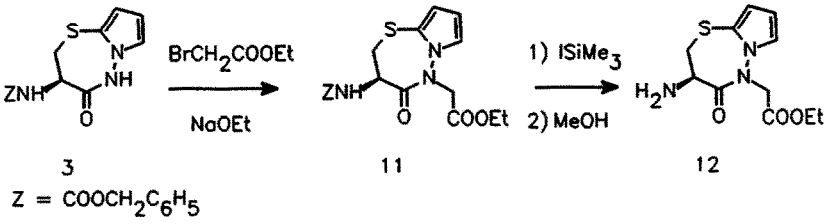


Scheme 3

table mixtures of degradation products. This inability to undergo the cyclization was attributed to an insufficient reactivity of the chloride as a leaving group. Consequently, it was decided to undertake the same synthetic sequence from the analogous iodide.

Iodide **7b** was prepared by treatment of chloride **7a** with excess sodium iodide in refluxing acetone. On treatment with thiocyanogen as before, the corresponding iodothiocyanate **9b** was obtained. In contrast to the chloroderivative **9a**, reductive treatment of **9b** with sodium borohydride did not allow isolation of the intermediate thiol since intramolecular nucleophilic displacement occurred under the reaction conditions, affording in one synthetic step the desired bicyclic derivative **3** (see Scheme 3). In the NMR spectrum of **3**, signals for the diastereotopic protons of position 2 at δ 2.51 and 3.60, with a geminal coupling constant of 11 Hz, were characteristic.

Introduction of the acetate chain on the endocyclic amide N was effected by treatment with ethyl bromoacetate in the presence of sodium ethoxide to give **11** in 84% yield. The acidity of its H allowed regioselective alkylation as reported for related compounds.[2,12] In the NMR spectrum appeared two doublets at δ 3.90 and 5.10 with a coupling constant of 17 Hz due to the diastereotopic protons of the acetate group. Moreover, the signal for the 7-H was shifted about 0.3 ppm downfield, which was attributed to a steric hindrance with the acetate chain.



3

Z = $COOCH_2C_6H_5$

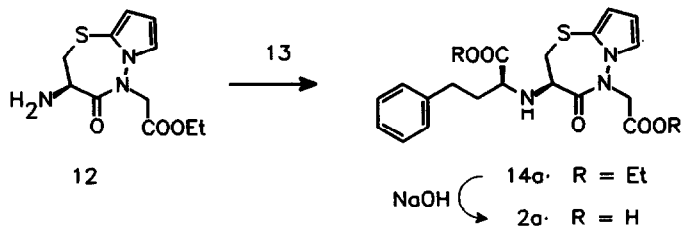
11

12

Scheme 4

Removal of the *N*-carbobenzoxy protective group was devised through a hydrolytic cleavage.[13] Since selectivity was required in the presence of other hydrolyzable groups, iodotrimethylsilane proved to be a useful reagent. This compound effects cleavage of several functional groups, such as esters, ethers, acetals, and carbamates, under mild, non aqueous conditions.[14] Among these groups, alkyl carbamates are reported to be more reactive than other functions,[15] thus allowing a high degree of selectivity. Particularly, benzyl- and *tert*-butylcarbamates readily react at room temperature. This has prompted the use of the reagent as a selective deblocking agent in peptide synthesis.[15b] Treatment of the alkyl carbamate with iodotrimethylsilane affords trimethylsilyl carbamate, which on addition of an alcohol suffers smooth decarboxylation to produce the free amine. In our case, treatment of carbamate **11** with $ISiMe_3$ at room temperature, followed by addition of methanol, afforded amine **12** in 85% yield. Neither the ester nor the lactam functions were affected under these conditions.

The last stage of our synthetic scheme involved diastereoselective introduction of a substituent with *S* configuration on the amino group. Alkylation of amines with the chiral triflates of α-hydroxycarboxylates has been reported to proceed with complete inversion of the configuration of alkylating compound.[16] Thus, alkylation of amine **12** with (*R*)-ethyl 4-phenyl-2-[(trifluoromethylsulfonyl)oxy]butanoate **13**[17] gave **14a**, therefore assumed to possess the 3*R*,1'*S* configuration. In the 300 MHz NMR spectrum of **14a**, a triplet at



Scheme 5

δ 3.16 was characteristic for the 1'-H of the carboxypropyl chain, and a doublet of doublets at 3.43 for the 3-H. As we have demonstrated for related structures,[2] the absence of formation of epimer (*S,S*)-**14** would provide evidence of the optical purity of amine **12**. In order to assess this, alkylation of **12** was effected with racemic ethyl 2-bromo-4-phenylbutanoate[18] to afford a mixture of diastereomeric **14a** and **14b** in about equal proportions. In the NMR spectrum of isomer **14b**, with *R,R* configuration, a triplet at δ 3.04 was characteristic of the 1'-H. Since these isomers could be easily differenciated on the 300 MHz NMR spectra and analytical TLC,[19] evidence was obtained of the absence of appreciable formation of diastereoisomer (*S,S*)-**14**[20] in the reaction with triflate **13**.

Finally, hydrolysis of diester **14a** under controlled conditions afforded the target diacid **2a**, with the desired 3*R*,1'*S* configuration. Furthermore, hydrolysis of diastereoisomer **14b** in an analytical scale afforded diacid **2b**. Comparison of the NMR spectra and analytical TLC[21] of **2a** and **2b** allowed confirmation of formation of a single isomer of **2** from pure **14a**. Thus, absence of epimerization during the hydrolysis was verified. Compounds **1** and **2** were tested for their biological activity and proved to be potent ACE inhibitors. The detailed biological results are to be reported on a separate paper.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. Infrared (IR) spectra were registered on a Perkin-Elmer 1710 spectrometer, and only noteworthy absorptions are listed. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Bruker WP80CW (80 MHz) or, when indicated, on a Varian Gemini 300 spectrometer, using TMS as internal standard. Chemical shifts are reported im ppm downfield (δ) from TMS. Microanalyses were performed on a Perkin-Elmer 2400 elemental analyzer. Optical rotations were measured on a Polartronic-D polarimeter, with a 1 dm pathlength cell. Column chromatography separations were performed on SiO_2 (silica gel 60, 0.063-0.200 mm, Merck). Analytical TLCs were run on silica gel 60 F_{254} (Merck) nanoplates, and the spots were visualized under UV light or on exposure to iodine vapor. Prior to evaporation, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate.

(*S*)-2-[(Benzyloxycarbonyl)amino]-3-hydroxy-*N*-(1-pyrrolyl)propanamide (5). To a solution of *N*-(benzyloxycarbonyl)-L-serine (**4**) (6 g, 25 mmol) and *N*-hydroxysuccinimide (3 g, 26 mmol) in anhydrous THF (40 mL), was added dropwise at 0 °C a solution of *N,N'*-dicyclohexylcarbodiimide (5.2 g, 25 mmol) in anhydrous

THF (40 mL). After stirring for 2 h at this temperature, and for further 1 h at room temperature, the resulting precipitate was removed by filtration. Then, a solution of *N*-aminopyrrole[4] (2.1 g, 25 mmol) in THF (5 mL) was added, and stirring was continued overnight. The solvent was evaporated *in vacuo*, and the residue was dissolved in refluxing EtOAc (10 mL), and hot filtered. On cooling, amide **5** (4.1 g, 54%) was obtained as white crystals of mp 151-153 °C. $[\alpha]^{20}_D$ -31 (MeOH, *c* 2%). IR (KBr) 3500-3200 (OH and NH), 1705 (NCOO), 1660 cm^{-1} (CON). NMR (CD_3OD) δ 3.80 (d, *J*=5 Hz, 2 H, 3-H), 4.28 (t, *J*=5 Hz, 1 H, 2-H), 4.60 (br s, 3 H, OH and NH), 5.10 (s, 2 H, CH_2Ph), 6.02 (t, *J*=2 Hz, 2 H, pyrrole-3H and -4H), 6.60 (t, *J*=2 Hz, 2 H, pyrrole-2H and -5H), 7.30 (s, 5 H, PhH). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.65; H, 5.92; N, 13.67.

2-[(Benzyloxycarbonyl)amino]-*N*-(1-pyrrolyl)propenamide (8). To a solution of **5** (1 g, 3.3 mmol) and triethylamine (0.34 g, 3.4 mmol) in dry CH_2Cl_2 (10 mL), was added dropwise at -20°C a solution of thionyl chloride (0.4 g, 3.4 mmol) in CH_2Cl_2 (10 mL). After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature, and was stirred for further 1 h. The solvent was evaporated *in vacuo* and the product was purified by column chromatography (Et_2O-$CHCl_3$ 3:7 as eluent) to give 0.4 g (45%) of **8**. IR (KBr) 2900-3700 (NH), 1720 (NCOO), 1670 (CON), 1640 (C=C). NMR (CD_3OD) δ 4.70 (s, 2 H, NH), 5.10 (s, 2 H, CH_2Ph), 5.45 (s, 1 H, =CH), 5.80 (s, 1 H, =CH), 6.05 (t, *J*=2 Hz, 2 H, pyrrole-3H and -4H), 6.60 (t, *J*=2 Hz, 2 H, pyrrole-2H and -5H), 7.30 (s, 5 H, PhH). Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.02; H, 5.46; N, 14.49.

(*R*)-2-[(Benzyloxycarbonyl)amino]-3-chloro-*N*-(1-pyrrolyl)propanamide (7a). To a solution of **5** (70 g, 0.23 mol) in anhydrous DMF (500 mL) and CCl_4 (700 mL) was added triphenylphosphine (70 g, 0.27 mmol), and the solution was stirred for 2 h at room temperature. After washing with water (3 x 700 mL), the solution was absorbed on silica gel (800 g) on a sintered glass funnel, washed with benzene (2 L), and then eluted with 1:3 Et_2O-C_6H_6 (2 L). Evaporation of this fraction afforded **9a** (62 g, 94%). An analytical sample was obtained by recrystallization from EtOAc: mp 154-156 °C. $[\alpha]^{20}_D$ -33 (MeOH, *c* 1.75%). IR (KBr) 3280 (NH), 1670 cm^{-1} (C=O). NMR (CD_3OD) δ 3.86 (d, *J*=6 Hz, 2 H, 3-H), 4.57 (t, *J*=6 Hz, 1 H, 2-H), 5.12 (s, 2 H, CH_2Ph), 6.05 (t, *J*=2 Hz, 2 H, pyrrole-3H and -4H), 6.60 (m, 2 H, pyrrole-2H and -5H), 7.31 (s, 5 H, PhH). Anal. Calcd for $C_{15}H_{16}N_3O_3Cl$: C, 55.99; H, 5.01; N, 13.06; Cl, 11.02. Found: C, 56.10; H, 4.93; N, 12.90; Cl, 10.81.

(*R*)-2-[(Benzyloxycarbonyl)amino]-3-iodo-*N*-(1-pyrrolyl)propanamide (7b). A mixture of chloride **7a** (62 g, 0.19 mol) and sodium iodide (160 g, 1.07 mol) in acetone (2 L) was heated to reflux for 48 h. After concentration to half the initial volume, water (2 L) was cautiosly added. The resulting precipitate was collected by filtration, washed with 1:2 acetone-water, and vacuum dried, to afford **7b** (36 g, 45%): mp 172−174 °C (benzene). $[\alpha]^{20}_D$ -37 (MeOH, *c* 1.8%). IR (KBr) 3280 (NH), 1670 cm^{-1} (C=O). NMR (CD_3OD) δ 3.55 (m, 2 H, 3-H), 4.47 (br t, *J*=6.5 Hz, 1 H, 2-H), 5.15 (s, 2 H, CH_2Ph), 6.05 (t, *J*=2 Hz, 2 H, pyrrole-3H and −4H), 6.60 (m, 2 H, pyrrole-2H and -5H), 7.30 (s, 5 H, PhH). Anal. Calcd for $C_{15}H_{16}N_3O_3I$: C, 43.60; H, 3.90; N, 10.17; I, 30.71. Found: C, 43.88; H, 3.91; N, 10.13; I, 30.38.

(*R*)-2-[(Benzyloxycarbonyl)amino]-3-chloro-*N*-(2-thiocyanato-1-pyrrolyl)propanamide (9a). To a suspension of potassium thiocyanate (2.6 g, 27 mmol) in MeOH (6 mL), was added dropwise at -70 °C a

solution of bromine (1.9 g, 12 mmol) in MeOH (6 mL), and was stirred at this temperature for 15 min longer. Then, a solution of **7a** (3.9 g, 12 mmol) in MeOH (35 mL) was added at a temperature below -60 °C. The mixture was stirred at -70 °C for 2 h, and allowed to warm to room temperature. Then, was poured onto ice-water, and extracted with CH_2Cl_2. After evaporation of the dried organic extracts, the product was purified by column chromatography (Et_2O-benzene 2:8 as eluent) to afford 3.3 g (72%) of **9a**, as a solid: mp 119-121 °C. IR (KBr) 3280 (NH), 2160 (SCN), 1720 (NCOO), 1680 cm^{-1} (CON). NMR ($CDCl_3$) δ 3.80-4.10 (*m*, 2 H, 3-H), 4.82 (*m*, 1 H, 2-H), 5.13 (s, 2 H, CH_2Ph), 5.90 (*br* d, J=8 Hz, 1 H, NHCOO), 6.20 (t, J=3.5 Hz, 1 H, pyrrole-4H), 6.63 (dd, J=3.5 and 2 Hz, 1 H, pyrrole-3H), 6.85 (dd, J=3.5 and 2 Hz, 1 H, pyrrole-5H), 7.30 (s, 5 H, PhH), 9.75 (br s, 1 H, CONH). Anal. Calcd for $C_{16}H_{15}N_4O_3ClS$: C, 50.73; H, 3.99; N, 14.79; Cl, 9.36; S, 8.46. Found: C, 50.93; H, 3.97; N, 14.64; Cl, 9.11; S, 8.19.

(*R*)-2-[(Benzyloxycarbonyl)amino]-3-iodo-*N*-(2-thiocyanato-1-pyrrolyl)propanamide (9b). Operating as above, from 5.2 g (53 mmol) of potassium thiocyanate, 3.8 g (24 mmol) of bromine, and 10 g (24 mmol) of **7b**, 7.8 g (68%) of thiocyanate **9b** was obtained: mp 148-150 °C (dec). $[\alpha]^{20}_D$ -32 (MeOH, *c* 1.3%). IR (KBr) 3280 (NH), 2160 (SCN), 1720 (NCOO), 1680 cm^{-1} (CON). NMR ($CDCl_3$) δ 3.50 (d, J=6 Hz, 2 H, 3-H), 4.65 (m, 1 H, 2-H), 5.13 (s, 2 H, CH_2Ph), 6.20 (t, J=3.5 Hz, 1 H, pyrrole-4H), 6.40 (br d, J=8 Hz, 1 H, NHCOO), 6.63 (dd, J=3.5 and 2 Hz, 1 H, pyrrole-3H), 6.90 (br, 1 H, pyrrole-5H), 7.30 (s, 5 H, PhH). Anal. Calcd for $C_{16}H_{15}N_4O_3IS$: C, 40.86; H, 3.25; N, 11.91; I, 26.98; S, 6.82. Found: C, 40.94; H, 3.22; N, 11.63; I, 26.60; S, 6.55.

(*R*)-2-[(Benzyloxycarbonyl)amino]-3-chloro-*N*-(2-mercapto-1-pyrrolyl)propanamide (10). To a solution of **9a** (1 g, 2.6 mmol) in absolute EtOH (20 mL), sodium borohydride (0.25 g, 6.6 mmol) was added in one portion at -15 °C, and the solution was stirred for 1 h at 0 °C, and for further 2 h at room temperature. The reaction mixture was poured onto ice-water and was extracted with CH_2Cl_2. Evaporation of the dried organic extracts provided an oil, which was purified on preparative TLC with Et_2O-benzene (1:1) as eluent to afford 0.1 g of **10** (11%). IR (KBr) 3280 (NH), 1720-1680 cm^{-1} (C=O). NMR ($CDCl_3$) δ 3.75 (m, 2 H, 3-H), 4.60 (m, 1 H, 2-H), 5.10 (s, 2 H, CH_2Ph), 5.75 (br d, J=8 Hz, 1 H, NHCOO), 6.10 (t, J=4 Hz, 1 H, pyrrole-4H), 6.38 (dd, J= 4 and 2 Hz, 1 H, pyrrole-3H), 6.85 (dd, J=4 and 2 Hz, 1 H, pyrrole-5H), 7.30 (s, 5 H, PhH), 9.05 (br s, 1 H, CONH). Anal. Calcd for $C_{15}H_{16}N_3O_3ClS$: C, 50.92; H, 4.56; N, 11.88; Cl, 10.02; S, 9.06. Found: C, 50.57; H, 4.70; N, 11.65; Cl, 9.92; S, 8.87.

(*R*)-3-[(Benzyloxycarbonyl)amino]-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepin-4-one (3). To a solution of **9b** (7.8 g, 16.6 mmol) in absolute EtOH (350 mL), sodium borohydride (1.6 g, 41.5 mmol) was added at -10 °C. The solution was allowed to warm to room temperature, and was stirred for 2 h longer. Then, was poured on water, acidified to pH 5-6 with HCl, and extracted with CH_2Cl_2. The crude product was purified by column chromatography ($CHCl_3$ as eluent), to give **3** (3.6 g, 68%) as a solid: mp 233-235 °C (*i*-PrOH). $[\alpha]^{20}_D$ -124 ($CHCl_3$, *c* 1%). IR (KBr) 3300-3150 (NH), 1725 (NCOO), 1680 cm^{-1} (CON). NMR ($CDCl_3$) δ 2.50 (t, J=11 Hz, 1 H, 2-H_A), 3.56 (dd, J=11 and 7 Hz, 1 H, 2-H_B), 4.20 (m, 1 H, 3-H), 5.02 (s, 2 H, CH_2Ph), 5.82 (br d, J=8 Hz, 1 H, NHCOO), 6.15 (t, J=3.5 Hz, 1 H, 8-H), 6.37 (dd, J=3.5 and 2 Hz, 1 H, 9-H), 6.87 (dd, J=3.5 and 2 Hz, 1 H, 7-H), 7.30 (s, 5 H, PhH), 8.95 (s, 1 H, 5-H). Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.94; H, 4.71; N, 13.10; S, 10.36.

(*R*)-Ethyl 3-[(Benzyloxycarbonyl)amino]-4-oxo-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepine-5-acetate (11). A solution of **3** (0.8 g, 2.5 mmol), sodium ethoxide (0.2 g, 2.9 mmol), and ethyl bromoacetate (0.6 g, 3.7 mmol) in absolute EtOH (80 mL) was stirred overnight at 40 °C. After vacuum evaporation of the solvent, water was added, and was extracted with benzene. Evaporation of the dried extracts provided pure **11** (0.85 g, 84%) as an oil. An analytical sample was obtained by column chromatography, with EtOAc-benzene (2:8) as eluent. $[\alpha]^{20}_D$ -176 ($CHCl_3$, *c* 1%). IR (neat) 3320 (NH), 1745 (COOEt), 1725 (NCOO), 1690 cm^{-1} (CON). NMR ($CDCl_3$) δ 1.28 (t, J=7.5 Hz, 3 H, CH_3), 2.51 (t, J=11 Hz, 1 H, 2-H_A), 3.60 (dd, J=11 and 7 Hz, 1 H, 2-H_B), 3.90 (d, J=17 Hz, 1 H, CH_ACOO), 4.10 (m, 1 H, 3-H), 4.24 (q, J=7.5 Hz, 2 H, $O\underline{CH_2}CH_3$), 5.02 (s, 2 H, CH_2Ph), 5.10 (d, J=17 Hz, 1 H, CH_BCOO), 5.70 (br d, J=8 Hz, 1 H, NH), 6.17 (t, J=3.5 Hz, 1 H, 8-H), 6.36 (dd, J=3.5 and 2 Hz, 1 H, 9-H), 7.15 (dd, J=3.5 and 2 Hz, 1 H, 7-H), 7.30 (s, 5 H, PhH). Anal. Calcd for $C_{19}H_{21}N_3O_5S$: C, 57.56; H, 5.25; N, 10.42; S, 7.95. Found: C, 57.26; H, 5.20; N, 10.14; S, 7.60.

(*R*)-Ethyl 3-Amino-4-oxo-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepine-5-acetate (12). To a solution of **11** (2 g, 5 mmol) in dry CH_2Cl_2 (15 mL), iodotrimethylsilane (1 mL, 7.3 mmol) was added dropwise, and the solution was stirred under N_2 for 1 h at room temperature. Then, MeOH (4 mL) was added, the mixture was stirred for 15 min, and the solvent removed in vacuo. The residue was dissolved in 1 N HCl (25 mL), washed with Et_2O, basified with $NaHCO_3$, and extracted with CH_2Cl_2. Evaporation of the dried organic extracts afforded **12** (1.2 g, 85%). An analytical sample was obtained by crystallization from Et_2O-hexane: mp 77-79 °C. $[\alpha]^{20}_D$ -133 (MeOH, *c* 3.2%). IR (neat) 3380 (NH), 1745 (COO), 1690 (CON), 1210 cm^{-1} (OEt). NMR ($CDCl_3$) δ 1.28 (t, J=7.5 Hz, 3 H, CH_3), 2.49 (t, J=9 Hz, 1 H, 2-H_A), 3.1-3.6 (m, 2 H, 3-H and 2-H_B), 3.90 (d, J=17 Hz, 1 H, CH_ACOO), 4.25 (q, J=7.5 Hz, 2 H, OCH_2), 5.15 (d, J=17 Hz, 1 H, CH_BCOO), 6.15 (t, J=3.5 Hz, 1 H, 8-H), 6.32 (dd, J=3.5 and 2 Hz, 1 H, 9-H), 7.13 (dd, J=3.5 and 2 Hz, 1 H, 7-H). Anal. Calcd for $C_{11}H_{15}N_3O_3S$: C, 49.06; H, 5.61; N, 15.60; S, 11.91. Found: C, 49.34; H, 5.80; N, 15.39; S, 11.69.

Ethyl3-[(1-Ethoxycarbonyl-3-phenylpropyl)amino]-4-oxo-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepine-5-acetate (14). Method A. A solution of **12** (1 g, 3.4 mmol), (*R*)-ethyl 4-phenyl-2-[(trifluoromethylsulfonyl)oxy]butanoate[17] (**13**) (1.16 g, 3.4 mmol), and NEt_3 (0.5 mL, 3.4 mmol) in CH_2Cl_2 (50 mL) was stirred overnight at 40 °C. The solution was washed with water, dried, and evaporated. The residue was purified by column chromatography (1:9 EtOAc-C_6H_6 as eluent), to afford **(3*R*,1'*S*)-ethyl 3-[(1-ethoxycarbonyl-3-phenylpropyl)amino]-4-oxo-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepine-5-acetate (14a)** (0.93 g, 60%) as an oil. IR (neat) 3150 (NH), 1740 (COO), 1690 (CON), 1200, 1040 cm^{-1} (OEt). NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J=7.1 Hz, 3 H, CH_3), 1.31 (t, J=7.1 Hz, 3 H, CH_3), 1.80-2.00 (m, 2 H, 2'-H), 2.30 (br s, 1 H, NH), 2.53 (t, J=11.1 Hz, 1 H, 2-H_A), 2.65 (t, J=8.2 Hz, 2 H, 3'-H), 3.01 (dd, J=11.1 and 6.8 Hz, 1 H, 2-H_B), 3.16 (t, J=6.5 Hz, 1 H, 1'-H), 3.43 (dd, J=11.1 and 6.8 Hz, 1 H, 3-H), 3.88 (d, J=17.5 Hz, 1 H, 5-N-CH_ACOO), 4.09 (q, J=7.1 Hz, 2 H, OCH_2), 4.26 (m, 2 H, OCH_2), 5.22 (d, J=17.5 Hz, 1 H, 5-N-CH_BCOO), 6.18 (t, J=3.6 Hz, 1 H, 8-H), 6.36 (dd, J=3.6 and 1.6 Hz, 1 H, 9-H), 7.13-7.29 (m, 6 H, 7-H and PhH). Anal. Calcd for $C_{26}H_{29}N_3O_5S$: C, 60.11; H, 6.36; N, 9.14; S, 6.98. Found: C, 59.86; H, 6.45; N, 9.12; S, 6.87.

Method B. A solution of **12** (0.27 g, 1 mmol), (±)-ethyl 2-bromo-4-phenylbutanoate[18] (0.32 g, 1.2 mmol), KI (0.05 g, 0.3 mmol), and NEt_3 (0.10 g, 1 mmol) in acetonitrile (15 mL) was heated to reflux overnight. Then the solvent was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic extracts consisted of a mixture of two isomers,[19] which were separated on preparative TLC with 3:7 hexane-EtOAc as eluent. The lower R_f isomer was identical to **14a** obtained in method A (0.11 g, 27%). The higher R_f isomer was identified as **(3*R*,1'*R*)-ethyl 3-[(1-ethoxycarbonyl-3-phenylpropyl)amino]-4-oxo-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepine-5-acetate (14b)** (0.12 g, 29%). NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, *J*=7.1 Hz, 3 H, CH_3), 1.30 (t, *J*=7.1 Hz, 3 H, CH_3), 1.61 (br s, 1 H, NH), 1.80-1.90 (m, 2 H, 2'-H), 2.55 (t, *J*=11.1 Hz, 1 H, 2-H_A), 2.55-2.65 (m, 2 H, 3'-H), 2.96 (dd, *J*=11.1 and 6.9 Hz, 1 H, 2-H_B), 3.04 (t, *J*=6.5 Hz, 1 H, 1'-H), 3.40 (dd, *J*=11.1 and 6.9 Hz, 1 H, 3-H), 3.86 (d, *J*=17.5 Hz, 1 H, 5-N-CH_ACOO), 4.14 (m, 2 H, OCH_2), 4.24 (m, 2 H, OCH_2), 5.21 (d, *J*=17.5 Hz, 1 H, 5-N-CH_BCOO), 6.18 (t, *J*=3.6 Hz, 1 H, 8-H), 6.37 (dd, *J*=3.6 and 1.6 Hz, 1 H, 9-H), 7.10-7.28 (m, 6 H, 7-H and PhH).

(3*R*,1'*S*)-3-[(1-Carboxy-3-phenylpropyl)amino]-4-oxo-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepine-5-acetic acid (2a). To a solution of **14a** (0.5 g, 1.1 mmol) in MeOH (20 mL), was added 1 N NaOH (3 mL), and was stirred at 50 °C for 90 min. After cooling, was added 1 N H_2SO_4 (3 mL), and the solvent was removed in vacuo at room temperature. The residue was extracted with MeOH (3 x 15 mL), and the extracts were concentrated to a volume of 10 mL, and precipitated by addition of Et_2O. The precipitate was recrystallized from MeOH-Et_2O to afford **2a** (0.17 g, 40%): mp 215-216 °C (dec). $[\alpha]^{20}_D$ -63.7 (1:1 MeOH-DMF, *c* 0.53%). IR (KBr) 3400 and 2450 (OH, NH), 1720 (COOH), 1680 cm^{-1} (CON). NMR (CD_3OD, 300 MHz) δ 2.00 (m, 2 H, 2'-H), 2.65-2.75 (m, 2 H, 3'-H), 2.76 (t, *J*=11 Hz, 1 H, 2-H_A), 3.40 (dd, *J*=11 and 7 Hz, 1 H, 2-H_B), 3.51 (t, *J*= 5.5 Hz, 1 H, 1'-H), 3.57 (dd, *J*=11 and 7 Hz, 1 H, 3-H), 3.63 (d, *J*=17 Hz, 1 H, 5-N-CH_ACOO), 5.04 (d, *J*=17 Hz, 1 H, 5-N-CH_BCOO), 6.19 (app t, *J*=3.6 Hz, 1 H, 8-H), 6.37 (dd, *J*=3.9 and 1.6 Hz, 1 H, 9-H), 7.10-7.25 (m, 5 H, PhH), 7.39 (dd, *J*=3.2 and 1.8 Hz, 1 H, 7-H). Anal. Calcd for $C_{19}H_{21}N_3O_5S$: C, 56.56; H, 5.25; N, 10.42; S, 7.95. Found: C, 56.38; H, 5.10; N, 10.04; S, 8.03.

(3*R*,1'*R*)-3-[(1-Carboxy-3-phenylpropyl)amino]-4-oxo-2,3,4,5-tetrahydropyrrolo[2,1-*b*][1,3,4]thiadiazepine-5-acetic acid (2b). Operating as above, from **14b** (100 mg, 0.2 mmol), 40 mg of **2b** (47%) was obtained. IR (KBr) 3400 and 2500 (OH, NH), 1720 (COOH), 1680 cm^{-1} (CON). NMR (CD_3OD, 300 MHz) δ 1.86 (m, 2 H, 2'-H), 2.58 (t, *J*=11 Hz, 1 H, 2-H_A), 2.60-2.80 (m, 2 H, 3'-H), 3.18 (dd, *J*=11 and 6.8 Hz, 1 H, 2-H_B), 3.24 (t, *J*=6 Hz, 1 H, 1'-H), 3.47 (dd, *J*=11 and 6.8 Hz, 1 H, 3-H), 3.94 (d, *J*=17.6 Hz, 1 H, 5-N-CH_ACOO), 5.57 (d, *J*=17.6 Hz, 1 H, 5-N-CH_BCOO), 6.23 (app t, *J*=3.4 Hz, 1 H, 8-H), 6.40 (dd, *J*=3.9 and 1.6 Hz, 1 H, 9-H), 7.10-7.20 (m, 5 H, PhH), 7.24 (dd, *J*=3.3 and 1.6 Hz, 1 H, 7-H). Anal. Calcd for $C_{19}H_{21}N_3O_5S$: C, 56.56; H, 5.25; N, 10.42; S, 7.95. Found: C, 56.68; H, 5.05; N, 10.25; S, 7.76.

Acknowledgment. This work was done with support of the Plan de Fomento a la Investigación (Farma II) from the Ministerio de Industria, Comercio y Turismo (1991-93). We are grateful to Mr. Joan Nieto for skillful experimental contribution. We also thank Mr. José M. Fernández and his staff for the analytical and spectral determinations.

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19. TLC: 3:7 EtOAc-hexane. R_f 0.35 for the *R,S* isomer (**14a**), and 0.40 for the *R,R* isomer (**14b**).
20. Isomer (*S,S*)-**14** would be the enantiomer of (*R,R*)-**14**, thus having the same R_f and NMR spectrum.
21. TLC: 1:1:1:5 AcOH-H_2O-*n*-BuOH-EtOAc. R_f 0.52 for the *R,S* isomer (**2a**), and 0.37 for the *R,R* isomer (**2b**).