at this temperature for an additional 1.0 h, cooled to 5 °C, and diluted with 150 mL of H_2O. Stirring was continued at 5 °C for 1.0 h, and the product was collected by filtration. It was washed with 300 mL of H_2O followed by cold (5 °C) acetone (3 × 100 mL) to give 81.9 g (75.2%) of 1, mp 198–199 °C, homogeneous by TLC (silica gel; 95:1:7:1 $CHCl_3$–CH_3OH–NH_4OH): UV (EtOH) 230 (sh, ϵ = 19 200), 289 (ϵ = 6780) nm; IR 3525, 3425, 1620, 1130 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.54 (2 H, s), 3.65 (3 H, s), 3.73 (6 H, s), 5.83 (2 H, s), 6.16 (2 H, s), 6.53 (2 H, s), 7.55 (1 H, s); MS m/z 290 (100, M^+), 275 (20), 259 (20), 243 (7). Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.23; N, 19.30. Found: C, 57.66; H, 6.30; N, 19.58. Trimethoprim prepared above may be recrystallized from aqueous EtOH, 95% return, mp 199–200 °C.

Enamine 24. A stirred solution of NaOMe in MeOH (from 4.6 g of Na and 62.0 mL of MeOH) was treated under Ar with 24.7 g (0.1 mol) of cinnamonitrile **20** and 50.0 mL of DMF. The mixture was stirred at 98 °C for 18 h, cooled to room temperature, poured into 200 mL of brine, and extracted with Et_2O (2 × 200 mL). The extract was washed with 250 mL of brine, dried ($MgSO_4$), and evaporated to give 26 g of a brown semisolid, which gave 10 g of a solid on trituration with 50 mL of ether. Repeated crystallizations from MeOH/Et_2O, and finally MeOH, gave 5.0 g (19%) of **24**, mp 85–86 °C: UV (EtOH) 230 (ϵ = 9850), 285 (ϵ = 21 400) nm; IR 2170, 1625, 1090 cm^{-1}; NMR δ 1.98 (6 H, s), 2.23 (3 H, s), 3.26 (2 H, s), 3.83 (6 H, s), 6.11 (1 H, s), 6.65 (1 H, s), 6.71 (1 H, s); MS m/z 260 (100, M^+), 245 (57), 229 (20), 164 (70). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.19; H, 7.80; N, 10.83.

The sample of **24** prepared above was identical (mmp, mixed TLC, UV, IR, NMR) with a substance isolated from a preparation of **2** when DMF was used as a solvent and with the product derived from the NaOEt-catalyzed condensation of **18** with 3-(dimethylamino)propanenitrile[11] in DMSO.

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Registry No. **1**, 738-70-5; **2**, 6981-18-6; **9**, 110-67-8; (*Z*)-**10**, 50744-71-3; (*E*)-**10**, 39800-76-5; **11**, 7515-08-4; **12**, 494-99-5; (*Z*)-**13**, 68640-16-4; (*E*)-**13**, 141292-60-6; **14**, 7520-76-5; **15**, 54236-98-5; **16**, 141292-61-7; **17**, 86-81-7; **18**, 7721-62-2; **19**, 141292-62-8; **20**, 7520-75-4; (*E*)-**21**, 141292-63-9; (*Z*)-**21**, 141292-66-2; **22**, 7520-70-9; (*E*)-**23**, 141292-64-0; (*Z*)-**23**, 141292-67-3; **24**, 141292-65-1; **26**, 104-93-8; HCO_2Me, 107-31-3; $(NH_2)_2C{=}NH{\cdot}H_2CO_3$, 100224-74-6; $(NH_2)_2C{=}NH{\cdot}HCl$, 50-01-1; $H_2C{=}CHCN$, 107-13-1; 3-bromo-4-methoxytoluene, 22002-45-5.

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Asymmetric Synthesis of Pyrrolo[1,2-*b*][1,2]diazepine Derivatives as Potential Antihypertensive Drugs

Jordi Bolôs, Ângel Pêrez, Santiago Gubert, Luîs Anglada, Aurelio Sacristân, and Josê A. Ortiz*

Medicinal Chemistry Department, Centro de Investigaciôn Grupo Ferrer, Juan de Sada, 32, 08028 Barcelona, Spain

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The asymmetric synthesis of compound **1**, with potential angiotensin-converting enzyme inhibitory activity, is reported. From the chiral precursor **5**, readily available from L-glutamic acid, two strategies to the key heterocyclic system pyrrolo[1,2-*b*][1,2]diazepine have been developed. The first one is based on the formation of the pyrrole nucleus in the early stages of the synthesis. The second strategy is based on the formation of the pyrrole in the final stages and can be regarded as a two-step Paal–Knorr *N*-aminopyrrole synthesis, in which intermediate N-protection is unnecessary.

Introduction

Angiotensin-converting enzyme (ACE; EC 3.4.15.1) is a peptidase which removes the carboxy-terminal dipeptide from several peptidic substrates.[1] ACE plays important physiological actions. The most relevant are the formation of the potent vasoconstrictor angiotensin II from the decapeptide angiotensin I[2] and the degradation of the vasodilating peptide bradykinin.[3] Compounds with inhibitory activity on ACE have application against hypertension[4] and congestive heart failure[5] in man, and several of them have been marketed. Captopril,[6] a thiol-containing compound, was the first orally effective ACE inhibitor; however, the incidence of some side effects was attributed to the mercapto function.[7] This led to the introduction of a new class of ACE inhibitors, the carboxyalkyl dipeptides, such as enalapril,[8] and more recently its conformationally restricted derivatives, the bicyclic lactams, such as benazepril[9] and cilazapril.[10]

Among the conformationally restricted derivatives, a seven-membered lactam is the common feature for the most active compounds. Furthermore, a benzo fusion

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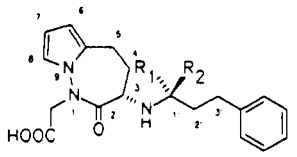
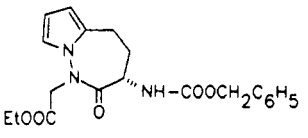
enhances the inhibitory potency.[9] However, heterocycle-fused lactams have not yet been investigated. In this context, as a part of a program aimed at preparing new antihypertensive drugs, we planned the synthesis of compound **1a** as a potential ACE inhibitor. This compound contains as a characteristic feature the lactamic framework pyrrolo[1,2-*b*][1,2]diazepin-2-one. Since some of the stereochemical requirements of the enzyme are known,[11] the synthesis was planned in a stereospecific way in order to assure the required *S* configuration in both chiral centers.





1a, R_1 = COOH, R_2 = H
1b, R_1 = H, R_2 = COOH

2

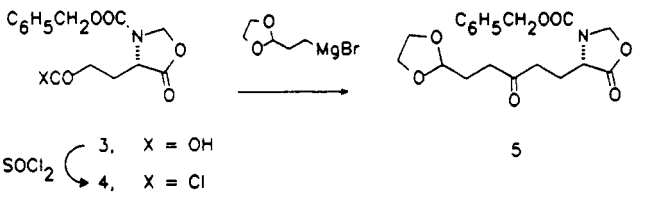
Compound **2**, the key intermediate in the synthesis of the target molecules, shows the characteristic pyrrolo-[1,2-*b*][1,2]diazepine heterocyclic nucleus. There are no reports in the literature concerning the preparation of this class of heterocycle.[12] In this paper, we describe two different synthetic strategies leading to compound **2** that consist of the formation of the pyrrole nucleus in either the early or in the final steps.

Results and Discussion

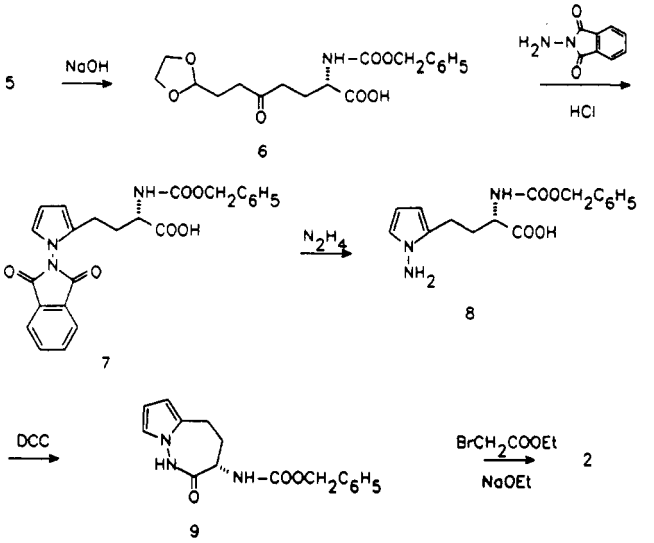
Pyrroles have been synthesized[13] from primary amines and 1,4-dicarbonyl compounds (Paal–Knorr synthesis)[14] or their cyclic acetal forms (Clauson–Kaas synthesis).[15] In an analogous manner, formation of *N*-aminopyrroles has been accomplished from N-protected hydrazines.[12a,16] In our case, the optically active, protected dicarbonyl compound **5** was the common intermediate in both strategies. Its synthesis is depicted in Scheme I. Oxazolidinone **3**,[17] an easily accessible, protected derivative of L-glutamic acid, was selected as the chiral precursor. On treatment with thionyl chloride at room temperature, the corresponding acid chloride **4**[18] was obtained as a solid, in almost quantitative yields. Grignard reagents of 2-(2-bromoethyl)-1,3-dioxane[19] and 2-(2-bromoethyl)-1,3-dioxolane[20] are known to react with acid chlorides to give ketones without appreciable formation of the tertiary alcohol resulting from the diaddition process. Thus, reaction of the acid chloride **4** with the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxolane gave the ketone **5** in 90% yield.

The first synthetic strategy to the bicyclic system (Scheme II) is based on the initial formation of the pyrrole

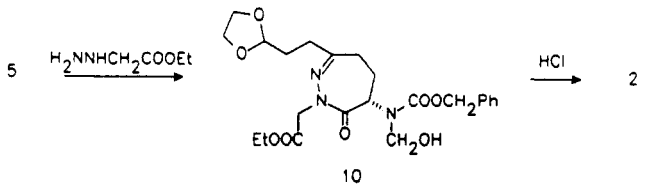
Scheme I



Scheme II



Scheme III



nucleus and leads to the N-1-unsubstituted compound, thus allowing the introduction of the acetate chain or, eventually, of more complex substituents. Due to its high reactivity, it was found advisable to first hydrolyze the oxazolidinone ring.[21] As reported in similar cases, alkaline hydrolysis of this function is accompanied by spontaneous elimination of the formaldehyde unit.[17] Thus, treatment of oxazolidine **5** with NaOH under controlled conditions gave the optically active *N*-carbobenzoxy amino acid **6**. Reaction of this acid with *N*-aminophthalimide in the presence of hydrochloric acid afforded the phthalimidopyrrole **7** in 23% yield. Subsequent deprotection of the phthaloyl group by treatment with hydrazine hydrate gave the aminopyrrole **8**. By treatment with dicyclohexylcarbodiimide, cyclization to the pyrrolodiazepinone **9** was effected in 53% yield. In the IR spectrum of **9**, a carbonyl absorption at 1680 cm^{-1} was observed, corresponding to the 7-membered lactam. The NMR spectrum shows the three characteristic pyrrole protons at δ 5.90, 6.05, and 6.63, appearing at somewhat lower fields than in the open structure **8** due to the acylation of the *N*-aminopyrrole system. Regioselective alkylation on the endocyclic amide N was conducted in the presence of sodium ethoxide by taking advantage of the acidity of its H[22] to afford the

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(21) When the reaction with *N*-aminophthalimide was conducted on **5**, only a complex mixture of products was obtained, showing a partial opening of the oxazolidinone ring.

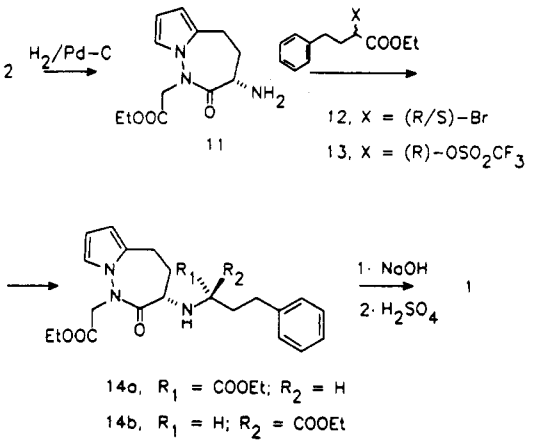
desired intermediate **2**. The NMR spectrum of **2** shows two doublets at δ 4.47 and 4.67, being characteristic of the diastereotopic methylene protons of the acetate chain.

An alternative and direct route to **2** has been developed (Scheme III), which consists of the final formation of the pyrrole nucleus. This approach can be regarded as a variant of the Paal–Knorr synthesis involving two separate steps from the unprotected hydrazine and the monoacetal of the dicarbonyl compound **5**. In the first step, formation of the hydrazone function and simultaneous N-protection as the required hydrazide was achieved by formation of the diazepinone **10**, on treatment of **5** with ethyl hydrazinoacetate. No loss of the *N*-hydroxymethyl moiety took place in this case, as evidenced by the two diastereotopic protons at δ 4.72 and 5.00 in the 500-MHz NMR spectrum. This fact has been reported in similar cases[18a] of opening of the oxazolidinone ring with amines. Previous removal of this formaldehyde unit was found to be unnecessary. Thus, the subsequent treatment of **10** with hydrochloric acid led to the pyrrolodiazepinone **2**, with concomitant loss of the hydroxymethyl group. Although isolation of the unstable diazepinone **10** is a tedious process, both steps can be effected in a more convenient procedure, without purification of this intermediate, in a 16% overall yield (see Experimental Section).

Deprotection of the *N*-benzyloxycarbonyl group of **2** was achieved by catalytic hydrogenolysis under the usual conditions to give the free amine **11** in 89% yield. The optical purity of the product from both synthetic routes was calculated by conversion to the diastereomeric (*R*)- and (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl derivatives (MPTA, Mosher amides).[23] The 500-MHz NMR spectrum of the (*S*)-MPTA-amide showed a signal at δ 3.44 for the methoxy group, whereas the (*R*)-MPTA-amide showed a signal at δ 3.27. By integration of the signals corresponding to the minor diastereoisomeric impurities in each case, an enantiomeric excess higher than 98% was estimated for the amine **11** from both synthetic strategies. Moreover, the chemical shift for the 3-H in the (*S*)-amide (δ 4.38) is higher than the corresponding shift for the (*R*)-amide (δ 4.35), whereas for all the 4-H and 5-H, the chemical shift is lower in the (*S*)-amide. These differences agree with those reported in a recent paper[24] dealing with the elucidation of the absolute configuration of α-amino acid derivatives and are consistent with the *S* configuration of amine **11**.

Alkylation of amine **11** was effected either with the racemic bromide **12**[25] or with the enantiomerically pure (*R*)-triflate **13**[26] (Scheme IV). As expected, racemic bromide gave a mixture of two diastereoisomers, **14a** and **14b**, in about equal proportions,[27] which were separated on column chromatography. Alkylation of amines with the triflates of α-hydroxy carboxylates has been reported to proceed with complete inversion of the configuration of the alkylating agent.[26,28] Thus, reaction between amine

Scheme IV



11 and triflate **13** gave a single isomer (**14a**), which was assumed to have the desired *S,S* configuration. The absence of appreciable formation of the diastereoisomer **14b**[29] provided further evidence for the high optical purity of amine **11**. In the NMR spectra, a triplet at δ 3.23 was characteristic for the 1′-H of isomer **14a**, and a triplet at δ 3.07 for the isomer **14b**. The 3-H appears as a doublet of doublets at δ 3.09 for the isomer **14a** and at δ 3.04 for **14b**.

Finally, hydrolysis of the diastereomeric diesters **14**, under controlled conditions, provided the respective diacids **1**. Each isomer was completely free from the other, as evidenced by analytical TLC.[30] Thus, the absence of epimerization during the hydrolysis was confirmed.

Each isomer was tested for its ACE inhibitory activity. Compound **1a**, with *S,S* configuration, is a powerful ACE inhibitor in vitro, about twice as potent as captopril, whereas, as expected, its epimer **1b** is about 20 times less potent.[31]

Experimental Section

General Methods. Melting points were determined in open capillary tubes and are uncorrected. ^{1}H-NMR spectra were recorded at 80 or, when indicated, at 500 MHz. Optical rotations were measured with a 1-dm cell. Column chromatography separations were carried out on SiO_2 (silica gel 60, 0.063–0.200 mm, Merck). Preparative HPLC was performed with a Waters PrepPak 500 cartridge (Porasil 125 A, 15–20 μm), and the peaks were located with a UV detector at 280 nm. Analytical TLCs were performed on silica gel 60 F_{254} (Merck) nanoplates, and the spots were visualized under UV light or on exposure to iodine vapor. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder.

(*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidinepropanoyl Chloride (4).[18] To a solution of acid **3**[17] (120 g, 0.41 mol) in dry CH_2Cl_2 (500 mL) was added thionyl chloride (33 mL, 53.8 g, 0.45 mol) dropwise. After addition of DMF (0.5 mL), the solution was stirred at room temperature for 2 h. Vacuum evaporation of the solvent at room temperature afforded an oily residue that solidified on standing. The residue was triturated with anhydrous Et_2O, filtered under N_2, and vacuum dried, affording 126.5 g (99%) of acid chloride **4** that was used without further purification in the next step: mp 72–74 °C (THF–hexane) (lit. mp 64–65 °C,[18a] 76–78 °C[18b]); $[\alpha]^{20}_D$ +88 (*c* 1%, CH_2Cl_2) (lit. $[\alpha]^{20}_D$ +69.3,[18a] +93[18b]).

(*S*)-3-(Benzyloxycarbonyl)-4-(6,6-(ethylenedioxy)-3-oxohexyl)oxazolidin-5-one (5). To a mixture of magnesium turnings

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(27) TLC: C_6H_6–Et_2O (1:1). R_f 0.42 for the isomer **14a** and 0.46 for the isomer **14b**.

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(29) Compound from racemized (*R*)-amine **11** and (*R*)-triflate **13** would be the enantiomer of **14b** and have the same R_f on TLC.

(30) TLC: AcOH–H_2O–*n*-BuOH–EtOAc (1:1:1:5). R_f 0.32 for the isomer **1a** and 0.23 for the isomer **1b**.

(31) Detailed biological results will be published in a separate paper.

(19.8 g, 0.81 mol) and anhydrous THF (150 mL) under N_2 was added dropwise a solution of 2-(2-bromoethyl)-1,3-dioxolane (79.2 g, 0.44 mol) in anhydrous THF (250 mL), keeping the temperature between 22 and 26 °C. After being stirred for 30 min at room temperature, the solution was filtered under N_2 through glass wool and transferred to a dropping funnel. This solution was added dropwise during a period of 3 h, under N_2, to a cooled solution of acid chloride 4 (126.5 g, 0.41 mol) in anhydrous THF (300 mL), keeping the temperature below −65 °C. The solution was stirred for an additional 1 h at this temperature and allowed to warm slowly to rt. Then, water (250 mL) was added, and the solution was extracted with EtOAc. The extracts were washed with brine and evaporated to give 138 g of 5 (90%) as an oil: IR (neat) 1800, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (m, 2 H, 5-H), 2.25 (m, 2 H, 1-H), 2.50 (m, 4 H, 2-H and 4-H), 3.85 (m, 4 H, OCH_2CH_2O), 4.32 (t, J = 6 Hz, 1 H, NCHCOO), 4.87 (t, J = 4 Hz, 1 H, 6-H), 5.18 (s, 2 H, $PhCH_2$), 5.19 (d, J = 5 Hz, 1 H, NCH_AO), 5.50 (d, J = 5 Hz, 1 H, NCH_BO), 7.37 (s, 5 H, ArH). An analytical sample was obtained by column chromatography with 1:3 EtOAc–$CHCl_3$ as eluent: $[\alpha]^{20}_D$ +60.5 (c 1%, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.18; H, 6.35; N, 3.40.

(S)-2-((Benzyloxycarbonyl)amino)-8,8-(ethylenedioxy)-5-oxooctanoic Acid (6). A solution of oxazolidine 5 (26.6 g, 70 mmol) in MeOH (200 mL) and 1 N NaOH (80 mL) was stirred overnight at room temperature. After removal of the MeOH in vacuo at rt, water (250 mL) was added, the pH was adjusted to 3 by addition of HCl, and the solution was extracted with EtOAc to give 21.5 g (83%) of acid 6 as an oil: IR (neat) 3360 (NH), 3400–2800 (OH), 1720–1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.80–2.20 (m, 4 H, 3-H and 7-H), 2.30–2.70 (m, 4 H, 4-H and 6-H), 3.85 (m, 4 H, OCH_2CH_2O), 4.40 (m, 1 H, 2-H), 4.87 (br t, J = 4 Hz, 1 H, 8-H), 5.10 (s, 2 H, $PhCH_2$), 5.80 (br s, 1 H, NH), 7.30 (s, 5 H, ArH), 8.70 (br s, 1 H, OH). An analytical sample was obtained by column chromatography with EtOAc as eluent: $[\alpha]^{20}_D$ +10.8 (c 3%, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.35; N, 3.83. Found: C, 59.31; H, 6.47; N, 3.67.

(S)-2-((Benzyloxycarbonyl)amino)-4-(1-phthalimido-2-pyrrolyl)butanoic Acid (7). A mixture of acid 6 (7.67 g, 21.5 mmol) and *N*-aminophthalimide (3.44 g, 21.2 mmol) in THF (50 mL) was heated at 50 °C. After addition of 20% HCl (3.8 mL), the mixture was stirred at this temperature for 15 min and then cooled. Ethyl ether (80 mL) was added, and the solution was washed with water. Evaporation of the dried organic layer gave a foam that was purified on column chromatography with 3:1 $CHCl_3$–EtOAc as eluent to afford 2.2 g (23%) of 7 as a white solid: mp 179–181 °C (EtOAc); $[\alpha]^{20}_D$ +5.8 (c 0.5%, 9:1 MeOH–DMF); IR (KBr) 3360 (NH), 3600–2800 (OH), 1790, 1740 (CONCO), 1720 (NCOO), 1690 cm^{-1} (COOH); NMR ($CDCl_3$) δ 1.80–2.20 (m, 2 H, 3-H), 2.30–2.60 (m, 2 H, 4-H), 4.30 (m, 1 H, 2-H), 5.00 (s, 2 H, $PhCH_2$), 5.45 (br d, J = 7 Hz, 1 H, NH), 6.05 (dd, J = 3.5 and 1.5 Hz, 1 H, pyrrole-3H), 6.20 (t, J = 3.5 Hz, 1 H, pyrrole-4H), 6.57 (dd, J = 3.5 and 1.5 Hz, 1 H, pyrrole-5H), 7.27 (s, 5 H, PhH), 7.80 (m, 4 H, phthalimide-H). Anal. Calcd for $C_{24}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92. Found: C, 62.16; H, 4.93; N, 9.67.

(S)-2-((Benzyloxycarbonyl)amino)-4-(1-amino-2-pyrrolyl)butanoic Acid (8). A solution of 7 (3.17 g, 7.1 mmol) and hydrazine hydrate (0.76 mL, 0.78 g, 15.6 mmol) in MeOH (50 mL) was stirred at room temperature for 1 h. After removal of the solvent in vacuo, the residue was dissolved in water (50 mL) and washed with EtOAc. The aqueous solution was brought to pH 3 by addition of HCl and extracted with EtOAc. Evaporation of the extracts gave 1.69 g (75%) of 8 as a syrup. A sample was purified by column chromatography (EtOAc as eluent): IR (KBr) 3350 (NH), 2600 (OH), 1710 cm^{-1} (COO); NMR ($CDCl_3$) δ 1.80–2.40 (m, 2 H, 3-H), 2.40–3.30 (m, 2 H, 4-H), 4.35 (dd, J = 13 and 7 Hz, 1 H, 2-H), 5.05 (s, 2 H, $PhCH_2$), 5.60 (br s, 1 H, NH), 5.74 (dd, J = 3.5 and 1.5 Hz, 1 H, pyrrole-3H), 5.90 (t, J = 3.5 Hz, 1 H, pyrrole-4H), 6.53 (dd, J = 3.5 and 1.5 Hz, 1 H, pyrrole-5H), 6.98 (br s, 3 H, NH_2 and COOH), 7.30 (s, 5 H, PhH). Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.85; H, 6.24; N, 13.05.

(S)-3-((Benzyloxycarbonyl)amino)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepin-2-one (9). To a solution of 8 (1 g, 3.2 mmol) in dry CH_2Cl_2 (25 mL) was added DCC (0.66 g, 3.2 mmol), and the solution was stirred at room temperature for 30 min. After filtering off the resulting precipitate and evaporation, the product was purified on column chromatography with 3:1 $CHCl_3$–EtOAc as eluent to afford 0.5 g (53%) of 9 as a solid: mp 174–176 °C; $[\alpha]^{20}_D$ −38.5 (c 1%, MeOH); IR (KBr) 3300 (NH), 1730 (NCOO), 1680 cm^{-1} (CONH); NMR ($CDCl_3$) δ 1.70–2.40 (m, 2 H, 4-H), 2.60–3.00 (m, 2 H, 5-H), 4.25 (m, 1 H, 3-H), 5.05 (s, 2 H, $PhCH_2$), 5.60 (br d, J = 7 Hz, 1 H, NHCOO), 5.90 (dd, J = 3.5 and 1.5 Hz, 1 H, 6-H), 6.05 (t, J = 3.5 Hz, 1 H, 7-H), 6.63 (dd, J = 3.5 and 1.5 Hz, 1 H, 8-H), 7.30 (s, 5 H, PhH), 8.87 (br s, 1 H, 1-H). Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.05; H, 5.83; N, 13.97.

(S)-Ethyl 6-((Benzyloxycarbonyl)(hydroxymethyl)amino)-3-((3,3-ethylenedioxy)propyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-1,2-diazepine-1-acetate (10). A mixture of 5 (10 g, 26.5 mmol), ethyl hydrazinoacetate hydrochloride (4 g, 26 mmol), and sodium acetate (4 g, 48.8 mmol) in MeOH (100 mL) was heated at 50 °C for 30 min. After evaporation of the solvent, water was added and the solution was extracted with CH_2Cl_2. Evaporation of the solvent gave 11.3 g of an oil which was used without further purification in the next step. In another run, from 2 g (5.3 mmol) of 5 and 0.8 g (5.2 mmol) of ethyl hydrazinoacetate hydrochloride, the crude product was purified by preparative HPLC (EtOAc as eluent), affording 0.3 g (12%) of 10 as an oil: $[\alpha]^{20}_D$ −186 (c 1%, $CHCl_3$); IR (neat) 3430 (OH), 1750 (COOEt), 1720 (NCOO), 1685 cm^{-1} (NCO); NMR ($CDCl_3$, 500 MHz) δ 1.20 (t, J = 7.2 Hz, 3 H, CH_3), 1.90–2.00 (m, 2 H, 2′-H), 2.20–2.30 (m, 2 H, 4-H_A and 5-H_A), 2.35 (td, J = 12.8 and 8.5 Hz, 1 H, 5-H_B), 2.53 (t, J = 7.7 Hz, 2 H, 1′-H), 3.03 (td, J = 15.5 and 8.5 Hz, 1H, 4-H_B), 3.70–3.90 (m, 4 H, OCH_2CH_2O), 3.96 (d, J = 17 Hz, 1 H, CH_ACOO), 4.10 (m, 2 H, OCH_2CH_3), 4.72 (d, J = 11 Hz, 1 H, NCH_AO), 4.88 (d, J = 17 Hz, 1 H, CH_BCOO), 4.90 (t, J = 4 Hz, 1 H, 3′-H), 5.00 (d, J = 11 Hz, 1 H, NCH_BO), 5.08 (d, J = 12.5 Hz, 1 H, CH_APh), 5.16 (d, J = 12.5 Hz, 1 H, CH_BPh), 7.20–7.30 (m, 5 H, PhH). Anal. Calcd for $C_{23}H_{31}N_3O_8$: C, 57.85; H, 6.54; N, 8.80. Found: C, 58.04; H, 6.65; N, 8.97.

(S)-Ethyl 3-((Benzyloxycarbonyl)amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepine-1-acetate (2). Method A. From Compound 9. To a solution of 9 (0.77 g, 2.6 mmol) and NaOEt (0.18 g, 2.6 mmol) in absolute EtOH (80 mL) was added ethyl bromoacetate (0.4 mL, 0.6 g, 3.6 mmol), and the solution was stirred overnight at 40 °C. After evaporation of the solvent, water (150 mL) was added, and the solution was extracted with benzene. Evaporation of the dried organic extracts gave 0.6 g (61%) of 2 as an oil. An analytical sample was obtained by column chromatography, on eluting with CH_2Cl_2: $[\alpha]^{20}_D$ −54 (c 1%, $CHCl_3$); IR (neat) 3360 (NH), 1740 (COOEt), 1720 (NCOO), 1690 (NCO), 1210 cm^{-1} (OEt); NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H, CH_3), 1.90 (td, J = 12.5 and 7.7 Hz, 1 H, 4-H_A), 2.52 (tt, J = 12.5 and 7.7 Hz, 1 H, 4-H_B), 2.76 (dd, J = 14.5 and 7.7 Hz, 1 H, 5-H_A), 3.15 (ddd, J = 14.5, 12.5, and 7.7 Hz, 1 H, 5-H_B), 4.20 (m and q, J = 7.2 Hz, 3 H, 3-H and CH_2CH_3), 4.47 (d, J = 17.6 Hz, 1 H, CH_ACOO), 4.67 (d, J = 17.6 Hz, 1 H, CH_BCOO), 5.06 (s, 2 H, CH_2Ph), 5.55 (br d, J = 7 Hz, 1 H, NH), 5.90 (ddd, J = 3.8, 1.6, and 0.8 Hz, 1 H, 6-H), 6.11 (app t, J = 3.5 Hz, 1 H, 7-H), 6.75 (dd, J = 3.2 and 1.6 Hz, 1 H, 8-H), 7.34 (s, 5 H, ArH). Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.02; N, 10.90. Found: C, 62.09; H, 5.93; N, 10.95.

Method B. From Compound 10. The crude diazepinone (10) from 10 g of 5 was dissolved in THF (100 mL) and heated at 50 °C. Then, 20% HCl (2 mL) was added, and the solution was stirred at this temperature for an additional 15 min. The reaction mixture was poured onto ice–water and extracted with benzene. The extracts were washed with water, dried, and absorbed on silica gel (50 g) on a sintered glass funnel. After being washed with benzene (100 mL), the product was eluted with 9:1 CH_2Cl_2–Et_2O (250 mL), affording 1.5 g (16%) of crude 2. In one run, from pure 10 (0.15 g, 0.31 mmol), after column chromatography (CH_2Cl_2 as eluent), 80 mg (66%) of pure 2 was obtained.

(S)-Ethyl 3-Amino-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepine-1-acetate (11). A solution of 2 (0.12 g, 0.31 mmol) in EtOH (10 mL) was stirred in the presence of 10% Pd–C (20 mg) under H_2 at room temperature and atmospheric pressure for 2 h. The catalyst was filtered off, the solution was evaporated, and the residue was triturated with Et_2O to give 70 mg (89%) of 11: mp 130–132 °C dec (THF–Et_2O); $[\alpha]^{20}_D$ −75 (c 0.4%, MeOH); IR (KBr) 3370 (NH), 1740 (COOEt), 1695 (NCO), 1210 cm^{-1} (OEt); NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H, CH_3),

1.50–2.50 (m, 2 H, 4-H), 2.50–3.00 (m, 2 H, 5-H), 3.00–3.40 (m, 1 H, 3-H), 4.20 (q, J = 7 Hz, 2 H, O-CH_2), 4.55 (s, 2 H, CH_2COO), 5.85 (dd, J = 3.5 and 1.5 Hz, 1 H, 6-H), 6.07 (t, J = 3.5 Hz, 1 H, 7-H), 6.72 (dd, J = 3.5 and 1.5 Hz, 1 H, 8-H). Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.61; H, 6.68; N, 16.43.

Mosher Amide Derivatives of 11. To a solution of amine 11 (50 mg, 0.21 mmol) and NEt_3 (21 mg, 0.21 mmol) in dry CH_2Cl_2 (10 mL) was added (*R*)-MTPA-Cl (53 mg, 0.21 mmol), and the mixture was stirred at rt for 30 min. The organic solution was washed 3 times with $NaHCO_3$ solution and 2 times with HCl solution. Evaporation gave 70 mg (75%) of crude (*S*)-MPTA-amide: NMR ($CDCl_3$, 500 MHz) δ 1.20 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.73 (td, J = 12 and 8 Hz, 1 H, 4-H_A), 2.45 (tt, J = 12 and 8 Hz, 1 H, 4-H_B), 2.68 (dd, J = 15 and 8 Hz, 1 H, 5-H_A), 3.13 (ddd, J = 15, 12 and 8 Hz, 1 H, 5-H_B), 3.44 (d, J = 1.5 Hz, 3 H, OCH_3), 4.14 (m, 2 H, OCH_2), 4.34 (d, J = 17.5 Hz, 1 H, CH_ACOO), 4.38 (dt, J = 12 and 8 Hz, 1 H, 3-H), 4.66 (d, J = 17.5 Hz, 1 H, CH_BCOO), 5.82 (ddd, J = 3, 1.5, and 1 Hz, 1 H, 6-H), 6.05 (t, J = 3.5 Hz, 1 H, 7-H), 6.69 (dd, J = 3.5 and 1.5 Hz, 1 H, 8-H), 7.31 (m, 3 H, PhH), 7.44 (m, 2 H, PhH).

In an analogous manner, from amine 11 (50 mg, 0.21 mmol) and (*S*)-MTPA-Cl (53 mg, 0.21 mmol), 72 mg (77%) of (*R*)-MPTA-amide was obtained: NMR ($CDCl_3$, 500 MHz) δ 1.20 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.89 (td, J = 12 and 8 Hz, 1 H, 4-H_A), 2.54 (tt, J = 12 and 8 Hz, 1 H, 4-H_B), 2.73 (dd, J = 15 and 8 Hz, 1 H, 5-H_A), 3.14 (ddd, J = 15, 12, and 8 Hz, 1 H, 5-H_B), 3.27 (d, J = 1.5 Hz, 3 H, OCH_3), 4.14 (m, 2 H, OCH_2), 4.35 (dt, J = 12 and 8 Hz, 1 H, 3-H), 4.36 (d, J = 17.5 Hz, 1 H, CH_ACOO), 4.64 (d, J = 17.5 Hz, 1 H, CH_BCOO), 5.82 (ddd, J = 3.5, 1.5, and 1 Hz, 1 H, 6-H), 6.03 (t, J = 3.5 Hz, 1 H, 7-H), 6.60 (dd, J = 3.5 and 1.5 Hz, 1 H, 8-H), 7.31 (m, 3 H, PhH), 7.45 (m, 2 H, PhH), 7.59 (br d, J = 8 Hz, 1 H, NH).

Ethyl 3-((1-(Ethoxycarbonyl)-3-phenylpropyl)amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepine-1-acetate (14). Method A. A solution of 11 (2 g, 8 mmol), (*R*)-ethyl 4-phenyl-2-(((trifluoromethyl)sulfonyl)oxy)butanoate (13)[26] (3 g, 8.8 mmol) and NEt_3 (0.89 g, 8.8 mmol) in CH_2Cl_2 was heated at reflux for 1 h. The solution was washed with water and evaporated. The product was purified on column chromatography with 9:1 C_6H_6–Et_2O as eluent to afford 1.8 g (51%) of **(3*S*,1′*S*)-ethyl 3-((1-(ethoxycarbonyl)-3-phenylpropyl)amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepine-1-acetate (14a)** as an oil: $[\alpha]^{20}_D$ −56 (*c* 1%, MeOH); IR (neat) 3320 (NH), 1740 (COO), 1685 cm^{-1} (NCO); NMR ($CDCl_3$, 500 MHz) δ 1.19 t, J = 7.2 Hz, 3 H, CH_3), 1.27 (t, J = 7.5 Hz, 3 H, CH_3), 1.62 (br s, 1 H, NH), 1.90 (m, 2 H, 2′-H), 1.98 (m, 1 H, 4-H_A), 2.31 (tt, J = 12.5 and 7.5 Hz, 1 H, 4-H_B), 2.68 (m, 2 H, 3′-H), 2.72 (dd, J = 15 and 7.5 Hz, 1 H, 5-H_A), 3.03 (ddd, J = 15, 12.5, and 7.5 Hz, 1 H, 5-H_B), 3.09 (dd, J = 11.5 and 7.5 Hz, 1 H, 3-H), 3.23 (t, J = 6.5 Hz, 1 H, 1′-H), 4.09 (m, 2 H, OCH_2), 4.21 (m, 2 H, OCH_2), 4.55 and 4.56 (AB system, J = 17.2 Hz, 2 H, CH_2COO), 5.86 (ddd, J = 3.5, 1.5, and 1 Hz, 1 H, 6-H), 6.09 (t, J = 3.5 Hz, 1 H, 7-H), 6.75 (dd, J = 3.5 and 1.5 Hz, 1 H, 8-H), 7.17 (m, 3 H, Ph-2H, -4H, and -6H), 7.26 (t, J = 7.5 Hz, 2 H, Ph-3H and -5H). Anal. Calcd for $C_{24}H_{31}N_3O_5$: C, 65.29; H, 7.08; N, 9.52. Found: C, 65.46; H, 7.38; N, 9.38.

Method B. A solution of 11 (1.5 g, 6 mmol), (±)-ethyl 2-bromo-4-phenylbutanoate (12)[25] (2.5 g, 9.2 mmol), KI (0.17 g, 1 mmol), and NEt_3 (1.3 mL) in acetonitrile (30 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 were absorbed on silica gel, washed with C_6H_6 (150 mL) and with CH_2Cl_2 (150 mL), and then eluted with Et_2O (250 mL). The ethereal fraction on TLC analysis showed a mixtured of two isomers in roughly equal amounts.[27] The mixture was separated on column chromatography, eluting with 9:1 C_6H_6–Et_2O. The first-eluting isomer was identified as **(3*S*,1′*R*)-ethyl 3-((1-(ethoxycarbonyl)-3-phenylpropyl)-amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]-diazepine-1-acetate (14b)** (0.5 g, 19%): $[\alpha]^{20}_D$ −58 (*c* 1%, MeOH); IR (neat) 3320 (NH), 1740 (COO), 1685 cm^{-1} (CON); NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, J = 7 Hz, 3 H, CH_3), 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 1.55 (br s, 1 H, NH), 1.87 (m, 3 H, 2′-H and 4-H_A), 2.28 (tt, J = 12.5 and 7.5 Hz, 1 H, 4-H_B), 2.63 (m, 2 H, 3′-H), 2.72 (dd, J = 15 and 7.5 Hz, 1 H, 5-H_A), 3.03 (ddd, J = 15, 12.5, and 7.5 Hz, 1 H, 5-H_B), 3.04 (dd, J = 11 and 7.5 Hz, 1 H, 3-H), 3.07 (t, J = 6.5 Hz, 1 H, 1′-H), 4.13 (m, 2 H, OCH_2), 4.20 (m, 2 H, OCH_2), 4.53 (s, 2 H, CH_2COO), 5.87 (ddd, J = 3.8, 1.8, and 1 Hz, 1 H, 6-H), 6.10 (app t, J = 3.5 Hz, 1 H, 7-H), 6.74 (dd, J = 3.3 and 1.8 Hz, 1 H, 8-H), 7.11 (d, J = 7.5 Hz, 2 H, Ph-2H and -6H), 7.16 (t, J = 7.5 Hz, 1 H, Ph-4H), 7.24 (t, J = 7.5 Hz, 2 H, Ph-3H and -5H). Anal. Calcd for $C_{24}H_{31}N_3O_5$: C, 65.29; H, 7.08; N, 9.52. Found: C, 65.47; H, 7.23; N, 9.37.

The second-eluting isomer was identical to **(3*S*,1′*S*)-ethyl 3-((1-(ethoxycarbonyl)-3-phenylpropyl)amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepine-1-acetate (14a)** obtained in method A (0.6 g, 23%).

(3*S*,1′*S*)-3-((1-Carboxy-3-phenylpropyl)amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepine-1-acetic Acid (1a). A solution of **14a** (0.44 g, 1 mmol) in MeOH (15 mL) and 1 N NaOH (3 mL) was stirred overnight at rt. Then, 1 N H_2SO_4 (3 mL) was added, and the solution was evaporated in vacuo. The residue was extracted with 3 20-mL portions of MeOH, and the extracts were filtered and evaporated, affording a solid that was recrystallized from MeOH–Et_2O to give 0.22 g (57%) of **1a** as a solid: mp 236–238 °C dec; $[\alpha]^{20}_D$ −37 (*c* 0.15%, 1:1 MeOH–DMF); IR (KBr) 3600–2400 (NH, OH), 1700 cm^{-1} (CON); NMR (CD_3OD, 500 MHz) δ 2.21 (m, 2 H, 2′-H), 2.31 (td, J = 12 and 7.5 Hz, 1 H, 4-H_A), 2.62 (tt, J = 12 and 7.5 Hz, 1 H, 4-H_B), 2.84 (m, 2 H, 3′-H), 2.97 (dd, J = 15 and 7.5 Hz, 1 H, 5-H_A), 3.15 (ddd, J = 15, 12, and 7.5 Hz, 1 H, 5-H_B), 3.75 (dd, J = 11 and 7 Hz, 1 H, 3-H), 3.81 (t, J = 6.5 Hz, 1 H, 1′-H), 4.68 (d, J = 17.5 Hz, 1 H, CH_ACOO), 4.79 (d, J = 17.5 Hz, 1 H, CH_BCOO), 6.02 (dd, J = 3.8 and 1.5 Hz, 1 H, 6-H), 6.21 (app t, J = 3.5 Hz, 1 H, 7-H), 7.00 (dd, J = 3.2 and 1.5 Hz, 1 H, 8-H), 7.28 (d, J = 7 Hz, 2 H, Ph-2H and -6H), 7.31 (t, J = 7 Hz, 1 H, Ph-4H), 7.37 (t, J = 7 Hz, 2 H, Ph-3H and -5H). Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.02; N, 10.90. Found: C, 62.07; H, 6.15; N, 10.69.

(3*S*,1′*R*)-3-((1-Carboxy-3-phenylpropyl)amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2]diazepine-1-acetic Acid (1b). Operating as above, from **14b** (0.25 g, 0.57 mmol), 70 mg (32%) of **1b** was obtained: mp 163–165 °C dec (MeOH–Et_2O); $[\alpha]^{20}_D$ −75 (*c* 0.3%, 1:1 MeOH–DMF); IR (KBr) 3600–2400 (NH, OH), 1700 cm^{-1} (CON); NMR (CD_3OD, 500 MHz) δ 2.17 (dd, J = 15 and 8 Hz, 2 H, 2′-H), 2.30 (td, J = 12 and 7.7 Hz, 1 H, 4-H_A), 2.57 (tt, J = 12 and 7.7 Hz, 1 H, 4-H_B), 2.80 (m, 2 H, 3′-H), 2.98 (dd, J = 15 and 7.7 Hz, 1 H, 5-H_A), 3.38 (ddd, J = 15, 12, and 7.7 Hz, 1 H, 5-H_B), 3.77 (dd, J = 11 and 7.7 Hz, 1 H, 3-H), 3.92 (t, J = 6.5 Hz, 1 H, 1′-H), 4.68 (d, J = 17.5 Hz, 1 H, CH_ACOO), 4.77 (d, J = 17.5 Hz, 1 H, CH_BCOO), 6.05 (dd, J = 3.8 and 1.5 Hz, 1 H, 6-H), 6.25 (app t, J = 3.5 Hz, 1 H, 7-H), 7.02 (dd, J = 3.2 and 1.5 Hz, 1 H, 8-H), 7.24 (d, J = 7 Hz, 2 H, Ph-2H and -6H), 7.30 (t, J = 7 Hz, 1 H, Ph-4H), 7.38 (t, J = 7 Hz, 2 H, Ph-3H and -5H). Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.02; N, 10.90. Found: C, 62.15; H, 6.05; N, 10.73.

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Registry No. **1a**, 140677-42-5; **1b**, 140677-52-7; **2**, 140677-43-6; **3**, 23632-67-9; **4**, 58456-26-1; **5**, 140677-44-7; **6**, 140696-60-2; **7**, 140677-45-8; **8**, 140677-46-9; **9**, 140677-47-0; **10**, 140677-48-1; **11**, 140677-49-2; **11** (*S*)-MTPA-amide, 140677-53-8; **11** (*R*)-MTPA-amide, 140677-54-9; (±)-**12**, 80828-27-9; **13**, 88767-98-0; **14a**, 140677-50-5; **14b**, 140677-51-6; (*R*)-MTPA-Cl, 39637-99-5; (*S*)-MTPA-Cl, 20445-33-4; $H_2NNHCH_2C(O)OEt$·HCl, 6945-92-2; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4; *N*-aminophthalimide, 1875-48-5; ethyl bromoacetate, 105-36-2.