Synthesis of 1,2,4-Oxadiazole-, 1,3,4-Oxadiazole-, and 1,2,4-Triazole-Derived Dipeptidomimetics

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Three series of heterocyclic dipeptidomimetics have been synthesized. The compounds were designed as amino acid–glycine mimetics containing 1,2,4-oxadiazole, 1,3,4-oxadiazole, and 1,2,4-triazole ring systems, useful as building blocks in the synthesis of modified peptides. The heterocyclic moieties were chosen according to their geometrical, electrostatical, and hydrogen-bonding properties together with the synthetic accessibility. The syntheses started with Boc-protected L-amino acids (Ala, Gly, Asp, Phe, Ser, Arg, Cys, and Pro), and the reaction conditions were chosen to allow for the formation of products with high enantiopurity. The enantiomeric excess was determined by HPLC using chiral stationary phases.

Introduction

Peptide bonds and peptide fragments have been replaced with a wide variety of structural moieties[1] in attempts to convert peptides into chemically stable and orally available molecules. Recently, reports on the use of heterocyclic rings in peptidomimetics have appeared in the literature.[2–5] To the best of our knowledge, 1,2,4-oxadiazole and 1,3,4-oxadiazole moieties have not been used in the construction of peptide mimics despite their frequent use as ester and amide bioisosteres.[6,7] We find these ring systems as well as the 1,2,4-triazole moiety[8,9] attractive for the synthesis of X-Gly dipeptidomimetics because (i) retrosynthetically, they may be derived in optically active form from appropriately protected and activated natural or unnatural amino acids, (ii) they form dipeptidomimetics with adequate geometrical and electrostatical properties,[10] and (iii) they possess certain properties which make them potentially useful in establishing key intermolecular features in interactions between peptides and biological targets; whereas all three ring systems can act as hydrogen bond acceptors, only the 1,2,4-triazole moiety is able to donate a hydrogen bond.

In an initial study, we failed to obtain optically active 1,2,4-oxadiazole derivatives using Boc-L-phenylalanine as the starting material.[11] Most likely, the strong basic

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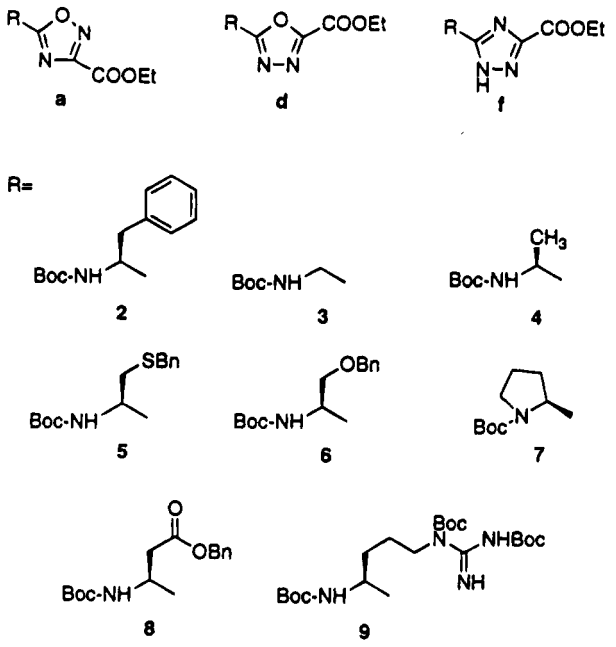
conditions used in the cyclization reaction (NaH or BuLi in THF) promoted the formation of achiral tautomeric forms.[12] We now report the facile synthesis of a range of optically active amino acid-Gly mimetics using milder conditions.[13] The 1,2,4-oxadiazole derivatives are obtained from activated α-amino acids and an amidoxime in a one-pot reaction in pyridine without the use of any strong base to promote the cyclization. In the synthesis of the 1,3,4-oxadiazole derivatives, mild dehydrating conditions are used in the cyclization step, whereas the 1,2,4-triazole derivatives are obtained by thermal dehydration. The compounds described herein constitute a set of potentially useful building blocks in the synthesis of modified peptides.[14]



Results and Discussion

Synthesis. Three series of heterocyclic derivatives were synthesized from Boc-protected L-amino acids. The synthetic routes to afford the heterocycles were applied on appropriately protected lipophilic (glycine, alanine, phenylalanine, and proline), polar (cysteine and serine), acidic (aspartate), and basic (arginine) amino acids. The enantiomeric purities were determined by HPLC using a chiral stationary phase. All eight amino acids were used in the synthesis of the 1,2,4-oxadiazoles. In the case of the 1,3,4-oxadiazoles and the 1,2,4-triazoles, neither aspartate nor arginine was used as starting material.[15] Aspartate was not suitable because of the reactivity of the ester functionality in the side chain, and arginine was avoided because of the difficulties we experienced in optimizing the reaction conditions in the 1,2,4-oxadiazole synthesis. The physical data of the synthesized heterocyclic derivatives are presented in Table 1.

1,2,4-Oxadiazoles[16] are most commonly synthesized from amidoximes and acetylating agents such as carboxylic acid chlorides or anhydrides.[17-19] In this study, we treated symmetrical anhydrides of the different Boc-protected L-amino acids[20] with an amidoxime in pyridine in a one-pot reaction (Scheme 1). The cyclization took place when the reaction mixture was heated to reflux. The *O*-acylamidoxime intermediate did not need to be isolated, nor was a dehydrating agent required. The 1,2,4-oxadiazole derivatives were obtained in 20–81% yield. In the synthesis of the aspartate derivative, **8a**, two different methods were used to activate the carboxylic acid function; in addition to the symmetrical anhydride, also the Boc-L-Asp(Bn)-nitrophenyl ester was used as starting material. The yields in the two reactions were similar (66 and 58%, respectively), but differences in optical rotations and melting points suggested that the stereoselectivity of the two routes differed, the use of the symmetrical anhydride providing a product with higher optical purity (Table 1).

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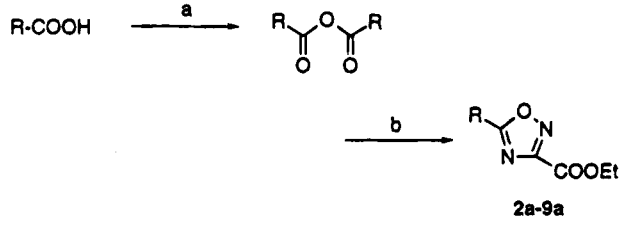
Table 1. Physical Data of the Novel Dipeptidomimetics 2a–9a, 2d–7d, and 2f-7f

compd	yield[a] (%)	mp (°C)	$[\alpha]_D$	t_R(min)[b]	% ee	formula[c]
2a	72	75–76[d]	−29.4[e]	17.2/19.5[f,g]	93	$C_{18}H_{23}N_3O_5$
2d	30	122–123[h]	-31.9[e]	45.7/42.5[i,g]	>95	$C_{18}H_{23}N_3O_5 \cdot {}^1/_4H_2O$
2f	52	154–154.5[h]	−22.8[j]	11.6/8.2[k,l]	>95	$C_{18}H_{24}N_4O_4 \cdot {}^1/_4H_2O$
3a	63	81–82[m]	–	–	–	$C_{11}H_{17}N_3O_5 \cdot {}^1/_8H_2O$
3d	17	62–64[m]	–	–	–	$C_{11}H_{17}N_3O_5$
3f	28	156–157[n]	–	–	–	$C_{11}H_{18}N_4O_4 \cdot {}^1/_2H_2O$
4a	76	73–74[h]	−51.0[j]	14.6/16.8[f,g]	>95	$C_{12}H_{19}N_3O_5$
4d	17	66–67[h]	−43.5[j]	21.8[f,g]/ND[o]	>95	$C_{12}H_{19}N_3O_5 \cdot {}^1/_4H_2O$
4f	39	97–98[p]	−92.6[j]	16.7[f,q]/ND[o]	>95	$C_{12}H_{20}N_4O_4 \cdot {}^1/_2H_2O$
5a	81	115–116[r]	−29.8[s]	ND[o]	ND[o]	$C_{19}H_{25}N_3O_5S$
5d	6	74.5–75.5[d]	−21.2[t]	ND[o]	ND[o]	$C_{19}H_{25}N_3O_5S$[u]
5f	13	181–182[p]	−28.8[v]	ND[o]	ND[o]	$C_{19}H_{26}N_4O_4S \cdot {}^1/_4H_2O$
6a	54	oil	−16.1[j]	23.5/22.2[f,g]	72	$C_{19}H_{25}N_3O_6$
6d	20	84–86[h]	−32.8[j]	ND[o]	ND[o]	$C_{19}H_{25}N_3O_6 \cdot {}^1/_4H_2O$
6f	15	153–153.5[w]	−22.8[x]	20.8[y,q]/ND[o]	>95	$C_{19}H_{26}N_4O_5$
7a	38	oil	−62.7[v]	17.3[f,g]/ND[o]	>95	$C_{14}H_{21}N_3O_5$[z]
7d	6	oil	−60.8[j]	25.3[f,g]/ND[o]	>95	$C_{14}H_{21}N_3O_5$[aa]
7f	26	131–134[n]	−199.3[j]	24.7[f,q]/ND[o]	>95	$C_{14}H_{22}N_4O_4$
8a[bb]	66	118.5–119.5[m]	−38.4[e]	20.8/22.1[y,g]	>95	$C_{20}H_{25}N_3O_7$
8a[cc]	58	105–106[m]	−8.7[e]		20	
9a	20	120–121[dd]	−14.7[j]	20.0[f,g]/ND[o]	>95	$C_{25}H_{42}N_6O_9 \cdot {}^1/_2H_2O$

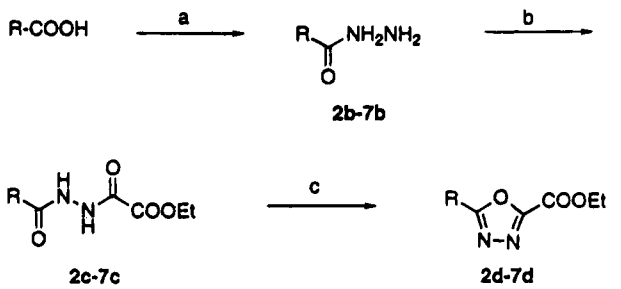
[a] Overall yield calculated from Boc-protected L-amino acid. [b] t_R for both enantiomers, if determined, given as L/D. [c] Except when noted, the compounds gave elemental analyses for C, H, and N (see supplementary material) within 0.4% of the theoretical values. [d] Recrystallized from Et_2O/hexane. [e] c 1.0, MeOH. [f] Hexane/2-propanol/Et_2NH (90:10:0.1), 0.5 mL/min. [g] Analysis run at ambient temperature. [h] Recrystallized from CH_2Cl_2/pentane. [i] Hexane/2-propanol/Et_2NH (95:5:0.1), 0.5 mL/min. [j] c 1.0, $CHCl_3$. [k] Hexane/2-propanol/Et_2NH (90:10:0.1), 1.0 mL/min. [l] Analysis run at 35 °C. [m] Recrystallized from Et_2O/pentane. [n] Recrystallized from $CHCl_3$/pentane. [o] Not determined. [p] Recrystallized from Et_2O/$CHCl_3$/pentane. [q] Analysis run at 30 °C. [r] Recrystallized from Et_2O/CH_2Cl_2/pentane. [s] c 0.9, MeOH. [t] c 0.3, $CHCl_3$. [u] N: calcd 10.3, found 9.85. [v] c 1.1, $CHCl_3$. [w] Recrystallized from Et_2O/MeOH/pentane. [x] c 0.7, $CHCl_3$. [y] Hexane/2-propanol/Et_2NH (80:20:0.2), 0.5 mL/min. [z] Characterized by MS. [aa] N: calcd 13.5, found 13.0. [bb] Boc-L-Aspartic acid anhydride used as starting material. [cc] Boc-L-aspartic acid nitrophenyl ester used as starting material. [dd] Recrystallized from pentane.

Scheme 1[a]



[a] (a) DCC, CH_2Cl_2, 0 °C; (b) EtOOCC(NOH)NH_2 (**1**), pyridine, reflux.

Scheme 2[a]



[a] (a) (i) DCC, DMAP, EtOH, Et_2O, rt; (ii) $NH_2NH_2 \cdot H_2O$, EtOH, rt; (b) ClCOCOOEt, Et_3N, THF, −30 °C to rt; (c) (i) $SOCl_2$, pyridine, Et_2O, 0 °C; (ii) toluene, reflux.

1,3,4-Oxadiazoles[21] are obtained by dehydration of diacylhydrazines.[22] In this study, the 1,3,4-oxadiazoles were synthesized via the corresponding Boc-L-amino acid hydrazides (Scheme 2).[23] The amino acids were first esterified[24] and then treated with hydrazine hydrate. An exception was Boc-L-Pro which was first activated as a mixed anhydride and then treated with hydrazine hydrate. The resulting hydrazides were treated with ethyl oxalyl chloride to give diacylhydrazines.[25] The cyclization conditions had to be mild, and since the derivatives contained acid sensitive Boc groups, the use of acidic dehydrating agents was not possible. Hence, the diacylhydrazines were treated with thionyl chloride and pyridine, giving 1,2,3,4-oxathiadiazole-*S*-oxide intermediates; the 1,3,4-oxadiazoles were formed by thermal elimination of sulfur dioxide.[26-29] The overall yields of the 1,3,4-

(21) For reviews about 1,3,4-oxadiazoles, see: (a) Behr, L. C. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; Wiley: New York, 1962; Vol. 17, pp 263–282. (b) Nesynov, E. P.; Grekov, A. P. *Russ. Chem. Rev. (Engl. Transl.)* **1964**, *33*, 508–514. (c) Hetzheim, A.; Möckel, K. *Adv. Heterocycl. Chem.* **1966**, *7*, 183–224. (d) Hill, J. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; Vol. 6, pp 427–446.

(22) For examples of dehydration of acylhydrazines, see: (a) Stollé, R. *Chem. Ber.* **1899**, *32*, 797–798. (b) Cauliez, P.; Couturier, D.; Rigo, B.; Fasseur, D.; Halama, P. *J. Heterocycl. Chem.* **1993**, *30*, 921–927 and references therein. (c) Carlsen, P. H. J.; Jørgensen, K. B. *J. Heterocycl. Chem.* **1994**, *31*, 805–807.

(23) For general references about amino acid hydrazides, see: (a) Stetzel, P. In *Methoden der Organischen Chemie (Houben-Weyl)*; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1974; Vol. XV/2, pp 296–322. (b) Rzeszotarska, B.; Nadolska, B.; Tarnawski, J. *Liebigs Ann. Chem.* **1981**, 1294–1302.

(24) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475–4478.

(25) Boesch, R. Ger. Pat. 28 08 842, 1978.

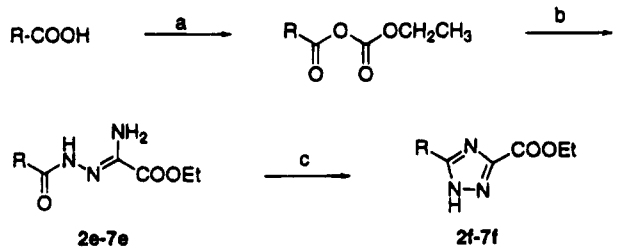
(26) Golfier, M.; Guillerez, M.-G. *Tetrahedron Lett.* **1976**, 267–270.

(27) For examples of the synthesis of other 1,3,4-oxadiazole-2-carboxylic acid esters, see: (a) Werber, G.; Buccheri, F. *Ann. Chim.* (Rome) **1968**, *58*, 810–822. (b) Werber, G.; Buccheri, F.; Marino, M. L. *Ann. Chim.* (Rome) **1971**, *61*, 587–599. (c) Werber, G.; Buccheri, F.; Marino, M. L. *Atti Accad. Sci., Lett. Arti Palermo, Parte 1* **1971**, *30*, 189–198. (d) Werber, G.; Buccheri, F.; Noto, R.; Gentile, M. *J. Heterocycl. Chem.* **1977**, *14*, 1385–1388. (e) Dost, J.; Heschel, M.; Stein, J. *J. Prakt. Chem.* **1985**, *327*, 109–116. See also ref 7b.

(28) For examples of 1,3,4-oxadiazoles synthesized from tetrazoles and acid chlorides or anhydrides, see: (a) Heller, G. *Chem. Ber.* **1907**, *40*, 114–119. (b) Huisgen, R.; Sauer, J.; Sturm, H. J.; Markgraf, J. H. *Chem. Ber.* **1960**, *93*, 2106–2124. (c) Ogilvie, W.; Rank, W. *Can. J. Chem.* **1987**, *65*, 166–169. (d) Jursic, B. S.; Zdravskovski, Z. *Synth. Commun.* **1994**, 24, 1575–1582. See also refs 7a, 7b, 17e, 17f, and 17h.

(29) For examples of other synthetic routes to 1,3,4-oxadiazoles, see: (a) Golfier, M.; Milcent, R. *Synthesis* **1979**, 946–948. (b) Pochat, F. *Synthesis* **1984**, 146–148. (c) Rigo, B.; Cauliez, P.; Fasseur, D.; Couturier, D. *Synth. Commun.* **1986**, *16*, 1665–1669. (d) El-Abadelah, M. M.; Nazer, M. Z.; Hussein, A. Q.; Awadallah, A. M. *J. Heterocycl. Chem.* **1991**, *28*, 1229–1234. (e) Reynaud, P.; El Hamad, Y.; Davrinche, C.; Nguyen-Tri-Xuong, E.; Tran, G.; Rinjard, P. *J. Heterocycl. Chem.* **1992**, *29*, 991–993. (f) Jedlovská, E.; Leško, J. *Synth. Commun.* **1994**, *24*, 1879–1885. See also refs 6d, 6f, 6j, and 17h.

Scheme 3[a]



[a] (a) EtOCOCl, Et_3N, THF, −5 °C; (b) EtOOCC(NH)$NHNH_2$ (**10**), THF, rt; (c) xylenes, Δ.

oxadiazole derivatives as calculated from the protected amino acids were 6−30%.

1,2,4-Triazoles[30] are generated by an intramolecular condensation of acylamidrazones.[31] The required acylamidrazones were formed by treatment of mixed anhydrides of the Boc-L-amino acids with an amidrazonate (Scheme 3).[32,33] The acylamidrazones were all solids, and some did precipitate in the reaction mixtures as they were soluble only in very polar solvents. Purified acylamidrazones were obtained in good yields (67−86%). The cyclizations[34] were performed at temperatures above the melting points of the acylamidrazones (180−200 °C) in xylenes (mixture of isomers). The use of crude acylamidrazones in the cyclization did not affect the overall yields calculated from the protected amino acids (13−52%).

Structural Aspects of the 1,2,4-Triazoles. The structure of 1,2,4-triazole **6f** was analyzed by X-ray crystallography[35] (Figure 1a) which confirmed the absolute configuration. As expected, the stereochemistry was retained during the reaction sequence resulting in the *R* configuration. In the crystal of **6f**, an extensive hydrogen-bonding pattern forms antiparallel strands of molecules packed in almost perpendicular layers (Figure 1b). Each molecule donates hydrogen bonds via N-1−H and the carbamate N−H and accepts hydrogen bonds to N-2, N-4, and the carbonyl oxygen (Figure 1b). It is noteworthy that only one triazole tautomer was observed in the crystal of **6f**. Also, ^{13}C NMR spectra of **6f** and **7f** indicated only one tautomeric form since signals due to C-3 and C-5 appeared as sharp peaks. This is in contrast with ^{13}C NMR spectra of **2f**−**5f** in which C-3 and C-5 appeared as broad peaks of low intensity or were not visible, indicating the presence of several tautomeric forms in equilibrium. These results may indicate that hydrogen bonding is less favored in **2f**−**5f** than in **6f** and **7f**.

Stereochemical Aspects. The enantiomeric excess (% ee) of the dipeptidomimetics was determined by analysis of the purified and characterized derivatives on chiral stationary phases[36] using a straight phase HPLC system. Data from the HPLC analyses are listed in Table 1. For the Phe-Gly analogues, **2a**, **2d**, and **2f**, the retention times for both the L- and the D-enantiomer were determined. In the cases where the retention time is determined only for the L-enantiomer, the % ee was estimated by assuming a similar separation factor and detection limit as in chromatograms of **2a**, **2d**, and **2f** (Figure 2).

Racemization of the stereogenic center of the 1,2,4-oxadiazole derivatives might occur either during the generation of the symmetrical anhydride with *N,N'*-dicyclohexylcarbodiimide (DCC) or during the cyclization. Two compounds, **2a** and **4a**, were racemized,[37] which allowed for an unambiguous determination of the stereochemical purity of L-**2a** and L-**4a** (93 and >95% ee, respectively). The % ee of the cysteine derivative **5a** could not be determined since we were unable to obtain reproducible chromatograms. The chromatogram of **6a** showed two peaks in a 6:1 relationship. In contrast, chromatograms of **7a** and **9a** showed only one peak each, indicating high enantiopurity. As mentioned above, **8a** was synthesized from two differently activated Boc-L-Asp(Bn) derivatives. When the chromatograms from the two syntheses were compared, it was apparent that the symmetrical anhydride gave a significantly higher % ee (>95%) than the nitrophenyl ester (20% ee). This confirms that different modes of activation in the synthesis of 1,2,4-oxadiazoles result in different enantiopurities.

Racemization of the stereogenic center of the 1,3,4-oxadiazoles might occur during the cyclization. We were, however, unable to racemize these compounds. Several different conditions were tried, e.g., tetrabutylammonium fluoride in THF, BuLi in THF, and NaOEt in EtOH at room temperature. Either no racemization occurred (tetrabutylammonium fluoride) or the 1,3,4-oxadiazole ring decomposed (BuLi and NaOEt). Racemic **2d** was

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(31) For reviews about amidrazones, see: (a) Watson, K. M.; Neilson, D. G. In *The Chemistry of Amidines and Imidates* (The Chemistry of Functional Groups); Patai, S., Ed.; John Wiley & Sons: New York, 1975; pp 491−544. (b) Neilson, D. G.; Roger, R.; Heatlie, J. W. M.; Newlands, L. R. *Chem. Rev.* **1970**, *70*, 151−170.

(32) For examples of 1,2,4-triazole-3-carboxylic acid esters derived from ethyl oxamidrazonate and an acid chloride or an anhydride, see: (a) Ün, R. *Chim. Acta Turc.* **1974**, *2*, 115−129. (b) Dost, J.; Stein, J.; Heschel, M. *Z. Chem.* **1986**, *26*, 203−204. (c) Dost, J.; Heschel, M.; Stein, J. *J. Prakt. Chem.* **1986**, *328*, 551−557. (d) Heschel, H.; Stein, J.; Dost, J. *Wiss. Z. Paedagog. Hochsch. "Karl Liebknecht" Potsdam* **1987**, *31*, 45−52.

(33) For examples of other routes providing 1,2,4-triazole-3-carboxylic acid esters, see: (a) Reimlinger, H.; Lingier, W. R. F.; Vandewalle, J. J. M. *Chem. Ber.* **1971**, *104*, 639−644. (b) Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1973**, *38*, 1437−1438. (c) Ito, Y.; Nii, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1979**, 2521−2524. (d) Poonian, M. S.; Nowoswiat, E. F. *J. Org. Chem.* **1980**, *45*, 203−208. (e) Schmidt, R. R.; Heermann, D. *Chem. Ber.* **1981**, *114*, 2825−2833. (f) Vaněk, T.; Velková, V.; Gut, J. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2492−2495. (g) Vemishetti, P.; Leiby, R. W.; Abushanab, E.; Panzica, R. P. *J. Heterocycl. Chem.* **1988**, *25*, 651−654. See also ref 19b.

(34) Francis, J. E.; Gorczyca, L. A.; Mazzenga, G. C.; Meckler, H. *Tetrahedron Lett.* **1987**, *28*, 5133−5136.

(35) Crystallographic data including the fractional atomic coordinates, referring to the 6(*R*) enantiomer, together with distances and angles of covalent bonds and of possible hydrogen bonds for **6f** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. Lists of the atomic displacement parameters and final F_{obs}/F_{calc} values are available directly from the authors (I.C.).

(36) The samples were dissolved either in the mobile phase or in EtOH. Samples dissolved in the mobile phase had to be fresh when injected since the use of old sample solutions did not give reproducable chromatograms. For compounds **2a**−**9a** and **2d**−**7d**, the samples were dissolved in the mobile phase. The analyses were run on a Chiracel OD-H column obtained from J. T. Baker, Holland. Hexane/2-propanol/Et_2NH (80:20:0.2, 90:10:0.1, or 95:5:0.1) at a flow rate of 0.5 mL/min were used as mobile phases. The detection wavelength was 254 nm. For compound **2f**−**7f**, the samples were dissolved in EtOH. The analyses were run on a Chiralpak AD column at J. T. Baker, Holland. Hexane/2-propanol/Et_2NH (90:10:0.1 or 80:20:0.1) at flow rates of 0.5 or 1 mL/min were used as mobile phases. The detection wavelength was 225 nm.

(37) The procedure for racemization of 1,2,4-oxadiazole derivatives is as follows: 1 equiv of the ethyl 1,2,4-oxadiazole-3-carboxylate and 2 equiv of 1 M tetrabutylammonium fluoride in THF were stirred at room temperature for 2 h. The solvent was stripped. The residue was dissolved in Et_2O and washed with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was redissolved in EtOAc/pentane (1:1) and filtered through a Pasteur pipet with silica.

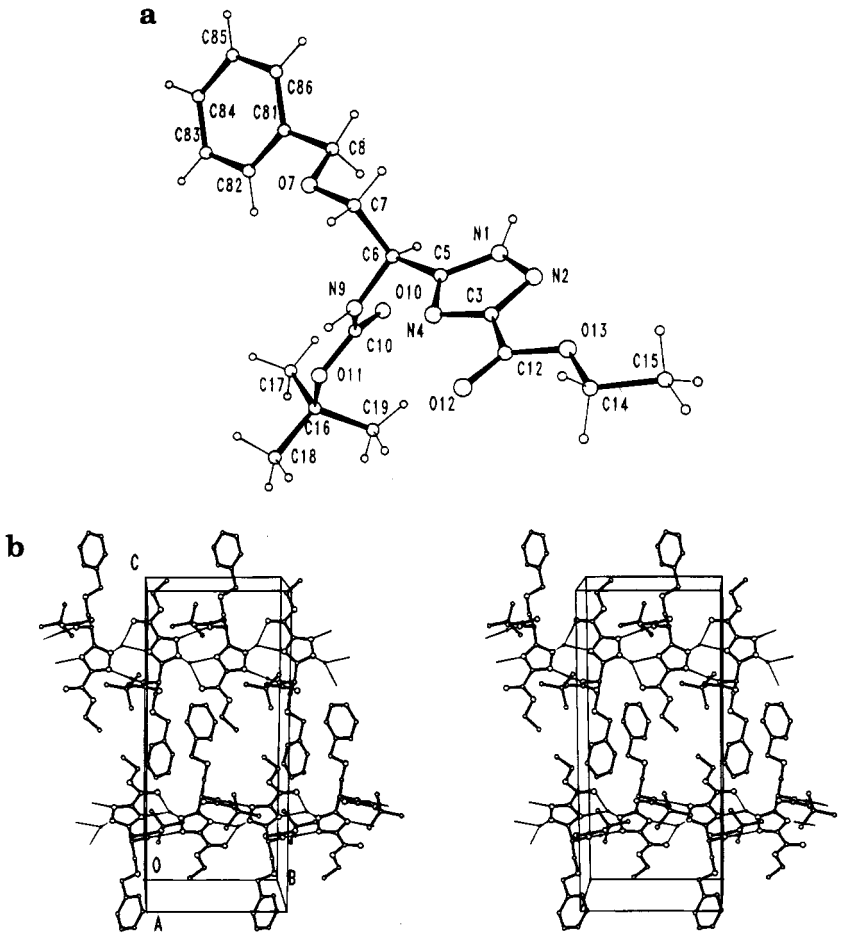

Figure 1. (a) Perspective view of **6f** with crystallographic labeling of the atoms. (b) Stereoscopic view of the crystal packing of **6f**.

therefore synthesized from Boc-DL-Phe, and the enantiopurity of L-**2d** was established to be >95% ee.

As with 1,2,4-oxadiazole **5a**, it was impossible to determine the % ee for the cysteine derivative **5d** since we did not obtain reproducible chromatograms. Also, the % ee for **6d** was impossible to determine. In the chromatograms of the other 1,3,4-oxadiazole derivatives, the enantiomers had different retention times and the % ee for the compounds varied between 90 and 95%.

None of the 1,2,4-triazole derivatives could be racemized. Several conditions were tried, e.g., tetrabutylammonium fluoride in THF, LiH in THF, and NaOEt in EtOH at room temperature, but no racemization occurred. Racemic **2f** was synthesized from Boc-DL-Phe, and the % ee of L-**2f** was found to be >95%. To be able to chromatographically analyze the 1,2,4-triazole derivatives, a different stationary phase was used (Chiralpak AD). Also here, the % ee of the cysteine derivative **5f** was impossible to determine. All other compounds showed chromatograms indicating high enantiopurities (>95% ee).

Conclusions

The compounds synthesized in this study represent a novel class of dipeptidomimetics useful as building blocks which can replace amino acid-Gly moieties in modified peptides. The reactions producing 1,2,4-oxadiazoles, 1,3,4-oxadiazoles, and 1,2,4-triazoles are versatile and can be performed starting from most of the natural amino acids. Although overall yields of the dipeptidomimetics are moderate to low, the synthetic sequences are short and facile. In addition, the chirality of the starting material is retained during the cyclization reactions. The reaction conditions used are compatible with Boc protection of the amino acids, but the use of other protecting groups may require modifications of the reaction conditions. We are presently synthesizing modified peptides containing the mimetic structures presented herein to evaluate their biological significance.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 270 and 67.5 MHz with tetramethylsilane as internal standard. Optical rotations were measured at ambient temperature in a 10 cm cell, and *c* is expressed in g/100 mL. Thin layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm, E. Merck); the spots were visualized with UV detection and by spraying with a 2% EtOH solution of ninhydrin, followed by heating. Column chromatography was performed on silica using Kieselgel 60 (230–400 mesh, E. Merck). The elemental analyses were performed by MikroKemi AB, Uppsala, Sweden, and Analytische Laboratorien, Gummersbach, Germany. Solvents were in some cases dried prior to use. THF and Et_2O were distilled from sodium/benzophenone, and CH_2Cl_2 was dried over $MgSO_4$. Ethyl 2-amino-2-(hydroxyimino)acetate[38] (**1**) and ethyl oxamidrazonate[39] (**10**) were prepared according to known procedures. Data on elemental analyses, optical rotations, and melting points of **2a–9a**, **2d–7d**, and **2f–7f** are listed in Table 1. In the ^{13}C spectra of **2f–7f**, weak signals are noted w.

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(39) (a) Schmidt, P.; Druey, J. *Helv. Chim. Acta* **1955**, *38*, 1560–1564. (b) Rätz, R.; Schroeder, H. *J. Org. Chem.* **1958**, *23*, 1931–1934.

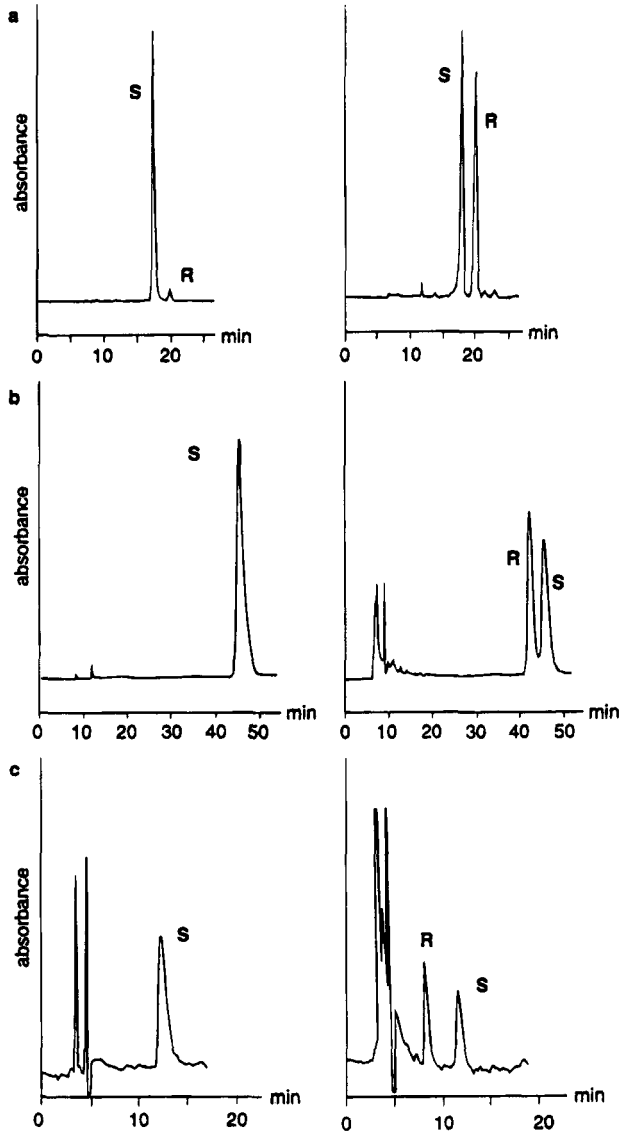

Figure 2. Enantiopurities of (a) **2a**, (b) **2d**, and (c) **2f** determined by HPLC on a chiral stationary phase and compared with the corresponding racemates (right). See Table 1 and ref 36 for the experimental conditions.

General Procedure for the Synthesis of Ethyl 1,2,4-Oxadiazole-3-carboxylate Derivatives 2a–9a. The symmetrical anhydride of the *tert*-butyloxycarbonyl-(Boc) protected L-amino acid was prepared by addition of *N,N'*-dicyclohexylcarbodiimide (DCC) to a solution of the Boc-L-amino acid in dry CH_2Cl_2. The mixture was stirred at 0 °C for 1 h. The resulting *N,N'*-dicyclohexylurea (DCU) was filtered off, and the filtrate was concentrated. The residue was redissolved in pyridine, and a solution of **1** in pyridine was added dropwise. The mixture was heated to reflux. The reaction was monitored by TLC (pentane/EtOAc, 3:2). When the reaction was complete, water was added and the solvent was evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with saturated aqueous $NaHCO_3$, aqueous HCl (pH = 2), brine, and water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified as indicated.

Ethyl 5-[(*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-phenylethyl]-1,2,4-oxadiazole-3-carboxylate (2a). The symmetrical anhydride was formed from Boc-L-phenylalanine (614 mg, 2.32 mmol) and DCC (239 mg, 1.16 mmol). A mixture of **1** (102 mg, 0.77 mmol) and the crude anhydride in pyridine was refluxed for 2 h. Purification by column chromatography (pentane/EtOAc, 8.5:1.5) afforded 200 mg (72%) of pure **2a**: ^{1}H NMR ($CDCl_3$) δ 7.30–7.00 (m, 5H), 5.39 (m, 1H), 5.17 (br d, 1H), 4.51 (q, J = 7.2 Hz, 2H), 3.27 (AB system, 2H), 1.44 (t, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 180.9, 161.8, 157.5, 154.7, 134.6, 129.2, 128.9, 127.6, 80.8, 63.2, 49.5, 39.9, 28.2, 14.1.

Ethyl 5-[[(*tert*-Butyloxycarbonyl)amino]methyl]-1,2,4-oxadiazole-3-carboxylate (3a). The symmetrical anhydride was formed from Boc-glycine (199 mg, 1.13 mmol) and DCC (117 mg, 0.57 mmol). A mixture of **1** (50 mg, 0.38 mmol) and the crude anhydride in pyridine was refluxed for 1.5 h. Purification by column chromatography (Et_2O/hexane, 1:1) afforded 65 mg (63%) of pure **3a**: ^{1}H NMR ($CDCl_3$) δ 5.34 (m, 1H), 4.67 (br d, 2H), 4.51 (q, J = 7.1 Hz, 2H), 1.46 (s, 9H), 1.45 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 178.6, 161.9, 157.4, 155.3, 81.0, 63.2, 37.2, 28.2, 14.1.

Ethyl 5-[(*S*)-1-[(*tert*-Butyloxycarbonyl)amino]ethyl]-1,2,4-oxadiazole-3-carboxylate (4a). The symmetrical anhydride was formed from Boc-L-alanine (379 mg, 2.00 mmol) and DCC (206 mg, 1.00 mmol). A mixture of **1** (50 mg, 0.38 mmol) and the crude anhydride in pyridine was refluxed for 1.5 h. Purification by column chromatography (pentane/EtOAc, 8.5:1.5) afforded 82.6 mg (76%) of pure **4a**: ^{1}H NMR ($CDCl_3$) δ 5.20 (m, 2H), 4.48 (q, J = 7.1 Hz, 2H), 1.59 (d, J = 7.0 Hz, 3H), 1.41 (s, 9H), 1.40 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 182.1, 161.8, 157.5, 154.6, 80.7, 63.0, 44.2, 28.2, 19.8, 14.0.

Ethyl 5-[(*R*)-2-(Benzylthio)-1-[(*tert*-butyloxycarbonyl)-amino]ethyl]-1,2,4-oxadiazole-3-carboxylate (5a). The symmetrical anhydride was formed from Boc-L-cysteine(Bn) (353 mg, 1.13 mmol) and DCC (117 mg, 0.57 mmol). A mixture of **1** (50 mg, 0.38 mmol) and the crude anhydride in pyridine was refluxed for 1.5 h. After addition of water to the pyridine solution, the mixture was kept in the refrigerator. The precipitate was filtered off to afford 125 mg (81%) of pure **5a**: ^{1}H NMR ($CDCl_3$) δ 7.35–7.25 (m, 5H), 5.39 (br d, 1H), 5.29 (m, 1H), 4.51 (q, J = 6.9 Hz, 2H), 3.68 (s, 2H), 2.97 (d, J = 6.0 Hz, 2H), 1.45 (t, 3H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 180.2, 161.8, 157.4, 154.7, 137.0, 128.9, 128.7, 127.5, 81.0, 63.2, 48.0, 36.5, 34.7, 28.2, 14.1.

Ethyl 5-[(*S*)-2-(Benzyloxy)-1-[(*tert*-butyloxycarbonyl)-amino]ethyl]-1,2,4-oxadiazole-3-carboxylate (6a). The symmetrical anhydride was formed from Boc-L-serine(Bn) (591 mg, 2.00 mmol) and DCC (206 mg, 1.00 mmol). A mixture of **1** (50 mg, 0.38 mmol) and the crude anhydride in pyridine was refluxed for 2 h. Purification by column chromatography (pentane/EtOAc, 8.5:1.5) afforded 80 mg (54%) of pure **6a** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.32–7.18 (m, 5H), 5.59 (br d, 1H), 5.29 (m, 1H), 4.51 (q, J = 7.1 Hz, 2H), 4.49 (s, 2H), 3.95 (dd, J = -9.5, 3.4 Hz, 1H), 3.83 (dd, J = 4.0 Hz, 1H), 1.44 (s, 9H), 1.43 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 179.9, 161.8, 157.4, 155.0, 136.8, 128.5, 128.0, 127.6, 80.8, 73.4, 70.0, 63.0, 49.2, 28.2, 14.0.

Ethyl 5-[(*S*)-1-(*tert*-Butyloxycarbonyl)pyrrolidin-2-yl]-1,2,4-oxadiazole-3-carboxylate (7a). The symmetrical anhydride was formed from Boc-L-proline (429 mg, 1.99 mmol) and DCC (206 mg, 1.00 mmol). A mixture of **1** (50 mg, 0.38 mmol) and the crude anhydride in pyridine was refluxed for 3 h. Purification by column chromatography (pentane/EtOAc, 3:1) afforded 44 mg (38%) of pure **7a** as an oil. ^{1}H NMR ($CDCl_3$) rotamers δ 5.15 (m, 1H), 4.55 (m, 2H), 3.75–3.40 (m, 2H), 2.50–1.90 (m, 4H), 1.44–1.27 (m, 12H); ^{13}C NMR ($CDCl_3$) rotamers δ 182.4, 182.1, 161.8, 157.5, 154.1, 153.2, 80.7, 80.5, 63.0, 62.9, 53.8, 53.7, 46.6, 46.3, 32.5, 31.5, 28.2, 28.0, 24.3, 23.6, 14.0; MS m/z 312.16 (MH^+); mass calcd for $C_{14}H_{21}N_3O_5$ 311.34.

Ethyl 5-[(*S*)-2-(Benzyloxycarbonyl)-1-[(*tert*-butyloxycarbonyl)amino]ethyl]-1,2,4-oxadiazole-3-carboxylate (8a). Method A. The symmetrical anhydride was formed from Boc-L-aspartate(Bn) (734 mg, 2.27 mmol) and DCC (234 mg, 1.14 mmol). A mixture of **1** (100 mg, 0.78 mmol) and the crude anhydride in pyridine was refluxed for 1 h. After addition of water to the pyridine solution, the mixture was kept in the refrigerator. The precipitate was filtered off to afford 208 mg (66%) of pure **8a**.

Method B. A mixture of **1** (50 mg, 0.38 mmol) and Boc-L-aspartate(Bn)-ONp (33.6 mg, 0.76 mmol) in pyridine was refluxed for 3 h. Purification by column chromatography (pentane/EtOAc, 8.5:1.5) afforded 92 mg (58%) of pure **8a**: ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5H), 5.73 (br d, 1H), 5.43 (m, 1H), 5.11 (AB system, 2H), 4.50 (q, J = 7.0 Hz, 2H), 3.31 (dd, J = −17.5, 4.5 Hz, 1H), 3.10 (dd, J = 5.0 Hz, 1H), 1.46 (s, 9H),

1.44 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 180.2, 169.9, 161.9, 157.4, 154.8, 135.0, 128.7, 128.6, 128.5, 81.1, 67.2, 63.1, 45.3, 37.7, 28.2, 14.1.

Ethyl 5-[(*S*)-4-[1,3-Bis(*tert*-butyloxycarbonyl)-1-guanidino]-1-[(*tert*-butyloxycarbonyl)amino]butyl]-1,2,4-oxadiazole-3-carboxylate (9a). The symmetrical anhydride was formed from $(Boc)_3$-L-arginine (30 mg, 0.73 mmol) and DCC (80 mg, 0.38 mmol). A mixture of **1** (53 mg, 0.40 mmol) and the crude anhydride in pyridine was refluxed for 4 h. Purification by column chromatography (pentane/EtOAc, 4:1) afforded 40 mg (20%) of pure **9a**: ^{1}H NMR ($CDCl_3$) δ 9.2 (br, 2H), 6.29 (br d, 1H), 5.15 (m, 1H), 4.50 (q, J = 7.2 Hz, 2H), 4.21–3.56 (m, 2H), 2.18–1.67 (m, 4H), 1.52–1.40 (m, 30H); ^{13}C NMR ($CDCl_3$) δ 181.8, 163.3, 161.8, 160.6, 157.6, 155.2, 154.8, 84.0, 80.2, 79.1, 63.0, 48.6, 43.8, 29.0, 28.3, 28.1, 28.0, 24.8, 14.1.

General Procedure for the Synthesis of Boc-Protected L-Amino Acid Hydrazides 2b–7b. DCC, 4-(dimethylamino)-pyridine (DMAP), and EtOH were added to a solution of the Boc-L-amino acid in dry Et_2O. The mixture was stirred at room temperature, and the reaction was followed by TLC (Et_2O/pentane, 1:1). The resulting DCU was filtered off. The filtrate was extracted with 1 M $NaHSO_4$, saturated aqueous $NaHCO_3$, and water, dried ($MgSO_4$), filtered, and concentrated. The residue was redissolved in EtOH and treated with hydrazine hydrate. The mixture was stirred at room temperature, and the reaction was followed by TLC ($CHCl_3$/MeOH, 9:1). The hydrazide was, if possible, isolated and characterized. Otherwise, it was used without further purification.

[(S)-2-[(*tert*-Butyloxycarbonyl)amino]-3-phenylpropanoyl]hydrazine (2b).[40] A solution of Boc-L-phenylalanine methyl ester (14 g, 0.05 mol) in MeOH was treated with hydrazine hydrate (7.3 mL, 0.15 mol). After stirring for 18 h, the mixture was kept in the refrigerator for 1 h. The product precipitated, and filtration afforded 11.5 g (82%) of pure **3b**: mp 120–122 °C; $[\alpha]_D$ +9.7 (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.70 (br s, 1H), 7.30–7.15 (m, 5H), 5.32 (br d, 1H), 4.36 (dd, 1H), 3.81 (br s, 2H), 3.02 (AB system, 2H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.9, 155.2, 136.4, 129.2, 128.8, 127.1, 80.5, 54.8, 38.4, 28.3. Anal. Calcd for $C_{14}H_{21}N_3O_3$: C, 60.2; H, 7.6; N, 15.0. Found: C, 60.4; H, 7.8; N, 15.0.

[2-[(*tert*-Butyloxycarbonyl)amino]acetyl]hydrazine (3b).[41] A mixture of Boc-glycine (500 mg, 2.85 mmol), DCC (648 mg, 3.14 mmol), DMAP (34.9 mg, 0.28 mmol), and EtOH (366 μL, 6.28 mmol) was stirred for 70 min. The crude ethyl ester was treated with hydrazine hydrate (416 μL, 8.56 mmol) for 36 h. The solvent was evaporated. Recrystallization (EtOAc/pentane) of the residue provided 312 mg (58%) of pure **3b**: mp 115–116 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (br s, 1H), 5.48 (br s, 1H), 3.92 (br s, 2H), 3.81 (d, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.4, 156.2, 80.5, 43.0, 28.3. Anal. Calcd for $C_7H_{15}N_3O_3$: C, 44.4; H, 8.0; N, 22.2. Found: C, 44.6; H, 7.9; N, 22.6.

[(S)-2-[(*tert*-Butyloxycarbonyl)amino]propanoyl]hydrazine (4b).[42] A mixture of Boc-L-alanine (500 mg, 2.64 mmol), DCC (600 mg, 2.91 mmol), DMAP (32.3 mg, 0.26 mmol), and EtOH (338 μL, 5.82 mmol) was stirred for 70 min. The crude ethyl ester was treated with hydrazine hydrate (385 μL, 7.93 mmol) for 36 h. The solvent was evaporated. Recrystallization (EtOAc/pentane) of the residue provided 312 mg (51%) of pure **4b**: mp 95.5–96.5 °C; $[\alpha]_D$ –25.4 (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.99 (br s, 1H), 5.25 (br d, 1H), 4.19 (app quin, 1H), 3.93 (br s, 2H), 1.44 (s, 9H), 1.36 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.6, 155.5, 80.3, 48.8, 28.3, 18.4. Anal. Calcd for $C_8H_{17}N_3O_3$: C, 47.3; H, 8.4; N, 20.7. Found: C, 47.6; H, 8.3; N, 21.0.

[(*R*)-3-(Benzylthio)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (5b). A mixture of Boc-L-cysteine(Bn) (500 mg, 1.60 mmol), DCC (364 mg, 1.77 mmol), DMAP (19.6 mg, 0.16 mmol), and EtOH (103 μL, 1.77 mmol) was stirred for 50 min. The crude ethyl ester was treated with hydrazine hydrate (234 μL, 4.82 mmol) for 19 h and was then kept in the refrigerator. The product precipitated, and filtration afforded 338 mg (65%) of pure **5b**: mp 109–110 °C; $[\alpha]_D$ –4.7 (*c* 0.98, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.78 (br s, 1H), 7.35–7.25 (m, 5H), 5.36 (app d, 1H), 4.22 (dd, 1H), 3.90 (br s, 2H), 3.72 (s, 2H), 2.79 (AB system, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.6, 155.6, 138.1, 129.3, 128.9, 127.6, 80.8, 53.0, 36.8, 33.9, 28.6. Anal. Calcd for $C_{15}H_{23}N_3O_3S$: C, 55.4; H, 7.1; N, 12.9. Found: C, 55.7; H, 7.0; N, 12.6.

[(*S*)-3-(Benzyloxy)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (6b). A mixture of Boc-L-serine(Bn) (500 mg, 1.62 mmol), DCC (385 mg, 1.85 mmol), DMAP (20 mg, 0.17 mmol), and EtOH (125 μL, 1.85 mmol) was stirred for 2 h. The crude ethyl ester was treated with hydrazine hydrate (240 μL, 4.93 mmol) for 20 h. The residue was used in the next step without further purification.

[(*S*)-1-(*tert*-Butyloxycarbonyl)-2-pyrrolidinoyl]hydrazine (7b). Ethyl chloroformate (312 μL, 3.25 mmol) was added to a solution of Boc-L-proline (700 mg, 3.25 mmol) and Et_3N (453 μL, 3.25 mmol) in dry THF. The mixture was stirred at –15 °C for 30 min. The resulting triethylammonium hydrochloride was filtered off, and the filtrate was added to hydrazine hydrate (316 μL, 6.50 mmol) in THF. The mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was used in the next step without further purification.

General Procedure for the Synthesis of Diacylhydrazides 2c–7c. The reaction was carried out in dry THF under a nitrogen atmosphere. Ethyl oxalyl chloride was added to a chilled (–30 °C) mixture of the Boc-L-amino acid hydrazide and Et_3N in THF. The mixture was gradually warmed to room temperature and was then kept at ambient temperature. The reaction was followed by TLC ($CHCl_3$/MeOH, 9:1). The resulting triethylammonium hydrochloride was filtered off, and the filtrate was concentrated. The residue was partitioned between Et_2O and water. The organic layer was extracted with saturated aqueous $NaHCO_3$ and 1 M $NaHSO_4$, dried ($MgSO_4$), filtered, and concentrated. The residue was purified as indicated or used in the next reaction step without further purification.

1-(Ethoxyoxalyl)-2-[(S)-2-[(*tert*-butyloxycarbonyl)amino]-3-phenylpropanoyl]hydrazine (2c). A mixture of ethyl oxalyl chloride (624 μL, 5.58 mmol), **2b** (1.30 g, 4.65 mmol), and Et_3N (777 μL, 5.58 mmol) was stirred for 20 h. Crystallization of the residue in Et_2O/hexane provided 1.06 g (60%) of pure **2c**: mp 88–89 °C; $[\alpha]_D$ –21.7 (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.20 (br s, 2H), 7.35–7.20 (m, 5H), 5.07 (br d, 1H), 4.51 (m, 1H), 4.37 (q, J = 7.0 Hz, 2H), 3.18 (dd, 1H), 3.05 (dd, J = –14.0, 6.0 Hz, 1H), 1.39 (s, 9H), 1.38 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0, 158.7, 155.7, 152.9, 136.0, 129.3, 128.7, 127.1, 80.8, 65.6, 54.3, 37.9, 28.3, 13.9. Anal. Calcd for $C_{18}H_{25}N_3O_6$: C, 57.0; H, 6.6; N, 11.1. Found: C, 56.6; H, 6.8; N, 11.0.

1-(Ethoxyoxalyl)-2-[2-[(*tert*-butyloxycarbonyl)amino]acetyl]hydrazine (3c). A mixture of ethyl oxalyl chloride (89 μL, 0.79 mmol), **3b** (100 mg, 0.53 mmol), and Et_3N (110 μL, 0.79 mmol) was stirred for 20 h. Extraction and concentration of the organic layer afforded 128 mg (84%) of pure **3c**: mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 9.56 (br s, 2H), 5.63 (br s, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.95 (app bd, 2H), 1.44 (s, 9H), 1.37 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 168.1, 158.7, 156.3, 154.0, 80.5, 63.5, 42.8, 28.2, 13.8. Anal. Calcd for $C_{11}H_{19}N_3O_6$: C, 45.7; H, 6.6; N, 14.5. Found: C, 45.4; H, 6.8; N, 14.1.

1-(Ethoxyoxalyl)-2-[(S)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (4c). A mixture of ethyl oxalyl chloride (235 μL, 2.10 mmol), **4b** (407 mg, 2.00 mmol), and Et_3N (293 μL, 2.10 mmol) was stirred for 3 h. The residue was redissolved in EtOAc and extracted with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was used in the next step without further purification.

1-(Ethoxyoxalyl)-2-[(*R*)-3-(benzylthio)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (5c). A mixture of ethyl oxalyl chloride (52 μL, 0.41 mmol), **5b** (100 mg, 0.31 mmol), and Et_3N (64.2 μL, 0.41 mmol) was stirred for 5 h. Extraction and concentration of the organic layer afforded 100 mg (76%) of pure **5c**: mp 63.5–65.5 °C; $[\alpha]_D$ –27.7 (*c* 0.84,

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(41) Bailey, W.; Griffith, J. R. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1964**, *5*, 266–278.
(42) Tesser, G. I.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 53–66.

MeOH); ^{1}H NMR ($CDCl_3$) δ 9.49 (br s, 2H), 7.35–7.25 (m, 5H), 5.44 (br d, 1H), 4.30 (m, 3H), 3.75 (s, 2H), 2.84 (br d, J = 6.5 Hz, 2H), 1.44 (s, 9H), 1.36 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 168.2, 158.5, 155.5, 152.9, 137.6, 129.0, 128.6, 127.2, 80.9, 63.5, 52.4, 36.4, 33.1, 28.2, 13.9. Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.6; H, 6.4; N, 9.9. Found: C, 53.2; H, 6.4; N, 9.3.

1-(Ethoxyoxalyl)-2-[(*S*)-3-(benzyloxy)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (6c). A mixture of ethyl oxalyl chloride (184 μL, 1.65 mmol), crude **6b**, and Et_3N (230 μL, 1.65 mmol) was stirred for 3 h. The crude product was used in the next step without further purification.

1-(Ethoxyoxalyl)-2-[(*S*)-1-(*tert*-butyloxycarbonyl)-pyrrolidinoyl]hydrazine (7c). A mixture of ethyl oxalyl chloride (389 μL, 3.48 mmol), crude **7b**, and Et_3N (485 μL, 3.48 mmol) was stirred for 40 min. The crude product was used without further purification.

General Procedure for the Synthesis of Ethyl 1,3,4-Oxadiazole-2-carboxylate Derivatives 2d–7d.[43] The first step of the ring closure was carried out in dry Et_2O under a nitrogen atmosphere. $SOCl_2$ was added to a chilled (0 °C) solution of the diacylhydrazide and pyridine in dry Et_2O. The mixture was stirred at 0 °C for 2 h. The resulting salt was filtered off, and the filtrate was concentrated in vacuo without heating. The residue was redissolved in toluene and the solution heated to reflux. The reaction was followed by TLC ($CHCl_3$/MeOH/hexane, 9:1:1). The solvent was evaporated and the residue purified by column chromatography.

Ethyl 5-[(*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-phenylethyl]-1,3,4-oxadiazole-2-carboxylate (2d). A solution of **2c** (1 g, 2.64 mmol), pyridine (550 μL, 6.85 mmol), and $SOCl_2$ (250 μL, 3.43 mmol) was stirred for 2 h. The residue was refluxed in toluene for 2 h. Purification by column chromatography (CH_2Cl_2/EtOAc, 19:1) afforded 593 mg (62%) of pure **2d**: ^{1}H NMR ($CDCl_3$) δ 7.35–7.05 (m, 5H), 5.36 (m, 1H), 5.09 (br d, 1H), 4.51 (q, J = 7.2 Hz, 2H), 3.32 (dd, 1H), 3.22 (dd, 1H), 1.45 (t, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.5, 156.9, 154.6, 154.1, 134.7, 129.2, 128.8, 127.4, 80.8, 63.6, 48.6, 39.6, 28.2, 14.0.

Ethyl 5-[[(*tert*-Butyloxycarbonyl)amino]methyl]-1,3,4-oxadiazole-2-carboxylate (3d). A solution of **3c** (121 mg, 0.42 mmol), pyridine (101 μL, 1.25 mmol), and $SOCl_2$ (46 μL, 0.63 mmol) was stirred for 2 h. The residue was refluxed in toluene for 2 h. Purification by column chromatography (CH_2Cl_2/EtOAc, 19:1) afforded 40 mg (35%) of pure **3d**: ^{1}H NMR ($CDCl_3$) δ 5.18 (br s, 1H), 4.62 (app br d, 2H), 4.50 (q, J = 7.0 Hz, 2H), 1.44 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 166.2, 157.1, 155.3, 154.1, 80.8, 63.6, 36.0, 28.2, 14.0.

Ethyl 5-[(*S*)-1-[(*tert*-Butyloxycarbonyl)amino]ethyl]-1,3,4-oxadiazole-2-carboxylate (4d). A solution of crude **4c**, pyridine (387 μL, 4.79 mmol), and $SOCl_2$ (174 μL, 2.40 mmol) was stirred for 2 h. The residue was refluxed in toluene for 12 h. Purification by column chromatography (pentane/EtOAc, 7:3) afforded 188 mg (33% overall yield in two steps) of pure **4d**: ^{1}H NMR ($CDCl_3$) δ 5.18 (m, 2H), 4.55 (q, J = 7.2 Hz, 2H), 1.63 (d, J = 6.8 Hz, 3H), 1.45 (s, 9H), 1.44 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 169.7, 156.9, 154.7, 154.2, 80.7, 63.6, 43.4, 28.2, 19.7, 14.1.

Ethyl 5-[(*R*)-2-(Benzylthio)-1-[(*tert*-butyloxycarbonyl)-amino]ethyl]-1,3,4-oxadiazole-2-carboxylate (5d). A solution of **5c** (106 mg, 0.25 mmol), pyridine (44 μL, 0.55 mmol), and $SOCl_2$ (20 μL, 0.27 mmol) was stirred for 2 h. The residue was refluxed in toluene for 2 h. Purification by column chromatography (CH_2Cl_2/EtOAc, 97:3) afforded 12 mg (12%) of pure **5d**: ^{1}H NMR ($CDCl_3$) δ 7.30–7.25 (m, 5H), 5.3 (br, 2H), 4.52 (q, J = 7.1 Hz, 2H), 3.70 (s, 2H), 2.98 (m, 2H), 1.46 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 167.8, 157.0, 154.7, 154.1, 137.1, 129.0, 128.8, 127.4, 81.0, 63.6, 47.2, 36.6, 34.4, 28.2, 14.1.

Ethyl 5-[(*S*)-2-(Benzyloxy)-1-[(*tert*-butyloxycarbonyl)-amino]ethyl]-1,3,4-oxadiazole-2-carboxylate (6d). A solution of half the amount of the crude **6c**, pyridine (116 μL, 1.44 mmol), and $SOCl_2$ (52 μL, 0.72 mmol) was stirred for 2 h. The residue was refluxed in toluene for 8 h. Purification by column chromatography (pentane/EtOAc, 7:3) afforded 65 mg (20% overall yield in three steps) of pure **6d**: ^{1}H NMR ($CDCl_3$) δ 7.32–7.19 (m, 5H), 5.55 (br d, 1H), 5.26 (m, 1H), 4.55–4.47 (m, 4H), 3.94 (dd, J = –9.4, 3.8 Hz, 1H), 3.84 (dd, J = 3.8 Hz, 1H), 1.45 (s, 9H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 157.0, 155.0, 154.1, 136.9, 128.5, 128.0, 127.7, 80.8, 73.4, 69.7, 63.5, 48.1, 28.2, 14.0.

Ethyl 5-[(*S*)-1-(*tert*-Butyloxycarbonyl)pyrrolidin-2-yl]-1,3,4-oxadiazole-2-carboxylate (7d). A solution of crude **7c**, pyridine (787 μL, 9.76 mmol), and $SOCl_2$ (354 μL, 4.88 mmol) was stirred at 0 °C for 2 h. The residue was refluxed in toluene for 2 h. Purification by column chromatography (CH_2Cl_2/EtOAc, 9:1 and Et_2O/pentane, 7:3) afforded 60 mg (6% overall yield in three steps) of pure **7d** as an oil: ^{1}H NMR ($CDCl_3$)[44] rotamers δ 5.22–5.06 (m, 1H), 4.52 (app q, 2H), 3.70–3.40 (m, 2H), 2.49–1.92 (m, 4H), 1.45 (m, 7H), 1.33 (s, 5H); ^{13}C NMR ($CDCl_3$)[44] rotamers δ 169.8, 156.6, 154.2, 153.4, 80.7, 80.5, 63.6, 63.4, 52.8, 46.6, 46.4, 32.0, 31.3, 28.3, 28.2, 24.3, 23.7, 14.0.

General Procedure for the Synthesis of Acylamidrazones 2e–7e. The Boc-protected L-amino acid was converted to a mixed anhydride by addition of ethyl chloroformate to a chilled solution (–5 °C) of the amino acid and Et_3N in dry THF. The mixture was stirred at –5 °C for 30 min. The resulting triethylammonium hydrochloride was filtered off, and a solution of **10** in dry THF was added to the filtrate at room temperature. In the cases where the acylamidrazone precipitated during the reaction, the pure product was easily isolated by filtration. Those compounds were fully characterized. If the acylamidrazone did not precipitate, the crude product was used in the cyclization reaction without purification. ^{1}H and ^{13}C NMR spectra showed that tautomeric mixtures were obtained in all the isolated compounds.

1-(Ethoxyoxalimidyl)-2-[(*S*)-2-[(*tert*-butyloxycarbonyl)amino]-3-phenylpropanoyl]hydrazine (2e). The mixed anhydride was formed from Boc-L-phenylalanine (111 mg, 0.42 mmol), Et_3N (48 μL, 0.50 mmol), and ethyl chloroformate (70 μL, 0.50 mmol). Compound **10** (46 mg, 0.35 mmol) was added to the filtrate, and the mixture was stirred for 5 h. Filtration of the reaction mixture afforded 106 mg (80%) of pure **2e**: mp 176–178 °C (EtOH/pentane); $[\alpha]_D$ +105.7 (c 1.05, DMF); ^{1}H NMR (DMSO-d_6) δ 9.96 (br s, 0.5H), 9.84 (br s, 0.5H), 7.42–7.13 (m, 5H), 7.08 (br d, 0.5H), 6.94 (br d, 0.5H), 6.50 (br s, 2H), 4.86 (m, 0.5H), 4.37–4.17 (m, 2.5H), 3.07–2.54 (m, 2H), 1.29 (s, 9H), 1.38–1.24 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 173.3, 168.1, 162.2, 161.9, 155.6, 155.4, 139.6, 139.3, 137.9, 136.1, 129.2, 128.1, 127.9, 126.3, 126.2, 78.1, 77.8, 61.8, 61.6, 54.9, 54.2, 37.5, 35.9, 28.2, 14.1. Anal. Calcd for $C_{18}H_{26}N_4O_5$: C, 57.1; H, 6.9; N, 14.8. Found: C, 57.0; H, 6.9; N, 14.7.

1-(Ethoxyoxalimidyl)-2-[2-[(*tert*-butyloxycarbonyl)-amino]acetyl]hydrazine (3e). The mixed anhydride was formed from Boc-glycine (146 mg, 0.83 mmol), Et_3N (139 μL, 1.00 mmol), and ethyl chloroformate (96 μL, 1.00 mmol). Compound **10** (91 mg, 0.69 mmol) was added to the filtrate, and the mixture was stirred for 3 h. After evaporation of the solvent, the crude acylamidrazone was used in the cyclization without further purification.

1-(Ethoxyoxalimidyl)-2-[(*S*)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (4e). The mixed anhydride was formed from Boc-L-alanine (128 mg, 0.68 mmol), Et_3N (113 μL, 0.81 mmol), and ethyl chloroformate (78 μL, 0.81 mmol). Compound **10** (74 mg, 0.56 mmol) was added to the filtrate, and the mixture was stirred for 18 h. Filtration of the reaction mixture afforded 146 mg (86%) of pure **4e**: mp 183–184 °C; $[\alpha]_D$ +37.8 (c 0.98, DMF); ^{1}H NMR (DMSO-d_6) δ 9.84 (br s, 0.5H), 9.76 (br s, 0.5H), 6.94 (br d, 0.5H), 6.74 (br d, 0.5H), 6.44 (br d, 2H), 4.73 (m, 0.5H), 4.22 (q, J = 7.2 Hz, 2H), 4.04 (m, 0.5H), 1.37 (s, 9H), 1.26 (t, 3H), 1.20 (d, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 174.3, 169.3, 162.2, 161.7, 155.1, 139.5, 136.2, 78.0, 77.8, 61.6, 61.5, 48.8, 28.2, 18.1, 16.9, 14.0, 13.9.

(43) The yield did not decrease when the crude diacylhydrazines were used in the cyclization step, but it was important to have dry conditions and high-quality thionyl chloride and pyridine. The pyridinium salt resulting from formation of the oxathiadiazole *S*-oxide had to be carefully filtered off to improve the yield.

(44) According to the ^{1}H and ^{13}C NMR spectra of the proline derivatives **7d** and **7f**, the *cis*-carbamate is the major isomer in the 1,3,4-oxadiazole derivative and the *trans*-carbamate is the major isomer in the 1,2,4-triazole derivative. For ^{1}H and ^{13}C NMR on *cis*- and *trans*-isomers of L-proline derivatives, see: Luthman, K.; Hacksell, U. *Acta Chem. Scand.* **1993**, *47*, 461–468.

Anal. Calcd for $C_{12}H_{22}N_4O_5$: C, 48.0; H, 6.9; N, 18.1. Found: C, 47.7; H, 7.3; N, 18.5.

1-(Ethoxyoxalimidyl)-2-[(*R*)-3-(benzylthio)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (5e). The mixed anhydride was formed from Boc-L-cysteine(Bn) (100 mg, 0.32 mmol), Et_3N (54 μL, 0.38 mmol), and ethyl chloroformate (37 μL, 0.38 mmol). Compound **10** (35 mg, 0.27 mmol) was added to the filtrate, and the mixture was stirred for 22 h. Filtration of the reaction mixture afforded 85 mg (75%) of pure **5e**: mp 200–202 °C; $[\alpha]_D$ +19.0 (*c* 1.02, DMF); ^1H NMR (DMSO-d_6) δ 10.02 (br s, 0.5H), 9.92 (br s, 0.5H), 7.32–7.20 (m, 5H), 7.04 (br d, 0.5H), 6.77 (br d, 0.5H), 6.52 (br d, 2H), 5.09 (m, 0.5H), 4.28–4.13 (m, 2.5H), 3.91–3.77 (m, 2H), 2.67–2.59 (m, 2H), 1.39 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 1.5H), 1.23 (t, 1.5H); ^{13}C NMR (DMSO-d_6) δ 172.2, 166.9, 162.1, 161.7, 155.4, 155.2, 140.0, 138.7, 138.2, 136.5, 129.0, 128.8, 128.4, 128.3, 126.9, 126.8, 78.3, 78.0, 61.7, 52.9, 50.6, 35.2, 35.0, 33.0, 32.1, 28.2, 14.0, 13.8. Anal. Calcd for $C_{19}H_{28}N_4O_5S$: C, 53.8; H, 6.6; N, 13.2. Found: C, 53.8; H, 6.6; N, 13.2.

1-(Ethoxyoxalimidyl)-2-[(*S*)-3-(benzyloxy)-2-[(*tert*-butyloxycarbonyl)amino]propanoyl]hydrazine (6e). The mixed anhydride was formed from Boc-L-serine(Bn) (174 mg, 0.59 mmol), Et_3N (98 μL, 0.70 mmol), and ethyl chloroformate (68 μL, 0.70 mmol). Compound **10** (59 mg, 0.45 mmol) was added to the filtrate, and the mixture was stirred for 7 h. Filtration of the reaction mixture afforded 124 mg (67%) of pure **6e**: mp 179–180 °C; $[\alpha]_D$ +26.2 (*c* 0.97, DMF); ^1H NMR (DMSO-d_6) δ 10.05 (br s, 1H), 7.31–7.13 (m, 5H), 6.88 (br d, 0.5H), 6.66 (br d, 0.5H), 6.52 (br d, 2H), 5.14 (m, 0.5H), 4.59–4.44 (m, 2H), 4.34 (m, 0.5H), 4.28–4.14 (m, 2H), 3.64 (br dd, 2H), 1.38 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.2, 166.4, 162.1, 161.6, 155.3, 155.2, 139.8, 138.4, 138.0, 136.3, 128.2, 128.1, 127.5, 127.4, 78.3, 78.1, 72.1, 71.5, 69.7, 69.1, 61.6, 61.5, 53.3, 51.3, 28.2, 14.0, 13.9. Anal. Calcd for $C_{19}H_{28}N_4O_6$: C, 55.6; H, 7.1; N, 13.4. Found: C, 55.9; H, 6.9; N, 13.7.

1-(Ethoxyoxalimidyl)-2-[(*S*)-1-(*tert*-butyloxycarbonyl)-2-pyrrolidinoyl]hydrazine (7e). The mixed anhydride was formed from Boc-L-proline (157 mg, 0.73 mmol), Et_3N (122 μL, 0.88 mmol), and ethyl chloroformate (84 μL, 0.88 mmol). Compound **10** (80 mg, 0.61 mmol) was added to the filtrate, and the mixture was stirred for 7 h. After evaporation of the solvent, the crude acylamidrazone was used in the cyclization without further purification.

General Procedure for the Synthesis of Ethyl 1,2,4-Triazolecarboxylate Derivatives 2f–7f. The acylamidrazone was heated in xylenes (mixture of isomers) with a Dean–Stark apparatus, using a silicon oil bath. The oil bath temperature was kept above the melting point of the acylamidrazone.[45] The reaction was followed by TLC ($CHCl_3$/MeOH/pentane, 9:1:1). When the reaction was complete, the solvent was evaporated and the residue purified by column chromatography.

Ethyl 5-[(*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-phenylethyl]-1,2,4-triazole-3-carboxylate (2f). Compound **2e** (318 mg, 0.84 mmol) was heated at an oil bath temperature of 190 °C for 6 h. Purification of the residue by column chromatography (pentane/EtOAc, 7:3) afforded 196 mg (65%) of pure **2f**: ^1H NMR ($CDCl_3$) δ 13.0 (br, 1H), 7.60–7.00 (m, 5H), 5.76 (br d, 1H), 5.25 (app dd, 1H), 4.48 (q, *J* = 7.0 Hz, 2H), 3.26 (AB system, 2H), 1.41 (t, 3H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.6, 159.5 (w), 155.8, 153.9, 136.2, 129.2, 128.6, 127.0, 80.6, 62.2, 49.2, 40.3, 28.2, 14.2.

(45) The fact that the reaction temperature had to be kept around 200 °C may have decreased the yields because of decomposition reactions.

Ethyl 5-[[(*tert*-Butyloxycarbonyl)amino]methyl]-1,2,4-triazole-3-carboxylate (3f). Crude **3e** was heated at an oil bath temperature of 180 °C for 3 h. Purification of the residue by column chromatography (EtOAc/pentane, 9:1) afforded 52 mg (28% overall yield in two steps) of pure **3f**: ^1H NMR ($CDCl_3$) δ 13.5 (br, 1H), 5.9 (br, 1H), 4.55 (app d, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.40 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 160.5, 159.8, 156.5, 154.0 (w), 80.5, 62.1, 36.5, 28.2, 14.1.

Ethyl 5-[(*S*)-1-[(*tert*-Butyloxycarbonyl)amino]ethyl]-1,2,4-triazole-3-carboxylate (4f). Compound **4e** (146 mg, 0.48 mmol) was heated at an oil bath temperature of 195 °C for 6 h. Purification of the residue by column chromatography (EtOAc/pentane, 7:3) afforded 62 mg (45%) of pure **4f**: ^1H NMR ($CDCl_3$) δ 13.7 (br, 1H), 5.91 (br d, 1H), 5.13 (m, 1H), 4.47 (q, *J* = 6.8 Hz, 2H), 1.62 (d, *J* = 7.0 Hz, 3H), 1.40 (t, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 160.5, 160.0, 155.6, 154.0 (w), 80.2, 62.1, 43.4, 28.2, 20.1, 14.1.

Ethyl 5-[(*R*)-2-(Benzylthio)-1-[(*tert*-butyloxycarbonyl)-amino]ethyl]-1,2,4-triazole-3-carboxylate (5f). Compound **5e** (91 mg, 0.21 mmol) was heated at an oil bath temperature of 195 °C for 4 h. Purification of the residue by column chromatography (EtOAc/pentane, 2:3) afforded 15 mg (17%) of pure **5f**: ^1H NMR ($CDCl_3$) δ 12.6 (br, 1H), 7.28–7.20 (m, 5H), 5.65 (br d, 1H), 5.10 (dd, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 3.11–2.92 (AB system, 2H), 1.43 (s, 9H), 1.42 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 159.5 (w), 155.7, 137.6, 128.9, 128.7, 127.3, 80.9, 62.3, 47.6, 36.5, 35.0, 28.3, 14.2.

Ethyl 5-[(*R*)-2-(Benzyloxy)-1-[(*tert*-butyloxycarbonyl)-amino]ethyl]-1,2,4-triazole-3-carboxylate (6f). Compound **6e** (113 mg, 0.28 mmol) was heated at an oil bath temperature of 190 °C for 5 h. Purification of the residue by column chromatography (EtOAc/pentane, 3:2) afforded 24 mg (22%) of pure **6f**: ^1H NMR ($CDCl_3$) δ 12.3 (br, 1H), 7.29–7.26 (m, 5H), 5.71 (bs, 1H), 5.16 (m, 1H), 4.52 (s, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 4.03–3.73 (m, 2H), 1.41 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 159.7, 158.2, 155.8, 153.7, 137.1, 128.8, 128.0, 127.8, 80.8, 73.5, 70.2, 62.1, 48.0, 28.2, 14.2.

Ethyl 5-[(*S*)-1-(*tert*-Butyloxycarbonyl)pyrrolidin-2-yl]-1,2,4-triazole-3-carboxylate (7f). The crude **7e** was heated at an oil bath temperature of 190 °C for 4 h. Purification of the residue by column chromatography (EtOAc/pentane, 9:1) afforded 49 mg (26% yield in two steps) of pure **7f**: ^1H NMR ($CDCl_3$)[44] rotamers δ 12.4 (br, 1H), 5.15–4.98 (m, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 3.66–3.35 (m, 2H), 2.94–2.79 (m, 1H), 2.49–1.89 (m, 3H), 1.48, 1.32 (2s, 9H), 1.42 (t, 3H); ^{13}C NMR ($CDCl_3$)[44] rotamers δ 160.1, 159.4, 156.1, 153.7, 80.0, 61.8, 54.8, 52.6, 47.2, 46.8, 32.9, 28.8, 28.3, 24.6, 23.5, 14.2.

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Supplementary Material Available: Assignments of ^1H and ^{13}C NMR signals of compounds described above, X-ray experimental data, and elemental analyses (calculated and found) of the compounds listed in Table 1 (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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