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Synthesis of Various 3-Substituted 1,2,4-Oxadiazole-Containing Chiral β^3- and α-Amino Acids from Fmoc-Protected Aspartic Acid

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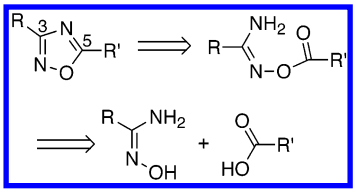
Various 3-substituted chiral 1,2,4-oxadiazole-containing Fmoc-β^3- and -α-amino acids were synthesized from Fmoc-(L or D)-Asp(O*t*Bu)-OH and Fmoc-L-Asp-O*t*Bu, respectively, in three steps (i.e., condensation of an aspartyl derivative with differentially substituted amidoximes, formation of the 1,2,4-oxadiazole, and cleavage of the *tert*-butyl ester). These compounds represent new series of nonnatural amino acids, which could be used in combinatorial synthesis. A simple protocol has been developed to generate the 1,2,4-oxadiazole ring. Indeed, common methods resulted in cleavage of the Fmoc group or required long reaction times. We found that sodium acetate in refluxing ethanol/water (86 °C) was a convenient and efficient catalyst to promote conversion of Fmoc-amino acyl amidoximes to 1,2,4-oxadiazoles, and this procedure proved to be compatible with Fmoc protection. It is shown that these compounds can be prepared without significant loss of enantiomerical purity. Furthermore, the alkaline conditions used to cleave the Fmoc protecting group from these compounds did not induce epimerization of their chiral center.

Introduction

In an effort to develop new chiral nonproteinogenic α- and β-amino acids that could be incorporated into biologically relevant peptides, as well as into protease inhibitor structures, we focused on the synthesis of heterocycle-containing amino acids. In the case of peptides, new properties could be expected from such compounds and remain to be investigated. The use of heterocycles as scaffolds to optimally place substituents in protease pockets is an important strategy for the search of protease inhibitors with improved pharmacokinetic properties. Heterocycle-containing amino acids would facilitate incorporation of the scaffold while offering several possibilities of variation.

One such heterocycle is the well-known 1,2,4-oxadiazole (Scheme 1).[1] It has been frequently used as ester or amide bioisostere[2] and was found to help in the design of compounds with improved physicochemical properties and bioavailability.[3] One interesting feature is the possible participation in hydrogen bonding (as acceptor) with a target (the active site of a protease, for instance) as observed for compounds containing 1,3,4-oxadiazole.[4] Furthermore, usual synthetic methods (see below) allow preparation of heterocycles with substituents in positions 3 and 5 (Scheme 1). Several papers have reported the use of 1,2,4-oxadiazole in peptide mimetics, including the design of amino acyl-Gly dipeptidomimetics,[5] signal transduction inhibitors,[6] or cell adhesion inhibitors.[7] 1,2,4-Oxadiazole-containing amino acids are prepared from amino diacid compounds (e.g., aspartyl and glutamyl derivatives). Several examples of aspartyl-derived 1,2,4-

SCHEME 1[a]



[a] 1,2,4-Oxadiazole is substituted in **5** by the acyl-derived moiety (R′) and in **3** by the amidoxime substituent (R).

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oxadiazole compounds can be found in the literature, with in addition to references already mentioned,[5a,7] the synthesis of phenolic amino acids,[8] alanine analogues,[9] or the synthesis of combinatorial libraries of oxadiazole compounds on solid support.[10]

1,2,4-Oxadiazoles are most commonly synthesized in solution and on solid support[10−13] from amidoximes and carboxylic acid derivatives in two steps (Scheme 1). During the first step, the amidoxime prepared by the addition of hydroxylamine to a nitrile compound is O-acylated by an activated carboxylic acid derivative. Preactivation or in situ activation protocols have been reported, including the use of acid chloride,[11] acid fluoride,[12] symmetrical anhydride,[3b,5,14] active ester,[6] ester with sodium ethoxide,[13] CDI,[15,16] acyl-palladium complex,[17] UNCA,[18] carbodiimides (DCC,[9,15] DIC,[10a] and EDC[6,15,19]), BOP-Cl,[15] and TBTU.[20] The heterocycle is subsequently formed by intramolecular cyclodehydration. This can be performed either after isolation of the O-acylated amidoxime precursor or immediately following its formation in a one-pot reaction. Numerous conditions of dehydration have been reported, mostly involving heating (above 100 °C) in solvents such as DMF,[16,20] diglyme,[10,15] pyridine,[5,6] in the presence or not[5,6,9,10,15,20] of additives such as EDC,[7] CDI,[16] or Burgess reagent.[19] Cyclization could also proceed at room temperature when a strong basic reagent (NaOEt[13] or TBAF[11,21]) is present. All of these approaches generally require long reaction times.

Most amino acid derived 1,2,4-oxadiazoles are synthesized by coupling the α-carboxylic group of an α-amino acid to amidoximes, leading to heterocycles in which the amino acyl derived moiety is attached at the C-5 position (Scheme 1). It is also possible to obtain the regioisomer with attachment at the C-3 position when the α-carboxyl group is first converted into nitrile, the amino acyl derived amidoxime precursor.[22] These derivatives are usually obtained from Boc-protected amino acids. One group reported the use of Fmoc-amino acids in the synthesis of oxadiazole libraries.[10] Cyclization is performed on a solid support by heating in a neutral solvent without the need of a dehydrating agent, conditions that are compatible with Fmoc protection. However, reaction time is rather long (6 h) and no yield has been precisely presented.

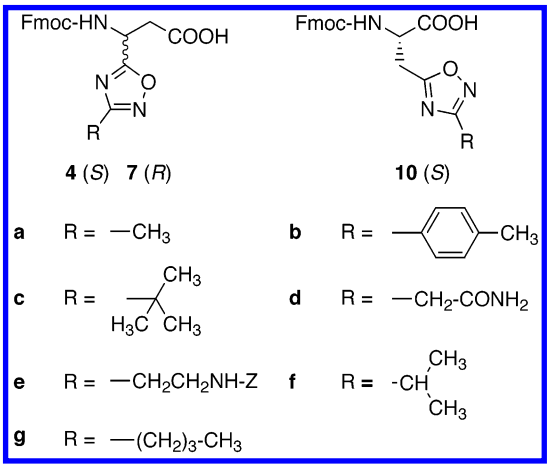

FIGURE 1. Structure of Fmoc-protected 1,2,4-oxadiazole-containing β^3- (*S* enantiomer, compounds **4a**−**g**; *R* enantiomer, compounds **7a**−**f**) and α- (*S* enantiomer, compounds **10a**−**d**) amino acids.

This paper describes the preparation of chiral 1,2,4-oxadiazole-containing Fmoc-β^3- and -α-amino acids from Fmoc-Asp protected on its β- and α-carboxylic group, respectively. Fmoc is a protecting group more suitable than Boc for the use of these derivatives in combinatorial synthesis.

Results and Discussion

Two series of 1,2,4-oxadiazole-containing amino acids have been synthesized from Fmoc-protected aspartyl derivatives (Figure 1). The condensation of differentially substituted amidoximes to the α- or β-carboxylic group of an aspartyl residue followed in both cases by the formation of the heterocyclic ring and the deprotection of the remaining carboxylic group led to the Fmoc-protected 1,2,4-oxadiazole-containing β^3- or α-amino acids, respectively.[23] Physical data of the synthesized Fmoc-amino acid derivatives are presented in Table 1.

Synthesis of 1,2,4-Oxadiazole-Containing Fmoc-β^3-Amino Acids. 1,2,4-Oxadiazole compounds **4a**−**g** and **7a**−**f** were synthesized in three steps from an aspartyl derivative (Scheme 2).[24] The α-carboxylic group of Fmoc-L-Asp(O*t*Bu)-OH (or Fmoc-D-Asp(O*t*Bu)-OH) was first condensed to variously substituted amidoximes, which have been prepared using classical procedures, i.e., treatment of nitrile compounds with hydroxylamine in refluxing ethanol.[25]

Several coupling conditions have been examined for O-acylation of acetamidoxime (**1a**). We first used HBTU

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(24) Similar β^3-amino acids could also be prepared from β-HomoAsp (β-amino-glutaric acid). In this case, the symmetry of this derivative allows the preparation of both enantiomers following homologation of an L-aspartyl derivative used as a single precursor. See: Hamzé, A.; Hernandez, J.-F.; Martinez, J. *Tetrahedron Lett.* **2003**, *44*, 6079−6082.
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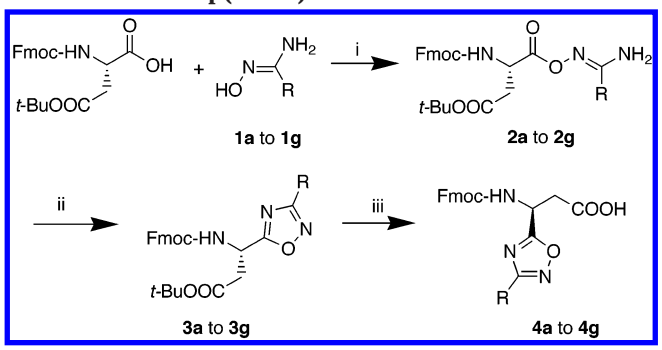
TABLE 1. Physical Data of 1,2,4-Oxadiazole-Containing Amino Acids

compound	$[\alpha]_D$[a]	mp (°C)[b]	t_R (min)[c]	yield (%)[d]
4a	−33	117−119	2.85	71
7a	+33	128−130	2.74	73
4b	−49	180−182	3.43	71
7b	+49	186−188	3.45	84
4c	−35	179−181	3.28	42
7c	+34	182−184	3.25	69
4d	−36	172−174	2.42	25
7d	+36	190−192	2.46	50
4e	−27	79−81	3.18	59
7e	+27	112−114	3.16	59
4f	−40	171−173	3.04	54
7f	+40	172−174	3.10	76
4g	−32	153−155	3.28	55
10a	−18	168−170	2.81	35
10b	−14	nd[e]	3.46	38
10c	−14	nd[e]	3.29	56
10d	−13	176−178	2.42	20

[a] t = 20 °C, c = 0.01, MeOH. [b] Melting points were measured using a Kofler apparatus and are uncorrected. [c] Reverse-phase HPLC analyses were run on a Chromolith SpeedRod C18 column (0.46 cm × 5 cm); gradient 0−100% CH_3CN/H_2O/0.1% TFA over 5 min, 3 mL/min flow rate; the slight differences in retention times observed between the enantiomers (**4a**/**7a** to **4f**/**7f**) are not significant. [d] Overall yield calculated from Fmoc-protected aspartyl derivative. [e] Not determined, hygroscopic powder.

SCHEME 2. Synthesis of 1,2,4-Oxadiazole-Containing Fmoc-β^3-Amino Acids from Fmoc-L-Asp(O*t*Bu)-OH[a,b]



[a] Reagents and conditions: (i) DIC, HOBt, DCM; (ii) CH_3COONa, $EtOH/H_2O$, 86 °C, 2 h; (iii) TFA/DCM (50:50). [b]The same synthetic pathway starting from Fmoc-D-Asp(O*t*Bu)-OH, was used for acyl amidoximes **5a**−**f**, fully protected oxadiazoles **6a**−**f**, and final compounds **7a**−**f**.

and the even more reactive HBTU/HOBt pair (1 equiv of each), which are very efficient coupling reagents and represent conditions close to those utilized successfully by Poulain et al.[20] (i.e., TBTU/HOBt) for coupling of amidoximes to carboxylic acid derivatives. These conditions led to the expected O-acylated compounds albeit with significant contamination. The widely used EDC/HOBt[6,15,19] gave similar results. However, the O-acylated amidoxime derivative **2a**, characterized by mass spectrometry and ^{1}H NMR analyses was the sole product when DIC or DIC/HOBt was used. The latter was preferred over DIC alone to limit the possible deactivation into *N*-acylurea and the loss of enantiomeric purity during coupling (see below) and was used for the synthesis of all compounds.

The *O*-acyl amidoximes were isolated before subsequently being cyclized. Several cyclization conditions were applied to check their compatibility with the Fmoc protecting group. Heating the acyl acetamidoxime **2a** in DMF at 110 °C, conditions that have been used successfully in the case of Boc-protected amino acyl amidoximes derivatives,[20] did not allow recovery of the desired protected oxadiazole **3a**. Instead, we isolated a compound that was identified as dibenzofulvene by ^{1}H NMR spectroscopy,[26,27] showing that cleavage of the Fmoc group had occurred. This cleavage was probably promoted by dimethylamine, which might be produced from thermal decomposition of DMF. Another method allowing the synthesis of 1,2,4-oxadiazoles from Boc-amino acids uses refluxing pyridine.[5] In the case of Fmoc-protected derivatives these conditions cannot be applied, and we observed extensive cleavage of the protecting group together with the appearance of dibenzofulvene. One possible explanation is the potential presence of amino contaminants in commercially available pyridine. The Fmoc group is very but not entirely resistant to pyridine. Traces of dibenzofulvene have been detected in pyridine solutions of Fmoc derivatives after 10 h at room temperature.[28] Pyridine itself might also induce Fmoc cleavage at high temperature. The catalytic use of a strong base such as TBAF at room temperature has also been documented for the conversion of Boc-protected amino acyl amidoximes.[18] However, the use of similar conditions in our study (0.1 equiv of TBAF in THF for 48 h) produced a heterogeneous reaction mixture where the presence of **2a** could be evidenced. Exposure to higher quantities of TBAF would not be relevant as this strong base can easily remove the Fmoc group.[29] In addition, Borg et al. observed that TBAF induced racemization of the α-carbon of a Boc-Phe-derived 1,2,4-oxadiazole.[5b] Finally, treatment with a tertiary amine (TEA, 1 equiv) at room temperature left the starting material unchanged.

Other described methods were thought to be Fmoc-incompatible or required long reaction times. Therefore, we searched for suitable conditions to achieve both Fmoc integrity and fast conversion. Sodium acetate appeared to us as a possible candidate, since we already noted its use in a dehydration reaction such as the formation of semicarbazone from aldehyde and semicarbazide.[30] In fact, cyclic dehydration of acyl amidoxime **2a** to oxadiazole **3a** in the presence of sodium acetate (1−1.1 equiv in ethanol/water at 86 °C) was found to proceed cleanly with good yield (75% after crystallization). Monitoring by reverse-phase HPLC showed that **2a** was totally consumed within 2 h, whereas less than 50% of **2a** was converted into **3a** in the absence of sodium acetate during the same period (Figure 2). This result showed that sodium acetate dramatically increased the dehydration rate. The completely protected oxadiazole compounds **3a**−**g** and **6a**−**f** were generated under these suitably mild conditions in good yields (50−84%), suggesting the general use of this method. Thus, it is shown that this procedure is compatible with the widely used protecting

(26) ^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2H), 7.63 (d, J = 6.6 Hz, 2H), 7.37−7.28 (ddd, J = 1.2 Hz, 2H), 7.25−7.20 (ddd, J = 1.2 Hz, 2H), 6.01 (s, 2 olefinic H).

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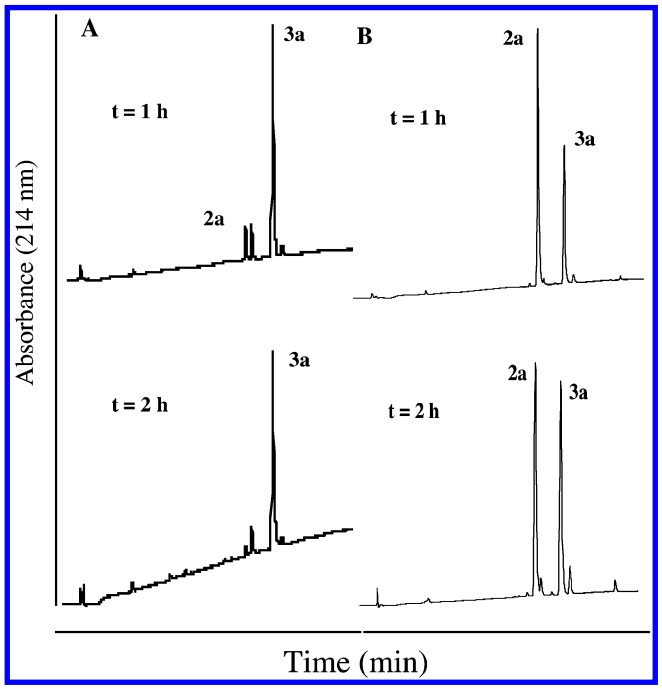
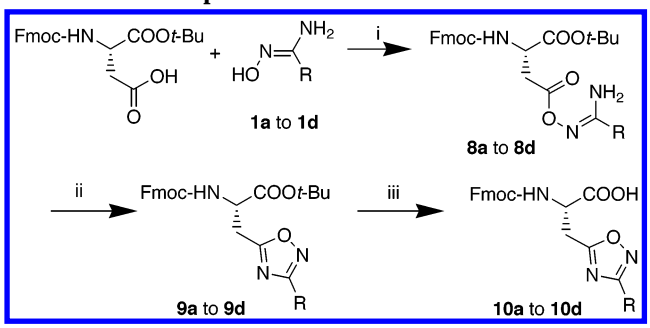


FIGURE 2. Reverse-phase HPLC monitoring of the conversion of compound **2a** to the oxadiazole **3a**, in the presence (A) or the absence (B) of sodium acetate (HPLC conditions are indicated in footnote c of Table 1).

SCHEME 3. Synthesis of 1,2,4-Oxadiazole-Containing Fmoc-α-Amino Acids from Fmoc-L-Asp-O*t*Bu[a]



[a] Reagents and conditions: (i) DIC, HOBt, DCM; (ii) CH_3COONa, $EtOH/H_2O$, 86 °C, 4−5 h; (iii) TFA/DCM (50:50).

groups, Fmoc, *t*-Bu ester, Boc (results not shown), Z (compounds **3e**, **6e**), benzyl and allyl ester (results not shown), as well as with functionalities such as amides (compounds **3d**, **6d**).

The final removal of the *t*-Bu ester protecting group from oxadiazoles **3a**−**g** and **6a**−**f** afforded the chiral Fmoc-β^3-amino acids **4a**−**g** and **7a**−**f**, respectively (Scheme 2). Satisfying overall yields (approximately 50−80% yields) were obtained for all compounds except for those with R = $-CH_2CONH_2$ (compounds **4d**, **7d**, **10d**. Table 1). The latter result was partly explained by the difficulty to obtain pure synthetic amidoxime **1d**.

Synthesis of 1,2,4-Oxadiazole-Containing Fmoc-α-Amino Acids. Chiral 1,2,4-oxadiazole derivatives **10a**−**d** were synthesized in three steps as described above starting from Fmoc-L-Asp-O*t*Bu (Scheme 3).

Various amidoximes (**1a**−**d**) were condensed to the β-carboxylic group of the aspartyl moiety. Here, the subsequent conversion of the resulting acyl amidoximes **8** to the oxadiazoles **9** required longer reaction times (4−5 h) compared to the cyclization involving the α-carboxyl group. The mechanism of ring closure implies an initial attack of the amidine group on the carbonyl of the acyl group. The observed lower reactivity could be explained by the lower electrophilic character of the β-carboxylic group compared to the α-one. Despite this difference, the reaction went to completion, leading to similar yields of oxadiazoles (43−82%).

The final deprotection step using TFA in DCM generated Fmoc-α-amino acids **10a**−**d**. Lower overall yields were obtained in the α-amino acid series compared to the β^3-amino acid series (Table 1). This result is mainly the consequence of a less efficient condensation of the aspartyl β-carboxylic group with amidoximes.

Stereochemical Aspects. Optical purity is an essential characteristic of amino acids. Synthesis from enantiopure aspartyl derivatives should lead to oxadiazole compounds without any significant epimerization. Epimerization might occur during the activation of the α-carboxylic group of aspartic acid derivatives and/or condensation with amidoximes[31] as already mentioned[5a] and depends on the activation procedure. In addition, once the 1,2,4-oxadiazole ring is formed, the amino acyl derived chiral αCH, adjacent to the heterocycle, might be subject to racemization under acidic or alkaline conditions (see below). To check the preservation of chiral integrity during the synthesis, compound **4a** was coupled to L-Phe-OMe. Reverse-phase HPLC analysis of the resulting dipeptide showed that no significant epimerization occurred during the synthesis of **4a** as more than 97% of the expected (*S*,*S*) diastereoisomer was recovered. In this context, it is of interest to note that optical rotation of the *S* (**4a**−**f**) and *R* (**7a**−**f**) derivatives have, as expected, opposite signs, and for an identical R substituent, very close absolute values (Table 1).

It was reported that the deprotection of Boc-protected 1,2,4-oxadiazole-derived dipeptidomimetics using TFA, following their incorporation on solid support, resulted in epimerization.[5b] No mechanism was proposed to explain this surprising finding. Furthermore, as mentioned above, the same group of investigators reported that racemization could be induced by TBAF.[5b] This could be prevented using adapted conditions, but it points out the lability of the amino acyl derived α-proton when it is adjacent to the heterocycle. The electron-attracting properties of the oxadiazoles, which have been exploited in the design of α-keto-oxadiazole inhibitors of serine proteases,[32] might be responsible for the observed epimerizations. This phenomenon was also observed for α-keto carbonyl inhibitors of proteases where the chiral center (αCH) adjacent to the electrophilic carbonyl group is subject to racemization under alkaline conditions.[33]

(31) Acylation by the β-carboxylic group of Asp does not induce epimerization.

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Therefore, we checked if removal of the Fmoc protecting group using a 20% piperidine solution in DMF could also induce epimerization. Using standard solid-phase peptide synthesis protocols, **4a** has been attached to a solid support, deprotected, and coupled with Fmoc-L-Phe-OH. The Fmoc was removed, and the pseudodipeptide was cleaved from the resin. Reverse-phase HPLC analysis of the resulting free compound showed almost the sole presence (>95%) of the expected (*S*,*S*) and no (*S*,*R*) diastereoisomer, indicating that no significant epimerization occurred during Fmoc deprotection.

Finally, we have to point out that the side chain orientation of the obtained β^3-amino acids is opposite to that of the starting aspartyl derivatives. Indeed, the α-carboxylic group of Asp is the precursor of the oxadiazole side chain, while the β-carboxylic group becomes part of the main peptide chain. Thus, if a topology similar to that of L-amino acid is desired, the precursor must be a D-aspartyl derivative.

Conclusion

New series of β^3- and α-amino acids containing different 3-substituted 1,2,4-oxadiazole heterocycles have been synthesized. They represent an original addition to the list of available nonnatural amino acids. Their preparation as Nα-Fmoc-protected derivatives and retention of chirality during all steps allow their use in peptide and peptidomimetic syntheses, as well as in solution- and solid-phase combinatorial syntheses. Although a limited number of different and representative substituents are presented here, it is obvious that a much larger diversity can be easily achieved. The use of sodium acetate in refluxing ethanol/water during the key cyclic dehydration step proved to be convenient and Fmoc-compatible and enables a short, clean, and inexpensive reaction. These mild conditions represent a very interesting alternative for the synthesis of 1,2,4-oxadiazoles.

Experimental Section

(A) General Procedure for Preparation of *O*-Amino Acyl Amidoximes (Compounds 2a−g, 5a−f, 8a−d). To a solution of Fmoc-amino acid (1 equiv) and amidoxime **1** (1.2 equiv) in DCM/DMF (9:1) (15 mL/g) were added HOBt (1.2 equiv) and DIC (1.2 equiv) at −10 °C. The reaction was stirred for 20 min at this temperature and then for 1.5 h at room temperature. The solvents were concentrated in vacuo, and the residue was dissolved in ethyl acetate. The organic layer was washed with $NaHCO_3$ (twice), H_2O, $KHSO_4$ 0.5 M (twice), and brine and dried over $MgSO_4$. Evaporation to dryness afforded *O*-amino acyl amidoxime, which was used without further purification in the next step, unless otherwise indicated.

1,1-Dimethylethyl-3-(*S*)-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-4-[[(1-amino-ethyl)imino]oxy]-4-oxobutanoate (2a, R = CH₃). Compound **2a** was prepared from Fmoc-L-Asp(O*t*Bu)-OH (0.7 g, 1.7 mmol), and *N*-hydroxyethanimidamide **1a** (0.151 g, 2.04 mmol). Purification by column chromatography (EtOAc/hex, 8:2) afforded 0.75 g (95%) of **2a** as a white solid: R_f 0.38 (EtOAc/hex, 7:3); *m*/*z* (ES+) 468.21 (M + H$^+$), 411.94 (M-*t*Bu + H$^+$), 935.34 (2M + H$^+$); HPLC t_R 3.2 min; ^{1}H NMR ($CDCl_3$) δ 7.8 (d, J = 7.5 Hz, 2H), 7.6 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 5.90 (d, J = 8.4 Hz, 1H), 4.75 (m, 1H), 4.4 (m, 2H), 4.21 (t, J = 7.1 Hz, 1H), 3.0 (dd, J = 5.0, 16.6 Hz, 1H), 2.8 (dd, J = 5.5, 16.6 Hz, 1H), 2.0 (s, 3H), 1.48 (s, 9H).

1,1-Dimethylethyl-2-(*S*)-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-4-[[(1-amino-ethyl)imino]oxy]-4-oxobutanoate (8a, R = CH₃). Compound **8a** was prepared from Fmoc-L-Asp-O*t*Bu (0.5 g, 1.22 mmol) and *N*-hydroxyethanimidamide **1a** (0.1 g, 1.34 mmol). Purification by column chromatography (EtOAc/hex, 7:3) afforded 0.34 g (61%) of pure product as a colorless oil: R_f 0.26 (EtOAc/hex, 7:3); *m*/*z* (ES+) 468.2 (M + H$^+$), 412.1 (M-*t*Bu + H$^+$), 935.3 (2M + H$^+$); HPLC t_R 3.05 min; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2H), 7.6 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 5.78 (d, J = 8.3 Hz, 1H), 4.65 (m, 1H), 4.4 (m, 2H), 4.3 (t, J = 7.1 Hz, 1H), 3.1 (m, 2H), 1.97 (s, 3H), 1.50 (s, 9H).

(B) General Procedure for Preparation of 1,2,4-Oxadiazoles (Compounds 3a−g, 6a−f, 9a−d). Sodium acetate (1 or 1.1 equiv) dissolved in water was added to a stirred solution of the Fmoc-aminoacyl amidoxime (1 equiv) in ethanol, and the resulting mixture was heated at 86 °C for 2 or 5 h. After this period, the solution was allowed to cool to room temperature. When crystallization occurred, the solid was collected by filtration. If not, the solvents were removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The aqueous layer was then extracted, and the subsequent organic layer was dried ($MgSO_4$) and filtered. Evaporating the solvent under vacuum afforded a crude product, which was generally purified by column chromatography.

1,1-Dimethylethyl-3-(*S*)-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-3-[3-methyl-1,2,4-oxadiazol-5-yl]-propionate (3a, R = CH₃). Heating a mixture of **2a** (1.9 g, 4.07 mmol) in ethanol (20 mL) and sodium acetate (0.608 g, 4.47 mmol) in water (3 mL) for 2 h afforded **3a**, which crystallized upon cooling as white crystals (1.34 g, 75%): mp 122−124 °C; *m*/*z* (ES+) 450.28 (M + H$^+$), 394.00 (M-*t*Bu + H$^+$), 899.30 (2M + H$^+$), 921.26 (2M + Na$^+$); HPLC t_R 3.71 min; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 7.2 Hz, 2H), 7.61 (m, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.32 (m, 2H), 6.2 (d, J = 8.3 Hz, 1H), 5.38 (m, 1H), 4.42 (m, 2H), 4.28 (t, J = 7.1 Hz, 1H), 3.1 (dd, 1H), 2.9 (dd, 1H), 2.4 (s, 3H), 1.4 (s, 9H).

1,1-Dimethylethyl-2-(*S*)-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-3-[3-methyl-1,2,4-oxadiazol-5-yl]-propionate (9a, R = CH₃). Heating a mixture of **8a** (0.31 g, 0.664 mmol) in ethanol (10 mL) and sodium acetate (0.091 g, 0.664 mmol) in water (1.5 mL) for 5 h afforded crude **9a**. Purification by column chromatography (EtOAc/hex, 2:8) yielded 0.185 g (62%) of the desired product as a colorless oil: R_f 0.42 (EtOAc/hex, 2:8); *m*/*z* (ES+) 450.2 (M + H$^+$), 471.7 (M + Na$^+$), 393.9 (M-*t*Bu + H$^+$), 899.4 (2M + H$^+$), 921.3 (2M + Na$^+$); HPLC t_R 3.56 min; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 2H), 7.5 (d, J = 7.5 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.4 Hz, 2H), 5.8 (d, J = 7.7 Hz, 1H), 4.7 (m, 1H), 4.35 (m, 2H), 4.21 (t, J = 7.1 Hz, 1H), 3.4 (dd, 1H), 3.3 (dd, J = 5.0 Hz, 21 Hz, 1H), 2.3 (s, 3H), 1.35 (s, 9H).

(C) General Procedure for Removal of *tert*-Butyl Ester (Compounds 4a−g, 7a−f, 10a−d). The *tert*-butyl-protected compounds were dissolved in TFA/DCM (50:50, 20−30 mL/g of compound), and the mixtures were stirred for 2 h at room temperature. After this period, the solvents were removed under reduced pressure, and the resulting residues were taken up in hexane/diethyl ether. The products precipitated and were collected by filtration.

3-(*S*)-[[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino]-3-[3-methyl-1,2,4-oxadiazol-5-yl]-propionic Acid (4a, R = CH₃). Compound **3a** (0.20 g, 0.44 mmol) was converted to **4a** as described in Method C to yield a white powder (0.174 g, 100%): mp 117−119 °C; $[\alpha]_D = -33$ (*c* 0.01, MeOH); *m*/*z* (ES+) 393.94 (M + H$^+$), 787.11 (2M + H$^+$), 809.25 (2M + Na$^+$); HPLC t_R 2.85 min; ^{1}H NMR ($CDCl_3$) δ 7.5 (d, J = 7.4 Hz, 2H), 7.4 (d, J = 7.1 Hz, 2H), 7.18 (t, J = 7.3 Hz, 2H), 7.1 (t, J = 7.3 Hz, 2H), 5.82 (d, J = 9.0 Hz, 1H), 5.2 (m, 1H), 4.2 (m, 2H), 4.1 (t, J = 7.0 Hz, 1H), 3.0 (dd, 1H), 2.88 (dd, 1H), 2.1 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 179.4, 171.7, 167.8, 156.4, 144.6, 144.5, 141.6, 128.5, 127.9, 126.0, 121.0, 66.8, 47.4, 45.7, 37.6, 12.0.

2-(*S*)-[[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino]-3-[3-methyl-1,2,4-oxadiazol-5-yl]-propionic Acid (10a, R = CH_3). Compound **9a** (0.175 g, 0.38 mmol) was converted to **10a** as described in Method C to yield a white powder (0.142 g, 93%): mp 168−170 °C; $[\alpha]_D = -18$ (*c* 0.01, MeOH); *m*/*z* (ES+) 394.1 ($M + H^+$), 416.2 ($M + Na^+$), 787.1 ($2M + H^+$), 809.4 ($2M + Na^+$); HPLC t_R 2.81 min; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, $J = 7.5$ Hz, 2H), 7.5 (d, $J = 7.3$ Hz, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.25 (t, $J = 7.4$ Hz, 2H), 5.88 (d, $J = 7.1$ Hz, 1H), 4.75 (m, 1H), 4.35 (m, 2H), 4.2 (t, $J = 6.8$ Hz, 1H), 3.48 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 177.5, 172.5, 167.6, 156.7, 144.6, 144.5, 141.6, 128.5, 127.9, 126.1, 126.0, 121.0, 66.7, 52.3, 47.4, 29.1, 12.0.

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Supporting Information Available: (1) General experimental procedures; experimental procedures for synthesis of amidoximes **1a**−**g**; synthetic details and analytical data for all other compounds. (2) Copies of ^{1}H NMR spectra of final compounds **4a**−**g**, **7a**−**f**, and **10a**−**d**. (3) Copies of ^{13}C NMR spectra of final compounds **4a**−**g**, **7a**−**f**, and **10a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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