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The preparation of optically active α-amino 4*H*-[1,2,4]oxadiazol-5-ones from optically active α-amino acids

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ABSTRACT

Optically active α-amino 4*H*-[1,2,4]oxadiazol-5-ones (oxadiazolones) were prepared from optically active α-amino acids in five synthetic steps. The oxadiazolone moiety serves as a bioisosteric replacement for the carboxylic acid. Incorporation of an α-amino oxadiazolone into a representative dipeptide mimic is described.

1. Introduction

The structure and function of α-amino acids and peptides have long fascinated chemists. Alteration of the peptide backbone through peptide mimetic design with a view on subsequent function continues to be a richly explored area of research.[1] Isosteric replacements for the carboxylic acid of α-amino acids or the C-terminus of peptides have been less explored with tetrazoles being the dominant replacement.[2] 4*H*-[1,2,4]Oxadiazol-5-ones (oxadiazolones) have been employed as isosteric replacements for carboxylic acids.[3] However, α-amino oxadiazolones have been rarely described in the literature, with a few examples without side chains,[4] and only one citation with side chains.[5] The use of oxadiazolones as a carboxylic acid isostere of α-amino acids or peptides may find wider use if efficient syntheses and knowledge about their properties were readily available. This note outlines the preparation of five representative α-amino oxadiazolones derived from optically active natural amino acids. This straight-forward sequence using readily available starting materials, and here determined to be stereospecific, to our knowledge has not been previously reported. To further develop the knowledge base of this class of compounds, analog **6a** was chosen for determination of selected physical properties and for the potential of its incorporation into peptides via standard coupling methodology.

2. Results and discussion

Commercially available, suitably-protected α-amino acids **1a–e** were converted to α-amino oxadiazolones **6a–e** (Fig. 1). Representative examples included lipophilic amino acids (phenylalanine and valine), an acidic amino acid (aspartic acid), and a basic amino acid (lysine). A general synthetic route was developed and is depicted in Scheme 1. The protected amino acids **1a–e** were converted to amides **2a–e** by a water soluble carbodiimide mediated coupling. The amides **2a–e** were conveniently dehydrated to nitriles **3a–e** by action of cyanuric chloride in DMF. This simple and general procedure has been reported to proceed without racemization and is consistent with our results (vide infra).[6] The reaction of nitriles **3a–e** with aqueous hydroxylamine provided hydroxyamidines **4a–e**. Oxadiazolones **5a–e** were formed by refluxing **4a–e** with carbonyldiimidazole in THF. Deprotection, and in some cases global deprotection, of **5a–e** was affected by exposure to ethereal hydrogen chloride to furnish the desired α-amino 4*H*-[1,2,4]oxadiazol-5-ones **6a–e** as their hydrochloride salts. The product oxadiazolone hydrochlorides **6a–e** were found to be stable, solid materials. Reanalysis by ^{1}H NMR of a nine-month-old batch of **6a** revealed no decomposition.

The overall route shown in Scheme 1 is efficient and in many cases the intermediates could be purified by recrystallization. The

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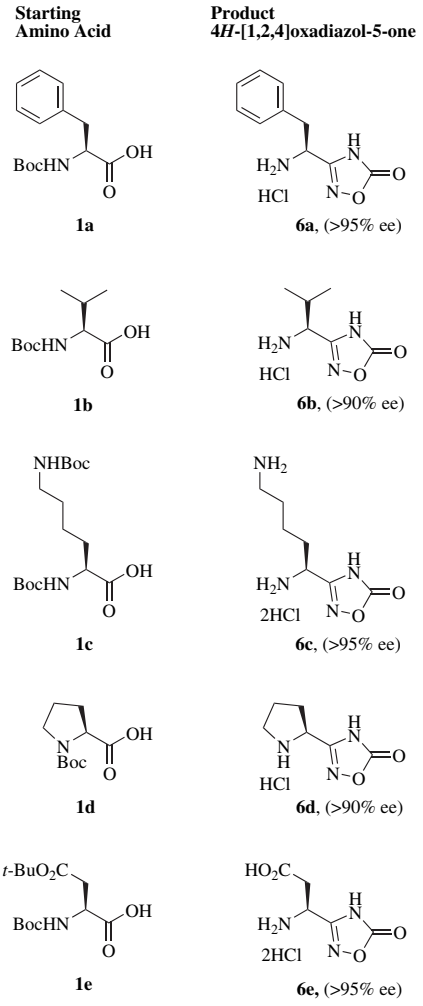
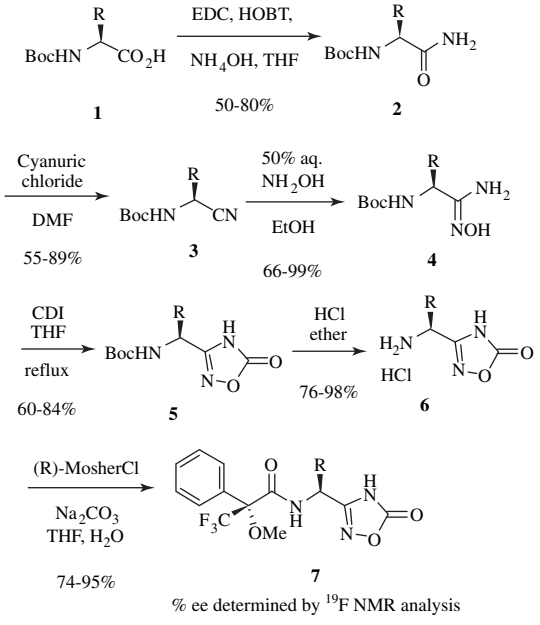


Figure 1.

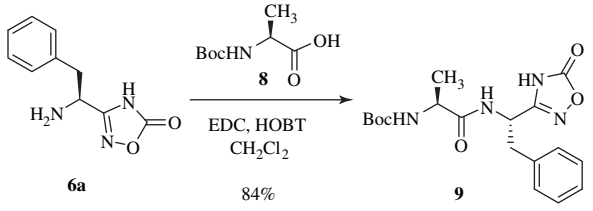


Scheme 1.

route is fairly general, without any interference from the various substituents defined in Figure 1. With the availability of optically active α-aminonitriles, for example, from various asymmetric Strecker reactions,[7] the scope of available substituents could be readily extended beyond the standard amino acids. One apparent limitation observed was an attempt to transform *S*-benzyl *N*-Boc-cysteine through the same general sequence. Although the oxadiazolone could be formed in low yield (21%, structure not shown) from the hydroxyamidine intermediate, all attempts to remove the Boc-protecting group led to non-specific decomposition.

The chiral integrity of oxadiazolones **6a–e** was determined by preparing their Mosher amides.[8] Oxadiazolones **6a–e** were coupled with (*R*)-Mosher chloride to furnish amides **7a–e**; **7c** (derived from lysine) was prepared as the bis-Mosher amide. Analysis of **7a–e** by ^{19}F NMR demonstrated negligible loss of optical purity during the synthetic sequence. Analysis of **7d** by ^{1}H and ^{19}F NMR demonstrated greater than 90% ee. Accurate quantification beyond this level was not possible due to broadening of signals, most likely due to rotomers.

The utility of α-amino oxadiazolones would be enhanced if they could be readily incorporated into peptides. To further demonstrate the potential of α-amino oxadiazolones, optically active **6a**, derived from phenylalanine, was coupled with *N*-Boc-alanine **8** by action of a water soluble carbodiimide to give dipeptide isostere **9** in good yield (Scheme 2). Notably, protection of the oxadiazolone functionality was not required for efficient coupling.



Scheme 2.

As a representative example, the pK_a′s and log *P* for compound **6a** were determined to exemplify this class of compound and to compare with its natural amino acid counterpart, phenylalanine. Two pK_a′s for compound **6a** were determined by potentiometry: pK_a=7.34 (±0.12) and 3.03 (±0.09) compared with phenylalanine pK_a=9.2 and 2.6. Based on these data, the oxadiazolone moiety of **6a** appears to be comparable or slightly less acidic than the carboxylic acid function of phenylalanine. Interestingly, the amino group of **6a** is considerably less basic than in phenylalanine. Although other factors may be at play, this latter observation may be partly attributable to the aromatic character of the oxadiazolone ring, depicted in Figure 2 as the hydroxyoxadiazole tautomer. In a similar fashion, simple replacement of the carboxyl group of glycine (pK_a=10.06) with a benzene ring (benzylamine pK_a=9.46) shows some decrease in pK_a.[9] The partitioning coefficient (log *P*) for compound **6a** was determined to be −1.56 by the shake flask method compared with the literature value of −1.44 for the zwitterionic form of phenylalanine.[10]

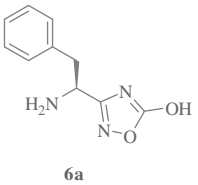


Figure 2.

In conclusion, an efficient synthetic route for the preparation of optically active α-amino oxadiazolones from optically active α-amino acids was developed. The oxadiazolone moiety can be considered as an isosteric replacement of the carboxylic acid. Efficient incorporation of a representative α-amino oxadiazolone into

a dipeptide mimic was exemplified. The use of α-amino oxadiazolones in peptide mimetic design remains to be more fully investigated.

3. Experimental

3.1. General

All reactions were performed under a dry nitrogen or argon atmosphere. Melting points are uncorrected. Proton NMR spectra were recorded at 300 MHz and Fluorine NMR spectra at 282 MHz. HPLC analysis was run on a Waters Symmetry C18 column (4.6×2 mm) with a flow rate of 1 mL/min and UV detection at 254 nM using a standard solvent gradient program (method A).

Method A:

Time (min)	%A	%B
0	90	10
20	10	90
30	10	90

Solvent A=0.05% trifluoroacetic acid in water.
Solvent B=0.05% trifluoroacetic acid in acetonitrile.

3.2. General procedure for the preparation of amide (2)

To a solution of amino acid (1.0 equiv) in tetrahydrofuran (c=0.07 M) was added 1-hydroxybenzotriazole (HOBT, 1.0 equiv) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.15 equiv). After stirring for 0.5 h, concentrated ammonium hydroxide (2.0 equiv) was added and the reaction mixture was stirred for 16–60 h. The mixture was concentrated and the residue was diluted with ethyl acetate. The suspension was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, filtered, and concentrated to afford the desired product **2**.

3.3. General procedure for the preparation of nitrile (3)[6]

To a solution of the amide **2** (1.0 equiv) in *N*,*N*-dimethylformamide (c=0.2 M) at 0 °C was added cyanuric chloride (1.4 equiv). After stirring for 1 h at 0 °C, the reaction mixture was quenched with a cold 0.5 M sodium hydroxide solution and the mixture extracted with ethyl acetate (3×). The organic layers were combined and washed with water and brine (2×), dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by silica gel chromatography to afford the desired nitrile **3**.

3.4. General procedure for the preparation of hydroxyamidine (4)

To a solution of nitrile **3** (1.0 equiv) in ethanol (c=0.25 M) was added 50% w/w aqueous hydroxylamine (4.0 equiv). After stirring for 18 h at room temperature, the reaction mixture was concentrated, the residue suspended in water, and extracted with diethyl ether (2×). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated to afford the desired product **4**.

3.5. General procedure for the preparation of *N*-Boc-oxadiazolone (5)

To a solution of hydroxyamidine **4** (1.0 equiv) in tetrahydrofuran (c=0.08 M) was added 1,1′-carbonyldiimidazole (1.5 equiv) and the mixture was heated at reflux for 5–18 h. The reaction mixture was cooled and concentrated. The residue was dissolved in ethyl acetate and extracted with a 1 M sodium hydroxide solution. The aqueous layer was diluted with methylene chloride, carefully acidified with 1 M hydrochloric acid to pH 3–4 with ice bath cooling and extracted with dichloromethane (2×). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and evaporated to afford the desired product **5**.

3.6. General procedure for the preparation of oxadiazolone hydrochloride (6)

To *N*-Boc-oxadiazolone **5** was added a 2 M solution of hydrogen chloride in diethyl ether and the mixture was stirred for 18 h. The precipitated solid was filtered, washed with diethyl ether, and dried to afford the desired product as a white solid **6**.

3.7. General procedure for the preparation of oxadiazolone Mosher amide (7)

To oxadiazolone **6** (1 equiv) in THF and water (1:1 vol, c=0.1 M) was added sodium carbonate (2 equiv), followed by *R*(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (1 equiv). The reaction mixture was stirred at room temperature for 2–18 h. The mixture was diluted with ethyl acetate and 1 N HCl. The organic layer was washed with 1 N HCl, dried over sodium sulfate, filtered, and evaporated to provide **7**.

*3.7.1. (S)-[1-(N-Hydroxycarbamimidoyl)-2-phenylethyl]-carbamic acid tert-butyl ester (**4a**)[11].* Compound **3a**, used to prepare **4a**, was prepared according to a literature procedure.[6] According to the general procedure described, **3a** (4.60 g, 18.7 mmol) was converted to **4a** (4.4 g, 85%) as a white solid: mp=158–161 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.14–7.28 (m, 5H), 6.85 (d, J=9.6 Hz, 1H), 5.34 (s, 2H), 4.10–4.19 (m, 1H), 2.79–3.03 (m, 2H), 1.29 (s, 9H); ESI: m/z=280 (M+H)$^+$; $[\alpha]_D^{25}$ +0.86 (c 1.05, MeOH). Anal. Calcd $C_{14}H_{21}N_3O_3$: C, 60.20; H, 7.58; N, 15.04. Found: C, 60.21; H, 7.64; N, 14.97.

*3.7.2. (S)-[1-(5-Oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-2-phenylethyl]-carbamic acid tert-butyl ester (**5a**).* According to the general procedure described, **4a** (1.80 g, 6.44 mmol) was converted to **5a** (1.51 g, 77%) as a white solid: mp=151–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.5 (br s, 1H), 7.46 (d, J=8.1 Hz, 1H), 7.19–7.32 (m, 5H), 4.64 (m, 1H), 3.08 (dd, J=5.6, 13.7 Hz, 1H), 2.94 (dd, J=9.7, 13.7 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 160.5, 159.6, 154.8, 136.7, 129.1, 128.1, 126.5, 78.5, 48.2, 36.7, 28.0; ESI: m/z=304 (M−H)$^-$; IR 3335, 3122, 1782, 1697, 1525, 1168, 972 cm^{-1}; $[\alpha]_D^{25}$ −24.93 (c 1.02, MeOH). Anal. Calcd $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.83; H, 6.27; N, 13.63.

*3.7.3. (S)-3-(1-Amino-2-phenylethyl)-4H-[1,2,4]oxadiazol-5-one hydrochloride (**6a**).* According to the general procedure described, **5a** (1.34 g, 4.39 mmol) was converted to **6a** (1.05 g, 99%) as a white solid: mp=168–171 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.33–7.43 (m, 3H), 7.26–7.29 (m, 2H), 4.69 (t, J=7.3 Hz, 1H), 3.18–3.36 (m, 2H, overlapping with MeOD peak); ^{1}H NMR (300 MHz, D_2O) δ 7.29–7.37 (m, 3H), 7.19–7.22 (m, 2H), 4.70 (m, 2H, overlapping with HOD peak), 3.29 (dd, J=7.0, 14.3 Hz, 1H), 3.21 (dd, J=7.5, 14.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 158.7, 156.7, 134.0, 129.2, 128.6, 127.3, 47.1, 35.8; APCI: m/z=206 (M+H)$^+$; IR 1770 cm^{-1}; $[\alpha]_D^{25}$ −23.12 (c 1.00, MeOH). Anal. Calcd $C_{10}H_{11}N_3O_2\cdot 1.05HCl$: C, 49.33; H, 4.99; N, 17.26, Cl, 15.29. Found: C, 49.08; H, 4.68; N, 17.30; Cl, 14.97.

*3.7.4. (R)-3,3,3-Trifluoro-2-methoxy-N-(S)-[1-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-2-phenylethyl]-2-phenyl-propionamide (**7a**).* According to the general procedure described, **6a** (50 mg, 0.21 mmol) was converted to **7a** (81 mg, 93%) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.50 (br s, 1H), 8.95 (d, J=8.7 Hz, 1H),

7.37 (m, 1H), 7.15–7.35 (m, 7H), 7.03 (d, J=7.7 Hz, 1H), 5.25 (ddd, J=4.6, 8.7, 10.8 Hz, 1H), 3.38 (s, 3H), 3.19 (dd, J=4.6, 13.9 Hz, 1H), 3.07 (dd, J=10.8, 13.9 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ −68.86 (98% ee); ESI: m/z=422 $(M+H)^+$; HPLC analysis: 99.3%, 25.09 min retention time. The other diastereomer of **7a** derived from D-phenylglycine (structure not shown) was prepared by analogous procedures to validate the enantiomeric excess determination. ^{19}F NMR (282 MHz, DMSO-d_6) δ −69.07 (98% ee).

*3.7.5. (S)-(1-Carbamoyl-2-methyl-propyl)-carbamic acid tert-butyl ester (**2b**)*[12]. Compound **2b** was prepared according to the general procedure described, using **1b** (4.00 g, 18.4 mmol) and affording **2b** (3.2 g, 80%) as a white solid: mp 155–157 °C (lit. 157 °C); $[\alpha]_D^{25}$ −0.4 (c 1.46, MeOH), (lit. $[\alpha]_D^{23}$ 0.3 (c 2.67, EtOH)).

*3.7.6. (S)-(1-Cyano-2-methyl-propyl)-carbamic acid tert-butyl ester (**3b**).* According to the general procedure described, **2b** (3.10 g, 14.3 mmol) was converted to **3b** (2.25 g, 80%) as a white solid: mp 69–71 °C; ^{1}H NMR ($CDCl_3$) δ 4.92 (br d, J=9.0 Hz, 1H), 4.49–4.44 (m, 1H), 2.02 (octet, J=6.7 Hz, 1H), 1.46 (s, 9H), 1.08 (t, J=6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 154.8, 118.4, 81.5, 48.8, 32.2, 28.8, 28.6, 28.3, 18.9, 18.3; IR (ATR) 3348, 2973, 1689, 1514, 1341, 1306, 1246, 1155, 1050 cm^{-1}; $[\alpha]_D^{25}$ −67.6 (c 1.07, MeOH); MS (APCI) 197 $[C_{10}H_{18}N_2O_2-H]^-$; MS (ESI) m/z 199 $[C_{10}H_{18}N_2O_2+H]^+$. Anal. Calcd for $C_{10}H_{18}N_2O_2\cdot 0.05H_2O$: C, 60.31; H, 9.16; N, 14.07. Found: C, 60.63; H, 9.56; N, 14.09.

*3.7.7. (S)-[1-(N-Hydroxycarbamimidoyl)-2-methyl-propyl]-carbamic acid tert-butyl ester (**4b**).* According to the general procedure described, **3b** (2.10 g, 10.6 mmol) was converted to **4b** (2.07 g, 84%) as a white solid: mp 138–141 °C; ^{1}H NMR ($CDCl_3$) δ 5.43 (br d, J=6.7 Hz, 1H), 4.90 (br s, 2H), 4.68 (br s, 1H), 3.78 (t, J=8.5 Hz, 1H), 2.11–1.88 (m, 1H), 1.44 (s, 9H), 0.95 (t, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 156.5, 154.7, 80.2, 58.2, 30.9, 28.7, 19.9, 18.9; IR (ATR) 3477, 3359, 2980, 1665, 1518, 1368, 1327, 1273, 1247, 1169, 1043 cm^{-1}; $[\alpha]_D^{25}$ −20.9 (c 1.02, MeOH); MS (APCI) m/z 232 $[C_{10}H_{21}N_3O_3+H]^+$, 463 $[(2\times C_{10}H_{21}N_3O_3)+H]^+$. Anal. Calcd for $C_{10}H_{21}N_3O_3$: C, 51.93; H, 9.15; N, 18.17. Found: C, 52.20; H, 9.51; N, 18.04.

*3.7.8. (S)-[2-Methyl-1-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-propyl]-carbamic acid tert-butyl ester (**5b**).* According to the general procedure described, **4b** (1.8 g, 7.6 mmol) was converted to **5b** (1.70 g, 88%) as a white solid: mp 120–121 °C; ^{1}H NMR ($CDCl_3$) δ 10.93–9.42 (br s, 1H), 5.21 (br d, J=8.1 Hz, 1H), 4.37 (t, J=7.6 Hz, 1H), 2.36–2.22 (m, 1H), 1.45 (s, 9H), 1.04–1.00 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 160.5, 159.6, 156.4, 81.7, 53.3, 31.4, 28.6, 19.4, 18.4; IR (ATR) 3737, 3337, 3144, 2983, 1802, 1781, 1688, 1514, 1469, 1283, 1159 cm^{-1}; $[\alpha]_D^{25}$ −44.1 (c 1.04, MeOH); MS (APCI) m/z 256 $[C_{11}H_{19}N_3O_4-H]^-$, 513 $[(2\times C_{11}H_{19}N_3O_4)-H]^-$. Anal. Calcd for $C_{11}H_{19}N_3O_4$: C, 51.35; H, 7.44; N, 16.33. Found: C, 51.28; H, 7.49; N, 16.26.

*3.7.9. (S)-3-(1-Amino-2-methyl-propyl)-4H-[1,2,4]-oxadia-zol-5-one hydrochloride (**6b**).* According to the general procedure described, **5b** (1.6 g, 6.2 mmol) was converted to **6b** (0.7 g, 60%) as a white solid: mp 176–180 °C; ^{1}H NMR ($CDCl_3$) δ 4.33 (d, J=5.8 Hz, 1H), 2.33 (octet, J=6.6 Hz, 1H), 1.10 (t, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 161.5, 157.8, 53.7, 31.9, 18.6, 18.3; IR (ATR) 3155, 2815, 2715, 2617, 1764, 1728, 1595, 1525, 1494, 1268, 1049 cm^{-1}; $[\alpha]_D^{25}$ −14.7 (c 1.04, MeOH); MS (ESI) m/z 158 $[C_6H_{11}N_3O_2+H]^+$. Anal. Calcd for $C_6H_{11}N_3O_2\cdot HCl$: C, 37.22; H, 6.25; N, 21.70; Cl, 18.31. Found: C, 37.19; H, 6.19; N, 21.37; Cl, 18.42.

*3.7.10. (S)-2-Methoxy-N-[(S)-2-methyl-1-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-propyl]-2-phenyl-2-trifluoromethoxy-acetamide (**7b**).* Yield 28 mg (57%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.57–7.40 (m, 5H), 4.68 (d, J=8.4 Hz, 1H), 3.44 (s, 3H), 2.22 (octet, J=6.7 Hz, 1H), 1.04 (d, J=6.7 Hz, 3H), 1.00 (d, J=6.7 Hz, 3H); ^{19}F NMR (282 MHz, CD_3OD) δ −70.78 (>90% ee); MS (ESI) m/z 374 $[C_{16}H_{18}F_3N_3O_4+H]^+$. The other diastereomer of **7b** derived from D-valine (structure not shown) was prepared by analogous procedures to validate the enantiomeric excess determination. ^{19}F NMR (282 MHz, CD_3OD) δ −70.82 (>95% ee).

*3.7.11. (S)-(5-tert-Butoxycarbonylamino-5-carbamoyl-pentyl)carbamic acid tert-butyl ester (**2c**)*[13]. L-Amino acid **1c** was prepared by dissolving its dicyclohexyl amine salt (12.0 g, 22.7 mmol) in toluene (200 mL) and washing with a 10% w/w aqueous solution of potassium hydrogen sulfate (3×75 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated at reduced pressure. Reaction of **1c** with 1-hydroxybenzotriazole (3.18 g, 23.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.17 g, 27.0 mmol), and concentrated ammonium hydroxide (3.20 mL, 47.4 mmol) in tetrahydrofuran (250 mL) and workup as described in the general procedure followed by recrystallization from hexanes/ethyl acetate afforded amide **2c** (6.01 g, 76%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.21 (br s, 1H), 5.51 (br s, 1H), 5.22–5.10 (m, 1H), 4.62 (br s, 1H), 4.22–4.01 (m, 1H), 3.15–3.09 (m, 2H), 1.92–1.81 (m, 1H), 1.72–1.62 (m, 2H), 1.56–1.32 (m, 21H); $[\alpha]_D^{25}$ +0.3 (c 1.005, methanol); MS (APCI) m/z 345 $[C_{16}H_{31}N_3O_5+H]^+$.

*3.7.12. (S)-(5-tert-Butoxycarbonylamino-5-cyanopentyl)-carbamic acid tert-butyl ester (**3c**).* Reaction of amide **2c** (5.43 g, 15.7 mmol) with cyanuric chloride (4.03 g, 21.8 mmol) in *N*,*N*-dimethylformamide (80 mL) followed by workup as described in the general procedure and silica gel chromatography (eluent: 75:25 hexanes/ethyl acetate) afforded nitrile **3c** (3.31 g, 64%) as a white solid. Recrystallization from hexanes/ethyl acetate afforded analytically pure **3c** (2.50 g, 48%): mp 79–82 °C; ^{1}H NMR ($CDCl_3$) δ 5.05 (br s, 1H), 4.62–4.47 (m, 2H), 3.20–3.08 (m, 2H), 1.89–1.79 (m, 2H), 1.57–1.38 (m, 22H); ^{13}C NMR (DMSO-d_6) δ 155.5, 154.7, 119.8, 79.1, 77.3, 41.8, 31.3, 28.6, 28.2, 27.9, 27.3, 22.2; $[\alpha]_D^{25}$ −38.7 (c 1.018, CH_2Cl_2); IR (ATR) 3357, 2982, 2951, 2288, 1698, 1685, 1522, 1365, 1246, 1164, 947 cm^{-1}. Anal. Calcd for $C_{16}H_{29}N_3O_4$: C, 58.69; H, 8.93; N, 12.83. Found: C, 58.61; H, 9.12; N, 12.67.

*3.7.13. (S)-[5-tert-Butoxycarbonylamino-5-(N-hydroxycarbamimidoyl)pentyl]carbamic acid tert-butyl ester (**4c**).* Reaction of nitrile **3c** (2.40 g, 7.33 mmol) with 50% w/w aqueous hydroxylamine (2.43 mL, 39.6 mmol) in ethanol (30 mL) followed by dilution with water (30 mL) did not provide a solid as described in the general procedure. The solution was concentrated to half of its original volume and extracted with dichloromethane (2×50 mL). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The foamy residue was redissolved in methanol and concentrated again to remove residual solvents to afford hydroxyamidine **4c** (2.40 g, 91%) as a white solid: mp 54–58 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (br s, 1H), 5.05 (br s, 1H), 4.84 and 4.76 (2 s, 3H), 4.10–3.98 (m, 1H), 3.13–2.98 (m, 2H), 1.90–1.54 (2m, 4H), 1.54–1.25 (m, 20H); ^{13}C NMR (DMSO-d_6) δ 155.4, 154.7, 153.0, 77.8, 77.2, 51.0, 32.6, 29.0, 28.2, 28.1, 27.5, 22.8; $[\alpha]_D^{25}$ −6.2 (c 1.01, methanol); IR (ATR) 3343, 2978, 1655, 1511, 1365, 1162 cm^{-1}; MS (ESI) m/z 361 $[C_{16}H_{32}N_4O_5+H]^+$. Anal. Calcd for $C_{16}H_{32}N_4O_5\cdot 0.3H_2O$: C, 52.53; H, 8.98; N, 15.31. Found: C, 52.62; H, 8.83; N, 15.28.

*3.7.14. (S)-[5-tert-Butoxycarbonylamino-5-(5-oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)pentyl]carbamic acid tert-butyl ester (**5c**).* Reaction of hydroxyamidine **4c** (2.20 g, 6.10 mmol) with 1,1′-carbonyldiimidazole (1.50 g, 9.15 mmol) in tetrahydrofuran (75 mL) as described in the general procedure afforded oxadiazolone **5c** (1.42 g, 60%) as a white solid: mp (DSC) 122.3–125.2 °C; ^{1}H NMR ($CDCl_3$)

δ 9.49 (br s, 1H), 5.41 (br s, 1H), 4.68 (br s, 1H), 4.48 (q, *J*=7.0 Hz, 1H), 3.23–3.06 (m, 2H), 2.08–1.81 (m, 2H), 1.61–1.33 (m, 22H); ^{13}C NMR (DMSO-d_6) δ 160.9, 159.8, 155.5, 155.0, 78.5, 77.3, 46.7, 30.8, 28.9, 28.2, 28.0, 27.5, 22.3; $[\alpha]_D^{25}$ −27.2 (*c* 1.04, CH_2Cl_2); IR (ATR) 3366, 3129, 2982, 2936, 1787, 1748, 1683, 1518, 1366, 1248, 1158, 975, 855 cm^{-1}; MS (ESI) *m*/*z* 385 $[C_{17}H_{30}N_4O_6-H]^-$. Anal. Calcd for $C_{17}H_{30}N_4O_6$: C, 52.84; H, 7.82; N, 14.50. Found: C, 52.53; H, 8.00; N, 14.56.

*3.7.15. 3-(1,5-Diaminopentyl)-4H-[1,2,4]-oxadiazol-5-one dihydrochloride (**6c**).* Reaction of oxadiazolone **5c** (0.82 g, 2.1 mmol) with a 2 M hydrogen chloride solution in ether (50 mL) as described in the general procedure followed by lyophilization afforded oxadiazolone **6c** (0.42 g, 76%) as a tan solid: mp (DSC) 152.1–152.3 °C (endotherm), 235.2–236.3 °C (endotherm); ^{1}H NMR (D_2O) δ 4.48 (t, *J*=6.6 Hz, 1H), 2.88 (t, *J*=7.6 Hz, 2H), 2.05–1.86 (m, 2H), 1.61 (quint, *J*=7.8 Hz, 2H), 1.38 (quint, *J*=7.8 Hz, 2H); ^{13}C (D_2O) δ 162.1, 157.5, 46.8, 39.3, 30.3, 26.6, 21.4; $[\alpha]_D^{25}$ −20.9 (*c* 0.11, methanol); IR (ATR) 2919, 1765, 1602, 1492, 949 cm^{-1}; MS (APCI) *m*/*z* 187 $[C_7H_{14}N_4O_2+H]^+$. Anal. Calcd for $C_7H_{14}N_4O_2\cdot 2HCl\cdot H_2O$: C, 30.34; H, 6.55; N, 20.22. Found: C, 30.61; H, 6.47; N, 20.29.

*3.7.16. (2R,2′R)-N,N′-((S)-1-(5-Oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-pentane-1,5-diyl)bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanamide) (**7c**).* ^{1}H NMR ($CDCl_3$) δ 7.61 (d, *J*=8.5 Hz, 1H), 7.48–7.36 (m, 10H), 7.21 (t, *J*=6.2 Hz, 1H), 4.80 (td, *J*=8.6, 5.1 Hz, 1H), 3.45, 3.31 and 3.28 (2s, m, 8H), 2.03–1.88 (m, 1H), 1.84–1.69 (m, 1H), 1.66–1.49 (m, 2H), 1.49–1.29 (m, 2H); ^{19}F ($CDCl_3$) δ −69.07, −69.40 (>95% ee); MS (ESI) *m*/*z* 619 $[C_{27}H_{28}F_6N_4O_6+H]^+$; HPLC (Waters Symmetry C18 Column, Detector @ 254 nm) >99%, t_R=11.1 min. The other diastereomer of **7c** derived from D-lysine (structure not shown) was prepared by analogous procedures to validate the enantiomeric excess determination. ^{19}F NMR (282 MHz, CD_3OD) δ −69.04, −69.13 (>95% ee).

*3.7.17. (S)-2-Carbamoylpyrrolidine-1-carboxylic acid tert-butyl ester (**2d**).* CAS Registry Number 35150-07-3, 54503-10-5, 70138-72-6. Following the general procedure described above, amino acid **1d** (8.00 g, 37.2 mmol) afforded the desired product **2c** (4.0 g, 50%) as a white solid, which was used without purification: mp (DSC) 103.6–107.7 °C; ^{1}H NMR (CD_3OD) δ 4.15–4.05 (m, 1H), 3.65–3.35 (m, 2H), 2.24–2.15 (m, 1H), 2.00–1.70 (m, 3H), 1.42 and 1.40 (2s, 9H); IR (ATR) 3375, 3203, 2974, 1672, 1660, 1406, 1361, 1167, 1118, 636 cm^{-1}; MS (APCI) *m*/*z* 115 $[C_{10}H_{18}N_2O_3-Boc+H]^+$; $[\alpha]_D^{25}$ −42.4 (*c* 1.0, methanol).

*3.7.18. (S)-2-Cyanopyrrolidine-1-carboxylic acid tert-butyl ester (**3d**)*[14]. Following the general procedure described above and purification by silica gel chromatography (eluent: 1:10 ethyl acetate/hexanes), amide **2d** (3.0 g, 14 mmol) afforded the desired nitrile **3d** (1.5 g, 55%) as a thick liquid: ^{1}H NMR (CD_3OD) δ 4.60–4.50 (m, 1H), 3.59–3.31 (m, 2H), 2.20–1.81 (m, 4H), 1.52 and 1.50 (2s, 9H); $[\alpha]_D^{25}$ −95.5 (*c* 1.3, methanol); IR (ATR) 2978, 1697, 1384, 1366, 1158, 771 cm^{-1}; MS (ESI) *m*/*z* 197 $[C_{10}H_{16}N_2O_2+H]^+$.

*3.7.19. (S)-2-(N-Hydroxycarbamimidoyl)pyrrolidine-1-carboxylic acid tert-butyl ester (**4d**)*[15]. Following the general procedure described above, nitrile **3d** (1.1 g, 5.6 mmol) afforded the desired hydroxyamidine **4d** (0.85 g, 66%) as a white solid: mp (DSC) 155.5–158.1 °C; ^{1}H NMR (CD_3OD) δ 4.25–4.10 (m, 1H), 3.61–3.39 (m, 2H), 2.30–1.71 (m, 4H), 1.51 (s, 9H); $[\alpha]_D^{25}$ −34.6 (*c* 1.015, methanol); IR (ATR) 3342, 2973, 1670, 1404, 1165, 1129, 774 cm^{-1}; MS (ESI) *m*/*z* 230 $[C_{10}H_{19}N_3O_3+H]^+$. Anal. Calcd for $C_{10}H_{19}N_3O_3$: C, 52.39; H, 8.35; N, 18.33. Found: C, 52.52, H, 8.61, N, 18.15.

*3.7.20. (S)-2-(5-Oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)pyrrolidine-1-carboxylic acid tert-butyl ester (**5d**).* Following the general procedure described above, hydroxyamidine **4d** (0.67 g, 2.9 mmol) afforded the desired oxadiazolone **5d** (0.47 g, 63%) as a white solid: mp (DSC) 131.8–134.7 °C and 191.1–191.8 °C; ^{1}H NMR (CD_3OD) δ 4.8–4.7 (m, 1H), 3.54–3.45 (m, 2H), 2.41–1.82 (m, 4H), 1.46 and 1.37 (2s, 9H); ^{13}C NMR (DMSO-d_6, rotational isomers) δ 161.8, 161.3, 159.7, 153.3, 152.6, 79.2, 52.3, 52.1, 46.4, 46.2, 31.4, 30.4, 28.0, 27.8, 23.6, 22.9; $[\alpha]_D^{25}$ −85.7 (*c* 1.15, methanol); IR (ATR) 2980, 1773, 1666, 1412, 1159, 1128, 958, 760 cm^{-1}; MS (ESI) *m*/*z* 156 $[C_{11}H_{17}N_3O_4-Boc+H]^+$. Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.88; H, 6.76; N, 16.45.

*3.7.21. (S)-3-Pyrrolidin-2-yl-4H-[1,2,4]oxadiazol-5-one hydrochloride (**6d**).* Following the general procedure described above, oxadiazolone **5d** (0.40 g, 1.6 mmol) afforded the desired product **6d** (0.28 g, 90%) as a white solid: mp (DSC) 178.8–187.5 °C; ^{1}H NMR (CD_3OD) δ 4.81 (m, 1H), 3.49 (t, *J*=7.2 Hz, 2H), 2.45–2.37 (m, 1H), 2.22–2.13 (m, 3H); ^{13}C NMR (CD_3OD) δ 161.7, 157.4, 54.9, 47.6, 29.7, 24.6; $[\alpha]_D^{25}$ −43.3 (*c* 1.055, methanol); IR (ATR) 2923, 1769, 1501, 1370, 1268, 942, 892, 728 cm^{-1}; MS (APCI) *m*/*z* 156 $[C_6H_9N_3O_2+H]^+$. Anal. Calcd for $C_6H_9N_3O_2\cdot HCl$: C, 37.61; H, 5.26; N, 21.93; Cl, 18.50. Found: C, 37.51; H, 5.24; N, 21.68; Cl, 18.60.

*3.7.22. (S)-3-[1-(3,3,3-Trifluoro-2-methoxy-2-phenyl-propionyl)-(S)-pyrrolidin-2-yl]-4H-[1,2,4]oxadiazol-5-one (**7d**).* Yield 20 mg (52%): ^{1}H NMR (300 MHz $CDCl_3$) δ 9.83 (br s, 1H), 7.45–7.38 (m, 5H), 5.13 (dd, *J*=7.9, 2.6 Hz, 1H), 3.66 (t, *J*=1.6 Hz, 3H), 3.53–3.43 (m, 1H), 2.76–2.78 (m, 1H), 2.48–2.35 (m, 1H), 2.11–1.87 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.84; MS (ESI) *m*/*z* 372 $[C_{16}H_{16}F_3N_3O_4+H]^+$. The other diastereomer of **7d** derived from D-proline (structure not shown) was prepared by analogous procedures to validate the enantiomeric excess determination. ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.72 (>90% ee).

*3.7.23. (S)-3-tert-Butoxycarbonylamino-succinamic acid tert-butyl ester (**2e**).* Following the general procedure described above, amino acid **1e** (4.67 g, 16.1 mmol) afforded the desired amide **2e** (3.10 g, 67%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 6.56 (br s, 1H), 5.90 (br s, 1H), 5.76–5.73 (m, 1H), 4.49 (br s, 1H), 2.85 (dd, *J*=16.9, 4.8 Hz, 1H), 2.60 (dd, *J*=16.8, 6.1 Hz, 1H), 1.45 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 171.1, 155.5, 81.7, 80.3, 50.5, 37.3, 28.3, 28.0; IR (ATR) 3332, 2979, 1674, 1502, 1366, 1249, 1153, 1049, 1025 cm^{-1}; $[\alpha]_D^{25}$ −6.0 (*c* 0.100, MeOH); MS (APCI) *m*/*z* 288 $[C_{13}H_{24}N_2O_5+H]^+$. Anal. Calcd for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72. Found: C, 54.45; H, 8.61; N, 9.46.

*3.7.24. (S)-3-tert-Butoxycarbonylamino-3-cyano-propionic acid tert-butyl ester (**3e**).* Following the general procedure described above, amide **2e** (3.00 g, 10.4 mmol) afforded the desired nitrile **3e** (2.50 g, 89%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 5.73–5.70 (m, 1H), 4.89 (br s, 1H), 2.78–2.75 (m, 2H), 1.49 (s, 9H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.2, 154.1, 117.9, 82.8, 81.2, 38.5, 38.3, 28.1, 27.9; IR (ATR) 3345, 2980, 2935, 1719, 1510, 1368, 1285, 1249, 1149, 1048 cm^{-1}; $[\alpha]_D^{25}$ −43.6 (*c* 0.174, MeOH); MS (ESI) *m*/*z* 271 $[C_{13}H_{22}N_2O_4+H]^+$. Anal. Calcd for $C_{13}H_{22}N_2O_4\cdot 0.25H_2O$: C, 56.80; H, 8.25; N, 10.09. Found: C, 56.81; H, 8.25; N, 10.19.

*3.7.25. (S)-3-tert-Butoxycarbonylamino-3-(N-hydroxycarbamimidoyl)-propionic acid tert-butyl ester (**4e**).* Following the general procedure described above, nitrile **3e** (2.25 g, 8.30 mmol) afforded the desired hydroxyamidine **4e** (2.50 g, >99%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 8.48 (br s, 1H), 5.92 (d, *J*=8.8 Hz, 1H), 5.31 (s, 2H), 5.63–4.61 (m, 1H), 2.69 (d, *J*=6.7 Hz, 2H), 1.44 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 171.0, 157.0, 154.3, 81.8, 80.5, 48.5, 38.0, 28.7, 28.3; IR (ATR) 3360, 2978, 2933, 1698, 1663, 1512.0, 1366, 1248, 1156, 1049 cm^{-1}; $[\alpha]_D^{25}$ −20.9 (*c* 1.03, MeOH); MS (ESI) *m*/*z* 304

$[C_{13}H_{25}N_3O_5+H]^+$. Anal. Calcd for $C_{13}H_{25}N_3O_5$: C, 51.47; H, 8.31; N, 13.85. Found: C, 51.47; H, 8.56; N, 13.53.

*3.7.26. (S)-3-tert-Butoxycarbonylamino-3-(5-oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)-propionic acid tert-butyl ester (**5e**).* Following the general procedure mentioned above, hydroxyamidine **4e** (2.11 g, 6.96 mmol) afforded the desired oxadiazolone **5e** (1.92 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.80 (br s, 1H), 5.90 (d, J=8.1 Hz, 1H), 5.03–5.00 (m, 1H), 2.87 (d, J=5.8 Hz, 2H), 1.45 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 169.5, 159.7, 158.9, 155.5, 82.5, 81.4 43.7, 36.4, 28.1, 27.9; IR (ATR) 3323, 2979, 2935, 1779, 1730, 1686, 1521, 1367, 1298, 1250, 1144, 1054 cm^{-1}; $[\alpha]_D^{25}$ −32.0 (*c* 1.06, MeOH); MS (ESI) *m*/*z* 330 $[C_{14}H_{23}N_3O_6+H]^+$. Anal. Calcd for $C_{14}H_{23}N_3O_6$: C, 51.06; H, 7.04; N, 12.76. Found: C, 51.09; H, 7.32; N, 12.70.

*3.7.27. (S)-3-Amino-3-(5-oxo-4,5-dihydro-[1,2,4]oxa-diazol-3-yl)-propionic acid (**6e**).* Following the general procedure described above, oxadiazolone **5e** (0.710 g, 2.16 mmol) afforded the desired amino acid **6e** (0.350 g, 78%) as an off-white solid: mp 196–198 °C; ^{1}H NMR (CD_3OD) δ 4.80 (dd, J=7.2, 5.6 Hz, 1H), 3.13 (dd, J=17.9, 5.6 Hz, 1H), 3.03 (dd, J=17.9, 7.2 Hz, 1H); ^{13}C NMR (CD_3OD) δ 171.6, 161.3, 157.7, 44.7, 35.4; IR (ATR) 2945.2, 1754.1, 1714.6, 1562.3, 1509.6, 1414.9, 1207.6, 1140.7, 1099.2 cm^{-1}; $[\alpha]_D^{25}$ −30.2 (*c* 1.00, MeOH); MS (APCI) *m*/*z* 173 $[C_5H_7N_3O_4+H]^+$. Anal. Calcd for $C_5H_7N_3O_4\cdot HCl\cdot 0.15H_2O$: C, 28.46; H, 4.13; N, 19.56; Cl, 16.87. Found: C, 28.29; H, 3.94; N, 19.79; Cl, 16.70.

*3.7.28. 3-(5-Oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-3-(3,3,3-trifluoro-2-methoxy-2-phenyl-propionylamino)-propionic acid (**7e**).* Following the general procedure mentioned above, amino acid **6e** (0.039 g, 0.188 mmol) and (*S*)-Mosher chloride afforded the desired amino acid derivative **7e** (0.054 g, 74%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (br s, 1H), 8.34 (br s, 1H), 8.10 (d, J=8.4 Hz, 1H), 7.57–7.38 (m, 5H), 5.41–5.30 (m, 1H), 3.32 (s, 3H), 3.07 (dd, J=18.0, 4.2 Hz, 1H), 2.95 (dd, J=18.0, 8.7 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.41 (96% ee); MS (ESI) *m*/*z* 390 [M+H]; The other diastereomer of **7e** derived from D-aspartic acid (structure not shown) was prepared by analogous procedures to validate the enantiomeric excess determination. ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.17 (98% ee).

*3.7.29. {1-[1-(5-Oxo-4,5-dihydro[1,2,4]oxadiazol-3-yl)-2-phenylethylcarbamoyl]ethyl}carbamic acid tert-butyl ester (**9**).* To a solution of BOC-L-alanine **8** (78 mg, 0.41 mmol) in dichloromethane (5 mL) cooled to 0 °C were added 1-hydroxybenzotriazole (73 mg, 0.54 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (103 g, 0.537 mmol), and 4-methylmorpholine (50 mg, 0.054 mL, 0.49 mmol). After stirring for 2 h at 0 °C, a solution of oxadiazolone **6a** (150 mg, 0.62 mmol) and 4-methylmorpholine (50 mg, 0.054 mL, 0.49 mmol) in dichloromethane (3 mL) was added. The mixture was allowed to warm to room temperature and stir overnight. The solvent was removed at reduced pressure, and the residue was dissolved in ethyl acetate and washed with a 10% potassium bisulfate solution, dried over sodium sulfate, filtered, and concentrated at reduced pressure. Silica gel chromatography (97:3 dichloromethane/methanol) afforded oxadiazolone **9** (131 mg, 84%) as a white solid. Recrystallization from ethyl acetate afforded analytically pure product: mp 236–238 °C; ^{1}H NMR (DMSO-d_6) δ 12.33 (s, 1H), 8.35 (d, J=7.7 Hz, 1H), 7.19–7.38 (m, 5H), 6.88 (d, J=7.4 Hz, 1H), 4.91 (td, J=8.0, 6.8 Hz, 1H), 3.84–4.00 (m, 1H), 3.12 (dd, J=13.8, 6.3 Hz, 1H), 3.03 (dd, J=13.8, 8.7 Hz, 1H), 1.37 and 1.24 (s and br s, 9H), 1.10 (d, J=7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.7, 160.0, 159.6, 155.0, 136.5, 129.1, 128.2, 126.7, 78.1, 49.6, 46.5, 36.7, 28.1, 17.9; $[\alpha]_D^{25}$ −56.4 (*c* 1.0, MeOH); IR (ATR) 3355, 3146, 2977, 1768, 1739, 1516, 1319, 1162, 975, 733 cm^{-1}; MS (APCI) *m*/*z* 375 $[C_{18}H_{24}N_4O_5-H]^-$. Anal. Calcd for: $C_{18}H_{24}N_4O_5$: C, 57.44; H, 6.43; N, 14.88. Found: C, 57.15; H, 6.27; N, 14.52.

References and notes

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