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Stereoselective Synthesis of Unnatural Spiroisoxazolinoproline-Based Amino Acids and Derivatives

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A route to spiroisoxazolinoproline-based amino acid derivatives is reported in which *exo*-methyleneprolinate **4** (*tert*-butyl ester) reacts as a dipolarophile with nitrile oxides to generate spiroisoxazolinoprolinates **7**/**10**/**11** in good yields (70−75%) and with ca. 1:4 cis:trans diastereoselectivity. *tert*-Butyl spiroisoxazolinoprolinates were separable by column chromatography and amenable to scale-up leading to single diastereoisomers of *N*-Boc and *N*-Fmoc protected spiroisoxazolinoproline amino acids.

Due to their intrinsic biological activities and applications as conformational modifiers for physiologically active peptides, unnatural and nonproteinogenic amino acids have become very important and attractive targets. Among amino acids, proline[1] analogues, with their unique structural constraints (cyclic and a secondary amine), play an important role in the investigation of structure, receptor affinity, and biological activity of amino acids chimeras and peptides.[2] Furthermore, heterocyclic pyrrolidine rings are valuable scaffolds and precursors in natural products and in drug discovery, i.e., kainoid,[3] carbapenems,[4] captopril,[5] and gramicidin.[6] Consequently, routes to and applications of proline-based amino acids and derivatives have received much attention in both chemistry and biochemistry.[1,7]

One of our research interests is the application of 1,3-dipolar cycloadditions to generate heterocyclic isoxazole and isoxazoline rings—substructures with inherent biological activity.[8] And while both spiroisoxazolines[9] and

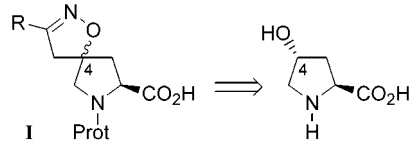

FIGURE 1. Spiroisoxazolinoprolines from 4-hydroxyproline.

modified prolines[1,10] have been studied, we are not aware of any reports regarding spiroisoxazolinoproline-based amino acids. In this paper, we report a straightforward synthetic route for combining these two interesting structural features within a single framework to form *N*-Boc- or *N*-Fmoc-protected *cis*- and *trans*-4-spiroisoxazilinoproline amino acid derivatives (**I**; Figure 1).

Our synthetic effort started with commercially available *trans*-4-hydroxyl-L-proline, which, following literature procedures[11] of *N*-Boc protection, oxidation (RuO_2/$NaIO_4$), and Wittig olefination, gave 1-*tert*-butoxycarbonyl-4-methylene-L-proline (**1**).[11] The key 1,3-dipolar cycloaddition reaction was conducted by treating *exo*-methyleneproline **1** with 2,6-dichlorobenzaldehyde oxime in the presence of NaOCl (i.e., the Huisgen method for in situ nitrile oxide generation)[12] and led to the desired spiroisoxazolinoproline amino acid **2** as an approximately 1:1

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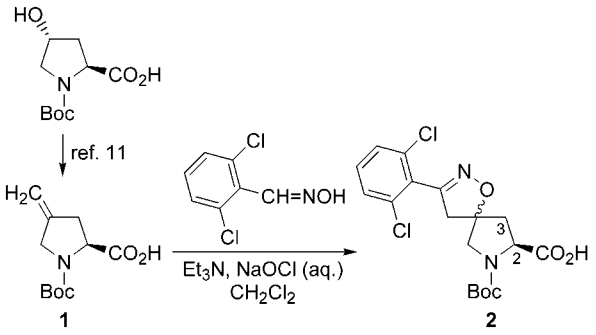
SCHEME 1. Spiroisoxazolinoproline Route

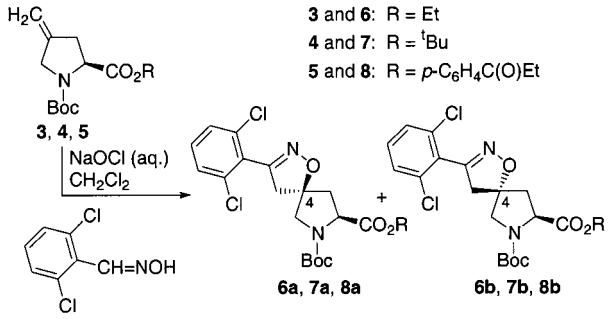


diastereomeric mixture in 76% yield (Scheme 1). On the basis of our previous experiences,[13] as well as that of others,[14] we were not surprised to find that **1** → **2** proceeds with excellent regioselectivity (none of the regioisomer could be detected). Given this result, we were intrigued with two pivotal questions regarding this cycloaddition reaction: (1) could the C2-stereogenic center be employed to effectively mediate the diastereoselectivity of the 1,3-dipolar cycloaddition and (2) is there a practical method to separate these spiroisoxazolinoproline diastereomers.

The latter point was accentuated by the fact that attempts to separate (routine column chromatographic and recrystallization techniques) the cis and trans isomers of **2** were unsuccessful. In addition, the ^{1}H NMR (ambient temperature) of **2** was complicated by the rotational isomerism[15] of the *N*-Boc protecting group; the 1:1 isomer ratio of crude **2** was determined by HPLC. Thus, while this 1,3-dipolar cycloaddition reaction was highly regioselective, its lack of stereoselectivity and separation problems prompted us to modify our dipolarophile system. The strategy we settled on was to convert *exo*-methyleneproline amino acid **1** to various *exo*-methyleneprolinates in the hopes that the subsequent cycloaddition would proceed with reasonable diastereoselectivity.

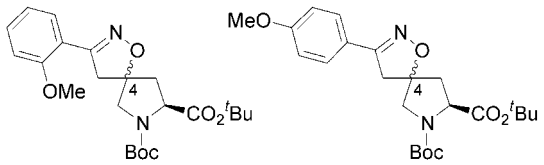
DCC-mediated esterification of **1** with three different alcohols afforded proline esters **3**−**5** in good yields [**3**, R = Et; **4**, R = ^{t}Bu; **5**, R = *p*-$C_6H_4C(=O)Et$ (selected because preliminary studies established that this ester moiety aided in the chromatographic separation of cycloadducts; see Scheme 2); 75−83%].[16] With these *exo*-methyleneprolinates in hand, we investigated their 1,3-dipolar cycloaddition reactions with the nitrile oxide generated in situ from 2,6-dichlorobenzaldehyde oxime (NaOCl). The targeted spiroisoxazolinoprolinates **6**, **7**, and **8** were obtained in good yields (73−80%) and the cis:trans ratios,

SCHEME 2. 1,3-Dipolar Cycloaddition Diastereoselectivity



[a] Determined by HPLC of the crude reaction mixture. [b]Product mixture after flash column chromatography.

SCHEME 3. Spiroisoxazolinoprolinates from Prolinate 4



product	*cis*:*trans* ratio[a]	combined yield (%)[b]
7a + **7b**	22:78	75
10a + **10b**	20:80	70
11a + **11b**	19:81	74

[a] Determined by HPLC of the crude reaction mixture. [b]Product mixture after flash column chromatography.

as determined by HPLC, were found to be **6a**:**6b** 1:1, **7a**:**7b** 1:4, and **8a**:**8b** 2:3 (Scheme 2). Clearly, the C2 ester moiety can, by steric effects, influence the stereoselectivity of these 1,3-dipolar cycloaddition reactions and prolinate **4**, with its bulky *tert*-butyl ester moiety, delivers the highest selectivity.

As with **2**, attempts to separate **6a** from **6b** failed. However, diastereoisomers **7a**/**7b** and **8a**/**8b** were separable by using routine column chromatography, which set the stage for the multigram preparation of pure spiroisoxazolinoproline amino acids and derivatives. The only reliable ^{1}H NMR spectral differences in the diastereomers of **7** and **8** are due to the diastereotopic C3 protons of the pyrrolidine ring: **7a** at δ 2.40 and 2.60 ppm/**7b** at δ 2.15 and 2.80 ppm; **8a** at δ 2.50 and 2.80 ppm/**8b** at δ 2.30 and 2.90 ppm. After hydrolysis of cycloadduct **7b** (aq NaOH/EtOH) and recrystallization of the resulting acid from MeOH, the stereochemistry (C2 carboxylic acid trans to the isoxazoline C−O bond) of pure spiroisoxazolinoproline amino acid **9b** was confirmed by X-ray crystallographic analysis.

At this point, nitrile oxides derived from *o*- and *p*-methoxybenzaldehyde oximes were reacted with *tert*-butyl prolinate **4** to give cycloadducts **10** and **11**, respectively, in good yields (70−75%; Scheme 3). As with **4** → **7**, diastereomer ratios of **10a**/**10b** and **11a**/**11b** were also 1:4. Again, the ^{1}H NMR spectra of **10a**/**10b** and **11a**/**11b** were differentiable by the diastereotopic C3 protons of the pyrrolidine ring: **10a** at δ 2.32 and 2.42 ppm/**10b** at

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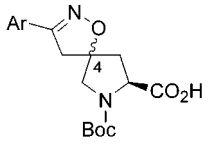
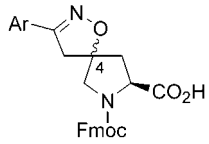


9a: *cis*, Ar = 2,6-dichlorophenyl
9b: *trans*, Ar = 2,6-dichlorophenyl
12a: *cis*, Ar = 2-methoxyphenyl
12b: *trans*, Ar = 2-methoxyphenyl
13a: *cis*, Ar = 4-methoxyphenyl
13b: *trans*, Ar = 4-methoxyphenyl

FIGURE 2. *N*-Boc protected spiroisoxazolinoproline amino acids.



14: *trans*, Ar = 2,6-dichlorophenyl
15: *cis*, Ar = 2-methoxyphenyl
16: *trans*, Ar = 4-methoxyphenyl

FIGURE 3. *N*-Fmoc protected spiroisoxazolinoproline amino acids.

δ 2.05 and 2.62 ppm; **11a** at δ 2.38 and 2.52 ppm/**11b** at δ 2.15 and 2.75 ppm.

Treating each pure diastereomer of **7**/**10**/**11** with aq NaOH/EtOH delivered the corresponding *N*-Boc protected spiroisoxazolinoproline amino acids (Figure 2): **9a** (90%), **9b** (92%), **12a** (83%), **12b** (85%), **13a** (91%), and **13b** (92%). Finally, the X-ray structure of acid **13a** (minor) verified that the carboxyl group is cis to the isoxazoline C−O bond.

An *N*-Boc protecting group was selected for the synthesis of acids **9**/**12**/**13** from 4-hydroxyproline because of its base stability. However, since *N*-Fmoc protected amino acids are more attractive and practical in peptide synthesis, we next set out to convert these *N*-Boc protected amino acids to *N*-Fmoc protected amino acids. *N*-Boc deprotection with TFA/CH_2Cl_2 (1/1) followed by solvent removal and addition of DMF/Na_2CO_3/FmocOSu allowed for the "one flask" conversion of **9b**/**12a**/**13b** to **14**/**15**/**16** (Figure 3).

In summary, the *exo*-methylenepyrrolidine system undergoes a highly regioselective 1,3-dipolar cylcoaddition reaction with nitrile oxides, the stereoselectivity of prolinate **4** is ca. 4:1, and these *tert*-butyl ester diasteroisomers are readily separable by column chromatography.

Experimental Section

General Procedures. All chemicals were obtained from commercial suppliers and used without purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70−230 mesh). NMR spectra (^{1}H at 300 or 400 MHz, ^{13}C at 75 or 100 MHz) were recorded in $CDCl_3$ or DMSO-d_6 as solvents, and chemical shifts are expressed in parts per million relative to internal TMS. Optical rotations were measured with a JASCO DIP-370 automatic polarimeter. CC refers to column chromatography. Concentration refers to rotary evaporation. The ratio of diastereoisomers was determinate by HPLC, using Symmetry C_{18} (4.6 × 250 mm, Waters) with linear gradient elution of 60−100% MeOH/water for 25 min, flow rate 1 mL/min, and detection 254 nm.

General Procedure for the Preparation of *exo*-Methylene-L-Prolinate-Based Amino Esters: Ethyl N^{α}-Boc-4-methylene-L-prolinate (3). *exo*-Methylene-L-proline **2** (1.0 g, 4.40 mmol) was dissolved in dry dichloromethane (20 mL) and cooled to 0 °C in an atmosphere of nitrogen. Ethanol (1.01 g, 22.0 mmol, 5 equiv) and 4-(dimethylamino)pyridine (54 mg, 0.44 mmol 10%) were added followed by *N*,*N*-dicyclohexylcarbodiimide (1.09 g, 5.3 mmol, 1.2 equiv) over 5 min. The mixture was stirred at room temperature for 8 h at which time the DCU was removed by filtration and the filtrate was concentrated. CC purification (20% EA in hexanes) gave **3** as a colorless oil (0.93 g, 3.65 mmol, 83%): $[\alpha]^{25}_D$ −19.1 (*c* 28.3, $CHCl_3$); IR ($CDCl_3$) 1747, 1708, 1652 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.07 (t, 3H, J = 5.7 Hz), 1.24 (s, 9H × $^3/_5$), 1.28 (s, 9H × $^2/_5$), 2.39−2.45 (m, 1H), 2.72−2.85 (m, 1H), 3.86−3.89 (m, 2H), 4.00 (q, 2H, J = 5.7 Hz), 4.18−4.29 (m, 1H), 4.80 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 171.9, 171.6, 153.7, 153.1, 142.9, 141.9, 107.3, 107.2, 79.5, 60.5, 58.7, 58.2, 50.3, 50.2, 36.4, 35.7, 28.0, 27.9, 13.9, 13.8. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16, H, 8.29, N, 5.49. Found: C, 60.99, H, 8.25, N, 5.44.

(4-Propionyl)phenyl N^{α}-Boc-4-methylene-L-prolinate (5). The preparation of **3** was modified as follows to give **5**. Compound **2** (2.0 g, 8.80 mmol), DCC (2.18 g, 10.56 mmol, 1.2 equiv), DMAP (110 mg, 0.88 mmol, 10%), 1-(4-hydroxyphenyl)-propan-1-one (1.72 g, 11.5 mmol, 1.3 equiv), and CC (20% EtOAc in hexanes) gave **5** (2.37 g, 6.6 mmol, 75%) as a colorless oil: $[\alpha]^{25}_D$ −17.2 (*c* 10.6, $CHCl_3$); IR ($CHCl_3$) 1772, 1687, 1600 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ambient temperature, mixture of conformers) δ 1.05 (t, 3H, J = 6 Hz), 1.37 (s, 9H × $^5/_9$), 1.40 (s, 9H × $^4/_9$), 2.79−2.89 (m, 1H), 3.02 (q, 2H, J = 6 Hz), 3.99 (s, 2H), 4.59−4.64 (m, 1H), 5.06 (s, 2H), 7.20−7.24 (m, 2H), 8.00−8.05 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, 100 °C) δ 198.4, 169.5, 153.0, 142.0, 134.0, 128.7, 120.6, 107.1, 79.1, 58.2, 50.1, 35.2, 30.7, 27.5, 7.5.

General Procedure for the Preparation of Spiroisoxazolinoprolinates: *tert*-Butyl (5*S*,8*S*)-3-(2,6-Dichlorophenyl)-1-oxa-2,7-diazaspiro[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (7a) and *tert*-Butyl (5*R*,8*S*)-3-(2,6-Dichlorophenyl)-1-oxa-2,7-diazaspiro[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (7b). Compound **4** (1.5 g, 5.30 mmol) and 2,6-dichlorobenzaldehyde oxime (2 equiv, 2.0 g, 10.6 mmol) were dissolved in methylene chloride (30 mL), and the solution was cooled to 0 °C. Aqueous NaOCl (32 g, 5%, 21.2 mmol, 4 equiv) was added dropwise over 30 min, and the reaction was stirred vigorously for 8 h (0 °C → room temperature). The layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried with $MgSO_4$ and concentrated. The crude sample was purified by CC (40% ethyl acetate in hexanes) to ester **7** (1.87 g, 4.0 mmol, 75%). Diastereoisomers **7a** and **7b** were separated from a mixture of **7** (1.87 g, 4.0 mmol) by CC (25% ethyl acetate in hexanes) to give **7a** (0.3 g, 16%) and **7b** (1.40 g, 75%).

7a: $[\alpha]^{25}_D$ +9.7 (*c* 29.0, $CHCl_3$); IR ($CHCl_3$) 1749, 1702, 1400 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.45−1.50 (m, 18H), 2.29−2.45 (m, 1H), 2.62 (dd, 1H, J = 13.3, 2.4 Hz), 3.14−3.34 (m, 2H), 3.65−3.97 (m, 2H), 4.29−4.41 (m, 1H), 7.24−7.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 170.3, 169.9, 153.7, 153.6, 153.4, 134.8, 131.0, 128.2, 127.9, 90.8 89.8, 81.6, 81.5, 80.1, 80.0, 59.0, 58.7, 55.9, 55.8, 45.4, 45.2, 41.9, 41.2, 28.4, 28.3, 27.9. Anal. Calcd for $C_{22}H_{28}Cl_2N_2O_5$: C, 56.06, H, 5.99, N, 5.94. Found: C, 55.67, H, 5.94, N, 5.80.

7b: $[\alpha]^{25}_D$ +2.2 (*c* 4.2, $CHCl_3$); IR ($CHCl_3$) 1749, 1702, 1400 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.41−1.43 (m, 18H), 2.06−2.16 (m, 1H), 2.70−2.81 (m, 1H), 3.12−3.29 (m, 2H), 3.58−3.64 (m, 1H, J = 11.7 Hz), 3.88−4.01 (m, 1H, J = 11.7 Hz), 4.31−4.38 (m, 1H), 7.23−7.34 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 75 °C) δ 170.1,

153.8, 152.4, 133.4, 131.5, 127.9, 127.5, 80.4, 78.9, 58.3, 55.7, 42.8, 27.6, 27.2. Anal. Calcd for $C_{22}H_{28}Cl_2N_2O_5$: C, 56.06, H, 5.99, N, 5.94. Found: C, 55.66, H, 6.01, N, 5.91.

(4-Propionyl)phenyl (5*S*,8*S*)-3-(2,6-Dichlorophenyl)-1-oxa-2,7-diaza-spiro[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (8a) and (4-Propionyl)phenyl (5*R*,8*S*)-3-(2,6-Dichlorophenyl)-1-oxa-2,7-diazaspiro[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (8b). The preparation of **7** was modified as follows to give **8**. Compound **5** (2.5 g, 7.0 mmol), 2,6-dichlorobenzaldehyde oxime (2 equiv., 2.66 g, 14.0 mmol), aqueous NaOCl (42 g, 5%, 28.0 mmol, 4 equiv), CH_2Cl_2 (40 mL), and CC (25% EtOAc in hexanes) gave **8a** (1.04 g, 1.90 mmol) and **8b** (1.75 g, 3.20 mmol) in a total yield of 73%.

8a: $[\alpha]^{25}_D$ +13.0 (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) 1779, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.15 (t, 3H, J = 7.2 Hz), 1.44 (s, 9H × $^1/_2$), 1.45 (s, 9H × $^1/_2$), 2.43−2.59 (m, 1H), 2.79−2.96 (m, 3H), 3.20−3.38 (m, 2H), 3.72 (dd, 1H, J = 12, 2.4 Hz), 4.05 (t, 1H, J = 12 Hz), 7.22−7.97 (m, 7H); ^{13}C NMR δ 199.1, 199.0, 169.6, 169.3, 154.1, 154.0, 153.9, 153.6, 153.0, 134.5, 134.3, 134.1, 131.1, 129.3, 129.2, 127.8, 121.5, 121.3, 90.05, 90.07, 80.5, 58.5, 58.2, 55.8, 55.7, 44.2, 44.1, 41.7, 41.2, 31.6, 28.2, 8.13. Anal. Calcd for $C_{27}H_{28}Cl_2N_2O_6$: C, 59.24; H, 5.16; N, 5.12. Found: C, 59.17; H, 5.10; N, 5.08.

8b: $[\alpha]^{25}_D$ −9.0 (*c* 5.1, $CHCl_3$); IR ($CHCl_3$) 1772, 1684 cm^{-1}; ^1H (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.01−1.11 (m, 3H), 1.37 (s, 9H × $^3/_5$), 1.39 (s, 9H × $^2/_5$), 2.27−2.35 (m, 1H), 2.79−2.90 (m, 3H), 3.16−3.27 (m, 2H), 3.59−3.70 (m, 1H), 3.91−4.05 (m, 1H), 4.61−4.66 (m, 1H), 7.11−7.98 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 198.7, 198.6, 169.7, 153.9, 153.8, 153.5, 153.4, 153.2, 152.6, 134.2, 134.1, 134.0, 131.0, 129.1, 129.0, 127.6, 121.1, 120.7, 90.6, 89.6, 80.5, 80.4, 58.3, 55.8, 43.1, 42.9, 40.9, 40.4, 31.3, 29.9, 7.9. Anal. Calcd for $C_{27}H_{28}Cl_2N_2O_6$: C, 59.24; H, 5.16; N, 5.12. Found: C, 59.36; H, 5.19; N, 5.10.

***tert*-Butyl (5*S*,8*S*)-3-(2-Methoxyphenyl)-1-oxa-2,7-diazaspiro[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (10a) and *tert*-Butyl(5*R*,8*S*)-3-(2-Methoxyphenyl)-1-oxa-2,7-diazaspiro-[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (10b)**. The preparation of **7** was modified as follows to give **10**. Compound **4** (0.5 g, 1.76 mmol), *o*-methoxybenzaldehyde oxime (2 equiv, 0.53 g, 3.52 mmol), aqueous NaOCl (10.5 g, 5%, 7.0 mmol, 4 equiv), CH_2Cl_2 (20 mL), and CC (25% EtOAc in hexanes) gave **10a** (0.10 g, 0.23 mmol) and **10b** (0.43 g, 1.0 mmol) in a total yield of 70%.

10a: $[\alpha]^{25}_D$ −19.8 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 1704, 1394 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.40−1.47 (m, 18H), 2.24−2.49 (m, 2H), 3.30−3.94 (m, 7H), 4.24−4.45 (m, 1H), 6.87−6.94 (m, 2H), 7.30−7.36 (m, 1H), 7.66−7.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 170.4, 170.1, 157.1, 155.7, 155.6, 153.7, 153.4, 131.3, 131.2, 128.9, 120.6, 118.2, 111.1, 89.7, 88.8, 81.3, 79.9, 79.8, 59.0, 58.7, 56.4, 55.9, 55.3, 46.2, 46.1, 41.9, 40.9, 28.36, 28.30, 27.9. Anal. Calcd for $C_{23}H_{32}N_2O_6 \cdot 0.3H_2O$: C, 63.08, H, 7.51, N, 6.39. Found: C, 63.30, H, 7.31, N, 6.16.

10b: $[\alpha]^{25}_D$ +1.1 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 1741, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.39−1.42 (m, 18H), 2.01−2.08 (dd, 1H, J = 13.2, 7.5 Hz), 2.61−2.65 (m, 1H), 3.31−3.55 (m, 3H), 3.75−3.87 (m, 4H), 4.27−4.34 (m, 1H, J = 7.5 Hz), 6.85−6.92 (m, 2H), 7.28−7.34 (m, 1H), 7.64−7.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 171.1, 171.0, 156.9, 155.7, 153.4, 153.1, 131.1, 128.7, 120.4, 117.9, 111.0, 89.7, 88.8, 80.9, 79.8, 79.6, 77.4, 58.8, 56.7, 56.2, 55.1, 44.7, 44.5, 41.5, 40.6, 28.1, 28.0, 27.76, 27.70. Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.87, H, 7.46, N, 6.48. Found: C, 64.00, H, 7.35, N, 6.21.

***tert*-Butyl (5*S*,8*S*)-3-(4-Methoxyphenyl)-1-oxa-2,7-diazaspiro[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (11a) and *tert*-Butyl (5*R*,8*S*)-3-(4-Methoxyphenyl)-1-oxa-2,7-diazaspiro-[4,4]non-2-ene-7-*N*-Boc-8-carboxylate (11b)**. The preparation of **7** was modified as follows to give **11**. Compound **4** (0.6 g, 2.12 mmol), *o*-methoxybenzaldehyde oxime (2 equiv, 0.64 g, 4.23 mmol), aqueous NaOCl (12.6 g, 5%, 8.50 mmol, 4 equiv), CH_2Cl_2 (20 mL), and CC (25% EtOAc in hexanes) gave **11a** (0.13 g, 0.27 mmol) and **11b** (0.61 g, 1.30 mmol) in a total yield of 74%.

11a: $[\alpha]^{25}_D$ −25.0 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 1747, 1741 1400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.46 (s, 9H), 1.50 (s, 9H), 2.36 (m, 1H), 2.51 (dd, 1H, J = 13.5, 3.5 Hz), 3.22−3.40 (m, 2H), 3.64 (m, 1H, J = 11.6 Hz), 3.83 (s, 3H), 3.86 (m, 1H), 4.34 (m, 1H), 6.91 (dd, 2H, J = 8.8, 2.6 Hz), 7.57 (dd, 2H, J = 8.8, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 170.6, 161.1, 155.8, 153.7, 128.1, 121.8, 114.1, 89.7, 88.8, 81.6, 80.2, 59.1, 58.8, 56.1, 55.3, 43.9, 42.2, 41.1, 28.3, 27.9. Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.87, H, 7.46, N, 6.48. Found: C, 63.79, H, 7.56, N, 6.18.

11b: $[\alpha]^{25}_D$ +8.3 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 1741, 1702, 1401 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.42 (s, 9H), 1.45 (s, 9H), 2.08 (m, 1H), 2.68 (m, 1H), 3.21 (dd, 1H, J = 16.8, 9.2 Hz), 3.34 (dd, 1H, J = 16.8, 6.0 Hz), 3.57 (dd, 1H, J = 11.5, 8.6 Hz), 3.80 (s, 3H), 3.86 (m, 1H), 4.34 (m, 1H), 6.88 (d, 2H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 171.5, 161.1, 156.0, 153.4, 128.0, 121.6, 114.0, 89.8, 88.9, 81.3, 80.2, 80.0, 58.9, 57.1, 56.4, 55.2, 42.5, 42.3, 41.8, 40.8, 28.2, 27.8. Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.87, H, 7.46, N, 6.48. Found: C, 63.78, H, 7.46, N, 6.42.

General Procedure for Hydrolysis of Spiroisoxazolinoprolinates to Spiroisoxazolinoproline Amino Acids: (5*R*,8*S*)-3-(2,6-Dichlorophenyl)-1-oxa-2,7-diazaspiro[4,4]non-2-ene-7-*N*-Boc-8-carboxylic Acid (9b). A mixture of compound **7b** (2.0 g, 4.24 mmol) and sodium hydroxide (0.34 g, 8.50 mmol) in EtOH/H_2O (10 mL/10 mL) was refluxed 6 h. The solvent was removed under reduced pressure, and 1 N HCl was added to the reaction mixture until the pH reached to 2−3. Ethyl acetate (20 mL × 2) extraction, drying over $MgSO_4$, and removal of solvent under reduced pressure gave **9b** (1.61 g, 3.90 mmol, 92%) as a solid: $[\alpha]^{25}_D$ +5.0 (*c* 0.8, MeOH); IR ($CHCl_3$) 1735, 1655, 1429 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 75 °C) δ 1.39 (s, 9H), 2.25 (dd, 1H, J = 13.2, 8.1 Hz), 2.70 (ddd, 1H, J = 13.2, 8.1, 1.8 Hz), 3.25−3.40 (m, 2H), 3.57 (d, 1H, J = 11.7 Hz), 3.78 (dd, 1H, J = 11.7, 1.8 Hz), 4.27 (t, 1H, J = 8.1 Hz), 7.46−7.57 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 75 °C) δ 172.4, 153.9, 152.5, 133.4, 131.6, 127.9, 127.6, 89.9, 79.0, 57.8, 55.6, 42.5, 40.0, 27.6.

(5*S*,8*S*)-3-(2,6-Dichlorophenyl)-1-oxa-2,7-diazaspiro-[4,4]non-2-ene-7-*N*-Boc-8-carboxylic Acid (9a). The preparation of **9b** was modified as follows to give **9a**. Compound **7a** (1.0 g, 2.31 mmol), sodium hydroxide (0.20 g, 5.00 mmol), EtOH/H_2O) (15 mL/15 mL), and CC (40% ethyl acetate in hexanes with 1% AcOH) gave **9a** (0.86 g, 2.08 mmol, 90%) as a solid: $[\alpha]^{25}_D$ −23.8 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$) 1702, 1430 cm^{-1}; 1H (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.40 (s, 9H × $^2/_3$), 1.43 (s, 9H × $^1/_3$), 2.44−2.52 (m, 1H), 2.62−2.73 (m, 1H), 3.15−3.32 (m, 2H), 3.62−3.72 (m, 1H), 3.86−3.96 (m, 1H), 4.39−4.55 (m, 1H), 7.22−7.32 (m, 3H), 9.83 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 176.0, 174.3, 153.8, 153.5, 134.7, 131.0, 128.0, 127.9, 90.3, 89.6, 81.3, 81.0, 58.0, 56.2, 55.8, 45.1, 44.9, 41.9, 41.1, 40.0, 28.3, 28.2.

(5*S*,8*S*)-3-(2-Methoxyphenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Boc-8-dicarboxylic Acid (12a). The preparation of **9b** was modified as follows to give **12a**. Compound **10a** (2.3 g, 5.32 mmol), sodium hydroxide (0.43 g, 10.75 mmol), EtOH/H_2O) (20 mL/20 mL), extraction, and concentration of organic layers gave **12a** (1.66 g, 4.41 mmol, 83%) as a solid: $[\alpha]^{25}_D$ −15.6 (*c* 0.16, MeOH); IR ($CHCl_3$) 1751, 1699, 1404 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 1.40 (s, 9H × $^3/_5$), 1.42 (s, 9H × $^2/_5$), 2.33−2.38

(m, 1H), 2.55−2.63 (m, 1H), 3.33−3.85 (m, 4H), 3.78 (s, 3H), 4.38−4.53 (m, 1H), 6.88 (m, 2H), 7.30 (m, 1H), 7.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 175.5, 174.1, 157.2, 155.8, 155.7, 154.7, 153.7, 131.4, 129.0, 120.6, 118.0, 111.2, 89.6, 88.8, 80.8, 80.6, 58.1, 57.9, 56.3, 55.4, 55.2, 45.5, 45.3, 41.2, 40.0, 28.1, 28.0. Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.46; H, 6.40; N, 7.43.

(5*R*,8*S*)-3-(2-Methoxyphenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Boc-8-carboxylic Acid (12b). The preparation of **9b** was modified as follows to give **12b**. Compound **10b** (2.8 g, 6.47 mmol), sodium hydroxide (0.52 g, 13.00 mmol), EtOH/H_2O) (25 mL/25 mL), extraction, and concentration of organic layers gave **12b** (2.06 g, 5.48 mmol, 85%) as a solid: $[\alpha]^{25}_D$ −3.1 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 1750, 1699, 1404 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 2.14−2.27 (m, 1H), 2.57−2.67 (m, 1H), 38−4.49 (9m, 1H), 3.38−3.57 (m, 4H), 6.80−6.91 (m, 2H), 7.27−7.33 (m, 1H), 7.62−7.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 175.5, 174.9, 157.0, 155.99, 155.95, 154.3, 153.3, 131.2, 128.6, 120.3, 117.7, 117.6, 111.0, 89.5, 89.0, 80.47, 80.43, 77.1, 58.3, 58.2, 56.5, 55.7, 55.0, 43.5, 43.3, 40.9, 39.9, 27.9, 27.7. Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.48; H, 6.49; N, 7.38.

(5*S*,8*S*)-3-(4-Methoxyphenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Boc-8-dicarboxylic Acid (13a). The preparation of **9b** was modified as follows to give **13a**. Compound **11a** (1.8 g, 4.16 mmol), sodium hydroxide (0.35 g, 8.75 mmol), EtOH/H_2O) (20 mL/20 mL), extraction, and concentration of organic layers gave **13a** (1.42 g, 3.79 mmol, 91%) as a solid: $[\alpha]^{25}_D$ −43.2 (*c* 3.8, $CHCl_3$); IR (neat) 1753, 1676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 1.41 (s, 9H), 2.28 (d, 1H, J = 13.6 Hz), 2.53 (d, 1H, J = 12.6 Hz), 3.38−3.64 (m, 4H), 3.80 (s, 3H), 4.31 (d, 1H, J = 9.2 Hz), 6.99 (d, 2H, J = 7.3 Hz), 7.57 (d, 2H, J = 7.1 Hz);^{13}C NMR (400 MHz, DMSO-d_6, 100 °C) δ 172.0, 160.5, 156.0, 152.8, 127.7, 121.6, 114.0, 89.0, 78.8, 57.7, 55.9, 55.0, 42.5, 40.4, 27.7. Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.32; H, 6.32; N, 7.44.

(5*R*,8*S*)-3-(4-Methoxyphenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Boc-8-carboxylic Acid (13b). The preparation of **9b** was modified as follows to give **13b**. Compound **11b** (2.1 g, 4.85 mmol), sodium hydroxide (0.40 g, 10.0 mmol), EtOH/H_2O) (20 mL/20 mL), extraction, and concentration of organic layers gave **13b** (1.67 g, 4.46 mmol, 92%) as a solid: $[\alpha]^{25}_D$ +9.2 (*c* 3.3, $CHCl_3$); IR (neat) 1743, 1675 cm^{-1}; ^{1}H (400 MHz, DMSO-d_6, 75 °C) δ 1.37 (s, 9H), 2.15 (dd, 1H, J = 12, 8.1 Hz), 2.54 (dd, 1H, J = 9.4, 1.3 Hz), 3.34−3.50 (m, 3H), 3.65 (d, 1H, J = 11.2 Hz), 3.77 (s, 3H), 4.21 (t, 1H, J = 8.2 Hz), 6.97 (d, 2H, J = 8.4 Hz), 7.54 (d, 2H, J = 8.4 Hz); ^{13}C NMR (400 MHz, DMSO-d_6, 75 °C) δ 172.9, 160.6, 156.2, 153.0, 127.8, 121.6, 114.1, 89.1, 79.1, 58.1, 55.9, 55.1, 40.4, 40.1, 27.7. Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.45; H, 6.39; N, 7.35.

General Procedure for Transformation from *N*-Boc Protected Spiroisoxazolinoproline Amino Acids to *N*-Fmoc Protected Spiroisoxazolinoproline Amino Acids: (5*R*,8*S*)-3-(2,6-Dichlorophenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Fmoc-8-carboxylic Acid (14). Compound **9b** (1.0 g, 2.40 mmol) was treated with the solution of CH_2Cl_2/TFA (15 mL/15 mL), and the reaction mixture was stirred at room temperature for 5 h. After removing the solvent under reduced pressure, the residue was treated with Na_2CO_3 (0.53 g, 5.0 mmol) in H_2O/DMF (5 mL/15 mL) for 30 min at 0 °C. FmocOSu (0.85 g, 2.52 mmol) in DMF (10 mL) was added to the reaction and the mixture was stirred at room temperature for 3 h. The reaction was quenched with 1 N HCl until the pH reached 2−3 and extracted with ethyl acetate (20 mL × 2). The organic layers were dried ($MgSO_4$) and concentrated to a pale-brown oil. The material was subjected to CC (50% ethyl acetate in hexanes with 1% acetic acid) to give **14** (0.9 g, 70%) as a white foam: $[\alpha]^{25}_D$ +13.4 (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 1708, 1430 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 2.20−2.42 (m, 1H), 2.79−2.91 (m, 1H), 3.14−3.29 (m, 2H), 3.60−3.67 (m, 1H), 4.03−4.15 (m, 1H), 4.23−4.46 (m, 3H), 4.54−4.67 (m, 1H), 7.27−7.74 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 176.8, 174.9, 155.7, 154.5, 154.3, 154.1, 143.8, 143.5, 143.4, 141.2, 134.9, 131.3, 131.2, 128.16, 128.10, 127.8, 127.6, 127.1, 125.0, 124.9, 124.8, 120.0, 119.9, 90.3, 89.8, 68.2, 67.8, 58.6, 57.9, 56.7, 56.4, 47.0, 46.9, 43.7, 43.4, 41.4, 39.4. Anal. Calcd for $C_{28}H_{22}Cl_2N_2O_5 \cdot 0.5H_2O$: C, 61.54, H, 4.16, N, 5.12. Found: C, 61.23, H, 4.39, N, 5.07.

(5*S*,8*S*)-3-(2-Methoxyphenyl)-1-oxa-2,7-diaza-spiro[4,4]-non-2-ene-7-*N*-Fmoc-8-carboxylic Acid (15). The preparation of **14** was modified as follows to give **15**. Compound **12a** (1.3 g, 3.45 mmol), CH_2Cl_2/TFA (20 mL/20 mL), Na_2CO_3 (0.74 g, 7.0 mmol) in H_2O/DMF (7 mL/15 mL), FmocOSu (1.18 g, 3.50 mmol) in DMF (10 mL), and CC (50% ethyl acetate in hexanes with 1% acetic acid) gave **15** (1.22 g, 2.45 mmol, 71%) as a solid: $[\alpha]^{25}_D$ +40.4 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 1739, 1660, 1442 cm^{-1}; ^{1}H (300 MHz, DMSO, 80 °C) δ 2.31−2.49 (m, 2H), 3.46 (s, 2H), 3.62 (s, 2H), 3.83 (s, 3H), 4.18−4.45 (m, 4H), 6.99 (t, 1H, J = 7.5 Hz), 7.11 (d, 1H, J = 8.1 Hz), 7.28−7.45 (m, 6H), 7.56−7.66 (m, 2H), 7.83 (d, 2H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ambient temperature, mixture of conformers) δ 174.9, 173.9, 157.4, 155.9, 155.2, 143.9, 143.8, 143.6, 143.5, 141.2, 131.6, 129.3, 127.69, 127.61, 127.1, 125.09, 125.00, 124.8, 120.9, 119.8, 118.0, 111.3, 89.6, 89.0, 77.5, 67.8, 67.6, 58.4, 58.1, 56.2, 56.0, 55.4, 47.1, 45.6, 45.1, 41.6, 40.2. Anal. Calcd for $C_{29}H_{26}N_2O_6 \cdot 0.1H_2O$: C, 69.61; H, 5.28; N, 5.60. Found: C, 69.39; H, 5.33; N, 5.47.

(5*R*,8*S*)-3-(4-Methoxyphenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Fmoc-8-carboxylic Acid (16). The preparation of **14** was modified as follows to give **16**. Compound **13b** (0.8 g, 2.12 mmol), CH_2Cl_2/TFA (15 mL/15 mL), Na_2CO_3 (0.45 g, 4.30 mmol) in H_2O/DMF (5 mL/15 mL), FmocOSu (0.74 g, 2.20 mmol) in DMF (8 mL), and CC (50% ethyl acetate in hexanes with 1% acetic acid) gave **15** (0.80 g, 1.60 mmol, 75%) as a solid: $[\alpha]^{25}_D$ +4.2 (*c* 0.3, $CHCl_3$); IR (KBr) 3440, 1702, 1608, 1515, 1423 cm^{-1}; ^{1}H (300 MHz, DMSO, 80 °C) δ 2.31 (br s, 1H), 2.70 (br s, 1H), 3.39 (d, 1H, J = 17.4 Hz), 3.51 (d, 1H, J = 17.4 Hz), 3.66 (d, 1H, J = 11.7 Hz), 3.78 (s, 3H), 3.87 (d, 1H, J = 11.7 Hz), 4.24−4.33 (m, 3H), 4.47 (br s, 1H), 6.98 (d, 2H, J = 8.7 Hz), 7.30−7.42 (m, 4H), 7.59 (d, 2H, J = 8.7 Hz), 7.66 (d, 2H, J = 7.2 Hz), 7.83 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO, 100 °C) δ 172.0, 160.3, 155.8, 153.3, 143.2, 140.2, 127.4, 127.0, 126.4, 124.4, 121.4, 119.3, 113.8, 89.1, 66.7, 58.0, 56.1, 54.9, 46.5, 40.3. Anal. Calcd for C $_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62. Found: C, 70.20; H, 5.41; N, 5.59.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **5**, **9a**, and **9b**, as well as X-ray crystal structures for **9b**, **13a**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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