Supporting Informations

A Simple One-Flask Method for the Preparation of Hydroxamic Acids.

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Experimental Section

The *N*-protected amino acids were prepared according standard methods and their purities were established before utilization by melting point and optical rotation.¹ The *N*-protected dipeptide, *N*-Boc-Leu-Gly-OH and *N*-Cbz-Pro-Gly-OH were prepared on solid phase.² Cyanuric chloride was purchased from Aldrich while the *N*-protected amino acids were purchase from Fluka. Elemental analyses were performed on a Perkin-Elmer 420 B analyser, optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter in a 1 dm tube. The ¹H NMR (300 MHz), ¹³C NMR (75.4 MHz) and ¹⁹F NMR (282.3 MHz) were obtained with a Varian VXR-300 spectrometer from CDCl₃ solutions.

The procedure for the preparation of **(*S*)-(*N*-benzyloxycarbonyl)proline hydroxamate, 3**, is representative for all cases. Cyanuric chloride (0.5 g, 3.0 mmol) was added to a solution of (*S*)-(N-benzyloxycarbonyl)proline (2.24 g, 9.0 mmol), NMM (1.0 g, 1.1 mL, 9.9 mmol), DMAP (0.01 g, 0.1 mmol) in CH₂Cl₂ (20 mL), containing hydroxylamine hydrochloride (0.68 g, 9.8 mmol), stirred and maintained at 0°C. After the addition, the mixture was warmed to room temperature, stirred for 12 h, then filtered on celite, and the organic phase washed threefold with 15 mL of 1 N HCl and then brine. The organic layer were dried (Na₂SO₄) and the solvent evaporated to yield compound **3** that was isolated without other purifications (2.3 g, 96%), [α]_D²⁵ −46.1 (*c* 0.5, methanol). ¹H NMR δ, 8.06 (s, 1H), 7.26-7.36 (m, 5H), 5.34 (s, 2H), 4.29 (t, 1H), 3.35 (t, 2H), 2.17 (s, 1H), 1.60-1.83 (m, 4H); ¹³C NMR δ, 170.0, 155.8, 137.0, 128.4, 127.8, 127.5, 67.0, 60.2, 40.9, 23.7, 20.1.

Benzoic hydroxamate, 1: (1.17 g, 95%), m. p. 123-124°C.³

Phenylacetic hydroxamate, 2: (1.22 g, 90%), oil; ¹H NMR δ, 8.09 (s, 1H), 7.26-7.33 (m, 5H), 3.65 (s, 2H), 2.17 (s, 1H); ¹³C NMR δ, 165.8, 129.7, 128.8, 127.5, 35.7.

¹ Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, 40, 4395.

² Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275.

³ Reddy, A. S.; Kumar, M. S.; Reddy, G. R. *Tetrahedron Lett.* **2000**, 41, 6285.

(S)-N-(Benzyloxycarbonyl)alanine hydroxamate, 4: [da (S)-N-(benzyloxycarbonyl)alanine, $[\alpha]^{20}_{\text{D}} -14.5$ (*c* 1, AcOH): 1.86 g, 87%], oil, $[\alpha]^{25}_{\text{D}} +10.4$ (*c* 1, methanol). ^1H NMR δ , 8.06 (s, 1H), 7.26-7.33 (m, 5H), 5.34 (s, 2H), 4.71 (q, 1H), 2.17 (s, 1H), 1.48 (d, 3H); ^{13}C NMR δ , 170.0, 155.8, 137.0, 128.4, 127.8, 127.5, 69.1, 50.8, 17.5. Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4$ (238.24): C, 55.46; H, 5.92; N, 11.76. Found C, 55.49, H, 5.91, N, 11.76.

(S)-N-(Benzyloxycarbonyl)valine hydroxamate, 5: [da (S)-N-(benzyloxycarbonyl)valine, $[\alpha]^{20}_{\text{D}} -3.8$ (*c* 2, AcOH): 2.25 g, 94%], oil, $[\alpha]^{25}_{\text{D}} -30.5$ (*c* 1, methanol). ^1H NMR δ , 8.07 (bs, 1H), 7.31-7.36 (m, 5H), 5.42 (d, 1H), 5.11 (s, 2H), 4.34 (dd, 1H), 2.24 (m, 1H), 2.07 (s, 1H), 0.98 (d, 6H); ^{13}C NMR δ , 170.0, 156.9, 140.0, 128.6, 127.5, 127.1, 70.0, 60.2, 28.0, 16.2. Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_4$ (266.29): C, 58.63; H, 6.81; N, 10.52. Found C, 58.69, H, 6.78, N, 10.52.

(S)-N-(Benzyloxycarbonyl)serine hydroxamate, 6: [da (S)-N-(benzyloxycarbonyl)serine, $[\alpha]^{20}_{\text{D}} +6.3$ (*c* 7, AcOH): 2.06 g, 90%], oil, $[\alpha]^{25}_{\text{D}} +15.87$ (*c* 1, methanol). ^1H NMR δ , 8.06 (s, 1H), 7.24-7.33 (m, 5H), 5.34 (s, 2H), 4.31 (t, 1H), 3.99 (m, 2H), 2.17 (s, 1H); ^{13}C NMR δ , 170.0, 155.8, 137.0, 128.4, 127.8, 127.5, 69.1, 50.8, 17.5. Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5$ (254.24): C, 51.97; H, 5.55; N, 11.02. Found C, 51.99, H, 5.51, N, 11.04.

(S)-N-(Benzyloxycarbonyl)phenylalanine hydroxamate, 7: [da (S)-N-(benzyloxycarbonyl)phenylalanine, $[\alpha]^{20}_{\text{D}} +5.0$ (*c* 5, AcOH): 2.60 g, 92%], oil, $[\alpha]^{25}_{\text{D}} -38.8$ (*c* 0.5, methanol). ^1H NMR δ , 8.09 (s, 1H), 7.26-7.33 (m, 10H), 5.34 (s, 2H), 4.71 (q, 1H), 3.84 (m, 1H), 3.56 (m, 1H), 2.07 (s, 1H); ^{13}C NMR δ , 171.9, 155.8, 139.8, 137.0, 129.0, 128.4, 128.3, 127.5, 127.3, 125.5, 69.8, 56.7, 39.0.⁴

(S)-N-Methyl-N-(benzyloxycarbonyl)valine hydroxamate, 8: (2.42 g, 96%), oil, $[\alpha]^{25}_{\text{D}} +10.0$ (*c* 1, methanol). ^1H NMR δ , 8.07 (bs, 1H), 7.33-7.36 (m, 5H), 5.28 (s, 2H), 4.35 (dd, 1H), 2.96 (s, 3H), 2.24 (m, 1H), 2.06 (s, 1H), 1.06 (d, 6H); ^{13}C NMR δ , 170.4, 157.2, 140.0, 128.6, 127.5, 127.1, 70.0, 59.8, 33.5, 28.0, 16.5. Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_4$ (280.32): C, 59.99; H, 7.19; N, 9.99. Found C, 59.99, H, 7.15, N, 10.00.

(S)-N-(tert-Butoxycarbonyl)proline hydroxamate, 9: [da (S)-N-(tert-butoxycarbonyl)proline, $[\alpha]^{20}_{\text{D}} -61.1$ (*c* 1, AcOH): 1.76 g, 85%], oil, $[\alpha]^{25}_{\text{D}} -57.1$ (*c* 1, methanol).⁴ ^1H NMR δ , 8.06 (s, 1H), 4.29 (t, 1H), 3.35 (t, 2H), 2.17 (s, 1H), 1.60-1.83 (m, 4H), 1.45 (s, 9H).

⁴ Thouin, E.; Lubell, W. D.. *Tetrahedron Lett.* **2000**, *41*, 457.

(S)-N-(tert-Butoxycarbonyl)alanine hydroxamate, 10: [da (S)-N-(tert-butoxycarbonyl)alanine, $[\alpha]^{20}_{\text{D}} -25.6$ (c 1, AcOH): 1.65 g, 90%], oil, $[\alpha]^{25}_{\text{D}} -36.0$ (c 1, methanol). ⁴ ¹H NMR δ , 8.09 (s, 1H), 4.71 (q, 1H), 2.17 (s, 1H), 1.48 (s, 9H), 1.39 (d, 3H).

(S)-N-(tert-Butoxycarbonyl)-O-benzyl glutamic acid hydroxamate, 11: (2.74 g, 90%), m. p. 82-83°C, $[\alpha]^{25}_{\text{D}} +27.7$ (c 1, methanol). ¹H NMR δ , 8.06 (s, 1H), 7.26-7.35 (m, 5H), 5.34 (s, 2H), 5.15 (t, 1H), 2.92 (s, 2H), 2.09 (s, 1H), 1.45 (s, 9H); ¹³C NMR δ , 173.1, 170.0, 156.44, 139.0, 128.8, 127.9, 127.2, 68.1, 49.8, 37.8, 28.3. Anal. Calcd. for C₁₆H₂₂N₂O₆ (338.36): C, 56.80; H, 6.55; N, 8.28. Found C, 56.85, H, 6.55, N, 8.32.

(S)-N-(tert-Butoxycarbonyl)leucine hydroxamate, 12: [da (S)-N-(tert-butoxycarbonyl)leucine, $[\alpha]^{20}_{\text{D}} -24.9$ (c 1, AcOH): 2.15 g, 97%, (%), oil, $[\alpha]^{25}_{\text{D}} -8.6$ (c 1, methanol). ¹H NMR δ , 8.05 (s, 1H), 4.43 (t, 1H), 2.20 (s, 1H), 1.85 (m, 1H), 1.76 (dd, 2H), 1.45 (s, 9H), 0.96 (d, 6H); ¹³C NMR δ , 170.1, 157.9, 71.0, 51.1, 41.6, 28.5, 23.1, 22.0. Anal. Calcd. for C₁₁H₂₂N₂O₄ (246.30): C, 53.64; H, 9.00; N, 11.37. Found C, 53.69, H, 9.05, N, 11.40.

(S)-N-(tert-Butoxycarbonyl)phenylalanine hydroxamate, 13: [da (S)-N-(tert-butoxycarbonyl)phenylalanine, $[\alpha]^{20}_{\text{D}} +25.2$ (c 1, EtOH): 2.41 g, 95%], oil. ¹H NMR δ , 8.09 (s, 1H), 7.26-7.33 (m, 5H), 4.13 (t, 1H), 3.84 (m, 1H), 3.56 (m, 1H), 2.04 (s, 1H), 1.45 (s, 9H).⁴

(9-Fluorenylmethoxycarbonyl)glycine, 14: (2.72 g, 97%), m. p. 116-118°C. ¹H NMR δ , 8.05 (s, 1H), 7.31-7.75 (m, 8H), 5.28 (t, 2H), 4.43 (d, 1H), 3.80 (s, 2H), 2.04 (s, 1H); ¹³C NMR δ , 166.1, 157.7, 141.8, 136.3, 128.2, 127.6, 126.3, 44.6, 38.0. Anal. Calcd. for C₁₇H₁₆N₂O₄ (312.32): C, 65.38; H, 5.16; N, 8.97. Found C, 65.38, H, 5.20, N, 8.98.

(S)-N-(9-Fluorenylmethoxycarbonyl)leucine hydroxamate, 15: [da (S)-N-(9-fluorenylmethoxycarbonyl)leucine, $[\alpha]^{20}_{\text{D}} -25.8$ (c 1, DMF): 3.25 g, 98%], m. p. 114-116°C, $[\alpha]^{25}_{\text{D}} -13.6$ (c 1, methanol). ¹H NMR δ , 8.05 (s, 1H), 7.31-7.75 (m, 8H), 5.28 (t, 2H), 4.43 (d, 1H), 4.32 (t, 1H), 2.20 (s, 1H), 1.85 (m, 1H), 1.76 (d, 3H), 0.96 (d, 6H); ¹³C NMR δ , 169.7, 156.4, 143.8, 141.1, 128.2, 127.6, 126.5, 67.9, 46.8, 37.9, 35.5, 23.1, 22.0. Anal. Calcd. for C₂₁H₂₄N₂O₄ (368.43): C, 68.46; H, 6.57; N, 7.60. Found C, 68.50, H, 6.56, N, 7.54.

(S)-N-(9-Fluorenylmethoxycarbonyl)phenylalanine hydroxamate, 16: [da (S)-N-(9-fluorenylmethoxycarbonyl)phenylalanine, $[\alpha]^{20}_{\text{D}} -39.8$ (c 1, DMF): 2.90 g, 80%], m. p. 150-152°C, $[\alpha]^{25}_{\text{D}} -68.9$ (c 1, methanol). ¹H NMR δ , 8.09 (s, 1H), 7.26-7.76 (m, 8H), 5.28 (d, 2H), 4.17 (t, 1H),

4.13 (d, 1H), 3.70 (d, 2H), 2.04 (s, 1H); ^{13}C NMR δ , 170.2, 157.2, 140.8, 137.1, 129.2, 128.2, 127.6, 127.1, 125.9, 125.3, 73.0, 55.1, 36.9. Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4$ (402.44): C, 71.63; H, 5.51; N, 6.96. Found C, 71.68, H, 5.56, N, 6.94.

(S)-N-(tert-Butoxycarbonyl)phenylglycine hydroxamate, 17: 5.0 g (19.9 mmol) of (S)-N-(tert-butoxycarbonyl)phenylglycine, $[\alpha]^{25}_{\text{D}} +145$ (c 1, ethanol) gave 4.77 g, 90% of **17**, m. p. 28-30°C, $[\alpha]^{25}_{\text{D}} +46.1$ (c 0.2, methanol). ^1H NMR δ , 7.92 (s, 1H), 7.32 (m, 5H), 5.21 (m, 1H), 1.48 (s, 9H); ^{13}C NMR δ , 167.8, 60.8, 137.1, 129.2, 128.2, 127.6, 79.0, 28.2. Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_4$ (266.29): C, 58.63; H, 6.81; N, 10.52. Found C, 58.60, H, 6.85, N, 10.54.

A sample of **17** (0.70 g, 0.26 mmol) and distilled (+)MPTACl (0.79 g, 0.31 mmol) were mixed in CCl_4 (1.0 mL) with dry pyridine (1.0 mL) and allowed to stand for 12 h. Water was then added, and the reaction mixture extracted with ether (15 mL), washed successively with diluted HCl, saturated Na_2CO_3 , water and dried (Na_2SO_4). TLC analysis showed the presence of only a compound. After removal of the solvent under vacuum, the residue was dissolved in CDCl_3 for ^{19}F NMR analysis [δ , -72.1 (s, ~ 0.01), -72.5 (s, ~ 0.99)].

The same procedure was repeated on a sample of racemic N-(tert-butoxycarbonyl)phenylglycine hydroxamate [δ , -72.1 (s, 0.5), -72.5 (s, 0.5)].

(S)-N-Boc-Leu-Gly-NHOH, 18; (1.99 g, 73%), m. p. 120-122°C, $[\alpha]^{25}_{\text{D}} -10.7$ (c 1, methanol).⁵ ^1H NMR δ , 8.09 (bs, 1H), 4.64 (t, 1H), 3.95 (s, 2H), 1.85 (m, 1H), 1.68 (m, 2H), 1.36 (s, 9H), 0.86 (d, 6H); ^{13}C NMR δ , 173.9, 167.0, 156.1, 73.9, 53.4, 41.4, 41.2, 28.3, 22.8, 21.7.

(S)-N-Cbz-Pro-Gly-NHOH, 19; (2.37 g, 82%), viscous oil, $[\alpha]^{25}_{\text{D}} -80.3$ (c 1, methanol). ^1H NMR δ , 8.06 (bs, 1H), 7.22-7.26 (m, 5H), 5.07 (s, 2H), 4.31 (t, 1H), 4.05 (s, 2H), 3.45 (t, 2H), 1.96 (m, 2H), 1.75 (m, 2H); ^{13}C NMR δ , 174.0, 170.0, 155.6, 136.1, 128.4, 127.8, 67.1, 60.2, 43.8, 41.1, 23.3, 20.0. Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_5$ (321.33): C, 56.07; H, 5.96; N, 13.08. Found C, 56.11, H, 5.96, N, 13.04.

All compounds **1-19** gave a positive test for hydroxamic acids on treatment with an iron(III) chloride solution.⁶

⁵ Odake, S.; Nakahashi, K.; Morikawa, T.; Takebe, S.; Kobashi, K. *Chem. Pharm. Bull.* **1992**, 40, 2764.

⁶ Vogel's *Textbook of Practical Organic Chemistry* Longman Ed. 5th ed, **1989**, p. 1222.