Methodology for the Preparation of N-Guanidino-Modified Arginines and Related Derivatives

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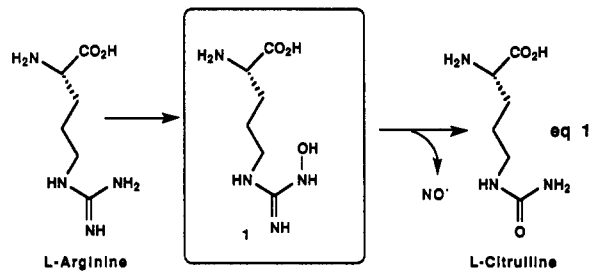
Methods for the preparation of N^G-modified arginines and N^δ-heterocyclic ornithines are described. The reactive cyanamide intermediate *tert*-butyl N^α-Boc-N^δ-cyano-L-ornithinate (**2**), prepared either by treatment of *tert*-butyl N^α-Boc-L-ornithinate (**5**) with cyanogen bromide or by dehydration of *tert*-butyl N^α-Boc-L-citrullinate (**6**), was utilized to prepare N^G-hydroxy-L-arginine, N^G-amino-L-arginine, and N^G-methoxy-L-arginine. Intermediates **3a** and **3b**, derived from treatment of **5** with diphenyl cyanocarbonimidate (**19**), reacted with nitrogen nucleophiles to produce novel N^G-cyano-L-arginine and N^δ-heterocyclic L-ornithine analogs.

Introduction

While there has been much research on the synthesis of guanidines there has been little research on the modification of the guanidino group in arginine. Our interest in modified arginines stems from the recent discovery of nitric oxide synthases (NOS) in vascular tissues, neuronal cells, and macrophages.[1-8] A few prototypical NOS inhibitors have been identified: N^G-methyl-L-arginine (NMA), N^G-nitro-L-arginine (NNA), and N^G-amino-L-arginine (NAA).[9-12] N^G-Hydroxy-L-arginine (NHA, **1**) had been proposed to be an intermediate in the biosynthesis of EDRF/nitric oxide (NO), eq 1;[13] recently,



the intermediacy of NHA in the biosynthesis of NO from L-arginine has been demonstrated.[14] Since L-arginine is utilized as a substrate by all of the known NOS isoenzymes, we hoped to derive modified arginines which would be selective inhibitors of the NOS isoenzymes. We sought to apply methodologies for the preparation of substituted guanidines to the synthesis of modified arginine derivatives.

Because of the biochemical and pharmacological importance of NHA and NAA we sought a synthetic route to these compounds and other analogs. Several reports of the synthesis of NAA,[15] NHA,[16,17] and N^G-hydroxy-N^G-methyl-L-arginine[17,18] have appeared. The protected cyanoornithine **2** has been utilized to prepare NHA[17,19,20] and N^G-hydroxy-N^G-methyl-L-arginine[17] for use as mechanistic probes. Our synthetic efforts also centered on the use of **2** for the preparation of NHA and NAA as well as other analogs.

We also sought to explore **3a** and **3b**, derived from protected ornithine and diphenyl cyanocarbonimidate (**19**) as versatile intermediates to various modified arginines. Reagent **19** has been used to produce novel cyanoguanidines,[21] heterocycles,[21,22] and cyanoarginine-containing peptides.[23] The unique reactivity of **3a** and **3b** should allow modification of the guanidine position to provide a diverse range of arginine analogs and heterocyclic isosteres of arginine.

Results and Discussion

The preparation of NHA, NAA, and other N^G-alkyl and N^G-aminoarginine analogs relied on the reaction of the cyanamide function of **2** with the appropriate amines and hydrazines.

Compound **2** was obtained by the two methods in Scheme I. First, *tert*-butyl N^α-Boc-N^δ-Cbz-L-ornithinate[16] was hydrogenated with Pd/C under 1 atm of H_2 to afford **5** in 98% yield. As previously reported for a similar

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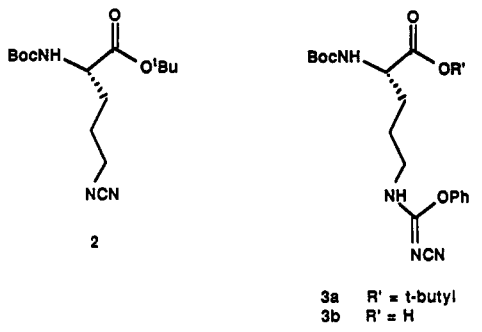
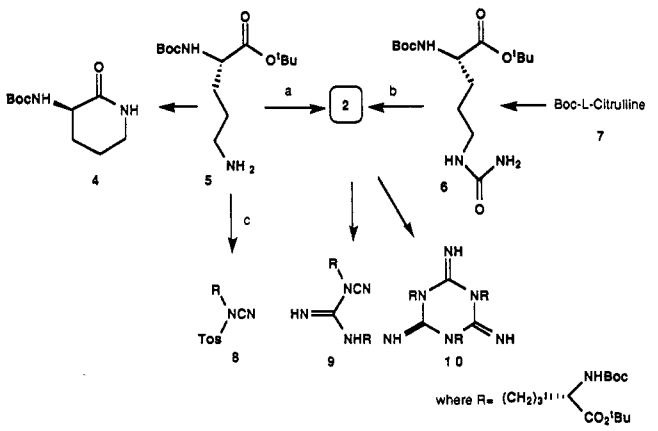


Figure 1.

Scheme I[a]



[a] Key: (a) CNBr/TEA; (b) TsCl/pyridine; (c) TsCl/CH_2Cl_2.

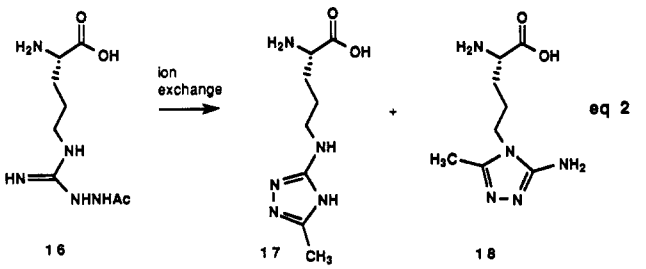
compound,[24] **5** readily cyclized to the lactam **4**, and therefore, the hydrogenolysis was generally done immediately prior to utilization.

Using a method similar to Pufahl et al.,[17] treatment of **5** with solid cyanogen bromide (BrCN) or, more conveniently, as a solution of BrCN in CH_2Cl_2 led to the formation of **2** within minutes providing a 57% yield after chromatography.

A second method to prepare **2** utilized the dehydration of protected L-citrullines in pyridine.[25] Treatment of L-citrulline with di-*tert*-butyl dicarbonate provided compound **7** in 65% yield. Reaction of **7** with *O*-*tert*-butyldicyclohexylisourea provided **6** in 80% yield. Dehydration of **6** with *p*-toluenesulfonyl chloride (TsCl) was complete within 1 h to afford the cyanamide **2** in 68% yield after chromatography. When **2** prepared by this route was stored neat, a large proportion was converted to the dimeric material **9** and cyclic trimer **10**.[26] This instability prompted the storage of **2** in ethanolic solution which was stable indefinitely (>1 year) at −20 °C. Alternatively, a nucleophile could be added to the crude reaction mixture in excess. When the dehydration with TsCl was performed in CH_2Cl_2 the only isolable product was the tosylated cyanoornithine **8**.[27]

Treatment of **2** with Me_3SiONH_2 in EtOH at room temperature (Scheme II) provided the protected NHA **11a** wherein the Me_3Si group had been cleaved under the reaction conditions. Direct treatment of compound **2** with NH_2OH·HCl in EtOH provided **11a** in 62–83% yield. To confirm the structure of **11a**, compound **2** was treated with $^{15}NH_2OH$·HCl to yield **11b** which displayed a ^{15}N–^{13}C coupling constant of 17.3 Hz, consistent with the product **11b**.[28] Treatment of **2** with $BzlONH_2$ overnight at room temperature provided **11c** in 67% yield. Hydrogenation of **11c** provided **11a** in quantitative yield. The Boc and *tert*-butyl ester protecting groups of compounds **11a** and **11b** were then removed by acid treatment with HCl–dioxane to provide NHA (**1a, b**).

The reaction of **2** with NH_2NH_2·HCl in refluxing EtOH provided the protected NAA **12** in 88% yield. Deprotection of compound **12** in 6 N HCl followed by ion exchange provided **13** in 61% yield. The preparation of NAA by this method does not generate L-arginine as with reductive methods using zinc[29] or PtO_2[15] nor N^G-(acetylamino)-L-arginine (**16**) which forms when NNA is reduced in the presence of HOAc.[29] In our hands, reduction of NAA was best performed in H_2O with 1 equiv of HCl to aid in solubility. Compound **16** further dehydrated to form **17** and **18** during ion-exchange purification (eq 2).



eq 2

Intermediate **2** was also reacted with MeNHOH·HCl in EtOH at 60 °C to afford **14** in 97% yield. Subsequent treatment of **14** with 4 N HCl in dioxane provided a 65% yield of N^G-methoxy-L-arginine (**15**).

To establish the enantiomeric purity of NHA and NAA produced by these methods, samples of the D-enantiomer of each compound were prepared using the same methodology, and the products were analyzed using chiral HPLC. The enantiomeric excesses observed were 97.8% and >98% for L-NHA and L-NAA, respectively.

Initial efforts to prepare N^G-cyano-L-arginine utilized the intermediate **3a** derived from **5** and diphenyl *N*-cyanocarbonimidate (**19**) (Scheme III). The reaction of *tert*-butyl N^α-Boc-L-ornithinate and **19** proceeded smoothly to provide a 76% yield of product. Compound **3a** was recrystallized from hexane–EtOAc and was stable at room temperature.

Compound **3a** was treated with NH_4OH in EtOH at 60 °C overnight or, alternatively, with a saturated solution of NH_3 in EtOH to yield the protected parent cyano-L-arginine **20a**. Deprotection was attempted with a variety of acidic reagents: TFA/CH_2Cl_2, 6 N HCl, 4 M HCl in dioxane or HOAc, and Me_3SiI. Regardless of the method, two product spots were always detected by TLC, and the crude product was difficult to characterize unambiguously. In several instances an ion at *m/e* 218 was observed indicating hydrolysis of the *N*-cyano function to the N^G-carboxamide **21**, consistent with a recent literature report.[23]

Compound **3a** reacted with 40% aqueous CH_3NH_2 to provide the protected N^G-cyano-$N^{G'}$-methylarginine **22a**

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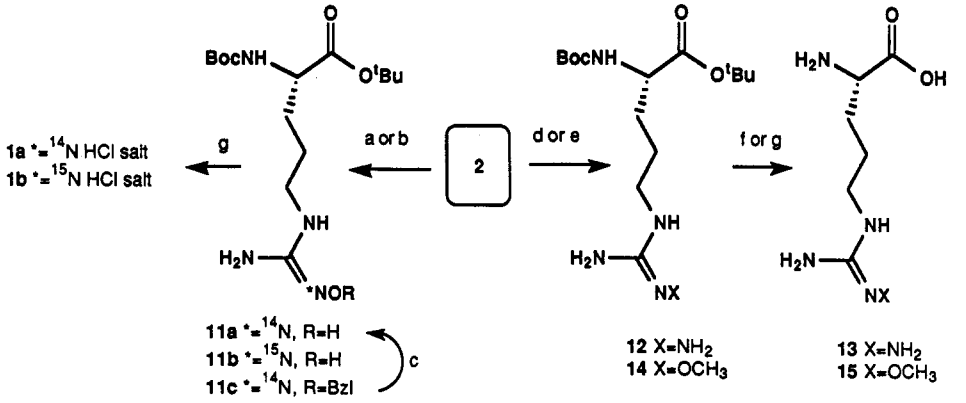
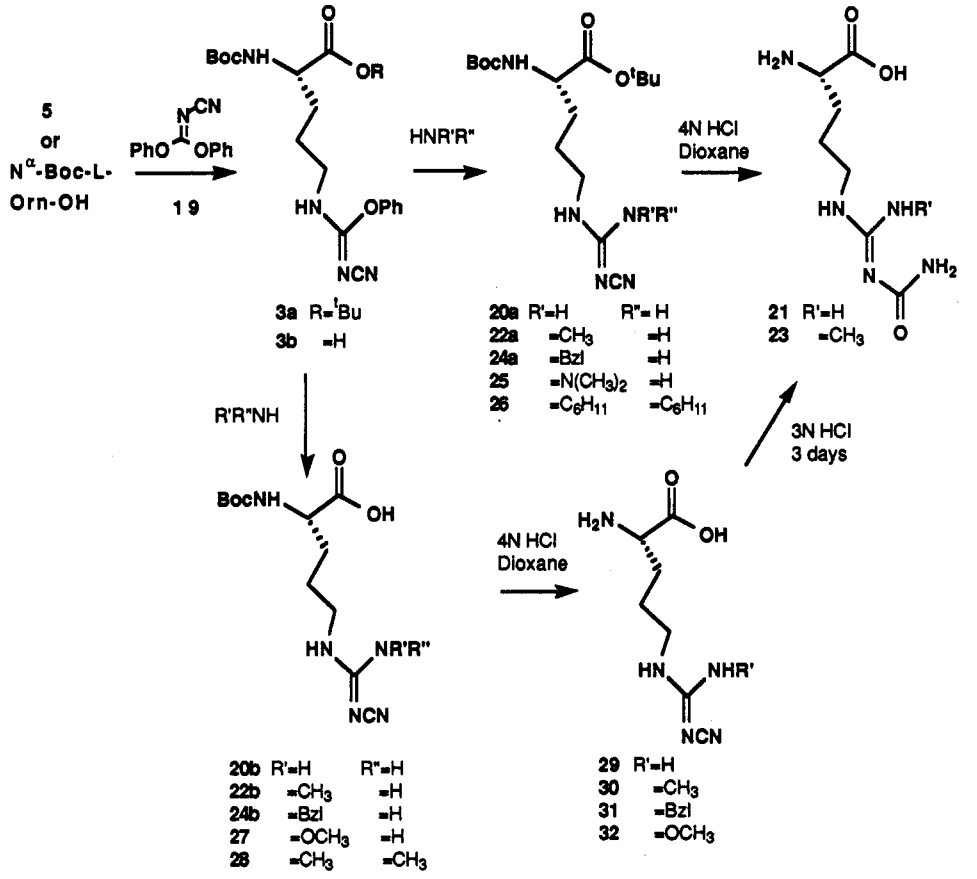
Scheme II[a]



[a] Key: (a) $TMSONH_2$ or HO^*NH_2HCl/TEA; (b) $BzlONH_2$; (c) H_2/Pd/C; (d) NH_2NH_2·HCl; (e) $MeONH_2$·HCl; (f) 6 N HCl; (g) 4 N HCl/dioxane.

Scheme III

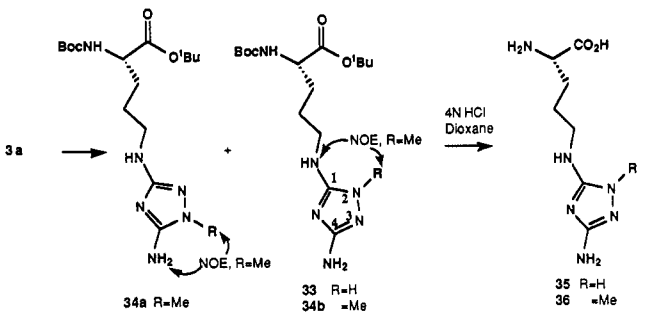


in 96% yield. Removal of the Boc protecting group with 4 N HCl yielded 15% of **23**. Reaction of **3a** with $BzlNH_2$ in refluxing EtOH for 3 h gave a quantitative yield of **24a**. Treatment with Me_2NNH_2 at room temperature provided a 70% yield of **25**. Compound **3a** could also be reacted with the secondary amine dicyclohexylamine to provide a 31% yield of **26**.

Due to hydrolysis of the cyano function of **20a** and **22a**, an alternative intermediate **3b** was prepared from Boc-L-ornithine and **19** in 79% yield. Treatment of **3b** with NH_3 in EtOH at room temperature yielded the **20b** in 84%. TFA treatment of **20b** in CH_2Cl_2 for 5 min resulted in complete deprotection providing **29** in 90% purity. A sample of **29**, dissolved in 1 N HCl, slowly transformed to compound **21**. Treatment of **20b** with Me_3SiI yielded only **21**. Deprotection of **20b** with HCl in dioxane at room temperature for 5 min yielded homogeneous **29** as a very hygroscopic solid. Compound **29** was neutralized by dissolution in 1 M NH_4HCO_3 and purified by ion exchange to provide a nonhygroscopic solid after lyophilization. Reaction of **3b** with CH_3NH_2 in EtOH resulted in **22b** in 55% yield. Compound **22b** when treated with HCl provided a quantitative yield of **30**. Similarly, **3b** was reacted with $BzlNH_2$ to provide **24b** in 55% yield and with CH_3ONH_2·HCl and Et_3N in a sealed tube at 60 °C to provide **27** in 75% yield. Compounds **24b** and **27** were deprotected by HCl in dioxane to provide **31** in 62% yield and **32** in 50% yield, respectively. Treatment of **3b** with saturated ethanolic solution of $(CH_3)_2NH$ provided a 32% yield of **28**.

Treatment of **3a** with hydrazines lacking 1,1-disubstitution resulted in cyclic products arising from attack of

Scheme IV



the intermediate aminoguanidine at the cyano function. Reaction of **3a** with NH_2NH_2 yielded 62% of **33** (Scheme IV). Treatment of **3a** with $MeNHNH_2$ resulted in **34a** and **34b**. The regiochemistry of the methylhydrazine addition was determined by a 2D-ROESY NMR study. An NOE was observed between ^1NH–$^2NCH_3$ in **34b** but not in **34a**; similarly, an NOE between the $^4NH_2$–$^3NCH_3$ was observed in **34a** and not in the other isomer. The cyclized compounds **33** and **34b** could be deprotected to provide **35** and **36** in 78% and 79% yield, respectively.

The D-enantiomer of compound **35** was also synthesized using the same methodology, and analysis by chiral HPLC demonstrated an enantiomeric excess for L-**35** of >98%.

In conclusion, NHA and NAA have been prepared by the aminolysis of *tert*-butyl N^{α}-Boc-N^{δ}-cyano-L-ornithinate (**2**). Intermediate **2** has been prepared by two routes in good yield and can be reacted with nitrogen nucleophiles directly in situ or after purification. Use of intermediate **2** provides an attractive avenue for NHA synthesis and allows for convenient preparation of a variety of additional derivatives in good yields. The methodology provides significant advantages over the direct reduction of NNA for NAA preparation in ease of synthesis and purification and in the versatility which should allow for the synthesis of a wide range of NAA derivatives. Methodology utilizing intermediates **3a** and **3b** allows for the preparation N^{G}-cyano-L-arginine and a variety of related analogs and, when ring closure on the cyano function is possible, N^{δ}-heterocyclic ornithine derivatives. Hydrolysis of the N^{G}-cyano function under the acidic conditions used to remove protecting groups was minimized by using intermediate **3b** which allowed for isolation of nonhygroscopic products after ion-exchange chromatography. Both methods, from intermediates **2** or **3a**, have been demonstrated to provide product without loss of enantiomeric purity and should be applicable to a wide variety of amines and hydrazines. The biological data for these compounds will be reported elsewhere.

Experimental Section

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting point apparatus or a Buchi 510 capillary melting point apparatus. TLC was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (E. Merck; 230–400 mesh) was used for flash chromatography eluting with 5–10 psi of air pressure. EtOAc–PAW elution solvent was the specified ratio of EtOAc to a stock solution of 10:3:5 pyridine–HOAc–H_2O. Chiral HPLC was performed using a Daicel Crownpack CR(+) 4.6 × 150-mm column and 0.01 M perchloric acid mobile phase at 0.5 mL/min flow rate at 5 °C and UV detection at 200 nm. Ion exchange was performed with commercial Dowex 50 × 8–100 resin (50–100 mesh) washed with 1 N NH_4OH and H_2O and used immediately (NH_4 form) or reprotonated with 1 N HCl and H_2O for storage or use (H^+ form). Optical rotations were determined in a Perkin-Elmer 241 polarimeter using the sodium D line. Proton NMR spectra were obtained at 300 MHz in $CDCl_3$ referenced to Me_4Si at room temperature unless otherwise indicated; spectra obtained in D_2O were referenced to Me_3SiCD_2-CD_2CO_2Na (TSP). ^{15}N NMR spectra utilized NH_4NO_2 in 10% HNO_3 as an external standard with NH_4 at 21.6 ppm. Mass spectra were obtained using desorption chemical ionization (DCI), fast atom bombardment (FAB^+) or plasma desorption MS (PDMS). Solvents and other reagents were reagent grade and were used without further purification unless otherwise noted.

N^{α}-Boc-L-citrulline (7).[30,31] L-Citrulline (12 g, 69 mmol) was dissolved in 150 mL of 2:1 EtOH–H_2O and treated with di-*tert*-butyl dicarbonate (18 g, 82 mmol) and Et_3N (11.4 mL, 82 mmol) at room temperature. After 1 h, the reaction became homogeneous. The reaction was acidified with 1 M H_3PO_4 after 3 h, and the product was extracted into CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and evaporated to provide 12.5 g, 45 mmol, 65% yield. Further extraction of the aqueous layer yielded an additional 3.4 g of desired product (12.4 mmol, 18%): R_f 0.2 (80:20:1 $CHCl_3$–MeOH–NH_4OH); ^1H NMR (DMSO-d_6) δ 1.38 (s, 11H), 1.47–1.69 (m, 2H), 2.88–2.96 (m, 2H), 3.80–3.87 (m, 1H), 5.40 (s, 2H), 5.96 (t, J = 5 Hz, 1H), 7.06 (d, J = 8 Hz, 1H), 11.5 (bs, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 26.8, 28.2, 28.3, 38.8, 53.4, 77.9, 155.5, 158.8, 174.2; MS (FAB^+) calcd for $C_{11}H_{22}N_3O_5$ m/e 276.1559, found 276.1560; MS (DCI) 276 (M + H)$^+$, 293 (M + NH_4)$^+$, 237; $[\alpha]^{23}_D$ −0.9° (c = 1.03, MeOH).

***tert*-Butyl N^{α}-Boc-L-citrullinate (6).** Compound **7** (10 g, 36 mmol) was dissolved in 200 mL of 1:1 CH_2Cl_2–dioxane and *O*-*tert*-butyl dicyclohexylisourea (13 mL, 54 mmol) added. After 1 day, an additional 7 mL of the isourea was added and the reaction was stirred for 3 days. After filtration of the precipitate, the solvent was evaporated in vacuo and the resulting residue purified by preparative HPLC (silica gel eluted with EtOAc) to yield 9.6 g, 29 mmol, 80%: R_f 0.15 (1:2 hexane–EtOAc); oil; ^1H NMR δ 1.43 (s, 9H), 1.47 (s, 9H), 1.53–1.85 (m, 4H), 3.14–3.21 (m, 2H), 4.08–4.17 (m, 1H), 4.88 (s, 2H), 5.38 (d, J = 8 Hz, 1H), 5.59 (bs, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 27.7, 28.3, 28.7, 30.0, 40.5, 55.7, 80.4, 82.5, 158.0, 162.2, 173.6; MS (DCI) 332 (M + H)$^+$, 276, 232, 220; $[\alpha]^{23}_D$ −19.3° (c = 1.18, MeOH). Anal. Calcd for $C_{15}H_{29}N_3O_5$ 0.2 H_2O: C, 53.78; H, 8.85; N, 12.54. Found: C, 53.83; H, 8.56; N, 12.55.

***tert*-Butyl N^{α}-Boc-N^{δ}-cyano-L-ornithine (2).** Compound **6** (2.2 g, 6.6 mmol) was dissolved in 10 mL of pyridine, and TsCl (3.8 g, 20 mmol) in pyridine (10 mL) was added dropwise over 5 min at 5 °C. After 30 min, the solvent was evaporated and the resulting crude residue chromatographed on silica gel eluted with 4:1 hexanes–EtOAc to yield 1.41 g, 4.5 mmol, 68%. When stored neat as an oil, the product dimerized to give after chromatography 112 mg of monomer **2** and 563 mg of dimer **9**. The monomer could be stored indefinitely in EtOH at −20 °C. For **2**: R_f 0.6 (1:1 hexane–EtOAc); R_f 0.6 (9:1 $CHCl_3$–MeOH); ^1H NMR δ 1.45 (s, 9H), 1.48 (s, 9H), 1.68–1.74 (m, 3H), 1.81–1.92 (m, 1H), 3.13–3.20 (m, 2H), 4.10–4.19 (m, 2H), 5.16–5.19 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.2, 28.0, 28.3, 30.0, 45.6, 53.1, 80.0, 82.4, 116.3, 155.5, 171.3; IR ($CHCl_3$) 2220 cm^{-1}; MS (FAB^+) calcd for $C_{15}H_{28}N_3O_4$ m/e 314.2080, found 314.2081; MS (DCI) 314 (M + H)$^+$, 331 (M + NH_4)$^+$, 275. For **9**: purified by column chromatography on silica gel eluted with 2:1 hexane–EtOAc; R_f 0.25 (1:1 hexanes–EtOAc); ^1H NMR δ 1.44 (s, 9H), 1.47 (s, 9H), 1.60–1.70 (m, 2H), 1.72–1.86 (m, 2H), 3.07–3.18 (m, 1H), 3.21 (bs, 2H), 3.56–3.63 (m, 1H), 4.13 (bs, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8, 24.7, 25.8, 28.0, 28.3, 29.3, 29.7, 30.4, 31.2, 41.6, 46.1, 46.5, 47.0, 53.3, 53.6, 60.3, 79.7, 81.9, 82.2, 111.6, 143.8, 151.4, 155.4, 171.4, 172.0; IR ($CHCl_3$) 2218 cm^{-1}; MS (DCI) 627 (M + H)$^+$; $[\alpha]^{23}_D$ −16.4° (c = 0.7, MeOH). For **10**: also purified by column chromatography eluted with 1:1 hexane–EtOAC; mp 67–70 °C; R_f 0.2 (1:2 hexanes–EtOAc); ^1H NMR δ 1.45 (s, 9H), 1.47 (s, 9H), 1.63–1.9 (m, 4H), 3.9–4.0 (m, 2H), 4.18–4.26 (m, 1H), 5.33 (d, J = 8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.4, 27.9, 28.3, 30.1, 43.8, 53.3, 79.6, 81.9, 146.4, 155.5, 171.6; MS (FAB^+) 940 (M + H)$^+$; $[\alpha]^{23}_D$ − 13.2° (c = 1.3, MeOH). Anal. Calcd for

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(31) Visser, S.; Kerling, K. E. T. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 880–4.

$C_{45}H_{81}N_9O_{12}$: C, 57.49; H, 8.68; N, 13.41. Found: C, 57.20; H, 8.74; N, 13.17.

Synthesis of 2 from 5. Prepared by modification of the literature method[17] wherein compound 5 (5.8 g, 20 mmol) was dissolved in 250 mL of Et_2O and BrCN (7.3 mL, 22 mmol, 3 M in CH_2Cl_2) was added in one portion, followed by Et_3N (3.1 mL, 22 mmol) added over 10 min. A precipitate formed immediately. After 1 h, the crude reaction mixture was placed on silica gel and eluted with 2:1 hexanes–EtOAc to yield 2.90 g, 9.2 mmol, 46%: R_f 0.5 (1:1 hexanes–EtOAc); R_f 0.8 (Et_2O); ^{1}H NMR δ 1.44 (s, 9H), 1.48 (s, 9H), 1.54–1.93 (m, 4H), 3.13–3.20 (m, 2H), 4.13–4.25 (m, 2H), 5.14–5.21 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.2, 28.0, 28.3, 30.1, 45.6, 53.0, 80.0, 82.4, 116.2, 155.6, 171.3; IR ($CHCl_3$) 2224 cm^{-1}; MS (DCI) 314 (M + H)$^+$, 331 (M + NH_4)$^+$, 275; $[\alpha]^{23}_D$ −19.6° (c = 0.85, EtOH).

***tert*-Butyl N^{α}-Boc-N^{δ}-(*p*-toluenesulfonyl)-N^{δ}-cyano-L-ornithinate (8).** Compound 6 (106 mg, 0.32 mmol) was dissolved in 5 mL of CH_2Cl_2, treated with Et_3N (167 μL, 1.2 mmol) and TsCl (122 mg, 0.64 mmol), and then refluxed for 3 h. Additional TsCl (122 mg) and Et_3N (167 μL) were added, and reflux was continued overnight. After cooling, the crude reaction mixture was chromatographed on silica gel eluted with 3:1 hexanes–EtOAc to yield 149 mg, 0.305 mmol, 96%: mp 60–70 °C; R_f 0.6 (2:1 hexane–EtOAc); ^{1}H NMR δ (s, 9H), 1.46 (s, 9H), 1.6–1.85 (m, 4H), 2.48 (s, 3H), 3.41 (t, J = 6 Hz, 2H), 4.16 (m, 1H), 5.06 (d, J = 7 Hz, 1H), 7.42 (d, J = 8 Hz, 2H), 7.84 (dt, J = 8, 1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 23.8, 27.9, 28.3, 29.5, 49.8, 53.0, 79.9, 82.5, 108.3, 127.8, 130.5, 133.4, 146.3, 155.8, 172.1; MS (DCI) calcd for $C_{22}H_{34}N_3O_6S$ m/e 468.2168, found 468.2167; MS (DCI) 468 (M + H)$^+$, 485 (M + NH_4)$^+$, 429, 412, 373; $[\alpha]^{23}_D$ −12.3° (c = 1.15, MeOH).

***tert*-Butyl N^{α}-Boc-N^{G}-hydroxy-L-arginate (11a).** In a modification of the literature method,[17] intermediate 2 (500 mg, 1.6 mmol) was dissolved in 4 mL of EtOH and treated with NH_2-OH·HCl (222 mg, 3.2 mmol) and Et_3N (223 μL, 1.6 mmol) for 1 h. The solvents were evaporated and the residue chromatographed on silica gel eluted with 6:1 CH_2Cl_2–EtOH to yield 379 mg, 1.1 mmol, 66%: R_f 0.3 (5:1 EtOAc–PAW); ^{1}H NMR (CD_3-OD) δ 1.43 (s, 9H), 1.46 (s, 9H), 1.62–1.83 (m, 4H), 3.21–3.27 (m, 2H), 3.93–3.98 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 26.5, 28.3, 28.8, 29.8, 41.9, 55.4, 80.6, 82.8, 158.1, 160.3, 173.3; MS (DCI) calcd for $C_{15}H_{31}N_4O_5$ m/e 347.2294, found 347.2285; MS (DCI) 347 (M + H)$^+$; $[\alpha]^{23}_D$ −18.2° (c = 1.1, MeOH).

Synthesis of 11a from 6. Compound 6 (674 mg, 2.0 mmol) was dissolved in 20 mL of pyridine and treated with TsCl (763 mg, 4.0 mmol). After 1 h, NH_2OH·HCl (278 mg, 4.0 mmol) was added and the reaction stirred overnight. After evaporation of the solvent, the residue was chromatographed on silica gel eluted with 10:1 EtOAc–PAW to yield 447 mg, 1.29 mmol, 65%: R_f 0.3 (5:1 EtOAc–PAW).

Synthesis of 11a from 11c. Compound 11c (260 mg, 0.60 mmol) was dissolved in 50 mL of MeOH and treated with 50 mg of 10% Pd/C and 1 atm of hydrogen gas overnight. The reaction mixture was filtered through Celite and concentrated, and the crude product was chromatographed on silica gel eluted with 10:1 EtOAc–PAW to yield 158 mg, 0.46 mmol, 77%: R_f 0.3 (5:1 EtOAc–PAW); ^{1}H and ^{13}C NMR spectra were consistent with previously prepared material; MS (FAB$^+$) calcd for $C_{15}H_{31}N_4O_5$ m/e 347.2294, found 347.2296; MS (DCI) 347 (M + H)$^+$, 331; $[\alpha]^{23}_D$ −15.6° (c = 0.57, MeOH).

Synthesis of 11a via Me_3SiONH_2. Intermediate 2 (200 mg, 0.64 mmol) was dissolved in 20 mL of EtOH and treated with Me_3SiONH_2 (135 mg, 1.28 mmol) at ambient temperature overnight. The crude residue from solvent evaporation was chromatographed on silica gel eluted with 5:1 EtOAc–PAW to provide 183 mg, 0.53 mmol, 83%; R_f 0.3 (5:1 EtOAc–PAW); ^{1}H NMR was consistent with previously prepared material; MS (FAB$^+$) 347 (M + H)$^+$, 331.

Synthesis of D-Isomer of 11a. The D-isomer of compound 5 (300 mg, 1.0 mmol) was dissolved in 10 mL of Et_2O and treated with BrCN (381 mL, 1.14 mmol) and Et_3N (294 μL, 2.1 mmol). After 10 min, the reaction was diluted with 10 mL of EtOH and treated with NH_2OH·HCl (102 mg, 1.6 mmol and Et_3N (223 μL, 1.6 mmol). After 2 h, the crude reaction mixture was chromatographed on silica gel eluted with 5:1 EtOAc–PAW to provide 217 mg, 0.62 mmol, 62% yield: R_f 0.3 (5:1 EtOAc–PAW); ^{13}C NMR was consistent with the spectrum of 11a; MS(DCI) 347 (M + H)$^+$, 331; $[\alpha]^{23}_D$ +18.0° (c = 1.1, MeOH).

***tert*-Butyl N^{α}-Boc-$^{15}N^{G}$-hydroxy-L-arginate (11b).** Compound 6 (155 mg, 0.47 mmol) was dissolved in 2 mL of pyridine and treated with TsCl (95 mg, 0.50 mmol) for 45 min at room temperature. $^{15}NH_2OH$·HCl (70 mg, 1.0 mmol) was then added and the reaction warmed to 60 °C for 2 h. The crude residue after concentration was chromatographed on silica gel eluted with 5:1 EtOAc–PAW to yield 87 mg, 0.25 mmol, 53%: R_f 0.3 (5:1 EtOAc–PAW); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.48 (s, 9H), 1.59–1.70 (m, 3H), 1.80–1.86 (m, 1H), 3.08–3.13 (m, 1H), 3.19 (bs, 1H), 4.18 (bs, 1H), 5.25–5.28 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.0, 27.9, 28.3, 30.0, 40.7, 53.5, 79.8, 82.0, 156.1, 157.9 (d, J = 14.7 Hz), 171.9; ^{15}N NMR (30.4 MHz, $CDCl_3$) δ 205.0; MS (FAB$^+$) calcd for $C_{15}H_{31}{}^{14}N_3{}^{15}N_1O_5$ m/e 348.2265, found 348.2265; MS (DCI) 348 (M + H)$^+$, 332, 292; $[\alpha]^{23}_D$ −16.7° (c = 0.15, MeOH).

***tert*-Butyl N^{α}-Boc-N^{G}-(benzyloxy)-L-arginate (11c).** Compound 6 (115 mg, 0.35 mmol) was dissolved in 2 mL of pyridine and treated with TsCl (66 mg, 0.35 mmol) followed, after 45 min, by the addition of BzlONH$_2$·HCl (560 mg, 3.5 mmol). After stirring overnight, the crude residue after solvent evaporation was chromatographed on silica gel eluted with 10:1 EtOAc–PAW to yield 103 mg, 0.24 mmol, 67%: R_f 0.75 (9:1 $CHCl_3$–MeOH); R_f 0.75 (5:1 EtOAc–PAW); ^{1}H NMR (CD_3OD) δ 1.44 (s, 9H), 1.46 (s, 9H), 1.53–1.66 (m, 3H), 1.72–1.78 (m, 1H), 3.12 (t, J = 7 Hz, 2H), 3.92–3.96 (m, 1H), 4.83 (s, 2H), 7.32–7.46 (m, 5H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 26.4, 28.3, 28.7, 29.8, 41.8, 55.4, 79.2, 80.5, 82.7, 126.9, 129.5, 129.7, 129.8, 130.5, 136.8, 158.1, 159.4, 173.3; MS (FAB$^+$) calcd for $C_{17}H_{37}N_6O_7$ m/e 437.2724, found 437.2733; MS (DCI) 437 (M + H)$^+$, 381, 325; $[\alpha]^{23}_D$ −7.2° (c = 2.23, MeOH).

N^{G}-Hydroxy-L-arginine Dihydrochloride Salt (1a). In a similar manner to that of Feldman,[16] compound 11a (1.1 g, 3.18 mmol) was treated with 10 mL of 4 N HCl in dioxane for 24 h. The resulting solid was collected and rinsed with Et_2O and then dried in vacuo to yield 0.7 g, 2.9 mmol, 91%: mp 178–80 °C dec; R_f 0.4 (6:2:2 CH_3CN–AcOH–H_2O); ^{1}H NMR (D_2O) δ 1.64–1.88 (m, 2H), 1.91–2.11 (m, 2H), 3.32 (t, J = 6 Hz, 2H), 4.10 (t, J = 6 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.7, 29.9, 43.2, 55.6, 161.6, 174.8; MS (FAB$^+$) calcd for $C_6H_{15}N_4O_3$ m/e 191.1144, found 191.1144; MS (DCI) 191 (M + H)$^+$; $[\alpha]^{23}_D$ +21.1° (c = 1.07, MeOH).[32] Anal. Calcd for $C_6H_{14}N_4O_3$·2HCl·0.1pyridine: C, 28.05; H, 6.05; N, 20.63. Found: C, 28.04; H, 6.00; N, 20.64.

Synthesis of the D-Enantiomer of 1a. Compound D-11a (100 mg, 0.28 mmol) was treated with 2 mL of 4 N HCl in dioxane in a manner similar to that for the L-isomer to provide 60 mg, 0.23 mmol, 82% yield: R_f 0.4 (6:2:2 CH_3CN–HOAc–H_2O); ^{1}H and ^{13}C NMR correlated with L-1a; MS (DCI) 191 (M + H)$^+$; $[\alpha]^{23}_D$ −17.8 (c = 1.16, MeOH). Anal. Calcd for $C_6H_{14}N_4O_3$·2HCl: C, 27.39; H, 6.13; N, 21.29. Found: C, 27.29; H, 5.89; N, 20.91.

Chiral HPLC results: D-1a, t_R = 4.9 min, L-1a, t_R = 7.7 min. For L-1a: peak area ratio L/D 98.9/1.1 = 97.8% ee. For D-1a: no L-isomer detected, >98% ee.

$^{15}N^{G}$-Hydroxy-L-arginine (1b).[17] Compound 11b (92 mg, 0.27 mmol) was treated with 10 mL of 4 N HCl in dioxane for 23 h. The resulting solid was filtered under N_2 and rinsed with Et_2O to yield 58.3 mg, 0.22 mmol, 81%: R_f 0.5 (6:2:2 CH_3CN–AcOH–H_2O); R_f 0.5 (1:2 EtOAc–PAW); ^{1}H NMR (D_2O) δ 1.68–1.92 (m, 2H), 1.96–2.16 (m, 2H), 3.36 (t, J = 7 Hz, 2H), 4.16 (t, J = 6 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.7, 29.9, 43.2, 55.6, 161.6 (d, J = 17.3 Hz), 174.8; ^{15}N NMR (30.4 MHz) δ 135.2; MS (FAB$^+$) calcd for $C_6H_{15}{}^{14}N_3{}^{15}N_1O_3$ m/e 192.1114, found 192.113; MS (FAB$^+$) 192 (M + H)$^+$; $[\alpha]^{23}_D$ +21.6° (c = 0.55, MeOH).

***tert*-Butyl N^{α}-Boc-N^{G}-amino-L-arginate (12).** Intermediate 2 (462 mg, 1.5 mmol) was dissolved in 10 mL of EtOH and treated with NH_2NH_2·HCl (103 mg, 1.5 mmol) at reflux. After 1 day, additional NH_2NH_2·HCl (206 mg) was added and reflux continued for 3 h. After the solution was cooled to room temperature, the solvent was evaporated and the residue was chromatographed on silica gel eluted with 5:1 EtOAc–PAW to yield 503 mg, 1.32 mmol, 88%: R_f 0.15 (5:1 EtOAc–PAW); ^{1}H NMR δ 1.43 (s, 9H), 1.47 (s, 9H), 1.56–1.83 (m, 4H), 3.1 (bs, 1H), 3.32–3.43 (m, 1H),

(32) The residual pyridine was carried from the purification of 11a (from 5) and was also observed in the ^{1}H NMR.

4.12 (bs, 1H), 5.32 (bs, 0.5H), 5.79 (bs, 1H), 6.0 (bs, 0.5H), 6.45 (bs, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.0, 27.9, 28.3, 30.2, 40.4, 53.1, 79.9, 82.2, 158.7, 171.8, 178.1; MS (FAB$^+$) calcd for $C_{15}H_{32}N_5O_4$ *m/e* 346.2454, found 346.2452; MS (FAB$^+$) 346 (M + H)$^+$, 290, 234; $[\alpha]^{23}_D$ −16.7° (*c* = 0.70, MeOH). Anal. Calcd for $C_{15}H_{31}N_5O_4 \cdot 2.0H_2O \cdot 0.25HCl \cdot 0.75Pyr \cdot 1.0HOAc$: C, 48.87; H, 8.50; N, 15.79. Found: C, 48.79; H, 8.82; N, 15.45.

Synthesis of the D-Enantiomer of 12. In a manner similar to that for the L-**12**, compound D-**5** (150 mg, 0.52 mmol) was treated with BrCN (173 μL, 0.52 mmol) and Et_3N (145 μL, 1.04 mmol) followed by $NH_2NH_2 \cdot HCl$ to provide, after chromatography, 91 mg, 0.26 mmol, 50% yield: R_f 0.3 (5:3 EtOAc–PAW); MS (DCI) 346 (M + H)$^+$, 317, 289; $[\alpha]^{23}_D$ +16.5 (*c* = 0.77, MeOH).

***N*^{G}-Amino-L-arginine (13).** Compound **12** (100 mg, 0.263 mmol) was treated with 5 mL of 6 N HCl for 30 min. The crude reaction mixture was purified by ion exchange (NH_4 form) eluted with 0.5 M NH_4OAc to yield 50 mg, 0.19 mmol, 72%: R_f 0.4 (6:2:2 CH_3CN–AcOH–H_2O); ^{1}H NMR (D_2O) δ 1.56–1.80 (m, 2H), 1.88–1.95 (m, 2H), 1.92 (s, 3H, acetate), 3.37 (t, *J* = 6 Hz, 2H), 3.77 (t, *J* = 6 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.9, 30.4, 43.0, 57.2, 160.8, 177.3; MS (FAB$^-$) 188; $[\alpha]^{23}_D$ +7.4 (*c* = 0.46, MeOH). Anal. Calcd for $C_6H_{15}N_5O_2 \cdot 1.5 \cdot H_2O \cdot 1.25HOAc$: C, 35.05; H, 7.96; N, 24.04. Found: C, 34.92; H, 7.41; N, 24.29.

Synthesis of the D-Enantiomer of 13. The D-enantiomer of **12** (29 mg, 0.08 mmol) was treated with 5 mL of 4 N HCl for 4 h. The reaction mixture was diluted with H_2O and lyophilized to provide 8.3 mg, 0.03 mmol, 40% yield: R_f 0.4 (6:2:2 CH_3CN–HOAc–H_2O); ^{1}H NMR spectral data correlated with L-**13** previously prepared; MS (FAB$^+$) 190 (M + H)$^+$; crude product was used directly for chiral HPLC.

Chiral HPLC results: D-**13**, t_R = 6.6 min; L-**13**, t_R = 9.9 min. For L-**13**: no D-enantiomer detected, >98% ee. For D-**13**: no L-enantiomer detected, >98% ee.

***tert*-Butyl *N*$^\alpha$-Boc-*N*^{G}-methoxy-L-arginate (14).** Intermediate **2** (310 mg, 1.0 mmol) in 30 mL of EtOH was treated with $MeONH_2 \cdot HCl$ (417 mg, 5.0 mmol) and Et_3N (697 μL, 5.0 mmol). No reaction was noted after 12 h at 23 °C, and the reaction was heated to reflux for 5 h. After evaporation of the solvent, the residue was chromatographed on silica gel eluted with 5:1 EtOAc–PAW. The product fractions were combined, concentrated, mixed with H_2O, and lyophilized to give 407 mg, 0.97 mmol, 97%: R_f 0.25 (5:1 EtOAc–PAW); ^{1}H NMR (CD_3OD) δ 1.44 (s, 9H), 1.46 (s, 9H), 1.6–1.88 (m, 4H), 3.17–3.22 (m, 2H), 3.72 (s, 3H), 3.94–3.99 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 26.3, 28.2, 28.7, 29.8, 41.8, 55.4, 64.8, 80.5, 82.7, 158.1, 159.4, 173.3; MS (FAB$^+$) calcd for $C_{16}H_{33}N_4O_5$ *m/e* 361.2451, found 361.2445; MS (DCI) 361 (M + H)$^+$; $[\alpha]^{23}_D$ −10.4° (*c* = 1.12, MeOH).

***N*^{G}-Methoxy-L-arginine (15).** Compound **14** (230 mg, 0.64 mmol) was treated with 10 mL of 4 N HCl in dioxane for 2 h during which time the reaction mixture became heterogeneous. The reaction mixture was concentrated, and the residue was purified by ion exchange (NH_4 form) eluted with 0.1 M NH_4HCO_3 to give 100.5 mg, 0.42 mmol, 65% yield. A portion (80 mg) was further purified by recrystallization from EtOH to yield 17 mg of crystalline product: mp 175–80 °C dec; R_f 0.3 (6:2:2 CH_3CN–HOAc–H_2O); ^{1}H NMR (D_2O) δ 1.53–1.73 (m, 2H), 1.82–1.94 (m, 2H), 3.10 (t, *J* = 6 Hz, 2H), 3.62 (s, 3H), 3.73 (t, *J* = 6 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 27.3, 30.9, 43.2, 57.4, 64.1, 161.7, 177.9; MS (FAB$^+$) calcd for $C_7H_{17}N_4O_3$ m/e 205.1301, found 205.1313; MS (FAB$^+$) 205 (M + H)$^+$; $[\alpha]^{23}_D$ +8.7° (*c* = 0.23, MeOH).

***tert*-Butyl *N*$^\alpha$-Boc-*N*$^\delta$-((cyanoimino)phenoxymethyl)-L-ornithinate (3a).** Compound **5** (2.4 g, 8.32 mmol) was dissolved in 50 mL of 2-propanol and treated with Et_3N (1.17 mL, 8.4 mmol) and **19** (2.0 g, 8.4 mmol). After 1 h, the solvent was evaporated and the residue chromatographed on silica gel (4:1 hexane–EtOAc) to provide 1.6 g, 3.70 mmol, 44% yield: mp 92–4 °C; R_f 0.15 (2:1 hexane–EtOAc); ^{1}H NMR δ 1.42 (s, 9H), 1.48 (s, 9H), 1.6–1.95 (m, 4H), 3.46–3.54 (m, 2H), 4.17–4.27 (m, 1H), 5.14 (d, *J* = 7 Hz, 1H), 7.08 (d, *J* = 8 Hz, 2H), 7.23–7.29 (m, 1H), 7.38 (t, *J* = 7 Hz, 2H), 7.53 (bs, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.4, 27.9, 28.2, 30.0, 42.0, 53.4, 79.7, 82.0, 115.6, 121.4, 126.4, 129.4, 151.0, 155.3, 163.8, 171.5; IR ($CHCl_3$) 2180 cm^{-1}; MS (FAB$^+$) 433 (M + H)$^+$, 377, 321, 303, 277, 214; $[\alpha]^{23}_D$ −11.8 (*c* = 1.06, MeOH). Anal. Calcd for $C_{22}H_{32}N_4O_5$: C, 61.09; H, 7.46; N, 12.95. Found: C, 61.10; H, 7.40; N, 12.82.

***N*$^\alpha$-Boc *N*$^\delta$-((cyanoimino)phenoxymethyl)-L-ornithine (3b).** N^α-Boc-L-ornithine (5.0 g, 21.5 mmol) in 2-propanol (100 mL) was treated with **19** (5.1 g, 21.5 mmol) at reflux for 3 h. The solvent was evaporated, and the residue was chromatographed on flash silica gel eluted with 80:20:1 $CHCl_3$–MeOH–NH_4OH to yield 6.3 g, 17 mmol, 79%: mp 119–124 °C dec; R_f 0.3 (80:20:1 $CHCl_3$–MeOH–NH_4OH); ^{1}H NMR (DMSO-d_6) δ 1.38 (d, *J* = 5 Hz, 9H), 1.48–1.78 (m, 4H), 3.13–3.22 (m, 1H), 3.26–3.32 (m, 1H), 3.62–3.72 (m, 1H), 6.18 (dd, *J* = 7, 17 Hz, 1H), 7.17 (t, *J* = 7 Hz, 1H), 7.25–7.31 (m, 1H), 7.39–7.48 (m, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6)[33] δ 24.4, 25.5, 28.2, 29.9, 42.1, 42.5, 54.5, 77.5, 114.4, 114.8, 119.6, 121.7, 125.9, 126.2, 129.5, 130.2, 151.3, 151.8, 154.9, 159.5, 162.6, 174.9; MS (DCI) 377 (M + H)$^+$, 394 (M + NH_4)$^+$, 338, 321, 271; $[\alpha]^{23}_D$ +15.7 (*c* = 1.00, MeOH). Anal. Calcd for $C_{16}H_{30}N_5O_4$: C, 53.91; H, 8.48; N, 19.65. Found: C, 53.88; H, 8.25; N, 19.37.

***tert*-Butyl *N*$^\alpha$-Boc-*N*^{G}-cyano-L-arginate (20a).** Compound **3a** (432 mg, 1.0 mmol) in EtOH (10 mL) was treated with concentrated NH_4OH (2 mL) at 60 °C overnight. The solvents were evaporated, and the residue was chromatographed on silica gel eluted with 5% EtOH in CH_2Cl_2 to yield 316 mg, 0.89 mmol, 89%: mp 68–72 °C; R_f 0.2 (20:1 CH_2Cl_2–EtOH); ^{1}H NMR δ 1.44 (s, 9H), 1.48 (s, 9H), 1.56–1.7 (m, 2H), 1.73–1.85 (m, 1H), 3.23 (br s, 2H), 4.12 (br s, 1H), 5.38 (d, *J* = 7 Hz, 1H), 5.92 (br s, 3H), 6.47 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.0, 28.1, 28.4, 30.5, 41.1, 50.6, 80.2, 82.5, 123.8, 156.1, 161.4, 171.7; IR ($CHCl_3$) 2170 cm^{-1}; MS (DCI) 356 (M + H)$^+$, 373 (M + NH_4)$^+$, 300; $[\alpha]^{23}_D$ −15.6 (*c* = 1.09, MeOH). Anal. Calcd for $C_{16}H_{29}N_5O_4$ 0.25 H_2O: C, 53.39; H, 8.26; N, 19.46. Found: C, 53.37; H, 8.40; N, 19.22. Alternatively, intermediate **3a** (537 mg, 1.24 mmol) was dissolved in 25 mL of EtOH, and the solution was saturated with NH_3(g). After 3 days, the solvent was evaporated and the residue was chromatographed on flash silica gel eluted with 20:1 CH_2Cl_2–EtOH to provide 337 mg, 0.95 mmol, 77% yield: R_f 0.2 (20:1 CH_2Cl_2–EtOH); oil; ^{1}H NMR (CD_3OD) δ 1.45 (s, 9H), 1.47 (s, 9H), 1.54–1.82 (m, 4H), 3.17 (t, *J* = 6 Hz, 2H), 3.94–3.98 (m, 1H); IR ($CHCl_3$) 2170 cm^{-1}; MS (FAB$^+$) calcd for $C_{16}H_{30}N_5O_4$ *m/e* 356.2298, found 356.2310; MS (DCI) 356 (M + H)$^+$, 373 (M + NH_4)$^+$, 300; $[\alpha]^{23}_D$ −15.0 (*c* = 0.50, MeOH). Anal. Calcd for $C_{16}H_{29}N_5O_4$: C, 54.07; H, 8.22; N, 29.70. Found: C, 53.88; H, 8.25; N, 19.37.

***N*$^\alpha$-Boc-*N*^{G}-cyano-L-arginine (20b).** Intermediate **3b** (376 mg, 1.0 mmol) in EtOH (15 mL) was cooled to 4 °C and saturated with NH_3(g) by bubbling for 1 min. The flask was sealed and stirred at room temperature for 24 h. The solvent was evaporated and the residue dissolved in H_2O and extracted with EtOAc. The aqueous layer was then lyophilized to yield 250 mg, 0.84 mmol, 84%: mp 120 °C dec; R_f 0.2 (70:30:1 $CHCl_3$–MeOH–NH_4OH); ^{1}H NMR (DMSO-d_6) δ 1.33 (s, 9H), 1.38–1.63 (m, 4H), 2.92–2.98 (m, 2H), 3.59–3.66 (m, 1H), 6.31 (d, *J* = 7 Hz, 1H), 6.78 (s, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 26.7, 28.8, 31.1, 42.1, 56.1, 88.8, 120.5, 157.9, 163.1, 178.8; IR (film) 2180 cm^{-1}; MS (FAB$^-$) calcd for $C_{12}H_{20}N_5O_4$ 298.1515, found 298.1516; MS (FAB$^-$) 298 (M − H)$^-$; $[\alpha]^{23}_D$ +7.88 (*c* = 1.46, MeOH).

***N*^{G}-Carbamoyl-L-arginine (21).** Compound **20a** (143 mg, 0.40 mmol) was treated with 5 mL of 4 N HCl in dioxane for 6 h. The reaction mixture, which had some precipitate present, was mixed with Et_2O, and the solid was collected to yield 102 mg, 0.36 mmol, 91%: mp 127 °C dec; R_f 0.2 (1:1 EtOAc–PAW); R_f 0.75 (6:2:2 CH_3CN–HOAc–H_2O); ^{1}H NMR (D_2O) δ 1.67–2.1 (m, 4H), 3.37 (t, *J* = 7 Hz, 2H), 4.08 (t, *J* = 6 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.3, 29.9, 43.4, 55.6, 156.6, 158.9, 174.9, MS (DCI) 200 (M + H)$^+$, 175, 157; $[\alpha]^{23}_D$ +20.0 (*c* = 1.45, MeOH). Anal. Calcd for $C_7H_{13}N_5O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 28.10; H. 6.06; N, 23.41. Found: C, 28.33; H, 6.12; N, 23.35.

***tert*-Butyl *N*$^\alpha$-Boc-*N*^{G}-cyano-*N*$^{G'}$-methyl-L-arginate (22a).** Intermediate **3a** (432 mg, 1.0 mmol) was dissolved in 5 mL of EtOH and treated with 40% aqueous $MeNH_2$ (344 μL, 10 mmol) overnight at room temperature. The crude residue after solvent evaporation was chromatographed on flash silica gel eluted with 10:1 CH_2Cl_2–EtOH to yield 356 mg, 0.96 mmol, 96%: R_f 0.5 (2:1 hexane–EtOAc); R_f 0.3 (20:1 CH_2Cl_2–EtOH; R_f 0.8 (5:1 EtOAc–PAW); ^{1}H NMR (CD_3OD) δ 1.43 (s, 9H), 1.46 (s, 9H), 1.56–1.68

(33) The ^{13}C NMR for **3b** displayed two conformational isomers whose signals did not coalesce when heated to 90 °C in DMSO-d_6.

(m, 3H), 1.73–1.82 (m, 1H), 2.78 (s, 3H), 3.21 (t, 2H), 3.44–4.0 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 26.8, 28.3, 28.7, 28.7, 29.2, 42.1, 55.4, 80.5, 82.6, 120.2, 158.0, 161.9, 173.5; MS (DCI) 370 (M + H)$^+$, 387 (M + NH_4)$^+$; $[\alpha]^{23}_D$ −13.8 (*c* = 1.35, MeOH). Anal. Calcd for $C_{17}H_{31}N_5O_4 \cdot 0.25H_2O$: C, 54.60; H, 8.49; N, 18.73. Found: C, 54.99; H, 8.44; N, 18.73.

N^{α}-Boc-N^{G}-cyano-$N^{G'}$-methyl-L-arginine (22b). Intermediate **3b** (300 mg, 0.80 mmol) was dissolved in 10 mL of EtOH and saturated with CH_3NH_2 (g). The solution was resaturated after 6 h and left sealed overnight at room temperature. The crude residue after concentration was chromatographed on silica gel eluted with 75:25:1 CH_2Cl_2–MeOH–NH_4OH to yield 138 mg, 0.44 mmol, 55%: R_f 0.2 (5:1 EtOAc–PAW); ^{1}H NMR (CD_3OD) δ 1.43 (s, 9H), 1.56–1.69 (m, 3H), 1.73–1.86 (m, 1H), 2.78 (s, 3H), 3.21 (t, *J* = 6 Hz, 2H), 3.98–4.04 (m, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 27.9, 30.5, 30.8, 31.9, 43.9, 58.5, 83.9, 123.8, 160.3, 163.1, 182.4; IR (film) 2170 cm^{-1}; MS (DCI) calcd for $C_{13}H_{24}N_5O_4$ *m/e* 314.1828, found 314.1804; MS (DCI) 314 (M + H)$^+$, 331 (M + NH_4)$^+$; $[\alpha]^{23}_D$ +7.7° (*c* = 1.1, MeOH). Anal. Calcd for $C_{13}H_{23}N_5O_4 \cdot 0.5H_2O \cdot 0.2NH_3$: C, 47.93; H, 7.61; N, 22.36. Found: C, 48.05; H, 7.62; N, 22.38.

N^{G}-Carbamoyl-$N^{G'}$-methyl-L-arginine (23). Compound **22a** (250 mg, 0.68 mmol) was treated with 5 mL of 4 N HCl in dioxane. After 1 day, the reaction was mixed with Et_2O and the resulting solid was filtered to yield 219 mg of semisolid. The crude product was chromatographed on silica gel eluted with 6:1:1 CH_3CN–HOAc–H_2O to provide first **30** (75 mg, 0.26 mmol, 39%), followed by mixed fractions (36 mg) and finally **23** (28 mg, 0.093 mmol, 14%). For **30**: R_f 0.6 (6:2:2 CH_3CN–AcOH–H_2O); ^{13}C NMR (75.5 MHz, D_2O)[34] δ 27.2, 30.4, 30.8, 43.6, 57.2, 163.2, 177.3; MS (PDMS) 214 (M + H)$^+$; $[\alpha]^{23}_D$ −0.24° (*c* = 1.26, MeOH). For **23**: R_f 0.4 (6:2:2 CH_3CN–AcOH–H_2O); R_f 0.25 (1:2 EtOAc–PAW); ^{1}H NMR (D_2O) δ 1.68–2.12 (m, 4H), 2.96 (s, 3H), 3.35–3.46 (m, 2H), 4.12 (t, *J* = 5 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.8, 29.8, 30.8, 43.5, 55.5, 156.2, 159.1, 174.8; MS (DCI) 232 (M + H)$^+$, 215, 185; $[\alpha]^{23}_D$ +9.4° (*c* = 1.24, MeOH). Anal. Calcd for $C_8H_{15}N_5O_2 \cdot 1.0HCl \cdot 1.4H_2O$: C, 34.95; H, 6.89; N, 25.47. Found: C, 35.31; H, 7.06; N, 25.08.

Synthesis of N^{G}-Cyano-$N^{G'}$-methyl-L-arginine (30) from 22b. Compound **22b** (60 mg, 0.19 mmol) was treated with 4 N HCl in dioxane and then sonicated for 5 min. The reaction mixture was filtered, and the resulting hygroscopic solid was dissolved in H_2O and purified by ion exchange (NH_4 form) eluted with 0.25 M NH_4HCO_3 to provide 48 mg (0.098 mmol, 51%). Further elution provided an additional 15 mg (0.03 mmol, 15%): R_f 0.4 (6:2:2 CH_3CN–HOAc–H_2O); ^{1}H NMR (D_2O) δ 1.52–1.74 (m, 2H), 1.79–1.97 (m, 2H), 2.79 (s, 3H), 3.25 (t, *J* = 6 Hz, 2H), 3.76 (t, 6H); ^{13}C NMR (75.5 MHz, D_2O, pH 6.4) δ 27.2, 30.4, 30.7, 43.6, 57.3, 124 (CN, very broad), 163.4, 177.3; ^{13}C NMR (75.5 MHz, D_2O, pH 8)[35] δ 30.6, 30.7, 43.6, 123.7, 163.4; IR (KBr) 2165 cm^{-1}; MS (FAB$^+$) 214 (M + H)$^+$; $[\alpha]^{23}_D$ −2.1° (*c* = 0.63, MeOH). Anal. Calcd for $C_8H_{15}N_5O_2 \cdot 4.75NH_4Cl \cdot 1.25H_2O$: C, 19.62; H, 7.51; N, 27.88. Found: C, 19.74; H, 7.37; N, 27.98.

Synthesis of 23 from 30. Compound **30** (10 mg, 0.05 mmol) was treated with 3 mL of 3 N HCl for 2 days. The solution was diluted with H_2O and lyophilized to provide 13 mg, 0.05 mmol, quantitative yield: R_f 0.4 (6:2:2 CH_3CN–AcOH–H_2O); R_f 0.25 (1:2 EtOAc–PAW); ^{1}H NMR (300 MHz, D_2O) δ 1.68–2.12 (m, 4H), 2.96 (s, 3H), 3.35–3.46 (m, 2H), 4.12 (t, *J* = 5 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.8, 29.8, 30.8, 43.5, 55.5, 156.2, 159.1, 174.8; MS (DCI) calcd for $C_8H_{18}N_5O_3$ *m/e* 232.1410, found 232.1398; $[\alpha]^{23}_D$ +6.4 (*c* = 0.28, MeOH).

***tert*-Butyl N^{α}-Boc-N^{G}-benzyl-$N^{G'}$-cyano-L-arginate (24a).** Intermediate **3a** (432 mg, 1.0 mmol) and $BzlNH_2$ (240 μL, 2.2 mmol) were refluxed in 5 mL of EtOH for 3 h. The residue after concentration was dissolved in EtOAc and washed with 0.1 M citric acid, brine, 0.5 M $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ to yield after filtration and evaporation of the volatiles 486 mg, 1.09 mmol, quantitative: R_f 0.5 (1:1 hexane–EtOAc); ^{1}H NMR δ 1.41 (s, 9H), 1.45 (s, 9H), 1.52–1.78 (m, 4H), 3.16–3.34 (m, 2H), 4.06 (bs, 1H), 4.34–4.52 (m, 2H), 5.25 (d, *J* = 7 Hz, 1 H), 5.77 (s, 1H), 6.26–6.31 (m, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$)[36] δ 25.0, 27.9, 28.3, 30.8, 41.2, 45.6, 52.8, 80.2, 82.5, 115.4, 118.7, 120.1, 127.4, 127.8, 128.8, 129.5, 137.0, 155.9, 156.3, 160.0, 171.4; IR ($CHCl_3$) 2162 cm^{-1}; MS (FAB$^+$) calcd for $C_{29}H_{36}N_5O_4$ *m/e* 446.2767, found 446.2753; MS (DCI) 446 (M + H)$^+$, 463 (M + NH_4)$^+$; $[\alpha]^{23}_D$ −9.95° (*c* = 2.2, MeOH).

N^{α}-Boc-N^{G}-benzyl-$N^{G'}$-cyano-L-arginine (24b). Intermediate **3b** (200 mg, 0.86 mmol) was dissolved in 5 mL of EtOH and treated with $BzlNH_2$ (942 μL, 8.6 mmol) for 1 day. The crude residue after solvent evaporation was chromatographed on silica gel eluted with 10:1 EtOAc–PAW to provide 183 mg, 0.47 mmol, 55% yield: R_f 0.5 (5:1 EtOAc–PAW); ^{1}H NMR (300 MHz, CD_3OD) δ 1.44 (s, 9H), 1.55–1.67 (m, 3H), 1.73–1.82 (m, 1H), 3.23 (t, *J* = 7 Hz, 2H), 4.03–4.1 (m, 1H), 4.43 (s, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 26.9, 28.7, 30.1, 42.2, 46.1, 54.6, 80.5, 128.1, 128.4, 129.6, 138.7, 158.0, 161.3, 176.0; IR (KBr) 2168 cm^{-1}; MS (FAB$^+$) calcd for $C_{19}H_{28}N_5O_4$: *m/e* 390.2141, found 390.2130; MS (DCI) 390 (M + H)$^+$, 407 (M + NH_4)$^+$, 347; $[\alpha]^{23}_D$ +4.5° (*c* = 1.0, MeOH).

***tert*-Butyl N^{α}-Boc-N^{G}-cyano-$N^{G'}$-(dimethylamino)-L-arginate (25).** Intermediate **3a** (129 mg, 0.3 mmol) in EtOH (3 mL) was treated with Me_2NNH_2 (60 μL, 0.8 mmol) for 7 h. The crude residue after solvent evaporation was chromatographed on silica gel eluted with 20:1 CH_2Cl_2–EtOH to yield 83 mg, 0.21 mmol, 70%: R_f 0.2 (1:1 hexane–EtOAc); ^{1}H NMR δ 1.38 (s, 9H), 1.40 (s, 9H), 1.48–1.78 (m, 4H), 2.51 (s, 6H), 3.17–3.24 (m, 2H), 4.06–4.14 (m, 1H), 5.04–5.10 (m, 1H), 6.26 (t, *J* = 5 Hz, 1H), 7.02 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.2, 27.9, 28.2, 30.0, 40.2, 47.2, 53.4, 79.7, 82.1, 117.4, 155.3, 158.8, 171.4; IR (film) 2175 cm^{-1}; MS (DCI) 399 (M + H)$^+$, 384, 343; $[\alpha]^{23}_D$ −11.1° (*c* = 1.08, MeOH). Anal. Calcd for $C_{18}H_{34}N_6O_4$: C, 54.25; H, 8.60; N, 21.09. Found: C, 54.08; H, 8.75; N, 20.80.

***tert*-Butyl N^{α}-Boc-N^{G}-cyano-$N^{G'}$,$N^{G'}$-dicyclohexyl-L-arginate (26).** Intermediate **3a** (500 mg, 1.16 mmol) in EtOH (5 mL) was treated with dicyclohexylamine (DCHA, 460 μL, 2.31 mmol), and the solution was heated to reflux. After 4 h, additional DCHA (460 μL) was added and reflux was continued overnight. The residue after evaporation of solvent was dissolved into EtOAc and washed with 0.1 M citric acid, brine, 0.5 M $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to yield 567 mg, 1.09 mmol, 94% of crude product oil: R_f 0.6 (1:1 hexane–EtOAc); ^{1}H NMR δ 1.13 (tt, *J* = 2, 13 Hz, 2H), 1.3–1.4 (m, 6H), 1.44 (s, 9H), 1.46 (s, 9H), 1.6–1.75 (m, 12H), 1.78–1.88 (m, 4H), 3.23–3.32 (m, 1H), 3.43–3.64 (m, 2H), 4.16 (bs, 1H), 4.92 (t, *J* = 3 Hz, 1H), 5.21 (d, *J* = 7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.3, 26.0, 26.1, 28.0, 28.3, 30.4, 31.7, 31.8, 43.2, 53.6, 57.9, 60.4, 79.9, 82.3, 117.7, 156.3, 159.4, 171.5; IR ($CHCl_3$) 2160 cm^{-1}; MS (FAB$^+$) calcd for $C_{28}H_{50}N_5O_4$ *m/e* 520.3863, found 520.3849; MS (DCI) 520 (M + H)$^+$; $[\alpha]^{23}_D$ −3.5° (*c* = 1.0, MeOH). Anal. Calcd for $C_{28}H_{49}N_5O_4 \cdot 0.5H_2O$: C, 63.61; H, 9.53; N, 13.25. Found: C, 63.74; H, 9.37; N, 13.50;

N^{α}-Boc-N^{G}-cyano-$N^{G'}$-dimethylarginine (28). Compound **3b** (155 mg, 0.67 mmol) in EtOH (5 mL) was saturated with $(CH_3)_2NH$ (g) and sealed overnight at room temperature. After solvent evaporation, the crude residue was chromatographed on silica eluted with 5:1 EtOAc–PAW to provide 71 mg, 0.22 mmol, 32% yield: R_f 0.2 (5:1 EtOAc–PAW); ^{1}H NMR (300 MHz, CD_3OD) δ 1.43 (s, 9H), 1.62–1.73 (m, 3H), 1.8–1.88 (m, 1H), 3.03 (s, 6H), 3.42 (t, *J* = 6 Hz, 2H), 4.03–4.08 (m, 1H); ^{13}C NMR (75.5 MHz, methanol-d_4) δ 27.6, 28.7, 30.3, 39.0, 43.5, 55.1, 80.4, 120.0, 158.0, 161.0, 176.8; IR (KBr) 2169 cm^{-1}; MS (DCI) calcd for $C_{14}H_{26}N_5O_4$ *m/e* 328.1985, found 328.1979; MS (DCI) 328 (M + H)$^+$, 345 (M + NH_4)$^+$, 384, 285, 272; $[\alpha]^{23}_D$ +10.4° (*c* = 1.4, MeOH).

N^{G}-Cyano-L-arginine (29). Compound **20b** (100 mg, 0.33 mmol) was treated with 4 mL of 4 N HCl in dioxane for 5 min. The reaction solution was mixed with Et_2O and filtered to provide a hygroscopic solid. The semisolid was dissolved into 2 mL of 1 M NH_4HCO_3 and purified by ion exchange (NH_4 form) eluted with H_2O to provide 50 mg, 0.13 mmol, 40%: mp >250 °C; R_f 0.7 (6:2:2 CH_3CN–AcOH–H_2O); ^{1}H NMR (D_2O) δ 1.53–1.78 (m, 2H), 1.78–2.0 (m, 2H), 3.23 (t, *J* = 6 Hz, 2H), 3.74 (m, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 27.2, 30.8, 43.8, 57.3, 123.3, 164.2, 177.9; IR (KBr) 2180 cm^{-1}; MS (DCI) 200 (M + H)$^+$, 217 (M + NH_4)$^+$;

(34) For complete ^{13}C NMR data see **30** from **22b** below.

(35) At pH 7, the remaining resonances were not observable although the cyano resonance was sharp; at pH 6.4, all peaks were sharp except the cyano resonance.

(36) The ^{13}C NMR for **24a** displayed two geometric isomers whose signals did not coalesce when heated to 130 °C in DMSO-d_6.

MS (FAB⁻) calcd for $C_7H_{12}N_6O_2$ *m/e* 198.0991, found 198.0990; $[\alpha]^{23}_D$ 2.1° (*c* = 1.0, H_2O). Anal. Calcd for $C_7H_{13}N_5O_2 \cdot 1.0H_2O \cdot 3.0NH_4Cl$: C, 22.26; H, 7.21; N, 29.67. Found: C, 22.22; H, 6.80; N, 29.72.

N^G-Benzyl-$N^{G'}$-cyano-L-arginine (31). Compound **24b** (50 mg, 0.13 mmol) was treated with 4 N HCl in dioxane for 5 min. The reaction mixture was diluted with 3 mL of H_2O and immediately placed onto ion exchange (H^+ form) and washed with H_2O. The product was eluted from the column with 0.5 N NH_4OH to provide 32 mg, 0.08 mmol, 62% yield: R_f 0.4 (1:1 EtOAc–PAW); ^1H NMR (300 MHz, D_2O) δ 1.66–2.0 (m, 4H), 3.23 (t, *J* = 7 Hz, 2H), 4.09–4.13 (m, 1H), 4.64 (s, 2H), 7.36–7.48 (m, 5H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.8, 29.5, 43.8, 47.7, 55.2, 129.9, 131.1, 132.0, 138.0, 155.6, 158.7, 174.1; IR (KBr) 2170 cm^{-1}; MS (FAB⁺) calcd for $C_{14}H_{20}N_5O_2$ *m/e* 290.1617, found 290.1610; MS (FAB⁺) 290 $(M + H)^+$, 247; $[\alpha]^{23}_D$ −0.93° (*c* = 0.75, 3:1 MeOH–H_2O).

N^a-Boc-N^G-cyano-$N^{G'}$-methoxy-L-arginine (27). Intermediate **3b** (100 mg, 0.26 mmol) in EtOH (5 mL) was treated with $CH_3ONH_2 \cdot HCl$ (217 mg, 2.6 mmol) and Et_3N (840 μL, 6 mmol) at 60 °C in a sealed tube overnight. After solvent evaporation, the crude residue was chromatographed on silica eluted with 5:1 EtOAc–PAW to yield 64 mg, 0.19 mmol, 75%: R_f 0.3 (5:1 EtOAc–PAW); ^1H NMR (300 MHz, CD_3OD) δ 1.44 (s, 9H), 1.6–1.7 (m, 3H), 1.78–1.87 (m, 1H), 3.27 (t, *J* = 6 Hz, 2H), 3.69 (s, 3H), 3.98–4.06 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 14.5, 22.0, 26.8, 28.8, 30.7, 41.6, 52.9, 55.7, 80.4, 158.0, 162.4; IR (KBr) 2178 cm^{-1}; MS calcd for $C_{13}H_{24}N_5O_5$ *m/e* 330.1777, found 330.1768; MS (DCI) 330 $(M + H)^+$, 347 $(M + NH_4)^+$, 233; $[\alpha]^{23}_D$ +6.8° (*c* = 0.22, MeOH).

N^G-Cyano-$N^{G'}$-methoxy-L-arginine (32). Compound **27** (24 mg, 0.073 mmol) was treated with 4 N HCl in dioxane (2 mL) under N_2 for 5 min. The reaction was mixed with Et_2O, and the resulting solid was collected by vacuum filtration. The crude product was dissolved in H_2O, purified by ion exchange (H^+ form), and eluted with 0.5 N NH_4OH to provide 8.3 mg, 0.036 mmol, 50% yield: R_f 0.2 (1:1 EtOAc–PAW); ^1H NMR (300 MHz, D_2O) δ 1.55–1.74 (m, 2H), 1.78–1.94 (m, 2H), 3.25–3.31 (m, 2H), 3.72 (s, 3H), 3.73 (t, *J* = 6 Hz, 1H); IR (KBr) 2175 cm^{-1}; MS (DCI) calcd for $C_8H_{16}N_5O_3$ *m/e* 230.1253, found 230.1251; MS (DCI) 230 $(M + H)^+$; $[\alpha]^{23}_D$ +1.4° (*c* = 0.22, H_2O).

***tert*-Butyl N^a-Boc-N^5-(5-amino-2*H*-1,2,4-triazol-3-yl)-L-ornithinate (33).** Intermediate **3a** (250 mg, 0.58 mmol) in EtOH (2 mL) was treated with $NH_2NH_2 \cdot H_2O$ (150 μL, 3.0 mmol). After 2 h, the solvent was evaporated and the residue chromatographed on silica gel eluted with 90:10:1 CH_2Cl_2–EtOH–NH_4OH to yield 134 mg, 0.36 mmol, 62%; R_f 0.5 (80:20:1 CH_2Cl_2–EtOH–NH_4OH); ^1H NMR δ 1.46 (s, 9H), 1.48 (s, 9H), 1.6–1.74 (m, 3H), 1.77–1.88 (m, 1H), 3.16–3.26 (m, 1H), 3.3–3.42 (m, 1H), 4.15–4.23 (m, 1H), 5.38 (d, *J* = 7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.8, 28.0, 28.4, 30.1, 42.9, 53.8, 79.9, 82.0, 155.9, 158.9, 159.1, 172.1; MS (DCI) 371 $(M + H)^+$; $[\alpha]^{23}_D$ −12.5 (*c* = 1.15, MeOH). Anal. Calcd for $C_{16}H_{30}N_6O_4 \cdot 0.8\ H_2O$: C, 49.93; H, 8.28; N, 21.84. Found: C, 50.07; H, 8.16; N, 21.49.

***tert*-Butyl N^a-Boc-N^5-(5-amino-2-methyl-2*H*-1,2,4-triazol-3-yl)-L-ornithinate (34b).** Intermediate **3a** (340 mg, 0.79 mmol) in EtOH (5 mL) was treated with $MeNHNH_2$ (82 μL, 1.5 mmol) for 3 days. After solvent evaporation, the residue was chromatographed on flash silica gel eluted with 20:1 CH_2Cl_2–EtOH to yield **34b**, 223 mg, 0.58 mmol, 74%. For **34b**: R_f 0.3 (9:1 $CHCl_3$–MeOH); ^1H NMR δ 1.44 (s, 9H), 1.46 (s, 9H), 1.66–1.78 (m, 3H), 1.80–1.90 (m, 1H), 3.32–3.42 (m, 5H), 3.40 (bs, 2H), 4.16–4.23 (m, 1H), 4.56–4.62 (m, 1H), 5.37 (d, *J* = 7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.2, 28.0, 28.2, 30.5, 32.5, 43.3, 53.2, 79.7, 82.0, 154.8, 155.6, 159.7, 171.6; MS (DCI) 385 $(M + H)^+$; $[\alpha]^{23}_D$ −15.0 (*c* = 0.40, MeOH). Anal. Calcd for $C_{17}H_{32}N_6O_4$ 0.5 H_2O: C, 51.89; H, 8.45; N, 21.36. Found: C, 51.88; H, 8.25; N, 21.22. Further elution from the column provided a mixture of **34b** and *tert*-Butyl N^a-Boc-N^5-(5-amino-1-methyl-1*H*-1,2,4-triazol-3-yl)-L-ornithinate (**34a**) (89 mg, 0.23 mmol, 29%). For **34a**: R_f 0.25 (9:1 $CHCl_3$–MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.45 (s, 9H), 1.6–1.74 (m, 3H), 1.8–1.9 (m, 1H), 3.18–3.22 (m, 2H), 3.45 (s, 3H), 4.18 (bs, 2H), 4.54 (bs, 1H), 5.21 (d, *J* = 6 Hz, 1H), 5.33 (d, *J* = 7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.8, 28.0, 28.3, 30.3, 33.1, 43.1, 53.8, 79.5, 81.7, 153.0, 155.4, 161.1, 171.9.

N^5-(5-Amino-2*H*-1,2,4-triazol-3-yl)-L-ornithine (35). Compound **33** (100 mg, 0.27 mmol) was treated with 5 mL of 1.4 M HCl in HOAc. After 1 h a solid had formed that was collected and rinsed with Et_2O. The crude product was chromatographed on neutral alumina eluted with 1:1 EtOAc–PAW to give 53 mg, 0.21 mmol, 78% yield. The product was then purified by ion exchange (H^+ form) eluted with 0.25 N NH_4OH to remove any alumina that might be present. The yield from the ion-exchange column was 30 mg: mp 250–5 °C; R_f 0.2 (1:2 EtOAc–PAW); ^1H NMR (D_2O–CD_3OD) δ 1.55–1.73 (m, 2H), 1.79–1.97 (m, 2H), 3.17 (t, *J* = 6 Hz, 2H), 3.70 (t, *J* = 6 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O/CD_3OD) δ 25.7, 29.2, 43.2, 55.6, 159.6, 160.6, 176.1; MS (FAB⁺) calcd for $C_7H_{15}N_6O_2$ *m/e* 215.1269, found 215.1256; MS (FAB⁺) 215 $(M + H)^+$; $[\alpha]^{23}_D$ +16.4 (*c* = 1.17, MeOH).

Synthesis of the D-Enantiomer of 35. The D-enantiomer of **5** (100 mg, 0.35 mmol was dissolved in 5 mL of 2-propanol and treated with **19** (91 mg, 0.38 mmol). After 2 h, the solvent was evaporated, and the resulting residue was dissolved in 5 mL of EtOH and treated with hydrazine hydrate (34 μL, 0.70 mmol) for 1 day. After solvent evaporation, chromatography of the residue on silica gel eluted with 80:20:1 $CHCl_3$–MeOH–NH_4OH provided D-**33**, 121 mg, 0.33 mmol, 94% yield: R_f 0.5 (80:20:1 $CHCl_3$–MeOH–NH_4OH); MS (DCI) 371 $(M + H)^+$; $[\alpha]^{23}_D$ +13.0 (*c* = 1.19, MeOH). Compound D-**33** was treated with 5 mL of 4 N HCl in dioxane for 3 h, and the resulting solid was collected and rinsed with Et_2O to provide D-**35**, 4.9 mg, 0.02 mmol, 37% yield: R_f 0.2 (1:2 EtOAc–PAW); MS (DCI) 215 $(M + H)^+$; $[\alpha]^{23}_D$ −14.5 (*c* = 0.38, MeOH).

Chiral HPLC Results: D-**35**, t_R = 5.6 min; L-**35**, t_R = 10.1 min. For L-**35**: peak area ratio L/D 99.25:0.75 = 98.5% ee. For D-**35**: no L-isomer detected, >98% ee.

N^5-(5-Amino-2-methyl-2*H*-1,2,4-triazol-3-yl)-L-ornithine (36). Compound **34b** (92 mg, 0.24 mmol) was treated with 5 mL of 1:1 TFA–CH_2Cl_2 for 2 h. The reaction was mixed with Et_2O, and the resulting solid was filtered to yield 44 mg, 0.13 mmol, 54%, of very hygroscopic solid: R_f 0.25 (6:2:2 CH_3CN–AcOH–H_2O); ^1H NMR (D_2O) δ 1.51–2.03 (m, 4H), 3.36 (t, *J* = 7 Hz, 2H), 3.43 (s, 3H), 3.88 (t, *J* = 5 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 27.2, 30.2, 36.2, 45.9, 56.7, 151.6, 153.8, 176.4; MS (FAB⁺) calcd for $C_8H_{17}N_6O_2$ *m/e* 229.1413, found 229.1396; MS (DCI) 229 $(M + H)^+$; $[\alpha]^{23}_D$ +8.7° (*c* = 0.94, MeOH).

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Supplementary Material Available: ^1H spectra for compounds **1a,b**, **6**, **7**, **11b**, **11c**, **14**, **15**, **20b**, **24a,b**, **27**, **28**, **29**, **31–32**, **35**, and **36**, ^{13}C spectra for compounds **1b**, **2**, **11a,c**, and **12**, ROESY spectrum for the mixture of compounds **34a,b**, and NOE data for compounds **17** and **18** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.