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Synthesis of cyclic and acyclic *N*α-methyl-*N*ω-alkyl-L-arginine analogues ☆

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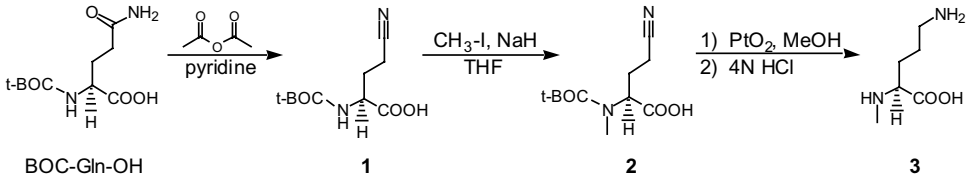
Abstract—A series of *N*α-methyl-alkyl-L-arginine (Arg) analogues have been synthesized from inexpensive, commercially available starting materials. These analogues, once incorporated into pharmaceutically relevant peptides, are expected to increase binding affinity, receptor selectivity, lipophilicity, and stability as demonstrated with analogues of similar design and structure.

In recent years, our laboratory has designed and synthesized a library of nonnatural analogues of the cationic amino acids Arg and lysine (Lys) in which the α-amines are modified with an array of alkyl groups.[1–5] These analogues were designed to improve fundamental parameters relevant to developing peptide-based pharmaceuticals, which include increasing the parent peptide's binding affinity and selectivity to its requisite receptor, increasing the peptide's lipophilicity to facilitate membrane partitioning, and increasing peptide stability to serum and intracellular proteases. Recent efforts have focused on incorporating these analogues into numerous pharmaceutically relevant peptides including neurotensin (NT),[6–11] bradykinin,[12] and tripeptide based thrombin inhibitors.[13] Modification of NT's C-terminal hexapeptide fragment, NT(8–13), demonstrated full proof of concept, in that binding affinity, selectivity,[11] stability,[11,10] and lipophilicity[9,6] (including blood brain barrier partitioning)[14] were all increased.

In this paper, techniques developed in this laboratory and others[15] are combined in order to synthesize a new series of ω-alkyl-L-Arg analogues in which a methyl group attached to the *N*α amine is incorporated. This serves to expand the structures and chemistry of the nonnatural Arg and Lys series.

Synthesis of the series of *N*α-methyl-alkyl-L-Arg analogues began with enantiomerically pure, commercially available Boc-L-glutamine (Gln). The first two steps of this synthesis followed the methods of Xue and DeGrado (1995) as illustrated in Scheme 1. Briefly, Boc-L-Gln was stirred overnight with 1.2 equiv of acetic



Scheme 1.

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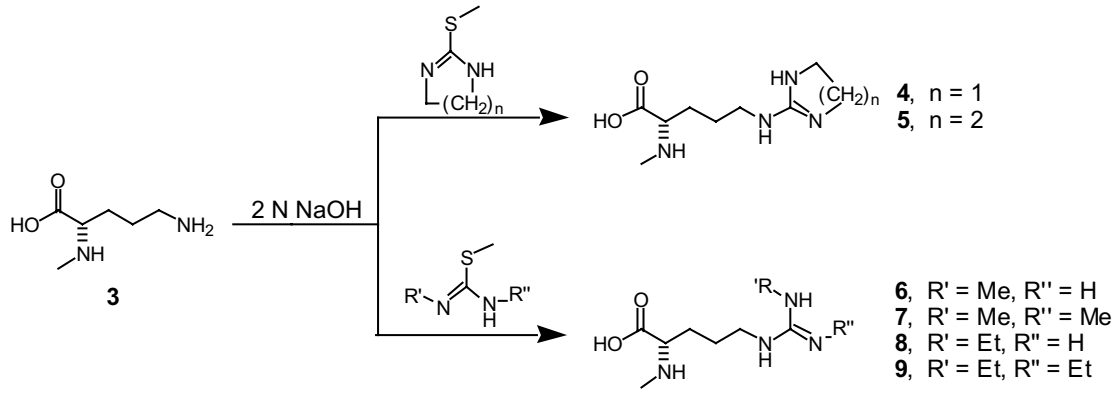

Scheme 2.

anhydride in pyridine. Following cleanup and column chromatography eluting with 10% MeOH/CH_2Cl_2, compound **1** was obtained in 80% yield as a viscous yellow oil. Compound **1** was then combined with 8 equiv of iodomethane in THF and cooled to 0 °C in an ice bath. Three equivalents of a 60% sodium hydride/mineral oil emulsion was added slowly to the mixture over 5 min. Following cleanup, compound **2** was crystallized from a 1:1 mixture of petroleum ether and ethyl acetate resulting in a 50% yield. Compound **2** (8.0 g, 33.0 mmol) was dissolved in 100 mL MeOH to which 1.0 g of PtO_2 was added under nitrogen. The hydrogenation flask was positioned on the Parr apparatus and subject to 30 psi of H_2 gas and shaken overnight. The PtO_2 was removed from the mixture via filtration and the resulting solution was evaporated to dryness under reduced pressure. The resulting oil was dissolved in 4 N HCl and stirred for 4 h at which time the resulting solution was evaporated to dryness under reduced pressure to produce compound **3**. Compound **3** (1.72 g, 9.4 mmol) was combined with 1 equiv of the requisite iodothiouronium salt and 9.4 mL of 2 N NaOH and stirred for 9 days as illustrated in Scheme 2. The resultant solution was chromatographed on a strongly acidic 50×8 Dowex ion exchange resin with sequential elution with 0.5 and 1 M NH_4OH. The resultant fractions were analyzed by TLC using a 3:1 phenol/water solvent system. The pure fractions containing the desired product were combined and concentrated to yield the desired *N*α-methyl-alkyl-L-Arg (40–90% yield). Confirmation of structure was determined with ^1H, gHMBC, and gHSQC NMR analysis. Enantiomeric purity is >95%. NMR data and optical rotation measurements of the novel amino acids are provided below:

(**3**) *N*α-Methyl-L-Orn: ^1H NMR (400 MHz, D_2O) δ 4.06 (dd, 1H, $J = 2.3, 4.83$), 3.02 (t, 2H, $J = 7.57$), 2.71 (s, 3H), 2.15–1.74 (m, 4H); ^{13}C NMR (100 MHz, D_2O, gHSQC, gHMBC) δ 170.8, 61.4, 40.2, 37.6, 27.3, 24.3.

(**4**) *N*α-Methyl-*N*ω-(CH_2CH_2)-*N*ω-L-Arg: ^1H NMR (400 MHz, D_2O) δ 3.52 (s, 4H), 3.44 (dd, 1H, $J = 1.94, 5.06$), 3.08 (t, 2H, $J = 7.07$), 2.54 (s, 3H), 1.83–1.64 (m, 2H), 1.57–1.38 (m, 2H); ^{13}C NMR (100 MHz, D_2O, gHSQC, gHMBC) δ 173.6, 160.13, 63.26, 42.88, 42.62, 31.85, 26.50, 24.09; $[\alpha]^{20}$ 21° (*c* 1, 6 N HCl).

(**5**) *N*α-Methyl-*N*ω-($CH_2CH_2CH_2$)-*N*ω-L-Arg: ^1H NMR (400 MHz, D_2O) δ 3.71 (dd, 1H, $J = 1.72, 5.12$), 3.14 (t, 4H, $J = 6.04$), 2.99 (t, 2H, $J = 7.01$), 2.56 (s, 3H), 1.9–1.63 (m, 2H), 1.73 (t, 2H, $J = 6.04$) 1.57–1.36 (m, 2H); ^{13}C NMR (100 MHz, D_2O, gHSQC, gHMBC) δ 172.18, 152.91, 61.77, 39.67, 38.30, 31.59, 25.97, 23.62, 19.56; $[\alpha]^{20}$ 25° (*c* 1, 6 N HCl).

(**6**) *N*α-Methyl-*N*ω-methyl-L-Arg: ^1H NMR (400 MHz, D_2O) δ 3.62 (dd, 1H, $J = 1.84, 5.11$), 3.03 (t, 2H, $J = 7.09$), 2.61 (s, 3H), 2.53 (s, 3H), 1.85–1.67 (m, 2H), 1.56–1.36 (m, 2H); ^{13}C NMR (100 MHz, D_2O, gHSQC, gHMBC) δ 172.77, 156.51, 62.41, 40.35, 38.35, 31.61, 27.34, 26.13, 23.68; $[\alpha]^{20}$ 29° (*c* 1, 6 N HCl).

(**7**) *N*α-Methyl-*N*ω,*N*ω-dimethyl-L-Arg: ^1H NMR (400 MHz, D_2O) δ 3.76 (dd, 1H, $J = 1.59, 5.25$), 3.06 (t, 2H, $J = 7.12$), 2.61 (s, 6H), 2.55 (s, 3H), 1.89–1.72 (m, 2H), 1.59–1.37 (m, 2H); ^{13}C NMR (100 MHz, D_2O, gHSQC, gHMBC) δ 172.4, 155.79, 62.01, 40.14, 31.6, 27.25, 26.02, 23.61; $[\alpha]^{20}$ 23° (*c* 1, 6 N HCl).

(**8**) *N*α-Methyl-*N*ω-ethyl-L-Arg: ^1H NMR (400 MHz, D_2O) δ 3.10 (t, 1H, $J = 6.35$), 3.01 (q, 4H, $J = 7.01$), 2.29 (s, 3H), 1.70–1.36 (m, 4H), 0.97 (t, 2H, $J = 7.01$); ^{13}C NMR (100 MHz, D_2O, gHSQC, gHMBC) δ 177.55, 155.55, 63.89, 40.52, 36.09, 32.17, 28.21, 24.10, 13.12; $[\alpha]^{20}$ 20° (*c* 1, 6 N HCl).

(**9**) *N*α-Methyl-*N*ω,*N*ω-diethyl-L-Arg: ^1H NMR (400 MHz, D_2O) δ 3.66 (t, 1H, $J = 5.8$), 3.07 (t, 2H, $J = 6.91$), 3.03 (q, 4H, $J = 7.23$), 2.54 (s, 3H), 1.86–1.68 (m, 2H), 1.58–1.36 (m, 2H), 0.97 (t, 6H, $J = 7.23$); ^{13}C NMR (100 MHz, D_2O, gHSQC, gHMBC) δ 171.97, 154.05, 61.57, 40.07, 36.18, 31.55, 25.89, 23.54, 13.41; $[\alpha]^{20}$ 26° (*c* 1, 6 N HCl).

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