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Progress toward a Novel C-Terminal Helix Capping Principle: Synthesis and Properties of (S)-α-(2-Aminoethyl)-Methionine

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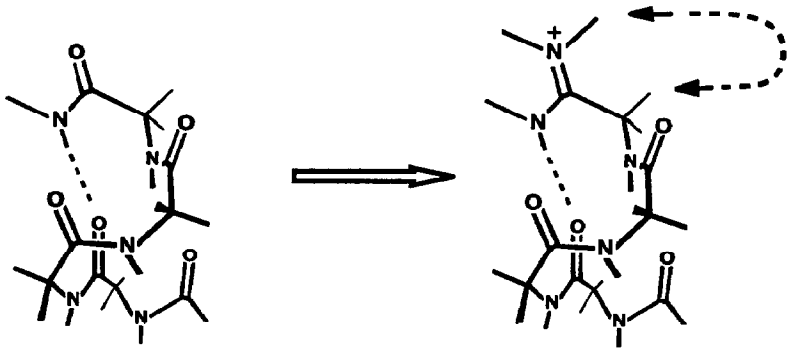
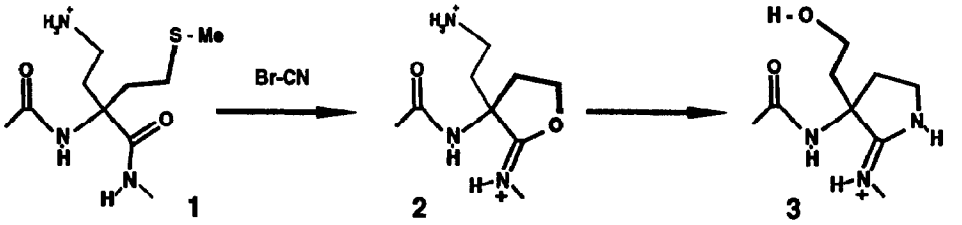
Abstract: (S)-α-(2-aminoethyl)-methionine **9** ((s)-2,4-diamino-2-(3-thiabutyl)-butanoic acid) is synthesized in three steps from 1-benzoyl-2-*tert*--btuyl-5-(3-thiabutryl)-oxazolidin-4-one. Neighboring group reactions of peptide derivatives of **9** are described.

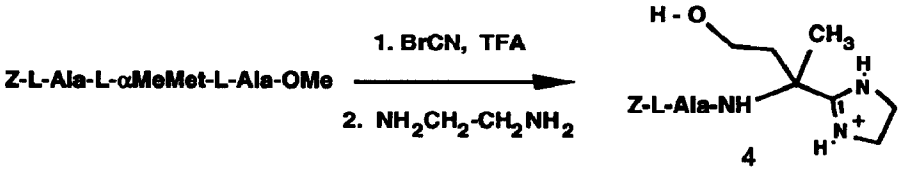
Conformational templates can provide unique insights into the properties of polypeptide helices.[1] In our previous studies the conformational constraints of pyrrolidine rings have been used to fix the orientation of N-terminal helical caps. The scope of the helix-capping principle could be extended by development of C-terminal caps. A normal peptide backbone does not permit introduction of local, small-ring conformational constraints at a helix C-terminus. We were struck by the possibility that replacement of a C-terminal amide by an amidinium residue could provide bonding linkages useful for defining cyclic constraints and place a helix-stabilizing positive charge in direct interaction with the helix dipole, unshielded by solvent.[2]



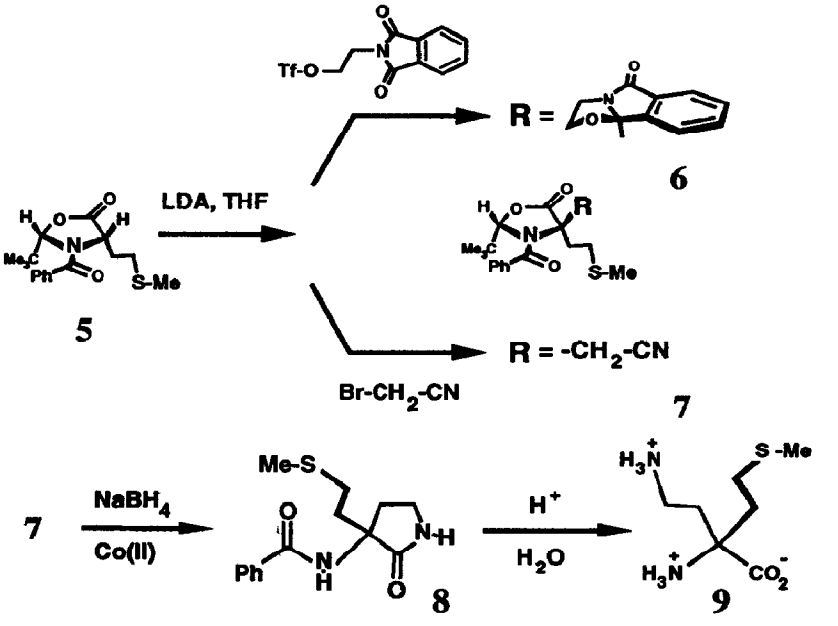
Peptide analogs in which acyclic amidines replace backbone amides have been studied previously by Eschenmoser[3] who found that the amidinium function complicates purification and enhances chiral lability at high pH. We sought routes that would generate cyclic amidines from a deblocked, fully formed peptide, allowing comparison of conformational properties with and without the cyclic constraint and charge-dipole interaction. The cleavage of methionine peptides by BrCN suggests the hypothetical sequence **1** -> **2** -> **3**, in which an iminoester **2** is trapped by a neighboring amine to generate the amidine **3**. Cleavage of methionine peptides by Br-CN is rapid only in aqueous solvents at low pH. The proposed sequence thus could fail if amine attack is not competitive with hydrolysis of **2**.



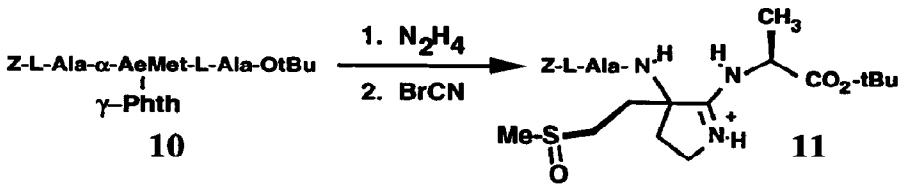
As a test of this issue and of the relevance of non-aqueous conditions, Z-L-Ala-L-α–MeMet-L-Ala-OMe was treated with BrCN in anhydrous TFA for 20 min at 25°C, followed by evaporation. Reaction with 1,2-diaminoethane generated the amidine **4** in 45 % yield. Strikingly, the analogous Met tripeptide failed to react with BrCN in 2 h under identical conditions.



Seebach and Beck have reported highly stereoselective methylation of the enolate anion derived from 1-benzoyl-2-*tert*-butyl-5-(3-thiabutyl)-oxazolidin-4-one, **5**, obtained readily from L-methionine.[4] We found that 2-phthalimidoethyl bromide or tosylate in THF failed to alkylate this enolate, and the triflate ester yields a novel product **6** in which enolate reacts at a carbonyl rather than at the primary alkyl carbon.[5] Enolate alkylation by $BrCH_2CN$ yields the expected product **7**, which is reduced by borohydride in the presence of Co(II) [6] to form an amine that spontaneously cyclizes to lactam **8**. This is hydrolyzable to the desired amino acid **9** (α–AeMet) in an overall yield of 18 % from the Seebach oxazolidinone.[7]



The hindered 2-amino-2,2-dialkylethanoic acids are well-known amino acid substitutes, and reports have dealt with their efficient chiral synthesis,[4] amide bond formation, and conformational biases in peptides.[8] The steric and inductive deactivation of the α–amino group of **9** permits unusually selective blocking of the γ–amino group. In water buffered with carbonate salts γ–phthalimido-α–AeMet was prepared in 67 % yield by reaction with N-carboethoxyphthalimide (1 equiv), and γ–Boc α–AeMet was obtained in 47 % yield with Boc dicarbonate. Unfortunately, these γ-blocked derivatives of **9** exhibit a dramatic tendency to undergo intramolecular cyclization reactions, compromising their synthetic utility. Peptides bearing a C-terminal γ–Boc-α–AeMet residue lactamized with loss of the Boc group upon attempted peptide coupling. Peptides bearing an N-terminal γ–phthalimido-α–AeMet residue underwent very slow peptide coupling with accompanying intramolecular attack of the α-amino group at a phthalimido carbonyl, forming a *bis*-lactam. Tripeptide **10** was formed in low and variable yield by a coupling of Z-L-Ala-OSu in DMSO with the tetramethylguanidine salt of γ–phthalimido-α–AeMet, followed by DCCI/HOBT coupling of the resulting dipeptide with H-L-Ala-OtBu.[9] Hydrazinolysis of the γ–phthalimido group generated complex products that were difficult to purify. Reaction of the major product of HPLC purification with excess BrCN in D_2O, pH 1-2 for 7 h at 25°C did not result in liberation of alanine, expected for a normal BrCN cleavage. Surprisingly this major product was identified by ^1H NMR, by the exceptional intensity of its MS molecular ion, and by detailed analysis of high resolution MS and MS-MS spectra as the cyclic amidinium ion **11**.[9] The ^1H NMR spectrum of **11** and of the hydrazinolysis product of **10** prior to BrCN treatment showed marked similarities, sharing resonances of Z-Ala and Ala-OtBu functions as well as corresponding resonances of 3-thiabutyl (δ 2.12 (s, 3H), 2.37-2.00 (m, 3H), m 1.92 (m,1H)) and 3-thiabutylsulfoxide functions (δ 2.73 (s, 3H), 2.71 m(1H), 2.45 (m,2H), 2.01 (m, 1H)). Resonances for the two α aminomethylene protons derived from the aminoethyl function appear in both derivatives in the range of 3.28-3.61 δ ,with chemical shifts of deshielded resonances consistent with those expected for the methylene bonded to a cyclic amidine (compare with 3.88 δ observed for the corresponding methylene of **4**). The most plausible interpretation of these observations is conversion to an amidinium ion prior to BrCN oxidation, which then takes an anomalous course at low pH in the absence of a suitable neighboring nucleophile. This interpretation implies that a BrCN-activated thioether function is not needed for the desired amidinium ion formation, which apparently occurs under acidic conditions with peptides derived from suitably constrained α-alkyl-α,γ-diaminobutanoic acids. Further experimentation is clearly needed to explore the scope of this unusually facile cyclization into the peptide backbone.



The above results establish the feasibility of the generation of cyclic amidines from polypeptides containing α,α-substituted amino acid derivatives bearing ω–functionalized alkyl chains. The extreme ease of 5-membered ring formation seen for α–AeMet derivatives materially assists the desired cyclization but also demonstrates that an exceptionally inert and therefore unconventional type of γ-amine protection will be required for practical synthetic applications. The azido group is a likely choice. Attenuation of the driving force for cyclization by replacement of 2-aminoethyl by 3-aminopropyl side chains is also planned.

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5. FAB MS for **6**: m/e 495 (MH^+); ^{13}C and ^1H NMR spectra of **6** showed the presence of the unperturbed 3-thiabutyloxazolidionone moiety with a deshielded methine hydrogen, together with a second function derived from the 2-(phthalimido)-ethyl moiety, which lacks C_2 symmetry, containing only 1 C=O ,with two CH_2s linked to O or N,. Calcd for $C_{27}H_{30}N_2O_5S{\cdot}H_2O$: C, 63.28, H, 6.25; N, 5.47; S, 6.25: Found: C, 63.33; H, 6.03; N, 5.28; S, 6.56.
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7. In dry THF (135 mL) at -78°C 6.4 g (20 mM) **5** was treated over 30 min with 24 mM LDA in hexane, then with 2.6 mL (37 mM) Br-CH_2CN, 5 h at -78°C. Workup gave **7**, 4.0 g tan needles (EtOH), 42%. Calcd for $C_{19}H_{24}N_2O_3$:C, 63.33; H, 6.66; N, 7.78; S, 8.89: Found: C, 63.07; H, 6.69; N, 8.17; S, 9.34. In MeOH (140 mL) at 25°C 2.0 g **7** (5.6 mM) was treated with 2.5 g (11 mM) $CoCl_2{\cdot}6H_2O$, then with 2.1 g (56 mM) $NaBH_4$ in small portions. After 35 min, 50 mL 6 *M* HCl was added. After extractive workup 0.70 g, 45 % of **8** was obtained as white needles from MeCN, mp 225-226°C,. MS m/e 276 (M^+) Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.43, H, 6.47; N, 10.07; S, 11.37: Found: C, 60.51; H, 6.55; N, 10.20; S, 11.37; A solution of 0.20 g, (0.72 mM) **8** in 12 mL 6 *M* HCl was refluxed for 3 h, then cooled, extracted with CH_2Cl_2, and evaporated to a white foam **9** (178 mg, 93 %) which was used without further purification. ^1H NMR (D_2O, 300 MHz) δ 3.27 (m,2H), 3.12 (m,1H), 2.68 (m,1H), 2.58 (m,1H), 2.38 (m,1H), 2.35 (t, J = 11 Hz, 2H), 2.23 (m, 1H), 2.13 (s,3H).
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9. For **10**, HPLC (50 % MeCN, 50 %0.1 % TFA, Vydac reverse phase C_{18} column) RT 15 min. FAB MS *m/e* 655 (MH^+); Calc for $C_{33}H_{43}N_4O_8S$, 655.2802, Found HRMS: 655.2839; Calc for $C_{33}H_{43}N_4O_8SNa$, 677.2620, Found: 677.2634. For **11**, HPLC (35 % MeCN, 65 %0.1 % TFA, Vydac reverse phase C_{18} column) RT 8 min; HRMS, Calc for $C_{25}H_{39}N_4O_6S$: 523.25903, Found: 523.26437. MS-MS: m/e 523 (MH^+) --> 467 (523 - C_4H_8) --> 403 (467 - CH_4SO) --> 376 (403 - C_2H_3); 523 --> 508 (523 - CH_3) --> 460 (508 - SO); 508 --> 452 (508 - C_4H_8); 508 --> 286 (508 - Z-Ala-NH_2); 523 --> 373 (523 - Z-NH) --> 317 (373 - C_4H_8). ^1H NMR for **11** (500 MHz D_2O) δ: 7.45 (m, 5H), 5.19 (s, 2H), 4.45 (m, 1H), 4.20 (m, 1H), 3.61 (d, 1H, J = 6.0 Hz), 3.35 (m, 1H), 3.16-3.02 (m, 1H), 3.02-2.88 (m, 1H), 2.73 (s, overlapping with next resonance, 3H), 2.71 (m, 1H), 2.45 (m, 2H), 2.01 (m, 1H), 1.55 (d, 3H, J = 7.0 Hz), 1.46 (s, 9H), 1.37 (d, 3H, J = 7.0 Hz).

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