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Facile syntheses of conformationally constrained analogues of lysine and homoglutamic acid

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Abstract—A facile divergent synthesis of the novel amino acid *trans*-4-aminoethyl-L-proline and *trans*-4-carboxymethyl-L-proline from commercially available *trans*-4-hydroxy-L-proline was developed. These conformationally constrained analogues of L-lysine and L-homoglutamic acid are useful proline templated amino acids (PTAAs) with potential applications in protein engineering and de novo protein design.
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The propensity of polyproline to adopt stable, helical structures in both aqueous and nonaqueous environments makes it an attractive scaffolding element suitable for exploitation in biological molecular recognition and synthetic protein engineering. To increase the diversity of proline structures available containing side chain amine and acid functionalization, we report here the development of a facile synthesis of *trans*-substituted prolines 4-carboxymethyl-L-proline[1] (Prc, **1**) and the novel amino acid 4-aminoethyl-L-proline (Pre, **2**) from commercially available *trans*-4-hydroxy-L-proline hydrochloride **3**.

In contrast to proline ring alkylation, few precedents describing aminoalkyl or carboxymethyl modification of the proline pyrrolidine side chain have been reported. Koskinen and Rapoport have developed a general method for synthesizing 4-substituted prolines from *N*-(9-(9-phenylfluorenyl))-protected glutamic acid esters.[2] Ezquerra et al. have also developed a general procedure for the synthesis of 4-substituted prolines by the regioselective alkylation of L-pyroglutamic acid derivatives followed by selective reduction of the lactam carbonyl.[1] Langlois and Rojas have extended the latter approach to the first stereoselective synthesis of the potential NMDA receptor antagonist/agonist, *trans*-4-carboxymethyl-L-proline, in six steps with a 26% overall yield from L-pyroglutamic acid.[3] Magdalengoitia and co-workers have prepared 3-substituted aminoalkyl proline derivatives (termed proline-templated amino acids or PTAAs) for use in polyproline mimetics.[4] Here, we describe an alternative improved synthesis of *trans*-4-carboxymethyl-L-proline **1** from amino acid **3** with a 64% overall yield. Also, we show that *trans*-4-aminoethyl-proline **2** could be obtained from the same starting material in 40% overall yield (Fig. 1).

4-Hydroxy-L-proline hydrochloride (**3**) was converted into its corresponding N^{α}-Boc-protected methylester[5] **4** by a two reaction, one pot treatment with methanolic HCl followed by Boc-anhydride/diisopropylethylamine in 91% overall yield. Dormoy and Castro have reported[5] the biphasic oxidation of *trans*-N^{α}-Boc-4-hydroxy-L-proline methyl ester **4** to N^{α}-Boc-4-oxo-L-proline methyl ester **5** in 94% yield using ruthenium tetroxide and

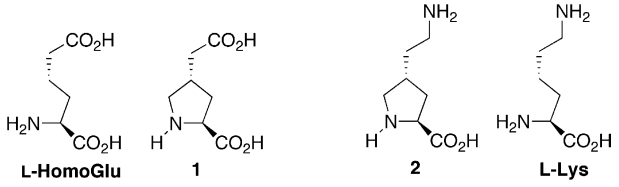

Figure 1. Structures of proline analogues **1** and **2** and their relationship to L-homoglutamic acid and L-lysine, respectively.

Keywords: Aminoethyl; Proline; Carboxymethyl; Amino acid; Polyproline.
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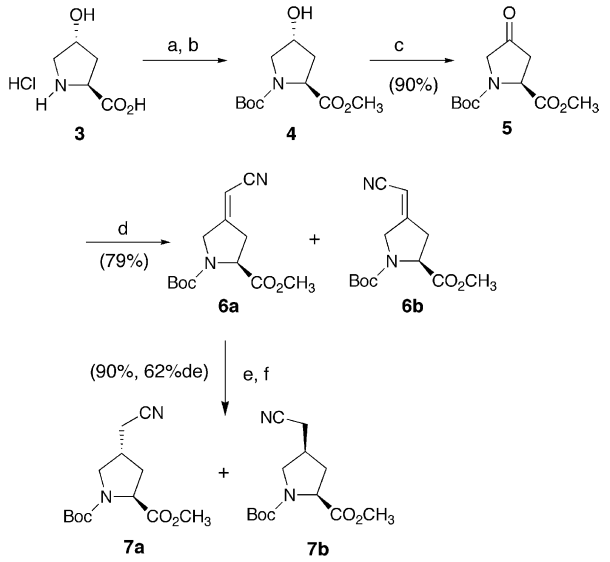


Scheme 1. Reagents and conditions: (a) MeOH/HCl, 4 Å mol. sieves, Δ (Soxhlet); (b) Boc_2O, NMM, DMF; (c) NMMO, TPAP (5 mol %), CH_2Cl_2, 4 Å mol. sieves; (d) $(EtO)_2P(O)CH_2CN$, LiHMDS, THF, 0 °C; (e) chromatographic separation; (f) $NaBH_4$, $PdCl_2$, H_2 (45 psi), MeOH.

sodium periodate. However, we were able to achieve similar yields (90%) of ketone **5** using the catalytic oxidant tetrapropylammonium perruthenate[6] (TPAP) with the stoichiometric co-oxidant *N*-methyl-morpholine-*N*-oxide (NMMO) in the presence of 4 Å molecular sieve dust (Scheme 1). Use of TPAP simplified workup as the crude product was freed of oxidant by passing the reaction mixture through a pad of silica gel. In addition to advantages with workup and purification, the potential hazard of performing preparative scale reactions with volatile RuO_4 was avoided.

The conversion of ketone **5** into cyanoolefins **6a** and **6b** was sluggish using stabilized Wittig conditions[7] with the reagent cyanomethyltriphenylphosphonium bromide and the bases sodium hydride, lithium diisopropyl amide, or lithium hexamethydisilazide. However, olefination under Horner–Wadsworth–Emmons conditions[8] (Scheme 1) proceeded smoothly at 0 °C to afford cyanoolefin **6** in 79% yield as a 2:1 mixture of (*E*) **6a** and (*Z*) **6b** isomers (based on ^1H NMR analysis of the crude product).

Unfortunately, two-dimensional NMR difference-NOE experiments could not be used to unequivocally determine the stereochemistry of compounds in this series as the protons that would normally exhibit observable NOE enhancements (H-3a, H-4, H-6) coincidentally resonated at 2.5 ppm. However, ^1H NMR and ^{13}C NMR analyses of compounds **5**, **6a**, and **6b** in $CDCl_3$ revealed that all three compounds exist as a 45:55 mixtures of, respectively, cis and trans urethane rotamers at room temperature. Furthermore, the stereochemistry assignment of compounds **6a** and **6b** were made based on coupling constant analysis of the vinyl proton and the diastereotopic methylene protons on C-3 and comparison to chemical shifts of related compounds.[1–3] The fixed geometric orientation of the anisotropic shielding cone of the nitrile of **6a** resulted in pronounced chemical shift differences in the NMR resonances of the C-3 and C-5 ring methylenes relative to the parent ketone that also facilitated discrimination of the regiochemistry associated with each isomer (see Supplementary data).

The exocyclic double bond of cyanoolefin **6a** was hydrogenated over sodium borohydride-reduced palladium chloride to afford the cyanomethyl derivatives **7a** and **7b** in 90% yield as a mixture of cis and trans diastereomers, with the trans isomer comprising ~80% of the mixture (62% diastereomeric excess). The stereochemical assignments for *anti* isomer **7a** and *syn* isomer **7b** were made based on comparison to literature examples of L-proline ester derivatives substituted at C-4 and by NMR chemical shift analyses. Depicted in Figure 2 is the structure of the global energy minimum conformation of **7a** and **7b** as calculated using AM1 semi-empirical methods. For compound **7b**, the energy-minimized structure clearly shows the proximal orientation of the nitrile to the methyl ester. Due to their *syn* relationship, not only are these two functional groups in potential van der Waals contact as evidenced by the presence of an ensemble of methyl ester resonances (conformers), but the resonance of the methyl ester is significantly downfield shifted due to the deshielding effect of nitrile anisotropy cone. In contrast, an *anti* stereochemical configuration for **7a** was deduced as the methyl ester resonance is neither influenced by the nitrile anisotropy cone, nor appears as multiple conformers on the NMR timescale.

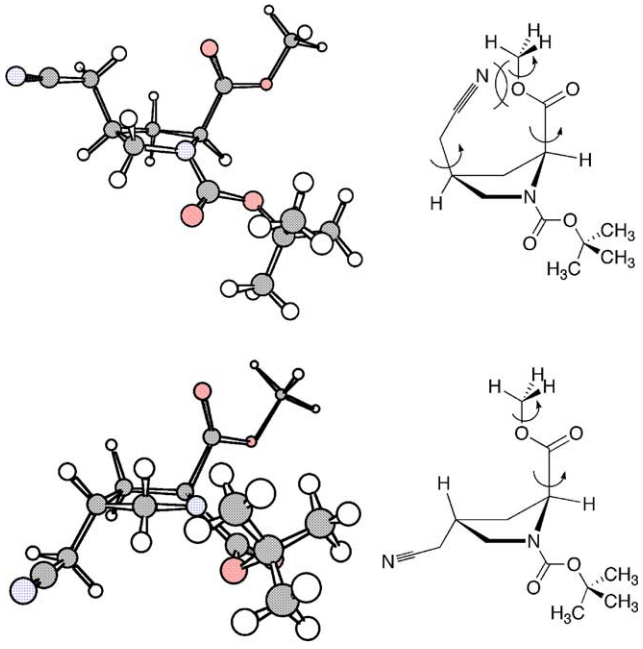
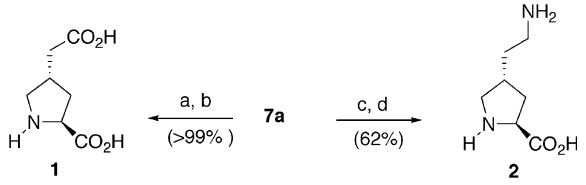


Figure 2. AM1 energy-minimized structure of **7a** (bottom) and **7b** (top) depicting the relative orientations of the cyanomethyl and methyl ester functional groups.



Scheme 2. Reagents and conditions: (a) 2 N NaOH; (b) TFA/DCM; (c) H_2/Pt_2O, EtOH/AcOH/H_2O (4:1:1 v/v/v); (d) 6 N HCl, propylene oxide, Dowex-50 ion-exchange chromatography.

Cyanomethyl derivative **7a** was converted quantitatively to the Boc-deprotected diacid **1** by alkaline hydrolysis 1 N NaOH and subsequent treatment with TFA (52% overall yield of the TFA salt from **3**) (Scheme 2). This compound is a constrained version of L-homoglutamic acid, and has identical spectroscopic data with reported values.[3] Moreover, the TFA salt of the novel *trans* 4-aminoethyl-L-proline **2** conformationally constrained analogue of L-lysine was also obtained through hydrogenation of **7a** on platinum oxide in 63% yield (40% overall yield from **3**).

In summary, we have described new and facile syntheses to both 4-carboxymethyl-L-proline **1** and 4-aminoethyl-L-proline **2** in four steps starting from the same commercially available 4-hydroxy-L-proline precursor **3** with excellent overall yields. These conformationally constrained analogues of L-homoglutamic acid and L-lysine will be of great utility in designing new polypeptides derived from the proline II motif.

Acknowledgments

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Supplementary data

Experimental procedures and characterization data for compounds are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.093.

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