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Synthesis and Structure Determination of (2*S*, 2′*S*)-3-Phenyl-2-(pyrrolidin-2′-yl)-propionic Acid

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ABSTRACT

Aβ^2,β^3-homoproline derivative, (2*S*, 2′*S*)-3-phenyl-2-(pyrrolidin-2′-yl)propionic acid, was synthesized starting from L-proline. After preparation of the (4*S*, 4a*S*)-4-benzyl-4a,5,6,7-tetrahydro-pyrrolo-[1,2-c]pyrimidine-1,3-dione under a mild condition, the absolute configuration of target compound was assigned using 2D H-H COSY and H-H NOESY technologies.

Key Words: Synthesis; β^2,β^3–Homoproline derivative; (2*S*, 2′*S*)-3-Phenyl-2-(pyrrolidin-2′-yl)propionic acid; (4*S*, 4a*S*)-4-Benzyl-4a,-5,6,7-tetrahydro-pyrrolo-[1,2-c]-pyrimidine-1,3-dione.

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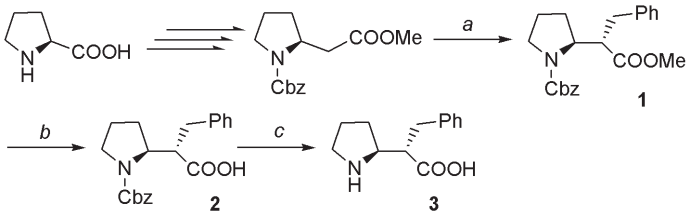
β-Peptides have particular appeal for extending our understanding of protein structure and stabilization into the realm of folded, nonbiological polymers, because β-amino acids represent the smallest step away from α-amino acids in ''backbone space''.[1] β-Amino acids, as the constructing units of β-peptides, have been invoked a great deal of synthetic interests.[2] Because proline, as the only proteinogenic amino acid with a secondary amino group, imparts special conformations on peptide backbone, its homologues, β^2- and β^3-homoprolines, have been synthesized to research their effects on the secondary structure of β-peptides.[3] Since C^2, C^3-disubstituted amino acids shown a different character in β-peptide self-assembly,[1] it is very interesting to synthesize β^2, β^3-homoproline homologues to explore their effects on β-peptide backbone. Here we report the synthesis and structure determination of (2*S*, 2′*S*)-3-phenyl-2-(pyrrolidin-2′-yl)propionic acid (compound **3**), a β^2, β^3-homoproline with highly substitution.

The target compound was synthesized starting from L-proline. After protecting the imino group of L-proline with benzyloxycarbonyl group (Cbz-), the precursor for benzylation was obtained through Arndt-Eistert homologation of the corresponding diazo ketone according to the Lit.[4] Benzylation using LHDMS occurred stereo-selectively and only one diastereomer (compound **1**) was obtained after silica gel column.[5] Following the hydrolysis with lithium hydroxide and deprotection on Pd-C, the target compound **3** was obtained.[6] (Sch. 1)

To determine the absolute configuration of compound **3**, we prepared a uracil derivative **4**, (4*S*, 4a*S*)-4-benzyl-4a,5,6,7-tetrahydropyrrolo[1,2-c]pyrimidine-1, 3-dione, under a mild condition to minimize the possibilities of racemization.[7] The initial formation of ureide can be anticipated according to the Lit.[8] And the subsequent formation of uracil derivatives may result as a condensation of the imino group with the ureide following by deamination. Compared to the formation of azabicyclo[3,2,0]heptan-7-one catalyzed by triethylamine (MeCN, 80°C),[9]



a. LHDMS, $PhCH_2Br$, -78 °C; b. LiOH, THF / MeOH / H_2O; c. 10 % Pd-C, H_2.

Scheme 1.

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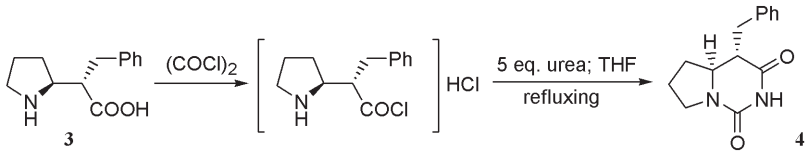

Scheme 2.

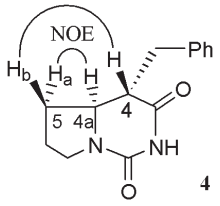

Figure 1.

our method provided not only a milder acidic condition to minimize the possibilities of racemization but also a modest yield (63%). And it also shown a possible synthetic approach to tetrahydropyrimidine, an important species for research the radical reactions involving DNA bases.[10] (Sch. 2)

The absolute configuration of compound **4** was assigned using 2D H-H COSY and H-H NOESY technologies.[11] The abstract signals of H-4, H-4a, and H-5 were determined according to the 2D H-H COSY spectrum, and then the H-5_a peak was differentiated according to the NOE effects with H-4a shown in the 2D H-H NOSEY spectrum. The other observed NOE effects between H-5_b and H-4 indicated the proximity of the two protons. These results support an anti-periplanar configuration of compound **4**. (Fig. 1) Therefore, the (2*S*, 2′*S*) configuration of compound **3** was determined.

In conclusion, we synthesized (2*S*, 2′*S*)-3-phenyl-2-(pyrrolidin-2′-yl)propionic acid stereo-selectively. To determination the absolute configuration, we developed a new mild method to prepare the corresponding uracil derivatives. The (2*S*, 2′*S*) configuration of target compound **3** was confirmed by H-H NOESY.

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5. Compound **1**: oil; yield: 70%. $[\alpha]_D^{20}$, −1.65 ($c = 0.5$, $CHCl_3$). IR (cm^{-1}, $CHCl_3$): 1731, 1699. HRMS, Cacld. for $C_{22}H_{25}NO_4$: 367.1784. Found: 367.1784. Compound **2**: white powder; m.p. 94–95°C. $[\alpha]_D^{20}$, −1.45 ($c = 0.5$, $CHCl_3$). IR (cm^{-1}, $CHCl_3$): 3062, 3031, 2973, 2887, 1700. Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.19; H, 6.49; N, 4.05. For both two compounds, the existence of rotator is observed in their NMR spectra.
6. Compound **3**: white powder, m.p. 248–249°C (Dec.). $[\alpha]_D^{20}$, −7.8 ($c = 0.1$, H_2O). IR (cm^{-1}, KBr): 3028, 2973, 2936, 1639, 1594. ^1H NMR (δ, D_2O, 400 MHz): 7.28–7.16 (m, 5H), 3.47–3.41 (m, 1H), 3.27–2.18 (m, 2H), 2.90–2.82 (m, 1H), 2.77–2.71 (m, 1H), 2.13–1.27 (m, 1H), 1.98–1.93 (m, 1H), 1.91–1.85 (m, 1H), 1.65–1.59 (m, 1H). ^{13}C NMR (δ, D_2O, 400 MHz): 177.57, 137.58, 127.60, 125.57, 60.45, 50.57, 44.34, 34.97, 26.65, 22.05. Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.87; H, 7.81; N, 6.45.
7. Compound **4**: oil, yield, 63 %. $[\alpha]_D^{20}$, −3.0° ($c = 0.2$, EtOAc). IR (cm^{-1}, $CHCl_3$): 1703, 1698, 1693. ^1H NMR (δ, $CDCl_3$, 300 MHz):

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7.50 (br, 1H), 7.29–7.18 (m, 5H), 3.57–3.53 (m, 1H), 3.45–3.38 (m, 2H), 3.28–3.24 (dd, 1H, $J = 5.0$, 14.5 Hz), 3.06–3.01 (dd, 1H, $J = 6.1$, 14.5 Hz), 2.64–2.58 (m, 1H), 2.03–1.94 (m, 2H), 1.87–1.69 (m, 1H), 1.40–1.34 (m, 1H). ^{13}C NMR (δ, $CDCl_3$, 400 MHz): 172.07, 150.55, 138.52, 129.68, 129.01, 127.21, 58.09, 48.49, 45.04, 33.12, 32.89, 23.65. HRMS, Cacld. for $C_{14}H_{16}N_2O_2$: 244.1212. Found: 244.1212.

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11. 2D H-H COSY (δ, $CDCl_3$, 500 MHz): 3.49–3.48 (m, H-4a); 2.65–2.57 (m, H-4); 2.08–1.98 (m, 1H, H-5); 1.28–1.23 (m, 1H, H-5). 2D H-H NOESY (δ, $CDCl_3$, 500 MHz): 2.08–1.98 (m, H-5_a); 1.28–1.23 (m, H-5_b). H-5_a of **4** was differentiated from the two protons of 5-position by the observed NOE effects with H-4a. The other observed NOE effects between H-4 and H-5_b supported the (4*S*, 4a*S*) configuration of **4**.

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