3,4-Methano-β-Proline: A Conformationally Constrained β-Amino Acid

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Abstract: An enantiomerically pure, conformationally constrained β-proline derivative, 3,4-methano-β-proline, was synthesized starting with a readily available bicyclic lactone by using a straightforward synthetic route.

Key words: 3,4-methano-β-proline, conformationally constrained β-amino acid, enantioselective synthesis

Conformationally constrained cyclic β-amino acids are useful building blocks for the preparation of β-peptide foldamers.[1] Secondary structures of β-peptide oligomers are governed by conformational preferences of the component monomers. For example, β-peptides that are composed of five-membered-ring β-amino acids (ACPC[2] or APC,[3] Figure 1) adopt 12-helical β-peptide structures, whereas analogous oligomers arising from six-membered-ring β-amino acids (ACHC) display stable 14-helical structures.[4]

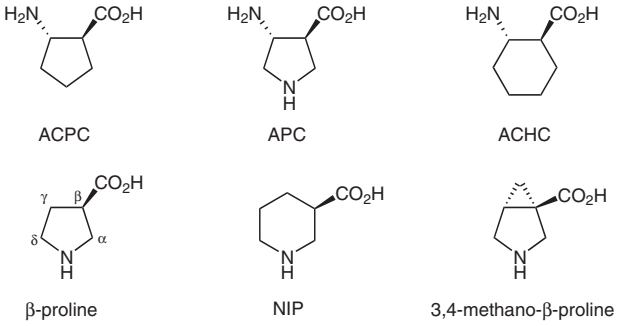

Figure 1 Structures of cyclic β-amino acids

β-Proline (pyrrolidine-3-carboxylic acid, PCA) and nipecotic acid (NIP) are examples of types of cyclic β-amino acids that are known to form oligomers with unique secondary structures.[5] Due to the lack of hydrogen-bonding donor sites in their backbones, oligomers arising from these monomers possess nonhydrogen-bonded helical structures that resemble natural polyproline helices. The results of a theoretical study by Carson and coworkers suggest that the nature of the substitution patterns of the side chains of β-prolines should influence the conformational properties of the resulting oligomers.[6] Indeed, Gellman and his coworkers have proven that the oligomers composed of δ,δ-disubstituted β-proline monomers can preferentially form *cis*-amide conformations that display different CD signals than those of poly-β-prolines.[7]

These findings suggest that β-proline analogues with different substitution patterns could give rise to new foldamer scaffolds with unique conformational properties. Systematic conformational studies exploring this issue require the availability of β-proline monomers with diverse substitution patterns. However, only a few reports exist describing the synthesis of substituted β-prolines.[8] In addition, β-proline has received a great deal of attention recently owing to its role as an organocatalyst in enantioselective C–C bond-forming reactions. For example, β-proline and its derivatives have been used as effecient catalysts for *anti*-selective Mannich-type reactions of aldehydes and ketones with imines.[9] Consequently, properly designed β-proline derivatives containing an array of different substitution patterns could have unique applications in the area of organocatalysis.

Stimulated by the recent dual interest in β-proline derivatives, we have designed a new, conformationally constrained, cyclic β-amino acid skeleton found in 3,4-methano-β-proline, where the methano bridge is located at C_β- and C_γ-positions of the amino acid. The structure of 3,4-methano-β-proline resembles that of both β-proline and NIP, but it is unique in that the pyrrrolidine-ring puckering is highly restricted. Owing to this structural feature, 3,4-methano-β-proline should serve as useful substance to explore the conformational space void that exists currently in peptidomimetic studies. In addition, it is anticipated that this substance will have unique organocatalytic properties that derive from the nucleophilicity and/or basicity of the nitrogen and orientation of the carboxylic acid group that differ from those of β-proline.[10]

Although a considerable effort has been given to the synthesis of natural and unnatural methano-α-prolines,[11] only a few reports exist describing the preparation of methano-β-prolines.[12] Below we present the results of an investigation that has led to the development of a straightforward route for the synthesis of the Boc-protected (3*R*,4*R*)-methano-β-proline (**1**, Figure 2) in enatiomerically pure form. Importantly, we have found that the approach can be applied to the preparation of the Boc-β-proline (**2**).[13]

The retrosynthetic plan outlined in Scheme 1 suggests that both Boc-(3*R*,4*R*)-methano-β-proline (**1**) and Boc-β-proline (**2**) can be generated from the respective bicyclic lactones (–)-**3** and (+)-**3**. The starting, enantiomerically pure

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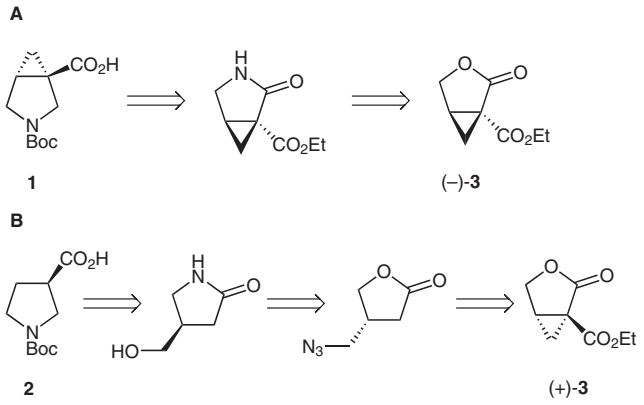
Figure 2 Structure of (3*R*,4*R*)-methano-β-proline (**1**) and β-proline (**2**)



Scheme 1 Retrosynthetic analysis

bicyclic lactones should be readily accessed on multigram scales by using the known[14] one-step synthetic protocol. Importantly, the carbon skeleton and all of the sterogenic centers of the target compound **1** already exist in the starting bicyclic lactone (–)-**3** (Scheme 1, A).

As shown in Scheme 1 (B), the route to β-proline **2** begins with the opposite enantiomer of the same bicyclic lactone (+)-**3** and employs selective manipulation of cyclopropane ring. For conformational analysis of the oligomer that is composed of the (3*R*,4*R*)-methano-β-proline monomer, the β-proline with *R*-configuration is needed as a reference, which will give the β-proline oligomer with the same helical sense as that of (3*R*,4*R*)-methano-β-proline. To synthesize β-proline with *R*-configuration, the bicyclic lactone (+)-**3**, the opposite enantiomer of (–)-**3**, is needed.

The sequence used to prepare enantiomerically pure Boc-(3*R*,4*R*)-methano-β-proline (**1**) is given in Scheme 2. The bicyclic γ-lactone ring in (–)-**3** was opened by treatment with TMSBr and ethanol to yield the bromide **4** (60%), which was then reacted with NaN_3 in DMF at 70 °C for 5 hours to generate the corresponding azide **5** (83%). Although reduction of the azide **5** can be accomplished using standard hydrogenation conditions (H_2, 10% Pd/C), the reaction is not reproducible on a large scale. As a result, the azide reduction was carried out using Ph_3P in THF–H_2O at reflux to furnish the desired γ-lactam **6** in 80% yield. The amide nitrogen was Boc-protected (forming **7**) prior to further manipulations. Initial attempts to chemoselectively reduce the amide carbonyl group in **7** were not successful. For example, no reaction was observed when **7** was treated 9-BBN, which is typically used for selective reduction of an amide group in the presence of an ester moiety.[15] Moreover, reaction of **7** with $BH_3{\cdot}SMe_2$ was sluggish at room temperature and when performed under refluxing THF conditions, the yield for the desired bicyclic pyrrolidine was only 15% (alcohol **8** was obtained as a major product in 57% yield). Although TLC analysis showed that amide reduction preceded ester reduction under these conditions, ester reduction could not be avoided. Therefore, complete reduction of both the lactam and ester groups in **7** was accomplished by using an excess of $BH_3{\cdot}SMe_2$ in refluxing THF. This process provided **8** in an 85% yield. Several methods were screened to transform **8** to the target carboxylic acid **1**. Reactions of **8** with Jones reagent or PDC were not clean. Although oxidation of **8** with $RuCl_3$ and $NaIO_4$ provided the desired acid **1** when carried out on a milligram scale,[16] the process was not efficient when performed on a gram scale. A two-step oxidation process was more reliable.

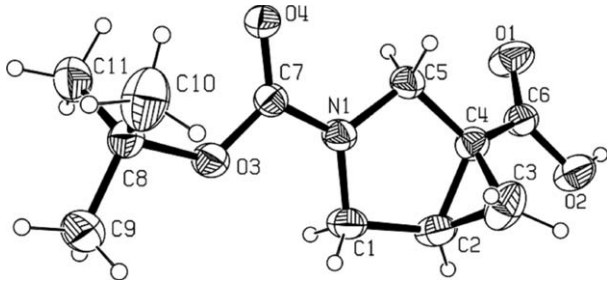
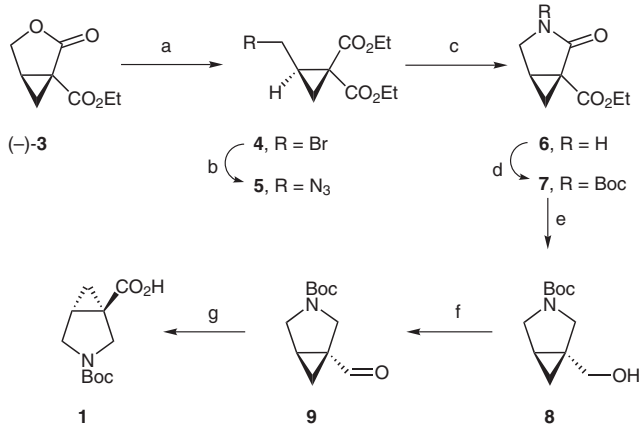


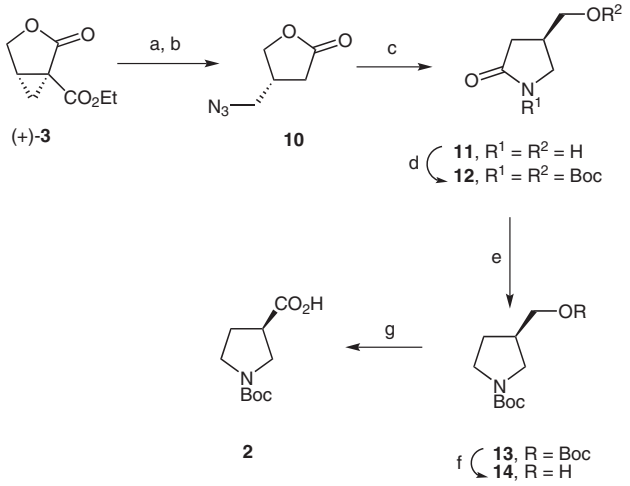
Figure 3 ORTEP plot of Boc-(3*R*,4*R*)-methano-β-proline (**1**) with 30% thermal ellipsoid probability.



Scheme 2 *Reagents and conditions*: (a) TMSBr (1.3 equiv), EtOH–CH_2Cl_2 (1:10), 0 °C to r.t., 24 h, 60%; (b) NaN_3 (8 equiv), 15-crown-5, DMF, 70 °C, 5 h, 83%; (c) Ph_3P (1.3 equiv), THF–H_2O (8:1), r.t., 3 h, and then 60 °C, 36 h, 80%; (d) $(Boc)_2O$ (2 equiv), Et_3N, DMAP, CH_2Cl_2, r.t., 2 h, 87%; (e) $BH_3{\cdot}SMe_2$ (7.5 equiv), THF, 55 °C, 2 h, 85%; (f) IBX (2.5 equiv), DMSO, r.t., 6 h, 83%; (g) $NaClO_2$, KH_2PO_4, *t*-BuOH, 2-methylbut-2-ene, H_2O, r.t., overnight, 70%.

Specifically, treatment of **8** with IBX proceeded smoothly to form aldehyde **9** (83%),[17] which was then converted into Boc-(3*R*,4*R*)-methano-β-proline (**1**, 70%, white crystalline solid) by treatment with $NaClO_2$. The methyl ester of Boc-(3*R*,4*R*)-methano-β-proline was prepared in order to determine the enantiomeric purity (>99%) by using chiral HPLC analysis.[18] Since the enantiomeric purity of

starting (–)-**3** is 99%, the configurations at all of the chiral centers are completely retained in this sequence. The crystal structure of **1** is shown in Figure 3,[19] and the absolute configuration of **1** was confirmed by using the Flack method.[20]



Scheme 3 *Reagents and conditions*: (a) NaN_3 (4 equiv), AcOH (0.1 equiv), Et_3N (0.1 equiv), DMSO, 75 °C, 4 h; (b) 6 N HCl, 120 °C, 18 h, 58% (in 2 steps); (c) H_2, 10% Pd/C, MeOH, r.t., overnight, 85%; (d) $(Boc)_2O$ (2.5 equiv), Et_3N, DMAP, CH_2Cl_2, r.t., 6 h, 74%; (e) $BH_3{\cdot}SMe_2$ (2.5 equiv), THF, 55 °C, 2 h, 98%; (f) KOH (4.5 equiv), MeOH, r.t., 18 h, 98%; (g) $RuCl_3$ (10 mol%), $NaIO_4$ (4 equiv), MeCN–CCl_4–H_2O (2:2:3), 0 °C to r.t., 2 h, 79%.

The enantiomerically pure β-proline **2** was synthesized starting with the bicyclic lactone (+)-**3** (Scheme 3). Opening of the cyclopropane ring in this substance was performed by using sodium azide to obtain the lactone intermediate which was then treated with 6 N HCl at 120 °C for 18 hours to produce the β-azidomethyl γ-butyrolactone (**10**) in 58% overall yield. After hydrogenolysis of the azide group in **10** by using H_2 and 10% Pd/C in MeOH, and stirring the resulting mixture overnight, the known γ-lactam **11** was generated as a white solid in 85% yield. Both the amide nitrogen and the primary alcohol of **11** were protected with Boc groups by treatment with $(Boc)_2O$ and DMAP to give **12** as a white solid in 74% yield. Reduction of lactam **12** with $BH_3{\cdot}SMe_2$ in refluxing THF efficiently provided **13** as an oil in 98% yield. Selective *O*-Boc deprotection **13** was performed by using methanolic KOH to furnish alcohol **14** in a quantitative yield. The $RuCl_3/NaIO_4$ oxidation of the alcohol moiety in **14** was successfully carried out to generate the desired Boc-protected amino acid **2** as a white solid in 79% yield. The enantiomeric purity of **2** was determined to be >99% by using chiral-HPLC.[21]

In summary, a new conformationally restricted β-proline derivative, Boc-(3*R*,4*R*)-methano-β-proline (**1**), has been synthesized in enantiomerically pure form in seven steps and a 17% overall yield starting with the readily available bicyclic lactone (–)-**3**. Boc-(*R*)-β-proline (**2**) was also prepared from the enantiomerically pure bicyclic lactone (+)-**3** in 28% overall yield. The organocatalytic properties of 3,4-methano-β-proline **1** and the effects of conformational constraints on the secondary structure of the β-proline oligomer derived from **1** are currently being investigated.

All compounds were characterized by analysis of their ^1H NMR, ^{13}C NMR, and HRMS properties.

Compound 1

White solid; mp 114–117 °C; $[\alpha]_D^{25}$ –87.3 (*c* 1.03, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 5.0 Hz, 3 H), 1.42 (s, 9 H), 1.64 (dd, *J* = 4.7, 8.2 Hz, 1 H), 2.10 (br, s, 1 H), 3.40–3.72 (m, 4 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 19.01/19.2 (1 CH_2), 27.7 (1 CH), 28.4 (3 CH_3), 28.9/29.7 (C), 47.0/47.2 (1 CH_2), 47.3/47.5 (1 CH_2), 79.9/80.0 (C), 154.9 (C), 178.2 (C). ESI-HRMS: *m/z* calcd for $[M + K]^+$ $C_{11}H_{17}NO_4K$: 266.0789; found: 266.0711.

Compound 2

White solid; mp 141–142 °C, $[\alpha]_D^{23}$ –13.8 (*c* 1.00, $CHCl_3$) { ref 13g: mp 139–141 °C; $[\alpha]_D^{22}$ –14.6 (*c* 1.00, $CHCl_3$)}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 2.13 (m, 2 H), 3.05 (m, 1 H), 3.34–3.57 (m, 4 H), 10.12 (br s, 1 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 28.1/28.7 (1 CH_2), 28.4 (3 CH_3), 42.2/43.0 (1 CH), 45.0/45.3 (1 CH_2), 47.8 (1 CH_2), 79.8 (C), 154.5 (C), 178.0 (C). HRMS (EI, pos. mode): *m/z* calcd for $[M]^+$ $C_{10}H_{17}NO_4$: 215.1158; found: 215.1159.

Acknowledgment

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(18) **HPLC Data for Boc-(3*R*,4*R*)-Methano-β-proline Methyl Ester**
t_R = 13.622 (min), area = 100%; OJ-H, IPA–*n*-hexane = 5:95; flow rate = 0.4 mL/min, 25 °C, λ = 220 nm.
(19) **Crystal Data for Compound 1**
$C_{11}H_{17}NO_4$, crystal size: 0.10 × 0.20 × 0.20 mm^3, M_r = 227.26 g mol^{-1}, monoclinic, space group *P*21, λ = 0.71073 Å, *a* = 6.1437 (8) Å, *b* = 11.3449 (17) Å, *c* = 9.3146 (13) Å, α = 90, β = 104.369 (10), γ = 90, *V* = 628. 92 (15) Å^3, *Z* = 2, ρ_{calcd} = 1.200 g cm^{-3}, μ = 0.091 min^{-1}, *T* = 293 (2) K, θ range = 3.6–33.2°; reflections collected: 10063, independent: 4247 (R_{int} = 0.037). The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0432, wR_2 = 0.1196 [$I > 2\sigma$ (I)]; maximal residual electron density: 0.12 e Å^{-3}. CCDC 710057 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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(21) **HPLC Data for Boc-(3*R*)-β-proline Methyl Ester**
t_R = 20.621 (min), area = 100%; racemic Boc-β-proline methyl ester, t_R = 15.985, 20.824 (min). OJ-H, IPA–*n*-hexane = 5:95; flow rate = 0.4 mL/min, 25 °C, λ = 220 nm.