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Synthesis of Racemic δ,δ-Dimethylproline Derivatives

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A versatile methodology for the preparation of racemic δ,δ-dimethylproline derivatives has been developed. Methyl *N*-Boc-δ,δ-dimethylprolinate was synthesized from a β-amino acid in six steps and 55 % overall yield. The route is amenable to the preparation of a broad range of δ,δ-disubstituted prolines by starting with the adequate β-amino acids. In addition, one of the intermediate compounds in the synthetic route has been used for the preparation of a δ,δ-dimethylproline derivative that is substituted at the β-position with a phenyl group. This has been achieved by coupling phenylboronic acid with a regioselectively generated vinyl triflate followed by a stereoselective hydrogenation.

Introduction

Proline is the only coded amino acid that exhibits a restricted conformational flexibility due to its cyclic structure. This unique structural feature explains its tendency to act as a β-turn inductor in peptides and proteins[1] as well as its ability to form *cis* peptide bonds.[2] These properties are the basis for the important role of proline in biology. Indeed, peptide turns are known to be propitious sites for molecular recognition,[3] and the *cis*/*trans* isomerization of a prolyl peptide bond is considered to be a molecular switch that controls important biological processes.[4]

Among proline analogues,[5] those that incorporate substituents at the δ-carbon atom are receiving increasing attention. Such analogues are able to stabilize the *cis* state of the peptide bond that involves the pyrrolidine nitrogen atom.[6] The *cis*/*trans* equilibrium of prolyl peptide bonds is governed by the different steric interactions established between the acyl substituent on the nitrogen atom and the α- or δ-positions of the pyrrolidine ring (see Figure 1). In the case of proline, the α-position is sterically more crowded than the δ-position, and, therefore, the *trans* prolyl amide geometry is preferred. Increasing the steric hindrance around the δ-carbon atom translates into a higher preference for the prolyl peptide bond to accommodate the *cis* arrangement. Thus, δ,δ-dimethylproline was reported to generate peptides with the prolyl amide bond locked in the *cis* geometry (see Figure 1).[7] Accordingly, δ,δ-dimethylproline is being used as a probe to explore the three-dimensional structure and folding pathways of therapeutic proteins,[4d,7,8] the mechanism of important receptors in neuroscience,[9] and the bioactive conformations of peptides.[7,10]

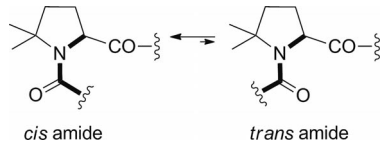

Figure 1. The *cis*/*trans* isomerism of the amide bond, which involves the pyrrolidine nitrogen, when δ,δ-dimethylproline is incorporated into a peptide chain.

For example, the rational replacement of a proline residue in bovine pancreatic ribonuclease A by δ,δ-dimethylproline led to faster folding and enhanced conformational stability of the protein.[8] Additionally, δ,δ-dimethylproline has been shown to be an excellent probe to build an experimental model of ion-channel gating for the 5-HT_3 receptor, which belongs to a cys-loop superfamily of neurotransmitter-gated ion channels.[9] The mutagenesis of a proline residue in a receptor loop with different analogues revealed that only modified prolines that favor the *cis* amide geometry produced functional channels.[9d] Remarkably, a ca. 60-fold increase in receptor activation was achieved with δ,δ-dimethylproline.[9d] Accordingly, the authors proposed that the *trans*-to-*cis* isomerization of a single proline residue provides the switch to interconvert the closed and open states of the channel. Moreover, some applications of δ,δ-dimethylproline have been reported such as in the design of bioactive compounds for the treatment of pain,[11] neurodegenerative disorders,[12] or bacterial infections.[13]

Despite its remarkable value, only few synthetic strategies have been developed for the preparation of δ,δ-dimethylproline (see Scheme 1). Some procedures make use of dimethyl-substituted pyrrolidine precursors, in which the carboxylic acid moiety is further installed. Thus, this strategy provides access to a racemic amino acid. In particular,

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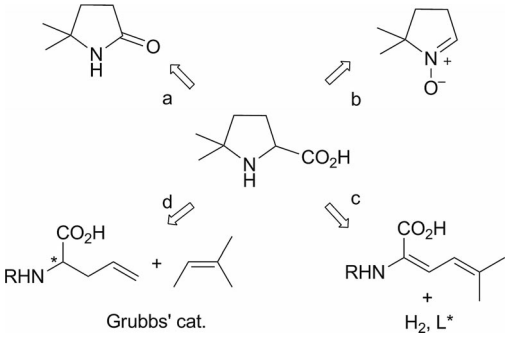
the pyrrolidone depicted in Scheme 1a was reported to undergo a selective reduction to form a Δ^1-pyrroline that was cyanated and hydrolyzed to the corresponding proline.[14] Alternatively, the substituted nitrone in Scheme 1b underwent an acid-catalyzed addition of cyanide to yield the *N*-hydroxy nitrile, which was further hydrolyzed and reduced to the amino acid,[15] along with the concomitant generation of a byproduct arising from an acid-catalyzed methyl migration from the δ-carbon atom to the pyrrolidine nitrogen atom.[10b,12] The racemic δ,δ-dimethylproline obtained in this manner was chemically resolved[7] by fractional crystallization of the diastereomeric tartrates. The resolution process delivered δ,δ-dimethyl-L-proline with > 98% enantiomeric purity. Additionally, the synthesis of enantioenriched δ,δ-dimethylproline has been achieved through an intramolecular cyclization procedure that involves the N–Cδ bond formation.[16] Specifically, a chiral prenylglycine intermediate, which was generated from two different precursors (see Scheme 1c and d), rendered δ,δ-dimethylproline in 98% *ee* upon heating under acidic conditions.[16]



Scheme 1. Reported strategies for the synthesis of δ,δ-dimethylproline.

Herein, we report an alternative preparation for δ,δ-dimethylproline through an intramolecular cyclization procedure that involves the formation of the N–Cα bond and makes use of a β-amino acid as the starting material.

Results and Discussion

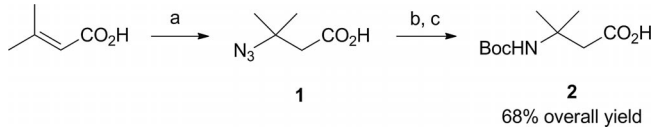
We have recently shown that a β-amino acid can be used as a suitable precursor to build the proline skeleton. Specifically, the proline analogue that contains a phenyl substituent attached to the pyrrolidine β-carbon atom was prepared from β-alanine in a highly efficient manner.[17] The starting β-amino acid was converted into an α-diazo-β-oxo ester derivative that underwent an intramolecular N–H insertion reaction upon generation of a metal carbenoid. The resulting oxoproline was further modified at the β-carbon atom to incorporate the desired aromatic functionality.[17]

We decided to explore whether δ,δ-dimethylproline could be synthesized by applying the aforementioned approach. In this case, the required β-amino acid (i.e., 3-amino-3-methylbutanoic acid; see Scheme 2) is not as readily available as β-alanine.

Scheme 2. Structure of the β-amino acid selected as a precursor of δ,δ-dimethylproline.

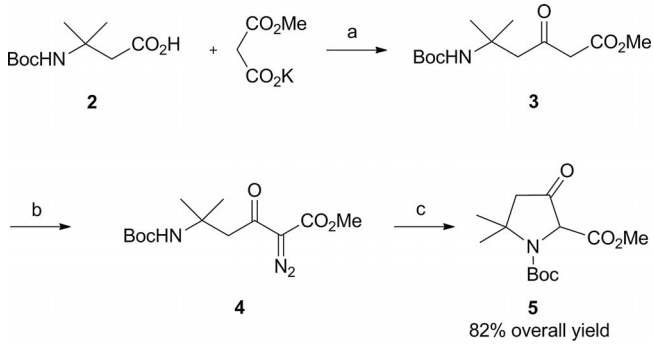
As this compound exhibits a geminal substitution pattern at the β-carbon atom (C-3), it belongs to the family of $\beta^{3,3}$-amino acids. These amino acids are targets of interest for the preparation of structurally defined oligomers as well as building blocks for bioactive molecules. Therefore, a variety of methods have been described for their preparation.[18]

The synthesis of 3-amino-3-methylbutanoic acid with the amino moiety protected by a *tert*-butoxycarbonyl (Boc) group could be attempted by the homologation of α-aminoisobutyric acid (Aib). However, the generation and rearrangement of the diazo ketones implicated in the homologation of α,α-disubstituted α-amino acids are reported to proceed with poor yields.[18] For this reason, we undertook an alternative three-step procedure (see Scheme 3) that started with the conjugate addition of sodium azide to 3-methyl-2-butenoic acid under acidic conditions.[19] The reduction of the azido group in **1** was then accomplished by hydrogenation at atmospheric pressure using palladium on carbon as the catalyst.[19] The introduction of the Boc protecting group at the amino functionality was carried out by treatment of the crude β-amino acid with di-*tert*-butyl dicarbonate under standard conditions. In this way, multigram quantities of **2** were prepared in 68% overall yield without purification of the intermediate compounds.



Scheme 3. Synthesis of the β-amino acid **2**. Reagents and conditions: (a) NaN_3, H_2O/AcOH, 95 °C; (b) H_2, Pd/C, EtOAc, room temp.; (c) Boc_2O, KOH, dioxane/H_2O, room temp.

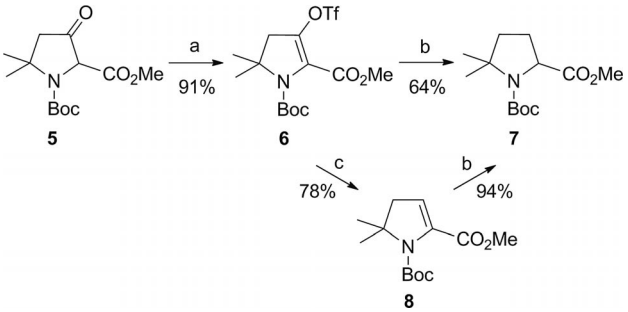
Once the β-amino acid precursor was obtained, it was converted into β-oxo ester **3** (see Scheme 4).[17] Thus, the carbonyl group in **2** was activated by treatment with *N*,*N*′-carbonyldiimidazole, and the resulting imidazolide was treated with a magnesium enolate that was generated from the potassium salt of monomethyl malonate. Upon spontaneous decarboxylation, the nucleophilic addition provided **3**. Next, the crude β-oxo ester **3** was submitted to a diazo-transfer reaction by treatment with 4-(acetamido)benzenesulfonyl azide.[20] The diazo group of the resulting α-diazo-β-oxo ester **4** successfully underwent decomposition, upon treatment with rhodium diacetate in toluene at 85–90 °C.[21] The intramolecular N–H insertion of the metal carbenoid generated in situ cleanly delivered δ,δ-dimethyloxoproline **5**, which was readily purified by column chromatography. The overall sequence in Scheme 4 provided this oxoproline in 82% yield from the starting β-amino acid **2**.



Scheme 4. Synthesis of δ,δ-dimethyl-oxoproline **5** from the β-amino acid **2**. Reagents and conditions: (a) *N*,*N*′-carbonyldiimidazole, $MgCl_2$, tetrahydrofuran (THF), room temp.; (b) 4-(acetamido)-benzenesulfonyl azide, Et_3N, CH_3CN, room temp.; (c) $Rh_2(OAc)_4$, toluene, 85–90 °C.

An alternative synthesis of a similar oxoproline, with *N*-acetyl protection, has previously been reported.[22] The strategy described by Sato et al. involved an intramolecular Dieckmann condensation reaction with the corresponding $\beta^{3,3}$-amino methyl ester. However, the process suffered from a low overall yield (26% yield of *N*-acetylated oxoproline from the β-amino ester). Therefore, the sequence reported herein (see Scheme 4) that involves the intramolecular N–H insertion of a metal carbenoid as the cyclization step represents a substantial improvement, in terms of efficiency, in comparison to the previous procedure.[22]

After the preparation of δ,δ-dimethyl-oxoproline **5**, we addressed its transformation into the desired δ,δ-dimethylproline derivative (see Scheme 5). First, the deprotonation of **5** with potassium hexamethyldisilazide (KHMDS) at room temperature gave an enolate that was then trapped with *N*-(5-chloro-2-pyridyl)triflimide to generate a vinyl triflate.[23] This combination of base and triflating agent, which proved optimal for achieving regiocontrol when working with 3-oxoproline,[17] rendered **6** in high yield as a single regioisomer.



Scheme 5. Synthesis of methyl *N*-Boc-δ,δ-dimethylprolinate (**7**) from δ,δ-dimethyl-oxoproline **5**. Reagents and conditions: (a) KHMDS, *N*-(5-chloro-2-pyridyl)triflimide, THF, room temp.; (b) H_2, Pd/C, MeOH, room temp.; (c) $Pd(PPh_3)_4$, Et_3SiH, LiCl, Et_3N, *N*,*N*-dimethylformamide (DMF), 60 °C.

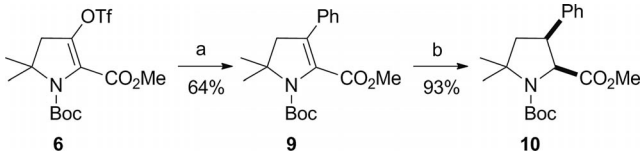
Although vinyl triflate **6** proved stable when stored at –20 °C, it was submitted to hydrogenation directly after its chromatographic purification. Thus, it was reduced to an alkane under atmospheric pressure of hydrogen gas in the presence of palladium on carbon (see Scheme 5b). This transformation, which has been proposed[24] to occur through a concerted hydrogenolysis of the C–O bond by a PdH_2 species followed by hydrogenation of the alkene, provided **7** in 64% yield, when the reaction was carried out on approximately a gram scale. However, concomitant deprotection of the amino group occurred upon scale-up as the reaction progressed, and the isolation of **7** became troublesome. To circumvent this inconvenience, we undertook the reduction of **6** through a two-step procedure that involved a palladium-catalyzed reductive removal of the triflate group by employing triethylsilane as the hydride source,[25] which was followed by hydrogenation of the resulting Δ^2-pyrroline **8** (see Scheme 5c and b). This procedure cleanly furnished **7** in 73% yield from **6**, without any isolation difficulties. Consequently, these transformations seem to be preferable for the preparation of **7**.

Therefore, we developed a methodology that renders racemic methyl *N*-Boc-δ,δ-dimethylprolinate (**7**) in a 55% overall yield through a six-step sequence that uses a β-amino acid as the starting material. The procedure seems to be a well-suited approach for the preparation of a broader range of δ,δ-disubstituted prolines, as the required β-amino acids should be accessible through a wide variety of methods.[18]

In addition, this synthetic route provides access to valuable intermediate compounds, namely, vinyl triflate **6** and Δ^2-pyrroline **8**. Thus, the latter could be used for the preparation of enantiopure or enantioenriched δ,δ-dimethylproline derivatives by means of asymmetric catalytic hydrogenations, as already tested for a 2,3-dehydroprolinate.[26] Moreover, both **8** and **6** could act as precursors of δ,δ-dimethylproline derivatives functionalized at the β-position. Specifically, vinyl triflate **6** and Δ^2-pyrroline **8** should be suitable substrates to carry out cross-coupling reactions and 1,4-conjugate additions, respectively. In fact, applying these strategies, we[17] and others[27] have successfully employed analogous compounds derived from proline in the synthesis of β-substituted prolines. The β-functionalization of δ,δ-dimethylproline is expected to render analogues that are able to combine the propensity of the parent amino acid to lock the prolyl amide bond in the *cis* geometry with the presence of new side chains. Such analogues are anticipated to be highly valuable for the development of pharmacologically active compounds. Until now, only few attempts have been made to access δ,δ-dimethylproline analogues with additional substituents at the β-carbon atom.[28]

We exemplified the value of these precursors (i.e., **6** and **8**) in the synthesis of a β-substituted δ,δ-dimethylproline derivative using vinyl triflate **6**. Specifically, we carried out the preparation of the analogue that has a phenyl substituent attached to the β-carbon atom, given the demonstrated utility of β-phenylproline in improving the pharmacological profile of biologically active peptides.[29] The incorporation of the aromatic substituent into the δ,δ-dimethylproline scaffold was achieved by means of a palladium-mediated cross-coupling reaction (see Scheme 6).[30] Treatment of vinyl triflate **6** with phenylboronic acid in the presence of

potassium carbonate, and a catalytic amount of dichlorido[1,1′-bis(diphenylphosphanyl)ferrocene]palladium(II) rendered Δ^2-pyrroline **9** in moderate yield. The presence of a double bond that connects the α- and β-carbon atoms in **9** ensured the relative *cis* disposition of the substituents upon reduction of the pyrroline. Thus, catalytic hydrogenation of **9** under standard conditions furnished **10** in high yield. This result emphasizes the importance of the regioselectivity previously attained in the generation of vinyl triflate **6** (see Scheme 5), which was not significant for the preparation of the parent δ,δ-dimethylproline, but becomes a key issue in a stereocontrolled synthesis of the β-substituted analogues. A copper-mediated 1,4-addition of a phenyl Grignard reagent to **8** would most probably render **10** as mixture of *cis*/*trans* isomers, as observed in the case of the Δ^2-pyrroline derived from proline.[27]



Scheme 6. Synthesis of the *cis*-β-substituted δ,δ-dimethylproline analogue **10**. Reagents and conditions: (a) $PhB(OH)_2$, $PdCl_2(dppf)$, K_2CO_3, toluene/MeOH, 80 °C; (b) H_2, Pd/C, MeOH, room temp.

Accordingly, **6** (and **8**) are suitable precursors to generate proline analogues with the prolyl amide bond stabilized in the *cis* geometry that incorporate additional functionality at the β carbon.[31]

Conclusions

A simple route for the preparation of methyl *N*-Boc-δ,δ-dimethylprolinate in racemic form has been developed. The procedure involves the construction of the pyrrolidine ring through an intramolecular cyclization reaction to form the N–Cα bond and makes use of a β-amino acid as the starting material. The methodology can adequately be extended to the preparation of other δ,δ-disubstituted prolines by using different starting β-amino acids. In addition, it provides access to valuable intermediates for the preparation of δ,δ-dimethylproline derivatives that are functionalized at the β-carbon atom. In particular, the *cis* stereoisomer of methyl *N*-Boc-δ,δ-dimethyl-β-phenylprolinate was obtained through a cross-coupling reaction of a vinyl triflate intermediate that was regioselectively generated. Such δ,δ-disubstituted prolines that are functionalized at the β-position combine the ability to stabilize the *cis* geometry of the prolyl amide bond with the presence of additional side-chain functionality. Efforts to obtain pure enantiomers of δ,δ-dimethylproline by HPLC resolution on a chiral column are underway.[32]

Experimental Section

General Methods: All reagents were used as received from commercial suppliers without further purification. Thin layer chromatography (TLC) was performed with Macherey–Nagel Polygram® SIL G/UV_{254} precoated silica gel polyester plates. The products were visualized by exposure to UV light or iodine vapor or by submersion in ninhydrin stain or an ethanolic solution of phosphomolybdic acid. Column chromatography was performed using 60 M (0.04–0.063 mm) silica gel from Macherey–Nagel. Melting points were determined with a Gallenkamp apparatus. IR spectra were registered with a Nicolet Avatar 360 FTIR spectrophotometer, and $\tilde{\nu}_{max}$ values are given for the main absorption bands. The ^1H and ^{13}C NMR spectroscopic data were recorded with a Bruker AV-400 or AV-500 instrument at room temperature with the residual solvent signal as the internal standard. The chemical shifts (δ) are expressed in parts per million, and the coupling constants (J) in Hertz. High-resolution mass spectra were obtained with a Bruker Microtof-Q spectrometer.

3-Amino-*N*-(*tert*-butoxycarbonyl)-3-methylbutanoic Acid (2): A solution of sodium azide (13.00 g, 199.97 mmol) in water (25 mL) was added dropwise by syringe to a solution of 3-methyl-2-butenoic acid (5.00 g, 49.94 mmol) in acetic acid (13 mL). After stirring of the mixture for 1 h, the temperature was raised to 95 °C, and the solution was stirred for an additional 2 d. The reaction mixture was diluted with water, and the resulting solution was extracted with diethyl ether (5 × 50 mL). The combined organic layers were dried with $MgSO_4$ and filtered. The solvent was concentrated in vacuo to afford a white solid (7.10 g) that was used without purification. A mixture of the solid and 10% Pd/C (700 mg) in ethyl acetate (100 mL) was stirred under an atmospheric pressure of hydrogen gas at room temperature for 24 h. The catalyst was removed by filtration and washed with ethyl acetate (100 mL). The resulting solution was washed with water (100 mL), and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The aqueous phase was lyophilized to afford 3-amino-3-methylbutanoic acid (4.80 g, 40.97 mmol) as a white solid. The crude compound was dissolved in dioxane (95 mL), and di-*tert*-butyl dicarbonate (17.80 g, 81.94 mmol) was added. The mixture was treated with potassium hydroxide (1 M aqueous solution, 42 mL), and the resulting mixture was stirred for 36 h. The reaction mixture was diluted with water and then basified with lithium hydroxide. After extraction with diethyl ether (3 × 50 mL), the aqueous phase was acidified by the addition of HCl (2 M solution), and the resulting solution was extracted several times with ethyl acetate. The combined organic extracts were concentrated to dryness to afford pure **2** (7.42 g, 34.15 mmol, 68% overall yield) as a white solid; m.p. 98 °C. IR (Nujol): $\tilde{\nu}$ = 3313, 3260, 3100–2500, 1701, 1652 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 6 H, C^{β}-CH_3), 1.44 (br. s, 9 H, *t*Bu CH_3), 2.72 (br. s, 2 H, H^{α}), 4.96 (br. s, 1 H, N*H*Boc), 10.08 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.88 (C^{β}-CH_3), 28.50 (*t*Bu CH_3), 44.33 (C^{α}), 51.24 (C^{β}), 79.74 (*t*Bu C), 155.14 (*t*BuO*C*O), 176.50 (CO_2H) ppm. HRMS (ESI): calcd. for $C_{10}H_{19}NNaO_4$ $[M + Na]^+$ 240.1206; found 240.1213.

Methyl *N*-(*tert*-Butoxycarbonyl)-5,5-dimethyl-3-oxopyrrolidine-2-carboxylate (5): A solution of **2** (6.00 g, 27.62 mmol) in anhydrous tetrahydrofuran (120 mL) under argon was treated with *N*,*N*′-carbonyldiimidazole (5.40 g, 33.30 mmol). After stirring at room temperature for 1 h, a mixture of previously combined magnesium chloride (2.00 g, 21.00 mmol) and monopotassium monomethyl malonate (6.50 g, 41.62 mmol) was added. The resulting mixture was stirred at room temperature for an additional 18 h. The solvent was evaporated, and the residue was dissolved in ethyl acetate (100 mL). The resulting solution was washed with 5% aqueous $KHSO_4$ (2 × 50 mL), 5% aqueous $NaHCO_3$ (2 × 50 mL), and then brine (2 × 50 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford a pale

orange oil (7.50 g, 27.43 mmol). The crude compound was dissolved in anhydrous acetonitrile (100 mL) under argon, and 4-(acetamido)benzenesulfonyl azide (6.90 g, 28.72 mmol) was added in one portion, which was followed by the addition of triethylamine (10.90 mL, 78.15 mmol). The resulting mixture was stirred at room temperature for 2 h. The solvent was concentrated in vacuo, and the residue was dissolved in diethyl ether (100 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), saturated aqueous NH_4Cl (2 × 50 mL), and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford an oil (7.80 g, 26.06 mmol) that was used in the next step without purification. The oil was dissolved in anhydrous toluene (300 mL) under argon, and $Rh_2(OAc)_4$ (56 mg, 0.127 mmol) was added. In a preheated oil bath, the reaction mixture was heated at 85–90 °C for approximately 40 min. The solvent was evaporated to dryness, and the residue was purified by column chromatography (hexanes/ethyl acetate, 2:1) to afford pure **5** (6.15 g, 22.67 mmol, 82% overall yield) as a white solid; m.p. 112 °C. IR (Nujol): $\tilde{\nu}$ = 1767, 1744, 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers, 2:1): δ = 1.39 (br. s, 6 H, *t*Bu CH_3) overlapped with 1.46–1.72 (m, 9 H, *t*Bu CH_3 and C^{δ}-CH_3), 2.51–2.73 (m, 2 H, H^{γ}), 3.79 (s, 3 H, OCH_3), 4.58 and 4.66 (2 br. s, 1 H, H^{α}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, duplicate signals observed for most carbon atoms, * = signal corresponding to minor rotamer): δ = 26.84, 27.48, and 27.87* (C^{δ}-CH_3), 28.30/28.52* (*t*Bu CH_3), 53.01/53.16* (OCH_3), 53.34/53.96* (C^{γ}), 58.72*/59.22 (C^{δ}), 68.28/68.42* (C^{α}), 80.87/81.58* (*t*Bu C), 152.59/154.33* (*t*BuO*C*O), 166.92*/167.25 (*C*O_2CH_3), 203.03*/203.72 (C^{β}=O) ppm. HRMS (ESI): calcd. for $C_{13}H_{21}NNaO_5$ $[M + Na]^+$ 294.1312; found 294.1301.

Methyl *N*-(*tert*-Butoxycarbonyl)-5,5-dimethyl-3-(trifluoromethylsulfonyl)-Δ²-pyrroline-2-carboxylate (6): A solution of KHMDS (0.5 M in toluene, 12.4 mL, 6.20 mmol) was added by syringe to a stirred solution of **5** (1.40 g, 5.16 mmol) in anhydrous tetrahydrofuran (16 mL) at room temperature. After stirring for 40 min, *N*-(5-chloro-2-pyridyl)triflimide (2.43 g, 6.20 mmol) was added, and the resulting solution was stirred for an additional 4 h. The solvent was evaporated to dryness, and the residue was purified by column chromatography (hexanes/ethyl acetate, 5:1) to afford pure **6** (1.90 g, 4.70 mmol, 91% yield) as an oil that solidified in the freezer. IR (neat): $\tilde{\nu}$ = 1750, 1716, 1429, 1387, 1370 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, *t*Bu CH_3), 1.56 (s, 6 H, C^{δ}-CH_3), 2.82 (s, 2 H, H^{γ}), 3.85 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.30 (C^{δ}-CH_3), 28.19 (*t*Bu CH_3), 45.40 (C^{γ}), 52.68 (OCH_3), 64.64 (C^{δ}), 82.38 (*t*Bu C), 118.41 (q, *J* = 320.4 Hz, CF_3), 128.38 (C^{α}), 133.55 (C^{β}), 150.97 (*t*BuO*C*O), 160.03 (*C*O_2CH_3) ppm. HRMS (ESI): calcd. for $C_{14}H_{20}F_3NNaO_7S$ $[M + Na]^+$ 426.0805; found 426.0795.

Methyl *N*-(*tert*-Butoxycarbonyl)-5,5-dimethylpyrrolidine-2-carboxylate (7)

Procedure A: A mixture of **6** (1.90 g, 4.70 mmol) and 10% Pd/C (0.19 g) in methanol (40 mL) was stirred under an atmospheric pressure of hydrogen gas at room temperature for 18 h. The catalyst was removed by filtration and then washed with methanol. The solvent was concentrated in vacuo, and the crude residue was purified by column chromatography (hexanes/diethyl ether, 5:1) to afford **7** (0.77 g, 3.00 mmol, 64% yield) as an oil.

Procedure B: A mixture of **8** (100 mg, 0.39 mmol) and 10% Pd/C (10 mg) in methanol (10 mL) was stirred under an atmospheric pressure of hydrogen gas at room temperature overnight. The catalyst was removed by filtration and then washed with methanol. The solvent was concentrated in vacuo, and the crude residue was purified by column chromatography (hexanes/ethyl acetate, 5:1) to afford **7** (94 mg, 0.37 mmol, 94% yield) as an oil. IR (neat): $\tilde{\nu}$ = 1752, 1706, 1686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers, 1.2:1): δ = 1.31 and 1.38 (2 s, 3 H, C^{δ}-CH_3), 1.39 and 1.48 (2 s, 9 H, *t*Bu CH_3), 1.49 and 1.53 (2 s, 3 H, C^{δ}-CH_3), 1.69–1.80 (m, 1 H, H^{γ}), 1.81–1.99 (m, 2 H, H^{β} and H^{γ}), 2.06–2.20 (m, 1 H, H^{β}), 3.71 and 3.72 (2 s, 3 H, OCH_3), 4.30 (dd, *J* = 8.8, 3.3 Hz, 0.54 H, H^{α}), 4.41 (dd, *J* = 8.7, 2.9 Hz, 0.46 H, H^{α}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, duplicate signals observed for all carbon atoms): δ = 26.07/26.92 (C^{δ}-CH_3), 26.34/26.90 (C^{γ}), 26.46/27.58 (C^{δ}-CH_3), 28.51/28.66 (*t*Bu CH_3), 40.19/41.02 (C^{β}), 52.00/52.16 (OCH_3), 60.90/61.67 (C^{δ}), 61.51/61.52 (C^{α}), 79.52/80.05 (*t*Bu C), 152.75/154.48 (*t*BuO*C*O), 173.85/174.25 (*C*O_2CH_3) ppm. HRMS (ESI): calcd. for $C_{13}H_{23}NNaO_4$ $[M + Na]^+$ 280.1519; found 280.1528.

Methyl *N*-(*tert*-Butoxycarbonyl)-5,5-dimethyl-Δ²-pyrroline-2-carboxylate (8): Triethylsilane (0.55 mL, 3.45 mmol) and triethylamine (0.97 mL, 6.95 mmol) were added dropwise to a solution of **6** (0.70 g, 1.74 mmol), lithium chloride (221 mg, 5.21 mmol), and $Pd(PPh_3)_4$ (27 mg, 0.17 mmol) in anhydrous DMF (28 mL). The reaction mixture was stirred at 60 °C for 1 h, and then the solvent was removed under reduced pressure. The solid residue was purified by column chromatography (hexanes/ethyl acetate, 5:1) to afford pure **8** (347 mg, 1.36 mmol, 78% yield) as an oil. IR (neat): $\tilde{\nu}$ = 1741, 1705, 1627 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *t*Bu CH_3), 1.47 (s, 6 H, C^{δ}-CH_3), 2.52 (d, *J* = 3.0 Hz, 2 H, H^{γ}), 3.78 (s, 3 H, OCH_3), 5.43 (t, *J* = 3.0 Hz, 1 H, H^{β}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.28 (C^{δ}-CH_3), 28.27 (*t*Bu CH_3), 45.82 (C^{γ}), 52.09 (OCH_3), 64.81 (C^{δ}), 80.92 (*t*Bu C), 113.36 (C^{β}), 136.33 (C^{α}), 151.46 (*t*BuO*C*O), 163.42 (*C*O_2CH_3) ppm. HRMS (ESI): calcd. for $C_{13}H_{21}NO_4$ $[M + H]^+$ 256.1543; found 256.1538.

Methyl *N*-(*tert*-Butoxycarbonyl)-5,5-dimethyl-3-phenyl-Δ²-pyrroline-2-carboxylate (9): To a solution of **6** (350 mg, 0.87 mmol) and phenylboronic acid (212 mg, 1.74 mmol) in a mixture of toluene/methanol (10:1, 5.5 mL) were added potassium carbonate (180 mg, 1.30 mmol) and dichlorido[1,1′-bis(diphenylphosphanyl)ferrocene]-palladium(II) (32 mg, 0.044 mmol). The reaction mixture was stirred at 80 °C for 1 h. The solvent was evaporated in vacuo, and the resulting residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 5:1) to afford pure **9** (185 mg, 0.56 mmol, 64% yield) as a white solid; m.p 108 °C. IR (Nujol): $\tilde{\nu}$ = 1734, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, *t*Bu CH_3), 1.59 (s, 6 H, C^{δ}-CH_3), 2.93 (s, 2 H, H^{γ}), 3.82 (s, 3 H, OCH_3), 7.20–7.41 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.29 (C^{δ}-CH_3), 28.42 (*t*Bu CH_3), 49.41 (C^{γ}), 52.46 (OCH_3), 63.23 (C^{δ}), 81.44 (*t*Bu C), 126.48 (Ar), 127.38 (Ar), 128.49 (Ar), 128.58 (C^{β}), 129.86 (C^{α}), 134.16 (Ar), 151.26 (*t*BuO*C*O), 164.75 (*C*O_2CH_3) ppm. HRMS (ESI): calcd. for $C_{19}H_{25}NO_4$ $[M + H]^+$ 332.1856; found 332.1837; calcd. for $C_{19}H_{25}NNaO_4$ $[M + Na]^+$ 354.1676; found 354.1660.

Methyl *cis*-*N*-(*tert*-Butoxycarbonyl)-5,5-dimethyl-3-phenylpyrrolidine-2-carboxylate (10): A mixture of **9** (166 mg, 0.50 mmol) and 10% Pd/C (17 mg) in methanol (5 mL) was stirred under an atmospheric pressure of hydrogen gas at room temperature overnight. The catalyst was removed by filtration and then washed with methanol. The solvent was evaporated in vacuo, and the crude residue was purified by column chromatography (hexanes/ethyl acetate, 5:1) to afford **10** (155 mg, 0.46 mmol, 93% yield) as an oil. IR (neat): $\tilde{\nu}$ = 1745, 1705, 1684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers, 1.2:1): δ = 1.37 and 1.49 (2 s, 9 H, *t*Bu CH_3), 1.43 and 1.47 (2 s, 3 H, C^{δ}-CH_3), 1.67 and 1.73 (2 s, 3 H, C^{δ}-CH_3), 1.89–2.02 (m, 1 H, H^{γ}), 2.48–2.73 (m, 1 H, H^{γ}), 3.22 and 3.25 (2 s,

3 H, OCH_3), 3.61–3.79 (m, 1 H, H^{β}), 4.53 (d, J = 8.8 Hz, 0.55 H, H^{α}), 4.62 (d, J = 8.7 Hz, 0.45 H, H^{α}), 7.16–7.36 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, duplicate signals observed for all carbon atoms): δ = 26.04/26.90 (C^{δ}-CH_3), 27.16/28.20 (C^{δ}-CH_3), 28.44/28.62 (*t*Bu CH_3), 43.07/43.62 (C^{β}), 43.71/44.51 (C^{γ}), 51.20/51.34 (OCH_3), 60.52/61.18 (C^{δ}), 66.70/66.84 (C^{α}), 79.68/80.24 (*t*Bu C), 127.45/127.51 (Ar), 127.96/128.00 (Ar), 128.38/128.41 (Ar), 136.74/136.77 (Ar), 152.47/154.26 (*t*BuO*C*O), 172.15/172.23 (CO_2CH_3) ppm. HRMS (ESI): calcd. for $C_{19}H_{27}NO_4$ $[M + H]^+$ 334.2013; found 334.1993; calcd. for $C_{19}H_{27}NNaO_4$ $[M + Na]^+$ 356.1832; found 356.1828.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **2**, **5**–**10**.

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[31] We confirmed that β-substituted analogue **10** exhibited a capacity to stabilize the *cis* state of the amide bond that involves the pyrrolidine nitrogen atom. To this end, we synthesized *N*-acetyl derivatives of **7** and **10** by acidic treatment followed by a reaction with acetic anhydride. Analysis of the two sets of resonances in the ^{1}H NMR spectra of **7** and **10** in $CDCl_3$ revealed a 67 and 70% *cis*-amide ratio, respectively, that is, a slightly superior tendency for the β-phenyl derivative to stabilize the *cis* amide geometry. Note that the remaining ca. 30% *trans* amide bond is a result of the small size of the methyl group in the *N*-acyl substituent. When δ,δ-dimethylproline is within a peptide chain, an amino acid is linked to the pyrrolidine nitrogen atom (instead of the acetyl group), and the higher steric hindrance prevents the *trans* arrangement of the prolyl peptide bond.
[32] Analytical assays have shown that benzyl *N*-benzyloxycarbonyl-δ,δ-dimethylprolinate (obtained by deprotection and further protection of the amino and carboxylic acid groups in **7** by following standard procedures) is well resolved by HPLC on a cellulose-derived Chiralpak® IB column (t_R = 4.6 and 6.7 min; *n*-hexane/2-propanol, 95:5; 150 × 4.6 mm column; flow rate 1.0 mL/min). Optimization of these preliminary results (mainly by testing the effect of other mobile phases on the enantioseparation) and subsequently extending them to a preparative scale would provide access to significant amounts of enantiopure δ,δ-dimethylproline (both enantiomers). For previous work from our group that describes the isolation of (multi)gram quantities of enantiomerically pure amino acids through the preparative HPLC resolution of racemic precursors, see: a) P. Fatás, A. M. Gil, M. I. Calaza, A. I. Jiménez, C. Cativiela, *Chirality* **2012**, *24*, 1082–1091; b) F. J. Sayago, M. J. Pueyo, M. I. Calaza, A. I. Jiménez, C. Cativiela, *Chirality* **2011**, *23*, 507–513; c) F. J. Sayago, A. I. Jiménez, C. Cativiela, *Tetrahedron: Asymmetry* **2007**, *18*, 2358–2364; d) S. Royo, A. I. Jiménez, C. Cativiela, *Tetrahedron: Asymmetry* **2006**, *17*, 2393–2400; e) M. Lasa, P. López, C. Cativiela, *Tetrahedron: Asymmetry* **2005**, *16*, 4022–4033; f) A. I. Jiménez, P. López, C. Cativiela, *Chirality* **2005**, *17*, 22–29; g) C. Cativiela, M. Lasa, P. López, *Tetrahedron: Asymmetry* **2005**, *16*, 2613–2623; h) A. M. Gil, E. Buñuel, P. López, C. Cativiela, *Tetrahedron: Asymmetry* **2004**, *15*, 811–819; i) C. Cativiela, P. López, M. Lasa, *Eur. J. Org. Chem.* **2004**, 3898–3908; j) M. Alías, M. P. López, C. Cativiela, *Tetrahedron* **2004**, *60*, 885–891; k) S. Royo, P. López, A. I. Jiménez, L. Oliveros, C. Cativiela, *Chirality* **2002**, *14*, 39–46; l) M. Alías, C. Cativiela, A. I. Jiménez, P. López, L. Oliveros, M. Marraud, *Chirality* **2001**, *13*, 48–55; m) A. I. Jiménez, P. López, L. Oliveros, C. Cativiela, *Tetrahedron* **2001**, *57*, 6019–6026; n) C. Cativiela, M. D. Díaz-de-Villegas, A. I. Jiménez, P. López, M. Marraud, L. Oliveros, *Chirality* **1999**, *11*, 583–590.

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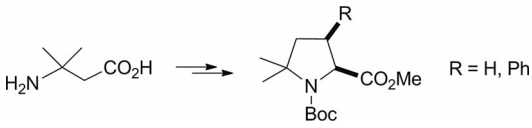

δ,δ-Dimethylproline derivatives have been efficiently synthesized by employing a β-amino acid as the starting material. The methodology is amenable to the preparation of other δ,δ-disubstituted prolines.

Keywords: Synthetic methods / Amino acids / Nitrogen heterocycles / Regioselectivity / Proline analogues

