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Improved synthesis of (2*S*,5*S*)-5-*tert*-butylproline

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We dedicate this work to our colleague Professor Stephen Hanessian on the occasion of his entering into his golden years

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Abstract—(2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline (**1**) was synthesized by an improved procedure featuring the conversion of (2*S*)-1-*tert*-butyldimethylsiloxy-2-*N*-(PhF)amino-5-oxo-6,6-dimethylheptane (**16**) into its corresponding imino alcohol followed by directed hydride delivery to reduce the imine functionality with a 95:5 diastereoselectivity. Ketone **16** was obtained from methyl 2-*N*-(PhF)amino-5-oxo-6,6-dimethylheptanoate (**13**), a previously reported precursor for the synthesis of (2*S*,5*R*)-5-*tert*-butylproline, by reduction to its corresponding diol, selective protection of the primary alcohol and oxidation of the secondary alcohol. This route provided (2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline (**1**) of >96% enantiomeric purity suitable for peptide chemistry in 39% overall yield from ketone **13**. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Amino acids possessing alkyl substituents have emerged as important tools for controlling peptide conformation. Because their steric interactions can restrict the motion about the backbone and side-chain dihedral angles within a peptide, alkyl-substituted amino acids may promote particular peptide secondary structures.[1–34] Although the steric bulk of the alkyl-substituted amino acid may interfere with binding and alter biological activity of a peptide analog, the structure–activity relationships of peptides possessing such alkyl-substituted amino acids have in some cases provided a better understanding of the biologically active conformation responsible for receptor recognition and signal transduction. Furthermore, the hydrophobic nature of the alkyl substituent may enhance affinity of conformations that favor antagonist activity at the receptor.[2,3]

Among the acyclic amino acids, α,α-dialkylglycines, such as α-aminoisobutyric acid (Aib), exert significant constraints on the backbone dihedral angles in a peptide[4] (Fig. 1) and many approaches for their stereoselective synthesis have been reported.[5] Replacement of the α-proton in an alanine residue with a methyl substituent restricts the ϕ- and ψ-torsion angles to regions that correspond to right- and left-handed α-helices and 3_{10}-helix geometry as demonstrated by computational analysis.[6] Naturally-occurring Aib-rich peptide antibiotics, peptaibols which produce voltage-gated ion channels in lipid membranes, have been shown to adopt helical conformations by X-ray analysis and NMR spectroscopy.[7] Related long synthetic peptides containing at least one Aib residue among 5–20 residues have been shown by X-ray analysis to adopt predominantly helical geometry.[8] Type III β-turn conformations have been observed by X-ray crystallography to be stabilized when Aib residues were introduced into shorter peptides composed of 2–4 amino acids.[4] α,α-Dialkylglycines containing larger α-alkyl substituents, such as α,α-diethylglycine (Deg), α,α-di-*n*-propylglycine (Dpg), α,α-di-*n*-butylglycine (Dbg), α,α-diphenylglycine (DΦg) and α,α-dibenzylglycine ($Db_z g$), have favored fully extended C_5 structures in peptides characterized by 180° ϕ- and ψ-dihedral angles and intramolecular H-bonds between the

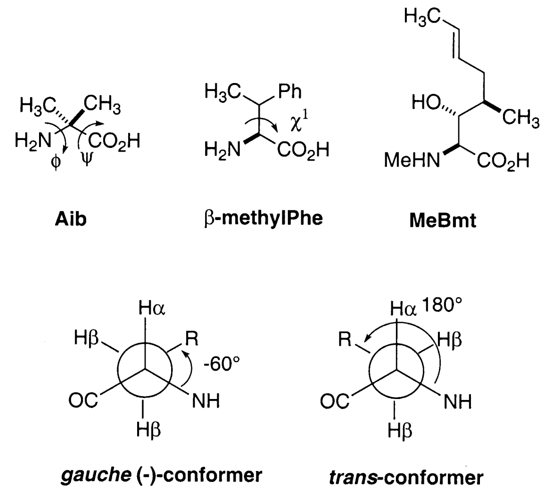

Figure 1. Representative examples of α-, β- and γ-alkyl substituted acyclic α-amino acids.

Keywords: steric effects; 5-*tert*-butylproline; *trans*-diastereomer; directed hydride addition; prolinol; imine; prolinal.

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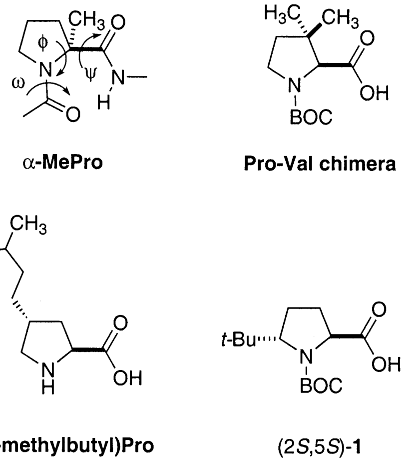
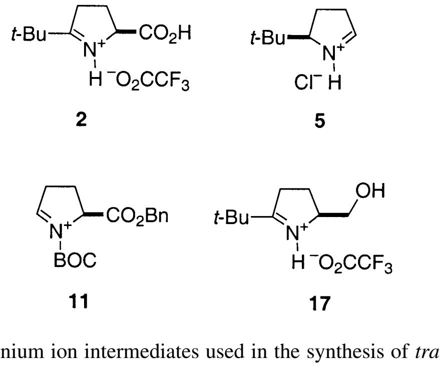


α-MePro **Pro-Val chimera**

γ-(3-methylbutyl)Pro **(2*S*,5*S*)-1**

Figure 2. Representative examples of α-, β-, γ- and δ-alkyl substituted cyclic α-amino acids.

amide hydrogen and carbonyl oxygen groups within the same residue.[9,10] 1-Aminocycloalkane-1-carboxylic acids of 3-, and 5- to 7-carbon ring-sizes have induced helical, β-turn and γ-turn conformations in peptides of 3–10 residues as observed in solution and in the solid state.[10,11] β-Alkyl substituents can influence significantly the side-chain dihedral angle and to some extent the backbone geometry of amino acid residues in peptides. Several β-methyl analogs of the naturally occurring amino acids (Asp, Glu, His, Phe, Trp and Tyr) have been stereoselectively synthesized for application in peptide mimics.[12–14] For example, β-methylphenylalanine has been employed to constrain the side-chain χ^1 dihedral angles in enkephalin and somatostatin analogs.[3,15] The steric effects of the β-methyl group are contingent on stereochemistry.[12,16] In (2*S*,3*R*)-β-MePhe, the side-chain χ^1 dihedral angle adopted the *trans*-conformer and in (2*S*,3*S*)-β-MePhe the *gauche* (−) conformer was preferred (Fig. 1).[15,16] γ-Alkyl substituents may also influence side-chain geometry of an amino acid residue in a peptide. Although several γ-alkyl analogs of the naturally occurring amino acids have been synthesized,[17–19,26,56a] their influence on peptide conformation and biology has been less thoroughly studied. Their significance to peptide biology has been illustrated in an analog of the natural cyclic peptide cyclosporine, where removal of the γ-alkyl substituents from the MeBmt residue caused a dramatic reduction in immunosuppressive activity (Fig. 1).[20]



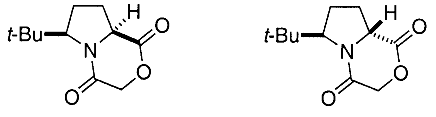
2 **5**

11 **17**

Figure 3. Iminium ion intermediates used in the synthesis of *trans*-5-*tert*-butylproline.

Among cyclic amino acids, azetidine-2-carboxylic acids, prolines and pipecolates possessing alkyl substituents have been synthesized and introduced into peptides.[1,2,21–38] In prolyl peptides, alkyl substituents can influence the ring puckering, the ψ-dihedral angle and the *N*-terminal amide equilibrium of the proline residue. For example, in *N*-acetyl α-methylproline *N*′-methylamide, only the *trans*-amide isomer was observed by NMR spectroscopy in $CDCl_3$ and in water (Fig. 2).[23] Several β-substituted azetidine-2-carboxylates, prolines and pipecolates have been synthesized to serve as amino acid chimeras in which the functional groups of the amino acid side-chain are combined with the conformational restrictions characteristic of the cyclic amino acid residue.[22a,24,35–37] Chimeras with proline bodies have been used to study the relationship of side-chain geometry to bioactivity in biologically active peptides such as angiotensin II, bradykinin, morphiceptin, and cholecystokinin.[24] Although β-substituents exhibited little effect on the populations of the prolyl amide isomers, they have influenced the proline ψ-dihedral angle as well as the energy barrier for amide isomerization. In the case of *N*-acetyl β-methylproline *N*′-methylamides, the *cis*-β-methyl substituent imposed steric interactions that restricted the ψ dihedral angle and prevented formation of a γ-turn conformation ($\psi \approx 80^\circ$) as observed by IR spectroscopy.[23a] A similar effect was observed in *N*-acetyl β,β-dimethylproline *N*′-methylamide; moreover, the presence of the two methyl substituents in this proline-valine chimera was shown to cause a nearly seven-fold reduction in the rate of prolyl amide isomerization as demonstrated by magnetization transfer experiments (Fig. 2).[25] γ-Alkylprolines have been stereoselectively synthesized and used to prepare proline oligomers because their ring substituents interact minimally with the prolyl residue conformation.[26–28] For example, natural poly-proline type II geometry was adopted by short oligomers composed of *trans*-4-(3-methylbutyl)-prolines as observed by NMR spectroscopy.[28] On the other hand, δ-alkyl substituents can exhibit significant steric interactions that may disturb the preferred conformation about the prolyl residue.[1,2,29–34,38] For example, replacement of proline by (2*S*,5*R*)-5-*tert*-butylproline in peptides has increased the prolyl amide *cis*-isomer population, diminished the barrier for prolyl amide isomerization and favored the formation of type VI β-turns.[2,30–33] In *N*-acetyl-proline *N*′-methylamides, (2*S*,5*S*)-5-*tert*-butylproline caused a greater increase in *cis*-isomer population relative to its *cis*-diastereomer counterpart without influencing the barrier for amide isomerization relative to proline.[30] In addition, *N*-acetyl-*trans*-5-*tert*-butylproline *N*′-methylamide was shown by IR spectroscopy not to adopt a seven member γ-turn conformation, which was a favored conformer for its natural proline and *cis*-diastereomer counterparts in $CHCl_3$.[30]

These examples demonstrate the ability of alkyl substituted amino acids to reinforce and to disturb natural peptide secondary structures. Improved methods for synthesizing alkyl substituted amino acids advance their use by making them more readily accessible for peptide science. In our own work with 5-*tert*-butylproline, we have until now focused primarily on the (2*S*,5*R*)-diastereomer, because it can be synthesized effectively via our high-yielding stereoselective sequence featuring acylation of γ-methyl *N*-(PhF)-L-glutamate



(2*S*,5*R*)-**3** (2*R*,5*R*)-**3**

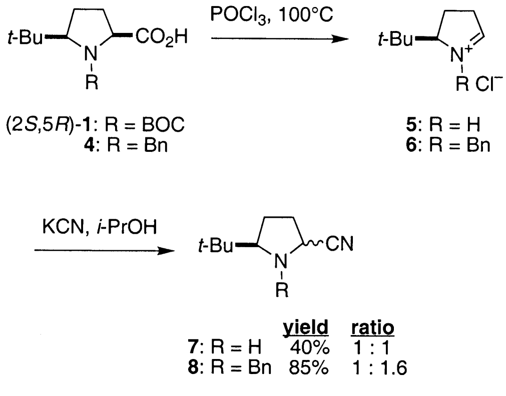
Figure 4. Prolyl lactam **3**.

followed by ester hydrolysis, decarboxylation and reductive amination.[21] Less attention has been given to the (2*S*,5*S*)-diastereomer because of drawbacks in its stereoselective synthesis. For example, although good diastereoselectivity was achieved in the hydride reduction of (2*S*)-5-*tert*-butyl-Δ^5-dehydroproline trifluoroacetate (**2**) to furnish the *trans*-diastereomer, the iminium ion intermediate **2** proved to be configurationally labile and racemized product was obtained (Fig. 3).[21] Although epimerization of the (2*S*,5*R*)-diastereomer of *N*-benzyl-5-*tert*-butylproline methyl ester could be used to provide enantiopure (2*R*,5*R*)-diasereomer, only a 1:1 ratio of (2*S*)-:(2*R*)-isomers was achieved under our best conditions: *t*-BuOK in *t*-BuOH at 50°C.[21] Encouraged by our success in the use of (2*S*,5*R*)-5-*tert*-butylproline in the synthesis of type VI β-turn mimics,[31,32] polyproline analogs[33] and biologically active derivatives of natural prolyl peptides such as oxytocin,[2] we chose to explore the attributes of its (2*S*,5*S*)-diastereomer for peptide mimicry. We present now an improved synthesis of (2*S*,5*S*)-5-*tert*-butylproline that provides enantiopure material (>96% ee) suitably protected for peptide synthesis.

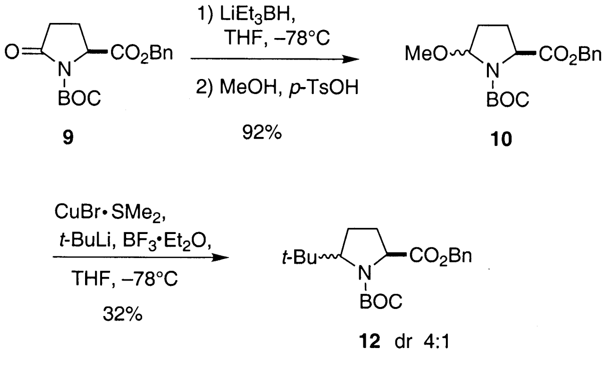
2. Results and discussion

Several approaches were considered for the synthesis of enantiopure *trans*-5-*tert*-butylproline. Because of limited success in the epimerization of (2*S*,5*R*)- to (2*R*,5*R*)-*N*-benzyl-5-*tert*-butylproline methyl ester, we examined epimerization of its bicyclic lactam counterpart, proline **3** (Fig. 4). Although protonation with inversion of configuration was considered for producing the *trans*-5-*tert*-butylproline, computational analysis of the *cis*- and *trans*-lactam diastereomers **3** indicated that the energy minimum for the *cis*-isomer was 0.9 kcal/mol lower than that of its *trans*-counterpart.[39] Opting for a new strategy for synthesizing *trans*-5-*tert*-butylproline, we examined the addition of cyanide ion to iminium salt **5** obtained from decarboxylation of the (2*S*,5*R*)-diastereomer. A similar approach had been used previously for the synthesis of *N*-benzyl-2-cyano-5-heptylpyrrolidine to afford a 3:1 mixture of *trans*:*cis* diastereomers for the preparation of 2,5-dialkylpyrrolidines found in ant venum.[40] We prepared both iminium salt **5** and its *N*-benzyl analog **6** by heating their respective *N*-protected-(2*S*,5*R*)-5-*tert*-butylproline (**1** and **4**) with POCl$_3$ at 100°C (Scheme 1). Although the bulky *tert*-butyl substituent was envisioned to direct attack towards the less hindered face of the iminium salt to provide the *trans*-isomer, the 2-cyano-5-*tert*-butylpyrrolidines (**7** and **8**) were obtained with low diastereoselectivity. For example, treatment of iminium salt **5** with KCN in isopropanol gave a 1:1 mixture of (2*S*,5*R*)- and (2*R*,5*R*)-2-cyano-5-*tert*-butylpyrrolidines in 40% yield. This ratio remained unchanged after attempts to equilibrate the mixture with silica gel in an isooctane/EtOAc solution.[40] Although the overall yield was increased to 58% when TMSCN in THF was used in the second step of the two step sequence, diastereomeric 2-cyano-5-*tert*-butylpyrrolidines **7** were obtained again as a 1:1 mixture. The yield of the sequence could be improved to 85% by employing *N*-(benzyl)proline **4**;[21] however, *N*-benzyl-2-cyano-5-*tert*-butylpyrrolidines (**8**) were produced non-selectively as a 1:1.6 mixture of diastereomers.

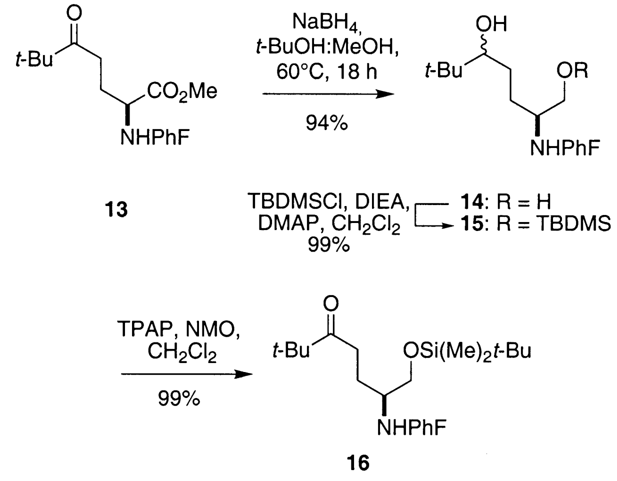
To improve diastereoselectivity, we investigated next the addition of a *tert*-butylcopper reagent to prolyl iminium ion **11** (Fig. 3). Less sterically bulky alkylcopper reagents, possessing *n*-propyl, *n*-butyl, *n*-heptyl, phenyl, benzyl and *iso*-propenyl substituents, have been reported to add diastereoselectively to iminium ions to afford 5-alkylprolines with the *trans* configuration.[41,42] Furthermore, the *tert*-butylcopper reagent prepared from CuI and *t*-BuLi had been reported to react quantitatively with benzoyl chloride in dimethylsulfide at −78°C to afford phenyl *tert*-butylketone.[43] Initially, *N*-Boc-5-methoxyproline benzyl ester (**10**) was synthesized as a 2:3 mixture of diastereomers in 92% yield by reduction of *N*-Boc-pyroglutamate benzyl ester[44] (**9**) with LiEt$_3$BH in THF followed by etherification of the aminal in MeOH with a catalytic amount of *p*-toluenesulfonic acid (Scheme 2).[45] Although several attempts to add a *tert*-butylcopper reagent to **11** failed, in one experiment, addition of a diastereomeric mixture of *N*-Boc-5-methoxyproline benzyl ester (**10**) to a suspension of *t*-BuLi, CuBr·SMe$_2$ and BF$_3$·OEt$_2$ in THF at −78°C provided protected 5-*tert*-butylproline **12** as a 1:4 mixture



Scheme 1. Synthesis of 2-cyano-5-*tert*-butylpyrrolidines **7** and **8**.



Scheme 2. Synthesis of *N*-Boc-5-*tert*-butylproline via addition of *tert*-butylcopper reagent.



Scheme 3. Synthesis of ketone **16**.

of diastereomers in 32% yield.[46] Because we could not later reproduce this result, we abandoned this approach involving *tert*-butylcopper reagents which were known to be sensitive to variations in reaction solvent and temperature.[43]

The less than satisfactory results we obtained in nucleophilic additions of cyanide ion and *tert*-butylcopper reagents respectively to iminium salts **5** and **11** (Fig. 3) made us reconsider our published strategy for synthesizing (2*S*,5*S*)-5-*tert*-butylproline with a significant modification. As mentioned, we found previously that hydride reduction of iminium acid **2** provided *trans*-5-*tert*-butylproline diastereoselectively with significant racemization due to the configurational lability of this intermediate under the acidic conditions for its production.[21] Attempts to circumvent racemization by using its more configurationally stable amide counterpart resulted in lower diastereoselectivity.[21] Reduction of the carboxylate to its respective alcohol has now been investigated as a means to alleviate the problem of racemization and to install an effective site for metal hydride coordination in order to direct iminium ion reduction to afford the *trans*-diastereomer. β-Hydroxy ketones have been reported to reduce diastereoselectively using tetramethylammonium triacetoxyborohydride to provide *anti* diols by directed intramolecular hydride delivery.[47] Furthermore, reduction of imino alcohols under similar conditions have been reported to produce predominantly *trans*-2-hydroxymethyl-5-alkylpyrrolidines possessing 5-methyl and 5-*n*-nonyl substituents in 83:17 and 70:30 respective ratios.[48] We pursued thus the synthesis and reduction of (2*S*)-5-*tert*-butyl-Δ^5-dehydroprolinol **19** in order to prepare (2*S*,5*S*)-5-*tert*-butylproline.

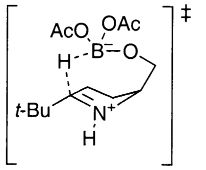
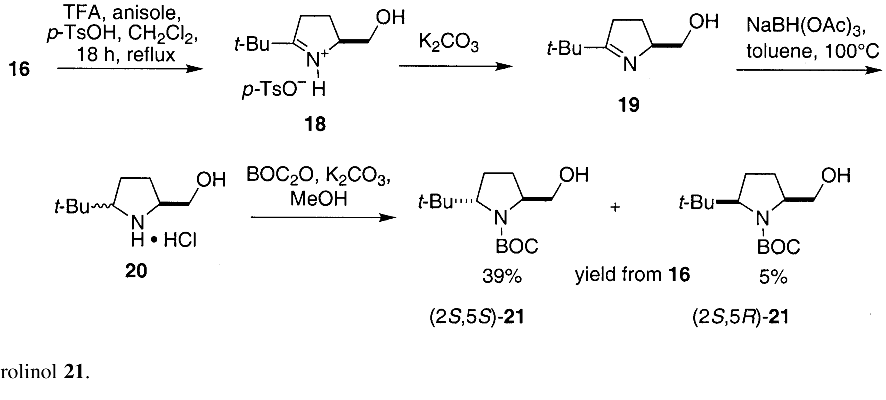


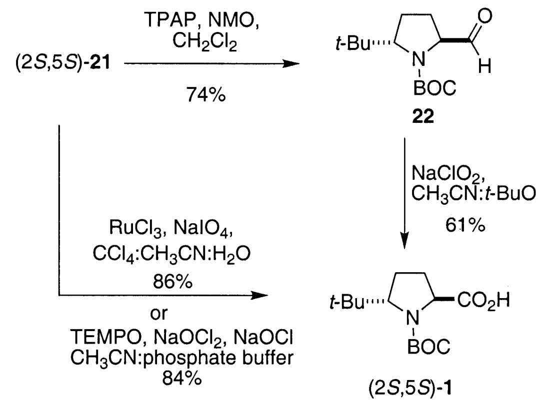
Figure 5. Proposed transition state for hydride addition to imine **19**.

The synthesis of (2*S*)-5-*tert*-butyl-Δ^5-dehydroprolinol (**19**) started with methyl 2-*N*-(PhF)amino-5-oxo-6,6-dimethylheptanoate (**13**), an intermediate in the synthesis of (2*S*,5*R*)-5-*tert*-butylproline derived from acylation of γ-methyl *N*-PhF-L-glutamate with pivaloyl chloride, ester hydrolysis, decarboxylation and esterification.[21] Sodium borohydride reduction of ketone **13** in a mixture of methanol/*tert*-butanol at 60°C gave 2-*N*-(PhF)amino-5-hydroxy-6,6-dimethylheptanol **14** in 94% yield as a 1:1 mixture of diastereomers (Scheme 3).[49] 1-*tert*-Butyldimethylsiloxy-2-*N*-(PhF)amino-5-oxo-6,6-dimethylheptane **16** was then synthesized in quantitative yield by selective protection of the primary alcohol of diol **14** with *tert*-butyldimethysilyl chloride, DIEA and DMAP in CH_2Cl_2 heated at a reflux,[49] followed by oxidation of neopentyl alcohol **15** with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine oxide in CH_2Cl_2.[50] Earlier attempts failed to oxidize the secondary alcohol of **15** to its corresponding ketone **16** using DMSO and oxalyl chloride in dichloromethane,[51] as well as using methylsulfide and *N*-chlorosuccinamide in toluene,[52] and only starting material was isolated after each reaction.

Concurrent deprotection of the silyl ether and PhF groups with formation of the iminium salt **17** was achieved on heating ketone **16** with anisole in a 1:3 TFA/CH_2Cl_2 solution at a reflux for 70 h (Scheme 4). Because trifluoroacetate **17** (Fig. 3) was volatile, the acidic counter ion was exchanged with *p*-toluenesulfonic acid as monitored by comparison of the integrations for the *tert*-butyl and methyl singlets respectively at 1.35 and 2.36 ppm in the proton NMR spectrum in $CDCl_3$. On larger scale, *p*-TsOH (100 mol%) was added at the start of the reaction to ketone **16** and anisole in 25% TFA/CH_2Cl_2 and the conversion to **18** was complete after 18 h. The configurational stability of



Scheme 4. Synthesis of prolinol **21**.



Scheme 5. Oxidation of **21** to (2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline.

iminium salt **18** was demonstrated by measuring the specific rotation of **18** after treatments with 25% TFA/CH_2Cl_2 at reflux for 18, 24, 48 and 72 h. Because the specific rotation value of **18** remained unchanged after these treatments, iminium salt **18** was concluded to be configurationally stable under these acidic conditions.

(2*S*,5*S*)-*N*-Boc-5-*tert*-butylprolinol (**21**) was obtained from *p*-toluenesulfonate **18** by a sequence commencing with liberation of imine **19** on washing with aqueous potassium carbonate, imine reduction with sodium triacetoxyborohydride in toluene at 100°C and *N*-acylation with di-*tert*-butyldicarbonate in acetonitrile (Scheme 4). Alcohol **21** was obtained in 68% overall yield from ketone **16** as a >95:5 diastereomeric mixture on small scale. Lower diastereoselectivity (87:13 *trans*/*cis*) was obtained when *p*-toluenesulfonate **18** was reduced under the same conditions. On larger scale, the diastereomeric *N*-(Boc)amino alcohols were separated by chromatography and (2*S*,5*S*)- and (2*S*,5*R*)-**21** were isolated in 39% and 5% respective overall yield from ketone **16**. The predominant *trans*-isomer is proposed to result from a transition state involving coordination of the borohydride by the alcohol and intramolecular hydride delivery to the *si* face of the iminium ion (Fig. 5).[47,48] For comparison, an authentic sample of the minor alcohol isomer (2*S*,5*R*)-**21** was synthesized by reduction of acid (2*S*,5*R*)-**1** using borane in THF.[53]

(2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline was produced by two different oxidation procedures. Direct oxidation of alcohol **21** to acid (2*S*,5*S*)-**1** was accomplished in 86% yield using ruthenium trichloride and sodium periodate in a solvent mixture of 2:2:3 CCl_4/CH_3CN/H_2O (Scheme 5).[54] On larger scale, alcohol **21** was oxidized to the corresponding acid in 84% yield using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), sodium chlorite and sodium hypochlorite in a sodium phosphate buffered acetonitrile solution.[55] Alternatively, oxidation of **21** to the prolinal **22** was achieved using TPAP and *N*-methylmorpholine oxide in CH_2Cl_2.[50] Subsequent oxidation to the corresponding acid was then performed using $NaClO_2$ in 1:1 CH_3CN/*t*-BuOH to provide (2*S*,5*S*)-**1** in 45% overall yield from the two step process.[56] Because no epimerization was observed after purification of aldehyde **22** on silica gel nor during conversion to acid **1**, prolinal **22** is an attractive intermediate for synthesizing analogs of prolyl residues having *C*-terminal modifications, such as those found in the dolastatins,[57] to study relationships between their amide isomer geometry and bioactivity.

The enantiomeric purity of (2*S*,5*S*)-5-*tert*-butylproline (**1**) was determined as described previously.[21] Formation of diastereomeric α-methylbenzylamides was first performed on coupling (*R*)- and (*S*)-methylbenzylamine to (2*S*,5*S*)-**1** using TBTU in acetonitrile, then the Boc group was removed with TFA in CH_2Cl_2.[21] Integration of the *tert*-butyl singlets (1.055 and 1.065 ppm) in the proton 600 MHz NMR spectra in CD_3OD revealed the amides to be of a >98:2 diastereomeric ratio. Hence, (2*S*,5*S*)-5-*tert*-butylproline is presumed to be of >96% enantiomeric purity.

In conclusion, we have developed an efficient synthesis of (2*S*,5*S*)-5-*tert*-butylproline. Starting from methyl 2-*N*-(PhF)amino-5-oxo-6,6-dimethylheptanoate (**13**), a precursor of (2*S*,5*R*)-5-*tert*-butylproline, (2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline was obtained in 39% overall yield and >96% enantiomeric purity via directed hydride addition to imine **19**. With an effective means for producing (2*S*,5*S*)-5-*tert*-butylproline in hand, we are now exploring its introduction into peptides in order to study the influence of this stereoisomer on peptide conformation and biology.

3. Experimental

3.1. General

Unless otherwise noted, all reactions were run under a nitrogen atmosphere and distilled solvents were transferred by syringe. Dichloromethane was distilled over P_2O_5, THF was distilled over sodium/benzophenone, toluene was distilled over sodium and DIEA was distilled over ninhydrin and CaH_2. Final reaction mixture solutions were dried over Na_2SO_4. Chromatography was on 230–400 mesh silica gel, and TLC was on aluminium-backed silica plates. Mass spectral data, HRMS (EI and FAB), were obtained by the Université de Montréal Mass Spectroscopy facility. ^1H and ^{13}C NMR experiments were performed on Brucker ARX400 and av400 spectrometers. The chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$). Coupling constants are in Hertz. Aromatic carbon resonances for PhF groups are not reported.

3.1.1. (2*S*,5*RS*)-2-*N*-(PhF)Amino-5-hydroxy-6,6-dimethylheptanol (14). A solution of ketone **13** (3.16 g, 7.16 mmol) in a mixture of *tert*-butanol (200 mL) and MeOH (12 mL) was treated with $NaBH_4$ (0.812 g, 300 mol%), stirred at 60°C for 4 h, cooled to room temperature and diluted with water (150 mL). The mixture was extracted with EtOAc (3×150 mL) and the organic phase was washed with brine, dried and evaporated to a residue that was purified by chromatography on silica gel using 25% EtOAc in hexane as eluant. Evaporation of the collected fractions furnished a 1:1 mixture of diastereomers **14** (2.80 g, 94% yield) as a white foam: ^1H NMR ($CDCl_3$) δ 0.79 (s, 9H), 0.83 (s, 9H), 0.98 (m, 2H), 1.18–1.28 (m, 4H), 1.48 (m, 2H), 2.13–2.20 (m, 2H), 2.27 (br s, 2H), 2.77–3.12 (m, 6H), 7.19–7.43 (m, 22H), 7.67–7.74 (m, 4H); ^{13}C NMR

($CDCl_3$) δ 25.5, 25.6, 27.5 (2C), 30.8, 31.4, 34.7, 34.8, 53.5, 54.0, 63.7, 64.0, 72.5, 72.6, 79.3, 79.9; HRMS calcd for $C_{28}H_{34}O_2N$ (MH^+) 416.2589, found 416.2602.

3.1.2. (2*S*,5*RS*)-1-*tert*-Butyldimethylsiloxy-2-*N*-(PhF)-amino-5-hydroxy-6,6-dimethylheptane (15). A solution of diol **14** (2.74 g, 6.6 mmol) in CH_2Cl_2 (70 mL) was treated with DIEA (4.6 mL, 26.4 mmol), DMAP (0.08 g, 0.66 mmol) and TBDMSCl (1.99 g, 13.2 mmol). The mixture was heated at a reflux for 6 h when complete consumption of the starting alcohol (R_f=0.18, 30% EtOAc in hexane) was observed by TLC. The solution was evaporated to a residue that was dissolved in EtOAc (100 mL) and washed with 0.1 M HCl (100 mL) and brine, dried and evaporated to a residue that was purified by chromatography on silica gel using 5% EtOAc in hexane as eluant. The alcohol **15**, an oil (3.50 g, 99% yield) was obtained as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ −0.09 (t, 12H, J=7.9 Hz), 0.84 (s, 18H), 0.85 (s, 9H), 0.89 (s, 9H), 1.03–1.10 (m, 2H), 1.25 (m, 4H), 1.42–1.52 (m, 2H), 2.12 (m, 1H), 2.20 (m, 1H), 2.70 (br s, 2H), 2.88 (dd, 3H, J=4.9, 9.6 Hz), 3.00 (m, 4H), 3.22 (dd, 1H, J=5.2, 9.9 Hz), 7.18–7.47 (m, 22H), 7.67–7.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.7, −5.6, −5.5, −5.4, 18.2 (2C), 25.7, 25.8, 27.3, 27.8, 30.7, 32.1, 34.7, 34.8, 53.8, 54.6, 65.4 (2C), 72.5, 72.7, 79.6, 80.2; HRMS calcd for $C_{34}H_{47}O_2NSi$ (MH^+) 530.3455, found 530.3445.

3.1.3. (2*S*)-1-*tert*-Butyldimethylsiloxy-2-*N*-(PhF)amino-5-oxo-6,6-dimethylheptane (16). A solution of diol **15** (3.50 g, 6.6 mmol) and *N*-methylmorpholine oxide (1.54 g, 13.2 mmol) in CH_2Cl_2 (66 mL) over powdered 4 Å molecular sieves (4.0 g) was treated with tetrapropylammonium perruthenate (0.23 g, 10 mol%) at room temperature, stirred for 3 h and filtered through a pad of silica gel using 5% EtOAc in hexanes as eluant. Evaporation of the filtrate gave ketone **16** (3.44 g, 99% yield) as an oil: $[\alpha]^{20}_D$=−115.3° (c 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ −0.07 (d, 6H, J=8.8 Hz), 0.87 (s, 9H), 1.16 (s, 9H), 1.41–1.48 (m, 1H), 1.53–1.62 (m, 1H), 2.16 (m, 1H), 2.40 (m, 1H), 2.42 (m, 2H), 2.98 (dd, 1H, J=5.3, 9.8 Hz), 3.11 (dd, 1H, J=3.7, 9.9 Hz), 7.21–7.48 (m, 11H), 7.70–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.5, 18.2, 25.8, 26.5, 28.5, 33.6, 43.9, 53.5, 65.5, 72.5, 216.3; HRMS calcd for $C_{34}H_{45}O_2NSi$ (MH^+) 528.3298, found 528.3288.

3.1.4. (2*S*)-5-*tert*-Butyl-Δ^5-dehydroprolinol *p*-toluenesulfonate (18). Ketone **16** (2.15 g, 4.08 mmol) was treated with 25% TFA in CH_2Cl_2 (41 mL), anisole (2.2 mL, 20.4 mmol) and *p*-TsOH (0.776 g, 4.08 mmol), heated at a reflux for 18 h, cooled to room temperature and evaporated. The residue was digested with MeOH (5 mL) and then triturated with hexane (3×5 mL) to furnish the iminium salt **18** as an oil that was used without further purification: $[\alpha]^{20}_D$=+34.7° (c 0.6, MeOH); ^{1}H NMR (CD_3OD) δ 1.35 (s, 9H), 2.28 (m, 2H), 2.36 (s, 3H), 3.00 (m, 1H), 3.16 (m, 1H), 3.66 (d, 1H, J=11.9 Hz), 4.30 (d, 1H, J=12.4 Hz), 4.60 (m, 1H), 7.18 (d, 2H, J=7.98 Hz), 7.38 (br s, 1H), 7.73 (d, 2H, J=7.99 Hz); ^{13}C NMR (CD_3OD) δ 20.3, 22.2, 26.4, 35.0, 37.3, 61.6, 69.1, 125.9, 128.9, 140.8, 142.7, 205.0; HRMS calcd for $C_9H_{18}ON$ (MH^+) 156.1388, found 156.1381.

3.1.5. (2*S*,5*S*)-*N*-Boc-5-*tert*-butylprolinol (21). *p*-Toluenesulfonate **18** (4.08 mmol) was dissolved in $CHCl_3$ (40 mL), washed with a saturated aqueous solution of K_2CO_3 (30 mL), dried and evaporated to imine **19**: $[\alpha]^{20}_D$=+45.9° (c 0.4, MeOH); ^{1}H NMR (CD_3OD) δ 1.18 (s, 9H), 1.78 (m, 1H), 2.00 (m, 1H), 2.62 (m, 1H), 2.71 (m, 1H), 3.54 (dd, 1H, J=5.6, 11.1 Hz), 3.69 (dd, 1H, J=4.3, 11.1 Hz), 4.06 (m, 1H); ^{13}C NMR (CD_3OD) δ 26.0, 28.7, 34.7, 37.1, 65.7, 74.8, 189.3. Imine **19** (4.08 mmol) was dissolved in toluene (40 mL), treated with $NaHB(OAc)_3$ (1.30 g, 6.12 mmol) and heated at a reflux for 18 h. The solution was cooled, treated with HCl (4 mL, 2 M) and evaporated to a residue that was dissolved in MeOH, filtered and evaporated to furnish (2*S*,5*S*)-5-*tert*-butylproline hydrochloride (**20**): ^{1}H NMR (CD_3OD) δ 1.18 (s, 9H), 1.75 (m, 1H), 2.00 (m, 1H), 2.64 (m, 2H), 3.16 (m, 1H), 3.55 (dd, 1H, J=5.6, 11.1 Hz), 3.70 (dd, 1H, J=4.4, 11.1 Hz), 4.06 (m, 1H). The hydrochloride **20** was dissolved in CH_3CN (30 mL), treated with K_2CO_3 (1.60 g, 11.3 mmol) and di-*tert*-butyldicarbonate (2.40 g, 11.3 mmol). After 18 h, the mixture was treated with K_2CO_3 (0.538 g, 3.8 mmol) and di-*tert*-butyldicarbonate (0.799 g, 3.8 mmol) and stirred for 2 h when complete consumption of the amine was observed by TLC (R_f=0.17, 10% MeOH in $CHCl_3$). Evaporation of the volatiles gave a residue that was purified by chromatography on silica gel using a gradient of 0–20% EtOAc in hexane as eluant. First to elute was (2*S*,5*R*)-**21** (45.9 mg, 5% yield) which exhibited the same spectral and physical characteristics as material synthesized as described below. Last to elute was (2*S*,5*S*)-**21** (375 mg, 39% yield): $[\alpha]^{20}_D$=−4.9° (c 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9H), 1.48 (s, 9H), 1.53 (m, 1H), 1.74 (m, 1H), 1.85 (m, 1H), 2.10 (m, 1H), 3.68 (m, 1H), 3.75 (m, 1H), 3.85 (m, 1H), 3.89 (dd, 1H, J=1.5, 8.8 Hz), 5.00 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 28.1, 28.2, 28.8, 29.9, 63.2, 67.5, 80.7, 211.0; HRMS calcd for $C_{14}H_{28}O_3N$ (MH^+) 258.2069, found 258.2075.

3.1.6. (2*S*,5*R*)-*N*-Boc-5-*tert*-butylprolinol (21). A solution of (2*S*,5*R*)-**1** (50.8 mg, 0.19 mmol) in THF (0.4 mL) was added to a solution of $BH_3{\cdot}SMe_2$ (46mL, 0.46 mmol) in THF (0.4 mL). The mixture was stirred and heated at a reflux for 18 h. The excess BH_3 was destroyed by addition of MeOH (0.2 mL) and the solvent was removed by evaporation. The residue was purified by chromatography on silica gel using a gradient of 0–20% EtOAc in hexane as eluant. Evaporation of the collected fractions provided (2*S*,5*R*)-**21** (40 mg, 83% yield) as an oil: $[\alpha]^{20}_D$=−8.2° (c 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.48 (s, 9H), 1.81 (m, 3H), 2.01 (m, 1H), 3.67 (m, 2H), 3.81 (m, 1H), 3.98 (m, 1H), 5.50 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.4, 28.1, 28.7, 35.9, 63.3, 68.2, 81.4, 159.8.

3.1.7. (2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline (2*S*,5*S*)-1 from direct oxidation of (2*S*,5*S*)-21 with $RuCl_3$. A solution of prolinol (2*S*,5*S*)-**21** (15.7 mg, 65 μmol) in 2:2:3 CCl_4/CH_3CN/H_2O (1 mL) was treated with $NaIO_4$ (57 mg, 267 μmol) and $RuCl_3$ (0.8 mg, 2 μmol) at room temperature and stirred for 90 min. The mixture was partitioned between water (1 mL) and CH_2Cl_2 (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine, dried and evaporated to a residue that was purified by chromatography on silica gel using an initial gradient of 0–75% EtOAc in hexane followed by 80–90% EtOAc in hexane containing

0.5% AcOH as eluant to furnish (2*S*,5*S*)-**1** (15.2 mg, 86% yield) as an oil: $[\alpha]^{20}_{D}=-38.1°$ (*c* 0.7, MeOH).

3.1.8. (2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline (2*S*,5*S*)-1 from direct oxidation of (2*S*,5*S*)-21 with TEMPO. A solution of (2*S*,5*S*)-**21** (0.172 g, 0.67 mmoL) in a mixture of CH_3CN (3.3 mL) and sodium phosphate buffer (0.67 M, pH=6–7, 2.7 mL) was treated with TEMPO (10 mol%, 10.4 mg), a solution of $NaClO_2$ (0.121 g, 1.3 mmol) in H_2O (0.66 mL) and a solution of NaOCl (0.1 mL, 2 mol%) in H_2O (0.33 mL). After stirring at 35°C for 18 h, the mixture was cooled, partitioned between 0.1 M HCl (10 mL) and EtOAc (10 mL) and the aqueous phase was extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine, dried and evaporated to a residue that was purified by chromatography on silica gel using a gradient of 5–90% EtOAc in hexane as eluant. Evaporation of the collected fractions gave (2*S*,5*S*)-**1** (152 mg, 84%) as an oil: $[\alpha]^{20}_{D}=-38.5°$ (*c* 0.7, MeOH). lit.[21] $[\alpha]^{20}_{D}=-16.3°$ (*c* 0.7, MeOH); spectroscopic values for (2*S*,5*S*)-**1** were identical with those reported in Ref. 21.

3.1.9. (2*S*,5*S*)-*N*-Boc-5-*tert*-butylproline (2*S*,5*S*)-1 via prolinal 22. Prolinol (2*S*,5*S*)-**21** (12 mg, 50 μmol) was oxidized to aldehyde **22** in 74% yield using the same conditions described for the oxidation of alcohol **15** to ketone **16**: minor carbamate isomers are reported in brackets, ^1H NMR ($CDCl_3$) δ [0.90 (s, 2.2H)] 0.92 (s, 6.8H), 1.41 (s, 5.6H) [1.47 (s, 3.2H)], 1.86 (m, 3H), 2.26 (m, 1H), [3.88 (br s, 0.39H)] 4.03 (br s, 0.60H), 4.17 (d, 0.64H, *J*=8.1 Hz) [4.25 (br s, 0.28H), 9.43 (d, 0.55H, *J*=2.7 Hz). Aldehyde **22** (9.5 mg, 37 μmol) was dissolved in 1:1 CH_3CN/*t*-BuOH (1 mL) and treated with a solution of $NaClO_2$ (45 mg, 500 μmol) and NaH_2PO_4 (54 mg, 450 μmol) in H_2O (0.25 mL). After 2 h, more $NaClO_2$ (50 mg) was added, the reaction was stirred for 30 min and another portion of $NaClO_2$ (50 mg) was added. After stirring for 30 min, the mixture was partitioned between ether (3 mL) and H_3PO_4 (2 mL, 1 M). The aqueous phase was extracted with Et_2O (3×3 mL). The combined organic layers were washed with brine, dried and evaporated to a residue that was purified by chromatography on silica gel using the same conditions reported above. Evaporation of the collected fractions gave (2*S*,5*S*)-**1** (6.1 mg, 61% yield) as an oil: $[\alpha]^{20}_{D}=-37.1°$ (*c* 0.5, MeOH), lit.[21] $[\alpha]^{20}_{D}=-16.3°$ (*c* 0.7, MeOH); spectroscopic values for (2*S*,5*S*)-**1** were identical with those reported in Ref. 21

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