5-*tert*-Butylproline

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Steric effects on the isomer equilibrium of amides *N*-terminal to proline can be explored with 5-alkylprolines having bulky 5-position substituents. Enantiopure 5-*tert*-butylprolines were thus synthesized from glutamic acid via an acylation/diastereoselective reductive amination sequence. Double deprotonation of γ-methyl *N*-(PhF)glutamate (**2**) with $LiN(SiMe_3)_2$ and *C*-acylation with pivaloyl chloride provided β-keto ester **3**, which upon γ-ester hydrolysis and decarboxylation gave δ-oxo-α-[*N*-(PhF)amino]heptanoic acid (**4**). Syntheses of (2*S*,5*R*)- and (2*R*,5*S*)-*N*-(BOC)-5-*tert*-butylprolines ((2*S*,5*R*)-**1** and (2*R*,5*S*)-**1**) were accomplished by catalytic hydrogenation of their respective (2*S*)- and (2*R*)-methyl δ-oxo-α-[*N*-(PhF)amino]heptanoates ((2*S*)-**5a** and (2*R*)-**5a**) in methanol with di-*tert*-butyl dicarbonate followed by chromatography and ester hydrolysis with potassium trimethylsilanolate. The 5-*tert*-butylproline *cis*-diastereomers were proven to be of >99% enantiomeric purity after their conversion to diastereomeric α-methylbenzylamides **10**. Good diastereoselectivity in favor of the *trans*-diastereomer was observed when (2*S*,5*S*)-5-*tert*-butylproline was synthesized from (2*S*)-δ-oxo-α-[*N*-(PhF)amino]heptanoate ((2*S*)-**4**) by solvolysis of the PhF group in trifluoroacetic acid and subsequent reduction of 5-*tert*-butyl-Δ^5-dehydroproline (**11**) with tetramethylammonium triacetoxyborohydride; however, imino acid **11** was shown to be configurationally labile and racemized under acidic conditions. 5-*tert*-Butyl-Δ^5-dehydroproline *N*′-methylamide **15** was configurationally stable in acid, yet preliminary attempts to reduce **15** favored *cis*-diastereomer **16**. Alternatively, enantiopure *trans*-diastereomer, (2*R*,5*R*)-methyl *N*-(BOC)-5-*tert*-butylprolinate (**9**) was prepared by epimerization of (2*S*,5*R*)-**9**. In summary, this synthetic methodology now provides access to all four enantiopure 5-*tert*-butylproline isomers from inexpensive L- and D-glutamate as chiral educts.

Introduction

Amides *N*-terminal to proline possess energetically similar *cis*- and *trans*-isomers that are separated by a significant barrier for isomerization (Figure 1).[1] Consequently, isomer geometry plays an important role in the recognition, reactivity, and stability of bioactive peptides and proteins that possess prolyl residues.[2−5] For example, proline-specific peptidases require the *trans*-isomer to hydrolyze X-Pro peptide bonds.[3] In addition, the acceleration of the folding of particular proteins by peptidyl prolyl *cis*/*trans* isomerase-catalyzed isomerization of X-Pro amide bonds may implicate substrate binding as X-Pro amide *cis*-isomers in type-VI β-turn conformations.[4,6,7]

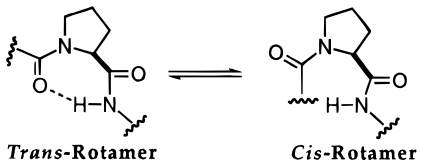

Figure 1. Amide isomer equilibrium *N*-terminal to proline derivatives.

The conformational heterogeneity of peptides possessing X-Pro residues has often confounded efforts to elucidate bioactive structures of native peptides using X-ray diffraction and NMR spectroscopy.[2] The identification of a bioactive structure is made more complicated due to influences on isomer geometry from environmental conditions such as solvent polarity and pH.[6,8] Because

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(1) MacArthur, M. W.; Thornton, J. M. *J. Mol. Biol.* **1991**, *218*, 397.

(2) Recent examples of bioactive peptides exhibiting X-Pro amide *cis*:*trans* isomer equilibrium include the following: oxytocin and vasopressin: (a) Larive, C. K.; Guerra, L.; Rabenstein, D. L. *J. Am. Chem. Soc.* **1992**, *114*, 7331. Morphiceptin: (b) Yamazaki, T.; Ro, S.; Goodman, M.; Chung, N. N.; Schiller, P. W. *J. Med. Chem.* **1993**, *36*, 708. Aureobasidin E: (c) Fujikawa, A.; In, Y.; Inoue, M.; Ishida, T., Nemoto, N.; Kobayashi, Y.; Kataoka, R.; Ikai, K.; Takesako, K.; Kato, I. *J. Org. Chem.* **1994**, *59*, 570. The *C*-terminal binding domain of *Pseudomonas aeruginosa*: (d) McInnes, C.; Kay, C. M.; Hodges, R. S.; Sykes, B. D. *Biopolymers* **1994**, *34*, 1221. Segatalin A: (e) Morita, H.; Yun, Y. S.; Takeya, K.; Itokawa, H.; Shiro, M. *Tetrahedron* **1995**, *51*, 5987.

(3) The relationship between the X-Pro isomer geometry and protease specificity is presented in: (a) Lin, L.-N.; Brandts, J. F. *Biochemistry* **1979**, *18*, 5037. (b) Lin, L.-N.; Brandts, J. F. *Biochemistry* **1979**, *18*, 43.

(4) X-Pro isomerization in protein folding is reviewed in: (a) Fischer, G.; Schmid, F. X. *Biochemistry* **1990**, *29*, 2205. X-Pro isomerization in protein denaturation is presented in: (b) Brandts, J. F.; Halvorson, H. R.; Brennan, M. *Biochemistry* **1975**, *14*, 4953. The role of *cis*−*trans* isomerization in the folding and renaturation of collagen is discussed in: (c) Heidemann, E.; Roth, W. *Adv. Polym. Sci.* **1982**, *43*, 143. X-Pro isomer geometry and the stability of staphylococcal nuclease is presented in: (d) Markley, J. L.; Hinck, A. P.; Loh, S. N.; Prehoda, K.; Truckses, D.; Walkenhorst, W. F.; Wang, J. *Pure Appl. Chem.* **1994**, *66*, 65. The importance of conformational changes of membrane-buried proline residues in transport proteins is presented in: (e) Williams, K. A.; Deber, C. M. *Biochemistry* **1991**, *30*, 8219. (f) Brandl, C. J.; Deber, C. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 917.

(5) The role of X-Pro isomer geometry in the antibody recognition of peptide antigens is presented in: (a) Richards, N. G. J.; Hinds, M. G.; Brennand, D. M.; Glennie, M. J.; Welsh, J. M.; Robinson, J. A. *Biochem. Pharm.* **1990**, *40*, 119. (b) A type VI β-turn conformation has been suggested as a requirement for thrombin-catalyzed cleavage of the V_3 loop of HIV gp120, a prerequisite to viral infection. See: Johnson, M. E.; Lin, Z.; Padmanabhan, K.; Tulinsky, A.; Kahn, M. *FEBS Lett.* **1994**, *337*, 4.

(6) PPIases are reviewed in: (a) Fischer, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1415. (b) Schmid, F. X.; Mayr, L. M.; Mücke, M.; Schönbrunner, E. R. *Adv. Protein Chem.* **1993**, *44*, 25. (c) Stein, R. L. *Adv. Protein Chem.* **1993**, *44* , 1.

(7) The importance of type VI β-turns in PPIase-catalyzed isomerization of X-Pro bonds is presented in: (a) Fischer, S.; Michnick, S.; Karplus, M. *Biochemistry* **1993**, *32*, 13830. (b) Fischer, S.; Dunbrack, R. L., Jr.; Karplus, M. *J. Am. Chem. Soc.* **1994**, *116*, 11931.

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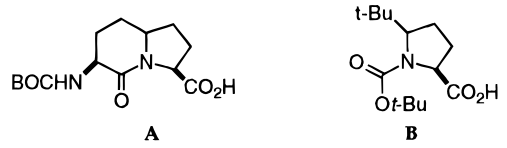

Figure 2. δ-Alkylprolines as conformationally rigid amide isomer surrogates.

knowledge of the bioactive conformation is principal to the rational design of therapeutics based on peptide leads, conformationally rigid surrogates of the *cis*- and *trans*-amide isomers of X-Pro residues have emerged as important tools for elucidating structure−activity relationships of peptides that possess prolyl residues.[9]

We are exploring the relationship between X-Pro amide conformation and peptide bioactivity through the use of 5-alkylprolines that function as fixed *trans*- and *cis*-isomer surrogates (Figure 2). We recently reported the synthesis of enantiopure 2-oxo-3-*N*-[(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylic acid in which the amide is locked in the *trans*-isomer by linking the 5-position of proline to its *N*-terminal amino acid in a six-membered lactam (Figure 2A).[10] We are currently investigating incorporation of this indolizidinone amino acid into peptides in order to examine its potential to serve as a conformationally fixed surrogate of β- and γ-turn conformations.[11]

In this paper, we report methodology for synthesizing 5-alkylprolines possessing bulky 5-position substituents.[12] All four stereoisomers of 5-*tert*-butylproline can now be synthesized in >99% enantiomeric purity from inexpensive glutamic acid as chiral educt. By allowing for the selective introduction of sterically demanding tertiary alkyl substituents at the proline 5-position, our process offers a unique advantage when compared to previous methods to synthesize 5-alkylprolines.[15,16] Furthermore, our method provides *N*-(BOC)-5-*tert*-butylprolines (**1**) that are suitable for incorporation into peptides using standard coupling techniques.[12a]

Since the steric interactions between the 5-position substituent and the *N*-terminal residue disfavor the X-Pro amide *trans*-isomer, they increase the *cis*-isomer population.[12−14] We synthesized 5-*tert*-butylprolines specifically in order to study the importance of X-Pro amide *cis*-isomer populations to the activity of prolyl peptides (Figure 2B). We have also synthesized and examined the conformational preferences of *N*-acetyl-5-*tert*-butylproline *N*′-methylamides.[14] Besides increasing the X-Pro *cis*-amide isomer population, incorporation of 5-*tert*-butylprolines into peptides influences the proline ψ dihedral angle and alters the energy barrier for X-Pro isomeri-

(8) The relationship between pH and the X-Pro amide isomer equilibrium of angiotensin II and thyrotropin-releasing hormone (TRH) is presented in: (a) Liakopoulou-Kyriakides, M.; Galardy, R. E. *Biochemistry* **1979**, *18*, 1952. (b) Unkefer, C. J.; Walker, R. D.; London, R. E. *Int. J. Peptide Protein Res.* **1983**, *22*, 582.

(9) Conformationally rigid amide surrogates have been used to study the importance of X-Pro amide isomer geometry in the following compounds. TRH: (a) Mapelli, C.; van Halbeek, H.; Stammer, C. H. *Biopolymers* **1990**, *29*, 407. Morphiceptin: (b) Yamazaki, T.; Pröbstl, A.; Schiller, P. W.; Goodman, M. *Int. J. Peptide Protein Res.* **1991**, *37*, 364. β-Casomorphin-5: (c) Tourwé, D.; Van Betsbrugge, J.; Verheyden, P.; Hootelé, C. *Bull. Soc. Chim. Belg.* **1994**, *103*, 201. Cyclic somatostatin analogues: (d) Brady, S. F.; Paleveda, W. J., Jr.; Arison, B. H.; Saperstein, R.; Brady, E. J.; Raynor, K.; Reisine, T.; Veber, D. F.; Freidinger, R. M. *Tetrahedron* **1993**, *49*, 3449. (e) Beusen, D. D.; Zabrocki, J.; Slomczynska, U.; Head, R. D.; Kao, J. L.-F.; Marshall, G. R. *Biopolymers* **1995**, *36*, 181. (f) Elseviers, M.; van der Auwera, L.; Pepermans, H.; Tourwé, D.; van Binst, G. *Biochem. Biophys. Res. Commun.* **1988**, *154*, 515. Bradykinin and angiotensin II: (g) Juvvadi, P.; Dooley, D. J.; Humblet, C. C.; Lu, G. H.; Lunney, E. A.; Panek, R. L.; Skeean, R.; Marshall, G. R. *Int. J. Peptide Protein Res.* **1992**, *40*, 163. Bradykinin: (h) Zabrocki, J.; Dunbar, J. B.; Marshall, K. W.; Toth, M. V.; Marshall, G. R. *J. Org. Chem.* **1992**, *57*, 202. A peptide substrate of HIV protease: (i) Garofolo, A.; Tarnus, C.; Remy, J.-M.; Leppik, R.; Piriou, F.; Harris, B.; Pelton, J. T. In *Peptides: Chemistry, Structure and Biology*; Rivier, J. E., Marshall, G. R., Eds.; ESCOM Science Publishers B.V.: Leiden, The Netherlands, 1990; pp 833−834. Conformationally rigid X-Pro amide isomer surrogates have also been designed to inhibit PPIases: (j) Andres, C. J.; Macdonald, T. L.; Ocain, T. D.; Longhi, D. *J. Org. Chem.* **1993**, *58*, 6609. (k) Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett.* **1994**, *35*, 6033.

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(11) (a) Lombart, H.-G.; Lubell, W. D. In *Peptides 1994* (*Proceedings of the 23rd European Peptide Symposium*); Maia, H. L. S., Ed.; ESCOM: Leiden, The Netherlands, 1995; p 696. (b) Lombart, H.-G.; Lubell, W. D. In *Peptides: Chemistry, Structure and Biology*; Kaumaya, P. T. P., Hodges, R. S., Eds.; ESCOM Sci. Pub. B.V.: Leiden, The Netherlands, 1995; pp 695−696.

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(13) The effects of 5-methyl substituents on the X-Pro amide isomer equilibrium are presented in: (a) Delaney, N. G.; Madison, V. *Int. J. Peptide Protein Res.* **1982**, *19*, 543. (b) Magaard, V. W.; Sanchez, R. M.; Bean, J. W.; Moore, M. L. *Tetrahedron Lett.* **1993**, *34*, 381. A *cis*-amide isomer is also present in the X-ray structure of Fmoc-Ala-Dmt-OH in which Dmt is the 2,2-dimethylthiazolidine derivative of cysteine: (c) Nefzi, A.; Schenk, K.; Mutter, M. *Protein Peptide Lett.* **1994**, *1*, 66. *N*-Acetyl-2,2-dimethylthiazolidine-4-carboxylic acid has also been reported to be locked in the *cis*-isomer: (d) Savrda, J. In *Peptides 1976*; Loffet, A., Ed.; Edition de l'Université de Bruxelles: Brussels, 1976; p 653.

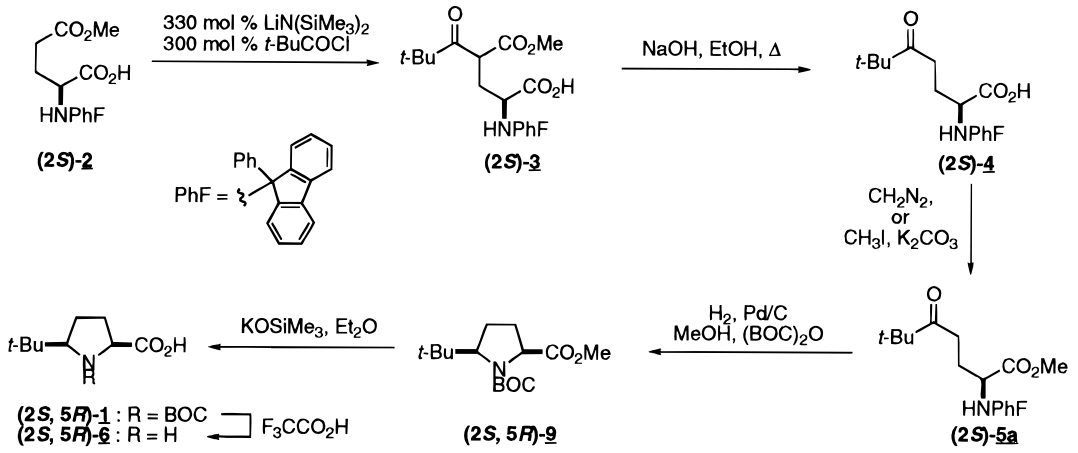
(14) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12901−12908.

(15) Synthetic methods to prepare racemic 5-alkylproline have been reviewed in: (a) Mauger, A. B.; Witkop, B. *Chem. Rev.* **1966**, *66*, 47. Recent methods to synthesize optically active 5-alkylprolines include the following examples. Tandem Horner−Emmons−Michael reaction on a 5-hydroxyproline: (b) Collado, I.; Ezquerra, J.; Vaquero, J. J.; Pedregal, C. *Tetrahedron Lett.* **1994**, *35*, 8037. Nucleophilic addition to *N*-acyl Δ^1-pyrroline-5-carboxylates: (c) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573. (d) Manfré, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060. (e) Thaning, M.; Wistrand, L. -G. *Acta Chem. Scand.* **1992**, *46*, 194. (f) Manfré, F.; Pulicani, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 235. (g) Célimène, C.; Dhimane, H.; Le Bail, M.; Lhommet, G. *Tetrahedron Lett.* **1994**, *35*, 6105. (h) McClure, K. F.; Renold, P.; Kemp, D. S. *J. Org. Chem.* **1995**, *60*, 454. (i) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011. Condensation of nitromethane to a pyroglutamate-derived alkyliminum salt and hydrogenation of the resulting enamine: (j) Jain, S.; Sujatha, K.; Krishna, K. V. R.; Roy, R.; Singh, J.; Anand, N. *Tetrahedron* **1992**, *48*, 4985. 1,3-Dipolar cycloadditions of azomethine ylides: (k) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817. (l) Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527. (m) Waldmann, H.; Bläser, E.; Jansen, M.; Letschert, H.-P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 683. (n) Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.* **1995**, *60*, 5005. Intramolecular *N*-alkylation: (o) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859. (p) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K *Tetrahedron Lett.* **1989**, *30*, 3805. (q) Ohta, T.; Hosoi, A.; Kimura, T.; Nozoe, S. *Chem. Lett.* **1987**, 2091. (r) Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948. Intramolecular reductive amination: (s) Ho, T. L.; Gopalan, B.; Nestor, J. J., Jr. *J. Org. Chem.* **1986**, *51*, 2405. (t) Fushiya, S.; Chiba, H.; Otsubo, A.; Nozoe, S. *Chem. Lett.* **1987**, 2229. Sulfide contraction on a pyroglutamate-derived thioamide and hydrogenation of the resulting enamine. (u) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229.

(16) 3,4-Dialkyl-5-*tert*-butylproline derivatives have been synthesized in good yield via diastereoselective Michael addition of a glycine enolate to α,β-unsaturated esters followed by intramolecular cyclization of imine intermediates: (a) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411. (b) Tatsukawa, A.; Dan, M.; Ohbatake, M.; Kawatake, K.; Fukata, T.; Wada, E.; Kanemasa, S.; Kakei, S. *J. Org. Chem.* **1993**, *58*, 4221. A 2,4-dialkyl-5-*tert*-butylproline derivative was synthesized in low yield via a diastereoselective 1,3-dipolar cycloaddition of an azomethine ylide: (c) Waldmann, H.; Bläser, E.; Jansen, M.; Letschert, H.-P. *Chem. Eur. J.* **1995**, *1*, 150.

(17) Azabicycloalkane Gly-Pro type VI β-turn peptidomimetics are described in: (a) Dumas, J.-P.; Germanas, J. P. *Tetrahedron Lett.* **1994**, *35*, 1493. (b) Gramberg, D.; Robinson, J. A. *Tetrahedron Lett.* **1994**, *35*, 861. Bicyclic X-Pro peptidomimetics with constrained *cis*-isomers are also presented in: (c) Curran, T. P.; McEnaney, P. M. *Tetrahedron Lett.* **1995**, *36*, 191. (d) Lenman, M. M.; Ingham, S. L.; Gani, D. *Chem. Commun.* **1996**, 85.

Scheme 1. Synthesis of (2*S*,5*R*)-5-*tert*-Butylproline 1



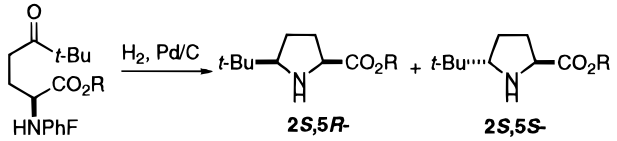
zation.[12−14] *N*-(BOC)-5-*tert*-butylproline should thus be useful for examining X-Pro amide *cis*-isomers in bioactive peptides as well as for synthesizing type-VI β-turn mimetics.[17]

Results and Discussion

***cis*-*N*-(BOC)-5-*tert*-butylprolines ((2*S*,5*R*)-1 and (2*R*,5*S*)-1).** We demonstrated previously that acylation of the lithium γ-enolate of α-*tert*-butyl γ-methyl *N*-(9-(9-phenylfluorenyl))glutamate with different acid chlorides provides β-keto esters.[18] Hydrolysis and decarboxylation of the γ-ester then furnishes enantiomerically pure δ-oxo α-amino esters possessing alkyl and aromatic δ-substituents.[18] In the acylation of the γ-enolate to prepare β-keto ester, we have found that α-carboxylate protection and pyroglutamate formation can both be avoided and high yields can be achieved by double deprotonating γ-methyl *N*-(PhF)glutamate (**2**, Scheme 1, PhF = 9-(9-phenylfluorenyl)).[19] Treatment of **2** with 200 mol % of lithium bis(trimethylsilyl)amide deprotonates the α-carboxylate and generates the γ-enolate, which reacts with pivaloyl chloride to provide β-keto ester **3** after aqueous workup and chromatography.[20] We have optimized acylation of **2** to furnish β-keto ester **3** in 75% yield by using ∼300 mol % of both $LiN(SiMe_3)_2$ and pivaloyl chloride. β-Keto ester **3** was observed by proton NMR as a mixture of diastereomers, each exhibiting a γ-proton appearing as a doublet of doublets in the region between 4 and 4.7 ppm.

Hydrolysis and decarboxylation of β-keto ester **3** with sodium hydroxide provided the δ-oxo α-*N*-(PhF)amino acid **4** in 78% yield after chromatography. Esterification of acid **4** was accomplished quantitatively with diazomethane in ether as well as with iodomethane and potassium carbonate in acetonitrile, providing methyl δ-oxo-α-[*N*-(PhF)amino]heptanoate **5a** after chromatography. On a large scale, chromatographic isolation of acids **3** and **4** was shown to be unnecessary. Multigram quantities of δ-oxo α-amino ester **5a** can now be obtained in ∼50% overall yield from glutamate **2** by the acylation, hydrolysis, decarboxylation, and esterification sequence presented in Scheme 1.

Table 1. Influence of α-Carboxylate Protection in the Diastereoselective Hydrogenation of 4, 5a and 5b[a]



	2*S*,5*R*-		2*S*,5*S*-
4 : R = H	86	**6** : R = H	14
5a : R = Me	90	**7** : R = Me	10
5b : R = *t*-Bu	>99	**8** : R = *t*-Bu	<1[b]

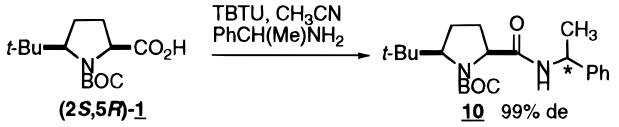
[a] Performed in a 9.6 M 9:1 MeOH:AcOH solution with 5 mol % Pd/C at 4 atm of H_2. [b] (2*S*,5*S*)-**8** was not detected.

Hydrogenations of δ-oxo-α-[*N*-(PhF)amino]heptanoic acid (**4**), methyl ester **5a**, and *tert*-butyl ester **5b**[18] were examined in order to study the influence of the α-carboxylate on the diastereoselectivity of the reductive amination. We performed our study in 0.6 M 9:1 methanol:acetic acid solutions with palladium-on-carbon as catalyst under 4 atm of hydrogen for 24 h (Table 1). Under these conditions, hydrogenation of δ-oxoheptanoates **4**, **5a**, and **5b** proceeds by cleavage of the phenylfluorenyl group, intramolecular imine formation, protonation, and hydrogen addition to the iminium ion intermediate.[15s] The diastereomeric ratios of (2*S*,5*R*)- and (2*S*,5*S*)-5-*tert*-butylprolines **6**−**8** were ascertained by proton NMR of the crude product after removal of the catalyst by filtration and evaporation of the volatiles under vacuum. The stereochemistry of esters **7** and **8** was assigned on the basis of analogy with our previous work.[18] Deprotection of (2*S*,5*R*)-*tert*-butyl ester **8** with trifluoroacetic acid gave an authentic sample of (2*S*,5*R*)-*tert*-butylproline ((2*S*,5*R*)-**6**). Our examination demonstrates clearly that steric bulk at the α-carboxylate favors hydrogen addition to the less hindered face of the iminium ion, providing the *cis*-diastereomers (Table 1). Hydrogenation of (2*S*)-*tert*-butyl ester **5b** proceeds diastereospecifically, furnishing (2*S*,5*R*)-*tert*-butylproline **8**.[12b]

We next employed a one-pot reductive amination/nitrogen protection process in order to prepare (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*R*)-**1**). Hydrogenation of (2*S*)-δ-oxo-α-[*N*-(PhF)amino]heptanoate (2*S*)-**5a** with palladium-on-carbon and di-*tert*-butyl dicarbonate in methanol without acetic acid proceeds by cleavage of the PhF protection, cyclization, *N*-acylation, and hydrogen addition, furnishing selectively (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline methyl ester ((2*S*,5*R*)-**9**) in 77% yield after

(18) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438.
(19) Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 3184.
(20) In a preliminary investigation a mixed anhydride was formed by reacting **2** with pivaloyl chloride and triethylamine in THF. When the mixed anhydride was treated with 100 mol % of $LiN(SiMe_3)_2$ in THF at −78 °C, the formation of β-keto ester **3** was observed by ^1H NMR examination of the crude product. Acylation of the dianion of **2** may thus proceed in part by *O*-acylation to provide a transient anhydride that undergoes intramolecular *C*-acylation via a six-membered transition state.

Scheme 2. Enantiomeric Purity of (2*S*,5*R*)-5-*tert*-Butylproline 1



chromatography. Since hydrogenation of Δ^1-pyrrolidine in alcoholic solvents without acid is normally a poor reaction,[15s] in this one-pot process, an *N*-acyliminium salt is presumably reacting with hydrogen in the presence of the palladium catalyst. Examination of **9** by proton NMR prior to chromatography showed a 97:3 ratio of *cis:trans* diastereomers and demonstrated that hydrogenation of **5a** via the *N*-acyliminium proceeded with higher diastereoselectivity than the hydrogenation of **5a** via the protonated iminium ion (90:10, Table 1). Hydrolysis of methyl ester (2*S*,5*R*)-**9** with potassium trimethylsilanolate (150 mol %) in Et_2O furnished (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*R*)-**1**) as a crystalline solid after aqueous extraction.[21] Removal of the BOC protecting group with trifluoroacetic acid in dichloromethane and evaporation of the volatiles under vacuum provided quantitatively (2*S*,5*R*)-5-*tert*-butylproline ((2*S*,5*R*)-**6**) as a TFA salt that was free based by ion-exchange chromatography on a Dowex 1-X8 resin (Scheme 1). When D-glutamic acid was employed in the same sequence of reactions, (2*R*,5*S*)-**1** was obtained in comparable overall yield.

In order to ascertain if any racemization had occurred during the syntheses of the 5-*tert*-butylproline *cis*-diastereomers from glutamic acid, the enantiomeric purity of proline (2*S*,5*R*)-**1** was investigated after conversion to diastereomeric α-methylbenzylamides **10** (Scheme 2). Both (*R*)- and (*S*)-α-methylbenzylamine were coupled to proline (2*S*,5*R*)-**1** in high yield using benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) in acetonitrile.[22] By integrating the diastereomeric 5-*tert*-butyl singlets ($\delta = 0.74, 0.93$), we established amide (1′*S*)-**10** to be of 99% diastereomeric purity. Since (*S*)-α-methylbenzylamine of 99% ee was used in the coupling step, proline (2*S*,5*R*)-**1** is presumed to be of >99% enantiomeric purity. Hence, no racemization was observed in the synthesis of *cis*-diastereomer **1**.

***trans*-*N*-(BOC)-5-*tert*-butylprolines (2*S*,5*S*)-1 and (2*R*,5*R*)-1.** With an efficient route in hand to synthesize enantiopure *cis*-diastereomers of 5-*tert*-butylproline, (2*S*,5*R*)- and (2*R*,5*S*)-**1**, we began the more formidable task to prepare *trans*-isomers (2*S*,5*S*)-**1** and (2*R*,5*R*)-**1**. In order to synthesize the *trans*-diastereomer, we investigated a novel approach involving carboxylate-directed hydride reduction of an iminium ion intermediate. (2*S*)-5-*tert*-Butyl-Δ^5-dehydroproline trifluoroacetate ((2*S*)-**11**) was synthesized in quantitative yield from δ-keto α-amino acid (2*S*)-**4** (Scheme 3). Treatment of (2*S*)-δ-oxo-α-[*N*-(PhF)amino]heptanoate ((2*S*)-**4**) with trifluoroacetic acid in dichloromethane effected solvolysis of the phenylfluorenyl group and intramolecular cyclization to imino acid (2*S*)-**11**, which was isolated as the trifluoroacetate after removal of the hydrocarbon impurities by trituration with hexanes. The zwitterionic form of imino acid **11** was also prepared by ion-exchange chromatography.

We hypothesized that coordination of a borohydride salt by the α-carboxylate of (2*S*)-**11** could direct hydride addition to the iminium ion and give *trans*-diastereomer (2*S*,5*S*)-**6**. Carboxylate complexation of metal ion has been suggested to bias the direction of organocuprate additions to *N*-acyl-Δ^5-dehydroprolinates.[15e] Since hydroxyl-directed reductions with tetramethylammonium triacetoxyborohydride proceed with good diastereoselectivity,[23] and because triacetoxyborohydrides effectively reduce imines,[24] we examined $Me_4NHB(OAc)_3$ in the reduction of **11** (Table 2).

tert-Butylprolines **6** were purified by ion-exchange chromatography; however, the diastereoselectivity of imine reductions was ascertained by proton NMR of the

Scheme 3. Synthesis of (2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline (1) via Iminium Ion 11

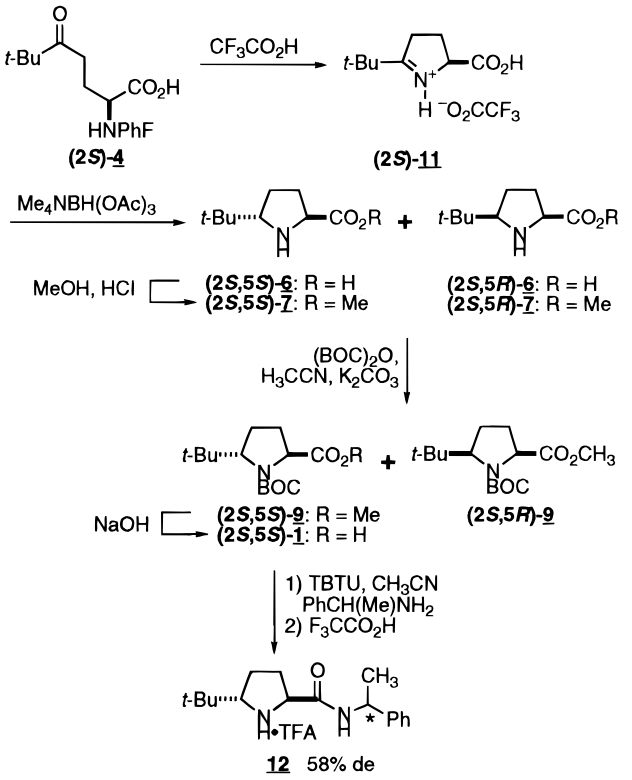
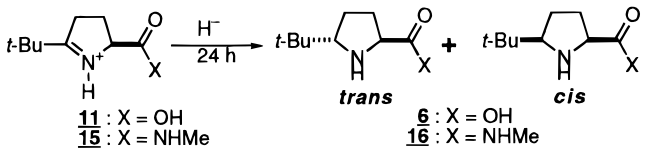


Table 2. Hydride Additions to Imino Acid 11 and Imino Amide 15[a]



entry	substrate	hydride	solvent	*T* (°C)	trans:cis
a	**11**·TFA	$NaCNBH_3$	THF	66	43:57
b	**11**·TFA	$Me_4NBH(OAc)_3$	THF	66	83:17[b]
c	**11**·TFA	$Me_4NBH(OAc)_3$	THF	0	66:33
d	**11**	$Me_4NBH(OAc)_3$	CH_3CN	−70	33:66
e	**11**	$NaCNBH_3$	CH_3CN	−40	50:50
f	**11**	$Me_4NBH(OAc)_3$	CH_3CN	0	58:42
g	**11**	$Me_4NBH(OAc)_3$	CH_3CN	−40	54:46
h	**15**·TFA	$Me_4NBH(OAc)_3$	THF	66	37:74
i	**15**·TFA	$Me_4NBH(OAc)_3$	CH_3CN	0	50:50[c]

[a] Unless noted 100% conversion. [b] 100% conversion after 6 h. [c] 66% conversion after 96 h.

(21) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
(22) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927.
(23) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(24) (a) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595. (b) Grandjean, C.; Rosset, S.; Célérier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1993**, *34*, 4517.

crude (2*S*,5*S*)- and (2*S*,5*R*)-*tert*-butylprolines (**6**) after addition of 1 M HCl and evaporation. The signals of the diastereomeric α-, *δ*-, and *tert*-butyl protons of **6** were all well resolved in CD_3OD acidified with TFA. In general, we have noted that the coupling pattern of the α-proton signal of 5-*tert*-butylproline analogues (**6**, **7**, and **16**) is different for the *cis*- and *trans*-diastereomers. In the ^1H NMR,the α-proton signal of the *trans*-diastereomer is observed as a triplet and that of the *cis*-diastereomer appears as a doublet of doublets.

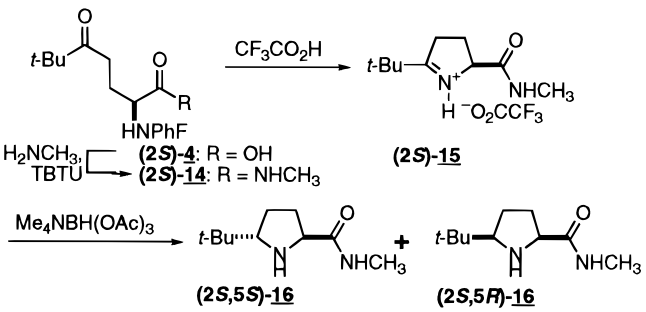
In our best conditions, solid $Me_4NHB(OAc)_3$ was added to a solution of 5-*tert*-butyl-Δ^5-dehydroproline trifluoroacetate (**11**) in THF at reflux (entry b in Table 2). We received an 86:14 ratio of *trans*:*cis* diastereomers (2*S*,5*S*)- and (2*S*,5*R*)-**6** in 96% yield after ion-exchange chromatography. The predominant formation of *trans*-diastereomer (2*S*,5*S*)-**6** is presumed to be due to a carboxyl-directed addition of hydride to the iminium. Employment of $NaCNBH_3$ in lieu of $Me_4NBH(OAc)_3$ under the same conditions gave a 43:57 ratio of (2*S*,5*S*)-**6**: (2*S*,5*R*)-**6**. Reduced diastereoselectivity also resulted at lower temperature. Similarly, the diastereoselectivity decreased in acetonitrile and when the zwitterionic form of **11** was employed.

Diastereomers (2*S*,5*S*)- and (2*S*,5*R*)-**6** were converted to *N*-(BOC)-5-*tert*-butylproline methyl esters (**9**) on treatment with methanolic HCl followed by acylation with di-*tert*-butyl dicarbonate in acetonitrile with potassium carbonate.[25] Separation of the diastereomers was then achieved by chromatography on silica gel with 0−2% EtOAc in hexanes as eluant. (2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline (**1**) was obtained on hydrolysis of methyl ester **9** using potassium hydroxide in dioxane (Scheme 3).

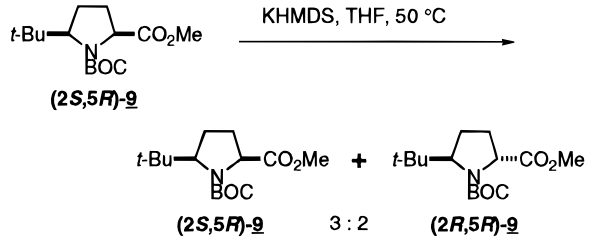
The enantiomeric purity of (2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline (**1**) was next ascertained by the preparation of diastereomeric amides **12**. Acid **1** was coupled to both (*R*)- and (*S*)-α-methylbenzylamine using TBTU in acetonitrile, and the BOC group was subsequently removed using TFA. Examination of the *tert*-butyl singlets (1.02 and 1.03 ppm) as well as the α-proton signals in the 400 MHz ^1H NMR in CD_3OD indicated that amides **12** were of only 58% diastereomeric excess. Racemization had obviously occurred after the removal of the PhF protection during either the deprotection or the reduction steps to produce (2*S*,5*S*)-**1**. By monitoring the decrease in the value of the specific rotation of **11** upon exposure to the deprotection conditions (TFA in CH_2Cl_2 at reflux),[26] we confirmed that imino acid **11** was configurationally labile under the acidic conditions.

In light of these results, we decided to explore amide-directed hydride addition to 5-*tert*-butyl-Δ^5-dehydroproline *N*′-methylamide trifluoroacetate (**15**) (Scheme 4). Since racemization of imino acid **11** presumably arose from enolization toward the α-carbon on protonation of the carboxylate, we expected **15** to be more configurationally stable than **11** because the amide would be less prone to enolize under acidic conditions.[27] (2*S*)-*N*′-Methyl-*δ*-oxo-α-[*N*-(PhF)amino]heptanamide ((2*S*)-**14**) was synthesized in 78% yield from acid (2*S*)-**4** and methylamine using TBTU in acetonitrile. Solvolysis of the PhF group

Scheme 4. Synthesis of (2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline 1 via Iminium Ion 15



Scheme 5. Epimerization of (2*S*,5*R*)-5-*tert*-Butylprolinates 9



and imine formation proceeded slowly when amide (2*S*)-**14** was treated with TFA in CH_2Cl_2 at reflux, yet furnished imino amide **15** in 92% yield. Examination of **15** after exposure to TFA in refluxing CH_2Cl_2 for 24 and 48 h showed no decrease in its specific rotation. Although amide **15** was shown to be of greater configurational stability than acid **11**, in preliminary studies, hydride reduction of imino amide **15** proceeds slowly and tends to favored *cis*-diastereomer **16** (entry h, Table 2).[28]

In order to synthesize enantiomerically pure *trans*-diastereomer, we examined epimerization of *N*-protected *cis*-5-*tert*-butylproline methyl esters (Scheme 5). Overall, the epimerization route to *trans*-isomers provided at best a 1:1 ratio of (2*S*,5*R*)- and (2*R*,5*R*)-isomers. For example, treatment of (2*S*,5*R*)-**9** with potassium bis(trimethylsilyl)-amide (125 mol %) in THF for 16 h at 50 °C followed by a methanol quench and aqueous workup gave a separable 3:2 mixture of (2*S*,5*R*)- and (2*R*,5*R*)-esters **9** in 97% yield. Epimerization of (2*S*,5*R*)-methyl *N*-benzyl-5-*tert*-butylprolinate using potassium *tert*-butoxide in 2-methyl-2-propanol at 50 °C for 16 h yielded a 1:1 *cis*:*trans* diastereomeric mixture.[29,30] Treatment of (2*S*,5*R*)-5-*tert*-butylproline ((2*S*,5*R*)-**6**) with acetic anhydride in acetic acid at 50 °C, conditions previously used to racemize L-proline,[31] provided a 3:1 *cis*:*trans* ratio of diastereomers **6**. Among these epimerization methods, the most practical in our hands was epimerization of *N*-(BOC)amino

(25) Kemp, D. S.; Curran, T. P. *J. Org. Chem.* **1988**, *53*, 5729.

(26) The specific rotation of **11** $[[\alpha]^{20}_D$ 56.8 (c = 1.0, CH_2Cl_2)] decreased to 43.5° after 24 h and to 32.8° after 48 h of exposure to TFA in CH_2Cl_2.

(27) Homer, R. B.; Johnson, C. D. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970; pp 188−197.

(28) The *trans*:*cis* ratio of diastereomers **16** was determined by measuring the peak height of the *tert*-butyl singlets (δ = 1.14 and 1.17 ppm) as well as integrating the area of the α-proton signals (δ = 4.43 and 4.53 ppm) in the proton NMR. Assignments of the stereoconfiguration of **16** were made on the basis of a comparison with authentic material prepared as described in ref 14.

(29) Lowe, G.; Ridley, D. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2024.

(30) (2*S*,5*R*)-Methyl *N*-benzyl-5-*tert*-butylprolinate was prepared from (2*S*,5*R*)-**9** by removal of the BOC group with TFA and *N*-benzylation as described for the synthesis of (2*S*)-*cis*-1-benzyl-5-heptylproline *tert*-butyl ester in ref 15u: ^1H NMR ($CDCl_3$) δ 1.01 (s, 9 H, 1.79−1.96, (m, 5 H), 2.75−2.79 (t, 1 H, J = 6.3 Hz), 3.34 (s, 3 H), 3.66 (d, 1 H, J = 13.9 Hz), 4.18 (d, 1 H, J = 13.9 Hz), 7.19−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 26.8, 27, 30.1, 30.2, 36, 51, 63.1, 74.7, 126.8, 127.8, 129, 139.3, 175.4.

(31) Price, V. E.; Levintow, L.; Greenstein, J. P.; Kingsley, R. B. *Arch. Biochem.* **1950**, *26*, 92.

ester (2*S*,5*R*)-**9** with $KN(Si(CH_3)_3)_3$ as described below in the Experimental Section.

Conclusion

We have developed efficient methodology for synthesizing enantiopure 5-alkylprolines possessing tertiary 5-position substituents. All four stereoisomers of 5-*tert*-butylproline can be synthesized from glutamic acid via our acylation/diastereoselective reductive amination sequence. Because the 5-*tert*-butyl substituent can effect the X-Pro amide geometry to favor the *cis*-isomer and because *N*-(BOC)-5-*tert*-butylproline may be introduced into a variety of peptides via standard coupling techniques, these 5-alkylprolines should find general use in the conformational analysis of bioactive peptides possessing energetically similar *cis*- and *trans*-isomers *N*-terminal to prolyl residues.

Experimental Section

General. Unless otherwise noted, all reactions were run under nitrogen atmosphere and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately before use; 1,1,1,3,3,3-hexamethyldisilazane (HMDS), CH_3CN, and CH_2Cl_2 were distilled from CaH_2; Et_3N was distilled from BaO. Final reaction mixture solutions were dried over Na_2SO_4. Chromatography was on 230−400 mesh silica gel; TLC on aluminum-backed silica plates. Melting points are uncorrected. Mass spectral data, HRMS (EI and FAB), were obtained by the Université de Montréal Mass Spectroscopy facility. ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$). *J* values are given in Hz. Chemical shifts for aromatic PhF carbons are not reported. The chemical shifts for the carbons and protons of minor isomers are respectively, reported in parentheses and in brackets.

(2*S*)-Methyl 6,6-Dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoate (5a). A −10 °C solution of HMDS (20 mL, 95.9 mmol) in 20 mL of THF was treated with *n*-butyllithium (34 mL of a 2.5 M solution in hexane, 85 mmol), stirred for 30 min, cooled to −78 °C, and treated with a solution of γ-methyl *N*-(9-(9-phenylfluorenyl))-L-glutamate (**2**, 10.3 g , 25.7 mmol)[15o] in THF (30 mL). The reaction mixture was stirred at −78 °C for 1.5 h, treated with a −78 °C solution of trimethylacetyl chloride (9 mL, 73.2 mmol) in THF (6 mL), stirred for an additional 45 min, and poured into 1 M NaH_2PO_4 (50 mL). The mixture was extracted with EtOAc (4 × 50 mL), and the combined organic phases were washed with cold water (3 × 20 mL) and brine (2 × 30 mL), dried, filtered, and evaporated. The residue was normally used without purification in the next reaction. Purification of the residue by chromatography on silica gel with an eluant of 17−60% EtOAc in hexane provided a 1.5:1 mixture of diastereomers, **(2*S*,4*RS*)-6,6-dimethyl-5-oxo-4-[(methyloxy)carbonyl]-2-[(*N*-(PhF)amino] heptanoic acid** (**3**, 75%): ^{1}H NMR δ 1.07 (s, 9 H), 1.22 (s, 9 H), 1.55 (m, 2 H), 2.03 (m, 1 H), 2.25 (m, 1 H), 2.5 (m, 2 H), 3.47 (s, 3 H), 3.7 (s, 3 H), 3.87 (dd, 1 H, *J* = 2.8, 8.8), 4.37 (dd, 1 H, *J* = 2.6, 10), 7.1−7.6 (m, 26 H); ^{13}C NMR δ 25.9, 26, 33, 33.6, 45.3, 45.6, 48, 49.7, 52.1, 52.3, 53.9, 54.6, 72.6, 72.7, 170.1, 170.2, 178.2, 178.3, 210, 210.2; HRMS calcd for $C_{30}H_{32}NO_5$ (MH^+) 486.2280, found 486.2250.

Crude β-keto ester **3** was dissolved in EtOH (125 mL), treated with 2 N NaOH (125 mL), and stirred at a reflux for 48 h. The mixture was cooled to room temperature and brought to pH 5 using 10% HCl. The solution was extracted with EtOAc (4 × 75 mL), and the combined organic phases were washed with brine, dried, filtered, and evaporated to a residue that was normally used without purification in the next reaction. When pure β-keto ester **3** was used, purification by chromatography on silica gel using 1:1 EtOAc:hexane gave a 78% yield of **(2*S*)-6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]-heptanoic acid** (**4**): mp 170 °C; $[\alpha]^{20}_D$ −61.1° (*c* 1.1, MeOH); ^{1}H NMR δ 1.12 (s, 9 H), 1.7 (m, 2 H), 2.5 (m, 2 H), 2.6 (dd, 1 H, *J* = 4.7, 6.6), 7.2−7.8 (m, 13 H); ^{13}C NMR δ 26.5, 27.37, 33.4, 44.2, 56, 72.8, 175.4, 212.2; FT-IR ($CHCl_3$) 2971, 1708, 1704, 1447, 1368, 1284; HRMS calcd for $C_{28}H_{30}NO_3$ (MH^+) 428.2226, found 428.2205.

Crude acid **4** was dissolved in acetonitrile (190 mL), treated with K_2CO_3 (6.5 g, 47.2 mmol) and MeI (5 mL, 80.1 mmol), and stirred at room temperature for 19 h. Brine (200 mL) was added to the reaction mixture, which was extracted with EtOAc (3 × 100 mL). The organic phases were combined, washed with 0.65 M sodium thiosulfate (200 mL) and brine, dried, filtered, and evaporated to an oil that was purified by chromatography on silica gel using a gradient of 0−25% EtOAc in hexane. Evaporation of the collected fractions gave 5.5 g (12.5 mmol, 49% overall from **2**) of **(2*S*)-methyl 6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoate (5a)** as a thick oil: $[\alpha]^{20}_D$ −137.7° (*c* 1, MeOH); ^{1}H NMR δ 1.11 (s, 9 H), 1.63 (m, 2 H), 2.3 (ddd, 1 H, *J* = 6, 9, 15), 2.54 (dd, 1 H, *J* = 5, 8), 2.7 (ddd, 1 H, *J* = 5.6, 9, 15), 3 (br s, 1 H), 3.27 (s, 3 H), 7.14−7.44 (m, 11 H), 7.17 (m, 2 H); ^{13}C NMR δ 26.5, 29.1, 33.1, 44, 51.5, 55, 72.9, 176.5, 215.2; FT-IR ($CHCl_3$) 2965, 1732, 1704, 1477, 1448, 1197, 1168; HRMS calcd for $C_{29}H_{32}NO_3$ (MH^+) 442.2382, found 442.2365. Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.9; H, 7.1; N, 3.2. Found: C, 78.7; H, 7.2; N, 3.

(2*R*)-Methyl 6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino] heptanoate ((*R*)-5a) was prepared by the same procedure in similar yield from γ-methyl *N*-(9-(9-phenylfluorenyl))-D-glutamate: $[\alpha]^{20}_D$ 159.5° (*c* 1, MeOH).

(2*S*,5*R*)-*N*-(BOC)-5-*tert*-Butylproline Methyl Ester ((2*S*,5*R*)-9). A solution of (2*S*)-methyl 6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoate (**5a**, 0.73 g, 1.66 mmol) and di-*tert*-butyldicarbonate (1g, 4.6 mmol) in MeOH (50 mL) was treated with palladium-on-carbon (10 wt %, 90 mg), and stirred under 4 atm of hydrogen for 48 h. The mixture was filtered on celite, the catalyst was washed with MeOH (2 × 30 mL), and the combined organic phase was evaporated to a residue that was purified by chromatography on silica gel using a gradient of 0−25% EtOAc in hexane. Evaporation of the collected fractions gave 400 mg (85%) of (2*S*,5*R*)-**9** as an oil. On larger scale, hydrogenation of **5a** (4.5 g ,10.3 mmol) under similar conditions [500 mg of 10 wt % Pd/C, 4 atm H_2 and 5.8 g (26.6 mmol) of $(BOC)_2O$ in 70 mL of MeOH] and purification gave 2.1 g (71%) of (2*S*,5*R*)-**9**: $[\alpha]^{20}_D$ -32.2° (*c* 1, MeOH); ^{1}H NMR δ 0.88 (s, 9 H), 1.35 (s, 9 H), 1.84 (m, 3 H), 2.13 (m, 1 H), 3.65 (s, 3 H), 3.73 (br d, 1 H, *J* = 6.4), 4.22 (m, 1 H); ^{13}C NMR δ 26.6, 27.3, 28.1, 29.4, 36.2, 51.6, 61.4, 66.5, 79.8, 155.9, 173.7; HRMS calcd for $C_{15}H_{28}NO_4$(MH^+) 286.2018, found 286.2025. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.1; H, 9.5; N, 4.9. Found: C, 63.4; H, 9.3; N, 4.9. **(2*R*,5*S*)-*N*-(BOC)-5-*tert*-butylproline methyl ester ((2*R*,5*S*)-9)** was prepared by the same procedure from heptanoate (2*R*)-**5a** in 84% yield: $[\alpha]^{20}_D$ 30.3° (*c* 1, MeOH).

(2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*R*)-1). Methyl ester *cis*-**9** (0.4 g, 1.4 mmol) was dissolved in 10 mL of Et_2O, treated with $KOSi(Me)_3$ (200 mg, 1.56 mmol), and stirred for 22 h at room temperature. Another 200 mg of $KOSi(Me)_3$ was added, and the reaction was stirred for an additional 2 h. The reaction mixture was extracted with water (5 × 20 mL), and the aqueous phases were combined, acidified with citric acid to pH 2, saturated with NaCl, and extracted with EtOAc (3 × 50 mL). The organic phases were combined, dried, filtered, and evaporated to give 0.36 g (1.33 mmol, 94%) of (2*S*,5*R*)-**7**: mp 119−121 °C; $[\alpha]^{20}_D$ −22.5° (*c* 1, MeOH); ^{1}H NMR (CD_3OD) δ 0.95 (s, 9 H), 1.43 (s, 9 H), 1.95 (m, 3 H), 2.27 (m, 1 H), 3.77 (br d, 1 H, *J* = 7.6), 4.27 (m, 1 H); ^{13}C NMR (CD_3OD) δ 27.7, 28.1, 28.7, 30.6, 37.3, 62.8, 68.3, 81.4, 158, 176.6; HRMS calcd for $C_{14}H_{26}NO_4$ (MH^+) 272.1862, found 272.1848. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 62; H, 9.3; N, 5.2. Found: C, 61.7; H, 9.1; N, 5.1. The same conditions provided **(2*R*,5*S*)-*N*-(BOC)-5-*tert*-butylproline ((2*R*,5*S*)-1)** from methyl ester ((2*R*,5*S*)-**9**) in similar yield: mp 120 °C; $[\alpha]^{20}_D$ 22.2° (*c* 0.5, MeOH).

(2*S*)-6,6-Dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoate (4) via Hydrolysis of 5a. A solution of methyl ester **5a** (1.9 g, 4.3 mmol) in EtOH (80 mL) was treated with 2 N NaOH (65 mL) and stirred at a reflux for 48 h. The solution was cooled to room temperature, acidified to pH 5 with 10%

HCl, saturated with NaCl, and extracted with EtOAc (2 × 250 mL). The organic phases were combined, washed with brine, dried, filtered, and evaporated to a minimum volume of EtOAc from which **4** was allowed to crystallize, giving 1.37 g (75%) of a white solid, mp 170 °C.

(2*S*,5*R*)-5-*tert*-Butylproline ((2*S*,5*R*)-6). A solution of (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*R*)-**1**, 90 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic acid (0.5 mL), stirred at room temperature for 12 h, and evaporated to a clear oil. (2*S*,5*R*)-5-*tert*-Butylproline trifluoroacetate: ^{1}H NMR δ 1.08 (s, 9 H), 1.68 (m, 1 H), 2.06 (m, 1 H), 2.44 (m, 2 H), 3.55 (m, 1 H), 4.44 (m, 1 H), 6.51 (br m, 1 H), 10.07 (br m, 1 H), 11.77 (br s, 1 H); ^{13}C NMR δ 25, 25.9, 29.1, 32, 58.9, 71.9, 172.7. The oil was dissolved in water and passed through an ion-exchange column of Dowex 1-X8 (hydroxide form) eluting with 0.01 M AcOH and provided **6** as a white solid: mp 265 °C dec; $[\alpha]^{20}_D$ −29.7° (*c* 0.26, 1 N HCl).

Hydrogenation of δ-Oxo-α-[*N*-(PhF)Amino]heptanoates 4, 5a, and 5b. A 0.6 M solution of (2*S*)-6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoates (**4**, **5a**, and **5b** (100 mol %) in 9:1 MeOH:AcOH was treated with palladium-on-carbon (10 wt %, 5 mol % of Pd) and stirred under 4 atm of hydrogen for 24 h. The mixture was filtered on Celite, the catalyst was washed with MeOH, and the combined organic phase was evaporated to a residue that was analyzed directly by ^{1}H NMR in order to determine the *cis*:*trans* ratios reported in Table 1.

(2*S*,5*R*)-5-*tert*-Butylproline Methyl Ester Trifluoroacetate ((2*S*,5*R*)-7). A sample for comparison was obtained as a low-melting solid from stirring a 0.1 M solution of (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline methyl ester ((2*S*,5*R*)-**9**) in 4:1 CH_2Cl_2:CF_3CO_2H for 18 h at room temperature followed by evaporation of the volatiles under vacuum; $[\alpha]^{20}_D$ −18.7° (*c* 0.4, MeOH); ^{1}H NMR δ 1.09 (s, 9 H), 1.67 (m, 1 H), 2.06 (m, 1 H), 2.3 (m, 1 H), 2.46 (m, 1 H), 3.64 (m, 1 H), 3.9 (s, 3 H), 4.58 (br d, 1 H, J = 9), 6.12 (br s, 1 H), 12 (br s, 1 H); ^{13}C NMR δ 25.2, 26.1, 29, 32.1, 54.2, 58.7, 71.3, 170.9.

(2*S*,5*R*)-5-*tert*-Butylproline *tert*-butyl ester ((2*S*,5*R*)-8): ^{1}H NMR δ 0.95 (s, 9 H), 1.46 (s, 9 H), 1.47 (m, 1 H), 1.75 (m, 2 H), 2.04 (m, 1 H) 2.84 (dd, 1 H, J = 6.2, 9.8), 3.65 (dd, 1 H, J = 5.5, 9); ^{13}C NMR δ 26.5, 26.6, 27.2, 27.9, 30.8, 60.4, 69.7, 81, 174.1.

(2*S*)-5-*tert*-Butyl-Δ^5-dehydroproline Trifluoroacetate (11). A solution of acid **4** (320 mg, 0.74 mmol) in CH_2Cl_2 (15 mL) was treated with TFA (0.76 mL) and anisole (0.38 mL), heated at reflux for 48 h, cooled to room temperature, and evaporated to a solid that was dissolved in a minimum volume of $CHCl_3$ and precipitated with excess hexane. The precipitate was recovered with the aid of a centrifuge, redissolved, and retreated in the same way two additional times to provide pure **11** (201 mg, 96%): $[\alpha]^{20}_D$ 81° (*c* 0.1, $CHCl_3$);[26] ^{1}H NMR (CD_3OD) δ 1.39 (s, 9 H), 2.37 (m, 2 H), 2.65 (m, 2 H), 5.05 (m, 1 H); ^{13}C NMR (CD_3OD) δ 25.6, 25.7, 27.6, 35.9, 38.7, 171.5, 208.1; HRMS calcd for $C_9H_{16}NO_2$ (M^+) 170.1181, found 170.1178.

Hydride Reduction of (2*S*)-10. A solution of (2*S*)-5-*tert*-butyl-Δ^5-dehydroproline (**10**, 141 mg, 0.5 mmol) in THF (30 mL) was heated to reflux, treated with solid $(H_3C)_4NHB(OAc)_3$ (197 mg, 0.75 mmol, 150 mol %), and stirred for 6 h. The solution was cooled to room temperature, treated with 1 N HCl (10 mL), and evaporated to a residue. The proton NMR spectrum of the residue exhibited a 85:15 *trans*:*cis* ratio of diastereomers. The residue was dissolved in water and purified on 11 g of Dowex 1-X8 ion-exchange resin (hydroxide form, 20−50 mesh) using a gradient of 0−10% acetic acid in water as eluant. Evaporation of the collected ninhydrin positive fractions gave 76 mg (96%) of solid (2*S*,5*RS*)-5-*tert*-butylprolines (**6**) possessing an 87:13 ratio of diastereomers.

(2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline Methyl Ester ((2*S*,5*S*)-9). A 0 °C solution of gaseous HCl (1g, 27 mmol) in 161 mL of MeOH was treated with a solution of 5-*tert*-butylproline (490 mg, 3.1 mmol, 5*R*:5*S* = 8.6:1) in MeOH (25 mL). The mixture was allowed to warm to rt, stirred for 16 h, and evaporated to a yellow solid containing an 8.6:1 mixture of (2*S*,5*R*)- and (2*S*,5*S*)-**7** (522 mg, 76%). The spectral characteristics of (2*S*,5*S*)-5-*tert*-butylproline methyl ester hydrochloride ((2*S*,5*S*)-**7**) are as follows: ^{1}H NMR ($CHCl_3$ acidified with TFA) δ 1.07 (s, 9 H), 1.9−2.2 (m, 3 H), 2.5 (m, 1 H), 3.65 (m, 1 H), 3.79 (s, 3 H), 4.51 (t, 1 H, J = 7.5), 9.0 (br s, 2 H); ^{13}C NMR (CD_3OD) δ 26.5, 27, 29.9, 33.7, 54.1, 61.4, 71.9, 170.2; HRMS calcd for $C_{10}H_{20}NO_2$ $[MH]^+$, 186.1494 found 186.1501.

A solution of **7** (100 mg, 0.45 mmol) in CH_3CN (3 mL) was then treated with solid K_2CO_3 (124 mg, 0.90 mmol, 200% mol), stirred for 30 min, and treated with a solution of di-*tert*-butyl dicarbonate (147 mg, 68 mmol, 150% mol) in CH_3CN (1 mL). After the solution was stirred for 24 h at rt, a second portion of di-*tert*-butyl dicarbonate (147 mg, 68 mmol, 150% mol) in CH_3CN (1 mL) was added, and the resulting solution was stirred 24 h, evaporated to a yellow solid, and chromatographed on silica gel using a gradient of 0−7% Et_2O in $CHCl_3$ as eluant. (2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline methyl ester ((2*S*,5*S*)-**9**, 99 mg, 77%) was first to elute: $[\alpha]^{20}_D$ −43.6° (*c* 0.94, CH_3OH); ^{1}H NMR δ 0.9 (s, 9 H), 1.51 (s, 9 H), 1.8−2.4 (m, 4 H), 3.74 (s, 3 H), 3.97 (d, 0.3 H, J = 8.4), 4.06 (d, 0.7 H, J = 8.5), 4.4 (d, 1 H, J = 9.5); ^{13}C NMR δ 25.2 (26.1), (27.3) 27.4, 27.5, (29) 30, (36.3) 37, (52.2) 52.4, (61.3) 61.7, (67.5) 67.6, (84.6) 84.7, (146.8) 149.9, (172.5) 172.8; HRMS calcd for $C_{18}H_{11}NO_3$ [M − O-*t*-Bu]$^+$, 212.1287 found 212.1275. Next to elute was (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline methyl ester (2*S*,5*R*)-**9** (11 mg, 9%).

Epimerization of (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline Methyl Ester ((2*S*,5*R*)-9). A solution of methyl ester (2*S*,5*R*)-**9** (143 mg, 0.5 mmol) in 10 mL of THF at −78 °C was treated with 1.2 mL of $KN(SiMe_3)_2$ (120 mol %, 0.5 M in toluene), heated to 50 °C, and stirred for 16 h. Methanol (6 mL) was added, and the mixture was partitioned between 1 M NaH_2PO_4 (15 mL) and EtOAc (15 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic phase was washed with brine, dried, evaporated and purified by chromatography using 0−25% EtOAc in hexanes. First to elute was (2*S*,5*R*)-**9** (84 mg, 59%) followed by (2*R*,5*R*)-**9** (54 mg, 38%): $[\alpha]^{20}_D$ 21.6° (*c* 0.25, CH_3OH). Last to elute was a mix of acids **1** (4 mg, 3%).

(2*S*,5*S*)-5-*tert*-Butyl-*N*-(BOC)proline ((2*S*,5*S*)-1). A solution of methyl ester (2*S*,5*S*)-**9** (50 mg, 0.18 mmol) in 1 mL of dioxane was treated with 1 mL of 1 N NaOH and stirred for 48 h at room temperature. The reaction mixture was extracted with water (5 × 1 mL), the aqueous phases were combined, acidified with citric acid to pH 2, saturated with NaCl, and extracted with EtOAc (3 × 2 mL). The organic phases were combined, dried, filtered, and evaporated to give 39 mg (82%) of (2*S*,5*S*)-**1**: $[\alpha]^{20}_D$ −16.3° (*c* 0.7, MeOH); ^{1}H NMR δ 0.9 (s, 9 H), 1.41 (s, 5.4 H), [1.46 (s, 3.6 H)], 1.90 (m, 2 H), 2.05 (m, 1 H), 2.30 (m, 1 H), [3.85 (d, 0.4 H, J = 8.5)] 3.98 (d, 0.6 H, J = 8.5), 4.28 (d, 0.6 H, J = 9.3) [4.34 (d, 0.4 H, J = 9.4)]; ^{13}C NMR δ 25.0 (26.1), 27.5, 28.1 (28.3), 29.1, 36.5 (36.8), 61.0, 66.2, 80.2 (80.6), 155.3, 179.9.

Enantiomeric Purity of (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*R*)-1). A room-temperature solution of (2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*R*)-**1**, 20 mg, 0.07 mmol) and either (*R*)- or (*S*)-α-methylbenzylamine (24 μL, 0.19 mmol) in 1 mL of acetonitrile was treated with benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (26 mg, 0.08 mmol) and stirred for 2 h when TLC showed complete disappearance of the starting acid. Brine (2 mL) was added to the reaction mixture that was then extracted with EtOAc (2 × 3 mL). The combined organic phase was extracted with 2 N HCl (2 × 2 mL) and $NaHCO_3$ (2 × 2 mL), washed with H_2O (2 × 2 mL) and brine, dried, filtered, and evaporated to a residue that was directly examined by ^{1}H NMR. When (*S*)-α-methylbenzylamine of 99% diastereomeric purity was used, examination of the *tert*-butyl singlets in the ^{1}H NMR in $CDCl_3$ demonstrated (*S*)-**10** to be of 99% diastereomeric purity. Hence, *cis*-**1** is presumed to be of >99% enantiomeric purity.

(1′*S*,2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline *N*′-α-methylbenzylamide ((*S*)-10): ^{1}H NMR δ 0.93 (s, 9 H), 1.34 (s, 9 H), 1.47 (d, 3 H, J = 6.9), 1.78 (m, 2 H), 2.2 (m, 2 H), 3.9 (dd, 1 H, J = 3, 7.7), 4.3 (t, 1 H, J = 8.8), 5.1 (quintet, 1 H, J = 6.9), 7.3 (m, 5 H).

(1′*R*,2*S*,5*R*)-*N*-(BOC)-5-*tert*-butylproline *N*′-α-methylbenzylamide ((*R*)-10): ^{1}H NMR δ 0.74 (s, 9 H), 1.47 (s, 9 H), 1.51 (d, 3 H, J = 7), 1.84 (m, 2 H), 2.1 (m, 1 H), 2.25 (m, 1 H), 3.83 (m, 1 H), 4.34 (t, 1 H, J = 8.7), 5.1 (quintet, 1 H, J = 7), 7.3 (m, 5 H).

Enantiomeric Purity of (2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*S*)-1). (2*S*,5*S*)-*N*-(BOC)-5-*tert*-butylproline ((2*S*,5*S*)-**7**, 22 mg, 0.06 mmol) was transformed into its respective (1′*R*)- and (1′*S*)-α-benzylamides **10** via the route described above for (2*S*,5*R*)-**1**. Amides **10** were then dissolved in CH_2Cl_2 (0.6 mL), treated with 45 μL (0.6 mmol, 1000 mol %) of trifluoroacetic acid, and stirred for 24 h. Evaporation of the volatiles gave amides **12** that were analyzed, without further purification, by ^{1}H NMR in CD_3OD via integration of the *tert*-butyl singlets.

(1′*S*,2*S*,5*S*)-5-*tert*-Butylproline *N*′-α-methylbenzylamide trifluoroacetate ((*S*)-12): ^{1}H NMR (CD_3OD) δ 1.02 (s, 9 H), 1.47 (d, 3 H, J = 7.0), 1.88 (m, 2 H), 2.14 (m, 2 H), 2.49 (m, 1 H), 3.61 (m, 1 H), 4.07 (m, 1 H) 5.03 (m, 1 H).

(1′*R*,2*S*,5*S*)-5-*tert*-Butylproline *N*′-α-methylbenzylamide trifluoroacetate ((*R*)-12): ^{1}H NMR (CD_3OD) δ 1,03 (s, 9 H), 1.49 (d, 3 H, J = 7.0), 1.9 (m, 2 H), 2.15 (m, 2 H), 2,42 (m, 1 H), 3,58 (m, 1 H), 4,14 (m, 1 H) 5.03 (m, 1 H).

(2*S*)-6,6-Dimethyl-*N*′-methyl-5-oxo-2-[*N*-(PhF)amino]-heptanamide ((2*S*)-14). A suspension of (2*S*)-6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoate ((2*S*)-**4**, 1.37 g, 3.2 mmol) and methylamine hydrochloride (238 mg, 3.52 mmol, 110 mol %) in acetonitrile (100 mL) at room temperature was treated with triethylamine (1.42 mL, 10.24 mmol, 320% mol) followed by TBTU (1.13 g, 3.52 mmol, 110% mol). The mixture was stirred for 48 h. The volatiles were removed under vacuum, leaving a residue that was purified by chromatography on silica gel using an eluant of 20−50% EtOAc in hexane. Evaporation of the collected fractions gave 1.094 g (78%) of (2*S*)-**14** as a white solid: $[\alpha]^{20}_D$ −28.7° (*c* 2.0, MeOH); mp 156−158 °C; ^{1}H NMR δ 1.05 (s, 9 H), 1.64 (q, 2 H, J = 6.7), 2.33 (t, 1H, J = 6.2), 2.43 (t, 2 H, J = 6.4), 2.49 (d, 3 H, J = 5), 3.2 (s, 1 H), 6.2 (d, 1 H, J = 4.7); ^{13}C NMR δ 25.6, 26.4, 29, 33.1, 43.9, 56.6, 72.9, 175.5, 216.4; HRMS calcd for $C_{29}H_{33}N_2O_2$ (MH^+) 441.2542, found 441.2552.

(2*S*)-5-*tert*-Butyl-Δ^5-dehydroproline *N*′-Methylamide Trifluoroacetate ((2*S*)-15). A solution of amide (2*S*)-**14** (100 mg, 0.23 mmol) in CH_2Cl_2 (11 mL) was treated with TFA (0.23 mL) and anisole (0.1 mL, 0.92 mmol), heated at reflux for 72 h, cooled to room temperature, and extracted with water (3 × 10 mL). The aqueous extractions were then evaporated to furnish (2*S*)-**15** as an oil (62 mg, 92%): $[\alpha]^{20}_D$ 86.6° (*c* 0.6, CH_2Cl_2); ^{1}H NMR δ 1.38 (s, 9 H); 2.33 (m, 1 H); 2.68 (m, 1 H); 2.81 (d, 3 H, J = 4.7), 3.04 (m, 1 H), 3.27 (m, 1 H), 5.13 (m, 1 H), 8.19 (m, 1 H); ^{13}C NMR (CD_3OD) δ 24.1, 26.5, 27.6, 35.4, 37.5, 69.1, 167.5, 202.3; HRMS calcd for $C_{10}H_{19}N_2O$ (MH^+) 183.1497, found 183.1503.

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Supporting Information Available: The ^{1}H and ^{13}C NMR spectra of **1**−**16** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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