Regioselective Enolization and Alkylation of 4-Oxo-*N*-(9-phenylfluoren-9-yl)proline: Synthesis of Enantiopure Proline−Valine and Hydroxyproline−Valine Chimeras

Raman Sharma and William D. Lubell*

Département de chimie, Université de Montréal, C. P. 6128, Succursale Centre Ville, Montréal, Québec, Canada H3C 3J7

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The regioselective enolization of 4-oxo-*N*-(9-phenylfluoren-9-yl)proline benzyl ester (**5**) followed by alkylation with different alkyl halides has been used to synthesize a variety of β-alkylproline derivatives. In particular, enolization of **5** with 400 mol % of $KN(SiMe_3)_2$ and alkylation with iodomethane provided 3,3-dimethyl-4-oxo-*N*-(9-phenylfluoren-9-yl)proline benzyl ester (**7a**) in excellent yield. Subsequent hydride reduction of ketone **7a** and protecting group exchange by hydrogenation in the presence of di-*tert*-butyl dicarbonate provided enantiopure (2*S*,4*R*)- and (2*S*,4*S*)-3,3-dimethyl-4-hydroxy-*N*-(BOC)prolines **2**. Hydroxyproline−valine chimeras (2*S*,4*R*)- and (2*S*,4*S*)-**2** are each synthesized from hydroxyproline in six steps and 27% respective overall yield. Deoxygenation of 3,3-dimethyl-4-hydroxy-*N*-(9-phenylfluoren-9-yl)proline benzyl esters **9** via their conversion to xanthates **10** followed by tributylstannane-mediated reduction provided 3,3-dimethyl-*N*-(9-phenylfluoren-9-yl)proline benzyl ester (**11**) in excellent yield. Hydrogenation of **11** with Pearlman's catalyst in the presence of di-*tert*-butyl dicarbonate then furnished (2*S*)-3,3-dimethyl-*N*-(BOC)proline (**1**) in the last step of an eight-step synthesis (41% overall yield) from hydroxyproline. Both proline−valine and hydroxyproline−valine chimeras **1** and **2** were designed to serve as tools for studying the conformational requirements of biologically active peptides.

Introduction

Proline analogues possessing the characteristics of other amino acids are important tools for studying the spatial requirements for receptor affinity and biological activity of natural amino acids[1] and peptides.[2−6] For example, the geometric relationship of the side-chain group to the peptide backbone can be explored using β-alkylprolines that combine amino acid side-chain functionality with proline conformational rigidity. Replacement of the natural amino acids in peptides for such proline−amino acid chimeras has led to better understanding of the bioactive conformations of cholecystokinin,[2] angiotensin II,[3] bradykinin,[4] and opioid peptides.[5] Furthermore, such β-alkylproline analogues have served in the development of enzyme inhibitors,[6] as well as peptidomimetics exhibiting improved bioactivity and greater metabolic stability.[3−5]

Among the many routes developed for synthesizing proline−amino acid chimeras,[1−7] few approaches provide general access to enantiopure β-alkylprolines in quanti-

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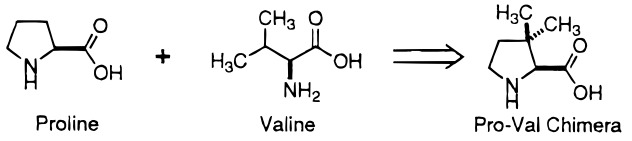


Figure 1. Design of a proline−valine chimera.

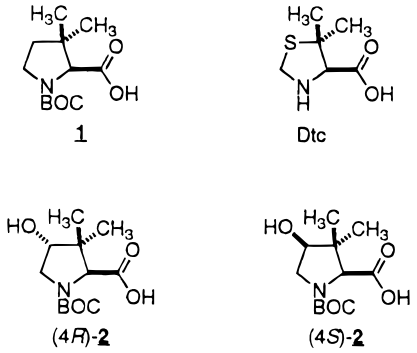


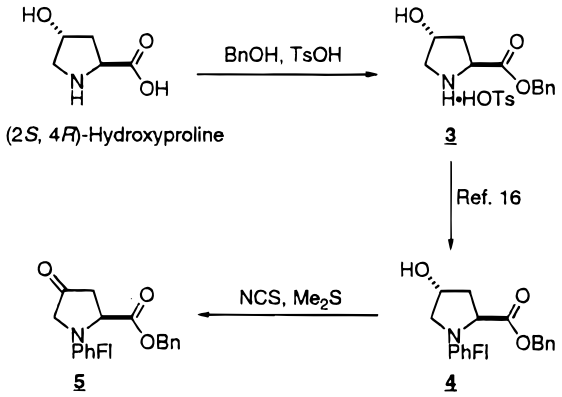
Figure 2. β,β-Dimethylproline derivatives.

ties suitable for incorporation into peptides. In order to furnish a variety of β-alkylprolines from an inexpensive source of chirality, we selected for use 4-hydroxy-L-proline as described in a previous synthesis of a proline−norleucine chimera.[2a] We have found that regioselective enolization and alkylation of a hydroxyproline-derived amino ketone is an effective way of preparing enantiopure β-alkylproline analogues. We recently communicated the application of this reaction in the synthesis of unique kainic acid derivatives.[8] In this paper, we now present details of the alkylation chemistry as well as syntheses of β,β-dimethylprolines **1** and **2**.

As part of a greater program to examine the influence of steric bulk on the conformation of prolyl residues in peptides, we are preparing various alkylproline derivatives. We first reported methodology for synthesizing 5-alkylprolines[9] and observed that steric repulsion between 5-alkyl and *N*-acyl substituents can disfavor the *trans*-rotamer and greatly increase the *cis*-rotamer population of the amide *N*-terminal to 5-alkylprolines that possess bulky 5-position substituents such as a *tert*-butyl group.[9b] With our methodology for synthesizing 5-alkylprolines in hand, we next pursued a complementary approach for synthesizing 3-alkylprolines in order to study the influence of β-alkyl substituents on the geometry of the prolyl ψ-dihedral angle and *C*-terminal residues.[10]

In this paper, we report the syntheses of enantiopure proline−valine and hydroxyproline−valine chimeras **1** and **2** (Figures 1 and 2). These β,β-dialkylprolines share a structural similarity with 5,5-dimethylthiazolidine-4-carboxylic acid (Dtc) which has been used extensively in conformational analyses of biologically active peptides.[11−13] For example, Dtc has been incorporated into angiotensin II agonists and antagonists,[11] as well as potent cholecystokinin-A receptor agonists.[2b] Lately, Dtc has found application in the design of potent peptide-based HIV protease inhibitors.[12] In these peptide analogues, steric interactions between the β-methyl substituents and the α-carboxylate restrict the ψ-dihedral angle of the Dtc residue, which can not adopt a seven member γ-turn conformation.[13] Since added conformational rigidity as well as metabolic stability should result from replacement of the thiazolidine sulfur with carbon, we synthesized 3,3-dimethylproline **1** and 3,3-dimethyl-4-hydroxyproline **2** that do not possess the masked aldehyde in Dtc. We are currently studying proline−valine chimeras **1** and **2** in order to determine the influence of the β-substituents on the geometries and barriers to rotation about the ω- and ψ-dihedral angles of prolyl and hydroxyprolyl residues in peptides.[10b]

Scheme 1. Synthesis of 4-Oxo-*N*-(PhFl)proline Benzyl Ester (5)



Results and Discussion

Synthesis, Enolization, and Alkylation of 4-Oxo-*N*-(PhFl)proline Benzyl Ester (5). Our method for synthesizing β-alkylproline derivatives begins with (2*S*,-4*R*)-hydroxyproline as a chiral educt that is converted in three steps to 4-oxoprolinate **5**. Regioselective enolization of this amino ketone and subsequent *C*-alkylation is the key step for synthesizing β-alkylproline derivatives. For this purpose, the proline nitrogen was protected with the 9-phenylfluoren-9-yl group (PhFl, Scheme 1), which prevents racemization during enolization and alkylation of α-amino ketones.[14] Judicious employment of a benzyl ester at the α-carboxylate allowed for one-pot *O*- and *N*-deprotection as well as *N*-protecting group shuffles via hydrogenolysis in the presence of di-*tert*-butyl dicarbon-

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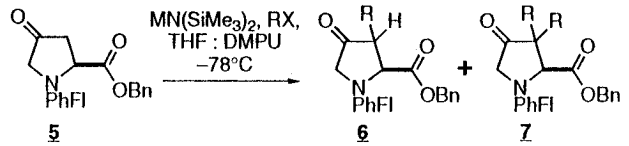
Table 1. Alkylation of 4-Oxoproline 5



entry	$MN(SiMe_3)_2$ (Mol %)	RX (Mol %)	THF / DMPU	% **6** [3*R* vs 3*S*][a]	% **7**[b]
a	Na (140)	H_3CI (500)	3	65 (82) [3 : 1][c]	14 (18)
b	K (200)	MeO_2CCH_2Br (220)	9	81 (91) [1 : 2][d]	-
c	Na (140)	$H_2C{=}CHCH_2I$ (500)	3	54 [> 6 : 1]	5
d	K (280)	$PhCH_2Br$ (300)	3	24 (28) [1 : 1]	2
e	K (400)	H_3CI (1000)	3	-	82
f	K (400)	EtO_2CCH_2I (1000)	3	-	52
g	K (400)	$H_2C{=}CHCH_2I$ (1000)	3	-	69
h	K (400)	$PhCH_2Br$ (670)	3	-	29[e]

[a]Isolated yields (unless noted). Stereochemical assignment at the 3-position was made as described in ref. 25. Ratios were determined by integration of ^1H NMR signals of crude **6**. Yields in parentheses are based on recovered **5**. Entries d & h were conducted at –55°C. [b]In e-g, **7** was the major isolated product. [c]NMR yield. [d]See ref. 8. [e]See text; *O*-benzyl enol ether **8** was the major product isolated in 48% yield.

ate and furnished the final products **1** and **2** as *N*-(BOC)-amino acids suitable for peptide synthesis.

The synthesis of the amino ketone 4-oxo-*N*-(PhFl)-proline benzyl ester (**5**) was best accomplished by a sequence of esterification, phenylfluorenation, and oxidation (Scheme 1).[8] Treatment of (2*S*,4*R*)-hydroxyproline with benzyl alcohol and stoichiometric *p*-toluenesulfonic acid in benzene with azeotropic removal of water gave hydroxyproline benzyl ester *p*-toluenesulfonate **3** in 98% yield after crystallization.[1m,15] Phenylfluorenation of **3** was performed according to the procedure for preparation of *N*-(PhFl)serine methyl ester and gave 4-hydroxy-*N*-(PhFl)proline benzyl ester (**4**) in 71% yield.[16] The secondary alcohol of **4** was then oxidized with *N*-chlorosuccinimide and methyl sulfide in toluene to furnish amino ketone **5** as a crystalline solid in 87% yield.[17] Alternatively, oxidation of **4** with $(COCl)_2$ and DMSO in dichloromethane provided ketone **5** in good yield on a larger scale.[18] We now use this three-step synthesis to provide 20 g batches of crystalline 4-oxo-*N*-(PhFl)proline **5** without chromatography in ~50% overall yield from hydroxyproline.

Regioselective enolization and alkylation of *N*-(PhFl)-amino ketone **5** provides mono- and bis-3-alkylprolines **6** and **7** in moderate to excellent yields (Table 1). Prior to the use of 4-oxo-*N*-(PhFl)prolines,[8,19] the enolization of *N*-acyl- and *N*-alkyl-3-pyrrolidinones under thermodynamically and kinetically controlled conditions was shown to proceed predominantly but not specifically away from the nitrogen-bearing carbon.[20] Selective alkylation of 4-oxoproline derivatives had thus required formation of an enamine and furnished 3-alkylproline product in low to moderate yield, sometimes accompanied by bis-alkylation.[2a,21] Recently, alkylation of the silyl enol ether of 4-oxo-*N*-(BOC)proline *tert*-butyl ester using fluoride ion and *tert*-butyl bromoacetate also gave low yields of bis-alkylated product.[22]

In our work, specific incorporation of deuterium at the proline 3-position (δ = 2.3 and 2.4 ppm) was observed on treatment of the enolate of **5** with CD_3OD. Enolization of **5** was accomplished using lithium, sodium, and potassium bis(trimethylsilyl)amide bases in THF at −78 °C. The addition of alkyl halide to the enolate in THF without cosolvant failed to yield product except in the case of α-bromoacetate. Alkylation did occur once DMPU was used as cosolvant,[20c] which was mixed with the base in THF at 0 °C prior to the addition of ketone **5** at −78 °C.[23] Decomposition with loss of the phenylfluorenyl group was observed at temperatures above −40 °C,[24] yet alkylation with benzyl bromide was successfully performed at −55 °C. The extent of alkylation was usually controlled by limiting the quantities of base and electrophile; however, complete conversion to monoalkylated product without dialkylation was difficult to achieve (Table 1). The 3-position stereochemistry in product **6** was assigned on the basis of the size of the vicinal coupling constant between the α- and β-protons as well as the chemical shift of the β-methyl group in **6a**.[2a,25] We also observed that the α-proton signals in the 3*S*-diastereomers appeared downfield from those of the 3*R*-isomers.[25] Although hydroxylation of the enolate of 4-oxo-*N*-(PhFl)proline methyl ester is reported to furnish only product with the 3-hydroxyl group *cis* to the α-carboxylate,[19] alkylation of benzyl ester **5** was less stereoselective. One-pot alkylation of **5** with excess base and excess electrophile gave generally good yields of dialkylprolines **7**. However, in the case of benzyl bromide *O*-alkylation competed with the second *C*-alkylation such that 3-benzyl 4-*O*-benzyl enol ether **8** was obtained in 48% yield and a separable 3:1 mixture of 3,3-dibenzylproline **7h** and (2*S*)-benzyl Δ^3-*N*-(PhFl)proline 4-*O*-benzyl enol ether was isolated in 29% yield.[26]

The synthesis of 3,3-dimethyl-4-oxo-*N*-(PhFl)proline benzyl ester (**7a**) was accomplished from **5** using 400 mol % of potassium bis(trimethylsilyl)amide and 1000 mol % of iodomethane in a 3:1 THF:DMPU solution. These conditions provided 3,3-dimethylproline **7a** contaminated with minor amounts of starting ketone **5** and 3-methylproline **6a**. Both **5** and **6a** could be conveniently sepa-

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(25) The chemical shifts and $J_{2,3}$ coupling constants from ^1H NMR spectra of **6** in $CDCl_3$ are as follows: (3*R*)-**6a**, 3.32 (6 Hz); (3*S*)-**6a**, 3.88 (8.5 Hz); (3*S*)-**6b**, 4.08 (8.3 Hz); (3*R*)-**6c**, 3.5 (4.3 Hz); (3*R*)-**6d**, 3.52 (4.7 Hz); (3*S*)-**6d**, 3.84 (7.8 Hz). The use of $J_{2,3}$ coupling constants in the assignment of the relative C2−C3 stereochemistry of 3-methylprolines is presented in: Mauger, A. B.; Irreverre, F.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 2019.
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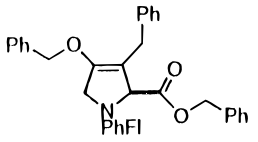

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rated from dimethylproline **7a** by taking advantage of their different solubilities in solutions of EtOAc in hexanes. In this way, the more soluble **5** and **6a** were removed and 3,3-dimethyl-4-oxoproline **7a** was obtained as a crystalline solid in 82% yield. 3-Methylproline **6a** could also be resubmitted to alkylation with iodomethane in order to yield additional 3,3-dimethylproline **7a**.

Synthesis of Hydroxyproline−Valine Chimeras 2. 3,3,-Dimethyl-4-hydroxy-*N*-(PhFl)proline (**9**) was obtained in excellent yield from the reduction of amino ketone **7a** with ordinary hydride reagents, albeit with low diastereoselectivity (Scheme 2). Reduction with $NaBH_4$ in MeOH at 0 °C provided quantitatively a 3:2 mixture of 4*R*:4*S* diastereomers **9**. On the other hand, $LiAlH_4$ in THF gave a 1:2 mixture of (4*R*)-**9**:(4*S*)-**9** in 90% yield. Diastereomeric alcohols **9** were readily separated by chromatography on silica gel.

The stereochemistry at the alcohol 4-position was assigned initially on the basis of chemical shift data for the hydroxyl group proton of **9** in $CDCl_3$. In the ^1H NMR spectrum of *cis*-diastereomer (4*S*)-**9**, the signal of the alcohol proton is observed downfield at 4.0 ppm due to a hydrogen bond with the ester carbonyl. The alcohol proton signal of *trans*-diastereomer (4*R*)-**9** appears at 1.5 ppm. This assignment was confirmed by X-ray analysis of crystals of alcohol (4*R*)-**9** that were grown from methanol.[27] We note again that in the crystal structure of (4*R*)-**9** (Figure 3) the α-proton and the α-ester carbonyl are almost coplanar. Such an arrangement has been observed previously in the X-ray analyses of α-*N*-(PhFl)-amino esters and acids,[28] as well as α-*N*-benzyl-*N*-(PhFl)-amino esters.[1c] This coplanar geometry has also been suggested to contribute to the configurational stability of α-*N*-(PhFl)amino carbonyl compounds, because α-deprotonation from this arrangement is stereoelectronically less favored than from an orthogonal geometry.[1c]

Hydroxyproline−valine chimeras, (4*R*)- and (4*S*)-3,3-dimethyl-4-hydroxy-*N*-(BOC)prolines ((4*R*)- and (4*S*)-**2**), were produced respectively in excellent yield from hydrogenation of (4*R*)- and (4*S*)-3,3-dimethyl-4-hydroxy-*N*-(PhFl)proline benzyl esters (**9**). In THF, hydrogenation of **9** at 5 atm of H_2 with catalytic palladium-on-carbon in the presence of di-*tert*-butyl dicarbonate caused deprotection of the amino and carboxylate groups and subsequent acylation of the amine such that pure **2** was obtained after filtration of the catalyst and removal of the hydrocarbon side product by trituration. In MeOH, the same reaction on (4*S*)-**9** occurred with acylation of the alcohol and gave mostly (4*S*)-4-*O*-BOC-**2** that was characterized as its *N*′-methyl amide.[29]

Synthesis and Enantiomeric Purity of Proline−Valine Chimera 1. We next explored the deoxygenation of alcohols **9** in order to furnish (2*S*)-3,3-dimethyl-*N*-(PhFl)proline **11** (Scheme 3). Early attempts to acylate as well as displace secondary alcohol **9** using various conditions were confounded by the steric effects of the adjacent *gem*-dimethyl center.[2a,30,31] However, xanthates (4*R*)- and (4*S*)-**10** were prepared in quantitative yield

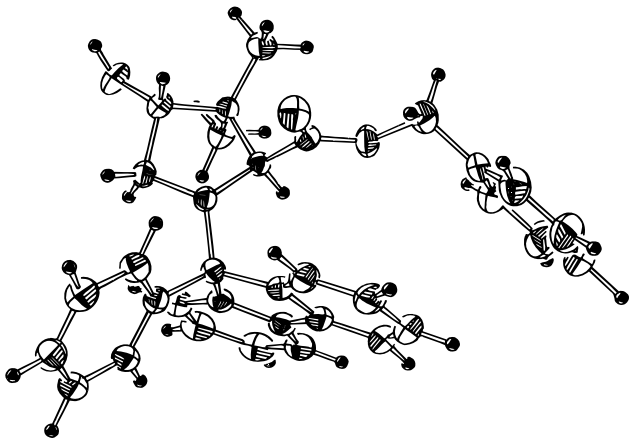
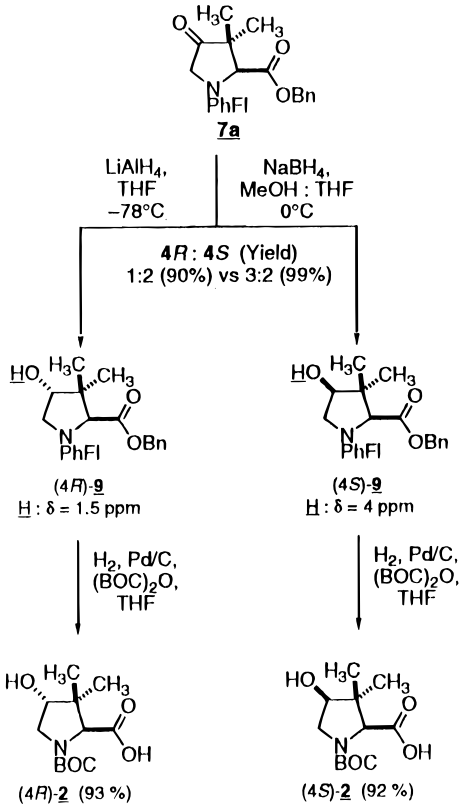


Figure 3. ORTEP drawing of (4*R*)-3,3-dimethyl-4-hydroxy-*N*-(PhFl)proline benzyl ester ((4*R*)-**9**). Nonhydrogen atoms are represented by ellipsoids corresponding to 40% probability. Hydrogen atoms are represented by spheres of arbitrary size.

Scheme 2. Synthesis of Hydroxyproline−Valine Chimeras 2



(27) The structure of (4*R*)-**9** was solved at l'Université de Montréal X-ray facility using direct methods (SHELXS 86). The author has deposited the atomic coordinates for the structure of (4*R*)-**9** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

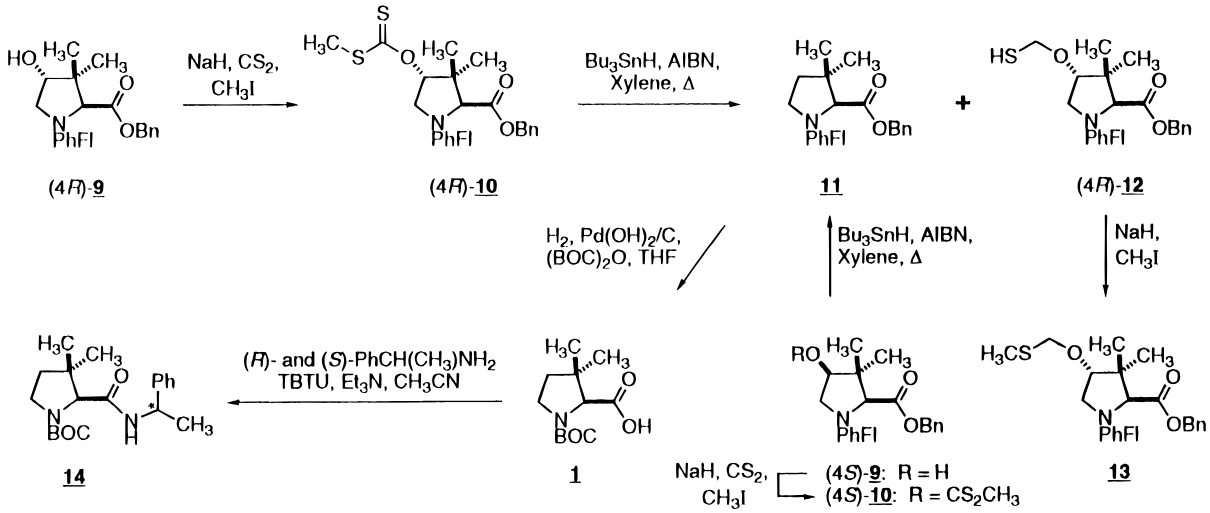
(28) Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 3184.

(29) (2*S*,4*S*)-3,3-Dimethyl-4-*O*-(*tert*-butyloxycarbonyloxy)-*N*-(BOC)-proline *N*'-methylamide was obtained from treatment of a mixture of (4*S*)-**2** and (4*S*)-4-*O*-BOC-**2** with methylamine hydrochloride, triethylamine, and TBTU in acetonitrile followed by purification on silica gel using EtOAc in hexane as eluant: ^1H NMR δ 1.0 (s, 3 H), 1.15 (s, 3 H), 1.38 (s, 9 H), 1.41 (s, 9 H), 2.78 (d, 3 H, J = 5), 3.65 (br m, 1 H), 3.75 (dd, 1 H, J = 4.6, 12.6), 3.8 (br s, 1 H), 4.72 (dd, 1 H, J = 4.6, 1.7), 6.1 (br m, 1 H); ^{13}C NMR δ 18.2, 25.7, 27.6, 27.9, 28.2, 45.6, 50.9, 70.4, 80.9, 81.2, 82.5, 152.5, 154.4, 171.2; HRMS calcd for $C_{18}H_{33}N_2O_6$ (MH^+) 373.2339, found 373.2354.

(30) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.

(31) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

Scheme 3. Synthesis and Enantiomeric Purity of Proline−Valine Chimera 1



from alcohols (4*R*)- and (4*S*)-**9** by acylation of the sodium alkoxide with carbon disulfide in THF and subsequent alkylation with iodomethane.[32] At first, xanthate (4*R*)-**10** was reduced with tributylstannane and AIBN as radical initiator in refluxing toluene.[33] Chromatography gave (2*S*)-3,3-dimethyl-*N*-(PhFl)proline **11** in 57% yield accompanied by a more polar side product, which was later determined to be hemithiol acetal (4*R*)-**12** (13%). A notable improvement in the xanthate reduction was obtained by switching to refluxing xylene.[33] This change decreased significantly the formation of hemithiol acetal **12** and gave excellent yield (91%) of dimethylproline **11**.

The structure of **12** was initially assigned on consideration of its molecular ion and ^{1}H,^{1}H and ^{1}H,^{13}C correlation spectra.[34] Additional structural proof came from treatment of **12** with citric acid in methanol which caused hydrolysis of the hemithiol acetal, returning alcohol (4*R*)-**9**. Alkylation of **12** with sodium hydride and iodomethane in THF furnished (methylthio)methyl ether **13** in 84% yield. Finally, a sample exhibiting an identical R_f value as **13** was synthesized for comparison by alkylation of the sodium alkoxide of (4*R*)-**9** with chloromethyl methyl sulfide.

Proline−valine chimera 3,3-dimethyl-*N*-(BOC)proline (**1**) was obtained from hydrogenation of (2*S*)-3,3-dimethyl-*N*-(PhFl)proline benzyl ester (**11**) in the presence of di-*tert*-butyl dicarbonate. Low yields of **1** were obtained when palladium-on-carbon was used as catalyst in the hydrogenation of **11** in THF under 5 atm of H_2. The major side product from hydrogenation under these conditions was (2*S*)-3,3-dimethyl-*N*-(BOC)proline benzyl ester which was obtained as the sole product from the same conditions in methanol.[35] An excellent yield (95%) of proline−valine chimera **1** was obtained upon switching to palladium-hydroxide-on-carbon as catalyst under the above conditions in THF.

The enantiomeric purity of dimethylproline **1** was ascertained via its conversion to α-methylbenzylamides **14** and examination of the diastereomers by ^{1}H NMR (Scheme 3). Both (*R*)- and (*S*)-α-methylbenzylamine were coupled to proline (2*S*)-**1** in high yield using benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate in acetonitrile.[36] Integration of the diastereomeric β-methyl group singlets (δ = 0.81, 1.03) in CD_3OD showed amide (1′*S*)-**14** to be of 97% diastereomeric purity. Since (*S*)-α-methylbenzylamine of 99% ee was used in the coupling step, dimethylproline (2*S*)-**1** as well as 4-hydroxy-3,3-dimethylprolines (2*S*,4*R*)- and (2*S*,4*S*)-**2** all are determined to be of 98% enantiomeric purity.

Conclusion

Regioselective enolization and alkylation of 4-oxo-*N*-(9-phenylfluoren-9-yl)proline benzyl ester (**5**) lays the foundation for building a variety of enantiopure β-alkylprolines and β-alkyl-γ-hydroxyprolines. Starting from (2*S*,4*R*)-hydroxyproline as an inexpensive source of chirality, we have demonstrated the utility of this method by synthesizing enantiopure (2*S*)-3,3-dimethyl-*N*-(BOC)proline (**1**) in eight steps with 41% overall yield, as well as (2*S*,4*R*)- and (2*S*,4*S*)-3,3-dimethyl-4-hydroxy-*N*-(BOC)-prolines ((2*S*,4*R*)- and (2*S*,4*S*)-**2**) in six steps with 27% respective overall yields. Because our strategy can be elaborated to furnish other β-alkylproline and β-alkyl-γ-hydroxyproline analogues possessing diverse side-chain functions, potential exists for the synthesis of an assortment of amino acid chimeras for studying the spatial requirements of various biologically active amino acids and peptides.

Experimental Section

General. Unless otherwise noted all reactions were run under a nitrogen atmosphere and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately before use. CH_3CN, CH_2Cl_2, Et_3N, and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were distilled from CaH_2. MeOH was distilled from $Mg(OCH_3)_2$. Toluene and xylene were distilled from sodium. CS_2 was distilled from P_2O_5. Final reaction mixture solutions were dried over Na_2SO_4. Chromatography

(32) Roberts, J. D.; Sauer, C. W. *J. Am. Chem. Soc.* **1949**, *71*, 3925.
(33) Reviewed in: Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.
(34) Barton, D. H. R.; Crich, D.; Löbberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329.
(35) (2*S*)-3,3-Dimethyl-*N*-(BOC)proline benzyl ester: ^{1}H NMR δ 0.97 (s, 3 H), 1.12 (s, 3 H), 1.3 (s, 6.3 H), 1.42 (s, 2.7 H), 1.6 (m, 1 H), 1.84 (m, 1 H), 3.45 (m, 1 H), 3.6 (m, 1 H), 3.89 (s, 0.7 H), 3.98 (s, 0.3 H), 5.2 (m, 2 H), 7.37 (m, 5 H); ^{13}C NMR δ (23.57) 23.62, (27.7) 27.8, 28.1 (28.3), 37.2 (38), (41.5) 42.5, 44.8 (45.1), 66.4, (68.7) 69.2, (79.7) 79.8, 128.3, 128.5, 128.6, 135.5, 154, 171.9; FAB MS *m/e* 334 $[MH]^+$, 278, 234, 198 $[M - CO_2CH_2Ph]^+$ 142 (100).
(36) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927.

was on 230−400 mesh silica gel. TLC on aluminum-backed silica plates. Melting points are uncorrected. Mass spectral data, HRMS (EI & FAB), were obtained by the Regional Center for Mass Spectroscopy at the Université de Montréal. ^{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 ($(CH_3)_4Si$), and coupling constants are given in hertz. Chemical shifts for aromatic carbons are not reported. The chemical shifts for the carbons of minor rotamers are reported in parentheses.

(2*S*,4*R*)-4-Hydroxyproline benzyl ester *p*-toluenesulfonate (3) was obtained as a white crystalline solid in 98% yield by treatment of (2*S*,4*R*)-4-hydroxyproline (25 g) according to the procedure for the preparation of (2*S*,4*S*)-4-hydroxyproline benzyl ester *p*-toluenesulfonate:[1m] mp 127−129 °C; $[\alpha]^{22}_D$ −19.4° (*c* 1.18, H_2O); ^{1}H NMR (D_2O with DOH as reference δ = 4.8) δ 2.2 (ddd, 1 H, *J* = 4, 10, 14), 2.3 (s, 3 H), 2.3 (ddt, 1 H, *J* = 2, 8, 14), 3.3 (dt, 1 H, *J* = 2, 12.6), 3.44 (dd, 1 H, *J* = 3.6, 12.6), 4.62 (m, 1 H), 4.66 (dd, 1 H, *J* = 8, 10.6), 5.2 (d, 1 H, *J* = 12), 5.27 (d, 1 H, *J* = 12), 7.34 (d, 2 H, *J* = 8), 7.4 (m, 5 H), 7.6 (d, 2 H, *J* = 8); ^{13}C NMR (D_2O with CH_3OH as reference δ = 49) 16, 32.2, 44.4, 53.6, 64.2, 64.9, 120.9, 124, 124.3, 124.4, 124.9, 130, 135.3, 137.6, 164.9.

(2*S*,4*R*)-4-Hydroxy-*N*-(PhFl)proline benzyl ester (4) was synthesized from (2*S*,4*R*)-4-hydroxyproline benzyl ester *p*-toluenesulfonate (**3**, 11.79 g, 30 mmol) using the procedure for the preparation of *N*-PhFl-L-serine methyl ester.[16] Purification by filtration through a column of silica gel using an eluant of EtOAc followed by recrystallization from EtOAc/hexane provided **4** (9.81 g, 71%): mp 151−152 °C; $[\alpha]^{22}_D$ 54.8° (*c* 1.16, $CHCl_3$); ^{1}H NMR δ 1.5 (br s, 1 H), 1.78 (ddd, 1 H, *J* = 6, 9, 13), 1.97 (dt, 1 H, *J* = 5.5, 13), 2.93 (dd, 1 H, *J* = 5, 10), 3.38 (dd, 1 H, *J* = 5, 9), 3.6 (dd, 1 H, *J* = 5.5, 10), 4.5 (m, 1 H), 4.54 (d, 1 H, *J* = 12.4), 4.8 (d, 1 H, *J* = 12.4), 7.1−7.8 (m, 18 H); ^{13}C NMR δ 39.8, 56.6, 59.4, 66, 70.1, 76.2, 175.4; HRMS calcd for $C_{31}H_{28}NO_3$ (MH^+) 462.2069, found 462.2093.

(2*S*)-4-Oxo-*N*-(PhFl)proline Benzyl Ester (5). A suspension of *N*-chlorosuccinimide (5.03 g, 38 mmol) in toluene (50 mL) was cooled to 0 °C, treated with methyl sulfide (3.3 mL, 45 mmol), stirred 20 min, and cooled to −20 °C. A solution of hydroxyproline benzyl ester **4** (6.92 g, 15 mmol) in toluene (40 mL) and CH_2Cl_2 (5 mL) was then added to the cooled solution. The mixture was stirred for 3 h, treated with triethylamine (5.25 mL, 38 mmol), and allowed to warm to rt with continued stirring. Water (100 mL) was added, and the mixture was extracted with EtOAc (3 × 40 mL). The organic extractions were combined, washed with brine, dried, and evaporated to a residue. The residue was chromatographed on silica gel using 10% EtOAc in hexane. Evaporation of the collected fractions gave 5.97 g (87%) of **5** as a white solid: mp 106−108 °C; $[\alpha]^{22}_D$ −32.6° (*c* 1.16, $CHCl_3$); ^{1}H NMR δ 2.3 (dd, 1 H, *J* = 3.2, 18.2), 2.4 (dd, 1 H, *J* = 8.4, 18.2), 3.5 (d, 1 H, *J* = 18), 3.81 (d, 1 H, *J* = 18), 3.82 (dd, 1 H, *J* = 3.2, 8.4), 4.67 (d, 1 H, 12.4), 4.74 (d, 1 H, *J* = 12.4), 7.1−7.7 (m, 18 H); ^{13}C NMR δ 41.4, 55.6, 58.3, 66.3, 76.4, 172.5, 213; HRMS calcd for $C_{31}H_{26}NO_3$ (MH^+) 460.1913, found 460.1926.

Alkylation of 4-Oxo-*N*-(PhFl)proline benzyl ester (5) was performed according to the general procedure for the alkylation of amino ketones as described in ref 14 using the conditions presented in Table 1. Chromatography with EtOAc in hexanes as eluant provided 3-alkylprolines **6**−**8**.

(2*S*,3*R*)- and (2*S*,3*S*)-3-Methyl-4-oxo-*N*-(PhFl)proline Benzyl Ester (6a). Spectral characterization of **6a** was performed on a 56:44 mixture of diastereomers: ^{1}H NMR δ 0.8 (d, 3 H, *J* = 7.1), 1.0 (d, 3 H, *J* = 7.3), 2.6 (m, 2 H), 3.32 (d, 1 H, *J* = 6), 3.38 (d, 1 H, *J* = 18), 3.62 (d, 1 H, *J* = 17.8), 3.81 (d, 1 H, *J* = 18), 3.87 (d, 1 H, *J* = 17.8), 3.88 (d, 1 H, *J* = 8.5), 4.36 (d, 1 H, *J* = 12.5), 4.53 (d, 1 H, *J* = 12.4), 4.62 (d, 1 H, *J* = 12.5), 4.64 (d, 1 H, *J* = 12.4), 7.1−7.7 (m, 18 H); ^{13}C NMR δ 8.4, 13.3, 46.1, 47.7, 54.2, 55.5, 63.4, 65.9, 66, 66.2, 75.4, 75.7, 171.3, 172.5, 213.8, 214.4; HRMS calcd for $C_{32}H_{28}NO_3$ (MH^+) 474.2069, found 474.2043.

(2*S*,3*R*)-3-Allyl-4-oxo-*N*-(PhFl)proline benzyl ester (6c) was isolated as a >6:1 mixture of diastereomers in 54% yield: ^{1}H NMR δ 2.14 (m, 1 H), 2.34 (m, 1 H), 2.47 (m, 1 H), 3.48 (dd, 1 H, *J* = 1, 18), 3.5 (d, 1 H, *J* = 4.3), 3.88 (d, 1 H, *J* = 18), 4.38 (d, 1 H, *J* = 12.5), 4.55 (d, 1 H, *J* = 12.5), 4.96 (m, 2 H), 5.55 (m, 1 H), 7.1−7.7 (m, 18 H); ^{13}C NMR δ 33.6, 52.2, 55.4, 62.9, 66.1, 75.5, 117.7, 172.5, 212.9.

(2*S*,3*R*)-3-Benzyl-4-oxo-*N*-(PhFl)proline benzyl ester (6d) was isolated as a mixture of diastereomers in 24% yield: ^{1}H NMR δ 2.64 (dd, 1 H, *J* = 8.5, 13.3), 2.76 (m, 1 H), 2.9 (dd, 1 H, *J* = 4.5, 13.3), 3.35 (d, 1 H, *J* = 17.8), 3.52 (d, 1 H, *J* = 4.7), 3.83 (d, 1 H, *J* = 17.8), 4.2 (d, 1 H, *J* = 12.5), 4.3 (d, 1 H, *J* = 12.5), 6.9−7.7 (m, 23 H); ^{13}C NMR δ 34.9, 54.2, 55.6, 63, 66, 75.5, 172.3, 212.9; HRMS calcd for $C_{38}H_{32}NO_3$ (MH^+) 550.2382, found 550.2404. **(2*S*,3*S*)-3-Benzyl-4-oxo-*N*-(PhFl)proline benzyl ester (6d)**: ^{1}H NMR δ 2.07 (dd, 1 H, *J* = 9.1, 14.8), 2.94 (m, 1 H), 3.04 (dd, 1 H, *J* = 4.5, 14.9), 3.62 (dd, 1 H, *J* = 1, 17.5), 3.84 (d, 1 H, *J* = 7.8), 3.9 (d, 1 H, *J* = 17.5), 4.5 (d, 1 H, *J* = 12.5), 4.55 (d, 1 H, *J* = 12.5), 6.9−7.7 (m, 23 H).

(2*S*)-3,3-Bis(ethoxycarbonylmethyl)-4-oxo-*N*-(PhFl)-proline benzyl ester (7f) (52%): $[\alpha]^{22}_D$ −204.9° (*c* 0.82, $CHCl_3$); ^{1}H NMR δ 1.02 (t, 3 H, *J* = 7.2), 1.27 (t, 3 H, *J* = 7.2), 2.24 (d, 1 H, *J* = 18), 2.83 (d, 1 H, *J* = 18), 3.04 (d, 1 H, *J* = 14), 3.1 (d, 1 H, *J* = 14), 3.8 (m, 3 H), 3.96, (s, 1 H), 4.12 (m, 4 H), 4.39 (d, 1 H, *J* = 12), 7−7.7 (m, 18 H); ^{13}C NMR δ 13.7, 14.1, 33.7, 39.1, 52.1, 52.3, 60.4, 60.9, 65.9, 66.2, 74.3, 169.8, 170.2, 170.3, 211.2; HRMS calcd for $C_{39}H_{38}NO_7$ (MH^+) 632.2648, found 632.2672.

(2*S*)-3,3-Diallyl-4-oxo-*N*-(PhFl)proline benzyl ester (7g) (69%): $[\alpha]^{22}_D$ −89.4° (*c* 0.62, $CHCl_3$); ^{1}H NMR δ 1.8 (dd, 1 H, *J* = 7, 15), 2.3 (ddd, 1 H, *J* = 1, 7.8, 15), 2.53 (dd, 1 H, *J* = 8.5, 14.1), 2.75 (dd, 1 H, *J* = 6.2, 14.1), 3.55 (s, 1 H), 3.76 (dd, 1 H, *J* = 1.4, 17.1), 4.1 (dd, 1 H, *J* = 0.8, 17.1), 4.3 (s, 2 H), 4.8 (d, 1 H, *J* = 18), 4.85 (d, 1 H, *J* = 10), 5.14 (d, 1 H, *J* = 17.3), 5.16 (d, 1 H, *J* = 10), 5.55 (m, 1 H), 5.74 (m, 1 H), 7.0−7.8 (m, 18 H); ^{13}C NMR δ 33.3, 38.5, 53.1, 55.2, 65.9, 66.7, 74.3, 118.6, 119, 170.9, 213.6; HRMS calcd for $C_{37}H_{34}NO_3$ (MH^+) 540.2539, found 540.2575.

(2*S*)-3,3-Dibenzyl-4-oxo-*N*-(PhFl)proline benzyl ester (7h): $[\alpha]^{22}_D$ −171° (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 2.5 (d, 1 H, *J* = 15.4), 3 (d, 1 H, *J* = 15.4), 3.07 (d, 1 H, *J* = 14), 3.12 (d, 1 H, *J* = 14), 3.65 (d, 1 H, *J* = 17.4), 3.92 (s, 1 H), 4.07 (d, 1 H, *J* = 17.4), 4.23 (d, 1 H, *J* = 12.6), 4.3 (d, 1 H, *J* = 12.6), 6.9−7.7 (m, 28 H); ^{13}C NMR δ 37, 41, 54, 58, 65.9, 67.4, 74.8, 170.6, 213.2; HRMS calcd for $C_{45}H_{38}NO_3$ (MH^+) 640.2852, found 640.2819.

(2*S*)-Benzyl 3-benzyl-Δ^3-*N*-(PhFl)proline 4-*O*-benzyl enol ether (8) (48%): $[\alpha]^{22}_D$ 7.6° (*c* 1, $CHCl_3$); ^{1}H NMR δ 2.89 (d, 1 H, *J* = 15.3), 3.45 (d, 1 H, *J* = 15.3), 3.78 (s, 1 H), 3.8 (m, 1 H), 4.25 (dd, 1 H, *J* = 5, 14), 4.64 (d, 1 H, *J* = 12.2), 4.67 (d, 1 H, *J* = 12.3), 4.8 (d, 1 H, *J* = 12.2), 4.84 (d, 1 H, *J* = 12.3), 6.7−7.7 (m, 28 H); ^{13}C NMR δ 29.4, 53.6, 65.9, 68.3, 71.3, 77.2, 111.2, 151, 173.9; HRMS calcd for $C_{45}H_{38}NO_3$ (MH^+) 640.2852, found 640.2833.

(2*S*)-3,3-Dimethyl-4-oxo-*N*-(PhFl)proline Benzyl Ester (7a). A mechanically stirred solution of $KN(SiMe_3)_2$ (64 mL, 0.5 M in toluene, 32 mmol) at 0 °C was treated with 31 mL of DMPU, stirred 10 min, cooled to −78 °C, and treated with a −78 °C solution of (2*S*)-4-oxo-*N*-(PhFl)proline benzyl ester (**5**, 3.76 g, 8 mmol) in 60 mL of THF. The solution was stirred 1 h, treated with iodomethane (5 mL, 80 mmol), and stirred 4.5 h, and the reaction was quenched with 1 M KH_2PO_4 (50 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic extractions were washed with H_2O (3 × 25 mL) and brine (25 mL), dried, and evaporated to a solid. The solid was suspended in a solution of 15% EtOAc in hexanes (10 mL), stirred 5 min, and decanted. The solid was resubmitted to this process four additional times and then four times using 10% EtOAc in hexanes (15 mL). The solid was dried under high vacuum, giving pure **7a** (3.24 g, 82%): mp 195−197 °C; $[\alpha]^{22}_D$ −254° (*c* 0.87, $CHCl_3$); ^{1}H NMR δ 0.78 (s, 3 H), 1.32 (s, 3 H), 3.46 (s, 1 H), 3.75 (d, 1 H, *J* = 17), 4.03 (d, 1 H, *J* = 17), 4.27 (d, 1 H, *J* = 12.4), 4.4 (d, 1 H, *J* = 12.4), 7.0−7.7 (m, 18 H); ^{13}C NMR δ 17.4, 25.5, 49, 52.7, 65.8, 69.3, 74.3, 171.7, 216; HRMS calcd for $C_{33}H_{30}NO_3$ (MH^+) 488.2226, found 488.2211.

(2*S*,4*R*)- and (2*S*,4*S*)-3,3-Dimethyl-4-hydroxy-*N*-(PhFl)-proline Benzyl Esters ((2*S*,4*R*)- and (2*S*,4*S*)-9) from Reduction with $NaBH_4$. A solution of (2*S*)-3,3-dimethyl-4-

oxo-*N*-(PhFl)proline benzyl ester (**7a**, 2.13 g, 4.37 mmol) in 70 mL of THF was added to a 0 °C suspension of $NaBH_4$ (662 mg, 17.5 mmol) in MeOH (40 mL), and the mixture was stirred 3.5 h. A second portion of $NaBH_4$ (332 mg, 8.7 mmol) was added, and the mixture was stirred an additional 2 h. The mixture was poured into a solution of 1 M KH_2PO_4 (100 mL) and extracted with EtOAc (4 × 50 mL), and the combined organic extractions were washed with brine (3 × 50 mL), dried, and evaporated to a solid that was purified by chromatography on silica gel using 15% EtOAc in hexane as eluant. First to elute was (2*S*,4*S*)-**9** (0.8 g, 38%): mp 173−174 °C; $[\alpha]^{22}_D$ 177° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 0.5 (s, 3 H), 0.82 (s, 3 H), 2.63 (s, 1 H), 3.33 (dd, 1 H, J = 3.4, 9.7), 3.45 (d, 1 H, J = 9.7), 3.5 (br s, 1 H), 4.03 (br d, 1 H), 4.55 (d, 1 H, J = 12), 4.94 (d, 1 H, J = 12), 7.0−7.8 (18 H); ^{13}C NMR δ 19.1, 27.1, 46.2, 54.7, 66.9, 69.2, 75.3, 79.8, 177.3; HRMS calcd for $C_{33}H_{32}NO_3$ (MH^+) 490.2382, found 490.2408. Next to elute was (2*S*,4*R*)-**9** (1.31 g, 61%): mp 193−194 °C; $[\alpha]^{22}_D$ 211° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 0.5 (s, 3 H), 0.78 (s, 3 H), 1.5 (br s, 1 H), 2.76 (s, 1 H), 2.98 (t, 1 H, J = 8.5), 3.6 (dd, 1 H, J = 6.5, 8.5), 4.18 (t, 1 H, J = 6.5), 4.65 (d, 1 H, J = 12.2), 4.86 (d, 1 H, J = 12.2), 7.0−7.8 (18 H); ^{13}C NMR δ 20.4, 21.9, 44, 52.1, 66, 70, 75.6, 76.2, 174.6; HRMS calcd for $C_{33}H_{32}NO_3$ (MH^+) 490.2382, found 490.2368.

(2*S*,4*R*)- and (2*S*,4*S*)-9 from reduction with $LiAlH_4$. A solution of **7a** (620 mg, 1.27 mmol) in 12 mL of THF at −78 °C was treated with $LiAlH_4$ (48 mg, 1.26 mmol) and stirred 30 min, and the reaction was quenched with a solution of 1 M KH_2PO_4 (20 mL). The mixture was allowed to warm to rt and extracted with EtOAc (3 × 25 mL). The combined organic extractions were washed with water (2 × 20 mL) and brine, dried, and evaporated to a solid that was purified by chromatography as described above to provide 358 mg (58%) of (2*S*,4*S*)-**9** and 201 mg (32%) of (2*S*,4*R*)-**9**.

(2*S*,4*R*)-3,3-Dimethyl-4-hydroxy-*N*-(BOC)proline ((2*S*,4*R*)-2). A solution of (2*S*,4*R*)-3,3-dimethyl-4-hydroxy-*N*-(PhFl)proline benzyl ester ((2*S*,4*R*)-**9**, 574 mg, 1.2 mmol) and di-*tert*-butyl dicarbonate (670 mg, 2.6 mmol) in 35 mL of THF was treated with palladium-on-carbon (70 mg, 10 wt %), and the mixture was stirred under 5 atm of hydrogen for 48 h. The catalyst was removed by filtration on Celite and washed with MeOH (3 × 10 mL) and THF (2 × 10 mL), and the combined organic phase was evaporated to a solid. The solid was triturated with hexane (20 mL), recovered by aid of a centrifuge, and treated in the same manner with five additional volumes of hexane (20 mL), providing (2*S*,4*R*)-**2** (283 mg, 93%): mp 253−255 °C; $[\alpha]^{22}_D$ 8.14° (*c* 1.2, CH_3OH); ^{1}H NMR δ (CD_3OD) 0.91 (s, 3 H), 1.06 (s, 3 H), 1.34 (s, 6.2 H), 1.38 (s, 2.8 H), 3.22 (m, 1 H), 3.63 (dd, 1 H, J = 5.7, 11.1), 3.83 (m, 1 H), 3.85 (s, 1 H); ^{13}C NMR δ (CD_3OD) 19.9, (20.9) 21, 27 (27.2), (43.6) 44.5, 51.2 (51.4), (67.5) 67.9, 75.2 (75.6), (79.8) 80.1, 154.7 (155), (173) 173.4; HRMS calcd for $C_{12}H_{22}NO_5$ (MH^+) 260.1498, found 260.1478.

(2*S*,4*S*)-3,3-Dimethyl-4-hydroxy-*N*-(BOC)proline ((2*S*,4*S*)-2) was prepared in 92% yield from (2*S*,4*S*)-**9** (250 mg, 0.5 mmol) by the same procedure as described for (2*S*,4*R*)-**2**: mp 173−175 °C; $[\alpha]^{22}_D$ −16.1° (*c* 1.4, CH_3OH); ^{1}H NMR δ (CD_3OD) 0.94 (s, 3 H), 1.11 (s, 3 H), 1.35 (s, 6.4 H), 1.39 (s, 2.6 H), 3.24 (m, 1 H), 3.65 (dd, 1 H, J = 6.3, 10.8), 3.73 (q, 1 H, J = 6), 3.8 (s, 1 H); ^{13}C NMR δ (CD_3OD) 19.4 (19.5), 28.3 (28.5), 30.2 (30.4), (47) 47.6, 54.3 (55), (70.8) 71.4, 79.1 (79.9), (83.2) 83.5, 157.8 (158.1), (176.6) 176.9; HRMS calcd for $C_{12}H_{22}NO_5$ (MH^+) 260.1498, found 260.1487.

(2*S*)-3,3-Dimethyl-*N*-(PhFl)proline Benzyl Ester ((2*S*)-11). A solution of (2*S*,4*R*)-3,3-dimethyl-4-hydroxy-*N*-(PhFl)-proline benzyl ester ((2*S*,4*R*)-**9**, 350 mg, 0.72 mmol) in THF (5 mL) was added to a suspension of NaH (114 mg, 2.86 mmol, 60% by weight which was prewashed with 10 mL of THF) in 5 mL of THF at 0 °C. The suspension was stirred for 30 min and treated with 5 mL of CS_2. The mixture was stirred 1 h at 0 °C, treated with iodomethane (0.44 mL, 7.2 mmol), stirred overnight at 4 °C, evaporated, and partitioned between EtOAc (50 mL) and H_2O (10 mL). The organic phase was washed with brine (10 mL), dried, and chromatographed on silica gel using 10% EtOAc in hexane as eluant. Evaporation of the collected fractions provided **xanthate** (2*S*,4*R*)-**10** (100%): ^{1}H NMR δ 0.84 (s, 3 H), 0.92 (s, 3 H), 2.46 (s, 3 H), 3.0 (s, 1 H), 3.26 (dd, 1 H, J = 5.4, 10.4), 3.98 (dd, 1 H, J = 6, 10.5), 4.61 (d, 1 H, J = 12.3), 4.79 (d, 1 H, J = 12.3), 5.75 (t, 1 H, J = 5.7), 7.0−7.8 (m, 18 H); ^{13}C NMR δ 19, 22.2, 22.6, 44.8, 50.5, 66, 69.9, 75.8, 87.4, 173.1, 215.2. **Xanthate** (2*S*,4*S*)-**10** was also prepared quantitatively from (2*S*,4*S*)-**9** according to the procedure described above: $[\alpha]^{22}_D$ 203° (*c* 0.4, CHCl3); ^{1}H NMR δ 0.73 (s, 3 H), 0.87 (s, 3 H), 2.59 (s, 3 H), 2.77 (s, 1 H), 3.47 (dd, 1 H, J = 4.8, 11.6), 3.72 (dd, 1 H, J = 5.7, 11.6), 4.63 (d, 1 H, J = 12.3), 4.82 (d, 1 H, J = 12.3), 5.4 (t, 1 H, J = 5), 7.0−7.8 (m, 18 H); ^{13}C NMR δ 18.7, 19, 27.1, 45.3, 51.9, 66, 69.8, 76.4, 88, 173.1, 215.4; HRMS calcd for $C_{35}H_{34}NO_3S_2$ (MH^+) 580.1980, found 580.2011.

A solution of xanthate (2*S*,4*R*)-**10** (51 mg, 0.09 mmol), AIBN (1−2 mg), and tri-*n*-butylstannane (0.05 mL, 0.2 mmol) in 2 mL of xylene was submitted to a bubbling of N_2 gas for 20 min. The solution was then transferred over 10 min into refluxing xylene (3 mL). The solution was heated at a reflux for 1 h when TLC showed complete consumption of the starting xanthate. The xylene was then removed by distillation under high vacuum, and the residue was purified by chromatography on silica gel using 4% EtOAc in hexanes as eluant. First to elute was (2*S*)-3,3-dimethyl-*N*-(PhFl)proline benzyl ester ((2*S*)-**11**, 38 mg, 91%): mp 131−132 °C; $[\alpha]^{22}_D$ 161° (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.55 (s, 3 H), 0.78 (s, 3 H), 1.4 (ddd, 1 H, J = 3, 6, 9), 1.87 (ddd, 1 H, J = 7, 10, 12), 2.6 (s, 1 H), 3.11 (dt, 1 H, J = 6, 9), 3.37 (ddd, 1 H, J = 3, 7, 9), 4.63 (d, 1 H, J = 12), 4.83 (d, 1 H, J = 12), 7.0−7.8 (m, 18 H); ^{13}C NMR δ 24.4, 27.7, 38.9, 42.3, 46.9, 65.8, 70.4, 76, 175.2; HRMS calcd for $C_{33}H_{32}NO_2$ (MH^+) 474.2433, found 474.2394. Next to elute was hemithiol acetal **12** (2 mg, 4%): ^{1}H NMR δ 0.47 (s, 3 H), 0.77 (s, 3 H), 2.04 (t, 1 H, J = 9.3), 2.68 (s, 1 H), 2.96 (t, 1 H, J = 8.3), 3.65 (dd, 1 H, J = 6.5, 8), 4.08 (dd, 1 H, J = 6.5, 8.5), 4.62 (d, 1 H, J = 12.1), 4.66 (dd, 1 H, J = 9.4, 11.1), 4.77 (dd, 1 H, J = 9.3, 11.1), 4.84 (d, 1 H, J = 12.2), 7.0−7.8 (m, 18 H); ^{13}C NMR δ 21.3, 22, 43.4, 49.5, 66.1, 67.6, 69.7, 75.5, 81.1, 174.5; FAB MS *m/e* 536 $[MH]^+$, 400 $[M - CO_2CH_2Ph]$, 241 (100); HRMS calcd for $C_{34}H_{34}NO_3S$ (MH^+) 536.2260, found 536.2233. When xanthates (2*S*,4*S*)- and (2*S*,4*R*)-**10** were reduced in refluxing toluene, **11** was obtained in 81% and 57% respective yields.

(2*S*)-3,3-Dimethyl-*N*-(BOC)proline ((2*S*)-1). A solution of (2*S*)-3,3-dimethyl-*N*-(PhFl)proline benzyl esters ((2*S*)-**11**, 107 mg, 0.23 mmol) and di-*tert*-butyl dicarbonate (67 mg, 0.31 mmol) in 10 mL of THF was treated with palladium-hydroxide-on-carbon (32 mg, 20 wt % in Pd), and the mixture was stirred under 5 atm of hydrogen for 25 h. The catalyst was removed by filtration on Celite and washed with THF (4 × 10 mL) and 1:1 THF:MeOH (2 × 10 mL), and the combined organic phase was evaporated to a residue that was purified by chromatography on silica gel. Initially an eluant of 10% EtOAc in hexane was used to elute the 9-phenylfluorene; afterward *N*-(BOC)-amino acid **1** was eluted from the column using 5% acetic acid in EtOAc. Evaporation of the ninhydrin positive fractions (visualized on TLC after treatment with TFA vapors) gave (2*S*)-**1** (52 mg, 95%): mp 130−131 °C; $[\alpha]^{22}_D$ 9.5° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.1 (s, 3 H), 1.2 (s, 3 H), 1.42 (s, 6.2 H), 1.46 (s, 2.8 H), 1.64 (m, 1 H), 1.89 (m, 1 H), 3.49 (m, 1 H), 3.6 (m, 1 H), 3.84 (s, 0.75 H), 3.94 (s, 0.25 H); ^{13}C NMR δ 23.6, 27.8, 28.2 (28.3), 37.3 (38), (41.3) 42.3, 44.8 (45.1), 69.1, (80.1) 80.3, 154.2 (154.8), (177) 177.8; MS *m/e* 244 $[MH]^+$, 188, 142 (100); HRMS calcd for $C_{12}H_{22}NO_4$ (MH^+) 244.1549, found 244.1556.

(2*S*,4*R*)-Benzyl 3,3-Dimethyl-*N*-(PhFl)prolinate 4-(Methylthio)methyl Ether ((2*S*,4*R*)-13). A solution of hemithiol acetal (2*S*,4*R*)-**12** (14 mg, 0.026 mmol) in 0.5 mL of THF was treated first with K_2CO_3 (4 mg, 0.03 mmol) and then with iodomethane (10 μL, 0.16 mmol). The mixture was stirred overnight at rt and then filtered through a pad of silica gel with THF as eluant. Evaporation gave 12 mg (84%) of (methylthio)methyl ether (2*S*,4*R*)-**13**: ^{1}H NMR δ 0.49 (s, 3 H), 0.77 (s, 3 H), 2.09 (s, 3 H), 2.69 (s, 1 H), 2.96 (t, 1 H, J = 8.3), 3.63 (dd, 1 H, J = 6.5, 8), 4.13 (dd, 1 H, J = 6.5, 8.5), 4.52 (d, 1 H, J = 11.3), 4.6 (d, 1 H, J = 11.3), 4.63 (d, 1 H, J = 12.3), 4.83 (d, 1 H, J = 12.3), 7.0−7.8 (m, 18 H); ^{13}C NMR δ 13.8, 21.3, 22.1, 43.5, 49.4, 65.9, 69.9, 75, 75.5, 80.7, 174.3.

Enantiomeric Purity of (2*S*)-3,3-Dimethyl-*N*-(BOC)-proline ((2*S*)-1). A room temperature solution of (2*S*)-3,3-dimethyl-*N*-(BOC)proline ((2*S*)-**1**, 5 mg, 0.02 mmol) and either

(*R*)- or (*S*)-α-methylbenzylamine (3 μL, 0.02 mmol) in 0.5 mL of acetonitrile was treated with benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (7 mg, 0.02 mmol) and stirred 12 h when TLC showed complete disappearance of the starting acid. The reaction mixture was partitioned between brine (0.7 mL) and EtOAc (3 mL), and the organic layer was washed with H_2O (2 × 3 mL), dried, filtered, and evaporated to a residue (7 mg) that was directly examined by ^{1}H NMR. When (*S*)-α-methylbenzylamine of 99% diastereomeric purity was used, examination of the β-methyl singlets in the ^{1}H NMR in CD_3OD demonstrated (*S*)-**14** to be of 97% diastereomeric purity. Hence, (2*S*)-**1** is determined to be of 98% enantiomeric purity.

(1′*S*,2*S*)-3,3-Dimethyl-*N*-(BOC)proline *N*′-α-methylbenzylamide ((*S*)-14): ^{1}H NMR δ (CD_3OD) 0.81 (s, 3 H), 1.08 (s, 3 H), 1.39 (s, 9 H), 1.46 (d, 3 H, J = 7.1), 1.52 (m, 1 H), 1.84 (m, 1 H), 3.33 (m, 1 H), 3.54 (m, 1 H), 3.73 (s, 1 H), 5.0 (m, 1 H), 7.1−7.4 (m, 5 H), 8.4 (br d, 1 H); HRMS calcd for $C_{20}H_{31}N_2O_3$ (MH^+) 347.2335, found 347.2333.

(1′*R*,2*S*)-3,3-Dimethyl-*N*-(BOC)proline *N*′-α-methylbenzylamide ((*R*)-14): ^{1}H NMR δ (CD_3OD) 1.03 (s, 3 H), 1.11 (s, 3 H), 1.19 (s, 9 H), 1.43 (d, 3 H, J = 7), 1.57 (m, 1 H), 1.93 (m, 1 H), 3.35 (m, 1 H), 3.56 (m, 1 H), 3.72 (s, 1 H), 5.04 (m, 1 H), 7.1−7.4 (m, 5 H), 8.4 (br d, 1 H); HRMS calcd for $C_{20}H_{31}N_2O_3$ (MH^+) 347.2335, found 347.2347.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and DEPT spectra of **1**−**14** and ^{1}H,^{1}H COSY and ^{1}H,^{13}C HETCOR spectra of **12** (65 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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