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Synthesis of Fused Heteroarylprolines and Pyrrolopyrroles

Guillaume Jeannotte and William D. Lubell*

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

lubell@chimie.umontreal.ca

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Fused heteroarylprolines were prepared starting from 4-oxo-*N*-(PhF)proline benzyl ester (**6**, PhF = 9-(9-phenylfluorenyl)) following two approaches. First, allylation of oxoproline **6** followed by Wacker oxidation gave 1,4-dione **8** that was selectively converted to pyrroloproline **10b**, pyrrolopyrrole **12**, and pyridazinoproline **9**. Second, aldol condensation of oxoproline **6** with a series of *N*-(Boc)-α-amino aldehydes **15a**−**e** and acid-catalyzed cyclization gave pyrroloprolines **17a**−**e** possessing a variety of pyrrole 5-position substituents. Conditions for the selective deprotection and alkylation of the pyrrole nitrogen of pyrroloprolines **17** were developed to expand the diversity of the heteoaryl systems. Finally, hydrogenolytic cleavage of the PhF and benzyl groups followed by subsequent protection with Boc, Fmoc, and Moz groups was performed to obtain analogues suitable for peptide synthesis. The enantiomeric purity of *N*-(Boc)pyrrolo-proline **21a** was ascertained by coupling to L- and D-phenylalanine methyl ester and examination of the diastereotopic pyrrole protons, which demonstrated the dipeptides to be of >99% diastereomeric purity. These approaches have thus delivered the first series of enantiopure fused arylprolines for application as arylglycine-proline chimeras in structure−activity studies of biologically active compounds.

Introduction

Fused arylprolines, such as **1** and **2** (Figure 1), are challenging synthesis targets that have potential to serve, respectively, as phenylalanine-proline and phenylglycine-proline chimeras in structure−activity studies of biologically relevant compounds. For example, asymmetric synthesis,[1−3] enzymatic resolution, and fractional recrystallization[4] all have furnished enantiomerically enriched analogues of indoline-2-carboxylate **1**, which has been used to develop angiotensin-converting enzyme inhibitors related to the drugs captopril[5,6] and enalapril.[7] Isoindoline-1-carboxylic acid **2** has been less well studied, and there exist presently no methods for its synthesis in enantiomerically pure form. Methyl isoindoline-1-carboxylates have been isolated as hydrochlorides yet reported to be "highly sensitive to air" and presumed to oxidize to the corresponding 1-carbomethoxyphthalimidines **3** and isoindoles **4**.[8] In light of the importance of arylglycines in medicine, such as their presence in common β-lactam antibiotics such as ampicillin[9] and amoxicillin,[10] enantiopure, conformationally rigid arylglycine analogues, like **2**, have desirable utility for studying and improving the pharmacological properties of contemporary drugs.

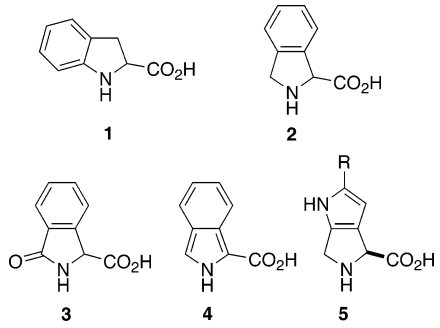

FIGURE 1. Representative fused arylproline analogues.

Prior to our studies, the synthesis of fused heteroarylprolines had yet to be reported. Pyrrole-prolines of general structure **5** were pursued as novel heteroarylglycine-proline chimeras that could be amenable for diversity oriented synthesis. In particular, *N*-alkylation was expected to allow synthesis of a variety of fused arylproline analogues from a common intermediate. The

(1) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.
(2) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614−7615.
(3) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163−168.
(4) Ramos Tombo, G. M.; Schär, H.-P.; Ghisalba, O. *Agric. Biol. Chem.* **1987**, *51*, 1833−1838.
(5) Kim, D. H.; Guinosso, C. J.; Buzby, G. C. J.; Herbst, D. R.; McCaully, R. J.; Wicks, T. C.; Wendt, R. L. *J. Med. Chem.* **1983**, *26*, 394−403.
(6) Stanton, J. L.; Gruenfeld, N.; Babiarz, J. E.; Ackerman, M. H.; Friedmann, R. C.; Yuan, A. M.; Macchia, W. *J. Med. Chem.* **1983**, *26*, 1267−1277.
(7) Gruenfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277−1282.
(8) Cignarella, G.; Cerri, R.; Grella, G.; Sanna, P. *Gazz. Chim. Ital.* **1976**, *106*, 65−75.
(9) Austin, K. W. B.; Marshall, A. C.; Smith, H. *Nature* **1965**, *208*, 999−1000.
(10) Long, A. A. W.; Nayler, J. H. C.; Smith, H.; Taylor, T.; Ward, N. *J. Chem. Soc. C* **1971**, 1920−1922.

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directionality of the pyrrole was expected to retard racemization and oxidation of the neighboring pyrrolidine ring. A methodology for making enantiopure pyrrole-prolines **5** has now been developed that allows modification of the steric and electronic properties of the aromatic component of the arylproline. Furthermore, conditions have been developed for alkylation of the pyrrole nitrogen. In addition to novel methodology for the synthesis of enantiopure pyrrole-prolines, protocols have been conceived for the preparation of pyridazinoproline and pyrrolopyrroles. A novel series of amino acid scaffolds has thus been synthesized for the study of biologically active compounds.

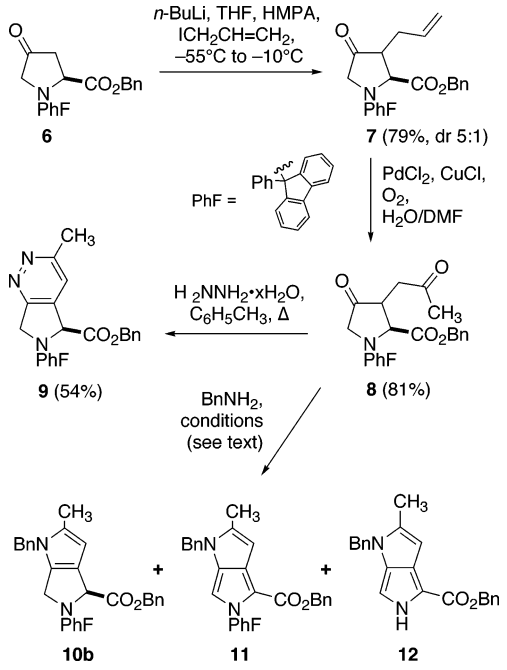
Results and Discussion

Past syntheses of dihydroisoindole-2-carboxylic acid **2** and its analogues have constructed the chiral α-center by amine alkylation with an α-halo acid equivalent,[8] by carbonylation of metalated phthalimidine[11] and isoindoline[12] intermediates, and by intramolecular arylation of glycine precursors.[13] Such approaches have thus far failed to deliver enantiopure product due to the inherent difficulty of constructing this stereocenter stereoselectively. In contrast, we pursued a route to heteroarylprolines in which hydroxyproline was used as chiral educt to provide enantiopure product. This approach was based on our previous methodology for the enolization and alkylation of 4-oxo-*N*-(PhF)proline benzyl ester to make a variety of Δ^3-dehydroproline analogues without loss of the configurational integrity at the α-center.[14,15]

Alkylation of the enolate of **6** with α-halo ketones was first pursued to construct a suitable 1,4-dione for pyrroloproline synthesis by condensation with amines according to the Paal−Knorr pyrrole synthesis.[16,17] Methyl bromoacetate had previously reacted with the potassium enolate of **6** to install the 3-position substituent for the synthesis of Δ^3-dehydrokainic acid analogues.[14,18] In contrast, attempts to perform similar chemistry with α-bromo ketones, such as α-bromo acetophenone, gave only trace amounts of 1,4-diones, perhaps due to deprotonation of the electrophile. Desired 1,4-dione **8** was synthesized from ketone **6** in 64% overall yield by alkylation with allyl iodide, followed by oxidation of the terminal olefin by a Wacker process using oxygen, $PdCl_2$, and CuCl in a mixture of DMF and water (Scheme 1).[19]

Considering the Paal−Knorr pyrrole synthesis with 1,4-dione **8** and our recently reported synthesis of 4-aminopyrrole-2-carboxylates[20] from 4-oxo-*N*-(PhF)proline esters such as **6**, we realized that there was a competition at hand and sought to develop selective conditions to prepare either pyrroloproline **10b** or pyrrolopyrroles **12**.

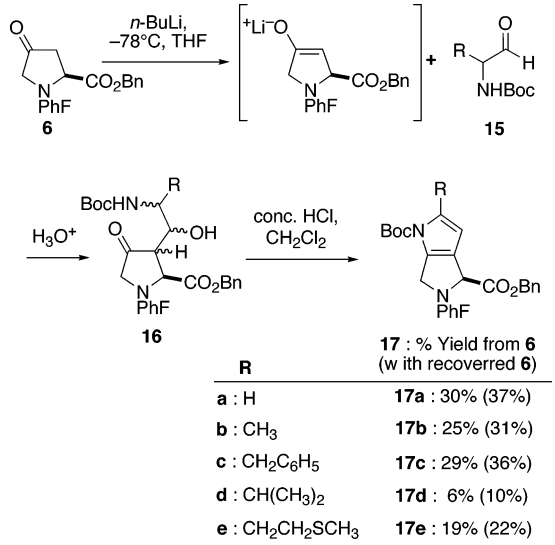
SCHEME 1. Paal−Knorr Approach to Heteroarylprolines



The latter was expected to be a thermodynamic product because of its fully aromatic character. To the best of our knowledge, the 2,4-dihydropyrrolo[3,4-*b*]pyrrole ring system had been reported only once before,[21] and the parent heterocycle was predicted to be unstable according to theoretical calculations of its resonance energy.[22] *N*-*p*-Methoxyphenysulfonylpyrrolo[3,4-*b*]pyrroles were synthesized by a retro-malonate addition reaction; however, attempts to deprotect the arylsulfonyl group led to decomposition of the product.[21] Condensation of 1,4-dione **8** with benzylamine was explored in different solvents (EtOH, CH_3CN, THF, toluene) with both *p*-toluenesulfonic and acetic acids. Varying ratios of pyrroloproline **10b** and pyrrolopyrrole **12** were obtained along with PhF-protected pyrrolopyrrole **11**,[23] as measured by proton NMR spectroscopy and integration of the pyrrole proton signals at 5.31, 6.35, and 6.12 ppm, respectively. The formation of PhF-protected **11** was minimized by performing the condensation under inert atmosphere in degassed solvent. The thermodynamic pyrrolo[3,4-*b*]-pyrrole **12** was obtained in a >14:1 ratio with pyrroloproline **10b** by reacting 1,4-dione **8** with 500 mol % of benzylamine in toluene at 50 °C for 24 h in the presence of 10 mol % of *p*-toluenesulfonic acid. After column chromatography, pure pyrrolopyrrole **12** was isolated in 60% yield as a yellow solid that turned brown when exposed to air and as a solution in $CDCl_3$. The presence of the electro-attractive ester moiety on the ring of the pyrrolopyrrole **12** may account for its enhanced stability. On the other hand, pyrroloproline **10b** was obtained in

(11) Couture, A.; Deniau, E.; Ionescu, D.; Grandclaudon, P. *Tetrahedron Lett.* **1998**, *39*, 2319−2320.
(12) Beeley, L. J.; Rockell, C. J. M. *Tetrahedron Lett.* **1990**, *31*, 417−420.
(13) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465−475.
(14) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658−2659.
(15) Rondeau, D.; Gill, P.; Chan, M.; Curry, K.; Lubell, W. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 771−773.
(16) Paal, C. *Chem. Ber.* **1884**, *17*, 2756.
(17) Knorr, L. *Chem. Ber.* **1884**, *17*, 2863.
(18) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202−209.
(19) Tsuji, J. *Synthesis* **1984**, 369−384.
(20) Marcotte, F.-A.; Lubell, W. D. *Org. Lett.* **2002**, *4*, 2601−2603.
(21) Sha, C.-K.; Liu, J.-M.; Chiang, R.-K.; Wang, S.-U. *Heterocycles* **1990**, *31*, 603−609.
(22) Gutman, I.; Milun, M.; Trinajstić, N. *J. Am. Chem. Soc.* **1977**, *99*, 1692−1704.
(23) 1-Benzyl-2-methyl-5-(PhF)-1,5-dihydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (**11**): ^{1}H NMR (300 MHz, $CDCl_3$) 2.25 (s, 3 H), 4.89 (s, 2 H), 5.12 (s, 2 H), 6.12 (s, 1 H), 7.0−7.7 (m, 23 H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.5, 49.1, 65.4, 78.1, 160.6; HRMS calcd for $C_{41}H_{32}N_2O_2$ (MH^+) 584.2464, found 584.2487.

SCHEME 2. Synthesis of Protected Pyrroloprolines 17

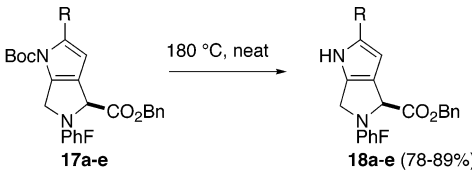


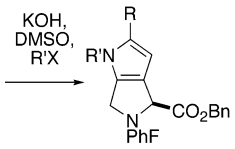
R	17 : % Yield from 6 (w ith recoverred 6)
a : H	**17a** : 30% (37%)
b : CH_3	**17b** : 25% (31%)
c : $CH_2C_6H_5$	**17c** : 29% (36%)
d : $CH(CH_3)_2$	**17d** : 6% (10%)
e : $CH_2CH_2SCH_3$	**17e** : 19% (22%)

a >3:1 ratio with pyrrolopyrrole **12** by reacting 1,4-dione **8** with 500 mol % of benzylamine and 3000 mol % of acetic acid in EtOH at 60 °C for 1.5 h. These mildly acidic conditions suppressed α-deprotonation with elimination of the PhF aromatic anion which leads to 4-aminopyrrole-2-carboxylates related to **12**,[20] such that pyrroloproline **10b** was isolated in 23% yield after column chromatography.

A more generally successful method for preparing pyrroloprolines was developed that involved the aldol condensation of ketone **6** with *N*-(Boc)-α-amino aldehydes **15**, followed by acid-induced cyclization of the *β*-hydroxyketone intermediate to yield the pyrrole[24] (Scheme 2). α-Substituted α-amino aldehydes **15b**−**e** were synthesized in >80% yields from their corresponding *N*-(Boc)-amino acids by acylation of *N*,*O*-dimethylhydroxylamine using TBTU, followed by reduction of the hydroxamate with lithium aluminum hydride.[25] Glycinal **15a** was prepared in two steps and 65% overall yield from 3-amino-1,2-propanediol by protection with $(Boc)_2O$ followed by periodate oxidation of the crude protected diol.[26] Previously, aldol adducts had been obtained by enolization of *N*-PhF-4-oxoproline esters with *n*-BuLi in THF at −55 °C and condensations with ordinary aromatic and aliphatic aldehydes.[27] Enolization of 4-oxoproline **6** under these conditions followed by treatment with *N*-Boc-α-amino aldehydes **15** at −78 °C gave crude mixtures that were observed by proton NMR spectroscopy and mass spectrometry to contain diastereomeric aldol products **16**, as well as starting 4-oxoproline **6** which could be recovered by column chromatography and recycled. Treatment of crude *β*-hydroxy ketone **16** with concentrated HCl in methylene chloride at room temperature afforded pyrroles **17a**−**e** in 10−37% overall yields accounting for recovered **6** (Scheme 2). Formation of the heterocycle was

SCHEME 3. Pyrrole Deprotection and Alkylation





R'X	% Yield from 18
19a : ICH_3	(92%)
10a : $BrCH_2C_6H_5$	(81%)
19b : ICH_3	(72%)
10b : $BrCH_2C_6H_5$	(63%)
20b : $BrCH_2CO_2t$-Bu	(49%)

indicated by the presence of a characteristic pyrrole aromatic singlet at around 5.5 ppm in the proton NMR spectrum.

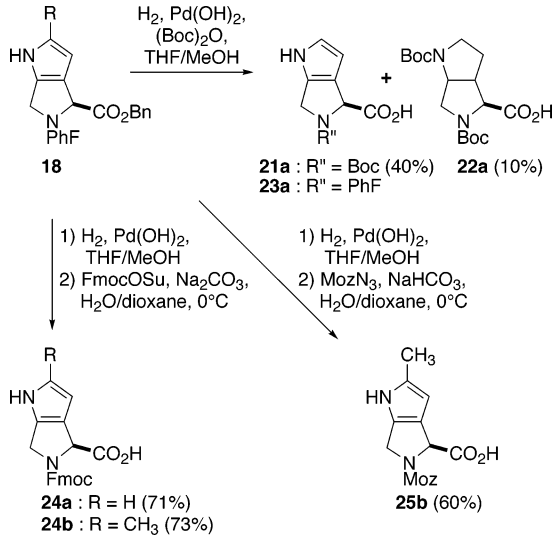
With effective methodology for preparing pyrroloprolines **17** in hand, our next objectives were the selective removal of the Boc group and alkylation of the pyrrole nitrogen to demonstrate the potential of our strategy for diversity-oriented synthesis (Scheme 3). Initially, pyrroloproline **17a** was treated with sodium methoxide in THF at room temperature and a 66% yield of deprotected product was isolated; however, trans-esterification occurred to give the pyrroloproline methyl ester.[28] Selective Boc group deprotection without trans-esterification was later accomplished by thermolysis at 180 °C for 30 min under a flow of argon.[29] All five pyrroloprolines **17a**−**e** were effectively converted to their *NH*-pyrrole counterparts **18a**−**e** by this method in 77−89% yields on a scale of 60 mg and 60−65% yields on 400 mg scale. The diversity of the pyrroloproline analogues was expanded by *N*-alkylation of the pyrrole ring. Alkylation of the nitrogen of both pyrrole **18a** and its 5-methyl counterpart **18b** was effectively accomplished in dimethyl sulfoxide at room temperature by sequential treatments with powdered potassium hydroxide and an alkyl halide followed by stirring at room temperature, aqueous workup, and purification by chromatography.[30] *N*-Alkylpyrrole-prolines **10a** and **10b**, **19a** and **19b**, and **20b** were prepared in 49−92% overall yields from **18** by this method using methyl iodide, benzyl bromide, and *tert*-butyl bromoacetate as electrophiles, respectively.

The next objective was to transform *N*-PhF-pyrroloproline benzyl ester **18** into analogues suitable for peptide synthesis. Previously, a one-pot hydrogenolytic cleavage of the PhF-amine and benzyl ester protecting groups in the presence of di-*tert*-butyl dicarbonate was used to synthesize Boc-protected proline-valine and hydroxyproline-valine chimeras suitable for peptide synthesis.[18,31] When pyrrole-proline **18a** was submitted to a similar hydrogenation protocol in the presence of $(Boc)_2O$ and

(24) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999−5003.
(25) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676−678.
(26) Dueholm, K. L.; Egholm, M.; Buchardt, O. *Org. Prep. Proc. Int.* **1993**, *25*, 457−461.
(27) Blanco, M.-J.; Paleo, M. R.; Penide, C.; Sardina, F. J. *J. Org. Chem.* **1999**, *64*, 8786−8793.

(28) (4*S*)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid methyl ester: ^1H NMR (400 MHz, $CDCl_3$) 3.43 (s, 3 H), 3.99 (d, 21 H, J = 12.4 Hz), 4.27 (d, 1 H, J = 2.4 Hz), 4.35 (dd, 1 H, J = 12.4, 2.4 Hz), 5.75 (s, 1 H), 6.54 (s, 1 H), 7.11−7.71 (m, 13 H), 7.89 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 49.8, 51.8, 63.2, 77.8, 174.9; HRMS calcd for $C_{27}H_{22}N_2O_2$ (M^+) 406.1681, found 406.1652.
(29) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141−6142.
(30) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499−500.
(31) Beausoleil, E.; Sharma, R.; Michnick, S. W.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 6572−6578.

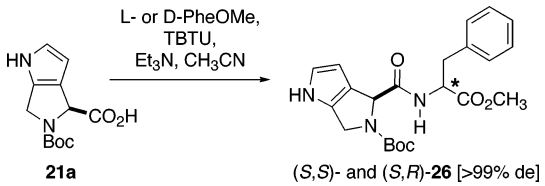
SCHEME 4. Synthesis of Protected Pyrroloprolines for Peptide Synthesis



palladium-on-carbon, in THF at 7 atm of hydrogen, starting material was predominantly recovered along with (4*S*)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid **23a**[32] from loss of the benzyl ester. Changing to palladium hydroxide as catalyst in a mixed MeOH/THF solvent system at 7 atm of hydrogen enhanced conversion; however, a considerable amount of bis-acylated reduced pyrrole **22a** was isolated as a mixture of diastereomers that were characterized by mass spectrometry (m/z = 352.2) and ^{1}H NMR spectroscopy.[33] To date, our best conditions for this one-pot conversion have featured hydrogenation of pyrrole-proline **18a** in the presence of di-*tert*-butyl dicarbonate and palladium hydroxide in a MeOH/THF mixture at 1 atm of hydrogen for 24 h to furnish the desired *N*-(Boc)amino acid **21a** in 40% yield along with 10% of the reduced pyrrole **22a** after purification by preparative liquid chromatography (Scheme 4).

Two alternative protecting groups, the Fmoc and *p*-methoxybenzyloxycarbonyl groups, were also installed on the proline nitrogen by a two-step processs featuring hydrogenation of pyrrole-proline **18** in the presence of palladium hydroxide at 1 atm of H_2 in 1:1 MeOH/THF for 3 h, followed by amine acylation after filtration of the catalyst and solvent exchange. (4*S*)-5-(Fmoc)-1,4,5,6-Tetrahydro-pyrrolo[3,4-*b*]pyrrole-4-carboxylic acid **24a** and its 5-methyl analogue **24b** were prepared in 71% and 73% overall yields, respectively, from **18a** and **18b** by suspension of the crude hydrogenation mixture in a dioxane/aqueous sodium carbonate solution, treatment with FmocOSu in dioxane at 0 °C for 30 min, aqueous workup, and chromatography on silica gel. Similar hydrogenation of **18b** and treatment with Moz-azide in dioxane gave the Moz-protected pyrrole-proline **25b** in 60% yield after work-up and chromatography.

SCHEME 5. Enantiomeric Purity of Pyrroloproline 21a



Finally, the potential for pyrroloprolines **21a** to serve in amide bond synthesis was evaluated in experiments to determine enantiomeric purity. *N*-(Boc)-Pyrroloproline **21a** was coupled to both L- and D-phenylalanine methyl ester using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and triethylamine in acetonitrile (Scheme 5). Measurement of the diastereotopic pyrrole proton signals at 6.69 and 6.59 ppm during incremental additions of the (*S*,*R*)-isomer into the (*S*,*S*)-dipeptide established the limits of detection of any (*R*,*S*)-isomer from racemization of the pyrroloproline during synthesis and coupling. In this way, *N*-(Boc)-pyrroloprolylphenylalanine methyl ester (*S*,*S*)-**26** was demonstrated to be of >99% diastereomeric purity. Fused pyrroloproline **21a** is thus considered to be of similarly high enantiomeric purity.

Conclusion

The first examples of enantiomerically pure fused heteroarylprolines have been synthesized by two approaches starting from 4-oxo-*N*-(PhF)proline benzyl ester **6**. In the first method, allylation of **6** followed by Wacker oxidation gave 1,4-dione **8** which was condensed with hydrazine to afford pyridazinoproline **9**, and with benzylamine to provide pyrroloproline **10b** and pyrrolopyrrole **12**. The competition between the Paal−Knorr condensation and the formation of aminopyrrole carboxylate[20] was controlled such that it was possible to obtain predominantly pyrroloproline **10b** or pyrrolopyrrole **12** by regulating the concentration of acid and amine nucleophile. Pyrroloprolines **17a**−**e** were synthesized by a general process featuring the aldol condensation of oxoproline **6** and *N*-(Boc)-α-amino aldehydes followed by acid-catalyzed cyclization. Selective modification of the pyrrole nitrogen of **17** was achieved by thermolytic cleavage of the Boc-group and *N*-alkylation. Diversity oriented methodology was thus developed for synthesizing a variety of fused heteroaryl-prolines from a common intermediate. *N*-(PhF)-pyrroloproline benzyl ester **18** was transformed into a series of analogues suitable for peptide synthesis, as demonstrated by the introduction of N-(Boc)pyrroloproline **21a** into a dipeptide of >99% diastereomeric purity. Pyrroloprolines are now being studied in model peptides to examine the influences of the aryl moiety and flattened pyrrolidine ring puckering on conformation and biological activity.

Experimental Section

(2*S*)-3-Allyl-4-oxo-*N*-(PhF)proline Benzyl Ester (7). A solution of (2*S*)-4-oxo-*N*-(PhF)proline benzyl ester (**6**, 4 g, 8.7 mmol) in a 10:1 mixture of THF/HMPA (34 mL/3.4 mL) was treated dropwise with *n*-BuLi (3.76 mL, 2.5 M in hexanes, 9.14 mmol) at −55 °C, stirred for 1 h, treated with allyl iodide (2.4

(32) (4*S*)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3, 4-*b*]pyrrole-4-carboxylic acid (**23a**): ^{1}H NMR (400 MHz, CD_3OD) 4.14 (m, 2 H), 4.54 (dd, 1 H, J = 13.4, 3.9 Hz), 5.69 (d, 1 H, J = 2.6 Hz), 6.58 (d, 1 H, J = 2.6 Hz), 7.1−7.8 (m, 13 H); ^{13}C NMR (100 MHz, CD_3OD) 50.7, 65.1, 78.7, 176.3; HRMS calcd for $C_{26}H_{21}N_2O_2$ (MH^+) 393.1603, found 393.1589.

(33) (4*S*)-1,5-Bis-(Boc)-octahydropyrrolo[3, 4-*b*]pyrrole-4-carboxylic acid (**22a**): ^{1}H NMR (400 MHz, CD_3OD) 1.46 (m, 18 H), 1.95 (m, 2 H), 3.26 (m, 2 H), 3.40 (m, 1 H), 3.42 (m, 1 H), 3.93 (m, 1 H), 4.31 (q, 1 H, J = 7.3 Hz), 4.44 (d, 1 H, J = 8.8 Hz); HRMS calcd for $C_{17}H_{29}N_2O_6$ (MH^+) 357.2026, found 357.1992.

mL, 26 mmol), and stirred for 2 h during which time the temperature rose slowly to −10 °C. The reaction mixture was treated with H_3PO_4 (10%, 6 mL) and poured into 150 mL of diethyl ether. The organic layer was washed with saturated sodium sulfite and brine, dried, and concentrated to a residue that was chromatographed eluting with 10% EtOAc in hexanes to furnish 3-allylproline **7** as a white foam that turned to dark yellow on standing, a 1:5 mixture of diastereomers (3.44 g, 79%). Spectral data for the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (m, 1 H), 2.32 (m, 1 H), 2.46 (m, 1 H), 3.45 (d, 1 H, J = 18 Hz), 3.48 (s, 1 H), 3.85 (d, 1 H, J = 18 Hz), 4.35 (d, 1 H, J = 12.5 Hz), 4.53 (d, 1 H, J = 12.5 Hz), 4.92 (m, 2 H), 4.52 (m, 1 H), 7.1−7.7 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 52.4, 55.5, 63.1, 66.3, 75.7, 117.9, 172.7, 213.2.

(2*S*)-4-Oxo-3-(2′-oxopropyl)-1-(PhF)-proline Benzyl Ester (8). In a 25 mL round-bottom flask under a rubber balloon filled with oxygen was stirred a mixture of palladium(II) chloride (14 mg, 0.08 mmol), copper(I) chloride (80 mg, 0.8 mmol), water (1 mL), and dimethylformamide (6 mL) for 1 h at room temperature during which time the solution turned to green. A solution of (2*S*)-3-allyl-4-oxo-*N*-(PhF)proline benzyl ester (**7**, 400 mg, 0.08 mmol, a 1:5 mixture of diastereomers) in DMF (3 mL) and water (0.3 mL) was added to the green solution, and the mixture was stirred vigorously for 24 h under oxygen, poured into cold 1 N HCl (50 mL), and extracted three times with EtOAc (50 mL). The combined organic layer was washed with saturated sodium bicarbonate and brine, dried, and concentrated to a residue that was chromatographed eluting with 10−25% EtOAc in hexanes to give dione **8** (336 mg, 81%) as a 1:5 mixture of diastereomers. First to elute was the minor isomer: ^{1}H NMR (300 MHz, C_6D_6) δ 1.34 (s, 3 H), 1.64 (dd, 1 H, J = 7.8, 18.6 Hz), 2.49 (dd, 1 H, J = 5.0, 18.6 Hz), 3.30 (m, 1 H), 3.59 (d, 1H, J = 17.0 Hz), 3.94 (d, 1 H, J = 17 Hz), 4.17 (d, 1 H, J = 8.3 Hz), 4.39 (d, 1 H, J = 12.3 Hz), 4.50 (d, 1 H, J = 12.3 Hz), 6.9−7.4 (m, 18 H); ^{13}C NMR (75 MHz, C_6D_6) δ 29.2, 38.6, 47.6, 54.3, 62.4, 66.1, 76.2, 171.6, 203.9, 211.8; HRMS calcd for $C_{34}H_{30}NO_3$ (MH^+) 515.2097, found 515.2077. Next to elute was the major isomer:^{1}H NMR (300 MHz, C_6D_6) δ 1.26 (s, 3 H), 1.89 (dd, 1 H, J = 7.4, 18.4 Hz), 2.16 (dd, 1 H, J = 3.8, 18.4 Hz), 3.08 (m, 1 H), 3.46, (d, 1 H, J = 7.4 Hz), 3.55 (d, 1 H, J = 17.8 Hz), 3.81 (d, 1 H, J = 17.8 Hz), 4.47 (d, 1 H, J = 12.4 Hz), 4.70 (d, 1 H, J = 12.4 Hz), 6.9−7.6 (m, 18 H); ^{13}C NMR (75 MHz, C_6D_6) δ 28.9, 41.4, 48.9, 57.1, 65.1, 66.7, 77.2, 172.7, 203.6, 211.1; HRMS calcd for $C_{34}H_{30}NO_3$ (MH^+) 515.2097, found 515.2085.

(5*S*)-3-Methyl-6-(PhF)-6,7-dihydro-5*H*-pyrrolo[3,4-*c*]-pyridazine-5-carboxylic Acid Benzyl Ester (9). Hydrazine hydrate (60 μL, 1.9 mmol) was added to a solution of dione **8** (100 mg, 0.19 mmol) in toluene (5 mL), and the mixture was heated to a reflux for 12 h, cooled to room temperature, diluted with EtOAc (10 mL), washed with 2 M NaH_2PO_4 and brine, dried, and concentrated to a residue that was purified by chromatography eluting with 50% EtOAc in hexanes to give pyridazine **9** (52 mg, 54%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 2.53 (s, 3 H), 4.47, (s, 1 H), 4.60 (d, 1 H, J = 16.1 Hz), 4.82 (d, 1 H, J = 16.1 Hz), 4.88 (d, 1 H, J = 12.2 Hz), 4.96, (d, 1 H, J = 12.2 Hz) 6.86 (s, 1 H), 7.2−7.8 (m, 18 H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 22.3, 55.0, 66.4, 67.3, 77.7, 171.1; HRMS calcd for $C_{34}H_{28}N_3O_2$ (MH^+) 510.2812, found 510.2175.

(4*S*)-1-*N*-Benzyl-2-methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid Benzyl Ester (10b). A stirred solution of dione **8** (50 mg, 0.097 mmol) in degassed anhydrous EtOH (2 mL) and acetic acid (150 μL, 3 mmol) was treated with benzylamine (24 μL, 0.2 mmol) in EtOH (1 mL), heated to 60 °C under argon atmosphere for 1.5 h, poured into water (5 mL), and extracted three times with EtOAc (5 mL). The combined organic phase was then washed with saturated $NaHCO_3$ and brine, dried, and evaporated to a residue that was chromatographed eluting with 5% EtOAc in hexanes. Evaporation of the collected fractions gave pyrroloproline **10b** (13 mg, 23%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3 H), 3.78 (d, 1 H, J = 11.6 Hz), 4.33 (m, 2 H), 4.72 (d, 1 H, J = 16.9 Hz), 4.83 (d, 1 H, J = 16.9 Hz), 4.90 (d, 1 H, J = 12.5 Hz), 5.98 (d, 1 H, J = 12.5 Hz), 5.31 (s, 1 H), 6.7−7.6 (m, 23 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 48.7, 49.9, 64.1, 66.1, 78.2, 174.3; HRMS calcd for $C_{41}H_{35}N_2O_2$ (MH^+) 587.2699, found 587.2685.

1-Benzyl-2-methyl-1,5-dihydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid Benzyl Ester (12). A solution of dione **8** (50 mg, 0.097 mmol) in toluene (5 mL) was treated with benzylamine (44 μL, 0.4 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol), heated to 50 °C under argon atmosphere for 24 h, cooled, and concentrated to a residue that was dissolved in EtOAc (10 mL) and washed with 2 M NaH_2PO_4, saturated $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed eluting with 10−30% EtOAc in hexanes. Evaporation of the collected fractions gave pyrroloproline **12** (20 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 5.03 (s, 2 H), 5.34 (s, 2 H), 6.10 (s, 1 H), 6.35 (s, 1 H), 7.0−7.5 (m, 10 H), 9.3 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.3, 48.7, 65.4, 95.2, 105.3, 126.8, 127.6, 127.9, 128.6, 128.8, 134.4, 137.3, 137.7, 142.8; HRMS calcd for $C_{22}H_{21}N_2O_2$ (MH^+) 345.1603, found 345.1557.

Typical Procedure for Pyrrole Preparation. (4*S*)-1-*N*-Boc-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid Benzyl Ester (17a). A stirred solution of (2*S*)-4-oxo-*N*-(PhF)proline benzyl ester (**6**, 3 g, 6.5 mmol) in 17 mL of THF was cooled to −78 °C under argon atmosphere, treated with *n*-BuLi (2.75 mL, 2.5 M in hexanes, 6.9 mmol), and stirred for 1 h at −55 °C. The mixture was cooled to −78 °C, treated via cannula with a −78 °C solution of *N*-(Boc)-glycinal (1.09 g, 6.9 mmol) in 5 mL of THF, stirred for 5 h at −55 °C, and poured into an ice-cold solution of 1 M NaH_2PO_4 (50 mL). The aqueous solution was extracted with ether (3 × 50 mL), and the combined organic phases were washed with brine, dried, and evaporated to a foam. The foam was chromatographed using 15% EtOAc in hexanes as eluent to recover 0.62 g of starting oxoproline **6** and a more polar fraction, that was isolated, dissolved in 50 mL of CH_2Cl_2, treated with 0.4 mL of conc HCl, and stirred for 12 h. The resulting brown mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (3 × 30 mL) and brine, dried, and concentrated to a residue that was chromatographed eluting with 10% EtOAc in hexanes. Evaporation of the collected fractions gave pyrroloproline **17a** as a white foam (1.11 g, 30 (37%)): $[\alpha]^{22}_D$ 107.7 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 4.23 (m, 2 H), 4.61 (m, 1 H), 4.80 (d, 1 H, J = 12 Hz), 4.97 (d, 1 H, J = 12 Hz), 5.73 (d, 1 H, J = 3.1 Hz), 6.96 (s, 1 H), 7.0−7.7 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 51.9, 63.1, 66.4, 77.8, 84.0, 147.0, 173.4; HRMS calcd for $C_{38}H_{35}N_2O_4$ (MH^+) 583.2597, found 583.2608.

(4*S*)-1-*N*-Boc-2-methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (17b) was isolated as a white foam in 25(31)% yield: $[\alpha]^{22}_D$ 104.8 (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 2.29 (s, 3 H), 4.20 (m, 2 H), 4.56 (dd, 1 H, J = 5.6, 15.3 Hz), 4.79 (d, 1 H, J = 12 Hz), 4.95 (d, 1 H, J = 12 Hz), 5.47 (s, 1 H), 7.0−7.9 (m 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 27.8, 53.1, 63.0, 66.2, 77.6, 83.5, 147.1, 173.6; HRMS calcd for $C_{39}H_{37}N_2O_4$ (MH^+) 597.2753, found 597.2773.

(4*S*)-1-*N*-Boc-2-benzyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo-[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (17c) was isolated as a white foam in 29(36)% yield: $[\alpha]^{22}_D$ 96.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9 H), 4.07 (s, 2 H), 4.22 (m, 2 H), 4.65 (dd, 1 H, J = 4.4, 14.9 Hz), 4.78 (d, 1 H, J = 12.2 Hz), 4.96 (d, 1 H, J = 12.2 Hz), 5.31 (s, 1 H), 7.0−7.7 (m, 23 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 35.6, 53.2, 63.2, 66.3, 77.7, 83.9, 143.3, 173.5; HRMS calcd for $C_{45}H_{41}N_2O_4$ (MH^+) 673.3066, found 673.3090.

(4*S*)-1-*N*-Boc-2-isopropyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (17d) was isolated as a white foam in 6(10)% yield: $[\alpha]^{22}_D$ 105.5 (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3 H, J = 2.6 Hz), 1.10 (d, 3 H, J = 2.6 Hz), 1.42 (s, 9 H), 3.38 (m, 1 H),

4.18 (m, 2 H), 4.54 (dd, 1 H, J = 5.1, 14.9 Hz), 4.78 (d, 1 H, J = 12.3 Hz), 5.01 (d, 1 H, J = 12.3 Hz), 5.50 (s, 1H), 7.0−7.7 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.3, 27.4, 27.9, 53.5, 63.2, 66.2, 77.7, 83.6, 146.8, 173.6; HRMS calcd for $C_{41}H_{41}N_2O_4$ (MH^+) 625.3066, found 625.3083.

(4*S*)-1-*N*-Boc-2-(2-methylthioethyl)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (17e) was isolated as a white foam in 19(22)% yield: $[\alpha]^{22}_D$ 104.1 (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 2.07 (s, 3 H), 2.63 (m, 2 H), 3.00 (t, 2 H, J = 7.3 Hz), 4.19 (m 2 H), 4.57 (d, 1 H, J = 9.5 Hz), 4.82 (d, 1 H, J = 11.9 Hz), 5.00 (d, 1 H, J = 11.9 Hz), 5.56 (s, 1 H), 7.0−7.7 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 28.0, 29.8, 33.7, 53.3, 63.2, 66.4, 77.7, 83.9, 147.2, 173.5; HRMS calcd for $C_{41}H_{41}N_2O_4S$ (MH^+) 657.2787, found 657.2774.

Typical Procedure for BOC Deprotection. (4*S*)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid Benzyl Ester (18a). A round-bottom flask containing (4*S*)-1-*N*-Boc-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (**17a**, 60 mg, 0.1 mmol) under an argon atmosphere was placed into a 180 °C oil bath for 35 min. The flask was removed from the oil bath, and the resulting product was purified by chromatography using 20% EtOAc in hexanes as eluent. Evaporation of the collected fractions gave **18a** (39 mg, 79%): $[\alpha]^{22}_D$ 61.8 (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (d, 1 H, J = 12.7), 4.33 (d, 1 H, J = 3.3 Hz), 4.41 (dd, 1 H, J = 3.8, 12.7), 4.82 (d, 1 H, J = 12.4), 4.97 (d, 1 H, J = 12.4), 5.73 (s, 1 H), 6.56 (s, 1 H), 6.5−7.7 (m, 18 H), 7.8 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.0, 63.4, 66.2, 78.0, 174.3; HRMS calcd for $C_{33}H_{27}N_2O_2$ (MH^+) 483.2073, found 483.2081.

(4*S*)-2-Methyl-5-(PhF)-1,4,5,6-tetrahydro-pyrrolo[3,4-*b*]-pyrrole-4-carboxylic acid benzyl ester (18b) was prepared from Boc-pyrroloproline **17b** (61 mg, 0.10 mmol) and isolated in 77% yield: $[\alpha]^{22}_D$ 79.9 (*c* 1.21, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3 H), 3.95 (d, 1 H, J = 12.4 Hz), 4.34 (m, 2 H, J = 3.3 Hz), 4.81 (d, 1 H, J = 12.4 Hz), 4.95 (d, 1 H, J = 12.4 Hz), 5.40 (s, 1 H), 7.0−7.7 (m, 19 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 50.2, 63.6, 66.2, 77.9, 174.5; HRMS calcd for $C_{34}H_{29}N_2O_2$ (MH^+) 497.2229, found 497.2211.

(4*S*)-2-Benzyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]-pyrrole-4-carboxylic acid benzyl ester (18c) was prepared from Boc-pyrroloproline **17c** (60 mg, 0.089 mmol) and isolated in 78% yield: $[\alpha]^{22}_D$ 80.3 (c 0.77, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 2 H), 3.91 (d, 1 H, J = 11.1 Hz), 4.31 (m, 2 H), 4.81 (d, 1 H, J = 12.4 Hz), 4.96 (d, 1 H, J = 12.4 Hz), 5.48 (s, 1 H), 7.0−7.7 (m, 24 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.7, 50.1, 63.6, 66.1, 77.9, 174.3; HRMS calcd for $C_{40}H_{33}N_2O_2$ (MH^+) 573.2542, found 573.2522.

(4*S*)-2-Isopropyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (18d) was prepared from Boc-pyrroloproline **17d** (60 mg, 0.091 mmol) and isolated in 79% yield: $[\alpha]^{22}_D$ 79.9 (*c* 0.95, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, 6 H, J = 6.8 Hz), 2.74 (m, 1 H), 3.98 (d, 1 H, J = 12.2 Hz), 4.30 (d, 1 H, J = 4.2 Hz), 4.35 (dd, 1 H, J = 4.2, 12.2 Hz), 4.79 (d, 1 H, J = 12.5 Hz), 4.97 (d, 1 H, J = 12.5 Hz), 5.39 (s, 1 H), 7.0−7.7 (m, 19 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 22.8, 27.7, 50.1, 63.6, 66.0, 77.8, 174.4; HRMS calcd for $C_{36}H_{33}N_2O_2$ (MH^+) 525.2542, found 525.2559.

(4*S*)-2-(2-Methylthioethyl)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (18e) was prepared from Boc-pyrroloproline **17e** (60 mg, 0.096) and isolated in 89% yield: $[\alpha]^{22}_D$ 81.2 (*c* 1.17, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.59 (t, 2 H, J = 6.7 Hz), 2.72 (t, 2 H, J = 6.6 Hz), 3.94 (d, 1 H, J = 11.1 Hz), 4.31 (m, 2 H), 4.80 (d, 1 H, J = 12.4 Hz), 4.95 (d, 1 H, J = 12.4 Hz), 5.44 (s, 1 H), 7.0−7.7 (m, 18 H), 8.00 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 28.2, 34.6, 50.1, 63.5, 66.2, 77.9, 174.4; HRMS calcd for $C_{36}H_{33}N_2O_2S$ (MH^+) 557.2263, found 557.2270.

Typical Procedure for *N*-Alkylation of the Pyrrole. (4*S*)-1-*N*-Methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]-pyrrole-4-carboxylic Acid Benzyl Ester (19a). At room temperature, a solution of KOH (9.3 mg, 0.17 mmol) in DMSO (500 μL) was treated with (4*S*)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (**18a**, 40 mg, 0.08 mmol), stirred for20 min, treated with iodomethane (20 μL, 0.32 mmol), and stirred for 2 h. Water (4 mL) was added to the mixture, which was extracted with three portions of EtOAc (10 mL). The combined organic phase was washed with water and brine, dried, and concentrated to a residue that was chromatographed eluting with 10% EtOAc in hexanes to give *N*-methylpyrrole **19a** (38 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3 H), 4.03 (d, 1 H, J = 12.4 Hz), 4.30 (d, 1 H, J = 2.4 Hz), 4.42 (dd, 1 H, J = 2.4, 12.4 Hz), 4.78 (d, 1 H, J = 12.4 Hz), 4.96 (d, 1 H, J = 12.4 Hz), 5.61 (d, 1 H, J = 2.1 Hz), 6.37 (s, 1 H), 7.0−7.7 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8, 49.2, 63.6, 66.2, 77.8, 174.2; HRMS calcd for $C_{34}H_{29}N_2O_2$ (MH^+) 497.2229, found 497.2222.

(4*S*)-1-*N*-Methyl-2-methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (19b) was isolated from the reaction of pyrroloproline **18b** (50 mg, 0.1 mmol) and iodomethane (25 μL, 0.4 mmol) in 72% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3 H), 3.26 (s, 3H), 4.03 (d, 1 H, J = 12.1 Hz), 4.29 (dd, 1 H, J = 1.5, 4.2 Hz), 4.42 (dd, 1 H, J = 4.2, 12.1 Hz), 4.77 (d, 1 H, J = 12.5 Hz), 4.94 (d, 1 H, J = 12.5 Hz), 5.39 (s, 1 H), 7.0−7.7 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 31.9, 49.7, 63.8, 66.2, 77.3, 174.4; HRMS calcd for $C_{35}H_{31}N_2O_2$ (MH^+) 511.2386, found 511.2371.

(4S)-1-*N*-Benzyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (10a) was isolated from the reaction of pyrroloproline **18a** (40 mg, 0.082 mmol) and benzyl bromide (20 μL, 0.164 mmol) in 81% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (m, 1 H), 4.32 (m, 2 H), 4.81−4.90 (m, 3 H), 4.98 (d, 1 H, J = 12.4 Hz), 5.71 (d, 1 H, J = 2.7 Hz), 6.45 (d, 1 H, J = 2.7 Hz), 6.8−7.6 (m, 23 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.4, 51.9, 63.7, 66.2, 78.1, 174.0; HRMS calcd for $C_{40}H_{33}N_2O_2$ (MH^+) 573.2542, found 573.2541.

(4*S*)-1-*N*-Benzyl-2-methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (10b) was isolated from the reaction of pyrroloproline **18b** (50 mg, 0.1 mmol) and benzyl bromide (24 μL, 0.2 mmol) in 63% yield and possessed the same spectral and physical properties as described above.

(4*S*)-1-*N*-(*tert*-Butyl acetate)-2-methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (20b) was isolated from the reaction of pyrroloproline **18b** (40 mg, 0.08 mmol) and *tert*-butyl bromoacetate (35.4 μL, 0.24 mmol) in 49% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9 H), 2.05 (s, 3 H), 4.04 (d, 1 H, J = 12.3 Hz), 4.15 (d, 1 H, J = 17.3 Hz), 4.23 (m, 2 H), 4.41 (dd, 1 H, J = 4.4, 12.4 Hz), 4.82 (d, 1 H, J = 12.5 Hz), 4.93 (d, 1 H, J = 12.5 Hz), 5.46 (s, 1 H), 7.0−7.7 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 28.1, 47.9, 49.9, 63.8, 66.1, 77.9, 82.5, 167.5, 174.2; HRMS calcd for $C_{40}H_{39}N_2O_4$ (MH^+) 611.2910, found 611.2909.

(4*S*)-5-(Boc)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid (21a). A solution of (4*S*)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (**18a**, 210 mg, 0.43 mmol) and di-*tert*-butyl dicarbonate (122 mg, 0.56 mmol) in 1:3 THF/MeOH (5 mL/15 mL) was treated with palladium hydroxide-on-carbon (60 mg, 20 wt % in palladium (wet)) and stirred under 1 atm of hydrogen for 24 h. The catalyst was removed by filtration on Celite and washed with MeOH. The filtrate was evaporated to dryness, and the residue was partitioned between saturated $NaHCO_3$ (10 mL) and Et_2O (15 mL). The aqueous phase was washed with Et_2O (2 × 15 mL), acidified to pH 2 with cold 1 N HCl, and extracted with $CHCl_3$ (4 × 15 mL). The combined organic extractions were washed with brine, dried, and concentrated to a residue that was purified by HPLC (20−80% CH_3CN in water, 0.01% TFA, C_{18} column) to provide pyrroloproline **21a** (44 mg, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) showed a 2:1 mixture of carbamate isomers δ 1.44 (s, 6 H) [1.48 (s, 3 H)], 4.50 (m, 2 H), 5.22 (d, 0.66 H, J = 2.9 Hz) [5.31 (d, 0.33, J = 2.4 Hz)], 6.03 (s, 0.66 H) [6.10 (s, 0.33 H)], 6.69 (s, 1 H), 8.69 (s, 0.66 H) [8.49 (s,

0.33 H)], 10.8 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (28.5), 46.5 (47.1), 61.1 (60.9), 81.2 (77.4), 102.4 (102.9), 119.3, 122.0, 130.4, 154.3 (155.2), 177.0, 175.4; HRMS calcd for $C_{12}H_{16}N_2O_4$ (M) 252.1110, found 252.1112.

Typical Procedure for Fmoc Protection of Pyrroloproline. (4*S*)-5-(Fmoc)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid (24a). A solution of (4*S*)-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (**18a**, 68 mg, 0.14 mmol) in 1:1 THF/MeOH (8 mL) was treated with palladium hydroxide-on-carbon (34 mg, 20 wt % in palladium (wet)) and stirred under 1 atm of hydrogen for 3 h. The catalyst was removed by filtration onto Celite and washed with MeOH. The filtrate was concentrated to a residue that was suspended in water (3 mL) containing 9% aqueous Na_2CO_3 (165 μL, 0.14 mmol), cooled to 0 °C, and treated with FmocOSu (53 mg, 0.15 mmol) in dioxane (3 mL) with vigorous stirring for 30 min. The reaction mixture was concentrated and partitioned between saturated $NaHCO_3$ (5 mL) and Et_2O (5 mL). The aqueous phase was washed with Et_2O (2 × 5 mL), acidified to pH 2 with cold 1 N HCl, and extracted with $CHCl_3$ (4 × 8 mL). The combined organic extractions were washed with brine, dried, and concentrated to a residue that was chromatographed eluting with 50−100% EtOAc in hexanes containing 1% AcOH to give Fmoc-pyrroloproline **24a** (37 mg, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) showed a 1:1 mixture of carbamate isomers δ 4.13 (t, 0.5 H, J = 6.1 Hz) [1.48 (t, 0.5 H, J = 6.6 Hz)], 4.41−4.63 (m, 4 H), 5.21 (d, 0.5 H, J = 2.2 Hz) [5.39 (d, 0.5, J = 2.0 Hz)], 6.07 (s, 0.5 H) [6.15 (s, 0.5 H)], 6.68 (s, 1 H) [6.72 (s, 0.5 H], 7.2−7.8 (m, 8 H), 8.15 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.9 (47.1), 47.2 (47.3), 61.0 (61.1), 67.8, 102.7 (103.0), 119.4 (119.3), 120.0 (120.1), 122.1 (122.2), 125.0 (124.9), 125.1 (125.3), 127.2 (127.1), 127.8 (127.9), 130.0, 141.4 (141.3), 143.4 (143.8), 143.97 (143.99), 154.8 (155.2), 175.4 (176.1); HRMS calcd for $C_{22}H_{19}N_2O_4$ (MH^+) 375.1267, found 375.1312.

(4*S*)-5-(Fmoc)-2-methyl-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid (24b) was isolated from reaction of (4*S*)-2-methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester **18b** (170 mg, 0.34 mmol) in 73% yield: ^{1}H NMR (400 MHz, $CDCl_3$) showed a 1:1 mixture of carbamate isomers δ 2.17 (s, 1.5 H) [2.21 (s, 1.5 H], 4.12 (t, 0.5 H, J = 6. Hz0) [4.26 (t, 0.5 H, J = 6.9 Hz)], 4.32−4.66 (m, 4 H), 5.20 (d, 0.5 H, J = 2.4 Hz) [5.32 (d, 0.5 H, J = 2.9 Hz)], 5.73 (s, 0.5 H) [5.79 (s, 0.5 H)], 7.2−7.8 (m, 8 H), 7.89 (s, 0.5 H) [7.94 (s, 0.5 H)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.57 (13.63), 47.03 (47.1), 47.2 (47.28), 60.9 (61.2), 67.78 (67.87), 100.3 (100.6), 119.3, 1210.1 (120.0), 125.0 (125.1), 125.2 (125.3), 127.2 (127.8), 127.9 (128.4), 132.5 (132.6), 141.4 (141.3) 143.8 (143.9), 144.0, 154.8 (155.2), 175.4 (176.1); HRMS calcd for $C_{23}H_{21}N_2O_4$ (MH^+) 388.1423, found 388.1492.

(4*S*)-5-(Methoxybenzyloxycarbonyl)-2-methyl-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid (25b). A solution of (4*S*)-2-methyl-5-(PhF)-1,4,5,6-tetrahydropyrrolo-[3,4-*b*]pyrrole-4-carboxylic acid benzyl ester (**18b**, 100 mg, 0.2 mmol) in 1:1 THF/MeOH (6 mL) was treated with palladium hydroxide-on-carbon (50 mg, 20 wt % in palladium (wet)), stirred under 1 atm of hydrogen for 3 h, filtered onto Celite, and washed with MeOH. The filtrate was concentrated to a residue that was suspended in water (4 mL), treated with $NaHCO_3$ (51 mg, 0.6 mmol), cooled to 0 °C, treated with 4-methoxybenzyloxycarbonyl azide (83 mg, 0.4 mmol) in dioxane (4 mL), stirred for 12 h, and concentrated to a residue that was partitioned between saturated $NaHCO_3$ (5 mL) and Et_2O (5 mL). The aqueous phase was washed with Et_2O (2 × 5 mL), acidified to pH 2 with cold 1 N HCl, and extracted with $CHCl_3$ (4 × 8 mL). The combined organic extractions were washed with brine, dried, and concentrated. Chromatography eluting with 50−100% EtOAc in hexanes containing 1% AcOH gave Moz-pyrroloproline **25b** (40 mg, 60%): ^{1}H NMR (400 MHz, MeOD) showed a 1:1 mixture of carbamate isomers δ 2.19 (s, 3 H), 4.43 (d, 1 H, J = 12.3 Hz), 4.52 (d, 1 H, J = 12.3 Hz), 5.00−5.15 (m, 3 H), 5.63 (s, 0.5 H) [5.66 (s, 0.5)], 6.87 (m, 2 H), 7.26 (d, 1 H, J = 8.3 Hz) [7.30 (d, 1 H, J = 8.4 Hz)], 10.1 (s, 0.5 H) [10.14 (s, 0.5 H]; ^{13}C NMR (100 MHz, MeOD) δ 13.5, 48.0 (48.2), 55.8, 62.67 (62.75), 68.36 (68.39), 100.2, 114.9 (115.0), 120.0 (120.4), 129.4 (130.0), 129.92 (129.87), 130.7 (130.9), 133.63 (133.59), 156.7 (156.9), 161.2 (161.3), 175.0 (175.3); HRMS calcd for $C_{17}H_{19}N_2O_5$ (MH^+) 331.1294, found 331.1281.

Enantiomeric Purity of (4*S*)-5-(Boc)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic Acid (21a). At room temperature, a solution of (4*S*)-5-(Boc)-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-4-carboxylic acid (**21a**, 5 mg, 0.02 mmol) and the HCl salt of either L- or D-phenylalanine methyl ester (4.3 mg, 0.02 mmol) in 0.5 mL of acetonitrile was treated with *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (7 mg, 0.02 mmol) and Et_3N (5.5 μL, 0.04 mmol). After being stirred for 12 h, the mixture was partitioned between brine (0.7 mL) and EtOAc (3 mL). The organic layer was washed with H_2O (2 × 3 mL) and brine, dried, and concentrated to a residue that was directly examined by ^{1}H NMR spectroscopy. Measurement of the diastereotopic pyrrole proton signals at 6.69 and 6.59 ppm during incremental additions of (*S*,*R*)-**26** in a sample of (*S*,*S*)-**26** demonstrated *N*-(Boc)-pyrroloprolylphenylalanine methyl ester (*S*,*S*)-**26** to be of >99% diastereomeric purity. Hence, fused pyrrole-proline **21a** is considered to be of the same high enantiomeric purity.

(*S*,*S*)-*N*-(Boc)-Pyrroloprolylphenylalanine methyl ester ((*S*,*S*)-26): ^{1}H NMR (400 MHz, MeOD) showed a 1:2 mixture of carbamate isomers δ 1.33 (s, 6 H) [1.49 (s, 3 H)], 3.04 (m, 2 H), 3.64 (s, 2 H) [6.62 (s, 1 H], 4.43−4.50 (m, 2 H), 4.67 (m, 1 H), 5.11 (d, 0.66 H, J = 2.3 Hz) [5.14 (d, 0.33 H, J = 2.0 Hz], 5.95 (s, 0.66 H) [5.98 (s, 0.33 H)], 6.69 (s, 0.66 H) [6.71 (s, 0.33 H)], 7.0−7.2 (m, 5 H), 8.22 (d, 0.66 H, J = 7.9 Hz) [8.08 (d, 0.33 H, J = 7.5 Hz)], 10.4 (s, 1 H); MS *m*/*z* 414.2 [MH^+].

(*S*,*R*)-*N*-(Boc)-pyrroloprolylphenylalanine methyl ester ((*S*,*R*)-26): ^{1}H NMR (400 MHz, MeOD)) showed a 1:2 mixture of carbamate isomers δ 1.42 (s, 6 H) [1.48 (s, 3 H)], 2.99 (m, 1 H), 3.15 (m, 1 H), 4.37 (m, 1 H), 4.52 (m, 1 H), 4.65 (m, 1 H), 5.14 (d, 1 H, J = 3.0 Hz), 5.57 (s, 0.66 H) [5.75 (s, 0.33 H)], 6.59 (s, 0.66 H) [6.63 (s, 0.33 H)], 7.1−7.3 (m, 5 H), 8.63 (d, 0.66 H, J = 7.8 Hz) [8.36 (d, 0.33 H, J = 7.7 Hz)], 10.3 (s, 1 H); MS *m*/*z* 414.2 [MH^+].

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Supporting Information Available: General experimental information, ^{1}H and ^{13}C NMR spectra for compounds **7**−**12**, **17a**−**e**, **18a**−**e**, **19a**,**b**, **20b**, **21a**, **23a**, **24a**,**b,** and **25b**, and ^{1}H NMR spectra for **22a** and **26** along with the limits of detection experiment for enantiomeric purity of **21a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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