Alkyl Substituent Effects on Pipecolyl Amide Isomer Equilibrium: Efficient Methodology for Synthesizing Enantiopure 6-Alkylpipecolic Acids and Conformational Analysis of Their *N*-Acetyl *N*′-Methylamides

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Enantiopure 6-alkylpipecolic acid hydrochlorides **1a**−**e** were synthesized in five steps and 15−59% overall yields from α-*tert*-butyl *β*-methyl *N*-(PhF)aspartate (**3**) via an approach featuring selective hydride reduction to the corresponding aspartate *β*-aldehyde **2**, aldol condensations with the enolates of various methyl alkyl ketones, and diastereoselective intramolecular reductive aminations. The influence of the 6-position substituent on the equilibrium and the energy barrier for isomerization of the amide *N*-terminal to pipecolate was then explored via the synthesis of *N*-acetyl *N*′-methylpipecolinamide (**16**) and its (2*S*,6*R*)-6-*tert*-butylpipecolinamide counterpart **17**, and their conformational analysis by proton NMR spectroscopy and coalescence experiments. The presence of the *tert*-butyl substituent augmented the population of the amide *cis*-isomer and lowered the barrier for pipecolyl amide isomerization in water. Compared with the results from our previous examination of *N*-acetyl-5-*tert*-butylproline *N*′-methylamides (Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12902), the consequences of the bulky 6-alkyl substituent on the acetamide geometry and isomerization barrier were less pronounced in the pipecolate series relative to the respective proline amides.

Introduction

Pipecolic acid (piperidine-2-carboxylic acid) is a widespread, naturally occurring nonproteinogenic amino acid found in many biologically interesting compounds. For example, pipecolate residues are components of the immunosuppressive drugs FK506[1] and rapamycin,[2] antibiotic peptides such as the virginiamycins[3] and the efrapeptins,[4] the antiprotozoal agent apicidin[5], and inhibitors of HIV protease.[6] Pipecolates have also served as proline substitutes in structure−activity studies of biologically relevant peptides.[7,8] Furthermore, alkyl-substituted pipecolic acids have been employed as dihydropicolinic acid (DHDPA) synthase inhibitors[9] and *N*-methyl-D-aspartic acid (NMDA) receptor agonists[10] and antagonists.[11] In addition, alkylpipecolates have served as starting materials for synthesizing biologically active piperidine alkaloids.[12,13] For example, *N*-(methoxycarbonyl)-6-*n*-propylpipecolate was used in the synthesis of the *N*-methyl derivative of coniine,[13] the principal toxic constituent of hemlock.

Concurrent with our research on employing alkylprolines in conformationally rigid mimics of peptide secondary structures,[14,15] we became interested in the effects of azacycloalkane amino acids of larger ring-size. We initiated a program to synthesize and study alkylpipecolates in peptide structures in order to examine the influence of ring-size, alkyl-substituent, and stereochemistry on peptide conformation.[16] Since 5-alkylprolines exhibited steric effects that greatly enhanced the *cis*-isomer of the amide *N*-terminal to prolyl residues in peptides,[14] 6-alkylpipecolates were chosen as our first targets in order to study the influence of bulky 6-position substituents on the equilibrium of pipecolyl amides.

The synthesis of alkylpipecolic acid derivatives[17] has received considerable attention;[18−22] however, few methods offer the potential for selective and stereocontrolled

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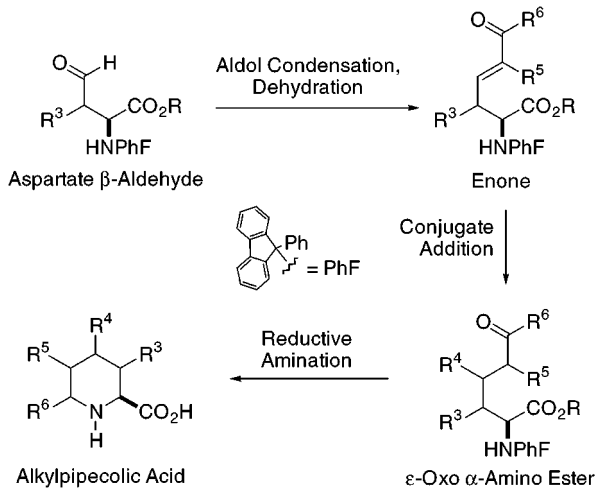
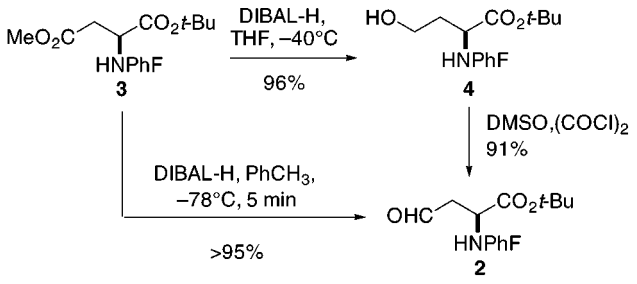
Scheme 1. General Strategy for Alkylpipecolate Synthesis



introduction of alkyl substituents at each of the ring carbons. We are exploring a biomimetic entry into this ring system in order to provide pipecolates with substituents at the 3-, 4-, 5-, and 6-positions (Scheme 1, PhF = 9-phenylfluoren-9-yl). In analogy to the diaminopimelate pathway for L-lysine biosynthesis, which features the enzyme catalyzed aldol condensation between pyruvate and aspartate β-aldehyde with subsequent cyclization to provide L-dihydropicolinic acid,[23] our route employs an aldol condensation/reductive amination sequence to transform *N*-(PhF)aspartate β-aldehyde **2** into alkylpipecolic acids. In principle, this route offers access to pipecolates with alkyl substituents at four of the five ring carbons by employment of β-alkyl-branched aspartates[24] and alkyl-substituted enolates, as well as by conjugate additions to the α,β-unsaturated ketone intermediate.[25] We report now the employment of this route for synthesizing enantiopure pipecolates with primary, secondary, and tertiary alkyl as well as aryl 6-position substituents.[16,26]

Scheme 2. Synthesis of *N*-(PhF)Aspartate β-Aldehyde 2



The influence of the 6-position substituent on the pipecolyl amide isomer equilibrium was studied via the synthesis and conformational analysis of *N*-acetyl *N*′-methylpipecolinamide (**16**) and its (2*S*,6*R*)-6-*tert*-butylpipecolinamide counterpart **17**. Using NMR spectroscopy and coalescence experiments, we observed that the consequences of the presence of the bulky (6*R*)-substituent on the pipecolyl amide isomer equilibrium in water were similar to those previously observed in our comparison of *N*-acetylproline *N*′-methylamide **18** with its (2*S*, 5*R*)-5-*tert*-butyl analogue **19**.[14] Steric interactions between the *N*-acetyl and 6-position substituents disfavored the amide *trans*-isomer and augmented the *cis*-amide population. In addition, the presence of the (6*R*)-*tert*-butyl substituent lowered the energy barrier for amide isomerization in **16** relative to **17**. On the other hand, the effects of the *tert*-butyl substituent were less pronounced in the pipecolate series relative to the respective proline amides. By elucidating their substituent effects on pipecolinamide conformation and by providing effective methodology for synthesizing 6-alkylpipecolates, our report is intended to further the employment of alkylpipecolates as tools for studying the structure–activity relationships of biologically relevant peptides.

Results and Discussion

Synthesis and Rearrangement of Aspartate β-Aldehyde. 6-Alkylpipecolic acids **1** were synthesized from aspartic acid via a route featuring aldol condensation on α-*tert*-butyl *N*-(PhF)aspartate β-aldehyde **2**, dehydration, and subsequent diastereoselective reductive amination of ϵ-oxo α-*N*-(PhF)amino esters **7** (Scheme 4). We reported previously on the Wittig and Horner–Wadsworth–Emmons olefination chemistry of (2*S*)-*tert*-butyl 2-[*N*-(PhF)-amino]-4-oxobutanoate (**2**),[27] and its synthesis from α-*tert*-butyl β-methyl *N*-(PhF)aspartate (**3**)[24b] by selective β-ester

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(20) Syntheses of 5-substituted pipecolates include the following: (a) Murray, P. J.; Starkey, I. D. *Tetrahedron Lett*. **1996**, *37*, 1875. (b) Hoarau, S.; Fauchère, J. L.; Pappalardo, L.; Roumestant, M. L.; Viallefont, P. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2585. (c) Adams, D. R.; Bailey, P. D.; Collier, I. D.; Heffernan, J. D.; Stokes, S. *Chem. Commun*. **1996**, 349. (d) Ezquerra, J.; Pedregal, C.; Escribano, A.; Carreño, M. C.; Ruano, J. L. G. *Tetrahedron Lett*. **1995**, *36*, 3247.

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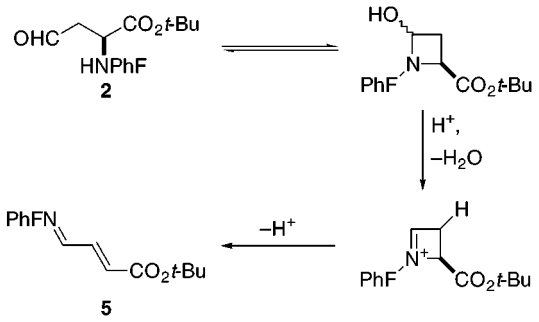
Scheme 3. Proposed Mechanism for the Rearrangement of Aldehyde 2 into Azadiene 5



reduction using DIBAL-H in THF at −40 °C to furnish *N*-(PhF)homoserine *tert*-butyl ester (**4**), followed by oxidation of the primary alcohol using DMSO and oxalyl chloride in dichloromethane. We report now that aldehyde **2** can be synthesized in one transformation and >95% yield from diester **3** by selective reduction with DIBAL-H in toluene at −78 °C for 5 min (Scheme 2).

As previously reported,[27] aldehyde **2** can be stored for several months at −20 °C without decomposition; however, when dissolved in $CDCl_3$, **2** was transformed into a new product **5** within a few hours as judged by the disappearance of the signals for the aldehyde, α- and *β*-protons, respectively, at 9.52, 3.04, and 2.40 ppm in the NMR spectrum. In the FT-IR spectrum of **5**, we observed bands at 1610 and 1714 cm^{-1} corresponding, respectively, to the stretches for an α,*β*-unsaturated imine and ester. Mass spectrometric analysis of **5** by fast atom bombardment gave a peak with $m/z = 396$, indicating loss of water from aldehyde **2** when nitrobenzyl alcohol was used as the matrix, and with thioglycerol as the matrix, a peak was obtained with $m/z = 504$ which indicated loss of water from **2** and formation of a thioglycerol adduct. Crystals of **5** were later grown from EtOAc−hexanes. Crystallographic analysis by X-ray diffraction demonstrated the product from decomposition of **2** to be *tert*-butyl *N*-(PhF)-5-azapenta-2,4-dienoate (**5**, Figure 1).[28] This conjugated imine is presumed to form by a process that commences with intramolecular attack of the *N*-(PhF)amine onto the *β*-aldehyde (Scheme 3). In the presence of trace amounts of acid in chloroform, the resulting aminol may lose water to provide a strained dehydroazetidine carboxylate that ring opens by elimination of the iminium ion nitrogen to furnish azadiene **5**. The thioglycerol adduct obtained in the mass spectral analysis of **5** may have thus resulted from 1,4- or 1,2-additions of this thiol to 5-azapenta-2,4-dienoate **5**.

Synthesis of 6-Alkylpipecolates. Aldol condensations with aldehyde **2** and the lithium enolates of a variety of methyl alkyl ketones furnished the respective ϵ-oxo γ-hydroxy α-*N*-(PhF)amino esters **6** in 61−93% yields (Scheme 4, Table 1). In the cases of 3-methylbutan-2-one and pentan-2-one, the enolate was generated under kinetically controlled conditions prior to the addition of aldehyde **2**.[29] Enones **7** were synthesized by dehydration of alcohols **6** using two different conditions. Initially, we subjected *β*-hydroxy ketones **6** to diisopropylcarbodiimide and catalytic copper(I) chloride in THF which furnished enones **7** in 62−87% yields.[30] Improved yields of enones **7b-f** were obtained via the elimination of the corresponding methanesulfonates using methanesulfonyl chloride and triethylamine in dichloromethane. Treatment of **6a** under the latter conditions provided enone **7a** in 64% yield accompanied by 32% yield of a single diastereomeric methanesulfonate, which suggested that steric crowding prevented this diastereomer from attaining the conformation required for elimination. In all cases, formation of olefin having only the (*E*)-configuration was indicated by the large (15.2−16.0 Hz) vicinal coupling constants between the vinyl protons.

Hydrogenations of enones **7** were originally performed using 10% palladium-on-carbon as catalyst in a solution of 10:1 methanol:acetic acid under 3 atm of hydrogen.[31] Under these conditions, concurrent hydrogenation of the double bond and cleavage of the PhF protecting group were followed by iminium ion formation and subsequent reduction from the side opposite the *tert*-butyl ester to selectively furnish the *cis*-6-alkylpipecolate *tert*-butyl esters **8**. The relative stereochemistry of the pipecolate 6-position substituent was assigned initially based on analogy with our studies on the hydrogenation of α-*tert*-butyl *δ*-oxo-α-*N*-(PhF)amino esters which produced 5-alkylprolines with high selectivity in favor of the *cis*-diastereomer.[31] Using similar hydrogenation conditions to prepare related fused-pipecolate analogues, we later confirmed the assignment of the 6-position stereochemistry by crystallization of the (2*S*,6*R*,8*S*)-methyl 9-oxo-8-*N*-(BOC)amino-1-azabicyclo[4.3.0]nonane-2-carboxylate and analysis by X-ray diffraction.[27]

6-*tert*-Butylpipecolate **8a** could be purified by chromatography after filtration and concentration; however, isolation of pure 6-alkylpipecolates **8b**−**d** was less straightforward, due largely to their volatility. Although chromatographic purification could be circumvented by partitioning the 9-phenylfluorene hydrocarbon into hexanes, subsequent concentration of the methanolic acetic acid solution under vacuum was accompanied by loss of material due to the volatility of the acetate salts of **8b**−**d**. Direct conversion of *tert*-butyl esters **8b**−**d** into amino acids **1b**−**d** was accomplished by treatment of the crude hydrogenation product with 1:1 trifluoroacetic acid:dichloromethane, extraction of the pipecolate trifluoroacetates into water, concentration, and ion-exchange chromatography which furnished zwitterionic 6-alkylpipecolates **1b**−**d** in respective yields of 59%, 61%, and 81%. Although amino acids **1b**−**d** were of adequate purity for subsequent use, their hygroscopic nature thwarted recrystallization. Hydrogenation of enones **7a**−**d** in the absence of acetic acid proved the most effective means for isolating 6-alkylpipecolates **8a**−**d**. Treatment of enones **7a**−**d** in methanol with palladium-on-carbon and 3 atm of hydrogen furnished *tert*-butyl 6-alkylpipecolates **8a**−**d** in 86−91% respective yields after chromatography with diethyl ether in dichlo-

(27) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463.

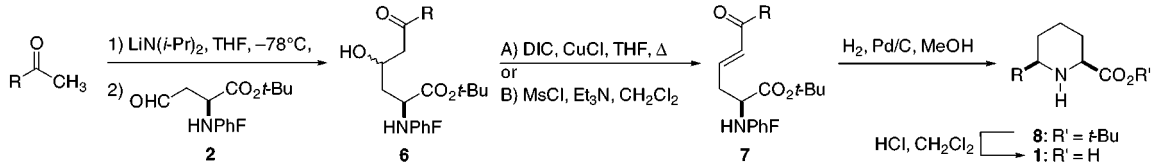
(28) The structure of **5** was solved at l′Université de Montréal X-ray facility using direct methods (SHELXS96) and refined with NRCVAX and SHELXL96: $C_{27}H_{25}NO_2$; $M_r = 395.480$; monoclinic, colorless crystal; space group P21; unit cell dimensions (Å) $a = 10.616(3)$, $b = 8.537(2)$, $c = 13.146(7)$; $\beta = 110.15(3)°$; volume of unit cell (Å^3) = 1118.5-(7); $Z = 2$; $R_1 = 0.0343$ for $I > 2\sigma(I)$, $wR_2 = 0.0584$ for all data; GOF = 0.990. The author has deposited the atomic coordinates for the structure of **5** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(29) For a review, see d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.

(30) Miller, M. J. *J. Org. Chem.* **1980**, *45*, 3131.

(31) (a) Beausoleil, E.; L′Archevêque, B.; Bélec, L.; Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447. (b) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438.

Scheme 4. Synthesis of 6-Alkylpipecolic Acid Hydrochloride Salts 1



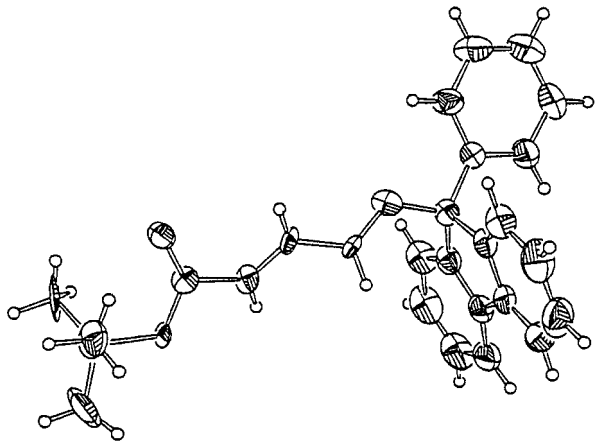
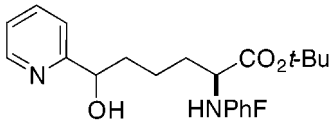


Figure 1. ORTEP view of *tert*-butyl *N*-(PhF)-5-azapenta-2,4-dienoate (**5**). Ellipsoids drawn at 40% probability level. Hydrogens represented by spheres of arbitrary size.[27]

romethane as eluant. The 6-alkylpipecolate hydrochlorides were then quantitatively obtained by exposure of *tert*-butyl esters **8** to HCl in dichloromethane.

The 9-phenylfluorene hydrocarbon was quantitatively recovered from the hydrogenation of ϵ-oxo-α-*N*-(PhF)-amino esters **7**. Endeavoring to recycle this hydrocarbon back to the protecting group precursor, 9-bromo-9-phenylfluorene, we found that simply heating 9-phenylfluorene with *N*-bromosuccinimide in carbon tetrachloride[32] provided the corresponding bromide in 96% yield after evaporation of the volatiles, digestion of the residue with hexanes, and filtration of the insoluble succinimide (Scheme 5). This efficient recycle of 9-phenylfluorene to 9-bromo-9-phenylfluorene has thus provided an economic means for extending the duration of utility of the 9-phenylfluorenyl protecting group.[33]

Synthesis of 6-Arylpipecolates. Hydrogenation of (2*S*,4*E*)-*tert*-butyl 6-oxo-6-phenyl-2-*N*-(PhF)-aminohex-4-enoate (**7e**) in the presence of acetic acid under the conditions described above for the synthesis of 6-alkylpipecolate did not furnish the desired 6-arylpipecolate **8e**; instead, (2*S*,6*RS*)-*tert*-butyl 2-amino-6-hydroxy-6-phenylhexanoate (**9**) was isolated as a 1:1 mixture of diastereomers in 46% yield (Scheme 6). Furthermore, no cleavage of the PhF protecting group was observed on hydrogenation of (2*S*,4*E*)-*tert*-butyl 6-oxo-6-(2′-pyridyl)-2-*N*-(PhF)aminohex-4-enoate (**7f**) under similar conditions; instead, (2*S*,6*RS*)-*tert*-butyl 2-[*N*-(PhF)amino]-6-hydroxy-6-(2′-pyridyl)hexanoate (**10**) was obtained as a 1:1 mixture of diastereomers in 58% yield. These results prompted



10

an investigation of the hydrogenation of **7e** in order to examine the competition between PhF group hydrogenolysis and aryl ketone reduction (Table 2).[34]

The rates of ketone hydrogenation and N−PhF bond hydrogenolysis were competitive using palladium and platinum catalysts such that *tert*-butyl 6-phenylpipecolate **8e** was isolated in low yield. The best yield (20%) of **8e** was obtained on hydrogenation of **7e** over palladium-on-carbon in methanol under 1 atm of hydrogen. Selective reduction of the double bond and aryl ketone without loss of the phenylfluorenyl group was achieved on hydrogenation of **7e** with Raney nickel as catalyst to give *N*-(PhF)-amino alcohol **11**. As previously noted,[35] selective olefin hydrogenation without PhF removal was accomplished with a platinum catalyst and gave (2*S*)-*tert*-butyl 6-oxo-6-phenyl-2-*N*-(PhF)aminohexanoate (**12**) from **7e**. Attempts to convert **12** to 6-arylpipecolate **8e** gave similar product distributions as those obtained from hydrogenations of **7e** under identical conditions. In summary, the reductive amination route proved more effective for preparing 6-alkyl rather than 6-arylpipecolates due to competitive aryl ketone reductions.

Enantiomeric Purity. Determination of the enantiomeric purity of 6-alkylpipecolate **1** by the preparation and analysis of diastereomeric derivatives proved more difficult than purity studies we had previously conducted on related 5-alkylprolines.[31] As noted in a failed attempt to determine the enantiomeric purity of an alkylpiperidine,[36] although amides and ureas could be synthesized by acylation of the piperidine nitrogen, analysis by proton NMR spectroscopy did not indicate sufficiently distinct diastereomeric signals for ascertaining the limits of detection of the minor isomer. Furthermore, these diastereomeric derivatives eluted with similar retention times in cursory examinations by reverse-phase HPLC.

The enantiomeric purity of 6-alkylpipecolate **1** was successfully determined after conversion to the respective *N*-benzylpipecolate and subsequent coupling to a chiral amine (Scheme 7). (2*S*,6*S*)-6-Methylpipecolate *tert*-butyl ester (**1d**) was treated with benzyl bromide and potassium carbonate in DMF to provide *N*-(benzyl)pipecolate **14** in 95% yield. Dipeptides **15** were synthesized by *tert*-butyl ester solvolysis on exposure of **14** to HCl gas in dichloromethane, followed by coupling to D- and L-phenylalanine methyl ester hydrochloride using benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)[37] and DIEA in acetonitrile. Measurement of the

(32) Buu-Höi, Ng. Ph. *Justus Liebigs Ann. Chem*. **1944**, *556*, 1.

(33) Although it is listed in the Aldrich Chemical Co. 1996−97 catalogue for $40.70 Canadian per gram, we synthesize >250 g batches of 9-bromo-9-phenylfluorene from inexpensive fluorenone, bromobenzene, butyllithium and HBr in >80% yield using the convenient protocol described in: Jamison, T. F.; Lubell, W. D.; Dener, J. M.; Krisché, M. J.; Rapoport, H. *Org. Synth*. **1992**, *71*, 220.

(34) Monographs include the following: (a) Rylander, P. N. *Catalytic Hydrogenation In Organic Synthesis*; Academic Press: New York, 1979. (b) Rylander, P. N. *Catalytic Hydrogenation Over Platinum Metals*; Academic Press: New York, 1967.

(35) (a) Lubell, W.; Rapoport, H. *J. Org. Chem*. **1989**, *54*, 3824. (b) Park, K. H.; Rapoport, H. *J. Org. Chem*. **1994**, *59*, 394.

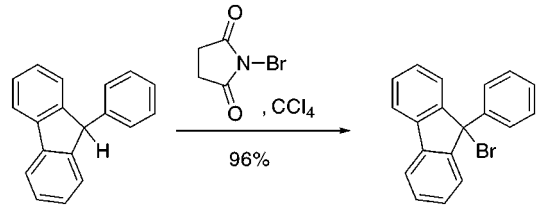
(36) Davis, F. A.; Szewczyk, J. M. *Tetrahedron Lett*. **1998**, *39*, 5951.

Table 1. Isolated Yields in the Synthesis of 6-Alkylpipecolates

entry	Ketone	R	% Yield **6** (dr)	A) % Yield **7**	B) % Yield **7**	% Yield **8**	% Yield **1**•HCl
a	Pinacolone	*t*-Bu	84 (1:1)	87	64[a]	86	98
b	3-Methyl-2-butanone	*i*-Pr	77 (2:1)	62	87	91	100
c	2-Pentanone	*n*-Pr	72 (2:1)	63	91	86	97
d	Acetone	Me	68 (2:1)	62	86	90	98
e	Acetophenone	Ph	93 (2:1)	81	92	20	96
f	2-Acetylpyridine	2-Pyridyl	61 (3:1)	–	80	–	–

[a]Recovered 32% methanesulfonate.

Scheme 5. Recycle of 9-Phenylfluorene to 9-Bromo-9-phenylfluorene



Scheme 6. Hydrogenation of Enone 7E

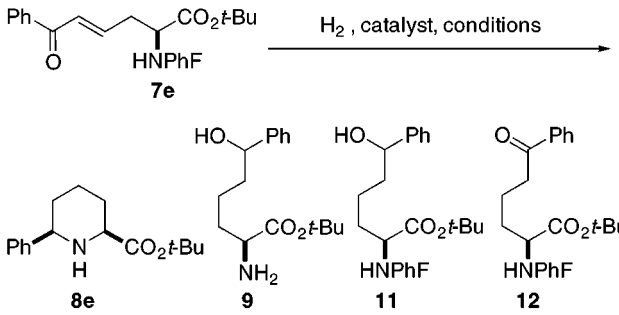
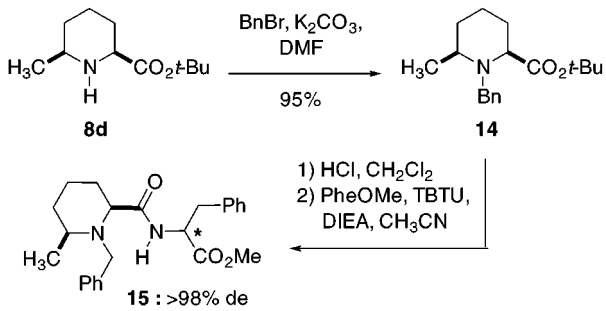


Table 2. Catalytic Hydrogenation of Enone 7e

entry	catalyst	solvent	H_2 (atm)	isolated yields % **8e**	% **9**	% **11**	% **12**
a	Pd/C	MeOH/AcOH	3	-	46	-	-
b	Pd/C	MeOH/AcOH	1	16	53	-	-
c	Pd/C	MeOH	1	20	13	31	-
d	Pt/C	MeOH/AcOH	3	9	-	9	64
e	Pt/C	EtOAc	2.75	-	-	14	84
f	Ra Ni	EtOH	3	-	-	95	-

Scheme 7. Enantiomeric Purity of (2*S*, 6*S*)-6-Methylpipecolate 8d



methyl ester singlets at 3.68 and 3.52 ppm in $CDCl_3$ by 400 MHz ^{1}H NMR spectroscopy and incremental additions of diastereomeric (2*S*,6*R*,2′*S*)-**15** demonstrated (2*S*,6*R*,2′*R*)-dipeptide **15** to be of >99% diastereomeric purity. Hence 6-alkylpipecolic acids **1** are presumed to be of >99% enantiomeric purity.

Conformational Analysis of *N*-Acetyl *N*′-Methyl Pipecolinamides. *N*-Acetyl *N*′-methyl pipecolinamide **16** and its (2*S*,6*R*)-6-*tert*-butyl counterpart **17** were synthesized in order to examine the influence of the bulky 6-position substituent on the amide isomer equilibrium and the rate of amide isomerization *N*-terminal to the pipecolyl residue. Pipecolic acid was *N*-protected with di-*tert*-butyl dicarbonate in an aqueous dioxane solution containing sodium hydroxide, and the resulting *N*-(BOC)-pipecolate was coupled to methylamine using TBTU in acetonitrile. Pipecolinamide **16** was then obtained after solvolysis of the BOC group with gaseous HCl in dichloromethane, followed by acetylation on heating in the presence of acetic anhydride and triethylamine in dichloromethane. (2*S*,6*R*)-*N*-Acetyl *N*′-methyl 6-*tert*-butylpipecolinamide was synthesized without *N*-protection by coupling to methylamine using TBTU in acetonitrile, followed by *N*-acetylation on heating with acetic anhydride, sodium acetate, and triethylamine in toluene at reflux.

The pipecolinamide isomer equilibrium and the energy barrier for amide isomerization were determined in water (D_2O) because of its physiological importance and for comparison with literature examples.[14] In comparison to reaction rates in nonprotic and nonpolar solvents, amide isomerization *N*-terminal to proline has been shown to proceed slower in water, which stabilizes the polar amide ground states relative to the less polar transition state.[38] The *cis*-isomer geometry was assigned based on the cross-peak arising from the nuclear Overhauser effect between the *N*-acetyl and prolyl α-hydrogens in the NOESY and ROESY spectra of **16** and **17** in water. The populations of the amide isomers were measured by integration of their isomeric acetyl methyl singlets in the ^{1}H NMR spectra. The energy barriers ($\Delta G^{\ddagger}$) for amide isomerization in **16** and **17** were determined by recording a series of ^{1}H NMR spectra at 400 MHz with increasing temperatures until the resonances for the two isomer populations were observed to coalesce. The energy barriers for amide isomerization in **16** and **17** were then calculated to, respectively, be 17.8 and 17.0 kcal/mol in D_2O.[39] For comparison, the isomer populations and the energy barriers for isomerization of **16** and **17** are listed next to the values for *N*-(acetyl)proline *N*′-methylamide (**18**) and its (2*S*,5*R*)-5-*tert*-butyl counterpart **19** in Table 3.[14]

(37) (a) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927. The crystal structure of HBTU, the corresponding PF_6 salt, substantiates a guanidinium-1-*N*-oxide salt for TBTU: (b) Abdelmoty, I.; Albericio, F.; Carpino, L. A.; Foxman, B.; Kates, S. A. *Lett. Peptide Sci.* **1994**, *1*, 57.

(38) Stein, R. L. *Adv. Protein Chem.* **1993**, *44*, 1.

(39) Sandström, J. *Dynamic NMR Spectroscopy*, Academic Press: London, 1982, ch. 6, p 79.

Table 3. Proline[14] and Pipecolate *N*-Acetyl-*N′*-Methyl Amide Equilibrium

trans-isomer *cis*-isomer

	n	R	%*cis*-isomer ±3%	T_c (°C)	$\Delta G^{\ddagger}$ ±0.3 kcal/mol
16	1	H	28	80[a]	17.8
17	1	*t*-Bu	43	70[a]	17.0
18	0	H	27	>85[b]	20.4
19	0	*t*-Bu	49	45[b]	16.5

[a]Measured at 400 MHz. [b]Measured at 300 MHz in ref. 14.

As observed in our comparison of *N*-acetyl *N′*-methylamides of proline and (2*S*,5*R*)-5-*tert*-butylproline, the bulky substituent caused steric interactions that disfavored the *trans*-isomer and increased the *cis*-amide isomer population. Furthermore, a lower barrier for amide isomerization was observed for the (6*R*)-*tert*-butylpipecolinamide **17** relative to the simple pipecolyl amide **16** (Table 3). The influences of the *tert*-butyl substituent were less pronounced in the pipecolinamides relative to their proline counterparts.

The 2.6 kcal/mol lower barrier for isomerization of pipecolinamide **16** relative to *N*-(acetyl)proline *N′*-methylamide (**18**) compared well with the 2.8 kcal/mol lower barrier for isomerization of *N*-acetyl 2-methylpyrrolidine (15.3 kcal/mol) relative to *N*-acetyl 2-methylpiperidine (18.1 kcal/mol).[40] The barrier for amide isomerization was also observed to be lower for pipecolyl than prolyl residues in peptides.[8] A tendency for greater amide *cis*-isomer populations *N*-terminal to pipecolyl versus prolyl residues has been recorded in peptides and attributed to increased steric interaction between the *N*-terminal amino acid and the bulkier piperidine ring.[8] Since the amount of *cis*-isomer exhibited by *N*-acetyl *N′*-methylpipecolinamide (**16**) is similar to that of *N*-(acetyl)-proline *N′*-methylamide (**18**) in water, the *N*-acetyl residue does not appear to have sufficient bulk to discriminate between the piperidine and pyrrolidine ring-sizes. The greater conformational liberty of the six- versus five-member ring may also account for the lower acetamide *cis*-isomer population for 6-*tert*-butylpipecolinamide **17** relative to 5-*tert*-butylproline amide **19**.

Conclusion

Our investigation has provided effective means for preparing novel alkylpipecolates and better understanding of their conformational effects in peptide structures. Enantiopure 6-alkylpipecolates were synthesized by employment of α-*tert*-butyl *N*-(PhF)aspartate *β*-aldehyde **2** in an aldol condensation, dehydration, reductive amination sequence. Primary, secondary, and tertiary alkyl as well as aromatic groups all were stereoselectively introduced at the 6-position of pipecolic acid. Furthermore, extension of this methodology offers potential to provide pipecolates with other substitution patterns. Comparison of *N*-acetyl *N′*-methyl pipecolinamide **16** and its (2*S*,6*R*)-6-*tert*-butyl counterpart **17** demonstrated that the 6-position substituent augmented the pipecolyl amide *cis*-isomer population and lowered the barrier for amide isomerization in a manner similar to albeit less pronounced than the influence of a 5-*tert*-butyl substituent on the amide of the corresponding proline series.[14] This approach has thus expanded our capacity for synthesizing and employing azacycloalkane carboxylates as tools for the exploration of conformation−activity relationships of biologically active peptides.

Experimental Section

General. Unless stated otherwise, solvents and reagents were used as supplied, and all reactions were carried out under nitrogen. Toluene was distilled from sodium, tetrahydrofuran from sodium/benzophenone, dichloromethane from P_2O_5, and the methyl ketones from $CaSO_4$, immediately prior to use. Diisopropylamine, DIEA, and triethylamine were distilled from CaH_2. Diisopropylcarbodiimide was distilled from $KMnO_4$. Copper(I) chloride was purified by precipitation from hydrochloric acid.[41] Methanesulfonyl chloride was passed through a pad of basic alumina immediately prior to use. *n*-Butyllithium was titrated using menthol in THF containing fluorene as indicator. Final reaction solutions were dried over Na_2SO_4. Flash-column chromatography[42] was performed on 230−400 mesh silica gel; TLC was performed on aluminum-backed silica plates with visualization by UV-light, iodine, or ninhydrin. Mass spectral data, and HRMS (FAB and ES) data, were obtained by the Université de Montréal Mass Spectroscopy facility. ^{1}H NMR and ^{13}C NMR spectra were, respectively, recorded at 400 and 100 MHz in $CDCl_3$. Chemical shifts are in ppm (δ units) relative to internal $(CH_3)_4Si$ or residual solvent for ^{1}H NMR spectra, and relative to solvant signals for ^{13}C NMR spectra. Chemical shifts for aromatic and vinyl carbons are not reported for PhF-containing compounds. Catalytic hydrogenation was conducted at 1 atm in a round-bottomed flask equipped with a balloon and at 3 atm in a high-pressure hydrogenation apparatus.

(2*S*)-*tert*-Butyl 2-[*N*-(PhF)amino]-4-oxobutanoate (2). Diisobutylaluminum hydride (46.6 mL of a 1.0 M solution in toluene, 0.047 mol) was added dropwise over 10 min to a stirred solution of (2*S*)-α-*tert*-butyl *β*-methyl-*N*-(PhF)aspartate (**3**, 18.8 g, 0.042 mol, prepared according to ref 26) in toluene (420 mL) at −78 °C. Upon complete addition, the reaction was stirred for an additional 5 min and quenched by the addition of acetone (10 mL) followed by water (10 mL). Sodium bicarbonate (approximately 45 g) was added to the mixture which was allowed to warm to room temperature with vigorous stirring and filtered through a pad of sodium bicarbonate on Celite. The filter cake was washed thoroughly with ethyl acetate, and the filtrate was concentrated in vacuo to furnish the title compound[26] in >95% yield as a viscous colorless oil which was subsequently used without further purification: TLC R_f = 0.44 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz) δ 1.21 (s, 9 H), 2.40 (m, 2 H), 3.03 (dd, 1 H, J = 7.4, 5.5), 3.34 (br s, 1 H), 7.15−7.72 (m, 13 H), 9.48 (dd, 1 H, J = 2.8, 2.2).

***tert*-Butyl *N*-(PhF)-5-azapenta-2,4-dienoate (5)** was isolated, after stirring **3** in $CDCl_3$, by chromatography using a gradient of 0−5% EtOAc in hexanes as eluant. Evaporation of the collected fractions and recrystallization from EtOAc and hexanes gave colorless needles: mp = 148−149 °C; TLC R_f = 0.57 (20% EtOAc in hexanes); ^{1}H NMR δ 7.83−7.74 (m, 3 H), 7.39−7.22 (m, 13 H), 6.04 (d, 1 H, J = 15.8), 1.49 (s, 9 H); ^{13}C NMR δ 28.0, 80.2, 81.1, 158.1, 164.9; FT-IR (Nujol, cm^{-1}) 1714, 1610; *m*/*z* (nitrobenzyl alcohol): 396 (MH^+); *m*/*z* (thioglycerol): 504 (M + 109).

General Procedure for Aldol Condensation of Aspartate *β*-Aldehyde 2 with 3-Methylbutan-2-one and Pentan-2-one. A solution of *n*-butyllithium (1.2 mmol) in hexanes was

(40) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 3385.
(41) Keller, R. N.; Wycoff, H. D. *Inorg. Synth.* **1946**, *2*, 1.
(42) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

added dropwise to a stirred solution of diisopropylamine (164 μL, 1.2 mmol) in THF (1 mL) at −10 °C to 0 °C. Upon complete addition, the solution was cooled to −78 °C, stirred for 15 min, and treated with the ketone (1.1 mmol, 110 mol %). After stirring an additional 15 min, the reaction mixture was treated dropwise via cannula with a solution of aldehyde **2** (414 mg, 1 mmol) in THF (1 mL) and stirred at −78 °C until analysis by TLC indicated the complete consumption of aldehyde **2** (1−2 h). The reaction was quenched by the addition of a solution of saturated aqueous sodium bicarbonate (0.5 mL), allowed to warm to room temperature, and treated with additional saturated aqueous sodium bicarbonate (10 mL). The mixture was separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried and concentrated in vacuo to a crude product which was purified by flash-column chromatography, eluting with an ethyl acetate:hexanes system of appropriate polarity.

General Procedure for Aldol Condensation of Aspartate *β*-Aldehyde 2 with Acetone, Pinacolone, Acetophenone, and 2-Acetylpyridine. A solution of *n*-butyllithium (1.4 mmol) in hexanes was added dropwise to a stirred solution of diisopropylamine (273 μL, 2.0 mmol) in THF (1 mL) maintaining the temperature between −10 °C and 0 °C. Upon complete addition, the solution was cooled to −78 °C, stirred for 15 min, treated with the ketone (1.4 mmol, 140 mol %), stirred 30 min, and treated dropwise via cannula with a solution of aldehyde **2** (414 mg, 1 mmol) in THF (1 mL). Stirring was continued at −78 °C until TLC analysis indicated complete consumption of aldehyde (1−2 h). Quench, workup, and purification all were performed in the same manner as described above.

(2*S*,4*RS*)-*tert*-Butyl 4-hydroxy-6-oxo-7,7-dimethyl-2-[*N*-(PhF)amino]octanoate (6a) was prepared as described above using pinacolone and isolated as a white foam containing an inseparable 2:1 mixture of diastereomers (84% from **2**): TLC R_f = 0.24 (20% ethyl acetate in hexanes); ^{1}H NMR (major isomer) δ 1.11 (s, 9 H), 1.15 (s, 9 H), 1.50−1.56 (m, 2 H), 2.36 (dd, 1 H, J = 17.2, 5.4), 2.70 (dd, 1 H, J = 17.2, 6.8), 2.71−2.75 (m, 1 H), 4.04−4.15 (m, 1 H), 7.18−7.38 (m, 10 H), 7.46−7.52 (m, 1 H), 7.67−7.72 (m, 2 H); ^{1}H NMR (minor isomer) δ 1.09 (s, 9 H), 1.23 (s, 9 H), 1.50−1.56 (m, 2 H), 2.44 (dd, 1 H, J = 17.4, 5.5), 2.63 (dd, 1 H, J = 17.4, 7.2), 2.71−2.75 (m, 1 H), 4.31−4.38 (m, 1 H), 7.18−7.38 (m, 10 H), 7.46−7.52 (m, 1 H), 7.67−7.72 (m, 2 H); ^{13}C NMR (major isomer) δ 26.1, 27.7, 40.0, 43.6, 55.8, 67.0, 72.9, 81.0, 174.1, 214.4; ^{13}C NMR (minor isomer) δ 26.1, 27.7, 39.7, 44.1, 53.8, 65.3, 72.9, 81.1, 174.5, 214.7; HRMS calcd for $C_{33}H_{40}NO_4$ (MH^+) 514.2957, found 514.2973.

(2*S*,4*RS*)-*tert*-Butyl 4-hydroxy-7-methyl-6-oxo-2-[*N*-(PhF)amino]octanoate (6b) was prepared as described above using 3-methylbutan-2-one and isolated as a pale-yellow, glassy solid containing an inseparable 2:1 mixture of diastereomers (77% from **2**): TLC R_f = 0.48 (30% ethyl acetate in hexanes); ^{1}H NMR (major isomer) δ 1.07 (d, 3H, J = 6.9), 1.08 (d, 3H, J = 6.9), 1.15 (s, 9H), 1.50−1.55 (m, 2H), 2.33 (dd, 1H, J = 16.3, 5.0), 2.51−2.64 (m, 2H), 2.70−2.74 (m, 1H), 4.02−4.08 (m, 1H), 7.20−7.75 (m, 13H); ^{1}H NMR (minor isomer) δ 1.06 (d, 3H, J = 6.9), 1.07 (d, 3H, J = 6.9), 1.24 (s, 9H), 1.50−1.55 (m, 2H), 2.39 (dd, 1H, J = 16.1, 4.9), 2.51−2.64 (m, 2H), 2.70−2.74 (m, 1H), 4.26−4.34 (m, 1H), 7.20−7.75 (m, 13H); ^{13}C NMR (major isomer) δ 17.8, 27.7, 39.9, 41.1, 47.5, 55.9, 67.2, 72.9, 81.0, 174.0, 213.2; ^{13}C NMR (minor isomer) δ 17.9, 27.7, 39.7, 41.3, 47.3, 53.9, 65.4, 72.9, 81.3, 174.3, 213.4; HRMS calcd for $C_{32}H_{38}NO_4$ (MH^+) 500.2801, found 500.2774. Anal. Calcd for $C_{32}H_{37}NO_4$: C, 76.92; H, 7.46; N, 2.80. Found C, 76.84; H, 7.55; N, 2.80.

(2*S*,4*RS*)-*tert*-Butyl 4-hydroxy-6-oxo-2-[*N*-(PhF)amino]nonanoate (6c) was prepared as described above using pentan-2-one and isolated as an off-white solid containing an inseparable 2:1 mixture of diastereomers (72% from **2**): TLC R_f = 0.30 (20% ethyl acetate in hexanes); ^{1}H NMR (major isomer) δ 0.91 (t, 3H, J = 7.4), 1.14 (s, 9H), 1.47−1.63 (m, 4H), 2.23−2.73 (m, 5H), 3.99−4.05 (m, 1H), 7.15−7.80 (m, 13H); ^{1}H NMR (minor isomer) δ 0.89 (t, 3H, J = 7.4), 1.23 (s, 9H), 1.47−1.63 (m, 4H), 2.23−2.73 (m, 5H), 4.25−4.30 (m, 1H), 7.15−7.80 (m, 13H); ^{13}C NMR (major isomer) δ 13.6, 16.9, 27.7, 39.8, 45.4, 49.9, 55.9, 67.4, 72.9, 81.1, 173.9, 209.7; ^{13}C NMR (minor isomer) 13.6, 16.9, 27.7, 39.6, 45.5, 49.7, 54.0, 65.5, 72.9, 81.4, 174.2, 209.8; HRMS calcd for $C_{32}H_{38}NO_4$ (MH^+) 500.2801, found 500.2815.

(2*S*,4*RS*)-*tert*-Butyl 4-hydroxy-6-oxo-2-[*N*-(PhF)amino]heptanoate (6d) was prepared as described above using acetone and isolated as a white solid containing an inseparable 2:1 mixture of diastereomers (68% from **2**): TLC R_f = 0.26 (30% ethyl acetate in hexanes); ^{1}H NMR (major isomer) δ 1.14 (s, 9 H), 1.47−1.52 (m, 2 H), 2.15 (s, 3 H), 2.29 (dd, 1 H, J = 16.0, 4.7), 2.51 (dd, 1 H, J = 16.0, 8.0), 2.69−2.73 (m, 1 H), 3.98−4.05 (m, 1 H), 7.14−7.73 (m, 13 H); ^{1}H NMR (minor isomer) δ 1.24 (s, 9 H), 1.47−1.52 (m, 2 H), 2.13 (s, 3 H), 2.34 (dd, 1 H, J = 16.5, 4.8), 2.54 (dd, 1 H, J = 16.0, 8.0), 2.69−2.73 (m, 1 H), 4.20−4.30 (1 H, m), 7.14−7.73 (m, 13 H); ^{13}C NMR (major isomer) δ 27.7, 30.5, 39.7, 50.8, 55.9, 67.4, 72.9, 81.2, 173.9, 207.6; ^{13}C NMR (minor isomer) δ 27.7, 30.7, 39.5, 50.7, 54.1, 65.4, 72.9, 81.4, 174.1, 207.5; HRMS calcd for $C_{30}H_{34}NO_4$ (MH^+) 472.2488, found 472.2505. Anal. Calcd for $C_{30}H_{34}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found C, 76.28; H, 7.15; N, 3.01.

(2*S*,4*RS*)-*tert*-Butyl 4-hydroxy-6-oxo-6-phenyl-2-[*N*-(PhF)amino]hexanoate (6e) was prepared as described above using acetophenone and isolated as a white solid containing an inseparable 2:1 mixture of diastereomers (93% from **2**): TLC R_f = 0.28 (20% ethyl acetate in hexanes); ^{1}H NMR (major isomer) δ 1.16 (s, 9 H), 1.60−1.70 (m, 2 H), 2.77 (dd, 1 H, J = 9.4, 5.4), 2.84 (dd, 1 H, J = 16.4, 5.4), 3.32 (t, 1 H, J = 7.1), 4.24−4.31 (m, 1 H), 7.12−7.96 (m, 18 H); ^{1}H NMR (minor isomer) δ 1.23 (s, 9 H), 1.60−1.70 (m, 2 H), 2.78 (m, 1 H), 2.92 (dd, 1 H, J = 16.6, 5.5), 3.36 (t, 1 H, J = 7.1), 4.46−4.54 (m, 1 H), 7.12−7.96 (m, 18 H); ^{13}C NMR (major isomer) δ 27.8, 40.1, 45.7, 55.8, 67.4, 73.0, 81.1, 174.1, 198.8; ^{13}C NMR (minor isomer) δ 27.7, 39.7, 45.8, 54.1, 65.8, 73.0, 81.4, 174.2, 198.7; HRMS calcd for $C_{35}H_{36}NO_4$ (MH^+) 534.2644, found 534.2662.

(2*S*,4*RS*)-*tert*-Butyl 4-hydroxy-6-oxo-6-(2-pyridyl)-2-[*N*-(PhF)amino]hexanoate (6f) was prepared as described above using 2-acetylpyridine and isolated as a white solid containing an inseparable 3:1 mixture of diastereomers (61% from **2**): TLC R_f = 0.33 (30% ethyl acetate in hexanes); ^{1}H NMR (major isomer) δ 1.15 (s, 9H), 1.57−1.68 (m, 2H), 2.75 (dd, 1H, J = 9.8, 4.8), 3.09 (dd, 1H, J = 16.1, 4.4), 3.30 (dd, 1H, J = 16.1, 8.1), 4.26−4.33 (m, 1H), 7.10−8.70 (m, 17H); ^{1}H NMR (minor isomer) δ 1.22 (s, 9H), 1.57−1.68 (m, 2H), 2.78−2.82 (m, 1H), 3.21 (dd, 1H, J = 16.5, 4.6), 3.30−3.35 (m, 1H), 4.48−4.56 (m, 1H), 7.10−8.70 (m, 17H); ^{13}C NMR (major isomer) δ 27.7, 40.2, 45.1, 55.8, 67.4, 73.0, 81.0, 174.1, 200.2; ^{13}C NMR (minor isomer) δ 27.7, 40.0, 45.5, 54.1, 65.7, 73.0, 81.2, 174.4, 200.2; HRMS calcd for $C_{34}H_{35}N_2O_4$ (MH^+) 535.2597, found 535.2612.

General Procedure A for the Dehydration of *β*-Hydroxy Ketones 6a−e. A solution of *β*-hydroxy ketone **6** (1 mmol, 100 mol %) in THF (8 mL) was treated with copper(I) chloride (40 mg, 0.4 mmol) and diisopropylcarbodiimide (470 μL, 3 mmol), and the suspension was heated at a reflux for 14 h. After cooling to room temperature, the solvent was removed in vacuo, and the residue was purified by flash-column chromatography, eluting with an ethyl acetate:hexanes system of appropriate polarity.

General Procedure B for the Dehydration of *β*-Hydroxy Ketones 6a−f. Methanesulfonyl chloride (85 μL, 1.1 mmol) was added dropwise to a stirred solution of *β*-hydroxy ketone **6** (1 mmol) and triethylamine (418 μL, 3 mmol) in dichloromethane (2.5 mL) at 0 °C. Upon complete addition, the reaction was stirred for 30 min at 0 °C, allowed to warm to room temperature, and stirred until TLC analysis indicated the consumption of the starting material (1−2 h). The reaction was diluted with dichloromethane (10 mL) and washed with water (10 mL). The aqueous phase was extracted with dichloromethane (3 × 5 mL), and the combined organic layer was dried and concentrated in vacuo to a crude oil that was purified by flash-column chromatography eluting with an ethyl acetate:hexanes system of appropriate polarity to furnish enones **7**.

(2*S*,4*E*)-*tert*-Butyl 6-oxo-7,7-dimethyl-2-[*N*-(PhF)amino]oct-4-enoate (7a) was isolated as an oil from **6a** in 87% yield with method A and 62% with method B: TLC $R_f = 0.57$ (20% EtOAc in hexanes); $[\alpha]^{20}_D$ −144.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.19 (s, 9 H), 1.23 (s, 9 H), 2.28−2.41 (m, 2 H), 2.73 (m, 1 H), 3.19 (d, 1 H, $J = 8.1$), 6.50 (d, 1 H, $J = 15.2$), 6.97 (dt, 1 H, $J = 15.1, 7.6$), 7.16−7.40 (m, 10 H), 7.45−7.48 (m, 2 H), 7.67−7.72 (m, 2 H); ^{13}C NMR δ 26.0, 27.7, 38.7, 42.6, 55.5, 72.8, 80.8, 173.8, 203.24; HRMS calcd. for $C_{33}H_{38}NO_3$ (MH^+) 496.2852, found 496.2836. Anal. Calcd for $C_{33}H_{37}NO_3$: C, 79.97; H, 7.52; N, 2.83. Found C, 80.21; H, 7.90; N, 2.96.

(2*S*,4*E*)-*tert*-Butyl 7-methyl-6-oxo-2-[*N*-(PhF)amino]-oct-4-enoate (7b) was isolated as a white solid from **6b** in 62% yield with method A and 87% yield with method B: TLC $R_f = 0.69$ (30% ethyl acetate in hexanes); mp 94−96 °C; $[\alpha]^{20}_D$ −145.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 1.11 (d, 3 H, $J = 7.0$), 1.12 (d, 3 H, $J = 6.9$), 1.18 (s, 9 H), 2.22−2.36 (m, 2 H), 2.67 (t, 1 H, $J = 6.2$), 2.84 (sept., 1 H, $J = 6.9$), 3.16 (br s, 1 H), 6.09 (d, 1 H, $J = 15.7$), 6.80 (dt, 1 H, $J = 15.7, 7.4$), 7.15−7.73 (m, 13 H); ^{13}C NMR δ 18.4, 27.8, 38.0, 38.8, 55.5, 72.9, 81.1, 173.8, 203.5; HRMS calcd for $C_{32}H_{36}NO_3$ (MH^+) 482.2695, found 482.2686.

(2*S*,4*E*)-*tert*-Butyl 6-oxo-2-[*N*-(PhF)amino]non-4-enoate (7c) was isolated as a white solid from **6c** in 63% yield with method A and 91% yield with method B: TLC $R_f = 0.50$ (20% ethyl acetate in hexanes); mp 88−89 °C; $[\alpha]^{20}_D$ −135.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 0.97 (t, 3 H, $J = 7.4$), 1.18 (s, 9 H), 1.67 (sex., 2 H, $J = 7.4$), 2.22−2.36 (m, 2 H), 2.52 (td, 2 H, $J = 7.4, 1.2$), 2.68 (t, 1 H, $J = 6.5$), 3.19 (br. s, 1 H), 6.03 (dt, 1 H, $J = 16.0, 1.4$), 6.74 (dt, 1 H, $J = 16.0, 7.4$), 7.15−7.70 (m, 13 H); ^{13}C NMR δ 13.8, 17.6, 27.8, 38.8, 41.6, 55.5, 72.9, 81.1, 173.8, 200.2; HRMS calcd for $C_{32}H_{36}NO_3$ (MH^+) 482.2695, found 482.2681.

(2*S*,4*E*)-*tert*-Butyl 6-oxo-2-[*N*-(PhF)amino]hept-4-enoate (7d) was isolated as a white solid from **6d** in 62% yield with method A and 86% yield with method B: TLC $R_f = 0.37$ (20% ethyl acetate in hexanes); mp 81−82 °C; $[\alpha]^{20}_D$ −148.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 1.19 (s, 9 H), 2.25 (s, 3 H), 2.31 (m, 2 H), 2.66 (t, 1 H, $J = 6.1$), 3.19 (br. s, 1 H), 6.00 (d, 1 H, $J = 15.9$), 6.70 (dt, 1 H, $J = 15.9, 7.4$), 7.15−7.73 (m, 13 H); ^{13}C NMR δ 26.5, 27.8, 38.8, 55.4, 72.9, 81.1, 173.8, 198.3; HRMS calcd for $C_{30}H_{32}NO_3$ (MH^+) 454.2382, found 454.2391.

(2*S*,4*E*)-*tert*-Butyl 6-oxo-7-phenyl-2-[*N*-(PhF)amino]-hept-4-enoate (7e) was isolated as a white solid from **6e** in 81% yield with method A and 92% yield with method B: TLC $R_f = 0.44$ (20% ethyl acetate in hexanes); mp 43−45 °C; $[\alpha]^{20}_D$ −108.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 1.18 (s, 9H), 2.32−2.46 (m, 2H), 2.71 (t, 1H, $J = 6.4$), 3.20 (br.s, 1H), 6.79 (dt, 1H, $J = 15.4, 1.2$), 6.95 (dt, 1H, $J = 15.4, 7.5$), 7.15−7.95 (m, 18H); ^{13}C NMR δ 27.8, 39.1, 55.7, 73.0, 81.1, 173.9, 190.6; HRMS calcd for $C_{35}H_{33}NO_3$ (MH^+) 454.2382, found 454.2391.

(2*S*,4*E*)-*tert*-Butyl 6-oxo-7-(2′-pyridyl)-2-[*N*-(PhF)amino]hept-4-enoate (7f) was isolated as an off-white solid from **6f** in 65−80% yield with method B: TLC $R_f = 0.53$ (30% ethyl acetate in hexanes); mp 118 °C (dec); $[\alpha]^{20}_D$ −91.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.18 (s, 9 H), 2.36−2.51 (m, 2 H), 2.72 (dd, 1 H, $J = 6.9, 5.9$), 3.21 (br s, 1 H), 7.14−7.70 (m, 14 H), 7.86 (m, 1 H), 8.14 (m, 1 H), 8.70 (m, 1 H); ^{13}C NMR δ 27.7, 39.1, 55.7, 72.9, 81.0, 173.9, 189.0; HRMS calcd for $C_{34}H_{33}N_2O_3$ (MH^+) 517.2492, found 517.2500.

General Procedure for the Hydrogenation of ϵ-Oxo-α-*N*-(PhF)amino Acid Analogues 7a−f over Palladium and Platinum Catalysts. A solution of enone **7** (1 mmol) in either ethyl acetate (20 mL), methanol (20 mL), or 10:1 methanol/acetic acid (22 mL) was treated with either palladium-on-carbon (10 wt %, 100 mg) or platinum-on-carbon (5 wt %, 200 mg). The reaction vessel (see general experimental details) was filled, vented, and refilled with hydrogen three times, and the suspension was stirred under hydrogen at room temperature for 14 h. The catalyst was filtered onto Celite and washed thoroughly with methanol (**7e** and **7f**) or dichloromethane (**7a**−**d**). The filtrate was concentrated in vacuo, and the residue was purified by flash-column chromatography with 9-phenylfluorene as the first product to elute. In cases where the filter cake had been washed with methanol, subsequent washing with dichloromethane provided an additional crop of 9-phenylfluorene hydrocarbon.

(2*S*,6*R*)-*tert*-Butyl 6-(1,1-dimethylethyl)-2-piperidinecarboxylate (8a) was isolated as a colorless oil in 86% yield from **7a**: TLC $R_f = 0.24$ (5% Et_2O in CH_2Cl_2); $[\alpha]^{20}_D$ −19.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 0.93 (s, 9 H), 1.13−1.02 (m, 1 H), 1.22−1.44 (m, 2 H), 1.47 (s, 9 H), 1.65 (m, 1 H), 1.92 (m, 2 H), 2.23 (dd, 1 H, $J = 2.2, 11.3$), 3.17 (dd, 1 H, $J = 2.6, 11.5$); ^{13}C NMR (CD_3OD) δ 25.9, 27.0, 27.1, 28.4, 29.8, 34.3, 61.5, 67.2, 82.1, 173.8; HRMS calcd for $C_{14}H_{28}NO_2$ (MH^+) 242.21201, found 242.21130.

(2*S*,6*R*)-*tert*-Butyl 6-(1-methylethyl)-2-piperidinecarboxylate (8b) was isolated as a colorless oil in 91% yield from **7b**: TLC $R_f = 0.22$ (10% diethyl ether in dichloromethane); $[\alpha]^{20}_D$ −19.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.88 (d, 3H, $J = 6.7$), 0.91 (d, 3H, $J = 6.7$), 1.00 (dtd, 1H, $J = 11.1, 8.8, 4.0$), 1.21−1.39 (m, 2H), 1.42 (s, 9H), 1.58 (sept, 1H, $J = 6.7$), 1.59−1.65 (m, 1H), 1.82−1.99 (m, 3H), 2.19 (ddd, 1H, $J = 11.1, 6.5, 2.5$), 3.15 (dd, 1H, $J = 11.3, 2.8$); ^{13}C NMR δ 18.7, 19.1, 24.7, 28.0, 28.4, 29.3, 33.1, 60.0, 62.3, 80.7, 172.7; HRMS calcd for $C_{13}H_{26}NO_2$ (MH^+): 228.1964, found 228.1957.

(2*S*,6*S*)-*tert*-Butyl 6-propyl-2-piperidinecarboxylate (8c) was isolated as a colorless oil in 90% yield from **7c**: TLC $R_f = 0.20$ (20% diethyl ether in dichloromethane); $[\alpha]^{20}_D$ −13.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR 0.89 (t, 3H, $J = 7.0$), 0.98−1.09 (m, 1H), 1.23−1.44 (m, 6H), 1.45 (s, 9H), 1.61−1.67 (m, 1H), 1.84−1.90 (m, 1H), 1.95−2.00 (m, 1H), 2.51 (dtd, 1H, $J = 11.0, 5.9, 2.6$), 3.22 (dd, 1H, $J = 11.3, 2.9$); ^{13}C NMR δ 14.2, 19.0, 24.6, 28.0, 29.3, 31.9, 39.3, 56.1, 59.7, 80.8, 172.6; HRMS calcd for $C_{13}H_{26}NO_2$ (MH^+) 228.1957, found 228.1964.

(2*S*,6*S*)-*tert*-Butyl 6-methyl-2-piperidinecarboxylate (8d) was isolated as a colorless oil in 86% yield from **7d**: TLC $R_f = 0.28$ (10% diethyl ether in dichloromethane); $[\alpha]^{20}_D$ −7.4 (*c* 1.04, $CHCl_3$); ^{1}H NMR δ 0.94−1.06 (m, 1H), 1.08 (t, 3H, $J = 6.2$), 1.21−1.45 (m, 2H), 1.43 (s, 9H), 1.53−1.59 (m, 1H), 1.78−1.85 (m, 2H), 1.90−1.96 (1H, m), 2.61 (dqd, 1H, $J = 10.9, 5.7, 2.6$), 3.21 (dd, 1H, $J = 11.3, 2.8$); ^{13}C NMR δ 22.7, 24.6, 28.0, 28.9, 33.7, 51.7, 59.7, 80.7, 172.5; HRMS calcd for $C_{11}H_{22}NO_2$ (MH^+) 200.1651, found 200.1644.

(2*S*,6*R*)-*tert*-Butyl 6-phenyl-2-piperidinecarboxylate (8e) was isolated as a white solid: mp = 74−75 °C; TLC $R_f = 0.57$ (20% ethyl acetate in hexanes); $[\alpha]^{20}_D$ −28.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 1.40 (s, 9H), 1.38−1.52 (m, 3H), 1.68−1.74 (m, 1H), 1.89−2.00 (m, 2H), 2.18 (br. s, 1H), 3.31 (dd, 1H, $J = 11.1, 2.7$), 3.57 (dd, 1H, $J = 10.8, 2.3$), 7.19−7.45 (m, 5H); ^{13}C NMR δ 25.1, 28.0, 28.5, 34.2, 60.3, 61.7, 76.7, 126.7, 127.1, 128.3, 144.6, 172.2; HRMS calcd for $C_{16}H_{24}NO_2$ (MH^+) 262.1807, found 262.1813.

(2*S*,6*RS*)-*tert*-Butyl 2-amino-6-hydroxy-6-phenylhexanoate (9) was isolated as a viscous colorless oil containing an inseparable 1:1 mixture of diastereomers (46% from **7e**): TLC $R_f = 0.33$ (10% Et_3N in Et_2O); ^{1}H NMR δ 1.34−1.58 (m, 3H), 1.41 (s, 9H), 1.63−1.81 (m, 3H), 2.15 (br.s, 3H), 3.24−3.29 (m, 1H), 4.62−4.68 (m, 1H), 7.21−7.36 (m, 5H); ^{13}C NMR (second diastereomer in parentheses where resolved) δ 21.7, (21.8), 27.9, 29.6, 34.3, (34.5), 38.7, 54.6, (54.7), 73.9, 81.0, 125.8, 127.3, 128.3, 144.8, (144.9), 175.2; HRMS calcd for $C_{16}H_{26}NO_3$ (MH^+) 280.1913, found 280.1905.

(2*S*,6*RS*)-*tert*-Butyl 6-hydroxy-2-[*N*-(PhF)amino]-6-(2′-pyridyl)hexanoate (10) was isolated as a viscous colorless oil containing an inseparable 1:1 mixture of diastereomers (67% from **7f**): TLC $R_f = 0.37$ (40% EtOAc in hexanes); ^{1}H NMR (second diastereomer in brackets where resolved) δ 1.10 (s, 9H), [1.11 (s, 9H)], 1.25−1.70 (m, 6H), 2.44−2.49 (m, 1H), 4.64−4.70 (m, 1H), 7.15−7.80 (m, 16H), 8.51−8.56 (m, 1H); ^{13}C NMR (second diastereomer in parentheses where resolved) δ 21.0, (21.1), 27.8, 35.6, 38.1, 55.8, 72.4, (72.5), 73.0, 80.3, 175.4; HRMS calcd for $C_{34}H_{37}N_2O_3$ (MH^+) 521.2804, found 521.2795.

(2*S*)-*tert*-Butyl 6-oxo-6-phenyl-2-[*N*-(PhF)amino]hexanoate (12) was isolated as a white solid in 84% yield from **7e**: mp = 91−92 °C; TLC $R_f = 0.44$ (20% EtOAc in hexane); $[\alpha]^{20}_D$ −159.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 1.19 (s, 9H), 1.40−1.57 (m, 2H), 1.76−1.88 (m, 2H), 2.54 (br. s, 1H), 2.71 (ddd, 1H, $J = 17.0, 7.0, 6.6$), 2.79 (ddd, 1H, $J = 17.0, 8.3, 6.7$); ^{13}C

NMR δ 19.9, 27.6, 34.9, 38.0, 55.3, 72.9, 80.4, 175.2, 199.9; HRMS calcd for $C_{35}H_{36}NO_3$ (MH^+) 518.2695, found 518.2686.

(2*S*,6*RS*)-*tert*-Butyl 6-hydroxy-6-phenyl-2-[*N*-(PhF)-amino]hexanoate (11). To a stirred suspension of Raney nickel (ca.. 10 mg of a 50% slurry in water, pore size 50 μm, surface area 80−100 m^2/g, washed three times with ethanol) in ethanol (4 mL) was added a solution of (2*S*,4*E*)-*tert*-butyl 6-oxo-7-phenyl-2-[*N*-(PhF)amino]hept-4-enoate (**7e**, 445 mg, 0.86 mmol) in ethanol (5 mL). The resulting suspension was stirred under 3 atm of hydrogen at room temperature for 14 h. Careful filtration followed by concentration furnished **11** (425 mg, 95%) as a white foam containing an inseparable 1:1 mixture of diastereomers: TLC R_f = 0.18 (10% EtOAc in hexanes): ^{1}H NMR δ 1.15 (s, 9 H), 1.32−2.07 (m, 6 H), 2.46−2.50 (m, 1 H), 3.05 (br. s, 1 H), 4.59−4.65 (m, 1 H), 7.15−7.71 (m, 18 H); ^{13}C NMR (second diastereomer in parentheses where resolved) δ 21.6, (21.7), 27.8, 35.5, 38.7, 55.9, 73.0, 74.3, 80.4, 175.4; HRMS calcd for $C_{35}H_{38}NO_3$ (MH^+) 520.2852, found 520.2834.

General Method for the Deprotection of *tert*-Butyl 6-Alkylpipecolates 8. Dry HCl gas was bubbled through a solution of 6-alkylpipecolate *tert*-butyl ester **8** (0.5 mmol) in dichloromethane (2−3 mL) at 0 °C until complete disappearance of the *tert*-butyl ester singlet was observed by ^{1}H NMR analysis (2−4 h). Removal of the solvent in vacuo furnished pipecolate hydrochlorides **1**·HCl.

(2*S*,6*R*)-6-(1,1-Dimethylethyl)-2-piperidinecarboxylic acid hydrochloride (1a·HCl) was isolated as a white powder in 98% yield from **8a**: mp > 220 °C dec; $[\alpha]^{20}_D$ −25.4 (*c* 0.7, 0.1 N HCl); ^{1}H NMR (CD_3OD) δ 1.08 (s, 9H), 1.44−1.57 (m, 1H), 1.63−1.82 (m, 2H), 1.99−2.06 (m, 2H), 2.28−2.34 (m, 1H), 3.02 (dd, 1H, J = 12.5, 2.5), 3.97 (dd, 1H, J = 12.7, 3.3); ^{13}C NMR (CD_3OD) δ 23.9, 24.7, 26.9, 27.0, 34.5, 60.7, 68.0, 171.2; HRMS calcd for $C_{10}H_{20}NO_2$ (MH^+) 186.1494, found 186.1499.

(2*S*,6*R*)-6-(1-Methylethyl)-2-piperidinecarboxylic acid hydrochloride (1b·HCl) was isolated as a white powder in 100% yield from **8b**: mp > 215 °C dec; $[\alpha]^{20}_D$ −18.8 (*c* 0.6, 0.1 N HCl); ^{1}H NMR (CD_3OD) δ 0.88 (d, 3H, J = 6.7), 0.91 (d, 3H, J = 6.7), 1.00 (dtd, 1H, J = 11.1, 8.8, 4.0), 1.21−1.39 (m, 2H), 1.42 (s, 9H), 1.58 (sept., 1H, J = 6.7), 1.59−1.65 (m, 1H), 1.82−1.99 (m, 3H), 2.19 (ddd, 1H, J = 11.1, 6.5, 2.5), 3.15 (dd, 1H, J = 11.3, 2.8); ^{13}C NMR (CD_3OD) δ 18.0, 19.7, 23.6, 25.5, 27.2, 32.3, 59.6, 64.1, 171.3; HRMS calcd for $C_9H_{18}NO_2$ (MH^+) 172.1338, found 172.1330.

(2*S*,6*S*)-6-Propyl-2-piperidinecarboxylic acid hydrochloride (1c·HCl) was isolated as a white powder in 97% yield from **8c**: mp > 209 °C dec; $[\alpha]^{20}_D$ −13.0 (*c* 1.0, 0.1 N HCl); ^{1}H NMR (CD_3OD) δ 0.99 (t, 3H, J = 7.3), 1.34−1.78 (m, 7H), 1.95−2.07 (m, 2H), 2.30−2.39 (m, 1H), 3.11−3.19 (m, 1H), 3.94 (dd, 1H, J = 12.4, 3.2); ^{13}C NMR (CD_3OD) δ 14.2, 19.6, 23.5, 27.4, 28.8, 36.7, 58.2, 58.9, 171.3; HRMS calcd for $C_9H_{18}NO_2$ (MH^+) 172.1338, found 172.1343.

(2*S*,6*S*)-6-Methyl-2-piperidinecarboxylic acid hydrochloride (1d·HCl) was isolated as a white powder in 98% yield from **8d**: mp > 212 °C dec; $[\alpha]^{20}_D$ −11.7 (*c* 1.1, 0.1 N HCl); ^{1}H NMR (CD_3OD) δ 1.37 (d, 3H, J = 6.6), 1.41−1.50 (m, 1H), 1.58−1.74 (m, 2H), 1.89−1.99 (m, 2H), 2.29−2.36 (m, 1H), 3.22−3.29 (m, 1H), 3.94 (dd, 1H, J = 12.4, 3.3); ^{13}C NMR (CD_3OD) δ 19.4, 23.6, 27.1, 31.1, 54.4, 58.7, 171.3; HRMS calcd for $C_7H_{14}NO_2$ (MH^+) 144.1025, found 144.1020.

(2*S*,6*R*)-6-Phenyl-2-piperidinecarboxylic acid hydrochloride (1e·HCl) was isolated as a white powder in 96% yield from **8e**: mp >230 °C dec; $[\alpha]^{20}_D$ −17.0 (*c* 0.4, 0.1 N HCl); ^{1}H NMR (CD_3OD) δ 1.81−2.14 (m, 5H), 2.38−2.45 (m, 1H), 4.18 (dd, 1H, J = 12.4, 3.4), 4.35 (dd, 1H, J = 11.6, 3.0), 7.41−7.57 (m, 5H); ^{13}C NMR (CD_3OD) δ 24.1, 26.9, 30.9, 59.7, 62.4, 128.6, 130.5, 130.7, 137.9. 171.0; HRMS calcd for $C_{12}H_{16}NO_2$ (MH^+) 206.1181, found 206.1171.

(2*S*,6*S*)-*tert*-Butyl *N*-Benzyl-6-methylpiperidine-2-carboxylate (14). Benzyl bromide (34 μL, 0.29 mmol, 120 mol %) and potassium carbonate (66 mg, 0.48 mmol, 200 mol %) were added to a solution of (2*S*,6*S*)-*tert*-butyl 6-methylpiperidine-2-carboxylate (**8d**, 48 mg, 0.24 mmol) in DMF (0.2 mL). After stirring for 36 h, the suspension was diluted with ethyl acetate (5 mL), washed successively with water (3 × 5 mL) and brine (5 mL), dried, and concentrated in vacuo to give a pale yellow oil (79 mg). Purification by flash-column chromatography (dichloromethane followed by 5% diethyl ether in dichloromethane) furnished (2*S*,6*S*)-*tert*-butyl *N*-benzyl-6-methylpiperidine-2-carboxylate (**14**, 66 mg, 95%) as a colorless oil: TLC R_f = 0.64 (10% diethyl ether in dichloromethane); $[\alpha]^{20}_D$ −24.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.00 (d, 3H, J = 6.3), 1.21−1.36 (m, 1H), 1.38 (s, 9H), 1.49−1.55 (m, 1H), 1.60−1.69 (m, 2H), 1.74−1.81 (m, 1H), 2.36 (dqd, 1H, J = 9.6, 6.2, 2.9), 3.01 (dd, 1H, J = 10.5, 3.3), 3.65 (d, 1H, J = 15.9), 3.84 (d, 1H, J = 15.9), 7.15−7.38 (m, 5H); ^{13}C NMR δ 21.2, 23.0, 27.8, 30.2, 34.1, 56.2, 56.4, 66.5, 80.5, 126.3, 127.7, 128.7, 139.5, 173.5; HRMS calcd for $C_{18}H_{28}NO_2$ (MH^+) 290.2120, found 290.2130.

Enantiomeric Purity of (2*S*,6*S*)-*tert*-Butyl *N*-Benzyl-6-methylpiperidine-2-carboxylate (14). Dry HCl gas was bubbled through a stirred solution of (2*S*,6*S*)-*tert*-butyl *N*-benzyl-6-methylpiperidine-2-carboxylate (**14**, 36 mg) in dichloromethane at 0 °C for 2 h. Evaporation of the volatiles in vacuo gave a white solid from which portions (10 mg, 0.04 mmol) were dissolved in acetonitrile (0.5 mL) and treated with D- or L-phenylalanine methyl ester hydrochloride (11 mg, 0.05 mmol, 120 mol %), TBTU (16 mg, 0.05 mmol, 120 mol %), and diisopropylethylamine (35 μL, 0.20 mmol, 500 mol %) at room temperature. After stirring for 1 h, the yellow solution was diluted with ethyl acetate (5 mL), washed sequentially with water (2 × 5 mL) and brine (5 mL), dried, and concentrated in vacuo to a crude viscous yellow oil which was directly examined by ^{1}H NMR spectroscopy. The limits of detection were determined by measuring the diastereomeric methyl ester singlets at 3.52 and 3.68 ppm in $CDCl_3$ in the 400 MHz ^{1}H NMR spectra. Less than 1% of (2′*S*)-**15** was detected in the spectrum of (2′*R*)-**15**. Purification by chromatography using a gradient of 0−5% diethyl ether in dichloromethane as eluant gave dipeptides having the following spectra.

(2*S*,6*S*)-*N*-Benzyl-6-methylpipecolyl-D-phenylalanine methyl ester ((2′*R*)-15): ^{1}H NMR δ 1.11 (d, 3 H, J = 6.1), 1.15−1.36 (m, 2 H), 1.53−1.67 (m, 4 H), 1.83−1.87 (m, 1 H), 2.36−2.45 (m, 1 H), 2.81 (dd, 1 H, J = 13.9, 7.6), 2.96 (dd, 1 H, J = 13.9, 6.2), 3.01 (dd, 1 H, J = 9.9, 3.7), 3.47 (d, 1 H, J = 15.4), 3.67 (d, 1 H, J = 15.4), 3.68 (s, 3H), 4.78 (td, 1 H, J = 8.0, 6.2), 7.00−7.31 (m, 10 H).

(2*S*,6*S*)-*N*-Benzyl-6-methylpipecolyl-L-phenylalanine methyl ester ((2′*S*)-15): ^{1}H NMR δ 1.05 (d, 3 H, J = 6.1), 1.15−1.39 (m, 3 H), 1.55−1.68 (m, 3 H), 1.83−1.90 (m, 1 H), 2.32−2.41 (m, 1H), 3.01 (dd, 1 H, J = 10.6, 3.4), 3.06 (dd, 1 H, J = 13.9, 6.7), 3.14 (dd, 1 H, J = 13.9, 6.7), 3.52 (s, 3 H), 3.67 (d, 1H, J = 15.5), 3.85 (d, 1 H, J = 15.5), 4.79 (dt, 1 H, J = 8.1, 6.2), 7.11−7.53 (m, 10 H).

Recycle of 9-phenylfluorene to 9-bromo-9-phenylfluorene was accomplished by heating a mixture of 9-phenylfluorene (969 mg, 4.00 mmol) and *N*-bromosuccinimide (711 mg, 4.00 mmol) in CCl_4 (4 mL) at a reflux for 1 h. After cooling, the reaction was concentrated in vacuo, and the residue was successively digested with volumes of hexanes until TLC analysis showed that no UV-active material was contained in the hexanes. Concentration of the combined hexane volumes gave 9-bromo-9-phenylfluorene as a yellow solid (1.23 g, 96%): mp 98−100 °C (lit.[43] mp 99 °C).

***N*-Acetyl *N*′-Methylpipecolinamide (16).** A solution of pipecolic acid (1.0 g, 7.7 mmol) in dioxane (15 mL) and water (8 mL) was treated with NaOH (12 mL, 1 M) followed by di-*tert*-butyl dicarbonate (4.06 g, 18.6 mmol, 240 mol %), stirred for 48 h at room temperature, and evaporated to a 5 mL volume that was diluted with EtOAc (20 mL) and acidified with 5% HCl to pH 2−3. The aqueous layer was saturated with solid NaCl and extracted with EtOAc until TLC of the organic layer showed no ninhydrin-active material. The combined organic layers were washed with brine (5 mL), dried, and evaporated to a solid residue that was dried for 48 h in a drying pistol. *N*-(BOC)-Pipecolic acid (1.62 g, 91%) was obtained as a white powder: mp 125 °C; HRMS calcd for $C_{11}H_{20}NO_4$ (MH^+) 230.1392, found 230.1388.

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A solution of *N*-(BOC)-pipecolic acid (500 mg, 2.18 mmol), TBTU (1.05 g, 3.3 mmol, 150 mol %), and methylamine hydrochloride (295 mg, 4.36 mmol, 200 mol %) in acetonitrile (20 mL) was then treated with DIEA (1.33 mL, 7.6 mmol, 350 mol %), stirred for 24 h at room temperature, and evaporated to a residue that was dissolved in EtOAc (40 mL), washed with 5% HCl (2 × 5 mL), H_2O (5 mL), $NaHCO_3$ (2 × 5 mL, saturated solution), H_2O (2 × 5 mL), and brine (5 mL), dried, and evaporated to give *N*-(BOC)-pipecolate *N*′-methylamide (393 mg, 74%) as a clear crystalline solid: mp = 86−88 °C; ^{1}H NMR (CD_3OD) δ 4.61 (bs, 1 H), 3.94 (m, 1 H), 2.99 (t, 1 H, J = 13), 2.72 (s, 3H), 2.12 (d, 1 H, J = 13), 1.60 (m, 3 H), 1.43 (s, 9 H), 1.48−1.31 (m, 3 H); HRMS calcd for $C_{12}H_{23}N_2O_3$ (MH^+) 243.1709, found 243.1701.

N-(BOC)-Pipecolate *N*′-methylamide (390 mg, 1.6 mmol) was dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C, treated with gaseous HCl bubbles for 5 min, stirred for 1 h at room temperature, and evaporated to a residue that was dissolved in CH_2Cl_2 (8 mL) and treated with Et_3N (444 μL, 3.2 mmol, 200 mol %) and acetic anhydride (302 μL, 3.2 mmol, 200 mol %). The mixture was heated at a reflux overnight and evaporated to dryness. Chromatography of the residue using a gradient of 0−5% MeOH in $CHCl_3$ as eluant gave **16** (128 mg, 65%) as a white crystalline solid: mp = 99−100 °C; ^{1}H NMR (D_2O, *trans*-isomer) δ 1.38−1.46 (m, 1H), 1.51−1.66 (m, 1H), 1.68−1.71 (m, 4H), 2.22 (s, 3H), 2.78 (s, 3H), 3.21 (m, 1H), 3.87 (bd, 1H, J = 14.7), 5.09 (bd, 1H, J = 2.2); (*cis*-isomer) δ 1.38−1.46 (m, 1H), 1.51−1.66 (m, 1H), 1.68−1.71 (m, 4H), 2.13 (s, 3H), 2.18 (bm, 1H), 2.28 (bm, 1H), 2.71 (bm, 1H), 2.81 (s, 3H), 4.30 (bd, 1H, J = 13.7), 4.65 (bd, 1H); ^{13}C NMR (D_2O, *trans*-isomer) δ 20.0, 21.2, 24.6, 26.2, 26.8, 45.1, 53.8, 173.8, 174.6; (*cis*-isomer) δ 20.2, 21.0, 24.3, 26.3, 26.4, 40.4, 58.5, 173.2, 174.4; HRMS calcd for $C_9H_{17}N_2O_2$ (MH^+) 185.1290, found 185.1285.

(2*S*,6*R*)-*N*-Acetyl *N*′-Methyl 6-*tert*-Butylpipecolinamide (17). To a solution of acid **1a** (100 mg, 0.33 mmol), TBTU (159 mg, 0.495 mmol, 150 mol %), and methylamine hydrochloride (44.6 mg, 0.66 mmol, 200 mol %) in acetonitrile (2.3 mL) was added Et_3N (229 μL, 1.65 mmol, 500 mol %). The clear solution was stirred for 24 h at room temperature and then evaporated to a residue that was treated with an ion-exchange resin (3 g, Dowex SBR) in H_2O (20 mL) to remove excess methylamine hydrochloride. The resin was filtered, and the solution was evaporated to dryness. The crude amide product was heated for 1 week in the presence of acetic anhydride (5 mL) and sodium acetate (82 mg, 1 mmol) in toluene (5 mL). Evaporation of the volatiles and chromatography of the residue using a gradient of 0−5% MeOH in $CHCl_3$ as eluant gave **17** (36 mg, 28%) as a viscous oil: ^{1}H NMR (D_2O, *trans*-isomer) δ 0.96 (s, 9 H), 1.23−1.40 (m, 1 H), 1.69−1.84 (m, 2 H), 1.86−2.09 (m, 3 H), 2.33 (s, 3 H), 2.76 (s, 3 H), 4.01 (m, 1H), 5.04 (dd, 1 H, J = 8.4, 8.2); (*cis*-isomer) δ 0.91 (s, 9 H), 1.23−1.40 (m, 1 H), 1.69−1.84 (m, 2 H), 1.86−2.09 (m, 3 H), 2.22 (s, 3 H), 2.79 (s, 3 H), 4.57 (m, 1 H), 4.71 (dd, 1 H, J = 7.6, 7.3); ^{13}C NMR (D_2O, *trans*-isomer,) δ 17.7, 23.8, 24.0, 25.0, 26.2, 27.2, 36.7, 54.9, 61.9, 175.2, 177.9; (*cis*-isomer) δ 17.9, 22.6, 23.5, 25.2, 26.4, 27.1, 36.3, 56.7, 58.1, 174.2, 177.5; HRMS calcd for $C_{13}H_{25}N_2O_2$ (MH^+) 241.1916, found 241.1907.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1a**−**e**, **7b**−**f**, and **8a**−**e**; crystallographic data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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