Rigid Dipeptide Mimetics: Efficient Synthesis of Enantiopure Indolizidinone Amino Acids

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An effective means to synthesize indolizidinone amino acids has been developed and furnishes all possible stereoisomers of these conformationally rigid mimetics of peptide secondary structures. Inexpensive glutamic acid was employed as chiral educt in a Claisen condensation/reductive amination/lactam cyclization sequence that furnished stereoselectively azabicyclo[3.4.0]alkane amino acid **1**. Enantiopure (3*S*,6*S*,9*S*)- and (3*R*,6*R*,9*R*)-2-oxo-3-*N*-(BOC)amino-1-azabicyclo[4.3.0]nonane-9-carboxylic acids ((3*S*,6*S*,9*S*)- and (3*R*,6*R*,9*R*)-**1**) were respectively synthesized from L- and D-*N*-(PhF)glutamates **2** (PhF = 9-(9-phenylfluorenyl)). Slow addition of sodium bis(trimethylsilyl)amide to **2** provided good to excellent yields of *β*-keto esters **3**, which were subsequently hydrolyzed and decarboxylated to give symmetric α,*ω*-bis[*N*-(PhF)amino]azelate *δ*-ketones **5**. Augmentation of hydrogen pressure increased diastereoselectivity in reductive aminations with **5** and afforded 5-alkylprolines **8** and **10**. Lactam formation on exposure of **10** to triethylamine and *N*-protection with di-*tert*-butyl dicarbonate gave methyl 2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate (**12**) which on *C*-terminal ester hydrolysis with hydroxide ion gave enantiopure [*N*-(BOC)amino]indolizidinone acid **1**. Alternatively, hydride addition to ketone **5a** gave symmetric α,*ω*-bis[*N*-(PhF)amino]azelate *δ*-alcohol **7a**, which upon mesylation and intramolecular S_N2 displacement by the PhF amine gave specifically *cis*-5-alkylproline **15** that was similarly converted to (3*S*,6*S*,9*S*)-**1**. In addition, epimerization of the C-9 stereocenter of (3*S*,6*S*,9*S*)-[*N*-(BOC)amino]-indolizidinone methyl ester **12** with $NaN(SiMe_3)_2$ and ester hydrolysis gave (3*S*,6*S*,9*R*)-indolizidinone amino acid (3*S*,6*S*,9*R*)-**1**. By providing efficient methodology for synthesizing all of the possible stereoisomers of enantiopure indolizidinone amino acid **1**, our route is specifically designed to enhance the general use of these peptide mimetics in the exploration of conformation−activity relationships of various biologically active peptides.

Introduction

Azabicyclo[*X*.*Y*.0]alkane amino acids are an important class of dipeptide analogues having restrained backbone and side-chain conformations (Figure 1).[1−17] The growing use of these dipeptide surrogates in the investigation of structure−activity relationships of various biologically active peptides has created a demand for new methodology for synthesizing these peptide mimetics.[1−17] Ideally, approaches for making azabicycloalkane amino acids should overcome three important challenges. First, the fused azacycloalkane heterocycle should be synthesized unambiguously in a predictable manner. Second, chiral centers should be introduced with stereocontrol at the

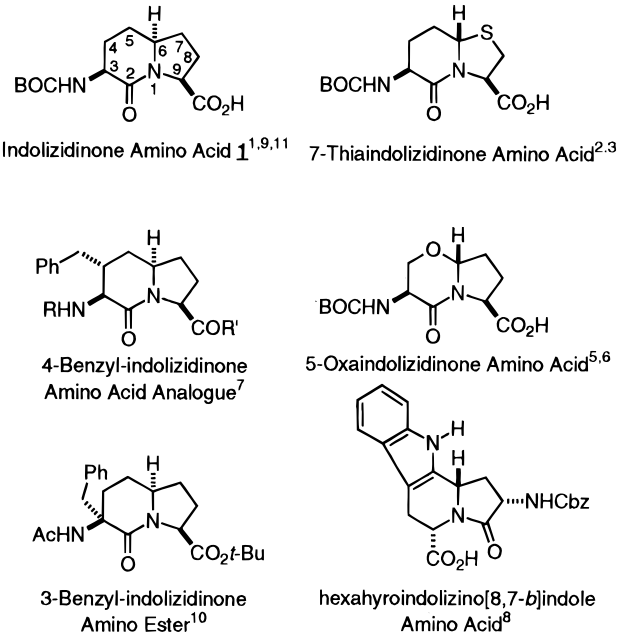

Figure 1. Representative examples of indolizidinone amino acid analogues.

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(1) We have adopted the nomenclature and ring system numbering previously used in refs 3a and 5a in order to maintain clarity and consistency when comparing these different heterocyclic systems.

(2) Synthesis and use of 2-oxo-3-phthalimido-7-thia-1-azabicyclo-[4.3.0]nonane-9-carboxylic acid are described in: (a) Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647. (b) Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577.

(3) The use of 2-oxo-3-amino-7-thia-1-azabicyclo[4.3.0]nonane-9-carboxylic acid in peptide analogues includes: gramicidin *S*-analogues: (a) Sato, K.; Nagai, U. *J. Chem. Soc., Perkin Trans. I* **1986**, 1231. (b) Bach, A. C., II; Markwalder, J. A.; Ripka, W. C. *Int. J. Pept. Protein Res.* **1991**, *38*, 314. Growth hormone-releasing factor analogues: (c) Sato, K.; Hotta, M.; Dong, M.-H.; Hu, H.-Y.; Taulene, J. P.; Goodman, M.; Nagai, U.; Ling, N. *Int. J. Pept. Protein Res.* **1991**, *38*, 340. Cyclosporin A analogues: (d) Belshaw, P. J.; Meyer, S. D.; Johnson, D. D.; Romo, D.; Ikeda, Y.; Andrus, M.; Alberg, D. G.; Schultz, L. W.; Clardy, J.; Schreiber, S. L. *Synlett* **1994**, 381. Tendamistat mimetic: (e) Etzkorn, F. A.; Guo, T.; Lipton, M. A.; Goldberg, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1994**, *116*, 10412. Cyclic RGD peptides: (f) Haubner, R.; Schmitt, W.; Hölzemann, G.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7881. Additional examples, such as enkephalin, LRF, GRF, dermorphin, and somatostatin, are reviewed in ref 2b.

(4) (a) Synthesis of 2-oxo-3-amino-8,8-dimethyl-7-thia-1-azabicyclo-[4.3.0]nonane-9-carboxylic acid is described in: Nagai, U.; Kato, R.; Sato, K.; Ling, N.; Matsuzaki, T.; Tomotake, Y. In *Peptides: Chemistry and Biology, Proceedings of the Tenth American Peptide Symposium;* Marshall, G. R., Ed.; ESCOM: Leiden, 1988; pp 129−130. (b) Synthesis of 2-oxo-3-amino-8-phenyl-7-thia-1-azabicyclo[4.3.0]nonane-9-carboxylic acid is described in: Nagai, U.; Kato, R. *Peptides: Chemistry and Structural Biology, Proceedings of the Eleventh American Peptide Symposium*; Rivier, J. E.; Marshall, G. R., Eds.; ESCOM: Leiden, 1989; pp 653−654.

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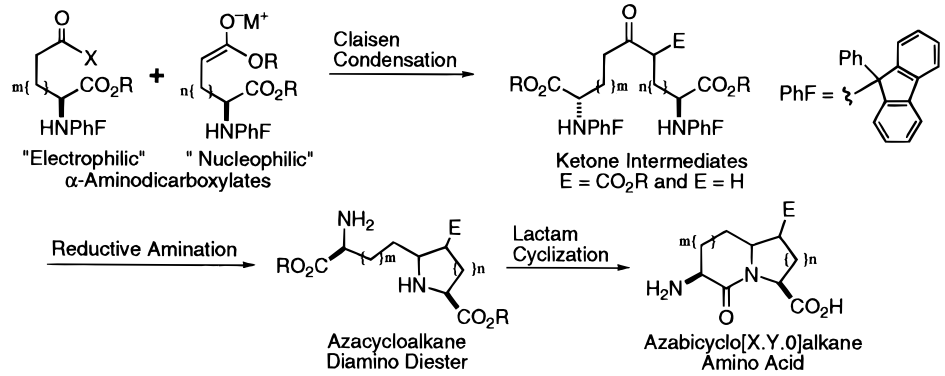
Scheme 1. General Approach for Synthesizing Azabicyclo[*X.Y.*0]alkane Amino Acids



α- and bridge-head carbons. Finally, the appendage of side chains onto the heterocycle is desired in order to synthesize analogues that mimic both peptide backbone and side-chain geometries.[4,7,8,10]

By targeting initially on the synthesis of azabicyclo-[3.4.0]alkane amino acids, we are developing a general approach in order to meet this criterion. Our method utilizes configurationally stable *N*-(9-(9-phenylfluorenyl))-amino dicarboxylates in a Claisen condensation/reductive amination/lactam cyclization sequence in order to furnish stereoselectively azabicycloalkane amino acids (Scheme 1, PhF = 9-(9-phenylfluorenyl)).[11] Employment of different amino dicarboxylates, such as glutamate, aspartate, and longer amino dicarboxylates, in this scheme is designed to provide a variety of heterocyclic ring sizes. In theory, side chains may be added to the heterocycle via alkylations and additions on the *N*-(PhF)amino ketone intermediates.[18] By employing inexpensive glutamic acid as chiral educt in this approach, we have developed an efficient synthesis of enantiopure indolizidinone amino acid **1** that gives access to all of the possible stereoisomers of these interesting dipeptide mimetics.

Indolizidinone amino acid **1** was selected as our first target because azabicyclo[3.4.0]alkane amino acids have been well studied in peptide structures, and because their different configurational isomers have been used to illustrate the importance of particular conformations for peptide bioactivity. For example, a thiaindolizidinone amino acid with 3*S*,6*R*,9*R*-stereochemistry was recently used to stabilize the active conformation in a potent analogue of cyclosporin A.[3d] Indolizidinone amino acids with 3*S*,6*R*,9*S*-stereochemistry have also been shown to adopt both type II′ β-turn and γ-turn conformations in mimetics of different biologically active peptides.[3a,b,e] The all-carbon indolizidinone system was selected for synthesis,[7−12] instead of thia and oxaanalogues,[2−6] because of three reasons. First, the methylene protons add increased rigidity to the indolizidinone by creating additional gauche interactions. Side-chain functional groups may be appended at the ring carbons. Finally, analogues possessing saturated thiazo and oxazo ring systems are inherently more prone to degradation via processes that may hydrolyze the masked aldehyde during metabolism in vivo as well as during peptide synthesis.

We now provide full details of our method for synthesizing indolizidinone amino acid **1**.[11] Several observations have led to improvements in overall yield and efficiency. For example, a relationship between hydrogen pressure and diastereoselectivity in the reductive amination step was observed and employed to control the bridge-head carbon stereochemistry. A new route featuring the activation and intramolecular displacement of a symmetric alcohol has been explored to stereospecifically synthesize (3*S*,6*S*,9*S*)-**1**. Regioselective enolization of indolizidinone amino ester now gives access to epimers at C-9. Moreover, the number of steps to synthesize **1** has been reduced via the employment of dimethyl *N*-(PhF)glutamate (**2b**) in the Claisen condensation/reductive amination/lactam cyclization sequence. Because indolizidinone amino acid **1** is suitable for incorporation into peptides using standard techniques,[12] our route is specifically designed to enhance the general use of these

(5) Syntheses of 2-oxo-5-oxa-3-amino-1-azabicyclo[4.3.0]nonane-9-carboxylic acids are reported in: (a) Baldwin, J. E.; Hulme, C.; Schofield, C. J.; Edwards, A. J. *J. Chem. Soc., Chem. Commun.* **1993**, 935. (b) Slomczynska, U.; Chalmers, D. K.; Cornille, F.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Org. Chem.* **1996**, *61*, 1198.

(6) Synthesis and analysis of Leu-enkephalin analogues containing 2-oxo-5-oxa-3-amino-1-azabicyclo[4.3.0]nonane-9-carboxylic acid are reported in: Claridge, T. D. W.; Hulme, C.; Kelly, R. J.; Lee, V.; Nash, I. A.; Schofield, C. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 485.

(7) The synthesis of a 2-oxo-3-amino-4-benzyl-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid analogue that serves as a model antagonist of the tachykinin NK-2 receptor is reported in: Hanessian, S.; Ronan, B.; Laoui, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1397.

(8) The synthesis of 2(*S*)-amino-3-oxo-11b(*R*)-hexahydroindolizino-[8,7-*b*]indole-5(*S*)-carboxylate is reported in: (a) de la Figuera, N.; Rozas, I.; García-López, M. T.; González-Muñiz, R. *J. Chem. Soc., Chem. Commun.* **1994**, 613. (b) de la Figuera, N.; Alkorta, I.; Rozas, I.; García-López, M. T.; Herranz, R.; González-Muñiz, R. *Tetrahedron* **1995**, *51*, 7841.

(9) An alternative strategy to prepare 2-oxo-3-amino-1-azabicyclo-[4.3.0]nonane-9-carboxylic acid is reported in: Mueller, R.; Revesz, L. *Tetrahedron Lett.* **1994**, *35*, 4091.

(10) The synthesis of a 2-oxo-3-amino-3-benzyl-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid analogue is reported in: Colombo, L.; Di Giacomo, M.; Scolastico, C.; Manzoni, L.; Belvisi, L.; Molteni, V. *Tetrahedron Lett.* **1995**, *36*, 625.

(11) Preliminary results were reported in part: (a) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147. (b) Lombart, H.-G.; Lubell, W. D. In *Peptides 1994 (Proceedings of the 23rd European Peptide Symposium)*; Maia, H. L. S., Ed.; ESCOM: Leiden 1995; p 696.

(12) Lombart, H.-G.; Lubell, W. D. In *Peptides: Chemistry, Structure and Biology*; Kaumaya, P. T. P, Hodges, R. S., Eds.; ESCOM Sci. Pub. B. V.: Leiden, 1996; p 695.

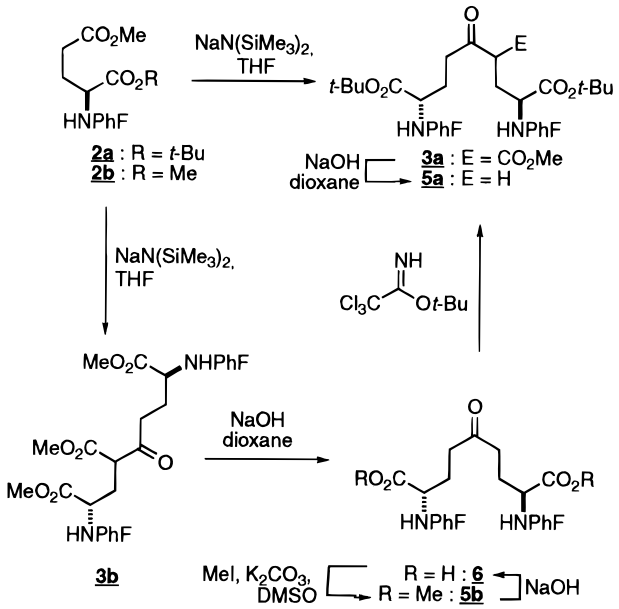
(13) Synthesis of 5-amino-9-oxo-1-azabicyclo[4.3.0]nonane-8-carboxylic acid analogues are described in: Dominguez, M. J.; García-López, M. T.; Herranz, R.; Martin-Martinez, M.; González-Muñiz, R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2839 and references therein.

(14) Synthesis and use of 2-oxo-3-amino-1-azabicyclo[4.3.0]nonane-6-carboxylic acid analogues as type VI β-turn peptide mimetics are described in: (a) Dumas, J.-P.; Germanas, J. P. *Tetrahedron Lett.* **1994**, *35*, 1493. (b) Gramberg, D.; Robinson, J. A. *Tetrahedron Lett.* **1994**, *35*, 861. (c) Kim, K.; Dumas, J.-P.; Germanas, J. P. *J. Org. Chem.* **1996**, *61*, 3138. (d) Gramberg, D.; Weber, C.; Beeli, R.; Inglis, J.; Bruns, C.; Robinson, J. A. *Helv. Chim. Acta* **1995**, *78*, 1588.

(15) 1,4-Diazabicyclo[4.3.0]nonane-9-carboxylic acid analogues are described in: Fobian, Y. M.; d'Avignon, D. A.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 315.

(16) [4.3.0]Pyrazolidinones 2-carboxylic acid analogues have been synthesized as potential antibacterial agents: Ternansky, R. J.; Draheim, S. E. *Tetrahedron Lett.* **1988**, *29*, 6569.

Scheme 2. Synthesis of 5-Oxo-2,8-bis[*N*-(PhF)amino]azelates 5 via Claisen Condensations of *N*-(PhF)Glutamates 2

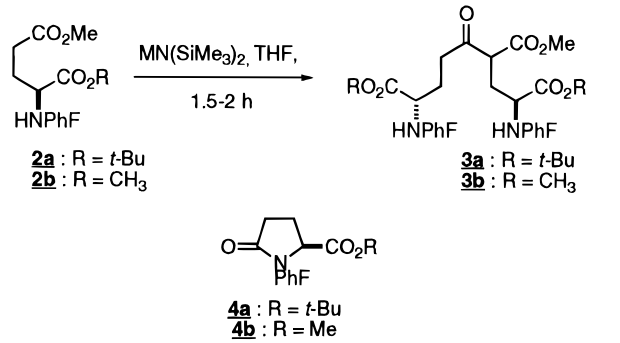


peptide mimetics in the exploration of conformation–activity relationships of various biologically active peptides.

Results and Discussion

Synthesis of α,ω-Diamino Dicarboxylate via Claisen Condensation of *N*-(PhF)Glutamates. The Claisen condensation of *N*-(PhF)amino dicarboxylates is an effective means for preparing functionalized α,ω-diamino dicarboxylates (Scheme 2). For example, slow addition of sodium bis(trimethylsilyl)amide (1 M in THF) to a solution of (2*S*)-α-*tert*-butyl γ-methyl *N*-(PhF)glutamate ((2*S*)-**2a**) in THF at −30 °C provided (2*S*,4*RS*,8*S*)-di-*tert*-butyl 4-carbomethoxy-5-oxo-2,8-bis[*N*-(PhF)amino]azelate ((2*S*,4*RS*,8*S*)-**3a**) in 80% yield (Table 1, entry d). Like the alkylation,[19] acylation,[20] aldol,[21] and Dieckmann[22] reactions of amino dicarboxylates, this Claisen condensation proceeds via regioselective enolization of the ω-ester. Sodium enolates generated with $NaN(SiMe_3)_2$ as base gave the best yields of β-keto ester **3**. Lithium enolates were less reactive, and potassium enolates gave no condensation products at all in reactions using bis(trimethylsilyl)amide bases. Although potassium enolates react well under alkylation conditions,[19] we have yet to acylate the potassium enolate of *N*-(PhF)glutamate **2a**.[20a] Attempts were also unsuccessful to effect Claisen condensation with methoxide in methanol. The Claisen condensation was usually complete after 2 h. Since enolization of the condensation product depletes base, and since excess base consumes electrophile, the stoichiometry and the rate of addition of $NaN(SiMe_3)_2$ to **2a** were both important for obtaining good yields of β-keto ester **3** (Table 1, entries b, f, and g).

Table 1. Claisen Condensation of *N*-(PhF)Glutamates[a]



entry	R	$MN(SiMe_3)_2$ (mol %)	temp (°C)	[**2**]	% **3**	% rcvd **2**	% **4**
a	*t*-Bu	Li (110)	−78	0.3	52	45	2
b	*t*-Bu	Na (110)	−78	0.5	69	27	2
c	*t*-Bu	K (110)	−78	0.3		100	
d	*t*-Bu	Na (110)	−30	0.5	80	2	10
e	*t*-Bu	Na (110)	−20	0.5	77		15
f	*t*-Bu	Na (50)	−78	0.3	24	69	6
g	*t*-Bu	Na (220)	−78	0.7	52	42	6
h	*t*-Bu	Na (110)	−30	0.1	75		25
i	*t*-Bu	Na (110)	−30	1.0	69	5	25
j	Me	Na (110)	−50	0.45	65	13	22

[a] Isolated yields.

Dimethyl *N*-(PhF)glutamate (**2b**) was employed next in the Claisen condensation using conditions optimized with α-*tert*-butyl γ-methyl *N*-(PhF)glutamate (**2a**) at −50 °C (Table 1, entry j). Synthesis of **2b** proceeded in excellent yield by esterification of glutamate in methanolic HCl followed by phenylfluorenation.[23] Because the kinetic γ-esterification as well as the α-*tert*-butyl esteri-

(17) Recent representative examples of other azabicyclo[*X*.*Y*.0]-alkane amino acid derivatives include the following: (a) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914. (b) Flynn, G. A.; Beight, D. W.; Mehdi, S.; Koehl, J. R.; Giroux, E. L.; French, J. F.; Hake, P. W.; Dage, R. C. *J. Med. Chem.* **1993**, *36*, 2420. (c) Attwood, M. R.; Hassall, C. H.; Kröhn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc., Perkin Trans. I* **1986**, 1011. (d) Thomas, W. A.; Whitcombe, I. W. A. *J. Chem. Soc., Perkin Trans. II* **1986**, 747. (e) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393. (f) Thorsett, E. D. *Actual. Chim. Thér.* **1986**, *13*, 257. (g) Cornille, F.; Slomczynska, U.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 909.

(18) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447. (b) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511. (c) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *60*, 202. (b) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658.

(19) (a) Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467. (b) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068. (c) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164. (d) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859. (e) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239.

(20) (a) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438. (b) Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 3184. (c) Zee-Cheng, R. K.-Y.; Olson, R. E. *Biochem. Biophys. Res. Commun.* **1980**, *94*, 1128.

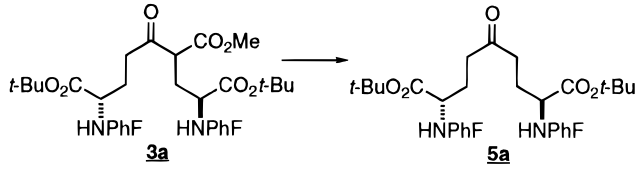
(21) (a) Baldwin, J. E.; North, M.; Flinn, A.; Moloney, M. G. *Tetrahedron* **1989**, *45*, 1453. (b) Baldwin, J. E.; North, M.; Flinn, A.; Moloney, M. G. *Tetrahedron* **1989**, *45*, 1465.

(22) Bergmeier, S. C.; Cobás, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.

(23) Dimethyl *N*-(PhF)glutamate was prepared according to the procedure described for dimethyl *N*-(PhF)aspartate: (a) Jamison, T. F.; Rapoport, H. *Org. Synth.* **1992**, *71*, 226. (b) Paz, M. M.; Sardina, J. *J. Org. Chem.* **1993**, *58*, 6990. γ-Methyl *N*-(PhF)glutamate was prepared by esterification according to: (c) Hanby, W. E.; Waley, S. G.; Watson, J. *J. Chem. Soc.* **1950**, 3239. Phenylfluorenation was according to refs 19d and 23a.

(24) Three different *tert*-butyl esterification methods were examined in order to synthesize α-*tert*-butyl γ-methyl *N*-(PhF)glutamate (**2a**). γ-Methyl *N*-(PhF)glutamate was initially prepared by reaction of *O*-*tert*-butyl *N*,*N*′-diisopropylisourea and γ-methyl *N*-(PhF)glutamate in 75% yield as described in ref 19d. Comparable yields were obtained, and **2a** was conveniently purified when the acid was treated with 400 mol % of *N*,*N*-dimethylformamide di-*tert*-butyl acetal in benzene according to the general procedure described in: (a) Widmer, U. *Synthesis* **1983**, 135. In our hands, the most efficient and least expensive method to prepare **2a** employed *O*-*tert*-butyl trichloroacetimidate as described in the Experimental Section. This procedure was modified from the methods described in: (b) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483. (c) Yue, C.; Thierry, J.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 323. (d) Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

Table 2. Hydrolysis and Decarboxylation of Ester 3a[a]



entry	conditions	temp (°C)	solvent	*n* (mol %)	% **5a**	% **4a**
a	NaOH (2 N)	66	THF	2000	52	12
b	NaOH (2 N)	25	THF	1000	68	*e*
c	LiOH (2 N)	25	THF	2000	58	9
d	LiOH (2 N)	25	THF	1000	67	4
e	LiOH (2 N)	66	THF	1000	70	12
f	LiOH (2 N)	66	THF	500	77	5
g	LiOH (2 N)	66	THF	300	74	20
h	NaOH (2 N)	25[b]	dioxane	500	99	
i	NaOH (2 N)	101	dioxane	500	99	
j	$KO(SiMe_3)_2$	25	Et_2O	150	*c*	
k	DMSO−H_2O	160	DMSO		*d*	

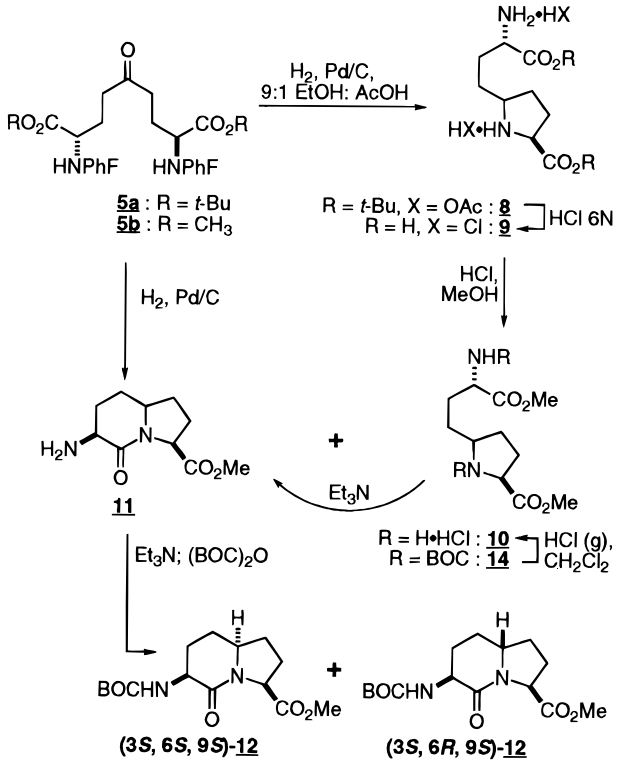
[a] Isolated yields. [b] Reaction time was 24 h. [c] **3a** was recovered unchanged. [d] **3a** decomposed. [e] **4a** was not isolated.

fication steps are avoided, the preparation of **2b** is simpler and higher yielding than that for **2a** (**2a** = three steps, 44% yield; **2b** = two steps, 88% yield).[23,24] With the conditions optimized on **2a**, the Claisen condensation of dimethyl ester **2b** gave lower yields than the reaction with **2a**; however, multigram quantities of β-keto ester **3b** could be obtained in 60% yield after chromatography.

N-(PhF)pyroglutamate **4** was isolated from the Claisen condensation reaction mixtures. Pyroglutamate formation was favored at higher temperatures. For example, the condensation of dimethyl ester **2b** at 0 °C gave *N*-(PhF)pyroglutamate methyl ester (**4b**) as the major product. Glutamate **2** was destroyed when the Claisen condensation was run at room temperature leaving behind considerable amounts of base-line material on TLC. Pyroglutamate **4** most likely arises from decomposition of the enolate with loss of methoxide to form a ketene intermediate that undergoes intramolecular cyclization onto the phenylfluorenyl nitrogen. The steric bulk of the α-*tert*-butyl ester seems to retard the formation of *N*-(PhF)pyroglutamate **4a**, which was a minor component of the product from the condensation of α-*tert*-butyl γ-methyl *N*-(PhF)glutamate (**2a**).

(2*S*,8*S*)-Di-*tert*-butyl 5-oxo-2,8-bis[*N*-(PhF)amino]azelate ((2*S*,8*S*)-**5a**) was synthesized via hydrolysis and decarboxylation of β-keto ester **3a** (Table 2). When the hydrolysis was conducted in refluxing THF, pyroglutamate **4a** was again isolated. Its formation may result from a retro-Claisen reaction and subsequent cyclization via the mechanism described above. β-Keto ester **3a** remained unchanged after treatment with potassium trimethylsilanolate in ether for 24 h[25] and decomposed on heating in wet DMSO at 160 °C.[26] The best conditions for decarboxylation of β-keto ester **3a** employed 2 N NaOH in dioxane and afforded quantitatively azelate **5a**. In addition, we found that isolation of β-keto ester **3a** was unnecessary, and glutamate (2*S*)-**2a** could be converted to symmetric azelate (2*S*,8*S*)-**5a** in 75% overall yield after Claisen condensation, hydrolysis, decarboxylation, and chromatography. (2*R*,8*R*)-Di-*tert*-butyl diaminoazelate (2*R*,8*R*)-**5a** was prepared in similar

Scheme 3. Synthesis of [*N*-(BOC)amino]indolizidinone Methyl Ester 12 via Reductive Amination with Azelate 5



yield by employing D-glutamate in the sequence described above (Scheme 2).

(2*S*,8*S*)-Dimethyl 5-oxo-2,8-bis[*N*-(PhF)amino]azelate ((2*S*,8*S*)-**5b**; Scheme 2) was obtained in 81% overall yield after chromatography via hydrolysis and decarboxylation of β-keto ester **3b** followed by esterification of 2,8-diaminoazelaic acid **6** with iodomethane and potassium carbonate in dimethyl sulfoxide. Hydrolysis of dimethyl azelate **5b** with NaOH in DMSO regenerated 2,8-diamino azelaic acid **6** in 95% yield after precipitation and recrystallization. Treatment of azelaic acid **6** with *tert*-butyl trichloroacetimidate in dichloromethane:cyclohexane provided an alternative means to synthesize di-*tert*-butyl diaminoazelate **5a** which was furnished in 76% yield.[24b−d]

A streamlined process gave 2,8-diaminoazelate dimethyl ester **5b** in 51% overall yield from dimethyl *N*-(PhF)glutamate (**2b**) via a sequence in which β-keto ester **3b** and 2,8-diaminoazelaic acid **6** were not isolated (Scheme 3). The added advantage was the ability to recoup 39% of starting dimethyl *N*-(PhF)glutamate (**2b**) as the other product isolated from chromatography of **5b**. Evidently, pyroglutamate **4b** was hydrolyzed to *N*-(PhF)-glutamate during the decarboxylation of **3b** with NaOH in dioxane. Subsequent esterification of *N*-(PhF)glutamate provided **2b** for reuse in the Claisen condensation. Accounting for the recovery of starting **2b**, the overall yield of (2*S*,2*R*)-**5b** from L-glutamic acid was 72%.

Synthesis of Indolizidinone Amino Acid 1. Indolizidinone amino acid **1** was synthesized from diaminoazelate **5** via two different routes: one featuring reductive amination of symmetric δ-amino ketone **5** (Schemes 3), the other involving hydride reduction of **5** followed by activation and intramolecular displacement of symmetric δ-amino alcohol **7** (Scheme 5). In the reductive amination sequence, hydrogenation of diami-

(25) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
(26) (a) Krapcho, A. P. *Synthesis* **1982**, 805. (b) Krapcho, A. P. *Synthesis* **1982**, 893.

Scheme 4. Synthesis of 12 via Reductive Amination of 5a

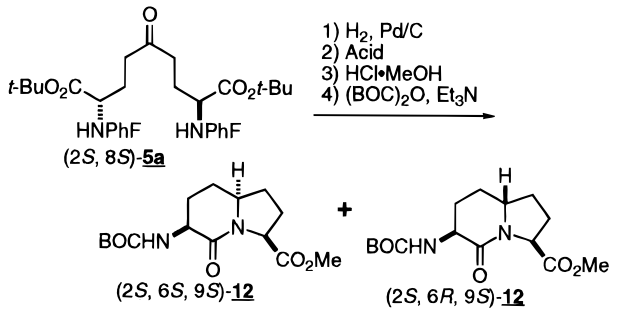


Table 3. Influence of H_2 Pressure on Reductive Amination of 5a[a]

entry	H2 P (atm)	acid	% (6*S*)-**12**	% (6*R*)-**12**	dr
a	1	TFA	41	22	65:35
b	6	TFA	52	10	84:16
c	11	TFA	54	6	90:10
d	1	6 N HCl	45	22	67:33
e	6	6 N HCl	64	8	89:11
f	11	6 N HCl	66	3	96:4

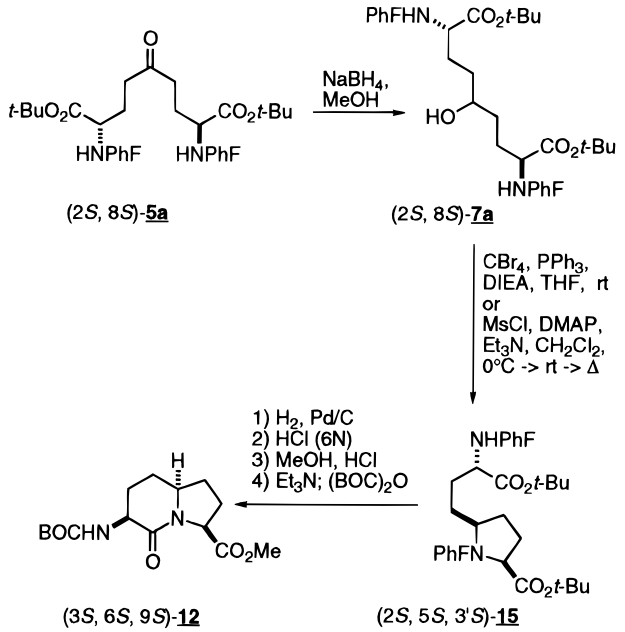
[a] Isolated yields.

noazelate **5a** with palladium-on-carbon as catalyst in 9:1 EtOH:AcOH proceeded by cleavage of the phenylfluorenyl groups, intramolecular imine formation, protonation, and hydrogen addition to the iminium ion intermediate. Because of symmetry, either amine of azelate **5** can condense with the δ-ketone in order to furnish the same 5-alkylproline *tert*-butyl ester **8**. Diamino diester **8** was not isolated at this time; instead, the *tert*-butyl esters were removed by acid solvolysis with either TFA or 6 N HCl to furnish diamino acid **9**. Methyl 2-oxo-3-[*N*-(BOC)-amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate (**12**) was then obtained in 60−70% overall yields from **5a** after esterification of **9** with methanolic HCl, lactam cyclization, *N*-acylation of ester **11** with di-*tert*-butyl dicarbonate and Et_3N in CH_2Cl_2, and chromatography (Scheme 4).

A study of the influence of hydrogen pressure on the diastereoselectivity of the reductive amination was performed by measuring the ratio of (2*S*,6*S*,9*S*)- and (2*S*,6*R*,9*S*)-[*N*-(BOC)amino]indolizidinone methyl esters **12** after their isolation from the reaction sequence described above (Table 3). We used this indirect method for ascertaining the diastereoselectivity of hydrogenation because 5-alkylprolines **8** and **9** were inseparable by chromatography and because their NMR spectra lacked distinguishable diastereomeric signals. [*N*-(BOC)amino]-indolizidinone methyl esters **12** were conveniently separated by chromatography with 1:1 EtOAc:hexanes as eluant. Increased hydrogen pressure was found to augment the diastereoselectivity in the reductive amination step with (2*S*,8*S*)-**5a** such that the ratio of (6*S*)-**12** to (6*R*)-**12** rose from 2:1 up to 24:1 as H_2 pressure was increased from 1 to 11 atm. In addition, we observed that [*N*-(BOC)amino]indolizidinone methyl esters **12** were obtained in higher yields when 6 N HCl was used to deprotect **8** instead of TFA (Table 3). Employment of (2*R*,8*R*)-**5a** in this reaction sequence gave similar yields and diastereomeric ratios of (3*R*,6*R*,9*R*)- and (3*R*,6*S*,9*R*)-[*N*-(BOC)amino]indolizidinone methyl esters **12**.

Methyl 5-[3′-[*N*-(BOC)amino]-3′-[(methyloxy)carbonyl]-propyl]-*N*-(BOC)prolinate (**14**) was isolated in varying yields from the reaction sequence to synthesize **12**. The formation of **14** is due to incomplete lactam formation and subsequent *N*-acylation of the secondary amine with

Scheme 5. Synthesis of [*N*-(BOC)amino]indolizidinone Methyl Ester 12 via Alcohol 7a

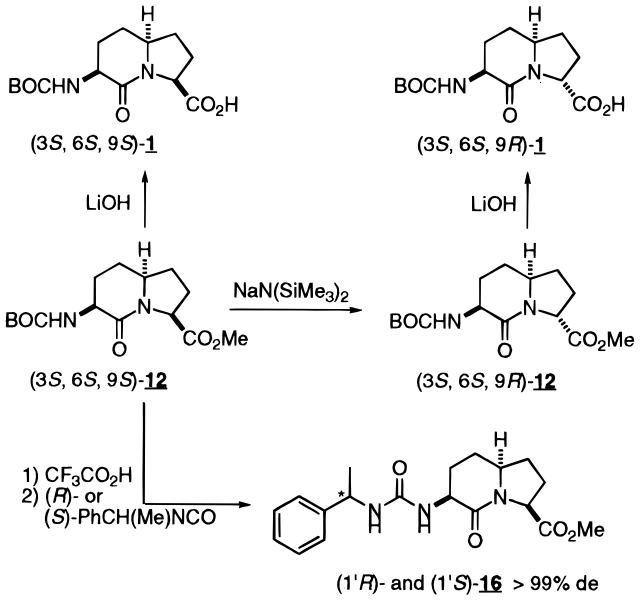


di-*tert*-butyl dicarbonate. In order to recycle **14** into [*N*-(BOC)amino]indolizidinone methyl ester **12**, the BOC groups were first removed with HCl gas in CH_2Cl_2 to provide 5-alkylproline **10** as the hydrochloride salt. Triethylamine in CH_2Cl_2 at room temperature was then used to liberate the amine and convert **10** into lactam **11** (Scheme 3). Conversion was monitored by proton NMR on examination of the disappearance of the methyl ester singlets for **10** (3.87 and 3.89 ppm) and the augmentation of the methyl ester singlet for **11** (3.73 ppm). By following lactam cyclization with ^1H NMR, we could time the addition of di-*tert*-butyl dicarbonate to the reaction mixture in order to avoid formation of **14** and thereby enhance the overall yield of [*N*-(BOC)amino]-indolizidinone methyl esters **12**.

(2*S*,8*S*)-2,8-Diaminoazelate dimethyl ester **5b** was next transformed into [*N*-(BOC)amino]indolizidinone methyl ester **12** using the experience gained with azelate **5a**. Treatment of (2*S*,8*S*)-**5b** with palladium-on-carbon under 6 atm of H_2 in 10:1 EtOH:AcOH furnished primarily indolizidinone **11** with some 5-alkylproline **10** after removal of the catalyst by filtration and evaporation of solvent. Without further purification, the mixture was first exposed to Et_3N in CH_2Cl_2 for 3 h at room temperature and then *N*-acylated with di-*tert*-butyl dicarbonate. Purification by chromatography provided respectively (2*S*,6*S*,9*S*)- and (2*S*,6*R*,9*S*)-[*N*-(BOC)amino]indolizidinone methyl esters **12** in 81% and 2% overall yields (Scheme 3).

An alternative method to prepare indolizidinone amino ester **12** was studied that featured activation and intramolecular displacement of symmetric alcohol **7**. The intramolecular S_N2 displacement was specifically examined with (2*S*,8*S*)-di-*tert*-butyl 5-hydroxy-2,8-bis[*N*-(PhF)-amino]azelate ((2*S*,8*S*)-**7a**) which was synthesized in 89% yield from reduction of diamino ketone **5a** with $NaBH_4$ in MeOH. Treatment of **7a** with carbon tetrabromide, triphenylphosphine, and diisopropylethylamine in THF at 25 °C for 1 h provided stereospecifically (2*S*,5*S*,3′*S*)-*tert*-butyl 5-[3′-[*N*-(PhF)amino]-3′-[(methyloxy)carbonyl]-propyl]-*N*-(PhF)prolinate ((2*S*,5*S*,3′*S*)-**15**) in 86% yield.[19d]

Scheme 6. Synthesis and Enantiomeric Purity of Indolizidinone Amino Acid 1



Stereospecific formation of *cis*-5-alkylproline (2*S*,5*S*,3′*S*)-**15** was also achieved in quantitative yield by mesylation of **7a** with methanesulfonyl chloride, Et_3N, and DMAP in CH_2Cl_2 at 0 °C followed by heating at reflux. Since the steric effects of the nitrogen- and carboxylate-protecting groups may alter the relative energies of the diastereomeric transition states for intramolecular S_N2 displacement, we are presently examining other derivatives of **7** in order to prepare *trans*-5-alkylproline (2*S*,5*R*,3′*S*)-**15**. *N*-PhF-5-alkylproline (2*S*,5*S*,3′*S*)-**15** was transformed into [*N*-(BOC)amino]indolizidinone methyl ester **12** by hydrogenolysis of the PhF groups with palladium-on-carbon as catalyst to give **8**, which was converted to **12** as previously described.

[*N*-(BOC)amino]indolizidinone acid **1** was synthesized via hydrolysis of ester **12** (Scheme 6). Epimerization of the C-9 center competed with ester hydrolysis and afforded mixtures of 9*S*- and 9*R*-diastereomers **12** that were separated by chromatography on silica gel using AcOH in EtOAc as eluant.[27] By controlling the stoichiometry of hydroxide ion in the hydrolysis of (3*S*,6*S*,9*S*)-**12**, the amount of epimerization was significantly reduced and (3*S*,6*S*,9*S*)-**1** was furnished in >90% yields (Table 4). Furthermore, hydrolysis of (3*R*,6*R*,9*R*)- and (3*S*,6*R*,9*S*)-[*N*-(BOC)amino]indolizidinone methyl esters **12** with LiOH furnished respectively (3*R*,6*R*,9*R*)- and (3*S*,6*R*,9*S*)-**1** in similar yields. Alternatively, enolization of ester (3*S*,6*S*,9*S*)-**12** with $NaN(SiMe_3)_2$ in THF provided a 10:1 mixture of (3*S*,6*S*,9*R*)- and (3*S*,6*S*,9*S*)-**12** in 92% yield. (3*S*,6*S*,9*R*)-Methyl 2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*R*)-**12**) was then hydrolyzed quantitatively with LiOH in dioxane to afford (3*S*,6*S*,9*R*)-[*N*-(BOC)amino]indolizidinone acid ((3*S*,6*S*,9*R*)-**1**.

Assignment of Stereochemistry and Enantiomeric Purity of Indolizidinone Amino Acid 1. The bridge-head stereochemistry of [*N*-(BOC)amino]indolizidinone acid **1** was originally assigned based on analogy with our previous work in which the reductive amination of δ-keto α-amino ester with hydrogen and palladium-on-carbon as catalyst gave predominantly 5-alkylprolines with *cis*-stereochemistry.[20a] Configurational assignments were supported by NMR experiments in which the nuclear Overhauser effects were measured when the signals of the C-3, C-6, and C-9 protons were irradiated in methyl 2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]-nonane-9-carboxylates **12**.[11a] For example, irradiation of the bridge-head proton (C-6, $\delta = 3.7$) of (3*S*,6*S*,9*S*)-**12** produced significant nuclear Overhauser effects at the C-3 ($\delta = 4.15$) and C-9 ($\delta = 4.5$) protons. On the other hand, irradiation of the C-6 ($\delta = 3.64$) proton of (3*S*,6*S*,9*R*)-**12** produced a significant nuclear Overhauser effect only at the C-3 ($\delta = 3.93$) proton. Crystallization of (3*S*,6*S*,9*S*)-methyl 2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo-[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*S*)-**12**) from methanol and X-ray crystallographic analysis confirmed the NMR assignments (Figure 2).[28]

Table 4. Synthesis of 1 via Hydrolysis of Methyl Ester 12[a]

entry	12	base	mol %	solvent	% yield[b] (9*S*)-**1**	% yield[b] (9*R*)-**1**
a	(3*S*,6*S*,9*S*)	LiOH (2 N)	1000	THF	52	29
b	(3*S*,6*S*,9*S*)	LiOH (2 N)	2000	THF	64	36
c	(3*S*,6*S*,9*S*)	LiOH (1 N)	200	THF	97	
d	(3*S*,6*S*,9*S*)	LiOH (2 N)	200	THF	83	6
e	(3*S*,6*S*,9*S*)	LiOH (1 N)	120	THF	74	13
f	(3*S*,6*S*,9*S*)	LiOH (2 N)	200	dioxane	95	5
g	(3*S*,6*S*,9*S*)	NaOH (2 N)	1000	THF	60	30
h	(3*S*,6*S*,9*S*)	NaOH (2 N)	200	dioxane	92	5
i	(3*R*,6*R*,9*R*)	LiOH (2 N)	200	THF	10	84
j	(3*S*,6*R*,9*S*)	LiOH (1 N)	150	THF	82	5
k	(3*S*,6*R*,9*S*)	LiOH (2 N)	200	dioxane	86	6
l	(3*S*,6*S*,9*R*)	NaOH (2 N)	200	dioxane		95

[a] Unless noted, the reaction was conducted for 1-2 h at rt in 1:1 (v:v) base:solvent. [b] Isolated yields. [c] Heated at reflux.

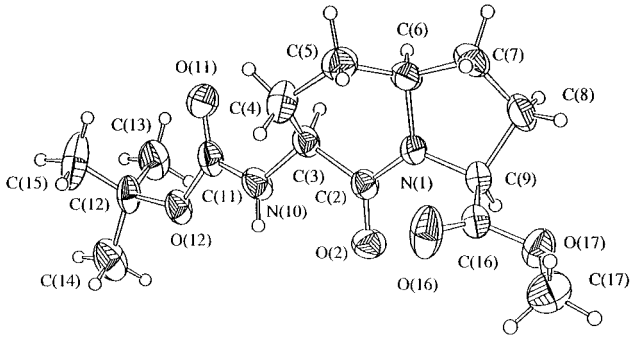


Figure 2. ORTEP view of indolizidinone methyl ester **12**. Ellipsoids drawn at 40% probability level. Hydrogens represented by spheres of arbitrary size.[28]

In the crystal structure of (3*S*,6*S*,9*S*)-indolizidinone **12**, the dihedral angles of the backbone atoms constrained inside the heterocycle ($\psi = -176°$ and $\phi = -78°$) resemble the values of the central residues in an ideal type II′ β-turn ($\psi_2 = -120°$ and $\phi_3 = -80°$).[29] Furthermore, these values compare well with those observed in the crystal

(27) Epimerization of **12** during basic hydrolysis is similar to racemization of *N*-methylamino esters under similar conditions; see, for examples: Boger, D. L.; Chen, J.-H.; Saionz, K. W. *J. Am. Chem. Soc.* **1996**, *118*, 1629 and ref 24 therein.

(28) The structure of **12** was solved at l'Université de Montréal X-ray facility using direct methods (SHELXS 86): $C_{15}H_{24}N_2O_5$; $M_r = 312.36$; orthorhombic, colorless crystal; space group $P2_12_12_1$; unit cell dimensions (Å) $a = 6.793(2)$, $b = 14.847(3)$, $c = 16.712(4)$; volume of unit cell (Å^3) 1685.5(7); $Z = 4$; $R_1 = 0.0353$ for $I > 2\sigma(I)$, $wR_2 = 0.0828$ for all data; GOF = 0.869. The author has deposited the atomic coordinates for the structure of **12** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(29) Ball, J. B.; Alewood, P. F. *J. Mol. Recogn.* **1990**, *3*, 55.

structure of a (3*S*,6*R*,9*S*)-6-thiaindolizidinone β-turn dipeptide analogue ($\psi = -161°$ and $\phi = -69°$).[2b] The observed value of the ϕ dihedral angle of (3*S*,6*S*,9*S*)-**12** is also similar to that of an ideal inverse γ-turn conformation ($\psi_2 = -80°$).[30]

The enantiomeric purity of (6*S*)-**12**, produced from both α-*tert*-butyl γ-methyl *N*-(PhF)glutamate (**2a**) and dimethyl *N*-(PhF)glutamate (**2b**), was determined after conversion to (1′*R*)- and (1′*S*)-*N*-(α-methylbenzyl)ureas **16**. Trifluoroacetic acid in CH_2Cl_2 removed quantitatively the *N*-BOC protecting group, and the TFA salt was acylated with either (*R*)- or (*S*)-α-methylbenzyl isocyanate in THF with triethylamine (Scheme 6).[20a] Observation of the diastereomeric methyl ester singlets by 400 MHz ^{1}H NMR spectroscopy in C_6D_6 during incremental additions of the opposite isomer demonstrated **16** to be of >99% diastereomeric excess. Hence ester **12,** azelates **5**, and 2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylic acids **1** are all presumed to be of >99% enantiomeric purity.

Conclusion

In the context of our research on general methods for making azabicyclo[*X*.*Y*.0]alkane amino acids, we have developed an efficient process for synthesizing enantiopure indolizidinone amino acid **1** ($X = 4$, $Y = 3$). (2*S*)-*N*-(PhF)glutamates (2*S*)-**2a** and (2*S*)-**2b** were used in a Claisen condensation/reductive amination/lactam cyclization sequence to provide enantiopure (3*S*,6*S*,9*S*)-indolizidinone amino acid **1** in 61% (7 steps) and 41% (5 steps, 64% accounting for recovery of **2b**) respective overall yields. By employing D-glutamate, (3*R*,6*R*,9*R*)-**1** was synthesized in similar yield. The indolizidinone C-6 bridge-head center was created with stereocontrol in favor of the concave *cis*-isomer by augmenting hydrogen pressure in the reductive amination step as well as by mesylation of alcohol **7a** and intramolecular S_N2 displacement by the PhF amine. Convex (3*S*,6*R*,9*S*)-**1** was synthesized, albeit with less stereocontrol, by lowering hydrogen pressure in the reductive amination step. Regioselective enolization of indolizidinone amino ester **12** gave access to C-9 epimers and was specifically used to synthesize (3*S*,6*S*,9*R*)-**1**. All of the possible configurations of indolizidinone amino acid **1** can therefore be stereoselectively generated via this approach.

Furthermore, because alkylation of amino ketones **3** and **5** may be used to add side chains with stereocontrol at different positions on the indolizidinone,[18] and because different length α-amino dicarboxylates may be employed to make alternative heterocycles,[31] our strategy has great potential for preparing a variety of azabicyclo[*X*.*Y*.0]-alkane amino acids. This efficient method for synthesizing rigid dipeptide mimetics should thus be of general utility for the study of structure−activity relationships in peptide chemistry and biology.

Experimental Section

General. Unless otherwise noted all reactions were run under argon atmosphere and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately before use; 1,1,1,3,3,3-hexamethyldisilazane and CH_2Cl_2 were distilled from CaH_2 and $CHCl_3$ from P_2O_5; triethylamine (Et_3N) was distilled from BaO. Final reaction mixture solutions were dried over Na_2SO_4. The solvent systems used are as follows: eluant A, EtOAc:hexanes (1:5); eluant B, EtOAc:hexanes (1:9); eluant C, EtOAc:hexanes (1:2); eluant D, $CHCl_3$:MeOH:AcOH (8:1:0.5); eluant E, EtOAc:hexanes (1:3); eluant F, *n*-BuOH:AcOH:H_2O (4:1:1); eluant G, EtOAc:hexanes (1:1); eluant H, EtOAc:hexanes (2:1); eluant I, EtOAc:AcOH (20:1). Melting points are uncorrected. Mass spectral data, HRMS and MS (EI and FAB), were obtained by the Université de Montréal Mass Spec. facility. Unless otherwise noted, ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$), residual $CHCl_3$ (δ 7.27 and 77), or residual MeOH (δ 3.31 and 49.15), and coupling constants are reported in hertz. Chemical shifts of PhF aromatic carbons are not reported for the ^{13}C NMR spectra. Analytical thin-layer chromatography (TLC) was performed by using 2 × 6 cm aluminum-backed silica gel plates coated with a 0.2 mm thickness of silica gel 60 F_{254} (Merck). Chromatography was performed using Kieselgel 60 (230−400 mesh).

(2*S*)-α-*tert*-Butyl γ-Methyl *N*-(PhF)Glutamate ((2*S*)-2a).[24] A solution of γ-methyl *N*-(PhF)glutamate (16.1 g, 40 mmol) in CH_2Cl_2 (40 mL) was treated with a solution of *O*-*tert*-butyl trichloroacetimidate [17.5 g, 80 mmol, 200 mol %, prepared as described for *O*-benzyl trichloroacetimidate in ref 23d: $R_f = 0.26$ in eluant A; ^{1}H NMR δ 1.58 (s, 9 H)] in cyclohexane (160 mL). The mixture was stirred for 3 days, filtered, and treated with a second solution of imidate (17.5 g, 80 mmol, 200 mol %) in cyclohexane (160 mL). After stirring for 2 days at room temperature (rt), the precipitate was removed by filtration and the solution was evaporated under vacuum leaving a residue that was purified by chromatography using 9:1 hexane:EtOAc as eluant. Evaporation of the collected fractions gave a white solid that was recrystallized from isooctane, (2*S*)-**2a**: 14.8 g (81%); $R_f = 0.55$ in eluant A, $R_f = 0.50$ in eluant B; mp 99−100 °C (lit.[19d] mp 100 °C); $[\alpha]^{20}_D$ −246° (*c* 1.08, $CHCl_3$); HRMS calcd for $C_{29}H_{32}NO_4$ (MH^+) 458.2352, found 458.2331.

(2*R*)-α-*tert*-Butyl γ-methyl *N*-(PhF)glutamate ((2*R*)-2a): synthesized from (2*R*)-γ-methyl *N*-(PHF)glutamate (2 g, 5 mmol) in the same way which gave 1.71 g (75%) of (2*R*)-**2a**; $[\alpha]^{20}_D$ 248° (*c* 1.04, $CHCl_3$).

(2*S*,8*S*)-Di-*tert*-butyl 5-Oxo-2,8-bis[*N*-(PhF)amino]azelate ((2*S*,8*S*)-5a). A solution of $NaN(SiMe_3)_2$ (5.95 mL, 5.95 mmol, 110 mol %, 1 M in THF) was added over 30 min to a −30 °C solution of (2*S*)-**2a** (2.44 g, 5.41 mmol, 100 mol %) in THF (5.5 mL). The reaction mixture was stirred for an additional 1.5 h at −30 °C and then partitioned between EtOAc (30 mL) and 1 M NaH_2PO_4 (50 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL), and the organic layers were combined and evaporated to a residue which was normally used in the next reaction without purification.

Purification by chromatography on silica gel using a gradient of 10−30% EtOAc in hexanes as eluant gave first recovered **2a** (25%, $R_f = 0.50$ in eluant B) followed by a 1.2:1 mixture of (2*S*,4*RS*,8*S*)-di-*tert*-butyl 4-carbomethoxy-5-oxo-2,8-bis[*N*-(PhF)-amino]azelate ((2*S*,4*RS*,8*S*)-**3a)** (74%): $R_f = 0.44$ in eluant A, $R_f = 0.40$ in eluant B; ^{1}H NMR δ 1.2 (s, 36 H), 1.6−1.75 (m, 4 H), 1.9 (t, 2 H), 2.3−2.6 (m, 4 H), 2.7−2.95 (m, 2 H), 3.15 (s, 2 H), 3.6 (s, 3 H), 3.75 (br s, 3 H), 3.95 (m, 2 H), 7.2−7.7 (m, 52 H); ^{13}C NMR δ 27.78, 27.8, 29, 29.1, 33.3, 33.4, 38.4, 38.6, 52.1, 52.3, 54.9, 55, 55.6, 55.9, 72.85, 72.91, 80.7, 80, 169.6, 170.2, 174.82, 174.85, 204, 204.8; HRMS calcd for $C_{57}H_{59}N_2O_7$ (MH^+) 883.4323, found 883.4327.

On larger scale and at elevated temperatures, we isolated (2*S*)-*tert*-butyl *N*-(PhF)pyroglutamate ((2*S*)-**4a**): $R_f = 0.45$ in eluant C; mp 203−205 °C) lit.[19d] mp 199−202 °C); $[\alpha]^{20}_D$ −120.6° (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 1.23 (s, 9 H), 1.85 (m, 1 H), 2.15−2.4 (m, 2 H), 2.67 (m, 1 H), 3.9 (d, 1 H), 7.2−7.8 (m, 13 H); ^{13}C NMR δ 25, 27.4, 30.9, 61.5, 73, 81.2, 171.3, 176.3; HRMS calcd for $C_{28}H_{27}NO_3$ (M^+) 425.1991, found 425.1981.

The crude condensation product was dissolved in dioxane (7 mL), treated with 2 M NaOH (6.75 mL, 500 mol %), and

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(31) We have recently reported a method to prepare L- and D-α-amino dicarboxylates of six to eight carbon chain lengths with high enantiomeric purities: Pham, T.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 3676.

stirred at reflux for 1 h when TLC (eluant B) showed complete disappearance of starting **2a**. The mixture was partitioned between EtOAc (15 mL) and NaH_2PO_4 (1 M, 15 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried, and evaporated to a foam that was purified by chromatography using a gradient of 10−20% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave 1.66 g (75%) of (2*S*,8*S*)-di-*tert*-butyl 5-oxo-2,8-bis[*N*-(PhF)amino]azelate ((2*S*,8*S*)-**5a**) which recrystallized from hexane:Et_2O: R_f = 0.52 in eluant A, R_f = 0.48 in eluant B; mp 129 °C; $[\alpha]^{20}_D$ −174.9° (*c* 2.2, MeOH); $[\alpha]^{20}_D$ −224.1° (*c* 2.2, $CHCl_3$); ^{1}H NMR δ 1.05 (s, 9 H), 1.55 (m, 2 H), 2.25 (m, 1 H), 2.4 (m, 2 H), 3 (br s, 1 H), 7−7.6 (m, 13 H); ^{13}C NMR δ 27.8, 29.3, 38.9, 55.1, 72.9, 80.6, 174.9, 209.8; HRMS calcd for $C_{55}H_{57}N_2O_5$ (MH^+) 825.4267, found 825.4230. Anal. Calcd for $C_{55}H_{56}N_2O_5$: C, 79.96; H, 6.96; N, 3.39. Found: C, 79.97; H, 7.04; N, 3.40. When pure **3a** was used, (2*S*,8*S*)-**5a** was obtained in 99% yield.

(2*R*,8*R*)-Di-*tert*-butyl 5-Oxo-2,8-bis[*N*-(PhF)amino]azelate ((2*R*,8*R*)-5a). This compound was prepared from (2*R*)-α-*tert*-butyl γ-methyl *N*-(PhF)glutamate ((2*R*)-**2a**; 0.914 g, 2 mmol, 100 mol %) in a similar manner using a solution of $NaN(Si(CH_3)_3)_2$ (110 mol %) in THF at −78 °C for the condensation and 1 M LiOH (500 mol %) in refluxing THF for 12 h for hydrolysis and decarboxylation. Evaporation of the collected fractions gave first 315 mg (38%) of (2*R*,8*R*)-**5a**, $[\alpha]^{20}_D$ 224.4° (*c* 2.2, $CHCl_3$), followed by 310 mg (37%) of (2*R*)-**4a**.

(2*S*,8*S*)-Dimethyl 5-Oxo-2,8-bis[*N*-(PhF)amino]azelate ((2*S*,8*S*)-5b). A solution of $NaN(SiMe_3)_2$ (7.9 mL, 7.9 mmol, 110 mol %, 1 M in THF) was added over 30 min to a −50 °C solution of (2*S*)-dimethyl *N*-(PhF)glutamate ((2*S*)-**2b**; 2.97 g, 7.15 mmol, 100 mol %)[23] in THF (7.15 mL). The reaction mixture was stirred for 2 h at −50 °C and then partitioned between EtOAc (30 mL) and 1 M NaH_2PO_4 (30 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine, dried, and evaporated to a residue that was directly used in the next reaction.

Purification of the residue by chromatography on silica gel using a gradient of 10−30% EtOAc in hexanes as eluant gave first recovered **2b** (35%, R_f = 0.55 in eluant C) followed by (2*S*,4*RS*,8*S*)-dimethyl 4-carbomethoxy-5-oxo-2,8-bis[*N*-(PhF)-amino]azelate ((2*S*,4*RS*,8*S*)-**3b**; 65%): R_f = 0.28 in eluant A; ^{1}H NMR δ 1.2 (s, 36 H), 1.6−1.75 (m, 4 H), 1.9 (t, 2 H), 2.3−2.6 (m, 4 H), 2.7−2.95 (m, 2 H), 3.15 (s, 2 H), 3.6 (s, 3 H), 3.75 (br s 3 H), 3.95 (m, 2 H), 7.2−7.7 (m, 52 H); ^{13}C NMR δ 28.2, 28.4, 32.4, 32.7, 37.8, 38.1, 51.3, 51.4, 51.5, 51.5, 52.1, 52.5, 53.4, 54.2, 54.5, 54.5, 54.9, 55.9, 72.85, 72.91, 169.2, 170.0, 175.6, 175.9, 176.0, 176.0, 204.0, 203.9; HRMS calcd for $C_{51}H_{47}N_2O_7$ (MH^+) 799.3411, found 799.3383.

Last to elute was (2*S*)-methyl *N*-(PhF)pyroglutamate ((2*S*)-**4b**) which was recrystallized from $CHCl_3$/Et_2O: $[\alpha]^{20}_D$ −105° (*c* 1, $CHCl_3$); mp 201−202 °C; ^{1}H NMR δ 1.85 (m, 1 H), 2.18 (m, 1 H), 2.37 (m, 1 H), 2.71 (m, 1 H), 3.31 (s, 3 H), 3.65 (dd, 1 H, *J* = 1.1, 9.3), 7.1−7.7 (m, 13 H); ^{13}C NMR δ 23.9, 30.5, 51.5, 60.1, 72.8, 172.6, 176; HRMS calcd for $C_{25}H_{22}NO_3$ (MH^+) 384.1560, found 384.1586.

The crude condensation product was dissolved in dioxane (32 mL), treated with 2 M NaOH (32 mL, 64.4 mmol, 900 mol %), and stirred at reflux for 2 h when TLC (eluant A) showed complete disappearance of starting **2b**. The mixture was acidified with citric acid, and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine, dried, and evaporated to a solid that was directly used in the next reaction.

Purification of the hydrolysis product from pure (2*S*,4*RS*,8*S*)-**3b** (2.68 g, 3.36 mmol) using a gradient of 0−10% MeOH in $CHCl_3$ as eluant gave 1.86 g (78%) of (2*S*,8*S*)-5-oxo-2,8-bis[*N*-(PhF)amino]azelate **(6)**, which recrystallized from $CHCl_3$/Et_2O: R_f = 0.77 in eluant D; mp 158 °C dec; $[\alpha]^{20}_D$ −32.8° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.62 (m, 1 H), 1.74 (m, 1 H), 2.32−2.45 (m, 2 H), 2.66 (t, 1 H, *J* = 5.5), 7.1−7.8 (m, 13 H), 8.1 (br s 1 H); ^{13}C NMR δ 27.2, 38.7, 55.8, 73.0, 175.4, 213.2; HRMS calcd for $C_{47}H_{41}N_2O_5$ (MH^+) 713.2984, found 713.3016.

The crude hydrolysis product was dissolved in dimethyl sulfoxide (33 mL), treated with K_2CO_3 (988 mg, 7.15 mmol, 100 mol %) and iodomethane (0.89 mL, 14.3 mmol, 200 mol %), and stirred at rt for 3 h. Brine (50 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 0.65 M sodium thiosulfate and brine, dried, and evaporated to a foam that was purified by chromatography using a gradient of 10−30% EtOAc in hexanes as eluant. First to elute was recovered (2*S*)-**2b** (1.14 g, 39%) followed by (2*S*,8*S*)-**5b** (1.34 g, 51%): R_f = 0.38 in eluant E; mp 135−136 °C; $[\alpha]^{20}_D$ −259.5° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.61−1.66 (m, 2 H), 2.29−2.49 (m, 2 H), 2.53 (t, 1 H, *J* = 6.5), 2.95 (br s 1 H), 3.26 (s, 3 H), 7.1−7.7 (m, 13 H); ^{13}C NMR δ 28.7, 38.7, 55.5, 54.8, 72.8, 176.4, 208.9; HRMS calcd for $C_{49}H_{45}N_2O_5$ (MH^+) 741.3328, found 741.3352. Esterification of pure **6** and chromatography gave (2*S*,8*S*)-**5b**, which recrystallized from hexane/Et_2O in 86% yield.

(3*S*,6*S*,9*S*)- and (3*S*,6*R*,9*S*)-Methyl 2-Oxo-3-[*N*-(BOC)-amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*S*)- and (3*S*,6*R*,9*S*)-12). A solution of azelate (2*S*,8*S*)-**5a** (1.78 g, 2.16 mmol) in anhydrous EtOH (60 mL) and AcOH (6 mL) was treated with palladium-on-carbon (10 wt %, 219 mg) and stirred under 6 atm of hydrogen for 24 h. The mixture was filtered on Celite, the catalyst was washed with EtOH (60 mL), and the combined organic phase was evaporated to give (2*S*,5*RS*,3′*S*)-*tert*-butyl 5-[3′-amino-3′-(*tert*-butyloxycarbonyl)propyl]prolinate bisacetate ((2*S*,5*RS*,3′*S*)-**8**): R_f = 0.46 in eluant F; ^{1}H NMR δ 1.50 (m, 18 H), 1.60−1.90 (m, 4 H), 2.0 (s, 6 H), 2.0−2.2 (m, 3 H), 2.3 (m, 1 H), 3.45 (m, 1 H), 3.55−3.70 (m, 2H), 4.10 (m, 1 H), 4.45 (d, 1 H); ^{13}C NMR δ 21.9, 26.5, 27.8, 28.9, 30.9, 31.0, 31.7, 49.0, 57.5, 59.2, 69.1, 81.5, 170.6, 176.0.

Ester **8** was dissolved in a solution of 6 N HCl (24 mL) and CH_2Cl_2 (24 mL). After stirring for 15 h, TLC (eluant F) showed complete disappearance of the starting ninhydrin positive material (R_f = 0.46) and formation of a new ninhydrin positive product (R_f = 0.22). Removal of the volatiles under vacuum gave (2*S*,5*RS*,3′*S*)-5-[3′-amino-3′-(hydroxycarbonyl)propyl]-*N*-prolinate (2*S*,5*RS*,3′*S*)-**9**: R_f = 0.22 in eluant F; ^{1}H NMR (CD_3OD) δ 1.60 (m, 2 H), 1.60−1.80 (m, 2 H), 1.9 (m, 1 H), 2.05−2.25 (m, 4 H), 2.4 (m, 1 H), 3.65 (m, 1 H), 3.80 (m, 1 H), 4.35 (d, 1 H).

The residue was dissolved in a premixed 0 °C solution of acetyl chloride (9.9 mL) in MeOH (46 mL), and the solution was stirred at rt for 24 h when TLC (eluant F) showed conversion to a new ninhydrin positive product. The volatiles were removed under vacuum. The crude amino ester hydrochloride residue was dissolved in CH_2Cl_2 (36 mL), treated with Et_3N (2.97 mL, 6.48 mmol, 300 mol %), and stirred at rt for 4 h. Di-*tert*-butyl dicarbonate (2.3 g, 10.8 mmol, 500 mol %) was added, and the solution was stirred at rt for 2 h. The mixture was partitioned between $CHCl_3$ (20 mL) and 1 M NaH_2PO_4 (20 mL), and the aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine, dried, and evaporated to an oil that was chromatographed using eluant G. Evaporation of the collected fractions gave first (2*S*,5*RS*,3′*S*)-methyl 5-[3′-[*N*-(BOC)amino-3′-[(methyloxy)carbonyl]propyl]-*N*-(BOC)prolinate ((2*S*,5*RS*,3′*S*)-**14**; 180 mg, 18%): R_f = 0.56 in eluant G; ^{1}H NMR δ 1.34 (s, 36 H), 1.58−1.63 (m, 4 H), 1.73−1.86 (m, 8 H), 2.13 (m, 2 H), 3.63 (s, 12 H), 4.11−4.18 (m, 3 H), 4.24 (m, 1 H), 5.11 (br d, 1 H), 5.16 (br d); ^{13}C NMR δ 27.78, 28.07, 28.13, 28.51, 28.95, 29.08, 29.52, 30.02, 30.22, 30.41, 51.75, 51.95, 53.12, 53.29, 57.52, 57.64, 59.19, 59.61, 79.29, 79.42, 79.70, 79.90, 153.54, 154.08, 155.30, 172.99, 173.09, 173.69, 173.55; HRMS calcd for $C_{21}H_{36}N_2O_8$ (MH^+) 445.2550, found 445.2536.

Next to elute was (3*S*,6*S*,9*S*)-methyl 2-oxo-3-[*N*-(BOC)-amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*S*)-**12**; 452 mg, 67%) as a white solid that recrystallized from hexane/Et_2O: R_f = 0.23 in eluant G; mp 111−112 °C; $[\alpha]^{20}_D$ −17.6° (*c* 1, $CHCl_3$); $[\alpha]^{20}_D$ −47.9° (*c* 6.12, MeOH); ^{1}H NMR δ 1.45 (s, 9 H), 1.7 (m, 3 H), 2.1 (m, 4 H), 2.45 (m, 1 H), 3.7 (m, 1 H), 3.75 (s, 3 H), 4.15 (m, 1 H), 4.5 (d, 1 H, *J* = 7.5), 5.5 (d, 1 H, *J* = 4.4); ^{13}C NMR δ 26.8, 27.2, 28.3, 28.9, 32.0, 49.9, 52.2, 56.4, 58.1, 79.4, 155.6, 169.1, 172.1; HRMS calcd for $C_{15}H_{25}N_2O_5$ (MH^+) 313.1764, found 313.1785. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.66; H, 7.75; N, 8.97. Found: C, 57.82; H, 7.76; N, 8.87.

Last to elute was convex (3*S*,6*R*,9*S*)-**12** as an oil (14 mg, 2%): R_f = 0.08 in eluant G; $[\alpha]^{20}_D$ −25.3° (*c* 1.1, MeOH); ^{1}H NMR δ 1.4 (s, 9 H), 1.69 (m, 1 H), 1.83 (m, 1 H), 1.92−2.05 (m, 2 H), 2.09−2.21 (m, 2 H), 2.44 (m, 1 H), 3.64 (m, 1 H), 3.72 (s, 3 H), 3.93 (m, 1 H), 4.43 (d, 1 H, *J* = 9.7), 5.36 (br s, 1 H); ^{13}C NMR δ 27.6, 28.16, 28.23, 28.50, 31.4, 52, 52.0, 57.9, 60.4, 79.3, 155.8, 168.2, 172.1; HRMS calcd for $C_{15}H_{25}N_2O_5$ (MH^+) 313.1764, found 313.1720.

(3*R*,6*R*,9*R*)- and (3*R*,6*S*,9*R*)-Methyl 2-oxo-3-[*N*-(BOC)-amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*R*,6*R*,9*R*)- and (3*R*,6*S*,9*R*)-12) were prepared from (2*R*,8*R*)-**5a** (250 mg, 0.30 mmol) in the same manner which gave (3*R*,6*R*,9*R*)-**12** [54.5 mg, 60%, $[\alpha]^{20}_D$ 17° (*c* 1.1, $CHCl_3$)] and (3*R*,6*S*,9*R*)-**8** [4.6 mg, 5%, $[\alpha]^{20}_D$ 16° (*c* 0.46, $CHCl_3$)].

(3*S*,6*S*,9*S*)-Methyl 2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*S*)-12) from Dimethylazelate (2*S*,8*S*)-5b. A solution of azelate (2*S*,8*S*)-**5b** (675 mg, 0.91 mmol) in anhydrous EtOH (23 mL) and AcOH (2.3 mL) was treated with palladium-on-carbon (20 wt %, 184 mg) and stirred under 6 atm of hydrogen for 48 h. The mixture was filtered on Celite, the catalyst was washed with EtOH (30 mL), and the combined organic phases were evaporated to a solid. The amino ester was dissolved in CH_2Cl_2 (15 mL), treated with Et_3N (0.83 mL, 1.82 mmol, 200 mol %), and stirred at rt for 3 h. Di-*tert*-butyl dicarbonate (993 mg, 4.55 mmol, 500 mol %) was added, and the solution was stirred at rt for another 2 h. The mixture was partitioned between $CHCl_3$ (15 mL) and 1 M NaH_2PO_4 (15 mL), and the aqueous phase was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with brine, dried, and evaporated to an oil that was chromatographed using eluant G. First to elute was (3*S*,6*S*,9*S*)-ethyl 2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate: 10 mg (5%); R_f = 0.29 in eluant G; $[\alpha]^{20}_D$ −13.8° (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 1.28 (t, 3H, *J* = 7.1), 1.44 (s, 9 H), 1.60−1.79 (m, 4 H), 2.03−2.33 (m, 3 H), 2.1 (m, 4 H), 2.45 (m, 1 H), 3.73 (m, 1 H), 4.15 (2, 1 H), 4.17 (qd, 1 H, *J* = 7.1, 1.2), 4.49 (d, 1 H, *J* = 7.8), 5.52 (br s, 1 H); ^{13}C NMR δ 14.1, 26.8, 27.2, 28.3, 29.1, 32.1, 50.0, 56.5, 58.3, 61.3, 79.4, 155.7, 169.1, 171.6; HRMS calcd for $C_{16}H_{27}N_2O_5$ (MH^+) 327.1920, found 327.1936. Next to elute was (3*S*,6*S*,9*S*)-**12** (230 mg, 81%) followed by (3*S*,6*R*,9*S*)-**12** (6.4 mg, 2%).

(3*S*,6*S*,9*R*)-Methyl 2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*R*)-12) via Epimerization of (3*S*,6*S*,9*S*)-12. A solution of $NaN(SiMe_3)_2$ (0.26 mL, 0.26 mmol, 200 mol %, 1 M in THF) was added over 15 min to a −50 °C solution of (3*S*,6*S*,9*S*)-**12** (40 mg, 0.13 mmol, 100 mol %) in THF (0.2 mL). The reaction mixture was stirred for 1 h at −50 °C followed by 1 h at −20 °C and then partitioned between EtOAc (5 mL) and 1 M NaH_2PO_4 (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL). The organic layers were combined, washed with brine, dried, and evaporated to an oil (36.6 mg, 92% of a 1:10 ratio of (3*S*,6*S*,9*S*)-**12**:(3*S*,6*S*,9*R*)-**12** as determined by ^{1}H NMR) that was chromatographed using eluant H. Evaporation of the collected fractions gave first (3*S*,6*S*,9*S*)-**12** (2 mg, 5%; R_f = 0.4 in eluant H) followed by (3*S*,6*S*,9*R*)-methyl 2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*R*)-**12**; 30 mg, 75% of >92% de by ^{1}H NMR): R_f = 0.37 in eluant H; ^{1}H NMR δ 1.8 (s, 9 H), 1.4−1.6 (m, 4 H), 1.85 (m, 1 H), 2.12−2.26 (m, 2 H), 2.37 (m, 1 H), 3.67 (s, 3 H), 3.75 (m, 1 H), 4.1 (m, 1 H), 4.5 (t, 1 H, *J* = 7.5), 5.5 (br s, 1 H); ^{13}C NMR δ 26.2, 28.0, 28.3, 28.4, 32.6, 50.1, 52.4, 56.4, 58.4, 79.7, 155.7, 169.0, 172.1; HRMS calcd for $C_{15}H_{25}N_2O_5$ (MH^+) 313.1764, found 313.1754.

(3*S*,6*S*,9*S*)-2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]-nonane-9-carboxylic Acid ((3*S*,6*S*,9*S*)-1). (3*S*,6*S*,9*S*)-Methyl 2-oxo-3-[*N*-(BOC)amino]indolizidine-9-carboxylate ((3*S*,6*S*,9*S*)-**12**; 563 mg, 1.8 mmol) in dioxane (1.8 mL) was treated with 2 M LiOH (1.8 mL, 200 mol %) and stirred at rt for 2 h when TLC (eluant G) showed complete disappearance of starting **12**. The mixture was partitioned between EtOAc (6 mL) and 1 M NaH_2PO_4 (6 mL). The aqueous phase was extracted with EtOAc (3 × 6 mL), and the organic layers were combined, washed with brine, dried, and evaporated to an oil that was chromatographed with 20:1 EtOAc:AcOH as eluant. Evaporation of the collected fractions gave 511 mg (95%) of (3*S*,6*S*,9*S*)-**12**: R_f = 0.46 in eluant E; $[\alpha]^{20}_D$ −44.7° (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 1.44 (s, 9 H), 1.65−1.75 (m, 3 H), 2.10−2.30 (m, 4 H), 2.42 (m, 1 H), 3.71 (dddd, 1 H, *J* = 10, 10, 5, 5), 4.22 (m, 1 H), 4.54 (d, 1 H, *J* = 8.6), 5.66 (d, 1 H, *J* = 4.8); ^{13}C NMR δ 26.4, 26.8, 28.1, 28.4, 31.8, 49.6, 56.8, 58.5, 79.6, 155.7, 170.3, 174.2; HRMS calcd for $C_{14}H_{23}N_2O_5$ (MH^+) 299.1607, found 299.1596.

This was followed by 27 mg (5%) of (3*S*,6*S*,9*R*)-2-oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ((3*S*, 6*S*, 9*R*)-**1**): R_f = 0.28 in eluant I; $[\alpha]^{20}_D$ −6.5° (*c* 1.7, $CHCl_3$); ^{1}H NMR δ 1.42 (s, 9 H), 1.65−1.8 (m, 2 H), 1.89 (m, 2 H), 2 (m, 3 H), 2.25 (m, 1 H), 3.6 (br s, 1 H), 3.95 (br s, 1 H), 4.35 (br s, 1 H), 5.86 (br s, 1 H); ^{13}C NMR δ 27.4, 28.9, 29.1, 30.2, 31.3, 51.5, 60, 60.6, 79.4, 156, 169.7, 176.5; HRMS calcd for $C_{14}H_{23}N_2O_5$ (MH^+) 299.1607, found 299.1619.

Isomeric indolizidinone amino acids **1** were similarly obtained from hydrolysis of **12** with hydroxide ion (Table 4) and purified by chromatography with 20:1 EtOAc:AcOH as eluant.

(3*S*,6*R*,9*S*)-2-Oxo-3-[N-(BOC)amino]-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid ((3*S*,6*R*, 9*S*)-1): $[\alpha]^{20}_D$ −20.3° (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 1.41 (s, 9 H), 1.55−1.8 (m, 2 H), 1.85−2.05 (m, 2 H), 2.05−2.15 (m, 3 H), 2.28 (br m, 1 H), 3.63 (br m, 1 H), 3.90 (m, 1 H), 4.44 (t, 1 H, *J* = 5.3), 5.61 (br s, 1 H), 8.2 (br s, 1H); ^{13}C NMR δ 27.7, 28.3, 29.7, 31.5, 31.5, 51.8, 59.5, 60.7, 79.5, 156.0, 169.8, 175.9; HRMS calcd for $C_{14}H_{23}N_2O_5$ (MH^+) 299.1607, found 299.1594.

(3*S*,6*R*,9*R*)-2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid ((3*S*,6*R*,9*R*)-1): ^{1}H NMR (showed a 5.4:1 ratio of diastereomers, resonances of the major isomer are as follows) δ 1.39 (s, 9 H), 1.5−1.7 (m, 3 H), 1.9−2.1 (m, 2 H), 2.1−2.35 (m, 2 H), 2.45 (m, 1 H), 3.6 (m, 1 H), 4.2 (m, 1 H), 4.5 (d, 1 H, *J* = 8.7 Hz), 5.4 (m, 1 H).

(3*R*,6*R*,9*R*)-2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid ((3*R*,6*R*,9*R*)-1): $[\alpha]^{20}_D$ 45.6° (*c* 0.8, $CHCl_3$).

(3*R*,6*R*,9*S*)-2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid ((3*R*,6*R*,9*S*)-1): $[\alpha]^{20}_D$ 20.5° (*c* 0.8, $CHCl_3$).

(3*S*,6*S*,9*S*)-Methyl 2-Oxo-3-amino-1-azabicyclo[4.3.0]-nonane-9-carboxylate Hydrochloride ((3*S*,6*S*,9*S*)-11). Through a solution of (3*S*,6*S*,9*S*)-**12** (0.32 mmol, 100 mg) in CH_2Cl_2 (2 mL) was bubbled a stream of HCl gas with stirring at rt for 15 min when TLC (eluant G) showed complete disappearance of starting **12**. The white precipitate was filtered to give 80 mg (100%) of (3*S*,6*S*,9*S*)-**11**: R_f = 0.35 in eluant F; mp 85−90 °C; $[\alpha]^{20}_D$ −54.9° (*c* 1, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.66−1.79 (m, 2 H), 1.93 (m, 1 H), 2.09 (m, 1 H), 2.17−2.34 (m, 3 H), 2.46 (m, 1 H), 3.73 (s, 3 H), 3.71 (dddd, 1 H, *J* = 10.1, 10.1, 5, 5), 4.04 (t, 1 H, *J* = 8.6), 4.49 (d, 1 H, *J* = 8.7); ^{13}C NMR δ 23.9, 26.6, 29.11, 31.8, 49.0, 52.6, 57.1, 58.6, 167.1, 172.0; HRMS calcd for $C_{10}H_{17}N_2O_3$ (MH^+) 213.1239, found 213.1246.

Recycle of (2*S*,5*RS*,3′*S*)-Methyl 5-[3′-[*N*-(BOC)amino]-3′-[(methyloxy)carbonyl]propyl]-*N*-(BOC)prolinate ((2*S*,5*RS*,3′*S*)-14) into (3*S*,6*S*,9*S*)- and (3*S*,6*R*,9*S*)-12. Through a solution of 5-alkylprolinate **14** (2.82 mmol, 1.25 g) in CH_2Cl_2 (10 mL) was bubbled a stream of HCl gas with stirring at rt for 30 min when TLC (eluant C) showed complete disappearance of starting **14**. The precipitated was filtered to give a white solid, (2*S*,5*RS*,3′*S*)-methyl 5-[3′-amino-3′-[(methyloxy)carbonyl]propyl]prolinate hydrochloride ((2*S*,5*RS*, 3′*S*)-**10**): 892 mg, 100%; R_f = 0.14 in eluant F; ^{1}H NMR (CD_3OD) δ 1.72−1.83 (m, 1 H), 1.90−2.10 (m, 4 H), 2.24−2.43 (m, 3 H), 3.70 (m, 1 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.15 (dd, 1 H), 4.50 (dd, 1 H); ^{13}C NMR (CD_3OD) δ 28.1, 28.5, 28.6, 29.8, 53.6, 53.9, 54.1, 60.9, 61.9, 170.5, 170.6; HRMS calcd for $C_{11}H_{21}N_2O4$ (MH^+) 245.1577, found 245.1501.

Amino ester hydrochloride **10** (303 mg, 0.95 mmol) was then dissolved in CH_2Cl_2 (5 mL) with Et_3N (396 μL, 2.85 mmol, 200 mol %) and stirred at rt for 4 h. Di-*tert*-butyl dicarbonate (623 mg, 2.85 mmol, 300 mol %) was added, and the solution was stirred at rt for another 2 h. The mixture was partitioned between $CHCl_3$ (10 mL) and 1 M NaH_2PO_4 (10 mL), and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried, and evaporated to an oil that was chromatographed with 1:1

hexanes:EtOAc as eluant. Evaporation of the collected fractions gave first recovered **14** (58 mg, 12%) followed by (3*S*,6*S*,9*S*)-**12** (175 mg, 59%) and (3*S*,6*R*,9*S*)-**12** (15 mg, 5%).

(2*S*,8*S*)-Di-*tert*-butyl 5-Hydroxy-2,8-bis[*N*-(PhF)amino]-azelate ((2*S*,8*S*)-7a). Sodium borohydride (790 mg, 2.04 mmol, 50 mol %) was added over a period of 5 min to a stirred solution of (2*S*,8*S*)-**5a** (3.36 g, 4.08 mmol) in EtOH (25 mL). After stirring for 30 min at rt, TLC (eluant A) showed complete disappearance of starting **5a**. The reaction mixture was concentrated on a rotary evaporator and then partitioned between EtOAc (15 mL) and water (25 mL). The aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried, and evaporated to a foam that was purified by chromatography using a gradient of 10−30% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave 3.01 g (89%) of **7a** as a white solid: $R_f = 0.28$ in eluant A; mp 84−86 °C; ^{1}H NMR δ 1.18 (s, 9 H), 1.20 (s, 9 H), 1.31−1.55 (m, 8 H), 2.47−2.55 (m, 2 H), 3.35−3.40 (m, 1 H), 7.1−7.7 (m, 26 H); ^{13}C NMR δ 27.9, 31.5, 31.6, 33.1, 33.2, 55.9, 56.0, 71.1, 73.1, 80.6, 80.7, 175.0, 175.1; HRMS calcd for $C_{55}H_{60}N_2O_5$ (MH^+) 828.4502, found 828.4538.

(2*S*,5*S*,3′*S*)-*tert*-Butyl 5-[3′-[*N*-(PhF)amino]-3′-(*tert*-butyloxycarbonyl)propyl]-*N*-(PhF)prolinate ((2*S*,5*S*,3′*S*)-15). A stirred 0 °C solution of (2*S*,8*S*)-**7a** (83 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was treated with methanesulfonyl chloride (16 μL, 0.2 mmol, 200 mol %), DMAP (1.2 mg, 0.01 mmol, 10 mol %), and Et_3N (24 μL, 0.30 mmol, 300 mol %), stirred for 1 h, brought to rt, stirred for 1 h, and heated at reflux for 24 h. EtOAc (3 mL) and H_2O (1 mL) were added to the reaction mixture, and the organic layer was sequentially washed with 2 N HCl (1 mL), 5% $NaHCO_3$ (1 mL), H_2O (1 mL), and brine, dried, evaporated, and purified by chromatography with 1:5 EtOAc:hexanes as eluant. Evaporation of the collected fractions gave 80.2 mg (99%) of **15** as a white solid: $R_f = 0.75$ in eluant A; mp 110−111 °C; $[\alpha]^{20}_D$ −133° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.14 (s, 9 H), 1.39 (s, 9 H), 1.35−1.45 (m, 3 H), 1.52−1.75 (m, 3 H), 1.92 (m, 1 H), 2.35 (m, 1 H), 2.73 (m, 1 H), 3.61 (dd, 1 H, J = 9, 5.8), 7.1−7.7 (m, 26 H); ^{13}C NMR δ 28.8, 30.0, 30.6, 32.8, 32.9, 56.0, 61.9, 64.7, 73.0, 78.3, 79.5, 79.9, 175.4, 175.5; HRMS calcd for $C_{55}H_{57}N_2O_4$ (MH^+) 809.4318, found 809.4324.

(3*S*,6*S*,9*S*)-Methyl 2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*S*)-12) from (2*S*,5*S*,3′*S*)-15. A solution of (2*S*,5*S*,3′*S*)-**15** (71 mg, 0.09 mmol) in EtOH (3 mL) and AcOH (0.3 mL) was treated with palladium-on-carbon (10 wt %, 10 mg) and stirred under 6 atm of hydrogen for 24 h. The mixture was filtered on Celite, the catalyst was washed with EtOH (3 mL), and the combined organic phase was evaporated to a solid. The solid was dissolved in a solution of 6 N HCl (1 mL) and CH_2Cl_2 (1 mL). After stirring for 15 h, TLC (eluant F) showed complete disappearance of the starting ninhydrin positive material (R_f = 0.46) and formation of a new ninhydrin positive product (R_f = 0.22). The volatiles were removed under vacuum, the residue was dissolved in a 0 °C solution of acetyl chloride (0.16 mL) in MeOH (1.92 mL), and the solution was stirred at rt for 24 h when TLC (eluant F) showed complete conversion to a new ninhydrin positive product ($R_f = 0.38$). The volatiles were removed under vacuum. The crude amino ester hydrochloride residue was dissolved in CH_2Cl_2 (1.5 mL), treated with Et_3N (0.12 mL, 0.27 mmol, 300 mol %), and di-*tert*-butyl dicarbonate (96 mg, 0.45 mmol, 500 mol %), and stirred at rt for 2 h. The mixture was partitioned between $CHCl_3$ (2 mL) and 1 M NaH_2PO_4 (2 mL), and the aqueous phase was extracted with $CHCl_3$ (3 × 2 mL). The combined organic layers were washed with brine, dried, and evaporated to an oil that was chromatographed with 1:1 hexanes:EtOAc as eluant. Evaporation of the collected fractions gave first (2*S*,5*S*,3′*S*)-**14** (6 mg, 15%) followed by (3*S*,6*S*,9*S*)-**12** (18 mg, 66%).

Enantiomeric Purity of (3*S*,6*S*,9*S*)-Methyl 2-Oxo-3-[*N*-(BOC)amino]-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,9*S*)-12). A solution of (3*S*,6*S*,9*S*)-**12** (0.06 mmol, 18 mg) in CH_2Cl_2 (1 mL) was treated with TFA (0.5 mL) and stirred for 4 h when TLC (eluant F) showed complete disappearance of starting **12**. The volatiles were removed under vacuum, and the residue was dissolved in 1 mL of THF. The solution was treated with either (*R*)- or (*S*)-α-methylbenzyl isocyanate (16 μL, 0.12 mmol, 200 mol %) and Et_3N (8 μL, 0.06 mmol, 100 mol %) and heated at reflux for 3 h. The mixture was cooled. The volatiles were removed under vacuum, and the residue was directly examined by NMR. The limits of detection were determined by observation of the diastereomeric methyl ester singlets in the 400 MHz ^{1}H NMR in benzene-d_6 during incremental additions of diastereomeric urea which demonstrated (1′*S*)- and (1′*R*)-**16** to be of >99% diastereomeric purity.

Urea (1′*R*)-16: ^{1}H NMR (C_6D_6) δ 1.21 (m, 3 H), 1.33 (d, 3 H, J = 6.9), 1.47 (m, 3 H), 1.6 (m, 1 H), 2.38 (m, 1 H), 2.83 (m, 1 H), 3.33 (s, 3 H), 4.21 (d, 1 H, J = 8.2), 4.34 (m, 1 H), 5.13 (m, 1 H), 5.5 (br s, 1 H), 6.05 (br s, 1 H), 7.15 (m, 5 H).

Urea (1′*S*)-16: ^{1}H NMR (C_6D_6) δ 1.23 (m, 2 H), 1.33 (m, 2 H), 1.39 (d, 3 H, J = 6.8), 1.47 (m, 1 H), 1.63 (m, 1 H), 2.3 (m, 1 H), 2.81 (m, 1 H), 3.3 (s, 3 H), 4.24 (d, 1 H, J = 8), 4.45 (m, 1 H), 5.16 (m, 1 H), 5.55 (br s, 1 H), 6.06 (br s, 1 H), 7.15 (m, 5 H).

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Supporting Information Available: Experimental details for **2b** and γ-methyl *N*-(PhF)glutamate, ^{1}H and ^{13}C NMR spectra of **1** and **3**−**15**, ^{1}H NMR spectra of **16**, and crystallographic data for **12** (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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