An Olefination Entry for the Synthesis of Enantiopure α,ω-Diaminodicarboxylates and Azabicyclo[*X.Y.*0]alkane Amino Acids†

Francis Gosselin and William D. Lubell*

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

Received July 24, 1998

A new approach for synthesizing α,ω-diaminodicarboxylates of various chain lengths has opened the way for making a series of azabicyclo[*X.Y.*0]alkane amino acids of different ring sizes. β-Keto phosphonates **21**−**23** were synthesized in 71−90% yield by the addition of the lithium anion of dimethyl methyl phosphonate to the ω-methyl ester of α-*tert*-butyl *N*-(PhF)aspartate **3**, glutamate **9**, and aminoadipate **12** (PhF = 9-phenylfluoren-9-yl). α,ω-Diaminodicarboxylates **24**−**26** of nine to eleven carbon chain lengths were prepared in 78−87% yield from the Horner−Wadsworth−Emmons olefination of α-*tert*-butyl *N*-(PhF)aspartate β-aldehyde (**5**) with aminodicarboxylate-derived β-keto phosphonates **21**−**23**. The power of this approach for making azabicyclo[*X.Y.*0]alkane amino acid was then illustrated by the first synthesis of enantiopure indolizidin-9-one amino acid **2** in nine steps and >25% overall yield from inexpensive aspartic acid as chiral educt. Hydrogenation of (2*S*,8*S*)-di-*tert*-butyl 4-oxo-2,8-bis[*N*-(PhF)amino]non-4-enedioate (**24**) in 9:1 EtOH:AcOH furnished a 9:1 diastereomeric mixture of 6-alkylpipecolate **28** that was subsequently transformed into azabicyclo[4.3.0]alkane amino acid **2** via lactam cyclization and protecting group manipulations. Because α,ω-diaminodicarboxylates **25** and **26** may be similarly converted to heterocycles of larger ring sizes and because alkylation of similar ketones can be used to attach side-chains at different points on the heterocycle, this olefination strategy greatly expands our methodology for synthesizing azabicyclo[*X.Y.*0]alkane amino acids for the exploration of conformation−activity relationships of various biologically active peptides.

Introduction

The synthesis of azabicyclo[*X.Y.*0]alkanes has stimulated over a hundred years of innovative chemistry.[1,2] Organic chemists were first attracted to these structures because of their importance as components of biologically active natural products, such as the families of indolizidine, pyrrolizidine, and quinolizidine alkaloids.[1] In recent years, peptide chemists have revived interest in their synthesis as constituents of azabicyclo[*X.Y.*0]alkane amino acids that restrain the backbone and side-chain geometry of native proteins.[2] These bicyclic amino acids act as valuable building blocks for constructing conformationally rigid surrogates of peptide structures that have served to probe and mimic the spatial requirements for protein chemistry and biology.[2] Because azabicyclo[*X.Y.*0]alkane amino acids possess spatially defined amine and carboxylate handles suitable for functionalization by combinatorial technology, medicinal chemists have also become drawn toward their synthesis as inputs for generating libraries on which different pharmacophores are systematically displayed for studying recognition events.[2]

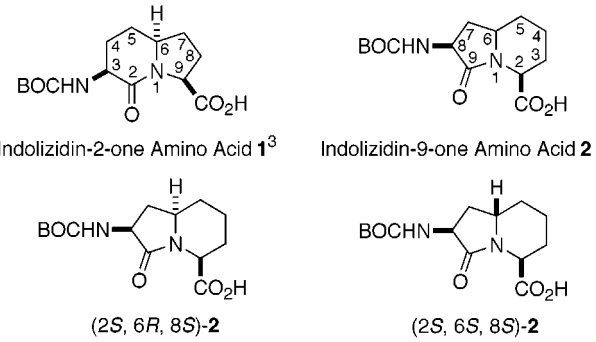


Figure 1. Indolizidinone amino acids **1** and **2**.

Engaged in the use of azabicyclo[*X.Y.*0]alkane amino acids in both peptide mimicry and combinatorial technology, we have strived to develop a general and practical synthesis to furnish a variety of these interesting ring systems.[3−5] Initially, we introduced a Claisen condensation/reductive amination/lactam cyclization sequence for stereoselectively synthesizing azabicyclo[*X.Y.*0]alkane amino acid (Scheme 1, PhF = 9-(9-phenylfluorenyl)).[4] Our route gave access to all of the possible stereoisomers of enantiopure indolizidin-2-one amino acid **1** by employing

† This paper is dedicated to Professor Henry Rapoport on the occasion of his 80th birthday.

(1) (a) Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413. (b) Wróbel, J. T. In *The Alkaloids*; Brossi, A., Ed.; Acad. Press: New York, 1986; Vol. 26, pp 327−384. (c) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 535. (d) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Acad. Press: New York, 1986; Vol. 28, pp 183−308. (e) Takahata, H.; Momose, T. In *The Alkaloids* Cordell, G. A., Ed. Acad. Press: New York, 1993; Vol. 44, pp 189−256.

(2) Reviewed in Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. We have adopted the nomenclature and ring system numbering used in this reference in order to maintain clarity and consistency when comparing these different heterocyclic systems.

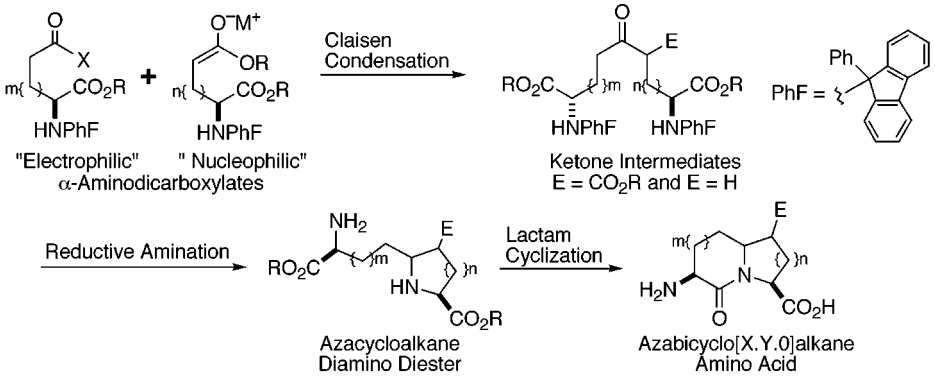
(3) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9437.

(4) (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, The Netherlands, 1995; p 696.

(5) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937.

S0022-3263(98)01460-1 CCC: $15.00
Published on Web 09/24/1998

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



inexpensive glutamic acid as chiral educt (Figure 1).[3] Lately, we have expanded our route to allow different amino acid side-chains to be appended onto the heterocyclic dipeptide surrogate via the alkylation of the ketone intermediate produced from decarboxylation of the Claisen condensation product.[5] In this report, we now present research to employ different aminodicarboxylates, such as aspartate and α-aminoadipate, in Scheme 1 in order to generate a variety of azabicyclo[*X.Y.*0]alkane heterocycle ring-sizes.

We have investigated the Claisen condensation between *N*-(PhF)aminodicarboxylates of three different chain lengths.[6−8] Using aspartate, glutamate, and α-aminoadipate in Claisen condensations, we have demonstrated the unique reactivity of *N*-(PhF)glutamate and have illustrated aspects that interfere with the condensations of the other two aminodicarboxylates. Examination of an alternative strategy to link *N*-(PhF)aminodicarboxylates of different chain lengths opened a new route for synthesizing several of the key amino ketone intermediates involved in our original design. This new entry features olefination of *N*-(PhF)aspartate *β*-aldehyde and has furnished three different α,*ω*-diaminodicarboxylate intermediates for the synthesis of azabicyclo[*X.Y.*0]alkane amino acid.

We have illustrated the utility of these new α,*ω*-diaminodicarboxylate intermediates by the synthesis of a novel azabicyclo[4.3.0]alkane amino acid. Enantiopure indolizidin-9-one amino acid **2** was synthesized for the first time in nine steps and >25% overall yield from aspartic acid via reductive amination and lactam cyclization of a *γ*-oxo-α,*ω*-diaminoazelate intermediate (Figure 1). Because the longer α,*ω*-diaminodicarboxylate intermediates may be similarly converted to heterocycles of larger ring sizes and because modification of these ketone intermediates may lead to the attachment of side-chains at different points on the azabicyclo[*X.Y.*0]alkane heterocycle, the olefination strategy greatly expands our methodology for constructing these important tools for studying the structure−activity relationships of biologically relevant peptides.

Results and Discussion

In principle, the Claisen condensations of the *ω*-carboxylates of aspartate, glutamate, and α-aminoadipate followed by decarboxylation could provide six different α,*ω*-diaminodicarboxylates with chain lengths between seven and eleven carbons (Scheme 1). Subsequent reductive aminations and lactam cyclizations would then furnish nine different azabicyclo[*X.Y.*0]alkane amino acid heterocycles in which X varies from three to five and Y from two to four carbons. Symmetrical α,*ω*-diaminodicarboxylates provide a single heterocycle as demonstrated in the synthesis of indolizidin-2-one amino acid **1** from *δ*-oxo-α,*ω*-diaminoazelate. Unsymmetrical α,*ω*-diaminodicarboxylates may yield two possible heterocycles from reductive aminations between the ketone and one of two different amines. The three stereocenters at the ring-fusion and peptide backbone carbons offer eight possible configurations per heterocycle. In sum, a library of 72 unique azabicyclo[*X.Y.*0]alkane amino acids may be generated by employing the L- and D-enantiomers of the three most common α-aminodicarboxylates, aspartate, glutamate, and α-aminoadipate, in Scheme 1. Because each azabicycloalkane amino acid is expected to adopt a preferred set of dihedral angle geometries when incorporated into a peptide framework, this library of rigid dipeptide surrogates should mimic a comprehensive spectrum of peptide conformations.

Suitably protected α-aminodicarboxylates were initially required for employment in Claisen condensations. Diesters of *N*-(PhF)aspartate[6] and *N*-(PhF)glutamate[3,7] were obtained using literature methods. Enantiopure *δ*-methyl α-*tert*-butyl *N*-(PhF)-α-aminoadipate (**9**)[8,9] was synthesized by an improved method in seven steps and 47% overall yield from aspartic acid (Schemes 2 and 3). *β*-Methyl *N*-(PhF)aspartate[6b] was esterified using *O*-*tert*-butyl trichloroacetimidate in dichloromethane which gave α-*tert*-butyl ester **3** in 84% yield after chromatography.[10] Treatment of a solution of α-*tert*-butyl *β*-methyl *N*-(PhF)-aspartate (**3**) in THF with DIBAL-H at −40 °C caused selective reduction of the *β*-methyl ester and provided

(6) Dimethyl *N*-(PhF)aspartate was prepared as described in (a) Jamison, T. F.; Rapoport, H. *Org. Synth.* **1992**, *71*, 226. *β*-methyl *N*-(PhF)aspartate was prepared as described in (b) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068.

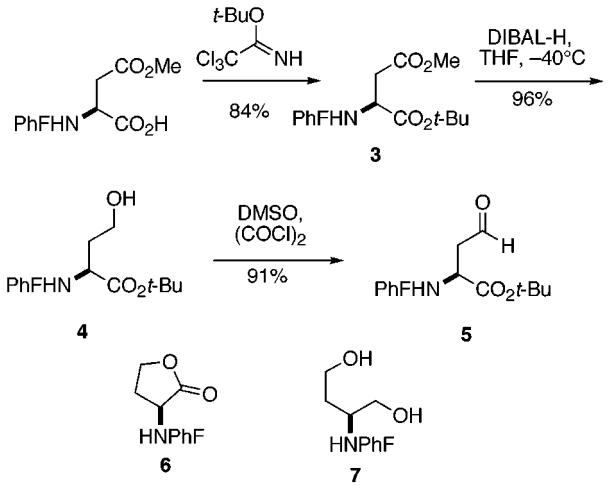
(7) Dimethyl *N*-(PhF)glutamate and α-*tert*-butyl *γ*-methyl *N*-(PhF)-glutamate were prepared as described in ref 3 above. (a) Paz, M. M.; Sardina, J. *J. Org. Chem.* **1993**, *58*, 6990. (b) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859.

(8) α-*tert*-Butyl *δ*-methyl L-*N*-(PhF)-α-aminoadipate was first reported in Bergmeier, S. C.; Cobás, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.

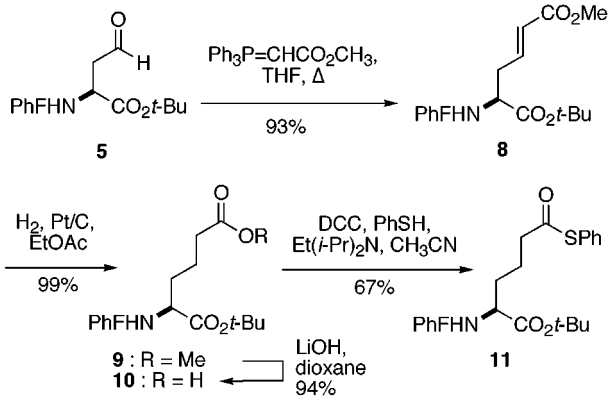
(9) Syntheses of optically active α-aminoadipate are reviewed in Pham, T.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 3676 and ref 3 therein.

(10) *tert*-Butyl esterification using *O*-*tert*-butyl trichloroacetimidate was conducted as described in the Experimental Section. This procedure was modified from ref 3 above using *O*-*tert*-butyl trichloroacetimidate that was synthesized as described in Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

Scheme 2. Synthesis of *N*-(PhF)Aspartate β-Aldehyde 5



Scheme 3. Synthesis of *N*-(PhF)Aminoadipate Esters



homoserine **4** in excellent yield (96%, Scheme 2).[11] In agreement with a previous report demonstrating that *N*-(PhF)amine protection inhibits γ-lactone formation,[12] the DIBAL-H reduction was found to be sensitive to concentration. γ-Lactone **6** and 2-aminobutane-1,4-diol **7** were isolated in variable amounts when the reduction was conducted at higher concentrations. It is interesting to note that the corresponding reduction of *N*-trityl aspartate diesters has been reported to furnish *N*-(trityl)-homoserine γ-lactone in good yield.[13] *N*-(PhF)Homoserine *tert*-butyl ester (**4**) showed no tendency to lactonize on standing nor during chromatography on silica gel. Subsequent oxidation of primary alcohol **4** using DMSO−oxalyl chloride in dichloromethane gave (2*S*)-*tert*-butyl 2-[*N*-(PhF)amino]-4-oxobutanoate (**5**) in 91% yield after chromatography on silica gel.[14] Aldehyde **5** was stable for several weeks under argon at −20 °C, but samples of aldehyde dissolved in $CDCl_3$ decomposed within a few hours as judged by ^1H NMR spectroscopy. Because decomposition of aldehyde **5** was presumed to be due to traces of acid in this solvent, exposure of **5** to chloroform was strictly avoided.

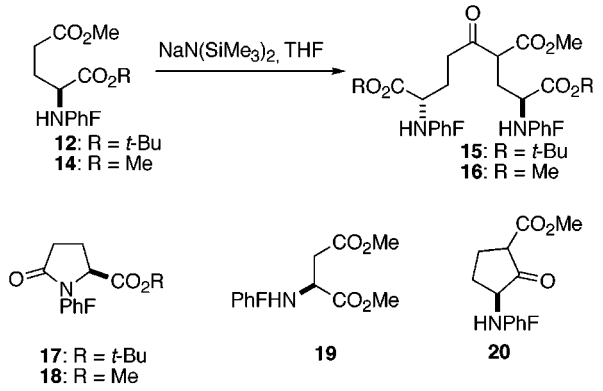


Figure 2. Claisen condensation substrates and products.

Wittig reaction with aldehyde **5** and methyl (triphenylphosphoranylidene)acetate in THF provided α,β-unsaturated ester **8** in 93% yield after chromatography (Scheme 3).[15,16] The formation of the *E*-isomer was confirmed by proton NMR which showed a vicinal coupling constant of 15.7 Hz between the vinyl protons. (2*S*)-δ-Methyl α-*tert*-butyl *N*-(PhF)aminoadipate (**9**) was then obtained in 99% yield from hydrogenation of olefin **8** using platinum-on-carbon as catalyst in EtOAc followed by removal of the catalyst by filtration through Celite.[17] Hydrogenolysis of the phenylfluorenylamine was not observed under these conditions. Selective hydrolysis of the methyl ester of **9** was readily accomplished with hydroxide ion and provided α-*tert*-butyl *N*-(PhF)-α-aminoadipate (**10**) in 94% yield. Acylation of thiophenol with **10** and DCC−DMAP in CH_3CN gave (2*S*)-α-*tert*-butyl *N*-(PhF)amino adipate δ-thiophenyl ester **11** in 67% yield.[18]

Prior to the present investigation, we found that self-condensations of *N*-(PhF)glutamate diesters **12** and **14** provided, respectively, β-ketoesters **15** and **16** in 82% and 75% yields accompanied by minor amounts of *N*-(PhF)-pyroglutamates **17** and **18** (Figure 2).[3,4] The self-condensations of (2*S*)-α-*tert*-butyl β-methyl *N*-(PhF)-aspartate (**3**), (2*S*)-dimethyl *N*-(PhF)aspartate (**19**), and (2*S*)-α-*tert*-butyl δ-methyl *N*-(PhF)aminoadipate (**9**) were thus examined using conditions previously optimized for the condensation of (2*S*)-α-*tert*-butyl γ-methyl *N*-(PhF)-glutamate (**12**). Treatment of either aspartate diester **3** or **19** with $NaN(SiMe_3)_2$ in THF at −30 °C returned only starting material. Exposure of α-aminoadipate **9** to the same conditions gave no Claisen condensation product;

(11) (a) Direct conversion of α-*tert*-butyl β-methyl *N*-(PhF)aspartate (**3**) into *N*-(PhF)aspartate β-aldehyde **5** with DIBAL-H has also been accomplished: Swarbrick, M. E.; Gosselin, F.; Lubell, W. D. Manuscript in preparation. Attempts failed to convert **3** to **5** using the conditions described for the preparation of glutamate γ-aldehyde in (b) Bach, A. C., II; Markwalder, J. A.; Ripka, W. C. *Int. J. Pept. Protein Res.* **1991**, *38*, 314. (c) Diol **7** was isolated as the major product from attempts selectively reduce diester **3** using $NaBH_4$−LiI in THF under conditions described in Benz, G. *Liebigs Ann. Chem.* **1984**, 1424.

(12) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164.

(13) Baldwin, J. E.; North, M.; Flinn, A. *Tetrahedron Lett.* **1987**, *28*, 3167.

(14) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

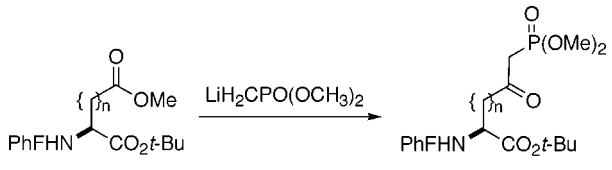
(15) The phosphonium ylide was prepared according to Isler, O.; Gutmann, H.; Montavon, M.; Rüegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *40*, 1242.

(16) (a) α-*tert*-Butyl *N*-(BOC)aspartate β-aldehyde has been used in Wittig condensations to prepare α-aminoadipic acid: see ref 8 and Ramsamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42; α-aminosuberic acid: (b) Wernic, D.; DiMaio, J.; Adams, J. *J. Org. Chem.* **1989**, *54*, 4224. Alternative examples of aspartate semialdehyde include: α-*tert*-butyl *N*-(BOC)aspartate β-aldehyde (c) Tong, G.; Perich, J. W.; Johns, R. B. *Tetrahedron Lett.* **1990**, *31*, 3759. *N*-(Cbz)aspartate β-aldehydes: Fushiya, S.; Nakatsuyama, S.; Sato, Y.; Nozoe, S. *Heterocycles* **1981**, *15*, 819.

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

(18) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

Table 1. Synthesis of β-Ketophosphonates 21−23



3 : n = 1
12 : n = 2
9 : n = 3

21 : n = 1
22 : n = 2
23 : n = 3

entry	n	Base	Solvent	M[a]	% ketone	% rcvd diester	% **17**	% **20**
a	1	*n*-BuLi	$PhCH_3$	0.1	71	-	-	-
b	1	*n*-BuLi	Et_2O	0.05	71	8	-	-
c	2	*n*-BuLi	Et_2O	0.05	84	4	12	-
d	2	*n*-BuLi	THF	0.1	52	15	34	-
e	2	*n*-BuLi	THF	0.5	28	50	22	-
f	2	*n*-BuLi	THF	1.0	25	57	18	-
g	2	$LiN(SiMe_3)_2$	THF	1.0	-	<5	>90	-
h	2	*n*-BuLi•KO*t*-Bu	THF	0.1	-	-	>90	-
i	3	*n*-BuLi	$PhCH_3$	0.1	90	5	-	5
j	3	*n*-BuLi	Et_2O	0.05	40	54	-	6

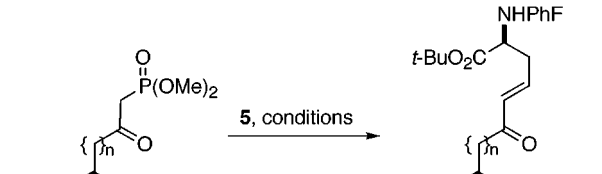
[a]Concentration of $H_3CPO(OCH_3)_2$ (250 mol%).

however, the Dieckmann cyclization product, cyclic β-keto ester **20**, was isolated in less than 10% yield along with recovered starting material. Dieckmann cyclization of dimethyl *N*-(PhF)aminoadipate has previously been used in the synthesis of carbocyclic nucleosides.[8,17a] Although α-*tert*-butyl ester **9** was employed, the Dieckmann reaction was still favored over the Claisen condensation.

Crossed Claisen condensations between glutamate and the two other aminodicarboxylates were also unsuccessful as discussed in the Supporting Information. In summary, Claisen condensations failed to occur with aspartate diesters and returned starting material, glutamate diesters gave good yields of β-keto esters **15** and **16** in self-condensations, and α-aminoadipate diesters were not reactive in Claisen condensations and susceptible to Dieckmann condensation giving cyclic β-keto ester **20**. Attempts to use α-aminoadipate thioester **11** failed to provide the Claisen condensation products. Although continued investigation may eventually lead to conditions for Claisen condensations with aspartate and α-aminoadipate esters, we abandoned this approach in light of positive results from an alternative method for joining two amino dicarboxylates to make linear precursors for azabicycloalkane amino acid synthesis.

Successful olefination of aspartate β-aldehyde **5** in the synthesis of α-aminoadipate **9** inspired an investigation of the Horner−Wadsworth−Emmons olefination of **5** with aminodicarboxylate-derived β-keto phosphonates to synthesize α,ω-diaminodicarboxylates (Table 2). This olefination strategy overcomes the problems of regiocontrol inherent in the Claisen condensation approach, because different amino dicarboxylates are joined in a selective fashion.[19] All possible α,ω-diaminodicarboxylate configurations may thus be synthesized by combining D- and L-amino dicarboxylate starting materials. Furthermore, the geometry of the resulting olefin may later be used to direct the cyclization reactions of unsymmetrical α,ω-diaminodicarboxylate intermediates in order to form regioselectively azabicyclo[*X*.*Y*.0]alkane. Indeed, the resulting α,β-unsaturated ketone intermediates may also

Table 2. Synthesis of Diaminodicarboxylates 24−26



21 : n = 1
22 : n = 2
23 : n = 3

24 : n = 1
25 : n = 2
26 : n = 3

entry	n	Base	Solvent	Temp. °C	Time	% olefin
a	1	K_2CO_3	CH_3CN	25	72 h	87
b	2	K_2CO_3	CH_3CN	10	72 h	78
c	2	K_2CO_3	CH_3CN	25	48 h	52
d	2	Cs_2CO_3	CH_3CN	10	36 h	75
e	2	LiOH•H_2O	Et_2O	25	18 d	73
f	2	$Ba(OH)_2$•$8H_2O$	40:1 THF:H_2O	25	48 h	45
g	2	LiCl, DBU	CH_3CN	25	48 h	33
h	3	K_2CO_3	CH_3CN	25	96 h	78

be used to introduce side-chains onto the heterocycle by both alkylations and conjugate additions.[5,20]

The prerequisite β-keto phosphonates were synthesized from the addition of the lithium anion of dimethyl methyl phosphonate to the ω-methyl ester of the *N*-(PhF)-aminodicarboxylates **3**, **9**, and **12** (Table 1).[21] Initial investigations were conducted with (2*S*)-α-*tert*-butyl γ-methyl *N*-(PhF)glutamate (**12**) to provide (2*S*)-α-*tert*-butyl 2-*N*-(PhF)amino-5-oxo-6-(dimethylphosphonyl)hexanoate (**22**). At first, **22** was obtained in low yield from reactions performed in THF and (2*S*)-*tert*-butyl *N*-(PhF)-pyroglutamate (**17**) was isolated as a second product,[3] presumed to result from either direct deprotonation of the PhF amine and cyclization onto the methyl ester or by enolization of the glutamate ester, followed by decomposition to ketene and cyclization. Changes in the base favored the formation of pyroglutamate **17** (entries g and h). The yield of β-keto phosphonate **22** increased on lowering the concentration of dimethyl methyl phosphonate in THF. Switching solvents from THF to diethyl ether increased the reaction yield and selectivity such that β-keto phosphonate **22** was isolated in 84% yield, along with 12% of pyroglutamate **17**. Treatment of (2*S*)-α-*tert*-butyl β-methyl *N*-(PhF)aspartate (**3**) under similar conditions in diethyl ether gave (2*S*)-α-*tert*-butyl 2-*N*-

(19) Some alternative strategies for synthesizing α,ω-diaminodicarboxylate analogues include as follows: 2,5-Diaminoadipic acids: (a) Hiebl, J.; Blanka, M.; Guttman, A.; Kollmann, H.; Leitner, K.; Mayrhofer, G.; Rovenszky, F.; Winkler, K. *Tetrahedron* **1998**, *54*, 2059. 2,6-Diaminopimelic acids: (b) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133. (c) Jurgens, A. R. *Tetrahedron Lett.* **1992**, *33*, 4727. (d) Williams, R. M.; Yuan, C. *J. Org. Chem.* **1992**, *57*, 6519 and ref 3 therein. 2,7-Diaminosuberic acids: (e) Williams, R. M.; Liu, J. *J. Org. Chem.* **1998**, *63*, 2130. (f) Kremminger, P.; Undheim, K. *Tetrahedron* **1997**, *53*, 6925. (g) Nutt, R. F.; Strachan, R. G.; Veber, D. F.; Holly, F. W. *J. Org. Chem.* **1980**, *45*, 3078. (h) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689. (i) 2,9-Diaminosebacic acids: Andrews, M. J. I.; Tabor, A. B. *Tetrahedron Lett.* **1997**, *38*, 3063.

(20) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. Conjugate addition of $LiCuMe_2$ to dimethyl (2*S*)-*N*-(PhF)-3,4-didehydroglutamate has given good yield of the corresponding β-methylglutamate: see ref 7a above.

(21) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.

Table 3. Comparison of the Dihedral Angles from Azabicycloalkane X-ray Data and Ideal Peptide Turns

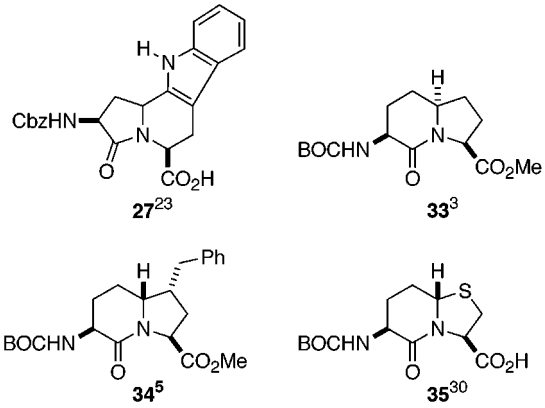
entry	ψ, deg	ϕ, deg
(2*S*,6*R*,8*S*)−8-*N*-(BOC)amino indolizidin-9-one 2-carboxylate **31**[27]	−141	−34
(3*S*,6*R*,7*S*,9*S*)−3-*N*-(BOC)amino 7-benzylindolizidin-2-one 9-carboxylate **34**[5]	−147	−56
(3*S*,6*R*,9*S*)−3-*N*-(BOC)amino 7-thiaindolizidin-2-one 9-carboxylate **35**[30]	−161	−69
(3*S*,6*S*,9*S*)−3-*N*-(BOC)amino indolizidin-2-one 9-carboxylate **33**[3]	−176	−78
Type II′ β-turn *i* + 1 and *i* + 2 residues[28]	−120	−80
inverse γ-turn *i* + 2 residue[29]		−80

(PhF)amino-4-oxo-5-(dimethylphosphonyl)pentanoate (**21**) in 71% yield. Pentanoate **21** was obtained in the same yield when toluene was employed as solvent at slightly higher concentration. Exposure of (2*S*)-α-*tert*-butyl δ-methyl α-*N*-(PhF)aminoadipate (**9**) under similar conditions in diethyl ether gave (2*S*)-α-*tert*-butyl 2-*N*-(PhF)-amino-6-oxo-7-(dimethylphosphonyl)heptanoate (**23**) in 40% yield contaminated with 6% of cyclic β-keto ester **20** as well as 54% of starting **9**. Alternatively, the use of toluene as solvent in the addition of dimethyl methyl phosphonate to aminoadipate **9** improved the yield of heptanoate **23** to 90% (Table 1).

With an efficient method for synthesizing β-keto phosphonates in hand, we explored next Horner−Wadsworth−Emmons olefinations with *N*-(PhF)aspartate β-aldehyde **5** (Table 2). (2*S*, 9*S*)-Di-*tert*-butyl 5-oxo-2,9-bis[*N*-(PhF)-amino]dec-4-enedioate (**25**) was initially synthesized from the reaction of β-keto phosphonate **22** with aldehyde **5** at room temperature using a variety of bases and conditions.[22] We found that olefination proceeded slowly using anhydrous potassium carbonate in CH_3CN at room temperature without any detectable decomposition of aldehyde **5** and gave unsaturated ketone **25** in up to 78% yield after chromatography. The reaction was accelerated by using cesium carbonate in CH_3CN which gave olefin **25** in similar yield. (2*S*,8*S*)-Di-*tert*-butyl 4-oxo-2,8-bis[*N*-(PhF)amino]non-4-enedioate (**24**) and (2*S*, 10*S*)-di-*tert*-butyl 6-oxo-2,10-bis[*N*-(PhF)amino]undec-4-enedioate (**26**) were then, respectively, obtained in 87% and 72% yields from the treatment of aspartate- and α-aminoadipate-derived β-keto phosphonates **21** and **23** with *N*-(PhF)aspartate β-aldehyde **5** using potassium carbonate in CH_3CN at room temperature. Olefins **24**−**26** all were of the *E*-configuration as indicated by the large (15.9−16.0 Hz) vicinal coupling constant for the vinyl protons.

α,ω-Diaminodicarboxylates of nine to eleven carbon chain lengths were effectively synthesized using the olefination sequence. Their introduction into Scheme 1 offers potential to prepare five azabicyclo[*X*.*Y*.0]alkane amino acids having different ring sizes. Presently pursuing the production of this spectrum of rigid dipeptides, we have illustrated the utility of the olefination route by the first synthesis of indolizidin-9-one amino acid **2**.

Interest in azabicyclo[*X*.*Y*.0]alkane amino acids such as **2** has grown since the synthesis of the related indole-fused analogue **27** via a sequence featuring a Pictet−Spengler reaction between a protected aspartate β-aldehyde and tryptophan and subsequent lactam cyclization



27[23] **33**[3] **34**[5] **35**[30]

Figure 3. Related indolizidinone aminocarboxylates.

(Figure 3).[23] In analogues of gramicidin S, indole-fused indolizidinone **27** has recently been shown to serve as a type II′ β-turn mimic contingent upon ring-fusion stereochemistry which influenced both the conformation and the bioactivity of the peptide antibiotic.[24] We selected to synthesize indolizidin-9-one amino acid **2** as our first target because of its structural similarities to indolizidin-2-one amino acid **1** and because, to the best of our knowledge, **2** had never been synthesized.[2]

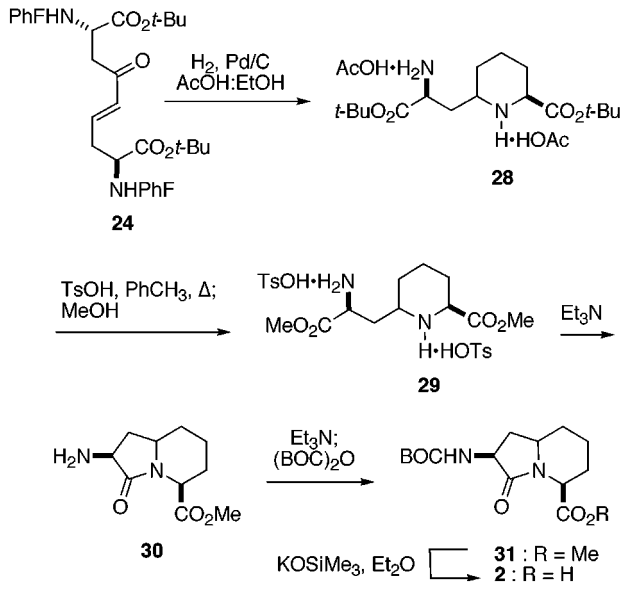
(2*S*,8*S*)-Di-*tert*-butyl 4-oxo-2,8-bis[*N*-(PhF)amino]non-4-enedioate (**24**) may be converted to both indolizidin-9-one amino acid **2** as well as an azabicyclo[5.2.0]alkane amino acid, subject to which amine reacts with the ketone at the azelate 4-position. Presuming that reductive amination would favor formation of the piperidine instead of the azetidine ring system, we subjected γ-oxo-α,ω-diaminoazelate **24** to the same reductive amination conditions used in the synthesis of **1**.[3] Hydrogenation of azelate **24** with palladium-on-carbon as catalyst in 9:1 EtOH:AcOH proceeded by reduction of the α,β-unsaturated ketone, cleavage of the phenylfluorenyl groups, intramolecular imine formation, protonation, and hydrogen addition to the iminium ion intermediate (Scheme 4). 6-Alkylpipecolate **28** was formed as a 9:1 mixture of diastereomers and was subsequently transformed into azabicyclo[4.3.0]alkane amino ester **30** by a one-pot three-step reaction sequence featuring *tert*-butyl ester solvolysis with *p*-toluenesulfonic acid, esterification in methanol, and lactam cyclization on addition of triethylamine. Lactam formation was monitored by proton NMR spectroscopy by measuring the disappearance of the methyl ester singlets at 3.80 and 3.88 ppm for **29** and the appearance of a new methyl singlet at 3.72 ppm for **30**

(22) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (c) Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501. (d) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774. (e) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374. (f) Blackwell, C. M.; Davidson, A. H.; Launchbury, S. B.; Lewis, C. N.; Morrice, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 1935.

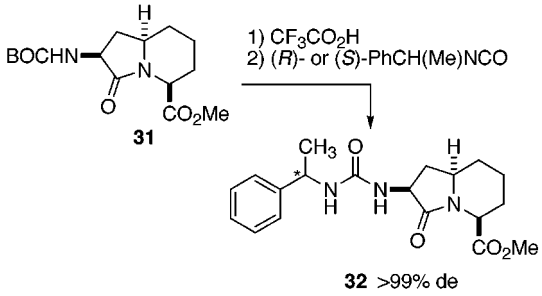
(23) The synthesis of 2(*S*)-amino-3-oxo-11b(*R*)-hexahydroindolizino-[8, 7-*b*]indole-5(*S*)-carboxylate is reported in (a) de la Figuera, N.; Rozas, I.; García-López, M. T.; González-Muñiz, R. *J. Chem. Soc., Chem. Commun.* **1994**, 613. (b) de la Figuera, N.; Alkorta, I.; Rozas, I.; García-López,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

(24) Andreu, D.; Ruiz, S.; Carreño, C.; Alsina, J.; Albericio, F.; Jiménez, M. A.; de la Figuera, N.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Am. Chem. Soc.* **1997**, *119*, 10579.

Scheme 4. Synthesis of Indolizidin-9-one *N*-(BOC)Amino Esters



Scheme 5. Enantiomeric Purity of Indolizidinone Ester 31



in CD_3OD. *N*-Protection of **30** with di-*tert*-butyl dicarbonate and triethylamine in dichloromethane provided *N*-(BOC)amino indolizidin-9-one ester **31** in 85% overall yield from ketone **24**. Hydrolysis of methyl ester **31** using $KOSiMe_3$ in ether gave *N*-(BOC)amino indolizidin-9-one acid **2** in 96% yield.[25]

The enantiomeric purity of (2*S*,6*R*,8*S*)-**31**, produced as the major diastereomer from the reductive amination/lactam cyclization sequence on **24**, was determined after conversion to (1′*R*)- and (1′*S*)-*N*-α-methylbenzylureas **32** (Scheme 5). 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.[3] Measurement of the diastereomeric methyl ester singlets at 3.56 and 3.52 ppm in C_6D_6 by 600 MHz ^1H NMR spectroscopy demonstrated **32** to be of >99% diastereomeric excess. Hence, diaminodicarboxylates **24**−**26**, *N*-(BOC)amino indolizidin-9-one ester **31**, and acid **2** are all are presumed to be of >99% enantiomeric purity.

The stereochemistry of the ring fusion carbon of *N*-(BOC)amino indolizidin-9-one acid (2*S*,6*R*,8*S*)-**2** was initially assigned based on analogy with *N*-(BOC)amino indolizidin-2-one acid (3*S*,6*S*,9*S*)-**1**.[3] Since hydrogenation of α-*tert*-butyl δ-oxo-α-*N*-(PhF)amino esters produces 5-alkylprolines with high selectivity in favor of the *cis*-

(25) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.

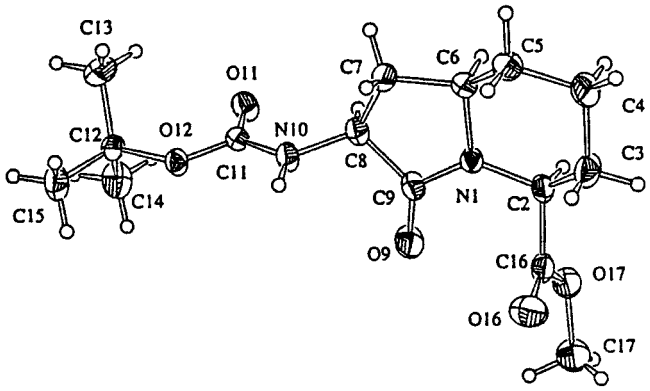


Figure 4. ORTEP view of *N*-(BOC)amino indolizidin-9-one methyl ester (2*S*,6*R*,8*S*)-**31**. Ellipsoids drawn at 40% probability level. Hydrogens represented by spheres of arbitrary size.[27]

diastereomer,[26] we presumed that reductive amination of amino ketone **24** proceeded to form *cis*-6-alkylpipecolate (2*S*,6*R*,2′*S*)-**28**. Crystallization of (2*S*,6*R*,8*S*)-methyl 9-oxo-8-*N*-(BOC)amino-1-azabicyclo[4.3.0]nonane-2-carboxylate ((2*S*,6*R*,8*S*)-**31**) from EtOAc and X-ray crystallographic analysis confirmed our hypothesis (Figure 4).[27] In the crystal structure of *N*-(BOC)amino indolizidin-9-one ester **31**, the dihedral angles of the backbone atoms constrained inside the heterocycle resemble the values of the central residues in an ideal type II′ β-turn. For comparison, we have listed in Table 1 the values for an ideal type II′ β-turn[28] and an ideal inverse γ-turn conformation[29] with the values for **31** and those observed in the crystal structures of the corresponding methyl esters of indolizidinone *N*-(BOC)amino acid, (3*S*,6*S*,9*S*)-**33**,[3] and (3*S*,6*R*,7*S*,9*S*)-3-*N*-(BOC)amino 7-benzylindolizidin-2-one 9-carboxylate **34**,[5] as well a (3*S*,6*R*,9*S*)-7-thiaindolizidin-2-one β-turn dipeptide analogue **35** (Figure 3).[30] Aside from crystal packing forces, this body of X-ray data begins to suggest that azabicycloalkane ring-size, stereochemistry, and alkyl substituents all may significantly influence peptide backbone geometry.

Conclusion

We have developed a new approach for synthesizing α,ω-diaminodicarboxylates of various chain lengths for the construction of azabicyclo[*X*.*Y*.0]alkane amino acids of different ring sizes. α,ω-Diaminodicarboxylates of nine to eleven carbon chain lengths were effectively synthesized by the Horner−Wadsworth−Emmons olefination of α-*tert*-butyl *N*-(PhF)aspartate β-aldehyde (**5**) with β-keto

(26) (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. (c) Ho, T. L.; Gopalan, B.; Nestor, J. J., Jr. *J. Org. Chem.* **1986**, *51*, 2405. (d) Fushiya, S.; Chiba, H.; Otsubo, A.; Nozoe, S. *Chem. Lett.* **1987**, 2229.

(27) The structure of **31** was solved at l'Université de Montréal X-ray facility using direct methods (SHELXS96) and refined with NRCVAX and SHELXL96: $C_{15}H_{24}N_2O_5$; M_r = 312.362; orthorhombic, colorless crystal; space group $P2_12_12_1$; unit cell dimensions (Å) a = 9.888(4), b = 12.234(2), c = 13.338(6); volume of unit cell (Å^3) 1613.5(10); Z = 4; R_1 = 0.0316 for $I > 2\ \sigma(I)$, wR_2 = 0.0728 for all data; GOF = 1.010. The author has deposited the atomic coordinates for the structure of **31** 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.

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

(29) Madison, V.; Kopple, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 4855.

(30) Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577.

phosphonates derived from aspartate, glutamate, and α-aminoadipate. Our approach has been used in the first synthesis of azabicyclo[4.3.0]alkane amino acid **2**. Enantiopure indolizidin-9-one *N*-(BOC)amino acid **2** was synthesized in nine steps and >25% overall yield from inexpensive aspartic acid as chiral educt via a route featuring reductive amination and lactam cyclization of γ-oxo-α,ω-diaminoazelate **24**. Because α,ω-diaminodicarboxylates **25** and **26** may be similarly converted to fused heterocycles having larger ring sizes and because alkylations and conjugate additions to **24**−**26** may be used to attach side-chains at different points on the heterocycle, this olefination strategy has greatly expanded our methodology for synthesizing azabicyclo-[*X*.*Y*.0]alkane amino acids for the exploration of conformation−activity relationships of biologically active peptides.

Experimental Section

General. Unless otherwise noted all reactions were run under nitrogen atmosphere and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately before use; toluene was distilled from sodium; CH_2Cl_2 and CH_3CN were distilled from CaH_2; $CHCl_3$ was distilled from P_2O_5; triethylamine (Et_3N) was distilled from BaO; CH_3CN was stored over 4 Å sieves. Potassium carbonate was dried at 120 °C for 18 h prior to use. Final reaction mixture solutions were dried over Na_2SO_4. 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 ($(CH_3)_4Si$), $CHCl_3$, and C_6H_6; coupling constants are reported in hertz. Chemical shifts of the vinyl carbons in **24**−**26** and of PhF aromatic carbons are not reported in the ^{13}C NMR spectra. Analytical thin-layer chromatography (TLC) was performed by using aluminum-backed silica 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*)-*tert*-Butyl β-Methyl *N*-(PhF)Aspartate (3). To a stirred suspension of β-methyl *N*-(PhF)aspartate (22 g, 56.4 mmol, prepared using the protocol in ref 6b) in CH_2Cl_2 (120 mL) was added *O*-*tert*-butyl trichloroacetimidate (112 mL, 200 mol %, 1 M in cyclohexane, prepared using the protocol in ref 10), the mixture was stirred for 3 days, filtered, and evaporated, and the residue was resubmitted to the same conditions as above for 2 days. Filtration and evaporation, followed by chromatography (5−10% EtOAc in hexanes), gave diester **3** (21 g, 84%) as a clear crystalline solid: mp = 75−76 °C, lit. 75−76 °C;[6b] TLC R_f = 0.40 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −233.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.71−7.67 (m, 2 H), 7.41−7.18 (m, 11 H), 3.67 (s, 3 H), 2.90 (t, 1 H, *J* = 5.7), 2.49 (dd, 1 H, *J* = 14.8, 5.8), 2.32 (dd, 1 H, *J* = 14.8, 5.6), 1.25 (s, 9 H); ^{13}C NMR δ 172.95, 171.17, 81.23, 72.93, 53.47, 51.49, 40.44, 27.71; HRMS calcd for $C_{28}H_{30}NO_4$ [M + 1]: 444.2175, found: 444.2157. Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.55; H, 6.79; N, 3.22.

(2*S*)-*tert*-Butyl 2-[*N*-(PhF)amino]-4-hydroxybutanoate (4). To a stirred solution of diester **3** (10.0 g, 22.6 mmol) in THF (760 mL) at −40 °C was added DIBAL-H (67.6 mL, 67.6 mmol, 300 mol %, 1.0 M in hexanes). The solution was stirred at −40 °C for 30 min, quenched with acetone (3.3 mL), diluted with MeOH (20 mL), and allowed to warm to room temperature and evaporated. The residue was dissolved in ether (200 mL), treated with NaH_2PO_4 (200 mL, 1 M) and sodium−potassium tartrate (10 g), stirred vigorously for 30 min, and filtered. The biphasic filtrate was saturated with solid NaCl, and the aqueous layer was extracted with ether until TLC showed no UV active material. The combined organic layers were washed with brine, dried, filtered, and evaporated. Chromatography (10−20% EtOAc in hexanes) afforded alcohol **4** as a white crystalline solid (9.0 g, 96% yield): mp = 121−122 °C; TLC R_f = 0.12 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −308.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.72−7.21 (m, 13 H), 3.71 (m 1 H), 3.59 (m, 1 H), 2.70 (dd, 1 H, *J* = 9.0, 4.3), 1.62 (m, 2 H), 1.17 (s, 9 H); ^{13}C NMR δ 174.25, 81.18, 73.16, 61.33, 56.07, 35.80, 27.81; HRMS calcd for $C_{27}H_{30}NO_3$ [M + 1]: 416.2226, found: 416.2240. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37. Found: C, 78.05; H, 7.22; N, 3.43.

Homoserine lactone **6** and diol **7** were encountered when the reduction was conducted at higher concentrations and with alternative reducing agents.

(2*S*)-*N*-(PhF)Homoserine γ-lactone (6) was obtained as a white solid: mp = 195 °C; TLC R_f = 0.27 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −299.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.75−7.66 (m, 2 H), 7.43−7.19 (m, 11 H), 4.11 (t, 1 H, *J* = 9.0), 3.72 (m, 1 H), 2.94 (dd, 1 H, *J* = 11.5, 8.1), 1.80 (m, 1 H), 1.29 (m, 1 H); ^{13}C NMR δ 178.0, 72.93, 65.67, 52.2, 32.95; HRMS calcd for $C_{23}H_{20}NO_2$ [M + 1]: 342.1494, found: 342.1482. Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.59; H, 5.58; N, 3.87.

(2*S*)-2-[*N*-(PhF)amino]-1,4-butanediol (7) was obtained as an oil: TLC R_f = 0.21 (4:1 EtOAc:hexanes); $[\alpha]^{20}_D$ −42.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.71−7.67 (m, 2 H), 7.40−7.18 (m, 11 H), 3.62 (dd, 1 H, *J* = 5.7, 5.1), 3.24 (br m, 2 H), 3.03 (dd, 1 H, *J* = 11.0, 2.9), 2.83 (dd, 1 H, *J* = 11.0, 4.4), 2.36 (br m, 1 H), 1.59 (m, 1 H), 1.37 (m, 1 H); ^{13}C NMR δ 72.64, 64.14, 60.49, 53.20, 35.72; HRMS calcd for $C_{23}H_{24}NO_2$ [M + 1]: 346.1807, found: 346.1813.

(2*S*)-*tert*-Butyl 2-[*N*-(PhF)amino]-4-oxobutanoate (5). A solution of oxalyl chloride (3.95 mL, 45 mmol, 250 mol %) in CH_2Cl_2 (97 mL) at −60 °C was treated with DMSO (4.47 mL, 63 mmol, 350 mol %) in CH_2Cl_2 (13.3 mL), stirred for 30 min, and treated dropwise with a solution of alcohol **4** (7.48 g, 18 mmol) in CH_2Cl_2 (25 mL). The clear solution was stirred for 4 h, treated with Et(*i*-Pr)$_2$N (18.8 mL, 108 mmol, 600 mol %), and warmed to room temperature over 60 min. The reaction mixture was added to aqueous NaH_2PO_4 (100 mL, 1 M), and the layers were separated. The aqueous layer was saturated with solid NaCl and extracted repeatedly with EtOAc (4 × 50 mL). The combined organic layers were then washed with H_2O (1 × 50 mL) and brine (60 mL). Aldehyde **5** was obtained as a colorless solid after chromatography using a gradient of 0−5% EtOAc in hexanes: 6.8 g, 91% yield; mp = 91−93 °C; TLC R_f = 0.41 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −263.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 9.52 (dd, 1 H, *J* = 2.1, 2.8), 7.74−7.69 (m, 2 H), 7.41−7.16 (m, 11 H), 3.04 (dd, 1 H, *J* = 5.3, 7.6), 2.40 (m, 2 H), 1.23 (s, 9 H); ^{13}C NMR δ 173.17, 158.10, 81.63, 72.94, 52.10, 48.34, 27.73; HRMS calcd for $C_{30}H_{36}NO_5S$ [M + 109 (thioglycerol)]: 522.2315, found: 522.2269. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.67; H, 6.58; N, 3.42.

(2*S*)-α-*tert*-Butyl δ-Methyl 2-[*N*-(PhF)Amino]-Δ^4-dehydroadipate (8). A solution of aldehyde **5** (2.0 g, 4.8 mmol) and methyl(triphenylphosphoranylidene) acetate[15] (2.4 g, 7.25 mmol, 150 mol %) in THF (48 mL) was stirred at a reflux for 24 h. Evaporation of the volatiles and chromatography (5−20% Et_2O in hexanes) of the residue furnished diester **8** (2.11 g, 93% yield) as a thick clear oil: TLC R_f = 0.43 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −116.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.71−7.67 (m, 2 H), 7.44−7.19 (m, 11 H), 6.91 (m, 1 H), 5.79 (d, 1 H, *J* = 15.7), 3.76 (s, 3 H), 2.67 (dd, 1 H, *J* = 6.4, 6.1), 2.19 (m, 2 H), 1.20 (s, 9 H). ^{13}C NMR δ 173.82, 166.58, 145.64, 122.90, 81.16, 72.98, 55.49, 51.39, 38.52, 27.82. HRMS calcd for $C_{30}H_{32}NO_4$ [M + 1]: 470.2331, found: 470.2314. Anal. Calcd for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98. Found: C, 77.16; H, 6.80; N, 2.81.

(2*S*)-α-*tert*-Butyl δ-Methyl 2-[*N*-(PhF)Amino]adipate (9). A solution of **8** (1.96 g, 4.18 mmol) and Pt/C (196 mg, 5 wt %) in ethyl acetate (85 mL) was stirred under 2.75 atm of H_2 for 16 h. The mixture was filtered through a plug of Celite, which was washed thoroughly with EtOAc. Evaporation of the volatiles gave α-aminoadipate **9** (1.95 g, 99% yield) as a thick clear oil: TLC R_f = 0.43 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$

−179.0 (*c* 4.4, $CHCl_3$); lit.[8] $[\alpha]^{25}_D$ −180 (*c* 4.4, $CHCl_3$); ^{1}H NMR δ 7.67−7.63 (m, 2 H), 7.43−7.13 (m, 11 H), 3.62 (s, 3 H), 2.50 (m, 1 H), 2.15−2.11 (m, 2 H), 1.71−1.63 (m, 2 H), 1.44−1.41 (m, 1 H), 1.39−1.21 (m, 1 H), 1.17 (s, 9 H); ^{13}C NMR δ 175.08, 173.73, 80.42, 72.90, 55.33, 51.29, 34.90, 33.58, 27.78, 20.77; HRMS calcd for $C_{30}H_{34}NO_4$ [M + 1] 472.2488, found: 472.2505. Anal. Calcd for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97. Found: C, 76.46; H, 7.15; N, 3.02.

(2*S*)-α-*tert*-Butyl 2-[*N*-(PhF)Amino]adipate (10). A stirred solution of diester **9** (504.8 mg, 1.07 mmol) in dioxane (10 mL) was treated with aqueous LiOH (2.70 mL, 500 mol %, 2 M), heated at a reflux for 2 h, cooled to room temperature, and acidified with concentrated H_3PO_4 to pH 2. The aqueous layer was saturated with NaCl and extracted with EtOAc until TLC of the organic layer showed no UV active material. The combined organic layers were washed with brine (5 mL), dried, and evaporated to an oil which was chromatographed using a gradient of 0−10% *i*-PrOH in $CHCl_3$ as eluant to afford **10** (459 mg, 94% yield) as an oil: TLC R_f = 0.42 (1:9 *i*-PrOH:$CHCl_3$); $[\alpha]^{20}_D$ −191.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.72−7.65 (m, 2 H), 7.53−7.13 (m, 12 H), 2.55 (m, 1 H), 2.21 (m, 2 H), 1.73 (m, 2 H), 1.48 (m, 2 H), 1.29 (s, 0.5 H), 1.22 (s, 8 H), 1.16 (s, 0.5 H). ^{13}C NMR δ 179.54, 175.03, 80.67, 73.01, 55.39, 34.65, 33.62, 27.83, 20.53. HRMS calcd for $C_{29}H_{32}N0_4$ [M + 1]: 458.2331, found: 458.2342.

(2*S*)-α-*tert*-Butyl δ-*S*-Phenyl 2-[*N*-(PhF)Amino]adipate (11). To a solution of adipate **10** (100 mg, 0.22 mmol) and TBTU (105 mg, 0.33 mmol, 150 mol %) in CH_3CN (2.2 mL) was added thiophenol (45 μL, 0.44 mmol, 200 mol %). The mixture was cooled to 0 °C, and Et(^{i}Pr)$_2$N (76 μL, 200 mol %) was added. A slow reaction followed; however, addition of DMAP (10 mol %) and DCC (150 mol %) accelerated the reaction as witnessed by TLC. After 24 h, the reaction mixture was filtered and evaporated to a residue that was chromatographed (5% EtOAc in hexanes) to give thioester **11** (80.6 mg, 67%) as a thick clear oil: ^{1}H NMR δ 7.71−7.68 (m, 2 H), 7.46−7.34 (m, 10 H), 7.27−7.20 (m, 7 H), 2.55−2.46 (m, 3 H), 1.85−1.74 (m, 2 H), 1.54−1.36 (m, 2 H), 1.21 (s, 9 H); ^{13}C NMR δ 196.98, 175.05, 80.62, 72.98, 55.41, 43.30, 34.77, 27.87, 21.5; HRMS calcd for $C_{35}H_{36}NO_3S$ [M + 1]: 550.2416, found: 550.2398.

(2S)-α-*tert*-Butyl 2-*N*-(PhF)Amino-4-oxo-5-(dimethylphosphonyl)pentanoate (21). A −78 °C solution of dimethyl methyl phosphonate (3.1 mL, 28,2 mmol, 250 mol %) in toluene (276 mL) was treated with *n*-butyllithium (11.4 mL, 28.2 mmol, 250 mol %, 2.5 M in hexanes), stirred for 20 min at −78 °C, and transferred by cannula dropwise over 30 min into a −78 °C solution of α-*tert*-butyl β-methyl *N*-(PhF)aspartate (**3**, 5.0 g, 11.29 mmol) in toluene (112 mL). The solution was stirred for 1 h, warmed to room temperature, quenched with aqueous NaH_2PO_4 (40 mL, 1 M), and diluted with EtOAc (50 mL). The aqueous layer was saturated with solid NaCl and extracted with EtOAc until TLC of the organic layer showed no UV-active material. The combined organic layers were washed with brine, dried, and evaporated to a residue that was chromatographed using 10−100% EtOAc in hexanes as eluant to give **21** as a colorless solid (4.28 g, 71%): mp 113−114 °C; TLC R_f = 0.17 (4:1 EtOAc:hexanes); $[\alpha]^{20}_D$ −136.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.69−7.66 (m, 2 H), 7.37−7.16 (m, 12 H), 3.78−3.74 (m, 6 H), 3.03 (s, 1 H), 2.97 (s, 1 H), 2.85 (dd, 1 H, *J* = 5.3, 5.5), 2.72 (dd, 1 H, *J* = 5.9, 16.1), 2.59 (dd, 1 H, *J* = 4.9, 16.0), 1.23 (s, 9 H); ^{13}C NMR (a mixture of keto−enol tautomers) δ 199.17, 199.11, 172.77, 81.39, 73.00, 53.09, 52.95, 52.89, 48.92, 42.25, 40.98, 27.67; HRMS calcd for $C_{30}H_{35}NO_6P$ [M + 1]: 536.2202, found: 536.2181. Anal. Calcd for $C_{30}H_{34}NO_6P$: C, 67.28; H, 6.40; N, 2.62. Found: C, 67.11; H, 6.70; N, 2.61.

(2*S*)-α-*tert*-Butyl 2-*N*-(PhF)Amino-5-oxo-6-(dimethylphosphonyl)hexanoate (22). A −78 °C solution of dimethyl methyl phosphonate (2.97 mL, 27.2 mmol, 250 mol %) in Et_2O (500 mL) was treated with *n*-butyllithium (11.0 mL, 27.2 mmol, 250 mol %, 2.5 M in hexanes), stirred for 20 min at −78 °C, and transferred by cannula dropwise over 60 min into a −78 °C solution of α-*tert*-butyl γ-methyl *N*-(PhF)glutamate **12** (4.98 g, 1.10 mmol, prepared according to ref 3) in Et_2O (50 mL). The solution was stirred for 2 h, quenched with aqueous NaH_2PO_4 (20 mL, 1 M), and diluted with EtOAc (100 mL). The aqueous layer was saturated with solid NaCl and extracted with EtOAc until TLC of the organic layer showed no UV-active material. The combined organic layers were washed with brine, dried, and evaporated to a residue that was chromatographed using a gradient of 5−100% EtOAc in hexanes as eluant. First to elute was glutamate **12** (188 mg, 4%), followed by α-*tert*-butyl *N*-(PhF)pyroglutamate (**17**,[3] 600 mg, 12−13%). Last to elute was β-ketophosphonate **22** (5.04 g, 84%, oil): TLC R_f = 0.19 (4:1 EtOAc:hexanes); $[\alpha]^{20}_D$ −168.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.68−7.65 (m, 2H), 7.39−7.17 (m, 13H), 3.79 (d, 3H, *J* = 11.2), 3.78 (d, 3 H, *J* = 11.2), 3.08 (m, 3H), 2.65 (m, 2H), 2.50 (dd, 1H, *J* = 5.3, 5.4), 1.66 (m, 2H), 1.18 (s, 9H); ^{13}C NMR (a mixture of keto−enol tautomers) δ 201.29, 201.23, 174.74, 80.81, 72.87, 54.88, 52.93, 52.87, 41.88, 40.60, 40.31, 40.30, 28.98, 27.77; HRMS calcd for $C_{31}H_{37}NO_6P$ [M + 1]: 550.2358, found: 550.2369. Anal. Calcd for $C_{31}H_{36}NO_6P$: C, 67.75; H, 6.60; N, 2.55. Found: C, 67.75; H, 6.74; N, 2.57.

(2*S*)-α-*tert*-Butyl 2-*N*-(PhF)Amino-6-oxo-7-(dimethylphosphonyl)heptanoate (23). A −78 °C solution of dimethyl methyl phosphonate (244 μL, 2.23 mmol, 250 mol %) in toluene (23 mL) was treated with *n*-butyllithium (898 μL, 2.23 mmol, 250 mol %, 2.5 M in hexanes), stirred for 20 min at −78 °C, and transferred by cannula dropwise over 60 min into a −78 °C solution of α-*tert*-butyl δ-methyl *N*-(PhF)aminoadipate (**9**, 423 mg, 0.89 mmol) in toluene (8.9 mL). The solution was stirred for 1 h, let warm to room temperature (ca 1 h), quenched with aqueous NaH_2PO_4 (5 mL, 1 M), and diluted with EtOAc (20 mL). The aqueous layer was saturated with solid NaCl and extracted with EtOAc until TLC of the organic layer showed no UV-active material. The combined organic layers were washed with 10 mL of brine, dried, and evaporated to a residue that was chromatographed using a gradient of 10−100% EtOAc in hexanes as eluant. First to elute was aminoadipate **9** (21 mg, 5%), followed by β-keto ester **20** (20 mg, 5%). Last to elute was β-keto phosphonate **23** (427 mg, 90%), an oil: TLC R_f = 0.16 (4:1 EtOAc:hexanes); $[\alpha]^{20}_D$ −144.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.69−7.65 (m, 2 H), 7.43−7.18 (m, 11 H), 3.77 (d, 3 H, *J* = 11.2), 3.75 (d, 3 H, *J* = 11.2), 3.05 (s, 1 H), 2.97 (s, 1 H), 2.49−2.34 (m, 3 H), 1.67−1.60 (m, 2 H), 1.44−1.26 (m, 2 H), 1.18 (s, 9 H); ^{13}C NMR (a mixture of keto−enol tautomers) δ 201.31, 201.25, 175.07, 80.54, 72.93, 55.37, 52.91, 52.85, 43.53, 41.74, 40.46, 34.52, 27.77, 19.19; HRMS calcd for $C_{32}H_{39}NO_6P$ [M + 1]: 564.2515, found: 564.2521. Anal. Calcd for $C_{32}H_{38}NO_6P$: C, 68.19; H, 6.80; N, 2.49. Found: C, 67.77; H, 7.17; N, 2.61.

(2*S*,8*S*)-Di-*tert*-butyl 4-Oxo-2,8-bis[*N*-(PhF)amino]non-4-enedioate (24). To a stirred solution of β-keto phosphonate **21** (1.20 g, 2.24 mmol) and aldehyde **5** (925 mg, 2.24 mmol, 100 mol %) in CH_3CN (16 mL) was added K_2CO_3 (326 mg, 2.35 mmol, 105 mol %). The mixture was stirred at room temperature for 72 h and evaporated to a residue that was suspended in toluene and added to a column of silica gel. Chromatography using a gradient of 0−10% EtOAc in hexanes and evaporation of the collected fractions gave **24** (1.61 g, 87%) as a white foam: TLC R_f = 0.34 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −160.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.68−7.61 (m, 4 H), 7.41−7.13 (m, 26 H), 6.54−6.50 (m, 1 H), 5.90 (d, 1 H, *J* = 16), 3.29 (br s, 1 H), 3.19 (br s, 1 H), 2.93 (t, 1 H, *J* = 5.4), 2.64 (m, 2 H), 2.54 (m, 1 H), 2.25 (m, 2 H), 1.21 (s, 9 H), 1.17 (s, 9 H); ^{13}C NMR δ 197.05, 173.76, 173.31, 81.09, 80.95, 72.97, 72.93, 55.46, 53.36, 45.05, 38.95, 27.82, 27.69; HRMS calcd for $C_{55}H_{55}N_2O_5$ [M + 1]: 823.4111, found: 823.4140.

(2*S*,9*S*)-Di-*tert*-butyl 5-Oxo-2,9-bis[*N*-(PhF)amino]dec-4-enedioate (25). To a stirred solution of β-keto phosphonate **22** (488 mg, 0.88 mmol) in CH_3CN (3.15 mL) was added K_2CO_3 (122 mg, 100 mol %). The suspension was stirred 30 min at room temperature, cooled to 0 °C, and treated with a solution of aldehyde **5** (367 mg, 0.88 mmol, 100 mol %) in CH_3CN (3.15 mL). The mixture was stirred at 10 °C for 72 h, diluted with EtOAc (15 mL), and quenched with NaH_2PO_4 (3 mL, 1 M). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic

layers were washed with brine, dried, and evaporated to give a yellowish oil that was chromatographed using a gradient of 5−20% Et_2O in hexanes. Evaporation of the collected fractions gave **25** (574 mg, 78%) as a white foam: ^{1}H NMR δ 7.71−7.66 (m, 5H), 7.43−7.15 (m, 28H), 6.70 (m, 1H), 6.00 (d, 1H, J = 15.9), 2.71−2.63 (m, 2H), 2.54−2.44 (m, 2H), 2.36−2.28 (m, 2H), 1.71−1.66 (m, 2H), 1.20 (s, 9H), 1.19 (s, 9H). ^{13}C NMR δ 199.67, 174.99, 173.86, 81.20, 80.75, 73.02, 55.66, 55.37, 38.97, 36.27, 29.60, 27.87. HRMS calcd for $C_{56}H_{57}N_2O_5$ [M + 1]: 837.4268, found: 837.4281.

(2*S*, 10*S*)-Di-*tert*-butyl 6-Oxo-2,10-bis[*N*-(PhF)amino]-undec-4-enedioate (26). To a stirred solution of β-ketophosphonate **23** (1.19 g, 2.11 mmol) and aldehyde **5** (874 mg, 2.11 mmol) in CH_3CN (20 mL) was added K_2CO_3 (293 mg, 2.22 mmol). The mixture was stirred at room temperature for 96 h and evaporated to a residue that was suspended in toluene and added to a column of silica gel. Chromatography using a gradient of 5−20% Et_2O in hexanes and evaporation of the collected fractions gave **26** (1.39 g, 78%) as a white foam: TLC R_f = 0.36 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −151.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.74−7.66 (m, 4 H), 7.48−7.17 (m, 26 H), 6.67 (m, 1 H), 6.01 (d, 1 H, J = 15.9), 3.21 (bs, 1 H), 2.70 (dd, 1 H, J = 6.0, 6.1), 2.56 (dd, 1 H, J = 4.9, 7.3), 2.41−2.27 (m, 4 H), 1.78−1.67 (m, 2 H), 1.51−1.38 (m, 2 H), 1.22 (s, 18 H); ^{13}C NMR δ 199.72, 175.25, 173.89, 81.11, 80.42, 72.92, 55.53, 55.42, 39.17, 38.86, 35.13, 27.82, 19.73.; HRMS calcd for $C_{57}H_{59}N_2O_5$ [M + 1]: 851.4423, found: 851.4444.

(2*S*,6*R*,8*S*)-Methyl 9-Oxo-8-*N*-(BOC)amino-1-azabicyclo-[4.3.0]nonane-2-carboxylate ((2*S*,6*R*,8*S*)-31) was obtained as a 9:1 diastereomeric mixture with (2*S*,6*S*,8*S*)-**31**. A solution of ketone **24** (375 mg, 0.456 mmol) in 15.4 mL of 9:1 EtOH:AcOH was transferred into a hydrogenation apparatus and treated with palladium-on-carbon (40 mg, 10 wt %). The pressure bottle was filled, vented, and refilled four times with 6 atm of H_2. The reaction mixture was stirred overnight, filtered onto a plug of Celite, and washed thoroughly with EtOH. Evaporation of the volatiles gave a crude residue that was dissolved in toluene (10 mL) and MeOH (1 mL) and treated with *p*-toluenesulfonic acid monohydrate (428 mg, 2.25 mmol, 500 mol %). The solution was heated at a reflux for 1 h using a Dean−Stark apparatus. The Dean−Stark trap was then emptied and Et_3N (200 mol %) was added to the solution, which was heated at a reflux for 48 h, cooled to room temperature, and evaporated to a residue that was immediately dissolved in CH_2Cl_2 (12 mL). The solution was treated with Et_3N (625 μL, 4.5 mmol, 1000 mol %) and di-*tert*-butyl dicarbonate (119 mg, 0.54 mmol, 120 mol %), stirred at room temperature for 4 h, and evaporated to a residue, that was chromatographed using a gradient of 0−100% EtOAc in hexanes. Evaporation of the collected fractions gave ester **31** (119.4 mg, 85% from ketone **24**) as a 9:1 mixture of diastereomers: TLC R_f = 0.43 (100% EtOAc); ^{1}H NMR (major isomer) δ 5.10 (bs, 1 H), 4.20 (bs, 1 H), 3.87 (dd, 1 H, J = 3.8, 9.4), 3.78 (s, 3 H), 3.32 (br m, 1 H), 2.81 (br m, 1 H), 1.97−1.12 (m, 7 H), 1.43 (s, 9 H); ^{13}C NMR (major isomer) δ 172.32, 171.45, 156.12, 80.04, 56.86, 55.52, 53.48, 52.62, 37.04, 30.62, 28.51, 27.32, 21.13. HRMS calcd for $C_{15}H_{25}N_2O_5$ [M + 1]: 313.1764, found: 313.1754. A sample of (2*S*,6*R*,8*S*)-**31** was obtained by HPLC purification using an isocratic solvent system of 45% CH_3CN: 55% H_2O on a reversed-phase C_{18} column. Crystals of (2*S*,6*R*,8*S*)-**31** were obtained from a 9:1 mixture of (2*S*, 6*RS*, 8*S*)-**31** in EtOAc.

(2*S*,6*RS*,8*S*)-9-Oxo-8-*N*-(BOC)amino-1-azabicyclo[4.3.0]-nonane-2-carboxylate ((2*S*,6*RS*,8*S*)-2). A solution of methyl ester **31** (9:1 6*R*:6*S*, 35 mg, 0.112 mmol) in Et_2O (4 mL) was treated with potassium trimethylsilanolate (21.6 mg, 0.168 mmol, 150 mol %), stirred for 30 min at room temperature, and treated with water (500 μL), followed by solid citric acid (32 mg, 0.168 mmol, 150 mol %). The layers were separated, and the aqueous layer was extracted repeatedly with Et_2O and then $CHCl_3$:*i*-PrOH (4:1) until TLC showed no ninhydrin active material. Evaporation of the combined organic layers, chromatography of the residue using 0−5% AcOH in ethyl acetate, and evaporation of the collected fractions gave **2** (32 mg, 96%) as a white solid: R_f = 0.29 (5% AcOH in EtOAc); ^{1}H NMR (CD_3OD, major isomer) δ 4.66 (d, 1 H, J = 5.3), 4.24 (dd, 0.6 H, J = 10.2, 8.3), 3.65 (br m, 1 H), 2.57 (br m, 1 H), 2.28 (d, 1 H, J = 12.7), 1.93 (d, 1 H, J = 12.3), 1.87−1.52 (m, 4 H), 1.45 (s, 9 H), 1.24 (m, 2 H); ^{13}C NMR (CD_3OD, major isomer) δ 174.90, 174.40, 158.07, 81.79, 79.62, 53.29, 53.07, 35.35, 33.47, 28.87, 27.56, 21.72; HRMS calcd for $C_{14}H_{23}N_2O_5$ [M + 1]: 299.1607, found: 299.1616.

Enantiomeric Purity of (2*S*,6*R*,8*S*)-Methyl 9-Oxo-8-*N*-(BOC)amino-1-azabicyclo[4.3.0]nonane-2-carboxylate ((2*S*, 6*R*,8*S*)-31). A solution of (2*S*,6*R*,8*S*)-**31** (8.1 mg) in CH_2Cl_2 (1 mL) was treated with TFA (1 mL) and stirred for 2.5 h at room temperature when TLC (100% EtOAc) showed complete disappearance of starting **31**. The volatiles were removed under vacuum, and the residue was dissolved in THF (1 mL), treated with either (*R*)- or (*S*)-α-methylbenzyl isocyanate (7.4 μL, 0.05 mmol, 200 mol %) and Et_3N (7.4 μL, 0.05 mmol, 200 mol %), and heated at a reflux for 3 h. The mixture was cooled, the volatiles were removed under vacuum, and the residue was directly examined by proton NMR. The limits of detection were determined by measuring the diastereomeric methyl ester singlets at 3.56 and 3.52 ppm in C_6D_6 in the 600 MHz ^{1}H NMR spectra. Less than 1% of the (1′*S*)-diastereomer was detected in the spectra for the (1′*S*)-urea **32**. Purification by chromatography using a gradient of pure hexanes to pure EtOAc as eluant gave ureas **32** having the following spectra.

Urea (1′*R*)-32: ^{1}H NMR δ 7.33−7.17 (m, 5 H), 5.45 (m, 1 H), 5.37 (d, 1 H, J = 5.3), 4.86 (m, 1 H), 4.22 (m, 1 H), 3.78 (m, 1 H), 3.76 (s, 3 H), 3.26 (m, 1 H), 2.77 (m, 1 H), 2.11 (m, 1 H), 1.98−1.44 (m, 4 H), 1.43 (d, 3 H, J = 6.9), 1.38−1.20 (m, 2 H).

Urea (1′*S*)-32: ^{1}H NMR δ 7.34−7.21 (m, 5H), 5.48 (d, 1 H, J = 7.4), 5.38 (d, 1 H), 4.88 (m, 1 H), 4.43 (m, 1 H), 3.85 (m, 1 H), 3.72 (s, 3H), 3.30 (m, 1 H), 2.75 (m, 1 H), 1.96−1.47 (m, 4 H), 1.44 (d, 3 H, J = 6.9), 1.21 (m, 3 H).

Acknowledgment. This research was supported in part by the Natural Sciences and Engineering Research Council (NSERC) of Canada, and the Ministère de l'Éducation du Québec. W. D. L. thanks Bio-Méga/Boehringer Ingelheim Recherche Inc. for a Young Investigator Award. The crystal structure analysis of compound **31** was performed by Francine Bélanger-Gariépy at l'Université de Montréal X-ray facility. F. G. thanks NSERC for a PGSB Scholarship (97-99) and FCAR for a M.Sc. Scholarship (96-97). We are grateful for a loan of Pd/C from Johnson Matthey PLC.

Supporting Information Available: Experimental details for attempted Claisen condensations and β-methyl *N*-(PhF)-aspartate;^{1}H and ^{13}C NMR spectra of ketones **24**−**26**; and crystallographic data for **31** (13 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.

JO9814602