Rigid Dipeptide Surrogates: Syntheses of Enantiopure Quinolizidinone and Pyrroloazepinone Amino Acids from a Common Diaminodicarboxylate Precursor

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A versatile and practical approach for synthesizing azabicyclo[*X.Y*.0]alkane amino acids of different ring sizes from a common diaminodicarboxylate precursor has been developed as a means for mimicking different peptide conformations. (2*S*,9*S*)-1-*tert*-Butyl 10-benzyl 5-oxo-2-[*N*-(PhF)amino] 9-[*N*-(BOC)amino]dec-4-enedioate (**18**) was first prepared in 83% yield by the Horner−Wadsworth−Emmons olefination of *N*-(PhF)aspartate *β*-aldehyde **8** with pyroglutamate-derived *β*-keto phosphonate **12** (PhF = 9-phenylfluoren-9-yl). The practicality of this approach for making azabicyclo[*X.Y*.0]alkane amino acids was then illustrated by the first synthesis of enantiopure quinolizidin-2-one amino acid **6** in seven steps and 40% overall yield from L-pyroglutamic acid. Hydrogenation of *δ*-keto α,*ω*-diaminosebacate **18**, followed by lactam cyclization and protection, gave quinolizidin-2-one amino acid **6** as a single diastereomer. The versatility of this approach was next demonstrated by the synthesis of both ring-fusion isomers of pyrroloazepin-2-one amino acid **6** in 11 steps and 13% overall yield from pyroglutamic acid. Hydride reduction of **18**, followed by methanesulfonate displacement, gave 5-alkylproline **22**. Protective group manipulations, lactam cyclization, and removal of the ester group afforded readily separable pyrroloazepinone amino acids (7*S*)- and (7*R*)-**7** in a 1:2 diastereomeric ratio. By introducing two new azabicycloalkane amino acids using our olefination approach, we have expanded the diversity of these important heterocycles for studying the conformational requirements for peptide biological activity.

Introduction

The biologically active conformation of a flexible peptide may be elucidated by using structural constraints to rigidify its backbone and side-chain geometries. For this endeavor, azabicyclo[*X.Y*.0]alkane amino acids have been used as rigid dipeptide surrogates that constrain three backbone dihedral angles within a fused bicyclic framework. Incorporation of these heterocyclic amino acids into a peptide can provide a better understanding of the spatial requirements for its biological activity.[1,2] Furthermore, these conformationally constrained dipeptide surrogates can serve as geometrically defined platforms onto which a variety of pharmacophores may be attached by modification of the amino and carboxylate handles using combinatorial techniques.[1,3] Their close structural relationship to the pyrrolizidine, indolizidine, and quinolizidine alkaloids suggests the use of the related azabicyclo[*X.Y*.0]alkane amino acids as scaffolds for generating libraries of lead compounds that may possess similar biological activities as members of these large classes of alkaloids.[4]

Ideally, the azabicycloalkane ring system should be formed unambiguously, with stereocontrol and the ability to append functional groups onto different positions of the heterocycle in order to mimic the side-chains of the common amino acids. Among the strategies for synthesizing azabicyclo[*X.Y*.0]alkane amino acid, methods based on *N*-acyl iminium ion cyclization as well as the condensation between a cysteine derivative and an amino acid *ω*-aldehyde have to date been the most successful for providing a variety of ring-systems.[5] Inability to control the stereochemistry of the ring-fusion center as well as low yields during the synthesis of alkyl-substituted analogues have, however, been drawbacks encountered

(1) 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.

(2) Some recent syntheses of azabicyclo[*X.Y*.0]alkane amino acids that have appeared since the writing of refs 1 and 9 include (a) Lindemann, U.; Wessig, P. *J. Inf. Rec. Mater.* **1998**, *24*, 441. (b) Geyer, A.; Bockelmann, D.; Weissenbach, K.; Fischer, H. *Tetrahedron Lett.* **1999**, *40*, 477. Recent examples of the use of azabicycloalkane amino acids to explore bioactive peptides include the following: (c) Interleukin-1*β*-converting-enzyme: Karanewski, D. S.; Bai, X.; Linton, S. D.; Krebs, J. F.; Wu, J.; Pham, B.; Tomaselli, K. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2757. (d) Farnesyl transferase: Liu, R.; Dong, D. L.-Y.; Sherlock, R.; Nestler, H. P.; Gennari, C.; Mielgo, A.; Scolastico, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 847. (e) Zinc finger of human YY1 protein: Viles, J. H.; Patel, S. U.; Mitchell, J. B. O.; Moody, C. M.; Justice, D. E.; Uppenbrink, J.; Doyle, P. M.; Harris, C. J.; Sadler, P. J.; Thornton, J. M. *J. Mol. Biol.* **1998**, *279*, 973. (f) Calcitonin-gene-related-peptide$_{8-37}$: Wisskirchen, F. M.; Doyle, P. M.; Gough, S. L.; Harris, C. J.; Marshall, I. *Br. J. Pharmacol.* **1999**, *126*, 1163. For additional examples see ref 2 in ref 9 below.

(3) Alternative examples of scaffolds for peptide mimicry and combinatorial chemistry include (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217. (b) Hirschmann, R.; Sprengeler, P. A.; Kawasaki, T.; Leahy, J. W.; Shakespeare, W. C.; Smith A. B., III. *J. Am. Chem. Soc.* **1992**, *114*, 9699. (c) Barry, J. F.; Davis, A. P.; Nieves Pérez-Payan, M.; Elsegood, M. R. J.; Jackson, R. F. W.; Gennari. C.; Piarulli, U.; Gude, M. *Tetrahedron Lett.* **1999**, *40*, 2849.

(4) Recent reviews include: (a) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 21. (b) Ohmiya, S.; Saito, K.; Murakoshi, I. In *The Alkaloids*; Cordell, G. A., Ed.; Acad. Press: New York, 1995; Vol. 47, pp 1−114. For additional examples see ref 1 in ref 10a below.

(5) For examples see refs 17, 19, 23, 26 and 41−49 in ref 1 above.

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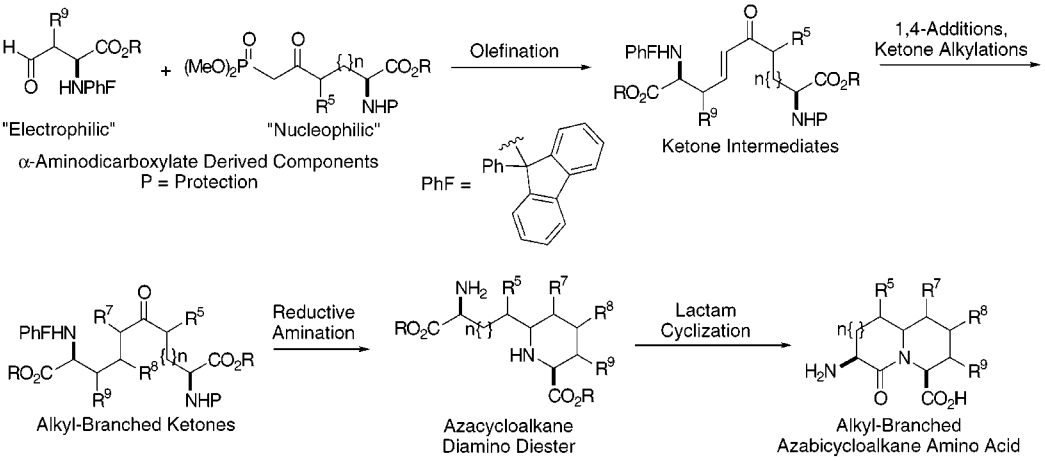
Scheme 1. Olefination Approach for Synthesizing Alkyl-Branched Azabicyclo[*X.Y.*0]alkane Amino Acids



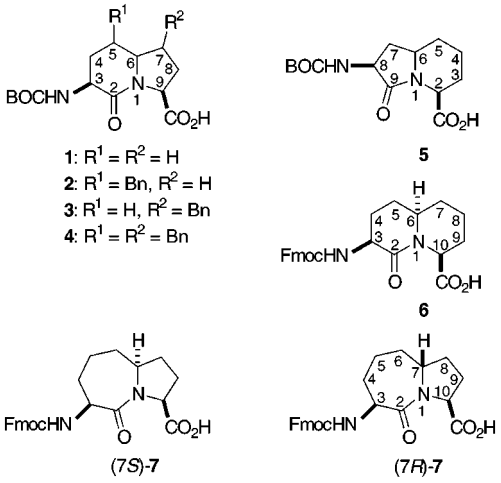
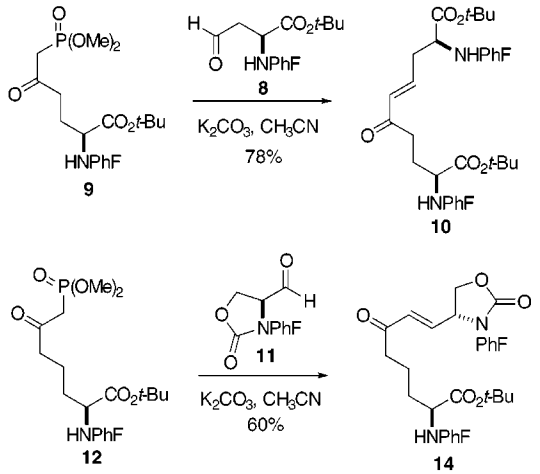


Figure 1. Indolizidinone, quinolizidinone, and pyrroloazepinone amino acids **1**−**7** (ref 1).

with these two strategies. For example, condensations between (*R*)-penicillamine and (*S*)-*β*-phenylcysteine with α-methyl-*N*-phthalyl-L-glutamate were plagued by low yields.[6] *N*-Acyl iminium ion cyclizations have given access to only one ring-fusion isomer in the synthesis of 5,7-fused pyrroloazepinone amino ester.[7] In the same light, although our Claisen condensation/alkylation/reductive amination/lactam cyclization strategy provided a stereoselective method for synthesizing indolizidin-2-one amino acid **1** and analogues **2**−**4** possessing amino acid side-chains at the 5- and 7-positions (Figure 1),[8,9] limitations in the Claisen condensation of aminodicarboxylates restricted this method's potential for generating a variety of ring-systems.[10a]

Scheme 2. Synthesis of Diaminodicarboxylates by Olefination of Amino Aldehydes with Diaminodicarboxylate-Derived *β*-Ketophosphonates.



Striving to expand the variety of heterocycles that can be made by our approach, we introduced next an olefination entry for making a series of linear precursors for azabicyclo[*X.Y.*0]alkane synthesis (Scheme 1).[10] Employing aspartic acid as an inexpensive chiral educt in this olefination/reductive amination/lactam cyclization sequence, we synthesized enantiopure indolizidin-9-one amino acid **5**.[10] We envisioned that alkylation and conjugate addition to the α,*β*-unsaturated ketone intermediate in the synthesis of amino acid **5** may be used to introduce side-chains onto this heterocycle.

Having employed the olefination strategy to selectively join different amino dicarboxylates,[10] we investigated using the (*E*)-geometry of the resulting double bond to direct the cyclization of the unsymmetrical α,*ω*−diaminodicarboxylate intermediate in order to regioselectively produce different azabicyclo[*X.Y.*0]alkanes. Our investigation has now led to the synthesis of two azabicycloalkane ring systems from a common linear olefin precursor. Quinolizidin-2-one amino acid **6** and pyrroloazepin-2-one amino acid **7** both were prepared from *δ*-keto α,*ω*-diaminosebacate **18** (Schemes 3−5). The former, azabicyclo[4.4.0]alkane amino acid **6** had previously never been synthesized. Although the latter, azabicyclo[5.3.0]alkane amino acid **7** had been made, only the concave (7*S*)-isomer was produced because of conformational preferences during a route involving an *N*-acyl

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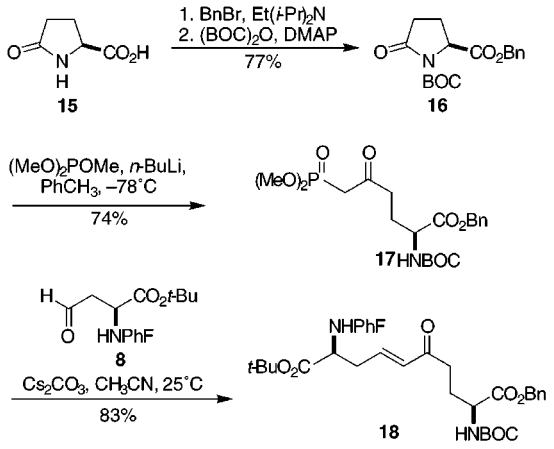
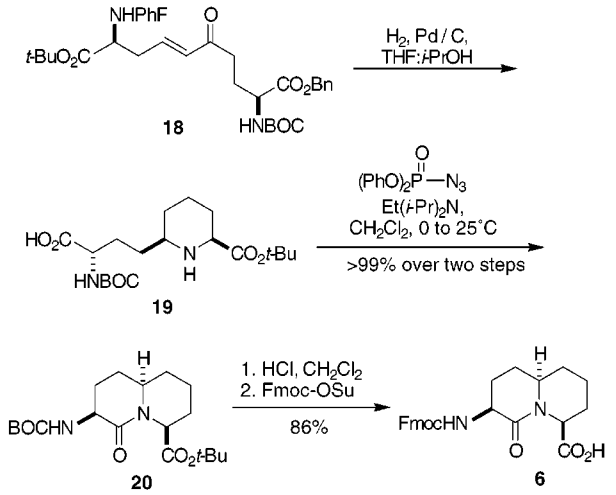
(10) (a) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463. (b) Gosselin, F.; Lubell, W. D. In *Peptides 1998*. Proceedings of the 25th European Peptide Symposium, Bajusz, S., Hudecz, F., Eds.; Akadémia Kiadó: Budapest, Hungary, 1998; p 660.

Scheme 3. Synthesis of δ-Keto α,ω-Diaminosebacate 18



Scheme 4. Synthesis of Quinolizidin-2-one Amino Acid 6



iminium ion cyclization,[7] and because of the precursor stereochemistry in a route featuring a radical cyclization of an *N*-acyl acrylamide.[11] Besides yielding the concave isomer,[7] our route has now, for the first time, furnished the convex (7*R*)-isomer of pyrroloazepin-2-one amino acid **7**.

Results and Discussion

Diaminodicarboxylate precursor synthesis was initially investigated using different amino acid-derived aldehydes in the Horner−Wadsworth−Emmons olefination (Schemes 2 and 3). For example, olefination of *N*-(PhF)aspartate β-aldehyde **8** with *N*-(PhF)glutamate-derived β-ketophosphonate **9** in acetonitrile with potassium carbonate as base was initially found to provide α,β-unsaturated ketone **10** in 78% yield.[10a] Similarly, the reaction of configurationally stable *N*-(PhF)serinal **11**[12] with α-amino adipate-derived β-ketophosphonate **12**[10] in acetonitrile with K_2CO_3 as base gave α,β-unsaturated ketone **14** in 60% yield as described in the Supporting Information. In both cases, only the (*E*)-olefin was formed as confirmed by the large coupling constant (J = 16.0 Hz) between the vinyl protons. Although 5-alkylproline and 6-alkylpipecolate intermediates could be respectively synthesized from α,β-unsaturated ketones **10** and **14**, we abandoned these approaches for preparing the 7,5- and 6,6-fused azabicycloalkanes because of difficulties encountered when trying to differentiate between the two *N*-(PhF)amines as well as between the two carboxylate functions.

We envisioned that a single linear olefin precursor could be used to synthesize both the 6,6- and 7,5-fused ring systems, if its amino and carboxylate functions were suitably protected. By employing a combination of *N*-BOC- and *N*-PhF-amines and *tert*-butyl and benzyl esters, we anticipated that acidic and hydrogenolytic conditions could be respectively used to unmask one member from each protected pair. Attention was thus turned toward the synthesis of 1-*tert*-butyl 10-benzyl 5-oxo-2-[*N*-(PhF)amino]-9-[*N*-(BOC)amino]dec-4-enedioate (**18**, Scheme 3).

Nucleophilic addition to *N*-carbamoyl pyroglutamate derivatives had previously been used to synthesize β-ketophosphonate.[13,14] Regioselective addition of diethyl methyl phosphonate to ethyl *N*-(BOC)pyroglutamate in THF afforded (2*S*)-α-ethyl 2-*N*-(BOC)amino-5-oxo-6-(diethylphosphonyl)hexanoate in 60% yield.[14b] In our route, benzyl *N*-(BOC)pyroglutamate **16** was first obtained in 77% overall yield by alkylative esterification of pyroglutamic acid with benzyl bromide and *N*,*N*-diisopropylethylamine (DIEA) in CH_2Cl_2, followed by *N*-protection using di-*tert*-butyl dicarbonate, DMAP, and Et_3N, in CH_3CN.[15,16] By substituting benzyl bromide for the less reactive chloride, we found that the alkylation was complete in less than 24 h, instead of the previously required 7 days.[15] (2*S*)-α-Benzyl 2-*N*-(BOC)amino-5-oxo-6-(dimethylphosphonyl)hexanoate (**17**) was then prepared by the addition of the lithium anion of dimethyl methylphosphonate to benzyl *N*-(BOC)pyroglutamate **16** in toluene in 74% yield.[17] Earlier attempts to react this nucleophile on pyroglutamate **16** using THF as solvent gave lower yields (40−50%) of β-ketophosphonate **17**.

The α,β-unsaturated ketone **18** was obtained by Horner−Wadsworth−Emmons olefination of *N*-(PhF)aspartate β-aldehyde **8** with β-ketophosphonate **17**.[10] Initially, longer times and high temperatures were required for the olefination reaction when K_2CO_3 was used as base alone as well as in the presence of 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane). Because of the limited stability of β-amino aldehyde **8** under these harsh conditions, α,β-unsaturated ketone **18** was isolated in less than 30% yield. Alternatively, the use of Cs_2CO_3 as base in

(11) Colombo, L.; Di Giacomo, M.; Belvisi, L.; Manzoni, L.; Scolastico, C.; Salimbeni, A. *Gazz. Chim. Ital.* **1996**, *126*, 543.

(12) Lubell, W. D.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824.

(13) The use of pyroglutamic acid in asymmetric synthesis has recently been reviewed: Nájera, C.; Yus, M. *Tetrahedron Asymmetry* **1999**, *10*, 2245.

(14) The addition of nucleophiles to *N*-carbamoyl pyroglutamates is described in (a) Ohta, T.; Hosoi, A.; Kimura, T.; Nozoe, S. *Chem. Lett.* **1987**, 2091. (b) Ezquerra, J.; de Mendoza, J.; Pedregal, C.; Ramirez, C. *Tetrahedron Lett.* **1992**, *33*, 5589. (c) Molina, M. T.; Valle, C. D.; Escribano, A. M.; Ezquerra, J.; Pedregal, C. *Tetrahedron*, **1993**, *49*, 3801. (d) Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J. H.; García Ruano, J. L. *Tetrahedron Lett.* **1993**, *34*, 4989. (e) Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; García, J. L.; Alvarez-Builla, N. J.; Vaquero, J. J. *Tetrahedron Lett.* **1993**, *34*, 6317. (f) Van Betsbrugge, J.; Van Den Nest, W.; Verheyden, P.; Tourwé, D. *Tetrahedron* **1998**, *54*, 1753.

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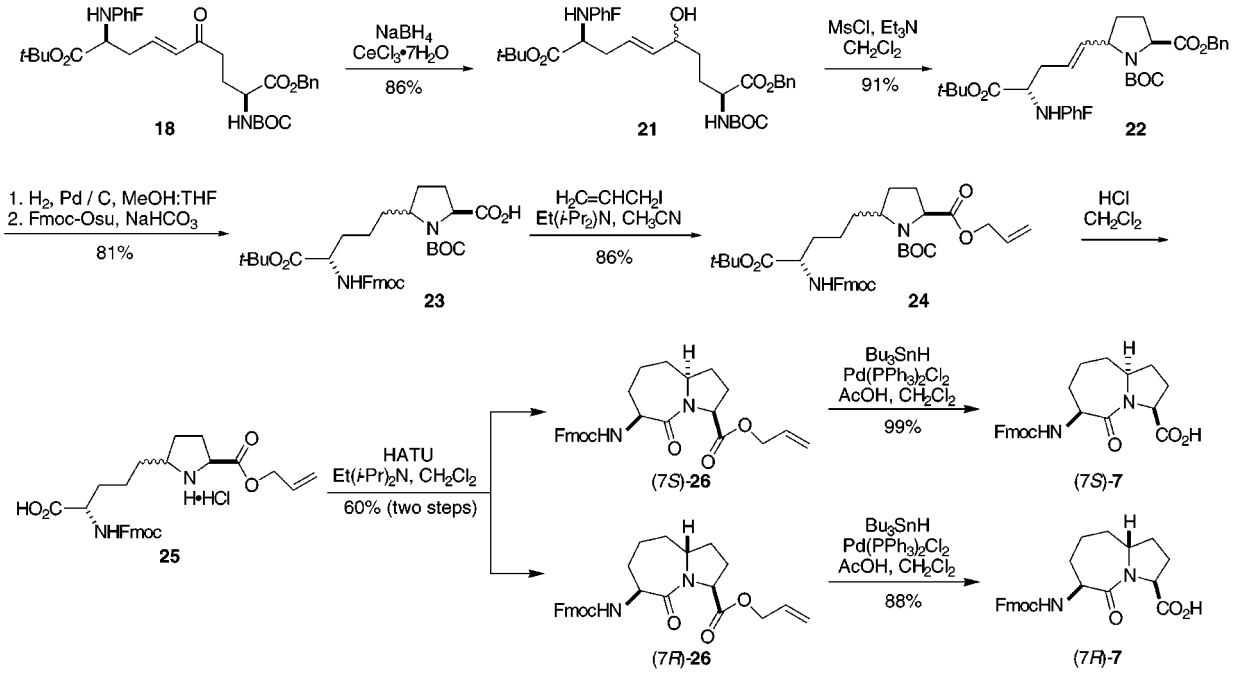
Scheme 5. Synthesis of Pyrroloazepin-2-one Amino Acid 7



CH_3CN cleanly afforded **18** in 83% yield after 4−5 h at room temperature. No decomposition of the aldehyde to *tert*-butyl *N*-(PhF)-5-azapenta-2,4-dienoate[18a] was observed under these conditions. The (*E*)-double bond geometry was confirmed by the $J = 16.0$ Hz coupling constant between the vinyl protons in α,*β*-unsaturated ketone **18**.

Quinolizidin-2-one amino acid synthesis was studied using a reductive amination approach to selectively unmask the *N*-(PhF)amine and furnish the 6-alkylpipecolate. Previously, we had shown that *δ*- and *ϵ*-keto α-amino esters can be effectively converted to their respective 5-alkylprolines and 6-alkylpipecolates by catalytic hydrogenation with high diastereoselectivity.[8−10,18,19] In the case of (2*S*, 9*S*)-1-*tert*-butyl 10-benzyl 5-oxo-2-[*N*-(PhF)amino] 9-[*N*-(BOC)amino]dec-4-enedioate (**18**, Scheme 4), treatment with palladium-on-carbon in an *i*-PrOH:THF solution at 6 atm of hydrogen caused reduction of the double bond, hydrogenolysis of the benzyl ester and the PhF group, imine formation, and reduction from the less-hindered face of the imine to afford pipecolate **19** as a single diastereomer. After filtration to remove the catalyst, the crude pipecolate mixture was then treated with diphenylphosphoryl azide (DPPA)[20] in CH_2Cl_2 in the presence of DIEA and provided crystalline azabicycloalkane *N*-(BOC)amino ester **20** in >99% yield from ketone **18** after chromatography.

Because of the growing importance of Fmoc-based solid-phase peptide synthesis, 6,6-fused azabicycloalkane *N*-(BOC)amino ester **20** was converted into its Fmoc derivative.[21,22] First, the BOC group and the *tert*-butyl ester were simultaneously removed with HCl gas in CH_2Cl_2. The amino acid hydrochloride was acylated with 9-fluorenylmethyloxycarbonyl hydroxysuccinimide (Fmoc-OSu), in the presence of $NaHCO_3$ in a solution of acetone and water.[23] Quinolizidinone *N*-(Fmoc)amino acid **6** was finally obtained in 86% yield after column chromatography.

Pyrroloazepin-2-one amino acid synthesis was next pursued using the same olefin precursor **18**. As mentioned, the concave (7*S*)-isomer of pyrroloazepin-2-one amino acid **7** had been previously synthesized by an *N*-acyl iminium ion cyclization from an allylglycine dipeptide precursor,[7] as well as by an intramolecular radical-mediated cyclization of a 5-alkylproline derivative.[11] This 7,5-fused azabicycloalkane amino acid and its 4-thiapyrroloazepin-10-one counterpart have been used as D-Ala-Pro mimics in the preparation of potent angiotensin-converting-enzyme inhibitors.[24,25] Furthermore, this constrained dipeptide surrogate has been shown to stabilize preferentially *γ*-turn conformations in short peptides.[26]

Previously, we have shown that methanesulfonate displacements can be effectively used for synthesizing the proline ring in indolizidin-2-one amino acid and its 5- and 7-benzyl, and 5,7-dibenzyl derivatives.[8a,9] Intramolecular attack of *N*-(PhF)amine onto secondary methanesulfonates

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has provided excellent yields of 5-alkylprolines by what appears to be a selective S_N2 process in these cases. To examine the methanesulfonate displacement for making the proline in the pyrroloazepin-2-one amino acid, ketone **18** was first transformed into its corresponding allylic alcohol by reduction with sodium borohydride in the presence of cerium trichloride in MeOH:THF to provide **21** as a 1:1 mixture of diastereomers in 86% yield (Scheme 5).[27] Treatment of the alcohol with methanesulfonyl chloride and triethylamine in CH_2Cl_2, afforded cyclization to 5-alkylprolines **22** in 91% yield. The (*E*)-olefin geometry of alcohol **21** excluded the attack of the *N*-(PhF)amine onto the methanesulfonate such that exclusive cyclization of the *N*-(BOC)amine occurred.

5-Alkylproline **22** was obtained as a 2:1 mixture of 5*R*:5*S* diastereomers as indicated by measurements of the *tert*-butyl ester singlets in the ^{1}H NMR spectra of analogues **23** and **24**. The enhanced stereochemical ratio relative to starting allylic alcohol **21** was ascribed to S_N1-type cyclization, presumably due to ionization of the methanesulfonates under the reactions conditions. As previously noted in a related synthesis of (−)-pyrrolidine-2,5-dicarboxylic acid,[28] the conformation of the allylic cation intermediate may have contributed to the enrichment of the 5*R* diastereomer of proline **22**.

Prior to the key lactam cyclization, the protecting groups were exchanged. First, the *N*-(PhF)amine and benzyl ester of **22** were cleaved with concurrent double bond reduction by catalytic hydrogenation in a THF/methanol solution. *N*-Acylation with Fmoc-OSu in an acetone/water solution gave prolines **23** in 81% overall yield from **22**. Alkylative esterification with allyl iodide in CH_3CN heated at a reflux afforded ester **24** in 86% yield. Simultaneous removal of the BOC group and *tert*-butyl ester with HCl in CH_2Cl_2 then gave amino acid hydrochloride **25**.

Lactam cyclization of **25** using either azabenzotriazolyl-1,1,3,3-tetramethylaminium hexafluorophosphate (HATU)[29,30] or benzotriazolyl-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU)[30,31] with DIEA in CH_2Cl_2 gave *N*-(Fmoc)-azabicycloalkane amino esters **26** in yields ranging between 50 and 60%.[32,33] Although TBTU gave essentially the same amount of conversion to lactam **26**, we found that the coupling reaction with HATU proceeded with an enhanced cyclization rate and yielded product of better purity.[29] Pyrroloazepin-2-one *N*-(Fmoc)-amino esters **26** were isolated as a 2:1 mixture of diastereomers that were easily separated by chromatography on silica gel. Pyrroloazepin-2-one *N*-(Fmoc)amino acids (7*S*)-**7** and (7*R*)-**7** were finally synthesized by palladium-catalyzed hydrostannolytic cleavage of their respective allyl esters (7*R*)-**26** and (7*S*)-**26** on treatment with $Pd(PPh_3)_2Cl_2$ and n-Bu_3SnH in a CH_2Cl_2/AcOH solution at room temperature in yields of 88% and 99% after chromatography.[34]

Relative stereochemistry at the ring-fusion center of the new azabicycloalkane amino acids was confirmed by spectroscopic and crystallographic methods. Because quinolizidin-2-one *N*-(BOC)amino ester (3*S*,6*R*,10*S*)-**20** was prepared by a reductive amination sequence, we assigned the stereochemistry of its ring-fusion carbon initially based on analogy with *N*-(BOC)amino indolizidin-9-one acid (2*S*,6*R*,8*S*)-**5** and 6-alkylpipecolates.[10,18]

Since hydrogenation of α-*tert*-butyl δ-oxo-α-*N*-(PhF)-amino ester produced 6-alkylpipecolates with high selectivity in favor of the *cis*-diastereomer, we presumed that the reductive amination with amino ketone **18** proceeded to form *cis*-6-alkylpipecolate (2*S*,6*R*,2′*S*)-**19**. Crystals of (3*S*,6*R*,10*S*)-*tert*-butyl 2-oxo-3-*N*-(BOC)amino-1-azabicyclo[4.4.0]decane-10-carboxylate **(20)** were later obtained from an EtOAc/hexanes solution. Subsequently, X-ray crystallographic analysis confirmed our hypothesis and indicated formation of the concave isomer (Figure 2).[35]

With both (7*S*)- and (7*R*)-pyrroloazepin-2-one *N*-(Fmoc)-amino acids (7*S*)-**7** and (7*R*)-**7** in hand, a series of two-dimensional NMR experiments were performed in order to assign the relative stereochemistry at the ring-fusion. First, the protons within the peptide backbone and at the ring-fusion of each isomer were identified using their COSY spectra. The stereochemistry at the ring-fusion was next determined by NOESY experiments (Figure 3). Transfer of magnetization was observed between the ring-fusion *C*-7 proton (3.86 ppm) and the backbone protons at *C*-3 (4.40 ppm) and *C*-10 (4.70 ppm) in the case of the (7*S*)-**7** minor diastereomer. By comparison, nuclear Overhauser effects were observed between the *C*-7 proton (3.70 ppm) and carbamate N−H (6.08 ppm) in the case of the (7*R*)-**7** major diastereomer.

Enantiomeric purity of quinolizidin-2-one amino ester (3*S*,6*R*,10*S*)-**20**, produced from the reductive amination/lactam cyclization sequence on ketone **18**, was determined after conversion to diastereomeric (1′*R*)- and

(27) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (c) The diastereomeric ratio of allylic alcohol **21** was determined by ^{1}H NMR of its *O*-acetyl derivative, prepared by treating **21** with Ac_2O in DMAP−pyridine at room temperature for 30 min; ^{1}H NMR δ 1.18 (s, 4.5 H), 1.19 (s, 4.5 H), 1.45 (s, 9 H), 1.50−1.68 (m, 3 H), 1.86 (m, 1 H), 2.02 (s, 1.5 H), 2.03 (s, 1.5 H), 2.12 (m, 2 H), 2.60 (m, 1 H), 4.35 (bm, 1 H), 5.05−5.28 (m, 3 H), 5.30−5.38 (m, 1 H), 5.63−5.69 (m, 1 H), 7.16−7.43 (m, 16 H), 7.66−7.69 (m, 2 H).

(28) For a related observation and an example of cyclization of a *N*-(Cbz)amine onto an allylic methanesulfonate see ref 14a above.

(29) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

(30) The crystal structures of HBTU, the corresponding PF_6 salt, and HATU indicate that these reagents exist in the form of aminium salts: Abdelmoty, I.; Albericio, F.; Carpino, L. A.; Foxman, B. M.; Kates, S. A. *Lett. Pept. Sci.* **1994**, *1*, 52.

(31) Knorr, R.; Trzreciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927

(32) In our hands, onium salt based coupling reagents were superior to all other methods. Earlier attempts provided lower yields of the desired seven-membered lactams using (a) catecholborane: Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 439, as well as peptide coupling reagents such as the following: (b) Carbodiimides: Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067. (c) (1-Azabenzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP): Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219. (d) Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl): Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342. (e) Diphenylphosphoryl azide (DPPA): see ref 20. For a discussion on the use of peptide coupling agents in synthesis, see (f) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.

(33) In comparison, formation of the seven-membered lactam by iminium ion cyclization and by radical-mediated cyclization went respectively in 79% and 42−61% yields, as discussed in refs 7 and 11.

(34) (a) Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984. (b) Loffet, A.; Zhang, H. X. *Int. J. Pept. Protein Res.* **1993**, *42*, 346.

(35) The structure of **20** was solved at the Université de Montréal X-ray facility using direct methods (SHELXS96) and refined with NRCVAX and SHELXL96: $C_{19}H_{32}N_2O_5$; M_r = 368.46; monoclinic, colorless crystal; space group $P2_1$; unit cell dimensions (Å) a = 9.773 (3), b = 10.201 (9), c = 11.064 (3), β = 105.01 (2)°; volume of unit cell (Å^3) 1065.4 (10); Z = 2; R_1 = 0.04 for $I > 2\,\sigma(I)$, wR_2 = 0.12 for all data; GOF = 1.065. The author has deposited the atomic coordinates for the structure of **20** 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, U.K.

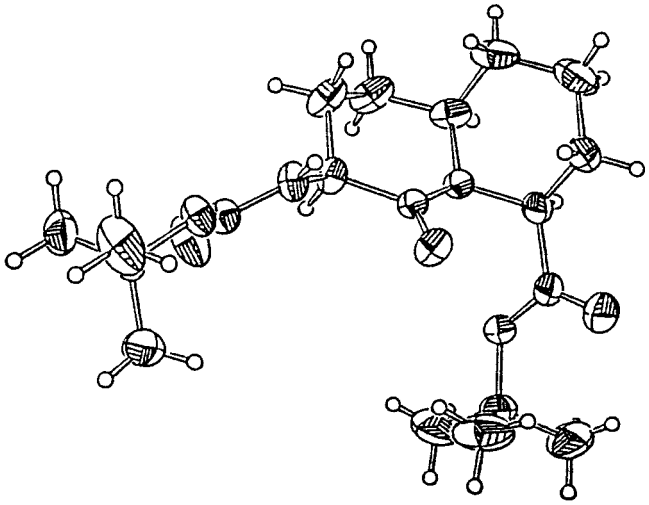


Figure 2. ORTEP view of N-(BOC)amino quinolizidin-2-one *tert*-butyl ester (3*S*,6*R*,10*S*)-**20**. Ellipsoids drawn at 40% probability level. Hydrogens represented by spheres of arbitrary size.[35]

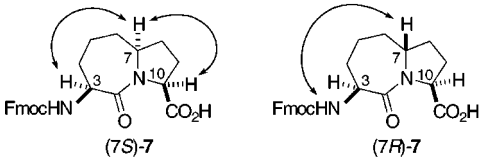
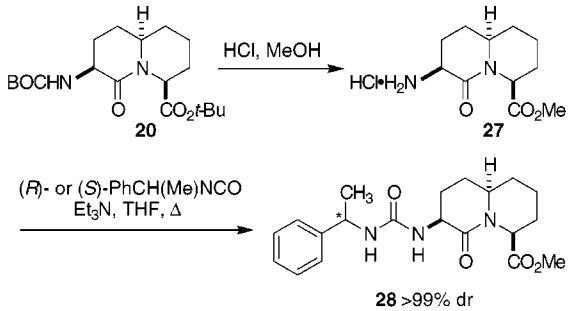


Figure 3. Observed diagnostic NOE's in NOESY experiments.

Scheme 6. Enantiomeric Purity of Quinolizidin-2-one Amino Ester 20



(1′*S*)-*N*-α-methylbenzylureas **28** by analysis using NMR spectroscopy (Scheme 6). Hydrogen chloride in methanol removed both the *N*-BOC and *tert*-butyl ester protecting groups and esterified the acid intermediate to quantitatively furnish methyl ester hydrochloride **27**. Acylation of **27** with either (*R*)- or (*S*)-α-methylbenzyl isocyanate and triethylamine in THF heated at a reflux gave α-methylbenzylureas **28** which were directly examined after evaporation of the volatiles. Measurement of the diastereomeric methyl ester singlets at 3.70 and 3.65 ppm in $CDCl_3$ by 400 MHz ^{1}H NMR spectroscopy demonstrated **28** to be of >99% in diastereomeric ratio. Hence diaminodicarboxylate **18**, *N*-(BOC)amino quinolizidin-2-one ester **20**, and its respective acid **6**, all are presumed to be of >99% enantiomeric purity. Because concurrent racemization of both stereocenters in ketone precursor **18** is very unlikely under the reaction conditions of the methanesulfonate displacement sequence, *N*-(Fmoc)-amino pyrroloazepinone-2-one acids **7** are also assumed to be of >99% enantiomeric purity.

Influences of Heterocycle Ring-Size on Peptide Back-Bone Conformation were illustrated on comparison of the dihedral angles of indolizidin-2-one, indolizidin-9-one, and quinolizidin-2-one *N*-(BOC)amino esters **1**, **5**, and **20** in the solid-state (Table 1). Because they possess the same relative stereochemistry, significant differences in the internal ψ and ϕ dihedral angles from the X-ray data of **1**, **5**, and **20** indicate that ring-size has a profound effect on conformation. Our data also indicates that a variety of azabicycloalkane amino acids of different ring-size may be used to mimic a comprehensive spectrum of peptide conformations. Because structure−activity relationship studies have already shown that peptides possessing γ-, δ-, and ϵ-lactams can differ in bioactivity,[36] the application of a series of azabicycloalkane amino acids toward the study of biologically relevant peptides should provide detailed pictures of the conformational requirements for activity.

Table 1. Comparison of the Dihedral Angles from Azabicycloalkane X-ray Data

entry	ψ, deg	ϕ, deg
(3*S*,6*R*,10*S*)-3-*N*-(BOC)amino quinolizidin-2-one-10-carboxylate **20**	−163	+48
(2*S*,6*R*,8*S*)-8-*N*-(BOC)amino indolizidin-9-one-2-carboxylate **5**[10]	−141	−34
(3*S*,6*S*,9*S*)-3-*N*-(BOC)amino indolizidin-2-one-9-carboxylate **1**[8]	−176	−78

Conclusion

We have expanded the diversity of azabicyclo[*X*.*Y*.0]-alkane amino acids by application of our olefination entry to synthesize their linear precursors. By taking advantage of the olefin geometry to direct the reductive amination and methanesulfonate displacement cyclizations on a common diaminodicarboxylate intermediate, two new ring systems of different sizes were prepared for the first time. Enantiopure (3*S*,6*R*,10*S*)-quinolizidin-2-one amino acid **6** was assembled in 7 steps and 40% overall yield from pyroglutamic acid. Convex (3*S*,7*R*,10*S*)-pyrroloazepin-2-one amino acid **7** was prepared as a 2:1 diastereomeric mixture with its previously synthesized concave counterpart in 11 steps and 13% overall yield from pyroglutamic acid.[38] Stereocontrol was achieved during the syntheses of **6** and **7** by selectively joining inexpensive aminodicarboxylate starting materials. Moreover, our approach is well poised for the introduction of side-chains onto the heterocycle framework through functionalization of the pyroglutamate and β-amino aldehyde precursors, as well as by conjugate additions and alkylations on the α,β-unsaturated ketone intermediate (Scheme 1). Our strategy now provides a series of azabicycloalkane amino acids for systematic mimicry of the backbone and side-chain conformations of biologically relevant peptides.

(36) Freidinger, R. M. In *Peptides: Synthesis, Structure, Function*. Proceedings of the 7th American Peptide Symposium, Rich, D. H., Gross, E., Eds., Pierce Chemical Company: Rockford, 1981; p 673.

(37) 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.

(38) By comparison, the iminium ion cyclization route required 11 steps and provided *N*-phthalyl pyrroloazepinone methyl ester in 23% overall yield from the more advanced intermediates *N*-phthalyl-L-allylglycine and *N*-phthalyl γ-benzyl glutamate. The radical cyclization based strategy took seven steps and provided *N*-acetyl pyrroloazepinone *tert*-butyl ester in 16−24% overall yield from the advanced intermediate (2*S*,5*S*)-diethyl *N*-benzylpyrrolidine 2,5-dicarboxylate.

Experimental Section

General. Unless otherwise noted all reactions were run under nitrogen atmosphere, and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately before use; toluene was distilled from sodium; CH_2Cl_2 was distilled from P_2O_5; commercial anhydrous CH_3CN was used without further purification; triethylamine (Et_3N) was distilled from BaO; *N*,*N*-diisopropylethylamine [Et(*i*-Pr)$_2$N, DIEA] was distilled from CaH_2 and ninhydrin. 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 Spectrometry facility. Unless otherwise noted, IR spectra were recorded in mineral oil; ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in $CDCl_3$. IR bands are reported in reciprocal centimeters (cm^{-1}). Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$), or residual $CHCl_3$; coupling constants are reported in hertz. Chemical shifts of the vinyl carbons in **18** and **21** 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), visualized with UV light, ninhydrin solution, and ceric ammonium molybdate solution. Chromatography was performed using Kieselgel 60 (230−400 mesh).

(2*S*)-Benzyl *N*-(BOC)-pyroglutamate (16). A solution of pyroglutamic acid (5.0 g, 38.75 mmol) and DIEA (13.5 mL, 77.5 mmol, 200 mol %) in CH_2Cl_2 (200 mL) was treated with benzyl bromide (18.5 mL, 155 mmol, 400 mol %), heated at a reflux for 12−24 h, cooled to room temperature, and washed with aqueous NaH_2PO_4 (50 mL, 1 M). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were washed with brine (50 mL), dried, filtered, and evaporated. The crude product (HRMS calcd for $C_{12}H_{14}NO_3$ [M + H]: 220.0974, found: 220.0967) was then dissolved in a solution of CH_3CN (100 mL) and Et_3N (5.4 mL, 100 mol %), treated with $(BOC)_2O$ (16.9 g, 200 mol %) and DMAP (473 mg, 10 mol %), and stirred at room temperature overnight. The colored mixture was washed with NaH_2PO_4 (50 mL, 1 M) and brine (50 mL), dried, filtered, and evaporated to a colored viscous solid that was filtered through a plug of silica gel using 1:1 EtOAc in hexanes as eluant. The collected fractions were evaporated to provide pyroglutamate **16** as a colorless crystalline solid: 9.56 g, 77%; mp 69−70 °C (lit. 57−59 °C;[14f] 72−74 °C[15]); TLC R_f = 0.19 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −37.8 (*c* 1.0, $CHCl_3$) (lit.[15] $[\alpha]^{25}_D$ −35.0 (*c* 0.98, $CHCl_3$); IR (cm^{-1}): 1782, 1739, 1702. ^{1}H NMR δ 1.42 (s, 9 H), 1.95−2.59 (m, 4 H), 4.64 (m, 1 H), 5.20 (s, 2 H), 7.36 (m, 5 H); ^{13}C NMR δ 21.7, 27.9, 31.3, 59.1, 67.5, 83.8, 128.7, 128.8, 128.9, 135.2, 149.4, 171.3, 173.4. HRMS calcd for $C_{17}H_{22}NO_5$ [M + H]: 320.1498, found: 320.1508. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.96; H, 6.94; N, 4.43.

(2*S*)-α−Benzyl 2-*N*-(BOC)Amino-5-oxo-6-(dimethylphosphonyl)hexanoate (17). A −78 °C solution of dimethyl methyl phosphonate (360 μL, 3.3 mmol, 105 mol %) in toluene (40 mL) was treated with *n*-butyllithium (2.53 mL, 3.3 mmol, 105 mol %, 1.3 M in hexanes), stirred for 20 min at −78 °C, and transferred by cannula dropwise over 60 min into a −78 °C solution of (2*S*)-benzyl *N*-(BOC)pyroglutamate (**16**, 1.0 g, 3.1 mmol) in toluene (30 mL). The solution was stirred for 1 h, warmed to room temperature over 30 min, quenched with aqueous NaH_2PO_4 (20 mL, 1 M), and diluted with EtOAc (50 mL). The aqueous layer was separated, saturated with solid NaCl, and extracted with EtOAc until TLC of the organic layer showed no material that stained with ceric ammonium molybdate. 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 afford a colorless oil that crystallized (**17**, 1.02 g, 74%): mp 81−83 °C; TLC R_f = 0.26 (EtOAc); $[\alpha]_D^{20}$ −4.8 (*c* 1.0, $CHCl_3$); IR (cm^{-1}): 3542, 1738, 1736, 1701, 1621. ^{1}H NMR (keto−enol mixture) δ 1.37 (s, 2 H), 1.42 (s, 7 H), 1.88−1.98 (m, 1 H), 2.14−2.18 (m, 1 H), 2.62−2.78 (m, 2 H), 3.04 (s, 1 H), 3.09 (s, 1 H), 3.66 (m, 1 H), 3.75 (d, 5 H, *J* = 11.2), 4.28 (dd, 1 H, *J* = 4.7, 8.1), 5.13 (d, 1 H, *J* = 12.3), 5.18 (d, 1 H, *J* = 12.3), 5.48 (bd, 1 H, *J* = 8.1), 7.34 (s, 5 H); ^{13}C NMR (keto−enol mixture) δ 27.7, 28.2, 39.7, 40.4, 41.7, 52.7, 52.8, 52.9, 53.4, 62.1, 66.9, 79.7, 135.3, 155.5, 172.0, 200.6. HRMS calcd for $C_{20}H_{31}NO_8P$ [M + H]: 444.1787, found: 444.1802.

(2*S*,9*S*)-1-*tert*-Butyl 10-Benzyl 5-Oxo-2-[*N*-(PhF)amino] 9-[*N*-(BOC)amino]dec-4-enedioate (18). To a stirred solution of β-keto phosphonate **17** (1.02 g, 2.3 mmol) and *N*-(PhF)-aspartate aldehyde **8** (950 mg, 2.3 mmol, 100 mol %, prepared according to refs 10 and 18a) in CH_3CN (20 mL) was added Cs_2CO_3 (899 mg, 2.76 mmol, 120 mol %). The mixture was stirred at room temperature for 4−5 h, quenched with aqueous NaH_2PO_4 (20 mL, 1 M), and diluted with EtOAc (25 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 solid residue that was chromatographed using a gradient of 10−50% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave ketone **18** as a white crystalline solid: 1.39 g, 83%; mp 144−145 °C; TLC R_f = 0.40 (1:4 EtOAc:hexanes); $[\alpha]^{20}_D$ −81.8 (*c* 1.0, $CHCl_3$); IR (cm^{-1}): 3359, 1736, 1709, 1678. ^{1}H NMR δ 1.20 (s, 9 H), 1.44 (s, 9 H), 1.96−2.04 (m, 1 H), 2.14−2.20 (m, 1 H), 2.22−2.36 (m, 1 H), 2.52−2.72 (m, 3 H), 3.21 (bs, 1 H), 4.37 (dd, 1 H, *J* = 5.2, 7.6), 5.14 (d, 1 H, *J* = 12.3), 5.20 (d, 1 H, *J* = 12.3), 5.28 (d, 1 H, *J* = 7.9), 5.99 (d, 1 H, *J* = 16.0), 6.69 (dt, 1 H, *J* = 7.4, 16.0), 7.19−7.43 (m, 16 H), 7.67−7.71 (m, 2 H); ^{13}C NMR δ 26.6, 28.0, 28.5, 35.8, 39.1, 53.4, 55.7, 67.3, 73.1, 80.1, 81.4, 155.6, 172.4, 174.1, 198.7. HRMS calcd for $C_{45}H_{51}N_2O_7$ [M + H]: 731.3696, found: 731.3676. Anal. Calcd for $C_{45}H_{50}N_2O_7$: C, 73.95; H, 6.90; N, 3.83. Found: C, 73.90; H, 7.10; N, 3.84.

(3*S*,6*R*,10*S*)-*tert*-Butyl 2-Oxo-3-*N*-(BOC)amino-1-azabicyclo[4.4.0]decane-10-carboxylate (20). A solution of ketone **18** (1.46 g, 2.0 mmol) in THF (30 mL) and *i*-PrOH (20 mL) was transferred into a hydrogenation apparatus and treated with palladium-on-carbon (200 mg, 10 wt %). The pressure bottle was filled, vented, and refilled four times with 6 atm of H_2. The reaction mixture was stirred for 18 h and filtered onto a plug of diatomaceous earth (Celite) that was washed thoroughly with MeOH. Evaporation of the volatiles gave crude pipecolate **19** (HRMS calcd for $C_{19}H_{35}N_2O_6$ [M + H]: 387.2495, found: 387.2507) that was dissolved in CH_2Cl_2 (50 mL), cooled to 0 °C, treated with DIEA (698 μL, 4 mmol, 200 mol %) and diphenylphosphoryl azide (862 μL, 4 mmol, 200 mol %), stirred for 30 min, warmed to room temperature, and left to stir for 16 h. Evaporation of the volatiles and chromatography of the residue using 0−100% EtOAc in hexanes as eluant gave quinolizidin-2-one amino ester **20** as a clear oil that crystallized on standing: 736 mg, 99%, mp 115−117 °C; TLC R_f = 0.47 (1:1 EtOAc:hexanes); $[\alpha]^{20}_D$ −1.6 (*c* 1.0, $CHCl_3$); IR (cm^{-1}): 3346, 1721, 1708, 1657. ^{1}H NMR δ 1.33 (s, 9 H), 1.35 (s, 9 H), 1.26−1.75 (m, 7 H), 1.80−1.93 (m, 3 H), 2.24−2.30 (m, 1 H), 3.38−3.45 (m, 1 H), 3.99−4.05 (m, 1 H), 4.19−4.22 (dd, 1 H, *J* = 5.7, 5.8), 5.50 (bs, 1 H); ^{13}C NMR δ 18.8, 24.3, 25.3, 27.4, 27.9, 28.0, 28.3, 29.1, 50.7, 52.7, 55.3, 79.3, 81.1, 155.6, 170.6. HRMS calcd for $C_{19}H_{33}N_2O_5$ [M + H]: 369.2390, found: 369.2403. Anal. Calcd for $C_{19}H_{32}N_2O_5$: C, 61.93; H, 8.75; N, 7.60. Found: C, 61.85; H, 9.04; N, 7.51.

(3*S*,6*R*,10*S*)-2-Oxo-3-*N*-(Fmoc)amino-1-azabicyclo[4.4.0]-decane-10-carboxylate (6). A solution of *N*-(BOC)amino-1-azabicyclo[4.4.0]decane-10-carboxylate **20** (350 mg, 0.95 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with HCl bubbles for 60 min, when TLC showed complete disappearance of the starting material. The volatiles were evaporated to give the crude hydrochloride as a white solid, that was dried under vacuum, dissolved in water (5 mL), treated with solid $NaHCO_3$ (160 mg, 1.9 mmol, 200 mol %), stirred for 10 min, and treated with a solution of Fmoc-OSu (320 mg, 0.95 mmol, 100 mol %) in acetone (10 mL). The mixture was stirred for 3 h at room temperature, acidified with H_3PO_4 to pH 4, and extracted with EtOAc until TLC of the aqueous layer showed no UV-active material. The combined organic layers were evaporated to a

residue that was chromatographed using 0−70% EtOAc in hexanes containing 2% AcOH as eluant. Evaporation of the collected fractions gave *N*-(Fmoc)amino acid **6** as a white foam: 356 mg, 86% TLC $R_f = 0.27$ (EtOAc + 1% AcOH); $[\alpha]^{20}_D$ −5.2 (*c* 1.0, $CHCl_3$); IR (cm^{-1}): 3290, 1717, 1648. ^1H NMR δ 1.50−1.80 (bm, 6 H), 2.02−2.09 (bm, 2 H), 2.34−2.39 (bm, 1 H), 3.52 (bs, 1 H), 4.25 (m, 1 H), 4.31 (m, 1 H), 4.34 (m, 1 H), 6.35 (bd, 1 H, $J = 6.0$), 7.18−7.78 (m, 8 H), 10.04 (bs, 1 H); ^{13}C NMR δ 19.4, 24.4, 25.0, 27.0, 29.3, 47.1, 51.1, 54.0, 55.9, 67.1, 119.9, 125.3, 127.1, 127.7, 128.2, 129.0, 137.8, 141.2, 143.8, 144.0, 156.4, 171.2, 174.9, 176.2. HRMS calcd for $C_{25}H_{27}N_2O_5$ [M + H]: 435.1920, found: 435.1938.

(2*S*,6*RS*,9*S*)-1-*tert*-Butyl 10-Benzyl 5-Hydroxy-2-[*N*-(PhF)amino]-9-[*N*-(BOC)amino]dec-4-enedioate (21). A solution of ketone **18** (2.0 g, 2.72 mmol) in MeOH (20 mL) and THF (20 mL) was treated with $CeCl_3 \cdot 7H_2O$ (1.12 g, 110 mol %) and stirred for 10 min. Solid $NaBH_4$ (255 mg, 6.8 mmol, 250 mol %) was added, and the solution was stirred for 10 min, quenched with aqueous NaH_2PO_4 (15 mL, 1 M), and diluted with EtOAc (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried, and evaporated to a residue that was chromatographed using 0−50% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave allylic alcohol **21** as a 1:1 mixture of diastereomers: 1.71 g, 86%, white foam; TLC $R_f = 0.58$ (1:1 EtOAc:hexanes); ^1H NMR δ 1.17 (s, 9 H), 1.42 (s, 9 H), 1.46−1.55 (m, 2 H), 1.57−1.99 (m, 2 H), 2.07−2.11 (bm, 3 H), 2.57 (ddd, 1 H, $J = 3.0, 6.0, 12.1$), 3.09 (bs, 1 H), 3.98 (m, 1 H), 4.35 (bm, 1 H), 5.05−5.20 (m, 2 H), 5.23−5.44 (m, 2 H), 5.56−5.66 (m, 1 H), 7.14−7.19 (m, 7 H), 7.21−7.28 (m, 9 H), 7.30−7.42 (m, 1 H), 7.63−7.66 (m, 1 H); ^{13}C NMR δ 28.0, 28.4, 32.7, 38.5, 38.6, 53.6, 56.2, 56.3, 65.1, 67.0, 72.0, 72.2, 73.1, 80.0, 80.8, 155.6, 172.7, 174.6. HRMS calcd for $C_{45}H_{53}N_2O_7$ [M + H]: 733.3853, found: 733.3869.

(2*S*,6*RS*,9*S*)-Benzyl 5-[4′-[*N*-(PhF)amino]-4′-(*tert*-butyloxycarbonyl)but-1-enyl]-*N*-(BOC)prolinate (22). A solution of allylic alcohol **21** (1.71 g, 2.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C was treated with Et_3N (2.26 mL, 16.3 mmol, 700 mol %) and methanesulfonyl chloride (1.06 mL, 13.6 mmol, 580 mol %). The stirred mixture was left to warm to room temperature for 20 h and evaporated to dryness, and the residue was chromatographed using a gradient of 0−20% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave a 2:1 diastereomeric mixture of prolines **22** (1.53 g, 91%, white foam): TLC $R_f = 0.57$ (1:4 EtOAc:hexanes); ^1H NMR δ 1.21 (s, 3 H), 1.23 (s, 4 H), 1.24 (s, 2 H), 1.32 (s, 1H), 1.41 (s, 2 H), 1.49 (s, 3 H), 1.50 (s, 3 H), 1.55−2.26 (m, 6 H), 2.66 (m, 1 H), 3.13 (bs, 1 H), 4.27−4.49 (m, 1 H), 5.15 (m, 2 H), 5.32 (m, 1 H), 5.45 (m, 1 H), 7.13−7.26 (m, 7 H), 7.31−7.49 (m, 9 H), 7.66−7.74 (m, 2 H); ^{13}C NMR δ 27.4, 27.5, 27.9, 28.3, 28.4, 29.3, 29.5, 30.1, 31.7, 34.3, 34.4, 38.3, 38.5, 52.2, 53.1, 55.7, 56.0, 58.3, 58.7, 59.0, 59.2, 59.5, 59.6, 59.9, 62.0, 62.2, 66.5, 66.6, 66.8, 67.0, 72.96, 73.0, 76.3, 77.4, 79.7, 80.0, 80.4, 80.7, 153.3, 154.4, 155.3, 172.2, 172.5, 172.8, 174.2, 174.3. HRMS calcd for $C_{45}H_{51}N_2O_6$ [M + H]: 715.3747, found: 715.3735.

(2*S*,6*RS*,9*S*)-5-[4′-[*N*-(Fmoc)amino]-4′-(*tert*-butyloxycarbonyl)butyl]-*N*-(BOC)proline (23). A solution of prolines **22** (1.53 g, 2.14 mmol) in THF (15 mL) and MeOH (15 mL) was transferred into a hydrogenation apparatus and treated with palladium-on-carbon (153 mg, 10 wt %). The pressure bottle was filled, vented, and refilled four times with 6 atm of H_2. The reaction mixture was stirred for 16 h and filtered onto a plug of diatomaceous earth (Celite) that was washed thoroughly with MeOH. Evaporation of the volatiles gave a crude residue that was dissolved in acetone (12 mL) and water (5 mL), treated with solid $NaHCO_3$ (180 mg, 2.14 mmol, 100 mol %) and Fmoc-OSu (721 mg, 2.14 mmol, 100 mol %), stirred for 2−3 h, acidified with solid citric acid to pH 4, saturated with solid NaCl, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried, and evaporated to a residue that was chromatographed using a gradient of 20−100% EtOAc in hexanes containing 1% AcOH as eluant. Evaporation of the collected fractions gave acid **23** as a 2:1 diastereomeric mixture: 1.05 g, 81%, white foam, TLC $R_f = 0.30$ (EtOAc + 1% AcOH); ^1H NMR δ 1.25−1.55 (bm, 4 H), 1.44 (s, 3 H), 1.48 (s, 6 H), 1.50 (s, 9 H), 1.58−1.71 (bm, 2 H), 1.84−1.99 (bm, 2 H), 2.03−2.33 (bm, 2 H), 3.80−4.10 (m, 1 H), 4.04−4.58 (bm, 5 H), 5.14 (bd, 0.2 H, $J = 7.4$), 5.53 (bd, 0.4 H, $J = 7.6$), 5.68 (bd, 0.2 H, $J = 8.0$), 6.12 (bs, 0.2 H), 7.14−7.78 (m, 8 H); ^{13}C NMR δ 22.3, 25.1, 25.3, 25.5, 28.1, 28.4, 28.5, 28.6, 29.1, 32.6, 32.8, 33.6, 33.9, 46.4, 47.3, 53.4, 54.3, 54.4, 58.0, 59.4, 59.6, 60.0, 67.5, 73.0, 80.1, 80.4, 80.8, 82.2, 151.7, 154.1, 155.7, 156.1, 156.3, 168.8, 172.1, 177.2. HRMS calcd for $C_{34}H_{44}N_2O_8Na$ [M + Na]: 631.2996, found: 631.3039.

(2*S*,6*RS*,9*S*)-Allyl 5-[4′-[*N*-(Fmoc)Amino]-4′-(*tert*-butyloxycarbonyl)butyl]-*N*-(BOC)prolinate (24). A solution of acid **23** (357 mg, 0.60 mmol) in CH_3CN (12 mL) was treated with allyl iodide (108 μL, 2.4 mmol, 400 mol %) and DIEA (210 μL, 1.2 mmol, 200 mol %), heated at a reflux for 3 h, cooled to room temperature, and evaporated to dryness. The crude residue was chromatographed using a gradient of 0−30% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave **24** as a 2:1 diastereomeric mixture: 334 mg, 86%, white foam, TLC $R_f = 0.37$ (1:4 EtOAc:hexanes); ^1H NMR δ 1.17−1.50 (m, 4 H), 1.37 (s, 3 H), 1.41 (s, 6 H), 1.43 (s, 9 H), 1.57−1.59 (bm, 2 H), 1.66−1.97 (bm, 3 H), 2.15 (bm, 1 H), 3.75−4.05 (bm, 1 H), 4.15−4.49 (bm, 5 H), 4.49−4.62 (bm, 2 H), 5.23 (bm, 2 H), 5.61 (bm, 0.6 H), 5.73 (bm, 0.3 H), 5.86 (m, 1 H), 7.23−7.26 (m, 2 H), 7.31−7.33 (m, 2 H), 7.55−7.57 (m, 2 H), 7.68−7.70 (m, 2 H); ^{13}C NMR δ 22.1, 24.9, 25.2, 27.3, 27.4, 27.9, 28.2, 28.3, 28.9, 32.3, 32.5, 33.4, 47.1, 53.4, 54.1, 54.2, 54.8, 57.5, 57.6, 57.8, 59.3, 59.6, 65.3, 65.5, 66.8, 79.5, 79.7, 79.8, 81.5, 81.7, 81.9, 153.7, 154.2, 155.3, 155.8, 156.0, 171.7, 171.8, 172.5, 172.7. HRMS calcd for $C_{37}H_{48}N_2O_8Na$ [M + Na]: 671.3308, found: 671.3333.

(3*S*,7*S*,10*S*)- and (3*S*,6*R*,10*S*)-2-Oxo-3-*N*-(Fmoc)amino-1-azabicyclo[5.3.0]decane-10-carboxylate (22). A solution of allyl ester **24** (793 mg, 1.25 mmol) in CH_2Cl_2 (40 mL) at 0 °C was treated with HCl bubbles for 1.5 h. The solution was stirred for 1.5 h at 0 °C, warmed to room temperature over 30 min, and evaporated to dryness. Hydrochloride **25** was obtained as a white glassy solid: HRMS calcd for $C_{28}H_{33}N_2O_6$ [M + H]: 493.2339, found: 493.2330. A solution of hydrochloride **25** (439 mg, 0.83 mmol) in CH_2Cl_2 (200 mL) was treated with azabenzotriazolyl-1,1,3,3-tetramethylaminium hexafluorophosphate (HATU, 631 mg, 1.66 mmol, 200 mol %) and DIEA (433 μL, 2.49 mmol, 300 mol %). The solution was stirred for 3 h at room temperature. The volatiles were evaporated, and the residue was chromatographed using 0−50% EtOAc in hexanes as eluant. First to elute was concave (3*S*,7*S*,10*S*)-**26**: 65 mg, 17%, white foam, TLC $R_f = 0.32$ (1:1 EtOAc:hexanes); TLC $R_f = 0.58$ (4:1 EtOAc:hexanes); $[\alpha]^{20}_D$ −37.8 (*c* 0.5, $CHCl_3$); ^1H NMR δ 1.61−1.90 (m, 5 H), 2.01−2.13 (m, 4 H), 2.23−2.31 (m, 1 H), 3.86 (m, 1 H), 4.22 (t, 1 H, $J = 7.2$), 4.31 (dd, 1 H, $J = 5.0, 6.1$), 4.34 (d, 2 H, $J = 7.3$), 4.66 (d, 2 H, $J = 5.9$), 4.67−4.70 (m, 1 H), 5.33 (m, 2 H), 5.97 (m, 1 H), 6.25 (d, 1 H, $J = 5.9$), 7.26−7.42 (m, 4 H), 7.60 (d, 2 H, $J = 7.4$), 7.76 (d, 2 H, $J = 7.5$); ^{13}C NMR δ 27.8, 31.8, 33.1, 34.4, 47.3, 55.0, 59.4, 60.7, 66.0, 67.1, 118.9, 120.1, 125.4, 127.2, 127.8, 131.9, 141.4, 144.1, 144.2, 155.7, 171.3, 171.8. HRMS calcd for $C_{28}H_{31}N_2O_5$ [M + H]: 475.2233, found: 475.2245.

Next to elute was convex (3*S*,7*R*,10*S*)-**26**: 129 mg, 33%, white foam; TLC $R_f = 0.19$ (1:1 EtOAc:hexanes); TLC $R_f = 0.45$ (4:1 EtOAc:hexanes); $[\alpha]^{20}_D$ −54.6 (*c* 0.5, $CHCl_3$); ^1H NMR δ 1.59−1.84 (m, 4 H), 1.97−2.11 (m, 5 H), 2.27 (m, 1 H), 3.78 (m, 1 H), 4.22 (t, 1 H, $J = 7.0$), 4.30 (bs, 1 H), 4.35 (d, 2 H, $J = 6.5$), 4.59−4.65 (bm, 3 H), 5.30 (m, 2 H), 5.93 (m, 1 H), 6.01 (bs, 1 H), 7.25−7.40 (m, 4 H), 7.61 (d, 2 H, $J = 7.4$), 7.75 (d, 2 H, $J = 7.5$); ^{13}C NMR δ 23.2, 26.7, 28.5, 34.3, 47.3, 53.3, 59.8, 61.3, 65.8, 67.0, 118.6, 120.1, 125.3, 127.2, 127.8, 132.0, 141.4, 144.0, 144.1, 156.1, 170.4, 172.3. HRMS calcd for $C_{28}H_{31}N_2O_5$ [M + H]: 475.2233, found: 475.2245.

(3*S*,7*S*,10*S*)-2-Oxo-3-*N*-(Fmoc)amino-1-azabicyclo[5.3.0]-decane-10-carboxylic acid ((7*S*)-7). A solution of (3*S*,7*S*,-10*S*)-**26** (60 mg, 0.126 mmol) in CH_2Cl_2 (2 mL) and AcOH (18 μL, 0.315 mmol, 250 mol %) was degassed by bubbling nitrogen for 5−10 min and then treated with $Pd(PPh_3)_2Cl_2$ (4 mol %) and *n*-Bu_3SnH (68 μL, 0.252 mmol, 200 mol %). The mixture

was stirred at room temperature for 1−2 min, when gas evolution was complete and the color of the solution changed from yellow to amber, and then it was evaporated to dryness. Chromatography of the residue using a gradient of 50−100% EtOAc in hexanes containing 1% AcOH and evaporation of the collected fractions gave (7*S*)-**7** as a foam: 54 mg, 99%; TLC R_f = 0.38 (1% AcOH in EtOAc); $[\alpha]^{20}_D$ −54.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 1.54−1.68 (m, 2 H), 1.83−1.85 (m, 3 H), 1.98−2.08 (m, 3 H), 2.11−2.35 (m, 2 H), 3.86 (m, 1 H), 4.21 (dd, 1 H, J = 7.1, 7.3), 4.35 (bd, 3 H, J = 7.5), 4.70 (d, 1 H, J = 7.7), 6.21 (d, 1 H, J = 6.2), 7.29−7.41 (m, 4 H), 7.60 (d, 2 H, J = 7.3), 7.76 (d, 2 H, J = 7.5); ^{13}C NMR δ 26.8, 27.4, 31.3, 32.9, 34.2, 47.0, 54.6, 59.5, 66.9, 119.9, 125.1, 126.9, 127.6, 141.1, 143.7, 143.8, 155.5, 172.4, 174.7. HRMS calcd for $C_{25}H_{27}N_2O_5$ [M + H]: 435.1920, found: 435.1929.

(3*S*,7*R*,10*S*)-2-Oxo-3-*N*-(Fmoc)amino-1-azabicyclo[5.3.0]-decane-10-carboxylic acid ((7*R*)-7) was prepared using the same procedure as described for (3*S*,7*S*,10*S*)-**26** using (3*S*,7*R*,-10*S*)-**26** (123 mg, 0.259 mmol). Evaporation of the collected fractions gave (7*R*)-**7** as a foam: 98 mg, 88%; TLC R_f = 0.19 (1% AcOH in EtOAc); $[\alpha]^{20}_D$ −40.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 1.57−2.29 (bm, 10 H), 3.69 (bm, 1 H), 4.21 (t, 1 H, J = 6.8), 4.31−4.35 (bm, 3 H), 4.58 (t, 1 H, J = 7.9), 6.08 (bs, 1 H), 7.25−7.46 (m, 4 H), 7.60 (d, 2 H, J = 7.3), 7.73 (d, 2 H, J = 7.4); ^{13}C NMR δ 23.0, 26.4, 28.4, 34.2, 47.3, 53.8, 59.7, 61.6, 67.1, 120.1, 125.4, 127.3, 127.8, 141.4, 144.0, 144.1, 156.3, 171.3, 176.0. HRMS calcd for $C_{25}H_{27}N_2O_5$ [M + H]: 435.1920, found: 435.1929.

Enantiomeric Purity of (3*S*,6*R*,10*S*)-*tert*-Butyl 2-Oxo-3-*N*-(BOC)amino-1-azabicyclo[4.4.0]decane-10-carboxylate ((3*S*,6*R*,10*S*)-20). A solution of (3*S*,6*R*,10*S*)-**20** (8.1 mg) in MeOH (5 mL) at 0 °C was treated with $SOCl_2$ (100 μL), stirred for 2.5 h at room temperature when TLC (100% EtOAc) showed complete disappearance of the starting material **20**. The volatiles were removed under vacuum, and the hydrochloride **27** was dissolved in THF (1 mL), treated with either (*R*)- or (*S*)-α-methylbenzylisocyanate (7.4 μL, 0.05 mmol, 200 mol %) and Et_3N (7.4 μL, 0.05 mmol, 200 mol %), heated at a reflux for 3 h, cooled, and evaporated to residue that was directly examined by proton NMR. The limits of detection were determined by measuring the diastereomeric methyl ester singlets at 3.71 and 3.65 ppm in $CDCl_3$ in the 400 MHz ^{1}H NMR spectrum. Less than 1% of the (1′*R*)-diastereomer was detected in the spectrum for the (1′*S*)-urea **28**. Purification by chromatography using a gradient of pure hexanes to pure EtOAc as eluant gave ureas **28** having the following spectra.

Urea (1′*R*)-28: ^{1}H NMR δ 1.45 (d, 3 H, J = 6.8), 1.46−1.69 (m, 4 H), 1.70−1.80 (m, 1 H), 1.81−2.05 (m, 4 H), 2.35 (m, 1 H), 3.50 (m, 1 H), 3.71 (s, 3 H), 4.15 (dd, 1 H, J = 5.3, 7.2), 4.25 (m, 1 H), 4.83 (bm, 1 H), 5.27 (bs, 1 H), 5.59 (bs, 1 H), 7.19−7.34 (m, 5 H); HRMS calcd for $C_{20}H_{28}N_3O_4$ [M + H]: 374.2080, found: 374.2077.

Urea (1′*S*)-28: ^{1}H NMR δ 1.45 (d, 3 H, J = 6.9), 1.51−1.59 (m, 2 H), 1.62−1.76 (m, 4 H), 1.81−2.06 (m, 3 H), 2.31 (m, 1 H), 3.51 (bd, 1 H, J = 4.9), 3.65 (s, 3 H), 4.14 (dd, 1 H, J = 5.3, 7.0), 4.34 (dd, 1 H, J = 6.0, 8.8), 4.88 (bs, 1 H), 5.37 (bs, 1 H), 5.69 (bs, 1 H), 7.20−7.40 (m, 5 H); HRMS calcd for $C_{20}H_{28}N_3O_4$ [M + H]: 374.2080, found: 374.2077.

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Supporting Information Available: Experimental details for the preparation of **14**, ^{1}H and ^{13}C NMR spectra of **6**, **7**, **17**, **21**, **22**, **24**, **26**, **28**, and crystallographic data for **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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