Mimicry of Peptide Backbone Geometry and Heteroatomic Side-Chain Functionality: Synthesis of Enantiopure Indolizidin-2-one Amino Acids Possessing Alcohol, Acid, and Azide Functional Groups

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Indolizidinone amino acids possessing various heteroatomic side chains at their 5- and 7-positions have been synthesized through modification of hydroxymethyl indolizidinone amino acids **5** and **6**. Displacements of the methanesulfonates from alcohols **5** and **6** with sodium azide, as well as oxidation of alcohol **5**, have been used to furnish orthogonally protected indolizidin-2-one diamino carboxylates **7** and **8**, and indolizidin-2-one amino dicarboxylate **9**. Both 5- and 7-hydroxymethylindolizidinone amino acids **5** and **6** were obtained from sequences commencing with the Claisen condensation of α-*tert*-butyl γ-methyl l-*N*-(PhF)-L-glutamate to furnish di-*tert*-butyl 4-carbomethoxy-5-oxo-2,8-di-[*N*-(PhF)amino]azelate **10** (PhF = 9-(9-phenylfluorenyl)). Subsequent hydride reduction of **10** to an isomeric mixture of diols **12**, selective protection of the primary alcohol as *tert*-butyldimethylsilyl ether **14** and oxidation of the secondary alcohol gave di-*tert*-butyl 4-*tert*-butyldimethylsilyloxymethyl-5-oxo-2,8-di-[*N*-(PhF)amino]azelate **15** as a separable diastereomeric mixture. Linear ketone **15** and alcohol **14** were then converted to the indolizidinone heterocycles by routes featuring reductive aminations, methanesulfonate displacements, and lactam cyclizations. A series of rigid scaffolds designed to mimic the conformations of dipeptides possessing serine, lysine, and glutamate residues has thus been synthesized by this new route for installing heteroatomic side-chain functional groups onto the indolizidin-2-one system.

Introduction

Azabicyclo[X.Y.0]alkane amino acids serve as tools for rigidifying peptide structures in order to probe conformation-activity relationships in peptide science.[1,2] They can also be employed in medicinal chemistry as inputs for targeted library synthesis in which different pharmacophores are systematically displayed for studying recognition events.[2,3] The sub-group of indolizidinone and quinolizidinone amino acids are particularly attractive scaffolds for functionalization by combinatorial technology, because of their relationship to indolizidine and quinolizidine ring systems which are present in the structures of up to 30% of all alkaloids.[4] Diversification of such azabicycloalkane amino acids by appendage of different pharmacophores onto the amine and carboxylate handles may thus provide library members exhibiting biological activity (i.e., cardiotonic, antiarrhythmic, uterotonic, immunostimulatory, and neuroexcitatory activity) which has inspired more than a century of research to synthesize their heterocycle counterparts (Figure 1).[4]

We have introduced methodology for synthesizing a variety of azabicyclo[X.Y.0]alkane amino acids stereoselectively from *N*-(PhF)aminodicarboxylates of different chain-lengths (Scheme 1, PhF = 9-(9-phenylfluorenyl)).[5−7]

(1) Reviewed in: Halab, L.; Gosselin, F.; Lubell, W. D. *Biopolymers, Peptide Science* **2000**, *55*, 101−122. We have adopted the nomenclature and ring system numbering used in ref 2 in order to maintain clarity and consistency when comparing these different heterocyclic systems.

(2) (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. Recent examples since the publication of this review include those cited in ref 2 of ref 8 below, as well as (b) syntheses of the 5, 5-, 5, 6- and 5,7-fused 1-azaoxobicycloalkane *N*-(BOC)amino *tert*-butyl esters: Angiolini, M.; Araneo, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2571−2581. (c) Synthesis of the 5,6-fused 1-azaoxobicycloalkane *N*-(Cbz)amino esters: Mulzer, J.; Schülzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289. (d) Synthesis of *N*-(BOC)amino Δ^5-dehydropyrroloazepinone methyl ester: Grossmith, C. E.; Senia, F.; Wagner, J. *Synlett* **1999**, 1660−1662. (e) Thiaindolizidinone peptide ORL1 receptor antagonist: Becker, J. A. J.; Wallace, A.; Garzon, A.; Ingallinella, P.; Bianchi, E.; Cortese, R.; Simonin, F.; Kieffer, B. L.; Pessi, A. *J. Biol. Chem.* **1999**, *274*, 27513−27522. (f) Spirocyclic thiaindolizidinone peptides with SH3 domain affinity: Witter, D. J.; Famiglietti, S. J.; Cambier, J. C.; Castelhano, A. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3137−3142. (g) Oxaindolizidinone amino acid: Estiarte, M. A.; Rubiralta, M.; Diez, A.; Thormann, M.; Giralt, E. *J. Org. Chem.* **2000**, *65*, 6992−6999.

(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 III, A. B.; 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 III, A. B. *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. (d) Eguchi, M.; Lee, M. S.; Nakanishi, H.; Stasiak, M.; Lovell, S.; Kahn, M. *J. Am. Chem. Soc.* **1999**, *121*, 12204. (e) Guan, Y.; Green, M. A.; Bergstrom, D. E. *J. Comb. Chem.* **2000**, *2*, 297 and refs 2−9 therein.

(4) Recent reviews include: (a) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905. (b) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 21. (c) Ohmiya, S.; Saito, K.; Murakoshi, I. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 47, pp 1−114. For additional examples see ref 1 in ref 6a below.

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

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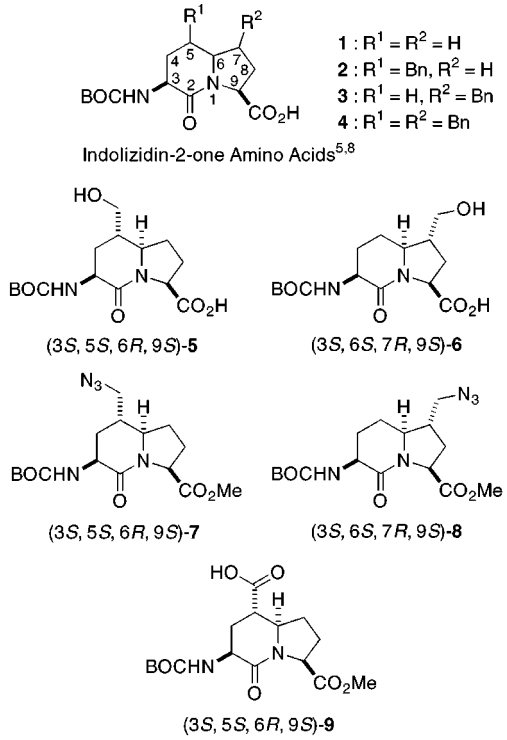


Figure 1. Indolizidin-2-one, 5- and 7-alkyl-, and 5,7-dialkylindolizidin-2-one amino acids **1**−**9**.

Stereocontrol has been attained at the ring-fusion and along the peptide backbone by employing L- and D-aminodicarboxylates in diastereoselective transformations.[1] For example, the employment of glutamic acid in our Claisen condensation/reductive amination/lactam cyclization sequence gave access to all of the possible stereoisomers of enantiopure azabicyclo[4.3.0]alkane, indolizidin-2-one amino acid **1** (Figure 1).[5] The use of aspartic acid in our olefination/reductive amination/lactam cyclization sequence has furnished the related azabicyclo[3.4.0]alkane, indolizidin-9-one amino acid in enantiopure form.[6] Employment of aspartate and pyroglutamate using the olefination entry has recently led to the syntheses of enantiopure azabicyclo[4.4.0]alkane, quinolizidinone amino acid as well as azabicyclo[5.3.0]alkane, pyrroloazepinone amino acid, both from the same linear precursor.[7]

In light of the importance of amino acid side chains as sites for interaction in various recognition events, we developed an approach for appending a variety of alkyl side chains onto the azabicyclo[X.Y.0]alkane heterocycle.[8] The power of this strategy was demonstrated by the syntheses of enantiopure 5-benzyl-, 7-benzyl-, and 5,7-dibenzyl indolizidin-2-one amino acids **2**−**4** via a route involving alkylation of a common *N*-(PhF)amino ketone intermediate **11**.[8] These benzyl indolizidinone amino acids may respectively serve as constrained dipeptide surrogates for Phe-Pro, Ala-Phe, and Phe-Phe.[9] Extending the versatility of our strategy for introducing alkyl side chains onto this heterocycle, we have now developed a method for synthesizing orthogonally protected indolizidin-2-one amino acids that possess heteroatomic side chains at the 5- and 7-positions.[10] Besides their homology with dipeptide structures possessing serine, lysine, and glutamate residues, these new scaffolds possess three sites suitable for diversification via combinatorial techniques.

Seeking to differentiate the side-chain functional group from the carboxylate groups destined to become the peptide backbone, we selected to introduce the side chain at the oxidation state of an alcohol. The product from the Claisen self-condensation of γ-methyl α-*tert*-butyl *N*-PhF-L-glutamate,[5] β-keto ester **10**, proved to be a practical starting material because its synthesis avoided the decarboxylation and alkylation steps for introducing groups onto δ-ketoazelate **11**[8] and because several stereoselective methods for β-keto ester reduction could be later employed to furnish specific isomers.[11] The syntheses of 5- and 7-hydroxymethyl indolizidinone amino acids **5** and **6** have now been accomplished by sequences that commence with the reduction of β-ketoester intermediate **10** to diol **12** and feature selective protection, reductive aminations, methanesulfonate displacements, and lactam cyclizations. The alcohol groups of 5- and 7-hydroxymethyl indolizidinone amino esters **16** and **17** have also been used for the introduction of other side-chain functionality including azido, formyl, and carboxylate groups.

Results and Discussion

Reduction of β-keto ester **10** with $NaBH_4$ in alcoholic solvents could be controlled to provide either diol **12** or β-hydroxy ester **13** as mixtures of diastereomers in 89% or 96% respective yields (Scheme 2).[12] Selective protection of the primary alcohol by silation of **12** with chloro *tert*-butyldimethylsilane (TBDMSCl), Et_3N, and DMAP in dichloromethane gave siloxymethyl ketone **14** in 96% yield.[13] Oxidation of the secondary alcohol of silyl ether **14** with oxalyl chloride and DMSO in dichloromethane gave ketones **15** in 97% yield as a mixture of diastereomers that were separable by column chromatography.[14]

Synthesis of 5- and 7-Hydroxymethyl and Methylindolizidinone Amino Esters 16−19 by Reductive Amination. Intramolecular reductive amination was examined to prepare the pyrrolidine ring of the hydroxymethyl indolizidinone system (Scheme 3). In the synthesis of 7-benzyl indolizidinones,[8] we found that treatment of diastereomerically pure (4*S*)- or (4*R*)-4-benzyl ketones with palladium-on-carbon at 9 atm of hydrogen in a 9:1 EtOH−AcOH solution, followed by lactam cyclization and protection, resulted in 5:1 to 8:1 ratios of (3*S*,6*S*,7*S*,9*S*)- and (3*S*,6*S*,7*R*,9*S*)-7-benzyl indolizidinones **3**. Epimerization of the alkyl-branched stereocenter was concluded to have occurred via an iminium ion−enaminium ion equilibrium prior to hydrogen addition to the dehydropyrrolidine.[8]

Considering epimerization as a means for controlling stereoselectivity in the synthesis of hydroxymethylin-

(6) (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; 660.

(7) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163.

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

(9) Polyak, F.; Lubell, W. D. In *Peptides 1998. Proceedings of the 25th European Peptide Symposium*; Bajusz, S., Hudecz, F., Eds; Akadémia Kiadó: Budapest, Hungary, 1998; 688.

(10) Preliminary results were reported: Polyak, F.; Lubell, W. D. In *Peptides: Chemistry, Structure and Biology*; Fields, G, Barany, G., Eds; ESCOM: Leiden, The Netherlands, 2000; 150−152.

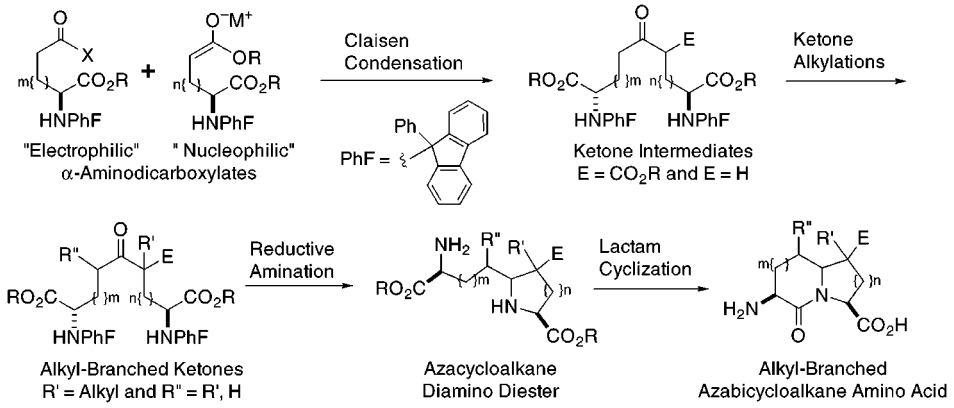
(11) Reviewed in: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

(12) Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.

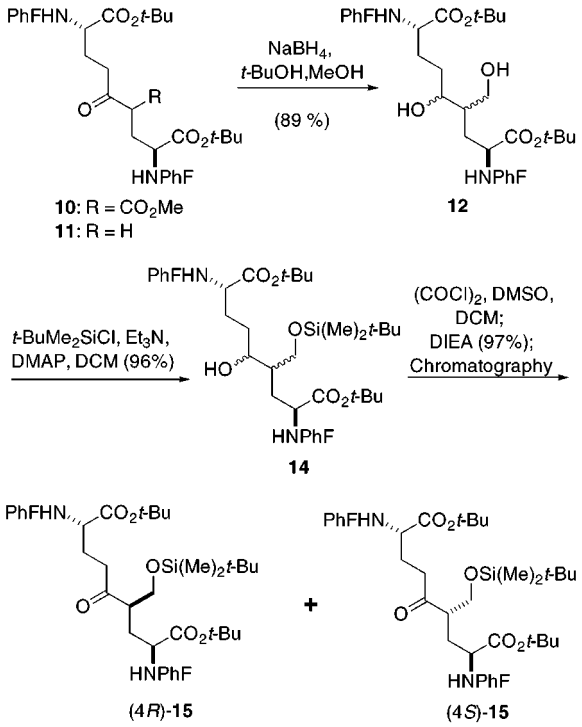
(13) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

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

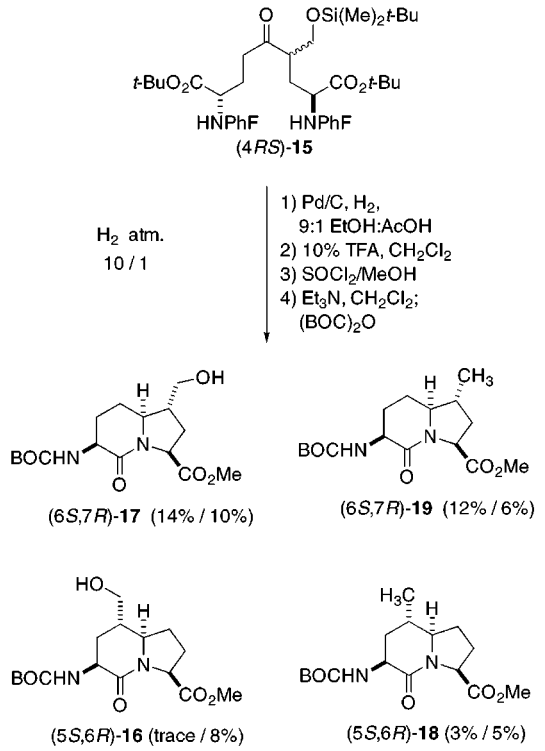
Scheme 1. General Approach for Synthesizing Alkyl-Branched Azabicyclo[X.Y.0]alkane Amino Acids



Scheme 2. Synthesis of Siloxymethyl δ-Ketoazelates 15



Scheme 3. Synthesis of 5- and 7-Hydroxymethyl- and Methylindolizidinone Amino Esters via Reductive Amination



dolizidinones, we exposed a diastereomeric mixture of siloxymethyl ketones **15** to our standard reductive amination/lactam cyclization/*N*-protection sequence. Hydrogenation of **15** with palladium-on-carbon in 9:1 EtOH−AcOH under hydrogen atmosphere caused removal of the phenylfluorenyl groups and conversion to the 5-alkylproline. The *tert*-butyl esters and *tert*-butyldimethylsilyl ether were removed with TFA in dichloromethane and the carboxylates were esterified using methanol and thionyl chloride. Treatment with triethylamine in dichloromethane caused lactam cyclization and liberation of the primary amine which was protected with di-*tert*-butyl dicarbonate to furnish *N*-(BOC)amino indolizidinone esters.

Four *N*-(BOC)amino indolizidinone esters were isolated by chromatography of the final reaction mixtures from this route. After hydrogenation at 10 atm of hydrogen followed by completion of the sequence, three *N*-(BOC)-amino methyl esters were isolated as major products: (3*S*,6*S*,7*R*,9*S*)-7-hydroxymethylindolizidinone (6*S*,7*R*)-**17** (14% yield), (3*S*,5*S*,6*R*,9*S*)-5-methylindolizidinone (5*S*,6*R*)-**18** (3% yield), and (3*S*,6*S*,7*R*,9*S*)-7-methylindolizidinone (6*S*,7*R*)-**19** (12% yield). The compound (3*S*,5*S*,6*R*,9*S*)-*N*-(BOC)amino 5-hydroxymethyl indolizidinone methyl ester (5*S*,6*R*)-**16** was obtained in trace amounts from the process at 10 atm of hydrogen and became a more significant product (8%) from the sequence featuring hydrogenation at 1 atm of hydrogen.

The formation of both 5- and 7-methyl indolizidinone amino esters **18** and **19** was most likely due to the elimination of the siloxy group via an enamine intermediate to form an α,*β*-unsaturated imine that was subsequently reduced (Figure 2). Their isolation adds additional proof of the existence of an imine to enamine equilibrium during the reductive amination of *δ*-keto α-amino esters.[8] Recently, we have taken advantage of this elimination process in order to form a related azadiene intermediate in a stereoconvergent approach to 5,6-dialkylpipecolates.[15]

(15) Swarbrick, M. E.; Lubell, W. D. *Chirality* **2000**, *12*, 366−373.

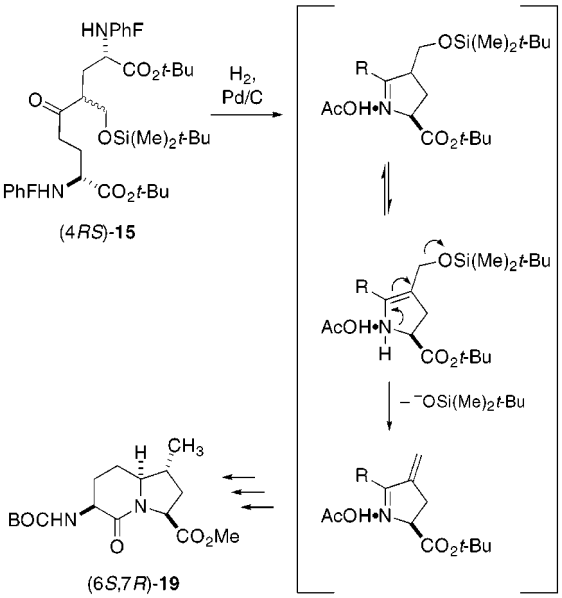


Figure 2. Mechanism for methylindolizidinone formation from the reductive amination of **15**.

Synthesis of 5- and 7-Hydroxymethylindolizidinone Amino Esters 16 and 17 by Methanesulfonate Displacements. Hydride reduction of δ-oxo azelates, methanesulfonation, and intramolecular displacement by the phenylfluorenylamine have proven effective for synthesizing 5-alkylproline intermediates for the preparation of indolizidinone amino acids.[5c,8,10] Specific formation of the *cis*-5-alkylproline diastereomer from symmetrical di-*tert*-butyl δ-hydroxy-α,ω-di-[*N*-(PhF)amino]azelate was first observed in the synthesis of the parent indolizidinone heterocycle and required the attack of each of the two amines fifty percent of the time in the S_N2 displacement of the methanesulfonate.[5c] A significant difference in the energy of the transition state leading to the favored *cis*- over the *trans*-5-alkylproline diastereomer was observed in the cyclizations of most of the δ-hydroxy α,β-diaminoazelates that we had previously studied.[5c,8] In the syntheses of 5- and 7-benzylindolizidinone amino esters of **2** and **3**, however, stereochemistry at the alkyl-branched 4-position influenced significantly the transition state for displacement of the 5*S*-methanesulfonate, and the 4*S* -benzyl group created a significant steric effect to promote a transition state providing the *trans*- rather than the *cis*-5-alkylproline diastereomer.[8] Continuing our investigation with δ-hydroxy α,β-diaminoazelate **14**, we have now found that the 4*S* and, to a lesser extent, the 4*R*-*tert*-butyldimethylsilyloxymethyl group both can exhibit sufficient steric effects to promote transition states that furnish the *trans*-5-alkylproline diastereomer in the cyclization of the 5*S*-methanesulfonate.

The influences of stereochemistry and substituent on the methanesulfonate displacements were examined as in the cyclization of the di-*tert*-butyl δ-hydroxy γ-benzyl α,ω-di-[*N*-(PhF)amino]azelates by the synthesis and cyclization of all four siloxymethyl alcohols **14**. As before, the four secondary alcohols **14** were obtained by independent reductions of ketones (4*S*)- and (4*R*)-**15** using sodium borohydride in ethanol with low diastereoselectivity (Scheme 4). Mixtures of (5*R*)- and (5*S*)-alcohols **14** were obtained from hydride reduction of both alkyl-branched isomers and were directly used in the subsequent reaction sequence, which featured activation with methanesulfonyl chloride, triethylamine, and DMAP in dichloromethane, followed by intramolecular substitution on heating at a reflux. The 5-alkylprolines were directly converted to the fully protected indolizidinone amino acids by *tert*-butyl ester, silyl ether and PhF group solvolysis with TFA, esterification with methanol and thionyl chloride, lactam cyclization on stirring with triethylamine in dichloromethane, and *N*-acylation with di-*tert*-butyl dicarbonate. The diastereomeric and regioisomeric hydroxymethylindolizidinone *N*-(BOC)amino esters **16** and **17** were finally separated by chromatography on silica gel.

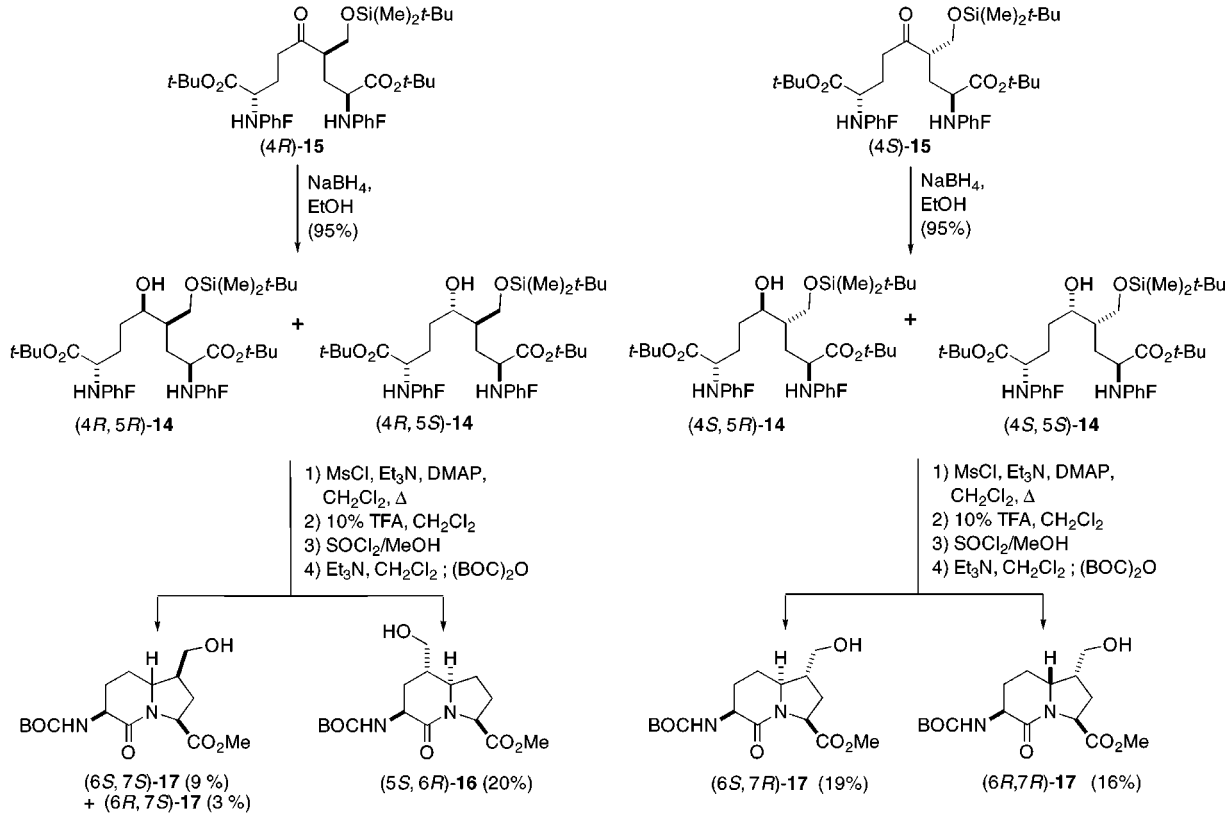
In total, this process has produced one 5-hydroxymethylindolizidinone amino ester **16** and four different 7-hydroxymethylindolizidinone amino ester diastereomers **17**. In three of the four cases, a single 5-alkylproline was synthesized from each alcohol diastereomer. As previously seen in the benzyl series, cyclizations with (4*R*,5*R*)- and (4*S*,5*R*)-**14** gave 4-substituted *cis*-5-alkylproline diastereomers that were respectively converted to 7-hydroxymethylindolizidinone amino esters (6*S*,7*S*)- and (6*S*,7*R*)-**17**. Furthermore, cyclization with (4*S*,5*S*)-**14** gave the 4-substituted 5-alkylproline *trans*-diastereomer, that was converted to (6*R*,7*R*)-**17**, and indicated that the steric effects from the 4*S*-group promoted a transition state providing *trans*- rather than *cis*-5-alkylproline diastereomer. Contrary to the stereoselective result of the benzyl series, the cyclization with (4*R*,5*S*)-**14** provided the less substituted 5-alkylproline *cis*-diastereomer along with a minor amount of the 4,5-dialkylproline *trans*-diastereomer, which were converted to their respective 5- and 7-hydroxymethylindolizidinone amino esters (5*S*,6*R*)-**16** and (6*R*,7*S*)-**17**. The formation of a mixture of 5-alkylprolines from cyclization of alcohol (4*R*,5*S*)-**14** demonstrated a competition of steric and stereochemical forces in the methanesulfonate displacement, which may be governed by varying the size of the protecting group on the hydroxymethyl substituent. In the siloxymethyl series, the methanesulfonate displacement approach has proven again to be an effective means for selectively generating alkyl-branched azabicyclo[4.3.0]-alkane ring systems. The final protected amino acid analogues, (3*S*,5*S*,6*R*,9*S*)- and (3*S*,6*S*,7*R*,9*S*)-3-*N*-(BOC)-amino-5-hydroxymethyl-indolizidin-2-one-9-carboxylic acids **5** and **6**, were respectively obtained in 86% and 85% yields from ester hydrolysis employing potassium trimethylsilanolate in ether without epimerization (Schemes 5 and 6).[16]

Synthesis of Indolizidinone Amino Acids Possessing Azide, Formyl, and Carboxylate Functions. With an effective method for synthesizing hydroxymethylindolizidinone amino esters **16** and **17** in hand, we began investigating the conversion of their alcohol groups into other side-chain functionality (Schemes 5 and 6). Two approaches have so far been investigated. One involving hydroxyl group activation as a methanesulfonate followed by displacement with sodium azide gave orthogonally protected diamino indolizidinone carboxylates **7** and **8**. The other employing a two step oxidation of the alcohol furnished indolizidinone amino dicarboxylate **9**.[10]

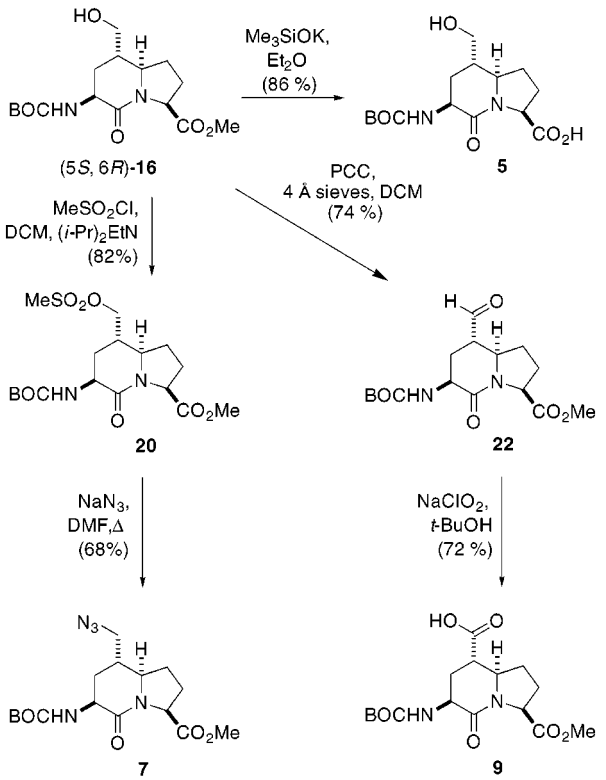
Activation of alcohols **16** and **17** with methanesulfonyl chloride and triethylamine in dichloromethane gave the respective methanesulfonates **20** and **21** in 82% and 79%

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

Scheme 4. Synthesis of 5- and 7-Hydroxymethylindolizidinone Amino Esters 16 and 17 via Methanesulfonate Displacements

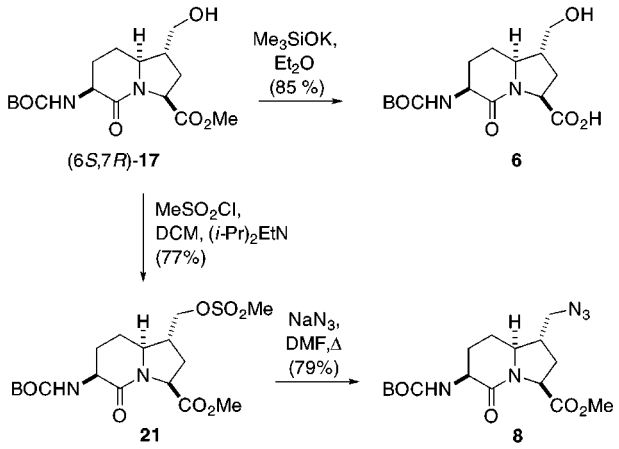


Scheme 5. Syntheses of Orthogonally Protected Indolizidinone Diamino Acid 7 and Indolizidinone Amino Dicarboxylate 9



yields. Displacement of the active ester with sodium azide in DMF at 80 °C furnished the respective azides **7** and **8** in 68% and 79% yields. Constrained Glu-Pro surrogate **9** was next synthesized by oxidation of 5-hydroxymethyl

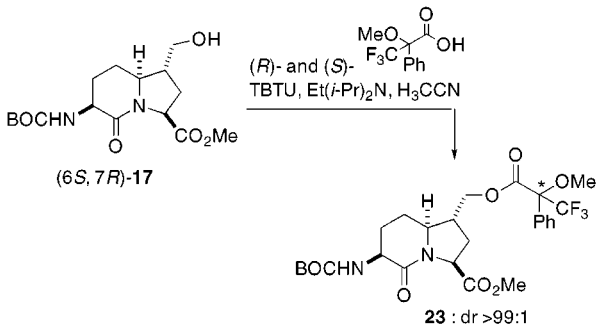
Scheme 6. Synthesis of Orthogonally Protected Indolizidinone Diamino Carboxylate 8



indolizidin-2-one *N*-(Boc)amino ester (5*S*)-**16** with pyridinium chlorochromate in dichloromethane containing 4 Å molecular sieves to furnish aldehyde **22** in 74% yield (Scheme 5).[17] Exposure of aldehyde **22** to $NaClO_2$ in a *t*-BuOH−MeCN solution buffered with aqueous NaH_2PO_4 yielded orthogonally protected carboxylate **9** in 72%.[18] Orthogonally protected with base-labile methyl ester, acid-labile BOC group, and reducible azide functionality, diamino indolizidinone carboxylates **7** and **8** and indolizidinone amino dicarboxylate **9** all offer diverse potential for elaboration into peptide mimics.

(17) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(18) (a) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511. (b) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. *Tetrahedron* **1981**, *37*, 2091.

Scheme 7. Enantiomeric Purity of 7-Hydroxymethylindolizidinone Amino Ester 17



Enantiomeric Purity and Stereochemical Assignments of 5- and 7-Hydroxymethyl Indolizidinone Amino Esters. The configurational integrity of this new indolizidin-2-one series was evaluated by determination of the enantiomeric purity of 7-hydroxymethyl indolizidinone *N*-(BOC)amino ester (3*S*,6*S*,7*R*,9*S*)-**17** produced from the methanesulfonate displacement/lactam cyclization sequence. Portions of alcohol **17** were acylated either with (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid using benzotriazolyl-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU)[19,20] and DIEA in MeCN.[21] Measurement of the diastereomeric trifluoromethyl singlets at −72.7 and −72.9 ppm in benzene with trifluoromethylbenzene as internal reference (−63.7 ppm) by ^{19}F NMR spectroscopy, using incremental additions of minor isomer to determine the limits of detection, demonstrated **23** to be of >99% diastereomeric excess. The high diastereomeric purity of ester **17** indicated that enantiopure material was produced from the methanesulfonate displacement. Hence, 7-hydroxymethyl indolizidinone *N*-(BOC)amino acids **5** and **6**, diamino indolizidinone carboxylates **7** and **8**, and indolizidinone amino dicarboxylate **9**, all are presumed to be of >99% enantiomeric purity.

As in the case of the benzyl series,[8] the position and relative stereochemistry of the hydroxymethyl and methyl carbons in indolizidinone *N*-(BOC)amino esters **16**−**19** were determined by two-dimensional NMR experiments. Although less distinct than in the benzyl series, the majority of the signals for each of the ring protons was well resolved at discrete chemical shifts (Table 1). The downfield chemical shifts for the proton signals of the three amine-bearing carbons appeared in the same order (C-9 > C-3 > C-6) as in the related benzyl series.[8] The C-3 proton was typically identified by its coupling to the carbamate proton. The C-9 proton was observed as a sharp triplet or apparent doublet. The point of union between the appending hydroxymethyl group and the indolizidinone heterocycle was established by assignment of the three ring protons exhibiting scalar couplings with the C-6 proton in the COSY spectra, followed by correlations of these protons to the protons of the appended methylene and either the C-3 or C-9 protons. Subsequently, the relative stereochemistry of the stereocenters at the 5-, 6-, and 7-positions was assigned by analysis of NOESY and ROESY spectra of **16**−**19**.

For example, in the COSY spectrum of (6*R*,7*S*)-**17** the C-7 proton (2.02 ppm) exhibited scalar couplings with the C-6, C-8, and methylene protons. In the NOESY spectrum of (6*R*,7*S*)-**17**, the C-7 proton exhibited significant nOes with the C-9 proton as well as the C-4$_\alpha$ proton. On the other face of the heterocycle, the C-4$_\beta$ proton exhibited nOes with the C-6 and hydroxymethyl protons. Additional nOes between the C-5$_\alpha$ proton and the C-3 proton as well as between the C-5$_\beta$ proton and the hydroxymethyl protons gave further support for the (6*R*,7*S*)-stereochemistry. In the case of the concave isomers, a clear nOe was observed between the C-3 and C-6 protons. The various two-dimensional NMR spectra that were used to assign the relative stereochemistry at the ring-fusion and alkyl-branched stereocenters of **16**−**19** are all provided in the Supporting Information. The stereochemical assignments made for the 5- and 7-positions of **16**−**19** were then used to deduce the relative stereochemistry at the hydroxymethyl branched 4-position of ketone **15** based on the fact that no epimerization happened during the reaction sequences featuring methanesulfonate displacements. The stereochemistry of alcohols **14** were similarly deduced from the assignments made for the ring-fusion 6-positions of **16**−**19** based on the assumption that complete inversion of stereochemistry occurred in the methanesulfonate displacement.

Crystallization of (3*S*,6*S*,7*R*,9*S*)-methyl 2-oxo-3-*N*-(BOC)amino-7-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*R*,9*S*)-**17**) from chloroform and X-ray crystallographic analysis confirmed the NMR assignments (Figure 3).[22] As in the crystal structures of related *N*-(BOC)amino indolizidin-2-one esters,[5c,8] the dihedral angles of the backbone atoms constrained inside the heterocycle of (3*S*,6*S*,7*R*,9*S*)-**17** resemble the values of the central residues in an ideal type II′ β-turn.[23] For comparison, we have listed in Figure 4 the values for **17** with those observed in the crystal structures of the corresponding methyl esters of the parent indolizidinone **24**[5c] and its 7-benzyl derivative **25**,[8] the acid of thiaindolizidinone **26**,[24] and the values for the central residues of an ideal type II′ β-turn[23] and an ideal inverse γ-turn conformation.[25] The presence of the hydroxymethyl substituent exhibited a noticeable yet relatively minor influence on the peptide backbone conformation compared to changes observed upon modification of the bicycle ring-size.[1,7]

Conclusion

Toward a general approach for constructing rigid dipeptide surrogates possessing heteroatomic side chains, we have developed effective methodology for synthesizing

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

(20) 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.

(21) (a) Reviewed in: Parker, D. *Chem. Rev.* **1991**, *91*, 1441. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(22) The structure of **17** was solved at l'Université de Montréal X-ray facility using direct methods (SHELXS 96) and refined with SHELXL 96: $C_{16}H_{26}N_2O_6$; M_r = 342.388; orthorhombic, colorless crystal; space group $P2_12_12_1$; unit cell dimensions (Å) a = 5.386(5), b = 8.891(2), c = 36.771(17); volume of unit cell (Å^3) 1760.9(19); Z = 4; R_1 = 0.0534 for $F^2 > 2\sum(F^2)$, wR_2 = 0.1283 for all data; GOF = 1.018. The author has deposited the atomic coordinates for the structure of **17** 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.

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

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

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

Table 1. ^{1}H NMR of 5- and 7-Hydroxymethyl and Methylindolizidinone Amino Esters 16−19 (R = CH'$_2$ for 16 and 17, CH_3 for 18 and 19)

	3α	4α	4β	5α	5β	6α/β	7α	7β	8α	8β	9α	*R*	OMe	O*t*-Bu	NH
(5*S*,6*R*)-**16**	4.17 m	2.35 m	1.86 m	-	2.25 m	3.66 m (α)	1.78 m	2.42 m	2.12 m	2.08 m	4.53 d 8.4	3.69 m	3.73	1.43	5.64
(6*S*,7*S*)-**17**	4.16 m	2.25 m	1.70 m	1.82 m	1.90 m	3.83 m (α)	2.57 dd 7.1, 5.2		2.37 m	1.97 m	4.30 dd 9.4, 4.7	3.55 dd 10.8, 7.4 3.69 dd 7.2, 2.9	3.71	1.39	5.80
(6*S*,7*R*)-**17**	4.08 bs	2.48 m	1.67 m	2.12 m	1.72 m	3.50 m (α)		2.30 m	2.11 m	2.08 m	4.40 d 6.0	3.58 t 4.3	3.65	1.35	5.30
(6*R*,7*R*)-**17**	4.10 bs	2.65 bs	1.71 m	1.74 m	1.98 m	3.87 m (β)		2.38 m	2.34 dd 8.1, 5.7	1.88 m	4.40 t 8.8	3.40 dd 11.0, 5.7 3.61 dd 10.7, 5.8	3.69	1.38	5.34
(6*R*,7*S*)-**17**	4.09 bs	2.54 bs	1.86 m	1.54 dd 13.6, 2.5	2.29 d 2.7	3.62 m (β)	2.02 m		2.49 m	1.70 m	4.48 t 8.5	3.62 m	3.75	1.44	5.26
(5*S*,6*R*)-**18**	4.20 m	2.03 m	1.95 m		2.00 m	3.32 m (α)	1.75 m	2.20 m	2.15 m	2.10 m	4.51 d 9.2	1.03 d 6.3	3.72	1.43	5.45
(6*S*,7*R*)-**19**	4.10 m	2.46 m	1.64 m	1.75 m	1.84 m	3.19 m (α)		2.06 m	2.14 m	1.86 dd 12.0, 9.1	4.49 d 9.0	1.07 d 6.3	3.74	1.45	5.50

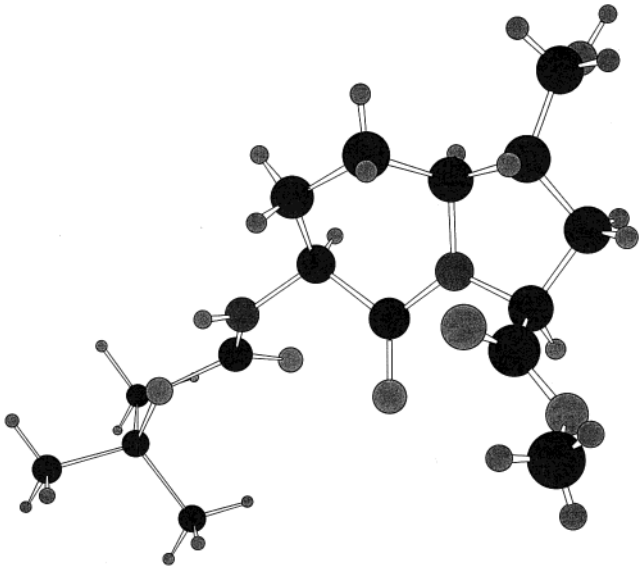


Figure 3. Ball and stick representation of 7-hyrdoxymethyl indolizidinone methyl ester (3*S*,6*S*,7*R*,9*S*)-**17**.[22]

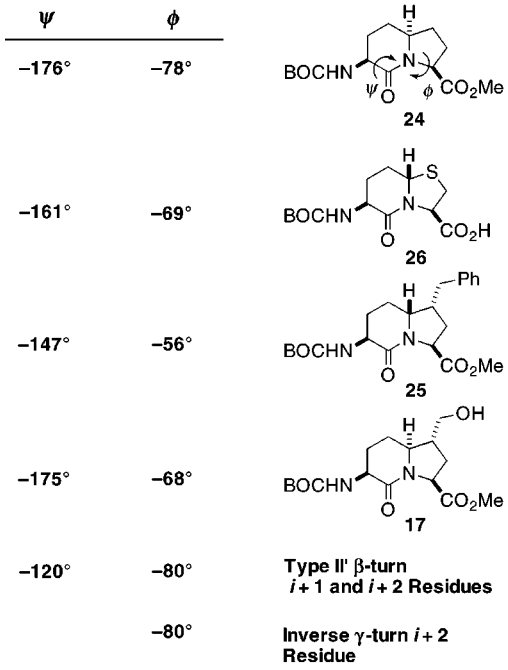


Figure 4. Dihedral angle values from azabicycloalkane *N*-(BOC)amino carboxylate X-ray data and ideal peptide turns.

5- and 7-hydroxymethyl indolizidinone amino acids **5** and **6** from β-ketoester **10** by strategies featuring reductive aminations, methanesulfonate displacements, and lactam cyclizations. Imine to enamine tautomerization during the hydrogenation of δ-ketoazelate **15** was accompanied by β-elimination of the hydroxyl substituent in the reductive amination sequence such that 5- and 7-hydroxymethyl indolizidinone amino esters **16** and **17** were produced with their 5- and 7-methyl counterparts **18** and **19** as side products. The importance of stereochemistry and steric bulk were illustrated in the route featuring a methanesulfonate displacement followed by lactam cyclization to selectively furnish 5- and 7-hydroxymethyl indolizidinone amino esters **16** and **17**. Modification of the alcohol functional group of **16** and **17** has furnished other side-chain functionality including azide and carboxylate groups in orthogonally protected diamino indolizidinone carboxylates **7** and **8** and indolizidinone amino dicarboxylate **9**. In summary, a spectrum of restrained scaffolds has thus been prepared with potential to replicate the backbone geometry and side-chain function of dipeptide residues possessing serine, lysine, glutamate, and related amino acids.

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; CH_2Cl_2 was distilled from CaH_2; $CHCl_3$ from P_2O_5; triethylamine (Et_3N) was distilled from BaO. 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 PhF aromatic carbons are not reported for 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*,4*RS*,5*RS*,8*S*)-Di-*tert*-butyl 4-Hydroxymethyl-5-hydroxy-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*RS*,5*RS*,8*S*)-12). A solution of β-keto ester **10** (3.6 g, 4.08 mmol, prepared according to ref 5c) in *tert*-butyl alcohol (150 mL) and MeOH (5 mL) was treated with $NaBH_4$ (1 g, 26.3 mmol, 645 mol %), stirred for 1 h at room temperature and for 6 h at 60 °C, cooled to room temperature, and diluted with water (100 mL). The volume was reduced using a rotary evaporator, and the remaining volume was extracted with EtOAc (2 × 200 mL). The combined organic phases were washed with brine, dried, and evaporated to a residue (3.1 g, 88.6%) that was shown by proton NMR analysis to contain a mixture of four diol diastereomers **12**, which was used without additional purification: R_f 0.08 (1:3 EtOAc−hexane); LRMS m/z = 857 (MH^+).

(2*S*,4*RS*,5*RS*,8*S*)-Di-*tert*-butyl 4-*tert*-Butyldimethylsiloxymethyl-5-hydroxy-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*RS*,5*RS*,8*S*)-14). A solution of diol **12** (1.0 g, 1.17 mmol) in CH_2Cl_2 (15 mL) was treated with Et_3N (0.655 mL, 4.68 mmol, 400 mol %), DMAP (14 mg, 0.11 mmol, 10 mol %), and TBDMSCl (387 mg, 2.57 mmol, 220 mol %), stirred for 6 h at room temperature, and diluted with water (20 mL). The layers were separated, and the organic phase was washed with brine, dried, and evaporated to a residue (1.2 g, 96%) that was shown by proton NMR analysis to contain a mixture of four silyl ether diastereomers **14**, which was used without additional purification: R_f 0.46 (1:3 EtOAc−hexane); LRMS m/z = 971 (MH^+).

(2*S*,4*R*,8*S*)- and (2*S*,4*S*,8*S*)-Di-*tert*-butyl 5-Oxo-4-*tert*-butyldimethylsiloxymethyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,8*S*)- and (2*S*,4*S*,8*S*)-15). A solution of oxalyl chloride (0.044 mL, 0.5 mmol, 250 mol %) in CH_2Cl_2 (1.5 mL) was cooled to −60 °C and treated with a solution of DMSO (0.05 mL, 0.7 mmol, 350 mol %) in CH_2Cl_2 (0.5 mL). The mixture was stirred for 30 min and treated dropwise with a solution of alcohol **14** (0.2 g, 0.2 mmol, 100 mol %) in CH_2Cl_2 (1 mL). The clear solution was stirred for 4 h, treated with $Et(i\text{-}Pr)_2N$ (0.21 mL, 1,2 mmol, 600 mol %), and allowed to warm to room temperature over 1 h. The reaction mixture was added to aqueous NaH_2PO_4 (2 mL), the layers were separated, and the aqueous layer was saturated with solid NaCl and extracted repeatedly with EtOAc (2 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried, and evaporated to give a residue that was purified by column chromatography using an eluant of 1:3 EtOAc−hexane to furnish ketone **15** (188 mg, 97%) as a colorless solid: R_f 0.66 (1:3 EtOAc−hexane); LRMS m/z 969 (MH^+). Diastereomers **15** (2.3 g) were separated by chromatography on silica gel using an eluant of hexane to dichloromethane. First to elute was (2*S*,4*S*,8*S*)-**15** (810 mg): $[\alpha]^{20}_D$ −46.15 (*c* 3.18, $CHCl_3$); ^1H NMR δ −0.02 (s, 3 H), −0.02 (s, 3 H), 0.82 (s, 9 H), 1.18 (s, 9 H), 1.24 (s, 9 H), 1.48 (m, 1 H), 1.72 (m, 1 H), 1.85 (m, 1 H), 2.30 (m, 1 H), 2.41 (m, 1 H), 2.54 (m, 1 H), 2.72 (m, 1 H), 2.90 (bs, 2 H), 3.00 (m, 1 H), 3.12 (m, 1 H), 3.48 (m, 1 H), 3.58 (m, 1 H), 7.05 (m, 2 H), 7.0−7.4 (m, 20 H), 7.65 (m, 4 H); ^{13}C NMR δ −5.6, −5.5, 18.1, 25.8, 27.9, 29.1, 34.2, 41.2, 55.0, 55.3, 65.1, 72.9, 73.5, 77.2, 80.5, 80.8, 174.6, 175.2, 212.5; followed by a 2:3 mixture of (4*S*)-**15** and (4*R*)-**15** (510 mg). Last to elute was (2*S*,4*R*,8*S*)-**15** (820 mg): $[\alpha]_D^{20}$ −41.04 (*c* 2.4, $CHCl_3$); ^1H NMR δ −0.12 (s, 3 H), −0.08 (s, 3 H), 0.76 (s, 9 H), 1.13 (s, 9 H), 1.15 (s, 9 H), 1.37 (m, 1 H), 1.50 (m, 2 H), 1.80 (m, 1 H), 2.27 (m, 1 H), 2.37 (m, 2 H), 2.47 (m, 2 H), 2.58 (dd, 1 H, J = 13.6, 8.5), 2.90 (bs, 2 H), 3.11 (m, 1 H), 7.05 (m, 2 H), 7.1−7.4 (m, 20 H), 7.65 (m, 4 H); ^{13}C NMR δ −5.7, −5.6, 18.2, 25.8, 27.8, 29.3, 31.9, 38.9, 50.1, 53.8, 55.4, 62.5, 72.9, 73.0, 77.2, 80.7, 175.1, 175.4, 212.1.

Synthesis of 5- and 7-Methyl and Hydroxymethylindolizidinone Amino Esters 16−19 via Reductive Amination Protocol. Hydrogenation was performed by stirring a solution of azelate **15** (ca. 1:1 mixture of diastereomers, 0.5 mmol, 100 mol %) in anhydrous EtOH (30 mL) and AcOH (3 mL) with palladium-on-carbon (10 wt %) under hydrogen atmosphere (10 atm) for 24 h. The mixture was filtered through Celite and washed with EtOH (30 mL). The combined organic solution was evaporated to dryness, and the residue was triturated with hexane (3 × 10 mL). The remaining solid was used without additional purification.

The *tert*-butyl esters and silyl ether were solvolyzed by dissolving the crude product in a 10% solution of TFA in CH_2Cl_2 (50 mL) and stirring overnight. Evaporation of the volatiles gave a residue which was used without further purification.

Esterification, lactam cyclization, and nitrogen protection commenced by treatment of the residue in MeOH (20 mL) at −5 °C with $SOCl_2$ (300 mol %). The solution was stirred at −5 °C for 1 h, at room temperature for 1 h, and at 50 °C for 2 h, then evaporated. The solid was dissolved in CH_2Cl_2 (15 mL), treated with Et_3N (500 mol %), stirred at room temperature for 24 h, treated with di-*tert*-butyl dicarbonate (500 mol %), and stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with a 1M solution of NaH_2PO_4 (5 mL) and brine (5 mL), dried, and evaporated. The residue was chromatographed with 3:2 hexanes−EtOAc as eluant. Three compounds were isolated and characterized by ^1H NMR spectroscopy (Table 1). First to elute was (5*S*,6*R*)-**18** (3% yield): $[\alpha]_D^{20}$ −1.31 (*c* 3.25, $CHCl_3$); ^{13}C NMR δ 16.2, 25.8, 27.4, 28.1, 37.3, 40.4, 50.2, 52.5, 57.8, 63.0, 79.7, 156.8, 168.2, 172.4; LRMS m/z 327 (MH^+). Second to elute was (6*S*,7*R*)-**19** (12% yield): $[\alpha]_D^{20}$ −12.2 (*c* 1.82, $CHCl_3$); ^{13}C NMR δ 17.3, 27.2, 28.8, 31.8, 34.0, 37.2, 49.6, 52.4, 58.5, 63.8, 79.8, 155.9, 168.4, 172.5; LRMS m/z 327 (MH^+). Last to elute was (6*S*,7*R*)-**17** (14% yield), which exhibited identical characteristics as material prepared by the methanesulfonate displacement route described below.

(2*S*,4*R*,5*RS*,8*S*)-Di-*tert*-butyl 4-*tert*-butyldimethylsiloxymethyl-5-hydroxy-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,5*SR*,8*S*)-14). A solution of ketone (4*R*)-**15** (12.0 g, 12.4 mmol) in EtOH (250 mL) was treated with $NaBH_4$ (2.36 g, 62 mmol, 500 mol %), stirred for 4 h at room temperature, and diluted with water (250 mL). The volume was reduced using a rotary evaporator, and the remaining volume was extracted with EtOAc (2 × 300 mL). The combined organic phases were washed with brine, dried, and evaporated to a residue which was shown by proton NMR analysis to contain a ca. 2:1 mixture of (5*R*)- and (5*S*)-alcohols **14** that were used in the subsequent reactions as a mixture without further purification. Yield 11.4 g (95%): ^1H NMR δ 0.03 (s, 6 H), 0.04 (s, 6 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.17 (s, 9 H), 1.18 (s, 9 H), 1.19 (s, 9 H), 1.20 (s, 9 H), 1.3−1.9, 2.5−2.7, 3.1, 3.4−3.7, 3.9 (multiplets from aliphatic protons of both diastereomers), 7.1−7.8 (multiplets from aromatic protons of both diastereomers).

(2*S*,4*S*,5*S*,8*S*)- and (2*S*,4*S*,5*R*,8*S*)-Di-*tert*-butyl 4-*tert*-butyldimethylsiloxymethyl-5-hydroxy-2,8-di-[*N*-(PhF)-amino]azelate ((2*S*,4*S*,5*S*,8*S*)- and (2*S*,4*S*,5*R*,8*S*)-14). These compounds were prepared by reduction of (4*S*)-**15** (4.7 g, 4.9 mmol) using the protocol described for ketone (4*R*)-**15** above ($NaBH_4$ 0.95 g, 25 mmol, 500 mol % in 50 mL of EtOH). A mixture of alcohols (4.5 g, 95%) was isolated from which analytical samples of pure diastereomers were obtained by column chromatography using 2:98 EtOH−CH_2Cl_2 as eluant. The first diastereomer to elute exhibited the following characteristics: ^1H NMR δ −0.18 (s, 3 H), −0.11 (s, 3 H), 0.80 (s, 9 H), 1.19 (s, 9 H), 1.22 (s, 9 H), 1.28−1.50 (m, 3 H), 1.52−1.78 (m, 3 H), 1.84−1.94 (m, 1 H), 2.38 (dd, 1 H, J = 11.9, 2.4), 2.58 (dd, 1 H, J = 7.6, 4.1), 2.77 (dd, 1 H, J = 10.5, 3.4), 3.31 (dd, 1 H, J = 10.5, 2.5), 3.74−3.80 (m, 1 H), 7.14−7.51 (m, 22 H), 7.66−7.72 (m, 4 H). The second eluting diastereomer showed: ^1H NMR δ −0.18 (s, 3 H), −0.11 (s, 3 H), 0.80 (s, 9 H), 1.18 (s, 9 H), 1.20 (s, 9 H), 1.22−1.38 (m, 2 H), 1.40−1.48 (m, 3 H), 1.57−1.78 (m, 4 H), 1.82−1.90 (m, 1 H), 2.41 (d, 1 H, J = 11.7), 2.52−2.60 (m, 1 H), 2.64 (d, 1 H, J = 10.7), 3.32−3.42 (m, 1 H), 3.52 (d, 1 H, J = 11.8), 7.18−7.49 (m, 22 H), 7.68−7.71 (m, 4 H).

General Procedure for the Synthesis of 5- and 7-Hydroxymethylindolizidinone Amino Esters 16 and 17 via Methanesulfonate Displacement. Methanesulfonation and displacement were performed by treating a magnetically stirred, 0 °C solution of alcohol **14** (0.2−0.3 mmol, 100 mol %) in CH_2Cl_2 (5 mL) with methanesulfonyl chloride (200 mol %), DMAP (10 mol %), and Et_3N (300 mol %). The solution was stirred for 1 h at 0 °C, the ice bath was removed, and the mixture was stirred an additional 1 h at room temperature. Toluene (10 mL) was added, and the reaction mixture was heated at a reflux for 24 h. The solution was allowed to cool to room temperature and partitioned between EtOAc (15 mL) and water (5 mL). The organic layer was washed with 2 N HCl (3 mL), 5% $NaHCO_3$ (3 mL), and water (3 mL), dried, and evaporated. The crude reaction product was used without further purification.

The *tert*-butyl esters, *tert*-butyldimethylsilyl ether, and PhF groups were solvolyzed by dissolving the crude reaction product in a 10% solution of TFA in CH_2Cl_2 (15 mL) and stirring the solution at room temperature for 48 h. Evaporation gave a residue which was triturated with hexane (3 × 10 mL) to furnish a solid that was used without further purification.

Esterification was performed on treatment of a solution of the crude product in MeOH at −5 °C with $SOCl_2$ (300 mol %). The reaction mixture was stirred at −5 °C for 1 h, then at room temperature for 1 h, and at 50 °C for 2 h. Evaporation of the volatiles gave a crude residue which was subsequently used without further purification.

Lactam cyclization and amine protection involved the treatment of the reaction product in CH_2Cl_2 (15 mL) with Et_3N (500 mol %) for 24 h at room temperature, followed by addition of $(BOC)_2O$ (500 mol %) and additional stirring at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 (15 mL), washed with a 1 M solution of NaH_2PO_4 (5 mL) and brine (5 mL), dried, and evaporated. The residue was chromatographed using 3:97 EtOH−$CHCl_3$ as eluant. Evaporation of the collected fractions gave the hydroxymethylindolizidinone amino esters; proton NMR spectra are recorded in Table 1.

(3*S*,5*S*,6*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-5-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,5*S*,6*R*,9*S*)-16). $[\alpha]_D^{20}$ −0.7 (*c* 1.45, $CHCl_3$);^{13}C NMR δ 20.8, 26.6, 28.2, 31.0, 42.9, 49.8, 52.4, 57.7, 58.3, 60.9, 79.6, 155.6, 169.1, 172.5; HRMS calcd for $C_{16}H_{27}N_2O_6$ (MH^+) 343.1869, found 343.1884.

(3*S*,6*S*,7*S*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,6*S*,7*S*,9*S*)-17). $[\alpha]_D^{20}$ −2.35 (*c* 2.02, $CHCl_3$); ^{13}C NMR δ 28.3, 29.1, 31.3, 31.7, 41.3, 49.7, 52.4, 57.9, 58.5, 64.2, 79.7, 155.8, 169.1, 172.1; HRMS calcd for $C_{16}H_{27}N_2O_6$ (MH^+) 343.1869, found 343.1855.

(3*S*,6*R*,7*S*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,6*R*,7*S*,9*S*)-17). $[\alpha]_D^{20}$ −14.3 (*c* 1.42, $CHCl_3$); ^{13}C NMR δ 27.1, 28.3, 28.6, 30.9, 42.8, 47.7, 52.3, 57.1, 62.2, 62.3, 79.6, 156.2, 168.0, 172.7; HRMS calcd for $C_{16}H_{27}N_2O_6$ (MH^+) 343.1869, found 343.1859.

(3*S*,6*S*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,6*S*,7*R*,9*S*)-17). $[\alpha]_D^{20}$ −6.17 (*c* 2.27, $CHCl_3$); ^{13}C NMR δ 26.0, 27.0, 28.1, 31.5, 47.1, 49.7, 52.2, 57.6, 58.7, 61.6, 79.4, 155.6, 169.1, 172.0; HRMS calcd for $C_{16}H_{27}N_2O_6$ (MH^+) 343.1869, found 343.1859.

(3*S*,6*R*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,6*R*,7*R*,9*S*)-17). $[\alpha]_D^{20}$ −19.2 (*c* 2.07, $CHCl_3$); ^{13}C NMR δ 23.1, 28.1, 28.8, 30.7, 42.7, 51.6, 52.2, 57.0, 60.7, 61.6, 79.5, 156.1, 168.4, 173.0; HRMS calcd for $C_{16}H_{27}N_2O_6$ (MH^+) 343.1869, found 343.1884.

(3*S*,5*S*,6*R*,9*S*)-2-Oxo-3-*N*-(BOC)amino-5-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylic Acid ((3*S*,5*S*,6*R*,9*S*)-5). Methyl ester (5*S*,6*R*)-**16** (10 mg, 0.03 mmol) in 3 mL of Et_2O was treated with $KOSiMe_3$ (5.8 mg, 0.045 mol), stirred for 10 h at room temperature, treated with a second portion of $KOSiMe_3$ (5.8 mg, 0.045 mol), and stirred overnight. The reaction solution was concentrated under reduced pressure. Water (10 mL) was added, and the pH was adjusted to ∼pH 2 using citric acid. After 10 min of stirring, the solution was saturated with NaCl and extracted with EtOAc (2 × 10 mL). The organic solutions were combined and purified by filtration through silica gel using 20:1 EtOAc−AcOH as eluant. Evaporation of the collected fractions gave 8.5 mg (86%) of acid **5**: $[\alpha]_D^{20}$ −2.9 (*c* 2.50, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9 H), 1.72−1.85 (m, 3 H), 1.98−2.16 (m, 2 H), 2.26−2.40 (m, 2 H), 3.63−3.71 (m, 3 H), 4.29 (dd, 1 H, J = 10.0, 6.2), 4.55 (d, 1 H, J = 8.7), 5.10 (bs, 2 H), 5.75 (d, 1 H, J = 6.2); ^{13}C NMR δ 28.3, 28.5, 29.7, 31.6, 41.1, 49.7, 58.6, 59.1, 63.9, 80.1, 155.9, 170.7, 173.0; HRMS calcd for $C_{15}H_{25}N_2O_6$ (MH^+) 329.1724, found 329.1713.

(3*S*,6*S*,7*R*,9*S*)-2-Oxo-3-*N*-(BOC)amino-5-hydroxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylic Acid ((3*S*,6*S*,7*R*,9*S*)-6). The compound was synthesized from 7-hydroxymethyl indolizidin-2-one *N*-(BOC)amino ester (6*S*,7*R*)-**17** (0.03 mmol) using the same protocol as that described above for the conversion of ester **16** to acid **5**: 85% yield; $[\alpha]_D^{20}$ −0.8 (*c* 1.58, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9 H), 1.63−1.80 (m, 2 H), 2.02−2.15 (m, 2 H), 2.18−2.30 (m, 2 H), 2.36−2.48 (m, 2 H), 3.52−3.63 (m, 1 H), 3.70−3.80 (m, 3 H), 4.18−4.30 (m, 1 H), 4.57 (d, 1 H, J = 8.6), 5.52−5.58 (bs, 1 H); ^{13}C NMR δ 27.5, 28.5, 29.1, 30.4, 47.4, 50.8, 58.7, 59.1, 64.8, 80.4, 156.8, 172.1, 173.5; HRMS calcd for $C_{15}H_{25}N_2O_6$ (MH^+) 329.1724, found 329.1714.

(3*S*,5*S*,6*R*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-5-methanesulfonyloxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,5*S*,6*R*,9*S*)-20). The compound was prepared from 5-hydroxymethyl indolizidin-2-one amino ester **16** (0.06 mmol) using the same procedure as that described below for the conversion of alcohol **17** to methanesulfonate **21**. The product was obtained in 82% yield and used directly in the nucleophilic displacement: ^{1}H NMR δ 1.44 (s, 9H), 1.75−1.90 (m, 2H), 2.13−2.20 (m, 1H), 2.23−2.45 (m, 2H), 3.03 (d, 1H, J = 7), 3.08 (s, 3H), 3.64 (dd, 1H, J = 9, 6), 3.74 (s, 3H), 3.75 (bs, 1H), 4.11−4.22 (m, 2H), 4.25 (d, 1H, J = 5), 4.55 (d, 1H, J = 7), 5.55 (bs, 1H); ^{13}C NMR δ 28.3, 28.9, 30.7, 31.5, 37.4, 38.9, 49.3, 52.4, 58.0, 58.4, 70.0, 79.7, 155.5, 168.7, 171.9.

(3*S*,6*S*,7*R*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-7-methanesulfonyloxymethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*R*,9*S*)-21). Methyl ester (6*S*,7*R*)-**17** (20 mg, 0.06 mmol) in 5 mL of CH_2Cl_2 at 0 °C was treated with DMAP (2 mg, 10 mol %), Et_3N (28 μL, 0.2 mmol, 300 mol %), and then with methanesulfonyl chloride (14 mg, 0.12 mmol, 200 mol %). The ice bath was removed and the mixture was stirred an additional 1 h at room temperature and partitioned between EtOAc (15 mL) and water (5 mL). The organic layer was washed with 2 N HCl (3 mL), 5% $NaHCO_3$ (3 mL), and water (3 mL), and dried and evaporated to yield 19 mg (77%) of **21**. The product was used directly in the nucleophilic displacement: ^{1}H NMR δ 1.45 (s, 9 H), 1.65−1.89 (m, 3 H), 2.10 (dd, 1 H, J = 12.4, 9.6), 2.18−2.26 (m, 2 H), 2.45−2−58 (m, 1 H), 3.05 (s, 3 H), 3.57 (dt,1 H, J = 9.7, 5.2), 3.76 (s, 3 H), 4.10−4.19 (m, 1 H), 4.27 (ddd, 2 H, J = 22.2. 10.4, 5.8), 4.56 (d, 1 H, J = 8.5), 5.12 (bs, 1 H); HRMS calcd for $C_{17}H_{29}N_2O_8S$ (MH^+) 421.1645, found 421.1627.

(3*S*,5*S*,6*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-5-azidomethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,5*S*,6*R*,9*S*)-7). The compound was synthesized from methanesulfonate **20** (0.06 mmol) using the same procedure as that described below for the conversion of methanesulfonate **21** into azide **8**: 68% yield; IR cm^{-1} 2109; ^{1}H NMR δ 1.45 (s, 9H), 1.72−1.91 (m, 2 H), 2.13 (dd, 1 H, J = 7, 2), 2.15−2.21 (m, 2 H), 2.23−2.29 (m, 1 H) 2.30−2.42 (m, 1 H), 3.44 (t, 2 H, J = 6), 3.50−3.62 (m, 1 H), 3.74 (s, 3 H), 4.26 (bs, 1 H), 4.53 (dd 1 H, J = 7, 1), 5.52 (bs, 1 H); ^{13}C NMR δ 28.9, 31.4, 32.1, 39.0, 49.3, 52.4, 53.9, 58.0, 59.2, 77.2, 79.7, 155.6, 168.9, 172.0.

(3*S*,6*S*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-azidomethyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,6*S*,7*R*,9*S*)-8). Methanesulfonate **21** was dissolved in DMF (3 mL) and treated with NaN_3 (15 mg, 0.225 mmol, 500 mol %), stirred at 80 °C for 4 h, cooled, and partitioned between EtOAc (10 mL) and water (5 mL). The organic layer was washed with 2 N HCl (3 mL), 5% $NaHCO_3$ (3 mL) and water (3 mL), and dried and evaporated to yield 13 mg (79%) of **8**: IR cm^{-1} 2099; ^{1}H NMR δ 1.45 (s, 9 H), 1.62−1.83 (m, 3 H), 2.01−2.22 (m, 2 H), 2.25−2.38 (m, 1 H), 2.40−2.55 (m, 1 H), 3.42−3.51 (m, 3 H), 3.76 (s, 3 H), 4.12−4.21 (m, 1 H), 4.54 (d, 1 H, J = 8.8), 5.48 (d, 1 H, J = 5.1); ^{13}C NMR δ 27.0, 28.3, 29.7, 32.7, 45.0, 50.0, 52.0, 52.5, 57.6, 59.0, 79.6, 155.7, 169.2, 171.9; HRMS calcd for $C_{16}H_{26}N_5O_5$ (MH^+) 368.1934, found 368.1926.

(3*S*,5*S*,6*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-5-formyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,5*S*,6*R*,9*S*)-22). A solution of alcohol (5*S*,6*R*)-**16** (20 mg, 0.058 mmol) in CH_2Cl_2 (2 mL) was treated with pyridinium chlorochromate (26 mg, 0.12 mmol, 200 mol %) and 3 Å molecular sieves, and the suspension was vigorously stirred for 6 h at room temperature. Then the suspension was filtered and evaporated. The residue was dissolved in EtOAc (5 mL) and filtered through a 1 g bed of silica gel on a glass filter with EtOAc (2 × 5 mL) as eluant. The combined organic solutions were evaporated to yield 15 mg (75%) of aldehyde **22**: ^{1}H NMR δ 1.45 (s, 9 H), 1.74−2.00 (m, 2 H), 2.11−2.18 (m, 1 H), 2.20−2.32 (m, 1 H), 2.47 (dd, 1 H, J = 12.6, 6.0), 2.82−2.96 (m, 1 H), 2.92−3.02 (m, 1 H), 3.75 (s, 3 H), 3.92−4.12 (m, 1 H), 4.20−4.29 (m, 1 H), 4.55 (d, 1 H, J = 8.7), 5.03 (bs, 1 H), 9.76 (s, 1 H); ^{13}C NMR δ 28.3, 28.9, 29.7, 31.5, 49.3, 51.7, 52.5, 55.4, 57.9, 79.9, 155.5, 168.4, 172.0, 200.1; HRMS calcd for $C_{16}H_{25}N_2O_6$ (MH^+) 341.1713, found 341.1722.

(3*S*,5*S*,6*S*,9*S*)-2-Oxo-3-*N*-(BOC)amino-1-azabicyclo[4.3.0]-nonane-9-carboxymethyl-5-carboxylate ((3*S*,5*S*,6*S*,9*S*)-9). A solution of $NaClO_2$ (270 mg, 3 mmol) and NaH_2PO_4 (380 mg, 2.7 mmol) in 1.5 mL of water was poured into a stirred solution of aldehyde **22** (10 mg, 0.3 mmol) in 1:1 acetonitrile−*tert*-butyl alcohol (6 mL). Stirring was continued for 30 min at room temperature, and the mixture was then partitioned between 10 mL of 1 M H_3PO_4 and 10 mL of ether. The aqueous layer was extracted with 3 × 10 mL of ether. The combined organic phase was washed with brine, dried, and evaporated to provide acid **9** (7.7 mg, 72%): ^{1}H NMR δ 1.44 (s, 9 H), 1.95−2.08 (m, 1 H), 2.06 (dd, 1H, J = 13, 7), 2.23 (dd, 1 H, J = 14, 6), 2.30 (d, 1 H, J = 6), 2.42−2.52 (m, 1 H), 2.55−2.65 (m, 1 H), 2.88 (d, 1 H, J = 14), 3.08 (d, 2 H, J = 4), 3.76 (s, 3 H), 4.12−4.22 (m, 1 H), 4.62 (d, 1 H, J = 9), 5.58 (bs, 1 H); ^{13}C NMR δ 27.0, 28.0, 28.2, 28.3, 35.1, 39.1, 52.6, 58.2, 77.2, 80.0, 155.3, 169.4, 171.4, 173.0.

Enantiomeric Purity of (3*S*,6*S*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-hydroxymethyl-1-azabicyclo[4.3.0]-nonane-9-carboxylate ((6*S*,7*R*)-17). A solution of (6*S*,7*R*)-**17** (3 mg, 0.0087 mmol) in 3 mL of MeCN was treated with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (2.3 mg, 0.01 mmol) followed by TBTU (4.2 mg, 0.013 mmol) and DIEA (2.1 mg, 0.016 mmol), stirred for 6 h at room temperature and partitioned between EtOAc (5 mL) and water (5 mL). The organic layer was washed with 10% citric acid (3 mL), 5% $NaHCO_3$ (3 mL) and water (3 mL), dried and evaporated to give a crude ester (*S*)-**23** that was directly examined by ^{19}F and ^{1}H NMR spectroscopy. The same experiment was performed on (6*S*,7*R*)-**17** using (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid to provide ester (*R*)-**23**.

(*R*)-23. ^{19}F NMR (C_6D_6 with $F_3CC_6H_5$ as internal reference, δ = −63.7) δ −77.94; ^{1}H NMR δ 1.45 (s, 9 H), 1.66−1.71 (m, 2 H), 1.89−2.10 (m, 2 H), 2.34−2.45 (m, 2 H), 3.34−3.52 (m, 1 H), 3.53 (s, 3 H), 3.75 (s, 3 H), 4.06−4.08 (m, 1 H), 4.33 (d, 2 H, J = 6), 4.50 (d, 2 H, J = 9), 5.43 (bs, 1 H), 7.28−7.51 (m, 5 H).

(*S*)-23. ^{19}F NMR (C_6D_6 with $F_3CC_6H_5$ as internal reference, δ = −63.7) δ −77.74; ^{1}H NMR δ 1.45 (s, 9 H), 1.59−1.69 (m, 3 H), 1.92−2.02 (m, 2 H), 2.04−2.15 (m, 2 H), 3.38−3.54 (m, 1H), 3.52 (s, 3 H), 3.74 (s, 3 H), 4.08−4.12 (m, 1 H), 4.21 (dd, 2 H, J = 12, 6), 4.47 (dd, 1H, J = 11, 5), 5.45 (bs, 1 H), 7.41−7.51 (m, 5 H).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5**−**8** and **15**−**23**, COSY and NOESY/ROESY spectra of **16**−**19**, and crystallographic data for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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