Rigid Dipeptide Mimics: Synthesis of Enantiopure 5- and 7-Benzyl and 5,7-Dibenzyl Indolizidinone Amino Acids via Enolization and Alkylation of δ-Oxo α,ω-Di-[*N*-(9-(9-phenylfluorenyl))amino]azelate Esters

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Azabicyclo[*X.Y.*0]alkane amino acids are tools for constructing mimics of peptide structure and templates for generating combinatorial libraries for drug discovery. Our methodology for synthesizing these conformationally rigid dipeptides has been elaborated such that alkyl groups can be appended onto the heterocycle to generate mimics of peptide backbone and side-chain structure. Inexpensive glutamic acid was employed as chiral educt in a Claisen condensation/ketone alkylation/reductive amination/lactam cyclization sequence that furnished alkyl-branched azabicyclo[4.3.0]-alkane amino acid. Enantiopure 5-benzyl-, 7-benzyl-, and 5,7-dibenzylindolizidinone amino acids **2**−**4** were stereoselectively synthesized via efficient reaction sequences featuring the alkylation of di-*tert*-butyl α,ω-di-[*N*-(PhF)amino]azelate δ-ketone **5**. A variety of alkyl halides were readily added to the enolate of ketone **5** to provide mono- and dialkylated ketones **6** and **7**. Hydride additions to **6** and **7**, methanesulfonations, and intramolecular S_N2 displacements by the PhF amine gave 5-alkylprolines that were converted by lactam cyclizations into 7- and 5-benzyl-, as well as 5,7-dibenzyl-2-oxo-3-*N*-(BOC)amino-1-azabicyclo[4.3.0]nonane-9-carboxylate methyl esters **10**, **11**, and **14**. Epimerization of the alkyl-branched stereocenter via an iminium−enaminium equilibrium proved effective for controlling diastereoselectivity in reductive aminations with **6** and **7** in order to furnish 5-alkylprolines that were similarly converted to 7- benzyl- and 5,7-dibenzylindolizidinone *N*-(BOC)amino esters **10** and **14**. Ester hydrolysis with hydroxide ion and potassium trimethylsilanolate then gave enantiopure indolizidinone amino acids **2**−**4**. Epimerization at C-9 of benzylindolizidinone amino esters was also used to provide alternative diastereomers of **10**, **11**, and **14**. This practical methodology for introducing side-chain groups onto the heterocycle with regioselective and diastereoselective control is designed to enhance the use of alkyl-branched azabicycloalkane amino acids for the exploration of conformation−activity relationships of various biologically active peptides.

Introduction

The spatial requirements for protein chemistry and biology may be explored through the employment of azabicyclo[*X.Y.*0]alkane amino acids as building blocks for the construction of conformationally rigid surrogates of peptide structures.[1,2] These unique dipeptide analogues can be used to restrain the backbone geometry and side-chain conformations of the native peptide in order to probe and elucidate structure−activity relationships.[1,2] Furthermore, because these scaffolds possess spatially defined amine and carboxylate handles suitable for functionalization by combinatorial technology, azabicyclo-[*X.Y.*0]alkane amino acids can also serve as inputs for generating libraries on which different pharmacophores are systematically displayed for studying recognition events in medicinal chemistry.[1,3]

Concurrent with increasing applications of these novel tools for studying peptide structure has grown a necessity for practical methodology for the stereocontrolled synthesis of azabicyclo[*X.Y.*0]alkane amino acid. Efficient technology is particularly necessary for appending side chains onto these heterocycle systems in order to generate mimics of both peptide backbone and side-chain properties. Since alkyl-branched azabicycloalkane amino acids have typically been prepared in the course of investigations of specific targets,[1] the current state of the art for their synthesis has usually involved multiple step sequences that provide a single alkyl-substituted framework in low overall yield. Because the future investigation of biologically relevant peptides can be advanced through routine employment of alkyl-branched azabicycloalkane amino acids, more proficient means are needed for obtaining a series of these dipeptide mimics from common intermediates via efficient reaction sequences.

Striving to develop such a versatile process for synthesizing azabicyclo[*X.Y.*0]alkane amino acid, we have introduced a Claisen condensation/reductive amination/lactam cyclization sequence to stereoselectively furnish these important targets.[4,5] Employment of different *N*-(9-(9-phenylfluorenyl))aminodicarboxylates (Scheme 1, PhF = 9-(9-phenylfluorenyl)), such as glutamate, aspartate, and longer aminodicarboxylates, in this scheme is designed to provide azabicycloalkane amino acid having a variety of heterocyclic ring sizes. Stereocontrol is attained at the ring-fusion and along the peptide backbone

(1) For a review, see: 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.

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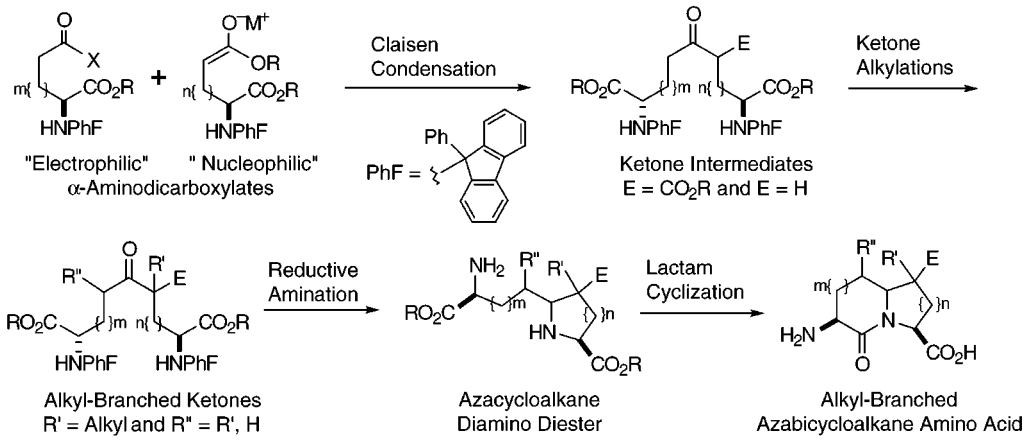
Scheme 1. General Approach for Synthesizing Alkyl-Branched Azabicyclo[*X.Y.*0]alkane Amino Acids



by employing L- and D-aminodicarboxylates to induce diastereoselectivity during the reductive amination reaction. By specifically employing inexpensive glutamic acid as chiral educt, we have developed an efficient synthesis of enantiopure indolizidinone amino acid **1** that gives access to all of the possible stereoisomers of this interesting dipeptide mimic (Figure 1).[4,5]

We have now elaborated our approach such that a variety of side chains may be added to the heterocycle via stereoselective alkylations of a common *N*-(PhF)-amino ketone intermediate (Scheme 1). Focusing on the benzyl side chain because of the significance of phenylalanine in biologically active peptides,[6−8] we have demonstrated the power of this strategy by furnishing three novel *C*-benzylated indolizidinone amino acid scaffolds

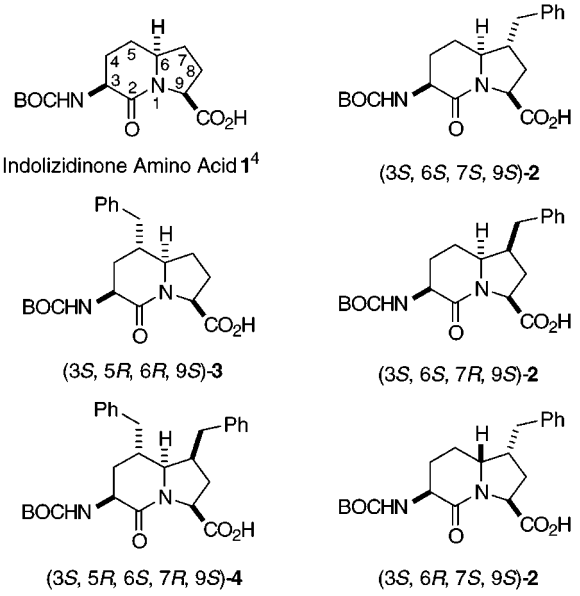


Figure 1. Indolizidinone, 5- and 7-benzylindolizidinone, and 5,7-dibenzylindolizidinone amino acids **1**−**4**.

(Figure 1). Enantiopure 5-benzyl-, 7-benzyl-, and 5,7-dibenzyl indolizidinone amino acids **2**−**4** were selectively synthesized via a sequence featuring alkylation of di-*tert*-butyl α,ω-di-[*N*-(PhF)amino]azelate δ-ketone **5**, cyclization to an alkylproline, and subsequent lactam formation.

Employing conditions that proved effective for the preparation of the parent indolizidinone amino acid **1**,[4] we have observed that alkyl substituents exhibited interesting effects during conversions of ketones **6** and **7** into alkylproline intermediates. Remarkable regioselectivity resulted from intramolecular displacements of methanesulfonates that were obtained from reduction of ketones **6** and **7** and activation of their respective alcohols. Epimerization of the alkyl-branched stereocenter via an iminium ion−enaminium ion equilibrium proved an effective means for controlling diastereoselectivity in the reductive amination of 4-benzyl ketones **6** to 4,5-dialkylproline intermediates. Furthermore, we found that epimerization at C-9 of benzylindolizidinone amino esters can be used to expand diversity by providing alternative diastereomeric frameworks.

One important practical aspect highlighted by our research was the capacity to transform selectively the major product from diastereoselective alkylation of ke-

(2) Some recent syntheses of azabicyclo[X. Y.0]alkane amino acids that have appeared since the writing of ref 1 include the following: (a) Lenman, M. M.; Lewis, A.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2297. (b) Kim, H.-Ok; Lum, C.; Lee, M. S. *Tetrahedron Lett.* **1997**, *38*, 4935. (c) Kim, H.-Ok; Kahn, M. *Tetrahedron Lett.* **1997**, *38*, 6483. (d) Siddiqui, M. A.; Préville, P.; Tarazi, M.; Warder, S. E.; Eby, P.; Gorseth, E.; Puumala, K.; DiMaio, J. *Tetrahedron Lett.* **1997**, *38*, 8807. (e) Colombo, L.; Di Giacomo, M.; Brusotti, G.; Sardone, N.; Angiolini, M.; Belvisi, L.; Maffioli, S.; Manzoni, L.; Scolastico, C. *Tetrahedron* **1998**, *54*, 5325. Recent examples of the use of azabicyclo-[X. Y.0]alkane amino acids in peptide mimicry include the following: (f) ($\alpha_v\beta_3$-receptor binders) Tran, T.-A.; Mattern, R.-H.; Zhu, Q.; Goodman, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 997. (g) Haubner, R.; Finsinger, D.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1374. (h) (gramicidin S analogues) 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. (i) (thrombin inhibitors) Salimbeni, A.; Paleari, F.; Canevotti, R.; Criscuoli, M.; Lippi, A.; Angiolini, M.; Belvisi, L.; Scolastico, C.; Colombo, L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2205. (j) (dopamine receptor modulators) Baures, P. W.; Ojala, W. H.; Costain, W. J.; Ott, M. C.; Pradhan, A.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1997**, *40*, 3594. (k) (dual metalloprotease inhibitors) Robl, J. A.; Sun, C.-Q.; Stevenson, J.; Ryono, D. E.; Simpkins, L. M.; Cimarutsi, M. P.; Dejneka, T.; Slusarchyk, W. A.; Chao, S.; Stratton, L.; Misra, R. N.; Bednarz, M. S.; Asaad, M. M.; Cheung, H. S.; Abboa-Offei, B. E.; Smith, P. L.; Mathers, P. D.; Fox, M.; Schaeffer, T. R.; Seymour, A. A.; Trippodo, N. C. *J. Med. Chem.* **1997**, *40*, 1570. (l) (interleukin-1β-converting enzyme inhibitors) Dolle, R. E.; Prasad, C. V. C.; Prouty, C. P.; Salvino, J. M.; Awad, M. M. A.; Schmidt, S. J.; Hoyer, D.; Ross, T. M.; Graybill, T. L.; Speier, G. J.; Uhl, J.; Miller, B. E.; Helaszek, C. T.; Ator, M. A. *J. Med. Chem.* **1997**, *40*, 1941.

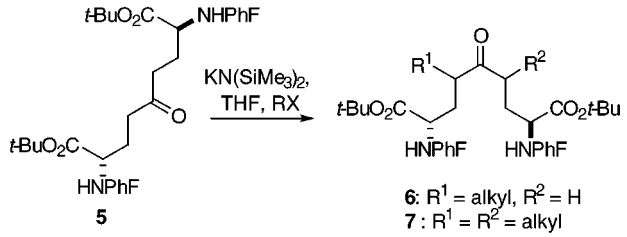
(3) For lead references on the use of templates for combinatorial chemistry, see: Falorni, M.; Giacomelli, G.; Nieddu, F.; Taddei, M. *Tetrahedron Lett.* **1997**, *38*, 4663 and refs 3−7 therein.

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

(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., Maia, Ed.; ESCOM: Leiden, The Netherlands, 1995; p 696.

(6) For numerous examples of bioactive peptides possessing phenylalanine see: Schmidt, G. *Top. Curr. Chem.* **1986**, *136*, 109. For additional examples see refs 1−6 in ref 8b below.

Table 1. Alkylation of Ketone 5



RX	mol% KHMDS	vol % DMPU	% conv. (4*S*-**6** : 4*R*-**6** : **7**)[a]	% Isolated Yield (4*S*)-**6**	(4*R*)-**6**	**7**
$PhCH_2Br$	110	10	63 (1 : 7.3 : 0)	5	45	
$PhCH_2Br$	160	10	91 (1 : 3.8 : 0)	14	54	
$PhCH_2Br$	160	–	>95 (1 : 7 : 0.5)		61[b]	
$PhCH_2Br$	210	10	86 (1 : 1.3 : 2)	10	28	31[c]
$H_2C{=}CHCH_2Br$	160	10	82 (1 : 1.8 : 0.5)		37	
$H_2C{=}CHCH_2Br$	160	–	>95 (1 : 3 : 0.5)			
MeO_2CCH_2Br	160	10	71 (1 : 1.8 : 0.2)	33[d]	14	
MeO_2CCH_2Br	160	–	>95 (1 : 4 : 0.3)	90[e]		
CH_3I	160	10	75 (1 : 4.2 : 1.4)			37[f]
CH_3CH_2I	160	10	74 (1 : 1.5 : 0)	21	51	
$(CH_3)_2CHI$	160	10	28 (-)			

[a]Determined by integration of *tert*-butyl ester siglets in the proton NMR spectrum of crude product. [b]Performed on 2 g of **5**. [c](4*R*,6*R*)-**7**, in addition 2% of (4*S*,6*R*)-**7** was also isolated. [d]Isolated as a 4:1 mixture with (4*S*)-**6**. [e]Isolated as a 5:1 mixture of (4*R*)-:(4*S*)-**6**. [f](4*R*,6*S*)-**7**.

tone **5**, 4-benzyl ketone (4*R*)-**6a**, into three different indolizidinone amino acids, (3*S*,6*S*,7*S*,9*S*)-**2**, (3*S*,6*S*,7*R*,9*S*)-**2** and (3*S*,5*R*,6*R*,9*S*)-**3** (Figure 1), via reagent control in sequences featuring methanesulfonate displacement and reductive amination. These features, combined with the versatility of the alkylation reaction for introducing a variety of side-chain groups onto the heterocycle, all illustrate the potential of this practical methodology for the synthesis of enantiopure 5-, 7-, and 5,7-alkyl-branched azabicyclo[4.3.0]alkane amino acids for use as building blocks for peptide mimicry and templates for combinatorial chemistry.

Results and Discussion

Alkylation of (2*S*,8*S*)-Di-*tert*-butyl 5-Oxo-2,8-di-[*N*-(PhF)amino]azelate (5). Alkylation of (2*S*,8*S*)-di-*tert*-butyl 5-oxo-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,8*S*)-**5**) was studied using various alkyl halides in order to open a general route for making alkyl-branched indolizidinone amino acids. Crystalline diaminoazelate δ-ketone **5** was synthesized in >30 mmol scale in five steps and >50% overall yield from L-glutamic acid via our reported route featuring the Claisen condensation of *N*-(PhF)glutamate, followed by hydrolysis and decarboxylation of the resulting β-keto ester.[4] The alkylation of azelate **5** was first explored with benzyl bromide, and similar conditions were then employed with a variety of alkyl halides (Table 1). Reaction conversion, the diastereomeric ratio of alkylated product **6**, and formation of dialkylated product **7** were ascertained by analysis of the crude reaction products using proton NMR spectroscopy and integration of the *tert*-butyl ester singlets which appeared at distinct chemical shifts (Table 2). Stereochemical assignments were made on the basis of analogy with benzylated ketones **6a** and **7a** which were characterized as described below. Mass recoveries were typically excellent; however, the reported isolated yields were lower than the amounts for conversion due to the difficulties of achieving complete separation of diastereomers by column chromatography and the exclusion of mixed fractions in the overall yields.

Initially, conditions that proved successful for the regioselective alkylations of *N*-(PhF)amino ketones were employed with **5** on small scale (100 mg, Table 1).[9] In a typical experiment, a solution of **5** in THF at −78 °C was converted into its enolate with potassium bis(trimethylsilyl)amide (KHMDS) and then treated with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and an alkyl halide for 1−2 h before aqueous workup. The conversion of **5** to alkylated material usually ranged from 63 to 95%, except in the reaction with isopropyl iodide which gave lower conversion (28%). Diastereoselectivity was typically low with these conditions. When the counterion was changed from potassium to sodium similar reactivity and selectivity were observed; switching to lithium retarded the rate of alkylation. In the reaction of the potassium enolate of **5** with benzyl bromide, we found that the ratio of mono- versus dialkylated product could be controlled by varying the stoichiometry of base. Higher diastereoselectivities and better conversions were obtained on larger scale in the absence of DMPU by allowing the reaction mixture to warm from −78 °C up to −10 °C after the addition of the alkyl halide (Table 1).

Silylenol ether **8** was prepared in order to study the geometry of the enolate formed under the conditions described above. Exposure of ketone **5** to KHMDS in

(7) (a) The synthesis of a 2-oxo-3-amino-4-benzyl-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid analogue that serves as a model antagonist of the tachykinin NK-2 receptor is reported in: Hanessian, S.; Ronan, B.; Laoui, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1397. (b) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567. (c) The synthesis of a 2-oxo-3-amino-3-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylic acid analogue is reported in: Colombo, L.; Di Giacomo, M.; Scolastico, C.; Manzoni, L.; Belvisi, L.; Molteni, V. *Tetrahedron Lett.* **1995**, *36*, 625.

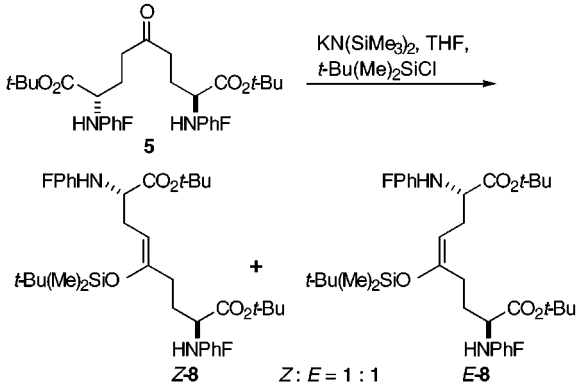
(8) Representative examples of constrained phenylalanine mimics include the following: (a) Gibson (née Thomas), S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447. (b) Collot, V.; Schmitt, M.; Marwah, A. K.; Norberg, B.; Bourguignon, J.-J. *Tetrahedron Lett.* **1997**, *38*, 8033. (c) Kazmierski, W. M.; Urbanczyk-Lipkowska, Z.; Hruby, V. J. *J. Org. Chem.* **1994**, *59*, 1789. (d) Cativiela, C.; Díaz-de-Villegas, M. D.; Avenoza, A.; Peregrina, J. M. *Tetrahedron* **1993**, *49*, 10987. (e) de Laszlo, S. E.; Bush, B. L.; Doyle, J. J.; Greenlee, W. J.; Hangauer, D. G.; Halgren, T. A.; Lynch, R. J.; Schorn, T. W.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 833. (f) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (g) Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270. (h) Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 351. (i) Belokon′, Y. N.; Bulychev, A. G.; Pavlov, V. A.; Fedorova, E. B.; Tsyryapkin, V. A.; Bakhmutov, V. A.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2075. (j) Sarges, R.; Tretter, J. R. *J. Org. Chem.* **1974**, *39*, 1710. (k) Semple, J. E.; Minami, N. K.; Tamura, S. Y.; Brunck, T. K.; Nutt, R. F.; Ripka, W. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2421. (l) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 8425. (m) Kühn, C.; Lindeberg, G.; Gogoll, A.; Hallberg, A.; Schmidt, B. *Tetrahedron* **1997**, *53*, 12497. (n) Liao, S.; Shenderovich, M. D.; Lin, J.; Hruby, V. J. *Tetrahedron* **1997**, *53*, 16645. (o) Van Betsbrugge, J.; Van Den Nest, W.; Verheyden, P.; Tourwé, D. *Tetrahedron* **1998**, *54*, 1753.

(9) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447. (b) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511. (c) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202. (d) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658.

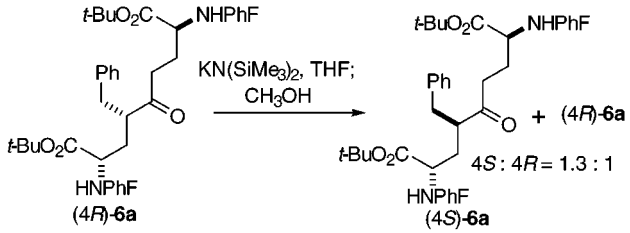
Table 2. Chemical Shifts (δ) of *tert*-Butyl Ester Singlets of 6 and 7

	R	(4*S*)-**6**	(4*R*)-**6**	(4*R*,6*R*)-**7**	(4*R*,6*S*)-**7**
a	$PhCH_2-$	1.05, 1.17	1.13, 1.15	1.11	1.08, 1.11
b	$CH2{=}CHCH_2-$	1.16, 1.22	1.14, 1.19	1.17	
c	$H_3CO_2CCH_2-$	1.17, 1.22	1.15, 1.21	1.20	
d	H_3C-	1.20, 1.23	1.18, 1.22	1.20	1.17, 1.25
e	CH_3CH_2-	1.18, 1.22	1.15, 1.20		

Scheme 2. Synthesis of Silylenol Ethers 8



Scheme 3. Epimerization of Alkyl-Branched Ketone (4*R*)-6a



THF at −78 °C for 2 h followed by addition of *tert*-butyldimethysilyl chloride furnished enol ether **8** as a 1:1 mixture of *E*:*Z* isomers (Scheme 2). Although the isomers were not separable by chromatography, spectral analysis confirmed their structure by revealing vinyl protons for each isomer as triplets at 4.48 and 4.52 ppm, as well as two sets of vinyl carbons at δ = 102.2, 103.5, 151.8, and 153.2 ppm.

Epimerization of benzyl ketone (4*R*)-**6a** was also examined in order to augment the amount of the minor diastereomer. Treatment of ketone (4*R*)-**6a** with KHMDS in THF at −78 °C for 2 h followed by addition of methanol furnished a 1.3:1 mixture of (4*S*)- and (4*R*)-**6a** (Scheme 3). Thus, although (4*S*)-**6a** was isolated as the minor diastereomer from the alkylation reaction, epimerization of the major diastereomer was successfully used to augment the quantity of this isomer.

Synthesis of 7- and 5-Benzylindolizidinone Amino Esters 10 and 11 by Methanesulfonate Displacements. In the preparation of indolizidinone amino acid **1**, hydride reduction of δ-oxo azelate **5**, methanesulfonylation, and S_N2 displacement by the phenylfluorenylamines proved to be an effective method for synthesizing 5-alkylproline intermediates.[4] Specific formation of the *cis*-5-alkylproline diastereomer from symmetrical di-*tert*-butyl δ-hydroxy-α,ω-di-[*N*-(PhF)amino]azelate was a noteworthy outcome that required the attack of each of the two amines 50% of the time in the S_N2 displacement of the methanesulfonate. This diastereospecificity indicated a significant difference in the energy of the transition states leading to the favored *cis*- over the *trans*-5-alkylproline diastereomer. In light of the excellent *cis*-diastereoselectivity in the cyclization of simple δ-hydroxy α,β-diaminoazelate,[4] we explored this reaction sequence to convert *C*-benzylated ketones **6a** into their respective indolizidinone amino esters. Since alkyl substituents can promote ring formation by steric interactions,[10] which may favor cyclization to form substituted prolines possessing 4-benzyl substituents, we considered that 7-benzylindolizidinone amino esters **10** and 5-benzylindolizidinone amino esters **11** might be formed by the influences of the benzyl substituent and stereochemistry in the displacement reaction.

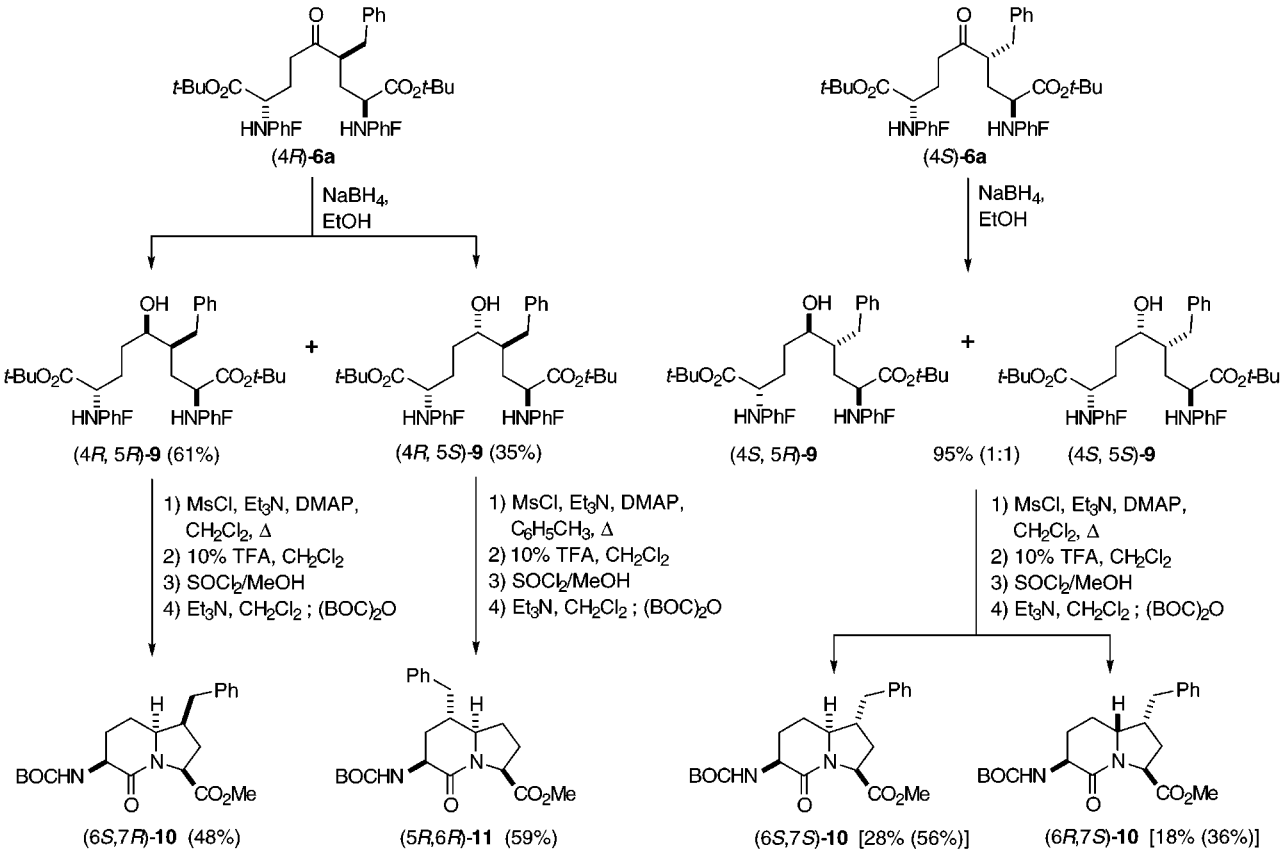
All four diastereomeric alcohols **9** were therefore synthesized by independent reductions of ketones (4*S*)- and (4*R*)-**6a** using sodium borohydride in ethanol to obtain low diastereoselectivity (Scheme 4). Sodium borohydride reduction of (4*R*)-**6a** gave a 2:1 mixture of (4*R*,5*R*)- and (4*R*,5*S*)-**9** alcohols that were separated by chromatography. Similar reduction of (4*S*)-**6a** yielded an inseparable 1:1 mixture of alcohols (4*S*,5*S*)- and (4*S*,5*R*)-**9**, that was directly used in the subsequent reaction sequence. Attempts to reduce ketone (4*R*)-**6a** diastereoselectively led to the discovery that sodium cyanoborohydride in ethanol with a catalytic amount of acetic acid gave a 5:1 ratio of (4*R*,5*S*)- and (4*R*,5*R*)-**9**.

5-Alkylproline intermediates were readily obtained by alcohol activation with methanesulfonyl chloride, triethylamine, and DMAP in dichloromethane, followed by intramolecular substitution on heating the solvent at a reflux. Cyclization of (4*R*,5*S*)-**9** occurred at higher temperature and required heating in boiling toluene. In all cases, each alcohol provided a single 5-alkylproline that was directly converted to the fully protected indolizidinone amino acid by *tert*-butyl ester 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. 7-Benzylindolizidinone amino esters (6*R*,7*S*)- and (6*S*,7*S*)-**10** were easily separated by chromatography on silica gel after their formation via cyclization of the 1:1 mixture of alcohols (4*S*,5*S*)- and (4*S*,5*R*)-**9**.

In total, three different 7-benzylindolizidinone amino ester diastereomers **10** and one 5-benzylindolizidinone amino ester **11** were selectively synthesized by this process. Cyclizations with (4*S*,5*R*)- and (4*R*,5*R*)-**9** gave 4-substituted *cis*-5-alkylproline diastereomers that were respectively converted to 7-benzylindolizidinone amino esters (6*S*,7*S*)- and (6*S*,7*R*)-**10** in 56% and 48% overall yields from their respective alcohols **9**. Cyclization with (4*S*,5*S*)-**9** gave the 4-substituted 5-alkylproline *trans*-diastereomer, that was converted to (6*R*,7*S*)-**10** in 36% overall yield from **9**, which indicated that the steric effects from the 4*S*-benzyl group were significant enough to promote a transition state providing the *trans*- rather than the *cis*-5-alkylproline diastereomer. On the other

(10) (a) For a review, see: Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205. (b) Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319.

Scheme 4. Synthesis of 5- and 7-Benzylindolizidinone Amino Esters 10 and 11 via Methanesulfonate Displacements



hand, the cyclization with (4*R*,5*S*)-**9** provided the less-substituted 5-alkylproline *cis*-diastereomer that was converted to 5-benzylindolizidinone amino ester (5*R*,6*R*)-**11** in 59% overall yield from **9**, which illustrated that the steric effects from the (4*R*)-benzyl group did not perturb the transition state favoring *cis*-5-alkylproline diastereomer. Thus, stereochemistry at the alkyl-branched 4-position influenced significantly the transition state for S_N2 displacement of the (5*S*)-methanesulfonate. The remarkable formation of only one 5-alkylproline from each diaminoazelate alcohol **9** implicates the importance of steric and stereochemical forces in the methanesulfonate displacements and underlines the power of this technique for selective generation of alkyl-branched azabicyclo[4.3.0]alkane ring systems.

Synthesis of 7-Benzylindolizidinone Amino Ester 10 by Reductive Amination. 7-Benzylindolizidinone amino ester **10** was also synthesized using the reductive amination/lactam cyclization strategy that had previously been developed for the synthesis of indolizidinone amino acid **1**.[4] A solution of **6a** in 10:1 EtOH:AcOH was treated with palladium-on-carbon under hydrogen atmosphere until TLC analysis showed complete disappearance of starting ketone. Hydrolysis of the *tert*-butyl esters with acid, esterification with MeOH and $SOCl_2$, lactam formation with Et_3N in dichloromethane, and protection with di-*tert*-butyl dicarbonate gave *N*-(BOC)amino 7-benzylindolizidinone ester **10** which was purified by column chromatography.

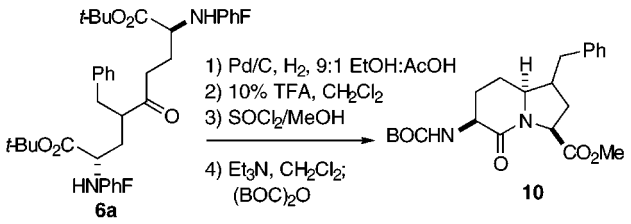
We noted several aspects of this reductive amination reaction that provided (3*S*,6*S*,7*R*,9*S*)- and (3*S*,6*S*,7*S*,9*S*)-**10** from hydrogenation of diastereomerically pure **6a**. In the first place, 7-alkylindolizidinone amino esters were formed instead of the 5-alkyl counterparts. Both steric promotion of ring formation,[10] as well as the formation of a more substituted enamine intermediate[11] during the reductive amination can account for the production of 4,5-dialkylprolines that lead to 7-alkylindolizidinones **10**. Furthermore, only 5-alkylproline *cis*-diastereomers, which yielded concave bicyclic ring systems, were isolated from hydrogenation of amino ketone **6a** at high hydrogen pressure. This result was consistent with the outcome of reductive amination of symmetrical (2*S*,8*S*)-di-*tert*-butyl 5-oxo-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,8*S*)-**5**) at high hydrogen pressure to form predominantly the concave indolizidinone system.[4] The steric bulk of the *tert*-butyl ester has previously been found to shield effectively one face of the dehydroproline intermediate such that *cis*-5-alkylprolines were the major products isolated from reductive amination of ordinary 5-keto esters.[12]

Finally, epimerization of the alkyl branched chiral center occurred via iminium ion−enaminium ion tautomerization during hydrogenation in the reductive amination, such that the reaction with pure (4*S*)- or (4*R*)-diastereomer **6a** and 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*)-**10** (Table 3). At 1 atm of hydrogen under the same conditions, the

(11) Shainyan, B. A.; Mirskova, A. N. *Russ. Chem. Rev.* **1979**, *48*, 107.

(12) (a) Beausoleil, E.; L'Archevêque, B.; Bélec, L.; Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447. (b) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438. (c) Ho, T. L.; Gopalan, B.; Nestor, J. J. Jr. *J. Org. Chem.* **1986**, *51*, 2405. (d) Fushiya, S.; Chiba, H.; Otsubo, A.; Nozoe, S. *Chem. Lett.* **1987**, 2229.

Table 3. Synthesis of 10 via Reductive Amination of 6a



		isolated yield of **10**	
substrate	H_2 atm	(6*S*,7*S*)-**10**	(6*S*,7*R*)-**10**
(4*R*)-**6a**	9	53	10
(4*R*)-**6a**	1	36	24
(4*S*)-**6a**	9	49	6
(4*S*)-**6a**	1	31	21

reductive amination of pure (4*S*)- or (4*R*)-diastereomer **6a** followed by conversion to indolizidinone ester produced a 1.5:1 ratio of (3*S*,6*S*,7*S*,9*S*)- and (3*S*,6*S*,7*R*,9*S*)-**10**.

The observed stereoselectivity of the hydrogenation at high pressure may be explained by a mechanism that implicates iminium ion−enaminium ion tautomerization as illustrated in Figure 2.[13,14] Among the possible intermediates leading to the hydrogenation transition state, the one labeled **B** may minimize the pseudo-1,3-diaxial interactions between the carboxylate and the 4-benzyl substituent by placing only the smallest substituent in an axial orientation. As mentioned above, *cis*-5-alkylprolines are produced from hydrogenation at high pressure due to the steric effects of the *tert*-butyl ester shielding attack of the upper face of the imine.[12] Relief of $A^{1,2}$ strain between the 4- and 5-position substituents in **B** would result from the catalyst delivering hydrogen to the underside of the imine.[15] Steric interactions between the *tert*-butyl ester and the 4-benzyl substituent most probably disfavor the (4*R*)-benzyl iminium intermediates that reduce to form the more congested (2*S*,4*R*,5*S*)-4,5-dialkylproline and furnish the minor (3*S*,6*S*,7*R*,9*S*)-7-benzylindolizidinone diastereomer **10** (Figure 2). At lower hydrogen pressure, reduced diastereoselectivity may be the consequence of competing palladium-catalyzed isomerization which leads to the minor (3*S*,6*S*,7*R*,9*S*)-diastereomer **10**.[16] Since the diastereoselectivity in the reductive amination of **6a** may also be observed in the hydrogenation of simpler γ-alkyl δ-oxo α-amino esters, this process exhibits potential as a complementary alternative to other approaches for synthesizing enantiopure 4,5-substituted prolinates, such as the addition of organocopper reagents to *N*-acyliminium ions and diastereoselective cycloadditions of azomethine ylides.[16b,17]

Synthesis of 5,7-Dibenzylindolizidinone Amino Ester 14. With successful means in hand for making 7- and 5-benzylindolizidinone amino esters **10** and **11**, we next investigated both the mesylate displacement and the reductive amination approaches with dibenzylazelate (4*R*,6*R*)-**7a** in order to synthesize 5,7-dibenzylindolizidinone amino ester **14** (Scheme 5). Symmetrical alcohol (4*R*,6*R*)-**12** was prepared in excellent yield by hydride reduction of ketone (4*R*,6*R*)-**7a** using sodium borohydride in ethanol. Methanesulfonylation of **12** using the conditions described above and heating in toluene furnished the *cis*-5-alkylproline intermediate which was converted to (5*R*,6*S*,7*R*)-5,7-dibenzylindolizidinone amino ester **14** in an overall yield of 26% from **12**. The same (5*R*,6*S*,7*R*)-5,7-dibenzylindolizidinone isomer **14** was also isolated as the only product in 20% overall yield from the reductive amination/lactam cyclization procedure using (4*R*,6*R*)-**7a** and hydrogenation at 9 atm with palladium-on-carbon.

Hydrolysis and Epimerization of 5- and 7-Benzyl- and 5,7-Dibenzylindolizidinone Amino Esters. *N*-(BOC)amino 7- and 5-benzylindolizidinone acids **2** and **3** as well as *N*-(BOC)amino 5,7-dibenzylindolizidinone acid **4** were synthesized via hydrolysis of their respective esters **10**, **11**, and **14** using conditions previously developed to generate (3*S*,6*S*,9*S*)-*N*-(BOC)amino indolizidinone acid (Table 4).[4] Quantitative hydrolysis was achieved using LiOH in dioxane; however, in certain cases, epimerization of the C-9 center competed with ester hydrolysis and afforded mixtures of (9*S*)- and (9*R*)-diastereomeric acids. For example, treatment of (3*S*,6*S*,7*R*,9*S*)-*N*-(BOC)-amino 7-benzylindolizidinone ester (3*S*,6*S*,7*R*,9*S*)-**10** with 200 mol % LiOH furnished a 3:2 mixture of (9*S*)- and (9*R*)-**2**. Exposure of (3*S*,5*R*,6*S*,7*R*,9*S*)-*N*-(BOC)amino 5,7-dibenzylindolizidinone ester (3*S*,5*R*,6*S*,7*R*,9*S*)-**14** to similar conditions gave a 55:45 mixture of (9*S*)- and (9*R*)-**4**. Ester hydrolysis without epimerization was achieved by employing potassium trimethylsilanolate in ether which furnished pure (3*S*,5*R*,6*S*,7*R*,9*S*)-**4** from its respective ester **14**.[12a,b] Similarly, treatment of ester (3*S*,6*S*,7*R*,9*S*)-**10** with 200 mol % $KOSiMe_3$ in ether gave pure (9*S*)-**2** in excellent yield without epimerization.

Since epimerization of esters **10**, **11**, and **14** can provide a means for generating benzylindolizidinone scaffolds having alternative configurations, we investigated conditions to transform (3*S*,6*S*,7*S*,9*S*)-*N*-(BOC)amino 7-benzylindolizidinone ester (3*S*,6*S*,7*S*,9*S*)-**10** into its corresponding (3*S*,6*S*,7*S*,9*R*)-**10** diastereomer. Epimerization of ester **10** was accomplished using KHMDS (200 mol %) in THF at −50 °C followed by an aqueous quench.[4] A separable 3:1 mixture of (9*R*)- and (9*S*)-**10** was isolated from this reaction.

Enantiomeric Purity and Stereochemical Assignments of 7- and 5-Benzyl- and 5,7-Dibenzylindolizidinone Amino Esters 10, 11, and 14. The enantiomeric purity of (3*S*,6*S*,7*S*,9*S*)-**10** produced from **5** via the alkylation/reductive amination/lactam cyclization sequence was determined after conversion to (1′*R*)- and (1′*S*)-*N*-α-methylbenzylureas **15** (Scheme 6). Trifluoroacetic acid in CH_2Cl_2 removed quantitatively the *N*-BOC

(13) Our process is related to the use of imine−enamine tautomerization for achieving diastereoselective Michael addition reactions. For example, see: (a) Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795 and refs 1 and 2 therein. For a review, see: (b) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

(14) Our process is also related to hydride additions to six-membered iminium ions, the stereochemical course of which has been discussed in the following: (a) Hart, D. J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757 and refs 4 and 19 therein. (b) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

(15) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 2017.

(16) (a) Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979; p 32. (b) To further probe the mechanism of this reductive amination reaction as well as to test the generality of this method, we are presently examining alternative hydrogenation conditions and simpler substrates.

(17) (a) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011 and refs therein. (b) Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.* **1995**, *60*, 5005 and refs therein.

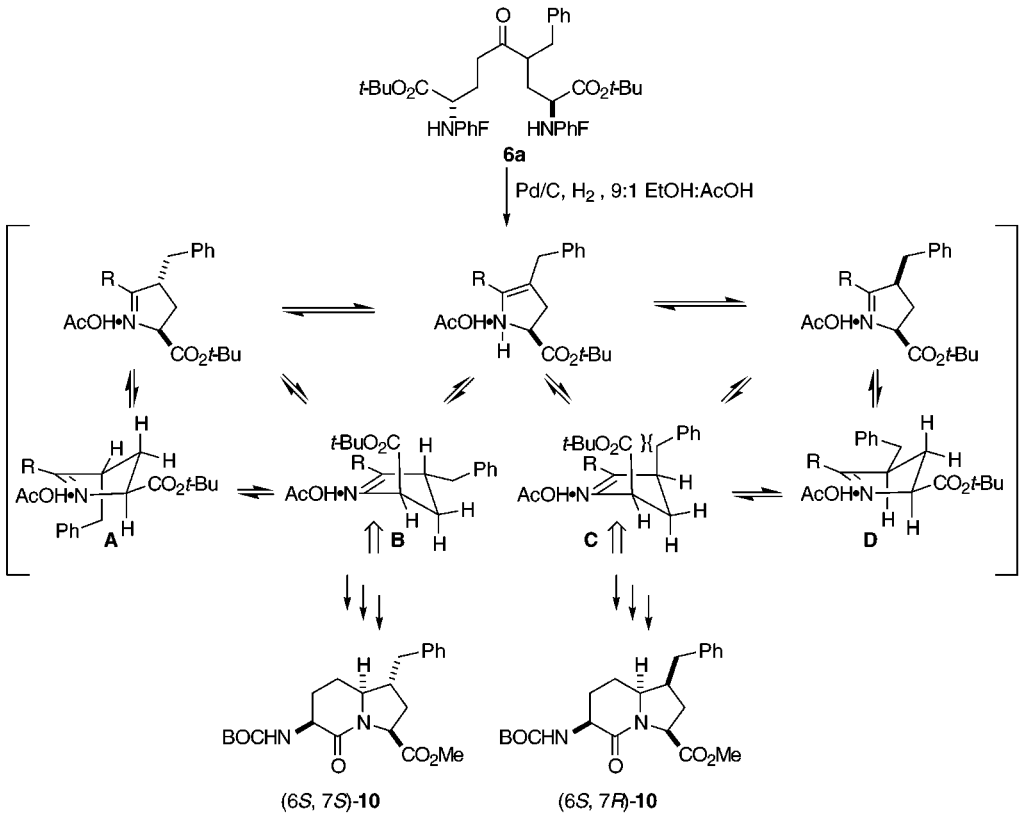
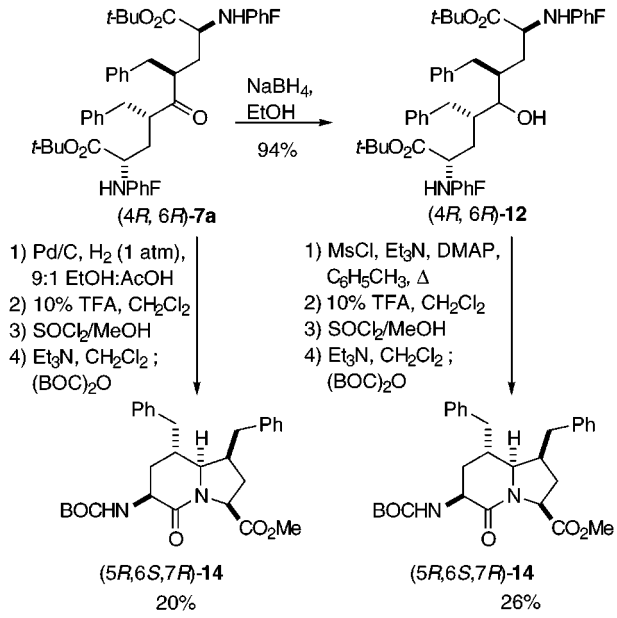


Figure 2. Mechanism of the reductive amination of **6a**.

Scheme 5. Synthesis of 5,7-Dibenzylquindolizidinone Amino Ester 14



protecting group, and the TFA salt was acylated with either (*R*)- or (*S*)-α-methylbenzyl isocyanate in THF with triethylamine.[4] Measurement of the diastereomeric methyl ester singlets at 3.67 and 3.70 ppm in $CDCl_3$ and at 3.28 and 3.38 in C_6D_6 by 400 MHz ^{1}H NMR spectroscopy demonstrated **15** to be of >99% diastereomeric excess.

The enantiomeric purity of (5*R*,6*S*,7*R*)-**14**, synthesized from **5** via the alkylation/methanesulfonate displacement/lactam cyclization sequence was determined in a similar fasion (Scheme 6). *N*-α-Methylbenzylureas **16** were prepared by BOC group solvolysis with TFA in CH_2Cl_2 followed by acylation with either (*R*)- or (*S*)-α-methylbenzyl isocyanate in THF with triethylamine. Measurement of the diastereomeric methyl ester singlets at 3.71 and 3.79 ppm in $CDCl_3$ and at 3.36 and 3.42 ppm in C_6D_6 by 400 MHz ^{1}H NMR spectroscopy demonstrated **16** to be of >99% diastereomeric excess.

The high diastereomeric purity of ureas **15** and **16** indicate that both routes, via reductive amination and via methanesulfonate displacement, provide enantiopure material. Hence, alkyl-branched intermediates **6** and **7**, benzylindolizidinone amino acid analogues **2**-**4**, and esters **10**, **11**, and **14** are all presumed to be of >99% enantiomeric purity.

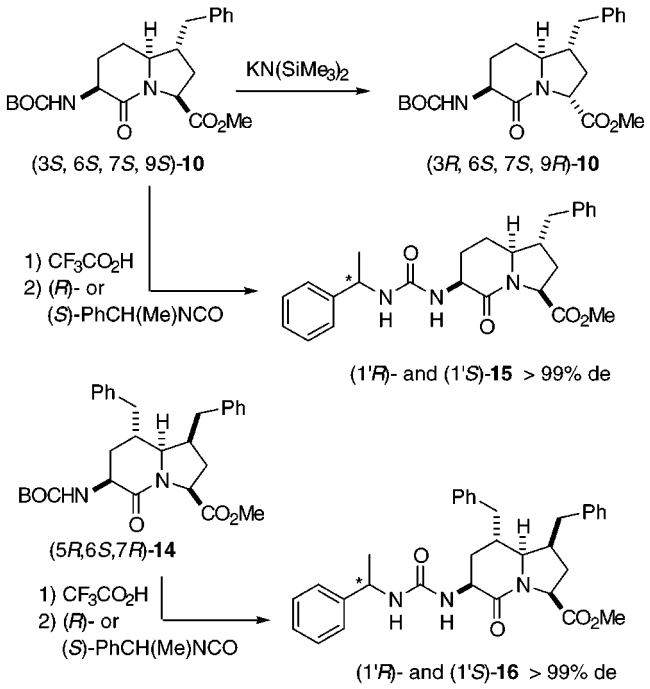
The position and relative stereochemistry of the benzylated carbons in indolizidinone *N*-(BOC)amino esters **10**, **11**, and **14** were conveniently determined by two-dimensional NMR experiments because the majority of the signals for each of the ring protons was well resolved at distinct chemical shifts (Table 5). The point of union between the benzyl group and the indolizidinone heterocycle was first established by systematic assignment of each of the ring protons in the COSY spectrum. For example, in the COSY spectrum of (3*S*,6*S*,7*S*,9*S*)-**10**, the presence of the benzyl substituent at the 7-position was confirmed by the coupling between the benzyl methylene protons at 2.7 and 2.8 ppm with the C7 proton at 2.3 ppm. Subsequently, the relative stereochemistry of the stereocenters at the 5-, 6-, and 7-positions was assigned by analysis of NOESY and ROESY spectra of **10**, **11**, and **14**. The various two-dimensional NMR spectra as well as the observed nuclear Overhauser effects that were used to assign the relative stereochemistry at the ring-fusion and alkyl-branched stereocenters of **10**, **11**, and **14**, all are illustrated in the Supporting Information. The stereochemical assignments made for the 5- and 7-posi-

Table 4. Synthesis of Amino Acids 2−4 by Ester Hydrolysis

ester	base	solvent	(9*S*):(9*R*)	yield (%)	acid
(3*S*,6*S*,7*S*,9*S*)-**10**	2 N LiOH	dioxane	99:1[a]	88	**2**
(3*S*,6*S*,7*R*,9*S*)-**10**	2 N LiOH	dioxane	60:40		**2**
(3*S*,6*S*,7*R*,9*S*)-**10**	$KOSiMe_3$	Et_2O	99:1[a]	77	**2**
(3*S*,6*R*,7*S*,9*S*)-**10**	2 N LiOH	dioxane	95:5	83	**2**
(3*S*,5*R*,6*R*,9*S*)-**11**	2 N LiOH	dioxane	99:1[a]	73	**3**
(3*S*,5*R*,6*S*,7*R*,9*S*)-**14**	2 N LiOH	dioxane	55:45		**4**
(3*S*,5*R*,6*S*,7*R*,9*S*)-**14**	$KOSiMe_3$	Et_2O	99:1[a]	83	**4**

a(9R)-Isomer was not detected.

Scheme 6. Enantiomeric Purity of 7-Benzylindolizidinone and 5,7-Dibenzylindolizidinone Amino Esters 10 and 14 and Epimerization of Ester 10



tions of **10**, **11**, and **14** were then used to deduce the relative stereochemistry at the benzyl branched 4- and 6-positions of ketones **6a** and **7a** based on the fact that no epimerization happened during the reaction sequences featuring methanesulfonate displacements. The stereochemistries of alcohols **9** were similarly deduced from the assignments made for the ring-fusion 6-positions of **10**, **11**, and **14** based on the actuality that the methanesulfonate displacements occurred with complete inversion of stereochemistry during this S_N2 reaction.

Crystallization of (3*S*,6*R*,7*S*,9*S*)-methyl 2-oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*R*,7*S*,9*S*)-**10**) from 1:1 EtOAc:hexane and X-ray crystallographic analysis confirmed the NMR assignments (Figure 3).[18] In the crystal structure of (3*S*,6*R*,7*S*,9*S*)-benzylindolizidinone **10**, the dihedral angles of the backbone atoms constrained inside the heterocycle resemble the values of the central residues in an ideal type II′ β-turn. For comparison, we have listed in Table 6 the values for **10** with those observed in the crystal structures of the corresponding methyl ester of indolizidinone amino acid (3*S*,6*S*,9*S*)-**1**, and a (3*S*,6*R*,9*S*)-6-thiaindolizidinone β-turn dipeptide analogue,[19] as well as the values for an ideal type II′ β-turn[20] and an ideal inverse γ-turn conformation.[21]

Conclusion

We have developed a practical method for synthesizing alkyl-branched azabicyclo[*X*.*Y*.0]alkane amino acids from α-aminodicarboxylates as inexpensive chiral educts. Alkylation of readily accessible (2*S*,8*S*)-di-*tert*-butyl 5-oxo-2,8-di-[*N*-(PhF)amino]azelate (**5**) permits a variety of substituents to be appended onto both linear and heterocycle dipeptide surrogates in order to mimic different amino acid side chains. Illustrating our method by the synthesis of 5- and 7-benzyl as well as 5,7-dibenzylindolizidinone amino acids **2**−**4**, we have prepared five new azabicyclo[*X*.*Y*.0]alkane amino acid scaffolds via efficient sequences featuring reductive aminations, methanesulfonate displacements, and lactam cyclizations. Because our routes are amenable to other amino acid side chains, and because the use of alternative α-aminodicarboxylates may furnish azabicyclo[*X*.*Y*.0]alkanes of various ring sizes, our methodology offers a versatile means for constructing these important tools for studying the spatial requirements for protein chemistry and biology.

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; 1,1,1,3,3,3-hexamethyldisilazane and CH_2Cl_2 were distilled from CaH; $CHCl_3$ was 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 Spectrometry facility. Unless otherwise noted, ^1H 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 (*J*) 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).

General Procedure for the Alkylation of (2*S*, 8*S*)-Di-*tert*-butyl 5-Oxo-2,8-di-[*N*-(PhF)amino]azelate (5). A −78

(18) The structure of **10** was solved at l'Université de Montréal X-ray facility using direct methods (SHELXS 96) and refined with SHELXL 96: $C_{22}H_{30}N_2O_5$; $M_r = 402.48$; monoclinic, colorless crystal; space group $P2_1$; unit cell dimensions (Å) $a = 5.928(2)$, $b = 10.207(3)$, $c = 17.964(7)$; $\beta = 93.45(3)°$; volume of unit cell (Å^3) 1085.0(6); $Z = 2$; $R_1 = 0.0599$ for $I > 2\ \sigma(I)$, $wR_2 = 0.1507$ for all data; GOF = 0.860. The author has deposited the atomic coordinates for the structure of **10** 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.

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

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

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

Table 5. ^{1}H NMR of 5- and 7-Benzyl- and 5,7-Dibenzylindolizidinone Amino Esters 11, 10 and 14

	3α	4α	4β	5α	5β	6α/β	7a	7β	8α	8β	9α/β	Bn	OMe	OtBu	NH
(6*S*,7*S*,9*S*)-**10**	4.09m	2.33m	1.62m	1.75m	1.56m	3.37m(α)		2.26m	1.95dd	2.06dd	4.49d(α)	2.75dd	3.70	1.43	5.50
									13.0, 9.1	13.1, 6.2	8.9	13.6, 6.7			
(6*S*,7*R*,9*S*)-**10**	4.20m	2.41m	1.62m	1.97m	1.97m	3.87dd(α)	2.73m		2.16m	1.83m	4.30dd(α)	2.82dd	3.78	1.44	5.50
						16.0, 7.2					8.8, 5.6	13.3, 5.5			
(6*R*,7*S*,9*S*)-**10**	4.13m	2.62m	1.81m	1.72m	2.0dd	3.98m(β)		2.54dd	2.06dd	1.69m	4.44t(α)	2.86dd	3.72	1.45	5.24
					10.4, 4.2			11.3, 6.3	4.9, 0.9		9.0	13.7, 4.7			
(6*S*,7*S*,9*R*)-**10**	4.11m	1.61	2.69m	1.91m	1.5m	3.5m(α)		2.07m	2.62dd	1.67dd	4.43t(β)	2.84dd	3.75	1.44	5.31
	4.9, 2.0								13.6, 8.7	11.2, 9.4	8.5	13.6, 5.8			
(5*R*,6*R*,9*S*)-**11**	4.23dd	2.12m	1.78m		2.27m	3.47m(α)	1.95m	1.64m	2.10m	2.07m	4.50dd(α)	2.80dd	3.73	1.43	5.40
	6.6, 3.0										8.4, 1.3	13.6, 6.3			
(5*R*,7*R*,9*S*)-**14**	4.32bs	2.08m	2.04m		2.61m	3.69dd(α)	2.36m		2.06dd	1.87d	4.44d(α)	2.99dd(5)	3.85	1.51	5.40
						9.5, 5.6			10.9, 6.7	14.0	10.5	13.7, 6.6			
												2.87dd(7)		2.57t(7)	
												13.6, 9.2		13.4	

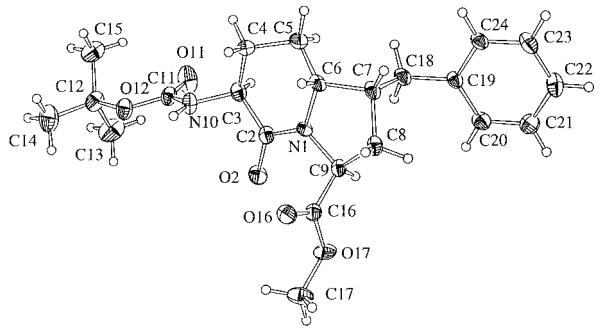


Figure 3. ORTEP view of indolizidinone methyl ester (3*S*,6*R*,7*S*,9*S*)-**10**. Ellipsoids are drawn at 40% probability level. Hydrogens are represented by spheres of arbitrary size.[18]

Table 6. Comparison of the Dihedral Angles from Azabicycloalkane X-ray Data and Ideal Peptide Turns

entry	ψ	ϕ
7-benzylindolizidinone (3*S*,6*R*,7*S*,9*S*)-**10**	−147°	−56°
indolizidinone (3*S*,6*S*,9*S*)-**1**[4]	−176°	−78°
(3*S*,6*R*,9*S*)−6-thiaindolizidinone[19]	−161°	−69°
Type II′ β-turn $i+1$ and $i+2$ residues[20]	−120°	−80°
inverse γ-turn $i+2$ residue[21]		−80°

°C solution of **5** (100 mg, 0.12 mmol, 100 mol %) in THF (1 mL) was treated with a 0.5 M solution of KHMDS in toluene, stirred for 30 min, and treated with DMPU (0.3 mL) and alkyl halide (170 mol %). After 1−2 h of stirring at −78 °C, the reaction mixture was partitioned between EtOAc (15 mL) and 1 M NaH_2PO_4 (15 mL). The aqueous layer was extracted with EtOAc (15 mL), and the combined organic layers were washed with brine, dried, and evaporated to a crude residue that was first analyzed by proton NMR spectroscopy and later chromatographed on silica gel using an eluant of hexane to 1:10 hexane:dichloromethane.

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 5-oxo-4-benzyl-2,8-di-[*N*-(PhF)-amino]azelate ((2*S*,4*R*,8*S*)-6a): $[\alpha]_D^{20}$ −178.5 (*c* 1.07, $CHCl_3$); ^{1}H NMR δ 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, 25 H), 7.65 (m, 4 H); ^{13}C NMR δ 27.8, 27.9, 28.4, 29.0, 36.6, 38.1, 39.8, 49.4, 54.3, 55.1, 72.9, 72.9, 80.6, 80.8, 175.0, 175.0, 213.2; HRMS calcd for $C_{62}H_{63}O_5N_2$ (MH^+) 915.4737, found 915.4707.

(2*S*,4*S*,8*S*)-Di-*tert*-butyl 5-oxo-4-benzyl-2,8-di-[*N*-(PhF)-amino]azelate ((2*S*,4*S*,8*S*)-6a): $[\alpha]_D^{20}$ −202.4 (*c* 0.77, $CHCl_3$); ^{1}H NMR δ 1.09 (s, 9 H), 1.17 (s, 9 H), 1.52 (m, 2 H), 1.76 (m, 1 H), 1.90 (m, 1 H), 2.03 (ddd, 1 H, J = 5.3, 11.6, 16.8), 2.37 (m, 2 H), 2.51 (t, 1 H, J = 5.0), 2.69 (m, 2 H), 2.95 (ddd, 1 H, J = 4.2, 11.6, 16.8), 3.1 (bs, 2 H), 7.03 (d, 2 H, J = 7.0), 7.1−7.5 (m, 25 H), 7.7 (m, 4 H); ^{13}C NMR δ 27.7, 27.9, 29.0, 36.6, 38.6, 40.6, 50.1, 55.0, 55.2, 72.9, 73.7, 80.6, 80.8, 174.4, 175.2, 213.2; HRMS calcd for $C_{62}H_{63}O_5N_2$ (MH^+) 915.4737, found 915.4716.

(2*S*,4*R*,6*R*,8*S*)-Di-*tert*-butyl 5-oxo-4,6-dibenzyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,6*R*,8*S*)-7a): $[\alpha]_D^{20}$ −93.9 (*c* 1.73, $CHCl_3$); ^{1}H NMR δ 1.03 (m, 2 H), 1.11 (s, 18 H), 1.15 (m, 2 H), 2.36 (m, 4 H), 2.45 (dd, 2 H, J = 9.6, 3.1), 3.05 (bs, 2 H), 3.26 (m, 2 H), 6.95 (m, 4 H), 7.1−7.4 (m, 28 H), 7.68 (m, 4 H); ^{13}C NMR δ 27.8, 35.2, 35.7, 48.8, 53.9, 72.8, 80.5, 175.2, 214.1; HRMS calcd for $C_{69}H_{69}O_5N_2$ (MH^+) 1005.5206, found 1005.5188.

(2*S*,4*S*,6*R*,8*S*)-Di-*tert*-butyl 5-oxo-4,6-dibenzyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*S*,6*R*,8*S*)-7a): $[\alpha]_D^{20}$ −125.3 (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 1.05 (m, 1 H), 1.08 (s, 9 H), 1.11 (s, 9 H), 1.25 (t, 1 H, J = 7.2), 1.33 (m, 1 H), 1.52 (m, 1 H), 1.86 (m, 1 H), 1.96 (m, 1 H), 2.19 (m, 2 H), 2.29 (m, 1 H), 2.45 (dd, 1 H, J = 9.5, 2.6), 2.55 (dd, 1 H, J = 13.7, 7.2), 2.67 (dd, 1 H, J = 7.3, 4.8), 2.87 (m, 1 H), 3.18 (m, 1 H), 6.72 (m, 2H), 6.93 (m, 2 H), 7.1−7.7 (m, 32 H); ^{13}C NMR δ 27.8, 27.8, 31.6, 35.3, 35.7, 36.1, 36.5, 48.2, 49.5, 54.2, 54.9, 72.8, 73.5, 80.4, 80.8, 174.5, 175.0, 213.5; HRMS calcd for $C_{69}H_{69}O_5N_2$ (MH^+) 1005.5206, found 1005.5178.

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 5-oxo-4-allyl-2,8-di-[*N*-(PhF)-amino]azelate ((2*S*,4*R*,8*S*)-6b): $[\alpha]_D^{20}$ −74.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 1.14 (s, 9 H), 1.19 (s, 9 H), 1.35 (m, 1 H), 1.65 (m, 3 H), 1.75 (m, 2 H), 2.35 (m, 1 H), 2.48 (m, 2 H), 2.65 (m, 1 H), 2.87 (m, 1 H), 4.86 (m, 2 H), 5.49 (m, 1 H), 6.0 (bs, 1 H), 6.7 (bs, 1 H), 7.2−7.4 (m, 22 H), 7.67 (d, 4 H, J = 7.4); ^{13}C NMR δ 27.8, 27.8, 29.1, 35.1, 36.0, 38.6, 47.4, 54.1, 55.3, 72.9, 73.0, 80.7, 175.0, 175.3, 212.8; HRMS calcd for $C_{58}H_{61}O_5N_2$ (MH^+) 865.4581, found 865.4609. (2*S*,4*S*,8*S*)-Di-*tert*-butyl 5-oxo-4-allyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*S*,8*S*)-**6b**) was isolated as a 3:1 mixture with the bis-alkylated product **7b**.

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 5-oxo-4-methyloxycarbonyl-methyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,8*S*)-6c) was isolated and characterized as a 4:1 mixture with (2*S*,4*S*,8*S*)-**6c**. Spectral data for the major product (2*S*,4*R*,8*S*)-**6c** are as follows: ^{1}H NMR δ 1.20 (s, 9 H), 1.26 (s, 9 H), 1.51−1.61 (m, 2 H), 1.62−1.70 (m, 1 H), 1.72−1.88 (m, 1 H), 2.36 (dd, 2 H, J = 10.8, 17.1), 2.52−2.64 (m, 2 H), 2.84−2.94 (m, 1 H), 3.20 (d, 1 H, J = 7.9), 3.26 (d, 1 H, J = 9.8), 3.40 (t, 1 H, J = 9.9), 3.67 (s, 3 H), 7.11−7.53 (m, 22 H), 7.72 (m, 4 H); ^{13}C NMR δ 27.7, 27.9, 29.2, 33.6, 36.3, 38.2, 43.3, 51.4, 53.6, 55.4, 72.8, 73.0, 80.7, 81.1, 172.3, 175.0, 175.1, 212.4; HRMS calcd for $C_{58}H_{61}O_7N_2$ (MH^+) 897.4479, found 897.4504.

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 5-oxo-4-methyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,8*S*)-6d) was isolated as a 9:1 mixture with (2*S*,4*R*,6*R*,8*S*)-**7d**. Spectral data for the major product (2*S*,4*R*,8*S*)-**6d** are as follows: ^{1}H NMR δ 0.61 (d, 3 H, J = 6.9), 1.17 (s, 9 H), 1.21 (s, 9 H), 1.64−1.76 (m, 3 H), 2.39−2.42 (m, 2 H), 2.44 (dd, 1 H, J = 3.2, 10.4), 2.51 (dd, 1 H, J = 4.9, 7.5), 2.64−2.73 (m, 1 H), 2.82−2.88 (m, 1 H), 7.18−7.70 (m, 26 H); ^{13}C NMR δ 15.6, 27.8, 27.9, 29.5, 37.2, 38.1, 42.6, 54.0, 55.4, 72.8, 73.1, 77.2, 80.6, 80.7, 175.1, 175.5, 213.9.

(2*S*,4*S*,6*R*,8*S*)-Di-*tert*-butyl 5-oxo-4,6-dimethyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*S*,6*R*,8*S*)-7d): $[\alpha]_D^{20}$ −160.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 0.42 (d, 3 H, J = 6.9), 0.95 (d, 3 H, J = 6.9), 1.17 (s, 9 H), 1.25 (s, 9 H), 1.46 (m, 2 H), 1.78 (dt, 2 H, J = 13.3, 1.2), 1.94 (m, 1 H), 2.36 (dd, 1 H, J = 11.4, 2.4), 2.61 (dd, 1 H, J = 7.0, 4.6), 2.66 (q, 1 H, J = 6.8), 3.11 (bs, 2 H), 7.1−7.5 (m. 22 H), 7.75 (m, 4 H); ^{13}C NMR δ 14.1, 14.8, 27.9, 28.0, 29.7, 37.7, 39.3, 40.9, 53.5, 55.0, 72.8, 73.5, 77.2, 80.6, 80.8, 174.8, 175.7, 216.8; HRMS calcd for $C_{57}H_{61}O_5N_2$ (MH^+) 853.4581, found 853.4548.

(2*S*,4*S*,8*S*)-Di-*tert*-butyl 5-oxo-4-ethyl-2,8-di-[*N*-(PhF)-amino]azelate ((2*S*,4*S*,8*S*)-6e): $[\alpha]_D^{20}$ −111.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 0.75 (t, 3 H, J = 7.4), 1.18 (s, 9 H), 1.22 (s, 9 H), 1.27 (m, 1 H), 1.42 (m, 2 H), 1.68 (m, 2 H), 1.88 (m, 1 H), 2.22 (ddd, 1 H, J = 4.6, 11.3, 18.0), 2.39 (m, 1 H), 2.43 (dd, 1 H, J = 4.3, 8.5), 2.50 (t, 1 H, J = 5.5), 2.80 (ddd, 1 H, J = 4.8, 11.7, 18.0), 3.20 (bs, 2 H), 7.1−7.4 (m, 22 H), 7.65 (m, 4 H); ^{13}C NMR δ 11.6, 25.3, 27.9, 29.1, 36.5, 39.5, 49.5, 55.1, 55.4, 72.9, 73.4, 76.7, 80.7, 80.8, 174.8, 175.2, 213.3; HRMS calcd for $C_{57}H_{61}O_5N_2$ (MH^+) 853.4581, found 853.4565.

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 5-oxo-4-ethyl-2,8-di-[*N*-(PhF)-amino]azelate ((2*S*,4*R*,8*S*)-6e): $[\alpha]_D^{20}$ −97.5 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 0.66 (t, 3 H, J = 7.3), 1.01 (m, 1 H), 1.15 (s, 9 H), 1.20 (s, 9 H), 1.31 (m, 2 H), 1.66 (m, 3 H), 2.40 (m, 1 H), 2.42 (dd, 1 H, J = 4.2, 10.2), 2.49 (dd, 1 H, J = 4.7, 7.5), 2.62 (m, 1 H), 2.72 (m, 1 H), 3.22 (bs, 2 H), 7.1−7.4 (m, 22 H), 7.67 (m, 4 H); ^{13}C NMR δ 11.2, 23.7, 27.8, 27.9, 29.3, 36.3, 38.5, 49.3, 54.2, 55.3, 72.9, 73.0, 80.7, 80.7, 175.1, 175.4, 213.6; HRMS calcd for $C_{57}H_{61}O_5N_2$ (MH^+) 853.4581, found 853.4556.

(2*S*,4*R*,8*S*)- and (2*S*,4*S*,8*S*)-Di-*tert*-butyl 5-Oxo-4-benzyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,8*S*)- and (2*S*,4*S*,8*S*)-6a). A solution of **5** (2.0 g, 2.4 mmol) in 7 mL of THF was cooled to −78 °C and treated with a 0.5 M solution of KHMDS in toluene (7.8 mL, 3.9 mmol, 160 mol %) dropwise over 30 min. The reaction mixture was stirred for 30 min at −78 °C, and benzyl bromide (1.71 mL, 14.4 mmol, 600 mol %) was added dropwise over 30 min. The reaction mixture was stirred for 1 h at −78 °C and allowed to warm to −10 °C over 45 min. The reaction mixture was stirred an additional 1 h at −10 °C and partitioned between EtOAc (15 mL) and 1 M NaH_2PO_4 (15 mL), and the separated aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried, and evaporated to a residue that was analyzed by proton NMR spectroscopy. Integration of the *tert*-butyl ester singlets indicated a 7:1:0.5 ratio of (4*R*)-**6a**:(4*S*)-**6a**:(4*R*,6*R*)-**7a** as well as trace amounts of starting ketone **5**. The residue was then chromatographed on silica gel (30 g per 1 g of residue) using a gradient of hexane to 1:10 hexane: dichloromethane. The collected fractions were combined into four portions: first an impure mix of (4*R*,6*R*)-**7a** and (4*S*)-**6a** (370 mg); second a 3.5:1 (4*R*)-**6a**:(4*S*)-**6a** mixture (580 mg, 27%); third a 9:1 (4*R*)-**6a**:(4*S*)-**6a** mixture (400 mg, 18%); fourth pure (4*R*)-**6a** (950 mg, 43%).

Epimerization of (2*S*,4*R*,8*S*)-Di-*tert*-butyl 5-Oxo-4-benzyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,8*S*)-6a). A −78 °C solution of (2*S*,4*R*,8*S*)-di-*tert*-butyl 5-oxo-4-benzyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,8*S*)-**6a**, 20 mg, 0.022 mmol, 100 mol %) in THF (1 mL) was treated with a 0.5 M solution of KHMDS in toluene (0.1 mL, 0.05 mmol, 227 mol %), stirred for 30 min, and quenched with CD_3OD (30 μL). After 1 h of stirring at −78 °C, the reaction mixture was partitioned between EtOAc (5 mL) and 1 M NaH_2PO_4 (5 mL). The aqueous layer was extracted with EtOAc (5 mL), and the combined organic layers were washed with brine, dried, and evaporated to a residue that was analyzed by proton NMR spectroscopy and showed a 1:1.3 ratio of the two pairs of diastereomeric *tert*-butyl singlets at 1.13 and 1.15 ppm ((4*R*)-**6a**) and 1.09 and 1.17 ppm ((4*S*)-**6a**).

(2*S*,4*S*,5*RS*,8*S*)-Di-*tert*-butyl 4-Benzyl-5-hydroxy-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*S*,5*RS*,8*S*)-9). A solution of (4*S*)-**6a** (300 mg, 0.33 mmol) in EtOH (15 mL) was treated with $NaBH_4$ (40 mg, 1 mmol, 300 mol %), stirred for 4 h at room temperature, and diluted with water (5 mL). The volume was reduced using a rotary evaporator, and the remaining volume was extracted with EtOAc (2 × 15 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 1:1 mixture of (5*R*)- and (5*S*)-alcohols **9** that were used in the subsequent reactions as a mixture without further purification: ^{1}H NMR δ 1.07 (s, 9 H), 1.12 (s, 9 H), 1.18 (s, 9 H), 1.22 (s, 9 H), 1.32−1.95 (m, 16 H), 2.19 (dd, 1 H), 2.30 (dd, 1 H), 2.52−2.80 (m, 6 H), 3.22−3.30 (m, 1 H), 3.38−3.47 (m, 1 H), 7.08−7.75 (m, 62 H).

(2*S*,4*R*,5*S*,8*S*)- and (2*S*,4*R*,5*R*,8*S*)-Di-*tert*-butyl 4-benzyl-5-hydroxy-2,8-di-[*N*-(PhF)amino]azelates ((2*S*,4*R*,5*S*,8*S*)- and (2*S*,4*R*,5*R*,8*S*)-9) were prepared using the protocol as described for the reduction of ketone (4*S*)-**6a**. Analysis of the crude residue by proton NMR spectroscopy showed a 2:1 ratio of 5*R*:5*S* diastereomeric alcohols **9** which were separated by chromatography on silica gel using a gradient of pure CH_2Cl_2 to 94:6 CH_2Cl_2:EtOAc. The first compound to elute was (4*R*,5*S*)-**9** (100 mg, 35%): $[\alpha]_D^{20}$ −113.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 1.09 (s, 9 H), 1.22 (s, 9 H), 1.26−1.80 (m, 7 H), 1.94 (bs, 1 H), 2.22−2.28 (m, 1 H), 2.34−2.36 (m, 2 H), 2.62−2.72 (m, 1 H), 3.39−3.40 (m, 1 H), 6.85 (d, 2 H, J = 6.9), 7.08−7.53 (m, 25 H), 7.66−7.71 (m, 4 H); ^{13}C NMR δ 27.7, 27.9, 29.3, 32.5, 34.4, 36.8, 42.5, 55.8, 56.4, 72.0, 73.0, 73.1, 80.4, 80.6, 175.1, 175.3; HRMS calcd for $C_{62}H_{65}N_2O_5$ (MH^+) 917.4893, found 917.4869.

The next compound to elute was (4*R*,5*R*)-**9** (180 mg, 61%): $[\alpha]_D^{20}$ −133.6 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 1.03 (s, 9 H), 1.23 (s, 9 H), 1.34−1.40 (m, 2 H), 1.50−1.72 (m, 6 H), 2.04−2.06 (m, 1 H), 2.11 (dd, 1 H, J = 14.5, 9.5), 2.60 (bs, 1 H), 2.66 (dd, 1 H, J = 13.2, 6.2), 3.35−3.38 (m, 1 H), 6.74 (d, 2 H, J = 7.0), 7.05−7.47 (m, 25 H), 7.65−7.73 (m, 4 H); ^{13}C NMR δ 27.7, 27.9, 30.7, 31.4, 36.3, 37.5, 42.6, 55.9, 56.9, 72.9, 73.1, 73.5, 77.2, 80.3, 80.7, 175.1, 175.2; HRMS calcd for $C_{62}H_{65}N_2O_5$ (MH^+) 917.4893, found 917.4915.

(2*S*,4*R*,5*R*,8*S*)- and (2*S*,4*R*,5*S*,8*S*)-Di-*tert*-butyl 5-Hydroxy-4-benzyl-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,5*R*,8*S*)- and (2*S*,4*R*,5*S*,8*S*)-9) by NaCNBH$_3$ Reduction of 6a. A solution of ketone (4*R*)-**6a** (300 mg, 0.33 mmol) in ethanol (10 mL) was cooled to −78 °C and treated with $NaCNBH_3$ (16.5 mg, 0.263 mmol, 300 mol %) in one portion, followed by several drops of acetic acid. The reaction mixture was stirred for 6 h at −78 °C, allowed to warm to room temperature over 45 min, diluted with water (5 mL), concentrated under vacuum, and extracted with EtOAc (2 × 15 mL). The combined organic

layers were washed with brine, dried, and evaporated to a residue which was analyzed to be a 1:5 mixture of (5*R*)- and (5*S*)-**9** by integration of the *tert*-butyl ester singlets in the NMR spectrum. The residue was chromatographed on silica gel (30 g per 1 g of residue) using a gradient of CH_2Cl_2 to 94:6 CH_2Cl_2:EtOAc. The collected fractions were combined into three portions: first (5*R*)-**9** (8 mg, 10%); second a 1:7 (5*R*)-**9**:(5*S*)-**9** mixture (22 mg, 28%); third (5*S*)-**9** (45 mg, 56%).

(2*S*,4*R*,6*R*,8*S*)-Di-*tert*-butyl 4,6-Dibenzyl-5-hydroxy-2,8-di-[*N*-(PhF)amino]azelate ((2*S*,4*R*,6*R*,8*S*)-12) was synthesized from dibenzyl ketone **7a** using the procedure described for the sodium borohydride reduction of ketone (4*S*)-**6a** and stirring the mixture overnight before dilution with water. The crude alcohol **12** (280 mg, 95%) was used in subsequent reactions without further purification. A crystalline sample of **12** was obtained from EtOH: mp 118−119 °C; $[\alpha]_D^{20}$ −62.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 1.03 (s, 9 H), 1.08 (s, 9 H), 1.30−1.38 (m, 1 H), 1.42−1.54 (m, 2 H), 1.78 (bs, 1 H), 1.82−1.98 (m, 2 H), 2.02−2.16 (m, 2 H), 2.38 (s, 2 H), 2.63 (dd, 1 H, J = 5.3, 3.5), 2.74−2.77 (m, 2 H), 3.26 (dd, 1 H, J = 7.5, 0.5), 6.62−6.64 (m, 2 H), 6.98−7.40 (m, 30 H), 7.53−7.73 (m, 4 H); ^{13}C NMR δ 27.7, 27.8, 34.3, 36.2, 37.4, 37.2, 38.6, 40.5, 55.2, 56.4, 72.9, 73.0, 77.2, 80.1, 80.2, 175.3, 175.5; HRMS calcd for $C_{69}H_{71}N_2O_5$ (MH^+) 1007.5363, found 1007.5389.

General Procedure for the Synthesis of 5- and 7-Benzyl and 5,7-Dibenzylindolizidinone Amino Esters 10, 11, and 14 via Methanesulfonate Displacement. Methanesulfonylation and S_N2 displacement were performed by treating a magnetically stirred, 0 °C solution of alcohol **9** or **12** (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 and heated at a reflux for 24 h (in the cases of alcohols (4*R*,5*S*)-**9** and (4*R*,6*R*)-**12**, the reaction was carried out in boiling toluene instead of CH_2Cl_2). 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 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 the crude reaction 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 2h. 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 40:60 hexanes:EtOAc as eluant. Evaporation of the collected fraction gave the indolizidinone amino ester.

(3*S*,6*S*,7*S*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*S*,9*S*)-10) was obtained in 23% (55%) overall yield from 400 mg of a 1:1 mixture of (4*S*,5*S*)- and (4*S*,5*R*)-**9**: $[\alpha]_D^{20}$ −3.6 (*c* 1.69, $CHCl_3$); ^{13}C NMR δ 25.9, 27.9, 28.3, 35.0, 38.2, 47.0, 50.0, 52.3, 57.4, 60.9, 79.4, 128.6, 128.7, 138.7, 155.6, 169.1, 172.0; HRMS calcd for $C_{22}H_{30}N_2O_5$ (MH^+) 403.2233, found 403.2216.

(3*S*,6*S*,7*R*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*R*,9*S*)-10) was obtained from 180 mg of (4*R*,5*R*)-**9** in 48% overall yield: $[\alpha]_D$ 20 27.4 (*c* 0.95, $CHCl_3$); ^{13}C NMR δ 21.4, 26.4, 28.3, 32.8, 34.2, 42.4, 50.2, 52.4, 58.0, 58.7, 79.6, 126.4, 128.6, 128.7, 139.4, 155.6, 169.4, 172.1; HRMS calcd for $C_{22}H_{30}N_2O_5$ (MH^+) 403.2233, found 403.2212

(3*S*,6*R*,7*S*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*R*,7*S*,9*S*)-10) was obtained from 400 mg of a 1:1 mixture of (4*S*,5*S*)- and (4*S*,5*R*)-**9** in 19% (37%) overall yield: mp 177−179 °C; $[\alpha]_D^{20}$ −86.7 (*c* 0.86, $CHCl_3$); ^{13}C NMR δ 23.2, 28.3, 28.7, 31.8, 33.8, 42.2, 52.1, 52.3, 56.3, 63.0, 79.6, 126.5, 128.7, 128.9, 139.0, 168.5, 172.7; HRMS calcd for $C_{22}H_{30}N_2O_5$ (MH^+) 403.2233, found 403.2216.

(3*S*,5*R*,6*R*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-5-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,5*R*,6*R*,9*S*)-11) was obtained from 190 mg of (4*R*,5*S*)-**9** in 59% overall yield: $[\alpha]_D^{20}$ 17.7 (*c* 1.63, $CHCl_3$); ^{13}C NMR δ 28.3, 28.9, 31.6, 34.2, 40.0, 40.7, 49.4, 52.3, 58.0, 61.8, 79.5, 126.4, 128.5, 129.0, 138.9, 155.7, 169.3, 172.2; HRMS calcd for $C_{22}H_{30}N_2O_5$ (MH^+) 403.2233, found 403.2216.

(3*S*,5*R*,6*S*,7*R*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-5,7-dibenzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate((3*S*,5*R*,6*S*,7*R*,9*S*)-14) was obtained from 280 mg of alcohol **12** in 26% overall yield: $[\alpha]_D^{20}$ 37.3 (*c* 0.64, $CHCl_3$); ^{13}C NMR δ 28.3, 30.8, 32.7, 33.1, 33.8, 40.1, 41.4, 49.7, 52.3, 56.6, 65.2, 79.7, 126.3, 126.7, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 138.6, 139.4, 155.6, 169.7, 172.0; HRMS calcd for $C_{29}H_{36}N_2O_5$ (MH^+) 493.2702, found 493.2698.

General Procedure for the Synthesis of 7-Benzyl and 5,7-Dibenzylindolizidinone Amino Esters 10 and 14 via Reductive Amination. Hydrogenation was performed by stirring a solution of azelate **6a** or **7a** (0.5 mmol, 100 mol %) in anhydrous EtOH (30 mL) and AcOH (3 mL) with palladium-on-carbon (10 wt %) under hydrogen atmosphere for 24 h. The mixture was filtered onto 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 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 and 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 1 M 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. Yields of (3*S*,6*S*,7*S*,9*S*)- and (3*S*,6*S*,7*R*,9*S*)-methyl 2-oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*S*,9*S*)- and (3*S*,6*S*,7*R*,9*S*)-**10**) obtained from hydrogenation of (4*R*)- and (4*S*)-**6a** at 1 and 9 atm of hydrogen are reported in Table 3. (3*S*,5*R*,6*S*,7*R*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-5,7-dibenzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,5*R*,6*S*,7*R*,9*S*)-**14**) was obtained in 20% overall yield from 280 mg of ketone **7a**.

General Procedure for the Hydrolysis of Methyl Esters 10, 11, and 14 with LiOH. A 0.012 M solution of indolizidinone amino ester **10**, **11**, or **14** (100 mol %) in dioxane (2 mL) was treated with 2 M LiOH (200 mol %), stirred at room temperature for 4 h, and partitioned between EtOAc (5 mL) and 1 M NaH_2PO_4 (5 mL). The aqueous layer was extracted with EtOAc (5 mL), and the combined organic layers were washed with brine, dried, and evaporated. The crude reaction mixtures were analyzed by proton NMR spectroscopy. Chromatography with 20:1 EtOAc:AcOH as eluant and evaporation of the collected fractions gave the pure indolizidinone amino acid.

(3*S*,6*S*,7*S*,9*S*)-2-Oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ((3*S*,6*S*,7*S*,9*S*)-2): 88% yield; $[\alpha]_D^{20}$ −5.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 1.44 (s, 9 H), 1.48−1.49 (m, 1 H), 1.71−1.72 (m, 1 H), 1.86−1.92 (m, 1

H), 2.27−2.40 (m, 3 H), 2.73 (d, 2 H, J = 6.3), 3.30−3.42 (m, 1 H), 4.14−4.26 (m, 1 H), 4.53 (d, 1 H, J = 8.9), 5.48 (d, 1 H, J = 5.5), 7.13 (d, 2 H, J = 7.0), 7.21−7.32 (m, 3 H); ^{13}C NMR δ 25.7, 26.9, 28.3, 34.1, 38.0, 46.9, 50.0, 58.3, 61.4, 79.9, 126.7, 128.7, 128.8, 131.9, 138.4, 155.7, 171.3, 172.8; HRMS calcd for $C_{21}H_{28}N_2O_5$ (MH^+) 389.2076, found 389.2062.

(3*S*,6*R*,7*S*,9*S*)-2-Oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ((3*S*,6*R*,7*S*,9*S*)-2): 83% yield; $[\alpha]_D^{20}$ −33.9 (*c* 0.38, $CHCl_3$); ^{1}H NMR δ 1.46 (s, 9 H), 1.78−1.87 (m, 2 H), 2.00−2.16 (m, 3 H), 2.39 (dd, 1 H, J = 8.3, 6.9), 2.52−2.68 (m, 1 H), 2.82 (dd, 1 H, J = 13.3, 5.5), 3.42−3.50 (m, 1 H), 4.12−4.33 (m, 1 H), 4.56 (d, 1 H, J = 8.5), 5.37 (bs, 1 H), 7.15−7.33 (m, 5 H); ^{13}C NMR δ 23.3, 25.8, 28.3, 29.7, 30.4, 33.9, 41.4, 57.7, 63.2, 77.2, 126.6, 128.7, 128.8, 138.6, 156.0, 170.8, 173.4; HRMS calcd for $C_{21}H_{29}N_2O_5$ (MH^+) 389.2076, found 389.2088.

(3*S*,5*R*,6*R*,9*S*)-2-Oxo-3-*N*-(BOC)amino-5-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ((3*S*,5*R*,6*R*,9*S*)-3): 73% yield; $[\alpha]_D^{20}$ 18.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9 H), 1.47−1.71 (m, 2 H), 1.96−2.06 (m, 2 H), 2.11−2.18 (m, 2 H), 2.39 (dd, 1 H, J = 8.3, 6.9), 2.52−2.68 (m, 1 H), 2.82 (dd, 1 H, J = 13.3, 5.5), 3.42−3.50 (m, 1 H), 4.12−4.33 (m, 1 H), 4.56 (d, 1 H, J = 8.5), 5.37 (bs, 1 H), 7.15−7.33 (m, 5 H); ^{13}C NMR δ 27.6, 28.3, 29.7, 31.7, 34.1, 39.8, 40.7, 49.4, 59.2, 62.6, 80.1, 126.6, 128.6, 129.0, 138.5, 155.6, 171.6; HRMS calcd for $C_{21}H_{29}N_2O_5$ (MH^+) 389.2076, found 389.2068.

(3*S*,5*R*,6*S*,7*R*,9*S*)-2-Oxo-3-*N*-(BOC)amino-5,7-dibenzyl-1-azabicyclo[4.3.0]nonane-9-carboxylic Acid ((3*S*,5*R*,6*S*,7*R*,9*S*)-4). Methyl ester **14** (10 mg, 0.02 mmol) in 5 mL of Et_2O was treated with $KOSiMe_3$ (2.9 mg, 0.022 mmol), stirred for 10 h at room temperature, treated with another portion (2.9 mg) of $KOSiMe_3$, 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 mg (83%) of acid **4**: $[\alpha]_D^{20}$ 52.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9 H), 1.72 (q, 1 H, J = 8.3), 1.92−2.14 (m, 3 H), 2.19−2.60 (m, 3 H), 2.65−2.93 (m, 3 H), 3.72 (dd, 1 H, J = 13.3, 5.5), 4.08−4.19 (m, 1 H), 4.52 (t, 1 H, J = 8.5), 5.37 (bs, 1 H), 6.90 (bs, 1 H), 7.15−7.33 (m, 10 H); ^{13}C NMR δ 28.3, 29.7, 30.2, 33.2, 33.7, 35.4, 40.4, 57.3, 68.2, 74.6, 126.6, 126.9, 128.7, 128.8, 128.9, 129.2, 138.1, 138.4, 156.2, 172.8; HRMS calcd for $C_{28}H_{35}N_2O_5$ (MH^+) 479.2546, found 479.2558.

(3*S*,6*S*,7*R*,9*S*)-2-Oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ((3*S*,6*S*,7*R*,9*S*)-2) was formed as a 60:40 mixture with (3*S*,6*S*,7*R*,9*R*)-**2** using the LiOH conditions for hydrolysis. Pure (3*S*,6*S*,7*R*,9*S*)-**2** was isolated from treatment of 0.01 mmol of (3*S*,6*S*,7*R*,9*S*)-**10** with one portion of $KOSiMe_3$ (0.02 mmol, 200 mol %) in ether under the conditions described above for acid **4**. Extraction with Et_2O, drying, evaporation, and filtration through silica gel using 20:1 EtOAc:AcOH as eluant gave 30 mg (77%) of acid (3*S*,6*S*,7*R*,9*S*)-**2**: mp 179−181 °C; $[\alpha]_D^{20}$ 98.0 (*c* 2.1, $CHCl_3$); ^{1}H NMR δ 1.44 (s, 9 H), 1.78−1.96 (m, 2 H), 1.99−2.11 (m, 3 H), 2.16 (dd, 1 H, J = 1.6, 13.7), 2.36−2.46 (m, 1 H), 2.53−2.59 (m, 1 H), 2.85 (dd, 1 H, J = 4.7, 13.5), 4.00 (dd, 1 H, J = 5.0, 11.1), 4.12−4.31 (m, 1 H), 4.53 (t, 1 H, J = 9.0), 5.60 (bs, 1 H), 7.14 (dd, 2 H, J = 6.8, 8.4), 7.17−7.34 (m, 3 H), 7.70 (bs, 1 H); ^{13}C NMR δ 20.6, 23.3, 28.3, 31.1, 33.8, 41.9, 51.8, 57.2, 63.1, 80.8, 126.5, 128.7, 128.9, 138.8, 156.4, 173.9, 176.3; HRMS calcd for $C_{21}H_{29}N_2O_5$ (MH^+) 389.2076, found 389.2088.

(3*S*,6*S*,7*S*,9*R*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*S*,9*R*)-10) Via Epimerization of (3*S*,6*S*,7*S*,9*S*)-10. A solution of $KN(SiMe_3)_2$ (0.3 mL, 0.15 mmol, 200 mol %, 1 M in toluene) was added over 15 min to a −50 °C solution of (3*S*,6*S*,7*S*,9*S*)-**10** (30 mg, 0.07 mmol, 100 mol %) in THF (1 mL). The reaction mixture was stirred for 1 h at −50 °C followed by 1 h at −20 °C and then partitioned between EtOAc (5 mL) and 1 M NaH_2PO_4 (5 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The organic layers were combined, washed with brine, dried, and evaporated to an oil (28 mg, 93% of a 1:3 ratio of (3*S*,6*S*,7*S*,9*S*)-**10**:(3*S*,6*S*,7*S*,9*R*)-**10** as determined by ^{1}H NMR) that was chromatographed using a gradient of hexane to 1:1 hexane:EtOAc as eluant. Evaporation of the collected fractions gave (3*S*,6*S*,7*S*,9*S*)-**10** followed by (3*S*,6*S*,7*S*,9*R*)-Methyl 2-oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo-[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*S*,9*R*)-**10**: $[\alpha]_D^{20}$ 33.2 (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 25.2, 26.9, 28.3, 34.7, 38.1, 48.4, 50.3, 52.4, 57.8, 61.4, 79.6, 126.6, 128.7, 128.8, 138.8, 155.7, 168.9, 172.1; HRMS calcd for $C_{28}H_{35}N_2O_5$ (MH^+) 479.2546, found 479.2558.

Enantiomeric Purity of (3*S*,6*S*,7*S*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,6*S*,7*S*,9*S*)-10). A solution of (3*S*,6*S*,7*S*,9*S*)-**10** (10 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.5 mL) and stirred for 4 h at room temperature. The volatiles were removed under vacuum. The residue was dissolved in THF (1 mL), treated with either (*R*)- or (*S*)-α-methylbenzyl isocyanate (7.3 mg, 0.05 mmol, 200 mol %) and Et_3N (7 μL, 0.05 mmol, 200 mol %), and heated at a reflux for 3 h. After cooling, the volatiles were removed under vacuum and the residue was directly examined by NMR. The limits of detection were determined by measuring the diastereomeric methyl ester singlets at 3.67 and 3.70 ppm in $CDCl_3$ and 3.28 and 3.38 in C_6D_6 in the 400 MHz ^{1}H NMR spectra. Less than 1% of the other diastereomer was detected in the spectra for ureas (1′*S*)- and (1′*R*)-**15**. Purification by chromatography using a gradient of pure hexane to pure EtOAc as eluant gave **15** having the following spectra.

Urea (1′*R*)-15: ^{1}H NMR δ 1.46 (d, 3 H, J = 6.8), 1.50−1.60 (m, 2 H), 1.82−1.93 (m, 1 H), 1.94 (dd, 1 H, J = 12.5, 9.2), 2.05 (dd, 1 H, J = 12.8, 6.1), 2.24−2.37 (m, 2 H), 2.65 (dd, 1 H, J = 13.7, 8.1), 2.76 (dd, 1 H, J = 13.4, 6.3), 3.32−3.38 (m, 1 H), 3.70 (s, 3 H), 4.20 (dd, 1 H, J = 5.4, 2.5), 4.41 (d, 1 H, J = 9.0), 4.83 (q, 1 H, J = 6.9), 5.11 (d, 1 H, J = 7.1), 5.51 (d, 1 H, J = 5.5), 7.12 (d, 2 H, J = 7.1), 7.20−7.34 (m, 8 H); ^{1}H NMR δ (C_6D_6) 1.18−1.21 (m, 1 H), 1.23 (d, 3 H, J = 6.8), 1.27−1.51 (m, 2 H), 1.71 (dd, 1 H, J = 13.2, 6.3), 1 97−2.06 (m, 1 H), 2.12−2.20 (m, 1 H), 2.25 (dd, 1 H, J = 13.5, 7.9), 2.37 (dd, 1 H, J = 13.7, 6.4), 2.87−2.93 (m, 1 H), 3.38 (s, 3 H), 4.02−4.12 (m, 1 H), 4.17 (d, 1 H, J = 9.2), 4.76−4.78 (m, 1 H), 4.98 (bs, 1 H), 5.50 (d, 1 H, J = 0.8), 6.61 (d, 1 H, J = 3.4), 6.86 (d, 2 H, J = 6.9), 6.98−7.36 (m, 8H).

Urea (1′S)-15: ^{1}H NMR δ 1.45 (d, 3 H, J = 6.8), 1.53−1.63 (m, 2 H), 1.74−1.78 (m, 1 H), 1.94 (dd, 1 H, J = 12.8, 8.8), 2.05 (dd, 1 H, J = 10.8, 6.0), 2.25−2.36 (m, 2 H), 2.65 (dd, 1 H, J = 13.8, 7.8), 2.76 (dd, 1 H, J = 13.7, 6.5), 3.34−3.39 (m, 1 H), 3.67 (s, 3 H), 4.25 (dd, 1 H, J = 5.5, 2.3), 4.42 (d, 1 H, J = 9.0), 4.83 (q, 1 H, J = 7.0), 5.10 (d, 1 H, J = 7.2), 5.51 (d, 1 H, J = 5.3), 7.12 (d, 2 H, J = 7.0), 7.21−7.33 (m, 8 H); ^{1}H NMR δ (C_6D_6): 1.29 (d, 3 H, J = 6.9), 1.30−1.55 (m, 3 H), 1.65 (dd, 1 H, J = 12.9, 6.1), 1.93−2.05 (m, 1 H), 2.12−2.24 (m, 2 H), 2.31 (dd, 1 H, J = 13.4, 7.5), 2.78−2.83 (m, 1 H), 3.28 (s, 3 H), 4.19 (d, 1 H, J = 9.2), 4.27 (dd, 1 H, J = 15.9, 6.6), 4.91 (q, 1 H, J = 7.3), 5.20 (bs, 1 H), 5.71 (d, 1 H, J = 3.2), 6.40 (d, 1 H, J = 1.4), 6.84 (d, 2 H, J = 6.9), 6.99−7.24 (m, 8 H).

Enantiomeric purity of (3*S*,5*R*,6*S*,7*R*,9*S*)-Methyl 2-oxo-3-*N*-(BOC)amino-5,7-dibenzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate ((3*S*,5*R*,6*S*,7*R*,9*S*)-14) was determined on 3 mg samples of **14** in a similar manner as described for **10** above. The limits of detection were determined on the crude residue by measuring the diastereomeric methyl ester singlets at 3.71 and 3.79 ppm in $CDCl_3$ as well as 3.36 and 3.42 ppm in C_6D_6 in the 400 MHz ^{1}H NMR. Less then 1% of the other diastereomer was detected in the spectra for ureas (1′*S*)- and (1′*R*)-**16**. Purification by chromatography using a gradient of pure hexane to pure EtOAc as eluant gave **16** having the following spectra.

Urea (1′*R*)-16: ^{1}H NMR δ 1.46 (d, 3 H, J = 6.9), 1.61 (m, 2 H), 1.77 (d, 1 H, J = 13.9), 1.88−2.08 (m, 4 H), 2.31−2.37 (m, 2 H), 2.46 (t, 1 H, J = 13.4), 2.65 (dd, 1 H, J = 8.3, 13.9), 2.72 (dd, 1 H, J = 3.4, 13.1), 2.89 (dd, 1 H, J = 13.5, 6.7), 3.55 (dd, 1 H, J = 10.0, 5.2), 3.79 (s, 3 H), 4.31−4.35 (m, 2 H), 4.84 (t,

1 H, J = 6.9), 5.0 (d, 1 H, J = 4.8), 5.45 (bs, 1 H), 6.9 (d, 2 H, J = 7.0), 7.15−7.36 (m, 10 H).

Urea (1′*S*)-16: ^{1}H NMR δ 1.4 (d, 3 H, J = 6.9), 1.53 (m, 2 H), 1.81 (dd, 1 H, J = 15.4, 1.4), 1.91−2.10 (m, 4 H), 2.33−2.39 (m, 1 H), 2.46−2.57 (m, 2 H), 2.70 (dd, 1 H, J = 8.0, 13.9), 2.81 (dd, 1 H, J = 4.0, 13.2), 2.94 (dd, 1 H, J = 13.8, 5.6), 3.60 (dd, 1 H, J = 10.0, 4.7), 3.71 (s, 3H), 4.32−4.37 (m, 2 H), 4.90 (t, 1 H, J = 6.9), 5.01 (d, 1 H, J = 4.8), 5.63 (bs, 1 H), 6.9 (d, 2 H, J = 7.0), 7.17−7.34 (m, 10 H).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **2**−**4**, **6**, **7**, **9**−**12**, and **14**; ^{1}H NMR spectra of **15** and **16**; COSY and NOESY/ROESY spectra of **10**, **11** and **14**; and crystallographic data for **10** (68 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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