JOC Article

Conformationally Constrained Dipeptide Surrogates with Aromatic Side-Chains: Synthesis of 4-Aryl Indolizidin-9-one Amino Acids by Conjugate Addition to a Common α,ω-Diaminoazelate Enone Intermediate

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Four methyl 9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylates (**11**, 4-Ph-I^{9}aa-OMe) were synthesized from (2*S*,8*S*,5*E*)-di-*tert*-butyl-4-oxo-5-ene-2,8-bis[*N*-(PhF)amino]azelate [(5*E*)-**7**, PhF = 9-(9-phenylfluorenyl)] via a seven-step process featuring a conjugate addition/reductive amination/lactam cyclization sequence. Various nucleophiles were used in the conjugate addition reactions on enone (5*E*)-**7** as a general route for making α,ω-diaminoazelates possessing different substituents in good yield albeit low diastereoselectivity except in the case of aryl Grignard reagents (9/1 to 15/1 drs). 6-Phenylazelates (6*S*)-**8d** and (6*R*)-**8d** were separated by chromatography and diastereoselective precipitation and independently transformed into 4-Ph-I^{9}aa-OMe. From (6*S*)-**8d**, (2*S*,4*R*,6*R*,8*S*)-4-Ph-I^{9}aa-OMe **11** was prepared selectively in 51% yield. Reductive amination of (6*R*)-**8d** provided the desired pipecolates **9** along with desamino compound **10**, which was minimized by performing the hydrogenation in the presence of ammonium acetate. Subsequent ester exchange, lactam cyclization, and amine protection provided three products (2*R*,4*S*,6*S*,8*R*)-, (2*R*,4*S*,6*S*,8*S*)-, and (2*S*,4*S*,6*R*,8*S*)-4-Ph-I^{9}aa-OMe **11** in 10, 6, and 6% yields, respectively, from (6*R*)-**8d**. Ester hydrolysis of (2*S*,4*R*,6*R*,8*S*)-**11** furnished 4-phenyl indolizidin-9-one *N*-(Boc)amino acid **3** as a novel constrained Ala-Phe dipeptide surrogate for studying conformation−activity relationships of biologically active peptides.

Introduction

Turn motifs play important roles in the recognition and activity of biologically relevant peptides and proteins.[1] Conformationally constrained mimics of peptide turns have thus become important synthesis targets because of their utility for studying the relationship between structure and function as well as their potential to improve the pharmacological properties of the native peptide.[2] Among turn mimics,[3] azabicyclo[X.Y.0]alkane amino acids have proven to be useful for constraining peptide backbone and side-chain geometry for studying structure−activity relationships.[4−9]

In the context of our research on peptide mimicry, we have employed different azabicyclo[X.Y.0]alkane amino acids in structure−activity studies of various peptides.[10−12] For example, introduction of indolizidin-9-one amino acid **1** (I^{9}aa) into a Leu-enkephalin (YGGFL) analogue as a rigid surrogate of its Gly-Gly residue produced an active mimic that exhibited greater duration of action relative to the parent peptide.[10] The circular dichroism spectrum of the indolizidin-9-one Leu-enkephalin analogue also exhibited a curve shape characteristic of a turn conformation in support of the importance of a turn about the glycine residues for activity of the native peptide.

Approaches for installing side-chain functionality at the different ring-positions on the indolizidin-9-one amino acid may furnish improved dipeptide surrogates for peptide mimicry. Although methodology is abundant for adding side-chain functionality to the 3-,[5e,i,x] 4-,[5a,b,d,l,s,v] 5-,[5c,6a,b] 6-,[5o] 7-,[5o,p,q,u,y,6a,b,c] and 8-positions[5u,v] of the related fused 6,5-ring system, indolizidin-2-one amino acid **2** (I^{2}aa), few methods have been reported for adding side-chains onto its fused 5,6-ring counterpart, indolizidin-9-one **1** (Figure 1).[7b,c] For example, we have previously reported on three effective routes for appending a series of aliphatic as well as a set of heteroatomic side chains onto the 5- and 7-positions of indolizidin-2-one amino acid, using a common β-keto ester starting material obtained from the Claisen condensation of α-*tert*-butyl γ-methyl *N*-(PhF)glutamate (Scheme 1).[6] On the other hand, Boc-IBTM **4** (Figure 1), a condensation product of the Asp-Trp dipeptide represents a rare example of an indolizidin-9-one amino acid possessing side-chain functionality.[7b] Replacement of the D-Phe-Pro residue of gramicidin S (*c*-[D-Phe-Pro-Val-Orn-Leu]$_2$) with IBTM has produced analogues with potency similar to the parent antibiotic,[13] contingent on the indolizidin-9-

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(4) Pyrrolizidinone amino acids: Dietrich, E.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6988−6996 and references therein.

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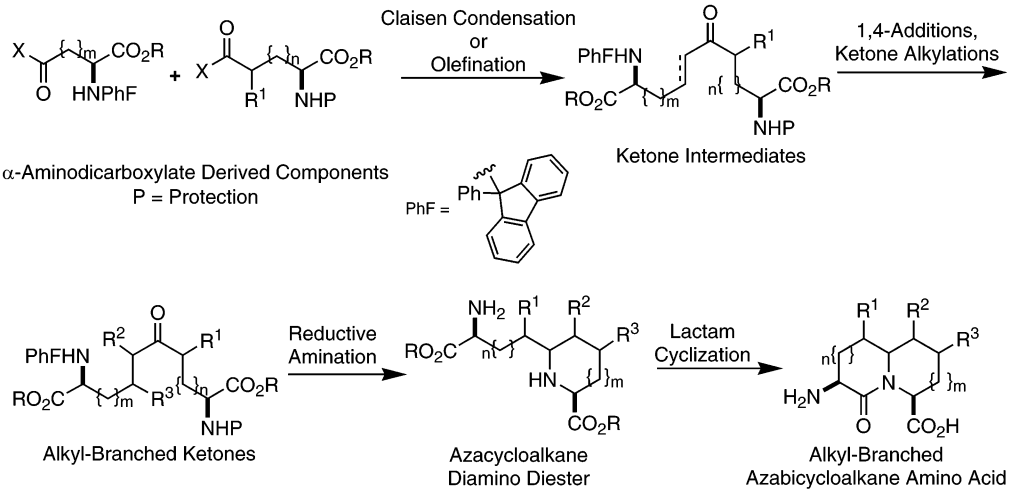
SCHEME 1. General Strategy for Azabicyclo[X.Y.0]alkane Amino Acid Synthesis



one ring-fusion stereochemistry. The promising biological activity of the enkephalin analogue (Tyr-I[9]aa-Phe-Leu) and antibiotic peptide analogue (*c*-[IBTM-Val-Orn-Leu-D-Phe-Pro-Val-Orn-Leu]), possessing indolizidin-9-one amino acids **1** and **4**, illustrates their effectiveness as mimics of secondary structure and suggests similar potential for peptide mimicry with related analogues possessing side-chain ring-substituents.

In our general strategy for constructing indolizidin-9-one amino acid systems, linear α,ω-diaminoazelate enone (5*E*)-**7** was converted to the heterocycle via a reductive amination/lactam cyclization sequence (Scheme 1).[7a] Conjugate addition (1,4-addition) reactions on enone (5*E*)-**7** have now provided a series of α,ω-diaminoazelate ketones **8** for conversion to a variety of substituted indolizidin-9-ones.[14] Conditions for the conversion of

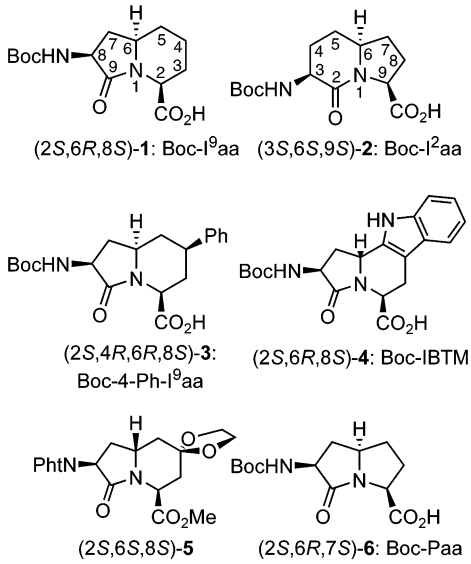


FIGURE 1. Representative azabicylo[X.Y.0]alkanone amino acids.[4,7a−c,9]

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SCHEME 2. Synthesis of 6-Substituted Diaminoazelates

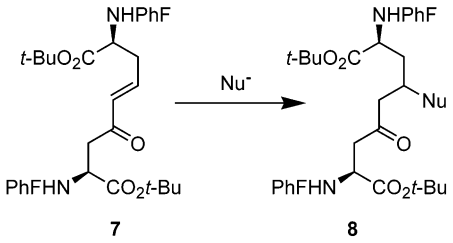

TABLE 1. Conjugate Addition on Enone 7

entry	nucleophile	product [% yield, dr]
1	$MeO_2CCH_2CO_2Me$/NaH	**8a** [77, 1:1]
2	KCN/18Crown6	**8b** [68, 1:1]
3	CH_3NO_2/DBU	**8c** [94, 2:1]
4	$Ph_2CuCN(MgBr)_2$	**8d** [98, 1:2]
5	$PhCu.S(CH_3)_2$	**8d** [74, 1:3]
6	$(p(CH_3O)\text{-}C_6H_4)_2CuCN(MgBr)_2$	**8e** [98, 1:2]
7	*i*-$Pr_2CuCN(MgBr)_2$	**8f** [80, 5:1]
8	*i*-PrMgBr/CuI (cat)	**8d** [83, 5:1]
9	PhMgBr	**8d** [86, 9:1]
10	$PhMgBr/MgBr_2$	**8d** [100[a], 15:1]
11	$p(CH_3O)\text{-}C_6H_4$-MgBr	**8e** [82, 10:1]
12	*i*-PrMgBr	**8f** [71[b], 3:1]
13	*i*-$PrMgBr/MgBr_2$	**8f** [80[a], 6:1]

[a] % conversion. [b] 1,2-Adduct (23%) was also isolated.

ketones **8** into 4-aryl indolizidin-9-one amino acids are now presented by the syntheses of constrained Ala-Phe dipeptide surrogate **3** (*N*-Boc-4-Ph-I[9]aa). In particular, we have developed an effective six-step synthesis of (2*S*,4*R*,6*R*,8*S*)-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylic acid **3** from (5*E*)-**7** with 42% overall yield.

Results and Discussion

Conjugate addition reactions on enone (5*E*)-**7** were studied using various nucleophiles as a general route for making α,ω-diaminoazelates possessing different substituents (Scheme 2). Various nucleophiles reacted effectively on enone (5*E*)-**7** in good yield albeit with low diastereoselectivity. For example, methylmalonate, cyanide, and nitromethane all were introduced onto ketone (5*E*)-**7** in good yield and from 1:1 to 2:1 diastereoselectivity (entries 1−3). Different alkyl and aryl substituents were introduced as organocopper species, namely, higher order cyano cuprates, aryl copper reagents, and Grignard reagents in the presence of catalytic amounts of copper. These various conditions employing copper reagents gave generally good yield and low diastereoselectivity (2/1 to 5/1, entries 4−8), with limited influence of the copper species on the diastereomeric ratio observed for the final ketone.[14]

Remarkable regio- and diastereoselectivity was observed when ordinary aryl Grignard reagents were added to ketone **7**.[14] For example, phenylmagnesium bromide added selectively in a 1,4 manner to provide a 9:1 ratio in favor of (6*R*)-**8d** (entry 9). Furthermore, the addition of metal salts to the reaction mixture was shown to give a significant improvement in the diastereoselectivity. For example, addition of magnesium bromide prior to reaction with the Grignard reagent increased the diastereoselectivity of the phenyl and *iso*-propyl products (6*R*)-**8d** and (6*R*)-**8f** up to ratios of 15:1 and 6.5:1, respectively (entries 10 and 13).

Diastereomeric mixtures from the conjugate addition were generally difficult to separate using chromatography. However, in the case of the phenyl analogue, a ternary eluant (45/45/10, *iso*-octane/toluene/*iso*-propyl ether) was developed that provided baseline separation of the diastereomers on 100 mg scale. Later, we found that 1.8 g of (6*S*)-**8d** could be precipitated diastereoselectively from 3.1 g of a 2/1 mixture of (6*S*)- and (6*R*)-**8d** in a 0.035 M solution of *i*-PrOH containing 1% H_2O. This method provided each isomer in a diastereomeric ratio of 13 to 1. Diastereomerically enriched samples (13:1 and 1:13) of (6*S*)- and (6*R*)-**8d** were used in subsequent reductive amination/lactam cyclization sequences described below. Stereochemical assignment at the 6-position of compound **8d** was made on the basis of assignments for (2*S*,4*R*,6*R*,8*S*)-4-phenylindolizidin-9-one **11**, from cyclization of (6*S*)-**8d**, as characterized below.

(2*S*,6*R*,8*S*)-Di-*tert*-butyl-4-oxo-6-phenyl-2,8-bis[*N*-(PhF)amino]azelate [(6*S*)-**8d** (13:1 dr)] was converted to (2*S*,4*R*,6*R*,8*S*)-methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylate [(2*S*,4*R*,6*R*,8*S*)-4-Ph-I[9]aa-OMe, **11**] in 51% overall yield by our reductive amination/lactam cyclization protocol (Scheme 3).[7a] Hydrogenation using 10% palladium-on-carbon in a mixture of EtOH and AcOH (9/1) provided the trisubstituted pipecolate (2*S*′,2*S*,4*R*,6*R*)-**9** as a single diastereoisomer as determined by ^1H and ^{13}C NMR spectroscopy. The *tert*-butyl esters were then removed using concentrated HCl and replaced by methyl esters using HCl gas in MeOH, as followed by ^1H NMR spectroscopy by monitoring the methyl ester singlets at 3.90 and 3.84 ppm, as well as by TLC. Lactam cyclization was performed by treating the diester in MeOH with Et_3N at reflux until NMR spectroscopy showed replacement of the two methyl ester singlets by a new singlet at 3.86 ppm (approximately 24 h). The amine was then protected with Boc_2O and Et_3N in CH_2Cl_2. Chromatography of the final residue provided (2*S*,4*R*,6*R*,8*S*)-4-Ph-I[9]aa-OMe **11** in 51% overall yield from ketone (6*S*)-**8d**.[15] Ester (2*S*,4*R*,6*R*,8*S*)-**11** was then converted to the corresponding *N*-(Boc)amino acid (2*S*,4*R*,6*R*,8*S*)-**3**, suitable for application in peptide synthesis, using potassium trimethylsilanolate in Et_2O for 1 h at room temperature (Scheme 3).

(2*S*,6*R*,8*S*)-Di-*tert*-butyl-4-oxo-6-phenyl-2,8-bis[*N*-(PhF)amino]azelate [(6*R*)-**8d** (13:1 dr)] was initially hydrogenated using the same conditions as in the synthesis of pipecolate (2*S*′,2*S*,4*R*,6*R*)-**9** from ketone (6*S*)-**8d**. The desired pipecolates **9** and their desamino counterparts **10** were isolated as mixtures of diastereoisomers in 27 and 56% respective yields (Scheme 4). Loss of the amine function was presumed to arrive from imine to enamine tautomerization followed by β-elimination of ammonium ion to form the α,β-unsaturated imine, which underwent subsequent reduction.[16] In related hydrogenation processes, we have reported β-elimination of nitrogen from a β-amino imine intermediate[4] and of oxygen

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(15) Using the 13/1 diastereomeric mixture, (2*R*,4*S*,6*R*,8*S*)-**11** was isolated in 3% yield from the residual (6*R*)-**8d**.

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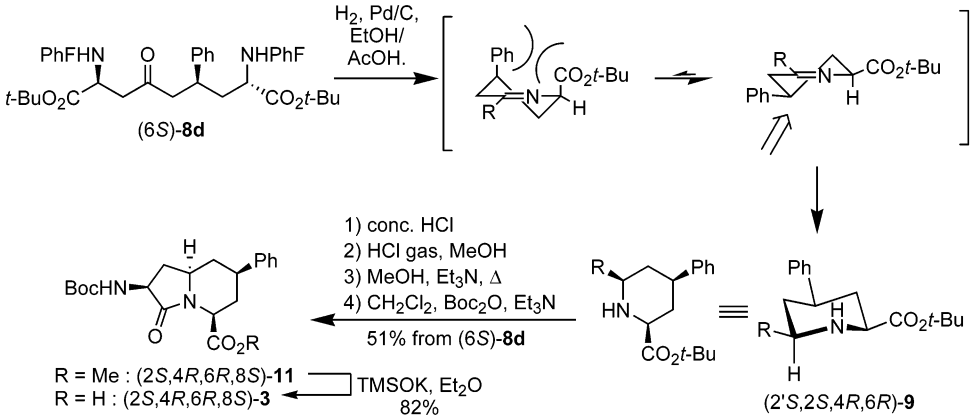
SCHEME 3. Synthesis of 4-Ph-I^{9}aa-OMe (2*S*,4*R*,6*R*,8*S*)-11 via Reductive Amination of (6*S*)-8d



SCHEME 4. Hydrogenation of (6*R*)-8d Proceeded with *β*-Elimination

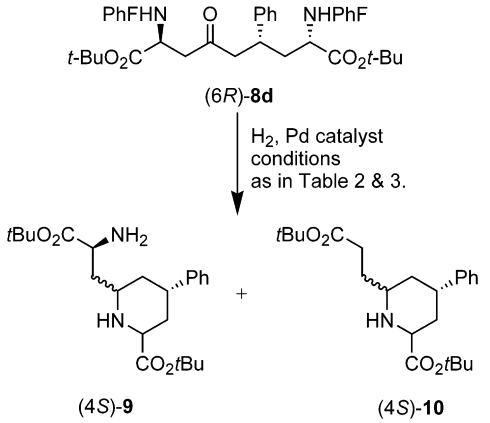


TABLE 2. Influence of Pd Catalyst on Hydrogenation of (6*R*)-8d

entry	catalyst[a]	dr of **9** (6*S*:6*R*)	ratio of **9**:**10**	dr of **10**
1	Pd/C 10% wet	1/3	1/1	1/3
2	Pd/C 10%	1/1	1/1	1/2
3[b]	$Pd(OH)_2$/C 20%	1/1	1/2[c]	1/2[d]
4	Pd/C 20% eggshell	3/1	1/4	3/1

[a] Hydrogenation was performed in EtOH/AcOH (9/1) under 9 atm of H_2. [b] When MeOH/EtOAC (7/3) was employed, the ratio for **9** was 1:4 and that for **10** was 1:4. [c] At 0 °C, a 1:4 ratio was obtained. [d] At 50 °C, a 9:1 ratio was obtained.

from *β*-hydroxy, *β*-silyloxy, and *β*-acetoxy imine intermediates.[6b,16] To prevent *β*-elimination, different proton sources, catalysts, and reaction temperatures were studied. For example, four forms of Pd catalyst were examined at 9 atm of H_2 in 9/1 EtOH/AcOH (Table 2). Their effect on the elimination process under these conditions was significant, and the ratio of pipecolate **9** to *β*-elimination product **10** changed from 1:1 with wet Pd/C (10% w/w) up to 1:4 using "eggshell" Pd/C (20 wt %).

In our synthesis of pyrrolizidinone amino acid **6**, a similar loss of amine due to a *β*-elimination process was inhibited significantly by diminishing the quantity of acid employed in the hydrogenation with Pd/C as catalyst.[4] In the case of (6*R*)-**8d**, no reaction was observed when using only 100 mol % AcOH, and a 1:1 ratio of **9** and **10** was obtained when using 100 mol % of pyridinium *para*-toluenesulfonate (Table 3, entries 2 and 3).

Practical conditions for obtaining the diamino compound **9** were found when the reaction mixture was saturated with ammonium acetate (entry 4), which according to Le Chatelier's law was expected to suppress the *β*-elimination product. In the absence of added AcOH, this saturation technique was not always reproducible (entries 4 and 5), such that a protocol was developed in which the ammonium acetate was first suspended in and dried by evaporation from toluene and then left to sit under high vacuum overnight. The resulting white crystalline solid was then employed in the hydrogenation of (6*R*)-**8d** using Pd/C in a solvent system of EtOH/THF/AcOH (7/3/0.1) for 48 h, which provided selectively the pipecolates **9**. Desamino compound **10** was not detectable by ^{1}H and ^{13}C NMR spectroscopy of the crude product, yet was visible when concentrated samples were spotted on TLC.

As described above for the synthesis of (2*S*,4*R*,6*R*,8*S*)-**11**, the *tert*-butyl esters of pipecolates **9** were removed using concentrated HCl and replaced with methyl esters employing HCl gas in MeOH (Scheme 5). Because the ^{1}H NMR spectrum was too complex, formation of methyl esters was best monitored by TLC. The lactam cyclization was then performed in MeOH at reflux with Et_3N for 48 h followed by amine protection using Et_3N and $(Boc)_2O$ in CH_2Cl_2 for 12 h. After two chromatographies, eluting first with 60/40 hexane/EtOAc, followed by 85/10/5 hexane/*i*-Pr_2O/*i*-PrOH, three diastereomeric products, (2*R*,4*S*,6*S*,8*S*)-, (2*R*,4*S*,6*R*,8*S*)-, and (2*R*,4*S*,6*S*,8*R*)-4-Ph-I^{9}aa **11** were isolated in 6, 6, and 10% overall yields, respectively, from (6*R*)-**8d**.

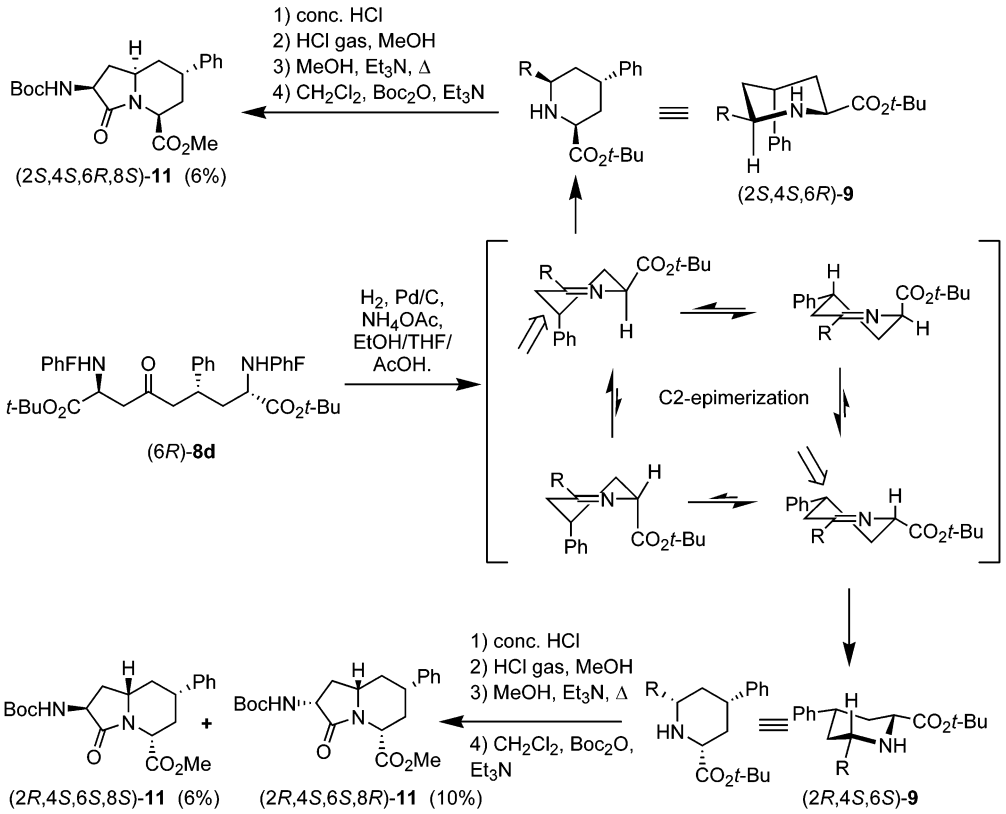
Enantiomeric Purity and Stereochemical Assignment of Indolizidines 11. The configurational integrity of the 4-phenyl-indolizidin-9-one amino acid was evaluated by the preparation and spectral analysis of diastereomeric *N*-(*p*-toluenesulfonyl)prolinamides **12** using (2*S*,4*R*,6*R*,8*S*)-4-Ph-I^{9}aa-OMe **11**, which was obtained from the hydrogenation/lactam cyclization sequence using (6*S*)-**8d**. After cleavage of the Boc protecting group using HCl gas, the resulting hydrochloride salt was treated with Et_3N and coupled respectively to L- and DL-*N*-(*p*-tolylsulfonyl)prolyl chloride in CH_2Cl_2 (Scheme 6). Observation of the diastereomeric methyl ester singlets at 3.75 and 3.73 ppm by 400 MHz ^{1}H NMR spectroscopy in C_6D_6 during incremental additions of the diastereomeric mixture demonstrated prolylamide (2′*S*)-**12** to be of >98% diastereomeric excess. Hence, (2*S*,4*R*,6*R*,8*S*)-4-

TABLE 3. Influence of the Proton Source on Hydrogenation of (6*R*)-8d

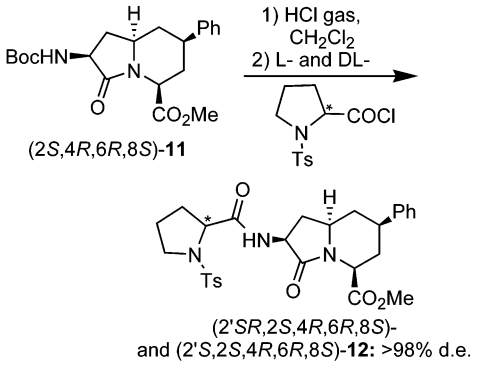
entry	catalyst	solvent	proton source	dr of **9** of (6*S*/6*R*)	ratio of **9**:**10**	dr of **10**
1	Pd/C 10%	EtOH	AcOH (excess)	1/1	1/2	2/1
2	Pd/C 10%	EtOH/THF (8/2)	AcOH (1 equiv)		nr	
3	Pd/C 10%	EtOH/THF (8/2)	PPTS (1 equiv)	1/4	1/1	1/4
4	Pd/C 10%	EtOH/THF (7/3)	NH_4OAc (200 equiv)	4/1	6/1	1/1
5	Pd/C 10%	EtOH/THF (7/3)	NH_4OAc (dry, 200 equiv)[a]		nr	
6	Pd/C 10%	EtOH/THF (7/3)	NH_4OAc (dry, 200 equiv)[a] AcOH (1%/solv)	3/1	>100/1	
7	$Pd(OH)_2$/C 20%	MeOH/EtOAc (7/3)	NH_4OAc (200 equiv)	3/1	4/1	1/1

[a] Ammonium acetate was dried as discussed in the Experimental Section.

SCHEME 5. Synthesis of (4*S*)-4-Ph-I[9]aa-)OMe 11 via Reductive Animation of (6*R*)-8d



SCHEME 6. Enantiomeric Purity of (2*S*,4*R*,6*R*,8*S*)-11



Ph-I[9]aa-OMe **11** as well as its corresponding acid (2*S*,4*R*,6*R*,8*S*)-**3** are presumed to be of similarly high enantiomeric purity.

The relative stereochemistry of the different diastereoisomers of **11** was established using one- and two-dimensional NMR experiments (Figure 2). The majority of the NMR signals were well resolved at distinct chemical shifts (Table 4). All protons were assigned using COSY and HMQC experiments, which established their linear sequence around the bicycle from the carbamate NH to the C-2 proton. Diastereomeric protons cis and trans to the carboxylate at C-2 are designated β and α, respectively. The assignments of the α and β protons at C-3, C-5, and C-7 were made using their signal multiplicity and coupling constants and supported by NOE observed in the NOESY experiments.

In the ^{1}H NMR spectrum of (2*S*,4*R*,6*R*,8*S*)-4-Ph-I[9]aa-OMe **11** in C_6D_6, the protons at C-2, C-3$_\beta$, C-4, C-5$_\beta$, and C-6 all exhibited large coupling constants (10.4−12.5 Hz) indicative of their axial position on the pipecolate, which adopted a chair conformation (Figure 2). For example, the C-2 proton was observed as a doublet of doublets and shared, respectively, vicinal coupling constants of 3.4 and 11.2 Hz with the C-3$_\alpha$ and C-3$_\beta$ protons, corresponding to dihedral angles of ±60° and ±160°.[17] The pseudoaxial conformation of the C-7$_\beta$ proton in the five-member lactam was assigned on the basis of observation of an

TABLE 4. ^{1}H NMR Data for *N*-(*Boc*)-4-Phenyl-indolizidin-9-one Amino Esters 11

	2	3α	3β	4	5α	5β	6	7α	7β	8	NH	Me	*t*-Bu
(2*S*,4*R*,6*R*,8*S*)-**11**	3.48 dd	1.70 d	1.80 q	2.08 t	1.31 d	1.00 q	2.34 t	2.25 br s	1.11 q	4.16 m	5.00 br d	3.62	1.42
(C_6D_6, 400 MHz)	3.4, 11.2	12.5	12.3	11.9	9.6	11.7	10.4		11.3		5.2		
(2*R*,4*S*,6*S*,8*S*)-**11**	3.88 dd	2.10 d	1.89 q	2.80 tt	2.06 d	1.52 q	3.74 m	2.24 t	4.17 m	5.01 br s	3.80	1.44	
($CDCl_3$,600 MHz)	3.5, 12.0	13.4	12.6	3.3, 12.4	12.9	12.3		6.9					
(2*S*,4*S*,6*R*,8*S*)-**11**	4.26 t	1.93 ddd	1.56 m	2.77 br t	1.56 m	1.82 ddd	2.91 m	2.42 m	1.16 q	4.35 m	5.12 d	3.37	1.43
(C_6D_6, 400 MHz)	5.0	3.7, 5.9, 9.6				9.7, 12.3, 13.9			11.0		6.0		

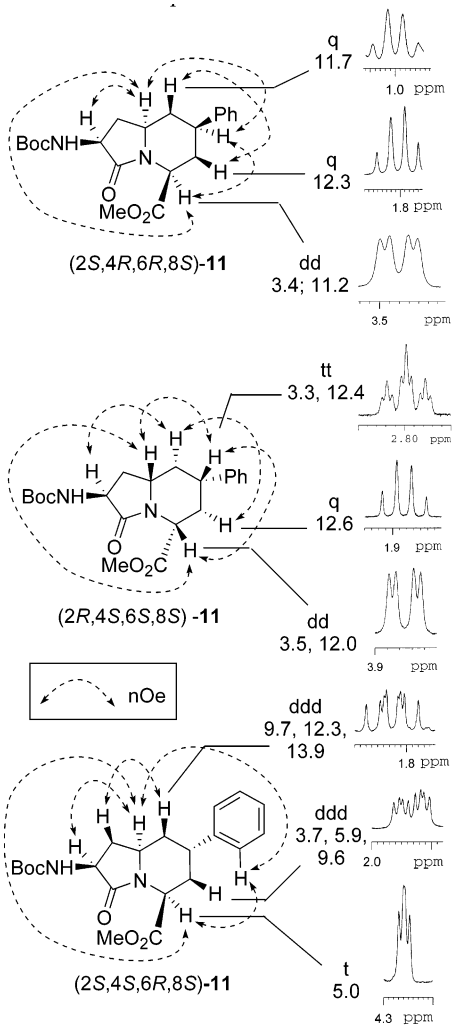


FIGURE 2. NOE correlations observed in the NOESY NMR spectra of **11**.

apparent quadruplet, due to similar vicinal couplings with the pseudoaxial C-8 proton and the axial C-6 proton as well as a geminal coupling with the C-7α proton. The concave shape of the bicyclic system and the (4*R*)-stereochemistry, which positions the C-2, C-4, C-6, and C-8 protons all on the same face, were supported by NOESY experiments. Characteristic NOE correlations were observed between the three piperidine axial protons at C-2, C-4, and C-6. In addition, NOE was measured between the C-6 and C-8 protons on one face as well as between the axial C-3$_\beta$ and C-5$_\beta$ protons on the other face.

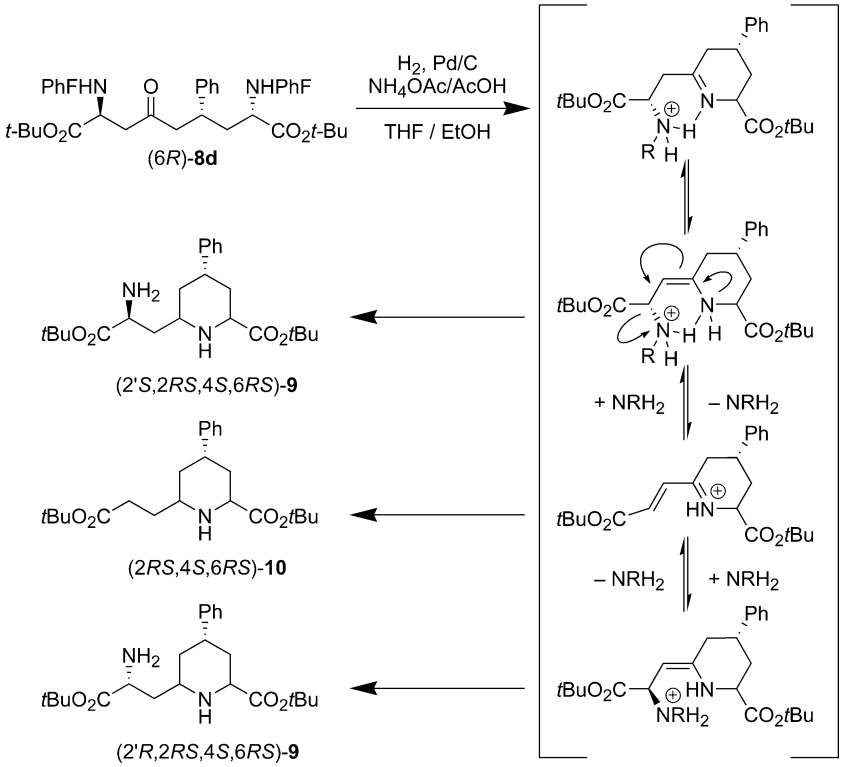
In the ^{1}H NMR spectrum of (2*R*,4*S*,6*S*,8*S*)-4-Ph-I^{9}aa-OMe **11**, the first of the two minor isomers from the cyclization of (6*R*)-**8d**, the C-2, C-3$_\beta$, C-4, and C-5$_\beta$ protons all exhibited large coupling constants in $CDCl_3$ (11.9 to 13.4 Hz), indicative of their axial position on the pipecolate, which adopted a chair conformation. For example, the C-4 proton was observed as a triplet of triplets with coupling constants of 3.3 and 12.4 Hz corresponding to dihedral angles close to ±61° with both the C-3α and C-5α protons and close to ±175° with both of the C-3β and C-5β protons.[16] With the (4*S*)-phenyl substituent sitting equatorial, the data suggested epimerization at C-2 and 2*R*,4*S*,6*S* stereochemistry for the pipecolate ring. The 2*R*,4*S*,6*S*,8*S* configuration was confirmed using NOESY experiments in which NOEs were observed between the axial C-2, C-4, and C-6 protons, confirming complete equatorial substitution about the piperidine cycle. Additional NOE between the C-5$_\beta$ and C-8 protons on the opposite face established the 8*S* stereochemistry.

In the ^{1}H NMR spectrum of the second minor isomer from cyclization of (6*R*)-**8d**, (2*S*,4*S*,6*R*,8*S*)-4-Ph-I^{9}aa-OMe **11**, in C_6D_6, the coupling constant pattern for protons in the piperidine cycle differed from that of a chair conformation. For example, the C-2 proton exhibited a small 5 Hz coupling constant and appeared as a triplet, suggesting an axial position for the ester function. The C-5β proton was observed as a double doublet of doublets (ddd) with three large coupling constants (9.7, 12.3, 13.9 Hz), indicative of a pseudoequatorial position for the phenyl ring. The C-7$_\beta$ proton exhibited an 11.0 Hz coupling constant and quadruplet multiplicity indicative of a trans relationship with the C-8 and C-6 protons. The C-6 stereocenter was assigned the 6*R* relative configuration because, in the NOESY spectrum, correlations were observed between the C-8 and C-6 protons and between the C-6 and C-2 protons, in agreement with the 2*S*,6*R*,8*S* relative stereochemistry. Additional NOEs were observed between the C-7β proton and both the carbamate NH and the C-5β protons, as well as between ortho aromatic protons and both C-2 and C-6 protons, which helped to confirm the stereochemistry of (2*S*,4*S*,6*R*,8*S*)-**11**.

The diverse NMR data confirmed the presence of (2*S*,4*R*,6*R*,8*S*)-4-Ph-I^{9}aa-OMe **11**, which might come from residual (6*S*)-**8d** in the hydrogenation of (6*R*)-**8d**; however, the mass of isolated product exceeded expectations. The presence of its enantiomer, (2*R*,4*S*,6*S*,8*R*)-**11**, coming from epimerization at both the C-2 and C-8 stereocenters during transformation of (6*R*)-**8d** was validated by coupling L-*N*-(*p*-tolylsulfonyl)-prolyl chloride to the isolated sample of (2*S*,4*R*,6*R*,8*S*)-4-Ph-I^{9}aa-OMe **11**; the amide products **12** were shown to be of only 33% diastereomeric excess (66:33 dr).

(17) Calculated using the equation $^3J = K\cos^2\phi$; where $K_{a-a} = 12.5$ Hz, $K_{a-e} = K_{e-a} = 14.3$ Hz, and $K_{e-e} = 12.9$ Hz. ϕ is the dihedral angle, and *K* values are calculated from 1,3,5-trimethyl-cyclohexane. (a) Xie, X.-Q.; Melvin, L. S.; Makriyannis, A. *J. Biol. Chem.* **1996**, *271*, 10640−10647. (b) Kriwacki, R. W.; Makriyannis, A. *Mol. Pharmacol.* **1989**, *35*, 495−503. (c) Booth, H. *Prog. NMR Spectrosc.* **1969**, *5*, 149−381.

SCHEME 7. Hydrogenation of (6*R*)-8d May Proceed with *β*-Elimination as well as C-2 and C-8 Epimerization



Stereoselection and Epimerization. In the synthesis of the parent indolizidin-9-one system, I[9]aa **1**, the six-membered ring iminium ion was preferentially reduced on the face opposite the ester, leading predominantly to the concave diastereomer (9:1).[7a] In the synthesis of (4*R*)-4-Ph-I[9]aa, the phenyl substituent works in harmony with the ester function to favor their pseudoequatorial orientation in the iminium ion such that attack occurs exclusively to give the concave 6*R* diastereoisomer (Scheme 3). In the case of the (4*R*)-phenyl isomer, the phenyl and carboxylate substituents battle to avoid pseudoaxial orientations in the iminium ion, such that two conformers exist in equilibrium, with a likely preference for the conformer having the phenyl group positioned equatorially (Scheme 5). Hydrogenation of the more stable iminium ion favored formation of the piperidine in a chair conformer having the C-4 and C-6 substituents positioned equatorially, which was transformed into (2*R*,4*S*,6*S*,8*R*)- and (2*R*,4*S*,6*S*,8*S*)-4-Ph-I[9]aa-OMe **11**.[18] Reduction of the less stable iminium ion having the phenyl group positioned pseudoaxially favored a piperidine in a chair conformer with the C-2 and C-6 substituents positioned equatorially, which furnished (2*S*,4*S*,6*R*,8*S*)-4-Ph-I[9]aa-OMe **11**.

Epimerization of one and both α-amino carboxylate centers of azelate (6*R*)-**8d** occurred during the synthesis of (2*R*,4*S*,6*S*,8*S*)- and (2*R*,4*S*,6*S*,8*R*)-4-Ph-I[9]aa-OMe **11**, respectively. Epimerization of different stereocenters has been sometimes reported in the syntheses of mono- and bicyclic amino acids. In particular, the α-proton of cyclic amino acids has been removed under basic conditions[7c,19,20] contingent on the nitrogen protecting group. Imine derivatives of α-amino acids are particularly sensitive to α-epimerization even in the absence of base[21] and as iminium ions in acidic conditions.[19] To the best of our knowledge, no α-epimerization of iminium ion intermediates has been previously reported in applications of reductive aminations to form substituted prolines and pipecolates using catalytic hydrogenation under mildly acidic conditions. Although a detailed assessment of the source of C-2 epimerization was not possible because the pipecolate diastereomers were inseparable, a driving force for epimerization during hydrogenation of the iminium ion would be the formation of the more stable intermediate having both substituents positioned pseudoequatorially (Scheme 5). A less likely alternative would involve C-2 epimerization by selective enolization of an α-ammonium carboxylate after hydrogenation during cleavage of the *tert*-butyl esters and formation of the methyl esters under acidic conditions. Epimerization at C-8 was only observed in the product from hydrogenation of (6*R*)-**8d** in the presence of excess NH_4OAc. Application of NH_4OAc to prevent formation of desamino pipecolate **10** apparently increased the potential for conjugate addition of ammonia to the unsaturated iminium ion, product from *β*-elimination, prior to reduction of the iminium ion intermediate (Scheme 7). The preferred formation of (2*R*,4*S*,6*S*,8*R*)-4-Ph-I[9]aa-OMe **11** instead of product epimerized only at C-8 remains inexplicable with our present data.

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Conclusion

Toward a general approach for constructing 4-substituted indolizidin-9-one amino acids, conjugate addition reactions on enone **7** were studied using various nucleophiles, and a versatile route has been developed for making 6-substituted α,ω-diaminoazelates in good yield and diastereomeric ratios from 1:1 to 15:1. 6-Phenyl-substituted diaminoazelates, (6*S*)- and (6*R*)-**8d**, were obtained in high diastereoselectivity (13:1 dr) by selective precipitation from a 0.035 M solution of *i*-PrOH/H_2O (99/1). Enantiopure (2*S*,4*R*,6*R*,8*S*)-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylic acid ((2*S*,4*R*,6*R*,8*S*)-**3**) was synthesized from (6*S*)-**8d** in six steps and 42% overall yield via a reductive amination/lactam cyclization sequence. On the other hand, reductive amination of (6*R*)-**8d** was accompanied by β-elimination leading to desamino analogue **10**. Although β-elimination could be avoided by performing the hydrogenation in the presence of excess ammonium acetate, epimerization during the conversion of (6*R*)-**8d** to **9** was detected at both the C-2 and C-8 stereocenters and three products, (2*R*,4*S*,6*S*,8*R*)-, (2*R*,4*S*,6*S*,8*S*)-, and (2*S*,4*S*,6*R*,8*S*)-**11**, were finally isolated from the lactam cyclization protocol. A novel synthesis methodology for preparing 4-substituted indolizidin-9-one amino acids has thus been demonstrated by the synthesis of 4-Ph-I[9]aa **3**, a new constrained Ala-Phe dipeptide surrogate for examining conformation−activity relationships of biologically active peptides.

Experimental Section

(2*S*,6*S*,8*S*)- and (2*S*,6*R*,8*S*)-Di-*tert*-butyl-4-oxo-6-phenyl-2,8-bis[*N*-(PhF)amino]-azelate [(6*S*)- and (6*R*)-8d]. Under an argon flow, CuCN (1.25 g, 240 mol %) was gently flame dried, allowed to cool to room temperature, cooled further to −48 °C, treated with a 0.5 M solution of PhMgBr in THF (48.5 mL, 400 mol %), stirred for 30 min, treated with a solution of enone (5*E*)-**7**[7a] (4 g, 4.8 mmol) in THF (50 mL), stirred for 2 h, and quenched with saturated NH_4Cl (20 mL). The resulting suspension was extracted with ether (3 × 20 mL), and the combined organic layers were washed with brine (30 mL), dried with Na_2SO_4, and concentrated on a rotary evaporator. The residue obtained was purified by column chromatography using hexane/EtOAc (90/10) as an eluant to give **8d** (3.2 g, 72%) as a 2/1 mixture of (6*S*)-/(6*R*)-**8d** as measured by the *tert*-butyl singlets at 1.16−1.12 and 1.16 ppm in the ^{1}H NMR spectrum. The mixture was dissolved in *i*-PrOH (100 mL, 0.035 M), treated with 1 mL of water, and stirred for 18 h. The mother liquor was decanted and evaporated to give a 1/13 mixture of [(6*S*)-/(6*R*)-**8d**,1.1 g, 25%]: R_f 0.12 (45/45/10 toluene/*iso*-octane/*i*-Pr_2O); R_f 0.31 (85/15, hexane/EtOAc); ^{1}H NMR δ ($CDCl_3$) 7.68−7.52 (m, 4 H), 7.44−7.05 (m. 27 H), 3.46 (t, 1H, J = 7.4 Hz), 3.15 (br s, 2 H), 2.73 (t, 1 H, J = 5.1 Hz), 2.47−2.35 (m, 3 H), 2.25−2.14 (m, 2 H), 1.79−1.64 (m, 2 H), 1.19 (s, 18 H); ^{13}C NMR δ ($CDCl_3$) 206.1, 175.0, 173.2, 80.9, 80.7, 72.9, 72.8, 54.2, 52.7, 49.4, 48.7, 42.7, 36.7, 27.9, 27.7; MS (FAB+) *m*/*z* 901.3 (M + H^+). The dry white precipitate was a 13/1 mixture of [(6*S*)-/(6*R*)-**8d**,1.8 g, 42%]: R_f 0.17 (45/45/10 toluene/*iso*-octane/*i*-Pr_2O); ^{1}H NMR δ ($CDCl_3$) 7.69−7.63 (m, 4 H), 7.37−7.12 (m. 27 H), 3.26 (m, 1 H), 2.95 (br s, 1 H), 2.79 (br t, 1 H), 2.47 (m, 3 H), 2.35 (dd, 1 H), 2.21 (dd, 1 H), 1.73 (t, 2 H), 1.20 (s, 9 H), 1.16 (s, 9 H); ^{13}C NMR δ ($CDCl_3$) 206.1, 175.0, 173.2, 80.9, 80.7, 72.9, 72.8, 54.8, 52.9, 50.5, 48.2, 42.4, 37.5, 27.8, 27.6; MS (FAB+) *m*/*z* 901.2 (M + H^+); $[\alpha]_D^{20}$ −136.1 (*c* 0.018, $CHCl_3$).

(2*S*,4*R*,6*R*,8*S*)-Methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4,3,0]nonane Carboxylate [(2*S*,4*R*,6*R*,8*S*)-11]. Ketone (6*S*)-**8d** (1.75 g, 1.94 mmol) was dissolved in a solution of THF (36 mL), EtOH 95% (126 mL), and AcOH (18 mL) and treated with palladium-on-carbon 10% (175 mg, 10 wt %). The vessel containing the suspension was filled, vented, and refilled three times with hydrogen. After stirring for 24 h under 9 atm of H_2, the suspension was filtered through Celite and concentrated on a rotary evaporator. The residue was partitioned between saturated $NaHCO_3$ (50 mL) and $CHCl_3$/*i*-PrOH (4/1, 50 mL). The aqueous phase was extracted (3 × 20 mL) with $CHCl_3$/*i*-PrOH (4/1). The organic phases were combined, dried with $MgSO_4$, and concentrated under vacuum to give the free amine as a colorless oil: TLC R_f 0.1 (90/9/1 hexane/*i*-PrOH/Et_3N); ^{1}H NMR ($CDCl_3$) δ 7.33−7.28 (m, 2H), 7.22 (m, 3H), 3.58 (br s, 1H), 3.42 (d, 1H, J = 11.0 Hz), 2.95 (br s, 1H), 2.73 (t, 1H, J = 12.2 Hz), 2.19 (d, 1H, J = 12.7 Hz), 2.07 (br s, 2H), 1.90 (m, 1H), 1.82 (d, 1H, J = 12.7 Hz), 1.61 (m, 1H), 1.52 (q, 1H, J = 12.0 Hz), 1.46 and 1.45 (2s, 18H), 1.43−1.33 (m, 2H); ^{13}C NMR δ 175.5, 172.2, 145.4, 128.4, 126.7, 126.3, 81.0 (2C), 59.3, 52.5, 51.9, 42.8, 40.8, 39.9, 36.7, 27.9 (2C). The oil was dissolved in 12 N HCl (30 mL) and stirred for 15 min, at which point ^{1}H NMR spectroscopy in CD_3OD showed the disappearance of the *tert*-butyl singlets at 1.55 and 1.51 ppm. Evaporation of the volatiles under vacuum gave the free diamino acid as the HCl salt: TLC R_f 0.05 (4/1/1 *n*-BuOH/H_2O/AcOH); ^{1}H NMR (CD_3OD) δ 7.36−7.23 (m, 5H), 4.26−4.22 (m, 2H), 3.88 (m, 1H), 3.10 (tt, 1H, J = 12.7, 2.9 Hz), 2.48 (m, 2H), 2.31 (d, 1H, J = 13.7 Hz), 2.21−2.15 (m, 2H), 1.90 (q, 1H, J = 13.7 Hz), 1.77 (q, 1H, J = 13.8 Hz); ^{13}C NMR (CD_3OD) δ 171.0, 170.8, 144.4, 130.0, 128.3, 128.0, 59.0, 55.4, 50.7, 41.2, 36.0, 35.0, 33.9. The crude white solid was dissolved in methanol (65 mL) and treated with bubbles of HCl gas until complete disappearance of starting material was observed by TLC (4/1/1 *n*-BuOH/H_2O/AcOH), approximately 1 h. The volatiles were removed under vacuum to give the diester as a white solid. TLC R_f 0.35 (4/1/1 *n*-BuOH/H_2O/AcOH); ^{1}H NMR (CD_3OD) δ 7.32−7.23 (m, 5H), 4.47−4.28 (m, 2H), 3.90 (s, 3H), 3.85 (m, 4H), 3.16 (m, 1H), 2.60 (m, 1H), 2.42 (m, 1H), 2.30 (m, 2H), 2.05−1.85 (m, 2H); ^{13}C NMR δ 170.8, 170.0, 144.4, 130.0, 128.4, 128.0, 58.9, 55.3, 54.5, 54.1, 50.7, 40.9, 35.8, 35.0, 33.8. The solid was dissolved in MeOH (45 mL), treated with Et_3N (0.54 mL, 200 mol %), and heated at reflux for 48 h at which point ^{1}H NMR spectroscopy in CD_3OD of an aliquot showed complete disappearance of the methyl singlets at 3.90 and 3.84 ppm and appearance of a new methyl singlet at 3.71 ppm. After removal of the volatiles under vaccum, the crude oil was dissolved in CH_2Cl_2 (45 mL), treated with Et_3N (2.7 mL, 1000 mol %) and Boc_2O (0.846 g, 200 mol %), stirred for 15 h, and concentrated on a rotary evaporator. Purification by column chromatography was performed using an eluant of hexane/EtOAc (70/30) as an eluant. First to elute was (2*R*,4*S*,6*S*,8*S*)-methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4,3,0]nonane carboxylate [(2*R*,4*S*,6*S*,8*S*)-**11**, 22 mg, 3%]: TLC R_f 0.1 (85/10/5 hexanes/*i*-Pr_2O/*i*-PrOH). Next to elute was (2*S*,4*R*,6*R*,8*S*)-methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylate [(2*S*,4*R*,6*R*,8*S*)-**11**, 340 mg, 51%]: TLC R_f 0.13 (70/30 Hex/EtOAc); $[\alpha]^{20}D$ −36.1; ^{13}C NMR (C_6D_6) δ 171.7 (2 C), 170.8 (C), 144.6 (C), 129.0 (2 CH), 128.5 (CH), 127.1 (2 CH), 79.4 (C), 56.4 (CH), 53.9 (CH), 52.6 (CH), 52.3 (CH), 40.6 (CH_2), 38.5 ($2CH_2$), 36.2 (2 CH_3), 28.6; MS (FAB+) *m*/*z* 389.1 (M + H^+); HRMS calcd for $C_{21}H_{28}N_2O_5$ (MH^+) 389.2077, found 389.2098.

(4*S*)-Methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylate [(4*S*)-11]. Ketone (6*R*)-**8d** (900 mg, 1 mmol) was dissolved in THF (15 mL) and treated with a solution of NH_4OAc (suspended in and dried by evaporation from toluene, and then left to sit under high vacuum overnight, 4.27 g, 5500 mol %) in 95% EtOH (35 mL) followed by AcOH (0.5 mL) and Pd/C 10% (90 mg, 10 wt %). The vessel containing the suspension was filled, vented, and refilled three times with hydrogen. After stirring for 24 h under 9 atm of H_2, the suspension was then filtered through Celite and concentrated on a rotary evaporator to give **9**: TLC R_f 0.1 (90/10 hexane/*i*-PrOH). Distinct signals for the major

isomer of (4*S*,6*S*)-**9**: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 3H), 7.20 (m, 2H), 3.40 (d, 2H, J = 10.3 Hz), 2.91 (m, 1H), 2.71 (t, 1H, J = 11.9 Hz), 2.20 (d, 1H, J = 12.8 Hz), 1.87 (m, 3H), 1.70−1.50- (m, 2H), 1.45 (s, 18H), 1.36 (q, 1H, J = 12.0 Hz); ^{13}C NMR ($CDCl_3$) δ 175.4, 172.1, 145.7, 128.5 (2C), 126.9 (2C), 125.8, 81.1 (2C), 59.5, 55.1, 54.2, 42.8, 41.1, 39.6, 36.4, 28.0 (6 CH_3); MS (FAB+) *m*/*z* 405.2 (M + H^+). As described above for the synthesis of (2*S*,4*R*,6*R*,8*S*)-**11**, ester exchange, lactam formation, and *N*-protection were performed to provide a residue that was purified by column chromatography using hexane/EtOAc (70/30) as an eluant, which gave (2*R*,4*S*,6*S*,8*S*)-methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylate [(2*R*,4*S*,6*S*,8*S*)-**11**, 18 mg, 6%]: TLC R_f 0.25 (85/10/5 hexane/*i*-Pr_2O/*i*-PrOH); ^{13}C NMR ($CDCl_3$) δ 170.3, 155.9, 129.0, 128.0, 127.1, 126.9, 80.2, 56.8, 56.5, 52.7, 51.5, 41.4, 38.9, 35.1, 33.6, 28.5; MS (FAB+) *m*/*z* 389.2 (M + H^+). HRMS calcd for $C_{21}H_{28}N_2O_5$ (MH^+) 389.2077, found 389.2085. A second fraction was collected containing a mixture of two compounds that were separated by column chromatography using hexane/*i*-Pr_2O/*i*-PrOH (85/10/5) as an eluant. First to elute was (2*S*,4*S*,6*R*,8*S*)-methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]-nonane carboxylate [(2*S*,4*S*,6*R*,8*S*)-**11**, 17 mg, 6%]: TLC R_f 0.22 (85/10/5 hexane/*i*-Pr_2O/*i*-PrOH); ^{13}C NMR (C_6D_6) δ 171.8, 171.7, 156.3, 146.3, 79.3, 63.9, 52.4, 52.1, 48.4, 38.2, 36.9, 34.7, 31.6, 28.6; MS (FAB+) *m*/*z* 389.1 (M + H^+); HRMS calcd for $C_{21}H_{28}N_2O_5$ (MH^+) 389.2077, found 389.2093. Second to elute was (2*R*,4*S*,6*S*,8*R*)-methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylate [(2*R*,4*S*,6*S*,8*R*)-**11**, 28 mg, 10%]: TLC R_f 0.17 (85/10/5 hexane/*i*-Pr_2O/*i*-PrOH); $[\alpha]_D^{20}$ +0.8. The NMR spectral data were identical with those of (2*S*,4*R*,6*R*,8*S*)-**11**. The enantiomeric purity of (2*R*,4*S*,6*S*,8*R*)-**11** was assessed by the preparation of diastereomeric prolyl amides (2′*S*,2*R*,4*S*,6*S*,8*R*)-**12** as described below and measured at 33% ee.

Enantiomeric Purity of (2*S*,4*R*,6*R*,8*S*)-Methyl-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane Carboxylate 11. Compound (2*S*,4*R*,6*R*,8*S*)-**11** (28 mg, 72 μmol) was dissolved in CH_2Cl_2 (5 mL) and treated with HCl gas for 1 h. The volatiles were removed under reduced pressure, and the product was dissolved in CH_2Cl_2 (3 mL), treated with DIEA (9 μL, 140 mol %) and either L- or DL-*N*-(*p*-toluenesulfonyl)prolyl chloride (10 mg, 100 mol %), stirred for 6 h at rt, diluted with CH_2Cl_2 (3 mL), and washed sequentially with 10% citric acid (3 mL), 1 N NaOH (3 mL), and brine (3 mL), dried ($MgSO_4$), filtered, and concentrated. In the case of the DL-diastereomer, 18 mg (93%) of (2′*RS*,2*S*,4*R*,6*R*,8*S*)-methyl-9-oxo-8-(*N*-(*p*-toluenesulfonyl)-prolinamido)-4-phenyl-1-azabicyclo[4,3,0]nonane carboxylate **12** was obtained as a 1:1 mixture of diastereoisomers as determined by measuring the signals of the methyl ester singlets at 3.75 and 3.73 ppm. For the (2′*S*)-diastereoisomer, 12 mg (62%) of (2′*S*,2*S*,4*R*,6*R*,8*S*)-methyl-9-oxo-8-(*N*-(*p*-toluenesulfonyl)prolinamido)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylate **12** was obtained: ^{1}H NMR (C_6D_6) δ 7.69 (d, 2H, J = 8.2 Hz), 7.57 (d, 1H, J = 6.5 Hz), 7.13−7.04 (m, 3H), 6.86 (d, 2H, J = 8.4 Hz), 6.80 (d, 2H, J = 8.0 Hz), 4.36 (m, 1H), 4.19 (dd, 1H, J = 3.0, 8.6 Hz), 3.66 (s, 3H), 3.53 (dd, 1H, J = 4.0, 11.0 Hz), 3.27 (m, 1H), 2.90 (m, 1H), 2.48 (m, 1H), 2.34 (m, 1H), 2.18−2.07 (m, 2H), 1.89 (s, 3H), 1.85 (m, 1H), 1.70 (dd, 1H, J = 1.5, 13.2 Hz), 1.67−1.52 (m, 2H), 1.33 (d, 1H, J = 11.1 Hz), 1.20−1.11 (m, 2H), 1.02 (m, 1H). The limits of detection were determined by observation of the diastereomeric singlets at 3.75 and 3.73 ppm in a 400 MHz ^{1}H NMR spectrum of (2′*S*)-**12** in C_6D_6 during incremental additions of the diastereomeric mixture (2′*RS*)-**12**, which demonstrated (2′*S*)-**12** to be of >98% diastereomeric purity. Distinct signals for (2′*R*)-**12** include: ^{1}H NMR (C_6D_6) δ 7.63 (d, 2H, J = 8.2 Hz), 7.47 (d, 1H, J = 8.2 Hz), 6.88 (d, 2H, J = 7.5 Hz)), 6.74 (d, 2H, J = 8.0 Hz), 4.78 (m, 1H), 3.64 (s, 3H), 1.85 (s, 3H).

(2*S*,4*R*,6*R*,8*S*)-9-Oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane Carboxylic Acid [(2*S*,4*R*,6*R*,8*S*)-3]. Ester (2*S*,4*R*,6*R*,8*S*)-**11** (519 mg, 1.34 mmol) in Et_2O (40 mL) was treated with potassium trimethylsilanolate (257 mg, 150 mol %), stirred for 2 h, quenched with water (1 mL), and evaporated to a residue that was partitioned between $CHCl_3$ (50 mL) and 10% citric acid solution (50 mL). The phases were separated, and brine (25 mL) was added to the aqueous phase, which was extracted with $CHCl_3$ (4 × 25 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to provide (2*S*,4*R*,6*R*,8*S*)-9-oxo-8-(*N*-(Boc)-amino)-4-phenyl-1-azabicyclo[4.3.0]nonane carboxylic acid [(2*S*,4*R*,6*R*,8*S*)-**3**, 410 mg, 82%]: ^{1}H NMR (C_6D_6) δ 9.84 (br s, 1H), 7.15 (m, 2H), 7.07 (m, 1H), 6.94 (m, 2H), 5.81 (d, 1H, J = 5.6 Hz), 5.10 (d, 1H, J = 5.6 Hz), 4.40 (br s, 1H), 3.58 (m, 1H), 2.66 (br t, 1H, J = 11.6 Hz), 2.43 (m, 2H), 1.57−1.48 (m, 3H), 1.45 (s, 9H), 1.08 (q, 1H, J = 11.8 Hz); ^{13}C (C_6D_6) δ 174.0, 173.2, 156.7, 145.1, 129.1, 127.5, 127.1, 80.0, 53.3, 52.5, 52.4, 39.3, 38.8, 35.2, 33.7, 28.8; MS (FAB+) *m*/*z* 375.1 (M + H^+); HRMS calcd for $C_{20}H_{26}N_2O_5$ (MH^+) 375.1920, found 375.1915.

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Supporting Information Available: ^{1}H, ^{13}C, COSY, and NOESY NMR spectra of (2*S*,4*R*,6*R*,8*S*)-**11**, (2*R*,4*S*,6*S*,8*S*)-**11**, and (2*S*,4*S*,6*R*,8*S*)-**11**; ^{1}H and ^{13}C NMR spectra of **3**, **8c**, **8b**, **8a**, **9**, **10**, and **12**; and Experimental for **8c**, **8b**, **8a**, (4*S*,6*R*)-**9**, (4*S*,6*S*)-**10**, and (4*S*,6*R*)-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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