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Efficient Synthesis of Enantiopure Pyrrolizidinone Amino Acid

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Enantiopure (3*S*,5*R*,8*S*)-3-[*N*-(Boc)amino]-1-azabicyclo[3.3.0]octan-2-one 8-carboxylic acid (**1**) was synthesized in nine steps and 16% overall yield from aspartate β-aldehyde **7**. Carbene-catalyzed acyloin condensation of **7**, followed by acetylation and samarium iodide reduction, gave linear precursor (2*S*,7*S*)-α,ω-diamino-4-oxosuberate **11**, which was converted to *N*-(Boc)aminopyrrolizidin-2-one carboxylic acid **1** by a reductive amination/lactam cyclization sequence. X-ray analysis of (3*S*,5*R*,8*S*)-methyl *N*-(Boc)aminopyrrolizidin-2-one carboxylate **21** showed that its internal backbone dihedral angles ($\psi = -149°$, $\phi = -49°$) were in good agreement with the ideal values for a type II′ β-turn. Proton NMR experiments on *N*′-methyl-*N*-(Boc)aminopyrrolizidin-2-one carboxamide **23** demonstrated significantly different NH chemical displacements and temperature coefficients suggestive of solvent shielded and exposed hydrogens indicative of a turn conformation. Because pyrrolizidinone amino acids can serve as conformationally rigid dipeptide surrogates, this synthesis should facilitate their application in the exploration of conformation−activity relationships of various biologically active peptides.

Introduction

Pyrrolizidinone amino acids are conformationally rigid dipeptide surrogates in which the peptide backbone is constrained within a fused 5,5-bicyclic structure (Figure 1).[1−11] These azabicyclo[3.3.0]octanone amino acids have been used to study conformation−activity relationships of biologically active peptides. For example, thiapyrrolizidinone **2** has been inserted into an active mimic of the dopamine receptor modulating peptide Pro-Leu-Gly-NH_2 (PLG) in support of the hypothesis that its bioactive conformation possesses a type II β-turn.[6] Interest in the synthesis of such bicyclic structures was initially evoked due to their structural relationship to β-lactam antibiotics, such as the penicillins and carbapenems.[12−32] In most cases, the antibacterial activity of these γ-lactams has been low due to their poor electrophilicity; however, pyrazolidinone **3**, bearing electron-withdrawing substituents, exhibited enhanced acylating potential and potent

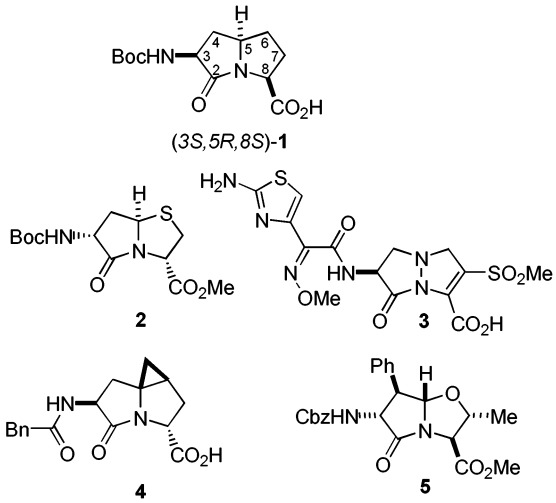

FIGURE 1. Representative azabicyclo[3.3.0]alkane amino acid analogues.[6,11,31,33]

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antibacterial activity.[31] Although the potency of pyrrolizidinone amino acids which do not encompass heteroatoms in the bicycle have been typically lower than their fused 4,5-bicyclic counterparts, a resurgence of attention toward constructing these γ-lactam analogues has been generated because they may serve as β-lactamase inhibitors, as suggested by the ability of tricyclic pyrrolizidinone **4** to improve the activity of the antibiotic ceftazidine against β-lactamase producing strains.[33] In addition, pyrrolizidinone amino acids share structural homology with pyrrolizidine alkaloids and may thus be employed as scaffolds in parallel syntheses to prepare libraries with members that may exhibit biological activity similar to that of their alkaloid counterparts.[34]

In the context of our program in peptide mimicry, we have employed related azabicyclo[*X*.*Y*.0]alkane amino acids as constrained dipeptide surrogates in order to systematically study structure−activity relationships of various biologically active peptides.[35−37] Having previously developed effective syntheses of indolizidinone,[38−43] quinolizidinone,[44] and pyrroloazepinone[44] amino acid analogues with stereocontrol and potential for adding side chains onto the heterocycle, we were interested in expanding this methodology to furnish pyrrolizidinone amino acids, because the smaller ring size of this heterocyclic system would favor alternative peptide backbone geometry. Although several syntheses of azabicyclo[3.3.0]octanone amino acids have been reported,[3,4,6−20,22,24−26,28,29,31−33,45,46] the majority provide analogues with multiple heteroatoms in the fused 5,5-bicycle. To our knowledge, only one synthesis of pyrrolizidinone amino acid **1** has been reported to provide entry to enantiomerically enriched material in the form of its *tert*-butyl ester.[10] This approach required pig-liver esterase mediated desymmetrization of 2,5-*cis*-dicarbethoxy-*N*-benzylpyrrolidine to provide the corresponding monocarboxylic acid with 80% ee and 13 additional steps with separation of diastereomeric mixtures to furnish the *tert*-butyl ester of **1** in an overall yield of 5%.[10] Because these approaches did not meet our requirements for producing sufficient quantity of enantiopure material in suitably protected form for peptide synthesis, we chose to develop a more effective method for synthesizing pyrrolizidin-2-one amino acid **1**.

As in our previous syntheses of heterocycle systems with larger ring sizes, we have pursued approaches to pyrrolizidinone amino acid **1** featuring preparation of a linear α,ω-diaminodicarboxylate precursor that could be converted to the bicycle by reductive aminations, methanesulfonate displacements, and lactam cyclizations. In pursuit of an α,ω-diaminosuberate for synthesizing the fused 5,5-bicycle, we found that crossed Claisen condensations between *N*-(PhF)aspartate diester **9** and *N*-(PhF)-glutamate diester **6** failed to provide β-ketoester **10**.[39] The more reactive aspartate β-aldehyde **7** was later found to undergo aldol condensation with the lithium enolate of glutamate diester **6** to provide β-hydroxyester **8** as a mixture of diastereomers. Oxidation of alcohol **8** using DMSO and oxalyl chloride followed by triethylamine furnished β-ketoester **10** (m/z = 869.5), which was then decarboxylated on treatment with 2 N sodium hydroxide in dioxane to provide ketone **11**. (2*S*,7*S*)-Di-*tert*-butyl 4-oxo-2,7-bis[*N*-(PhF)amino]suberate (**11**) was isolated from this unoptimized process in only 6% overall yield from glutamate **6** (Scheme 1, PhF = 9-(9-phenylfluorenyl)). Before trying to optimize this route, we considered another more convergent approach featuring acyloin condensation of aldehyde **7** in order to prepare ketone **11** by way of α-hydroxy ketone **15** (Scheme 2). Although reducing metals have been employed to effect dimerization of esters and aldehydes to provide acyloins and diols, respectively,[47−49] we selected instead to examine the use of stabilized carbenes as catalysts to effect the acyloin condensation.[50−53] This approach has now been developed

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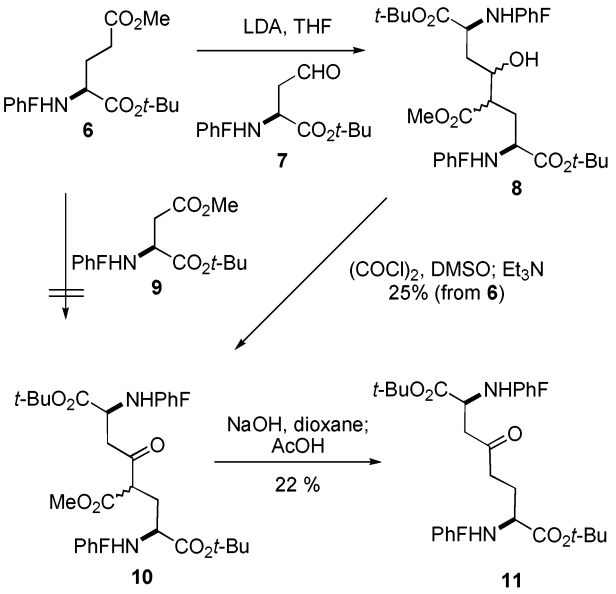
SCHEME 1. Claisen Condensation and Aldol Approaches to Diamino Suberate 11



to deliver multiple gram quantities of ketone **11** in three steps from aldehyde **7** and 44% overall yield. The synthesis of enantiopure pyrrolizidinone amino acid **1** was then accomplished by employing ketone **11** in a sequence featuring our reductive amination/lactam cyclization protocol.

Results and Discussion

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**12**, Figure 2) had previously been shown to catalyze the dimerization of butanal in EtOH with triethylamine at 80 °C to afford 5-hydroxyoctan-4-one in 71−74% yield.[51] Examination of the same conditions on the more functionalized four-carbon aldehyde **7** gave no reaction (Table 1, entry 1); however, increasing the stoichiometry of catalyst **12** up to 50 mol % raised the yield of α-hydroxy ketone **15** to 49% (Table 1, entry 3). Decomposition of aldehyde **7** was observed under these hot alkaline conditions; for example, *tert*-butyl *N*-(PhF)-5-azapenta-2,4-dienoate was isolated as one side product.[54] Switching to 5-methoxy-4,5-dihydro-1,3,4-triphenyl-1*H*-1,2,4-triazole (**13**)[52] as catalyst (25 mol %) in *tert*-butyl alcohol at 80 °C removed the need for base and gave a cleaner reaction at a higher substrate-to-catalyst ratio furnishing **15** in 63% yield after flash chromatography and precipitation from hexanes. The reaction yield was not improved using longer reaction times or lower and higher catalyst-to-substrate ratios. Switching to toluene as a nonpolar solvent slowed the reaction and resulted in lower yields. Conducting the reaction at a lower temperature after initial activation of the catalyst at 80 °C also reduced the reaction rate and produced lower yields of acyloin **15**. Finally, 5-ethoxy-4,5-dihydro-1,3,4-triphenyl-1*H*-1,2,4-triazole (**14**)[55] catalyzed the reaction in a similar way as triazole **13** (Table 1).

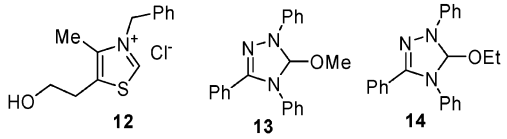


FIGURE 2. Catalysts used in acyloin condensation of aspartate β-aldehyde **7**.[51,52,55]

TABLE 1. Acyloin Condensations of Aspartate β-Aldehyde 7

entry	cat. (mol %)	base (mol %)	solvent	*T* (°C)	time (h)	isolated yield (%) of **15**
1	**12** (5)	Et_3N (30)	EtOH	80	2	no reaction
2	**12** (25)	NaOAc (50)	EtOH	80	2	37
3	**12** (50)	Et_3N (300)	EtOH	80	2	49
4	**12** (100)	Et_3N (300)	EtOH	80	3.5	24
5	**13** (10)		*t*-BuOH	80	4	30
6	**13** (10)		*t*-BuOH	80	24	33
7	**13** (20)		*t*-BuOH	80	4	57
8	**13** (25)		*t*-BuOH	80	4	63
9	**14** (25)		*t*-BuOH	80	4	57
10	**13** (75)		*t*-BuOH	80	4	26
11	**13** (50)		*t*-BuOH	80	4	51
12	**13** (50)		*t*-BuOH	50[a]	120	8
13	**13** (50)		toluene	80	24	34

[a] Reaction mixture was initially heated at 80 °C to activate catalyst.

(2*S*,7*S*)-Di-*tert*-butyl 4-oxo-2,7-bis[*N*-(PhF)amino]suberate (**11**) was synthesized from α-hydroxy ketone **15** in two steps and 70% overall yield using a samarium iodide induced α-dehydroxylation (Scheme 2). Although the α-hydroxyl group may later serve for the introduction of side-chain groups onto the pyrrolizidinone amino acid, for our initial goal, the synthesis and application of ordinary ketone **11** was pursued to avoid complications from the additional stereocenter and to furnish the parent heterocycle. Acetylation of alcohol **15** with acetic anhydride, pyridine, and DMAP furnished diastereomeric acetates **16** in 78% yield. The acetates were separable by chromatography; moreover, one diastereomically pure acetate could be selectively precipitated from methanol. Isomerically pure **16** and diastereomeric mixtures of acetates **16**, both could be converted effectively to ketone **11** in 90% yield using 220 mol % of freshly prepared SmI_2 in THF at −78 °C.[56,57]

Synthesis of Pyrrolizidinone Amino Ester 21. Pyrrolizidinone amino ester **21** was synthesized from diamino suberate **11** by a sequence featuring reductive amination and lactam cyclization (Scheme 2). In the reductive amination, hydrogenation of diamino suberate **11** with palladium-on-carbon as catalyst in 9:1 EtOH/AcOH proceeded by cleavage of the phenylfluorenyl groups, intramolecular imine formation, protonation, and

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(55) (a) Catalyst **14** was obtained by heating **13** in ethanol at reflux for 20 min, cooling, and filtration of the beige crystalline solid: mp 68−70 °C; ^{1}H NMR (C_6D_6) δ 1.00 (t, 3H, *J* = 7.1), 3.27−3.32 (m, 1H), 3.41−3.47 (m, 1H), 6.82−6.86 (m, 1H), 6.89−7.94 (m, 3H), 6.99−7.07 (m, 5H), 7.26−7.32 (m, 2H), 7.61−7.68 (m, 4H); ^{13}C NMR (C_6D_6) δ 15.0, 55.6, 100.6, 113.4, 120.4, 122.9, 124.9, 128.6, 128.8, 129.0, 129.2, 129.5, 140.9, 142.7, 145.0; MS 298.1 (M − EtOH + H)$^+$. (b) Trace amounts of acyloin **15** were observed by TLC from attempts to use chiral carbene catalysts under conditions reported in: Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. The authors thank T. Rovis for generous gifts of chiral carbene catalysts.

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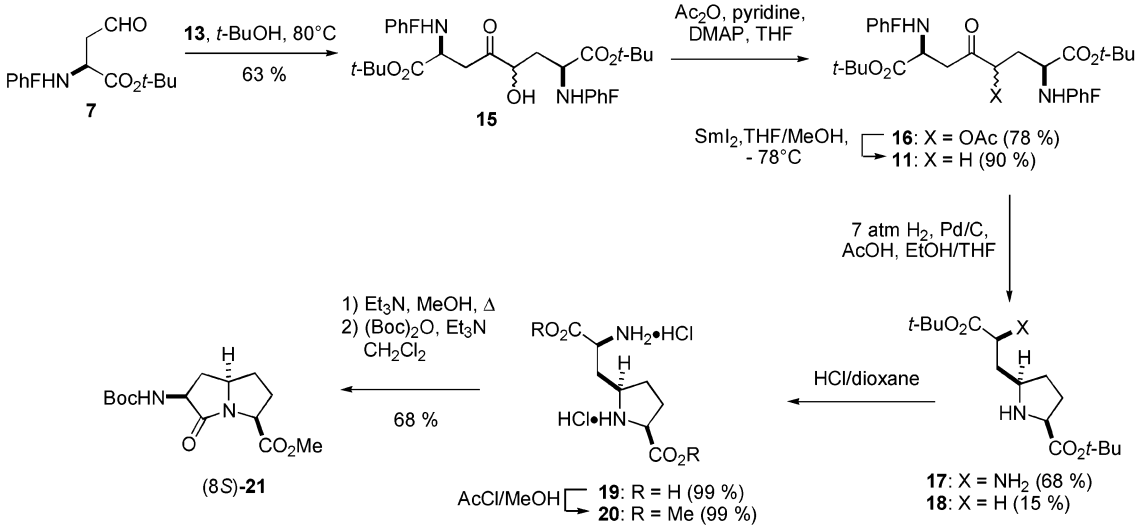
(57) In our hands, samarium iodide could not be generated from a sample of samarium obtained from Aldrich Chemicals.

SCHEME 2. Synthesis of Methyl *N*-(Boc)aminopyrrolizidin-2-one Carboxylate 21



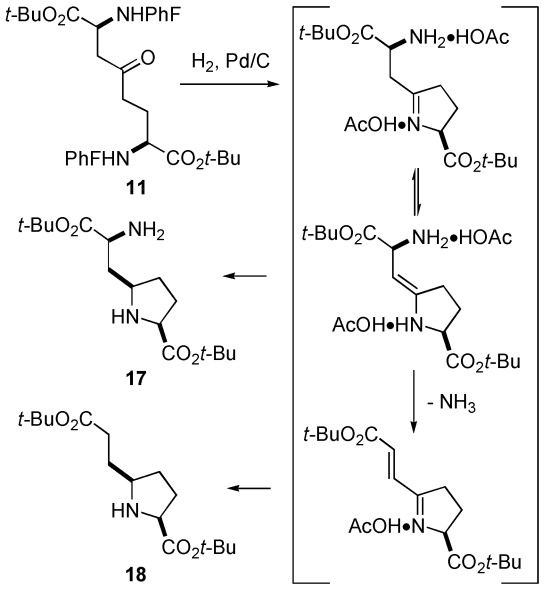


FIGURE 3. Proposed mechanism for loss of amine during reductive amination of **11**.

hydrogen addition to the iminium ion intermediate. The dehydro pyrrolidine intermediate was favored thermodynamically relative to its azetidine counterpart, and hydrogen addition to the iminium ion proceeded stereoselectively on the least hindered face to yield 5-alkylproline *tert*-butyl ester **17** as the cis diastereomer. Prolinate **17** was, however, not the major product when the hydrogenation was performed with a large excess of acetic acid; instead, propionate **18** from β-elimination of the primary amine was isolated in 58% yield. A plausible mechanism for the formation of **18** features imine formation, tautomerization to an enamine, β-elimination of the amine, and subsequent reduction of the resulting α,β-unsaturated imine intermediate (Figure 3). We have reported similar elimination reactions during reductive aminations with δ- and ϵ-amino ketones possessing hydroxy, silyloxy, and acetoxy groups at the β-position.[40,54,58] The propensity of the amine elimination was shown to be favored by protonation and the ratio of prolines **18** and **17** was inverted from 3.5:1 to 1:4.5 by diminishing the quantity of acid from 17 000 to 100 mol % in the reductive amination sequence. After hydrogenation of diamino suberate **11** with palladium-on-carbon as catalyst in 4:1 EtOH/THF containing 100 mol % AcOH, prolinate **17** could be isolated in 68% yield and was accompanied by 15% of β-elimination product **18**. Initially, (3*S*,5*R*,8*S*)-methyl 3-[*N*-(Boc)amino]-1-azabicyclo-[3.3.0]octan-2-one 8-carboxylate (**21**) was obtained in inconsistent overall yields, at best 42%, from proline **17** by removal of the *tert*-butyl esters of **17** with 220 mol % TsOH in toluene/methanol, lactam cyclization with excess triethylamine in toluene at reflux, and N-protection with di-*tert*-butyl dicarbonate and Et_3N in CH_2Cl_2, followed by chromatography. Attempting to optimize the transesterification sequence, we found that dimethyl ester **20** was obtained in purer form after treatment of proline **17** with 4.35 M HCl in dioxane followed by esterification with methanolic HCl. Low yields of product **21** were isolated after treatment of the hydrochloride salt of **20** with excess Et_3N in toluene at reflux followed by Boc protection. By changing the solvent from toluene to methanol at reflux, the yield of the lactam cyclization was significantly improved and pyrrolizidinone amino ester **21** could be reproducibly isolated in 68% yield. The best sequence for obtaining pyrrolizininone amino ester **21** from linear ketone **11** consisted of reductive amination using 100 mol % of acetic acid to obtain proline **17**, removal of *tert*-butyl esters with HCl in dioxane, esterification with methanolic HCl, lactam cyclization using excess triethylamine in methanol at reflux and Boc protection using di-*tert*-butyl dicarbonate and Et_3N in CH_2Cl_2. The overall yield of ester **21** using this five-step process was 45% from diaminosuberate **11**.

Synthesis, Assignment of Stereochemistry, and Enantiomeric Purity of Pyrrolizidinone Amino Acid 1. *N*-(Boc)aminopyrrolizidin-2-one acid **1** was synthesized via hydrolysis of ester **21** (Scheme 3). Epimerization of the C-8 center competed with ester hydrolysis, when using potassium trimethylsilanolate in ether, and afforded a 1.5:1 mixture of (8*S*)- and (8*R*)-**1** in quantita-

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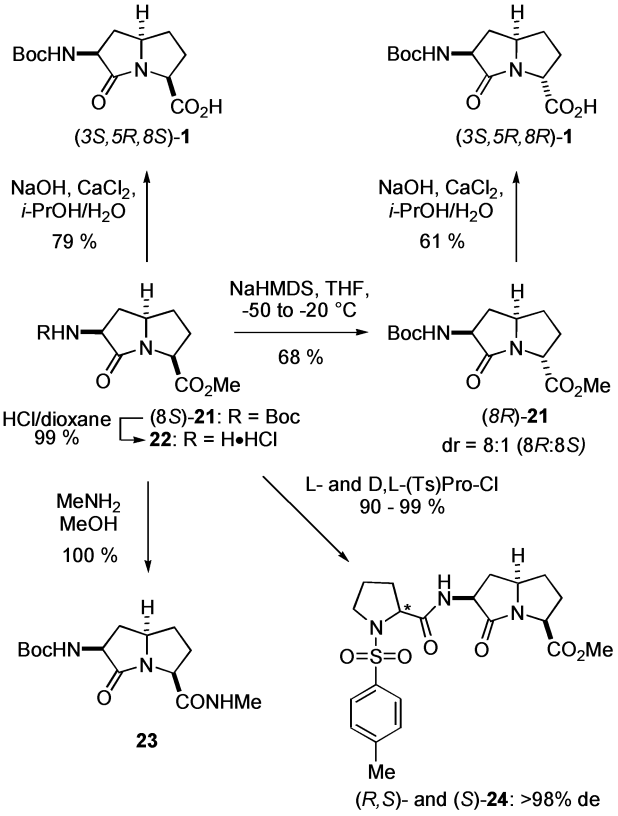
SCHEME 3. Synthesis and Enantiomeric Purity of (3*S*,5*R*,8*S*)-1 and Amide 23



tive yield.[38] This epimerization process demonstrated that our route can be used to synthesize alternative diastereomeric configurations of *N*-(Boc)aminopyrrolizidin-2-one acid **1**. By employing a premixed solution of NaOH and $CaCl_2$ in a 7:3 2-propanol−H_2O solution,[59] epimerization could be suppressed and (3*S*,5*R*,8*S*)-**1** was isolated in 79% yield.

Diastereomeric (8*R*)-**1** was pursued by a process featuring epimerization of ester (8*S*)-**21**. Enolization of ester (8*S*)-**21** with NaHMDS in THF provided an 8:1 mixture of (3*S*,5*R*,8*R*)- and (3*S*,5*R*,8*S*)-**21** in 68% yield. Hydrolysis of ester (8*R*)-**21** using a premixed solution of NaOH and $CaCl_2$ in a 7:3 2-propanol−H_2O solution provided isomerically pure acid (3*S*,5*R*,8*R*)-**1** in 61% yield after separation of the diatereoisomers by chromatography.

The ring-fusion stereochemistry of *N*-(Boc)aminopyrrolizidin-2-one acid **1** was originally assigned based on analogy with previous work in which the reductive amination of δ-keto α-amino ester with hydrogen and palladium-on-carbon as catalyst gave predominantly 5-alkylprolines with cis stereochemistry.[38,40,60,61] Crystallization of (3*S*,5*R*,8*S*)-methyl 3-*N*-[(Boc)amino]-1-azabicyclo[3.3.0]octan-2-one 8-carboxylate [(3*S*,5*R*,8*S*)-**21**] from hexanes and X-ray crystallographic analysis confirmed this assignment (Figure 4).[62] Configurational assignments were supported by NMR experiments. Initially, the signals of the ring protons of both isomers of

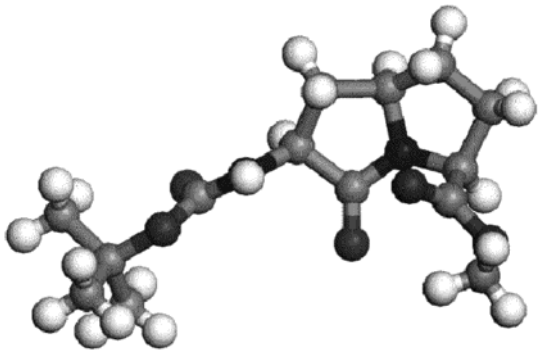
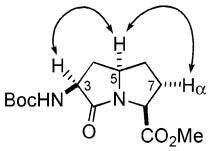
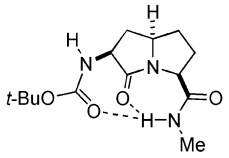


FIGURE 4. Structure of methyl *N*-(Boc)aminopyrrolizidin-2-one carboxylate **21** from X-ray crystallography (C, light gray; N, black; O, dark gray; H, white).



(8*S*)-**21**



23

δ (ppm)	$CDCl_3$	DMSO-d6	Δδ/Δsolvent
NHMe	7.32	7.77	-0.45
NH Paa	5.48	7.17	-1.69

FIGURE 5. Configurational and conformational analyses of pyrrolizidinone amino acid derivatives **21** and **23**. Long-distance NOE correlations indicated by double-tip arrows. Probable hydrogen bonds indicated by dotted lines, Paa = pyrrolizidinone amino acid.

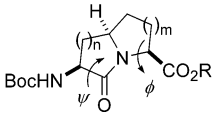
21 were assigned using COSY experiments. The NOESY spectra of both (3*S*,5*R*,8*S*)- and (3*S*,5*R*,8*R*)-**21** showed long-distance interactions between the ring fusion proton 5 and backbone proton 3. In addition, in the spectrum of (3*S*,5*R*,8*S*)-**21**, a second long-range NOE was observed between the 5 and 7α protons (*β*-protons are assigned to be on the same side as the amine function), consistent with concave geometry (Figure 5). In (8*S*)-**21**, the backbone proton at position 8 exhibited stronger NOE with the 7α relative to the 7*β* proton; the (8*R*)-isomer exhibited the opposite NOE intensities. The chemical displacements for the 7α and 7*β* protons were also indicative of the stereochemistry at the 8-position. For the (8*S*)-isomer, the 7α proton was observed upfield from the 7*β* proton, due to the anisotropic effect of the carboxylate group.[63] For the (8*R*)-isomer, the 7α proton was downfield from the 7*β* proton.

In the crystal structure of (3*S*,5*R*,8*S*)-pyrrolizidinone **21**, the dihedral angles of the backbone atoms constrained inside the heterocycle ($\psi = -149°$ and $\phi = -45°$)

(59) Pascal, R.; Sola, R. *Tetrahedron Lett.* **1998**, *39*, 5031−5034.
(60) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438−6441.
(61) Ho, T. L.; Gopalan, B.; Nestor, J. J., Jr. *J. Org. Chem.* **1986**, *51*, 2405−2408.

(62) The structure of **21** was solved at l'Université de Montréal X-ray facility using direct methods (SHELXS 97) and refined with SHELX L 97: $C_{14}H_{22}N_2O_5$; $M_r = 298.336$; monoclinic, colorless crystals; space group *C*2; unit cell dimensions (Å) $a = 18.601(13)$, $b = 6.823(2)$, $c = 15.622(7)$, $\beta = 124.96(4)°$; volume of unit cell (Å^3) = 1624.9(14); $Z = 4$; $R = 0.0472$ for $F^2 > 2\sigma(F^2)$, $\omega R(F^2) = 0.1091$ for all data; GOF = 1.007. The author has deposited the atomic coordinates for the structure of **21** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.
(63) Mauger, A. B.; Irreverre, F.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 2019−2024.

TABLE 2. Comparison of the Dihedral Angles from Azabicyclo[*X.Y.*0]alkane Amino Acids X-ray Data and Ideal Peptide Turns



entry	n	m	R	ψ, deg	ϕ, deg
21	1	1	Me	−149	−45
25[39]	1	2	Me	−141	−34
26[38]	2	1	Me	−176	−78
27[44]	2	2	*t*-Bu	−163	48
type II′ β-turn $i+1$ and $i+2$ residues[64]				−120	−80
inverse γ-turn $i+2$ residue[65]					−80

resembled the values of the central residues in an ideal type II′ β-turn ($\psi_2 = -120°$ and $\phi_3 = -80°$).[64] Comparison of the values for pyrrolizidinone **21** with those observed in the crystal structures of related indolizidinone and quinolizidinone analogues possessing the same relative stereochemistry demonstrated the influence of ring-size on conformation (Table 2).[38−40,44] Furthermore, the pyrrolizidinone amino acid appeared to adopt the most concave shape among these dipeptide surrogates suggesting interesting potential for turn mimicry.

The enantiomeric purity of (3*S*,5*R*,8*S*)-**21** was determined after conversion to (2′*S*)- and (2′*R*,*S*)-*N*′-(*p*-toluenesulfonyl)prolyl amides **24**. The Boc protecting group was removed with HCl in dioxane and the HCl salt was acylated with (*S*)- and (*R*,*S*)-*N*-(*p*-toluenesulfonyl)prolyl chlorides with Et_3N in CH_2Cl_2 (Scheme 3). Observation of the diastereomeric aromatic doublets centered at 6.76 and 6.82 ppm by 400 MHz ^{1}H NMR spectroscopy in C_6D_6 during incremental additions of the diastereomeric mixture demonstrated (2′*S*)-**24** to be of >98% diastereomeric excess. Hence ester **21**, suberate **11**, and *N*-(Boc)amino pyrrolizidin-2-one acid **1**, all are presumed to be of >98% enantiomeric purity.

Confomational Analysis of Methyl *N*-(Boc)aminopyrrolizidinone Carboxamide 23. Methyl *N*-(Boc)-aminopyrrolizidin-2-one carboxamide **23** was prepared quantitatively by treating ester **21** with methylamine gas in methanol (Scheme 3). Proton NMR experiments were then performed in order to determine if the amide hydrogen of **23** was involved in an intramolecular hydrogen bond. Typically, the chemical shifts of protons involved in hydrogen bonds exhibit little variation on changes in solvent composition and temperature.[66] Changing the solvent from deuterated chloroform to deuterated DMSO caused, respectively, 1.69 and 0.45 ppm downfield shifts of the signals for the carbamate and the amide protons, indicating that the later NH was more solvent shielded (Figure 5). The temperature coefficients of the NH chemical shifts were recorded in DMSO by heating at 5° intervals from 298 to 323 K. Although the temperature coefficient of the methyl amide proton ($\Delta\delta/\Delta T = -5.2$) was not in the reported range of a hydrogen bonded amide within cyclic peptides and larger proteins, it was much less influenced by the changes in temperature relative to the carbamate proton ($\Delta\delta/\Delta T = -10.2$, Figure 6). The results of the influence of solvent and temperature on the chemical shifts of the NH signals both supported the involvement of the methyl amide proton in an intramolecular hydrogen bond (Figure 5).

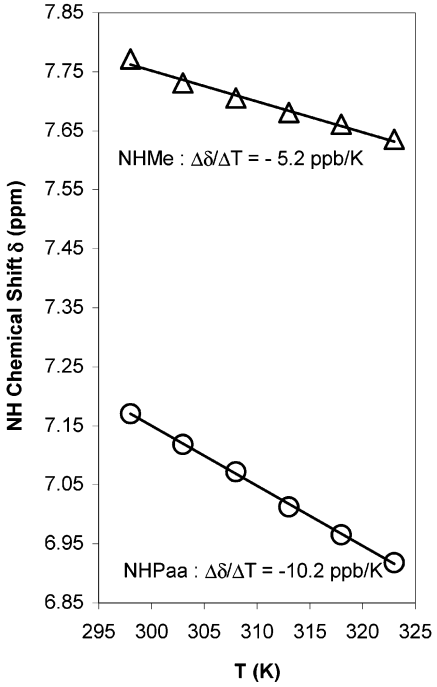


FIGURE 6. Influence of temperature on the N−H chemical shifts of *N*′-methyl *N*-(Boc)aminopyrrolizidin-2-one carboxamide **23** in DMSO-d_6; Paa = pyrrolizidinone amino acid.

Conclusion

Enantiopure (3*S*,5*R*,8*S*)-pyrrolizidin-2-one amino acid **1** was synthesized from aspartate β-aldehyde **7** via an acyloin condensation/reductive amination/lactam cyclization sequence in 9 steps and 16% overall yield. The pyrrolizidinone C-5 bridge-head center was created with stereocontrol in favor of the concave cis isomer in the reductive amination of ketone **11**. The relative stereochemistry was demonstrated by NOESY experiements and by X-ray analysis. The dihedral angles of the backbone atoms constrained inside the heterocycle ($\psi = -149°$ and $\phi = -45°$) resembled the values of the central residues in an ideal type II′ β-turn ($\psi_2 = -120°$ and $\phi_3 = -80°$) and proton NMR experiments demonstrated that *N*-(Boc)aminopyrrolizidin-2-one *N*′-methylamide **23** adopted an intramolecular hydrogen-bonded turn conformation. Epimerization of pyrrolizidinone amino ester **21** gave access to (3*S*,5*R*,8*R*)-**1** and demonstrated that all four concave diastereomers of **1** may be synthesized by employing L- and D-aspartate as chiral educts in this sequence. Furthermore, because modification of the α-hydroxyl group of ketone **15** and alkylation of amino ketone **11** may be used to add various side chains with stereocontrol at different positions on the pyrrolizidinone, our strategy offers potential for preparing a variety of azabicyclo[3.3.0]alkane amino acids posessing side-chain functional groups at different ring carbons. This efficient method for synthesizing pyrrolizidinone dipeptide sur-

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(65) Madison, V.; Kopple, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 4855−4863.
(66) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512−523.

rogates should thus be of general utility for the study of structure−activity relationships in peptide chemistry and biology.

Experimental Section

(2S,5*RS*,7*S*)-Di-*tert*-butyl 5-Hydroxy-4-oxo-2,7-bis[*N*-(PhF)amino]suberate (15). In a flame-dried three-necked flask equipped with a reflux condenser, (2*S*)-*tert*-butyl 2-[(*N*-PhF)amino]-4-oxobutanoate (**7**, prepared according to ref 54, 200 mg, 0.48 mmol) in dry ethanol (1.5 mL) was treated with 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**12**, prepared according to ref 51, 65 mg, 0.24 mmol) and Et_3N (201 μL, 1.44 mmol), heated at reflux for 1 h, cooled, and evaporated to dryness. The residue was partitioned between 25 mL of EtOAc and 25 mL of 1 M KH_2PO_4. The aqueous phase was extracted with EtOAc (2 × 25 mL). The organic phases were combined, washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography using a gradient of 5−10% EtOAc in hexanes as eluent. Evaporation of the collected fractions yielded 111 mg (56%) of acyloin **15** as a 1:1 mixture of diastereomers: $R_f = 0.18$ (10% AcOEt/hexanes, UV); ^{1}H NMR δ 1.15 (s, 9H), 1.19 (s, 9H), 1.20 (s, 9H), 1.23 (s, 9H), 1.25−1.30 (m, 1H), 1.30−1.52 (m, 1H), 1.73−1.77 (m, 2H), 2.48−2.56 (m, 2H), 2.70−2.79 (m, 4H), 2.89 (bs, 2H), 3.40 (bs, 3H, NH), 4.06 (d, 1H, J = 8.3 Hz), 4.35 (d, 1H, J = 7.8 Hz), 7.18−7.36 (m, 44H), 7.68−7.71 (m, 8H); ^{13}C NMR (300 MHz) δ 27.9, 28.0, 36.7, 38.0, 43.4, 43.5, 53.2, 53.6, 53.7, 55.5, 73.1, 73.2, 73.3, 75.2, 81.2, 81.4, 81.6, 173.3, 173.7, 174.0, 174.8, 209.8, 210.6; HRMS calcd for $C_{54}H_{55}N_2O_6$ $(MH)^+$ 827.4060, found 827.4080.

In a flame-dried, three-neck flask equipped with a reflux condenser, (2*S*)-*tert*-butyl 2-[(*N*-PhF)amino]-4-oxobutanoate (**7**, 8.37 g, 20.2 mmol) in dry *tert*-butyl alcohol (100 mL) was stirred at 50 °C and degassed with a stream of nitrogen bubbles for 15 min. 5-Methoxy 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazole (**13**, prepared according to ref 52, 1.66 g, 5.05 mmol) was added to the mixture, which was stirred at 80 °C for 4 h, cooled, and evaporated to dryness. The residue was purified by flash chromatography using 5% EtOAc in hexanes as eluent. Evaporation of the collected fractions followed by precipitation from hexanes and filtration yielded 5.30 g (63%) of the desired acyloin as a 1:1 mixture of diastereomers.

(2*S*,7*S*)-Di-*tert*-butyl 5-Acetoxy-4-oxo-2,7-bis[*N*-(PhF)-amino]suberate (16). Acyloin **15** (4.60 g, 5.56 mmol) in THF (60 mL) was treated with acetic anhydride (2.63 mL, 27.8 mmol), pyridine (1.35 mL, 16.7 mmol), and DMAP (68 mg, 0.56 mmol), stirred for 18 h at rt, diluted with 100 mL of EtOAc, washed with saturated $NaHCO_3$ (2 × 50 mL), 1 M aq $CuSO_4$ (2 × 50 mL), and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was suspended in 50 mL of methanol, stirred at reflux for 10 min and cooled to rt. The precipitate was isolated by filtration to afford 1.81 g (37%) of **16** (lower R_f) as a white solid and single diastereomer: $R_f = 0.17$ (25% Et_2O/hexanes, UV); mp 176−177 °C; $[\alpha]^{20}_D$ −250 (*c* 17.0, $CHCl_3$); ^{1}H NMR δ 1.17 (s, 9H), 1.23 (s, 9H), 1.55−1.66 (m, 2H), 1.77 (s, 3H), 2.54−2.61 (m, 3H), 2.90 (bs, 1H), 3.18 (bs, 1H), 3.37 (bs, 1H), 5.28 (d, 1H, J = 10.9 Hz), 7.13−7.37 (m, 22H), 7.66−7.68 (m, 4H); ^{13}C NMR δ 20.9, 27.9, 28.1, 35.7, 43.8, 52.8, 72.9, 73.4, 75.9, 170.2, 173.2, 175.2, 204.6; HRMS calcd for $C_{56}H_{57}N_2O_7$ $(MH)^+$ 869.4166, found 869.4181. The filtrate was concentrated and purified by flash chromatography using 15% Et_2O in hexanes as eluent to yield 1.97 g (41%) of **16** (higher R_f) as a white foam and single diastereomer: $R_f = 0.22$ (25% Et_2O/hexanes, UV); $[\alpha]^{20}_D$ −202 (*c* 14.4, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.22 (s, 9H), 1.23 (s, 9H), 1.70−1.82 (m, 2H), 1.98 (s, 3H), 2.31 (dd, 1H, J = 17.1, 4.5 Hz), 2.56 (dd, 1H, J = 17.2, 5.2 Hz), 2.67 (bs, 1H), 2.83 (bs, 1H), 3.26 (d, 1H, J = 6.5 Hz), 3.33 (bs, 1H), 5.43 (dd, 1H, J = 10.6, 3.1 Hz), 7.16−7.40 (m, 22H), 7.67−7.69 (m, 4H); ^{13}C NMR δ 20.7, 27.9, 28.0, 35.1, 43.8, 52.5, 52.9, 73.3, 75.5, 81.2, 81.4, 170.1, 173.2, 174.0, 204.3; HRMS calcd for $C_{56}H_{57}N_2O_7$ $(MH)^+$ 869.4166, found 869.4146.

(2*S*,7*S*)-Di-*tert*-butyl 4-Oxo-2,7-bis[*N*-(PhF)amino]suberate (11). In a flame-dried flask under N_2 atmosphere, samarium (1.71 g, 11.4 mmol) was suspended in dry THF (15 mL), stirred, and treated with a solution of 1,2-diiodoethane (2.86 g, 10.2 mmol) in THF (15 mL) which was slowly added via cannula. The olive green slurry was stirred for 1 h. The resulting dark-blue slurry of SmI_2 was cooled to −78 °C and treated over 10 min with a solution of (2*S*,5*RS*,7*S*)-di-*tert*-butyl 4-oxo-5-acetoxy-2,7-bis[*N*-(PhF)amino]suberate (**16**, 3.42 g, 3.94 mmol) in THF (30 mL) and methanol (10 mL). The resulting brown mixture was stirred at −78 °C for 15 min, warmed to rt, and poured into 100 mL of saturated K_2CO_3. The aqueous phase was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with 5% sodium thiosulfate solution (100 mL), dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by flash chromatography using 10% EtOAc in hexanes as eluent. Evaporation of the collected fractions yielded 2.89 g (90%) of linear ketone **11** as a white solid: $R_f = 0.29$ (15% AcOEt/hexanes, UV); mp 156−158 °C; $[\alpha]^{20}_D$ −225 (*c* 15.4, $CHCl_3$); ^{1}H NMR δ 1.20 (s, 9H), 1.26 (s, 9H), 1.60−1.65 (m, 2H), 2.08−2.14 (m, 1H), 2.31−2.60 (m, 4H), 2.86 (t, 1H, J = 5.6 Hz), 3.21 (bs, 2H), 7.18−7.40 (m, 22H), 7.70−7.73 (m, 4H); ^{13}C NMR δ 28.0, 28.1, 29.3, 40.3, 48.1, 53.8, 55.3, 73.1, 80.9, 81.3, 173.7, 175.3, 208.0; HRMS calcd for $C_{54}H_{54}N_2O_5$ (M^+) 811.4111, found 811.4093.

(2*S*,2′*S*,5*R*)-5-(2′-Amino-2′-*tert*-butoxycarbonylethyl)-proline *tert*-Butyl Ester (17). A suspension of ketone **11** (500 mg, 0.61 mmol) in 60 mL of a 4:1 solution of absolute ethanol/THF was treated with AcOH (35 μL, 0.61 mmol) and palladium-on-carbon (50 mg, 10% by wt). The reaction vessel was filled, vented, and filled three times under a hydrogen atmosphere; the reaction mixture was stirred under 7 atm of hydrogen for 24 h, after which time more catalyst (50 mg) was added; and the reaction was stirred under 7 atm of H_2 for another 24 h. The reaction mixture was filtered onto Celite and washed with methanol (3 × 10 mL). The combined organic phases were evaporated under reduced pressure to a residue that was dissolved in 0.1 M HCl (15 mL) and washed with Et_2O (3 × 10 mL). The aqueous phase was made alkaline to pH ∼ 9 by adding saturated $NaHCO_3$ solution and extracted with $CHCl_3$/*i*-PrOH (4:1, 4 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a residue that was purified by flash chromatography using a gradient of 2−5% MeOH in CH_2Cl_2. First to elute was (2*S*,5*R*)-5-(2′-*tert*-butoxycarbonylethyl)proline *tert*-butyl ester (**18**, 27 mg, 15%): $R_f = 0.25$ (5% MeOH/CH_2Cl_2); ^{1}H NMR (CD_3OD) δ 1.26−1.31 (m, 1H), 1.45 (s, 9H), 1.48 (s, 9H), 1.76−1.92 (m, 4H), 2.06−2.10 (m, 1H), 2.31−2.35 (m, 2H), 2.98−3.01 (m, 1H), 3.57−3.61 (m, 1H); ^{13}C NMR (CD_3OD) δ 28.4, 28.5, 31.3, 31.7, 32.4, 34.3, 60.8, 61.6, 81.6, 82.6, 174.5, 175.2; HRMS calcd for $C_{16}H_{30}NO_4$ $(MH)^+$ 300.2175, found 300.2178. Next to elute was (2*S*,2′*S*,5*R*)-5-(2′-amino-2′-*tert*-butoxycarbonylethyl)proline *tert*-butyl ester (**17**, 132 mg, 68%): $R_f = 0.07$ (5% MeOH/CH_2Cl_2); ^{1}H NMR (CD_3OD) δ 1.33−1.38(m, 1H), 1.49 (s, 18H), 1.71−1.75 (m, 1H), 1.91−1.97 (m, 3H), 2.08−2.11 (m, 1H), 3.15−3.19 (m, 1H), 3.44−3.47 (m, 1H), 3.60−3.63 (m, 1H); ^{13}C NMR (CD_3OD) δ 28.4, 31.2, 32.6, 40.9, 54.4, 58.1, 61.7, 82.6, 82.7, 175.4, 175.7; HRMS calcd for $C_{16}H_{31}NO_4$ $(MH)^+$ 315.2284, found 315.2284.

(2*S*,2′*S*,5*R*)-5-(2′-Amino-2′-hydroxycarbonylethyl)proline Hydrochloride (19). Di-*tert*-butyl ester **17** (220 mg, 0.70 mmol) was stirred for 6 h in a solution of 4.35 M HCl in dioxane (10 mL) and concentrated. The residue was coevaporated with water and then CH_2Cl_2 to afford hydrochloride **19** as a light yellow foam (194 mg, 99%): $R_f = 0.08$ (10% MeOH/CH_2Cl_2); ^{1}H NMR (CD_3OD) δ 1.83 (bs, 1H), 2.27 (bs, 2H), 2.41 (bs, 2H), 2.55−2.57 (m, 1H), 3.99 (bs, 1H), 4.16 (bs, 1H), 4.48 (bs 1H); ^{13}C NMR (CD_3OD) δ 28.1, 29.9, 33.5, 51.7, 59.2, 61.0, 170.8, 171.2; HRMS calcd for $C_8H_{15}N_2O_4$ $(MH - 2\ HCl)^+$ 203.1032, found 203.1037.

(2*S*,2′*S*,5*R*)-5-(2′-Amino-2′-methoxycarbonylethyl)proline Methyl Ester Hydrochloride (20). Methanol (14 mL) at 0 °C was treated dropwise with acetyl chloride (3.0 mL, 42.0 mmol) and stirred for 10 min. The resulting solution was added to hydrochloride **19** (194 mg, 0.70 mmol). The reaction was stirred at rt for 18 h and concentrated under vacuum to provide methyl ester hydrochloride **20** as an off-white foam (212 mg, 99%): R_f = 0.08 (4:1:1 *n*-BuOH/H_2O/AcOH); ^{1}H NMR (CD_3-OD) δ 1.83−1.85 (m, 1H), 2.28−2.31 (m, 2H), 2.38−2.50 (m, 2H), 2.56−2.63 (m, 1H), 3.87 (s, 3H), 3.91 (s, 3H), 3.97 (m, 1H), 4.23−4.26 (m, 1H), 4.55−4.57 (m, 1H); ^{13}C NMR (CD_3OD) δ 27.7, 29.6, 33.2, 51.4, 54.1, 54.3, 59.0, 59.2, 169.8, 170.1; HRMS calcd for $C_{10}H_{19}N_2O_4$ (MH − 2 HCl)$^+$ 231.1345, found 231.1340.

(3*S*,5*R*,8*S*)-Methyl 3-[*N*-(Boc)amino]-1-azabicyclo-[3.3.0]octan-2-one 8-Carboxylate [(3*S*,5*R*,8*S*)-21]. A solution of methyl ester hydrochloride **20** (212 mg, 0.70 mmol) in MeOH (14 mL) was treated with Et_3N (293 μL, 2.10 mmol), heated at reflux and stirred for 24 h, concentrated to a residue that was dissolved in CH_2Cl_2 (14 mL), treated with Et_3N (137 μL, 0.98 mmol) and di-*tert*-butyl dicarbonate (183 mg, 0.84 mmol), stirred at rt for 18 h, diluted with $CHCl_3$ (20 mL), and washed with 1 M NaH_2PO_4 (15 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated to a residue that was purified by flash chromatography using 50% EtOAc in hexanes as eluent. Evaporation of the combined collected fractions gave (3*S*,5*R*,8*S*)-methyl 3-[*N*-(Boc)amino]-1-azabicyclo[3.3.0]octan-2-one 8-carboxylate (**21**) as a white solid (143 mg, 68%): R_f = 0.17 (50% EtOAc/hexanes); $[\alpha]^{20}_D$ −72.6 (*c* 12.4, MeOH); ^{1}H NMR δ 1.44 (s, 9H), 1.67−1.76 (m, 2H), 2.05−2.09 (m, 1H), 2.18−2.25 (m, 1H), 2.34−2.48 (m, 1H), 2.95 (quintet, 1H, J = 5.8 Hz), 3.76 (s, 3H), 3.88 (heptet, 1H, J = 5.1 Hz), 4.18 (d, 1H, J = 8.9 Hz), 4.58−4.66 (m, 1H), 5.20−5.22 (m, 1H); ^{13}C NMR δ 28.5, 30.3, 33.7, 39.7, 52.7, 55.2, 56.7, 59.2, 80.0, 155.9, 171.5, 172.0; HRMS calcd. for $C_{14}H_{22}N_2O_5$ (M^+) 298.1529, found 298.1530.

(3*S*,5*R*,8*R*)-Methyl 3-[*N*-(Boc)amino]-1-azabicyclo[3.3.0]-octan-2-one 8-carboxylate [(3*S*,5*R*,8*R*)-21]. To a solution of ester (8*S*)-**21** (28 mg, 0.094 mmol) in THF (1 mL) at −50 °C was added dropwise a solution of 1 M NaHMDS in THF (188 μL, 0.188 mmol). The reaction mixture was stirred at −50 °C for 1 h, warmed to −20 °C, stirred for 1 h, and poured into aq 1 M NaH_2PO_4 (5 mL). The aqueous phase was extracted with EtOAc (6 × 5 mL), and the organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The ^{1}H NMR spectrum of the crude material in C_6D_6 showed an 8:1 mixture of (8*R*)-/(8*S*)-isomers based on the integration of the signals for the protons at the 8 position. The crude residue was purified by flash chromatography using 50% EtOAc in hexanes as eluent. Evaporation of the collected fractions yielded 19 mg (68%) of (3*S*,5*R*,8*R*)-**21** as a white foam (8:1 mixture): R_f = 0.17 (50% EtOAc/hexanes); ^{1}H NMR for the major isomer δ 1.43 (s, 9H), 1.46−1.64 (m, 2H), 2.06−2.22 (m, 2H), 2.46−2.50 (m, 1H), 2.93−2.99 (m, 1H), 3.73 (s, 3H), 3.94−3.99 (m, 1H), 4.47 (t, 1H, J = 7.8 Hz), 4.51−4.59 (m, 1H), 5.16 (bs, 1H); ^{13}C NMR for the major isomer δ 28.5, 31.7, 32.4, 38.6, 52.7, 55.2, 55.7, 58.2, 80.1, 155.8, 171.5, 172.0; HRMS calcd for $C_{14}H_{22}N_2O_5$ (M^+) 298.1529, found 298.1543.

(3*S*,5*R*,8*S*)-Methyl 3-amino-1-azabicyclo[3.3.0]octan-2-one 8-carboxylate hydrochloride (22). (3*S*,5*R*,8*S*)-Methyl 3-[*N*-(Boc)amino]-1-azabicyclo[3.3.0]octan-2-one 8-carboxylate (**21**, 11 mg, 0.036 mmol) was stirred in 5.70 M HCl in dioxane (1 mL) for 20 min and the volatiles were removed under reduced pressure to provide amine hydrochloride **22** as a colorless oil (9 mg, 99%): ^{1}H NMR (CD_3OD) δ 1.60−1.71 (m, 1H), 1.90−1.98 (m, 1H), 2.11−2.17 (m, 1H), 2.24−2.29 (m, 1H), 2.50−2.60 (m, 1H), 2.80−2.86 (m, 1H), 3.77 (s, 3H), 4.03−4.09 (m, 1H), 4.20 (d, 1H, J = 9.2 Hz), 4.40−4.45 (m, 1H); ^{13}C NMR (CD_3OD) δ 30.7, 34.7, 36.1, 53.3, 56.1, 56.3, 61.1, 169.2, 172.8; HRMS calcd for $C_9H_{14}N_2O_3$ (M − HCl)$^+$ 198.1004, found 198.1001.

(3*S*,5*R*,8*S*)-3-[*N*-(Boc)amino]-1-azabicyclo[3.3.0]octan-2-one 8-Carboxylic Acid [(3*S*,5*R*,8*S*)-1]. A 1 M aq solution of NaOH (201 μL, 0.20 mmol) was added to a solution of ester (8*S*)-**21** (50 mg, 0.17 mmol) in a 0.8 M solution of $CaCl_2$ in *i*-PrOH/H_2O (7:3, 5 mL). The reaction mixture was stirred for 4 h and then poured into aq 10% citric acid (15 mL). The aqueous phase was extracted with $CHCl_3$/*i*-PrOH (4:1, 5 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a residue that was purified by flash chromatography on silica gel using 2% MeOH in CH_2Cl_2 containing 1% AcOH as eluent to afford acid **1** (38 mg, 79%): R_f = 0.20 (10% MeOH/CH_2Cl_2 + 1% AcOH); $[\alpha]^{20}_D$ −80.6 (*c* 9.58, MeOH); ^{1}H NMR (CD_3OD) δ 1.45 (s, 9H), 1.53−1.79 (m 3H), 2.02−2.10 (m, 1H), 2.23 (dd, 1H, J = 13.4, 6.6 Hz), 2.43−2.57 (m, 1H), 2.63−2.71 (m, 1H), 3.90 (heptet 1H, J = 5.0 Hz), 4.11 (d, 1H, J = 9.2 Hz), 4.73 (dd, 1H, J = 12.0, 7.2 Hz); ^{13}C NMR (CD_3OD) δ 28.8, 30.9, 34.7, 38.5, 56.3, 60.3, 80.7, 158.1, 173.8, 174.3; HRMS calcd. for $C_{13}H_{21}N_2O_5$ 285.1450 (MH)$^+$, found 285.1452.

(3*S*,5*R*,8*R*)-3-[*N*-(Boc)amino]-1-azabicyclo[3.3.0]octan-2-one 8-Carboxylic Acid [(3*S*,5*R*,8*R*)-**1**] was synthesized from an 8:1 mixture of (8*R*)- and (8*S*)-**21** (19 mg, 0.064 mmol) using the procedure described above for (3*S*,5*R*,8*S*)-**1** and purified on silica gel using a gradient of 2−5% MeOH in CH_2-Cl_2 containing 1% AcOH as eluent. First to elute was (8*S*)-**1** (1 mg, 6%), followed by 3 mg (17%) of a 2:1 mixture of (8*R*)-/(8*S*)-isomers and (8*R*)-**1** (11 mg, 61%): R_f = 0.09 (10% MeOH/CH_2Cl_2 + 1% AcOH); $[\alpha]^{20}_D$ +79.4 (*c* 8.75, MeOH); ^{1}H NMR (CD_3OD) δ 1.40−1.51 (m, 1H), 1.45 (s, 9H), 1.77−1.80 (m, 1H), 2.02−2.24 (m, 2H), 2.57−2.73 (m, 2H), 3.91−3.96 (m, 1H), 4.37 (t, 1H, J = 8.1 Hz), 4.58 (dd, 1H, J = 11.2, 8.1 Hz); ^{13}C NMR (CD_3OD) δ 28.8, 33.1, 33.4, 36.7, 56.7, 57.1, 59.4, 80.7, 157.8, 174.0, 175.7; HRMS calcd for $C_{13}H_{21}N_2O_5$ 285.1450 (MH)$^+$, found 285.1438.

(3*S*,5*R*,8*S*)-*N*′-Methyl-3-[*N*-(Boc)amino]-1-azabicyclo-[3.3.0]octan-2-one 8-Carboxamide (23). An aqueous solution of methylamine (40 wt %) was slowly heated from 30°C to 60°C and the evolving methylamine gas was bubbled through a solution of (3*S*,5*R*,8*S*)-methyl 3-[*N*-(Boc)amino]-1-azabicyclo[3.3.0]octan-2-one 8-carboxylate (**21**, 19 mg, 0.064 mmol) in MeOH (2 mL) at 0 °C for 2 h. The reaction mixture was warmed to rt, capped, and left for 18 h. The volatiles were removed by bubbling argon and the residue was concentrated under vacuum, yielding carboxamide **23** as a white foam (19 mg, 99%): R_f = 0.51 (10% MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ −41.6 (*c* 4.33, MeOH); ^{1}H NMR δ 1.38 (s, 9H), 1.51−1.65 (m, 1H), 1.91−1.94 (m, 1H), 2.07 (q, 1H, J = 10.8 Hz), 2.29−2.37 (m, 2H), 2.58 (quintet, 1H, J = 6.1 Hz), 2.75 (d, 3H, J = 4.6 Hz), 3.72 (heptet, 1H, J = 5.1 Hz), 4.06 (d, 1H, J = 8.1 Hz), 4.19−4.27 (m, 1H), 5.29 (d, 1H, J = 6.4 Hz), 7.20 (s, 1H); ^{13}C NMR δ 26.7, 28.5, 29.6, 34.5, 35.7, 56.9, 58.1, 59.8, 80.5, 156.0, 170.5, 170.8; HRMS calcd for $C_{14}H_{24}N_3O_4$ 298.1767 (MH)$^+$, found 298.1774.

Enantiomeric Purity of (3*S*,5*R*,8*S*)-Methyl 3-[*N*-(Boc)-amino]-1-azabicyclo[3.3.0]nonane 8-Carboxylate 21. Ester (8*S*)-**21** (10 mg, 0.034 mmol) was treated with a 5.70 M solution of HCl in dioxane (1 mL) for 30 min. The solution was evaporated to amine hydrochloride **20**, which was dissolved in CH_2Cl_2 (1 mL) and treated with Et_3N (10 μL, 0.075 mmol) and either (*S*)- or (*RS*)-*N*-(*p*-toluenesulfony)prolyl chloride (12 mg, 0.041 mmol), stirred for 2 h at rt, diluted with EtOAc (5 mL), washed sequentially with 1 M NaH_2PO_4 (3 mL), saturated $NaHCO_3$ (3 mL), and brine (3 mL), dried (Na_2SO_4), filtered, and concentrated. In the case of the (*RS*)-diatereomers, the residue was purified by flash chromatography on silica gel using 2% MeOH in CH_2Cl_2 as eluent. Evaporation of the collected fractions yielded 14 mg (90%) of (2′*RS*,3*S*,5*R*,8*S*)-methyl 3-[*N*-(*p*-toluenesulfonyl)prolinamido]-1-azabicyclo[3.3.0]-octan-2-one 8-carboxylate [(2′*RS*)-**24**] as a 1:1 mixture of diastereomers as determined by measuring the signals of the diastereomeric aromatic doublets at 6.76 and 6.81 ppm: ^{1}H NMR (400 MHz, C_6D_6) δ 0.92−1.04 (m, 2H), 1.12−1.36 (m, 8H), 1.45−1.61 (m, 6H), 1.70−1.81 (m, 2H), 1.86 (s, 3H), 1.89 (s,

3H), 2.08−2.13 (m, 2H), 2.58−2.64 (m, 1H), 2.67−2.73 (m, 1H), 2.81−2.88 (m, 2H), 2.89−3.04 (m, 2H), 3.15−3.21 (m, 1H), 3.24−3.30 (m, 1H), 3.39 (s, 6H), 3.83−3.86 (m, 2H), 4.21 (dd, 2H, J = 8.6, 3.1 Hz), 4.31 (dd, 1H, J = 8.5, 3.2 Hz), 4.86−4.93 (m, 1H), 5.16−5.19 (m, 1H), 6.76 (d, 2H, J = 7.9 Hz), 6.81 (d, 2H, J = 7.9 Hz), 7.66 (d, 2H, J = 8.2 Hz), 7.72 (d, 2H, J = 8.2 Hz). The residue from the (*S*)-isomer, (2′*S*,3*S*,5*R*,8*S*)-methyl 3-[*N*-(*p*-toluenesulfonyl)prolinamido]-1-azabicyclo[3.3.0]octan-2-one 8-carboxylate [(2′*S*)-**24**, 99%], was not purified by chromatography and was directly analyzed by NMR spectroscopy: ^{1}H NMR (400 MHz, C_6D_6) δ 0.95−1.04 (m, 1H), 1.12−1.21 (m, 2H), 1.25−1.40 (m, 2H), 1.44−1.60 (m, 3H), 1.76 (quadruplet, 1H, J = 9.7 Hz), 1.88 (s, 3H), 2.07−2.14 (m, 1H), 2.67−2.73 (m, 1H), 2.86−2.94 (m, 1H), 2.96−3.04 (m, 1H), 3.13−3.19 (m, 1H), 3.39 (s, 3H), 3.85 (d, 1H, J = 8.3 Hz), 4.19 (dd, 1H, J = 8.6, 3.1 Hz), 4.85−4.90 (m, 1H), 6.80 (d, 2H, J = 7.9 Hz), 7.71 (d, 2H, J = 8.2 Hz). The limits of detection were determined by observation of the diastereomeric aromatic doublets at 6.76 and 6.81 ppm in the 400 MHz ^{1}H NMR spectrum of (2′*S*)-**24** in C_6D_6 during incremental additions of diastereomeric (2′*RS*)-**24** which demonstrated (2′S*S*)-**24** to be of >98% diastereomeric purity.

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Supporting Information Available: General experimental information, ^{1}H and ^{13}C NMR spectra of compounds (8*S*)- and (8*R*)-**1**, **11**, **15**, **16**−**20**, (8*S*)- and (8*R*)-**21**, **22**, and **23**; ^{1}H NMR spectra of compounds (2′*S*)- and (2′*RS*)-**24**; COSY and NOESY spectra of (8*S*)- and (8*R*)-**21**; crystallographic data for **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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