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Rigid Dipeptide Mimics: Synthesis of Enantiopure C6-Functionalized Pyrrolizidinone Amino Acids

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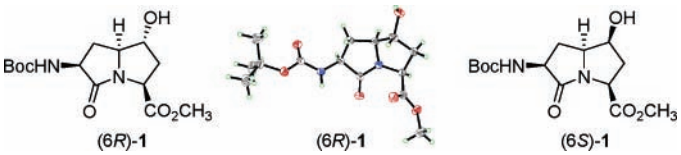

Enantiopure (3*S*,5*S*,6*R*,8*S*)- and (3*S*,5*S*,6*S*,8*S*)-6-hydroxypyrrolizidinone 3-*N*-(Boc)amino 8-methyl carboxylates (6*R*)- and (6*S*)-**1** were synthesized in seven steps starting from (2*S*)-α-*tert*-butyl *N*-(PhF) aspartate β-aldehyde (**10**). Carbene-catalyzed acyloin condensation of β-aldehyde **10** followed by acetylation provided a separable mixture of diastereomeric (2*S*,5*RS*,7*S*)-diamino-4-oxo-5-acetoxysuberates (**13**). Reductive amination and lactam annulation of the respective α-acetoxy ketones **13** provided hydroxypyrrolizidinones (6*R*)- and (6*S*)-**1** with retention of the C6-position stereochemistry. The X-ray crystallographic study of (6*R*)-**1** indicated dihedral angles constrained within the heterocycle that were consistent with the ideal values for the $i + 1$ and $i + 2$ residues of a type II′ β-turn. Hydrogen-bonding studies on *N*′-methyl-*N*-(Boc)aminopyrrolizidin-2-one carboxamides (6*R*)- and (6*S*)-**21** in DMSO-d_6, demonstrated different NH chemical shift displacements and temperature coefficients for the amide and carbamate protons, indicative of solvent shielded and exposed hydrogens in a turn conformation. 6-Hydroxy pyrrolizidinone amino carboxylate **1** may thus find application as a constrained alaninylhydroxyproline dipeptide mimic. In addition, alkylation of the hydroxyl group provided orthogonally protected pyrrolizidinone amino dicarboxylate (6*R*)-**25**, demonstrating potential for expanding the diversity of these rigid dipeptide surrogates for the exploration of peptide conformation−activity relationships.

Introduction

β-Turns are common structural motifs found in folded proteins and peptides. They play important roles in stabilizing tertiary structure, initiating folding, and facilitating intermolecular recognition.[1] Constrained analogues that resemble β-turn secondary structures have thus become valuable tools for the development of pharmaceuticals because they can provide information about the biologically active protein conformation in structure−activity relationship studies.[2]

Azabicycloalkane amino acids can serve as conformationally rigid backbone analogs of type II′ β-turn structure, contingent on stereochemistry and ring size[3] (Figure 1). Although the introduction of functional groups onto the azabicycloalkane ring system has typically proven more challenging and step intensive than the synthesis of the heterocycle, the potential for such scaffolds to serve as rigid peptide surrogates that mimic both the backbone and side-chain geometry makes them particularly interesting targets for peptide mimicry.

We have previously reported on the synthesis of the 5,5-fused azabicycloalkanone amino acid **2**[4] by complementary methodology to our earlier syntheses of related amino acids with fused 6,5-, 5,6-, 7,5-, and 6,6-ring systems.[5] Many mono- and multialkyl- and heteroalkyl-substituted indolizidinone amino acids[6] as well as 4-alkyl-substituted 6-oxa- and 6-thiapyrroliz-

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(2) (a) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R., Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J Med. Chem.* **1993**, *36*, 3039. (b) Marshall, G. R. *Tetrahedron* **1993**, *49*, 3547. (c) Hruby, V, J. *Nat. Rev. Drug Discovery* **2002**, *1*, 847.

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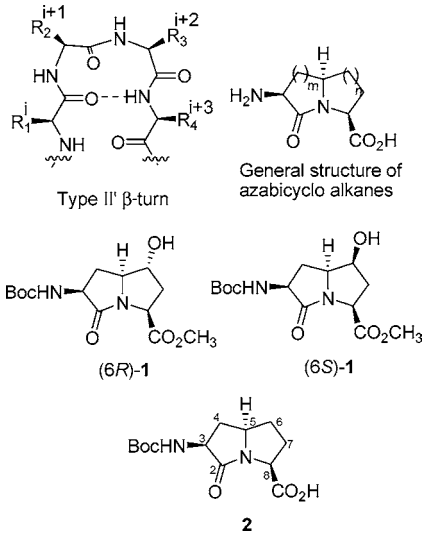

FIGURE 1. Representative β-turn and azabicyclo[*X*.*Y*.0] amino acid structures.

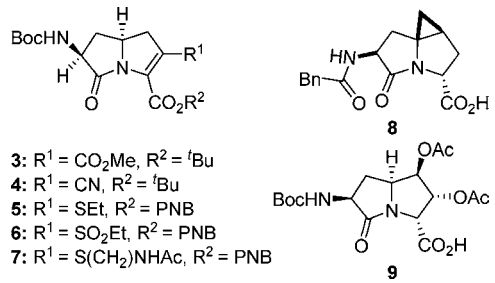

FIGURE 2. Representative pyrrolizidinone amino acids.

idinones[7] have been previously synthesized; however, few preparations of pyrrolizidinone amino acids bearing substitutents have provided enantiomerically pure product. As γ-lactam relatives of the β-lactam antibiotics, unsaturated pyrrolizidinones bearing ring substitutents have been more intensively studied than their saturated counterparts because of their relatively higher antibacterial activity. For example, unsaturated pyrrolizidinones **3**−**7** (Figure 2) have been synthesized by routes featuring [3 + 2] cyclizations,[8] Rh(II)-catalyzed insertions,[9] and homologation of L-aspartic acid.[10] Tricyclic pyrrolizidinone carboxylic acids **8** have been made by Hanessian et al., employing intramoleular cyclopropanation and enolization protocols in 19 steps starting with *N*-Boc pyrrolidinone.[11] In addition, 6,7-diacetoxypyrrolizidinone **9** was synthesized in 14 steps from tri-*o*-benzylarabinose in 5.8% overall yield.[12]

Pyrrolizidinone amino acid **2** was prepared by a route featuring the acyloin condensation of aspartate β-aldehyde **10** to provide (2*S*,5*R*,7*S*)-di-*tert*-butyl 5-hydroxy-4-oxo-2,7-bis[*N*-(PhF)amino]suberate **12** as a precursor to the bicyclic system. *N*-(Boc)Aminopyrrolizidinone acid **2** was then prepared employing a sequence featuring removal of the α-hydroxyl group, annulations by reductive amination, and lactam formation followed by ester hydrolysis. By performing the corresponding annulation chemistry on the α-acetoxy ketone, we envisioned that side chains could be directly introduced onto the 5,5-ring system in as many steps as were taken for the synthesis of the *N*-(Boc)aminopyrrolizidinone amino acid. We now report the synthesis of enantiopure (6*R*)- and (6*S*)-hydroxypyrrolizidin-2-one amino acids (6*R*)- and (6*S*)-**1**.

Results and Discussion

(2*S*,7*S*)-Di-*tert*-butyl 5-acetoxy-4-oxo-2,7-bis[*N*-(PhF)amino]-suberate (**13**) was obtained in 63% yield as a 1:1 mixture of diastereomers by acyloin condensation of aspartate β-aldehyde **10** and acetylation (Scheme 1).[4] Diastereomers (5*S*)- and (5*R*)-**13** were separated and respectively purified by fractional crystallization from methanol and column chromatography. Each was independently subjected to reductive amination, which was expected to proceed by hydrogenolytic cleavage of the phenylflorenyl groups, intramolecular imine formation, protonation, and hydrogen addition to the least hindered face of the iminium ion intermediate, to yield the 4-acetoxy-5-alkylprolines. In the case of the synthesis of the parent pyrrolizidinone amino acid **2**, however, during the hydrogenation, β-elimination of ammonium ion led to desamino side product, which was minimized by using 100 mol % of acetic acid in the reductive amination step. In contrast, the use of AcOH (100 mol %) in the reductive amination of (5*R*)-acetoxy diamino suberate (5*R*)-**13** did not prevent β-elimination, and *des*-amino side product (4*R*)-**14** was obtained as the major product, accompanied by a minor amount of diamino acetoxy prolinate (4*R*)-**15** (Scheme 1). Furthermore, the α-elmination product, 5-alkylproline *tert*-butyl ester **16** was exclusively isolated from application of the AcOH conditions in the reductive amination of (5*S*)-**13**.

A systematic investigation to minimize the formation of β- and α-elimination products from reductive amination of the diastereomers (5*R*)- and (5*S*)-**13** was undertaken. A plausible mechanism for the formation of β-elimination product (4*R*)-**14** entails imine to enamine tautomerization, followed by β-elimination of the primary amine to form an α,β-unsaturated imine that was subsequently reduced.[4] The propensity for amine elimination was favored by protonation. By employing HCl as proton source in the reductive amination, various concentrations of acid were studied by periodically monitoring crude fractions using LC−MS. At 0.1 M and at 0.01 M HCl complete conversion was achieved in 7 and 24 h, respectively; however, β-elimination product (4*R*)-**14** predominated. At 0.003 M HCl, the required diamino acetoxy prolinate (4*R*)-**15** was formed as major product containing trace amounts of monoamine (4*R*)-**14** after 48 h. Hydrogenation of suberate (5*R*)-**13** using palladium-on-carbon as catalyst in 4:1 EtOH/THF containing 0.003 M HCl afforded diamine (4*R*)-**15** in 67% isolated yield (Scheme 2). (6*R*)-Hydroxypyrrolizidinone (6*R*)-**1** was then synthesized in 23% overall yield starting from acetoxy diamino

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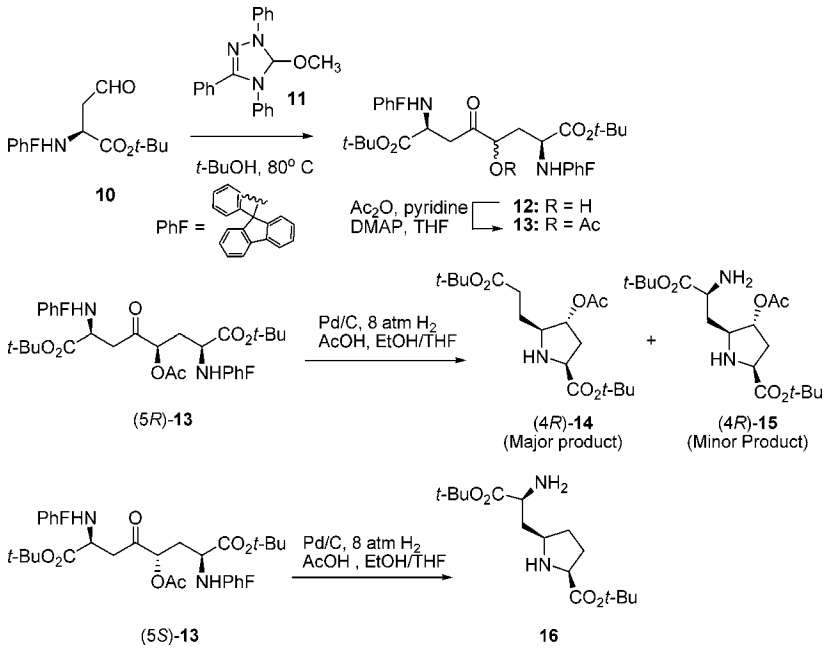
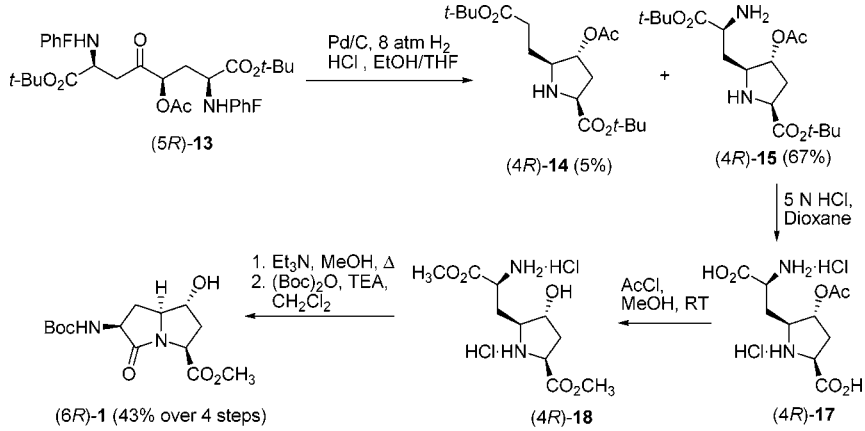
SCHEME 1. Synthesis of 13 and Reductive Amination of (5*R*)-13 and (5*S*)-13



SCHEME 2. Synthesis of Methyl *N*-(Boc)amino-(6*R*)-hydroxypyrrolizidinone Amino Carboxylate (6*R*)-1



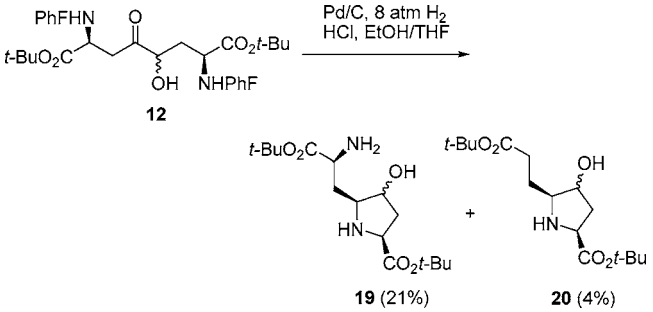
suberate (5*R*)-**13** by a five-step sequence featuring *tert*-butyl ester hydrolysis using 5 N HCl in dioxane, esterification with AcCl in MeOH, lactam formation using excess Et_3N in MeOH at reflux, and Boc protection using di-*tert*-butyl dicarbonate and Et_3N.

Attention was turned next to prevent formation of α-acetoxy elimination product **16**, during reductive amination of diastereomer (5*S*)-**13**. Hydrogenolysis of the acetoxy group[13] was considered to take place in the presence of Pd/C in EtOH/THF (4:1) with AcOH as proton source. The speculative mechanism for loss of acetoxy group could involve the tautomerization of the iminum ion intermediate to an enamine from which an acetoxy-Pd π-allyl complex could be formed and reduced (Figure 3). Although no π-2-aminoallyl Pd complexes have been reported to the best of our knowledge, the related π-2-alkoxyallyl Pd complexes have been employed in synthesis.[13] Product **16** from the loss of acetoxy group was confirmed by conversion to the *N*-(Boc)aminopyrrolizidinone amino acid **2**, by lactam cyclization and Boc protection.[4]

Considering that loss of the OH group would be less facile than the electron-deficient acetate, we performed the reductive amination on a diastereomeric mixture of **12** using the palladium-on-carbon and AcOH (50 mol %) conditions. A diastereomeric mixture of diamino alcohols **19** was isolated in only 21% yield and β-elimination product **20** was also obtained in 4% yield (Scheme 3).

In light of potential for the adsorption of alcohol onto Pd/C diminishing yield, we continued investigating the acetate (5*S*)-

SCHEME 3. Reductive Amination of Hydroxy Suberate 5



(13) Reviewed in (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1−24. (b) Muzart, J. *Tetrahedron* **2005**, *61*, 9423.

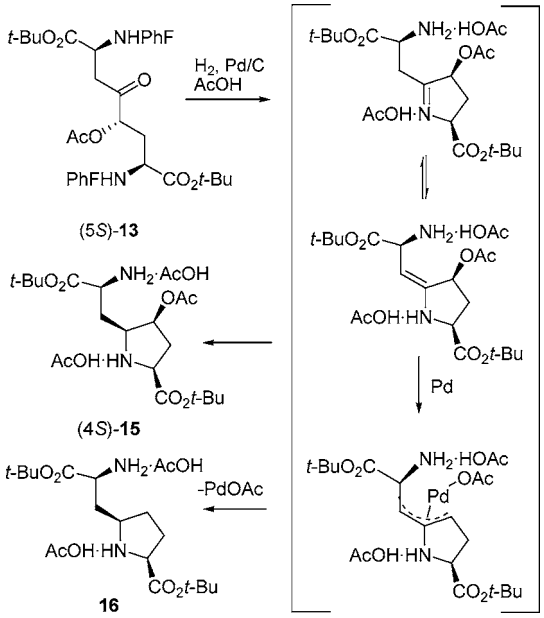


FIGURE 3. Proposed mechanism for the formation of **16**.

13 in the reductive amination. Considering that the elimination of α-acetoxy group could be influenced by the acid in the reductive amination reaction, we employed a series of proton sources: HCl, TFA, AcOH, H_3PO_4, and NH_4HCO_2. The catalyst was also varied from Pd/C to PtO_2 and $Pd(OH)_2$ (Table 1). By monitoring the reaction using LCMS analysis on crude samples, no variations of the acid and catalyst were observed to prevent loss of the acetate group.

In the reductive amination of (5*S*)-**13**, by employing palladium hydroxide-on-carbon in 7:1 EtOH/THF containing HCl (0.005 N) as proton source for 24 h (entry 13, Table 1), acetoxyproline (4*S*)-**15** and acetoxy eliminated product **16** were isolated in 43% and 5% isolated yields, respectively, without deaminated product (4*S*)-**14** (Scheme 4). Pyrrolizidinone (6*S*)-**1** was then synthesized from diamine (4*S*)-**15** by the same route described above for making (6*R*)-**1** and isolated in 11% overall yield starting from acetoxy diaminosuberate (5*S*)-**13**.

For the conformational analysis studies described below, *N*′-methyl-*N*-(Boc)-3-amino-6-hydroxypyrrolizidin-2-one 8-carboxamides (6*R*)- and (6*S*)-**21** were prepared quantitatively by

TABLE 1. Reductive Amination of (5*S*)-13

entry	acid source (quantity)	catalyst (20 w/w %)	time (h)	% ratio of products formed[a] (4*S*)-**15**	(4*S*)-**14**	**16**
1	AcOH (0.5 equiv)	Pd/C	24	1	4	95
2	TFA (1 equiv)	Pd/C	5	16	53	31
3	H_3PO_4 (1 equiv)	Pd/C	4	34	9	57
4	NH_4HCO_2 (1 equiv)	Pd/C	24	1.5	1.5	97
5	HCl (0.1 N)	Pd/C	7	44	34	22
6	HCl (0.01 N)	Pd/C	24	46	32	22
7	HCl (0.001 N)	Pd/C	24	59	23	17
8	HCl (0.1 N)	PtO_2/C	24	30	14	56
9	HCl (0.01 N)	PtO_2/C	24	14	17	69
10	HCl (0.001 N)	PtO_2/C	24	57	28	15
11	HCl (0.1 N)	$Pd(OH)_2$/C	14	29	35	36
12	HCl (0.01 N)	$Pd(OH)_2$/C	24	46	29	25
13	HCl (0.005 N)	$Pd(OH)_2$/C	24	94	<1	5
14	HCl (0.01 N), NH_4Cl	$Pd(OH)_2$/C	4	15	31	54
15	HCl (0.01 N), NH_4OAc	$Pd(OH)_2$/C	7	38	13	49

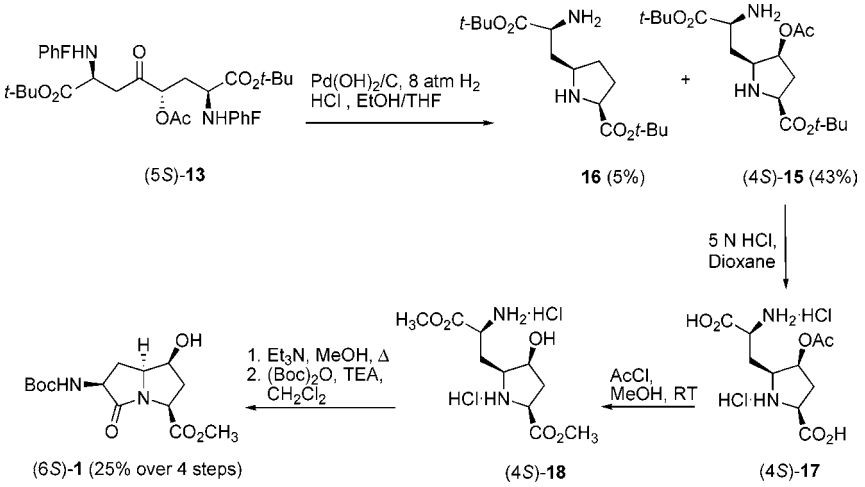
[a] Product ratios calculated from LC−MS.

treating (6*R*)- and (6*S*)-**1** with methylamine in methanol (Scheme 5). In cursory examinations at diversifying the (6*R*)-alcohol, hydroxylpyrrolizidinone (6*R*)-**1** was activated with methanesulfonyl chloride, triethylamine, and catalytic DMAP in dichloromethane to give the corresponding methansulfonate (6*R*)-**22** in 94% yield. Attempts to displace methanesulfonate with sodium azide and potassium cyanide were, however, unsuccessful, probably due to the steric hindrance of the concave face of (6*R*)-**22**. Furthermore, (6*R*)-**22** and hydroxy pyrrolizidinone (6*R*)-**1** were independently subjected to ester hydrolysis with LiOH in 1:1 dioxane and water mixture to afford carboxylic acids (6*R*)-**23** and (6*R*)-**24** in 86% and 67% respective yields, without epimerization of the C-8 center. Finally hydroxypyrrolizidinone (6*R*)-**1** was alkylated using *tert*-butyl bromoacetate and sodium hydride in THF at 0 °C to yield diester (6*R*)-**25** (30% yield).

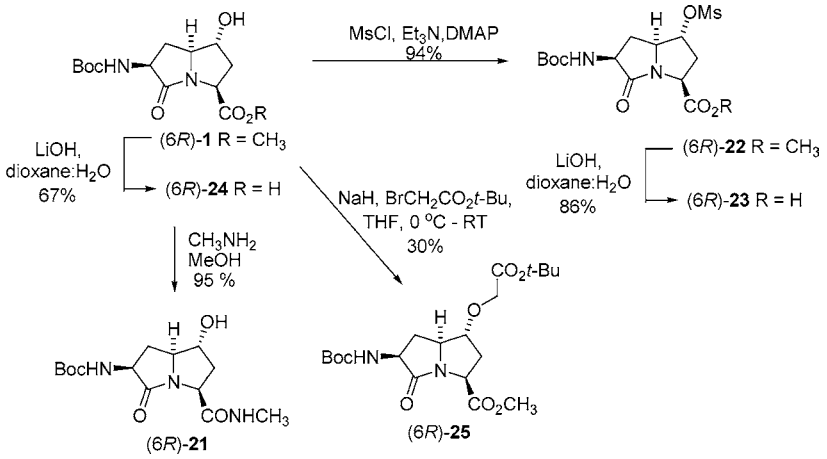
Configurational and Conformational Analysis of Hydroxypyrrolizidinone Amino Acids

The relative stereochemistry of hydroxypyrrolizidinone *N*-(Boc)amino esters and amides was initially determined by NMR spectroscopy. At first, a COSY spectrum was used to assign

SCHEME 4. Synthesis of Methyl *N*-(Boc)amino-(6S)-Hydroxypyrrolizidinone Amino Carboxylate (6*S*)-1



SCHEME 5. Modification of (6*R*)-Hydroxypyrrolizidinone (6*R*)-1



the through-bond couplings sequentially from the downfield carbamate NH proton. Subsequently the relative stereochemistry of the ring fusion and alcohol bearing carbons was assigned using a NOESY spectrum. In the case of the (5*S*,6*R*)-isomer (6*R*)-**1**, transfer of magnetization from the protons at C-3 and C-8, with chirality derived from L-Asp, to the ring fusion C-5 proton was indicative of their position on the same face of the bicycle and established the concave geometry of the pyrrolizidinone (Figure 4). The stereochemistry of the alcohol bearing carbon was assigned from the observed NOE between the C-6 proton and the C-4 β-proton.

In the case of the (5*S*,6*S*)-isomer (6*S*)-**21**, diagnostic NOEs were observed respectively between each of the backbone C3 and C8 protons and the ring fusion C5 proton similar to (6*S*)-**1** (Figure 4). Furthermore, the NOE between the C6 proton and both the C3 proton and C8 proton confirmed the stereochemistry of alcohol bearing carbon. The relative stereochemistry of the linear precursors, acetoxy suberates (5*R*)- and (5*S*)-**13**, was assigned based on the configurations of hydroxypyrrolizidinones (6*R*)-**1** and (6*S*)-**21**, respectively.

A comparison of the influence of temperature on the chemical shifts of the NH protons of *N*-(Boc)aminohydroxypyrrolizidinone *N*′-methylamides (6*R*)- and (6*S*)-**21** with those for the parent *N*-(Boc)aminopyrrolizidinone *N*′-methylamide in DMSO-d_6 was made to study the influence of the hydroxyl group on the propensity for hydrogen bonding in these β-turn mimics. The temperature coefficients ($\Delta\delta/\Delta T$) for the parent heterocycle were measure previously to be -5.2 and -10.2 ppb/K for the amide and carbamate protons, respectively, indicative of solvent shielded and solvent exposed hydrogens in a β-turn conformation.[4] Similar temperature coefficient trends were observed for the protons of hydroxypyrrolizidinones (6*R*)- and (6*S*)-**21** (Figure 5); however, the temperature coefficients for the amide and carbamate NH protons were respectively increased and decreased for (6*R*)-**21** ($\Delta\delta/\Delta T = -4.3$ and -8.4 ppb/K) and (6*S*)-**21** ($\Delta\delta/\Delta T = -5.3$ and -11.7 ppb/K). The variations in the temperature coefficients reflect the influence of the hydroxyl group, which was inductive in both cases. Hydrogen bonding of the hydroxyl group with the carbamate and amide was, however, only possible in the (6*S*)-**21** isomer. The inductive effect of the electron deficient hydroxyl group increased the acidity of the NH protons and thus favored their potential as hydrogen donors.[14] Hence, higher temperature coefficient values were observed for (6*R*)-**21** indicative of better intra- and intermolecular hydrogen bonds. On the other hand, in (6*S*)-**21**, the hydroxyl group may interact with the carbonyls and exchange with NHs of the carbamate and amide in ways that perturb their potential for hydrogen bonding and result in lower temperature coefficients.

In the crystal structure of (6*R*)-**1**, the backbone dihedral angles of the atoms constrained within the bicyclic ring system ($\psi =$

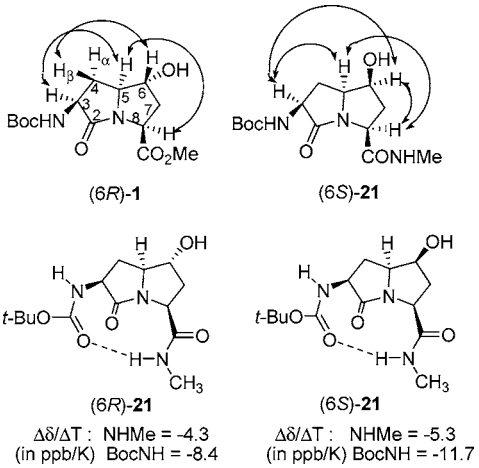


FIGURE 4. Conformational and configurational analysis of (6*R*)-**1**, (6*R*)-**21**, and (6*S*)-**21**. (Double headed arrows represent NOE and dotted lines represent hydrogen bonding.)

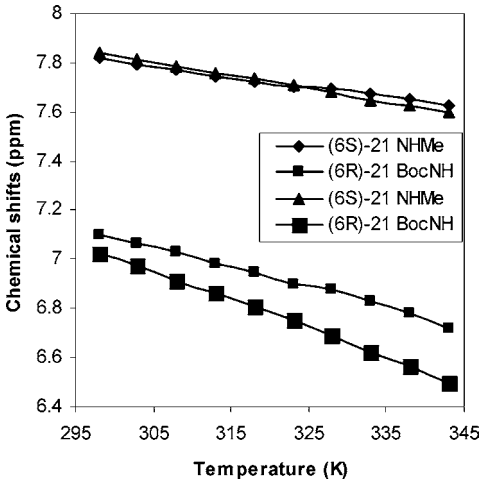


FIGURE 5. Variable-temperature studies for (6*R*)-**21** and (6*S*)-**21** in DMSO-d_6.

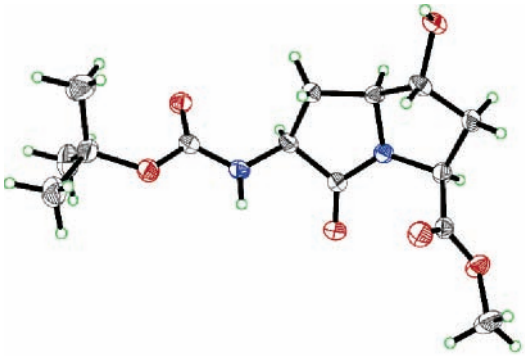
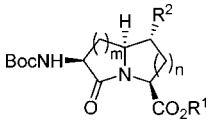


FIGURE 6. Ball and stick diagram of the X-ray structure of (6*R*)-3-*N*-(Boc)amino-6-hydroxypyrrolizidin-2-one 8-carboxylate (6*R*)-**1** (C, gray; H, green; N, blue; O, red).

TABLE 2. Comparison of the Dihedral Angles from Azabicyclo[*X.Y.*0]alkanone X-ray Data



entry	*n*	*m*	R^1	R^2	ψ, deg	ϕ, deg
(6*R*)-**1**	1	1	Me	OH	−141	−40
2[4]	1	1	Me	H	−149	−45
26[5c]	1	2	Me	H	−141	−34
27[5b]	2	1	Me	H	−176	−78
28[5d]	2	2	*t*-Bu	H	−163	48
type II′ β-turn $i+1$ and $i+2$ residues[16]					−120	−80

−141° and $\phi = -40°$, Figure 6) were in agreement with values of the central residues in an ideal type II′ β-turn ($\psi = -120°$ and $\phi = -80°$). Comparison of the values for hydroxypyrrolizidinone (6*R*)-**1** with those observed in the crystal structures of the parent pyrrolizidinone and relative indolizidinone and quinolizidinone analogues possessing the same relative stereochemistry demonstrated the influence of the ring size on conformation (Table 2).[4,5b−d] A subtle change in the dihedral angles was observed on addition of the hydroxyl group to the *N*-(Boc)aminopyrrolizidinone methyl carboxylate. The deviation in the backbone dihedral angles may be attributed to the influence of OH functionality on the ring puckering.[15]

Conclusion

Enantiopure (3*S*,5*S*,6*R*,8*S*)- and (3*S*,5*S*,6*S*,8*S*)-6-hydroxypyrrolizidin-2-one 3-*N*-(Boc)amino 8-methyl carboxylates (6*R*)- and (6*S*)-**1** were synthesized by five-step sequences in 23% and 14% respective overall yields from 4-acetoxy diaminosuberates (5*R*)- and (5*S*)-**13**. Conformational analysis of *N*-(Boc)amino-*N*′-methylamide derivatives of hydroxypyrrolizidinones (6*R*)- and (6*S*)-**21** by NMR spectroscopy and measurement of temperature coefficients indicated hydrogen bonding in a turn conformation. In comparisons of pyrrolizidinone and hydroxypyrrolizidinone amides, the inductive and hydrogen-bonding effects of the alcohol group were found to respectively raise and lower the NH temperature coefficients in (6*R*)- and (6*S*)-**21** relative to those for the parent pyrrolizidinone. Furthermore, X-ray crystallographic analysis demonstrated that the dihedral angles within the hydroxypyrrolizidinone ring carboxylate (6*R*)-**1** were consistent with those of the central residues of a type II′ β-turn. With potential for mimicry of the backbone and side chains of β-turn conformations, hydroxypyrrolizidinones (6*R*)- and (6*S*)-**1** should find utility for studying structure−activity relationships in peptide science.

Experimental Section

(2*S*,2′*S*,4*R*,5*S*)-*tert*-Butyl 5-(2′-*tert*-Butoxycarbonyl-2′-aminoethyl)-4-acetoxypyrrolidine 2-Carboxylate (4*R*)-15. A suspension of ketone (5*R*)-**13** (330 mg, 0.38 mmol, prepared according to reference 4) in 35 mL of a 4:1 solution of absolute ethanol/THF was treated with 12 N HCl (3 μL) and palladium-on-carbon (33 mg, 10 wt %). The reaction vessel was filled, vented, and filled three times with a hydrogen atmosphere. The reaction mixture was stirred under 8 atm of H_2 for 24 h, more catalyst (33 mg, 10 wt %) was added, and stirring under 8 atm of H_2 was continued for another 24 h. The reaction mixture was filtered onto Celite and washed with methanol (3 × 10 mL). The combined filtrate and washes were evaporated under vacuum 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 $NaHCO_3$ solution and extracted with $CHCl_3$/*i*-PrOH (4:1, 4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a residue that was purified by flash chromatography using a gradient 3−5% MeOH/CH_2Cl_2. First to elute was (2*S*,4*R*,5*S*)-5-(2′-(*tert*-butoxycarbonyl)ethyl)-4-acetoxypyrrolidine-2-*tert*-butyl carboxylate (4*R*)-**15** (5.1 mg, 5%): $[\alpha]^{20}_D$ −16.7 (*c* = 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.48 (s, 9H), 1.60−1.90 (m, 2H), 2.03 (s, 3H), 2.08−2.17 (m, 3H), 2.37 (dd, 2H, *J* = 6.7, 7.6 Hz), 3.08 (ddd, 1H, *J* = 3.7, 6.7, 7.6 Hz), 3.78 (t, 1H, *J* = 8.2 Hz), 4.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 28.2 (3C), 28.4 (3C), 29.8, 33.4, 36.9, 60.3, 65.0, 79.8, 81.5, 82.7, 172.2, 174.1, 174.1; HRMS calcd for $C_{18}H_{32}NO_6$ $(MH)^+$ 358.2224, found 358.2230. Second to elute was (2*S*,2′*R*,4*R*,5*S*)-*tert*-butyl 5-(2′-(*tert*-butoxycarbonyl)-2′-aminoethyl)-4-acetoxypyrrolidine-2-carboxylate (4*R*)-**14** (95 mg, 67%): $[\alpha]^{20}_D$ −5.7 (*c* = 1.4, $CDCl_3$); ^{1}H NMR (CD_3OD) δ 1.48 (s, 18H), 1.72−1.90 (m, 2H), 2.04 (s, 3H), 2.22−2.08 (m, 5H), 3.27 (ddd, 1H, *J* = 3.7, 5.3, 8.6 Hz), 3.50 (dd, 1H, *J* = 5.1, 8.0 Hz), 3.82 (t, 1H, *J* = 7.2 Hz), 4.87 (dt, 1H, *J* = 3.3, 6.2 Hz); ^{13}C NMR (DMSO-d_6) 21.0, 28.3 (6C), 36.6, 38.8, 53.7, 60.4, 62.6, 80.1, 83.3, 82.5, 172.2, 174.3, 175.6; HRMS calcd for $C_{18}H_{32}N_2O_6$ $(MH)^+$ 373.2333, found 373.2327.

(2*S*,2′*S*,4*R*,5*S*)-4-Acetoxy-5-(2′-amino-2′-carboxyethyl)pyrrolidine-2-carboxylic Acid (4*R*)-17. Di-*tert*-butyl ester (4*R*)-**15** (95 mg, 0.25mmol) was stirred in a solution of 5 M HCl in dioxane (dry HCl in dioxane) (10 mL) for 6 h, and the reaction volume was concentrated. The residue was coevaporated with water and then CH_2Cl_2 to afford hydrochloride (4*R*)-**17** as a white foam (82 mg, 99%): ^{1}H NMR (CD_3OD) δ 2.13 (s, 3H), 2.31 (ddd, 1H, *J* = 4.5, 8.2, 14.5 Hz), 2.50−2.69 (m, 3H), 3.58 (ddd, 1H, *J* = 1.1, 5.1, 5.4 Hz), 3.67 (m, 2H), 3.74 (ddd, 1H, *J* = 1.5, 5.0, 5.8), 4.20 (m, 1H), 4.29 (dd, 1H, *J* = 4.5, 9.4 Hz), 4.69 (t, 1H, *J* = 9.4 Hz), 5.31 (dt, 1H, *J* = 2.9, 5.4 Hz); ^{13}C NMR (CD_3OD) δ 22.7, 30.8, 35.6, 53.8, 58.2, 64.0, 73.3, 169.8, 169.8, 170.3; HRMS calcd for $C_{10}H_{17}N_2O_6$ $(MH)^+$ 261.1089, found 261.1085.

(2*S*,2′*S*,4*R*,5*S*)-Methyl 4-Hydroxy-5-(2′-methoxycarbonyl-2′-aminoethyl)pyrrolidine-2-carboxylate (4*R*)-18. Methanol (7 mL)

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at 0 °C was treated dropwise with acetyl chloride (1.5 mL, 42.0 mmol) and stirred for 10 min. The resulting solution was added to hydrochloride (4*R*)-**17** (73 mg, 0.24 mmol). The reaction was stirred at rt for 18 h and concentrated under vacuum to provide dimethyl ester hydrochloride (4*R*)-**18** as an off-white foam (85 mg, 99%): ^{1}H NMR (CD_3OD) δ 2.25 (ddd, 1H, J = 5.1, 8.1, 14.7 Hz), 2.39 (ddd, 1H, J = 3.7, 9.1, 13.7 Hz), 2.46−2.59 (m, 2H), 3.59 (dd, 1H, J = 4.5, 8.1 Hz), 3.64−3.69 (m, 2H), 3.75 (dd, 1H, J = 5.8, 10.9 Hz), 3.78−3.87 (m, 1H), 3.87 (s, 3H), 3.92 (s, 3H), 4.35 (dd, 1H, J = 5.2, 8.2 Hz), 4.39 (dd, 1H, J = 4.5, 9.2 Hz), 4.69 (t, 1H, J = 9.0 Hz); ^{13}C NMR (CD_3OD) δ 29.6, 36.3, 48.1, 52.3, 57.1, 57.1, 62.6, 72.1, 168.0, 168.2; HRMS calcd for $C_{10}H_{18}N_2O_5$ $(MH)^+$ 247.1288, found 247.1286.

(3*S*,5*S*,6*R*,8*S*)-Methyl 3-*N*-(Boc)amino-6-hydroxypyrrolizidinone-8-carboxylate (6*R*)-1. A solution of methyl ester hydrochloride (4*R*)-**18** (175 mg, 0.48 mmol) in MeOH (7 mL) was treated with Et_3N (201 μL, 1.45 mmol), heated at reflux, stirred for 24 h, cooled, and concentrated to a residue that was dissolved in CH_2Cl_2 (14 mL), treated with Et_3N (100 μL, 0.72 mmol) and di-*tert*-butyl dicarbonate (124 mg, 0.57 mmol), stirred at rt for 18 h, diluted with $CHCl_3$ (20 mL), and washed with 1 M NaH_2PO_4. The aqueous layer was extracted with $CHCl_3$, and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated to a residue that was purified by flash chromatography using 70% EtOAc in hexane as eluent. Evaporation of the combined collected fractions gave pyrrolizidinone (6*R*)-**1** as a white solid (65 mg, 43%): mp 137.5 °C; $[\alpha]^{20}_D$ −85.4 (c = 1.6, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.79 (ddd, 1H, J = 9.6, 11.5, 11.7 Hz), 2.34−2.37 (m, 2H), 2.95 (dt, 1H, J = 6.2,11.5 Hz), 3.08−3.29 (br s, 1H), 3.67 (ddd, 1H, J = 5.4, 7.8, 9.6 Hz), 3.75 (s, 3H), 4.13 (dd, 1H, J = 7.8, 11.8 Hz), 4.22 (t, 1H, J = 5.4 Hz), 4.57 (ddd, 1H, J = 6.4, 6.6, 11.5 Hz), 5.41 (d, 1H, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 28.0 (3C), 37.0, 39.6, 52.5, 54.2, 55.5, 62.4, 73.0, 79.8, 155.4, 171.1, 171.8; HRMS calcd for $C_{14}H_{22}N_2O_6$ $(MH)^+$ 315.1550, found 315.1545.

(2*S*,2′*S*,4*S*,5*S*)-*tert*-Butyl 5-(2′-(*tert*-Butoxycarbonyl)-2′-aminoethyl)-4-acetoxypyrrolidine-2-carboxylate (4*S*)-15. A suspension of ketone 5(*S*)-**6** (500 mg, 0.57 mmol) in 70 mL of a 7:1 solution of absolute ethanol/THF was treated with concentrated HCl (20 μL) and palladium-on-carbon (100 mg, 20 wt %). The reaction vessel was filled, vented, and filled three times with a hydrogen atmosphere. The reaction mixture was stirred under 8 atm of H_2 for 24 h, filtered onto Celite, and washed with methanol (3 × 10 mL). The combined filtrate and washings were evaporated under vacuum 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 using saturated $NaHCO_3$ solution and extracted with $CHCl_3$/*i*-PrOH (4:1, 4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a residue that was purified by flash chromatography using a gradient of 3−5% MeOH in CH_2Cl_2. First to elute was (2*S*,4*S*,5*S*)-*tert*-butyl 5-(2-*N*-(*tert*-butoxycarbonyl)aminoethyl)-4-acetoxypyrrolidine-2-carboxylate (4*S*)-**15** (91 mg, 43%): $[\alpha]^{20}_D$ +10 (c = 1.35, MeOH); ^{1}H NMR (CD_3OD) δ 1.48 (s, 9H), 1.49 (s, 9H), 1.78 (ddd, 1H, J = 6.0, 7.6, 14.1 Hz), 1.92 (ddd, 1H, J = 6.0, 7.7, 14.1 Hz), 2.02 (s, 3H), 2.03−2.09 (m, 1H), 2.48 (ddd, 1H, J = 5.1, 10.3, 14.6 Hz), 3.19 (ddd, 1H, J = 4.2, 6.0, 7.5 Hz), 3.46 (dd, 1H, J = 6.4, 7.5 Hz), 3.68 (dd, 1H, J = 4.1, 10.3 Hz), 5.14 (br t, 1H, J = 2.3 Hz); ^{13}C NMR (CD_3OD) δ 20.9, 28.2 (3C), 28.3 (3C), 34.9, 38.6, 54.0, 59.6, 61.1, 76.5, 82.5, 82.8, 171.9, 174.3, 175.6; HRMS calcd for $C_{18}H_{32}N_2O_6$ $(MH)^+$ 373.23331, found 373.23333. Second to elute was (2*S*,5*R*)-*tert*-butyl 5-(2-(*N*-(*tert*-butoxycarbonyl)aminoethyl)-pyrrolidine-2-carboxylate **16** (8 mg, 5%): $[\alpha]^{20}_D$ −11.1 (c = 1, MeOH); ^{1}H NMR (CD_3OD) δ 1.35−1.45 (m, 2H), 1.47 (s, 9H), 1.50 (s, 9H), 1.81 (ddd, 1H, J = 5.5, 8.0, 14.5 Hz), 1.87−2.03 (m, 3H), 2.13 (m, 1H), 3.72 (m, 2H); ^{13}C NMR (CD_3OD) 28.3 (6C), 31.3, 32.0, 38.8, 53.9, 57.9, 61.6, 82.6, 83.3, 174.1, 175.8; HRMS calcd for $C_{16}H_{31}N_2O_4$ $(MH)^+$ 315.2278, found 315.2284.

(2*S*,2′*S*,4*S*,5*S*)-4-Acetoxy-5-(2′-amino-2′-carboxyethyl)pyrrolidine-2-carboxylic Acid (4*S*)-17. Di-*tert*-butyl ester (4*S*)-**17** (91 mg, 0.24 mmol) was transformed to hydrochloride which was isolated as a white foam (78 mg, 99%) by following a similar procedure as used for (4*R*)-**17**: ^{1}H NMR (CD_3OD) δ 2.10 (s, 3H), 2.30−2.62 (m, 3H), 2.82 (ddd, 1H, J = 4.6, 10.5, 14.9 Hz), 3.58 (m, 1H), 3.67 (m, 1H), 3.74 (m, 1H), 4.15−4.24 (m, 2H), 4.63 (dd, 1H, J = 4.9, 14.9 Hz), 5.48 (t, 1H, J = 3.8 Hz); ^{13}C NMR (CD_3OD) δ 20.8, 28.4, 35.9, 59.2, 61.9, 64.3, 73.3, 170.8, 171.2 (2C); HRMS calcd for $C_{10}H_{17}N_2O_6$ $(MH)^+$ 261.1089, found 261.1081.

(2*S*,2′*S*,4*S*,5*S*)-Methyl 4-Hydroxy-5-(2′-methoxycarbonyl-2′-aminoethyl)pyrrolidine-2-carboxylate (4*S*)-18. Diester (4*S*)-**18** was isolated as an off-white foam (82 mg, 99%) from hydrochloride (4*S*)-**17** (78 mg, 0.23 mmol) following a similar procedure as used for the synthesis of (4*R*)-**18** as described above: ^{1}H NMR (CD_3OD) δ 2.42 (dd, 1H, J = 3.1, 14.1 Hz), 2.49 (t, 2H, J = 7.3 Hz), 2.62 (ddd, 1H, J = 3.1, 10.6, 14.1 Hz), 3.58 (m,1H), 3.67 (m, 1H), 3.75 (m, 1H), 3.86 (s, 3H), 3.90 (s, 3H), 4.26 (t, 1H, J = 6.7 Hz), 4.50 (t, 1H, J = 3.2 Hz), 4.62 (dd, 1H, J = 3.4, 10.5 Hz); ^{13}C NMR (CD_3OD) 28.6, 38.3, 51.2, 54.0, 54.2, 59.4, 63.3, 69.8, 170.0, 170.5; HRMS calcd for $C_{10}H_{18}N_2O_5$ $(MH)^+$ 247.1288, found 247.1284.

(3*S*,5*S*,6*S*,8*S*)-Methyl-3-*N*-(Boc)amino-6-hydroxypyrrolizidinone-8-carboxylate (6*S*)-1. A solution of methyl ester hydrochloride (4*S*)-**17** (82 mg, 0.22 mmol) in MeOH (7 mL) was treated with Et_3N (92 μL, 0.66 mmol), heated at reflux, stirred for 24 h, concentrated to a residue that was dissolved in CH_2Cl_2 (14 mL), treated with Et_3N (46 μL, 0.33 mmol) followed by di-*tert*-butyl dicarbonate (57 mg, 0.26 mmol), stirred at rt for 18 h, diluted with $CHCl_3$ (20 mL), worked up similar to (6*R*)-**1**, and purified by flash chromatography using 70% EtOAc in hexane as eluent. Evaporation of the combined collected fractions afforded (6*S*)-**1** as a white solid (19 mg, 28%): mp 131.7 °C; $[\alpha]^{20}_D$ −53.4 (c = 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.10 (ddd, 1H, J = 9.8, 11.6, 11.6 Hz), 2.20 (d, 1H, J = 14.8 Hz), 2.52 (ddd, 1H, J = 3.8, 9.4, 14.8 Hz), 2.61 (ddd, 1H, J = 3.1, 10.0, 12.9 Hz), 3.78 (s, 3H), 3.83 (ddd, 1H, J = 3.1, 5.6, 9.4 Hz), 4.01−4.07 (m, 1H), 4.08 (d, 1H, J = 9.5 Hz), 4.60 (dt, 1H, J = 7.1, 11.5 Hz), 5.07 (d, 1H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 28.3 (3C), 30.8, 40.3, 53.4, 53.9, 55.6, 63.4, 69.1, 80.9, 155.5, 174.5 (2C); HRMS calcd for $C_{14}H_{22}N_2O_6$-Na $(M + Na)^+$ 337.1381, found 337.1370.

(3*S*,5*S*,6*R*,8*S*)-*N*′-Methyl-3-[*N*-(Boc)amino]-6-hydroxy-1-azabicyclo[3.3.0]octan-2-one 8-Carboxamide (6*R*)-21. To a solution of (6*R*)-**1** (10 mg, 0.03 mmol) in MeOH at 0 °C was added a 2 N solution of methylamine in MeOH (10 mL). The reaction mixture was stirred for 18 h, evaporated under vacuum to a residue, and purified by flash chromatography to yield carbamate (6*R*)-**21** (9 mg, 95%): $[\alpha]^{20}_D$ −6.5 (c = 0.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 1.61−1.82 (br s, 1H), 2.08 (dd, 1H, J = 11.0, 21.7 Hz), 2.27 (dd, 1H, J = 10.9, 21.7 Hz), 2.55 (dd, 1H, J = 5.8, 12.5 Hz), 2.70 (ddd, 1H, J = 5.6, 8.4, 12.0 Hz), 2.75 (d, 3H, J = 4.6 Hz), 3.58 (ddd, 1H, J = 5.6, 8.7, 9.0 Hz), 4.02−4.29 (m, 3H), 5.16 (d, 1H, J = 5.5 Hz), 6.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3C), 29.7, 31.1, 34.3, 56.4, 57.1, 63.1, 72.9, 80.5, 155.7, 170.2, 170.7; HRMS calcd for $C_{14}H_{23}N_3O_5Na$ $(M + Na)^+$ 336.1529, found 336.1532.

(3*S*,5*S*,6*S*,8*S*)-*N*′-Methyl 3-[*N*-(Boc)amino]-6-hydroxy-1-azabicyclo[3.3.0]octan-2-one-8-carboxamide (6*S*)-21. Ester (6*S*)-**1** (9.2 mg, 0.029 mmol) was transformed following a procedure similar to (6*R*)-**21** to obtain (6*S*)-**21** (8 mg, 95%): $[\alpha]^{20}_D$ +6.5 (c = 0.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.19 (m, 1H), 2.38 (dd, 1H, J = 7.8, 14.7 Hz), 2.57 (m, 1H), 2.77 (d, 3H, J = 4.9 Hz), 3.90 (ddd, 3H, J = 2.7, 3.5, 7.6 Hz), 4.16 (t, 1H, J = 3.3 Hz), 4.40 (t, 1H, J = 8.9 Hz), 4.47 (t, 1H, J = 8.9 Hz), 5.34 (d, 1H, J = 7.8 Hz), 7.11 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3C), 29.7, 31.9, 38.8, 55.2, 55.5, 62.5, 70.0, 80.7, 155.8, 170.5, 174.3; HRMS calcd for $C_{14}H_{23}N_3O_5Na$ $(M + Na)^+$ 336.1529, found 336.1522.

(3*S*,5*S*,6*R*,8*S*)-Methyl 3-[*N*-(Boc)amino]-6-methanesulfonyloxy-1-azabicyclo[3.3.0]octane-2-one-8-carboxylate (6*R*)-22. A solution of alcohol (6*R*)-**1** (11 mg, 0.035 mmol) in 1 mL of CH_2-

Cl_2 at 0 °C was treated with DMAP (0.6 mg, 3.5×10^{-3} mmol), Et_3N (14.6 μL, 0.105 mmol), and methanesulfonyl chloride (5.4 μL, 0.07 mmol). After the mixture was stirred for 30 min at 0 °C, the ice bath was removed and the mixture was stirred for 2 h at room temperature. The solvent was evaporated under vacuo, and the residue was partitioned between EtOAc (10 mL) and water (5 mL). The organic layer was washed with 10% HCl (3 mL), 5% $NaHCO_3$ (3 mL), and water (3 mL), dried, and evaporated to yield 12 mg (94%) of (6*R*)-**22**: $[\alpha]^{20}_D$ −34.4 (*c* = 0.6, MeOH); ^{1}H NMR (CD_3OD) δ 1.45 (s, 9H), 1.94−2.02 (m, 1H), 2.61−2.65 (m, 2H), 3.09 (s, 3H), 3.11−3.16 (m, 1H), 3.77 (ddd, 1H, *J* = 5.5, 7.6, 9.5 Hz), 3.81 (s, 3H), 3.95 (dd, 1H, *J* = 3.2, 6.3 Hz), 4.32 (t, 1H, *J* = 5.2 Hz), 4.64 (dt, 1H, *J* = 6.3, 11.7 Hz), 4.92 (dd, 1H, *J* = 8.3, 16.2 Hz), 5.15 (d, 1H, 5.6 Hz); ^{13}C NMR (CD_3OD) δ 28.7 (3C), 30.1, 38.1, 38.6, 53.4, 54.8, 56.0, 61.2, 78.5, 80.5, 155.8, 171.1, 172.8; HRMS calcd for $C_{15}H_{25}N_2O_8S$ (MH^+) 393.1326, found 393.1331.

(3*S*,5*S*,6*R*,8*S*)-3-[*N*-(Boc)amino]-6-methanesulfonyloxy-1-azabicyclo[3.3.0]octane-2-one-8-carboxylic Acid (6*R*)-23. Methyl ester (6*R*)-**22** (23 mg, 0.059 mmol) was dissolved in a mixture of dioxane/water (1:1, 1.4 mL), treated with LiOH (2.3 mg, 0.096 mmol), and stirred at rt for 3 h. The reaction mixture was concentrated and purified by chromatography using a gradient of 2−5% MeOH in CH_2Cl_2. Evaporation of the collected fractions yielded 19 mg (86%) of acid (6*R*)-**23** as a yellowish oil: $[\alpha]^{20}_D$ −14.4 (*c* = 1, MeOH); ^{1}H NMR (CD_3OD) δ 1.47 (s, 9H), 1.94−2.03 (m, 1H), 2.57−2.65 (m, 2H), 2.76−2.82 (m, 1H), 3.15 (s, 3H), 3.61−3.92 (m, 2H), 3.92−4.01 (m, 1H), 4.10 (d, 1H, *J* = 8.6 Hz), 4.70 (dd, 1H, *J* = 7.5, 11.6 Hz), 4.94−4.97 (m, 1H); ^{13}C NMR (CD_3OD) δ 26.9 (3C), 35.1, 36.1, 37.8, 55.3, 57.1, 60.5, 78.2, 78.8, 156.2, 172.2, 175.1; HRMS calcd for $C_{14}H_{22}N_2O_8S$ (MH^+) 379.1169, found 379.1163.

(3*S*,5*S*,6*R*,8*S*)-3-[*N*-(Boc)amino]-6-hydroxy-1-azabicyclo[3.3.0]-octane-2-one-8-carboxylic Acid (6*R*)-24. Methyl ester (6*R*)-**1** (25 mg, 0.080 mmol) was hydrolyzed using LiOH (2.9 mg, 0.119 mmol) following a similar procedure as used for (6*R*)-**23** and purified by column chromatography (CH_2Cl_2/MeOH, 7:3) to obtain acid (6*R*)-**24** (16 mg, 67% yield): $[\alpha]^{20}_D$ −37.2 (*c* = 1, MeOH); ^{1}H NMR (CD_3OD) δ 1.47 (s, 9H), 1.83 (dd, 1H, *J* = 9.4, 11.5 Hz), 2.28−2.39 (m, 2H), 2.72 (m, 1H), 3.62 (dt, 1H, *J* = 5.2, 8.8 Hz), 4.08−4.14 (m, 2H), 4.66−4.72 (m, 1H), 6.96 (d, 1H, *J* = 9.4 Hz); ^{13}C NMR (CD_3OD) δ 27.7 (3C), 35.7, 40.0, 46.9, 56.1, 62.8, 73.2, 79.6, 156.9, 172.9 (2C); HRMS calcd for $C_{13}H_{20}N_2O_6$ (MH^+) 300.1321, found 300.1325.

(3*S*,5*S*,6*R*,8*S*)-Methyl 3-[*N*-(Boc)amino]-6-[1′-(4′,4′-dimethyl-2′-oxopentyloxy)]-1-azabicyclo[3.3.0]octane-2-one 8-Carboxylate (6*R*)-25. To a solution of hydroxypyrrolizidinone (6*R*)-**1** (10.2 mg, 0.032 mmol) in 0.5 mL of THF was added NaH (1.56 mg, 0.069 mmol, 60% dispersion) under argon atmosphere at 0 °C and the mixture stirred for 1 h. *tert*-Butyl bromoacetate (7.0 μL, 0.48 mmol) was added to the reaction mixture at 0 °C and stirred overnight at room temperature. The reaction was quenched with 5 mL of 0.1 N HCl, extracted with ethyl acetate (10 mL × 3), dried over Na_2SO_4, and evaporated under vacuum to a residue that was purified by column chromatography to obtain 4.1 mg of ether (6*R*)-**25** (0.009 mmol, 30% yield): $[\alpha]^{25}_D$ −22 (*c* = 0.6, MeOH); ^{1}H NMR ($CDCl_3$) 1.37 (s, 9H), 1.40 (s, 9H), 1.82 (ddd, 1H, *J* = 9.8, 11.6, 11.8 Hz), 2.40 (d, 1H, *J* = 8.0 Hz), 3.03 (dt, 1H, *J* = 6.0, 11.8 Hz), 3.70 (s, 3H), 3.74 (ddd, 1H, *J* = 5.4, 7.1, 10.3 Hz), 3. 85−3.95 (m, 3H), 4.18 (dd, 1H, *J* = 2.9, 7.0 Hz), 4.51 (dt, 1H, *J* = 6.4, 10.6 Hz), 5.09 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 28.1 (3C), 28.3 (3C), 29.7, 37.7, 38.6, 52.7, 54.4, 55.7, 61.5, 68.1, 77.2, 82.2, 155.4, 171.2 (2C), 171.9; HRMS calcd for $C_{20}H_{32}N_2O_8Na$ $(M + Na)^+$ 451.2050, found 451.2053.

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Supporting Information Available: General experimental procedure, ^{1}H and ^{13}C NMR spectra of compounds (6*R*)-**1,** (6*S*)-**1**, (4*R*)-**14**, (4*R*)-**15**, (4*R*)-**17**, (4*R*)-**18**, (4*S*)-**15**, **16**, (4*S*)-**17**, (4*S*)-**18**, (6*R*)-**21**, (6*R*)-**22**, (6*R*)-**23**, (6*R*)-**24**, (6*R*)-**25**, and (6*S*)-**21**, COSY and NOESY spectra of (6*R*)-**1** and (6*S*)-**21**, and crystallographic data for (6*R*)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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