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Substituted 2-Azabicyclo[2.1.1]hexanes as Constrained Proline Analogues: Implications for Collagen Stability

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Among the proteinogenic amino acids, only proline is a secondary amine and only proline has a saturated ring. Electronegative substituents on C-4 (that is, C^{γ}) have a substantial effect on the trans/cis ratio of the prolyl peptide bond and the pucker of the pyrrolidine ring. 2-Azabicyclo[2.1.1]-hexane is, in essence, a proline analogue with two C^{γ} atoms, one in each of the two prevalent ring puckers of proline. Here, 2-azabicyclo[2.1.1]hexane analogues of 2*S*-proline, (2*S*,4*S*)-4-hydroxyproline, and (2*S*,4*S*)-4-fluoroproline residues were synthesized, and their trans/cis ratios were shown to be invariant in a particular solvent. Thus, the substitution of a proline residue on C-4 affects the trans/cis ratio by altering the pucker of its pyrrolidine ring. This finding has implications for the conformation of collagen, which has an abundance of 2*S*-proline and (2*S*,4*R*)-4-hydroxyproline residues, and can be stabilized by (2*S*,4*R*)-4-fluoroproline and (2*S*,4*S*)-4-fluoroproline residues.

Introduction

Proline has two prominent attributes that are unique among the proteinogenic amino acids: only proline is a secondary amine, and only proline has a saturated ring.[1] These attributes make proline residues a key determinant of protein structure.[2,3] Accordingly, a deeper understanding of the conformational properties of proline would illuminate challenging problems in protein folding, stability, and design.

As a secondary amine, proline has a much greater propensity than other natural amino acids to form cis (that is, *E*) peptide bonds.[4−6] A variety of methods have been developed to control the trans/cis ratio, including buttressing the 2-,[7] 3-,[7,8] and 5-positions[9−12] with functional groups, replacing the prolyl peptide bond with an alkene isostere,[13−18] and including the amide in a ring system that is fused to the pyrrolidine ring.[11] These approaches endow torsional control of the amide bond but introduce steric bulk that could be undesirable.

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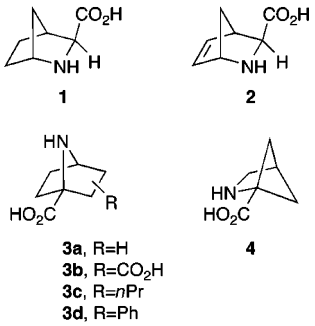
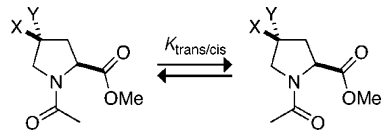
The pyrrolidine ring of proline exists in a variety of puckers, with C^{γ} being its most aplanar constituent.[19,20] A variety of bridged bicyclic proline mimics have been developed to control the conformation of the pyrrolidine ring (**1**−**4**).[21−27] All of these proline mimics are rigid enough to fix pyrrolidine ring pucker, but some include elements that make them suboptimal as proline mimics. Of those proline mimics, **3a**[28,29] and **4**[30] have been employed in the design of peptide-based enzyme inhibitors to reinforce a bioactive peptide conformation, with varying degrees of success.



2-Azabicyclo[2.1.1]hexane (as in **5**) is a proline analogue that displays *both* predominant puckers of the pyrrolidine ring.[31] This end is achieved by the addition of a single carbon atom to proline, a minimal perturbation. Substitution of a hydrogen at the $C^{\gamma 1}$ or $C^{\gamma 2}$ position of the bicyclic system with a hydroxyl or fluoro group yields mimics of 4-hydroxyproline (as in **6**) and 4-fluoroproline (as in **7**). (2*S*,4*R*)-4-Hydroxyproline (Hyp) residues are prevalent in collagen, which is the most abundant protein in animals.[32] Replacing the Hyp residues with (2*S*,4*R*)-4-fluoroproline (Flp) residues endows synthetic mimics of collagen with extraordinary stability.[33−35]

TABLE 1. Values of $K_{trans/cis}$ for 4-Substituted AcXaaOMe[a,b]



Xaa	X	Y	$K_{trans/cis}$
Flp	H	F	6.7
Hyp	H	OH	6.1
Pro	H	H	4.6
hyp	OH	H	2.4
flp	F	H	2.5

[a] Data are from ref 38. [b] Values were measured in D_2O at 25 °C by integration of ^1H NMR spectra.

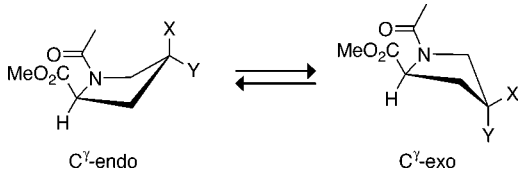
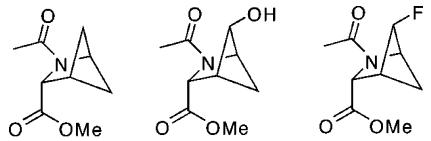


FIGURE 1. Ring puckers in 4-substituted Ac-Pro-OMe. C^{γ}-endo pucker is favored when X = H, OH, or F and Y = H. C^{γ}-exo pucker is favored when X = H and Y = OH or F.



Substitutions on C-4 (that is, C^{γ}) of proline residues are known to have a large effect on the trans/cis ratio.[36−39] For example, electronegative substituents in the 4*R*-position of Pro increase the stability of the trans isomer, whereas electronegative substituents in the 4*S*-position decrease that stability (Table 1). NMR analyses indicate that Ac-(2*S*,4*R*)-4-fluoroproline-OMe (Ac-Flp-OMe) resides predominantly (86%) in the C^{γ}-exo pucker in solution, whereas Ac-(2*S*,4*S*)-4-fluoroproline-OMe (Ac-flp-OMe) is found almost exclusively (95%) in the C^{γ}-endo pucker (Figure 1).[40] This dichotomy can be attributed to the gauche effect, which causes the pyrrolidine ring to adopt a pucker that places the nitrogen and fluorine in a gauche orientation about the $C^{\delta 2}-C^{\gamma}$ bond (for nomenclature, see Figure 2 and ref 41)[42] and has important

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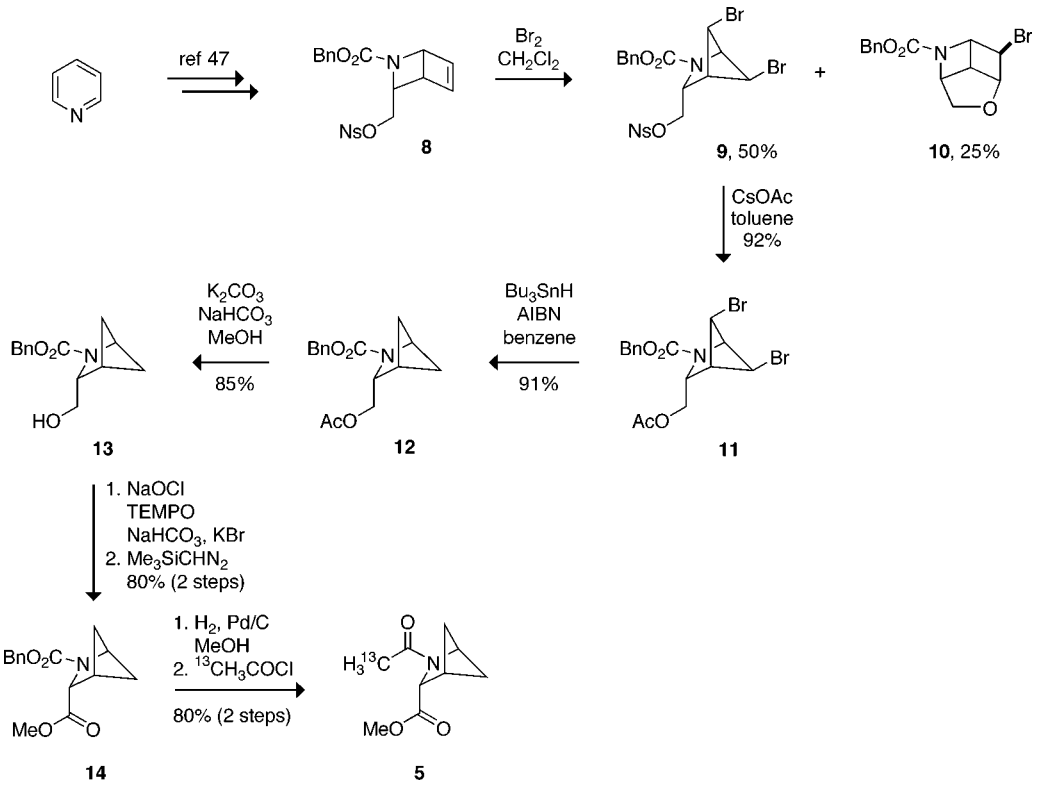
SCHEME 1. Synthetic Route to Ac-methano-Pro-OMe (5)



ramifications for the stability of collagen.[35,36,38,40,43−45] The relationship between the gauche effect and amide trans/cis isomerization in proline derivatives is thought to arise from both steric and electronic interactions. The stabilization of the trans conformer of Ac-Flp-OMe arises from an n → π^* interaction between the oxygen of the amide (the electron donor) and the carbon of the methyl ester (the electron acceptor).[38,40,46] The relative destabilization of the trans rotamer of Ac-flp-OMe arises from unfavorable steric interactions between the nonbonded electrons on the fluoro and ester groups, which disfavors the n → π^* interaction.[40]

We reasoned that constraining the pucker of proline with a one-carbon (that is, methano) bridge would allow us to dissect the relationship among ring pucker, inductive effects, and peptide backbone conformation in proline derivatives. Accordingly, we synthesized compounds **5**−**7** to isolate the influence of ring pucker (which is not variable) and inductive effects (which is variable) on the cis−trans isomerization of proline residues. The results provide insight on the origin of the preference for cis or trans prolyl peptide bonds and have important implications for the conformational stability of collagen.

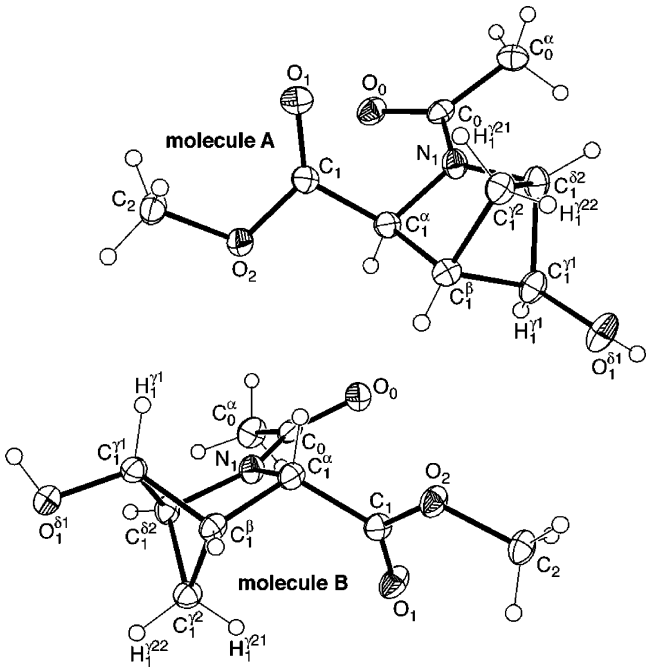


FIGURE 2. ORTEP diagrams showing the two crystallographically independent molecules in the unit cell of crystalline Ac-methano-hyp-OMe (**6**), drawn with 30% probability ellipsoids.

Results and Discussion

2-(2-^{13}C-Acetyl)-2-azabicyclo[2.1.1]hexane-3-carboxylic acid methyl ester (**5**, Ac-methano-Pro-OMe) was synthesized starting with intermediate **8** as shown in Scheme 1. Compound **8** was prepared from pyridine following an established procedure[47] and then reacted with bromine in dichloromethane to effect the key rearrangement, yielding the dibrominated bicyclo[2.1.1]-

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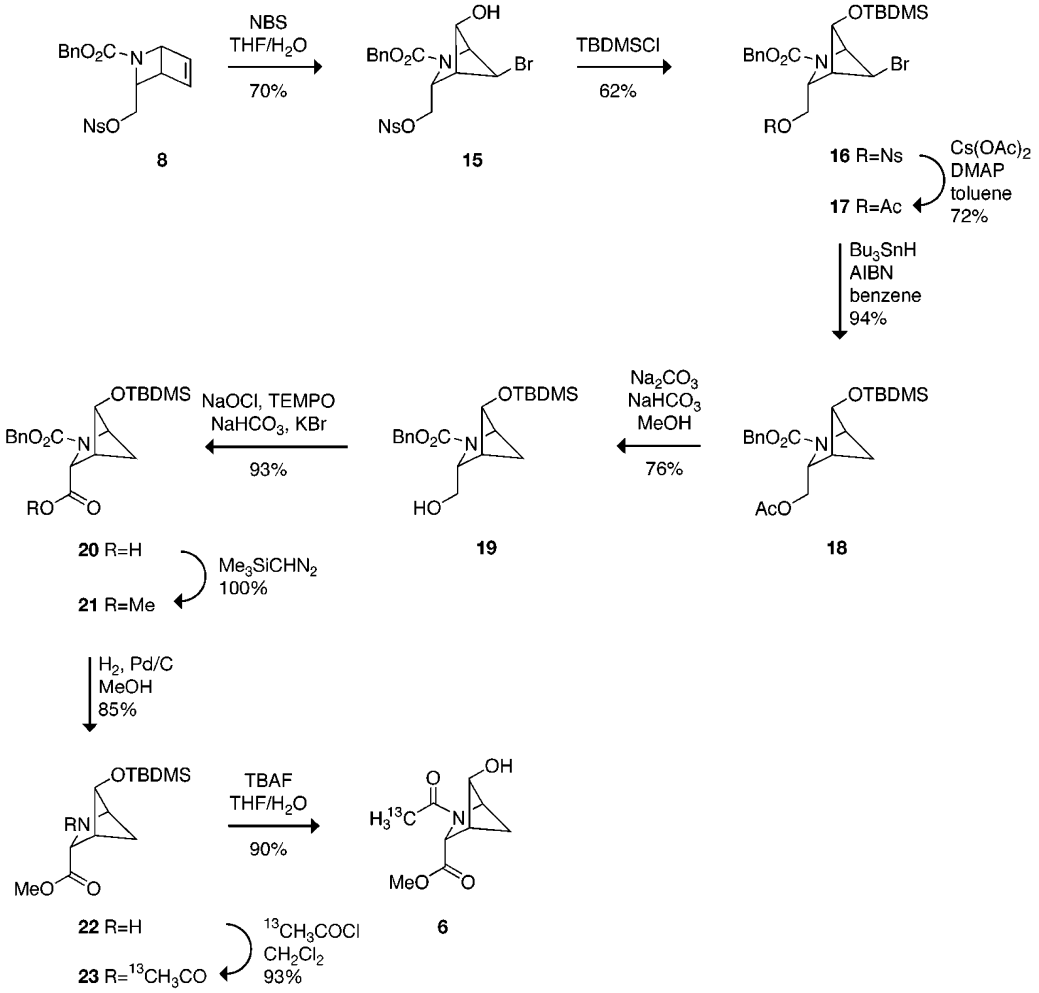
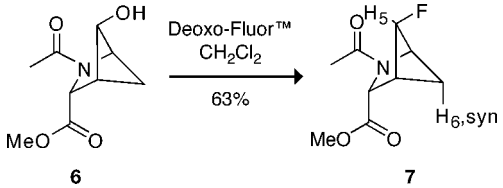
SCHEME 2. Synthetic Route to Ac-methano-hyp-OMe (6)



hexane **9** along with a tricyclic byproduct, **10**, in a ratio of 2:1.[48−50] To generate the hydroxyl group of alcohol **13** in high yield, the *p*-nitrobenzenesulfonyl (nosyl) group of **9** was replaced with an acetyl group by reaction with cesium acetate[51] to yield **11**. The bromine groups were then removed by reduction with tributyltin hydride initiated by AIBN[48,49] to give ester **12**. The acetate was hydrolyzed under mildly basic conditions to alcohol **13**, followed by oxidation of the alcohol to the carboxylic acid[52] and esterification with trimethylsilyldiazomethane[53] to yield compound **14**. The benzyloxycarbonyl group was removed by hydrogenolysis under standard conditions and acetylated with ^{13}C-labeled acetyl chloride to give the desired Ac-methano-Pro-OMe (**5**). The ^{13}C label was incorporated to enable facile measurement of amide trans/cis ratios by ^{13}C NMR spectroscopy (vide infra).

SCHEME 3. Synthetic Route to Ac-methano-flp-OMe (7)



The synthesis of 2-(2-^{13}C-acetyl)-5-hydroxy-2-azabicyclo-[2.1.1]hexane-3-carboxylic acid methyl ester (**6**, Ac-methano-hyp-OMe) was similar to that of methano-Pro. The key differences include effecting the rearrangement from **8** to **15** with NBS and H_2O in THF[50] and the need to protect the resulting alcohol with a TBDMS group, as shown in Scheme 2. The relative configuration at $C_1{}^{\gamma 1}$ (which bears the hydroxyl group) of **6** was determined by X-ray diffraction analysis (vide infra).

2-Acetyl-5-fluoro-2-azabicyclo[2.1.1]hexane-3-carboxylic acid methyl ester (**7**, Ac-methano-flp-OMe) was synthesized from unlabeled Ac-methano-hyp-OMe (**6**) by its reaction with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor), as shown in Scheme 3.[54] The reaction generally proceeds with the inversion of stereochemis-

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TABLE 2. Effect of Solvent on $K_{trans/cis}$ of AcXaaOMe[a]

Xaa	$K_{trans/cis}$		
	$CDCl_3$	1,4-dioxane-d_8	D_2O
methano-Pro (**5**)	2.4	2.2	3.5
methano-hyp (**6**)	2.4	2.1	3.6
methano-flp (**7**)	2.7	2.8	3.5

[a] Values of $K_{trans/cis}$ were measured in the indicated solvents at 25 °C by integration of ^{13}C or ^{19}F NMR spectra.

try,[55] but the configuration is retained here because neighboring-group participation of the nitrogen (or possibly the amide oxygen) leads to a double inversion of stereochemistry at the bridge carbon during the fluorination reaction. The stereochemistry of the fluorine on $C_1^{\gamma 1}$ (elsewhere, C-5[48,31]) was confirmed by analyzing the coupling constants between $H_1^{\gamma 1}$ (H-5) and $H_1^{\gamma 21}$ (H-6_{syn}), which is 7.4 Hz. This four-bond W-plan coupling was not observed between the fluorine and either proton on $C_1^{\gamma 2}$ (C-6), nor between $H_1^{\gamma 1}$ and $H_1^{\gamma 22}$ (H-6_{anti}), as the latter two sets of nuclei are not in the appropriate arrangement for such coupling.[56]

An attractive feature of the methanoproline derivatives is that both pyrrolidine ring puckers are incorporated into a single framework, which allows dissection of the relative contributions of ring pucker and inductive effects on the conformation of substituted prolines. The hydroxyl- and fluoro-substituted methanoprolines are analogues of (2*S*,4*S*)-4-hydroxyproline (hyp) and (2*S*,4*S*)-4-fluoroproline (flp), respectively, and the substituent is in an orientation analogous to the disfavored C^{γ}-exo pucker.[40,42] In other words, the bicyclic structure fixes the hydroxyl and fluoro groups of compounds **6** and **7** to be in an antithetical conformation—anti rather than gauche to the pyrrolidine nitrogen about the $C^{\delta 2}-C^{\gamma 1}$ bond.

We measured the amide trans/cis ratios of **5** and **6** by using NMR spectroscopy. We used ^{13}C NMR spectroscopy because the ^1H resonances of both methyl groups overlapped with those of other protons from the bicyclic ring system. ^{13}C NMR spectra were obtained with ^1H-decoupling enabled only during the acquisition phase of the pulse sequence, allowing for no NOE buildup and thus enabling quantitative integration of the relevant peaks. The trans/cis ratios were measured in $CDCl_3$, 1,4-dioxane-d_8, and D_2O and are listed in Table 2. The trans/cis ratios of **7** were measured by ^{19}F NMR spectroscopy, as the two ^{19}F resonances were well-resolved. We found little variation among the three derivatives in a particular solvent. The trans/cis ratios in deuterated 1,4-dioxane and chloroform were all similar, and the ratios in water were somewhat greater than those in the organic solvents.[36] These data demonstrate that rigidifying the pyrrolidine ring of proline derivatives by adding a methano bridge abolishes any inductive effect exerted by a fluoro- or a hydroxyl group on the trans/cis ratio of its peptide bond. Apparently, an electronegative substituent on the flexible pyrrolidine ring of proline affects the trans/cis ratio by altering the pucker of the ring.

Next, we determined the crystalline structure of Ac-methano-hyp-OMe (**6**) by X-ray diffraction analysis.

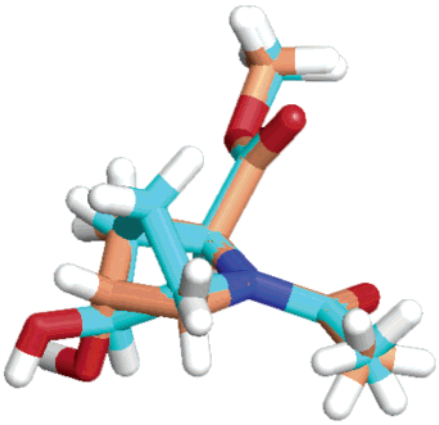

FIGURE 3. Superposition of crystalline structures of Ac-methano-hyp-OMe (**6**, cyan) and Ac-Hyp-OMe (orange).[57]

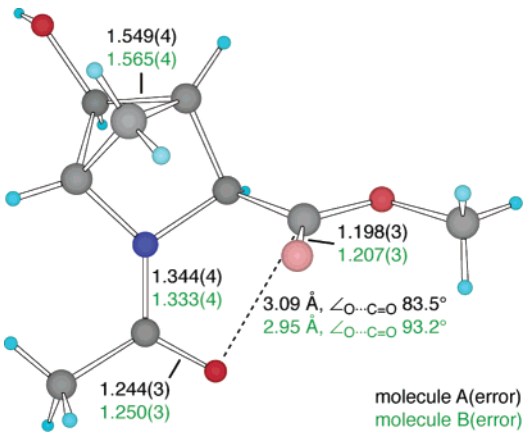

FIGURE 4. Ball-and-stick diagram showing bond lengths that differ statistically in the two molecules of the X-ray structure of crystalline Ac-methano-hyp-OMe (**6**). The $O_0\cdots C_1{=}O_1$ bond lengths and angles are also shown.

There are two crystallographically independent molecules in the unit cell, as shown in Figure 2. The ring structures of the two molecules are superimposable, while the ester and amide conformations vary slightly relative to one another. The ϕ angles ($C_{i-1}-N_i-C_i^{\alpha}-C_i$) differ by 3.1(3)°, the ψ angles (here, $N_i-C_i^{\alpha}-C_i-O_{i+1}$) differ by 18.0(4)°, and the ω angles ($C_i^{\alpha}-C_i-N_{i+1}-C_{i+1}^{\alpha}$) differ by 2.6(2)°. A superposition of the structures of Ac-methano-hyp-OMe (**6**) and Ac-Hyp-OMe[57] is shown in Figure 3 and clearly depicts the antipodal configuration of the hydroxyl groups on C^{γ}.

All relevant structural parameters support the presence of a stronger $n \rightarrow \pi^*$ interaction[38] in molecule B than in molecule A of crystalline Ac-methano-hyp-OMe (**6**), as shown in Figure 4.[40] For example, the $O_0\cdots C_1$ distance is 2.949(4) Å in molecule B, but 3.092(3) Å in molecule A. In addition, the $C_1{=}O_1$ bond length is 1.207(3) Å in molecule B, but 1.198(3) Å in molecule A, and the $^{+}N_1{=}C_0{-}O_0^{-}$ amidic resonance structure appears to be more prevalent in molecule B, which has a shorter N_1-C_0 bond and a longer C_0-O_0 bond than does molecule A. Finally, the $O_0\cdots C_1{=}O_1$ angle is closer to the Bürgi–Dunitz optimum of 109°[58–62] in molecule B [93.2(2)°] than in

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TABLE 3. Values of ϕ and ψ Dihedral Angles for the *trans*-Amide Isomers of Ac-Xaa-OMe[a]

Xaa	ring pucker	ϕ (deg)	ψ (deg)	ref
Pro	C^{γ}-exo	−58.6	143.0	40
Pro	C^{γ}-endo	−70.0	152.1	40
Hyp (1)	C^{γ}-exo	−62.0	156.4	57
Hyp (2)	C^{γ}-exo	−50.9	145.2	57
Flp	C^{γ}-exo	−59.2	140.8	40
flp	C^{γ}-endo	−76.4	169.0	40
methano-hyp (1) (**6**)		−65.0	169.0	this work
methano-hyp (2) (**6**)		−61.9	153.5	this work

[a] Dihedral angles of Xaa = Pro, Flp, and flp are from density functional theory calculations; dihedral angles of Xaa = Hyp and methano-hyp are from X-ray diffraction analysis of crystalline molecules.

molecule A [83.6(2)°]. All of these structural parameters are consistent with greater donation of electron density from the nonbonding electrons of O_0 to the antibonding orbital of the $C_1{=}O_1$ bond in molecule B, as expected from a stronger $n \rightarrow \pi^*$ interaction.[40] Moreover, the congruence of these five structural parameters (three bond lengths, an atom···atom distance, and an atom···atom−atom angle) provides additional support for the existence of a meaningful $n \rightarrow \pi^*$ interaction in Ac-methano-hyp-OMe (**6**) as well as a benchmark for detecting $n \rightarrow \pi^*$ interactions in other derivatives of proline.

The trans/cis ratios for compounds **5**−**7** in D_2O are intermediate between those of Ac-Pro-OMe and Ac-hyp-OMe or Ac-flp-OMe (Table 1), indicating that the $n \rightarrow \pi^*$ interactions in methanoproline derivatives are probably weaker than those found in Pro and 4*R*-substituted prolines but stronger than those in the 4*S*-substituted prolines. Likewise, the ϕ and ψ angles of Ac-methano-hyp-OMe (**6**) are intermediate between those of the endo- and exo-puckers of proline derivatives (Table 3), which is consistent with its intermediate trans/cis ratio.

Conclusions

Electronegative substituents in the 4-position of proline residues had been shown to have a substantial effect on the trans/cis ratio of their peptide bonds (Table 1).[36−39] Here, constraining the pucker of the pyrrolidine ring of 4-substituted proline residues with a one-carbon bridge, as in compounds **5**−**7**, was shown to abolish the effect of the electronegative substituents on the trans/cis ratio (Table 2). Thus, changes in trans/cis ratio arise from changes in ring pucker. This finding suggests that pyrrolidine ring pucker is a key determinant of the stability (or instability) endowed by 4-substituted proline residues on collagen.

Experimental Section

General Procedures. Thin-layer chromatography was performed on precoated plates of silica gel GF 250 μm. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). Reagent chemicals were obtained from commercial suppliers, and reagent grade solvents were used without further purification. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDC1_3$, unless noted otherwise. Both the ^{1}H and ^{13}C NMR spectra are often complicated by the presence of carbamate conformers and pairs of ^{13}C NMR lines due to a single carbon, identified using proton-carbon correlation experiments, have been presented as pairs. Chemical shifts are expressed in ppm relative to internal TMS (^{1}H) or solvent $CDCl_3$ (^{13}C). High-resolution mass spectra were performed at the University of Pennsylvania, Drexel University, or Merck Research Laboratories (West Point, PA) using FAB ionization methods.

For purposes of nomenclature, 3-*exo* orientation on 2-azabicyclo[2.1.1]hexanes refers to the 3-substituent oriented toward the bridge containing the lower priority attached 5- or 6-substituent. *N*-(Benzyloxycarbonyl)-2-hydroxymethyl-1,2-dihydropyridine and *N*-(benzyloxycarbonyl)-2-hydroxymethyl-2-azabicyclo[2.2.0]hex-5-ene were prepared according to our previously described procedures for *N*-(methoxycarbonyl)-2-hydroxymethyl-1,2-dihydropyridine and *N*-(methoxycarbonyl)-2-hydroxymethyl-2-azabicyclo[2.2.0]hex-5-ene.[47]

***N*-(Benzyloxycarbonyl)-5-*anti*,6-*anti*-dibromo-3-(*p*-nitrophenylsulfonyloxy)methyl-2-azabicyclo[2.1.1]hexane (9).** A solution of bromine (2.56 g, 1.7 equiv) in CH_2Cl_2 (50 mL) was added dropwise to a cold (−5 to 0 °C) solution of nosylate **8** (4.0 g, 9.3 mmol) in CH_2Cl_2 (50 mL), and the resulting solution was stirred for 2 h. The temperature was then raised to 25 °C, and the reaction mixture was stirred for an additional 10 h. The solution was diluted with ether and washed with aqueous sodium bisulfite (10% w/v) until no brown color remained. The organic layer was washed with water, dried over sodium sulfate, and filtered. The solvent was removed in vacuo to provide a crude oil. Purification by flash chromatography (4:1 hexane/EtOAc) afforded 2.74 g (50%) of rearranged dibromide **9** as the major product with $R_f = 0.47$ (1:1 ether/hexane): ^{1}H NMR δ 8.39 (br, 2H), 8.06 (br, 2H), 7.50−7.26 (m, 5H), 5.13 (s, 2H), 4.56 (m, 2H), 4.11 (m, 3H), 3.96 (d, $J = 7.8$ Hz, 1H), 3.19 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR δ 155.0, 150.9, 140.9, 135.2, 129.2, 128.7, 128.2, 125.5, 124.6, 68.1, 68.0, 66.1, 59.8, 51.7, 50.9, 46.5; HRMS *m/z* 610.9090, 612.9081, 614.9065, calcd for $C_{20}H_{18}N_2O_7S^{79}Br^{79}BrNa$ (M + Na) 610.9099, $C_{20}H_{18}N_2O_7S^{79}Br^{81}BrNa$ (M + Na) 612.9079; and $C_{20}H_{18}N_2O_7S^{81}Br^{81}BrNa$ (M + Na) 614.9058. In addition, 750 mg (25%) of azatricycle byproduct **10** was also isolated: $R_f =$ 0.40 (1:1 ether/hexane); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.16, 5.10 (two d, $J = 12.6$ Hz, 2H), 4.93 (dd, $J = 2.4$, 3.9, 5.4 Hz, 1H), 4.72 (dd, $J = 3.6$, 5.7 Hz, 1H), 4.64 (dd, $J = 3.9$, 10.2 Hz, 1H), 4.42 (dd, $J = 3.6$, 3.6 Hz, 1H), 4.21, 4.11 (s, 1H), 3.92 (ddd, $J = 3.6$, 5.4, 5.7 Hz, 1H), 3.76 (dd, $J = 2.4$, 10.2 Hz, 1H); ^{13}C NMR δ 153.4, 135.6, 128.0, 127.7, 127.3, (85.7, 85.5), (73.4, 72.5), (66.5, 66.2), (65.1, 64.4), (63.8, 63.0), (49.0, 48.5), 42.5; HRMS *m/z* 346.0055, calcd for $C_{14}H_{14}NO_3Na^{79}Br$ (M + Na), 346.0055; and 348.0036, calcd for $C_{14}H_{14}NO_3Na^{81}Br$ (M + Na), 348.0034.

***N*-(Benzyloxycarbonyl)-5-*anti*,6-*anti*-dibromo-3-acetoxymethyl-2-azabicyclo[2.1.1]hexane (11).** To the dibromide **9** (300 mg, 0.50 mmol) in dry DMF (10 mL) was added CsOAc (336 mg, 1.75 mmol, 3.5 equiv). The solution was heated to 60 °C for 30 h, cooled, filtered through Celite, and concentrated under reduced pressure. The reaction was diluted with EtOAc and washed with water and brine. The organic layer was dried over sodium sulfate and filtered. Removal of solvent in vacuo and flash chromatography (4:1 hexane/EtOAc) afforded 205.6 mg (92%) of acetate **11**: $R_f = 0.46$ (1:1 ether/hexane); ^{1}H NMR δ 7.41 (s, 5H), 5.22 (m, 2H), 4.62 (d, $J = 7.3$ Hz, 1H), 4.53 (d, $J = 6.2$ Hz, 1H), 4.35 (d, $J = 7.6$ Hz, 1H), 4.16 (b, 2H), 4.05 (d, $J = 7.6$ Hz, 1H), 3.19 (d, $J = 7.3$ Hz, 1H), 2.12 (s, 3H); ^{13}C NMR δ 170.4, 155.1, 135.8, 128.7, 128.5, 128.2, 67.9, 66.3, 62.7, 60.4, 52.3, 51.4, 47.3, 20.7; HRMS *m/z* 467.9411, 469.9405, 471.9391, calcd for $C_{16}H_{17}NO_4{}^{79}Br^{79}BrNa$

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(M + Na) 467.9422; $C_{16}H_{17}NO_4{}^{79}Br^{81}BrNa$ (M + Na) 469.9402; and $C_{16}H_{17}NO_4{}^{81}Br^{81}BrNa$ (M + Na) 471.9381.

***N*-(Benzyloxycarbonyl)-3-acetoxymethyl-2-azabicyclo-[2.1.1]hexane (12).** Dibromide **11** (474 mg, 1.06 mmol) and AIBN (47.4 mg, 0.29 mmol) were dissolved in benzene (25 mL), and the system was purged with Ar(g) for 10 min. Tributyltin hydride (713 ≥ L, 772 mg, 2.65 mmol) was added via syringe, and the resulting solution was heated at reflux for 2 h. The reaction mixture was cooled to rt, and the solvent was removed in vacuo. The residue was purified by flash chromatography (1:5 ether/hexane) to give 277 mg (91%) of acetate **12**: R_f = 0.46 (1:1 ether/hexane); ^{1}H NMR δ 7.42 (s, 5H), 5.21 (s, 2H), 4.50 (dd, J = 4.3, 6.7 Hz, 1H), 4.40 (d, J = 7.1 Hz, 1H), 4.14 (m, 1H), 3.96 (b, 1H), 2.83 (d, J = 7.1 Hz, 1H), 2.05 (s, 3H), 1.88−1.42 (m, 4H); ^{13}C NMR δ 170.7, 156.9, 136.7, 128.5, 128.0, 127.8, 66.8, 64.1, 61.3, 58.2, 41.8, 41.1, 36.4, 20.8; HRMS *m/z* 290.1386, calcd for $C_{16}H_{20}NO_4$ (M + H) 290.1392.

***N*-(Benzyloxycarbonyl)-3-hydroxymethyl-2-azabicyclo-[2.1.1]hexane (13).** To acetate **12** (300 mg, 1.04 mmol) in methanol (25 mL) were added K_2CO_3 (450 mg, 3.0 mmol) and $NaHCO_3$ (830 mg, 9.0 mmol). The solution was stirred at 25 °C for 2 h and then concentrated in vacuo to remove ca. 90% of the methanol. The resulting slurry was diluted with water and extracted with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4(s). The solvent was removed in vacuo, and the residue was purified by flash chromatography (1:1 ether/hexane) to afford 218 mg (85%) of alcohol **13**: R_f = 0.23 (1:2 hexane/ether); ^{1}H NMR δ 7.41 (s, 5H), 5.22 (s, 2H), 4.59 (b, 1H), 4.45 (d, J = 7.18 Hz, 1H), 3.96−3.79 (br, 2H), 2.75 (b, 1H), 2.02−1.50 (m, 4H); ^{13}C NMR δ 157.9, 136.4, 128.5, 128.1, 127.9, 67.3, 66.0, 62.8, 61.4, 42.6, 41.2, 37.7; HRMS *m/z* 270.1113, calcd for $C_{14}H_{17}NO_3Na$ (M + Na) 270.1106. Alcohol **13** was admixed with about 10% of a second inseparable alcohol in which the *N*-benzyloxycarbonyl group was exchanged for *N*-methoxycarbonyl as shown by a small peak at δ 3.80 (s). This impurity was removed at the next stage.

***N*-(Benzyloxycarbonyl)-3-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (14).** To a solution of the slightly impure alcohol **13** (600 mg, 2.45 mmol) in CH_2Cl_2 (7 mL) containing TEMPO (5 mg, 0.032 mmol) was added a solution of saturated aqueous $NaHCO_3$ (4.8 mL) containing KBr (26.4 mg, 0.22 mmol) and tetrabutylammonium chloride (35.2 mg, 0.13 mmol). The mixture was cooled to 0 °C, and a solution of NaOCl (4−6% w/v, 12 mL), saturated aqueous $NaHCO_3$ (2.64 mL), and brine (5.3 mL) was added dropwise over 45 min. The two layers were separated, and the organic layer was washed with water. The combined aqueous extracts were acidified with 4 M HCl and extracted extensively with ethyl acetate. The organic layer was dried over Na_2SO_4(s) and concentrated in vacuo. The crude acid was dissolved in isopropyl alcohol (15 mL) and hexane (15 mL), and trimethylsilyldiazomethane (2.0 M, 1.225 mL, 2.45 mmol) was added. The mixture was stirred at 25 °C for 30 min, and then the solvent was removed in vacuo. The residue was purified by flash chromatography, eluting with 4:1 hexane/ether to afford 539 mg (80%) of ester **14**: R_f = 0.40 (1:1 hexane/ether); ^{1}H NMR δ 7.37 (s, 5H), 5.22 (m, 2H), 4.53 (br, 1H), 4.34 (br, 1H), 3.79 (br, 3H), 3.05 (br, 1H), 2.11−1.48 (m, 4H); ^{13}C NMR δ 171.4, 156.8, 66.9, 60.9, 60.2, 52.2, 43.4, 42.9, 37.7; HRMS *m/z* 298.1070, calcd for $C_{15}H_{17}NO_4Na$ (M + Na) 298.1055. This ester contained 40 mg of a minor byproduct, the *N*-(methoxycarbonyl)-3-ester: R_f = 0.40 (1:1 hexane/ether); ^{1}H NMR δ 4.40 (br, 1H), 4.22 (br, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.97 (m, 1H), 2.03−1.39 (m, 4H); ^{13}C NMR δ 171.3, 156.2, 61.0, 60.1, 52.4, 52.1, 43.3, 42.7, 37.2; HRMS *m/z* 200.0918, calcd for $C_9H_{14}NO_4$ (M + H) 200.0923. A sample of the major product, ester **14** (25 mg), was separated from the mixture (60 mg) by collection of the first fraction upon chromatography (1:10 ether/hexane); the remainder (20 mg) was a mixture of esters. A pure sample of the minor ester was obtained following *N*-debenzylation of the major isomer (below).

***N*-$^{13}CH_3$-Labeled-acetyl-3-methoxylcarbonyl-2-azabicyclo[2.1.1]hexane (5).** To a solution of ester **14** (200 mg, 0.73 mmol) in methanol (20 mL) was added Pd/C (100 mg). The mixture was stirred at 25 °C under a H_2(g)-filled balloon for 2 h and then filtered through Celite. The solvent was removed in vacuo to afford 105 mg of crude amine: R_f = 0.60 (5:1 EtOAc/methanol); ^{1}H NMR ($CDCl_3$) δ 4.70 (br, 1H), 4.32 (d, J = 7.2 Hz, 1H), 3.84 (s, 3H), 3.18 (d, J = 7.2 Hz, 1H), 2.20 (d, J = 7.2 Hz, 1H), 2.16 (d, J = 7.2 Hz, 1H), 2.00 (dd, J = 10.6, 7.2 Hz, 1H), 1.63 (dd, J = 10.6, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.1, 60.4, 59.0, 52.2, 43.9, 42.2, 37.0; HRMS *m/z* 142.0873, calcd for $C_7H_{12}NO_2$ (M + H) 142.0868. To a solution of the amine in dry CH_2Cl_2 (10 mL) at 0 °C was added (dimethylamino)pyridine (DMAP, 759 mg, 6.21 mmol), followed by dropwise addition of $^{13}CH_3COCl$ (170.8 mg, 2.15 mmol). The mixture was stirred for an additional 30 min at 0 °C, allowed to warm slowly to 25 °C, and then stirred for 2 h. Water was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4(s) and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography eluting with EtOAc to give 107 mg (80%) of **5** as a colorless oil: R_f = 0.50 (15:1 EtOAc/MeOH); ^{1}H NMR δ 4.8−4.4 (m, 1H, two conformers), 4.34 (m, 1H), 3.80 (m, 3H), 3.06 (m, 1H), 2.36−1.40 (m, 7H); ^{13}C NMR δ (170.8, 169.4), 168.3 (d, J = 51.6 Hz), (62.5, 61.0), (59.6, 59.0), (52.5, 52.1), (44.0, 42.9), (42.6, 42.3), (37.8, 36.5) (21.6, 21.5, labeled ^{13}C); HRMS *m/z* 185.1002, calcd for $C_8{}^{13}CH_{14}NO_3$ (M + H) 185.1007.

***N*-(Benzyloxycarbonyl)-5-*anti*-hydroxy-6-*anti*-bromo-3-*endo*-(*p*-nitrophenylsulfonyloxy)methyl-2-azabicyclo-[2.1.1]hexane (15).** To the nosylate **8** (2.00 g, 4.65 mmol) in THF (16 mL) and H_2O (8 mL) at 0 °C was added *N*-bromosuccinimide (2.51 g, 13.9 mmol) in small portions so that the temperature never exceeded 0 °C. Upon completion of addition, the solution was warmed to rt and stirred for 2.5 h, diluted with water, and extracted extensively with chloroform. The combined organic layers were washed with brine and dried over Na_2SO_4(s). The solvent was removed in vacuo to give an oil, which was purified by flash chromatography (3:1 ether/hexane) to provide 1.71 g (70%) of bromohydrin **15**: R_f = 0.25 (3:1 ether/hexane); ^{1}H NMR δ 8.43 (br, 2H), 8.14 (br, 2H), 7.47−7.34 (m, 5H), 5.15 (s, 2H), 4.55 (br, 1H), 4.44 (d, J = 7.5 Hz, 1H), 4.22 (m, 2H), 4.10 (m, 2H), 3.43 (br, 1H), 3.08 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 155.1, 150.8, 141.0, 135.4, 129.2, 128.7, 128.5, 128.1, 124.6, 85.9, 68.2, 67.8, 65.8, 58.3, 51.8, 47.7; HRMS *m/z* 548.9953, calcd for $C_{20}H_{19}N_2O_8NaS^{79}Br$ (M + Na) 548.9943; *m/z* 550.9929, calcd for $C_{20}H_{19}N_2O_8NaS^{81}Br$ (M + Na) 550.9923.

***N*-(Benzyloxycarbonyl)-5-*anti*-(*tert*-butyldimethylsilyloxy)-6-*anti*-bromo-3-*endo*-(*p*-nitrophenylsulfonyloxy)-methyl-2-azabicyclo[2.1.1]hexane (16).** To a solution of nosylate **15** (2.33 g, 4.4 mmol) in DMF (5 mL) were added *tert*-butyldimethylsilyl chloride (TBDMSCl) (0.80 g, 5.3 mmol) and imidazole (0.76 g, 11 mmol). The resulting solution was stirred at rt until no starting material remained (21 h), as determined by TLC, and then diluted with diethyl ether (20 mL) and water (10 mL). The two layers were separated, and the aqueous layer was extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4(s), and filtered. The solvent was removed in vacuo to give the crude product, which was purified by flash chromatography to provide 1.76 g (62%) of the desired *O*-silyl ether **16** as an oily white solid: R_f = 0.64 (2:1 ether/hexane); ^{1}H NMR δ 8.42 (br, 2H), 8.13 (br, 2H), 7.40−7.31 (5H), 5.13 (m, 2H), 4.53 (m, 1H), 4.28 (d, J = 7.5 Hz, 1H), 4.20 (d, J = 7.8 Hz, 1H), 4.15 (d, J = 9.9 Hz, 1H), 4.12 (d (buried), J = 7.8 Hz, 1H), 4.06 (m, 1H), 2.90 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 157.7, 150.9, 140.9, 129.3, 124.6, 135.6, 128.7, 128.5, 128.1, 84.7, 68.4, 67.7, 66.2, 58.1, 51.6, 45.7, 25.6, 17.9, −5.04; HRMS *m/z* 663.0792, calcd for $C_{26}H_{33}N_2O_8NaSiS^{79}Br$ (M + Na), 663.0808; *m/z* 665.0773, calcd for $C_{26}H_{33}N_2O_8NaSiS^{81}Br$ (M + Na) 665.0788.

***N*-Benzyloxycarbonyl-5-*anti*-(*tert*-butyldimethylsilyloxy)-6-*anti*-bromo-3-*endo*-acetoxymethyl-2-azabicyclo[2.1.1]hexane (17).** To a solution of *O*-silyl ether **16** (128 mg, 0.20 mmol) in toluene (30 mL) were added cesium acetate (200 mg, 1.0 mmol, 5 equiv), DMAP (24.5 mg, 0.20 mmol), and 18-crown-6 (7 mg). The resulting solution was heated at reflux for 8 h and then cooled and filtered through Celite. The solvent was concentrated in vacuo, and the resulting slurry was diluted with EtOAc and then washed with water followed by brine. The organic layer was dried over Na_2SO_4(s) and filtered. Removal of solvent in vacuo and flash chromatography afforded 72 mg (72%) of acetate **17** as a yellow oil: $R_f = 0.32$ (1:2 ether/hexane); ^{1}H NMR δ 7.35 (s, 5H), 5.19 (dd, $J = 7.5$ Hz, 2H), 4.43 (dd, $J = 3.6$, 10.8 Hz, 1H), 4.28 (d, $J = 7.2$ Hz, 1H), 4.26 (d, $J = 7.2$ Hz, 1H), 4.14 (d, $J = 7.2$ Hz, 1H), 4.05 (br, 2H), 2.82 (d, $J = 7.2$ Hz, 1H), 2.06 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 170.4, 155.0, 135.9, 128.5, 128.2, 128.0, 84.8, 67.4, 66.1, 63.0, 58.5, 52.1, 46.5, 25.7, 20.7, 17.9, −5.1; HRMS *m/z* 520.2243, calcd for $C_{22}H_{32}NO_5NaSi^{79}Br$ (M + Na) 520.1131; *m/z* 522.1115, calcd for $C_{22}H_{32}NO_5NaSi^{81}Br$ (M + Na) 522.1110.

***N*-Benzyloxycarbonyl-5-*anti*-(*tert*-butyldimethylsilyloxy)-3-*exo*-acetoxymethyl-2-azabicyclo[2.1.1]hexane (18).** To a solution of acetate **17** (670 mg, 1.3 mmol) in benzene (50 mL) were added tributyltin hydride (1.18 g, 4.1 mmol) and AIBN (22 mg, 0.13 mmol). The resulting mixture was heated at reflux for 3 h. The solvent was removed in vacuo, and the crude product was purified by flash chromatography to give 540 mg (94%) of acetate **18** as a colorless oil: $R_f = 0.53$ (1:1 ether/hexane); ^{1}H NMR δ 7.40 (s, 5H), 5.20 (dd, $J = 12.3$ Hz, 2H), 4.44 (dd, $J = 11.1$, 4.2 Hz, 1H), 4.18 (d, $J = 7.2$ Hz, 1H), 4.17 (m, 1H), 4.11 (br, 1H), 3.97 (d, $J = 7.2$ Hz, 1H), 2.86 (br d, $J = 8.1$ Hz, 1H), 2.62 (dd, $J = 7.2$, 3.0 Hz, 1H), 2.09 (s, 3H), 1.84 (dd, $J = 8.1$, 7.2 Hz, 1H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR δ 170.6, 156.5, 136.5, 128.4, 128.0, 127.8, 82.4, 66.9, 64.2, 63.4, 56.8, 47.4, 32.8, 25.7, 20.8, 17.9, −4.96; HRMS *m/z* 442.2041, calcd for $C_{22}H_{33}N_5NaSi$ (M + Na) 442.2026.

***N*-Benzyloxycarbonyl-5-*anti*-*tert*-butyldimethylsilyloxy-3-*exo*-hydroxymethyl-2-azabicyclo[2.1.1]hexane (19).** To a solution of acetate **18** (302 mg, 0.72 mmol) in methanol (10 mL) were added potassium carbonate (357 mg, 2.2 mmol) and sodium bicarbonate (544 mg, 6.5 mmol). The resulting mixture was stirred at rt for 1 h. The bulk of the solvent was removed in vacuo, and the resulting mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4(s), and concentrated in vacuo to give crude product (240 mg). Flash chromatography provided 207 mg (76%) of alcohol **19** as a colorless liquid: $R_f = 0.30$ (1:1 ether/hexane); ^{1}H NMR δ 7.40 (m, 5H), 5.21 (m, 2H), 4.34 (br, 1H), 4.21 (dd, $J = 1.5$, 7.5 Hz, 1H), 4.03 (d, 1H, $J = 7.2$ Hz, 1H), 3.99 (br, 1H), 3.80 (br, 2H), 2.84 (dt, $J = 2.7$, 8.1, 1.5 Hz, 1H), 2.55 (m, 1H), 1.79 (dd, $J = 8.1$, 7.2 Hz, 1H), 0.94 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 157.7, 136.3, 128.5, 128.2, 127.9, 82.9, 67.3, 65.4, 64.5, 61.7, 47.3, 34.0, 25.7, 18.0, −4.9; HRMS *m/z* 400.1930, calcd for $C_{20}H_{31}NO_4NaSi$ (M + Na) 400.1920.

***N*-Benzyloxycarbonyl-5-*anti*-*t*-butyldimethylsilyloxy-3-*exo*-carboxy-2-azabicyclo[2.1.1]hexane (20).** To a solution of alcohol **19** (39 mg, 0.085 mmol) in dichloromethane (0.5 mL) containing TEMPO (0.1 mg) was added a solution of saturated $NaHCO_3$ (0.2 mL) containing KBr (0.9 mg) and tetrabutylammonium chloride (1.2 mg). The mixture was cooled to 0 °C, and a solution of NaOCl (0.21 mL), saturated $NaHCO_3$(aq) (0.1 mL), and saturated NaCl(aq) (0.18 mL) was added dropwise over 45 min. The two layers were separated, and the organic layer was extracted with water. The aqueous extracts were combined and acidified with aqueous HCl (10% w/v), and the resulting solution was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4(s). The solvent was removed to give 37 mg (93%) of the desired carboxylic acid **20**: ^{1}H NMR (75 °C) δ 10.48 (br, 1H), 7.39 (s, 5H), 5.25 (dd, $J = 12.3$ Hz, 2H), 4.37 (s, 1H), 4.26 (dd, $J = 7.5$, 1.2 Hz, 1H), 4.06 (dd, $J = 7.2$ Hz, 1H), 2.97 (d, br, $J = 8.1$ Hz, 1H), 2.94 (d, $J = 7.5$ Hz, 1H), 2.15 (dd, $J = 7.2$, 8.1 Hz, 1H), 0.96 (s, 9H), −0.13 (s, 6H); ^{13}C NMR δ 172.9, 156.9, 135.8, 128.4, 128.1, 127.8, 82.2, 67.3, 64.1, 59.4, 48.0, 34.5, 25.5, 17.9, −4.8; HRMS *m/z* 392.1894, calcd for $C_{20}H_{30}NO_5Si$ (M + H) 392.1893.

***N*-Benzyloxycarbonyl-5-*anti*-*t*-butyldimethylsilyloxy-3-*exo*-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (21).** To a solution of acid **20** (75 mg, 0.19 mmol) in hexane (1.5 mL) and 2-propanol (0.75 mL) was added a 2 M solution of trimethylsilyldiazomethane in hexane (383 μL, 0.766 mmol). The resulting mixture was stirred under argon for 0.5 h. The solvent was removed in vacuo to give 80 mg (100%) of ester **21**: $R_f = 0.35$ (1:2 ether/hexane); ^{1}H NMR (75 °C) δ 7.38 (s, 5H), 5.27 (d, $J = 12.3$ Hz, 1H), 5.16 (d, $J = 12.3$ Hz, 1H), 4.33 (s, 1H), 4.26 (dd, $J = 7.5$, 1.5 Hz, 1H), 4.05 (d, $J = 7.2$ Hz, 1H), 3.76 (s, 3H), 2.90 (ddd, $J = 8.1$, 3.3, 1.5 Hz, 1H), 2.82 (dd, $J = 7.5$, 3.3 Hz, 1H), 2.04 (dd, $J = 8.1$, 7.2 Hz, 1H), 0.97 (s, 9H), 0.1 (s, 6H); ^{13}C NMR δ 170.5, 156.7, 136.5, 128.4, 128.0, 127.7, 82.7, 67.0, (64.3 and 63.5), 58.7, 52.3, (49.1 and 48.8), (33.7, 33.2), 25.6, 18.0, −4.9; HRMS *m/z* 406.2046, calcd for $C_{21}H_{32}NO_5Si$ (M + H) 406.2049.

5-*anti*-*tert*-Butyldimethylsilyloxy-3-*exo*-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (22). To a solution of ester **21** (810 mg, 2.0 mmol) in methanol (40 mL) was added 10% Pd/C (200 mg). The solution was stirred at 25 °C under a H_2-(g)-filled balloon for 2 h and then filtered through Celite. The solvent was removed in vacuo to give an oil. Purification by flash chromatography (1:1 hexane/EtOAc) afforded 483 mg (85%) of the desired amine **22**: ^{1}H NMR δ 4.13 (m, 1H), 3.79 (m, 4H), 3.44 (m, 1H), 2.79 (m, 1H), 2.69 (m, 1H), 2.22 (br, 1H), 1.45 (m, 1H), 0.94 (s, 9H), 0.11 (s, 6H); ^{13}C NMR δ 174.1, 82.8, 62.8, 58.4, 52.3, 49.7, 33.0, (25.7 and 22.6), −4.9; HRMS *m/z* 272.1672, calcd for $C_{13}H_{26}NO_3Si$ (M + H) 272.1682.

***N*-(2-^{13}CH$_3$-Acetyl)-5-*anti*-*tert*-butyldimethylsilyloxy-3-*exo*-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (23).** To a solution of amine **22** (483 mg, 1.6 mmol) in dry methylene chloride (20 mL) at 0 °C was added DMAP (1.66 g, 13.6 mmol, 3 equiv), and then $^{13}CH_3COCl$ (372.7 mg, 4.69 mmol) was added dropwise, and the mixture was stirred for 30 min at 0 °C. The reaction mixture was then slowly warmed to 25 °C and stirred for an additional 2 h. Water (5 mL) was added to form two layers, and the water layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4(s) and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography to afford 484 g (93%) of amide **23**: $R_f = 0.20$ (1:1 hexane/EtOAc); ^{1}H NMR δ 4.57−4.24 (m, 1H), 3.98 (m, 2H), 3.71 (m, 3H), 2.84−2.75 (m, 2H), 2.04 and 1.93 (two d, $J = 128.1$ Hz, 3H), 2.06 (t, $J = 7.5$ Hz, 1H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (two conformations) δ 170.1 and 169.6, 169.3 (d, $J = 51.5$ Hz) and 168.1 (d, $J = 51.6$ Hz), 82.4 and 82.0, 65.6 and 62.6, 59.5 and 57.6, 52.5 and 52.2, 49.3 and 48.3, 34.0 and 32.7, 25.5, (21.2 and 21.0, labeled methyl), 17.9, −4.1; HRMS *m/z* 315.1830, calcd for $C_{14}{}^{13}CH_{28}NO_4Si$ (M + H) 315.1821.

***N*-(2-^{13}CH$_3$-Acetyl)-5-*anti*-hydroxy-3-*exo*-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (6).** To a solution of silyl ether **23** (486.4 mg, 1.48 mmol) in THF (10 mL) at 0 °C was added tetrabutylammonium fluoride monohydrate (TBAF·H_2O, 1.16 g, 4.44 mmol, 3 equiv). The reaction mixture was stirred at 0 °C for 5 min, and then warmed slowly to rt and stirred for an additional 30 min. Removal of solvent in vacuo and flash chromatography afforded 181 mg (90%) of alcohol **6** as a white solid: $R_f = 0.60$ (5:1 EtOAc/MeOH); ^{1}H NMR (500 MHz) δ (4.73, 4.68) (br, 1H), (4.55−4.53, 4.11−4.09) (m, 1H), (4.31, 4.28) (bs, 1H), (4.04, 3.98) (m, 1H), (3.78, 3.72) (s, 3H), 2.91−2.81 (m, 2H), 2.11 (m, 1H), (2.06, 1.94) (d, $J = 128.3$ Hz, 3H); ^{13}C NMR (125 MHz, two conformations) δ 170.0 (d, $J = 50.3$ Hz), 169.9, 168.4 (d, $J = 51.7$ Hz), 81.8, 81.3, 65.3, 62.5, 59.9, 57.9, 52.6, 52.3, 48.5, 47.4, 34.1, 32.8, 21.8, 21.65, (21.58, 21.4 labeled ^{13}C); HRMS *m/z* 201.0961, calcd for $C_8{}^{13}CH_{14}NO_4$ (M + H) 201.0956.

***N*-Acetyl-5-*anti*-fluoro-3-*exo*-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (7).** Bis(2-methoxyethyl)aminosulfur trifluoride (166 mg, 0.75 mmol) was added dropwise via syringe to a solution of *N*-acetyl-5-*anti*-hydroxy-3-*exo*-methoxycarbonyl-2-azabicyclo[2.1.1]hexane **6** (60 mg, 0.3 mmol) in dry CH_2Cl_2 (12 mL) under Ar(g) at −78 °C. The mixture was stirred for 2 h at rt and then heated at reflux for 8 h. The reaction was quenched with water, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined and washed with water and brine, dried over Na_2SO_4(s), and filtered. Removal of solvent in vacuo and flash chromatography (EtOAc) gave 38 mg (63%) of fluoride **7** as an oil: $R_f = 0.55$ (15:1 EtOAc/MeOH); ^{1}H NMR δ [4.77 (dd, $^2J_{H,F} = 61.6$ Hz, $J = 7.4$ Hz), 4.62 (dd, $^2J_{H,F} = 61.0$ Hz, $J = 7.4$ Hz), 1H], 4.33 (s, 1H), 4.24 (dd, $J = 7.2$, 1.5 Hz, 1H), 3.74 and 3.70 (two s, 3H), 3.01 (m, 1H), 2.79 (m, 1H), 2.25−2.22 (m, 1H), 2.11 and 1.99 (two s, 3H); ^{13}C NMR (100 MHz, two conformations) δ 169.6, 169.4, 169.2, 168.1, 97.9 (d, $J_{C,F} = 219.6$ Hz), 97.6 (d, $J_{C,F} = 218.7$ Hz), 63.5 (d, $J_{C,F} = 20.5$ Hz), 60.5 (d, $J_{C,F} = 20.8$ Hz), 58.6, 56.5, 52.8, 52.5, 47.6 (d, $J_{C,F} = 19.2$ Hz), 46.7 (d, $J_{C,F} = 18.7$ Hz), 34.2, 32.8, 30.9, 21.6, 21.6; HRMS *m/z* 202.0885, calcd for $C_9H_{13}NO_3F$ (M + H) 202.0879.

Measurement of $K_{trans/cis}$ Values of 5−7. Each compound (10−20 mg) was dissolved in $CDCl_3$ (approximately 1 mL) and the ^{13}C NMR (**5** and **6**) or ^{19}F NMR (**7**) spectrum recorded. The relaxation delay for the measurement of the spectra of **5** and **6** was 10−18 s to allow for full relaxation of the ^{13}C nuclei. The spectral baselines were corrected and peaks corresponding to the labeled carbon or the fluorine were integrated with the software package NUTS.[63] The samples were then concentrated under reduced pressure and placed under high vacuum overnight to ensure removal of all residual $CDCl_3$. The resulting samples were dissolved in 1,4-dioxane-d_8 (800 μL), and the spectra were recorded again. The samples were concentrated under reduced pressure and placed under high vacuum overnight. D_2O (800 μL) was then added to each sample followed by enough CD_3OD to effect full dissolution of the sample. The amount of added CD_3OD was less than 20% of the total volume in each case. The samples were filtered, their spectra were recorded, and the trans/cis ratios were determined by integration of the respective resonances.

Crystallization of Ac-methano-hyp-OMe (6). Racemic Ac-methano-hyp-OMe (**6**, 20−30 mg) was dissolved in dichloromethane, and the resulting solution was aliquotted into five vials. A cosolvent (10−20 drops) was added to each vial with a Pasteur pipet: vial 1, hexanes; vial 2, diethyl ether; vial 3, 1,4-dioxane; vial 4, no cosolvent; vial 5, ethyl acetate. The vials were capped loosely and allowed to sit at rt for approximately 2 days. Vial 5 contained the crystals most suitable for X-ray crystallography, and these crystals were used for X-ray diffraction analysis.

X-ray Diffraction Data Collection. An air-stable crystal of Ac-methano-hyp-OMe (**6**) with approximate dimensions 0.50 × 0.40 × 0.40 mm^3 was selected under oil at ambient conditions and attached to the tip of a glass capillary. The crystal was mounted in a stream of cold nitrogen at 173(2) K and centered in the X-ray beam by using a microscope.

Crystal evaluation and data collection were performed on a Bruker P4/CCD-1000 diffractometer with Mo Kα ($\lambda = 0.710\,73$ Å) radiation with a diffractometer-to-crystal distance of 4.999 cm.

Initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 20 frames collected at intervals of 0.3° in a 6° range about ω with an exposure time of 10 s per frame. A total of 69 reflections were obtained. The reflections were indexed successfully by an automated indexing routine built in the SMART program.[65] The final cell constants were calculated from a set of 4952 strong reflections from the actual data collection.

Data were collected by using the multirun data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of 0.80 Å. A total of 12437 data were harvested by collecting one set of 1250 frames with 0.3° scans in ϕ and four sets of 100 frames with 0.3° scans in ω with an exposure time 30 s per frame. This highly redundant data set was corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[64]

Structure Solution and Refinement. The systematic absences in the diffraction data were consistent for the space groups $P1$ and $P\bar{1}$.[65] The E-statistics strongly suggested the centrosymmetric space group $P\bar{1}$ that yielded chemically reasonable and computationally stable results of refinement.

A successful solution by direct methods provided most non-hydrogen atoms from the E-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. There were two chemically equivalent but crystallographically independent molecules of compound **6** in the asymmetric unit. Because compound **6** crystallized in a centrosymmetric space group, the crystal structure was a racemic mixture of stereoisomers. Several likely intermolecular hydrogen-bonding interactions were observed in the lattice, and formed a series of one-dimensional chains in the *ab* plane.

The final least-squares refinement of 259 parameters against 3638 data resulted in residuals R (based on F^2 for $I \geq 2\sigma$) and wR (based on F^2 for all data) of 0.0735 and 0.2199, respectively. The final difference Fourier map was featureless.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **5**−**23** and data from the X-ray diffraction analysis of Ac-methano-hyp-OMe (**6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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