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

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#### Abstract

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, $\mathrm{C}^{\gamma}$ ) 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 $\mathrm{C}^{\gamma}$ 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

[^0]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 $\mathrm{C}^{\gamma}$ 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 $(\mathbf{1}-\mathbf{4}) .{ }^{21-27}$ 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, $\mathbf{3} \mathbf{a}^{28,29}$ and $\mathbf{4}^{30}$ have been employed in the design of peptide-based enzyme inhibitors to reinforce a bioactive peptide conformation, with varying degrees of success.




3a, $\mathrm{R}=\mathrm{H}$
3b, $\mathrm{R}=\mathrm{CO}_{2} \mathrm{H}$
3c, $\mathrm{R}=n \mathrm{Pr}$
3d, $\mathrm{R}=\mathrm{Ph}$
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 $\mathrm{C}^{\gamma 1}$ or $\mathrm{C}^{\gamma 2}$ 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

[^1]TABLE 1. Values of $\boldsymbol{K}_{\text {trans/cis }}$ for 4-Substituted AcXaaOMe ${ }^{\text {a }, b}$

| Xaa | X | Y | $K_{\text {trans/cis }}$ |
| :--- | :--- | :--- | :--- |
| Flp | H | F | 6.7 |
| Hyp | H | OH | 6.1 |
| Pro | H | H | 4.6 |
| OH | H | H | 2.4 |
| flp | F | H | 2.5 |

${ }^{a}$ Data are from ref $38 .^{b}$ Values were measured in $\mathrm{D}_{2} \mathrm{O}$ at 25 ${ }^{\circ} \mathrm{C}$ by integration of ${ }^{1} \mathrm{H}$ NMR spectra.


FIGURE 1. Ring puckers in 4 -substituted Ac-Pro-OMe. $\mathrm{C}^{\gamma}-$ endo pucker is favored when $\mathrm{X}=\mathrm{H}, \mathrm{OH}$, or F and $\mathrm{Y}=\mathrm{H}$. $\mathrm{C}^{\gamma}$-exo pucker is favored when $\mathrm{X}=\mathrm{H}$ and $\mathrm{Y}=\mathrm{OH}$ or F .
mimics of collagen with extraordinary stability. ${ }^{33-35}$


5


6


7

Substitutions on C-4 (that is, $\mathrm{C}^{\gamma}$ ) 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 $\mathrm{C}^{\gamma}$-exo pucker in solution, whereas Ac-( $2 S, 4 S$ )-4-fluoroproline-OMe (Ac-flpOMe ) is found almost exclusively ( $95 \%$ ) in the $\mathrm{C}^{\gamma}$-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 $\mathrm{C}^{\delta 2}-\mathrm{C}^{\gamma}$ bond (for nomenclature, see Figure 2 and ref 41$)^{42}$ and has important

[^2]
## 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 $n \rightarrow \pi^{*}$ interaction between the oxygen of the amide


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.
(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 $\mathrm{n} \rightarrow$ $\pi^{*}$ 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.

## Results and Discussion

2-(2- ${ }^{13} \mathrm{C}$-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]-

[^3]
## SCHEME 2. Synthetic Route to Ac-methano-hyp-OMe (6)



hexane $\mathbf{9}$ along with a tricyclic byproduct, $\mathbf{1 0}$, 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 ${ }^{13} \mathrm{C}$-labeled acetyl chloride to give the desired Ac-methano-Pro-OMe (5). The ${ }^{13} \mathrm{C}$ label was incorporated to enable facile measurement of amide trans/cis ratios by ${ }^{13} \mathrm{C}$ NMR spectroscopy (vide infra).

[^4]SCHEME 3. Synthetic Route to Ac-methano-flp-OMe (7)


The synthesis of $2-\left(2-{ }^{13} \mathrm{C}\right.$-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 $\mathbf{1 5}$ with NBS and $\mathrm{H}_{2} \mathrm{O}$ in THF ${ }^{50}$ and the need to protect the resulting alcohol with a TBDMS group, as shown in Scheme 2. The relative configuration at $\mathrm{C}_{1}{ }^{\gamma 1}$ (which bears the hydroxyl group) of $\mathbf{6}$ 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-

[^5]TABLE 2. Effect of Solvent on $K_{\text {trans/cis }}$ of AcXaaOMe ${ }^{a}$

|  | $K_{\text {trans/cis }}$ |  |  |
| :--- | :---: | :---: | :---: |
| Xaa | $\mathrm{CDCl}_{3}$ | 1,4-dioxane- $d_{8}$ | $\mathrm{D}_{2} \mathrm{O}$ |
| 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 $K_{\text {trans/cis }}$ were measured in the indicated solvents at $25^{\circ} \mathrm{C}$ by integration of ${ }^{13} \mathrm{C}$ or ${ }^{19} \mathrm{~F}$ 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 $\mathrm{C}_{1}{ }^{\gamma 1}$ (elsewhere, C-5 ${ }^{48,31}$ ) was confirmed by analyzing the coupling constants between $\mathrm{H}_{1}{ }^{\gamma 1}(\mathrm{H}-5)$ and $\mathrm{H}_{1}{ }^{\gamma 21}\left(\mathrm{H}-6_{\text {syn }}\right)$, which is 7.4 Hz . This four-bond W-plan coupling was not observed between the fluorine and either proton on $\mathrm{C}_{1}{ }^{\gamma 2}$ (C-6), nor between $\mathrm{H}_{1}{ }^{\gamma 1}$ and $\mathrm{H}_{1}{ }^{\gamma 22}\left(\mathrm{H}-6_{\text {anti }}\right)$, 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 hy-droxyl- and fluoro-substituted methanoprolines are analogues of ( $2 S, 4 S$ )-4-hydroxyproline (hyp) and ( $2 S, 4 S$ )-4fluoroproline (flp), respectively, and the substituent is in an orientation analogous to the disfavored $\mathrm{C}^{\gamma}$-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 $\mathrm{C}^{\delta 2}-\mathrm{C}^{\gamma 1}$ bond.

We measured the amide trans/cis ratios of 5 and $\mathbf{6}$ by using NMR spectroscopy. We used ${ }^{13} \mathrm{C}$ NMR spectroscopy because the ${ }^{1} \mathrm{H}$ resonances of both methyl groups overlapped with those of other protons from the bicyclic ring system. ${ }^{13} \mathrm{C}$ NMR spectra were obtained with ${ }^{1} \mathrm{H}$-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 $\mathrm{CDCl}_{3}, 1,4$-di-oxane- $d_{8}$, and $\mathrm{D}_{2} \mathrm{O}$ and are listed in Table 2. The trans/ cis ratios of 7 were measured by ${ }^{19} \mathrm{~F}$ NMR spectroscopy, as the two ${ }^{19} \mathrm{~F}$ 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.

[^6]

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 $\mathrm{O}_{0} \cdots \mathrm{C}_{1}=\mathrm{O}_{1}$ 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 $\phi$ angles $\left(\mathrm{C}_{i-1}-\mathrm{N}_{i}-\mathrm{C}_{i}{ }^{\alpha}-\mathrm{C}_{i}\right)$ differ by $3.1(3)^{\circ}$, the $\psi$ angles (here, $\mathrm{N}_{i}-\mathrm{C}_{i}{ }^{\alpha}-\mathrm{C}_{i}-\mathrm{O}_{i+1}$ ) differ by $18.0(4)^{\circ}$, and the $\omega$ angles $\left(\mathrm{C}_{i}{ }^{\alpha}-\mathrm{C}_{i}-\mathrm{N}_{i+1}-\mathrm{C}_{i+1}{ }^{\alpha}\right)$ differ by 2.6(2) ${ }^{\circ}$. 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 $\mathrm{C}^{\gamma}$.

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 $\mathrm{O}_{0} \cdots \mathrm{C}_{1}$ distance is 2.949(4) $\AA$ in molecule B , but 3.092(3) $\AA$ in molecule A. In addition, the $\mathrm{C}_{1}=\mathrm{O}_{1}$ bond length is $1.207(3) \AA$ in molecule B, but 1.198(3) Å in molecule A, and the ${ }^{+} \mathrm{N}_{1}=$ $\mathrm{C}_{0}-\mathrm{O}_{0}{ }^{-}$amidic resonance structure appears to be more prevalent in molecule $B$, which has a shorter $N_{1}-C_{0}$ bond and a longer $\mathrm{C}_{0}-\mathrm{O}_{0}$ bond than does molecule A. Finally, the $\mathrm{O}_{0} \cdots \mathrm{C}_{1}=\mathrm{O}_{1}$ angle is closer to the Bürgi-Dunitz optimum of $109^{\circ 58-62}$ in molecule B [93.2(2) ${ }^{\circ}$ ] than in

[^7]TABLE 3. Values of $\phi$ and $\psi$ Dihedral Angles for the trans-Amide Isomers of Ac-Xaa-OMe ${ }^{a}$

| Xaa | ring pucker | $\phi(\mathrm{deg})$ | $\psi(\mathrm{deg})$ | ref |
| :--- | :---: | :---: | :---: | :---: |
| Pro | $\mathrm{C}^{\gamma}$-exo | -58.6 | 143.0 | 40 |
| Pro | $\mathrm{C}^{\gamma}$-endo | -70.0 | 152.1 | 40 |
| Hyp (1) | $\mathrm{C}^{\gamma}$-exo | -62.0 | 156.4 | 57 |
| Hyp (2) | $\mathrm{C}^{\gamma}$-exo | -50.9 | 145.2 | 57 |
| Flp | $\mathrm{C}^{\gamma}$-exo | -59.2 | 140.8 | 40 |
| flp | $\mathrm{C}^{\gamma}$-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) ${ }^{\circ}$. All of these structural parameters are consistent with greater donation of electron density from the nonbonding electrons of $\mathrm{O}_{0}$ to the antibonding orbital of the $\mathrm{C}_{1}=\mathrm{O}_{1}$ bond in molecule B , as expected from a stronger $\mathrm{n} \rightarrow \pi^{*}$ interaction. ${ }^{40}$ Moreover, the congruence of these five structural parameters (three bond lengths, an atom $\cdots$ atom distance, and an atom $\cdots$ atom-atom angle) provides additional support for the existence of a meaningful $\mathrm{n} \rightarrow \pi^{*}$ 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 $\mathrm{D}_{2} \mathrm{O}$ are intermediate between those of Ac-Pro-OMe and Ac-hypOMe 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 $\phi$ and $\psi$ angles of Ac-methano-hyp-OMe (6) are intermediate between those of the endoand 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 $5-\mathbf{7}$, 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 $250 \mu \mathrm{~m}$. Column chromatography was performed on silica gel, Merck grade 60

[^8](230-400 mesh). Reagent chemicals were obtained from commercial suppliers, and reagent grade solvents were used without further purification. ${ }^{1} \mathrm{H}$ NMR spectra were recorded at 300 MHz and ${ }^{13} \mathrm{C}$ NMR spectra were recorded at 75 MHz in $\mathrm{CDC1}_{3}$, unless noted otherwise. Both the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra are often complicated by the presence of carbamate conformers and pairs of ${ }^{13} \mathrm{C}$ 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 $\left({ }^{1} \mathrm{H}\right)$ or solvent $\mathrm{CDCl}_{3}\left({ }^{13} \mathrm{C}\right)$. Highresolution 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-aza-bicyclo[2.2.0]hex-5-ene were prepared according to our previously described procedures for N -(methoxycarbonyl)-2-hy-droxymethyl-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-ni-trophenylsulfonyloxy)methyl-2-azabicyclo[2.1.1]hexane (9). A solution of bromine ( $2.56 \mathrm{~g}, 1.7$ equiv) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ (50 mL ) was added dropwise to a cold $\left(-5\right.$ to $\left.0{ }^{\circ} \mathrm{C}\right)$ solution of nosylate $8(4.0 \mathrm{~g}, 9.3 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL})$, and the resulting solution was stirred for 2 h . The temperature was then raised to $25^{\circ} \mathrm{C}$, and the reaction mixture was stirred for an additional 10 h . The solution was diluted with ether and washed with aqueous sodium bisulfite ( $10 \% \mathrm{w} / \mathrm{v}$ ) 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 $2.74 \mathrm{~g}(50 \%)$ of rearranged dibromide $\mathbf{9}$ as the major product with $R_{f}=0.47$ (1:1 ether/hexane): ${ }^{1} \mathrm{H}$ NMR $\delta 8.39$ (br, 2H), 8.06 (br, 2H), $7.50-7.26(\mathrm{~m}, 5 \mathrm{H}), 5.13(\mathrm{~s}, 2 \mathrm{H}), 4.56(\mathrm{~m}, 2 \mathrm{H}), 4.11(\mathrm{~m}, 3 \mathrm{H})$, 3.96 (d, $J=7.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.19 (d, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR $\delta$ 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 $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{7} \mathrm{~S}^{79} \mathrm{Br}^{79} \mathrm{BrNa}(\mathrm{M}+\mathrm{Na})$ 610.9099, $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{7} \mathrm{~S}^{79} \mathrm{Br}^{81} \mathrm{BrNa}(\mathrm{M}+\mathrm{Na}) 612.9079$; and $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{7} \mathrm{~S}^{81} \mathrm{Br}^{81} \mathrm{BrNa}(\mathrm{M}+\mathrm{Na}) 614.9058$. In addition, 750 $\mathrm{mg}(25 \%)$ of azatricycle byproduct 10 was also isolated: $R_{f}=$ 0.40 (1:1 ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta 7.35(\mathrm{~m}, 5 \mathrm{H}), 5.16$, 5.10 (two d, $J=12.6 \mathrm{~Hz}, 2 \mathrm{H}$ ), 4.93 (dd, $J=2.4,3.9,5.4 \mathrm{~Hz}$, $1 \mathrm{H}), 4.72$ (dd, $J=3.6,5.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.64 (dd, $J=3.9,10.2 \mathrm{~Hz}$, $1 \mathrm{H}), 4.42$ (dd, $J=3.6,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.21,4.11$ (s, 1H), 3.92 (ddd, $J=3.6,5.4,5.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.76 (dd, $J=2.4,10.2 \mathrm{~Hz}, 1 \mathrm{H}$ ); ${ }^{13}$ C NMR $\delta 153.4,135.6,128.0,127.7,127.3,(85.7,85.5)$, (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 $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{NO}_{3} \mathrm{Na}^{79} \mathrm{Br}(\mathrm{M}+\mathrm{Na})$, 346.0055; and 348.0036, calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{NO}_{3} \mathrm{Na}^{81} \mathrm{Br}(\mathrm{M}+\mathrm{Na})$, 348.0034 .
$N$-(Benzyloxycarbonyl)-5-anti,6-anti-dibromo-3-ace-toxymethyl-2-azabicyclo[2.1.1]hexane (11). To the dibromide 9 ( $300 \mathrm{mg}, 0.50 \mathrm{mmol}$ ) in dry DMF ( 10 mL ) was added $\mathrm{CsOAc}(336 \mathrm{mg}, 1.75 \mathrm{mmol}, 3.5$ equiv). The solution was heated to $60^{\circ} \mathrm{C}$ 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); ${ }^{1} \mathrm{H}$ NMR $\delta 7.41$ (s, 5H), 5.22 (m, 2H), 4.62 (d, $J=7.3$ $\mathrm{Hz}, 1 \mathrm{H}), 4.53(\mathrm{~d}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.35(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H})$, 4.16 (b, 2H), 4.05 (d, $J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.19(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H})$, $2.12(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 170.4,155.1,135.8,128.7,128.5,128.2$, 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 $\mathrm{C}_{16} \mathrm{H}_{17} \mathrm{NO}_{4}{ }^{79} \mathrm{Br}^{79} \mathrm{BrNa}$
$(\mathrm{M}+\mathrm{Na}) 467.9422 ; \mathrm{C}_{16} \mathrm{H}_{17} \mathrm{NO}_{4}{ }^{79} \mathrm{Br}^{81} \mathrm{BrNa}(\mathrm{M}+\mathrm{Na})$ 469.9402; and $\mathrm{C}_{16} \mathrm{H}_{17} \mathrm{NO}_{4}{ }^{81} \mathrm{Br}^{81} \mathrm{BrNa}(\mathrm{M}+\mathrm{Na}) 471.9381$.
$N$-(Benzyloxycarbonyl)-3-acetoxymethyl-2-azabicyclo[2.1.1]hexane (12). Dibromide $11(474 \mathrm{mg}, 1.06 \mathrm{mmol})$ and AIBN ( $47.4 \mathrm{mg}, 0.29 \mathrm{mmol}$ ) were dissolved in benzene ( 25 mL ), and the system was purged with $\operatorname{Ar}(\mathrm{g})$ for 10 min . Tributyltin hydride ( $713 \geq \mathrm{L}, 772 \mathrm{mg}, 2.65 \mathrm{mmol}$ ) 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 $277 \mathrm{mg}(91 \%)$ of acetate 12: $R_{f}=$ 0.46 (1:1 ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\delta 7.42$ (s, 5H), 5.21 (s, 2H), 4.50 (dd, $J=4.3,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.40(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.14$ $(\mathrm{m}, 1 \mathrm{H}), 3.96(\mathrm{~b}, 1 \mathrm{H}), 2.83(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.05(\mathrm{~s}, 3 \mathrm{H})$, $1.88-1.42(\mathrm{~m}, 4 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta$ 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 $\mathrm{C}_{16} \mathrm{H}_{20} \mathrm{NO}_{4}(\mathrm{M}+\mathrm{H})$ 290.1392.

N-(Benzyloxycarbonyl)-3-hydroxymethyl-2-azabicyclo[2.1.1]hexane (13). To acetate $12(300 \mathrm{mg}, 1.04 \mathrm{mmol})$ in methanol ( 25 mL ) were added $\mathrm{K}_{2} \mathrm{CO}_{3}(450 \mathrm{mg}, 3.0 \mathrm{mmol})$ and $\mathrm{NaHCO}_{3}(830 \mathrm{mg}, 9.0 \mathrm{mmol})$. The solution was stirred at $25{ }^{\circ} \mathrm{C}$ 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 $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$. The solvent was removed in vacuo, and the residue was purified by flash chromatography (1:1 ether/hexane) to afford $218 \mathrm{mg}(85 \%)$ of alcohol 13: $R_{f}=0.23$ (1:2 hexane/ether); ${ }^{1} \mathrm{H}$ NMR $\delta 7.41$ (s, $5 \mathrm{H}), 5.22(\mathrm{~s}, 2 \mathrm{H}), 4.59(\mathrm{~b}, 1 \mathrm{H}), 4.45(\mathrm{~d}, J=7.18 \mathrm{~Hz}, 1 \mathrm{H}), 3.96-$ 3.79 (br, 2H), $2.75(\mathrm{~b}, 1 \mathrm{H}), 2.02-1.50(\mathrm{~m}, 4 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta$ $157.9,136.4,128.5,128.1,127.9,67.3,66.0,62.8,61.4,42.6$, 41.2, 37.7; HRMS $m / z 270.1113$, calcd for $\mathrm{C}_{14} \mathrm{H}_{17} \mathrm{NO}_{3} \mathrm{Na}(\mathrm{M}+$ 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 $\delta 3.80$ (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 $13(600 \mathrm{mg}, 2.45 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(7 \mathrm{~mL})$ containing TEMPO ( $5 \mathrm{mg}, 0.032 \mathrm{mmol}$ ) was added a solution of saturated aqueous $\mathrm{NaHCO}_{3}(4.8 \mathrm{~mL})$ containing $\mathrm{KBr}(26.4 \mathrm{mg}, 0.22$ mmol ) and tetrabutylammonium chloride ( $35.2 \mathrm{mg}, 0.13$ mmol ). The mixture was cooled to $0^{\circ} \mathrm{C}$, and a solution of $\mathrm{NaOCl}(4-6 \% \mathrm{w} / \mathrm{v}, 12 \mathrm{~mL})$, saturated aqueous $\mathrm{NaHCO}_{3}(2.64$ 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 $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$ and concentrated in vacuo. The crude acid was dissolved in isopropyl alcohol (15 mL ) and hexane ( 15 mL ), and trimethylsilyldiazomethane ( 2.0 $\mathrm{M}, 1.225 \mathrm{~mL}, 2.45 \mathrm{mmol}$ ) was added. The mixture was stirred at $25{ }^{\circ} \mathrm{C}$ 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 $539 \mathrm{mg}(80 \%)$ of ester 14: $R_{f}=0.40$ ( $1: 1$ hexane/ether); ${ }^{1} \mathrm{H}$ NMR $\delta 7.37$ ( $\mathrm{s}, 5 \mathrm{H}$ ), 5.22 $(\mathrm{m}, 2 \mathrm{H}), 4.53$ (br, 1H), 4.34 (br, 1H), 3.79 (br, 3 H ), 3.05 (br, $1 \mathrm{H}), 2.11-1.48(\mathrm{~m}, 4 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 171.4,156.8,66.9,60.9$, 60.2, 52.2, 43.4, 42.9, 37.7; HRMS $m / z$ 298.1070, calcd for $\mathrm{C}_{15} \mathrm{H}_{17} \mathrm{NO}_{4} \mathrm{Na}(\mathrm{M}+\mathrm{Na}) 298.1055$. This ester contained 40 mg of a minor byproduct, the $N$-(methoxycarbonyl)-3-ester: $R_{f}=$ 0.40 (1:1 hexane/ether); ${ }^{1} \mathrm{H}$ NMR $\delta 4.40$ (br, 1H), 4.22 (br, 1 H ), $3.73(\mathrm{~s}, 3 \mathrm{H}), 3.67(\mathrm{~s}, 3 \mathrm{H}), 2.97(\mathrm{~m}, 1 \mathrm{H}), 2.03-1.39(\mathrm{~m}, 4 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 171.3,156.2,61.0,60.1,52.4,52.1,43.3,42.7,37.2$; HRMS $m / z$ 200.0918, calcd for $\mathrm{C}_{9} \mathrm{H}_{14} \mathrm{NO}_{4}(\mathrm{M}+\mathrm{H}) 200.0923$. A sample of the major product, ester $14(25 \mathrm{mg})$, 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 - ${ }^{13} \mathrm{CH}_{3}$-Labeled-acetyl-3-methoxylcarbonyl-2-azabicyclo[2.1.1]hexane (5). To a solution of ester $14(200 \mathrm{mg}$, 0.73 mmol ) in methanol ( 20 mL ) was added $\mathrm{Pd} / \mathrm{C}(100 \mathrm{mg})$. The mixture was stirred at $25^{\circ} \mathrm{C}$ under a $\mathrm{H}_{2}(\mathrm{~g})$-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); ${ }^{1} \mathrm{H}$ NMR ( $\mathrm{CDCl}_{3}$ ) $\delta 4.70$ (br, 1 H ), 4.32 (d, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.84(\mathrm{~s}, 3 \mathrm{H}), 3.18(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.20$ (d, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.16(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.00(\mathrm{dd}, J=$ $10.6,7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.63 (dd, $J=10.6,7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta 171.1,60.4,59.0,52.2,43.9,42.2,37.0$; HRMS m/z 142.0873, calcd for $\mathrm{C}_{7} \mathrm{H}_{12} \mathrm{NO}_{2}(\mathrm{M}+\mathrm{H})$ 142.0868. To a solution of the amine in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ was added (dimethylamino)pyridine (DMAP, $759 \mathrm{mg}, 6.21 \mathrm{mmol}$ ), followed by dropwise addition of ${ }^{13} \mathrm{CH}_{3} \mathrm{COCl}(170.8 \mathrm{mg}, 2.15 \mathrm{mmol})$. The mixture was stirred for an additional 30 min at $0^{\circ} \mathrm{C}$, allowed to warm slowly to $25^{\circ} \mathrm{C}$, and then stirred for 2 h . Water was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$ and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography eluting with EtOAc to give $107 \mathrm{mg}(80 \%)$ of 5 as a colorless oil: $R_{f}=0.50(15: 1 \mathrm{EtOAc} /$ $\mathrm{MeOH}) ;{ }^{1} \mathrm{H}$ NMR $\delta 4.8-4.4(\mathrm{~m}, 1 \mathrm{H}$, two conformers), 4.34 (m, $1 \mathrm{H}), 3.80(\mathrm{~m}, 3 \mathrm{H}), 3.06(\mathrm{~m}, 1 \mathrm{H}), 2.36-1.40(\mathrm{~m}, 7 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR $\delta(170.8,169.4), 168.3(\mathrm{~d}, J=51.6 \mathrm{~Hz}),(62.5,61.0),(59.6,59.0)$, (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 $\mathrm{C}_{8}{ }^{13} \mathrm{CH}_{14} \mathrm{NO}_{3}$ (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 $8(2.00 \mathrm{~g}, 4.65 \mathrm{mmol})$ in THF ( 16 mL ) and $\mathrm{H}_{2} \mathrm{O}(8 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ was added N bromosuccinimide ( $2.51 \mathrm{~g}, 13.9 \mathrm{mmol}$ ) in small portions so that the temperature never exceeded $0{ }^{\circ} \mathrm{C}$. 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 $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$. The solvent was removed in vacuo to give an oil, which was purified by flash chromatography (3:1 ether/ hexane) to provide $1.71 \mathrm{~g}(70 \%)$ of bromohydrin 15: $R_{f}=0.25$ (3:1 ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\delta 8.43$ (br, 2H), 8.14 (br, 2H), $7.47-7.34(\mathrm{~m}, 5 \mathrm{H}), 5.15(\mathrm{~s}, 2 \mathrm{H}), 4.55(\mathrm{br}, 1 \mathrm{H}), 4.44(\mathrm{~d}, J=7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 4.22(\mathrm{~m}, 2 \mathrm{H}), 4.10(\mathrm{~m}, 2 \mathrm{H}), 3.43(\mathrm{br}, 1 \mathrm{H}), 3.08(\mathrm{~d}, J=$ $7.5 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 155.1,150.8,141.0,135.4,129.2,128.7$, 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 $\mathrm{C}_{20} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{8} \mathrm{NaS}^{79} \mathrm{Br}(\mathrm{M}+\mathrm{Na})$ 548.9943; m/z 550.9929, calcd for $\mathrm{C}_{20} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{8} \mathrm{NaS}^{81} \mathrm{Br}$ (M + Na) 550.9923.
$N$-(Benzyloxycarbonyl)-5-anti-(tert-butyldimethylsilyl-oxy)-6-anti-bromo-3-endo-(p-nitrophenylsulfonyloxy)-methyl-2-azabicyclo[2.1.1]hexane (16). To a solution of nosylate $15(2.33 \mathrm{~g}, 4.4 \mathrm{mmol})$ in DMF ( 5 mL ) were added tertbutyldimethylsilyl chloride (TBDMSCl) $(0.80 \mathrm{~g}, 5.3 \mathrm{mmol})$ and imidazole ( $0.76 \mathrm{~g}, 11 \mathrm{mmol}$ ). 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 $(10 \mathrm{~mL})$. The two layers were separated, and the aqueous layer was extracted with diethyl ether. The organic layer was washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$, and filtered. The solvent was removed in vacuo to give the crude product, which was purified by flash chromatography to provide $1.76 \mathrm{~g}(62 \%)$ of the desired $O$-silyl ether $\mathbf{1 6}$ as an oily white solid: $R_{f}=$ 0.64 (2:1 ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\delta 8.42$ (br, 2H), 8.13 (br, 2H), $7.40-7.31(5 \mathrm{H}), 5.13(\mathrm{~m}, 2 \mathrm{H}), 4.53(\mathrm{~m}, 1 \mathrm{H}), 4.28(\mathrm{~d}, J=7.5$ $\mathrm{Hz}, 1 \mathrm{H}), 4.20(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.15(\mathrm{~d}, J=9.9 \mathrm{~Hz}, 1 \mathrm{H})$, 4.12 (d (buried), $J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.06$ (m, 1H), 2.90 (d, $J=$ $7.2 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 157.7,150.9,140.9,129.3,124.6,135.6$, 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 $\mathrm{C}_{26} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{8} \mathrm{Na}-$ $\mathrm{SiS}^{79} \mathrm{Br}(\mathrm{M}+\mathrm{Na}), 663.0808 ; \mathrm{m} / \mathrm{z} 665.0773$, calcd for $\mathrm{C}_{26} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{8^{-}}$ $\mathrm{NaSiS}{ }^{81} \mathrm{Br}(\mathrm{M}+\mathrm{Na}) 665.0788$.
$N$-Benzyloxycarbonyl-5-anti-(tert-butyldimethylsilyl-oxy)-6-anti-bromo-3-endo-acetoxymethyl-2-azabicyclo[2.1.1]hexane (17). To a solution of $O$-silyl ether $16(128 \mathrm{mg}$, 0.20 mmol ) in toluene ( 30 mL ) were added cesium acetate ( 200 $\mathrm{mg}, 1.0 \mathrm{mmol}, 5$ equiv), DMAP ( $24.5 \mathrm{mg}, 0.20 \mathrm{mmol}$ ), 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 $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$ and filtered. Removal of solvent in vacuo and flash chromatography afforded $72 \mathrm{mg}(72 \%)$ of acetate 17 as a yellow oil: $R_{f}=0.32$ (1:2 ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\delta 7.35$ (s, 5H), 5.19 (dd, $J=7.5$ $\mathrm{Hz}, 2 \mathrm{H}$ ), 4.43 (dd, $J=3.6,10.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.28 (d, $J=7.2 \mathrm{~Hz}$, $1 \mathrm{H}), 4.26$ (d, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.14(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.05$ (br, 2H), 2.82 (d, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.06 (s, 3 H ), 0.91 (s, 9 H ), 0.07 ( $\mathrm{s}, 6 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR $\delta 170.4,155.0,135.9,128.5,128.2,128.0$, 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 $\mathrm{C}_{22} \mathrm{H}_{32} \mathrm{NO}_{5} \mathrm{NaSi}^{79} \mathrm{Br}(\mathrm{M}+\mathrm{Na})$ 520.1131; m/z 522.1115, calcd for $\mathrm{C}_{22} \mathrm{H}_{32} \mathrm{NO}_{5} \mathrm{NaSi}^{81} \mathrm{Br}(\mathrm{M}+$ Na) 522.1110 .
$N$-Benzyloxycarbonyl-5-anti-(tert-butyldimethylsilyl-oxy)-3-exo-acetoxymethyl-2-azabicyclo[2.1.1] hexane (18). To a solution of acetate $\mathbf{1 7}(670 \mathrm{mg}, 1.3 \mathrm{mmol})$ in benzene ( 50 $\mathrm{mL})$ were added tributyltin hydride ( $1.18 \mathrm{~g}, 4.1 \mathrm{mmol}$ ) and AIBN ( $22 \mathrm{mg}, 0.13 \mathrm{mmol}$ ). 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 $540 \mathrm{mg}(94 \%)$ of acetate 18 as a colorless oil: $R_{f}=0.53$ (1:1 ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\delta 7.40(\mathrm{~s}, 5 \mathrm{H}), 5.20$ (dd, $J=12.3 \mathrm{~Hz}$, $2 \mathrm{H}), 4.44$ (dd, $J=11.1,4.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.18(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H})$, $4.17(\mathrm{~m}, 1 \mathrm{H}), 4.11(\mathrm{br}, 1 \mathrm{H}), 3.97(\mathrm{~d}, \mathrm{~J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.86$ (br $\mathrm{d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.62(\mathrm{dd}, J=7.2,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.09(\mathrm{~s}, 3 \mathrm{H})$, $1.84(\mathrm{dd}, J=8.1,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 0.93(\mathrm{~s}, 9 \mathrm{H}), 0.10(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 170.6,156.5,136.5,128.4,128.0,127.8,82.4,66.9,64.2$, $63.4,56.8,47.4,32.8,25.7,20.8,17.9,-4.96$; HRMS m/z 442.2041, calcd for $\mathrm{C}_{22} \mathrm{H}_{33} \mathrm{~N}_{5} \mathrm{NaSi}(\mathrm{M}+\mathrm{Na}) 442.2026$.
$N$-Benzyloxycarbonyl-5-anti-tert-butyldimethylsilyloxy-3-exo-hydroxymethyl-2-azabicyclo[2.1.1]hexane (19). To a solution of acetate $18(302 \mathrm{mg}, 0.72 \mathrm{mmol})$ in methanol ( 10 mL ) were added potassium carbonate ( $357 \mathrm{mg}, 2.2 \mathrm{mmol}$ ) and sodium bicarbonate ( $544 \mathrm{mg}, 6.5 \mathrm{mmol}$ ). 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 $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$, and concentrated in vacuo to give crude product ( 240 mg ). Flash chromatography provided $207 \mathrm{mg}(76 \%)$ of alcohol $\mathbf{1 9}$ as a colorless liquid: $R_{f}$ $=0.30$ ( $1: 1$ ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\delta 7.40(\mathrm{~m}, 5 \mathrm{H}), 5.21(\mathrm{~m}$, $2 \mathrm{H}), 4.34(\mathrm{br}, 1 \mathrm{H}), 4.21$ (dd, $J=1.5,7.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.03(\mathrm{~d}, 1 \mathrm{H}$, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.99(\mathrm{br}, 1 \mathrm{H}), 3.80(\mathrm{br}, 2 \mathrm{H}), 2.84(\mathrm{dt}, J=2.7$, $8.1,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.55(\mathrm{~m}, 1 \mathrm{H}), 1.79(\mathrm{dd}, J=8.1,7.2 \mathrm{~Hz}, 1 \mathrm{H})$, 0.94 (s, 9H), 0.06 (s, 6H); ${ }^{13} \mathrm{C}$ NMR $\delta 157.7,136.3,128.5,128.2$, $127.9,82.9,67.3,65.4,64.5,61.7,47.3,34.0,25.7,18.0,-4.9$; HRMS $m / z 400.1930$, calcd for $\mathrm{C}_{20} \mathrm{H}_{31} \mathrm{NO}_{4} \mathrm{NaSi}(\mathrm{M}+\mathrm{Na})$ 400.1920 .
$N$-Benzyloxycarbonyl-5-anti-t-butyldimethylsilyloxy3 -exo-carboxy-2-azabicyclo[2.1.1]hexane (20). To a solution of alcohol $19(39 \mathrm{mg}, 0.085 \mathrm{mmol})$ in dichloromethane ( 0.5 mL ) containing TEMPO ( 0.1 mg ) was added a solution of saturated $\mathrm{NaHCO}_{3}(0.2 \mathrm{~mL})$ containing $\mathrm{KBr}(0.9 \mathrm{mg})$ and tetrabutylammonium chloride $(1.2 \mathrm{mg})$. The mixture was cooled to $0{ }^{\circ} \mathrm{C}$, and a solution of $\mathrm{NaOCl}(0.21 \mathrm{~mL})$, saturated $\mathrm{NaHCO}_{3}(\mathrm{aq})(0.1 \mathrm{~mL})$, and saturated $\mathrm{NaCl}(\mathrm{aq})(0.18 \mathrm{~mL})$ 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 $\mathrm{HCl}(10 \%$ w/v), and the resulting solution was extracted with EtOAc. The combined organic extracts were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$. The solvent was removed to give 37 mg ( $93 \%$ ) of the desired carboxylic acid 20: ${ }^{1} \mathrm{H}$ NMR $\left(75{ }^{\circ} \mathrm{C}\right) \delta 10.48$ (br, 1 H ), 7.39 (s, 5 H ), 5.25 (dd, $J=12.3 \mathrm{~Hz}, 2 \mathrm{H}$ ), 4.37 ( $\mathrm{s}, 1 \mathrm{H}$ ), 4.26 (dd, $J=7.5$,
$1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.06 (dd, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.97 (d, br, $J=8.1 \mathrm{~Hz}$, $1 \mathrm{H}), 2.94$ (d, $J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.15$ (dd, $J=7.2,8.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), $0.96(\mathrm{~s}, 9 \mathrm{H}),-0.13(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 172.9,156.9,135.8$, $128.4,128.1,127.8,82.2,67.3,64.1,59.4,48.0,34.5,25.5,17.9$, -4.8 ; HRMS $m / z$ 392.1894, calcd for $\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{NO}_{5} \mathrm{Si}(\mathrm{M}+\mathrm{H})$ 392.1893.
$N$-Benzyloxycarbonyl-5-anti-t-butyldimethylsilyloxy-3-exo-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (21). To a solution of acid $20(75 \mathrm{mg}, 0.19 \mathrm{mmol})$ in hexane ( 1.5 mL ) and 2-propanol ( 0.75 mL ) was added a 2 M solution of trimethylsilyldiazomethane in hexane ( $383 \mu \mathrm{~L}, 0.766 \mathrm{mmol}$ ). The resulting mixture was stirred under argon for 0.5 h . The solvent was removed in vacuo to give $80 \mathrm{mg}(100 \%)$ of ester 21: $R_{f}=0.35$ ( $1: 2$ ether/hexane); ${ }^{1} \mathrm{H}$ NMR $\left(75{ }^{\circ} \mathrm{C}\right.$ ) $\delta 7.38$ ( s , $5 \mathrm{H}), 5.27(\mathrm{~d}, J=12.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.16(\mathrm{~d}, J=12.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.33$ ( $\mathrm{s}, 1 \mathrm{H}$ ) , 4.26 (dd, $J=7.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.05(\mathrm{~d}, J=7.2 \mathrm{~Hz}$, 1 H ), 3.76 (s, 3 H ), 2.90 (ddd, $J=8.1,3.3,1.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.82 (dd, $J=7.5,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.04(\mathrm{dd}, J=8.1,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 0.97$ (s, $9 \mathrm{H}), 0.1$ (s, 6 H ); ${ }^{13} \mathrm{C}$ NMR $\delta 170.5,156.7,136.5,128.4,128.0$, 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 $\mathrm{C}_{21} \mathrm{H}_{32} \mathrm{NO}_{5} \mathrm{Si}(\mathrm{M}+\mathrm{H}) 406.2049$.

5-anti-tert-Butyldimethylsilyloxy-3-exo-methoxycar-bonyl-2-azabicyclo[2.1.1]hexane (22). To a solution of ester $21(810 \mathrm{mg}, 2.0 \mathrm{mmol})$ in methanol ( 40 mL ) was added $10 \%$ $\mathrm{Pd} / \mathrm{C}(200 \mathrm{mg})$. The solution was stirred at $25^{\circ} \mathrm{C}$ under a $\mathrm{H}_{2}-$ (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: ${ }^{1} \mathrm{H}$ NMR $\delta 4.13(\mathrm{~m}, 1 \mathrm{H}), 3.79$ $(\mathrm{m}, 4 \mathrm{H}), 3.44(\mathrm{~m}, 1 \mathrm{H}), 2.79(\mathrm{~m}, 1 \mathrm{H}), 2.69(\mathrm{~m}, 1 \mathrm{H}), 2.22(\mathrm{br}$, $1 \mathrm{H}), 1.45(\mathrm{~m}, 1 \mathrm{H}), 0.94(\mathrm{~s}, 9 \mathrm{H}), 0.11(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\delta 174.1$, 82.8, 62.8, 58.4, 52.3, 49.7, 33.0, (25.7 and 22.6), -4.9; HRMS $\mathrm{m} / \mathrm{z} 272.1672$, calcd for $\mathrm{C}_{13} \mathrm{H}_{26} \mathrm{NO}_{3} \mathrm{Si}(\mathrm{M}+\mathrm{H})$ 272.1682.
$\boldsymbol{N}$-(2- ${ }^{13} \mathbf{C H}_{3}$-Acetyl)-5-anti-tert-butyldimethylsilyloxy-3-exo-methoxycarbonyl-2-azabicyclo[2.1.1]hexane (23). To a solution of amine $\mathbf{2 2}(483 \mathrm{mg}, 1.6 \mathrm{mmol})$ in dry methylene chloride ( 20 mL ) at $0{ }^{\circ} \mathrm{C}$ was added DMAP $(1.66 \mathrm{~g}, 13.6 \mathrm{mmol}$, 3 equiv), and then ${ }^{13} \mathrm{CH}_{3} \mathrm{COCl}(372.7 \mathrm{mg}, 4.69 \mathrm{mmol})$ was added dropwise, and the mixture was stirred for 30 min at 0 ${ }^{\circ} \mathrm{C}$. The reaction mixture was then slowly warmed to $25{ }^{\circ} \mathrm{C}$ 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 $\mathrm{Na}_{2}-$ $\mathrm{SO}_{4}(\mathrm{~s})$ and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography to afford $484 \mathrm{~g}(93 \%)$ of amide 23: $R_{f}=0.20$ ( $1: 1$ hexane/EtOAc); ${ }^{1} \mathrm{H}$ NMR $\delta 4.57-4.24(\mathrm{~m}, 1 \mathrm{H}), 3.98(\mathrm{~m}, 2 \mathrm{H}), 3.71(\mathrm{~m}, 3 \mathrm{H}), 2.84-$ $2.75(\mathrm{~m}, 2 \mathrm{H}), 2.04$ and 1.93 (two d, $J=128.1 \mathrm{~Hz}, 3 \mathrm{H}), 2.06(\mathrm{t}$, $J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 0.86(\mathrm{~s}, 9 \mathrm{H}), 0.04(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (two conformations) $\delta 170.1$ and $169.6,169.3(\mathrm{~d}, J=51.5 \mathrm{~Hz})$ and 168.1 (d, $J=51.6 \mathrm{~Hz}$ ), 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 $\mathrm{C}_{14}{ }^{13} \mathrm{CH}_{28} \mathrm{NO}_{4} \mathrm{Si}(\mathrm{M}+\mathrm{H})$ 315.1821.

N -(2- ${ }^{13} \mathrm{CH}_{3}$-Acetyl)-5-anti-hydroxy-3-exo-methoxycar-bonyl-2-azabicyclo[2.1.1]hexane (6). To a solution of silyl ether 23 ( $486.4 \mathrm{mg}, 1.48 \mathrm{mmol}$ ) in THF ( 10 mL ) at $0{ }^{\circ} \mathrm{C}$ was added tetrabutylammonium fluoride monohydrate (TBAF$\mathrm{H}_{2} \mathrm{O}, 1.16 \mathrm{~g}, 4.44 \mathrm{mmol}, 3$ equiv). The reaction mixture was stirred at $0{ }^{\circ} \mathrm{C}$ 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 $181 \mathrm{mg}(90 \%)$ of alcohol 6 as a white solid: $R_{f}=0.60$ ( $5: 1 \mathrm{EtOAc} / \mathrm{MeOH}$ ); ${ }^{1} \mathrm{H}$ NMR ( 500 $\mathrm{MHz}) \delta(4.73,4.68)(\mathrm{br}, 1 \mathrm{H}),(4.55-4.53,4.11-4.09)(\mathrm{m}, 1 \mathrm{H})$, $(4.31,4.28)(\mathrm{bs}, 1 \mathrm{H}),(4.04,3.98)(\mathrm{m}, 1 \mathrm{H}),(3.78,3.72)(\mathrm{s}, 3 \mathrm{H})$, $2.91-2.81(\mathrm{~m}, 2 \mathrm{H}), 2.11(\mathrm{~m}, 1 \mathrm{H}),(2.06,1.94)(\mathrm{d}, J=128.3 \mathrm{~Hz}$, $3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz , two conformations) $\delta 170.0$ (d, $J=$ 50.3 Hz ), 169.9, 168.4 (d, $J=51.7 \mathrm{~Hz}$ ), 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 ${ }^{13} \mathrm{C}$ ); HRMS $m / z 201.0961$, calcd for $\mathrm{C}_{8}{ }^{13} \mathrm{CH}_{14} \mathrm{NO}_{4}$ $(\mathrm{M}+\mathrm{H}) 201.0956$.

N-Acetyl-5-anti-fluoro-3-exo-methoxycarbonyl-2azabicyclo[2.1.1]hexane (7). Bis(2-methoxyethyl)aminosulfur trifluoride ( $166 \mathrm{mg}, 0.75 \mathrm{mmol}$ ) was added dropwise via syringe to a solution of $N$-acetyl-5-anti-hydroxy-3-exo-meth-oxycarbonyl-2-azabicyclo[2.1.1] hexane $6(60 \mathrm{mg}, 0.3 \mathrm{mmol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(12 \mathrm{~mL})$ under $\operatorname{Ar}(\mathrm{g})$ at $-78{ }^{\circ} \mathrm{C}$. 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The organic extracts were combined and washed with water and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}(\mathrm{~s})$, 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); ${ }^{1} \mathrm{H}$ NMR $\delta\left[4.77\left(\mathrm{dd},{ }^{2} J_{\mathrm{H}, \mathrm{F}}=61.6 \mathrm{~Hz}, J\right.\right.$ $\left.=7.4 \mathrm{~Hz}), 4.62\left(\mathrm{dd},{ }^{2} J_{\mathrm{H}, \mathrm{F}}=61.0 \mathrm{~Hz}, J=7.4 \mathrm{~Hz}\right), 1 \mathrm{H}\right], 4.33(\mathrm{~s}$, $1 \mathrm{H}), 4.24(\mathrm{dd}, J=7.2,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.74$ and 3.70 (two s, 3 H ), $3.01(\mathrm{~m}, 1 \mathrm{H}), 2.79(\mathrm{~m}, 1 \mathrm{H}), 2.25-2.22(\mathrm{~m}, 1 \mathrm{H}), 2.11$ and 1.99 (two s, 3H); ${ }^{13} \mathrm{C}$ NMR ( 100 MHz , two conformations) $\delta 169.6$, $169.4,169.2,168.1,97.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=219.6 \mathrm{~Hz}\right), 97.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=\right.$ $218.7 \mathrm{~Hz}), 63.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=20.5 \mathrm{~Hz}\right), 60.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=20.8 \mathrm{~Hz}\right)$, $58.6,56.5,52.8,52.5,47.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=19.2 \mathrm{~Hz}\right), 46.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=\right.$ $18.7 \mathrm{~Hz}), 34.2,32.8,30.9,21.6,21.6$; HRMS $m / z 202.0885$, calcd for $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{3} \mathrm{~F}(\mathrm{M}+\mathrm{H}) 202.0879$.

Measurement of $\boldsymbol{K}_{\text {trans/cis }}$ Values of 5-7. Each compound ( $10-20 \mathrm{mg}$ ) was dissolved in $\mathrm{CDCl}_{3}$ (approximately 1 mL ) and the ${ }^{13} \mathrm{C}$ NMR (5 and 6) or ${ }^{19} \mathrm{~F}$ NMR (7) spectrum recorded. The relaxation delay for the measurement of the spectra of 5 and 6 was $10-18 \mathrm{~s}$ to allow for full relaxation of the ${ }^{13} \mathrm{C}$ 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 $\mathrm{CDCl}_{3}$. The resulting samples were dissolved in 1,4 -dioxane- $d_{8}(800 \mu \mathrm{~L})$, and the spectra were recorded again. The samples were concentrated under reduced pressure and placed under high vacuum overnight. $\mathrm{D}_{2} \mathrm{O}(800 \mu \mathrm{~L})$ was then added to each sample followed by enough $\mathrm{CD}_{3} \mathrm{OD}$ to effect full dissolution of the sample. The amount of added $\mathrm{CD}_{3} \mathrm{OD}$ 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 $\times 0.40 \times 0.40 \mathrm{~mm}^{3}$ 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 $\mathrm{Mo} \mathrm{K} \alpha(\lambda=0.71073$ Å) radiation with a diffractometer-to-crystal distance of 4.999 cm .

Initial cell constants were obtained from three series of $\omega$ scans at different starting angles. Each series consisted of 20 frames collected at intervals of $0.3^{\circ}$ in a $6^{\circ}$ range about $\omega$ with an exposure time of 10 s per frame. A total of 69 reflections
(63) NUTS-NMR Utility Transform Software, Acorn NMR Inc., 7670 Las Positas Road, Livermore, CA 94551.
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 $0.80 \AA$. A total of 12437 data were harvested by collecting one set of 1250 frames with $0.3^{\circ}$ scans in $\phi$ and four sets of 100 frames with $0.3^{\circ}$ scans in $\omega$ 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 $P 1$ and $P \overline{1} .{ }^{65}$ The $E$-statistics strongly suggested the centrosymmetric space group $P \overline{1}$ that yielded chemically reasonable and computationally stable results of refinement.

A successful solution by direct methods provided most nonhydrogen 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 $\mathbf{6}$ 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 hy-drogen-bonding interactions were observed in the lattice, and formed a series of one-dimensional chains in the $a b$ 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 $w R$ (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: ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ 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.

## JO049242Y

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(65) All software and sources of the scattering factors are contained in the SHELXTL (version 5.1) program library: Sheldrick, G., Ed. Bruker Analytical X-ray Systems, Madison, WI.

Vol. 61, 1996
Thomas R. Hoye* and Matthew K. Renner. MTPA (Mosher) Amides of Cyclic Secondary Amines: Conformational Aspects and a Useful Method for Assignment of Amine Configuration.

Page 2062. The structures for $\mathbf{1 5}$ and $\mathbf{1 6}$ should be interchanged in Figure 5. They are correctly described in Table 6.

Page 2062. " $(R)$-MTPA-Cl" should be changed to " $(S)$ -MTPA-Cl" (18 lines from the bottom of column two). This is correctly stated 28 lines from the top of the same column.

Page 2062. "IPEA" should be changed to the more conventional "DIEA" eight lines from the bottom of column two.
Page 2063. The header "( $\mathbf{6} \boldsymbol{R}$ )-2,6-Dimethyl-1,4,5,6-tetrahydropyridine $-(\boldsymbol{R})$-MTPA Amide (12) and -(S)-MTPA Amide (13)" should be changed to "( $6 R$ )- and ( $6 S$ )-2,6-Dimethyl-1,4,5,6-tetrahydropyridine-( $R$ )-MTPA Amides (12 and 13, Respectively)" in column two.

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Cara L. Jenkins, Guoliang Lin, Jingqi Duo, Deepa Rapolu, Ilia A. Guzei, Ronald T. Raines,* and Grant R. Krow*. Substituted 2-Azabicyclo[2.1.1]hexanes as Constrained Proline Analogues: Implications for Collagen Stability.

Page 8573. The Acknowledgment should begin: "We are grateful to Drs. C. W. Ross, III, and J. A. Hodges for helpful discussions."

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