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# Synthesis of Conformationally Constrained 5-Fluoro- and 5-Hydroxymethanopyrrolidines. Ring-Puckered Mimics of *Gauche*- and *Anti*-3-Fluoro- and 3-Hydroxypyrrolidines

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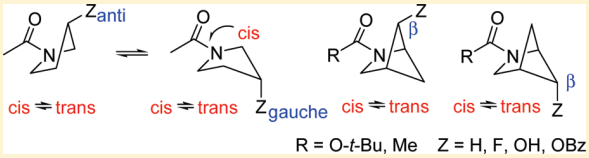
Supporting Information

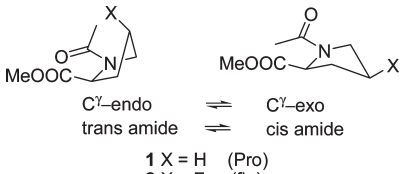
**ABSTRACT:** *N*-Acetylmethanopyrrolidine methyl ester and its four 5-*syn*/*anti*-fluoro and hydroxy derivatives have been synthesized from 2-azabicyclo[2.2.0]hex-5-ene, a 1,2-dihydropyridine photoproduct. These conformationally constrained mimics of idealized $C^{\beta}$-gauche and $C^{\beta}$-anti conformers of pyrrolidines were prepared in order to determine the inherent bridge bias and subsequent heteroatom substituent effects upon trans/cis amide preferences. The bridgehead position and also the presence of *gauche*(*syn*)/*anti*-5-fluoro or 5-hydroxy substituents have minimal influence upon the $K_{T/C}$ values of *N*-acetylamide conformers in both $CDCl_3$ (43−54% trans) and $D_2O$ (53−58% trans). *O*-Benzoylation enhances the trans amide preferences in $CDCl_3$ (65% for a *syn*-OBz, 61% for an *anti*-OBz) but has minimal effect in $D_2O$. The synthetic methods developed for *N*-BOC-methanopyrrolidines should prove useful in the synthesis of more complex derivatives containing α-ester substituents. The $K_{T/C}$ results obtained in this study establish baseline amide preferences that will enable determination of contributions of α-ester substituents to *trans*-amide preferences in methanoprolines.






## INTRODUCTION

The ability of amides to exist as cis−trans isomers has important implications for protein structure and function.[1] The particular behavior of amides derived from the secondary amine proline has engendered much interest in this regard because of the importance of proline cis−trans isomerization to biological functions[2] and structure of proteins.[3] There is an emerging interest in bioengineering applications of proline and substituted prolines.[4−6]




*N*-Acetylproline methyl ester (Pro) **1** not only is present as a mixture of cis−trans isomers but also exists in a variety of ring conformations. Two of these in which $C^{\gamma}$ experiences a large out-of-plane displacement are major,[7] and we refer to them as $C^{\gamma}$-endo ($C^{\gamma}$-pucker toward the ester) and $C^{\gamma}$-exo ($C^{\gamma}$-pucker away from the ester). Substituents at $C^{\gamma}$, as in (2*S*,4*S*)-4-fluoroproline (flp) **2** and (2*S*,4*S*)-4-hydroxyproline (hyp) **3**, affect the direction of ring pucker and also influence amide cis/trans conformational preferences.[3] The two effects appear to be correlated.[3a,4,8] In an effort to control the ring pucker variable and isolate the remaining effect of a substituent upon amide cis−trans preferences, we synthesized the 2-azabicyclo[2.1.1]hexanes **4**−**6** (Table 1),[9] analogues of Pro **1**, flp **2**, and hyp **6**. *N*-Acetylmethanoproline methyl ester (MetPro) **4** displays a Pro **1** residue with *both* idealized $C^{\gamma}$-exo and $C^{\gamma}$-endo ring puckers. The substituted 4-*anti*-fluoromethanoproline (Metflp) **5** and 4-*anti*-hydroxymethanoproline (Methyp) **6**, when viewed from the perspective of the substituent-bearing bridges, are pyrrolidines (bolded bonds) with constrained $C^{\gamma}$-exo ring puckers. The relative substituent effects on $K_{T/C}$ for these methanoprolines **4**−**6** was essentially invariant in $D_2O$, although in the less polar aprotic solvents $CDCl_3$ and 1,4-dioxane-$d_8$ Metflp **5** had a slightly larger trans preference than the others.

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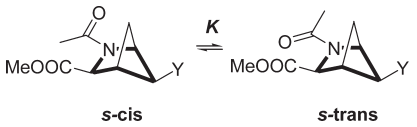
**Table 1. $K_{T/C}$ of Methanoprolines 4−6**




| compd | Y | $K_{T/C}$[a] $D_2O$ | $CDCl_3$ | dioxane-$d_8$ |
|---|---|---|---|---|
| MetPro **4** | H | 3.5 | 2.4 | 2.2 |
| Metflp **5** | F | 3.5 | 2.7 | 2.8 |
| Methyp **6** | OH | 3.6[b] | 2.4 | 2.1 |

[a] Values of $K_{T/C}$ were measured at 25 °C using $^{19}F$ NMR spectra for fluoro isomers and $^{13}C$ NMR for MetPro **4** and Methyp **6** (see ref 9). [b] Values in ref 9 were measured in $D_2O/CD_3OD \sim 4:1$.

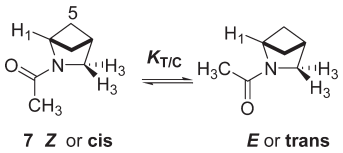
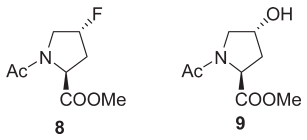



**Figure 1.** Amide equilibrium for a methanopyrrolidine **7**.

**Scheme 1. Retrosynthesis of Methanoprolines 14−17 Related to Flp 8 and Hyp 9**

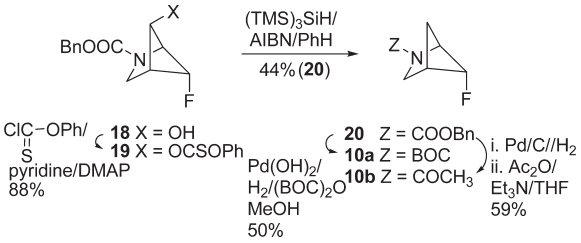


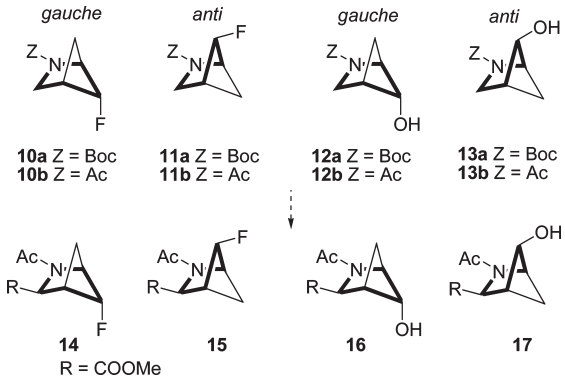

This result was taken to indicate that the γ-substituent effect is primarily related to ring pucker and a resultant enhancement of the interaction between the amide carbonyl oxygen and ester carbonyl carbon.

Our previous study[9] did not identify unresolved issues associated with using methanoprolines **4**−**6** as mimics of prolines **1**−**3**. For example, it is not known if the carbonyl group of the amides in the mimics **4**−**6** has a structurally−related preference to be adjacent to the bridgehead $H_1$ or the methylene $H_3$ position. Knowledge of the amide preference of a methanopyrrolidine (Metpyr) **7** that is missing the α-ester adjacent to nitrogen (Figure 1) is necessary in order to determine the effect of a 3-ester substituent upon amide conformations.

Additionally, the scope of the methanoproline substituent effect study was limited to the Metflp **5** and Methyp **6** stereoisomers related to flp **2** and hyp **3** by the synthetic approach available at that time. Thus, we were unable to address the generality of the finding for other methanoproline stereoisomers related to (2*S*,4*R*)-4-fluoroproline **8** (Flp) and the biologically relevant (2*S*,4*R*)-4-hydroxyproline (Hyp) **9** as to whether $K_{T/C}$ values are always independent of substituent and depend mainly on ring pucker. To answer these questions, a different synthetic approach is needed to prepare methanofluoroprolines (MetFlps) **14** and **15**, whose idealized $C^\gamma$ ring puckers contain either exo(gauche)- or endo(anti)-Flp **8** conformers, embedded in bold for emphasis in Scheme 1. The same is true for methanohydroxyprolines (MetHyps) **16** and **17**, related to Hyp **9**. A possible synthetic approach to methanoprolines could utilize as key synthons the methanopyrrolidines **10a**−**13a** or related *O*-protected derivatives.

**Scheme 2. Synthetic Route to *N*-Protected 5-*syn*-Fluoromethanopyrrolidines**




Herein, we describe 1,2-dihydropyridine-based syntheses of Metpyr **7** as well as *N*-acetyl-5-*syn*- and 5-*anti*-F(OH)-substituted methanopyrrolidines **10b**−**13b**. The configurational preferences determined for these amides reveal that only small inherent trans/cis amide biases accompany the use of methanoprolines as idealized $C^\gamma$-puckered proline mimics. In a separate paper, we shall show how *N*-Boc-methanopyrrolidines **10a**−**13a**, or related *O*-silylated derivatives, can serve as key synthons for a directed lithiation approach to the desired methanoproline derivatives **14**−**17**.[10,11]

## RESULTS AND DISCUSSION

Metpyr **7** was prepared in 70% yield from *N*-Boc-methanopyrrolidine[10] by removal of the Boc group with trifluoroacetic acid followed by acetylation with acetyl chloride.

**Synthesis of 5-Fluoromethanopyrrolidines.** *N*-Boc-5-*syn*-fluoro-Metpyr **10a** was synthesized, as shown in Scheme 2, from pyridine-derived intermediate **18** that was prepared by a second-chance rearrangement route.[12] Conversion of fluoro alcohol **18** to the thionocarbonate **19** using *O*-phenyl chlorothionoformate[13] followed by reductive deoxygenation afforded the *N*-benzyloxycarbonyl fluoride **20**. Reductive removal of the protecting group using $H_2/Pd(OH)_2$ in methanol in the presence of $(BOC)_2O$ afforded the *N*-BOC-5-*syn*-fluoro synthon **10a**. The reduction of **20** in methanol followed by addition of acetyl chloride afforded the *N*-acetyl-5-*syn*-fluoroamide **10b**.

In the 5-*anti*-fluoro series, *N*-Boc-5-*anti*-fluoro-methanopyrrolidine **11a** was synthesized from 1,2-dihydropyridine photoproduct **21** as shown in Scheme 3.[14,15] Addition of BrF to **11a** was accompanied by rearrangement to afford the 5-*anti*-bromo-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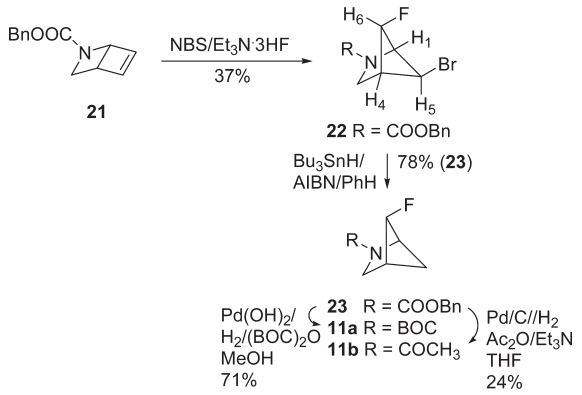
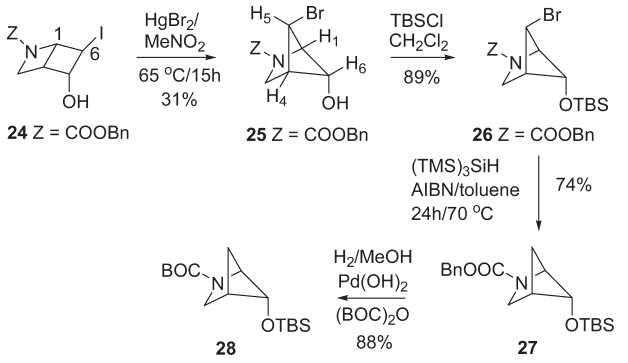
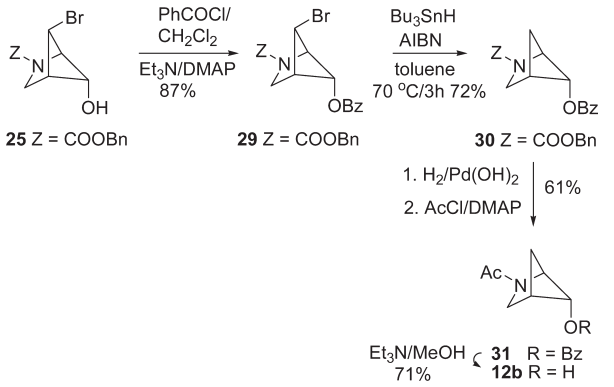
**Scheme 3. Synthetic Route to *N*-Protected 5-*anti*-Fluoromethanopyrrolidines**



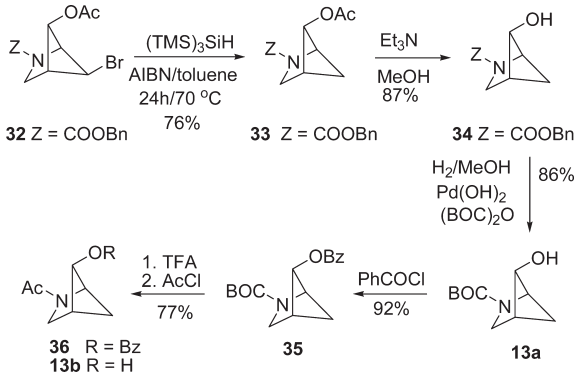

**Scheme 4. Synthetic Route to *N*-BOC-5-*syn*-*O*-TBS-methanopyrrolidine 28**




**Scheme 5. Synthetic Route to *N*-Acetyl-5-*syn*-hydroxymethanopyrrolidines**




**Scheme 6. Synthetic Route to *N*-Protected 5-*anti*-Hydroxymethanopyrrolidines**




6-*anti*-fluoro azabicycle **22**. Characteristic for the rearranged 2-azabicyclo[2.1.1]hexane structure for **22** was the $^1$H NMR W-plan coupling between the bridgehead proton $H_1$ at $\delta$ 4.61 with $H_4$ at $\delta$ 3.20 ($J_{1,4}$ = 7.2 Hz). Similarly, the 5-*anti*-6-*anti* stereochemistry for **22** was demonstrated by its W-plan coupling of proton $H_5$ at $\delta$ 4.18 with $H_6$ at $\delta$ 5.07 ($J_{5,6}$ = 7.5 Hz), as well as their vanishingly small couplings to the flanking bridgehead protons $H_1$ and $H_4$.[12,14] Bromo fluoride **22** was reductively debrominated to give 5-*anti*-fluoride **23**. Reductive removal and reprotection, as described above for fluoride **20**, afforded either the *N*-BOC-5-*anti*-fluoro synthon **11a**[16] or the *N*-acetyl fluoride **11b**.

**Synthesis of 5-Hydroxymethanopyrrolidines.** For the 5-*syn*-hydroxy series, a silylated derivative of alcohol **12a**, *N*-Boc-5-*syn*-OTBS-methanopyrrolidine **28**, was synthesized from iodohydrin **24** as shown in Scheme 4.[12,14] An inefficient, but necessary, mercuric bromide-mediated nucleophilic substitution reaction, during which nitrogen has migrated from $C_1$ to $C_6$, afforded the bromohydrin **25**. The rearranged 2-azabicyclo-[2.1.1]hexane structure of **25** was confirmed by the characteristic $^1$H NMR W-plan coupling between bridgehead proton $H_1$ at $\delta$ 4.44 with $H_4$ at $\delta$ 2.92 ($J_{1,4}$ = 6.8 Hz) and a geminal $H_3$ proton at $\delta$ 3.41 (d, $J_{3,3'}$ = 11.3 Hz) that is not further coupled to $H_4$. The singlet at $\delta$ 3.57 identifies $H_5$ as syn, since there is no coupling with $H_1$ or $H_4$. Also, the absence of W-plan coupling between $H_5$ and $H_6$ at $\delta$ 4.77 identifies $H_6$ as anti. With the crucial 5-*syn*-alcohol in place, protection of the alcohol as the TBS ether **26** followed by reductive debromination gave the ether **27**. Hydrogenolysis in the presence of $(BOC)_2O$ gave *N*-BOC-5-*syn*-OTBS synthon **28**.

*N*-Acetyl-5-*syn*-*O*-benzoate **29** and *N*-acetyl-5-*syn*-alcohol **12a** were prepared from **25** as shown in Scheme 5. Benzoylation of alcohol **25** gave a benzoate **29** that was reductively debrominated to afford benzoate **30**. Hydrogenolysis and acetylation afforded the amide ester **31**, which upon methanolysis afforded 5-*syn*-alcohol **12b**.

For the 5-*anti*-hydroxy series, *N*-BOC-5-*anti*-alcohol **13a** was prepared from bromoacetate **32**,[17] as shown in Scheme 6. Reductive debromination gave acetate **33**. Methanolysis to **34** and then hydrogenolysis in the presence of $(BOC)_2O$ gave *N*-BOC alcohol **13a**. For investigation of trans/cis amide preferences, alcohol **13a** was converted to the *N*-acyl benzoate[18] **36**, and this was converted by methanolysis to the alcohol **13b**.

**NMR Analysis of $K_{T/C}$ for Substituted Methanopyrrolidines.** A planar amide carbonyl in methanopyrrolidine **7** might be eclipsed with $H_1$ in a cis conformation or staggered between the two $H_3$ methylene protons in a trans orientation (Figure 2). Further, substituents might alter whatever inherent stereochemical preference might exist for **7**. To resolve these issues, and to establish baseline amide conformational preferences for conformationally constrained methanoprolines with heteroatom substituents, we determined $K_{T/C}$ for the 5-*syn*- and 5-*anti*-fluoro-, hydroxy-, and benzoyloxymethanopyrrolidines in Figure 2.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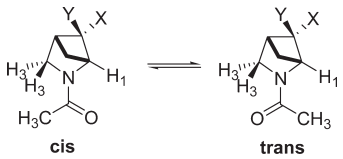
Amide trans/cis ratios shown in Table 2 were obtained by integration of nonoverlapping $^1$H or $^{19}$F NMR peaks. The percentages of trans isomers obtained by separate $^1$H NMR integrations are reliable ±1%. For an individual structure, isomer ratios can depend on the protons chosen to be integrated and compared and the percentage of trans isomer can vary from the average by ± 1.5%. $^{19}$F and $^1$H ratios ($K_{T/C}$) differ by no more than 0.1.

There is only a slight solvent dependence for methanopyrrolidine amide preferences of **7** and **10b**−**13b** (entries 1−5 Table 2). In polar protic $D_2O$, the 54% trans amide preference shown by MetPyr **7** is relatively unchanged (±1%) by either the syn or anti, fluoro or hydroxy, heteroatom substituents of **10b**−**13b**. In $CDCl_3$ solvent there is a bit more sensitivity to solvent (43−54% trans). The 5-*syn*-F **10b** and 5-*anti*-F isomers **11b** (entries 2 and 3) show essentially the same trans preferences in $CDCl_3$ within a few percent as the parent substrate **9** (entry 1), indicating that the dipolar C−F bond *does not* have a significant effect on amide preference for these methanopyrrolidine derivatives. With alcohol substitution, the 5-*syn*-OH **12b** (entry 4) in $CDCl_3$ has a clear cis amide preference, while the 5-*anti*-OH **15b** (entry 5) has little amide preference.

The $K_{T/C}$ results in Table 2 in apolar $CDCl_3$ solvent are in somewhat qualitative agreement with gas-phase relative energy calculations that generally favor small trans amide preferences. Only the 5-*syn*-OH **12b**, in agreement with experiment, is calculated to have a cis amide preference. An X-ray analysis of **12b** shows that that there is no unusual distortion of the ring or internal hydrogen bonding interaction in the solid phase; the amide nitrogen is nearly flat in both the cis and trans amide forms (see the Supporting Information).

Benzoylation of the alcohol groups results in little change in preference for trans amides in $D_2O$ for both the 5-*syn*-OBz **31** (entry 6) and 5-*anti*-OBz **36** (entry 7) isomers. However, upon benzoylation the trans preference is enhanced in the less polar aprotic solvent $CDCl_3$. Especially noteworthy is the switch from a cis amide preference for 5-*syn*-OH **12b** (entry 4) to a clear trans amide preference for the 5-*syn*-OBz **31**. In this constrained ring system a change in preferred ring pucker upon *O*-acylation can be ruled out as the cause of the enhancement effect.[5b,f]




**7** X = Y = H
**10b** X = F, Y = H
**11b** X = H, Y = F
**12b** X = OH, Y = H
**13b** X = H, Y = OH
**31** X= OBz, Y = H
**36** X = H, Y = OBz

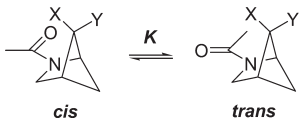
**Figure 2.** Amide conformations for methanopyrrolidines.

## CONCLUSION

*N*-Acetylmethanopyrrolidine and its 5-*syn*/5-*anti*-F(OH) derivatives have been synthesized from pyridine via a 1,2-dihydropyridine photoproduct. The trans/cis amide preferences ($K_{T/C}$) for the parent **7** were compared with those of the stereoisomeric pairs of 5-*syn*(*gauche*)/*anti*-fluoro **10b**/**11b**, hydroxy **12b**/**13b**, and O-Bz isomers **31**/**36** in both $D_2O$ and $CDCl_3$ solvent. The substituent effect differences ($K_{T/C}$ functionalized isomer − $K_{T/C}$ for **7**) were extremely small ($\Delta K_{T/C}$ = −0.3 to +0.1) for all cases studied, with the single minor exception of the OBz isomers in $CDCl_3$ ($\Delta K_{T/C}$ = 0.5−0.7). Further, in all of the pairs of stereoisomers studied the trans/cis amide preference was minimally influenced by the stereochemical orientation of the substituent ($K_{T/C}$ *syn*-isomer − $K_{T/C}$ *anti*-isomer = $\Delta K_{T/C}$ = −0.2 to +0.3).

The small trans amide preferences for methanopyrrolidine **7** in $CDCl_3$ or $D_2O$ show that it is the interaction of the α-ester group and the amide of MetPro **4** that plays a major role in determining trans/cis ratios. Further, the small trans amide preferences for the substituted fluoro- and hydroxy-methanopyrrolidines is confirmation of previous work with the stereoisomers Metflp **5** and Methyp **6** that indicated the remote anti heteroatom has little additional effect upon trans amide preferences.[9] The findings with rigid methanopyrrolidines are consistent with the proposal for prolines that substituent influences upon the pucker energetics of ring conformations, and the resulting impact upon the amide carbonyl and proline side-chain

**Table 2. $K_{trans/cis}$ for *N*-Acetylmethanopyrrolidine Derivatives**




| | | | | $K_{trans/cis}$ | | dipole moment ($\mu$) | | |
|---|---|---|---|---|---|---|---|---|
| entry | substrate | X | Y | $D_2O$[a] | $CDCl_3$[a] | trans | cis | $K_{trans/cis}$ calcd[b] |
| 1 | parent **7** | H | H | 1.2 (54:46) | 1.1 (52:48) | 4.34 | 4.30 | 1.2 |
| 2 | *syn*-F **10b** | F | H | 1.1 (53:47) | 0.9 (48:52)[c] | 5.05 | 4.61 | 1.2 |
| 3 | *anti*-F **11b** | H | F | 1.2 (55:45)[d] | 1.2 (54:46)[e] | 2.40 | 4.36 | 2.0 |
| 4 | *syn*−OH **12b** | OH | H | 1.2 (54:46) | 0.8 (43:57) | 5.51 | 2.90 | 0.06 |
| 5 | *anti*−OH **13b** | H | OH | 1.2 (54:46) | 1.0 (51:49) | 3.91 | 2.93 | 1.2 |
| 6 | *syn*-OBz **31** | OBz | H | 1.4 (58:42) | 1.8 (64:36) | | | |
| 7 | *anti*-OBz **36** | H | OBz | 1.3 (56:44) | 1.6 (61:39) | | | |

[a] Ratios were obtained from $^1$H NMR spectra. [b] MP2/6-31G(d,p)//RHF/6-31G(d) level. [c] $K_{trans/cis}$ 0.9 (46:54) by $^{19}$F NMR. [d] $K_{trans/cis}$ = 1.3 (56:44) by $^{19}$F NMR. [e] $K_{trans/cis}$ = 1.3 (57:43) by $^{19}$F NMR.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carbonyl interaction, play the major role in determining trans/cis amide equilibria.[3a,4,8]

For the four possible *N*-acetyl-5-fluoro- and -5-hydroxymethanopyrrolidines, we now have obtained $K_{T/C}$ values that establish baseline amide preferences in the absence of α-ester functionality. With this evidence, it will be possible to determine the contribution to trans amide preferences by α-ester substituents when other methanoprolines are synthesized. The *N*-BOC-methanopyrrolidines **10b**, **11b**, **28**, and **13b** should prove useful in this endeavor to prepare fluoro- and hydroxymethanoprolines **14**−**17**, constrained mimics of Flp and Hyp in idealized $C^{\gamma}$-exo and $C^{\gamma}$-endo conformations through which insights may be gained concerning amide preferences of prolines.

## EXPERIMENTAL SECTION

**General Methods.** 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. The standard for $^1$H NMR was $CHCl_3$ δ 7.26, for $^{13}$C NMR $CDCl_3$ δ 77.0, and for $^{19}$F NMR $CFCl_3$ δ 0.00; undecoupled $^{19}$F spectra were referenced indirectly against a D-lock and required minor shift correction. Some NMR resonances appear as pairs because of carbamate conformations and italics denote minor rotamer peaks. Assignments of NMR resonances, where necessary, were facilitated by NOE, $^1$H−$^1$H-COSY, and HETCOR experiments. The trans/cis amide assignments were based upon observations of an NOE effect on either the characteristic bridgehead $H_1$ hydrogen or alternatively at the $H_3$ methylene hydrogen signals upon irradiation of the major or minor acetyl methyl singlets; italics denote minor rotamer peaks. Amide trans/cis ratios were obtained by integration of nonoverlapping $^1$H or $^{19}$F NMR peaks. Throughout this paper, we have chosen to use syn/anti nomenclature to identify the stereochemistry of substituents on the non-nitrogen containing bridges. This is to avoid the use of exo/endo nomenclature, confusing to those accustomed to naming related all-carbon-bridged bicyclic structures. The bridge with the nitrogen heteroatom is always the main bridge of highest priority. Thus, all substituents anti to nitrogen are endo.

***N*-Acetyl-2-azabicyclo[2.1.1]hexane (7).** To a solution of *N*-BOC-2-azabicyclo[2.1.1]hexane[10] (42 mg, 0.229 mmol) in $CH_2Cl_2$ (5.0 mL) was added TFA (261 mg, 2.29 mmol) at rt under argon. After 6 h, the crude amine obtained upon workup was dissolved in $CH_2Cl_2$ (7.5 mL) to which DMAP (84 mg, 0.69 mmol) was added. The solution was cooled to 0 °C, and AcCl (54 mg, 0.69 mmol) was added to the reaction mixture. After being stirred for 3 h at room temperature, the reaction mixture was washed with water (2 × 5 mL) and then the combined aqueous layer was backwashed with $CH_2Cl_2$ (4 mL). The organic layer was dried over $Na_2SO_4$ and filtered, and the solvent was removed in vacuo. Preparative TLC (1:9 MeOH/EtOAc) afforded 20 mg (70%) of **39** as a colorless oil at $R_f$ = 0.39 (1:9 MeOH/ethyl acetate): $^1$H NMR (400 MHz, $D_2O$) (italics denote minor rotamer peaks) δ *4.64 (dt, J = 6.9, 1.8 Hz, 1H, $H_1$)*, 4.46 (dt, J = 6.9, 1.8 Hz, 1H, $H_1$), *3.54 (s, 2H, $H_3$)*, 3.36 (s, 2H, $H_3$), 2.93 (m, 1H, $H_4$), 2.11 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.07 (m, 2H, $H_{5anti}$), 2.04 (m, 2H, $H_{5anti}$), 1.44 (m, 2H, $H_{5syn}$), *1.37 (m, 2H, $H_{5syn}$)*; NOE ($D_2O$) the major $H_1$ signal at δ 4.46 on irradiation sees the acetyl signal at δ 2.11 and the minor $H_1$ signal at δ 4.64 sees no acetyl signal. The minor $H_3$ signal at δ 3.54 on irradiation enhances the acetyl signal at δ 2.07 and the major $H_3$ signal at δ 3.36 on irradiation enhances no acetyl signal. $K_{trans/cis}$ = 52/48 ($CDCl_3$) based upon $H_1$ integrations; the major upfield $H_1$ is trans. $K_{trans/cis}$ = 54/46 ($D_2O$) based upon $H_1$ integrations.

***N*-Acetyl-2-azabicyclo[2.1.1]hexane (9):** $^1$H NMR (400 MHz, $CDCl_3$) (italics denote minor rotamer peaks) δ *4.78 (dt, J = 6.9, 1.8 Hz, 1H, $H_1$)*, 4.25 (dt, J = 6.9, 1.8 Hz, 1H, $H_1$), 3.39 (s, 2H, $H_3$), *3.38 (s, 2H, $H_3$)*, 2.89 (m, 1H, $H_4$), *2.06 (s, 3H, $COCH_3$)*, 2.01 (s, 3H, $COCH_3$), 1.98 (m, 2H, $H_{5anti}$), *1.93 (m, 2H, $H_{5anti}$)*, 1.43 (m, 2H, $H_{5syn}$), *1.33 (m, 2H, $H_{5syn}$)*; $^{13}$C NMR (400 MHz, $CDCl_3$) δ *168.6* and 168.0, 62.5 and *59.1*, *50.1* and 48.3, 41.1 and *40.2*, *38.7* and 37.9, 21.6 and *21.5*; HRMS *m/z* found 125.0834, calcd for $C_7H_{11}NO$ (M) 125.0836.

***N*-(Benzyloxycarbonyl)-5-*syn*-fluoro-6-*anti*-(phenoxycarbonothioyloxy)-2-azabicyclo[2.1.1]hexane (19).** To 5-*syn*-fluoro-6-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane[12] **18** (170 mg, 0.68 mmol) in $CH_2Cl_2$ (15 mL) were added pyridine (219 μL, 2.7 mmol) and a catalytic amount of DMAP. To the resulting solution was added *O*-phenyl chlorothionoformate (111 μL, 1.02 mmol) carefully under argon at rt.[13] After 2 h, the reaction mixture was quenched with satd $NH_4Cl$ (aq) (5 mL) and diluted with $CH_2Cl_2$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL), and all of the $CH_2Cl_2$ layers were combined and dried using $Na_2SO_4$. Removal of the solvent in vacuo followed by silica gel flash chromatography gave 230 mg (88%) of **19** at $R_f$ = 0.60 (1:1 hexane/diethyl ether): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37−7.01, 5.12 (dd, J = 56.4, 6.8 Hz, 1H, $H_5$), 5.11 (s, 2H), 4.86 (d, J = 20.8 Hz, 1H, $H_6$), 4.78 (dd, J = 21.1, 6.8 Hz, 1H, $H_1$), 3.61 (two d, J = 9.0 Hz, 1H, $H_3$), 3.45 (d, J = 9.0 Hz, 1H, $H_3$), 3.27 (br, 1H, $H_4$); $^{13}$C NMR (100 MHz) δ 194.1 (C═S), 156.9, 156.3 (C═O), 153.5, 136.69, 130.1, 128.9, 128.6, 128.5, 128.3, 127.3, 122.0, 85.9, 83.5, 78.9, 78.7, 67.7, 64.6, 64.4, 47.3, 47.1, 44.3, 44.3; HRMS *m/z* 388.1019, calcd for $C_{20}H_{19}FNO_4S$ (M + H), *m/z* 388.1014, calcd for 410.0844 $C_{20}H_{18}FNaNO_4S$ (M + Na) 410.0833.

***N*-(Benzyloxycarbonyl)-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (20).** Compound **19** (129 mg, 0.33 mmol) was dissolved in dry toluene (8.3 mL) and degassed for 1 h with Ar. Separately, AIBN (8.2 mg, 0.05 mmol) and $(TMS)_3SiH$ (100 mg, 0.5 mmol) were dissolved in dry toluene (13.7 mL) and degassed for 1 h with Ar. The flask was then lowered into a 90 °C oil bath, and the AIBN/$(TMS)_3SiH$ solution was added slowly via canula. The reaction was monitored by TLC for disappearance of starting material at $R_f$ = 0.6 (1:1 hexane/ether). After 22 h, a second portion of AIBN/TTMSS dissolved in dry toluene degassed for 1 h with Ar was added to the flask. After 3 h, TLC showed no remaining starting material. Solvent was removed *in vacuo* resulting in a pale yellow oil. The crude material after preparative TLC at $R_f$ = 0.3 (1:1 hexane/ether) yielded 53 mg (71%) of **20**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 5H), 5.02 (s, 2H), 4.36 (br, 1H, $H_1$), 4.27 (d, J = 58.8 Hz, 1H, $H_5$), 3.37, 3.35 (two d, J = 8.0, 7.6 Hz, 1H, $H_3$), 3.19, 3.17 (two d, J = 7.6, 7.6 Hz, 1H, $H_3$), 2.77 (br, 1H, $H_4$), 1.12 (dd, J = 37.2, 5.9 Hz, 1H, $H_6$), 1.14 (s, $H_6$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.3, 137.2, 129.0, 128.8, 128.6, 128.4, 128.3, 128.2, 85.0, 84.9, 82.7, 82.7, 67.2, 62.6, 62.5, 62.2, 62.1, 45.3, 42.4, 42.2, 42.0, 29.9, 26.7, 26.6, 26.4; HRMS *m/z* 258.0898, calcd for $C_{13}H_{14}FNO_2Na$ (M + Na) 258.0901.

***N*-(*tert*-Butoxycarbonyl)-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (10a). General Procedure for *N*-COOBn to *N*-BOC Conversion.** To a solution of **20** (190 mg, 0.81 mmol) in MeOH (10 mL) was added $Pd(OH)_2$ (56 mg, 10 mol %) followed by $(BOC)_2O$ (231 mg, 1.1 mmol). The resulting solution was stirred at rt for 2 h under hydrogen. Filtration of the catalyst followed by silica gel flash chromatography gave 80 mg (50%) of the fluoride **10a** at $R_f$= 0.45 (1:1 hexane/diethyl ether): $^1$H NMR (500 MHz, $CDCl_3$) δ 4.46 (br, 1H, $H_1$), 4.41 (d, J = 58.8 Hz, 1H, $H_5$), 3.41 (dd, J = 23.5, 7.5 Hz, 1H, $H_{3n}$), 3.24 (br, 1H, $H_{3x}$), 2.88 (br, 1H, $H_4$), 1.46 (s, 9H), 1.29 (m, 2H, $2H_6$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.2, 85.2, 82.8, 79.9, 62.8, 62.6, 61.7, 61.6, 45.5, 44.9, 42.3, 42.1, 29.0, 28.8, 28.6, 28.4, 26.8, 26.6, 26.4; HRMS *m/z* 224.1072, calcd for $C_{10}H_{16}FNO_2$ Na (M + Na) 224.1063.

***N*-Acetyl-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (10b). General Procedure for Acetylation.** Carbamate **20** (56 mg, 0.24 mmol) and 10% Pd/C (13 mg, 0.012 mmol) were placed under Ar and suspended in dry THF (5.6 mL). The vessel was repeatedly evacuated and placed

under $H_2$ six times. $H_2$ was bubbled through the suspension for 15 min followed by capping with a $H_2$−filled balloon (2 L). Acetic anyhdride (0.025 mL, 0.26 mmol) and TEA (0.033 mL, 0.024 mmol) freshly distilled from $CaH_2$ were added via syringe. After being sitrred for 3 h, the Pd/C was filtered through a Celite plug, and the solvent was removed in vacuo. The crude oil purified by silica gel flash chromatography at $R_f$ = 0.14 (1% MeOH in DCM) gave 19.5 mg (59%) of amide **10b**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.88 (dm, $J$ = 6.9 Hz, 1H, major $H_1$), 4.49 (ddd, $J$ = 58.4, 2.8, 2.3 Hz, 1H, minor $H_5$), 4.46 (ddd, $J$ = 58.3, 2.9, 2.0 Hz, 1H, major $H_5$), 4.33 (dddd, $J$ = 6.4, 1.8, 1.74, 1.74 Hz, 1H, minor $H_1$), 3.54 (d, $J$ = 9.7 Hz, 1H, minor $H_3$), 3.50 (d, $J$ = 8.0 Hz, 1H, major $H_3$), 3.37 (overlapping d, 2H, $H_3$), 2.98 (m, 1H, $H_4$), 2.07 (two s, 6H, $COCH_3$). 1.45−1.23 (m, 2H, $H_6$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 169.7, 83.8 (d, $J$ = 241.1 Hz), 83.2 (d, $J$ = 240.8 Hz), 63.86 (d, $J$ = 17.4 Hz), 60.67 (d, $J$ = 17.0 Hz), 45.91 (d, $J$ = 3.3 Hz), 44.29 (d, $J$ = 2.8 Hz), 42.42 (d, $J$ = 18.4 Hz), 41.75 (d, $J$ = 18.6 Hz), 27.43 (d, $J$ = 17.6 Hz), 26.26 (d, $J$ = 18.0 Hz), 22.10, 21.70; $^1$H NMR (500 MHz, $D_2O$) $\delta$ 4.72 (1H, minor $H_1$), 4.67 (ddd, $J$ = 58.9, 3.1, 2.0, 1H, $H_5$), 4.65 (major coupling from HSQC $J$ = 59 Hz, 1H, $H_5$), 4.56 (dq, $J$ = 6.3, 1.82 Hz, 1H, major $H_1$), 3.56 (dt, $J$ = 8.7, 1.1 Hz, 1H, minor $H_3$), 3.53 (dd, $J$ = 8.7, 0.7 Hz, 1H, minor $H_3$), 3.41 (d br, $J$ = 9.7 Hz, 1H, major $H_3$), 3.34 (d, $J$ = 9.7 Hz, 1H, major $H_3$), 3.08 − 3.04 (m, 1H, $H_4$), 3.04 − 3.01 (m, 1H, $H_4$), 2.1 (s, 3H, major $COCH_3$), 2.09 (s, 3H, minor $COCH_3$), 1.47 (dm, $J$ = 9.3 Hz, 1H, $H_{6eq}$), 1.42 (dm, $J$ = 9.3 Hz, 1H, $H_{6eq}$), 1.42 (dd, $J$ = 9.3 Hz, 1H, $H_{6ax}$), 1.34 (dd, $J$ = 9.3 Hz, 1H, $H_{6ax}$); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −177.2 and −177.6 (ratio 1:1.16); $^{19}$F NMR (376 MHz, $D_2O$) $\delta$ −176.9 (br, overlapping conformers); $^1$H NMR NOE ($CDCl_3$) pulse $\delta$ 4.33 ppm (minor $H_1$) hits $\delta$ 2.09, 4.57, 1.38. Pulse $\delta$ 4.88 (major $H_1$) hits $\delta$ 4.46 ($H_5$ major), 1.33; NOE ($D_2O$) pulse $\delta$ 1.97 hits $\delta$ 3.55 and 4.57. and pulse $\delta$ 2.04 hits $\delta$ 4.57 only; $K_{trans/cis}$ = 48/52 ($CDCl_3$) and 53/47 ($D_2O$) based upon $H_1$ integrations or $K_{trans/cis}$ = 46/54 ($CDCl_3$) based upon $^{19}$F integrations; HRMS $m/z$ 144.0823, calcd for $C_7H_{10}FNO$ (M + H) 144.0819.

***N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (22).** To a solution of alkene[14] **21** (398 mg, 1.85 mmol) in $CH_3NO_2$ (15 mL) was added NBS (461 mg, 2.6 mmol) at 0 °C followed by $Et_3N\cdot 3HF$ (753 $\mu$L, 4.62 mmol) dropwise over a period of 10 min.[15] The reaction mixture was brought to rt and stirred for 16 h, after which it was diluted with $CH_2Cl_2$ (40 mL), washed with $NaHCO_3$ (15 mL) and brine (15 mL), and dried over $Na_2SO_4$ to give 876 mg of a crude oil. Silica gel flash column chromatography gave 150 mg of the unreacted olefin **21** (37%) and 212 mg (38%) of **22** at $R_f$ = 0.45 (1:1 hexane/ether); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (m, 5H), 5.22 (s, 2H), 5.07 (dd, $J$ = 59.4, 7.5 Hz, $H_6$), 4.61 (d, $J$ = 7.2 Hz, 1H, $H_1$), 4.18 (dd, $J$ = 7.5, 3.0 Hz, $H_5$), 3.68 (dd, $J$ = 12.0, 1.8 Hz, $H_3$), 3.58 (d, $J$ = 12.0 Hz, $H_3$), 3.20 (br, 1H, $H_4$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.5, 136.8, 128.8, 128.3, 128.2, 100.2 ($J$ = 224 Hz), 65.1, 64.8, 50.3, 49.6, 48.5; HRMS $m/z$ found 336.0014, calcd for $C_{13}H_{13}NO_2FNaBr^{79}$ (M + Na) 336.0011.

***N*-(Benzyloxycarbonyl)-5-*anti*-fluoro-2-azabicyclo[2.1.1]-hexane (23). General Procedure for Reductive Debromination.** To a solution of **22** (222 mg, 0.71 mmol) in benzene (25 mL) were added *n*-$Bu_3SnH$ (263 $\mu$L, 0.98 mmol) and AIBN (21 mg). The resulting solution was refluxed for 16 h. Solvent was removed in vacuo, and the crude was chromatographed to give 130 mg (78%) of **23** at $R_f$ = 0.39 (1:1 hexane/ether): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34 (m, 5H), 5.15 (s, 2H), 4.80 (dd, $J$ = 62.1, 7.2 Hz, $H_5$), 4.41 (brd, $J$ = 6.0 Hz, 1H, $H_1$), 3.45 (s, 2H, $2H_3$), 2.86 (brm, 2H, $H_4$ and $H_{6x}$), 1.74 (ddd, $J$ = 7.8, 7.7, 2.6 Hz, $H_{6n}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.3, 136.3, 128.8, 128.3, 128.2, 98.4 (d, $J_{CF}$ = 209 Hz), 66.9 and 66.8, 62.0, 47.3, 43.4 and 43.1, 36.7; HRMS $m/z$ found 258.0907, calcd for $C_{13}H_{14}NO_2FNa$ (M + Na) 258.0907.

***N*-(*tert*-Butoxycarbonyl)-5-*anti*-fluoro-2-azabicyclo[2.1.1]-hexane (11a)[16].** According to the general procedure for **10a**, to carbamate **23** (42 mg, 0.18 mmol) in MeOH (10 mL) was added $Pd(OH)_2$ (15 mg) followed by $(BOC)_2O$ (47 mg, 2.15 mmol). After the mixture was stirred at rt for 2 h under hydrogen there was obtained 25 mg (71%) of **11a**: $R_f$ = 0.39 (1:1 hexane/ether); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.80 (dd, $J$ = 62, 7.9 Hz, $H_5$), 4.30 (br, $H_1$), 3.36 (q, $J$ = 9.7 Hz, $2H_3$), 2.83 (m, 2H, $H_4$ and $H_{6x}$), 1.70 (ddd, $J$ = 7.9, 7.3, 2.7 Hz, $H_{6n}$), 1.45 (s, 9H, BOC); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.4, 98.6 (d, $J_{CF}$ = 210 Hz, $C_5$), 79.9, 62.2, 47.2, 43.4 and 43.2, 36.7, 28.4; HRMS $m/z$ found 224.1052, calcd for $C_{10}H_{16}FNO_2$ [M + Na] 224.1063.

***N*-(Acetyl)-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (11b).** According to the general procedure, carbamate **23** (96 mg, 0.41 mmol) and 10% Pd/C (22 mg, 0.02 mmol) were placed under Ar and suspended in dry THF (5.6 mL). Hydrogenation, followed by addition of acetic anyhdride (0.042 mL, 0.45 mmol) and TEA (0.056 mL, 0.41 mmol), and workup afforded 14 mg (24%) of amide **11b**: $R_f$ = 0.16 (1% MeOH in DCM); $^1$H NMR (500 MHz, $CDCl_3$) 4.82 (dd, $J$ = 62.4, 7.2 Hz, 1H, $H_5$ major), 4.78 (dd, $J$ = 62.2, 7.3 Hz, 1H, $H_5$ minor) 4.77(1H, $H_1$, minor) 4.26 (d, $J$ = 6.7 Hz, 1H, $H_1$ major), 3.49 (m, 2H, $H_3$), 2.91 (m, 2H, $H_4$, $H_6$) 1.78 (td, $J$ = 7.8, 2.4 Hz, 1H, $H_{6x}$) 1.71 (td, $J$ = 7.8, 2.4 Hz, 1H, $H_{6y}$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.17, 168.72, 98.51 (d, $J$ = 214.2 Hz), 98.43 (d, $J$ = 213.3 Hz), 64.13 (d, $J$ = 21.8 Hz), 60.76 (d, $J$ = 21.9 Hz), 48.62 (d, $J$ = 5.1 Hz), 46.79 (d, $J$ = 4.9 Hz), 43.79 (d, $J$ = 18.4 Hz), 43.15 (d, $J$ = 17.8 Hz), 37.70, 36.70; HRMS $m/z$ 144.0823, calcd for $C_7H_{10}FNO$ (M + H) 144.0819. $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −206.1 and −206.8 (ratio =1.3:1.0); $^{19}$F NMR (376 MHz, $D_2O$) $\delta$ −205.2 and −206.8 (ratio =1.0:0.79); $^1$H NMR (500 MHz, $D_2O$) $\delta$ 4.89 (dd, $J$ = 62.1, 7.3 Hz, 1H, $H_5$ major), 4.87 (dd, $J$ = 62.2, 7.3 Hz, 1H $H_1$ minor), 4.62 (ddd, $J$ = 7.4, 1.9, 1.1 Hz, 1H, $H_1$ minor), 4.48 (ddd, $J$ = 7.1, 1.9, 1.0 Hz, 1H, $H_1$ major), 3.62 (m, 1H, $H_{3,3'}$, minor), 3.45 (dd, $J$ = 10.0, 3.5 Hz, 1H, $H_3$, major), 3.41 (d, $J$ = 10.2 Hz, 1H, $H_{3'}$, major), 2.97 (m, 1H, $H_4$), 2.89 (m, 1H, $H_{6anti}$), 2.08 (s, 3H), 2.03 (s, 3H), 1.80 (ddd, $J$ = 8.5, 7.3, 2.7 Hz, 1H, $H_{6syn}$, major), 1.74 (ddd, $J$ = 8.5, 7.3, 2.7 Hz, 1H, $H_{6syn}$, minor); NOE ($D_2O$) pulse $\delta$ 2.03 hits $\delta$ 3.62 ($H_3$ minor); pulse $\delta$ 2.08 (pulls 2.03 into pulse) hits $\delta$ 3.62, 4.47 ($H_1$ major). NOE ($CDCl_3$): pulse $\delta$ 2.02 hits $\delta$ 3.48; pulse $\delta$ 2.06 (pulls 2.02 into pulse) hits $\delta$ 4.25 (major $H_1$), $\delta$ 3.48; $K_{trans/cis}$ = 54/46 ($CDCl_3$) and $K_{trans/cis}$ = 55/45 ($D_2O$) based upon $H_1$ integrations or $K_{trans/cis}$ = 57/43 ($CDCl_3$) and 56:44 ($D_2O$) based upon $^{19}$F integrations.

***N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*syn*-hydroxy-2-azabicyclo[2.1.1]hexane (25).** To a stirred solution of iodohydrin **24** (1000 mg, 2.784 mmol) in $MeNO_2$ (100 mL) was added mercuric bromide (2509 mg, 6.961 mmol, 2.5 equiv).[12,14] The solution was heated at 65 °C for 15 h. The mixture was diluted with brine (50 mL) and extracted with ether (4 × 150 mL). The ether extracts were combined, washed with brine (2 × 100 mL), dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (gradient: 25−40% ether in hexanes) to afford 269 mg (31%) of rearranged bromohydrin **25** as a colorless oil: $R_f$= 0.44 (2:3 ethyl acetate/hexanes) (unreacted $HgBr_2$ is UV active and NMR blind, and separation was difficult); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.29 (m, 5H), 5.15 (br, 2H), 4.77 (br, 1H, $H_6$), 4.44 (dd, $J$ = 6.8, 1.7 Hz, 1H, $H_1$), *4.41 (dd, J = 6.8, 1.7 Hz, 1H, $H_1$)*, 3.57 (s, 1H, $H_5$), *3.58−3.51 (m, 3H, $2H_3$ and $H_5$)*, 3.41 (d, $J$ = 11.3 Hz, 1H, $H_3$), 3.36 (d, $J$ = 11.9 Hz, 1H, $H_{3'}$), 3.13 (br, 1H, OH), 2.92 (m, 1H, $H_4$), *2.87 (m, 1H, $H_4$)*; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.8, 136.3, 128.5, 128.1, 127.9, *71.4* and 70.2, *67.4* and 67.3, *49.9* and 49.7, 45.5, 43.1, 14.7; HRMS $m/z$ found 334.0045, calcd for $C_{13}H_{14}BrNO_3Na$ (M + Na) 334.0049.

***N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*syn*-(*tert*-butyldimethylsilyloxy)-2-azabicyclo[2.1.1]hexane (26).** To a solution of bromohydrin **25** (257 mg, 0.823 mmol) in dry $CH_2Cl_2$ (10 mL) under argon was added imidazole (280 mg, 4.116 mmol, 5.0 equiv) followed by TBSCl (149 mg, 0.988 mmol, 1.2 equiv) in small portions. The resulting solution was stirred at rt for 6 h. The solvent was removed in vacuo and then chromatographed (10% ethyl acetate in hexanes) on silica gel to gave 312 mg (89%) of bromo-*O*-silyl ether **26** as a colorless oil: $R_f$ = 0.44 (1:5 ethyl acetate/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.27


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(m, 5H), 5.21−5.00 (m, 2H), *4.67 (br s, 1H, $H_6$)*, 4.65 (br s, 1H, $H_6$), *4.44 (dd, J = 6.9, 1.4 Hz, 1H, $H_1$)*, 4.38 (dd, *J* = 6.9, 1.4 Hz, 1H, $H_1$), 3.58 (s, 1H, $H_5$), 3.57−3.28 (m, 2H, $2H_3$), 2.91−2.79 (m, 1H, $H_4$), 0.91−0.78 (m, 9H), 0.09−0.01 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 156.7 and *156.1*, 136.6 and 136.4, 128.4, 128.1, 128.0, *127.9*, *127.8*, 70.4 and *70.3*, 68.0 and *67.6*, 67.0 and *66.8*, *50.4* and 50.3, *45.7* and 45.6, *43.2* and 43.0, 25.5, 17.8, −5.1 and -5.2; HRMS *m*/*z* found 448.0923, calcd for $C_{19}H_{28}BrNO_3SiNa$ (M + Na) 448.0914.

***N*-(Benzyloxycarbonyl)-5-*syn*-(*tert*-butyldimethylsilyloxy)-2-azabicyclo[2.1.1]hexane (27).** According to the general reductive procedure for **23**, to a solution of bromo-*O*-silyl ether **26** (304 mg, 0.713 mmol) in dry toluene (20 mL) were added $(TMS)_3SiH$ (440 *μ*L, 1.426 mmol, 2.0 equiv) and AIBN (30 mg). After 2 h at 70 °C, workup and flash chromatography (1:9 ethyl acetate/hexanes) gave 183 mg (74%) of *O*-silyl ether **27** as a colorless oil: $R_f$ = 0.41 (1:6 ethyl acetate/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.41−7.22 (m, 5H), 5.21−5.01 (m, 2H,), *4.29 (dt, J = 6.7, 1.5 Hz, 1H, $H_1$)*, 4.23 (dt, *J* = 6.7, 1.5 Hz, 1H, $H_1$), 3.69 (m, 1H, $H_5$), *3.47 (d, J = 8.4 Hz, 1H, $H_3$)*, 3.45 (d, *J* = 8.4 Hz, 1H, $H_3$), 3.22 (d, *J* = 8.4 Hz, 1H, $H_{3'}$), 3.19 (d, *J* = 8.3 Hz, 1H, $H_{3'}$), 2.64 (m, 1H, $H_4$), 1.28 (m, 1H, $H_{6anti}$), *1.26 (m, 1H, $H_{6anti}$)*, 1.20 (d, *J* = 8.1 Hz, 1H, $H_{6syn}$), *1.17 (d, J = 8.1 Hz, 1H, $H_{6syn}$)*, 0.84 (s, 9H,), 0.04 (s, 6H), *0.03 (s, 6H)*; $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 157.4 and *156.9*, *137.2* and 137.0, 128.3, *127.9*, 127.7, 69.6 and *69.5*, 66.5 and *66.4*, 63.7 and *63.4*, 45.3 and *45.2*, *42.8* and 42.7, 28.6 and *28.2*, 25.6, 17.8, *-5.1* and −5.2; HRMS *m*/*z* found 348.1994, calcd for $C_{19}H_{30}NO_3Si$ (M + H) 348.1989.

***N*-(*tert*-Butoxycarbonyl)-5-*syn*-(*tert*-butyldimethylsilyloxy)-2-azabicyclo[2.1.1]hexane (28).** To a solution of *O*-silyl ether **27** (231 mg, 0.665 mmol) in MeOH (10 mL) was added $Pd(OH)_2$ (50 mg) followed by $(BOC)_2O$ (174 mg, 0.798 mmol, 1.2 equiv). After 3 h under hydrogen at rt, workup and silica gel chromatography gave 184 mg (88%) of carbamate **28** as a colorless oil: $R_f$ = 0.52 (1:6 ethyl acetate/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) *δ 4.21 (dt, J = 6.8, 1.6 Hz, 1H, $H_1$)*, 4.11 (dt, *J* = 6.8, 1.6 Hz, 1H, $H_1$), 3.65 (m, 1H, $H_5$), *3.36 (d, J = 8.3 Hz, 1H, $H_3$)*, 3.31 (d, *J* = 8.3 Hz, 1H, $H_3$), *3.13 (d, J = 8.3 Hz, 1H, $H_{3'}$)*, 3.09 (d, *J* = 8.3 Hz, 1H, $H_{3'}$), 2.60 (m, 1H, $H_4$), *1.45 (s, 9H, Boc)*, 1.44 (s, 9H, Boc), *1.23 (m, 1H, $H_{6anti}$)*, 1.21 (m, 1H, $H_{6anti}$), 1.56 (d, *J* = 8.9 Hz, 1H, $H_{6syn}$), *1.13 (d, J = 8.9 Hz, 1H, $H_{6syn}$)*, 0.86 (s, 9H, TBS), 0.04 (s, 6H, TBS); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 156.7 and *156.4*, 78.8, 69.6, 63.8 and *62.7*, 45.2 and *44.6*, 42.8, 28.7, 28.5, 25.7, 17.9, −5.0; HRMS *m*/*z* found 314.2154, calcd for $C_{16}H_{32}NO_3Si$ (M + H) 314.2146.

***N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*syn*-benzoyloxy-2-azabicyclo[2.1.1]hexane (29).** Bromohydrin **25** (51 mg, 0.163 mmol) was dissolved in dry $CH_2Cl_2$ (2.5 mL). The solution was cooled to 0 °C and treated sequentially with triethylamine (115 *μ*L, 0.817 mmol), DMAP (22 mg, 0.180 mmol), and benzoyl chloride (40 *μ*L, 0.327 mmol).[18] The reaction mixture was stirred for 30 min at 0 °C, allowed to come to room temperature, and then stirred for 3 h. The reaction mixture was quenched with water (2 × 1 mL) and extracted with $CH_2Cl_2$ (2 × 0.5 mL). The combined organic layers were dried and evaporated to dryness. The residue was purified by chromatography on silica gel (prep TLC: 1:4 ethyl acetate/hexanes) to afford 59 mg (87%) bromobenzoate ester **29** as a light orange oil at $R_f$ = 0.33 (4:1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.10 − 7.17 (m, 10H), 5.70 (br s, 1H, $H_6$ and its rotamer), 5.09 (m, 2H), *4.80 (d, J = 6.6 Hz, 1H, $H_1$)*, 4.74 (d, *J* = 6.6 Hz, 1H, $H_1$), 3.78 (s, 1H, $H_5$), 3.69 − 3.47 (m, 3H, $2H_3$ and $H_5$ rotamer), 3.28 (dd, *J* = 6.6, 2.7 Hz, 1H, $H_4$), *3.23 (dd, J = 6.6, 2.7 Hz, 1H, $H_4$)*; $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 165.0, 156.7, 136.0, 133.5, 129.6, 128.9, 128.5, 128.4, 128.1, 127.8, *72.0* and 70.9, 67.3 and *67.1*, 66.9 and *66.3*, *49.5* and 49.2, 46.0, *43.5* and 43.2; HRMS *m*/*z* found 416.0510, calcd for $C_{20}H_{19}BrNO_4$ (M + H) 416.0492.

***N*-(Benzyloxycarbonyl)-5-*syn*-benzoyloxy-2-azabicyclo[2.1.1]-hexane (30).** According to the general procedure, to a solution of bromobenzoate ester **29** (223 mg, 0.536 mmol) in dry toluene (15 mL) were added $Bu_3SnH$ (285 *μ*L, 1.072 mmol) and AIBN (9 mg). After 3 h at 70 °C, workup and flash chromatography (1:5 ethyl acetate/hexanes) gave 130 mg (72%) of benzoate ester **30** as a light orange oil: $R_f$ = 0.34 (1:3 ethyl acetate/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.96−7.20 (m, 10H), 5.08 (d, *J* = 12.4 Hz, 1H), 5.02 (d, *J* = 12.3 Hz, 1H), 4.8 (m, 1H, $H_5$ and its conformer), *4.67 (brd, J = 6.6 Hz, 1H, $H_1$)*, 4.61 (brd, *J* = 6.6 Hz, 1H, $H_1$), 3.59 (d, *J* = 9.1 Hz, 1H, $H_3$), *3.50 (d, J = 9.1 Hz, 1H, $H_3$)*, 3.40 (d, *J* = 9.1 Hz, 1H, $H_{3'}$), *3.37 (d, J = 9.1 Hz, 1H, $H_{3'}$)*, 3.07 (m, 1H, $H_4$), 1.64 (m, 1H, $H_{6anti}$ and its conformer), 1.47 (m, 1H, $H_{6syn}$ and its conformer); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 165.4 and *165.3*, 157.5 and *156.8*, 136.8 and 136.6, 133.3, 129.6, 128.5, 128.3, 127.8, 127.7, 69.4, 66.8 and *66.7*, 62.6 and *62.0*, 45.9 and *45.6*, *42.0* and 41.6, 30.1 and *29.8*; HRMS *m*/*z* found 338.1386, calcd for $C_{20}H_{20}NO_4$ (M + H) 338.1387.

***N*-Acetyl-5-*syn*-benzoyloxy-2-azabicyclo[2.1.1]hexane (31).** According to the general procedure, to a solution of benzoate ester **30** (102 mg, 0.302 mmol) in MeOH (2 mL) was added $Pd(OH)_2$ (30 mg). After 3 h under hydrogen at RT workup gave a crude amine that was dissolved in dry $CH_2Cl_2$ (10 mL) and cooled to 0 °C. DMAP (110 mg, 0.907 mmol, 3 equiv) and AcCl (65 *μ*L, 0.907 mmol, 3 equiv) was added to the reaction mixture maintained for 30 min at 0 °C and then brought to RT. After 3 h at RT workup and chromatography (1:4 hexanes/ethyl acetate) afforded 45 mg (61%) of **31** as a light orange oil at $R_f$ = 0.24 (ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.93 (m, 2H), 7.54 (m, 1H), 7.40 (m, 2H), *4.98 (dt, J = 6.8, 1.8 Hz, 1H, $H_1$)*, *4.75 (dd, J = 3.0, 1.9 Hz, 1H, $H_5$)*, 4.72 (dd, *J* = 3.0, 1.9 Hz, 1H, $H_5$), 4.50 (dt, *J* = 6.4, 1.8 Hz, 1H, $H_1$), 3.60 (brd, *J* = 9.7 Hz, 1H, $H_3$), 3.40 (m, 1H, $H_3$ conformer and 1H, $H_{3'}$ and its conformer), *3.15 (m, 1H, $H_4$)*, 3.08 (m, 1H, $H_4$), *2.05 (s, 3H, Ac)*, 2.00 (s, 3H, Ac), 1.69 (m, 1H, $H_{6anti}$), *1.63 (m, 1H, $H_{6anti}$)*, 1.51 (d, *J* = 8.6 Hz, 1H, $H_{6syn}$), *1.39 (d, J = 8.7 Hz, 1H, $H_{6syn}$)*; $^{13}$C NMR (100 MHz, $CDCl_3$) *δ 169.9* and 169.5, 165.6 and *165.3*, 133.4 and *133.3*, 129.6 and *129.5*, *129.3* and 129.0, 128.5 and *128.4*, 69.8 and 69.1, 64.0 and *60.3*, *46.1* and 44.7, *42.2* and 41.0, 30.9 and *29.6*, 21.6 and *21.4*; HRMS *m*/*z* found 246.1125, calcd for $C_{14}H_{16}NO_3$ (M + H) 246.1125; $^1$H NMR (400 MHz, $D_2O$) *δ* 7.93 (m, 2H, Bz), 7.68 (m, 1H, Bz), 7.51 (m, 2H, Bz), *4.86 (dt, J = 6.8, 1.7 Hz, 1H, $H_1$)*, 4.78 (m, 1H, $H_5$ and its conformer, some part of signal is under $D_2O$ peak), 4.71 (dt, *J* = 6.4, 1.7 Hz, 1H, $H_1$), 3.62 − 3.36 (m, 2H, $2H_3$ and their conformers), 3.17 (m, 1H, $H_4$), *2.05 (s, 3H, Ac)*, 2.03 (s, 3H, Ac), 1.81 (m, 1H, $H_{6anti}$), *1.76 (m, 1H, $H_{6anti}$)*, 1.58 (d, *J* = 9.1 Hz, 1H, $H_{6syn}$), *1.49 (d, J = 9.0 Hz, 1H, $H_{6syn}$)*; NOE (500 MHz, $CDCl_3$) the major acetyl signal at *δ* 2.00 on irradiation enhances major $H_1$ at *δ* 4.50. The minor acetyl signal at *δ* 2.05 on irradiation enhances minor $H_3$ at *δ* 3.40; NOE (500 MHz, $D_2O$) the major acetyl signal at *δ* 2.03 on irradiation enhances the major $H_1$ at *δ* 4.71. The minor acetyl signal at *δ* 2.05 on irradiation enhances the minor $H_3$ at *δ* 3.60. $K_{trans/cis}$ = 64/36 ($CDCl_3$); $K_{trans/cis}$ = 58/42 ($D_2O$) based on $H_{6syn}$ peaks.

***N*-Acetyl-5-*syn*-hydroxy-2-azabicyclo[2.1.1]hexane (12b). General Procedure for Benzoate Removal.** $Et_3N$ (770 *μ*L, 5.504 mmol) was added to the benzoate **31** (27 mg, 0.110 mmol) in methanol (1 mL) and stirred at room temperature for 1 day under argon. After the solvent was removed in vacuo, the crude was chromatographed (prep TLC: 9:1 ethyl acetate/MeOH) to afford 11 mg (71%) of alcohol **12b** as an off-white solid: $R_f$ = 0.29 (9:1 ethyl acetate/MeOH); mp 52−54 °C (ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) *δ* 4.60 (dt, *J* = 6.8, 1.7 Hz, 1H, $H_1$), 4.55 (d, *J* = 4.2 Hz, 1H, $H_5$), *4.27 (bd, J = 6.9 Hz, 1H, $H_5$)*, *4.16 (dt, J = 6.6, 1.8 Hz, 1H, $H_1$)*, 3.84 (m, 1H, OH), 3.50 (brd, *J* = 7.9 Hz, 1H, $H_3$), *3.46 (brd, J = 9.8 Hz, 1H, $H_3$)*, 3.27 (m, 1H, $H_{3'}$ and its conformer), 2.78 (m, 1H, $H_4$ and its conformer), 2.05 (s, 3H, Ac), *2.04 (s, 3H, Ac)*, *1.39 (m, 1H, $H_{6anti}$)*, 1.34 (m, 1H, $H_{6anti}$), *1.23 (d, J = 8.6 Hz, 1H, $H_{6syn}$)*, 1.14 (d, *J* = 8.6 Hz, 1H, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 170.5 and *169.8*, *70.1* and 68.9, *65.1* and 62.0, 46.1 and *44.1*, 42.1 and *42.0*, *29.6* and 28.6, *21.9* and 21.4; HRMS *m*/*z* found 164.0682, calcd for $C_7H_{11}NO_2$-Na (M + Na) 164.0682. $^1$H NMR (400 MHz, $D_2O$) *δ 4.55 (dt, J = 6.7, 1.8 Hz, 1H, $H_1$)*, 4.37 (dt, *J* = 6.5, 1.8 Hz, 1H, $H_1$), 3.95 (bdd, *J* = 3.1, 1.8

Hz, 1H, $H_5$), *3.93 (dd, J = 3.1, 1.8 Hz, 1H, $H_5$)*, *3.48 (s, 2H, $H_3$)*, 3.32 (two d, J = 9.8, 9.7 Hz, 2H, $H_3$), 2.84 (m, 1H, $H_4$ and its conformer), *2.09 (s, 3H, Ac)*, 2.08 (s, 3H, Ac), 1.51 (m, 1H, $H_{6anti}$), *1.45 (m, 1H, $H_{6anti}$)*, 1.29 (d, J = 8.8 Hz, 1H, $H_{6syn}$), *1.21 (d, J = 8.8 Hz, 1H, $H_{6syni}$)*; NOE (500 MHz, $CDCl_3$, some $C_6D_6$ added to resolve peaks) the minor $H_1$ signal at $\delta$ 4.16 on irradiation enhances the minor $COCH_3$ at $\delta$ 2.04 and vice versa; NOE (500 MHz, $D_2O$) the major $H_1$ resonance at $\delta$ 4.37 on irradiation enhances the major $COCH_3$ at $\delta$ 2.08. The minor $H_3$ resonance at $\delta$ 3.48 on irradiation enhances the minor $COCH_3$ at $\delta$ 2.09. $K_{T/C}$ = 43/57 ($CDCl_3$) and $K_{T/C}$ = 54/46 ($D_2O$) based on $H_{6syn}$ peaks.

***N*-(Benzyloxycarbonyl)-5-*anti*-acetoxy-2-azabicyclo[2.1.1]-hexane (33).** According to the general procedure, AIBN (600 mg) and $(TMS)_3SiH$ (10.45 mL, 33.8 mmol) were added to bromoacetate[17] **32** (6.00 g, 16.9 mmol) in dry toluene (300 mL). The resulting solution was stirred vigorously at 70 °C for 3 h under an argon-filled balloon. Workup and chromatography (10% and then 25% ether in hexanes) afforded 3.52 g (76%) of acetate **33** as a light yellow oil at $R_f$ = 0.44 (1:1 ether/hexanes): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30−7.18 (m, 5H, Ph), 5.07 (s, 2H, $OCH_2$), 4.48 (d, J = 7.3 Hz, 1H, $H_5$), 4.34 (br dd, J = 7.1, 1.2 Hz, 1H, $H_1$), 3.43 (d, J = 9.0 Hz, 1H, $H_3$), 3.37 (d, J = 9.0 Hz, 1H, $H_{3'}$), 2.78 (dd, J = 7.1, 2.8 Hz, 1H, $H_4$), 2.60 (br d, J = 8.1 Hz, 1H, $H_{6anti}$), 2.00 (s, 3H, $COCH_3$), 1.52 (dd, J = 8.1, 7.3 Hz, 1H, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 155.5 (br), 136.5, 128.2, 127.8, 127.6, 81.8, 65.6, 61.8 (br), 47.9, 42.4, 36.7, *24.9* and 20.6; HRMS *m/z* found 298.1060, calcd for $C_{15}H_{17}NO_4Na$ (M + Na) 298.1055.

***N*-(Benzyloxycarbonyl)-5-*anti*-hydroxy-2-azabicyclo[2.1.1]-hexane (34).** According to the general procedure, $Et_3N$ (15 mL, 0.109 mol) was added to acetate **33** (3.00 g, 0.011 mol) in methanol (270 mL) and the mixture stirred at rt for 12 h. Workup and chromatography (1:1 ethyl acetate/hexanes) afforded 2.20 g (87%) of alcohol **34** as a light yellow oil at $R_f$ 0.50 (2:1 ethyl acetate/hexanes): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38−7.25 (m, 5H), 5.12 (s, 2H), 4.42 (br, 1H, OH), 4.18 (dd, J = 7.2, 1.2 Hz, 1H, $H_1$), 4.03 (d, J = 7.1 Hz, 1H, $H_5$), 3.37 (s, 2H, $H_3$), 2.89 (br, 1H, $H_{6anti}$), 2.63 (dd, J = 7.2, 3.1 Hz, 1H, $H_4$), 1.60 (dd, J = 7.8, 7.1 Hz, 1H, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.6, 136.6, 128.4, 127.9, 127.7, 80.9, 66.7, *63.6* and 63.2, 48.2 (br), 43.8, 36.7 (br); HRMS *m/z* found 256.0946, calcd for $C_{13}H_{15}NO_3Na$ (M + Na) 256.0950.

***N*-(*tert*-Butoxycarbonyl)-5-*anti*-hydroxy-2-azabicyclo-[2.1.1]hexane (13a).** According to the general procedure, $(Boc)_2O$ (954 mg, 4.37 mmol) and $Pd(OH)_2$ (150 mg) were added to alcohol **34** (1.00 g, 4.28 mmol) in methanol (40 mL) and stirred at rt for 2 h under a $H_2$-filled balloon. Workup and chromatography (1:2 ethyl acetate/hexanes) afforded 733 mg (86%) of alcohol **13a** as an off-white solid: $R_f$ = 0.32 (2:3 ethyl acetate/hexanes); mp 113−114 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.07 (br d, J = 7.3 Hz, 1H, $H_1$), 4.03 (br d, J = 6.8 Hz, 1H, $H_5$), 3.66 (br, 1H, OH), 3.29 (s, 2H, $H_3$), 2.86 (br, 1H, $H_{6anti}$), 2.61 (br d, J = 6.8 Hz, 1H, $H_4$), 1.57 (dd, J = 7.3, 7.3 Hz, 1H, $H_{6syn}$), 1.43 (s, 9H, Boc); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$155.7, 81.0, 79.6, *63.8* and 62.9 (br), *48.6* and 48.0 (br), 43.9, 36.8, 28.4; HRMS *m/z* found 222.1104, calcd for $C_{10}H_{17}NO_3Na$ (M + Na) 222.1104.

***N*-(*tert*-Butoxycarbonyl)-5-*anti*-benzoyloxy-2-azabicyclo-[2.1.1]hexane (35).** Alcohol **34** (85 mg, 0.427 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL) under argon. The reaction mixture was cooled to 0 °C and sequentially treated with triethylamine (300 $\mu$L, 2.133 mmol), DMAP (57 mg, 0.469 mmol), and benzoyl chloride (125 $\mu$L, 1.067 mmol). The mixture was stirred for 30 min at 0 °C, allowed to come to room temperature, and then stirred for 3 h. The solution was washed with water (3 × 2 mL), and the combined organic layers were dried and evaporated to dryness. The residue was purified by chromatography on silica gel (10% ethyl acetate in hexanes) to afford 119 mg (92%) of benzoate **35** as a light orange oil: $R_f$ = 0.54 (4:1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09−8.03 (m, 2H), 7.62−7.56 (m, 1H), 7.50−7.43 (m, 2H), 4.81 (d, J = 7.3 Hz, 1H, $H_5$), 4.45 (br, 1H, $H_1$), 3.53 (br d, J = 9.0 Hz, 1H, $H_3$), 3.45 (br d, J = 9.0 Hz, 1H, $H_{3'}$), 2.99 (dd, J = 7.2, 2.8 Hz, 1H, $H_4$), 2.79 (d, J = 8.1 Hz, 1H, $H_{6anti}$), 1.67 (dd, J = 8.1, 7.3 Hz, 1H, $H_{6syn}$), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.3, 155.6, 133.3, 129.8, 129.6 and 128.5, 82.6, 79.8, 62.2, 48.2, 43.0, 37.1, 28.5; HRMS *m/z* found 326.1367, calcd for $C_{17}H_{21}NO_4Na$ (M + Na) 326.1363.

***N*-Acetyl-5-*anti*-benzoyloxy-2-azabicyclo[2.1.1]hexane (36).** To a solution of carbamate **35** (108 mg, 0.356 mmol) in dry $CH_2Cl_2$ (10 mL) was added TFA (275 $\mu$L, 3.559 mmol) at rt. The solution was stirred for 6 h at room temperature under argon, and then solvent was removed in vacuo to afford the 173 mg of crude amine as an orange oil. To the crude amine in dry $CH_2Cl_2$ (15 mL) was added DMAP (130 mg, 1.068 mmol) under argon, and the solution was cooled to 0 °C. AcCl (75 $\mu$L, 1.068 mmol) was added to the reaction mixture that was maintained for 30 min at 0 °C and then brought to rt. After being stirred for 4 h at rt, the reaction mixture was washed with water (2 × 5 mL) and then the combined aqueous layer was backwashed with $CH_2Cl_2$ (4 mL). The organic layer was dried over $Na_2SO_4$ and filtered, and the solvent was removed in vacuo. The crude (122 mg) was chromatographed (prep tlc, 1:9 hexanes/ethyl acetate) to afford 67 mg (77%) of amide **36** as a light orange oil: $R_f$ = 0.22 (1:9 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06−8.01 (m, 2H), 7.61−7.55 (m, 1H), 7.48−7.42 (m, 2H), *4.89 (dd, J = 7.4, 1.8 Hz, 1H, $H_1$)*, *4.77 (d, J = 7.3 Hz, 1H, $H_5$)*, 4.76 (d, J = 7.3 Hz, 1H, $H_5$), 4.41 (dd, J = 7.0, 1.8 Hz, 1H, $H_1$), 3.65−3.51 (m, 2H, $2H_3$), 3.06 (m, 1H, $H_4$), 2.84 (m, 1H, $H_{6anti}$), 2.10 (s, 3H), *2.05 (s, 3H)*, 1.72 (dd, J = 8.3, 7.3 Hz, 1H, $H_{6syn}$), *1.65 (dd, J = 8.3, 7.3 Hz, 1H, $H_{6syn}$)*; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ *168.7* and 168.5, 166.2 and *166.1*, 133.4 and 133.3, 129.6 (2C), 128.5 and *128.4*, 82.4 and *82.0*, 63.8 and *60.4*, *49.0* and 47.1, *43.1* and 42.0, 37.6 and *36.7*, 21.6 and *20.9*; HRMS *m/z* found 246.1125, calcd for $C_{14}H_{16}NO_3$ (M + H) 246.1125.

***N*-Acetyl-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (13b).** $Et_3N$ (450 $\mu$L, 3.180 mmol) was added to the benzoate **36** (52.0 mg, 0.212 mmol) in methanol (5 mL) and stirred at room temperature for 17 h under argon. After the solvent was removed in vacuo, the crude was chromatographed (9:1 ethyl acetate/MeOH) to afford 23.6 mg (79%) of alcohol **13b** as a colorless oil: $R_f$ = 0.26 (9:1 ethyl acetate/MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.69 (br, 1H, OH), *4.48 (dd, J = 7.3, 1.7 Hz, 1H, $H_1$)*, *4.05 (d, J = 7.0 Hz, 1H, $H_5$)*, 4.04 (dd, J = 7.0, 1.9 Hz, 1H, $H_1$), 3.98 (d, J = 7.0 Hz, 1H, $H_5$), *3.40 (s, 2H, $H_3$)*, 3.37 (s, 2H, $H_3$), 2.94 (br dd, J = 8.1, 8.1 Hz, 1H, $H_{6anti}$), *2.71 (dd, J = 7.1, 3.2 Hz, 1H, $H_4$)*, 2.67 (dd, J = 7.0, 3.3 Hz, 1H, $H_4$), 2.01 (s, 3H, $COCH_3$), *1.98 (s, 3H, $COCH_3$)*, 1.62 (dd, J = 8.0, 7.0 Hz, 1H, $H_{6syn}$), 1.55 (dd, J = 8.0, 7.0 Hz, 1H, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.9 and 168.3, 80.9 and 80.5, 65.5 and 62.3, 49.4 and 47.6, 43.8 and 43.4, 37.3 and 36.3, 21.4 and 20.8); HRMS *m/z* found 164.0692, calcd for $C_{17}H_{11}NO_2Na$ (M + Na) 164.0687. $^1$H NMR (400 MHz, $D_2O$) *$\delta$ 4.46 (dd, J = 7.3, 1.8 Hz, 1H, $H_1$)*, 4.29 (dd, J = 7.1, 1.9 Hz, 1H, $H_1$), 4.08 (d, J = 7.1 Hz, 1H, $H_5$), *4.05 (d, J = 7.1 Hz, 1H, $H_5$)*, *3.61 (s, 2H, $2H_3$)*, 3.42 (s, 2H, $2H_3$), 2.88 (m, 1H, $H_4$), 2.78 (m, 1H, $H_{6anti}$), 2.09 (s, 3H, $COCH_3$), *2.06 (s, 3H, $COCH_3$)*, 1.74 (dd, J = 7.5, 7.1 Hz, 1H, $H_{6syn}$), *1.68 (dd, J = 7.5, 7.1 Hz, 1H, $H_{6syn}$)*; NOE ($CDCl_3$) the major acetyl signal at $\delta$ 2.01 on irradiation sees the major $H_1$ at $\delta$ 4.04. The minor acetyl signal at $\delta$ 1.98 on irradiation sees the minor $H_3$ at $\delta$ 3.40. NOE ($D_2O$): the major acetyl signal at $\delta$ 2.09 on irradiation enhances the major $H_1$ at $\delta$ 4.29. The minor acetyl signal at $\delta$ 2.06 on irradiation enhances the minor $H_3$ at $\delta$ 3.61. $K_{T/C}$ = 50.5/49.5 ($CDCl_3$) based on $H_{6syn}$ and 54/46 ($D_2O$) based on $H_1$.

***N*-Acetyl-5-*anti*-benzoyloxy-2-azabicyclo[2.1.1]hexane (36):** $^1$H NMR (400 MHz, $D_2O$) $\delta$ 8.14−8.09 (m, 2H), 7.77−7.71 (m, 1H), 7.62−7.56 (m, 2H), 4.80 (m, 2H, $H_5$ and $H_1$ rotamer are under $D_2O$ peak), 4.66 (dd, J = 7.0, 1.7 Hz, 1H, $H_1$), *3.80 (d, J = 9.1 Hz, 1H, $H_3$)*, *3.75 (d, J = 9.1 Hz, 1H, $H_{3'}$)*, 3.61 (d, J = 9.9 Hz, 1H, $H_3$), 3.56 (d, J = 9.9 Hz, 1H, $H_{3'}$), 3.16 (m, 1H, $H_4$), 2.96 (m, 2H, $H_{6anti}$ both conformers), 2.17 (s, 3H), *2.13 (s, 3H)*, 1.81 (dd, J = 8.0, 8.0 Hz, 1H, $H_{6syn}$), *1.75 (dd, J =*

*8.0, 8.0 Hz, 1H, $H_{6syn}$*); NOE ($CDCl_3$) the major acetyl signal at $\delta$ 2.10 on irradiation sees the major $H_1$ at $\delta$ 4.41 and vice versa. The minor $H_1$ signal at $\delta$ 4.89 on irradiation sees no proton. NOE ($D_2O$): the major acetyl signal at $\delta$ 2.17 on irradiation enhances the major $H_1$ at $\delta$ 4.66. The minor acetyl signal at $\delta$ 2.13 on irradiation enhances the $H_3$ signal $\delta$ 3.80 and the $H_3$ signal $\delta$ 3.75. $K_{T/C}$ = 61/39 ($CDCl_3$) based on $H_1$ and 56/44 ($D_2O$) based on $H_3$.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Coordinates of optimized geometries, selected angles, and energy calculations for **9** and **10b**−**13b**; data from the X-ray diffraction analysis of *syn*-alcohol **12b**, copies of $^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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