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Synthesis of 5-Fluoro- and 5-Hydroxymethanoprolines Via Lithiation of *N*-BOC-Methanopyrrolidines. Constrained Cγ-Exo and Cγ-Endo Flp and Hyp Conformer Mimics

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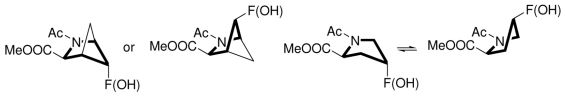
Abstract



Proline derivatives with a Cγ-exo pucker typically display a high amide bond trans:cis ($K_{T/C}$) ratio. This pucker enhances n→π* overlap of the amide oxygen and ester carbonyl carbon, which favors a trans amide bond. If there were no difference in n→π* interaction between the ring puckers, then the correlation between ring pucker and $K_{T/C}$ might be broken. To explore this possibility, proline conformations were constrained using a methylene bridge. We synthesized discrete gauche and anti 5-fluoro and 5-hydroxy *N*-acetyl-methanoproline methyl esters from 3-syn and 3-anti fluoro and hydroxyl methanopyrrolidines, using directed α-metallation to introduce the α-ester group. NBO calculations reveal minimal n→π* orbital interactions, so contributions from other forces might be of greater importance in determining $K_{T/C}$ for the methanoprolines. Consistent with this hypothesis, greater trans amide preferences were found in $CDCl_3$ for anti isomers en-MetFlp and en-MetHyp (72-78% trans) than for the syn stereoisomers ex-MetFlp and ex-MetHyp (54-67% trans). These, and other, $K_{T/C}$ results that we report here indicate how substituents on proline analogues can affect amide preferences by pathways other than ring puckering and n→π* overlap and suggest that caution should be exercised in assigning enhanced pyrrolidine Cγ-exo ring puckering based solely on enhanced trans amide preference.

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Supporting Information Available. Gaussian-03 energies for structures in Tables 2, 3, and 5. Data base for Table 4, calculated $K_{T/C}$ of methanoprolines, X-ray parameters for **25** and ^{1}H, ^{13}C, and ^{19}F NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Introduction

Proline (Pro) is distinct among the twenty common amino acids because the C^{α}-alkyl side chain is covalently linked to the nitrogen atom in the amino acid backbone. In a peptide context, the cyclic nature of Pro results in formation of tertiary amide bonds rather than the secondary amide bonds observed for the other nineteen amino acids. The presence of tertiary amide bonds to Pro residues has important effects on protein structure and folding.[1] Specifically, Pro amides have a high population of the cis peptide bond, whereas amino acids that form secondary amides exist nearly exclusively in the trans peptide bond conformation.[2]

The five-membered pyrrolidine ring in Pro exists primarily in two favored ring puckers. C^{γ} experiences a large out-of-plane displacement in these puckers,[3] and thus we refer to the two major conformations as C^{γ}-endo and C^{γ}-exo (see Table 1). The predominant ring pucker for a particular Pro derivative can be controlled by hydrogen bonding,[4] or by functionalization of C^{γ} with either spatially demanding functional groups or electronegative substituents that result in a conformation-controlling gauche effect.[5] In addition to ring puckering, there is a concurrent trans/cis equilibrium of amide conformations. Previous work suggests that Pro ring pucker and amide trans/cis ratios ($K_{T/C}$) for Pro derivatives are strongly correlated (Table 1).[5,6]

Pro derivatives whose C^{γ}-exo ring puckers are highly populated (Flp 1) have a higher $K_{T/C}$, whereas Pro derivatives whose C^{γ}-endo ring puckers are highly populated (Pro **3** and flp **4**) have a lower K (Table 1).[5,6] T/C A rationalization of this observation is that the higher $K_{T/C}$ of C^{γ}-exo puckered Pro derivatives is due to a greater stabilizing $n\rightarrow\pi^{*}$ orbital interaction between O_0 of a trans prolyl peptide bond with $C_1{=}O_1$. This interaction is favored by the ϕ and ψ angles enforced by a C^{γ}-exo ring pucker for Flp **1**, rather than those enforced by a C^{γ}-endo ring pucker in flp **4**.[5b,7,8b] These relationships are shown in Figure 1A. An exception to the relationship between favored C^{γ}-exo ring pucker and higher $K_{T/C}$ preferences has been noted for hyp 5 ($K_{T/C}$ = 4.7-5.0) in $CDCl_3$ solvent.[4] A transannular hydrogen bond between the 4-hydroxyl group and the ester carbonyl oxygen distorts the main chain ϕ and ψ torsion angles of the C^{γ}-endo ring pucker toward those typical of C^{γ}-exo ring puckers. The same hydrogen bond also enhances an $n\rightarrow\pi^{*}$ orbital interaction that stabilizes the trans amide conformation.

Of course, trans amide preferences can be influenced as well by other often interrelated forces, such as steric, dipolar, and solvent effects.[4,5g,5i] These features of γ-substituted Pro derivatives, as depicted in Figure 1A, are useful for many protein engineering applications, including modulation of the structure and stability of collagen, elastin, and many other peptides and proteins.[5,8]

An alternative scenario depicted in Figure 1B is a conformationally constrained system in which the gauche and anti conformations are not in equilibrium, but are isomeric structures. In such a system, the contribution of $n\rightarrow\pi^{*}$ orbital interactions to amide preferences $K_{T/C}$ may be equal for the two isomers or perhaps be of an unimportant magnitude. Such structures would provide experimental insight into other substituent-related forces that influence amide trans preferences.

The 2-azabicyclo[2.1.1]hexane ring system, a methanoproline (MetPro), was previously selected as a constrained proline model that fulfills the requirements of Figure 1B.[10] Because of the methylene bridge, the syn(gauche) or anti orientations of substituents in methanoprolines are fixed and can not interconvert. As depicted in Figure 2, substituted

methanoproline derivatives can be created that display either the idealized C^{γ}-exo or the C^{γ}-endo ring pucker of a 4-substituted proline derivative. For example, replacement of a hydrogen atom by a fluorine at the appropriate $C^{\gamma syn}$ or $C^{\gamma anti}$ position of MetPro generates the constrained mimics ex-MetFlp **6** and en-MetFlp **7** that correspond to idealized embedded conformations for ex-Flp **1** (exo pucker) and en-Flp **1** (endo pucker), shown by the bold outlines. Similarly, ex-MetHyp **8** and en-MetHyp **9** are constrained versions of ex-Hyp **2** (exo pucker) and en-Hyp **2** (endo pucker), respectively. Previously, we used this Pro model system to demonstrate that by constraining the pucker of the pyrrolidine ring in MetPro **10** and the γ-substituted derivatives, ex-Metflp **11** and ex-Methyp **12**, the substituent effect on $K_{T/C}$ was essentially abolished.[10]

To assess the $n\rightarrow\pi^*$ orbital contribution to $K_{T/C}$ for the methanoprolines, we performed geometry optimizations and frequency calculations on the favored trans distal (td) and trans proximal (tp) conformations for each of the MetPro derivatives **6**-**12**, and the optimized geometries were subjected to NBO analysis.[11] Our calculations revealed no significant $n\rightarrow\pi^*$ stabilization for any of the isomers studied (shown in Table 2). Moreover, the differences in $n\rightarrow\pi^*$ stabilization within pairs of MetFlp isomers **6**/**7** and MetHyp isomers **8**/**9** is minimal (≤0.3 kcal/mol). The impact of these calculations is that the trans amide preferences for structures **6**-**12** should be mainly a function of the "other forces;" e.g., dipolar, steric, and solvent effects (as depicted in Figure 1B).

The scope of our original study with methanoprolines was limited to MetPro **10** and the anti stereoisomers of ex-Metflp **11** and ex-Methyp **12** by synthetic considerations at that time, and we were unable to explore the generality of the finding that $K_{T/C}$ values of other methanoprolines are independent of substituent and position.[10] We now report a different synthetic approach to methanoprolines using directed lithiations of isomeric *N*-Boc-5-fluoro and 5-hydroxymethanopyrrolidines to introduce the 3-ester substituent.[12,13] By this method, we have synthesized and characterized in detail ex-MetFlp **6** and en-MetFlp **7** that contain embedded exo and endo conformations of Flp **1**. We have also prepared ex-MetHyp **8** and en-MetHyp **9** that contain exo and endo conformations of Hyp **2** (see Figure 1). The trans amide preferences of these methanoprolines have been determined in $CDCl_3$ and D_2O. The results provide fresh insights on an issue of importance to peptide and protein chemists.

Results and Discussion

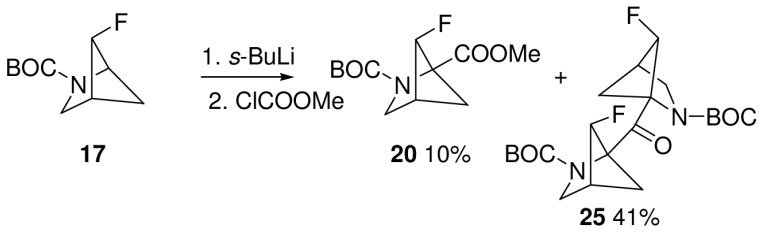
Synthesis of Fluoromethanoprolines

The ex-MetFlp derivative **6** was prepared from the fluorinated methanopyrrolidine **13** using directed α-metallation (Scheme 1).[13] Treating compound **13** with *s*-BuLi at −78 °C yielded a mixture of C_1 and C_3 anions.[12] These carbanions were transformed to the desired C_3-methyl esters by one of two methods: treatment with CO_2, acidification, and then esterification with TMS-diazomethane (Method A); or treatment with methyl chloroformate (Method B). Method A afforded a desired 3-ester **14** (27%) and the 1-ester **15** (17%), whereas method B gave the same esters **14** (24%) and **15** (26%). We were unable to separate the esters, but isomer ratios could be determined by integration of non-overlapping H_4 resonances for the two esters and the unique resonances for the methylene protons H_{3s} and H_{3a} of the 1-ester **15**. Of the two possible 3-esters only **14**, the ester farther from the 5-*syn*-F substituent, was observed. The stereochemistry for the 3-exo ester **14** was assigned based upon the proton H_{3n} (δ 4.32 and 4.22, conformations) showing an NOE enhancement with H_4 (δ 3.05), but not with the H_{6s} proton. For 1-ester **15**, H_{3x} at δ 3.41 has an NOE enhancement with H_4 (δ 2.82) and H_{6s} (δ 1.76). Deprotection and subsequent acetylation of a 1:1 mixture of esters afforded a 1.1:1 mixture of the desired ex-MetFlp **6** along with the 1-ester **16**. Isomer and conformer ratios again were determined by integration of non-

overlapping H_4 resonances for the two esters **6** and **16** and the unique resonances for H_{3s} and H_{3a} of the 1-ester **16**. The isomer ratios were confirmed by ^{19}F NMR integrations (See Table 3).

The en-MetFlp derivative **7** was prepared as shown in Scheme 2 by directed metallation of the fluorinated methanopyrrolidine **17**[13,14] followed by either a CO_2 quench and esterification (Method A) or by reaction with DMF followed by oxidation of the resultant aldehyde to the acid and esterification with TMS-diazomethane (Method C). Method A gave a poorly separated 5:5:3 mixture of 3-esters **18** and **19**, and 1-ester **20** (31%); there was an additional amount of **20** (17%) at a slightly lower R_f value. Method C gave a 1:1 mixture of 3-alcohols **21** and **22** (34%) that was separable from the 1-alcohol **23** (22%). Oxidation of the 3-alcohols to the acids and esterification with TMS-diazomethane gave a mixture of 3-esters **18** and **19**. The ester mixture (from Method A or C) was treated with TFA to remove the BOC protecting group and then acetylated to afford a mixture of the desired en-MetFlp **7**, its stereoisomer ex-Metflp **11**, and the 1-ester **24**. NMR analysis of the 3-ester mixture was enabled by a clear separation of the H_{5syn} protons next to fluorine in the two isomers and the previous preparation of ex-Metflp **11**.[10] The en-MetFlp **7** was also prepared independently from alcohol **9** (see below).

The method B procedure with fluoride **17** was designed to trap the *s*-BuLi generated 3-anions with methyl chloroformate, but it did not provide the 3-esters (eq 1). Instead, we isolated only the 1-ester **20** (10%) and the ketone **25** (41%), whose crystalline sample used for X-ray analysis was found to have C_2 symmetry. Thus, in forming ketone **25** the 1-anion of **17** and its reactive partner ester **20** must be derived from the same enantiomer of **17**.



17 **20** 10% **25** 41%

Synthesis of Hydroxymethanoprolines

The ex-MetHyp structure **8** was prepared from the protected 5-*syn*-hydroxymethanopyrrolidine **26** (Scheme 3).[13] Method A gave a separable mixture of 3-ester **27** (30%) and 1-ester **28** (40%), identified by the absence of an H_1 proton and the pair of H_3 protons (δ 3.60-3.38 and 3.30). The ester **27** was reduced to give alcohol **29**; confirming 3-*exo*-hydroxymethyl stereochemistry, the proton H_{6s} (δ 1.34) showed an NOE enhancement with the hydroxymethylene protons (δ 3.76) and the proton H_{6a} (δ 1.16) gave a positive NOE enhancement with proton H_{5a} (δ 3.72). The usual *N*-deprotection and *N*-acetylation of ester **27** gave amide **30** that was desilylated using tetrabutylammonium fluoride trihydrate in THF (89%) to give ex-MetHyp **8**. Benzoylation of alcohol **8** afforded benzoate ester **31**.

The en-MetHyp structure **9** was prepared from the unprotected 5-*anti*-hydroxy-methanopyrrolidine **32** (Scheme 4).[13] Following the Method A procedure, alcohol **32** gave a mixture of alcohol esters that was immediately esterified with benzoyl chloride to give a 1:1 mixture of benzoates **33** and **34** (28%, 50% BORSM), which differed only in the stereochemistry at C_3. The substitution was regioselective and introduction of an ester group at C_1 was not observed.[15] The *N*-BOC protections of the benzoates were removed and

subsequent acetylation afforded a separable mixture of 3-endo ester **35** (47%) and 3-exo ester **36** (34%). Selective removal of the benzoate esters was effected using methanol/triethylamine to give the new en-MetHyp **9** (87%) along with its previously described stereoisomer ex-Methyp **12** (85%).[10] Alcohol **9** was converted to the fluoride **7** by reaction with BAST.[10]

NMR Analysis of $K_{T/C}$ Values for Substituted for Methanoprolines. Embedded Flp and Hyp Conformers

With the requisite methanoprolines **6**-**9** in hand, the integrated intensities of non-overlapping ^{1}H peaks were compared to find amide trans/cis ratios in both $CDCl_3$ and D_2O. The results are shown by entries 1-4 in Table 3[13]. The percentages of trans isomers obtained from averaged separate ^{1}H NMR integrations are reliable to ±1.2% or better. However, isomer ratios did depend slightly on the atom chosen to be integrated and compared; the percentage of trans isomers determined by ^{19}F NMR ratios were within 2% of values determined using ^{1}H NMR ratios.

In aprotic $CDCl_3$, the C$^\gamma$-exo mimetics ex-MetFlp **6** (entry 1) and ex-MetHyp **8** (entry 3), have clearly *lower* trans amide preferences than the C$^\gamma$-endo mimetics en-MetFlp **7** (entry 2) and en-MetHyp **9** (entry 4). In polar D_2O there is a leveling effect upon amide preferences, but lower trans amide preferences, slightly outside or close to the range of experimental error, are again seen for ex-MetFlp **6** (entry 1) and ex-MetHyp **8** (entry 3) compared to their stereoisomers en-MetFlp **7** (entry 2) and en-MetHyp **9** (entry 4).

The $K_{T/C}$ values for **6**-**9** also can be compared with those of MetPro **10** (entry 5). In D_2O, introduction of a heteroatom at any position results in a slight enhancement (81-84% trans) of the trans amide preference relative to the parent **10** (79% trans). In $CDCl_3$, however, one of the gauche isomers, ex-MetFlp **6** (67% trans, entry 1), has a similar trans amide preference and the other, ex-MetHyp **8** (54% trans, entry 3), has a *lower* trans amide preference than shown by MetPro **10** (71% trans, entry 5). On the other hand, the anti heteroatom isomers en-MetFlp **7** (78% trans, entry 2) and en-MetHyp **9** (72% trans, entry 4) have slightly *higher* trans amide preferences than MetPro **10**. Surprisingly, individual comparisons of $K_{T/C}$ values in both $CDCl_3$ and D_2O show that the C$^\gamma$-exo conformer mimics ex-Metflp **11** and ex-Methyp **12** have slightly *lower* (3-5%) trans amide preferences than the C$^\gamma$-endo conformer mimics en-MetFlp **7** and en-MetHyp **9**.[10] Both sets of exo conformer proline mimics have anti orientations for their substituents.

Effect of the hydroxyl moiety on $K_{T/C}$ values

The hydroxyl proton is not wholly responsible for the low $K_{T/C}$ = 1.2 (54% trans) in aprotic $CDCl_3$ for the gauche alcohol ex-MetHyp **8** (entry 3). Its *O*-silyl ether ex-Hyp-X **30** (entry 8) showed a somewhat *higher* $K_{T/C}$ = 1.4 (58% trans), but this value was still below $K_{T/C}$ = 2.4 (71% trans) for MetPro **10** (entry 5). As with ex-MetHyp **8** in the protic and more polar solvent D_2O, the $K_{T/C}$ = 4.1 (80% trans) for the silyl ether MetHyp-X **30** (entry 8) was substantially increased relative to $K_{T/C}$ = 1.4 (58% trans) in $CDCl_3$.

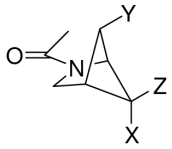
In apolar $CDCl_3$, benzoylation resulted in higher trans amide preferences in comparison to the parent alcohols. *O*-Benzoylation of ex-MetHyp **8** (X = OH, $K_{T/C}$ = 1.2, 54% trans) formed the *syn*-benzoate ex-MetHyp-X **31** (X = OBz) that showed a large increase in trans preference ($K_{T/C}$ = 4.1, 80% trans, entry 9). Similarly, the anti esters en-MetHyp-Y **35** (Y = OBz, $K_{T/C}$ = 3.2, 76% trans, entry 10), and ex-MetHyp-Z **36** (Z = OBz, $K_{T/C}$ = 3.2, 76% trans, entry 11), both showed higher trans preferences than their related free alcohols, en-MetHyp **9**, ($K_{T/C}$ = 2.7, 72% trans, entry 4), and ex-Methyp **12**, ($K_{T/C}$ = 2.2, 68% trans, entry 7), respectively.[16] These results with hydroxymethanoprolines are cautionary in

showing that an increased $K_{T/C}$ value upon *O*-acylation does not need to be related to the presence or absence of a particular favored ring pucker.[17]

The higher trans amide preferences noted in $CDCl_3$ for the benzoates relative to the free alcohols were not observed in a polar protic solvent. In D_2O the 80-83% observed trans preferences for ex-MetHyp-X **31** (X = OBz, entry 9), en-MetHyp-Y **35** (Y = OBz, entry 10), and ex-Methyp-Z **36** (Z = OBz, entry 11) were similar to those of their parent alcohols ex-MetHyp **8** (X = OH, 81% trans, entry 3), en-MetHyp **9** (Y = OH, 83% trans, entry 4), and ex-Methyp **12** (Z = OH, 80% trans, entry 7), respectively.

Comparison of $K_{T/C}$ between *N*-acetyl-methanoprolines and *N*-acetyl-methanopyrrolidines

Previously, we observed for the *N*-acetyl-methanopyrrolidines **37–41** that neither the methylene bridge nor the 5-fluoro- or 5-hydroxy substituent (or stereochemistry) had much of an effect upon trans amide preferences [$CDCl_3$ (43–54% trans) and D_2O (53–58% trans)].[13] Comparisons of trans preferences for methanoproline esters and their corresponding C_3-unsubstituted methanopyrrolidines generated the trans isomer enhancements (Δ% trans) listed in Table 4. These enhancements are a measure of what we term the "α-ester effect".



37 X = F, Y = Z = H
38 X = Y = H, Z = F*
39 X = OH, Y = Z = H
40 X = Y = H, Z = OH*
41 X = Y = Z = H
*Y and Z are interchangeable

The α-ester effects for entries 1-7 in Table 4 are always positive. In D_2O there is a 23– 28% increase (entries 1-7) in the amount of trans isomer upon the introduction of the α-ester. Notably, there is little variance in Δ% trans values between fluoro and hydroxyl substituents despite a range of three separate stereochemistries.

The α-ester effect is smaller in $CDCl_3$ solvent than in D_2O. The trans enhancement (Δ% trans) is on average 9% lower in $CDCl_3$ for combined entries **1–7** (18% increased trans amide) compared to that in D_2O (27% increased trans amide). The lowest trans amide enhancement (11% in $CDCl_3$) was with ex-MetHyp **8** (entry 3). This case is somewhat unique, since the parent *N*-acetyl-5-*syn*-hydroxymethanopyrrolidine **39** showed a cis amide preference prior to introduction of the α-ester to give alcohol **8**.

Calculations of methanoproline geometries

Why is the $n\rightarrow\pi^*$ interaction weak for methanoprolines (see Table 2 for NBO energies)? One way to crudely evaluate the potential for $n\rightarrow\pi^*$ stabilization is to determine the angle between the amide oxygen and the ester carbonyl, and also the distance between the amide oxygen and the ester carbon.[18] The best stabilization should involve angles similar to tetrahedral and distances ≤300 pm,[10] although stabilizations have been validated for protein structures at angles of 109.5° ± 15° and distances of 320 pm.[18] To assess potential $n\rightarrow\pi^*$ interactions within our compounds, we performed geometry optimizations and frequency calculations on four conformational energy minima for each of the MetPro derivatives **6-12**. In the four conformations modeled, the ester alkoxy group is either distal ($\psi \sim 155°$) or proximal ($\psi \sim 15°$), and the amide bond is either trans or cis. Results for the most populated trans conformers for each MetPro derivative are summarized in Table 5.

The bond angle and distance parameters for the favored trans distal conformations of ex-MetFlp **6** (entry 1) and en-MetFlp **7** (entry 2) indicate that although the two structures have similar angle parameters, θ = 97.2° and 96.4°, respectively, the syn (gauche) fluoride ex-MetFlp **6** has a longer distance (322 pm) for the n→π* interaction than en-MetFlp **7**, (309 pm). By comparison, the calculated parameters for exo puckered Flp **1** (trans distal) that accompany favorable n→π* interactions are θ = 100.6° and distance = 287 pm; these values can be compared to the measured values θ = 99.08° and 97.39° and distances = 275.2 pm and 277.8 pm, determined by x-ray structure analysis (two different trans distal geometries in the crystal).[19] Clearly, the distance relationships in methanoprolines are distorted from those that allow for more favorable n→π* overlap in C^{γ}-exo ring puckers of Flp **1** (Figure 3). One source of this difference is revealed by the sum of the calculated angles around nitrogen for the trans conformers of ex-MetFlp **6**: td = 353.5° and tp = 352.5° (see Supporting Information).[20] The syn fluorine on ex-MetFlp **6** repels the nitrogen-π electrons so that the acyl substituents on nitrogen are then bent toward the fluorine substituent and away from the adjacent ester; this lengthens the O···CO distance.[9b]

The *syn*-alcohol ex-MetHyp **8,** whose calculated angles at nitrogen deviate little from planarity (td = tp = 359.7°), has a favorable distance (296 pm), but a poor vector angle (90.7°) for n→π* stabilization.[18] The NBO analysis in Table 2 identified a weak n→π* stabilization of 0.68 kcal/mol for this alcohol that is the highest calculated value for the methanoprolines **6-12** in Table 2; yet **8** has the *lowest* experimentally observed $K_{T/C}$ value (Table 3). This decoupling of $K_{T/C}$ from the n→π* orbital interaction is consistent with "other forces" (Figure 1B) as being dominant in determining conformational preferences of these methanoprolines in nonpolar solvents.[21]

The calculated gas phase trans mole fractions (td + tp) in Table 5 qualitatively mirror the experimental $K_{T/C}$ values for some of the methanoprolines in Table 3 ($CDCl_3$), i.e., en-MetFlp **7** (entry 2, 85% trans) > ex-MetFlp **6** (entry 1, 75% trans) and en-MetHyp **9** (entry 4, 91% trans) > ex-MetHyp **8** (entry 3, 66% trans). However, the calculated trans mole fractions for ex-Metflp **11** (entry 6, 87% trans) and ex-Methyp **12** (entry 7, 42% trans) do not mirror the relative observed trans values in solution. The calculated trans mole fraction for ex-Metflp **11** is slightly higher than that of en-MetFlp **7**, but 6% less trans isomer was observed in solution (Table 3, entries 6 and 2). Also, the cis distal conformer of ex-Methyp **12** was calculated to be the major conformer, but 68% trans isomer was found experimentally (Table 3, entry 7).

Intermolecular influences on conformational preferences

One force that might influence amide preferences in solution is the drive to minimize unfavorable intramolecular dipole–dipole interactions. This might be accomplished by optimizing conformations with favorable intramolecular interactions (dipole–dipole orientations and orbital overlaps).[21,22] The lowest energy trans-distal (td) conformations in the calculations (Table 5) usually also have the lowest calculated molecular dipoles (μ). Exceptions are the minor cis proximal (cp) conformations of the 5-*syn* isomers, ex-MetFlp **6** (6% cp, entry 1) and ex-MetHyp **8** (8% cp, entry 3), and MetPro **10** (9% cp, entry 5) that have slightly lower calculated dipole moments than their trans distal (td) conformers. Thus, for ex-MetFlp **6**, $\Delta\mu = (\mu_{cp} - \mu_{td}) = -1.2$ D, for ex-MetHyp **8**, $\Delta\mu = (\mu_{cp} - \mu_{td}) = -1.0$ D, and for MetPro **10**, $\Delta\mu = (\mu_{cp} - \mu_{td}) = -1.8$ D. These dipole moment considerations support higher amounts of cis conformations in non-polar solvents and, although energy considerations indicate these conformations are of minor importance in the gas phase, might be a factor in the smaller trans preferences in $CDCl_3$ for syn (gauche) ex-MetFlp **6**, ex-MetHyp **8**, and MetPro **10**.

It has been suggested for Flp **1** that a perpendicular arrangement of the C-F and amide dipoles favors a C$^{\gamma}$-exo ring pucker, while a C$^{\gamma}$-endo ring pucker has an unfavorable antiparallel orientation of these dipoles.[5i] The C$^{\gamma}$-exo ring pucker is associated with *higher* $K_{T/C}$. For ex-MetFlp **6** and ex-MetHyp **8**, where ring puckers are constrained and amide preferences are not a function of substituent effect on ring pucker, *lower* $K_{T/C}$ values are associated with the perpendicular orientation of dipoles.

Trans amide preferences for methanoprolines are generally enhanced in polar protic D_2O where hydration competes with other forces.[8p] A hydrogen bonding interaction with solvent is one way to augment the π-acceptor ability or dipolar character of the α-ester carbonyl carbon. Enhancement of the ester carbonyl dipole by electrophilic complexation with D_2O would facilitate interaction between a trans amide carbonyl oxygen and the ester carbonyl carbon. This factor could underlie the globally observed leveling effect in D_2O upon $K_{T/C}$ values of methanoprolines. The C$^{\gamma}$-endo mimetics with anti substituents, en-MetFlp **7** and en-MetHyp **9**, reveal only slightly higher $K_{T/C}$ values (2% and 2% more trans isomer, respectively) than their C$^{\gamma}$-exo mimetic counterparts ex-MetFlp **6** and ex-MetHyp **8**, whose substituents are gauche.

Conclusion

Constrained MetFlp and MetHyp mimics do not permit significant n→π* interactions. The conformational distortions needed to attain favored angle and distance parameters for amide/ester orbital overlap interactions are too difficult. Thus, knowledge of the trans amide preferences for substituted methanoprolines enables an evaluation of substituent effects on $K_{T/C}$ that are largely exclusive of n→π* interactions.

Comparison of $K_{T/C}$ values between *N*-acetyl-methanoproline methyl esters and *N*-acetyl-methanopyrrolidines revealed a solvent dependent α-ester effect with greater enhanced trans amide preferences in D_2O +(24–29% trans) compared to those in $CDCl_3$ +(11–24% trans). The trans enhancement effect is similar for both syn and anti isomers in D_2O, but is larger for the anti isomers in $CDCl_3$.

In summary, our results indicate that other trans amide stabilizing interactions are important in the absence of dominant n→π* stabilization of the trans conformation in *N*-acyl proline derivatives. However, our results should not be interpreted to imply that such stabilization is not dominant when allowed by geometric considerations. The relationships we describe between proline substitution, ring pucker, and $K_{T/C}$ are an important consideration when designing Pro derivatives for protein engineering. Our findings here inform the continued development of novel Pro derivatives with well-defined conformational preferences.[5,7b,8,17]

Experimental

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 standards for ^{1}H NMR were C$\underline{H}Cl_3$ δ 7.26 and D$\underline{H}$O δ 4.80, for ^{13}C NMR $\underline{C}DCl_3$ δ 77.0, and for ^{19}F NMR C$\underline{F}Cl_3$ 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. Amide trans/cis ratios were obtained by integration of non-overlapping ^1H peaks, acetyl peaks if possible. Spectra were obtained using delay times of $5 \times T_1$ to ensure adequate relaxation of nuclei. Experiments with amides **7** and **11** (D_2O) and **8**, **9**, and **12** ($CDCl_3$) yielded T_1 of 1.1-2.3 sec; thus 15-20 second delay times were used for other spectra; ^{19}F NMR spectra were measured using default 5 sec delay times. The amide ratios obtained with these relaxation times were the same as those obtained using 1 sec default delay times. Integrated intensities were obtained following line fitting of appropriate acetyl methyl peaks using NUTS software[23] where possible. The reported error range for $K_{T/C}$ is one standard deviation of the average amide ratio; the trans amide percentage and its error limits were calculated from the average of the amide ratio and the average ± one standard deviation. Throughout this paper we have chosen to use syn/anti nomenclature to identify the stereochemistry of substituents on the non-nitrogen containing bridges. This choice avoids 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-3-carboxymethyl-2-azabicyclo[2.1.1]hexane 10.[10]

^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (dt, J = 7.5, 1.7 Hz, 1H, H_1), 4.33 (s, 1H, H_3), 4.28 (dt, J = 7.2, 1.6 Hz, 1H, H_1), 4.26 (s, 1H, H_3), 3.76 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.05 (dtd, J = 7.5, 2.9, 1.3 Hz, 1H, H_4), 2.98 (dtd, J = 7.2, 3.0, 1.2 Hz, 1H, H_4), 2.09 (ddd, J = 7.6, 3.0, 1.6 Hz, 1H, H6anti), 2.07 (s, 3H, Ac), 2.03 (ddd, J = 7.6, 2.9, 1.7 Hz, 1H, H6anti), 1.96 (dd, J = 10.3, 7.8 Hz, 1H, H_{5syn}), 1.94 (s, 3H, Ac), 1.91 (dm, 1H, J = 7.8 Hz, H5anti), 1.85 (dm, 1H, J = 8.0 Hz, H5anti), 1.67 (dd, J = 10.6, 8.0 Hz, 1H, H_{5syn}), 1.47 (ddd, J = 10.3, 7.6, 0.9 Hz, 1H, H_{6syn}), 1.40 (dd, J = 10.6, 7.6 Hz, 1H, H 1 6syn). H NMR (400 MHz, D_2O) δ *4.69 (dt, J = 7.1, 1.7, 1H)*, *4.68 (s, 1H)*, 4.51 (dt, J = 7.1, 1.7 Hz, 1H), 4.42 (s, 1H), *3.82 (s, 3H)*, 3.78 (s, 3H), *3.15 (m, 1H)*, 3.07 (m, 1H), 2.21 (m, 1H), *2.15 (m, 1H)*, 2.14 (s, 3H), 2.09 – 2.02 (m, 1H), *2.00 (s, 3H)*, 1.77 (dd, J = 10.6, 8.5 Hz, 1H), *1.71 (m, 1H)*, 1.55 (dd, J = 10.7, 7.9 Hz, 1H), *1.47 (dd, J = 10.7, 7.6 Hz, 1H)*. $K_{T/C}$ = 2.4 ± 0.03 (70.6 ± 0.2% trans) in $CDCl_3$ and $K_{T/C}$ = 3.7 ± 0.1 (78.8 ± 0.5% trans) in D_2O were determined from relative H_4 integrations.

N-(*tert*-Butoxycarbonyl)-3-*exo*-carboxymethyl-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (14) and *N*-(*t*-Butoxycarbonyl)-1-carboxymethyl-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (15). General Procedure for Electrophilic Substitution Next to Nitrogen. Method A.[12]

Carbamate **13** (160 mg, 0.80 mmol), TMEDA (144 μL, 1.11 mmol) in ether (10 mL) was cooled to −78 °C and *s*-BuLi (680 μL, 0.96 mmol) was added dropwise. The solution was stirred 2 h and quenched with CO_2 (g) bubbled for 20 min. The ether layer was extracted with water (3 H 10 mL). The aqueous layers were combined and acidified with aqueous HCl (pH 3). The aqueous layer was extracted with ethyl acetate (3 H 10 mL), and the organic layer was concentrated to give 120 mg (62%) of the mixture of acids. The crude mixture of acids was dissolved in hexane (5 mL) and *i*-PrOH (5 mL) and to this solution was added $TMSCHN_2$ (245 mL, 0.49 mmol). The solution was stirred at rt for 12 h. Removal of the solvent in vacuo gave as a light colored oil 90 mg (71%) of an inseparable 3:2 mixture of esters **14** and **15** at R_f = 0.39 (3:1 hexane/ethyl acetate). For the 3-ester **14**, ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (ddd, J = 55.5, 1.8, 1.8 Hz, 1H, H_5), 4.47 and 4.35 (brd, H_1), 4.32 and 4.22 (two s, 1H, H_3), 3.77 (multiple s, 3H), 3.05 (m, 1H, H_4), 1.73 (m, 1H, H_{6syn}), 1.32 (multiple s, 9H), 1.20 (m, 1H, H_6). For 1-ester **15**, ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, J = 57.6, 3.0 Hz, 1H, H_5), 3.77 (multiple s, 3H), 3.58 (brd, J = 8.8 Hz, 1H, H_{3n}), 3.41 (d, J = 8.8 Hz, 1H, H_{3x}), 2.82 (br, 1H, H_4), 1.76 (m, 1H, H_{6syn}), 1.48 (m, 1H, H6anti), 1.32 (multiple s, 9H). For the mixture of **14**/**15**, ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 167.1,

157.7, 156.8, 155.3, 28.2, and 28.1; for 3-isomer **14**, δ 85.2 and 84.9 (two d, *J* = 244 Hz), 80.5 and 80.3, 62.7 and 61.3 (two d, *J* = 18 Hz), 56.5 (d, *J* = 4 Hz), 52.3 (d, *J* = 16 Hz), 46.5 and 46.2 (d, *J* = 18 Hz), 23.6 and 22.9 (two d, *J* = 16 Hz), and for 1-isomer **15**, δ 84.2 (d, *J* = 243 Hz), 81.0, 71.8 (br), 52.1, 48.3 (d, *J* = 3.9 Hz), 38.8 (d, *J* = 19 Hz), 31.0. For 1-ester **15**, H_{3x} at δ 3.41 has an NOE enhancement with H_4 (δ 2.82) and H_{6syn} (δ 1.76). For 3-*exo*-ester **14**, H_{3n} (δ 4.32 and 4.22) has an NOE enhancement with H_4 (δ 3.05), but not with an H_6 (δ 1.76-1.20). For the **14**/**15** mixture, HRMS *m/z* 282.1108, calcd for $C_{12}H_{18}FNO_4Na$ (M + Na) 282.1118. **Method B.** Carbamate **13** (140 mg, 0.7 mmol) and TMEDA (97 mg, 125 μL, 3.5 mmol) in ether (10 mL) in a lithiation vial were cooled to −78 °C and *s*-BuLi (600 μL, 0.84 mmol, 1.4 M solution in cyclohexane) to prepare the anion as described in Method A. The solution was stirred 2 h at −78 °C and methyl chloroformate (331 mg, 3.5 mmol) was injected quickly into the reaction vial. After 30 min the solution was allowed to warm to rt. The solution was washed with saturated ammonium chloride (3 H 5 mL), brine (5 mL) and then dried over Na_2SO_4. Filtration and removal of solvent in vacuo afforded as a light yellow oil 90 mg (50%) of a 1.1:1 mixture of **14** and **15**.

N-Acetyl-3-*exo*-carboxymethyl-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (6) and *N*-Acetyl-1-carboxymethyl-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (16)

To a 1.1:1 mixture of esters **14** and **15** (90 mg, 0.35 mmol) (Method B) in CH_2Cl_2 (6 mL) was added TFA (270 L, 3.5 mmol), and the resulting solution was stirred at rt for 4 h. Workup gave 40 mg (73%) of an amine that without further purification was dissolved in CH_2Cl_2 (10 mL) at 0 °C. To this solution was added DMAP (92 mg, 1.1 mmol) followed by acetyl chloride (54 L, 1.1 mmol) dropwise. The resulting solution stirred at 0 °C for 30 min and was slowly brought to room temperature and stirred for 12 h. The reaction mixture was washed with water (3 × 5 mL) and dried with Na_2SO_4. The solvent was removed in vacuo to give a residue that upon silica gel flash chromatography gave 40 mg (50%) of a 1.2:1 mixture of amides **6** and **16** as a light yellow oil at R_f = 0.17 (2:1 ethyl acetate/hexane). For 3-isomer **6**, ^{1}H NMR (300 MHz, $CDCl_3$) δ *4.86* and 4.30 (dq, *J* = 7.2, 1.7 Hz, 1H, H_1), 4.51 and *4.48* (minor) (dt, *J* = 58, 2.8, 2.8 Hz, 1H, H_5), 4.39 and *4.27* (two s, 1H, H_3), 3.82 and *3.77* (s, 3H), *3.00* and 2.93 (br, 1H, H_4), 2.03 (multiple singlets, 3H), 1.76 and *1.52* (dd, *J* = 30.0, 9.5 Hz, 1H, H_{6syn}), 1.24 (brm, 1H, H6anti); NOE: Irradiation in $CDCl_3$ of the major acetyl peak at δ 2.03 enhances the H_1 signal at δ 4.30 indicating the trans conformer of **6** to be major. For 1-isomer **16**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (dd, *J* = 58, 3 Hz, 1H, H_5), 3.75 (s, 3H), 3.53 (br d, *J* = 7.8 Hz, 1H_3), 3.45 (d, *J* = 7.8 Hz, 1H_3), 2.87 (br, 1H, H_4), 2.03 (multiple singlets, 3H), 1.67 (dd, *J* = 27.5, 9 Hz, 1H, H_{6syn}), 1.48 (d, *J* = 9.0 Hz, 1H, H6anti). From the mixture of **6** and **16**, ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.5, 169.9, 166.8, 84.5, 84.1, and 83.7 (three d, *J* = 241 Hz), 52.7, 52.4, and 52.3, 21.6, 21.4, and 21.3; for 3-isomer **6**, δ 63.5 and 60.8 (two d, *J* = 17 Hz), 57.2 and 55.4 (two d, *J* = 4 Hz), 47.5 and 47.2 (two d, *J* = 18 Hz), 24.0 and 22.6 (two d, *J* = 16 Hz); for the 1-isomer **16**, δ 71.1 (br), 53.2, 47.5, 38.8 (d, *J* = 16 Hz), 29.8 (*J* = 16 Hz). The ^{19}F NMR for **6** (282 MHz, $CDCl_3$) δ −177.1 (dd J = 59 and 30 Hz) and *−177.7* (dd, J = 58, 28 Hz); for **16** δ –178.7 (dd, J = 56, 29 Hz); HRMS *m/z* 202.0865, calcd for $C_9H_{13}FNO_3$ (M + H) 202.0874. A trans/cis isomer ratio in $CDCl_3$ of 2.1 (68% trans) was determined for **6** from fluorine spectra following line shape fitting; a trans/cis isomer ratio of 2.02 ± 0.05 (66.9 ± 0.5 % trans) was determined from comparisons using H_4. Also, ^{1}H NMR of the mixture of **6**/**16** (400 MHz, D_2O) δ 4.89–4.63 (m, 3H), 4.44 (s, 1H, H_3 for **6**), 3.84 and 3.79 (two s, 6H, two OMe), 3.68 (two d, *J* = 9.1 Hz, 2H, H_3 of **16**), 3.32 minor and 3.26 major (two m, 1H, H_4 for **6**), 3.03 (br, 1H, H_4 of **16**), 2.14, 2.10, 2.07 (three s, 2CH_3), 1.84–1.40 (m, 4H). For the mixture of **6** and **16**, ^{13}C NMR (100 MHz, D_2O) δ 175.4, 175.1, 173.7, 172.6, 169.7; for 3-ester **6**, δ 85.2 and 84.7 (two d, *J* = 239 Hz), 65.0 and 61.2 (two d, *J* = 17 Hz), 58.3 and 56.4 (two d, *J* = 4 Hz), 53.9 and 53.6, 47.3 and 46.4 (two d, *J* = 18 Hz), 23.6 and 22.4 (two d, *J* = 17 Hz), 21.3 and 21.1; also for 1-ester **16**, δ 84.6 (d, *J* = 239 Hz), 71.6, 53.4, 48.2 (d, *J* = 4 Hz), 39.1 (d, *J* = 18.4

Hz), 29.7 (d, *J* = 14.8 Hz), 20.9; ^{19}F NMR for 3-ester **6** (282 MHz, D_2O) δ −179.1 (dd, *J* = 58, 32 Hz) and −*179.4* (dd, *J* = 58, 32 Hz) and for 1-ester **16**, δ −180.5 (dd, *J* = 58, 32 Hz). A trans/cis isomer ratio for **6** in D_2O of 4.0 (80 ± 1 % trans) was determined from the fluorine spectrum. The NUTS[23] package was used to obtain the Gaussian resolution enhanced proton spectrum. This permitted iterative line fitting of partially overlapped H_4 multiplets; a trans/cis ratio for **6** of 4.61 ± 0.34 (82.1 ± 1.0% trans) (D_2O) was obtained after adding the fitted intensities.

N-(*tert*-Butoxycarbonyl)-5-*anti*-fluoro-3-*endo*-carbomethoxy-2-azabicyclo[2.1.1]hexane (18), *N*-(*tert*-Butoxycarbonyl)-5-*anti*-fluoro-3-*exo*- carbomethoxy-2-azabicyclo[2.1.1]hexane (19), and *N*-(*tert*-Butoxycarbonyl)-1-carbomethoxy-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (20)

According to General Procedure Method A, to a solution of fluoride **17** (365 mg, 1.8 mmol) in ether (25 mL) at −78 °C was added TMEDA (300 L, 2.0 mmol) dropwise. The resulting solution was stirred for 15 min followed by the addition of *s*-BuLi (1.8 mL, 2.5 mmol). The mixture was then allowed to stir for 2 h at the same temperature, and the anion was quenched by bubbling CO_2 for 20 min. Workup afforded 412 mg (93%) of a light yellow oily mixture of acids. To this mixture in *i*-PrOH (7 mL) and hexane (7 mL), $TMSCHN_2$ (1 mL, 2 mmol) was added at rt. After stirring for 1 h, removal of solvent, then silica gel flash chromatography gave 137 mg (31%) of a 5:5:3 mixture of **18**, **19** and **20** as a light yellow oil at R_f = 0.53 (1:1 hexanes/ether) and 73 mg (17%) of **20** at R_f = 0.56. For the mixture of esters **18**/**19**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (br d, *J* = 61.8 Hz, 1H, H_5) and 4.75 (dd, *J* = 61.8, 7.2 Hz, 1H, H_5), 4.36 (br, 2H, $2H_1$), 4.24 (brm, 2H, $2H_3$), 3.75 and 3.76 (two s, 6H), 2.98 (m, 3H), 2.78 (m, 1H), 2.13 (ddd, *J* = 8.0, 8.0, 2.4 Hz, 1H, H_{6syn}), 1.75 (m, 1H, H_6), 1.43 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 153.9 (2C), 98.2 (d, *J* = 218 Hz), 95.8 (d, *J* = 210 Hz), 80.5 (2C), 62.1, 60.8, 59.7, 57.3, 52.1 (2C), 47.4 (d, *J* = 16.6 Hz), 47.2 (d, *J* = 16.6 Hz), 38.8, 33.4, 28.1 (2C); HRMS *m/z* found 224.0330, calcd for $C_8H_8FNO_4Na$ (M + Na − *tert*-Bu – H) 224.0335. For **20**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (dd, *J* = 60.8, 6.8 Hz, H_5), 3.80 (s, 3H), 3.49 (dd, *J* = 8.8, 4.4 Hz, H_3), 3.43 (d, *J* = 8.8 Hz, H_3), 2.97 (ddd, *J* = 8.4, 4.5, 4.0, 1H, H_6), 2.81 (t, *J* = 3.6 Hz, H_4), 1.92 (ddd, *J* = 8.0, 7.6, 2.4 Hz, 1H, H_6), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 156.1, 99.4 (d, *J*CF = 217 Hz, C_5), 81.3, C_1 (not visible, see **24** below), 52.1, 48.9 and 48.8 (C_3), 39.7 (d, *J* = 17.5 Hz, C_4), 37.7 (C_6), 28.2; HRMS *m/z* found 282.1112, calcd for $C_{12}H_{18}NO_4FNa$ (M + Na) 282.1112.

N-(*tert*-Butoxycarbonyl)-3-*endo*- and 3-*exo*-hydroxymethyl-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexanes (21) and (22) and *N*-(*tert*-Butoxycarbonyl)-1-hydroxymethyl-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (23). Method C

According to the general procedure, to the carbamate **17** (174 mg, 0.87 mmol) and TMEDA (156 L, 1.2 mmol) in ether (25 mL) at −78 °C was added *s*-BuLi (867 L, 1.2 mmol). The solution was stirred for 2 h and to this mixture was added DMF (341 L, 4.33 mmol). The solution was warmed slowly to rt and washed with NH_4Cl (2 H 10 mL). The ether layer was diluted, washed with water (5 mL) and brine (5 mL). After drying over Na_2SO_4, the solution was filtered and concentrated to give 176 mg (92%) of a mixture of aldehydes. Without further purification the mixture was taken up in MeOH (10 mL) and cooled to 0 °C. $NaBH_4$ (147 mg, 3.9 mmol) was added slowly; the reaction was stirred for 15 min then warmed to rt and satd. NH_4Cl (5 mL) was added slowly, followed by CH_2Cl_2 (3 mL). The aqueous layer was extracted with CH_2Cl_2 (2 H 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to furnish 163 mg of a light yellow oily mixture of alcohols which on silica gel flash chromatography gave 45 mg (22%) of 1-CH_2OH **23** and 69 mg (34%) of a 1:1 mixture of 3-*endo*-CH_2OH **21** and 3-*exo*-CH_2OH **22** as clear oils. For **23**: R_f = 0.57 (2:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (dd, J = 62.7, 6.9 Hz, H_5), 4.59 (br, 1H, OH), 3.93 (m, 2H), 3.42 (dd, J = 9.6, 3.0 Hz, H_3), 3.36 (d, J = 9.0

Hz, H_3), 2.80 (brt, J = 3.6, 3.0 Hz, 1H, H_4), 2.59 (ddd, J = 8.4, 4.5, 4.0 Hz, 1H, H6anti), 1.78 (ddd, J = 7.8, 7.2, 2.4 Hz, H_{6syn}), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 96.8 (d, J_{CF} = 213 Hz, C_5), 81.1, 74.6 and 74.4, 57.7 (C_1), 49.4 (C_3), 39.6 and 39.5 (C_4), 37.7 (C_6), 28.8; HRMS m/z found 230.1187, calcd for $C_{11}H_{17}N_1O_3F$ [M − H] 230.1192 and m/z 232.1338, calcd for $C_{11}H_{19}N_1O_3F$ [M + H] 232.1349. For the mixture of alcohols **21**/**22**: *R* = *f* 0.36 (2:1 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (br dd, *J* = 62.4, 7.6 Hz, 1H, H_{5syn}), 4.76 (dd, *J* = 62.4, 7.6 Hz, 1H, H_{5syn}), 4.45 (br, integrates for only 1H, OH), 4.29 (brd, *J* = 7.5 Hz, 1H, H_1), 4.25 (d, *J* = 7.5 Hz, 1H, H_1), 3.89–3.74 (m, 6H), 2.86 and 2.75 (two m, 4H), 1.89 (m, 1H, H_6), 1.71 (ddd, *J* = 8.0, 7.6, 3.2 Hz, 1H, H_6), 1.46 (s, 18H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 157.3, 156.9, 98.9 (d, *J* = 215 Hz, 1C, C_5), 96.3 (d, *J* = 209 Hz, 1C, C_5), 81.1 (2C), 64.6 (br, C_1, 2C), 62.6 (2C, C_3), 60.1 (2C), 46.1 (d, *J* = 17.4 Hz, 1C, C_4), 45.7 (d, *J* = 18.1 Hz, 1C, C_4), 38.7 and 37.3 (2C, C_6), 28.4; HRMS *m/z* found 232.1348, calcd for $C_{11}H_{19}N_1O_3F$ [M + H] 232.1344, *m/z* found 170.0724, calcd. for (M + H − *tert*-butyl) 170.0729, *m/z* found 200.1087, calcd. for (M + H − MeOH) 200.1087.

N-(*tert*-Butoxycarbonyl)-3-*endo*- and 3-*exo*-methoxycarbonyl-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexanes (18) and (19) from alcohols 21 and 22

To a solution of the alcohols **21**/**22** (69 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) containing TEMPO (3 mg) was added a solution of saturated $NaHCO_3$ (6 mL) containing KBr (2 mg) and tetrabutylammonium iodide (4 mg). The mixture was cooled to 0 °C and a solution of NaOCl (0.67 mL), saturated $NaHCO_3$ (aq) (0.3 mL), and saturated NaCl (aq) (0.7 mL) was added dropwise over 45 min. The two layers were separated, and the organic layer was extracted with water (3 H 5 mL). The aqueous extracts were combined and acidified with aqueous HCl (10% w/v), and the resulting solution was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4. The solvent was removed to give 56 mg (77%) of the desired carboxylic acids as a light yellow oil. To a solution of these acids in hexane (6 mL) and isopropanol (6 mL) was added a 2M solution of $TMSCHN_2$ in hexane (115 μL, 2.3 mmol). The resulting mixture was stirred under argon for 0.5 h. The solvent was removed in vacuo to give 56 mg (95%) of a 1:1 mixture of esters **18** and **19** as a light yellow oil at R_f = 0.51 (1:1 hexane/ether).

N-Acetyl-3-*endo*-carbomethoxy-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (7), *N*-Acetyl-3-*exo*-carbomethoxy-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (11) and *N*-Acetyl-1-carbomethoxy-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (24)

According to the general procedure, to the mixture of **18**, **19** and **20** (59 mg, 0.25 mmol) in CH_2Cl_2 (8 mL) prepared by Method A there was added TFA (3 mL), and the resulting solution was stirred at rt for 1h. Workup afforded 32 mg (54%) of an oily mixture of amines that without further purification was dissolved in methylene chloride (8 mL) at 0 °C. To this solution was added DMAP (122 mg, 1.0 mmol), followed by dropwise addition of acetyl chloride (43 L, 0.6 mmol). The resulting solution was stirred at 0 °C for 30 min and then was slowly brought to rt and stirred for 3 h. Workup by the general procedure gave a crude amide which upon silica gel flash chromatography gave 19 mg (48%) of an inseparable 1:1 mixture of 3-isomers **7**/**11** as a light yellow oil at R_f = 0.32 (2:1 ethyl acetate/hexane), and 8 mg (15%) of 1-isomer **24** as a light yellow oil at R_f = 0.26 (1:3 ethyl acetate/hexane). For 3-*endo*-ester **7**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 and *5.12* (two dd, *J* = 62.1, 7.2 Hz, 1H, H_5), *4.85* and 4.34 (d, *J* = 7.2 Hz, 1H, H_1), 4.43 (s, 1H, H_3), *3.83* and 3.78 (two s, 3H, CH_3), 3.05 (m, 2H, H_4 and H6anti), 2.11 and *1.96* (two s, 3H, CH_3), 1.82 (m, 1H, H_{6syn}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.4, 95.5 (d, J_{CF} = 212.6 Hz, C_5), *95.4* (d, J_{CF} = 211.7 Hz, C_5), 63.5 (d, J_{CF} = 21.8 Hz, C_1), *60.7* (d, J_{CF} = 3.4 Hz, C_3), *60.6* (d, J_{CF} = 21.8 Hz, C_1), 58.7 (d, J_{CF} = 3.4 Hz, C_3), *52.9,* 52.6, *48.0* (d, J_{CF} = 19.0 Hz, C_4), 46.9 (d, J_{CF} = 18.5 Hz, C_4), 39.2 (C_6), *38.5* (C_6), 21.4, *20.9*. For 7, ^{19}F NMR (282 MHz, $CDCl_3$) δ –219.0 (d, *J* = 62 Hz), *−221.9* (d, *J* = 61 Hz); also for **7**, ^{1}H NMR (400 MHz, D_2O) δ ^{1}H NMR 5.24 (dd, *J* =

61.5, 7.3 Hz, 1H, H_5), *5.09* (dd, *J* = 61.2, 7.3 Hz, 1H, H_5), *4.83* (t, *J* = 1.7 Hz, 1H, H_3), *4.75* (dt, *J* = 7.8, 1.6 Hz, 1H, H_1), 4.62 (ddd, *J* = 7.4, 1.7, 1.0 Hz, 1H, H_1), 4.53 (br s, 1H, H_3), 3.86 (s, 3H, OMe), 3.81 (s, 3H, OMe), *3.27* (m, 1H, H_4), 3.19 (m, 1H, H_4), 3.06 (m, 1H, H6anti), *3.01* (m, 1H, H6anti), 2.16 (s, 3H), *2.00* (s, 3H), 1.93 (ddd, J = 10.9, 7.4, 3.4 Hz, 1H, H_{6syn}), *1.87* (ddd, *J* = 10.9, 7.4, 3.4 Hz, 1H, H_{6syn}); ^{13}C NMR (100 MHz, D_2O) δ 172.1, 172.0, 96.0 (d, J_{CF} = 210.8 Hz, C_5), 64.5 (d, J_{CF} = 22.3 Hz, C_1), 59.5 (d, J_{CF} = 4.3 Hz, C_3), 53.5, 47.0 (d, J_{CF} = 19.3 Hz, C_4), 38.8 (C_6), 20.8; ^{19}F NMR (282 MHz, D_2O) δ – 211.5 (d, *J* = 62 Hz), *−213.7* (d, *J* = 62 Hz). For 3-*exo*-ester **11**,[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (major) and *4.75* (minor) (two dd, *J* = 61.8, 7.5 Hz, 1H, H_5), 4.39 (s, 1H, H_3), 4.31 (dd, *J* = 7.2, 1.6 Hz, 1H, H_1), *3.81* and 3.76 (two s, 3H), 3.01 (m, 1H, H_4), 2.79 (m, 1H, H_6), 2.30 (ddd, *J* = 7.8, 7.5, 3.0, 1H, H_6), 2.11 and *1.99* (two s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 and 168.1, 170.0, 95.5 (d, J_{CF} = 210 Hz, C_5) and 95.4 (d, J_{CF} = 211 Hz, C_5), 63.6 (d, J_{CF} = 20.5 Hz, C_1) and 60.7 (d, J_{CF} = 20.8 Hz, C_1), 58.6 and 56.6 (C_3), 52.8 and 52.5, 48.0 (d, J_{CF} = 19.2 Hz) and 47.0 (d, J_{CF} = 18.7 Hz, C_4), 38.5 and 34.2 (C_6), 21.6 and 21.6. Also for 3-*exo*-ester **11**,[10] ^{19}F NMR (282 MHz, $CDCl_3$) δ –212.9 (d, *J* = 62 Hz) and *–214.2* (d, *J* = 62 Hz); shifts corrected to $CFCl_3$. Also for **11**, ^{1}H NMR (400 MHz, D_2O) δ 4.94 (dd, *J* = 61.4, 7.6 Hz, 1H, H_5), *4.90* (dd, *J* = 61.4, 7.6 Hz, 1H, H_5), 4.78 (s, 1H, H_3), *4.74* (dd, *J* = 7.4, 1.7 Hz, 1H, H_1), 4.59 (dd, *J* = 7.4, 1.7 Hz, 1H, H_1), 4.50 (s, 1H, H_3), *3.85* (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.26 (m, 1H, H_4), 3.20 (m, 1H, H_4), 2.90 (m, 1H, H6anti), *2.81* (m, 1H, H6anti), 2.16 (s, 3H, $COCH_3$), 2.12 (ddd, *J* = 9.8, 7.5, 2.6 Hz, 1H, H_{6syn}), *2.03* (s, 3H, $COCH_3$), *1.90* (ddd, *J* = 9.8, 7.5, 2.6 Hz, 1H, H_{6syn}); ^{13}C NMR (100 MHz, D_2O) δ 172.1, 171.5, 98.3 (d, J_{CF} = 216.7 Hz, C_5), 97.8 (d, J_{CF} = 216.7 Hz, C_5), 64.6 (d, J_C F = 22.1 Hz, C_1), 61.5 (d, J_{CF} = 22.1 Hz, C_1), 59.5 (d, J_{CF} = 4.6 Hz, C_3), 57.4 (d, J_{CF} = 4.6 Hz, C_3), 53.8, 53.5, 47.7 (d, J_{CF} = 19.0 Hz, C_4), 46.9 (d, J_{CF} = 19.0 Hz, C_4), 33.8 (C_6), 32.8 (C_6), 21.1, 20.8; ^{19}F NMR (282 MHz, D_2O) δ – 205.8 (d, *J* = 62 Hz) and *– 206.7* (d, *J* = 62 Hz); NOEs in D_2O: irradiation of the major acetyl signal for **7** at δ 2.16 enhances the major H_1 signal at δ 4.62, and irradiation of the minor acetyl signal at δ 2.00 enhances the minor H_3 signal at δ 4.83. Irradiation of the acetyl signal for **11** at δ 2.16 enhances the major H_1 signal at δ 4.59. HRMS of the **7**/**11** mixture *m/z* 202.0875, calcd for $C_9H_{13}FNO_3$ (M + H) 202.0874. For spectral and analytical data for 1-ester **24**, see below. The reported trans/cis ratios in Table 3 were those obtained by proton integration of fluorides **7** and **11** prepared independently from alcohols **9** and **12**, respectively (See below).

N-Acetyl-1-carbomethoxy-2-azabicyclo-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (24) from 20

According to the general procedure, to a solution of 1-ester **20** (73 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) there was added TFA (4 mL), and the resulting solution was stirred at rt for 1 h. Workup afforded 18 mg (40%) of the amine as light yellow oil. Without further purification the amine was dissolved in CH_2Cl_2 (5 mL) and was cooled to 0 °C. To this solution was added DMAP (67 mg, 0.55 mmol) followed by slow addition of acetyl chloride (24 L, 0.34 mmol). The resulting solution was stirred at 0 °C for 0.5 h and then was slowly brought to rt and stirred for 2 h. The reaction mixture after workup and flash chromatography gave 12 mg (52%) of 1-ester **24** as a light yellow oil at R_f = 0.26 (1:3 ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dd, *J* = 61.6, 7.2 Hz, H_5), 3.81 (s, 3H), 3.55 (m, 2H, $2H_3$), 3.01 (ddd, *J* = 8.4, 4.7, 3.6 Hz, 1H, H6anti), 2.89 (dd, *J* = 3.2, 3.6 Hz, 1H, H_4), 2.02 (s and m, 4H, CH_3 and H_{6syn}); ^{13}C NMR δ (100 MHz, $CDCl_3$) 170.0, 166.2, 98.3 (*J* = 216 Hz), 70.0 (d, *J* = 23.1 Hz, C_1), 52.4 and 52.1, 49.9 (C_3), 39.5 (d, *J* = 17.5 Hz, C_4), 38.0 (C_6), 21.0; HRMS m/z found 202.0879, calcd for $C_9H_{13}FNO_3$ (M + H) 202.0874, m/z found 425.1517, calcd for $C_{18}H_{26}F_2N_2O_6Na$ (2M + Na) 425.1494.

N-(*tert*-Butoxycarbonyl)-1-carbomethoxy-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (20) and non-symmetrical Di-*tert*-butyl-1,1′-dicarbonyl-*bis*-(5-a*nti*-fluoro-2-azabicyclo[2.1.1]hexane-2-carboxylate) (25) from 17. General Procedure Method B

According to the general procedure, to a solution of **17** (140 mg, 0.70 mmol) and TMEDA (115 L, 76 mmol) in ether (10 mL) at 0 °C was added s-BuLi (600 L, 0.84 mmol) dropwise. The mixture was stirred for 2 h followed by the addition of methyl chloroformate (270 L, 3.5 mmol). The reaction mixture was diluted with ether (10 mL) and workup upon silica gel flash chromatography gave as a light yellow oil 14 mg (10%) of 1-ester **20**, as a white solid 79 mg (41%) of ketone **25** and as a light yellow oil 13 mg (9%) of unreacted starting material **17**. For **20**: R_f = 0.35 (6:4 hexane/ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (dd, J = 60.8, 6.8 Hz, H_5), 3.80 (s, 3H, 3.49 (dd, J = 8.8, 4.4 Hz, H_3), 3.43 (d, J = 8.8 Hz, H_3), 2.97 (ddd, J = 8.4, 4.5, 4.0, 1H, H6anti), 2.81 (t, J = 3.6 Hz, H_4), 1.92 (ddd, J = 8.0, 7.6, 2.4 Hz, 1H, H_{6syn}), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 156.1, 99.4 (d, J_{CF} = 217 Hz, C_5), 81.3, 52.1, 48.9 and 48.8 (C_1), 39.8 (C_3), 39.6 (C_4), 37.7 (C_6), 28.2; HRMS *m/z* found 282.1112, calcd for $C_{12}H_{18}NO_4FNa$ (M + Na) 282.1112. For ketone **25**, mp 185–186 °C: R_f = 0.29 (3:2 hexane/ether); ^{1}H NMR δ 4.90 (dd, J = 61.2, 7.2 Hz, 2H, $2H_5$), 3.46 (dd, J = 8.8 Hz, H_3), 3.39 (dd, J = 9.6, 2.8 Hz, H_3), 3.19 and 3.16 (two m, 2H, 2H6anti), 2.67 (brm, 2H, $2H_4$), 2.10 (m, 2H, $2H_{6syn}$), 1.38 (s, 18 H, two BOC); ^{13}C NMR δ 194.0, 154.0, 95.8 (d, J_{CF} = 300 Hz, C_5), 83.5, 71.3 and 71.0 (C_1), 47.3 (C_3), 38.1 (C_4), 37.4 and 37.2 (C_6), 25.6; HRMS *m/z* found 451.2020, calcd for $C_{21}H_{30}N_2O_5F_2Na$ (M + Na) 451.2037.

N-(*tert*-Butoxycarbonyl)-3-*exo*-carboxymethyl-5-*syn*-(*tert*-butyldimethylsilyloxy)-2-azabicyclo[2.1.1]hexane (27) and *N*-(*tert*-Butoxycarbonyl)-1-carboxymethyl-5-*syn*-(*tert*-butyldimethylsilyloxy)-2-azabicyclo[2.1.1]hexane (28)

According to Method A, carbamate **26** (150 mg, 0.479 mmol) was dissolved in dry diethyl ether (4 mL). TMEDA (90 L, 0.574 mmol, 1.2 eq.) was added to the resulting solution, which was cooled to −78 °C; s-BuLi in cyclohexane (415 L, 0.574 mmol, 1.4 M) was added dropwise, and the solution was stirred 2 h at −78 °C. Excess CO_2 gas was blown through the flask for approximately 10 min. The solution was stirred at −78 °C for 30 min. and warmed to rt. The ether was extracted with distilled water (3 H 2.5 mL), and the combined aqueous layers were then acidified with dilute HCl to pH = 3. The aqueous layer was extracted with ethyl acetate (5 H 4 mL), which was then concentrated. The crude yellow oil was then taken up in hexanes (7.5 mL) and isopropyl alcohol (7.5 mL). Trimethylsilyldiazomethane (66 mg, 0.574 mmol, 1.2 eq. 2.0 M solution in hexanes) was added, and the reaction was stirred 12 h at room temperature. Workup and chromatography using a pencil column on silica gel (gradient up to 8:1 hexanes/ethyl acetate) furnished 71 mg (40%) of 1-ester **28** as a colorless oil at R_f = 0.37 (7:1 hexanes/ethyl acetate), 53 mg (30%) of 3-ester **27** as a colorless oil at R_f = 0.31 (7:1 hexanes/ethyl acetate), and small amounts of trimethylsilylmethyl esters at higher R_f values. For **27**, ^{1}H NMR (400 MHz, $CDCl_3$) δ *4.26* (dt, J = 7.1, 1.8 Hz, 1H, H_1), 4.25 (s, 1H, H_5), *4.19* (s, 1H, H_5), 4.17 (dt, J = 7.1, 1.8 Hz, 1H, H_1), 3.80 (m, 1H, H_3), 3.74 (s, 3H, OMe, both conformers), 2.80 (m, 1H, H_4), *1.58* (d, J = 8.8 H, 1H, H6anti), 1.56 (d, J = 8.8 H, 1H, H_{6anti}), *1.44* (s, 9H), 1.42 (s, 9H) *1.20* (m, 1H, H_{6syn}), 1.18 (m, 1H, H_{6syn}), *0.87* (s, 9H), 0.86 (s, 9H), 0.06 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 and *172.4*, *156.6* and 155.5, *79.7* and 79.5, *71.7* and 71.5, 64.3, 63.0, 57.1 and *56.8*, *52.1* and 51.9, 47.9 and *47.8*, 28.4 and *28.3*, *25.7* and 25.6, *18.0* and 17.9, −5.0 and *−5.2*; HRMS *m/z* 372.2196, calcd for $C_{18}H_{34}NO_5Si$ (M + H) 372.2201. For **28**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (d, J = 3.0 Hz, 1H, H_5), 3.74 (s, 3H), 3.60–3.38 (br, 1H, H_3), 3.30 (br, 1H, $H_{3'}$), 2.51 (s, 1H, H_4), 1.59 (br, 1H, H_6), 1.39 (br, 10H, Boc and H_6), 0.87 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 157.7, 80.2 (br), 72.8 (br), 70.4, 51.6, 48.3, >39.8, 33.9 (br), 28.3, 25.7, 18.1, -4.9 and *-5.2*; HRMS *m/z* 372.2203, calcd for $C_{18}H_{34}NO_5Si$ (M + H) 372.2201.

N-(*tert*-Butoxycarbonyl)-3-*exo*-hydroxymethyl-5-*syn*-(*tert*-butyldimethylsilyloxy)-2-azabicyclo[2.1.1]hexane (29)

LAH (9 L, 0.018 mmol, 2.0 M solution in THF) was added dropwise to a solution of carbamate 27 (11 mg, 0.030 mmol) in dry THF (600 L) at −78 °C. The reaction mixture was maintained at −78 °C for 1 h and then brought to room temperature. After stirring for 2 h, the reaction mixture was quenched with a 1:1 mixture of water and THF (10 L). The resulting solution was dried over Na_2SO_4, filtered and washed with THF (600 L). Solvent was removed in vacuo to afford 9 mg (89%) of pure alcohol **29** as a colorless oil at R_f = 0.42 (1:4 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (br, 1H, H_1), 3.87 (br, 1H, H_3), *3.78* (br, 1H, H_5), 3.76 and 3.72 (two m, 2H, CH_2), 3.72 (brs, 1H, H_5), 2.69 (br, 1H, OH), 2.51 (m, 1H, H_4), 1.46 (s, 9H), 1.34 (d, J = 8.9, 1H, H_{6syn}), 1.16 (dbr, J = 9.0, 2.4, 1H, H6anti), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 80.3, 71.1 (C_5), 65.5, 64.3 (C_1), 58.2 (C_3), 45.6 (C_4), 28.4, 26.4 (C_6), 25.7, 17.9, −5.06; HRMS *m/z* 366.2092, calcd for $C_{17}H_{33}NO_4SiNa$ (M + Na) 366.2071. The hydroxymethyl stereochemistry was confirmed by NOE and HSQC experiments. The H_{6syn} signal at δ 1.34 on irradiation enhances the CH_2 signals at δ 3.76 and 3.72. The H6anti signal at δ 1.16 on irradiation enhances the H_5 signal at δ 3.72.

N-Acetyl-3-*exo*-carboxymethyl-5-*syn*-(*tert*-butyldimethylsilyloxy)-2-azabicyclo[2.1.1]hexane (30)

According to the general procedure, to a solution of carbamate **27** (35 mg, 0.094 mmol) in CH_2Cl_2 (2 mL) there was added TFA (110 L, 1.413 mmol) at rt. The solution was stirred for 7 h and then solvent was removed in vacuo to afford 55 mg of crude amine as an orange oil. To the crude amine in CH_2Cl_2 (4 mL) there was added DMAP (35 mg, 0.283 mmol), and the solution was cooled to 0 °C. Acetyl chloride (20 L, 0.283 mmol) was added to the reaction mixture, which was maintained for 30 min at 0 °C and then brought to rt. After stirring overnight, the reaction mixture was diluted with CH_2Cl_2 (4 mL) and workup afforded after chromatography (prep TLC, 1:2 hexanes/ethyl acetate) 22 mg (75%) of **30** as a colorless oil at R_f = 0.41 (1:2 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ *4.69* (dt, J = 7.2, 1.7 Hz, 1H, H_1), 4.38 (s, 1H, H_3), 4.12 (dt, J = 7.0, 1.7 Hz, 1H, H_1), *4.26* (s, 1H, H_3), 3.87 (m, 1H, H_5), *3.82* (m, 1H, H_5), *3.79* (s, 3H), 3.75 (s, 3H), *2.93* (m, 1H, H_4), 2.87 (m, 1H, H_4), 2.05 (s, 3H), *2.00* (s, 3H), 1.73 (d, J = 9.1 Hz, 1H, H_6), *1.46* (d, J = 9.1 Hz, 1H, H_6), 1.28 (br, 2H, H_6), 0.85 (s, 9H), 0.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 and 171.7, 171.1 and 170.7, 71.5 and 70.8, 65.4 and 62.8, 58.0 and 56.2, 52.4 and 52.2, 48.4 and 47.4, 29.7, 25.6 and 25.5, 21.9 and 21.7, 17.8 and 17.8, −5.0 and −5.0, −5.2 and −5.2 (one carbon TBS); ^{1}H NMR (400 MHz, D_2O) δ 4.60 (br d, J = 7.2 Hz, 1H, H_1), 4.55 (s, 1H, H_3), 4.43 (br d, J = 7.0 Hz, 1H, H_1), 4.34 (s, 1H, H_3), 4.16 (m, 1H, H_5), 4.11 (m, 1H, H_5), 3.82 (s, 3H), 3.78 (s, 3H), 3.09 (m, 1H, H_4), 3.04 (m, 1H, H_4), 2.12 (s, 3H), 2.05 (s, 3H), 1.57 (d, J = 9.8 Hz, 1H, H_6), 1.48 (d, J = 9.8 Hz, 1H, H_6), 1.44 (d, J = 9.8 Hz, 1H, H_6), 1.36 (d, J = 9.8 Hz, 1H, H_6), 0.85 (s, 9H, both rotamers), 0.12 (s, 6H), 0.11 (s, 6H); HRMS m/z 314.1795, calcd for $C_{15}H_{28}NO_4Si$ (M + H) 314.1782. The major H_1 signal at δ 4.43 shows an NOE enhancement with the major acetyl at δ 2.12. The minor acetyl signal at δ 2.05 on irradiation does not show an NOE enhancement. Amide isomer ratios for **30** were determined by comparison of Ac and H_1 major/Ac and H_1 minor in $CDCl_3$ ($K_{T/C}$ = 1.36 ± 0.04, 57.7 ± 0.7% trans) and comparison of Ac peaks in D_2O ($K_{T/C}$ = 4.05 ± 0.08 , 80.2 ± 0.3% trans).

N-Acetyl-3-*exo*-carboxymethyl-5-*syn*-hydroxy-2-azabicyclo[2.1.1]hexane (8)

To a solution of silyl ether **30** (16 mg, 0.051 mmol) in THF (250 L) at 0 °C there was added a solution of tetrabutylammonium fluoride trihydrate (TBAF·$3H_2O$) (48 mg, 0.153 mmol) in THF (250 L). The reaction mixture was stirred at 0 °C for 30 min, warmed slowly to rt, and then stirred an additional 30 min. The solvent was removed in vacuo and chromatographed

(prep TLC, 1:9 MeOH/ethyl acetate) to afford 9 mg (89%) of alcohol **8** as a colorless oil at R_f = 0.41 (1:9 MeOH/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ *4.63* (dt, *J* = 6.8, 1.7 Hz, 1H, H_1), 4.41 (s, 1H, H_3), *4.37* (s, 1H, H_3), 4.20 (dt, *J* = 6.8, 1.7 Hz, 1H, H_1), 3.99 (m, 1H, H_5), *3.95* (m, 1H, H_5), *3.78* (s, 3H, OMe), 3.74 (s, 3H, OMe), *2.98* (m, 1H, H_4), 2.92 (m, 1H, H_4), 2.07 (s, 3H), *2.02* (s, 3H), 1.73 (d, *J* = 9.1 Hz, 1H, H_{6syn}), *1.46* (d, *J* = 9.1 Hz, 1H, H_{6syn}), 1.33 (dt, *J* = 9.1, 2.2 Hz, 1H, H6anti), *1.29* (dt, *J* = 9.1, 2.2 Hz, 1H, H6anti); ^{13}C NMR (100 MHz, $CDCl_3$) δ *172.6*, *171.4*, 171.3, 171.0, 71.4 and *70.4*, 65.3 and *62.8*, *58.1* and 55.9, *52.6* and 52.3, *47.3* and 46.8, 26.4 and *25.2*, 21.8 and *21.7*; ^{1}H NMR (400 MHz, D_2O) δ *4.62* (d, *J* = 6.8 Hz, 1H, H_1), *4.53* (s, 1H, H_3), 4.34 (d, *J* = 6.8 Hz, 1H, H_1), 4.35 (s, 1H, H_3), 4.10 (br, 1H, H_5), *4.06* (br, 1H, H_5), *3.83* (s, 3H), 3.78 (s, 3H), *3.09* (m, 1H, H_4), 3.03 (m, 1H, H_4), 2.12 (s, 3H), *2.05* (s, 3H), 1.61 (d, *J* = 9.5 Hz, 1H, H_{6syn}), 1.49 (br d, J = 9.5 Hz, 1H, H6anti), *1.45* (br d, *J* = 9.5 Hz, 1H, H6anti), *1.40* (d, *J* = 9.5 Hz, 1H, H_{6syn}); HRMS m/z 200.0923, calcd for $C_9H_{14}NO_4$ (M + H) 200.0917. The major acetyl signal (D_2O) at δ 2.12 on irradiation shows an NOE enhancement with the major H_1 at δ 4.34 and vice-versa. The trans/cis isomer ratio was determined to be $K_{T/C}$ = 1.20 ± 0.06 (54.4 ± 1.2 % trans by acetyl, H_3, H_6 and OMe peaks) in $CDCl_3$ and $K_{T/C}$ = 4.29 ± 0.23 (81.1 ± 0.9 % trans) in D_2O.

N-Acetyl-3-*exo*-carboxymethyl-5-*syn*-benzoyloxy-2-azabicyclo[2.1.1]hexane (31)

According to the general procedure, the *syn*-alcohol **8** (5mg, 0.025 mmol) was dissolved in dry CH_2Cl_2 (250 L), cooled to 0 °C and treated sequentially with dry triethylamine (15 L, 0.100 mmol), DMAP (4 mg, 0.028 mmol) and benzoyl chloride (6 L, 0.050 mmol). The reaction mixture was stirred for 30 min at 0 °C, allowed to come to rt, and then stirred for 3 h. Workup and chromatography (prep tlc: 4:1 ethyl acetate/hexanes) afforded 7 mg (92%) of *syn*-benzoate **31** as a colorless oil at R_f = 0.49 (4:1 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–7.37 (m, 5H), *5.04* (dt, *J* = 7.1, 1.7 Hz, 1H, H_1), 4.88 (s, 1H, H_3 or H_5), 4.55 (dt, *J* = 7.1, 1.7 Hz, 1H, H_1), 4.54 (s, 1H), *4.27* (s, 1H), *3.81* (s, 3H), 3.78 (s, 3H), 3.35 (m, 1H, H_4), 3.27 (m, 1H, H_4), 2.07– 2.01 (m, 4H, $COCH_3$ and H_{6syn}), *1.76* (d, *J* = 9.3 Hz, 1H, H_{6syn}), 1.66 (dt, *J* = 9.3, 2.2 Hz, 1H, H6anti), *1.60* (dt, *J* = 9.3, 2.2 Hz, 1H, H6anti); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.3 and *170.6*, 170.3, 165.5 and *165.1*, 133.7 and *133.6*, 129.7 and *129.6*, 128.7 and *128.6* (C on Ph, one carbon buried), 71.2 and *70.6*, 64.2 and *61.0*, *57.9* and 56.3, *52.7* and 52.5, *47.2* and 45.7, 27.9 and *26.4*, 21.6; ^{1}H NMR (400 MHz, D_2O) δ 7.98–7.89 (m, 2H), 7.73–7.66 (m, 1H), 7.57–7.46 (m, 2H), 4.99 (s, 1H, H_5), 4.96–4.92 (m, 2H, H_1 and H_5), 4.86–4.73 (under D_2O peak, m, 2H, H_1 and H_3 conformer), 4.54 (s, 1H, H_3), *3.85* (s, 3H), 3.81 (s, 3H), *3.46* (m, 1H, H_4), 3.40 (m, 1H, H_4), 2.09 (s, 3H), *2.03* (s, 3H), 1.89–1.75 (m, 2H, H6anti and its conformer and H_{6syn}), *1.65* (brd, *J* = 9.8 Hz, 1H, H_{6syn}); HRMS *m/z* found 326.0990, calcd for $C_{16}H_{17}NO_5Na$ (M + Na) 326.0999. NOE (C_6D_6:$CDCl_3$ 1:1): the major H_1 signal at δ 4.12 on irradiation enhances the major H_5 signal at δ 4.50 and the major $COCH_3$ signal at δ 1.81. The major $COCH_3$ signal at δ 1.81 on irradiation enhances the major H_1 signal at δ 4.12; the minor H_1 signal at δ 4.92 on irradiation sees no methyl signal. Noe (D_2O): the major acetyl signal at δ 2.09 on irradiation enhances the major H_1 signal at δ 4.78; the minor acetyl signal at δ 2.03 on irradiation enhances the minor H_3 signal at δ 4.71. $K_{T/C}$ = 4.08 ± 0.04 (80.3 ± 0.2% trans) was determined from relative integration of Ac peaks in $CDCl_3$ and $K_{T/C}$ = 3.92 ± 0.18 (79.7 ± 0.7% trans) in D_2O was determined from relative Ac/COOMe integrations. HRMS *m/z* found 326.0990, calcd. for $C_{16}H_{17}NO_5Na$ (M + Na) 326.0999.

N-(*tert*-Butoxycarbonyl)-3-*endo*- and 3-*exo*-carboxymethyl-5-*anti*-benzoyloxy-2-azabicyclo[2.1.1]hexane mixture (33 and 34)

Following the general procedure for lithiation, to carbamate **32** (1.0 g, 5.03 mmol) in dry diethyl ether (25 mL) with a positive pressure of argon at −78 °C there was added TMEDA (1.7 mL, 11.06 mmol) followed by s-BuLi in cyclohexane (7.9 mL, 11.06 mmol) dropwise

via syringe at −78 °C. After 4h at −45 to −50 °C the reaction mixture was then recooled to −78 °C. Excess CO_2 gas was blown through the flask for approximately 5 min, stirred at −78 °C for 30 min and then allowed to come to rt. Extraction with water (2 H 20 mL) followed by back-extraction of the combined water layers with ether (2 H 20 mL) afforded, after drying and removal of solvent, 440 mg (44%) of starting material **32**. The aqueous layer was acidified with dilute HCl until approximately pH = 3 and then was extracted with ethyl acetate (5 H 40 mL). The combined extracts were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated in vacuo to yield a light orange oil. The crude oil was then taken up in 1:1 mixture of hexanes and isopropanol (80 mL), trimethylsilyldiazomethane (1.7 mL, 3.38 mmol, 2.0 M solution in hexanes) was added under argon, and the reaction was stirred 12 h at rt. The solvent was removed in vacuo to afford 748 mg of crude ester as light orange oil. Since the mixture of hydroxyester components could not easily be separated, the crude alcohol was dissolved in dry CH_2Cl_2 (35 mL), cooled to 0 °C and treated sequentially with triethylamine (1.9 mL, 14.06 mmol), DMAP (380 mg, 3.09 mmol) and benzoyl chloride (820 L, 7.03 mmol). The reaction mixture was stirred 30 min at 0 °C, allowed to come to room temperature, and then stirred for 3 h. Workup and chromatography on silica gel (gradient, 10–20 % ethyl acetate in hexanes) afforded 508 mg (28%) (50% BORSM) of a mixture of 3- and 3′-methyl ester benzoates **33**/**34** as a light orange oil at R_f = 0.43 (4:1 hexanes/ethyl acetate). Based on proton integration (H_5), the ratio of the mixture is **49**/**51**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.01 (m, 4H), 7.62– 7.54 (m, 2H), 7.50–7.41 (m, 4H), 5.22 (br, 1H, H_5), 4.78 (br d, J = 7.0 Hz, 1H, H_5), 4.52 (br, 2H, $2H_1$), 4.41 (br, 1H, H_3), 4.35 (br, 1H, H_3), 3.80 (s, 3H), 3.77 (s, 3H), 3.15 (br, 2H, $2H_4$), 2.92 (br d, J = 7.5 Hz, 1H, H_{6anti}), 2.75 (br d, J = 8.4 Hz, 1H, H_{6anti}), 2.12 (t, J = 8.0 Hz, 1H, H_{6syn}), 1.72 (br, 1H, H_{6syn}), 1.46 (br s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 and 170.3, 166.0 and 166.0, 155.1 (br) and 153.9 (br), 133.4 and 133.3, 129.6 and 129.6 (2C), 128.5 and 128.5, 82.9, 80.6, 79.8, 62.6 (br), 61.1 (br), 60.2 (br), 58.4, 52.4, 52.3, 47.0 (br), 39.3, 33.9 (br), 28.3; HRMS *m/z* 384.1419, calcd for $C_{19}H_{23}NO_6Na$ (M + Na) 384.1418.

N-Acetyl-3-*endo*-carboxymethyl-5-*anti*-benzoyloxy-2-azabicyclo[2.1.1]hexane (35) and *N*-Acetyl-3-*exo*-carboxymethyl-5-*anti*-benzoyloxy-2-azabicyclo[2.1.1]hexane (36)

According to the general procedure, to a solution of a mixture of carbamates **33**/**34** (455 mg, 1.26 mmol) in dry CH_2Cl_2 (45 mL) was added TFA (970 L, 12.60 mmol) at rt. The solution was stirred for 6 h at rt under an argon balloon and then solvent was removed in vacuo to afford 785 mg of crude amine as an orange oil. To the crude amine in dry CH_2Cl_2 (60 mL) there was added DMAP (462 mg, 3.78 mmol), and the solution was cooled to 0 °C. Acetyl chloride (270 L, 3.78 mmol) was added to the reaction mixture that was maintained for 30 min at 0 °C and then brought to rt. After 3 h under an argon-filled balloon, workup and chromatography (1:4 hexanes/ethyl acetate) gave 179 mg (47%) of **35** as an orange oil at R_f = 0.38 (1:4 hexanes/ethyl acetate) and 130 mg (34%) of **36** as an orange oil at R_f = 0.28 (1:4 hexanes/ethyl acetate). For 3-*endo*-ester **35**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.01 (m, 2H), 7.63–7.57 (m, 1H), 7.51–7.43 (m, 2H), 5.28 (d, J = 7.3 Hz, 1H, H_5), *5.01* (d, J = 7.3 Hz, 1H, H_5), *5.00* (dd, J = 7.5, 1.4 Hz, 1H, H_1), 4.52 (dd, J = 7.5, 1.4 Hz, 1H, H_1), *4.51* (s, 1H, H_3), 4.45 (s, 1H, H_3), *3.87* (s, 3H), 3.81 (s, 3H), *3.28* (ddd, J = 7.4, 3.3, 0.9 Hz, 1H, H_4), 3.21 (ddd, J = 7.4, 3.3, 0.9 Hz, 1H, H_4), 3.02–2.93 (br, 1H, H6anti both conformers), 2.15 (s, 3H), *2.01* (s, 3H), 1.77 (dd, J = 7.8, 7.8 Hz, 1H, H_{6syn}), *1.72* (dd, J = 7.8, 7.8 Hz, 1H, H_{6syn}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 and *169.7*, 168.4, 166.0 and 165.9, 133.5 and *133.4*, 129.6 (2C), 128.5 and *128.1*, 79.7 and *79.2* (C_5), 63.6 and *61.1* (C_1), *60.7* and 58.9 (C_3), *52.8* and 52.5, *47.6* and 46.3, 39.5 and *38.8*, 21.4 and *21.1*; ^{1}H NMR (400 MHz, D_2O) δ 8.11–8.06 (m, 2H), 7.76–7.570 (m, 1H), 7.60–7.53 (m, 2H), 5.16 (d, J = 7.5 Hz, 1H, H_5), 4.*95* (d, J = 7.5 Hz, 1H, H_5), *4.90* (dd, J = 7.5, 1.7 Hz, 1H, H_1), *4.75* (dd, J = 7.5, 1.7 Hz, 1H, H_1), 4.75 (s, 1H, H_3), 4.62 (s, 1H, H_3), *3.91* (s, 3H), 3.86 (s, 3H), *3.39* (ddd, J = 7.3, 3.3, 1.2

Hz, 1H, H_4), 3.33 (ddd, *J* = 7.3, 3.3, 1.2 Hz, 1H, H_4), 3.14–3.09 (m, 1H, H6anti), *3.07–3.03* (m, 1H, H6anti), 2.21 (s, 3H), *2.06* (s, 3H), 1.90 (dd, *J* = 7.9, 7.5 Hz, 1H, H_{6syn}), *1.83* (dd, *J* = 7.9, 7.5 Hz, 1H, H_{6syn}); HRMS m/z 304.1182, calcd for $C_{16}H_{18}NO_5$ (M + H) 304.1179. For exo-ester **36**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.02 (m, 2H), 7.64–7.57 (m, 1H), 7.50– 7.44 (m, 2H), *4.96* (dd, *J* = 7.7, 1.8 Hz, 1H, $H_{1,}$), *4.76* (d, *J* = 7.4 Hz, 1H, H_5), 4.73 (d, *J* = 7.4 Hz, 1H, H_5), 4.55 (s, 1H, H_3), *4.50* (s, 1H, H_3), 4.46 (dd, *J* = 7.3, 1.9 Hz, 1H, H_1), *3.81* (s, 3H), 3.77 (s, 3H), *3.27* (ddd, *J* = 7.3, 3.3, 1.3 Hz, 1H, H_4), 3.20 (ddd, *J* = 7.3, 3.3, 1.3 Hz, 1H, H_4), 2.81 (dt, *J* = 8.5, 2.3, 2.3 Hz, 1H, H6anti), *2.78* (dt, *J* = 8.5, 2.3, 2.3 Hz, 1H, H6anti), 2.25 (dd, *J* = 8.5, 7.5 Hz, 1H, H_{6syn}), 2.16 (s, 3H), *2.02* (s, 3H), *2.00* (dd, *J* = 8.5, 7.5 Hz, 1H, H_{6syn}); ^{13}C NMR (100 MHz, $CDCl_3$) δ *169.7* and 169.6, 168.6, 166.1 and *166.0*, 133.6 and *133.5*, 129.7 (2C), 128.6, 82.7 and *82.3* (C_5), 63.8 and *60.7* (C_1), *59.6* and 57.5 (C_3), *52.7* and 52.4, *47.6* and 46.2, 34.5 and *33.2*, *21.7* and 21.5; ^{1}H NMR (400 MHz, D_2O) δ 8.12–8.07 (m, 2H), 7.75–7.70 (m, 1H), 7.60–7.54 (m, 2H), *4.92* (br, 1H, H_3), *4.89* (dd, *J* = 7.6, 1.8 Hz, 1H, $H_{1,}$), 4.85 (d, *J* = 7.6 Hz, 1H, H_5), 4.73 (dd, *J* = 7.4, 1.8 Hz, 1H, H_1), 4.65 (s, 1H, H_3), 3.82 (s, 3H), *3.77* (s, 3H), 3.39 (ddd, *J* = 7.3, 3.4, 1.1 Hz, 1H, H_4), 3.33 (ddd, *J* = 7.3, 3.4, 1.1 Hz, 1H, H_4), 2.94 (dt, *J* = 9.2, 2.4, 2.4 Hz, 1H, H6anti), *2.92* (dt, *J* = 9.2, 2.4, 2.4 Hz, 1H, H6anti), 2.21 (s, 3H), *2.08* (s, 3H), 2.08 (dd, *J* = 9.1, 7.8 Hz, 1H, H_{6syn}), *1.86* (dd, *J* = 9.3, 7.7 Hz, 1H, H_{6syn}); HRMS m/z 304.1181, calcd for $C_{16}H_{18}NO_5$ (M + H) 304.1179. Amide isomer ratios for **35** were determined by comparison of Ac major/ Ac minor in both solvents; the ratio in $CDCl_3$ is $K_{T/C}$ = 3.21 ± 0.03 (76.2 ± 0.1% trans isomer) and in D_2O $K_{T/C}$ = 4.98 ± 0.15 (83.3 ± 0.4% trans isomer). The amide isomer ratios for **36** were determined by comparison of acetyl peaks in $CDCl_3$ and COOMe peaks in D_2O. The amide ratio $K_{T/C}$ = 3.22 ± 0.09 (76.3 ± 0.5% trans isomer) in $CDCl_3$ and $K_{T/C}$ = 3.99 ± 0.04 (80.0 ± 0.2% trans isomer) in D_2O.

N-Acetyl-3-*endo*-carboxymethyl-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (9)

According to the general procedure, Et_3N (660 L, 4.70 mmol) was added to the benzoate **35** (95 mg, 0.31 mmol) in methanol (9 mL), and the solution was stirred at rt for 17 h under argon. Workup and chromatography (gradient, 0 to 6% MeOH in ethyl acetate) gave 54 mg (87%) of alcohol **9** as a colorless oil at R_f = 0.58 (5:1 ethyl acetate/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ *4.60* (dd, J = 7.3, 1.5 Hz, 1H, H_1), 4.58 (d, *J* = 7.1 Hz, 1H, H_5), 4.38 (s, 1H, H_3), *4.35* (d, J = 7.1 Hz, 1H, H_5), *4.34* (s, 1H, H_3), 4.14 (dd, *J* = 7.3, 1.5 Hz, 1H, H_1), *3.79* (s, 3H), 3.75 (s, 3H), 3.13 and *3.09* (m, 1H, H_4), *2.94* (ddd, J = 7.3, 3.3, 0.9 Hz, 1H, H6anti), 2.87 (ddd, *J* = 7.3, 3.3, 0.9 Hz, 1H, H_{6anti}) 2.09 (s, 3H, $COCH_3$), *1.95* (s, 3H, $COCH_3$), 1.69 (dd, *J* = 7.7, 7.3 Hz, 1H, H_{6syn}), *1.64* (dd, J = 7.7, 7.3 Hz, 1H, H_{6syn}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.6, 77.2 and *76.6*, 65.2 and *62.2* (C_1), *61.1* and 59.1 (C_3), *52.4* and 52.0, *48.3* and 47.3, 39.1 and *38.3*, 21.0 and *20.8*; ^{1}H NMR (400 MHz, D_2O) δ *4.78* (s, 1H, H_3), *4.54* (dd, *J* = 7.6, 1.7 Hz, 1H, $H_{1,}$), 4.39 (d, *J* = 7.1 Hz, 1H, H_5), 4.50 (s, 1H, H_3), 4.38 (dd, *J* = 7.4, 1.8 Hz, 1H, H_1), 4.22 (d, *J* = 7.3 Hz, 1H, H_5), *3.84* (s, 3H), 3.80 (s, 3H), 3.05 (brm, two conformers, 1H, H_4), 2.96 (ddd, *J* = 7.3, 3.3, 1.2 Hz, 1H, H6anti), 2.14 (s, 3H), *2.00* (s, 3H), 1.82 (two d, *J* = 7.3, 7.3 Hz, 1H, H_{6syn}), *1.76* (two d, *J* = 7.3, 7.3 Hz, 1H, H_{6syn}); NOE: The major acetyl signal at δ 2.14 on irradiation enhances the major H_1 at δ 4.38 and vice-versa. $K_{T/C}$ = 2.59 ± 0.07 (72.1 ± 0.6 trans, $CDCl_3$) by relative Ac and COOMe integrations and $K_{T/C}$ = 4.72 ± 0.11 (82.5 ± 0.4% trans, D_2O) by relative line fit acetyl integrations. HRMS *m/z* 222.0740, calcd for $C_9H_{13}NO_4Na$ (M + Na) 222.0737.

N-Acetyl-3-*exo*-carboxymethyl-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (12).[10]

Following the general procedure, Et_3N (1.0 mL, 7.43 mmol) was added to the benzoate **36** (150 mg, 0.50 mmol) in methanol (15 mL), and the mixture was stirred at rt for 17 h under argon. Workup and chromatography afforded 84 mg (85%) of alcohol **12** as an off-white solid at R_f = 0.59 (5:1 ethyl acetate/MeOH). NOE (D_2O): the major acetyl signal at δ 2.14 on irradiation enhances the major H_1 at δ 4.38 and vice-versa; the minor acetyl signal at δ

2.00 on irradiation enhances no proton. The major H_3 at δ 4.50 on irradiation enhances no proton. $K_{T/C}$ = 2.15 ± 0.02 (68.2 ± 0.2 from the acetyl methyls, H_3, and COOMe peaks, $CDCl_3$) and $K_{T/C}$ = 4.04 ± 0.10 (80.2 ± 0.4 from H_1, H_5, Ac, and OMe peaks, D_2O).

Alternative synthesis of *N*-Acetyl-3-*endo*-carboxymethyl-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (7) from alcohol 9.[10]

Bis(2-methoxyethyl)aminosulfur trifluoride (39 mg, 0.176 mmol) was added dropwise via syringe to a solution of alcohol **9** (14 mg, 0.070 mmol) in dry CH_2Cl_2 (3 mL) under argon at −78 °C. The mixture was stirred for 2 h at rt and then heated at reflux for 8 h. The reaction mixture was quenched with water (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 H 2 mL). The organic extracts were combined and washed with brine (2 mL), dried over Na_2SO_4, and filtered. Removal of the solvent in vacuo and chromatography (prep tlc, 3% MeOH in EtOAc) afforded 8 mg (57%) of fluoride **7** as a light yellow oil at R_f = 0.44 (3% MeOH in EtOAc); ^{19}F NMR (282 MHz, $CDCl_3$)δ −219.0 (d, J = 62 Hz), *−221.9* (d, J = 61 Hz); ^{19}F NMR (376 MHz, D_2O) δ −211.5 and *−213.7* (5.2:1 ratio). Noe (D_2O): The major acetyl signal at δ 2.16 on irradiation enhances the major H_1 at δ 4.62, and the minor acetyl signal at δ 2.00 on irradiation enhances the minor H_3 at δ 4.83. $K_{T/C}$ = 3.52 ± 0.08 (77.9 ± 0.4% trans by integration of major/minor H_5, OMe, or acetyl methyls, $CDCl_3$) and 5.11 ± 0.13 (83.6 ± 0.3 % trans by integration of major/minor Ac and COOMe protons, D_2O). In $CDCl_3$, the characteristic downfield acetyl peak at δ 2.11 for the trans isomer (major) and the upfield peak at δ 1.96 for the cis isomer were used to assign the trans amide isomer as major. Slightly higher trans/cis isomer ratios for **7** of 3.7 (79% trans) in $CDCl_3$ and 5.6 (85% trans) in D_2O were determined by fluorine NMR.

Alternate Synthesis of *N*-Acetyl-3-*exo*-carboxymethyl-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (11) from Alcohol 12.[10]

Fluoride **11** was prepared according to the published procedure; ^{19}F NMR (282 MHz, $CDCl_3$) δ −212.7 (d, J = 62 Hz) and *−214.1* (d, J = 62 Hz); ^{19}F NMR (376 MHz, D_2O) δ −205.8 and *−206.7*. Noe (D_2O): The major acetyl signal at δ 2.16 on irradiation enhances the major H_1 at δ 4.59. $K_{T/C}$ = 2.56 ± 0.02 (71.9 ± 0.1 % trans calculated from H_5 major at δ 4.72 vs minor at δ 4.68, $CDCl_3$) or 2.9 (74% trans by F integration, $CDCl_3$) and 3.69 ± 0.11 (78.7 ± 0.5% trans by integration of major/minor H_5 peaks, D_2O) or 4.2 (81% trans by F integrations, D_2O).

Supplementary Material

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Acknowledgments

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Morokuma, K.; Voth, GA.; Salvador, P.; Dannenberg, JJ.; Zakrzewski, VG.; Dapprich, S.; Daniels, AD.; Strain, MC.; Farkas, O.; Malick, DK.; Rabuck, AD.; Raghavachari, K.; Foresman, JB.; Ortiz, JV.; Cui, Q.; Baboul, AG.; Clifford, S.; Cioslowski, J.; Stefanov, BB.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, RL.; Fox, DJ.; Keith, T.; Al-Laham, MA.; Peng, CY.; Nanayakkara, A.; Challacombe, M.; Gill, PMW.; Johnson, B.; Chen, W.; Wong, MW.; Gonzalez, C.; Pople, JA. Geometries and energies were calculated with B3LYP/6-311+G(2d,p)//HF/6-31G(d) using Gaussian 03. Revision E.01. Gaussian, Inc.; Wallingford CT: 2004.

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16. These results can be contrasted with a finding of *no effect* upon $K_{T/C}$ values in dioxane at 37 °C upon *O*-acylation or *O*-trifluoroacylation of Hyp **2** or hyp **5**. (ref. 5c).
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20. For ex-MetFlp **6** (td) δ = −22.18° (See ref. 19). In ex-Flp **1** the innate flexibility of the pyrrolidine ring prevents observation of the F–N lone-pair interaction seen in **6**.[5a] Idealized C^{γ}-exo puckers are therefore not readily accessible for the more flexible Flp **1** because the molecule can distort to avoid the fluorine)(nitrogen lone pair repulsive interaction..
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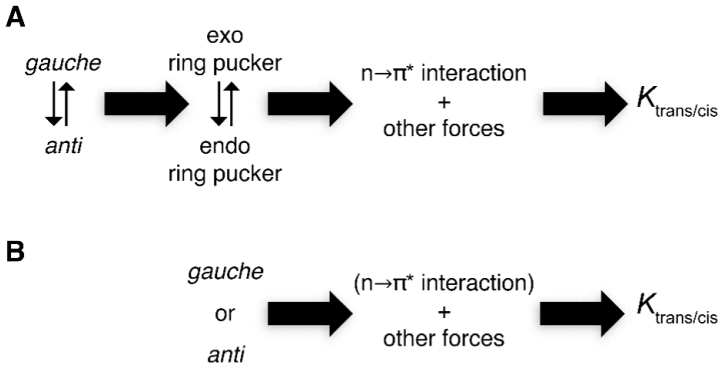


Figure 1.

(A) The relationship between ring conformations and $K_{trans/cis}$ in proline derivatives. (B) The relationship between substituent orientation (gauche or anti) and $K_{trans/cis}$ in conformationally constrained proline derivatives.

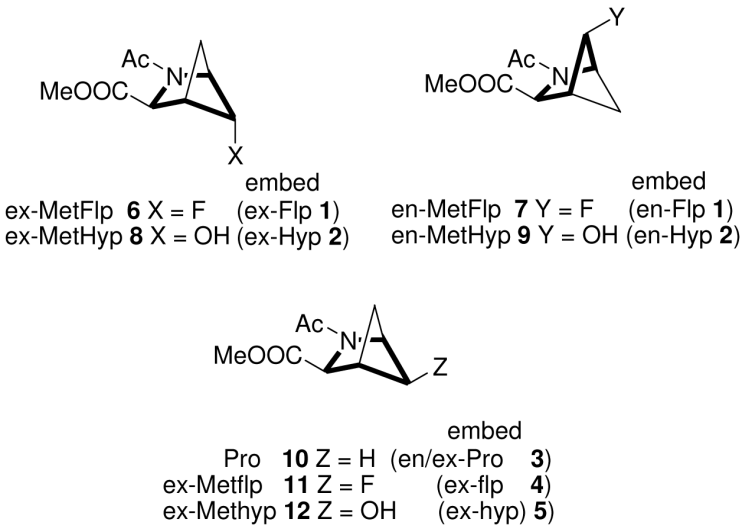


Figure 2.
Structures of methanoproline mimics **6-12** showing embedded prolines **1-5**.

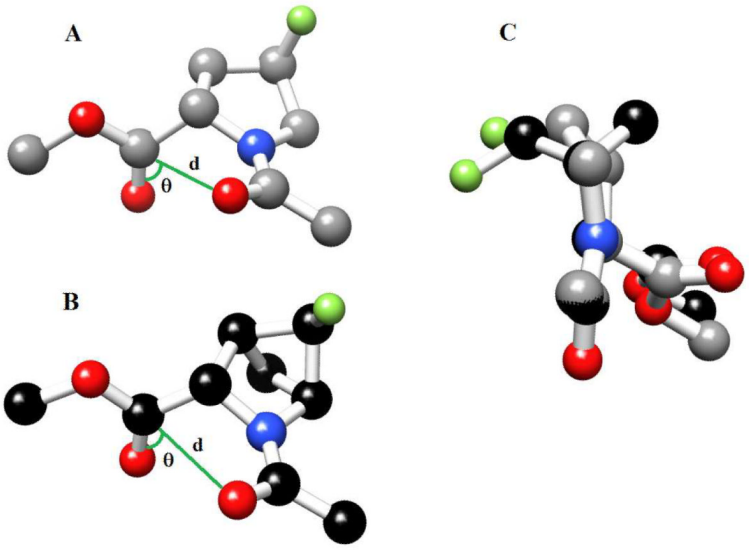
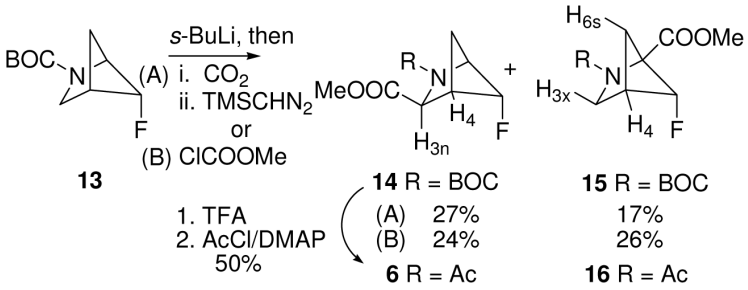
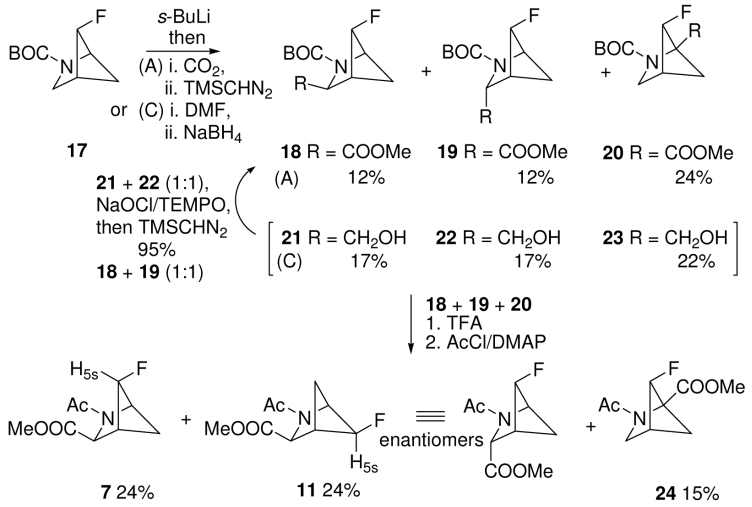


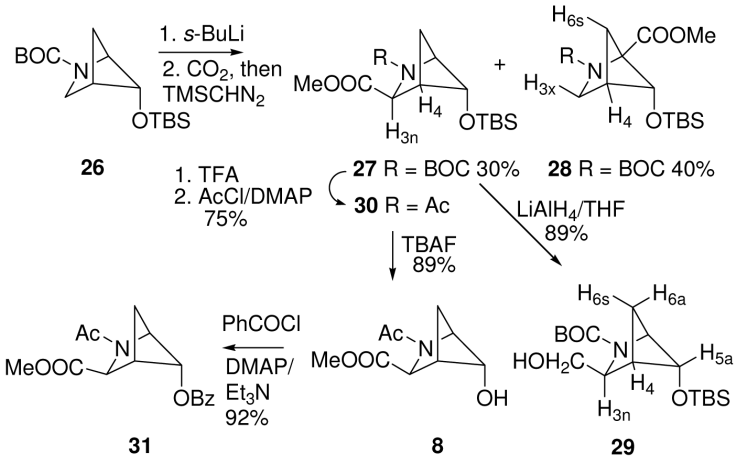
Figure 3.
Calculated structures of ex-Flp **1** (A), ex-MetFlp **6** (B) and overlapped ex-Flp **1** and ex-MetFlp **6** (C) in their trans distal conformations.



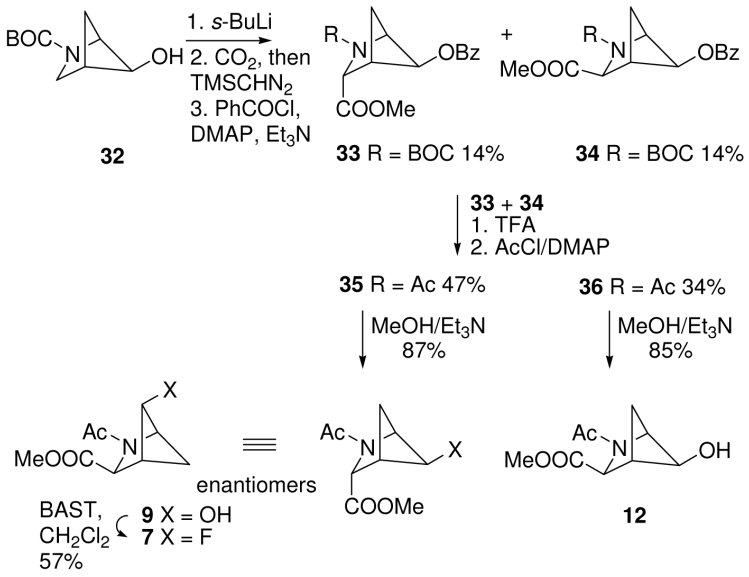
Scheme 1.
Synthetic Route to ex-MetFlp 6.



Scheme 2.
Synthetic Routes to en-MetFlp 7 and ex-Metflp 11.



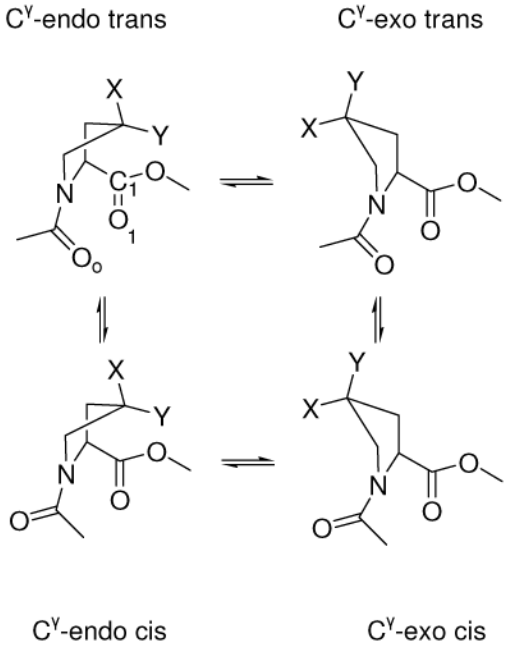
Scheme 3.
Synthetic Route to ex-MetHyp 8.



Scheme 4.
Synthetic Route to en-MetHyp 9 and ex-Methyp 12.

Table 1

Amide Conformational Preferences for N-Acetyl Substituted-Proline Methyl Esters in Dioxane (25 °C).[8b]



compound	X	Y	$K_{T/C}$ [a]	ring pucker[b]
Flp[c] **1**	F	H	6.7	86% exo
Hyp[d] **2**	OH	H	6.1	
Pro **3**	H	H	4.6	66% endo
flp[e] **4**	H	F	2.5	95% endo
hyp[f] **5**	H	OH	2.4	

[a] Data collected in D_2O (see ref. 8b). Methyl ester derivatives of prolines were employed for these analyses to avoid γ-turn formation, as described previously by Gellman and co-workers (see ref. 9a). The esters are arbitrarily drawn in the distal conformation with the OMe of the ester directed away from the amide nitrogen; proximal has the OMe directed toward the nitrogen.

[b] Data collected in dioxane (see ref. 5b).

[c] Flp = N-acetyl-(2S,4R)-4-fluoroproline.

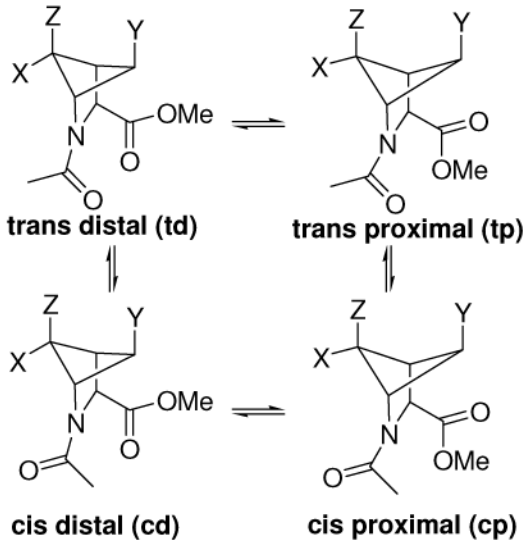
[d] Hyp = N-acetyl-(2S,4R)-4-hydroxyproline.

[e] flp = N-acetyl-(2S,4S)-4-fluoroproline.

[f] hyp = N-acetyl-(2S,4S)-4-hydroxyproline.

Table 2

Selected Calculated Structural Parameters for the Major Contributing Conformers of MetPro Derivatives.[a]



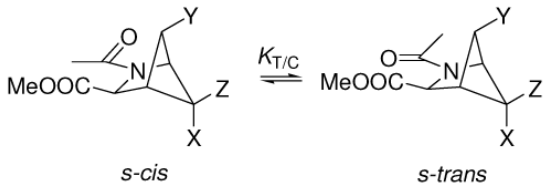
entry	compound	X	Y	Z	isomer	n→π* (kcal/mol)[b]
1	ex-MetFlp **6**	F	H	H	td	0.13
2	en-MetFlp **7**	H	F	H	td	0.38
3	ex-MetHyp **8**	OH	H	H	td	0.68
4	en-MetHyp **9**	H	OH	H	td	0.35
5	MetPro **10**	H	H	H	td	0.24
6	ex-Metflp **11**	H	H	F	td	0.30
7	ex-Methyp **12**	H	H	OH	td	0.25

[a]Calculated using geometry calculation HF/6-31G(d) and single point energy calculation at B3LYP/6-311+G(2d,p).

[b]The value is the sum of interactions of the amide oxygen p and sp lone pair interactions with the ester carbonyl carbon. A 0.01 kcal/mol interaction minimum value was reported.

Table 3

$K_{T/C}$ of Methanoproline and Diverse Derivatives.



					$K_{T/C}$[a] (trans %)	
entry	**compound**	**X**	**Y**	**Z**	**$CDCl_3$**	**D_2O**
1	ex-MetFlp **6**	F	H	H	2.0[b] (67)	4.6[c] (82)
2	en-MetFlp **7**	H	F	H	3.5[d] (78)	5.1[e] (84)
3	ex-MetHyp **8**	OH	H	H	1.2 (54)	4.3 (81)
4	en-MetHyp **9**	H	OH	H	2.6 (72)	4.7 (83)
5	MetPro **10**	H	H	H	2.4[f] (71)	3.7[g] (79)
6	ex-Metflp **11**	H	H	F	2.6[h] (72)	3.7[i] (79)
7	ex-Methyp **12**	H	H	OH	2.2[j] (68)	4.0[k] (80)
8	ex-MetHyp-X **30**	OTBS	H	H	1.4 (58)	4.1 (80)
9	ex-MetHyp-X **31**	OBz	H	H	4.1 (80)	3.9 (80)
10	en-MetHyp-Y **35**	H	OBz	H	3.2 (76)	5.0 (83)
11	ex-Methyp-Z **36**	H	H	OBz	3.2 (76)	4.0 (80)

[a] Values of $K_{T/C}$ measured at 25 °C using ^1H NMR integrated intensities were used to calculate the trans preferences, range ± 1.5 %.

[b] By ^{19}F NMR integrations $K_{T/C}$ = 2.1 (68% trans).

[c] The value obtained from ^{19}F NMR integrations 4.0 (80% trans).

[d] By ^{19}F NMR integrations $K_{T/C}$ = 3.7 (79% trans).

[e] By ^{19}F NMR integrations $K_{T/C}$ = 5.6 (85% trans).

[f] This work; ref 10 value by ^{13}C NMR $K_{T/C}$ = 2.4 (71% trans).

[g] This work; ref 10 value by ^{13}C NMR $K_{T/C}$ = 3.5 (78% trans).

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[h] By ^{19}F NMR integrations 2.9 (74% trans), prior report (ref. 10), $K_{T/C}$ = 2.7 (73% trans).

[i] By ^{19}F NMR integrations $K_{T/C}$ = 4.2 (81% trans), prior report (ref. 10) $K_{T/C}$ = 3.5 (78% trans).

[j] Prior report by ^{13}C NMR integration (ref. 10) $K_{T/C}$ = 2.4 (71% trans).

[k] Prior report by ^{13}C NMR integration (ref. 10) $K_{T/C}$ = 3.6 (78% trans). Values in ref. 10 were measured in D_2O:CD_3OD ~ 4:1.

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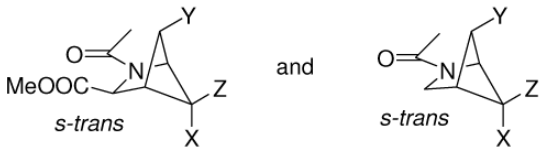
Table 4

Methanoproline–Methanopyrrolidine Relative Trans Amide Preferences.[a]



Metpro 6-12 **Metpyr 37-41**

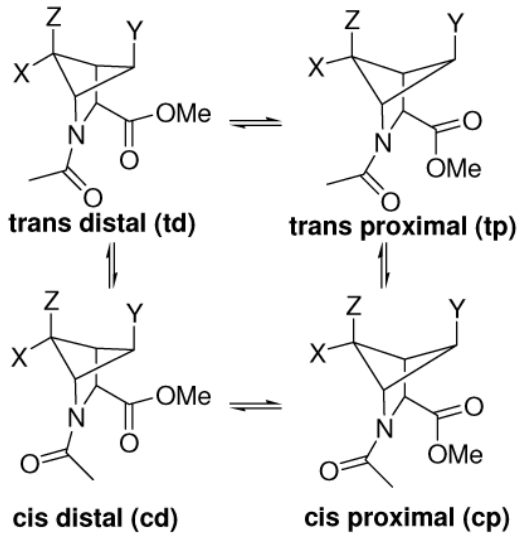
entry	MetPro Metpyr	X	Y	Z	Δ trans[a] D_2O	change (%)[b]	Δ trans[a] $CDCl_3$	change (%)[b]
1	**6** and **37**	F	H	H	29	55	19	40
2	**7** and **38**	H	F	H	29	53	24	44
3	**8** and **39**	OH	H	H	27	50	11	26
4	**9** and **40**	H	OH	H	29	54	21	41
5	**10** and **41**	H	H	H	25	46	19	37
6	**11** and **38**	H	H	F	24	44	18	33
7	**12** and **40**	H	H	OH	26	48	17	33

[a] Δ trans = % trans MetPro − % trans Metpyr. Trans isomer ratios for methanopyrrolidines are from reference 13. Methanoproline trans isomer ratios are from Table 3. See Supporting information.

[b] (%) = the percentage increase in trans isomer ratio when Δ trans is compared to % trans for Metpyr.

Table 5

Selected Calculated Structural Parameters for the Major Contributing Conformers of Methanoproline Derivatives.[a]



entry	compound	X	Y	Z	isomer	mole[b] fraction	μ[c] (D)	O…C=O[d] angle (θ)	O…C=O[e] distance (pm)
1	ex-MetFlp **6**	F	H	H	**td**	**0.52**	4.6	97.2°	322
					tp	0.23	5.8	130.3°	327
					cp	0.06	3.4		
2	en-MetFlp **7**	H	F	H	**td**	**0.70**	2.5	96.4°	309
					tp	0.15	3.6	123.9°	312
3	ex-MetHyp **8**	OH	H	H	**td**	**0.57**	2.8	90.7°	296
					tp	0.09	5.2	123.1°	300
					cp	0.08	1.8		
4	en-MetHyp **9**	H	OH	H	**td**	**0.74**	3.6	96.5°	310
					tp	0.17	4.0	128.8°	318
5	MetPro **10**	H	H	H	**td**	**0.56**	4.3	94.6°	313
					tp	0.17	4.9	127.4°	317

entry	compound	X	Y	Z	isomer	mole[b] fraction	μ^c (D)	O…C=O[d] angle (θ)	O…C=O[e] distance (pm)
					cp	0.09	2.5		
6	ex-Metflp **11**	H	H	F	**td**	**0.75**	2.3	92.9°	310
					tp	0.12	3.9	127.3°	314
7	ex-Methyp **12**	H	H	OH	td	0.08	3.6	94.1°	310
					tp	0.34	3.8	128.8°	317
					cd	**0.53**	4.3		

[a] Geometries were optimized with HF/6-31G(d) and energies were then obtained with single point calculations using B3LYP/6-311+G(2d,p). See ref. 11.

[b] Only those cis conformers which are major or with μ smaller than the major trans conformer are listed (see: Supporting Information).

[c] Calculated dipole moment.

[d] Angle for three given atoms .

[e] Interatom amide carbonyl oxygen to ester carbon distance.