Published in final edited form as:
J Org Chem. 2011 May 20; 76(10): 3626–3634. doi:10.1021/jo200117p.

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

Grant R. Krow[*,†], **Matthew D. Shoulders**[‡], **Ram Edupuganti**[†], **Deepa Gandla**[†], **Fang Yu**[†], **Matthew Sender**[†], **Philip E. Sonnet**[†], **Michael J. Zdilla**[†], **Charles DeBrosse**[†], **Kevin C. Cannon**[§], **Charles W. Ross III**[đ], **Amit Choudhary**[≠], and **Ronald T. Raines**[‡]
Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania 19486-004, Department of Chemistry, Penn State Abington, Abington, Pennsylvania, 19001, and the Departments of Chemistry and Biochemistry, University of Wisconsin–Madison, Madison, Wisconsin 53706

Abstract

N-Acetylmethanopyrrolidine 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^{β}-*gauche* and C^{β}-*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 $K_{T/C}$ 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 a trans-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.

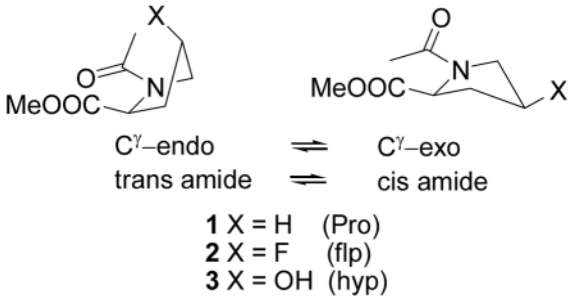
Introduction

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]

Corresponding Author: grkrow@temple.edu.
[†]Department of Chemistry, Temple University
[đ]Department of Medicinal Chemistry, Merck Research Laboratories
[§]Penn State Abington
[‡]Departments of Chemistry and Biochemistry, University of Wisconsin–Madison
[≠]Graduate Program in Biophysics, University of Wisconsin–Madison.

ASSOCIATED CONTENT

Supporting Information. Coordinates of optimized geometries, selected angles, and energy calculations for **9** and **10b–13b**; data from the X-ray diff raction 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.



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^{γ} experiences a large out-of-plane displacement are major,[7] and we refer to them as C^{γ}-endo (C^{γ}-pucker toward the ester) and C^{γ}-exo (C^{γ}-pucker away from the ester. Substituents at C^{γ}, as in (2*S*, 4*S*)-4-fluoroproline **2** (flp), 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 for 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^{γ}-exo and C^{γ}-endo ring puckers. The substituted *anti*-4-fluoromethanoproline (Metflp) **5** and *anti*-4-hydroxymethanoproline (Methyp) **6**, when viewed from the perspective of the substituent-bearing bridges, are pyrrolidines (bolded bonds) with constrained C^{γ}-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. 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 indentify unresolved issues associated with using methanopyrrolidines **4**–**6** as mimics of pyrrolidines **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 value–added 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) **14–15**, whose idealized C^{γ} 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) **16–17**, related to the biologically relevant Hyp **9**. A possible synthetic approach to methanoprolines could utilize as key synthons the methanopyrrolidines **10a–13a**, or related *O*-protected derivatives.

Herein, we describe 1,2-dihydropyridine-based syntheses of Metpyr **7** as well as *N*-acetyl-5-*syn*- and 5-*anti*-F(OH)-substituted Metpyrs **10b**–**13b**. The configurational preferences

determed for these amides reveal that only small inherent trans/cis amide biases accompany the use of methanoprolines as idealized C^{γ}-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 fluoroalcohol **18** to the thionocarbonate **19** using phenylchlorothionocarbonate[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**. In the alternative 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-Metpyr **11a** was synthesized from 1,2-dihydropyridine photoproduct **21** by addition of BrF accompanied by rearrangement as shown in Scheme 3.[14,15] The 5-*anti*-bromo,6-*anti*-fluoro azabicycle **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 ^1H NMR W-plan coupling between bridgehead proton H_1 at δ 4.44 with H_4 at δ 2.92 ($J_{1,4}$ = 6.8 Hz) and a geminal H_3 proton at δ 3.41 (d, $J_{3,3'}$ = 11.3 Hz) that is not further coupled to H_4. The singlet at δ 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 δ 4.77 identifies H_6 as *anti*. With the crucial *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*-acylbenzoate[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 benzoyloxy-methanopyrrolidines in Figure 2. Amide trans/cis ratios show in Table 2 were obtained by integration of nonoverlapping ^1H or ^{19}F NMR peaks. The percentages of trans isomers obtained by separate ^1H 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 ^1H 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 the *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 2–3) 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 MetPyr 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 *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 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 *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]

Conclusion

N-Acetylmethanopyrrolidine and its 5-*syn*/5-*anti*-F(OH) derivatives have been synthesized from pyridine via a 1,2-dihydropyridine photoproduct. MetPyr **7** has only a slight trans amide conformer preference in both aprotic $CDCl_3$ and polar protic D_2O solvents. Introduction of 5-*syn*(*gauche*)/*anti*-F or 5-*syn*/*anti*-OH groups in **10b–13b** has little influence on the small equilibrium trans preferences in D_2O solvent. In $CDCl_3$ trans amides continue to be slightly favored for the anti isomers, *anti*-F **11b** and *anti*-OH **13b**; however, there is a small selection favoring cis amides with *syn*-F **10b** and *syn*-OH **12b**. It has been shown that *O*-benzoylation enhances trans amide preferences in $CDCl_3$ for both *syn* and *anti* 5-hydroxymethanopyrrolidines. 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,5f]

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 ring preferences. This is confirmation of findings for the stereoisomers Metflp **5** and Methyp **6**[9] that indicated the remote *anti* heteroatom has little additional effect upon trans amide preferences.

For the four possible 5-substituted fluoro and 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 value–added contribution to trans amide preferences by α-ester substituents when other methanoprolines are synthesized. The *N*-BOC-MetPyr **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^{γ}-exo and C^{γ}-endo conformations. By introducing substituents into stereochemically defined positions of methanoprolines, insights may be gained about their influence upon 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 $C\underline{H}Cl_3$ δ 7.26, 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 run versus 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 non-overlapping ^{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) there 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 stirring 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, 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) 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 sees the acetyl signal at δ 2.07 and the major H_3 signal at δ 3.36 on irradiation sees 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, H1)*, 4.25 (dt, *J* = 6.9, 1.8 Hz, 1H, H_1), 3.39 (s, 2H, H_3), *3.38 (s, 2H, H3)*, 2.89 (m, 1H, H_4), *2.06 (s, 3H, COCH3)*, 2.01 (s, 3H, $COCH_3$), 1.98 (m, 2H, H_{5anti}), *1.93 (m, 2H, H5anti)*, 1.43 (m, 2H, H_{5syn}), *1.33 (m, 2H, H5syni)*; ^{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) there was 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 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 hr 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 hr 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 the reaction 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 stirring for 3h 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) δ 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, $CDCl_3$) δ −177.2 and −177.6 (ratio 1:1.16); ^{19}F NMR (376 MHz, D_2O) δ −176.9 (br, overlapping conformers). ^{1}H NMR NOE ($CDCl_3$) Pulse δ 4.33 ppm (minor H_1) hits δ 2.09, 4.57, 1.38; pulse δ 4.88 (major H_1) hits δ 4.46 (H_5 major), 1.33; NOE (D_2O) pulse δ 1.97 hits δ 3.55 and 4.57; and pulse δ 2.04 hits δ 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 μL, 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) and washed with $NaHCO_3$ (15 mL), 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) there was added *n*Bu_3SnH (263 μL, 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) there was added $Pd(OH)_2$ (15 mg) followed by $(BOC)_2O$ (47 mg, 2.15 mmol). After stirring at RT for 2 h under hydrogen there was obtained 25 mg (71%) of **11a** at R_f = 0.39 (1:1 hexane/ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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** at 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, $CDCl_3$) δ 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, $CDCl_3$) δ −206.1 and −206.8 (ratio = 1.3:1.0); ^{19}F NMR (376 MHz, D_2O) −205.2 and −206.8 (ratio = 1.0:0.79); ^{1}H NMR (500 MHz, D_2O) δ 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 δ 2.03 hits δ 3.62 (H_3 minor); pulse δ 2.08 (pulls 2.03 into pulse) hits δ 3.62, 4.47 (H_1 major). NOE ($CDCl_3$): pulse δ 2.02 hits δ 3.48; pulse δ 2.06 (pulls 2.02 into pulse) hits δ 4.25 (major H_1), δ 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 at R_f = 0.44 (2:3 ethyl acetate/hexanes) (Unreacted $HgBr_2$ is UV active, NMR blind and separation was difficult); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, H1)*, 3.57 (s, 1H, H_5), *3.58–3.51 (m, 3H, 2H3 and H5)*, 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, H4)*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 at R_f = 0.44 (1:5 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 5.21–5.00 (m, 2H), *4.67 (br s, 1H, H6)*, 4.65 (br s, 1H, H_6), *4.44 (dd, J = 6.9, 1.4 Hz, 1H, H1)*, 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) was added $(TMS)_3SiH$ (440 μL, 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 at 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, H1)*, 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, H3)*, 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, H6anti)*, 1.20 (d, J = 8.1 Hz, 1H, H_{6syn}), *1.17 (d, J = 8.1 Hz, 1H, H6syn)*, 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 at 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, H1)*, 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, H3)*, 3.31 (d, J = 8.3 Hz, 1H, H_3), *3.13 (d, J = 8.3 Hz, 1H, H3′)*, 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, H6anti)*, 1.21 (m, 1H, H_{6anti}), 1.56 (d, J = 8.9 Hz, 1H, H_{6syn}), *1.13 (d, J = 8.9 Hz, 1H, H6syn)*, 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 indry CH_2Cl_2 (2.5 mL). The solution was cooled to 0 °C and treated sequentially with triethylamine (115 μL, 0.817 mmol), DMAP (22 mg, 0.180 mmol) and benzoyl chloride (40 μL, 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) was added Bu_3SnH (285 μL, 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 colored oil at 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) there 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 μL, 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 sees major H_1 at *δ* 4.50. The minor acetyl signal at *δ* 2.05 on irradiation sees minor H_3 at *δ* 3.40. NOE (500 MHz, D_2O): the major acetyl signal at *δ* 2.03 on irradiation sees the major H_1 at *δ* 4.71. The minor acetyl signal at *δ* 2.05 on irradiation sees 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 μL, 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 removing the solvent *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 at 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 $C_7H_{11}NO_2Na$ (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 *δ* 4.16 on irradiation sees the minor $COCH_3$ at *δ* 2.04 and vice versa. NOE (500 MHz, D_2O): the major H_1 resonance at *δ* 4.37 on irradiation sees the major $COCH_3$ at *δ* 2.08. The minor H_3 resonance at *δ* 3.48 on irradiation sees the minor $COCH_3$ at *δ* 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 colored oil at R_f = 0.44 (1:1 ether/hexanes); (Italics denote minor rotamer peaks.) ^{1}H NMR (400 MHz, $CDCl_3$)*δ* 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, $CDCl_3$) δ 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 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 colored oil at R_f 0.50 (2:1 ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$)*δ* 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, $CDCl_3$) δ 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 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 at R_f = 0.32 (2:3 ethyl acetate/hexanes); mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$)δ 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, $CDCl_3$) δ155.7, 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 μL, 2.133 mmol), DMAP (57 mg, 0.469 mmol) and benzoyl chloride (125 μL, 1.067 mmol). The mixture was stirred for 30 min at 0 °C and 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 at R_f = 0.54 (4:1 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$)δ 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, $CDCl_3$) δ 166.3, 155.6, 1333, 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 μL, 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 μL, 1.068 mmol) was added to the reaction mixture that was maintained for 30 min at 0 °C and then brought to RT. After stirring 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, 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 at R_f = 0.22 (1:9 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$)δ 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, $CDCl_3$) δ *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 μL, 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 removing the solvent *in vacuo*, crude was chromatographed (9:1 ethyl acetate/MeOH) to afford 23.6 mg (79%) of alcohol **13b** as a colorless oil at R_f = 0.26 (9:1 ethyl acetate/MeOH); (Italics denote minor rotamer peaks) ^{1}H NMR (400 MHz, $CDCl_3$)δ 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, $CDCl_3$) δ 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)*δ 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 *δ* 2.01 on irradiation sees the major H_1 at *δ* 4.04. The minor acetyl signal at *δ* 1.98 on irradiation sees the minor H_3 at *δ* 3.40. NOE (D_2O): the major acetyl signal at *δ* 2.09 on irradiation sees the major H_1 at δ 4.29. The minor acetyl signal at *δ* 2.06 on irradiation sees the minor H_3 at *δ* 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)*δ* 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 *δ* 2.10 on irradiation sees the major H_1 at *δ* 4.41 and vice-versa. The minor H_1 signal at *δ* 4.89 on irradiation sees no proton; NOE (D_2O): the major acetyl signal at *δ* 2.17 on irradiation sees the major H_1 at *δ* 4.66. The minor acetyl signal at *δ* 2.13 on irradiation sees the H_3 signal *δ* 3.80 and the H_3 signal *δ* 3.75. $K_{T/C}$ = 61/39 ($CDCl_3$) based on H_1 and 56/44 (D_2O) based on H_3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support was provided by the National Science Foundation (CHE 0515635) and (DGE-0841377). M.D.S. was supported by a U.S.A. Department of Homeland Security Graduate Fellowship; MS was supported by a Der Min Fan Fellowhip. We thank Alex Shaffer and Zilun Hu for assistance and Hans Reich and David Dalton for helpful discussions.

References

1. (a) Lu KP, Finn G, Lee TH, Nicholson L. Nat Chem Biol. 2007; 3:619–629. [PubMed: 17876319] (b) Dugave C, Demange L. Chem Rev. 2003; 103:2475–2532. [PubMed: 12848578] (c) Fischer G. Chem Soc Rev. 2000; 29:119–127.(d) Andreotti AH. Biochemistry. 2003; 42:9515–9542. [PubMed: 12911293] (e) Wedemeyer WJ, Welker E, Scheraga HA. Biochemistry. 2002; 41:14637–14644. [PubMed: 12475212]

2. (a) Lummis SCR, Beene DL, Lee LW, Lester HA, Broadhurst RW, Dougherty DA. Nature. 2005; 438:248–252. [PubMed: 16281040] (b) Lin LN, Brandts JF. Biochemistry. 1979; 18:43–47. [PubMed: 570405]

3. For a review of prolines and collagen, see: (a) Shoulders MD, Raines RT. Annu Rev Biochem. 2009; 78:929–958. [PubMed: 19344236] (b) Shoulders MD, Satyshur KA, Forest KT, Raines RT. Proc Natl Acad Sci USA. 2010; 107:559–564. [PubMed: 20080719]

4. (a) Eberhardt ES, Panasik N Jr, Raines RT. J Am Chem Soc. 1996; 118:12261–12266. [PubMed: 21451735] (b) DeRider ML, Wilkens SJ, Waddell MJ, Bretscher LE, Weinhold F, Raines RT, Markley JL. J Am Chem Soc. 2002; 124:2497–2505. 7. [PubMed: 11890798] (d) Kuemin M, Nagel YA, Schweizer S, Monnard FW, Ochsenfeld C, Wennemers H. Angew Chem Int Ed. 2010; 49:1–5. (e) Bretscher LE, Jenkins CL, Taylor KM, DeRider ML, Raines RT. J Am Chem Soc. 2001; 123:777–778. [PubMed: 11456609] (f) Renner C, Alefelder S, Bae JH, Budisa N, Huber R, Moroder L. Angew Chem Int Ed. 2001; 40:923–925.(g) Hodges JA, Raines RT. J Am Chem Soc. 2003; 125:9262–9263. [PubMed: 12889933] (h) Doi M, Nishi Y, Uchiyama S, Nishiuchi Y, Nakazawa T, Ohkubo T, Kobayashi Y. J Am Chem Soc. 2003; 125:9922–9923. [PubMed: 12914445] (i) Hodges JA, Raines RT. J Am Chem Soc. 2005; 127:15923–15932. [PubMed: 16277536] (j) Kim W, McMillan RA, Snyder JP, Conticello VP. J Am Chem Soc. 2005; 127:18121–18132. [PubMed: 16366565] (k) Doi M, Nishi Y, Uchiyama S, Nishiuchi Y, Nishio H, Nakazawa T, Ohkubo T, Kobayashi YJ. Pept Sci. 2005; 11:609–616.(l) Horng JC, Raines RT. Protein Sci. 2006; 15:74–83. [PubMed: 16373476] (m) Kim W, Hardcastle KI, Conticello VP. Angew Chem Int Ed. 2006; 45:8141–8145.(n) Shoulders MD, Kamer KJ, Raines RT. Bioorg Med Chem Lett. 2009; 19:3859–3862. [PubMed: 19423349] (o) Kubik S, Goddard R. Proc Natl Acad Sci USA. 2002; 99:5127–5132. [PubMed: 11943849] (p) Buechter DD, Paolella DN, Leslie BS, Brown MS, Mehos KA, Gruskin EAJ. Biol Chem. 2003; 278:645–650.(q) Mizuno K, Hayashi T, Bachinger HP. J Biol Chem. 2003; 278:32373–32379. [PubMed: 12807876] (r) Gauba V, Hartgerink JD. J Am Chem Soc. 2007; 129:15034–15041. [PubMed: 17988128] (s) Gauba V, Hartgerink JD. J Am Chem Soc. 2008; 130:7509–7515. [PubMed: 18481852] (t) Gauba V, Hartgerink JD. J Am Chem Soc. 2007; 129:2683–2690. [PubMed: 17295489] (u) Erdmann RS, Wennemers J. Am Chem Soc. 2010; 132:13957–13959.(v) Rele S, Song Y, Apkarian RP, Zheng Q, Conticello VP, Chaikof EL. J Am Chem Soc. 2007; 129:14780–14787. [PubMed: 17985903]

5. For derivatized hydroxyprolines, see: (a) Jenkins CL, McCloskey AI, Guzei IA, Eberhardt ES, Raines RT. Biopolymers: Pept Sci. 2005; 80:1–8.(b) Owens NW, Braun C, O'Neill JD, Marat K, Schweizer F. J Am Chem Soc. 2007; 129:11670–11671. [PubMed: 17764180] (c) Bann JG, Bachinger HP. J Biol Chem. 2000; 275:24466–24469. [PubMed: 10827193] (d) Kotch FW, Guzei IA, Raines RT. J Am Chem Soc. 2008; 130:2952–2953. [PubMed: 18271593] (e) Naduthambi D, Zondlo NJ. J Am Chem Soc. 2006; 128:12430–12431. [PubMed: 16984189] (f) Thomas KM, Naduthambi D, Tririya G, Zondlo NJ. Org Lett. 2005; 7:2397–2400. [PubMed: 15932207] (g) Owens NW, Lee A, Marat K, Schweizer F. Chem Eur J. 2009; 15:10649–10657. [PubMed: 19739208]

6. For prolines other than 4-F or 4-OH, see: (a) Mollica A, Paradisi MP, Varani K, Spisani S, Lucente G. Bioorg Med Chem. 2006; 14:2253–2265. [PubMed: 16303307] (b) Cadamuro SA, Reichhold R, Kusebauch U, Musiol H-J, Renner C, Tavan P, Moroder L. Angew Chem Int Ed. 2008; 47:2143–2146.(c) Babu IR, Ganesh KN. J Am Chem Soc. 2001; 123:2079–2080. [PubMed: 11456840] (d) Beausoleil E, Sharma R, Michnick WW, Lubell WD. J Org Chem. 1998; 63:6572–6578.(e) Curran TP, Chandler NM, Kennedy RJ, Keaney MT. Tetrahedron Lett. 1996; 37:1933–1936.(f) Kümin M, Sonntag LS, Wennemers H. J Am Chem Soc. 2007; 129:466–467. [PubMed: 17226990] (g) Shoulders MD, Hodges JA, Raines RT. J Am Chem Soc. 2006; 128:8112–8113. [PubMed: 16787056] (h) Sonntag LS, Schweizer S, Ochsenfeld C, Wennemers H. J Am Chem Soc. 2006; 128:14697–14703. [PubMed: 17090057] (i) Shoulders MD, Guzei IA, Raines RT. Biopolymers. 2008; 89:443–454. [PubMed: 17937398] (j) Koskinen AMP, Heliaja J, Kumpulainen ETT, Koivisto J, Manisikkamacki H, Rissanen K. J Org Chem. 2005; 70:6447–6453. [PubMed: 16050708]

7. Giacovazzo, C.; Monaco, HL.; Artioli, G.; Viterbo, D.; Ferraris, G.; Gilli, G.; Zanotti, G.; Catti, M. Fundamentals of Crystallography. 2. Oxford University Press; Oxford, UK: 2002. p. 492-499.

8. Holmgren SK, Taylor KM, Bretscher LE, Raines RT. Nature. 1998; 392:666–667. [PubMed: 9565027]

9. Jenkins CL, Lin G, Duo J, Rapolu D, Guzei IA, Raines RT, Krow GR. J Org Chem. 2004; 69:8565–8573. [PubMed: 15575731]
10. Krow GR, Herzon SB, Lin F, Qiu G, Sonnet PE. Org Lett. 2002; 4:3151–3154. [PubMed: 12201739]
11. (a) Sunose M, Peakman TM, Charmant JPH, Gallagher T, Macdonald SJF. J Chem Soc, Chem Commun. 1998:1723–1724.(b) Pandey G, Chakrabarti D. Tetrahedron Lett. 1996; 37:2285–2288.
12. Krow GR, Lin G, Yu F, Sonnet PE. Org Lett. 2003; 5:2739–2741. [PubMed: 12868903]
13. (a) Gandon LA, Russell AG, Guveli T, Brodwolf AE, Kariuki BM, Spencer N, Snaith JS. J Org Chem. 2006; 71:5198–5207. [PubMed: 16808507] (b) Oba M, Nishiyama K. Tetrahedron. 1994; 50:10193–10200.
14. Krow GR, Lin G, Rapolu D, Fang Y, Lester WS, Herzon SB, Sonnet PE. J Org Chem. 2003; 68:5292–5299. [PubMed: 12816491]
15. (a) Alvernhe G, Laurent A, Haufe G. Synthesis. 1987:562–564.(b) Shellhamer DF, Horney MJ, Pettus BJ, Pettus TL, Stringer JM, Heasley VL, Syvret RG, Dobroldky JM Jr. J Org Chem. 1999; 64:1094–1098.
16. Krow GR, Huang Q, Lin G, Centafont RR, Thomas AM, Gandla D, DeBrosse C, Carroll PJ. J Org Chem. 2006; 71:2090–2098. [PubMed: 16496997]
17. Krow GR, Lee YB, Lester WS, Christian H, Shaw DA, Yuan J. J Org Chem. 1998; 63:8558–8560.
18. Pichlmair S, Ruiz MDL, Vilotijevic I, Paquette LA. Tetrahedron. 2006; 62:5791–5802.

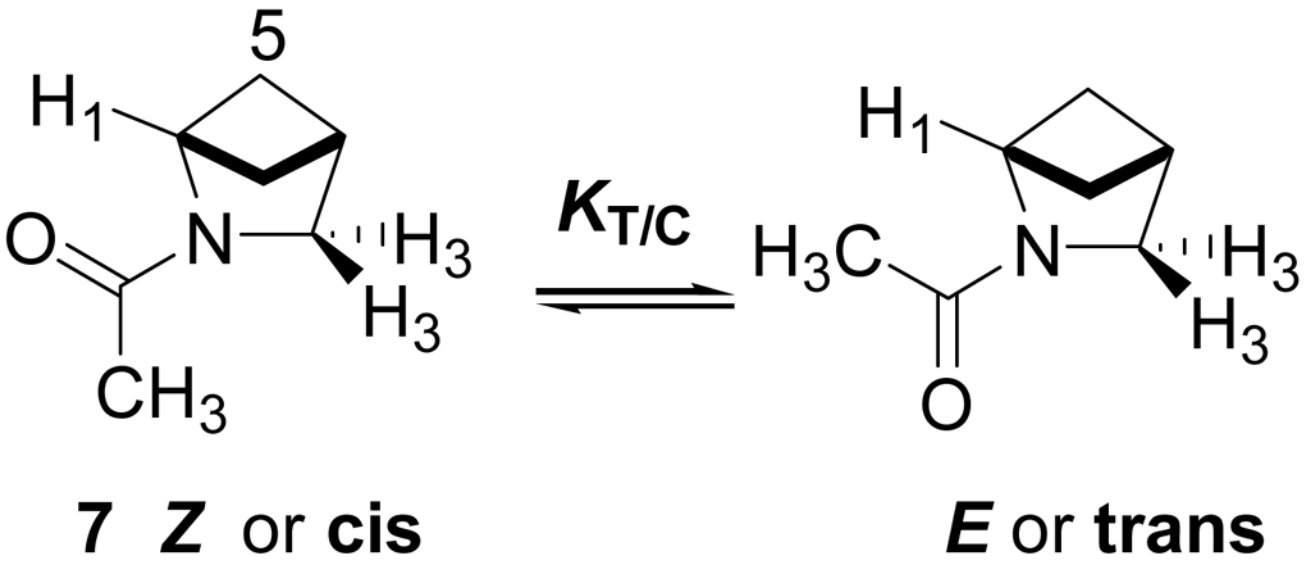
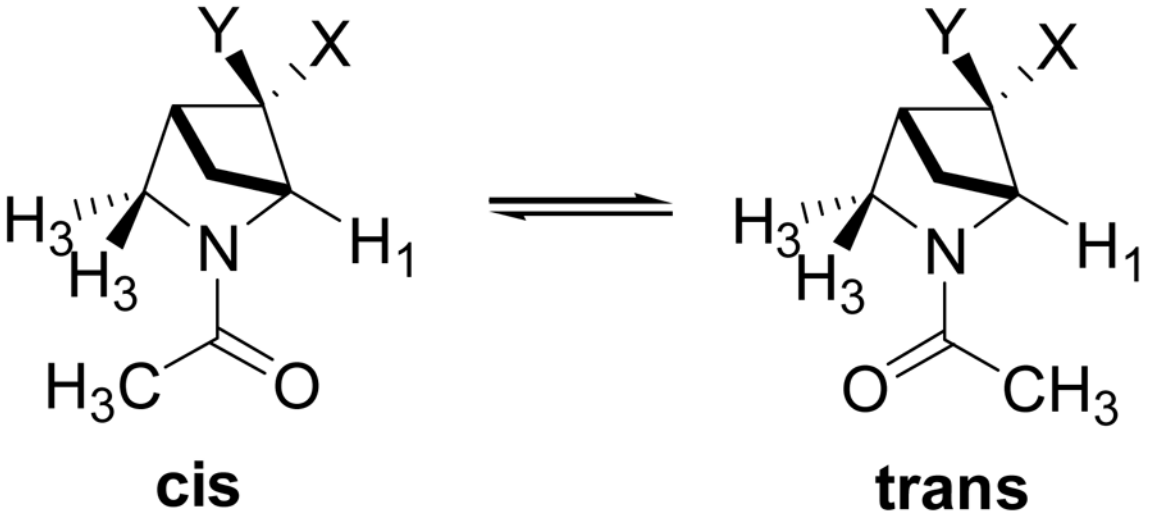
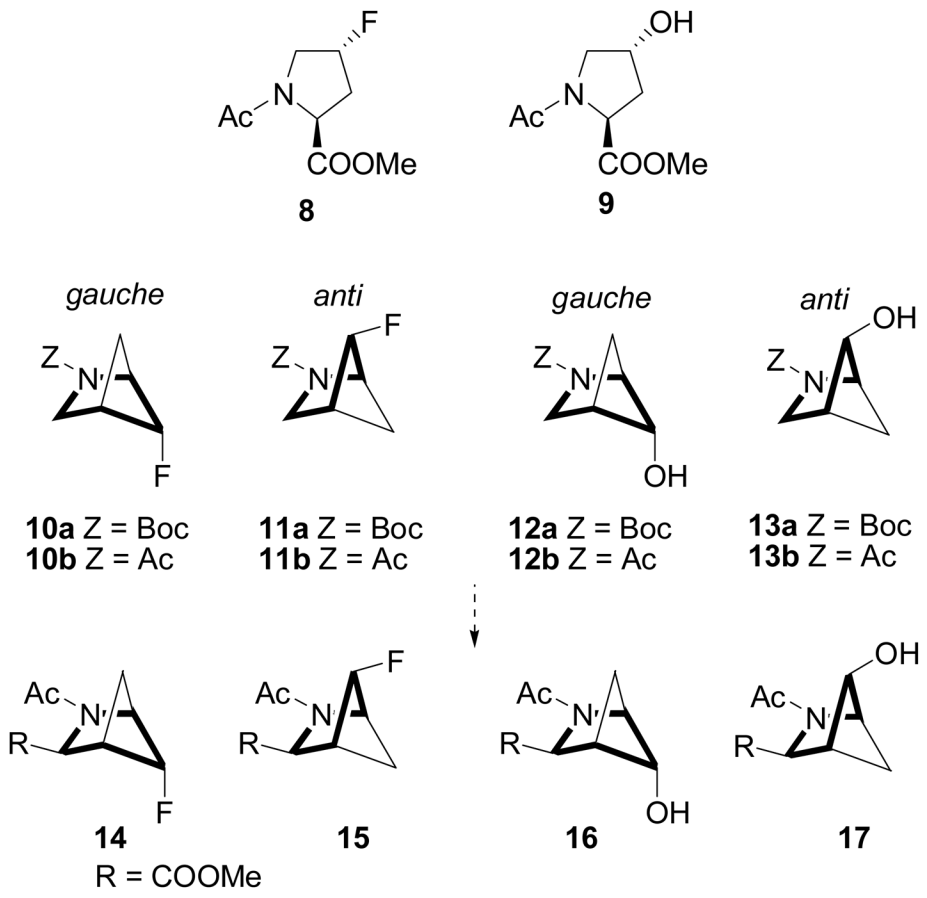


Figure 1.
Amide equilibrium for a methanopyrrolidine **7**.

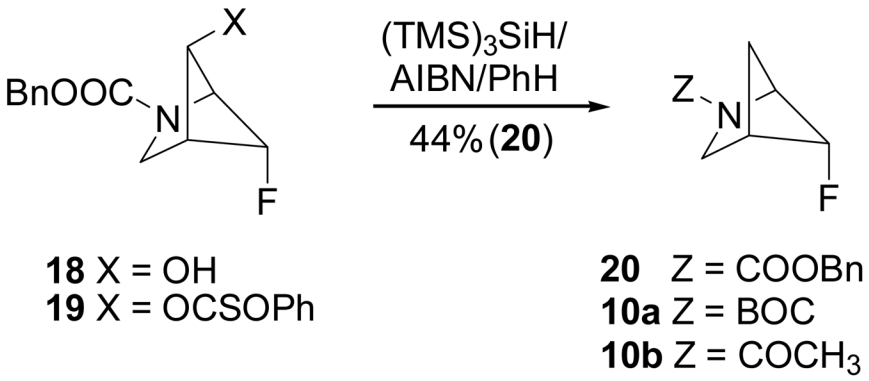


7 X = Y = H
10b X = F, Y = H
11b X = H, Y = F
12b X = OH, Y = H
13b X = H, Y = OH
31 X= OBz, Y = H
36 X = H, Y = OBz

Figure 2.
Amide conformations for methanopyrrolidines.



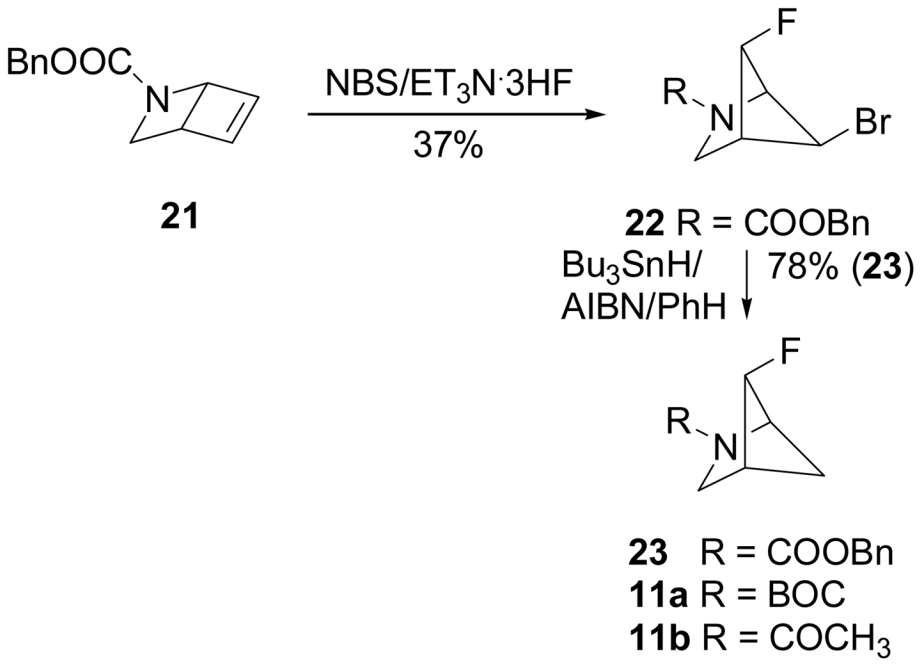
Scheme 1.
Retrosynthesis of Methanoprolines **14**–**17** Related to Flp **8** and Hyp **9**



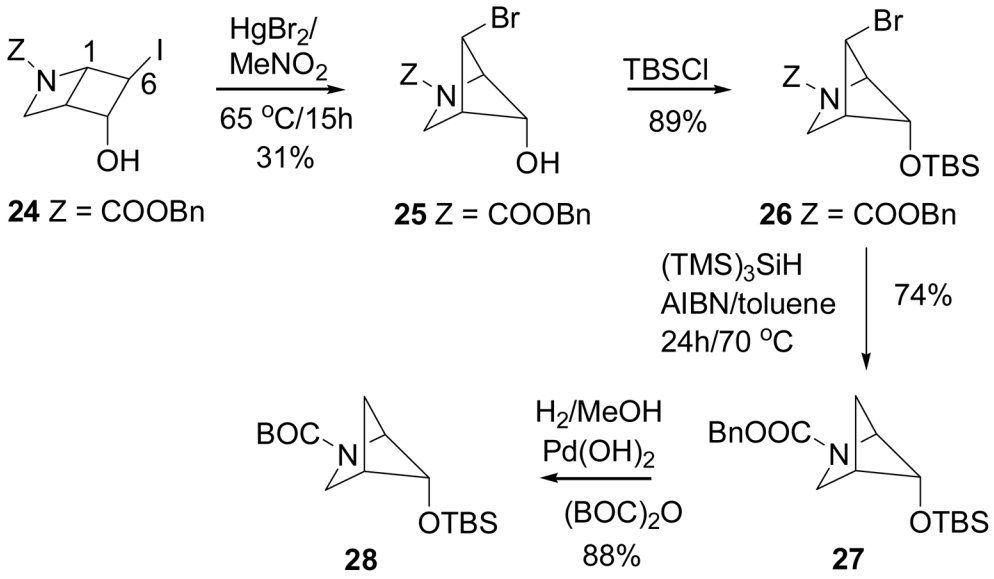
18 X = OH
19 X = OCSOPh

20 Z = COOBn
10a Z = BOC
10b Z = $COCH_3$

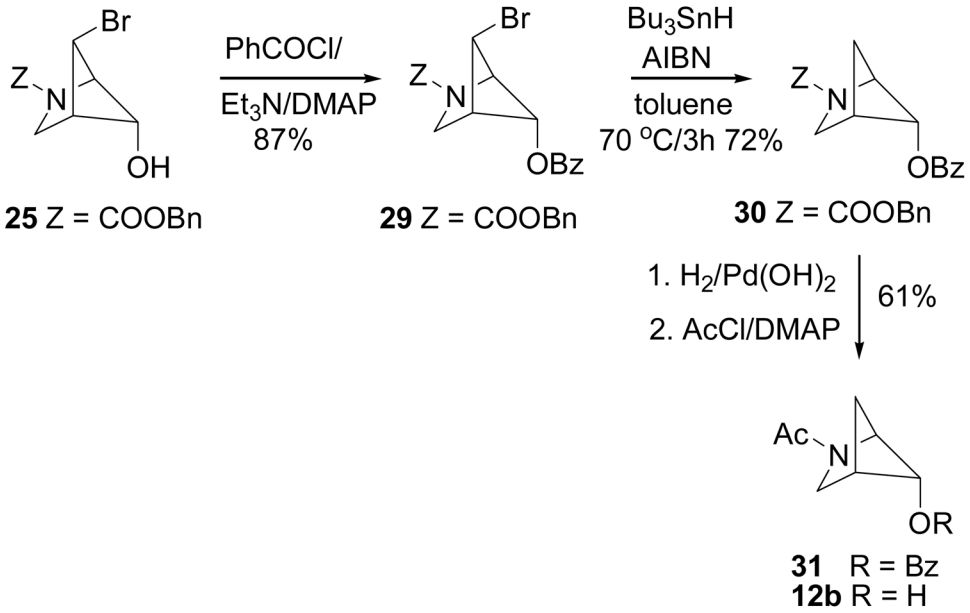
Scheme 2.
Synthetic Route to *N*-Protected-5-*syn*-Fluoromethanopyrrolidines



Scheme 3.
Synthetic Route to *N*-Protected-5-*anti*-fluoromethanopyrrolidines



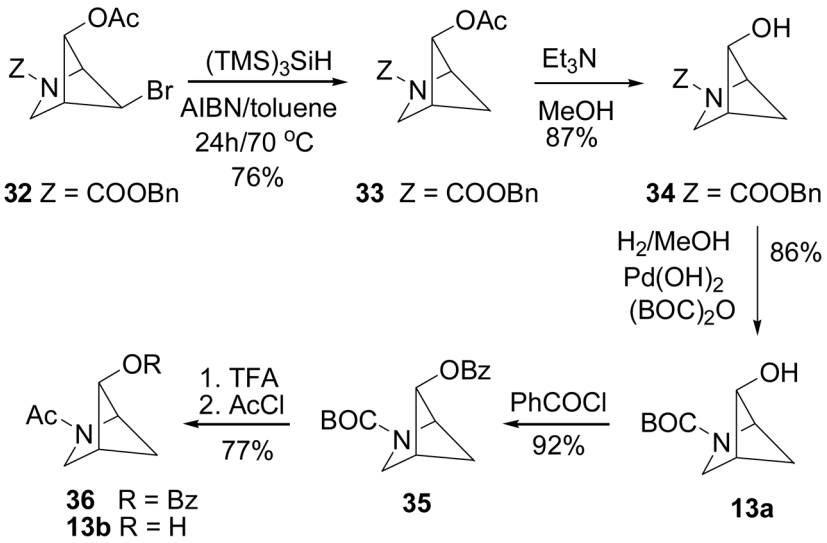
Scheme 4.
Synthetic Route to *N*-BOC-5-*syn*-*O*-TBS-methanopyrrolidine **28**



25 Z = COOBn **29** Z = COOBn **30** Z = COOBn

31 R = Bz
12b R = H

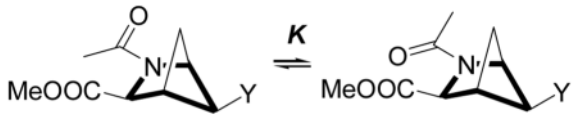
Scheme 5.
Synthetic Route to *N*-Acetyl-5-*syn*-hydroxymethanopyrrolidines



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

Table 1

$K_{T/C}$ of Methanoprolines **4**–**6**



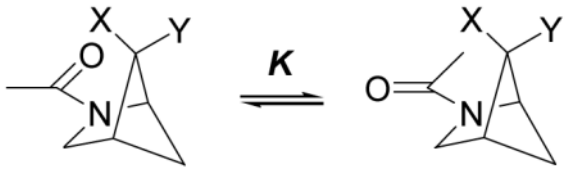
	s-cis			s-trans	
			$K_{T/C}$[a]		
entry	**compound**	**Y**	**D_2O**	**$CDCl_3$**	**dioxane-d_8**
1	MetPro **4**	H	3.5	2.4	2.2
2	Metflp **5**	F	3.5	2.7	2.8
3	Methyp **6**	OH	3.6[b]	2.4	2.1

[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 ~4:1.

Table 2

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



cis ***trans***

entry	substrate	X	Y	$K_{trans/cis}$		dipole moment (μ)		$K_{trans/cis}$ calculated[b]
				D_2O[a]	$CDCl_3$[a]	trans	cis	
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 ^1H 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.

J Org Chem. Author manuscript; available in PMC 2012 March 15.