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# 5(6)-*anti*-Substituted-2-azabicyclo[2.1.1]hexanes: A Nucleophilic Displacement Route

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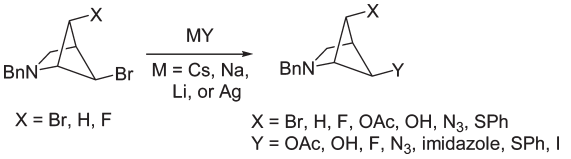
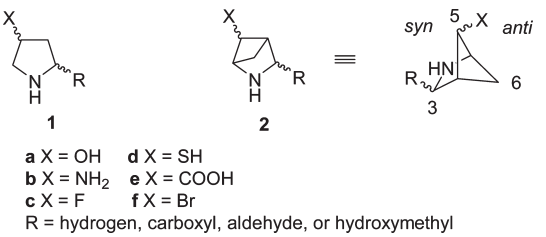



Nucleophilic displacements of 5(6)-*anti*-bromo substituents in 2-azabicyclo[2.1.1]hexanes (methanopyrrolidines) have been accomplished. These displacements have produced 5-*anti*-X-6-*anti*-Y-difunctionalized-2-azabicyclo[2.1.1]hexanes containing bromo, fluoro, acetoxy, hydroxy, azido, imidazole, thiophenyl, and iodo substituents. Such displacements of *anti*-bromide ions require an amine nitrogen and are a function of the solvent and the choice of metal salt. Reaction rates were faster and product yields were higher in DMSO when compared to DMF and with CsOAc compared to NaOAc. Sodium or lithium salts gave products, except with NaF, where silver fluoride in nitromethane was best for substitution by fluoride. The presence of electron-withdrawing F, OAc, $N_3$, Br, or SPh substituents in the 6-*anti*-position slows bromide displacements at the 5-*anti*-position.

## Introduction

Pyrrolidines **1**, especially those with hydroxy,[1] amino,[2] fluoro,[3] or thio[4] substituents in a 1,2-relationship $\beta$ to the nitrogen atom, are a valuable source of biologically significant molecules. One strategy in the search for new bioactive molecules is to incorporate key pharmacophoric units into inflexible structures.[5−7] Viewed in this light, methano-bridged pyrrolidines **2** (2-azabicyclo[2.1.1]hexanes) that display their functionalities in defined spatial orientations are of interest. Such molecules may prove to be valuable scaffolds for incorporation into proteins,[8] for drug discovery, or for other purposes.[3b] To realize this potential there is a need for practical methods to introduce a diverse array of heteroatom substituents onto these structures.[9]




Heteroatoms at $C_5(C_6)$ of *N*-acyl-2-azabicyclo[2.1.1]hexanes have been introduced by rearrangement routes (X = *syn*- or

(1) (a) For a review of nonproteinogenic amino acids from 4-hydroxyproline, see: Remuzon, P . *Tetrahedron* **1996**, *52*, 13803. (b) For examples of the utility of 4-hydroxyprolines, see also: Krow, G. R.; Lin, G.; Yu, F. *J. Org. Chem.* **2005**, *70*, 590. References 2−12. Trabocchi, A.; Rolla, M.; Menchi, G.; Guarno, A. *Tetrahedron Lett.* **2005**, *46*, 7813.

(2) For a recent example, see : (a) Deppermann, N.; Prenzel, A. H. G. P.; Beitat, A.; Maison, W. *J. Org. Chem.* **2009**, *74*, 4267. (b) Zanardi, F.; Burreddu, P.; Rassu, G.; Auzzas, L.; Battistini, L.; Curti, C.; Sartori, A.; Nicastro, G.; Menchi, G.; Cini, N.; Bottonocetti, A.; Raspanti, S.; Casiraghi, G. *J. Med. Chem.* **2008**, *51*, 1771. For further references, see: (c) Krow, G. R.; Huang, Q.; Lin, G.; Centafont, R. A.; Thomas, A. M.; Gandla, D.; DeBrosse, C.; Carroll, P. J. *J. Org. Chem.* **2006**, *71*, 2090,especially refs 1−6.

(3) For fluoropyrrolidines, see: (a) Giardina, G.; Dondio, G.; Grugni, M. *Synlett*. **1995**, *43*, 55. (b) For leading references to 4-fluoroprolines and 5-fluoromethanoproline, see: Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2004**, *69*, 8565.



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*anti*-halogen, hydroxyl),[10] nucleophilic ring closure of cyclobutanes (X = *syn*-SePh),[6a] or a thermal 2 + 2 cycloaddition (X/H = difluoride).[11] There are a few examples of *N*-acyl monoheteroatom-substituted *anti*-5-hydroxy-2-azabicyclo[2.1.1]hexanes **2a** (X = OH) formed by reductive dehalogenation of 5-*anti*,6-*anti*-bromohydrins.[3b,10a,10d]

Recently, we described the preparation of *N*-BOC-5-*syn*- and 5-*anti*-carboxy-2-azabicyclo[2.1.1]hexanes **2e** (R = H, X = COOH), isolated mainly as the *syn*-5-carboxy isomers,[12] and their use for introduction of heteroatom functionality into this ring system.[2c] The Curtius rearrangement was especially useful for the stereospecific conversion of 5-*syn*- and 5-*anti*-acids to the corresponding 5-*syn*- and 5-*anti*-amines, isolated as their carbamates **2b** [R = H, X = NHCOOBn(Et)]. The major 5-*syn*-carboxylic acid **2e** has been used to introduce other 5-heteroatoms by radical decarboxylative substitutions of either the acid or its Barton ester. Reactions led to mainly 5-*syn*-chloro, 5-*syn*-bromo, 5-*syn*-iodo, and 5-*syn*-pyridylthioether substitution products admixed with only minor amounts of the 5-*anti* isomers (0−11%); an exception was the iodide, which gave 17−44% 5-*anti*-isomer. Yields were generally poor, and this nonstereospecific method is not of general utility as a source of halide or thioether substitution. The rearrangement route remains the most useful for introduction of 5-*anti*-hydroxy and 5-*anti*-bromine groups as in **2a** and **2e**. Thus, methods to displace these substituents by other nucleophiles are welcome.

Nucleophilic substitution reactions of 5-tosylbicyclo[2.1.1]hexanes, the parent carbon bicycle of structures **2**, provide insights into the reactivity of 5-substituents in this strained ring system. The substitution reactions of 5-*syn*-substituents occur fairly easily and proceed with retention of configuration but are accompanied by rearrangement products. The *syn*-5-alcohol **3a** and phosphorus tribromide afforded a product assigned as the 5-*syn*-bromide **3b** (17%) admixed with some 4-bromocyclohexene, while *syn*-5-tosylate **3c** reacts with tetrabutylammonium chloride at 5 °C for 29 h to afford a product assigned as 5-*syn*-chloro[2.1.1]hexane **3d** (43%) with retained stereochemistry.[13a] Both of these products are suggestive of neighboring group participation by the neighboring methanobridge.[13b] On the other hand, nucleophilic displacement of 5-*anti*-substituents, our goal, is more difficult. The *syn*-tosylate **3c** reacted at a rate $3 \times 10^6$ time that of the 5-*anti*-tosylate **4**.[13b,c] To induce a reasonable rate for acetic acid solvolysis of the *anti*-tosylate **4**, a temperature of 164 °C was required. More importantly, none of the products retained the bicyclo[2.1.1]hexane structure. Acetolysis of **4** produced 4-cyclohexenyl tosylate (80%), 4-cyclohexenyl acetate (8%), and bicyclo[3.1.0]hex-2-yl acetate (8%) as the major products.[13c]


**3a** X = OH
**3b** X = Br
**3c** X = OTs
**3d** X = Cl


**4** X = OTs

Nevertheless, there are two examples of nucleophilic displacement reactions of 5-*anti*-substituents in *N*-acyl-2-azabicyclo[2.1.1]hexanes by fluoride in which products have been isolated that maintain the integrity of the heterobicyclic structure. The conversion of alcohol **5a** to fluoride **6a** was carried out using bis(2-methoxyethyl)aminosulfur trifluoride [BAST or Deoxo-Fluor] in refluxing methylene chloride (63%) (eq 1).[3b] Limited success was observed with the replacement of the 5-*anti*-iodo substituent of **5b** by fluoride using AgF/nitromethane at 80 °C/4 h to give **6b** (19%) (eq 2).[2c] Retention of stereochemistry was observed in both cases of displacement reactions of $C_5$-*anti*-substituents. We have not been successful in nucleophilic displacements of

(4) For 4-thioprolines, see: (a) Williams, J. M.; Brands, K. M. J.; Skerlj, R. T.; Jobson, R. B.; Marchesini, G.; Conrad, K. M.; Pipik, B.; Savary, K. A.; Tsay, F.-R.; Houghton, P. G.; Sidler, D. R.; Dolling, U.-H.; DiMichele, L. M.; Novak, T. J. *J. Org. Chem.* **2005**, *70*, 7479. (b) Azami, H.; Barrett, D.; Tanaka, A.; Sasaki, H.; Matsuda, K.; Chiba, T.; Matsumoto, Y.Matsumoto, S.; Morinaga, C.; Ishiguro, K.; Tawara, S.; Sakane, K.; Takasugi, H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2199. (c) Kemp, D. S.; Curran, T. P.; Davis, W. M.; Boyd, J. G.; Muendel, C. *J. Org. Chem.* **1991**, *56*, 6672. For a 4-thiopyrrolidine, see: (d) Shibata, T.; Iono, K.; Sugimura, Y. *Heterocycles* **1986**, *24*, 1331.

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(8) Kim, W.; George, A.; Evans, M.; Conticello, V. P. *ChemBioChem.* **2004**, *5*, 928.

(9) For a review of synthetic approaches to 2-azabicyclo[2.1.1]hexanes, see: Krow, G. R.; Cannon, K. C. *Heterocycles* **2004**, *62*, 877.

(10) For 3-alkyl(aryl),5(6)-heteroatom-substituted methanopyrrolidines, see : (a) Krow, G. R.; Lin, G.; Yu, F. *J. Org. Chem.* **2005**, *70*, 590. (b) Krow, G. R.; Yuan, J.; Lin, G.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 1259. (c) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Liu, N.; Yuan, J.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Zacharias, D. *J. Org. Chem.* **2001**, *66*, 1805. (d) Krow, G. R.; Lester, W. S.; Liu, N.; Yuan, J.; Hiller, A.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Cannon, K. *J. Org. Chem.* **2001**, *66*, 1811. For other 5(6)-heteroatom substituted methanopyrrolidines, see: (e) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558. (f) Krow, G. R.; Lin, G.; Moore, K. P.; Thomas, A. M. C.; DeBrosse, C.; Ross, C. W. III; Ramjit, H. G. *Org. Lett.* **2004**, *6*, 1669. (g) Krow, G. R.; Lin, G.; Yu, F.; Sonnet, P. E. *Org. Lett.* **2003**, *5*, 2739.

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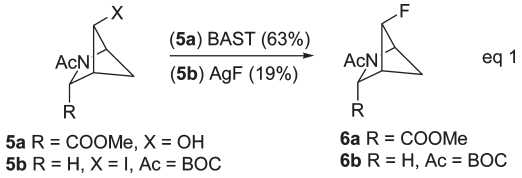
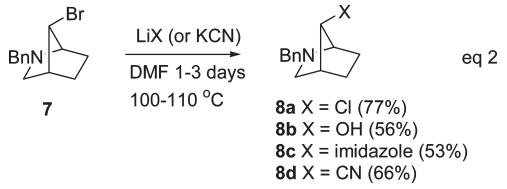
5-*anti*-bromo substituents in *N*-acyl-5-*anti*-bromo-2-azabicyclo[2.1.1]hexanes (see Supporting Information).




It occurred to us that replacement of the *N*-acyl substituent by an *N*-alkyl group might facilitate nucleophilic substitution reactions. Malpass and White[14] have shown that a free amine can facilitate displacements in a normally slow-reacting 7-norbornyl position.[13] The 7-bromo group in *N*-benzyl-*anti*-7-bromo-2-azabicyclo[2.2.1]heptane **7** was displaced by various nucleophiles at 100−110 °C in DMF to give products **8**. Only products with retained stereochemistry were observed, presumably the result of neighboring group participation.[14]

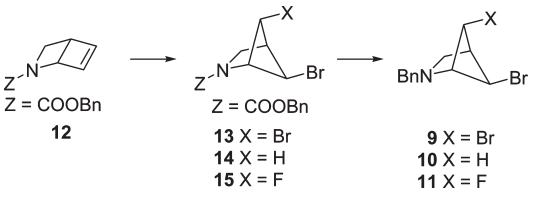



The key objective of this work was to see if replacement of *N*-acyl groups by *N*-benzyl in readily available 5-*anti*-bromo- and 5-*anti*-,6-*anti*-dibromo-2-azabicyclo[2.1.1]hexanes would allow for displacement of the bromine atom by useful heteroatom nucleophiles.[15] Specifically, dibromide **9**, monobromide **10**, and fluorobromide **11** have been chosen as substrates. We now describe conditions that enable preparation of 5(6)-*anti*-substituted-2-azabicyclo[2.1.1]hexanes with halogen-, nitrogen-, sulfur-, and oxygen-containing groups X starting from these bromides. Since preparation of 5-*anti*-bromides with compatible substituents at other ring positions is feasible,[3b,9,10] the functional group modifications described for these bromides should prove useful in the preparation of more highly functionalized 5(6)-substituted-2-azabicyclo[2.1.1]hexanes **2**. Some of these structures can be precursors of methanoprolines **2** (R = COOH);[3b,16] we especially desired to prepare novel 5,6-dihydroxy-, 5,6-difluoro-, 5,6-diamino-, and mixed 5,6-hydroxyfluorides that are not available by other synthetic routes.[7b]

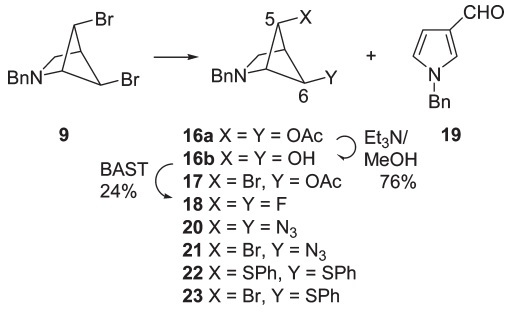
## Results and Discussion

The requisite *N*-benzyl dibromides **9**−**11** were prepared from the *N*-alkoxycarbonyl dihydropyridine photoproduct **12** (Scheme 1).[7b] The known dibromide **13**[7b] was selectively monodebrominated using $(TMS)_3SiH$/toluene/70 °C to give monobromide **14** (74%). Conversion of alkene **12** to bromofluoride **15** (53%) was carried out using NBS/nitromethane/$Et_3N\cdot 3HF$.[17] Hydrogenolysis of the carbobenzyloxy protecting groups of **13**−**15** with $H_2$/$Pd(OH)_2$/MeOH and subsequent benzylation with benzyl bromide/$Et_3N$/$CH_3CN$ afforded the *N*-benzyl compounds **9**−**11** in 51−69% overall yields for the two steps.

**SCHEME 1. Synthesis of *N*-Benzylbromides**




**SCHEME 2. Reactions of Dibromide 9**




Our first attempts to effect nucleophilic displacements of dibromide **9** (Scheme 2) were carried out in DMF under conditions used successfully by Malpass[14] for halide displacements with bromide **5** (R = Bn, Y = H). The results are shown in Table 1. Dibromide **9** was slowly converted to its diacetate **16a** using excess cesium acetate[18] (entry 1), but displacement of the second bromine was difficult. Even after 5 days there was unreacted starting material and a large amount of bromoacetate **17** in the reaction mixture. For the stereochemical assignment of diacetate **16**, the protons $H_5/H_6$ are identical and appear as a singlet in the $^1H$ NMR spectrum. The retained 5-*anti*,6-*anti* stereochemistry is apparent from the absence of coupling between $H_1$ or $H_4$ and their vicinal *syn* protons $H_5/H_6$. In this ring system these *syn* protons characteristically do not show vicinal coupling.[2c] For bromoacetate **18**, there is the characteristic W-plan coupling between the *syn* protons $H_5$ and $H_6$ ($J$ = 7.2 Hz).[7b] Methanolysis of the diacetate **16a** afforded diol **16b**. Attempted preparation of difluoride **18** from dibromide **9** using AgF/DMF formed instead the pyrrole aldehyde **19** (entry 2).[19]

To introduce nitrogen functionality, bromide **9** was reacted with sodium azide in DMF (entry 3) to give diazide **20** and azidobromide **21**. As noted with CsOAc (entry 1), it was difficult to replace the second bromine in azidobromide **21** despite extended reaction times (8 days). The symmetrical diazide **20** gave a singlet for $H_5/H_6$, while bromoazide **21**

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(15) We did not expect to isolate aziridinium ion salts. Aziridinium salts are preferred for 6-*anti*-bromo-2-azabicyclo[2.2.1]heptanes, although not the 7-*anti*-isomers. See ref [14a] and (a) Sosonyuk, S. E.; Bulanov, M. N.; Leshcheva, I. F.; Zyk, N. V. *Russ. Chem. Bull.* **2002**, *51*, 1254. (b) Bulanov, M. N.; Sosonyuk, S. E.; Zyk, N. V.; Zefirov, N. S. *Russ. J. Org. Chem.* **2003**, *39*, 415.

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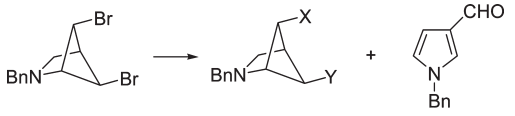
**TABLE 1. Nucleophilic Substitutions of Dibromide 9**




**9** **19**

| entry | substrate | reagent | conditions | product | X | Y | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **9** | CsOAc | DMF/60 °C/5 d | **16a** | OAc | OAc[a] | 40 |
| | | | | **17** | Br | OAc | 42 |
| 2 | **9** | AgF | DMF/50 °C/8 h | **19** | | | 72 |
| 3 | **9** | $NaN_3$ | DMF/60 °C/8 d | **20** | $N_3$ | $N_3$ | 34 |
| | | | | **21** | Br | $N_3$ | 49[b] |
| 4 | **9** | CsOAc | DMSO/60 °C/5 d | **16a** | OAc | OAc | 89 |
| 5 | **9** | NaOAc | DMSO/60 °C/5 d | **16a** | OAc | OAc | 14[c] |
| | | | | **17** | Br | OAc | 59 |
| 6 | **9** | NaF | DMSO/70 °C/5 d | **19** | | | 22[d] |
| 7 | **16b** | BAST | $CH_2Cl_2$/25 °C/12 h | **18** | F | F | 24 |
| | | | | **19** | | | 40 |
| 8 | **9** | AgF | $CH_3NO_2$/50 °C/8 h | **18** | F | F | 52 |
| | | | | **19** | | | 24 |
| 9 | **9** | $NaN_3$ | DMSO/60 °C/2d | **20** | $N_3$ | $N_3$ | 87 |
| 10 | **9** | NaSPh | DMSO/60 °C/5 h | **22** | SPh | SPh | 37 |
| | | | | **23** | Br | SPh | 29 |

[a]Also 10% dibromide **9**. [b]Also 17% of dibromide **9**. [c]Also 15% dibromide **9**. [d]Also 50% dibromide **9**.

showed the characteristic W-plan coupling for $H_5/H_6$ indicating that both structures have 5-*anti*,6-*anti* stereochemistry. The long reaction times and low yields in DMF solvent for preparation of desired diacetate **16a** and diazide **20**, along with the failure to prepare the desired difluoro isomer **18**, initiated a search for alternative superior reaction conditions.

Dimethylsulfoxide was found to be a superior solvent for nucleophilic displacement reactions of dibromide **9** (entry 4).[20] The substitution of DMSO for DMF, and otherwise the same reaction conditions in entry 1 for the reaction with CsOAc, resulted in complete conversion to the diacetate **16a** in a suitable yield after 5 days. The use of cesium acetate was clearly superior to sodium acetate in this reaction (entry 5). Our pleasure was tempered somewhat by the failure of DMSO as solvent to enable dibromide **9** to be converted to a desired difluoride **18** in the presence of NaF (entry 6); again only the pyrrole aldehyde **19** was obtained. However, it was discovered that difluoride **18** could be obtained in small yield (24%) by reaction of diol **16b** with BAST (entry 7).[3b] The symmetrical difluoride evidenced the expected multiplet AA′XX′ pattern in the $^1H$ NMR spectrum shown in Figure 1. The main product in the reaction was the oxidized ring-cleaved pyrrole aldehyde **19**. Later, it was found that the difluoride **18** could be made directly from the dibromide **9** in better yield by reaction with silver fluoride in nitromethane as solvent (entry 8).

The symmetrical diazide **20** also was prepared from dibromide **9** in both vastly improved yield (87%) and in shorter time (2 days) simply by replacing DMF with DMSO solvent (entry 9). With DMSO solvent it was also possible to prepare the symmetrical thiophenyl ether **22**, although after 5 h some bromothiophenyl ether **23** and unreacted dibromide **9** remained (entry 10).

(20) (a) Creary, X.; Burtch, E. A.; Jiang, Z. *J. Org. Chem.* **2003**, *68*, 1117. (b) Creary, X.; Burtch, E. A. *J. Org. Chem.* **2004**, *69*, 1227.

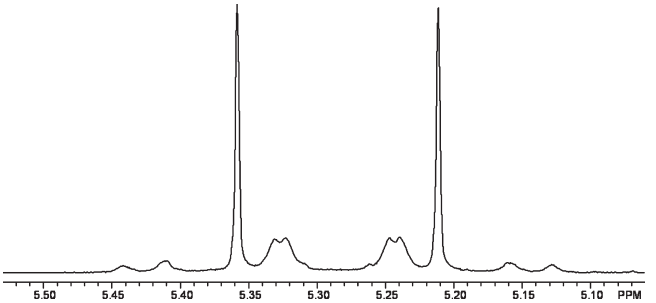
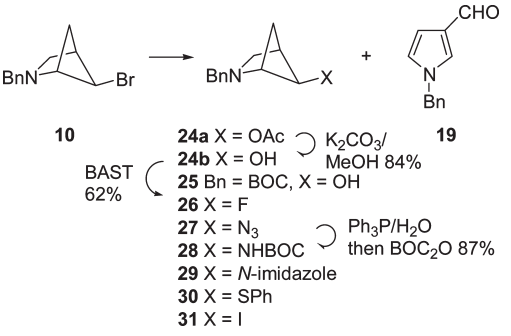



**FIGURE 1.** $^1H$ NMR spectrum (400 MHz) for $H_5/H_6$ protons in difluoride **18** ($CDCl_3$).

**SCHEME 3. Reactions of Monobromides 10**

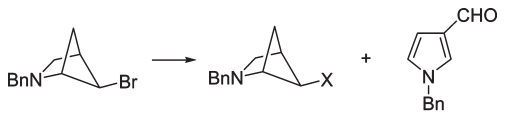



**Reactions of Monobromides 10 and 11.** We next turned our attention to the monobromide **10** (Scheme 3). Its substitution reactions are tabulated in Table 2. Our initial efforts again focused upon reactions in DMF solvent because of precedent.[14] With silver acetate in DMF bromide **10** gave acetate **24a** in moderate yield (entry 1). This was methanolyzed using $K_2CO_3$/methanol to give alcohol **24b** (84%). To show that the benzyl group could be removed without destruction of the strained ring, alcohol **24** was hydrogenolyzed and the resulting amine was protected by reaction with $(BOC)_2O$ to give *N*-BOC alcohol **25** (92%).

Monobromide **10** and AgF in DMF gave the same ring-opened and oxidized pyrrole aldehyde **19** (entry 2) observed upon reaction of dibromide **9** under these conditions. Bromide **10** in DMF did not react with NaF (entry 3) but did react with $NaN_3$ and gave azide **27** in moderate yield (entry 4). The azide **27** was reduced using triphenylphosphine/water, and the resultant amine was reacted with $(BOC)_2O$ to afford the protected carbamate **28**. An *N*-imidazole ring could be introduced by generation of lithium imidazole in DMF and reaction with bromide **10** to give amine **29** (entry 5). Sodium iodide (3 equiv) effected partial displacement of bromide ion to give an inseparable 50:50 mixture of bromide **10** and iodide **31** (entry 6).

DMSO again proved to be a superior solvent for the replacement of bromide using cesium acetate (entry 7), and bromide **10** produced acetate **24a** in high yield. Cesium acetate was found to be a better salt for the displacement than NaOAc. NaF in DMSO did not yield a fluoride with bromide **10** (entry 8). The desired fluoride **26** could be obtained from alcohol **24b** upon reaction with BAST (entry 9), but the fluoride **26** was obtained in higher yield from bromide **10** using AgF in nitromethane (entry 10). DMSO was shown to be a better solvent for bromide **10** in

**TABLE 2. Nucleophilic Substitutions of Bromide 10**




**10** **19**

| entry | substrate | reagent | conditions | product | X | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **10** | AgOAc | DMF/60 °C/12 h | **24a** | OAc | 54 |
| 2 | **10** | AgF | DMF/70 °C/24 h | **19** | | 42[a] |
| 3 | **10** | NaF | DMF/70 °C/12 h | **10** | Br | 88 |
| 4 | **10** | $NaN_3$ | DMF/70 °C/12 h | **27** | $N_3$ | 51 |
| 5 | **10** | LiNu[b] | DMF/70 °C/8 d | **29** | Nu[b] | 55 |
| 6 | **10** | NaI[c] | DMF/70 °C/3 d | **31** | I | 50[d] |
| 7 | **10** | CsOAc[e] | DMSO/70 °C/6 h | **24a** | OAc | 90 |
| 8 | **10** | NaF | DMSO/70 °C/12 h | **10** | Br | 82 |
| 9 | **24b** | BAST | $CH_2Cl_2$/40 °C/12 h | **26** | F | 62 |
| 10 | **10** | AgF | $CH_3NO_2$/50 °C/12 h | **26** | F | 80 |
| 11 | **10** | $NaN_3$ | DMSO/70 °C/5 h | **27** | $N_3$ | 88 |
| 12 | **10** | NaSPh | DMSO/60 °C/5 h | **30** | SPh | 77 |
| 13 | **10** | NaI[f] | acetone/reflux/4 d | **31** | I | 74[g] |

[a]Bromide **10** was stable in DMF/70 °C/12 h; 90% recovery, no **19** formed. [b]Nu = *N*-imidazole. [c]3 equiv. [d]Admixed with unreacted bromide **10**. [e]To separate samples of the monobromide **10** in DMSO-$d_6$ was added 1.5 equiv of either NaOAc (sample A) or CsOAc (sample B). After 6 h the conversion to acetate **24a** was 39% for sample A and 66% for sample B by NMR analysis. [f]20 equiv. [g]Total conversion of **10**.

its reactions with $NaN_3$ to give the azide **27** (entry 11) or with NaSPh to give the thiophenyl ether **30** (entry 12). It was possible to convert the bromide **10** to the iodide **31** using excess NaI/acetone after extended reflux (entry 13). $^1$H NMR indicated complete conversion of the bromide. The 5-*anti* stereochemistry for all new compounds in Table 2 was indicated by the observation of W-plan $^1$H NMR couplings ($J_{5,6}$ = 6.9−7.6 Hz).

The next substrate investigated was the bromofluoride **11** (Scheme 4), and its reactions are tabulated in Table 3. The bromofluoride **11** reacted slowly with CsOAc in DMF to give fluoroacetate **32a** (entry 1). A sequence of methanolysis of the acetate **32a** to alcohol **32b** and then hydrogenolysis followed by acylation with $(BOC)_2O$ gave a desired fluoroalcohol **33** (86%). Formation of azide **34** from bromofluoride **11** was also a slow reaction (entry 2) and was accompanied by decomposition. The azide **34** was converted to the amine **35** using triphenylphosphine/water, and the amine was acylated to give the acetamide **36**.

While fluoroalcohol **32b** showed coupling between OH-F ($J$ = 3.9 Hz),[21] there was no evidence for such coupling in either the fluorine or proton NMR spectra of amine **35** or amide **36**. Molecular models indicate the 5-*anti*- and 6-*anti*-substituents are not actually parallel but point slightly away from each other. The 5-*anti*,6-*anti* arrangement of halogen substituents was again indicated by W-plan couplings ($J_{5,6}$ = 7.1−7.8 Hz).

Replacement of solvent DMF by DMSO facilitated the displacement reactions of **11** to give fluoroacetate **32a** with either NaOAc (entry 3) or more effectively with CsOAc (entry 4). The same solvent effect was observed in the improved yields in formation of azide **34** upon

**SCHEME 4. Reactions of Fluorobromide 11**

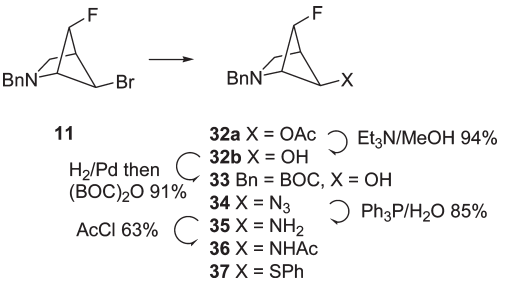
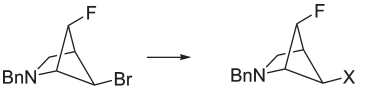



**TABLE 3. Nucleophilic Substitutions of Bromofluoride 11**




**11**

| entry | substrate | reagent | conditions | product | X | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **11** | CsOAc | DMF/70 °C/5 d | **32a** | OAc | 30[a] |
| 2 | **11** | $NaN_3$ | DMF/70 °C/5 d | **34** | $N_3$ | 43[b] |
| 3 | **11** | NaOAc | DMSO/70 °C/5 d | **32a** | OAc | 33[c] |
| 4 | **11** | CsOAc | DMSO/70 °C/5 d | **32a** | OAc | 90 |
| 5 | **11** | $NaN_3$ | DMSO/70 °C/7 d | **34** | $N_3$ | 67 |
| 6 | **11** | NaSPh | DMSO/60 °C/5 h | **37** | SPh | 15[d] |
| 7 | **11** | NaSPh | DMSO/60 °C/9 d | **37** | SPh | 69[e] |

[a]Also 64% unreacted **11**. [b]Also 31% unreacted **11**. [c]Also 64% unreacted **11**. [d]Also 66% unreacted **11**. [e]Also 4% unreacted **11**.

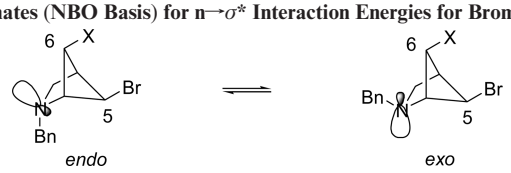
reaction of **11** with $NaN_3$ in DMSO (entry 5). It was also possible to prepare the fluorothioether **37** using NaSPh in DMSO, although the reaction was quite slow (entries 6 and 7).

The ease of bromide displacements in bromides **9**−**11** was dependent upon the adjacent substituent X. Monitoring of the disappearance of starting bromides indicated a relative reactivity order monobromide **10** > dibromide **9** > fluorobromide **11** (see Supporting Information). Nucleophilic substitution reactions with the bromide **10** in DMSO solvent with CsOAc or $NaN_3$ required hours for completion, with the dibromide **9** a few days, and with the fluorobromide **11** 5−7 days. In addition, upon displacement of one of the bromides of dibromide **9** by acetate, azide, or thiophenyl it took longer to displace the remaining bromides of bromoacetate **17**, bromoazide **21**, or bromo(phenylthio) ether **23** (Table 1). These reactivity orders indicate that all parallel heteroatom substituents in the adjacent methyl bridge, so far investigated, are rate-retarding for bromide substitution.

One plausible explanation for the rate-retarding effects of heteroatom groups is that electron withdrawal of the nitrogen lone pair by a second atom X reduces the ability for nitrogen atom interaction with the leaving bromide. In molecular orbital terms the nitrogen's lone pair of electrons could interact with the $\sigma^*$ orbitals of the C−Br bond. On the basis of the electronegativity of the non-reacting C−X bond (H < Br < F), it might be predicted that the n→$\sigma^*$ overlap for the reacting C−Br bond should follow the order monobromide **10** > dibromide **9** > fluorobromide **11**. To gain evidence about the substituent effect upon lone pair n→$\sigma^*$ interactions, NBO calculations were performed for

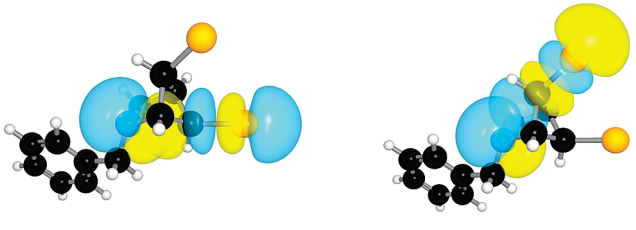
(21) Krow, G. R.; Gandla, D.; Guo, W.; Centafont; Lin, G.; DeBrosse, C.; Sonnet, P. E.; Ross, C. W. III; Ramjit, H.; Cannon, K. C. *J. Org. Chem.* **2008**, *73*, 2122.

**TABLE 4. Second-Order Perturbative Estimates (NBO Basis) for n→σ* Interaction Energies for Bromides 9−11**




| | | | n→σ* (kcal/mol)[a] | | | n→σ* (kcal/mol) | |
|---|---|---|---|---|---|---|---|
| entry | substrate | X | N→$C_5$−Br | N→$C_6$-X[b] | substrate | N→$C_5$−Br | N→$C_6$-X |
| 1 | **9***endo-N*-Bn[c] | Br | 1.71 | 0.96 | **9** *exo-N*-Bn | 0.96 | 1.71 |
| 2 | **10***endo-N*-Bn | H | 1.75 | (0.28) | **10** *exo-N*-Bn | 0.89 | (0.55) |
| 3 | **11***endo-N*-Bn | F | 1.63 | (0.69) | **11** *exo-N*-Bn | 0.92 | (1.63) |

[a]Geometry optimizations, frequency calculations, and NBO analyses were performed at the B3LYP/6-311+G(2d,p) level of theory on **9**−**11**.[22,23] [b]Those bonds that do not have leaving groups for substitutions are in parentheses. [c]The benzyl group has been arbitrarily assigned as *endo* (or *exo*) to enable us to distinguish the two bromides as $C_5$ and $C_6$ for purposes of this analysis.

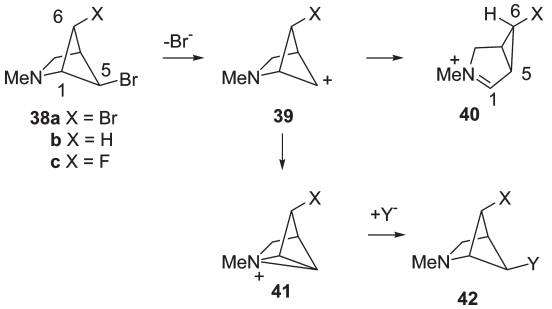


**Rear lobe → Proximal Bromide** **Large lobe → Distal Bromide**

**FIGURE 2.** n→σ* Orbital overlaps for C−Br bonds in benzyl dibromide **9**.

structures **9**−**11**.[22,23] The calculations, shown in Table 4, indicate the nitrogen lone pair electrons, front lobe and rear lobe, interact with the σ* orbitals of *both* $C_5$ and $C_6$ substituents. Pictures in Figure 2 show the orbital overlap for the two lobes of the nitrogen lone pair orbital in the dibromide **9**.[23d] The larger n→σ* interaction in each case occurs from the *endo-N*-benzyl conformer with the rear lobe (yellow) of the nitrogen atom overlapping (N→$C_5$Br).[24] While it is true that the calculated relative overlap stabilization energies (**10** > **9** > **11**) are consistent with the observed reactivity order (**10** > **9** > **11**) with nucleophiles, the ground state interaction energies are too similar for this factor alone to explain the large relative rate differences. Indeed, the relative stabilization energies may differ appreciably as the corresponding transition state energies are approached. Electron lone pair orbital interactions would be expected to become more important as positive charge is created at $C_5$.

**SCHEME 5. Calculated Ionic Intermediates for Reactions of *N*-Methyl-azabicyclic Bromides 38−40**




To gain information on charged intermediates derived from *N*-methyl substrates **38a**−**c**, we performed single point energy calculations of *N*-methyl carbocations **39a**−**c** (Scheme 5) by two different means: (1) Hartree−Fock 6-31+G(d,p)[25] and (2) B3LYP/6-31+G(d,p)[26] methods/basis sets using the Gaussian 03 suite of computations.[22] We then optimized these structures for geometry using the same two methods. In all instances, save one, each optimization of a cation **39** led to an iminium ion **40**; *exo* and *endo* isomers led to the same ions. The one exception occurred with bromofluoride **38c** using method 2 in which the aziridinium ion **41c** was the outcome of the calculation. Independently, we optimized iminium ion **40c** using method 2. The fluoro aziridinium ion **41c** was calculated to be 43.5 kcal/mol less

(22) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford CT, **2004**.

(23) (a) Weinhold, F. Natural Bond Orbital Methods. In *Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Shaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, UK, 1998; Vol. 3, p 1792. (b) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. *NBO 5.0*; **2001**. (c) Weinhold, F.; Landis, C. R. *Valency and Bonding: A Natural Bond Orbital Donor−Acceptor Perspective*; Cambridge University Press: Cambridge, U.K., 2005. (d) Depictions of orbital overlap were generated using NBOview 1.1: Wendt, M.; Weinhold, F. *NBOView 1.1*; Theoretical Chemistry Institute, University of Wisconsin, Madison: Madison, WI, 2001.

(24) Crystals of dibromide **9** were subjected to X-ray analysis (see Supporting Information). It was envisioned that an especially significant and equal interaction of the nitrogen lone pair electrons with the C−Br σ* orbitals might lead at the extreme to a symmetrical structure for dibromide **9** with a planar nitrogen atom. However, nitrogen is tetrahedral and the sum of the bond angles including the nitrogen atom is 330.1°. The C−Br bond proximal to the *N*-benzyl group is 1.945 Å, and the distal C−Br bond is 1.942 Å. While suggestive of an n→σ* interaction for the longer proximal bond distance, these bond lengths are essentially identical within experimental error (0.002 Å).

(25) McWeeny, R.; Dierksen, G. *J. Chem. Phys.* **1968**, *49*, 4852.

(26) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

stable than fluoroiminium ion **40c**. See Supporting Information for details on aziridinium ions **41a,b**.[27]

Considering the large energy preference calculated for the gas phase iminium ions **40** versus the aziridinium ions **41**, it is perhaps surprising that the 5-*anti*-bromo-2-azabicyclo-[2.1.1]hexanes **9**−**11**, related to **38a**−**c**, can undergo nucleophilic substitutions to afford unrearranged 5(6)-*anti* products related to **42**. A 1,2-alkyl shift of $C_6$ from $C_1$ to $C_5$ on the *anti* face of a cationic species **39** leads to iminium ion **40**. Unrearranged products **42** that have retained stereochemistry are consistent with an intermediate ion that under suitable conditions is resistant to rearrangement. Such an ion in solution might be an aziridinium ion such as **41**, associated with its counterion.

Solvent effects are consistent with the need to stabilize a transition state leading to charged intermediates, such as **41a**−**c**. The more polar DMSO was a more effective solvent than DMF for the displacement reactions of all substrates **9**−**11**.[20,28] A "cesium ion effect" was also noted for acetate displacements.[28−30] Reactions of fluorobromide **11** with CsOAc and NaOAc are illustrative. This substrate remained 64% unreacted (Table 4, entry 3) with NaOAc in DMSO solvent at 70 °C after 5 days, but with CsOAc and the same temperature/solvent conditions fluorobromide **11** reacted completely (Table 3, entry 4). These reactions were run under heterogeneous conditions, and thus the salt solutions were concentrated. The greater solubility of CsOAc than NaOAc in DMSO and DMF, as well as lesser ion pairing of cesium salts, increases the ionic strength of the CsOAc reaction solutions and facilitates the formation of charged ions in the polar solvents.[30]

Silver ions facilitated bromide displacements. The outcomes of the silver salt reactions we investigated were dependent upon counterion and solvent. Illustrative are the conversions of monobromide **10** in Table 2. AgOAc/DMF gave acetate **20a** (entry 1). However, with AgF/DMF the reaction took a different course, and an oxidative rearrangement occurred to give pyrrole aldehyde **19** (entry 2). The sodium salt NaF/DMF was unreactive with bromide **10** over 12 h (entry 3), but the silver salt $AgF/CH_3NO_2$ provided fluoride **26** (entry 10).

Reactions of the alcohols **16b** (25 °C) and **24b** (40 °C) with $BAST/CH_2Cl_2$ to give fluorides **18** and **26** were markedly easier than conversion of bromides **9** (50 °C) or **10** (70 °C) to the fluorides, even with $AgF/CH_3NO_2$ (Table 1, entries 7, 8 and Table 2, entries 10, 11). The hydroxyl groups are activated for displacement by BAST after formation of O-sulfur bonds; fluorination reactions occurred in $CH_2Cl_2$ in a few hours.

The oxidative ring-opening reaction to form the aromatic aldehyde **19** occurred under a variety of conditions. Reactions of dibromide **9** in Table 1 are informative. AgF/DMF afforded the aldehyde **19** (entry 1), but so did NaF/DMSO (entry 6). $AgF/CH_3NO_2$ gave a mixture of difluoride **18** and aldehyde **19** (entry 8). In two trials with $NaN_3$/DMF similar to entry 3, but using less pure noncrystalline dibromide **9**, a small amount (< 6%) of aldehyde **19** was obtained with air as the only recognized oxidant. Aldehyde **19** also formed during reactions of BAST with diol **16b** (Table 1, entry 7). For proposed mechanisms to this oxidized ring-cleaved aldehyde **19**, see Supporting Information.

## Conclusion

The novel *N*-benzyl-5-*anti*,6-*anti*-dibromo-2-azabicyclo-[2.1.1]hexane nitrogen mustard **9**, the bromide **10**, and bromofluoride **11** react with nucleophiles to give products with retained stereochemistry. We have observed single bromide displacement reactions, and somewhat slower displacements of two bromides by appropriate oxygen (acetate), nitrogen (azide, imidazole), thioether (phenylthio), and halide (fluoride, iodide) nucleophiles. The present synthetic route describes the first reported examples of 5-*anti*,6-*anti*-diols, -difluorides, -diazides, -dithioethers, -fluoroamines, and -fluorothioethers, as well as the first 5-*anti*-imidazoles. We presently envision use of the diols, fluoroalcohols, and difluorides as key intermediates for the preparation of methanoproline derivatives, desired in order to study substituent effects on amide conformations.

## Experimental Section

***N*-Benzyl-5-*anti*,6-*anti*-dibromo-2-azabicyclo[2.1.1]hexane (9).** To a solution of dibromide **13**[7b] (1000 mg, 2.67 mmol) in methanol (75 mL) was added $Pd(OH)_2$ (150 mg). The solution was degassed and stirred under a $H_2$-filled balloon for 1 h at rt. The reaction mixture was filtered through Celite, the filtrate was evaporated, and the residue was chromatographed on silica gel (9:1 EtOH/MeOH) to give 513 mg (80%) of dibromoamine **13-int** at $R_f = 0.58$ (2:1 EtOH/MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.11 (s, 2H, $H_5$ and $H_6$), 3.87 (d, $J = 6.0$ Hz, 1H, $H_1$), 3.35 (br s, 1H, NH), 3.17 (s, 2H, $2H_3$), 3.10 (d, $J = 6.0$ Hz, 1H, $H_4$); $^{13}$C NMR (100 MHz, $CDCl_3$, rt) $\delta$ 66.2, 52.3, 51.2, 47.1; HRMS *m*/*z* 239.9014, 241.9001, 243.8983, calcd for $C_5H_8N^{79/79,\,79/81,\,81/81}Br_2$ (M + H) 239.9023, 241.9003, 243.8983. To a solution of amine (0.50 g, 2.08 mol) in acetonitrile (20 mL) were added $Et_3N$ (1.69 g, 16.60 mol) and then BnBr (1.42 g, 8.30 mol) dropwise at rt. The reaction mixture was stirred at rt for 36 h. Solvent was removed in vacuo, ether (75 mL) was added, the mixture was stirred for 10 min at rt and then filtered, and the residue was washed with ether (25 mL). Solvent again was removed in vacuo to afford crude dibromide **9**. This was chromatographed on silica gel (hexanes/ether 4:1) to afford 590 mg (86%) of an off-white solid dibromide **9** at $R_f = 0.75$ (1:1 hexanes/ether); mp 68−70 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.27 (m, 5H, Ph), 4.32 (s, 2H, $H_5$ and $H_6$), 3.85 (s, 2H, $CH_2Ph$), 3.61 (d, $J = 6.6$ Hz, 1H, $H_1$), 3.12 (dd, $J = 6.6$, 0.9 Hz, 1H, $H_4$), 2.92 (s, 2H, $2H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.8, 128.5, 127.4, 70.1, 58.6, 55.1, 52.4, 51.1; HRMS *m*/*z* 329.9482, 331.9472, 333.9453, calcd for $C_{12}H_{14}N^{79/79,79/81,81/81}Br_2$ (M + H) 329.9493, 331.9473, 333.9453. Hexanes (0.3 mL) were added to a vial with a syringe that contained about 5 mg of dibromide **9** dissolved in ether (0.2 mL). The vial was wrapped with aluminum foil, small holes were made with a syringe, and the solution was allowed to sit for 3 d to give crystals suitable for X-ray crystallography.

***N*-(Benzyloxycarbonyl)-5-*anti*-bromo-2-azabicyclo[2.1.1]hexane (14).** To a solution of dibromide **13** (693 mg, 1.8 mmol) in toluene (50 mL) were added $(TMS)_3SiH$ (596 $\mu$L, 1.9 mmol) and AIBN (40 mg). The resulting solution was allowed to stir at 70 °C for 3 h. The solvent was concentrated in vacuo, and flash chromatography

(27) Independently, the aziridinium ions **41a,b** were drawn and their geometries were optimized using both methods 1 and 2. The aziridinium ions **41a,b** were calculated to be 42−46 kcal/mol less stable than the corresponding iminium ions. See Supporting Information for details.

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gave 407 mg (74%) of the monobromide **14** at $R_f = 0.39$ (2:1 hexanes/ether); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.11 (m, 5H), 4.91 (s, 2H), 4.19 (br d, $J = 6.3$ Hz, $H_5$), 3.58 (d, $J = 8.4$ Hz, $H_1$), 3.27 (d, $J = 9.0$ Hz, $H_3$), 3.23 (d, $J = 9.0$ Hz, $H_3$), 2.79 (dm, $J = 8.1$ Hz, $H_{6anti}$), 2.67 (br, 1H, $H_4$), 1.40 (dd, $J = 8.1$, 6.3 Hz, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.5, 136.9, 128.9, 128.5, 128.4, 68.6, 65.2, 55.2, 49.4, 46.3, 39.3 and 25.5; HRMS *m*/*z* found 296.0284, calcd for $C_{13}H_{14}NO_2Br$ (M + H) 296.0281, *m*/*z* 318.0105 calcd for $C_{13}H_{13}NO_2BrNa$ (M + Na) 318.0105.

***N*-Benzyl-5-*anti*-bromo-2-azabicyclo[2.1.1]hexane (10).** To a solution of the monobromide **14** (708 mg, 2.4 mmol) in MeOH (40 mL) was added $Pd(OH)_2$ (71 mg), and the resulting solution was degassed and allowed to stir for 1 h at rt under hydrogen. After 1 h the catalyst was filtered via Celite, and the solvent was removed in vacuo to give 500 mg of the crude amine. Without further purification the amine was dissolved in acetonitrile (20 mL), and to the resulting solution were added $Et_3N$ (405 mg, 4.0 mmol) and BnBr (328 mg, 1.9 mmol). The resultant solution was stirred at rt for 3 days. Solvent was removed in vacuo to give an oil that on flash chromatography gave 351 mg (58%) of the bromide **10** at $R_f = 0.40$ (1:1 hexane/ether); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.24 (m, 5H), 4.11 (d, $J = 8.4$ Hz, 1H, $H_5$), 3.81 (s, 2H), 3.46 (dd, $J = 6.9$, 1.9 Hz, $H_1$), 2.88 (m, 4H, $2H_3$, $H_4$, $H_{6anti}$), 1.76 (t, $J = 8.1$ Hz, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 139.0, 128.5, 128.3, 127.0, 68.8, 59.0, 55.3, 54.6, 48.0, 35.8; HRMS *m*/*z* found 252.0383, calcd for $C_{12}H_{15}NBr$ (M + H) 252.0383.

***N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*anti*-fluoro-2-azabicyclo-[2.1.1]hexane (15).** To a solution of 2-azabicyclo[2.2.0]hex-5-ene **12**[7b] (1.30 g, 0.006 mol) in $MeNO_2$ (50 mL) was added NBS (2.15 g, 0.012 mol) at 0 °C followed by $Et_3N \cdot 3HF$ (2.92 g, 0.018 mol) dropwise over a period of 10 min.[12] The reaction was brought to rt and stirred for 20 h. Then the reaction mixture was diluted with $CH_2Cl_2$ (125 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo, and the residue was purified by flash chromatography (1:3 ether/hexanes) to afford 997 mg (53%) of bromofluoride **15** as a colorless oil at $R_f = 0.49$ (1:1 ether/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.29 (m, 5H), 5.18 (d, $J = 12.3$ Hz, 1H), 5.14 (d, $J = 12.3$ Hz, 1H), 4.99 (dd, $J = 59.1$, 7.3 Hz, 1H, $H_5$), 4.55 (br d, $J = 7.2$ Hz, 1H, $H_6$), 4.11 (dd, $J = 7.3$, 3.1 Hz, 1H, $H_1$), 3.61 (ddd, $J = 9.1$, 3.2, 1.2 Hz, 1H, $H_3$), 3.51 (dt, $J = 9.1$, 1.3 Hz, 1H, $H_{3'}$), 3.13 (brdd, $J = 7.3$, 3.6 Hz, 1H, $H_4$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.9, 136.0, 128.5, 128.3, 128.0, 99.7 ($J_{C,F} = 226.8$ Hz), 67.4, 64.6, 49.8, 49.1 ($J_{C,F} = 17.5$ Hz), 48.1; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −204.75 (d, $J = 58.9$ Hz), −205.83 (d, $J = 58.9$ Hz); HRMS *m*/*z* found 336.0014, 338.0005, calcd for $C_{13}H_{13}NO_2FBr^{79}$ and $^{81}$Na (M + Na) 336.0011, 337.9991.

***N*-Benzyl-5-*anti*-bromo-6-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (11).** To a solution of fluorobromide **15** (990 mg, 3.2 mmol) in methanol (25 mL) was added $Pd(OH)_2$ (99 mg). The solution was degassed in vacuo for 5 min and stirred at rt under a $H_2$ balloon for 1 h. The reaction mixture was then filtered through Celite, the solvent was removed in vacuo, the crude amine was dissolved in $CH_3CN$ (17 mL), and then $Et_3N$ (1.3 g, 4 mmol) followed by BnBr (807 mg, 1.5 mmol) were added dropwise. The solution was stirred at rt for 3 days followed by removal of solvent in vacuo to give the residue, which was chromatographed to give 494 mg (58%) of bromoamine **11** as a light orange oil at $R_f = 0.79$ (1:5 ether/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.25 (m, 5H), 5.17 (dd, $J = 60.6$, 7.3 Hz, 1H, $H_5$), 4.39 (dd, $J = 7.4$, 3.2 Hz, 1H, $H_6$), 3.88 (d, $J = 13.2$, 1H), 3.77 (d, $J = 13.2$, 1H), 3.55 (dd, $J = 6.8$, 1.8 Hz, 1H, $H_1$), 3.07 (ddt, $J = 6.8$, 4.4, and 1.2 Hz, 1H, $H_4$), 3.03 (dt, $J = 9.0$ and 1.2 Hz, 1H, $H_3$), 2.74 (ddd, $J = 9.0$, 4.0, 1.2 Hz, 1H, $H_{3'}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.9, 128.4 (2C overlap), 127.3, 100.1 ($J_{C,F} = 222.3$ Hz), 68.4 ($J_{C,F} = 18.7$ Hz, $C_1$), 58.5, 52.9 ($J_{C,F} = 5.0$ Hz), 51.4 ($J_{C,F} = 17.1$ Hz, $C_4$), 49.4 ($J_{C,F} = 3.0$ Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −208.68 (d, $J = 60.6$ Hz); HRMS *m*/*z* 270.0275, calcd for $C_{12}H_{13}BrFN$ (M) 270.0288.

***N*-Benzyl-5-*anti*,6-*anti*-diacetoxy-2-azabicyclo[2.1.1]hexane (16a) and *N*-Benzyl-5-*anti*-acetoxy-6-*anti*bromo-2-azabicyclo-[2.1.1]hexane (17). General Method A (DMF).** To a solution of dibromide **9** (200 mg, 0.604 mmol) in DMF (20 mL) under argon was added cesium acetate (696 mg, 3.63 mmol). After stirring at 60 °C for 5 days, the reaction mixture was allowed to reach rt. Brine (10 mL) was added, and the solvent was extracted with ether (3 × 20 mL). The combined ether extracts were washed with water (20 mL) and dried over $Na_2SO_4$. The dried ether was evaporated, and the residue was chromatographed on silica gel (hexanes/ether 2:1) to give 70 mg (40%) of diacetate **16a** as an orange colored oil at $R_f = 0.27$ (1:1 hexanes/ether), 78 mg (42%) of bromoacetate **17** as an orange colored oil at $R_f = 0.53$ (1:1 hexanes/ether), and 19 mg (10%) of starting material. For diacetate **16a**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.23 (m, 5H, Ph), 4.99 (s, 2H, $H_5$ and $H_6$), 3.91 (s, 2H, $CH_2Ph$), 3.56 (d, $J = 6.9$ Hz, 1H, $H_1$), 3.04 (d, $J = 6.9$ Hz, 1H, $H_4$), 3.03 (s, 2H, $2H_3$), 2.10 (s, 6H, $2COCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$170.8, 138.2, 128.7, 128.4, 127.3, 81.7 ($C_5$ and $C_6$), 65.5, 58.6, 52.2, 47.7, 21.0; HRMS *m*/*z* 290.1399, calcd for $C_{16}H_{20}NO_4$ (M + H) 290.1392. For bromoacetate **17**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.27 (m, 5H, Ph), 4.91 (d, $J = 7.0$ Hz, 1H), 4.34 (d, $J = 7.1$ Hz, 1H), 3.94 (d, $J = 13.1$ Hz, 1H), 3.86 (d, $J = 13.1$ Hz, 1H), 3.62 (d, $J = 6.7$ Hz, 1H, $H_1$), 3.11 (d, $J = 6.7$ Hz, 1H, $H_4$), 3.04 (d, $J = 8.8$ Hz, 1H, $H_3$), 2.92 (br, 1H, $H_{3'}$), 2.13 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$170.9, 137.7, 128.6, 128.5, 127.4, 82.3, 68.2, 58.4, 53.7, 50.3, 50.0, 21.2; HRMS *m*/*z* 310.0410, 312.0424, calcd for $C_{14}H_{17}NO_2{}^{79,81}Br$ (M + H) 310.0443, 312.0422.

***N*-Benzyl-5-*anti*,6-*anti*-dihydroxy-2-azabicyclo[2.1.1]hexane (16b).** To a solution of diacetate **16a** (50 mg, 0.173 mmol) in methanol (3 mL) under argon was added triethylamine (175 mg, 1.728 mmol). The solution was stirred at rt overnight and concentrated under reduced pressure. Purification of the obtained residue by flash chromatography (9.5:0.5 $CH_2Cl_2$/MeOH) afforded 27 mg (76%) of diol **16b** as a light orange oil at $R_f = 0.54$ ($CH_2Cl_2$/MeOH 9:1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.28 (m, 5H), 4.59 (s, 2H, $H_5$ and $H_6$), 3.89 (s, 2H), 3.57 (br, 2H, 2OH), 3.21 (d, $J = 7.0$ Hz, 1H, $H_1$), 2.97 (s, 2H, $2H_3$), 2.64 (d, $J = 6.9$ Hz, 1H, $H_4$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.7, 128.8, 128.5 and 127.4, 81.9 ($C_5$ and $C_6$), 67.9, 58.9, 52.7, 50.4; HRMS *m*/*z* 206.1173, calcd for $C_{12}H_{16}NO_2$ (M + H) 206.1181.

***N*-Benzyl-5-*anti*,6-*anti*-difluoro-2-azabicyclo[2.1.1]hexane (18) and *N*-Benzyl-3-formylpyrrole (19) (from diol 16b).** To a solution of diol **16b** (25 mg, 0.122 mmol) in $CH_2Cl_2$ (0.7 mL) under argon was added BAST (81 mg, 0.365 mmol) dropwise at −78 °C. The resulting mixture was brought to rt and stirred overnight. The solution was diluted with $CH_2Cl_2$ (1.3 mL) and washed with brine (0.5 mL) and water (0.5 mL), and then the $CH_2Cl_2$ layer was dried over $Na_2SO_4$. The organic layer was concentrated under reduced pressure, and purification of obtained residue by preparative TLC (1:1 hexanes/ether) gave 6 mg (24%) of difluoro compound **18** at $R_f = 0.37$ (1:1 hexanes/ether) and 9 mg (40%) aldehyde **19** at $R_f = 0.13$ (1:1 hexanes/ether). For **18**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.25 (m, 5H), 5.34 (m, AA′XX′ pattern, 2H, $H_5$ and $H_6$), 3.82 (s, 2H), 3.45 (dt, $J = 7.2$, 1.9 Hz, 1H, $H_1$), 2.99 (m, 1H, $H_4$), 2.92 (s, 2H, $2H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.1, 128.4 (2C), 127.3, 100.6, and 98.3 (m, AA′XX′ pattern, 2C, $C_5$ and $C_6$), 65.5 (t, $J = 18.2$ Hz, $C_1$), 58.7, 50.5 (t, $J = 7.3$ Hz), 49.2 (t, $J = 18.1$ Hz, $C_4$); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −217.3 (m). HRMS *m*/*z* 210.1089, calcd for $C_{12}H_{14}NF_2$ (M + H) 210.1094.

***N*-Benzyl-5-*anti*,6-*anti*-diazido-2-azabicyclo[2.1.1]hexane (20) and *N*-Benzyl-6-*anti*-azido-5-*anti*-bromo-2-azabicyclo[2.1.1]hexane (21) (DMF).** According to general method A, sodium azide (15 mg, 0.24 mmol) was added to a solution of crystalline

dibromide **9** (15 mg, 0.045 mmol) in DMF (2.5 mL) under an air atmosphere. The mixture was allowed to stir at 60 °C for 8 d. Workup and chromatography of the residue using silica gel (5:1 hexane/ether) gave 9.3 mg of a mixture of dibromide **9** (2.6 mg), 2.8 mg (34%) of diazide **20** at $R_f = 0.5$ (1:1 hexane/ether), and 4.0 mg (49%) of bromoazide **21** at $R_f = 0.6$. In two trials with noncrystalline dibromide **9** a small amount ( < 6%) of aldehyde **19** was observed at $R_f = 0.35$. For diazide **20**: $^1$H NMR ($CDCl_3$, 400 Hz) $\delta$ 7.25 (m, 5H), 4.14 (s, 2H), 3.75 (s, 2H), 3.31(d, $J = 7.0$ Hz, 1H, $H_1$), 2.85 (s, 2H, $2H_3$), 2.81(d, $J = 7.0$ Hz, 1H, $H_4$); $^{13}$C NMR ($CDCl_3$, 100 Hz) $\delta$ 138.4, 128.9, 128.9, 127.8, 68.4, 67.3, 59.0, 53.9, 48.2; HRMS *m*/*z* calcd for $C_{12}H_{14}N_7$ (M + H) 256.1259, found 256.1263. For bromoazide **22**: $^1$H NMR ($CDCl_3$, 400 Hz) $\delta = 7.25$ (m, 5H), 4.22 (d, $J = 7.0$ Hz, 1H), 4.18 (d, $J = 7.0$ Hz, 1H), 3.77 (two d, $J = 13.2$ Hz, 2H, $CH_2$Ph), 3.41 (d, $J = 6.6$ Hz, 1H, $H_1$), 2.93 (m, 2H, $H_3$+$H_4$), 2.72 (d, $J = 9.1$ Hz, 1H, $H_3$); $^{13}$C NMR ($CDCl_3$, 100 Hz) $\delta$ 138.3, 128.9, 128.9, 127.8, 69.8, 68.9, 59.0, 54.8, 50.5 (2C); HRMS *m*/*z* 294.0483, calcd for $C_{12}H_{14}N_4Br$ ($MBr^{79}$ + H) 294.0481 and 296.0465, calcd for $C_{12}H_{14}N_4Br$ ($MBr^{81}$ + H) 296.0461.

***N*-Benzyl-5-*anti*-6-*anti*-di(phenylthio)-2-azabicyclo[2.1.1]hexane (22) and *N*-Benzyl-5-*anti*-bromo-6-*anti*-(phenylthio)-2-azabicyclo-[2.1.1]hexane (23). General Method B (DMSO).** To a solution of dibromide **9** (50 mg, 0.15 mmol) in dry DMSO (1 mL) was added NaSPh (120 mg, 0.906 mmol) under argon, and the reaction mixture was maintained at 60 °C for 5 h. The usual workup and chromatography (prep TLC, 1:2 ether/hexanes) gave di(phenylthio) ether **22** (22 mg, 37%) at $R_f = 0.53$ (1:2 ether/hexanes) and bromo(phenylthio) ether **23** (16 mg, 29%) at $R_f =$ 0.59 (1:2 ether/hexanes) as light orange-colored oils and the starting dibromide **9** (2 mg, 4%) at $R_f$ 0.73 (1:2 ether/hexanes) as an off-white solid. For di(phenylthio) ether **22**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.23 (m, 15H), 3.94 (s, 2H, $H_5$ and $H_{5'}$), 3.80 (s, 2H, $CH_2$Ph), 3.71 (d, $J = 6.6$ Hz, 1H, $H_1$), 3.16 (d, $J = 6.6$ Hz, 1H, $H_4$), 306 (s, 2H, $H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.5 (br, 2C), 129.2, 129.0, 128.5, 128.4, 127.2, 126.1, 71.3, 58.9, 56.8, 56.6, 51.6; HRMS *m*/*z* 390.1361 calcd for $C_{24}H_{24}NS_2$ (M + H) 390.1345. For bromo(phenylthio) ether **23**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.18 (m, 10H), 4.27 (d, $J = 7.3$ Hz, 1H, $H_6$), 3.88 (d, $J = 13.3$ Hz, 1H, $CH_2$Ph), 3.83 (d, $J = 13.3$ Hz, 1H, $CH_2$Ph), 3.74 (d, $J = 7.3$ Hz, 1H, $H_5$), 3.64 (d, $J = 6.5$ Hz, 1H, $H_1$), 3.13 (d, $J = 6.5$ Hz, 1H, $H_4$), 2.97 (d, $J = 8.9$ Hz, 1H, $H_3$), 2.94 (d, $J = 8.9$ Hz, 1H, $H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 139.1, 138.0, 129.3, 129.0, 128.5, 128.5, 127.4, 126.2, 71.2, 58.8, 58.3, 55.9, 52.7, 52.0; HRMS *m*/*z* 360.0433 calcd for $C_{18}H_{19}BrNS$ (M + H) 360.0416.

***N*-Benzyl-5-*anti*-acetoxy-2-azabicyclo[2.1.1]hexane (24a) (DMF).** Following general method A, to a solution of bromide **10** (14 mg, 0.06 mmol) in DMF (8 mL) under argon was added (72 mg, 0.5 mmol) of AgOAc. The resulting solution was heated for 12 h at 70 °C. Workup and chromatography gave 7 mg (54%) of acetate **24a** at $R_f = 0.28$ (1:1 hexane/ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.24 (m, 5H), 4.73 (d, $J = 7.5$ Hz, $H_5$), 3.82 (d, $J = 13.1$ Hz, 1H, $CH_2$), 3.74 (d, $J = 13.1$ Hz, 1H, $CH_2$), 3.39 (dd, $J = 6.6$, 1.5 Hz, $H_1$), 2.88 (d, $J = 8.7$ Hz, $H_3$), 2.74 (m, 2H, $H_4$ and $H_3$), 2.42 (d, $J = 7.8$ Hz, $H_{6anti}$), 2.03 (s, 3H), 1.73 (dd, $J = 7.8$, 7.5 Hz, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.1, 130.0, 128.8, 128.4, 127.2, 81.4, 65.5, 58.5, 54.0, 44.4, 32.3, 21.0; HRMS *m*/*z* found 232.1315, calcd for $C_{14}H_{18}NO_2$ (M + H) 232.1315.

***N*-Benzyl-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (24b).** To a solution of acetate **24a** (3 mg, 0.002 mmol) in methanol (3 mL) was added $K_2CO_3$ (138 mg, 0.01 mmol), and the solution was stirred at rt for 1 h. After 1 h the base was filtered, and the solvent was removed in vacuo to give 2.1 mg (84%) of the alcohol **24b** at $R_f = 0.20$ (1:2 hexane/ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36 (m, 5H), 4.18 (brd, $J = 7.2$ Hz, $H_5$), 3.78 (d, $J = 12.9$ Hz, 1H, $CH_2$), 3.69 (d, $J = 12.9$ Hz, 1H, $CH_2$), 3.19 (d, $J =$ 6.8, 1.8 Hz, $H_1$), 2.96 (d, $J = 8.8$ Hz, $H_3$), 2.64 (brd, $J =$ 8.1 Hz, $H_{6anti}$), 2.54 (dd, $J = 6.8$, 3.0 Hz, 1H, $H_4$), 2.48 (d, $J = 8.8$ Hz, $H_3$), 1.74 (dd, $J = 8.1$, 7.2 Hz, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 128.7, 128.3, 126.9, 80.6, 67.3, 59.1, 55.0, 46.1, 32.3; HRMS *m*/*z* 190.1212, calcd for $C_{12}H_{15}NO$ (M + H) 190.1227.

***N*-(*tert*-Butoxycarbonyl)-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (25).** To a solution of alcohol **24b** (25 mg, 0.13 mmol) in MeOH (8 mL) was added $Pd(OH)_2$ (5 mg) and $(BOC)_2O$ (54 mg, 0.25 mmol). The solution was stirred under 1 atm of hydrogen for 7 h at rt. Afterward, the solution was diluted with 10 mL of MeOH and filtered through Celite. Evaporation of the solvent followed by column chromatography gave 24 mg (92%) of the pure alcohol **25** at $R_f = 0.31$ (2:1 hexane/ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.17 (m, 2H, $H_1$ and $H_5$), 3.32 (s, 2H, $2H_3$), 2.93 (dm, $J = 7.5$ Hz, 1H, $H_4$), 2.70 (m, 1H, $H_{6anti}$), 1.81 (br, OH), 1.61 (t, $J = 7.5$ Hz, 1H, $H_{6syn}$), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.7, 81.4, 79.5, 63.4, 48.3, 44.1, 36.9, 28.5; HRMS *m*/*z* found 222.1104, calcd for $C_{10}H_{17}NO_3Na$ (M + Na) 222.1104.

***N*-Benzyl-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (26) (from bromide 10 using AgF).** To a solution of bromide **10** (33 mg, 0.13 mmol) in $CH_3NO_2$ (8 mL) at rt under argon was added AgF (83 mg, 0.65 mmol), and the reaction mixture was heated at 50 °C for 12 h. The AgF was filtered via Celite, and the solvent was removed in vacuo to give 20 mg (80%) of pure fluoride **26** at $R_f = 0.20$ (1:2 hexane/ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36 (m, 5H), 4.90 (dd, $J = 64$, 7.2 Hz, $H_5$), 3.74 (d, $J = 13.8$ Hz, 1H, $CH_2$), 3.65 (d, $J = 13.8$ Hz, 1H, $CH_2$), 3.35 (brd, $J = 6.4$ Hz, $H_3$), 2.88 (b, $J = 8.8$ Hz, $H_3$), 2.72 (br, $H_4$), 2.51 (m, 2H, $H_3$ and $H_{6anti}$), 1.90 (ddd, $J = 8.0$, 7.2, 2.4 Hz, $H_{6syn}$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 138.6, 128.7, 128.4, 127.2, 98.8 (d, $J =$ 208 Hz), 65.8 and 65.6, 58.9, 53.5, 45.3, 32.1; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −220.1 (d, $J = 64.7$ Hz); HRMS *m*/*z* found 192.1191, calcd for $C_{12}H_{14}NF$ (M + H) 192.1188.

***N*-Benzyl-5-*anti*-azido-2-azabicyclo[2.1.1]hexane (27). Method A (DMF).** To a solution of bromide **10** (65 mg, 0.24 mmol) in DMF (10 mL) under argon was added sodium azide (84 mg, 1.3 mmol). The resulting solution was heated for 12 h at 70 °C. The usual workup and flash chromatography gave 28 mg (51%) of the azide **27** at $R_f = 0.39$ (1:1 hexane/ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38 (m, 5H), 3.86 (br, $J = 7.5$ Hz, $H_5$), 3.72 (d, $J = 13.2$ Hz, 1H), 3.65 (d, $J = 13.2$ Hz, 1H), 3.32 (dd, $J = 6.3$, 2.0 Hz, $H_1$), 2.86 (brd, $J = 9.3$ Hz, $H_3$), 2.67 (m, $H_4$), 2.61 (d, $J = 9.3$ Hz, $H_3$), 2.38 (brd, $J = 7.8$ Hz, $H_{6anti}$), 1.69 (dd, $J = 7.8$, 7.5 Hz, $H_{6syn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 129.0, 128.8, 127.5, 69.5, 67.0, 59.2, 54.9, 45.2 and 33.8; HRMS *m*/*z* found 215.1291, calcd for $C_{12}H_{15}N_4$ (M + H) 215.1282; *m*/*z* found 256.1551, calcd for $C_{14}H_{18}N_5$ (M + $CH_3CN$ + H) 256.1556.

***N*-Benzyl-5-*anti*-(*tert*-butoxycarbonylamino)-2-azabicyclo-[2.1.1]hexane (28).** To a solution of azide **27** (29 mg, 0.13 mmol) in toluene (8 mL) were added $PPh_3$ (71 mg, 0.27 mmol) and water (1 mL), and the resultant solution was heated at 60 °C for 4 h. After cooling, the two layers were separated, and the water layer was extracted with $CH_2Cl_2$ (3 × 5 mL). All organic layers were combined and dried over $Na_2SO_4$. Solvent was removed in vacuo, and the amine was dissolved in MeOH to which were added $Et_3N$ (18 $\mu$L, 0.26 mmol) and $(BOC)_2O$ (28 mg, 0.13 mmol). Removal of the solvent followed by flash chromatography gave 34 mg (87%) of the BOC protected amine **28** at $R_f =$ 0.37 (1:3 hexane/ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.44 (m, 5H), 4.92 (br, 1H, NH), 3.82 (s, 2H), 3.76 (br, $H_5$), 3.40 (br, $H_1$), 2.86 (d, $J = 8.1$ Hz, $H_3$), 2.72 (br, 2H, $H_3$ and $H_4$), 2.32 (brd, $J = 7.8$ Hz, $H_{6anti}$), 1.74 (dd, $J = 7.8$, 8.1 Hz, $H_{6syn}$), 1.35 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.4, 139.3, 128.9 and 128.8, 127.5, 119.5, 79.9, 66.5, 59.0, 55.2, 44.7, 34.3, 34.2, 28.8; HRMS *m*/*z* found 289.1917, calcd for $C_{17}H_{25}N_2O_2$ (M + H) 289.1911; *m*/*z* found 311.1749, calcd for $C_{17}H_{24}N_2O_2Na$ (M + Na) 311.1730.

***N*-Benzyl-5-*anti*-imidazol-1-yl-2-azabicyclo[2.1.1]hexane (29).** Butyllithium (90 $\mu$L, 2.5 M solution in hexanes, 0.226 mmol) was added dropwise to imidazole (15 mg, 0.226 mmol) in anhydrous DMF (0.5 mL) under argon, and the mixture was stirred at 20 °C for 0.25 h. A solution of bromide **10** (19 mg, 0.075 mmol) in anhydrous DMF (0.5 mL) was added, and after stirring at 70 °C for 8 days, workup, and chromatography ($CH_2Cl_2$/ MeOH/ $NH_4OH$ 90: 10: 1) the imidazolyl compound **29** was isolated as a light orange-colored oil (10 mg, 55%) at $R_f = 0.60$ ($CH_2Cl_2$/MeOH/$NH_4OH$, 90:10:1); $^1$HNMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (s, 1H), 7.43−7.25 (m, 5H), 7.09 (s, 1H), 6.94 (s, 1H), 4.30 (d, $J = 7.3$ Hz, 1H, $H_5$), 3.91 (d, $J = 13.2$ Hz, 1H, Bn), 3.83 (d, $J = 13.2$ Hz, 1H, Bn), 3.70 (dbr, $J = 6.8$ Hz, 1H, $H_1$), 3.14−3.07 (m, 2H, $H_3$), 2.79 (d, $J = 8.7$ Hz, 1H, $H_{6anti}$), 2.13 (m, 1H, $H_4$), 1.88 (two d, $J = 8.5, 8.5$ Hz, 1H, $H_{6syn}$); $^{13}$CNMR (100 MHz, $CDCl_3$) $\delta$ 138.7, 136.8, 129.4, 128.6, 128.5, 127.3, 119.0, 66.1, 64.4, 58.9, 54.6, 44.1, 33.4; HRMS *m*/*z* 240.1495, calcd for $C_{15}H_{18}N_3$ (M + H) 240.1495.

***N*-Benzyl-5-*anti*-phenylthio-2-azabicyclo[2.1.1]hexane (30).** Following method B, to a solution of monobromide **10** (22 mg, 0.087 mmol) in dry DMSO (0.6 mL) was added NaSPh (35 mg, 0.262 mmol), and the reaction mixture was maintained at 60 °C for 5 h under argon. Workup and chromatography (prep TLC, 1:1 ether/hexanes) afforded phenylthio ether **30** (19 mg, 77%) at $R_f = 0.42$ (1:1 ether/hexanes) as a light orange colored oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50−7.23 (m, 10H), 3.96 (d, $J = 13.3$ Hz, 1H, $CH_2Ph$), 3.91 (d, $J = 13.3$ Hz, 1H, $CH_2Ph$), 3.72 (d, $J = 8.0$ Hz, 1H, $H_5$), 3.54 (dbr, $J = 6.6, 1.8$ Hz, 1H, $H_1$), 2.99 (dd, $J = 8.7, 1.0$ Hz, 1H, $H_3$), 2.93 (dd, $J = 8.7, 1.0$ Hz, 1H, $H_3$), 2.88 (m, 1H, $H_{6syn}$), 2.84 (m, 1H, $H_4$), 1.81 (t, $J = 8.0$ Hz, 1H, $H_{6yn}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.9, 136.9, 128.9, 128.7, 128.6, 128.4, 127.1, 125.8, 67.3, 58.8, 55.8, 54.4, 45.0, 35.7; HRMS *m*/*z* 282.1321 calcd for $C_{18}H_{20}NS$ (M + H) 282.1311.

***N*-Benzyl-5-*anti*-iodo-2-azabicyclo[2.1.1]hexane (31).** A solution of NaI (190 mg, 1.269 mmol) in acetone (750 $\mu$L) was added to bromide **10** (16 mg, 0.063 mmol) under argon. The reaction mixture was maintained at reflux for 4 days. The solvent was removed in vacuo, and the crude was dissolved in $CH_2Cl_2$ (4 mL) and washed with water (2 mL). The organic layer was separated, and the aqueous layer was washed with $CH_2Cl_2$ (2 × 2 mL). The organic extracts were combined and dried over $Na_2SO_4$. The solvent was removed in vacuo, and the crude was chromatographed (prep TLC, 1:1 ether/hexanes) to give iodide **31** (14 mg, 74%) at $R_f = 0.74$ (1:1 ether/hexanes) as a light orange-colored oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.24 (m, 5H), 3.95 (d, $J = 9.0$ Hz, 1H, $H_5$), 3.80 (two d, $J = 13.3, 13.3$ Hz, 2H, Bn), 3.46 (dd, $J = 6.5, 1.8$ Hz, 1H, $H_1$), 2.86−2.77 (m, 4H, $2H_3$, $H_4$ and $H_{6anti}$), 1.75 (dd, $J = 9.0, 8.0$ Hz, 1H, $H_{6syn}$); $^{13}$CNMR (100 MHz, $CDCl_3$) $\delta$139.0, 128.5, 128.4, 127.1, 69.5, 59.1, 54.1, 48.5, 37.9, 30.1; HRMS *m*/*z* 300.0243, calcd for $C_{12}H_{15}IN$ (M + H) 300.0244.

***N*-Benzyl-6-*anti*-acetoxy-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (32a). Method A (DMF).** To a solution of bromofluoride **11** (900 mg, 3.33 mmol) in DMF (55 mL) under argon was added cesium acetate (1279 mg, 6.66 mmol). The solution was maintained at 70 °C for 5 days. The usual workup and flash chromatography (1:3 ether/hexanes) afforded 578 mg (64%) of unreacted fluorobromide **11** at $R_f = 0.61$ (1:1 ether/hexane) and 249 mg (30%) (84% BORSM) of fluoroacetate **32a** at $R_f = 0.44$ (1:1 ether/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.22 (m, 5H), 5.29−5.08 (m, ABX pattern, 2H, $H_5$ and $H_6$) (see Supporting Information), 3.88 (d, $J = 13.2$, Hz, 1H), 3.82 (d, $J = 13.2$, Hz, 1H), 3.48 (dd, $J = 7.1, 2.2$ Hz, 1H, $H_1$), 3.05−2.95 (m, 2H, $H_3 + H_4$), 2.88 (ddd, $J = 9.0, 3.7, 1.2$ Hz, 1H, $H_3$), 2.12 (s, 3H); $^1$H NMR (400 MHz, $CDCl_3$/$C_6D_6$ 1:1 mixture) $\delta$ 7.41−7.22 (m, 5H), 5.26−4.99 (m, ABX pattern, 2H, $H_5$ and $H_6$), 3.73 (d, $J = 13.2$, Hz, 1H), 3.66 (d, $J = 13.2$, Hz, 1H), 3.48 (dd, $J = 7.1, 2.2$ Hz, 1H, $H_1$), 2.86 (t, $J = 6.0$ Hz, 1H, $H_4$), 2.79−2.62 (m, 2H, $2H_3$), 2.01 (s, 3H); $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 7.44−7.22 (m, 5H), 5.21−4.96 (m, ABX pattern, 2H, $H_5$ and $H_6$), 3.61 (d, $J = 13.2$, Hz, 1H), 3.55 (d, $J = 13.2$, Hz, 1H), 3.51 (dd, $J = 7.1, 2.1$ Hz, 1H, $H_1$), 2.78 (m, 1H, $H_4$), 2.57 (br d, $J = 9.0$ Hz, 1H, $H_3$), 2.50 (ddd, $J = 9.0, 3.6, 1.2$ Hz, 1H, $H_3$), 1.92 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.2, 138.2, 128.5, 128.4 and 127.2, 99.5 ($J_{C,F} = 219.0$ Hz, $C_5$), 81.3 ($J_{C,F} = 3.6$ Hz), 65.5 ($J_{C,F} = 18.4$ Hz, $C_1$), 58.7, 51.4 ($J_{C,F} = 6.7$ Hz), 48.4 ($J_{C,F} = 17.7$ Hz, $C_4$), 21.0; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −214.63 (d, $J = 60.9$ Hz); HRMS *m*/*z* 250.1224, calcd for $C_{14}H_{17}FNO_2$ (M + H) 250.1238.

***N*-Benzyl-5-*anti*-fluoro-6-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (32b).** To a solution of fluoroacetate **32a** (575 mg, 2.306 mmol) in methanol (35 mL) under argon was added $Et_3N$ (3212 $\mu$L, 23.066 mmol). The solution was stirred at rt for 20 h and concentrated under reduced pressure. Purification of the obtained residue by flash chromatography (0.5:9.5 MeOH/$CH_2Cl_2$) afforded 459 mg (96%) of fluoroalcohol **32b** at $R_f = 0.62$ (1:9 MeOH/$CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.19 (m, 5H), 5.41 (dd, $J = 61.8, 8.0$ Hz, 1H, $H_5$), 4.56 (d, $J = 8.0$ Hz, 1H, $H_6$), 3.83 (s, 2H), 3.33 (dd, $J = 7.2, 2.1$ Hz, 1H, $H_1$ and br, 1H, OH), 2.93 (s, 2H, $2H_3$), 2.82 (brdd, $J = 7.2, 5.2$, Hz, 1H, $H_4$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.8, 128.6, 128.5 and 127.4, 102.2 ($J_{C,F} = 208.7$ Hz, $C_5$), 82.4, 66.9 ($J_{C,F} = 16.3$ Hz, $C_1$), 58.8, 51.6 ($J_{C,F} = 7.8$ Hz), 50.2 ($J_{C,F} = 16.3$ Hz, $C_4$); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −213.63 (dd, $J = 62.4, 3.9$ Hz); the extra 3.9 Hz may be due to H-bonding. Calculated couplings for the related *N*-methyl fluoroalcohol are 62.53 and 11.8 Hz; HRMS *m*/*z* 208.1109, calcd for $C_{12}H_{15}FNO$ (M + H) 208.1132.

***N*-(*tert*-Butoxycarbonyl)-5-*anti*-fluoro-6-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (33).** To a solution of fluoroalcohol **32b** (250 mg, 1.206 mmol) in MeOH (10 mL) were added palladium hydroxide (20 wt % Pd on carbon) (38 mg) and $(Boc)_2O$ (316 mg, 1.447 mmol). The resulting solution was stirred at rt under hydrogen for 6 h. Then the solution was filtered through Celite and washed with MeOH (10 mL). The filtrate was evaporated to give an oily solid, *n*-heptane (20 mL) was added to the residue, and solvent was again evaporated. Then *n*-heptane (30 mL) was added to the residue, and after 2 h of stirring at rt, the separated solid was filtered and dried under reduced pressure to afford 237 mg (91%) of fluoroalcohol **33** as an off-white solid at $R_f = 0.71$ (1:9 MeOH/$CH_2Cl_2$); mp 95−97 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.10 (dd, $J = 60.8, 7.8$ Hz, 1H, $H_5$), 4.28 (d, $J = 7.7$ Hz, 1H, $H_6$), 4.22 (br s, 1H, $H_1$), 3.47 (d, $J = 9.1$ Hz, 1H, $H_3$), 3.40 (d, $J = 9.0$ Hz, 1H, $H_{3'}$), 3.08 (br s, 1H, OH), 2.83 (br t, $J = 6.1$ Hz, 1H, $H_4$), 1.43 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.9, 101.9 ($J_{C,F} = 214.2$ Hz, $C_5$), 84.1, 80.4, 63.8 (br), 48.1 ($J_{C,F} = 16.3$ Hz), 46.0 (br), 28.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −209.3 (d, $J = 57.6$ Hz), −210.3 (d, $J = 57.6$ Hz) (no F-HO splitting was observed.); HRMS *m*/*z* 240.1018, calcd for $C_{10}H_{16}FNO_3Na$ (M + Na) 240.1012.

***N*-Benzyl-6-*anti*-azido-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (34). Method A (DMF).** Sodium azide (144 mg, 2.22 mmol) and tetrabutylammonium chloride (30 mg) were added to a solution of fluorobromide **11** (200 mg, 0.740 mmol) in dry DMF (15 mL) under argon. The reaction mixture was maintained at 70 °C for 5 days. Workup and flash chromatography (1:4 ether/hexanes) afforded 74 mg (43%) (62% BORSM) of fluoroazide **34** as an oil at $R_f = 0.59$ (1:1 ether/hexanes) and 62 mg (31%) of starting material **11** at $R_f = 0.69$; after two column separations, for **34**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.27 (m, 5H), 5.21 (dd, $J = 60.9, 7.1$ Hz, 1H, $H_5$), 4.31 (dd, $J = 7.1, 2.9$ Hz, 1H, $H_6$), 3.85 (d, $J = 13.1$, 1H), 3.79 (d, $J = 13.2$, 1H), 3.43 (dd, $J = 7.1, 2.0$ Hz, 1H, $H_1$), 3.00 (dt, $J = 9.0, 1.3$ Hz, 1H, $H_3$), 2.96 (ddt, $J = 7.1, 4.7, 1.2$ Hz, 1H, $H_4$), 2.85 (ddd, $J = 9.1, 3.7, 1.2$ Hz, 1H, $H_{3'}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.0, 128.5, 128.4 and 127.4, 99.6 ($J_{C,F} = 220.2$ Hz, $C_5$), 67.7 ($J_{C,F} = 4.2$ Hz), 66.3 ($J_{C,F} = 18.1$ Hz), 58.7, 52.1 ($J_{C,F} = 7.1$ Hz), 48.4 ($J_{C,F} = 17.3$ Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −216.11 (d, $J = 60.4$ Hz); HRMS *m*/*z* 233.1202, calcd for $C_{12}H_{14}FN_4$ (M + H) 233.1202.

***N*-Benzyl-6-*anti*-amino-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (35).** To a solution of fluoroazide **34** (70 mg, 0.301 mmol) in toluene (20 mL) and water (2.5 mL) was added triphenylphosphine (166 mg, 0.633 mmol). The reaction mixture was heated to 60 °C for 5 h. After cooling to rt the organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 5 mL). The combined organic layers were dried over $Na_2SO_4$. Filtration, removal of solvent, and purification by flash chromatography (1−10% methanol in methylene chloride) afforded 53 mg (85%) of fluoroamine **35** at $R_f$ = 0.40 (1:9 MeOH/$CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.23 (m, 5H), 5.27 (dd, $J$ = 62.3, 7.4 Hz, 1H, $H_5$), 3.83 (d, $J$ = 13.3, 1H), 3.78 (d, $J$ = 13.3, 1H), 3.73 (dd, $J$ = 7.5, 1.3 Hz, 1H, $H_6$), 3.20 (dd, $J$ = 7.0, 2.1 Hz, 1H, $H_1$), 2.89−2.83 (m, 2H, $H_3$), 2.68 (ddt, $J$ = 7.1, 5.2, 1.2 Hz, 1H, $H_4$), 2.20 (br s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.6, 128.4, 128.2 and 127.0, 101.9 ($J_{C,F}$ = 212.1 Hz, $C_5$), 67.7 ($J_{C,F}$ = 16.2 Hz), 63.8 ($J_{C,F}$ = 2.1 Hz), 58.8, 52.9 ($J_{C,F}$ = 8.2 Hz), 50.3 ($J_{C,F}$ = 16.3 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −213.55 (brd, $J$ = 63.1 Hz); HRMS $m/z$ 207.1301, calcd for $C_{12}H_{16}FN_2$ (M + H) 207.1298.

***N*-Benzyl-6-*anti*-acetamido-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (36).** DMAP (44 mg, 0.3636 mmol) was added to the solution of fluoroamine **35** (25 mg, 0.1212 mmol) in dry methylene chloride (3 mL) under argon. The resulting solution was cooled to 0 °C, and acetyl chloride (26 $\mu$L, 0.3636) was added dropwise. The reaction mixture was allowed to rt and stirred for 3 h. The reaction mixture was then diluted with $CH_2Cl_2$ (7 mL), washed with water (3 × 5 mL), and dried over $Na_2SO_4$. Filtration, removal of solvent and purification by preparative thin layer chromatography (1:9 MeOH/$CH_2Cl_2$) afforded 19 mg (63%) of fluoroacetamide **36** at $R_f$=0.54 (1:9 MeOH/$CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.22 (m, 5H), 6.54 (br s, 1H, NH), 5.34 (dd, $J$=62.5, 7.4 Hz, 1H, $H_5$), 4.79 (ddd, $J$=9.3, 7.4, 1.8 Hz, 1H, $H_6$), 3.91 (d, $J$ = 13.2, 1H), 3.84 (d, $J$ = 13.2, 1H), 3.33 (dd, $J$ = 7.1, 2.5 Hz, 1H, $H_1$), 3.07 (br d, $J$ = 9.1, Hz, 1H, $H_3$), 2.85 (br dd, $J$=9.1, 4.1 Hz, 1H, $H_{3'}$), 2.78 (ddt, $J$= 7.1, 5.7, 1.2 Hz, 1H, $H_4$), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 138.1, 128.6, 128.4 and 127.3, 101.8 ($J_{C,F}$ = 209.0 Hz, $C_5$), 67.0 ($J_{C,F}$ = 18.6 Hz), 58.8, 58.6 ($J_{C,F}$ = 3.2 Hz), 52.5 ($J_{C,F}$ = 7.1 Hz), 49.2 ($J_{C,F}$ = 16.4 Hz), 23.7; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −211.80 (brd, $J$ = 63.0 Hz); HRMS $m/z$ 249.1414, calcd for $C_{14}H_{18}FN_2O$ (M + H) 249.1403.

***N*-Benzyl-5-*anti*-fluoro-6-*anti*-phenylthio-2-azabicyclo[2.1.1]hexane (37).** According to method B, to a solution of bromofluoride **11** (26 mg, 0.096 mmol) in dry DMSO (0.6 mL) was added NaSPh (38 mg, 0.289 mmol), and the reaction mixture was maintained at 60 °C for 9 days under argon. The usual workup and chromatography (prep TLC, 1:3 ether/hexanes) afforded fluoro(phenylthio) ether **37** (20 mg, 69%) at $R_f$=0.26 (1:3 ether/hexanes) as a light orange-colored oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.18 (br, 10H), 5.13 (dd, $J$ = 61.8, 6.7 Hz, 1H, $H_5$), 3.88 (d, $J$=13.2 Hz, 1H), 3.88−3.84 (m, 1H, $H_6$), 3.81 (d, $J$= 13.2 Hz, 1H), 3.54 (dd, $J$=6.8, 2.1 Hz, 1H, $H_1$), 3.11 (dt, $J$=9.0, 1.2 Hz, 1H, $H_3$), 3.01 (m, 1H, $H_4$), 2.78 (ddd, $J$=9.0, 3.9, 1.2 Hz, 1H, $H_{3'}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.2, 129.1, 129.0, 128.5, 128.4, 127.3, 126.1, 99.9 (d, $J$=216.4 Hz), 68.5 (d, $J$=18.7 Hz), 59.9, 54.6 (d, $J$ = 4.6 Hz), 53.6 (d, $J$ = 6.4 Hz), 50.3 (d, $J$ = 17.0 Hz); $^{19}$F NMR (282 Hz, $CDCl_3$) $\delta$ −210.2 (d, $J$=62.4 Hz); HRMS $m/z$ 300.1226 calcd for $C_{18}H_{19}FNS$ (M + H) 300.1217.

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**Supporting Information Available:** General experimental procedures; control reactions with dibromide **13**; reactions in DMSO to prepare **16a**, **18**, **19**, **20**, **24a**, **27**, **32a**, and **34**; reaction with BAST to prepare **26** and attempted preparation of **26** using AgF/DMF; variance of PhSNa concentrations (Table S-5) with monobromide **10** to give thioether **30**; comparison of reactivities for reaction of bromides **9**, **10**, **11**, and **23** with PhSNa (Table 6); proposed mechanisms for formation of aldehyde **19**, X-ray diffraction analysis of dibromide **9**; copies of $^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR for new compounds; a calculated spectrum for *N*-methyl-6-*anti*-fluoro-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane **32c**; SCF Energies and coordinates of optimized geometries for amine invertomers of bromides **9**−**11** shown in Table 4 along with pictures of orbitals for dibromide **9**; and energy minimizations of ions derived from N-methyl-2-azabicyclo[2.1.1]hexyl-5-cations **39**. This material is available free of charge via the Internet at http://pubs.acs.org.