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Selectfluor as a Nucleofuge in the Reactions of Azabicyclo[*n*.2.1]alkane *β*-Halocarbamic Acid Esters (*n* = 2,3)

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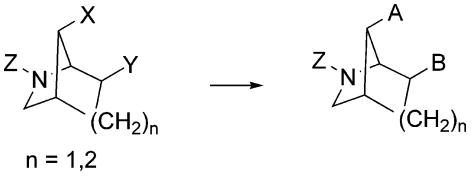

The ability of Selectfluor to act as a nucleofuge for hydrolysis of *β*-*anti*-halides was investigated with *N*-alkoxycarbonyl derivatives of 6-*anti*-Y-7-*anti*-X-2-azabicyclo[2.2.1]heptanes and 4-*anti*-Y-8-*anti*-X-6-azabicyclo[3.2.1]octanes. The azabicycles contained X = I or Br groups in the methano bridge and Y = F, Br, Cl, or OH substituents in the larger bridge. The relative reactivities of the halides were a function of the azabicycle, the halide, and its bridge and the addition of Selectfluor or HgF_2 as a nucleofuge. All halide displacements occurred with retention of stereochemistry. Selectfluor with sodium bromide or sodium chloride, but not sodium iodide, competitively oxidized some haloalcohols to haloketones. A significant 15.6 Hz F···HO NMR coupling was observed with 4-*anti*-fluoro-8-*anti*-hydroxy-6-azabicyclo-[3.2.1]octane.

Introduction

As part of a synthetic effort to prepare methanopyrrolidine structures **2**,[1] it was discovered that Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] in water/acetonitrile can be substituted for mercury or silver salts as a nucleofuge in the hydrolysis−rearrangement of *N*-alkoxycarbonyl-6-*exo*-iodo-2-azabicyclo[2.2.0]hexanes **1a**−**c** (X = I) to form the novel structures **2a**−**c** (X = OH) (eq 1).[2] As a source of alcohols from halides, Selectfluor has the advantage of not being a toxic or expensive metal salt.[3] The Selectfluor-mediated reaction was not effective with the related 6-*exo*-bromides **1d** (X = Br), however. Nor did Selectfluor facilitate

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(1) (a) Krow, G. R.; Lin, G.; Yu, F. *J. Org. Chem.* **2005**, *70*, 590−595. (b) Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2004**, *69*, 8565−8573. (c) Krow, G. R.; Lin, G.; Rapolu, D.; Fang, Y.; Lester, W.; Herzon, S. B.; Sonnet, P. E. *J. Org. Chem.* **2003**, *68*, 5292−5299. (d) Krow, G. R.; Yuan, J.; Lin, G.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 1259−1262. (e) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558−8560. (f) 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*, 1811−1817. (g) 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*, 1805−1810.

(2) (a) Krow, G. R.; Lin, G.; Moore, K. P.; Thomas, A. M.; DeBrosse, C.; Ross, C. W., III; Ramjit, H. G. *Org. Lett.* **2004**, *6*, 1669−1672. (b) Krow, G. R.; Lin, G.; Yu, F.; Sonnet, P. E. *Org. Lett.* **2003**, *5*, 2739−2741.

(3) For reviews of reactions with Selectfluor, see: (a) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31−44. (f) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192−212.

(4) 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 the related all-carbon-bridged bicyclic structures. The bridge with the nitrogen heteroatom is always the main bridge of highest priority before the bridge with fewest members. Thus, all substituents *anti* to nitrogen are *endo*, even when pointed toward a methylene bridge. Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; John Wiley & Sons, Inc.: New York, 1991; pp 49−50.

(5) 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*, 2090−2098.

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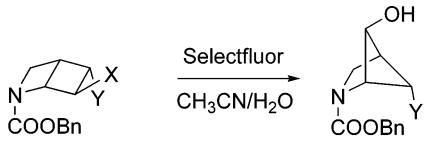
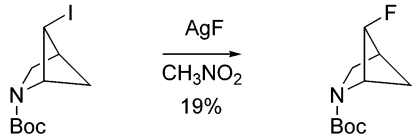
displacement of the 5-*anti*-iodide[4] in the methanopyrrolidine **2d**, although silver fluoride afforded **2e** in low yield (eq 2).[5]



(1)

1a X = I, Y = OH
1b X = I, Y = F
1c X = I, Y = Cl
1d X = Br, Y = OH

2a Y = OH 68%
2b Y = F 84%
2c Y = Cl 75%



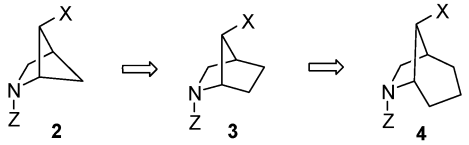
(2)

2d **2e**

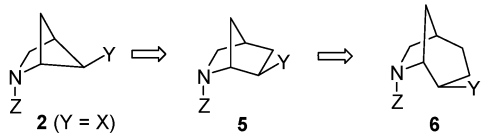
The above results leave several unanswered questions concerning Selectfluor-assisted hydrolyses of *N*-acyl-*β*-haloamines incorporated into bridged pyrrolidines. As depicted in Scheme 1, first, what influence would replacement of the one-atom methylene bridge of generalized structures **2** by additional methylenes have on these hydrolysis reactions (type 1)? Second, what effect would lengthening of the halomethylene bridge with retention of the *β*-leaving group X have on these hydrolysis reactions (type 2)? Third, does Selectfluor only facilitate iodide displacements, or can other halides be hydrolyzed?

SCHEME 1. Homologous *β*-Haloazabicycloalkanes

Type 1. Expansion of the Methylene Bridge.

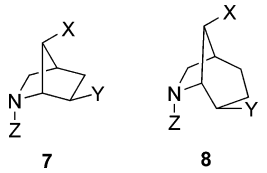


Type 2. Expansion of the Halomethylene Bridge.



Azabicyclic substrates **7** and **8** (X or Y = halogen) are especially interesting because they have one or more leaving groups in non-symmetric *β*-positions *anti* to nitrogen and combine the elements of both type 1 and type 2 reactions of Scheme 1. Both structures have the leaving group (X or Y) and the nitrogen atom in an antiperiplanar orientation, as required for neighboring group participation. Additionally, for such structures **7** and **8** in which both X and Y are halogen, there now is an opportunity to compare the relative reactivity of the two halogens in *N*-acylated nitrogen mustards as a function of both the halogen and its bridge position in the azabicycle.[6] The halides with skeletons **7**[7,8] and **8**[9,10] might also serve as precursors of useful stereochemically defined alcohols or other functionalities.[8a,b,11,12]

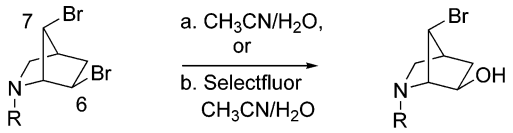
(6) Levi, I.; Blondal, H.; Weed, J. W. R.; Frosst, A. C.; Reilly, H. C.; Schmid, F. A.; Sugira, K.; Tarnowski, G. S.; Stock, C. C. *J. Med. Chem.* **1965**, *8*, 715−718.



7 **8**

Results and Discussion

Azabicyclo[2.2.1]heptanes 7. The requisite structures **7** were prepared as previously described.[13] We first carried out a control experiment on the dibromide **9a** in acetonitrile/water (Table 1, entry 1) since it was uncertain if either bromine would be reactive (eq 3).[8a] The 6-*anti*-bromide was displaced easily to afford the bromohydrin **10a**; the 7-*anti*-bromine was unreactive.[14] Heating of dibromide **9b** at 65 °C still did not enable displacement of the 7-bromide (entry 2) nor did the addition of Selectfluor to dibromide **9a** in acetonitrile/water facilitate reaction of the 7-bromide (entry 3).



(3)

9a R = Boc
9b R = Cbz

10a R = Boc
10b R = Cbz

Although we initially saw no reason to add excess bromide ion to these reactions, subsequent experiments with dibromo-

(7) (a) Raasch, M. S. *J. Org. Chem.* **1975**, *40*, 161−172. (b) Hursthouse, M. B.; Malik, K. M. A.; Hibbs, D. E.; Roberts, S. M.; Seago, A. J. H.; Sik, V.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2419−2425.

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(9) (a) Krow, G. R.; Shaw, D. A.; Jovais, C. S.; Ramjit, H. G. *Synth. Commun.* **1983**, *13*, 575−579. (b) Krow, G. R.; Raghavachari, R.; Shaw, D. A.; Zacharias, D. E. *Trends Heterocycl. Chem.* **1990**, *1*, 1−7. (c) Krow, G. R.; Lee, Y. B.; Raghavachari, R.; Szczepanski, S. W.; Alston, P. V. *Tetrahedron* **1991**, *47*, 8499−8514. (d) Krow, G. R.; Shaw, D. A.; Szczepanski, S.; Ramjit, H. G. *Synth. Commun.* **1984**, *14*, 429−433.

(10) For 4,8-disubstituted *N*-alkyl-2-azabicyclo[3.2.1]octanes, see: ref 11 and Hutchins, R. O.; Rua, L., Jr. *J. Org. Chem.* **1975**, *40*, 2567−2568.

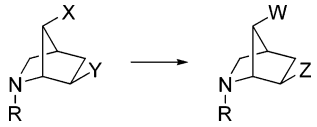
(11) Malpass, J. R.; White, R. *J. Org. Chem.* **2004**, *69*, 5328−5334.

(12) For 8-*anti*-hydroxy-6-azabicyclo[3.2.1]octanes: Peduncularine: (a) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342−11348. (b) Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621−623. Norsecurinine skeleton: (c) Magnus, P.; Rodriguez-Lopez, J.; Mulholland, K.; Matthews, I. *J. Am. Chem. Soc.* **1992**, *114*, 382−383. Actinobolamine: (d) Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1412−1414. For 8-*syn*-hydroxy-6-azabicyclo[3.2.1]-octanes: Peduncularine: (e) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588−2595. (f) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 1581−1584. (g) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333−2337. (h) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523−3525. Catharanthine byproduct: (i) Trost, B. M.; Godleski, S. A.; Belletire, J. L. *J. Org. Chem.* **1979**, *44*, 2052−2054.

(13) Krow, G. R.; Gandla, D.; Guo, W.; Centafont, R. A.; Lin, G.; DeBrosse, C.; Sonnet, P. E.; Ross, C. W., III; Ramjit, H. G.; Carroll, P. J.; Cannon, K. C. *J. Org. Chem.* **2008**, *73*, 2114−2121.

(14) (a) For unsuccessful nucleophilic displacement reactions of a 7-*anti*-bromo-2,6-ethanobridged-2-azabicyclo[2.2.1]heptane, see: Wilson, S. R.; Sawicki, R. A.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 3887−3891. (b) However, for successful nucleophilic displacements with 8-*anti*-bromo-*N*-benzyl-2-azabicyclo[2.2.1]heptane with retention of stereochemistry, see ref 8a. (c) Ni(0)-catalyzed couplings of arylboronic acids with *N*-Boc-7-*anti*-bromo-2-azabicyclo[2.2.1]heptane give 7-*syn*/*anti*-aryl mixtures. Malpass, J. R.; Handa, S.; White, R. *Org. Lett.* **2005**, *7*, 2759−2762.

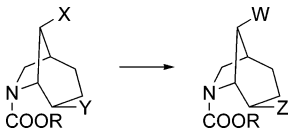
TABLE 1. *β*-Halo-*N*-Alkoxycarbonyl-2-azabicyclo[2.2.1]heptane Hydrolyses with Selectfluor



no.	halide	R	X	Y	reagents/temp/time	product	W	Z	yield (%)
1	**9a**	Boc	Br	Br	CH_3CN/H_2O/25 °C/12 h	**10a**	Br	OH	94
2	**9b**	Cbz	Br	Br	CH_3CN/H_2O/65 °C/12 h	**10b**	Br	OH	80
3	**9a**	Boc	Br	Br	$F^{+a}/CH_3CN/H_2O$/25 °C/24 h	**10a**	Br	OH	60
4	**9b**	Cbz	Br	Br	$F^{+a}/CH_3CN/NaBr^b/H_2O$/25 °C/24 h	**10b**	Br	OH	66
5	**10a**	Boc	Br	OH	$F^{+c}/CH_3CN/NaBr^b/H_2O$/25 °C/24 h	**11**	Br	=O	32[d]
6	**12a**	Boc	I	Cl	CH_3CN/H_2O/25 °C/12 h	**13a**	I	OH	5
7	**12a**	Boc	I	Cl	$F^{+e}/CH_3CN/H_2O$/60 °C/20 h	**13a**	I	OH	35
						14a	OH	OH	45
8	**13a**	Boc	I	OH	$F^{+b}/CH_3CN/H_2O$/25 °C/12 h	**14a**	OH	OH	80
9	**15a**	Boc	I	F	$F^{+f}/CH_3CN/H_2O$/25 °C/12 h	**16a**	OH	F	86

[a] Selectfluor = [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] = F^+, 5−6 equiv of reagent. [b] 2 equiv of reagent. [c] 3 equiv of reagent. [d] Unreacted **10a** (57%). [e] 1.3 equiv of reagent. [f] 1.0 equiv of reagent.

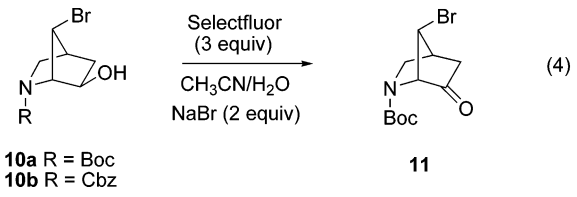
TABLE 2. Selectfluor as Nucleofuge and Oxidant with *β*-Halo-*N*-alkoxycarbonyl-2-azabicyclo[3.2.1]octanes



no.	halide	R	X	Y	reagents/temp/time	product	W	Z	yield (%)
1	**17a**	Et	Br	Br	CH_3CN/H_2O/25 °C/24 h	**18a**	Br	OH	82
2	**17a**	Et	Br	Br	$F^{+a}/CH_3CN/H_2O$/25 °C/24 h	**19a**	Br	=O	91
3	**18a**	Et	Br	OH	$F^{+a}/CH_3CN/H_2O$/25 °C/24 h	NR[c]			
4	**18a**	Et	Br	OH	$F^{+a}/NaBr^b/CH_3CN/H_2O$/25 °C/24 h	**19a**	Br	=O	99
5	**18a**	Et	Br	OH	$F^{+a}/NaI^b/CH_3CN/H_2O$/25 °C/3 days	NR[c]			
6	**18a**	Et	Br	OH	$F^{+a}/NaCl^b/CH_3CN/H_2O$/25 °C/3 days	**19a**	Br	=O	17[d]
7	**20a**	Et	I	Cl	CH_3CN/H_2O/60 °C/12 h	**21a**	I	OH	56[e]
8	**20a**	Et	I	Cl	$F^{+a}/CH_3CN/H_2O$/60 °C/12 h	**21a**	I	OH	77
9	**23a**	Et	I	F	$F^{+a}/CH_3CN/H_2O$/80 °C/12 h	NR[c]			
10	**21b**	Bn	I	OH	$F^{+a}/NaBr^b/CH_3CN/H_2O$/25 °C/24 h	**24b**	I	=O	20[e,f]

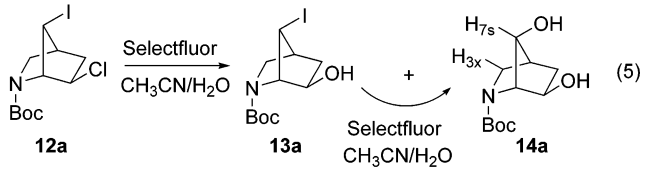
[a] Selectfluor = F^+, 2 equiv of reagent. [b] 2 equiv of reagent. Note: $Br_2/CH_3CN/H_2O$/25 °C/24 h gave ketone **19a** (99%). [c] No reaction. [d] Determined by NMR integration. [e] In addition, starting material (20%) and *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene **22** (14%) were isolated. [f] $Br_2/CH_3CN/H_2O$/25 °C/24 h gave ketone **24b** (65%). The same oxidation with iodoalcohol **21a** gave ketone **24a** (84%).

2-azabicyclo[3.2.1]octanes **17a** (see below, Table 2, entry 2) led us to react dibromide **9b** with Selectfluor and NaBr (2 equiv each) in an effort to observe oxidation (entry 4). Again only bromohydrin **10b** was isolated. When this bromohydrin **10b** was reacted independently with Selectfluor (3 equiv) and NaBr (2 equiv) (entry 5), we were able to isolate a bromoketone **11** in small 32% yield after 24 h, but mainly starting material was retained (eq 4). When viewed together, entries 4 and 5 show that the Selectfluor-facilitated bromide hydrolysis in this ring system is faster than the subsequent oxidation of the 4-hydroxyl group.



(4)

The iodochloride **12a** is a modified nitrogen mustard with two different halogens in separate bridges. A control experiment with acetonitrile/water showed that the 7-*anti*-iodide was unreactive and the 6-*anti*-chlorine was displaced only slowly with retention of stereochemistry to give a trace of the iodoalcohol **13a** (entry 6). Iodochloride **12a** was next mixed in the same solvent system with less than sufficient Selectfluor (1.2 equiv) to react with both halides (eq 5). There was now total displacement of the more reactive 6-*anti*-chlorine, but only partial displacement of the 7-*anti*-iodine (entry 7) to give a mixture of iodohydrin **13a** and diol **14a**. Significantly, this is the first example where Selectfluor aided hydrolysis of a halide other than iodide. Also, because the 6-*anti*-chloride is in the longer ethylene bridge, it reacted even faster than the 7-*anti*-iodide in the methylene bridge.

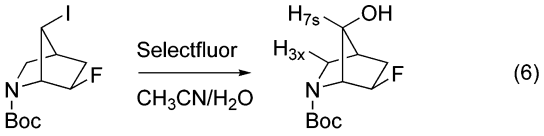


(5)

The 6-*anti*,7-*anti*-diol stereochemistry of **14a** was assigned by means of NOE experiments; the H_{7s} and H_{3x} protons were

shown to be near each other. The iodoalcohol **13a** with Selectfluor (2 equiv) independently afforded the diol **14a** by displacement of the 7-*anti*-iodide with retention of configuration (entry 8).

The iodofluoride **15a** (eq 6) reacted with Selectfluor to give the fluoroalcohol **16a** (entry 9). NOE experiments correlated H_{7s} and H_{3x}, as expected for 6-*anti*-F,7-*anti*-OH stereochemistry. The ^{19}F NMR spectrum (ddd, $J = 18$, 36, 54 Hz) was invariant upon addition of D_2O and thus did not indicate intramolecular F···HO coupling (see Supporting Information).[15]

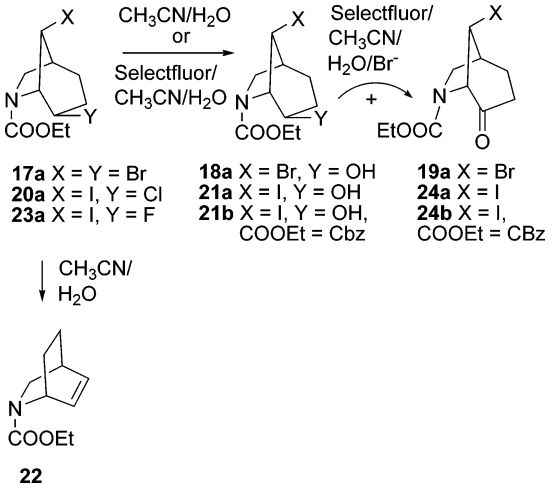


(6)

15a **16a**

Azabicyclo[3.2.1]octanes 8. With success in displacing the 7-*anti*-iodine in structures **12a**, **13a**, and **15a**, our attention turned to Selectfluor-mediated hydrolyses of homologous 6-azabicyclo-[3.2.1]octyl halides **8**. The requisite azabicycles listed in Table 2 were prepared as previously described.[13] At the outset of this study, several routes to 8-hydroxy-6-azabicyclo[3.2.1]octanes, prepared as intermediates during multistep natural product syntheses,[12] were known. However, there were no reports of intermolecular nucleophilic displacements of groups at the 8-positions in these ring systems.[16] The results of hydrolysis efforts with bromides and iodides are shown in Scheme 2 and Table 2.

SCHEME 2. Hydrolysis Reactions of 6-Azabicyclo[3.2.1]octanes



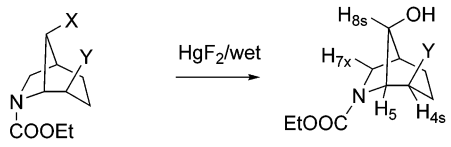
In an initial control experiment, the dibromide **17a** was added to acetonitrile/water and stirred for 24 h (entry 1).[9a] The 4-*anti*-bromide was displaced even at rt to afford the bromoalcohol **18a**,[9d] but the 8-*anti*-bromide remained. When Selectfluor (2 equiv) was added to dibromide **17a** (entry 2), the 8-*anti*-bromide again was not displaced, but now a bromoketone **19a** was obtained!

Our previous Selectfluor reaction with the 2-azabicyclo[2.2.1]-heptane dibromide **9a** to afford bromoalcohol **10a** (prior Table 1, entry 3) had not prepared us to expect this oxidation. It was initially thought that Selectfluor had oxidized the alcohol, but the bromoalcohol **18a** was unreactive with Selectfluor (entry 3). However, when NaBr was added to this same mixture (entry 4), the bromoketone **19a** was again isolated. Taken together, these results suggest that Selectfluor oxidizes bromide ion to bromine, which then results in oxidation of the alcohol. Indeed, bromine in acetonitrile/water oxidized bromoalcohol **18a** in quantitative yield to bromoketone **19a**. The Selectfluor-mediated oxidation was shown to be halide dependent. Bromoalcohol **18a** with NaI/Selectfluor in acetonitrile/water resulted in no change at 24 °C after 3 days (entry 5), while NaCl/Selectfluor in acetonitrile/water after 3 days (entry 6) afforded a 4:1 mixture of unreacted alcohol **18a** and bromoketone **19a**.

The acylated iodochloride **20a** (entry 7) was first tested in acetonitrile/water at 60 °C as a control. Appreciable displacement of the 4-*anti*-chlorine was observed under these forcing conditions with formation of the iodoalcohol **21a** (56%), but some starting material **20a** (20%) remained even after 12 h. Surprisingly, reversible elimination of ICl and regeneration of 2-azabicyclo[2.2.2]oct-5-ene **22**, the starting material for synthesis of **20a**, was also noted in small yield (14%). Under these same conditions, but with added Selectfluor, the iodoalcohol **21a** was obtained in better yield (entry 8).

The iodofluoride **23a** was unreactive with Selectfluor (entry 9), as expected. Iodoalcohol **21b** with Selectfluor and NaBr (2 equiv) after 24 h (entry 10) afforded mostly unreacted iodoalcohol along with a low yield (20%) of the iodoketone **24b**. There was again no evidence for displacement of the 8-*anti*-iodide on the methylene bridge. The low efficiency of the alcohol oxidation was surprising given the ease of oxidation of the bromoalcohol **18a** (entry 4). Indeed, oxidations of the iodoalcohols **21a**/**21b** were more successful using bromine in acetonitrile/water. Since only the oxidation of iodoalcohol **19b** with Selectfluor/NaBr and not that with molecular bromine was slowed, perhaps the Selectfluor reagent complexed to the 8-iodide, sterically retarded subsequent bromine oxidation, and then was removed upon aqueous workup.

Moist Mercuric Fluoride as Nucleofuge with 8-*anti*-Halo-6-azabicyclo[3.2.1]octanes. In an effort to see if an 8-*anti*-halide could be induced by another nucleofuge to undergo hydrolysis, reactions were attempted using hygroscopic HgF_2 (eq 7). The results are shown in Table 3. Indeed, bromoalcohol **18a** reacted with moist mercuric fluoride in nitromethane (entry 1) to provide diol **25a**. When iodochloride **20a** was reacted with moist mercuric fluoride in nitromethane (entry 2), both halides were displaced to give a mixture of diol **25a,** and also fluoroalcohol **26a**.



(7)

18a X = Br, Y = OH
20a X = I, Y = Cl

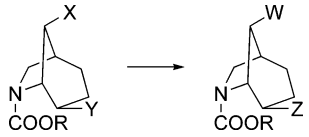
25a Y = OH
26a Y = F

The stereochemistry at C_8 for diol **25a** was shown by observation of an NOE between H_{8s} and H_{7x}. Independently,

(15) (a) Biamonte, M. A.; Vasella, A. *Helv. Chim. Acta* **1998**, *81*, 695−717. (b) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613−12622. (c) Carosati, E.; Sciabola, S.; Cruciani, G. *J. Med. Chem.* **2004**, *47*, 5114−5125. (d) Shimoni, L.; Glucker, J. P. *Struct. Chem.* **1994**, *5*, 383−397. For reviews, see: (e) Desiraju, G. R. *Acc. Chem. Res.* **2002**, *35*, 565−573. (f) Dunitz, J. D.; Taylor, R. *Chem.—Eur. J.* **1997**, *3*, 89−98. (g) Jackel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483−4503.

(16) (a) For an example of intramolecular nucleophilic displacement of an 8-*syn*-bromine in a 6-azabicyclo[3.2.1]octane, see: Davies, H. M. L.; Cao, G. *Tetrahedron Lett.* **1998**, *39*, 5943−5946.

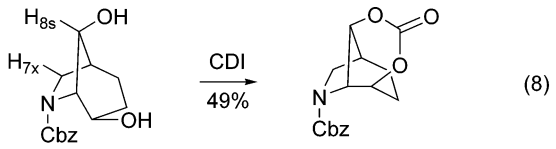
TABLE 3. Mercuric Fluoride and Deoxo-Fluor as Nucleofuges with β-Halo-*N*-alkoxycarbonyl-2-azabicyclo[3.2.1]octanes



no.	halide	R	X	Y	reagents/temp/time	product	W	Z	yield (%)
1	**18a**	Et	Br	OH	HgF_2[a]/CH_3NO_2/60 °C/12 h	**25a**	OH	OH	52
2	**20a**	Et	I	Cl	HgF_2[a]/CH_3NO_2/60 °C/12 h	**25a**	OH	OH	20 (16)[b]
						26a	OH	F	33 (25)[b]
3	**21b**	Bn	I	OH	HgF_2[a]/CH_3NO_2/60 °C/12 h	**25b**	OH	OH	64
4	**23a**	Et	I	F	HgF_2[c]/CH_3NO_2/60 °C/12 h	**26a**	OH	F	36 (47)[b]
						28a	=O	F	46 (6)[b]
5	**26a**	Et	OH	F	HgF_2[a]/CH_3NO_2/60 °C/12 h	NR[d]			
6	**21a**	Et	I	OH	R_2NSF_3[e]/CH_2Cl_2/25 °C/1 h	**23a**	I	F	85
7	**26a**	Et	OH	F	R_2NSF_3[e]/CH_2Cl_2/25 °C/12 h	NR[f]			

[a] 2.8 equiv of moist reagent. [b] A fresh bottle of HgF_2 was used for the reactions in parentheses in entries 1 and 3. [c] 2.8 equiv of moist reagent. [d] No reaction. [e] R_2NSF_3 = Deoxo-Fluor (R = $MeOCH_2CH_2$). [f] Reflux for an additional 12 h afforded starting fluoroalcohol (26%) and unidentified decomposition products.

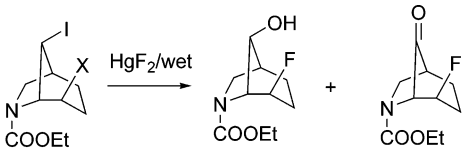
the related diol **25b** was prepared from the iodoalcohol **21b** (entry 3) for which the 4-*anti* stereochemistry of the hydroxyl group was known.[13] The diol was converted to its carbonate **27b** using CDI (1,1′-carbonyldiimidazole) to confirm the 4-*anti*-8-*anti*-diol orientation (eq 8).



25b **27b** (8)

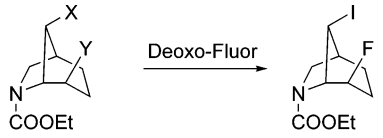
The NMR of the fluoroalcohol structure **26a** was quite surprising. The hydroxyl proton at δ 3.02/2.98 appeared as two resonances consistent with carbamate conformational isomers. Each pattern in $CDCl_3$ is a dd (J = 15.6 and 8.5 Hz). The larger 15.6 Hz coupling is the result of a CF···HO hydrogen interaction; the smaller 8.5 Hz coupling is due to the vicinal H−C−OH coupling (see Supporting Information). This exceptionally large proton−fluorine coupling[15a] was confirmed by ^{19}F NMR (two dddd patterns; see Supporting Information). Addition of D_2O to the sample resulted in loss of the hydroxyl proton coupling to leave two ddd patterns (J = 49, 49, 22 Hz). Computational modeling suggests the absence of coupling between H_{4s} and H_5 (see Supporting Information).

When we next reacted the iodofluoride **29a** with moist mercuric fluoride by heating in nitromethane (entry 4),[2b] we were surprised by the results. A mixture of fluoroalcohol **26a** and mainly an unexpected fluoroketone **28a** was obtained (eq 9).[17] Why did the fluoroalcohol **26a** fail to oxidize when it was prepared from the iodochloride **20a** (entry 1)? In an attempt to shed light on this problem, reactions of iodochloride **20a** and iodofluoride **23a** were repeated using a brand new bottle of HgF_2. The yields of fluoroalcohol **26a** (entries 1 and 3, yields in parentheses) showed little change. However, the reaction of iodofluoride **23a** (entry 3) now yielded only a small amount (6%) of fluoroketone **28a**. Independently, the fluoroalcohol **26a** (entry 4) was unreactive using this fresh bottle of mercuric fluoride in the presence or absence of water (1 equiv). Some unknown factor in the one bottle of HgF_2 was responsible for the oxidation. The fluoroketone **28a** was prepared independently by Dess−Martin periodinane oxidation of the fluoroalcohol **26a**.



23a X = F **26a** **28a** (9)

To determine if hydroxyl groups could be readily displaced in this ring system, we used the reagent Deoxo-Fluor [bis(2-methoxyethyl)aminosulfur trifluoride][2a,18] in methylene chloride (eq 10). The 4-*anti*-hydroxyl group of iodoalcohol **21a** reacted readily under these conditions at room temperature to provide the iodofluoride **23a** in excellent yield (entry 6).[19] By contrast, the 8-*anti*-hydroxyl of fluoroalcohol **26a** was unreactive even after 12 h at room temperature; upon prolonged heating with Deoxo-Fluor (entry 7), the fluoroalcohol decomposed.



21a X = I, Y = OH
26a X = OH, Y = F
23a (10)

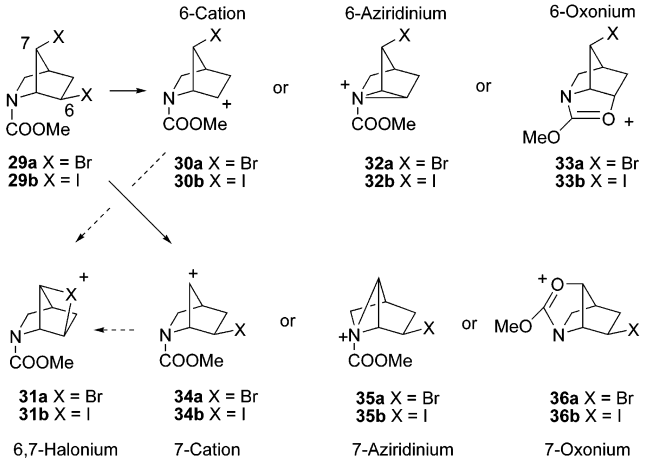
Potential Ionic Reaction Intermediates. For purposes of discussion and molecular energy calculations, potentially rel-

(17) Mercury salt oxidations of alcohols are not common. (a) McKillop, A.; Young, D. W. *Synth. Commun.* **1977**, *7*, 467−474. (b) Habibi, M. H.; Farhadi, S. *Pol. J. Chem.* **2004**, *78*, 741−744.

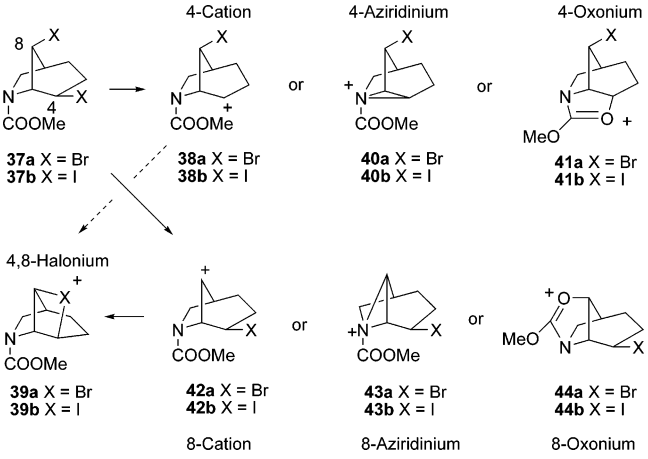
(18) For a review of the reactions with Deoxo-Fluor and the related DAST (diethylaminosulfur trifluoride), see: Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561−2578.

(19) Reactions of *N*-protected amino alcohols with DAST have been observed both with and without neighboring group participation. (a) De Jonghe, S.; Overmeire, I. V.; Van Calenbergh, S.; Hendrix, C.; Busson, R.; de Keukeleire, D.; Herdewijn, P. *Eur. J. Org. Chem.* **2000**, 3177−3183. (b) Hallett, D. J.; Gerhard, U.; Goodacre, S. C.; Hitzel, L.; Sparey, T. J.; Thomas, S.; Rowley, M.; Ball, R. G. *J. Org. Chem.* **2000**, *65*, 4984−4993. (c) Golubev, A. S.; Schedel, H.; Radics, G.; Sieler, J.; Burger, K. *Tetrahedron Lett.* **2001**, *42*, 7941−7944.

SCHEME 3. Potential Ions from the Ionization of *β,β′*-Dihalides of *N*-Methoxycarbonyl-2-azabicyclo[2.2.1]heptanes



SCHEME 4. Potential Ions from the Ionization of *β,β′*-Dihalides of *N*-Methoxycarbonyl-6-azabicyclo[3.2.1]octanes



evant ions for reaction of identically halogenated 6-*anti*-7-*anti*-dihalo-2-azabicyclo[2.2.1]heptanes **29a**,**b** are shown in Scheme 3. The experimental results in Table 1, for structures related to **29**, have shown that 6-*anti*-halides are more reactive than are 7-*anti*-halides and that all reactions occur with retention of configuration. These findings are most consistent with generation of 6-aziridinium ions **32** or oxonium ions **33** in preference to the 7-aziridinium ions **35** or 7-oxonium ions **36**. Only these ions would be expected to give solely stereochemical retention upon attack at C_6 by water nucleophile. The secondary cations **30**/**34** likely would give stereochemical mixtures, and the bridged halonium ions **31** should lead to inverted stereochemistry upon attack by water. Calculations of the relative energies of the ions in Scheme 3 support aziridinium ions **32** and **35** as the most favored ionic intermediates (see the Supporting Information).

Similarly, for discussion and calculation purposes, the potentially relevant ions for reaction of identically substituted 4-*anti*-8-*anti*-dihalo-6-azabicyclo[3.2.1]heptanes **37** are shown in Scheme 4. The findings in Tables 2 and 3, for azabicycles related to **37**, showed preferential reaction of 4-*anti*-halides over 8-*anti*-halides and stereochemical retention at both C_4 and C_8. These results are most consistent with generation of 4-aziridinium ions **40** or oxonium ions **41** faster than the 8-aziridinium ions **43** or 8-oxonium ions **44**. Calculations predict oxonium ions **41** to be more stable than aziridinium ions **40**, but aziridinium ions **43** are more stable than oxonium ions **44**. There is no evidence to confirm the kinetic preference for ions in these reactions (see the Supporting Information).

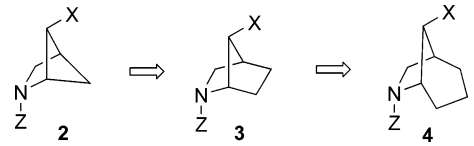


FIGURE 1. Homologous *β*-haloazabicycloalkanes type 1. Expansion of the methylene bridge.

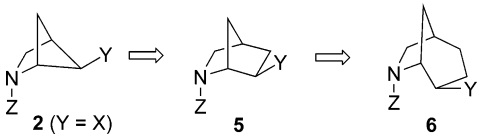


FIGURE 2. Homologous *β*-haloazabicycloalkanes type 2. Expansion of the halomethylene bridge.

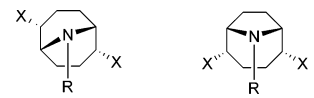
Conclusions

We have determined the scope of Selectfluor-mediated hydrolysis reactions of two classes of azabicyclic systems. For type 1 reactions (Figure 1), the methylene bridge of **2** was expanded. Substrate **2** (X = I) was known to be unreactive toward Selectfluor in acetonitrile/water. For substrates **3** (X = Br, I), Selectfluor has been shown to readily facilitate hydrolysis of a 7-*anti*-iodide but not a 7-*anti*-bromide. Formal addition of an additional methylene to generate **4** (X = Br, I) resulted in a substrate in which both of these 8-*anti*-halides on the methylene bridge failed to hydrolyze using Selectfluor. Deoxo-Fluor with **4** (Y = OH) did not facilitate replacement of an 8-*anti*-hydroxyl by fluoride. Replacement of either an 8-*anti*-bromide or 8-*anti*-iodide from **4** by hydroxyl can be effected with retention using wet mercuric fluoride as nucleofuge.

For type 2 reactions (Figure 2), the halomethylene bridge of **2** (Y = X) was formally expanded. With azabicycle **5** (Y = Br, Cl), a 6-*anti*-bromide was readily displaced at room temperature in acetonitrile/water without added nucleofuge, while a 6-*anti*-chloride reacted more slowly under these conditions. Selectfluor facilitated hydrolysis of such a chloride.

Formal addition of a second flanking methylene group to **5** gives substrates **6**. For these less reactive 6-azabicyclo[3.2.1]-octanes, a 4-bromide (Y = Br) was hydrolyzed in acetonitrile/

(20) Haufe, G.; Rolle, U.; Kleinpeter, E.; Kiviloski, J.; Rissanen, K. *J. Org. Chem.* **1993**, *58*, 7084−7088. Halogen substitution in the conversion of *anti*,*anti*-2,6-dibromo-*N*-cyano-9-azabicyclo[3.3.1]nonane (**i**) and *anti*, *anti*-2,5-dibromo-*N*-cyano-9-azabicyclo[4.2.1]nonane (**ii**) to the corresponding *N*-acetyl-2,6- or 2,5-diacetates using silver acetate has been reported to occur with retention at one carbon and inversion at another. The NMR and symmetry properties of each amide structure are more consistent with a pair of *N*-acetyl conformational isomers having either two retained configurations or two inverted configurations. Our results that show the importance of nitrogen participation in bridged azabicyclic systems suggest doubly retained *anti* configurations **iii** and **iv** for the diacetates. Dr. Haufe is currently reinvestigating this problem (personal communication).



i X = I, R = CN
iii X = OAc, R = COMe
ii X = I, R = CN
iv X = OAc, R = COMe

water at 60 °C, but a 4-chloride (Y = Cl) reacted more slowly under these conditions. Selectfluor facilitated displacement of the 4-*anti*-chloride. Deoxo-Fluor facilitated replacement of a 4-*anti*-hydroxyl from **6** (Y = OH) by a 4-*anti*-fluoride.

Caution must be exercised in the use of Selectfluor in reactions that generate bromide ion since generation of bromine under these conditions may result in unwanted oxidations. Rearrangement products and retention of configuration in all displacement reactions indicate the importance of neighboring group participation in these ring systems.[20] The reactivity with Selectfluor of the 7-*anti*-iodide in the *N*-acyl-2-azabicyclo[2.2.1]-heptanes should prove useful in the synthesis of 7-*anti*-alcohols. Similarly, the 8-*anti*-iodides in the *N*-acyl-6-azabicyclo[3.2.1]-octanes now provide a new precursor to 8-*anti*-alcohols in this ring system.

Experimental Section

***N*-(*tert*-Butoxycarbonyl)-7-*anti*-bromo-6-*anti*-hydroxy-2-azabicyclo[2.2.1]heptane (10a) with Selectfluor.** Dibromide **9a** (225 mg, 0.64 mmol) and Selectfluor (1.35 g, 3.8 mmol) in a 1:1 CH_3CN/H_2O (14 mL) were stirred for 24 h, after which water (25 mL) was added. The solution was extracted with 3:1 $CHCl_3$/isopropanol (3 × 50 mL); the organic phases were combined and dried with $MgSO_4$, solvent was removed, and column chromatography yielded 112 mg of bromoalcohol **10a** (77%).

***N*-(*tert*-Butoxycarbonyl)-7-*anti*-bromo-2-azabicyclo[2.2.1]-heptan-6-one (11).** Sodium bromide (0.031 g, 0.302 mmol) was added as a solid to bromoalcohol **10a** (0.044 g, 0.151 mmol) in 1:1 acetonitrile/water (14 mL). Selectfluor (0.107 g, 0.302 mmol) was added at room temperature, and the flask was capped. The reaction mixture was stirred for 24 h, after which time the acetonitrile was removed in vacuo. The aqueous phase was extracted with ether (3 × 20 mL). The combined ether extracts were dried with Na_2SO_4. Removal of solvent and purification by thin layer chromatography (2:1 ether/hexane) afforded 0.025 g of unreacted alcohol **10a** at R_f 0.43, and 0.014 g of ketone **11** (32%) at R_f 0.5 and (2:1 ether/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16−4.15 (m, 2 H), 3.54 (br d, J = 9.4 Hz, 1 H), 3.33 (br d, J = 9.4 Hz, 1 H), 2.94 (br s, 1 H), 2.75 (ddd, J = 1.2, 4.8, 18.1 Hz, 1 H), 2.05 (dd, J = 2.0, 18.1 Hz, 1 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 153.7, 81.7, 66.2 and 65.9, 49.9, 48.4, 41.1 and 40.7, 39.1, 28.6; HRMS *m*/*z* 312.0211, calcd for $C_{11}H_{16}BrNNaO_3$ (M + Na) 312.0196.

***N*-(*tert*-Butoxycarbonyl)-6-*anti*-hydroxy-7-*anti*-iodo-2-azabicyclo[2.2.1]heptane (13a) and *N*-(*tert*-Butoxycarbonyl)-6-*anti*-7-*anti*-dihydroxy-2-azabicyclo[2.2.1]heptane (14a) from *N*-(*tert*-Butoxycarbonyl)-6-*anti*-chloro-7-*anti*-iodo−2-azabicyclo-[2.2.1]heptane (12a).** According to the general procedure, iodochloride **12a** (72 mg, 0.2 mmol) and Selectfluor (92 mg, 0.26 mmol) in 1:1 acetonitrile/water (10 mL) after 12 h afforded after chromatography 24 mg (35%) of iodoalcohol **13a** and 21 mg (45%) of diol **14a** at R_f 0.25 (4:1 ether/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 and 4.11 (two s, 1H), 4.02 and 3.92 (two br, 1H), 3.89 and 3.82 (two s, 1H), 3.11 (br, 1H), 2.81 and 2.75 (two d, J = 9.8 Hz, 1H), 2.43 (br, 1H), 1.99 and 1.88 (two br, 3 H), 1.39 and 1.36 (two s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 and 154.2, 80.0, 74.0 and 73.4, 60.5 and 59.3, 49.9 and 49.0, 41.2 and 40.7, 37.6 and 37.0, 30.3 and 28.5; HRMS *m*/*z* 254.1214, calcd for $C_{11}H_{19}NO_4Na$ (MNa^+) 254.1206.

***N*-(*tert*-Butoxycarbonyl)-6-*anti*-7-*anti*-dihydroxy-2-azabicyclo-[2.2.1]heptane (14a).** Iodoalcohol **13a** (170 mg, 0.5 mmol) was dissolved in acetonitrile (5 mL), and Selectfluor (354 mg, 1 mmol) was added. After 5 min, water (5 mL) was added and stirring was continued for 12 h at 25 °C. The solution was extracted with ether (3 × 100 mL), the combined extracts were dried over $MgSO_4$, solvent was removed in vacuo, and the residual oil was chromatographed using silica gel (3:1 hexane/ether) to give 92 mg (80%) of diol **55**.

***N*-(*tert*-Butoxycarbonyl)-6-*anti*-fluoro-7-*anti*-hydroxy-2-azabicyclo[2.2.1]heptane (16a).** According to the general procedure, iodofluoride **15a** (180 mg, 1 mmol) and Selectfluor (354 mg, 1 mmol) in 1:1 acetonitrile/water (10 mL) after 12 h afforded after chromatography 100 mg (86%) of fluoroalcohol **16a** at R_f 0.30 (1:2 hexane/ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.7 and 4.63 (two dd, J = 54, 6.4 Hz, 1H), 4.16 and 4.04 (two br s, 1H), 4.12 (s, 1H), 3.13 (m, 1H), 2.80 and 2.72 (d, J = 9.6 Hz, 1H), 2.48 (br, 1H), 2.20−2.02 (br, 3 H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 92.9 and 92.6 (d J = 190 Hz), 80.4 and 80.2, 59.5 and 59.3, 58.4 and 58.1, 49.5 and 48.7, 41.1 and 40.7, 35.2 and 25.0, 28.4; HRMS *m*/*z* 254.1165, calcd for $C_{11}H_{18}FNO_3Na$ (MNa^+) 254.1163.

CH_3CN/Water Control Experiment on the *N*-(Ethoxycarbonyl)dibromide 17a. Synthesis of Bromoalcohol 18a.[9d] A solution of dibromide **17a** (60 mg, 0.17 mmol) in 1:1 acetonitrile/water (10 mL) was stirred for 24 h at rt. Acetonitrile was removed in vacuo, and the water layer was extracted with ether (3 × 10 mL). The ether layers were combined and dried with Na_2SO_4. Solvent was removed in vacuo to give 40 mg (82%) of the known bromoalcohol **18a** at R_f 0.54 (6:4 hexane/ethyl acetate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (m, 5H, OCH_2 and H_5, H_4, H_8), 3.33 (dd, J = 10.5, 5.1 Hz, 1H), 3.20 and 3.18 (two d, J = 10.8 Hz, 1H), 3.10 (d, J = 8.5 Hz, 1H), 2.36 (br, 1H), 2.16 (m, 1H), 1.74 (m, 1H), 1.53 (dd, J = 6.0, 15.6 Hz, 1H), 1.35 (m, 1H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 153.4 and 153.3, 67.6 and 67.1, 60.9, 56.4, 47.0 and 46.8, 46.1 and 45.6, 37.7 and 37.0, 25.1, 20.7, 14.1.

Selectfluor Experiment on the Dibromide 17a To Make *N*-(Ethoxycarbonyl)-8-*anti*-bromo-6-azabicyclo[3.2.1]octan-4-one (19a). According to the general procedure, the solution of the dibromide **17a** (65 mg, 0.18 mmol) and Selectfluor (105 mg, 0.36 mmol) in a 1:1 mixture of acetonitrile/water (10 mL) after 24 h at rt gave 48 mg (91%) of the bromoketone **19a** at R_f 0.45 (6:4 hexane/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (t, J = 5.8 Hz, H_8), 4.32 and 4.22 (br d, J = 6.0 Hz, H_5), 4.12 (m, 2H), 3.75 (ddd, J = 10.4, 4.8, 1.2 Hz, 1H, H_7), 3.70 (d, J = 10.8 Hz, 1H, H_7), 2.69 (br, 1H, H_1), 2.51 (m, 1H, H_{2x}), 2.34 (m, 2H, $2H_3$), 2.01 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 154.0, 66.2, 62.1, 49.2, 48.7, 37.4, 33.2, 26.1, 14.5; HRMS *m*/*z* 298.0055, calcd for $C_{10}H_{14}BrNO_3Na$ (M + Na) 298.0045.

Oxidation of Bromoalcohol 18a to Ketone 19a with Selectfluor/NaBr. To the solution of the bromoalcohol **18a** (70 mg, 0.25 mmol) in a 1:1 mixture of acetonitrile/water (16 mL) were added Selectfluor (150 mg, 0.50 mmol) and sodium bromide (52 mg, 0.50 mmol). The resulting yellow solution was stirred for 24 h at rt, the acetonitrile was removed in vacuo, and the water layer was extracted with ether (3 × 10 mL). The ether layers were combined, dried with Na_2SO_4, and concentrated to give after flash silica gel chromatography 69 mg (99%) of the bromoketone **19a**.

Reaction of Bromoalcohol 18a with Mercuric Fluoride. *N*-(Ethoxycarbonyl)-4-*anti*-8-*anti*-dihydroxy-6-azabicyclo[3.2.1]-octane (25a). The bromoalcohol **18a** (140 mg, 0.49 mol) and HgF_2 (336 mg, 1.24 mmol) in CH_3NO_2 (15 mL) were stirred at 60 °C for 12 h, after which mercuric fluoride was filtered through Celite and the solvent was removed in vacuo. The crude oil was subjected to silica gel flash chromatography to afford 55 mg (52%) of the diol **25a** at R_f 0.56 (1:2 hexane/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 4.20 (br, 1H), 4.16 (m and q, J = 7.1 Hz, 3H), 4.04 (br, 1H), 3.51 (ddd, J = 11.8, 5.3, 0.9 Hz, 1H), 3.35 (br d, J = 11.8 Hz, 1H), 2.37 (br, 1H), 2.30 (m, 1H), 1.88 (m, 1H), 1.75 (dd, J = 15.5, 6.0 Hz, 1H), 1.44 (br, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 73.3 and 73.1, 69.9 and 69.6, 61.4, 54.5 and 54.4, 47.6 and 47.4, 37.1 and 36.3, 26.3 and 25.9, 19.3, 14.7; HRMS *m*/*z* 216.1237, calcd for $C_{10}H_{17}NO_4$ (MH^+) 216.1231; *m*/*z* 238.1049, calcd for $C_{10}H_{17}NO_4Na$ (MNa^+) 238.1050.

Reaction of Iodochloride 20a with Mercuric Fluoride. *N*-(Ethoxycarbonyl)-4-*anti*-8-*anti*-dihydroxy-6-azabicyclo[3.2.1]-octane (25a) and *N*-(Ethoxycarbonyl)-4-*anti*-fluoro-8-*anti*-hydroxy-6-azabicyclo[3.2.1]octane (26a). By the general procedure, the iodochloride **20a** (160 mg, 0.47 mmol) was dissolved in nitromethane (20 mL), and to this was added HgF_2 (316 mg, 1.16 mmol) in one lot. The reaction mixture was then heated at 60 °C for 12 h to afford after workup 20 mg (20%) of the diol **25a** at R_f 0.56 and 34 mg (33%) of the fluoroalcohol **26a** at R_f 0.28 (1:2 hexane/ethyl acetate): ^{1}H NMR (400 MHz, DMSO-d_6, 108 °C) δ 4.67 (br d, J = 48.7 Hz, 1H, H_4), 4.06 (q and m, J = 7.1 Hz, 3H, OCH_2 and H_8), 3.92 (m, 1H, H_5), 3.42 (m, 1H, H_{7x}), 3.20 (d, J = 10.7 Hz, 1H, H_{7n}), 2.2 (br, 2H), 1.79 (br, 2H), 1.31 (br, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.96 and 4.85 (two br d, J = 48.4 Hz, 1H), 4.17 and 4.05 (m, J = 4.8, 4.4 Hz, 3 H), 3.44 (m, 1H), 3.25 (two d, J = 10.8 Hz, 1H), 3.02 and 2.98 (two dd, J = 15.6, 8.5 Hz, 1H, OH), 2.34 (br, 1H), 2.15 (m, 1H), 1.89 (m, 1H), 1.42 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 91.1 and 90.8 (J = 172 Hz), 72.5 and 72.3, 61.5, 53.3, 47.6 and 47.5, 36.7 and 35.9, 23.9 and 23.7, 18.9, 14.7; HRMS m/z 218.0767, calcd for $C_{10}H_{17}NO_3F$ (MH^+) 218.0753. Attempted reactions of iodochloride **20a** with HgF_2 in CH_2Cl_2, $CHCl_3$, and acetonitrile resulted in only recovery of starting iodochloride accompanied by some decomposition. However, the iodochloride (104 mg, 0.31 mmol) in CH_3CN (15 mL) with HgF_2 (206 mg, 0.76 mmol) and water (5 μL, 0.30 mmol, 1 equiv) after stirring at 60 °C for 12 h and the usual purification afforded 10 mg (10%) of unreacted **20a** and 71 mg (72%) of the iodoalcohol **21a**.

***N*-(Benzyloxycarbonyl)-4-*anti*-8-*anti*-dihydroxy-6-azabicyclo-[3.2.1]octane (25b).** The pure iodoalcohol **21b** (407 mg, 1.05mmol) was dissolved in nitromethane (25 mL), and to this was added mercuric fluoride (713 mg, 2.63 mmol) all in one lot. The reaction mixture was then heated at 60 °C for 12 h, after which the reaction mixture was washed with aqueous sodium bromide (2 × 15 mL) and brine (10 mL) and dried with sodium sulfate. The solvent was removed in vacuo to give 285 mg of the crude oil, which upon silica gel flash chromatography gave 175 mg (64%) of the pure diol **25b** at R_f 0.28 (1:4 hexane/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.04 (s, 2H), 4.60 (d, J = 5.6 Hz), 4.18 and 4.13 (s and m, 1H), 4.13 and 4.05 (two m, 1H), 3.93 (m, 1H), 3.86 (d, J = 5.6 Hz, OH), 3.43 (br, 1H), 3.29 (d, J = 10.8 Hz), 2.97 (br, 1H), 2.29 (br, 1H), 2.19 (m, 1H), 1.79 (m, 1H), 1.63 (m, 1H), 1.34 (m, 1H); ^{1}H NMR (400 MHz, DMSO, 96 °C) δ 7.32 (m, 5H), 5.05 (s, 2H), 4.07 (br, 1H), 3.90 (br, 1H), 3.77 (dd, J = 4.8, 4.7 Hz, 1H), 3.39 (br m, 1H), 3.24 (d, J = 10.8 Hz), 2.20 (br, 1H), 2.09 (m, 1H), 1.68 (m, 1H), 1.53 (dd, J = 14.6, 5.9 Hz), 1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 139.9, 128.9, 128.5 and 128.3, 128.2, 73.7 and 73.4, 70.4 and 69.6, 67.4, 55.0, 48.1, 37.5 and 36.7, 26.7 and 26.4, 19.7 and 19.6; HRMS m/z 278.1376, calcd for $C_{15}H_{20}NO_4$ (M + H) 278.1387; m/z 300.1203, calcd for $C_{15}H_{19}NO_4Na$ (M + Na) 300.1206.

***N*-(Benzyloxycarbonyl)-4-*anti*-8-*anti*-dihydroxy-6-azabicyclo-[3.2.1]octane carbonate (27b).** To a solution of the diol **25b** (80 mg, 0.3 mmol) in dry methylene chloride (10 mL) was added DMAP (10 mg) followed by addition of triethylamine (167 μL, 1.2 mmol). The resulting solution was stirred at room temperature for 10 min, after which carbodiimidazole (100 mg, 0.6 mmol) was added. The reaction mixture was then stirred at room temperature for 12 h. The solution was then washed with water (10 mL) and brine (10 mL) and dried over sodium sulfate. The solvent was removed in vacuo to give an oil that upon silica gel flash chromatography gave 43 mg (49%) of the pure diol carbonate **27b** at R_f 0.50 (1:2 hexane/ethyl acetate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 5H), 5.20 (br s, 2H), 4.84 (t, J = 5.2 Hz, H_8), 4.68 (br s) and 4.48 (d, J = 5.7 Hz, 1H, H_4), 4.37 and 4.30 (two t, J = 5.4 Hz, 1H, H_5), 3.65 (m, 1H, H_{7x}), 3.51 (two d, J = 11.1 Hz, 1H, H_{7n}), 2.77 (br, 1H, H_1), 2.12−1.87 (br m, 3H), 1.69 (m, 1H, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 147.7, 136.0, 128.7, 128.5, 128.2 and 128.0, 76.3 and 75.9, 75.6 and 75.3, 67.8 and 67.6, 47.9 and 47.6, 43.7, 36.9 and 35.9, 24.4, 20.9; HRMS m/z 304.1177, calcd for $C_{16}H_{18}NO_5$ (M + H) 304.1184.

Reaction of Iodofluoride 23a with Mercuric Fluoride. *N*-(Ethoxycarbonyl)-4-*exo*-fluoro-8-*anti*-hydroxy-6-azabicyclo-[3.2.1]octane (26a) and *N*-(Ethoxycarbonyl)-4-*exo*-fluoro-6-azabicyclo[3.2.1]octan-8-one (28a). Following the procedure for iodochloride **20a**, iodofluoride **23a** (85 mg, 0.23 mmol) in nitromethane (15 mL) and mercuric fluoride (176 mg, 0.65 mmol) was heated at 60 °C for 12 h. Preparative TLC gave 20 mg (36%) of fluoroalcohol **26a** at R_f 0.32 and 26 mg (46%) of fluoroketone **28a** at R_f 0.41 (1:1 hexane/ethyl acetate): ^{1}H NMR (300 MHz, $CDCl_3$, 58 °C) δ 5.20 (br d, J = 48 Hz, 1H, H_4), 4.06 (q and br, J = 7.1 Hz, 3H, OCH_2 and H_5), 3.64 (dd, J = 10.7, 5.4 Hz, 1H, H_{7x}), 3.52, (d, J = 10.7 Hz, 1H, H_{7n}), 2.65 (m, 1H, H_1), 2.21 (m, 1H), 2.00 to 1.86 (br m, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 155.2, 96.0/95.8 and 94.2/94.0 (J = 172 Hz), 62.3, 60.7 and 60.4, 46.8 and 46.5, 45.8 and 45.1, 30.6, 24.2 and 24.0, 15.0; HRMS m/z 216.1024, calcd for $C_{10}H_{15}NO_3F$ (MH^+) 216.1037.

***N*-(Ethoxycarbonyl)-4-*exo*-fluoro-8-*anti*-iodo-6-azabicyclo-[3.2.1]octane (23a). From Iodoalcohol 21a.** To a solution of iodoalcohol **21a** (27 mg, 0.07 mmol) in methylene chloride (10 mL) at −76 °C was added Deoxo-Fluor (26 μL, 0.14 mmol). The resulting solution was warmed to 25 °C and stirred for 1 h. The mixture was then washed with water (2 × 5 mL) and dried over sodium sulfate. Solvent was removed in vacuo to give after chromatography 23 mg (85%) of iodofluoride **23a**.

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Supporting Information Available: General experimental and procedures for preparation of **28a**; control experiments with **9a**, **12a**, **17a** (to **18a**); Selectfluor or bromine with **9b**, **18a** (to **19a**), **20a** (to **21a**), **23a**, **24a**,**b** and HgF_2 and Deoxo-Fluor with **26a**; Gaussian 98 derived energies for all structures in Schemes 3 and 4; calculated energy profiles for OH rotation and calculated spectroscopic data for *N*-methoxycarbonyl fluorohydrins **15e** and **26e**, copies of ^{1}H NMR and ^{13}C NMR for all new compounds, ^{19}F NMR spectra of fluoroalcohols **15a** and **26a**, and expansion of the OH peak in the ^{1}H NMR for **26a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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