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Neighboring Group Participation in the Additions of Iodonium and Bromonium Ions to *N*-Alkoxycarbonyl-2-azabicyclo[2.2.*n*]alk-5-enes (*n* = 1,2)

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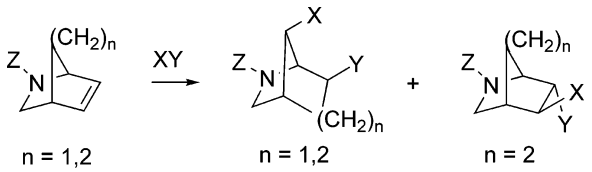

Additions of iodonium-X reagents to *N*-alkoxycarbonyl-2-azabicyclo[2.2.1]hept-5-enes and the homologous 2-azabicyclo[2.2.2]oct-5-enes have been found to mirror the outcomes of additions of bromonium-X reagents. Only rearranged products were observed for reactions of either of these halonium ion reagents with the azabicylo[2.2.1]hept-5-enes. For the azabicyclo[2.2.2]oct-5-enes, nitrogen participation in addition of IOH or BrOH was dependent on the *N*-alkoxycarbonyl group. With larger *N*-Boc, *N*-Cbz, or *N*-Troc protecting groups, unrearranged 5-*anti*-hydroxy-6-*syn*-I(or Br)-2-azabicyclo[2.2.2]octanes were formed by nucleophilic attack at C_5 on *syn*-halonium ions. The structure of *N*-methyl-8-*anti*-bromo-4-*anti*-hydroxy-2-azabicyclo[3.2.1]octane has been reassigned by X-ray analysis.

Introduction

The addition of bromine to *N*-alkoxycarbonyl-2-azabicyclo-[2.2.0]hex-5-enes **1** (Scheme 1) can form unrearranged *N*-alkoxycarbonyl-5,6-disubstituted-2-azabicyclo[2.2.0]hexanes **2a** and **3a** (Table 1, entries 1−5) as well as rearranged *N*-alkoxycarbonyl-2-azabicyclo[2.1.1]hexanes **4a**.[1a,b] The outcomes of such competitions between nucleophilic trapping of bromonium ions and nitrogen neighboring group participation via aziridinium ions are under subtle solvent control, as shown in Table 1 (entries 1−5).[1] By contrast, the homologous *N*-alkoxycarbonyl-2-azabicyclo[2.2.1]hept-5-enes **5**[2−4] (entry 6) are known to react with bromonium ions to afford only rearranged products **7**, and unrearranged adducts of type **6** have not been reported.[5] The next larger homologue, *N*-alkoxycarbonyl or *N*-sulfonyl-2-azabicyclo[2.2.2]oct-5-enes **8**,[6,7] reacts with bromonium ions to give mainly rearranged *N*-alkoxycarbonyl(or sulfonyl)-6-azabicyclo[3.2.1]octanes **10** (entries 7 and 8). There is evidence for minor amounts of dibromides **9**[6a−c] of undetermined stereochemistry.[8,9] Alkene substituents that can stabilize halonium ions interfere with the propensity for aziridinium ion formation.[6b,c]

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(1) (a) 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. (b) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558−8560. (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.; 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. (f) Krow, G. R.; Lin, G.; Yu, F. *J. Org. Chem.* **2005**, *70*, 590−595. (g) 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.

(2) (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. (c) For addition of bromine to an *N*-*O*-tosyl-2-azabicyclo[2.2.1]hept-5-ene without rearrangement, see: Biehler, J.-M.; Bleury, J.-P. *Tetrahedron* **1971**, *27*, 3171−3196.

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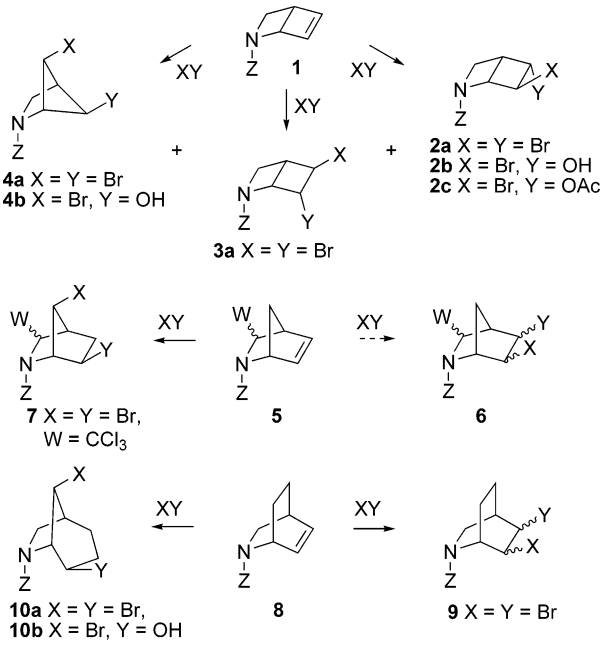
TABLE 1. Bromonium Ion Additions to *N*-Alkoxycarbonyl-2-azabicyclo[2.2.*n*]alkenes

no.	substrate	reagents	Z	addition (%)	rearrangement (%)
1	**1**	Br_2/CH_2Cl_2	COOBn	**2a** (41), **3a** (14)	**4a** (45)[a]
2	**1**	$Br_2/CH_3NO_2/CH_2Cl_2$	COOBn	−	**4a** (100)[a]
3	**1**	NBS/DMSO/H_2O	COOEt	**2b** (76)	**4b** (24)[a]
4	**1**	NBS/THF/H_2O	COOBn	**2b** (44)	**4b** (56)[a]
5	**1**	NBS/HOAc	COOBn	**2c** (11)	**4c** (89)[a]
6	**5**	Br_2/CH_2Cl_2	COOMe	−	**7a** (100)[b]
7	**8**	Br_2/CH_2Cl_2	COOEt	**9a** (10)[c]	**10a** (90)[d]
8	**8**	$NBS/DMSO_{wet}$	COOEt	−	**10b** (100)[e]

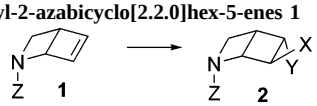
[a] From ref 1c. [b] From ref 2a. [c] From ref 6a. [d] Not isolated. [e] From ref 6d.

SCHEME 1. Halonium Ion Additions to *N*-Acylazabicyclo[2.2.*x*]alk-5-enes



Unlike bromonium ion additions, neighboring group interception of iodonium ions in the reactions of *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes **1** with IX and IOH species has not been observed.[1c,10] In both nonpolar organic solvents and polar protic solvents, iodonium ion species afford solely the unrearranged addition products of type **3d**−**g** (Table 2). We are aware of no reported additions of iodonium ion species to non-lactam *N*-acylated one- or two-atom-bridged azabicycles **5** or **8**.[4,5]

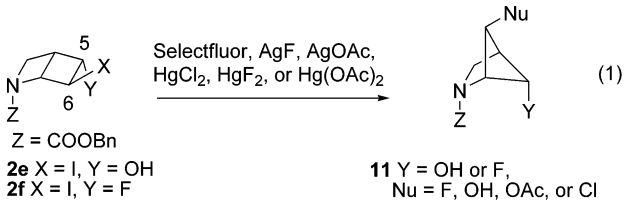
TABLE 2. Iodonium Ion Additions to *N*-Alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes 1



no.	substrate	reagents	Z	X	Y	addition (%)
1	**1**	ICl/CH_2Cl_2	COOBn	I	Cl	**2d** (100)[a]
2	**1**	NIS/DMSO/H_2O	COOBn	I	OH	**2e** (100)[a]
3	**1**	NIS/HOAc/Ac_2O	COOBn	I	F	**2f** (100)[a]
4	**1**	$I_2/HgF_2/MeNO_2/CH_2Cl_2$	COOBn	I	OAc	**2g** (100)[a]

[a] From ref 1c.

Although iodonium ions are not intercepted by neighboring nitrogen atoms in the reactions of *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes **1**, the unrearranged 6-*exo*-iodo-5-*endo*-halo(hydroxy)-2-azabicyclo[2.2.0]hexanes **2e**,**f** are useful methanopyrrolidine intermediates. Ionization of iodide ion provides a second chance for nitrogen participation in these systems.[11] For example, iodide displacement can be facilitated by Selectfluor, mercury salts, or silver ion nucleofuges to give the various combinations of rearranged *N*-alkoxycarbonyl-5,6-disubstituted-2-azabicyclo[2.1.1]hexanes **11** in which one substituent is 5(6)-*syn* and the other is 5(6)-*anti* (eq 1).



The goal in this paper is to extend studies of iodonium ion additions with the fused 2-azabicyclo[2.2.0]hex-5-ene system

(3) For addition of bromine reagents to related 2-azabicyclo[2.2.1]hept-5-ene-2-ones with rearrangement, see: (a) Faith, W. C.; Booth, C. A.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 1983−1985. (b) Evans, C.; McCague, R.; Roberts, S. M.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 656−657. (c) Palmer, C. F.; McCague, R. M. *Perkin Trans.* **1998**, *1*, 2977−2978. (d) Palmer, C. F.; Parry, K. P.; Roberts, S. M.; Sik, V. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1021−1028.

(4) For addition of molecular fluorine to related 2-azabicyclo[2.2.1]hept-5-ene-2-ones to give both rearranged and non-rearranged products, see: (a) Toyota, A.; Aizawa, M.; Habutani, C.; Katagiri, N.; Kaneko, C. *Tetrahedron* **1995**, *51*, 8783−8798. (b) Toyota, A.; Habutani, C.; Katagiri, N.; Kaneko, C. *Tetrahedron Lett.* **1994**, *35*, 5665−5668.

(5) For iodofluorination of related *N*-acylated-2-azabicyclo[2.2.1]hept-5-ene-2-ones to give unrearranged *cis* addition products, see: Toyota, A.; Ono, Y.; Kaneko, C. *Tetrahedron Lett.* **1995**, *36*, 6123−6126.

(6) (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.

(7) For rearrangement of an *N*-tosyl-2-azabicyclo[2.2.2]hex-5-ene, see: (a) Holmes, A. B.; Raithby, P. R.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1983**, 1490−1492. (b) For rearrangement of a related epoxide, see: Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1412−1414. (c) For a related *N*-*O*-tosyl structure, see: Bussmann, R.; Heesing, A. *Tetrahedron Lett.* **1986**, *27*, 561−564.

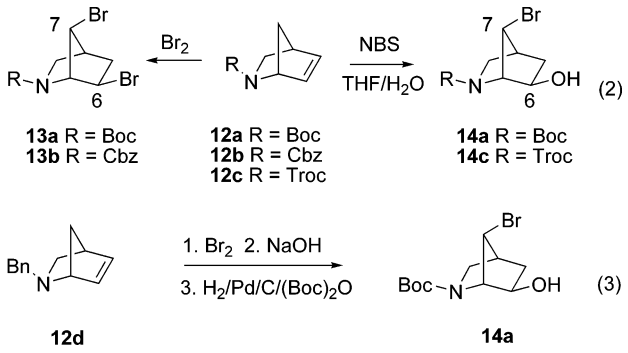
(8) For rearrangement of *N*-alkyl-2-azabicyclo[2.2.1]hept-5-enes upon addition of bromine reagents, see: (a) Malpass, J. R.; White, R. *J. Org. Chem.* **2004**, *69*, 5328−5334. (b) Sosonyuk, S. E.; Bulanov, M. N.; Leshcheva, I. F.; Zyk, N. V. *Russ. Chem. Bull.* **2002**, *51*, 1254−1261. (c) Bulanov, M. N.; Sosonyuk, S. E.; Zyk, N. V.; Zefirov, N. S. *Russ. J. Org. Chem.* **2003**, *39*, 415−421. (d) Mitch, C. H.; Quimby, S. J. Patent WO 00/75140 A1, 2000.

(9) For rearrangement of *N*-alkyl-2-azabicyclo[2.2.2]oct-5-enes upon addition of bromine reagents, see ref 7b and Hutchins, R. O.; Rua, L., Jr. *J. Org. Chem.* **1975**, *40*, 2567−2568.

1 to homologous one-atom-bridged *N*-alkoxycarbonyl-2-azabicyclo[2.2.1]hept-5-enes **12**, which lack the 3-substitution of **5**, and to two-atom-bridged 2-azabicyclo[2.2.2]oct-5-enes **8**. How will the bridging atoms affect the reaction dynamics in these *N*-acylated systems between halonium ions and aziridinium ions? Additionally, rearranged dihalides derived from **12** and **8** are non-symmetric nitrogen mustards. We desired these structures as substrates for comparison of the propensity for neighboring group carbamate participation as a function of ring size to determine the relative leaving ability of *β-anti*-halides as a function of the halides and their ring positions and to study the effects of different nucleofuges upon substrate reactivity. The iodides especially might also serve as precursors for generation of other useful functionalized azabicyclic structures.

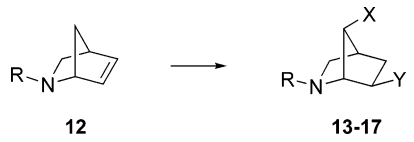
Results and Discussion

Halonium Ion Additions to *N*-Alkoxycarbonyl-2-azabicylo-[2.2.1]alkenes. At the outset of this work, it was known that reaction of 3-substituted *N*-acyl-2-azabicyclo[2.2.1]hept-5-enes with bromonium ion species occurs with nitrogen participation to give products of rearrangement, rather than 1,2-additions.[2] To demonstrate that the rearrangements did not require 3-substituents and were applicable to a range of *N*-alkoxycarbonyl protecting groups, we reacted *N*-Boc alkene **12a** (Table 3, entry 1) and *N*-CBz alkene **12b** (entry 2) with bromine/CH_2Cl_2 to prepare the rearranged dibromides **13a** and **13b**, respectively (eq 2). Similarly, *N*-Boc alkene **12a** (entry 3) and *N*-Troc alkene **12c** (entry 4, Troc = 2,2,2-trichloroethoxycarbonyl) with NBS/THF/water afforded only rearranged bromohydrins **14a** and **14c**, respectively (eq 2). The bromohydrin **14a** was prepared independently from *N*-benzyl-2-azabicyclo[2.2.1]hept-5-ene **12d** by reactions known to give 6-anti,7-anti stereochemistry (eq 3).[8a,b,12]



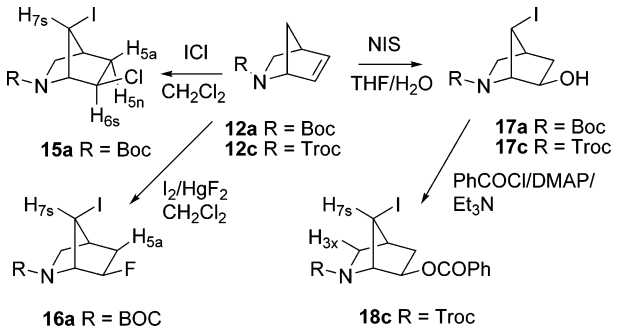
With the rearranged dibromides **13a**,**b** and bromohydrins **14a**,**c** characterized, we next investigated addition of iodonium ion sources to alkenes **12a**,**c** (Scheme 2 and Table 3). In either aprotic or protic solvents, only the rearranged *N*-alkoxycarbonyl-6-*anti*-7-*anti*-disubstituted-2-azabicyclo[2.2.1]heptanes **15**−**17** were observed (Scheme 2). The 6-*anti* substituent orientations in the structures **15**−**17** were confirmed by the absence of significant coupling between H_{6s} and H_1,[8b] consistent with protons that have nearly 90° dihedral angles in molecular models. The iodochloride **15a** (entry 5) and iodoalcohol **17a** (entry 7) have slightly broadened singlets for H_{7s} as expected for rearranged structures.[8b] Consistent with a 7-*anti*-I orientation, the iodochloride **15a** (entry 5) shows small long-range ^{1}H NMR coupling between H_{7s} at δ 3.85 and H_{5s} at δ 2.27. The iodofluoride **16a** (entry 6) also shows small long-range coupling for H_{7s} at δ 3.65 ($J_{5s,7}$ = 1.8 Hz). Additional evidence for a

TABLE 3. ***N*-Alkoxycarbonyl-2-azabicyclo[2.2.1]hept-5-enes and Halonium Ions**

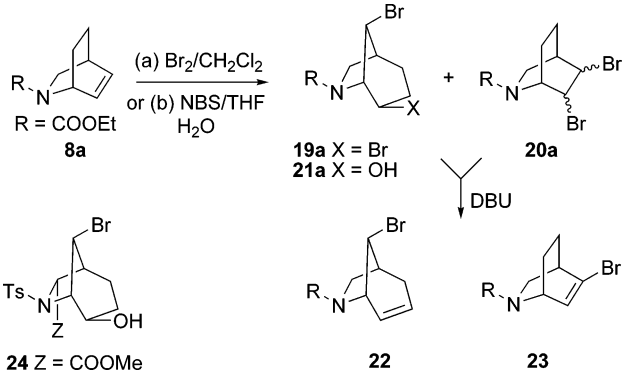


entry	reactant	R	reagents	X	Y	product (yield, %)
1	**12a**	Boc	Br_2/CH_2Cl_2	Br	Br	**13a** (93)
2	**12b**	Cbz	Br_2/CH_2Cl_2	Br	Br	**13b** (54)
3	**12a**	Boc	NBS/2:1 THF/H_2O	Br	OH	**14a** (63)
4	**12a**	Troc	NBS/2:1 THF/H_2O	Br	OH	**14c** (35)
5	**12a**	Boc	ICl/CH_2Cl_2	I	Cl	**15a** (76)
6	**12a**	Boc	I_2/CH_2Cl_2 and HgF_2/CH_3NO_2	I	F	**16a** (50)
7	**12a**	Boc	NIS/2:1 THF/H_2O	I	OH	**17a** (80)
8	**12c**	Troc	NIS/2:1 THF/H_2O	I	OH	**17c** (62)

SCHEME 2. Iodonium Ion Additions to Azabicycle 12



SCHEME 3. Bromonium Ion Additions to *N*-Acyl-2-azabicyclo[2.2.2]oct-5-enes

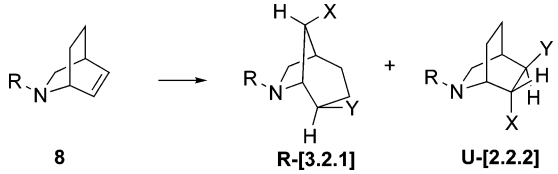


(10) See ref 1c. *N*-Chlorosuccinimide and Selectfluor react with alkene **1** to give ring-opened 5-aminopenten-2-al by electrophilic attack of halonium ion on nitrogen.

(11) (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.

(12) 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.

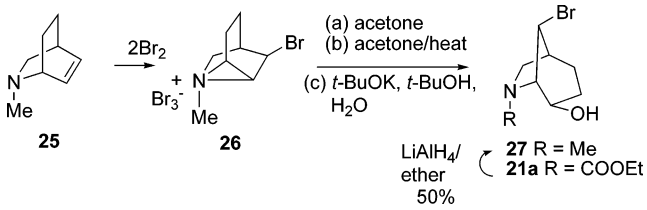
TABLE 4. ***N*-Alkoxycarbonyl-2-azabicyclo[2.2.2]oct-5-enes 8 Reactions with Halonium Ions**



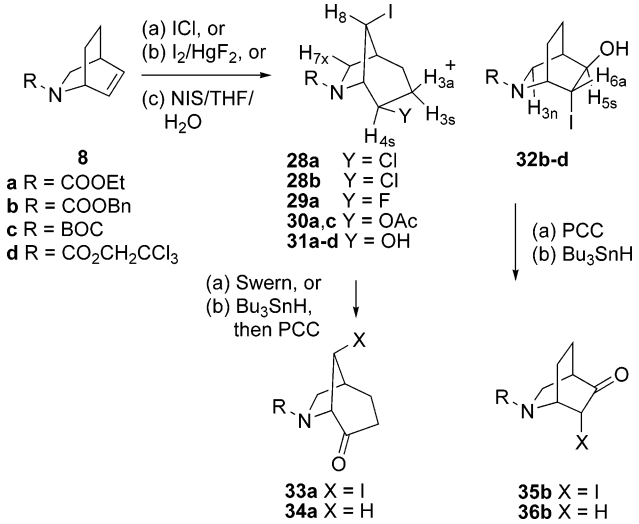
						products (yield, %)[a]	
no	reactant	R	reagents	X	Y	R-[3.2.1]	U-[2.2.2]
1	**8a**	COOEt	Br_2/CH_2Cl_2	Br	Br	**19a** (71)	**20a** (8)[b]
2	**8a**	COOEt	NBS/DMSO/H_2O	Br	OH	**21a** (62)	
3	**8a**	CO_2Et	ICl/CH_2Cl_2	I	Cl	**28a** (72)[c]	
4	**8a**	CO_2Et	$I_2/HgF_2/CH_3NO_2/CH_2Cl_2$	I	F	**29a** (30)	
5	**8a**	CO_2Et	NIS/HOAc/NaOAc	I	OAc	**30a** (92)	
6	**8a**	CO_2Et	NIS/2:1 DMSO/H_2O	I	OH	**31a** (77)[d]	
7	**8b**	Cbz	NIS/2:1 DMSO/H_2O	I	OH	**31b** (53)[d]	**32b** (17)
8	**8c**	Boc	NIS/2:1 DMSO/H_2O	I	OH	**31c** (36)[d]	**32c** (8)
9	**8d**	Troc	NIS/2:1 DMSO/H_2O	I	OH	**31d** (12)[d]	**32d** (29)
10	**8d**	Troc	NBS/THF/H_2O	Br	OH	**21d** (18)	**32e** (14)
11	**8c**	Boc	NIS/HOAc/NaOAc	I	OAc	**30c** (72)	

[a] R = rearranged; U = Unrearranged. Isolated yields. [b] The bromide mixture was not separable, so the stereochemistry of **20a** could not be assigned. See Scheme 3 and ref 6a. [c] R = COOBn (**8b**) gave **28b** (72%). [d] Similar results were noted in THF/H_2O solvent (see the supplementary experimental section).

SCHEME 4. Reassignment of the Bromohydrin 27 from Azabicycloalkene 25



SCHEME 5. Addition of Iodonium Ions to Azabicycles 8



6-*anti*-F in **16a** is found in its smaller J_{F-H} coupling with the *trans* proton H_{5s} at δ 1.85 (J_{HF} = 13.6 Hz) compared to that with the *cis* proton H_{5a} at δ 2.10 (J_{HF} = 33.0 Hz). To remove resonance overlaps, the iodoalcohol **17c** (entry 8) was converted to its benzoate ester **18c** (82%). Consistent with the assigned stereochemistry, positive NOE effects for ester **18c** are seen between H_{3x} at δ 3.45 and H_{7s} at δ 4.03, as well as between H_{3n} at δ 3.19 and H_{5n} at δ 2.37.

Halonium Ion Additions to *N*-Alkoxycarbonyl-2-azabicylo-[2.2.2]oct-5-enes. Previously, the azabicycle *N*-ethoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene **8a** was reacted with bromine/methylene chloride to prepare the rearranged dibromide **19a**, apparently admixed with 10% of an inseparable unrearranged dibromide **20a** (Table 4, entry 1).[6a] The stereochemistries of both bromines in **19a** and **20a** were not proven at the time because the mixture was reacted with base and only the rearranged vinyl bromides **22** and **23** were identified and isolated.[6a] However, the 4-*anti*,8-*anti* stereochemistry of substituents for the rearranged *N*-tosylbromohydrin **24** has been shown by X-ray crystallographic analysis.[7a] As well, alkene **8a** and NBS/DMSO/water gave the rearranged bromohydrin **21a** (entry 2).[6d]

In light of a report that addition of bromine to *N*-methyl-2-azabicyclo[2.2.2]oct-5-ene **25** might give rise to a rearranged bromohydrin with an 8-*syn*-bromine,[9] and to confirm the structure of **21a**, we have repeated the experiments shown in Scheme 4. A salt **26** was formed by addition of 2 equiv of bromine to alkene **25**. As described,[9] the salt was converted to a bromohydrin **27**, which we now have shown to have 8-*anti*-bromo,4-*anti*-hydroxy stereochemistry by X-ray crystallographic analysis. This defines the bromine substituent as *anti* in salt **26**, consistent with more recent NMR evidence.[8b] We have now confirmed the structure of *N*-ethoxycarbonyl bromohydrin[6d] **21a** by chemical correlation with *N*-methyl bromohydrin **27**.

With the structure of the rearranged bromohydrin **21a** assured, we next turned our attention to the addition of iodonium ions to *N*-alkoxycarbonyl-2-azabicyclo[2.2.2]oct-5-enes **8** shown in Scheme 5 and Table 2. Reaction of alkenes **8a** and **8b** (entry 3) with iodine chloride in the aprotic solvent methylene chloride afforded only rearranged products **28a** and **28b**, respectively. The iodine of these structures was determined to be *anti* to nitrogen on the basis of an NOE between the *syn*-H_8 and H_{7x} hydrogens. Assignment of the 4-*anti*-chlorine stereochemistry was more involved. There is an NOE between H_{7n} and H_{3s} (proton toward the nitrogen-containing bridge) and a large coupling between H_{3s} and H_{4s} (J = 6 Hz). The coupling is characteristic of a *cis* H_{3s}/H_{4s} relationship and a dihedral angle of 35.5° based upon modeling. This places the C_4-chlorine of **28a**,**b** *anti* to the nitrogen bridge. In confirmation, protons H_{3a}

and H_{4s} do not appear to be coupled, consistent with a calculated dihedral angle of 80.4°.

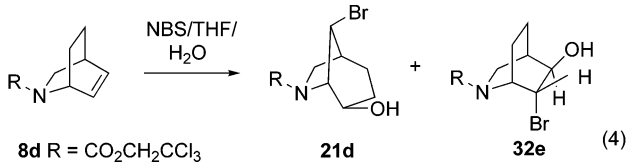
The alkene **8a** (entry 4) with moist mercuric fluoride in nitromethane/methylene chloride afforded a low yield of the iodofluoride **29a**. Spectral comparison to the other iodohalides indicated the rearranged structure.[13]

Reaction of NIS/HOAc with alkene **8a** (entry 5) afforded a rearranged iodoacetate **30a**. This acetate could be hydrolyzed to the iodoalcohol **31a** (92%), identical to that formed by reaction of alkene **8a** with NIS/THF/water[1c] or NIS/DMSO/water (entry 6).[6d,14] Although there is a striking similarity for the NMR spectrum of **31a** and that of rearranged bromohydrin **21a**, an exact structural assignment for **31a** was made difficult by overlapping NMR resonances. The rearranged structure was confirmed by oxidation of the iodoalcohol **31a** to the iodoketone **33a** (89%) and by conversion to the known rearranged ketone **34a** (76%).[6d]

In an effort to improve NMR resolution to obtain stereochemical assignments, we decided to modify the protecting group on nitrogen. As an immediate benefit, isolation of crystalline rearranged iodoalcohol **31c** enabled its 4-*anti*-hydroxy-8-*anti*-iodo structure to be confirmed by X-ray crystallographic analysis. Additionally, and surprisingly, we now found that the results of the iodohydrin syntheses are a function of the *N*-protection. With *N*-Cbz on **8b** (entry 7) or *N*-Boc on **8c** (entry 8), NIS/solvent/water reactions afforded mixtures containing unrearranged iodohydrins **31b**,**c** and **32b**,**c**, respectively. With the *N*-Troc group of **8d** (entry 9), the unrearranged iodohydrin **32d** became the major isolated product.

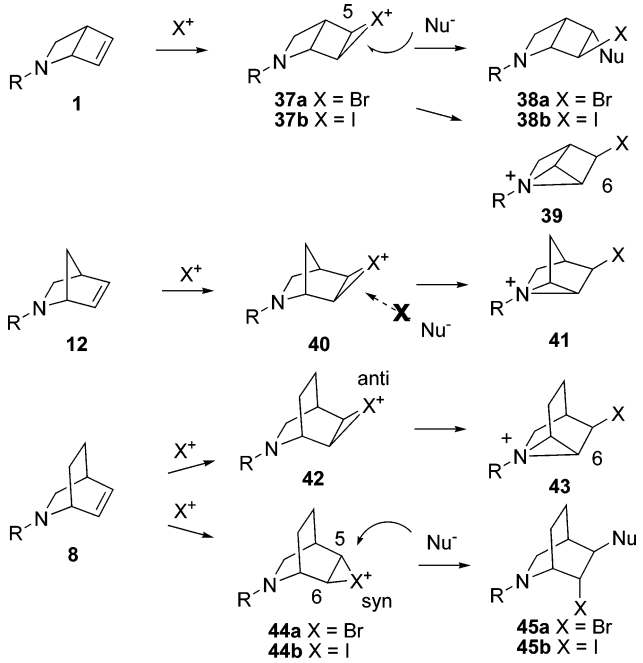
To determine the regiochemical structure of the unrearranged iodohydrins, **32b** was oxidized to iodoketone **35b** (49%), and this was reduced to the known ketone **36b** (Scheme 5).[15] To assign stereochemistry, the ^{1}H NMR of iodohydrin **32d** (two conformers) was most helpful. The C_5 hydroxyl is *anti*, for there is an NOE between H_{5s} at δ 4.59(4.56) and H_{3n} at δ 3.59(3.50). The C_6 iodine is *syn* based upon an NOE between H_{6a} at δ 4.08(4.07) and H_{7a} at δ 2.06−1.81, as well as the small *trans* coupling between H_{5s} and H_{6a} (J = 2.4 Hz).

To show that the isolation of unrearranged bromoalcohols **32b**−**d** with the bulkier protecting groups was not solely a function of NIS as reactant, NBS/THF/water was stirred with alkene **8d** (eq 4). A mixture of rearranged bromoalcohol **21d** and unrearranged bromoalcohol **32e** was isolated, although in low yields (entry 10). Finally (entry 11), it was shown that the choice of solvent was critical to these reactions. When NIS was reacted with alkene **8c** (R = BOC) in HOAc/NaOAc, the conditions of entry 5 (R = COOEt), again only rearranged iodoacetate **30c** was obtained.[1c]



8d R = $CO_2CH_2CCl_3$ **21d** **32e** (4)

SCHEME 6. The Observed Fates of Halonium Ions from Zero-, One-, or Two-Atom-Bridged *N*-R-Azabicycloalkenes (R = Alkoxycarbonyl); (a) X = Br, (b) X = I



As noted previously for reactions of the 2-azabicyclo[2.2.1]-hept-5-ene **5**, there is a tendency for yields of azabicycles to decrease as the protecting group on nitrogen becomes larger. This is especially true in polar protic solvents. A competing process that involves attack of the electrophile on the *N*-protecting group and ring opening has been identified previously.[10]

Mechanistic Considerations. The results of this study allow us to depict the fate of halonium ions formed from 2-azabicyclo-[2.2.*x*]alkenes (x = 0, 1, 2) as shown in Scheme 6. Previously, it was known for the fused azabicycle **1** that the preferred halonium ion **37** has halogen on the less hindered *exo* face.[1] This ion is preferentially attacked by external nucleophile at the C_5 carbon distal to the nitrogen atom to give products **38**. With *anti*-iodonium ions **37b**, the external attack occurs faster than the iodonium ion can rearrange to the aziridinium ion **39b** (X = I).[1c]

In this and other work, the methylene-bridged azabicycles **12** only yielded rearranged products.[2] One possibility is for *anti*-halonium ion **40** to undergo rapid intramolecular attack by nitrogen to give aziridinium ion **41**, the precursor of rearranged products, faster than it can be attacked by external nucleophile. In the alternative, the isolation of only rearranged products is also consistent with reaction of substrate **12** in a synchronous manner with an external halonium ion to give the aziridinium ion **41**, without intervention of halonium ion **40**.

The ethylene-bridged azabicycle **8** might form both an *anti*-halonium ion **42** and a *syn*-halonium ion **44**. In one scenario, there could be reversible formation of halonium ions **42**/**44** but a dominant fast rearrangement from *anti*-halonium ion **42** to aziridinium ion **43**. In this case, only rearranged azabicycles will be observed. This first scenario is consistent with the results in Table 4 in apolar solvents (entries 1, 3, and 4) or acetic acid (entries 5 and 11) or in protic solvent with *N*-COOEt protection (entries 2 and 6).

In a second scenario with larger *N*-protecting groups, and either aqueous DMSO or THF as solvents, the *anti*-halonium

(13) The iodofluoride **29a** has also been prepared from the iodoalcohol **31b**. See the accompanying manuscript: Krow, G. R.; Gandla, D.; Guo, W.; Centafont, R. A.; Lin, G.; DeBrosse, C.; Sonnet, P. E.; Ross, C. W., III; Ramjit, H. G.; Cannon, K. C. *J. Org. Chem.* **2008**, *73*, 2122−2129.

(14) Dalton, D. R.; Rodebaugh, R. K.; Jefford, C. W. *J. Org. Chem.* **1972**, *37*, 362−367.

(15) Krow, G. R.; Johnson, C. *Synthesis* **1979**, 50−51.

ion **42** again rearranges to the aziridinium ion **43**, but now a *syn*-halonium ion **44** undergoes competitive attack by water to give halohydrin **45**. This scenario is noted in Table 4 (entries 7−9). Consistent with the principle of least motion, the larger bulk for *N*-Cbz, *N*-Boc, and *N*-Troc (**8b**−**d**) relative to *N*-COOEt (**8a**) should retard the neighboring group movement necessary to form aziridinium ion **43** from halonium ions **42**.[16] The electron-withdrawing R = trichloroethoxycarbonyl group of **8d** may further retard neighboring group nucleophilic participation required for generation of ions **43**, making formation of unrearranged adducts **45** more competitive. An additional factor opposing nitrogen migration exists in aqueous solvent. Water, through hydrogen bonding to the carbamate, facilitates charge donation from nitrogen to carbonyl oxygen. This effect could serve to reduce the nucleophilicity of nitrogen and retard intramolecular neighboring group participation and rearrangement.

The *trans* stereochemistry of the unrearranged azabicycles **38** and **45** rules out attack by nucleophiles at C_6 on aziridinium ions **39** and **43**.[17] Nucleophilic displacement is preferred at the C_5 position for both *anti*-halonium ions **37** and the *syn*-halonium ions **44**.[18] For preferential *syn*-face attack upon an ion **37** at C_5, it has been argued that, despite greater positive charge density at C_6, the external nucleophile avoids the nearby nitrogen lone pair and the *N*-substituent.[1c] However, for *syn*-halonium ion **44**, there is an ethano bridge facing a nucleophile for *anti*-face attack. Calculations with *syn*-bromonium ion **46c′** and *syn*-iodonium ion **46d′** indicate stronger C_6−X bonds, and this may account for C_5 attack on these ions by water (see Supporting Information).[19]

Conclusions

In summary, the propensity for neighboring group rearrangement upon addition of iodonium ions to *N*-alkoxycarbonyl-2-azabicyclo[2.2.*n*]alk-5-enes as a function of bridge size was found to be $n = 1 > 2 > 0$. With a one-atom bridge, iodohalides and iodohydrins (IX) gave solely rearranged 6-*anti*-X-7-*anti*-iodo-2-azabicyclo[2.2.1]heptanes. With a two-atom bridge, the same species IX added to give rearranged 4-*anti*-X-8-*anti*-iodo-2-azabicyclo[2.2.2]octanes, except for the additions of NIS or NBS in aqueous THF or aqueous DMSO to *N*-R-2-azabicyclo-[2.2.2]oct-5-enes with *N*-alkoxycarbonyl groups [R = Cbz, Boc, or Troc ($CO_2CH_2CCl_3$)]. These gave rearranged iodohydrins accompanied by regioselective and 1,2-stereoselective addition to form 5-*anti*-hydroxy-6-*syn*-halides. The previously erroneous structure of *N*-methyl-8-*anti*-bromo-4-*anti*-hydroxy-2-azabicyclo-[3.2.1]octane **27** has been reassigned.

Experimental Section

***N*-(*tert*-Butoxycarbonyl)-6-*anti*-7-*anti*-dibromo-2-azabicyclo-[2.2.1]heptane (13a).** Bromine (0.620 g, 3.85 mmol) in CH_2Cl_2 (5 mL) was added over 45 min to alkene[20] **12a** (0.625 g, 3.20 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The mixture was maintained at −78 °C for 6 h and was then allowed to warm to room temperature overnight. The organic layer was washed with saturated aqueous $NaHCO_3$ (25 mL). Evaporation of the organic phase and purification of the residue by column chromatography afforded 1.026 g of **13a** (93%) as an oil at R_f 0.51 (1:1 ether/hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 and 4.39 (two br s, 1H), 4.13 (br s, 1H), 3.97 (br, 1H), 3.38 and 3.35 (two dt, J = 9, 3, 3 Hz, 1H), 3.06 and 3.02 (two d, J = 9.6 Hz, 1H), 2.77 (br, 1H), 2.67 (br, 1H), 2.46 and 2.42 (two dd, J = 13.8 and 8.4 Hz, 1H), 1.46 and 1.49 (two s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 80.9, 64.1 and 62.9, 50.0 and 49.3, 47.9 and 47.6, 45.0 and 44.5, 43.0 and 42.9, 39.0 and 38.9, 28.4; HRMS m/z 375.9529, calcd for $C_{11}H_{17}NO_2Na^{79}Br_2$ 375.9524.

***N*-(*tert*-Butoxycarbonyl)-7-*anti*-bromo-6-*anti*-hydroxy-2-azabicyclo[2.2.1]heptane (14a). From alkene 12a.** NBS (0.733 g, 4.12 mmol) was added over 45 min to **12a** (402 mg, 2.06 mmol) in 2:1 THF/water (30 mL) at 0 °C. The mixture was maintained at 0 °C for 2 h and was then allowed to warm to room temperature overnight. Following addition of 10 wt % aq $Na_2S_2O_3$ (100 mL), the aqueous phase was extracted with ether (4 × 100 mL), and the combined organic layers were dried with $MgSO_4$. Removal of solvent in vacuo afforded 0.583 g of white oil, which upon column chromatography gave 0.379 g of **14a** (63%) at R_f 0.45 (2:1 ether/hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 and 4.07 (br, 1H), 3.93 (br s, 1H), 3.83 (br, 1H), 3.10 (br, 1H), 2.81 (br, 1H), 2.60 (br, 1H), 2.28 (br, 1H), 2.09 (br, 1H), 1.99 (br, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 80.6, 74.7, 63.2, 50.1 and 49.9, 49.2, 42.9, 39.2 and 38.8, 28.4 and 28.3; HRMS 314.0361, calcd for $C_{11}H_{18}NO_3Na^{79}Br_2$ 314.0368.

***N*-(*tert*-Butoxycarbonyl)-6-*anti*-chloro-7-*anti*-iodo-2-azabicyclo-[2.2.1]heptane (15a).** Alkene **12a** (97.5 mg, 0.5 mmol) was dissolved in methylene chloride (10 mL). A solution of iodine chloride (89.3 mg, 0.55 mmol) in methylene chloride (5 mL) was added dropwise at 0 °C, and the solution was stirred for an additional 10 h at 25 °C. It was then washed with 10% sodium sulfite until colorless (2 × 5 mL), extracted with ether (3 × 25 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. Column chromatography using silica gel (1:5 ether/hexane) afforded 130 mg (76%) of iodochloride **15a** at R_f 0.4 (1:2 ether/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 and 4.20 (br, 1H, H_1), 3.90 and 3.85 (br, 1H, H_6), 3.85 (br s, 1H, H_{7s}), 3.20 and 3.18 simplifies on heating (dt, J = 9.6, 3.0 Hz, 1H, H_{3x}), 2.86 and 2.81 (d, J = 9.6 Hz, 1H, H_{3n}), 2.63 (br, 1H, H_4), 2.45 (d br, J = 14.0 Hz, 1H, H_{5a}), 2.27 (ddd, J = 14.0, 8.0, 1.2 Hz, 1H, H_{5s}), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 79.9 and 80.4, 64.7 and 63.4, 55.9, 48.8 and 49.0, 46.0 and 45.5, 39.9, 28.5 and 28.3, 19.1 and 18.8; HRMS m/z 379.9917, calcd for $C_{11}H_{17}NO_2ClINa$ (MNa^+) 379.9884.

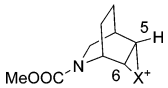
***N*-(*tert*-Butoxycarbonyl)-6-*anti*-fluoro-7-*anti*-iodo-2-azabicyclo-[2.2.1]heptane (16a).** Alkene **12a** (585 mg, 3.0 mmol) was dissolved in nitromethane (10 mL), and mercuric fluoride (1.47 g, 6 mmol) was added. A solution of iodine (1.56 g, 6 mmol) in

(16) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 782. "Those reactions are favored which involve the least change in atomic position and electronic configuration."

(17) Unrearranged *cis* products have been observed for additions of IX (X = F, OH) to an azabicyclic lactam; see ref 5. For 1,2-*cis* additions of bromine to alkene facilitated by neighboring oxygen, see: (a) Menzek, A.; Altundas, A.; Coruh, U.; Akbulut, N.; Vazquez Lopez, E. M.; Hokelek, T.; Erdonmez, A. *Eur. J. Org. Chem.* **2004**, 1143−1148. (b) Menzek, A.; Altundas, A. *Tetrahedron* **2006**, *62*, 12318−12325. For a 1,2-*cis* addition of bromine to alkene facilitated by a neighboring arene, see: (c) Dastan, A. *J. Chem. Res.* **2005**, 608−612.

(18) Oxymercuration/demercuration of azabicycle **18a** affords a 1:1 mixture of 5-*syn* and 5-*anti* alcohols. This indicates that water attacks mercurinium ions regioselectively at C_5 distal from nitrogen. Krow, G.; Rodebaugh, R.; Grippi, M.; Carmosin, R. *Synth. Commun.* **1972**, *2*, 211−214.

(19) Calculated bond distances at RHF/3-21G level for the isomeric *syn*-bromonium ion **46c′** from *N*-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene are 2.04 Å for C_6-Br and 2.13 Å for C_5-Br. For the *syn*-iodonium ion **46d′**, the distances are 2.29 Å for C_6-I and 2.49 Å for C_5-I.



46c' X = Br
46d' X = I

(20) Arakawa, Y.; Yasuda, M.; Ohnishi, M.; Yoshifuji, S. *Chem. Pharm. Bull.* **1997**, *45*, 255−259.

methylene chloride (10 mL) was added dropwise, and the solution was stirred for 3 h at 25 °C. It was then washed with 10% sodium sulfite (2 × 20 mL), extracted with ether (3 × 100 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. Column chromatography using silica gel (1:4 ether/hexane) afforded 500 mg (50%) of iodofluoride **16a** at R_f 0.6 (1:2 ether/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 and 4.56 (two dd br, J = 54, 6 Hz, 1H), 4.1 and 4.23 (two br s, 1H), 3.65 (br s, 1H), 2.97 (m, 1H), 2.57 and 2.62 (two d, J = 9.5 Hz, 1H), 2.46 (br, 1H), 2.10 (dd br, J = 33, 13.6 Hz, 1H), 1.85 (dt, J = 13.6, 13.6, 6.8 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 91.6 (d, J = 199 Hz), 80.7 and 80.4, 62.5, 62.3, 61.4, and 61.2, 49.7 and 48.9, 44.2 and 43.7, 37.1 and 36.9, 28.5, 28.3, and 28.0, 20.0, 19.5, 19.2, and 19.0; HRMS m/z 364.0187, calcd for $C_{11}H_{17}NO_2FINa$ (MNa^+) 364.0180.

***N*-(*tert*-Butoxycarbonyl)-6-*anti*-hydroxy-7-*anti*-iodo-2-azabicyclo[2.2.1]heptane (17a).** By the above procedure, alkene **12a** (195 mg, 1.0 mmol) in 1:1 THF/ water (10 mL) and *N*-iodosuccinimide (450 mg, 2 mmol) after 12 h at 25 °C gave after chromatography on silica gel (3:1 hexane/ether) 288 mg (80%) of iodoalcohol **17a** at R_f 0.77 (1:4 hexane/ether): ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 4.16 (br s, 1H), 3.85 (br, 1H), 3.81 (s, 1H), 3.17 (br d, J = 9.5, 1H), 2.83 (d, J = 9.5 Hz, 1H), 2.62 (br, 1H), 2.12 (br, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1 and 152.9, 80.4 and 80.1, 74.9 and 74.1, 63.7 and 63.6, 49.7 and 48.7, 44.4 and 43.9, 39.9 and 39.3, 28.9 and 28.5, 22.6 and 22.1; HRMS m/z 362.0222, calcd for $C_{11}H_{18}NO_3INa$ (MNa^+) 362.0223.

***N*-(Ethoxycarbonyl)-4-*anti*-bromo-8-*anti*-bromo-6-azabicyclo-[3.2.1]octane (19a).** By the procedure for **13a**, olefin **8a**[21] (887 mg, 4.9 mmol) and bromine (338 μL, 5.9 mmol) in CH_2Cl_2 (40 mL) at −78 °C at rt for 12 h afforded 1.65 g (99%) of the pure dibromide **19a** at R_f 0.33 (2:1 hexane/ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 and 4.32 (two m, 1H), 4.28 and 4.20 (two m, 1H), 4.13 (m and q, J = 6.8 Hz, 3H), 3.50 (m, 1H, H_6), 3.32 (dd, J = 10.4, 6.4 Hz, 1H, H_6), 2.51 (br, 1H, H_1), 2.42 (m, 1H, H_2), 2.30 (m, 1H, H_3), 2.08 (dd, J = 1.0, 5.6 Hz, 1H, H_{3n}), 1.49 (m, H_2), 1.23 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 61.6/61.5, 57.4/57.2, 47.9/47.8, 45.2, 42.3/41.8, 37.8/36.9, 27.1, 20.9, 14.6; HRMS m/z found 339.9540, calcd for $C_{10}H_{15}{}^{79}Br_2NO_2$ (M+H) 339.9542.

Conversion of Bromohydrin 21a to *N*-Methyl-8-*anti*-bromo-4-*anti*-hydroxy-6-azabicyclo[3.2.1]octane (27). To a solution of bromohydrin **21a**[6d] (149 mg, 0.54 mmol) in ether (25 mL) was added $LiAlH_4$ (40 mg, 1.1 mmol) in ether (25 mL), and the mixture was refluxed for 2 h. Water (40 μL), 15% NaOH solution (40 μL), and water (120 μL) were added. The solution was dried using sodium sulfate and then filtered via Celite. Removal of solvent in vacuo and chromatography of the residue (2:1 hexane/ethyl acetate) gave unreacted **21a** (57 mg). Flushing of the column with methanol gave 58 mg (50%, 79% based on recovered **21a**) of *N*-methyl bromoalcohol **27** at R_f 0.45 (6:4 ethyl acetate/hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (dd, J = 4.5, 4.5 Hz, H_8), 3.77 (br, H_4), 2.99 (s and m, J = 9.9 Hz, 2H, H_5 and H_{7x}), 2.78 (br, OH), 2.56 (dd, J = 9.9, 5.7 Hz, H_{7n}), 2.42 (s and m, 4H, Me and H_1), 2.16 (ddd, J = 5.7, 14.1, 14.1 Hz, H_{2a}), 1.95 (m, H_{3s}), 1.61 (dd, J = 15.0, 5.7 Hz, H_{3a}), 1.35 (m, H_{2s}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.9, 64.6, 55.4, 48.7, 44.2, 40.2, 28.2, 21.0. The structure was confirmed by X-ray.

***N*-(Ethoxycarbonyl)-4-*exo*-chloro-8-*anti*-iodo-6-azabicyclo-[3.2.1]octane (28a).** By the procedure for **15a**, alkene **8a** (170 mg, 0.7 mmol) and iodine monochloride (135 mg, 0.84 mmol) in CH_2Cl_2 (30 mL) after 16 h at room temperature gave upon flash chromatography on silica gel 205 mg (72%) of iodochloride **28a** at R_f 0.47 (3:1 hexane/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 4.35 (br, 1H, H_5), 4.27 (br, 1H, H_4), 4.19 (q, J = 7.1 Hz, OCH_2), 4.13 (t, J = 4.5 Hz, 1H, H_8), 3.54 (ddd, J = 10.3, 5.6, 1.2 Hz, 1H, H_{7x}), 3.37 (d, J = 10.3 Hz, 1H, H_{7n}), 2.52 (m, 1H, H_1), 2.47 (ddd, J = 14, 12, 6 Hz, 1H, H_{2a}), 2.25 (dddd, J = 16, 12, 6, 6 Hz, 1H, H_{3s}), 2.00 (dd, J = 16, 6 Hz, 1H, H_{3a}), 1.60 (m, 1H, H_{2s}), 1.25 (t, J = 7.1 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 4.28 and 4.22 (dd, J = 4.3, 3.8 Hz, 1H), 4.14−4.09 (m, 3H), 4.03 (dd, J = 4.7, 4.0 Hz, 1H), 3.44 (m, 1H), 3.29 and 3.27 (d, J = 10.3 Hz, 1H), 2.44 (br, 1H), 2.33 (m, 1H), 2.11 (m, 1H), 1.87 (dd, J = 15.7, 5.4 Hz), 1.53 (m, 1H), 1.04 (t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 61.7 and 61.6, 57.3 and 57.2, 53.4 and 53.0, 47.6 and 47.5, 39.5 and 38.6, 26.9, 23.0, 17.3, 14.7; HRMS m/z 343. 9906, calcd for $C_{10}H_{16}NO_2ICl$ (MH^+) 343.9909; m/z 365.9730, calcd for $C_{10}H_{15}NO_2IClNa$ (MNa^+) 365.9728.

***N*-(Benzyloxycarbonyl)-4-*exo*-chloro-8-*anti*-iodo-6-azabicyclo-[3.2.1]octane (28b).** According to the above procedure, alkene **8b** (300 mg, 1.65 mmol) and iodine monochloride (332 mg, 1.98 mmol) after 16 h afforded 652 mg of crude oil, which upon chromatography afforded 420 mg (72%) of iodochloride **28b** at R_f 0.78 (1:1 hexane/ethyl acetate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 5H), 5.06 (m, 2H), 4.28, 4.22, 4.1, and 4.0 (four br, 3H), 3.42 (dd, J = 10.5, 5.7 Hz, 1H), 3.29 (d, J = 10.5 Hz, 1H), 2.41 (br, 1H), 2.30 (m, 1H), 2.06 (m, 1H), 1.86 (m, 1H), 1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 136.1, 128.6, 128.3, 128.2, 128.0, 127.9, 67.4 and 67.3, 57.5 and 57.4, 53.5 and 52.9, 47.7, 39.5 and 38.6, 26.9, 22.9, 17.1 and 16.9; HRMS m/z 427.9879, calcd for $C_{15}H_{17}NO_2IClNa$ (MNa^+) 427.9890.

***N*-(Ethoxycarbonyl)-4-*exo*-fluoro-8-*anti*-iodo-6-azabicyclo-[3.2.1]octane (29a). (a) From Alkene 8a.** By the procedure for **16a**, to olefin **8a** (220 mg, 1.22 mmol) and mercury fluoride (1.64 g, 6.07 mmol) in nitromethane (25 mL) was added iodine (369 mg, 1.46 mmol) in methylene chloride (15 mL). After 12 h at rt, there was obtained upon flash chromatography 120 mg (30%) of **29a** at R_f 0.55 (1:1 ethyl acetate/hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 and 4.65 (two br d, J = 48 Hz, H_4), 4.34 and 4.26 (two t, J = 3.9 Hz, H_5), 4.08 (q, J = 7.1 Hz, OCH_2), 4.00 (br, H_8), 3.45 (br m, H_{7x}), 3.31 and 3.27 (two d, J = 10.5 Hz, H_{7n}), 2.44 (br, H_1), 2.26 (m, H_{2a}), 1.80 (m, 2H, H_3), 1.50 (m, 1H, H_{2s}), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 87.4 and 87.1 (J = 180 Hz), 62.1, 56.5, 47.6 and 47.5, 39.7 and 38.8, 30.1 and 29.8, 24.1 and 24.0, 18.1 and 17.9, 15.1 and 14.6; HRMS m/z 328.0205, calcd for $C_{10}H_{16}NO_2IF$ (MH^+) 328.0210.

***N*-(Ethoxycarbonyl)-4-*anti*-acetoxy-8-*anti*-iodo-6-azabicyclo-[3.2.1]-octane (30a).** To a solution of alkene **8a** (86 mg, 0.48 mmol) in acetic acid was added sodium acetate (97 mg, 1.2 mmol), followed by *N*-iodosuccinimide (213 mg, 0.95 mmol). The mixture was stirred at room temperature for 16 h, then was diluted with CH_2Cl_2 (15 mL), washed with 10% sodium bicarbonate (10 mL), and dried over magnesium sulfate. The solvent was then removed in vacuo to give 319 mg of a crude oil, which upon flash silica gel chromatography gave 160 mg (92%) of the rearranged iodoacetate **30a** at R_f 0.68 (1:1 hexane/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 4.91 (br, 1H, H_4), 4.32 (dd, J = 4, 4 Hz, 1H, H_5), 4.13 (q, J = 7.1 Hz, 2H), 4.05 (m, 1H, H_8), 3.47 (dd, J = 10.3, 5.4, 1.5 Hz, 1H, H_{7x}), 3.34 (d, J = 10.3 Hz, 1H, H_{7n}), 2.46 (m, 1H, H_1), 2.25 (dddd, J = 14.0, 13.3, 6.6, 1.8 Hz, 1H, H_{2a}), 2.08 (s, 3H), 1.85 (m, 1H, H_{3s}), 1.67 (dd, J = 15.7, 6.0 Hz, 1H, H_{3a}), 1.53 (m, 1H, H_{2s}), 1.25 (t, J = 7.1 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (br) and 4.89 (dd, J = 4, 4 Hz, 1H), 4.34 (br) and 4.32 (t, J = 4.0, 4.0 Hz, 1H), 4.13 (q, J = 7 Hz, 2H), 4.06 (dd, J = 4, 4 Hz, 1H), 3.50 (dd, J = 5, 10 Hz, 1H), 3.36 and 3.33 (two d, J = 10 Hz, 1H), 2.48 (br, 1H), 2.24 (ddd, J = 14, 14, 7 Hz, 1H), 2.10 (s, 3H), 1.88 (m, 1H), 1.66 (dd, J = 16, 6 Hz, 1H), 1.59 (m, 1H), 1.27 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 and 169.7, 153.5 and 153.4, 68.3 and 67.9, 61.5, 55.2 and 55.0, 47.3 and 47.1, 39.3 and 38.5, 23.5, 22.9, 21.5, 19.0 and 19.2, 18.7, 14.5; HRMS m/z 368.0366, calcd for $C_{12}H_{19}NO_4I$ (M + H) 368.035 and m/z 390.0192, calcd for $C_{12}H_{18}NO_4NaI$ (M + Na) 390.0178.

***N*-(Ethoxycarbonyl)-4-*anti*-hydroxy-8-*anti*-iodo-6-azabicyclo-[3.2.1]octane (31a). (a) From alkene 8a in THF/Water.** By the procedure for preparation of **14a**, a solution of alkene **27a** (340 mg, 1.87 mmol) in 2:1 water/THF (22.5 mL) and *N*-iodosuccinimide

(21) Cava, M. P.; Wilkins, C. K., Jr.; Dalton, D. R.; Bessho, K. *J. Org. Chem.* **1965**, *30*, 3772−3775.

(844 mg, 3.8 mmol) after 16 h gave upon chromatography 420 mg (69%) of rearranged iodoalcohol **31a** at R_f 0.43 (1:1 hexane/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 4.17 (br, 1H, H_4), 4.14 (d, J = 7.1 Hz, 2H), 4.06 (dd, J = 4.4, 4.4 Hz, 1H, H_5), 3.99 (dd, J = 4.8, 4.4 Hz, 1H, H_8), 3.49 (ddd, J = 10.3, 4.6, 1.2 Hz, 1H, H_{7x}), 3.36 (d, J = 10.3 Hz, 1H, H_{7n}), 2.48 (br, 1H, H_1), 2.31 (m, 1H, H_{2a}), 2.07 (br, 1H), 1.91 (m, 1H, H_{3s}), 1.68 (ddd, J = 15.8, 6.2, 1.0 Hz, 1H, H_{3a}), 1.47 (m, 1H, H_{2s}), 1.25 (t, J = 7.1 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 68.5 and 67.8, 61.4, 57.0, 46.9 and 46.2, 39.5 and 38.6, 25.8, 23.5, 20.2 and 19.5, 14.6; HRMS m/z 326.0256, calcd for $C_{10}H_{17}NO_3I$ (M + H) 326.0253 and m/z 348.0075, calcd for $C_{10}H_{16}NO_3NaI$ (M + Na) 348.0073.

***N*-(Benzyloxycarbonyl)-4-*exo*-hydroxy-8-*anti*-iodo-6-azabicyclo-[3.2.1]octane (31b) and *N*-(Benzyloxycarbonyl)-5-*exo*-hydroxy-6-*endo*-iodo-2-azabicyclo[2.2.2]octane (32b). (a) THF/Water.** According to the general procedure, alkene **8b**[15] (1 g, 0.4 mmol) in a 2:1 THF/water (48 mL) and *N*-iodosuccinimide (1.85 g, 8.2 mmol) was stirred at room temperature for 16 h. Workup and chromatography gave 407 mg (26%) of the rearranged iodoalcohol **31b** at R_f 0.34 (6:4 hexane/ethyl acetate) and 548 mg (35%) of the unrearranged iodoalcohol **32b** at R_f 0.29 (1:1 hexane/ethyl acetate). For the rearranged iodoalcohol **31b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.11 (s, 2H), 4.27 and 4.21 (two br, 1H), 4.1 and 4.04 (two br, 1H), 4.04 and 4.00 (br, 1H), 3.52 (m, 1H), 3.40 (m, 1H), 2.50 (br, 1H), 2.27 (m, 1H), 2.19 (m, 1H), 1.90 (m, 1H), 1.63 (m, 1H); ^{1}H NMR (400 MHz, DMSO, 100 °C) δ 7.31 (s, 5H), 5.07 (s, 2H), 4.14 (dd, J = 4.2, 4.0 Hz, H_4), 4.00 (dd, J = 4.1, 4.2 Hz, H_5), 3.85 (br, H_8), 3.44 (dd, J = 10.0, 5.3 Hz, H_{7x}), 3.29 (d, J = 10.0 Hz, H_{7n}), 2.97 (br, 1H), 2.37 (br, H_1), 2.14 (m, H_3), 1.69 (m, H_2), 1.47 (m, H_3 and H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 139.3 and 136.2, 128.4, 128.1 and 128.0, 127.8, 68.7 and 67.9, 67.2 and 67.0, 57.2 and 57.1, 47.2 and 46.9, 39.5 and 38.6, 25.8, 23.5, 20.1 and 19.4; HRMS m/z 388.0404, calcd for $C_{15}H_{19}NO_3I$ (M + H) 388.0404; m/z 410.0243, calcd for $C_{15}H_{18}NO_3INa$ (M + Na) 410.0223. For the unrearranged iodoalcohol **32b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.21 (m, 1H) and 5.12 (d, J = 12.3 Hz, 1H), 4.54 (m, 1H), 4.31 and 4.22 (two m, 1H), 4.09 and 4.06 (two t, J = 2.5 Hz, 1H), 3.53 (m, 1H), 3.45 (dd, J = 11.7, 2.7 Hz, 1H), 3.06 (br, 1H), 1.99 (m, 4H), 1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 and 155.4, 136.8 and 136.5, 128.4, 127.9, 127.7, 80.7 and 80.6, 67.1 and 67.0, 53.0 and 52.5, 46.5, 35.1 and 34.9, 34.2, 27.2 and 27.0, 15.4; HRMS m/z 410.0237, calcd for $C_{15}H_{18}NO_3INa$ (M + Na) 410.0229.

***N*-(2,2,2-Trichloroethoxycarbonyl)-4-*anti*-hydroxy-8-*anti*-iodo-6-azabicyclo[3.2.1]octane (21d) and *N*-(2,2,2-Trichloroethoxycarbonyl)-5-*anti*-hydroxy-6-*syn*-iodo-2-azabicyclo[2.2.2]octane (32e).** By the usual procedure, alkene **8d** (445 mg, 1.6 mmol) at 0 °C in 1:1 THF/water (20 mL) with NBS (557 mg, 3.1 mmol) at rt for 16 h afforded upon flash silica gel chromatography 105 mg (18%) of the rearranged bromoalcohol **21d** at R_f 0.67 (2:1 hexane/ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 and 4.66 (two d, J = 12 Hz, 1H), 4.77 and 4.71 (two d, J = 12 Hz, 1H), 4.34 and 4.31 (two t, J = 4.4 Hz, 1H, H_4), 4.22 (m, 1H, H_5), 4.10 (m, 1H, H_8), 3.63 and 3.56 (ddd, J = 10.4, 5.6, 1.2 Hz, H, H_6), 3.53 and 3.46 (two d, J = 10.8 Hz, 1H, H_6), 2.60 (br, 1H, H_1), 2.37 (m, 1H, H_2), 1.95 (m, 1H, H_3), 1.77 (dd, J = 15.6, 6.0 Hz, 1H, H_3), 1.58 (m, 1H, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 95.6 and 95.3, 74.9, 68.9 and 68.1, 57.2, 47.8, 46.5 and 46.3, 38.1 and 37.4, 25.6, 21.2; HRMS m/z 401.9022, calcd for $C_{10}H_{13}BrCl_3NO_3Na$ (M + Na) 401.9042. Also obtained was 84 mg (14%) of the unrearranged bromoalcohol **32e** at R_f 0.48 (2:1 hexane/ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (q, J = 11.6 Hz, 1H), 4.67 (s, 1H), 4.29 and 4.26 (two br, 1H, H_5), 4.23 (ddd, J = 3.6, 1.6 Hz, 1H, H_1), 3.90 and 3.87 (two t, J = 2.2 Hz, 1H, H_6), 3.53 and 3.43 (ddd, J = 11.6, 2.4, 2.4 Hz, 1H, H_3), 3.47 and 3.38 (dd, J = 11.6, 2.8 Hz, 1H, H_3), 2.20 (br, 1H), 1.96 (m, 2H), 1.77 (m, 1H), 1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 105.2, 78.9/78.7, 75.0, 56.8/56.7, 52.1/51.7, 46.7/46.5, 33.9/33.8, 26.6/26.3, 15.6; HRMS m/z 401.9024, calcd for $C_{10}H_{13}BrCl_3NO_3Na$ (M + Na) 401.9042.

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Supporting Information Available: General experimental and procedures for preparation of **13b**, **14b**−**d**, **17c**, **18c**, **8b**, **21a**, **21d**/**32e**, **27**, **30c**, **31a**, **31b**, **31c**,**d**/**32c**,**d**, **33a**,**b**, **34a**, **35b**, **36b**; Gaussian 98 derived energies for structures related to those in Mechanistic Scheme 6 and footnote 18 are tabulated in the supplement; X-ray diffraction analysis of *N*-methyl bromohydrin **27** and *N*-ethoxycarbonyl iodohydrin **31a**, copies of ^{1}H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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