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The Rearrangement Route to 2-Azabicyclo[2.1.1]hexanes. Solvent and Electrophile Control of Neighboring Group Participation

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The reactions of *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **5** with halonium ion electrophiles were studied in polar and nonpolar aprotic solvents and also in protic media with the aim of controlling nitrogen neighboring group participation. Specifically, for bromonium ions nitrogen participation is facilitated by the polar aprotic solvent nitromethane and by the poorly nucleophilic protic solvent acetic acid. Alkene **5b** and bromine/nitromethane afford only the rearranged *anti,anti*-5,6-dibromo-2-azabicyclo[2.1.1]hexane **6b**, and NBS/acetic acid gives an 8:1 mixture favoring rearranged 5-bromo-6-acetate **6f**. Conversely, pyridinium bromide perbromide/CH_2Cl_2 is selective for only unrearranged 5,6-dibromide **7**. Iodonium and phenylselenonium ions react with alkenes **5** to give only unrearranged 1,2-addition products **9** and **10**, regardless of solvent. Chloronium and fluoronium ions react with alkenes **5** to give 4-aminomethyl-3-hydroxycyclobutene **11**, derived by ring cleavage.

Introduction

Pyrrolidines are common to many biologically significant molecules.[1] In the search for selective bioactive molecules one useful strategy is to incorporate this key pharmacophoric entity into a less flexible structure.[2] The 2-azabicyclo[2.1.1]hexane (**1**), if envisaged as a 2,4-methanopyrrolidine (pyrrolidine numbering), is one example of an inflexible model for pyrrolidines.[3] Of the several methods available for synthesis of 2-azabicyclo-[2.1.1]hexanes, bromine-mediated additions of BrX (X = Br, OH) to 2-azabicyclo[2.2.0]hex-5-enes **2** is the one pathway that has allowed useful heteroatom functionality to be easily introduced in the 5- and 6-methano bridges.[4,5] The requisite alkenes **2** are readily synthesized from pyridines via 1,2-dihydropyridines.[4,6] The synthetic

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(5) For a summary of nucleophilic ring closure approaches to 2-azabicyclo[2.1.1]hexanes, see refs 3n−q and 4a (footnote 6 therein). For photochemical approaches to 2-azabicyclo[2.1.1]hexanes, see ref 4a (footnote 5 therein), and also: (a) Kwak, Y.-S.; Winkler, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 7429. (b) Toda, F.; Miyamoto, H.; Takeda, K.; Matsugawa, R.; Maruyama, N. *J. Org. Chem.* **1993**, *58*, 6208. (c) Vogler, B.; Bayer, R.; Meller, M.; Kraus, W. *J. Org. Chem.* **1989**, *54*, 4165.

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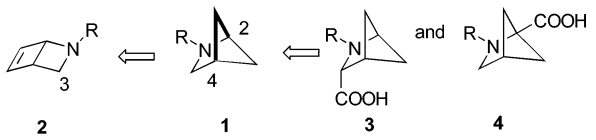
TABLE 1. Bromine Additions to *N*-(Alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes 5

no.	reactant	solvent (salt)	Z	X	products (ratio)	yield (%)
1	**5a**	CH_2Cl_2	COOEt	Br	**6a** (45):**7a** (55)	61−78[a]
2	**5b**	CH_2Cl_2	COOBn	Br	**6b** (45):**7b** (41):**8b** (14)	73
3	**5b**	CH_3CN/CH_2Cl_2[b]	COOBn	Br	**6b** (81):**7b** (19)	91
4	**5b**	$MeNO_2/CH_2Cl_2$[c]	COOBn	Br	**6b**	89
5	**5b**	$MeNO_2/CH_2Cl_2$[c] (HgF_2)	COOBn	Br	**6b**	80
6	**5b**	$MeNO_2/CH_2Cl_2$[c] ($HgCl_2$)	COOBn	Cl	**6c**	81
7	**5b**	CH_2Cl_2/(PBPB)[d]	COOBn	Br	**7b**	92

[a] See refs 4b,c. [b] 10:3 solvent ratio. [c] 8:5 solvent ratio. [d] Pyridinium bromide perbromide.

potential of this rearrangement route from alkene **2** to bridged azabicycles **1** has been limited somewhat, however, by the general inability to drive the rearrangements to completion in the absence of an endo substituent in the azetidine ring at C_3 of **2**.[4b,d] In such cases the bridged structures **1** are admixed with significant amounts of unrearranged structural isomers. We recently showed that azabicycles **1** are precursors of desirable methanoproline structures **3** and **4**.[7] Clearly, an improved protocol for formation of **1** is important if it is to fulfill its potential as a methanopyrrolidine synthon.

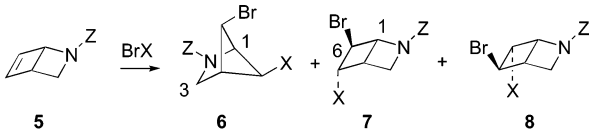


Results and Discussion

N-(Alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **5**[6] were initially reacted with a variety of sources of bromonium ions in either protic or aprotic solvents. Subsequently, alkenes **5** were reacted with other electrophilic species: I^+, Cl^+, F^+, and $PhSe^+$. The results of our investigations of solvent and electrophile influences on the competition between simple 1,2-additions to alkenes **5** and additions accompanied by rearrangement follow.

Brominations of 5 in Aprotic Solvent. In Table 1 the results of bromine-mediated additions to alkenes **5** are shown. At the outset of this work it was known that bromine/CH_2Cl_2 reacts with the *N*-ethoxycarbonyl-substituted alkene **5a** to give rearranged dibromide **6a** as the minor product admixed with unrearranged dibromide **7a** (entry 1).[4b,c] The use of a larger *N*-benzyloxycarbonyl protecting group with azabicycle **5b** (entry 2) again results in rearrangement to give **6b** as a minor isomer; but now two unrearranged dibromides **7b** and **8b** are isolated. The rearranged dibromide **6b** can be assigned by comparison with the known **6a**; for example, the singlet for H_3 at δ 3.61 is a result of symmetry and the coupling between H_1 at δ 4.63 and H_4 at δ 3.20 ($J_{1,4}$ = 6.3 Hz) is the result of W-plan coupling.[4b] The unrearranged structure **7b** can be assigned by comparison with the known **7a**;[4b] importantly, there is an absence of coupling between the endo H_6 proton at δ 4.60 and H_1 at δ 4.74 ($J_{1,6}$ = 0 Hz) and there is trans coupling with H_5 at δ 4.96 ($J_{5,6}$ = 5.1 Hz). Dibromide **8b** has coupling of the exo proton H_6 at δ 4.80 with both H_1 at δ 4.94 ($J_{1,6}$ = 4.8 Hz) and the trans-endo H_5 at δ 4.62 ($J_{5,6}$ = 6 Hz).

Upon switching to the more polar solvent acetonitrile for reaction of bromine with azabicycle **5b** (entry 3), a much improved 4:1 ratio of rearranged dibromide **6b** to unrearranged dibromide **7b** results; no dibromide **8b** is observed. The same reaction in polar nitromethane (entry 4) now affords only the desired rearranged dibromide **6b** in 89% isolated yield.



a Z = COOEt
b Z = COOBn
a Z = COOEt, X = Br
b Z = COOBn, X = Br
c Z = COOBn, X = Cl
d Z = COOEt, X = OH
e Z = COOBn, X = OH
f Z = COOBn, X = OAc

In an effort to prepare mixed halides mercury(II) salts were used as promoters in 8:5 nitromethane:CH_2Cl_2. Bromine/HgF_2 (entry 5) affords only the rearranged dibromide **6b** with none of the expected trapping by fluoride nucleophile.[8] Bromine/$HgCl_2$ (entry 6), however, does afford a new rearranged *anti*,*anti*-bromochloro structure **6c** with participation by chloride. The ^1H NMR of **6c** shows a characteristic doublet for H_4 at δ 3.13 ($J_{1,4}$ = 6.8 Hz), and doublets for H_6 at δ 4.14 and H_5 at δ 4.06 ($J_{5,6}$ = 7.3 Hz). The H_3 protons appear as separate doublets at δ 3.63 and 3.57 (J = 9.0 Hz), as expected for a molecule lacking an internal symmetry plane.

As a corollary effort to enhancing the formation of rearranged dibromide, it was desired to find conditions that would favor the formation of unrearranged dibromide. Indeed, reaction of alkene **5b** with pyridinium bromide perbromide in CH_2Cl_2 afforded the single unrearranged dibromide **7b** (entry 7).

Brominations in Protic Solvent. In Table 2 the results of bromine-mediated additions to alkenes **5** are shown. At the outset of this work it was known that NBS in 2:1 DMSO/water reacts with the *N*-ethoxycarbonyl-substituted alkene **5a** to give rearranged bromo alcohol **6d** as the minor product admixed with unrearranged bromo alcohol **7d** (entry 1).[4b,d]

Reaction of alkene **5b** with NBS in 2:1 THF/water gives improved 9:7 selectivity for the rearranged isomer **6e** compared to the unrearranged isomer **7e** (entry 2). Use of sodium acetate buffered acetic acid[10] gives a more desirable 8:1 selectivity for the rearranged bromoacetate

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TABLE 2. Reaction of NBS with *N*-(Alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes 5

no.	reactant	solvent	Z	X	products (ratio)	yield (%)
1	**5a**	DMSO/water 2:1	COOEt	Br	**6d** (17):**7d** (53)	70[a]
2	**5b**	THF/water 2:1	COOBn	Br	**6e** (45):**7e** (35)	80
3	**5b**	HOAc/NaOAc/Ac_2O	COOBn	Br	**6f** (80):**7f** (10)	90

[a] References 4b and 9.

TABLE 3. Reaction of Electrophilic Iodine, Selenium, and Sulfur Species with *N*-(Alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes 5

no.	reactant	reagent/solvent	Z	X	Y	products (ratio)	yield (%)
1	**5a**	NIS/DMSO/water 2:1	COOEt	I	OH	**9a**	97
2	**5b**	NIS/THF/water 2:1	COOBn	I	OH	**9b**	91
3	**5b**	NIS/HOAc/NaOAc/Ac_2O	COOBn	I	OAc	**9c**	90
4	**5a**	$I_2/HgF_2/MeNO_2/CH_2Cl_2$[a]	COOEt	I	F	**9d**	72
5	**5b**	$I_2/HgF_2/MeNO_2/CH_2Cl_2$[a]	COOBn	I	F	**9e**	68
6	**5b**	$PhSeBr/CH_2Cl_2$	COOBn	PhSe	Br	**9f** (72) **10f** (11)	83
7	**5b**	$PhSeBr/MeNO_2$	COOBn	PhSe	Br	**9f** (67) **10f** (23)	90
8	**5c**	RSCl[b]	COOMe	RS	Cl	**9g** (57) **10g** (10)	67

[a] 8:5 solvent ratio. [b] R = *N*-succinimido, refs 4b and 14.

6f relative to the unrearranged isomer **7f**. The structures of the acetates **6e**/**6f** were confirmed by acetylation of alcohols **6e** and **7e**.

Reactions of I^+, $PhSe^+$, and RS^+ Electrophiles with Alkene 5b. The reactions of several other soft electrophiles[11] with alkenes **5** are shown in Table 3. We first looked at NIS in polar media.[12] Alkene **5a** and NIS in DMSO/water (entry 1) afford only unrearranged 5-*endo*-hydroxy-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane **9a**, and similarly alkene **5b** and NIS/THF/water (entry 2) afford unrearranged **9b**. Alkene **5b** and NIS in buffered acetic acid afford only unrearranged iodoacetate **9c** (entry 3). The 5-exo,6-endo stereochemical assignments to iodo alcohols **9a**,**b** and iodoacetate **9c** were made by ^1H NMR; i.e., especially notable in alcohol **9b** is the absence of coupling between endo proton H_6 and bridgehead H_1 indicative of an exo iodine substituent. The 5-acetate can be assigned an endo orientation on the basis of a large coupling ($J = 7.5$ Hz) between H_{5x} and bridgehead proton H_4 and a smaller coupling ($J = 3.9$ Hz) between H_{5x} and H_{6n}. Alcohol **9b** was readily acetylated to afford acetate **9c**.

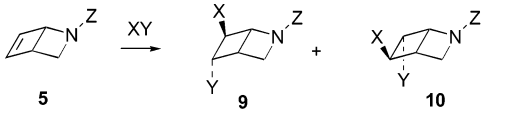
In the aprotic solvent system 8:5 nitromethane/CH_2Cl_2 iodine in the presence of HgF_2 reacted with alkene **5a** (entry 4) or **5b** (entry 5) to afford 6-*exo*-iodo-5-*endo*-fluoro addition products **9d** and **9e**, respectively.[8] The structures were readily assigned on the basis of the absence of coupling between H_{6n} and H_1, which places the iodo group exo, and the large coupling ($J = 6.8$ Hz) between H_{5x} and H_4, which places the F endo.

Alkene **5b** and PhSeBr in aprotic CH_2Cl_2 give a 7:1 mixture of unrearranged bromoselenides **9f** and **10f** (entry 6).[13] The same reaction performed in the more polar solvent system 8:5 nitromethane/CH_2Cl_2 again affords only these unrearranged bromoselenides (entry 7). For comparison, Tsuchiya and co-workers have reported that alkene **5c** reacts with succinimide-*N*-sulfenyl chloride in CH_2Cl_2 to give a 6:1 mixture of unrearranged chlorothio isomers **9g** and **10g** (entry 8).[4c,14]

TABLE 4. Reaction of Fluoronium and Chloronium Ion Electrophiles with *N*-(Alkoxycarbonyl)-2-azabicyclo-[2.2.0]hex-5-enes 5

no.	reactant	reagent/solvent	Z	product	yield (%)
1	**5c**	F-TEDA/CH_3CN/water[a]	COOMe	**11c**	76
2	**5b**	F-TEDA/CH_3CN/water[a]	COOBn	**11b**	74
3	**5b**	NCS/THF/water[b]	COOBn	**11b**	24
4	**5b**	NCS/DMSO/water[b]	COOBn	**11b**	31
5	**5c**	NCS/THF/waterat 35 °C[c]	COOMe	**12**	40
6	**11c**	NCS/THF/waterat 35 °C[c]	COOMe	**12**	55

[a] 1:1 solvent ratio, F-TEDA. [b] 2:1 solvent ratio. [c] 1:1 solvent ratio, 3 equiv of NCS.



a Z = COOEt
b Z = COOBn
c Z = COOMe

a Z = COOEt, X = I, Y = OH
b Z = COOBn, X = I, Y = OH
c Z = COOBn, X = I, Y = OAc
d Z = COOEt, X = I, Y = F
e Z = COOBn, X = I, Y = F
f Z = COOBn, X = PhSe, Y = Br
g Z = COOMe, X = S-*N*-succinimido, Y = Cl

Reactions of F^+ and Cl^+ with Alkenes 5. The results for reaction of the harder fluoronium and chloronium ions with alkenes **5** are shown in Table 4. The reagent F-TEDA (Selectfluor),[15] a source of positive

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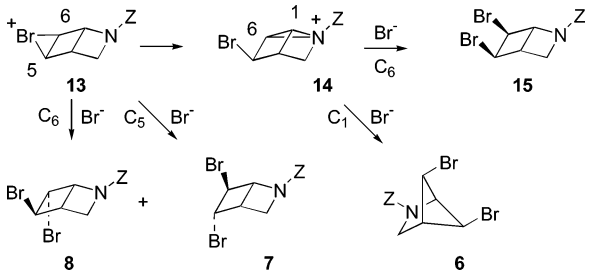
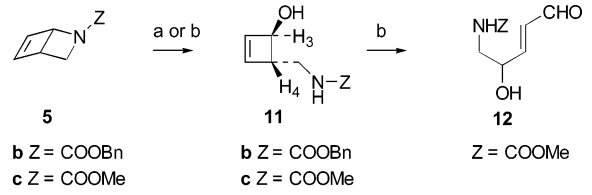
SCHEME 1



fluorine, reacts with alkene **5c** in aqueous acetonitrile to afford the cyclobuten-3-ol **11c** (entry 1). The olefinic protons appeared as two doublets with a small $J = 2.8$ Hz expected for the vinyl protons on a cyclobutene. The H_3 proton at δ 4.70 (d, $J = 2.9$ Hz) exhibited the small coupling expected if the relationship of substituents on the cyclobutene ring is trans. The *N*-benzyloxycarbonyl structure **5b** reacts in a similar fashion to give **11b** (entry 2). Electrophilic chlorine generated from NCS in THF/water (entry 3) or DMSO/water (entry 4) also furnishes cyclobuten-3-ol **11b**, although in poorer yield. When the alkene **5c** is reacted with excess NCS in THF/water and heat is applied, hydroxyaldehyde **12** is obtained. This further oxidized and ring-opened product is identified by ^{1}H NMR. The vinyl H_2 proton at δ 6.29 ($J = 15.6$, 7.5 Hz) is coupled to the aldehyde proton at δ 9.57 and the trans H_3 vinyl proton at δ 6.77. The H_3 proton is also coupled ($J = 6.9$ Hz) to the H_4 proton at δ 4.65 adjacent to the hydroxyl group.



b Z = COOBn
c Z = COOMe

b Z = COOBn
c Z = COOMe

Z = COOMe

(a) Selectfluor, CH_3CN/water, (b) NCS, THF/water

Mechanistic Discussion: Soft Electrophiles. A mechanism for addition of bromine to azabicycles **5** is shown in Scheme 1;[4b,c] it serves as a model for the results in Tables 1 and 2 and for addition of other soft electrophiles in Table 3.[11] The key intermediate is the bromonium ion **13**. Dibromides **7** and **8** are formed by bromide attack on the bromonium ion, while dibromide **6**, and potentially dibromide **15**, is formed by bromide attack on the aziridinium ion **14**. To estimate the relative energies of the key dibromides the calculations shown in Table 5 were performed.

(a) Stereochemical Preferences for Unrearranged Dibromides. The gas-phase data in Table 5 reveal the most stable dibromide to be **8c** (entry 1), formed by *endo* bromide attack on bromonium ion **13c** at C_6. However, the experimental results (Table 1, entry 2) reveal only a minor amount of dibromide **8b** is formed compared with the stereoisomeric **7b**, formed by *endo* bromide attack on a bromonium ion **13** at C_5.

In an effort to explain the preference for unrearranged dibromides **7** versus **8** (Table 1, entries 1−3) charge density calculations were carried out for the bromonium ion **13a** (Z = COOEt).[16−18] The selected values shown in Table 6 indicate that even though greater positive charge

TABLE 5. Relative Energies of the Dibromides Likely To Be Formed from Bromonium Ion 13c and Its Derived Aziridinium Ion 14c (Z = COOMe)

entry	dibromide structure	calculation method (kcal/mol)[a] RHF/6-31G(d)[b]	B3LYP/6-31G(d,p)[c]
1	5-*exo*-6-*endo* **8c**	0.0	0.0
2	5-*endo*-6-*exo* **7c**	0.3	1.1
3	5-*anti*-6-*anti* **6c**	1.1	1.4
4	5-*exo*-6-*exo* **15c**	2.9	3.2

[a] All values are relative to the lowest energy of each set. See refs 16−18. [b] Full optimization (uncorrected). [c] Single point energy at RHF/6-31G(d) geometry.

TABLE 6. Calculated Charge Densities for Relevant Atoms of Bromonium Ion 13a (Z = COOEt)[a]

heavy atom[b]	charge analysis method: Mulliken[c]	Mertz, Kollman, Singh[d]
C_5	0.171014	0.099466
Br	0.251049	0.326648
C_6	0.205296	0.121956
C_3	0.349061	0.125282
N	−0.547941	−0.090945

[a] Calculations were performed with Gaussian 98. See refs 16−18. [b] The attached hydrogen charges are summed into those of the carbons. [c] Mulliken charges were obtained from structures optimized for geometry with RHF/6-31G(d). [d] The RHF geometry was employed to obtain electron density with MP2/6-31G(d,p).

resides on C_6 relative to C_5, this charge density factor is countered by the negative charge density on the nitrogen atom. This deters attack of a negatively charged nucleophile at C_6 and favors formation of a dibromide **7** by attack of bromide ion at the adjacent C_5 position.

(b) Rearranged versus Unrearranged Dibromides. What explains the preferential formation in polar solvents of rearranged dibromide **6c**, the third most stable species in Table 5? Calculations[16] shown in Table 7 indicate that the necessary aziridinium ion **14c** (entry 2) is more stable than the bromonium ion **13c** (entry 1)—a useful insight.

For a bromonium ion **13** to form a more stable aziridinium ion **14** by a k_Δ process it first is necessary to avoid competitive trapping of ion **13** by external nucleophile by a k_{Nu} process.[19] In CH_2Cl_2 both k_Δ and k_{Nu} processes compete to give product mixtures (Table 1, entries 1 and 2). The polar solvents acetonitrile or nitromethane (Table 1 entries 3−6) stabilize the transition state for interconversion of ions sufficiently enough to allow the bromonium ion **13** to aziridinium ion **14** rearrangement to

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(17) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(18) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *94*, 6081.

(19) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 341.

TABLE 7. Relative Energies (kcal/mol) of Potential Ions Formed by Addition of a Bromonium Ion to *N*-(Methoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (5c)

entry	structure calculation method[a]	RHF/ 6-31G(d)[b]	B3LYP/ 6-31G(d,p)[c]
1	**13c**, bromonium ion	19.1	18.1
2	**14c**, aziridinium ion	4.6	7.1
3	**16X**, *exo*-*N*-bromo	28.0	23.2
4	**16N**, *endo*-*N*-bromo	29.1	23.8
5	**17**, allylic cation	—[d]	—[d]
6	**18**, oxonium ion	0.0	0.0

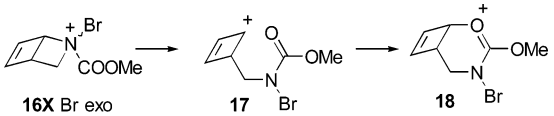
[a] All values are relative to the lowest energy of each set. See refs 16−18. [b] Full optimization (uncorr.). [c] Single point energy with the geometry of RHF/6-31G(d) (uncorr.). See Supporting Information. [d] Ion **18** is the calculation output.

compete favorably with external nucleophilic attack on the bromonium ion **13**.

Once the aziridinium ion **14** is formed, bromide ion prefers to attack at C_1 to form the rearranged azabicycle **6**, rather than at C_6 to form the unrearranged dibromide **15**. Because attack of bromide at C_6 must occur adjacent to an eclipsing bromine substituent at C_5, it is not surprising that **15** is not formed in any reaction studied.[20]

It follows also that in a nonpolar solvent containing a good nucleophile a k_{Nu} process may dominate. This was shown to be the case in the reaction of alkene **5b** with pyridinium bromide perbromide/CH_2Cl_2 (Table 1 entry 7) to give only unrearranged dibromide 7b.

(c) Dibromides versus Ring Cleavage. Why does *N*-bromination of alkene **5** not occur to give ions **16X** and/or **16N**, the precursors of ring-opened allylic ion **17** and oxonium ion **18**? The Table 7 calculations again provide insight. The most stable ion derived from alkene **5c** is the oxonium ion **18** (entry 6), an outcome from attempts to calculate the energy of the allylic cation **17** (entry 5). However, the *N*-bromo ions **16X**/**16N** (entries 3 and 4) are less stable than bromonium ion **13c** (entry 1). Thus, failure to observe products derived from oxonium ion **18** can be attributed to the lower possibility of its precursor *N*-bromo ions to form.



16X Br exo **16N** Br endo **17** **18**

(d) Reactions with Nonbromonium Ion Soft Electrophiles. Why does rearrangement not occur upon addition of other soft electrophiles to alkenes **5**? We attempted to gain insight from comparison calculations[16] performed for the series of bridged ions **13a** and **19**−**21** shown in Table 8. The calculations, except for the selenonium ion **21** (entry 4), again showed the aziridinium ions **14a**, **22**, and **24** to be the more stable species. But the products formed from the soft electrophiles in Table 3, either in nonpolar CH_2Cl_2, polar nitromethane, or aqueous media, are not derived from aziridinium ions.

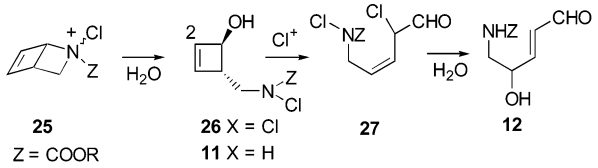
(20) An examination of the LUMO of the aziridinium ion **14c** (Z = COOMe) suggests that the preferential nucleophilic attack at C_1 might be due to the greater size and accessibility of the LUMO at C_1. *PCSpartan Plus* version 2.0; Wavefunction, INC., Irvine, CA 92612. (See Supporting Information.)

TABLE 8. Comparative Energies of Bridged Onium Ions from Alkene 5a (Z = COOEt) and Their Rearranged Aziridinium Ions

			comparison	
entry	onium ion	rel energy,[a] kcal/mol	aziridinium ion	rel energy
1	**13a**, bromonium	+16.0	**14a**	0.0
2	**19**, episulfonium	+8.8	**22**	0.0
3	**20**, iodonium	—[b]	**23**	0.0
4	**21**, selenonium	−6.1	**24**	0.0

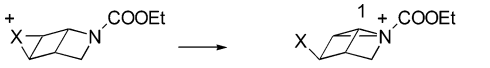
[a] RHF/6-31G(d) (uncorr.). See refs 16−18. Comparison is between the onium ion for each entry with the aziridinium ion **14a** or **22**−**24** of its row. [b] The aziridinium ion **23** rather than the unrearranged iodonium ion **20** was the output of the calculation.

SCHEME 2



25 Z = COOR **26** X = Cl **11** X = H **27** **12**

Thus, unlike the case for bromonium ion **13a**, which rearranges to aziridinium ion **14a**, the formation of unrearranged 1,2-addition products from bridged ions **19**−**21** can be attributed to an unfavorable energy barrier for the k_Δ process leading to aziridinium ions **22**−**24**.[21]



13a X = Br
19 X = S-*N*-succinimidyl
20 X = I
21 X = SePh

14a X = Br
22 X = S-*N*-succinimidyl
23 X = I
24 X = SePh

Mechanistic Discussion: Hard Electrophiles. The additions of the harder chloronium and fluoronium ion electrophiles to azabicycles **5** occur on nitrogen rather than the softer alkene moiety.[6b,22] A mechanism for conversion of *N*-chloronium ion **25** to hydroxycyclobutenes **11** and aldehyde **12** (Z = COOMe) is shown in Scheme 2. Ring opening of ion **25** and attack of water affords a chloramine **26**; the *N*-chloro substituent is lost to aqueous medium to afford alcohol **11**. Aldehyde **12** might be formed by addition of a chloronium ion to alkene **26** mediating a ring opening to give chloroaldehyde **27**. Chloride displacement by attack at the olefin terminus and loss of the *N*-chloro group to solvent would afford hydroxyaldehyde **12**.

(a) Chemoselectivity of Halonium Ion Additions. Why is cyclobutenol **11** formed in the reaction of alkenes **5** with F^+ and Cl^+? To determine the relative stabilities of the key intermediate ions, energies shown in Table 9 were calculated for the bridged halonium ions (**13c** and **28**−**30**) and the *N*-halo ions (**16**, **25**, **34**, and **35**). The observed products with alkenes **5** and each halonium ion

(21) Hassner, A.; Boerwinkle, F. P.; Levy, A. B. *J. Am. Chem. Soc.* **1970**, *92*, 4879. There is evidence to indicate that iodonium ions are more stable than bromonium ions.

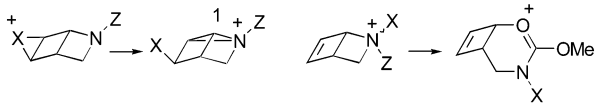
(22) Krow, G. R.; Lester, W. S.; Lin, G.; Fang, Y.; Carroll, P. J. *J. Org. Chem*. **2003**, *68*, 1626. Chlorosulfonyl isocyanate also adds to the nitrogen atom of alkenes **5**.

TABLE 9. Comparison of the Relative Energies for Key Ions Potentially Formed during Additions of Halonium Ions to Alkene 5c (Z = COOMe)

		ion and relative energy (kcal/mol)[a]				
entry	halogen (X)	halonium	aziridinium	*N-exo*-halo	*N-endo*-halo	oxonium
1	F	**28** (−)[b]	**31** (0.0)	**34X** (42.6)	−	**36** (16.4)
2	Cl	**29** (−)[b]	**32** (9.7)	**25X (**31.7)	−	**37** (0.0)
3[c]	Br	**13c** (19.1)	**14c** (4.6)	**16X** (28.0)	**16N** (29.1)	**17** (0.0)
4	I	**30** (−)[b]	**33** (27.2)	**35X** (33.2)	**35N** (33.6)	**38** (0.0)

[a] The energies are relative to the lowest for each entry (0.0 kcal/mol for a given halogen), and were computed with RHF/6-31G for all but entry 4 (iodine), which was RHF/3-21G. Iodine is not available with the 6-31 basis sets in Gaussian 98. See ref 16. [b] The aziridinium ion was the output of the bridged halonium ion calculation. [c] See Table 7.

studied (Tables 1−4) are ultimately derived from one of these two kinds of halonium ions.



28 X = F
29 X = Cl
13c X = Br
30 X = I

31 X = F
32 X = Cl
14c X = Br
33 X = I

34X X = *exo*-F
34N X = *endo*-F
25X X = *exo*-Cl
25N X = *endo*-Cl
16X X = *exo*-Br
16N X = *endo*-Br
35X X = *exo*-I
35N X = *endo*-I

36 X = F
37 X = Cl
17 X = Br
38 X = I

The calculations indicate that all of the *N*-halo ions, if formed, have an energetic driving force to ring open and to then form oxonium ions (entries 1−4). The experimental data in Tables 1-4 indicate that this ring opening occurs when the halo group is F or Cl, but not when the halo group is Br or I. Also, in agreement with experiment (Tables 1−3), the calculated energy for bromonium ion **13c** is shown to be lower than that of the *N*-bromo ions **16X**/**16N** (entry 3). It is unfortunate that the energies of the *N*-halo ions (X = F, Cl, I) are not available for comparison with those of the competitive halonium-bridged ions (entries 1, 2, and 4). Attempts to calculate energies for the bridged ions **28**−**30** resulted in outputs of energies for the aziridinium ions **31**−**33**.

Conclusions

Selective rearrangement reactions from *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5enes **5** to 5-*anti*,6-*anti*-dibromo(chlorobromo)- and 5-*anti*-bromo-6-*anti*-hydroxy-*N*-(alkoxycarbonyl)-2-azabicyclo[2.1.1]hexanes **6** have been described. From the same substrates **5** there are described selective 1,2-addition reactions to prepare 5-*endo*-(bromo, iodo, hydroxy)-6-*exo*-(bromo, iodo)-*N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hexanes **9** as well as a selective ring cleavage reaction to afford 4-aminomethyl-3-hydroxycyclobutene **11**. The outcomes of the reactions with alkenes **5** are both electrophile and solvent dependent. The chemoselective methods enhance the utility of alkenes **5** for synthesis of highly functionalized azabicyclohexanes.

Experimental Section

General Procedure for Addition of Bromine to *N*-(Alkoxyoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes 5. Method A: A solution of bromine (419 mg, 2.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a 0 °C solution of *N*-(alkoxycarbonyl)-2-azabicyclohex-5-ene **5** (560 mg, 2.6 mmol) in CH_2Cl_2 (30 mL) under argon.[6] After being stirred for 2 h the reaction was allowed to come to rt while stirring was continued for an additional 16 h. The solution was diluted with CH_2Cl_2 (20 mL), washed with 10% aqueous sodium bisulfite (25 mL) and water (25 mL), dried over $MgSO_4$, and filtered and solvent was removed in vacuo to provide an oil, which was chromatographed (1−4:1 hexane:ether). **Method B:** The procedure of Method A was changed by using acetonitrile or nitromethane as solvent for the alkene **5**. After addition of bromine the solution was stirred for 1 h at rt and the reaction was diluted with ether (20 mL) prior to washing. **Method C:** The procedure of Method A was changed by using nitromethane as the solvent for alkene **9** and adding 2.5 equiv of a mercuric salt.[8]

Preparation of *N*-(Benzyloxycarbonyl)-5-*anti*-6-*anti*-dibromo-2-azabicyclo[2.1.1]hexane (6b), *N*-(Benzyloxycarbonyl)-5-*endo*-6-*exo*-dibromo-2-azabicyclo[2.2.0]-hexane (7b), and *N*-(Benzyloxycarbonyl)-5-*exo*-6-*endo*-dibromo-2-azabicyclo[2.2.0]hexane (8b). From alkene **5b** (445 mg, 2 mmol) and bromine (320 mg, 2 mmol) there was obtained according to the general procedure (Method A) following chromatography 249 mg (33%) of rearranged dibromide **6b** at R_f 0.27 (2:1 hexane:ether), 221 mg (30%) of unrearranged dibromide **7b** at R_f 0.34, and 77 mg (10%) of the minor unrearranged dibromide **8b** at R_f 0.17. The dibromide **6b**: ^{1}H NMR δ 7.4 (s, 5 H), 5.16 (s, 2 H), 4.63 (d, J = 6.3 Hz, 1 H), 4.07 (s, 2 H), 3.61 (s, 2 H), 3.20 (d, J = 6.3 Hz, 1 H); ^{13}C NMR δ 154.7, 128.6, 128.3, 128.1, 67.5, 66.3, 50.9, 50.8, 50.1; HRMS *m*/*z* 373.9395, 375.9358, 377.9352, calcd for $C_{13}H_{14}NO_2{}^{79/79,79/81,81/81}Br_2$ (M + H) 373.9391, 375.9371, 377.9350. The unrearranged dibromide **7b**: ^{1}H NMR δ 7.39 (5 H), 5.23 (d, J = 12 Hz, 1 H), 5.17 (d, J = 12 Hz, 1 H), 4.96 (dd, J = 5.1, 4.8 Hz, 1 H), 4.74 (d, J = 4.2 Hz, 1 H), 4.60 (d, J = 5.1 Hz, 1 H), 4.57 (dd, J = 9.6, 2.7 Hz, 1 H), 4.36 (dd, J = 9.3, 7.2 Hz, 1 H), 3.40 (m, 1 H); ^{13}C NMR δ 154.6, 128.5, 128.2, 127.8, 67.8 and 67.4, 67.0, 53.2 and 52.3, 51.8 and 51.2, 35.9; HRMS *m*/*z* 373.9404, 375.9365, 377.9348, calcd for $C_{13}H_{14}NO_2{}^{79/79,79/81,81/81}Br_2$ (M + H) 373.9391, 375.9371, 377.9350. The unrearranged dibromide **8b**: ^{1}H NMR δ 7.36 (s, 5 H), 5.14, s (2 H), 4.94 (dd, J = 4.8, 3.9 Hz, 1 H), 4.80 (dd, J = 6.0, 4.8 Hz, 1 H), 4.62 (dd, J = 6.0, 2.4 Hz, 1 H), 4.34 (dd, J = 9.3, 6.9 Hz, 1 H), 4.02 (dd, J = 9.3, 1.5 Hz, 1 H), 3.25 (m, 1 H); ^{13}C NMR δ 155.8, 128.4, 128.1, 67.1, 66.0, 57.3 and 56.4, 52.5, 51.7, 41.0; HRMS *m*/*z* 373.9375, 375.9371, 377.9365, calcd for $C_{13}H_{14}NO_2{}^{79/79,79/81,81/81}Br_2$ (M + H) 373.9391, 375.9371, 377.9350.

Selective Preparations of Rearranged Dibromide 6b. Acetonitrile cosolvent: Following the general procedure Method B, a solution of alkene **5b** (215 mg, 1 mmol) and bromine (208 mg. 1.3 mmol) in 10:3 acetonitrile:CH_2Cl_2 (13 mL) was reacted for 20 min at rt to afford 270 mg (72%) of rearranged dibromide **6b** and 68 mg (19%) of unrearranged dibromide **7b**. **Nitromethane cosolvent:** Following the general procedure of Method B, bromine (104 mg. 0.65 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of alkene **5b** (107 mg, 0.5 mmol) in nitromethane (8 mL). After 20 min at rt there was isolated 158 mg (89%) of dibromide **6b**. **Nitromethane cosolvent-mercuric fluoride salt:** Following the general procedure of Method C, bromine (80 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added to a solution of alkene **5b** (107

mg, 0.5 mmol) and mercuric fluoride (300 mg, 1.25 mmol) in nitromethane (8 mL). After 1 h at rt there was isolated 140 mg (80%) of dibromide **6b**.

Selective Preparation of Rearranged *N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*anti*-chloro-2-azabicyclo[2.1.1]hexane (6c). Following the general procedure of Method C, bromine (80 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added to a solution of alkene **5b** (100 mg, 0.48 mmol) and mercuric chloride (332 mg, 1.25 mmol) in nitromethane (8 mL). After 1 h at rt there was isolated 127 mg (81%) of bromochloride **6c** at R_f 0.51 (1:1 hexane:ether): ^{1}H NMR δ 7.36 (br, 5H), 5.13 (s, 2H), 4.57 (br, 1 H), 4.13 (d, J = 7.3 Hz, 1 H), 4.06 (d, J = 7.3 Hz, 1 H), 3.63 (d, J = 9.0 Hz, 1H), 3.57 (d, J = 9.0 Hz, 1H), 3.13 (d, J = 6.8 Hz, 1 H); ^{13}C NMR δ 154.8, 135.9, 128.6, 128.1, 128.0, 67.5, 66.5, 64.3, 50.9, 50.4, 50.3; HRMS *m*/*z* 351.9717, 353.9694, calcd for $C_{13}H_{13}NO_2{}^{35}Cl^{79,81}BrNa$ (M + Na) 351.9716, 353.9695.

Selective Preparation of Unrearranged 5-*endo*-6-*exo*-Dibromo-2-azabicyclo[2.2.0]hexane 7b. Pyridinium bromide perbromide (558 mg, 2.16 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 0.5 h to a solution of alkene **5b** (310 mg, 1.4 mmol) in CH_2Cl_2 (15 mL) under argon at 0 °C. The mixture was then stirred at rt for 16 h, washed with $NaHCO_3$ (25 mL) and brine (15 mL), and dried over $MgSO_4$, solvent was removed in vacuo, and the residue was chromatographed to afford 390 mg (92%) of unrearranged dibromide **7b**.

General Procedure for *N*-Halosuccinimide/*N*-(Alkoxycarbonyl)-2-azabicyclo-[2.2.0]hex-5-ene 5 Reactions. To the 2-azabicyclo[2.2.0]hex-5-ene **5** (1.0 mmol) in a solution of the appropriate solvent at −5 °C was added *N*-halosuccinimide (2.5−3 mmol) in small portions so that the temperature did not exceed 0 °C. Upon completion of the addition, the solution was stirred an additional 2−36 h, diluted with water (5−20 mL), and extracted with ether (5 × 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered and solvent was removed in vacuo to provide an oil, which was chromatographed on silica gel (2:1 ether/hexane).

Preparation of *N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (6e) and *N*-(Benzyloxycarbonyl)-6-*exo*-bromo-5-*endo*-hydroxy-2-azabicyclo[2.2.0]hexane (7e). From alkene **5b** (215 mg, 1 mmol) and NBS (445 mg, 2.5 mmol) in 2:1 THF/water (30 mL) after 16 h was obtained according to the general procedure following chromatography 140 mg (45%) of rearranged bromohydrin **6e**, R_f 0.35 (2:1 hexane:ether): ^{1}H NMR δ 7.26 (s, 5H), 5.07 (s, 2H), 4.37 (d, J = 5.4 Hz, 1H), 4.19 (d, J = 7 Hz, 1H), 4.01 (d, J = 7.5 Hz, 1H), 3.53 (d, J = 8.8 Hz, 1H), 3.47 (d, J = 8.8 Hz, 1H), 3.5−3.4 (br, 1H), 2.92 (d, J = 7 Hz, 1H); ^{13}C NMR δ 155.7, 136.5, 129.0, 128.7, 128.5, 85.4, 67.8, 66.4, 65.9, 52.4, 50.4, 49.7; HRMS *m*/*z* 334.0067, 336.0038, calcd for $C_{13}H_{14}NO_3{}^{79/81}BrNa$ (MNa^+) 334.0055, 336.0034. Also obtained was 109 mg (35%) of unrearranged bromohydrin **7e**, R_f 0.32: ^{1}H NMR δ 7.27 (s, 5H), 5.02 (s, 2H), 4.59 (br, 1H), 4.42 (m, 1H), 4.35−4.23 (m, 2H), 4.05 (m, 1H), 3.80−3.40 (br, 1H), 3.25 (m, 1H).; ^{13}C NMR δ 155.7, 136.6, 129.0, 128.6, 128.2, 75.9, 67.8, 64.3 and 64.0, 52.7 and 52.1, 48.5 and 47.7, 35.8; HRMS *m*/*z* 312.0227, 314.0227, calcd for $C_{13}H_{15}NO_3{}^{79/81}Br$ (MH^+) 312.0235, 314.0215.

Preparation of *N*-(Benzyloxycarbonyl)-5-*anti*-bromo-6-*anti*-acetoxy-2-azabicyclo[2.1.1]hexane (6f) and *N*-(Benzyloxycarbonyl)-6-*exo*-bromo-5-*endo*-acetoxy-2-azabicyclo-[2.2.0]hexane (7f). Alkene **5b** (215 mg, 1 mmol) and NBS (445 mg, 2.5 mmol) in a solution of acetic acid (8 mL), sodium acetate (205 mg, 2.5 mmol), and acetic anhydride (0.2 mL, 2 mmol) were stirred at 25 °C for 1 h. With use of the general procedure there was obtained after chromatography 275 mg (80%) of rearranged bromoacetate **6f**, R_f 0.37 (2:1 hexane/ether): ^{1}H NMR δ 7.27 (m, 5H), 5.08 (s, 2H), 4.63 (d, J = 7.1 Hz, 1H), 4.53 (d, J = 7.1 Hz, 1H), 3.96 (d, J = 7.1 Hz, 1H), 3.53 (s, 2H), 3.10 (d, J = 7.1 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR δ 171.0, 155.6, 136.5, 129.0, 128.7, 128.5, 128.0, 83.4, 67.9 and 67.4, 65.7 and 65.3, 50.8, 49.3, 48.6, 21.1 and 20.9; HRMS *m*/*z* 376.0176, 378.0148, calcd for $C_{15}H_{16}NO_4{}^{79/81}BrNa$ (MNa^+) 376.0160, 378.0140. There also was present, as shown by NMR of the crude mixture, 35 mg (10%) of unrearranged bromoacetate **7f**, R_f 0.38 (2:1 hexane/ether): ^{1}H NMR δ 7.26 (m, 5H), 5.24 (br, 1H), 5.07 (d, J = 12.4 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.40−4.30 (br, 2H), 4.08 (br, 2H), 2.02 (s, 3H); ^{13}C NMR δ 169.8, 155.3, 136.6, 129.0, 128.6, 128.2, 76.5 and 76.1, 67.4, 65.6 and 65.3, 49.3 and 48.5, 47.9, 34.7, 20.9; HRMS *m*/*z* 376.0163, 378.0139, calcd for $C_{15}H_{16}NO_4{}^{79/81}BrNa$ (MNa^+) 376.0160, 378.0140. Difficult to obtain separately from the rearranged bromoacetate **6f**, the identity of bromo alcohol **7f** was confirmed by acetylation of the bromo alcohol **7d**.

Preparation of *N*-(Benzyloxycarbonyl)-6-*exo*-iodo-5-*endo*-hydroxy-2-azabicyclo[2.2.0]hexane (9b). THF/water: From alkene **5b** (500 mg, 2.3 mmol) and NIS (1.04 g, 4.6 mmol) in 2:1 THF/water (45 mL) after 24 h at 25 °C there was obtained according to the general procedure following chromatography 750 mg (91%) of unrearranged iodohydrin **9b**, R_f 0.5 (1:5 hexane:ether): ^{1}H NMR δ 7.34 (s, 5H), 5.12 (dd, J = 12.4 Hz, 2H), 4.79 (br, 1H), 4.52 (dd, J = 9.3, 2.5 Hz, 1H), 4.40 (m, 1H), 4.31 (br, 1H), 4.08 (m, 1H), 3.22 (br, 2H), HRMS *m*/*z* 381.9911, calcd for $C_{13}H_{14}NO_3INa$ (MNa^+) 381.9916. **DMSO/water:** From alkene **5b** (713 mg, 3.3 mmol) and NIS (2.35 g, 10.0 mmol) in 1:1 DMSO/water (30 mL) after 24 h at 25 °C there was obtained according to the general procedure following chromatography 1.153 g (97%) of unrearranged iodohydrin **9b**.

Preparation of *N*-(Benzyloxycarbonyl)-6-*exo*-iodo-5-*endo*-acetoxy-2-azabicyclo[2.2.0]hexane (9c). From alkene **5b** (215 mg, 1 mmol) and NIS (450 mg, 2 mmol) in a solution of acetic acid (8 mL), sodium acetate (205 mg, 2.5 mmol), and acetic anhydride (0.2 mL, 2 mmol) at 25 °C after 1 h was obtained according to the general procedure following chromatography 300 mg (78%) of unrearranged iodoacetate **9c**, R_f 0.36 (2:1 hexane/ether): ^{1}H NMR δ 7.34 (m 5H), 5.35 (br, 1H), 5.11 (m, 2H), 4.57−4.44 (br, 2H), 4.21 (m, 2H), 3.44 (br, 1H), 2.15 (s, 3H); ^{13}C NMR δ 169.9, 155.3, 136.6, 129.0, 128.6, 128.3, 67.4, 66.6, 49.3, 48.5, 36.1, 20.9, 20.3; HRMS *m*/*z* 402.0200, calcd for $C_{15}H_{17}NO_4$ (MH^+) 402.0202.

Preparation of *N*-(Benzyloxycarbonyl)-6-*exo*-iodo-5-*endo*-acetoxy-2-azabicyclo[2.2.0]hexane (9c) from the Iodo Alcohol 9b. To a solution of iodo alcohol **9b** (359 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added pyridine (131 mg, 1.8 mmol). Acetyl chloride (214 mg, 2.7 mmol) was added dropwise and the mixture was stirred for 30 min, then warmed slowly to rt and stirred an additional 2 h. Water (15 mL) was added, the organic layer was separated, and the water layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and chromatographed to afford 398 mg (100%) of iodoacetate **9c**.

Selective Preparation of Unrearranged *N*-(Benzyloxycarbonyl)-5-*endo*-fluoro-6-*exo*-iodo-2-azabicyclo-[2.2.0]hexane (9e). Following the above procedure of Method C, iodine (150 mg, 0.6 mmol) in CH_2Cl_2 (5 mL), alkene **5b** (107 mg, 0.5 mmol), and mercuric fluoride (300 mg, 1.25 mmol) in nitromethane (15 mL) after 1 h at rt afforded 115 mg (68%) of iodofluoride **9e** at R_f 0.46 (1:1 hexane:ether): ^{1}H NMR δ 7.26 (m, 5H), 5.34 (dbr, J = 50.2 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.97 (d, J = 12.4 Hz, 1H), 4.6 (br, 1H), 4.5 (br, 1H), 4.4 (dd, J = 9.1, 2.8 Hz, 1H), 4.15 (m, 1H), 3.30 (m, 1H); ^{13}C NMR 155.2, 136.6, 129.0, 128.7, 128.5, 128.3, 96.2/95.5 and 93.9/93.2 ($J_{F,C}$ = 230 Hz), 67.5, 65.1 and 65.0, 48.3 and 47.6, 36.4 and 36.2, 21.3, 21.1; HRMS *m*/*z* 362.0058, calcd for $C_{13}H_{14}NO_2FI$ (MH^+) 362.0053.

Preparation of *N*-(Benzyloxycarbonyl)-5-*endo*-bromo-6-*exo*-phenylseleno-2-azabicyclo[2.2.0]hexane (9f) and *N*-(Benzyloxycarbonyl)-6-*endo*-bromo-5-*exo*-phenylseleno-2-azabicyclo[2.2.0]hexane (10f). CH_2Cl_2: To a solution of alkene **5b** (800 mg, 3.7 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added dropwise phenylselenium bromide (1.05 g, 4.46 mmol) in CH_2Cl_2 (25 mL) over 25 min. After an additional 1 h at 25

°C the mixture was washed with 5% aqueous $NaHCO_3$ (25 mL), water (2 × 25 mL), and brine (25 mL) and dried over $MgSO_4$, and solvent was removed in vacuo. The residue was chromatographed on silica gel (3:1 hexane/ether) to give 1.2 g (72%) of the major isomer **9f** at R_f 0.39 (2:1 hexane/ether): ^{1}H NMR (60 °C) δ 7.60 (br s, 1H), 7.51 (sbr, 1H), 7.33 (m, 7H), 7.29 (sbr, 1H), 5.13 (s, 2H), 4.71 (dd, J = 6.9, 6.6 Hz, H_5), 4.62 (d overlaps m, J = 2.7 Hz, H_1 and H_3), 4.37 (d, J = 9.0, 7.5 Hz, 1H), 4.28 (br, 1H), 3.27 (m, H_4); NOESY H_5 and H_4, H_1 and H_4; ^{13}C NMR δ 155.2, 136.8, 134.6, 134.2, 129.7, 128.9, 128.6, 128.4 (one C overlaps), 67.2 and 66.7, 53.9, 52.9, 50.5, 49.8 and 49.4, 36.5; HRMS m/z 449.9759, 451.9758, 453.9753, calcd for $C_{19}H_{19}NO_2{}^{78/80}Se^{79/81}BrNa$ (MNa^+) 449.9772, 451.9764/451.9752, 453.9744. There also was obtained 179 mg (11%) of the minor isomer **10f** at R_f 0.20: ^{1}H NMR (60 °C) δ 7.60 (br s, 1H), 7.51 (sbr, 1H), 7.33 (m, 7H), 7.29 (sbr, 1H), 5.13 (s, 2H), 4.77 (dd, J = 4.5, 4.2 Hz, 1H), 4.63 (t, J = 6.9, 4.5 Hz, 1H), 4.31 (dd, J = 8.7, 6.9 Hz, 1H), 4.16 (dd, J = 6.9, 3.0 Hz, 1H), 4.01 (dd, J = 8.7, 1.5 Hz, 1H), 3.00 (m, 1H); ^{13}C NMR δ 156.3, 136.7, 135.7, 135.2, 134.6, 129.3, 128.9, 128.7, 128.4, 66.5 and 66.3, 58.5 and 57.6, 53.9, 49.8, 38.4; HRMS m/z 449.9780, 451.9767, 453.9756, calcd for $C_{19}H_{19}NO_2{}^{78/80}Se^{79/81}BrNa$ (MNa^+) 449.9772, 451.9764/451.9752, 453.9744. **Nitromethane:** Reaction of alkene **5b** (100 mg, 0.47 mmol) in nitromethane (15 mL) with phenylselenium bromide (130 mg, 0.56 mmol) according to the above conditions afforded 140 mg (67%) of the major isomer **9f** and 48 mg (23%) of the minor isomer **10f**.

Preparation of *trans*-*N*-(Benzyloxycarbonyl)-4-aminomethyl-3-hydroxycyclobutene (11b). F-TEDA: From alkene **5b** (215 mg, 1.0 mmol) and F-TEDA (461 mg, 1.3 mmol) in acetonitrile (10 mL) and water (10 mL) after 3 h at 25 °C was obtained following extraction with CH_2Cl_2 (4 × 10 mL) and then workup according to the general procedure 172 mg (74%) of cyclobutenol **11b**, R_f 0.14 (2:1 EtOAc/hexane): ^{1}H NMR δ 7.23 (m, 5H), 6.11 (d, J = 2.8 Hz, 1H), 6.06 (br, 1H), 5.27 (br, 1H), 5.01 (s, 2H), 4.66 (t, J = 3.9 Hz, 1H), 3.41 (m, 1H), 3.30 (m, 2H), 3.02 (m, 1H); ^{13}C NMR δ 157.4, 141.2, 139.6, 136.9, 128.9, 128.5, 128.4, 72.2, 67.2, 51.1, 42.5; HRMS m/z 256.0944, calcd for $C_{13}H_{15}NO_3Na$ (MNa^+) 256.0950. **NCS/THF/water:** From alkene **5b** (215 mg, 1.0 mmol) and NCS (334 mg, 2.5 mmol) in THF (10 mL) and water (5 mL) after 36 h at 25 °C there was obtained after workup according to the general procedure 43 mg (20%) of unreacted alkene **5b** and 30 mg (13%) of cyclobutenol **11b**. **NCS/DMSO/water:** From alkene **5b** (215 mg, 1.0 mmol) and NCS (334 mg, 2.5 mmol) in DMSO (8 mL) and water (4 mL) at 25 °C was obtained after 36 h and workup with the general procedure 80 mg (31%) of cyclobutenol **11b** and 32 mg (15%) of unreacted alkene **5b**.

Preparation of *trans*-*N*-(Methoxycarbonyl)-4-aminomethyl-3-hydroxycyclobutene (11c). F-TEDA: From alkene **5c** (136 mg, 1.0 mmol) and F-TEDA (461 mg, 1.3 mmol) in acetonitrile (10 mL) and water (10 mL) after 3 h at 25 °C was obtained following extraction with CH_2Cl_2 (4 × 10 mL) and then workup according to the general procedure 117 mg (76%) of cyclobutenol **11c**, R_f 0.12 (2:1 EtOAc/hexane): ^{1}H NMR δ 6.15 (d, J = 2.8 Hz, 1H), 6.09 (d, J = 2.8 Hz, 1H), 5.32 (br, 1H), 4.70 (d, J = 2.9 Hz, 1H), 3.59 (br, 4H), 3.38 (m, 1H), 3.28 (m, 1H), 3.06 (m, 1H); ^{13}C NMR δ 158.1, 141.1, 139.6, 72.1, 52.6, 51.1, 42.4; HRMS m/z 158.0820, calcd for $C_7H_{12}NO_3$ (MH^+) 158.0817.

Preparation of *N*-(Methoxycarbonyl)-*cis*-4-hydroxy-6-amino-2-pentenal (12). From alkene **5c** (136 mg, 1.0 mmol) and NCS (400 mg, 3.0 mmol) in THF (10 mL) and water (5 mL) after 7.5 h at 35 °C was obtained after the general workup procedure 68.5 mg (40%) of the aldehyde **12**, R_f 0.49 (1:3 hexane/ether): ^{1}H NMR δ 9.57 (d, J = 7.5 Hz, 1H), 6.77 (dd, J = 15.6, 6.9 Hz, 1H), 6.29 (dd, J = 15.6, 7.5 Hz, 1H), 5.89 (br, 1H), 5.19 (br, 1H), 4.65 (m, 1H), 3.79−3.46 (br, 5H); ^{13}C NMR δ 193.0, 157.4, 150.9, 134.4, 58.9, 53.5, 46.9; HRMS m/z 174.0768, calcd for $C_7H_{12}NO_4$ (MH^+) 174.0766.

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Supporting Information Available: Experimental details for conversion of alcohols **7d** and **9b** to acetates **7f** and **9c**, formation of iodohydrin **9a** and iodofluoride **9d**, ^{1}H and ^{13}C NMR spectra for all new structures, and computational methods and data for Tables 5−9 and footnote 20. This material is available free of charge via the Internet at http://pubs.acs.org.

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