2-Azabicyclo[2.1.1]hexanes. 2. Substituent Effects on the Bromine-Mediated Rearrangement of 2-Azabicyclo[2.2.0]hex-5-enes

Grant R. Krow,*,† Yoon B. Lee,† Walden S. Lester,† Nian Liu,† Jing Yuan,† Jingqi Duo,† Seth B. Herzon,† Yen Nguyen,† and David Zacharias‡

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, and The Institute for Cancer Research, Fox Chase, Philadelphia, Pennsylvania 19111

grantkrow@aol.com

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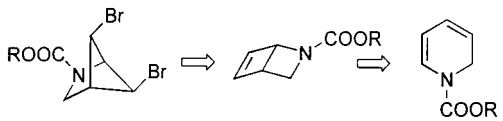
Methyl- and phenyl-substituted *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **6** have been prepared by photoirradiation of appropriately substituted 1,2-dihydropyridines. Torquoselectivity is observed in the synthesis of the 3-*endo*-methyl- and 3-*endo*-phenyl-2-azabicyclo[2.2.0]hexenes **6c**−**e** from 2-methyl- and 2-phenyl-1,2-dihydropyridines **5c**−**e**. Products formed upon addition of bromine to 3-*endo*-, 4-, and 5-methyl- and 3-*endo*-phenyl-substituted *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **6a**−**f** were substituent dependent. For **6a**,**b**, which lack substituents at C_3 or C_5, mixtures of unrearranged dibromides **8a**,**b** and rearranged dibromides **9a**,**b** were obtained. With the 3-*endo*-substituents in **6c**−**e**, only rearranged dibromides **9c**−**e** were formed; 5-methyl substitution afforded mainly unrearranged dibromide **8f** and some allylic bromide **10**. Both unrearranged 5-*endo*,6-*exo*-dibromo-2-azabicyclo[2.2.0]hexanes **8** and rearranged 5-*anti*-6-*anti*-dibromo-2-azabicyclo[2.1.1]hexanes **9** are formed stereoselectively. The dibromoazabicyclo[2.1.1]-hexanes **9** have been reductively debrominated to afford the first reported 2-azabicyclo[2.1.1]hexanes **11** with alkyl or aryl substituents at C-3.

Introduction

The 2-azabicyclo[2.1.1]hexane ring system **1** has recently been prepared by bromine-mediated rearrangement of *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene **2**.[1] The latter structures **2** are conveniently prepared by photoirradiation of *N*-(alkoxycarbonyl)-1,2-dihydropyridines **3**.[2] The synthetic potential of this route to the 2-azabicyclo[2.1.1]hexane structure[3] **1** has prompted us to investigate the influences of sterically demanding alkyl substituents at C_3 and C_4 and a carbocation stabilizing substituent at C_5 of the alkene **2** upon reaction outcomes.[4] The results of these substituent effect studies are relevant to projected syntheses of azabicyclic structures related to **1**, but containing multiple functional groups, each one amenable to subsequent functionalization, for formation of combinatorial libraries.[5]



1 2 3

Results and Discussion

Preparation of 2-Azabicyclo[2.2.0]hex-5-enes. Pyridines **4a**−**c** were reduced with sodium borohydride in methanol in the presence of ethyl chloroformate according to the procedure of Fowler[2a−b] to give the N-(ethoxycarbonyl)-1,2-dihydropyridines **5a**, **5b**, and **5f** (Scheme 1). Pyridines **4a**,**b** were admixed with MeMgBr,[6a] and pyridine **4a** was admixed with PhMgBr[6b] in the presence of ethyl chloroformate to afford N-(ethoxycarbonyl)-1,2-dihydropyridines **5c**, **5d** and **5e**. Because of the difficulty in purifying the 1,2-dihydropyridines **5**, they were di-

† Temple University.
‡ The Institute for Cancer Research.

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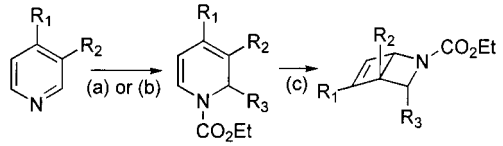
Scheme 1

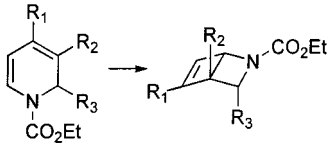


(a) $NaBH_4$/MeOH. (b) MeMgBr or PhMgBr. (c) Irradiation

	R_1	R_2
a	H	H
b	H	CH_3
c	CH_3	H

	R_1	R_2	R_3
a	H	H	H
b	H	CH_3	H
c	H	H	CH_3
d	H	CH_3	CH_3
e	H	H	Ph
f	CH_3	H	H

Table 1. Photocyclization of 1,2-Dihydropyridines 5 to 2-Azabicyclo[2.2.0]hex-5-enes 6



		substituents			product(s)	
entry	substrate[a]	R^1	R^2	R^3	(ratio)	yield (%)
1	**5a**	H	H	H	**6a**	50
2	**5b**	H	Me	H	**6b**	16
3	**5c**	H	H	Me	**6c**	21
4	**5d**	H	Me	Me	**6d**	13
5	**5e**	H	H	Ph	**6e**	15
6	**5f**	Me	H	H	**6f**	25

[a] See ref 1.

rectly irradiated in acetone to provide 2-azabicyclo[2.2.0]-hex-5-enes **6**, shown in Table 1.[2a−d]

Of especial interest in Table 1 is the stereochemical assignment to the methyl group in structure **6c** (entry 3), which followed from its ^{1}H NMR spectrum. The H_3 proton at δ 4.28 was a quintet (J = 6 Hz), resulting from its coupling with H_4 and the adjacent methyl group. Because H_4 and the H_3 endo proton (syn to the olefinic bridge) have a dihedral angle near 90° and would not be expected to show such a large coupling, H_3 must be exo-oriented (anti to the olefinic bridge); thus, the C_3 methyl group must be endo. Consistent with this assignment, the corresponding ^{1}H NMR couplings for the parent structure **6a** (entry 1) are J (H_3 exo/H_4) = 7.2 Hz and J (H_3 endo/H_4) = 2.4 Hz.

The preference for formation of only the 3-*endo*-methyl stereoisomer **6c** is an example of torquoselectivity[7] for one of the possible disrotatory cyclizations of 1,2-dihydropyridine **5c**. In this kind of torquoselectivity (Figure 1), the alkyl group of interest is not attached directly to the diene, but rather is one atom removed and is merely attached to the ring tether. The stereochemical result is explicable in terms of a least motion ring closure pathway shown in Figure 1.[8] The favored conformation of 1,2-dihydropyridine **5c** should have a pseudoaxial methyl group at C_2 pointed away from the ethoxycarbonyl substituent.[9] Photoexcitation of this conformation might be followed by disrotatory twisting of vinyl protons H_b and H_c either away from the C_2 methyl group (anti) or toward it (syn). Initially, H_a and H_b are at an angle close to 30° in the 1,2-dihydropyridine **5c**. Models indicate these hydrogens have moved about 20° toward eclipsing in the 3-*endo*-methyl cycloadduct **6c**, but need to move over 100° away from each other to form the stereoisomeric 3-*exo*-methyl stereoisomer **7**. Also, models indicate less movement of the 2-methyl group of **5c** occurs as H_b twists (about 40°) away from the pseudoaxial methyl substituent at C_2 in going to structure **6c** via the anti ring closure pathway. In the syn pathway leading to **7**, the 3-*exo*-methyl and H_b become nearly eclipsed, requiring about 90°of twist of these groups compared to **5c**.[10] The structures of the 3-*endo*-4-dimethyl analogue **6d** (entry 4) and 3-*endo*-phenyl stereoisomer **6e** (entry 5) were assigned by analogy to **6c**; their behavior upon reaction with bromine is consistent with these stereochemical assignments (Table 2, entries 4 and 5).

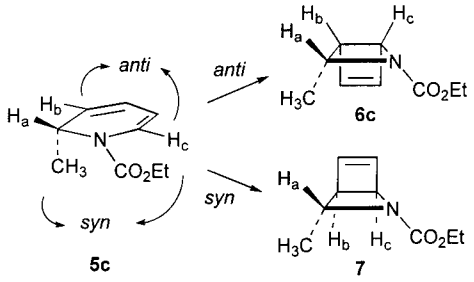


Figure 1. Alternate electrocyclic ring closure pathways.

Brominations of 2-Azabicyclo[2.2.0]hex-5-enes 6. The results of the addition of bromine to the alkenes **6** at −5 °C in methylene chloride (eq 1) are shown in Table 2. The parent olefin **6a** (entry 1) has previously been shown to afford a 55:45 mixture of unrearranged 5-*endo*-6-*exo*-dibromide **8a** in addition to the rearranged 5-*anti*-6-*anti*-dibromide **9a**.[1] The ^{1}H NMR couplings for the parent dibromides **8a** and **9a** are important in making subsequent assignments of structure to the methyl analogues. For dibromide **8a**, the absence of coupling between H_1 and H_6 is consistent with a nearly 90° dihedral angle relationship for H_1 and H_6, which is possible if H_6 is endo oriented and the bromine is 6-exo. The coupling of H_5 with H_6 (J = 5.1 Hz) and with H_4 (J = 7.8 Hz) is consistent with a trans relationship between H_5 and H_6 and a cis relationship for H_5 and H_4; this requires a 5-endo bromine. For the rearranged dibromide **9a**, there is 4-bond coupling between H_1 and H_4 (J = 6.9 Hz) and an absence of coupling between H_4 and its vicinal protons H_3, H_5, and H_6. This result is

(7) Torquoselectivity refers to the twist or torsion preference in an electrocyclic process. (a) Kirmse, Q.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Lopez, S.; Rey, J. G.; Rodriquez, J.; de Lera, A. R. *Tetrahedron Lett.* **1995**, *36*, 4669. (c) Evanseck, J. D.; Thomas IV, B. E.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1995**, *60*, 7134.

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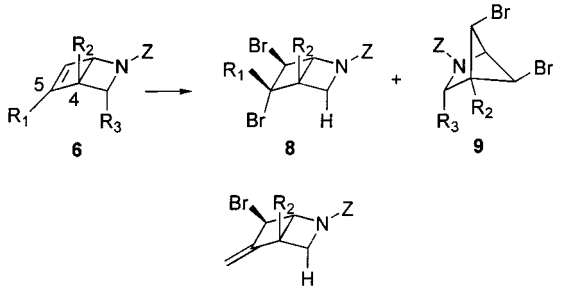
(9) Krow, G. R.; Raghavachari, Siatkowski, Chodosh, D. F. *J. Org. Chem.* **1986**, *51*, 1916. In its crystalline form the 2-aryl substituent of 1-phenoxycarbonyl-2-*p*-chlorophenyl-1,2-dihydropyridine is approximately orthogonal to the plane of the diene.

(10) For an example of torquoselectivity preferences which place allylic substituents exo in the cyclobutenes formed upon irradiation of cyclohexa-1,3-dienes, see: Dauben, W. C.; Kellog, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 4456.

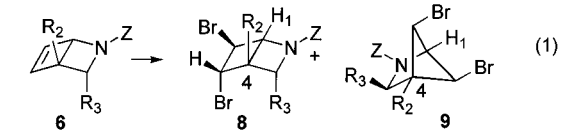
Table 2. Products Formed during Reaction of 2-Azabicyclo[2.2.0]hex-5-enes 6 with Bromine



entry	substrate[a]	substituents R1	R2	R3	product(s) (ratio)	yield (%)
1	**6a**	H	H	H	**8a** + **9a** (55:45)	61−78
2	**6b**	H	Me	H	**8b** + **9b** (27:73)	73
3	**6c**	H	H	Me	**9c**	99
4	**6d**	H	Me	Me	**9d**	89
5	**6e**	H	H	Ph	**9e**	80
6	**6f**	Me	H	H	**8f** + **10** (80:20)[b]	59

[a] Z = COOEt; see ref 1. [b] 70:30 after chromatography.

consistent with dihedral angles close to 90° and anti bromine orientations at C_5 and C_6.



	R_2	R_3
a	H	H
b	CH_3	H
c	H	CH_3
d	CH_3	CH_3
e	H	Ph

Z = COOEt

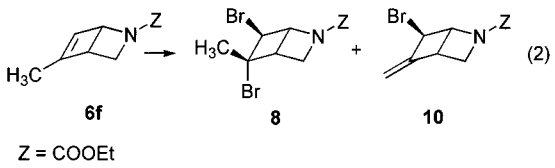
Bromination of 4-Me olefin **6b** (entry 2) afforded a 27:75 mixture of unrearranged dibromide **8b** and rearranged dibromide **9b**. The dibromide **8b** was assigned the 5-*endo*-6-*exo*-dibromo stereochemistry because of the absence of coupling between H_1 and H_6 and the coupling between H_5 and H_6 (J = 5.1 Hz), which were identical to that found in the ^{1}H NMR spectrum of the parent 5-*endo*-6-*exo*-dibromide **8a**. The rearranged dibromide **9b** had a singlet at δ 4.51 for H_1, consistent with the absence of coupling between H_1 and H_6 found in the parent **9a**. The ^{13}C NMR spectra of **9b** consisted of eight lines; the single carbon resonance at δ 56.0 for C_5/C_6 is consistent with the symmetry of this isomer.

Bromination of 3-*endo*-methyl olefin **6c** (entry 3) afforded dibromide **9c**, which showed mutually coupled doublets for H_5 and H_6 at δ 4.29 and δ 4.10 (J = 7.5 Hz) and also for H_4 and H_1 at δ 2.92 and δ 4.55 (J = 7.2 Hz).[12]

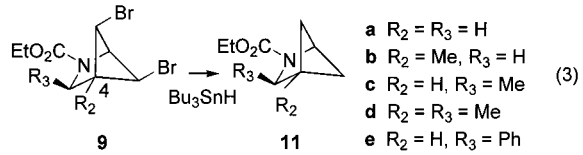
(11) Tsuchiya and co-workers (refs 2c, 2d) have observed the same torquoselectivity in the synthesis of 3-*endo*-phenyl-*N*-(benzyloxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes. The 3-phenyl stereochemistry was assigned by these authors on the basis of a presumed shielding effect on a neighboring methyl group by a 3-*endo*-phenyl substituent.[2d] The reported coupling constants, J (H_3/H_4) = 7 Hz for derived 3-aza-7-oxatricyclo[4.1.0.0^{2,5}]heptanes and J (H_3/H_4) = 8 Hz for derived 3,7-diazatricyclo-[4.1.0.0^{2,5}]heptanes[2c] are consistent with an exo orientation of H_3 and thus an endo orientation for the 3-phenyl groups.

The absence of coupling between bridgehead protons H_1 or H_4 and any of their vicinal hydrogens H_3, H_5, or H_6 is consistent with the ^{1}H NMR of the parent 5-*anti*-6-*anti*-dibromide **9a**. Bromination of 3-*endo*,4-dimethyl olefin **6d** (entry 4) gave a single dibromide **9d** with a singlet for H_1 at δ 4.55 and a pair of doublets for H_5 and H_6 at δ 4.23 and δ 3.97 (J = 7.5 Hz). Similarly, 3-*endo*-phenyl olefin **6e** (entry 5) afforded the single rearranged dibromide **9e**, characterized by the mutually coupled doublets for H_4 and H_1 at δ 3.30 and δ 4.76 (J = 7.5 Hz).

The 5-methyl olefin **6f** (entry 6) afforded mainly the unrearranged dibromide **8f** (eq 2). The exo stereochemistry of the methyl group at C_5 was assigned on the basis of NOE effects observed between H_4 and the C_5-Me hydrogens. Allyl bromide **10** could be assigned the 6-*exo*-bromo orientation on the basis of the absence of coupling between H_6 and H_1, consistent with a 90° dihedral angle for these hydrogens.



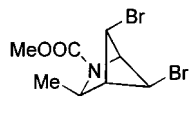
Reductive Debrominations. Tributyltin hydride in refluxing benzene removed the bromine atoms from rearranged dibromides **9a**−**e** to give azabicyclo[2.1.1]-hexanes **11a**−**e** in yields of 74−97% (eq 3).[1] These are the first examples of nonhalogenated 2-azabicyclo[2.1.1]-hexanes to be alkyl or aryl substituted at C_3.



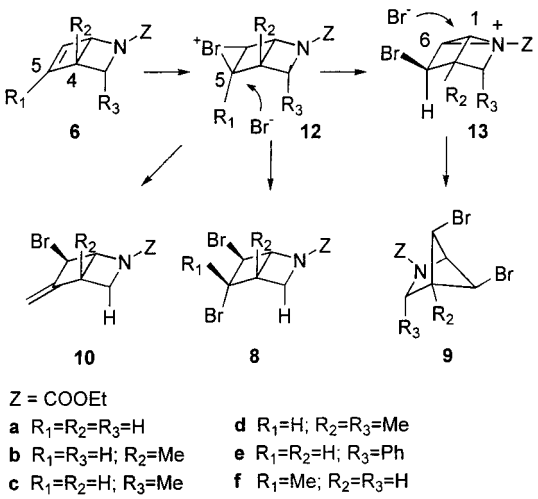
Mechanistic Discussion. An explanation for the electrophilic bromination outcomes is depicted in Scheme 2.[1] Addition of bromine to the open exo face of olefins **6** affords bromonium ions **12**. Selective attack of bromide at C_5 on the endo face of **12** remote from the *N*-ethoxycarbonyl group provides unrearranged dibromides **8**. Competitively, neighboring group particpation by nitrogen can lead to the formation of aziridinium ion **13**. Regioselective attack of bromide ion on intermediate **13**, at the C_1 position farthest from the bromine at C_5, gives the rearranged dibromides **9**.

Introduction of a methyl substituent at C_4 in alkene **6b** (Table 2, entry 2) results in an increase in the rearranged **8**/unrearranged **9** dibromide product ratio relative to the unsubstituted parent alkene **6a** (entry 1). Relief of strain between the 4-methyl substituent and the *exo*-bromonium ion bridge in intermediate **12** may drive rearrangement to the aziridinium ion **13**, the precursor

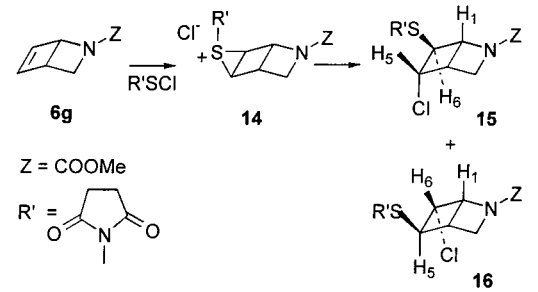
(12) The structure of the **9c′** (R = COOMe) the *N*-methoxycarbonyl analogue of **9c** was confirmed by X-ray structure analysis. Interestingly, the nitrogen atom of **9c** was found to deviate from planarity as measured by θ = 353.6°, where θ is the sum of the three valence angles around nitrogen.[13]



Scheme 2



Scheme 3



of the rearrangement product **9b**. Of greater significance to the reaction outcome is the presence of the 3-*endo*-substituents in alkenes **6c**−**e** (Table 2, entries 3−5). These groups block nucleophilic bromide ion attack on the endo C_5 position of intermediates **12**. Bromide ion attack from an endo direction at C_6 on an exo bromonium ion **12** is also blocked by the conformationally mobile ethoxycarbonyl group on nitrogen. Thus, bromonium ion **12** converts to aziridinium ion **13**. Attack of bromide ion on aziridinium ion **13** occurs regioselectively at the less hindered C_1 position, which leads to the more stable 2-azabicyclo[2.1.1]hexane structures **9c**−**e**. The preference for rearranged product **9d** from alkene **6d** (entry 4) is consistent with its provisional 3-*endo*-4-dimethyl stereochemical assignment.

A C_5 methyl group (Table 2, entry 6) stabilizes positive charge at C_5 in intermediate **12**, or its cationic equivalent, and aziridinium ion **13** is not formed. Only unrearranged dibromide **8f** and allylic bromide **10** are observed. The isomer ratios for all of the unrearranged/rearranged dibromides **8**/**9** are kinetically determined, since the purified dibromides are stable at 25 °C in $CDCl_3$.

Tsuchiya and co-workers[2c] have reported that *N*-(methoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (**6g**) reacts with succinimide-*N*-sulfenyl chloride in CH_2Cl_2 to give two adducts, found to have exo *N*-succinimidothio groups on the basis of subsequent chemistry, in 57% and 10% yields (Scheme 3). The minor adduct was assigned as the 5-*endo*-chloro-6-*exo*-*N*-succinimidothio stereoisomer **15**, and the major adduct was assigned the 6-*endo*-chloro-5-*exo*-*N*-succinimidothio structure **16.** Since the addition shown in Scheme 3 presumably occurs via an episulfonium ion **14** similar to the bromonium ion **12** in Scheme 2, the results of Tsuchiya were reinvestigated. Kurita and Yasuike have determined that the original stereochemical assignments should be reversed on the basis of 400 MHz NMR coupling constants obtained at 50 °C to remove the ambiguities of overlapping carbamate conformers.[14] The proton H_6 of the actual major isomer **15** at δ 4.14 showed only one large coupling (J = 6.6 Hz) consistent with an endo orientation for H_6 and a 6-*exo*-*N*-succinimidothio group. The proton H_6 of the actual minor isomer **16** at δ 4.60 appeared as a triplet (J = 6.5 Hz) coupled to H_1 and H_5; this is consistent with an exo orientation for H_6 and a 6-*endo*-chloro substituent.

We attribute the preference for nucleophilic attack upon bridged bromonium ion **12** and episulfonium ion **14** at C_5 to the greater positive character at C_5 compared to that at C_6 in these structures. The electron-withdrawing 2-aza-substituent inductively destabilizes a positive charge at C_6 with a resultant strengthening of the C_6-hetereoatom bond.[15] A steric effect due to the tetrahedral carbamate substituent cannot be discounted, however.[16] The episulfonium ion **14** is attacked to a minor extent by chloride ion at C_6, but it does not undergo intramolecular nucleophilic attack by nitrogen, as does the bromonium ion **12** to give aziridinium ion **13**. This suggests that the episulfonium ion is more stable than a bridged aziridinium ion.

Conclusion

A rearrangement route to 2-azabicyclo[2.1.1]hexanes **9** has provided the first examples of this ring system with alkyl or aryl substitution at C_3 and also with the possibility of halogen functionality at C_5 and C_6. The latter provide potential for further synthetic manipulations.

Experimental Procedures[1]

N-(Ethoxycarbonyl)-1,2-dihydropyridines **5a**,[1] **5c**, and **5d**,[6a] and *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene **6a** have been prepared previously.[1] The *N*-(ethoxycarbonyl)-1,2-dihydropyridines **5b** and **5f** were prepared according to the procedure of Fowler.[1] The *N*-(ethoxycarbonyl)-2-phenyl-1,2-dihydropyridine **5e** was prepared according to the literature procedure for the *N*-benzyloxycarbonyl analogue.[2c] In accordance with the procedure of Tsuchiya,[2c] the 1,2-dihydropyridines **5** were irradiated as crude mixtures because of their ready decomposition during isolation by chromatography. Brominations of alkenes **6** were carried out as described for olefin **6a**.[1] Reductive debrominations were carried out as described for dibromide **9a**.[1]

General Procedure for Preparation of *N*-(Ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes 6. Following the procedure of Fowler,[2a,b] a 5% solution of the 1,2-dihydropyridine **5** (3.3 mmol) in acetone (10 mL) was irradiated for 48 h in a Rayonet photochemical reactor using RP-3000 lamps. After

(13) (a) Ohwada, T.; Achiwa, T.; Okamoto, I.; Shudo, K. *Tetrahedron Lett.* **1998**, *39*, 865. (b) A slightly larger θ = 356.6° has been observed at the ring nitrogen of *N*-acetyl-2,4-methanoproline-*N*-methylamide (proline ring numbering), which has been described as pyramidal. See: Talluri, S.; Montelione, G. T.; van Duyne, G.; Piola, L.; Clardy, J. Scheraga, H. A. *J. Am. Chem. Soc.* **1987**, *109*, 4473; Piela, L.; Nemethy, G.; Scheraga, H. A. *J. Am. Chem. Soc.* **1987**, *109*, 4477.

(14) We thank J. Kurita and S. Yasuike, School of Pharmacy, Hokuriku University, Japan, for this personal communication.

(15) The propensity for oxymercuration and PhSeCl additions to *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.2[oct-5-enes to add the electrophile at C_6 and the nucleophile at C_5 has been noted: (a) Krow, G. R.; Fan, D. M. *J. Org. Chem.* **1974**, *39*, 2674.

(16) The carbamate substituent of *N*-(methoxycarbonyl)-3-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hex-5-ene has been shown to be pyramidal by X-ray analysis: *Tetrahedron* **2000**, *56*, 9227. See also ref 13.

removal of solvent in vacuo, chromatography of the residue on basic alumina gave photoproducts **6**.

***N*-(Ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (6a).** Irradiation of 1,2-dihydropyridine **5a** (500 mg, 3.3 mmol) for 24 h afforded 252 mg (50%) of photoproduct **6a** (R_f = 0.56, 1:1 hexane/ether): ^{1}H NMR δ 1.23 (t, J = 7.2 Hz, 3H), 3.39 (m, 1H), 3.48 (ddd, J = 8.7, 2.4, 1.5 Hz, 1H), 3.94 (dd, J = 8.7, 7.2 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 4.81 (m, 1H), 6.49 (m, 2H); ^{13}C NMR δ 14.5, 38,3, 49.6, 60.6, 65.5, 140.6, 142.9, 157.2; HRMS *m/z* 153.0797, calcd for $C_8H_{11}NO_2$, 153.0790.

***N*-(Ethoxycarbonyl)-4-methyl-2-azabicyclo[2.2.0]hex-5-ene (6b).** According to Fowler's procedure 3-picoline (30 g, 0.32 mmol) afforded 17.0 g (32%) of crude clear liquid 3-methyl-1,2-dihydropyridine **5b** (R_f = 0.47, 4:1 hexane/ether): ^{1}H NMR δ 1.20 (t, J = 7.2 Hz, 3H), 1.61 (s, 3H), 4.11 (m, 4H), 4.99 (m, 1H), 5.48 (m, 1H), 6.54 (m, 1H). Upon irradiation of crude **5b** (500 mg, 3.0 mmol), there was afforded 105 mg (16%) of photoproduct **6b** (R_f = 0.51, 1:1 hexane/ether): ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 1.37 (s, 3H), 3.59 (d, J = 8.4, 1.2 Hz, 1H), 3.66 (d, J = 8.4 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.48 (d, J = 3.3, 1.2 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 3.3, 2.4 Hz, 1H); ^{13}C NMR δ 14.6, 17.7, 46.5, 55.2, 60.6, 68.3, 137.6, 146.2, 157.1; HRMS *m/z* 167.0934, calcd for $C_9H_{13}NO_2$, 167.0946.

***N*-(Ethoxycarbonyl)-3-methyl-2-azabicyclo[2.2.0]hex-5-ene (6c).** Irradiation of 2-methyl-1,2-dihydropyridine **5c** (500 mg, 3.0 mmol) afforded 105 mg (21%) of photoproduct **6c** (R_f = 0.47, 1:1 hexane/ether): ^{1}H NMR δ 1.25 (t, J = 7.2 Hz, 3H), 1.33 (d, J = 6.3 Hz, 3H), 3.51 (m, J = 7.5, 7.5, 3.0, 1.8 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.28 (qd, J = 7.5, 6.3 Hz, 1H), 4.74 (dd, J = 3.3, 3.0 Hz, 1H), 6.38 (dd, J = 3.3, 2.4 Hz, 1H), 6.58 (dd, J = 2.4, 1.8 Hz, 1H); ^{13}C NMR δ 14.6, 16.0, 43.0, 56.1, 60.0, 63.0, 140.0, 142.7, 155.8; HRMS *m/z* 167.0945, calcd for $C_9H_{13}NO_2$, 167.0946.

***N*-(Ethoxycarbonyl)-3-*endo*-4-dimethyl-2-azabicyclo-[2.2.0]hex-5-ene (6d).** Irradiation of 2,3-dimethyl-1,2-dihydropyridine **5d** (500 mg, 2.76 mmol) afforded 65 mg (13%) of photoproduct **6d** (R_f = 0.51, 1:1 hexane/ether): ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 6.6 Hz, 3H), 1.34 (s, 3H), 3.94 (q, J = 6.6 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.39 (d, J = 3.6 Hz, 1H), 6.36 (dd, J = 3.6, 2.4 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 14.7, 15.8, 17.7, 50.5, 60.4, 61.9, 65.6, 139.6, 144.0, CO lost; HRMS *m/z* 181.1104, calcd for $C_{10}H_{15}NO_2$, 181.1105.

***N*-(Ethoxycarbonyl)-3-*endo*-phenyl-2-azabicyclo[2.2.0]-hex-5-ene (6e).** Irradiation of crude 2-phenyl-1,2-dihydropyridine **6e** (8.79 g, 37 mmol)[2c] for 21 h afforded after chromatography 941 mg (11%) of photoproduct **6e** (R_f = 0.43, 2:1 ether/hexane): ^{1}H NMR δ 1.21 (t, J = 7.0 Hz, 3H), 3.81 (d, J = 7.4 Hz, 1H), 4.10 (br, 2H), 4.98 (s, 1H), 5.26 (d, J = 7.8 Hz, 1H), 6.00 (br, 1H), 6.59 (br, 1H), 7.29 (m, 5H); ^{13}C NMR δ 44,6, 60.8, 63.1, 126.1, 127.1, 127.8, 128.5, 140.7, 141.9, 155.9; HRMS *m/z* 230.1177, calcd for $C_{14}H_{16}NO_2$ (M + H), 230.1181.

***N*-(Ethoxycarbonyl)-5-methyl-2-azabicyclo[2.2.0]hex-5-ene (6f).** According to the general procedure, 4-picoline (30 g, 0.33 mmol) afforded 18.1 g (33%) of clear liquid 4-methyl-1,2-dihydropyridine **5e** (R_f = 0.47, 4:1 hexane/ether): ^{1}H NMR δ 1.22 (t, J = 7.2 Hz, 3H), 1.62 (s, 3H), 4.13 (s, 2H), 4.22 (s, 2H), 4.92 (m, 1H), 5.11 (m, 1H), 6.64 (m, 1H). Upon irradiation of crude **5c** (500 mg, 3.0 mmol), there was afforded 125 mg (25%) of photoproduct **6c** (R_f = 0.40, 1:1 hexane/ether): ^{1}H NMR δ 1.27 (t, J = 7.2 Hz, 3H), 1.84 (s, 3H), 3.22 (m, 1H), 3.42 (dd, J = 8.7, 2.4 Hz, 1H), 3.85 (dd, J = 8.7, 7.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 4.63 (m, 1H), 6.16 (s, 1H); ^{13}C NMR δ 14.3, 14.9, 39.5, 48.7, 60.4, 61.8, 133.0, 153.5, 157.3; HRMS *m/z* 167.0943, calcd for $C_9H_{13}NO_2$, 167.0946.

General Procedure for Addition of Bromine to *N*-(Ethoxycarbonyl)-2-azabicyclo[2.2.0]hexenes 6b−f. The previously described procedure was followed[1] in which a solution of bromine (1 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a cold (−5 °C) solution of the alkene **6** (1 mmol) in CH_2Cl_2 (10 mL) under argon, and the resulting solution was stirred for 2 h and then allowed to come to room temperature and stirred for an additional 16 h. The solution was diluted with ether (25 mL), washed with 10% aqueous sodium bisulfite (10 mL) and water (10 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to provide product oils, which were chromatographed using 1:1 hexane/ether.

Preparation of *N*-(Ethoxycarbonyl)-5-*endo*-6-*exo*-dibromo-4-methyl-2-azabicyclo[2.2.0]hexane (8b) and *N*-(Ethoxycarbonyl)-5-*anti*-6-*anti*-dibromo-4-methyl-2-azabicyclo[2.1.1]hexane (9b). From 4-methyl-2-azabicyclo[2.2.0]-hexene **6b** (59 mg, 0.35 mmol) and bromine (56 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) there were obtained according to the general procedure 22 mg (19%) of unrearranged dibromide **8b** at R_f = 0.63 and 61 mg (54%) of rearranged dibromide **9b** at R_f = 0.55. The dibromide **8b**: ^{1}H NMR δ 1.27 (t, J = 7.2 Hz, 3H), 1.45 (s, 3H), 3.92 (d, J = 9.3 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.37 (d, J = 5.1 Hz, 1H), 4.45 (s, 1H), 4.52 (d, J = 9.3 Hz, 1H), 4.57 (1H, d, J = 5.1 Hz, 1H); ^{13}C NMR δ 14.6, 20.8, 44.1, 48.3, 57.6, 58.4, 62.2, 70.3, 155.6; HRMS *m/z* 325.9378, 327.9407, 329.9334, calcd for C_9H_{14}79/79, 79/81, 81/81Br_2NO_2, 325.9391, 327.9371, 329.9350. The rearranged dibromide **9b**: ^{1}H NMR δ 1.27 (t, J = 7.2 Hz, 3H), 1.34 (s, 3H), 3.46 (s, 2H), 4.04 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.51 (s, 1H); ^{13}C NMR δ 12.3, 14.6, 29.6, 54.5, 56.0, 61.8, 64.1, 155.0; HRMS *m/z* 325.9396, 327.9366, 329.9282, calcd for C_9H_{14}79/79, 79/81, 81/81Br_2NO_2, (M + H), 325.9391, 327.9370, 329.9350.

Preparation of *N*-(Ethoxycarbonyl)-5-*anti*-6-*anti*-dibromo-3-methyl-2-azabicyclo-[2.1.1]hexane (9c). From 3-*endo*-methyl-2-azabicyclo[2.2.0]hexene **6c** (300 mg, 1.8 mmol) and bromine (287 mg, 1.8 mmol) in CH_2Cl_2 (10 mL) there was obtained according to the general procedure 580 mg (99%) of rearranged dibromide **9c** (R_f = 0.49): ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 1.41 (d, J = 6.6 Hz, 3H), 2.92 (d, J = 7.2 Hz, 1H), 4.10 (d, J = 7.5 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.29 (d, J = 7.5 Hz, 1H), 4.55 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 14.5, 18.0, 48.3, 52.4, 54.8, 58.1, 61.7, 66.8, 155.3; HRMS (EI) *m/z* 246.0124, 248.0149, calcd for $C_9H_{13}{}^{79/81}BrNO_2$ − Br, 246.0129, 248.0109.

Preparation of *N*-(Ethoxycarbonyl)-5-*anti*-6-*anti*-dibromo-3,4-dimethyl-2-azabicyclo[2.1.1]hexane (9d). From 3-*endo*-4-dimethyl-2-azabicyclo[2.2.0]hexene **6d** (100 mg, 0.55 mmol) and bromine (88 mg, 0.55 mmol) in CH_2Cl_2 (10 mL) there was obtained according to the general procedure 168 mg (89%) of rearranged dibromide **9d** (R_f = 0.66): ^{1}H NMR δ 1.24 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H), 3.79 (q, J = 6.3 Hz, 3H), 3.97 (d, J = 7.5 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.23 (d, J = 7.5 Hz, 1H), 4.55 (s, 1H); ^{13}C NMR δ 11.5, 14.5, 15.8, 52.8, 55.7, 57.5, 60.6, 61.6, 64.1, 155.4; HRMS (EI) *m/z* 260.0284, 262.0251, calcd for $C_{10}H_{15}{}^{79/81}BrNO_2$ − Br, 260.0286, 262.0266.

Preparation of *N*-(Ethoxycarbonyl)-5-*anti*-6-*anti*-dibromo-3-phenyl-2-azabicyclo[2.1.1]hexane (9e). From 3-*endo*-phenyl-2-azabicyclo[2.2.0]hexene **6e** (114 mg, 0.50 mmol) and bromine (80 mg, 0.50 mmol) in CH_2Cl_2 (13 mL) there was obtained according to the general procedure 165 mg (85%) of rearranged dibromide **9e** (R_f = 0.55, 2:1 ether/hexane): ^{1}H NMR δ 1.28 (br, 3H), 3.30 (d, J = 7.5 Hz, 1H), 4.23 (m, 4H), 4.76 (d, J = 7.5 Hz, 1H), 5.17 (s, 1H), 7.44 (m, 5H); ^{13}C NMR δ 1.5, 47.1, 51.5, 55.4, 62.2, 64.4, 66.9, 126.2, 127.8, 128.7, 137.4, 156.3; mp 187.5−189.0 °C (ether). HRMS (FAB) *m/z* 387.9572, calcd for $C_{14}H_{16}{}^{79/79}Br_2NO_2$ (M + H), 387.9548.

Preparation of *N*-(Ethoxycarbonyl)-5-*endo*-6-*exo*-dibromo-5-*exo*-methyl-2-azabicyclo[2.2.0]hexane (8f) and *N*-(Ethoxycarbonyl)-6-*exo*-bromo-5-methylene-2-azabicyclo[2.2.0]hexane (10). (Method A). From 5-methyl-azabicyclo-[2.2.0]hexene **6f** (221 mg, 1.32 mmol) and bromine (211 mg, 1.32 mmol) in CH_2Cl_2 (25 mL) there was obtained according to the general procedure 172 mg of an oil with a minor component **10** inseparable by column chromatography. Reflux of the mixture in benzene (3 h) decomposed the minor component, and chromatography gave 82 mg (43%) of unrearranged dibromide **8f** at R_f = 0.50: ^{1}H NMR (70 °C) δ 1.27 (t, J = 7.2 Hz, 3H), 2.00 (s, 3H), 3.07 (ddd, J = 7.2, 4.5, 2.7 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.28 (dd, J = 9.6, 7.2 Hz, 1H), 4.46 (dd, J = 9.6, 2.7 Hz, 1H), 4.54 (d, J = 4.5 Hz, 1H), 4.93 (s, 1H); an NOE of 11% was observed for the peak at δ 3.07 (H4) upon irradiation of the methyl group at δ 3.00; ^{13}C NMR δ 14.6, 32.3, 44.6, 54.8, 55.6, 59.6, 61.5, 66.2, 155.3; HRMS *m/z* 325.9379, 327.9370, 329.9359, calcd for $C_9H_{14}{}^{79/79,}$

$^{79/81,\ 81/81}Br_2NO_2$, (M + H), 325.9391, 327.9371, 329.9350. **(Method B).** From 5-methylazabicyclo[2.2.0]hexene **6f** (173 mg, 1.03 mmol) and bromine (160 mg, 1.0 mmol) in CH_2Cl_2 (15 mL) there was obtained according to the general procedure 310 mg of a 3.2−5.4:1 oily mixture of dibromide **6f** and allylic bromide **10**. Column chromatography on silica gel (hexane: ether 3:1) afforded 180 mg (59%) of a 2.1−2.7 mixture of **8f** and **10**. **(Method C).** From alkene **6f** (221 mg, 1.32 mmol) and bromine (211 mg, 1.32 mmol) in THF (25 mL) after 14 h at 25 °C there was obtained after the usual workup and chromatography 81 mg (25%) of a 1:7 mixture of dibromide **8f** and allylic bromide **10**: ^{1}H NMR (70 °C) δ 1.26 (t, J = 7.2 Hz, 3H), 3.62 (dd, J = 6.3, 4.2 Hz, 1H), 3.91 (d, J = 8.1 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 4.30 (dd, J = 8.1, 6.3 Hz, 1H), 4.67 (d, J = 4.2 Hz, 1H), 4.97 (s, 1H), 5.27 (d, J = 1.2 Hz, 1H), 5.40 (d, J = 1.2 Hz, H); ^{13}C NMR δ 14.6, 39.2, 47.8, 54.9, 61.2, 67.4, 113.6, 116.2, 155.4; HRMS m/z 246.0130, calcd for $C_9H_{13}{}^{79}BrNO_2$, (M + H), 246.0147.

General Procedure for Debrominations of 5,6-Dibromo-2-azabicyclo[2.1.1]hexanes 9. Preparation of *N*-(Ethoxycarbonyl)-4-methyl-2-azabicyclo[2.1.1]hexanes 11. The previously described procedure[1] was followed in which the dibromide **9** (176 mg, 0.56 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN) (90 mg, 0.54 mmol) were dissolved in benzene (10 mL), the system was purged with argon for 15 min, tributyltin hydride (454 μL, 491 mg, 1.69 mmol) was added through a rubber septum, and the resulting solution was heated to 80 °C for 2 h. The reaction mixture was cooled to room temperature, and the benzene was removed in vacuo to give a residue that upon chromatography (10:1 hexane/ether) gave compounds **11**, R_f (1:1 hexane/ether).

Preparation of *N*-(Ethoxycarbonyl)-4-methyl-2-azabicyclo[2.1.1]hexane (11b). From dibromide **9b** (76 mg, 0.23 mmol), AIBN (3 mg, 0.02 mmol), and tributyltin hydride (213 mg, 0.73 mmol) there was obtained according to the general procedure 36 mg (92%) of a clear oil **11b** (R_f = 0.40): ^{1}H NMR δ 1.22 (t, J = 7.2 Hz, 3H), 1.26 (s, 3H), 1.41 (m, 2H), 1.62 (m, 2H), 3.12, (s, 2H), 4.10 (q, J = 7.2 Hz, 2H), 4.31 (bs, 1H); ^{13}C NMR δ 14.7, 17.0, 45.1, 46.7, 53.9, 58.5, 60.7, 155.8; HRMS (EI) m/z 169.1103, calcd for $C_9H_{15}NO_2$, 169.1092.

Preparation of *N*-(Ethoxycarbonyl)-3-methyl-2-azabicyclo[2.1.1]hexane (11c). From dibromide **9c** (415 mg, 1.27 mmol), AIBN (30 mg, 0.18 mmol), and tributyltin hydride (1024 μL, 3.80 mmol) there was obtained according to the general procedure 209 mg (97%) of a clear oil **11c** (R_f = 0.49): ^{1}H NMR δ 1.22 (t, J = 7.2 Hz, 3H), 1.28 (d, J = 6 Hz, 3H), 1.32 (dd, J = 10.5, 7.5 Hz, 1H), 1.57 (dd, J = 10.2, 7.8 Hz, 1H), 1.76 (m, 1H), 1.88 (m, 1H), 2.51 (m, 1H), 3.80 (q, J = 6.0 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.39 (br, 1H); ^{13}C NMR δ 14.6, 17.9, 36.4, 42.2, 43.8, 55.5, 60.4, 61.1, 156.7; HRMS (EI) m/z 169.1105, calcd for $C_9H_{15}NO_2$, 169.1093.

Preparation of *N*-(Ethoxycarbonyl)-3,4-dimethyl-2-azabicyclo[2.1.1]hexane (11d). From dibromide **9d** (252 mg, 0.74 mmol), AIBN (17 mg, 0.11 mmol), and tributyltin hydride (596 μL, 2.22 mmol) there was obtained according to the general procedure 115 mg (85%) of a clear oil **11d** (R_f = 0.60): ^{1}H NMR δ 1.13 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.20 (bs, 3H), 1.37 (dd, J = 10.2, 7.2 Hz, 1H), 1.47 (m, 1H), 1.57 (m, 1H), 1.61 (m, 1H), 3.42 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 4.25 (br, 1H); ^{13}C NMR δ 14.7, 15.1, 16.0, 40.1, 46.7, 49.7, 57.9, 58.8, 60.4, 156.3; HRMS (EI) m/z 183.1273, calcd for $C_{10}H_{17}NO_2$, 183.1260.

Preparation of *N*-(Ethoxycarbonyl)-3-phenyl-2-azabicyclo[2.1.1]hexane (11e). From dibromide **9e** (130 mg, 0.33 mmol), AIBN (6 mg, 0.04 mmol), and tributyltin hydride (250 μL, 270 mg, 0.93 mmol) there was obtained according to the general procedure, after washing with concentrated aqueous KF solution (5 mL), 57 mg (74%) of a clear oil **11e** (R_f = 0.40, 1:1 hexane/ether: ^{1}H NMR δ 7.32 (m, 5H), 4.88 (s, 1H), 4.30 (d, J = 6.6 Hz, 1H), 4.16 (d, J = 5.7 Hz, 1H), 4.12 (br, 2H), 3.77 (br, 1H), 2.72 (d, J = 6.6 Hz, 1H), 2.71 (d, J = 7.5 Hz, 1H), 1.77 (dd, J = 5.7, 7.5 Hz, 1H), 1.20 (m, 3H); ^{13}C NMR δ 157.6, 140.7, 128.0, 126.7, 126.4, 62.8, 61.3, 61.0, 45.3, 42.5, 35.6, 14.7; HRMS m/z 232.1345, calcd for $C_{14}H_{18}NO_2$ (M + 1) 232.1338.

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Supporting Information Available: The experimental procedure, tables of the crystal data, bond lengths and angles, atomic coordinates, and anisotropic thermal parameters accompany the ORTEP drawing for the *N*-(methoxycarbonyl)-3-methyl-2-azabicyclo[2.1.1]hexane dibromide **9c′**; ^{1}H spectra for the crude dihydropyridines **5** and ^{1}H and ^{13}C spectra for other new structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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