(10), 190 (70), 161 (37), 160 (47), 104 (65), 91 (100); mol wt 242.1427 (calcd for $C_{15}H_{18}N_2O$ 242.1419).

Acknowledgment. We thank The Robert A. Welch Foundation for their generous support of this research. We also express our appreciation to Dr. Gary Martin of the Department of Medicinal Chemistry, University of Houston, for conducting the high field NMR studies reported herein.

Registry No. **5**, 34657-68-6; **6**, 96040-47-0; **7**, 2301-40-8; **8**, 96040-48-1; **9**, 96040-49-2; **10**, 96040-50-5; **11**, 96040-51-6; **12**, 96040-52-7; **13**, 34164-50-6; **14**, 96040-53-8; **15a**, 96040-54-9; **15b**, 96040-55-0; **18**, 96040-56-1; **19**, 96040-57-2; $PhCH_2Br$, 100-39-0; BuMgCl, 693-04-9; o-$CH_3C_6H_4(CH_2)_2OH$, 19819-98-8; $Br(CH_2)_3CH{=}CH_2$, 1119-51-3; 5,5-dimethyl-2,4-imidazolidinedione, 77-71-4; 2,4-imidazolidinedione, 461-72-3; diethyl azodicarboxylate, 1972-28-7; 5-methylimidazolidine-2,4-dione, 616-03-5.

Supplementary Material Available: The experimental protocol utilized as well as figures showing the high field ^1H, ^{13}C, 2D-J-resolved ^{13}C and 2D-NOE spectra of compounds **15a,b** are reported herein (7 pages). Ordering information is given on any current masthead page.

Heterodienophiles. 10.[1] Stereoselectivity in the 1,4-Cycloaddition of *N*-(Ethoxycarbonyl)-*C*-alkylaldiminium Ions with Cyclohexa-1,3-diene

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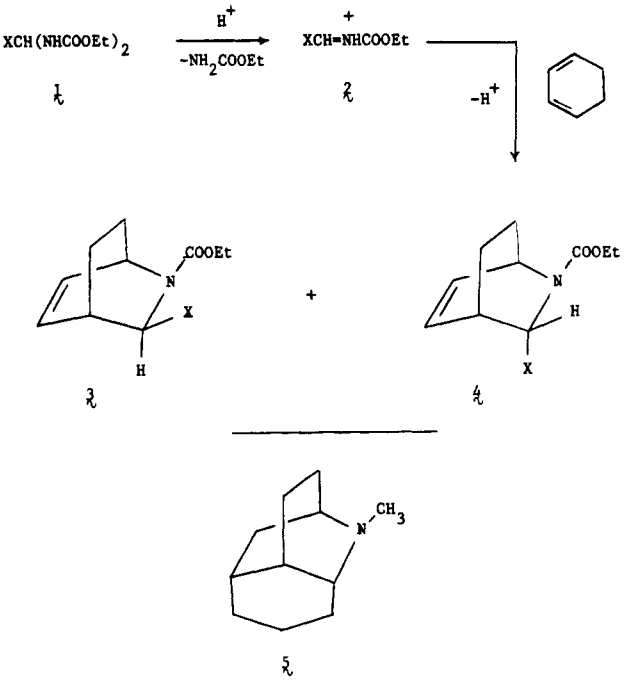
The first systematic investigation of the stereochemistry of cycloaddition reactions of *C*-alkylaldiminium ions **2** is described. *N*-(Ethoxycarbonyl)-3-*exo*- and *N*-(ethoxycarbonyl)-3-*endo*-alkyl-5,6-dehydroisoquinuclidines **3** and **4** are formed from alkylidenebis(urethanes) **1** and cyclohexa-1,3-diene under the influence of boron trifluoride catalysis. ^1H NMR chemical shift and coupling information and, in several cases, independent syntheses of 3-*endo*-alkyl isomers **4** were used to make stereochemical assignments. Major amounts of 3-*exo*-alkyl adducts **3** were found in all cases where the 3-alkyl group was primary (methyl, ethyl, propyl, isobutyl, 3-chloropropyl, and benzyl). When the 3-alkyl group was secondary (isopropyl, cyclohexyl), the percentage of 3-*endo*-alkyl adducts **4** was increased. A proposed reaction model involving cycloaddition via N-protonated (*E*)-aldiminium ions **2**-*E*, in which the allylic moiety reacts through a favored hydrogen/imine eclipsed conformation, is consistent with the observed stereochemical results. The 3-(3-chloropropyl) adduct **4h** has been reported previously as an intermediate in a discredited preparation of **5**, once proposed to be dihydrocannivonine. Our ^1H NMR and mass spectral data for **4h** are generally inconsistent with the previously reported values.

Alkylidenebis(urethanes) **1**, which are readily prepared from aldehydes and urethane,[2] undergo fragmentation in solutions containing catalytic amounts of Lewis acids to afford dienophilic *N*-(alkoxycarbonyl)iminium ions **2**. Thus, cyclohexa-1,3-diene reacts with alkylidenebis(urethanes) **1** to provide 3-substituted 5,6-dehydroisoquinuclidines (2-azabicyclo[2.2.2]oct-5-enes) **3** and **4**.[3] The stereochemical outcomes for a number of such cycloadditions are reported in Table I. For alkylidenebis(urethanes) **1a–e**, in which substituents X are aryl, carbonyl,[3b] and alkoxycarbonyl,[1] a kinetic preference[3b] for 3-exo orientation of substituents as in **3a–e** has been noted. Cycloaddition of *N*-(ethoxycarbonyl)(trichloromethyl)methanimine, the deprotonated form of **2f**, has been effected thermally without acid catalysis[4] and provides mainly 3-*endo*-(trichloromethyl) adduct **4f** with cyclohexa-1,3-diene. We have recently described a cycloaddition of alkylidenebis(urethane) **1g**, in which X is alkyl,[5] and have found mainly 3-*exo*-methyl adduct **3g** to be formed.



A second reported example in which X was alkyl utilized **1h**, X = (3-chloropropyl),[6] to give mainly 3-*exo*-alkyl adduct **3h**. The structure **3h** was described as part of a

(1) For the preceding paper in this series, see: Krow, G.; Johnson, C.; Boyle, M. *Tetrahedron Lett.* **1978**, 1971.
(2) Kraft, F.; Herbst, R. *J. Org. Chem.* **1945**, *10*, 483.
(3) (a) Cava, M.; Wilkens, C.; Dalton, D.; Bessho, K. *J. Org. Chem.* **1965**, *30*, 3772. (b) Krow, G.; Rodebaugh, R.; Carmosin, R.; Figures, W.; Pannella, H.; DeVicaris, G.; Grippi, M. *J. Am. Chem. Soc.* **1973**, *95*, 5273. (c) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (d) Weinreb, S. M.; Steib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(4) Krow, G.; Pyun, C.; Rodebaugh, R.; Marakowski, J. *Tetrahedron* **1974**, *30*, 2977.
(5) Krow, G. R.; Shaw, D. A.; Johnson, C. A.; Henz, K. J.; Guare, J. P.; Kubrak, D.; Szczepanski, S. W.; Carey, J. T. *J. Org. Chem.* **1982**, *47*, 5239.
(6) Jankowski, K.; Jankowski, I. *Experientia* **1971**, *27*, 1383.

0022-3263/85/1950-1888$01.50/0

Table I. Stereochemical Preferences at Carbon 3 in the Formation of Cycloadducts 3 and 4 from Cyclohexa-1,3-diene and Alkylidenebis(urethanes) 1

bis(urethane) 1, X	% 3-*exo*-X 3
a, COOEt[a]	70
b, COOMe[a]	80
c, Ph[b]	80
d, *p*-NO_2Ph[b]	80
e, COMe[b]	67
f, CCl_3[c]	38
g, Me[d]	80
h, $(CH_2)_3Cl$[e]	80

[a] Iminium ion **2a** was prepared from the *N*-(alkoxycarbonyl)-2-methoxyglycinate as was **2b**; see ref 1. [b] Reference 3b. [c] The preformed imine was utilized without acid catalysis; see ref 4. [d] Reference 5. [e] Reference 6.

synthesis of the purported structure **5**, proposed to be dihydrocannivonine.[6] Evans[7] and Kozikowski,[8] by independent syntheses of **5** which did not utilize **4h**, have shown that Jankowski did not actually synthesize **5**, but it is not known whether or not Jankowski actually had **4h**.

On the basis of our stereochemical result for cycloaddition using bis(urethane) **1g** in Table I, we became intrigued about the general question of stereochemical preferences for formation of cycloadducts **3** and **4** when the substituent X of alkylidenebis(urethane) **1** was alkyl. The failure of Jankowski's synthetic route to **5** also casts doubt upon the structures of **3h** and **4h** and required a reinvestigation. Additionally, Baxter and Holmes[10] have shown that 5,6-dehydroisoquinuclidines **3** and **4**, stereoselectivity alkyl substituted at C-3, are synthons for stereospecific syntheses of 2,6-disubstituted piperidines.

Reactions of Alkylidenebis(urethanes) 1 with Cyclohexa-1,3-diene. Aldiminium ions **2** were generated in situ from the corresponding alkylidinebis(urethanes) **1** in refluxing chloroform solution using boron trifluoride etherate as catalyst.[2b] Cyclohexa-1,3-diene was added to this solution and cycloaddition was effected over 1–2 h of reflux. Yields of **3** and **4** are shown in Table II. Reaction mixtures were purified by Kugelrohr distillation of crude material followed by column chromatography or preparative thin-layer chromatography of the distillate. Although yields of cycloadducts **3** and **4** were low, they were fairly uniform for each adduct as shown by the range of observed yields.

The mass spectra of all of the cycloadduct mixtures of **3** and **4** were characteristic for *N*-(ethoxycarbonyl)-5,6-dehydroisoquinuclidines.[3b] As shown in Scheme I, in addition to unique parent ions, common ions were noted at m/z 180, for loss of the alkyl side chain at C-3, and m/z 79, for loss of an XCHNHCOOEt radical. Common fragments at m/z 152 (180 – C_2H_4), 124 (152 – C_2H_4), 108 (124 – CO_2), and 80 (108 – C_2H_4) characterize breakdown of carbamate and loss of ethylene by cycloreversion pathways.

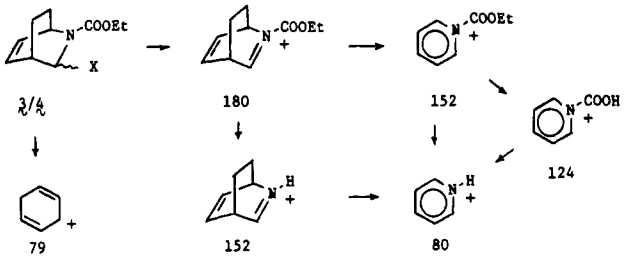
Determination of Ratios of Stereoisomeric Cycloadducts 3 and 4. Chemical shift assignments to the cycloadducts **3g–n** and **4g–n** were made with the aid of decoupling experiments and the most important ^{1}H NMR resonances are shown in Table III. The structures **3g**, X = *exo*-methyl, and **4g**, X = *endo*-methyl, can be used to indicate the method of structure analysis. The ^{1}H NMR spectrum of **3g** at 105 °C was characterized by a quartet of doublets of doublets, J(3n, Me) = 6.3 Hz, J(3n, 4) = 2.5 Hz, and J(3*n*, 8a) = 1 Hz, at δ 3.38 for proton H-3*n*. W-plan coupling J(3*n*, 8a) has been noted previously for 3-exo-substituted stereoisomers **3a–f**.[3b] The 3-*endo*-methyl cycloadduct **4g** was characterized by a quartet of doublets, J(3x, Me) = 6.3 Hz and J(3x, 4) = 2.5 Hz, at δ 3.67 for proton H-3x.

Table II. Yields and Stereochemical Outcomes in the Synthesis of *C*-3-Alkyl Cycloadducts 3 and 4 from Cyclohexa-1,3-diene and Alkylidenebis(urethanes) 1

reactant[a]	product	X	yield, %	% *exo*-X 3	runs
1g	**3g/4g**	methyl	36–43	82 ± 6	3[b]
1h	**3h–4h**	3-chloropropyl	20–35	81 ± 8	3[c]
1i	**3i/4i**	ethyl	6–15	81 ± 8	3
1j	**3j/4j**	propyl	32	81 ± 11	2
1k	**3k/4k**	isobutyl	35–42	79 ± 5	3
1l	**3l/4l**	benzyl	6–10	95 + 5[d]	3
1m	**3m/4m**	isopropyl	7–25	36 ± 7[e]	4
1n	**3n/4n**	cyclohexyl	20–34	54 ± 6	3

[a] Chloroform/boron trifluoride. [b] One run, methylene chloride/boron trifluoride, 84 ± 9% *exo*-X **3**. [c] One run, benzene/boron trifluoride, 81 ± 6% *exo*-X **3**. [d] The *endo*-benzyl isomer **4l** has not been positively identified in the mixtures. [e] One trial gave 58 ± 5% **3m**.

Scheme I. Common Mass Spectral Ions from Cycloadducts 3 and 4

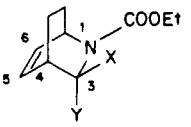


In addition to the coupling information, characteristic chemical shifts for **3** and **4** were observed. Notably, the chemical shifts for H-3n (δ 3.38) and H-4 (δ 2.39) of the 3-*exo*-methyl adduct **3g** are upfield of those for H-3x (δ 3.67) and H-4 (δ 2.54) of the 3-*endo*-methyl adduct **4g**. Additionally, there is a small upfield chemical shift for H-5 (δ 6.40) of the 3-*endo*-methyl adduct **4g** relative to H-5 (δ 6.48) of the 3-*exo*-methyl isomer **3g**. These characteristic chemical shifts shown in Table III were useful in assigning stereochemistry to other cycloadducts **3h–n** and **4h–n**.

For several examples it was difficult to determine unequivocally the complete ^{1}H NMR spectrum of the minor 3-*endo*-alkyl cycloadduct **4** from the spectrum of the mixture of **3** and **4**. This was not a problem, however, since a stereoselective route from *N*-(ethoxycarbonyl)-2-alkyl-1,2-dihydropyridines **6** to stereoisomerically pure adducts **4g** (X = methyl), **4i** (X = ethyl), **4j** (X = propyl), and **4m** (X = isopropyl)[11b] has been reported and the chemical shift values for these adducts were available. It was necessary to prepare the 3-*endo*-benzyl adduct **4l** by this alternative route shown in Scheme II, since it was not clear that any of **4l** was present in the cycloaddition mixture from bis(urethane) **11**. Thus, *N*-(ethoxycarbonyl)-2-benzyl-1,2-dihydropyridine (**6a**) was reacted with phenyl vinyl sufone in refluxing xylene to afford, as a single stereoisomer, the

(7) Evans, D.; Golob, A.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1978**, *100*, 8170.
(8) (a) Kozikowski, A.; Schmiesing, R. *J. Chem. Soc., Chem. Commun.* **1979**, 106. (b) Kozikowski, A.; Schmiesing, R. J. *J. Org. Chem.* **1983** *48*, 1000.
(9) Rearrangement of 2-azabicyclo[2.2.2]oct-5-enes **3** and **4** to 7-azabicyclo[3.2.1]oct-2-enes has been described: Krow, G. R.; Rodebaugh, R.; Hyndman, C.; Carmosin, R.; DeVicaris, G. *Tetrahedron Lett.* **1973**, 2175.
(10) Baxter, A.; Holmes, A. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2343.
(11) (a) Fraenkel, G.; Cooper, J. W.; Fink, C. M. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 523. (b) Krow, G. R.; Carey, J. T.; Cannon, K. C.; Henz, K. J., *Tetrahedron Lett.* **1982**, 2527.

Table III. Selected ^{1}H NMR Chemical Shift Data for 3-*exo*- and 3-*endo*-Alkyl-*N*-(ethoxycarbonyl)-5,6-dehydroisoquinuclidines 3 and 4



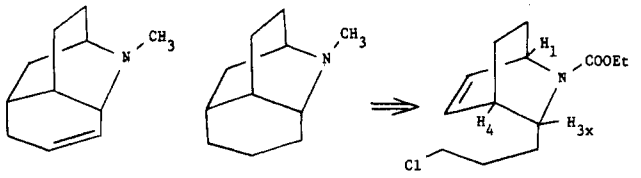
adduct	substituent X	substituent Y	chemical shift,[a] δ H-1	H-3x	H-3n	H-4	H-5	H-6
3g	methyl[b]	H	4.70		3.38[c]	2.39	6.48	6.48
3h	3-chloropropyl[b]	H	4.71		3.20	2.60	6.46	6.46
3i	ethyl	H	4.70		3.08	2.64	6.46	6.46
3j	propyl	H	4.69		3.17	2.60	6.43	6.43
3k	isobutyl[d]	H	4.70		3.28	2.60	6.47	6.44
3l	benzyl[b]	H	4.76		3.42[e]	2.36	6.35[f]	6.41[g]
3m	isopropyl	H	4.73		3.02	2.70	6.46	6.46
3n	cyclohexyl	H	4.71		3.07	2.71	6.45	6.45
4g	H	methyl[b,h]	4.70	3.67[i]		2.54	6.40	6.48
4h	H	3-chloropropyl[b,h]	4.71	3.52		2.72	6.29	6.46
4i	H	ethyl[h]	4.70	3.42		2.77	6.29	6.46
4j	H	propyl[h]	4.69	3.53		2.73	6.29	6.43
4k	H	isobutyl[d]	4.70	3.43		2.75	6.31	6.44
4l	H	benzyl[b,h]	4.72	3.69		2.46	6.30	6.45
4m	H	isopropyl[h]	4.73	3.42		2.80	6.30[j]	6.38[j]
4n	H	cyclohexyl[d]	4.71	3.43		2.80	6.32	6.38

[a] 360 MHz, 60–70 °C, $CDCl_3$. The NMR absorptions are generally broadened due to conformational effects unless otherwise stated. [b] The spectrum was carefully observed at elevated temperature (105 °C) and was decoupled to determine coupling constants for H-5, H-6, H-3x, or H-3n. [c] ddq, J(8a, 3n) = 1.0, J(3n, 4) = 2.5, J(3n, Me) = 6.2 Hz, δ(H-8a) = 1.29. [d] Stereochemical assignments were made on the basis of the relative downfield chemical shifts for H-3n and H-4 and the upfield chemical shifts for H-5 of the 3-*endo*-alkyl stereoisomers 4 relative to the 3-*exo*-alkyl isomers 3. [e] dt, J(3n, CH_2Ph) = 10, 4, J(3n, 4) = 4 Hz. [f] dd, J = 7.5, 7.0 Hz. [g] dd, J = 7.5, 6.0 Hz. [h] This adduct was prepared independently as described in the text and Scheme II. [i] dq, J = 6.2, 2.5 Hz. [j] t, J = 6.0 Hz.

cycloadduct **7a**. Reductive desulfonylation of **7a** with 6% sodium amalgam[11b] provided **41**.

The stereochemical ratios **3g–n/4g–n** from the cycloadditions of bis(urethanes) **1** were remarkably consistent, considering the yields given in Table II, and fell within expected error of the NMR method of analysis in nearly all cases studied. An exception was the formation of **3m/4m** (X = isopropyl), in which 3-*exo*-isopropyl **3m** percentages of 23%, 24%, 40%, and 58% were observed from separate runs. The 40% value, nearly the average value, was observed on the run that provided the best yield (25%) of all the trials.

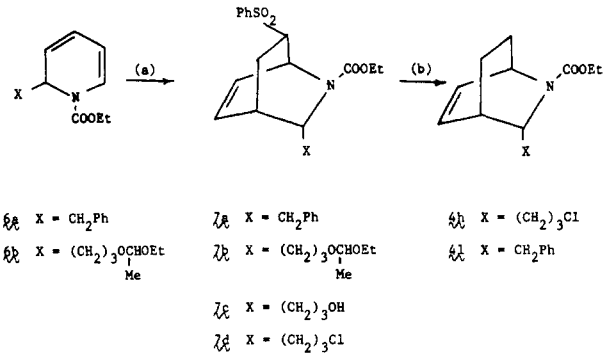
Spectral Properties of Cycloadduct 4h. Jankowski[6] assigned a structure **8** to an alkaloid, cannivonine, isolated from the New Brunswick cranberry. A purported synthesis of **5**, the dihydro derivative of structure **8**, was reported by Jankowski; however, cannivonine was not hydrogenated for comparison with this synthetic material **5**.[6] Subsequently, Evans[7] and Kozikowski[8] each independently synthesized **5** and found it to be different from the structure reported by Jankowski.[6] Since Jankowski utilized the 3-*endo*-(3-chloropropyl) cycloadduct **4h** in his



discredited route to **5**, we have reinvestigated the synthesis and spectral properties of **4h**.

There are significant differences between the reported proton spectral data for **4h**[6] and our observed values for **4h** shown in Table III. One questionable element in the reported spectrum[6] for **4h** is the downfield position of H-5 at δ 6.97 relative to H-6 at δ 6.31. With 3-endo substituents in cycloadducts **4**, H-5 invariably appears upfield of H-6.

Scheme II. Stereoselective Route to 3-*endo*-Alkyl Cycloadducts 4[a]



4e X = CH_2Ph **4f** X = $(CH_2)_3OCHOEt$ (Me)

4g X = CH_2Ph **4h** X = $(CH_2)_3OCHOEt$ (Me) **4i** X = $(CH_2)_3OH$ **4j** X = $(CH_2)_3Cl$

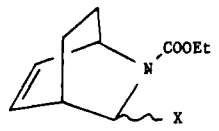
4k X = $(CH_2)_3Cl$ **4l** X = CH_2Ph

[a] (a) $PhSO_2CH{=}CH_2$; (b) Na(Hg).

This has been observed with 3-*endo*-acyl-, trichloromethyl-, aryl-, alkoxycarbonyl-,[4] and, of most relevance, alkyl-substituted **4** in Table III. Other unusual elements in the literature spectrum for **4h** are the differences reported for the chemical shifts of H-1 (δ 3.45) and H-3x (δ 3.17)[6] and the same shifts found in this work for H-1 (δ 4.71) and H-3x (δ 3.52). Notably, in this work H-3x cannot be cleanly observed since its NMR absorbance is buried in an envelope with the methylene protons adjacent to chlorine at δ 3.50. The spectral data for **3h** in Table III is also inconsistent with the reported spectral data for **4h**.[6]

Despite the spectral differences, we observed the same 4:1 ratio of 3-*exo*-/3-*endo*-(3-chloropropyl) cycloadducts **3h/4h** as reported by Jankowski.[6] To confirm this ratio the mixture of cycloadducts **3h/4h** was refluxed with sodium iodide in acetone[12] and the resulting iodides obtained in 41% yield were reduced with sodium cyanoborohydride in hexamethylphosphoramide[13] to afford, despite material

(12) Schurink, H. "Organic Syntheses; Wiley: New York, 1943; Collect. Vol. II, p 476.
(13) Hutchins, R.; Kandasamy, P.; Maryanoff, C.; Masilamani, D.; Maryanoff, B. *J. Org. Chem.* **1977**, *42*, 82.



3h/4h X = $(CH_2)_3$-Cl

3i/4i X = $(CH_2)_2$-CH_3

losses in the transformations, 47% yield of a 4:1 mixture of 3-*exo*-/3-*endo*-propyl cycloadducts **3j**/**4j**.

Because we could not carry out an efficient separation of the cycloadducts **3h**/**4h**, an independent synthesis of the minor stereoisomer **4h** was effected by the route shown in Scheme II. Cycloadduct **7b** was obtained as a single stereoisomer by reaction of 1,2-dihydropyridine **6b** with phenyl vinyl sulfone in toluene for 2 weeks at 210 °C in a sealed tube.[11b,14] Dilute aqueous hydrochloric acid treatment deprotected the acetal **7b**[14] to give 97% of the alcohol **7c**. Conversion of **7c** to the chloride **7d** was effected in 46% yield by reaction of the methanesulfonate ester of **8b** with lithium chloride in HMPA/ether.[15] Desulfonylation of **7d** with 6% sodium amalgam[11b] afforded the cycloadduct **4h** in 19% isolated yield. The ^1H NMR spectrum of **4h** was identical with that of the minor component **4h** from the cycloaddition of alkylidenebis(urethane) **1h** with cyclohexa-1,3-diene. A high-resolution mass spectrum of the isomerically pure adduct **4h** showed, in addition to the parent ion at *m*/*z* 257.1166, the major fragments shown in Scheme I that are expected for a 3-substituted *N*-(ethoxycarbonyl)-5,6-dehydroisoquinuclidine **4h**. These peaks were *m*/*z* 180 (22%), 152 (100%), 108 (12%), 80 (51%), and 79 (19%). By comparison, Jankowski[6] reported at 70 eV *m*/*z* 257 (17%), 180 (100%), 212 (45%), 214 (12%), and 182 (40%) for the same structure **4h**. Although we observed peaks at *m*/*z* 214 (1%), 212 (2.6%), and 182 (1%), these were not significant.

Discussion of the Stereochemistry of Intermolecular Cycloadditions of Cyclohexa-1,3-diene with Aldiminium Ions 2. Available data on the stereochemistry of intermolecular cycloadditions of dienes upon reaction with alkylidenebis(urethanes) **1** in the presence of Lewis acids is consistent with N-protonated (*E*)-aldiminium ions **2** as the primary reactive species in acyclic systems.[2b-d,4] In a concerted process[16] for cycloadduct formation the 3-*exo*-alkyl cycloadduct **3** would be formed from a transition state having the ethoxycarbonyl of **2** endo oriented toward the diene as in 3-TS, while the 3-*endo*-alkyl cycloadduct **4** would be obtained when the ethoxycarbonyl of **2** is exo oriented away from the diene as in 4-TS of Scheme III. The exo/endo stereochemical preferences for **3** and **4** according to this model reflect the relative preferences of the ethoxycarbonyl on nitrogen and the substituent X of **2** for an endo-transition-state orientation.[17]

Data in Table I show that the ethoxycarbonyl on nitrogen of an iminium ion **2** is a better endo director than

Scheme III. Cyclic Transition States for (*E*)-Iminium Ion 2 Cycloadditions with Cyclohexa-1,3-diene

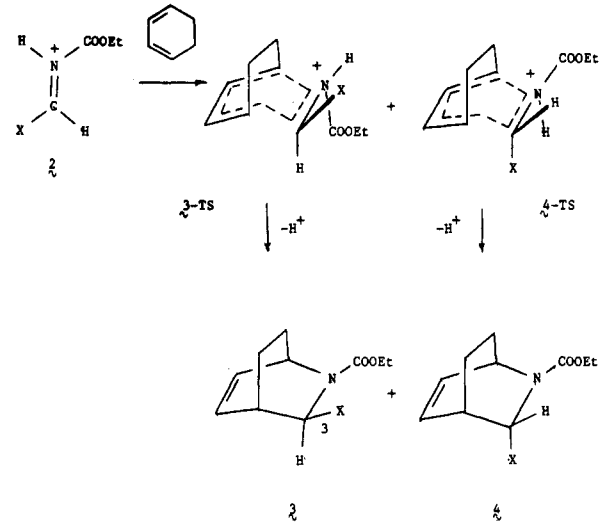


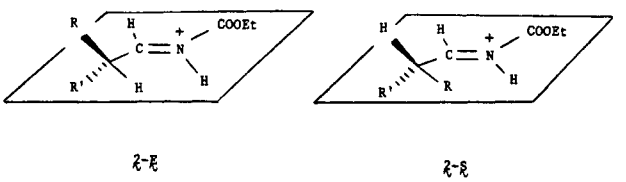
Table IV. Allylic Substituents for the Conformers 2-*E* and 2-*S*

iminium ion	X (-CHRR′)	R	R′
2f[a]	trichloromethyl	Cl	Cl
2g	methyl	H	H
2h	3-chloropropyl	2-chloroethyl	H
2i	ethyl	methyl	H
2j	propyl	ethyl	H
2k	isobutyl	isopropyl	H
2l	benzyl	phenyl	H
2m	isopropyl	methyl	methyl
2n	cyclohexyl	$-(CH_2)_4-$	

[a] The imine rather than the iminium ion **2f** was studied. H in structures 2-*E* and 2-*S* should be chlorine.

aryl, acetyl, or alkoxycarbonyl on carbon of the iminium ion but a poorer endo director than trichloromethyl on the imine carbon of a deprotonated imine.[18] The results of the present study indicate the ethoxycarbonyl of ion **2** to be a better endo director than any primary alkyl substituent on carbon but that secondary alkyl substitution of the aldimine increases the relative amount of 3-*endo*-alkyl adduct **4**.

Facial selectivities in hydroboration,[19a] epoxidation,[19a] and osmium tetraoxide[19b] additions to olefins have been rationalized successfully for allyl moieties by assuming that those factors which determine relative ground-state preference for the hydrogen/olefin eclipsed conformation of an allylic substituent are also of significance in the transition states for additions to the olefin. Such a model has met with predictive success. Application of a similar conformational model to the protonated iminium ions **2** suggests limiting conformations 2-*E*, in which an allylic H



2-E 2-S

is eclipsed with the iminium bond, and 2-*S*, in which an

(14) Eaton, P.; Cooper, G.; Johnson, R.; Mueller, R. *J. Org. Chem.* **1972**, *37*, 1947.

(15) Stork, G.; Grieco, P.; Gregson, M. *Tetrahedron Lett.* **1969**, 1393.

(16) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209. A concerted reaction is one that takes place in a single kinetic step but is not necessarily synchronous. All bond-making and bond-breaking processes take place in unison in a synchronous reaction.

(17) Stereochemical ratios are of kinetic origin.[3b,4] When isomerization at C-3 is possible as in **3e** (R = $COCH_3$), 3-endo isomer **4e** is found to predominate.[3b] We found no change in the isomer ratio when a 4:1 mixture of **3g**/**4g**, enriched in the 3-*exo*-methyl isomer **3g**, was resubjected to the reaction conditions. Nor did we find isomerization of 3-*endo*-benzyl isomer **4l** to the kinetically favored 3-*exo*-benzyl isomer **3l** upon reflux in boron trifluoride etherate in chloroform.

(18) Boron trifluoride catalysis for cycloaddition of the isolated imine formally derived by deprotonation of **2f** also affords mainly 3-*endo*-(trichloromethyl) cycloadduct **4f**.[4]

(19) (a) Kishi, Y. *Aldrichimica Acta* **1980**, *13*, 26. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

H is staggered and a larger substituent R or R′ is eclipsed with the iminium bond. Conformer **2**-*E* should be favored.[20]

In the transition state for a concerted cycloaddition of conformer **2**-*E* the ethano bridge of cyclohexa-1,3-diene will sterically interact with the substituent R or R′ when the ethoxycarbonyl on nitrogen is endo. As the sizes of R and R′ increase the steric interaction with the ethano bridge should increase in magnitude and the tendency for the alkyl substituent to assume the less sterically demanding endo orientation as in 4-TS of Scheme III should increase. The identities of R and R′ of the aldiminium ion **2**-*E* are shown in Table IV.

When one of the substituents R or R′ in Table IV is hydrogen, the diene can always attack this less hindered face of the iminium ion **2**-*E*, and steric interactions between the substituent hydrogen and the diene bridge is insufficient to overcome the endo-directing effects of the *N*-(ethoxycarbonyl). When both R and R′ are methyl (**2m**) or chlorine (**2f**), the steric interactions of the substituent groups with the ethano bridge of the diene become dominant and 3-*endo*-alkyl cycloadducts **4m** (Table II) and **4f** (Table I) are the major stereoisomers. For the example **2n**, when R = R′ = $(CH_2)_4$, nearly equal amounts of 3-*exo*- and 3-*endo*-alkyl cycloadducts **3n** and **4n** were observed; this result again reflects a lessened influence of the ethoxycarbonyl substituent on the nitrogen of **2**-*E* in controlling the stereochemical outcome of the cycloaddition than when R or R′ = hydrogen.

The interaction between a 3-*exo*-alkyl substituent of **3** and a methylene hydrogen at C-8 appears similar to a 1,3-diaxial interaction in a cyclohexane ring. Conformational free-energy differences between equatorial and axial substituents on a cyclohexane ring or *A* values are measures of a pair of such 1,3-diaxial interactions. Steric *A* values for the smaller of the two substituents R and R′ of iminium ion **2**-*E* do not correlate with observed stereochemical preferences in the formation of adducts **3** and **4**, however. Ethoxycarbonyl (A = 1.1–1.2)[21] is predicted on the basis of *A* values to be of smaller effective steric size than alkyl (A = 1.74–1.75 for methyl and ethyl, an extended alkyl chain). However, in the formation of **3m**/**4m** (R′ = methyl) isopropyl is a better endo director than is ethoxycarbonyl, while for formation of **3n**/**4n** (R = R′ = $(CH_2)_4$) cyclohexyl and ethoxycarbonyl show about the same endo preference.[22]

Within the bounds of the proposed conformation model **2**-*E*, failure of steric *A* values to predict the observed stereochemical outcomes for formation of **3** and **4** is related to the occurrence of the cycloaddition transition state before the 1,3-steric interactions in **3**-TS and **4**-TS are fully developed. Additionally, attractive transition-state interactions between the diene and endo-oriented ethoxycarbonyl or alkyl substituents may play an important role.[23] Although other models might be used to explain the stereochemical results in formation of **3** and **4**,[24] the model of these cycloadditions occurring through a favored hydrogen-eclipsed conformation of an (*E*)-aldiminium ion **2**-*E* is a useful one in rationalizing observed reaction stereochemistry. The predictive ability of the model, especially with primary alkyl substituents, is remarkable when one considers the potential for contributions from stepwise ionic pathways[3b] to the mixture of cycloadducts and the possibility of *E*/*Z* isomerization of aldiminium ions **2** with the concomitant potential for some cycloadduct formation from (*Z*)-iminium ions.

Experimental Section

Infrared spectra were measured with a Perkin-Elmer 137 sodium chloride spectrophotometer. Elemental analyses were performed by Micro Analysis, Inc., Wilmington, DE. Proton NMR spectra were obtained in $CDCl_3$ solutions with tetramethylsilane as an internal standard by using a Perkin-Elmer R-32 90-MHz spectrometer and a Varian XL-100-15 spectrometer fitted with a Nicolet FT computer. High-resolution (360 MHz) NMR spectra were recorded at the University of Pennsylvania Middle Atlantic NMR facility, G. McDonald, Director. Exact mass measurements were taken on an RMH-2 Hitachi Perkin-Elmer mass spectrometer at an ionization energy of 70 eV at the University of Pennsylvania Mass Spectrometry Center, D. T. Terwilliger, Director. The parent peak plus the most intense fragments are reported. Routine mass spectra were obtained by R. Dumphy on a Perkin-Elmer mass RMU-6H spectrometer. Dry-column chromatography was performed by using Woelm dry column silica gel (activity III) with a fluorescent indicator. Thin-layer chromatography was conducted by using Analtech silica gel GF plates containing a fluorescent indicator.

The following bis(urethanes) have been previously reported: ethylidene (**1g**),[5] (4-chlorobutylidene) (**1h**),[6] propylidene (**1i**),[2] butylidene (**1j**),[2] isopentylidene (**1k**),[2] isobutylidene (**1m**).[2] The following *N*-(ethoxycarbonyl)-3-*exo*-alkyl-2-azabicyclo[2.2.2]-oct-5-enes **3** have been reported previously: **3g** (methyl)[5] and **3h** (3-chloropropyl).[6] The following *N*-(ethoxycarbonyl)-3-*endo*-alkyl-2-azabicyclo[2.2.2]oct-5-enes **4** have been reported previously: **4g** (methyl),[11b] **4h** (3-chloropropyl),[6] **4i** (ethyl),[11b] **4j** (propyl),[11b] **4m** (isopropyl).[11b] The ^1H NMR of each **3** and **4** is more extensively characterized in Table III.

General Procedure for the Synthesis of Bis(urethanes) 1. Urethane (1.0 mol), aldehyde (0.5 mol), and boron trifluoride etherate (5–10 mL) in ether (500 mL) were stirred for 2–3 h during which time a solid formed. The solvent was removed by suction filtration and the solid **1** was washed with ether, 5% sodium bicarbonate, and ether and dried in vacuo.

(2-Phenylethylidene)bis(urethane) (11). Reaction of 2-phenylacetaldehyde (8.0 g, 0.066 mol) and urethane (10.6 g, 0.13 mol) according to the general procedure afforded 8.28 g (44%) of **11** as a white solid: mp 165–167 °C (methanol); IR (KBr) 3350, 1700 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (br s, 5 H), 5.60 (br d, J = 7 Hz, 2 H), 5.20 (m, J = 7 Hz, 1 H), 4.09 (q, J = 7 Hz, 4 H), 3.06 (d, J = 7 Hz, 2 H), 1.22 (t, J = 7 Hz, 6 H); low-resolution mass spectrum, m/z 197 (13%), 189 (100%), 117 (26%), 91 (35%), 89 (25%). Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.71; H, 7.17; N, 9.89.

(Cyclohexylmethylene)bis(urethane) (1n). Reaction of cyclohexanecarboxaldehyde (4.48 g, 0.04 mol) and urethane (7.0 g, 0.08 mol) according to the general procedure afforded 10.1 g (92%) of **1n** as a white solid: mp 200–201 °C (methanol): IR (KBr) 3350, 1700 cm^{-1}; NMR ($CDCl_3$) δ 5.42 (br d, J = 7 Hz, 2 H), 4.69 (m, 1 H), 4.12 (q, J = 7 Hz, 4 H), 1.60–1.95 (br, 6 H), 1.0–1.4 (br, 10 H); low-resolution mass spectrum, m/z 189 (100%), 117 (15%), 95 (90%), 89 (11%). Anal. Calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.06; H, 8.79; N, 10.02.

(20) Hehre, W. J.; Pople, J. A.; Devaquet, A. J. P. *J. Am. Chem. Soc.* **1976**, *98*, 664. Ketimines are also predicted to be more stable if they are in H-eclipsed conformations. Although conformational preferences are small, the stereochemical preferences for **3** or **4** are often small as well.

(21) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw Hill: New York, 1977; p 130.

(22) Similar reasoning applies to the formation of **3f**/**4f** from thermal cycloaddition using *N*-(ethoxycarbonyl)(trifluoromethyl)methanimine (Tables II and V). An *E* imine in an imine/chlorine eclipsed conformation would have chlorine substituents out of the plane of the imine. Chlorine has an *A* value of 0.52,[21] which is *smaller* than that of ethoxycarbonyl (1.1–1.2), yet trichloromethyl is a *better* endo director than is ethoxycarbonyl. A chlorine–diene attractive effect is implied.

(23) In this regard, failure to observe 3-*endo*-benzyl cycloadduct **41** may be due to repulsive transition-state interaction of the aromatic and dienic moieties.

(24) A model in which one substituent is perpendicular to the imine bond, and in which the diene attacks from the face anti to this substituent R or R′, would experience greatest steric hindrance when *both* R and R′ were larger than hydrogen as occurs when a secondary alkyl group is attached to carbon of the imine, just as in the present instance. See: Kozikowski, A. P.; Chen, Y.-Y.; Wang, B. C.; Xu, Z.-B. *Tetrahedron* **1984**, *40*, 2345.

General Procedure for the Synthesis of 3-Substituted-*N*-(Ethoxycarbonyl)-2-azabicyclo[2.2.2]oct-5-enes 3 and 4 from Alkylidenebis(urethanes) 1. A solution of cyclohexa-1,3-diene (2.0 g, 25 mmol), boron trifluoride etherate (0.15 mL/mmol), and the bis(urethane) 1 (22 mmol) in dry chloroform, methylene chloride, or benzene (250 mL) was refluxed for 1–3 h. The solution was cooled, washed with water, aqueous sodium bicarbonate, and water, and dried over magnesium sulfate. Filtration and removal of solvent in vacuo afforded an oil which was chromatographed on silica gel to afford a mixture of 3 and 4. Samples were purified for analysis by gas chromatography on a Varian A-90 gas chromatograph [5 ft × 0.25 in. 5% SE-52/Chromosorb G (60-80 mesh) at column temperature of 175 °C, flow rate 60 mL/min, retention times, **3g/4g** 3.5 min, **3i/4i**, 3.5 min, **3j/4j**, 3.5 min, **3k/4k**, 4.5 min, **31/41**, 25 min, **3m/4m**, 3.5 min, and, **3n/4n**, (15 min)]. Isomer ratios of **3/4** in Table II were determined from the ^{1}H NMR spectra of mixtures of crude material before chromatography and on purified material where possible. The integral for H-3n of the 3-*exo*-alkyl isomers **3g–n** was compared with the total integral for H-1 of both isomers **3g–n** and **4g–n**. Use of methylene chloride (**3g/4g**) or benzene (**3h/4h**) as reaction solvents did not alter the isomer ratios observed when chloroform was used as solvent. The general reaction conditions were found to be optimum for formation of cycloadduct from methylenebis(urethane) and cyclohexadiene.

***N*-(Ethoxycarbonyl)-3-*exo*-methyl-2-azabicyclo[2.2.2]-oct-5-ene (3g) and *N*-(Ethoxycarbonyl)-3-*endo*-methyl-2-azabicyclo[2.2.2]oct-5-ene (4g).** Bis(urethane) **1g** (4.4 g, 21 mmol) and cyclohexa-1,3-diene (2.0 g) in methylene chloride after 3 h afforded following column chromatography an 84:16 ± 9% mixture of **3g/4g**: bp 85–87 °C (0.3 mm); IR (neat) 2950, 1690 cm^{-1}; low-resolution mass spectrum, *m/z* 195 (17%), 152 (100%), 116 (38%), 108 (20%), 80 (100%), 79 (14%); NMR ($CDCl_3$) Table III and δ 4.10 (q, *J* = 7 Hz, 2 H), 1.1–2.0 (br, 10 H). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.05. Found: C, 67.48; H, 8.87; N, 7.15.

Repeat runs in chloroform gave the following results: trial 2, 1 h, 36%, 84 ± 3% **3g**; trial 3, 1 h, 41%, 80 ± 5% **3g**.

Reflux of an 80:20 mixture of **3g/4g** in chloroform (4 mL) with boron trifluoride etherate (0.1 mL) for 1 h gave 0.20 g (87%) recovery of an 80:20 mixture of **3g/4g**.

***N*-(Ethoxycarbonyl)-3-*exo*-(3-chloropropyl)-2-azabicyclo[2.2.2]oct-5-ene (3h) and *N*-(Ethoxycarbonyl)-3-*endo*-(3-chloropropyl)-2-azabicyclo[2.2.2]oct-5-ene (4h).** According to literature[3a,6] and the general procedure, bis(urethane) **1h** (1.35 g, 5.0 mmol) and cyclohexa-1,3-diene (1.0 g) in refluxing benzene (40 mL) after 1 h afforded after Kugelrohr distillation [140–150 °C (0.15 mm)] and column chromatography 290 mg (21%) of an 81:19 ± 6% mixture of **3h** and **4h**:[6] IR (neat) 1690 cm^{-1}; NMR ($CDCl_3$) Table IV; high-resolution mass spectrum, see the text. Repeat runs in chloroform gave the following results: trial 2, 0.75 h, 20%, 82 ± 11% **3h**; trial 3, 2.3 h, 35%, 82 ± 7% **3h**.

***N*-(Ethoxycarbonyl)-3-*exo*-ethyl-2-azabicyclo[2.2.2]oct-5-ene (3i) and *N*-(Ethoxycarbonyl)-3-*endo*-ethyl-2-azabicyclo[2.2.2]oct-5-ene (4i).** Bis(urethane) **1i** (1.38 g, 6.4 mmol) and cyclohexa-1,3-diene (0.7 g) in chloroform after 2 h afforded following Kugelrohr distillation at 80–95 °C (0.5 mm) and column chromatography (2:1 petroleum ether/ether) 200 mg (15%) of an 81:19 ± 6% mixture of **3i** and **4i** as a yellow oil: NMR ($CDCl_3$) Table III and δ 4.10 (q, *J* = 7 Hz, 2 H), 1.15–2.20 (br, 9 H), 0.94 (t, *J* = 7 Hz, 3 H); IR (neat) 1680 cm^{-1}; high-resolution mass spectrum, *m/z* 209.1423 (calcd for $C_{12}H_{19}NO_2$, 209.1416), 180 (41%), 152 (100%), 108 (24%), 80 (100%). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.67; H, 9.53; N, 6.33.

Repeat runs using the same conditions gave the following results: trial two, 6%, 80 ± 10% **3i**; trial three, 15%, 83 ± 9% **3i**.

***N*-(Ethoxycarbonyl)-3-*exo*-propyl-2-azabicyclo[2.2.2]-oct-5-ene (3j) and *N*-(Ethoxycarbonyl)-3-*endo*-propyl-2-azabicyclo[2.2.2]oct-5-ene (4j).** Bis(urethane) **1j** (4.57 g, 19 mmol) and cyclohexa-1,3-diene (1.6 g) in chloroform after 2 h afforded after silica gel column chromatography (7:3 pentane/ether) 1.37 g (32%) of an 80:20 ± 3% mixture of **3j** and **4j** as an oil: NMR ($CDCl_3$) Table III and δ 4.10 (q, *J* = 7 Hz, 2 H), 1.10–2.15 (complex 11 H), 0.98 (t, *J* = 7 Hz, 3 H); IR (neat) 1700 cm^{-1}; high-resolution mass spectrum, *m/z* 223.1579 (calcd for $C_{13}H_{21}NO_2$, 223.1572), 180 (63%), 152 (100%), 144 (21%), 108 (14%), 80 (93%). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.09; H, 9.46; N, 6.26.

A repeat run gave the same result.

***N*-(Ethoxycarbonyl)-3-*exo*-isobutyl-2-azabicyclo[2.2.2]-oct-5-ene (3k) and *N*-(Ethoxycarbonyl)-3-*endo*-isobutyl-2-azabicyclo[2.2.2]oct-5-ene (4k).** Bis(urethane) **1k** (1.40 g, 5.6 mmol) and cyclohexa-1,3-diene (0.7 g) in chloroform after 2 h afforded upon silica gel chromatography (3:1 petroleum ether/ether) 0.56 g (42%) of an 82:18 ± 5% mixture of **3k/4k** as an oil: NMR ($CDCl_3$) Table III and δ 4.10 (q, *J* = 7 Hz, 2 H), 1.10–2.00 (br, 10 H), 0.98 (d, *J* = 7 Hz, 6 H); IR (neat) 1700 cm^{-1}; high-resolution mass spectrum, *m/z* 237.1699 (calcd for $C_{14}H_{23}NO_2$, 237.1729), 180 (58%), 152 (100%), 80 (85%). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.73; H, 9.72; N, 5.71. Repeat runs afforded the following results: trial two, 42%, 80 ± 6% **3k**, trial three, 35%, 79 ± 5% **3k**.

***N*-(Ethoxycarbonyl)-3-*exo*-benzyl-2-azabicyclo[2.2.2]-oct-5-ene (31) and *N*-(Ethoxycarbonyl)-3-*endo*-benzyl-2-azabicyclo[2.2.2]oct-5-ene (41).** Bis(urethane) **11** (1.12 g, 4.0 mmol) and cyclohexa-1,3-diene (0.7 g) in chloroform after 2 h afforded upon silica gel chromatography (2:1 petroleum ether/ether) followed by preparative TLC (2:1 petroleum ether/ether) 100 mg (10%) of an oil containing at least 95% of **31** with perhaps a small amount of **41**: NMR ($CDCl_3$) Table III and δ 7.23 (br s, 5 H), 4.18 (q, *J* = 7 Hz, 2 H), 3.55 (d, *J* = 12 Hz, 1 H), 2.56 (t, *J* = 12 Hz, 1 H), 2.10–1.10 (br, 6 H); IR (neat) 1690 cm^{-1}; high-resolution mass spectrum, *m/z* 271.1600 (calcd for $C_{17}H_{21}NO_2$, 271.1573), 180 (66%), 152 (100%), 91 (59%), 80 (85%), 79 (39%). Repeat determinations using the same conditions afforded yields of 6% and 9% with the same isomer ratios.

***N*-(Ethoxycarbonyl)-3-*exo*-isopropyl-2-azabicyclo-[2.2.2]oct-5-ene (3m) and *N*-(Ethoxycarbonyl)-3-*endo*-isopropyl-2-azabicyclo[2.2.2]oct-5-ene (4m).** Bis(urethane) **1m** (1.17 g, 5.1 mmol) and cyclohexa-1,3-diene (0.7 g) in chloroform after 1.2 h afforded upon silica gel chromatography (3:1 petroleum ether/ether) 284 mg (25%) of a 40:60 ± 5% mixture of **3m/4m**: NMR ($CDCl_3$) Table III and δ 4.00–4.25 (br, 2 H), 0.8–2.0 (br, 14 H); IR (neat) 1690 cm^{-1}; high-resolution mass spectrum, *m/z* 223.1565 (calcd for $C_{13}H_{21}NO_2$, 223.1572), 180 (60%), 152 (100%), 108 (20%), 80 (85%), 79 (16%). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.68; H, 9.37; N, 6.03. Repeat determinations in chloroform gave the following results: trial two, 1.3 h, 10%, 76 ± 6% **4m**; trial 3, 1.3 h, 7%, 77 ± 11% **4m**; trial 4, 1 h, 16%, 42 ± 5% **4m**: It is conceivable, but not confirmed, that the column was incompletely eluted in the trial with 42% **4m**, since the later fractions contained larger amounts of **4m**.

***N*-(Ethoxycarbonyl)-3-*exo*-cyclohexyl-2-azabicyclo-[2.2.2]oct-5-ene (3n) and *N*-(Ethoxycarbonyl)-3-*endo*-cyclohexyl-2-azabicyclo[2.2.2]oct-5-ene (4n).** Bis(urethane) **1n** (2.26 g, 8.3 mmol) and cyclohexa-1,3-diene (1 g) in chloroform after 2 h afforded upon silica gel chromatography (3:1 petroleum ether/ether) 729 mg (34%) of a 52:48 ± 6% mixture of **3n/4n**: NMR ($CDCl_3$) Table III and δ 4.10 (br, 2 H), 1.05–1.90 (br, 18 H); IR (neat) 1700 cm^{-1}; high-resolution mass spectrum, *m/z* 263.1891 (calcd for $C_{16}H_{25}NO_2$, 263.1885), 180 (78%), 152 (100%), 108 (13%), 80 (77%), 79 (25%). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.73; H, 9.84; N, 5.16. Repeat trials in chloroform gave the following results: trial 2, 32%, 56 ± 9% **3n**; trial 3, 22%, 56 ± 5% **3n**.

***N*-(Ethoxycarbonyl)-7-(phenylsulfonyl)-3-*endo*-benzyl-2-azabicyclo[2.2.2]oct-5-ene (7a).** Pyridine (1.87 g, 23.7 mmol) in ether (10 mL) was added dropwise to a preformed solution of benzylmagnesium chloride, prepared from benzyl chloride (3.0 g, 23.7 mmol), and magnesium (580 mg, 23.7 mmol) in dry ether (30 mL), at 0 °C over 1.5 h, and then ethyl chloroformate (2.57 g, 23.7 mmol) in ether (10 mL) was added over 0.5 h.[11] Saturated aqueous ammonium chloride was added, the layers were separated, and the organic layer was washed with water, dried over magnesium sulfate, filtered, and solvent was removed in vacuo to yield 4.02 g (70%) of a 1:2 mixture of *N*-(ethoxycarbonyl)-2-benzyl-1,2-dihydropyridine **6a** and its 1,4-dihydropyridine isomer: NMR ($CDCl_3$), for **6a**, δ 7.20 (m, 5 H), 6.80 (br, H-6), 6.00–5.65 (m, H-3), 5.50–5.05 (br, H-4, H-5), 4.80 (m, H-2), 4.30–3.95 (m, OCH_2), 2.90–2.50 (br, CH_2Ph), 1.15 (m, 3H), the resonance for H-3 was

compared to that of OCH_2 to determine the 1,2- to 1,4-dihydropyridine ratio; IR (film) 1705 cm^{-1}; low-resolution mass spectrum, m/z 152 ($M^+ - CH_2Ph$).

A solution of 3 g of the mixture of dihydropyridines containing **6a** (1.0 g) and phenyl vinyl sulfone (1.5 g, 8.9 mmol) was refluxed in xylene (40 mL) for 36 h. The solvent was removed and the residue was purified by flash column chromatography (silica gel 60, 230–400 mesh, 2:1 ether/hexane) to give 460 mg (30%) of **7a** as an oil: NMR ($CDCl_3$) δ 7.85, 7.55 (m, 5 H), 7.20 (m, 5 H), 6.46 (m, 2 H), 4.95 (br m, 1 H), 4.10 (br, 2 H), 3.80–3.40 (m, 2 H), 3.30–2.95 (m, 1 H), 2.70 (m, 1 H), 2.65–2.30 (m, 1 H), 1.95–1.70 (m, 2 H), 1.45–1.00 (m, 3 H); IR ($CHCl_3$) 1685 cm^{-1}; high-resolution mass spectrum, m/z 411.1497 (calcd for $C_{23}H_{25}NO_4S$, 411.1505).

***N*-(Ethoxycarbonyl)-3-*endo*-benzyl Adduct 4l by Desulfonylation of 7a.** To a cold (0 °C) solution of the sulfone **7a** (0.37 g, 0.90 mmol) in dry methanol (50 mL) containing disodium hydrogen phosphate (2.04 g, 14.40 mmol) was added 5% sodium amalgam (3.32 g, 7.21 mmol, 8 equiv). The reaction was stirred at 0 °C for 10 h, then an additional 10 h at 25 °C. Water (10 mL) was added and the solution was decanted from the residual mercury. After solvent was removed in vacuo the residue was taken up in dichloromethane, washed with water, and dried over magnesium sulfate, and solvent was removed to give 240 mg of a crude oil. The residue was dissolved in toluene (20 mL) and refluxed with maleic anhydride (500 mg) for 12 h.[11b] Solvent was removed, the residue was taken up in dichloromethane, washed with 3 N sodium hydroxide and water, and dried over magnesium sulfate, and the solvent was removed to give 170 mg of an oil. Flash chromatography (1:1 ether/hexane) gave 138 mg (57%) of **4l** as an oil: NMR ($CDCl_3$) Table III and δ 7.29–7.18 (m, 5 H), 4.18 (br q, J = 7 Hz, 2 H), 3.23 and 3.06 (two d, J = 12 Hz, 1 H), 2.35 (two overlapping t, J = 12 Hz, 1 H), 1.50–1.21 (m, 6 H); IR (film) 1690 cm^{-1}; high-resolution mass spectrum, m/z 271.1565 (calcd for $C_{17}H_{21}NO_2$, 271.1572). Reflux of **4l** (76 mg) in chloroform (5 mL) with boron trifluoride etherate (0.05 mL) for 1 h afforded solely unchanged **4l**; no isomerization to **3l** was observed.

Conversion of Cycloadducts 3h/4h to 3j/4j. A solution of a 4:1 mixture of **3h/4h** (930 g, 40 mmol) in acetone (8 mL) was added to a solution of sodium iodide (2.16 g, 10 mmol) in dry acetone (15 mL) and the mixture was refluxed for 12 h.[12] The solution was cooled and filtered, acetone was removed in vacuo, and chloroform (20 mL) and water were added. The layers were separated and the organic layer was dried over magnesium sulfate and filtered, and the residue, after chromatography on silica gel (7:3 pentane/ether), yielded 520 mg (41%) of a yellow oily iodide: NMR ($CDCl_3$) δ 6.40 (br, 1.6 H), 6.29 (br, 0.4 H), 4.68 (br, 1 H), 4.10 (q, J = 7 Hz, 2 H), 3.53–3.20 (br, 3 H), 1.10–2.05 (br, 11 H); IR (neat) 1690 cm^{-1}; low-resolution mass spectrum, m/z 349 (M^+, 3%), 180 (94%), 152 (100%), 108 (19%), 80 (100%), 79 (42%). According to the procedure of Hutchins,[13] a solution of the iodide (400 mg, 1.14 mmol) and sodium cyanoborohydride (300 mg, 4.76 mmol) in hexamethylphosphoramide (10 mL) was heated at 70 °C for 4.5 h. After cooling, water (40 mL) was added, and the solution was extracted twice with cyclohexane (30 mL). The combined organic layers were washed with water, solvent was removed, and the residue was eluted through a short alumina column (2:1 petroleum ether/ether) to afford 120 mg (47%) of a 4:1 mixture of **3j/4j**: NMR ($CDCl_3$) identical with that of the **3j/4j** mixture prepared directly from bis(urethane) **1j**.

***N*-(Ethoxycarbonyl)-2-[3-(1-ethoxyethoxy)propyl]-1,2-dihydropyridine (6b).** Addition of 1-lithio-3-(1-ethoxyethoxy)propane, prepared from 1-(3-bromopropoxy)-1-ethoxyethane (3.17 g, 20 mmol) according to Eaton's procedure,[14] to pyridine (79 mg, 10 mmol) and trapping with ethyl chloroformate (1.08 g, 10 mmol) according to the method of Fraenkel,[11a] afforded 1.87 g (66%) of *N*-(ethoxycarbonyl)-2-[3-(1-ethoxyethoxy)propyl]-1,2-dihydropyridine (**6b**) as an oil: NMR ($CDCl_3$) δ 6.70 (br, 1 H), 5.91 (dd, J = 9 Hz, 5 Hz, 1 H), 5.55 (dd, J = 9 Hz, 5 Hz, 1 H), 5.20 (br, 1 H), 4.75 (br, 1 H), 4.62 (q, J = 6 Hz, 1 H), 4.20 (q, J = 7 Hz, 2 H), 3.3–3.65 (br, 4 H), 1.55 (br, 4 H), 0.9–1.4 (br, 9 H); IR (neat) 1710 cm^{-1}; high-resolution mass spectrum, m/z 283.1727 (calcd for $C_{21}H_{25}NO_4$, 283.1783).

***N*-(Ethoxycarbonyl)-7-(phenylsulfonyl)-3-*endo*-(3-hydroxypropyl)-2-azabicyclo[2.2.2]oct-5-ene (7c).** A mixture of the oil **6b** (1.75 g, 6.18 mmol) and phenyl vinyl sulfone (1.18 g, 7 mmol) was dissolved in toluene (10 mL) and, after freezing in liquid nitrogen and evacuation of the tube in vacuo, was sealed in a heavy-walled glass tube. After heating at 200–210 °C for 14 days, the tube was opened, solvent was removed, and the residue wa columned on basic alumina (1:1 pet ether/ether, then 2:1:1 chloroform/petroleum ether/ether, then 1:1 chloroform/methylene chloride). The first solvent removed unreacted phenyl vinyl sulfone, the next removed ketal **7b**: NMR ($CDCl_3$) δ 7.89–7.62 (5 H), 6.40 (br, 2 H), 4.89 (br, 1 H), 4.62 (q, J = 5 Hz, 1 H), 4.08 (br, 3 H), 3.48 (br, 5 H), 2.94 (br, 1 H), 1.10–2.05 (br, 15 H); IR (neat) 1690 cm^{-1}; high-resolution mass spectrum, m/z 378.1394 (M^+ - CHMeOEt, 26.5%), 210 (20%), 152 (100%). The third solvent eluted alcohol **7c**: NMR ($CDCl_3$) δ 7.89–7.63 (5 H), 6.42 (2 H), 4.87 (1 H), 4.07 (3 H), 3.4–3.85 (3 H), 2.94 (1 H), 1.10–2.10 (9 H); IR (neat) 3400, 1690 cm^{-1}; high-resolution mass spectrum, m/z 379.1459 (calcd for $C_{19}H_{25}NO_5S$, 379.1453), 152 (100%), 80 (21%), 79 (15%). The ketal **7b** (1.52 g, 0.336 mmol) was dissolved in 60:40 water/ethanol (25 mL) and added to 50:50 tetrahydrofuran/water (12 mL) containing concentrated hydrochloric acid (1.0 mL).[14] After stirring for 20 min, solid potassium carbonate was used to neutralize the solution and solvent was removed in vacuo. The residue was taken up in chloroform, washed with water, dried over magnesium sulfate, and filtered, and solvent was removed to afford 1.23 g (50%) of alcohol **7c**.

***N*-(Ethoxycarbonyl)-7-(phenylsulfonyl)-3-(3-chloropropyl)-2-azabicyclo[2.2.2]oct-5-ene (7d).** According to the procedure of Stork,[15] to alcohol **7c** (500 mg, 1.2 mmol) in benzene (20 mL) containing pyridine (0.3 mL) there was added methanesulfonyl chloride (420 mg, 3.6 mmol). The mixture was stirred for 25 h at 25 °C, solvent was removed, chloroform (20 mL) and water (20 mL) were added to the residue, the organic layer was separated and dried over magnesium sulfate, and solvent was again removed. Chromatography of the resultant oil on silica gel (4:1:1 chloroform/petroleum ether/ether, afforded 231 mg (41%) of a mesylate, R_f 0.35, IR (neat) 1690 cm^{-1}, absence of hydroxyl absorption. A solution of this oil (180 mg, 0.4 mmol) and lithium chloride (20 mg, 0.42 mmol) in hexamethylphosphoramide (0.7 mL) and ether (1.5 mL) was stirred at 25 °C under nitrogen for 19 h. Ether (10 mL) and 1 N hydrochloric acid (10 mL) were combined with the mixture, the layers were separated and the aqueous layer was washed with ether (10 mL). The combined organic layers were washed with water, dried over magnesium sulfate, and filtered, and solvent was removed to provide an oil. Elution of the oil through silica gel using 4:1:1 chloroform/petroleum ether/ether provided 150 mg (94%) of chloride **7d**: NMR ($CDCl_3$) δ 7.90–7.60 (5 H), 6.40 (2 H), 4.87 (1 H), 4.04 (3 H), 3.44 (3 H), 2.91 (1 H), 1.05–2.10 (9 H), all peaks were broadened or complex; IR (neat) 1690 cm^{-1}; high-resolution mass spectrum, m/z 397.1107, 399.1094 (calcd for $C_{19}H_{24}NO_4S^{35}Cl$, 397.1114; $C_{19}H_{24}NO_4{}^{37}Cl$, 399.1084), 152 (100%), 80 (26%), 79 (20%).

Desulfonylation of Chloride 7d to Chloride 4h. Chloride **7d** (500 mg, 1.2 mmol) was desulfonylated according to the procedure described for **7a** to provide 130 mg (40%) of **4h**; NMR (Table IV) was identical with that obtained for **4h** from bis(urethane) **1h**; IR (neat) 1690 cm^{-1}; high resolution mass spectrum, m/z 257.1166 (calcd for $C_{13}H_{20}NO_2Cl$, 257.1182).

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Registry No. **1g**, 539-71-9; **1h**, 61936-69-4; **1i**, 5336-11-8; **1j**, 96151-93-8; **1k**, 96151-94-9; **1l**, 96151-95-0; **1m**, 40589-04-6; **1n**, 96151-96-1; **3g**, 83187-89-7; **3h**, 96193-49-6; **3i**, 83187-90-0; **3j**, 83187-91-1; **3k**, 96151-97-2; **3l**, 96151-98-3; **3m**, 83187-92-2; **3n**, 96151-99-4; **4g**, 83213-95-0; **4h**, 61936-70-7; **4i**, 83213-96-1; **4j**, 83213-97-2; **4k**, 96193-50-9; **4l**, 96193-51-0; **4m**, 83213-98-3; **4n**, 96193-52-1; **6a**, 96152-00-0; **6b**, 96152-01-1; **7a**, 96152-02-2; **7b**, 96152-03-3; **7c**, 96152-04-4; **7c** mesylate, 96152-05-5; **7d**, 96152-06-6; 2-phenylacetaldehyde, 122-78-1; urethane, 51-79-6; cyclohexanecarboxaldehyde, 2043-61-0; cyclohexa-1,3-diene, 592-57-4; pyridine, 110-86-1; benzyl chloride, 100-44-7; ethyl chloroformate, 541-41-3; ethyl 2-benzyl-1,4-dihydropyridine-1-carboxylate, 96152-07-7; phenyl vinyl sulfone, 5535-48-8; ethyl 3-(3-iodopropyl)-2-azabicylco[2.2.2]oct-5-ene-2-carboxylate, 96152-08-8; 1-lithio-3-(1-ethoxyethoxy)propane, 37494-03-4.