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Steric Control in the Thermal Rearrangement of a Bicyclo[3.1.0]hex-2-ene Substituted at a Radical-Nonstabilizing Position

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Abstract: Introduction into the long-known bicyclo[3.1.0]hex-2-ene system of a large substituent in an electronically inactive, interconnected pair of positions brings to light the importance of sterics as a major factor in the determination of products. Far from the "flat" surface that so well describes the caldera of diradicals of the archetype, a "bumpy" surface is required as the conceptual scheme. The relief of "compressional" strain serves to explain the dramatic effect on kinetics and composition at equilibrium.

Introduction

Until the revelation of Baldwin and Keliher,[1] and the qualitatively and quantitatively remarkable theoretical explanation provided for it by Doubleday, Suhrada, and Houk,[2] the thermal reorganization of bicyclo[3.1.0]hex-2-ene might have been thought degenerate. The surprise lay in the discovery of large differences among the relative rates of the three paths open to **1-exo** and **1-trans** (48%, 36%, and 16%) made observable through deuterium labeling (Figure 1). They might have been expected to be 33%, 33%, and 33% had the diradical $\mathbf{C_{2v}}$ been a common intermediate!

The dynamical calculation of Doubleday, Suhrada, and Houk, as great a triumph as it is quantitatively, does not come in terms that allow translation into a conceptual scheme for the qualitative prediction of the response of distribution of product to constitutional perturbations. It comes in terms of a dynamical trajectory model in which the distribution among vibrational states of entry into the caldera of diradicals predetermines the channels of exit. This concept may be expressed as diradicals-in-transit. Figure 1 is cast according to Figure 2 of Doubleday, Suhrada, and Houk[2] to show the "flat" cross-over region, including $\mathbf{C_{2v}}$ between the isoconformation, $\mathbf{(C_s)_{iso}}$, and anti-conformation, $\mathbf{(C_s)_{anti}}$, of the diradical in the caldera.[3]

This paper focuses on a previously explicitly uninvestigated effect of substituents only in inactive positions, defined as positions where radical-stabilizing effects are excluded. The purpose is to uncover any effect on product distribution associated with changes in the frequencies of normal vibrational modes. The qualifying positions for substituents in bicyclo-[3.1.0]hex-2-ene are the pair at C4 and C6 as well as C2 (*nodal* in the developing allylic radical of the hypothetical intermediary diradical). Substituents at these three positions cannot exercise

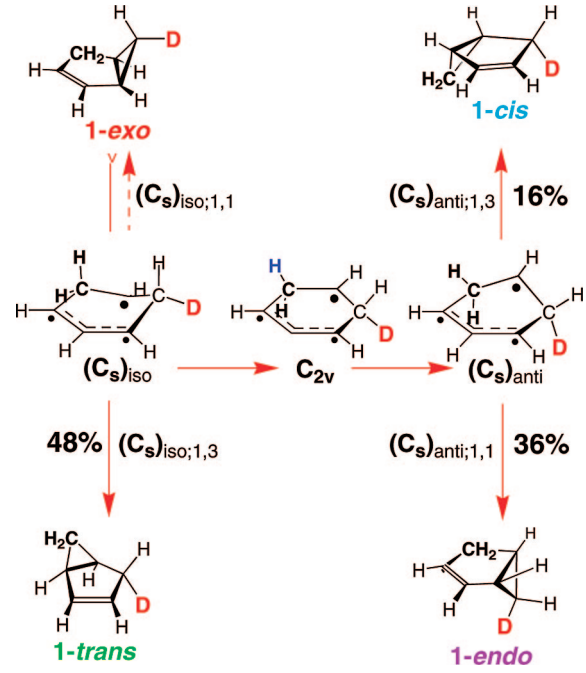


Figure 1. Kinetically controlled distribution among the three reaction pathways of deuteriobicyclo[3.1.0]hex-2-enes, **1-exo** (**6-exo**-D in Baldwin and Keliher), of Baldwin and Keliher is shown.

significant electronic radical-stabilizing effects in the diradical. They contrast with vulnerable positions C1, C3, and C5 (Scheme 1).

Interest in the bicyclo[3.1.0]hex-2-ene system begins in the early years of the twentieth century, the period in which dicyclic, C10 terpenes were discovered and had their constitutions and configurations elucidated.[4] Kinetic studies followed and included α-thujene (5-isopropyl-2-methylbicyclo[3.1.0]hex-2-ene)[5b] (Figure 2), *β*-thujene (1-isopropyl-4-methylbicyclo[3.1.0]hex-2-

(1) Baldwin, J. E.; Keliher, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 380–381.
(2) Doubleday, C., Jr.; Suhrada, C. P.; Houk, K. N *J. Am. Chem. Soc.* **2006**, *128*, 90–94.
(3) It is suggested the reader be familiar with refs 1 and 2 before proceeding.

(4) Simonsen, J. L. *The Dicyclic Terpenes and their Derivatives, Vol. II*, 2nd ed.; University Press: Cambridge, U.K., 1949; pp 10–16..

10.1021/ja7104812 CCC: $40.75

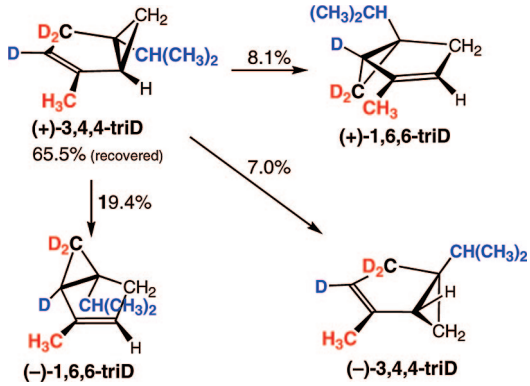
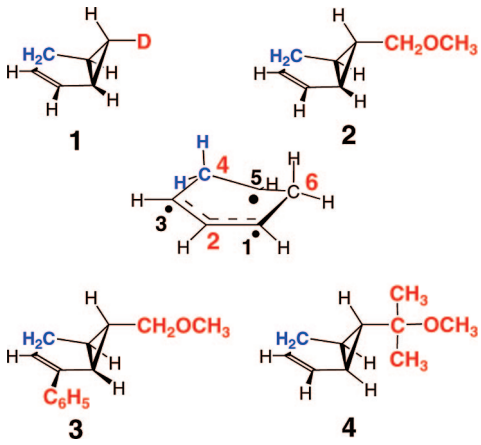


Figure 2. Relative rates of rearrangement of α-thujene (196 min at 240 °C) are given.

Scheme 1



ene)[5c] (Figure 3), a 5,6-diphenyl derivative (Figure 9),[6] and the parent (Figure 1).[1,7] The resulting pieces of information relevant to the phenomenon discovered by Baldwin and Keliher are collected in Table 1. Each member of the quartet of isomers comprising each system can rearrange with retention of conformation (isoconformer) and reformation of bond at position 3 of the allylic component [$(Cs)_{iso;1,3}$] or at position 1 [$(Cs)_{iso;1,1}$], this latter path being unobservable, or with inversion of conformation (anticonformer) by passage over conformation C_{2v} of the diradical and reformation of bond at position 3 [$(Cs)_{anti;1,3}$] or at position 1 [$(Cs)_{anti;1,1}$] (cf. Figure 1).

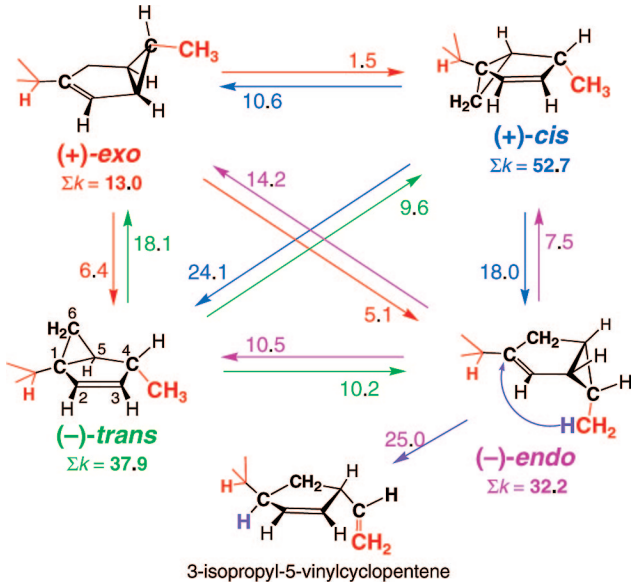


Figure 3. Specific rate constants for the rearrangement pathways of the β-thujenes at 237 °C in the gas phase are given in units of 10^{-6} s^{-1}.

Table 1. Relative Rates of Formation (in %) of the Three Products from Substituted Bicyclo[3.1.0]hex-2-enes (see Figure 1)

compound	$(Cs)_{iso;1,3}$	$(Cs)_{anti;1,1}$	$(Cs)_{anti;1,3}$	ref
4- and 6-D-	48	36	16	1
2-Me-5-*i*-Pro[a]	49	32	19	5a
2-Me-5-*i*-Pro[b]	56	20	24	5b
(−)-*trans*[c]	48	25	27	5c
(+)-*exo*[d]	49	39	12	5c
(−)-*endo*[d]	23	44	33	5c
(+)-*cis*[c]	34	46	20	5c
5-Ph-6-endo-Ph[e]	98	2 × (f)	2 × (1−f)	6

[a] α-Thujene; 485 °C. [b] α-Thujene; 240 °C. [c] β-Thujene. [d] 3-*i*-Pro-6-Me-bicyclo[3.1.0]hex-2-ene. [e] Figure 9.

In none of these examples are the perturbations confined to radical *nonstabilizing* positions (see Scheme 1). In α-thujene, the isopropyl group is at position C5 and the methyl group is at position C2 (Figure 2), while, in β-thujene, the isopropyl group is at position C1 and the methyl group is at position C4 or C6 (Figure 3). Although the isopropyl group is only weakly stabilizing of a radical, these examples do not represent the pure type sought here.

The present work is prompted by a curiosity about the possible effect on the kinetically controlled ratios among the three products that may result from alteration by substitution of the set of normal vibrational modes. Factors that affect the energies of stabilization of the secondary and the allyl free radicals are excluded in the selected examples. However, no way of avoiding the classical steric factors thereby introduced can be envisaged. The selected derivatives of the paradigm (**1**) are 6-methoxymethyl- (**2**), 2-phenyl-6-methoxymethyl- (**3**), and 6-dimethylmethoxymethyl-bicyclo[3.1.0]hex-2-ene (**4**) (Scheme 1).

Results

6-*exo*-Methoxymethylbicyclo[3.1.0]hex-2-ene (**2-exo**) was prepared in an unexceptional manner from 6-*exo*-carboethoxybicyclo[3.1.0]hexan-2-one, a known compound the structure of which has been determined by single crystal X-ray analysis (Scheme 2).[8] A minor product (30%) of the preparation was the endo isomer, 6-*endo*-carboethoxybicyclo[3.1.0]hexan-2-one (**2-endo**). On being heated at 245 °C for 96 h, **2-exo** escapes irreversibly from the closed system of four components in Figure 4 by a facile 1,5 H shift in **2-endo** to 3-(2′-methoxyvinyl)cyclopentene in high yield (see also Figure 3). As a consequence, further investigation of this system was not pursued.

(5) (a) Doering, W. v. E.; Lambert, J. B *Tetrahedron* **1963**, *19*, 1989–1994. (b) Doering, W. v. E.; Schmidt, E. K. G *Tetrahedron* **1971**, *27*, 2005–2030. (c) Doering, W. v. E.; Zhang, T.-h.; Schmidt, E. K. G. *J. Org. Chem.* **2006**, *71*, 5688–5693.
(6) Swenton, J. S.; Wexler, A. J. *J. Am. Chem. Soc.* **1971**, *93*, 3066–3068.
(7) (a) Grimme, W. cited in: Doering, W. von E.; Roth, W. R *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 115–122. (b) Cooke, R. S.; Andrews, U. H. *J. Am. Chem. Soc.* **1974**, *96*, 2974–2980.
(8) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. *J. Med. Chem.* **1997**, 528–537.

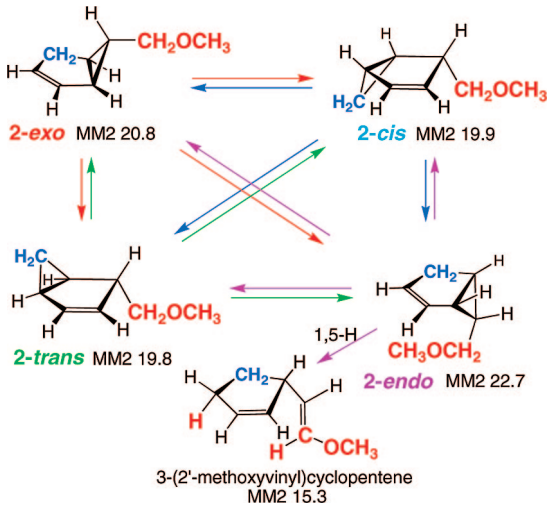
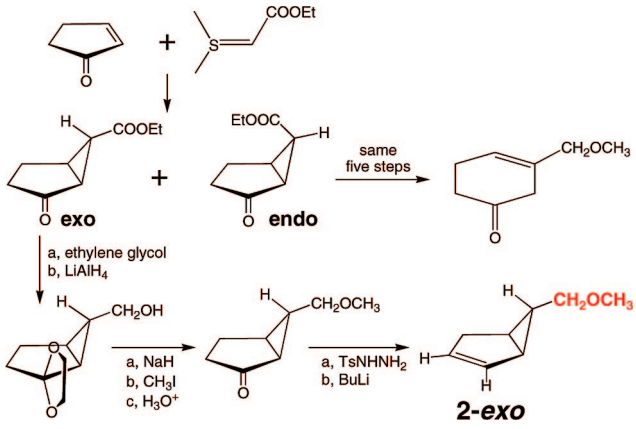


Figure 4. Thermal rearrangement of 6-*exo*-methoxymethylbicyclo[3.1.0]hex-2-ene (**2-exo**) to the other three products of the system, and the ultimate product, 3-(2′-methoxyvinyl)cyclopentene, are shown. Included are calculated steric energies in kcal mol^{-1}.

Scheme 2



The 2-phenyl-6-methoxymethyl system (**3**) was examined next (Figure 5) with the thought that the conjugative interaction of the phenyl group with the double bond might impede the 1,5 H shift from **3-endo**. Whereas the preparation of **3-exo** was unexceptional (Schemes 2 and 3), the attempted preparation of the corresponding **3-endo**, 2-phenyl-6-*endo*-methoxymethylbicyclo[3.1.0]hex-2-ene, foundered when the attempted preparation from 6-*endo*-ethoxycarbonylbicyclo[3.1.0]hexan-2-one following the procedure in Scheme 2 led instead to 3-methoxymethyl-2-cyclohexen-1-one.

Thermal rearrangement of **3-exo** is initially clean but leads over time to ever larger amounts of byproduct, including biphenyl. Kinetics are based on the data in Tables S5 and S6. The two sets of three specific rate constants at 216 and 245 °C given in Table 2 are calculated by the method of extrapolation to zero time.[9] Arrhenius values are included in Table 2.

In a final effort, the dimethylmethoxymethyl group (**4**) was selected to guarantee exclusion of the 1,5 H shift. Preparations of **4-exo** and **4-endo** were accomplished by the sequence in Scheme 4. Thermal rearrangements were quite clean. Kinetic data are collected in the Supporting Information, Tables S1 and S2 (**4-endo**) and Tables S3 and S4 (**4-exo**).

(9) Young, W. G.; Winstein, S.; Goering, H. L. *J. Am. Chem. Soc.* **1951**, *73*, 1958–1963.

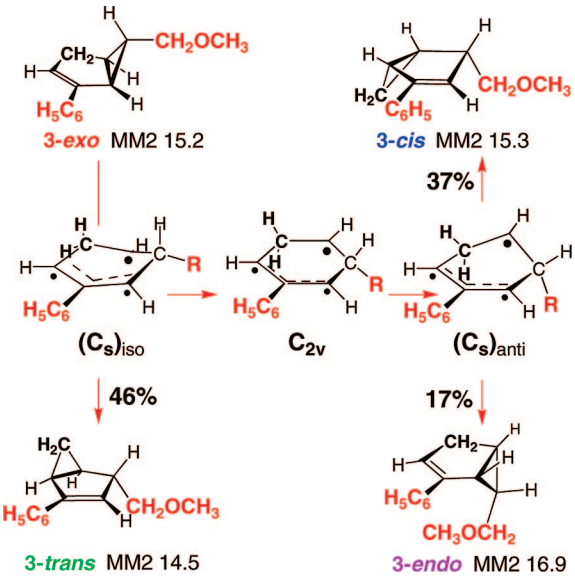


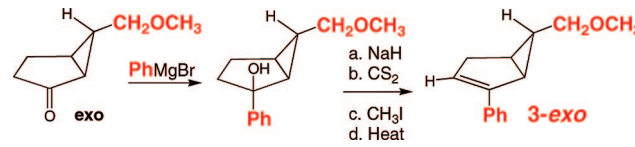
Figure 5. Thermal rearrangements of 2-phenyl-6-*exo*-methoxymethylbicyclo-[3.1.0]hex-2-ene (**3-exo**) to **3-trans**, **3-cis**, and **3-endo** at 216.5 °C are shown. Included are MM2 steric energies in kcal mol^{-1}.

Table 2. Specific Rate Constants[a] for Three Isomerizations of **3-exo**

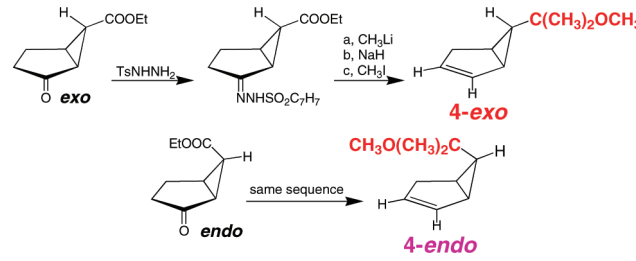
temp, °C	**3-*exo*** [b]	**3-*trans*** [c]	**3-*cis*** [c]	**3-*endo*** [c]
216.5	0.38	0.182 (47%)	0.143 (37%)	0.065 (16%)
244.6	4.5	2.4 (52%)	1.42 (31%)	0.8 (17%)
E_a [d]	42.9 ± 2			
log *A*	13.9			

[a] In units of 10^{-6} s^{-1}. [b] Rate of disappearance. [c] Assignments of structure to the three products are arbitrary (see text). [d] kcal mol^{-1}.

Scheme 3



Scheme 4



Starting from either **4-exo** or **4-endo**, the ratios at 216.5 and 244.6 °C at equilibrium are **4-exo**, 64.5%; **4-trans**, 30%; **4-cis**, 5.5%; and **4-endo**, 0%. Under kinetic control, the rearrangement of **4-exo** leads only to **4-trans** and **4-cis**. It has not been possible to separate either of the isomers in this pair in pure form. As a consequence, assignment of configuration is essentially arbitrary. It is based on the inference that the cis configuration should be assigned to that isomer which rearranges faster than the other isomer (see below) and appears to have a higher steric energy as estimated by force field calculations (MM2; see Figure 7).

From the kinetic data in Tables S3 and S4, specific rate constants for the thermal conversions of **4-exo** are estimated

Table 3. Specific Rate Constants[a] for the Thermal Rearrangements of **4-exo** and **4-endo**

temp, °C	*4-exo*	*4-trans*	*4-cis*[c]	*4-endo*[c]
starting compd	***4-exo***			
216.5	0.87[b]	0.76,[e] 0.73 ± 0.05[c,f]	0.135,[e] 0.127 ± 0.05[c,f]	0.0
244.6	12.2[b]	8.6,[e] 8.23 ± 0.6[c,f]	1.42,[e] 1.46 ± 0.6[c,f]	0.0
E_a kcal mol^{-1}		43.4 ± 2.5	43.8 ± 9	
log *A*		13.3	12.6	
starting compd				**4-endo**
153.9	1.85 ± 0.067[c]	1.64 ± 0.06[c,f]	1.38 ± 0.067[18,18]	5.097[d]
185.6	34.8 ± 1.2[c]	33.0 ± 1.2,[f]	28.7 ± 1.2,[f]	101.8[d]
E_a kcal mol^{-1}		36.8 ± 2.0		
log *A*		13.5		
starting compd[g]	**4-exo** (36.3%)	**4-trans** (32.9%)	**4-cis** (30.8%)	
244.6			47.5[h]	

[a] In units of 10^{-6} s^{-1}. [b] Rates of disappearance to ***4-trans*** and **4-cis** (for assignment between configurations, see text). [c] Rates of appearance. [d] Rates of disappearance of **4-endo** to **4-exo**, **4-trans**, and ***4-cis***. [e] Estimated by extrapolation to zero time (see text). [f] Estimated by the program Kinetic (see text). [g] The kinetically controlled mixture obtained from **4-endo**. [h] Rate of disappearance of **4-cis** to **4-exo** and **4-trans**.

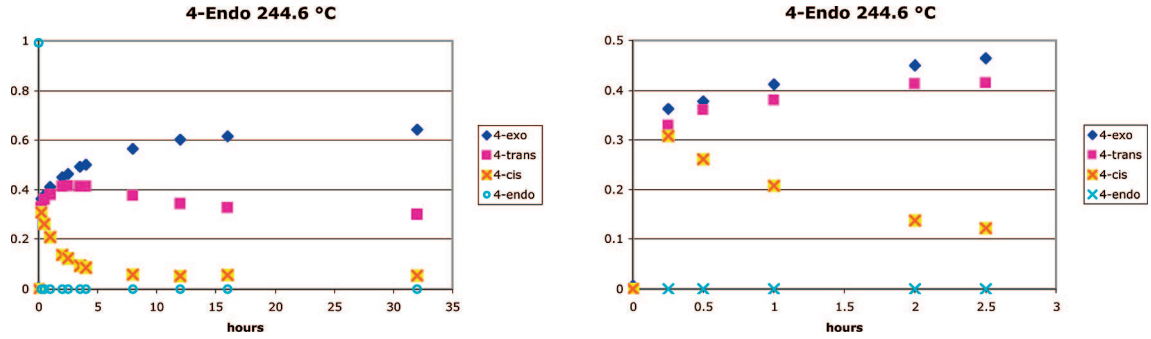


Figure 6. The distribution of products from **4-endo** at 244.6 °C is shown at the left, while an expanded plot from 15 min through 2.5 h of reaction is shown at the right.

by extrapolation to zero time of tangents to the curve fitting best to the plot of data relating concentration to time[9] and by applying the program Kinetic[10] to a simplified kinetic scheme, based on the assumption that early points can be handled as first-order reactions of disappearance or appearance. Agreement is good (see Table 3).

The **4-endo** isomer rearranges much faster than **4-exo**, **4-trans**, or **4-cis**. Only a few minutes at 244.5 °C suffices to produce a mixture of these three isomers, which then rearrange much more slowly as they approach equilibrium. Although the kinetic data are collected in Table S2, the graphic representation in Figure 6 is more immediately revealing. The plot at the left depicts the much slower progress of the kinetically controlled, rapidly formed, initial mixture from **4-endo** toward equilibrium, while, from the expansion at the right, one can imagine an extrapolation back to zero time. At 153.9 and185.6 °C,temperatures at which further transformation of the initial mixture of products toward equilibrium is very slow, the kinetics of the rearrangements of **4-endo** can be followed conveniently. Specific rate constants are derived from the data in Table S1 and given in Table 3, along with the derived Arrhenius constants, and their uncertainties are estimated in a previously described manner.[11]

Table 4. Kinetically Controlled Ratios among the Three Products of the Rearrangement of **4-endo**

temp, °C	*4-exo*	*4-trans*	*4-cis*
153.9	39.6	33.1	27.3
185.6	36.7	33.7	29.6
216.5	36.0	32.7	31.3
244.5	36.3	32.9	30.8
	37.1[a]	33.1	29.8

[a] Mean values.

The rearrangement of **4-endo** at 244.6 °C gives a mixture consisting of **4-exo** 36.3%, **4-trans** 32.9%, and **4-cis** 30.8%,[12] in comparison to the equilibrium values of 64.5%, 30%, and 5.5%, respectively. At the other temperatures, the composition of the initial mixture is essentially the same within experimental uncertainties (Table 4). This kinetically controlled mixture can serve in partial compensation for the unavailability of a pure sample of **4-cis** for the determination of the kinetics of its rearrangement. The concentration of **4-cis**, ~30%, is sufficiently greater than its concentration at equilibrium, 5.5%, to support elucidation of the kinetics (cf. Figure 6, right). The same is not true of **4-trans**, which, at ~33%, is already present at essentially its equilibrium concentration of 30% (Figure 6, left) and cannot serve as a reliable entry into the kinetics of its further rearrangements.

Extraction of a specific rate constant for the disappearance of **4-cis** is effected by fitting the five points from 15 min to

(10) (a) Roth, W. R.; Fink, R.,unpublished. (b) Marquardt, D. W. *J. Soc. Ind. Appl. Math.* **1963**, *11*, 431–441.
(11) Doering, W. von E.; Keliher, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 2488–2495.
(12) Not having pure samples on hand, we have not determined GC response factors. In one instance analysis by GC and NMR were in excellent agreement.

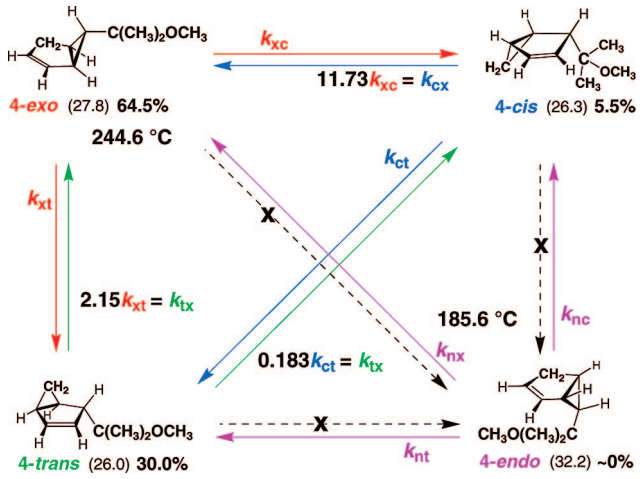


Figure 7. Kinetic relations among the four isomers of system **4** are shown along with their relative concentrations at equilibrium and steric energies (MM2) in kcal mol^{-1}.

2.5 h to a curve by the program Origin, estimating the slopes of the tangents at the five points, plotting these against the time of reaction, and extrapolating the resulting linear plot to zero time.[9] The rate constant at 244.6 °C thus derived is the sum of the rates of appearance of **4-exo** and **4-trans** from **4-cis** ($[k_{cx} + k_{ct}] = 47.5 \times 10^{-6}$ s^{-1}) (see Figure 7). Similarly derived, the specific rate constants for the rearrangements of **4-cis** to **4-trans** are 23.2×10^{-6} s^{-1} and 19.5×10^{-6} s^{-1} to **4-exo**. This latter value for k_{cx} may be compared with that of $(17.1 \pm 7.0) \times 10^{-6}$ s^{-1} for the reaction of **4-exo** to **4-cis**; that is, $(1.46 \pm 0.6) \times 10^{-6}$ s^{-1} (see Table 3) times the equilibrium constant, $K = 11.73$. Subtraction of this value from the more precise specific rate constant of 47.5×10^{-6} s^{-1} above leads to a value of 30.4×10^{-6} s^{-1} for the conversion of **4-cis** to **4-trans** (k_{ct}) and a value of 5.6×10^{-6} sec^{-1} for the reverse ($0.183\ k_{tc}$).

Discussion

The Arrhenius values from the reaction of 2-phenyl-6-*exo*-methoxymethylbicyclo[3.1.0]hex-2-ene, **3-exo** (Table 2), serve to confirm the expected freedom from the electronic effect of substituents in the 4/6 and 2 positions of the bicyclic system (Scheme 1). The values of $E_a = 42.9 \pm 2$ kcal mol^{-1} and log $A = 13.9$ are close to those found by Baldwin and Keliher for the parent substituted by deuterium: E_a 43.4 ± 1 kcal mol^{-1} and log $A = 14.1$.[1] The ratios of products from **3-exo** are surprisingly close to those obtained for the archetype by Baldwin and Keliher but are not as significant as they might be owing to the problematic assignments of structure.

Separations of pure samples for spectroscopic analysis have not been achieved. Assignments are based on relative steric energies estimated by force field calculations (MM2) but are doubtful because the differences are smaller than the uncertainties in the method. If the same order is assumed as that seen below for compounds **4**, the assignments are made as indicated in Figure 5. The three rate constants at 216.5 °C, for example, are then in the ratios 46, 37, 17%. It can be said with certainty that they are not all of equal value! On this basis, the slowest of the rearrangements would be assigned to the conversion of **3-exo** to **3-endo**, the fastest, to **3-trans**, and the intermediate, to **3-cis**.

The bicyclo[3.1.0]hex-2-ene system substituted by the dimethylmethoxycarbinyl group is no longer threatened by a 1,5 hydrogen shift from its endo isomer, **4-endo**. Structural assignments to **4-endo** and its exo isomer, **4-exo**, are firm, based as they are on the known configurations of the esters from which their preparations start (Scheme 4), but those of **4-cis** and **4-trans** are tentative, being based on the small differences in calculated steric energies shown in Figure 7 and their relative concentrations at equilibrium (5.5% and 30% at 244.6 °C, respectively).

The dimethylmethoxy group introduces a large steric effect. This factor is reflected in the failure (within the limits of the analytical procedure) to detect any **4-endo** in the equilibrium mixture, which consists only of **4-exo**, **4-trans**, and **4-cis**. Consistently, the steric energy of **4-endo** calculated by the force field program MM2 is 4.4 kcal mol^{-1} higher than that calculated for **4-exo**.[13] Not only does this difference in steric energy thwart the observation of **4-endo** at equilibrium, but it leads to a remarkable acceleration of the rate of rearrangement of **4-endo**. Necessarily determined at lower temperatures, 153.9 and 185.6 °C, Arrhenius parameters of $E_a = 36.8 \pm 2.0$ kcal mol^{-1} and log $A = 13.5$ allow calculation of a rate constant at 244.6 °C for the disappearance of **4-endo** (9.27×10^{-3} s^{-1}) greater by a factor of 760 than that for the disappearance of **4-exo** (1.22×10^{-5} s^{-1}). Described in more qualitative terms, **4-endo** has reacted completely at 244.6 °C within 15 min to a nonequilibrium mixture of **4-exo**, **4-trans**, and **4-cis**, which then requires ~60 h to reach equilibrium, no **4-endo** being detectable (see Figure 6). The difference in rate is so great that no direct experimental connection can be made between **4-exo**, which is confined observationally to a three-component system, and **4-endo**, which participates in a purely kinetically controlled four-component system. Conceivably a much more sensitive analytical method might bridge the gap by revealing the very small amounts of **4-endo** present at equilibrium in the four-component system. The use of radioactivity comes to mind![14] On a guess that the difference in free energy of formation between **4-exo** and **4-endo** might be 6.7 kcal mol^{-1}, the concentration of **4-endo** at 244.6 °C would be about 0.15%.

The driving force behind the acceleration of the rate of breaking the cyclopropane bond comes from the relief of the substantial, energy-raising, steric interaction of the dimethylmethoxymethyl group with the inside face of the bicyclo[3.1.0]hex-2-ene system. It can be estimated to be 6.7 kcal mol^{-1} from the enthalpies of activation of the disappearance of **4-exo** and **4-endo** (Table 3). This driving force appears to be an example of steric acceleration by H. C. Brown's "back (B) strain".[15] The well-known original examples involved the effect of steric bulk on the rates of the S_N1 solvolysis of tertiary carbinyl compounds. Replacement of the methyl groups in *tert*-butyl *p*-nitrobenzoate by Bartlett and Tidwell each by a *tert*-butyl, for example, led to an acceleration in rate by a factor of 13 500.[16] Interpretation, however, was complicated by the role of the solvent and its own susceptibility to the steric factor. The present seems to be an uncomplicated example, striking in its magnitude. Other clear

(13) For further calibration, the following differences in steric energy calculated by MM2 for **6-*endo*/6-exo** pairs are recorded in kcal mol^{-1}: methyl, 2.1; ethyl, 2.1; *n*-propyl, 2.0; isopropyl, 2.4; phenyl, 2.3; and *tert*-butyl, 6.1.

(14) (a) Wolfgang, R.; MacKay, C. F. *Nucleonics* **1958**, *16*, 69–73. (b) MacKay, C.; Wolfgang, R. *J. Am. Chem. Soc.* **1965**, *148*, 899–907.
(15) Brown, H. C.; Fletcher, R. S. *J. Am. Chem. Soc.* **1949**, *71*, 1845–1854, and references therein.
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(17) (a) Doering, W. von E.; Sachdev, K. *J. Am. Chem. Soc.* **1974**, *96*, 1168–1187. (b) Doering, W. von E.; Mastrocola, A. R. *Tetrahedron, Suppl. 1* **1981**, *37*, 329–344.

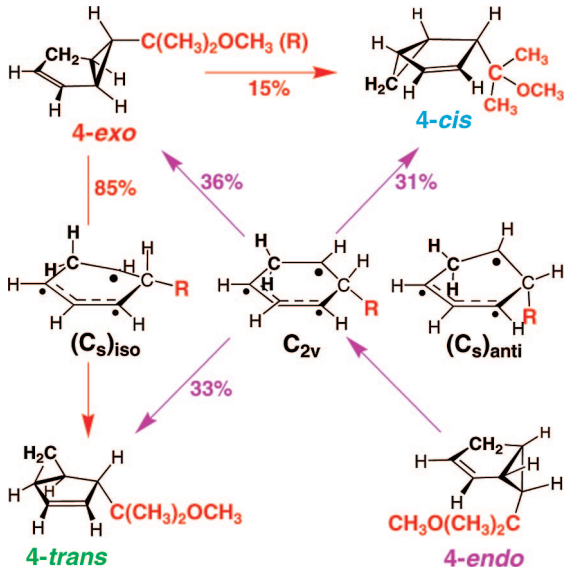

Figure 8. Thermal rearrangement of **4-exo** at 244.6 °C under kinetic control leads to **4-trans** and **4-*cis*** (no **4-endo**), while **4-endo** leads to all three isomers in close to equal amount.

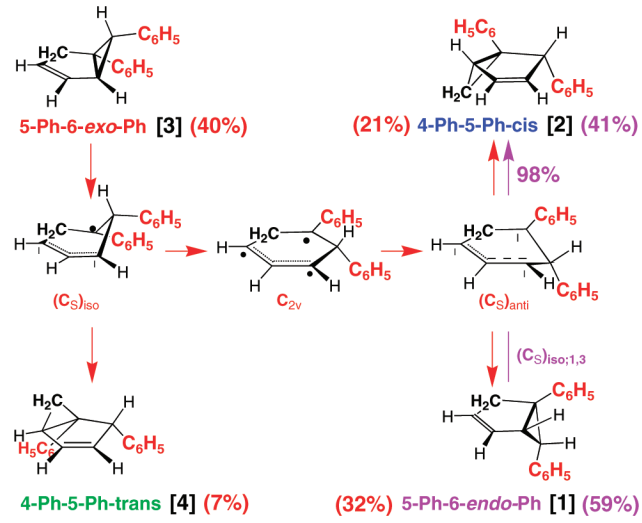

Figure 9. The Swenton−Wexlar example of diphenylbicyclo[3.1.0]hexenes (their numbering system in brackets) is shown, as are relative concentrations (in parentheses) at equilibrium from [**3**] and at pseudo equilibrium from [**1**].

examples of acceleration by relief of "compressional" strain are rare. An impressive example provided by Swenton and Wexlar is discussed below.

A dramatic feature of the rearrangement of **4-endo** is the unique composition of its initially formed products. At 216.5 °C, this kinetically controlled mixture consists of **4-cis** 31%, **4-trans** 33%, and **4-exo** 36%. The nearly equal quantities are a striking departure from the other sets of values in Table 1 and are far removed from the equilibrium values of 5.5%, 30%, and 64.5%, respectively, reached only after many hours of further heating. A graphic picture is given in Figure 6. That the composition is independent of temperature is supported in Table 4. Under this hypothesis, at least 90% (3 × 30%) of the reaction passes through $\mathbf{C_{2v}}$ as an intermediate in common. In early studies of not obviously concerted rearrangements, the possibility of a diradical-in-common between two or more products has been considered and held wanting as more than a partial explanation. The maximum possible participations that have been noted are 63%,[17a] 83%, and 64%.[14b]

A plausible explanation involves combination of the breaking of the cyclopropane bond in **4-endo** with the breathing vibrational component that leads directly to the planar intermediary diradical represented by $\mathbf{C_{2v}}$ in Figure 8, that is, bypassing the diradical of the iso conformation (from **4-endo**). In this manner, more of the steric repulsion between the dimethylmethoxymethyl group and the five-membered ring is relieved than by stopping at the iso conformation. The near equality among the three products requires additionally the plausible assumption that differences in steric interaction among the three products do not make themselves felt at the beginning of the four highly exothermic bond-reforming steps.

A fine example of a large steric perturbation is that of two adjacent phenyl groups provided by Swenton and Wexlar (Figure 9).[6] In the time it takes the endo isomer [**1**] to reach a pseudo equilibrium at 130 or 170 °C with [**2**] of 59% and 41%, respectively, less than 2% of [**3**] and [**4**] has been formed. Arrhenius values for k_{12} are $E_a = 32.4$ kcal mol^{-1} and log A = 12.6. In contrast, the much more slowly reacting exo isomer [**3**] leads to the equilibrium mixture of all four isomers shown in Figure 9. In the range of temperature 180 to 212 °C, Arrhenius values for the rate of disappearance of [**3**] are $E_a = 36.7$ kcal mol^{-1} and log A = 13.1. It would have been informative had the specific rate constants for the appearance of the other isomers starting from [**1**] ([**2**]) and [**3**] been determined for comparison with concentrations at equilibrium.

We ascribe the lowering by 4.3 kcal mol^{-1} of the activation energy in [**1**] to the relief of the same type of compressional strain as in our example. In their exemplary discussion, Swenton and Wexlar propose that the immediate diradical of the iso conformation is hindered from passing to the planar diradical and thence to that of the anti conformation leading to isomers [**3**] and [**4**] by sterically unfavorable eclipsing between the two phenyl groups. This is an example of steric repulsion leading to a deceleration of movement within the caldera relative to bond reformation.

The sensitivity of the steric factor revealed in these examples points to a reconsideration of the assumption that the small difference between hydrogen and deuterium plays no significant role in the Baldwin−Keliher case.[1,2] Today it is unrealistic to suggest that replacement of deuterium by tritium might be contemplated! But a theoretical calculation can be contemplated.

The original purpose of the present investigation having been diverted by the recognition that substitution in the 6-position introduces major steric complications, there remain derivatives substituted in the 2 (nodal) position such as 2-phenyl-6-deuteriobicyclo[3.1.0]hex-2-ene to be explored.

Conclusion

The large enhancement in the rate of rearrangement apparent in the endo isomer of 6-endodimethylmethoxybicyclo[3.1.0]hex-2-ene is a rare and dramatic example of steric acceleration.

Perhaps more surprising is the dramatic influence of this endo steric effect on distribution among products. The operation of this factor can be interpreted in terms of a direct passage to a planar diradical intermediate during transit on the surface of the caldera.

In a general sense, this work provides encouragement to consider traversing the caldera in the classical terms of overcoming barriers on a bumpy surface. The concept of the "flat surface" as a general description has evolved largely

because contemporary theoretical calculations have understandably concentrated on the simplest archetypal systems. The usefulness of the archetype may be limited by its extreme position as the flattest along the caldera. As substituents are introduced, this "flat" surface gives way to bumpier surfaces. A role for classical steric factors in accelerating and decelerating the rates of competing pathways then becomes useful. Although the role of electronic effects in determining the rate of entry into the caldera remains secure and unaffected, its role, if any, in determining ratios among products has not been defined.

Experimental Section

General Methods. ^{1}H NMR (600 MHz) and ^{13}C NMR (100.4 MHz) spectra were measured in solution in $CDCl_3$ or benzene-d_6 on Varian Unity/Inova or Varian Mercury Instruments. Chemical shifts are reported in ppm relative to the residual CH peak of the solvent (δ). Preparative GC on a Varian Aerograph A90-P3 instrument employed a 3-m column of 20% Carbowax 20 M on Anachrom AS with He as carrier gas. Kinetic data are acquired by heating samples sealed in ampoules of lead-potash glass (Corning 0120, no longer available) in the vapors of compounds boiling under reflux: 153.9 °C, anisole; 185.6 °C, diethyl oxalate; 216.5 °C, *n*-dodecane; 244.6 °C, 1-methylnaphthalene. The ampoules (4 mm o.d. by 10 cm) were prepared by soaking in conc. ammonia, washing successively with water and acetone, and drying for 24 h at 120 °C. After being degassed by three freeze/thaw cycles at 10^{-3} mmHg, ampoules were sealed under vacuum.

6-*exo*-Ethoxycarbonylbicyclo[3.1.0]hexan-2-one. A solution of 2-cyclopenten-1-one (4.0 g, 49 mmol) and ethyl (dimethylsulfuranylidene)-acetate[18] (8.2 g, 56 mmol) in anhydrous toluene (20 mL) was heated at 100 °C for 17 h. After being cooled to room temperature, the solution was diluted with ethyl acetate (20 mL) and then washed successively with water (20 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated, and subjected to column chromatography (silica gel, hexane/ethyl acetate: 6/1 to 5/1) to give 3.9 g of 6-*exo*-ethoxycarbonylbicyclo[3.1.0]hexan-2-one as a colorless oil, which solidified on standing (68% of theoretical yield) (R_f = 0.31, hexane/ethyl acetate: 4/1): ^{1}H NMR ($CDCl_3$) 1.27 (t, J = 7.03 Hz, 3H), 2.00–2.29 (m, 6H), 2.50–2.52 (m, 1H), 4.15 (q, J = 7.03 Hz, 2H); ^{13}C NMR ($CDCl_3$) 14.19, 22.50, 26.47, 29.25, 31.92, 35.78, 61.24, 170.45, 211.75.

In addition, 1.7 g of 6-*endo*-ethoxycarbonylbicyclo[3.1.0]hexan-2-one was isolated as a colorless oil (R_f = 0.23, hexane/ethyl acetate: 4/1): ^{1}H NMR ($CDCl_3$) 1.27 (t, J = 7.32 Hz, 3H), 2.06–2.09 (m, 1H), 2.21–2.37 (m, 4H), 2.40–2.46 (m, 2H), 4.16 (q, J = 7.03 Hz, 2H); ^{13}C NMR ($CDCl_3$) 14.25, 20.09, 28.74, 30.01, 34.30, 38.04, 61.25, 169.91, 213.52.

6-*exo*-Methoxymethylbicyclo[3.1.0]hexan-2-one. In a round-bottomed flask equipped with a Dean–Stark device, a mixture of 6-*exo*-ethoxycarbonylbicyclo[3.1.0]hexan-2-one (7.2 g, 39 mmol), *p*-toluenesulfonic acid (0.83 g, 4.4 mmol), and ethylene glycol (16 mL) in toluene (65 mL) was heated in the vapors under reflux for 3 h. The cooled reaction mixture was extracted with diethyl ether (80 mL). The organic phase was washed successively with saturated $NaHCO_3$ (30 mL), water (30 mL), and brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated to a yellow oil (6.6 g). This oil, dissolved in anhydrous diethyl ether (15 mL), was added dropwise to an ethereal suspension (45 mL) of lithium aluminum hydride (1.9 g, 50 mmol) at 0 °C. The reaction was stirred for 2 h at room temperature, then quenched with $Na_2SO_4 \cdot 10H_2O$, filtered, and washed several times with diethyl ether. The combined ethereal solutions were dried over anhydrous Na_2SO_4, filtered, and concentrated to a yellow oil (4.6 g).

To an ethereal solution (40 mL) of this oil, sodium hydride (2.2 g, 60% in mineral oil) was added slowly. After 0.5 h of standing, methyl iodide (7.7 g) was added. The reaction mixture was stirred for 48 h at room temperature, then quenched with water, and extracted several times with diethyl ether. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to a yellow oil (4.8 g). To this oil, dissolved in acetone (20 mL), 2 mL of 1 N HCl were added. After being stirred overnight, the reaction mixture was treated with water (10 mL) and extracted three times with ether (20 mL each). The combined ethereal solutions were dried over anhydrous Na_2SO_4, filtered, concentrated, and subjected to column chromatography (silica gel, hexane/ethyl acetate: 4/1 to 2/1) to afford 3.0 g (55%) of 6-*exo*-methoxymethylbicyclo[3.1.0]hexan-2-one as a colorless oil: ^{1}H NMR ($CDCl_3$) 1.57–1.60 (m, 1H), 1.69–1.71 (m, 1H), 2.02–2.15 (m, 5H), 3.21–3.24 (m, 1H), 3.34 (s, 3H), 3.40–3.43 (m, 1H); ^{13}C NMR ($CDCl_3$) 22.55, 26.16, 26.64, 32.34, 32.55, 58.52, 72.96, 213.73.

6-*exo*-Methoxymethylbicyclo[3.1.0]hex-2-ene (2-*exo*). To a solution of 6-*exo*-methoxymethylbicyclo[3.1.0]hexan-2-one (1.2 g, 8.6 mmol) in anhydrous THF (12 mL), *p*-toluenesulfonylhydrazine (1.7 g, 9 mmol) was added in one portion. The reaction mixture was stirred with a 3 Å molecular sieve at room temperature and monitored by GC until all 6-*exo*-methoxymethyl bicyclo[3.1.0]hexan-2-one had been consumed. The mixture was filtered, and the filtrate was concentrated by rotary evaporation to afford a yellow solid. The crude tosylhydrazone of 6-*exo*-methoxymethylbicyclo[3.1.0]hexan-2-one was dissolved in anhydrous THF (30 mL) and treated with butyllithium (12 mL, 2 M in pentane, 24 mmol) by dropwise addition at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2 h, and then cooled to 0 °C, and quenched with water. The resulting mixture was extracted three times with ether (20 mL each), dried over anhydrous Na_2SO_4, filtered, and concentrated by distillation with a 12-cm Vigreux column. The residue was purified by preparative GC at 72 °C to give 0.35 g (33% of the theoretical yield) of 6-*exo*-methoxymethylbicyclo-[3.1.0]hex-2-ene as a colorless oil: ^{1}H NMR (benzene-d_6) 0.58–0.60 (m, 1H), 1.34–1.36 (m, 1H), 1.70–1.72 (m, 1H), 2.19–2.23 (m, 1H), 2.42–2.46 (m, 1H), 2.99–3.02 (m, 1H), 3.08–3.09 (m, 1H), 3.11 (s, 3H), 5.28–5.29 (m, 1H), 5.84–5.86 (m, 1H); ^{13}C NMR (benzene-d_6) 20.89, 29.59, 29.84, 35.91, 57.94, 74.57, 128.71, 133.77.

3-Methoxymethyl-2-cyclohexen-1-one. When 6-*endo*-ethoxycarbonylbicyclo[3.1.0]hexan-2-one was subjected to the same procedure as its exoisomer above, 3-methoxymethyl-2-cyclohexen-1-one was the major product, instead of the desired 6-*endo*-methoxymethyl bicyclo[3.1.0]hexan-2-one: ^{1}H NMR ($CDCl_3$) 2.02–2.04 (m, 2H), 2.26–2.28 (m, 2H), 2.39–2.42 (m, 2H), 3.37 (s, 3H), 4.00 (d, J = 0.7 Hz, 2H), 6.07 (d, J = 1.47 Hz, 1H); ^{13}C NMR ($CDCl_3$) 22.56, 26.30, 37.90, 58.78, 74.50, 124.60, 161.48, 199.48.

2-Phenyl-6-*exo*-methoxymethylbicyclo[3.1.0]hexan-2-ol. To a solution of freshly prepared phenylmagnesium bromide (prepared from 0.07 g of magnesium and 0.38 g of bromobenzene), 6-*exo*-methoxymethylbicyclo[3.1.0]hexan-2-one (0.17 g, 1.2 mmol) in anhydrous THF (3 mL) was added dropwise at 0 °C. After being stirred at 0 °C for 15 min and room temperature for another 15 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL), followed by water (5 mL), and then extracted three times with ether (30 mL each). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated, and subjected to column chromatography (silica gel, hexane/ethyl acetate, 4/1 to 2/1) to afford 0.21 g (80% of the theoretical yield) of 2-phenyl-6-*exo*-methoxymethylbicyclo[3.1.0]-hexan-2-ol as a colorless oil: ^{1}H NMR ($CDCl_3$) 1.48–1.58 (m, 3H), 1.63–1.68 (m, 1H), 1.79–1.92 (m, 3H), 3.26–3.29 (m, 1H), 3.31–3.35 (m, 1H), 3.36 (s, 3H), 7.25–7.28 (m, 1H), 7.36 (t, J = 7.32 Hz, 2H), 7.55 (dt, J_1 = 7.32 Hz, J_2 = 1.17 Hz, 2H); ^{13}C NMR ($CDCl_3$) 19.08, 24.55, 25.88, 33.87, 38.36, 58.47, 75.07, 82.55, 124.94, 126.92, 128.37, 148.61.

2-Phenyl-6-*exo*-methoxymethylbicyclo[3.1.0]hex-2-ene (3-*exo*). To a solution of 2-phenyl-6-*exo*-methoxymethylbicyclo[3.1.0]hexan-2-ol (0.54 g, 2.5 mmol) in anhydrous ether (30 mL), sodium hydride

(18) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351–3355.

(0.2 g, 60% in mineral oil, 5 mmol) was added in portions. The resulting solution was stirred for 15 min, treated with carbon disulfide (0.42 g, 5.5 mmol), and boiled under reflux for 0.5 h prior to the addition of methyl iodide (0.78 g, 5.5 mmol). The reaction mixture was refluxed for 16 h, cooled to 0 °C, and quenched with water. After separation of the organic layer, the aqueous layer was extracted with ether. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated, and subjected to column chromatography (silica gel, hexane/ethyl acetate, 40/1) to afford 0.21 g (42% of the theoretical yield) of 2-phenyl-6-*exo*-methoxymethylbicyclo[3.1.0]hex-2-ene as a colorless oil: ^{1}H NMR (benzene-d_6) 0.75–0.77 (m, 1H), 1.40–1.42 (m, 1H), 2.07–2.09 (m, 1H), 2.35–2.39 (m, 1H), 2.54–2.59 (m, 1H), 3.00–3.03 (m, 1H), 3.14 (s, 3H), 3.19–3.23 (m, 1H), 5.55 (s, 1H), 7.07 (t, J = 7.32 Hz, 1H), 7.17 (t, J = 7.62 Hz, 2H), 7.58 (d, J = 7.03 Hz, 2H); ^{13}C NMR (benzene-d_6) 21.00, 28.95, 30.21, 36.18, 58.02, 74.66, 122.54, 126.27, 127.39, 128.62, 136.63, 146.78; exact mass HRMS (ESI) calcd for $C_{14}H_{16}O$, 201.12739, found 201.12662.

For a study of the kinetics, a stock solution was prepared from 42.5 mg of **3-exo**, 118.6 mg of diphenylamine as inhibitor, and 10.0 μL of *n*-heptadecane as internal standard in 4.0 mL of *n*-dodecane. For each run, 0.1 mL was placed in the ampule of lead-potash glass. Analysis was by GC: 30-m by 0.53 mm i.d. capillary column coated with either DB-I or DB-225 (J & W Scientific, Inc.; 1 mm thickness). For each point, three analyses were averaged. Retention times in min on the DB-1 column at 150 °C and He at 20 mL/min (20 psi, split 10 psi) follow: **3-exo**, 12.27; **3-trans**, 10.92; **3-cis**, 12.86; **3-endo**, 14.69.

6-*exo*- and 6-*endo*-Dimethylmethoxymethylbicyclo[3.1.0]hex-2-ene (4-*exo*), 4-*endo*). To a solution of 6-*exo*-ethoxycarbonylbicyclo-[3.1.0]hexan-2-one (vide supra) (0.5 g, 3 mmol) in anhydrous methanol (10 mL), *p*-toluenesulfonylhydrazine (1.7 g, 9 mmol) was added in one portion at room temperature. The reaction mixture was monitored periodically by GC until no more starting ester remained (24 h). After standing overnight at 0 °C, the solution deposited crystals of 6-*exo*ethoxycarbonylbicyclo[3.1.0]hexan-2-hydrazone. These were filtered, washed with pentane, and dried to give 0.75 g (74% of theoretical yield).

To a solution of the hydrazone in freshly distilled THF (20 mL), methyllithium (8.2 mL, 1.6 M in pentane) was added dropwise at 0 °C under nitrogen. The reaction mixture was kept at room temperature for 2 h, cooled to 0 °C, quenched with water (2 mL), and extracted three times with ether (20 mL each). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to a pale yellow oil, which was dissolved in anhydrous ethyl ether (15 mL) and treated with a single portion of NaH (0.26 g, 6.6 mmol) under nitrogen. After 0.5 h of standing, the reaction mixture was treated with methyl iodide (7.7 g), boiled under reflux for 24 h, then quenched with water, and extracted three times with ether (20 mL each). Dried over Na_2SO_4, and filtered, the combined organic phases were subjected to column chromatography (basic alumina, pentane/diethyl ether, 10/1) to give 0.30 g (90% of theoretical yield) of 6-*exo*-dimethylmethoxymethylbicyclo[3.1.0]hex-2-ene as a clear liquid: ^{1}H NMR (benzene-d_6) 0.38–0.39 (m, 1H), 1.00 (s, 3H), 1.01 (s, 3H), 1.49–1.51 (m, 1H), 1.81–1.83 (m, 1H), 2.18–2.22 (m, 1H), 2.47–2.51 (m, 1H), 3.10 (s, 3H), 5.33–5.36 (m, 1H), 5.88–5.91 (m, 1H); ^{13}C NMR (benzene-d_6) 19.30, 24.12, 24.39, 28.46, 36.49, 39.09, 49.31, 73.49, 128.90, 134.42.

The endo isomer, 6-*endo*-dimethylmethoxymethylbicyclo[3.1.0]hex-2-ene, was obtained from 6-*endo*-ethoxycarbonylbicyclo[3.1.0]hexan-2-one (vide supra) following the same procedure. Steps b and c were much slower, and the final product was much more volatile: ^{1}H NMR (benzene-d_6) 0.83–0.85 (m, 1H), 1.14 (s, 3H), 1.18 (s, 3H), 1.45–1.48 (m, 1H), 1.85–1.87 (m, 1H), 2.37–2.39 (m, 2H), 3.23 (s, 3H), 5.32–5.34 (m, 1H), 5.54–5.56 (m, 1H); ^{13}C NMR (benzene-d_6) 21.18, 26.37, 27.40, 29.66, 30.70, 33.01, 49.65, 76.65, 120.52, 132.20.

For a study of the kinetics, a stock solution was prepared from 27.85 mg of **4-exo** and 15.0 μL of *tert*-butylbenzene as internal standard in 0.30 mL of benzene. For each run, 10 μL were sealed in an ampule of lead-potash glass. Analysis was by GC: 30-m by 0.53 mm i. d. capillary column coated with either DB-1 or DB-225 (J & W Scientific, Inc.; 1 mm thickness). Retention times in min on the DB-1 column at 80 °C and He at 20 mL/min (20 psi, split 10 psi) follow: **4-exo**, 7.64; **4-trans**, 8.12; **4-cis**, 9.53; **4-endo**, 9.85. For each point three analyses were averaged. Similarly a stock solution was prepared from 15 μL of **4-endo** and 10 μL of *tert*-butylbenzene in 0.60 mL of benzene. Otherwise the procedure is the same as that above.

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Supporting Information Available: Six tables of kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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