Stereoselectivity in 1,4-Elimination Reactions. The Gas-Phase Reactivity of Deuterium-Labeled 1-Methoxy-2-cyclohexene and 6,6-Dimethyl-1-methoxy-2-cyclohexene

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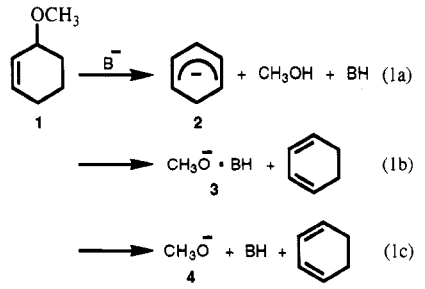
Received November 13, 1992

Elimination reactions are one of the most studied transformations in all of chemistry. Numerous aspects of the mechanism have been probed, and a tremendous wealth of information has been obtained.[1] The selectivity in these processes is often influenced by solvation, aggregation, and counterion effects. The intrinsic reactivity, therefore, is of special interest. Ab initio molecular orbital calculations and gas-phase ion molecule investigations are noteworthy in this regard. In this paper the first stereochemical information on 1,4-eliminations in the gas phase is presented. Strong bases (amide and hydroxide) are found to be relatively nonselective whereas weaker bases (*tert*-butoxide and fluoride) display a strong preference for the syn pathway.

Elimination reactions, somewhat surprisingly, have only recently been examined with high-level computations,[2] but they have been the subject of numerous gas-phase studies.[3] Many questions remain unanswered, however, in part because substitutions and eliminations both afford the same ionic products (which are what is detected). One method for overcoming this difficult is to design substrates so that the ions "tell" how they are formed. For example, 1-methoxy-2-cyclohexene (**1**) reacts with a number of bases (B^-) to afford cyclohexadienide (**2**), methoxide clusters ($CH_3O^-{\cdot}BH$, **3**), and free methoxide (**4**, eq 1).[4] The former two species must result from an elimination reaction and cannot be due to substitution. We have previously examined the regiochemistry in this system, 1,2- vs 1,4-elimination, by labeling **1** with deuterium at either C4 or C6. Strong bases were found to induce 1,4-eliminations,



as in solution,[5] whereas the 1,2-pathway successfully competes with weaker bases. This change in selectivity as a function of the base strength is indicative of a change in mechanism and led us to suggest that strong bases react via an $E1_{cb}$-type pathway whereas weaker bases proceed by an E2-type elimination.

In order to examine the stereoselectivity of a 1,4-elimination reaction, several deuterium-labeled 1-methoxy-2-cyclohexenes were prepared. The synthetic sequence for *trans*-4-deuterio-1-methoxy-2-cyclohexene (**5**) is shown in Scheme I. 1,3-Cyclohexadiene was converted to the *trans*-diacetate **6** by a palladium acetate catalyzed oxidation.[6] Subsequent hydrolysis and methylation with 1 equiv of dimethyl sulfate gave **7** in multigram quantities. This trans-alcohol was transformed into its cis-allylic chloride **12** using *N*-chlorosuccinimide and dimethyl sulfide.[7] Lithium triethylborodeuteride (Super Deuteride) reduction of the chloride occurs stereospecifically to afford the trans-labeled methoxycylohexene **5**. The cis-isomer **8** was prepared in an identical fashion, except that a catalytic amount of lithium chloride was used in the first step so as to produce the *cis*-1,4-diacetate.

The expected course of the reaction of **5** and **8** with amide and hydroxide is illustrated in Scheme II, and the stereochemical outcome is summarized in Table I. Anti elimination is favored for the cis isomer **8** with both bases (~2–3:1) whereas there is essentially no overall selectivity with the trans-compound. This difference can be accounted for by the observed isotope effects, i.e., syn elimination is retarded in **8** and anti elimination is hindered in **5**, and suggests that there is a slight preference for the anti pathway. Both telltale products (cyclohexadienide (**2**) and the methoxide–water cluster **3**) arise from syn and anti eliminations so their formation, in the absence of a labeling study, cannot be used to draw any stereochemical conclusions. In addition, both ions (**2** and **3**) do not always give rise to the same syn to anti ratios which indicates that there is a product-forming isotope effect; i.e., ion/neutral complexes **A** and **B** are subject to a partitioning isotope effect.

In order to study a wider range of bases and still avoid any possible contributions from 1,2-elimination (which competes with the 1,4-pathway when weaker bases are used), we synthesized the 6,6-dimethyl derivatives of **5** and **8** (**9** and **10**, respectively). The syntheses were carried

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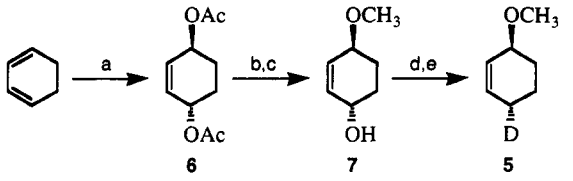
Scheme I[a]



[a] Key: (a) $Pd(OAc)_2$, MnO_2, *p*-benzoquinone, LiOAc, HOAc; (b) NaOH, CH_3OH; (c) $(CH_3O)_2SO_2$, NaOH; (d) NCS, $(CH_3)_2S$; (e) $LiEt_3BD$.

Scheme II

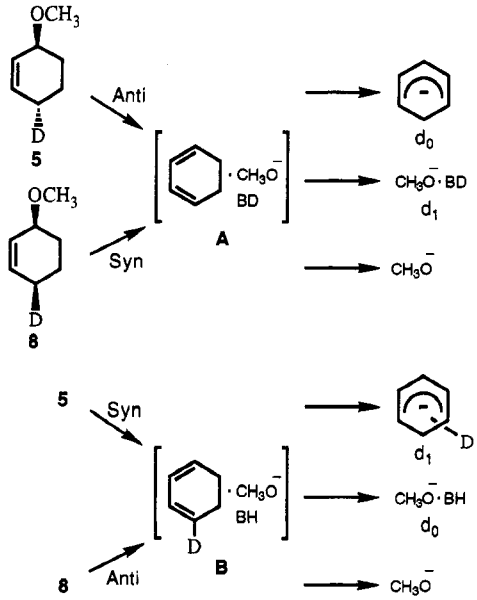
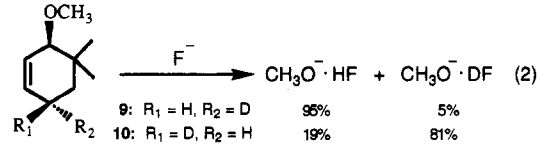


Table I. Stereoselectivity in the 1,4-Elimination Reactions of 1-Methoxy-2-cyclohexene Derivatives[a]

		products[c]					
		2		3			
compd[b]	base	syn	anti	syn	anti	3:2	k_H/k_D[d]
5	NH_2^-	57	43			0:100	1.10 ± 0.22
	OH^-	41	59	58	42	64:36	1.15 ± 0.07
8	NH_2^-	25	75			0:100	1.06 ± 0.22
	OH^-	29	71	33	67	64:36	1.10 ± 0.07
9	NH_2^-	51	49			0:100	1.28 ± 0.11
	OH^-	52	48	61	39	52:48	1.27 ± 0.09
	MeO^-	54	46	69	31	78:22	1.17 ± 0.08
	t-BuO^-	57	43	85	15	86:14	1.05 ± 0.15
	F^- [e]			95	5	100:0	1.09 ± 0.16
10	NH_2^-	33	67			0:100	1.24 ± 0.12
	OH^-	36	64	33	67	51:49	1.18 ± 0.14
	MeO^-	17	83	18	82	77:23	1.02 ± 0.04
	t-BuO^-	58	42	44	56	84:16	1.54 ± 0.11
	F^- [e]			81	19	0:100	1.20 ± 0.19

[a] The normalized product distributions and the isotope effects have not been corrected for the deuterium content and the stereospecificity of the starting compounds or the occurrence of the competing (syn/anti) elimination. [b] **5**: ≥98% D and 90% trans. **8**: ≥98% D and 95% cis. **9**: ≥98% D and 95% trans. **10**: ≥98% D and 98% cis. NMR and MS were used to determine the deuterium content and its location. [c] The product ratios correspond to the initial product distributions. [d] The reported errors are the standard deviations in our measurements, but it is unlikely that the isotope effects are more reliable than ±20%. [e] The major product (~60%) is an adduct ion.

out just as for the deuterium-labeled 1-methoxy-2-cyclohexenes, but 5,5-dimethyl-1,3-cyclohexadiene (**15**) was used as the starting material. The results with amide and hydroxide are similar to those for the unmethylated derivatives.[8] Upon decreasing the base strength, however, there is a gradual shift toward the syn pathway. Fluoride is the weakest base which was used, and it gives a ≥95:5 and ≥80:20 preference for syn elimination with **9** and **10**, respectively (eq 2).[9] This change in selectivity as a function



of the base strength is in accord mechanistically with the observed regioselectivity; i.e., strong bases react via an $E1_{cb}$-like mechanism and weaker bases proceed by an E2-like pathway.[10] The exact mechanistic details, however, are undoubtedly much more complex.

Our results corroborate molecular orbital predictions by Fukui and Anh,[11] and Tee's analysis based on the principle of least motion.[12] It is harder to compare this work to liquid-phase investigations since both syn and anti 1,4-eliminations have been observed in solution. Nevertheless, it appears that the former pathway is favored in condensed media as well.[13] This study can be extended to 1,2-eliminations, and the results of this work, along with MO calculations which address the reaction mechanisms, will be reported in due course.[14]

Experimental Section

General Methods. Nuclear magnetic resonance spectra were obtained in $CDCl_3$ or CD_3COCD_3 on IBM NR/200, IBM NR/300, or Varian VXR-500S spectrometers and are reported in ppm (δ). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra were obtained on an AEI MS-30 and/or Finnigan MAT 95 mass spectrometer. Preparative gas–liquid chromatography (GLC) was carried out on a Varian Aerograph gas chromatograph with a helium flow of 60 mL min^{-1}. Reactions were carried out under a nitrogen atmosphere. Reagents were purchased from Aldrich, except for sodium hydride (Alfa) and *tert*-butyldimethylchlorosilane (Hüls), and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, methylene chloride from phosphorous pentoxide, pyridine from barium oxide, and DMF from barium oxide.

***cis*-4-Methoxy-2-cyclohexen-1-ol (11).** Sodium hydroxide (6 g in 15 mL water) and dimethyl sulfate (7.2 g, 57 mmol) were alternately added in three batches to a solution of *cis*-2-cyclohexene-1,4-diol[6] (6.0 g, 53 mmol) and 95% ethanol (45 mL). Additional NaOH (3.0 g in 6.0 mL H_2O) was subsequently added to make the solution alkaline, and the reaction mixture was then

(8) The product distributions are also similar except that less methoxide is formed (≤5%). When weaker bases are used the proportion of the cluster increases, the dienide decreases, and the methoxide disappears entirely. This change in the product ratio simply reflects the reaction thermodynamics.

(9) The product ratios are given as lower limits because they have not been corrected for the deuterium content and location (syn/anti contamination) in the starting material.

(10) It is interesting to note that the change in mechanism occurs in going from hydroxide to methoxide, which coincides with the base's ability to abstract an allylic proton.

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(14) The computational work is being carried out in collaboration with Prof. Scott Gronert.

refluxed for 3 h. Upon cooling, the solution was saturated with sodium chloride and extracted with ethyl acetate. The organic material was washed with saturated sodium bicarbonate and water. Drying over anhyd $MgSO_4$ and removal of the solvent under reduced pressure afforded 5.1 g of a dark oil which showed three spots on TLC (silica gel, 5:1 ethyl acetate/hexane). Separation of the components was accomplished with a silica gel column by eluting first with 10:1 hexane/ethyl acetate to obtain the cis-dimethylated product (800 mg) and then with 5:1 ethyl acetate/hexane to afford 11 (2.1 g) and starting material (2.7 g). The recovered diol was resubjected to the reaction conditions, and the same workup yielded an additional 600 mg of 11 to give a total of 2.7 g (40%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 2 H), 4.11 (m, 1 H), 3.67 (br s, 1 H), 3.36 (s, 3 H), 1.72 (m, 5 H).

***trans*-4-Methoxy-2-cyclohexen-1-ol (7).**[15] The same methylation conditions described above for the synthesis of 11 were followed. A 6.5-g portion of *trans*-2-cyclohexene-1,4-diol[6] yielded 2.1 g (29%) of the *trans*-monomethyl ether 7 after the recovered starting material was resubjected to the reaction conditions three times: ^1H NMR (200 MHz, $CDCl_3$) δ 5.58 (s, 2 H), 4.27 (m, 1 H), 3.38 (m, 1 H), 3.37 (s, 3 H), 2.12 (dt, 2 H, J = 10.7 and 3.5 Hz), 1.50 (m, 3 H).

***cis*-4-Methoxy-1-chloro-2-cyclohexene (12).** The chlorination procedure developed by Corey was used.[7] Dimethyl sulfide (1.2 mL, 16 mmol) was added via syringe to a 0 °C solution of *N*-chlorosuccinimide (1.85 g, 13.8 mmol) and freshly distilled methylene chloride (57 mL). Upon completion of the addition, the temperature was lowered to −25 °C (CCl_4/dry ice) and a methylene chloride (6.0 mL) solution of 7 (1.35 g, 10.5 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C and was stirred for 6 h (reaction progress was monitored by TLC, 1:1 hexane/ethyl acetate). The cold solution was poured into cold brine (80 mL), and the two layers were separated. The aqueous phase was extracted with ether, and the combined organic material was washed with saturated sodium chloride, dried over anhyd $MgSO_4$, and concentrated under reduced pressure to yield 1.40 g of a yellow oil. Proton NMR indicated that both diastereomeric chlorides as well as the chloride resulting from an S_N2' process were formed. The crude product was successfully separated by MPLC (silica gel, 3% ethyl acetate in hexane) to give 700 mg (45%) of 12, 200 mg of 13, and 300 mg of the S_N2' product. 12: ^1H NMR (200 MHz, $CDCl_3$) δ 5.88 (s, 2 H), 4.52 (m, 1 H), 3.80 (t, 1 H, J = 6.4 Hz), 3.38 (s, 3 H), 2.07 (m, 2 H), 1.91 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.1, 129.9, 74.0, 55.8, 54.2, 29.6, 23.8.

***trans*-4-Methoxy-1-chloro-2-cyclohexene (13).** The same Corey chlorination procedure described above was followed. A 2.40-g (19 mmol) portion of *cis*-methoxy alcohol 11 yielded 1.35 g (47%) of clean chloride 13 after MPLC purification: ^1H NMR (200 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.93 (s, 1 H), 4.58 (t, 1 H, J = 5.0 Hz), 3.77 (t, 1 H, J = 4.8 Hz), 3.36 (s, 3 H), 2.26 (m, 1 H), 2.09 (m, 1 H), 1.88 (m, 1 H), 1.72 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.9, 129.9, 72.4, 56.1, 54.4, 29.0, 24.7.

***cis*-1-Methoxycyclohex-2-ene-4-d_1 (8).** Lithium triethylborodeuteride (1 M) in THF (16.0 mL, 16 mmol) was added dropwise to a solution of *trans*-methoxy chloride 13 (1.20 g, 8.0 mmol) and freshly distilled THF (30 mL), and the resulting mixture was allowed to stir at room temperature overnight (16 h). Water was added to quench excess deuteride, and then 3 N sodium hydroxide (8.0 mL) and 30% hydrogen peroxide (8.0 mL) were added to oxidize the boranes. The aqueous layer was extracted with pentane, and the combined organic material was washed with water to remove ethanol. The resulting solution was dried over anhyd $MgSO_4$, and the solvent was removed by an atmospheric distillation. The residue was purified by preparative GLC (20% SE-30, 95 °C) to yield 520 mg (56%) of 8. The fully resolved 500-MHz ^1H NMR showed that the deuterium incorporation was >95% cis:[16] ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, 1 H, J = 7.3 and 9.8 Hz), 5.77 (d, 1 H, J = 9.8 Hz), 3.72 (br s, 1 H), 3.34 (s, 3 H), 1.91 (br s, 1 H), 1.80 (m, 1 H), 1.71 (m, 1 H), 1.64 (m, 1 H), 1.52 (m, 1 H). Mass spectral analysis indicated ≥98% d_1.

***trans*-1-Methoxycyclohex-2-ene-4-d_1 (5).** The same procedure used for the synthesis of 8 was followed except that the reaction was complete after 8 h. Starting with 680 mg of 12, 270 mg (51%) of purified product (5) was obtained. The fully resolved 500-MHz ^1H NMR indicated that the deuterium incorporation was 90% trans and 10% cis,[16] while the mass spectrum showed the product to be ≥98% d_1: ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, 1 H, J = 7.3 and 9.8 Hz), 5.77 (d, 1 H, J = 9.8 Hz), 3.72 (br s, 1 H), 3.34 (s, 3 H), 2.00 (br s, 1 H), 1.80 (m, 1 H), 1.71 (m, 1 H), 1.63 (m, 1 H), 1.51 (m, 1 H).

1-Acetoxy-4,4-dimethyl-2-cyclohexene (14). 4,4-Dimethyl-2-cyclohexen-1-ol (58.5 g, 0.464 mol) in pyridine (195 mL) was added dropwise to a room-temperature solution of acetic anhydride (292 mL) and freshly distilled pyridine (292 mL). The reaction mixture was heated at 70 °C for 16 h and then was quenched with water (300 mL), diluted with ether, and acidified with 3 N HCl (300 mL). The aqueous phase was extracted with ether, and the combined organic material was washed with 3 N HCl, sodium bicarbonate, and saturated sodium chloride. It was then dried over anhyd $MgSO_4$ and concentrated under reduced pressure to afford a yellow oil (14) (69.5 g, 89%). The crude material was pyrolyzed in the next step without further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, 1 H, J = 9.8 Hz), 5.51 (d, 1 H, J = 9.8 Hz), 5.17 (m, 1 H), 2.02 (s, 3 H), 1.84 (m, 1 H), 1.70 (m, 1 H), 1.55 (m, 1 H), 1.44 (m, 1 H), 1.00 (s, 3 H), 0.95 (s, 3 H).

5,5-Dimethyl-1,3-cyclohexadiene (15).[17] Acetate 14 (69.0 g, 0.411 mol) was allowed to slowly drip into a hot (410–420 °C) vertical quartz tube filled with quartz chips under a constant flow of nitrogen over a 4-h period. The product was collected in a dry ice/acetone trap and was subsequently diluted with pentane and washed with water and sodium bicarbonate. Simple atmospheric distillation of the dried solution (anhyd $MgSO_4$) afforded 23.8 g (54%) of diene 15: bp 104–108 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 5.75 (m, 3 H), 5.49 (d, 1 H, J = 9.3 Hz), 2.08 (d, 2 H, J = 5.1 Hz), 0.99 (s, 6 H).

***trans*-1,4-Diacetoxy-5,5-dimethyl-2-cyclohexene (16).** The procedure developed by Bäckvall[6] was followed: Activated MnO_2 (13.6 g, 0.156 mol) immediately followed by a pentane (420 mL) solution of diene 15 (14.1 g, 0.131 mol) were added to a solution of $Pd(OAc)_2$ (1.46 g, 6.5 mmol), lithium acetate dihydrate (14.2 g, 0.139 mol), 1,4-benzoquinone (4.0 g, 0.037 mol), and glacial acetic acid (210 mL). The resulting mixture was stirred for 48 h, and then the two liquid layers were separated. The acetic acid solution was diluted with saturated sodium chloride (250 mL) and extracted with pentane followed by a 1:1 pentane/ether mixture. The combined organic material was washed with brine, water, and 2 M sodium hydroxide until the extracts became clear and colorless. Concentration of the dried organic solution (anhyd $MgSO_4$) under reduced pressure afforded 17.2 g (58%) of crude 16. ^1H NMR showed the presence of a small amount (<5%) of the cis-isomer; therefore, the crude product was passed through a silica gel column (30% ethyl acetate in hexane) to yield 16.5 g (56%) of pure 16: ^1H NMR (200 MHz, $CDCl_3$) δ 5.75 (m, 2 H), 5.36 (m, 1 H), 5.18 (d, 1 H, J = 2.2 Hz), 2.08 (s, 3 H), 2.04 (s, 3 H), 1.94 (dd, 1 H, J = 6.0 and 13.4 Hz), 1.56 (dd, 1 H, J = 8.7 and 13.4 Hz), 0.98 (s, 6 H).

***trans*-5,5-Dimethyl-2-cyclohexene-1,4-diol (17).** A solution of diacetate 16 (16.5 g, 0.073 mol) and methanol (345 mL) darkened immediately upon adding 86 mL of 2 M sodium hydroxide. The resulting mixture was refluxed for 1 h, and then it was concentrated to a volume of ~50 mL with a rotary evaporator. Sodium hydroxide pellets were added to saturate the solution which was then extracted with ethyl acetate. The black organic material was treated with decolorizing carbon and concentrated under reduced pressure to yield 9.32 g (90%) of 17 as a yellow oil. Crystallization from acetone afforded 8.6 g (83%)

(15) This compound has been alternatively prepared: Bäckvall, J. E.; Nordberg, R. E.; Björkman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, *20*, 943.

(16) The stereochemical assignment is consistent with the known mechanism (anti displacement) for this type of reaction (see: Kirshnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1983**, *48*, 3085), the chemical shifts (see ref 13c), and 2D-NOESY experiments.

(17) A different procedure for the preparation of this compound has been reported. See: Dauben, W. G.; Lorber, M. E.; Vietmeyer, N. D.; Shapiro, R. H.; Duncan, J. H.; Tomer, K. *J. Am. Chem. Soc.* **1968**, *90*, 4762.

of 17: mp 108 °C; bp 115–120 °C (0.1 mm); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 5.63 (dd, 1 H, J = 1.8 and 10.2 Hz), 5.51 (dd, 1 H, J = 1.8 and 10.2 Hz), 4.18 (m, 1 H), 3.90 (m, 1 H), 3.74 (d, 1 H, J = 6.2 Hz), 3.68 (d, 1 H, J = 6.0 Hz), 1.79 (dd, 1 H, J = 1.48 and 12.8 Hz), 1.34 (dd, 1 H, J = 9.7 and 12.8 Hz), 1.01 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 132.8, 132.1, 74.8, 65.8, 46.5, 37.6, 28.7, 19.3; IR (neat, mixture of isomers) 3334, 3027, 2954, 1652, 1384, 1365, 1094, 1031, 758.

***trans*-1-(*tert*-Butyldimethylsiloxy)-5,5-dimethyl-2-cyclohexen-4-ol (18).** A solution of trans-diol 17 (4.35 g, 30.6 mmol), freshly distilled DMF (17.0 mL), *tert*-butyldimethylsilyl chloride (5.54 g, 36.8 mmol) and imidazole (5.21 g, 76.5 mmol) was allowed to stir at 35 °C overnight (~12 h). Water was added to the reaction mixture which was subsequently extracted with ether. The resulting ethereal solution was washed with cold $NaHCO_3$, water, and brine. After drying with anhyd sodium sulfate, the solvent was removed at aspirator pressure to afford a yellow oil. Vacuum distillation yielded 7.31 g (93%) of 18: bp 99–104 °C (0.1 mm); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (m, 2 H), 4.27 (m, 1 H), 3.97 (br s, 1 H), 1.73 (dd, 1 H, J = 5.7 and 6.5 Hz), 1.44 (dd, 1 H, J = 6.5 and 9.3 Hz), 1.03 (s, 3 H), 0.92 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 131.1, 74.7, 66.6, 45.6, 36.9, 28.1, 25.9, 19.2, 18.2, −4.6, −4.5; IR (neat) 3384, 3030, 2955, 1654, 1389, 1362, 1006.

***trans*-1-(*tert*-Butyldimethylsiloxy)-4-methoxy-5,5-dimethyl-2-cyclohexene (19).** To a warm solution (50 °C) of sodium hydride (60% oil dispersion, 4.0 g, 0.10 mol), iodomethane (13.0 g, 0.092 mol), and THF (60 mL) was added 18 (15.0 g, 0.059 mol) in THF (20 mL) dropwise. The reaction mixture was allowed to stir for an additional 4 h at 50 °C, and after cooling, water was added until all of the solid material dissolved. The resulting layers were separated, the aqueous material was extracted with ether, and the combined organic solution was washed with brine and dried over anhyd $MgSO_4$. Removal of the solvent under vacuum afforded 15.2 g (96%) of 19. This crude material was carried onto the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 2 H), 4.27 (m, 1 H), 3.43 (s, 1 H), 3.40 (s, 3 H), 1.70 (dd, 1 H, J = 5.8 and 6.5 Hz), 1.42 (dd, 1 H, J = 6.5 and 9.3 Hz), 1.03 (s, 3 H), 0.90 (s, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

***trans*-4-Methoxy-5,5-dimethyl-2-cyclohex-1-ol (20).** A solution of crude 19 (7.60 g, 0.028 mol), freshly distilled THF (50 mL), and 1.0 M tetrabutylammonium fluoride in THF (58 mL) was allowed to stir at room temperature for 48 h. Water was then added, the aqueous layer was extracted with ether, and the combined organic material was washed with water, dried over anhyd magnesium sulfate, and concentrated under reduced pressure. Distillation of the residue yielded 3.40 g (77%) of 20: bp 50–53 °C (0.3 mm); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.75 (s, 2 H), 4.26 (m, 1 H), 3.42 (s, 1 H), 3.41 (s, 3 H), 1.86 (dd, 1 H, J = 5.5 and 6.4 Hz), 1.54 (br s, 1 H), 1.33 (dd, 1 H, J = 9.6 and 6.4 Hz), 1.05 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.4, 128.1, 84.5, 65.6, 58.3, 45.8, 37.1, 28.6, 19.5; IR (neat) 3375, 3027, 2927, 1649, 1379, 1364, 1037; HRMS-EI (mixture of isomers) calcd for $C_9H_{16}O_2$ 156.1150, found 156.1150.

***cis*-4-Methoxy-5,5-dimethyl-1-chloro-2-cyclohexene (21).** The Corey chlorination procedure described above was followed: 3.60 g (23.1 mmol) of trans-alcohol 20 yielded 3.81 g (95%) of crude *cis*-chloride 21. MPLC purification (silica gel, 3% ethyl acetate in hexane) yielded 1.50 g (37%) of pure *cis*-chloride 21, 500 mg of pure *trans*-chloride 24 (12%), 300 mg (7%) of the chloride product from an SN_2' reaction, and 600 mg (15%) of a mixture of 21 and 24. Separation of the cis/trans chlorides is difficult; TLC did not give any separation, and MPLC did not give base-line separation. The above quantities were obtained only after cycling the mixture through the MPLC three times: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (dd, 1 H, J = 3.66 and 11.0 Hz), 5.83 (dd, 1 H, J = 2.44 and 11.0 Hz), 4.50 (t, 1 H, J = 6.1 Hz), 3.38 (s, 3 H), 3.10 (d, 1 H, J = 3.66 Hz), 1.95 (dd, 1 H, J = 13.4 and 7.3 Hz), 1.80 (dd, 1 H, J = 6.1 and 13.4 Hz), 1.00 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3, 128.3, 80.6, 57.9, 54.0, 41.6, 35.0, 25.5, 24.7; IR (neat) 3037, 2955, 1383, 1365, 1011, 724; HRMS-CI (CH_4) M + H$^+$ calcd for $C_9H_{17}ClO$ 175.0890, found 175.0887.

***trans*-1-Methoxy-6,6-dimethyl-2-cyclohexene-4-*d*$_1$ (9).** The previously described deuteride displacement of an allylic chloride was followed: 1.45 g (8.3 mmol) of *cis*-chloride 21 was allowed to react at room temperature for 16 h and yielded, after preparative GLC (SE-30, 130 °C), 550 mg (47%) of pure 9. The fully resolved 500-MHz ^{1}H NMR showed that the deuterium was 95% trans/5% cis,[16] and mass spectral analysis indicated ≥98% d_1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 2 H), 3.39 (s, 3 H), 3.25 (s, 1 H), 2.00 (m, 1 H), 1.45 (dd, 1 H, J = 4.88 and 13.4 Hz), 1.33 (dd, 1 H, J = 8.5 and 13.4 Hz), 0.94 (s, 3 H), 0.87 (s, 3 H).

***cis*-4-Methoxy-5,5-dimethyl-2-cyclohexen-1-ol (22).** DEAD (10 mL) was added dropwise via syringe to a −78 °C solution of 20 (6.70 g, 42.9 mmol), triphenylphosphine (13.6 g, 52 mmol), benzoic acid (6.70 g, 52 mmol), and freshly distilled THF (167 mL). The reaction mixture was allowed to slowly rise to room temperature after the addition was complete and then was stirred for an additional 3 h. Concentration of the reaction mixture under reduced pressure followed by column chromatography (silica gel, 20% ethyl acetate in hexane) afforded 10.80 g (97%) of the *cis*-benzoate (23). This compound was dissolved in methanol (122 mL), and sodium hydride (1.0 g, 25 mmol, 60% dispersion in oil) was carefully added in small portions to the solution. After the solution was stirred for 12 h at 25 °C, aqueous acetic acid was added and the resulting solution was washed with dichloromethane. The combined organic extracts were washed with water and saturated sodium bicarbonate, dried over anhyd magnesium sulfate, and concentrated under reduced pressure. The resulting oil was purified by column chromatography (silica gel, 15% ethyl acetate in hexane) to yield 4.97 g (77%) of the cis-alcohol 22: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.88 (m, 2 H), 4.12 (m, 1 H), 3.40 (s, 3 H), 3.11 (d, 1 H, J = 3.3 Hz), 1.62 (m, 2 H), 1.37 (d, 1 H, J = 13.4 Hz), 1.0 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.7, 127.1, 81.4, 65.8, 58.0, 41.0, 34.6, 25.7, 25.6; IR (neat) 3375, 3027, 2927, 1647, 1379, 1364, 1037; HRMS-EI (mixture of isomers) calcd for $C_9H_{16}O_2$ 156.1150, found 156.1150.

***trans*-4-Methoxy-5,5-dimethyl-1-chloro-2-cyclohexene (24).** The usual Corey chlorination with 4.90 g (31.4 mmol) of *cis*-methoxy alcohol 22 yielded 5.10 g (94%) of the crude *trans*-chloride 24. MPLC purification (3% ethyl acetate in hexane) gave 2.10 g (38%) of pure *trans*-methoxy chloride 24: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (d, 1 H, J = 11.0 Hz), 5.75 (d, 1 H, J = 11.0 Hz), 4.55 (m, 1 H), 3.45 (s, 1 H), 3.39 (s, 3 H), 2.02 (dd, 1 H, J = 4.9 and 13.4 Hz), 1.74 (dd, 1 H, J = 9.8 and 13.4 Hz), 1.04 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.4, 129.0, 83.4, 58.2, 54.7, 46.4, 37.4, 27.9, 19.0; IR (neat) 3038, 2929, 1380, 1364, 1036, 638; HRMS-CI (CH_4) M + H$^+$ calcd for $C_9H_{17}ClO$ 175.0890, found 175.0893.

***cis*-1-Methoxy-6,6-dimethyl-2-cyclohexene-4-*d*$_1$ (10).** The Super Deuteride reaction conditions described above were used, and 1.90 g (11 mmol) of 24 yielded, after stirring for 30 h at room temperature, 1.60 g of crude material. Preparative gas–liquid chromatography (SE-30, 120 °C) afforded 780 mg (51%) of 10. The fully resolved 500-MHz ^{1}H NMR indicated that the deuterium label was 98% cis/2% trans,[16] while mass spectral analysis indicated ≥98% d_1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 2 H), 3.39 (s, 3 H), 3.25 (s, 1 H), 1.91 (m, 1 H), 1.45 (dd, 1 H, J = 6.1 and 13.4 Hz), 1.33 (dd, 1 H, J = 6.1 and 13.4 Hz), 0.94 (s, 3 H), 0.87 (s, 3 H).

Acknowledgment. Support from the National Science Foundation (CHE-8907198) and the donors of the Petroleum Research Foundation, administered by the American Chemical Society, is gratefully acknowledged.

Supplementary Material Available: ^{1}H NMR spectra of compounds 1, 5, 7, 8, 1-methoxy-6,6-dimethyl-2-cyclohexene, 9, 10–13, 16–18, 20–22, and 24, ^{13}C NMR spectrum of 20, and 2D NOESY spectrum of 1-methoxy-6,6-dimethyl-2-cyclohexene (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.