# Stereochemistry of the Claisen Rearrangement of Derivatives of 5-*tert*-Butyl-1-(hydroxymethyl)-1-cyclohexene: Preferred Axial Attachment of the Side Chain[1]

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The Claisen rearrangement of vinyl ethyl derivatives of 5-*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene is reported. The standard allyl vinyl ether conditions as well as the triethyl orthoacetate and ester enolate variants of the Claisen rearrangement all resulted in the formation of *cis*(axial)-4-*tert*-butylcyclohexyl-substituted systems. Thus, in sterically unbiased cases, this [3,3] sigmatropic process results in the axial attachment of the side chain in a cyclohexyl system.

The Claisen rearrangement is a synthetically useful transformation,[2] and most of its stereochemical aspects are now well understood.[3] One stereochemical point that has not been addressed directly in the public literature[4,5] is whether there is a preference for axial or equatorial attachment of the side chain that results from such a rearrangement in certain cyclohexene series. In an earlier sterically biased case reported from these laboratories,[6] only the axially oriented product was observed (see below).
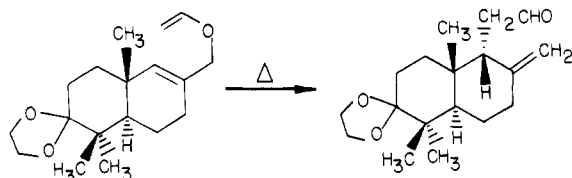


Since it was not clear if this result was the consequence of the steric congestion on the top face of this dicyclic molecule or a preferred stereoelectronically controlled quasi-axial approach of the vinyl ether to the cyclohexene ring system, it was decided to investigate the rearrangement in a stereochemically defined but sterically unbiased situation. The substrate chosen for this work was 5-

**Scheme I. Claisen Rearrangements with 5-*tert*-Butyl-1-(hydroxymethyl)-1-cyclohexene (2)**[a]



[a] (a) C₂H₅COCl, pyr; (b) [Cp₂Ti structure]; C₆H₅CH₃;
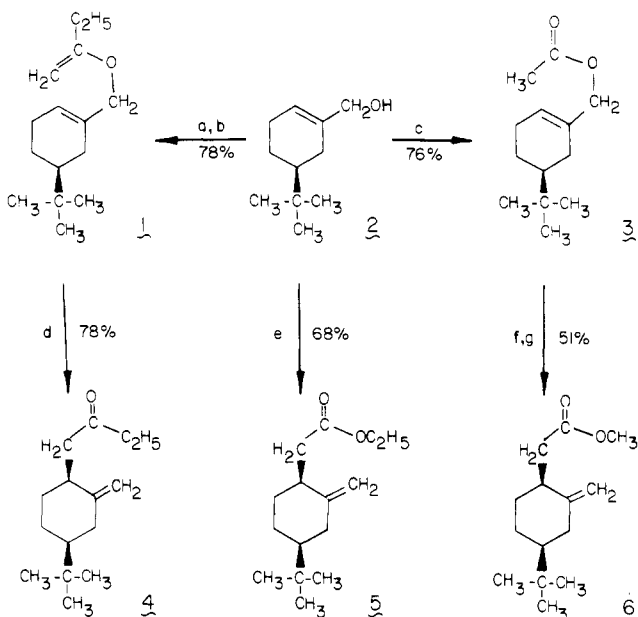
(c) CH₃COCl, pyr; (d) 142 °C (sealed tube), 6 h; (e) CH₃C(OC₂H₅)₃, C₅H₁₁CO₂H, 166 °C, 44 h; (f) LDA, THF, HMPA; *t*-BuMe₂SiCl; 60 °C; H₃O⁺; (g) CH₂N₂, Et₂O.

*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene (2),[7] and several variations of the Claisen rearrangement were explored (Scheme I).

In one instance, the ketone 4 was prepared through the standard[6,13] allyl vinyl ether type rearrangement of the vinyl ether 1. Alternately, direct formation of the ethyl ester 5 was accomplished through application of the Johnson[8] triethyl orthoacetate variant of the rearrange-

(1) Contribution No. 6697. Grateful acknowledgement is made for the support of this investigation through National Science Foundation Grant CHE-78-21066.

(2) (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975,** *22,* 1. (b) Bennett, G. B. *Synthesis* **1977,** 589. (c) Ziegler, F. E. *Acc. Chem. Res.* **1977,** *10,* 227. (d) Bartlett, P. A. *Tetrahedron* **1980,** *36,* 1–72.

(3) (a) Gill, G. B. *Q. Rev., Chem. Soc.* **1968,** *22,* 338. (b) Hansen, H. J. Schmidt, H. *Tetrahedron* **1974,** *30,* 1959. (c) Takahashi, H.; Oshima, K.; Yamamoto, H.; Nazaki, H. *J. Am. Chem. Soc.* **1973,** *95,* 5803. (d) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962,** *18,* 67. (e) Vittovelli, P.; Winkler, T.; Hansen, H. J.; Schmidt, H. *Helv. Chim. Acta* **1968,** *51,* 1457. (f) Sucrow, W.; Richter, W. *Chem. Ber.* **1971,** *104,* 3679. (g) Faulkner, D. J.; Peterson, M. R. *Tetrahedron Lett.* **1969,** 3243. (h) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979,** *44,* 882.

(4) Dr. A. A. Panaras has informed us that his research group is investigating similar systems. See also ref 2c and 5.

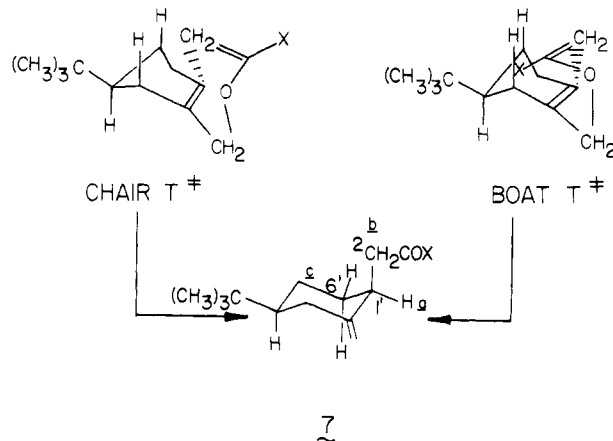(5) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975,** *40,* 86.

(6) Ireland, R. E.; Marshall, J. A.; Church, R. F. *J. Org. Chem.* **1962,** *27,* 1118.

(7) Gream, G. E.; Serelis, A. K. *Aust. J. Chem.* **1978,** *31,* 863–91.

ment to the allylic alcohol 2. Finally, the methyl ester 6 was formed after diazomethane esterification of the acid from the ester enolate Claisen rearrangement[9] of the acetate 3. In each instance, the steric congestion associated with the addition of the $CH_2COX$ side chain to the ring system should be minimal, and on the assumption[10] that the C5 *tert*-butyl grouping is sufficiently bulky to maintain a rigid cyclohexene conformation, the stereochemistry of these products should reflect the preferred mode of orientation for the rearrangement transition state.

The required stereochemical determination of the rearrangement products was accomplished through 500-MHz ^{1}H NMR analysis[11] of the individual diastereomers. In each instance, the two possible products (axial and equatorial side-chain attachment) were detected through the appearance of multiplet resonances for the C1′ allylic methine hydrogen at 2.89 and 2.46 ppm. That one isomer was by far the predominant product of the rearrangements was apparent from the ≥87:13 ratio observed on integration of the two peaks in the analytical VPC trace in each of the three products. After decoupling the C1′-methine hydrogen (a) from the C2 methylene hydrogens (b) of the side chain, it was possible to determine the stereochemistry at the C1′ center by analysis of the coupling between the C1′ methine hydrogen (a) and the adjacent C6′ methylene hydrogens (c). These coupling constants for the resonance

(8) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970,** *92,* 741.

(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976,** *98,* 2868.

(10) Allinger, N. L.; Eliel, E. L. *Top. Stereochem.* **1967,** *1,* 199.

(11) Southern California Regional NMR Facility, NSF Grant CHE-79-16324.

(12) Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Varian EM-390 (^{1}H NMR) or a Bruker WM500 (500-MHz ^{1}H NMR) spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assigned protons).

Silica gel columns for chromatography utilized E. Merck silica gel 60, 70–230-mesh ASTM, or for flash chromatography silica gel 60, 230–400-mesh ASTM, was used.

Analytical vapor-phase chromatographic (VPC) analyses were performed on a Hewlett-Parkard 5750 gas chromatograph, equipped with a flame-ionization detector (335 °C) and using helium carrier gas at a flow rate of 60 mL/min. The column size was 6 ft × 1/8 in. and was packed with 10% SE-30 absorbed on 60–80-mesh Chromosorb W AW DMCS. Injector temperature was 330 °C. The column temperature and retention times are as indicated in each experimental.

Preparative vapor-phase chromatographic separations were performed on a Varian 920 gas chromatograph, equipped with a thermal-conductivity detector (230 °C) and using helium carrier gas at a flow rate of 60 mL/min. The column size was 6 ft × 0.25 in. and was packed with 10% SE-30 absorbed on 60–80-mesh Chromosorb W AW DMCS. The injector temperature was 230 °C. The column temperature and retention times are as indicated for each experiment.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether and tetrahydrofuran (THF) were distilled under argon from sodium metal in the presence of benzophenone. Benzene and pyridine were distilled from powdered calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. Hexamethylphosphoramide (HMPA) was distilled at 1.0 mmHg from powdered calcium hydride and stored over 4-Å molecular sieves. Diisopropylamine was distilled under argon from sodium metal.

Lithium diisopropylamide (LDA) was prepared by adding a titrated hexane solution of *n*-butyllithium to a mixture of diisopropylamine in THF at 0 °C under argon and stirring the mixture for 5 min.

All other reactants and solvents were "reagent grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction, bp 35–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, NJ, and was not further purified.

Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

(13) (a) Tebbe, F. N.; Parshall, G. W.; Ready, G. S. *J. Am. Chem. Soc.* **1978,** *100,* 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980,** *102,* 3270.

(14) Prepared as described in ref 7. The data (IR, NMR) for alcohol 2 was identical in all respects to those given.

at 2.89 ppm of the major product were 0 and 5 Hz. The resonance at 2.46 ppm of the minor product was a large multiplet and was determined to be both the C1′ and the C3′ equatorial hydrogens. That the C1′ hydrogen was in fact axial in the minor product was determined from its 12-Hz coupling constant to the C6′ axial hydrogen at 0.95 ppm. For the expected chair conformation of the cyclohexene ring system, these coupling constants indicate that the C1′ methine hydrogen of the major product is equatorial (dihedral angles: $H_aH_c(ax) = 38°$; $H_aH_c(eq) = 75°$) and that of the minor product is axial (dihedral angles: $H_aH_c(ax) = 170°$). Therefore, in each case, the Claisen rearrangement has resulted in the attachment of the $CH_2COX$ side chain predominately on the β face of the cyclohexene ring in the *axial orientation*, as shown in structure 7. Apparently, stereoelectronically controlled



CHAIR T[‡]          BOAT T[‡]

7

axial approach during rearrangement is favored, and the steric bias of the earlier observed[6] system served only to augment this effect.

Ziegler's suggestion[2c] that this preference for axial approach is a result of the $A^{(1,3)}$ strain experienced in the trans (equatorial) products does not seem likely. Literature values for this interaction (~1.3 kcal/mol)[15] indicate that the product resulting from equatorial approach is still thermodynamically more stable than the product resulting from axial approach whose 1,3-diaxial interactions are on the order of 1.8 kcal/mol.[10]

Two limiting transition states (CHAIR T[‡] and BOAT T[‡]) can be envisaged to account for this result. Molecular models, as reflected in the drawings above, make it apparent that in these cases where the vinyl ether portion of the allyl vinyl ether system terminates in a $CH_2$ grouping, the CHAIR T[‡] arrangement is less hindered. In order to ascertain the effect of a substituent at this position on the preferred chair conformation of the transition state and hence the stereochemical effect that results, we prepared the corresponding allylic propionate 9 (Scheme II).

After enolization of this propionate 9, the derived silyl ketene was rearranged at 50 °C, and the resulting silyl ester was hydrolyzed. Esterification with diazomethane then produced a stereoisomeric mixture of the esters 11 and 12. Even though these esters are isomeric at both C2 and C1′, it was possible to analyze this mixture for the cis (axial side chain) and trans (equatorial side chain) components in the same fashion described above for the acetates. Again, the predominate component was assigned the structure 11 with an axial side chain by virtue of the equatorial C1′ hydrogen doublet of doublets at 2.36 ppm ($J = 11, 5$ Hz). This C1′ hydrogen appears at 2.05 ppm ($J = 7.5, 11, 3.5$ Hz) in the ^{1}H NMR spectrum of the minor isomers 12.

(15) Johnson, F. *Chem. Rev.* **1968,** *68,* 375.

**Scheme II. Ester Enolate Claisen Rearrangement of (5-*tert*-Butyl-1-cyclohexenyl)methyl Propionate (9)$^a$**
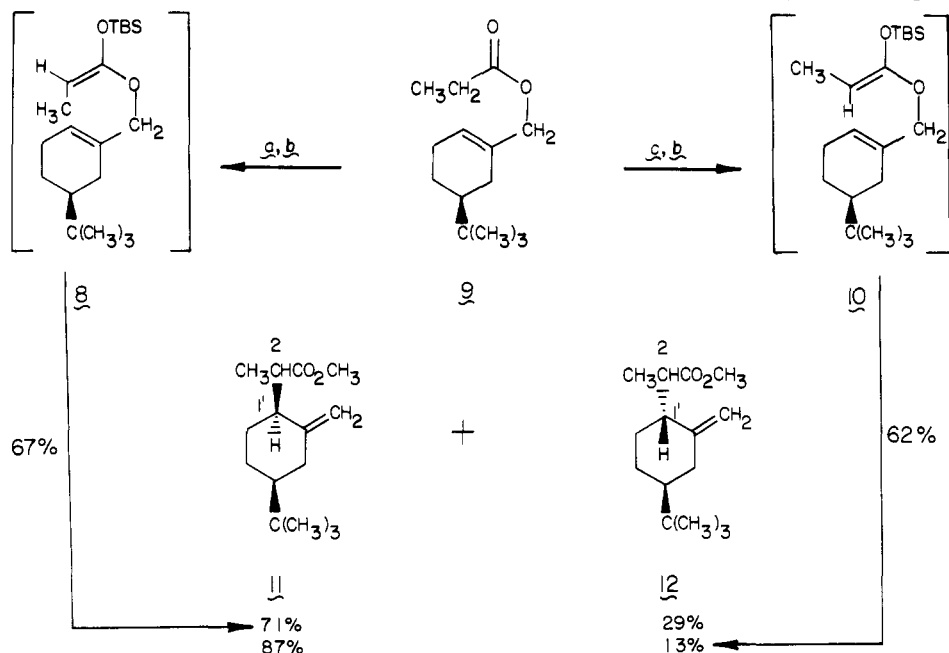


$^a$ (a), LDA, THF, −78 °C; TBSCl, HMPA; 50 °C; $H_3O^+$; (b) $CH_2N_2$, $Et_2O$; (c) LDA, 23% HMPA/THF, −78 °C; TBSCl; 50 °C; $H_3O^+$.

While rearrangement still occurs so as to attach the side chain predominately in the axial orientation, there is an interesting effect that results from the terminal methyl substituent on the vinyl ether portion of the molecule. Now, two geometrically isomeric enolates are possible. On the basis of prior results from these laboratories,[9] it is expected that enolization of the ester 9 in pure THF and then silylation would lead to the ketene acetal 8 (predominately), while the use of 23% HMPA–THF as the solvent for enolization will ultimately result in the ketene acetal 10 (predominately). For the Z form 10 of the ketene acetal, the CHAIR (axial) T* orientation seems to be favored, as the product ratio favors the ester 11 quite significantly. For the E form 8 of the ketene acetal, the steric congestion in the transition states is not nearly as obvious, and now equatorial attachment of the side chain competes significantly. For *either* the CHAIR T* or the BOAT T* conformation for the axial approach, this (E)-ketene acetal isomer 8 will require that a bulky vinyl substituent be buried in the cyclohexene ring (C2 $CH_3$ in the CHAIR T* and C1 OTBS in the BOAT T*). While similar destabilization is apparent in both the chair and boat transition states for equatorial attack, the overall effect must result in the narrowing of the energy difference between axial and equatorial attack so that more trans (equatorial) product is formed. The steric effects are also manifest in the ratio of the isomers at C2 in the cis (axial) products 11. Independent $^1H$ NMR analysis indicates a virtual 1:1 ratio of the R* and S* isomers at C2 of the esters 11; this is apparent from the two methyl doublets at 1.03 and 1.13 ppm and probably reflects a lack of preference for the energetically nearly equal CHAIR T* and BOAT T* conformations.

Thus, while axial attachment of the side chain by Claisen rearrangement is preferred in these cyclohexenylmethanol systems, relatively minor substitution of the vinyl ether portion of the molecule can significantly alter this generalization.

## Experimental Section[12]

**(5′-*tert*-Butyl-1′-cyclohexenyl)methyl Propionate (9).** To a rapidly stirred solution of 1.53 g (9.1 mmol) of allylic alcohol

$2^{7,14}$ in 50 mL of dry dichloromethane at 0 °C under an argon atmosphere was added 0.81 mL (10.0 mmol) of pyridine and 0.87 mL (10.0 mmol) of propionyl chloride. After 2 h, the reaction mixture was allowed to warm to room temperature. After an additional hour, the reaction mixture was poured into 200 mL of saturated $NaHCO_3$, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 200 mL portions), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (200 g) with 1:50 ether/petroleum ether. In this manner, there was obtained 1.85 g (91%) of the desired ester as a colorless oil: IR ($CHCl_3$) 2970, 1750 (C=O), 1375, 1180 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.70 (br s, 1 H), 4.44 (br s, 2 H, $OCH_2$), 2.35 (q, 2 H, $J$ = 8 Hz, O=CHCH$_2$), 1.3–2.2 (m, 7 H), 1.13 (t, 3 H, $J$ = 8 Hz, $CH_3$), 0.88 (s, 9 H, C($CH_3$)$_3$). Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this oil provided an analytical sample. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.04; H, 10.69.

**(5′-*tert*-Butyl-1′-cyclohexyl)methyl Buten-2-yl Ether (1).** According to the procedure of Grubbs et al.,[13b] 303 mg (1.34 mmol) of the above propionate ester 9 in 3 mL of THF was cooled to −40 °C under an argon atmosphere. To this mixture there was added 4.5 mL (1.48 mmol) of a 0.33 M solution of the "Tebbe"[13a] reagent in toluene over a 3-min period. After 1 h, the reaction mixture was allowed to warm to room temperature and stirred an additional 1.5 h. The reaction was quenched with 0.5 mL of 10% NaOH. After dilution with 100 mL of ether, the mixture was dried ($Na_2SO_4$) and then filtered through a pad of Celite. After removal of the solvent at reduced pressure, the crude residue was filtered through alumina (activity III, 30 g) with hexane. In this manner, there was obtained 257 mg (86%) of the desired enol ether as a colorless oil: IR ($CHCl_3$) 2975, 1650, 1610, 1470, 1365 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.72 (br s, 1 H, C=CHC), 4.05 (br s, 2 H, $H_2$C=C), 3.82 (br s, 2 H, $CH_2$O), 1.0–2.35 (m, 12 H), 0.88 (s, 9 H, ($CH_3$)$_3$C). Distillation [Kugelrohr, 60 °C (0.1 mmHg)] of this oil provided an analytical sample. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.16; H, 11.61.

**2-Methylene-1-(2-oxobutyl)-4-*tert*-butylcyclohexane (4).** According to the procedure of Ireland and Marshall,[6] 102 mg (0.46 mmol) of the enol ether 1 was sealed in a glass tube coated with dry KOH and heated at 142 °C for 6 h. After cooling, the crude product was diluted with ether and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with 12:1 petroleum ether/ether. In this manner, there was obtained 79.2 mg (78%) of a mixture of the two diastereomeric ketones in a ratio of 87:13 (by analytical VPC) with retention times of 9.21 and 11.83 min.,

respectively, at a column temperature of 142 °C. Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.95; H, 11.68.

A portion of this mixture was separated via preparative VPC (column temperature 160 °C) to give pure samples of the two diastereomeric ketones for 500-MHz $^1H$ NMR analysis. For the major diastereomer 4 (retention time 24 min): IR (CHCl$_3$) 2980, 1715 (C=O), 1654 (C=C) cm$^{-1}$; 500-MHz $^1H$ NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$), 1.02 (t, 3 H, $J$ = 7 Hz, CH$_3$), 1.09 (dddd, 1 H, $J$ = 12, 12, 3.5, 5.0 Hz, H-6$_{ax}$), 1.21 (dddd, 1 H, $J$ = 12, 12, 12, 3.5 Hz, H-5$_{ax}$), 1.54 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-4), 1.60 (ddd, 1 H, $J$ = 12, 3.5, 3.5 Hz, H-6$_{eq}$), 1.69 (dddd, 1 H, $J$ = 12, 3.5, 3.5, 3.5 Hz, H-5$_{eq}$), 1.85 (dd, 1 H, $J$ = 12, 12 Hz, H-3$_{ax}$), 2.9 (ddd, 1 H, $J$ = 12, 3, 3 Hz, H-3$_{eq}$), 2.40 (dq, 2 H, $J$ = 2, 7 Hz, CH$_2$CH$_3$), 2.47 (dd, 1 H, $J$ = 7.5, 15 Hz, HCHC=O), 2.54 (dd, 1 H, $J$ = 7.5, 15 Hz, HCHC=O), 2.89 (dt, $J$ = 5, 7.5 Hz, H-1$_{eq}$), 4.61 (s, 1 H, C=CH), 4.68 (s, 1 H, C=CH). For the minor diastereomer (retention time 27 min): IR (CHCl$_3$) 2980, 1730 (C=O), 1654 (C=C) cm$^{-1}$; 500-MHz $^1H$ NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$C), 0.95 (dddd, 1 H, $J$ = 12, 12, 12, 3.5 Hz, H-6$_{ax}$), 1.06 (t, 3 H, $J$ = 7.5 Hz, CH$_3$), 1.10 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-4$_{ax}$), 1.23 (dddd, 1 H, $J$ = 12, 12, 12, 3.5 Hz, H-5$_{ax}$), 1.79 (m, 2 H, H-3$_{ax}$, H-5$_{eq}$), 1.85 (dddd, 1 H, $J$ = 12, 3.5, 3.5, 3.5 Hz, H-6$_{eq}$), 2.34 (dd, 1 H, $J$ = 7.5, 16 Hz, HCHC=O), 2.38 (m, 2 H, CH$_2$C=O), 2.46 (m, 2 H, H-3$_{eq}$, H-1$_{ax}$), 2.70 (dd, 1 H, $J$ = 16, 5.5 Hz, HCHC=O), 4.39 (s, 1 H, C=CH), 4.66 (s, 1 H, C=CH).

As a control experiment, pure cis (axial) 4 was resubjected to the reaction conditions, and the material was recovered unchanged (analytical VPC).

**(5′-*tert*-Butyl-1′-cyclohexenyl)methyl Acetate (3).** To a rapidly stirred solution of 508 mg (3.0 mmol) of the allylic alcohol 2 in 20 mL of dry dichloromethane at 0 °C under an argon atmosphere was added 0.3 mL (3.6 mmol) of dry pyridine and 0.25 mL (3.6 mmol) of acetyl chloride. After 1 h, the reaction mixture was allowed to warm to room temperature, and after an additional hour, the reaction mixture was poured into 100 mL of saturated NaHCO$_3$, and the aqueous layer was extracted with ether (2 × 100 mL portions). The combined organic extracts were dried (MgSO$_4$), and after removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (50 g) with 99:1 petroleum ether/ether. In this manner, there was obtained 447 mg (76%) of the desired ester as a colorless oil: IR (CHCl$_3$) 2950, 1720, 1360, 945 cm$^{-1}$; $^1H$ NMR (CDCl$_3$) δ 5.70 (br s, 1 H, HC=CC), 4.44 (br s, 2 H, CH$_2$O), 2.04 (s, 3 H, CH$_3$C=O), 1.0–1.9 (m, 7 H), 0.88 (s, 9 H). Distillation [Kugelrohr, 55 °C (0.1 mmHg)] of this oil provided an analytical sample. Anal. Calcd for C$_{13}$H$_{22}$O$_2$: C, 74.24; H, 10.54. Found: C, 74.01; H, 10.41.

**Ethyl (4-*tert*-Butyl-2-methylenecyclohexyl)acetate (5).** According to the procedure of Johnson and Faulkner,[8] a solution of 56.8 mg (0.33 mmol) of the allylic alcohol 2[7] and triethyl orthoacetate containing 20 mg (0.16 mmol) of hexanoic acid was heated at 166 °C under an argon atmosphere. After 44 h, the excess orthoacetate was removed at reduced pressure. The crude residue was chromatographed on silica gel (10 g) with 99:1 petroleum ether/ether. In this manner, there was obtained 55 mg (68%) of a mixture of the two diastereomeric esters in a ratio of 91:9 (by analytical VPC) with retention times of 10.19 and 12.58 min, respectively, at a column temperature of 150 °C. Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.79; H, 10.88.

A portion of this mixture was separated via preparative VPC (column temperature 160 °C) to give pure samples of each diastereomeric ester suitable for 500-MHz $^1H$ NMR analysis. For the major diastereomer 5 (retention time 16 min): IR (CHCl$_3$) 2960, 1725 (C=O), 1648 (C=C) cm$^{-1}$; 500-MHz $^1H$ NMR (CDCl$_3$) δ 0.87 (s, 9 H, (CH$_3$)$_3$C), 1.09 (dddd, 1 H, $J$ = 12, 12, 3.5, 5.0 Hz, H-6$_{ax}$), 1.24 (t, 3 H, $J$ = 7.5 Hz, CH$_3$), 1.23 (m, 1 H, H-5$_{ax}$), 1.56 (dddd, 1 H, $J$ = 12, 12, 3.5, 5 Hz, H-4$_{ax}$), 1.60 (m, 1 H, H-6$_{eq}$), 1.74 (dm, 1 H, $J$ = 12, H-5$_{eq}$), 1.87 (dd, 1 H, $J$ = 12, 12 Hz, H-3$_{ax}$), 2.19 (dd, 1 H, $J$ = 12, 3.5 Hz, H-3$_{eq}$), 2.40 (dd, 1 H, $J$ = 7, 14 Hz, HCHC=O), 2.45 (dd, 1 H, $J$ = 7, 14 Hz, HCHC=O), 2.86 (dt, 1 H, $J$ = 5, 7 Hz, H-1$_{eq}$), 4.11 (q, 2 H, $J$ = 7 Hz, OCH$_2$), 4.64 (s, 1 H, C=CH), 4.71 (s, 1 H, C=CH). For the minor diastereomer (retention time 19 min): IR (CHCl$_3$) 2970, 1730 (C=O), 1645

(C=C) cm$^{-1}$; 500-MHz $^1H$ NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$C), 1.01 (dddd, 1 H, $J$ = 12, 12, 12, 3.5 Hz, H-6$_{ax}$), 1.11 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-4$_{ax}$), 1.23 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-5$_{ax}$), 1.26 (t, 3 H, $J$ = 7 Hz, CH$_3$), 1.78 (dd, 1 H, $J$ = 12, 12 Hz, H-3$_{ax}$), 1.82 (dddd, 1 H, $J$ = 12, 3.5, 3.5, 3.5 Hz, H-5$_{eq}$), 1.91 (dddd, 1 H, $J$ = 12, 3.5, 3.5, 3.5 Hz, H-6$_{eq}$), 2.24 (dd, 1 H, $J$ = 15, 7.5 Hz, HCHC=O), 2.38 (m, 2 H, H-1, H-3$_{eq}$), 2.60 (dd, 1 H, $J$ = 15, 6 Hz, HCHC=O), 4.14 (dq, 2 H, $J$ = 7, 2.5 Hz, OCH$_2$CH$_3$), 4.47 (s, 1 H, C=CH), 4.68 (s, 1 H, C=CH).

**Methyl (4-*tert*-Butyl-2-methylenecyclohexyl)acetate (6).** According to the procedure of Ireland and Willard,[9] a solution of 100 mg (0.47 mmol) of the acetate 3 and 1 mL of THF was added dropwise via a cannula to 3.5 mL (0.79 mmol) of a 0.23 M solution of LDA in THF at –78 °C under an argon atmosphere. After the mixture was stirred for 5 min, a solution of 127 mg (0.84 mmol) of *tert*-butyldimethylsilyl chloride in 1 mL of THF was added all at once. The solution was allowed to warm to room temperature and was then heated at 60 °C for 4 h. After dilution with 50 mL of water, the mixture was separated, the aqueous layer was extracted with pentane (3 × 75 mL portions), and then the combined organic extracts were dried (Na$_2$SO$_4$). After removal of the solvent at reduced pressure, the crude residue was dissolved in 3 mL of THF, and to this solution there was added 0.5 mL of 5% HCl. The resulting mixture was stirred at room temperature for 45 min and then diluted with 200 mL of 10% NaOH. After extraction with 50 mL of ether, the aqueous layer was acidified with concentrated HCl and then extracted with ether (3 × 100 mL portions). The combined organic layers were dried (MgSO$_4$) and filtered. After removal of the solvent at reduced pressure, the crude residue was esterified with excess ethereal diazomethane. The esters were chromatographed on silica gel (10 g) with 99:1 petroleum ether/ether. In this manner, there was obtained 54 mg (51%) of a mixture of the two diastereomeric esters in a ratio of 91:9 (by analytical VPC) with retention times of 8.28 and 10.40 min, respectively, at a column temperature of 140 °C. Distillation [Kugelrohr, 60 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for C$_{14}$H$_{24}$O$_2$: C, 74.95; H, 10.78. Found: C, 74.96; H, 10.73.

A portion of this mixture was separated via preparative VPC (column temperature 149 °C) to give pure samples of each diastereomeric ester suitable for 500-MHz $^1H$ NMR analysis. For the major diastereomer 6 (retention time 16 min): IR (CHCl$_3$) 2960, 1730 (C=O), 1645 (C=C), 910 cm$^{-1}$; 500-MHz $^1H$ NMR (CDCl$_3$) δ 0.87 (s, 9 H, (CH$_3$)$_3$C), 1.09 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-6$_{ax}$), 1.23 (dddd, 1 H, $J$ = 12, 12, 12, 4 Hz, H-5$_{ax}$), 1.57 (dddd, 1 H, $J$ = 12, 12, 5, 5 Hz, H-4$_{ax}$), 1.60 (m, 1 H, H-6$_{eq}$), 1.73 (dm, 1 H, $J$ = 12 Hz, H-5$_{eq}$), 1.86 (dd, 1 H, $J$ = 12, 12 Hz, H-3$_{ax}$), 2.19 (dd, 1 H, $J$ = 12, 3.5 Hz, H-3$_{eq}$), 2.42 (dd, 1 H, $J$ = 7.5, 14 Hz, HCHC=O), 2.46 (dd, 1 H, $J$ = 7.5, 14 Hz, HCHC=O), 2.85 (dt, 1 H, $J$ = 5, 7.5 Hz, H-1$_{eq}$), 3.65 (s, 3 H, OCH$_3$), 4.64 (s, 1 H, C=CH$_2$), 4.71 (s, 1 H, C=CH$_2$). For the minor diastereomer (retention time 18 min): IR (CHCl$_3$) 2980, 1730 (C=O), 1645 (C=D), 930 cm$^{-1}$; 500-MHz $^1H$ NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$C), 1.01 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-6$_{ax}$), 1.11 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-4$_{ax}$), 1.23 (dddd, 1 H, $J$ = 12, 12, 3.5, 3.5 Hz, H-5$_{ax}$), 1.78 (dd, 1 H, $J$ = 12, 12 Hz, H-3$_{ax}$), 1.82 (m, 1 H, H-5$_{eq}$), 1.91 (dddd, 1 H, $J$ = 12, 3.5, 3.5, 3.5 Hz, H-6$_{eq}$), 2.26 (dd, 1 H, $J$ = 7.5, 15 Hz, HCHC=O), 2.39 (m, 2 H, H-3$_{eq}$, H-3$_{eq}$), 2.62 (dd, 1 H, $J$ = 5.5, 15 Hz, HCHC=O), 3.67 (s, 3 H, OCH$_3$), 4.47 (s, 1 H, C=CH), 4.68 (s, 1 H, C=CH).

**Methyl Methyl(4-*tert*-Butyl-2-methylenecyclohexyl)acetates (11 and 12).** According to the procedure of Ireland and Willard,[9] a solution of 250 mg (1.1 mmol) of the propionate ester 9 and 2 mL of THF was added dropwise via a cannula to 4.7 mL (1.3 mmol) of a 0.28 M solution of LDA in 4:1 THF/HMPA at –78 °C under an argon atmosphere. After the mixture was stirred for 10 min, a solution of 202 mg (1.3 mmol) of *tert*-butyldimethylsilyl chloride in 2 mL of THF was added all at once. After the solution was stirred for an additional 5 min, it was allowed to warm to room temperature and then heated at 50 °C for 2 h. The mixture was then diluted with 200 mL of pentane and washed once with ice water (50 mL). After removal of the solvent at reduced pressure, the crude residue was dissolved in 5 mL of THF, and to this solution there was added 1 mL of 1 N HCl. The resulting mixture was stirred at room temperature for 45 min and then diluted with 50 mL of 1 N NaOH. After extraction with

pentane (50 mL), the aqueous layer was acidified with 6 N HCl and then extracted with ether (3 × 100 mL portions). The combined organic layers were dried (MgSO$_4$) and filtered. After removal of the solvent at reduced pressure, the crude residue was esterified with excess ethereal diazomethane. The esters were chromatographed on silica gel (20 g) with 98:2 petroleum ether/ether. In this manner, there was obtained 164 mg (62%) of a mixture of the diastereomeric esters **11** and **12** in a ratio of 87:13 (by analytical VPC) with retention times of 7.65 and 10.64 min, respectively, at a column temperature of 150 °C. Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.41; H, 10.89.

A portion of this mixture was separated via preparative VPC (column temperature 156 °C) to give pure samples of the esters **11** and **12** suitable for 500-MHz $^1$H NMR analysis. For the major diastereomer **11** (retention time 17 min): IR (CHCl$_3$) 2970, 1730 (C=O), 1650 (C=C) cm$^{-1}$; 500-MHz $^1$H NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$C), 1.09 (m, 2 H, H-5 and H-6$_{ax}$), 1.13 (d, 3 H, J = 7.5 Hz, CH$_3$), 1.44 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4$_{ax}$), 1.58 (m, 1 H, H-5$_{eq}$), 1.92 (m, 2 H, H-6$_{eq}$ and H-3$_{ax}$), 2.18 (dd, 1 H, J = 12, 3.5 Hz, H-3$_{eq}$), 2.36 (dd, 1 H, J = 11, 5 Hz, H-1$_{eq}$), 2.73 (dq, 1 H, J = 11, 7.5 Hz), 3.58 (s, 3 H, OCH$_3$), 4.59 (t, 1 H, J = 1 Hz, C=CH$_2$), 4.62 (t, 1 H, J = 1 Hz, C=CH$_2$). For the minor diastereomer **12** (retention time 21 min): IR (CHCl$_3$) 2960, 1730 (C=O), 1645 (C=C) cm$^{-1}$; 500-MHz $^1$H NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$C), 0.99 (dddd, 1 H, J = 12, 12, 12, 3.5 Hz, H-6$_{ax}$), 1.11 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4$_{ax}$), 1.18 (d, 3 H, J = 7 Hz, CH$_3$), 1.78 (dd, 1 H, J = 12, 12 Hz, H-3$_{ax}$), 1.86 (dm, 1 H, J = 12 Hz, H-5$_{eq}$), 1.94 (dddd, 1 H, J = 12, 3.5, 3.5, 3.5 Hz, H-6$_{eq}$), 2.28 (m, 1 H, H-6$_{eq}$), 2.35 (ddd, 1 H, J = 12, 3.5, 3 Hz, H-3$_{eq}$), 2.70 (dq, 1 H, J = 7.5, 7.5 Hz, HCC=O), 3.67 (s, 3 H, OCH$_3$), 4.53 (s, 1 H, C=CH$_2$), 4.54 (s, 0.25 H, C=CH$_2$), 4.70 (s, 1 H, C=CH$_2$), 4.77 (s, 0.25 H, C=CH$_2$). This is a 4:1 mixture (determined by NMR) of the R* and S* isomers at the C-2 methyl center.

**Methyl Methyl(4-*tert*-butyl-2-methylenecyclohexyl)acetates (11 and 12). Enolization without HMPA.** According to the procedure of Ireland and Willard,[9] a solution of 250 mg (1.1 mmol) of the propionate ester **9** and 2 mL of THF was added dropwise via a cannula to 4.7 mL (1.3 mmol) of a 0.28 M solution of LDA in THF at −78 °C under an argon atmosphere. After the mixture was stirred for 10 min, a solution of 202 mg (1.3 mmol) of *tert*-butyldimethylsilyl chloride in 3 mL THF containing 1.0 mL of HMPA was added all at once. After the solution was stirred for an additional 5 min, it was allowed to warm to room temperature and then heated at 50 °C for 2 h. The mixture was then

diluted with 200 mL of pentane and washed once with ice–water (50 mL). After removal of the solvent at reduced pressure, the crude residue was dissolved in 5 mL of THF, and to this solution there was added 1 mL of 1 N HCl. The resulting mixture was stirred at room temperature for 45 min and then diluted with 50 mL of 1 N NaOH. After extraction with pentane (50 mL), the aqueous layer was acidified with 6 N HCl and then extracted with ether (3 × 100 mL portions). The combined organic layers were dried (MgSO$_4$) and filtered. After removal of the solvent at reduced pressure, the crude residue was esterified with excess ethereal diazomethane. The esters were chromatographed on silica gel (20 g) with 98:2 petroleum ether/ether. In this manner, there was obtained 177 mg (67%) of a mixture of the diastereomeric esters **11** and **12** in a ratio of 71:29 (by analytical VPC) with retention times of 7.68 and 10.01 min, respectively, at a column temperature of 150 °C.

A portion of this mixture was separated via preparative VPC (column temperature 156 °C) to give pure samples of the esters **11** and **12** suitable for 500-MHz $^1$H NMR analysis. For the major diastereomers **11** (retention time 17 min): IR (CHCl$_3$) 2970, 1730 (C=O), 1650 (C=C) cm$^{-1}$; 500-MHz $^1$H NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$C), 1.03 (d, 3 H, J = 7.5 Hz, CH$_3$), 1.11 (m, 2 H, H-5 and H-6$_{ax}$), 1.13 (d, 3 H, J = 7.5 Hz, CH$_3$), 1.30 (dddd, 1 H, J = 12, 12, 12, 3.5 Hz, H-5$_{ax}$), 1.47 (m, 2 H, H-4$_{ax}$), 1.66 (m, 2 H, H-3$_{ax}$), 1.96 (m, 2 H, H-6$_{eq}$), 2.18 (dd, 2 H, J = 12, 3.5 Hz, H-3$_{eq}$), 2.36 (dd, 1 H, J = 11, 5 Hz, H-1$_{eq}$), 2.39 (dd, 1 H, J = 11, 5 Hz, H-1$_{eq}$), 2.67 (dq, 1 H, J = 11, 7.5 Hz, CHC=O), 2.73 (dq, 1 H, J = 11, 7.5 Hz, CHC=O), 3.59 (s, 3 H, OCH$_3$), 3.69 (s, 3 H, OCH$_3$), 4.59 (s, 1 H, C=CH$_2$), 4.62 (s, 1 H, C=CH$_2$), 4.71 (s, 1 H, C=CH$_2$), 4.75 (s, 1 H, C=CH$_2$). This is a 1:1 mixture (determined by NMR) of the R* and S* epimers at the C-2 center adjacent to the ester function. For the minor diastereomer **12** (retention time 21 min): IR (CHCl$_3$) 2970, 1730 (C=O), 1645 (C=C) cm$^{-1}$; 500-MHz $^1$H NMR (CDCl$_3$) δ 0.86 (s, 9 H, (CH$_3$)$_3$C), 1.15 (m, 2 H, H-5, H-6$_{ax}$), 1.24 (d, 3 H, J = 7.5 Hz, CH$_3$), 1.73 (dd, 1 H, J = 12, 12 Hz, H-3$_{ax}$), 1.76 (m, 1 H, H-6$_{eq}$), 1.81 (m, 1 H, H-5$_{eq}$), 2.05 (ddd, 1 H, J = 7.5, 11, 3.5 Hz, H-1$_{ax}$), 2.36 (dd, 1 H, J = 12, 3.5 Hz, H-3$_{eq}$), 2.69 (dq, 1 H, J = 7.5, 7.5 Hz, CHC=O), 3.67 (s, 3 H, OCH$_3$), 4.54 (s, 1 H, C=CH$_2$), 4.77 (s, 1 H, C=CH$_2$).