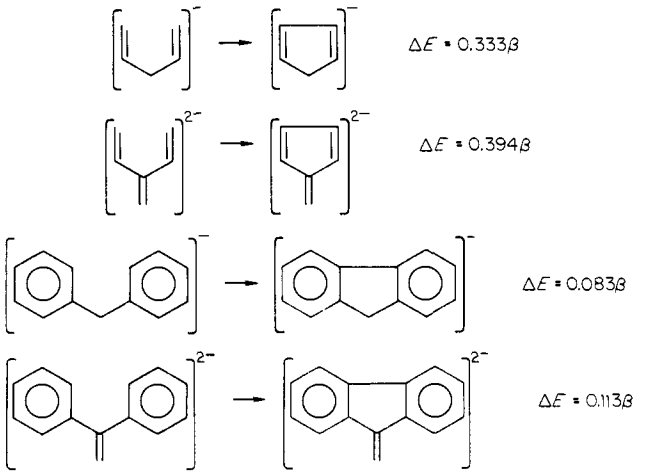
$$\Delta E = \beta_{rs} p_{rs}$$

ΔE can be easily evaluated by using data in existing tables[20,21] for molecules with isoelectronic π systems to those in question. Thus



The topological effect of changing the five-membered aromatic rings to dibenzo derivatives is to markedly decrease the π-electron stabilization afforded by cyclization, e.g., to reduce the aromaticity of the central ring. In the model isoelectronic hydrocarbon π systems the ones isoelectronic to the thiophene *S*-oxides are in both cases *more* aromatic than the ones isoelectronic to the thiophenes themselves! The result of replacing one or more carbon atoms in these systems with heteroatoms will decrease the ΔE values and, therefore, the aroamticity. Each of the π-orbitals has a plane passing through the heteroatoms. A heteroatom, more electronegative than carbon, will inductively polarize the π electrons toward it. This effect will be largest in π orbitals with non-zero coefficients at the heteroatom site. These, however, must by symmetry have coefficients with identical signs at the sites to be joined in the hypothetical cyclization. They must therefore contribute positive terms to the bond order. The inductive polarization will decrease the magnitude of these coefficients at the junction points, and thus this replacement will decrease the bond order and the aromaticity. The extent of this decrease can not be unequivocally determined. It will certainly be larger for O-substitution than for S-substitution because O is more electronegative (relative to C) than is S. The decrease will also be larger in magnitude for the smaller thiophene system than for the larger dibenzothiophene because the later has a larger π-electron source to disperse the charge. If the destabilization is sufficiently large to change the sign of the bond order the systems could be considered antiaromatic. The theoretical determination of aromaticity or antiaromaticity is very model dependent, and the question can only be finally settled by detailed thermochemical data which are now being determined.

(20) Heilbronner, E.; Bock, H. "The HMO Model and its Application"; Wiley-Interscience: New York, 1976.
(21) Coulson, C. A.; Streitweriser, A., Jr. "Dictionary of π-Electron Calculations"; W. H. Freeman: San Francisco, 1965.

Supplementary Material Available: Listings of structure factor tables for compounds I and II (34 pages). Ordering information is given on any current masthead page.

Optical Rotatory Dispersion Studies. 132.[1] Conformational Isotope Effect in Deuterium-Substituted Cyclohexanones

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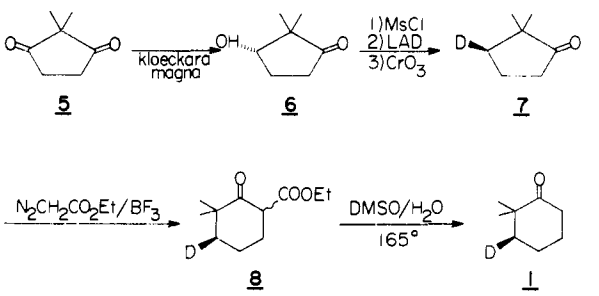
Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received June 9, 1980*

Abstract: The observed temperture dependence of the circular dichroism spectra of (3*R*)-2,2-dimethyl-3-deuteriocyclohexanone (**1**), (4*S*)-2,2-dimethyl-4-deuteriocyclohexanone (**2**), and (5*S*)-2,2-dimethyl-5-deuteriocyclohexanone (**3**) is interpreted as reflecting a conformational isotope effect which biases the equilibrium of the two chair conformers toward that conformation in which the deuterium substituent is axially oriented. With use of the estimates for the rotational strengths of the involved conformers as obtained from stereochemically rigid reference compounds, energy differences of −9.5, −4.2, and −2.7 cal/mol were calculated for the equilibria of **1**, **2**, and **3**, respectively. Empirical force field calculations show that the configuration of 2,2-dimethylcyclohexanone is slightly distorted from the symmetrical chair form. With use of the smaller nonbond interaction for C···D and H···D, energy differences were calculated for **1**, **2**, and **3** which are in qualitative agreement with the experimental ones.

Introduction

In two preliminary communications[2,3] we have reported the temperature-dependent circular dichroism spectra of four deuterium-substituted cyclohexanones, (3*R*)-2,2-dimethyl-3-deuteriocyclohexanone (**1**), (4*S*)-2,2-dimethyl-4-deuteriocyclohexanone (**2**), (5*S*)-2,2-dimethyl-5-deuteriocyclohexanone (**3**), and (3*S*)-3-deuterio-4,4-dimethylcyclohexanone (**4**). We associated the observed temperature variation of the rotational strength with the presence of a steric isotope effect: in the chair ⇄ chair equilibrium the conformation with the deuterium in the axial positions becomes energetically preferred. We now report the

Scheme I



(1) For preceding paper see: Sing, L. Y.; Lindley, M.; Sundararaman, P.; Barth, G.; Djerassi, C. *Tetrahedron*, in press.
(2) Lee, S.-F.; Barth, G.; Kieslich, K.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 3965-3966.
(3) Lee, S.-F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 8010-8012.

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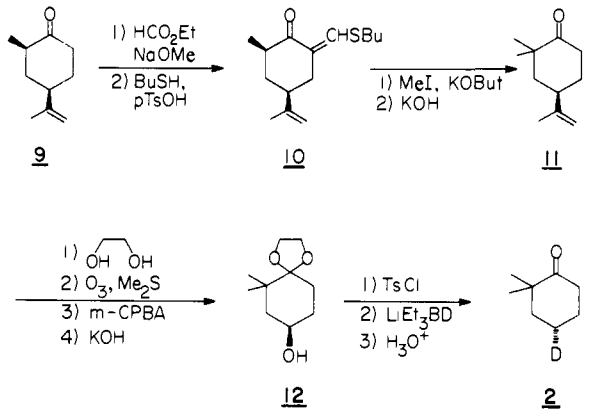
Scheme II



detailed synthesis of these compounds and the recalculation of the enthalpy differences using more accurate values for the rotational strengths of the involved conformers as obtained from a recent study.[4] We also present the results of empirical force field (EFF) calculations in an attempt to find an explanation for the variation of $\Delta H°$ with the site of substitution of deuterium in the cyclohexanone ring system.

Synthesis

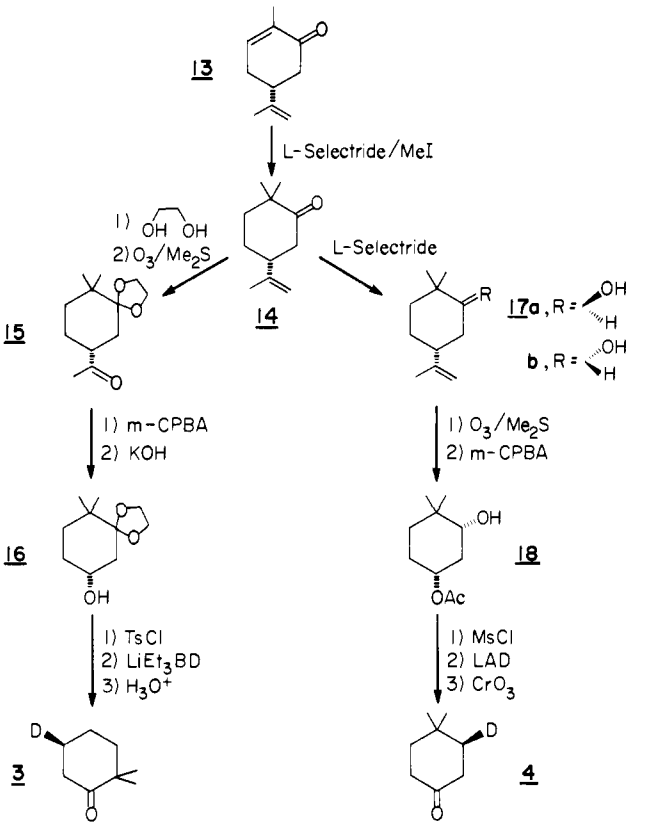
(3*R*)-2,2-Dimethyl-3-deuteriocyclohexanone (**1**) was synthesized (Scheme I) by microbiological reduction of 2,2-dimethylcyclopentane-1,3-dione (**5**) with Kloeckera magna (ATCC 20109) to (3*S*)-2,2-dimethyl-3-hydroxycyclopentanone (**6**) (enantiomeric excess >95%). The 3*S* configuration follows from the stereochemical course of similar reductions[5] with the identical organism in the steroid series. Subsequent mesylation, LAD reduction, and CrO_3 oxidation yielded ketone **7**. Ring expansion of this cyclopentanone with diazoacetate[6] gave **8** which was decarboxylated[7] to the desired cyclohexanone **1**.

(4*S*)-2,2-Dimethyl-4-deuteriocyclohexanone (**2**) was synthesized (Scheme II) by methylation (Ireland's method)[8] of (+)-(2*R*,4*R*)-2-methyl-4-isopropenylcyclohexanone (**9**)[9] (enantiomeric excess >99%) to give **11**. Ketalization, ozonolysis, Bayer–Villiger oxidation, and saponification of the intermediate acetate gave the alcohol **12** which was converted to **2** via tosylation, $LiEt_3BD$ reduction, and hydrolysis of the ketal group.

The chiral starting material for (5*S*)-2,2-dimethyl-5-deuteriocyclohexanone (**3**) was (−)-carvone **13** (enantiomeric excess >95%) (Scheme III) which was methylated with L-selectride/MeI to give **14**. Conversion to **3** was achieved by the same reaction sequence as employed in the synthesis of **2** (Scheme II). (3*S*)-3-Deuterio-4,4-dimethylcyclohexanone (**4**) was also obtained (Scheme III) from **14** via initial L-selectride reduction to the two diasteriomeric alcohols **17a,b**. After column chromatographic purification, the cis isomer **17b** was converted to **18** by ozonolysis and Bayer–Villiger oxidation. Mesylation, reduction with LAD, and subsequent CrO_3 oxidation provided **4**. Conversion of the trans alcohol (**17a**), using the same reaction steps, yielded the enantiomer of **4** which exhibited a mirror-image circular dichroism spectrum.

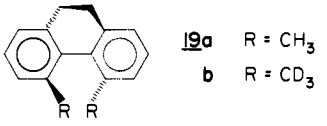
Both the Bayer–Villiger oxidation[10] and the LAD reduction[11] of the tosylates or mesylates proceed with high, but possibly not complete, stereospecificity, and the enantiomeric excess of compounds **1–4** is estimated therefore to be 90 ± 10%.

Scheme III



Results and Discussion

The steric isotope effect, i.e., the differences in "effective size" of isotopic atoms, has primarily been investigated by means of kinetic studies.[12] A relevant example is the work of Mislow et al.[13] on the rate of racemization of 9,10-dihydro-4,5-dimethylphenanthrene (**19a,b**) for which a rate ratio (k_D/k_H) of 1.17 was

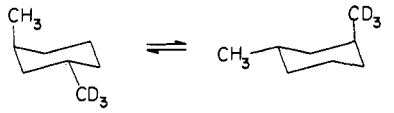


determined. From this and other work the concept has evolved of viewing the heavier isotope as being of "smaller size", i.e., that the sum of all nonbond interactions with its neighboring atoms is smaller for deuterium as compared to hydrogen. The quantitative evaluation of these terms from kinetic studies requires that the configuration of the transition state be known with certainty—information which is only rarely available.

Alternatively the steric isotope effect can be determined from the shift of a dynamic conformational equilibrium prompted by isotopic substitution, provided that the isotope occupies positions of sufficiently different nonbond strain in the participating conformers. Such an approach does not require any knowledge about the transition-state geometry and would lead directly to the conformational free-energy difference (i.e., differences in nonbond interactions). Knowing the stereochemistry of the conformers, one is then in a position to associate this value with the steric "size" difference between deuterium and hydrogen. Since these energy differences must be assumed to be very small—at best on the order of a few calories per mole—the associated equilibrium shift introduced by isotopic substitution can be expected to be less than 0.5% and therefore to be difficult to verify experimentally. Using

(4) Konopelski, J. P.; Sundararaman, P.; Barth, G · Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 2737–2745.
(5) Kosmol, H.; Kieslich, K.; Vössing, R.; Koch, H. J.; Petzold, K.; Gibian, H. *Justus Liebigs Ann. Chem.* **1976**, *701*, 198–205.
(6) Liu, H. J.; Majumdar, S. P. *Synth. Commun.* **1975**, *5*, 125–130.
(7) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957–960.
(8) Ireland, R. E.; Marshall, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 6336–6337.
(9) Takagi, Y.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 517–521. We are indebted to Dr. Takagi for a generous gift of this starting material.
(10) Mislow, K.; Brenner, J. *J. Am. Chem. Soc.* **1953**, *75*, 2318–2322.
(11) Sanderson, W. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1966**, *88*, 4185–4190.
(12) For a recent review on this subject see: Carter, R. E.; Melander, L. *Adv. Phys. Org. Chem.* **1973**, *10*, 1–27.
(13) Mislow, K.; Graeve, R.; Gordon, A. J.; Wahl, G. H., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1733–1741.

^{13}C NMR chemical shift studies, Baldry and Robinson[14] have concluded that for *trans*-1-methyl-d_3-3-methylcyclohexane (**20**)



20

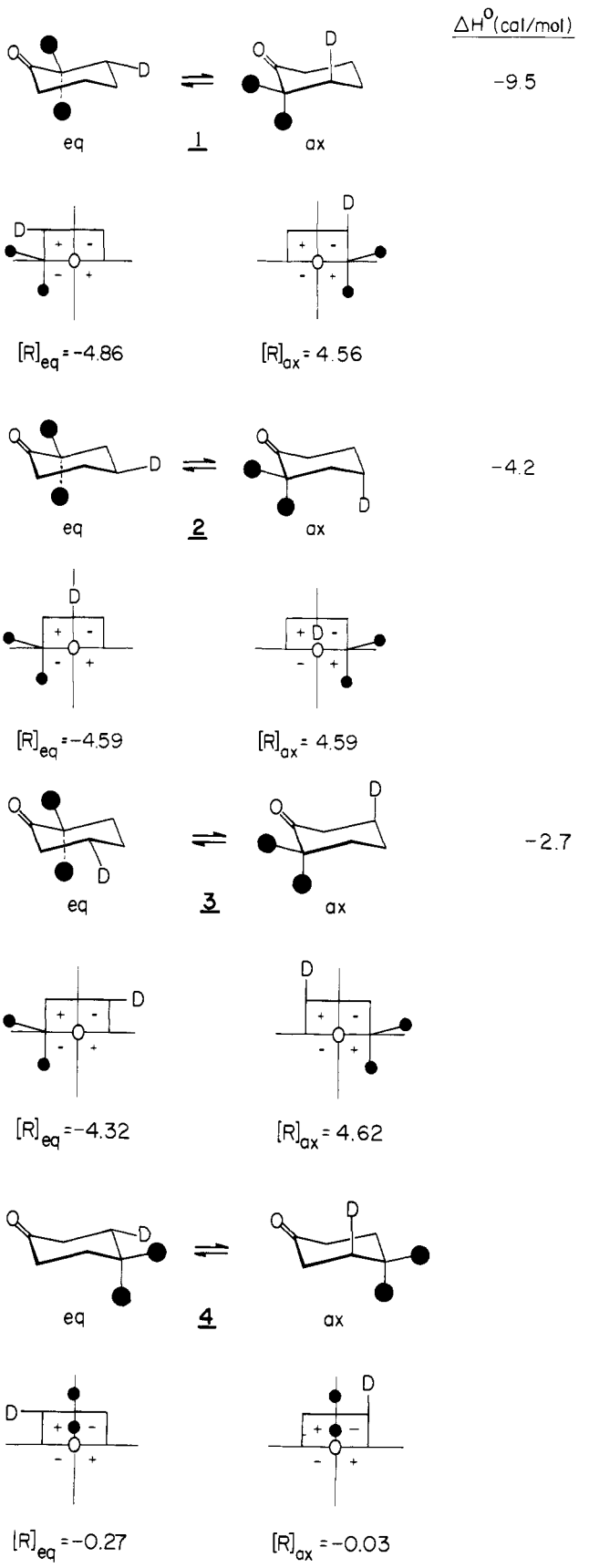
the conformation with the CD_3 substituent in the axial position (**20**ax) is favored by ca. 11 cal/mol over **20**eq. This value corresponds to an equilibrium shift of 0.5% toward **20**ax at room temperature and is in agreement with the results of the kinetic studies in that the heavier isotope behaves as being of "smaller size" and, therefore, occupying preferentially the position of larger nonbond strain (axial in this example). Two other studies[15,16] have interpreted the unusually large ^1H NMR chemical shifts introduced through deuterium substitution in terms of a conformational isotope effect but did not attempt to evaluate the conformational energy differences.

In our preliminary reports[2,3] on this subject we reported the temperature-dependent circular dichroism spectra of **1**, **2**, and **3**. The chosen molecular system is ideally suited for such an investigation. First, the molecule can be assumed to exist in a dynamic equilibrium between only two (chair) conformations having the deuterium substituent in the axial and equatorial positions respectively (Scheme IV). Second, the introduction of the α-*gem*-dimethyl group, which by itself does not contribute to any preference of one conformation over the other, causes the rotational strengths of both conformers to be *large numbers of opposite sign*. Therefore even a small change in the conformational equilibrium position (caused by variation of the temperature) will result in a measurable change of the observed rotational strength. For this reason we have termed the α-*gem*-dimethyl group a "chiral probe". Finally, good estimates for the rotational strengths of the appropriate conformers are obtainable from conformationally fixed reference compounds, thus permitting a quantitative evaluation of the enthalpy differences of the conformational equilibria (Scheme IV).

Before discussing the experimental results it is worthwhile to provide some justification for the above made assumptions—in particular the proposition that the presence of conformations other than the chair forms and/or solvent–solute interactions can be neglected—since it is clear that the analysis is valid only if the observed changes of the rotational strength with temperature ($[R]_{obsd}^T$) are solely, or at least predominantly, associated with the proposed equilibrium shifts between the chair conformations as shown in Scheme IV. Alternative conformational forms for the cyclohexanone ring are the twist and boat forms. Since the twist conformations can exhibit rotational strengths of extraordinary amplitude,[4,17,18] it is conceivable that the presence at room temperature of even a few percent of such a nonchair conformation could be responsible for the observed temperature changes of the rotational strength. From EFF calculations the energy difference between the twist and chair conformations of cyclohexanone was calculated[19] to be 2.72 kcal/mol (corresponding to the presence of 1% twist form at room temperature). Even if one assumes that this value is reduced through the introduction of the *gem*-dimethyl group to say 1 kcal/mol, the expected variation of $[R]_{obsd}^T$ with temperature would be very different from the observed one; i.e., the main intensity changes would take place between room temperature and 150 K at which temperature the twist form would be "frozen out" from 15 to less than 4%. Experimentally, however, the main intensity changes take place between 150 and 77 K (Table I).

To assess the possibility of temperature-dependent solvent–solute equilibria, which also have been shown[20] to give rise to temper-

Scheme IV



(14) Baldry, K. W.; Robinson, M. J. T. *Tetrahedron* **1977**, *33*, 1663–1668.
(15) Calvert, R. B.; Shaply, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 7726–7727.
(16) Anet, F. A. L.; Dekmezian, A. H. *J. Am. Chem. Soc.* **1979**, *101*, 5449–5451.
(17) Djerassi, C.; Warawa, E. J.; Berdahl, J. M.; Eisenbraun, E. J. *J. Am. Chem. Soc.* **1961**, *83*, 3334–3335.
(18) Djerassi, C.; Klyne, W. *Proc. Natl. Acad. Sci. U.S.A.* **1962**, *48*, 1093–1098.
(19) Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1972**, *28*, 1173–1190.

Table I. Experimental Rotational Strengths[a]

compd	$[R]_{obsd}^{T}$ (T, K)[b]
1	−0.103 (293), −0.100 (253), −0.072 (163), −0.020 (93), 0.003 (77)
2	0.011 (293), 0.015 (228), 0.018 (180), 0.026 (128), 0.034 (113), 0.058 (77)
3	0.134 (293), 0.133 (203), 0.141 (133), 0.161 (77)
4	−0.112 (293), −0.108 (77)

[a] $[R]_{obsd}^{T}$ is the reduced rotational strength (integration range 340–240 nm) as obtained from the circular dichroism date given in ref 2 and 3. [b] The experimental error of these values is estimated to be ±0.005.

ature-dependent circular dichroism spectra, we have carried out all measurements in two solvent systems of different polarity, namely, EPA (ether, isopentane, ethanol) and IPM (isopentane, methylcyclohexane), a polar and nonpolar solvent, respectively. Within the experimental error the same temperature dependence of $[R]_{obsd}^{T}$ was observed. Although this does not necessarily exclude the possibility of the presence of a solvent–solute equilibrium, it makes it unlikely.

In order to provide further evidence for the correctness of our basic assumption, we have measured the circular dichroism spectrum of **4**, a compound which is structurally similar to **1**, **2**, and **3**. However, since the *gem*-dimethyl group is now located in the 4-position, i.e., in the symmetry plane of the octant diagram (Scheme IV), it does not act as a "chiral probe" and the rotational strengths of the conformers **4**ax and **4**eq are now only determined by the contributions from the β-axial and β-equatorial deuterium atoms; the differences between these values are smaller by a factor of ca. 38 as compared to the ones for the conformers of **1**, **2**, and **3**. Consequently, even if a similar energy difference exists for **4**ax/**4**eq as compared to the 2,2-dimethyl isomers **1**–**3**, the expected change of $[R]_{obsd}^{T}$ between room temperature and 77 K of **4** will be lower than the experimental error limit; this is actually observed experimentally (see Table I). For the same reason no temperature dependence of $[R]$ was observed[21] with (3*S*)-3-deuteriocyclohexanone. We conclude that the sum of the evidence supports our interpretation that the temperature variation of the rotational strength of **1**, **2**, and **3** originates in the conformational equilibrium shift resulting from a steric isotope effect.

The circular dichroism spectra of **1**, **2**, **3**, and **4** at various temperatures between 293 and 77 K were already reported in our preliminary communications,[2,3] and the corresponding $[R]_{obsd}^{T}$ values are summarized in Table I. To obtain more accurate values for the rotational strengths of the conformers, we have recently[4] reported the circular dichroism spectrum of (*R*)-2,2-dimethyl-4-*tert*-butylcyclohexanone and have used the rotational strength of this conformationally rigid molecule as a reference value for the octant contribution of an α-*gem*-dimethyl group (Table II). Using this value in conjunction with the octant contributions of deuterium in the various positions[22,23] with respect to the carbonyl group, we arrive at the estimates for $[R]_{ax}$ and $[R]_{eq}$ listed underneath each octant diagram representation (Scheme IV) of the various chair conformations of **1**, **2**, **3**, and **4**. With these values we have recalculated $\Delta H°$ from a linear least-squares fit to the data points in an Arrhenius diagram (Figure 1) and listed in Table III by using the relationships (1) and (2), where c_{ax} and k are the mole

$$c_{ax} = ([R]_{obsd}^{T} - [R]_{eq})/([R]_{ax} - [R]_{eq}) \quad (1)$$

$$K = c_{ax}/(1 - c_{ax}) \quad (2)$$

Table II. Substituent Octant Contributions, δ[R], in Cyclohexanone

substituent	δ[R]	lit. ref
α-dimethyl	4.59 (con)[a]	4
γ-dimethyl	0.0	assumed
β_{ax}-deuterium	0.03 (con)[a]	22
β_{eq}-deuterium	0.27 (dis)	23
γ-deuterium	0.0	assumed

[a] con = consignate and dis = dissignate. The meaning of this nomenclature has been defined by: Klyne, W.; Kirk, D. N. *Tetrahedron Lett.* 1973, 1483–1486; i.e., a group or atom is termed consigate when the sign of its contribution to the rotational strength is equal to the sign of the octant in which it is located and vice versa. It should be pointed out that, since the experimentally determined rotational strength can be considered as resulting from the sum of contributions from all atoms, the consignate/dissignate nomenclature is based on a relative scale with the contribution from hydrogen arbitrarily set to zero (see: Kirk, D. N. *J. Chem. Soc., Perkin Trans. 1* 1976, 2171–2177). In the case of a molecule which owes its chirality to deuterium substitution the assignment of deuterium as a dissignate perturber can therefore equally be expressed by stating that the octant contribution from deuterium is smaller as compared to that of hydrogen at the same or the mirror-image position within the octant diagram.

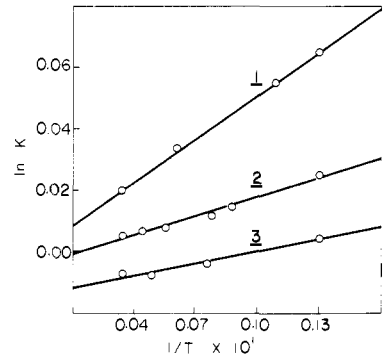


Figure 1. Arrhenius plots for (3*R*)-2,2-dimethyl-3-deuteriocyclohexanone (**1**), (4*S*)-2,2-dimethyl-4-deuteriocyclohexanone (**2**), and (5*S*)-2,2-dimethyl-5-deuteriocyclohexanone (**3**). The equilibrium constants *K* were obtained from the rotational strengths at various temperatures (given in Table I, using eq 1 and 2).

fraction of the axial conformer and the equilibrium constant, respectively. The good linearity of the data points represents a further validation for the assumption that we are dealing with a two-state equilibrium.

All three examples (Table III) display negative enthalpy values—in other words the conformation with the deuterium in the axial position is energetically preferred over the alternative one with equatorial deuterium. Thus, this result is entirely consistent with the interpretation that the isotope of "smaller size" (deuterium) preferentially occupies the position of larger nonbond strain, in these examples the axial position.

Quantitatively the largest energy difference is found for the 3(β)-position (compound **1**) and the smallest for the 5(β′)-position (compound **3**). From other studies[23–25] it is well-known that the α, β, and γ positions of cyclohexanone are not equivalent as far as the energy difference between an axial and equatorial substituent is concerned; e.g., for a methyl group values of −1.6, −0.6, and −1.1 kcal/mol have been determined experimentally for those respective positions. In one respect, the energy differences obtained for **1**–**3** are not readily interpretable—why is $\Delta H°$ for the β-position (**1**) 3.5 times as large as for the β′-position (**3**)—since the additional gauch interactions with the α-*gem*-dimethyl group (one for the β-axial and two for the β-equatoriol position) would

(20) Rassat, A. (pp 314–328); Moscowitz, A. (pp 329–334) In "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry"; Snatzke, G., Ed.; Heyden & Son: London, 1967.
(21) Djerassi, C.; VanAntwerp, C. L.; Sundararaman, P. *Tetrahedron Lett.* **1978**, 535–538. The magnitude of the Cotton effect ([θ] = 48) of (3*S*)-3-deuteriocyclohexanone as reported in this paper has been found to be too low. Repetition of the synthesis and measurement gave a value of [θ] = 160.
(22) Sundararaman, P.; Djerassi, C. *Tetrahedron Lett.* **1978**, 2457–2460. Errata: *Ibid.* **1979**, 4120.
(23) Edgar, M. T.; Barth, G.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 2680–2684.
(24) Eliel, L. E. "Stereochemistry of Carbon Compounds"; McGraw-Hill: London, 1962, p 240.
(25) Heywood, P. J.; Rassing, J. E.; Wyn-Jones, E. *Adv. Mol. Relaxation Processes* **1975**, *6*, 307–317.

Table III. Experimental and Calculated Conformational Energy Differences

compd	exptl			calcd[b]		
	$\Delta H°$,[a] cal/mol	% axial conformer 293 K	% axial conformer 77 K	shorter C-D only	smaller deuterium nonbond interact	shorter C-D plus smaller nonbond interact
1	−9.5	50.41	51.55	10	−76	−62
2	−4.2	50.18	50.69	−10	−84	−94
3	−2.7	50.12	50.44	10	−55	−56
2,2-dimethyl-6-deuteriocyclohexanone				−18	−127	−146

[a] The error of $\Delta H°$ is estimated to be approximately 10%. [b] The calculations were carried out with the program MOLBD2 described by: Boyd, R. H. *J. Chem. Phys.* **1968**, *49*, 2574-2583. The parameters for the bond deformation modes were taken from ref 19 and those for the nonbond interactions from ref 28.

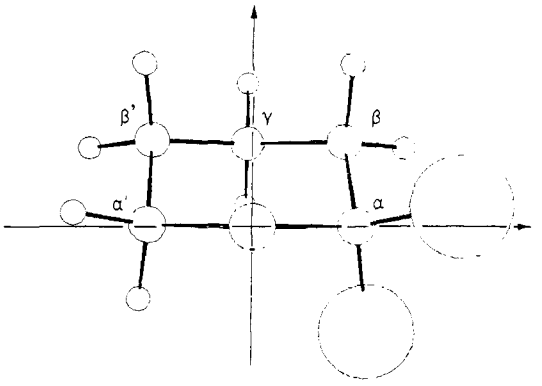


Figure 2. Energy minimum configuration for 2,2-dimethylcyclohexanone as obtained by EFF calculations. The molecule is viewed along the C=O bond, and the methyl groups are represented as large circles. (The atomic coordinates are available on request from the authors.)

seem to make the β-equatorial/β-axial energy difference smaller rather than larger as compared to the case for the β'-position.

To gain a more detailed insight into the stereochemical situation, we have carried out EFF calculations[26] on 2,2-dimethylcyclohexanone, whose energy minimum configuration is reproduced in Figure 2. The results indeed reveal a small distortion of the chair; in particular the dihedral angle between the α-equatorial methyl group and the β-axial hydrogen is found to be narrowed by 11.8° from its tetrahedral value of 60° and the corresponding angle to the β-equatorial hydrogen was found to be 68.3°. The calculations reveal that the β-axial position receives additional nonbond strain causing the axial vs. equatorial energy difference to be larger as compared to the β'-position. Since EFF calculations have been shown to reproduce conformational energy differences quite accurately,[27-29] we have made an attempt to calculate the energy differences for compounds **1**, **2**, and **3**. This approach requires some physically reasonable assumptions about the differences between hydrogen and deuterium. The force field as employed in these calculations is commonly[26] separated into bond deformation (bond stretch, bend, and twist) and nonbond interactions. In order to simulate the "size" differences between hydrogen and deuterium, we have made the following two approximations. (a) The equilibrium bond length of the C-D bond was shortened by 0.02 Å vs. the corresponding C-H bond length by adjustment of parameter B in eq 3, where U_{st} is the bond stretch

$$U_{st}\ (\text{kcal/mol}) = (144)(0.5)A(R_{ij} - B)^2 \qquad (3)$$

potential, R_{ij} is the internuclear distance, and A and B are the bond force constant and equilibrium distance, respectively. (b) The nonbond interactions between C···D and H···D were reduced as compared to those for the C···H and H···H interactions. The

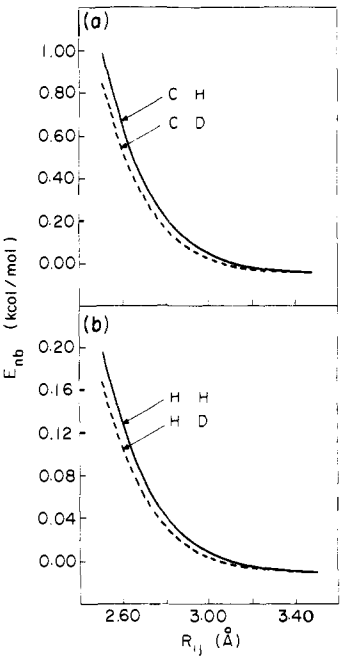


Figure 3. (a) Functional plot for the Buckingham eq 4 employed for the nonbond interactions between C···H (A = 135.40, B = 3.75, C = 1.076) and C···D (A = 121.90, B = 3.75, C = 1.076) interactions. (b) Same for the H···H (A = 14.72, B = 3.40, C = 0.3333) and H···D (A = 13.25, B = 3.40, C = 0.3333) interactions.

nonbond potential U_{nb} is described by a three-parameter Buckingham equation, eq 4, where A, B, and C are empirically chosen

$$U_{nb}\ (\text{kcal/mol}) = 144[A \exp(-BR_{ij}) - C/R_i^6] \qquad (4)$$

parameters. Reducing the magnitude of A results in a "softer" nonbond interaction, i.e., a smaller potential energy for a given atomic distance R_{ij}. The chosen values for deuterium and hydrogen and the corresponding potential energy functions are shown in parts a and b of Figure 3. Approximation a was intended to simulate the experimentally found[30] shorter equilibrium bond distance (Δ = 0.004 Å) resulting from the anharmonicity of the stretch potential, whereas approximation b was introduced to reflect the smaller vibrational amplitudes (experimental Δ = 0.01 Å)[30] between C-D as compared to the C-H bond. In order to assure computational accuracy, we have exaggerated the "size" differences between hydrogen and deuterium and place therefore no particular significance to the magnitude of the computed energy differences but rather wish to emphasize the relationship between them. We performed the EFF calculations on the conformers of **1**, **2**, and **3** (Scheme IV) introducing each assumption separately and in combination (see Table III). Whereas assumption a led to partial disagreement with the experimental values (note that for **1** and **3** the conformations with the deuterium in the equatorial

(26) For a recent review article see: Altona, C.; Faber, H. D. *Fortschr. Chem. Forsch.* **1974**, *45*, 1-38.
(27) Engler, E. M.; Andose, J. D.; Schleyer, P. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005-8025.
(28) Fitzwater, S.; Bartell, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 5107-5115.
(29) Osawa, E.; Collins, J. B.; Schleyer, P. R. *Tetrahedron* **1977**, *33*, 2667-2675.
(30) Bartell, L. S.; Kuchitsu, K.; DeNeui, R. J. *J. Chem. Phys.* **1961**, *35*, 1211-1218.

positions are predicted to be of lower energy), assumption b alone or in combination with a leads to a qualitative agreement in that a negative energy difference is obtained for all three deuterated ketones. Although ΔE for the β-position (**1**) is calculated to be somewhat larger as compared to the β'-position (**3**), the difference is considerably smaller than found experimentally. Nevertheless, considering the crudeness of the applied approximations, the agreement between experimental and calculated energy differences seems acceptable. Table III also includes the calculated energy difference for the as yet undescribed 2,2-dimethyl-6-deuteriocyclohexanone (with the deuterium substituent in the α'-position) which is calculated to possess the largest value of all compounds so far investigated. It would be interesting to verify this prediction through synthesis.

Conclusion

The experiments described in this paper again offer dramatic proof for the sensitivity and utility of chiroptical methods such as circular dichroism for the detection and quantitative analysis of conformational changes. The use of "chiral probes" such as the α,α-dimethyl grouping may find utility in other stereochemical problems, and experiments are under consideration to examine the scope of this tool.

Experimental Section

Magnetic resonance spectra were determined on a Varian T-60 and infrared spectra on a Perkin-Elmer 700A spectrometer. The mass spectra were recorded on an AEI MS-9 spectrometer and a Varian MAT-711 instrument interfaced with a Hewlett-Packard gas chromatograph through an all-glass Watson-Bieman molecular separator. The circular dichroism spectra were recorded on a JASCO J-40 circular dichrometer using an earlier[31] described cell for the variable-temperature measurements. Rotations were taken on a Perkin-Elmer 141 polarimeter. The elemental analyses were performed by the Microanalytical Laboratory at the Department of Chemistry of Stanford University.

Since the rotational strengths of compounds which owe their asymmetry to isotopic substitution are at least 1–2 orders of magnitude smaller as compared to those of other chiral molecules, particular care was taken in the purification of **1–4** since even trace amounts of optically active impurities could lead to large errors in the determined CD spectra. Therefore, compounds **1–4** were purified repeatedly by GLC, and their purity was considered as satisfactory when no changes in the CD spectral amplitudes were observed after each purification step.

(3*S*)-2,2-Dimethyl-3-hydroxycyclopentanone (6).[32] A 500-mL fermentation medium consisting of 50 g/L commercial glucose and 20 g/L cornsteep liquor in a 2-L Erlenmeyer flask was inoculated with Kloeckera Magna (ATCC 20109) rinsed off with 3 mL of physiological NaCl solution. The mixture was shaken for 48 h at 30 °C at 140 revolutions per min; 250 mL of this culture was used as seed for a 20-L jar fermentor filled with 15 L of the same medium. The fermentor was stirred at 200 revolutions per min under aeration. After 24-h germination time 900 mL of the culture was transferred to a second fermentor started under the same conditions. After 6 h 17.5 g of 2,2-dimethylcyclopentane-1,3-dione (**5**)[33] dissolved in 50 mL of DMF was added and the aeration rate reduced. After an additional 14 h the fermentation was terminated and the biomass removed by centrifugation. The broth was extracted three times with 5 L of ethyl acetate, and the combined extracts were concentrated under reduced pressure at 35 °C. The oily residue was purified by column chromatography on silica gel (hexane, methylene chloride) to yield 11.7 g of 6: bp 67–70 °C (0.7mmHg); $[\alpha]^{22}_D$ +8° ($CHCl_3$); IR (neat) 3420, 2870–2970, 1730 cm^{-1}; ^1H NMR (pyridine-d_5) δ 1.09 (s, 3 H), 1.24 (s, 3 H), 1.93–2.71 (m, 4 H), 4.18 (m, 1 H); mass spectrum, m/z (relative intensity) 128 (M^+, 43), 126 (8), 124 (5), 110 (8), 109 (2), 108 (**4**), 95 (16), 85 (14), 83 (12), 73 (12), 72 (14), 70 (10), 69 (100).

(3*R*)-2,2-Dimethyl-3-deuteriocyclopentanone (7). To a stirred solution of 6 (1.24 g, 9.69 mmol) in CH_2Cl_2 (30 mL) containing 2 mL of triethylamine was added dropwise methanesulfonyl chloride (1.24 g, 10.8 mmol) at 0 °C. After a stirring period of 30 min the reaction mixture was worked up by standard procedures to yield 2.28 g of the mesylate as an oil. This product was dissolved in anhydrous ether (10 mL) and added to a slurry of LAD (1.2 g) in ether (30 mL) at 0 °C. The reaction was stirred at 0 °C for 10 h followed by 3 h at room temperature. Excess LAD was decomposed with wet ether/water, and after filtration and evaporation of the solvent a mixture of alcohols was obtained (870 mg). Without further purification the mixture was subjected to a Jones oxidation to give 110 mg of **7** after gas chromatographic purification (15% Carbowax on Chromosorb W): IR ($CHCl_3$) 2200, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 6 H), 1.92 (m, 3 H), 2.26 (m, 2 H); mass spectrum, m/z (relative intensity) 113 (M^+, 16), 98 (5), 95 (3), 80 (5), 70 (10), 69 (11), 57 (100), 56 (35) (isotopic purity: 98%).

Ethyl (3*R*)-2,2-Dimethyl-3-deuteriocyclohexanone-6-carboxylate (8). To a solution of **7** (300 mg) in anhydrous ether (15 mL) containing BF_3–ether (0.5 mL) at 0 °C was added dropwise ethyldiazoacetate (0.5 mL). The solution was stirred at room temperature for 4 days. The reaction mixture was diluted with ether and then washed with aqueous $NaHCO_3$ and water. After the mixture was dried and evaporated, 470 mg of the β-keto ester **8** was obtained: IR ($CHCl_3$) 1750, 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3 H), 1.07 (s, 3 H), 1.25 (t, 3 H), 2.28 (m, 2 H), 3.58 (q, 1 H), 4.15 (q, 3 H); mass spectrum, m/z (relative intensity) 127 (M^+ – 72).

(3*R*)-2,2-Dimethyl-3-deuteriocyclohexanone (1). A solution of **8** (470 mg) and sodium chloride (138 mg) in Me_2SO (2.5 mL) containing 0.1 mL of water was heated to 180–185 °C for 3.5 h. Thereafter the reaction mixture was cooled, diluted with ether, washed, and dried and the solvent evaporated to yield 138 mg of **1**. Final purification was carried out by gas chromatography (15% Carbowax on Chromosorb W); IR ($CHCl_3$) 2200, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 6 H), 1.66 (m, 5 H), 2.36 (m, 2 H); mass spectrum, m/z (relative intensity) 127 (M^+, 43), 84 (16), 83 (100), 82 (88), 70 (30), 69 (25), 68 (52), 57 (46), 56 (51), 55 (18).

(+)-2,2-Dimethyl-4-isopropenylcyclohexanone (11). To a solution of *t*-BuOK prepared from K (3.7 g) and *t*-BuOH (100 mL) was added **10** (5 g, 0.02 mol) prepared from **9**, as described by Takagi et al.,[9] and the reaction mixture was stirred under N_2 for 10 min at room temperature. Subsequently MeI (4 mL) was added dropwise over a period of 5 min and stirring was continued for another 30 min. After standard workup an oil was obtained (5.3 g) which was dissolved in a mixture of 20 mL of 25% KOH and ethylene glycol (20 mL) and refluxed under N_2 for 48 h. The cooled reaction mixture was diluted with water and extracted with ether. The ether solution was washed with water, dried, and evaporated to yield 2.36 g of **11** which was purified by distillation (74 °C (0.4 mmHg)): IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.21 (s, 3 H), 1.73 (b s, 3 H), 4.75 (s, 2 H); mass spectrum, m/z (relative intensity) 166 (M^+, 67), 151 (4), 133 (5), 123 (11), 111 (19), 110 (77), 109 (45), 108 (3), 107 (27), 95 (50), 81 (26), 68 (100), 67 (77), 55 (43); $[\alpha]^{22}_D$ +90° (*c* 3.28, $CHCl_3$).

(4*R*)-2,2-Dimethyl-4-hydroxycyclohexanone Ethylene Ketal (12). A mixture of **11** (2 g, 12 mmol), ethylene glycol (2 mL), and *p*-TsOH (20 mg) in anhydrous benzene (40 mL) was refluxed for 2 h with continuous azeotropic removal of water. The cooled reaction mixture was diluted with ether and washed with saturated $NaHCO_3$ solution and water. After drying and evaporation of the solvent, the residue was distilled (74 °C (0.4mmHg)) to give 2.4 g of the ketal. The product was dissolved in methanol (15 mL) and the solution saturated with ozone at –78 °C until a permanent blue color was obtained. The excess ozone was removed by passing N_2 through the solution. After addition of Me_2S (0.5 mL) the solution was stirred at room temperature for 12 h. After removal of the methanol the residue was taken up in ether, the ether solution washed with brine, dried and evaporated, and the crude product (980 mg) purified by column chromatography (silica gel, EtOAc/benzene). The product was dissolved in methylene chloride (15 mL) and *m*-chloroperbenzoic acid (1.1 g) added and stirred for 24 h at room temperature. Following standard workup and chromatography on silica gel (5% EtOAc/benzene) 600 mg of the acetate was obtained as an oil; 460 mg of this product was treated with 5% KOH/MeOH (10 mL) at room temperature for 30 min. The reaction mixture was poured into water and extracted with chloroform, and the extracts were dried, washed, and evaporated to yield 360 mg of **12**: IR (neat) 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 1.03 (s, 3 H), 3.90 (s, 4 H); mass spectrum, m/z (relative intensity) 186 (M^+, 6), 168 (9), 125 (23), 114 (19), 99 (100); $[\alpha]^{22}_D$ +33.5° (*c* 4, $CHCl_3$).

(4*S*)-2,2-Dimethyl-4-deuteriocyclohexanone (2). A mixture of **12** (360 mg, 1.9 mmol) and *p*-toluenesulfonyl chloride (720 mg) in pyridine (5 mL) was stirred at room temperature for 12 h. After standard workup and chromatography (silica gel, 2% EtOAc/benzene) 600 mg of the tosylate was obtained. The product was dissolved in 10 mL of anhydrous THF and added dropwise under N_2 at 0 °C to a solution of $LiEt_3BD$ (7 mL, 1 M in THF).[34] The reaction mixture was refluxed for 24 h. After the mixture was cooled, the excess hydride was decomposed with water. The organoborane was oxidized with 10 mL of 30% H_2O_2 and 10 mL of

(31) Barth, G.; Dawson, J. H.; Dolinger, P. M.; Linder, R. E.; Bunnenberg, E.; Djerassi, C. *Anal. Biochem.* **1975**, *65*, 100–108.

(32) The microbiological reduction was carried out at the Pharma Forschung Schering AG., D1000 Berlin 65, West Germany under the direction of Dr. K. Kieslich (cf. ref 2 and 5).

(33) Agosta, W. C.; Smith, A. B. *J. Org. Chem.* **1970**, *35*, 3856–3860.

(34) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1975**, *40*, 1864–1865.

3 N NaOH for 10 min at 0 °C, the organic layer separated, and the aqueous layer extracted with pentane. The combined extracts were washed with water, most of the solvent was removed by distillation, and the residue was treated with 10% HCl (5 mL) for 12 h. The reaction mixture was diluted with ether, washed with brine, dried, and concentrated by distillation (yield 60%). Pure samples of **2** were obtained by gas chromatography (15% Carbowax on Chromosorb W): IR ($CHCl_3$) 2200, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 6 H), 2.35 (t, 2 H); mass spectrum, m/z (relative intensity) 127 (M^+, 41), 85 (6), 84 (18), 83 (100), 82 (85), 56 (60), 55 (26).

(+)-2,2-Dimethyl-5-isopropenylcyclohexanone (14). To a solution of (−)-carvone **13** (Farmers Chemical Co., Inc., $[\alpha]_D$ −60.5°) (3.75 g, 24.9 mmol) in dry THF (25 mL) under N_2 at −78 °C was added dropwise L-selectride (Aldrich, 27.4 mL) over a period of 5 min. After 1 h at −78 °C, MeI (2.0 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for another 1.5 h. The reaction mixture was poured into water and the organoborane was oxidized with 30% H_2O_2/3 N NaOH (1:1) for 10 min at 0 °C. The solution was extracted with pentane. The combined extracts were washed with water, dried, and evaporated. The crude product was chromatographed on silica gel (2% EtOAc/benzene) to give 3.53 g of **14**: IR ($CHCl_3$) 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.15 (s, 3 H), 1.75 (b s, 3 H), 4.73 (b s, 2 H); mass spectrum, m/z (relative intensity) 166 (M^+, 33), 108 (37), 95 (47), 69 (100), 68 (42), 67 (45), 55 (31); $[\alpha]^{22}_D$ +91.2° (c 11, $CHCl_3$).

(+)-2,2-Dimethyl-5-acetylcyclohexanone Ethylene Ketal (15). A mixture of **14** (7.5 g, 45 mmol), ethylene glycol (11 mL), and p-TsOH (100 mg) in dry benzene (200 mL) was refluxed in a Dean–Stark apparatus for 2 h. The solution was then cooled, diluted with water, and washed with saturated $NaHCO_3$ and water. After the mixture was dried and evaporated, the remaining liquid was distilled at 74 °C (0.4mmHg) to give 9.8 g of ketal. The product was dissolved in MeOH (180 mL) and the solution saturated with ozone at −78 °C. The excess ozone was removed by passing N_2 through the solution. The solution was stirred at room temperature for 16 h after addition of 8 mL of Me_2S. The excess Me_2S and the solvent were removed under reduced pressure. The residue was taken up in ether, washed, and dried. Solvent removal and vacuum distillation afforded 8.5 g of **15** as an oil (bp 95 °C (0.4mmHg)): IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 1.00 (s, 3 H), 2.11 (s, 3 H), 2.60 (m, 1 H), 3.97 (s, 4 H); mass spectrum, m/z (relative intensity) 212 (M^+, 3), 170 (12), 169 (100), 155 (5), 154 (13), 113 (11), 111 (14), 99 (21), 86 (13); $[\alpha]^{22}_D$ +10.6° (c 10.3, $CHCl_3$).

(−)-2,2-Dimethyl-5-hydroxycyclohexanone Ethylene Ketal (16). A mixture of **15** (6.5 g, 31 mmol) and m-chloroperbenzoic acid (11 g) in 120 mL of CH_2Cl_2 was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2, washed with 5% KOH until the solution was basic, then washed with brine, dried, and evaporated to give 7.77 g of an acetate. The crude product was treated with KOH/MeOH (3 g in 30 mL) at room temperature for 30 min. The reaction mixture was poured into water and extracted with chloroform, and the extract washed with brine, dried, and evaporated to give 5.25 g of crystalline **16** which was further purified by crystallization from ether/pentane (mp 82–83 °C): IR ($CHCl_3$) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 6 H), 3.98 (s, 4 H), 4.00 (m, 1 H); mass spectrum, m/z (relative intensity) 186 (M^+, 3), 168 (2), 116 (6), 115 (100), 114 (5), 99 (3), 87 (6), 86 (22); $[\alpha]^{22}_D$ −13.5 (c 10.2, $CHCl_3$). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.48, H, 9.74. Found: C, 64.70, H, 9.78.

(5*S*)-2,2-Dimethyl-5-deuteriocyclohexanone (3). A mixture of **16** (2 g, 10.7 mmol) and p-toluenesulfonyl chloride (4 g, 20 mmol) in 20 mL of pyridine was stirred at room temperature for 20 h. After standard workup the crude product was purified by chromatography on silica gel (5% EtOAc/benzene) to yield 3.5 g of the tosylate. The product was dissolved in 10 mL of anhydrous THF, and to the solution was added dropwise 33 mL of $LiEt_3BD$ (9 M in THF) over a period of 5 min at 0 °C under N_2. The reaction mixture was refluxed for 24 h. After the mixture was cooled, the excess hydride was decomposed with water. The solution was oxidized with 20 mL of 30% H_2O_2 and 20 mL of 3 N NaOH for 10 min at 0 °C. The organic layer was separated, the aqueous layer was extracted with pentane, and the combined extracts were washed with water, dried, and concentrated. The crude product was distilled (40 °C (0.4mmHg)) to give 1.6 g of ketal which was dissolved in 5 mL of ether and stirred with 5 mL of 10% aqueous HCl for 24 h. The reaction mixture was diluted with ether, then washed with brine, and dried. The crude product (yield 80%) was purified by gas chromatography (15% Carbowax on Chromosorb W): IR ($CHCl_3$) 2200, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 6 H), 1.66 (m, 5 H), 2.36 (m, 2 H); mass spectrum, m/z (relative intensity) 127 (M^+, 26), 84 (12), 83 (100), 82 (4), 70 (11), 69 (28), 57 (12), 56 (30), 55 (22), isotopic purity 98%.

(1*S*,5*R*)-(+)-2,2-Dimethyl-5-isopropenylcyclohexanol (17a) and (1*R*,5*R*)-(+)-2,2-dimethyl-5-isopropenylcyclohexanol (17b). To a solution of **14** (2.98 g, 17.9 mmol) in 20 mL of dry THF under N_2 at −78 °C was added 35 mL (1 M in THF) of L-Selectride. The reaction was stirred at −78 °C for 4 h. Excess hydride was decomposed with water and the organoborane oxidized with 30% H_2O_2/3 N NaOH (1:1) for 10 min at 0 °C. The solution was then extracted with pentane. The combined extracts were washed with water, dried, and concentrated. The crude residue was distilled (72–74 °C (0.2mmHg)) to give a mixture of **17a** and **17b**. This mixture was carefully separated by column chromatography on silica gel (5% EtOAc/benzene) to give 1.86 g of **17a** and 0.93 g of **17b**. **17a**: $[\alpha]^{22}_D$ +32.9 (c 7.5, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 3 H), 0.96 (s, 3 H), 3.50 (t, 1 H, J = 3 Hz), 4.70 (s, 2 H); mass spectrum, m/z (relative intensity) 168 (M^+, 1), 150 (26), 135 (18), 121 (11), 107 (43), 97 (19), 95 (39), 69 (100), 68 (43), 67 (46). **17b**: $[\alpha]^{22}_D$ +4.4 (c 6, $CHCl_3$); IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3 H), 1.00 (s, 3 H), 3.35 (dd, 1 H, J = 10, 3 Hz), 4.70 (s, 2 H); mass spectrum, m/z (relative intensity) 168 (M^+, 1), 150 (14), 135 (20), 121 (17), 107 (57), 97 (35), 95 (30), 69 (100), 68 (45), 67 (43). The stereochemistry of the hydroxyl group was assigned from the ^1H NMR spectra. The vicinal coupling constant[35] for an axial C*H*–OH proton in **17b** is larger than for **17a**. In addition, this signal for the axial proton of **17b** is located at higher field as compared to the corresponding signal of **17a**.[36,37]

(1*R*,5*R*)-(+)-2,2-Dimethyl-5-acetoxycyclohexanol (18). A solution of **17b** (0.9 g) in 30 mL of MeOH was saturated with ozone at −78 °C and the excess ozone removed by passing N_2 through the solution followed by the addition of Me_2S. After 16 h at room temperature the solution was concentrated and the residue dissolved in $CHCl_3$. The solution was washed with water, dried, and evaporated and the residue purified by chromatography on silica gel (10% EtOAc/benzene). The product (0.87 g, 5 mmol) and m-chloroperbenzoic acid (1.3 g) were dissolved in 20 mL of CH_2Cl_2 and stirred at room temperature for 2 days. The reaction mixture was diluted with CH_2Cl_2, washed with diluted aqueous KOH until basic, washed with brine, and dried. After solvent removal and chromatography on silica gel (5% EtOAc/benzene) 0.8 g of **18** was obtained as an oil: $[\alpha]^{22}_D$ −5.5 (c 5.35, $CHCl_3$); IR (neat) 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 1.00 (s, 3 H), 2.01 (s, 3 H), 3.56 (q, 1 H); mass spectrum, m/z (relative intensity) 126 (M^+, 27), 111 (19), 108 (14), 93 (16), 82 (38), 43 (100).

(3*S*)-3-Deuterio-4,4-dimethylcyclohexanone (4). To a solution of **18** (660 mg, 3.54 mmol) in CH_2Cl_2 (20 mL) containing 0.73 mL of triethylamine was added at 0 °C 609 mg of methanesulfonyl chloride. The reaction mixture was stirred at 0 °C for 1 h. After standard workup and chromatography on silica gel (2% EtOAc/benzene) 814 mg of mesylate was obtained. An aliquot of 700 mg of this product was dissolved in 5 mL of dry ether and added to a slurry of $LiAlD_4$ (400 mg) in 20 mL of dry ether. The reaction mixture was refluxed for 24 h and excess hydride decomposed with wet ether and water. After filtration and removal of the solvent the residue was dissolved in 5 mL of acetone and subjected to a Jones oxidation at 0 °C. After standard workup (yield 60%) pure samples of **4** were obtained by gas chromatography (15% Carbowax on Chromosorb W): IR ($CHCl_3$) 2200, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 6 H), 1.63 (m, 3 H), 2.33 (m, 4 H); mass spectrum, m/z (relative intensity) 127 (M^+, 42), 112 (15), 84 (19), 70 (74), 69 (100), 68 (71), 55 (71), 56 (90); isotopic purity 90%.

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(35) Schroeter, S. H.; Eliel, E. L. *J. Org. Chem.* **1965**, *30*, 1–7.
(36) Neikam, W. C.; Dailey, B. P. *J. Chem. Phys.* **1963**, *38*, 445–447.
(37) Williams, D. H.; Fleming, I. In "Spectroscopic Methods in Organic Chemistry"; McGraw-Hill: New York, 1973; p 104.