of ether. The ether extracts were combined, and the ether was removed by distillation. Concentrated aqueous ammonia (15 mL) was added to dissolve the small amount of liquid residue. The removal of liquid from the solution produced 317 mg (80%) of ammonium trifluoroacetate (mp 122–123 °C) which was dried 30 min at 100 °C under 5 mm of pressure and found to be identical with an authentic sample.

Kinetic Procedure. The concentrations of amine buffer in all solutions were maintained in large excess over that of trifluoroacetanilide in order to provide a strong buffering capacity. Except for trimethylamine, buffered solutions were prepared shortly before use by the addition of calculated amounts of standardized hydrochloric acid solution to weighed amounts of freshly distilled amine. For trimethylamine buffers, calculated amounts of standardized aqueous potassium hydroxide were added to aqueous solutions containing weighed amounts of trimethylamine hydrochloride. The water employed was doubly distilled from glass. A dilute solution of trifluoroacetanilide was prepared in ethanol. The reactions were initiated by addition of about 0.01 mL of trifluoroacetanilide solution to a cuvette containing 3 mL of amine buffer solution. The amine buffer had been previously thermostated in the Cary instrument and after momentary agitation was returned to that position where the disappearance of absorption at 262 nm was followed spectrophotometrically. Pseudo-first-order rate constants (k_{obsd}) were determined from the slopes of log $(A_0 - A_\infty)/(A_t - A_\infty)$ vs. time. All actual computations were carried out on an Olivetti-Underwood Programma 100 computer utilizing a weighted least-squares program written by Dr. Donald Tanner. Representative numbers of these computations were plotted to ensure that the reactions were indeed conducted under first-order conditions.

Acknowledgment. The financial support of the Northern Arizona University Institutional Research Committee is gratefully acknowledged.

Registry No. I, 404-24-0; trifluoroacetic anhydride, 407-25-0; aniline, 62-53-3; aniline hydrochloride, 142-04-1; ammonium trifluoroacetate, 3336-58-1; morpholine, 110-91-8; trimethylamine, 75-50-3; *n*-butylamine, 109-73-9; piperidine, 110-89-4.

Optical Rotatory Dispersion Studies. 130.[1] Additivity of Deuterium Octant Contributions in Cyclohexanone

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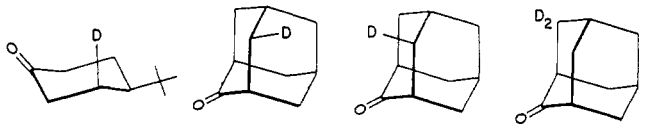
Received January 22, 1980

A comparison between the circular dichroism spectra of (4*S*)-3,3-dideuterio-4-methylcyclohexanone (1), (3*R*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (2), and (3*S*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (3) leads to the conclusion that the octant contributions of deuterium in the β-equatorial and β-axial positions of the cyclohexanone ring are additive. From the temperature-dependent circular dichroism spectra of 1 an energy difference of −1.1 kcal/mol was obtained for the conformations with the 4-methyl substituent in the axial and equatorial position, respectively.

The octant contributions of isotopes toward the rotational strength of the n → π* Cotton effect of ketones have formed the subject of several recent experimental studies.[2-5] From them a picture has emerged which permits accurate predictions of the rotational strength of such molecules by viewing the isotope as a perturber which has a certain (experimentally determined) group contribution in different locations of the molecule. This interpretation has been substantiated by recent CNDO/S calculations[5] which have previously[6] been shown to yield reliable rotational strengths for substituents such as the methyl group. In general the C–D bond has been found to make a dissignate contribution; i.e., it is a weaker perturber when compared to the C–H bond at the same or the mirror-image location of the octant diagram. In this publication we address ourselves to the question of additivity of contributions when more than one hydrogen is substituted by deuterium. As an example we have chosen to synthesize (4*S*)-3,3-dideuterio-4-methylcyclohexanone (1) (Scheme I).

The octant contributions for a β-equatorial and β-axial deuterium in the conformationally rigid cyclohexanones (3*R*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (2) (Scheme II) and (3*S*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (3)



3 4 5 6

have been reported previously by us,[3] and we compare our results with those obtained for the corresponding adamantanones 4, 5, and 6 reported by Lightner[2] and Wynberg.[4] The synthesis of 2 was repeated via a different synthetic route which resulted in a more reliable determination of its enantiomeric excess. In addition, we report the synthesis of (4*S*)-2,2,3,3,4,6,6-heptadeuterio-4-methylcyclohexanone (7) (Scheme I), the perdeuterated analogue of 1, which can formally be considered to owe its chirality to the substitution of deuterium vs. hydrogen.

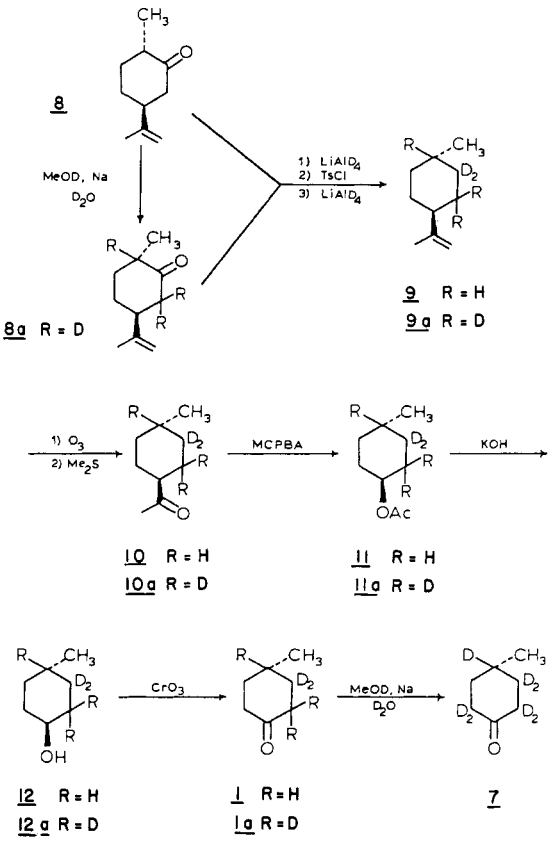
Synthesis

(4*S*)-3,3-Dideuterio-4-methylcyclohexanone (1) was synthesized from dihydrocarvone (8)[7] (containing 10–18% of the cis diastereomer) as outlined in Scheme I. Reduc-

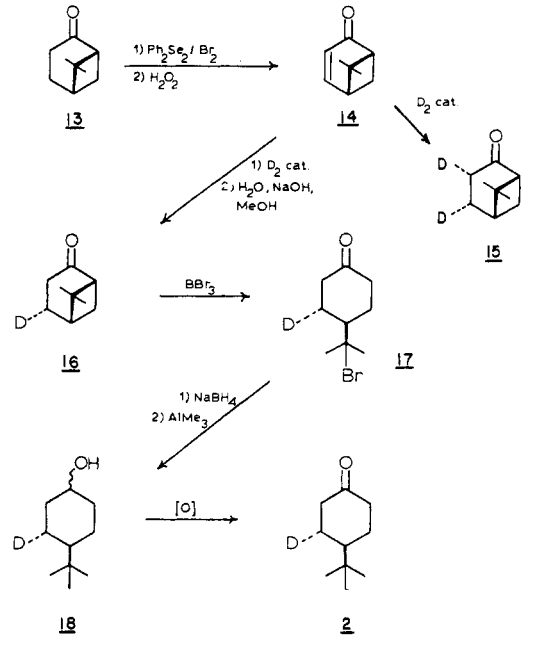
(1) For preceding paper, see: Lee, S.-F.; Edgar, M. T.; Pak, C. S.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.*, in press.
(2) Lightner, D. A.; Chang, T. C.; Horwitz, J. *Tetrahedron Lett.* **1977**, 3019–3023; errata. *Ibid.* **1978**, 696.
(3) Sundararaman, P.; Djerassi, C. *Tetrahedron Lett.* **1978**, 2457–2460; errata. *Ibid.* **1979**, 4120.
(4) Numan, H.; Wynberg, H. *J. Org. Chem.* **1978**, *43*, 2232–2236.
(5) Lightner, D. A.; Gawronski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.*, **1980**, *102*, 1983–1990.
(6) Bouman, T. D.; Lightner, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 3145–3154.
(7) Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647–4648.

0022-3263/80/1945-2680$01.00/0

Scheme I



Scheme II



tion of **8** with $LiAlD_4$, tosylation of the intermediate alcohol, and renewed reduction with $LiAlD_4$ gave **9**. Conversion of the isopropenyl group was achieved by ozonolysis[8] to **10**, Baeyer–Villiger oxidation[9] to the acetate **11**, and saponification to the alcohol **12**, which was oxidized[10] to **1**. Gas chromatographic analysis of **12** afforded a

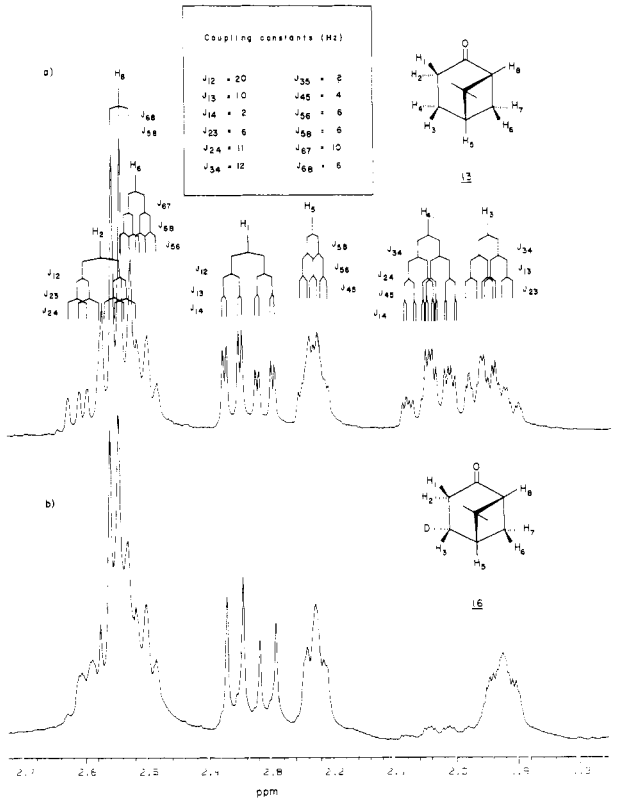


Figure 1. 360-MHz ^1H NMR spectra of (a) nopinone (**13**) and (b) nopinone-d_1 (**16**) in chloroform-*d* as solvent and tetramethylsilane as internal standard. Methyl singlets at δ 1.33 and 0.86 and H_7 resonances (d, J_{67} = 10 Hz, δ 1.58) are not shown.

quantitative value for the amount of the cis diastereomer of this compound (1.5%)[11] and therefore the enantiomeric excess of **1** (97%). By use of the same reaction sequence the heptadeuterio ketone **7** was synthesized. Deuterium exchange of the carbonyl α-protons of dihydrocarvone (**8**) led to **8a**, and the final product (**1a**) was again subjected to deuterium exchange to yield **7**. The enantiomeric excess of **7**, determined as above for **1**, was found to be 92%.

For the synthesis of (3*R*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (**2**), the reaction sequence as outlined in Scheme II was applied. (–)-Nopinone (**13**) of known optical purity[12] (90%) was converted to apoverbenone (**14**) and catalytically hydrogenated with deuterium to yield **15**; α-proton exchange then provided the monodeuterated nopinone **16**. Ring opening with BBr_3[13] led to **17** which was converted to **2** by $NaBH_4$ reduction, alkylation with $Al(CH_3)_3$, and reoxidation[10] of the intermediate alcohol **18**. Since we have previously shown[12] that the reaction steps **16** → → → **2** proceed with complete stereospecificity, it was only necessary to establish the stereospecificity of the hydrogenation reaction in order to determine the enantiomeric excess of **2**. This was achieved through a detailed analysis of the 360-MHz ^1H NMR spectra of **13**, **15**, and **16**.

Because of the complexity of the ^1H NMR spectrum of nopinone the spectra of both **15** and **16** played a major role

(8) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273–4278.
(9) Mislow, K.; Brenner, J. *J. Am. Chem. Soc.* **1953**, *75*, 2318–2322.
(10) Brown, H. C.; Garg, C. P.; Liu, K. T. *J. Org. Chem.* **1971**, *36*, 387–390.
(11) A separation of the diastereomers at this stage was not feasible on a preparative scale. That the amount of the cis diastereomer was less than in the starting material dihydrocarvone (**8**) was due to a partial separation of both in the reaction **8** → **9**; the cis diastereomer, with the hydroxyl group in the axial position, is only incompletely tosylated and is removed in the subsequent purification of the tosylate.
(12) Konopelski, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.*, **1980**, *102*, 2737–2745.
(13) Levine, S. G.; Gopalakrishnan, B. *Tetrahedron Lett.* **1979**, 699–702.

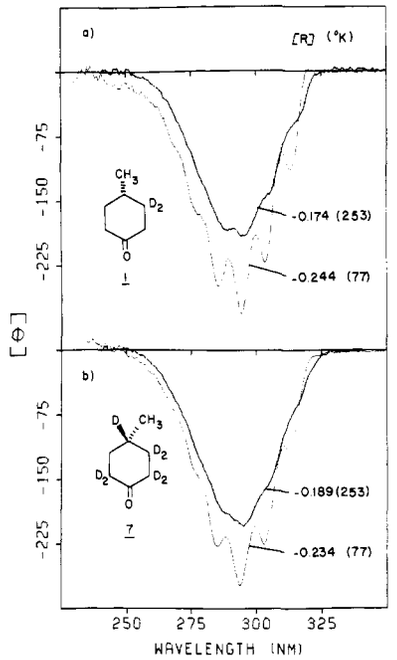


Figure 2. Circular dichroism spectra of (a) (4*S*)-3,3-dideuterio-4-methylcyclohexanone (1) and (b) (4*S*)-2,2,3,3,4,6,6-heptadeuterio-4-methylcyclohexanone (7) in EPA (ether–isopentane–ethanol 5:5:2 vvv) at room temperature (heavy line) and at 77 K (thin line). The spectra are corrected to 100% enantiomeric excess and isotopic purity.

in identifying the resonances. In chloroform-*d* protons 1, 3, 4, 5, and 7 were cleanly separated while protons 2, 6, and 8 overlap (see Figure 1). Conversely, in benzene-d_6 all protons were resolved except for H-3 and H-4. Introduction of a deuterium atom at C-4 greatly simplified the analysis of the spectra in both solvents. Comparison of the spectra of nopinone and nopinone-d_1 (**16**) immediately demonstrates the position of the H-4 resonance. Furthermore, it showed that H-3 and H-4 coincide in benzene-d_6 and that H-4 was coupled to H-1, H-2, H-3, and H-5. Decoupling experiments on nopinone and nopinone-d_1 (**16**) in benzene-d_6 established several proton interrelationships while other coupling constants were elucidated or confirmed from decoupling experiments in chloroform-*d*. The $J_{3,5}$ coupling constant and another, possibly long-range, coupling of H-3 were not determined. The complete coupling pattern of nopinone is given schematically in Figure 1a. Analysis of the spectrum of nopinone-d_1 (**16**) (Figure 1b) permits determination of the stereospecificity of the hydrogenation reaction. The signal for the H-4 proton in nopinone (**13**) is reduced to 9% compared to the signal intensity for the H-3 proton. This value is identical with the presence of nondeuterated nopinone as determined from the mass spectrum of **16**. We note further that the residual H-4 signal shows the geminal coupling constant $J_{3,4}$ of 10 Hz, supporting the interpretation that it is due to the presence of the undeuterated nopinone rather than belonging to the diastereomer of **16**. We therefore conclude that the hydrogenation proceeds with complete stereoselectivity and that the enantiomeric excess of **2** is therefore equal to that of the starting compound nopinone (**13**), i.e., 90%.

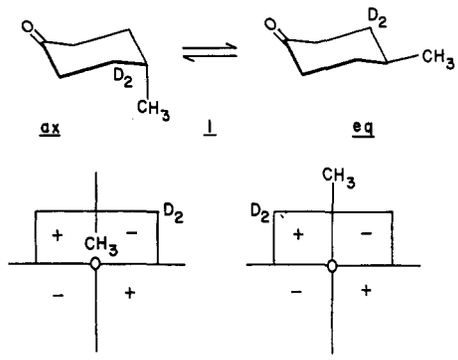
Results and Discussion

The circular dichroism spectra of 1 are shown in Figure 2a. A negative Cotton effect is observed at room temperature, the rotational strength of which decreases on lowering the temperature to 77 K. This temperature dependence is most likely associated with the shift of the conformational equilibrium toward the conformation with the 4-methyl group in the equatorial position (1-eq).

Table I. Deuterium Octant Contributions $\delta[R]$ [a]

	adamantanone [b] (compd no.)	cyclohexanone (compd no.)
β-equatorial	−0.34 (4)	−0.27 [c] (2)
β-axial	−0.07 (5)	0.03 [d] (3)
β,β	−0.35 (6)	−0.24 (1)

[a] Values are expressed in terms of the difference of the rotational strength between the contribution of the heavier isotope and the lighter one at the same or the mirror image position of the octant diagram. [b] Obtained by integration of the spectra given in ref 4 and corrected to 100% enatiomeric excess. [c] This value is 21% lower than that reported previously,[3] but due to the better determination of the enantiomeric excess of **2**, it is considered to be more reliable. [d] Taken from ref 3.



If one assumes that the rotational strengths of both conformers are only opposite in sign but are equal in intensity (the methyl substituent presumably exerts no effect since it lies in a symmetry plane of the octant diagram), an energy difference of −1.1 kcal/mol is obtained for the equilibrium of **1**, corresponding to the presence of 86.9% of 1-eq at room temperature and 99.9% at 77 K. This result is in agreement with the energy difference obtained for 4-methylcyclohexanone (−1.1 kcal/mol) by using ultrasonic relaxation spectrometry.[14]

We conclude that the rotational strength at 77 K represents the octant contribution of the deuterium substituents in the chair conformation 1-eq. As can be seen from the values given in Table I, the sum of the contributions for **2** and **3** is equal to that of **1**. Therefore, the deuterium octant contributions are found to be additive. This comparison also confirms, although indirectly, the normal octant behavior (consignate) of a β-axial deuterium found for (3*S*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (**3**).[3] Comparing these values with those reported for the β-deuterium-substituted adamantanones **4**, **5**, and **6** (Table I),[2,4] we note that for this molecular system the sum of the contributions is somewhat larger than the value for the dideuterated ketone **6**. Provided the accuracy of the data for **4**, **5**, and **6** permits such a comparison, it is conceivable that structural factors are responsible for this difference, since it is well-known[15,16] that in cyclohexanone the ring is flattened as compared to the adamantane structure. Such an explanation has been proposed by Lightner et al.[5] in their interpretation of the opposite behavior of a β-axial deuterium substituent (consignate in **3** and dissignate in **5**). These authors suggested that due to the close proximity of the substituent to the local symmetry plane which

(14) Heywood, P. J.; Rassing, J. E.; Wyn-Jones, E. *Adv. Mol. Relaxation Processes* **1975**, *6*, 307–317.
(15) Lectard, A.; Lichanot, A.; Metras, F.; Gaultier, J.; Hauw, C. *Cryst. Struct. Commun.* **1975**, *4*, 527–530.
(16) Donahue, J.; Goodman, S. H. *Acta Crystallogr.* **1967**, *22*, 352–354.

separates the front from the rear quadrants even a small displacement in position could lead to a sign inversion of its octant contribution. The circular dichroism spectra of 7 are shown in Figure 2b. Within the experimental error the same rotational strength and temperature dependence as for 1 (Figure 1a) are observed. Although one might suspect that, as a result of the deuterium substitution, the energy difference between the two chair conformations of 7 is not identical with that of 1, such a "conformational isotope effect" is in the range of a few calories per mole, which is far beyond the accuracy of the present measurement.[17]

Experimental Section

A Varian Aerograph Series 2700 thermal conductivity instrument with a 10 ft × $^1/_4$ in. column (column A) of 15% Carbowax 20-M on 60/100 Chromosorb W was used for preparative VPC. Analytical VPC analysis was performed on a Hewlett-Packard 402 FID instrument employing a 6 ft × $^1/_{16}$ in. glass column (column B) of 10% Carbowax 20-M on Chromosorb W A/W. The circular dichroism spectra were measured with a JASCO J-40 circular dichrometer using a previously described cell[18] for the low-temperature measurements. Nuclear magnetic resonance spectra were measured on a Varian T-60, a Varian XL-100, and a 360-MHz Bruker HXS-360 using chloroform-*d* and benzene-d_6 as solvents with tetramethylsilane as internal standard. A Perkin-Elmer 700A infrared spectrophotometer was used to measure the infrared spectra. Mass spectra were determined on either an AEI MS-9 or a Varian MAT-44. Rotations were taken on a Perkin-Elmer 141 polarimeter in chloroform as solvent. Lithium aluminum deuteride was purchased from Stohler Isotope Chemicals. Extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. Merck silica gel 60 (230–400 mesh) was used for column chromatography (dry packed) unless otherwise indicated.

(1*S*,4*S*)-1-Isopropenyl-3,3-dideuterio-4-methylcyclohexanone (9). To a slurry (under nitrogen) of lithium aluminum deuteride (1.26 g, 30 mmol) in ether (250 mL) was added an ether (50 mL) solution of dihydrocarvone (8; 7.90 g, 52 mmol). After the mixture was stirred at room temperature for 3 h, the excess lithium aluminum deuteride was destroyed, and the reaction mixture was filtered, concentrated, and distilled (64 °C/0.5 mm) to give 6.7 g of a mixture of four isomeric alcohols which was dissolved in pyridine (90 mL) and treated with tosyl chloride (16.5 g, 74 mmol) for 6.5 h at room temperature. After the mixture was concentrated to one-fourth of its volume, 120 mL of water was added and the mixture extracted with methylene chloride (100 mL). The extract was washed with 10% hydrochloric acid and brine, dried, and concentrated to an oil which was chromatographed on silica gel (100 g, 70–230 mesh; 5% ethyl acetate–hexane) to yield 13 g of the crystalline tosylate: ^{1}H NMR 7.58 (br dd, aromatic), 4.66 (br s, $=CH_2$), 2.41 (s, aromatic CH_3), 1.64 (br s, vinyl CH_3), 0.80 ppm (d, J = 6 Hz, CH_3). Addition of the tosylate (13.0 g, 42 mmol) in ether (50 mL) to a suspension of lithium aluminum deuteride (3.53 g, 84 mmol) in 250 mL of ether (72 h at room temperature under nitrogen) furnished after workup an oil composed of three components (86:6:6, column A, 90 °C). The major product was the isopropenylcyclohexane 9 (1.46 g), and a minor product arose from tosylate elimination. Pure samples of 9 were isolated by preparative VPC (column A, 90 °C): IR (film) 3100, 2900, 2850, 2175, 2075, 1650 cm^{-1}; ^{1}H NMR 4.66 (br s, $=CH_2$), 1.70 (m, vinyl CH_3), 0.88 ppm (d, J = 6 Hz, CH_3); mass spectrum (70 eV), m/z (relative intensity) 140 (M^+, 38), 139 (0.8), 97 (100).

(1*S*,4*S*)-1-Acetyl-3,3-dideuterio-4-methylcyclohexane (10). Isopropenylcyclohexane 9 (978 mg, 7.0 mmol) in methanol (30 mL) was cooled to −78 °C and treated with excess ozone. After removal of excess ozone with nitrogen, methyl sulfide (1.5 mL, 20 mmol) was introduced, and the resulting mixture was stirred for 23 h at room temperature. Chromatographic separation (5% ethyl acetate–hexane) provided the acetylcyclohexane 10 (663 mg): IR (film) 2900, 2850, 2175, 2075, 1715 cm^{-1}; ^{1}H NMR 2.13 (s, $COCH_3$), 0.87 ppm (d, J = 6 Hz, CH_3); mass spectrum (70 eV), m/z (relative intensity) 142 (M^+, 19), 141 (0.5), 140 (0.5), 43 (100).

(1*S*,4*S*)-1-Acetoxy-3,3-dideuterio-4-methylcyclohexane (11). To a solution of the acetylcyclohexane 10 (612 mg, 4.3 mmol) in methylene chloride was added *m*-chloroperbenzoic acid (80–90% pure, 1.5 g). After being stirred for 17 h at room temperature, the reaction mixture was diluted with methylene chloride (40 mL), washed with 10% KOH and brine, dried, and concentrated to give the acetoxycyclohexane 11 (772 mg): IR (film) 2940, 2875, 2180, 2090, 1740 cm^{-1}; ^{1}H NMR 2.02 (s, OAc), 0.88 ppm (d, J = 6 Hz, CH_3); mass spectrum (70 eV), m/z (relative intensity) 158 (M^+, 1), 98 (38), 43 (100).

(1*S*,4*S*)-3,3-Dideuterio-4-methylcyclohexan-1-ol (12). Acetoxycyclohexane 11 (403 mg, 2.6 mmol) in methanol was mixed with KOH (280 mg, 5.0 mmol) for 30 min at 23 °C. The reaction mixture was diluted with water (20 mL) and extracted with methylene chloride. The organic extract was washed with brine, dried, and concentrated to a liquid (334 mg), which was composed of a 24:1 mixture of trans and cis isomers. Methylcyclohexanol 12 containing 1.4% (column B, 70 °C) cis isomer was isolated by preparative VPC (column A, 140 °C): IR (film) 3350, 2940, 2870, 2180, 2080 cm^{-1}; ^{1}H NMR 3.56 (m, CHOH), 0.87 ppm (d, J = 6 Hz, CH_3); mass spectrum (70 eV), m/z (relative intensity) 116 (M^+, 1), 59 (100), 57 (94).

(4*S*)-3,3-Dideuterio-4-methylcyclohexanone (1). A chromic acid solution (86 drops, excess) was added dropwise to a solution of 4-methylcyclohexanol 12 (76 mg, 0.66 mmol) at 5 °C. After being stirred for 90 min, the reaction mixture was washed with a saturated bicarbonate solution (until colorless) and brine, dried, and concentrated to give methylcyclohexanone 1 (63 mg). Samples were isolated by VPC (column A, 130 °C): IR (film) 3000, 2900, 2215, 2140, 1740 cm^{-1}; ^{1}H NMR 2.36 (m, CH_2COCH_2), 1.02 ppm (d, J = 6 Hz, CH_3); mass spectrum (70 eV), m/z (relative intensity) 114 (M^+, 66), 113 (1), 57 (100), 55 (97).

Dihydrocarvone-*2,6,6*-d_3 (8a). A solution (under nitrogen) of sodium deuterioxide was prepared by dissolving sodium (1.3 g) in methanol-d_1 (120 mL) followed by the addition of D_2O (75 mL). Dihydrocarvone (8; Fritsche Brothers, Inc.; 9.1 g, 60 mmol) was introduced, and the resulting solution was heated under reflux for 15 h. The reaction mixture was concentrated to remove methanol and then extracted with ether. Solvent removal from the ether extract gave an oil. The exchange procedure was repeated twice, and the final product was isolated after removal of methanol by distillation under atmospheric pressure, saturation of the resulting aqueous phase with solid sodium chloride, and removal of the aqueous phase. The organic phase (an oil) was purified by Kugelrohr distillation to provide 5.5 g (35 mmol) of *d*-carvone-*2,6,6*-d_3 (8a).

(1*S*,4*S*)-1-Isopropenyl-2,2,3,3,4-pentadeuterio-4-methylcyclohexanone (9a) was synthesized from 8a as described above for 9. A pure sample of 9a was isolated by preparative VPC (column A, 90 °C): IR (film) 3100, 2925, 2850, 2180, 2100, 1650 cm^{-1}; ^{1}H NMR 4.62 (br s, $=CH_2$), 1.69 (br s, vinyl CH_3), 0.87 ppm (s, CH_3); mass spectrum (70 eV), m/z (relative intensity) 143 (M^+, 55), 142 (3.5), 70 (100).

(1*S*,4*S*)-1-Acetyl-2,2,3,3,4-pentadeuterio-4-methylcyclohexane (10a) was synthesized as described above for 10: IR (film) 2925, 2860, 2180, 2090, 1710 cm^{-1}; ^{1}H NMR 2.10 (s, $COCH_3$), 0.88 ppm (s, CH_3); mass spectrum (70 eV), m/z (relative intensity) 145 (M^+, 29), 144 (1.5), 43 (100).

(1*S*,4*S*)-1-Acetoxy-2,2,3,3,4-pentadeuterio-4-methylcyclohexane (11a) was synthesized as described above for 11: IR (film) 2950, 2875, 2200, 2100, 1730 cm^{-1}; ^{1}H NMR 4.66 (m, CHOAc), 2.00 (s, $COCH_3$), 0.87 ppm (s, CH_3); mass spectrum (70 eV), m/z (relative intensity) 119 (M^+ − 42) (1), 43 (100).

(1*S*,4*S*)-2,2,3,3,4-Pentadeuterio-4-methylcyclohexanol (12a) was synthesized as described above for 12: IR (film) 3350, 2925, 2850, 2175, 2100 cm^{-1}; ^{1}H NMR 3.46 (m, CHOH), 0.87 ppm (s, CH_3); mass spectrum (70 eV), m/z (relative intensity) 119 (M^+, 2), 60 (94), 57 (100).

(17) The fact that such small isotope effects are measurable by temperature-dependent circular dichroism measurements (see ref 1 and references cited therein) relies on the large and oppositely signed rotational strengths of the involved conformers ($[R] \simeq \pm 5$); for 1 and 7 these values are smaller by a factor of ca. 20, thereby reducing the sensitivity of measurement toward small energy differences correspondingly.

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

(4*S*)-2,2,3,4,6,6-Heptadeuterio-4-methylcyclohexanone (7). To a solution of the deuterated methylcyclohexanol **12a** (400 mg, 3.36 mmol), containing 4.2% of the *cis*-methyl diastereomer, in ether (60 mL) at 5 °C was added dropwise a chromic acid solution (460 drops, excess). After 3 h, the reaction mixture was poured into a saturated sodium bicarbonate solution. The organic phase was washed with a saturated bicarbonate solution until no yellow color remained. Drying and concentration furnished (4*S*)-2,2,3,3,4-pentadeuterio-4-methylcyclohexane (**1a**, 291 mg) which was added to a solution prepared by addition of sodium (80 mg) to methanol-d_1 (10 mL) and subsequent addition of D_2O (2 mL). A 16-h reflux period was followed by removal of methanol through distillation at atmospheric pressure. The aqueous residue was extracted with dry ether. After removal of the ether the above procedure was repeated twice. Samples of the thus-produced methylcyclohexanone **7** were purified by preparative VPC (KOD Carbowax pretreated with D_2O, 150 °C): IR (film) 2950, 2870, 2190, 2100, 1710 cm^{-1}; ^1H NMR 1.98 (d, J = 13 Hz, one methylene H), 1.39 (d, J = 13 Hz, one methylene H), 1.01 ppm (s, CH_3); mass spectrum (70 eV), m/z (relative intensity) 119 (M^+, 54), 118 (6), 117 (1), 58 (100), 56 (98).

Apoverbenone (14). (-)-Nopinone (**13**; 1.0 g, 7.2 mmol) in THF (5 mL) was added to a solution of diisopropylamine (1.2 mL, 8.6 mmol) in THF (30 mL) at -78 °C. After the mixture was stirred for 2 h, PhSeBr (generated from 1.88 g of Ph_2Se_2 and 0.96 g of bromine) in 5 mL of THF was added. After a 30-min stirring period at -78 °C, the solution was warmed to room temperature. At this time the reaction mixture was poured into dilute HCl/ether. The organic layer was washed with saturated bicarbonate and brine, dried, and concentrated to an oil. This was chromatographed on 100 g of silica by using hexane followed by 5% ethyl acetate–hexane to give 1.1 g of selenide. The selenide was dissolved in methylene chloride (12 mL) and pyridine (0.6 mL) at 0 °C. Hydrogen peroxide (1.15 g of 30% H_2O_2 in 1 mL of H_2O) was added, followed by 0.5 h of stirring. The reaction mixture was washed with saturated bicarbonate and brine, dried, and concentrated to give 591 mg of crude enone **14**. This material was distilled several times to give pure **14** (this compound must be purified by preparative GC just prior to use since it turns yellow). All spectral data were in accordance with those reported in the literature[19] except the rotation: $[\alpha]^{21}_D$ +286° (*c* 10.5, $CHCl_3$) [lit. $[\alpha]^{25}_D$ +319° ($CHCl_3$)].

(+)-(4*R*)-4-Deuterionopinone (16). Apoverbenone (206 mg, 1.5 mmol) was dissolved in ether (5 mL), and rhodium on alumina (37 mg) was added. The reaction flask was evacuated and purged several times with deuterium gas. The reaction mixture was allowed to stir under an atmosphere of deuterium (balloon pressure) for about 24 h (although it appears to be complete in 2 h). A small sample of the dideuterio compound **15** was isolated by preparative GC (Carbowax, 180 °C) for ^1H NMR studies. To the reaction mixture (filtered) was added methanol (20 drops) and 10 drops of NaOH (29 g in 500 mL of H_2O), and the mixture was stirred for 4 h. About 1 mL of H_2O was added and then removed, and fresh methanol and NaOH were added as before. After 14 h, the layers were separated, and the ether phase was extracted with H_2O. The aqueous phases were back-extracted with ether, and the combined ether extract was washed with brine, dried, and concentrated to an oil which was Kugelrohr distilled (100 °C/0.05 mm) to give **16** (176 mg) as a colorless liquid: IR (neat) 2170, 1710 cm^{-1}; $[\alpha]^{21}_D$ +32° (*c* 9.2, $CHCl_3$); mass spectrum, m/z (relative intensity) 140 (1.7), 139 (M^+, 8.8), 138 (1.3), 83 (100), 55 (85).

(3*R*)-3-Deuterio-4-(2-bromoprop-2-yl)cyclohexanone (17). Nopinone-d_1 (**16**; 176 mg, 1.27 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C under nitrogen. Boron tribromide (Aldrich; 0.15 mL, 1.6 mmol) was introduced, and the resulting light brown solution was stirred for 1.75 h at -78 °C. Pyridine (0.39 mL, 4.8 mmol) and subsequently methanol (0.54 mL, 13.4 mmol) were added. The cold, colorless reaction mixture was poured into water, and the mixture was extracted with ether. The ether extract was washed with saturated oxalic acid (or dilute HCl) and brine, dried, and concentrated. Chromatography on silica gel (20 g, 230–400 mesh, 5% ethyl acetate–hexane) gave 211 mg of a crystalline solid which could be further purified by sublimation (50 °C/0.05 mm): mp 71–74 °C; IR (CCl_4) 2250, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 2.40 (m, 4 H), 1.81 (s, 6 H); mass spectrum, m/z (relative intensity) 221 (M^+, 2.5), 219 (M^+, 2.6), 140 (45), 84 (62), 83 (44), 69 (72), 70 (68), 56 (83), 55 (100).

(3*R*)-3-Deuterio-4-*tert*-butylcyclohexanone (2). The bromo ketone **17** (211 mg, 0.96 mmol) was dissolved in methanol (5 mL) at 5 °C, and sodium borohydride (62 mg, 1.6 mmol) was introduced. After 3 min, TLC (20% ethyl acetate–hexane) showed no ketone, and after a total reaction time of 15 min, the reaction mixture was poured into cold ether–5% HCl. The aqueous phase was extracted with ether, and the combined ether extracts were washed with brine and dried. Concentration gave 153 mg of colorless solid.

The alcohol (153 mg, 0.69 mmol) was placed in a three-necked, 50-mL, round-bottomed flask equipped with a stirring bar, a dry ice condenser (which was connected to an argon source), a gas inlet valve, and a septum. The flask and condenser were cooled to -78 °C, and methyl chloride (~7 mL) was introduced. After addition of trimethylaluminum (25% in hexane, 3.9 mL, 9.4 mmol), the dry ice bath was removed from the flask, and the methyl chloride was allowed to reflux (-23 °C) for 2.5 h. The flask was cooled to -78 °C, and methanol (2.8 mL) was *slowly* added, followed by 5% HCl (5 mL) and ether (5 mL). The methyl chloride was removed by warming to 25 °C. The product was isolated with ether. The ether extract was washed with dilute HCl and brine. After the extract was dried and concentrated, **18** was isolated as a white solid (118 mg).

The crude product was dissolved in ether (10 mL) at 5 °C, and a chromic acid solution[10] (150 drops) was added. After a 3-h stirring period, the reaction mixture was poured into water (10 mL)/ether (5 mL) containing solid Na_2CO_3. This was stirred until the color became green and the ether layer was colorless. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated to give a solid (102 mg). Preparative VPC (Carbowax, 190 °C) followed by sublimation (25 °C/0.08 mm) gave colorless crystals of **2**: mp 50–51.5 °C; IR (CCl_4) 2160, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 2.35 (m, 4 H), 0.90 (s, 9 H); mass spectrum, m/z (relative intensity) 156 (3.6), 155 (M^+, 18.9), 154 (1.5), 99 (78), 57 (100).

Acknowledgment. We acknowledge the valuable technical assistance of Ms. Ruth Records and thank Professor David Lightner (University of Nevada) for providing us with a preprint of ref 5. Partial financial support was provided by grants from the National Science Foundation (CHE 78-27413) and the National Institutes of Health (GM 20276-06). The 360-MHz NMR spectra were measured by Dr. Lois Durham on an instrument funded by the National Science Foundation (Grant No. GP-23633) and the National Institutes of Health (Grant No. RR-0711).

Registry No. **1**, 73687-65-7; **1a**, 73687-66-8; **2**, 68778-92-7; **7**, 73687-67-9; **8**, 5524-05-0; **8a**, 73687-68-0; **9**, 73687-69-1; **9a**, 73687-70-4; **10**, 73687-71-5; **10a**, 73687-72-6; **11**, 73687-73-7; **11a**, 73687-74-8; **12**, 73687-75-9; **12a**, 73687-76-0; **13**, 38651-65-9; **14**, 35408-03-8; **16**, 73687-77-1; **17**, 73687-78-2; **18**, 73687-79-3.

(19) Reich, J. H.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5446.