Photoaddition of 1a to 1,6-Heptadiene. Irradiation (1.5 h) of a solution of 1,6-heptadiene (0.144 g, 1.5 mmol) and **1a** (0.312 g, 1.0 mmol) in 1 mL of carbon tetrachloride gave, upon workup, an oily residue (0.423 g) that could be separated into three fractions by chromatography on silica gel using benzene, methylene chloride, and chloroform successively as eluants. The compounds eluted were as follows: (a) An oil (0.136 g), assigned the structure 6-(phenylseleno)-7-(*p*-tolylsulfonyl)-1-heptene (**18**): IR (neat) 3060, 2920, 2855, 1633, 1590, 1572, 1473, 1437, 1398, 1311, 1298 (s, SO_2), 1140 (s, SO_2), 1081, 1018, 996, 910, 813, 738, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75–7.10 (m, 9 H), 6.1–5.4 (br m, 1 H, C*H*=CH_2), 5.2–4.7 (m appearing as a d, 2 H, CH_2=CH), 3.42 (m, 3 H, CHSePh and CH_2SO_2Ar), 2.43 (s, 3 H, C$H_3C_6H_4$), 2.20–1.65 (m, 6 H, —$(CH_2)_3$—). (b) An oil (0.036 g), which is 1-((phenylseleno)methyl)-2-((*p*-tolylsulfonyl)methyl)cyclopentane 1-((phenylseleno)methyl)-2-((*p*-tolylsulfonyl)methyl]cyclopentane (**19**): IR (neat) 3057, 3026, 2955, 2874, 1597, 1577, 1477, 1452, 1437, 1404, 1313, 1302, 1288 (s, SO_2), 1147 (s, SO_2), 1087, 1022, 817, 758, 738, 692, 689, 632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.10 (m, 9 H), 3.55–2.65 (two m, 4 H, CH_2SePh and CH_2SO_2Ar), 2.43 (s, 3 H, C$H_3C_6H_4$), 2.40 (m, 2 H, C*H*CH_2SO_2Ar and C*H*CH_2SePh), 2.00–1.35 (m, 6 H). Anal. Calcd for $C_{20}H_{24}O_2SSe$: C, 58.96% H, 5.93. Found: C, 58.74; H, 6.16. (c) An oil (0.038 g), assigned the structure 2,6-bis(phenylseleno)-1,7-bis(*p*-tolylsulfonyl)heptane (**20**): IR (neat) 3050, 2915, 2850, 1590, 1575, 1473, 1435, 1398, 1312, 1298 (s, SO_2), 1140 (s, SO_2), 1081, 1018, 813, 739, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.2 (m, 18 H), 3.42 (m, 6 H, 2 CHSePh and 2 CH_2SO_2Ar), 2.43 (s, 6 H, 2 C$H_3C_6H_4$), 2.25–1.50 (m, 6 H, —$(CH_2)_3$—).

To study the effect of a change in the initial concentration of **1a** on the product distribution more dilute solutions of **1a** and 1,6-heptadiene were irradiated. A solution of 1.0 mmol of **1a** and 1.5 mmol of 1,6-heptadiene in 5 mL of carbon tetrachloride gave 0.146 g of **18**, 0.071 g of **19**, and 0.042 g of **20**, while a solution of 5.0 mmol of **1a** and 7.5 mmol of 1,6-heptadiene in 50 mL of carbon tetrachloride gave 0.329 g of **18**, 0.283 g of **19**, and 0.051 g of **20**.

Oxidative Elimination of the Phenylseleno Groups in 18, 19, and 20. Each of the 1,6-heptadiene–**1a** adducts (**18**, **19**, **20**) was subjected to the same oxidative procedure described for the conversion of **14** to **15**.

Formation of 21. Upon workup of the reaction mixture from the oxidation of 0.407 g (1.0 mmol) of **18** there was obtained, after chromatography on silica gel using ethanol as eluant, 0.181 g (73%) of (*E*)-1-(*p*-tolylsulfonyl)-1,6-heptadiene (*E*-**21**) as an oil: IR (neat) 3060, 3043, 2925, 2860, 1635, 1595, 1490, 1450, 1433, 1311, 1300, 1280 (s, SO_2), 1143 (s, SO_2), 1085, 1014, 995, 967, 915, 814, 658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.2 (AA′BB′ pattern, 4 H), 6.93 (dt, J_1 = 15 Hz, J_2 = 6 Hz, 1 H, C*H*=CHSO_2Ar), 6.28 (dt, J_1 = 15 Hz, J_2 = 1.5 Hz, 1 H, CH=C*H*SO_2Ar), 6.1–5.4 (br m, 1 H, C*H*=CH_2), 5.2–4.7 (2 H, CH_2=CH), 2.43 (s, 3 H, C$H_3C_6H_4$), 2.33–1.33 (m, 6 H, —$(CH_2)_3$—). Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25. Found: C, 66.97; H, 7.18.

Formation of 22. Workup of the reaction mixture from the oxidation of 0.180 g (0.25 mmol) of **20** gave 0.064 g (75%) of a gummy solid whose structure was assigned to be (*E*,*E*)-1,7-di-(*p*-tolylsulfonyl)-1,6-heptadiene on the basis of its IR and ^1H NMR spectra: IR (neat) 3061, 3043, 2928, 2860, 1928, 1815, 1718, 1635, 1595, 1494, 1450, 1433, 1311, 1300, 1280 (s, SO_2), 1143 (s, SO_2), 1086, 1014, 981 (s, *trans* C=C), 868, 814, 738, 659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.2 (AA′BB′ pattern, 8 H) 6.89 (dt, J_1 = 15 Hz, J_2 = 6 H, 2 H, 2 C*H*=CHSO_2Ar), 6.25 (dt, J_1 = 15 Hz, J_2 = 1.5 Hz, 2 H, 2 CH=C*H*SO_2Ar), 2.43 (s, 6 H, 2 C$H_3C_6H_4$), 2.35–1.30 (m, 6 H, —$(CH_2)_3$—).

Formation of 23. Oxidation of **19** (0.306 g, 0.75 mmol) gave upon workup a yellow oil that could be separated into two fractions by TLC (SiO_2, CH_2Cl_2–benzene, 1:1, with two drops of EtOH per 5 mL of solvent). The higher R_f value was diphenyl diselenide (0.01 g), and the lower R_f value fraction was an oil (0.175 g) that consisted primarily of 1-methylene-2-(*p*-tolylsulfonylmethyl)-cyclopentane (**23**), but with the latter still contaminated with a small amount of **19**. Since a variety of attempts to separate **23** from **19** by preparative TLC were unsuccessful, an analytically pure sample of **23** could not be obtained. The structure for **23** was assigned on the basis of the following spectral data: IR (neat) 3068, 2957, 2872, 1653, 1597, 1315, 1302, 1288 (s, SO_2), 1145 (s, SO_2) 1087, 885, 817, 761, 659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07–7.15 (AA′BB′ pattern, 4 H), 4.98 (d, J = 2 Hz, 1 H), 4.79 (d, J = 2 Hz, 1 H), 3.5–1.35 (series of m, 12 H). The yield of **23** (71%) was determined from the total weight of the second fraction and the integrated intensity of the signals for the CH_2=C group in **23** in the ^1H NMR spectrum of the fraction.

Acknowledgment. The support of this research by the Robert A. Welch Foundation (Grant D-650) is gratefully acknowledged.

Registry No. **1a**, 68819-94-3; **6a**, 89165-51-5; **6b**, 89165-52-6; **7**, 60513-62-4; **8**, 89165-53-7; **9**, 89165-55-9; **10**, 89165-54-8; **11**, 89165-56-0; **13**, 89165-57-1; **14**, 89165-58-2; **15**, 89165-59-3; **18**, 89165-60-6; **19**, 89165-61-7; **20**, 89165-62-8; (*E*)-**21**, 89165-63-9; (*E*,*E*)-**22**, 89165-64-0; **23**, 89165-65-1; benzeneseleninic acid, 6996-92-5; 1-dodecanesulfinic acid, 26535-63-7; phenylmethanesulfinic acid, 4403-73-0; *p*-toluenesulfinic acid, 536-57-2; selenium dioxide, 7446-08-4; cyclohexene, 110-83-8; styrene, 100-42-5; phenyl benzyl selenide, 18255-05-5; β-pinene, 127-91-3; 1,6-heptadiene, 3070-53-9.

Optical Rotatory Dispersion Studies. 137.[1] Synthesis and Chiroptical Properties of α- and β-Deuterium Substituted Aliphatic Aldehydes and Ketones

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The synthesis and chiroptical properties of (2*R*)-2-deuterio-3-hexanone (**8a**), (2*R*)-2-deuterio-4-methylpentanone (**8b**), (2*R*)-2-deuteriopentanal (**9a**), (2*R*)-2-deuterio-3-methylbutanal (**9b**), and (3*R*)-3-deuteriohexanal (**13**) are described. All exhibit Cotton effects consistent with the preferred eclipsed conformation of the carbonyl/α-alkyl moiety. The β-deuterio aldehyde **13** shows a sign change in accordance with the "proximity rule" previously observed in CD studies.

Introduction

In spite of the large amount of work published on the chiroptical properties of cyclic carbonyl compounds, relatively little has been done in acyclic systems. Because of their conformational mobility, the latter are expected to give rotations substantially lower than those of their cyclic counterparts, as was borne out by Djerassi and Geller in their early (1959) study of a series of optically active methyl-substituted aldehydes and ketones.[2] The rotations

(1) For the preceding paper, see Lu, Y.; Barth, G.; Kieslich, K.; Strong, P. S.; Duax, W. L.; Djerassi, C. *J. Org. Chem.* **1983**, *48*, 4549.

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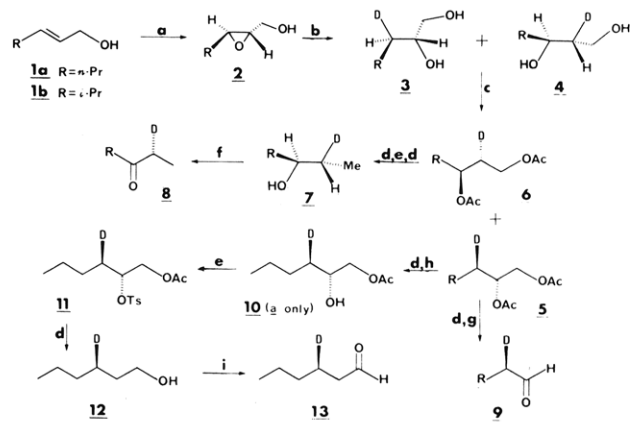
Scheme I[a]



[a] a, *t*-BuOOH, (+)-diethyl tartrate, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, −23 °C; b, $LiAlD_4$, ether; c, Ac_2O, pyr; chromatography; d, $LiAlH_4$, ether; e, TsCl, pyr; f, CrO_3/Celite, CH_2Cl_2/ether; g, H_5IO_6, ether; h, Ac_2O, pyr; i, PCC, CH_2Cl_2.

observed were not so low as to be insignificant, however, and further studies on acyclic carbonyl compounds (generally carboxylic acids) have appeared from time to time,[3,4] including, recently, one in which the optical activity was due to isotopic substitution.[4] In this work, Ringdahl et al. reported the circular dichroism spectra of a series of optically active α-deuterium-substituted carboxylic acids in H_2O. In previous papers[5] we have focused on the chiroptical properties of cyclic compounds (cyclohexanones, cyclopentanones,[6] and, more recently, cyclobutanones[7]) with isotopically engendered chirality. Having examined most of the major ring systems, we therefore wished to extend these studies to acyclic compounds and to this end synthesized a series of optically active α-deuterium-substituted aldehydes and ketones **8** and **9** (see Scheme I) and measured their CD spectra in a variety of solvents and at different temperatures. We also prepared one β-deuterium-substituted aldehyde, **13**, and were able to observe the "proximity effect" discussed by Djerassi and Geller[2] and later by Potapov et al.[3b]

Synthesis

The three aldehydes and two ketones were synthesized from *trans*-2-hepten-1-ol and *trans*-5-methyl-2-hexen-1-ol as outlined in Scheme I. Asymmetric epoxidation of the allylic alcohols **1** by the Sharpless method[8] gave the epoxides **2**, whose enantiomeric purity was estimated from the 360 MHz NMR spectra of their (+)-MTPA esters[9] (see, for example, Figure 1). Ring opening of the epoxy alcohols

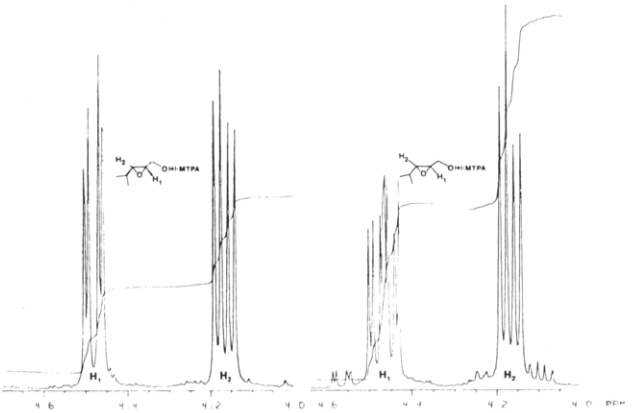


Figure 1. Partial 360-MHz NMR spectra of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetic (MTPA) esters of (a) optically active and (b) racemic **2b**.

with LAD gave a mixture of 1,2- and 1,3-diols. Separation of the diols proved difficult, so the mixture was acetylated and the acetates separated by slow column chromatography on silica gel. The diols **3** and **4** were regenerated by LAH reduction or saponification. The 1,2-diol could then be oxidized to the α-deuterio aldehyde **9** by periodic acid in wet ether.[6] The 1,3-diol was converted to **7** by tosylation of the primary alcohol and subsequent reduction with LAH; the secondary alcohol could then be converted to the corresponding α-deuterio ketone **8** by CrO_3/Celite oxidation.[10]

The β-deuterio aldehyde **13** was prepared from the 1,2-diol **3a** as follows. The diol was acetylated, giving the primary acetate **10** as the major product. It could be separated from the secondary acetate and diacetate by column chromatography on silica gel, but it was easier to delay purification until later in the sequence. The remaining hydroxyl group was tosylated; the tosyl and acetyl groups were then both reduced with LAH to give (3*R*)-3-deuterio-1-hexanol (contaminated with (3*R*)-3-deuterio-2-hexanol from the secondary acetate mentioned above). The primary alcohol **12** was isolated by preparative gas chromatography and oxidized with pyridinium chlorochromate[11] to give the aldehyde **13**.

Optical and Isotopic Purities

Integration (by computer) of the 300-MHz NMR spectrum of **8b** showed the compound to be 100% d_1 within the limits of integration. Furthermore, the α-proton (at the chiral center) appears as a clean quartet of triplets (vicinal splitting from the methyl group plus geminal splitting from the deuterium), while the methyl group appears accordingly as a doublet of triplets. The 300-MHz NMR spectrum of **9a** was difficult to integrate due to the large amount of ether present, but the splittings of the α-proton and the aldehydic proton are consistent with the α-deuterated structure.

NMR spectra of the primary alcohols produced by LAH reduction of **9a,b** show doublets for the protons adjacent to the hydroxyl group, while the corresponding protic compounds give triplets. The splitting patterns and/or integration of the NMR spectra of various deuterated intermediates (e.g., **3**, **7**, **11**, and **12**) also suggest that their isotopic purities are close to 100%.

Attempts to use mass spectra of the alcohols **7** and of their THP ethers to determine isotopic purity failed due to weak molecular ions and lack of reproducibility in the

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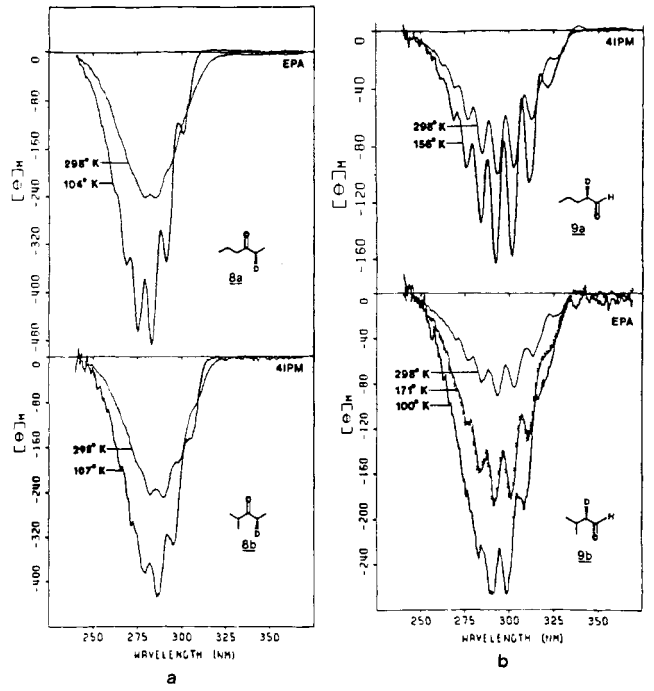

Figure 2. (a) CD spectra of (2*R*)-2-deuterio-3-hexanone (**8a**) in EPA (5:5:2 ether/isopentane/ethanol) and of (2*R*)-2-deuterio-4-methylpentanone (**8b**) in 4IPM (4:1 isopentane/methylcyclohexane) at various temperatures between 100 and 298 K. (b) CD spectra of (2*R*)-2-deuteriopentanal (**9a**) in 4IPM and of (2*R*)-2-deuterio-3-methylbutanal (**9b**) in EPA at various temperatures between 100 and 298 K.

peak heights. The mass spectra of the 1,2-diacetates **5**, however, give an M + 1 ion indicating an isotopic purity of approximately 99%.

Since little or no deuterium was lost in the sequence of reactions leading from **3** and **4** to **9** and **8**, respectively, the optical purities of the latter should be equal to that of **2**, if one assumes that the epoxide ring-opening reaction is completely stereospecific. The optical purities of **2a** and **2b** were determined via their (+)-MTPA esters to be 93% and 98%, respectively.

The CD spectra were always measured immediately after preparation of the carbonyl compounds to minimize the threat of racemization as well as evaporation and (in the case of the aldehydes) oxidation. This precaution was especially necessary for the spectra run in the more polar solvents EPA (5:5:2 ether:isopentane:ethanol) and 2-propanol. Generally the [Θ] values of samples in these solvents decreased in magnitude by several percent over the course of a few hours, while in the hydrocarbon solvents they remained the same (within experimental error). Another experimental difficulty should be briefly mentioned. Due to the high volatility and small quantities of the final compounds, it was very difficult to remove all of the reaction solvent (ether); consequently, the concentrations of the CD samples were determined by recording their UV spectra and comparing them to a series of standards of the corresponding protic compounds run in the same solvents.

Results and Discussion

α-Deuterated Compounds. The CD spectra of the α-deuterated compounds **8** and **9** are shown in Figures 2 and 3. The most salient feature of the spectra is that the Cotton effects are all negative. The generalized octant diagrams given in Figure 4 show that the deuterium atom falls into a positive octant when the compound assumes the conformation in which the α-alkyl group is eclipsed

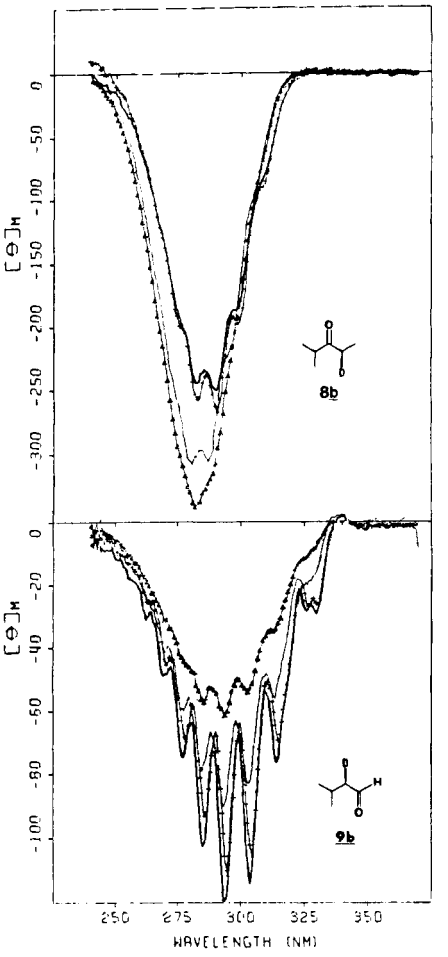

Figure 3. CD spectra of (2*R*)-2-deuterio-4-methylpentanone (**8b**) and (2*R*)-2-deuterio-3-methylbutanal (**9b**) in various solvents: 4IPM (heavy line), isooctane (+++), EPA (thin line), and 2-propanol (ΔΔΔ).

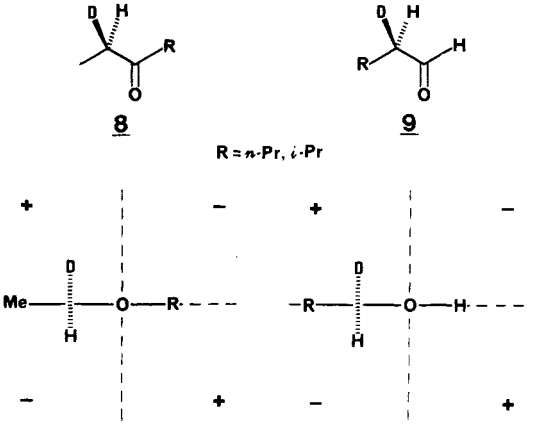

Figure 4. Octant representations of ketones **8a,b** and aldehydes **9a,b**.

with the carbonyl bond. This conformation has been found to be the predominant one for acyclic carbonyl compounds in numerous cases.[12] The dissignate or "anti-octant" behavior of deuterium has been documented many times[5] and operates here as expected. This interpretation cor-

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Table I. Rational Strengths and Molar Ellipticities (Corrected to 100% Enantiomeric Excess)[a]

compd	solvent	temp, K	$[R]^b$	$[\Theta]^c$	compd	solvent	temp, K	$[R]$	$[\Theta]$
8a	*i*-PrOH	298	−0.299	−304	9a	isooctane	298	−0.155	−161
	isooctane	298	−0.284	−290		EPA	298	−0.121	−111
	EPA	298	−0.266	−260			215	−0.180	−167
		226	−0.322	−328			181	−0.208	−191
		183	−0.377	−396			100	−0.246	−217
		104	−0.433	−525		4IPM	298	−0.119	−120
	4IPM	298	−0.250	−258			213	−0.164	−174
		219	−0.316	−344			156	−0.223	−247
		181	−0.348	−387	9b	*i*-PrOH	298	−0.0685	−61
		146	−0.370	−414		isooctane	298	−0.107	−108
8b	*i*-PrOH	298	−0.344	−357		EPA	298	−0.0972	−92
	isooctane	298	−0.258	−281			208	−0.153	−143
	EPA	298	−0.323	−322			171	−0.200	−188
		221	−0.386	−398			100	−0.281	−268
		173	−0.441	−518		4IPM	298	−0.123	−120
	4IPM	298	−0.254	−260			228	−0.139	−145
		208	−0.315	−337			161	−0.210	−220
		148	−0.383	−429			107	−0.239	−262
					13	EPA	298	+0.0178	+20
							203	+0.0113	+14
							148	+0.0110	+13
						4IPM	298	+0.0282	+27
							223	+0.0177	+17

[a] Figures 2, 3, and 7 are uncorrected for enantiomeric excess. [b] Units for $[R]$ are 10^{-2} Debye·Bohr magneton. [c] Units for $[\Theta]$ are those of molar absorptivity ϵ (L/mol cm)/3300.

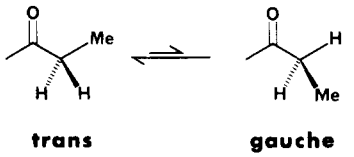

Figure 5. The trans and gauche conformers of butanone.

responds to that of Ringdahl et al.,[4] who obtained positive signals from α-deuterated carboxylic acids of the opposite configuration.

The magnitudes of the signals and their strong temperature dependence are also worthy of comment. The rotational strengths of the ketones **8a** and **8b** at room temperature in EPA (see Table I) are comparable to that obtained for *trans*-(*R*)-2-deuterio-4-*tert*-butylcyclohexanone ($[R] = -0.25$),[13] a conformationally rigid molecule in which the deuterium atom is situated similarly with respect to the octant planes. These large rotational strengths suggest that there is a high preference for the eclipsed conformer in the acyclic compounds, as has already been determined in numerous studies by other physical techniques. Thus, a ratio of approximately 95:5 was proposed for the trans:gauche (see Figure 5) ratio in butanone as determined by electron diffraction[12a] and infrared spectroscopy;[12b] Pierce et al.[12c] observed only transitions corresponding to the trans form of butanone in its microwave spectrum. The energy difference between the two forms was estimated to be approximately 1.0–1.2 kcal/mol in these studies. Pierce also estimated the trans–gauche energy difference in propionaldehyde to be 0.9 kcal/mol, while Chapput et al.[12d] reported a value of 1.2 kcal/mol.

Before discussing the variable-temperature effects observed, it should be emphasized that it is often very difficult to separate the effects of conformational and solvational equilibria.[14] Solvational equilibria have been found to cause profound changes in the CD spectra of conformationally rigid ketones;[15] these changes are due to

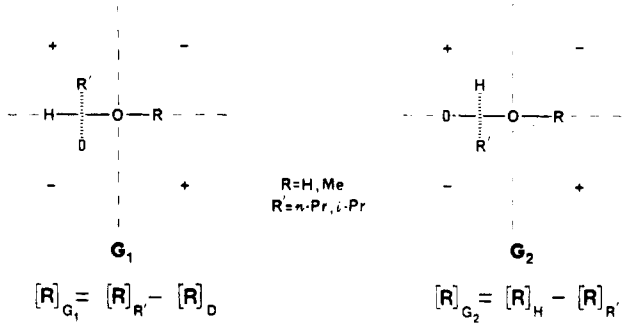

Figure 6. Octant representations of the two gauche conformers of ketones **8a,b**.

the presence of solvated and unsolvated species with different (oppositely signed in the above case) rotational strengths. A change in solvent can also affect the conformational equilibrium, thus complicating matters still further.[16] Furthermore, solvent effects may not be consistent from one compound to another, even when the compounds are very similar.[17]

With these considerations in mind, we shall first discuss conformational equilibria. An examination of the two possible gauche conformers (Figure 6) shows that their rotational strengths will be of opposite sign and nearly equal magnitude. Their overall contribution to the rotational strength of the molecule (assuming they are present in equal amounts[18]) will be positive and equal in magnitude to $[R]_H - [R]_D$ (where $[R]_X$ = the absolute contribution of

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(16) (a) Moscowitz, A. in ref 15, p 333. (b) Reference 3b, p 1662.

(17) Reference 14, p 2742.

(18) There will probably be a slight difference in the populations of the two gauche conformers due to a conformational isotope effect (see: S. F. Lee et al. *J. Am. Chem. Soc.* **1978**, *100*, 1965; **1978**, *100*, 8010; **1981**, *103*, 295. Also ref 6 and 7, this paper). However, in previous cases such population differences have been found to be less than 1% at room temperature, involving only a few calories difference in energy, while the trans/gauche energy difference is on the order of a kilocalorie. Therefore this effect may be safely neglected here.

X to the rotational strength). Thus $[R]_{trans} = -[R]_{gauche}$ (see also Figure 4). We can expect the positive contribution of the gauche conformers to disappear as the temperature is lowered, thus making [R] more negative, as is observed. (Rotamers not involving the chiral center may be neglected since they will cancel out, just as the two gauche conformers would cancel each other out were it not for the deuterium substitution.) Since only a small amount of gauche conformer is present at room temperature, however, its disappearance will not account for such a large change in [R] as is observed. Therefore it is reasonable to expect that some solvational equilibrium comes into play. This assumption is supported by the presence of a blue shift (a sign of increased solvation[19]) in the low-temperature spectra. The blue shift is generally more pronounced in EPA than in the less polar hydrocarbon solvent. The change in [R] with temperature is generally greater in EPA as well (see table), though the differences are only slight.

A blue shift is also observed in the room temperature spectra of the compounds as one proceeds from nonpolar to polar solvents. The variations in [R] from one solvent to another correspond roughly to the variations in ϵ_{max} in the UV spectra and are therefore likely to be due more to electronic and solvent effects than to changes in conformation. There is no evidence, for example, of an effect such as that observed by Potapov et al.,[3b,c] in which a polar solvent increases the effective bulk of the carbonyl oxygen, thus making the gauche conformers more energetically favorable. For our α-deuterated compounds this would result in a more positive signal. The aldehydes do give a weaker (and thus more positive) signal in polar solvents, but this can largely be explained by acetal or hemiacetal formation in the presence of alcohol[20] (no signal is observed in methanol). The ketones actually give a stronger (more negative) signal in polar solvents, as is commonly observed in CD studies.

β-Deuterated Aldehyde. Increasing the distance between the carbonyl chromophore and the asymmetric center in aliphatic compounds greatly decreases the rotational strength. The relationship between the intensity and/or sign of the Cotton effect and the proximity of the chiral center to the chromophore has been noted by other authors[2] and in other systems, such as carboxylic acids,[3d] substituted phenylethylamines,[21] and metal peptide complexes.[22] For the sake of completeness, we decided to examine one such example where deuterium is the asymmetric perturber.

As can be seen in Figure 7, the β-deuterated aldehyde **13** gives a weak positive signal, roughly one-fifth the magnitude of that given by its α-deuterated homologue **9a** and opposite in sign. The octant representations (Figure 8) show that when the carbonyl group is displaced one carbon further from the chiral center, maintaining the *R* configuration and trans (eclipsed) conformation, the deuterium atom moves from the top left to the bottom left rear octant, thus changing the sign of the Cotton effect.

Only a weak temperature dependence is observed for **13**, in contrast to the strong dependence shown by the α-deuterated compounds. The lack of an observable conformational equilibrium could be due to the remoteness of the chiral center from the chromophore and the consequent increase in the number of relatively stable conformers involving the chiral center.

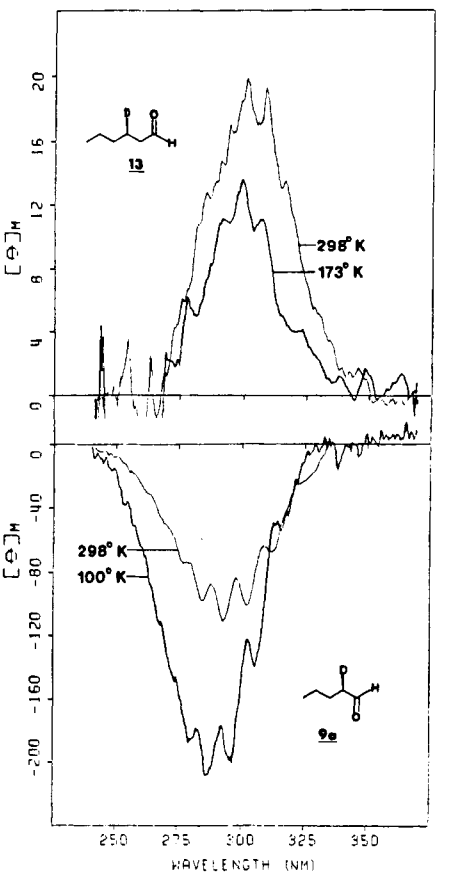

Figure 7. CD spectra of (3*R*)-3-deuteriohexanal (**13**) and (2*R*)-2-deuteriopentanal (**9a**) in EPA at various temperatures between 100 and 298 K.

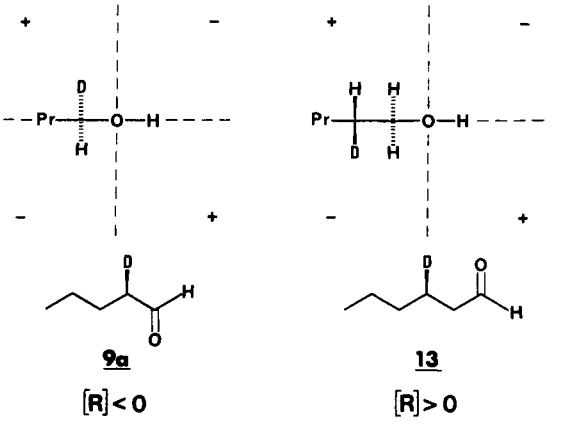

Figure 8. Octant representations of aldehydes **9a** and **13**.

Conclusion

This study has demonstrated that chiroptical studies of acyclic compounds are indeed feasible even when the chirality is solely due to isotopic substitution. The high preference of acyclic carbonyl compounds for the eclipsed conformation of the carbonyl and α-alkyl groups enables one to predict the sign of the Cotton effect. Changes in solvent polarity did not appear to affect the conformational preference in this series of compounds, though variable-temperature effects were observed. The application of the "proximity rule" to homologous compounds with isotopically engendered chirality has also been demonstrated for the first time.

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Experimental Section

Circular dichroism spectra were measured on a JASCO J-40 instrument, using a previously described[23] cell for the low-temperature measurements. Absorption spectra were measured with a Hewlett-Packard HP 8450 A UV–vis spectrophotometer. Optical rotations were measured on a Rudolf Autopol III polarimeter in a thermostated 10-cm cell. Infrared spectra were recorded as neat liquid films between NaCl plates using a Beckman Acculab 3 infrared spectrophotometer. ^{1}H NMR spectra were obtained on either a Varian T-60, a 100-MHZ Varian XL-100, or a 300-MHz Nicolet NT 300 WB spectrometer and are given as δ values with $CDCl_3$ as solvent and residual $CHCl_3$ as internal standard. Mass spectra were obtained on either a Ribermag R 10-10B or a Varian MAT-44 spectrometer. Preparative gas chromatography was performed with a Varian Aerograph Series 2700 gas chromatograph on a 10-ft column of 20% Carbowax 20M on 80/100 Chromosorb W.

***trans*-4-Methyl-2-penten-1-ol (1b).** Methyl 4-methylpentenoate (17.0 g) was added dropwise with stirring to a solution of 37.9 g of Dibal in hexane under a nitrogen atmosphere at 0 °C. The solution was stirred at room temperature for 16 h. Excess Dibal was quenched by careful addition of 6 mL of saturated Na_2SO_4 solution, followed by 100 mL of 10% HCl. The mixture was stirred until it became clear, at which point it was saturated with NaCl. The organic layer was separated and the aqueous layer extracted three times with hexane. The combined organic solutions were washed with brine and dried over Na_2SO_4. The solvent was removed by fractional distillation and the residue distilled. 9.27 g (69.8%) of **1b**, boiling between 140 and 150 °C, was collected: ^{1}H NMR 1.00 (d, J = 3.5 Hz, 6 H), 2.31 (m, 1 H), 3.33 (s, 1 H), 4.02 (d, J = 2 Hz, 2 H), 5.60 (m, 2 H); IR 3350, 2980, 1400, 1390, 1025, 980 cm^{-1}; MS, m/z 101 (1.8), 100 (1.2, M$^+$), 99 (6), 81 (28), 55 (42), 43 (100).

Asymmetric Epoxidation of 1: Typical Procedure. Titanium tetraisopropoxide (17.8 mL) was transferred to a dropping funnel via a cannula and subsequently added dropwise with stirring under a nitrogen atmosphere to 600 mL of dry CH_2Cl_2 in a dry 1-L flask at −23 °C (dry ice/CCl_4 bath); 10.8 mL of (+)-diethyl tartrate, 6.0 g of *trans*-2-hexen-1-ol (Aldrich), and 48.0 mL of 2.5 M *tert*-butyl hydroperoxide in 1,2-dichloroethane[24] were then added sequentially via syringes. The flask was then stored in a similar bath in a Dewar in the refrigerator for 22 h. Me_2S (3.36 g) was added, and the mixture was removed from the bath, stirred for 45 min, and then poured into 1 L of saturated NaF solution with vigorous stirring. After stirring for 14 h the mixture was saturated with NaCl and filtered through a pad of Celite. The aqueous layer was extracted three times with CH_2Cl_2, and the extracts were combined with the organic layer, dried over Na_2SO_4, and concentrated to 19.26 g of oily residue. This material was distilled under reduced pressure to give 4.62 g, bp 55–57 °C (1.2 mmHg), plus 0.45 g, bp 57 °C (1.2 mmHg), (64%) of **2a**: $[\alpha]^{20}_D$ −41.6 (c 0.0563, $CHCl_3$); ^{1}H NMR 0.93 (t, J = 6 Hz, 3 H), 1.50 (m, 4 H), 2.50 (s, 1 H), 2.90 (m, 2 H), 3.55 (d of d, J = 12 Hz, J = 5 Hz, 1 H), 3.87 (d of t, J = 12 Hz, J = 3 Hz, 1 H; IR 3450, 2890, 1065, 910, 860 cm^{-1}; MS, m/z 116 (M$^+$, <1), 73 (13), 45 (100).

Similar oxidation of **1b** gave **2b** in 66% yield: $[\alpha]^{20}_D$ −32.5 (c 0.0621, $CHCl_3$); ^{1}H NMR 1.40 (d, J = 3 Hz, 3 H), 1.61 (m, 1 H), 1.70 (d, J = 3 Hz, 3 H), 2.93 (dd, J = 6 Hz, J = 2.5 Hz, 1 H), 3.02 (m, 1 H), 3.60 (d of d, J = 13 Hz, J = 5 Hz, 1 H), 3.96 (d of d, J = 13 Hz, J = 4 Hz, 1 H); IR 3400, 2980, 1390, 1370, 1070, 890 cm^{-1}; MS, m/z 116 (3, M$^+$), 73 (75), 56 (100).

(+)-MTPA Esters: Typical Procedure. A 155-mg (1.23 mmol) sample of (+)-MTPA chloride was placed in a dry 5-mL flask, which was then evacuated and filled with nitrogen. A solution of 139 mg of **2a** (1.20 mmol) in 2 mL of dry pyridine was added, causing a small amount of white precipitate to form. The solution was stirred at room temperature for 6 h and then stored in the refrigerator for 14 h. It was then diluted with 25 mL of ether, washed with cold 2% HCl, water, saturated $NaHCO_3$ solution, and water again, dried over Na_2SO_4, and concentrated to 145 mg of oil: ^{1}H NMR 0.939 (t, J = 7.6 Hz, 3 H), 1.45 (m, 2 H), 1.52 (m, 2 H), 2.844 (d of d of d, J = 10 Hz, J = 5 Hz, J = 3.6 Hz, 1 H), 3.01 (m, 1 H), 3.568 (s, 3 H), 4.219 (d of d, J = 12.2 Hz, J = 5.8 Hz, 1 H), 4.574 (d of d, J = 12.2 Hz, J = 3.2 Hz, 1 H), 7.417 (m, 3 H), 7.529 (m, 2 H).

(+)-MTPA ester of **2b**: ^{1}H NMR 0.860 (d, J = 6.8 Hz, 3 H), 0.828 (d, J = 6.8 Hz, 3 H), 1.476 (m, J = 6.8 Hz, 1 H), 2.573 (d of d, J = 6.8 Hz, J = 1.8 Hz, 1 H), 2.994 (m, 1 H), 3.501 (s, 3 H), 4.164 (d of d, J = 11.9 Hz, J = 6 Hz, 1 H), 4.480 (d of d, J = 11.9 Hz, J = 3.6 Hz, 1 H), 7.350 (m, 3 H), 7.465 (m, 2 H). The corresponding racemic (+)-MTPA esters were prepared similarly; the starting epoxides were obtained via MCPBA oxidation of the appropriate olefins.

(+)-MTPA ester of racemic **2a**: ^{1}H NMR same as optically active compound except for 7th and 8th signals reported above. New signals are 4.219 (d of d of d, J = 12.2 Hz, J = 5.8 Hz, J = 4.3 Hz, 1 H) and 4.574 (d of d of d, J = 12.6 Hz, J = 12.2 Hz, J = 3.2 Hz, 1 H), respectively.

(+)-MTPA ester of racemic **2b**: ^{1}H NMR same as optically active except for 7th signal reported above. New signal is 4.463 (ddd, J = 12.6 Hz, J = 9.7 Hz, J = 3.6 Hz, 1 H).

(2*R*,3*R*)-3-Deuterio-1,2-hexanediol (3a) and (2*R*,3*S*)-2-Deuterio-1,3-hexanediol (4a). (i). LAD Ring Opening of 2a. A solution of 3.48 g (30 mmol) of **2a** in 50 mL of dry ether was added dropwise to a stirred suspension of 2.52 g (60 mmol) of LAD in a dry 500-mL flask with reflux condenser. The mixture was refluxed for 16 h, quenched with 5 mL of saturated Na_2SO_4 solution, and stirred for 1 h. The separated white solid was filtered and the filtrate dried over Na_2SO_4; the filter cake was then extracted with $CHCl_3$ in a Soxhlet apparatus for 14 h. The combined organic phase was concentrated to 3.31 g (93%) of a ~1:1 mixture of **3a** and **4a**.

(ii). Acetylation of Diol Mixture 3a and 4a; Separation of Diacetates 5a and 6a. Acetic anhydride (30 mL) was added dropwise to a solution of the crude diol mixture in 30 mL of pyridine. The solution was refluxed for 15 min and then treated with 150 mL of ice water. After 15 min the mixture was extracted twice with ether, and the extracts were washed with 5% HCl, water, saturated $NaHCO_3$ solution, and water and dried over $MgSO_4$. Removal of the solvent gave 5.19 g (92%) of the acetate mixture. This material was chromatographed slowly on 130 g of activated silica gel, eluting first with 350 mL of CH_2Cl_2 over 17 h to obtain 1.48 g of pure **5a** and then with $CHCl_3$ to recover the rest of the material (3.70 g), which was eluting as a mixture. The latter fraction was rechromatographed on a similar column, eluting with CH_2Cl_2, to give 1.96 g of pure **5a**, 0.65 g of **5a** and **6a**, and 2.52 g of **6a** containing a trace of **5a**.

5a: $[\alpha]^{20}_D$ +5.5 ($CHCl_3$); ^{1}H NMR 0.883 (t, J = 6.8 Hz, 3 H), 1.298 (m, 4 H), 1.554 (m, 1 H), 2.050 (s, 3 H), 2.056 (s, 3 H), 4.015 (d of d, J = 11.9 Hz, J = 6.5 Hz, 1 H), 4.209 (d of d, J = 11.9 Hz, J = 3.2 Hz, 1 H), 5.050 (m, 1 H); MS, m/z 203 (<1, M$^+$), 129 (100), 116 (36), 100 (29).

6a: ^{1}H NMR 0.903 (d, J = 7.2 Hz, 3 H), 1.32 (m, 2 H), 1.53 (m, 2 H), 1.82 (m, 1 H), 2.03 (s, 6 H), 4.07 (d, J = 5.8 Hz, 2 H), 4.98 (d of t, J = 7.9 Hz, J = 5.8 Hz, 1 H); MS, m/z 204 (4, M + 1), 144 (45, M − OAc), 84 (37), 43 (100).

(iii). LAH Reduction of Diacetates. A 1.875-g (9.5 mmol) sample of **5a** in dry ether was added dropwise to a stirred suspension of 0.71 g (19 mmol) of LAH in the same solvent. The mixture was refluxed for 4 h and then quenched with saturated Na_2SO_4 solution. The white precipitate was filtered and washed with ether, and the combined ether solutions were concentrated to 1.04 g (94.6%) of a colorless oil.

3a: ^{1}H NMR 0.897 (t, J = 6 Hz, 3 H), 1.36 (m, 5 H), 2.82 (s, 2 H), 3.54 (d of d, J = 19 Hz, J = 8 Hz), 3.5 (m, 1 H). **6a** was reduced in a similar manner to give a quantitative yield of **4a**.

Monotosylation of 4a,b. A solution of 1.33 g of *p*-toluenesulfonyl chloride (7 mmol) in 10 mL of dry pyridine was added dropwise to a strirred solution of 0.833 g of **4a** (7 mmol) in 10 mL of the same solvent at −23 °C under a nitrogen atmosphere. The solution was stirred at −23 °C for 30 min and then poured over ice. The resulting mixture was extracted twice with ether, and the extracts were washed with cold 10% HCl, water, saturated $NaHCO_3$ solution, and water and dried over $MgSO_4$. Removal of the solvent under vacuum gave 1.103 g (54%) of a colorless oil: ^{1}H NMR 0.93 (t, J = 5 Hz, 3 H), 1.38 (m, 4 H), 1.86 (m, 2

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H), 2.47 (s, 3 H), 3.62 (m, 1 H), 4.15 (d of t, J = 4 Hz, J = 1 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H), 7.73 (d, J = 8 Hz, 2 H). Similar reaction of **4b** with *p*-toluenesulfonyl chloride gave a 53% yield of monotosylate: ^{1}H NMR 0.89 (d, J = 6 Hz, 6 H), 1.39 (m, 1 H), 1.88 (m, 2 H), 2.46 (s, 3 H), 3.46 (d of d, J = 10 Hz, J = 5 Hz, 1 H), 4.19 (m, 2 H), 7.37 (d, J = 9 Hz, 2 H), 7.84 (d, J = 9 Hz, 2 H).

(2*R*,3*S*)-2-Deuterio-3-hexanol (7a). $LiAlH_4$ (0.366 g) was added gradually to a solution of 1.1 g of the monotosylate derived from **4a** (above) in 150 mL of anhydrous ether. The mixture was then refluxed for 4 h, quenched with saturated Na_2SO_4 solution, and filtered. The filtered solid was washed with ether and the combined ether solutions washed with saturated $NaHCO_3$ solution and brine and dried over Na_2SO_4. The solvent was removed by fractional distillation and the residue short-path distilled to give 0.378 g (98%) of **7a**: ^{1}H NMR 0.935 (m, 6 H), 1.41 (m, 6 H), 3.53 (m, 1 H). **7b** was prepared similarly in 95% yield from the corresponding monotosylate: ^{1}H NMR 0.905 (d, J = 6.4 Hz, 6 H), 0.942 (d, J = 6.9 Hz, 3 H), 1.37 (m, 2 H), 1.66 (m, 1 H), 3.268 (d of d, J = 7.3 Hz, J = 5.2 Hz, 1 H).

(2*R*)-2-Deuterio-3-hexanone (8a) and (2*R*)-2-Deuterio-4-methyl-3-pentanone (8b). Dry CrO_3 (200 mg) was added to a stirred suspension of 200 mg of Celite and 90 mg of **7a** or **7b** in 3 mL of dry 3:1 CH_2Cl_2/ether. A serum cap was fitted, and stirring was continued for 45 min. Ether (2 mL) and Celite (200 mg) were then added, and the mixture was allowed to settle for 10 min. The supernatant was pipetted and filtered through a short column (Pasteur pipette) of Celite and $MgSO_4$; the residue was washed with ether and the washings likewise filtered. Most of the solvent was removed by gently blowing nitrogen on the solution and allowing the solvent to condense in a cold trap connected to the first flask via a short-path distillation apparatus (drying tube connected to vacuum inlet). Subsequently a new collecting flask was attached and the residue was vacuum distilled without heat to give **8a** or **8b** (contaminated with varying amounts of ether). This material was used immediately for CD measurements. **8b**: ^{1}H NMR 1.026 (d of t, J = 7.5 Hz, J = 0.9 Hz, 3 H), 1.081 (d, J = 7.2 Hz, 6 H), 2.434 (q of t, J = 7.2 Hz, J = 2.7 Hz, 1 H), 2.599 (heptet, J = 6.9 Hz, 1 H).

(2*R*)-2-Deuteriopentanal (9a) and (2*R*)-2-Deuterio-3-methylbutanal (9b). Periodic acid (190 mg) and a stirring bar were placed in a 5-mL flask, and it was flushed with nitrogen through a serum cap. "Wet" ether (1 mL, anhydrous grade exposed to the air for 20 min) was added via syringe with stirring, followed by 100 mg of **3a** or **3b** in 2 mL of the same solvent. After 1 h of stirring, the ether solution was decanted, washed with brine, dried briefly over $MgSO_4$ and filtered. The product was isolated (along with some residual ether) as described for **8a,b** above and used immediately for CD measurements. **9b**: ^{1}H NMR 0.925 (t, J = 7.2 Hz, 3 H), 1.360 (m, 2 H), 1.60 (m, 2 H), 2.402 (t of d of t, J = 7.5 Hz, J = 2.4 Hz, J = 2.4 Hz, 1 H) (geminal splitting from deuterium), 9.767 (d, J = 1.8 Hz, 1 H).

Acetylation of 3a. A 275-mg sample of **3a** was dissolved in 5 mL of pyridine; 0.25 mL of Ac_2O were added, and the solution was cooled in an ice–salt bath. A few additional drops of Ac_2O were added after 45 min and then again at 1 h. After $1^1/_2$ h the reaction mixture was poured into ice water and extracted three times with ether. The ether extracts were washed several times with saturated $CuSO_4$ solution (to remove pyridine), dried over $MgSO_4$, and concentrated to 205 mg of yellowish oil. 51 mg of **10** and 45 mg of **10** contaminated with secondary acetate were isolated by column chromatography on silica gel, eluting with hexane/EtOAc mixtures of increasing polarity (0–30% EtOAc). The diacetate (30 mg) and a trace of the diol were also obtained. **10**: ^{1}H NMR 0.908 (t, J = 4.5 Hz, 3 H), 1.405 (m, 5 H), 1.84 (br s, 1 H), 2.093 (s, 3 H), 4.03 (m, 3 H) (superimposed signals).

Tosylation of 10. A 51-mg (0.32 mmol) sample of (2*R*,3*R*)-1-acetoxy-3-deuterio-2-hexanol (**10**) was dissolved in 2 mL of dry pyridine with 171 mg (0.89 mmol) of *p*-toluenesulfonyl chloride. The flask was stoppered and stored in the refrigerator for 48 h, after which time a crystalline precipitate had formed. The reaction mixture was poured into ice water and extracted three times with ether, and the ether extracts were washed with saturated $CuSO_4$ solution, dried over $MgSO_4$, and concentrated to 146 mg (91% crude) of yellow oil. **11**: ^{1}H NMR 0.830 (t, J = 5.8 Hz, 3 H), 1.203 (m, 4 H), 1.58 (m, 1 H), 1.934 (s, 3 H), 2.441 (s, 3 H), 4.103 (m, 2 H), 4.608 (d of t, J = 6.5 Hz, J = 3.6 Hz, 1 H), 7.329 (d, J = 8.2 Hz, 2 H), 7.801 (d, J = 8.2 Hz, 2 H); IR 2860, 1740, 1590, 1370, 1230, 1175, 920 cm^{-1}. (The reaction was repeated on primary/secondary acetate mixtures. Since the respective reduction products of the two acetoxy tosylates (2-hexanol and 1-hexanol) are easily separable by preparative GC, no attempt was made to purify the tosylate mixtures.)

(3*R*)-3-Deuterio-1-hexanol (12). A solution of 146 mg of **11** (contaminated with the 1-tosyl-2-acetoxy isomer) in dry ether was added to a stirred suspension of 65 mg of $LiAlH_4$ in 6 mL of the same solvent. After $1^1/_2$ h the reaction was quenched by addition of water, 15% NaOH solution, and wet ether. The resulting mixture was extracted with ether, and the extracts were dried over $MgSO_4$. Most of the ether was removed by fractional distillation, and the residue was purified by preparative GC on a 20% Carbowax 20M column at 150 °C to give 16 mg (34%) of **12**: ^{1}H NMR 0.889 (t, J = 6.6 Hz, 3 H), 1.298 (m, 6 H), 1.533 (dt, J = 6 Hz, J = 6.6 Hz, 2 H), 3.637 (t, J = 6.6 Hz, 3 H).

(3*R*)-3-Deuteriohexanal (13). A solution of 16 mg of **12** in CH_2Cl_2 was added to a stirred solution of pyridinium chlorochromate (freshly recrystallized and dried) in a few millileters of CH_2Cl_2. After 2 h, a few milliliters of ether were added, and the mixture was stirred for a few minutes more and then allowed to settle. The supernatant was pipetted and filtered through a short column (Pasteur pipette) of Florisil, followed by two washings of the residue. The filtrate was dried over $MgSO_4$ and the product isolated as previously described for the aldehydes **9** and ketones **8**.

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Registry No. **1a**, 928-95-0; **1b**, 69143-05-1; (±)-**2a**, 89395-00-6; **2a**, 89321-71-1; **2a** ((+)-MTPA ester), 89321-72-2; (*R*,*R*)-**2a** ((+)-MTPA ester), 89394-97-8; (±)-**2b**, 89459-99-4; **2b**, 89459-98-3; **2b** ((+)-MTPA ester), 89321-73-3; (*R*,*R*)-**2b** ((+)-MTPA ester), 89394-98-9; **3a**, 89321-74-4; **3b**, 89321-88-0; **4a**, 89321-75-5; **4a** (monotosylate), 89321-78-8; **4b**, 89321-91-5; **4b** (monotosylate), 89345-77-7; **5a**, 89321-76-6; **6a**, 89321-77-7; **7a**, 89321-79-9; **7b**, 89394-99-0; **8a**, 89321-80-2; **8b**, 89321-81-3; **9a**, 89321-82-4; **9b**, 89321-83-5; **10**, 89321-84-6; **10** (2-acetate), 89321-90-4; **10** (diacetate), 89321-76-6; **11**, 89321-85-7; **11** (1-tosyl-2-acetoxy deriv.), 89321-89-1; **12**, 89321-86-8; **13**, 89321-87-9; (+)-MTPA-Cl, 20445-33-4; *trans-i*-PrCH=CHCO$_2$Me, 20515-15-5.