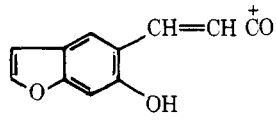
concentration) in solutions where a_{D^+} is high enough to protonate most of the 8-MOP.

Although we have made no real attempt to characterize the products of the slower reactions, both UV and NMR spectra show that substantial changes in the structure occur. We suspect that ring opening occurs to give either *cis*- and/or *trans*-6-hydroxy-5-benzofuranylacrylic acid, which would exist as carboxy-protonated conjugate acids or the related acylium ions in the strongly acidic media.



The rates in sulfuric acid solutions were highest in 95% acid, the highest concentration at which the changes were monitored. However, the most rapid change of all was observed in 72% $HClO_4$. Although the rate variation in H_2SO_4 solutions could be correlated by a mechanism involving attack of a second proton on (8-MOP)H^+, the same line of reasoning cannot account for the high rate in $HClO_4$.

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The Octant Rule. 7.[1] Deuterium as an Octant Perturber

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Abstract: (1*S*)-*exo*-2-Deuteriobicyclo[2.2.1]heptan-7-one (**1**) and (1*S*)-*endo*-2-deuteriobicyclo[2.2.1]heptan-7-one (**2**) were synthesized, and their circular dichroism spectra were measured and analyzed. Both ketones show dissignate Cotton effects near 295 nm corresponding to their n–π* electronic transitions: **1** ($\Delta\epsilon_{296}$ = +0.033) and **2** ($\Delta\epsilon_{292}$ = +0.132). The nature of the isotopic perturbation on the n–π* transitions of **1** and **2**, related β-deuterioadamantanones and cyclohexanones, and α-deuteriocyclohexanones is treated theoretically. The net contribution to the sign of the rotatory strength is determined by the relatively more consignate contribution of the C–H bond that is located in an oppositely signed octant relative to the C–D bond.

Until recently, application of the octant rule to interpret the n–π* Cotton effects (CEs) of chiral ketones with deuterium perturbers had received very little experimental justification. During the past several years, however, an increasing interest has focused on this aspect of isotopic stereochemistry with the result that an ever-growing body of circular dichroism (CD) data is becoming available. The first attempt to study the influence of deuterium on a ketone carbonyl n–π* Cotton effect (CE) was published by Djerassi, Closson, and Lippman in 1956.[3] No difference could be detected between the optical rotatory dispersion (ORD) spectra of 3β-acetoxy-6β-deuteriocholestan-7-one and its protio analogue. However, results derived by difference measurements of large values are not entirely satisfactory, especially since the two systems measured must be of the same concentration and optical purity, and they must have identical geometries. In an effort to overcome such shortcomings, Djerassi and Tursch[4] attempted the first direct measurement of a ketone (CE) where chirality was due to a single deuterium perturber, i.e., where the protio analogue is achiral. They prepared (3*S*)-deuteriocyclopentanone of known absolute configuration and measured its ORD spectrum but found no rotation (<42°) down to 280 nm. Subsequently, Meyer and Lobo[5] prepared (+)-camphor-*9,9,9-d*$_3$ which had a molecular amplitude[6] (+60.92°) 3% smaller than that of the protio compound. On the basis of this observation and the fact that the atomic refractivity of deuterium is less than hydrogen, the authors[5] concluded that deuterium, like fluorine,[7,8] makes an antioctant[6,9] contribution to the octant rule.[6,9,10]

The fruitfulness of employing a stereochemically rigid framework in detecting circular dichroism (CD) CEs due only to deuterium substitution was impressively demonstrated with (1*R*)-[1-^{2}H]-α-fenchocamphoronequinone[11] and (−)-(*S*)-4-deuterio[2.2]paracyclophane.[12] Weak but well-resolved CEs ($|\Delta\epsilon| \approx 0.02$) were observed in both examples. However, the first monoketone n–π* CE due solely to deuterium was observed only recently in a reinvestigation of (3*R*)-deuteriocyclopentanone,[13] which gave a (−)-CD CE [$\Delta\epsilon_{304}$ = −0.019 (25 °C) and $\Delta\epsilon_{302}$ = −0.021 (−196 °C)]. That important observation indicated that deuterium is an "antioctant" [9] perturber. It also initiated a series of interesting and valuable papers on the CD CEs of conformationally mobile[14-16] and locked[17] cyclic deuterio ketones from the Djerassi group. In those papers, deuterium was found usually but not always[17] to exhibit an "antioctant" effect and to prefer the axial (or more hindered) configuration relative to hydrogen.[15] Other work[18] has been reported on similar systems.[17] Prior to this work[14-18] we reported on the CD CE of a conformationally immobile β-equatorial deuterioadamantanone (**5**) in which the deuterium exhibits an "antioctant" effect, in hydrocarbon solvent.[1] Subsequently, Numan and Wynberg[19] reported on their syntheses and CD spectra of **4** and **5**.

In our work on chiral perturbers we have focused on the synthesis and CD analysis of stereochemically rigid structures that are achiral when the isotope under study (e.g., deuterium) is replaced by the more abundant isotope (e.g., hydrogen). In this way the inherent effect of the isotope perturber may be

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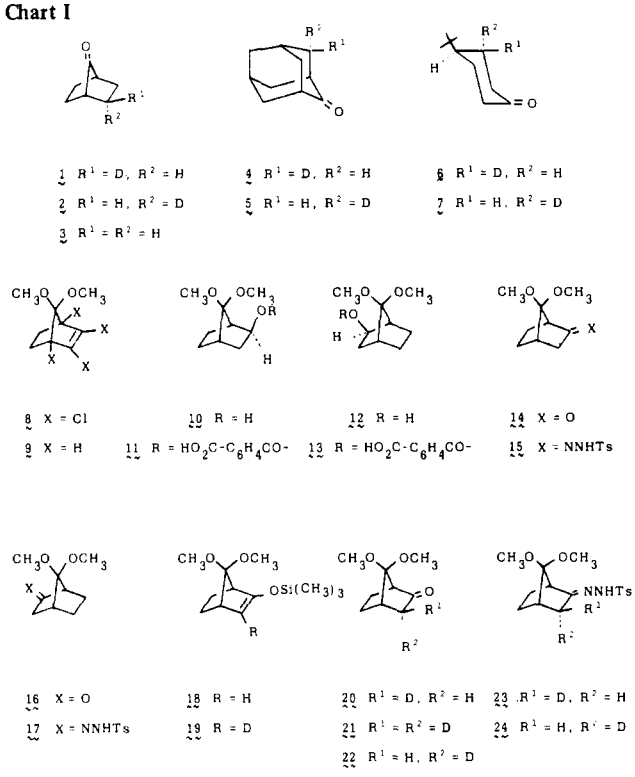
Chart I



recognized and analyzed without resort to comparisons of the CD spectra of, e.g., chiral deuterio vs. chiral protio analogues and without the necessity of conformational analysis. The latter, of course, becomes an intriguing study when CE signs and magnitudes for the perturbers are known with the certainty provided in judiciously chosen, stereochemically immobile structures. In the present work, we describe the preparations and CD spectra of (1*S*)-[2-*exo*-^{2}H]bicyclo[2.2.1]heptan-7-one (**1**) and (1*S*)-[2-*endo*-^{2}H]bicyclo[2.2.1]heptan-7-one (**2**), β-deuterio ketones that contain stereochemically rigid skeletons and whose chirality is due only to deuterium substitution. We provide as well a theoretical basis for understanding the contribution of deuterium as an octant perturber.

Synthesis and Stereochemistry

Optically active deuterio ketones **1** and **2** were prepared from the key intermediate hydroxy ketal (**10**),[20,21] which could be obtained from a racemic mixture of **10** + **12** by resolution of the corresponding half-acid phthalate ester racemate (**11** + **13**) with *l*-ephedrine.[20] Racemic **10** + **12** was conveniently prepared in high yield with >99% epimeric purity by oxymercuration of the known 7,7-dimethoxybicyclo[2.2.1]heptene (**9**), prepared from perchlorocyclopentadiene and ethylene with an improved[22] dechlorination step by reaction of **8** with sodium in liquid ammonia. The absolute configuration (1*S*) of **12** was determined by LIS-NMR measurements of its Mosher ester derivative.[23] This confirmed the earlier chemical determination of absolute configuration determination of **10** (1*R*) which was converted to (−)-norcamphor via transthioketalization, Raney-nickel desulfurization, and oxidation.[20] The optical purity or enantiomeric excess (ee) in a sample of **10** + **12** could be determined by use of the Mosher ester[23] or by addition of a chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III). By these two techniques, the diastereotopic syn OCH_3 group of the ketal separated cleanly and could be integrated accurately. We determined, thus, that enantiomerically pure **10** has $[\alpha]_D^{CH_2Cl_2}$ +50° and pure **14** has $[\alpha]_D^{CH_2Cl_2}$ −59°.

We had originally hoped to introduce one deuterium atom in a stereospecific way by deuteride displacement of tosylate or methanesulfonate from those corresponding esters of exo alcohol **10** or **12** (to give *endo*-d_1) and the corresponding endo alcohol (to give *exo*-d_1). Unfortunately, treatment of the tosylate or mesylate of **10** + **12** with lithium aluminum deuteride or lithium triethylborodeuteride ("super deuteride") in refluxing tetrahydrofuran led mainly to recovered starting material and some alcohol (**10** + **12**). Prolonged reaction with super deuteride led to not only the isolation of more **10** + **12** but also, curiously, to *p*-[$^2H_1$]toluene. The latter presumably arises via deuteride attack at aromatic carbon with cleavage of the C–S bond to give alcoholate (of **10** + **12**) and SO_2, which reacts with excess super deuteride to give diethyl disulfide, as noted by NMR. Steric crowding by the syn OCH_3 group apparently alters the normal reaction course, since methyl tosylate reacts with super hydride to give methane and lithium tosylate, and lithium tosylate and "super deuteride" do not react to produce toluene. Similarly, the endo tosylate and methanesulfonate do not react to give the desired product. Therefore, we had to devise an alternative stereospecific synthetic method.

Work on the base-catalyzed enolization–exchange of 2-norbornanones, which showed a k_{exo}/k_{endo} = 650[24a] or 715,[24b] and camphor, which showed a k_{exo}/k_{endo} = 12.4,[24b] 19.1,[24c] or 27.1,[24d] led us to believe that we might succeed in introducing deuterium stereospecifically exo by quenching the lithium enolate of **14** or **16** with DCl. Similarly, quenching the lithium enolate derived from **14**-*3,3*-d_2 or **16**-*3,3*-d_2 with HCl would be expected to lead to the *endo*-d_1 epimer. The remaining task would then be reduction of the ketone carbonyl group to a methylene group—without exchanging or epimerizing at the neighboring α-C bearing stereospecifically introduced deuterium. To accomplish this objective, we turned to tosylhydrazone formation and reduction. Since it had been shown previously that reaction of *exo*-3-deuteriocamphor with *p*-toluenesulfonylhydrazine led to tosylhydrazone with no deuterium loss and no epimerization,[25] we believed that the major uncertainty would be the tosylhydrazone reduction step. Many different reduction procedures (involving $NaBH_4$/THF, $NaBH_4/CH_3OH$, super hydride/THF, BH_3/THF, and $LiAlH_4/NiCl_2$/glyme) were unsuccessful and led either to no reduction or to undesired side reactions with extremely low yields of reduction. We succeeded in our objective, however, with the previously untried diisobutylaluminum hydride (DIBAL) and recommend this novel, facile method for reducing tosylhydrazones. We found that DIBAL reduced camphor tosylhydrazone in high yield (>67%, isolated product) and cholestan-3-one tosylhydrazone to give the corresponding hydrocarbons. It also reduced the tosylhydrazones of α,β-unsaturated ketones with double-bond migration: Δ^1-cholesten-3-one tosylhydrazone to Δ^2-cholestene and Δ^4-cholesten-3-one tosylhydrazone to Δ^3-coprostene (9:1 5β:5α).[26] Our task in reducing **15** + **17** was made more difficult by the penchant DIBAL exhibits toward ketal group cleavage. However, at low temperatures and short reaction times, we could achieve a >66% yield of the dimethyl ketal of **3** from reduction of **15** + **17**. The corresponding ketone **3** was isolated following deketalization in acetic acid.

Stereospecific introduction of deuterium was accomplished by kinetic deuteration of the lithium enolate of ketone **14.** Thus, deuterium chloride quenching of the lithium enolate, prepared by treatment of **14** with lithium diisopropylamide in tetrahydrofuran, afforded a 63:3:34 ratio of *exo*-d_1 (**20**):d_2 (**21**):d_0 (**14**) in quantitative yield. Presumably, the unexpectedly large amount of d_0 (**14**) arose from rapid D–H exchange with isopropylamine present during quenching of the enolate. A more effective preparation of *exo*-d_1 ketone **20** was accomplished by conversion of **14** to its trimethylsilyl enol ether (**18**), reaction of the latter with 1 equiv of methyllithium, and quenching with deuterium chloride to give a 92:2:6 ratio of *exo*-d_1 (**20**):d_2

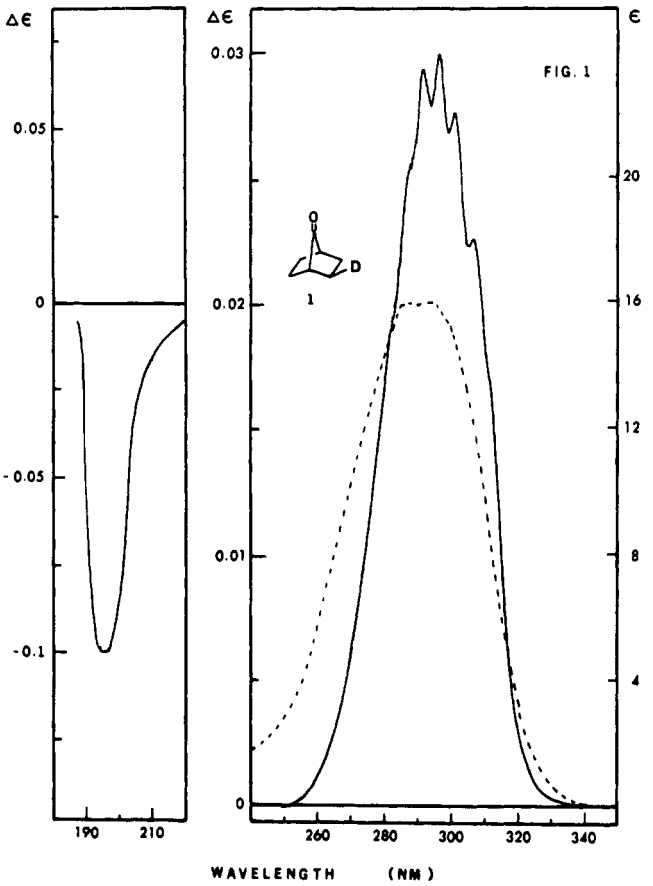


Figure 1. Circular dichroism (—) and ultraviolet (- - - -) spectra of (1*S*)-*exo*-2-deuteriobicyclo[2.2.1]heptan-7-one (**1**) in *n*-heptane at 25 °C. Corrections are made to 100% enantiomeric excess and 100% d_1. Base lines were obtained using equivalent concentrations of (achiral) 7-norbornanone (**3**) with no difference from pure *n*-heptane.

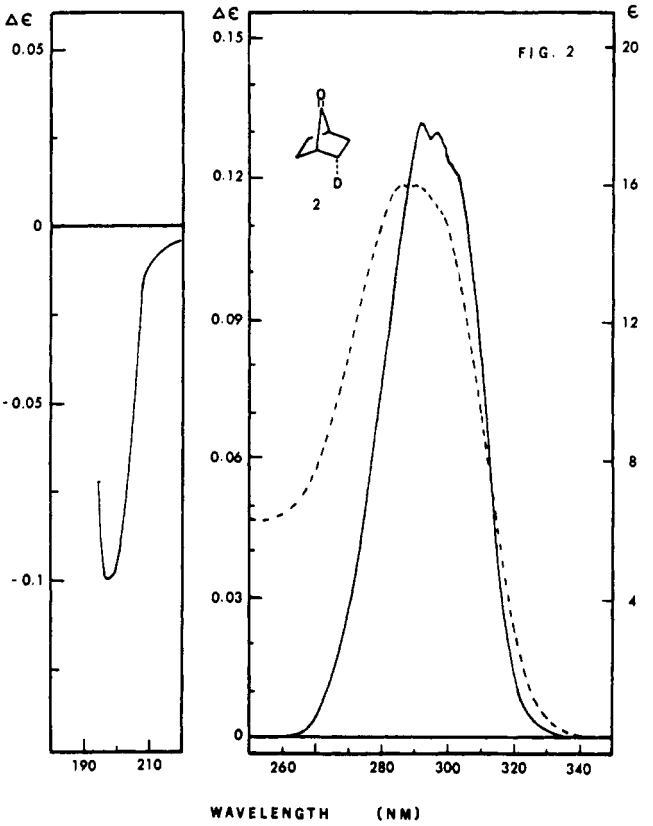


Figure 2. Circular dichroism (—) and ultraviolet (- - - -) spectra of (1*S*)-*endo*-2-deuteriobicyclo[2.2.1]heptan-7-one (**2**) in *n*-heptane at 25 °C. Corrections are made to 100% enantiomeric excess and 100% d_1. Base lines were obtained using equivalent concentrations of (achiral) 7-norbornanone (**3**) with no difference from pure *n*-heptane.

(**21**):d_0 (**14**). Similarly, the *endo*-d_1 ketone (**22**) (>97% *d*) was prepared by quenching the enolate from **19** with hydrochloric acid. The deuterated trimethylsilyl enol ether (**19**) was conveniently prepared following base-catalyzed exchange of **15** in D_2O/NaOD.

Conversion of **20** and **22** to their corresponding tosylhydrazones (**23** and **24**) was shown to involve no exchange of or epimerization of D. Interestingly, racemic tosylhydrazone is much more crystallizable then either enantiomer. Thus, crystallization of the tosylhydrazone with 48% enantiomeric excess (ee) of **15** led to crystals of nearly racemic material (**15** + **17**) with the mother liquors containing 95% ee of **15.** Similarly, crystallization of tosylhydrazone-d_1 (48% ee of **23**) gave mother liquors containing 91.5% ee of **23.** With this method of optical enrichment, nearly optically pure products could be obtained. The ee's of **15, 23,** and **24** could be determined by a convenient method of converting tosylhydrazones back to their parent ketones with *N*-bromosuccinimide.[25,27]

The key reaction, reduction of **23** and **24** to the dimethyl ketals of **1** and **2**, respectively, was accomplished with DIBAL at low temperatures and short reaction times. Deketalization in acetic acid gave the desired ketones (**1** and **2**) which were purified to >99.9% purity by preparative gas chromatography.

Ketones **1** and **2** were >99% *exo*-d_1 and 99% *endo*-d_1, respectively, as ascertained by LIS-NMR. By this method addition of Eu(fod)$_3$ resulted in the clean separation of the three sets of protons of **3** in the expected ratio 1:2:2 for the sets of hydrogens at C_1 + C_4, exo at C_2, C_3, C_5, C_6 and endo at C_2, C_3, C_5, C_6, with the endo signals at highest field. The method is essentially the same as that developed by Stothers and Tan[28] for their adamantanone work, and one we found useful in our adamantanone work.[1] It clearly showed epimeric purity in the 2.0:4.0:3.0 ratio of H signals for **1** and 2.0:3.0:4.0 ratio for **2**.

Attempts to make shorter the sequence of reactions leading to **1** involved direct deuteration of the dianion of **15** (from reaction with 2 equiv of CH_3Li at −60 to −10 °C) with DCl at −50 °C, followed by the usual DIBAL treatment and deketalization, and led to a 4:1 mixture of **1**:**2** containing 28:70:2 d_0:d_1:d_2.

Results and Discussion

Circular Dichroism Spectra, Rotatory Strengths, and Molecular Geometries. The CD and UV curves for long-wavelength n-π^* and shorter wavelength transitions were measured in *n*-heptane and are displayed in Figures 1 and 2. Attempts to measure accurate CD and UV spectra of **1** and **2** in 95% ethanol were thwarted because the compounds tended to undergo rapid (hemi)ketalization—an observation consistent with the preference for C-7 to relieve angle strain in going from sp^2 to sp^3 hybridization. Very rapidly obtained CD measurements in 95% ethanol gave CE curves with the same signs and nearly the same magnitudes as those of Figures 1 and 2 (see Experimental Section). The exo isomer **1** exhibits much better resolved vibrational fine structure (spacing ~550 cm^{-1}) on its n-π^* CD band (Figure 1) than the endo isomer **2** (Figure 2). Contrasting behavior can be found in comparing the CD spectra of the β-deuterioadamantanones[1,19] of which the equatorial-d_1 (endo-like) isomer **4** has clearly developed vibrational fine structure (spacing ~1050 cm^{-1}) whereas the axial-d_1 (exo-like) isomer **5** does not. The CD spectra of adamantanones **4** and **5**, which have their deuterium perturbers

Table I

compd	exptl[d] R	exptl[d] temp, °C	exptl[d] solvent	calcd[d] R^r	calcd[d] R^∇	D coordinates, Å[c] X	Y	Z
[(1*R*)[*exo*-2-D]bicyclo[2.2.1]heptan-7-one (**1**)	+0.073	(25)	*n*-heptane	+0.02	+0.07	2.118	−1.169	−1.358
(1*R*)[*endo*-2-D]bicyclo[2.2.1]heptan-7-one (**2**)	+0.338	(25)	*n*-heptane	+0.28	+0.51	1.197	−1.232	−1.822
(1*R*)[4(*R*)(a)-D]adamantan-2-one (**4**)	+0.06[a]	(25)	isooctane	−0.03	−0.00	2.132	−1.258	−1.161
(1*R*)[4(*S*)(e)-D]adamantan-2-one (**5**)	+0.28[a]	(25)	isooctane	+0.21	+0.32	1.258	−2.132	−2.395
[(3*S*)(a)-D]-(4*R*)-*tert*-butylcyclohexanone (**6**)	−0.027[b]	(25)	EPA	−0.03	+0.01	1.900	−1.288	−1.517
	−0.026[b]	(−197)	EPA					
[(3*R*)(e)-D]-(4*R*)-*tert*-butylcyclohexanone (**7**)	+0.318[b]	(25)	EPA	+0.22	+0.34	0.846	−2.093	−2.527
	+0.328[b]	(−197)	EPA					
[(2*S*)(a)-D]-(4*R*)-isopropylcyclohexanone	−0.119[b]	(25)	EPA	−0.28	−0.52	−0.938	−1.378	−1.299
	−0.113[b]	(−197)	EPA					
[(2*R*)(e)-D]-(4*R*)-isopropylcyclohexanone	−0.024[b]	(25)	EPA	+0.10	+0.17	0.078	−2.107	−0.130

[a] Values determined from the CD spectra of ref 19. [b] Values determined from the reduced rotatory strength data reported in ref 17. The CE of **6** in 5:1 isopentane-methylcyclohexane is also (−), with a somewhat weaker **R** (C. Djerassi, personal communication). [c] Origin at carbonyl carbon; C=O group in *Y*-*Z* plane. See text for model geometries used. [d] Rotatory strength (**R**), value $\times 10^{-40}$ cgs.

at nearly the same locations (relative to C=O) as **1** and **2**, were reported earlier.[1,19]

The rotatory strengths *R* for the n-π^* transitions of **1** and **2** are compared with those of adamantanones **4** and **5** and other relevant conformationally locked ketones[17] in Table I. Aside from the quite comparable $|R|$ values for axial and exo β-D perturbers and for equatorial and endo β-D perturbers, Table I also reveals the great similarity in D-perturber location among **1**, **4**, and **6** (*exo*-*d* $\approx$ β-axial D), and octant projection diagrams[6,10] for **1** and **2** and for **4**–**7** are consistent with all D perturbers being in a (−) back octant. It is therefore important to note that in each example, except **6**, the CE signs are opposite to those predicted by the classical octant rule, and deuterium may be viewed as making an "antioctant" or dissignate contribution. The apparent consignate behavior of the deuterium perturber in **6** is puzzling;[17] however, it lies near a CE sign-change region[9] and its inherent octant contribution will depend crucially on small changes in its coordinates and/or solvation. For example, *tert*-butylcyclohexanone is believed[29] to have a somewhat flattened six-membered ring as compared to cyclohexanone (or adamantanone), which would lead to small differences in the β-axial D coordinates of **4** and **6**. Also solvation played a sign-determining role in the CD spectra of (1*S*)-4(a)-methyladamantanone [($\Delta\epsilon$ is (+) in ethanol and (−) in isooctane)].[30] Whether **4** exhibits similar solvent effects will be examined in our future work; we know that **1** and **6** do not.

Theoretical Considerations. The rotatory strength R_{0b}, i.e., the integrated CD intensity over an electronic absorption band, is expressible theoretically (in cgs units) in either of the two forms

$$R^r_{0b} = \frac{e^2\hbar}{2mc}\langle 0|\mathbf{r}|b\rangle\cdot\langle 0|\mathbf{r}\times\nabla|b\rangle \quad \text{(length form)} \quad (1)$$

$$R^\nabla_{0b} = \frac{e^2\hbar^3}{2m^2c\Delta E_{0b}}\langle 0|\nabla|b\rangle\cdot\langle 0|\mathbf{r}\times\nabla|b\rangle \quad \text{(velocity form)} \quad (2)$$

where the transition is from the ground state ψ_0 to the *b*th excited state, and ΔE_{0b} is the excitation energy. The two forms yield identical results when exact wave functions are used, while the usual, approximate calculations may lead to discrepancies between them. Thus we compute both forms (reported as R^r and R^∇ in Table I), and use the agreement between them as a check on the quality of the results.

In an ordinary optically active molecule, the chirality is already evident in the nuclear geometry corresponding to the minimum of the adiabatic (Born-Oppenheimer) potential energy surface. For the molecules under consideration here, however, this equilibrium nuclear geometry is achiral, because the Born-Oppenheimer potential energy surface is unaffected by isotopic substitution. Hence the effects of nuclear vibrations play a crucial role in considerations of optical activity induced by isotopic substitution.

In the Born-Oppenheimer approximation, the vibronic wave functions are written as product functions

$$\Psi_{b\beta}(q,Q) = \psi_b(q,Q)\chi_\beta{}^b(Q) \quad (3)$$

where the electronic wave functions ψ_b are explicit functions of the electronic coordinates *q*, and depend parametrically on the nuclear coordinates *Q*. The vibrational functions $\chi_\beta{}^b$ are determined separately using the potential-energy surface defined by the eigenvalues corresponding to $\psi_b(q,Q)$. Using the vibronic wave functions, eq 3, and assuming that the excitations originate in the lowest vibrational level of the electronic ground state, $\chi_0{}^0$, we can write the rotatory strength for the absorption band in the general form

$$R_{0b} = \text{const} \times \langle\chi_0{}^0|\mathbf{D}_{0b}(Q)\cdot\mathbf{M}_{0b}(Q)|\chi_0{}^0\rangle_Q \quad (4)$$

Here $\mathbf{D}_{0b}(Q) = \langle\psi_0|\hat{\mathbf{D}}|\psi_b\rangle_q$, where $\hat{\mathbf{D}} = \mathbf{r}$ or $\hat{\nabla}$, $\mathbf{M}_{0b}(Q) = \langle\psi_0|\mathbf{r}\times\hat{\nabla}|\psi_b\rangle_q$, and the subscripts *q* and *Q* respectively designate integrations over electronic and nuclear coordinates. The electronic transition moments are functions of the nuclear coordinates through the nuclear dependence of the functions $\psi_i(Q)$, and for semirigid molecules, where average displacements are small, these transition moments can be expanded in a Taylor series in the nuclear displacements about a reference configuration Q' to yield (apart from a constant)

$$R_{0b} = \mathbf{D}_{0b}(Q')\cdot\mathbf{M}_{0b}(Q') + \sum_\xi \left\{\left[\frac{\partial\mathbf{D}_{0b}}{\partial Q_\xi}\right]'\mathbf{M}_{0b}(Q') + \mathbf{D}_{0b}(Q')\cdot\left[\frac{\partial\mathbf{M}_{0b}}{\partial Q_\xi}\right]'\right\}\langle\chi_0{}^0|Q_\xi - Q'_\xi|\chi_0{}^0\rangle_Q + \text{higher order terms} \quad (5)$$

If the expansion center is taken to be the equilibrium nuclear geometry Q^0, then the first term vanishes by assumption for the molecules we consider, and the second term is nonzero only for an anharmonic vibration. Qualitatively, however, one can see that, for an anharmonic vibration, the difference in zero-point energies for two isotopes will lead to a slight difference in the *average* values of the nuclear coordinates, $\overline{Q}_\xi = \langle\chi_0{}^0|Q_\xi|\chi_0{}^0\rangle_Q$, $\xi = 1, \ldots, 3N-6$. If we now take the average geometry $\overline{Q}$ as the expansion center for the Taylor expansion, the first term is nonvanishing since the average geometry is now chiral, whereas the second term vanishes. The effects of nuclear vibrations may thus be taken into account (to first order) by the purely electronic term alone, provided that bond lengths are approximately adjusted for isotopic

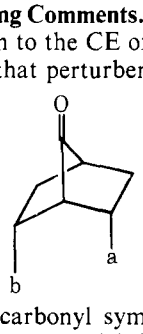
substitution. Differences in electronegativity among isotopes need not be invoked.[31] The qualitative features of this analysis, which leads to a shortening of a C–D bond relative to a C–H bond, were first used in calculations performed by one of us (T.D.B.) and reported by Simek, Mattern, and Djerassi.[13] The analysis was formalized by Dezentje and Dekkers,[32] and calculations using this method show the proper qualitative behavior.

The calculations reported here use the approximate CNDO/S molecular orbital method of DelBene and Jaffe,[33] and the $n\rightarrow\pi^*$ excited state is approximated as a single electron promotion from the n into the π^* orbital. Details of the computational method are given in ref 9. Geometries for the molecules considered (Table I) were adjusted so that the C–D bond length was taken rather arbitrarily to be 0.02 Å shorter than that of a C–H bond. This bond shortening exaggerates the actual change in the average molecular geometry,[34,35] but is used in the context of our approximate MO method to ensure that reasonable qualitative conclusions can be drawn.

Computations, as described above, were carried out for the compounds in Table I. In the absence of an experimental structure for the 7-norbornanone skeleton, geometrical parameters for **1** and **2** were taken from Dreiding models, with bond lengths C_1–C_2 = C_1–C_7 = 1.54 Å, C_2–C_3 = 1.58 Å, C–H = 1.08 Å, C–D = 1.06 Å, C–O = 1.22 Å, and angles $C_1C_7C_4$ = 94°, dihedral angle between $C_1C_2C_3C_4$ and $C_1C_4C_5C_6$ planes = 114.7°. These values are similar to electron-diffraction results for norbornane itself.[36] Geometries for **4** and **5** were based upon an idealized adamantane structure, with all C–C–C and H–C–H bond angles tetrahedral, and bond lengths C–C = 1.54 Å, C–O = 1.22 Å, C–H = 1.09 Å, and C–D = 1.07 Å. Geometries for a fully staggered conformation of the isopropylcyclohexanones were obtained from Dreiding models. The crystal structure[29] of *tert*-butylcyclohexanone was taken as the basis for the calculations on **6** and **7**.

The results are shown in Table I. The calculated results reproduce the qualitative features of the CD spectra quite well, with the exceptions of the very weak axial deuterium contribution in the adamantanone **4** and the α-equatorial deuterium in the isopropylcyclohexanone. These anomalies can be readily rationalized in terms of slight inaccuracies in the assumed geometry, since both substituents lie very close to regions of sign change in the octant rule.[9] In the other cases, the good quantitative agreement between the experimental and calculated rotatory strengths is probably fortuitous, but the overall agreement supports the hypothesis that the effect of deuterium substitution results primarily from a decrease in the mean C–D bond length, and further that a deuterium substituent exerts an effect opposite in sign to that of a hydrogen atom at the same site.

Concluding Comments. In the octant rule[9,10] the net signed contribution to the CE of a given perturber (a) is evaluated relative to that perturber (b) located in a position reflected



i, a = H; b = Cl
ii = **2**, a = D; b = H

across the carbonyl symmetry plane. The important contrasting features are (1) differences in the chemical nature of the perturbers and (2) differences in bond lengths. For most perturbers studied heretofore, differences in the *chemical* nature of the perturbers were sufficiently large as to be sign determining, i.e., a and b ordinarily need not be in exactly comparable positions in their respective octants. Thus, considerations of bond-length differences were rendered inconsequential. For example, in i with a = H and b = Cl the chemical difference between Cl and H is sufficient to allow correct prediction of the CE without resort to consideration of the different C–Cl and C–H bond lengths. This approximation and that of neglecting H contributions form the basis for the qualitative application of the classical octant rule.[10] The chemical nature of a deuterium perturber, however, is virtually indistinguishable from that of H, e.g., as in ii = **2**, and one must therefore resort to a consideration of bond-length differences. When the small difference between the C–D and C–H bond lengths is incorporated into our theoretical treatment, we conclude that the H perturber makes the sign-determining contribution to the observed CE because the C–D bond is shorter and D is closer to the carbonyl symmetry plane. (The reason for the latter observation can be discerned through an examination of the contribution of the C–D bond to the *z* component of the dipole velocity transition moment matrix element.[9]) In our computations, the C–D bond contributes *less* than its mirror image C–H counterpart bond; *thus, the net contribution to the sign of the rotatory strength is determined by the comparatively more consignate*[37,38] *contribution of the C–H bond that is located across the carbonyl mirror plane from the C–D bond.*

Experimental Section

General. Circular dichroism spectra were recorded on a JASCO J-40 instrument equipped with a photoelastic modulator, ultraviolet spectra were recorded on a Cary 219 spectrophotometer, and sodium D-line rotations were determined on a Perkin-Elmer 141 polarimeter. All nuclear magnetic resonance spectra (60 MHz) were determined on a Perkin-Elmer R-24B instrument, mass spectra were recorded at 70 eV on a JEOL JMS-07 spectrometer and infrared spectra were recorded on a Perkin-Elmer 599 spectrophotometer. All melting points are uncorrected and were determined on a Thomas-Hoover apparatus. Analytical gas chromatography (GC) was performed on column A (6 ft × 1/8 in., 5% SE-30 on Chromosorb W AW-DMCS), column B (6 ft × 1/8 in., 5% FFAP on Chromosorb W AW-DMCS), or column C (6 ft × 1/8 in., Carbowax 790 on Chromosorb W AW-DMCS) on a Varian-Serograph 2400 instrument. Preparative GC was performed on a Varian-Aerograph 1720 instrument using column D (6 ft × 3/8 in. 12% QF-1 on Chromosorb W). Combustion analyses were performed by Chemalytics, Tempe, Ariz. Spectral data were obtained using spectral-grade solvents (MCB). Other solvents were distilled and dried before use: diethyl ether and tetrahydrofuran (from $LiAlH_4$ under N_2) and dichloromethane (from P_2O_5) were used freshly distilled or stored over 4A molecular sieves (Linde). Tetramethylethylenediamine (TMEDA, Aldrich) was distilled twice from CaH_2 and stored over 5A molecular sieves. Pyridine was distilled from BaO and stored over KOH and dioxane was distilled from CaH_2 and stored over 4A molecular sieves. Deuterium oxide (D_2O) used in this work was 99.8% from Bio-Rad. Column chromatography was accomplished on Florisil (Floridin Co.) on Merck neutral alumina. Analytical thin layer chromatography (TLC) was carried out with a 125-μ layer silica gel F (M. Woelm, Eschwege).

7,7-Dimethoxybicyclo[2.2.1]heptene (9).[22b] 7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]heptene (**8**) was prepared according to the literature procedure from the Diels–Alder reaction of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene [from hexachlorocyclopentadiene (Aldrich), KOH–CH_3OH, and ethylene (Matheson)]. An improvement in the dechlorination step was achieved by using sodium–liquid ammonia.[22a]

Liquid ammonia (400 mL) was trapped in a 1-L three-neck round-bottom flask equipped with a mechanical stirrer (glass paddle), a cold finger dry ice condenser, and a gas inlet tube following distillation from the gas cylinder. Sodium (25 g, 1.09 g-atoms) was cut into pea-size chunks and added to the liquid ammonia. The gas inlet tube was replaced by a 500-mL pressure-equalized dropping funnel containing a solution of **8** (20.0 g, 68.5 mmol) in 110 g of anhydrous ethanol and 150 mL of dry ether. The solution was added dropwise over a period of 40 min to the sodium–liquid ammonia with stirring. A white precipitate formed during the addition. Stirring was continued for an additional 15 min; then the reaction was quenched by addition of solid ammonium chloride until the blue color of the mixture dis-

appeared. Ammonia was allowed to evaporate from the reaction following removal of the dry ice condenser. The remaining white slurry was dissolved in water and extracted with pentane (3 × 100 mL). The combined pentane extracts were washed twice with saturated aqueous NaCl and dried (Na_2SO_4). The solution was distilled to remove the pentane, and further distillation through a 225-mm Vigreux column gave the pure product, bp 65–70.5 °C (25–35 mm), 7.21 g (78%) [lit.[22b] bp 56–68 °C (17 mm)]. It had IR (neat) 1186, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (m, 2 H, endo C_5H and C_6H), 1.85 (m, 2 H, exo C_5H and C_6H), 2.71 (m, 2 H, >CH), 3.09 (s, 3 H, syn OCH_3), 3.13 (s, 3 H, anti OCH_3), 5.98 (t, 2 H, J = 2.2 Hz, =CH) ppm; MS *m/e* (rel intensity) 154 (27) [M^+·], 139 (17) [$M - CH_3$], 123 (34) [$M - OCH_3$], 107 (26), 79 (100).

7,7-Dimethoxybicyclo[2.2.1]heptan-*exo*-2-ol (10 + 12).[21,22c] Mercuric acetate (11.5 g, 36 mmol) was added to 35 mL of water in a 250-mL Erlenmeyer flask equipped for magnetic stirring. This mixture was cooled in ice-water for 10–15 min, then alkene **9** (5.55 g, 36 mmol) was added as a solution in 35 mL of tetrahydrofuran. After complete addition, the stirred mixture was allowed to warm to room temperature and stirred for an additional 30 min. Five milliliters of 3 M aqueous NaOH was added at once followed by the dropwise addition of a solution of 0.72 g (19 mmol) of sodium borohydride in 35 mL of 3 M aqueous NaOH. After complete addition, the mixture was stirred for 20 min and saturated with NaCl and the organic layer removed using a pipet. The aqueous layer was extracted with ether (2 × 50 mL). The organic layers were combined and allowed to stand to facilitate mercury precipitation. After 3 h, 2 g of NaCl was added followed by 2 g of anhydrous Na_2SO_4 1 h later. After standing for an additional 1 h, the liquid was decanted and the solvents were removed on a rotary evaporator. The residue was distilled through a 225-mm Vigreux column to give 5.1 g (85%) of a liquid (bp 101–102 °C, 2.6 mm) (lit.[22c] bp 62–72 °C, 0.6 mm]. GC analysis on column A, 122 °C, showed the liquid to be 97% pure. After standing for 1 day at room temperature, the liquid partially solidified. The solid, mp 37–39 °C, had identical spectral properties with the liquid, except that the latter had a weak IR band at 1730 cm^{-1} due to a trace of acetate contaminant. Spectral properties: IR (neat) 3540, 2830, 1110, 1060 cm^{-1}; NMR ($CDCl_3$) δ 0.71–2.29 (8 H), 3.21 (s, 3 H, OCH_3), 3.23 (s, 3 H, OCH_3), 3.64 (dd, 1 H, J = 3.6, 7.6 Hz, CHO) ppm; MS *m/e* (rel intensity) 172 (1.1) [M^+·], 155 (25) [$M - OH$], 154 (23) [$M - H_2O$], 108 (31), 101 (100), 91 (54), 55 (65).

7,7-Dimethoxybicyclo[2.2.1]heptan-*exo*-2-yl Half-Acid Phthalate (11 + 13). A mixture of 37.9 g of the alcohol (**10** + **12**), 39.0 g (2 equiv) of phthalic anhydride (recrystallized from CH_2Cl_2, mp 131.5–133.5 °C), and 200 mL of anhydrous pyridine was heated under N_2 at 90 ± 3 °C for 5 h and left overnight at room temperature. The pyridine was removed under reduced pressure, and the residue dissolved in 420 mL of 1 M $NaHCO_3$ and washed with light petroleum ether (2 × 100 mL) to remove starting olefin. The aqueous solution was acidified with cooling in an ice bath with 250 mL of 2 N HCl and extracted with CH_2Cl_2. After washing with water, drying (Na_2SO_4), and removing the solvent there was obtained a crystalline product, which was washed with ether, yield 59.15 g, mp 148.5–150 °C. The oily residue obtained from mother liquor crystallized from ether–light petroleum ether to give an additional 4.35 g of product, mp 147–149 °C. The total yield was 63.5 g (90%). It had IR (KBr) 3500–2800, 1718, 1116, 1060 cm^{-1}; NMR ($CDCl_3$) δ 0.94–2.48 (m, 8 H), 3.17 (s, 6 H, OCH_3), 4.83 (dd, 1 H, J = 4.4, 6.6 Hz, CO_2CH–), 7.24–7.88 (m, 4 H, ArH), 10.10 (s, 1 H, CO_2H) ppm; MS *m/e* (rel intensity) 320 (1.2) [M^+·], 155 (100), 149 (12), 104 (17), 101 (36).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 63.74; H, 6.29. Found: C, 63.53; H, 6.25.

Resolution of Half-Acid Phthalates 11 and 13. The racemic half-acid phthalate (133.75 g) and *l*-ephedrine (69.0 g) were dissolved in 1.6 L of hot dioxane and left for 24 h. The crystalline salt (159 g) was recrystallized three more times from dioxane–ethyl acetate to give 84.4 g of the salt (A), mp 157–158 °C, $[\alpha]_D$ −17.66° (*c* 0.99, CH_2Cl_2). Further fractional crystallization of the concentrated mother liquors gave the crops (B) 49.5 g, $[\alpha]_D$ −73.2 to −8.2° (*c* 1.0, CH_2Cl_2), and (C) 35.9 g, $[\alpha]_D$ −2.4 to −3.8° (*c* 0.94, CH_2Cl_2) and the mother liquors (D) 32.6 g, $[\alpha]_D$ +1.8 and +4.8° (*c* 1.44, CH_2Cl_2). Salts A–D were separately hydrolyzed by extracting twice with cold 2 N aqueous HCl, evaporating the ether, and dissolving the residue (white solid) in 2 N aqueous NaOH. Continuous extraction with *n*-pentane for 2 × 6 h and evaporation of the dried ($MgSO_4$) extract afforded practically pure (GC, column B, 130 °C) alcohol with the yield 95%. Small samples of the alcohol were distilled (85 °C, 2 mm) for optical-purity determination. This was done by observing splitting of the –OMe signals in the ^1H NMR spectrum upon addition of Eu(facam)$_3$ (Aldrich) to the solution of the alcohol in $CDCl_3$.[20] Similarly, ^1H NMR or ^{19}F NMR of the Mosher esters gave the same result.[23] The recovered fractions of the alcohol had the following optical purities (enantiomeric excess, ee): (1) alcohol from A 30% ee, $[\alpha]_D$ −14.4° (*c* 2.3, CH_2Cl_2); (2) alcohol from B almost racemic, $[\alpha]_D$ +0.25° (*c* 7, pentane); (3) alcohol from C 24% ee, $[\alpha]_D$ +11.4° (*c* 1.7, CH_2Cl_2); (4) alcohol from D 48% ee, $[\alpha]_D$ +24.4° (*c* 3.7, CH_2Cl_2).

Absolute Configuration of (+)-7,7-Dimethoxybicyclo[2.2.1]heptan-*exo*-2-ol. The absolute stereochemistry of the (+) alcohol was previously[20] determined to be 1*R* by conversion of a sample to (−)-(1*S*)-norcamphor and reconfirmed using an LIS–NMR method on the Mosher ester.[23] Thus, for the former, to 200 mg (1.16 mmol) of (+) alcohol ($[\alpha]^{22}_D$ +6.0° (CH_2Cl_2)) in 3 mL of *n*-butanethiol was added 1 drop of boron trifluoride etherate, and the solution was heated at 110 °C for 16 h. After cooling, CH_2Cl_2 was added, the solution was washed with dilute aqueous K_2CO_3, and the solvent was removed on a rotary evaporator to give a dark, viscous oil, which was chromatographed on a short column of neutral alumina (activity II) to give the thioketal in petroleum ether and CH_2Cl_2 washings. Removal of the solvent on a rotary evaporator gave a light orange-brown oil which was treated directly with a large excess of Raney nickel[39] in ethanol at reflux for 20 min. After filtration, evaporation to 2 mL volume, and refiltration, water was added, and the mixture was extracted with light ether. GC (column C, 100 °C) showed a major peak and impurities totaling less than 1%. After removal of the petroleum ether on a rotary evaporator, the remaining oil was oxidized using excess chromium trioxide–pyridine in CH_2Cl_2. After 2 h, the solution was washed with 5% aqueous NaOH, then with 5% aqueous HCl and water. The organic layer was dried (Na_2SO_4) and evaporated to give (−)-norcamphor, which was >99% pure by GC (column C, 150 °C) and had a retention time identical with that of (±)-norcamphor (Aldrich). It gave a dinitrophenylhydrazone with the same silica gel TLC R_f (0.8, CH_2Cl_2) as that from (±)-norcamphor, and had a negative Cotton effect. The chiroptical properties establish the 1*S* configuration for the derived (−)-norcamphor[40] and hence the 1*R* configuration for (+) alcohol which has structure **10.**

The assignment of absolute stereochemistry was confirmed by LIS–NMR on the Mosher ester of **12.**

(1*R*)-7,7-Dimethoxybicyclo[2.2.1]heptan-2-one (14).[20] The (+) alcohol **10** (5.0 g, 29 mmol, $[\alpha]_D^{CH_2Cl_2}$ +24.4°, 48% ee) in 10 mL of dry CH_2Cl_2 was added to a mechanically stirred slurry of 10 g (1.4 equiv) of dry pyridinium chlorochromate[41] in dry CH_2Cl_2 at room temperature. The reaction mixture turned dark almost immediately, and soon an exothermic reaction began. Sodium acetate (0.25 g) was added, and the mixture was stirred for 2 h. An additional 0.5 g of pyridinium chlorochromate was added to complete the oxidation, as monitored by GC on column B, 130 °C. Stirring was continued for an additional 2 h, then the reaction mixture was diluted with 60 mL of ether and filtered through a short column of Florisil. The dark tars at the top of the column were washed with 3 × 25 mL of ether. The solvents were combined and evaporated under reduced pressure. The crude crystalline ketone was taken up in pentane–ether (3:1) and filtered through silica gel (activity II) to give a >99.9% pure product which solidified with a considerable exothermic effect upon solvent evaporation to give 4.7 g (95%) of **14,** mp 43–47 °C. It had $[\alpha]_D$ −28.4° (*c* 1.81, CH_2Cl_2); IR (neat) 2835, 1755, 1100, 1070 cm^{-1}; NMR (CCl_4) δ 3.18 (s, 6 H, OCH_3), 2.6–1.2 (m, 8 H) ppm; MS *m/e* (rel intensity) 170 [M^+·] (9), 101 (100), 97 (28), 55 (32).

Pure racemic ketone (**14** + **16**) was prepared as above in 93% yield, bp 95–98 °C (2 mm) (lit.[21] bp 52–55 °C, 0.2 mm) using Kugelrohr distillation in place of the silica filtration.

(1*R*)-7,7-Dimethoxy[2.2.1]heptan-2-one Tosylhydrazone (15). (−)-Ketone **14** (851 mg, 5 mmol, $[\alpha]_D^{CH_2Cl_2}$ −28.4°, 48% ee) was heated briefly to boiling with 931 mg (5 mmol) of *p*-toluenesulfonylhydrazine (Aldrich) in 5 mL of CH_3OH and let stand at room temperature for 24 h. Part of the tosylhydrazone crystallized and was removed by filtration and washed with ether–pentane to give 882 mg (52%) of material A with mp 188–190 °C dec and $[\alpha]_D$ +2.0° (*c* 1.2, $CHCl_3$). The mother liquor was evaporated to dryness to give a semisolid tosylhydrazone (B), 810 mg (48%), with $[\alpha]_D$ +22.0°(*c* 1.4, $CHCl_3$) and mp 125–128 °C.

In order to ascertain the ee of A and B, each was separately con-

verted back[25,27] to the corresponding 7,7-dimethoxybicyclo-[2.2.1]heptan-2-one. Tosylhydrazone (84.6 mg, 0.25 mmol) was dissolved in a mixture of 3.5 mL of acetone and 1 mL of H_2O, and the solution was cooled in an ice bath. *N*-Bromosuccinimide (178 mg, 1 mmol) was added with stirring, and stirring was continued for 2 min. Two milliliters of 0.5 M aqueous $Na_2S_2O_3$ was added followed by 2.5 mL of H_2O, and the reaction mixture was extracted with ether. The extracts were washed with 1 N aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$), and the ether was evaporated at room temperature. The crude product (81 mg) was purified by GC (column D) to give pure ketone. The ketone from A had $[\alpha]_D^{CH_2Cl_2}$ −2.78° (4.7% ee) and that from B had $[\alpha]_D^{CH_2Cl_2}$ −56.1° (95% ee).

Racemic tosylhydrazone (**15** + **17**) was prepared from racemic ketone (**9** + **11**) (170 mg, 1 mmol) and 186 mg (1 mmol) of *p*-toluenesulfonylhydrazine in 1 mL of CH_3OH. After 24 h at room temperature, the reaction mixture was evaporated to dryness under reduced pressure and washed with pentane to give a crystalline product, 338 mg (100%), mp 190–191 °C dec. (Tosylhydrazone of 48% ee had mp 175–182 °C dec.)

The tosylhydrazone had IR (Nujol) 3200, 2840, 1670, 1595, 1325, 1160 cm^{-1} and NMR ($CDCl_3$) δ 2.38 (s, 3 H, $ArCH_3$), 3.00 (s, 3 H, OCH_3), 3.16 (s, 3 H, OCH_3), 7.20 (d, J = 8 Hz, 2 H, ArH), 7.74 (d, J = 8 Hz, 2 H, ArH).

Anal. Calcd for $C_{16}H_{22}O_4N_2S$: C, 56.78; H, 6.55; N, 8.28. Found: C, 57.01; H, 6.41; N, 8.16.

Bicyclo[2.2.1]heptan-7-one (3).[42] To racemic tosylhydrazone (**15** + **17**) (338 mg, 1 mmol), prepared above under **15,** in 2 mL of dry CH_2Cl_2 was added at 0 °C under N_2 2.5 mL of 0.9 M diisobutylaluminum hydride (DBAL, Ventron) in hexane. The mixture turned bright yellow after ca. 1 mL of the DIBAL solution was added, and all the tosylhydrazone was dissolved during DIBAL addition. Stirring was continued for 15 min (subsequent reactions showed no increase in yield with extended reaction times), and the solution was carefully decomposed with 2.5 mL of 3 N aqueous NaOH. Extraction with pentane, drying ($MgSO_4$), and distillation of the solvents through an efficient Vigreux column gave a colorless solution containing 103 mg (66%) of 7,7-dimethoxybicyclo[2.2.1]heptane by GC analysis on column B, 80–100 °C. A sample of the product was purified by preparative GC on column D (110 °C). It had NMR (CCl_4) δ 0.9–1.4 (m, 4 H), 1.5–2.0 (m, 6 H), and 3.10 (s, 6 H, 2 OCH_3) ppm and MS *m/e* (rel intensity) 156 [M^+], 101 (100). There was no evidence by NMR or MS for the presence of olefinic impurities.

The alkaline extract, upon acidification with 6 N aqueous HCl and extraction with ether, gave 141 mg (90%) of *p*-toluenesulfinic acid.

A solution of 1 mmol of the ketal in 1 mL of 2 N aqueous HCl in glacial acetic acid was stirred under N_2 at room temperature for 10–16 h. The mixture was carefully extracted (while cooling) with pentane–ether and 7 mL of 3 N aqueous NaOH. The extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated by distillation through a Vigreux column. The product (**3**) was collected as a colorless solid by preparative GC on column D (110 °C), mp 79.5–80.5 °C, a waxy, highly volatile solid. It had UV (*n*-heptane) ϵ_{292} 16 (lit. ϵ_{292} 18 in isooctane,[42] ϵ_{292} 22 in $CHCl_3$,[42] and ϵ_{290} 14 in ethanol[43]); NMR ($CDCl_3$) δ 1.3–2.2 (m) with the signals being well separated into a 1:2:2 ratio having δ bridgehead > δ exo > δ endo upon addition of Eu(fod)$_3$ (Aldrich); MS *m/e* (rel intensity) 110 [M^+·], 67 (100), 54.

(1*R*)-2-Trimethylsilyloxy-7,7-dimethoxybicyclo[2.2.1] hept-2-ene (18). To a magnetically stirred solution (under argon) of 1.54 mL (11 mmol) of diisopropylamine (distilled from CaH_2) in 5 mL of THF (distilled twice from $LiAlH_4$ under N_2) was added 4.3 mL of 2.6 N (11 mmol) *n*-butyllithium in hexane with cooling in an ice bath. To this clear solution a solution of 1.70 g (10 mmol) of ketone **14** in 3 mL of THF was added followed by addition (at once) of 7.5 mL of the quenching solution (12 mL of freshly distilled trimethylsilyl chloride plus 3 mL of triethylamine, distilled from CaH_2, dissolved in 30 mL of THF; filtered prior to use). The ice-water bath was removed, and the solution was stirred at room temperature for 1 h, during which time a white precipitate of LiCl appeared. The mixture was diluted with pentane and extracted with 1 N aqueous $NaHCO_3$. The dried ($MgSO_4$) pentane solution upon evaporation gave an almost quantitative yield of the oily trimethylsilyl enol ether, practically pure by GC (column B, 130 °C) and IR; yield 97% after distillation, 100 °C (2.5 mm). It had IR (neat) 3080, 2830, 1620, 1255, 1095, 1070, 845 cm^{-1}; NMR (CCl_4) δ 0.18 (s, 9 H, $Si(CH_3)_3$), 3.04 (s, 6 H, 2 OCH_3), 4.5 (dd, J = 3.5, 1.5 Hz, 1 H, =CH) ppm and MS *m/e* (rel intensity) 242 [M^+·], 73 (100).

Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.70; H, 9.32.

(1*R*)-3-*exo*-Deuterio-7,7-dimethoxybicyclo[2.2.1]heptan-2-one (20). Trimethylsilyl enol ether (**18,** 1.128 g, 4.65 mmol) from 48% ee ketone **14** was dissolved in 5 mL of THF and treated at 0 °C under nitrogen with 2.9 mL of 1.6 M methyllithium in ether. After 15 min 1 mL of 5 N aqueous DCl was added at once, and the mixture was extracted immediately with pentane–aqueous $NaHCO_3$. The extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated to give 732 mg (92%) of colorless solid **20,** which was identical with **14** in most respects. Mass spectral analysis indicated it to be 92% d_1, 6% d_0, and 2% d_2.

(1*R*)-3,3-Dideuterio-7,7-dimethoxybicyclo[2.2.1]heptan-2-one (21). A two-phase mixture of 410 mg (2.41 mmol) of ketone **14** (48% ee) in 3 mL of THF and 1 mL of 1 M NaOD was stirred at room temperature for 4 days with 15 mg (2 molar equiv) of cetyltrimethylammonium bromide (phase transfer agent). Dried NaCl was added, and the organic phase was separated. It was stirred for another 4 days with fresh 1 N NaOD. Each NaOD solution was buffered (pD 7) with 2 mL of 0.8 M K_2HPO_4 and extracted with ether–pentane. The extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated to give a quantitative yield of colorless solid ketone **21** which was identical in most respects with **14.** MS analysis showed it to be 97% d_2 and 3% d_1.

(1*R*)-3-*endo*-Deuterio-7,7-dimethoxybicyclo[2.2.1]heptan-2-one (22). Ketone **21,** above, was converted to its trimethylsilyl enol ether (**19**) as described for **18.** The NMR of **19** showed the complete absence of the vinyl hydrogen signal at δ 4.5. This material (**19,** 1.580 g, 6.50 mmol) was treated in the same manner as in the synthesis of **20,** except that 7 mL of THF, 4.1 mL of 1.6 M methyllithium in ether, and 1.1 mL of 6 N HCl were used. The yield of **22** was 1.034 g (93%), which was 100% d_1 by MS.

(1*R*)-3-*exo*-Deuterio-7,7-dimethoxybicyclo[2.2.1]heptan-2-one *p*-Toluenesulfonylhydrazone (23). Ketone **20** (731 mg, 4.27 mmol, 48% ee), 795 mg (4.27 mmol) of *p*-toluenesulfonylhydrazine (recrystallized), 5 mL of anhydrous THF, and 1 g of 5A molecular sieves were stirred at room temperature for 24 h. The solution was separated from the sieves, evaporated to dryness, and left in a desiccator over KOH until the product fully crystallized. Recrystallization from CH_2Cl_2–CH_3OH gave 738 mg (51%) of tosylhydrazone A, mp 185–186 °C dec. The remaining product, B, obtained by evaporation of the mother liquor solvent, was a colorless, viscous semisolid showing negligible C=O absorption in the IR. Using the method described under **15** to convert tosylhydrazone back to ketone, and referring to the rotation of **14** (≃that of 20), A had an ee of 6%, whereas **B** had an ee of 91.5%. Thus, B was converted to ketone **20** and had $[\alpha]_D$ −54.0° (*c* 1.28, CH_2Cl_2), corresponding to 91.5% ee. Its mass spectrum was nearly identical with that of starting **20** and showed 92.5% d_1 and 1.5% d_2. Thus, neither tosylhydrazone formation nor this method of converting tosylhydrazone back to ketone encumbered any deuterium loss.

(1*S*)-2-*exo*-Deuteriobicyclo[2.2.1]heptan-7-one (1). Tosylhydrazone **23** (above) (641 mg, 1.89 mmol, 91.5% ee) was dissolved in 4 mL of dry CH_2Cl_2 and treated while stirring under N_2 at 0 °C with 5 mL of 0.9 M diisobutylaluminum hydride (DIBAL, Ventron) in hexane. After 15 min the bright yellow solution was quenched with 5 mL of 3 N aqueous NaOH while stirring. The mixture was extracted with pentane and the organic phase was dried ($MgSO_4$) and concentrated by distilling through a Vigreux column to remove volatiles. The remaining 3.2 mL of solution contained 228 mg (77%) of product ketal as determined by GC analysis (column B, 80 °C).

The ketal solution was heated at reflux under N_2 (oil bath 110 °C) with 1.8 mL of glacial acetic acid for 10 h while the solvents were allowed to distill partially through a 30-cm Vigreux column. The solution was then treated with 12 mL of 3 N aqueous NaOH and extracted with pentane. The pentane was dried ($MgSO_4$) and filtered through activity II silica gel, after addition of 10% volume of ether, to give a clear solution. It was concentrated by distillation through a Vigreux column and the residual solution purified by preparative GC (column D, 110 °C). The resulting crystalline ketone (**1**) was carefully rechromatographed on the GC to give 50 mg (24% overall yield from tosylhydrazone **18**-B) of >99.9% pure **1**. It has a GC retention time identical with that of pure bicyclo[2.2.1]heptan-7-one (**3**) on several columns (A, B, D). The epimeric purity was determined by use of

NMR with the aid of Eu(fod)$_3$ (Aldrich). Addition of the shift reagent led to clean separation of the pair of hydrogens at 1 and 4, the exo set and the endo set in the ratio 2.0:3.0:4.0. The α-H's move out first followed by the exo set, as anticipated from the work of Stothers[28] on adamantanone. Thus, the monodeuterated material (92% d_1, 6% d_0, 2% d_2) was 100% d_{exo} and the chiral material ($d_1 + d_2$) had 91.5% ee. The d_0 ketone is achiral. The ketone thus prepared had UV (*n*-heptane) $\epsilon_{292} = 16$ and (CH_3OH or 95% C_2H_5OH) λ_{max} 288 nm (in alcohol, a rapid ketalization ensues); CD (*n*-heptane) $\Delta\epsilon_{296}$ +0.033 (corrected to 100% ee and 100% *exo*-d_1) with vibrational spacing 580 cm^{-1}, $\Delta\epsilon_{195}$ −0.1, and (95% C_2H_5OH) $\Delta\epsilon_{292}$ +0.03; MS *m/e* (rel intensity) 111 [$M^{+\cdot}$], 68 (100), 55.

(1*R*)-*endo*-Deuterio-7,7-dimethoxybicyclo[2.2.1]heptan-2-one *p*-Toluenesulfonylhydrazone (24). Ketone **22** (955 mg, 5.58 mmol, 48% ee), 1.040 g (5.58 mmol) of *p*-toluenesulfonylhydrazine (recrystallized), and 6 mL of CH_3OH were mixed, heated briefly, and left at room temperature for 24 h. The solvent was evaporated under vacuum from the partially crystallized product, and the residue was washed with pentane and dried at 85 °C under vacuum to give 1.875 g (99%) of the product, mp 127–130 and ~160 °C dec. No fractional crystallization was attempted. The total material had the 48% ee of the starting ketone when converted back to it (see under **23**) by the NBS method.

(1*S*)-2-*endo*-Deuteriobicyclo[2.2.1]heptan-7-one (2). Tosylhydrazone **24** from above (1.87 g, 5.52 mmol, 48% ee) was partially dissolved in 12 mL of dry CH_2Cl_2 and treated under N_2 at 0 °C with 15 mL of 0.9 M DIBAL (Ventron) in hexane as described for **1**. The reaction was quenched after 15 min with 15 mL of 3 N aqueous NaOH and the mixture worked up as described under **1** to yield 4.9 mL of colorless solution containing (GC estimation using column B, 80 °C) 557 mg (64%) of the desired ketal.

Deketalization of the total material was effected by stirring the solution with 5 mL of glacial acetic acid and 1 mL of concentrated HCl. The two-phase reaction mixture was stirred for 24 h at room temperature, at which time GC (column B, 80 °C) showed deketalization to be complete. The reaction was worked up with 35 mL of 3 N aqueous NaOH and pentane–ether to give (after concentration of the extracts) 3 mL of solution containing 47% of desired ketone **2**. It was purified and collected by preparative GC (column D, 110 °C) to give initially 120 mg (65% recovery) of crystalline ketone which was further purified by additional preparative GC to give 80 mg of **2**, >99.9% pure, checked as under **1**. NMR analysis as with **1** showed an exo-H:endo-H ratio of 4:3, and the MS showed it to be >97% d_1. Thus the material is pure essentially *endo*-d_1. It had UV (*n*-heptane) ϵ_{291} 16 and CD (*n*-heptane) $\Delta\epsilon_{292}$ +0.132 (corrected to 100% ee and 100% d_1), $\Delta\epsilon_{196}$ −0.1, and (95% ethanol) $\Delta\epsilon_{292}$ +0.096.

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References and Notes

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