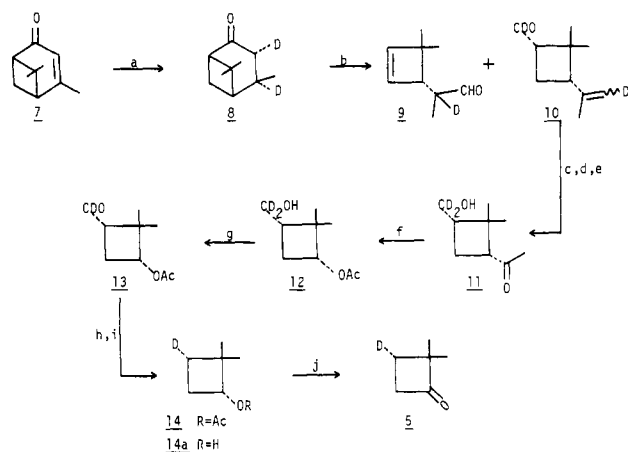


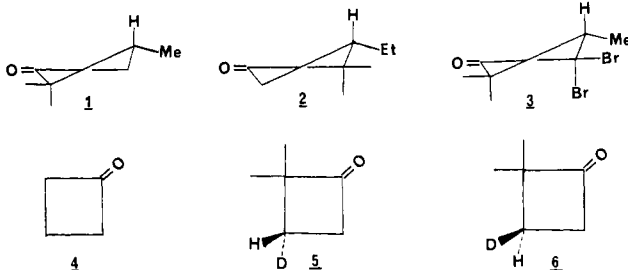
Scheme I



a. D_2 , Pd/C, EtOAc; b. $h\nu$, MeOH; c. $LiAlD_4$; d. D_2 , MeOH; e. Me_2S ; f. *m*-CPBA, CH_2Cl_2 ; g. PCC; h. $(Ph_3P)_3RhCl$, CH_2Cl_2 ; i. KOH, MeOH; j. Jones Ox.

most commonly employed isotope. Thus we have reported^{3,4} the synthesis and CD data of several conformationally mobile, chirally deuterated cyclohexanones and cyclopentanones and have found with the exception of one cyclopentanone^{4b} that deuterium relative to hydrogen prefers to occupy a conformational position having the greater nonbonded steric interactions. Furthermore, the energy differences between chair conformations in cyclohexanones and twist conformations in cyclopentanones were calculated to be on the order of 1–10 cal/mol in favor of axial and quasi-axial deuterium.^{3d,e}

Though there have been no reports of CD studies on optically active cyclobutanones in which the chirality is solely due to isotopic substitution, Conia and Goré⁵ have reported chiroptical studies on a series of alkylated and brominated cyclobutanones and we have reported magnetic circular dichroism properties of a series of alkyl substituted cyclobutanones.⁶ More recently, the CD and ORD spectra of (*R*)-2-methylcyclobutanone have been reported.²¹ From the CD studies of cyclobutanones 1–3,⁵ a consistent trend



emerged which indicated that these cyclobutanones were most likely puckered and that the bulkier group at position 3 preferred the pseudoequatorial orientation. Although a microwave study⁸ of the parent compound, cyclobutanone (4), indicated that it also was slightly puckered, an earlier liquid crystal NMR study⁷ of 4 predicted a flat structure.

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(5) (a) Conia, J. M.; Goré, J. *Bull. Soc. Chim. Fr.* **1964**, 1968–1975. (b) Conia, J. M.; Goré, J. *Tetrahedron Lett.* **1963**, 1379–1382.

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Scheme II

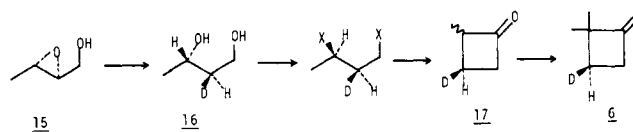
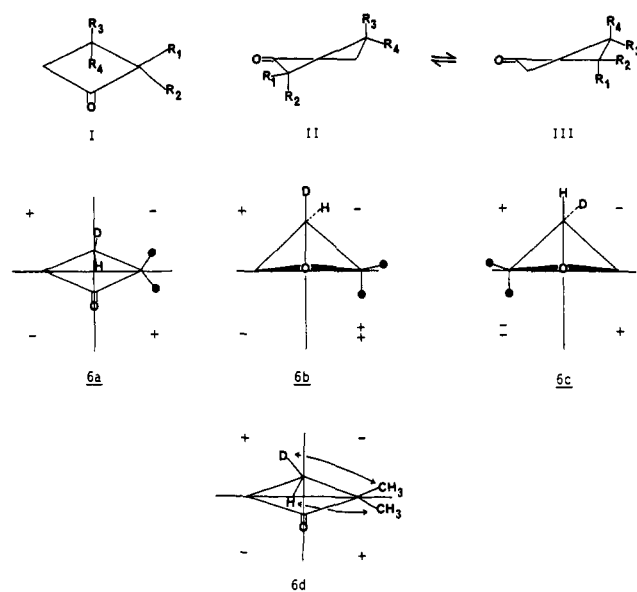


Chart I



ently gave poor yields of product which proved to be exceedingly difficult to purify. This method was abandoned in favor of a longer sequence¹⁷ which utilized the equally useful key *cis*-epoxy alcohol **20** (Scheme III). Thus starting from L-threonine (**18**), diazotization in the presence of KBr gave (2*S*,3*R*)-2-bromo-3-hydroxybutanoic acid¹³ which was treated with aqueous base to give the epoxy salt **19** as a hygroscopic solid. After reacting **19** with iodomethane in DMF,¹⁴ the resulting methyl ester was reduced with NaBH₄ to provide **20** as a rather volatile, water-soluble liquid. Reduction of **20** with LiAlH₄ according to a procedure previously reported for ethyl (*E*)-2,3-epoxybutyrate¹⁵ gave the two diols **22a** and **21a** in an approximate ratio of 2:1, respectively. Reduction of **20** in a similar manner with LiAlD₄ provided **22b** and **21b** in the even more favorable ratio of 5:1. The two isomers (**21b** and **22b**) were cleanly separated by careful silica gel chromatography, and the major isomer **22b**, after converting to the dimesylate and treating with LiBr,¹⁵ was transformed to the deuterated dibromobutane **23**. Ring closure was accomplished by reacting **23** with tosylmethyl isocyanide in the presence of excess NaH to give the cyclobutane derivative **24** which upon acid hydrolysis yielded (2*R*,3*R*)-3-deuterio-2-methylcyclobutanone (**25**).¹⁶

At this point, introduction of the second methyl group into **25** in a regioselective manner proved to be a formidable problem as noted in model experiments with unlabeled 2-methylcyclobutanone.¹⁸ Attempts to generate the thermodynamic enolate of 2-methylcyclobutanone with LiH-DME, NaH-DME, Et₂NLi-DME, Ph₃CLi-Et₂O, or LDA-Et₂O followed by trapping as the trimethylsilyl enol ether or quenching with iodomethane invariably led to unreacted starting material or intractable mixtures in which none of the desired product could be detected. However, it was found that by treating excess 2-methylcyclobutanone with lithium triphenylmethylide in THF at low temperature, followed by equilibration and quenching with iodomethane, a sufficient, unmaximized yield of 2,2-dimethylcyclobutanone could be obtained. To our knowledge, this is the first example of a direct regioselective alkylation of an unsymmetrically substituted cyclobutanone. Consequently, upon adding a 10–20% excess of **25** to lithium triphenylmethylide in THF at –78 °C, allowing equilibration of enolates at 0 °C and addition of iodomethane there was isolated as the major product pure (*R*)-3-deuterio-2,2-dimethylcyclobutanone (**6**) by preparative gas chromatography. Mass spectral analysis of **6** indicated a deuterium incorporation at C-3 of 97%. The enantiomeric excess of **6** was determined via the acetonides **26a,b** which in turn were prepared by treating diols **22a,b** with pivalaldehyde. In Figure 1 the partial 360-MHz ¹H NMR spectra of both **26a,b** in benzene-*d*₆ are shown. From the integral ratio of H5_{eq} to H5_{ax} in the spectrum of **26b** the optical purity at C-5 is ca. 97% and therefore the enantiomeric excess of **6** is 97%.

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(14) Buehler, C. A.; Pearson, D. E., Ed. "Survey of Organic Synthesis"; Wiley: New York, 1970; p 817.

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(17) Majetich, G.; Stork, G., personal communication.

(18) The 2-methylcyclobutanone was prepared as in ref 16.

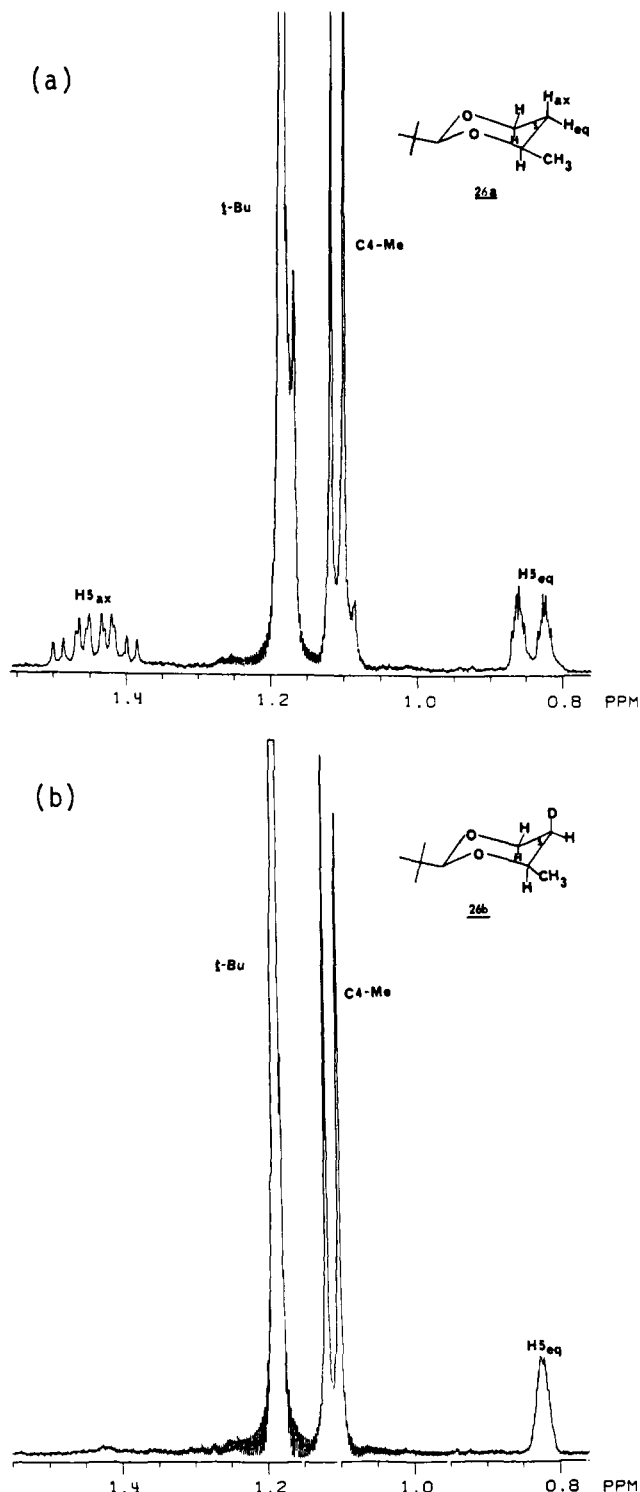


Figure 1. Partial 360-MHz ¹H NMR spectra of (a) (2*S*,4*R*)-2-*tert*-butyl-4-methyl-1,3-dioxane and (b) (2*S*,4*R*,5*R*)-2-*tert*-butyl-(5-²H)-4-methyl-1,3-dioxane, both in benzene-*d*₆.

Results and Discussion

When conformational effects in cyclobutanones are discussed, two main possibilities should be considered: (a) the cyclobutanone ring is flat, i.e., all ring carbon atoms lie in the same plane as in I (Chart I), or (b) the ring exists in a dynamic state of equilibrium between two "puckered" conformations which can be represented as II and III. The first possibility leads to the observation that all substituent positions in I would be conformationally equivalent whereas the second possibility (II and III) would lead to substituent positions which would be conformationally nonequivalent, i.e., pseudoaxial and pseudoequatorial. The molecular system chosen

here (**5** or **6**) is ideally suited to explore both possibilities. If the true representation of **6** is as shown in I ($R_1 = R_2 = \text{CH}_3$, $R_3 = \text{D}$, $R_4 = \text{H}$) then the back octant diagram can be drawn as in **6a** (Chart I). It is seen that the chiral center lies in a nodal plane and therefore makes no octant contribution while the two methyl substituents, being symmetrically disposed, contribute equal and opposite contributions and thus cancel each other. As a result there should be no observable CD effects in **6a**. Alternatively, if the true representation of **6** contains contributions from II and III, then the back octant diagram can be drawn as in **6b** and **6c**. In this case, although the α -gem-dimethyl group does not contribute to a conformational preference, it does cause the rotational strengths of both conformers to be large numbers of opposite sign. Therefore, even a small difference in the conformational population at equilibrium can be measured by way of the α -gem-dimethyl group which serves as a "chiral probe".^{3c}

The CD spectrum of (*R*)-3-deuterio-2,2-dimethylcyclobutanone (**6**) in various solvents (Figure 2) shows a negative Cotton effect at room temperature while that of the *S* enantiomer (**5**) shows a positive Cotton effect at room temperature. These results indicate that 3-deuterio-2,2-dimethylcyclobutanone cannot be totally flat but must exhibit some conformational mobility as implied in II and III.

An alternative explanation for the observed Cotton effects in **5** and **6** is a steric interaction between the α -gem-dimethyl group and the deuterium and hydrogen atoms at C-3. This possible interaction could lead to an out-of-plane bending of the C-3 substituents as shown in **6d** (Chart I). As a result both deuterium and hydrogen would then be pushed into positive and negative octants, respectively. Since in most cases it is observed that deuterium behaves in a dissignate manner² (i.e., deuterium provides less octant contribution than hydrogen), this possible steric distortion could lead to the observed Cotton effects in Figure 2. However, there is evidence on two accounts that dispels this possibility.

First, Conia and Goré⁵ observed positive and negative Cotton effects for the cyclobutanones **1** and **2**, respectively. If the steric interactions illustrated in **6d** are considered for **1** and **2**, then one would expect just the opposite, i.e., a negative Cotton effect for **1** and a positive Cotton effect for **2**. Indeed for these two cases an adjacent methyl-methyl or methyl-ethyl interaction would seem much more likely than the methyl-deuterium and methyl-hydrogen interactions depicted in **6d**. Second, in Figure 2d the CD of (*R*)-3-deuterio-2,2-dimethylcyclobutanone (**6**) is shown in isopentane-methylcyclohexane (4:1) mixture at increasingly lower temperatures. At 219 K the Cotton effect becomes weaker, at 153 K a bisignate signal is observed, and at 77 K the CD of **6** almost undergoes a complete sign inversion. Predictably, one would not expect such a temperature-dependent sign reversal for the flat structure shown as **6d**. This behavior, upon lowering the temperature, is taken to indicate a shift in the conformational equilibrium toward the thermodynamically favored conformer. Therefore, as further support for the equilibrium implied in II (= **6b**) and III (= **6c**, Chart I), we conclude that 3-deuterio-2,2-dimethylcyclobutanone exhibits a shift in the conformational equilibrium, upon lowering the temperature, toward the thermodynamically favored conformer in which deuterium occupies the pseudoaxial orientation, i.e., conformer II ($R_1 = R_2 = \text{CH}_3$, $R_3 = \text{D}$, $R_4 = \text{H}$).

The anomalous sign reversal in Figure 2d has been observed in only one other cyclic ketone whose chirality is solely due to isotopic substitution, that being the deuterated cyclohexanone **27**.^{3e} The change from a negative Cotton effect at room temperature to a bisignate Cotton effect at 77 K in the CD of **27** was attributed to a greater rotational strength contribution for conformer **27a** as compared to the thermodynamically favored conformer **27b**.^{3e} Assuming an almost 50:50 equilibrium mixture of **6b** and **6c** at room temperature,²² we likewise conclude that the conformer

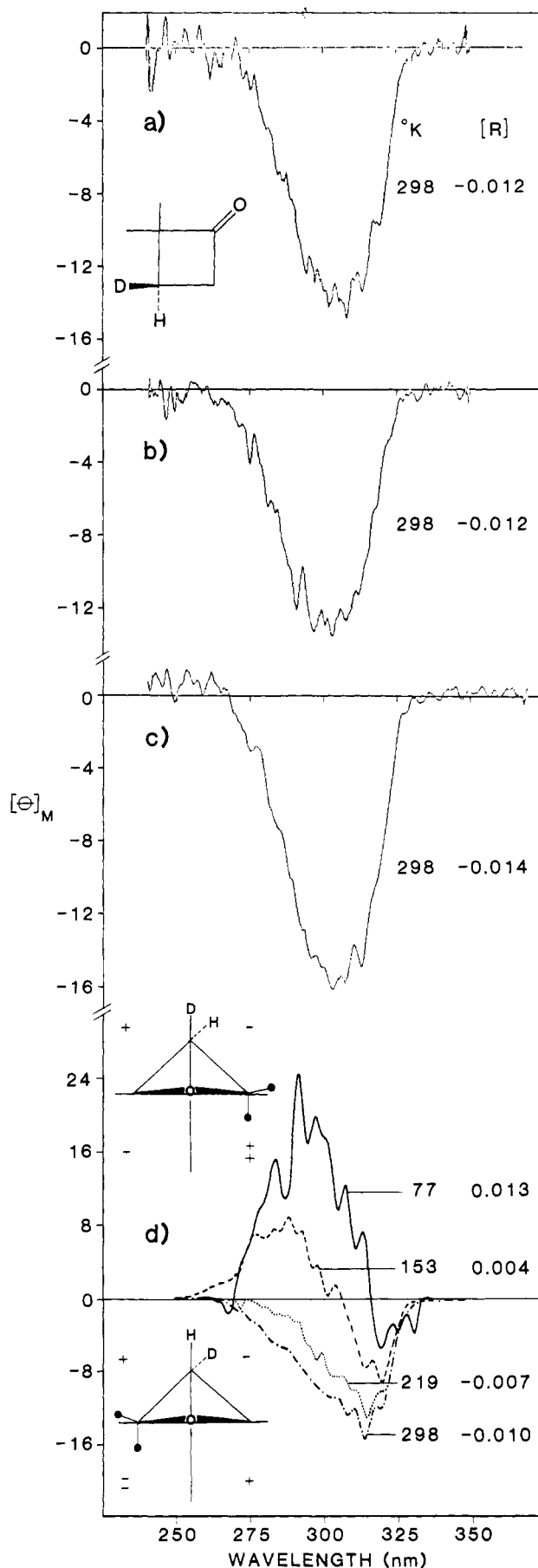
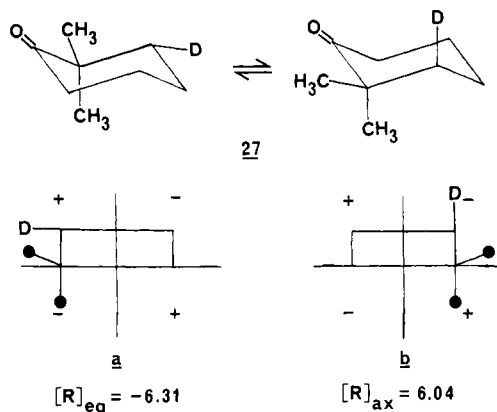


Figure 2. Circular dichroism spectra of (*R*)-(3-²H₁)-2,2-dimethylcyclobutanone (**6**) in (a) isooctane at room temperature, $c = 2.49$ g/L; (b) methanol at room temperature, $c = 3.01$ g/L; (c) ether, isopentane, ethanol (5:5:2) at room temperature, $c = 3.77$ g/L; (d) isopentane, methylcyclohexane (4:1) at various temperatures between 298 and 77 K, $c = 5.49$ g/L.

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(20) Possel, Cf. O.; van Leusen, A. M. *Tetrahedron Lett.* **1977**, 4229.



illustrated in **6c**, in which deuterium is in the pseudoequatorial orientation, has a greater rotational strength than the conformer illustrated in **6b**. This leads to our final conclusion: *due to steric and/or electronic effects, the chiral center (C-3) in (R)- and (S)-3-deuterio-2,2-dimethylcyclobutanone apparently makes a direct octant contribution to the observed Cotton effects in Figure 2.*

Experimental Section

Circular dichroism spectra were measured on a JASCO J-40 instrument, using a previously described¹⁹ 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 Rudolph Autopol III polarimeter in a thermostated 10-cm cell. Infrared (IR) spectra were recorded as neat liquid films between NaCl plates or as a solution in a NaCl cell with 1-mm path length, using a Beckman Acculab 3 infrared spectrophotometer. ¹H NMR spectra were obtained on either a Varian T-60, a 300-MHz Nicolet NT 300 WB, or a 360-MHz Bruker HXS-360 spectrometer and are given as δ values with deuteriochloroform as solvent and tetramethylsilane as internal standard. Mass spectra (MS) were obtained on a Ribermag R 10-10B spectrometer. High-resolution mass spectra were determined by A. Wegmann on a Varian MAT-711 spectrometer; both instruments operated at 70 eV with a direct inlet system. Preparative gas chromatography was performed with a Varian Aerograph Series 2700 gas chromatograph. The following columns were used: column A, 10 ft, 20% Carbowax 20M on 80/100 Chromosorb W; column B, 10 ft, 20% OV-101 on 100/120 Supelcoport.

2,3-Dideuterioverbanone (8). (–)-Verbanone (22 g, Aldrich, ee 90%) in ethyl acetate was reduced with deuterium gas, using 5% Pd/C as the catalyst to give 22 g of **8**: ¹H NMR 1.03 (s, 3 H), 1.36 (s, 3 H), 1.16 (s, 3 H), 2.00–2.80 (m, 4 H).

Photolysis of 8. Compound **8** (22 g) in 600 mL of methanol containing 0.1 g of NaHCO₃ was photolyzed to yield the two aldehydes **9** and **10** in the ratio of 1:7.5 as previously reported.⁹ Compound **9**: ¹H NMR 1.00 (s, 3 H), 1.06 (s, 3 H), 1.20 (s, 3 H), 5.96 (b s, 2 H), 9.80 (d, 1 H, $J = 2$ Hz). Compound **10**: ¹H NMR 0.90 (s, 3 H), 1.40 (s, 3 H), 1.66 (b s, 3 H), 4.60 (b s, 0.5 H), 4.76 (b s, 0.5 H).

(2,2-Dimethyl-3-acetylcyclobutyl)(α , α -²H₂)methanol (11). Aldehyde **10** (9.5 g) was reduced in ether with 0.65 g of LiAlD₄ at 0 °C to yield 8.2 g of 2,2-dimethyl-3-[1-methyl-(2-²H₁)ethenyl]cyclobutyl(α , α -²H₂)-methanol: $[\alpha]_D^{25} -10.51^\circ$ (c 1.90, CHCl₃); IR (film) 3150, 2100, 2050, 1650 cm⁻¹; ¹H NMR 0.83 (s, 3 H), 1.23 (s, 3 H), 1.63 (s, 3 H), 4.48 (b s, 0.5 H), 4.70 (b s, 0.5 H); MS, m/z 124 (17, M⁺ – CD₂OH), 123 (26), 86 (38), 73 (100), 72 (58), 71 (28), 70 (42), 69 (46), 68 (53), 67 (25).

This material (2.2 g) was ozonized in 100 mL of methanol at –78 °C until the first permanent blue color. The ozonide was decomposed with 5 mL of Me₂S, and after standard workup there was obtained 1.6 g of ketol **11**: $[\alpha]_D^{25} 100.87^\circ$ (c 9.20, CHCl₃); IR (film) 3200, 2100, 2050, 1740 1725 cm⁻¹; ¹H NMR 0.93 (s, 3 H), 1.70 (s, 3 H), 2.03 (s, 3 H), MS, m/z 125 (15, M⁺ – CD₂OH), 98 (21), 97 (37), 96 (25), 86 (22), 83 (100), 73 (80), 72 (57), 71 (31), 70 (54), 69 (52), 68 (16), 55 (36).

(2,2-Dimethyl-3-acetoxycyclobutyl)(α , α -²H₂)methanol (12). To a solution of 1.6 g of **11** in 50 mL of CH₂Cl₂ was added 2.9 g of *m*-chloroperbenzoic acid over a 5-min period. The mixture was stirred in

the dark for 2 days and washed with saturated NaHCO₃ and then saturated sodium thiosulfate. After the solution was washed again with saturated NaHCO₃ followed by water and brine and dried the solvent was evaporated to give 1.26 g of the acetate **12**: $[\alpha]_D^{25} -32.50^\circ$ (c 1.70, CHCl₃); IR (film) 3200, 2100, 2050, 1740, 1725 cm⁻¹; ¹H NMR 1.00 (s, 3 H), 1.20 (s, 3 H), 2.03 (s, 3 H); MS, m/z 114 (7, M⁺ – HOAc), 88 (37), 73 (100), 72 (63), 71 (36), 70 (34), 45 (27), 43 (71); isotopic purity, 97%.

(1S)-(2,2-Dimethyl-3-acetoxycyclobutyl)(α -²H₁)carboxaldehyde (13). To a suspension of pyridinium chlorochromate in 50 mL of CH₂Cl₂ was added 1.2 g of **12** in 2 mL of CH₂Cl₂. The mixture was stirred at room temperature for 3 h, poured into 200 mL of ether, and filtered through a column of Florisil. Evaporation of the filtrate gave a residue which was chromatographed on silica gel. Elution with hexane and increasing amounts of ether yielded 0.94 g of pure aldehyde **13**: $[\alpha]_D^{25} -109.7^\circ$ (c 1.10, CHCl₃); IR (film) 2050, 1740, 1700 cm⁻¹; ¹H NMR 1.06 (s, 3 H), 1.43 (s, 3 H), 2.06 (s, 3 H), 4.70 (dd, 1 H $J = 7$ Hz, 7 Hz); MS, m/z 111 (23, M⁺ – HOAc), 110 (3), 96 (24), 73 (20), 72 (30), 46 (38), 45 (47), 43 (100).

(3S)-(3-²H₁)-2,2-Dimethylcyclobutyl Acetate (14). To a solution of 0.4 g of aldehyde **13** in 6 mL of CH₂Cl₂ was added 5 g of tris(triphenylphosphine)rhodium chloride. The mixture was heated at reflux for 2 days and concentrated and the residue distilled at 150 °C. The distillate was chromatographed on silica gel and elution with pentane and increasing amounts of ether provided pure acetate **14**. A sample was purified free of solvent by preparative gas chromatography (column A, 120 °C): IR (CHCl₃) 2100, 1735 cm⁻¹; ¹H NMR 1.03 (s, 3 H), 1.13 (s, 3 H), 2.00 (s, 3 H), 4.76 (t, 1 H, $J = 7$ Hz); MS, m/z 100 (8, M⁺ – CH₃C≡O⁺), 87 (12), 86 (17), 83 (17), 82 (21), 72 (34), 67 (17), 45 (22), 44 (32), 43 (100); isotopic purity, 60%.

(S)-(3-²H₁)-2,2-Dimethylcyclobutanone (5). The acetate **14** was hydrolyzed with 10% methanolic KOH at 0 °C for 12 h. At the end of this time, the mixture was poured into water and extracted with three portions of ether. After drying (MgSO₄), the combined extracts were concentrated by distillation through a Vigreux column at atmospheric pressure. A sample of pure alcohol **14a** was obtained free of solvent by preparative gas chromatography (column A, 130 °C): IR (CHCl₃) 3310, 2100 cm⁻¹; ¹H NMR 1.06 (s, 3 H), 3.76 (t, 3 H, $J = 7$ Hz).

Alcohol **14a** was oxidized with Jones reagent to give a mixture of products from which pure **5** could be isolated by preparative gas chromatography (column A, 80 °C): MS, m/z 99 (19, M⁺); isotopic purity, 60%. For complete spectral data, see preparation of the *R* isomer to follow. The CD spectrum of **5** in isopentane–methylcyclohexane (4:1) mixture showed a mirror image Cotton effect to the CD spectrum of **6** in the same solvent mixture. The magnitude of the rotation however was somewhat less due to the lower isotopic purity of **5**.

(2R,3R)-Epoxybutan-1-ol (20).¹⁷ (2S,3R)-2-Bromo-3-hydroxybutanoic acid was prepared from L-threonine as previously described.¹³ This material (37.25 g) was dissolved in 50 mL of water and cooled in ice. With stirring, there was added 28.9 g of KOH pellets over a 30-min period and the resulting mixture was allowed to warm to room temperature. After stirring an additional 20 h, the pH of the mixture was adjusted to 8.0 by the addition of solid CO₂ and then evaporated under reduced pressure to a semisolid residue. The residue was taken up in hot absolute ethanol, filtered free of inorganic salts, decolorized with activated carbon, and concentrated to a syrupy residue. After pumping down under vacuum overnight, there was obtained 30 g of potassium salt **19** as a gum which slowly solidified to an off-white solid.

To 30 g of **19** in 100 mL of dry DMF was added 18 mL of iodomethane and the mixture was warmed at 50 °C with stirring for 3 h. After stirring at room temperature for an additional 18 h, the mixture was cooled in ice, 220 mL water was added and the mixture was extracted with five portions of pentane–ether (1:1). The combined extracts were washed once with saturated brine–water (1:1) and dried (MgSO₄) and the solvent removed by distillation through a Vigreux column at atmospheric pressure. There was recovered 16.5 g of methyl (2R,3R)-epoxybutanoate as a light yellow liquid which was pure enough for subsequent use. An analytical sample was obtained by chromatographing on silica gel and eluting with pentane–ether (7:3): $[\alpha]_D^{25} 4.22^\circ$ (c 0.925, CHCl₃); IR (film) 1745, 1260 cm⁻¹; ¹H NMR 1.39 (d, 3 H, $J = 5$ Hz), 3.30 (m, 1 H), 3.52 (d, 1 H, $J = 4$ Hz), 3.83 (s, 3 H); MS, m/z 116 (2, M⁺), 85 (5), 59 (100), 57 (21).

Into a mixture of 5.17 g of NaBH₄ in 50 mL of methanol–water (1:1) cooled to 0 °C was dropped a solution of 10.6 g of methyl (2R,3R)-epoxybutanoate in 10 mL of methanol–water (1:1) over a 15-min period. The mixture was stirred in the cold for 3 h after which time there was added 100 mL of water. After saturating with NaCl, the mixture was extracted with eight 50-mL portions of ether, the combined extracts dried (MgSO₄), and the solvents removed by distillation through a Vigreux column at atmospheric pressure. The remaining residue was chromatographed

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(22) To calculate the equilibrium position between the two conformers as we have previously done^{3,4} would require reference values for the ellipticities of the involved conformers. Since these data are not presently available, we are unable to perform these calculations.

graphed on silica gel through a water-cooled column at 18 °C. Elution first with pentane-ether (7:3) and then with pentane-ether (3:2) provided 2.45 g of pure (2*R*,3*R*)-epoxybutan-1-ol (**20**) as a colorless liquid. A sample was distilled: bp 55–57 °C (5 mm); $[\alpha]_D^{25}$ -4.26° (*c* 1.01, CHCl₃); IR (film) 3400, 1022 cm⁻¹; ¹H NMR 1.30 (d, 3 H, *J* = 5 Hz), 2.97–3.32 (m, 2 H), 3.62–3.95 (m, 2 H); MS, *m/z* 88 (2, M⁺), 70 (10), 59 (10), 57 (26), 45 (100), 44 (51), 43 (50).

(2*R*,3*S*)-(3-²H₁)-1,2-Butanediol (21b) and (2*R*,3*R*)-(2-²H₁)-1,3-Butanediol (22b).¹⁵ Into a stirring suspension of 2.8 g of LiAlD₄ in 125 mL of THF cooled to -78 °C under N₂ was dropped a solution of 3.22 g of **20** in 25 mL of THF over a 2-h period. The mixture was stirred at -78 °C for an additional 3.5 h, allowed to warm to room temperature, and then stirred for an additional 17 h. After cooling in ice, there was added dropwise 2.4 mL of water, 2.4 mL of 15% NaOH, and 5.15 mL more of water. Stirring was continued at room temperature for 15 min, MgSO₄ was added, and the mixture was filtered through a Celite pad. Evaporation of the filtrate gave a viscous pale yellow oil which was chromatographed on 160 g of silica gel 60 under a slight N₂ pressure. Elution was affected with hexane-ethyl acetate (1:3) in 40-mL fractions. In fractions 31–35 there was eluted 0.44 g of pure **21b**: $[\alpha]_D^{27}$ 9.69° (*c* 0.805, EtOH); IR (film) 3380, 2180 cm⁻¹; ¹H NMR 0.93 (d, 3 H, *J* = 7 Hz), 1.45 (m, 1 H), 3.33–3.77 (br m, 5 H); MS, *m/z* 91 (<1, M⁺), 73 (26), 61 (20), 60 (100), 59 (31), 58 (25), 45 (25), 43 (25).

Continued elution provided in fractions 36–54 pure **22b** (2.13 g): $[\alpha]_D^{27}$ -23.42° (*c* 0.41, EtOH); IR (film) 3350, 2180 cm⁻¹; ¹H NMR 1.22 (d, 3 H, *J* = 6 Hz), 1.67 (m, 1 H), 3.82 (d, 2 H, *J* = 5 Hz), 4.03 (m, 1 H); MS, *m/z* 91 (1, M⁺), 76 (17), 73 (73), 58 (38), 46 (31), 45 (70), 44 (38), 43 (100).

(2*R*,3*S*)-(2-²H₁)-1,3-Dibromobutane (23).¹⁵ To 2.0 g of **22b** in 8 mL of dry pyridine cooled at -15 °C was added dropwise methanesulfonyl chloride (5.02 g) over a 1-h period with stirring. The mixture was stored at -20 °C for 3 days, poured on crushed ice, and extracted with three portions of CH₂Cl₂. The combined extracts were washed with ice cold 5% HCl, dried (MgSO₄), and evaporated under reduced pressure to give a light yellow oil. The oil was dissolved in 45 mL of dry dioxane, 9 g of anhydrous LiBr was added, and the mixture heated at reflux for 18 h. After cooling, the mixture was poured into 50 mL of ice water and extracted with three portions of pentane. The combined extracts were washed with two portions of ice water and the combined aqueous layers washed with one portion of pentane. After all organic layers were combined, and the mixture dried the solvent was removed by distillation through a Vigreux column at atmospheric pressure. The remaining residue was distilled under reduced pressure to give 3.96 g of pure **23**: bp 84–85 °C (40 mm); $[\alpha]_D^{28}$ 58.08° (*c* 0.52, CHCl₃); ¹H NMR 1.75 (d, 3 H, *J* = 6 Hz), 2.30 (m, 1 H), 3.53 (dd, 2 H, *J* = 5 Hz, 1 Hz), 4.28 (dq, 1 H, *J* = 6 Hz, 2 Hz); MS, *m/z* 217 (5, M⁺), 215 (3), 139 (6), 138 (93), 136 (100), 135 (5).

(2*R*,3*R*)-(3-²H₁)-2-Methylcyclobutanone (25). Compound **25** was prepared as previously described¹⁶ for the undeuterated compound.

Into a suspension of 1.73 g of 57% NaH (free from oil, 0.041 mol of NaH) in 36 mL of dry Me₂SO and 13 mL of anhydrous ether was dropped over 1.5 h a solution of 3.1 g of tosylmethyl isocyanide²⁰ and 3.7 g of **23** in 11 mL of Me₂SO and 5 mL of ether, all under N₂ and stirring. After the addition, the mixture was stirred for 1.5 h longer and there was slowly added 11 mL of water. The mixture was extracted with ether ((2×) 18 mL, (1×) 11 mL, and (1×) 8 mL), the combined extracts washed with saturated brine ((3×) 8 mL), dried (Na₂SO₄) and evaporated to give a yellow oil. The oil was dissolved in 7.5 mL of ether, diluted with 12.5 mL of petroleum ether (bp 36–45 °C) and the clear solution stored at -20 °C overnight. The solid was filtered to give 2.24 g of **24** as white crystals. A sample was recrystallized from the same

solvent mixture: mp 110–112 °C dec; $[\alpha]_D^{28}$ -17.82° (*c* 0.55, CHCl₃); IR (CCl₄) 2140, 1605, 1345 cm⁻¹; ¹H NMR 1.05 (d, 3 H, *J* = 6 Hz), 2.18 (m, 1 H), 2.47 (s, 3 H), 2.62–3.58 (m, 2 H); MS, *m/z* 266 (<1, M⁺), 233 (24), 141 (13), 140 (44), 82 (33), 78 (42), 68 (100), 65 (21).

Acid hydrolysis of **24** (2.24 g) as previously described¹⁶ for the undeuterated **24** provided 0.74 g of pure (2*R*,3*R*)-(3-²H₁)-2-methylcyclobutanone (**25**): $[\alpha]_D^{28}$ 12.77° (*c* 0.595, CHCl₃); IR (CCl₄) 2210, 1785 cm⁻¹; ¹H NMR 1.18 (d, 3 H, *J* = 7.3 Hz), 1.58 (m, 1 H), 2.23 (m, 1 H), 2.78–3.62 (m, 2 H); MS, *m/z* 85 (36, M⁺), 57 (17), 56 (49), 55 (8), 48 (14), 43 (57), 42 (100); isotopic purity, 97%.

(*R*)-(3-²H₁)-2,2-Dimethylcyclobutanone (6). Lithium triphenylmethylide (2.5 mmol) was prepared by adding 1.06 mL of a 2.35 M solution of *n*-BuLi in hexane to 0.75 g of triphenylmethane in 8 mL of dry THF under N₂ with stirring.

After the lithium triphenylmethylide solution was cooled to -78 °C, there was added dropwise 0.288 g (3.4 mmol) of **25**. The deep red color of the triphenylmethylide anion was discharged and the solution was warmed to 0 °C and allowed to stir for 2.5 h. There was then added 0.37 mL of iodomethane and the mixture warmed to room temperature and stirred in the dark overnight. Most of the THF was distilled out of the mixture through a Vigreux column at atmospheric pressure, and the cyclobutanones remaining in the residue were isolated as a mixture by vacuum distillation at 70 °C (0.075 mm) and collecting the distillate in a trap immersed in liquid N₂. Gas chromatographic analysis of the distillate (column B, 90 °C) indicated a mixture of unreacted starting material (**25**, 20%), (*R*)-(3-²H₁)-2,2-dimethylcyclobutanone (**6**, 50%), and four other minor components (30%). Pure **6** was isolated by preparative gas chromatography: yield, 50 mg; IR (CCl₄) 2210, 1785 cm⁻¹; ¹H NMR 1.20 (s, 6 H), 1.81 (t, 1 H, *J* = 8.4 Hz), 3.03 (d, 2 H, *J* = 8.4 Hz); MS, *m/z* 99 (40, M⁺), 71 (47), 70 (52), 57 (100), 56 (55), 41 (88), 40 (49); isotopic purity, 97%.

(2*S*,4*R*,5*R*)-2-*tert*-Butyl-(5-²H₁)-4-methyl-1,3-dioxane (26b). In 0.75 mL of CH₂Cl₂ was dissolved 16.6 mg of **22b**, 0.040 mL of pivalaldehyde, and 4 mg of TsOH. The mixture was stirred for 5 h, diluted with 3 mL of CH₂Cl₂, washed with saturated NaHCO₃, dried (MgSO₄), and evaporated to give 25.5 mg of oil. Pure **26b** was obtained by preparative gas chromatography (column A, 125 °C): ¹H NMR (C₆D₆) see Figure 1b 0.82 (m, 1 H), 1.11 (d, 3 H, *J* = 6.2 Hz), 1.18 (s, 9 H), 3.31–3.37 (m, 2 H), 3.85 (d, 1 H, *J* = 11.3 Hz), 4.05 (s, 1 H); MS, *m/z* 159 (1, M⁺), 158 (5), 103 (10), 102 (100), 70 (6), 57 (37), 56 (64), 55 (15).

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