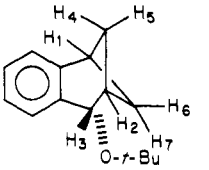
6.79, 7.28, 7.78, 8.58, 9.82, 10.60, 13.12, 13.55 μm; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.00–7.32 (m, aryl, 4 H), 3.25–3.45 (m, bridgeheads, 2 H), 1.20–2.05 (m) overlapping 1.33 (s, methyl) overlapping 1.25 (s, methyl) (12 H total); *m/e* 202.137 (calcd for $C_{14}H_{18}O$, *m/e* 202.136). The compound was independently synthesized by Wittig olefination of 2-benzonorbornen-2-one with ethyltriphenylphosphonium iodide, hydroboration, Jones oxidation, and Grignard addition of methylmagnesium iodide (a mixture of "**3**" and "**4**" is obtained).[75]

Preparative Photolysis of exoClBNB in *tert*-Butyl Alcohol. Irradiation of an argon degassed, 0.075 M solution of exoClBNB (45 mL) in a Vycor photolysis tube for 5 h with 15 254-nm lamps in the Rayonet gave a solution which was neutralized with solid $NaHCO_3$ (300 mg), evaporated in vacuo, taken up in ether (100 mL), washed with water (1 × 60 mL), and dried over $MgSO_4$. Removal of solvent left 531 mg of a yellow oil. Five of the seven photoproducts detected in the photoproduct mixture had already been isolated by VPC and structurally characterized in detail: **1**, **5**, and **8** from the photoreaction of exoClBNB in methanol, and *exo*-benzonorbornen-2-yl *tert*-butyl ether ("**6**") and 1,3-methanonaphthalen-4-yl *tert*-butyl ether ("**7**") from the photoreaction of exoMsBNB in *tert*-butyl alcohol (see below). The remaining two photoproducts were isolated from column N, 160 °C. **1-(Benzonorbornen-*endo*-2-yl)-2-methyl-2-hydroxypropane** ("**4**") had IR (neat) 2.97, 3.40, 6.80, 7.25, 8.61, 8.88, 10.90, 13.24 μm; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.90–7.26 (m, aryl, 4 H), 3.12–3.32 (m, bridgeheads, 2 H), 2.00–2.55 (m, exo-2-H and exo-3-H, 2 H), 1.00–1.90 (m) overlapping 1.12 (s, 12 H total); *m/e* 213.152 (calcd for $C_{15}H_{20}O$, *m/e* 213.151).

1-Benzonorbornen-*exo*-2-yl)-2-methyl-2-hydroxypropane ("**3**") had IR (CCl_4) 2.97, 3.41, 6.79, 7.29, 8.65, 8.88, 10.42, and 10.95 μm; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.97–7.30 (m, aryl, 4 H), 3.29 (m, bridgehead 4H, 1 H), 3.08 (m, bridgehead 1H, 1 H), 1.41–1.87 (m, 7 H), 1.22 (s, methyls, 6 H); *m/e* 213.152 (calcd for $C_{15}H_{20}O$, *m/e* 216.151). This compound was independently synthesized by oxidation of *endo*-benzonorbornen-2-yl-methanol (**4**) with pyridinium chlorochromate, Wittig olefination with isopropyltriphenylphosphonium iodide, and oxymercuration–demercuration.

Preparative Photolysis of exoMsBNB in *tert*-butyl Alcohol. Irradiation of 150 mL of a 0.011 M exoMsBNB solution in *tert*-butyl alcohol, in two 50-mL and three 25-mL Vycor photolysis tubes (after degassing 15 min with argon), with 16 254-nm lamps in the Rayonet reactor for 8 h, gave a solution which was diluted with 200 mL of water and extracted with ether (4 × 100 mL). The ether layers were combined and washed with water (2 × 60 mL) and 5% $NaHCO_3$ (1 × 60 mL) and dried over $MgSO_4$. Removal of ether in vacuo left 432.2 mg of an orange-yellow oil which by VPC on column A (170 °C) showed four products, two of which had been characterized as **5** and **8** (t_R 13 and 18 min, respectively). The remaining two photoproducts were isolated from column A (170 °C). (No photoproducts derived from a free radical process could be detected on columns H or K.) ***exo*-Benzonorbornen-2-yl *tert*-butyl ether ("6")** (t_R 28 min): IR (neat) 3.36, 6.01, 7.22, 7.34, 8.36, 8.60, 9.28, 9.44, 9.75, 10.00, 10.22, 13.21, 13.34 μm; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.90–7.25 (m, aryl, 4 H), 3.61 (m, endo-2-H, 1 H), 3.20 (m, bridgehead-4-H, 1 H), 3.08 (m, bridgehead-1-H, 1 H), 1.48–2.16 (m, 4 H), 1.19 (s, *t*-Bu, 9 H); *m/e* 216.150 (calcd for $C_{15}H_{20}O$, *m/e* 213.151). This compound was independently synthesized via ground-state solvolysis of ExoMsBNB. **1,3-Methanonaphthalen-4-yl *tert*-butyl ether ("7")**: IR (neat) 3.40, 6.70, 6.83, 7.30, 8.10, 8.34, 9.38, 9.74, 13.14, 13.56 μm; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.75–7.35 (m, aryl, 4 H), δ_3 4.83 (d, J_{32} = 3.2 Hz), δ_1 3.00 (q, $J_{12} \simeq J_{15} = J_{16} \simeq 5.8$ Hz), δ_2 2.69 (m, $J_2 \simeq 5.8$, $J_{23} = 3.2$, $J_{25} = J_{26} \simeq 7.0$ Hz), δ_5 2.42 (m, $J_{51} \simeq 5.8$, $J_{52} \simeq 7.0$, $J_{54} \simeq 8.3$ Hz), δ_6 2.26 (m, $J_{61} \simeq 5.8$, $J_{62} \simeq 7.0$, $J_{67} \simeq 8.3$ Hz), δ_7 1.72 (t, $J_{74} = J_{76} \simeq 8.3$ Hz), δ_4 1.53 (t, $J_{45} = J_{47} \simeq 8.3$ Hz), δ 1.35 (s, *t*-Bu, 9 H), where the following numbering applies:



m/e 216.151 (calcd for $C_{15}H_{20}O$, *m/e* 216.151).

Acknowledgment. We thank the U.S. Army Research Office, Texaco Oil Co., and the National Science Foundation (Grant 7926499) for support of this research. The high-field NMR data were obtained from the Prudue facility supported by NIH Research Grant PR 01077 from the division of Research Sources. We are grateful to Professor William Jorgensen for his assistance in our theoretical studies, Professors Ken Houk and Michael Paddon-Row for the PES spectra, and John Saddler for the high-field NMR spectra.

Registry No. 1, 4486-29-7; **3**, 73176-49-5; "**3**" (R′ = Cl), 7605-04-1; "**3**" (R′ = CH_3SO_2O), 31351-14-1; "**3**" (R′ = OH), 13153-47-4; "**3**" (R′ = OPr), 84988-56-7; "**3**" (R′ = $C(CH_3)_2OH$), 85027-46-9; "**3**" (R′ = *t*-BuO), 73151-76-5; **4**, 69103-46-4; "**4**" (R′ = Cl), 7605-05-2; "**4**" (R′ = CH_3SO_2O), 31351-15-2; "**4**" (R′ = OH), 13153-75-8; "**4**" (R′ = $C(CH_3)_2OH$), 84988-58-9; "**4**" (R′ = $CH_2C(CH_3)_2OH$), 84988-59-0; **5**, 4453-90-1; **6**, 73151-73-2; **7**, 73151-74-3; "**7**" (R″ = Pr), 84988-57-8; "**7**" (R″ = *t*-Bu), 73151-75-4; 2-chlorobenzonorbornadiene, 7605-08-5; benzonorbornen-2-one tosylhydrazone, 84988-55-6; benzonorbornen-2-one, 7374-90-5; 2-methylenebenzonorbornene, 7525-44-2; ethyltriphenylphosphonium iodide, 4736-60-1; (*E*)-2-heptene, 14686-13-6; oxygen, 7782-44-7; water, 7732-18-5; PrSH, 107-03-9; MeOH, 67-56-1; *i*-PrOH, 67-63-0; *t*-BuOH, 75-65-0.

Optical Rotatory Dispersion Studies. 135.[1] Synthesis and Chiroptical Properties of (*S*)- and (*R*)-(3-$^2H_1$)-2,2-Dimethylcyclobutanone. Evidence for Conformational Effects in Substituted Cyclobutanones

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Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received August 30, 1982*

Abstract: The synthesis, proof of absolute configuration, and other chiroptical properties of both (*S*)- and (*R*)-(3-$^2H_1$)-2,2-dimethylcyclobutanone (**5** and **6**) are reported. Both **5** and **6** exhibited temperature-dependent Cotton effects in their CD spectra characteristic of compounds having conformational mobility.

The use of circular dichroism (CD) as a tool for studying subtle conformational effects in cyclic ketones having isotopically engendered chirality is now well established.[2] However, of the examples reported so far, attention has focused mainly on the cyclohexanone and cyclopentanone systems with deuterium as the

(1) For preceding paper, see ref 4b.

(2) For review, see: Barth, G.; Djerassi, C. *Tetrahedron* **1981**, *37*, 4123–4142.

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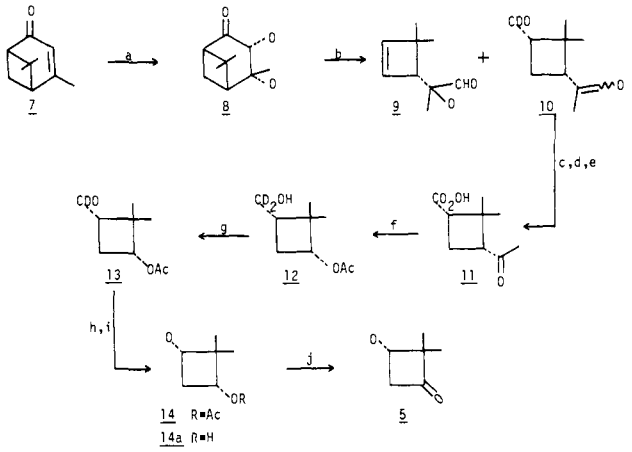
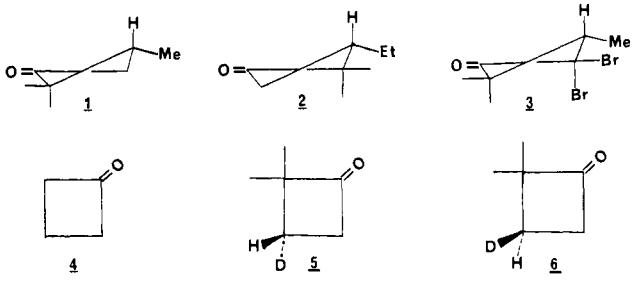
Scheme I



a. O_2,Pd/C,EtOAc; b. hν,MeOH; c. $LiAlO_4$; d. O_3,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.

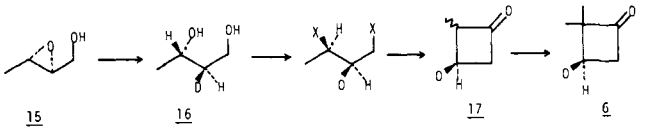
most commonly employed isotope. Thus we have reported[3,4] the synthesis and CD data of several conformationally mobile, chirally deuterated cyclohexanones and cyclopentanones and have found with the exception of one cyclopentanone[4b] that deuterium relative to hydrogen prefers to occupy a conformational 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 Gorē[5] 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

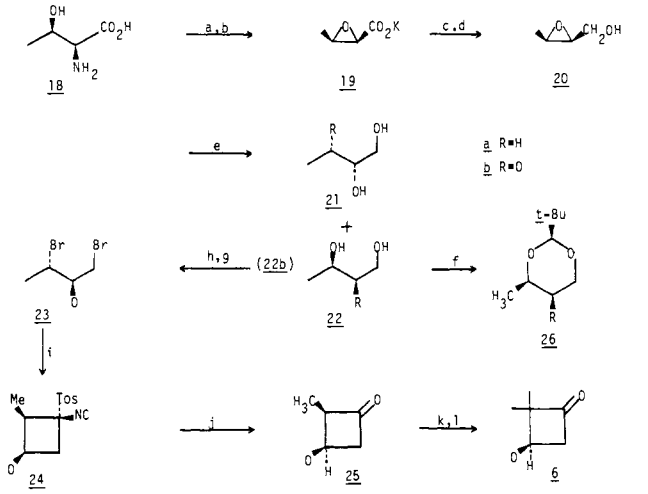


emerged which indicated that these cyclobutanones were most likely puckered and that the bulkier group at position 3 preferred the pseudoequatorial orientation. Although a microwave study[8] of the parent compound, cyclobutanone (**4**), indicated that it also was slightly puckered, an earlier liquid crystal NMR study[7] of **4** predicted a flat structure.

Scheme II



Scheme III



a. HONO,KBr; b. KOH,H_2O; c. CH_3I,DMF; d. $NaBH_4$,MeOH,H_2O; e. $LiAlO_4(LiAlH_4)$; f. $(CH_3)_3CCHO$,TsOH,CH_2Cl_2; g. MsCl,Pyr.; h. LiBr,dioxane; i. $TosCH_2NC$,NaH,DMSO, Et_2O; j. H_3O^+; k. Ph_3CLi,THF,-78°; l. CH_3I.

In order to gain more insight into isotopically induced conformational effects in cyclobutanones, we now report the synthesis and chiroptical properties of both (*S*)- and (*R*)-3-deuterio-2,2-dimethylcyclobutanone (**5** and **6**).

Synthesis

The synthesis of the *S* isomer **5** proceeded from (−)-verbenone (**7**, Scheme I). Catalytic deuteration of **7** gave dideuterioverbanone (**8**) which was photolyzed to give a 1:7.5 mixture of the two aldehydes **9** and **10** as previously reported[9] for the undeuterated verbanone. The two aldehydes were separated by silica gel chromatography and the major component **10**, after reduction with $LiAlD_4$, was ozonized to give ketol **11**. Baeyer–Villiger oxidation of **11** then provided the acetate **12** which was 97% isotopically pure as demonstrated by mass spectral analysis. Further oxidation of **12** with pyridinium chlorochromate gave aldehyde **13**. It has been previously reported that Rh(I)-catalyzed decarbonylations of cyclopropyl carboxaldehydes occur with transfer of hydrogen from the aldehyde group to the cyclopropane via an intramolecular process which proceeds with retention of configuration.[10] Consequently, the deuterioaldehyde **13** was subjected to decarbonylation in the presence of tris(triphenylphosphine)rhodium chloride to give the acetate **14**. Base hydrolysis of **14** followed by Jones oxidation of the resulting alcohol provided **5** having 60% deuterium incorporation at C-3 as determined by mass spectral analysis.[11] Assuming 100% retention of configuration in the decarbonylation of **13**, the enantiomeric excess of **5** is that of the starting compound, i.e., 90%.

The initial attempts to prepare the *R* isomer **6** made use of the chiral epoxy alcohol **15** (Scheme II) as a key intermediate. It was anticipated that $LiAlD_4$ reduction of **15** would give predominately the 1,3-diol **16** which by proper functional group manipulation and ring closure with a carbonyl dianion equivalent would give the 2-methylcyclobutanone **17**. Regioselective alkylation with iodomethane would then give the desired epimer **6**.

Attempts to prepare sizable quantities of *trans*-epoxy alcohol **15** by the Sharpless asymmetric epoxidation of *trans*-crotyl alcohol[12] consist-

(3) (a) Sundararaman, P.; Barth, G.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 5231–5236. (b) Djerassi, C.; van Antwerp, C. L.; Sundararaman, P. *Tetrahedron Lett.* **1978**, 535–538. (c) Lee, S. F.; Barth, G.; Kieslich, K.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 3965–3966. (d) Lee, S. F.; Barth, G.; Djerassi, C. *Ibid.* **1978**, *100*, 8010–8012. (e) Lee, S. F.; Barth, G.; Djerassi, C. *Ibid.* **1981**, *103*, 295–301.

(4) (a) Lee, S. f.; Edgar, M.; Pak, C. S.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 4784–4790. (b) Sundararaman, P.; Barth, G.; Djerassi, C. *Ibid.* **1981**, *103*, 5004–5007.

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

(6) Dixon, S. J.; Linder, R. E.; Barth, G.; Bunnenberg, E.; Djerassi, C.; Seamans, L.; Moscowitz, A. *Spectrosc. Lett.* **1976**, *9(11)*, 777–778.

(7) d'Annibale, A.; Lunnazi, L.; Fronza, G.; Mondelli, R.; Bradamante, S. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1908–1911.

(8) Stigliani, W. M.; Laurie, V. W.; Scharpen, L. H. *J. Mol. Spectrosc.* **1976**, *62*, 85–89.

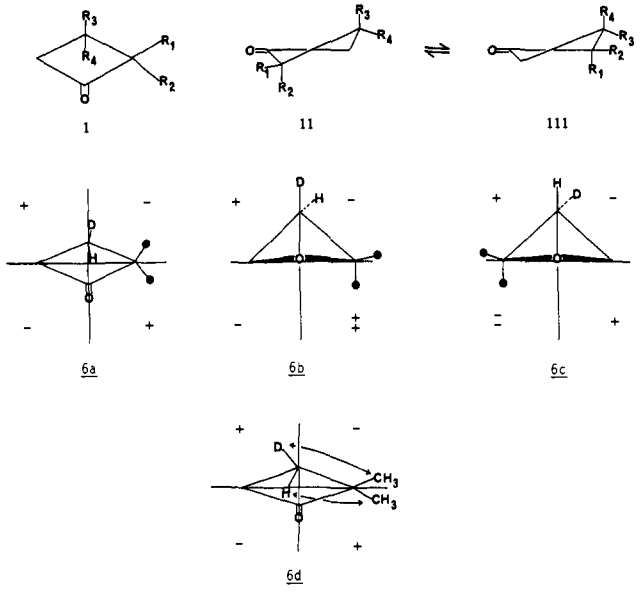
(9) Hobbs, P. D.; Magnus, P. D. *J. Am. Chem. Soc.* **1976**, *98*, 4594–4600.

(10) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465–5468.

(11) The apparent loss of deuterium can be attributed to reaction conditions in the decarbonylation step (**13** → **14**). The exact cause of deuterium loss was undetermined.

(12) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464–465. Katsuki, T.; Sharpless, K. B. *Ibid.* **1980**, *102*, 5975–5976.

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 sequence[17] 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 acid[13] 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 $NaBH_4$ to provide **20** as a rather volatile, water-soluble liquid. Reduction of **20** with $LiAlH_4$ according to a procedure previously reported for ethyl (*E*)-2,3-epoxybutyrate[15] gave the two diols **22a** and **21a** in an approximate ratio of 2:1, respectively. Reduction of **20** in a similar manner with $LiAlD_4$ 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 unlabled 2-methylcyclobutanone.[18] Attempts to generate the thermodynamic enolate of 2-methylcyclobutanone with LiH–DME, NaH–DME, Et_2NLi–DME, Ph_3CLi–Et_2O, or LDA–Et_2O 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%.

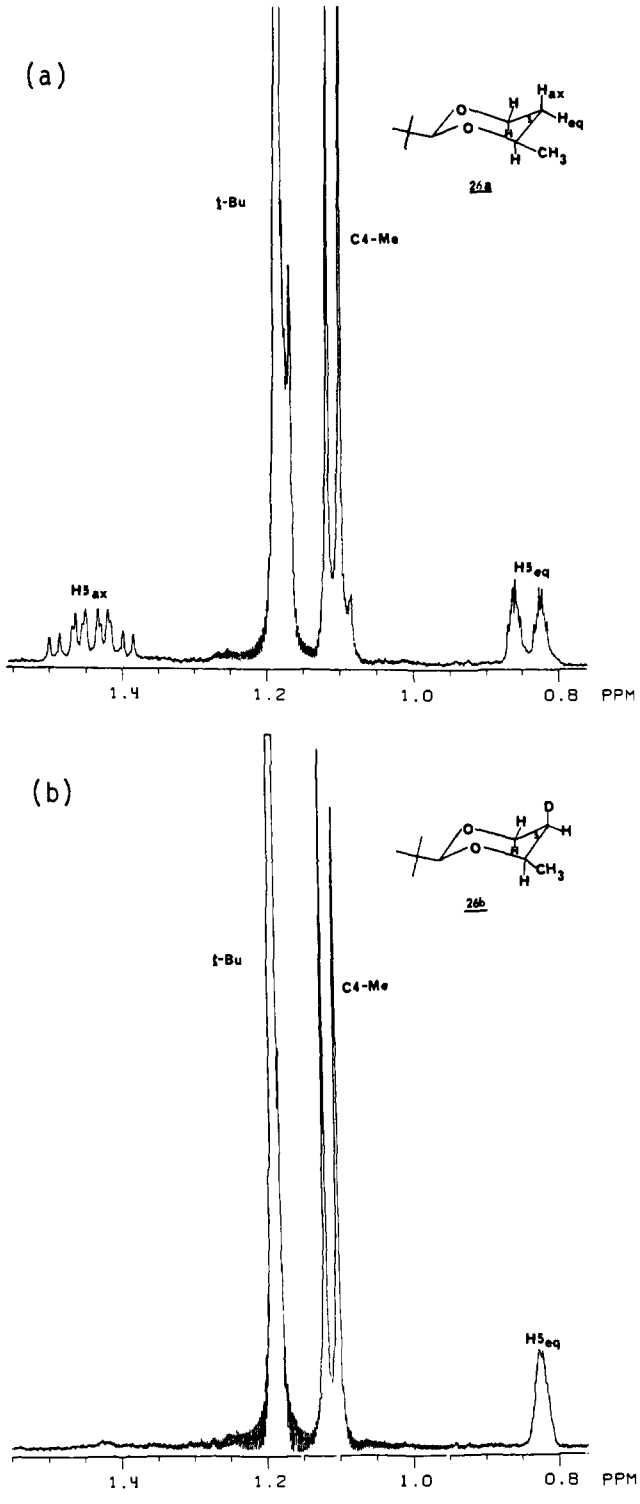


Figure 1. Partial 360-MHz ^1H NMR spectra of (a) (2*S*,4*R*)-2-*tert*-butyl-4-methyl-1,3-dioxane and (b) (2*S*,4*R*,5*R*)-2-*tert*-butyl-(5-$^2H_1$)-4-methyl-1,3-dioxane, both in benzene-d_6.

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

(13) Shimohigashi, Y.; Waki, M.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 945–950.
(14) Buehler, C. A.; Pearson, D. E., Ed. "Survey of Organic Synthesis"; Wiley: New York, 1970; p 817.
(15) Baldwin, J. E.; Fleming, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 5261–5266.
(16) van Leusen, D.; van Leusen, A. M. *Synthesis* **1980**, 325–326.
(17) Majetich, G.; Stork, G., personal communication.
(18) The 2-methylcyclobutanone was prepared as in ref 16.

here (**5** or **6**) is ideally suited to explore both possibilities. If the true representation of **6** is as shown in I ($R_1 = R_2 = CH_3$, R_3 = D, R_4 = 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 manner[2] (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 Goré[5] 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 ($R_1 = R_2 = CH_3$, R_3 = D, R_4 = 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

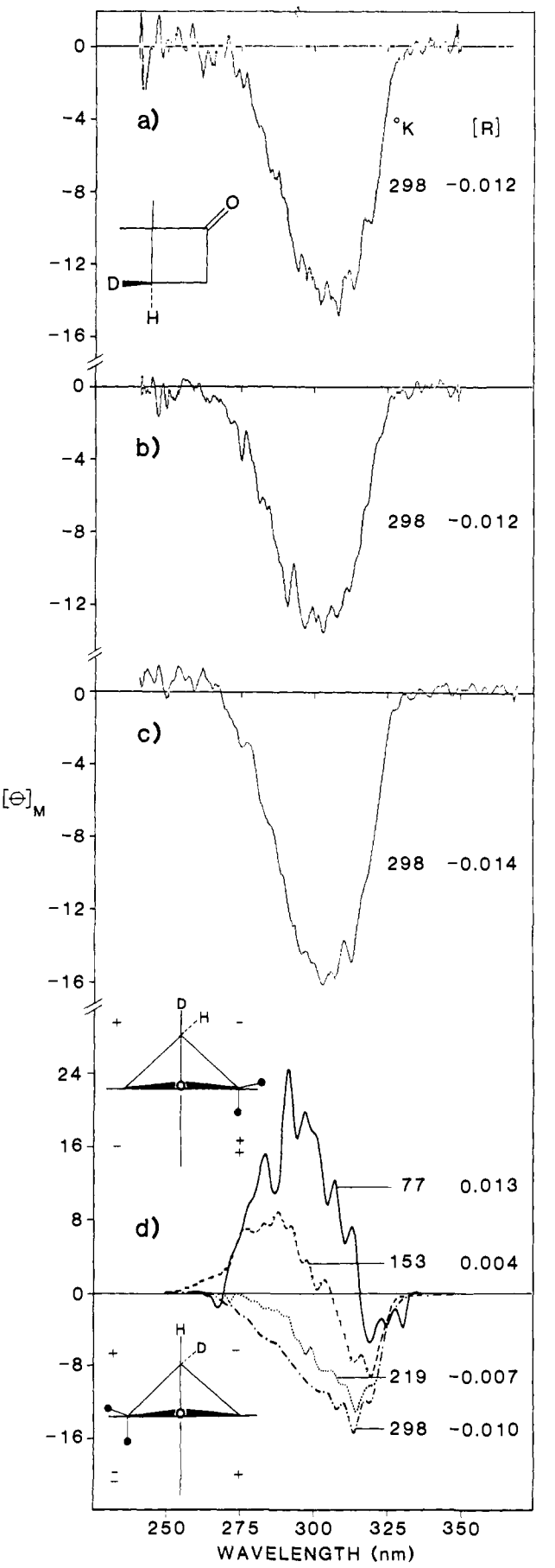


Figure 2. Circular dichroism spectra of (*R*)-(3-$^2H_1$)-2,2-dimethylcyclobutanone (**6**) in (a) isooctane at room temperature, c = 2.49 g/L; (b) methanol at room temperature, c = 3.01 g/L; (c) ether, isopentane, ethanol (5:5:2) at room temperature, c = 3.77 g/L; (d) isopentane, methylcyclohexane (4:1) at various temperatures between 298 and 77 K, c = 5.49 g/L.

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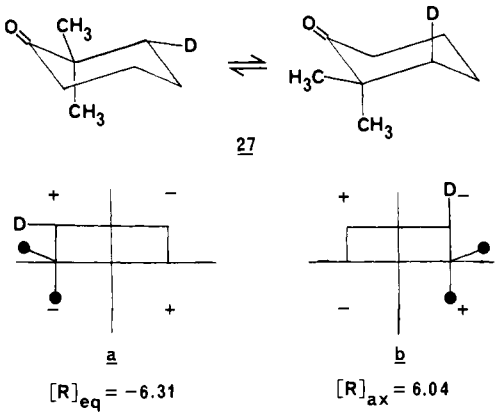
(20) Possel, Cf. O.; van Leusen, A. M. *Tetrahedron Lett.* **1977**, 4229.



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 described[19] 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 (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. ^{1}H 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). (−)-Verbenone (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**: ^{1}H 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 $NaHCO_3$ was photolyzed to yield the two aldehydes **9** and **10** in the ratio of 1:7.5 as previously reported.[9] Compound **9**: ^{1}H 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**: ^{1}H 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-$^2H_2$)methanol (11). Aldehyde **10** (9.5 g) was reduced in ether with 0.65 g of $LiAlD_4$ at 0 °C to yield 8.2 g of 2,2-dimethyl-3-[1-methyl(2-$^2H_1$)ethenyl]cyclobutyl(α,α-$^2H_2$)-methanol: $[\alpha]^{25}_D$ −10.51° (c 1.90, $CHCl_3$); IR (film) 3150, 2100, 2050, 1650 cm^{-1}; ^{1}H 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, $M^+ - CD_2OH$), 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 Me_2S, and after standard workup there was obtained 1.6 g of ketol **11**: $[\alpha]^{25}_D$ 100.87° (c 9.20, $CHCl_3$); IR (film) 3200, 2100, 2050, 1740 1725 cm^{-1}; ^{1}H NMR 0.93 (s, 3 H), 1.70 (s, 3 H), 2.03 (s, 3 H), MS, m/z 125 (15, $M^+ - CD_2OH$), 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-$^2H_2$)methanol (12). To a solution of 1.6 g of **11** in 50 mL of CH_2Cl_2 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 $NaHCO_3$ and then saturated sodium thiosulfate. After the solution was washed again with saturated $NaHCO_3$ followed by water and brine and dried the solvent was evaporated to give 1.26 g of the acetate **12**: $[\alpha]^{25}_D$ −32.50° (c 1.70, $CHCl_3$); IR (film) 3200, 2100, 2050, 1740, 1725 cm^{-1}; ^{1}H 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-acetoxycyclobutane(α-$^2H_1$)carboxaldehyde (13). To a suspension of pyridinium chlorochromate in 50 mL of CH_2Cl_2 was added 1.2 g of **12** in 2 mL of CH_2Cl_2. 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**: $[\alpha]^{25}_D$ −109.7° (c 1.10, $CHCl_3$); IR (film) 2050, 1740, 1700 cm^{-1}; ^{1}H 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-$^2H_1$)-2,2-Dimethylcyclobutyl Acetate (14). To a solution of 0.4 g of aldehyde **13** in 6 mL of CH_2Cl_2 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 ($CHCl_3$) 2100, 1735 cm^{-1}; ^{1}H 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^+ − $CH_3C{\equiv}O^+$), 87 (12), 86 (17), 83 (17), 82 (21), 72 (34), 67 (17), 45 (22), 44 (32), 43 (100); isotopic purity, 60%.

(S)-(3-$^2H_1$)-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 ($MgSO_4$), 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 ($CHCl_3$) 3310, 2100 cm^{-1}; ^{1}H 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 CO_2 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 ($MgSO_4$) 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): $[\alpha]^{25}_D$ 4.22° (c 0.925, $CHCl_3$); IR (film) 1745, 1260 cm^{-1}; ^{1}H 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 $NaBH_4$ 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 ($MgSO_4$), and the solvents removed by distillation through a Vigreux column at atmospheric pressure. The remaining residue was chromato-

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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); $[\alpha]^{25}_D$ −4.26° (*c* 1.01, $CHCl_3$); 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-$^2H_1$)-1,2-Butanediol (21b) and (2*R*,3*R*)-(2-$^2H_1$)-1,3-Butanediol (22b).[15] Into a stirring suspension of 2.8 g of $LiAlD_4$ in 125 mL of THF cooled to −78 °C under N_2 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, $MgSO_4$ 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 N_2 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**: $[\alpha]^{27}_D$ 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): $[\alpha]^{27}_D$ −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-$^2H_1$)-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 CH_2Cl_2. The combined extracts were washed with ice cold 5% HCl, dried ($MgSO_4$), 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); $[\alpha]^{28}_D$ 58.08° (*c* 0.52, $CHCl_3$); ^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-$^2H_1$)-2-Methylcyclobutanone (25). Compound **25** was prepared as previously described[16] 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 Me_2SO and 13 mL of anhydrous ether was dropped over 1.5 h a solution of 3.1 g of tosylmethyl isocyanide[20] and 3.7 g of **23** in 11 mL of Me_2SO and 5 mL of ether, all under N_2 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 (Na_2SO_4) 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; $[\alpha]^{28}_D$ −17.82° (*c* 0.55, $CHCl_3$); IR (CCl_4) 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 described[16] for the undeuterated **24** provided 0.74 g of pure (2*R*,3*R*)-(3-$^2H_1$)-2-methylcyclobutanone (**25**): $[\alpha]^{28}_D$ 12.77° (*c* 0.595, $CHCl_3$); IR (CCl_4) 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-$^2H_1$)-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 N_2 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 N_2. Gas chromatographic analysis of the distillate (column B, 90 °C) indicated a mixture of unreacted starting material (**25**, 20%), (*R*)-(3-$^2H_1$)-2,2-dimethylcyclobutanone (**6**, 50%), and four other minor components (30%). Pure **6** was isolated by preparative gas chromatography: yield, 50 mg; IR (CCl_4) 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-$^2H_1$)-4-methyl-1,3-dioxane (26b). In 0.75 mL of CH_2Cl_2 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 CH_2Cl_2, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 25.5 mg of oil. Pure **26b** was obtained by preparative gas chromatography (column A, 125 °C): ^1H NMR (C_6D_6) 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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